In order to create an initial conceptual model of stimulant overdose for the purpose of informing hypothesis-driven selection of variables into the predictive model, it is necessary to examine a wide array of literature to find potential predictors of stimulate overdose. In reviewing the literature, there seemed to be three main areas of work that examine stimulant overdose. First is looking at trends in stimulant overdose over time and association with variables such as age, sex, race, and ethnicity. The second is literature examining the role of co-use of opioids and stimulants in overdoses. Since co-use is common in overdoses, examining attempts to predict opioid overdose through predictive modeling may also point to some variables that could be useful in predicting stimulant. There are also some geographical analyses and related analyses of social determinants data that point to other important variables for consideration.

*Trends over Time*

There have been several papers that have examined trends in stimulant overdoses from 2000 through 2019.1–10 In general, the papers observe that there have been significant increases in stimulant overdose deaths over time and over sex, race, ethnicity, sexuality, and age subgroups.1,3 However, the size of the increase in the rates of overdose varies between groups. The papers seem to indicate that American Indian and Alaska Natives have the highest rates of death due to methamphetamine overdose, followed by non-Hispanic Whites, and that men have higher death rates than women.1,10 One paper observed that in Washington State from 2010-2017 that the highest increase was in persons older than 55.4 Also, while psychostimulant overdose has historically been associated with the western United States, psychostimulant overdoses have been increasing in states most affected by the opioid epidemic.5

Cocaine overdoses have also increased over this time period, and they seem to be primarily affecting people who are older, Black, or with lower education.7,10 Over these time period, polysubstance, usually co-use of an opioid with cocaine or a psychostimulant, overdoses have been increasing, as well.9,10 The papers indicate that age, race, ethnicity, sex are variables with potential associations with stimulant overdose, as well as heterogeneous associations with cocaine and psychostimulant overdose. Co-use of opioids is another trend that has been noticed, and it will be discussed in the following section.

*Co-Use of Opioids*

A significant proportion of stimulant overdose deaths also involve opioids. One study found that increases in cocaine overdoses were also largely driven by co-use of opioids, especially since 2013.10 Another paper by Jones, Baldwin and Compton illustrated a similar phenomenon.8 Goodwin et al found that co-use of both heroin and cocaine increased linearly from 2002 to 2017.11 A similar phenomenon has been seen with methamphetamines as well.12 In 2016, non-fatal cocaine and psychostimulant overdoses had a 27% and 14% chance of involving an opioid, respectively.9 When looking at fatal overdoses, those numbers rise to 72.7% for cocaine and 50.3% for psychostimulants.9 A study looking at New York City from 2006 to 2016 observed a similar phenomenon with cocaine and opioid use.13 In a 2006 study, Galea et al found that the vast majority of the study sample used both heroin and cocaine, and suggested that interventions should target co-use of heroin and cocaine. 14 Another study from 2007 based in Vancouver, similarly found that polysubstance use was a significant predictor of non-fatal overdose in injecting drug users.15 Because of the increasing role of opioids in stimulant overdoses and the overlap of the stimulant and opioid using populations, it is reasonable to look to models and studies that predict opioid overdoses for candidate variables.

*Predictive Models of Opioid Overdose*

Attempts at making predictive models of opioid overdose are also a useful source for variables to include in a conceptual model of stimulant overdose. One study from Maryland found that male sex, diagnosis of opioid use in a hospital, release from prison, and receiving Medication-Assisted Treatment had statistically significant associations in a predictive, logistic regression model.16 Another study using electronic health record [EHR] data listed several diagnoses and clinical events that may be predictive of opioid overdoses in their machine learning models, which included random forest, decision trees, logistic regression, and deep learning models..17 Some of these are diagnoses of related conditions such as other substance abuse and mental health conditions.17 Others include clinical data in EHRs such as BMI, pulse, respiratory rate, hypertension, and history of pain.17 History of being injured in a motor vehicle collision as a pedestrian were also influential in their machine learning models.17 There was also a study using predictive modeling based on Prescription Drug Monitoring Program data to predict fatal opioid overdose.18 Their model achieved an AUC of 0.81 for overdose on any use of opioids resulting in a fatal overdose and 0.77 for illicit use of opioids resulting in a fatal overdose.18 They found that male sex, a fill of 1 or more long-acting opioids, 1 or more buprenorphine fills, 2 or more short-acting opioid fills, large fills of opiates (91 or more days), average morphine milligram equivalent daily dose, 2 or more benzodiazepine fills, and 1 or more fills of muscle relaxants were significant predictors of fatal opioid overdose.18 They also found that older age was protective.18 A systematic review of literature on opioid predictive models found that the significant predictors included, demographics (age, race, sex, and socioeconomic status), comorbid psychiatric conditions, substance abuse disorders, chronic pain, lung disease, prescribing data related to opioids, living with people who are prescribed opioids, and co-use of other sedatives.19

*Analysis of Social Determinants of Health and Geospatial Data*

A review of the literature has resulted in some potential social determinants of health variables to include in a model of stimulant overdose. In a 2006 study, Galea et al found that lower educational attainment and homelessness were associated with cocaine overdoses.14 A 2019 paper by Han et al, found associations between male sex, mid age, and Black race with cocaine overdoses.13 They also found that Bronx residence was associated with cocaine overdoses.13 The Bronx is known as a socioeconomically struggling borough withing New York City, and the variables that characterize its deprivation may be useful. Criminal justice involvement may also be useful, based on findings in a paper looking at opioid overdoses in Maryland.16 The same 2007 study in Vancouver found that homelessness, street injecting, and recent incarceration were also associated with non-fatal overdose.15

In a geospatial analysis of electronic health record data and neighborhood deprivation from drug-related admissions in the Duke University Health System, Cobert et al examined the association of neighborhood deprivation and other geographic socioeconomic variables, with drug-related admission and overdose rates.20 In their analyses, they used a composite variable, the Area Deprivation Index [ADI], rather than multiple variables measuring socioeconomic conditions.

The ADI is a validated, composite index based on 17 United States Census variables, whose construction and validation has been discussed elsewhere.21 According to Singh, use of the ADI may be more valid than using the individual variables due to its ability to better capture the nuances of an area’s socioeconomic conditions.21

The variables used include the following21:

* Proportion of the population aged 25 years or older with less than 9 years of education
* Proportion of the population aged 25 years or older with at least a high school diploma
* Proportion of employed persons aged 16 years or older in white-collar occupations
* Median family income
* Income disparity
* Median home value
* Median gross rent
* Median monthly mortgage,
* Proportion of housing units which are owner-occupied
* Proportion of civilian labor force population aged 16 years or older that is unemployed
* Proportion of families below the poverty level
* Proportion of the population below 150% of the poverty threshold
* Proportion of households that are single-parent households with children aged less than 18 years
* Proportion of households without a motor vehicle
* Proportion of households without a telephone
* Proportion of occupied housing units without complete plumbing
* Proportion of households with more than 1 person per room.

Cobert et al, found that there was a 97% chance of a positive effect of ADI on overdose rates, and that a 20% increase in the percentile was associated with a 3% increase in the rate of overdose admissions, and that this difference is statistically significant.20 They also observed that some geographic heterogeneity remained after adjustment and that there may be an effect of urbanicity, but that this has been inconsistent in the literature.20 Even though the authors hold that the use of multiple individual socioeconomic variables has led to conflicting conclusions on socioeconomic predictors of overdose and that a composite index may work better20, a geospatial model for stimulant overdoses should assess both the composite measure and its constituent variables in order to optimize model fit.

Bibliography

1. Han B, Cotto J, Etz K, Einstein EB, Compton WM, Volkow ND. Methamphetamine Overdose Deaths in the US by Sex and Race and Ethnicity. JAMA Psychiatry. 2021 May 1;78(5):564–567. PMCID: PMC8100861

2. Jones CM, Compton WM, Mustaquim D. Patterns and Characteristics of Methamphetamine Use Among Adults - United States, 2015-2018. MMWR Morb Mortal Wkly Rep. 2020 Mar 27;69(12):317–323. PMCID: PMC7725509

3. Han B, Compton WM, Jones CM, Einstein EB, Volkow ND. Methamphetamine Use, Methamphetamine Use Disorder, and Associated Overdose Deaths Among US Adults. JAMA Psychiatry. 2021 Sep 22; PMCID: PMC8459304

4. Njuguna H, Gong J, Hutchinson K, Ndiaye M, Sabel J, Wasserman C. Increasing rates of methamphetamine/amphetamine-involved overdose hospitalizations in Washington State, 2010-2017. Addict Behav Rep. 2021 Dec;14:100353. PMCID: PMC8185143

5. Cano M, Huang Y. Overdose deaths involving psychostimulants with abuse potential, excluding cocaine: State-level differences and the role of opioids. Drug Alcohol Depend. 2021 Jan 1;218:108384. PMID: 33158665

6. Kariisa M, Scholl L, Wilson N, Seth P, Hoots B. Drug Overdose Deaths Involving Cocaine and Psychostimulants with Abuse Potential - United States, 2003-2017. MMWR Morb Mortal Wkly Rep. 2019 May 3;68(17):388–395. PMCID: PMC6541315

7. Cano M, Oh S, Salas-Wright CP, Vaughn MG. Cocaine use and overdose mortality in the United States: Evidence from two national data sources, 2002-2018. Drug Alcohol Depend. 2020 Sep 1;214:108148. PMCID: PMC7423708

8. McCall Jones C, Baldwin GT, Compton WM. Recent Increases in Cocaine-Related Overdose Deaths and the Role of Opioids. Am J Public Health. 2017 Mar;107(3):430–432. PMCID: PMC5296707

9. Hoots B, Vivolo-Kantor A, Seth P. The rise in non-fatal and fatal overdoses involving stimulants with and without opioids in the United States. Addiction. 2020 May;115(5):946–958. PMID: 31912625

10. Kariisa M, Seth P, Scholl L, Wilson N, Davis NL. Drug overdose deaths involving cocaine and psychostimulants with abuse potential among racial and ethnic groups - United States, 2004-2019. Drug Alcohol Depend. 2021 Oct 1;227:109001. PMID: 34492555

11. Goodwin RD, Moeller SJ, Zhu J, Yarden J, Ganzhorn S, Williams JM. The potential role of cocaine and heroin co-use in the opioid epidemic in the United States. Addict Behav. 2021 Feb;113:106680. PMID: 33022537

12. Al-Tayyib A, Koester S, Langegger S, Raville L. Heroin and Methamphetamine Injection: An Emerging Drug Use Pattern. Subst Use Misuse. 2017 Jul 3;52(8):1051–1058. PMCID: PMC5642954

13. Han BH, Tuazon E, Kunins HV, Mantha S, Paone D. Unintentional drug overdose deaths involving cocaine among middle-aged and older adults in New York City. Drug Alcohol Depend. 2019 May 1;198:121–125. PMCID: PMC6467745

14. Galea S, Nandi A, Coffin PO, Tracy M, Markham Piper T, Ompad D, Vlahov D. Heroin and cocaine dependence and the risk of accidental non-fatal drug overdose. J Addict Dis. 2006;25(3):79–87. PMID: 16956872

15. Kerr T, Fairbairn N, Tyndall M, Marsh D, Li K, Montaner J, Wood E. Predictors of non-fatal overdose among a cohort of polysubstance-using injection drug users. Drug and Alcohol Dependence. 2007 Feb 23;87(1):39–45.

16. Saloner B, Chang H-Y, Krawczyk N, Ferris L, Eisenberg M, Richards T, Lemke K, Schneider KE, Baier M, Weiner JP. Predictive Modeling of Opioid Overdose Using Linked Statewide Medical and Criminal Justice Data. JAMA Psychiatry. 2020 Nov 1;77(11):1155–1162. PMCID: PMC7315388

17. Dong X, Rashidian S, Wang Y, Hajagos J, Zhao X, Rosenthal RN, Kong J, Saltz M, Saltz J, Wang F. Machine Learning Based Opioid Overdose Prediction Using Electronic Health Records. AMIA Annu Symp Proc. 2020 Mar 4;2019:389–398. PMCID: PMC7153049

18. Ferris LM, Saloner B, Krawczyk N, Schneider KE, Jarman MP, Jackson K, Lyons BC, Eisenberg MD, Richards TM, Lemke KW, Weiner JP. Predicting Opioid Overdose Deaths Using Prescription Drug Monitoring Program Data. Am J Prev Med. 2019 Dec;57(6):e211–e217. PMCID: PMC7996003

19. Tseregounis IE, Henry SG. Assessing opioid overdose risk: a review of clinical prediction models utilizing patient-level data. Transl Res. 2021 Aug;234:74–87. PMCID: PMC8217215

20. Cobert J, Lantos PM, Janko MM, Williams DGA, Raghunathan K, Krishnamoorthy V, JohnBull EA, Barbeito A, Gulur P. Geospatial Variations and Neighborhood Deprivation in Drug-Related Admissions and Overdoses. J Urban Health. 2020 Dec;97(6):814–822. PMCID: PMC7704893

21. Singh GK. Area Deprivation and Widening Inequalities in US Mortality, 1969–1998. Am J Public Health. American Public Health Association; 2003 Jul 1;93(7):1137–1143.