Temporal trend of drug overdose-related deaths and excess deaths during the COVID-19 pandemic: a population-based study in the United States from 2012 to 2022

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Summary

Background Drug overdose is an escalating public health crisis in the United States (U.S.). This study evaluated the temporal trend of drug overdose-related deaths in the U.S., with an emphasis on identifying disparities across subpopulations and the contributing drugs.

Methods Using the nationwide death dataset from the National Vital Statistics System (NVSS), we estimated the drug overdose-related age-standardized mortality rate (ASMR) and temporal trends for individuals aged 12 and older from 2012 to 2022. Excess mortality during the Coronavirus disease 2019 (COVID-19) pandemic was evaluated based on the pre-pandemic trends using predictive modeling analysis.

Findings Among 809,967 overdose-related deaths during 2012–2022, ASMR increased by 8.9% [95% confidence interval (CI): 6.0%–11.9%] per year from 2012 to 2019 and increased to 12.9% (95% CI: 2.1%–24.8%) from 2019 to 2022, with the excess ASMR of 16.9% in 2020, increased to 26.4% in 2021 and then decreased to 19.3% in 2022. Significant age, sex, racial/ethnic and geographic disparities were demonstrated, with adolescents (annual percentage change [APC]:21.6%) and males (APC:13.6%) having the most pronounced increase during the pandemic. Ethnic minorities especially the non-Hispanic American Indian/Alaska Native experienced the highest excess ASMR (33.1% in 2020). Illicit fentanyl and synthetics starting with the lowest ASMR in 2012 (1.0 per 100,000), marked the most dramatic increase and became the leading cause of overdose-related death since 2016 (7.5 per 100,000), leading to the highest ASMR by 2022 (27.4 per 100,000). All drug types except heroin experienced varying degrees of excess ASMRs, with prescription opioid pain relievers (23.5%–55.1%), benzodiazepines (27.4%–40.9%) and antidepressants (10.4%–17.8%) exhibiting consistent increases from 2020 to 2022, while the excess ASMRs for illicit fentanyl and synthetics (25.3%–10.0%), psychostimulants (32.8%–14.6%) and methadone (35.0%–33.3%) decreased between 2021 and 2022.

Interpretation Overdose-related mortality is increasing at an alarming rate, and the stark differences point to the need for targeted interventions to reduce the burden of drug overdose deaths.

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Research in context

Evidence before this study

Drug overdose deaths continue to contribute to overall mortality and decline in life expectancy in the United States, resulting in substantial costs to society. During the Coronavirus disease 2019 (COVID-19) pandemic, the drug overdose crisis in the United States has further intensified. A search was conducted on PubMed and Web of Science for studies on overdose-related deaths in the United States from January 2020 to December 2022, without any language restrictions. The search terms were: ("overdose" OR "drug overdose" OR "overdose deaths") AND ("US" OR "the United States") AND ("COVID-19" OR "SARS-CoV-2" OR "Coronavirus disease 2019"). To our knowledge, studies have reported a significant increase in drug overdose deaths in the United States during the pandemic, with the largest increases in deaths due to overdoses of fentanyl and other synthetic opioids. However, the extent of excess deaths related to drug overdose during the pandemic and how they vary across demographic groups and specific drug type remains unclear.

Added value of this study

Using the National Vital Statistics System (NVSS) in the United States, we searched for multiple cause of drug overdose related deaths (12 years of age or older) (1/1/2012–12/31/2022) and calculated age-standardized mortality rate (ASMR). Overall, the ASMR of drug overdose has significant increased in the past decade, with the annual percentage change (APC) of 8.9% from 2012 to 2019 and at an alarm rate of 12.9% during the pandemic, corresponding to excess ASMRs of 16.9%–26.4% in 2020–2022. The excess ASMR was consistent across all demographic and racial/ethnic groups, with the highest excess ASMR found in adolescents (over 100% in 2021 and 2022), females (over 36% in 2021 and 2022), ethnic minorities especially the non-Hispanic American Indian/Alaska Native (33% in 2020). Illicit fentanyl and synthetic drugs showed a significantly upward trend throughout the study period, although it slowed down during the pandemic. The excess ASMR of overdoses due to prescription opioid (23.5%–55.1%), benzodiazepines (27.4%–40.9%) and antidepressants (10.4%–17.8%) continued to be elevated during the pandemic.

Implications of all the available evidence

The findings underscore the critical need for an integrated public health response that targets both the supply of illicit drugs and addresses the root causes of substance misuse. There is a need for reinforcement of nationwide strategies that prioritize comprehensive access to substance use treatment, mental health support, and targeted interventions aimed at reducing the impact of social determinants on drug misuse behaviors.

Introduction

In recent years, drug overdose has become a major public health challenge in the United States, with heavy burdens for individuals, families and communities.[1,2] Overall, the age-adjusted overdose mortality rate in the United States rose between 1999 and 2006, remained stable from 2006 to 2013, then experienced a significant upward trend from 2013 to 2019, albeit with a slight decrease in 2018.[3] Since 2013, the sharp increase in overdose deaths related to synthetic opioids (primarily illegal fentanyl and analogs) has been the most significant cause of overdose deaths in the United States.[4] Fentanyl, a highly potent synthetic opioid, possesses an efficacy that surpasses morphine by 50–100 times.[5] Illicit fentanyl's manufacturing simplicity, addictive nature, and low production cost provide significant profit potential for illicit drug suppliers.

Since 2020, the crisis has been further exacerbated with the emergence of the Coronavirus disease 2019 (COVID-19) pandemic.[6] Data showed that the number of overdose-related deaths in the United States reached above 90,000 in 2020, which was a 31% increase compared to 2019, and deaths due to synthetic opioid (primarily fentanyl) use increased by 56%.[7] In 2021, the number of overdose deaths reached a new record high of more than 100,000, representing a 14% increase compared to 2020.[8] During the pandemic, closure of substance use treatment clinics, focus of emergency departments on COVID-19 patients, social distancing and shelter in place orders affecting mental health, reduced access to health care and availability of naloxone, threats to income and supply of substances for people who use them, may all have resulted in more overdoses and fewer rescue opportunities.[9] Our study aimed to comprehensively update the data on drug overdose deaths in the United States, analyze the differences among subpopulations and the contributing drugs, as well as present the dynamic trends of drug overdose deaths, in hope to inform the development of targeted health policies.

Using the National Vital Statistics System (NVSS) in the United States, we provided the latest overdose mortality trends from 2012 to 2022 and calculated excess mortality to reflect the difference between actual and predicted values during the pandemic based on forecast analysis. We further provided data striated by demographic group (sex, age, race/ethnicity, geographic areas) and by specific drug type.

Methods

Data source

We conducted a cross-sectional study using mortality and demographic data from the NVSS, which is available on the Center for Disease Control and Prevention Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) website.[10] The CDC WONDER website includes over 99% of death certificates issued over all 50 continental states of the United States and the District of Columbia. It contains comprehensive, unidentified mortality data for all individuals in the United States.

Study population

The study population included decedents aged 12 years or older whose cause of death included drug overdose-related death between January 1, 2012 and December 31, 2022. Drug overdose deaths were identified using the International Classification of Diseases 10th edition (ICD-10) codes X40–X44 (unintentional), X60–X64 (suicide), X85 (homicide), or Y10–Y14 (undetermined intent). All mentioned categories were included in our assessment without distinction.

We calculated overdose-related deaths and corresponding age-standardized mortality rate (ASMR) overall and by sex (male, female), age (in years) (12–19 years, 20–34 years, 35–49 years, 50–64 years, and ≥65 years), race/ethnicity (non-Hispanic American Indian/Alaska Native, non-Hispanic Asian, non-Hispanic Black, non-Hispanic White, Hispanic), and states. Among deaths with drug overdose as one of the multiple cause-of-death, CDC identified the type of drug involved based on ICD-10 codes, and we focus on the T40 class (poisoning by narcotics and hallucinogens) which includes the relevant subclasses heroin (T40.1), prescription opioids (T40.2), methadone (T40.3), fentanyl (T40.4), cocaine (T40.5). We also pay attention to other subclass included benzodiazepines (T42.4), antidepressants (T43.0–T43.2), psychostimulants (T43.6) and other prescription drugs (T36–T39, T41–T42, T43.3–T43.5, T43.8–T50.8) (Supplementary Table S1). Race/ethnicity subgroup analysis covered the period from 1/1/2012 to 12/31/2020 by year and 1/1/2018 to 12/31/2022 by month. The CDC restructured their classification system for race/ethnicity in 2021, which complicates data comparison between the two eras. Our analysis and presentation followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[11]

Statistical analysis

We calculated age-adjusts death rates using the direct method. That is, by applying age-specific death rates to the U.S. standard population age distribution. The calculation formula is as follows:

$$ASMR = \sum_{i=1}^{N} (Di \,/\, Pi) wi$$

(Di) is the actual number of deaths in age group (i), (Pi) is the number of the population in age group (i), (wi) is the weight of age group (i) (based on 2000 U.S. Census Standard Population distribution), (N) is the total number of age groups.

Excess mortality was defined as the difference between the total number of deaths that have occurred and the number of deaths that are expected in the absence of a pandemic. We calculated excess mortality by subtracting the projected mortality rate from the observed values based on forecast analysis. Linear regression models were used to estimate the predicted mortality rates via the ordinary least squares method.[12] The R-squared statistic was employed to assess the fitness of the model, and the choice of models was determined based on the trend of mortality rates.

To assess the temporal trend for drug overdose deaths in United States populations aged 12 and over from 2012 to 2022, we employed Joinpoint analysis, a piecewise regression technique that examines whether the trend can be explained by one or multiple segments.[13] Monte Carlo permutation method was used to determine the effect size and significance.

We used the SPSS version 26.0 (IBM Corp. Released 2019. Armonk, NY, United States: IBM Corp), the Joinpoint analysis software (version 4.9.1.0; National Cancer Institute, Bethesda, MD, United States), and R 4.3.2 software for all analyses in our study. A two-sided p value of less than 0.05 was considered statistically significant.

Ethics statement

Since the data are available for the general public and have been fully de-identified, we did not seek approval from the Institutional Review Board.

Role of the funding source

There was no funding source for this study.

Results

Study population

A total of 809,967 overdose-related deaths aged 12 and older were identified between January 1, 2012 and December 31, 2022 (Supplementary Table S2). Males accounted for two-thirds of deaths. The majority of these deaths occurred in the 35–49 year age group (34.5%), followed by the 50–64 year age group (29.6%) and the 20–34 year age group (28.1%). Deaths in non-Hispanic White accounted for 75.7%, followed by non-Hispanic Black (12.7%) and Hispanic (9.2%). Furthermore, 87.8% of the deaths were unintentional, and 7.3% were suicide. We observed that 50.6% of deaths occurred at the decedent's home, 23.9% at medical facility, and 23.5% at other/unknown locations.

	Age-standardized mortality rate (ASMR, per 100,000 persons)															
	2012		2019		2020				2021				2022			
	Death counts	ASMR [95% CI]	Death counts	ASMR [95% CI]	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)
Overall																
Multiple cause of death	44,760	17.0 [16.9–17.2]	75,456	27.8 [27.6–28.0]	97,080	36.0 [35.8–36.2]	30.8 [28.1–33.5]	**16.9 [6.8–28.9]**	112,612	41.2 [41.0–41.4]	32.6 [29.4–35.8]	**26.4 [14.4–41.0]**	113,395	41.0 [40.8–41.3]	34.4 [30.7–38.1]	**19.3 [7.1–34.5]**
Sex																
Female	17,588	13.0 [12.9–13.2]	24,242	17.6 [17.3–17.8]	29,705	21.8 [21.5–22.0]	18.1 [15.2–20.9]	**20.2 [2.9–44.8]**	34,303	25.0 [24.7–25.2]	18.0 [13.7–22.4]	**38.7 [17.3–54.3]**	33,900	24.4 [24.2–24.7]	17.9 [11.7–24.0]	**36.4 [14.2–61.7]**
Male	27,172	21.0 [20.7–21.2]	51,214	38.3 [37.9–38.6]	67,375	50.4 [50.0–50.8]	42.5 [38.5–46.4]	**18.6 [7.8–31.9]**	78,309	57.5 [57.1–57.9]	45.3 [40.7–49.9]	**26.9 [14.4–42.2]**	79,495	57.7 [57.3–58.2]	48.1 [42.8–53.5]	**20.1 [7.2–35.9]**
Age																
12~19 years	737	2.1 [2.0–2.3]	925	2.7 [2.6–2.9]	1684	5.0 [4.8–5.2]	2.6 [1.9–3.4]	**92.3 [74.9–99.1]**	1862	5.4 [5.2–5.7]	2.5 [1.4–3.7]	**116.4 [104.0–146.3]**	1824	5.3 [5.0–5.5]	2.4 [0.8–4.1]	**118.8 [106.2–155.7]**
20~34 years	11,836	19.2 [13.6–27.1]	21,194	33.1 [25.3–42.3]	28,293	44.0 [35.0–54.5]	35.0 [24.9–45.2]	**25.7 [12.5–43.3]**	30,862	48.6 [39.0–59.4]	35.0 [19.5–50.6]	**39.0 [33.7–44.2]**	28,952	45.5 [36.2–55.9]	34.5 [12.3–56.8]	**31.8 [26.9–37.1]**
35~49 years	15,907	25.7 [19.6–32.7]	25,679	41.1 [33.7–49.8]	33,814	54.0 [45.5–63.9]	45.0 [41.3–48.8]	**20.0 [9.6–34.6]**	39,528	62.0 [53.0–72.5]	47.6 [43.2–52.0]	**30.3 [26.2–34.6]**	40,435	63.1 [53.7–73.3]	50.2 [45.1–55.3]	**25.7 [21.9–29.7]**
50~64 years	13,708	23.4 [17.6–30.7]	22,467	37.1 [29.9–45.9]	27,299	45.2 [37.0–54.5]	39.7 [37.3–42.0]	**13.7 [10.6–46.1]**	32,783	53.0 [44.3–63.2]	41.7 [38.9–44.5]	**27.2 [22.8–31.6]**	33,635	53.6 [44.7–63.7]	43.8 [40.6–47.0]	**22.4 [18.6–26.6]**
≥65 years	2572	5.9 [5.6–6.1]	5191	9.1 [8.9–9.4]	5990	10.2 [9.9–10.4]	9.9 [9.6–10.3]	**3.0 [0.6–8.6]**	7577	12.6 [12.3–12.8]	10.9 [10.4–11.5]	**15.6 [9.4–23.8]**	8549	13.9 [13.6–14.2]	11.9 [11.2–12.7]	**17.6 [11.3–25.7]**

Note: Excess (%) is calculated as (Observed – Predicted)/Predicted. Predicted value for 2020–2022 was based on 2012–2019 trend for each subgroup.

Table 1: **Multiple cause of drug overdose-related deaths and age-standardized mortality rate (per 100,000 persons) in the United States populations (≥12 years) overall, by sex and by age, 2012–2022.**

Temporal trend of drug overdose-related mortality and excess mortality during the COVID-19 pandemic

Before the pandemic, overdose-related ASMR increased from 17.0 (per 100,000 persons) in 2012 to 27.8 in 2019. During the pandemic, the mortality rate surged to 36.0 in 2020 and 41.2 in 2021, translating to a 16.9% (2020) and 26.4% (2021) increase in observed ASMR compared to the projected trend. From 2021 to 2022, the mortality rate remained stable (41.0 in 2022), while the excess ASMR decreased to 19.3% (2022) (Table 1, Supplementary Fig. S1). For Joinpoint analysis, the ASMR of drug overdose increased by 8.9% [95% confidence interval (CI): 6.0%–11.9%] per year from 2012 to 2019 and by 12.9% (95% CI: 2.1%–24.8%) from 2019 to 2022 (Supplementary Table S3).

Drug type subgroup analysis

During the pandemic, the percentage differences between the observed and projected ASMRs were considerable across all drug types except heroin and cocaine. Notably, the excess ASMR for prescription opioid pain relievers (23.5% in 2020, 43.9% in 2021 and 55.1% in 2022), benzodiazepines (27.4% in 2020, 39.1% in 2021 and 40.9% in 2022) and antidepressants (10.4% in 2020, 13.6% in 2021 and 17.8% in 2022) displayed continued increases from 2020 to 2022. In addition, from 2021 to 2022, the excess ASMRs were decreased for illicit fentanyl and synthetics (25.3%–10.0%), psychostimulants (32.8%–14.6%) and methadone (35.0%–33.3%) (Table 2). For Joinpoint analysis, the ASMR of prescription drugs shown an upward trend from 2012 to 2022, with the annual percentage change (APC) of 8.2% (95% CI: 6.7%–9.6%). The ASMR of illicit fentanyl and synthetics increased by 64.8% (95% CI: 46.7%–85.1%) from 2012 to 2019, then slowed down with an APC of 22.9% (95% CI, 9.4%–38.1%) from 2019 to 2022. The ASMR of heroin was increased from 2012 to 2016 (APC: 26.2%; 95% CI: 19.3%–33.4%), plateaued from 2016 to 2020, then decreased from 2020 to 2022 (APC: −34.8%; 95% CI: −45.4% to −22.2%). The ASMR of cocaine remain stable from 2012 to 2014, increased from 2014 to 2017 (APC: 33.3%; 95% CI: 10.3%–61.3%), then slowed down from 2017 to 2022 (APC: 14.0%; 95% CI: 9.3%–19.0%). The ASMRs of benzodiazepines, antidepressants, and psychostimulants showed upward trends throughout the whole study period, with the APC of 5.5% (95% CI: 2.8%–8.1%), 2.4% (95% CI: 1.8%–3.1%) and 28.6% (95% CI: 26.8%–30.5%) from 2012 to 2022, respectively (Fig. 1, Table 3).

We further analyzed mortalities among drug types and stratified by sex, age and race/ethnicity, significant disparities in the percentage change of mortalities during the study period were observed (Supplementary Table S4). Notably, across all drug types, the highest percentage increase was observed in illicit fentanyl and synthetics-related deaths. Specifically, the most pronounced

percentage increase in illicit fentanyl and synthetics-related deaths were observed in males, 12–19-year-old age group and non-Hispanic Black (Supplementary Table S4).

Sex subgroup analysis

From 2012 to 2022, the burden of overdose deaths for males was generally higher than that of females. However, females experienced more excess ASMR than males during the pandemic (20.2% vs.18.6% in 2020 and 38.7% vs. 26.9% in 2021, respectively) (Table 1). From 2021 to 2022, the excess ASMR remained stable for females (36.4% in 2022), while it decreased for males (20.1% in 2022) (Table 1, Fig. 2A). For Joinpoint analysis, the APC of ASMR was almost twice as large for males than females from 2012 to 2019 (10.8% vs. 5.5%, respectively), while this gap narrowed between 2019 and 2022 (13.6% vs.10.8%, respectively) (Supplementary Table S3).

Age subgroup analysis

From 2020 to 2022, the ASMR of drug overdose was highest for adults aged 35–49 (54.0 in 2020 to 63.1 in 2022 per 100,000) and lowest for people aged 12–19 (5.0 in 2020 to 5.3 in 2022 per 100,000) (Table 1, Fig. 2B). When compared to predicted values, people aged 12–19 experienced the most pronounced excess mortality (92.3% in 2020 and 116.4% in 2021). Furthermore, the excess ASMR continued increasing for the 12–19 year age group (118.8% in 2022) and the ≥65 year age group (17.6% in 2022) from 2021 to 2022, while it was decreased for other age groups during the same period (Table 1). Joinpoint analysis demonstrated the ASMR of drug overdose increased to varying degrees during the past decade in all age groups, with people aged 12–19 experiencing the greatest percentage change from 2018 to 2022 (APC: 21.6%; 95% CI: 3.5%–42.9%) (Supplementary Table S3).

Race/ethnicity subgroup analysis

The observed mortality rates in 2020 were significantly higher when compared to projected mortality rates in all races/ethnicities. This trend was particularly noted for non-Hispanic American Indian/Alaska Native with an excess ASMR of 33.1%, followed by non-Hispanic Black (22.1%) and Hispanic (21.1%), while non-Hispanic White was the lowest (20.1%) (Supplementary Table S5). When grouped by race and sex, the excess ASMRs for males were higher than females across all races/ethnicities, except for non-Hispanic American Indian/Alaska Native (41.9% in females vs. 28.0% in males) (Supplementary Table S5). In addition, we analyzed the trends of ASMR across all race/ethnic subgroups between 1/2018 and 12/2022 by month. Similar trends to the previous analyses by year were observed, with the highest mortality observed in non-Hispanic American Indian/Alaska Native and then non-Hispanic Black (Supplementary Fig. S2).

	Age-standardized mortality rate (ASMR, per 100,000 persons)																	
	2012		2019		2020			2021				2022						
	Death counts	ASMR [95% CI]	Death counts	ASMR [95% CI]	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)	Death counts	Observed ASMR [95% CI]	Predicted ASMR [95% CI]	Excess ASMR [95% CI] (%)
Prescription drugs	12,106	4.6 [4.5–4.7]	18,985	6.9 [6.8–7.0]	23,963	8.8 [8.7–8.9]	7.3 [6.0–8.5]	**20.6 [2.3–48.6]**	27,012	9.8 [9.7–9.9]	7.4 [5.4–9.4]	**32.6 [22.0–44.3]**	26,314	9.4 [9.3–9.6]	7.4 [4.6–10.1]	**27.5 [17.4–38.6]**
Prescription OPR	11,562	4.4 [4.3–4.5]	12,392	4.5 [4.4–4.6]	13,920	5.1 [5.0–5.2]	4.1 [2.9–5.3]	**23.5 [12.4–40.3]**	14,099	5.0 [5.0–5.1]	3.5 [1.7–5.3]	**43.9 [26.3–60.6]**	12,296	4.3 [4.3–4.4]	2.8 [0.2–5.3]	**55.1 [33.9–72.5]**
Illicit fentanyl and synthetics	2710	1.0 [1.0–1.1]	36,598	13.9 [13.7–14.0]	56,956	21.6 [21.4–21.8]	17.8 [13.7–21.9]	**21.4 [15.6–28.1]**	71,071	26.6 [26.4–26.8]	21.2 [14.9–27.6]	**25.3 [19.8–31.9]**	74,105	27.4 [27.2–27.6]	24.9 [15.8–33.9]	**10.0 [6.6–14.5]**
Heroin	5958	2.3 [2.3–2.4]	14,105	5.3 [5.2–5.4]	13,291	5.0 [4.9–5.1]	4.8 [3.9–5.7]	**4.1 [0.5–14.3]**	9230	3.4 [3.3–3.5]	3.9 [2.6–5.3]	**-12.8 [-27.4 (-4.2)]**	5887	2.1 [2.1–2.2]	2.8 [0.9–4.7]	**-25.0 [-44.9 (-10.7)]**
Cocaine	4922	1.9 [1.8–1.9]	16,720	6.2 [6.1–6.3]	20,357	7.5 [7.4–7.6]	7.6 [5.8–9.4]	**-1.3 [-7.1-(-0.1)]**	25,477	9.2 [9.1–9.3]	8.7 [5.9–11.4]	**6.0 [1.9–12.9]**	28,520	10.2 [10.1–10.3]	9.9 [5.9–13.7]	**2.8 [0.6–8.6]**
Methadone	4025	1.5 [1.5–1.6]	2832	1.0 [1.0–1.1]	3646	1.3 [1.3–1.4]	1.0 [0.8–1.2]	**33.1 [6.7–65.2]**	3806	1.4 [1.3–1.4]	1.0 [0.7–1.3]	**35.0 [12.2–73.8]**	3411	1.2 [1.2–1.2]	0.9 [0.5–1.3]	**33.3 [7.5–70.1]**
Benzodiazepines	6773	2.6 [2.5–2.7]	10,032	3.7 [3.6–3.8]	12,621	4.7 [4.6–4.8]	3.7 [2.6–4.8]	**27.4 [13.8–44.1]**	12,799	4.7 [4.7–4.8]	3.4 [1.7–5.0]	**39.1 [22.2–56.4]**	11,224	4.1 [4.0–4.2]	2.9 [0.5–5.4]	**40.9 [23.5–61.1]**
Antidepressants	4447	1.7 [1.6–1.7]	5389	1.9 [1.9–2.0]	5807	2.1 [2.0–2.2]	1.9 [1.7–2.1]	**10.4 [1.3–33.1]**	6088	2.2 [2.1–2.2]	1.9 [1.6–2.1]	**13.6 [3.4–39.6]**	6028	2.1 [2.1–2.2]	1.8 [1.4–2.2]	**17.8 [3.6–41.4]**
Psychostimulants	3196	1.2 [1.2–1.3]	18,107	6.8 [6.7–6.9]	26,211	9.9 [9.7–10.0]	8.3 [7.9–8.6]	**18.8 [13.3–26.3]**	35,392	13.1 [13.0–13.3]	9.9 [9.5–10.5]	**32.8 [23.9–39.8]**	36,715	13.5 [13.4–13.7]	11.8 [11.1–12.5]	**14.6 [7.1–23.1]**

Note: OPR, opioid pain relievers. Excess (%) is calculated as (Observed−Predicted)/Predicted. Predicted value for 2020–2022 was based on 2012–2019 trend for each subgroup.

Table 2: **Multiple cause of drug overdose-related deaths and age-standardized mortality rate (per 100,000 persons) in the United States populations (≥12 years) by drug type, 2012–2022.**

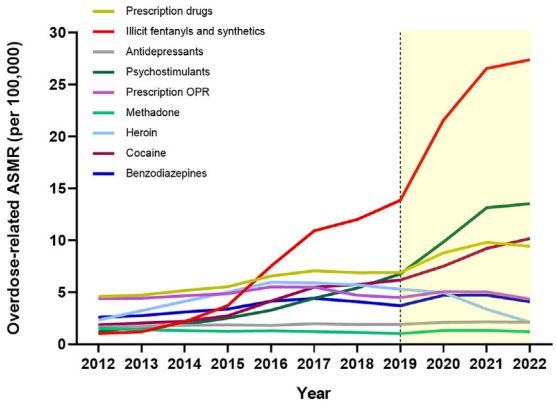

Fig. 1: **All-cause age-standardized mortality rate (ASMR) for drug overdose per 100,000 persons in the United States (≥ 12 years) by drug type, 2012–2022.** Drug overdose deaths were identified using International Classification of Diseases 10th Revision (ICD-10) multiple cause-of-death codes X40–X44, X60–X64, X85 and Y10–Y14. Among these deaths, the following ICD-10 multiple cause-of-death codes indicate the drug types involved: heroin (T40.1), prescription opioids (T40.2), methadone (T40.3), fentanyl (T40.4), cocaine (T40.5), benzodiazepines (T42.4), antidepressants (T43.0–T43.2), psychostimulants (T43.6) and other prescription drugs (T36–T39, T41–T42, T43.3–T43.5, T43.8–T50.8). Age-standardized mortality rate were calculated using the direct method and the 2000 U.S. standard population. OPR: opioid pain relievers.

Geographic area subgroup analysis

Significant geographic variation in overdose-related mortality was observed during the pandemic, with the highest ASMR observed in West Virginia (increase from 88.2 in 2020 to 97.3 in 2021, and decrease to 91.3 in 2022 per 100,000), followed by the District of Columbia, Louisiana, and Tennessee. However, the top three states with excess ASMR were Vermont, Virginia, and South Carolina (Fig. 3, Supplementary Table S6).

Discussion

In recent years, the United States has witnessed a significant increase in overdose-related deaths. The purpose of this study was to provide insight into the temporal trend of drug overdose-related deaths and excess deaths during the COVID-19 pandemic in the United States. Our study revealed that overdose-related deaths significantly increased in the United States during the past decade. The ASMR of drug overdose increased by 8.9% from 2012 to 2019 and increased to 12.9% during 2019–2022. Overall, excess ASMR during the pandemic increased from 16.9% in 2020 to 26.4% in 2021 and decreased to 19.3% in 2022, with excess ASMR being higher in females than in males. Age subgroup analysis showed that the excess ASMRs were most pronounced in the adolescent population (about 100% in 2020–2022). Furthermore, the greatest excess ASMR occurred in the non-Hispanic American Indians/American Native group (above 30% in 2020) and the lowest in the non-Hispanic White group (20% in 2020). Illicit fentanyl and synthetics showed a significant growth trend through the study period, accounting for over 60% of total mortality during the pandemic.

During the pandemic, the excess mortality due to drug overdose in the United States significantly increased, especially among adolescents. Fentanyl was identified in 77.1% of adolescent drug overdose deaths in 2021, and the increasing presence of fentanyl in counterfeit medications such as prescription opioids, benzodiazepines, and other drugs may have played a pivotal role in this shift.[14,15] Adolescents in particular are

Type of drugs	Trend segment	Segment endpoints		APC (95% CI)	*p* value
		Lower	Upper		
Prescription drugs	1	2012	2022	8.2 (6.7–9.6)	<0.001
Prescription OPR	1	2012	2022	0.3 (−1.6 to 2.3)	0.696
Illicit fentanyls and synthetics	1	2012	2019	64.8 (46.7–85.1)	<0.001
	2	2019	2022	22.9 (9.4–38.1)	0.005
Heroin	1	2012	2016	26.2 (19.3–33.4)	0.001
	2	2016	2020	−5.2 (−13.2 to 3.6)	0.153
	3	2020	2022	−34.8 (−45.4 to −22.2)	0.005
Cocaine	1	2012	2014	8.2 (−10.5 to 30.9)	0.277
	2	2014	2017	33.3 (10.3–61.3)	0.017
	3	2017	2022	14.0 (9.3–19.0)	0.002
Methadone	1	2012	2022	−1.7 (−3.8 to 0.3)	0.090
Benzodiazepines	1	2012	2022	5.5 (2.8–8.1)	0.001
Antidepressants	1	2012	2022	2.4 (1.8–3.1)	<0.001
Psychostimulants	1	2012	2022	28.6 (26.8–30.5)	<0.001

Note: OPR, opioid pain relievers.

Table 3: **Trend segment analysis and annual percentage change (APC) in multiple cause of drug overdose-related age-standardized mortality rate in the United States by drug type, 2012–2022.**

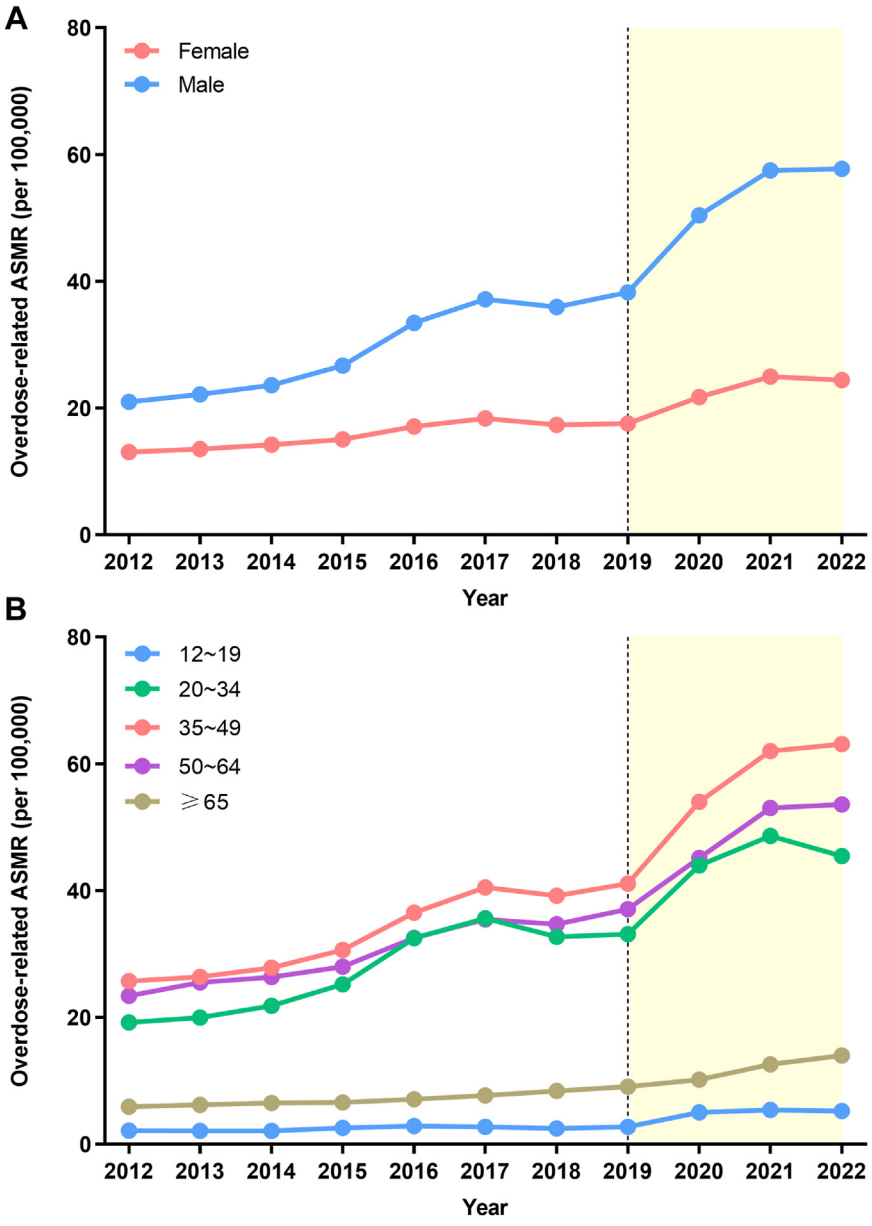

Fig. 2: **All-cause age-standardized mortality rate (ASMR) for drug overdose per 100,000 persons in the United States (≥ 12 years) by sex (A) and by age (B), 2012–2022.**

vulnerable to substance use and are at increased risk for long-term problems. Furthermore, the stress related to the social isolation and lockdown measures during the pandemic increased the prevalence of depression, suicidal ideation, and suicide attempts among teenagers.[16] Böttcher et al. provide a more effective age-stratified prediction method based on an ensemble Kalman filter, which shows that the deaths of drug overdoses will continue to increase in all relevant age groups in 2023–2024, with the most significant deaths occurring in those under 30 years of age.[17] Amidst the escalating supply of illegal fentanyl, the increasing number of adolescent overdose deaths underscores the urgent need to strengthen mental health education for this vulnerable group, and combining prescription monitoring programs to facilitate greater services for adolescent substance use behaviors.

The emergence of synthetic opioids has characterized the third wave of the opioid crisis that began in 2013, particularly involving the illicit manufacture of fentanyl.[18] The Department of Health and Human Services (DHHS) of the United States formally announced

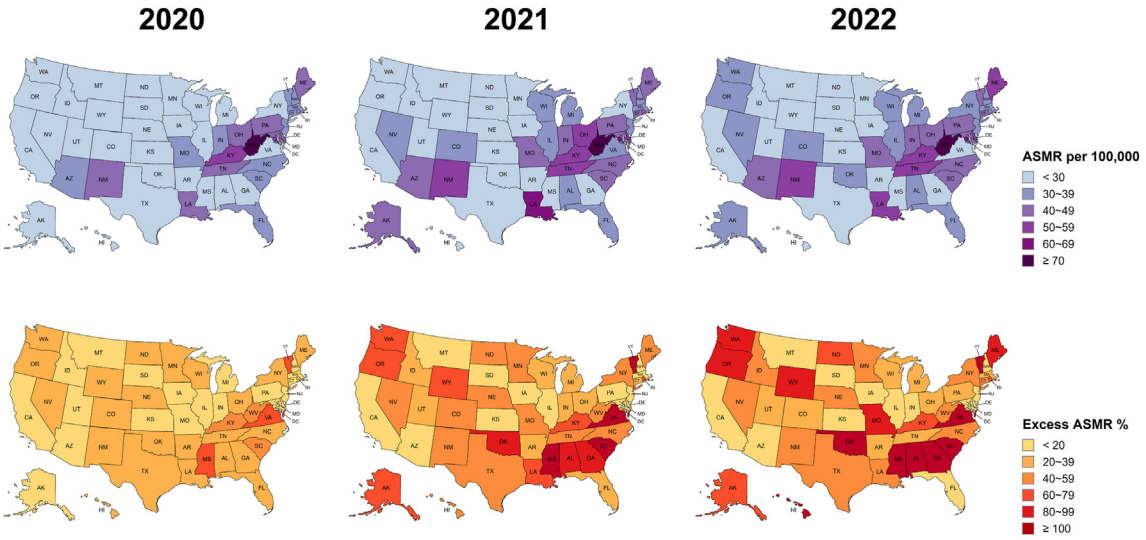

Fig. 3: **All-cause age-standardized mortality rate (ASMR) for drug overdose per 100,000 persons and excess ASMR in the United States by states, 2020–2022.** (Top) State-level observed ASMR per 100,000 in 2020–2022; (Bottom) State-level excess ASMR in 2020–2022. The excess ASMR in 2020–2022 was calculated by subtracting the projected ASMR, predicted using a linear regression model with ordinary least squares based on data from 2012 to 2019, from the observed ASMR values.

the opioid crisis in 2017 and enacted appropriate measures aimed at stemming the tide of this crisis. However, these endeavors were disrupted by the unexpected COVID-19 pandemic. Reductions in general services during the pandemic such as naloxone accessibility and needle exchange services, and reduced access to emergency care among overdoses, may put these vulnerable populations at greater risk.[19] Furthermore, the closure of substance use treatment clinics and the accessibility of telemedicine services posed a number of challenges for people with opioid use disorder (OUD).[20] Research indicates a sharp decline in methadone supply at the pandemic's onset, despite with relaxed regulations by Substance Abuse and Mental Health Service Administration, barriers to methadone use persist.[21] In addition, a study from the Rhode Island Data Ecosystem (RIDE) found that 53% of people who died from overdose were in their personal residences, suggested that social isolation, reduced social support, and increased use of drugs alone may all exacerbate overdose risk.[22] Study has predicted that by the end of 2030, 1.2 million people in the United States will die from overdoses of opioids, primarily due to fentanyl.[23] Comprehensive measures urgently needed to be taken, including expanding health services for patients with OUD, and monitor the availability of illicit drugs to alleviate the severity of the opioid crisis.

Racial/ethnic disparities in overdose-related mortality during the pandemic have been exacerbated.[24–26] Our study confirmed a disproportionate increase in excess all-cause overdose related mortality among ethnic minorities during the pandemic. Yet what are the potential reasons behind this troubling trend? Studies have shown that minority groups are less likely to receive behavioral health telehealth services and to seek treatment for OUD; additionally, minority groups face a lack of culturally appropriate services and discrimination within the healthcare system, which may make it difficult for individuals to access treatment for addiction leading to an increased risk of overdose.[27] Furthermore, overdose deaths from fentanyl during the pandemic disproportionately affected Black communities. Black people who use drugs are likely to be exposed to fentanyl, which is often unintentional and may reflect a reduced ability to avoid unwanted exposure.[28] Nonetheless, minority populations have been largely ignored in the drug overdose crisis, which has been overwhelmingly portrayed on the national political stage as a "White problem" in recent years.[29,30] Targeted interventions are needed to address the differences in access to treatment for drug overdoses, prevention of drug abuse, and recovery support services among minority groups.

Our study revealed that the pandemic further exacerbated the burden of overdose-related deaths, with excess deaths peaking in 2021 (26.4%). As the impact of the pandemic lessened and medical and nursing services returned to normal, the overall excess mortality showed a decreasing trend in 2022 (19.3%). However, the overdose-related excess deaths continued to increase in 2022 among certain populations, including females, adolescents and ethnic minorities. Our findings suggested that the continuing impact of the post-pandemic phase on these populations still requires further

attention, and targeted intervention measures need to be implemented as soon as possible.

We acknowledged the following limitations. We identified decedents with an overdose-related diagnosis through the ICD-10 codes, which is prone to misclassification bias. Using the CDC WONDER database, we discussed overdose-related deaths during the COVID-19 pandemic, which cannot reflect other possible factors that may influence trends in overdose-related deaths, such as policy changes, socioeconomic status, and societal pressures. The data used in the study were based on death certificates, which may not always accurately reflect the true cause of death. For example, some people may have died from an overdose due to multiple drugs, but their death certificates only listed one drug, resulting in underestimates of drug-induced deaths.

In conclusion, in this cross-sectional study, the burden of drug overdose-related deaths in the United States has significantly increased from 2012 to 2022 and exacerbated during pandemic, with excess ASMRs of 16.9%–26.4% in 2020–2022. During the pandemic, major disparities existed with the highest excess ASMR found in adolescents, females, ethnic minorities especially the non-Hispanic American Indian/Alaska Native group. Illicit fentanyl and synthetic drugs are the primary cause of drug overdose deaths during the pandemic. Comprehensive measures are needed to reduce the burden of drug overdose deaths.

Contributors

YZ, YL, YHY and FJ conceptualized the study. YZ, XH, WHN, SQ, LZ, ZX and YG collected the data. YZ and XH verified the data. YZ, YL, FL and JZ performed the data analysis. YZ wrote the first draft of the manuscript. All authors reviewed and edited the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data sharing statement

The NVSS can be accessed through this website: https://wonder.cdc.gov/mcd-icd10-provisional.html.

Declaration of interests

Professor Ji has received speaker fees from Gilead Sciences, MSD, and Ascletis, in addition to consulting or advisory board fees from Gilead and MSD. All other authors report no potential conflicts.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102752.

References

1 US drug overdose deaths: a global challenge. *Lancet*. 2016;387(10017):404.
2 Scholl L, Seth P, Kariisa M, Wilson N, Baldwin G. Drug and opioid-involved overdose deaths-United States, 2013-2017. *MMWR Morb Mortal Wkly Rep*. 2018;67(5152):1419–1427.
3 Hedegaard H, Miniño AM, Warner M. Drug overdose deaths in the United States, 1999-2019. *NCHS Data Brief*. 2020;394:1–8.
4 Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. *Curr Opin Psychiatry*. 2021;34(4):344–350.
5 *DEA: fentanyl*; 2022. http://www.dea.gov/factsheets/fentanyl. Accessed June 23, 2024.
6 Cartus AR, Li Y, Macmadu A, et al. Forecasted and observed drug overdose deaths in the US during the COVID-19 pandemic in 2020. *JAMA Netw Open*. 2022;5(3):e223418.
7 Hedegaard H, Miniño AM, Spencer MR, Warner M. Drug overdose deaths in the United States, 1999-2020. *NCHS Data Brief*. 2021;426:1–8.
8 Spencer MR, Miniño AM, Warner M. Drug overdose deaths in the United States, 2001-2021. *NCHS Data Brief*. 2022;457:1–8.
9 Ross JA, Malone PK, Levy S. The impact of the severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) pandemic on substance use in the United States. *Clin Infect Dis*. 2022;75(Suppl 1):S81–S85.
10 *Prevention tCfDCa. CDC WONDER*; 2023. https://wonder.cdc.gov/. Accessed July 31, 2023.
11 Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in Epidemiology (STROBE): explanation and elaboration. *Epidemiology*. 2007;18:805–835.
12 Stone MB,RJ. Cross-validated sequentially constructed prediction embracing ordinary least squares, partial least squares and principal components regression. *J Roy Stat Soc*. 1990;52:237–258.
13 Kim HJ, Fay MP, Feuer EJ, Midthune DN. Permutation tests for joinpoint regression with applications to cancer rates. *Stat Med*. 2000;19(3):335–351.
14 Friedman J, Godvin M, Shover CL, et al. Trends in drug overdose deaths among US adolescents, January 2010 to June 2021. *JAMA*. 2022;327(14):1398–1400.
15 Green TC, Gilbert M. Counterfeit medications and fentanyl. *JAMA Intern Med*. 2016;176(10):1555–1557.
16 Anderson KN, Johns D, Holland KM, et al. Emergency department visits involving mental health conditions, suicide-related behaviors, and drug overdoses among adolescents-United States, January 2019-February 2023. *MMWR Morb Mortal Wkly Rep*. 2023;72(19):502–512.
17 Böttcher L, Chou T, D'Orsogna MR. Forecasting drug-overdose mortality by age in the United States at the national and county levels. *PNAS Nexus*. 2024;3(2):pgae050.
18 Cook JL. The opioid epidemic. *Best Pract Res Clin Obstet Gynaecol*. 2022;85(Pt B):53–58.
19 Mellis AM, Kelly BC, Potenza MN, Hulsey JN. Factors associated with drug overdoses during the COVID-19 pandemic. *J Addict Med*. 2022;16(1):e67–e69.
20 Khatri UG, Perrone J. Opioid use disorder and COVID-19: crashing of the crises. *J Addict Med*. 2020;14(4):e6–e7.
21 Chen AY, Powell D, Stein BD. Changes in buprenorphine and methadone supplies in the US during the COVID-19 pandemic. *JAMA Netw Open*. 2022;5(7):e2223708.
22 Macmadu A, Batthala S, Correia Gabel AM, et al. Comparison of characteristics of deaths from drug overdose before vs during the COVID-19 pandemic in Rhode Island. *JAMA Netw Open*. 2021;4(9):e2125538.
23 Rao IJ, Humphreys K, Brandeau ML. Effectiveness of policies for addressing the US opioid epidemic: a model-based analysis from the stanford-lancet commission on the North American opioid crisis. *Lancet Reg Health Am*. 2021;3:100031.
24 Han B, Einstein EB, Jones CM, et al. Racial and ethnic disparities in drug overdose deaths in the US during the COVID-19 pandemic. *JAMA Netw Open*. 2022;5(9):e2232314.
25 Friedman JR, Hansen H. Evaluation of increases in drug overdose mortality rates in the US by race and ethnicity before and during the COVID-19 pandemic. *JAMA Psychiatr*. 2022;79(4):379–381.
26 Jones AA, Waghmare SA, Segel JE, et al. Regional differences in fatal drug overdose deaths among Black and White individuals in the United States, 2012-2021. *Am J Addict*. 2024. https://doi.org/10.1111/ajad.13536.
27 Khan MR, Hoff L, Elliott L, et al. Racial/ethnic disparities in opioid overdose prevention: comparison of the naloxone care cascade in White, Latinx, and Black people who use opioids in New York City. *Harm Reduct J*. 2023;20(1):24.
28 D'Orsogna MR, Böttcher L, Chou T. Fentanyl-driven acceleration of racial, gender and geographical disparities in drug overdose deaths in the United States. *PLoS Glob Public Health*. 2023;3(3):e0000769.
29 Friedman J, Hansen H. Far from a "white problem": responding to the overdose crisis as a racial justice issue. *Am J Public Health*. 2022;112(S1):S30–S32.
30 Netherland J, Hansen H. White opioids: pharmaceutical race and the war on drugs that wasn't. *BioSocieties*. 2017;12(2):217–238.