Title: Substance Use Disorders and risk of Cardiovascular and Cerebrovascular disease: Analysis of the Nationwide Inpatient Sample database

Running title: Risk of stroke and sudden cardiac death and Recreational Substance abuse

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Table 1: Demographics of SUDs amongst USA hospitalizations

Table 2: Incidence and Prevalence of CeVDs and CVDs amongst active SUDs patients

Table 3: Odds of having hospitalizations with new onset of CeVD and CVD amongst active SUDs patients

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ABSTRACT

Background: Substance use continues to be on the rise in the United States and has been linked to new onset cardiovascular (CVDs) and cerebrovascular disorders (CeVDs) leading to hospitalizations. We aimed to study the association of different subtypes of substance use disorders (SUDs) among hospitalized patients, with the different subtypes of CVDs and CeVDs, using the National Inpatient Sample (NIS) Database. Additionally, we aimed to assess the odds of hospitalizations with new onset CVDs and CeVDs among patients with different types of SUDs.

Methods: A retrospective study of the NIS database (2016-2017) using the ICD-10-CM codes was performed. The hospitalizations with a secondary diagnosis of SUDs were identified. Weighted univariate analysis using the chi-square test and multivariate survey logistic regression analysis was performed to evaluate for the incidence, prevalence, and odds of association between vascular events and SUDs.

Results: There were a total of 58,259,589 hospitalizations, out of which 21.42% had SUDs. Out of all the hospitalized patients between the age 18-50, more patients had SUDs than not (31.83%, $p< 0.0001$). This difference existed for all the different subtypes of SUDs including alcohol related disorder (42.61%), amphetamine dependence (76.17% vs 31.83%), cannabis related disorder (75.17%), cocaine related disorders (57.87%), hallucinogen related disorder (82.91%), inhalant related disorders (67.25%), opioid related disorders (52.86%), and nicotine dependence (35.72%). We found a significant association of acute ischemic stroke with amphetamine dependence (OR 1.23, 95%CI 1.14-1.33), cocaine related disorders (1.17, 1.12-1.23) and nicotine dependence (1.42, 1.40-1.43). Similarly, the association of intracerebral hemorrhage was higher with amphetamine dependence (2.58, 2.26-2.93), and cocaine related disorders (1.62, 1.46-1.79). The association of subarachnoid hemorrhage was noted to be higher with amphetamine

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dependence (1.82, 1.48-2.24) and nicotine dependence (1.47, 1.39-1.55). In terms of association of cardiovascular disorders with SUDs,the patients with myocardial infarction had higher odds of nicotine dependence (1.85, 1.83-1.87) than not, Similarly, the patients with angina pectoris were noted to have a higher association with cocaine related disorders (2.21, 1.86-2.62), and those with atrial fibrillation had a higher association alcohol related disorders (1.14, 1.11-1.17).

Conclusion:

Our study demonstrates the variability of CVD and CeVD in patients hospitalized for SUD. Findings from our study may help promote increased awareness and early management of these events. Further studies are needed to evaluate specific effects of frequency and dose on the incidence and prevalence of CVD and CeVD in patients with SUD.

Keywords: Recreational substance abuse, drug abuse, marijuana, amphetamine, acute ischemic stroke, risk factors, young adult, NIS, Stroke, Sudden Cardiac Death

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INTRODUCTION

The past few decades have seen a rise in the incidence and prevalence of cardiovascular disease concomitant with substance use disorders (SUDs) among younger adults aged 18 - 45 years of age (Andersson 2017)[1]. In the United States (US), common substances reportedly used include alcohol, tobacco, marijuana, sedatives, hallucinogens, cocaine, amphetamines, inhalants and opioids (SAMHSA, 2019)[2].

SUD comprises an estimated 6.7% of all inpatient admissions and has been associated with greater costs and longer hospitalizations relative to non-SUD admissions (Heslin, 2015)[3]. A recent epidemiological study in British Columbia, Canada found SUD to be an independent risk factor associated with a greater prevalence and incidence of cardiovascular (CV) disease on cross-sectional and longitudinal analysis respectively (Gan, 2021)[4]. Accelerated atherosclerotic cardiovascular disease (ASCVD) is broadly suggested as a mechanism for increased CV events (Mahtta, 2021)[5] in patients with SUD.

However, there is known variability in the types of CV events, depending on the use of the agent. For instance, an analysis of the National Health and Nutrition Examination Survey (NHANES) revealed a statistically significant association of non-fatal myocardial infarction with lifetime users of cocaine, when compared with non-users. The study did not reveal a significant association of ischemic stroke with cocaine users (Qureshi, 2001)[6]. We therefore sought to investigate the spectrum of CV and Cerebrovascular (CeV) events in SUD among hospitalized patients in the United States.

METHODS

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Details of Data

Data was obtained from the Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project (HCUP) Nationwide inpatient sample files between January 2016 and December 2017. The NIS is the largest publicly available all-payer inpatient care database in the United States and contains discharge-level data provided by states that participate in the HCUP (including a total of 46 in 2011). This administrative dataset contains data on approximately 8 million hospitalizations in 1,000 hospitals that were chosen to approximate a 20% stratified sample of all US community hospitals, representing more than 95% of the national population. Criteria used for stratified sampling of hospitals into the NIS include hospital ownership, patient volume, teaching status, urban or rural location, and geographic region. Discharge weights are provided for each patient discharge record, which allow extrapolation to obtain national estimates. Each hospitalization is treated as an individual entry in the database and is coded with one principal diagnosis, up to 24 secondary diagnoses, and 15 procedural diagnoses associated with that stay. Detailed information on NIS is available at http://www.hcup-us.ahrq.gov/db/nation/nis/nisdde.jsp.

Demographic characteristics of population

We performed a retrospective cross-sectional observational study on adult hospitalizations in the USA from 2016-2017. Secondary diagnoses of SUDs were identified using ICD-10-CM code. SUDs include Alcohol related disorder, Amphetamine dependence, Cannabis related disorders, Cocaine related disorders, Hallucinogen related disorders, Inhalant related disorders, Opioid related disorders, and Nicotine dependence.

The comparison was made between US hospitalizations with history of SUDs and hospitalizations without history of SUDs. In each group primary and secondary diagnosis with CVDs and CeVDs were identified. We considered angina pectoris, myocardial infarction (STEMI), sudden cardiac

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arrest, ischemic heart disease, and atrial fibrillation as CVDs and acute ischemic stroke, transient ischemic attack, hemorrhagic stroke as CeVDs. ICD-10-CM codes for vascular diseases are described in Table 1. We used ICD-10-CM codes to identify comorbidities of hypertension, diabetes mellitus, obesity, dyslipidemia, renal failure, HIV/AIDS, solid tumor, depression, ischemic heart disease, atrial fibrillation, and congestive heart failure. Age<18 years and admissions with missing data for age, sex, and race were excluded. We obtained patient characteristics of interest (age, sex, race, insurance status, admission day, admission type, median household income category, and concomitant diagnoses) and hospital characteristics (hospital size, hospital region, and teaching versus nonteaching hospital).

Outcomes

Primary aim of this study was to evaluate the incidence and prevalence of CVDs and CeVDs amongst patients with SUDs. The secondary aim of this study was to evaluate odds of CVDs and CeVDs amongst SUDs.

Statistical analysis

We analyzed the data using SAS software (Version 9.4). We performed univariate analysis to find association of SUDs with CVDs and CeVDs. Categorical variables were evaluated using chi-square and t-test was used for continuous variables. Multivariable survey logistic regression models were generated to predict the association of CVDs and SUDs as well as CeVDs and SUDs after adjusting for confounding variables. There was no pre-decided sample size calculation. The p-value <0.05 was considered significant and OR with its 95%CI were calculated.

Details of confounders

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In regression analysis, the models were adjusted with socio demographic variables like, age, race, ethnicity, annual household income, education status, and comorbidities like diabetes, cholesterol, hypertension cardiovascular health, obesity, and preventive aspirin use.

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RESULTS

Disease hospitalizations

We found 58,259,589 hospitalizations [weighted-after removing missing data for age, sex and race (unweighted:11,651,925)] from January 2016 to December 2017 after excluding patients with age <18 years. Out of these hospitalizations, 21.42% had a history (secondary diagnosis) of major substance use disorders (SUDs). The prevalence of alcohol related disorders was 5.87%, amphetamine dependence was 0.51%, cannabis related disorders was 1.84%, cocaine related disorders was 0.59%, hallucinogen related disorders was 0.01%, opioid related disorders was 1.53%, and nicotine dependence was 11.07%.

Demographic characteristics of patients with history of substance abuse (Table 1)

Alcohol related disorder (42.61%), amphetamine dependence (76.17%), cannabis related disorder (75.17%), cocaine related disorders (57.87%), hallucinogen related disorder (82.91%), inhalant related disorders (67.25%), opioid related disorders (52.86%), nicotine dependence (35.72%) were higher in the 18-50 years age group compared to their non-SUD cohort (31.83%) ($p<0.0001$). A significantly higher proportion of patients within the age group of 50-75 years had SUDs, including alcohol related disorders (52.67%), opioid related disorders (41.74%), and nicotine dependence (55.73%) than not having them. (40.88%) ($p<0.0001$).

Among males, there was a higher prevalence of alcohol related disorders (71.81%), amphetamine dependence (59.02%), cannabis related disorder (57.54%), cocaine related disorders (59.05%), hallucinogen related disorder (62.42%), inhalant related disorders (60.09%), opioid related disorders (44.67%), and nicotine dependence (49.84%) in comparison to those males not having a diagnosis of SUD (38.14%) ($p<0.0001$). Opioid (77.09%) abuse prevalence was higher amongst Caucasians with SUDs in comparison to those with no SUDs (74.30%) ($p< 0.0001$). Similarly,

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Cannabis (32.24%), cocaine (48.64%), and hallucinogen (43.50%) abuse prevalence was higher in African-americans with a diagnosis of SUDs in comparison to those without SUDs (17.27%) ($p< 0.0001$). Amphetamine (14.96%) and hallucinogen (16.49%) were more prevalent in those Hispanics with SUDs when compared to those without SUDs (12.11%) ($p< 0.0001$). Amongst the patients diagnosed with SUDs in the lowest median household income group (0-25th percentile), there was a higher prevalence of alcohol (34.77%), amphetamine (39.52%), cannabis (42.33%), cocaine (52.87%), hallucinogen (46.09%), inhalant (40.68%), opioid (35.33%), and nicotine (38.80%) abuse when compared to those without a diagnosis of SUDs. (29.12%) ($p< 0.0001$).

Incidence and prevalence of cerebrovascular disorders (Table 2)

The incidence of AIS was higher in patients with cocaine related disorders (1.71%), nicotine dependence (2.28%) when compared to those without SUDs (1.70%) ($p<0.0001$). The incidence of intracerebral hemorrhage (ICeH) was higher in patients with amphetamine dependence (0.40%), cocaine related disorders (0.35%) in comparison to those without SUDs (0.29%). ($p<0.0001$) The incidence of SAH was higher in patients admitted with alcohol related disorders (0.27%), amphetamine dependence (0.40%), cocaine related disorders (0.35%) when compared to those with no SUDs (0.24%). ($p<0.0001$) The prevalence of a history of AIS was higher in patients admitted with cocaine related disorders (2.22%) in comparison to those with no SUDs (2.14%) ($p<0.0001$). There was a higher prevalence of history of intracerebral hemorrhage (ICeH) in patients admitted with alcohol related disorders (0.42%), amphetamine dependence (0.60%), cocaine related disorders (0.53%) in comparison to those patients with no SUDs (0.33%) ($p<0.0001$). The prevalence of a history of SAH was higher among patients with amphetamine dependence (0.23%), cocaine related disorders (0.23%), and nicotine dependence (0.18%) in comparison to those without SUDs (0.14%) ($p<0.0001$).

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Incidence and prevalence of cardiovascular disorders (Table 2)

The incidence (0.06% vs 0.05%) and prevalence (0.79% vs 0.67%) of SCA was higher in alcohol related disorders (p<0.0001). The incidence of angina pectoris was higher in patients with cocaine related disorders (0.14%) and nicotine dependence (0.08%) in comparison to those without SUDs (0.06%) (p<0.0001). Similarly, the prevalence of angina pectoris was higher in patients with cocaine related disorders (0.54%), nicotine dependence (0.25%) in comparison to those with no SUDs (0.19%) (p<0.0001). The prevalence of a history of MI was higher in patients with cocaine related disorders (3.60%), nicotine dependence (5.31%) in comparison to those with no SUDs (3.33%) (p<0.0001). The incidence (1.71% vs 1.70%) and prevalence (2.22% vs 2.14%) of AIS was higher amongst patients with cocaine related disorders compared to those without SUDs.

Multivariable regression showing odds of hospitalizations with new onset of cerebrovascular disorders and cardiovascular amongst SUDs patients (Table 3)

The odds of having hospitalizations with new onset of acute ischemic stroke was higher in patients with amphetamine dependence (OR 1.23, 95%CI 1.14-1.33; p<0.0001), cocaine related disorders (1.17, 1.12-1.23; p<0.0001), nicotine dependence (1.42, 1.40-1.43; p<0.0001). The odds of having hospitalizations with new onset intracerebral hemorrhage was higher in patients with amphetamine dependence (2.58, 2.26-2.93; p<0.0001), cocaine related disorders (1.62, 1.46-1.79; p<0.0001) and alcohol related disorder (1.35, 1.01-1.82; p=0.0439). The odds of having hospitalizations with new onset subarachnoid hemorrhage was higher in patients with amphetamine dependence (1.82, 1.48-2.24; p<0.0001), and nicotine dependence (1.47, 1.39-1.55; p<0.0001). The odds of having hospitalizations with new onset myocardial infarction was higher in patients with nicotine dependence (1.85, 1.83-1.87 p<0.0001) and cocaine related disorders (1.09, 1.04-1.14; p=0.0002). The odds of having hospitalizations with new onset angina pectoris was higher in patients with

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cocaine related disorders (2.21, 1.86-2.62; p<0.0001). The odds of having hospitalizations with new onset atrial fibrillation was higher in patients with alcohol related disorders (1.14, 1.11-1.17; p <0.0001).

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DISCUSSION

Our analysis of 58,259,589 hospitalizations revealed the following findings: (1) amphetamine and cocaine use were associated with ischemic stroke and intracerebral hemorrhage, (2) cocaine but not amphetamine use was associated with angina and acute MI, (3) alcohol use was associated with intracerebral hemorrhage and atrial arrhythmias, (4) nicotine use was associated with ischemic stroke, acute MI and sudden cardiac arrest (SCA).

Both amphetamine and cocaine are vasoactive agents that exert their effect through catecholaminergic modulation and have previously been associated with both ischemic and hemorrhagic stroke[7]. A retrospective study in young adults by Westover et al. noted a statistically significant association between cocaine use and both ischemic and hemorrhagic stroke[8]. Amphetamine use was only associated with hemorrhagic strokes and not ischemic strokes[8]. In addition, a review of cases reported in the literature also found a preponderance of amphetamines for hemorrhagic stroke [9]. Our analysis echoed these trends, whereby a stronger association was demonstrated between amphetamine use and hemorrhagic stroke (2.58, 2.26-2.93) as compared to ischemic stroke (1.23, 1.14-1.33), albeit both associations were statistically significant. Compared to the study by Westover et al, statistical significance of the latter is likely due to the larger sample size, considering the lower event rate of ischemic strokes demonstrated in prior studies. Mechanistically, cocaine and amphetamines can cause hemorrhagic stroke through acute hypertension, aneurysm formation and rupture. For ischemic strokes, common mechanisms include arrhythmias with cardio-embolism, severe vasospasm and accelerated atherosclerosis[7]. Cocaine additionally may trigger platelet hyper-aggregation and arterial dissections as additional mechanisms for ischemic stroke[7]. We also found a statistically significant association between

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amphetamine and SAH, which lends support to a recent retrospective study by Noblett et al. that indicated increased risk of rupture and SAH at smaller aneurysmal size in patients with a history of methamphetamine use[10].

In terms of involvement of the cardiovascular system, hospitalization with angina pectoris and acute myocardial infarction was greater in patients with cocaine use (1.09, 1.04-1.14; p=0.0002) but not amphetamine use. This is contrasted to the findings by Westover et al. who found a statistically significant association of acute MI with both cocaine and amphetamine use among hospitalizations in Texas (Westover, 2008)[11]. Their study also demonstrated regional variation in the strength of association between amphetamine use and acute MI, suggesting areas with heavier use might be more susceptible to cardiovascular events. Further studies investigating this association in other regions and the frequency/amount of amphetamine use with incident events will lend more clarity to the discrepancy observed between our findings and that of Westover et al.

The increased legalization of marijuana and rising prevalence has led to increased concern regarding its long-term effects on the cardiovascular system (World Drug report 2019, United Nations)[12]. Our study revealed that while there was a statistically significant increase in both incidence and prevalence of ischemic heart disease and myocardial infarction in hospitalized patients with cannabis use, no significant association was noted when adjusted for potential confounders. Our results are consistent with data from the Behavioral Risk Factor Surveillance System (BRFSS) by Jivanji et al (2020)[13] that also failed to reveal an association between cardiovascular disease and cannabis use. Furthermore, longitudinal studies investigating marijuana use and development of cardiovascular disease in 18-30 year olds also showed no change in risk of development of cardiovascular disease later in life[14].

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We found significantly increased odds of hospitalization with intracerebral hemorrhage in patients with alcohol related disorders (1.35, 1.01-1.82; p=0.0439). A prior retrospective study by Casolla et al. demonstrated similar findings with the proposed mechanism being through coagulopathy and platelet dysfunction[15]. In keeping with previous studies, we also demonstrated a statistically significant association between atrial arrhythmias and alcohol use[16]. This is proposed to occur through alcohol mediated myocyte injury and autonomic dysfunction leading to increased likelihood for formation of atrial re-entry circuits, precipitating atrial fibrillation[17]. Chelikam et al., in NHANES study evaluated 263465 respondents with CVDs, in which marijuana (1.98, 1.98-1.98), injectable illegal drug use (2.15, 2.14-2.15), cigarette smoking (1.55, 1.55-1.55) had significantly increased the risk CVDs [18].

Tobacco use is a well-established risk factor and has been shown to have a dose-dependent effect on risk of ischemic stroke, myocardial infarction and ruptured cerebral aneurysms[19–21]. Our findings are in agreement with prior studies, nicotine use was independently associated with ischemic stroke (1.23, 1.14-1.33; p<0.0001), myocardial infarction (1.09, 1.04-1.14; p=0.0002) and SAH (1.47, 1.39-1.55; p<0.0001). Nicotine causes an increased adrenergic drive, combined with the toxic and prothrombotic effects of oxidant chemicals and carbon-monoxide lead to ischemic events[22]. The increased shear stress and endothelial inflammation are also suspected to be the mechanisms behind aneurysm formation and rupture in aneurysmal SAH [21].

Strengths & Limitations

We highlighted that, on a national level, there is a higher risk of cardiovascular diseases among patients with substance use disorders, even though the evidence described in our findings is based on administrative billing codes, producing a decreased overall sensitivity when compared with

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clinical diagnosis. The data we provided, together with the relevant literature, shows the importance of better education about drug use problems and the effects they have on cardiovascular health. While we were able to demonstrate association of different types of SUDs with different sub-types of CVDs and CeVDs, our study was limited in further delineating the specific doses or frequency of drug uses and their association with CVDs and CeVDs. Moreover, the study was designed to establish association and not causality.

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CONCLUSION

In conclusion, our study highlights the significant variability among CVD and CeVD events among patients hospitalized for SUD. The results of our studies may aid in raising the index of suspicion and early management, especially in young adults hospitalized for SUD. Further studies are needed to evaluate other parameters such as frequency and dose-relationship of different substances and their effect on CVD and CeVD in hospitalized patients.

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Table 1 Demographics of SUDs amongst USA hospitalizations

Variables	Alcohol related disorders (n=3420548) (5.87%)	Amphetamine dependence (n=295060) (0.51%)	Cannabis related disorders (n=1072879) (1.84%)	Cocaine related disorders (n=341745) (0.59%)	Hallucinogen related disorders (n=7345) (0.01%)	Inhalant related disorders (n=2305) (0.0%)	Opioid related disorders (n=889520) (1.53%)	Nicotine dependence (n=6451382) (11.07%)	No-SUDs* (n=45,778,806) (78.58%)
Demographic and Socioeconomic Characteristics (%)									
Age Groups (%)									
Age Group 18-50 years	42.61	76.17	75.17	57.87	82.91	67.25	52.86	35.72	31.83
Age Group 50-75 years	52.67	23.64	24.22	41.75	16.34	29.93	41.74	55.73	40.88
Age Group >75 years	4.73	0.19	0.62	0.38	0.75	2.82	5.41	8.55	27.29
Sex									
Male	71.81	59.02	57.54	59.05	62.42	60.09	44.67	49.84	38.14
Female	28.19	40.98	42.46	40.95	37.58	39.91	55.33	50.16	61.86
Race (%)									
White	69.97	70.81	55.70	40.05	38.45	72.41	77.09	74.30	69.31
Black	16.83	9.97	32.24	48.64	43.50	13.25	13.40	17.27	14.76
Hispanic	10.70	14.96	10.07	10.34	16.49	10.82	7.98	6.46	12.11

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Asian or Pacific Islander	0.99	2.41	0.99	0.55	1.28	2.21	0.67	1.21	3.27
Native American	1.51	1.85	1	0.42	0.28	1.32	0.86	0.75	0.54
Median household income for patient's ZIP Code (%)									
0-25th percentile	34.77	39.52	42.33	52.87	46.09	40.68	35.33	38.80	29.12
26th to 50th percentile (median)	25.51	28.40	25.31	21.00	19.32	26.36	26.31	28.22	25.70
51st to 75th percentile	22.28	21.00	19.71	15.61	18.76	18.86	22.24	20.70	24.08
76th to 100th percentile	17.43	11.08	12.65	10.51	15.83	14.09	16.12	12.28	21.10
Primary Payer Insurance (%)									
Medicare	28.96	14.64	18.82	22.11	14.66	25.81	36.38	41.29	51.04
Medicaid	33.08	57.05	44.59	49.56	51.06	31.24	38.60	24.92	15.19
Private	22.71	11.03	21.63	12.26	19.02	25.16	16.74	23.08	28.13
Self	15.25	17.27	14.96	16.07	15.27	17.79	8.28	10.71	5.63
Admission Type (%)									
Emergency & Urgent	90.68	90.82	87.00	91.42	89.84	84.13	85.49	82.08	73.86

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Elective	9.32	9.18	13.00	8.58	10.16	15.87	14.51	17.92	26.14
Admission Day (%)									
Weekdays (Monday-Friday)	75.71	75.14	77.44	74.62	75.43	79.18	76.92	78.58	80.15
Weekends (Saturday-Sunday)	24.49	24.86	22.56	25.38	24.57	20.82	23.08	21.42	19.85
Bedsize (%) (Hospital size by number of beds)									
Small	20.24	17.70	18.56	19.59	24.23	23.64	19.99	19.36	19.43
Mediam	29.75	24.71	28.43	30.28	28.25	34.27	28.11	28.96	29.51
Large	50.02	57.59	53.01	50.14	47.52	42.08	51.90	51.69	51.06
Location and Teaching Status (%)									
Rural	7.95	9.31	7.30	4.05	4.08	11.26	7.70	11.31	8.95
Urban, non-teaching	24.39	28.34	21.78	19.06	20.63	17.79	26.35	25.19	24.926
Urban, teaching	67.66	62.35	70.90	76.89	75.29	70.93	65.95	63.50	66.13
Hospital Region (%)									
Northeast	21.91	3.32	18.86	27.58	31.93	18.66	22.35	16.28	19.52
Midwest or North Central	21.95	14.46	24.12	20.79	18.58	18.87	20.27	25.45	20.97

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South	35.85	28.13	35.35	42.63	36.15	49.46	34.92	42.74	40.23
West	20.30	54.09	21.67	9.01	13.34	13.02	22.26	14.53	19.28
Concurrent comorbidities (%)									
Diabetes (%)	16.20	16.10	15.30	21.58	12.73	15.40	21.38	27.42	27.65
HTN (%)	51.86	30.81	31.96	47.29	28.25	33.62	43.87	57.10	56.29
Obesity (%)	8.88	8.36	11.27	9.79	8.51	9.76	13.75	15.95	15.88
Dyslipidemia (%)	19.90	10.12	14.16	16.84	8.85	16.27	18.34	33.22	33.65
Renal Failure (%)	17.19	16.65	13.74	24.06	15.52	14.75	20.40	20.18	25. 22
Smoking (%)	46.54	57.52	49.39	56.77	41.87	41.00	42.92	100.00	0.00
AIDS (%)	100.00	1.04	0.76	2.27	0.68	1.30	0.69	0.41	0.17
Metabolic Syndrome (%)	0.09	0.08	0.11	0.07	0.07	0.00	0.13	0.17	0.18

*No-SUDs defined by the hospitalizations/patients who is not having Alcohol related disorder, Amphetamin related disorders, Cocaine related disorders, Hallucinogen related disorders, Inhalant related disorders, Opic Nicotine dependence

Column (%) comparison were made between Individual SUD vs no-SUD

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Table 2: Incidence and Prevalence of CeVDs and CVDs amongst active SUDs patients

Outcomes	Alcohol related disorders (n=3420548) (5.87 %)	Amphetamine dependence (n=295060) (0.51 %)	Cannabis related disorders (n=1072879) (1.84%)	Cocaine related disorders (n=341745) (0.59%)	Hallucinogen related disorders (n=7345) (0.01%)	Inhalant related disorders (n=2305) (0.0%)	Opioid related disorders (n=889520) (1.53%)	Nicotine dependence (n=6451382) (11.07%)	No-SUDs* (n=45,778,806) (78.58%)
Incidence (New primary diagnosis) of Cerebrovascular disorders (%)									
Acute Ischemic Stroke (AIS) **(%)**	1.29	1.13	**1.12**	1.71	0.48	≤10 (–)	0.54	2.28	1.70
Transient Ischemic Attack (TIA) **(%)**	0.18	0.09	0.19	0.18	≤10 (–)	≤10 (–)	0.13	0.37	0.41
Intracerebral hemorrhage (ICeH) **(%)**	0.2	0.40	0.13	0.35	≤10 (–)	≤10 (–)	0.07	0.18	0.29
Subarachnoid hemorrhagic (SAH) **(%)**	0.27	0.40	0.13	0.35	≤10 (–)	≤10 (–)	0.07	0.18	0.24
Prevalence (Primary and secondary diagnosis) of Cerebrovascular disorders (%)									
Acute ischemic stroke (AIS) **(%)**	1.69	1.64	**1.35**	2.22	0.95	0.87	0.95	0.69	2.14
Transient ischemic attack (TIA) **(%)**	0.29	0.16	0.25	0.28	≤10 (–)	≤10 (–)	0.23	0.56	0.67

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Intracerebral Hemorrhage (ICeH) **(%)**	0.42	0.60	0.22	0.53	≤10 (–)	≤10 (–)	0.14	0.16	0.33
Subarachnoid hemorrhagic (SAH) **(%)**	0.13	0.23	0.13	0.23	≤10 (–)	≤10 (–)	0.9	0.18	0.14
Incidence (New primary diagnosis) of Cardiovascular disorders (%)									
Sudden cardiac arrest (SCA) **(%)**	0.06	0.04	0.03	0.09	≤10 (–)	≤10 (–)	0.04	0.04	0.05
Ischemic heart disease (IHD) **(%)**	1.81	1.75	2.28	2.97	1.09	0.65	1.24	5.74	3.32
Myocardial infarction (MI) **(%)**	1.21	1.38	1**.62**	2.01	1.02	≤10 (–)	0.78	3.97	2.01
Angina pectoris **(%)**	0.04	0.04	0.05	0.14	≤10 (–)	≤10 (–)	0.03	0.08	0.06
Atrial fibrillation (Afib) **(%)**	0.99	0.35	0.39	0.41	0.20	≤10 (–)	0.31	0.85	1.18
Prevalence (Primary and secondary diagnosis) of Cardiovascular disorders (%)									
Sudden cardiac arrest (SCA) **(%)**	0.79	0.77	0.42	0.95	0.68	≤10 (–)	0.75	0.63	0.67
Ischemic heart disease (IHD) **(%)**	13.41	9.80	**9.87**	16.60	5.85	10.85	14.10	25.03	22.84
Myocardial infarction (MI) **(%)**	2.18	2.57	**2.30**	3.60	1.70	1.30	1.85	5.31	3.33
Angina pectoris **(%)**	0.16	0.14	0.18	0.54	0.34	≤10 (–)	0.14	0.25	0.19

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Atrial fibrillation (Afib) **(%)**	7.03	2.77	**2.77**	3.94	1.57	3.47	5.41	7.65	12.21

≤10 (-) indicated unidentified lower frequencies
Column (%) comparison were made between Individual SUD vs no-SUD

Table 3: Risk of having hospitalizations with new onset of CeVD and CVD amongst active SUDs patients

Outcomes	Alcohol related disorder aOR (95%CI) p-value	Amphetamine dependence aOR (95%CI) p-value	Cannabis related disorders aOR (95%CI) p-value	Cocaine related disorder aOR (95%CI) p-value	Hallucinogen related disorder aOR (95%CI) p-value	Inhalant related disorder aOR (95%CI) p-value	Opioid related disorder aOR (95%CI) p-value
Model 1 Acute Ischemic stroke (AIS)	0.68 (0.61-0.76) <.0001	**1.23 (1.14-1.33) <.0001**	1.03 (0.99-1.06) 0.2058	**1.17 (1.12-1.23) <.0001**	0.43 (0.28-0.67) 0.0002	0.39 (0.14-1.05) 0.0619	0.38 (0.36-0.40) <.0001
Model 2 Transient Ischemic Attack (TIA)	0.72 (0.54-0.96) <.0001	0.64 (0.50-0.82) 0.0233	0.86 (0.78-0.95) 0.0032	0.77 (0.67-0.89) 0.0002	0.59 (0.22-1.58) 0.2967	0.56 (0.08-3.97) 0.5596	0.43 (0.38-0.49) <.0001
Model 3 Intracerebral Hemorrhage (ICeH)	**1.35 (1.01-1.82) 0.0439**	**2.58 (2.26-2.93) <.0001**	0.78 (0.71-0.87) <.0001	**1.62 (1.46-1.79) <.0001**	0.34 (0.11-1.07) 0.0650	-	0.37 (0.32-0.43) <.0001
Model 4 Subarachnoid Hemorrhage (SAH)	0.82 (0.50-1.35) 0.4345	**1.82 (1.48-2.24) <.0001**	0.94 (0.82-1.08) 0.3917	1.09 (0.91-1.31) 0.3551	0.52 (0.13-2.08) 0.3524	-	0.38 (0.31-0.47) <.0001
Model 5 Sudden Cardiac Arrest (SCA)	1.23 (0.73-2.05) 0.4404	1.01 (0.68-1.48) 0.9731	0.95 (0.78-1.17) 0.6571	1.24 (0.99-1.55) 0.0581	1.91 (0.71-5.13) 0.1983	2.45 (0.34-17.4) 0.3723	1.20 (1.00-1.43) 0.0460

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Model 7 Myocardial Infarction (MI)	0.47 (0.43-0.52) <.0001	0.90 (0.84-0.96) 0.0013	0.96 (0.93-0.99) 0.0124	**1.09 (1.04-1.14) 0.0002**	0.64 (0.46-0.90) 0.0090	0.40 (0.18-0.90) 0.0266	0.37 (0.36-0.39) <.0001
Model 8 Angina Pectoris	0.49 (0.29-0.84) 0.0095	0.76 (0.50-1.14) 0.1803	0.74 (0.61.0.89) 0.0013	**2.21 (1.86-2.62) <.0001**	0.70 (0.18-2.79) 0.6147	-	0.46 (0.36-0.58) <.0001
Model 9 Atrial Fibrillation (AFib)	**1.14 (1.11-1.17) <.0001**	0.97 (0.86-1.09) 0.5864	0.90 (0.84-0.95) 0.0002	0.93 (0.86-1.01) 0.0987	0.56 (0.29-1.06) 0.0758	0.77 (0.29-2.04) 0.5921	0.39 (0.36-0.41) <.0001