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Dissecting polysubstance use disorders via polygenic risk scoring

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To model the phenotypic complexity of polysubstance use disorder (PSU), we applied a latent class analysis (LCA) to five substance dependencies (SD; alcohol, AD; cannabis, CaD; cocaine, CoD; nicotine, ND; and opioids, OD) across 20,740 participants. Accounting for potential biases affecting LCA (e.g., case-control ratio and SUD prevalence), we observed the best fit for 4 latent classes: 1) “no-SD” class with 71% (ND) to 100% (CaD) probability of not having any of the SDs; 2) “all-SD” class with 54% (OD) to 97% (AD) probability to have all SDs; 3) “alcohol-nicotine” class with 65% and 69% probabilities to have AD and ND, respectively; 4) “high addiction risk” class with 76%, 82%, and 100% probabilities to have ND, CoD, and OD, respectively. For these latent classes, we tested polygenic risk scores (PRS) for neuroticism, risk-taking behaviors, psychopathology, cognitive ability, educational attainment, socioeconomic status, and subjective well-being. The strongest PRS associations were observed for educational attainment and cognitive ability for the “no-SD” class (positive effect size association, 3.21e-5>p>1.32e-18), the “all-SD” class (negative association, 0.003>p>8.22e-10), and the “high addiction risk” class (negative association, 6.81e-5>p>5.93e-9). PRS related to neuroticism, risk-taking behaviors, and subjective well-being showed the strongest association with the “all-SD” latent class (neuroticism: z=2.66, p=0.007) and “no-SD” latent class (risk-taking: z=-2.99, p=0.003; subjective well-being: z=3.49, p=5e-4). To understand the biology underlying these PRS associations, we additionally investigated gene ontologies and molecular pathways, observing enrichments for synaptic GABAergic transmission, immunological synapse formation, axon morphogenesis, and neuron differentiation.