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Genome-wide meta-analysis of quantitatively measured generalized anxiety symptoms in individuals of European ancestry

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Anxiety is heritable and exists on a continuum, with symptoms ranging from adaptive threat response to clinical disorder. Here we performed a genome-wide association meta-analysis of generalized anxiety symptom severity in 693,869 individuals of European ancestry from 14 cohorts. We identified 80 independent genome-wide significant variants within 74 loci, 39 of which were newly associated with anxiety. SNP-based heritability was 5.9% (posterior s.d. = 0.15%). Polygenic scores were significantly associated with anxiety symptom severity and disorder in European, African and South Asian ancestry samples (R^2 = 1.2–2.9%). Significant genetic correlations (r_g) were estimated with mental and physical health traits, including case–control anxiety, neuroticism and depression (r_g = 0.71–0.85), irritable bowel syndrome (r_g = 0.57), coronary artery disease, endometriosis and migraine (r_g = 0.20–0.27). Gene-based and pathway analyses implicated synaptic and axonal processes, with enriched expression in the brain. These findings highlight the discovery power gained from analysing a quantitative trait rather than a case–control phenotype in anxiety genetics.

Anxiety disorders are the most prevalent mental health conditions worldwide[1] and rates are rising[2–4]. Anxiety is associated with reduced quality of life[5], elevated mortality[6,7] and is frequently comorbid with other mental[8–12] and physical[13] health conditions, ranging from irritable bowel syndrome to cancer. When co-occurring with other conditions, anxiety symptoms can exert an independent and sometimes greater impact on quality of life and functioning than the primary diagnosis[8], as has been reported in autism[14] and bipolar disorder[15].

Twin and family studies estimate the heritability of anxiety disorders at 20–60% (ref. 13), with measures capturing stable anxiety typically showing higher heritability[16]. Early case–control genome-wide association studies (GWAS)[17–19], which aggregated across anxiety subtypes, identified a handful of risk loci. More recent large-scale efforts using a range of analytical approaches have reported between 14 and 51 associated loci[20–22]. A recent GWAS[23] of anxiety disorders from the Anxiety Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ANX) identified 58 independent loci from over 120,000 cases. Across these studies, single nucleotide polymorphism (SNP)-based heritability estimates ranged from 5% to 10% (refs. 20,22,23).

Fear and worry serve an evolutionary function by promoting vigilance and caution in response to potential threats[24]. Variation in threat sensitivity across individuals may be adaptive at the group level and, consistent with this, anxiety symptoms exist in the population along a continuum of frequency and severity. Clinical anxiety represents a practical threshold at the upper extreme of this distribution based on levels of distress and functional impairment. GWAS of anxiety using quantitative symptom scores capture genetic variation across the full phenotypic range, not only at clinical thresholds. This approach can offer greater statistical power[25] and a more comprehensive representation of genetic associations with anxiety traits. The degree of genetic overlap between quantitative anxiety symptom severity and disorder status has received little study. A GWAS of a 2-item anxiety scale in the

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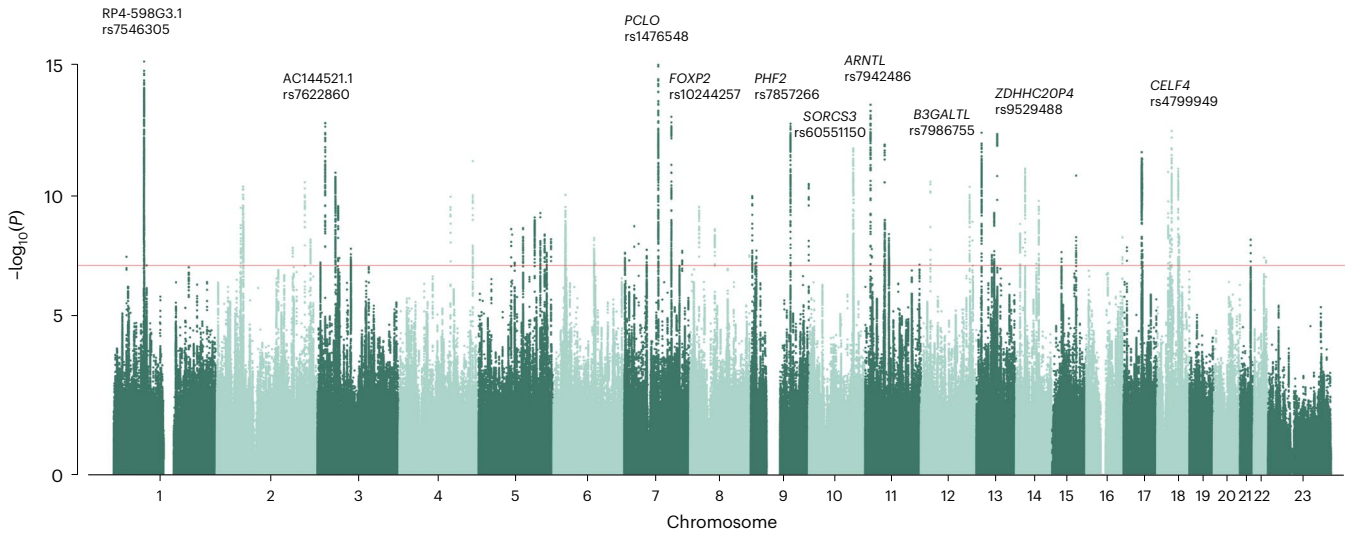

Fig. 1 | Manhattan plot of the genome-wide association meta-analysis of generalized anxiety symptom severity. Variants are represented as points plotted against their respective genomic location and association significance value (two-tailed test). The red line indicates the genome-wide significant threshold ($P < 5 \times 10^{-8}$). Sample size, $N = 693{,}869$.

European ancestry subsample of the Million Veteran Program (MVP) identified 5 significant loci[26] and moderate-to-strong genetic correlations with lifetime anxiety disorder ($r_g = 0.59–0.87$)[13,26]. However, the brevity of the measure may have limited the potential to comprehensively capture phenotypic variance. Additional support for shared genetic signal across the anxiety continuum, including above and below diagnostically relevant thresholds, comes from a UK Biobank study[19] reporting high genetic correlations between mild, moderate and severe anxiety symptom groupings ($r_g = 0.76–0.98$). Among individuals with lifetime anxiety or depression, anxiety symptom severity has also shown a significant genetic correlation with functional impairment ratings ($r_g = 0.79$)[27], which have clinical relevance.

These findings provide preliminary evidence that a well-powered GWAS of quantitative anxiety would identify variants relevant to both symptom severity and clinically defined anxiety. Aside from the MVP analysis of a two-item scale, previous quantitative anxiety GWAS[28,29] have incorporated other psychiatric or personality traits to maximize statistical power, resulting in findings relating to a broader construct than anxiety symptoms specifically. To address this, we performed a genome-wide association meta-analysis of generalized anxiety disorder (GAD) symptom severity in 693,869 individuals of inferred European ancestry across 14 cohorts from PGC-ANX, building on our previous study[23] of individuals with anxiety disorder. Most cohorts used the GAD 7-item scale (GAD-7) or conceptually similar self-report measures of recent GAD symptoms. In addition to identifying associated loci, we performed variant- and gene-level investigations, estimated genetic correlations with relevant traits and evaluated polygenic score prediction in independent samples of European, African and South Asian ancestry.

Results

Genome-wide association meta-analysis

We performed a genome-wide association meta-analysis of GAD symptom severity in 693,869 individuals of European ancestry across 14 cohorts from 8 countries (see Supplementary Tables 1–3 for cohort, phenotype and GWAS details). The analysis identified 80 independent genome-wide significant variants ($P < 5 \times 10^{-8}$) across 74 loci (Fig. 1, Supplementary Fig. 1 and Supplementary Table 4. Effect sizes (β) represent the associated change in standard deviation units of generalized anxiety symptom score per additional copy of the effect allele. The top signal came from an intergenic locus near the long non-coding RNA *RP4-598G3.1* on chromosome 1 (lead SNP rs7546305; $P = 3.8 \times 10^{-15}$; $\beta = -0.014$; 95% confidence interval (CI), −0.017 to −0.010), followed by a locus within an intron of *PCLO* on chromosome 7 (lead SNP rs1476548; $P = 4.9 \times 10^{-15}$; $\beta = -0.014$; 95% CI, −0.017 to −0.010). These loci have both previously been associated with internalizing traits, including anxiety (Supplementary Table 5).

Of the 74 loci, 16 had no previous associations with internalizing trait GWAS, including neuroticism, anxiety or depression, at any variant in linkage disequilibrium (LD; defined as $r^2 > 0.1$) with the lead SNP (Methods and Supplementary Table 5a). Thirty-nine loci were novel for anxiety specifically, measured either as a diagnosis or symptom severity phenotype. Of the 58 loci previously identified in the PGC-ANX anxiety disorder study[23], all showed the same direction of association in the present analysis, with 19 (33%) reaching genome-wide significance and a further 33 (57%) showing nominal significance ($P < 0.05$) (Supplementary Table 5b). Nine of the 14 cohorts included here also contributed to the PGC-ANX anxiety disorders study, although cohort sample composition differed somewhat due to the availability of symptom score versus diagnostic information. Power calculations[30] confirmed increased power in the present analysis relative to the anxiety disorder study (Supplementary Table 6).

Among the 6,012 genome-wide significant SNPs, between-study heterogeneity accounted for a moderate proportion of variance in effect size estimates (measured with I^2), with a median I^2 across cohorts of 29.7%. In contrast, the median I^2 for the 80 LD-independent genome-wide significant SNPs was 0%, indicating highly consistent effect size estimates across cohorts. Heterogeneity statistics for the lead SNPs are presented in Supplementary Table 4. Genetic correlations between sufficiently powered cohorts, estimated using LD score regression (LDSC), ranged from 0.64 to 0.97 (significant at a Bonferroni-corrected threshold $P < 4.6 \times 10^{-4}$; Supplementary Table 7). As a sensitivity analysis, we categorized cohorts by generalized anxiety symptom severity measure (for example, GAD-7; six subgroups) and by ascertainment method (community and clinical subgroups) (Supplementary Table 2). Subgroup meta-analyses were performed as per the main analysis, and genetic correlations between subgroups were estimated with LDSC. While most subgroup comparisons were underpowered, including by ascertainment method, the genetic correlation between the 2 most frequently used measures was high (GAD-7 and GAD-2, $r_g = 0.86$; 95% CI, 0.79–0.92; $P = 9.6 \times 10^{-166}$, significant at a Bonferroni-corrected threshold $P < 5 \times 10^{-3}$; Supplementary Table 8).

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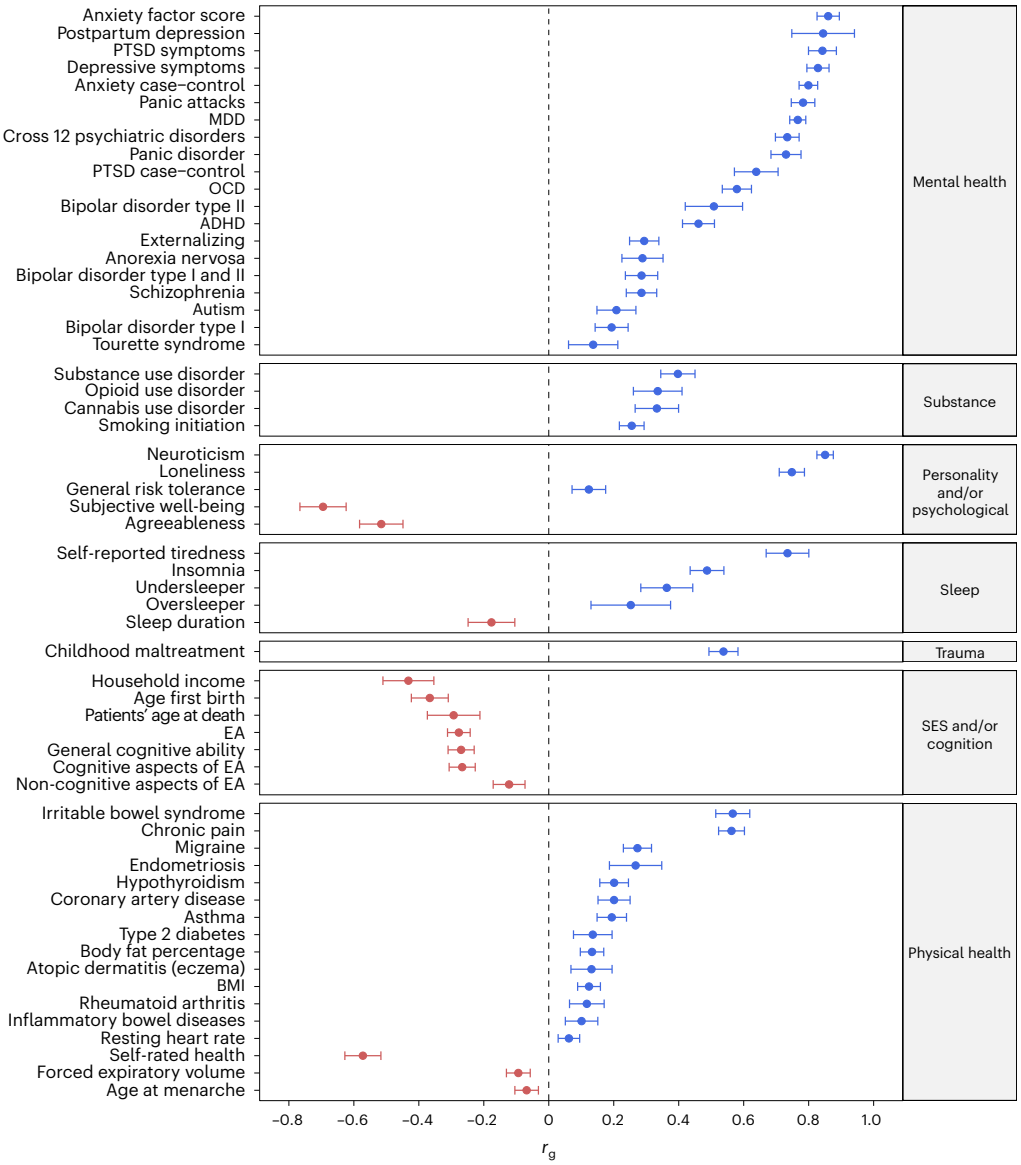

Fig. 2 | Genetic correlations between generalized anxiety symptom severity meta-analysis and a range of traits from existing GWASs. Genetic correlations estimated using LDSC (N = 693,869). All correlations shown are significant at a Bonferroni-corrected threshold for 105 tests (2-tailed $P < 4.76 \times 10^{-4}$). Points represent genetic correlation estimates and bars represent 95% CIs. Exact P values and full results for all tested traits are provided in Supplementary Table 9. Forced expiratory volume is a measure of lung function. ADHD, attention-deficit/hyperactivity disorder; BMI, adult body mass index; EA, educational attainment; MDD, major depressive disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder; SES, socio-economic status.

SNP-based heritability and genetic correlations with external traits

The SNP-based heritability estimate from SBayesRC was 5.90% (posterior s.d. = 0.146%). SBayesRC was selected due to the known underestimation of heritability from LDSC[31]. LDSC[32] indicated that genomic inflation was largely not attributable to confounding (intercept = 1.03; 95% CI, 1.01–1.05). To characterize the broader genetic architecture of GAD symptoms, we used LDSC[33] to estimate genetic correlations with 105 traits spanning mental and physical health, personality, cognitive and socio-economic domains (Supplementary Table 9). Following Bonferroni correction ($P < 4.8 \times 10^{-4}$), 64 associations remained significant (Fig. 2, omitting 4 traits represented by multiple studies).

The strongest correlations were observed with quantitative internalizing traits, including neuroticism, depressive symptoms and a genetic anxiety factor (r_g = 0.83–0.86), and with case–control phenotypes for anxiety and depression (r_g = 0.71–0.80). Moderate-to-strong estimates were also found for post-traumatic stress disorder (r_g = 0.64), insomnia (r_g = 0.49), irritable bowel syndrome (r_g = 0.57) and chronic pain (r_g = 0.56). Negative correlations were observed with socio-economic status indicators including household income (r_g = −0.43). Smaller but significant correlations were identified with coronary artery disease, endometriosis, hypothyroidism and migraine (r_g = 0.20–0.27). Most other associations with physical traits and illnesses were comparatively weaker and included positive correlations with resting heart rate, rheumatoid arthritis and atopic dermatitis, and a negative correlation with lung function (absolute r_g = 0.06–0.13).

Conditional analyses

To assess whether genome-wide significant loci for generalized anxiety symptoms represented associations unique to this phenotype, we performed multi-trait conditional and joint analysis (mtCOJO)[34], conditioning on highly genetically correlated traits. mtCOJO uses Generalized Summary-data-based Mendelian Randomization (GSMR) to estimate the effect of a conditioning trait on an outcome (b_{xy}). Conditioning

on neuroticism (67 instruments, GSMR $b_{xy} = 0.47 \pm 0.02$) resulted in 9 remaining genome-wide significant SNPs across 2 loci ($P < 5 \times 10^{-8}$; Supplementary Table 10). Conditioning on case–control anxiety (11 instruments, $b_{xy} = 0.22 \pm 0.02$) yielded 66 significant SNPs across 6 loci, and conditioning on case–control depression (98 instruments, $b_{xy} = 0.31 \pm 0.01$) produced 76 SNPs across 6 loci. Approximately half of SNP effect sizes were attenuated and standard errors had a median inflation of 7–9%, suggesting the loss of significance was not solely attributable to reduced power. Sign changes were observed in 17–20% of variants for each trait, consistent with instability, as expected under high genetic correlations. The LDSC SNP-based heritability (h^2) estimates of the conditioned summary statistics were significant (neuroticism $h^2 = 0.014$; 95% CI, 0.012–0.016; $P = 1.02 \times 10^{-42}$; case–control anxiety $h^2 = 0.018$; 95% CI, 0.016–0.020; $P = 1.54 \times 10^{-59}$; case–control depression $h^2 = 0.017$; 95% CI, 0.015–0.019; $P = 7.34 \times 10^{-51}$), but block jack-knifing confirmed that each was significantly lower than the original estimate (Z-statistic = 33.24, $P = 3.3 \times 10^{-242}$; $Z = 28.61$, $P = 5.0 \times 10^{-180}$; $Z = 30.48$, $P = 4.24 \times 10^{-204}$, respectively).

Polygenic risk scores

To evaluate the within- and cross-ancestry generalizability of our GWAS findings, we generated a polygenic risk score (PRS) for GAD symptom severity using SBayesRC[35] and tested its association with both quantitative and case–control anxiety outcomes in independent samples across ancestry groups (Supplementary Table 11). A Bonferroni-corrected significance threshold of $P < 1.7 \times 10^{-2}$ was applied, accounting for 3 ancestry groups tested per outcome. The PRS significantly explained 2.9% of the variance (R^2) in generalized anxiety symptom scores in an independent European ancestry sample ($\beta = 0.55$; 95% CI, 0.44–0.65; $P = 8.9 \times 10^{-24}$), 1.4% in an African ancestry sample ($\beta = 0.48$; 95% CI, 0.28–0.67; $P = 2.9 \times 10^{-6}$) and 1.2% in a South Asian ancestry sample ($\beta = 0.45$; 95% CI, 0.27–0.64; $P = 2.0 \times 10^{-6}$). For case–control anxiety, assuming 20% prevalence, the PRS explained 1.8% ($\beta = 0.25$; 95% CI, 0.14–0.36; $P = 1.2 \times 10^{-5}$) of the variance on the liability scale in a European ancestry sample, 1.7% ($\beta = 0.27$; 95% CI, 0.10–0.44; $P = 2.0 \times 10^{-3}$) in an African ancestry sample and 1.4% ($\beta = 0.25$; 95% CI, 0.10–0.41; $P = 1.3 \times 10^{-3}$) in a South Asian ancestry sample. These R^2 values represent the variance explained by the PRS beyond that accounted for by covariates.

Positional and functional annotation

Functionally informed fine-mapping using PolyFun[36] and SuSiE[37] identified 4 putative causal variants with posterior inclusion probabilities (PIP) ≥0.95. Two of these were index variants for genome-wide significant loci: rs2392289 at locus 31 (PIP = 0.983) and rs72676302 at locus 58 (PIP = 0.978). The remaining two variants were in loci that did not reach genome-wide significance. One variant, rs72676302, had a high Combined Annotation Dependent Depletion (CADD) score of 19.78, suggesting a deleterious effect (above the suggested threshold of 12.37 (ref. 38)), although there was little biological evidence that it is within a regulatory element (regulomeDB score = 5). In addition, we identified 24 small credible causal sets (<10 variants each) that cumulatively met the PIP threshold (Supplementary Table 12).

SNP-level gene annotation was performed using FUMA[39] based on positional, expression quantitative trait loci (eQTL), and chromatin interaction (Hi-C) mapping (Supplementary Table 13). We identified genes annotated by more than one method, with this convergence providing greater support for their involvement. This approach again highlighted *PCLO* and *CRHR1*, a key regulator of the stress response, along with *TMEM106B*, which has been repeatedly associated with anxiety[18,19,23] and with depression[40]. *SORCS3* was implicated by both positional and chromatin interaction mapping and has also been reported in a previous anxiety GWAS[23]. In addition, multiple genes were identified that have previously been implicated in depression (for example, *ERBB4*, *GRM7*, *VRK2*, *DCC*, *LRFN5*, *PCLO* and *NEGR1*) and schizophrenia (for example, *ERBB4*, *VRK2* and *NEGR1*). *MAD1L1* (refs. 17–19,26) was supported only by positional mapping in our analysis but has been linked to anxiety phenotypes in previous GWAS, lending further support to its potential relevance. Although detailed functional information was limited for many mapped genes, several are posited to play roles in key neurotransmitter systems, including glutamatergic (*GRM7* and *HOMER1*), GABAergic (*ERBB4*) and dopaminergic (*DRD1*) signalling. In contrast, gene annotations for loci novel for internalizing traits did not map clearly to defined neurobiological pathways relevant to anxiety. For example, rs58179213 is proximal to multiple genes implicated in diverse biological processes, including lung function (*SFTPC*), intestinal barrier function and immunoprotective inflammation (*FHIP2B*), and hair growth (*HR*). While such processes could influence anxiety via indirect pathways (for example, gut–brain interactions or somatic symptoms), independent replication will be required to provide the greater power necessary to determine their robustness and relevance.

Gene-based associations and enrichment

Gene-based association analysis was conducted using MAGMA[41], which aggregates trait–SNP associations across all SNPs within a gene while accounting for LD. In total, 197 genes across 80 independent loci surpassed the Bonferroni-corrected significance threshold ($P < 2.5 \times 10^{-6}$; Supplementary Table 14). The top associated gene was *PCLO* ($P = 2.5 \times 10^{-21}$), mirroring the SNP-based results.

To assess biological pathways significantly enriched for associations with GAD symptom severity, we performed pathway analysis in MAGMA with predefined gene sets (MsigDB[42]; curated and Gene Ontology terms; Supplementary Table 15,a). Six gene sets passed Bonferroni correction ($P < 2.9 \times 10^{-6}$): postsynaptic membrane (271 genes, $P = 2.6 \times 10^{-8}$), synaptic membrane (383 genes, $P = 7.1 \times 10^{-8}$), axon (627 genes, $P = 5.3 \times 10^{-7}$), neurogenesis (1,627 genes, $P = 8.6 \times 10^{-7}$), postsynapse (648 genes, $P = 9.2 \times 10^{-7}$) and generation of neurons (1,412 genes, $P = 1.0 \times 10^{-6}$). These results were unaffected by the exclusion of the major histocompatibility complex region, although the number of genes per set slightly decreased (Supplementary Table 15b).

Gene–tissue expression analysis was conducted using catalogues of gene expression levels across different human tissues (Supplementary Fig. 2–5), with a Bonferroni correction applied for the number of tests within each tissue set. Among brain samples from 11 developmental stages (BrainSpan), only the 2 prenatal samples were significant ($P = 6.3 \times 10^{-4}$ and 2.5×10^{-3}). In adult tissues (GTEx v.8 (ref. 43)), significant enrichment was observed in brain ($P = 3.0 \times 10^{-9}$) and pituitary ($P = 4.9 \times 10^{-5}$) tissues. Analysis of more specific tissue types revealed enrichment in 11 brain regions, most strongly in the frontal cortex, cortex, cerebellum, anterior cingulate cortex and nucleus accumbens (all $P < 9.3 \times 10^{-4}$; Supplementary Table 16).

Drug targets

To explore therapeutic relevance, we ran DrugTargetor[44] to identify drug priorities with potential utility for clinical anxiety, based on their relevance for GAD symptom severity. We did not observe any significant enrichment of anxiety associations for the 1,551 drug targets tested (Supplementary Table 17). However, at the drug class level, we identified significant associations for Anatomical Therapeutic Chemical classifications N06 'psychoanaleptics', including N06A antidepressants, N02A 'opioids' and N06B 'psychostimulants' (Bonferroni-adjusted $P < 0.05$; Supplementary Table 18). With the exception of psychostimulants, these classes include drugs that have been used clinically to treat anxiety[45]. The enrichment for psychostimulants probably reflects shared dopaminergic and noradrenergic pathways involved in arousal and vigilance and underlying both anxiety and attention, consistent with pleiotropic genetic associations rather than direct therapeutic action.

Discussion

In this genome-wide association meta-analysis of 693,869 individuals from 14 cohorts, we identified 80 genome-wide significant variants

across 74 loci associated with quantitative measures of GAD symptom severity. Approximately half of the identified loci replicated associations reported in previous anxiety GWAS[19–23,46], while the remainder were newly identified associations.

The strongest intragenic association was estimated for rs1476548 within *PCLO*, which was also implicated through positional mapping, eQTL mapping and gene-based association testing. *PCLO* encodes a protein involved in regulating presynaptic structure and neurotransmitter release. This gene has long been of interest in major depressive disorder[47], with recent evidence also linking it to anxiety disorders[20,23]. Another gene of interest from our analysis was *SORCS3*, which was supported by multiple lines of evidence in the recent PGC-ANX case–control anxiety GWAS[23]. *SORCS3* plays a role in postsynaptic functioning and glutamate receptor regulation, particularly in the hippocampus[48]. It has been linked to memory and learning processes, specifically synaptic depression and fear extinction[49], and mental health and neurodevelopmental conditions, including major depressive disorder, Tourette syndrome, attention deficit hyperactivity disorder and autism[50,51].

Our SNP-based heritability estimate (5.9%) aligned with an existing GWAS of GAD symptom severity (5.6%)[26] while remaining lower than liability scale estimates from case–control anxiety meta-analyses[23]. In contrast to traditional case–control phenotyping, which aims to maximize clinical specificity through diagnostic thresholds, our approach leveraged the full spectrum of symptom variability, increasing power for discovery[52] and capturing genetic risk relevant to both subclinical and clinical presentations. The key differences between clinical diagnoses and symptom severity measures relate to the presence of distress and impairment and to symptom duration. While subclinical symptoms can still cause distress and impairment, this is not always true for lower levels of anxiety severity, potentially contributing to some diagnosis-specific genetic variance. Similarly, diagnostic tools often assess lifetime occurrence and require symptoms to be present for a minimum period of time (6 months for GAD), whereas symptom severity scales typically capture recent experiences (for example, the past 2 weeks), introducing greater susceptibility to transient fluctuations and measurement noise. Consistent with this, GWAS[53–55] of depression symptom severity typically yield lower SNP-based heritability estimates than case–control analyses. We aimed to partially address and control for temporal fluctuations and better approximate a stable underlying trait[16] by incorporating assessments from multiple time points into our analysis, where available. In addition, our meta-analysis combined data from multiple cohorts with differences in phenotype definitions, genotyping arrays, imputation methods, quality control procedures and population structure adjustments, which may have introduced further heterogeneity and reduced the observed SNP-based heritability. By contrast, single-cohort studies with individual-level data are more homogeneous and can implement alternatives to summary-statistics-based methods. Despite our lower heritability estimate, the strong genetic correlation observed between our phenotype and case–control anxiety suggests that GAD symptom severity captures much of the same genetic risk. This finding is consistent with a recent analysis of obsessive–compulsive symptoms[56]. Quantitative, symptom-based approaches may be particularly well suited to genetic studies of anxiety, given the high burden of anxiety symptoms observed across other mental health conditions[8–11]. In this context, efforts to isolate 'pure' anxiety cases may be both methodologically challenging and capture an unusual clinical phenotype that is unrepresentative for most individuals with anxiety.

There was a broad range of significant genetic correlations across both mental and physical health conditions, consistent with the frequent co-occurrence with anxiety symptoms and widespread pleiotropy. A strong genetic correlation was observed with neuroticism, a well-established risk factor for anxiety[23]. This probably reflects both genuine shared liability and conceptual or item-level overlap between the measures. Conditional analyses indicated extensive overlap between loci associated with generalized anxiety symptoms and those implicated in neuroticism, case–control anxiety and depression. Many genome-wide significant loci may therefore index a broader neuroticism-related liability, although the presence of anxiety-specific associations cannot be excluded due to the statistical noise introduced by conditioning on highly genetically correlated traits. Many of the genetic correlations aligned with findings from a genomic structural equation modelling analysis of anxiety symptoms and disorder[22], including strong associations with irritable bowel syndrome and chronic pain, and a moderate association with migraine. These results do not necessarily indicate horizontal pleiotropy but could instead arise from the experience of these conditions eliciting uncertainty and worry that contribute to anxiety.

Polygenic scores derived from our genome-wide association meta-analysis demonstrated within- and cross-ancestry generalizability, significantly explaining 1.2–2.9% of the variance in GAD symptom severity in European, African and South Asian ancestry samples. Across these samples, the PRS also accounted for 1.4–1.8% of the variance in case–control anxiety on the liability scale. While broadly consistent with the 0.5–2.3% range reported in the PGC-ANX case–control analysis[23], direct comparisons are limited by methodological differences in PRS construction and target sample composition. A key limitation of the present meta-analysis is its restriction to cohorts of European ancestry, due to lack of data for other ancestries at sufficient scale for GWAS analysis. Our PRS findings support a degree of shared genetic architecture with African and South Asian populations. Ancestry-specific modelling across diverse populations remains necessary to identify population-specific risk loci, such as that identified in a previous analysis[26] of African American participants, and ensure equitable benefits from genetic discoveries. Overall, these findings provide additional evidence that quantitative phenotyping can effectively capture genetic signal relevant to clinical anxiety.

The GAD symptom severity measures and ascertainment methods varied across contributing cohorts, although most assessed symptoms using the GAD-7. While widely adopted across clinical and research contexts, the GAD-7 does not comprehensively assess all GAD symptoms from the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[57]—omitting sleep, fatigue and concentration problems—and is not designed to capture symptoms of fear-based anxiety (that is, phobias and social anxiety disorder) or panic disorder. This limits the generalizability of our findings across anxiety disorders, particularly in light of evidence for partially distinct phenotypic and genetic contributions to GAD compared with fear-based disorders[58,59]. Expanding future studies to incorporate a broader range of anxiety symptom measures will enable more robust, transdiagnostic translation of these findings. Furthermore, future work could examine the genetic architecture of individual symptom domains, such as cognitive versus physiological symptoms, to better understand the biological specificity of these. Our subgroup analyses based on measure and ascertainment method were largely underpowered to reliably estimate SNP-based heritability or correlations. Although sufficiently powered comparisons indicated high genetic overlap, we cannot be certain that all cohorts captured the same underlying genetic architecture. While population-based cohorts allow assessment of the full range of symptoms, symptom severity measures typically better distinguish variation at the upper end of the distribution. This results in highly skewed symptom severity scores, as most participants report few or no symptoms, whereas individuals in clinical cohorts typically report more symptoms. Combining population-based cohorts with studies selecting on diagnosis introduces some heterogeneity and may limit generalizability to broader populations, but it can help yield a more normally distributed phenotype for GWAS analysis. This combination may have improved statistical power for detecting associations in our study.

Our quantitative GWAS of GAD symptom severity identified more genome-wide significant loci than a slightly larger and mostly

overlapping case–control anxiety study (N = 852,222; 122,341 cases)[23], with many loci replicated across the 2 methods. This aligns with expectations under the liability-threshold model when considering common conditions such as anxiety, whereby quantitative traits generally offer greater statistical power than case–control designs of equal sample size[52]. Beyond identifying anxiety-associated loci, our results implicate key neurobiological pathways, including synaptic function and neurotransmission, and notable genes such as *PCLO* and *SORCS3*. These findings demonstrate that a quantitative anxiety symptom-based phenotype can reveal biologically meaningful signals and complements insights from case–control designs. Clinically ascertained samples remain essential for identifying disorder-specific biology and mapping genetic risk to diagnostic presentations; however, obtaining clinical cases at sufficient scale for binary genome-wide analyses is challenging. Although electronic health records offer an efficient option, these are limited to individuals seeking and receiving medical attention. Quantitative, symptom-based approaches within biobanks and population studies therefore offer a promising scalable alternative for advancing the field of anxiety genetics. Moving forwards, the combination of these with deeply phenotyped clinical cohorts will be crucial for translating genetic insights into diagnostic and therapeutic advances. Together, these approaches can elucidate the biological continuum of anxiety, from healthy stress responses to debilitating disorder. Given the high and rising rates of anxiety, especially in young adults, it is more important than ever to improve our ability to identify and understand sources of risk. Despite its public health impact, progress in anxiety genetics lags behind other major mental health conditions. We hope our findings encourage genome-wide investigations leveraging existing but potentially underutilised anxiety severity data in genotyped cohorts, accelerating our progress in understanding the genetic architecture of anxiety.

Methods

Participants and measures

We meta-analysed data from 14 international cohorts (N = 693,869): 13 PGC-ANX studies with generalized anxiety symptom data and summary statistics from a pre-existing GWAS[26]. Details of each study and sample descriptives are provided in Supplementary Table 1. We performed a meta-analysis with access to individual participant data[60], such that each PGC-ANX cohort performed genome-wide association analyses specifically for this study and shared summary statistics with the core analytical team. The majority of the sample (70%) had completed the GAD-7 or closely related brief self-report measures assessing recent anxiety symptoms. The remaining 30% used other brief self-report anxiety scales (Supplementary Table 1), each available in at least 3,000 individuals. We analysed total sum scores, with higher scores indicating greater severity of symptoms. If participants were missing data on <25% of measure items, the missing scores were imputed with the participant's mean score of the other items. Participants with ≥25% missing data were excluded from analysis. Several cohorts had assessed anxiety symptoms on two or more occasions. Longitudinal twin studies have shown that symptom stability is primarily driven by genetic factors[16,61,62] and that stability extracted from repeated assessments yields higher heritability estimates than single time points[16]. For cohorts with anxiety assessments from 3 or more time points (12% of the sample), a latent factor was created in R with the package lavaan[63], the predict function and a maximum likelihood estimator. For cohorts with 2 time points (44%), a mean score was calculated. All scores, whether single time point, mean or factor score, were standardized to have a mean of zero and a standard deviation of one. Given the high comorbidity of anxiety and other mental health conditions, no additional exclusions were applied beyond those defined by each study. For two cohorts—Genetic Links to Anxiety and Depression Study (GLAD+) and the UK Biobank—individual-level data were merged before the GWAS. Participants from clinical cohorts had been recruited based on a lifetime history of depression or anxiety, as assessed by self-reported diagnostic questionnaires.

Meta-analysis

Supplementary Table 3 provides details of the studies that contributed to this meta-analysis, which were: Australian Genetics of Depression Study (AGDS)[64], Avon Longitudinal Study of Parents and Children (ALSPAC)[65,66], CoLaus|PsyCoLaus[67], Estonian Biobank[68], Generation Scotland[69], NIHR Bioresource GLAD+[70], Lifelines[71], MEGA TRR58[72], MVP[26], Norwegian Mother, Father and Child Cohort Study[73], Providing Tools for Effective Care and Treatment of Anxiety Disorders (PROTECT-AD)[74], Twins Early Development Study (TEDS)[75], Tracking Adolescents' Individual Lives' Survey (TRAILS)[76] and UK Biobank[77]. Each cohort performed genotyping using microarray platforms and imputed genotypes using ancestry-matched panels, primarily the Haplotype Reference Consortium[78]. Standard quality control procedures were applied, including filters on sample and variant call rates, sex concordance and excessive heterozygosity (full details in Supplementary Table 3). The one set of pre-existing summary statistics was from an analysis in the MVP, obtained through the database of Genotypes and Phenotypes (dbGaP; phs001672). Most groups adopted a mixed linear model approach and retained related individuals in their GWAS. Where applicable, covariates such as ancestry principal components and genotyping batch were included. We did not include age or sex as covariates, as they are not confounders of genetic effects and may represent effect moderators of interest warranting dedicated follow-up investigation, rather than variables to be adjusted for. All resulting summary statistics were on the GRCh37 genome assembly (build 37, hg19). Before meta-analysis, variant-level quality control was performed across the summary statistics, excluding those with minor allele frequency <1% or imputation accuracy score <0.6. Variants present in fewer than half of the contributing cohorts were excluded, resulting in a total of 7,499,431 autosomal SNPs. X-chromosome data were analysed from 7 cohorts (166,852 variants), with male genotypes coded as diploid (0/2) and sex included as a covariate. The meta-analysis was conducted in METAL (v.2020-05-05)[79] using an inverse-variance-weighted, standard-error-based approach. The β values from the meta-analysis represent the associated change in standard deviation units of generalized anxiety symptom score per additional copy of the effect allele. All statistical tests conducted in this study were two tailed.

Heterogeneity across cohorts was assessed by inspecting the P values from Cochran's Q test as implemented in METAL. In addition, we calculated the median I^2 values (HetISq in METAL) for SNPs reaching genome-wide significance ($P < 5 \times 10^{-8}$) and for independent lead SNPs. We also estimated genetic correlations between contributing cohorts using LDSC[33]. The inclusion of clinical alongside community-based cohorts offered greater representation across the full range of anxiety symptom severity, increasing statistical power as evidenced in a recent depression GWAS[80]. However, due to the risk of bias or confounding from differences in study design and phenotyping, we performed subgroup meta-analyses stratified by anxiety measure and excluding clinical cohorts (Supplementary Table 2). Meta-analyses of the measure and ascertainment subgroups were performed in METAL, and genetic correlations between the groups estimated using LDSC[33]. For both cohort and subgroup genetic correlations, most pairwise comparisons were not sufficiently powered (that is, heritability z-scores <4 for 1 or both sets of summary statistics[81]) to draw conclusions.

To identify LD-independent significant SNPs and loci, clumping was performed in FUMA (v.1.6.5)[39]. The r^2 threshold for independent significant SNPs was 0.1, and was 0.05 for lead SNPs, within a 500-kb window. Genome-wide significance was defined using the conventional threshold ($P < 5 \times 10^{-8}$).

To identify novel loci in our results, we cross-referenced significant loci with published trait associations from the GWAS Catalog[82] using LDTrait[83] (date accessed 2 September 2025), applying an r^2 threshold of >0.1 and a 500-kb window. Novelty was strictly defined as having no previous associations with internalizing traits including anxiety, depression, neuroticism and worry. To supplement this, we compared

our results with recent anxiety and depression studies[23,80] not yet available in the GWAS Catalog. Overlapping significant loci were identified with BEDtools (v.2.31.0)[84] and LD assessed using a threshold of $r^2 > 0.1$. The investigation of novel loci also revealed the extent to which our results replicated previous findings. We also determined novel loci specifically for anxiety, whether assessed as symptom severity or a case–control phenotype. Many of the 14 cohorts in our meta-analysis overlap with previous case–control anxiety meta-analyses, with the exception of GLAD+, Lifelines, PROTECT-AD, TEDS and MEGA (approximate $N = 110{,}000$). In some instances, the cohort sample composition differs due to the availability of quantitative versus diagnostic information.

SNP-based heritability and genetic correlations with external traits

We estimated SNP-based heritability via SBayesRC (v.0.2)[35]. This provided an estimate of the proportion of variance in quantitative anxiety attributable to variation in the common SNPs present in this meta-analysis. We inspected the LDSC[32] genomic inflation factor (λ_{GC}) and intercept to evaluate the contribution of potential confounding relative to polygenicity. Genetic correlations were also computed using LDSC with 105 GWAS summary statistics covering a broad range of phenotypes and applying a Bonferroni-corrected P value threshold of 4.76×10^{-4}.

High genetic correlations, such as those often observed between anxiety, depression and neuroticism, do not necessarily indicate identical biology; even when most loci are shared, traits may involve different biological pathways, tissue enrichments or show individual patterns of relationships with other traits. Identifying unique genetic influences on anxiety is important to better understand its specific aetiology and inform potential treatment pathways. However, conditional analyses, especially in the presence of strong genetic correlations, are statistically challenging and require substantial power, and therefore should be interpreted cautiously. We used the mtCOJO[34] tool from GCTA (v.1.94.1), which performs conditional analyses between summary statistics to provide marginal effect estimates for the trait of interest. We conditioned our anxiety meta-analysis on depression diagnosis[80] (98 index SNPs), neuroticism[85] (67 index SNPs) and anxiety diagnosis[23] (11 index SNPs). Depression symptoms[86] was underpowered (two index SNPs) for the analysis. We also estimated the SNP-based heritability of each set of conditioned summary statistics with LDSC and used block jack-knifing to compare these to the unconditioned heritability estimate.

PRSs

To evaluate the within- and cross-ancestry validity of our GWAS, we calculated GAD symptom severity PRSs in independent samples from the UK Biobank[77] and Prospective Imaging Study of Ageing (PISA)[87]. We then performed regressions between our PRS and quantitative anxiety, using GAD-7 scores, and case–control anxiety, as defined by a self-reported diagnostic questionnaire or self-report of a diagnosis from a health professional. Specifically, we used SBayesRC[35] to calculate PRSs in European, African and South Asian ancestry samples, excluding related individuals. SBayesRC is a Bayesian regression method that uses GWAS summary statistics to estimate SNP effect sizes while accounting for LD and polygenic architecture. It extends the SBayesR framework by incorporating functional annotations or prior biological information, improving the detection of probable causal variants and enhancing predictive accuracy for complex traits. We conducted linear regressions to assess the variance explained in GAD symptom severity by the PRS in each sample (European $N = 3{,}452$; African $N = 1{,}581$; South Asian $N = 1{,}813$). For case–control status, we performed logistic regressions to estimate associations in the target samples (European total $n = 3{,}107$, case $n = 407$; African total $n = 1{,}303$, case $n = 218$; South Asian total $n = 1{,}549$, case $n = 265$). We calculated Nagelkerke's R^2 for our PRS on the liability scale using the observed linear regression R^2 and corresponding formula[88], assuming a population prevalence of 20%. All regressions included the first ten ancestry-specific principal components and genotyping batch as covariates. The variance explained by the PRS was calculated as the difference in R^2 between a full model, including the PRS and covariates, and a null model with only covariates.

Positional and functional annotation

We used PolyFun (v.1.0.0)[36] to estimate per-SNP heritabilities, leveraging a regularized extension of stratified-LDSC applied to the v.2.2UKB baseline-LF model annotations, which captures heritability enrichment related to allele frequency, LD and variant function. These prior causal estimates were then used for fine-mapping in SuSiE (v.0.11.92)[37], limiting to a maximum of one causal SNP per locus. We extracted annotations at a PIP threshold of ≥0.95 and created credible causal sets containing the minimum set of ranked variants that cumulatively met this threshold. Unlike standard definitions of credible causal sets in SuSiE, we did not require a minimum pairwise r^2 between variants in a set, as the PolyFun + SuSiE pipeline does not incorporate LD estimates.

We performed SNP-level gene annotation using FUMA (v.1.6.5)[39], integrating three complementary methods: positional mapping (based on physical proximity to genes), eQTL mapping (linking variants to gene expression) and chromatin interaction mapping (using Hi-C data to identify regulatory interactions). eQTL mapping used significant SNP–gene pairs and eQTLs from the brain tissue datasets GTEx v.8 Brain[43] (13 regions) and BRAINEAC[89] (10 regions), and averaged expressions across these, applying a false discovery rate (FDR) threshold of $P < 0.05$. Chromatin interaction mapping used Hi-C brain tissue data (dorsolateral prefrontal cortex, hippocampus and left and right ventricles)[90] and adult and fetal cortex[91], with an FDR threshold of $P < 1 \times 10^{-6}$. These methods differ in their underlying biological rationale and may implicate different genes. Genes identified by two or more mapping approaches were therefore highlighted, as convergence across the methods increased our confidence in the potential functional relevance of a gene.

Gene-based associations and enrichment

Gene-based association, gene-set and gene–tissue expression enrichment analyses were performed in MAGMA (v.1.08)[41] via FUMA (v.1.6.5)[39]. These analyses aimed to identify genes associated with GAD symptom severity, biological pathways enriched for associated genes and relevant tissues where genes are preferentially expressed, offering insight into the potential biological mechanisms underlying our findings. For gene-based associations, we tested 19,954 genes, applying a Bonferroni-corrected significance threshold of $P < 2.5 \times 10^{-6}$. SNPs were mapped to genes using a 35-kb upstream and 10-kb downstream window. Gene-set analyses were performed using 6,494 curated gene sets (c2.all) and 10,529 Gene Ontology terms (c5.bp, c5.cc and c5.mf) from the Molecular Signatures Database (MSigDB; v.2023.1.Hs)[42]. Significance was determined by a Bonferroni-corrected threshold of $P < 2.9 \times 10^{-6}$. For tissue enrichment, we tested relationships between trait-associated genes and gene expression in human tissues, using data from BrainSpan (brain samples from 11 general developmental stages and 29 specified ages) and GTEx v.8 (covering 30 general and 54 specific tissue types).

Drug targets

We examined whether genes associated with GAD symptom severity were associated with individual drugs and drug classes using the DrugTargetor (v.1.3)[44] method. DrugTargetor integrates MAGMA gene-level association results with curated drug–gene interaction databases (ChEMBL[92,93] and DGIdb[94]). We used MAGMA (v.1.10) to prioritize associated genes within windows 35 kb upstream and 10 kb downstream. We restricted our analysis to hypothesized drug action within the nervous system, a maximum of 1,551 unique drugs and 163 drug classes. To assess the enrichment of drug classes, we calculated the area under the

enrichment curve (AUC), where 50% indicates random enrichment and 100% optimal enrichment, and AUC significance was assessed using one-sided Wilcoxon–Mann–Whitney tests.

Ethics

This study analysed pre-existing data from cohort studies. Each contributing study obtained ethical approval from the relevant institutional ethics committee, and participants provided informed consent permitting genetic and health-related research. Details of all ethical approvals are provided in Supplementary Table 1, and data application numbers where applicable.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

Summary statistics are available on the PGC download page (https://pgc.unc.edu/for-researchers/download-result). Individual study data can be accessed following review and approval by the individual study cohorts; see https://pgc.unc.edu/for-researchers/individual-level-data-access/ for more information. Summary statistics for the genetic correlations are available following the procedure detailed within the relevant publications (searchable using the PMID in Supplementary Table 9) or via GWAS Catalog (https://www.ebi.ac.uk/gwas/home).

Code availability

Analytical code is available via GitHub at: https://github.com/megskelton/gad-sympt-metagwas.

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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection for the purpose of this specific study; pre-existing data was used. The contributing cohort studies used questionnaire software such as Qualtrics, OpenClinica, and REDCAP, as detailed in their original publications.
Data analysis	This information is provided in the Methods and Supplementary Tables. Individual GWAS were performed with REGENIE (v3.1 or 3.2; https://rgcgithub.github.io/regenie/), SAIGE (v 1.3; https://saigegit.github.io/SAIGE-doc/), or PLINK (2.0; https://www.cog-genomics.org/plink/). The meta-analysis was performed in METAL (v2020-05-05; https://csg.sph.umich.edu/abecasis/metal/download/). Estimates of genetic correlations, genomic inflation factor and LD score intercept were made using LDSC (v1.0.1; https://github.com/bulik/ldsc). Clumping, SNP-level gene annotation were performed in FUMA (v1.6.5; https://fuma.ctglab.nl/). Gene-based associations, gene-set and gene-tissue expression enrichment analyses were performed in MAGMA (v1.08; https://cncr.nl/research/magma/) via FUMA. LDTrait (https://ldlink.nih.gov/?tab=ldtrait) was used to cross-reference significant loci with those from the GWAS Catalog. BEDtools (v2.31.0) was used to inspect the overlap of loci with relevant studies unavailable in the GWAS Catalog. SBayesRC (v0.2; https://github.com/zhilizheng/SBayesRC) provided an estimate of SNP-based heritability and the calculation of polygenic scores. Conditional analyses were performed with the mtCOJO tool from GCTA software (v1.94.1). Fine-mapping was performed using PolyFun (v1.0.0; https://github.com/omerwe/polyfun) and SuSiE (v0.11.92; https://stephenslab.github.io/susieR/). DrugTargetor (v1.3; https://drugtargetor.com/) was used to identify associations with individual drugs and drug classes. Data were prepared, described and visualised using R (v4; https://www.r-project.org/), the psych (https://cran.r-project.org/web/packages/psych/index.html), lavaan (https://cran.r-project.org/web/packages/lavaan/index.html) and tidyverse (https://cran.r-project.org/web/packages/tidyverse/index.html) packages. Analytical code for this study is available on Github: https://github.com/megskelton/gad-sympt-metagwas.

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Policy information about availability of data

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As per the data availability statement: Summary statistics will be made available on the PGC data-download page (https://pgc.unc.edu/for-researchers/download-result). Bona fide researchers can apply to access raw genomic data from the individual cohorts by contacting the relevant team or through the study website.

Research involving human participants, their data, or biological material

Policy information about studies with human participants or human data. See also policy information about sex, gender (identity/presentation), and sexual orientation and race, ethnicity and racism.

Reporting on sex and gender	Genetically inferred sex, based on the X chromosome, was used as part of the quality control procedure in each cohort, as is typical in GWAS. Specifically, concordance between self-reported sex and genetically inferred sex was examined, and individuals with mismatches were removed, as these can indicate genotyping errors or sample contamination. For X chromosome analyses, cohorts either stratified by genetically inferred sex or included it as a covariate. The proportion of females in each contributing sample is provided in Table S1, with the overall proportion 48%. Sex and/or gender based analyses were not performed.
Reporting on race, ethnicity, or other socially relevant groupings	We used genetically inferred ancestry estimates based on the 1000 Genomes reference panel. All participants in the main analyses were of European inferred ancestry. Polygenic risk score analysis was performed in participant samples of South Asian and African inferred ancestry to test cross-ancestry transferability of our findings. No race, ethnicity, or other socially relevant groupings were shared for this project.
Population characteristics	A total of 14 cohorts contributed to this meta-analysis and characteristics varied across each of these. Information on individual study-specific inclusion criteria is available in Table S1 e.g. lifetime experience of anxiety or depression, country population-based. Sample descriptives (mean (SD) age and percentage female) are also provided in Table S1. The total sample was 693,869 individuals, 48% female, mean age 44 years (SD = 14). Information on genotyping methods for each cohort can be found in Table S3.
Recruitment	This information is detailed for each of the 14 cohorts in Table S1. In brief, recruitment methods included online recruitment, recruitment into national biobank studies, or within clinical settings via health service providers.
Ethics oversight	Details on the ethical approval for each contributing cohort study are provided in Table S1 (e.g. "Ethical approval for the GLAD Study and NBR COPING study was obtained from the London-Fulham Research Ethics Committee (REC reference 18/LO/1218 and 20/SW/0078, respectively, COPING project no. 282754.)."). This is referred to at the start of the Methods section of the manuscript.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

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Behavioural & social sciences study design

All studies must disclose on these points even when the disclosure is negative.

Study description	Quantitative
Research sample	Participants from established cohort studies who had previously provided generalised anxiety disorder symptom scores. This includes population-based cohort studies, studies recruiting based on a lifetime history of anxiety or depression, a population-based military veterans study, and a pregnancy-based population-based cohort study.
Sampling strategy	We identified samples with data on generalised anxiety symptom severity from communications within PGC-ANX and used as many as possible to maximise our sample size, excluding where a symptom measure had been used only in a small sample of participants as this would make subgroup measure-based secondary analyses underpowered for any meaningful conclusion. Convenience sampling was used in many cohorts, which relies on participants volunteering in response to recruitment materials, although some cohorts used population-based sampling whereby they invited all individuals within a defined population e.g. MoBa, TEDS. A power

	calculation using the GCTA calculator can be found in Table S6.
Data collection	Across cohorts, symptom measures were self-report questionnaires and are detailed in Table S1. Most were provided online. Genetic data was provided via blood or saliva samples.
Timing	This varies across cohorts but broadly the start and end dates for data collection are 2007 and 2023, respectively.
Data exclusions	This varies per cohort and is detailed in the supplementary tables and original cohort publications. Quality control exclusions included missingness of genetic or phenotypic data above a specified threshold, or evidence of contamination of genetic data.
Non-participation	This is a meta-analysis of pre-existing study data and therefore no dropout occurred in respect to this specific analysis.
Randomization	All participants were analysed as a single group.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

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☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern
☒	☐ Plants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Plants

Seed stocks	N/A
Novel plant genotypes	N/A
Authentication	N/A