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Phenome-wide association studies of polygenic liability for externalizing in a European cohort reveals sex- and age-differentiated associations with numerous medical outcomes

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Externalizing (EXT) refers to psychiatric disorders and behaviors such as substance use disorders (SUD) and aggression, exhibiting variations by sex and age and are associated with elevated morbidity rates. This may stem from shared genetic factors influencing both EXT and morbidity or associations between EXT and morbidity mediated through EXT-related traits. The Externalizing Consortium performed phenome-wide association studies (PheWAS) to assess relationships between polygenic scores (PGS) for EXT derived from the latest genome-wide association study (N=1,492,085) and numerous clinical EHR-based diagnoses from BioVu (N=66,915). Up to 255 significant disease phenotypes were identified; however, sex and age differences were not assessed. This study addresses the gap by conducting sex- and age-differentiated PheWAS and sex-differentiated interaction tests (Sex*PGS) to examine whether genetic liability to EXT on clinical diagnoses vary by sex and age. Of the 1,378 disease phenotypes assessed, up to 418 were associated with the PGS-EXT (FDR 5%). The most abundant associations were with mental and behavioral disorders, such as SUD, mood disorders, and suicidal ideation. Worse health was also identified in nearly every bodily system including infectious disease, cardio-endocrine conditions, and respiratory conditions. Ischemic heart disease was the only trait found to be more strongly associated in females compared to males (female OR=1.17, p=4.23E-16; male OR=1.09, p=1.87E-07) in the sex-differentiated interaction tests. These results suggest that the EXT polygenic score manifests similarly across sex and age groups, underscoring its robust association with diverse health outcomes.