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TITLE: Using Neuroticism as a model phenotype to compare and contrast genome-wide associations from structural equation models

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ABSTRACT:

Several methods have emerged to conduct genome wide association studies using structural equation modeling (SEM). We will use the moderately heritable personality trait Neuroticism as a model phenotype to compare and contrast the SEM methods, focusing on potential differential interpretations to elucidate the strengths and weaknesses of each method. Specifically, we will compare GW-SEM (Verhulst et al., 2017), genomicSEM (Grotzinger et al., 2018), and TATES (van der Sluis et al., 2013).

**Participants:** Analyses will be conducted on up to 379,153 unrelated respondents with northern European ancestry from the UK Biobank.

**Statistical Analyses:** We will conduct univariate GWAS analyses on the 12 Neuroticism items and use the summary statistics for the genomicSEM and TATES analyses. We will compare these results with those using raw data conducted with GW-SEM.

We expect the pattern of genetic associations from different software will be broadly consistent, however possible differences may emerge based on methodological variation. These potential methodological differences are not currently understood but may have

considerable implications for the utility of the specific methods.

Verhulst, et al., (2017). GW-SEM: A statistical package to conduct genome-wide structural equation modeling. *Beh Gen*, 47(3), 345–359.

Grotzinger, et al. (2019). Genomic structural equation modelling provides insights into the multivariate genetic architecture of complex traits. *Nat Hum Behav*, 3(5), 513–525.

van der Sluis et al (2013) TATES: Efficient Multivariate Genotype-Phenotype Analysis for Genome-Wide Association Studies. *PLOS GEN*.

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