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Trans-ancestry GWAS meta-analysis of tobacco and alcohol use

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ABSTRACT:

The use and abuse of nicotine and alcohol account for >100 million disability-adjusted life years across the globe, constituting one of the world's leading public health problems. Despite this, the vast majority of genome-wide association studies thus far have been restricted to individuals of European ancestry, representing <1% of known worldwide genetic variation. Here, we leveraged a trans-ancestry GWAS of nicotine and alcohol use from up to 3.4 million individuals from 81 studies with recent ancestry from Africa (N=121,858), America (285,155), East Asia (298,624), and Europe (2,669,029). Overall, we identified 1,449 loci and 3,842 conditionally independent variants associated with our five substance use phenotypes: 33 loci (39 variants) for age of initiation of regular smoking, 738 (2,489) for smoking initiation, 138 (245) for cigarettes per day, 132 (217) for smoking cessation, and 408 (852) for alcoholic drinks per week. Using trans-ancestry fine-mapping methods, we identified 653 loci with 90% credible intervals containing <5 variants. Approximately 18% of sentinel variants showed differential effects across ancestry. Polygenic risk score prediction accuracy in European ancestries ranged from 1.2 to 7.7%, which attenuated to 0.6-5.1% in the remaining ancestries. Taken together, our results highlight the value of diverse ancestry inclusion in genetic studies.

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