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Comorbidity alters the genetic relationship between anxiety disorders and major depression

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Key Points

Question Is the high genetic correlation between anxiety disorders (ANX) and major depression (MD) due to phenotypic overlap (comorbidity) and will disorder-specific (non-comorbid) analysis provide insight into their underlying causal factors?

Findings: Applying statistical genetics tools in two large population samples (UK Biobank, n=500,000; and MoBa, n= 130,000), we found a smaller genetic correlation between MD and ANX when comorbid cases were excluded. Additionally, after excluding comorbid cases, Mendelian randomization revealed that genetic liability to ANX is causally linked to MD but not *vice versa*.

Meaning: The genetic overlap between ANX and MD may be driven by phenotypic comorbidity, which inflates their genetic correlation. The results support that ANX has a causal link to MD, suggesting that early interventions for ANX may prevent subsequent development of MD. Further, investigating the genetic underpinnings of ANX and MD, while excluding their comorbid states, may help advance precision medicine and uncover novel biological mechanisms.

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Abstract

Importance:- There is extensive comorbidity between anxiety disorders (ANX) and major depression (MD). Most studies on the genetics of ANX do not exclude comorbid cases of MD, and *vice versa*, therefore confounding genetic association analyses. Disorder-specific analysis of genomic data may reveal more precise biological pathways and causal relationships.

Objective:- To investigate the genetic relationship between disorder-specific ANX and MD compared to samples with comorbidity, including their causal relationship.

Design, Setting, and Participants:- Data from UK Biobank was used to perform genome-wide association studies (GWAS) of ANX-only and MD-only, and generate disorder-specific polygenic risk scores (PRS). The Norwegian Mother, Father, and Child Cohort (MoBa) was used to test the associations of PRS with diagnosis and symptoms. MD and ANX GWAS data including comorbidities (MD-co and ANX-co) were used as comparators. Genetic correlation was assessed using LDSC, and Mendelian randomization was employed to infer causal relationships.

Main Outcomes and Measures GWAS of ICD-10 diagnoses of ANX, MD, or both. Genetic correlations between pairs of ANX and MD phenotypes. PRS associations with diagnoses of ANX, MD, and their comorbid states, and anxiety or depressive symptoms.

Results:- The GWAS of ANX-only (9,980 cases and 179,442 controls) and MD-only (15,301 cases and 179,038 controls) showed a lower genetic correlation (0.53) than the one between ANX-co and MD-co (0.90). ANX-only showed a causal relationship with MD-only (P_{FDR}=1.5e-02), but not *vice versa*, while comorbid cases showed a significant bidirectional causal relationship (P_{FDR}=2.9e-12, P_{FDR} =9.3e-06). The PRS-MD-only were differentially associated with MD-only compared to ANX-only cases (β= -0.08; 95%CI: -0.11, -0.03); however, this differential association was not observed for the PRS-MD-co. A similar pattern of differential association with anxiety and depressive symptoms was observed for PRS-ANX-only, but not for PRS-MD-co.

Conclusions and Relevance:- The genetics and underlying biology of ANX and MD are more distinct when comorbid cases are excluded from analyses and reveals that ANX may be causal for MD. This confounding of genetic relationships as a result of comorbidity is likely to apply to other psychiatric disorders. Disorder-specific genetic studies may help uncover more relevant biological mechanisms and guide more targeted clinical interventions.

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Introduction

Anxiety disorders (ANX) and major depression (MD) are the most prevalent psychiatric conditions, making a substantial contribution to poor health and disability globally.[1] Both ANX and MD are more prevalent among women.[1-3] Comorbidity between the two disorders occurs in over half of all cases,[2,3] and is associated with greater morbidity, worse treatment response, and higher suicide risk.[4-6] Overlapping symptomatology, causal relationships, and shared environmental risk factors[7-10] as well as shared genetic risk and neurobiology may explain the high comorbidity.[9,11-13]

Both ANX and MD exhibit moderate heritability,[14,15] and consistently show high genetic correlations.[9,13,16] However, the high comorbidity makes these genetic associations difficult to interpret. The largest genome-wide association study (GWAS) for ANX did not exclude cases of MD, and *vice versa*.[17,18] Polygenic risk scores (PRS) derived from these GWASs exhibit strong associations with comorbid ANX and MD cases,[19] and the PRS of MD was a stronger predictor of ANX than the PRS of ANX.[9,13] While including individuals with comorbidity may improve the power of GWAS to identify genetic loci,[20] such approaches fail to distinguish genes specific to ANX from those specific to MD. Consequently, identifying distinct, disorder-specific, biological mechanisms may be hampered.[21] Therefore, GWAS of anxiety and depressive disorders with better stratification of case definitions are needed.[19,20]

Here, we investigated the genetic relationship between ANX and MD using two large population-based genotyped samples with clinical psychiatric diagnoses. We conducted non-comorbid ANX-only and MD-only GWAS of the UK Biobank sample and compared them with GWAS including comorbid cases (ANX-co and MD-co). We investigated the genetic relationship between ANX-only and MD-only compared to ANX-co and MD-co, and how the respective PRS associated with ANX and MD diagnoses and symptoms in an independent sample (Norwegian Mother, Father and Child Study, MoBa). We also explored differences in biological pathways and how comorbidity affected causal relationships between ANX and MD using Mendelian Randomization (MR).[22,23]

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Methods

We used two large genotyped cohorts with data on relevant mental phenotypes in Europeans for training and testing: the UK Biobank (UKB; Project No. 27412) for GWAS (training) (eAppendix 1 in Supplement 1), and the Norwegian Mother, Father, and Child Cohort (MoBa) for independent testing (eAppendix 2 in Supplement 1). These cohorts are linked to clinical diagnoses from national healthcare records. We used publicly available GWAS summary data without the testing sample (MoBa) of ANX-co (cases=31,977, controls=82,114),[24] and MD-co (cases=170,756, controls=329,443)[25] as comparators. These GWAS did not exclude cases with ANX and MD comorbidity (eAppendix 3 in Supplement 1).

GWAS Dataset (Training)

We used UK Biobank data to perform GWAS for ANX-only (cases = 9,980) and MD-only (cases = 15,301). Individuals with a history of diagnoses of organic mental disorders (F00 – F09), psychotic disorders (F20 – F29), bipolar disorders (F30.0 – F30.9 and F31.0 – F31.9), or mixed anxiety and depressive disorder (F41.2) were excluded from all analyses. The ANX-only cases were diagnosed with agoraphobia (F40.0), social phobia (F40.1), panic disorder (F41.0), generalized anxiety disorder (F41.1), or other anxiety disorders (F41.3 - F41.9), excluding those with 'MD-only' diagnoses (see below). MD-only cases had a diagnosis of any depressive episode (F32.0 - F32.9), or recurrent depressive disorder (F33.0 - F33.9), excluding those with 'ANX-only' diagnoses (see above). Controls for ANX-only (n=179,442) and MD-only (n=179,038) were randomly selected and did not overlap. Individuals with MD were excluded from the ANX-only GWAS control group, and those with ANX were excluded from the MD-only GWAS control group.

Polygenic risk score dataset (Testing)

We obtained genotype and phenotype data on mothers and fathers (n = 130,992) who participated in MoBa.[26,27] All study participants provided written informed consent upon recruitment and those who withdrew during follow-up were excluded from our analyses. The Regional Committee for Medical and Health Research Ethics approved the present study (2016/1226/REK sør-øst C).

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Data on previous or current diagnoses of mental disorders were obtained from the Norwegian Patient Registry (2008 - 2022). We excluded individuals who withdrew their consent (n=484), with missing covariates (n=1,590), and related individuals. We excluded individuals with a diagnosis of organic mental disorders (F00 – F09), psychotic disorders (F20 – F29), or bipolar disorders (F30.0 – F30.9 and F31.0 – F31.9) (eFigure 1 in Supplement 1).

Diagnoses

We classified the cases within the MoBa sample into three disorder-specific subgroups: 1. Dx-ANX-only (n=1,992) with the same criteria as in the UKB and excluding individuals with MD. 2. Dx-MD-only (n=7,486) using the same criteria as in the UKB and excluding individuals with ANX. 3. Dx-ANX-MD (n=3,468) comprising individuals with both MD and ANX or a mixed anxiety and depressive disorder (F41.2). The number of excluded individuals and the corresponding numbers of controls are provided in the supplement (eFigure 1 in Supplement 1).

ANX and MD symptoms

Symptoms of ANX and MD were assessed using the validated 8-item Hopkins Symptom Checklist (SCL-8), which correlates highly with the original 25-item HSCL.[28] Responses were rated on a Likert scale from 1 to 4 reflecting how much respondents were bothered by specific symptoms in the preceding two weeks. Pregnant women participating in MoBa (n = 67,219) completed the SCL-8 during the 30th week of gestation. After excluding individuals with missing covariates (n=787) and related individuals (n=11,570), the analysis included 54,862 mothers (eFigure 2 in Supplement 1).

Genome-wide association study (GWAS)

We performed GWAS for ANX-only and MD-only using version 3 of the UKB imputed genetic data among individuals of “white British” ancestry classified according to self-declared ethnicity and genetic principal component (PC) analysis (UKB data field 22006). The GWAS was done with REGENIE v3.4.1 including related individuals. Variants with an imputation INFO score < 0.8 and minor allele count < 20 were excluded. Age, sex, and the first 20 genotype PCs were used as covariates.

Polygenic risk score (PRS) calculation

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PRS were calculated using ANX-only and MD-only GWAS summary statistics. Additionally, a PRS was calculated from the summary statistics of a case-case GWAS (CC-GWAS) performed on ANX-only and MD-only GWAS. Further PRSs were derived from GWAS that included comorbidity i.e., ANX-co[24] and MD-co.[25] All PRSs were computed using the PRS-PCA approach, extracting PCs PRSs generated by PRSice (2.3.3) for a set of *p*-value cut-offs (1.0e-06, 1.0e-05, 1.0e-04, 1.0e-03, 1.0e-02, 5.0e-02, 1.0e-01, 5.0e-01, 1.0).[29] In logistic regression models, the first PC was used for the prediction of phenotypes in the MoBa sample.

Statistical analysis

PRS Associations

Logistic regression analyses were performed to test the association between each PRS (i.e., ANX-only, MD-only, MD-co, ANX-co, and CC-ANX-MD), and each diagnostic category (i.e., Dx-ANX-only, Dx-MD-only, and Dx-ANX-MD) compared to controls. Additionally, logistic regression was used to assess whether each PRS is differentially associated with one diagnostic category over another. For depression and anxiety symptoms, responses were dichotomized into '1' for '3- Quite bothered' or '4- Very bothered', and '0' for '1- Not bothered' or '2- A little bothered'. Logistic regressions were then used to analyze the association between each PRS and the dichotomized symptom responses. All regression models were adjusted for age, sex, and the first 10 genotype PCs. Only one of the related individuals with a kinship coefficient greater than 0.05 was kept, prioritizing cases. Effect sizes were represented as standardized β values with 95% confidence intervals. Bonferroni correction was applied to *p*-values to account for multiple comparisons.

Genetic Correlations

Linkage disequilibrium score regression[30] was applied to the GWAS summary data to estimate genetic correlations between ANX and MD with or without comorbid cases. The single nucleotide polymorphism (SNP) heritability for each phenotype was also computed.

Mendelian Randomization (MR)

We applied MR analyses using the R package TwoSampleMR[31] to examine causal associations between ANX and MD. To enhance result reliability, multiple MR methods were applied:

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inverse variance weighted (IVW),[22] weighted median,[32] and MR Egger.[33] Instruments were selected at a *p*-value threshold of 1e-05 to account for the low power of the ANX-only and MD-only GWASs,[34] following previous studies' application of more relaxed p-value threshold for low-power GWASs.[35,36] Furthermore, the Causal Analysis Using Summary Effect estimates (CAUSE) method was applied to further assess causality and distinguish horizontal pleiotropy.[23]

Functional Enrichment of Genes

To explore biological differences between ANX and MD, we employed GSA-MiXeR which can provide more specific genes and pathways relevant to a given phenotype. GSA-MiXeR estimates gene-level heritability to compute fold enrichment from the respective GWAS summary statistics,[37] with reliability assessed using Akaike Information Criterion (AIC) values. We compared the enriched genes for ANX-only and MD-only as well as ANX-co and MD-co based on AIC and fold enrichment values.

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Results

Sample characteristics

UKB data: ANX-only GWAS consisted of 189,422 (54.0 % females) with a mean age(SD) of 56.8 (8.0) years. MD-only GWAS comprised 194,339 participants (54.1 % females) with a mean age (SD) of 56.7 (8.0) years. *MoBa data:* A total of 128,918 individuals (58.9% females) with a mean age (SD) of 49.0 (5.4) years had genetic and phenotype data for analysis. For the prediction of symptoms of anxiety and depression, the sample included 54,862 mothers with a mean age (SD) of 48.1 (5.0) years.

PRS associations with diagnoses vs controls in MoBa

Almost all PRSs were positively associated with all three diagnostic categories (i.e. Dx-ANX-only, Dx-MD-only, and Dx-ANX-MD). However, CC-ANX-MD PRS exhibited a negative association with Dx-MD-only and no significant association with Dx-ANX-MD. MD-only PRS had stronger associations with Dx-MD-only (β=0.13; 95%CI: 0.10, 0.15) and Dx-ANX-MD (β=0.15; 95%CI: 0.12, 0.18) than with Dx-ANX-only (β=0.05; 95%CI: 0.01, 0.08). ANX-co PRS and MD-co PRS showed stronger associations than the ANX-only PRS and MD-only PRS when comparing Dx-ANX-MD or Dx-ANX-only cases to controls (Figure 1, Panel A).

PRS associations between diagnoses in MoBa

We assessed the association of PRSs with each diagnostic group, using another diagnostic group as a control. As expected, MD-only PRS and MD-co PRS were associated with Dx-ANX-MD compared to Dx-ANX-only. Notably, MD-co PRS was associated with Dx-ANX-MD compared to Dx-MD-only. Unlike MD-co PRS, MD-only PRS showed a positive association with Dx-MD-only compared to Dx-ANX-only. The association of ANX-only PRS with Dx-ANX-only compared to Dx-MD-only appeared consistent but was not statistically significant after correction for multiple testing. CC-ANX-MD PRS was associated with Dx-ANX-only compared to Dx-MD-only (Figure 1, Panel B).

PRS associations with symptoms of anxiety and depression in MoBa

MD-co PRS was associated with all eight symptoms on SCL-8 consistent with the large GWAS sample size and inclusion of comorbid ANX. ANX-only PRS was associated with all anxiety items but only two depression symptoms (worry and hopelessness). The item ‘suddenly scared

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for no reason' had the lowest endorsement (1%) which may have contributed to the low precision and non-significant associations with ANX-co PRS and MD-only PRS (Figure 2). Overall, all PRSs generated from the GWAS of a range of diagnostic categories exhibited a similar pattern of prediction of anxiety and depressive symptoms. In contrast, CC-ANX-MD PRS was not associated with any SCL-8 items, highlighting that the symptoms span the ANX and MD continuum.

Genetic Correlation and Mendelian Randomization (MR)

The genetic correlation between MD-co and ANX-co was higher 0.90 (p = 5.4e-196) than that between MD-only and ANX-only, 0.53 (p = 2.7e-06). SNP heritability was 8.4% for MD-co, 9.5% for ANX-co, 10.5% for MD-only, and 5.4% for ANX-only.

At least two MR methods showed evidence of a bidirectional causal association between MD-co and ANX-co. In contrast, only ANX-only had a significant causal association with MD-only (Table 1). The CAUSE-MR method, which accounts for potential horizontal pleiotropy suggested causal associations of ANX-co and MD-co, however, these results were not statistically significant after correction for multiple testing (Table 1).

Enrichment of Genes and Pathways

GSA-MiXeR analyses identified significant fold enrichment for 148 genes in ANX-only and 155 genes in MD-only, with 13 genes enriched in both (*ERBB4*, *ACSL3*, *TPRG1*, *MAML3*, *KCNQ5*, *INSIG1*, *KCNB2*, *FER1L6*, *B3GLCT*, *IRX6*, *TSHZ3*, *TOX2*, and *FAM110A*). Enriched pathways for ANX-only included: microvesicle, CCR6 chemokine receptor binding, and cardiac muscle myoblast proliferation (Table S1 in Supplement 2). For MD-only, pathways included negative regulation of myoblast proliferation, interleukin 21 production, protein-O-linked fucosylation, and positive regulation of 3-UTR-mediated mRNA stabilization (Table S2 in Supplement 2). More genes showed enrichment in ANX-co (n=190) and MD-co (n=331) (Tables S3 & S4 in Supplement 2) with 48 genes common to both (Figure 3).

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Discussion

Here, we dissected the genetic relationship between ANX and MD using GWAS with and without comorbid cases. ANX-only and MD-only showed lower genetic correlations compared to ANX-co and MD-co. MD-only PRS was differentially associated with Dx-MD-only compared to Dx-ANX-only, while MD-co PRS was associated with both. Our results suggest ANX-only is causally associated with MD-only but not *vice versa*, whereas ANX-co and MD-co support a bidirectional causal association. Additionally, ANX-co PRS and MD-co PRS had a stronger association with Dx-ANX-MD and did not differentiate between Dx-ANX-only and Dx-MD-only.

The high comorbidity between ANX and MD, and the inclusion of comorbid cases in major GWAS, can confound the reported genetic overlap between the two disorders.[9,13,16,24,38] Our findings show lower genetic correlations when comorbid cases are excluded, aligning with a recent family-based adoption study.[39] Since the SNP heritabilities for ANX-only and MD-only were comparable to previous reports,[24,25] low power alone is unlikely to explain the diminished genetic correlation.[30,40]

Our MR results from ANX-only and MD-only suggest a direction of causation aligning with epidemiological data,[7,10,41] unlike the bidirectional causal association observed using GWAS including comorbid cases. Thus, investigating the genetic relationships between diagnoses with pervasive comorbidity without removing comorbid cases from the initial GWAS may be misleading. Epidemiological studies show that ANX often precedes MD,[10,42,43] and longitudinal clinical data support that ANX causes MD but not *vice versa*.[7] A large proportion of individuals with MD (46 – 75%) have a history of ANX, which is associated with greater severity, chronicity, and impairment.[43-46] Furthermore, the importance of anxiety symptoms in MD has also been highlighted with the anxious distress specifier in DSM-5.[47,48] Therefore, targeting ANX symptoms in the early phase of MD may improve clinical outcomes.

The MD-co PRS[25] showed the strongest association with Dx-ANX-only, Dx-MD-only, and Dx-ANX-MD cases compared to controls. The MD-co PRS also demonstrated the greatest prediction of ANX caseness, probably because of its large sample size and inclusion of comorbid ANX in the GWAS.[9] Consistent with our findings, a stronger association of MD-co PRS with Dx-ANX-MD than with Dx-MD-only was reported using electronic health records data from the US.[19] This

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may be attributed to a stronger genetic burden among comorbid cases,[49] an overrepresentation of comorbid cases in samples included in the GWAS.[25] The difference in the associations of the ANX-co PRS with Dx-ANX-MD and those with Dx-ANX-only were not as large, which may be due to the lower power of the ANX-co GWAS.[24] Additionally, diagnostic hierarchy requires the exclusion of MD before making a diagnosis of ANX but not *vice versa*,[48] which may lead to underreporting of ANX among individuals with MD.[50]

Taken together, our findings indicate that the genetic underpinnings of ANX and MD are more distinct than previously suggested.[19] Thus, the disease pathways of ANX-only may be different from MD-only or their comorbid state which is relevant for clinical translation and precision psychiatry. Notably, less than 10% of genes enriched based on the heritabilities of MD-only and ANX-only were common to both. This contrasts with our recent report of many shared genetic loci and extensive overlap (85%) of trait-influencing variants between ANX and MD without excluding comorbid cases.[9,13] GSA-MiXeR showed 25% of genes enriched in ANX-co were also enriched in MD-co. GWAS of strictly defined MD diagnosis can help identify disorder-specific biological mechanisms.[21] For example, our data suggests that immune pathways, such as CCR6-chemokine receptor binding, are implicated in ANX-only, while interleukin-21 production was enriched in MD-only. Intriguingly, interleukin-21 production was also enriched in ANX-co. MD-only PRS and CC-ANX-MD PRS may facilitate the differentiation of clinical subgroups. Notably, the CC-ANX-MD PRS showed a negative association with Dx-MD-only suggesting that it could be a marker of resilience to MD for individuals with ANX.

The pattern of positive association between symptoms (SCL-8) and the range of PRS highlights the pervasive overlap between these disorders at the symptom level.[48] Also, anxiety and depressive symptoms have significant correlations with each other.[51] The deviation of associations with the item ‘feeling suddenly scared for no reason’ may be related to its low prevalence and large confidence intervals. The CC-ANX-MD PRS showed no association with any symptom suggesting that all eight symptoms span across the ANX – MD dichotomy.

Current efforts to improve genetic discoveries from GWAS of complex phenotypes such as mental disorders emphasize the need for increasing sample sizes.[52] However, the current findings support that more narrowly defined, homogeneous phenotypes are more likely to enable the identification of specific genetic variants with significant functional effects.[20] The observed

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differential association of the MD-only PRS and CC-ANX-MD PRS with Dx-MD-only compared to Dx-ANX-only provide support for disorder-specific genetic risk which may have implications for the prediction of treatment outcome.[53,54]

Our findings should be interpreted in the light of some limitations. The cases identified for the UKB and MoBa data were defined based on available health registry data and may still include some comorbid cases. However, this would bias the results of disorder-specific GWAS towards those of comorbid ones. The results are based on European populations and may not be generalizable to other ancestries. The limitations of our ANX-only GWAS may be biased by low power. Accordingly, the effect directions were consistent with expectations even though these associations did not stand correction for multiple testing. As better powered GWAS of more deeply phenotyped cases become available, the utility of genetic factors in treatment selection and outcome prediction can be realized. Hence, global efforts for genetic discoveries with better phenotypic characterization are needed for precision psychiatry.

Conclusions

Our findings suggest that the genetic liabilities for ANX and MD are more distinct than has been inferred from GWAS where comorbid cases were included, implicating more separate underlying biological pathways. Further, we show that ANX may have a causal link to MD, suggesting that targeting ANX symptoms in early phase MD can be an effective intervention. Together, genetic factors derived from ANX and MD excluding comorbidities may be useful in developing precision medicine approaches and uncovering novel biological mechanisms for drug targets.

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Authors' Contributions

Dr. Tesfaye had full access to all of the data in the study and takes full responsibility for the integrity of the data and the accuracy of data analyses. Concept and design: Tesfaye, Parker, Jaholkowski, O'Connell, Andreassen. Acquisition, analysis, or interpretation of data: Tesfaye, Shadrin, Jaholkowski, Parker, Smeland, Parekh, Kutrolli, Birkenæs, Bakken, Ask, Frei, Dale, O'Connell, Andreassen. Drafting of the manuscript: Tesfaye, Shadrin, Parker, Andreassen. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Tesfaye, Shadrin, Parker, Jaholkowski. Obtained funding: Andreassen. Administrative, technical, or material support: Kutrolli, Parekh, Bakken, Birkenæs, Ask, O'Connell, Shadrin, Andreassen. Supervision: Frei, O'Connell, Andreassen.

Conflict of Interest Disclosures

Ole A. Andreassen is a consultant for Cortechs.ai and Precision Health and has received speaker's honoraria from Lundbeck, Janssen, Otsuka, and Sunovion. Srdjan Djurovic has received speaker's honoraria from Lundbeck. Dr. Anders M. Dale is the Founding Director, holds equity in CorTechs Labs, Inc. (DBA Cortechs.ai), and serves on its Board of Directors and the Scientific Advisory Board. He is an unpaid consultant for Oslo University Hospital. The terms of these arrangements have been reviewed and approved by the University of California, San Diego in accordance with its conflict-of-interest policies. Dr. Frei is a consultant to Precision Health. The other authors have no conflicts of interest to declare.

Funding/Support

The authors received support support from the Research Council of Norway (324252, 324499, 300309, 273291, 223273, 248778, 273446, 326813, 334920, 271555/F21, 324620), NordForsk (grant 156298), the European Economic Area and Norway Grants (EEA-RO-NO-2018-0535, EEA-RO-NO-2018-0573), the South-East Norway Regional Health Authority (2022-087 and 2022-073), The University of Oslo, KG Jebsen Stiftelsen (SKGJ-MED-021), the European Union's Horizon 2020 research and innovation program (847776, 964874), and Marie Skłodowska-Curie grant (801133), and the US National Institutes of Health (R01MH123724-01, R01MH124839-02, U24DA041123, R01AG076838, U24DA055330, and OT2 HL161847). The Norwegian Mother, Father and Child Cohort Study is supported by the Norwegian Ministry of Health and Care Services and the Ministry of Education and Research. This research is part of the HARVEST collaboration, supported by the Research Council of Norway (grant 229624). The Norwegian Centre for Mental Disorders Research (NORMENT) provided genotype data, funded by the Research Council of Norway (grant 223273), South East Norway Health Authorities, and Stiftelsen Kristian Gerhard Jebsen. The Center for Diabetes Research, the University of Bergen, provided genotype data funded by the ERC AdG project SELECTionPREDISPOSED, Stiftelsen Kristian Gerhard Jebsen, the Trond Mohn Foundation, the Research Council of Norway, the

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Novo Nordisk Foundation, the University of Bergen, and theWestern Norway Health Authorities.

Role of the Funder/Sponsor:

The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: We are grateful to all individuals who participated in the Norwegian MoBa study. We thank the Norwegian Institute of Public Health for generating high-quality genomic data. We also thank the research participants and employees of the Psychiatric Genomic Consortium (Anxiety Disorders, and Major Depressive Disorder Working Groups), the UK Biobank, and iPSYCH.

Additional Information: This work was performed on the TSD (Tjeneste for Sensitive Data) facilities, owned by the University of Oslo, operated and developed by the TSD service group at the University of Oslo, IT-Department (USIT) (tsd-drift@usit.uio.no). This research has been conducted using the UK Biobank Resource under Application Number 27412.

Disclaimer: Data from the Norwegian Patient Registry has been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Norwegian Patient Registry is intended nor should be inferred.

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Figure Legends:

Figure 1. The association of PRS of differently defined anxiety and depressive disorders with anxiety disorder only (Dx-ANX-only), major depression only (Dx-MD-only), or comorbid anxiety and depression (Dx-ANX-MD) compared to controls (CTRL) (Panel A) or compared to each of the other diagnostic categories (Panel B). PRS: polygenic risk score; CI: confidence interval, ANX-co: anxiety disorder including comorbid depression, MD-co: major depression including comorbid anxiety, CC-ANX-MD: case-case GWAS of ANX-only and MD-only. Phenotypes are displayed on the x-axis and PRS on the y-axis.

Figure 2. The association of polygenic scores (PRS) of differently defined anxiety and depressive disorders with symptoms of depression (Blue, Effort, Hopeless, Worry) and symptoms of anxiety (Nervous, Fearful, Scared, Tension) reported by mothers from MoBa. ANX-co: anxiety disorder including comorbid depression, MD-co: major depression including comorbid anxiety, ANX-only: anxiety disorder only, MD-only: major depression only, CC-ANX-MD: case-case GWAS of ANX-only and MD-only.

Figure 3. Venn diagram – The numbers of genes that showed enrichment in GSA-MiXeR analyses using GWAS data for different diagnoses. ANX-co: anxiety disorder including comorbid depression, MD-co: major depression including comorbid anxiety, ANX-only: anxiety disorder only, MD-only: major depression only.

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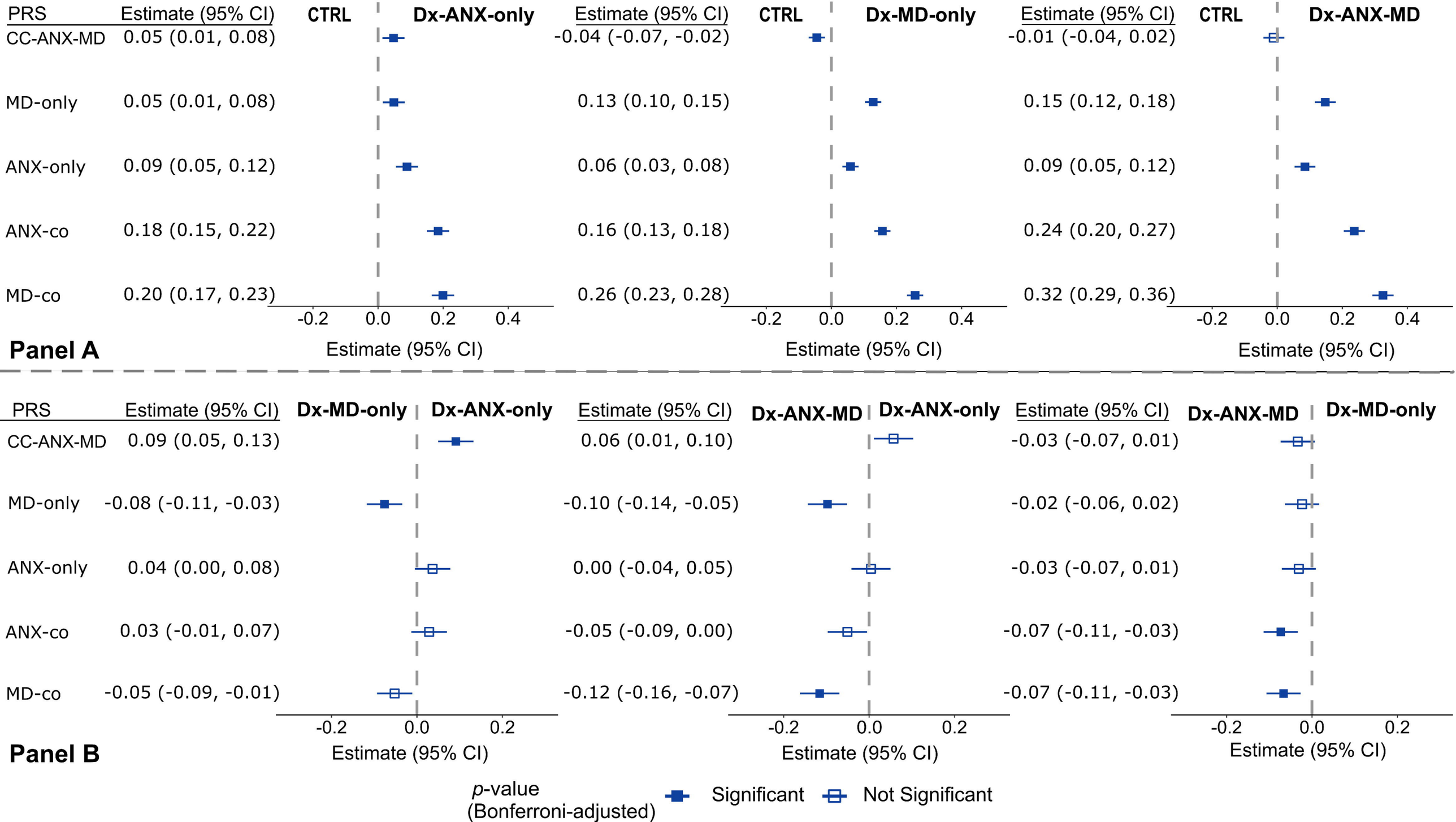
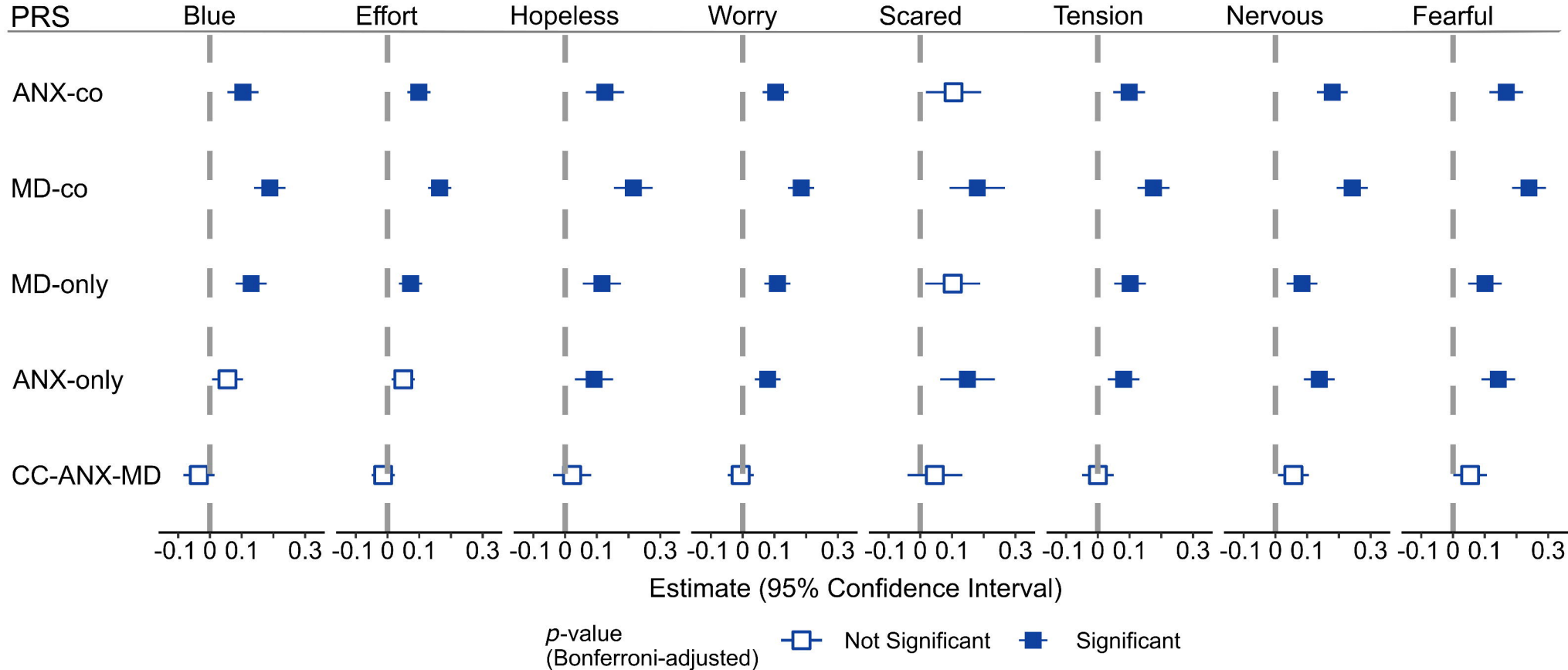
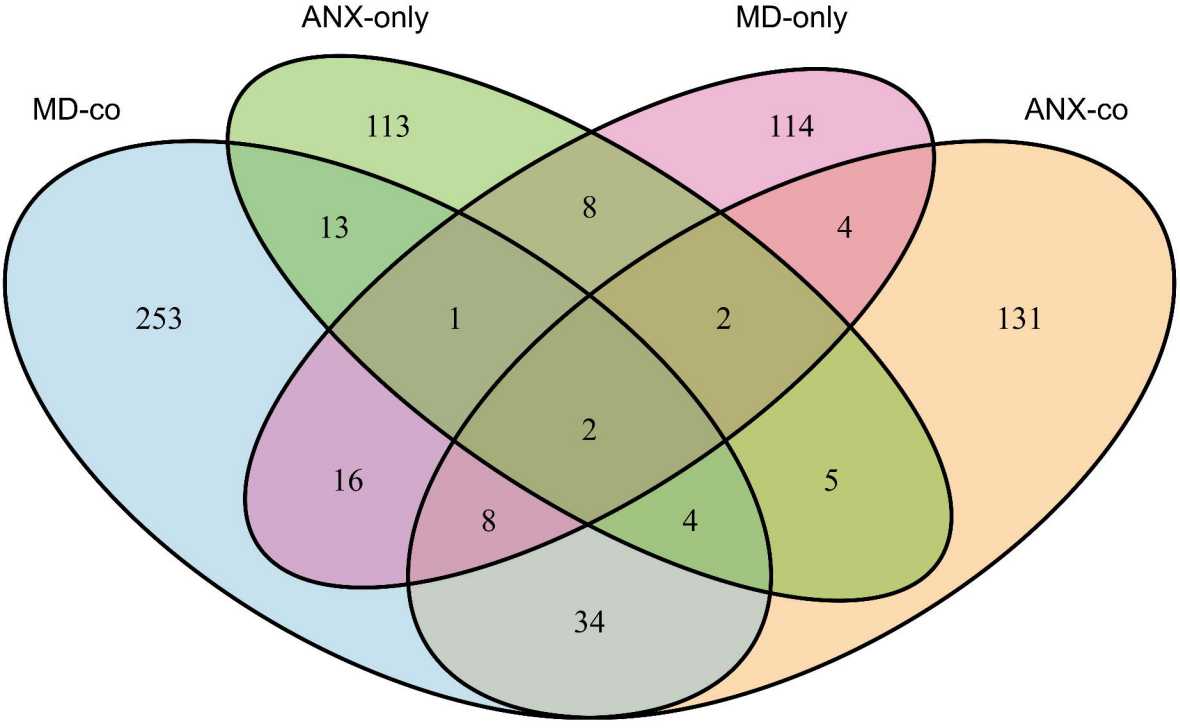
Table 1. Bidirectional Mendelian Randomization Analyses of Anxiety Disorders and Major Depression

Exposure	Outcome	Method	SNPs	Beta /gamma	SE / 95%CI	P-value	P_{FDR}
		IVW	**47**	**0.48**	**0.06**	**2.17e-14**	**1.73e-13**
MD-co[1]	ANX-co	MR Egger	47	0.03	0.20	0.88	0.93
		Weighted Median	**47**	**0.37**	**0.08**	**2.33e-06**	**9.31e-06**
		IVW	**39**	**0.26**	**0.03**	**2.17e-24**	**3.47e-23**
ANX-co[1]	MD-co	MR Egger	39	-0.19	0.25	0.46	0.73
		Weighted Median	**39**	**0.11**	**0.02**	**5.40e-13**	**2.88e-12**
		IVW	25	0.01	0.05	0.78	0.89
MD-only[1]	ANX-only	MR Egger	25	0.01	0.13	0.93	0.93
		Weighted Median	25	0.02	0.07	0.78	0.89
		IVW	**23**	**0.10**	**0.04**	**1.43e-02**	**3.81e-02**
ANX-only[1]	MD-only	MR Egger	23	-0.13	0.10	0.18	0.36
		Weighted Median	**23**	**0.15**	**0.05**	**4.79e-03**	**1.53e-02**
MD-co	ANX-co	CAUSE MR	1158	0.09	(-0.70, 0.25)	0.55	0.73
ANX-co	MD-co	CAUSE MR	1088	0.09	(0.04, 0.15)	0.045	0.10
MD-only	ANX-only	CAUSE MR	1491	0.11	(-0.08, 0.29)	0.55	0.73
ANX-only	MD-only	CAUSE MR	1480	0.10	(-0.06, 0.27)	0.51	0.73

[1] Instruments were selected at a *p*-value threshold of 1e-05; *p*-values < 0.05 after correction are in bold.
ANX-co: anxiety disorder including comorbid depression, MD-co: major depression including comorbid anxiety, ANX-only: anxiety disorder only, MD-only: major depression only, SE – standard error, CI – confidence interval, IVW – inverse variance weighted, MR – mendelian randomization, CAUSE - causal analysis using summary effect estimates, SNP – single nucleotide polymorphism


PRS
Estimate (95% CI)
CC-ANX-MD
MD-only
ANX-only
ANX-co
MD-co
0.05 (0.01, 0.08)
0.05 (0.01, 0.08)
0.09 (0.05, 0.12)
0.18 (0.15, 0.22)
0.20 (0.17, 0.23)
CTRL
Dx-ANX-only
-0.04 (-0.07, -0.02)
0.13 (0.10, 0.15)
0.06 (0.03, 0.08)
0.16 (0.13, 0.18)
0.26 (0.23, 0.28)
Dx-MD-only
-0.01 (-0.04, 0.02)
0.15 (0.12, 0.18)
0.09 (0.05, 0.12)
0.24 (0.20, 0.27)
0.32 (0.29, 0.36)
Dx-ANX-MD
-0.2
0.0
0.2
0.4
Estimate (95% CI)
Panel A
PRS
Estimate (95% CI)
CC-ANX-MD
MD-only
ANX-only
ANX-co
MD-co
0.09 (0.05, 0.13)
-0.08 (-0.11, -0.03)
0.04 (0.00, 0.08)
0.03 (-0.01, 0.07)
-0.05 (-0.09, -0.01)
Dx-MD-only
Dx-ANX-only
0.06 (0.01, 0.10)
-0.10 (-0.14, -0.05)
0.00 (-0.04, 0.05)
-0.05 (-0.09, 0.00)
-0.12 (-0.16, -0.07)
Dx-ANX-MD
-0.03 (-0.07, 0.01)
-0.02 (-0.06, 0.02)
-0.03 (-0.07, 0.01)
-0.07 (-0.11, -0.03)
-0.07 (-0.11, -0.03)
-0.2
0.0
0.2
Estimate (95% CI)
Panel B
p-value
(Bonferroni-adjusted)
Significant
Not Significant


PRS
Blue
Effort
Hopeless
Worry
Scared
Tension
Nervous
Fearful
ANX-co
MD-co
MD-only
ANX-only
CC-ANX-MD
-0.1 0 0.1 0.3
Estimate (95% Confidence Interval)
p-value
(Bonferroni-adjusted)
Not Significant
Significant


ANX-only
MD-only
MD-co
ANX-co
113
114
13
8
4
253
1
2
131
2
16
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8
4
34