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Epigenetic profiles of latent classes for polysubstance use disorder

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In this study, we used latent class analysis (LCA) to identify distinct combinations of five substance use disorders - alcohol, cannabis, cocaine, opioid, and tobacco and subsequently performed an epigenome-wide association study (EWAS) of pSUD latent classes using DSM-IV criteria in 31,197 individuals. After quality control of the variables, we identified a five-class model: Class1 (Alcohol-Tobacco, n= 6487), Class 2 (Cocaine-Tobacco, n=1170), Class 3 (Polysubstance use (PSU): Alcohol, cocaine, opioid, tobacco, n= 2090), Class 4 (Controls, n= 11759), and Class 5 (Tobacco, n = 1162). We extracted individuals with genotype, and methylation data (n = 1072). We conducted an EWAS in three genetically defined ancestry groups (European (EUR); African (AFR), n= 501, Hispanic (HIS), n= 175) at 657,226 CpG sites using regression models, with adjustment for technical artifacts, age, sex, blood cell type proportion, and ten principal components of within-genetic ancestry. Comparing the latent-class control sample with the PSU latent class, we found 2, 1, and 0 differentially methylated sites in EUR, AFR, and HIS populations, respectively. The cg05575921 in *AHRR* (5p15.33) was significantly hypomethylated in the PSU class (AFR p = 3.63e-09; EUR p= 7.35e-09). Comparing the control latent-class with alcohol-tobacco class, we found 2, 80, and 1 differentially methylated sites in EUR, AFR, and HIS populations, respectively. The cg02833127 in *SPATA4* (4q34.2) was significantly hypomethylated in alcohol & tobacco class (AFR p = 6.05e-08; EUR p= 3.668915e-26; HIS p= 1.00e-17). These findings highlight the role of methylation in pSUD profiles in multiple population groups.