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A Mediating Role for Epigenetic Aging in the Relationship Between People Who Inject Drugs with HCV and All-Cause Mortality

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Background: Injection drug use is the principal risk factor for hepatitis C virus (HCV) infection mostly due to needle sharing. People who inject drugs (PWID) comorbid with HCV infection (PWID-HCV) leads to high mortality, causing more than 500,000 deaths per year globally.

Rationale/significance: Understanding the relationship between PWID-HCV and biological age is important for decreasing mortality in this population. Epigenetic age is a biomarker for chronological age and has been applied to predict disease progression and all-cause mortality risk. The five commonly used epigenetic clocks (i.e., MonoDNAMAge, HorvathDNAMAge, HannumDNAMAge, PhenoDNAMAge, GrimDNAMAge) employ differing sets of DNA methylation sites that show minimum overlap in included CpGs and may provide correlated but potentially different facets of chronological age. Our prior work demonstrated that aberrant DNA methylation is associated with PWID-HCV.

Hypothesis: In this study, we hypothesized that an increased mortality risk among PWID-HCV is partially mediated by epigenetic age in the Veteran Aging Cohort Study (N=927).

Results: Using a Cox proportional hazards model, we first found that PWID-HCV significantly increased risk of mortality in PWID-HCV (HR: 2.23; 95% confidence interval [CI]: 1.61, 3.09; $p=1.03E-06$). Furthermore, using the five established epigenetic clocks, our results showed that PWID-HCV was associated with statistically significantly increased epigenetic age acceleration with 3 out of 5 clocks, adjusting for age, race, BMI, smoking status, alcohol consumption (i.e., HannumDNAMAge: $p=4.39E-04$, PhenoDNAMAge: $p=9.40E-04$, GrimDNAMAge: $p=4.28E-12$). Importantly, using a mediation analysis, we found that these three clocks partially mediated the relationship between PWID-HCV status and all-cause mortality with average mediation effects of 0.05 (5.95% of total effect) for HannumDNAMAge, 0.05 (6.51%) for PhenoDNAMAge, and 0.12 (14.33%) for GrimDNAMAge.

Discussion: Our results suggest that an acceleration of epigenetic age by PWID-HCV partially contributes to high all-cause mortality in this population.