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## Shared genetic and phenotypic risk factors in pain and psychological conditions

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### ABSTRACT:

Chronic pain and psychological conditions show substantial phenotypic and genetic overlap. Our goal was to find and characterize the shared genetic risk components underlying these conditions. Using the UK Biobank dataset, we selected chronic conditions marked by persistent pain across body sites and suspected etiologies. We ran a genome-wide association study (GWAS) on each condition and estimated their genetic correlations, which we compared to phenotypic correlations. Next, we performed confirmatory factor analysis (CFA) to test two hypotheses -- anatomic and etiologic groupings of conditions -- and exploratory factor analysis (EFA) followed by CFA. The EFA-CFA pipeline was validated using a split-genome approach with model discovery and validation in odd and even autosomes, respectively. All confirmatory analyses were performed using the genomic structural equation modeling (gSEM) framework. Furthermore, we plotted genetic correlations between all pain traits as a network, extracting graph properties. Our gSEM results show evidence of a bifactor structure, with a prominent general factor explaining most of the shared genetic variance and two specific factors with significant loadings from musculoskeletal and cranio-visceral disorders. Network visualization reveals a large cluster of highly inter-connected conditions that share genetic associations. Including psychosocial traits into the phenotypic analysis showed an effect of neuroticism on correlations among symptom-based pain traits, which were likewise positively and negatively correlated with depression and happiness, respectively. Our findings suggest a common genetic predisposition for etiologically distinct pain conditions, which may indicate shared pathophysiology. Overall, we report evidence for chronic pain as a systemic condition modulated by psychosocial traits.

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