Men have approximately 2- to 3-fold greater overdose mortality than women for synthetic opioids, heroin and psychostimulants including cocaine across the lifespan: Analysis of state-level CDC data for 2020-2021

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Abbreviations:

95%CI**:** 95% confidence interval

DF: degrees of freedom

CDC: Centers for Disease Control and Prevention

MOP-r: μ-opioid receptor

NS: not significant

SUD: Substance use disorders

Abstract

Drug overdoses are an escalating cause of mortality in the United States, with potential sex differences across the lifespan. The objective of this study was to use state-level nationally representative data that includes the COVID-19 pandemic period to determine overdose mortality for specific drug categories across the lifespan of men and women. We used Centers for Disease Control and Prevention (CDC) Multiple Cause of Death 2020-2021 data on overdose mortality, for 50 states and District of Columbia, across 10-year age bins (age range: 15-74). The outcome measure was sex-specific crude overdose death rate (per 100,000) for: synthetic opioids excluding methadone (ICD-10 code: T40.4; e.g., fentanyl), heroin (T40.1), psychostimulants with abuse potential (T43.6; e.g., methamphetamine), and cocaine (T40.5). Multiple regression analyses adjusted for ethnic-cultural background and household net worth from Census data, and sex-specific rate of misuse of the relevant substances, from the National Survey on Drug Use and Health (2019-2020). For each of these major drug categories, men had greater overall overdose mortality than women. Although overall rates of mortality differed across jurisdictions, the sex ratio of mortality for each drug category was relatively stable (≈2- to 3-fold greater mortality in men vs women). These findings survived adjustment for state-level ethnic-cultural and economic variables, and for sex-specific misuse of each drug type (especially in the 25-34, 35-44, 45-54 and 55-64 age bins). These findings underscore the need for research into sex- and gender-based mechanisms underlying differential vulnerability in overdose mortality for these drugs, based on their diverse pharmacodynamics and pathophysiology.

Introduction

Overdose deaths due to the use of opioids [μ-opioid receptor (MOP-r) agonists such as fentanyl and heroin], or psychostimulants such as methamphetamine and cocaine, have increased considerably in recent years in the United States [1-3]. Starting in 2020, and following the onset of the COVID-19 pandemic, there has been a further increase in overdose mortality for some substances (e.g., synthetic opioids such as fentanyl or the psychostimulant methamphetamine), but not others (e.g., heroin and other opiates) [4-6].

Identification of vulnerability to overdose mortality in the population at risk is crucial for targeted prevention and intervention efforts and for saving lives. A large number of experimental studies (in preclinical models and humans) examined sex differences, including the potential role of ovarian hormones, in abuse liability of MOP-r agonists or psychostimulants, with conflicting results [7-11]. While some preclinical studies report that females show greater responsiveness to the reinforcing effects or escalation of MOP-r agonists or psychostimulants, other studies do not show such sex differences [7,9,12-16]. Similarly, some cohort studies in humans show that women escalate their intake of MOP-r agonists or psychostimulants more rapidly than men, but this is not found in all studies [17-23]. As indicated by an extensive recent review of preclinical and clinical data, sex differences in vulnerability to withdrawal and relapse-like behaviors for MOP-r agonists or psychostimulants were also not robust overall, particularly in humans [11]. However, given methodological and ethical reasons, experimental investigations do not typically examine overdoses directly [8,11,24].

Nevertheless, epidemiological studies have shown gaps in overdose mortality between men and women. A recent report from the CDC, summarizing data from 2019 and 2020, including the COVID-19 pandemic, for 25 states and the District of Columbia, showed an overall increase in overdose mortality for all drugs combined, with a greater rate in men versus women [25]. Similarly, a United States nation-level analysis of mortality data, stratified as ages 15-34 or 35-64, found that overdoses from synthetic opioids (including fentanyl but not heroin) and psychostimulants (including methamphetamine but not cocaine) increased from March 2018 to March 2021 (i.e., covering the onset of the COVID-pandemic [4]), again with highest mortality was in men with minority status (e.g., African-American) [4]. Prior to the COVID-19 pandemic, a national-level

report of CDC data from 2017-2018 showed that men compared to women had greater overdose mortality for all opioids combined, and also for prescription opioids (e.g., oxycodone) [6].

Given the differential pharmacodynamics and pathophysiology underlying these different types of drugs, it is important to examine their associated overdose mortality separately. Acute overdose mortality caused by MOP-r agonists is primarily attributed to respiratory depression mediated by several brainstem nuclei [26,27]. Ascribed in part to greater rapidity of onset or chest rigidity, recent studies suggest that fentanyl may pose greater overdose risk than heroin or morphine derivatives [28-30]. It is unclear if there is sexually dimorphic vulnerability or resilience to the respiratory depressant effects of MOP-r agonists in humans [31-34].

By contrast, acute overdose mortality caused by psychostimulants such as methamphetamine and cocaine is primarily attributed to cardiovascular events, strokes, or seizures [35,36]. Psychostimulants primarily target transporters for the monoamines dopamine, serotonin and norepinephrine [37,38]. Methamphetamine acts both to increase monoamine release and inhibit reuptake through these transporters [24], whereas cocaine primarily functions through the latter mechanism [37], and there is greater neurotoxicity caused by methamphetamine than cocaine exposure [37,39,40]. Sex differences have been observed in the cardiovascular effects of cocaine in some, but not all experimental studies in humans [12,41-43]. Thus, cocaine increases heart rate and blood pressure of both men and women [44], and a subset of studies reported that women had either more prolonged or greater cardiovascular effects than men [41,42,45,46], possibly varying due to route of administration [12,47]. Sex differences in methamphetamine-induced cardiovascular effects such as hypertension and cardiac function also depend on variables studied and methodological factors [24,43].

As mentioned above, there has been an increase in overdoses due to synthetic opioids during recent years, especially 2020 and thereafter, coinciding with the COVID-19 pandemic [1,4,48]. COVID-19 mortality, which is greater in men versus women, also involves respiratory distress [49-51], and the presence of specific SUD is also noted as a risk factor for COVID-19 infection [51,52]. However, we are not aware of studies that examined if COVID-19 infection *per se* is involved in the increases in opioid-induced overdoses at the patient

level (as opposed to the system-wide impact of multiple environmental, healthcare and patient-level changes that occurred during the pandemic) [51,53-57].

Opioid or psychostimulant use disorders can have long-term trajectories over the lifespan [19,58-60], and sex differences in overdose vulnerability may change through adolescence, adulthood and menopause or aging, potentially depending on multiple underlying mechanisms [12,24,35]. Also, men and women could differ in their risk of overdose mortality based in part on gendered factors that may also change over the lifespan, such as family and social interactions and related trauma [61,62], risky behaviors (e.g., injecting alone) [63], and interaction with healthcare systems [64-69]. We therefore studied the potential for a sexually dimorphic overdose mortality risk as a function of selected drug categories across the lifespan. We also considered environmental differences as reflected across states, as these could encompass illicit drug market supply, socioeconomic factors, and availability of evidence-based care [70-74]. Overall, using state-level nationally representative CDC data for 2020-2021, the goal of this study was to determine if there are stable sex differences in overdose mortality across the lifespan for synthetic opioids, heroin, psychostimulants and cocaine, studied as mutually exclusive categories.

Patients and Methods

This was an observational study of de-identified publicly available data from the CDC “multiple cause mortality” data, obtained from the CDC WONDER platform (https://wonder.cdc.gov/mcd.html), which provides information based on death certificates in the United States. Values that were “suppressed” (due to n<10 per cell) or deemed “unreliable” in CDC WONDER were considered missing. Data were analyzed in October-December 2022.

Data set: The main analyzed outcome was crude death rates per 100,000 population for Drug Poisonings (ICD-10 codes for overdoses; unintentional X40-X44, suicide X60-X64, homicide X85, undetermined Y10-Y14). Data were obtained separately for: synthetic opioids other than methadone (“synthetic opioids” hereafter; this includes fentanyl and its analogs but also compounds from other scaffolds; T40.4) [55], heroin (T40.1), psychostimulants with abuse potential (“psychostimulants” hereafter; including methamphetamine; T43.6) and

cocaine (T40.5). Data were stratified by sex and by six consecutive 10-year age bins (i.e., 15-24, 25-34, 35-44, 45-54, 55-64 and 65-74) obtained for 51 jurisdictions (50 states and the District of Columbia) for 2020-2021 (2021 includes provisional data) [75,76]. To minimize the number of cells with suppressed data, analysis with greater granularity (e.g., county level) was not attempted.

Data Analyses: All analyses were carried out with GraphPad Prism V.9, using jurisdiction-level data. Univariate analyses included four Spearman correlations on raw overdose mortality data (crude death rate/100,000) for men and women, per jurisdiction. Univariate mixed effects ANOVAs (sex x age bin) then analyzed log-transformed overdose mortality rate across the lifespan, stratified in six consecutive 10-year age bins; significant effects were followed by post-hoc Bonferroni tests. Outliers (>1.96 standard deviations from the mean) were excluded from the ANOVAs. If there were less than 10 jurisdictions in which data were available for both men and women for a given age bin and drug category, the whole age bin was excluded from the ANOVA, in order to maintain representativeness of sex comparisons. The overall alpha level of significance was set at the p=0.05 level.

Separately for each drug category and age bin, multivariate analyses were then carried out with multiple linear (least squares) regressions, to assess the effect of sex and selected potential covariates on the outcome, log-transformed death rates. Thus, the independent variables included: sex (M/F), percent of the population who is white, percent of the population who is black (from the 5-year American Community Survey for 2020 from the U.S. Census Bureau; from https://worldpopulationreview.com/states/states-by-race), and median household net worth in 2020 (www.census.gov/data/tables/2020/demo/wealth/state-wealth-asset-ownership.html). Using data from the National Survey on Drug Use and Health (NSDUH) for the years 2019-2020, we also controlled for overall levels of misuse of the relevant drugs (https://rdas.samhsa.gov/#/survey/NSDUH-2019-2020-RD02YR). Thus, the multiple linear regressions for both synthetic opioids and heroin included percent of the population who reported past year misuse of opioids (item OPINMYR in the NSDUH survey). Likewise, the regressions for psychostimulants or cocaine included the percent in the population who reported past year misuse of these types of drugs (items AMMEPDPYMU and COCMYR in the NSDUH survey, respectively). In all the multiple regressions, outliers (>1.96 standard deviations from the mean of the outcome value), were removed. As above, multiple regressions for a given age

bin are not reported if there were less than 10 jurisdictions in which data were available for both men and women. In a supplementary follow-up analysis, we also examined analogously overdoses caused by both synthetic opioids and psychostimulants (a common poly-drug pattern of overdose) [3,77].

Results:

Overall overdose mortality profiles (all ages combined): With all ages combined, there was a broad range of raw overdose mortality rates for all four drug categories, across jurisdictions (i.e., individual symbols in Figure 1). There were positive Spearman correlations, nearing unity, in the rate of overdose mortality for men and women in the same jurisdiction, for the different drug categories (Spearman r-values ranged from +0.94 to +0.97; all $p<0.0001$) (see Figure 1). Simple linear regressions provided a strong fit for these within-jurisdiction data (R^2 values of 0.95, 0.88, 0.92 and 0.95, for synthetic opioids, heroin, psychostimulants and cocaine respectively). Importantly, the mean ratios for mortality in men:women (all ages combined) across jurisdictions exhibited a relatively small range, 2.4 to 2.9 for the four drug categories. Thus, the mean ratio of mortality in men:women was 2.5 (95%CI 2.4-2.7) for synthetic opioids, 2.9 (95%CI: 2.7-3.1) for heroin, 2.4 (95%CI: 2.3-2.5) for psychostimulants and 2.8 (95%CI: 2.6-2.9) for cocaine.

Univariate analyses across the lifespan: Analyses were then stratified over six consecutive 10-year age bins (Figure 2), using log-transformed mortality rates as the outcome, after excluding age bins for which insufficient data was available (see Methods and Table 1). Separate 2-way mixed effects ANOVAs (sex X age bin) were carried out for each drug category. For synthetic opioids, psychostimulants and cocaine, there were significant main effects of sex and age bin, and also sex x age bin interactions (see Table 1). For heroin, there were significant main effects of sex and age bin, but the interaction was non-significant. Post-hoc Bonferroni tests for gender at each age bin (Table 1 and Figure 2) showed that with few exceptions (typically for the youngest and oldest age bins, 15-24 and 65-74 years), men had greater mortality than women. Furthermore, women did not have significantly greater mortality than men for any of the age bins, in any of the drug categories, based on these post-hoc tests.

Multivariate analyses across the lifespan: Multiple linear regressions for log overdose mortality rate were carried out for each drug category separately, per age bin. Significant beta parameters (±95%CI), p-values and overall model R^2, as well as effect size for sex (eta^2) [78,79] are provided (Table 2). For all the available multiple regressions, sex remained a significant factor after adjustment for jurisdiction-level demographic variables (ethnic-cultural group and median household net worth) and for percent of men and women reporting past year misuse of the relevant drugs. Of note, sex also remained a significant factor in overdose mortality for all drug categories in the 55-64 age bin, a post-menopausal range [80].

Supplementary analysis of overdoses caused by *both* synthetic opioids and psychostimulants: We also analyzed overdoses caused by a commonly reported pattern of poly-drug use (combining synthetic opioids and psychostimulants; i.e., ICD-10 codes T40.4 and T43.6 as multiple causes of death) [3,77,81]. Overdose mortality due to this poly-drug combination generally followed a similar sex profile across the lifespan, with men having greater mortality than women in the age range 25-64 (see Supplementary data at the bottom of the document).

Discussion

To our knowledge, this is the first state- and age- specific examination of differences between men and women in overdose mortality due to synthetic opioids, heroin, and psychostimulants including cocaine, using a nationally representative sample, for 2020-2021 (thus covering the COVID-19 pandemic period). This analysis showed that across these four mutually exclusive drug categories in CDC data, and across the lifespan, men are dying from overdoses at an approximately 2-3 greater rate than women, as generalized across geographical jurisdictions, and controlling for demographics (household net worth and ethnic-cultural group) and past-year drug misuse.

This robust pattern of greater mortality in men across the lifespan, for each of these drug categories, was observed for all but the youngest and oldest age bins (15-24 and 65-74; which were also the bins with lowest overdose mortality overall). Greater overdose mortality in men versus women was also observed in the 55-64 age bin, for all drug categories. Since women typically reach menopause before the age of 55 [80,82], fluctuations in ovarian hormones are unlikely to account for this sex difference in overdose mortality. However, potential post-menopausal effects of progesterone cannot be fully excluded [12,83,84]. It should also be noted that the age trajectory of these SUD typically commences earlier in the lifespan [19,20,60], and that the lower mortality occurring in post-menopausal women could be a “carryover” of sexually dimorphic bio-behavioral factors that occur prior to menopause.

Since MOP-r agonists and psychostimulants including cocaine produce overdoses by different pharmacological and pathophysiological mechanisms [29,35,85,86], it is unlikely that a single underlying biological mechanism could account for sexual dimorphism in overdose mortality across the lifespan for these drug categories. Furthermore, even within these major categories, the pharmacodynamics and pathophysiological effects of fentanyl vs heroin and other μ-agonists [29,30,87], or methamphetamine vs cocaine [36,39,88], are not necessarily identical. Instead, multiple sex- or gender- related mechanisms, potentially with different expressions/contributions, could underlie the risk of overdose mortality, at different stages in the life-long trajectories of these substance use disorders [24,35,89-93]. At a behavioral level, men could more frequently reach patterns of drug exposure associated with greater overdose risk (e.g., due to high

doses, or frequency of use) despite negative consequences such as withdrawal (e.g., sex differences in positive or negative reinforcement) [94,95]. There could also be gendered differences in protective factors such as the impact of family and social relationships [96,97], or vulnerability factors such as injecting drugs alone and other risky behaviors [63,98].

Limitations: We focused separately on each of these four mutually exclusive major drug categories, because they are involved in a large number of overdoses in the United States, and because of their different pharmacological and pathophysiological effects [3,4,24,99,100]. Analogous examination for other drug categories would also be valuable, for example prescription opioids [6]. Overall, epidemiological studies from other countries would also be important, to understand how generalizable these findings are. As a further potential limitation, it cannot be fully excluded that some of the sex differences in overdose mortality are due to reporting bias [101-103].

As mentioned in the Introduction, there have been increases in overdose mortality for both synthetic opioids and psychostimulants during the COVID-19 pandemic period [1,4,51]. Furthermore, mortality due to COVID-19 is also greater in men versus women [50,104], and substance use disorders have been detected as a comorbidity with this viral infection [51,56]. In a follow-up to this study, we found that COVID-19 (ICD-10 code: U07.1) was infrequently reported as one of “multiple causes of mortality” in the overdoses reported here for synthetic opioids or psychostimulants (not shown). Therefore, based on these data, it does not appear that these overdoses were principally due to an acute interaction of pathophysiological effects of these drugs and COVID-19 infection *per se* [51,56].

Conclusions: This state-level analysis of recent nationally representative data showed that, compared to women, men have approximately 2-3 fold greater rate of overdose mortality from synthetic opioids, heroin and psychostimulants including cocaine. Notably, these sex differences were relatively invariant across jurisdictions and across the lifespan (especially in the range of 25-64 years of age), even after controlling for major ethnic-cultural and economic factors, and levels of drug misuse. Together with the recent escalating trends in mortality, these findings suggest that sex and gender differences are important targets for investigation at

multiple biological and behavioral levels, potentially leading to optimized and drug-specific prevention and intervention approaches to mitigate risk of overdose mortality across the lifespan.

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Table 1: Univariate mixed effects ANOVAs (sex x age bin) to examine sex-related overdose mortality for specific drug categories across the lifespan (analysis of data in Figure 2, after log transformation).

Drug Category	**Sex** **Main effect**	**Age bin** **Main effect**	**Interaction** **(Sex x** **Age bin)**	**Significant post-hoc tests** **for sex x age bin**
Synthetic opioids	F (1, 209) = 2291; p<0.0001	F (5, 248) = 31.9; p<0.0001	F (5, 209) = 6.35; p<0.0001	Male>Female at age bins: • 15-24 • 25-34 • 35-44 • 45-54 • 55-64 • 65-74
Heroin (excluded 15-24 and 65-74 age bins[a])	F (1, 77) = 1209; p<0.0001	F (3, 134) = 4.85; P=0.0031	F (3, 77) = 2.06; NS	• N/A (sex x age bin interaction not significant)
Psychostimulants (excluded 65-74 age bin[a])	F (1, 160) = 1736; p<0.0001	F (4, 201) = 30.44; p<0.0001	F (4, 160) = 16.35; p<0.0001	Male>Female at age bins: • 15-24 • 25-34 • 35-45 • 45-54 • 55-64
Cocaine (excluded 65-74 age bin[a])	F (1, 119) = 1295; p<0.0001	F (4, 170) = 17.62; P<0.0001	F (4, 119) = 5.29; p=0.0006	Male>Female at age bins: • 15-24 • 25-34 • 35-45 • 45-54 • 55-64

[a]Age bins excluded from analysis if there were less than 10 jurisdictions with available data in both men and women (see Methods).

Table 2: Multiple linear regressions for state-level log mortality rate for specific drug categories, by age bin*

Table 2.1 Synthetic Opioids	**Significant β (beta) parameter Estimates [95%CI] and p-value**					Model R^2 (DF)
Age bin	Sex (Men); Women as reference	State Median Household Net Worth	State %White	State %Black	State and sex past year opioid misuse (%)[a]	
15-24	β=0.31 [0.22-0.38] p<0.0001 eta^2=0.42[b]	NS	NS	NS	NS	0.48 (69)
25-34	β=0.37 [0.26-0.47] p<0.0001 eta^2=0.33	NS	β=0.010 [0.0022-0.018] p=0.013	β=0.012 [0.0028-0.021] p=0.010	NS	0.40 (82)
35-44	β=0.37 [0.24-0.49] p<0.0001 eta^2=0.26	NS	β=0.013 [0.0062-0.021] p=0.0004	β=0.017 [0.0084-0.026] p=0.0002	NS	0.41 (80)
45-54	β=0.36 [0.23-0.49] P<0.0001 eta^2=0.25	NS	β=0.014 [0.0046-0.023] p=0.0039	β=0.019 [0.0092-0.030] p=0.0004	NS	0.39 (76)
55-64	β=0.35 [0.21-0.48] p<0.0001 eta^2=0.24	NS	NS	β=0.013 [0.001-0.024] p=0.034	NS	0.31 (74)
65-74	β=0.47 [0.30-0.64] p<0.0001 eta^2=0.40	β=1.77 X 10^{-6} [4.12 X 10^{-7} – 3.14 X 10^{-6}] P=0.012	β=0.013 [0.0009-0.025] p=0.036	β=0.018 [0.0034-0.032] p=0.016	NS	0.56 (34)

*Outcome: Log mortality rate

[a]State level of past year opioid misuse was from NSDUH, Restricted-Use Data Analysis System, item "OPINMYR" (2019-2020), per sex.

[b]eta^2 for sex (i.e., sum of $squares_{gender}$ / sum of $squares_{total}$); to measure effect size for the main variable of interest [78].

Table 2.2 Heroin	**Significant β (beta) parameter Estimates [95%CI] and p-value**					Model R^2 (DF)
Age bin	Sex (Men); Women as reference	State Median Household Net Worth	State %White	State %Black	State and sex past year opioid misuse (%)[a]	
15-24	Insufficient data for regression[c]					N/A
25-34	β=0.38 [0.28-0.48] p<0.0001 eta^2=0.50	NS	NS	NS	NS	0.51 (53)
35-44	β=0.40 [0.28-0.51] p<0.0001 eta^2=0.49	NS	NS	NS	NS	0.52 (50)
45-54	β=0.38 [0.25-0.51] p<0.0001 eta^2=0.39	NS	NS	NS	NS	0.46 (47)
55-64	β=0.46 [0.29-0.63] p<0.0001 eta^2=0.42	NS	NS	NS	NS	0.53 (33)
65-74	Insufficient data for regression[c]					N/A

[a]State level of past year opioid misuse was from NSDUH, Restricted-Use Data Analysis System, item "OPINMYR" (2019-2020), per sex.

[c]Less than 10 States had available data in both men and women (see Methods).

Table 2.3 Psychostimulants	**Significant β (beta) parameter Estimates [95%CI] and p-value**					Model R^2 (DF)
Age bin	Sex (Men); Women as reference	State Median Household Net Worth	State %White	State %Black	State and sex past year stimulant misuse (%)[d]	
15-24	β=0.22 [0.11-0.33] p<0.0001 eta^2=0.25	NS	NS	NS	NS	0.34 (44)
25-34	β=0.33 [0.24-0.42] p<0.0001 eta^2=0.36	β=-1.62 X 10^{-6} [-8.45 X 10^{-7} – -2.40 X 10^{-6}] p=0.0001	β=0.0076 [0.00066-0.015] p=0.032	NS	NS	0.60 (58)
35-44	β=0.35 [0.24-0.46] p<0.0001 eta^2=0.34	β=-1.64 X 10^{-6} [-7.34 X 10^{-7} – -2.55 X 10^{-6}] p=0.0006	NS	NS	NS	0.52 (59)
45-54	β=0.38 [0.24-0.51] p<0.0001 eta^2=0.29	β=-1.74 X 10^{-6} [-6.22 X 10^{-7} – -2.87 X 10^{-6}] p=0.0029	NS	β=-0.019 [-0.029 – -0.008] p=0.0006	NS	0.51 (58)
55-64	β=0.37 [0.24-0.50] P<0.0001 eta^2=0.25	β=-1.78 X 10^{-6} [-5.87 X 10^{-7} – -2.97 X 10^{-6}] p=0.0041	β=-0.012 [-0.021 – -0.0036] p=0.0066	β=-0.028 [-0.039 – -0.017] p>0.0001	NS	0.51 (58)
65-74	Insufficient data for regression[c]					N/A

[c]Less than 10 States had available data in both males and females (see Methods).

[d]State level of past year stimulant misuse was from NSDUH, Restricted-Use Data Analysis System, item "APPEPDPYMU" (2019-2020), per sex.

Table 2.4 Cocaine	**Significant β (beta) parameter Estimates [95%CI] and p-value**					Model R^2 (DF)
Age bin	Sex (Men); Women as reference	State Median Household Net Worth	State %White	State %Black	State and sex past year cocaine misuse (%)[e]	
15-24	β=0.26 [0.15-0.38] p<0.0001 eta^2=0.29	NS	NS	NS	NS	0.58 (30)
25-34	β=0.20 [0.10-0.37] p=0.011 eta^2=0.064	β=1.23 X 10^{-6} [2.30 X 10^{-7} – 2.99 X 10^{-6}] p=0.017	β=0.015 [0.0059-0.025] p=0.0020	β=0.017 [0.0055-0.028] P=0.0039	β=0.25 [0.075-0.42] p=0.0056	0.43 (61)
35-44	β=0.22 [0.047-0.39] p=0.013 eta^2=0.069	NS	β=0.020 [0.0084-0.031] p=0.0009	β=0.023 [0.01-0.035] p=0.0006	NS	0.34 (62)
45-54	β=0.28 [0.12-0.44] p=0.0011 eta^2=0.11	β=1.44 X 10^{-6} [2.38 X 10^{-7} – 2.64 X 10^{-6}] p=0.020	β=0.017 [0.0059-0.027] p=0.0029	β=0.022 [0.011-0.034] p=0.0003	NS	0.44 (61)
55-64	β=0.28 [0.13-0.43] p=0.0012 eta^2=0.11	β=1.95 X 10^{-6} [8.66 X 10^{-7} – 3.04 X 10^{-6}] p=0.0007	β=0.015 [0.0051-0.0258] p=0.0037	β=0.025 [0.014-0.035] p<0.0001	β=0.20 [0.039-0.36] P=0.016	0.54 (53)
65-74	Insufficient data for regression[c]					N/A

[c]Less than 10 States had available data in both males and females (see Methods).

[e]State level of past year cocaine misuse was from NSDUH, Restricted-Use Data Analysis System, item “COCYR” (2019-2020), per sex.

References

1 Brown KG, Chen CY, Dong D, Lake KJ, Butelman ER. Has the United States Reached a Plateau in Overdoses Caused by Synthetic Opioids After the Onset of the COVID-19 Pandemic? Examination of Centers for Disease Control and Prevention Data to November 2021. Frontiers in psychiatry. 2022; https://www.frontiersin.org/articles/10.3389/fpsyt.2022.947603/full.

2 Mattson CL, Tanz LJ, Quinn K, Kariisa M, Patel P, Davis NL. Trends and Geographic Patterns in Drug and Synthetic Opioid Overdose Deaths — United States, 2013–2019. MMWR Morbidity and mortality weekly report. https://doi.org/http://dx.doi.org/10.15585/mmwr.mm7006a4.

3 Kariisa M, Seth P, Scholl L, Wilson N, Davis NL. Trends in drug overdose deaths involving cocaine and psychostimulants with abuse potential among racial and ethnic groups – United States, 2004–2019. Drug Alc Depend. 2021:109001.

4 Han B, Einstein EB, Jones CM, Cotto J, Compton WM, Volkow ND. Racial and Ethnic Disparities in Drug Overdose Deaths in the US During the COVID-19 Pandemic. JAMA Netw Open. 2022; 5(9):e2232314.

5 Glicksberg L, Dempsey SK, Casey BK. Heroin and fentanyl in Dallas County: A 5-year retrospective review of toxicological, seized drug, and demographical data. J Forensic Sci. 2022; DOI: 10.1111/1556-4029.15155.

6 Wilson N, Kariisa M, Seth P, Smith Ht, Davis NL. Drug and Opioid-Involved Overdose Deaths - United States, 2017-2018. MMWR Morbidity and mortality weekly report. 2020; 69(11):290-97.

7 Carroll ME, Collins M, Kohl EA, Johnson S, Dougen B. Sex and menstrual cycle effects on chronic oral cocaine self-administration in rhesus monkeys: Effects of a nondrug alternative reward. Psychopharmacology. 2016; 233:2973-84.

8 Roth ME, Carroll ME. Sex differences in the escalation of intravenous cocaine intake following long- or short-access to cocaine self-administration. Pharmacology, biochemistry, and behavior. 2004; 78(2):199-207.

9 Anker JJ, Carroll ME. Females are more vulnerable to drug abuse than males: evidence from preclinical studies and the role of ovarian hormones. Current topics in behavioral neurosciences. 2011; 8:73-96.

10 Diester CM, Banks ML, Neigh GN, Negus SS. Experimental design and analysis for consideration of sex as a biological variable. Neuropsychopharmacol. 2019; 44(13):2159-62.

11 Nicolas C, Zlebnik NE, Farokhnia M, Leggio L, Ikemoto S, Shaham Y. Sex Differences in Opioid and Psychostimulant Craving and Relapse: A Critical Review. Pharmacological reviews. 2022; 74(1):119-40.

12 Evans SM, Foltin RW. Does the response to cocaine differ as a function of sex or hormonal status in human and non-human primates? Hormones and behavior. 2010; 58(1):13-21.

13 Alonso-Caraballo Y, Guha SK, Chartoff EH. The neurobiology of abstinence-induced reward-seeking in males and females. Pharmacology, biochemistry, and behavior. 2020:173088.

14 George BE, Barth SH, Kuiper LB, Holleran KM, Lacy RT, Raab-Graham KF, Jones SR. Enhanced heroin self-administration and distinct dopamine adaptations in female rats. Neuropsychopharmacol. 2021; 46(10):1724-33.

15 Malone SG, Keller PS, Hammerslag LR, Bardo MT. Escalation and reinstatement of fentanyl self-administration in male and female rats. Psychopharmacology. 2021; 238(8):2261-73.

16 Mavrikaki M, Lintz T, Constantino N, Page S, Chartoff E. Chronic opioid exposure differentially modulates oxycodone self-administration in male and female rats. Addict Biol. 2021; 26(3):e12973.

17 Kosten TA, Gawin FH, Kosten TR, Rounsaville BJ. Gender differences in cocaine use and treatment response. J Subst Abuse Treat. 1993; 10(1):63-6.

18 McCance-Katz EF, Carroll KM, Rounsaville BJ. Gender differences in treatment-seeking cocaine abusers--implications for treatment and prognosis. Am J Addict. 1999; 8(4):300-11.

19 Butelman ER, Chen CY, Brown KG, Kreek MJ. Escalation of drug use in persons dually diagnosed with opioid and cocaine dependence: Gender comparison and dimensional predictors. Drug Alcohol Depend. 2019; 205:107657.

20 Butelman ER, Chen CY, Conybeare RA, Brown KG, Fry RS, Kimani R, Correa da Rosa J, Ott J, Kreek MJ. Are trait impulsivity and exposure to cannabis or alcohol associated with the age of trajectory of cocaine use? A gender-specific dimensional analysis in humans with cocaine dependence diagnosis. Experimental and clinical psychopharmacology. 2019:10.1037/pha0000314.

21 Hernandez-Avila CA, Rounsaville BJ, Kranzler HR. Opioid-, cannabis- and alcohol-dependent women show more rapid progression to substance abuse treatment. Drug Alcohol Depend. 2004; 74(3):265-72.
22 Stoltman JJ, Woodcock EA, Lister JJ, Greenwald MK, Lundahl LH. Exploration of the telescoping effect among not-in-treatment, intensive heroin-using research volunteers. Drug Alcohol Depend. 2015; 148:217-20.
23 Anglin MD, Hser YI, McGlothlin WH. Sex differences in addict careers. 2. Becoming addicted. The American journal of drug and alcohol abuse. 1987; 13(1-2):59-71.
24 Daiwile AP, Jayanthi S, Cadet JL. Sex differences in methamphetamine use disorder perused from pre-clinical and clinical studies: Potential therapeutic impacts. Neuroscience and biobehavioral reviews. 2022; 137:104674.
25 Kariisa M, Davis NL, Kumar M, Seth P, Mattson CL, Chowdhury F, Jones CM. Vital Signs: Drug Overdose Deaths, by Selected Sociodemographic and Social Determinants of Health Characteristics — 25 States and the District of Columbia, 2019–2020. 2022. https://www.cdc.gov/mmwr/volumes/71/wr/mm7129e2.htm.
26 Baldo BA, Rose MA. Mechanisms of opioid-induced respiratory depression. Archives of Toxicology. 2022.
27 Liu S, Kim DI, Oh TG, Pao GM, Kim JH, Palmiter RD, Banghart MR, Lee KF, Evans RM, Han S. Neural basis of opioid-induced respiratory depression and its rescue. Proc Natl Acad Sci USA. 2021:118(23):e2022134118.
28 Britch SC, Walsh SL. Treatment of opioid overdose: current approaches and recent advances. Psychopharmacology. 2022; 239:2063-81.
29 Kelly E, Sutcliffe K, Cavallo D, Ramos-Gonzalez N, Alhosan N, Henderson G. The anomalous pharmacology of fentanyl. British journal of pharmacology. 2021; doi: 10.1111/bph.15573.
30 Torralva PR, Janowsky A. Noradrenergic Mechanisms in Fentanyl-Mediated Rapid Death Explain Failure of Naloxone in the Opioid Crisis. The Journal of pharmacology and experimental therapeutics. 2019; DOI: 10.1124/jpet.119.258566.
31 Roy S, Bruehl S, Feng X, Shotwell MS, Van De Ven T, Shaw AD, Kertai MD. Developing a risk stratification tool for predicting opioid-related respiratory depression after non-cardiac surgery: a retrospective study. BMJ open. 2022; 12(9):e064089.
32 Khanna AK, Bergese SD, Jungquist CR, Morimatsu H, Uezono S, Lee S, Ti LK, Urman RD, McIntyre R, Jr., Tornero C, Dahan A, Saager L, Weingarten TN, Wittmann M, Auckley D, Brazzi L, Le Guen M, Soto R, Schramm F, Ayad S, Kaw R, Di Stefano P, Sessler DI, Uribe A, Moll V, Dempsey SJ, Buhre W, Overdyk FJ. Prediction of Opioid-Induced Respiratory Depression on Inpatient Wards Using Continuous Capnography and Oximetry: An International Prospective, Observational Trial. Anesthesia and analgesia. 2020; 131(4):1012-24.
33 Garrett J, Vanston A, Ogola G, da Graca B, Cassity C, Kouznetsova MA, Hall LR, Qiu T. Predicting opioid-induced oversedation in hospitalised patients: a multicentre observational study. BMJ open. 2021; 11(11):e051663.
34 Pleym H, Spigset O, Kharasch ED, Dale O. Gender differences in drug effects: implications for anesthesiologists. Acta anaesthesiologica Scandinavica. 2003; 47(3):241-59.
35 Bachi K, Mani V, Jeyachandran D, Fayad ZA, Goldstein RZ, Alia-Klein N. Vascular disease in cocaine addiction. Atherosclerosis. 2017; 262:154-62.
36 Jayanthi S, Daiwile AP, Cadet JL. Neurotoxicity of methamphetamine: Main effects and mechanisms. Experimental neurology. 2021; 344:113795.
37 Fleckenstein AE, Gibb JW, Hanson GR. Differential effects of stimulants on monoaminergic transporters: pharmacological consequences and implications for neurotoxicity. Eur J Pharmacol. 2000; 406(1):1-13.
38 Ritz MC, Lamb RJ, Goldberg SR, Kuhar MJ. Cocaine receptors on dopamine transporters are related to self-administration of cocaine. Science (New York, NY). 1987; 237(4819):1219-23.
39 Dietrich JB. Alteration of blood-brain barrier function by methamphetamine and cocaine. Cell and tissue research. 2009; 336(3):385-92.
40 Fowler JS, Volkow ND, Logan J, Alexoff D, Telang F, Wang G-J, Wong C, Ma Y, Kriplani A, Pradhan K, Schlyer D, Jayne M, Hubbard B, Carter P, Warner D, King P, Shea C, Xu Y, Muench L, Apelskog K. Fast uptake and long-lasting binding of methamphetamine in the human brain: Comparison with cocaine. NeuroImage. 2008; 43(4):756-63.
41 Lukas SE, Sholar M, Lundahl LH, Lamas X, Kouri E, Wines JD, Kragie L, Mendelson JH. Sex differences in plasma cocaine levels and subjective effects after acute cocaine administration in human volunteers. Psychopharmacology. 1996; 125(4):346-54.

42 Kosten TR, Kosten TA, McDougle CJ, Hameedi FA, McCance EF, Rosen MI, Oliveto AH, Price LH. Gender differences in response to intranasal cocaine administration to humans. Biological psychiatry. 1996; 39(2):147-8.
43 Mayo LM, Paul E, DeArcangelis J, Van Hedger K, de Wit H. Gender differences in the behavioral and subjective effects of methamphetamine in healthy humans. Psychopharmacology. 2019; 236(8):2413-23.
44 Mendelson JH, Mello NK, Sholar MB, Siegel AJ, Kaufman MJ, Levin JM, Renshaw PF, Cohen BM. Cocaine Pharmacokinetics in Men and in Women During the Follicular and Luteal Phases of the Menstrual Cycle. Neuropsychopharmacol. 1999; 21(2):294-303.
45 Evans SM, Haney M, Fischman MW, Foltin RW. Limited sex differences in response to "binge" smoked cocaine use in humans. Neuropsychopharmacol. 1999; 21(3):445-54.
46 Singha AK, McCance-Katz EF, Petrakis I, Kosten TR, Oliveto A. Sex Differences in Self-Reported and Physiological Response to Oral Cocaine and Placebo in Humans. The American journal of drug and alcohol abuse. 2000; 26(4):643-57.
47 Collins SL, Evans SM, Foltin RW, Haney M. Intranasal cocaine in humans: effects of sex and menstrual cycle. Pharmacology, biochemistry, and behavior. 2007; 86(1):117-24.
48 Garcia GP, Stringfellow EJ, DiGennaro C, Poellinger N, Wood J, Wakeman S, Jalali MS. Opioid overdose decedent characteristics during COVID-19. Annals of medicine. 2022; 54(1):1081-88.
49 Oliván-Blázquez B, Bartolomé-Moreno C, Gericó-Aseguinolaza J, Méndez-López F, Lerma-Irureta D, Lamiquiz-Moneo I, Fernández-Martínez S, Magallón-Botaya R. Relationship between initial symptoms and the prognosis, sex, and demographic area of patients with COVID-19. Frontiers in Medicine. 2022; 9.
50 Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M. Risk Factors Associated With Mortality Among Patients With COVID-19 in Intensive Care Units in Lombardy, Italy. JAMA internal medicine. 2020; 180(10):1345-55.
51 Volkow ND. Collision of the COVID-19 and Addiction Epidemics. Annals of internal medicine. 2020; 173(1):61-62.
52 Wang QQ, Kaelber DC, Xu R, Volkow ND. COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States. Molecular psychiatry. 2020; doi: 10.1038/s41380-020-00880-7.
53 Slavova S, Rock P, Bush HM, Quesinberry D, Walsh SL. Signal of increased opioid overdose during COVID-19 from emergency medical services data. Drug Alc Depend. 2020; 214:108176.
54 Root ED, Slavova S, LaRochelle M, Feaster DJ, Villani J, Defiore-Hyrmer J, El-Bassel N, Ergas R, Gelberg K, Jackson R, Manchester K, Parikh M, Rock P, Walsh SL. The impact of the National Stay-at-Home Order on Emergency Department Visits for Suspected Opioid Overdose During the First Wave of the COVID-19 Pandemic. Drug Alc Depend. 2021:108977.
55 Skolnick P. Treatment of overdose in the synthetic opioid era. Pharmacology & therapeutics. 2021:108019.
56 Schimmel J, Manini AF. Opioid Use Disorder and COVID-19: Biological Plausibility for Worsened Outcomes. Substance use & misuse. 2020; 55(11):1900-01.
57 Hurd YL, Brennan T. A Perfect Storm. Cerebrum. 2022; 2022.
58 Butelman ER, Chen CY, Lake KJ, Brown KG, Kreek MJ. Bidirectional influence of heroin and cocaine escalation in persons with dual opioid and cocaine dependence diagnoses. Experimental and clinical psychopharmacology. 2020.
59 Woodcock EA, Lundahl LH, Stoltman JJ, Greenwald MK. Progression to regular heroin use: examination of patterns, predictors, and consequences. Addictive behaviors. 2015; 45:287-93.
60 Rodriguez-Cintas L, Daigre C, Grau-Lopez L, Barral C, Perez-Pazos J, Voltes N, Braquehais MD, Casas M, Roncero C. Impulsivity and addiction severity in cocaine and opioid dependent patients. Addictive behaviors. 2016; 58:104-09.
61 Luthar SS, Gushing G, Rounsaville BJ. Gender differences among opioid abusers: Pathways to disorder and profiles of psychopathology. Drug Alc Depend. 1996; 43(3):179-89.
62 Bagley SM, Gai MJ, Earlywine JJ, Schoenberger SF, Hadland SE, Barocas JA. Incidence and Characteristics of Nonfatal Opioid Overdose Among Youths Aged 11 to 24 Years by Sex. JAMA Netw Open. 2020; 3(12):e2030201.

63 Norton A, Hayashi K, Johnson C, Choi J, Milloy MJ, Kerr T. Injecting drugs alone during an overdose crisis in Vancouver, Canada. Harm reduction journal. 2022; 19(1):125.

64 Kaplovitch E, Gomes T, Camacho X, Dhalla IA, Mamdani MM, Juurlink DN. Sex Differences in Dose Escalation and Overdose Death during Chronic Opioid Therapy: A Population-Based Cohort Study. PloS one. 2015; 10(8):e0134550.

65 Ho JY. Cycles of Gender Convergence and Divergence in Drug Overdose Mortality. Popul Dev Rev. 2020; 46(3):443-70.

66 Moyo P, Eliot M, Shah A, Goodyear K, Jutkowitz E, Thomas K, Zullo AR. Discharge locations after hospitalizations involving opioid use disorder among medicare beneficiaries. Addiction science & clinical practice. 2022; 17(1):57.

67 Serdarevic M, Striley CW, Gurka KK, Leeman RF, Cottler LB. Sex differences in prescription opioid use patterns assessed through a community engagement program in Florida. Drug Alc Depend. 2019; 204:107568.

68 Hser YI, Anglin MD, McGlothlin W. Sex differences in addict careers. 1. Initiation of use. The American journal of drug and alcohol abuse. 1987; 13(1-2):33-57.

69 Goetz TG, Becker JB, Mazure CM. Women, opioid use and addiction. FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 2021; 35(2):e21303.

70 Shover CL, Falasinnu TO, Dwyer CL, Santos NB, Cunningham NJ, Freedman RB, Vest NA, Humphreys K. Steep increases in fentanyl-related mortality west of the Mississippi River: Recent evidence from county and state surveillance. Drug Alcohol Depend. 2020; 216:108314.

71 Althoff KN, Leifheit KM, Park JN, Chandran A, Sherman SG. Opioid-related overdose mortality in the era of fentanyl: Monitoring a shifting epidemic by person, place, and time. Drug Alc Depend. 2020:108321.

72 Kilmer B, Pardo B, Pujol TA, Caulkins JP. Rapid changes in illegally manufactured fentanyl products and prices in the United States. Addiction (Abingdon, England). 2022; DOI: 10.1111/add.15942

73 Cano M, Oh S, Osborn P, Olowolaju SA, Sanchez A, Kim Y, Moreno AC. County-Level Predictors of US Drug Overdose Mortality: A Systematic Review. Drug Alc Depend. 2022; https://doi.org/10.1016/j.drugalcdep.2022.109714:109714.

74 Tabatabai M, Cooper RL, Wilus DM, Edgerton RD, Ramesh A, MacMaster SA, Patel PN, Singh KP. The Effect of Naloxone Access Laws on Fatal Synthetic Opioid Overdose Fatality Rates. J Prim Care Community Health. 2023; DOI: 10.1177/21501319221147246.

75 Ahmad FB, Rossen LM, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics. 2021. https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm.

76 Spencer MR, Ahmad F. Timeliness of Death Certificate Data for Mortality Surveillance and Provisional Estimates. 2016. https://www.cdc.gov/nchs/data/vsrr/report001.pdf.

77 Hedegaard H, Miniño AM, Warner M. Co-involvement of opioids in drug overdose deaths involving cocaine and psychostimulants; https://doi.org/10.15620/cdc:103966. 2021.

78 Lakens D. Calculating and reporting effect sizes to facilitate cumulative science: a practical primer for t-tests and ANOVAs. Frontiers in psychology. 2013; 4:863.

79 Richardson JTE. Eta squared and partial eta squared as measures of effect size in educational research. Educational Research Review. 2011; 6(2):135-47.

80 Gold EB. The timing of the age at which natural menopause occurs. Obstet Gynecol Clin North Am. 2011; 38(3):425-40.

81 Ciccarone D. The rise of illicit fentanyls, stimulants and the fourth wave of the opioid overdose crisis. Current opinion in psychiatry. 2021; 34(4):344-50.

82 Schoenbaum EE, Hartel D, Lo Y, Howard AA, Floris-Moore M, Arnsten JH, Santoro N. HIV infection, drug use, and onset of natural menopause. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2005; 41(10):1517-24.

83 Weinland C, Mühle C, Kornhuber J, Lenz B. Progesterone serum levels correlate negatively with craving in female postmenopausal in-patients with alcohol use disorder: A sex- and menopausal status-separated study. Progress in Neuro-Psychopharmacology and Biological Psychiatry. 2021; 110:110278.

84 Sinha R, Fox H, Hong K-I, Sofuoglu M, Morgan PT, Bergquist KT. Sex steroid hormones, stress response, and drug craving in cocaine-dependent women: implications for relapse susceptibility. Experimental and clinical psychopharmacology. 2007; 15(5):445.
85 Tas B, Jolley CJ, Kalk NJ, Van der Waal R, Bell J, Strang J. Heroin-induced respiratory depression and the influence of dose variation: within-subject between-session changes following dose reduction. Addiction (Abingdon, England). 2020:10.1111/add.15014.
86 Darke S, Duflou J, Kaye S. Prevalence and nature of cardiovascular disease in methamphetamine-related death: A national study. Drug Alcohol Depend. 2017; 179:174-79.
87 Hill R, Santhakumar R, Dewey W, Kelly E, Henderson G. Fentanyl depression of respiration: comparison with heroin and morphine. British journal of pharmacology. 2019; 177:254-66.
88 Kohno M, Link J, Dennis LE, McCready H, Huckans M, Hoffman WF, Loftis JM. Neuroinflammation in addiction: A review of neuroimaging studies and potential immunotherapies. Pharmacology Biochemistry and Behavior. 2019; 179:34-42.
89 Libert C, Dejager L, Pinheiro I. The X chromosome in immune functions: when a chromosome makes the difference. Nature Reviews Immunology. 2010; 10(8):594-604.
90 Yang B-Z, Zhou H, Cheng Z, Kranzler HR, Gelernter J. Genomewide Gene-by-Sex Interaction Scans Identify ADGRV1 for Sex Differences in Opioid Dependent African Americans. Scientific reports. 2019; 9(1):18070.
91 Becker JB, Chartoff E. Sex differences in neural mechanisms mediating reward and addiction. Neuropsychopharmacol. 2019; 44(1):166-83.
92 McLellan AT, Koob GF, Volkow ND. Preaddiction—A Missing Concept for Treating Substance Use Disorders. JAMA psychiatry. 2022; https://doi.org/10.1001/jamapsychiatry.2022.1652.
93 Valentino RJ, Koroshetz W, Volkow ND. Neurobiology of the Opioid Epidemic: Basic and Translational Perspectives. Biological psychiatry. 2020; 87(1):2-3.
94 Martinez S, Brandt L, Comer SD, Levin FR, Jones JD. The subjective experience of heroin effects among individuals with chronic opioid use: Revisiting reinforcement in an exploratory study. Addict Neurosci. 2022; 4.
95 Koob GF. The dark side of emotion: The addiction perspective. Eur J Pharmacol. 2015; 753:73-87.
96 Andersen SL. Stress, sensitive periods, and substance abuse. Neurobiology of stress. 2019; 10:100140.
97 Vannucci A, Fagle TR, Simpson EG, Ohannessian CM. Perceived Family and Friend Support Moderate Pathways From Peer Victimization to Substance Use in Early-Adolescent Girls and Boys: A Moderated-Mediation Analysis. The Journal of Early Adolescence. 2021; 41(1):128-66.
98 O'Donnell J, Tanz LJ, Gladden RM, Davis NL, Bitting J. Trends in and Characteristics of Drug Overdose Deaths Involving Illicitly Manufactured Fentanyls — United States, 2019–2020 2021; http://dx.doi.org/10.15585/mmwr.mm7050e3.
99 O'Donnell J, Gladden RM, Kariisa M, Mattson CL. Using death scene and toxicology evidence to define involvement of heroin, pharmaceutical morphine, illicitly manufactured fentanyl, and pharmaceutical fentanyl in opioid overdose deaths, 38 states and the District of Columbia, January 2018-December 2019. Addiction (Abingdon, England). 2021; DOI: 10.1111/add.15768.
100 Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, Marshall BDL, Tyndall M, Walsh SL. Opioid use disorder. Nature Reviews Disease Primers. 2020; DOI: 10.1038/s41572-019-0137-5.
101 Shai D. Problems of accuracy in official statistics on drug-related deaths. International Journal of the Addictions. 1994; 29(14):1801-11.
102 (CDC). National Center for Health Statistics. Guidance for certifying deaths due to COVID–19. 2020. https://www.cdc.gov/nchs/data/nvss/vsrg/vsrg03-508.pdf.
103 Brooks C. Medical Examiner and Coroner Offices, 2018. 2021. https://bjs.ojp.gov/content/pub/pdf/meco18.pdf. 2022.
104 Gebhard C, Regitz-Zagrosek V, Neuhauser HK, Morgan R, Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biology of sex differences. 2020; 11(1):29.

Figure 1

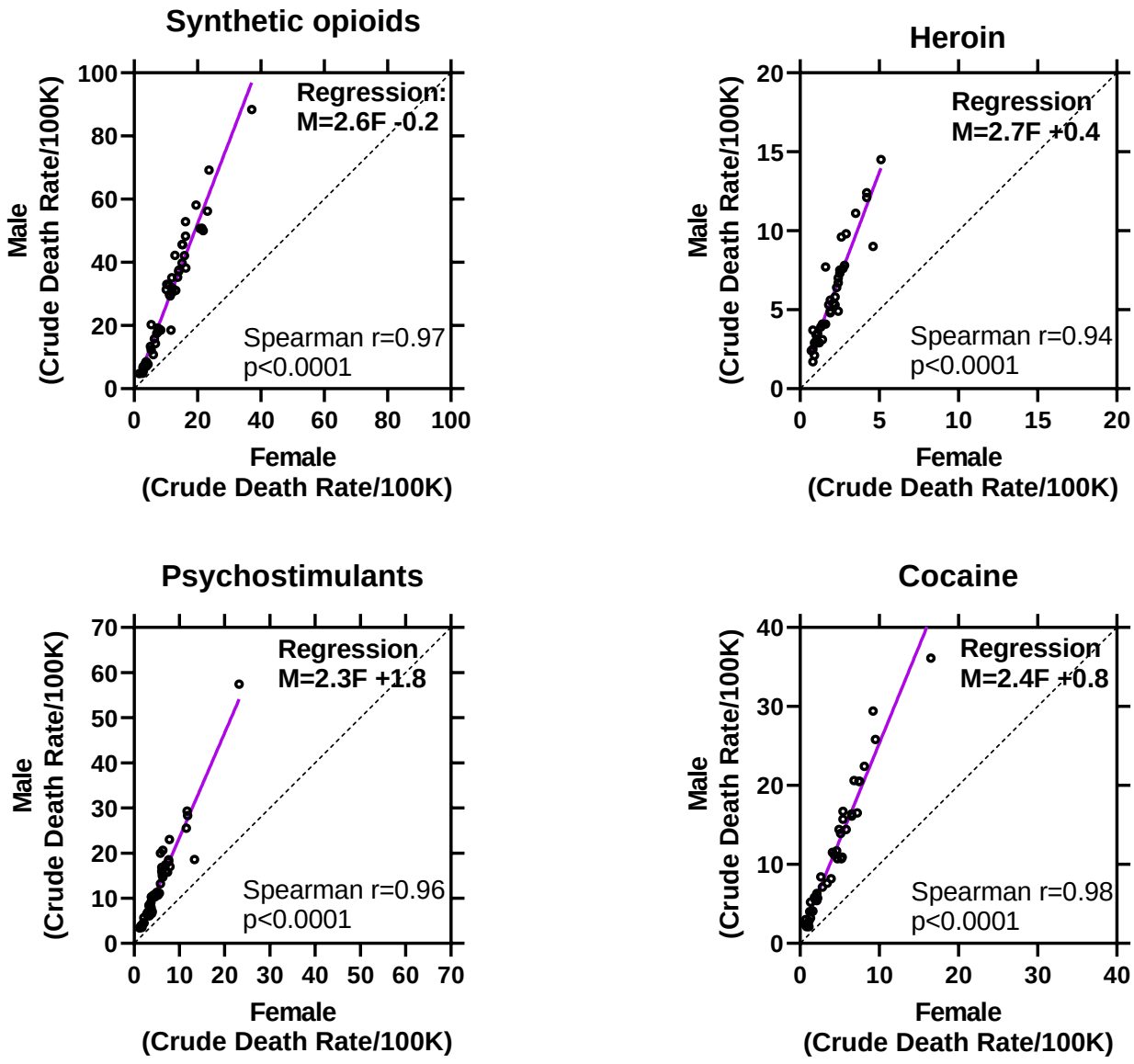


Figure 1: Overdose mortality per jurisdiction in men and women, due to synthetic opioids, heroin, psychostimulants and cocaine; all ages combined. Each symbol is one jurisdiction (i.e., 50 states and District of Columbia). Note different axis ranges in the panels. Spearman correlations for men and women in each jurisdiction are included. The purple line indicates the best-fit simple linear regression (M: male; F: female in the equation). Dashed black line indicates identity.

Figure 2

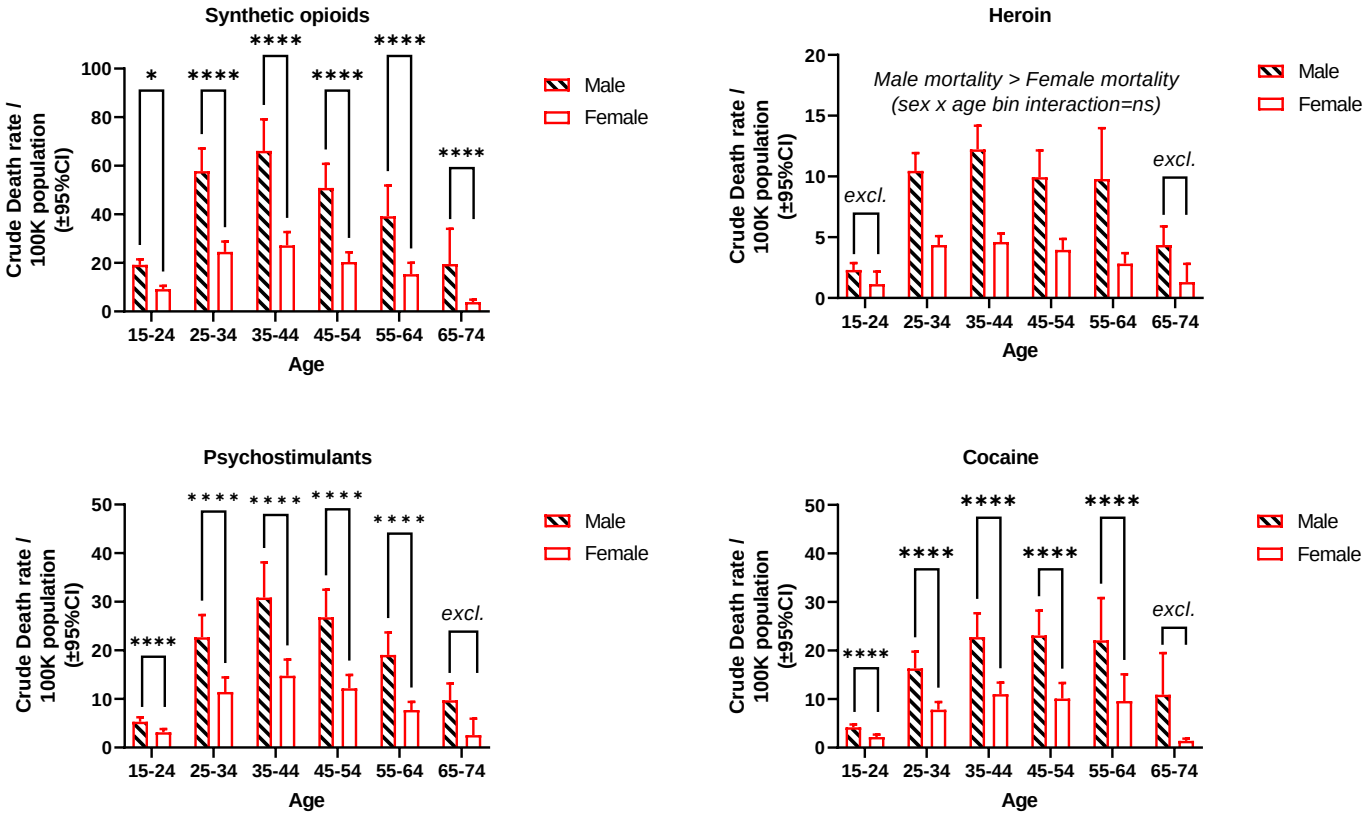
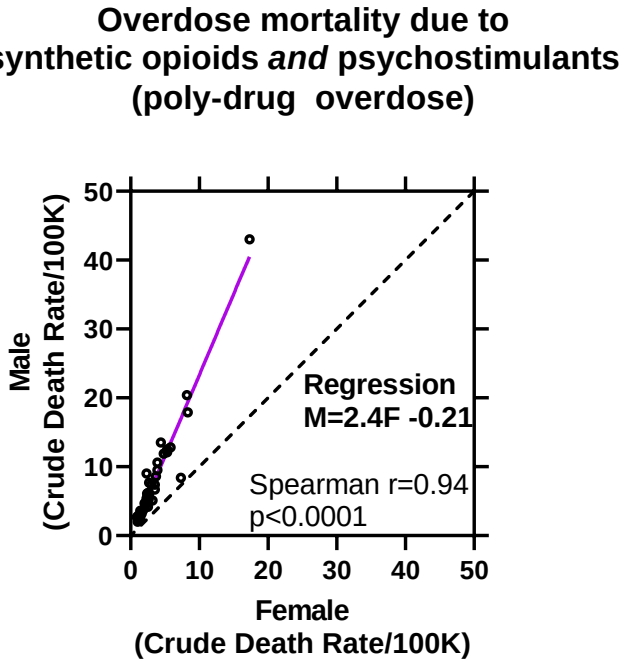
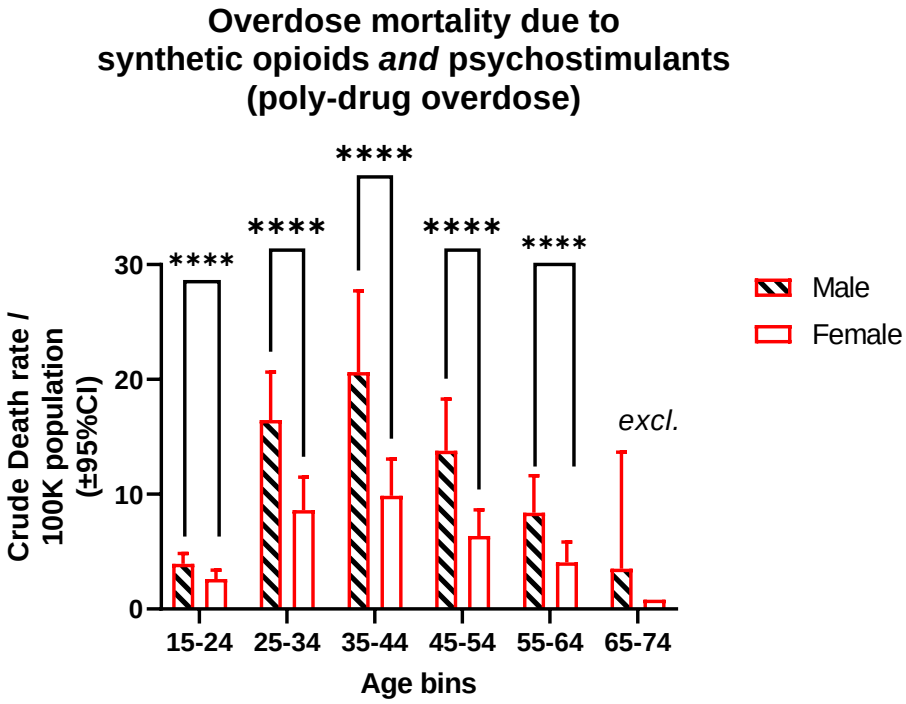


Figure 2: Overdose mortality in men and women, due to synthetic opioids, heroin, psychostimulants and cocaine, for consecutive 10-year age bins. Note different Y-axis ranges in the panels. Means and 95%CI are calculated across 51 jurisdictions. Log overdose data were analyzed in univariate mixed-effects effects ANOVAs (gender X age). Bonferroni post-hoc tests for sex at each age bin are shown with black brackets (* is $p<0.05$; **** is $p<0.0001$). The label "excl." indicates that the age bin was excluded from ANOVA analysis due to insufficient available data (see Methods and Table 1).

Supplement: Poly-drug overdose mortality due to *both* Synthetic Opioids (ICD-10 category T40.4) *and* Psychostimulants (T43.6)





Supplementary Figure: Upper panel: Mortality for poly-drug overdose (synthetic opioids *and* psychostimulants) in men and women, all ages combined. The purple line indicates the simple linear regression (M: male; F: female in the equation). Each symbol is one jurisdiction. Lower panel: Mortality for poly-drug overdose (synthetic opioids *and* psychostimulants) in men and women, in 10-year age bins. Log-transformed data were analyzed with a univariate mixed-effects ANOVAs (sex X age) for each drug category. The label "excl." indicates that the age bin was excluded from analysis due to insufficient data (i.e., less than 10 States had available data in both men and women; see Methods). Main effects of sex ($F[1,113]=934.6$) and age bin ($F[4,160]=19.37$ and a sex x age bin interaction ($F[4,113]=10.16$) were found (all $p<0.0001$). Bonferroni post-hoc tests are shown for gender x age bin (****; $p<0.0001$).

- *See multiple linear regressions of supplementary data in page below*

Supplementary Table: Multiple linear regression of State-level mortality rate for poly-drug overdoses caused by both synthetic opioids *and* psychostimulants

	Significant β Parameter Estimates [95%CI] and p-value						Model R^2 (DF)
Age bin	Sex (Men); Women as reference	State Median Household Net Worth	State %White	State %Black	State and sex past year opioid misuse (%)[a]	State and sex past year stimulant misuse (%)[b]	
15-24	NS	NS	NS	NS	NS	NS	0.33 (27)
25-34	β=0.32 [0.20-0.45] p<0.0001 eta^2=0.29	β=-1.19 X 10^{-6} [-8.75 X 10^{-8} – -2.30 X 10^{-6}] p=0.035	β=0.012 [0.0020-0.022] p=0.020	NS	NS	NS	0.50 (46)
35-44	β=0.31 [0.17-0.45] p<0.0001 eta^2=0.22	NS	β=0.017 [0.0055-0.028] p=0.0044	NS	NS	NS	0.48 (62)
45-54	β=0.33 [0.19-0.48] p<0.0001 eta^2=0.27	NS	β=0.012 [0.00078-0.024] p=0.037	NS	NS	NS	0.47 (44)
55-64	β=0.28 [0.043-0.51] p=0.022 eta^2=0.14	NS	NS	NS	NS	NS	0.29 (30)
65-74	Insufficient data for regression[c]						N/A

Outcome is log-transformed overdose mortality rate; see Methods; all details as in Table 2

[a]State level of past year opioid misuse was from NSDUH, Restricted-Use Data Analysis System, item "OPINMYR" (2019-2020), per sex.

[b]State level of past year stimulant misuse was from NSDUH, Restricted-Use Data Analysis System, item "APPEPDPYMU" (2019-2020), per sex.

[c]Less than 10 States had available data in both men and women (due to suppression based on low "n"; see Methods).

DF: degrees of freedom