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Alcohol and stress additively accelerate epigenetic cellular age

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Alcohol use and stress are partly entwined predictors of allostatic load and mortality. We measured their separate and combined effects on epigenetic age acceleration (EAA). A composite stress score (CSS) was computed from 13 clinical variables. We derived methylation indices of stress (MS Stress) and AUD (MS Alcohol) from methylome arrays. In 372 AUD patients and 243 healthy controls [NIAAA cohort] CSS or MS Stress, together with alcohol, additively accelerated epigenetic age (EAA). Telomere shortening highly correlated. Findings were replicated in Generation Scotland (GOS, set 1: N = 2578, set 2: N = 4450) and Grady Trauma Project (GTP, N = 795). In the NIAAA cohort, EAA [GrimAge] was 3.2 years higher in AUD than HCs ($p < 10\text{-}5$). MS Stress did not simply correlate with EAA or MS Alcohol.

Compared to low MS stress and low MS alcohol reference groups, EAA increased stepwise with higher MS stress, MS alcohol or both. Those with high MS stress/high MS alcohol exhibited a 3.9-year increase in GrimAge ($p <10\text{-}8$) and those with high MS stress/low MS alcohol exhibited only 2.2-year EAA ($p = .001$), and with similar findings for PhenoAge. Additive effects of stress and alcohol on EAA replicated. For example, in the GTP cohort, GrimAge was accelerated 4.6 yrs ($p < 10\text{-}15$) in the high MS stress/high MS alcohol group compared to low MS stress/low MS alcohol. These findings suggest that epigenetic measures of exposure together with polygenic scores (PGS) may better capture vulnerability than AUD PGS alone.