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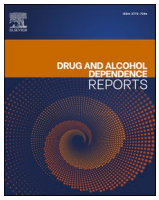

Drug supply measures and drug overdose mortality in the era of fentanyl and stimulants

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HIGHLIGHTS

- Fentanyl/fentanyl-related compounds were positively associated with overdose deaths.
- This association was observed in all subpopulations by sex, age, and race/ethnicity.
- Carfentanil drug reports were also positively associated with overdose deaths.
- The best-performing model included all proportional drug report measures examined.

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ABSTRACT

Background: Illicitly-manufactured fentanyl and stimulants have replaced prescription opioids as the primary contributors to fatal overdoses in the United States (US), yet the street supply of these substances is challenging to quantify. Building on the foundation of prior research on law enforcement drug reports, the present study compares publicly available forensic laboratory drug report measures to identify which measures account for the most variation in drug overdose mortality between states, within states over time, and in various demographic groups.

Methods: Drug reports from the National Forensic Laboratory Information System and drug overdose mortality rates from the Centers for Disease Control and Prevention were examined for all US states and the District of Columbia, 2013–2021 (459 state-years). State- and year- fixed effects models regressed drug overdose mortality rates (in the overall population and subpopulations by sex, age, and race/ethnicity) on various drug report measures, including rates per population and proportional shares of drug reports positive for fentanyl/fentanyl-related compounds, heroin, cocaine, methamphetamine, and xylazine.

Results: For drug overdose death rates in the overall population and nearly all subpopulations examined by sex, race/ethnicity, and age, the model including all drug report proportional measures represented the best-performing model (as identified via the lowest Akaike Information Criterion and highest within *R*-squared value), followed by the model including only the fentanyl/fentanyl-related compounds proportion.

Conclusions: Findings support the utility of publicly available drug report composition measures, particularly the proportion of fentanyl/fentanyl-related compounds, as predictors of drug overdose mortality in the US and in various subpopulations.

1. Introduction

Illicitly-manufactured drugs such as non-pharmaceutical fentanyl and stimulants have replaced prescription opioids as the drugs most frequently involved in fatal overdoses in the United States (Spencer et al., 2022). In 2021, for example, synthetic opioids (e.g., fentanyl) were reported in 70,601 overdose deaths, psychostimulants (e.g., methamphetamine) in 32,537 deaths, and cocaine in 24,486 deaths; in contrast, prescription opioid pain relievers were reported in 13,618 deaths (Spencer et al., 2022). The shift from prescription opioids to illicitly-manufactured drugs has required researchers to identify measures to assess the pervasiveness of these drugs in street drug supplies

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(Hall et al., 2021; Jalal and Burke, 2021; Rosenblum et al., 2020) in order to better understand, and respond to, ever-changing trends in overdose deaths.

Law enforcement forensic laboratory drug reports represent one available source of measures related to the illicit drug supply and non-pharmaceutical fentanyl. Several recent studies have examined associations between seized drug reports and measures of overdose mortality or have developed methods of using seized drug reports to forecast or predict overdose deaths as part of early warning systems. Many of these studies have focused on data from a single state or area (e.g., Hall et al., 2021; Mohler et al., 2021; Lowder et al., 2022; Ray et al., 2023; Rosenblum et al., 2020; Slavova et al., 2017; Tran et al., 2021; Zibbell et al., 2019, 2022), while fewer have examined multiple states or the entire US (Jalal and Burke, 2021; Gladden et al., 2016; Marks et al., 2021; Sumner et al., 2022; Zibbell et al., 2023; Zoorob et al., 2019). These studies have varied in terms of specific drug reports examined (e.g., opioids, stimulants), types of drug overdose mortality outcomes (e.g., drug overdose mortality overall, opioid-involved overdose mortality), and units of analysis (e.g., state-year, county-month).

The present study builds on the foundation of the aforementioned studies in several ways. *First*, this study examines associations between state-level seized drug report measures and drug mortality rates not only in the overall US population, but also within subpopulations based on sex, race, and age, in consideration of subpopulation differences in the drugs most frequently involved in overdose deaths (Cano, 2021). *Second*, the study examines the years 2013–2021, as 2013 approximates the beginning of the era of illicitly-manufactured fentanyl (Ciccarone, 2019), and 2021 represents the most recent (finalized, nonprovisional) data available. Prior national studies (e.g., Jalal and Burke, 2021; Sumner et al., 2022; Zibbell et al., 2023) have included data through the year 2019, providing valuable insights yet not capturing more recent trends such as the post-2019 spread of illicitly-manufactured fentanyl beyond the east into the west (Shover et al., 2020) or COVID-era and post-COVID changes in overdose mortality. *Finally*, this study also incorporates measures of xylazine reports, as xylazine has been identified as an emerging drug threat with a distinct geographic footprint (Kariisa et al., 2023).

Overall, the present study aims to identify the extent to which a variety of measures from the publicly accessible National Forensic Laboratory Information System account for variation in drug overdose mortality between states and within states over time in various subpopulations of the US. The study uses a national, publicly available data source to evaluate measures that are accessible to *all* researchers/agencies and available for all states in the US, as many prior studies (e.g., Lowder et al., 2022; Ray et al., 2023; Tran et al., 2021; Zibbell et al., 2019) have utilized state-specific data sources that are not nationally publicly available but include more detailed, in-depth measures (e.g., weekly or monthly data, weights or doses of drugs seized). Findings from the present study may serve as a reference for researchers seeking optimal nationally available measures of the illicit drug supply for statistical controls in evaluations of policy or socioeconomic influences on drug overdose, or for public health agencies considering measures to include in early warning systems (e.g., Hall et al., 2021; Marks et al., 2021; Sumner et al., 2022) for overdose mortality trends.

2. Methods

2.1. Data sources and measures

2.1.1. Dependent variables

The primary outcome of interest was the *drug overdose mortality* rate per 100,000 residents, in each of the 50 states and District of Columbia (DC) for each year from 2013 to 2021. Drug overdose mortality rates were obtained from the Centers for Disease Control and Prevention (CDC) WONDER online platform (CDC, 2023), consisting of crude rates for drug overdose deaths of any intent (identified via an underlying cause of death corresponding to International Classification of Diseases [ICD]-10 codes X40-44, X60-64, X85, or Y10-14). Overdose deaths involving any drug were the primary outcome of interest due to geographic and time variation in the extent to which specific drug types are identified and reported on death certificates (Jones et al., 2019). In a supplemental analysis, we also examined synthetic opioid-involved overdose death rates as a more specific outcome (identified via an ICD-10 code of T40.4 as a "multiple cause of death.")

Drug overdose mortality rates were examined for the overall resident population as well as for subpopulations identified as: male; female; ages 15–29; ages 30–44; ages 45–74; Non-Hispanic (NH) White; NH Black; and Hispanic. CDC mortality data guidelines required the suppression of data for state-years in which 1–9 drug overdose deaths occurred in the population examined. This resulted in reduced sample sizes for several subpopulations: female; NH Black; Hispanic; age 15–29; age 30–44; and age 45–74. In three of these subpopulations (female, age 30–44, and age 45–74), only one state-year was suppressed (resulting in a sample of 458 of 459 total state-years across 2013–2021). In the NH Black subpopulation model, the sample of 359 state-years accounted for 99.6 % of all NH Black overdose deaths from 2013 to 2021; in the Hispanic subpopulation model, the 335 state-years accounted for 99.1 % of all Hispanic overdose deaths from 2013 to 2021, and the 451 state-years for the age category 15–29 accounted for 99.9 % of all overdose deaths in this age category from 2013 to 2021. The specific state-years excluded from each model are listed in Supplemental Table S2, generally representing states with relatively small populations of the groups examined, such as states with small Hispanic or NH Black populations. Data suppression requirements also limited the study to three broad racial/ethnic groups, as overdose mortality rates were unavailable for other racial/ethnic groups in multiple states. Race-specific drug overdose mortality rates were based on bridged-race categories for years 2013–2020 and single-race categories for the year 2021 (Heron, 2021), in accordance with data availability (CDC, 2023).

2.1.2. Independent variables

Counts of law enforcement seized drug reports were obtained from the National Forensic Laboratory Information System (NFLIS-Drug) online Public Data Query System (NFLIS, 2023) as accessed on May 19, 2023. The NFLIS-Drug system compiles data from 286 forensic laboratories, representing approximately 98 % of all US drug cases analyzed (Drug Enforcement Administration, n.d.), and each count represents one documented report of a specific substance within seized drug samples submitted for laboratory analysis, regardless of the size or weight of the seizure. NFLIS uses the term "drug report," rather than "seizure," since not every seized drug seized is submitted for forensic analysis (Pitts et al., 2023). For each of the 50 states and DC, 2013–2021, we compiled state-by-year raw counts of seized drug reports positive for: fentanyl/fentanyl-related compounds (fentanyl, fentanyl analogs, and fentanyl precursors); heroin; methamphetamine; cocaine; xylazine; and carfentanil (also included in the fentanyl/fentanyl-related compounds category). We selected these particular substances since they are primarily sold illicitly and are frequently involved in overdose deaths nationwide or in specific regions. We did not examine reports of prescription opioids, benzodiazepines, or antidepressants, even though these substances are also involved in overdose deaths, since these substances are sourced both legally and illicitly, and as such, the extent to which prescription drugs are involved in law enforcement reports would not likely represent their overall availability (due to not directly accounting for availability via prescription).

We used counts of specific drug reports to compute two different measures for each drug type:

a) the specific drug report *rate*, comprising the yearly number of law enforcement seized drug reports for the specific drug divided by the population size, using population estimates from the National Center

for Health Statistics via CDC WONDER (CDC, 2023) and expressed per 1000 population; and

b) the specific drug report *percentage*, comprising the number of seized drug reports of the specific drug divided by the total summed count of drug reports of fentanyl/fentanyl-related compounds, heroin, methamphetamine, cocaine, and xylazine.

To provide a specific example, the heroin report *rate* in West Virginia, 2020, represents the number of heroin seized drug reports in West Virginia in 2020, divided by the population size of West Virginia in 2020, expressed per 1000. Alternately, the heroin report *percentage* in West Virginia, 2020, represents the number of heroin seized drug reports in West Virginia in 2020, divided by the total (summed) count of seized drug reports of heroin, fentanyl/fentanyl-related compounds, methamphetamine, cocaine, and xylazine in West Virginia in 2020, expressed as a percent.

2.2. Statistical analyses

Analyses were completed using Stata/MP 18.0, Stata's user-written program *heatplot* (Jann, 2019), and RStudio. We calculated descriptive statistics (minimum and maximum values, means, and standard deviations) for all measures used in the study. Next, we examined between-state variation in drug overdose mortality and seized drug reports, calculating zero-order Pearson correlation coefficients for states' levels of different types of drug reports and drug overdose mortality rates, year by year. We calculated the correlations for each year individually due to the non-independence of states' observations over time and the potential for correlations between different drug report measures and overdose mortality rates to shift over the years examined.

For the study's main analyses, we used two-way (state and year) fixed-effects regression models to predict log-transformed drug overdose mortality rates, overall and by subpopulation (sex, age, and racial/ethnic group), using panel data from 2013 to 2021 and robust standard errors clustered at the state level. Models comprised:

A Baseline models with no predictors beyond the state and year fixed effects;
B Models adding one seized drug report measure per model; and
C Models adding all seized drug report *rates* simultaneously *or* all seized drug report *percentages* simultaneously (with the carfentanil measure omitted, since already included in the fentanyl/fentanyl-related compounds category, and one additional category [heroin] omitted to avoid perfect collinearity in the percentage model).

In these models, all predictors (drug report measures) were standardized with a mean of zero and standard deviation of one. For each model, we report within-R-squared values (Allison, 2009) and Akaike Information Criterion (AIC) values for assessment of model fit, with lower AIC values within each set of models indicating greater predictive accuracy, while accounting for the number of parameters estimated (Cavanaugh et al., 2019). AIC values were selected due to their simulation-based validation with fixed effects regression models for panel data (Yum, 2022).

3. Results

Summary statistics for all measures in the study are presented in Table 1, and Fig. 1 depicts the percentage of US seized drug reports each year corresponding to the drug types examined in the study. As presented in Fig. 1, in the US overall, the proportional representation of cocaine and heroin (in the drug reports examined) decreased over time (2013–2021), while seized drug reports of fentanyl/fentanyl-related compounds, methamphetamine, and xylazine increased in relative representation over time. In the Supplemental Material, Figs. S1–S6 display state-year rates and percentages for each drug examined in the study.

Table 1
Descriptive characteristics of the state-level measures included in the study (United States, 2013–2021).

	Mean (SD)	Min, Max	SD, between	SD, within
Drug overdose mortality rates, per 100,000 population:				
for US, overall	21.95 (11.12)	2.76, 84.19	8.60	7.15
for male population	29.18 (16.64)	3.24, 115.40	12.76	10.82
for female population	14.99 (6.28)	4.81, 53.14	5.04	3.81
for NH White population	23.94 (11.38)	3.13, 85.54	9.35	6.61
for NH Black population	25.52 (21.00)	0.00, 137.36	15.60	15.36
for Hispanic population	13.03 (9.18)	0.00, 54.66	7.89	5.76
for population aged 15–29	19.49 (9.92)	3.35, 59.88	7.59	6.45
for population aged 30–44	41.92 (25.75)	7.28, 206.21	20.55	15.76
for population aged 45–74	28.00 (16.70)	5.08, 176.42	13.60	9.88
Law enforcement drug report measures:				
Fentanyl/FRC rate	0.26 (0.45)	0.00, 2.89	0.32	0.33
Fentanyl/FRC %	9.53 (13.13)	0.00, 60.56	8.84	9.78
Heroin rate	0.44 (0.45)	0.00, 3.15	0.38	0.24
Heroin %	19.86 (15.99)	0.30, 81.60	12.34	10.31
Methamphetamine rate	1.26 (1.20)	0.00, 6.07	1.10	0.49
Methamphetamine %	47.36 (29.38)	0.34, 96.41	28.75	7.17
Cocaine rate	0.49 (0.40)	0.01, 2.16	0.37	0.15
Cocaine %	22.95 (16.30)	2.06, 80.92	14.65	7.41
Xylazine rate	0.01 (0.02)	0.00, 0.28	0.01	0.02
Xylazine %	0.30 (1.32)	0.00, 17.48	0.66	1.15
Carfentanil rate	0.00 (0.02)	0.00, 0.39	0.01	0.02
Carfentanil %	0.07 (0.36)	0.00, 5.98	0.20	0.30

Notes. Based on publicly available data from the US National Forensic Laboratory Information System, Public Data Query System (Retrieved May 19, 2023) for the 50 states and District of Columbia. Seized drug report rates are expressed per 1000 population. *Abbreviations*: FRC, fentanyl-related compounds; NH, Non-Hispanic; US, United States; %, percentage; SD, standard deviation; SD between, standard deviation between states; SD within, standard deviation within states over time.

3.1. Variation between states

Fig. 2 presents yearly state-level Pearson correlation coefficients for the bivariate associations between seized drug report measures and drug overdose mortality rates, with darker colors indicating stronger correlations (positive correlations in red and negative correlations in blue). For nearly every drug type examined, stronger correlations were observed for drug report *percentages*, rather than *rates per population*. Correlations differed over time; for example, the correlation between state drug overdose mortality rates and heroin report percentages declined over time, from a peak of Pearson's $r = 0.56$ in 2015 to a correlation near zero in the years 2020 and 2021. For most other seized drug reports besides heroin, correlations with state drug overdose mortality rates peaked during the years 2016–2019 and were lower in the two most recent years examined (2020 and 2021).

3.2. Variation within states over time

Tables 2–4 provide results from state- and year- fixed effects regression models predicting state-level drug overdose mortality rates by various seized drug report measures. Table 2 includes results in the overall population and among male and female populations, Table 3

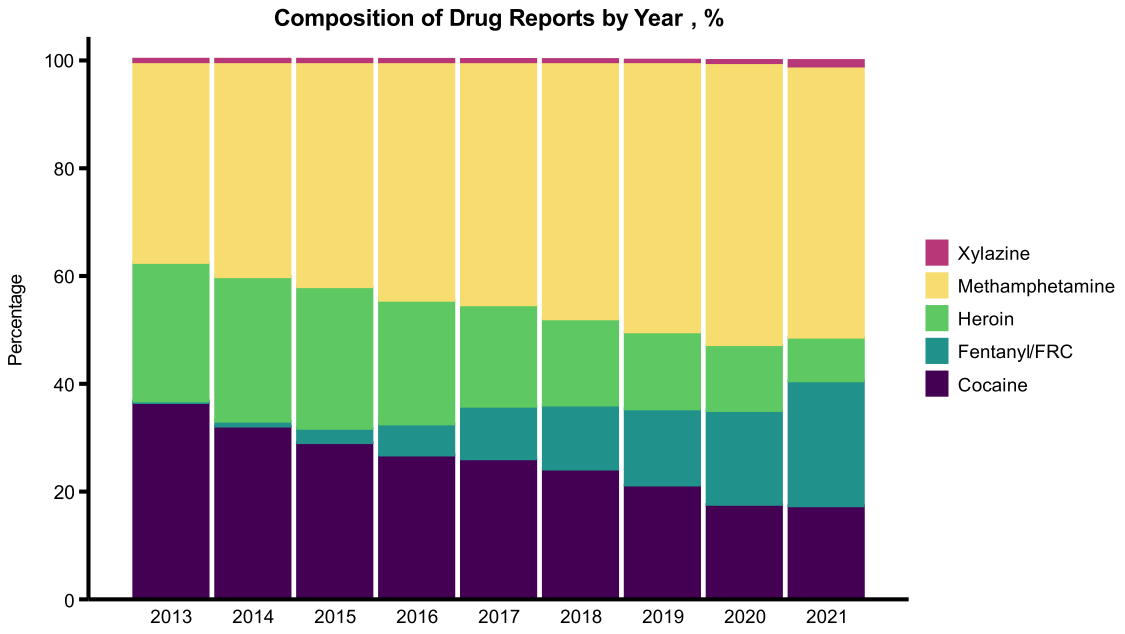

Fig. 1. Percentage of seized drug reports each year (United States, 2013–2021) corresponding to each of the drug types examined in the study.
Note. The drug categories examined do not represent all drug seizure types reported by the National Forensic Laboratory Information System, but only those included in the present study. *Abbreviations*: Fentanyl/FRC, fentanyl and fentanyl-related compounds.

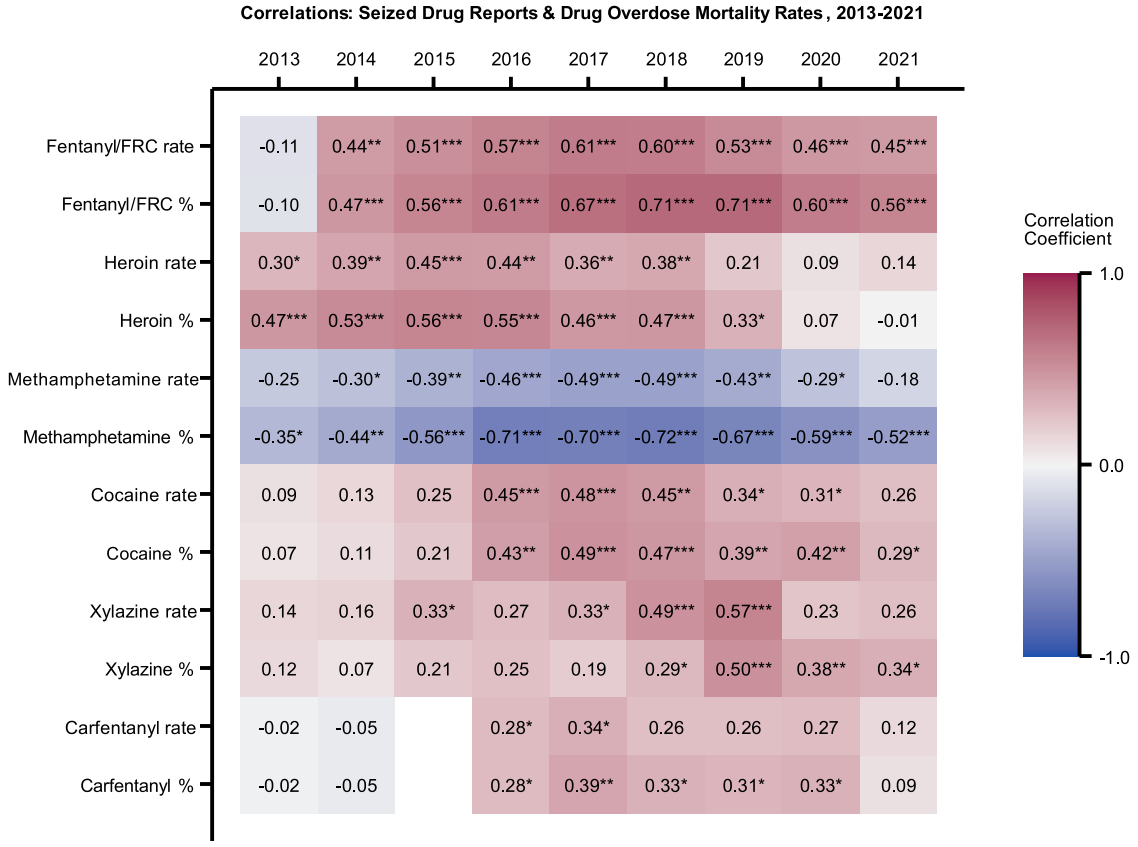

Fig. 2. Pearson correlation coefficients for bivariate yearly associations between annual seized drug reports and annual drug overdose mortality rates, United States, 2013–2021.
Note. Drug overdose mortality rates are per 100,000 population. Seized drug report rates are per 1000 population. Data unavailable for the associations between carfentanil measures and overdose mortality rate in 2015. *Abbreviations*: Fentanyl/FRC, fentanyl and fentanyl related compounds. *Symbols*: %, percentage.
*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Table 2
Results of state- and year- fixed effects regression models predicting drug overdose mortality rates in the US overall, and in male and female populations, by measures related to seized drug reports, 2013–2021.

	Overall			Male population			Female population		
	β (SE)	R^2	AIC	β (SE)	R^2	AIC	β (SE)	R^2	AIC
A. Baseline model									
State & Year Fixed Effects		0.73	−448.75		0.78	−413.26		0.56	−443.69
B. Baseline model + one seized drug report measure at a time									
Fentanyl/FRC rate	**0.08** (0.02)	0.76	−491.39	**0.07** (0.02)	0.79	−439.11	**0.09** (0.02)	0.62	−505.99
Fentanyl/FRC %	**0.14** (0.02)	0.79	−552.96	**0.12** (0.02)	0.81	−482.39	**0.15** (0.02)	0.68	−578.91
Heroin rate	−0.03 (0.02)	0.73	−450.62	−0.00 (0.02)	0.78	−411.27	−0.07 (0.02)	0.59	−466.52*
Heroin %	**−0.07** (0.02)	0.75	−477.40	**−0.04** (0.02)	0.78	−421.13	**−0.11** (0.02)	0.63	−520.57*
Meth. rate	−0.04 (0.04)	0.73	−450.02	−0.04 (0.04)	0.78	−414.55	−0.03 (0.04)	0.57	−444.14
Meth. %	0.05 (0.06)	0.73	−448.94	0.01 (0.06)	0.78	−411.29	**0.14** (0.06)	0.58	−459.47
Cocaine rate	−0.00 (0.03)	0.73	−446.76	−0.01 (0.03)	0.78	−411.43	0.01 (0.03)	0.56	−441.78
Cocaine %	**−0.11** (0.04)	0.75	−475.46	**−0.12** (0.04)	0.79	−439.55	**−0.12** (0.04)	0.59	−471.09
Xylazine rate	−0.01 (0.01)	0.73	−447.38	**−0.02** (0.01)	0.78	−415.10	0.01 (0.01)	0.57	−443.03
Xylazine %	0.01 (0.01)	0.73	−448.29	0.00 (0.01)	0.78	−411.27	**0.03** (0.01)	0.57	−450.38
Carfent. rate	**0.02** (0.00)	0.73	−451.62	**0.02** (0.00)	0.78	−415.31	**0.02** (0.00)	0.57	−447.08
Carfent. %	**0.02** (0.01)	0.73	−453.47	**0.02** (0.01)	0.78	−416.94	**0.02** (0.00)	0.57	−449.19
C. Baseline model + all seized drug report measures simultaneously									
Rates									
Fentanyl/FRC rate	**0.14** (0.03)	–	–	**0.14** (0.03)	–	–	**0.12** (0.03)	–	–
Heroin rate	0.07 (0.04)	–	–	**0.10** (0.04)	–	–	0.01 (0.04)	–	–
Meth. rate	**−0.08** (0.04)	–	–	**−0.08** (0.04)	–	–	−0.06 (0.03)	–	–
Cocaine rate	**−0.09** (0.03)	–	–	**−0.11** (0.03)	–	–	−0.06 (0.03)	–	–
Xylazine rate	**−0.02** (0.01)	–	–	**−0.02** (0.01)	–	–	−0.01 (0.01)	–	–
Model fit	–	0.77	−519.08	–	0.81	−482.66	–	0.63	−513.82
Percentages									
Fentanyl/FRC %	**0.13** (0.02)	–	–	**0.12** (0.02)	–	–	**0.15** (0.02)	–	–
Meth. %	−0.07 (0.08)	–	–	−0.14 (0.08)	–	–	0.06 (0.07)	–	–
Cocaine %	**−0.13** (0.05)	–	–	**−0.16** (0.06)	–	–	−0.08 (0.04)	–	–
Xylazine %	−0.00 (0.01)	–	–	−0.01 (0.01)	–	–	0.00 (0.01)	–	–
Model fit	–	0.80	−580.23	–	0.83	−520.23	–	0.70	−606.95

Notes. State-year observations: $n = 459$ for overall and male population models; $n = 458$ for female population models; *Rate* refers to the number of law enforcement seized drug reports of the specified drug per 1000 population. *Percentage* refers to the number of drug reports of the specified drug divided by all drug reports examined in the study, expressed as percent. Drug overdose mortality rates are per 100,000 population and are log-transformed. All predictors are standardized with a mean of 0 and standard deviation of 1. Robust standard errors are clustered at the state level. Coefficients in bold are significantly different from zero at $p < 0.05$. R^2 is for the within variation. *Abbreviations*: SE, standard error; AIC, Akaike information criterion; FRC, fentanyl-related compounds; %, percent; Meth, methamphetamine; Carfent, carfentanil. *Symbols*: −, not applicable.

presents results by racial/ethnic subgroup, and Table 4 provides results by age group.

In models examining one seized drug report measure per model, the fentanyl/fentanyl-related compounds percentage (and, to a lower extent, the fentanyl/fentanyl-related compounds rate and the carfentanil rate and percentage) was significantly positively associated with drug overdose mortality rates across all subgroups examined, while the cocaine percentage was significantly negatively associated with drug overdose mortality rates across all subgroups examined. Similar results were observed in the supplemental analysis examining synthetic opioid-involved overdose mortality as the outcome (Supplemental Table S1). The direction and significance of associations with other drug report measures differed between subgroups; for example, the heroin report percentage was significantly negatively associated with drug overdose mortality rates for all subgroups except ages 15–29, NH Black, and Hispanic. In models including all drug report measures simultaneously, fentanyl/fentanyl-related compound drug report measures (both as percentages and rates) remained consistently positively associated with drug overdose mortality rates across all populations, while results for other drugs varied between populations.

For nearly all populations examined (except for ages 15–29), the model that included *all* seized drug report *percentage* measures represented the best-performing model (as identified via the lowest AIC and highest within R-squared values), followed by the model including only the fentanyl/fentanyl-related compounds *percentage*. In contrast, in the population age 15–29, the best-performing model included all drug report *rates* (AIC = −250.43), closely followed by the model with all drug report *percentages* (AIC = −247.03).

4. Limitations

Although the data source used in the present study (NFLIS) is publicly accessible and available for all states (Drug Enforcement Administration, n.d.), it does not include the level of detail available in state-specific data sources examined in prior studies, such as weights/-quantities/doses within each drug submitted for analysis, the county, zip code area, or address corresponding to the seizure, "true" combinations of drugs, or the type of law enforcement agency involved. Not all forensic laboratories are represented in the NFLIS, not all drugs seized are analyzed, and laboratories may differ in terms of which drugs are analyzed and reported. Exact counts of drug reports depend on the date results are retrieved, due to periodic updates of delayed data (Drug Enforcement Administration, n.d.), and these drug reports represent raw counts that are not adjusted for differences in laboratory reporting (Pitts et al., 2023).

The state- and year- fixed effects models used in the present study included a variety of drug report measures, yet not all drug types were included, and models did not account for availability of prescription drugs, given the present study's focus on illicit drugs, even though overdose deaths may involve both illicit and prescription drugs. Finally, in preliminary analyses examining variation between states, correlation coefficients were computed for each year independently in consideration of temporal, yet not spatial, dependence of observations.

5. Discussion

The present study examined the extent to which measures from publicly accessible law enforcement drug reports account for differences

Table 3
Results of state- and year- fixed effects regression models predicting drug overdose mortality rates for Non-Hispanic (NH) White, NH Black, and Hispanic populations, by measures related to seized drug reports, 2013–2021.

	White, Non-Hispanic			Black, Non-Hispanic			Hispanic		
	β (SE)	R^2	AIC	β (SE)	R^2	AIC	β (SE)	R^2	AIC
A. Baseline model									
State & Year Fixed Effects		0.66	−510.57		0.89	−232.75		0.74	−58.19
B. Baseline model + one seized drug report measure at a time									
Fentanyl/FRC rate	**0.09** (0.02)	0.71	−575.95	**0.06** (0.03)	0.90	−242.42	**0.11** (0.03)	0.76	−79.33
Fentanyl/FRC %	**0.13** (0.02)	0.73	−621.60	**0.10** (0.03)	0.90	−256.74	**0.16** (0.04)	0.77	−96.04
Heroin rate	−0.03 (0.02)	0.66	−513.87	−0.02 (0.03)	0.89	−231.96	−0.03 (0.05)	0.74	−57.50
Heroin %	**−0.08** (0.02)	0.69	−551.42	−0.05 (0.03)	0.89	−237.56	−0.06 (0.05)	0.74	−61.10
Meth. rate	−0.01 (0.03)	0.66	−508.77	0.01 (0.05)	0.89	−230.98	0.04 (0.07)	0.74	−56.96
Meth. %	0.06 (0.06)	0.66	−512.81	0.06 (0.06)	0.89	−232.85	0.04 (0.10)	0.74	−56.69
Cocaine rate	0.03 (0.03)	0.66	−511.88	−0.00 (0.04)	0.89	−230.76	0.03 (0.06)	0.74	−56.72
Cocaine %	**−0.09** (0.04)	0.68	−530.02	**−0.10** (0.04)	0.90	−243.15	**−0.22** (0.07)	0.76	−85.78
Xylazine rate	−0.01 (0.01)	0.66	−509.88	−0.02 (0.01)	0.89	−233.82	−0.01 (0.01)	0.74	−56.37
Xylazine %	0.00 (0.01)	0.66	−508.67	−0.00 (0.01)	0.89	−230.81	0.00 (0.01)	0.74	−56.20
Carfent. rate	**0.02** (0.00)	0.66	−514.65	**0.02** (0.00)	0.89	−233.62	**0.02** (0.00)	0.74	−58.34
Carfent. %	**0.02** (0.00)	0.67	−516.93	**0.02** (0.01)	0.89	−234.92	**0.02** (0.01)	0.74	−58.93
C. Baseline model + all seized drug report measures simultaneously									
Rates									
Fentanyl/FRC rate	**0.13** (0.03)	–	–	**0.09** (0.04)	–	–	**0.17** (0.04)	–	–
Heroin rate	0.05 (0.04)	–	–	0.02 (0.04)	–	–	0.07 (0.07)	–	–
Meth. rate	−0.04 (0.03)	–	–	−0.02 (0.05)	–	–	−0.04 (0.08)	–	–
Cocaine rate	−0.05 (0.04)	–	–	−0.05 (0.04)	–	–	−0.07 (0.06)	–	–
Xylazine rate	**−0.02** (0.01)	–	–	**−0.03** (0.01)	–	–	−0.02 (0.01)	–	–
Model fit	–	0.72	−592.25	–	0.90	−244.73	–	0.76	−78.76
Percentages									
Fentanyl/FRC %	**0.13** (0.02)	–	–	**0.11** (0.03)	–	–	**0.15** (0.04)	–	–
Meth. %	−0.01 (0.07)	–	–	0.04 (0.07)	–	–	−0.12 (0.11)	–	–
Cocaine %	−0.08 (0.05)	–	–	−0.08 (0.05)	–	–	**−0.25** (0.08)	–	–
Xylazine %	−0.02 (0.01)	–	–	−0.02 (0.01)	–	–	−0.02 (0.01)	–	–
Model fit	–	0.75	−641.18	–	0.90	−267.26	–	0.79	−121.36

Notes. State-year observations: NH White, $n = 459$; NH Black, $n = 359$; Hispanic, $n = 335$. *Rate* refers to the number of law enforcement seized drug reports of the specified drug per 1000 population. *Percentage* refers to the number of drug reports of the specified drug divided by all drug reports examined in the study, expressed as percent. Drug overdose mortality rates are per 100,000 population and are log-transformed. All predictors are standardized with a mean of 0 and standard deviation of 1. Robust standard errors are clustered at the state level. Coefficients in bold are significantly different from zero at $p<0.05$. R^2 is for the within variation. *Abbreviations*: SE, standard error; AIC, Akaike information criterion; FRC, fentanyl-related compounds; %, percent; Meth, methamphetamine; Carfent, carfentanil. *Symbols*: –, not applicable.

in overall US drug overdose mortality rates between states, within states over time (2013–2021), and in various subpopulations. Study results indicated a consistent positive association between fentanyl/fentanyl-related compound seized drug reports and drug overdose mortality; this positive association was observed across all analyses in the study, including: models with one or multiple drug report measures; models for all populations examined by sex, age, and race/ethnicity; and models measuring fentanyl/fentanyl-related compounds as a rate per population or as a proportion of all drug reports examined. Drug reports involving carfentanil were also consistently positively associated with drug overdose mortality rates. In contrast, the proportional representation of cocaine in seized drug reports was negatively associated with drug overdose mortality rates in all populations examined, and results were mixed for heroin, methamphetamine, and xylazine reports.

In this study, seized drug report measures were conceptualized as proxies for the composition of illicit drug supplies, consistent with numerous prior studies (e.g., Gladden et al., 2016; Jalal and Burke, 2021; Sumner et al., 2022; Zibbell et al., 2019, 2023; Zoorob, 2019). In contrast, several studies (e.g., Lowder et al., 2022; Mohler et al., 2021; Ray et al., 2023) have examined seized drug reports as law enforcement operations with the potential to either reduce overdose deaths (by limiting the availability and use of potentially lethal substances) or increase overdose deaths (by disrupting opioid tolerance levels and shifting individuals who use drugs to less familiar drug sources and products of unknown potency). The present study, however, was not based on the notion that seized drug reports directly impact rates of drug overdose mortality, but rather that higher proportional representation of potent substances (e.g., fentanyl, carfentanil) in seized drug reports is indicative of greater pervasiveness of these substances in street drug supplies, accompanied by more use of (or exposure to) these substances relative to others, and a higher rate of fatal overdoses.

In a recent analysis of 2014–2019 US opioid overdose deaths by state and quarter, seized drug report measures expressed as *counts* were more strongly associated with changes in opioid overdose deaths, compared to drug report measures expressed as *percentages* (Zibbell et al., 2023). In the present study, drug report measures expressed as *percentages* of total examined drug reports accounted for more variation in drug overdose mortality between and within states (in most, yet not all models), relative to measures expressed as drug report *rates* per population. It is plausible that drug report rates per population may be more sensitive to year-by-year or between-state differences in drug enforcement, while percentage-based measures may more stably reflect the extent to which one substance is more common than another in street drug supplies, regardless of variation in law enforcement activities (Zibbell et al., 2023). For example, a state's increase in overall enforcement activities following a policy change may be reflected in higher *rates* of drug reports, but such increases in overall enforcement activities would not likely impact the *percentage* of drug reports involving a certain substance. With the exception of a few studies that have included percentage-based measures (Zibbell et al., 2019, 2023) the majority of studies on associations between seized drug reports and overdose mortality have examined counts or rates (Gladden et al., 2016; Hall et al., 2021; Jalal and Burke, 2021; Lowder et al., 2022; Rosenblum et al., 2020; Slavova et al., 2017; Sumner et al., 2022; Tran et al., 2021; Zibbell et al., 2022; Zoorob, 2019). Findings from the present study, however, support the potential utility of proportion-based drug report measures.

Of the state- and year- fixed effects models examined in this study, the best-performing model for the overall population (and nearly all

Table 4
Results of state- and year- fixed effects regression models predicting drug overdose mortality rates for populations age 15–29, 30–44, and 45–74, by measures related to seized drug reports, 2013–2021.

	Ages 15–29			Ages 30–44			Ages 45–74		
	β (SE)	R^2	AIC	β (SE)	R^2	AIC	β (SE)	R^2	AIC
A. Baseline model									
State & Year Fixed Effects		0.60	−172.70		0.71	−283.72		0.64	−429.08
B. Baseline model + one seized drug report measure at a time									
Fentanyl/FRC rate	**0.06** (0.02)	0.61	−184.29	**0.09** (0.02)	0.73	−325.31	**0.08** (0.02)	0.68	−472.93
Fentanyl/FRC %	**0.08** (0.03)	0.61	−188.17	**0.17** (0.02)	0.77	−396.82	**0.15** (0.03)	0.73	−543.53
Heroin rate	**0.06** (0.03)	0.61	−181.57	−0.04 (0.02)	0.71	−287.33	**−0.07** (0.02)	0.67	−453.45
Heroin %	0.02 (0.03)	0.60	−172.54	**−0.09** (0.02)	0.73	−318.23	**−0.11** (0.02)	0.70	−500.65
Meth. rate	−0.03 (0.04)	0.60	−171.64	−0.04 (0.04)	0.71	−284.73	−0.01 (0.05)	0.65	−427.48
Meth. %	−0.10 (0.08)	0.60	−176.13	**0.13** (0.06)	0.71	−292.71	**0.13** (0.05)	0.66	−442.79
Cocaine rate	0.05 (0.03)	0.60	−173.96	−0.01 (0.03)	0.71	−281.95	−0.03 (0.03)	0.65	−428.57
Cocaine %	**−0.11** (0.05)	0.61	−185.56	**−0.18** (0.04)	0.74	−334.03	**−0.11** (0.04)	0.66	−450.57
Xylazine rate	**−0.04** (0.01)	0.61	−187.04	−0.01 (0.01)	0.71	−282.90	0.02 (0.01)	0.65	−430.47
Xylazine %	**−0.04** (0.01)	0.61	−185.21	0.01 (0.01)	0.71	−282.27	**0.04** (0.01)	0.66	−444.15
Carfent. rate	**0.02** (0.00)	0.60	−173.14	**0.02** (0.00)	0.71	−286.68	**0.02** (0.00)	0.65	−430.56
Carfent. %	**0.02** (0.01)	0.60	−174.96	**0.03** (0.01)	0.71	−289.02	**0.02** (0.00)	0.65	−431.30
C. Baseline model + all seized drug report measures simultaneously									
Rates									
Fentanyl/FRC rate	**0.17** (0.03)	–	–	**0.16** (0.03)	–	–	**0.10** (0.03)	–	–
Heroin rate	**0.17** (0.05)	–	–	0.07 (0.05)	–	–	0.00 (0.04)	–	–
Meth. rate	**−0.09** (0.04)	–	–	−0.08 (0.05)	–	–	−0.03 (0.05)	–	–
Cocaine rate	**−0.09** (0.04)	–	–	**−0.11** (0.04)	–	–	**−0.08** (0.04)	–	–
Xylazine rate	**−0.04** (0.02)	–	–	**−0.02** (0.01)	–	–	−0.00 (0.01)	–	–
Model fit[a]	–	0.67	−250.43	–	0.75	−353.31	–	0.69	−481.35
Percentages									
Fentanyl/FRC %	**0.09** (0.03)	–	–	**0.17** (0.02)	–	–	**0.14** (0.02)	–	–
Meth. %	**−0.27** (0.09)	–	–	−0.03 (0.08)	–	–	0.05 (0.07)	–	–
Cocaine %	**−0.22** (0.07)	–	–	**−0.18** (0.06)	–	–	−0.07 (0.05)	–	–
Xylazine %	**−0.04** (0.02)	–	–	−0.01 (0.01)	–	–	0.01 (0.01)	–	–
Model fit[a,b]	–	0.66	−247.03	–	0.80	−450.90	–	0.74	−567.37

Notes. State-year observations: Ages 15–29, $n = 451$; Ages 30–44, $n = 458$; Ages 45–74, $n = 458$. *Rate* refers to the number of law enforcement seized drug reports of the specified drug per 1000 population. *Percentage* refers to the number of drug reports of the specified drug divided by all drug reports examined in the study, expressed as percent. Drug overdose mortality rates are per 100,000 population and are log-transformed. All predictors are standardized with a mean of 0 and standard deviation of 1. Robust standard errors are clustered at the state level. Coefficients in bold are significantly different from zero at $p < 0.05$. R^2 is for the within variation. *Abbreviations*: SE, standard error; AIC, Akaike information criterion; FRC, fentanyl-related compounds; %, percent; Meth, methamphetamine; Carfent, carfentanil. *Symbols*: −, not applicable.

subgroups examined) included *percentage* measures for seized drug reports involving fentanyl/fentanyl-related compounds, cocaine, methamphetamine, and xylazine (with the percentage involving heroin omitted to avoid perfect collinearity). When examining only one drug-report measure at a time, models with the fentanyl/fentanyl-related compound *percentage* accounted for the largest extent of variation in state-level drug overdose mortality rates. Fentanyl's high potency, wide availability (Kilmer et al., 2022), and involvement in an estimated two thirds of all drug overdose deaths (Spencer et al., 2023) may explain the strong performance of fentanyl/fentanyl-related compound reports as predictors of overall drug overdose mortality rates. The results of multiple prior studies support the positive association between seized fentanyl/fentanyl-related compound reports and drug overdose deaths in individual states and the US overall (Gladden et al., 2016; Rosenblum et al., 2020; Slavova et al., 2017; Zibbell et al., 2019, 2023; Zoorob, 2019), and results of the present study add that this association is observed across subpopulations based on sex, race/ethnicity, and age. The present study also documented significant positive associations between state-level carfentanil reports and drug overdose mortality rates, consistent with several prior studies (Jalal and Burke, 2021; Tran et al., 2021).

With respect to stimulants, prior studies report mixed or inconsistent associations between seized stimulant reports and overdose mortality outcomes (Ray et al., 2023; Lowder et al., 2022; Zibbell et al., 2022, 2023). The present study's correlation analyses examining between-state variation suggested that states with higher proportions of methamphetamine in seized drug reports were states with lower drug overdose mortality rates, possibly because methamphetamine is most concentrated in the western US (Supplemental Fig. S3), where non-pharmaceutical fentanyl is relatively less prevalent (Supplemental Fig. S1) and overdose death rates are lower (Wilson et al., 2020). Conversely, states with higher rates/proportions of cocaine seized drug reports were also generally states with higher drug overdose mortality rates, plausibly because cocaine is concentrated in the eastern US (Supplemental Fig. S1), where non-pharmaceutical fentanyl is also concentrated (Supplemental Fig. S4) and increases risk of fatality. When utilizing *panel data* to examine within-state variation over time, however, the proportional representation of cocaine in seized drug reports was negatively associated with drug overdose mortality in multiple models examined, consistent with a recent national analysis of opioid overdose mortality (Zibbell et al., 2023). Regarding methamphetamine, results from the study's panel data models did not provide consistent evidence of an association between methamphetamine drug reports and drug overdose mortality rates. Although the data source used in the present study did not provide information about combinations of drugs reported in seizures, prior research suggests the relevance of considering drug combinations (Zibbell et al., 2022). In one Ohio-based study, for example, stimulant deaths were positively associated with seized reports of cocaine or methamphetamine *with* fentanyl but negatively associated with seized reports of methamphetamine *without* fentanyl (Zibbell et al., 2022).

In the present study, state-level correlations between drug report measures and drug overdose mortality rates differed over the individual years examined. The attenuation over time of the state-level correlation between heroin report measures and drug overdose mortality rates is consistent with documented trends in drug availability and overdose deaths, as heroin has diminished in availability and in involvement in overdose deaths over time, virtually replaced by fentanyl (Pardo et al.,

2021). The relatively weaker correlations between most drug report measures and drug overdose mortality rates in the years 2020–2021, compared to 2019, may also possibly reflect COVID-19-related disruptions in drug markets or increased contributions of social factors to drug overdose mortality during the unique circumstances of the pandemic (Imtiaz et al., 2021). Nonetheless, further research would be necessary to test these potential explanations or to clarify post-COVID trends as more recent data become available.

6. Implications and conclusions

Law enforcement drug report data are often available relatively more quickly than overdose mortality data (Hall et al., 2021), and many forensic laboratories test for emerging substances of concern before these substances are included in routine postmortem testing or reporting (Zibbell et al., 2023). Based on results from the present study, as well as prior studies (Gladden et al., 2016; Rosenblum et al., 2020; Slavova et al., 2017; Zibbell et al., 2019, 2023; Zoorob, 2019), fentanyl/fentanyl-related compounds in seized drug reports represent potential indicators to include in overdose early warning systems alongside additional data sources such as community drug-checking programs (Dasgupta and Figgatt, 2022) or clinical samples (Whitley et al., 2022). Considering that new substances are frequently introduced in illicit drug supplies, overdose early warning systems may also adapt by adding indicators of the proportion of seized drug reports positive for whichever novel substances are identified as most potent and lethal.

Although drug supplies affect risk of fatal overdose (Ruhm, 2019), a sole focus on supply-side interventions can lead to increases in the availability and use of more dangerous and potent drugs, ultimately increasing deaths (Beletsky and Davis, 2017; Lowder et al., 2022; Maclean et al., 2020; Rosenblum et al., 2020). While examining seized drugs may emphasize *supply*-side influences on drug overdose mortality, seized drug report measures can also facilitate evaluations of *demand*-side policies (e.g., naloxone access laws, Good Samaritan laws, cannabis legalization; Maclean et al., 2020) and social/economic influences (e.g., unemployment, poverty, incarceration), since "isolating the effects" of such policies and socioeconomic factors may require statistical adjustment for supply-side factors such as illicit drug market characteristics (Hall et al., 2021). Overall, findings of the present study support the potential utility of publicly available seized drug proportional measures (i.e., percentages of drug reports involving various drug types), especially the proportion of fentanyl/fentanyl-related compounds, for overdose early warning systems (e.g., Hall et al., 2021; Marks et al., 2021; Sumner et al., 2022), as well as research into contextual-level risk factors and interventions, with the overarching aim of reducing the number of lives lost to drug overdoses each year in the US.

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CRediT authorship contribution statement

Manuel Cano: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Visualization. **Patricia Timmons:** Validation, Writing – review & editing. **Madeline Hooten:** Validation, Writing – review & editing. **Kaylin Sweeney:** Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dadr.2023.100197.

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