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TIME ZONE OF PRESENTING AUTHOR:
Australian Eastern Standard

TYPE OF SUBMISSION:
Oral paper

MEMBER STATUS:
Associate

ELIGIBLE FOR THOMPSON AWARD: Yes
ELIGIBLE FOR ROWEWARD: No

TITLE:
Symptom-level genetic modelling identifies novel risk loci and unravels the shared genetic architecture of anxiety and depression

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KEYWORDS:
Depression Anxiety GWAS Symptom-level Overlap

ABSTRACT:
Depression and anxiety are highly prevalent and comorbid psychiatric traits that cause considerable burden worldwide. Previous studies have revealed substantial genetic overlap between depression, anxiety, and a closely related personality trait – neuroticism. Here, we use factor analysis and genomic structural equation modelling (Genomic SEM) to investigate the genetic factor structure underlying 28 items assessing depression, anxiety and neuroticism. Symptoms of depression and anxiety loaded on two distinct, although genetically correlated factors, while neuroticism items were partitioned between them. We leveraged this factor structure to conduct multivariate genome-wide association analyses on latent factors of anxiety symptoms and depressive symptoms, using data from over 400,000 individuals in the UK Biobank. We identified 89 independent variants for the depressive factor (61 genomic loci) and 102 independent variants for the anxiety factor (73 loci). Of these variants, 72% and 78%, respectively, replicated in an independent 23andMe cohort of ~1.9 million individuals with self-reported diagnosis of depression (634,037 cases) and anxiety (624,615 cases). A pairwise GWAS analysis revealed substantial genetic overlap between anxiety and depression but also showed trait-specific genetic influences; e.g. genomic regions specific to depressive symptoms were associated with hypertriglyceridemia, while regions specific to anxiety symptoms were linked to blood pressure phenotypes. The substantial genetic overlap between the two traits was further evidenced by a lack of trait-specificity in polygenic prediction of depressive and anxiety symptoms. Our results provide novel insight into the genetic architecture of depression and anxiety and comorbidity between them.

GRANT SUPPORT:
J.G.T. and A.I.C. are supported by a UQ Research Training Scholarship from The University of Queensland (UQ). N.G.M. received funding from the Australian National Health & Medical Research Council (NHMRC) to conduct surveys in the Australian Twin Registry. S.M. is supported by an NHMRC Fellowship.

