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**Genetic association of phenotypic typologies of polysubstance use disorders:  
A latent class approach**

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Polysubstance use disorder (PSU) is highly prevalent among individuals with substance use disorders and co-occurs with several mental and physical morbidities. The phenotypic heterogeneity that arises inevitably from the use of multiple substances creates a substantial challenge in identifying replicable polygenic effects for polysubstance use disorder. We addressed this heterogeneity by employing latent class analysis to categorize latent (unobserved) relationships among five diagnosis of substance use disorders - alcohol, cannabis, cocaine, nicotine, and opioids. Our initial cohort consisted of unfiltered individual-level genotype and clinical data of approximately 35,000 individuals from 14 PSU cohorts. The quality control and SNP marker imputation of genotype datasets within and across cohort merging were performed using RICOPIIL (Rapid Imputation and COmputational PipeLine). The PSU phenotype profiles were harmonized and imputed using PHENIX (PHENotype Imputation eXpediated). Latent classes of PSU phenotype profiles were derived using Mplus and poLCA with multiple iterations and the optimal number of classes was estimated using a combination of the Bayesian information criterion, the Akaike information criterion, the Lo–Mendell–Rubin adjusted likelihood ratio test, and the bootstrap likelihood ratio test. Multinomial regression was employed to test for genetic association with latent profiles followed by conditioning on a single substance to identify its relationship with latent PSU profiles. The results obtained provide information regarding the genetic correlations of PSU profiles with neuropsychiatric phenotypes, enrichment with brain morphology, and gene ontology of neuronal functions, providing novel insights related to the specific molecular architecture of the traits investigated.