



Published in final edited form as:

*Circ Popul Health Outcomes*. 2026 April ; 19(4): e012683. doi:10.1161/CIRCOUTCOMES.125.012683.

## Cardiovascular Conditions and Symptoms in Deaths Attributed to Acute Stimulant Toxicity

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### Abstract

**Background:** The underlying etiology of deaths attributed to acute stimulant (methamphetamine or cocaine) toxicity is poorly understood, although cardiovascular events are believed to contribute.

**Methods:** We analyzed psychological autopsy data from acute stimulant toxicity deaths in San Francisco from 2022-2023. Sources included vital records, autopsies, medical records, and mixed methods interviews with informants (e.g., family, friends) who knew decedents in the year preceding death. We compared sociodemographic characteristics and cardiovascular measures (autopsy, electrocardiogram, echocardiogram, or lab abnormalities; diagnoses; acute care visits; symptoms) by fentanyl involvement. Age was skewed and compared with a Wilcoxon rank sum test. Proportions were compared with Chi-square or Fisher's exact tests. Qualitative thematic analyses identified themes related to cardiovascular health in interviews.

**Results:** Among 101 deaths, 70 involved stimulants without opioids and 31 also involved fentanyl. Median age at death was higher among stimulant without opioids compared to fentanyl-involved decedents (58 vs 50 years,  $p=0.02$ ). A plurality were White (44%) and 36% were Black. Most (69%) were unhoused or marginally housed. Cardiovascular conditions were identified in records among 93% of stimulant without opioids and 71% of fentanyl-involved decedents ( $p<0.01$ ), and symptoms were reported by informants for 76% of stimulant without

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**DECLARATIONS OF COMPETING INTEREST:** The authors have declared that no competing interests exist.

opioids and 52% of fentanyl-involved decedents ( $p=0.02$ ). Specific conditions more prevalent among stimulant without opioid decedents were cardiac enlargement ( $p=0.04$ ), coronary artery disease ( $p=0.01$ ), prolonged QTc interval ( $p=0.03$ ), and hypertension ( $p=0.02$ ). Themes from 140 informant interviews included family history of cardiovascular disease, cardiovascular symptoms, comorbid conditions, reluctance to seek care, and poor health contributing to social isolation.

**Conclusions:** Pre-mortem cardiovascular conditions and symptoms were common among stimulant decedents, and more prevalent among deaths attributed to stimulants without opioids compared to those involving fentanyl. In addition to opioid overdose prevention efforts, people who use stimulants might benefit from aggressive prevention and treatment of cardiovascular disease.

### Keywords

methamphetamine; cocaine; fentanyl; cardiovascular; overdose; acute toxicity

## INTRODUCTION

Since 2021, there has been a sharp increase in deaths attributed to acute toxicity from methamphetamine or cocaine (stimulants) in the United States.(1) Most of these deaths were also attributed to fentanyl, while deaths attributed to stimulants without opioid involvement have increased much less during that same period. For opioids, there is a clearly defined mechanism of overdose death, a process involving respiratory depression eventually resulting in cardiac arrest, and early evidence that deaths involving both opioids and stimulants have a similar etiology.(2, 3) However, the etiology of stimulant deaths that do not involve opioids is poorly understood.

Stimulant use is associated with a wide range of cardiovascular conditions. Coronary artery disease, congestive heart failure, electroconductive abnormalities, valvular disorders, aortic and coronary artery dissections, and both ischemic and hemorrhagic strokes can all result from long-term stimulant use, and raise the risk for future death from cardiovascular disease.(4-7) Studies in Australia identified cardiovascular disease, most commonly coronary artery disease, in 54% of methamphetamine deaths(8) and 51% of cocaine deaths(9); cerebrovascular disease was also more prevalent in stimulant compared to opioid deaths. An analysis of additional causes of death and significant contributing conditions among deaths attributed to acute toxicity from opioids or stimulants found similar odds of cardiovascular, cerebrovascular, and other medical contributors among opioid and opioid-stimulant deaths, and much higher odds among deaths attributed to stimulants alone.(10) Investigators have suggested that many deaths attributed to acute stimulant toxicity may actually be better attributed to chronic cardiovascular disease exacerbated by stimulant use.(11)

We analyzed data from a psychological autopsy study of deaths attributed to acute stimulant toxicity to understand the prevalence of pre-mortem cardiovascular disease in stimulant deaths by fentanyl involvement.

## METHODS

Because of the sensitive nature of the data collected for this study, requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the corresponding author.

### Study Sample and Procedures

The Leveraging Psychological Autopsies to Advance Stimulant Overdose Research (LASSO) study is described in detail in a previous manuscript.(12) As a brief overview, we identified decedents whose death was attributed to stimulants through record review from the California Electronic Death Registry System (EDRS) and San Francisco Office of the Chief Medical Examiner (OCME) from June 2022 through December 2023. We intentionally selected 70 decedents attributed to acute toxicity from stimulants without opioids (“stimulant-no-opioid”) and 31 attributed to both fentanyl and stimulants (“fentanyl-stimulant”) in order to compare the groups. We reached out to informants (largely family or friends) with contact information who were listed in EDRS, OCME, or medical records, and considered a decedent “enrolled” once one informant interview was completed. Slightly over a quarter of decedents (38, 27%) had more than one interview; a total of 140 interviews available for analysis.

Informant interviews were semi-structured, mixed methods interviews lasting 1-2 hours, including 14 thematic sections with quantitative and qualitative questions addressing sociodemographic characteristics, neighborhood and housing, adverse childhood and adult experiences, physical and emotional/psychological health, substance use, social environment, and the fatal event. Interviews were audio-recorded and transcribed by [Rev.com](#). After informant interviews, we collected medical examiner and chart data. All data were collected using REDCap.(13, 14)

The study was approved by the University of California San Francisco, Human Research Protection Program (#21-35305) and the State of California Health and Human Services Agency Committee for the Protection of Human Subjects (#2022-091).

### Measures

Data sources for this analysis included death records, OCME autopsy reports, medical charts, and informant interviews. Sociodemographic characteristics that were ascertained from death records included age at death, gender (female, male), race/ethnicity (Asian/ Pacific Islander, Black/African American, Hispanic/Latine, White, Multiracial), and housing status (unhoused [living on the streets or in a vehicle], marginally housed [living in temporary housing], and stably housed [living in one’s own place, staying with family, living in an adult residential facility]). Gender was determined by the medical examiner and may represent gender at death or sex at birth. When housing status was not present on death records, informant interviews were used for this measure.

We included results from autopsies that involved at least chest imaging or internal examination; we excluded visual inspections. Autopsy measures included in this analysis were evidence of cardiac enlargement / ventricular hypertrophy, occurrence of

a cerebrovascular accident, peripheral vascular disease, and coronary artery disease. All cases with valvular disease also had ventricular hypertrophy, thus we were able to include autopsies based on imaging only which all included comments on heart size and coronary disease. We derived a binary variable for presence of each cardiac sign on autopsy.

Electronic medical record data included ICD-10 codes for cardiac disease, the etiology of the most recent three emergency department visits and inpatient admissions in the three years preceding death, latest electrocardiogram and echocardiogram results, and latest troponin and brain natriuretic peptide results. We reviewed ICD-10 codes listed in decedent medical records for cardiac-related codes (atrial fibrillation, hypertension, coronary artery disease, congestive heart failure, cerebral hemorrhage, ischemic stroke, and other cardiovascular disease [not otherwise specified]) and developed a binary variable of the presence of any such code. We categorized up to the three most recent pre-mortem emergency and inpatient visits as related to a cardiac complaint or another reason. We created a binary measure of any abnormal electrocardiogram (ECG) finding, including rhythm (abnormal included atrial fibrillation/flutter, bundle branch block, ectopic atrial rhythm; normal included normal sinus rhythm, sinus tachycardia, sinus bradycardia), QTc interval ( $\geq 450$  msec), or anatomic abnormalities (atrial or ventricular dilation or hypertrophy; reports of prior myocardial infarction were not included due to limited reliability of that finding on automated reports). Because not all decedents had data for all outcomes, the denominator presented for each data source varies; a summary variable including any medical record or OCME evidence of cardiovascular disease was tabulated for all decedents.

Informant interview data included if the decedent had told the informant they had experienced symptoms that may be associated with cardiovascular disease in the year before death (chest pain or pressure, shortness of breath, calf or leg pain or cramps when walking, leg swelling, losing consciousness for a reason other than opioid overdose, or rapid heartbeat / palpitations). Informants reported if the decedent had experienced each cardiac symptom in the 30 days or year before death, depending on the last time they had been in contact with the decedent. Response time periods were combined to represent informant-reported cardiac symptoms experienced by the decedent in the year before death.

## Analysis

We conducted a descriptive analysis of sociodemographic characteristics and cardiac measures by involvement of fentanyl in death. We reported a median for age, which was skewed, and compared it by fentanyl involvement using a Wilcoxon rank sum test. The remaining quantitative measures were categorical and thus presented as proportions. Proportions were compared across fentanyl involvement in death using Pearson's Chi-square tests and Fisher's exact tests for expected cell counts less than five. All quantitative analyses were conducted in Stata 17 and  $p$ -values  $< 0.05$  were considered significant.

The qualitative data in interview transcripts were reviewed and coded by five researchers including four co-authors (VMM, YGC, XLM, and MAM). An initial *a priori* codebook was generated for qualitative coding, and additional emergent codes were added during the coding process. Eleven transcripts were reviewed and coded together by the five coders

until they reached consensus on the codebook. Then the team coded transcripts separately, meeting weekly to review any questions that emerged from coding and updating the codebook and transcripts already coded as needed. The transcripts were coded and analyzed in ATLAS.ti using a thematic analysis framework.<sup>(15)</sup> Transcripts were analyzed for salient and recurring themes regarding cardiac health.

## RESULTS

Decedent demographics are provided in Table 1. Median age was 58 years; 75% were male; 44% were White, 36% Black/African American, 14% Hispanic/Latine, and 4% Asian/Pacific Islander; 20% were unhoused and 49% were marginally housed. Stimulant-no-opioid deaths were significantly older (58 vs 50 years,  $p=0.02$ ); other sociodemographic characteristics were similar by fentanyl involvement.

Overall, 86% of decedents had clinical evidence of pre-mortem cardiovascular disease and 68% had informant-reported pre-mortem potential cardiovascular symptoms (Table 2). Cardiovascular conditions were more common among stimulant-no-opioid decedents compared to fentanyl-stimulant decedents by record review ( $p<0.01$ ) and informant report ( $p=0.02$ ). The individual conditions that were significantly more prevalent among stimulant-no-opioid decedents were cardiac enlargement/ventricular hypertrophy (by autopsy,  $p=0.04$ ), coronary artery disease (by autopsy,  $p=0.01$ ), prolonged QTc interval (by electrocardiogram,  $p=0.03$ ), and hypertension (by diagnostic code,  $p=0.02$ ); shortness of breath in the year prior to death (by informant report) was marginal ( $p=0.05$ ).

### Qualitative Informant Interview Findings

Cardiac health codes were identified 261 times in 81 of 140 available transcripts, including interviews for 46 of 70 stimulant-no-opioid and 18 of 31 fentanyl-stimulant decedents. Common themes included a family history of cardiovascular problems; reports of cardiac symptoms such as shortness of breath, chest pain, and a racing heart; reports of strokes, heart attacks, or hypertension; recent declines in health and impaired mobility; poor mental health as evidenced by suicidality, hallucinations, and anxiety; reluctance to seek medical care; using drugs to cope with medical issues; and social isolation.

**Personal and Family History of Cardiovascular Events:** Informants commonly reported a personal and family history of cardiovascular events among the decedents, including strokes and heart attacks. In some cases, these events were proximal to their death.

“I have actually had a stroke. My grandmother had a stroke. There were a few other folks in our family that have suffered either hypertension or things that contribute to poor cardiovascular health. And so, I know that [decedent], he can't run away from the DNA, that's for sure.”

Nephew of decedent; 66-year-old Non-Hispanic Black/  
African American male, Cocaine-no-opioid

“About a week before he died [decedent] had a stroke and his mom had a stroke, so strokes run on their side of the family. So after [his] stroke, his heart only worked at like 15% or something... And so, I'm sure he did meth because that's what was found in the coroner report. And I'm sure with his heart not functioning good and that, heart couldn't take it. But his mom also had the same problem... Her heart only works at like 20%. She had a stroke at the same exact age [decedent] did at 54.”

Former spouse of decedent; 54-year-old Non-Hispanic  
White male, Methamphetamine-no opioid

“[Decedent] had a couple of strokes, couple heart attacks [in the year before he died]. His DNA, genetically, he had had a bad heart. It went from his mother. His mother, she had a bad heart too.... His cousin had suffered a stroke and his cousin's son passed away in his sleep [before that]. A lot of family members were dying.”

Partner of decedent; 60-year-old Non-Hispanic Black/  
African American male, Cocaine-no opioid

**Decedent Cardiovascular Symptoms:** In addition to histories of cardiovascular events among decedents and their families, informants commonly reported that decedents had symptoms that may represent cardiovascular disease, such as shortness of breath, chest pain, a racing heart, or leg swelling in the year preceding death.

“He had high blood pressure, his heart beat faster, and a lot of times he sweat for no reason. He started getting an eye problem due to the blood pressure, blurry eyes. He started accumulating water in his legs.”

Friend of decedent; 55-year-old Hispanic/Latino male,  
Cocaine-no-opioid death

“[In the 30 days before she died] she complained of chest pains a lot... She was concerned about her breathing, and her heart was... She was having problems with her chest and her heart... When she did the ECG with her counselor at the methadone clinic a few times, they were telling her that she's got problems with her heart. It's very weak.”

Partner of decedent; 40-year-old Non-Hispanic White  
female, Fentanyl-cocaine-methamphetamine death

“She was complaining about chest pains... My granny always had a shortness of breath. I don't want to say it like that, but for a period of time, she was a heavier set woman. But even when she was back smaller now, she had breathing problems, and she coughed a lot... she was saying that her legs were hurting a lot and that she was going to take some time off.”

Granddaughter of decedent; 61-year-old Non-Hispanic  
Black/African American female, Cocaine-no-opioid  
death

**Physical and Mental Health Comorbidities:** Informants reported being aware of or observing a history of serious chronic health issues among decedents, including highly prevalent and symptomatic chronic obstructive pulmonary disease (COPD), obesity, HIV, and vision problems. Comorbid conditions also involved mental health, including paranoia, anxiety, and depression.

“He was HIV positive. He's been living with AIDS since '95. And at the end, I guess he just stopped taking his medication and so he developed a whole bunch of problems. So, he said that his heart was always beating... he couldn't catch his breath. He was, legs were swollen, he was having trouble walking, he was having trouble controlling his bowels. It sounded like his body was just shutting down and then it didn't help with all the drug use.”

Sister of decedent; 58-year-old Non-Hispanic White male, Methamphetamine-no-opioid death

“His health [was] just so declined. His COPD was so advanced. He's had untreated cardiac issues and his depression. He just was so depressed. I think that he just wasn't as clear as he had been. I think that the [drug] use would just ... He was too dependent on it and so, it was so hard to find any way to maybe help him feel better physically, emotionally.”

Case manager of decedent, 60-year-old Non-Hispanic White male, Cocaine-methamphetamine-no-opioid death

“He had heart arrhythmia, high blood pressure. He may have had some other elements and issues going on too because of the medication he had been taking related to his heart. But he hadn't given me any other indications outside of just his anxiety really bothering him. And he had really bad anxiety... And then just his diet in general, how he ate.”

Daughter of decedent; 59-year-old Non-Hispanic Black/African American male, Cocaine-no-opioid death

**Poor Health as a Contributor to Substance Use and Social Isolation:** Informants described how poor health was a contributor to substance use, mainly to cope with their declining health.

“[The decedent] had this chronic fatigue kind of issue, and I don't know if it's Epstein Barr or' He never really espoused on it, but he said he had constant fatigue and so he self-medicated with alcohol and cocaine.”

-Friend of decedent; 55-year-old Hispanic/Latino male, Cocaine-no-opioid death

“Because [my dad's] diabetes and his high blood pressure had gotten worse in the last year and especially in the last 30 days before his death. And I believe that that probably caused him to get depressed again, to get in a situation where maybe he felt using the drugs helped him to cope. It was more like a coping mechanism because if he couldn't get his medication refilled, or if he didn't get a doctor's

appointment timely, he could always trust on drugs to help him feel like he could cope.”

Daughter of decedent; 75-year-old Non-Hispanic Black/  
African American male, Cocaine-no-opioid death

“I watched her, I watched, really watched her disease. I used to get on her about it. I used to find some different doctors. Because these doctors you mess with them, they're not... this is why she was fucking with the coke because she was in pain. One nurse said she couldn't get no... They wouldn't give her nothing it. This is why she was smoking coke.”

Friend of decedent; 61-year-old Non-Hispanic Black/  
African American female, Cocaine-no-opioid death

In addition to contributing to substance use, informants reported that poor health among the decedents resulted in increased social isolation.

“He wouldn't come out [of his van] after his stroke, and he didn't even bathe. He'd always kept himself clean. He just let himself go.... He didn't want to see anybody running in the neighborhood. He was... ashamed I guess.”

Friend of decedent; 64-year-old Non-Hispanic White  
male, Methamphetamine-no-opioid death

“He'd been having a lot of health issues over the last years, and it was really, really hard for him and I think it contributed to his stimulant use [...] He couldn't even sort of use the way he wanted to use anymore, and he relied on sort of his healthy self to get by and get through and form relationships and have people depend on him and he was less able to be reliable and be there because of his illnesses. And so, he really felt, I think, depressed and alone and yeah [...]. He'd actually, historically, sort of been much more involved.”

Case manager of decedent, 60-year-old Non-Hispanic  
White male, Cocaine-methamphetamine-no-opioid  
death,

**Reluctance to Seek Medical Care:** Most decedents had complex health issues, but informants frequently noted observing decedents avoiding or expressing reluctance to seek healthcare prior to their death. In some cases, decedents' health issues contributed to limited mobility, resulting in decedents not leaving their homes for extended periods of time. Many decedents were reported to leave care or treatment against medical advice.

“I mean he would be having symptoms, and he didn't want to go to the doctor. He had a provider, a primary care provider. But there would be symptoms that would happen, and he wouldn't want to seek medical treatment for it... He had chronically high blood pressure. Like every time we'd go to the doctor, [we'd] have the conversation about blood pressure and he wasn't interested in having it treated.”

Case manager of decedent, 60-year-old Non-Hispanic  
White male, Cocaine and methamphetamine-no-opioid  
death

“The heart problems, he’d been having it for the last year or two... He couldn’t breathe and swolleness... He’ll be on the street, and he’ll call 911 because he just didn’t feel... Like he couldn’t breathe.... See, I don’t know too much of the diagnostic. They say that he had some kind of disease of the heart. He had to do some kind of treatment, but he never followed up.”

Brother of decedent, 55-year-old Hispanic/Latino male,  
Methamphetamine-no-opioid death

“He wasn’t always following through on his medical care. So, he always had concerns about it; he would miss a lot of appointments. Sometimes he just didn’t care about following through or not. His doctors would call because they wanted to check his heart, they wanted to check his blood pressure... He definitely had high blood pressure and that was a big concern for his provider, which he wasn’t following through with as he should have.”

Case manager of decedent, 56-year-old Non-Hispanic  
Black/African American Male, Cocaine-no-opioid death

“When he would go to the hospital... his blood pressure was not quite as high as he was when he came in with the stroke, but it was high... So, they immediately put him on, it was probably a combination of ACE inhibitor and whatever else... He was taking one or two meds. And then when he ran out [of blood pressure lowering medication], probably in August, when he was being treated for his leg fracture... he just never went back to being treated.”

Mother of decedent; 37-year-old Non-Hispanic White  
male, Methamphetamine-no-opioid

One reason informants reported for why decedents did not seek or comply with recommended medical care was a mistrust of providers and institutions.

“I think it was little things [that she would not get medical care for], and I can’t even remember exactly what it was as recently as this summer. It was things like maybe extreme tiredness, sleeping too much. And she was very hesitant to ever try to seek medical care. She didn’t have a great faith in doctors. And she got that from her mother. Her mother also said, “Oh, they can’t do anything for me.” So, she kind had that attitude. So, she would go to doctors... Unless it was absolutely necessary.”

Father of decedent; 31-year-old Non-Hispanic White  
female, Cocaine-no-opioid

In some cases, this lack of recommended medical compliance was considered as a contributor to the decedents’ death.

“Well, yeah, because there was these compounding factors together. She didn’t have her medication for her heart. Her blood pressure was high. She should have stayed

in the hospital and left, then she went out and did cocaine, then that caused [the fatal] stroke.”

Sister of decedent; 43-year-old Non-Hispanic Black/  
African American female, Cocaine-no-opioid

## DISCUSSION

Our mixed-methods findings strongly support chronic cardiovascular disease, including cerebrovascular disease, as the primary etiology of deaths attributed to acute stimulant toxicity in the absence of opioids. While cardiovascular disease was prevalent among all deaths involving stimulants, findings on medical record review, as well as by informant report of symptoms, were greater among stimulant-no-opioid deaths than among fentanyl-stimulant deaths, further supporting the hypothesis that these categories of deaths are due to distinct processes.

We identified several specific cardiovascular signs and symptoms that were more prominent among stimulant deaths in the absence of opioids. Cardiac enlargement / left ventricular hypertrophy and coronary artery disease as found on autopsy, prolonged QTc interval as found on clinically-obtained electrocardiograms, and clinically-diagnosed hypertension were all highly prevalent and more frequently reported for stimulant-no-opioid deaths compared to fentanyl-stimulant deaths. These differences suggest potential targets for intervention, such as screening electrocardiograms for people who report stimulant use; more aggressive management of hypertension, coronary artery disease, and congestive heart failure; and a lower threshold for deploying strategies – such as statin therapies – to prevent or slow the progression of cardiovascular disease.(16) Shortness of breath was frequently reported and may represent a potential target for more aggressive diagnostic and therapeutic strategies.

Informants reported that cardiovascular disease (by family history and decedents’ symptoms at the time), poor mental health, recent declines in health, avoidance of non-urgent medical care, and social isolation were common among decedents at the time of death. Notably, all exemplar quotes were from informants for stimulant-no-opioid deaths. Informants generally felt that medical causes, such as heart attacks or strokes, were main contributors to the death of decedents rather than attributing their death to a single incident involving use of too much of a stimulant. While the symptoms themselves could have been related to an array of medical problems, not just cardiovascular disease, these findings overall support chronic disease as the major contributor to death, and reinforce the importance of interventions to engage people who use stimulants in primary care, cardiovascular specialty care, and substance use disorder treatment interventions.

The hypothesis that chronic disease is the underlying etiology of deaths attributed to acute toxicity from stimulants in the absence of opioids is now supported by multiple studies. From this same cohort, we found that deaths involving stimulants without opioids had less evidence of drug use on the scene of unwitnessed deaths and less drug use prior to events that led to death among witnessed deaths, when compared with fentanyl-stimulant deaths.(3) While stimulants can be directly responsible for acute myocardial infarctions, arrhythmias, or cerebrovascular accidents, the occurrence of these events is strongly associated with

both aging and cumulative exposure to the substance(17); this extends to prescribed psychostimulants, for which duration of use is also associated with cardiovascular outcomes. (18)

The substantial prevalence of cardiovascular disease in fentanyl-stimulant deaths supports similar intervention efforts for this population as well. Nonetheless, other analyses of this dataset suggest that the mechanism of acute death in fentanyl-stimulant cases was more likely opioid-induced respiratory depression,(3) thus opioid-based overdose prevention interventions like naloxone provision are also critical for people who use stimulants. People who use stimulants may use fentanyl intentionally, and thus should be aware of opioid overdose risks. However, about a third of paramedic-managed opioid overdoses in San Francisco were among people who used stimulants and did not intend to use any opioid – these events were attributed to unintentional fentanyl use.(19) Interviews suggest that these patients had used drugs that they thought were stimulants, but were in fact fentanyl, or had used drug paraphernalia that they did not know had been used for fentanyl administration. (19) Broad opioid overdose education and naloxone provision for people who access any non-prescribed drugs is critical to reduce fentanyl-involved deaths, and strategies to slow or reverse cardiovascular disease are critical for people who use stimulants regardless of other substances used.

The question of how stimulants contribute to opioid overdose deaths remains poorly understood. While stimulants may merely be a bystander, some have suggested that, by increasing myocardial demand, stimulants increase susceptibility to opioid-induced respiratory depression. This hypothesis is belied by decades of anesthesiology and other research suggesting that stimulants often raise the threshold for respiratory depression from opioids.(20-22) A corollary hypothesis suggests that, by increasing cardiovascular disease, chronic stimulant use creates a physiologic milieu more susceptible to cardiac arrest when respiratory depression occurs from opioid use; i.e., rather than acutely contributing to an opioid death, stimulants contribute through the pathway of chronic disease. A different set of hypotheses suggests that the higher risk of opioid overdose death among persons who also use stimulants is due to behavioral factors. Stimulant use is associated with high risk sexual behaviors,(23-25) which may extend to opioid use practices that increase overdose risk. Alternatively, by raising the threshold for respiratory depression from opioids, (20-22) stimulant use may allow people to use higher doses of opioids (supported by studies demonstrating a median dose of fentanyl of >1.5 grams with near-universal stimulant use(26)); this apparent protection, however, would be dependent on the presence and dose of stimulants. Thus the risk of opioid overdose may increase not only due to shifts in the potency of the available opioid,(27) but simultaneous shifts in the presence and potency of stimulants, making street opioid use increasingly perilous to titrate.

The primary limitations of this study were the small sample size and single geographic location, both of which limit generalizability. A larger sample size or more geographic diversity may have identified more varied medical backgrounds among decedents. In addition, only decedents for whom an informant could be found to interview were included in the study, which could underestimate the degree of social isolation in the overall population. Informant accounts may also be subject to recall bias or influenced by social

desirability, leading to a desire to attribute a loved one's death to less stigmatized medical causes. Finally, while the high prevalence of pre-mortem cardiovascular disease was likely contributed to by stimulant use, it may have also involved other factors; low income, racial/ethnic minority status,(28) and housing challenges(29) have all been associated with accelerated cardiovascular disease. While efforts to address substance use are critical, more comprehensive efforts addressing broader social determinants of health may be necessary to reduce adverse cardiovascular outcomes.

In summary, we found a high prevalence of pre-existing cardiovascular disease and potential cardiovascular symptoms among deaths attributed to acute stimulant toxicity, with an even greater prevalence among those deaths attributed to stimulants in the absence of opioids. These findings support the hypothesis that stimulant deaths in the absence of opioids are distinct from those involving fentanyl. Moreover, findings suggest that preventing these deaths would require aggressively screening for, preventing, and treating chronic cardiovascular conditions.

## ACKNOWLEDGMENTS:

Authors would like to acknowledge the contributions of the entire research team to this study, as well as informants who provided interviews about loved ones they had lost.

## SOURCES OF FUNDING:

Centers for Disease Control and Prevention grant # R01CE003364 and National Institute on Drug Abuse grant #2K24DA042720

## Non-standard Abbreviations and Acronyms:

|              |                                                                                 |
|--------------|---------------------------------------------------------------------------------|
| <b>LASSO</b> | Leveraging Psychological Autopsies to Advance Stimulant Overdose Research study |
| <b>EDRS</b>  | California Electronic Death Registry System                                     |
| <b>OCME</b>  | San Francisco Office of the Chief Medical Examiner                              |
| <b>ECG</b>   | electrocardiogram                                                               |
| <b>COPD</b>  | chronic obstructive pulmonary disease                                           |
| <b>IQR</b>   | interquartile range                                                             |

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**What is Known:**

- Deaths attributed to acute stimulant toxicity often involve cardiovascular disease or events.

**What the Study Adds:**

- The vast majority of decedents whose deaths were attributed to stimulants in the absence of opioids had evidence of pre-mortem cardiovascular disease and associated symptoms.
- Interventions to address these deaths may be more effective if focused on prevention of cardiovascular disease.

**Table 1:**

Sociodemographic characteristics of decedents from acute stimulant toxicity without opioids and with fentanyl in San Francisco, June 2022-December 2023 (N=101)

|                             | All deaths (N=101) |       | Stimulant-no-opioid<br>(n = 70) |       | Fentanyl-stimulant<br>(n = 31) |       | p-value |
|-----------------------------|--------------------|-------|---------------------------------|-------|--------------------------------|-------|---------|
| <b>Age [median (IQR *)]</b> | 58                 | 47-61 | 58                              | 52-61 | 50                             | 43-59 | 0.02    |
| <b>Sex †</b>                |                    |       |                                 |       |                                |       | 0.51    |
| Female                      | 25                 | 25%   | 16                              | 23%   | 9                              | 29%   |         |
| Male                        | 76                 | 75%   | 54                              | 77%   | 22                             | 71%   |         |
| <b>Race/ethnicity</b>       |                    |       |                                 |       |                                |       | 0.12    |
| Asian/Pacific Islander      | 4                  | 4%    | 4                               | 6%    | 0                              | 0%    |         |
| Black /African American     | 36                 | 36%   | 29                              | 41%   | 7                              | 23%   |         |
| Hispanic/Latine             | 14                 | 14%   | 7                               | 10%   | 7                              | 23%   |         |
| White                       | 44                 | 44%   | 28                              | 40%   | 16                             | 52%   |         |
| Multiracial                 | 3                  | 3%    | 2                               | 3%    | 1                              | 3%    |         |
| <b>Housing status ‡</b>     |                    |       |                                 |       |                                |       | 0.39    |
| Unhoused                    | 20                 | 20%   | 12                              | 17%   | 8                              | 26%   |         |
| Marginally housed           | 49                 | 49%   | 37                              | 53%   | 12                             | 39%   |         |
| Stably housed               | 32                 | 32%   | 21                              | 30%   | 11                             | 35%   |         |

\* IQR=interquartile range

† Sex was determined by medical examiner and may represent sex at birth or gender at death.

‡ Unhoused included living on streets or in a vehicle. Marginally housed included temporary housing (e.g., halfway house, hotel). Stably housed included owning or renting one's own place, staying with family, or living in an adult residential facility.

**Table 2:**

Cardiovascular conditions among decedents from acute stimulant toxicity without opioids and with fentanyl in San Francisco, June 2022-December 2023 (N=101)

|                                                                                    |                                                                      | All deaths<br>(N=101) | Stimulant-no-opioid<br>(n=70) | Fentanyl-stimulant<br>(n=31) | p-value         |
|------------------------------------------------------------------------------------|----------------------------------------------------------------------|-----------------------|-------------------------------|------------------------------|-----------------|
| <b>Cardiovascular conditions by medical record or medical examiner evaluation</b>  |                                                                      |                       |                               |                              |                 |
| <b>Any</b>                                                                         |                                                                      | <b>87/101 (86%)</b>   | <b>65/70 (93%)</b>            | <b>22/31 (71%)</b>           | <b>&lt;0.01</b> |
| <i>Autopsy (n=73 [37 full internal autopsies])</i>                                 |                                                                      |                       |                               |                              |                 |
|                                                                                    | Ventricular hypertrophy                                              | 52/73 (71%)           | 38/48 (79%)                   | 14/25 (56%)                  | 0.04            |
|                                                                                    | Valvular disease                                                     | 4/73 (5%)             | 2/48 (4%)                     | 2/25 (8%)                    | 0.60            |
|                                                                                    | Cerebrovascular accident                                             | 2/73 (3%)             | 2/48 (4%)                     | 0/25 (0%)                    | 0.54            |
|                                                                                    | Peripheral vascular disease                                          | 11/73 (15%)           | 10/48 (21%)                   | 1/25 (4%)                    | 0.09            |
|                                                                                    | Coronary artery disease                                              | 44/73 (60%)           | 34/48 (71%)                   | 10/25 (40%)                  | 0.01            |
| <i>Electrocardiogram (n=45)</i>                                                    |                                                                      |                       |                               |                              |                 |
|                                                                                    | Any of below electrocardiogram abnormalities                         | 36/45 (80%)           | 29/33 (88%)                   | 7/12 (58%)                   | 0.04            |
|                                                                                    | QTc ≥ 450                                                            | 31/45 (69%)           | 26/33 (79%)                   | 5/12 (42%)                   | 0.03            |
|                                                                                    | Other rhythm abnormality *                                           | 11/45 (24%)           | 9/33 (27%)                    | 2/12 (17%)                   | 0.70            |
|                                                                                    | Anatomic abnormality †                                               | 16/45 (36%)           | 13/33 (39%)                   | 3/12 (25%)                   | 0.49            |
| <i>Echocardiogram (any abnormality) (n=23)</i>                                     |                                                                      | 20/23 (87%)           | 16/18 (89%)                   | 4/5 (80%)                    | 0.54            |
| <i>Laboratory testing</i>                                                          |                                                                      |                       |                               |                              |                 |
|                                                                                    | Troponin > upper limit of normal (>19ng/L) (n=31)                    | 19/31 (61%)           | 16/25 (64%)                   | 3/6 (50%)                    | 0.65            |
|                                                                                    | Brain-natriuretic peptide > upper limit of normal (<100pg/mL) (n=23) | 17/23 (74%)           | 14/18 (78%)                   | 3/5 (60%)                    | 0.58            |
| <i>Medical record diagnoses (n=93)</i>                                             |                                                                      |                       |                               |                              |                 |
|                                                                                    | Atrial fibrillation                                                  | 2/93 (2%)             | 2/65 (3%)                     | 0/28 (0%)                    | 1.00            |
|                                                                                    | Hypertension                                                         | 44/93 (47%)           | 36/65 (55%)                   | 8/28 (29%)                   | 0.02            |
|                                                                                    | Coronary artery disease                                              | 6/93 (6%)             | 6/65 (9%)                     | 0/28 (0%)                    | 0.17            |
|                                                                                    | Congestive heart failure                                             | 22/93 (24%)           | 18/65 (28%)                   | 4/28 (14%)                   | 0.16            |
|                                                                                    | Other cardiovascular disease ‡                                       | 13/93 (14%)           | 9/65 (14%)                    | 4/28 (14%)                   | 1.00            |
|                                                                                    | Cerebral hemorrhage                                                  | 1/93 (1%)             | 0/65 (0%)                     | 1/28 (4%)                    | 0.30            |
|                                                                                    | Ischemic stroke                                                      | 7/93 (8%)             | 7/65 (11%)                    | 0/28 (0%)                    | 0.10            |
| <i>Emergency department visit for cardiovascular complaint (n=93)</i>              |                                                                      | 16/93 (17%)           | 14/65 (22%)                   | 2/28 (7%)                    | 0.14            |
| <i>Hospitalization for cardiovascular condition (n=93)</i>                         |                                                                      | 15/93 (16%)           | 12/65 (18%)                   | 3/28 (11%)                   | 0.54            |
| <b>Cardiovascular symptoms in the year preceding death, by informant interview</b> |                                                                      |                       |                               |                              |                 |
| <b>Any</b>                                                                         |                                                                      | <b>69/101 (68%)</b>   | <b>53/70 (76%)</b>            | <b>16/31 (52%)</b>           | <b>0.02</b>     |
|                                                                                    | Chest pain or pressure                                               | 32/101 (32%)          | 24/70 (34%)                   | 8/31 (26%)                   | 0.40            |
|                                                                                    | Shortness of breath                                                  | 44/101 (44%)          | 35/70 (50%)                   | 9/31 (29%)                   | 0.05            |
|                                                                                    | Calf or leg pain or cramps when walking                              | 44/101 (44%)          | 34/70 (49%)                   | 10/31 (32%)                  | 0.13            |

|                                                                       |  | <b>All deaths<br/>(N=101)</b> | <b>Stimulant-no-opioid<br/>(n=70)</b> | <b>Fentanyl-stimulant<br/>(n=31)</b> | <b>p-value</b> |
|-----------------------------------------------------------------------|--|-------------------------------|---------------------------------------|--------------------------------------|----------------|
| Leg swelling                                                          |  | 34/101 (34%)                  | 26/70 (37%)                           | 8/31 (26%)                           | 0.27           |
| Passed out/lost consciousness for a reason other than opioid overdose |  | 20/101 (20%)                  | 16/70 (23%)                           | 4/31 (13%)                           | 0.25           |
| Rapid heartbeat or palpitations                                       |  | 25/101 (25%)                  | 19/70 (27%)                           | 6/31 (19%)                           | 0.40           |

\* Rhythm abnormalities include atrial fibrillation/flutter, bundle branch block, ectopic atrial rhythm

† Anatomic abnormalities include atrial or ventricular dilation or hypertrophy

‡ Includes cardiovascular codes not otherwise specified