JACC: ADVANCES VOL. 2, NO. 8, 2023

ORIGINAL RESEARCH

Substance Use in Pregnancy and its Association With Cardiovascular Events

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ABSTRACT

BACKGROUND Substance use and cardiovascular (CV) events are increasing among pregnant women in the United States, but association between substance use in pregnancy and CV events remains unknown.

OBJECTIVES The purpose of this study was to examine the association between substance use and acute CV events in pregnancy.

METHODS We identified all women with a delivery hospitalization between 2004 and 2018 in the Nationwide Inpatient Sample, stratified on the presence or absence of substance use. The primary outcome was any acute CV event, defined as the presence of: acute myocardial infarction, stroke, arrhythmia, endocarditis, acute cardiomyopathy or heart failure, or cardiac arrest. Secondary outcomes were individual acute CV events, major adverse cardiac events, and maternal mortality. The association between substance use and outcomes were examined using multivariable logistical regression.

RESULTS A total of 60,014,368 delivery hospitalizations occurred from 2004 to 2018, with substance use complicating 955,531 (1.6%) deliveries. Substance use was independently associated with CV events (adjusted odds ratio [aOR]: 1.61; 95% CI: 1.53-1.70; $P < 0.001$), major adverse cardiac events (aOR: 1.53; 95% CI: 1.46-1.61; $P < 0.001$), and maternal mortality (aOR: 2.65; 95% CI: 2.15-3.25; $P < 0.001$) during delivery hospitalization. All individual substances had an increased association with CV events; however, amphetamine/methamphetamine had the strongest association (aOR: 2.71; 95% CI: 2.35-3.12; $P < 0.001$). All substances other than cocaine and cannabis had a significant association with maternal death.

CONCLUSIONS Substance use has a strong association with acute CV events and maternal mortality during hospitalization for delivery and women with substance use warrant increased surveillance for CV events during this time. (JACC Adv 2023;2:100619) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

The prevalence of substance use continues to increase in the United States and is a public health crisis due to its profound impact on morbidity and mortality.[1,2] The 2020 National Survey on Drug Use and Health reported that 1 in 2 survey respondents over the age of 12 used alcohol, and 1 in 5 used an illicit drug.[1] Similar increasing trends of substance use are reported amongst pregnant women;

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received February 23, 2023; revised manuscript received July 6, 2023, accepted July 17, 2023.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2023.100619

ABBREVIATIONS AND ACRONYMS

AMI = acute myocardial infarction

aOR = adjusted odds ratio

CM = cardiomyopathy

CV = cardiovascular

HF = heart failure

ICD-9-CM = International Classification of Diseases-9th Revision-Clinical Modification

ICD-10-CM = International Classification of Diseases-10th Revision-Clinical Modification

MACE = major adverse cardiac event(s)

NIS = National Inpatient Sample

PPCM = peripartum cardiomyopathy

with 1 in 6 pregnant women aged 15 to 44 reporting use illicit drugs or alcohol within the last 30 days.[1]

In the general population, substance use is well known to increase the risk of cardiovascular (CV) events due to increased oxidative stress, endothelial dysfunction, a hyperadrenergic state, shared risk factors such as tobacco use, and direct toxic effects of the substances.[3-5] The association of substance use and CV events in pregnancy, however, is not well defined, with prior reports focused on limited substances and limited CV outcomes.[6,7] The hemodynamic changes of pregnancy alone result in a unique cardiac stress due to the high volume, high output cardiac state, which can predispose pregnant women to adverse CV events, but concurrent substance use has the potential to increase the risk for such adverse events further.[8,9]

Given the increasing prevalence of substance use among pregnant women, we sought to determine the association between substance use and CV events in pregnancy during delivery hospitalization, including assessment of temporal trends. We hypothesize that substance use is associated with an increased risk of maternal CV events, which may contribute to the increasing maternal morbidity and mortality in the United States.

METHODS

DATA SOURCE. The National Inpatient Sample (NIS) of the Healthcare Cost and Utilization Project, sponsored by the Agency for Healthcare Research and Quality, is the largest publicly available all-payer inpatient health care database in the United States, providing annual information on nearly 8 million inpatient stays.[10] Before 2012, the NIS randomly sampled 20% of hospitals for all inpatient discharges; however in 2012, the NIS began systematically sampling 20% of discharges from all hospitals. NIS discharge level sampling weights based on the sampling schemes are used to obtain national estimates.[11]

Given that this study period included the switch (on October 1, 2015) from International Classification of Diseases-9th Revision-Clinical Modification (ICD-9-CM) to International Classification of Diseases-10th Revision-Clinical Modification (ICD-10-CM) coding, billing data from the NIS in the form of both ICD-9-CM and ICD10-CM codes were included in the analysis.[12] The ICD-9-CM codes were translated to ICD-10-CM codes with an algorithm; using the publicly available General Equivalence Mapping provided by the Centers for Medicare and Medicaid Services and the National Center for health statistics.[13,14]

Since the NIS database contains publicly available deidentified information, this study is exempt from review by the institutional review board at University of Arizona. Our study conforms to the Data Use Agreement for the Nationwide Databases from the Healthcare Cost and Utilization Project.

STUDY POPULATION. We identified all women with a delivery hospitalization between January 2004 and December 2018 using ICD-9-CM and ICD-10-CM diagnosis codes related to delivery, based on previously published protocols.[15,16] Hospital level discharge weights provided by the NIS were used to obtain national estimates of pregnancy-related delivery hospitalizations (n = 60,014,368).

We identified maternal substance use by using ICD-9-CM and ICD-10-CM codes for current substance use, abuse, dependence, or poisoning by amphetamine/methamphetamine, cocaine, opioid, cannabis, alcohol, or polysubstance use. There is not an ICD-9-CM or ICD-10-CM code specific for methamphetamine use; however, ICD-9-CM and ICD-10-CM codes associated with psychostimulant use have been shown to be highly predictive of methamphetamine use and were used as a surrogate marker for methamphetamine use in our study.[17] Hospitalizations were defined as substance use related if a diagnosis code of substance use was listed in any diagnosis field. Polysubstance use does not have a specific ICD-10-CM code, so for 2015 to 2018 polysubstance use was defined as the presence of 2 or more diagnosis codes for different substances of use in any diagnosis field. All substance use variables were binary.

Patient demographics extracted include: age, race, hospital region, hospital location (urban vs rural), household income quartile according to zip code, expected primary payer, and patient comorbidity conditions. Each discharge record included information on up to 30 diagnoses per patient (15 between 2004 and 2008, 25 between 2009 and 2013, and 30 between 2014 and 2018). We used ICD-9-CM and ICD-10-CM diagnosis codes to identify the comorbidity conditions recorded during the delivery hospitalization. Supplemental Table 1 includes a complete list of ICD-9-CM and ICD-10-CM codes utilized.

OUTCOMES MEASURED. The primary outcome measured was any CV event which included acute myocardial infarction (AMI), stroke, arrhythmia, endocarditis, any acute cardiomyopathy (CM) or heart failure (HF), or cardiac arrest. Secondary outcomes consisted of any of the individual CV events,

maternal mortality, and major adverse cardiac events (MACE). For this study, we used the same definition of MACE as previously published research from the NIS focusing on CV disease in pregnancy.[18] There, MACE was comprised of any of the following ICD-9-CM or ICD-10-CM coded diagnoses: in-hospital death, AMI, HF, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery. Each outcome was identified by ICD-9-CM and ICD-10-CM coding (Supplemental Table 1). Due to the relatively low prevalence of these events and the variability within how these diagnoses are coded, peripartum cardiomyopathy (PPCM), acute CM, and acute HF were grouped together into a group titled "acute CM/HF."

STATISTICAL ANALYSIS. Patient demographic, clinical risk factors, hospital characteristics, and clinical outcomes, for those with and without substance use, were reported as means (95% CI) for continuous variables and percentages or cases per 100,000 delivery hospitalizations for categorical variables. These descriptive statistics were further stratified by time (2004-2007, 2008-2011, 2012-2014, and 2015-2018). Univariable linear regression was used to compare the continuous variables, while chi-squared analyses were used to compare the categorical variables. Odds ratios (95% CI) were calculated using a multivariable logistic regression model fit to each CV outcome. All regression models were adjusted for sociodemographic, CV risk factors, and pre-existing conditions. For our primary and secondary outcomes, comparisons were made between pregnancies without substance use and pregnancies with substance use, either as a whole or by individual substance of use. Pregnancies with more than 1 substance of use were classified as polysubstance. Pregnancies without substance use were used as the reference group for each analysis. As a secondary analysis, trends in the prevalence of CV risk factors and comorbidities over time were analyzed using logistic regression models fit with categorized year, substance use, and their interaction. The *P* value from the interaction term was reported to determine whether trends differed between pregnancies with substance use and pregnancies without. All analyses were conducted following the implementation of population discharge weight provided by Healthcare Cost and Utilization Project. All *P* values were 2-sided and $P < 0.05$ was considered statistically significant. All analyses were conducted using STATA version 14 (STATA Corp).

TABLE 1 Demographics at Delivery Admission: 2004 to 2018

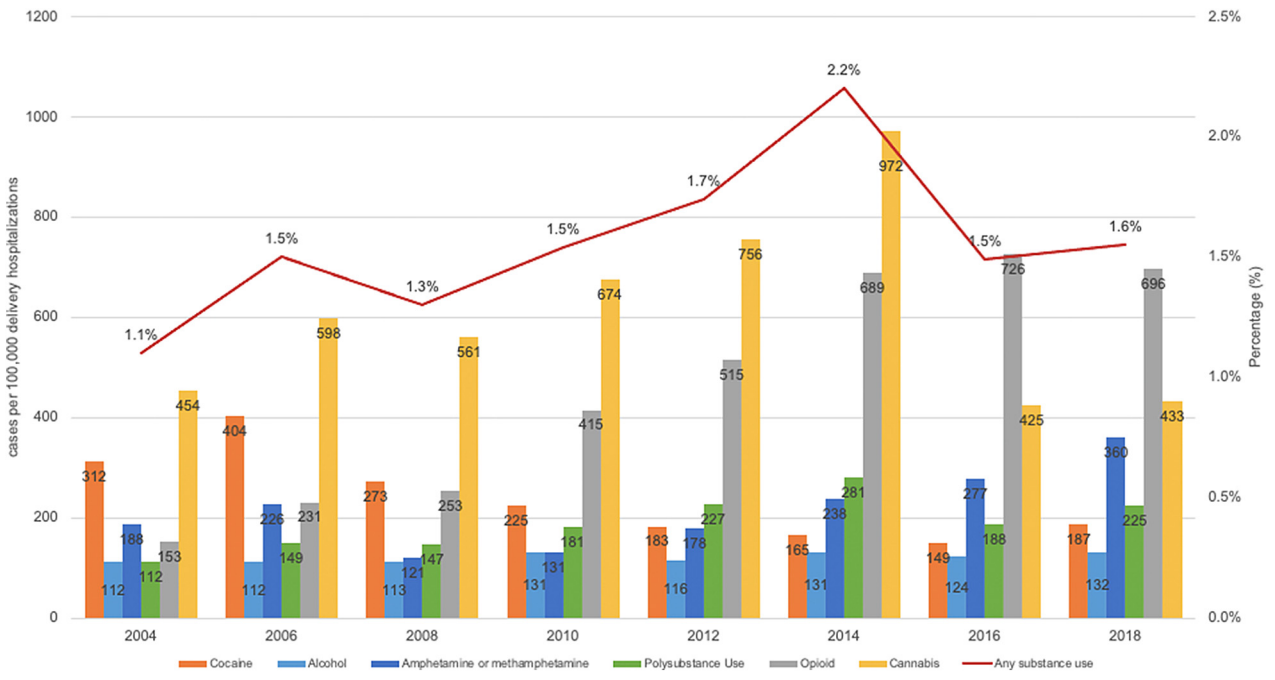
	Pregnancies Without Substance Use (n = 59,058,837)	Pregnancies With Substance Use (n = 955,531)	*P* Value
Sociodemographics			
Age, y	28.2 (28.1-28.2)	27.8 (27.7-27.9)	<0.0001
Race			<0.0001
White	45.6	53.9	
Black	12.2	19.3	
Hispanic	19.6	10.2	
Other	22.5	16.6	
Hospital region			0.1197
Northeast	16.3	16.9	
Midwest	21.2	22.5	
South	38.1	36.4	
West	24.4	24.3	
Hospital location—urban	89.5	87.0	<0.0001
Income quartile			<0.0001
1	27.5	42.6	
2	25.2	27.2	
3	24.7	19.8	
4	22.6	10.4	
Payer status %			<0.0001
Medicare	0.9	3.4	
Medicaid	42.1	74.7	
Private	51.2	14.8	
Self-pay	3.0	4.9	
Other	2.9	2.3	
Cardiovascular risk factors			
Obesity	5.1	6.4	<0.0001
Tobacco use	5.4	46.9	<0.0001
Chronic hypertension	2.5	5.3	<0.0001
Pregestational diabetes	1.2	2.0	<0.0001
Hyperlipidemia	0.3	0.8	<0.0001
Family history of cardiovascular disease	0.6	1.0	<0.0001
Any cardiovascular disease risk factor[a]	13.0	53.1	<0.0001
Pre-existing conditions			
Chronic renal disease	0.3	0.7	<0.0001
Congenital heart disease	0.1	0.2	<0.0001
Prior stroke	0.1	0.3	<0.0001
Chronic anemia	11.6	18.3	<0.0001
Depression	1.9	9.0	<0.0001
Anxiety	1.6	8.1	<0.0001
Substance use			
Amphetamine or methamphetamine	-	13.1	-
Cocaine	-	15.1	-
Opioid	-	28.6	-
Cannabis	-	39.8	-
Alcohol	-	9.3	-
Polysubstance use	-	12.2	-

Values are weighted mean (95% CI) or %. [a]Any cardiovascular disease risk factors = obesity, tobacco use, chronic hypertension, pregestational diabetes, hyperlipidemia, family history of cardiovascular disease.

RESULTS

A total of 60,014,368 delivery hospitalizations occurred from 2004 to 2018, with substance use complicating 955,531 (1.6%) deliveries. The baseline

FIGURE 1 Trend of Substance Use per 100,000 Delivery Hospitalizations and Percentage of all Delivery Hospitalizations Complicated by Substance Use: 2004 to 2018



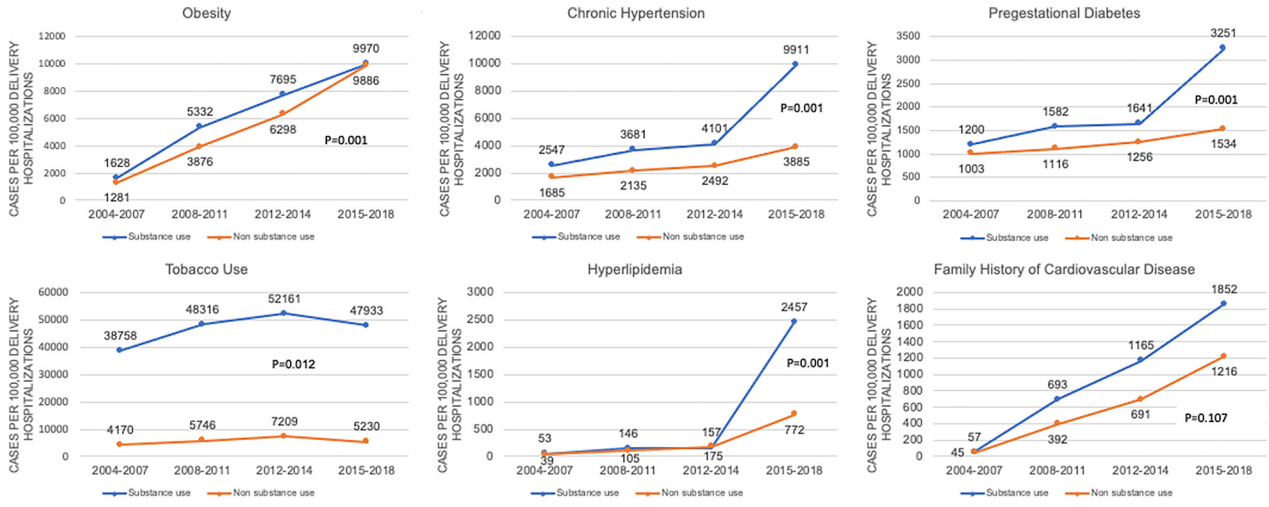
Bar/line graph depicting the prevalence of individual substances and the total percentage of substance use among all pregnant women at the time of delivery hospitalization from 2004 to 2018.

characteristics of delivery hospitalizations in those with and without substance use are shown in Table 1. When compared with deliveries without substance use, deliveries with substance use occurred in women who were younger (27.8 years vs 28.2 years; $P < 0.0001$), White (substance use: 53.9% vs no substance use: 45.6%; $P < 0.0001$) or Black (substance use: 19.3% vs no substance use: 12.3%; $P < 0.0001$), lowest income quartile (substance use: 42.6% vs no substance use: 27.5%; $P < 0.0001$), and using public health insurance (substance use: 78.1% vs no substance use: 42.9%; $P < 0.0001$). Cannabis and opioids were the most common substances reported (n = 380,312 [39.8%] and n = 273,234 [28.6%], respectively). Deliveries complicated by substance use increased over this 14-year period, from 1,126 per 100,000 deliveries in 2004 to 1,547 per 100,000 in 2018, peaking at 2,187 per 100,000 in 2014. This increasing trend persisted even when cannabis use, the most commonly used substance, was excluded from deliveries complicated by substance use, increasing from 769 per 100,000 deliveries in 2004 to 1, 225 per 100,000 in 2018, peaking at 1,333 per 100,000 in 2014 (data not shown). There was an increase in the use of amphetamine/methamphetamine, opioids, alcohol, and polysubstance use from 2004 to 2018. Cocaine use decreased from 2004 to 2018, while cannabis use increased from 2004 to 2015 and then decreased to 2004 levels by 2018. (Figure 1).

The prevalence of CV risk factors increased over time within the pregnant population at delivery hospitalization, irrespective of substance use (Figure 2). The prevalence of any CV risk factor was highest amongst deliveries with substance use compared with deliveries without substance use (substance use: 53.1% vs no substance use: 13.0%; $P < 0.0001$). Pre-existing medical conditions consisting of chronic renal disease, prior stroke, chronic anemia, depression, anxiety, and congenital heart disease also increased over time for both the deliveries with and without substance use (Figure 3).

Delivery hospitalizations with substance use were associated with a greater risk of any CV events after adjustment for age, race, traditional CV risk factors, and pre-existing medical conditions, compared to those without substance use (Table 2, Figure 4). The association between delivery hospitalizations with substance use and any CV event was strengthened with the exclusion of cannabis from the substance use

FIGURE 2 **Trends in CV Risk Factors at Delivery Hospitalization by Presence or Absence of Substance Use**



Line graphs comparing the prevalence of cardiovascular risk factors among pregnant women with and without substance use. *P* value represents whether trends differed between substance use and nonsubstance use population. CV = cardiovascular.

population (adjusted odds ratio [aOR]: 1.71; 95% CI: 1.62 to 1.80; $P < 0.001$) (data not shown). The incidence of any CV event increased over time, with an over 4-fold increase for deliveries with substance use and an over 2-fold increase for deliveries without substance use.

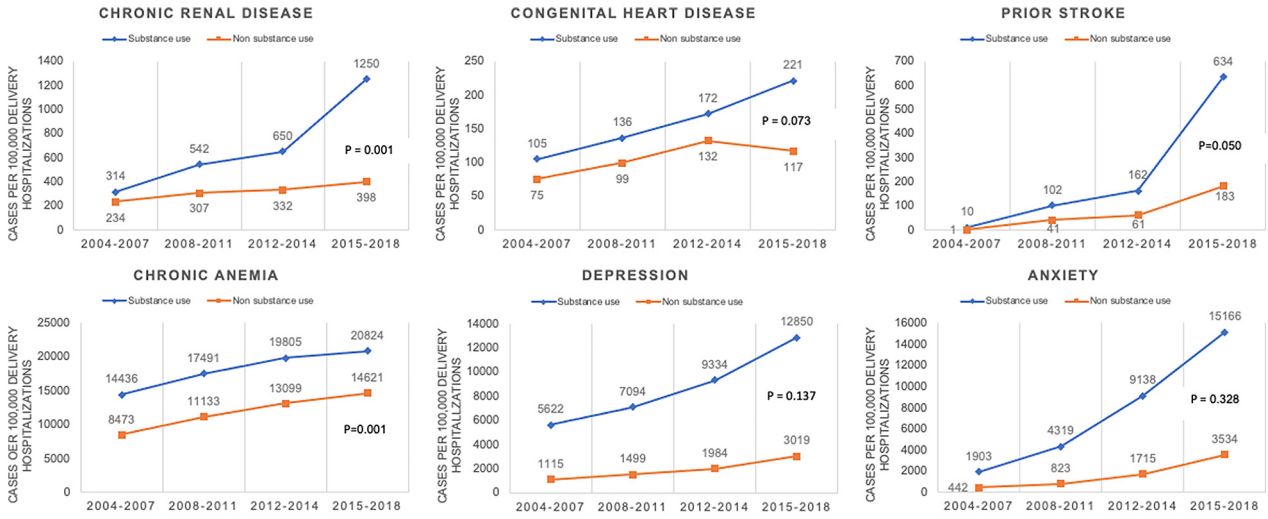
The type and incidence of CV events varied by the substance of use (Table 3). Amphetamine/methamphetamine use was associated with any CV event more than other substances (aOR: 2.71; 95% CI: 2.35 to 3.12; $P < 0.001$). Arrhythmias were the most common CV event at delivery hospitalization for every individual substance, with the exception of amphetamine/methamphetamine, which was most frequently associated with acute CM/HF (739 per 100,000 delivery hospitalizations).

Among the individual substances, amphetamine/methamphetamine was associated with the greatest risk of any acute CM/HF (aOR: 9.06; 95% CI: 7.52-10.93; $P < 0.001$), AMI (aOR: 7.57; 95% CI: 4.12-13.92; $P < 0.001$), cardiac arrest (aOR: 7.29; 95% CI: 4.19-12.68; $P < 0.001$), and maternal mortality (aOR: 3.20; 95% CI: 1.59-6.41; $P < 0.01$). Opioid use had the strongest association with endocarditis (aOR: 24.77; 95% CI: 16.55-37.09; $P < 0.001$), alcohol use had the strongest association with arrhythmia (aOR: 1.68; 95% CI: 1.48-1.91; $P < 0.001$), and cocaine use had the strongest association with stroke (aOR: 3.75; 95% CI: 2.14-6.54; $P < 0.001$). All substances were strongly associated with MACE, and all substances, except cocaine and cannabis, were associated with increased maternal mortality.

DISCUSSION

Using this large sample of the U.S. population, we have demonstrated a significant association between substance use and acute CV events and maternal mortality during delivery hospitalization. All substances—amphetamine/methamphetamine, cocaine, opioid, cannabis, and alcohol—were associated with an increased risk of acute CV events. The risk was greatest in those deliveries with documented amphetamine/methamphetamine use, with a 9-fold increased risk of acute CM/HF and a 7-fold increased risk of AMI and cardiac arrest. The increase in substance use from 2004 to 2018 parallels the increase in maternal CV events seen over the same time period. These findings have important public health implications, given that CV disease is the leading cause of maternal mortality, accounting for 1 in 4 pregnancy-related deaths[19] and substance use accounts for at least 1 in every 10 pregnancy-related deaths.[20] To our knowledge, this is the first study examining the association between all substance use and acute CV outcomes and maternal mortality for delivery hospitalizations in the United States.

FIGURE 3 Trends in Comorbid Conditions at Delivery Hospitalization by Presence or Absence of Substance Use



Line graphs comparing the prevalence of medical comorbid conditions among pregnant women with and without substance use. *P* value represents whether trends differed between substance use and nonsubstance use population.

Prior studies have attempted to examine this association but were limited in terms of documentation of CV outcomes or were specific to a single substance use.[6-8,21] In an older retrospective analysis using the NIS, an association between opioid, cocaine, or methamphetamine use and AMI or cardiac arrest during any pregnancy-related hospital admission was demonstrated.[7] However, other CV events and other substances were excluded from this analysis. The California Pregnancy-Associated Review examined maternal mortality from 2002 to 2006 and similarly demonstrated that substance use was a risk factor for pregnancy-related CV mortality but were unable to examine any other CV endpoints.[6]

The association between substance use and acute CV events in the general population has been well documented.[4,22-26] Methamphetamine activates the sympathetic nervous system, increasing heart rate, blood pressure, cardiac contractility, and myocardial oxygen demand, which ultimately increases the cardiac and metabolic workload. Additionally, methamphetamine may induce vasospasm and cause structural and electrical remodeling of the heart.[22] These pathways may contribute to methamphetamine's association with AMI, stroke, CM/HF, arrhythmia, and death in the general population.[4,22] Similarly, we demonstrated that the use of amphetamine/methamphetamine among women at delivery was associated with a greater risk of AMI, stroke, CM/HF, arrhythmia, and cardiac arrest.

Cocaine is known to stimulate the sympathetic system, induce vasospasm and alter electrical signaling. In the general population, cocaine is an established risk factor for AMI, stroke, arrhythmia, CM/HF, and cardiac arrest.[3,23] For pregnant women with reported cocaine use at delivery, we found an association with AMI, stroke, CM/HF, but not arrhythmias or cardiac arrest.

Opioid use alters cardiac physiology primarily through abnormal cardiac signaling by modifying electrical conduction and contractility, with a strong association with AMI, stroke, arrhythmia, CM/HF, cardiac arrest, and mortality.[27-29] Only an increased association with AMI, CM/HF, and cardiac arrest were increased in women who abused opioids at delivery hospitalization. Opioids, as well as other substances with an intravenous route of administration, such as methamphetamine and cocaine, have an established association with endocarditis.[30] This was similarly confirmed amongst pregnant women with opioid, cocaine, or methamphetamine use at delivery.

Alcohol use has routinely been associated with arrhythmias, CM/HF, AMI, and hemorrhagic stroke in the general population. Similar associations, with the exception of AMI, were confirmed in our study for women with alcohol use at delivery hospitalization.

Cannabis stimulates sympathetic activity and inhibits parasympathetic activity, primarily via the tetrahydrocannabinol component of cannabis, while also induces myocyte cell death, triggers endothelial

TABLE 2 Trends in CV Events Cases per 100,000 Delivery Hospitalizations Based on Presence or Absence of Substance Use

	2004-2007			2008-2011			2012-2014			2015-2018		
	No Substance Use (n = 17,016,721)	Substance Use (n = 222,741)	*P* Value	No Substance Use (n = 15,673,606)	Substance Use (n = 224,840)	*P* Value	No Substance Use (n = 11,433,984)	Substance Use (n = 229,110)	*P* Value	No Substance Use (n = 14,934,526)	Substance Use (n = 278,840)	*P* Value
Any CV event[a]	296.1	599.3	<0.0001	374.5	748.7	<0.0001	437.7	979.9	<0.0001	664.5	2,442.3	<0.0001
AMI	2.9	19.4	<0.0001	3.0	12.8	0.0002	3.7	10.9	0.0146	24.6	147.0	<0.0001
Stroke	7.6	27.0	<0.0001	8.8	32.0	<0.0001	10.8	28.4	0.0004	27.7	177.5	<0.0001
Arrhythmia	242.3	337.5	<0.0001	313.0	526.3	<0.0001	369.5	674.4	<0.0001	525.8	1,599.5	<0.0001
Acute CM/HF[b]	43.1	184.6	<0.0001	52.7	176.4	<0.0001	59.7	244.4	<0.0001	131.9	672.4	<0.0001
Endocarditis	1.4	27.7	< 0.0001	0.9	33.0	<0.0001	0.8	52.4	<0.0001	4.5	109.4	<0.0001
Cardiac arrest	6.5	30.7	<0.0001	7.4	17.4	0.0143	8.1	26.2	<0.0001	13.8	80.7	<0.0001
MACE[c]	348.3	678.4	<0.0001	429.9	871.5	<0.0001	494.2	1,047.5	<0.0001	825.1	2,930.0	<0.0001

Values are %. [a]Any CV event: AMI, stroke, arrhythmia, PPCM, HF, CM, endocarditis, cardiac arrest. [b]Acute CM/HF: PPCM, CM, HF. [c]MACE: in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery.

AMI = acute myocardial infarction; CM = cardiomyopathy; CV = cardiovascular; HF = heart failure; MACE = Major adverse cardiovascular event.

dysfunction, and promotes vascular smooth muscle hypertrophy.[25] An increasing association between cannabis use and CV events has been noted, and may correlate with increasing concentrations of tetrahydrocannabinol in cannabis products in recent years.[25] Among pregnant women at delivery hospitalization, cannabis use had an increased association with AMI, stroke, and arrhythmia.

We have demonstrated strong associations between substance use and acute CV events in this pregnant population at the time of delivery. These women are younger than the general population and are traditionally considered to be at low risk for acute CV events.[23,25,27-37] Pregnancy, in and of itself, increases the risk of CV events due to the normal pregnancy-related changes in CV hemodynamics and function,[8,9] however we have demonstrated that substance use in pregnancy increases that risk further. Ultimately, there are no studies to date directly comparing the pathophysiologic effect of substance use on the CV system in the pregnant and nonpregnant state, but it is possible that the combined, additive CV hemodynamic changes from pregnancy in addition to substance use may exceed what the CV system can tolerate and result in an increased susceptibility for acute CV events amongst substance user who are pregnant.[38-40] Further research and investigation into the role of pregnancy hemodynamics in the development of CV events among the pregnant women with substance use is warranted.

Traditional CV risk factors including obesity, tobacco use, chronic hypertension, pregestational diabetes, hyperlipidemia, and family history of CV disease, are rising among pregnant women but are more prevalent amongst women with substance use. This alone, however, cannot explain the increased association of CV events among pregnancies with substance use because this association persists even after adjustment for these CV risk factors.

Social determinants of health—such as unstable housing, lack of transportation, food insecurity, and racism—have a strong association with maternal mortality and CV disease.[41] As we highlighted in our study, there were significant differences in the sociodemographic data among pregnancies with and pregnancies without substance use. Although we adjusted for these variations in our regression models, it is important to acknowledge the additive role social determinants of health may play in CV disease and maternal mortality specifically for women with substance use.

Two substances demonstrated an association with acute CV events but did not demonstrate an association with maternal mortality, cocaine, and cannabis. Cocaine use has previously been associated with an increased risk of maternal mortality, so our lack of association was surprising.[42] Our finding of no association may be due to the decreasing number of pregnant women with cocaine use over our study timeframe, or related to dose/

FIGURE 4 Adjusted OR for CV Events Based on Type of Substance Use

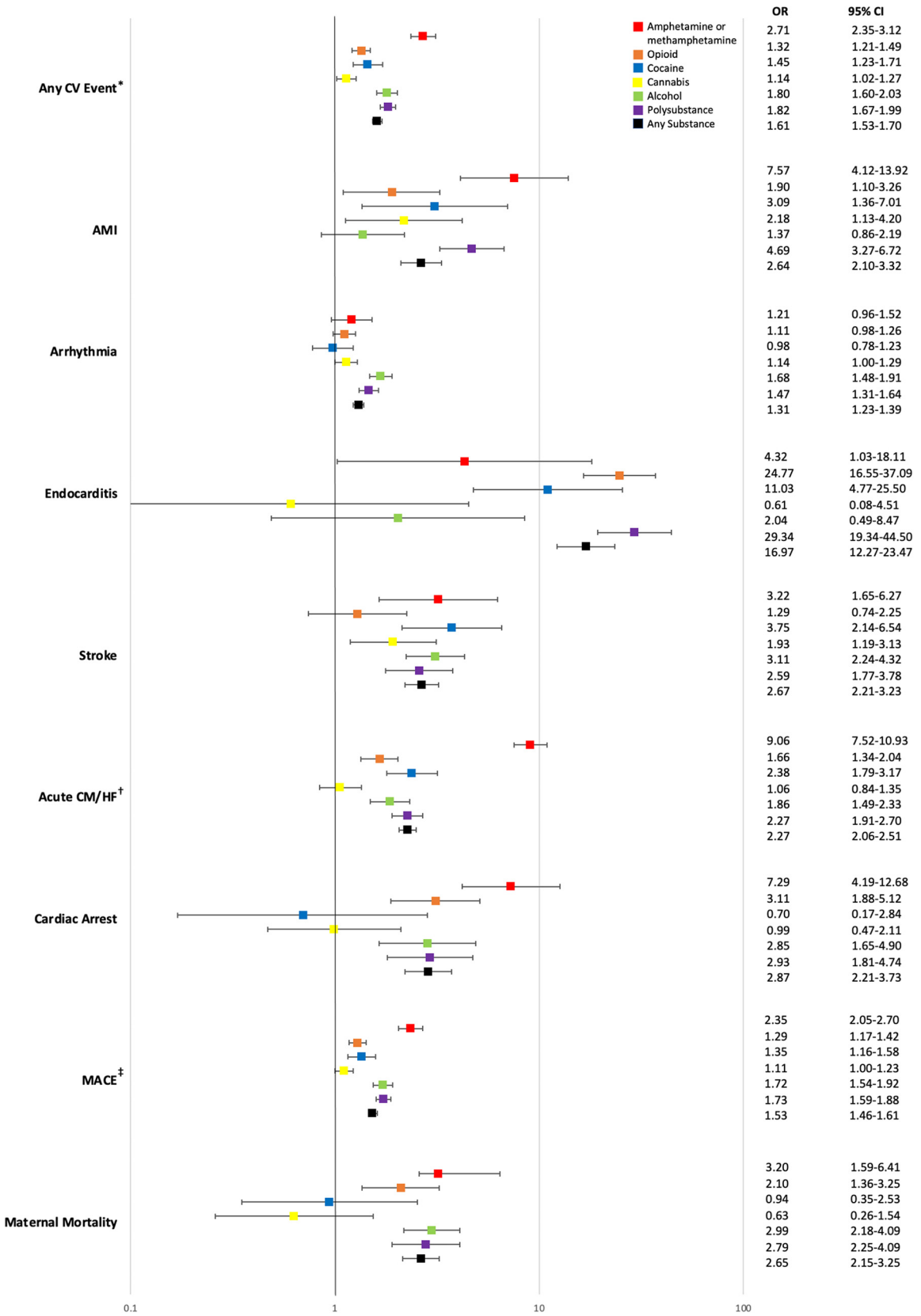


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TABLE 3 Cardiovascular Events in Cases per 100,000 Delivery Hospitalizations Based on Type of Substance Use: 2004 to 2018

	No Substance Use (n = 59,058,837)	Amphetamine or Methamphetamine (n = 125,260)	Cocaine (n = 144,621)	Opioid (n = 273,234)	Cannabis (n = 380,312)	Alcohol (n = 89,257)	Polysubstance Use (n = 116,559)
Any CV event[a]	437.5	1,427.6	1,142.3	1,265.5	738.5	3,888.3	1,253.6
AMI	8.6	66.6	54.7	45.3	28.6	184.4	81.8
Stroke	13.6	62.6	88.1	46.9	33.9	287.4	63.9
Arrhythmia	357.4	595.7	628.3	826.4	539.9	2,944.5	740.7
Acute CM/HF[b]	71.3	739.2	339.0	253.8	171.2	874.9	310.8
Endocarditis	1.9	72.0	101.9	153.3	6.5	39.3	141.3
Cardiac Arrest	8.9	65.0	36.9	54.0	14.4	100.3	38.7
MACE[c]	518.8	1,508.5	1,286.3	1,466.7	866.2	4,850.9	1,401.4

Values are %. [a]Any CV event: acute myocardial infarction, stroke, arrhythmia, peripartum cardiomyopathy, heart failure, cardiomyopathy, endocarditis, cardiac arrest. [b]Acute CM/HF: peripartum cardiomyopathy, cardiomyopathy, heart failure. [c]MACE: in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery.

AMI = acute myocardial infarction; CM = cardiomyopathy; CV = cardiovascular; HF = heart failure; MACE = major adverse cardiovascular events.

duration of use, which we were unable to assess in the NIS. For cannabis, there is a lack of understanding regarding why it does not have an association with maternal mortality; however, our findings are consistent with prior research, demonstrating no association.[43]

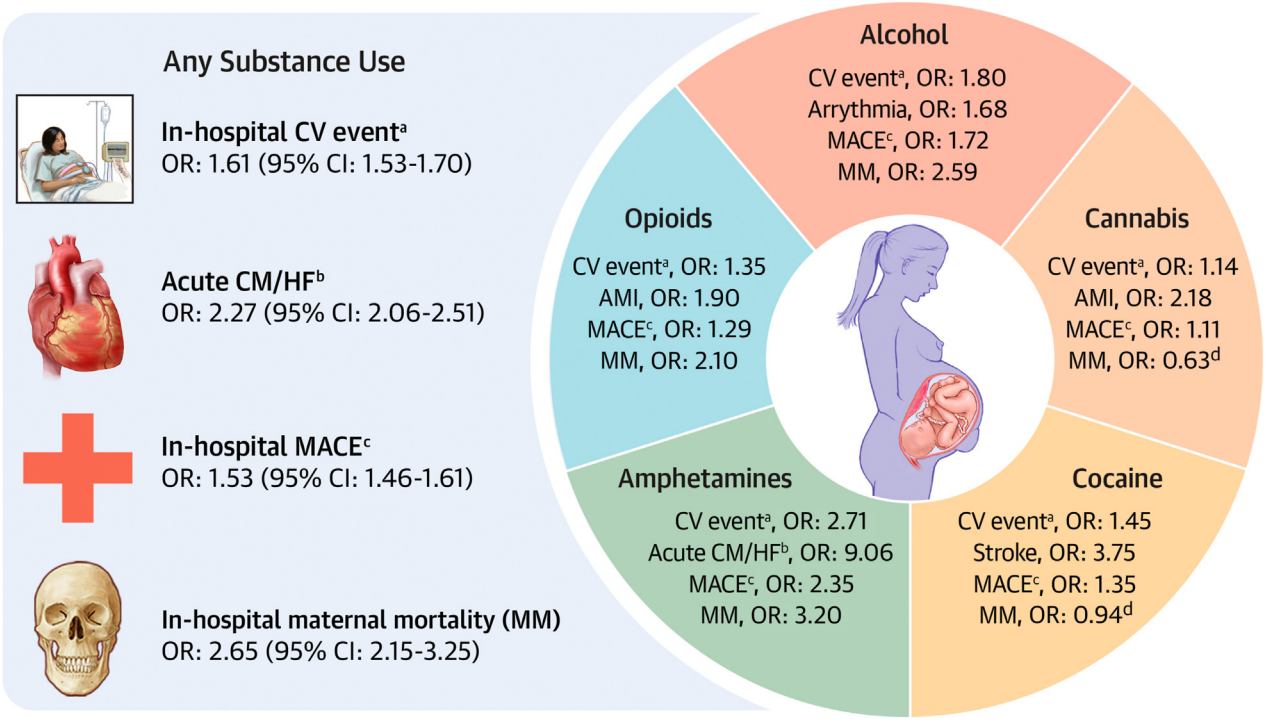
Our findings highlight the need for increased surveillance of pregnant women with substance use (**Central Illustration**). As the prevalence of substance use increases, it is likely that maternal CV events, and maternal, fetal, and neonatal morbidity and mortality will continue to increase as well. Prenatal care for women with substance use should include high risk pregnancy specialists and cardiologists to help identify and minimize these adverse outcomes, with a multidisciplinary cardio-obstetrics approach recommended to decrease cardiac complications.[44,45] Awareness of the risk of acute CV events is critical because an estimated one-quarter or more of all maternal deaths could be prevented if CV pathology was considered in the differential diagnosis by treating health care providers.[6,46] For the wellbeing of pregnant women and their children, substance use needs to be considered an independent risk factor for CV events in pregnancy.

STUDY LIMITATIONS. There are several limitations in our analysis. Inherent to using large administrative databases, coding errors are a potential source for bias with underreporting of diagnoses, or a lack of specificity of diagnoses. Additionally, our study spans the transition from ICD-9-CM to the more specific ICD-10-CM coding system, so temporal changes in coding, make the accuracy of evaluating trends difficult. In addition, for substance use coding, women with multiple diagnoses of substance use are included in the analysis for each substance for which they have a diagnosis. This can skew the prevalence and odds ratio of CV events for each substance since there may be influences from other substances confounding the result. It was not possible to assess the impact of dose, duration of use, method of use, or timing of use for any substance and its association with CV events. Coding for vaping was not introduced until 2019, so it was not possible to examine the effect of vaping on maternal CV events. Using the NIS, we were unable to differentiate hospitalizations for delivery that were complicated by CV events vs hospitalizations for CV events that prompted delivery. The findings of this study are limited to in-hospital delivery hospitalizations and did not include the

FIGURE 4 Continued

Multivariable logistical regression was fit for each cardiovascular outcome, adjusting for sociodemographics (age, race, hospital location, income quartile, payer status), cardiovascular risk factors (obesity, tobacco use, chronic hypertension, pregestational diabetes, hyperlipidemia, and family history of cardiovascular disease), and pre-existing conditions (chronic renal disease, congenital heart disease, prior stroke, chronic anemia, depression, and anxiety). [a]Any CV event: acute myocardial infarction, stroke, arrhythmia, peripartum cardiomyopathy, heart failure, cardiomyopathy, endocarditis, cardiac arrest. [b]Acute CM/HF: peripartum cardiomyopathy, cardiomyopathy, heart failure. [c]MACE: in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery. AMI = acute myocardial infarction; CM/HF = cardiomyopathy/heart failure; CV = cardiovascular; MACE = major adverse cardiac event.

CENTRAL ILLUSTRATION **Adjusted Odds of Adverse Events Associated With Substance Use During Pregnancy**



Evans K, et al. JACC Adv. 2023;2(8):100619.

Multivariable logistical regression was fit for each cardiovascular outcome, adjusting for sociodemographics (age, race, hospital location, income quartile, payer status), cardiovascular risk factors (obesity, tobacco use, chronic hypertension, pregestational diabetes, hyperlipidemia, and family history of cardiovascular disease), and pre-existing conditions (chronic renal disease, congenital heart disease, prior stroke, chronic anemia, depression, and anxiety). [a]Any CV event: acute myocardial infarction, stroke, arrhythmia, peripartum cardiomyopathy, heart failure, cardiomyopathy, endocarditis, cardiac arrest. [b]Acute CM/HF: peripartum cardiomyopathy, cardiomyopathy, heart failure. [c]MACE: in-hospital death, acute myocardial infarction, heart failure, arrhythmia, cerebrovascular events, pulmonary embolism, arterial embolism, atheroembolism, obstetric pulmonary embolism, and cardiac complications of anesthesia or other sedation in labor and delivery. [d]Odds ratio is not significant. AMI = acute myocardial infarction; CM/HF = cardiomyopathy/heart failure; CV = cardiovascular; MACE = major adverse cardiac event; OR = odds ratio.

postpartum period, where there is an established high rate of adverse CV events.[8,47-49] It should be noted that the overwhelming majority of CV related mortality can occur more than 42 days after delivery and may be seen up to 1 year postpartum.[6]

CONCLUSIONS

Substance use during pregnancy continues to rise, paralleling the rise in acute CV events associated with childbirth and maternal mortality in the United States. We have demonstrated a strong association between any substance use and acute CV events and maternal mortality during delivery hospitalization. As substance use continues to increase in pregnant women and maternal mortality continues to rise, these findings have important implications for maternal health. Further work is needed to address maternal care in this population, including an effective national policy to address this growing public health issue..

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Pregnant women with substance use at delivery hospitalization have an increased risk of acute CV events, MACEs, and maternal mortality. The pregnancy-related CV changes combined with the CV stress from substance use may explain the increased prevalence of CV events among pregnant women with substance use.

TRANSLATIONAL OUTLOOK 1: Further research is needed to evaluate the role of the pregnancy hemodynamics on the association between substance use and CV events.

TRANSLATIONAL OUTLOOK 2: Our findings support the implementation of multidisciplinary cardio-obstetric care teams for pregnant women with substance use due to their increased risk of CV events.

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KEY WORDS **cardiovascular, cardiovascular disease, maternal mortality, pregnancy, substance use**

APPENDIX **For a supplemental table, please see the online version of this paper.**