Excess Fatal Overdoses in the United States During the COVID-19 Pandemic by Geography and Substance Type: March 2020–August 2021

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See also Excess Mortality Calculations: Methods and Uses, pp. 575–609.

Objectives. To assess heterogeneity in pandemic-period excess fatal overdoses in the United States, by location (state, county) and substance type.

Methods. We used seasonal autoregressive integrated moving average (SARIMA) models to estimate counterfactual death counts in the scenario that no pandemic had occurred. Such estimates were subtracted from actual death counts to assess the magnitude of pandemic-period excess mortality between March 2020 and August 2021.

Results. Nationwide, we estimated 25 668 (95% prediction interval [PI] = 2811, 48 524) excess overdose deaths. Specifically, 17 of 47 states and 197 of 592 counties analyzed had statistically significant excess overdose-related mortality. West Virginia, Louisiana, Tennessee, Kentucky, and New Mexico had the highest rates (20–37 per 100 000). Nationally, there were 5.7 (95% PI = 1.0, 10.4), 3.1 (95% PI = 2.1, 4.2), and 1.4 (95% PI = 0.5, 2.4) excess deaths per 100 000 involving synthetic opioids, psychostimulants, and alcohol, respectively.

Conclusions. The steep increase in overdose-related mortality affected primarily the southern and western United States. We identified synthetic opioids and psychostimulants as the main contributors.

Public Health Implications. Characterizing overdose-related excess mortality across locations and substance types is critical for optimal allocation of public health resources. (*Am J Public Health*. 2024;114(6):599–609. https://doi.org/10.2105/AJPH.2024.307618)

Over the past 20 years, fatal drug overdoses have been rising at an alarming rate in the United States.[1] A triple wave epidemic, driven by changes in substance supply and demand, has been theorized.[2] The differing characteristics of the most recent, fourth substance overdose wave underscore that this multifaceted crisis is not caused by a single substance type.[3] In particular, the surge of synthetic opioids and psychostimulant use during the COVID-19 pandemic[3] has had both important repercussions on behavioral health and implications for resource allocation, especially in rural areas of the United States.[4]

Excess mortality, defined as the discrepancy between the number of observed deaths and expected deaths, has become commonly used to understand the full burden of the pandemic.[5] This metric can retrospectively quantify the impacts of the pandemic on cause-specific deaths (e.g., cancer, diabetes, overdose).[6] Thus far, pandemic-period changes in drug overdose–related mortality have primarily been examined nationwide,[7,8] among certain racial and ethnic groups,[9–12] or in a few states or cities.[11–14]

Two studies investigated 31 states[15] and all 50 states,[16] respectively, but did not model excess mortality and instead quantified percent changes and absolute increases in drug overdose–related deaths. From a public health and policy

AJPH June 2024, Vol. 114, No. 6

decision-making perspective, excess-mortality approaches generally have advantages over point-in-time comparisons (i.e., percent change), including estimation of the counterfactual, acknowledgment of seasonality and long-term trends, and inclusion of uncertainty bounds.

In 2020 to 2022, 3 studies evaluated excess mortality associated with drug overdoses; they did so at the national level and for a single state (California).[7–9] County-level heterogeneity and state-level substance-specific trends in overdose mortality have yet to be studied. In addition, the extent of overdose-related excess mortality by state and of potential interactions between geography and substance type remain to be investigated. Such information could help state and local health departments allocate resources, allowing them to identify treatment needs, deploy effective outreach strategies, and implement rehabilitative and nonrehabilitative interventions that may vary with urbanicity.[17] While previous work has resulted in national recommendations—including innovation in substance use disorder treatments and disbursement methods, expansion of telehealth opportunities, enhancement of harm reduction services such as naloxone delivery, and improved access to methadone and buprenorphine,[18] such solutions may not universally apply, and their meaningful combination may depend on the location.

In this study, we quantified national-, state-, and county-level distributions of excess fatal overdoses that occurred during the pandemic, overall and for specific substance types. Each geographical unit of analysis matters; public health agencies implement prevention and recovery programs at all levels. Such a comprehensive investigation is critical for targeted resource allocation.

METHODS

Using the publicly available Centers for Disease Control and Prevention (CDC) WONDER (Wide-ranging Online Data for Epidemiologic Research) data platform,[19] we extracted cause-specific death data across all ages nationwide, by state, and by county, between January 2015 and August 2021 (see the Methods section of the Appendix, available as a supplement to the online version of this article at https://ajph.org). We identified overdose-related deaths using the underlying cause-of-death field (see the Methods section of the Appendix). The relevant *International Classification of Diseases, 10th Revision* (*ICD-10*; https://www.cdc.gov/nchs/icd/icd10.htm) codes were X40–X45 (Accidental), X60–X65 (Suicide), X85 (Homicide), and Y10–Y15 (Unknown). In addition, using the contributing cause-of-death information, we identified overdoses involving at least 1 of the following substances: heroin (T40.1), natural and semisynthetic opioids (T40.2), synthetic opioids excluding methadone (T40.4), cocaine (T40.5), psychostimulants with abuse potential (T43.6), benzodiazepines (T42.4), and alcohol (T51; Appendix Figure A).

Notably, decedents for whom the coroner or medical examiner determined the presence of multiple substances at the time of death would have certificates listing multiple contributing causes. Therefore, substance-specific categories considered in this study are not mutually exclusive, and overall overdose-related excess mortality is lower than the sum of substance-specific excess mortality. Importantly, the CDC WONDER data do not allow distinction between prescription use and illicit use. Alone, the *ICD-10* codes for underlying and contributing causes of death are insufficient to examine the potential role of substance misuse. Although partial explanations about an individual's medical history might be available in the free text section of the death certificate titled "How Injury Occurred,"[20] this part of the record may not be well-documented, even when an autopsy is performed. Moreover, the amount of details being provided about an individual's medical history and the circumstances of their death can vary substantially across medical examiners and decedents.

We estimated excess fatal overdoses both overall and by substance type by comparing observed deaths to projections based on historical trends. Our national- and overall state-level analyses capture a relatively long horizon of 18 months. Specifically, for national- and state-level estimates across all drug types, we compared counts of deaths that occurred between March 2020 and August 2021 (inclusive) to projections for this same period based on monthly data from a 5-year prepandemic period spanning January 2015 through February 2020 (inclusive). For county-level estimates across all drug types and for state-level substance-specific estimates, we similarly compared deaths that occurred in 2020 to projections based on historical data for that year. This greater level of spatial or substance type granularity required us to use yearly rather than monthly data, because of privacy-protecting data suppression in areas with few deaths in a given timeframe. For these analyses, we thus used a longer 10-year timeframe for our counterfactual models (from 2010 to 2019, inclusive). Out of 3143 counties, 592 (representing 78%

AJPH June 2024, Vol. 114, No. 6

of the US population) had no missing data for 2010 to 2020 and were included in the monthly analyses; the remaining counties were excluded. Similarly, 3 states (North and South Dakota and Wyoming, representing less than 1% of the population) were excluded from the monthly analyses owing to missing data.

We used a seasonal autoregressive integrated moving average (SARIMA) model to estimate the expected number of deaths in the hypothetical scenario in which no pandemic occurred. Models were fitted separately for each substance type and geographical unit (county, state, country). Each model's parameters were chosen based on the Akaike information criterion (see Methods section in the Appendix). Once fitted to prepandemic data, the selected SARIMA model yielded projections during the pandemic period of interest, along with prediction intervals (see Methods section in the Appendix). When the observed number of deaths was outside the prediction interval (PI) for the projected number of deaths, the change in overdose-related mortality was deemed statistically significant. We conducted a sensitivity analysis to the type of model used to derive mortality projections based on prepandemic data, comparing locally estimated scatterplot smoothing models (Appendix Figure B) with the SARIMA models presented in the main analysis. We performed all analyses by using R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From March 2020 to August 2021, we estimated a total of 25 668 (95% PI = 2811, 48 524) excess deaths nationwide, equivalent to a mortality rate of 7.7 per 100 000 persons (95% PI = 0.9, 14.6) and 15% (95% PI = 1%, 29%) of 159 000 fatal overdoses overall. The start of the pandemic was marked by a dramatic rise in fatal overdoses: a 19% increase occurred in the 6 months that followed March 2020, relative to the counterfactual (Figure 1). Specifically, 17 out of 47 states and the District of Columbia, representing 45% of the US population, experienced a statistically significant increase in overdose-related mortality (Table 1, Figure 2). In particular, West Virginia (37 [95% PI = 2, 72] excess overdose-related deaths per 100 000), Louisiana (28; 95% PI = 16, 40), Tennessee (25; 95% PI = 18, 32), Kentucky (22; 95% PI = 1, 42), and New Mexico (20; 95% PI = 2, 38) had the highest overdose-related excess mortality rates (Table 1). These 5 states alone accounted for 21% of nationwide excess fatal overdoses (5060 in total), despite representing only 6% of the US population. These states had both high expected mortality levels and high excess mortality. Pacific coast states—including Oregon (12; 95% PI = 6, 19), Washington (11; 95% PI = 3, 18), and California (7; 95% PI = 3, 10)—also had high excess overdose-related death rates. In addition, 20 states without significant aggregate overdose-related excess mortality during the study period experienced significant excess mortality in specific months, especially either immediately following the start of the pandemic in March 2020 or 1 year later (March–May 2020 and March–May 2021).

Moreover, 197 of the 592 counties analyzed, representing 36% of the US population, had a statistically significant increase in overdose-related mortality in 2020 (Figure 3, Appendix Table A). Among the 50 counties with the highest overdose-related excess mortality, half were located in the 5 most-affected states. Geographical clustering was notable: the 4 counties with the largest excess mortality rates (65–78 excess deaths per 100 000) were all located in West Virginia. Many of these counties had both high expected drug overdose–related deaths and high excess mortality (Appendix Figure C). However, we also identified a few outlying counties with high excess mortality in states that overall did not exhibit such a pattern (e.g., Monroe County, Pennsylvania; see the Results section of the Appendix). Our results also highlighted county-level differences based on urbanicity, but with variations across states as illustrated by the case of Florida versus Texas (see the Results section of the Appendix).

Importantly, national-level excess overdose-related mortality also varied across substance types. The primary contributors were synthetic opioids (5.7 [95% PI = 1.0, 10.4] excess deaths per 100 000; 18 782), psychostimulants (3.1; 95% PI = 2.1, 4.2; 10 345), and alcohol poisoning (1.4; 95% PI = 0.5, 2.4; 4797; Figure 1, Appendix Figure D). Of the 50 states and DC, 40 (representing 95% of the US population) had statistically significant excess mortality involving synthetic opioids. In addition, mortality rates linked to psychostimulants, benzodiazepines, cocaine, and alcohol significantly exceeded projections in 29, 20, 18, and 18 states, respectively. However, mortality rates associated with heroin as well as with natural and semisynthetic opioids rose significantly in only 4 and 7 states, respectively. Interestingly, New York was one of the rare states significantly affected by both heroin (1.1 [95% PI = 0.2, 2.1] excess deaths per 100 000) and natural and semisynthetic opioids (1.4; 95% PI = 0.3, 2.6). West Virginia had the highest excess mortality for all

AJPH June 2024, Vol. 114, No. 6

FIGURE 1— Observed and Projected Overdose Mortality From (a) All Substance Types and (b) Psychostimulants: United States, March 2020–August 2021 (Inclusive)

Note. Substance-specific overdose mortality involving synthetic opioids, cocaine, heroin, benzodiazepines, natural and semisynthetic opioids, and alcohol are displayed in Appendix Figure D (available as a supplement to the online version of this article at https://ajph.org). The substance-specific categories are not mutually exclusive. Purple lines represent observed monthly deaths; green lines represent the fitted and projected fatal overdoses based on counterfactual estimates derived from prepandemic data (Jan 2015–Feb 2020) using a seasonal auto-regressive integrated moving average model. Dashed vertical line indicates transition between prepandemic and pandemic period, defined as starting on Mar 1, 2020. Shaded green area, during the pandemic period, corresponds to 95% prediction interval (PI) for absolute number of fatal overdoses at the national level, from Mar 2020–Aug 2021. The difference between the purple line and the green line to the right of the dashed line is the estimated excess mortality. The difference between the purple line and the lower and upper bounds of the PI results in a PI for excess mortality.

TABLE 1— Estimates of Overall Excess Fatal Overdoses for 47 US States and the District of Columbia: March 2020–August 2021, (Inclusive)

State	Expected No. of Fatal Overdoses (95% PI)	Observed No. of Fatal Overdoses	Ratio (Observed/ Expected)	Excess Deaths, No. (95% PI)	Excess Deaths per 100 000 Persons, No. (95% PI)	COVID-19 Deaths per 100 000 Persons, No.
US overall[a]	135 191 (112 334, 158 048)	160 859	1.19	25 668 (2 811, 48 524)	7.7 (0.9, 14.6)	181
Alabama[a]	1 318 (802, 1 833)	1 904	1.45	586 (71, 1102)	11.7 (1.4, 21.9)	252
Alaska	253 (112, 394)	354	1.40	101 (−40, 242)	13.8 (−5.5, 33)	62
Arizona	3 916 (3 088, 4 744)	4 523	1.16	607 (−221, 1 435)	8.5 (−3.1, 20.1)	217
Arkansas	858 (504, 1 211)	962	1.12	104 (−249, 458)	3.5 (−8.3, 15.2)	222
California[a]	13 496 (12 110, 14 883)	16 161	1.20	2 665 (1 278, 4 051)	6.7 (3.2, 10.2)	164
Colorado[a]	2 257 (1 751, 2 763)	2 849	1.26	592 (86, 1098)	10.3 (1.5, 19.0)	110
Connecticut	2 239 (1 585, 2 892)	2 239	1.00	0 (−653, 654)	0.0 (−18.1, 18.1)	214
Delaware	797 (520, 1 074)	723	0.91	−74 (−351, 203)	−7.5 (−35.4, 20.5)	168
District of Columbia	735 (282, 1 187)	656	0.89	−79 (−531, 374)	−11.4 (−77.1, 54.2)	171
Florida	10 363 (7 359, 13 367)	11 876	1.15	1 513 (−1 491, 4 517)	7.0 (−6.9, 21.0)	197
Georgia[a]	2 451 (1 745, 3 157)	3 468	1.42	1 017 (311, 1 723)	9.5 (2.9, 16.1)	180
Hawaii	414 (245, 582)	450	1.09	36 (−132, 205)	2.5 (−9.1, 14.1)	44
Idaho	462 (274, 650)	510	1.10	48 (−140, 236)	2.6 (−7.6, 12.8)	116
Illinois	5 738 (3 726, 7 750)	5 751	1.00	13 (−1 999, 2 025)	0.1 (−15.6, 15.8)	174
Indiana	3 522 (2 502, 4 542)	4 132	1.17	610 (−410, 1 630)	9.0 (−6.0, 24.0)	184
Iowa	823 (529, 1 117)	799	0.97	−24 (−318, 270)	−0.7 (−10, 8.5)	178
Kansas	768 (516, 1 020)	987	1.29	219 (−33, 471)	7.5 (−1.1, 16.0)	179
Kentucky[a]	2 605 (1 665, 3 544)	3 578	1.37	973 (34, 1 913)	21.6 (0.8, 42.5)	170
Louisiana[a]	2 330 (1 778, 2 883)	3 623	1.55	1 293 (740, 1 845)	27.8 (15.9, 39.6)	236
Maine	793 (409, 1 177)	813	1.03	20 (−364, 404)	1.5 (−26.7, 29.7)	70
Maryland	3 655 (2 138, 5 173)	4 396	1.20	741 (−777, 2 258)	12.0 (−12.6, 36.6)	153
Massachusetts	3 597 (2 463, 4 731)	3 759	1.05	162 (−972, 1 296)	2.3 (−13.8, 18.4)	179
Michigan	3 921 (2 384, 5 459)	4 548	1.16	627 (−911, 2 164)	6.2 (−9.0, 21.5)	175
Minnesota[a]	1 340 (958, 1 723)	1 944	1.45	604 (221, 986)	10.6 (3.9, 17.3)	122
Mississippi[a]	584 (352, 816)	1 089	1.86	505 (273, 737)	17.1 (9.2, 24.9)	269
Missouri	3 121 (2 353, 3 890)	3 453	1.11	332 (−437, 1 100)	5.4 (−7.1, 17.9)	194
Montana	242 (114, 371)	296	1.22	54 (−75, 182)	4.9 (−6.9, 16.8)	149
Nebraska	288 (167, 410)	381	1.32	93 (−29, 214)	4.7 (−1.5, 10.9)	139
Nevada[a]	1 194 (855, 1 532)	1 583	1.33	389 (51, 728)	12.5 (1.6, 23.4)	205
New Hampshire	588 (241, 936)	626	1.06	38 (−310, 385)	2.7 (−22.5, 28.0)	95
New Jersey	5 132 (3 251, 7 012)	4 530	0.88	−602 (−2482, 1279)	−6.5 (−26.7, 13.8)	245
New Mexico[a]	1 183 (789, 1 577)	1 584	1.34	401 (7, 795)	18.9 (0.3, 37.5)	205
New York	7 140 (5 391, 8 889)	8 271	1.16	1 131 (−618, 2 880)	5.6 (−3.1, 14.3)	256
North Carolina	4 227 (3 019, 5 436)	5 411	1.28	1 184 (−25, 2 392)	11.3 (−0.2, 22.9)	154
Ohio	7 182 (3 981, 10 384)	8 649	1.20	1 467 (−1735, 4 668)	12.4 (−14.7, 39.6)	182
Oklahoma	1 110 (522, 1 697)	1 484	1.34	374 (−213, 962)	9.5 (−5.4, 24.3)	234
Oregon[a]	1 035 (762, 1 309)	1 555	1.50	520 (246, 793)	12.3 (5.8, 18.7)	73
Pennsylvania	7 532 (3 283, 11 780)	8 317	1.10	785 (−3 463, 5 034)	6.0 (−26.6, 38.7)	201
Rhode Island	496 (305, 687)	646	1.30	150 (−41, 341)	13.7 (−3.7, 31.0)	204
South Carolina[a]	2 183 (1 553, 2 812)	2 991	1.37	808 (179, 1 438)	15.8 (3.5, 28.1)	207

Continued

TABLE 1— Continued

State	Expected No. of Fatal Overdoses (95% PI)	Observed No. of Fatal Overdoses	Ratio (Observed/ Expected)	Excess Deaths, No. (95% PI)	Excess Deaths per 100 000 Persons, No. (95% PI)	COVID-19 Deaths per 100 000 Persons, No.
Tennessee[a]	3 713 (3 217, 4 208)	5 420	1.46	1 707 (1 212, 2 203)	24.7 (17.5, 31.9)	191
Texas[a]	6 224 (5 198, 7 250)	7 788	1.25	1 564 (538, 2 590)	5.4 (1.8, 8.9)	203
Utah	843 (323, 1 363)	1 063	1.26	220 (−300, 740)	6.7 (−9.2, 22.6)	74
Vermont	289 (125, 454)	349	1.21	60 (−105, 224)	9.3 (−16.3, 34.9)	37
Virginia[a]	2 692 (1 833, 3 550)	3 738	1.39	1 046 (188, 1 905)	12.1 (2.2, 22.1)	129
Washington[a]	2 405 (1 795, 3 015)	3 215	1.34	810 (200, 1 420)	10.5 (2.6, 18.4)	75
West Virginia[a]	1 669 (1 047, 2 291)	2 330	1.40	661 (39, 1 283)	36.9 (2.2, 71.5)	169
Wisconsin	2 295 (1 580, 3 009)	2 568	1.12	273 (−441, 988)	4.6 (−7.5, 16.8)	126

Note. PI = prediction interval. Additional information about the calculation of point estimates and prediction intervals is provided in the Methods section of the Appendix (available as a supplement to the online version of this article at https://ajph.org). There were no statistically significant decreases. Three states (ND, SD, and WY), representing less than 1% of the US population, were excluded from the analysis owing to missing data: the CDC WONDER platform does not return any value for cells with a death count strictly lower than 10.
[a]States with statistically significant increases (n = 17).

AJPH June 2024, Vol. 114, No. 6

substances, except cocaine, for which Rhode Island was the most-affected state. The states most affected by cocaine-related excess mortality were primarily located in the central and northeastern parts of the country, in addition to Alaska and Hawaii.

The geographical distribution of psychostimulant-, benzodiazepine-, and alcohol-related overdose excess mortality followed the pattern of overall overdose-related excess mortality, with the addition of a few states in the Northeast (New York, Rhode Island, Pennsylvania) and Midwest (Nebraska, Wisconsin). Despite having nonsignificant excess mortality overall, Rhode Island had the fourth highest excess mortality rate related to synthetic opioids in the country (9.1 [95% PI = 5.8, 12.4] per 100 000). Vermont also had low excess fatal overdoses overall but significantly high excess mortality involving synthetic opioids (7.0 [95% PI = 2.8, 11.2] per 100 000), cocaine (4.0 [95% PI = 2.4, 5.6] per 100 000), and benzodiazepines (3.7 [95% PI = 1.2, 6.3] per 100 000). Additional visualizations and tables displaying substance-specific results are provided at https://github.com/jaychandra3/Drug_Overdose.

Furthermore, the repercussions of the COVID-19 pandemic on overdose-related mortality shifted over time. While excess mortality during the longer pandemic period spanning March 2020 to August 2021 was significant only for synthetic opioids, psychostimulants, and alcohol, the initial peak in fatal overdoses observed in May 2020 was unambiguous and affected all substance types (Figure 1, Appendix Figure D). Indeed, we found considerable excess mortality across all substance types during the first 3 months of the pandemic (March–May 2020), marking a clear divergence from prepandemic trends: increases were statistically significant for synthetic opioids (1.0 [95% PI = 0.7, 1.4] excess deaths per 100 000), cocaine (0.3; 95% PI = 0.1, 0.4), psychostimulants (0.4; 95% PI = 0.3, 0.5), benzodiazepines (0.3; 95% PI = 0.1, 0.4), alcohol (0.2; 95% PI = 0.1, 0.3), heroin (0.1; 95% PI = 0, 0.3), and natural and semisynthetic opioids (0.1; 95% PI = 0.0, 0.2). Following this 3-month period, overdose deaths involving benzodiazepines, natural and semisynthetic opioids, and cocaine returned nearly to the levels projected using prepandemic trends, while heroin overdose deaths dropped below projections. In contrast, fatal overdoses involving alcohol, psychostimulants, or synthetic opioids continued to outpace projections during the remainder of the 18-month study period, stressing the mid- to long-term effects of the pandemic on overdose-related absolute and excess mortality (Figure 1).

DISCUSSION

The steep increase in fatal overdoses in the months following March 2020 may indicate the rapid, substantial effect of the COVID-19 pandemic on substance use, especially in southern and Pacific coast states. Most previous work published in

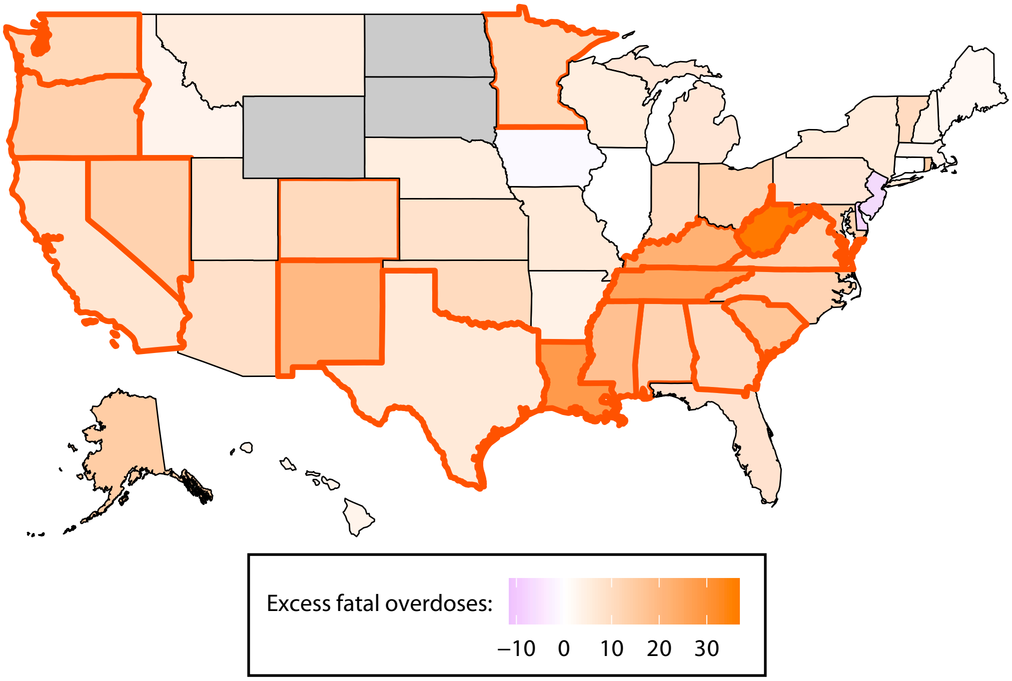

FIGURE 2— Excess Fatal Overdoses by State: United States, March 2020–August 2021 (Inclusive)

Note. States in gray (n = 3) lacked sufficient data for estimation. States with orange boundaries (n = 17) had a statistically significant increase in overdose-related mortality between Mar 2020 and Aug 2021. States in orange (n = 44) had an increase in overdose-related mortality (relative to the counterfactual). States in purple (n = 4) had a non–statistically significant decrease in overdose-related mortality.

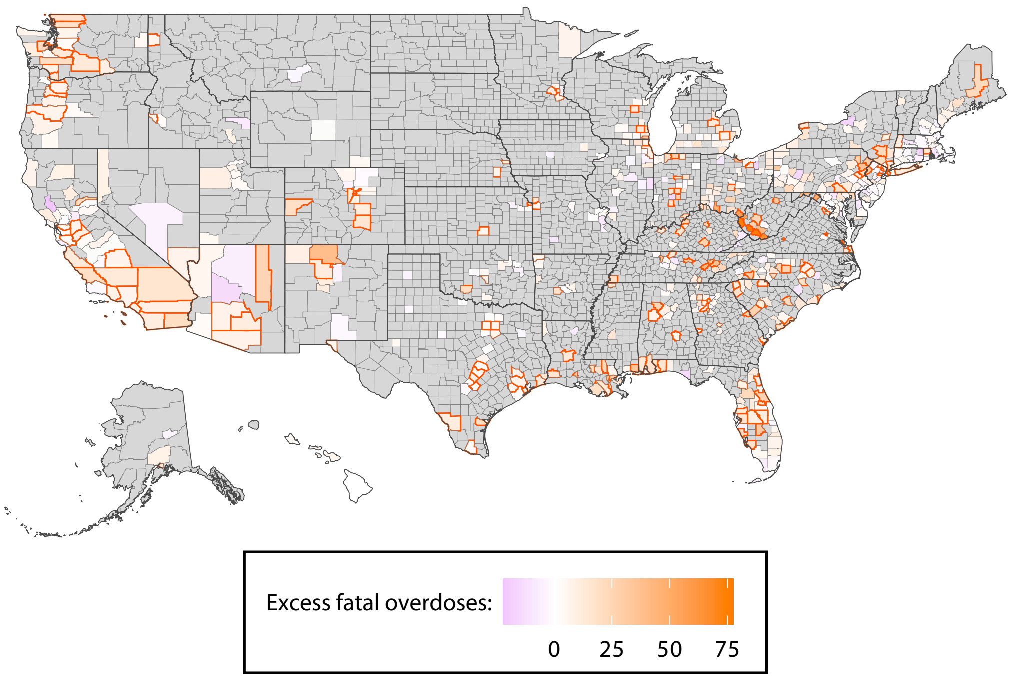

FIGURE 3— Excess Fatal Overdoses by County: United States, 2020

Note. Counties in gray (n = 2551) lacked sufficient data for estimation. Counties with orange boundaries (n = 197) had positive and statistically significant excess overdose-related mortality in 2020. Counties in orange (n = 487) had positive excess overdose-related mortality. Counties in purple (n = 105) had negative excess overdose-related mortality.

2020 to 2022 has analyzed overdose-related mortality at the national level only.[7,8] While examining macro-trends in substance-related mortality is important for nationwide public health decision-making, local analyses also matter as they provide valuable insights for tailored interventions. Our study acknowledges this trade-off by adopting a dual focus. Through modeling of absolute and excess fatal overdoses across US states and counties as well as by substance, our study expands upon previous research by analyzing nationwide trends by substance and demonstrating the importance of granular geographical characterization for postpandemic resource (re)allocation.

Future work could involve the development and implementation of methods to explicitly account for similarities among geographically proximal units. Notably, in 2019, Haffajee et al. had proposed a method to identify counties with high opioid overdose mortality, arguing that it could help target support programs toward areas with the greatest needs.[21] Following the pandemic shock, it is important to revisit this approach to account for changes in regional demographics and health behaviors, which are critical for resource allocation.[22] By contrasting prepandemic and pandemic-period fatal overdoses by substance type, we provide new information to assist with identifying high-risk counties. Resource allocation based solely on state-level data or ignoring yearly adjustments might overlook highly vulnerable counties. As an example, we show that individual counties in a given state can appear as outliers and present high excess mortality despite the state having low excess mortality in aggregate, underscoring the extent of geographical heterogeneity. The opposite pattern can also appear (i.e., states with high excess mortality overall but with counties that are not severely affected).

For public health officials, the geographical granularity of our study allows identification of adjacent counties that may benefit from pooling their resources. Quantifying the distributions of substance-specific overdose deaths among counties and states and pandemic-period shifts can also inform program design. We show that while almost all states had significant excess mortality associated with synthetic opioids, other substance types affected only specific regions or a small subset of states (e.g., cocaine: central and northeastern United States; heroin: Iowa, Georgia, South Carolina, and New York).

We hypothesize that several factors may have interacted and differentially affected certain states or counties owing to place-based, structural socioeconomic factors[23] and dynamic evolutions of the epidemic and labor market. First, the overburdened health system may have resulted in decreased attention to overdose-related morbidity and mortality. This burden has been primarily linked to synthetic opioids and psychostimulants. The growing availability of highly potent drugs such as fentanyl has largely contributed to drug overdose–related excess mortality,[24,25] but distinct geographical patterns have emerged, including greater involvement of psychostimulants in rural versus urban overdose deaths.[26]

Second, in regard to changes in socio-behavioral factors, the pandemic may have worsened individual-level correlates of substance use and risk of overdose, such as mental health issues, social isolation, and homelessness.[27] Survey respondents have reported that growing anxiety and lack of employment made them more likely to use drugs alone than before the pandemic, a setting that can, in turn, increase the risk of overdose.[28] The consumption of drugs or alcohol as a stress-induced coping mechanism[29] might explain the sudden increase in fatal overdoses, especially among individuals facing substance use disorder for the first time during the pandemic. Notably, we found that alcohol-related overdose deaths consistently outpaced projections over the considered time period, corroborating a previous study.[30] For relapsing individuals, shifts in lifestyle and economic insecurity may have compounded with limited access to substance use disorder treatment and support services.[31] The perception of changes to service provisions might also have increased self-stigma,[32] thereby lowering health care utilization. Further research is needed to elucidate the underlying socio-behavioral contexts and their interaction with biological and environmental factors.

Lastly, a decline in heroin-related overdose mortality was initiated in 2017. This prepandemic trend may in part explain the patterns we have observed over the study period, along with pandemic-period changes in supply and demand. Mobility restrictions, long-lasting border closures, and declines in world trade that affected global supply chains during the pandemic all significantly disrupted drug supply.[33] Indeed, most heroin and cocaine imports from Mexico, Colombia, Peru, and Southwest Asia[34] may have been substituted by either toxic and adulterated substances or by more potent drugs such as fentanyl, thereby amplifying the risk of fatal overdose.[35] Empirical evidence from surveys and qualitative interviews confirms that several factors contributed to increased exposure to fentanyl, including the scarcity of heroin, increasing cost of methamphetamine, and emergence of inexpensive fentanyl-derived products.[36] A rising number of fatalities have been attributed to counterfeit pills and heroin mixed with fentanyl, which could be transported in much smaller quantities when cross-border mobility was limited by border restrictions. This reality was more pronounced in regions close to Mexico.[37] In September 2023, a CDC report[38] quantified the impact: evidence of counterfeit pill use in overdose deaths more than doubled between July to September 2019 and October to December 2021 (from 2.0% to 4.7% of overall overdose deaths), and tripled in western US states (from 4.7% to 14.7%). Further research is needed to causally identify the relative contribution of increases in counterfeit pill supply on fatal overdoses.

Limitations

This study has 4 main limitations. First, death projections based on prepandemic trends are assumed to be valid counterfactuals from which excess mortality estimates are derived. The goodness-of-fit evaluation of our models resulted in a mean absolute percentage error (MAPE) of only 8% across the 47 considered states with a minimum MAPE of 3% (California) and a maximum MAPE of 17% (Delaware). For 90% of states (42 out of 47), the MAPE was lower than 13%. However, projections based on fluctuating levels of prepandemic mortality can be difficult to obtain in certain locations (e.g., Ohio, Pennsylvania). Furthermore, whether the increase or decrease in death counts is linear, polynomial, or exponential may be challenging to determine in certain states (e.g., California, Florida). Such uncertainties can yield wider PIs. Consequently, statistical significance is generally conservative in this study. Furthermore, the nonstatistical significance of excess mortality estimates in certain states (e.g., Rhode Island, Alaska) may owe in part to small population sizes and highly variable overdose-related mortality rates during the prepandemic period.

Despite this first limitation, our results about pandemic-period excess fatal overdoses seem robust to model choice. In sensitivity analyses involving models that overweigh proximal points and tend to project exponential rather than linear growth, the roster of states with significant overdose-related mortality was similar to that of the main analysis (76% overlap, see Methods section of the Appendix). Moreover, we confirmed that our model did not estimate significant excess mortality in any state before the pandemic (see Methods section of the Appendix). This validation provides further evidence that the magnitude of overdose-related excess mortality is strongly associated with the pandemic rather than an artifact of poor model fit.

Second, there are limitations associated with the reporting of causes of death in vital records. The heterogeneity in fatal overdoses observed across states might be influenced by differing practices among coroners and medical examiners. The quality of death certificate data can also vary over time as reporting practices and incentives evolve.[39] Additionally, toxicology assessments may not be conducted systematically, yielding variation in the proportion of death certificates with an "unknown/unspecified" drug code (T50.9) across states.[39] For instance, investigating the presence of fentanyl requires a second toxicology assessment, which incurs additional costs. Therefore, substance-specific excess mortality estimates presented in our study reflect only death certificates in which specific overdose-related labels are present. More efforts are needed to mitigate missing or poor-quality data in vital records.

Third, our study relied exclusively on *ICD-10* codes reported on death certificates and data queries from the CDC WONDER online platform. Thus, it does not allow examination of substance misuse. Going forward, an analysis attempting to link electronic health records or claims data with death certificates at the county or even zip code level may be warranted to learn more about the role of prescription drug use on excess mortality, identify any geographical differences, and potentially implement targeted interventions.

Fourth, in the present study, we have investigated differences in overdose-related excess mortality rates by age group across states only overall. Next, we plan to additionally study the 3-way interaction among substance type, geography, and socio-demographics (including age). In the future, the broader objective is to work closely with state departments of public health to allow for near-real-time monitoring of excess mortality patterns.

Conclusions

Overall, the COVID-19 pandemic had a disparate impact on overdose-related mortality. Our granular geographical analysis of the burden has identified areas that were more affected than others, including outlying counties. Furthermore, our work has revealed the emergence of new patterns by substance type and the increasing involvement of alcohol in overdose deaths. To complement the national recommendations of the Stanford-Lancet Commission for the North American Opioid Crisis,[18] we encourage the CDC to tailor public health messaging by geography and local departments of health to strengthen existing death investigation systems to characterize with precision the socioeconomic, psychosocial, and pharmacological needs of their populations. We hope our results will drive additional research into the state-specific mechanisms by which the pandemic and the substance overdose crisis interact and prompt changes to resource allocation to prevent overdose deaths in the most vulnerable communities. AJPH

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J. Chandra and M.-L. Charpignon equally contributed to this work. J. Chandra and A. Bhaskar participated in the conceptualization of the study, formal analysis, methodology, validation, and visualization. M.-L. Charpignon participated in the conceptualization of the study, formal analysis, methodology, project administration, validation, and visualization. A. Therriault participated in the conceptualization of the study and methodology. Y.-H. Chen participated in the methodology and supervision. M. A. Dahleh participated in the supervision. M. V. Kiang and F. Dominici participated in the methodology, project administration, and supervision. All authors participated in writing the original draft, reviewed and edited the article, and have read and agreed to the published version of the article. Mathew V. Kiang and Francesca Dominici were co-senior authors.

CONFLICTS OF INTEREST

We have no conflicts of interest to disclose.

HUMAN PARTICIPANT PROTECTION

This study used publicly available data and was not subject to human participant protection review at Harvard or the Massachusetts Institute of Technology.

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