

Submitter Name: Jessica Williams-Nguyen
Submitted email: jswn@uw.edu
PI Name: Heidi Crane
PI email: hcrane@uw.edu

The importance of measuring substance use: A Mendelian randomization of chronic Hepatitis C and myocardial infarction

Jessica Williams-Nguyen¹, Anshuman Sewda², Sara Lindström^{1,3}, Inga Peter², Robin M Nance^{1,4}, Susan R Heckbert^{1,5}, H Nina Kim^{4,6}, Bridget M Whitney¹, W Chris Mathews⁷, Edward R Cachay⁷, Matt Budoff⁸, Christopher B Hurt⁹, Peter W Hunt¹⁰, Elvin Geng¹⁰, Richard D Moore^{11,12}, Michael J Mugavero¹³, Stephen E Hawes¹, Joseph J Eron⁹, Bryan Lau^{11,12}, Mari M Kitahata^{4,6}, Michael S Saag¹³, Joseph A Delaney¹, Heidi M Crane^{4,6}

¹Department of Epidemiology, University of Washington; ²Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai; ³Public Health Sciences Division, Fred Hutchinson Cancer Research Center; ⁴Department of Medicine, University of Washington; ⁵Cardiovascular Health Research Unit, University of Washington; ⁶Center for AIDS Research, University of Washington; ⁷Department of Medicine, University of California San Diego; ⁸Department of Medicine, Los Angeles Biomedical Research Institute at Harbor – University of California at Los Angeles Medical Center; ⁹Institute for Global Health & Infectious Diseases, University of North Carolina Chapel Hill; ¹⁰Division of Experimental Medicine, University of California San Francisco; ¹¹Department of Medicine, Johns Hopkins University; ¹²Department of Epidemiology, Johns Hopkins University; ¹³Division of Infectious Disease, University of Alabama at Birmingham

Chronic hepatitis C virus (HCV), common in people living with HIV (PLWH), is associated with cardiovascular disease such as myocardial infarction (MI). The two most frequently occurring types of MI are atheroembolic Type 1 (T1MI) and oxygen supply-demand mismatch Type 2 (T2MI). Our recent study in PLWH found that chronic infection with HCV was associated with T2MI, particularly T2MI attributed to sepsis, but not T1MI. We hypothesize that this relationship is confounded by sociobehavioral factors, such as injection drug use, and accompanying risk of sepsis. We used Mendelian randomization (MR) to estimate the causal effect of chronic HCV infection on T2MI (n events = 143) in 6,116 PLWH in the CFAR Network of Integrated Clinical Systems (CNICS), a multi-center clinical cohort of PLWH. T2MI events were ascertained by centralized adjudication. Genotyping of four candidate variants with known association to HCV clearance in diverse populations was via the Illumina Multiethnic Global Array. MR estimates on the basis of each variant were combined via meta-analysis. Variants were associated with 17 to 32% higher odds of chronic HCV infection. Findings do not support a causal relationship between chronic HCV and T2MI (ratio of odds ratios (ORR): 0.78, 95% CI: 0.33, 1.83) or the subset of T2MI attributed to sepsis (ORR 1.13, 95% CI: 0.54, 2.36). This suggests that factors other than HCV infection, such as substance use, may explain the observed association between chronic HCV infection and T2MI, highlighting the importance of comprehensive longitudinal substance use assessments in clinical cohorts of PLWH.