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DNA methylation signature of Phosphatidylethanol Predicts Hazardous Alcohol Use

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Alcohol consumption has been associated with DNA methylation (DNAm) in blood and DNAm may serve as biomarkers for hazardous alcohol use (HA). Here, we report a 2-stage study for developing DNAm signature in blood to predict HA in two independent cohorts (N_{total} =1,226). First, we performed an epigenome-wide association study (EWAS) with over 450,000 CpGs on Phosphatidylethanol (PEth), a marker for short-term alcohol consumption in 720 samples (**Cohort 1**). Then, PEth-associated DNAm was applied to predict HA, measured by the Alcohol Use Disorders Identification Test-C (AUDIT-C >=4) in 506 samples (**Cohort 2**).

EWAS revealed 9 CpGs (ps<1E-07) for PEth including 2 previously reported CpG sites (cg06690548 (*SLC7A11*) (t=-6.44, p=2.80E-10) and cg11376147 (*SLC43A1*) (t=-5.14, p=3.90E-7) for HA. We identified 7 novel CpGs including cg17962756, cg13442969 (*DYRK2*), cg20525486 (*FOXP1*), cg26689780 (*WDR1*), cg04304130 (*HERV-FRD*), cg00220102 *(ABAT*), and cg18590502 (*CCDC71*). Of note, the effect size of individual CpG on PEth is small. To test whether PEth-related DNAm collectively predicted HA, we constructed a polygenic methylation score (PGMS) by summing weighted effect size of 179 CpGs. PGMS was highly correlated with AUDIT-C score in the cohort 2 (r^2=0.33, p=2.56E-6). The Area Under the Receiver Operating Characteristic Curve to predict HA was 0.72 (95% CI: 0.64-0.80), suggesting that a panel of the selected CpGs showed moderate discrimination between HA and non-HA.

Our results indicated that the objective test for alcohol consumption is a powerful phenotype to detect subtle methylation effect. PEth-associated DNAm may be a biomarker for future HA diagnosis and treatment.