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# Multi-ancestral genome-wide association study of nicotine dependence reveals strong genetic correlations with other substance use and psychiatric disorders

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There are many ways to define substance use traits and disorders (SUDs); for traits for which multiple definitions have been studied, the underlying biology may be heterogeneous. Our ability to clarify this heterogeneity for nicotine dependence has been limited by a lack of large genome-wide association studies (GWASs) of nicotine dependence defined using DSM criteria. Here, we present a genome-wide meta-analysis of DSM IV-defined nicotine dependence (NicDep) in 61,598 individuals (46,816 of European ancestry (EA), 10,231 of African ancestry, 4,551 of East Asian ancestry). We replicated the well-known genome-wide significant association at the *CHRNA5* gene on chromosome 15 (lead SNP: rs2036527, p-value=1.15e-12). NicDep shows strong positive genetic correlations with other SUDs (cannabis use disorder, opioid use disorder, problematic alcohol use), lung cancer, neighborhood deprivation, and psychiatric disorders (anxiety, attention deficit hyperactivity disorder, depression, post-traumatic stress disorder, and schizophrenia), and negative correlations with respiratory function and educational attainment. Genomic structural equation models show that NicDep loads more strongly on a previously identified factor of general addiction liability than does a “problematic tobacco use” factor (a combination of cigarettes per day and the Fagerström Test for Nicotine Dependence (FTND)). A polygenic score for NicDep was associated with DSM-5 nicotine use disorder in the independent NESARC sample (beta=0.10, SE=0.02, p=7.95e-6; $N_{cases}$ =4,205). Our findings suggest that NicDep defined by DSM criteria shares substantial genetic overlap with other SUDs and psychiatric disorders and may provide additional value beyond genetic studies of smoking behaviors (e.g., cigarettes per day) or common questionnaires (e.g., FTND).