Impact of Polysubstance Use on High-Sensitivity Cardiac Troponin I over Time in Homeless and Unstably Housed Women

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Abstract

Introduction: The use of controlled substances like cocaine increases the risk of cardiovascular disease (CVD) and myocardial infarction (MI). However, outside of alcohol and tobacco, substance use is not included in CVD risk assessment tools. We identified the effects of using multiple substances (nicotine/cotinine, cannabis, alcohol, cocaine, methamphetamine, heroin and other opioids) on cardiac injury measured by high-sensitivity troponin (hsTnI) in homeless and unstably housed women.

Methods: We recruited 245 homeless and unstably housed women from shelters, free meal programs and street encampments. Participants completed six monthly study visits. Adjusting for traditional CVD risk factors, we examined longitudinal associations between substance use and hsTnI.

Results: Median participant age was 53 years and 74% were ethnic minority women. At baseline, 76% of participants had hypertension, 31% were HIV-positive, 8% had a history of a prior MI and 12% of prior stroke. The most commonly used substances were cotinine/nicotine (80%), cannabis (68%) and cocaine (66%). HsTnI exceeding the 99th percentile (14.7 ng/L) – a level high enough to signal possible MI – was observed in 14 participants during ≥1 study visit (6%). In adjusted analysis, cocaethylene and fentanyl were significantly associated with higher hsTnI levels.

Conclusions: Fentanyl use and the co-use of cocaine and alcohol are associated with myocardial injury, suggesting that the use of these substances may act as long-term cardiac insults. Whether risk counseling on these specific substances and/or including their use in CVD risk stratification would improve CVD outcomes in populations where substance use is high merits further investigation.

Keywords

cardiovascular risk assessment; drug abuse; women; cardiac troponin

INTRODUCTION

Substance use increases the risk of CVD and cardiac events (Morentin and Callado, 2019; Zador et al., 2019). In addition to the more commonly studied effects of alcohol and tobacco, a variety of controlled substances have been linked to CVD but have received less attention (Mladenka et al., 2018), including heroin (Reece and Hulse, 2013), methamphetamine (Schurer et al., 2017), and cocaine (Havakuk et al., 2017; Richards et al., 2017).

The use of cocaine is particularly well-studied. Cocaine potentiates acute cardiovascular sympathetic effects (Vongpatanasin et al., 1999), leading to increased peripheral vasoconstriction. This vasoconstrictive response is accompanied by increased levels of endothelin-1 (Wilbert-Lampen et al., 1998), impaired acetylcholine-induced vasorelaxation (Havranek et al., 1996), altered intracellular calcium handling (Perreault et al., 1991), and blockade of nitric oxide (NO) synthase (Mo et al., 1998). Consequently, cocaine use is associated with a variety of myocardial complications (Lange and Hillis, 2001), including hypertension, cardiomyopathy, ischemia and arrhythmia (Havakuk et al., 2017), and events such as stroke, myocardial infarction (Havakuk et al., 2017), and sudden death caused by cocaine-induced arrhythmia (Hollander et al., 1994; Lange and Hillis, 2001).

Sixty to ninety percent of cocaine users engage in polysubstance use (i.e., the simultaneous use of multiple substances) often including alcohol (Heil et al., 2001). However, potential risks conferred by polysubstance use that are different than those conferred by individual drugs are rarely considered in research regarding substance-related CVD risk. Furthermore,

cardiovascular risks differ by sex (Mosca et al., 2011), and some studies do not include enough women to ensure statistical power (Bucholz and Krumholz, 2015). For example, a recent randomized trial reported that alcohol abstinence reduced arrhythmia recurrences in regular alcohol drinkers with atrial fibrillation (Voskoboinik et al., 2020). However, women only comprised 15% of study participants, and subgroup analyses showed that women may not have benefitted from alcohol abstinence (Gillis, 2020).

While abstinence is an important goal, research shows low quit rates and high relapse in high-risk women such as homeless and unstably housed women (Riley et al., 2015). A better understanding of the relationships between polysubstance use and CVD risk is needed for individuals currently unable to achieve abstinence (Hsue et al., 2012). Understanding the circumstances preceding acute drug-induced CVD events would facilitate better risk assessment and inform more effective prevention programs.

A cornerstone of CVD prevention is risk assessment tools that include biomarkers (Neumann et al., 2019; Ward-Caviness et al., 2017). Cardiac troponins detect myocardial injury, provide risk stratification in patients suspected of acute coronary syndromes, and add independent prognostic information to clinical variables when considered alongside other biomarkers (Gaggin et al., 2014). Troponin predicts clinical outcomes including death and first coronary heart disease event in individuals free from CVD at baseline, indicating the importance of silent cardiac damage in the development of coronary heart disease and mortality (Zethelius et al., 2006). In addition, several studies show that troponin outperforms echocardiographic parameters in predicting mortality (Bergenzaun et al., 2012).

The recent advent of highly-sensitive troponin assays has led to the understanding that persons with detectable values far below the traditional 99th percentile cutoff – signaling myocardial infarction (MI) – are at increased risk for morbidity and mortality (Jaffe, 2006; Waxman et al., 2006). Research consistently confirms the value of assessing even slight increases in high-sensitivity troponin to predict cardiovascular events (Beatty et al., 2013; Omland et al., 2009). Studies that employ troponin measurements at very low concentrations (i.e., 0.02 μg/L), will provide a better understanding of important influences on silent cardiac damage (Kavsak et al., 2007).

We conducted a prospective women's study to determine longitudinal associations between polysubstance use and cardiac injury measured by high-sensitivity troponin (hsTnI). The study draws on our prior cross-sectional research, which showed a significant association between cocaine and hsTnI in a mostly male sample of individuals seeking care in a safety net hospital (Riley et al., 2017).

The current study seeks to extend existing evidence in two ways. First, to address limitations in some prior studies related to CVD risk stratification which have under-enrolled women (Beatty et al., 2013), the current study was conducted exclusively in women. This is important for several reasons. From a physiological perspective, biomarkers vary between men and women (e.g., men have higher levels of naturally occurring cardiac troponin than women (Collinson et al., 2012)). From a population perspective, substance use – especially the use of crack cocaine – is common (>50%) in homeless and unstably housed women

(Riley et al., 2015), and cocaine-related acute intoxication is one of the leading causes of death in this group (Riley et al., 2013). From a clinical perspective, among individuals hospitalized for acute MI, women are more likely than men to present without chest pain, and their providers are less likely to conclude that symptoms experienced prior to hospitalization were heart-related (Lichtman et al., 2018). Thus, advances in biomarker research conducted exclusively in women may offer a novel tool to help women and their providers make informed health care decisions.

Second, almost all studies regarding cardiovascular risk stratification and substance use are among individuals recruited from health care establishments where they were receiving care at the point of recruitment. Although this may be an efficient research approach, it largely precludes assessment of subclinical disease (or is at least biased toward persons experiencing symptoms that prompt health care use) and overenrolls individuals with access to health care. This is important because prior studies report that cardiac biomarkers predict clinical outcomes in individuals *without* clinically diagnosed CVD, suggesting the important role of silent cardiac damage in the development of future disease and mortality (Zethelius et al., 2006). By conducting community-based recruitment to assess effects in individuals whose CVD status at enrollment was unknown, we sought a real-world understanding of associations between substance use and cardiac dysfunction in the larger population of homeless and unstably housed women, not only those receiving health care.

METHODS AND MATERIALS

1.1. Study design

Polysubstance Use and Health Outcomes Evaluation (PULSE) is a prospective study of women living in San Francisco. We collected PULSE study data between June 2016 and January 2019 to examine the influences of polysubstance use on cardiac dysfunction.

1.2. Study Participant Recruitment

Trained study team members recruited a sample of San Francisco homeless and unstably housed women from shelters, free meal programs, single room occupancy (SRO) hotels and street encampments. The number of people from each venue was not determined a priori. In addition, women living with HIV were recruited from the Zuckerberg San Francisco General Hospital HIV clinic ("Ward 86"),

Inclusion criteria included female sex at birth, age 18 years and a history of housing instability (i.e., slept in public or a homeless shelter, or stayed with a series of associates because there was no other place to sleep ["couch-surfed"]). HIV testing was conducted at screening, and HIV-positive persons were oversampled to accomplish HIV-related aims. CVD status at enrollment was unknown. Participants were reimbursed $40 for each study interview. We obtained free and informed consent from all study participants. All study procedures reported here were approved by the Institutional Review Board at the University of California, San Francisco.

1.3. Data Collection

Participants completed monthly study visits for six consecutive months, consisting of an interview, blood draw, assessment of blood pressure and assessment of height/weight, resulting in six longitudinal measurements of every factor considered. Questionnaires and study procedures were pilot-tested to ensure appropriateness for the target population. Socially sensitive questions were administered by audio computer-assisted self-interviewing (ACASI); all other questions were interviewer-administered.

1.4. Dependent Outcome Measures

We used serum samples to evaluate the level of hsTnI (Abbott Architect hsTnI; 99th percentile of myocardial injury for females in serum>14.7 ng/L), which changes as a function of cardiac injury, is detectable for 6–8 days following cardiac insult (Wu, 1999), and has a dose-response relationship with MI, heart failure, cardiovascular mortality and all-cause mortality (Li et al., 2019).

1.5. Independent Exposure Measures

Primary study exposures were toxicology-confirmed substance use and toxicology-confirmed use of prescribed pharmaceutical drugs influencing cardiovascular health. We tested hydrolyzed urine samples using a qualitative liquid chromatography-high resolution mass spectrometry (LC-HRMS) method. Data acquisition and generation of mass spectra took place using an SCIEX 5600 TripleTOF® LC-HRMS system. We used HRMS full scan mode with information-dependent acquisition of HRMS product ion spectra, which were searched against a mass spectral library for positive identification of each substance. This methodology has proven sensitive and specific for the detection of these compounds in urine (Thoren et al., 2016).

To increase test sensitivity, we conducted separate urine THC screening, which uses a liquid chromatography tandem mass spectrometry (LC-MS/MS) method to detect THC–COOH (>0.5 ng/mL) and THC-COOH-glucuronide (2.5 ng/mL) (Benowitz et al., 2019a). A full list of substances and pharmaceutical drugs is shown in Table 1, including cotinine (>10 pg/ml, a marker of smoking (Benowitz et al., 2019b)), ethylglucuronide (a marker for alcohol), cocaine, methamphetamine, opioids, beta blockers, calcium channel blockers and statins.

We considered five groups of exposure variables. Demographic variables (group 1) included age, race and menopausal status. Substance use (group 2), included controlled substances, drug adulterants and metabolites, which are detailed in Table 1. Commonly used pharmaceutical drugs related to CVD (group 3) are also detailed in Table 1. Chronic health conditions (group 4) included HIV infection, hepatitis C infection, diabetes, prior MI and prior stroke. Current health status (group 5) included body mass index (BMI), systolic blood pressure, diastolic blood pressure, total cholesterol (Cholesterol_2, Siemens ADVIA® Chemistry XPT), HDL cholesterol (Direct HDL cholesterol, Siemens ADVIA® Chemistry XPT), triglycerides (Triglycerides_2, Siemens ADVIA® Chemistry XPT), calculated LDL cholesterol (Friedewald equation), and high sensitivity C-reactive protein (CardioPhase™ hsCRP, Siemens ADVIA® Chemistry XPT).

1.6. Analysis

We considered descriptive statistics (e.g., frequency, percentage, interquartile range and median) before conducting comparative analyses. We then log-transformed biomarker outcomes and, in order to account for intra-individual correlation between subsequent visit measures, we used linear mixed models to determine effects over time between substance use and hsTnI measured at each of six study visits.

To clearly delineate effects, a series of models sequentially added variables from each of the five exposure variable groups. At each step, backward deletion was used to remove variables in the most recently added group with p-values>0.1. Variable significance within adjusted models was considered at the p<0.05 level. In addition, we used separate analyses to estimate associations between drug combinations and hsTnI. Analyses were done using Stata Version 15.0 (Stata Corp., College Station, TX). Finally, we conducted a sub-analysis to assess potential effects of substance use frequency by replacing all substance use toxicology results with (1) self-reported frequency of use in the prior week (every day, almost everyday, sometimes, not often or no use) and (2) number of uses per day (continuous variable),

RESULTS

We recruited 245 participants (77 from low-income hotels, 70 from free meal programs, 50 from the Ward 86 HIV clinic, 44 from homeless shelters and 4 from street encampments), with a median of 5 completed study visits each, resulting in 1,051 study visits total. The median participant age at baseline was 53 years and 74% were ethnic minority women (Table 2). Due to oversampling of women living with HIV, the prevalence of HIV (i.e., proportion of people living with) was 31% and the prevalence of hepatitis C infection was 32%. Prior physician-diagnosed heart attack and stroke were reported by 8.2% and 11.5% of participants, respectively. At baseline, 76% of participants had hypertension (i.e., systolic >120 mm Hg or diastolic>80 mm Hg) (Table 2).

The prevalence of toxicology-confirmed substances at baseline and at one or more study visit respectively included cotinine/nicotine (69% and 80%); cocaine (53% and 66%); cannabis (51% and 68%); methamphetamine (29% and 43%); glucuronide/alcohol (29% and 48%); cocaethylene, a metabolite formed when cocaine and alcohol are co-ingested (Jones, 2019) (17% and 28%); heroin (2% and 8%); and opioids other than heroin (22% and 36%). Almost 4 in 5 participants (77%) had evidence of polysubstance use at one or more study visits. (Table 2).

The baseline population median level of hsTnI was 2.0 ng/L (Table 2). A level of hsTnI exceeding the 99th percentile (14.7 ng/L) – a level high enough to signal possible MI – was observed in 14 participants during at least one study visit (6%). Using data from all study visits, Table 3 shows that, after adjusting for age, race/ethnicity and menopausal status (Model 1), the only substance-related metabolites significantly associated with hsTnI level over time (Model 2) were cocaethylene, which was associated with a 1.09-fold increase in log-transformed hsTnI, and fentanyl, which was associated with a 1.18-fold increase. Adjusting for chronic health conditions (Model 3), pharmaceutical drugs (Model 4), BMI,

and systolic blood pressure and LDL cholesterol (Model 5), slightly increased the magnitude of effect for both cocaethylene (Adjusted Linear Effect [ALE]:1.12; 95% CI:1.02–1.22) and fentanyl (ALE:1.20; 95% CI:1.02–1.41). A variety of factors known to increase cardiovascular events and conditions were not significantly associated with hsTnI in this population, including nicotine/cotinine, prior MI, prior stroke, HIV infection, HCV infection and hsCRP.

Additional models using data from all study visits considered combined substance use effects on hsTnI compared to effects from individual drugs over time and suggested that the combined effects of fentanyl + methamphetamine (interaction p= 0.006), fentanyl + opioids (interaction p=0.03), and fentanyl + methadone (interaction p=0.02) were lower than expected based on their independent effects. Similarly, while limited, there was evidence for negative interaction between cocaethylene and methadone (p=0.02).

Additional models using data from all study visits considered potential differences in hsTnI according to differing levels of substance use. Considering self-reported frequency of use in the prior week and number of uses per day, only cocaine use frequency (Daily Use vs. No Use Linear Effect:1.20; 95% CI:1.06–1.35), and number of cocaine uses per day (Linear Effect: 1.05; 95% CI:1.01–1.09) were significantly associated with hsTnI level. However, effects were non-significant after adjusting for age, race, menopausal status, statin use, BMI, blood pressure, cholesterol and CRP. Log-Likelihood results confirmed that model fit was improved in the presence of toxicology results compared to self-reported frequency of substance use (data not shown).

DISCUSSION

In this community-recruited sample of homeless and unstably housed women in their 40s and 50s without known CVD at enrollment, where one in two used cocaine and four in five used multiple substances, 8.2% had a prior heart attack and 11.5% had a prior stroke diagnosis. The proportion of women reporting a prior stroke is approximately four times higher than the general population of non-Hispanic white women, and twice as high as the general population of non-Hispanic black women over age 20 living in the United States (Writing Group et al., 2016). In addition, across the six monthly study visits, 6% of study participants had biomarker evidence of myocardial injury exceeding the hsTnI 99th percentile for women. Cocaethylene and fentanyl were independently associated with hsTnI concentration, even after adjusting for traditional risk factors. On the contrary, several factors included in standard CVD risk assessment tools (e.g., nicotine/cotinine, prior MI and prior stroke) were not significantly associated with hsTnI. Combined with previous reports showing that frequent substance use is common and sustained over years in some populations (Parker and Anthony, 2014), results presented here suggest the potential importance of considering cocaine, alcohol and fentanyl use, not only as episodic risk factors leading to acute health events like MI and stroke, but also as long-term factors leading to ongoing cardiac injury. Prior research indicates strong associations between substance use and high CVD risk scores, while also noting the absence of cocaine in standard risk calculators (Gozdzik et al., 2015; Lee et al., 2005). It acknowledges the need to supplement risk scores with clinical impressions of nontraditional factors, including cocaine,

that elevate risk (Gozdzik et al., 2015). Findings presented here suggest that, rather than augmenting risk scores with clinical impressions, it may be useful to systematically include substance use beyond alcohol and tobacco directly in CVD risk assessment tools.

This is the first study of which we are aware to report a significant association between hsTnI and cocaethylene, an observation occurring in the absence of significant associations between hsTnI and either cocaine or alcohol alone. This finding reinforces prior reports that cocaethylene –a metabolite formed when cocaine and alcohol are used within approximately 2 hours of each other --may be more cardiotoxic than either alone (Farooq et al., 2009; Lange and Hillis, 2001). Cocaethylene synergistically increases cocaine toxicity, due in part to slower drug clearance in the presence of other drugs (Laizure et al., 2003).

We added a sub-analysis in which we replaced toxicology-confirmed substance use with self-reported frequency of use for each substance. Adjusted analysis did not show significant associations between self-reported frequency of any substances used and level of troponin, and model fit was better when toxicology-confirmed substance use variables were included. Given that the strongest substance-related associations were between hsTnI and toxicology-confirmed cocaethylene (a metabolite that cannot be self-reported), and fentanyl (a substance often used as an adulterant of other drugs, making its presence unknown to the user and therefore impractical to self-report), the observed absence of significant relationships between self-reported frequency of substance use and hsTnI is not surprising. Our findings highlight the important role of toxicology-confirmed substances in substance-related research.

In addition to single drug effects, secondary analyses suggest differential effects from drug combinations. Results reported here should be replicated in additional diverse samples, but they provide initial evidence to suggest notable differences in cardiac injury depending on drug combinations used. In particular, our secondary analyses show that fentanyl interacts with multiple substances (methamphetamine, methadone, and opioids) to synergistically increase cardiac injury (interaction p-values<0.05). This combined with significant increases in hsTnI associated with cocaethylene, but not cocaine or alcohol alone, highlights the importance of polysubstance use in risk reduction counseling. For individuals who are unable to achieve abstinence, avoiding the co-use of cocaine and alcohol in the same two hour period reduces cocaethylene (Jones, 2019) and may potentially reduce CVD risk. Similarly, counseling people who use fentanyl, or heroin—which is sometimes adulterated with fentanyl—to reduce concurrently using other substances (polysubstance use) may reduce CVD risk.

Trends observed here are consistent with our prior research regarding the association between cocaine and hs-TnI from a mostly male cross-sectional study of hospital patients (Riley et al., 2017), although the observed associations were not as strong in the current study. On the other hand, the association between fentanyl and hsTnI was unexpected, because fentanyl used surgically is known to have minimal acute cardiovascular effects (Stanley, 2014), and even provides cardioprotective effects via δ- and κ-receptors (Tanaka et al., 2014; Xu et al., 2015). However, the effect may be modified by pharmacological actions of other drugs (Tanaka et al., 2014), which, given high levels of polysubstance use among

study participants, may be why our results do not suggest a cardioprotective effect from fentanyl. Perhaps more important to the direct influence on cardiac injury, opioids are associated with QT interval prolongation, the development of torsades de pointes (TdP) and arrhythmia (Aghadavoudi et al., 2015; Benyamin et al., 2008; Chen and Ashburn, 2015; Keller et al., 2016; Shirani et al., 2010). Most prior opioid-related findings come from clinical research of medically supervised opioid doses, while the current study considered *all* use (i.e., prescribed and non-prescribed), and therefore provides a new perspective that more fully represents real-world circumstances. Future research may help to clarify variations in findings between studies, but results presented here suggest that the inclusion of fentanyl use, along with co-use of cocaine and alcohol, in CVD risk assessment and risk counseling of women who use drugs may reduce CVD events.

While some studies report that cannabis use is associated with acute coronary syndromes (Richards et al., 2019), recent large prospective studies that have failed to show significant associations between lifetime cannabis use and cardiovascular events, and a review concluded that the relationships remain unclear (Ghosh and Naderi, 2019). Results presented here contribute prospective evidence to this ongoing dialog, finding no significant association between the toxicology-confirmed presence of cannabis and biomarkers of myocardial injury in homeless and unstably housed women. Future studies that distinguish frequency, duration and modes of cannabis use may help clarify seemingly disparate findings.

Standard cardiovascular risk assessment tools include risk factors with significant population-level influence, including tobacco use, prior MI and prior stroke (Goff et al., 2014). While established as the most important predictors of CVD and cardiovascular events in the general population, results presented here show that these factors do not have significant effects on cardiac injury in homeless and unstably housed women over a six-month period, but the use of fentanyl and the co-use of cocaine and alcohol do. Results may suggest the dominant effect of illegal substance use compared to many traditional risk factors. While the outcome predicted with a risk assessment tool is a cardiac event, the outcomes of the current study are predictors of such events, and are therefore one step removed. Nonetheless, our results suggest that adapting risk counseling and risk assessment tools for people who use controlled substances is worthy of further consideration, and may be useful in preventing cardiac events by helping to improve risk stratification. This possibility is consistent with risk stratification strategies for cocaine-using persons suggested by Sehatbakhsh et al., which may increase the accuracy of risk prediction and also reduce invasive procedures like cardiac catheterization when treating patients with chest pain (Sehatbakhsh et al., 2018).

Our study has several potential limitations. First, the number of comparisons made was large and the sample was modest. One way we controlled inflation of the type-I error rate was to only consider drug combinations as significant if their interaction terms were significant. While this may have reduced inflation, the technique was only applied to analyses concerning relative effects of polydrug use and did not completely ameliorate the problem. Future studies that confirm results presented here, assess more detail regarding substance use (e.g., frequency of current use) and assess markers of cardiac dysfunction beyond hsTnI,

would strengthen these initial findings. Also, the over-enrollment of women living with HIV had the potential to bias results. HIV status was not associated with hsTnI; however, residual confounding may have occurred.

Study strengths included a community-based sample of substance-using individuals rather than persons seeking medical care, which would have biased the sample toward sicker people and those with access to the U.S. health care system. In addition, a community-based approach naturally facilitated the inclusion of complex conditions uniquely common in low-income populations. For example, both food insecurity and BMI were high in this population. While this is seemingly contradictory, it is consistent with prior studies in low-income individuals, particularly low-income U.S. women, reporting the "food insecurity-obesity paradox" (i.e., the paradox of obesity despite deprivation, resulting from high-calorie foods with low nutritional value, which are more plentiful in "food desert" neighborhoods) (Dhurandhar, 2016). The fact that data were longitudinal was another strength, allowing for the consideration of varying substance use over time. In addition, few prior studies include substances as well as pharmaceutical drugs, and those that do usually use self-reported measures. Both substance use and pharmaceutical drug use were toxicology-confirmed here. Finally, the sample population was composed entirely of women, which allowed for the estimation of women-specific results rather than those common to both genders, which may be driven by men's risks.

CONCLUSION

Fentanyl use and the simultaneous use of cocaine and alcohol are associated with elevated levels of hsTnI in low-income women, suggesting that the use of these substances may be acting as long-term factors leading to ongoing cardiac insults. Considering the use of these substances as ongoing exposures leading to cardiac dysfunction may improve risk stratification and risk counseling in populations where controlled substance use is high, and merits further investigation.

Acknowledgements

REFERENCES

Aghadavoudi O, Eizadi-Mood N, Najarzadegan MR, 2015 Comparing cardiovascular factors in opium abusers and non-users candidate for coronary artery bypass graft surgery. Adv Biomed Res 4, 12. [PubMed: 25625118]

Beatty AL, Ku IA, Christenson RH, DeFilippi CR, Schiller NB, Whooley MA, 2013 High-sensitivity cardiac troponin T levels and secondary events in outpatients with coronary heart disease from the Heart and Soul Study. JAMA Intern Med 173, 763–769. [PubMed: 23568589]

Benowitz N, Nardone N, St Helen G, Addo N, Jacob P 3rd, Liakoni E, Jain S, Hooshfar S, Lynch K, 2019a Quantitative biochemical screening for marijuana use and concordance with tobacco use in urban adolescents. Drug Alcohol Depend 205, 107583 [Epub ahead of print]. [PubMed: 31600618]

Benowitz NL, Bernert JT, Foulds J, Hecht SS, Jacob P, Jarvis MJ, Joseph A, Oncken C, Piper ME, 2019b Biochemical Verification of Tobacco Use and Abstinence: 2019 Update. Nicotine Tob Res.

Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, Glaser SE, Vallejo R, 2008 Opioid complications and side effects. Pain Physician 11, S105–120. [PubMed: 18443635]

Bergenzaun L, Ohlin H, Gudmundsson P, During J, Willenheimer R, Chew MS, 2012 High-sensitive cardiac Troponin T is superior to echocardiography in predicting 1-year mortality in patients with SIRS and shock in intensive care. BMC Anesthesiol 12, 25. [PubMed: 23006477]

Bucholz EM, Krumholz HM, 2015 Women in clinical research: what we need for progress. Circ Cardiovasc Qual Outcomes 8, S1–3. [PubMed: 25714827]

Chen A, Ashburn MA, 2015 Cardiac Effects of Opioid Therapy. Pain Med 16 Suppl 1, S27–31. [PubMed: 26461073]

Collinson PO, Heung YM, Gaze D, Boa F, Senior R, Christenson R, Apple FS, 2012 Influence of population selection on the 99th percentile reference value for cardiac troponin assays. Clin Chem 58, 219–225. [PubMed: 22100808]

Dhurandhar EJ, 2016 The food-insecurity obesity paradox: A resource scarcity hypothesis. Physiol Behav 162, 88–92. [PubMed: 27126969]

Farooq MU, Bhatt A, Patel M, 2009 Neurotoxic and cardiotoxic effects of cocaine and ethanol. J Med Toxicol 5, 134–138. [PubMed: 19655286]

Gaggin HK, Szymonifka J, Bhardwaj A, Belcher A, De Berardinis B, Motiwala S, Wang TJ, Januzzi JL Jr., 2014 Head-to-head comparison of serial soluble ST2, growth differentiation factor-15, and highly-sensitive troponin T measurements in patients with chronic heart failure. JACC Heart failure 2, 65–72. [PubMed: 24622120]

Ghosh M, Naderi S, 2019 Cannabis and Cardiovascular Disease. Curr Atheroscler Rep 21, 21. [PubMed: 30980200]

Gillis AM, 2020 A Sober Reality? Alcohol, Abstinence, and Atrial Fibrillation. N Engl J Med 382, 83–84. [PubMed: 31893520]

Goff DC Jr., Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, Greenland P, Lackland DT, Levy D, O'Donnell CJ, Robinson JG, Schwartz JS, Shero ST, Smith SC Jr., Sorlie P, Stone NJ, Wilson PW, Jordan HS, Nevo L, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC Jr., Tomaselli GF, American College of Cardiology/American Heart Association Task Force on Practice, G., 2014 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 129, S49–73. [PubMed: 24222018]

Gozdzik A, Salehi R, O'Campo P, Stergiopoulos V, Hwang SW, 2015 Cardiovascular risk factors and 30-year cardiovascular risk in homeless adults with mental illness. BMC Public Health 15, 165. [PubMed: 25886157]

Havakuk O, Rezkalla SH, Kloner RA, 2017 The Cardiovascular Effects of Cocaine. J Am Coll Cardiol 70, 101–113. [PubMed: 28662796]

Havranek EP, Nademanee K, Grayburn PA, Eichhorn EJ, 1996 Endothelium-dependent vasorelaxation is impaired in cocaine arteriopathy. J Am Coll Cardiol 28, 1168–1174. [PubMed: 8890811]

Heil SH, Badger GJ, Higgins ST, 2001 Alcohol dependence among cocaine-dependent outpatients: demographics, drug use, treatment outcome and other characteristics. J Stud Alcohol 62, 14–22. [PubMed: 11271960]

Hollander JE, Hoffman RS, Gennis P, Fairweather P, DiSano MJ, Schumb DA, Feldman JA, Fish SS, Dyer S, Wax P, et al., 1994 Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. Acad Emerg Med 1, 330–339. [PubMed: 7614278]

Hsue PY, Deeks SG, Hunt PW, 2012 Immunologic basis of cardiovascular disease in HIV-infected adults. J Infect Dis 205 Suppl 3, S375–382. [PubMed: 22577211]

Jaffe AS, 2006 Chasing troponin: how low can you go if you can see the rise? J Am Coll Cardiol 48, 1763–1764. [PubMed: 17084246]

Jones AW, 2019 Forensic Drug Profile: Cocaethylene. Journal of analytical toxicology 43, 155–160. [PubMed: 30796807]

Kavsak PA, Newman AM, Lustig V, MacRae AR, Palomaki GE, Ko DT, Tu JV, Jaffe AS, 2007 Long-term health outcomes associated with detectable troponin I concentrations. Clin Chem 53, 220–227. [PubMed: 17204519]

Keller GA, Alvarez PA, Ponte ML, Belloso WH, Bagnes C, Sparanochia C, Gonzalez CD, Villa Etchegoyen MC, Diez RA, Di Girolamo G, 2016 Drug-Induced QTc Interval Prolongation: A Multicenter Study to Detect Drugs and Clinical Factors Involved in Every Day Practice. Curr Drug Saf 11, 86–98. [PubMed: 26537523]

Laizure SC, Mandrell T, Gades NM, Parker RB, 2003 Cocaethylene metabolism and interaction with cocaine and ethanol: role of carboxylesterases. Drug Metab Dispos 31, 16–20. [PubMed: 12485948]

Lange RA, Hillis LD, 2001 Cardiovascular complications of cocaine use. N Engl J Med 345, 351–358. [PubMed: 11484693]

Lee TC, Hanlon JG, Ben-David J, Booth GL, Cantor WJ, Connelly PW, Hwang SW, 2005 Risk factors for cardiovascular disease in homeless adults. Circulation 111, 2629–2635. [PubMed: 15897342]

Li Y, Pei H, Zhou C, 2019 Cardiac troponins predict adverse clinical outcomes in stable coronary artery disease: a dose-response meta-analysis of prospective studies. Biomarkers 24, 556–565. [PubMed: 30974974]

Lichtman JH, Leifheit EC, Safdar B, Bao H, Krumholz HM, Lorenze NP, Daneshvar M, Spertus JA, D'Onofrio G, 2018 Sex Differences in the Presentation and Perception of Symptoms Among Young Patients With Myocardial Infarction: Evidence from the VIRGO Study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients). Circulation 137, 781–790. [PubMed: 29459463]

Mladenka P, Applova L, Patocka J, Costa VM, Remiao F, Pourova J, Mladenka A, Karlickova J, Jahodar L, Voprsalova M, Varner KJ, Sterba M, Tox OER, Researchers, C.H.K., Collaborators, 2018 Comprehensive review of cardiovascular toxicity of drugs and related agents. Med Res Rev 38, 1332–1403. [PubMed: 29315692]

Mo W, Singh AK, Arruda JA, Dunea G, 1998 Role of nitric oxide in cocaine-induced acute hypertension. Am J Hypertens 11, 708–714. [PubMed: 9657630]

Morentin B, Callado LF, 2019 Sudden cardiac death associated to substances of abuse and psychotropic drugs consumed by young people: A population study based on forensic autopsies. Drug Alcohol Depend 201, 23–28. [PubMed: 31174141]

Mosca L, Barrett-Connor E, Wenger NK, 2011 Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. Circulation 124, 2145–2154. [PubMed: 22064958]

Neumann JT, Twerenbold R, Ojeda F, Sorensen NA, Chapman AR, Shah ASV, Anand A, Boeddinghaus J, Nestelberger T, Badertscher P, Mokhtari A, Pickering JW, Troughton RW, Greenslade J, Parsonage W, Mueller-Hennessen M, Gori T, Jernberg T, Morris N, Liebetrau C, Hamm C, Katus HA, Munzel T, Landmesser U, Salomaa V, Iacoviello L, Ferrario MM, Giampaoli S, Kee F, Thorand B, Peters A, Borchini R, Jorgensen T, Soderberg S, Sans S, Tunstall-Pedoe H, Kuulasmaa K, Renne T, Lackner KJ, Worster A, Body R, Ekelund U, Kavsak PA, Keller T, Lindahl B, Wild P, Giannitsis E, Than M, Cullen LA, Mills NL, Mueller C, Zeller T, Westermann D, Blankenberg S, 2019 Application of High-Sensitivity Troponin in Suspected Myocardial Infarction. N Engl J Med 380, 2529–2540. [PubMed: 31242362]

Omland T, de Lemos JA, Sabatine MS, Christophi CA, Rice MM, Jablonski KA, Tjora S, Domanski MJ, Gersh BJ, Rouleau JL, Pfeffer MA, Braunwald E, Prevention of Events with Angiotensin Converting Enzyme Inhibition Trial, I., 2009 A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 361, 2538–2547. [PubMed: 19940289]

Parker MA, Anthony JC, 2014 Should anyone be riding to glory on the now-descending limb of the crack-cocaine epidemic curve in the United States? Drug Alcohol Depend 138, 225–228. [PubMed: 24629632]

Perreault CL, Morgan KG, Morgan JP, 1991 Effects of cocaine on intracellular calcium handling in cardiac and vascular smooth muscle. NIDA Res Monogr 108, 139–153. [PubMed: 1749409]

Reece AS, Hulse GK, 2013 Impact of opioid pharmacotherapy on arterial stiffness and vascular ageing: cross-sectional and longitudinal studies. Cardiovasc Toxicol 13, 254–266. [PubMed: 23456431]

Richards JR, Bing ML, Moulin AK, Elder JW, Rominski RT, Summers PJ, Laurin EG, 2019 Cannabis use and acute coronary syndrome. Clinical toxicology 57, 831–841. [PubMed: 30964363]

Richards JR, Hollander JE, Ramoska EA, Fareed FN, Sand IC, Izquierdo Gomez MM, Lange RA, 2017 beta-Blockers, Cocaine, and the Unopposed alpha-Stimulation Phenomenon. J Cardiovasc Pharmacol Ther 22, 239–249. [PubMed: 28399647]

Riley ED, Cohen J, Shumway M, 2013 Overdose fatality and surveillance as a method for understanding mortality trends in homeless populations. JAMA Intern Med 173, 1264.

Riley ED, Hsue PY, Wu AH, Coffin PO, Moore PK, Lynch KL, 2017 Higher prevalence of detectable troponin I among cocaine-users without known cardiovascular disease. Drug Alcohol Depend 172, 88–93. [PubMed: 28157591]

Riley ED, Shumway M, Knight KR, Guzman D, Cohen J, Weiser SD, 2015 Risk factors for stimulant use among homeless and unstably housed adult women. Drug Alcohol Depend 153, 173–179. [PubMed: 26070454]

Schurer S, Klingel K, Sandri M, Majunke N, Besler C, Kandolf R, Lurz P, Luck M, Hertel P, Schuler G, Linke A, Mangner N, 2017 Clinical Characteristics, Histopathological Features, and Clinical Outcome of Methamphetamine-Associated Cardiomyopathy. JACC Heart failure 5, 435–445. [PubMed: 28571597]

Sehatbakhsh S, Kushnir A, Furlan S, Donath E, Ghumman W, Chait R, 2018 Importance of a Risk Stratification Strategy to Identify High-risk Patients Presenting With Cocaine-associated Acute Coronary Syndrome. Crit Pathw Cardiol 17, 147–150. [PubMed: 30044255]

Shirani S, Shakiba M, Soleymanzadeh M, Esfandbod M, 2010 Can opium abuse be a risk factor for carotid stenosis in patients who are candidates for coronary artery bypass grafting? Cardiol J 17, 254–258. [PubMed: 20535715]

Stanley TH, 2014 The fentanyl story. J Pain 15, 1215–1226. [PubMed: 25441689]

Tanaka K, Kersten JR, Riess ML, 2014 Opioid-induced cardioprotection. Curr Pharm Des 20, 5696–5705. [PubMed: 24502571]

Thoren KL, Colby JM, Shugarts SB, Wu AH, Lynch KL, 2016 Comparison of Information-Dependent Acquisition on a Tandem Quadrupole TOF vs a Triple Quadrupole Linear Ion Trap Mass Spectrometer for Broad-Spectrum Drug Screening. Clin Chem 62, 170–178. [PubMed: 26453698]

Vongpatanasin W, Mansour Y, Chavoshan B, Arbique D, Victor RG, 1999 Cocaine stimulates the human cardiovascular system via a central mechanism of action. Circulation 100, 497–502. [PubMed: 10430763]

Voskoboinik A, Kalman JM, De Silva A, Nicholls T, Costello B, Nanayakkara S, Prabhu S, Stub D, Azzopardi S, Vizi D, Wong G, Nalliah C, Sugumar H, Wong M, Kotschet E, Kaye D, Taylor AJ, Kistler PM, 2020 Alcohol Abstinence in Drinkers with Atrial Fibrillation. N Engl J Med 382, 20–28. [PubMed: 31893513]

Ward-Caviness CK, Xu T, Aspelund T, Thorand B, Montrone C, Meisinger C, Dunger-Kaltenbach I, Zierer A, Yu Z, Helgadottir IR, Harris TB, Launer LJ, Ganna A, Lind L, Eiriksdottir G, Waldenberger M, Prehn C, Suhre K, Illig T, Adamski J, Ruepp A, Koenig W, Gudnason V, Emilsson V, Wang-Sattler R, Peters A, 2017 Improvement of myocardial infarction risk prediction via inflammation-associated metabolite biomarkers. Heart 103, 1278–1285. [PubMed: 28255100]

Waxman DA, Hecht S, Schappert J, Husk G, 2006 A model for troponin I as a quantitative predictor of in-hospital mortality. J Am Coll Cardiol 48, 1755–1762. [PubMed: 17084245]

Wilbert-Lampen U, Seliger C, Zilker T, Arendt RM, 1998 Cocaine increases the endothelial release of immunoreactive endothelin and its concentrations in human plasma and urine: reversal by coincubation with sigma-receptor antagonists. Circulation 98, 385–390. [PubMed: 9714087]

Wilson LD, French S, 2002 Cocaethylene's effects on coronary artery blood flow and cardiac function in a canine model. J Toxicol Clin Toxicol 40, 535–546. [PubMed: 12215047]

Writing Group, M., Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW, Turner MB, American Heart Association Statistics, C., Stroke Statistics, S., 2016 Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 133, e38–360. [PubMed: 26673558]

Wu AH, 1999 A comparison of cardiac troponin T and cardiac troponin I in patients with acute coronary syndromes. Coron Artery Dis 10, 69–74. [PubMed: 10219511]

Xu YC, Li RP, Xue FS, Cui XL, Wang SY, Liu GP, Yang GZ, Sun C, Liao X, 2015 kappa-Opioid receptors are involved in enhanced cardioprotection by combined fentanyl and limb remote ischemic postconditioning. J Anesth 29, 535–543. [PubMed: 25808344]

Zador Z, Landry A, Cusimano MD, Geifman N, 2019 Multimorbidity states associated with higher mortality rates in organ dysfunction and sepsis: a data-driven analysis in critical care. Crit Care 23, 247. [PubMed: 31287020]

Zethelius B, Johnston N, Venge P, 2006 Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 113, 1071–1078. [PubMed: 16490824]

HIGHLIGHTS

- Cocaethylene and fentanyl are associated with higher levels of hsTnI in poly-drug using women

- Counseling to avoid using cocaine and alcohol in the same two hour period may reduce cardiovascular events

- Including substance use in cardiac risk stratification tools may be warranted

Table 1.

Substances Assessed

Drug or Drug Class	Individual Drugs and Drug Metabolites
Cocaine	Benzoylecgonine, Cocaine, Ecgonine methyl ester, Norcocaine
	Cocaethylene
Amphetamines	Methamphetamine, methamphetamine, MDMA (?)
Antiarrhythmic	Lidocaine
Opioid antagonist	Methadone, , EDDP buprenorphine, Norbuprenorphine
Heroin	6-Monoacetylmorphine, Heroin
Opioids	6-Monoacetylmorphine, Heroin, Morphine, Codeine, Hydrocodone, Hydromorphone, Dihydrocodeine, Glucuronide, Codeine Glucuronide, Oxycodone, Oxymorphone
Fentanyl	F entanyl, Norfentanyl
Naloxone	Naloxone
Benzodiazepines	Clonazepam, Diazepam, Lorazepam, Nordazepam, Temazepam, Oxazepam, Alprazolam alpha-hycroxyalprazolam, Flurazepam, 2-Hydroxyethylflurazepam, Desalkylflurazepam, Flunitrazepam, 7-Aminoflunitrazepam, N-Desmethylflunitrazepam, Midazolam, 7-Aminonitrazepam, Etizolam
Alcohol	Ethyl Glucuronide
Cannabis (THC)	Tetrahydrocannabinol (THC) –COOH and THC–COOH glucuronide
Nicotine	Cotinine, Nicotine
Beta Blockers	Metoprolol, Atenolol, Carvedilol, Labetalol
Calcium Channel Blockers	Amlodipine, Diltiazem, Verapamil
Diuretic	Furosemide, Hydrochlorothiazide
Nitrate	Isosorbide mononitrate
Antihypertensive Agents	Clonidine, Lisinopril, Losartan
Statins	Atorvastatin, Pravastatin, Simvastatin
Vasodilator	Sildenafil
Blood thinner	Coumadin
Analgesic	Acetaminophen

Table 2.

Baseline Characteristics of Study Participants (N=245)

Study Characteristic	Median (IQR) or Proportion (%)
Demographic	
Age (years)	Median=53.4 (45.7–59.5)
Race/Ethnicity	
White	64 (26.1%)
Black/African American	92 (37.6%)
Latina	37 (15.1%)
Multiracial	29 (11.8%)
Other	23 (9.4%)
Post-menopausal[c]	154 (63.1%)
Substance Use	
Cotinine/Nicotine[e]	169 (69.0%)
Cocaine/Benzoylecgonine[e]	129 (52.7)%
Cannabis (THC)[e]	125 (51%)
Levamisole[e]	83 (33.9%)
Methamphetamine[e]	71 (29.0%)
Alcohol (as determined by ethyl glucuronide)[e]	71 (29.0%)
Opioids other than heroin[e]	55 (22.4%)
Cocaethylene[e]	42 (17.1%)
Heroin/Monoacetylmorphine-6[e]	5 (2.0%)
Fentanyl/Norfentanyl[e]	6 (2.4%)
History of Chronic Health Conditions	
Diabetes[f]	37 (15.2%)
Prior myocardial infarction[f]	20 (8.2%)
Prior stroke[f]	28 (11.5%)
HIV-positive[g]	77 (31.4%)
HCV-positive[f]	78 (32.0%)
Pharmaceutical Drug Use	
Acetaminophen[e]	64 (26.1%)
Methadone[e]	53 (21.6%)
Lidocaine[e]	38 (15.5%)
Benzodiazepine[e]	21 (8.6%)

Study Characteristic	Median (IQR) or Proportion (%)
Beta blocker[e]	14 (5.7%)
Antihypertensive[e]	11 (4.5%)
Calcium channel blocker[e]	10 (4.1%)
Buprenorphine/Norbuprenorphine[e]	1 (0.4%)
Statin[e]	0 (0.0%)
Naloxone[e]	0 (0.0%)
Current Health Status	
Body Mass Index (BMI)	Median=27.9 (23.2–34.0)
Systolic Blood Pressure	Median=129.0 (115.0–145.0)
Diastolic Blood Pressure	Median=85.0 (77.0–93.5)
Hypertension	
No hypertension	58 (23.5%)
Elevated blood pressure (systolic 120 mm Hg or diastolic 80 mm Hg)	12 (4.9%)
Stage 1 hypertension (systolic 130 mm Hg or diastolic 80 mm Hg)	70 (28.3%)
Stage 2 hypertension (systolic 140 mm Hg or diastolic 90 mm Hg)	102 (41.3%)
Hypertensive crisis (systolic 180 mm Hg or diastolic 120 mm Hg)	5 (2.0%)
LDL cholesterol (mg/dL)	Median=93.0 (77.0–117.0)
HDL cholesterol (mg/dL)	Median=61.0 (47.0–73.0)
High-sensitivity C-Reactive Protein (hsCRP) (mg/L)	Median=3.1 (0.9–8.9)
High-sensitivity Troponin I (ng/L)	Median=2.0 (1.0–3.0)

[c]>1 year since last menstrual period

[e]Positive toxicology results

[f]Self-reported

[g]ELISA test results

Table 3.

Associations between Study Factors and High-Sensitivity Cardiac Troponin I (hsTnI) (ng/L) Across Six Study Visits (N=245; 1,051 study visits total)

	Unadjusted Effects[a] (95% CI)	Model 1 Adjusted Effects (95% CI) Demographic	Model 2 Adjusted Effects (95% CI) Substance Use	Model 3 Adjusted Effects (95% CI) Pharmaceutical Drug Use	Model 4 Adjusted Effects (95% CI) History of Chronic Health Conditions	Model 5 Adjusted Effects (95% CI) Current Health Status
Age (years)	1.28 (1.18–1.38) **	1.21 (1.11–1.32) **	1.21 (1.11–1.33) **	1.21 (1.10–1.32) **	1.21 (1.11–1.32) **	1.21 (1.11–1.31) **
Race/Ethnicity						
White	(ref)	(ref)		(ref)	(ref)	(ref)
Black/African American	1.36 (1.09–1.70) **	1.30 (1.05–1.60) **	1.27 (1.03–1.56) **	1.26 (1.03–1.55) **	1.27 (1.03–1.57) **	1.18 (0.97–1.44) **
Latina	1.32 (0.99–1.76) **	1.35 (1.03–1.76) **	1.34 (1.03–1.75) **	1.34 (1.03–1.75) **	1.35 (1.03–1.77) **	1.27 (0.99–1.63) **
Multiracial	1.50 (1.10–2.05) **	1.57 (1.18–2.09) **	1.58 (1.19–2.10) **	1.56 (1.17–2.08) **	1.57 (1.17–2.10) **	1.43 (1.09–1.86) **
Other	1.48 (1.05–2.07) **	1.43 (1.05–1.95) **	1.41 (1.03–1.92) **	1.40 (1.03–1.91) **	1.42 (1.04–1.95) **	1.38 (1.03–1.83) **
Post-menopausal[b]	1.42 (1.25–1.62) **	1.24 (1.07–1.43) **	1.22 (1.06–1.44) **	1.22 (1.06–1.40) **	1.22 (1.06–1.41) **	1.22 (1.06–1.40) **
Cotinine/Nicotine[e]	0.96 (0.88–1.05)		0.90 (0.78–1.04)	--	--	--
Cocaine/Benzoylecgonine[e]	1.08 (0.99–1.18)		1.06 (0.96–1.16)	--	--	--
Cannabis (THC)[e]			1.03 (0.95–1.11)	--	--	--
Levamisole[e]	1.04 (0.97–1.12)		0.99 (0.91–1.07)	--	--	--
Methamphetamine[e]	1.01 (0.93–1.10)		1.10 (0.94–1.08)	--	--	--
Alcohol (as determined by ethyl glucuronide)[e]	1.06 (0.98–1.14)		1.04 (0.96–1.12)	--	--	--
Opioids other than heroin[e]	1.04 (0.95–1.14)		1.02 (0.93–1.12)	--	--	--
Cocaethylene[e]	1.13 (1.04–1.24) **		1.09 (0.99–1.20)	1.10 (1.01–1.20) **	1.09 (1.00–1.19) **	1.12 (1.02–1.22) **
Heroin/Mono-acetylmorphine-6[e]	1.15 (0.97–1.36)		1.14 (0.96–1.36)	--	--	--
Fentanyl/Norfentanyl[e]	1.19 (1.02–1.40) **		1.18 (1.00–1.40)	1.22 (1.04–1.44) **	1.22 (1.04–1.44) **	1.20 (1.02–1.41) **

	Unadjusted Effects[a] (95% CI)	Model 1 Adjusted Effects (95% CI) Demographic	Model 2 Adjusted Effects (95% CI) Substance Use	Model 3 Adjusted Effects (95% CI) Pharmaceutical Drug Use	Model 4 Adjusted Effects (95% CI) History of Chronic Health Conditions	Model 5 Adjusted Effects (95% CI) Current Health Status
Diabetes[f]	0.90 (0.77–1.05)			--	0.89 (0.76–1.03)	--
Prior myocardial infarction[f]	0.99 (0.92–1.05)			--	0.98 (0.92–1.04)	--
Prior stroke[f]	1.00 (0.96–1.04)				0.99 (0.96–1.03)	--
HIV-positive[g]	1.01 (0.78–1.31)			--	0.96 (0.80–1.15)	--
HCV-positive[f]	0.99 (0.88–1.11)			--	0.98 (0.87–1.11)	--
Acetaminophen[e]	0.98 (0.93–1.04)			0.97 (0.92–1.03)		--
Methadone[e]	0.97 (0.86–1.10)			0.97 (0.86–1.10)		--
Lidocaine[e]	**1.09 (1.01–1.18)** **			1.07 (0.99–1.16)	1.07 (0.99–1.16)	1.07 (0.99–1.16)
Benzodiazepine[e]	0.97 (0.86–1.09)			0.96 (0.85–1.07)		--
Beta blocker[e]	1.04 (0.89–1.20)			1.01 (0.88–1.18)		--
Antihypertensive[e]	1.04 (0.89–1.23)			1.06 (0.90–1.25)		--
Calcium channel blocker	1.06 (0.91–1.23)			1.01 (0.86–1.17)		--
Buprenorphine/Norbuprenorphine[e]	1.20 (0.87–1.66)			1.14 (0.81–1.61)		--
Statin[e]	**1.58 (1.23–2.03)** **			**1.55 (1.21–2.00)** **	**1.56 (1.21–2.01)** **	**1.55 (1.20–2.00)** **
Naloxone[e]	1.33 (0.58–3.03)			1.20 (0.50–2.90)		--
Body Mass Index (BMI)	1.01 (100–1.01)					**1.01 (1.00–1.02)** **
Systolic Blood Pressure	**1.04 (1.02–1.06)** **					**1.03 (1.01–1.05)** **
Diastolic Blood Pressure	**1.04 (1.02–1.07)** **					1.02 (0.98–1.05)
LDL cholesterol (mg/dL)	**1.02 (1.00–1.03)** **					**1.01 (1.00–1.03)** **
HDL cholesterol (mg/dL)	1.01 (0.99–1.04)					0.99 (0.97–1.02)
High-sensitivity C-Reactive Protein (hsCRP) (mg/L)	1.01 (1.00–1.03)					1.02 (1.00–1.04)

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**
p<0.05

[a] Adjusted for visit only

[b] >1 year since last menstrual period

[e] Positive toxicology results

[f] Self-reported

[g] ELISA test results