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Increased Risks of Major Cardiac Adverse Events in Stimulant Use Disorder as Compared With Other Substance Use Disorders: A Propensity-score Matching Cohort Study

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Objectives: Individuals with stimulant use disorders (StSUDs) present an elevated risk of cardiovascular complications compared with the general population. However, it remains unclear whether, within the subpopulation of individuals with substance use disorders (SUDs), those specifically affected by StSUDs face even higher cardiovascular complications.

Methods: We conducted a retrospective cohort study using the EVERSANA databank, spanning from January 2015 to December 2023. The EVERSANA data set comprises deidentified electronic health record data aggregated and standardized across the United States. Participants included patients diagnosed with SUDs, encompassing alcohol, cannabis, opioids, stimulants, tobacco, hallucinogens, sedative-hypnotics, or inhalants. We employed the International Classification of Disease 10th (ICD-10) version codes to define the presence of StSUD and SUD. Major adverse cardiac events (MACE) were assessed, and Cox proportional hazard ratios were adjusted using high-dimensional propensity score (hdPS) matching to account for potential confounders.

Results: Among 137,106 patients with SUD, 7706 (5.6%) had StSUD. The cohort was 50.2% female, 53.0% non-White, with a mean age of 49.1 years (SD ± 15). After adjustment, stimulant users exhibited significantly higher MACE rates (HR = 1.37, 95% CI: 1.22–1.53, $P < 0.001$), including an elevated risk of death (HR = 1.23, 95% CI: 1.02–1.47, $P = 0.026$).

Conclusion: Individuals with StSUD face increased MACE compared with those with nonstimulant SUDs.

Key Words: stimulants, substance use disorders, myocardial infarction, stroke, death

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The global prevalence of substance use disorders (SUDs) continue to surge.[1] In the United States alone, 48.7 million Americans aged 12+ report a past-year history of SUD in 2022.[2] Medical complications linked to substance use, including cardiovascular disease (CVD), have been rising since 1999.[3–5] Alcohol, tobacco, methamphetamine, and cocaine are well-known to be associated with cardiac sequelae, but significant cardiac complications with opioids, cannabis, and prescription stimulant have also now been reported.[3–7] Based on US prevalence rates, alcohol represents roughly 65% of the leading causes of death associated with SUD. Opioids are the second-leading cause (14%), followed by cocaine (10%) and other stimulants (6.5%).[3] Although cannabis is minimally associated with death (< 1%), there has been a notable increase in recent years of cannabis-related CVD, likely related to widespread legalization leading to increased use.[3,8] These substances all contribute to the

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Abbreviations: MACE, Major Adverse Cardiac Events; StSUD, stimulant substance use disorder; SUD, substance use disorder

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development of acute and/or chronic CVD through independent mechanisms. For instance, psychostimulants may induce vasoconstriction and hypertension via endothelin-1 upregulation and nitric oxide reduction, promote thrombosis through platelet activation and precipitate arrhythmias by blocking ion channels. Alcohol's cardiotoxic effects, mediated by ethanol metabolites, lead to oxidative stress, mitochondrial dysfunction, and disruption of calcium homeostasis, which can result in arrhythmias and dilated cardiomyopathy. Furthermore, tobacco and cannabis have been shown to accelerate atherosclerosis and increase the risk of stroke and myocardial infarction. In addition, long-acting opioid misuse has been associated with conditions such as QTc prolongation, torsade de pointes, ventricular arrhythmias, and cardiac arrest.[5] In recent years, as use of stimulants (ie, cocaine, amphetamine, methamphetamine, and prescription psychostimulants) have again begun to rise relative to other substances in Europe and the United States, especially on the West Coast,[9–11] complications related to stimulant use disorder (StSUD) have been sharply increasing,[9,12] including cardiomyopathy, heart failure, and death.[3] Indeed, methamphetamine-associated cardiomyopathy and heart failure (HF) hospitalizations surged by 600% between 2008 and 2018 in California, in stark contrast to a 6.0% decrease observed in HF cases not related to stimulants.[10] Moreover, individuals with cardiomyopathy associated with StSUD are nearly 4 times more likely to be hospitalized within 30 days of discharge.[13]

Data on cardiac outcomes across individuals with SUDs are lacking, even though people with SUDs represent the highest-risk group for prioritizing preventive measures due to the rising prevalence of SUD,[9–11] the younger demographic affected, the potential for modifying risks and the link to poor social determinants of health (SDOH).[14,15] These factors collectively underscore the urgency and potential impact of targeted interventions in this high-risk cohort. The purpose of this study was to assess if patients with StSUDs are at higher risk of major adverse cardiac events (MACE) than patients with nonstimulant SUDs, employing a retrospective longitudinal cohort design with a rigorous matching methodology to control for multiple confounding variables. MACE is a composite endpoint commonly used in cardiovascular research to assess the overall impact of interventions or risk factors on cardiac health. While there is not a universally standardized definition,[16] we chose to use a 5-point MACE outcome, which encompasses myocardial infarction (MI), stroke, heart failure (HF) hospitalization, and death.

METHODS

Study Setting

We conducted a retrospective cohort study using electronic health records (EHR) collected in the EVERSANA databank between January 2015 and December 2023. This databank is a collection of deidentified EHR data that has been aggregated and standardized from various sources and contains data from >120 million patients in the United States. The data originate from diverse EHR systems, collected from >2000 outpatient/ambulatory health centers, over 500 hospitals, and more than 30 health systems, including academic medical centers.[17] This data set offers a representative overview of healthcare activities across the US population, and the overall distributions of patient demographics align reasonably well with major geographic trends. EHR data were mapped to the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) version 5.3 such that standardized vocabularies, including the Anatomical Therapeutic Chemical (ATC) classification system, the RxNORM, the International Classification for Diseases, tenth revision (ICD-10) and the LOINC could be used to define patients and their conditions. The Stanford Health Care Institutional Review Board granted an informed consent waiver for the examination of EHR data. This study used STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) Guidelines[18]

Sample

Patients with at least one EHR-documented SUD diagnosis were included in the cohort (ie, alcohol, cannabis, opioids, stimulants, tobacco, hallucinogens, sedative-hypnotics, and inhalants). Patients were considered in the exposed group if they received an initial diagnosis of StSUD. Other SUD diagnoses for patients in the StSUD group thus occurred after the initial StSUD diagnosis. The control group was constituted of patients with single or comorbid SUD diagnoses who had never received a diagnosis of StSUD, stimulant intoxication, or stimulant poisoning (see Table S1 for standardized code definitions, Supplemental Digital Content, http://links.lww.com/JAM/A603). Patients were required to have a SUD diagnosis for at least 90 days before inclusion and have a valid "record end." The analysis included patient data from 18 to 90 years old. Patients who were 90 years old at any point during the study were excluded from the survival analysis. Patients in both groups StSUD and SUD were similar in several characteristics (Table 1) and deemed comparable in one crucial aspect: their significantly higher prevalence of adverse health outcomes compared with the general population, which are linked to SDOH, including housing, food insecurity, and systemic racism.[14,15]

Outcomes and Measures

MACE lacks a universally standardized definition, with variations across studies.[16] However, in many studies, MACE typically includes myocardial infarction (MI) and death. In our present investigation, MACE was denoted by a composite of events, encompassing MI, stroke, HF, hospitalization, or death as defined in other meta-analyses,[19] and enriched through a process of tokenization, linking it to government records and obituary data (see Tables S1–S5 for standardized code definitions, Supplemental Digital Content 1, http://links.lww.com/JAM/A603).

TABLE 1. Baseline Clinical and Demographic Characteristics of Stimulant Use Disorder and Nonstimulant Use Disorder Patients Before and After Propensity Score Matching

	Nonstimulant use disorder*	Stimulant use disorder*	Nonstimulant use disorder PS matched	Stimulant use disorder PS matched
	(N = 129,400)	(N = 7706)	(N = 7676)	(N = 7676)
Female, n (%)	65,279 (50.4)	3596 (46.7)	3544 (46.2)	3584 (46.7)
Mean age, y (SD)†	49.1 (15.1)	42.3 (12.9)	41.3 (14.8)	42.4 (12.9)
18–29	17,836 (13.8)	1529 (19.8)	2109 (27.5)	1515 (19.7)
30–39†	21,561 (16.7)	2141 (27.8)	1846 (24)	2132 (27.8)
40–49	23,287 (18)	1684 (21.9)	1382 (18)	1680 (21.9)
50–59	30,224 (23.4)	1559 (20.2)	1293 (16.8)	1556 (20.3)
60–69†	26,642 (20.6)	687 (8.9)	838 (10.9)	687 (8.9)
70–79	9840 (7.6)	106 (1.4)	208 (2.7)	106 (1.4)
80–89	10 (0)	0 (0)	0 (0)	0 (0)
Race, n (%)‡				
White	68,974 (53.3)	3751 (48.7)	3655 (47.6)	3739 (48.7)
Other	48,885 (37.8)	3222 (41.8)	3327 (43.3)	3206 (41.8)
Black	10,341 (8)	683 (8.9)	624 (8.1)	681 (8.9)
Asian	1200 (0.9)	50 (0.6)	70 (0.9)	50 (0.7)
Hispanic ethnicity, n (%)	7357 (5.7)	498 (6.5)	498 (6.5)	495 (6.4)
Index year ranges, n (%)				
2010–2014	0	0	0	0
2015–2029	70,229 (54.3)	3767 (48.9)	3654 (47.6)	3752 (48.9)
2020–present	59,171 (45.7)	3939 (51.1)	4022 (52.4)	3924 (51.1)
Mean preindex days (SD)§	3420.3 (3268.6)	3711.7 (3127.5)	3501.7 (3147.4)	3708.4 (3128.3)
Mean follow-up days (SD)‖	1044.5 (816.9)	932.3 (782.8)	956.7 (785.1)	931.5 (783.1)
Charlson Comorbidity score (SD)¶	1.9 (2.2)	1.6 (2.4)	1.5 (2.2)	1.6 (2.4)
Selected comorbidities, n (%)#				
Malignancy	6501 (5.02)	297 (3.9)	398 (5.2)	294 (3.8)
Diabetes	18,032 (13.9)	894 (11.6)	998 (13.0)	890 (11.6)
Peripheral vascular disease	6683 (5.16)	248 (3.2)	295 (3.8)	244 (3.2)
Chronic pulmonary disease	32,074 (24.8)	1947 (25.3)	1965 (25.6)	1939 (25.3)
HIV†	891 (0.7)	362 (4.7)	91 (1.2)	359 (4.7)
Rheumatic disease	3122 (2.4)	124 (1.6)	171 (2.2)	122 (1.6)
Dementia	575 (0.4)	40 (0.5)	27 (0.4)	40 (0.5)
Mild liver disease†	8245 (6.4)	1047 (13.6)	605 (7.9)	1041 (13.6)
Severe liver disease	843 (0.7)	89 (1.2)	79 (1.0)	89 (1.2)
Renal disease	4588 (3.6)	260 (3.4)	244 (3.2)	257 (3.4)
Substance use disorder, n (%)#				
Alcohol	21,534 (16.6)	2011 (26.1)	1330 (17.3)	2001 (26.1)
Tobacco	92,898 (71.8)	3640 (47.2)	5264 (68.6)	3615 (47.1)
Cannabis	8110 (6.3)	1778 (23.1)	888 (11.6)	1761 (22.9)
Opioids	10,272 (7.9)	2019 (26.2)	730 (9.5)	2000 (26.1)
Sedative/hypnotics	2493 (1.9)	495 (6.4)	144 (1.9)	491 (6.4)
Inhalants	87 (0.07)	18 (0.2)	7 (0.1)	17 (0.2)
Hallucinogens	110 (0.09)	105 (1.4)	18 (0.2)	103 (1.3)
Other psychoactives substances	6501 (5.0)	2250 (29.2)	573 (7.5)	2229 (29.0)
Stimulants				
Cocaine	0 (0)	2963 (38.5)	0 (0)	2949 (38.4)
Other stimulants	0 (0)	5148 (66.8)	0 (0)	5130 (66.8)

*The cohort included patients with a diagnosis of any substance use disorder and were separated in 2 groups according to the presence of a stimulant use disorder defined by the International Classification of Diseases 10th Revision [ICD-10] codes.

†Characteristics that exhibited statistically significant differences between groups (standardized mean difference >0.25)

‡Self-reported and imputed race and ethnicity.

§Defined by the average number of days each cohort had before the index; the "follow up" is the amount of data after (marker of utilization that is corrected for in the propensity score match).

‖Defined by the average number of days each cohort had after the index date (marker of utilization that is corrected for in the propensity score match).

¶Validated score that is a weighted sum of 17 comorbidities, factoring the number and severity of comorbidities and age such that the final score provides a way to stratify mortality risk.

#Defined by the International Classification of Diseases 10th Revision [ICD-10] codes.

PS indicates propensity score.

Statistical Analysis

We computed Cox proportional hazard ratios to compare MACE occurrences between patients with StSUDs and controls without StSUD. Patients were followed to the end of their available data with right-censoring. E-values were calculated for each outcome, representing the effect size of an unmeasured confounder on the risk ratio scale that would be required to negate the

observed results.[20,21] A high E-value (> 2) suggests lower susceptibility to residual confounding, as a significant level of confounding would be required to negate the observed effect. Pretreatment confounders included demographics, diagnostic, procedure and medication codes, the number of observed encounters, and Charlson comorbidity scores. The Charlson comorbidity score aims to forecast a patient's likelihood of 1-year mortality by assessing the quantity and severity of diverse comorbidities.[22] This weighted sum of 17 comorbidities, adjusted for both their number, severity, and age offers a practical and easily interpretable means of categorizing mortality risk. Since its inception, the Charlson comorbidity score has gained widespread acceptance in epidemiological studies as a tool to succinctly represent health status by considering existing health conditions and their severity, with continuous adjustments to accommodate the growing use of administrative billing codes in both ICD9 and ICD10.[22] In our recent analysis, we employed the prevailing method for calculating the Charlson score. We identified 17 comorbidities based on ICD10 codes and then tallied comorbidities using an updated weighted scheme.[22] This computation demonstrated an 84% AUC (*C*-statistic) in predicting in-hospital mortality.[22] To control for confounders, the exposed group was matched with the control group using 1:1 matching on age and sex, or high dimensional propensity score (hdPS) considering all baseline confounders listed above.[20] The propensity score (PS) provided a composite score of the baseline confounders such that when the PS is balanced (within a caliper of 0.25), baseline confounders between the groups approach being balanced. The PS model of the hdPS covariates was fitted using a logistic regression with regularization that penalizes low-weight variables down to zero weight, such that the resulting parsimonious model has equivalent predictive performance without overfitting covariates in a high dimensional setting.[20] Analyses were performed using R version 4.2. A 2-sided *P*-value of ≤ 0.05 was considered statistically significant. The primary research question and analysis plan have not been preregistered on a publicly available platform. As such, the results should be considered exploratory.

RESULTS

The cohort comprised 137,106 patients with SUD, of which 7706 (5.6%) had StSUD, which aligns with estimates from National Surveys on Drug Use and Health (NSDUH, 2016). The sample was 50.2% female, 53.0% non-White, with a mean age of 49.1 years (SD ± 15) (Table 1). After hdPS-matching, the StSUD and control groups differed on a few variables (Table 1).

Hazard ratios (HR) for MACE occurrence were significantly greater in the exposed (StSUD) group according to unmatched (HR = 1.22 [95% CI: 1.16, 1.25, $P < 0.001$]), basic matched (HR = 1.75 [95% CI: 1.55, 1.97, $P < 0.001$]) and hdPS-matched (HR = 1.37 [95% CI: 1.22, 1.53, $P < 0.001$]) analyses (Fig. 1). All E-values were in the moderate to high range. The numbers of events are detailed in Table 2 for each analysis. HRs for MI, stroke, HF hospitalization, and death were each significantly greater in the exposed group compared with the control group (see supplement for individual outcomes analysis details), including after hdPS matching for MI (HR = 1.46 [95% CI: 1.17, 1.83, $P < 0.001$]), stroke (HR = 1.48 [95% CI: 1.15, 1.89, $P = 0.002$]), HF hospitalization (HR = 1.57 [95% CI: 1.18, 2.08, $P < 0.001$]) and death (HR = 1.23 [95% CI: 1.02, 1.47, $P = 0.026$]).

DISCUSSION

Our study found that among patients with SUDs, those with StSUD face a 37% higher risk of MACE, including a 23% higher risk of death. The highest increase was observed in patients with heart failure hospitalizations, with a 57% higher risk of being hospitalized for heart failure in the StSUD cohort compared with those with nonstimulant SUDs. The results must be interpreted under the lenses of a methodological approach that includes both an expansive definition of MACE (5-point outcome, encompassing myocardial infarction [MI], stroke, heart failure [HF] hospitalization, and death, which differs from other studies using 3 or 4 point MACE definitions) and a rigorous matching algorithm for robust comparison of groups (basic matching plus high dimensional Propensity score matching based on the Charlson comorbidity score).

While preventive cardiovascular efforts to date have focused on well-known risk factors like tobacco exposure in the general population, the present findings emphasize the significantly higher cardiovascular risks of StSUDs even among the high-risk population of individuals with SUDs. These results shine a much-needed light on the increased cardiac morbidity and mortality among patients with StSUD as compared with patients with other SUDs, including substances with known cardiac risk factors, like tobacco, alcohol, and opioids.

Stimulants have multiple potential pathophysiological mechanisms of heart disease resulting from their use, including direct toxic effects, endothelial dysfunction effects, pro-thrombotic effects, sodium channel blockade, catecholamine surges, and hyperadrenergic states.[4] Addiction and nonaddiction clinicians alike would benefit from appreciating the cardiac complications associated with StSUD and the early signs of disease, especially as many stimulant users are younger and hence the cardiac consequences of stimulants are both reversible and easily overlooked.[23]

Patients with stSUD are vulnerable to CVD progression both by drug effects and by their difficulty with engaging with medical care, as nonadherence to treatment is among the main challenges in this population.[12,22] The integration of cardiology and addiction treatment is thus imperative in devising innovative models of care to effectively address CVD associated with StSUD. By collaboratively combining expertise, these disciplines could provide holistic and evidenced-based care in parallel to enhance patient outcomes. One such innovative approach involves implementing contingency management (CM) interventions, the most evidence-based intervention for

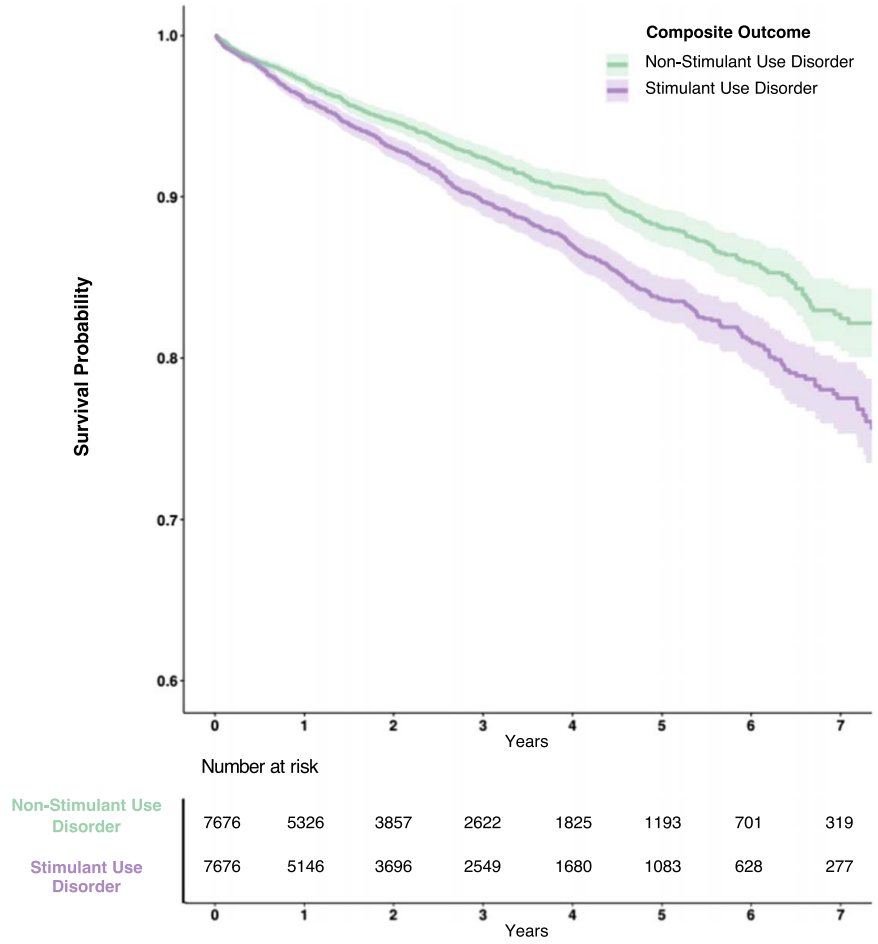

FIGURE 1. Propensity score matched survival analysis of major adverse cardiac events in patients suffering from stimulant use disorder versus nonstimulant use disorder. Kaplan-Meier survival curve showing time to first major cardiac event, in years, with a hazard ratio of 1.37 (95% CI: 1.22, 1.53, $P < 0.001$). The numbers below the Kaplan-Meier curves represent the numbers of patients followed up and the numbers censored at each timepoint.

StSUD, with adaptation to this specific context by targeting specific behaviors including attendance at cardiology appointments. A recent project of this type in California has shown promise in decreasing utilization of acute care services and stimulant consumption, while also promoting greater engagement with outpatient care and adherence to cardiology treatment.[13] By leveraging the strengths of both specialties and incorporating evidence-based interventions, healthcare providers can thus deliver more effective and tailored care.

TABLE 2. Unmatched, Basic Matched, and High Dimensional Propensity Score Matched Hazard Ratios for the Composite Outcome (Myocardial Infarction, Stroke, Heart Failure Hospitalization, and Death) in Patients With Stimulant Use Disorder and Patients With Nonstimulant Substance Use Disorder

Major adverse cardiac event composite outcome						
	N	**Events**	**HR (95% CI)**	**RMST (95% CI), days**	***P***	**E**
Unmatched						
Nonstimulant use disorder	129400	11078	NA	2631.9 (2627.8, 2636.1)	NA	NA
Stimulant use disorder	7706	677	1.16 (1.07, 1.25)	2583.2 (2565.2, 2601.3)	<0.001	1.4 (M)
Basic matched						
Nonstimulant use disorder	7706	439	NA	2739.3 (2724.8, 2753.8)	NA	NA
Stimulant use disorder	7706	677	1.75 (1.55, 1.97)	2579.7 (2561.7, 2597.7)	<0.001	2.5 (H)
High dimensional propensity score matched						
Nonstimulant use disorder	7676	516	NA	2681.3 (2665.2, 2697.5)	NA	NA
Stimulant use disorder	7676	676	1.37 (1.22, 1.53)	2577.7 (2559.7, 2595.8)	<0.001	1.7 (M)

CI indicates confidence interval; H, high; HR, hazard ratios; L, low; M, medium; NA, not applicable; RMST, restricted mean survival time.

Limitations

While the study provides valuable insights, certain limitations must be acknowledged. The inclusion of the sample required one outpatient diagnosis at a minimum, and StSUD was not compared with specific SUDs, given the high rates of polysubstance use in the addiction population, which limits direct comparison between substances. In addition, the databank captures a preindex on 90 days, requiring less history, allowing the capture of more patients and having less selection bias while this parameter is relatively high across both cohorts. Furthermore, despite propensity score matching analysis, residual confounding persisted, including higher rates of different substance use in the StSUD group. On the other hand, tobacco use was higher in the control group, which raises the possibility that our study underestimates the cardiac harms of stimulants. Such limitations are inherent to this type of study design, and we believe our numerous analyses being aligned across many outcomes inspires confidence in our results. Finally, the MACE data from a decade ago may not be reflective of the evolving landscape of increasing illicit stimulant potency and toxicity.

CONCLUSIONS

Ours is the first study to examine stimulant-associated cardiotoxicity in people with StSUD as compared with people with nonstimulant SUDs. Those with SUDs face a 37% higher risk of MACE and a 23% higher risk of death. The heightened risk or adverse cardiac outcomes among those with StSUD in an already vulnerable population of people with SUDs can inform the development of screening and treatment guidelines tailored to specifically address cardiovascular complications arising in this population. An accelerated and sustained research effort is required to provide the much-needed evidence base to guide such public health initiatives.

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REFERENCES

1. Canton H. *United Nations Office on drugs and crime—UNODC The Europa Directory of International Organizations 2021*. Routledge; 2021:240–244.
2. SAMHSA. Results from the 2022 National Survey on Drug Use and Health: summary of national findings. *NSDUH Series H-48, HHS Publication No(SMA) 14-4863*. 2022:1-143.
3. Minhas AMK, Kewcharoen J, Hall ME, et al. Temporal trends in substance use and cardiovascular disease–related mortality in the United States. *J Am Heart Assoc*. 2024;13:e030969.
4. Gagnon LR, Sadasivan C, Perera K, et al. Cardiac complications of common drugs of abuse: pharmacology, toxicology, and management. *Can J Cardiol*. 2022;38:1331–1341.
5. Mehta A, Patel BM. Long-acting opioids and cardiovascular diseases: help or hindrance! *Vascul Pharmacol*. 2023;149:107144.
6. Drake LR, Scott PJ. DARK classics in chemical neuroscience: cocaine. *ACS Chem Neurosci*. 2018;9:2358–2372.
7. Manja V, Nrusimha A, Gao Y, et al. Methamphetamine-associated heart failure: a systematic review of observational studies. *Heart*. 2023;109:168–177.
8. Goyal H, Awad HH, Ghali JK. Role of cannabis in cardiovascular disorders. *J Thorac Dis*. 2017;9:2079.
9. Han B, Jones CM, Einstein EB, et al. Use of medications for alcohol use disorder in the US: results from the 2019 National Survey on Drug Use and Health. *JAMA Psychiatry*. 2021;78:922–924.
10. Zhao SX, Deluna A, Kelsey K, et al. Socioeconomic burden of rising methamphetamine-associated heart failure hospitalizations in California from 2008 to 2018. *Circ Cardiovasc Qual Outcomes*. 2021;14:e007638.
11. Citaristi I. *United Nations Office on Drugs and Crime—UNODC The Europa Directory of International Organizations 2022*. Routledge; 2022:248–252.
12. Das LT, Kutscher E, editors. Stimulant use disorders in the United States—is another epidemic on the horizon? JAMA Health Forum. 2020. American Medical Association.
13. Davis JD, Bepo L, Suen LW, et al. Implementing heart plus: design and early results of a novel comanagement clinic for patients with stimulant-associated cardiomyopathy. *J Card Fail*. 2024;30:869–876.
14. Doe J, Smith A, Johnson M. Understanding substance use disorders: social determinants and health outcomes. *J Sub Abuse Res*. 2022;45:123–140.
15. Brown S, Garcia L, Lee K. Structural racism, access to medical care, and health equity in substance use disorder populations. *Health Equity Soc Determ*. 2024;12:210–225.
16. Bosco E, Hsueh L, McConeghy KW, et al. Major adverse cardiovascular event definitions used in observational analysis of administrative databases: a systematic review. *BMC Med Res Methodol*. 2021;21:1–18.
17. Jackson M, Gombar S, Manickam R, et al. Testing an informatics consulting service for systematic bias using negative control reference sets. 2024.
18. Benchimol EI, Smeeth L, Guttmann A, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. *PLoS Med*. 2015;12:e1001885.
19. Heianza Y, Ma W, Manson JE, et al. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. *J Am Heart Assoc*. 2017;6:e004947.
20. Callahan A, Gombar S, Cahan EM, et al. Using aggregate patient data at the bedside via an on-demand consultation service. *NEJM Catal Innov Care Deliv*. 2021;2.
21. VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. *Ann Intern Med*. 2017;167:268–274.
22. Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med Care*. 2005;43:1130–1139.
23. Schwarzbach V, Lenk K, Laufs U. Methamphetamine-related cardiovascular diseases. *ESC Heart Fail*. 2020;7:407–414.