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Epigenome-wide association meta-analysis of DNA methylation with lifetime cannabis use

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Cannabis use and its links to adverse health outcomes is a pressing public health question, highlighting the urgent need for reliable biomarkers that reflect cannabis exposure. Growing evidence suggests that DNA methylation can serve as a reliable exposure biomarker. We conducted an epigenome-wide association study (EWAS) of peripheral blood-based CpG methylation and lifetime cannabis use (ever vs. never) in a meta-analysis including 9,480 participants (7,739 European- and 1,741 African-ancestry) from 6 cohorts. Our EWAS meta-analysis revealed four CpG sites significantly associated with lifetime cannabis use at a false discovery rate of 0.05 ($p < 5.85 \times 10^{-7}$): cg22572071 near gene *ADGRF1*, cg15280358 in *ADAM12*, cg00813162 in *ACTN1*, and cg01101459 near *LINC01132*. Previous EWAS findings showed tobacco smoking was a big confounding factor for cannabis use, but none of the four CpGs has been reported as genome-wide significant hits in EWAS for smoking. Although our EWAS model accounted for tobacco smoking as a covariate, we further investigated the associations between CpGs and lifetime cannabis use in the subset of participants who never smoked tobacco (N=3,861). All four top CpGs from the overall analysis remained significantly associated with cannabis use in never smokers ($p < 0.05$). Additionally, the EWAS meta-analysis for cannabis use in never smokers identified another epigenome-wide significant CpG, cg14237301 annotated to *APOBR*, which has been found significantly associated with lifetime cannabis use in a genome-wide association study ($p = 7.56 \times 10^{-9}$), suggesting the observed differential DNA methylation at *APOBR* was likely driven by genetic factors. These findings support developing a peripheral blood-based biomarker indicative of lifetime cannabis use.