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# Cocaine Use is Associated With Increased LVMI in Unstably Housed Women With Polysubstance Use

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## Abstract

**Background:** While substance use is known to influence cardiovascular health, most prior studies only consider one substance at a time. We examined associations between the concurrent use of multiple substances and left ventricular mass index (LVMI) in unhoused and unstably housed women.

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Author Contributions

Dr. Riley was the principal investigator of the PULSE study and was heavily involved in the design, execution, and conceptualization of the analysis presented here. Dr. Ravi led the design, analysis, interpretation, and initial draft of this manuscript. Drs. Kazi, Win, Hsue, Lynch, Coffin, Suen, Wu, and Vittinghoff participated in the discussion and interpretation of the findings, and edited the final manuscript. Dr. Kazi additionally performed all echocardiography reported in the study. Dr. Vittinghoff additionally performed primary statistical analyses presented. And all authors contributed substantially to and approved the final version.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Compliance, Ethical Standards, and Ethical Approval

Institutional Review Board approval was not required.

**Methods:** Between 2016 and 2019, we conducted a cohort study of unstably housed women in which measurements included an interview, serum/urine collection, vital sign assessment, and a single transthoracic echocardiogram at baseline. We evaluated independent associations between 39 separate substances confirmed through toxicology and echocardiography-confirmed LVMI.

**Results:** The study included 194 participants with a median age of 53.5 years and a high proportion of women of color (72.6%). Toxicology-confirmed substance use included: 69.1% nicotine, 56.2% cocaine, 28.9% methamphetamines, 28.9% alcohol, 23.2% opioid analgesics, and 9.8% opioids with catecholaminergic effects. In adjusted analysis, cocaine was independently associated with higher LVMI (Adjusted linear effect: 18%; 95% CI 9.9, 26.6). Associations with other substances did not reach levels of significance and did not significantly interact with cocaine.

**Conclusion:** In a population of vulnerable women where the use of multiple substances is common, cocaine stands out as having particularly detrimental influences on cardiac structure. Blood pressure did not attenuate the association appreciably, suggesting direct effects of cocaine on LVMI. Routinely evaluating stimulant use as a chronic risk factor during risk assessment and preventive clinical care planning may reduce end organ damage, particularly in highly vulnerable women.

### Keywords

polysubstance use; stimulant use; women’s health; cardiac remodeling; homeless; unhoused and unstably housed

## Background

In 2021 stimulant overdose deaths hit record highs across the country and exceeded 93 000.[1,2] This follows trends of increased hospital readmission rates among people with cocaine, amphetamine or opioid disorders, and increased mortality among emergency department patients who use cocaine with alcohol and/or cannabis.[3,4] Use and consequences of use have traditionally been disproportionately high in certain vulnerable populations compared to the general population; however, contributing factors are often unclear, which makes risk assessment unreliable.

While acute toxicity is a known contributor to death in vulnerable populations, influences from co-occurring conditions are rarely considered. This is important because pre-existing cardiovascular conditions are common but often undetected among people who use stimulants.[5,6] Similarly, “silent” cardiovascular disease (CVD) frequently goes undiagnosed until an individual presents to an emergency department with an acute event.[7] Research acknowledging polysubstance use in high-risk individuals, could facilitate better risk assessment.

Cocaine use has been associated with cardiac events including myocardial infarction and sudden cardiac death,[8,9] and conditions known to precede them such as left ventricular mass index (LVMI),[10,11] a measure of cardiac structure that independently predicts adverse cardiovascular events.[12–15] Notably, these studies do not account for other substances, which is salient given rising trends of overdose death associated with polysubstance use.[16–19] Furthermore, it has become clear that current CVD risk scores, often derived from study

populations composed mostly of men, do not accurately predict CVD risk in women[20] and that non-traditional risk factors are more common in women.[21] Despite known sex differences in CVD risk factors, left ventricular (LV) remodeling, and a higher risk of death associated with LV hypertrophy in women, much of the existing evidence comes from predominantly male study populations.[22–24] Sex-specific research that leads to sex-specific risk assessment models may improve risk prediction, particularly in women.[25]

Our previous work showed that cocaine use is significantly associated with high-sensitivity cardiac troponin (hsTnI) in hospitalized patients. Similarly, we found that toxicology-confirmed substance use is associated with higher levels of hsTnI in non-hospitalized, unstably housed women,[18,26] suggesting potential ongoing cardiac injury in chronic users. The present study extends these findings to investigate structural evidence of end organ damage by examining the independent effects of stimulants and other substances on LVMI.

## Materials and Methods

The present study is based on a cross sectional analysis of data from "Polysubstance Use and Health Outcomes Evaluation," a previously described cohort study of unhoused and unstably housed women in San Francisco.[18] Women were sampled from homeless shelters, free meal programs, single room occupancy hotels, and street encampments.[27] Women living with HIV were also oversampled from the Zuckerberg San Francisco General Hospital HIV clinic ("Ward 86") to achieve HIV-related objectives of the parent study. Study participants completed 6 consecutive monthly study visits conducted between June 2016 and January 2019 and were reimbursed $40 for each interview. All study procedures were approved by the Institutional Review Board at the University of California, San Francisco (IRB# 14–13868).

Inclusion criteria were female sex at birth; age >17 years; and history of housing instability, including to sleeping in public, in a homeless shelter, or staying with a series of associates out of necessity ("couch surfing").

Study measurements included an interview, serum/urine collection, vital sign assessment, and a baseline transthoracic echocardiogram. Median time between the baseline study visit and the baseline echocardiogram was 76.5 days. Baseline data were used in the current study; blood pressure was averaged across all study visits to reduce bias from a single transient spike.

LVMI was the primary study outcome. Echocardiography-confirmed LV mass (g) was calculated by the Devereux and Reichek "cube" formula and indexed to body surface area (BSA) to obtain the LVMI ($g/m^2$).[28] Echocardiograms were read by a single cardiologist who was blinded to any identifying variables.

Primary exposure variables included 39 separate substances confirmed through urine toxicology (Table 1).[29,30] Assessments were made using qualitative liquid chromatography-high resolution mass spectrometry (LC-HRMS) on hydrolyzed urine samples. Information-dependent product ion mass spectra were obtained using a SCIEX 5600 Triple TOF®

LC_HRMS system. Notably, this methodology cannot distinguish between prescribed or unprescribed ("illicit") medications.

Additional exposures included demographic variables; self-reported chronic health conditions (diabetes, prior myocardial infarction, prior stroke, hepatitis C); serum-confirmed presence of commonly used pharmaceutical drugs related to cardiovascular health (Table 1); and additional CVD risk factors including body mass index (BMI), systolic and diastolic blood pressure, total cholesterol (Cholesterol_2, Siemens ADVIA® Chemistry XPT), HDL cholesterol (Direct HDL cholesterol, Siemens ADVIA® Chemistry XPT), and calculated LDL cholesterol (Friedewald equation).

We used linear regression to estimate independent associations in all models where multiple variables were considered. Specifically, we used linear regression to estimate associations between substances used and LVMI, which was log-transformed to meet normality assumptions. We exclude BMI from the model assessing LVMI because it is highly correlated with BSA, a component of the formula defining LVMI. We also excluded blood pressure from the main model because stimulant use increases blood pressure[31] and hypertension drives cardiac remodeling,[32] thus making it part of the causal pathway and consequently not recommended for inclusion in cross-sectional analyses.[33] In post-hoc analysis, hypertension reintroduced into the model as a possible effect modifier.

For all models, we first estimated unadjusted associations with all exposure variables. Exposure variables that were significant with a *P*-value <.1 in the unadjusted analysis were considered for inclusion in the final models, which were selected using backwards deletion. Variable significance within adjusted models was considered at the $P < .05$ level. To delineate the effects of hypertension more clearly, we estimated adjusted effects with and without hypertension in a post-hoc analysis. All analyses were done using Stata Version 15.0 (Stata Corp., LLC, College Station, TX).

## Results

Of 245 women recruited, 194 received a baseline echocardiogram and were included in this analysis. Baseline characteristics of included participants are detailed in Table 1. The median age of participants was 53.5 years (interquartile range [IQR]: 46.5–59.5 years), and 72.6% were women of color. The median BMI was 27.8 kg/m$^2$ (IQR 23–34.5 kg/m$^2$). Median average systolic and diastolic blood pressures were 130 mmHg (IQR 116–142 mmHg) and 86 mmHg (IQR 78.5–93.5 mmHg) respectively, and 82% of participants met criteria for hypertension based on at least 2 blood pressure readings greater than 130/80 mmHg during the study period.[34] One-third (32%) of participants tested positive for HIV antibody. Self-reported chronic health conditions included diabetes (12.4%), prior myocardial infarction (9.3%), prior stroke (12.4%), and hepatitis C (31.4%).

Toxicology-confirmed substances and metabolites included nicotine (69.1%); cotinine (68.0%); cocaine (56.2%); cannabis (50.0%); methamphetamine (28.9%); alcohol (28.9%); opioid analgesics (23.2%); cocaethylene, a metabolite formed during the co-use of cocaine and alcohol (18.0%); heroin (2.1%); and fentanyl (1.5%). Toxicological analysis also

identified several pharmaceutical drugs including methadone (20.6%), benzodiazepines (8.8%), beta blockers (6.2%), calcium channel blockers (4.1%), and other antihypertensives (3.6%).

Median LVMI was 86.8 g/m$^2$ (IQR 72.9–100 g/m$^2$) with 34.4% of the study population meeting criteria for LV hypertrophy (LVMI > 95 g/m$^2$) (Table 1).[35] Table 2 shows independent associations between study factors and LVMI. Here, effect size represents the percent difference in log LVMI associated with the presence of each exposure variable. Adjusting for other significant variables, including menopause, prior myocardial infarction, and the presence of antihypertensive medications and tenofovir, cocaine was associated with an 18.0% higher log LVMI (Table 2, Model 2; 18.0%, 95% CI 9.9, 26.6, $P <$ .01). Associations did not reach levels of significance for other substances, diabetes, prior myocardial infarction, HIV, or hepatitis C (Table 2). Cocaine effects did not interact significantly with other substances.

Adding hypertension to the final model slightly reduced cocaine's magnitude of effect, but it was still associated with a significant 15% difference (Table 2, Model 3; 15.3%, 95% CI 7.7, 23.4, $P <$ .01).

## Conclusion

In this population of unhoused and unstably housed women with high rates of polysubstance use, one-third had abnormal LVMI suggestive of hypertrophy, which is 12% to 16% higher than women of a similar age range from the general population.[36] Cocaine was the only substance independently associated with LVMI, even after adjusting for age and blood pressure. These findings are consistent with our prior work showing strong associations between cocaine and cardiac injury.[18,26] In combination they are significant because both increased troponin and LV structural abnormalities have known prognostic implications for cardiovascular morbidity and mortality.[12–14] Routine assessment of cocaine in safety net patients and unstably housed women may improve CVD risk assessment in these populations.

Building on previous studies implicating cocaine in wide ranging adverse cardiovascular events,[8] our study confirms that cocaine is also associated with increased LVMI, a chronic marker of cardiovascular remodeling and antecedent of cardiovascular morbidity and mortality.[13,14] Results presented here are also consistent with prior work which highlighted the centrality of cocaine in cardiac injury as evidenced by hsTnI.[18] Taken together, the existing evidence indicates that cocaine is associated with conditions preceding cardiovascular morbidity and mortality, suggesting opportunities for prevention. This is notable because prior studies have found that risk management is linked to reversal of LVMI over time.[15]

Prior studies have also described gender differences in LV response to chronic pressure overload in scenarios like chronic hypertension or aortic stenosis.[37,38] Notably, female sex was independently associated with LV hypertrophy, early myocardial scarring, and less regression of LV hypertrophy after treatment compared to men. Given cocaine's

known associations with increased blood pressure and aortic stiffness, chronic cocaine use may lead to physiologically similar states of chronic pressure overload. In our study, the outsized impact of cocaine on LVMI may suggest further exacerbation by these sex-specific differences in LV response to pressure overload. Further longitudinal studies are needed, especially in light of calls for sex-specific research.[20,25]

The finding that cocaine is especially detrimental to cardiovascular health compared with other substances is consistent with prior research showing that, among people using cocaine or heroin, those using cocaine have a higher likelihood of LV hypertrophy.[39] Similarly, compared to opioid-related emergency department presentations, those related to cocaine more often require interventions for acute cardiopulmonary complications.[40] Moreover, cocaine deaths are more likely than methamphetamine/amphetamine deaths to involve significant contributing cardiac conditions.[5] Future studies focused on mechanisms of action and potential mediation by patterns of substance use could help further elucidate the disproportionate effects of cocaine on cardiovascular outcomes.

Data presented here suggest that cocaine has an outsized impact on LVMI, even compared to traditional risk factors like hypertension or tobacco use. However, while traditional medical education and current risk assessment tools often include tobacco use, they rarely include other substances. Our results suggest that tobacco use and other commonly assessed risk factors may not perform as well as cocaine in women who use multiple substances. For frontline clinicians caring for this uniquely vulnerable population with limited time per patient, these results suggest that an emphasis on stimulant use for risk stratification and CVD prevention may be appropriate.

Our study has several potential limitations. The relatively small sample size limits power, and outcome measurement at a single time point does not allow the assessment of change in LV mass. In addition, the sample population is a subgroup that experiences high levels of stress and other unmeasured risks, which could limit the generalizability of our findings. The intentional oversampling of women living with HIV may also limit generalizability; however, HIV was not associated with LVMI in this study suggesting that these effects were minimal. Our toxicology testing methodology also cannot distinguish between the prescribed versus unprescribed use of drugs like amphetamines, cannabis, and fentanyl, though this does not change the echocardiographic associations presented here. Furthermore, explicit diagnosis of substance use disorder was not performed, which limits the understanding of chronicity of substance use in this population. Finally, inclusion of men in future studies will help to assess applicability of these findings to men. Study strengths include a community-based sample of polysubstance-using women, toxicology confirmation of multiple substances, and echocardiographic confirmation of cardiac structure.

Among a diverse population of unstably housed women where the use of multiple substances is common, cocaine use is strongly associated with higher LVMI. Our findings suggest the centrality of stimulant use to the cardiac health of unstably housed women. Routinely evaluating stimulant use alongside traditional CVD risk factors during primary care visits and considering them as potential chronic cardiovascular risk factors in preventive

clinical care plans, may improve patients' cardiovascular health, particularly in highly vulnerable women.

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**Table 1.**

Baseline Patient Characteristics.

| Characteristics | Median (IQR) or N (%) |
|---|---|
| Age | 53.5 (46.5–59.5) |
| Race | |
| White | 53 (27.3) |
| Black/AA | 76 (39.2) |
| Latina | 28 (14.4) |
| Multiracial | 21 (10.8) |
| Other | 16 (8.2) |
| Post-menopausal[a] | 124 (64.2) |
| Body Mass Index (BMI) (kg/m$^2$) | 86 (78.5–93.5) |
| Average systolic blood pressure (mmHg) | 130 (116–142) |
| Average diastolic blood pressure (mmHg) | 86 (78.5–93.5) |
| Hypertension (≥130/80 mmHg) | 159 (82.0) |
| LDL cholesterol (mg/dL) | 93 (76.5–118) |
| HDL cholesterol (mg/dL) | 60 (47–73) |
| Diabetes[b] | 24 (12.4) |
| Prior MI[b] | 18 (9.3) |
| Prior stroke[b] | 24 (12.4) |
| Hep C[b] | 61 (31.4) |
| HIV[c] | 62 (32) |
| Cocaine[d,e] | 109 (56.2) |
| Cocaethylene[d] | 35 (18.0) |
| Levamisole[d] | 73 (37.6) |
| Methamphetamine[d] | 56 (28.9) |
| Heroin[d,f] | 4 (2.1) |
| Fentanyl[d] | 3 (1.5) |
| Opioid analgesics[d,g] | 45 (23.2) |
| Alcohol[d,h] | 56 (28.9) |
| Cannabis[d,i] | 97 (50) |
| Nicotine[d] | 134 (69.1) |
| Cotinine[d] | 132 (68) |
| Promethazine[j] | 4 (2.1) |
| Methadone[j] | 40 (20.6) |
| Buprenorphine[j] | 0 (0) |
| Naloxone[j] | 0 (0) |
| Benzodiazapines[j,k] | 17 (8.8) |

| Characteristics | Median (IQR) or N (%) |
|---|---|
| Beta blockers[j,l] | 12 (6.2) |
| Calcium channel blockers[j,m] | 8 (4.1) |
| Other antihypertensive agents[j,n] | 7 (3.6) |
| Statins[j,o] | 0 (0) |
| Isosorbide Mononitrate[j] | 0 (0) |
| Acetaminophen[j] | 51 (26.3) |
| Lidocaine[j] | 32 (16.5) |
| Tenofovir[j] | 9 (4.6) |
| Emtricitabine[j] | 21 (10.8) |
| Darunavir[j] | 6 (3.1) |
| Raltegravir[j] | 1 (0.5) |
| Dolutegravir[j] | 26 (13.4) |
| LVMI ($g/m^2$) | 86.8 (72.9–100) |

[a] >1 year since last menstrual period;

[b] Self reported history;

[c] Immunoassay positive result;

[d] Toxicology confirmed;

[e] Cocaine, Benzoylecgonine, Ecgonine methyl ester or Norcocaine;

[f] 6-Monoacetylmorphine, Heroin;

[g] Morphine, Codeine, Hydrocodone, Hydromorphone, Dihydrocodeine, Morphine Glucuronide, Codeine Glucuronide, Oxycodone or Oxymorphone;

[h] Determined by Ethyl Glucuronide;

[i] Tetrahydrocannabinol (THC) −COOH and THC−COOH glucuronide;

[j] Drug level confirmed;

[k] 7-Aminoclonazepam, Clonazepam, Diazepam, Lorazepam, Nordiazepam, Temazepam, Oxazepam, Alprazolam, alpha-hycroxyalprazolam, Flurazepam, 2-Hydroxyethlflurazepam, Desalkylflurazepam, Flunitrazepam, 7-aminoflunitrazepam, N-Desmethylflunitrazepam, Midazolam, 7-aminontrazepam or Etizolam;

[l] Metoprolol, Atenolol, Carvedilol, Labetolol;

[m] Amlodipine, Diltiazem, Verapamil;

[n] Clonidine, Lisinopril or Losartan;

[o] Atorvastatin, Pravastatin or Simvastatin.

**Table 2.**

Associations Between Study Factors and Log-Transformed LVMI (g/m$^2$) in Homeless and Unstably Housed Women (N = 194).

| Exposure variables | Model 1: unadjusted linear effect (95% CI) | *P*-value | Model 2: adjusted linear effect (95% CI) without hypertension[o] | *P*-value | Model 3: adjusted linear effect (95% CI) with hypertension[o,p] | *P*-value |
|---|---|---|---|---|---|---|
| Age (per 10 years) | 6.2% (2.4, 10.1) | <0.01 | - | - | - | - |
| Race | | | | | | |
| White | Ref | | Ref | | Ref | |
| Black/AA | 14.5% (4.3, 25.6) | <0.01 | - | - | - | - |
| Latina | 7.6% (−4.7, 21.5) | 0.24 | - | - | - | - |
| Multiracial | 2.0% (−10.8, 16.7) | 0.77 | - | - | - | - |
| Other | 23.8% (6.7, 43.6) | <0.01 | - | - | - | - |
| Post-menopausal[a] | 13.8% (5.3, 23.1) | <0.01 | 11.4% (3.5, 20.0) | <0.01 | 7.7% (0.2, 15.7) | 0.04 |
| LDL cholesterol (mg/dL) | −2.4% (−6.3, 1.6) | 0.23 | - | - | - | - |
| HDL cholesterol (mg/dL) | 2.6% (−1.4, 6.6) | 0.21 | - | - | - | - |
| Diabetes[b] | 1.6% (−9.6, 14.1) | 0.79 | - | - | - | - |
| Prior myocardial infarction[b] | 11.9% (−1.9, 27.6) | 0.09 | 12.6% (−0.3, 27.0) | 0.06 | 12.6% (0.4, 26.3) | 0.04 |
| Prior stroke[b] | −0.9% (−6.5, 5.1) | 0.76 | - | - | - | - |
| Hep C[b] | 5.6% (−2.8, 14.6) | 0.2 | - | - | - | - |
| HIV[c] | 3.0% (−5.1, 11.8) | 0.48 | - | - | - | - |
| Cocaine[d,e] | 18.7% (10.3, 27.8) | <0.01 | 18.0% (9.9, 26.6) | <0.01 | 15.3% (7.7, 23.4) | <0.01 |
| Cocaethylene[d] | 11.7% (1.2, 23.2) | 0.03 | - | - | - | - |
| Levamisole[d] | 13.4% (5.0, 22.5) | <0.01 | - | - | - | - |
| Methamphetamine[d] | −0.8% (−8.9, 7.9) | 0.85 | - | - | - | - |
| Heroin[d,f] | −6.8% (−28.8, 22.1) | 0.61 | - | - | - | - |
| Fentanyl[d] | 6.0% (−22.3, 44.6) | 0.71 | - | - | - | - |
| Opioid analgesics[d,g] | −0.3% (−9.0, 9.2) | 0.95 | - | - | - | - |
| Alcohol[d,h] | 0.7% (−7.5, 9.6) | 0.87 | - | - | - | - |
| Cannabis[d,i] | −1.6% (−8.8, 6.3) | 0.68 | - | - | - | - |

| Exposure variables | Model 1: unadjusted linear effect (95% CI) | *P*-value | Model 2: adjusted linear effect (95% CI) without hypertension[o] | *P*-value | Model 3: adjusted linear effect (95% CI) with hypertension[o,p] | *P*-value |
|---|---|---|---|---|---|---|
| Nicotine[d] | 5.0% (−3.3, 14.0) | 0.25 | - | - | - | - |
| Cotinine[d] | 5.6% (−2.7, 14.6) | 0.19 | - | - | - | - |
| Promethazine[j] | 22.8% (−6.1, 60.6) | 0.13 | - | - | - | - |
| Methadone[j] | 7.8% (−1.9, 18.4) | 0.12 | - | - | - | - |
| Benzodiazapines[j,k] | 6.0% (−7.4, 21.4) | 0.4 | - | - | - | - |
| Beta blockers[j,l] | 14.4% (−2.3, 34.0) | 0.09 | - | - | - | - |
| Calcium channel blockers[j,m] | 12.7% (−7.0, 36.5) | 0.22 | - | - | - | - |
| Other antihypertensive agents[j,n] | 22.4% (−0.2, 50.0) | 0.05 | 20.9% (0.0, 46.2) | 0.05 | 23.0% (2.7, 47.4) | 0.03 |
| Acetaminophen[j] | 5.0% (−3.7, 14.5) | 0.27 | - | - | - | - |
| Lidocaine[j] | 15.0% (3.9, 27.2) | <0.01 | - | - | - | - |
| Tenofovir[j] | −17.8% (−31.3, −1.6) | 0.03 | −13.6% (−26.9, 2.1) | 0.09 | - | - |
| Emtricitabine[j] | −4.5% (−15.6, 8.0) | 0.46 | - | - | - | - |
| Darunavir[j] | 1.7% (−18.5, 27.0) | 0.88 | - | - | - | - |
| Raltegravir[j] | −20.4% (−53.4, 35.8) | 0.4 | - | - | - | - |
| Dolutegravir[j] | −3.9% (−14.2, 7.5) | 0.48 | - | - | - | - |
| Average systolic blood pressure (per 10 mmHg) | 0.6% (0.4, 0.8) | <0.01 | - | - | 0.7% (0.4, 1.0) | <0.01 |
| Average diastolic blood pressure (per 10 mmHg) | 0.6% (0.2, 0.9) | <0.01 | - | - | −0.5% (−1.0, 0.1) | 0.08 |
| Hypertension | 12.5% (1.9, 24.1) | 0.02 | - | - | - | - |

[a] >1 year since last menstrual period;

[b] Self reported history;

[c] Immunoassay positive result;

[d] Toxicology confirmed;

[e] Cocaine, Benzoylecgonine, Ecgonine methyl ester or Norcocaine;

[f] 6-Monoacetylmorphine, Heroin;

[g] Morphine, Codeine, Hydrocodone, Hydromorphone, Dihydrocodeine, Morphine Glucuronide, Codeine Glucuronide, Oxycodone or Oxymorphone;

[h] Determined by Ethyl Glucuronide;

[i] Tetrahydrocannabinol (THC) −COOH and THC−COOH glucuronide;

[j] Drug level confirmed;

[k] 7-Aminoclonazepam, Clonazepam, Diazepam, Lorazepam, Nordiazepam, Temazepam, Oxazepam, Alprazolam, alpha-hycroxyalprazolam, Flurazepam, 2-Hydroxyethlflurazepam, Desalkylflurazepam, Flunitrazepam, 7-aminoflunitrazepam, N-Desmethylflunitrazepam, Midazolam, 7-aminontrazepam or Etizolam.

[l] Metoprolol, Atenolol, Carvedilol, Labetolol;

[m] Amlodipine, Diltiazem, Verapamil;

[n] Clonidine, Lisinopril or Losartan;

[o] Final model built using backwards deletion to select from exposure variables that were significant with a *P*-value <0.1 in unadjusted analysis;

[p] Hypertension was incorporated into this additional model as 3 distinct variables: Systolic Blood Pressure (per 10 mmHg), Diastolic Blood Pressure (per 10 mmHg), and Hypertension at baseline defined as blood pressure greater than or equal to 130/80 on 2 separate visits.