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Historical epidemiological trends in opioid-only and opioid/polysubstance–related death rates among American Indian/Alaska Native populations: a longitudinal ecological study

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Abstract

Objectives: The rate of drug overdose deaths in the U.S. has more than tripled since the turn of the century, and rates are disproportionately high among the American Indian/Alaska Native (AI/AN) population. Little is known about the overall historical trends in AI/AN opioid-only and opioid/polysubstance–related mortality. This study will address this gap.

Design: This is a retrospective longitudinal ecological study that uses serial cross-sectional data.

Setting: U.S. death records from 1999 to 2019 using the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) .

Participants: U.S. Non-Hispanic AI/AN people age 12 years and older.

Measures: The primary outcomes, identified via the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, included death due to (1) opioids only, opioids in combination with any other substance, all-opioid related instances; (2) combinations of opioids and alcohol, opioids and methamphetamine, opioids and cocaine, opioids and benzodiazepines; and (3) opioids by indivdiual types.

Results: From 1999-2019, opioid-only mortality rates increased from 2.8 to 15.8 per 100,000 ($P<0.001$) for AI/AN women, and 4.6 to 25.6 per 100,000 ($P<0.001$) for AI/AN men. All opioid-related mortality rates increased significantly ($P<0.001$) from 5.2 to 33.9 per 100,000 AI/AN persons, 3.9 to 26.1 for women, and 6.5 to 42.1 for men. AI/AN also exhibited significant increases in mortality rates due to opioids and alcohol, opioids and benzodiazepines, opioids and methamphetamines, and AI/AN men experienced significant increases in mortality due to opioids and cocaine. Mortality rates by individual opioid types increased signficiantly over time for Heroin, natural and semi-synthetic (prescription), and synthetic opioids other than Methadone.

Conclusions: These findings highlight magnification over time in opioid-related deaths and may point to broader systemic factors that may disproportionately affect members of AI/AN communities and drive inequities.

Strengths and limitations of this study

- This is one of the first studies to consider the historical trends pertaining to opioid overdose mortality in the AI/AN population across the United States, with special attention given to how co-use of opioids with alcohol, benzodiazepines, cocaine, or methamphetamines may be contributing to drug overdose mortality in this population.
- This study stratify results by sex, and compares opioid-only and opioid-combination mortality rates between NH AI/AN populations and other race/ethnicity groups.
- This study provides an insight towards historical trends pertaining to opioid overdose mortality in the AI/AN population by individual opioid types (Heroin, natural and semi-synthetic (prescription) opioids [e.g. oxycodone, hydrocodone], Methadone, and synthetic opioids other than Methadone [e.g. fentanyl, tramadol]).
- Subgroup data with small counts were aggregated due to data-use agreement requirements.
- To capture as much AI/AN data as possible, age-adjusted results were not obtained because they required suppressing AI/AN-specific results.

Keywords: American Indian/Alaska Native; opioid use; opioid-related mortality, polysubstance use; epidemiology; trends

INTRODUCTION

Over the past two decades, the rate of drug overdose deaths in the United States (U.S.) has more than tripled.[1] This spike in overdoses, which has been described as a public health crisis, has grown more destructive with time.[1,2] The American Indian(s)/Alaska Native(s) (AI/AN) population has been disproportionately affected by drug-related mortality. From 1999 to 2015, drug overdose mortality among metropolitan AI/AN populations increased from 7.1 per 100,000 to 22.1 per 100,000, representing a 261% change from 1999. A magnified pattern was observed in non-metro AI/AN populations, whose overdose mortality rate climbed steeply from 3.9 per 100,000 in 1999 to 19.8 per 100,000 in 2015, representing a 519% increase. Other groups also experienced rises in drug overdoses over this same period but at lower rates of change.[3]

Opioid overdose fatalities among AI/AN and non-Hispanic white populations both rose dramatically since 1999, surpassing national rates in all years since 2002. While non-Hispanic white populations exhibit the highest rates since 2014, AI/AN populations demonstrate the second highest opioid overdose mortality across U.S. racial and ethnic groups. In 1999, the AI/AN opioid overdose mortality rate was 2.9 per 100,000 and has risen to 17.0 deaths per 100,000 in 2019.[4] Regional variations also exist in this trend among AI/AN populations. From 1999-2016, higher mortality rates from opioids among AI/AN were observed in states in the Pacific Northwest and Great Lakes Region.[5] During 2013–2015, mortality rates among AI/AN populations in Washington state were 2.7 higher than rates among non-Hispanic white populations for all opioid-involved overdoses.[6]

The literature also points to variations in overdose rates from specific opioid types. Increases in synthetic opioids other than methadone have contributed to the bulk of US opioid-involved fatalities in recent years. From 2017 to 2018, overdose death rates from synthetic

opioids other than methadone among AI/AN increased from 6.5 per 100,000 to 7.3 per 100,000 deaths. Compared to non-Hispanic Whites and non-Hispanic Blacks, AI/AN overdose rates from synthetic opioids were lower but higher than Hispanic and Pacific Islander rates.[7] Additionally, while the US has seen recent declines in heroin overdoses, decreases observed among AI/AN are modest compared to other racial and ethnic populations.[7]

Regarding polysubstance use, the literature suggests that opioid users often use other drugs simultaneously with opioids, thereby creating increased difficulties in curbing the opioid crisis.[8] Among AI/AN, the co-use of opioids with other drugs may be higher than other races. Treatment admission data from the Treatment Episode Data Set (TEDS) demonstrated that each year from 2008 to 2017, AI/AN consistently had the highest percentage of individuals entering treatment with co-use of methamphetamine and heroin.[9]

Although previous reports show AI/AN populations across the U.S. have experienced elevated rates of drug overdose deaths, the significance of historical trends in drug-related death rates among AI/AN populations remain unclear, especially regarding trends in deaths related to polysubstance use, which have risen dramatically in the general U.S. population in recent years. Deaths involving psychostimulants increased by over 30% between 2016 and 2017 across the U.S. and in 2017, over 70% of cocaine-involved deaths and 50% of other psychostimulant-involved overdose deaths involved at least one opioid.[10] This study provides foundational knowledge on opioid and polysubstance use deaths involving opioids among AI/AN populations by analyzing the historical patterns of opioid-only and opioid/polysubstance–related deathamong AI/AN populations.

METHODS

Settings

This is a retrospective longitudinal ecological study that uses serial cross-sectional data to analyze historical patterns of opioid-only and polysubstance-involved opioid overdose deaths among AI/AN populations. Specifically, this retrospective observational study used publicly available data from the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. Data on drug overdose deaths due to opioids and combinations of opioids with either alcohol, benzodiazepines, cocaine, or methamphetamine were obtained from the CDC WONDER's National Center for Health Statistics Mortality database. The data spanned from 1999 to 2019, included all United States, all urbanization categories, all weekdays, all autopsy values, and all place of death categories. The population of interest was U.S. Non-Hispanic (NH) AI/AN of the age of 12 and older.

Measures

All deaths were identified by underlying cause of death and multiple cause of death with *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. The outcomes of interest were separated into 3 scenarios: (1) overdose deaths relating to opioids alone (opioid-only), opioids in combination with any other substances (opioid/polysubstance), the sum of opioid-only and opioid/polysubstance cases (all-opioid related) (2) overdose deaths relating to opioids in combination with each of the other substance types and (3) overdose deaths separated by individual opioid types (Heroin, natural and semi-synthetic (prescription) opioids [e.g. oxycodone, hydrocodone], Methadone, and synthetic opioids other than Methadone [e.g. fentanyl, tramadol]). Opium (multiple cause code T40.0) and unknown opioids (T40.6) were not displayed alone because counts were too small. The specific substance-related overdose death types and corresponding ICD-10 codes are displayed by outcome scenario below in List 1.

List 1: Substance-related overdose death types, and associated ICD-10 codes, by outcome scenario

	Underlying Cause of Death ICD-10	Multiple Cause of Death ICD-10[1]
Scenario 1		
Opioid-only	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6
Opioid/polysubstance	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9
All-opioid related[2]	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 OR (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9)
Scenario 2		
Opioids and Methamphetamine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T43.6
Opioids and Cocaine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5
Opioids and Benzodiazepines	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T42.4
Opioids and Alcohol	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T51.0, T51.1, T51.9
Scenario 3		
Heroin	X40-44, X60-64, X85, Y10-Y14	T40.1
Natural and semi-synthetic (prescription) opioids	X40-44, X60-64, X85, Y10-Y14	T40.2
Methadone	X40-44, X60-64, X85, Y10-Y14	T40.3
Synthetic opioids (other than Methadone)	X40-44, X60-64, X85, Y10-Y14	T40.4

[1] Any of prescribed codes, if an "AND" is included then at least 1 from first code group AND 1 from other code group;
[2] Sum of opioid-only and opioid/polysubstance

For multiple cause of death codes, any one qualifying code from the list of available codes was counted towards the outcome. In the case of opioids in combination with another substance, any one qualifying code from the list of available opioid multiple cause of death codes (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6) *and* any one code from the other substance(s) list was counted towards the outcome. The count of deaths was divided by the population of interest to provide a mortality rate per 100,000 NH AI/AN 12 and older. Per the data use agreement of CDC Wonder, all counts 9 and lower were classified as 10. Predictors included year (1999-2019), and sex (female, male). Supplemental analyses looked at age groups (15-24, 25-34, 35-44, 45+) and race/ethnicity (NH AI/AN, NH Asian or Pacific Islander (API), NH Black, NH White,

Hispanic/Latino). Because age groupings were allowed only in 5 and 10-year increments, the age group predictor was restricted to those 15 years and older instead of 12 years and older.

Statistical Analysis

Overdose death rates per 100,000 NH AI/AN population 12 and older, relating to the 3 outcome scenarios, were presented over time from 1999 to 2019. Figures and tables were constructed with 95% Wilson binomial confidence intervals. To assess significant trends over time, non-parametric Jonckheere-Terpstra tests were performed for each substance type because rates exhibited non-normal distributions. All analysis results were presented overall as well as stratified by sex to identify sex-specific trends in the outcomes of interest. Supplementary figures were displayed for mortality rates due to opioids-only as well as due to opioids in combination with each other substance. Rates were stratified by age groups as well as by race/ethnicity. Racial comparisons were performed to assess how NH AI/AN rates compared to those of other racial groups.

All hypothesis tests were two-sided with a significance level of 5%. R version 3.6.1 (R Foundation for Statistical Computing) was used to perform all analyses.

Patient and public involvement

No patient involved.

RESULTS

From 1999-2019 (Figure 1, Table 1), NH AI/AN opioid mortality rates increased significantly (all $P<0.001$) overall and for both women and men. All opioid-related mortality rates increased from 5.2 to 33.9 per 100,000 overall, 3.9 to 26.1 per 100,000 women, and 6.5 to 42.1 per 100,000 men. Opioid-only rates increased from 3.7 to 20.6 per 100,000 overall, 2.8 to 15.8 per 100,000 women, and 4.6 to 25.6 per 100,000 men. Opioid/polysubstance rates increased

from 1.5 to 13.3 per 100,000 overall, 1.1 to 10.3 per 100,000 women, and 1.9 to 16.5 per 100,000 men. Significant trends were also observed for mortality due to opioids in combination with other specific substances, with the exception of opioids and cocaine overall and among women (Figure 2, Table 2). Significantly increasing mortality rates were seen overall in NH AI/AN due to opioids and alcohol (rates per 100,000: 1.1 to 4.2, P<0.001), opioids and benzodiazepines (rates per 100,000: 1.1 to 2.6, P<0.001), and opioids and methamphetamine (rates per 100,000: 1.2 to 6.7, P=0.02). By sex, NH AI/AN men and women both exhibited significant increases in mortality rates due to opioids and alcohol (rates per 100,000 women: 1.1 to 2.1, P=0.01; rates per 100,000 men: 1.2 to 6.5, P<0.001), opioids and benzodiazepines (rates per 100,000 women: 1.1 to 2.0, P=0.01; rates per 100,000 men: 1.2 to 3.1, P<0.001), and opioids and methamphetmaine (rates per 100,000 women: 1.1 to 6.2, P=0.02; rates per 100,000 men: 1.2 to 7.1, P=0.02). Only NH AI/AN men exhibited significantly increasing mortality rates due to opioids and cocaine (rates per 100,000 men: 1.2 to 3.2, P=0.02).

When looking deeper into individual opioid types (Figure 3, Table 3) there was a significant rise in natural and semi-synthetic (prescription) opioid death rates (rates per 100,000 overall: 1.4 to 5.1, P<0.001; rates per 100,000 women: 1.1 to 4.8, P<0.001; rates per 100,000 men: 1.6 to 5.4, P<0.001) and Heroin (rates per 100,000 overall: 1.2 to 6.3, P<0.001; rates per 100,000 women: 1.1 to 4.9, P=0.056 [on the boundary of significance]; rates per 100,000 men 1.3 to 7.7, P<0.001). Death rates due to synthetic opioids (other than Methadone) saw a drastic increase in recent years (2013 to 2019 rates per 100,000 overall: 1.5 to 12.5, P<0.001; 2013 to 2019 rates per 100,000 women: 1.5 to 8.6, P<0.001; 2013 to 2019 rates per 100,000 men: 1.5 to 16.5, P<0.001).

Supplemental analyses, by age groups, revealed that NH AI/AN ages 25-44 had higher opioid-only and opioid-combination mortality rates than those 15-24 and older than 44 (Supplemental Figures 1a and 1b). Overall and across both sexes, NH AI/AN populations generally exhibited opioid-only and opioid-combination mortality rates as high or higher than other races. Death rates across all years, relating to opioids and methamphetamine, remained consistently higher for NH AI/AN compared to all other races. However in more recent years, NH White rates exceeded those of the NH AI/AN population, as seen in opioid-only and opioid-benzodiazepine mortality rates. NH Black men, additionally, saw higher opioid-only mortality rates than NH AI/AN men in recent years. Opioid and cocaine-related death rates among the NH Black population also exceeded rates of the NH AI/AN population overall and for men across most years and more recently for women. NH AI/AN exhibited higher opioid and alcohol mortality than other races, with NH Blacks showing slightly higher rates in recent years (Supplemental Figures 2a-2e).

DISCUSSION

This study provides a comprehensive historical overview of fatal drug overdose trends for NH AI/AN populations in the U.S. with particular attention to the role of opioids and combinations of opioids with alcohol, benzodiazepines, methamphetamines, and cocaine. We found that among NH AI/AN, mortality rates due to opioids have increased significantly over time. The trend of rising opioid-overdose mortality remains when data are stratified by sex and across age categories. Deaths due to polysubstance use involving opioids have also increased significantly over time among NH AI/AN populations. Among specific opioid types, Heroin and natural/semi-synthetic (prescription) opioid-related deaths have risen across the years, however synthetic opioid-related deaths have spiked just in recent years alone. When comparing across

U.S. racial and ethnic groups, NH AI/AN exhibit rising opioid-overdose mortality rates that have generally been higher than other groups, but in recent years NH AI/AN men's rates were below those of NH white and NH Black men, and NH AI/AN also display lower rates of death related to opioids and cocaine than NH Blacks. However, NH AI/AN populations exhibit higher mortality rates of opioid combinations with methamphetamines and alcohol than all other U.S. groups.

In general, the increasing opioid overdose mortality from 1999-2019 among NH AI/AN observed in our analysis mirror the rising opioid overdose trends in the US general population.[1,7,11] Similarly, deaths resulting from opioids combinations with other drugs among AI/AN follow an increasing trend that is supported by prior research.[10] In particular, our results showed an escalation in mortality due to opioids in combination with methamphetamines from 1999 to 2019. Consistent with our findings, data from the CDC reported that roughly half of all psychostimulant deaths in 2017 also involved an opioid. Additionally, they observed a significant rise in deaths due to opioids in combination with psychostimulants from 2015 to 2017.[10]

Regarding trends in specific opioid types, our finding that AI/AN deaths resulting from synthetic opioids have increased sharply in recent times is worrisome. In our analysis, this group of opioids contains fentanyl, a highly potent synthetic opioid. Due to its potency, the risk of overdose and mortality may be heightened among users.[12,13] Current evidence points to increased use of fentanyl in the US, especially in combination with other drugs. For instance, in a study consisting of 10 US states, close to 60% of individuals who succumbed to drug overdoses tested positive for fentanyl and fentanyl analogs in addition to cocaine, methamphetamine, and heroin.[14] Furthermore, overdose deaths resulting from fentanyl increased nearly 12 fold from

2013 to 2019.[15] These results demonstrate the need for increased education about the dangers of fentanyl, especially among at-risk individuals along with improved access to treatment programs and overdose reversal interventions involving naloxone.[16]

These findings highlight existing inequities in drug-related deaths and may point to broader systemic factors that disproportionately affect members of AI/AN communities. American Indians and Alaska Natives continue to encounter stressors that stem from diminished socioeconomic prospects, racism, and historical trauma from colonization. These stressors often contribute significantly to the heightened drug use and related overdoses in theAI/AN population.[17,18] Leverage points for intervention must therefore look at the root causes and structural factors that shape substance use and addiction.

Furthermore, sex differences were apparent throughout our results. In our primary analysis and supplemental analysis, male populations tended to experience higher rates and higher increases in drug overdose deaths than female populations. Sex differences observed in drug overdose studies are often characterized by higher rates in men.[19,20] However, historical trends are not uniform, and gaps between male and female populations have narrowed at specific periods during the drug overdose crisis and widened at other points.[20] Our observed results may reflect differential attitudes towards risk and varying social expectations for males and females in AI/AN communities and may suggest the need for targeted gender-sensitive interventions.

Our findings should be considered within the constraints of certain limitations. First, subgroup data with small counts were aggregated due to data-use agreement requirements. Additionally, to capture as much AI/AN data as possible, age-adjusted results were not obtained because they required suppressing AI/AN-specific results. However, in comparing age-adjusted and raw rates, we found rates to be reasonably similar. On the other hand, our study is one of the

initial studies to investigate AI/AN opioid overdose historical trends across the United States, with emphasis on the implications of the simultaneous use of opioids and alcohol, benzodiazepines, cocaine, or methamphetamines.

CONCLUSIONS

Overall, our results suggest that AI/AN populations continue to face rising levels of overdose mortality due to opioids alone and in combination with other substances, with rates as high or higher than all other racial/ethnic groups. AI/AN men and those age 25-44 are especially impacted. While the prevailing opioid type has changed over the years, underlying factors that drive these patterns have not, and may include disparities in socioeconomic status, persistent effects of historical trauma, and disparities in access to healthcare and treatment programs. Interventions for American Indians and Alaska Natives with substance use disorders will be more impactful if they are comprehensive, culturally centered, and address social determinants of health, including SES, and racial and ethnic discrimination.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics statements

Patient consent for publication

Not required.

Contributors

FQ, EFM, KLV, KE, and AD contributed to the concept and study design. BT, and FQ contributed to acquisition, curation and analysis of data. FQ, EFM, NAM, BT, and AD drafted

the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Data statement

Data are publicly available at the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database: https://wonder.cdc.gov/mcd.html

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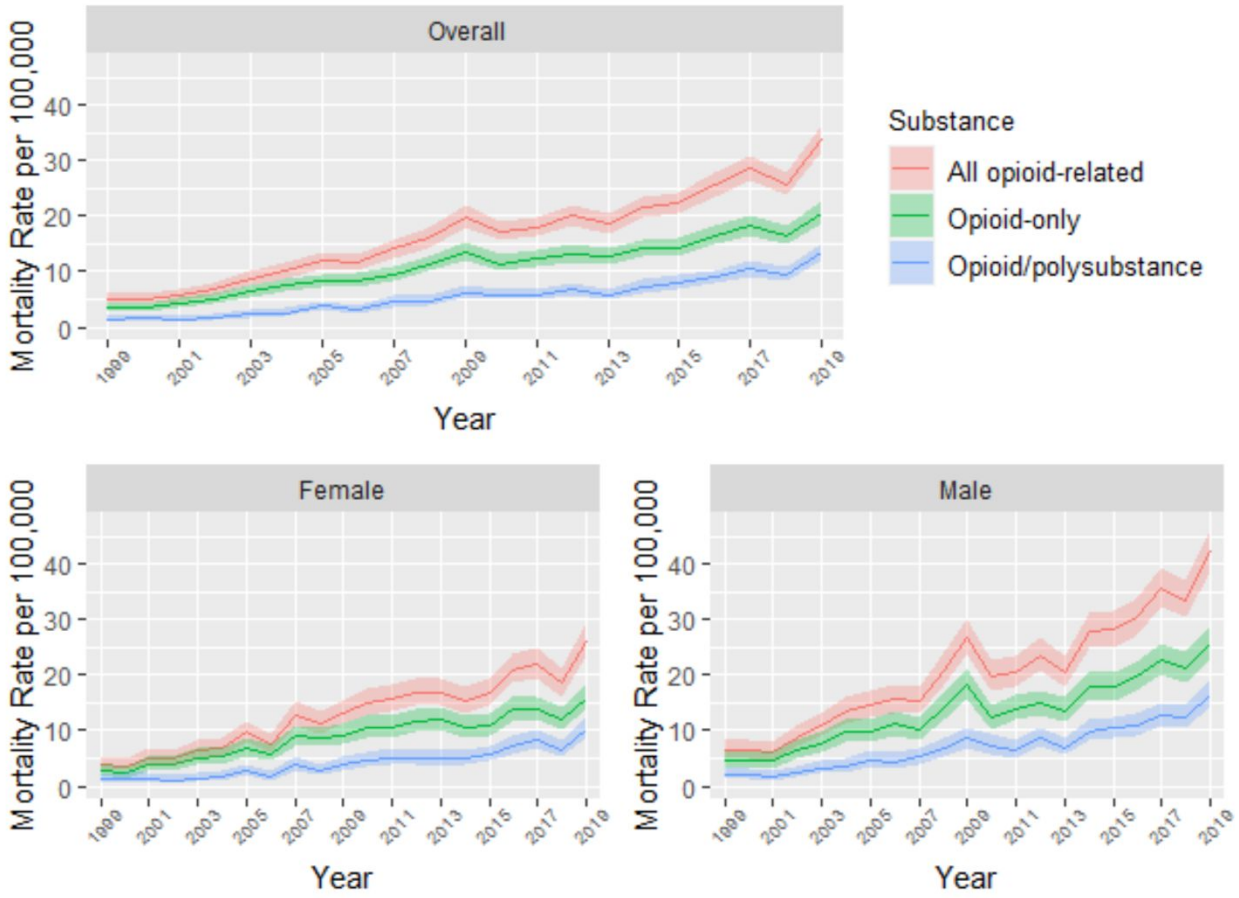

Figure 1: Trends in opioid death rates among US NH-AIAN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);
Opioid/polysubstance (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T51.0, T51.1, T51.9);
All-opioid related: sum of “opioid-only” and “opioid/polysubstance”

Table 1: Trends in opioid death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
All opioid-related	5.2 (4.2, 6.3)	5.0 (4.1, 6.2)	5.7 (4.7, 6.9)	6.8 (5.7, 8.1)	8.6 (7.4, 10.0)	10.0 (8.7, 11.5)	12.0 (10.5, 13.6)	11.5 (10.1, 13.1)	14.1 (12.5, 15.8)	16.0 (14.4, 17.8)	19.8 (17.9, 21.8)	17.3 (15.6, 19.2)	18.0 (16.3, 19.9)	20.0 (18.2, 22.0)	18.5 (16.8, 20.5)	21.5 (19.6, 23.5)	24.2 (22.3, 26.3)	25.6 (23.5, 27.7)	28.6 (26.5, 30.9)	25.8 (23.8, 28.0)	33.9 (31.6, 36.3)	<0.001
Opioid-only	3.7 (2.9, 4.7)	3.3 (2.6, 4.3)	4.2 (3.4, 5.2)	5.1 (4.2, 6.2)	6.4 (5.3, 7.6)	7.5 (6.4, 8.8)	8.2 (7.0, 9.6)	8.4 (7.2, 9.8)	9.6 (8.3, 11.0)	11.3 (10.0, 12.9)	13.5 (12.0, 15.2)	11.4 (10.1, 13.0)	12.2 (10.8, 13.8)	13.2 (11.8, 14.9)	12.7 (11.3, 14.3)	14.2 (12.7, 15.8)	15.3 (13.8, 17.0)	16.6 (15.0, 18.4)	18.2 (16.5, 20.0)	16.5 (14.9, 18.2)	20.6 (18.8, 22.5)	<0.001
Opioid/polysubstance	1.5 (1.0, 2.2)	1.7 (1.2, 2.4)	1.5 (1.0, 2.1)	1.7 (1.2, 2.4)	2.2 (1.7, 3.0)	2.5 (1.9, 3.3)	3.8 (3.0, 4.7)	3.1 (2.4, 3.9)	4.5 (3.7, 5.5)	4.7 (3.8, 5.7)	6.2 (5.2, 7.4)	5.9 (4.9, 7.0)	5.8 (4.8, 6.9)	6.8 (5.8, 8)	5.9 (4.9, 7.0)	7.3 (6.3, 8.5)	8.9 (7.9, 10.2)	9.0 (7.8, 10.3)	10.4 (9.2, 11.9)	9.4 (8.2, 10.7)	13.3 (11.9, 14.9)	<0.001
Female																						
All opioid-related	3.9 (2.8, 5.4)	3.6 (2.6, 5.1)	5.2 (3.9, 6.8)	4.9 (3.7, 6.5)	6.4 (5.0, 8.2)	6.8 (5.4, 8.7)	9.6 (7.9, 11.7)	7.6 (6.1, 9.5)	12.9 (10.9, 15.3)	11.3 (9.4, 13.6)	13.1 (11.1, 15.5)	15.0 (12.8, 17.5)	15.7 (13.5, 18.3)	16.8 (14.5, 19.4)	16.7 (14.4, 19.3)	15.3 (13.2, 17.8)	16.7 (14.5, 19.2)	21.0 (18.5, 23.8)	22.1 (19.5, 25.0)	18.5 (16.2, 21.1)	26.1 (23.3, 29.2)	<0.001
Opioid-only	2.8 (1.9, 4.1)	2.2 (1.5, 3.5)	3.9 (2.8, 5.4)	3.8 (2.8, 5.3)	5.1 (3.9, 6.7)	5.2 (4.0, 6.9)	6.8 (5.4, 8.7)	5.9 (4.6, 7.6)	9.0 (7.3, 11)	8.6 (7.0, 10.6)	9.1 (7.5, 11.1)	10.6 (8.8, 12.7)	10.6 (8.8, 12.7)	11.7 (9.9, 14)	11.9 (10, 14.1)	10.5 (8.7, 12.6)	11.0 (9.2, 13.1)	13.8 (11.8, 16.1)	13.8 (11.8, 16.2)	12.0 (10.1, 14.1)	15.8 (13.7, 18.2)	<0.001
Opioid/polysubstance	1.1 (0.6, 2.1)	1.4 (0.8, 2.4)	1.3 (0.7, 2.2)	1.0 (0.5, 1.9)	1.3 (0.8, 2.3)	1.6 (1.0, 2.6)	2.8 (1.9, 4.0)	1.8 (1.1, 2.8)	3.9 (2.8, 5.3)	2.7 (1.8, 3.9)	4.0 (2.9, 5.4)	4.4 (3.3, 5.9)	5.1 (3.9, 6.7)	5.0 (3.9, 6.6)	4.8 (3.7, 6.3)	4.8 (3.7, 6.3)	5.7 (4.4, 7.3)	7.2 (5.8, 8.9)	8.3 (6.8, 10.1)	6.5 (5.2, 8.2)	10.3 (8.6, 12.3)	<0.001
Male																						
All opioid-related	6.5 (5.0, 8.5)	6.5 (5.0, 8.4)	6.2 (4.7, 8)	8.8 (7.1, 10.9)	10.9 (9.0, 13.2)	13.4 (11.2, 15.9)	14.4 (12.2, 17.1)	15.5 (13.2, 18.2)	15.4 (13.1, 18.0)	20.9 (18.3, 24.0)	26.8 (23.8, 30.2)	19.7 (17.1, 22.6)	20.4 (17.8, 23.4)	23.5 (20.7, 26.6)	20.5 (17.9, 23.5)	27.9 (24.9, 31.3)	28.1 (25.1, 31.4)	30.4 (27.3, 33.9)	35.5 (32.1, 39.2)	33.6 (30.3, 37.2)	42.1 (38.4, 46.1)	<0.001
Opioid-only	4.6 (3.4, 6.3)	4.5 (3.3, 6.1)	4.5 (3.3, 6.2)	6.4 (4.9, 8.3)	7.7 (6.1, 9.7)	9.9 (8.1, 12.1)	9.7 (7.9, 11.9)	11.1 (9.2, 13.4)	10.2 (8.4, 12.4)	14.2 (12.0, 16.8)	18.2 (15.7, 21.0)	12.3 (10.3, 14.7)	14.0 (11.9, 16.5)	14.8 (12.6, 17.3)	13.5 (11.5, 16)	18.0 (15.6, 20.8)	17.7 (15.4, 20.4)	19.6 (17.1, 22.4)	22.8 (20.1, 25.8)	21.2 (18.7, 24.1)	25.6 (22.8, 28.8)	<0.001
Opioid/polysubstance	1.9 (1.1, 3.1)	2.0 (1.3, 3.2)	1.7 (1.0, 2.8)	2.4 (1.6, 3.6)	3.2 (2.2, 4.6)	3.5 (2.5, 4.9)	4.8 (3.6, 6.4)	4.4 (3.3, 6.0)	5.2 (3.9, 6.8)	6.7 (5.3, 8.6)	8.6 (7.0, 10.6)	7.3 (5.9, 9.2)	6.5 (5.1, 8.2)	8.7 (7.1, 10.7)	7.0 (5.5, 8.8)	9.9 (8.2, 12.0)	10.4 (8.6, 12.5)	10.8 (9.0, 13.0)	12.7 (10.8, 15.0)	12.3 (10.4, 14.6)	16.5 (14.2, 19.0)	<0.001

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);
Opioid/polysubstance(underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T51.0, T51.1, T51.9);
All-opioid related: sum of "opioid-only" and "opioid/polysubstance"

[2] Non-parametric Jonckheere-Terpstra Test for trend

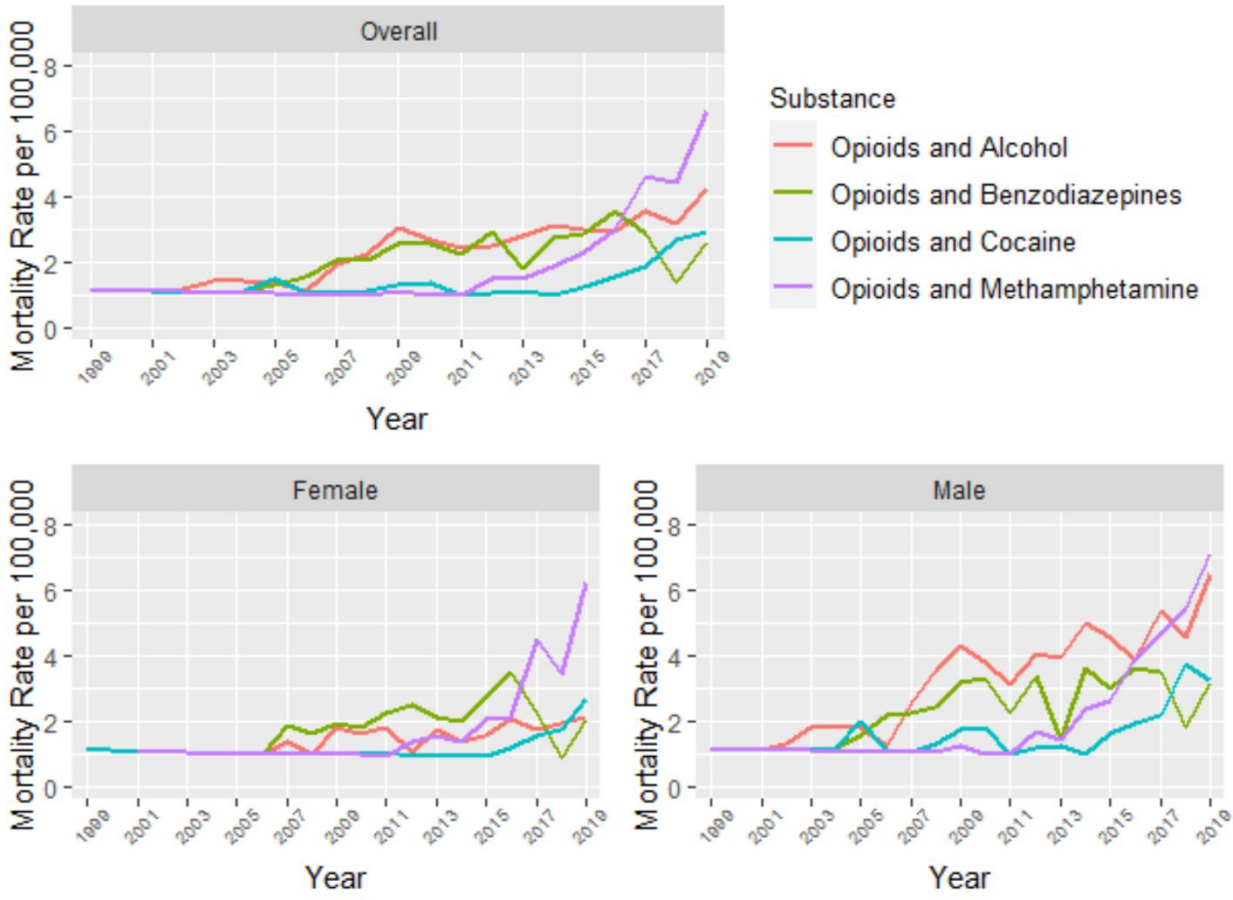

Figure 2: Trends in opioid combination[1] death rates among US NH-AI/AN 12 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

Table 2: Trends in opioid combination[1] death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by substance combination type

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Opioids and Alcohol	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)	1.4 (1.0, 2.1)	1.4 (0.9, 2.0)	1.4 (0.9, 2.0)	1.1 (0.7, 1.7)	1.9 (1.4, 2.7)	2.2 (1.6, 3.0)	3.0 (2.4, 3.9)	2.7 (2.0, 3.5)	2.4 (1.8, 3.2)	2.5 (1.9, 3.3)	2.8 (2.2, 3.6)	3.1 (2.5, 4.0)	3.0 (2.4, 3.8)	2.9 (2.3, 3.7)	3.5 (2.8, 4.4)	3.2 (2.5, 4.0)	4.2 (3.5, 5.2)	<0.001
Opioids and Benzodiazepines	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.0 (0.7, 1.6)	1.1 (0.7, 1.7)	1.3 (0.9, 1.9)	1.6 (1.1, 2.2)	2.0 (1.5, 2.8)	2.0 (1.5, 2.7)	2.5 (1.9, 3.3)	2.5 (1.9, 3.3)	2.2 (1.7, 3.0)	2.9 (2.3, 3.7)	1.8 (1.3, 2.4)	2.8 (2.1, 3.6)	2.9 (2.2, 3.7)	3.6 (2.9, 4.4)	2.9 (2.2, 3.7)	1.3 (0.9, 1.9)	2.6 (2.0, 3.3)	<0.001
Opioids and Cocaine	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.0 (0.7, 1.6)	1.1 (0.7, 1.7)	1.5 (1.0, 2.1)	1.1 (0.7, 1.6)	1.0 (0.7, 1.6)	1.1 (0.7, 1.7)	1.3 (0.9, 1.9)	1.4 (0.9, 2.0)	1.0 (0.6, 1.5)	1.0 (0.7, 1.6)	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	1.2 (0.8, 1.8)	1.5 (1.1, 2.1)	1.9 (1.4, 2.5)	2.7 (2.1, 3.5)	2.9 (2.3, 3.7)	0.14
Opioids and Methamphetamine	1.2 (0.6, 2.2)	-	1.1 (0.7, 1.7)	1.1 (0.6, 2.0)	1.0 (0.7, 1.6)	1.0 (0.7, 1.6)	1.0 (0.6, 1.6)	1.0 (0.6, 1.6)	1.0 (0.5, 1.9)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.5 (1.1, 2.1)	1.5 (1.0, 2.1)	1.8 (1.3, 2.5)	2.3 (1.8, 3.1)	3.0 (2.3, 3.8)	4.6 (3.8, 5.6)	4.4 (3.6, 5.4)	6.7 (5.7, 7.8)	0.02
Female																						
Opioids and Alcohol	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	1.4 (0.8, 2.3)	1.0 (0.5, 1.8)	1.8 (1.1, 2.8)	1.6 (1.0, 2.6)	1.8 (1.1, 2.8)	1.0 (0.5, 1.8)	1.7 (1.1, 2.7)	1.3 (0.8, 2.2)	1.5 (0.9, 2.4)	2.0 (1.3, 3.1)	1.7 (1.1, 2.7)	1.9 (1.2, 2.9)	2.1 (1.4, 3.2)	0.01
Opioids and Benzodiazepines	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	1.8 (1.2, 2.9)	1.6 (1.0, 2.6)	1.9 (1.2, 3.0)	1.8 (1.1, 2.8)	2.2 (1.5, 3.3)	2.5 (1.7, 3.6)	2.1 (1.4, 3.2)	2.0 (1.3, 3.0)	2.7 (1.9, 3.9)	3.5 (2.6, 4.8)	2.3 (1.5, 3.3)	0.9 (0.4, 1.6)	2.0 (1.4, 3.1)	0.01
Opioids and Cocaine	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	1.1 (0.6, 1.9)	1.0 (0.5, 1.8)	0.9 (0.5, 1.8)	0.9 (0.5, 1.8)	1.0 (0.6, 1.9)	0.9 (0.5, 1.7)	0.9 (0.5, 1.7)	1.0 (0.5, 1.8)	0.9 (0.5, 1.7)	1.1 (0.7, 2.0)	1.6 (1.0, 2.5)	1.7 (1.1, 2.7)	2.6 (1.9, 3.8)	0.49
Opioids and Methamphetamine	-	-	1.1 (0.5, 2.0)	-	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	-	1.0 (0.5, 1.8)	0.9 (0.5, 1.8)	0.9 (0.5, 1.8)	0.9 (0.5, 1.7)	1.4 (0.8, 2.3)	1.5 (0.9, 2.5)	1.3 (0.8, 2.2)	2.0 (1.3, 3.1)	2.1 (1.4, 3.2)	4.5 (3.4, 5.9)	3.4 (2.5, 4.7)	6.2 (4.9, 7.8)	0.02
Male																						
Opioids and Alcohol	1.2 (0.6, 2.2)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.3 (0.7, 2.3)	1.8 (1.1, 2.9)	1.8 (1.1, 2.9)	1.8 (1.1, 2.9)	1.2 (0.7, 2.2)	2.5 (1.7, 3.8)	3.5 (2.5, 4.9)	4.3 (3.2, 5.8)	3.8 (2.7, 5.2)	3.1 (2.2, 4.4)	4.1 (3.0, 5.5)	3.9 (2.9, 5.3)	5.0 (3.8, 6.6)	4.6 (3.5, 6.1)	3.9 (2.9, 5.3)	5.4 (4.2, 7.0)	4.5 (3.4, 6.0)	6.5 (5.1, 8.2)	<0.001
Opioids and Benzodiazepines	1.2 (0.6, 2.2)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.6, 2)	1.2 (0.6, 2.1)	1.6 (0.9, 2.6)	2.2 (1.4, 3.3)	2.2 (1.5, 3.4)	2.4 (1.6, 3.6)	3.2 (2.3, 4.5)	3.3 (2.3, 4.6)	2.2 (1.5, 3.4)	3.4 (2.4, 4.7)	1.4 (0.9, 2.4)	3.6 (2.6, 4.9)	3.0 (2.1, 4.2)	3.6 (2.6, 4.9)	3.5 (2.5, 4.8)	1.8 (1.2, 2.8)	3.1 (2.3, 4.4)	<0.001
Opioids and Cocaine	1.2 (0.6, 2.2)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)	1.2 (0.6, 2.1)	2.0 (1.2, 3.1)	1.1 (0.6, 2.1)	1.0 (0.5, 1.9)	1.3 (0.7, 2.3)	1.7 (1.0, 2.8)	1.8 (1.1, 2.9)	1.0 (0.5, 1.8)	1.2 (0.6, 2.1)	1.2 (0.7, 2.2)	0.9 (0.5, 1.8)	1.6 (1.0, 2.6)	1.9 (1.3, 3.0)	2.2 (1.5, 3.3)	3.7 (2.7, 5.1)	3.2 (2.3, 4.5)	0.02
Opioids and Methamphetamine	1.2 (0.6, 2.2)	-	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.2 (0.7, 2.1)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	1.6 (1.0, 2.7)	1.4 (0.9, 2.4)	2.4 (1.6, 3.5)	2.6 (1.8, 3.8)	3.9 (2.9, 5.3)	4.7 (3.5, 6.2)	5.4 (4.2, 7.0)	7.1 (5.7, 8.9)	0.02

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

[2] Non-parametric Jonckheere-Terpstra Test for trend

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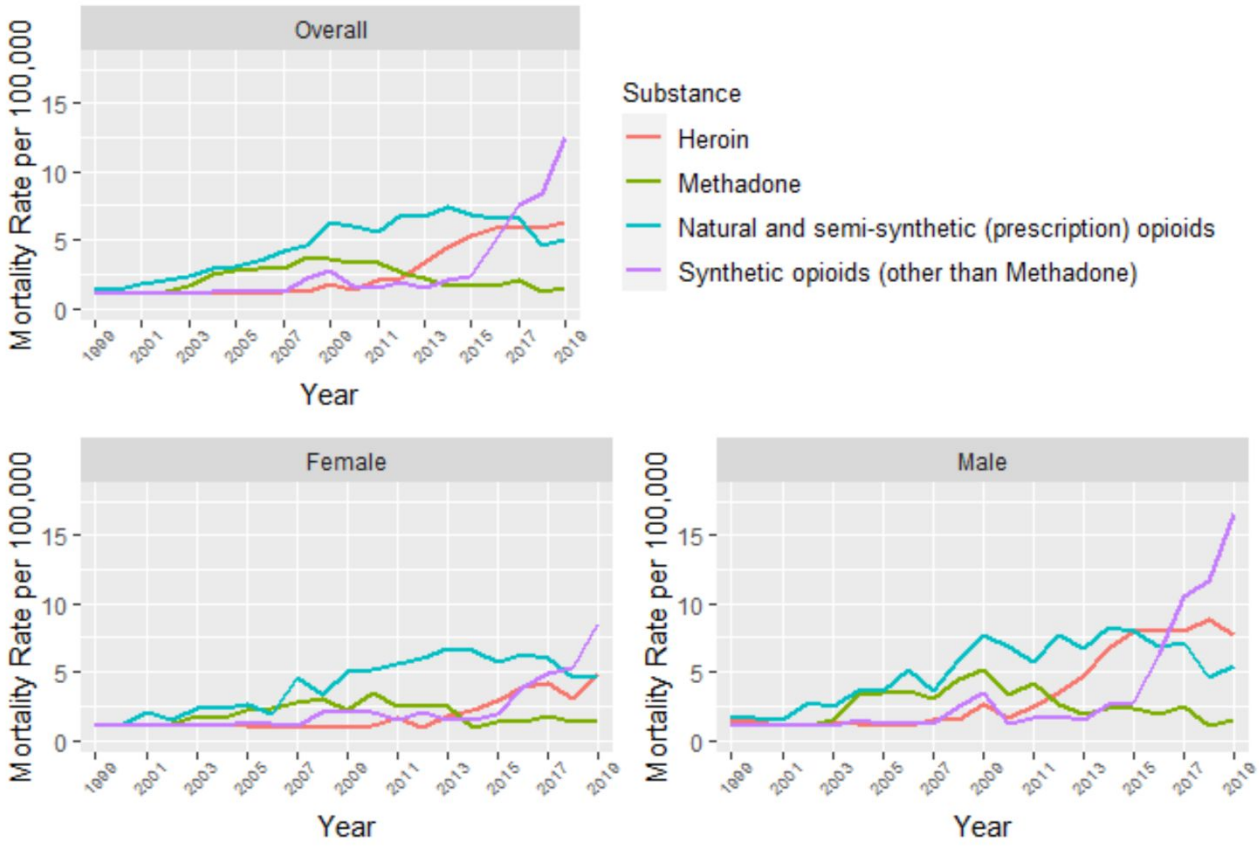

Figure 3: Trends in opioid death rates among US NH-AIAN 12 and older by individual opioid types[1]

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.1);
Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.2);
Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.3);
Synthetic opioids other than Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.4)

Table 3: Trends in opioid death rates per 100,000 (95% CI) among US NH-AIAN 12 and older by individual opioid type[1]

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Heroin	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)	1.1 (0.7, 1.7)	1.0 (0.6, 1.6)	1.1 (0.7, 1.6)	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	1.8 (1.3, 2.4)	1.4 (0.9, 2.0)	2.1 (1.6, 2.8)	2.2 (1.6, 2.9)	3.3 (2.6, 4.1)	4.4 (3.6, 5.4)	5.3 (4.4, 6.4)	5.9 (5.0, 7.0)	6.1 (5.1, 7.2)	5.9 (5.0, 7.0)	6.3 (5.3, 7.4)	<0.001
Methadone	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.2 (0.8, 1.8)	1.6 (1.1, 2.3)	2.5 (1.9, 3.3)	2.8 (2.1, 3.6)	3.0 (2.3, 3.8)	2.9 (2.2, 3.7)	3.7 (2.9, 4.6)	3.7 (2.9, 4.6)	3.4 (2.7, 4.3)	3.3 (2.6, 4.2)	2.6 (2.0, 3.4)	2.2 (1.7, 3.0)	1.6 (1.1, 2.2)	1.8 (1.3, 2.5)	1.7 (1.2, 2.3)	2.1 (1.6, 2.8)	1.2 (0.8, 1.7)	1.4 (1.0, 2.0)	0.70
Natural and semi-synthetic (prescription) opioids	1.4 (0.9, 2.0)	1.3 (0.9, 2.0)	1.8 (1.3, 2.5)	2.1 (1.6, 2.9)	2.4 (1.8, 3.2)	2.9 (2.3, 3.8)	3.1 (2.4, 4.0)	3.5 (2.8, 4.4)	4.2 (3.4, 5.2)	4.6 (3.7, 5.6)	6.3 (5.3, 7.5)	6.0 (5.0, 7.2)	5.6 (4.7, 6.7)	6.9 (5.8, 8.1)	6.7 (5.7, 7.9)	7.4 (6.3, 8.6)	6.8 (5.8, 8.0)	6.5 (5.5, 7.7)	6.6 (5.6, 7.7)	4.5 (3.7, 5.5)	5.1 (4.2, 6.1)	<0.001
Synthetic opioids (other than Methadone)	1.1 (0.7, 1.8)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)	1.0 (0.7, 1.6)	1.2 (0.8, 1.8)	1.3 (0.9, 1.9)	1.3 (0.9, 1.9)	1.1 (0.8, 1.7)	2.2 (1.6, 3.0)	2.8 (2.1, 3.6)	1.6 (1.1, 2.3)	1.5 (1.1, 2.2)	1.9 (1.4, 2.6)	1.5 (1.1, 2.2)	2.0 (1.5, 2.7)	2.3 (1.8, 3.1)	5.1 (4.2, 6.1)	7.6 (6.6, 8.9)	8.4 (7.3, 9.7)	12.5 (11.1, 14.0)	<0.001
Female																						
Heroin	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.8)	0.9 (0.5, 1.8)	1.0 (0.6, 1.9)	1.7 (1.0, 2.7)	0.9 (0.5, 1.7)	1.8 (1.2, 2.8)	2.2 (1.5, 3.3)	2.8 (2.0, 4.0)	3.9 (2.9, 5.2)	4.2 (3.1, 5.5)	3.1 (2.2, 4.3)	4.9 (3.7, 6.3)	0.056
Methadone	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.2 (0.7, 2.2)	1.7 (1.1, 2.8)	1.6 (1.0, 2.6)	2.2 (1.4, 3.3)	2.3 (1.6, 3.5)	2.7 (1.9, 3.9)	3.0 (2.1, 4.2)	2.2 (1.4, 3.3)	3.5 (2.5, 4.8)	2.5 (1.7, 3.7)	2.6 (1.8, 3.7)	2.5 (1.7, 3.7)	0.9 (0.5, 1.7)	1.3 (0.8, 2.2)	1.4 (0.8, 2.3)	1.7 (1.1, 2.7)	1.4 (0.8, 2.3)	1.4 (0.9, 2.3)	0.32
Natural and semi-synthetic (prescription) opioids	1.1 (0.6, 2.1)	1.1 (0.6, 2)	2.0 (1.3, 3.2)	1.4 (0.8, 2.5)	2.3 (1.5, 3.5)	2.3 (1.5, 3.5)	2.6 (1.7, 3.8)	2.0 (1.3, 3.1)	4.6 (3.5, 6.2)	3.4 (2.4, 4.7)	5.0 (3.8, 6.6)	5.2 (4.0, 6.8)	5.6 (4.3, 7.2)	6.1 (4.8, 7.7)	6.7 (5.3, 8.4)	6.5 (5.2, 8.2)	5.7 (4.4, 7.3)	6.2 (4.9, 7.9)	6.0 (4.7, 7.6)	4.6 (3.5, 6.0)	4.8 (3.7, 6.2)	<0.001
Synthetic opioids (other than Methadone)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.5, 2.0)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.0 (0.5, 1.9)	1.3 (0.7, 2.2)	1.3 (0.7, 2.2)	1.1 (0.6, 1.9)	2.0 (1.3, 3.1)	2.2 (1.4, 3.3)	2.0 (1.3, 3.1)	1.5 (0.9, 2.4)	2.1 (1.4, 3.2)	1.5 (0.9, 2.5)	1.5 (0.9, 2.5)	1.9 (1.2, 2.9)	3.9 (2.9, 5.3)	4.9 (3.7, 6.3)	5.3 (4.2, 6.9)	8.6 (7.1, 10.5)	<0.001
Male																						
Heroin	1.3 (0.7, 2.3)	1.3 (0.7, 2.4)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.4 (0.8, 2.4)	1.3 (0.7, 2.2)	1.0 (0.5, 2.0)	1.1 (0.6, 2.1)	1.5 (0.9, 2.6)	1.5 (0.9, 2.5)	2.6 (1.8, 3.8)	1.7 (1.0, 2.7)	2.5 (1.7, 3.8)	3.5 (2.5, 4.8)	4.8 (3.6, 6.3)	6.7 (5.3, 8.5)	7.9 (6.4, 9.8)	8.0 (6.5, 9.9)	8.1 (6.5, 9.9)	8.8 (7.2, 10.7)	7.7 (6.3, 9.6)	<0.001
Methadone	1.2 (0.6, 2.2)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.5 (0.9, 2.5)	3.4 (2.4, 4.8)	3.4 (2.4, 4.8)	3.6 (2.6, 5.0)	3.1 (2.1, 4.4)	4.4 (3.3, 6.0)	5.2 (4.0, 6.8)	3.3 (2.3, 4.6)	4.2 (3.1, 5.7)	2.6 (1.8, 3.8)	1.9 (1.2, 3.0)	2.3 (1.5, 3.4)	2.3 (1.6, 3.5)	1.9 (1.3, 3.0)	2.5 (1.7, 3.6)	1.0 (0.5, 1.8)	1.4 (0.9, 2.4)	>0.99
Natural and semi-synthetic (prescription) opioids	1.6 (0.9, 2.8)	1.6 (0.9, 2.7)	1.5 (0.9, 2.6)	2.8 (1.9, 4.2)	2.5 (1.6, 3.7)	3.6 (2.6, 5.0)	3.6 (2.6, 5.1)	5.1 (3.9, 6.8)	3.7 (2.6, 5.1)	5.8 (4.5, 7.6)	7.7 (6.2, 9.6)	6.9 (5.4, 8.7)	5.7 (4.4, 7.3)	7.7 (6.2, 9.6)	6.7 (5.3, 8.5)	8.3 (6.7, 10.2)	8.0 (6.5, 9.9)	6.8 (5.4, 8.6)	7.1 (5.7, 8.9)	4.5 (3.4, 6.0)	5.4 (4.2, 7.0)	<0.001
Synthetic opioids (other than Methadone)	1.2 (0.6, 2.2)	1.1 (0.6, 2.1)	1.1 (0.6, 2.1)	1.1 (0.6, 2.0)	1.1 (0.6, 2.0)	1.5 (0.9, 2.5)	1.2 (0.7, 2.2)	1.3 (0.8, 2.3)	1.2 (0.7, 2.2)	2.4 (1.6, 3.6)	3.4 (2.4, 4.8)	1.2 (0.7, 2.1)	1.6 (0.9, 2.6)	1.7 (1.1, 2.8)	1.5 (0.9, 2.5)	2.5 (1.7, 3.7)	2.8 (2.0, 4.0)	6.3 (4.9, 8.0)	10.5 (8.8, 12.6)	11.7 (9.8, 13.9)	16.5 (14.3, 19.1)	<0.001

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.1); Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.2); Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.3); Synthetic opioids other than Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.4);[2] Non-parametric Jonckheere-Terpstra Test for trend

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Supplement

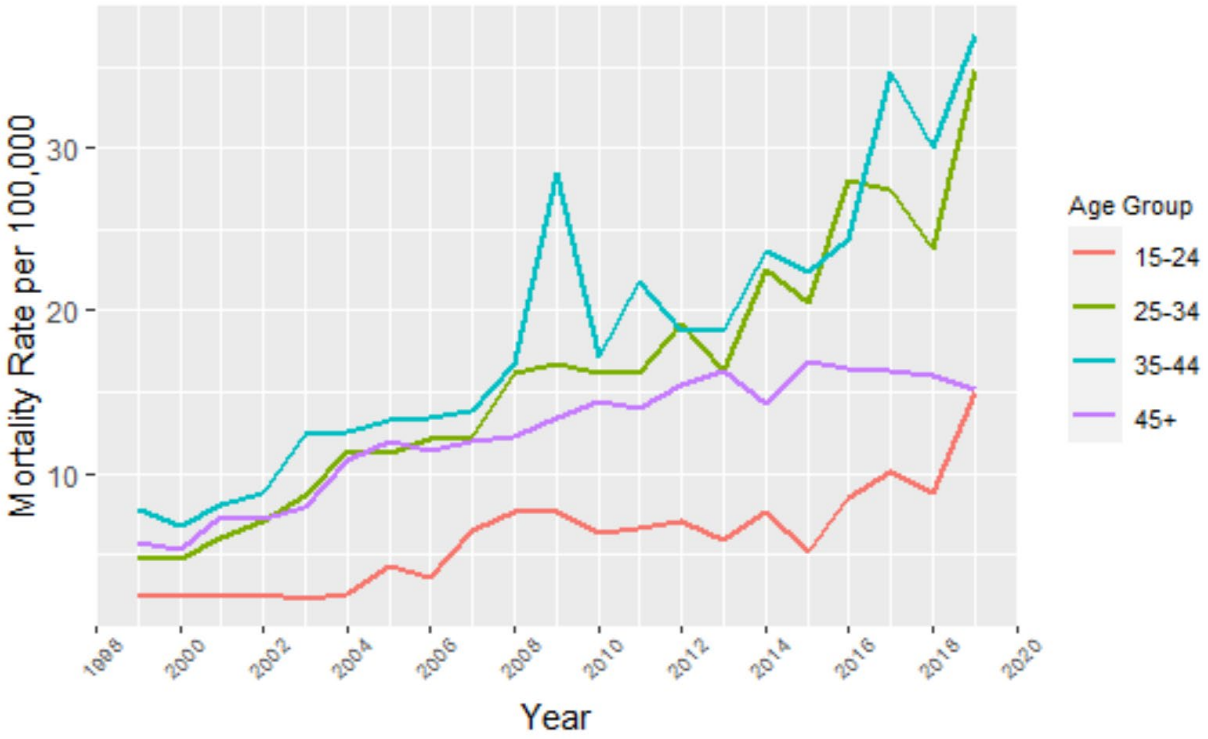

Figure 1a: Trends in opioid-only[1] death rates among US NH-AIAN 15 and older by age groups

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

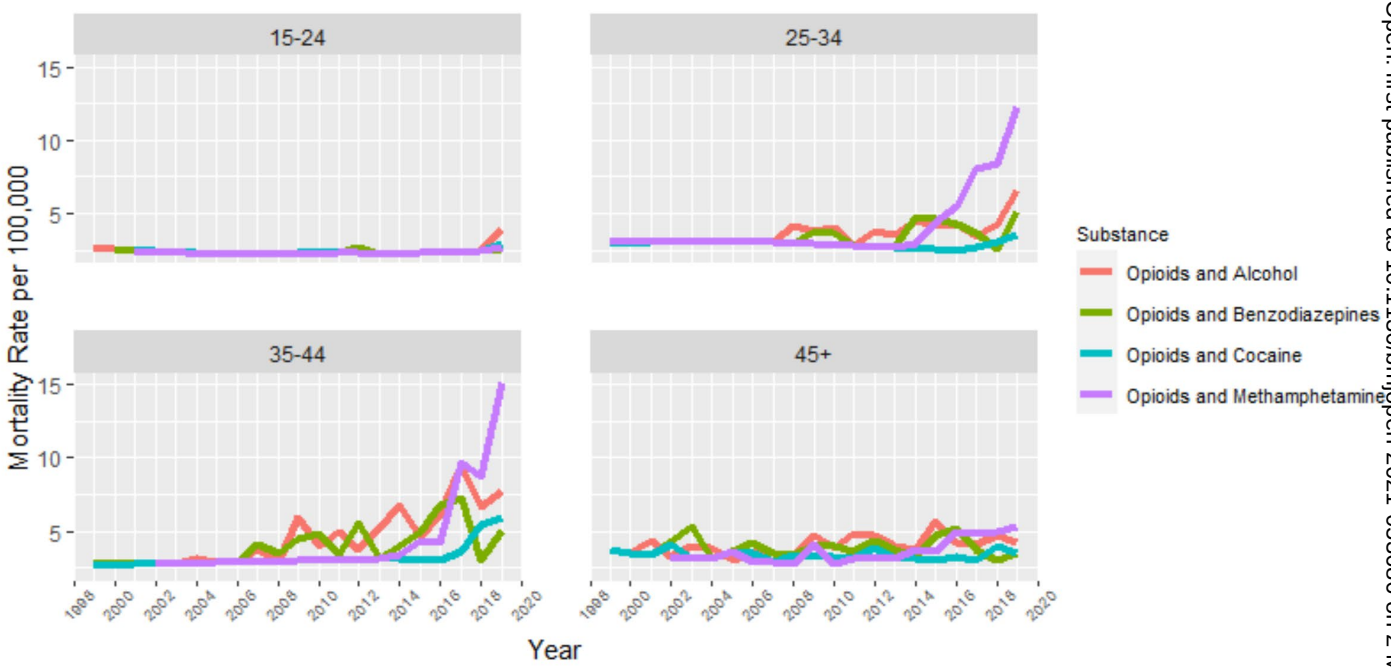

Figure 1b: Trends in opioid combination[1] death rates among US NH-AIAN age groups 15 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9)

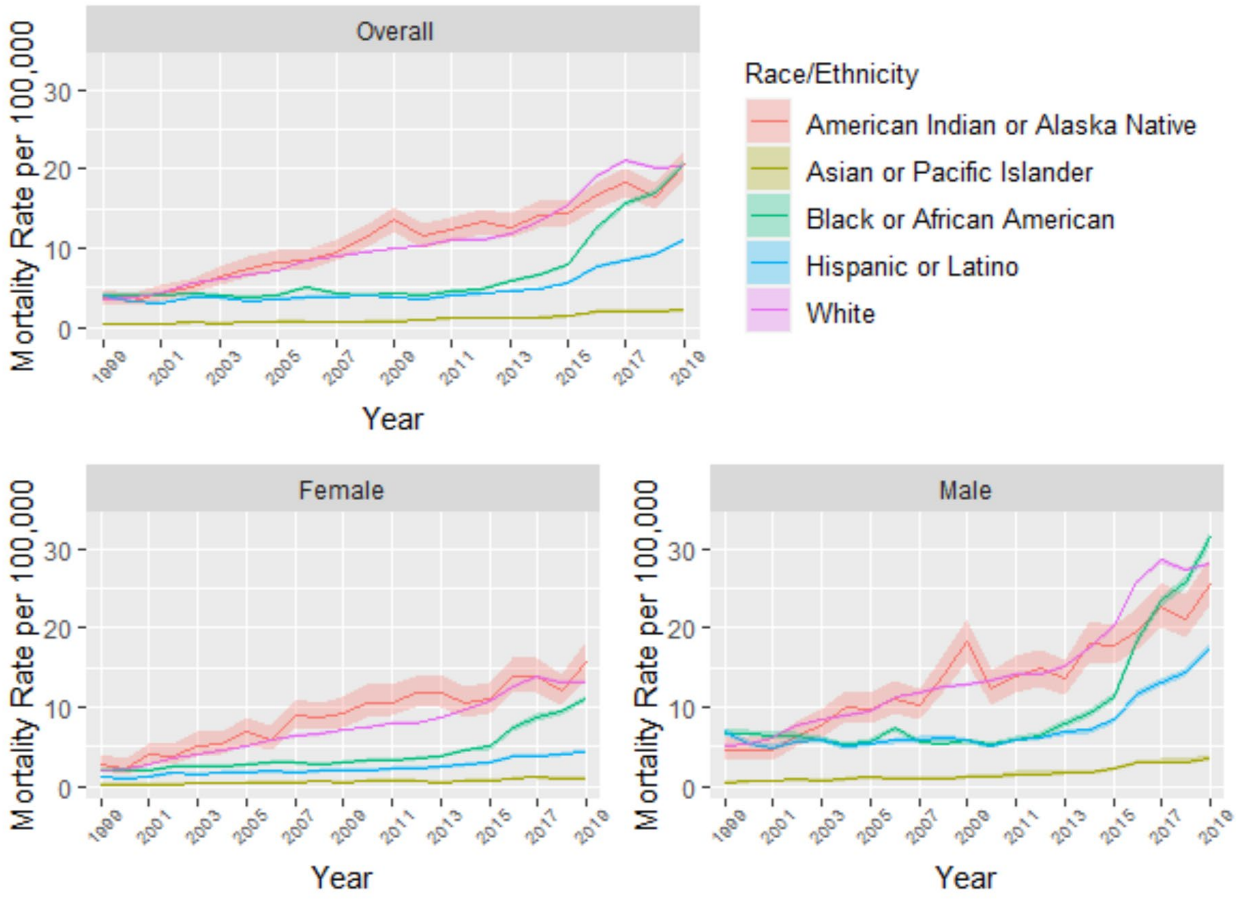

Figure 2a: Trends in opioid-only[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

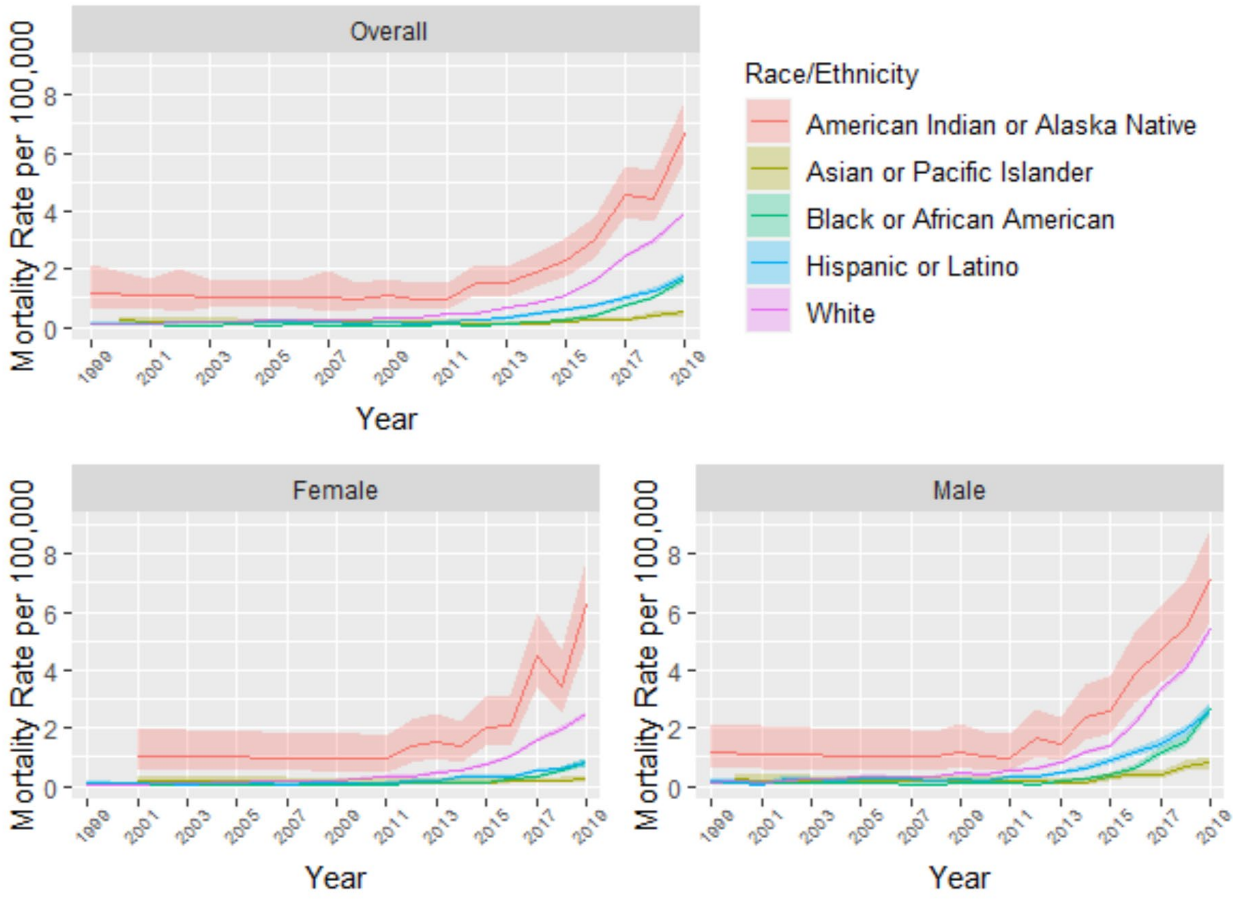

Figure 2b: Trends in opioid and methamphetamine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);

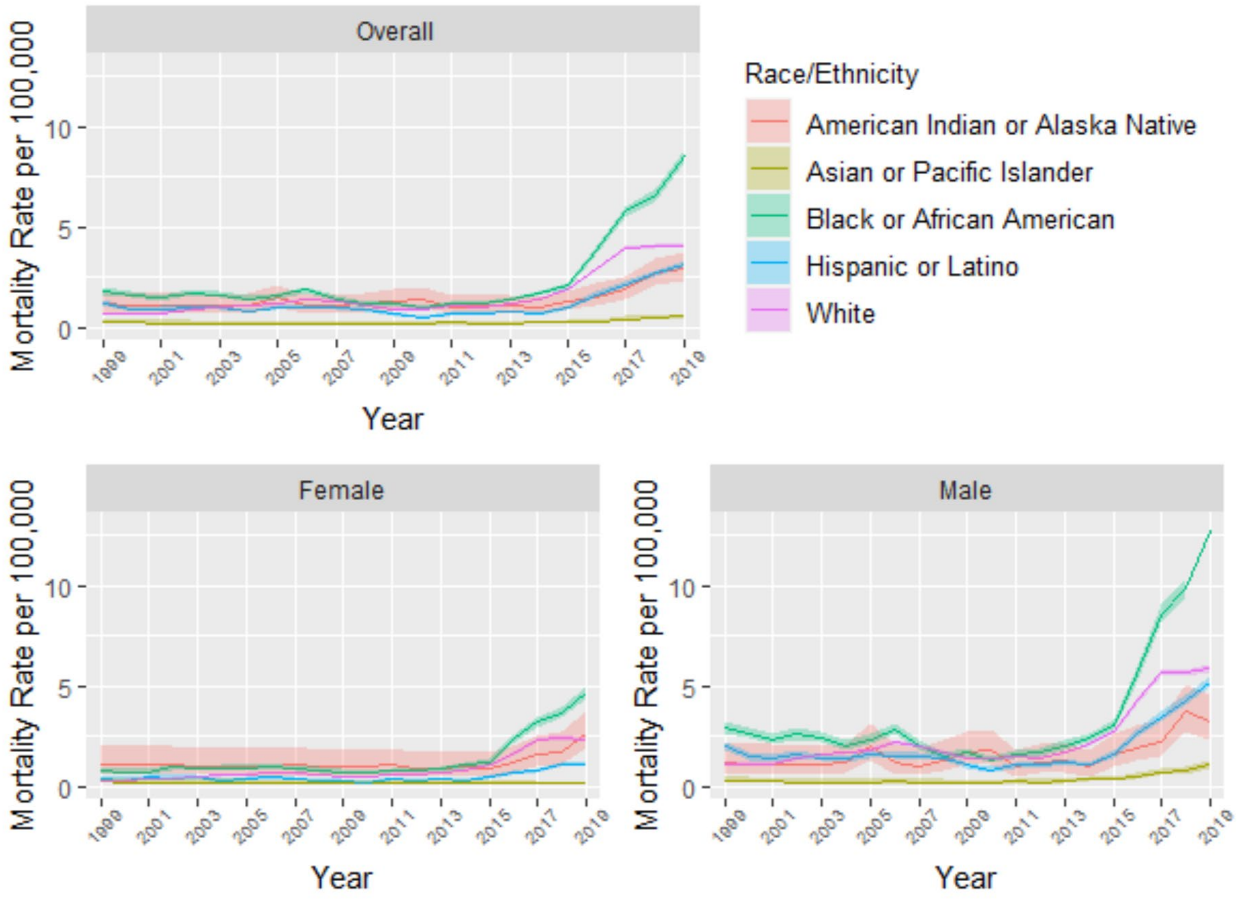

Figure 2c: Trends in opioid and cocaine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5)

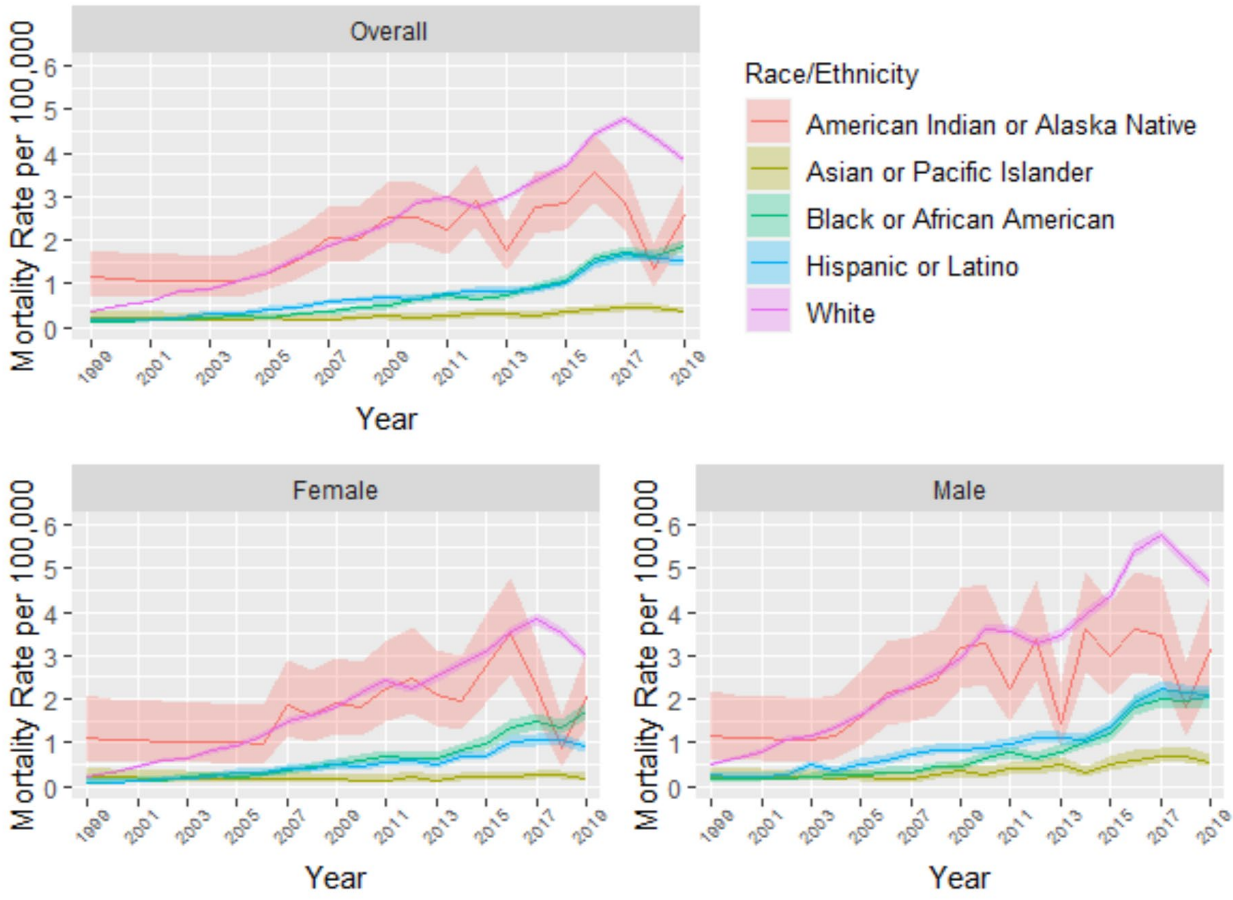

Figure 2d: Trends in opioid and benzodiazepine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4)

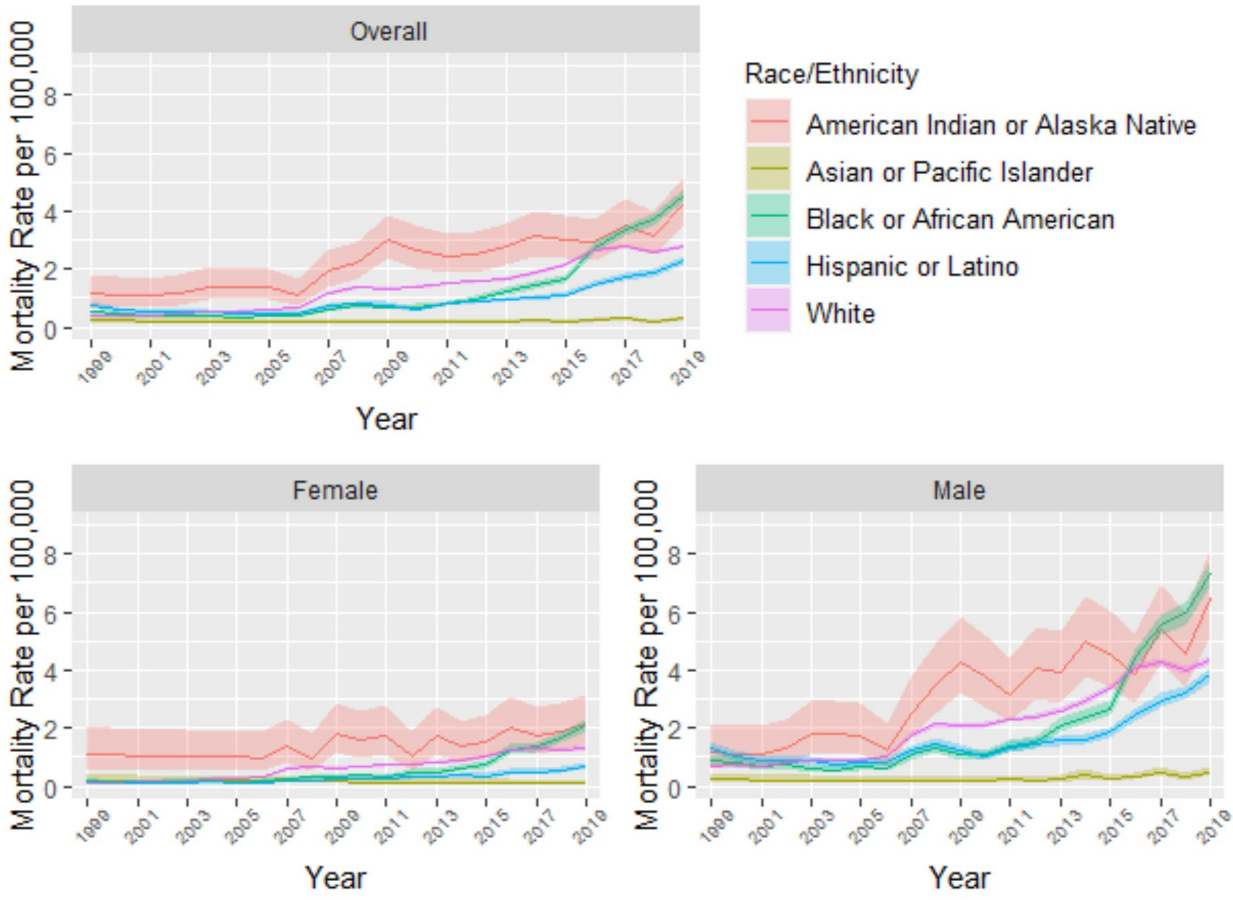

Figure 2e: Trends in opioid and alcohol[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Manuscript page 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Manuscript page 2
Methods			
Study design	4	Present key elements of study design early in the paper	Manuscript page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Manuscript page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Manuscript page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Manuscript page 3-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Manuscript page 3-5
Bias	9	Describe any efforts to address potential sources of bias	Manuscript page 4-5
Study size	10	Explain how the study size was arrived at	Manuscript page 3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Manuscript page 3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Manuscript page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Manuscript page 3-5
		(*c*) Explain how missing data were addressed	Manuscript page 4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Manuscript page 5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	All data captured on aggregate and each analysis scenario looked at different sub-population of patients within AIANs, eligibility criteria described in Manuscript page 3-5
		(b) Give reasons for non-participation at each stage	Manuscript page 3
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Manuscript page 4-7
		(b) Indicate number of participants with missing data for each variable of interest	Manuscript page 4
Outcome data	15*	Report numbers of outcome events or summary measures	Manuscript page 5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Manuscript page 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Manuscript page 7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	_
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Manuscript page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Manuscript page 7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Manuscript page 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Manuscript page 8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Manuscript page 8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	Manuscript page 11

applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Epidemiological trends in opioid-only and opioid/polysubstance–related death rates among American Indian/Alaska Native populations from 1999 – 2019: a retrospective longitudinal ecological study

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Epidemiological trends in opioid-only and opioid/polysubstance–related death rates among American Indian/Alaska Native populations from 1999 – 2019: a retrospective longitudinal ecological study

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Abstract

Objectives: The rate of drug overdose deaths in the U.S. has more than tripled since the turn of the century, and rates are disproportionately high among the American Indian/Alaska Native (AI/AN) population. Little is known about the overall historical trends in AI/AN opioid-only and opioid/polysubstance–related mortality. This study will address this gap.

Design: This is a retrospective longitudinal ecological study.

Setting: U.S. death records from 1999 to 2019 using the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER).

Participants: U.S. Non-Hispanic AI/AN people age 12 years and older.

Measures: The primary outcomes, identified via the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, included overdose deaths due to (1) opioids only, opioids in combination with any other substance, all-opioid related overdoses; (2) combinations of opioids and alcohol, opioids and methamphetamine, opioids and cocaine, opioids and benzodiazepines; and (3) specific types of opioids.

Results: From 1999-2019, opioid-only mortality rates increased from 2.8 to 15.8 per 100,000 ($P<0.001$) for AI/AN women and 4.6 to 25.6 per 100,000 ($P<0.001$) for AI/AN men. All opioid-related mortality rates increased significantly ($P<0.001$) from 5.2 to 33.9 per 100,000 AI/AN persons, 3.9 to 26.1 for women, and 6.5 to 42.1 for men. AI/AN also exhibited significant increases in mortality rates due to opioids and alcohol, opioids and benzodiazepines, opioids and methamphetamine, and AI/AN men experienced substantial increases in mortality due to opioids and cocaine. Mortality rates by individual opioid types increased significantly over time for heroin, natural and semi-synthetic (prescription), and synthetic opioids (fentanyl/fentanyl analogs) other than methadone.

Conclusions: These findings highlight magnification over time in opioid-related deaths and may point to broader systemic factors that may disproportionately affect members of AI/AN communities and drive inequities.

Strengths and limitations of this study

- This is one of the first studies to consider the historical trends of opioid overdose mortality in the AI/AN population across the United States, with particular attention given to how co-use of opioids with certain substances contributes to drug overdose mortality in this population.
- This study offers stratified results by sex and compares mortality rates between NH AI/AN populations and other race/ethnicity groups to better identify sub-populations at risk of overdose death.
- This study provides insight into trends about opioid overdose mortality in the AI/AN population by specific opioid types, which can help guide harm reduction and public health prevention efforts for AI/AN communities.
- Due to data-use agreement requirements, subgroup data with small counts could not be disaggregated.
- Age-adjusted rates could not be obtained because they require larger sample sizes to avoid data suppression for small sample sizes.

Keywords: American Indian/Alaska Native; opioid use; opioid-related mortality, polysubstance use; epidemiology; trends

INTRODUCTION

Over the past two decades, the rate of drug overdose deaths in the United States (U.S.) has more than tripled.[1] This spike in overdoses, described as a public health crisis, has grown more destructive with time.[1,2] The American Indian(s)/Alaska Native(s) (AI/AN) population has been disproportionately affected by drug-related mortality. From 1999 to 2015, drug overdose mortality among metropolitan AI/AN populations increased from 7.1 per 100,000 to 22.1 per 100,000, representing a 261% change from 1999. [3] A magnified pattern was observed in non-metro AI/AN populations, whose overdose mortality rate climbed steeply from 3.9 per 100,000 in 1999 to 19.8 per 100,000 in 2015, representing a 519% increase. [3] Other groups also experienced rises in drug overdoses over this same period but at lower rates of change.[3]

Opioid overdose fatalities among AI/AN and non-Hispanic White populations both rose dramatically since 1999, surpassing national rates in all years since 2002. [4] While non-Hispanic White populations exhibit the highest rates since 2014, AI/AN populations demonstrate the second highest opioid overdose mortality across U.S. racial and ethnic groups. In 1999, the AI/AN opioid overdose mortality rate was 2.9 per 100,000 and had risen to 17.0 deaths per 100,000 by 2019.[4] Regional variations also exist in this trend among AI/AN populations. From 1999-2016, higher mortality rates from opioids among AI/AN were observed in states in the Pacific Northwest, and Great Lakes Region.[5] During 2013–2015, mortality rates among AI/AN populations in Washington state were 2.7 higher than rates among non-Hispanic White populations for all opioid-involved overdoses.[6]

The literature also points to variations in overdose rates from specific opioid types. Increases in overdose due to synthetic opioids, primarily driven by illicitly manufactured fentanyl, have contributed to the bulk of U.S. opioid-involved fatalities in recent years.[7,8] From

2017 to 2018, overdose death rates from synthetic opioids other than methadone among AI/AN populations increased from 6.5 per 100,000 to 7.3 per 100,000 deaths.[9] Compared to non-Hispanic Whites and non-Hispanic Blacks, AI/AN overdose rates from synthetic opioids were lower, but AI/AN rates were higher than Hispanic and Pacific Islander rates.[9] Additionally, while the U.S. has seen recent declines in heroin overdoses, decreases observed among AI/AN populations are modest compared to other racial and ethnic populations.[9]

Regarding polysubstance use, the literature suggests that people who use opioids often use other drugs concurrently, thereby creating drug interactions that can increase overdose risk.[10] The co-use of opioids with some other drugs may be of particular concern for AI/AN populations, as treatment admission data from the Treatment Episode Data Set (TEDS) demonstrated that among U.S. racial groups, AI/AN respondents consistently reported the highest rates of individuals entering treatment with concurrent use of methamphetamine and heroin each year from 2008 to 2017.[11]

The reasons for higher rates of drug overdose among Indigenous people are many but likely originate from a persistent legacy of colonialism, racism and intergenerational trauma.[12,13] This legacy is often complicated by current social, economic, and health disadvantages experienced by many AI/AN populations.[12-14] Taken together, these circumstances provide the ideal for increased risk of overdose.[12,15]

Although previous reports show AI/AN populations across the U.S. have experienced elevated rates of drug overdose deaths, the significance of historical trends in drug-related death rates among AI/AN populations remains unclear, especially regarding trends in deaths related to polysubstance use, which have risen dramatically in the general U.S. population in recent years. Deaths involving psychostimulants (e.g., cocaine, methamphetamine, MDMA, and prescription

stimulants) increased by over 30% between 2016 and 2017 across the U.S., and in 2017, over 70% of cocaine-involved overdose deaths and 50% of other psychostimulant-involved overdose deaths involved at least one opioid.[16] This study provides foundational knowledge on overdose deaths involving opioids among AI/AN populations by analyzing the historical patterns of opioid-only and opioid/polysubstance–related deaths.

METHODS

Settings

This is a retrospective longitudinal ecological study that uses serial cross-sectional data to analyze historical patterns of opioid-only and polysubstance-involved opioid overdose deaths among AI/AN populations. Specifically, this retrospective observational study used publicly available data from the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. Data on drug overdose deaths due to opioids and combinations of opioids with either alcohol, benzodiazepines, cocaine, or methamphetamine were obtained from the CDC WONDER's National Center for Health Statistics Mortality database (NCHS). This database contains county-level data comprising both mortality and population counts across all fifty United States and the District of Columbia. Mortality data were captured by either 1) being coded by states and provided to NCHS per the Vital Statistics Cooperative Program or 2) state registration offices providing copies of physical death certificates to the NCHS to be coded by the NCHS itself. The mortality data in CDC Wonder are based on information from all death certificates across the U.S. Mortality information from individuals classified as nonresidents (i.e., nonresident aliens, citizens living abroad, residents of Puerto Rico, Guam, the Virgin Islands, other territories of the U.S.) as well as fetal deaths were excluded from capture. Population data were captured from the U.S. Census Bureau and comprise mid-year census, estimates of

national, state, and county resident populations. Additional information such as time and place of death, place of residence, age, sex, race, and ethnicity are also provided with the demographic data being captured on the death certificate for mortality data and by self-reporting for population data. The data spanned from 1999 to 2019, included all United States, all urbanization categories, all weekdays, all autopsy values, and all place of death categories. The population of interest was U.S. Non-Hispanic (N.H.) AI/AN of the age of 12 and older. Ethical approval was not required for this secondary analysis of publicly available aggregate county-level national data, in which no individual information would be identifiable.

Measures

All deaths were identified from the NCHS Mortality database by the underlying cause of death and multiple causes of death with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. The outcomes of interest were separated into three scenarios: (1) overdose deaths relating to opioids alone (opioid-only), opioids in combination with any other substances (opioid/polysubstance), the sum of opioid-only and opioid/polysubstance cases (all-opioid related) (2) overdose deaths relating to opioids in combination with each of the other substance types and (3) overdose deaths separated by individual opioid types (heroin natural and semi-synthetic (prescription) opioids [e.g., oxycodone, hydrocodone], methadone, and synthetic opioids other than methadone[e.g., fentanyl, tramadol]). Opium(multiple cause code T40.0) and unknown opioids (T40.6) were not displayed alone because counts were too small. The specific substance-related overdose death types and corresponding ICD-10 codes are displayed by the outcome scenario below in List 1. While types of opioids are differentiated by these ICD codes, whether an opioid was prescribed or obtained via unregulated sources is not discernable using these data.

List 1: Substance-related overdose death types, and associated ICD-10 codes, by outcome scenario

	Underlying Cause of Death ICD-10	Multiple Cause of Death ICD-10[1]
Scenario 1		
Opioid-only	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6
Opioid/polysubstance	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9
All-opioid related[2]	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 OR (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9)
Scenario 2		
Opioids and Methamphetamine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T43.6
Opioids and Cocaine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5
Opioids and Benzodiazepines	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T42.4
Opioids and Alcohol	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T51.0, T51.1, T51.9
Scenario 3		
Heroin	X40-44, X60-64, X85, Y10-Y14	T40.1
Natural and semi-synthetic (prescription) opioids	X40-44, X60-64, X85, Y10-Y14	T40.2
Methadone	X40-44, X60-64, X85, Y10-Y14	T40.3
Synthetic opioids (other than methadone)	X40-44, X60-64, X85, Y10-Y14	T40.4

[1] Any of prescribed codes, if an "AND" is included then at least 1 from first code group AND 1 from other code group;
[2] Sum of opioid-only and opioid/polysubstance

For multiple causes of death codes, any qualifying code from the list of available codes was counted towards the outcome. In the case of opioids in combination with another substance, any qualifying code from the list of available opioid multiple causes of death codes (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6) *and* any code from the other substance(s) list was counted towards the outcome. The count of deaths was divided by the population of interest and multiplied by 100,000 to provide a mortality rate per 100,000 NH AI/AN 12 years and older. Per the data use agreement of CDC Wonder, all counts 9, and lower were classified as 10. Predictors included year (1999-2019) and sex (female, male). Supplemental analyses looked at age groups (15-24, 25-34, 35-44, 45+) and race/ethnicity (NH AI/AN, NH Asian or Pacific Islander (API),

NH Black, NH White, Hispanic/Latino). Because age groupings were allowed only in 5 and 10-year increments, the age group predictor was restricted to those 15 years and older instead of 12 years and older.

Statistical Analysis

Overdose death rates per 100,000 NH AI/AN population 12 and older, relating to the three outcome scenarios, were presented over time from 1999 to 2019. Figures and tables were constructed with 95% exact Poisson confidence intervals. To assess significant trends over time, non-parametric Jonckheere-Terpstra tests were performed for each substance type because rates exhibited non-normal distributions. All analysis results were presented overall and stratified by sex to identify sex-specific trends in the outcomes of interest. Supplementary figures were displayed for mortality rates due to opioids-only and due to opioids in combination with each other substance. Rates were stratified by age groups as well as by race/ethnicity. Racial comparisons were performed to assess how NH AI/AN rates compared to those of other racial groups.

All hypothesis tests were two-sided with a significance level of 5%. R version 3.6.1 (R Foundation for Statistical Computing) was used to perform all analyses.

Patient and public involvement

No patient was involved.

RESULTS

From 1999-2019 (Figure 1, Table 1), NH AI/AN opioid mortality rates increased significantly (all $P<0.001$) overall and for both women and men. All opioid-related mortality rates increased from 5.2 to 33.9 per 100,000 overall, 3.9 to 26.1 per 100,000 women, and 6.5 to 42.1 per 100,000 men. Opioid-only rates increased from 3.7 to 20.6 per 100,000 overall, 2.8 to

15.8 per 100,000 women, and 4.6 to 25.6 per 100,000 men. Opioid/polysubstance rates increased from 1.5 to 13.3 per 100,000 overall, 1.1 to 10.3 per 100,000 women, and 1.9 to 16.5 per 100,000 men. Rates increased significantly even with total population counts of NH AI/AN increasing across 1999-2019 from 1,764,431 to 2,285,417 overall, from 902,815 to 1,173,309 for males, and from 861,616 to 1,112,108 for females.

Significant trends were also observed for mortality due to opioids in combination with other specific substances, with the exception of opioids and cocaine overall and among women (Figure 2, Table 2). Significantly increasing mortality rates were seen overall in NH AI/AN due to opioids and alcohol (rates per 100,000: 1.1 to 4.2, P<0.001), opioids and benzodiazepines (rates per 100,000: 1.1 to 2.6, P<0.001), and opioids and methamphetamine (rates per 100,000: 0.6 to 6.7, P=0.001). By sex, NH AI/AN men and women both exhibited significant increases in mortality rates due to opioids and alcohol (rates per 100,000 women: 1.1 to 2.1, P=0.01; rates per 100,000 men: 1.2 to 6.5, P<0.001), opioids and benzodiazepines (rates per 100,000 women: 1.1 to 2.0, P=0.01; rates per 100,000 men: 1.2 to 3.1, P<0.001), and opioids and methamphetamine (rates per 100,000 women: 1.1 to 6.2, P=0.02; rates per 100,000 men: 1.2 to 7.1, P=0.02). Only NH AI/AN men exhibited significantly increasing mortality rates due to opioids and cocaine (rates per 100,000 men: 1.2 to 3.2, P=0.02).

When looking deeper into individual opioid types (Figure 3, Table 3) there was a significant rise in natural and semi-synthetic (prescription) opioid death rates (rates per 100,000 overall: 1.4 to 5.1, P<0.001; rates per 100,000 women: 1.1 to 4.8, P<0.001; rates per 100,000 men: 1.6 to 5.4, P<0.001) and heroin (rates per 100,000 overall: 1.2 to 6.3, P<0.001; rates per 100,000 women: 1.1 to 4.9, P=0.056 [on the boundary of significance]; rates per 100,000 men 1.3 to 7.7, P<0.001). Death rates due to synthetic opioids (other than methadone) saw a drastic

increase in recent years (2013 to 2019 rates per 100,000 overall: 1.5 to 12.5, P<0.001; 2013 to 2019 rates per 100,000 women: 1.5 to 8.6, P<0.001; 2013 to 2019 rates per 100,000 men: 1.5 to 16.5, P<0.001).

Supplemental analyses, by age groups, revealed that NH AI/AN ages 25-44 had higher opioid-only and opioid-combination mortality rates than those 15-24 and older than 44 (Supplemental Figures 1a and 1b). Overall and across both sexes, NH AI/AN populations generally exhibited opioid-only and opioid-combination mortality rates as high or higher than other races. Death rates across all years relating to opioids and methamphetamine remained consistently higher for NH AI/AN compared to all other races. However, in more recent years, NH White rates exceeded those of the NH AI/AN population, as seen in opioid-only and opioid-benzodiazepine mortality rates. NH Black men, additionally, saw higher opioid-only mortality rates than NH AI/AN men in recent years. Opioid and cocaine-related death rates among the NH Black population also exceeded rates of the NH AI/AN population overall and for men across most years and more recently for women. NH AI/AN exhibited higher opioid and alcohol mortality than other races, with N.H. Blacks showing slightly higher rates in recent years (Supplemental Figures 2a-2e).

DISCUSSION

This study provides a comprehensive historical overview of fatal drug overdose trends for NH AI/AN populations in the U.S., with particular attention to the role of opioids and combinations of opioids with alcohol, benzodiazepines, methamphetamine, and cocaine. We found that among NH AI/AN, mortality rates due to opioids have increased significantly over time. The trend of rising opioid-overdose mortality remains when data are stratified by sex and across age categories. Deaths due to polysubstance use involving opioids have also increased

significantly over time among NH AI/AN populations. Among specific opioid types, heroin and natural/semi-synthetic (prescription) opioid-related deaths have risen across the years, however, synthetic opioid-related deaths have spiked just in recent years alone. When comparing across U.S. racial and ethnic groups, NH AI/AN populations exhibit rising opioid-overdose mortality rates that have generally been higher than other groups, but in recent years NH AI/AN men's rates were below those of NH White and NH Black men, and NH AI/AN populations also display lower rates of death related to opioids and cocaine than NH Black populations. However, NH AI/AN populations exhibit higher mortality rates of opioid combinations with methamphetamine and alcohol than all other U.S. racial/ethnic groups.

In general, the increasing opioid overdose mortality from 1999-2019 among NH AI/AN populations observed in our analysis mirror the rising opioid overdose trends in the U.S. general population.[1,9,17] Similarly, deaths resulting from opioid combinations with other drugs among AI/AN populations follow an increasing trend that is supported by prior research.[16] The combination of opioids with other substances can be a potent inducer of drug overdose. Alcohol, opioids (heroin/morphine, tramadol, oxycodone, etc.), and benzodiazepines depress the central nervous system when used alone.[18,19] However, the combination of opioids with other substances may generate complex drug interactions associated with a heightened risk of fatal overdose.[10,20] Consequently, our results showed an escalation in mortality due to opioids in combination with methamphetamine and opioids in combination with alcohol from 1999 to 2019. Consistent with our findings, data from the CDC reported that roughly half of all psychostimulant deaths in 2017 also involved an opioid. Additionally, they observed a significant rise in deaths due to opioids in combination with psychostimulants from 2015 to 2017.[16] Aside from the elevated risk of overdose, the co-use of opioids with other substances has been shown to negatively impact

treatment outcomes,[21] including lower rates of treatment retention.[22] Similarly, co-use of alcohol with other substances has been associated with increased relapse rates.[23] Given the increased risk of overdose and poor treatment outcomes, it is essential that substance use treatment programs, interventions, and policies consider the complexities surrounding polysubstance, including identifying and addressing the root causes of such polysubstance use.

Regarding trends in specific opioid types fueling overdose mortality, our finding that AI/AN deaths resulting from synthetic opioids have increased sharply in recent years indicates AI/AN communities have experienced similar drivers of mortality as the general U.S. population. This group of opioids contains illicitly manufactured fentanyl, a highly potent synthetic opioid that can increase the risk of overdose and mortality in unregulated and unknown quantities.[24,25] While we cannot determine from these data whether the fentanyl involved in an overdose was prescribed or unregulated, current evidence points to increased illicit fentanyl poisoning in the U.S.[26,27], especially in combination with other drugs, as a key engine of drug poisoning deaths. Numerous analyses indicate a growing role for fentanyl in drug overdose deaths. A study consisting of toxicology data from 10 U.S. states showed that close to 60% of individuals who died of drug overdoses tested positive for fentanyl and fentanyl analogs in addition to cocaine, methamphetamine, and heroin.[28] Furthermore, overdose deaths resulting from fentanyl increased nearly 12 fold from 2013 to 2019.[8] Qualitative and mixed methods studies indicate that illicitly manufactured fentanyl, as opposed to prescription synthetic opioids, drive these trends.[29,30] Our results demonstrate the need for harm reduction interventions to mitigate the dangers of fentanyl, especially among individuals using unregulated drugs (e.g., naloxone training and safe drug supplies), along with improved access to evidence-based treatment programs that offer opioid agonist treatment.[31]

These findings highlight existing inequities in drug-related deaths and may point to broader systemic factors that disproportionately affect members of AI/AN communities. American Indians and Alaska Natives continue to encounter stressors that stem from diminished socioeconomic prospects, racism, and historical trauma from colonization. These stressors often contribute significantly to the heightened drug use and related overdoses in the AI/AN population.[13,15] Despite this disproportionate burden, indigenous communities continue to encounter significant challenges in treatment access, availablity[32], and quality.[33] A recent study using 2017 and 2018 data showed that only 22% of A.I./AN-serving treatment centers offer opioid agonists. Furthermore, they found that only 40% of AI/AN persons in specialty treatment receive medication-assisted treatment for opioid use disorder.[32] To mitigate the impact of drug overdoseon AI/AN communities, leverage points for intervention must look at the root causes and structural factors that shape substance use and addiction and seek to expand specialty treatment programs for AI/AN communities.

Furthermore, sex differences were apparent throughout our results. In our primary and supplemental analysis, male populations tended to experience higher rates and higher increases in drug overdose deaths than female populations. Sex differences observed in drug overdose studies are often characterized by higher rates in men.[34,35] However, historical trends are not uniform, and gaps between male and female populations have narrowed at specific periods during the drug overdose crisis and widened at other points.[35] Our observed results may reflect differential attitudes towards risk and varying social expectations for males and females in AI/AN communities and may suggest the need for targeted gender-sensitive interventions.

Finally, two essential observations in our study may shed light on the critical role of socioeconomic status in overdose deaths. In our supplemental analysis of opioid only deaths, we

found that individuals aged 35-44 carried the highest burden of death rates for most of the years from 1999-2010. Additionally, among this same age, overdose death rates spiked immediately following 2008. The period between 2008 and 2009 was defined by a worldwide economic crisis characterized by high unemployment rates.[36] Furthermore, most overdose deaths during the same period occurred among individuals who often bear the financial responsibility for their families (i.e., 35-44 age group). While additional studies will be needed to ascertain the relationship between the 2008 financial crises and the escalation in drug overdose deaths among AI/AN communities, our findings offer compelling insights into the importance of socioeconomic wellbeing in the context of substance use. Our findings should be considered within the constraints of certain important limitations. First, to capture as much AI/AN data as possible, age-adjusted results were not obtained because they required suppressing AI/AN-specific results. However, in comparing age-adjusted and raw rates, we found rates to be reasonably similar. Second, subgroup data with small counts were aggregated due to data-use agreement requirements. Third, due to the different demographic reporting techniques between the mortality data from death certificates (reported by surviving next of kin or funeral director observation)[37] and population data from the U.S. Census Bureau (self-reporting), inconsistencies could arise between the two groups, which could translate into biased mortality rates[38,39] across certain demographic groups (especially race and ethnicity). Fourth, deaths with specific demographics reported as "not stated" or unknown were not included in demographic-specific analyses.

On the other hand, our study has some unique strengths worth mentioning. First, this is one of the first studies to investigate AI/AN opioid overdose trends over time across the U.S., with emphasis on the drug overdose implications of the concurrent use of opioids with alcohol, benzodiazepines, cocaine, or methamphetamine contributes in this population. Second, by

stratifying our findings by sex and comparing mortality rates between NH AI/AN groups, our findings are mainly presented to better identify subpopulations at risk of overdose. Finally, our results highlight the historical trends of opioids overdose mortality among AI/AN populations by specific opioid types, including heroin, natural and semi-synthetic (prescription) opioids [e.g., oxycodone, hydrocodone], methadone, and synthetic opioids other than methadone [e.g., fentanyl, tramadol]). Providing these distinctions is essential for public health prevention and harm reduction strategies directed towards AI/AN communities.

CONCLUSIONS

Overall, our results suggest that AI/AN populations continue to face rising levels of overdose mortality due to the use of opioids alone and in combination with other substances, with rates as high or higher than all other racial/ethnic groups. AI/AN men and those aged 25-44 are especially impacted. While the type of opioid driving these trends has changed over the years, many underlying social factors that drive these patterns have not, including inequities in socioeconomic status, persistent effects of historical trauma, and inequities in healthcare access and treatment programs. Interventions for AI/AN populations with substance use disorders will be more impactful if they are comprehensive, culturally centered, and address social determinants of health, including socioeconomic factors and racial and ethnic discrimination.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics statements

Patient consent for publication

Not required.

Contributors

FQ, EFM, KLV, KE, and AD contributed to the concept and study design. BT, and FQ contributed to acquisition, curation and analysis of data. FQ, EFM, NAM, BT, and AD drafted the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Data Availablity statement

Data are publicly available at the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database: https://wonder.cdc.gov/mcd.html

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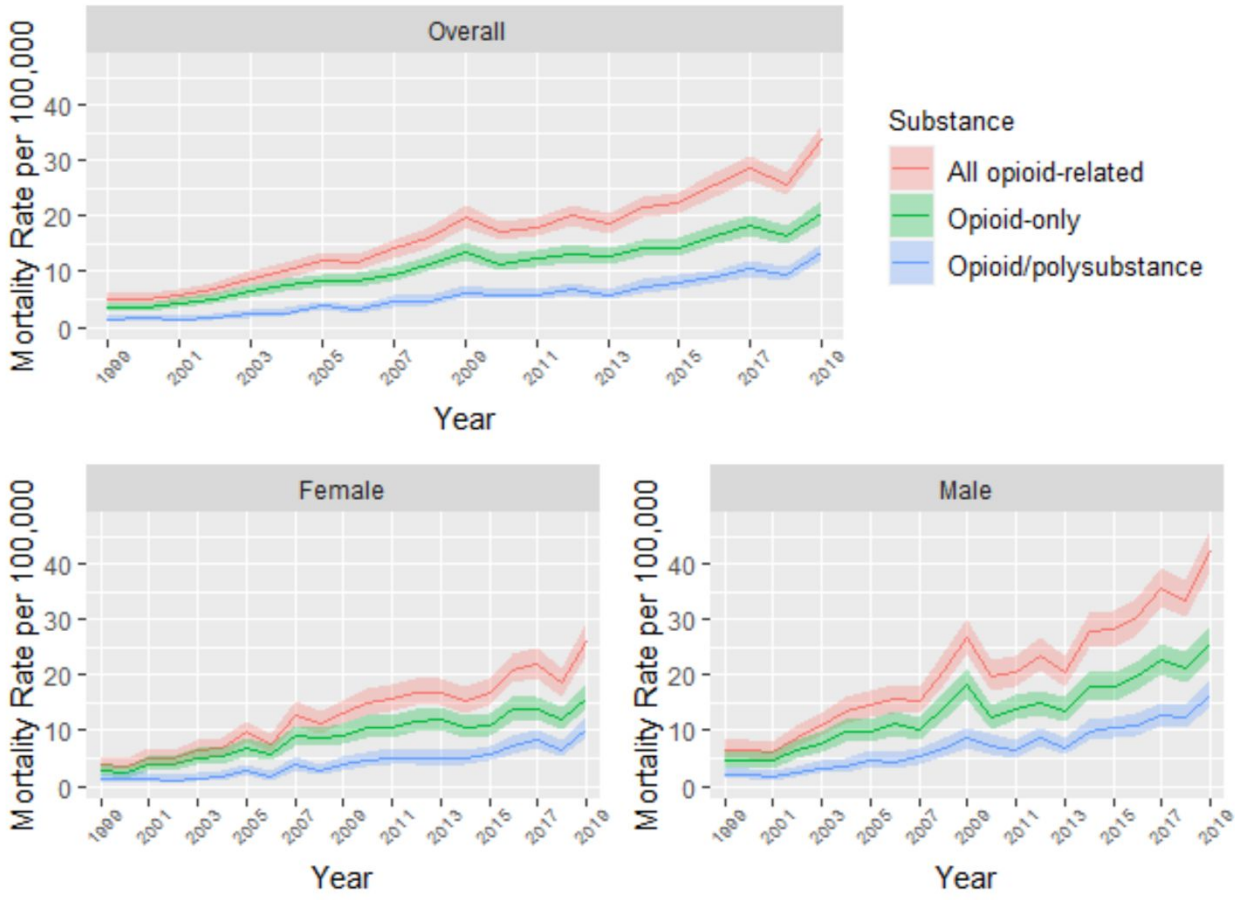

Figure 1: Trends in opioid death rates among US NH-AI/AN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);
Opioid/polysubstance (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T51.0, T51.1, T51.9);
All-opioid related: sum of "opioid-only" and "opioid/polysubstance"

Table 1: Trends in opioid death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
All opioid-related	5.2 (4.2, 6.3)	5.0 (4.1, 6.1)	5.7 (4.6, 6.8)	6.8 (5.7, 8.0)	8.6 (7.3, 10.0)	10 (8.7, 11.5)	12.0 (10.5, 13.5)	11.5 (10.0, 13.0)	14.1 (12.5, 15.8)	16.0 (14.3, 17.8)	19.8 (17.9, 21.7)	17.3 (15.5, 19.1)	18.0 (16.2, 19.9)	20.0 (18.2, 22.0)	18.5 (16.8, 20.4)	21.5 (19.6, 23.4)	22.2 (20.3, 24.2)	25.6 (23.5, 27.7)	28.6 (26.4, 30.9)	25.8 (23.8, 28.0)	33.9 (31.5, 36.3)	<0.001
Opioid-only	3.7 (2.8, 4.6)	3.3 (2.5, 4.2)	4.2 (3.3, 5.2)	5.1 (4.1, 6.1)	6.4 (5.3, 7.5)	7.5 (6.3, 8.8)	8.2 (7.0, 9.5)	8.4 (7.2, 9.7)	9.6 (8.3, 11.0)	11.3 (9.9, 12.9)	13.5 (12.0, 15.2)	11.4 (10.0, 12.9)	12.2 (10.8, 13.8)	13.2 (11.7, 14.8)	12.7 (11.2, 14.2)	14.2 (12.6, 15.8)	14.3 (12.7, 15.9)	16.6 (15.0, 18.3)	18.2 (16.5, 20.0)	16.5 (14.8, 18.2)	20.6 (18.7, 22.5)	<0.001
Opioid/polysubstance	1.5 (1.0, 2.1)	1.7 (1.2, 2.3)	1.5 (1.0, 2.1)	1.7 (1.2, 2.3)	2.2 (1.6, 3.0)	2.5 (1.9, 3.3)	3.8 (2.9, 4.7)	3.1 (2.3, 3.9)	4.5 (3.6, 5.5)	4.7 (3.8, 5.6)	6.2 (5.2, 7.4)	5.9 (4.9, 6.9)	5.8 (4.8, 6.8)	6.8 (5.8, 8.0)	5.9 (4.9, 6.9)	7.3 (6.2, 8.5)	8.0 (6.8, 9.2)	9.0 (7.8, 10.2)	10.4 (9.1, 11.8)	9.4 (8.1, 10.7)	13.3 (11.8, 14.8)	<0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2199588	2222736	2243570	2265155	2285417	
Female																						
All opioid-related	3.9 (2.7, 5.3)	3.6 (2.5, 5.0)	5.2 (3.8, 6.7)	4.9 (3.6, 6.4)	6.4 (4.9, 8.1)	6.8 (5.3, 8.5)	9.6 (7.8, 11.6)	7.6 (6.0, 9.4)	12.9 (10.8, 15.2)	11.3 (9.4, 13.4)	13.1 (11, 15.4)	15.0 (12.8, 17.4)	15.7 (13.4, 18.1)	16.8 (14.4, 19.3)	16.7 (14.4, 19.2)	15.3 (13.1, 17.7)	16.7 (14.4, 19.1)	21.0 (18.4, 23.7)	22.1 (19.4, 24.9)	18.5 (16.1, 21.0)	26.1 (23.2, 29.1)	<0.001
Opioid-only	2.8 (1.8, 4.0)	2.2 (1.4, 3.3)	3.9 (2.7, 5.2)	3.8 (2.7, 5.2)	5.1 (3.8, 6.6)	5.2 (3.9, 6.7)	6.8 (5.3, 8.5)	5.9 (4.5, 7.4)	9.0 (7.3, 10.9)	8.6 (6.9, 10.5)	9.1 (7.4, 11)	10.6 (8.7, 12.6)	10.6 (8.7, 12.6)	11.7 (9.8, 13.9)	11.9 (9.9, 14)	10.5 (8.7, 12.5)	11.0 (9.1, 13)	13.8 (11.7, 16)	13.8 (11.8, 16.0)	12.0 (10.1, 14)	15.8 (13.6, 18.1)	<0.001
Opioid/polysubstance	1.1 (0.5, 1.9)	1.4 (0.7, 2.2)	1.3 (0.7, 2.1)	1.0 (0.5, 1.8)	1.3 (0.7, 2.1)	1.6 (0.9, 2.5)	2.8 (1.8, 3.9)	1.8 (1.0, 2.7)	3.9 (2.8, 5.2)	2.7 (1.8, 3.8)	4.0 (2.9, 5.3)	4.4 (3.3, 5.8)	5.1 (3.8, 6.5)	5.0 (3.8, 6.5)	4.8 (3.6, 6.2)	4.8 (3.6, 6.2)	5.7 (4.4, 7.1)	7.2 (5.7, 8.8)	8.3 (6.7, 10.0)	6.5 (5.2, 8.1)	10.3 (8.6, 12.2)	<0.001
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
All opioid-related	6.5 (4.9, 8.3)	6.5 (4.9, 8.3)	6.2 (4.7, 7.9)	8.8 (7.0, 10.8)	10.9 (8.9, 13.1)	13.4 (11.1, 15.8)	14.4 (12.1, 16.9)	15.5 (13.1, 18.1)	15.4 (13.0, 17.9)	20.9 (18.2, 23.9)	26.8 (23.7, 30.1)	19.7 (17.0, 22.5)	20.4 (17.8, 23.3)	23.5 (20.6, 26.5)	20.5 (17.9, 23.3)	27.9 (24.8, 31.2)	28.1 (25.0, 31.3)	30.4 (27.2, 33.7)	35.5 (32.1, 39.1)	33.6 (30.2, 37.1)	42.1 (38.4, 46.0)	<0.001
Opioid-only	4.6 (3.3, 6.2)	4.5 (3.2, 6.0)	4.5 (3.2, 6.0)	6.4 (4.9, 8.1)	7.7 (6.0, 9.6)	9.9 (8.0, 12)	9.7 (7.8, 11.7)	11.1 (9.1, 13.3)	10.2 (8.3, 12.3)	14.2 (12.0, 16.6)	18.2 (15.6, 20.9)	12.3 (10.2, 14.6)	14.0 (11.8, 16.4)	14.8 (12.5, 17.2)	13.5 (11.4, 15.9)	18.0 (15.5, 20.6)	17.7 (15.3, 20.3)	19.6 (17.0, 22.3)	22.8 (20.0, 25.7)	21.2 (18.6, 24.0)	25.6 (22.7, 28.7)	<0.001
Opioid/polysubstance	1.9 (1.1, 2.9)	2 (1.2, 3.0)	1.7 (0.9, 2.6)	2.4 (1.5, 3.5)	3.2 (2.2, 4.4)	3.5 (2.4, 4.8)	4.8 (3.5, 6.3)	4.4 (3.2, 5.8)	5.2 (3.9, 6.7)	6.7 (5.2, 8.5)	8.6 (6.9, 10.5)	7.3 (5.8, 9.1)	6.5 (5.0, 8.1)	8.7 (7.0, 10.6)	7.0 (5.5, 8.6)	9.9 (8.1, 11.9)	10.4 (8.5, 12.4)	10.8 (8.9, 12.8)	12.7 (10.7, 14.9)	12.3 (10.3, 14.5)	16.5 (14.2, 18.9)	<0.001
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072179	1083032	1092738	1102570	1112108	

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);
Opioid/polysubstance(underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T51.0, T51.1, T51.9);
All-opioid related: sum of "opioid-only" and "opioid/polysubstance"

[2] Non-parametric Jonckheere-Terpstra Test for trend

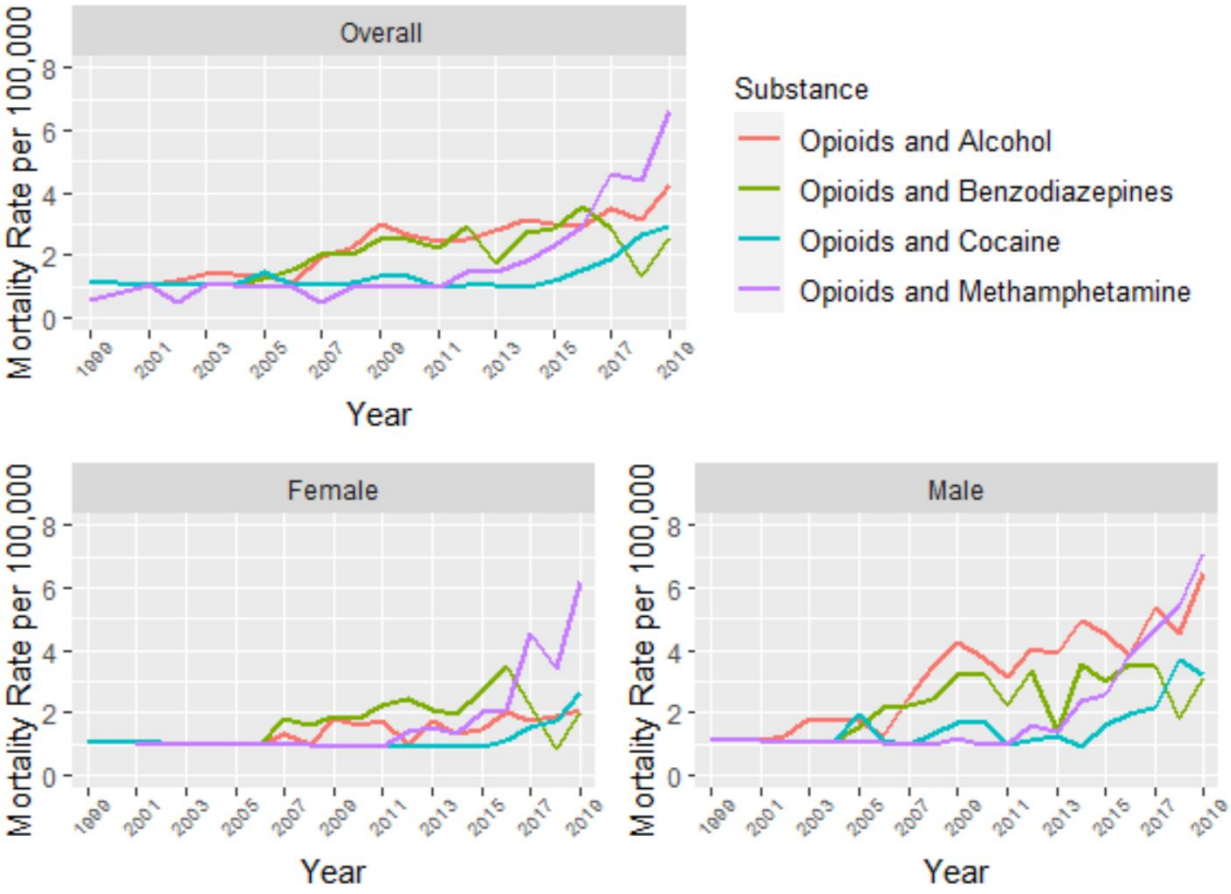

Figure 2: Trends in opioid combination[1] death rates among US NH-AI/AN 12 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

Table 2: Trends in opioid combination[1] death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by substance combination type

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Opioids and Alcohol	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.2 (0.7, 1.7)	1.4 (0.9, 2.0)	1.4 (0.9, 2.0)	1.4 (0.9, 1.9)	1.1 (0.7, 1.6)	1.9 (1.4, 2.6)	2.2 (1.6, 2.9)	3.0 (2.3, 3.8)	2.7 (2.0, 3.4)	2.4 (1.8, 3.1)	2.5 (1.9, 3.2)	2.8 (2.1, 3.5)	3.1 (2.4, 3.9)	3.0 (2.3, 3.8)	2.9 (2.3, 3.7)	3.5 (2.8, 4.3)	3.2 (2.5, 4.0)	4.2 (3.4, 5.1)	<0.001
Opioids and Benzodiazepines	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.3 (0.8, 1.8)	1.6 (1.1, 2.1)	2.0 (1.5, 2.7)	2.0 (1.4, 2.7)	2.5 (1.9, 3.3)	2.5 (1.9, 3.2)	2.2 (1.6, 2.9)	2.9 (2.2, 3.7)	1.8 (1.3, 2.4)	2.8 (2.1, 3.5)	2.9 (2.2, 3.6)	3.6 (2.8, 4.4)	2.9 (2.2, 3.6)	1.3 (0.9, 1.8)	2.6 (2.0, 3.3)	<0.001
Opioids and Cocaine	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.5 (1.0, 2.1)	1.1 (0.7, 1.5)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.3 (0.9, 1.9)	1.4 (0.9, 1.9)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.1 (0.7, 1.5)	1.0 (0.6, 1.4)	1.2 (0.8, 1.7)	1.5 (1.1, 2.1)	1.9 (1.3, 2.5)	2.7 (2.1, 3.4)	2.9 (2.3, 3.7)	0.14
Opioids and Methamphetamine	0.6 (0.3, 1.0)	-	1.1 (0.7, 1.6)	0.5 (0.3, 0.9)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	0.5 (0.2, 0.8)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.0 (0.6, 1.4)	1.0 (0.6, 1.4)	1.5 (1.0, 2.1)	1.5 (1.0, 2)	1.8 (1.3, 2.4)	2.3 (1.7, 3.1)	3.0 (2.3, 3.7)	4.6 (3.7, 5.5)	4.4 (3.6, 5.3)	6.7 (5.6, 7.7)	0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2199688	2222736	2243570	2265155	2285417	
Female																						
Opioids and Alcohol	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.4 (0.7, 2.2)	1.0 (0.5, 1.6)	1.8 (1.1, 2.7)	1.6 (0.9, 2.5)	1.8 (1.1, 2.6)	1.0 (0.5, 1.7)	1.7 (1.0, 2.6)	1.3 (0.8, 2.1)	1.5 (0.9, 2.3)	2.0 (1.3, 2.9)	1.7 (1.1, 2.6)	1.9 (1.2, 2.8)	2.1 (1.4, 3.0)	0.01
Opioids and Benzodiazepines	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.8 (1.1, 2.8)	1.6 (0.9, 2.5)	1.9 (1.2, 2.8)	1.8 (1.1, 2.7)	2.2 (1.4, 3.2)	2.5 (1.6, 3.5)	2.1 (1.3, 3.0)	2 (1.2, 2.9)	2.7 (1.9, 3.9)	3.5 (2.5, 4.7)	2.3 (1.5, 3.2)	0.9 (0.4, 1.5)	2.0 (1.3, 2.9)	0.01
Opioids and Cocaine	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.1 (0.5, 1.8)	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	1.0 (0.5, 1.7)	0.9 (0.4, 1.6)	0.9 (0.4, 1.5)	1.0 (0.5, 1.6)	0.9 (0.4, 1.6)	1.1 (0.6, 1.8)	1.6 (0.9, 2.4)	1.7 (1.1, 2.6)	2.6 (1.8, 3.7)	0.49
Opioids and Methamphetamine	-	-	1.1 (0.5, 1.8)	-	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	-	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.4, 1.6)	1.4 (0.8, 2.2)	1.5 (0.9, 2.4)	1.3 (0.8, 2.1)	2.0 (1.3, 3.0)	2.1 (1.3, 3.0)	4.5 (3.4, 5.8)	3.4 (2.5, 4.6)	6.2 (4.9, 7.7)	0.02
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
Opioids and Alcohol	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.3 (0.7, 2.1)	1.8 (1.1, 2.8)	1.8 (1.0, 2.7)	1.8 (1, 2.7)	1.2 (0.6, 2.0)	2.5 (1.6, 3.6)	3.5 (2.5, 4.8)	4.3 (3.1, 5.7)	3.8 (2.7, 5.1)	3.1 (2.1, 4.3)	4.1 (2.9, 5.4)	3.9 (2.8, 5.2)	5.0 (3.7, 6.4)	4.6 (3.4, 5.9)	3.9 (2.8, 5.1)	5.4 (4.1, 6.9)	4.5 (3.4, 5.9)	6.5 (5.1, 8.1)	<0.001
Opioids and Benzodiazepines	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.2 (0.6, 1.9)	1.6 (0.9, 2.4)	2.2 (1.3, 3.2)	2.2 (1.4, 3.3)	2.4 (1.5, 3.5)	3.2 (2.2, 4.4)	3.3 (2.3, 4.5)	2.2 (1.4, 3.3)	3.4 (2.4, 4.6)	1.4 (0.8, 2.2)	3.6 (2.5, 4.8)	3.0 (2.0, 4.2)	3.6 (2.6, 4.8)	3.5 (2.5, 4.7)	1.8 (1.1, 2.7)	3.1 (2.2, 4.3)	<0.001
Opioids and Cocaine	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.2 (0.6, 1.9)	2.0 (1.2, 3.0)	1.1 (0.6, 1.9)	1.0.0 (0.5, 1.7)	1.3 (0.7, 2.1)	1.7 (1.0, 2.6)	1.8 (1.1, 2.7)	1.0 (0.5, 1.7)	1.2 (0.6, 1.9)	1.2 (0.7, 2.0)	0.9 (0.5, 1.6)	1.6 (0.9, 2.5)	1.9 (1.2, 2.9)	2.2 (1.4, 3.2)	3.7 (2.7, 4.9)	3.2 (2.3, 4.4)	0.02
Opioids and Methamphetamine	1.2 (0.6, 2.0)	-	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.8)	1 (0.5, 1.7)	1.0 (0.5, 1.7)	1.2 (0.6, 2.0)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.6 (1.0, 2.5)	1.4 (0.8, 2.2)	2.4 (1.5, 3.4)	2.6 (1.7, 3.9)	3.9 (2.8, 5.1)	4.7 (3.5, 6.0)	5.4 (4.2, 6.9)	7.1 (5.6, 8.8)	0.02
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072179	1083032	1092738	1102570	1112108	

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

[2] Non-parametric Jonckheere-Terpstra Test for trend

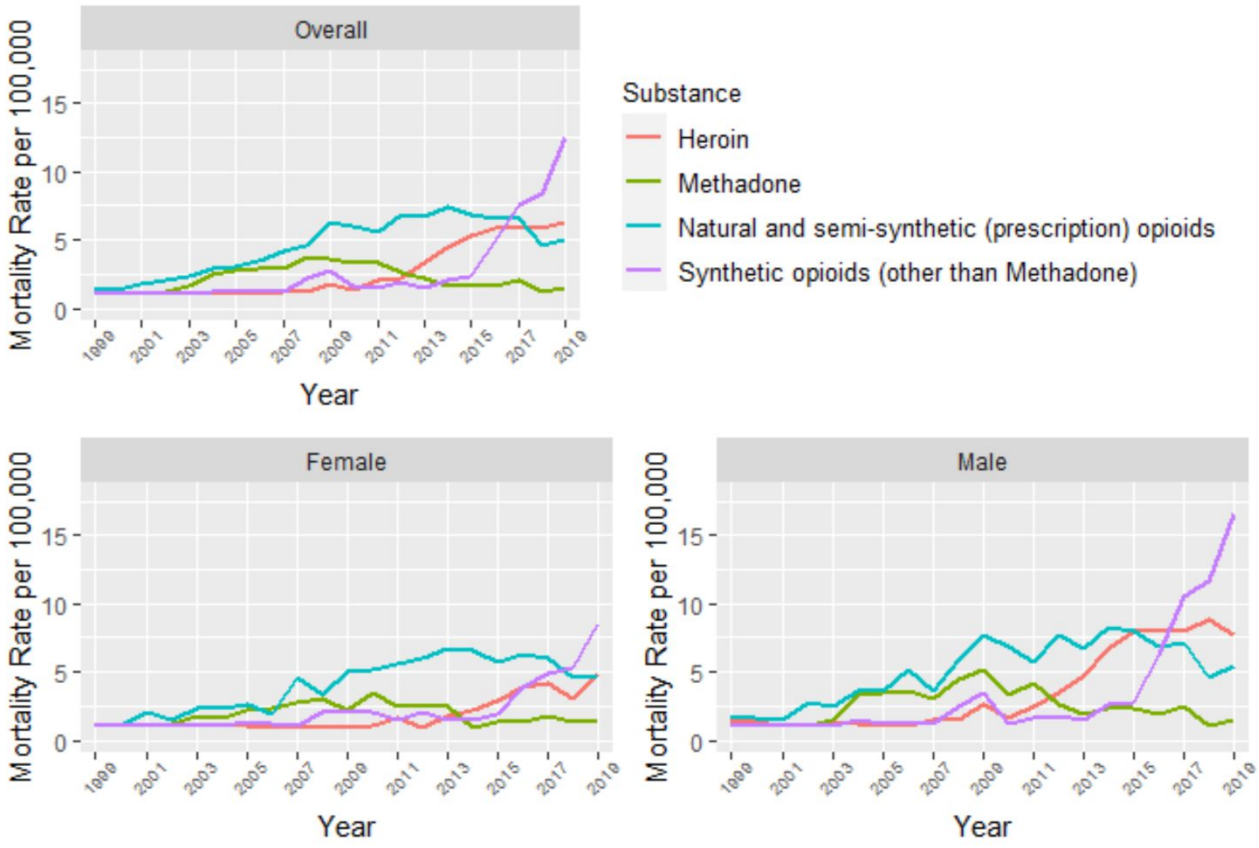

Figure 3: Trends in opioid death rates among US NH-AI/AN 12 and older by individual opioid types[1]

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.1);
Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.2);
Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.3);
Synthetic opioids other than methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.4)

Table 3: Trends in opioid death rates per 100,000 (95% CI) among US NH-AIAN 12 and older by individual opioid type[1]

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Heroin	1.2 (0.7, 1.8)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.2 (0.8, 1.7)	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.5)	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	1.8 (1.2, 2.4)	1.4 (0.9, 1.9)	2.1 (1.5, 2.8)	2.2 (1.6, 2.8)	3.3 (2.5, 4.1)	4.4 (3.6, 5.3)	5.3 (4.4, 6.3)	5.9 (4.9, 6.9)	6.1 (5.1, 7.1)	5.9 (4.9, 6.9)	6.3 (5.3, 7.3)	<0.001
Methadone	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.2 (0.7, 1.7)	1.6 (1.1, 2.2)	2.5 (1.8, 3.2)	2.8 (2.1, 3.6)	3.0 (2.3, 3.8)	2.9 (2.2, 3.7)	3.7 (2.9, 4.6)	3.7 (2.9, 4.5)	3.4 (2.6, 4.2)	3.3 (2.6, 4.2)	2.6 (1.9, 3.3)	2.2 (1.6, 2.9)	1.6 (1.1, 2.1)	1.8 (1.3, 2.4)	1.7 (1.2, 2.2)	2.1 (1.5, 2.7)	1.2 (0.8, 1.7)	1.4 (1.0, 2.0)	0.70
Natural and semi-synthetic (prescription) opioids	1.4 (0.9, 2.0)	1.3 (0.8, 1.9)	1.8 (1.2, 2.4)	2.1 (1.5, 2.8)	2.4 (1.8, 3.1)	2.9 (2.2, 3.7)	3.1 (2.4, 3.9)	3.5 (2.7, 4.4)	4.2 (3.3, 5.1)	4.6 (3.7, 5.5)	6.3 (5.3, 7.5)	6.0 (5.0, 7.1)	5.6 (4.7, 6.7)	6.9 (5.8, 8.0)	6.7 (5.6, 7.8)	7.4 (6.3, 8.6)	6.8 (5.8, 8.0)	6.5 (5.5, 7.6)	6.6 (5.5, 7.7)	4.5 (3.7, 5.5)	5.1 (4.2, 6.0)	<0.001
Synthetic opioids (other than methadone)	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.2 (0.8, 1.8)	1.3 (0.8, 1.8)	1.3 (0.9, 1.8)	1.1 (0.7, 1.7)	2.2 (1.6, 2.9)	2.8 (2.1, 3.5)	1.6 (1.1, 2.2)	1.5 (1.0, 2.1)	1.9 (1.4, 2.6)	1.5 (1.1, 2.1)	2.0 (1.5, 2.7)	2.3 (1.7, 3.0)	5.1 (4.2, 6.1)	7.6 (6.5, 8.8)	8.4 (7.3, 9.7)	12.5 (11.1, 14.0)	<0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2159688	2222736	2243570	2265155	2285417	
Female																						
Heroin	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	1.0 (0.5, 1.7)	1.7 (1.0, 2.5)	0.9 (0.4, 1.6)	1.8 (1.1, 2.7)	2.2 (1.4, 3.2)	2.8 (1.9, 3.9)	3.9 (2.8, 5.1)	4.2 (3.1, 5.4)	3.1 (2.2, 4.2)	4.9 (3.7, 6.2)	0.056
Methadone	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.2 (0.6, 2.0)	1.7 (1, 2.6)	1.6 (0.9, 2.5)	2.2 (1.4, 3.2)	2.3 (1.5, 3.4)	2.7 (1.8, 3.8)	3.0 (2.0, 4.1)	2.2 (1.4, 3.2)	3.5 (2.5, 4.7)	2.5 (1.7, 3.5)	2.6 (1.7, 3.6)	2.5 (1.7, 3.6)	0.9 (0.4, 1.5)	1.3 (0.7, 2.0)	1.4 (0.8, 2.2)	1.7 (1.1, 2.6)	1.4 (0.8, 2.1)	1.4 (0.8, 2.2)	0.32
Natural and semi-synthetic (prescription) opioids	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	2.0 (1.2, 3.0)	1.4 (0.8, 2.3)	2.3 (1.5, 3.4)	2.3 (1.5, 3.3)	2.6 (1.7, 3.7)	2.0 (1.2, 2.9)	4.6 (3.4, 6.1)	3.4 (2.3, 4.6)	5.0 (3.8, 6.5)	5.2 (3.9, 6.6)	5.6 (4.3, 7.1)	6.1 (4.7, 7.6)	6.7 (5.3, 8.3)	6.5 (5.1, 8.1)	5.7 (4.4, 7.1)	6.2 (4.9, 7.8)	6.0 (4.7, 7.5)	4.6 (3.4, 5.9)	4.8 (3.6, 6.1)	<0.001
Synthetic opioids (other than methadone)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.3 (0.7, 2.1)	1.3 (0.7, 2.1)	1.1 (0.5, 1.8)	2.0 (1.2, 3.0)	2.2 (1.4, 3.2)	2.0 (1.2, 2.9)	1.5 (0.8, 2.3)	2.1 (1.3, 3.1)	1.5 (0.9, 2.4)	1.5 (0.9, 2.3)	1.9 (1.2, 2.7)	3.9 (2.9, 5.2)	4.9 (3.7, 6.2)	5.3 (4.1, 6.7)	8.6 (7.0, 10.4)	<0.001
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
Heroin	1.3 (0.6, 2.1)	1.3 (0.7, 2.2)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.4 (0.7, 2.2)	1.3 (0.7, 2.1)	1.0 (0.5, 1.8)	1.1 (0.6, 1.9)	1.5 (0.9, 2.4)	1.5 (0.8, 2.4)	2.6 (1.7, 3.7)	1.7 (1.0, 2.6)	2.5 (1.7, 3.6)	3.5 (2.4, 4.7)	4.8 (3.5, 6.2)	6.7 (5.2, 8.3)	7.9 (6.3, 9.6)	8.0 (6.4, 9.8)	8.1 (6.5, 9.8)	8.8 (7.1, 10.6)	7.7 (6.2, 9.5)	<0.001
Methadone	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.5 (0.8, 2.4)	3.4 (2.3, 4.6)	3.4 (2.4, 4.7)	3.6 (2.5, 4.9)	3.1 (2.1, 4.2)	4.4 (3.2, 5.8)	5.2 (3.9, 6.7)	3.3 (2.3, 4.5)	4.2 (3.0, 5.5)	2.6 (1.7, 3.7)	1.9 (1.2, 2.8)	2.3 (1.4, 3.3)	2.3 (1.5, 3.3)	1.9 (1.2, 2.9)	2.5 (1.6, 3.5)	1.0 (0.5, 1.7)	1.4 (0.8, 2.2)	>0.99
Natural and semi-synthetic (prescription) opioids	1.6 (0.9, 2.6)	1.6 (0.9, 2.5)	1.5 (0.8, 2.4)	2.8 (1.8, 4.0)	2.5 (1.6, 3.6)	3.6 (2.5, 4.9)	3.6 (2.5, 4.9)	5.1 (3.8, 6.7)	3.7 (2.6, 4.9)	5.8 (4.4, 7.4)	7.7 (6.1, 9.5)	6.9 (5.3, 8.6)	5.7 (4.3, 7.2)	7.7 (6.1, 9.5)	6.7 (5.2, 8.3)	8.3 (6.7, 10.1)	8.4 (6.8, 9.9)	6.8 (5.4, 8.5)	7.1 (5.6, 8.8)	4.5 (3.4, 5.9)	5.4 (4.1, 6.8)	<0.001
Synthetic opioids (other than methadone)	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.5 (0.8, 2.3)	1.2 (0.6, 2.0)	1.3 (0.7, 2.2)	1.2 (0.6, 2.0)	2.4 (1.5, 3.5)	3.4 (2.4, 4.6)	1.2 (0.6, 2.0)	1.6 (0.9, 2.4)	1.7 (1.0, 2.6)	1.5 (0.9, 2.4)	2.5 (1.7, 3.6)	2.8 (1.9, 3.9)	6.3 (4.9, 7.9)	10.5 (8.7, 12.5)	11.7 (9.8, 13.8)	16.5 (14.2, 19.0)	<0.001
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072079	1083032	1092738	1102570	1112108	

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.1); Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.2); Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.3); Synthetic opioids other than methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.4);[2] Non-parametric Jonckheere-Terpstra Test for trend

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Supplement

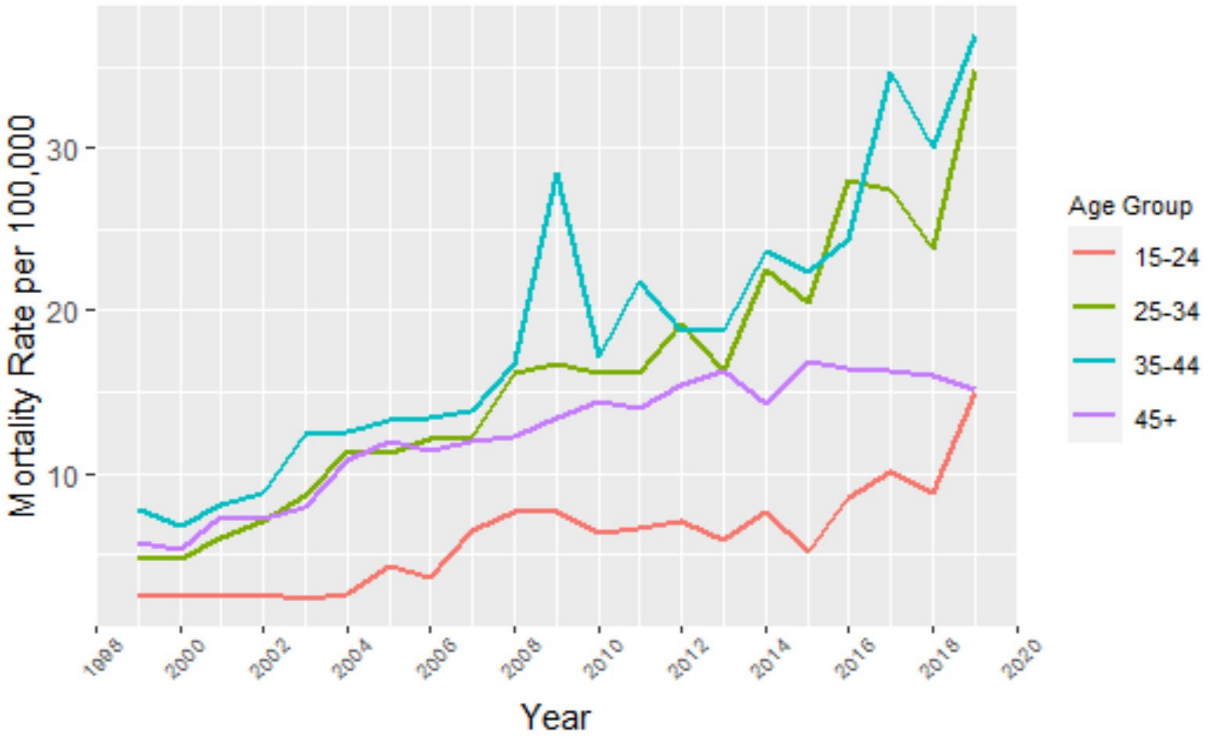

Figure 1a: Trends in opioid-only[1] death rates among US NH-AIAN 15 and older by age groups

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

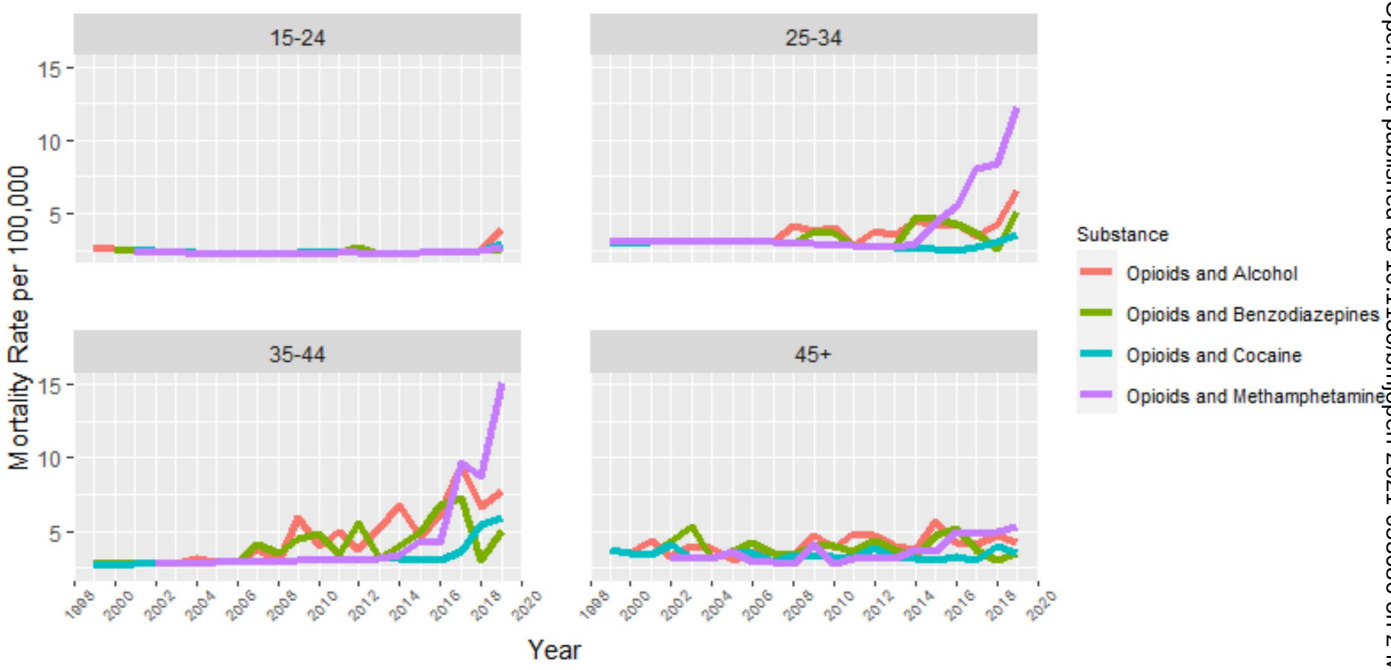

Figure 1b: Trends in opioid combination[1] death rates among US NH-AIAN age groups 15 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9)

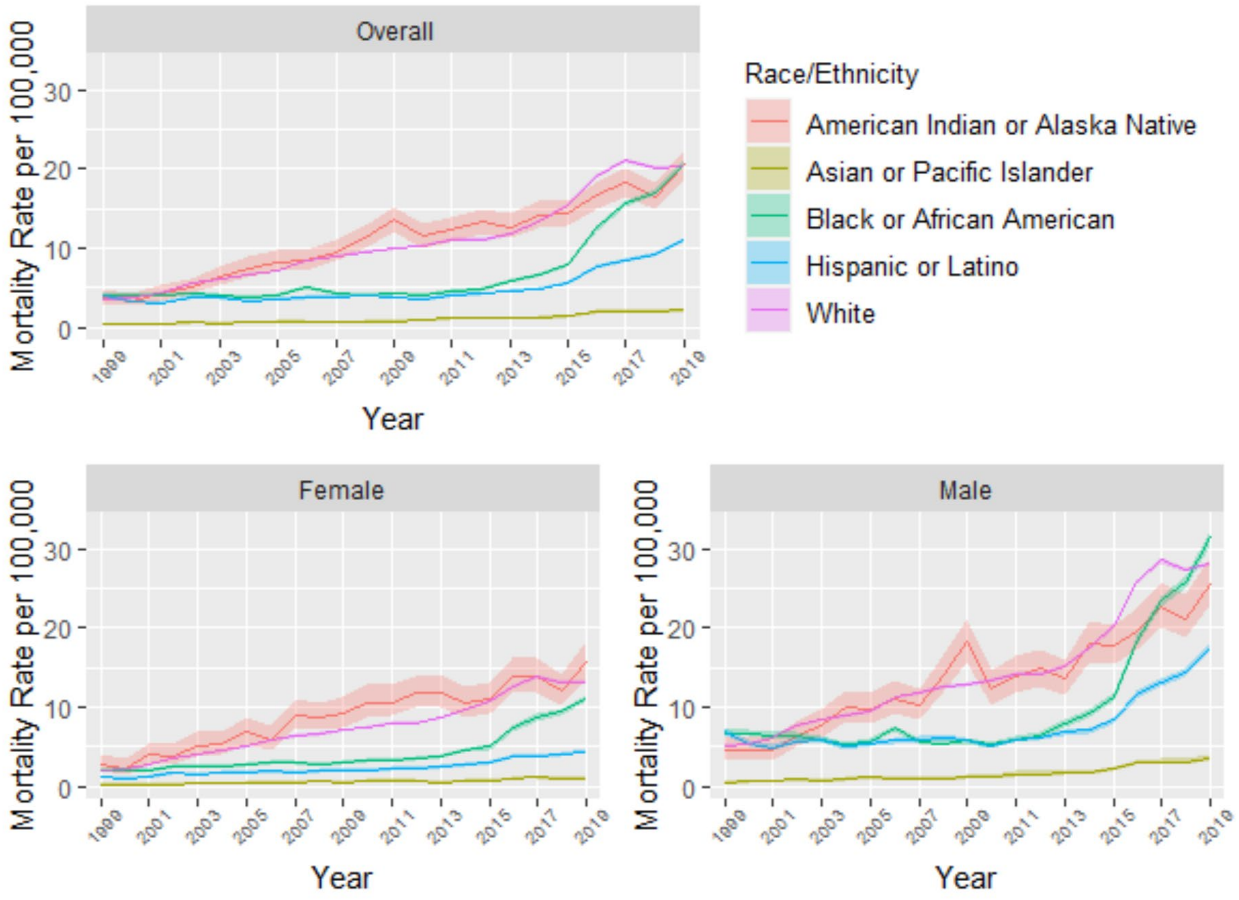

Figure 2a: Trends in opioid-only[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

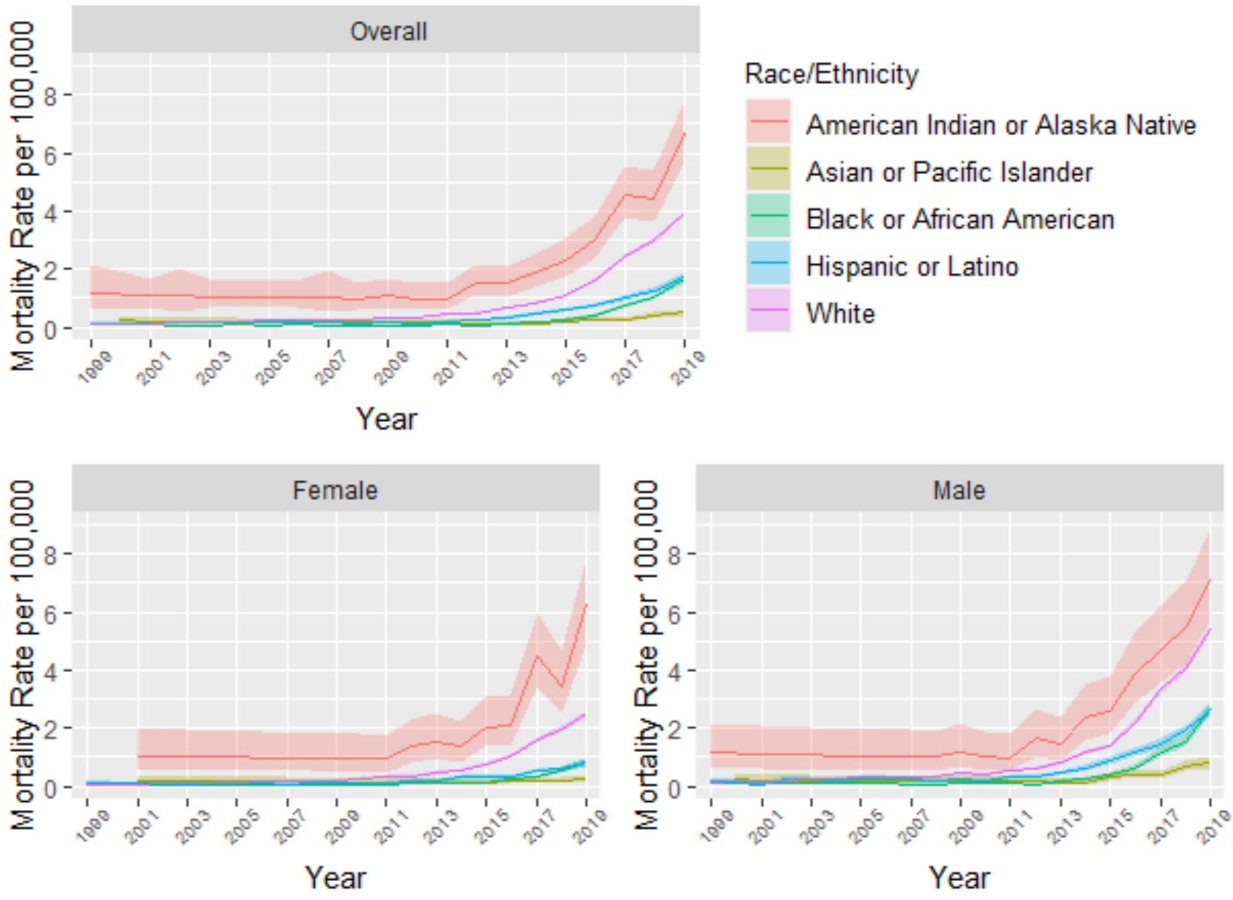

Figure 2b: Trends in opioid and methamphetamine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);

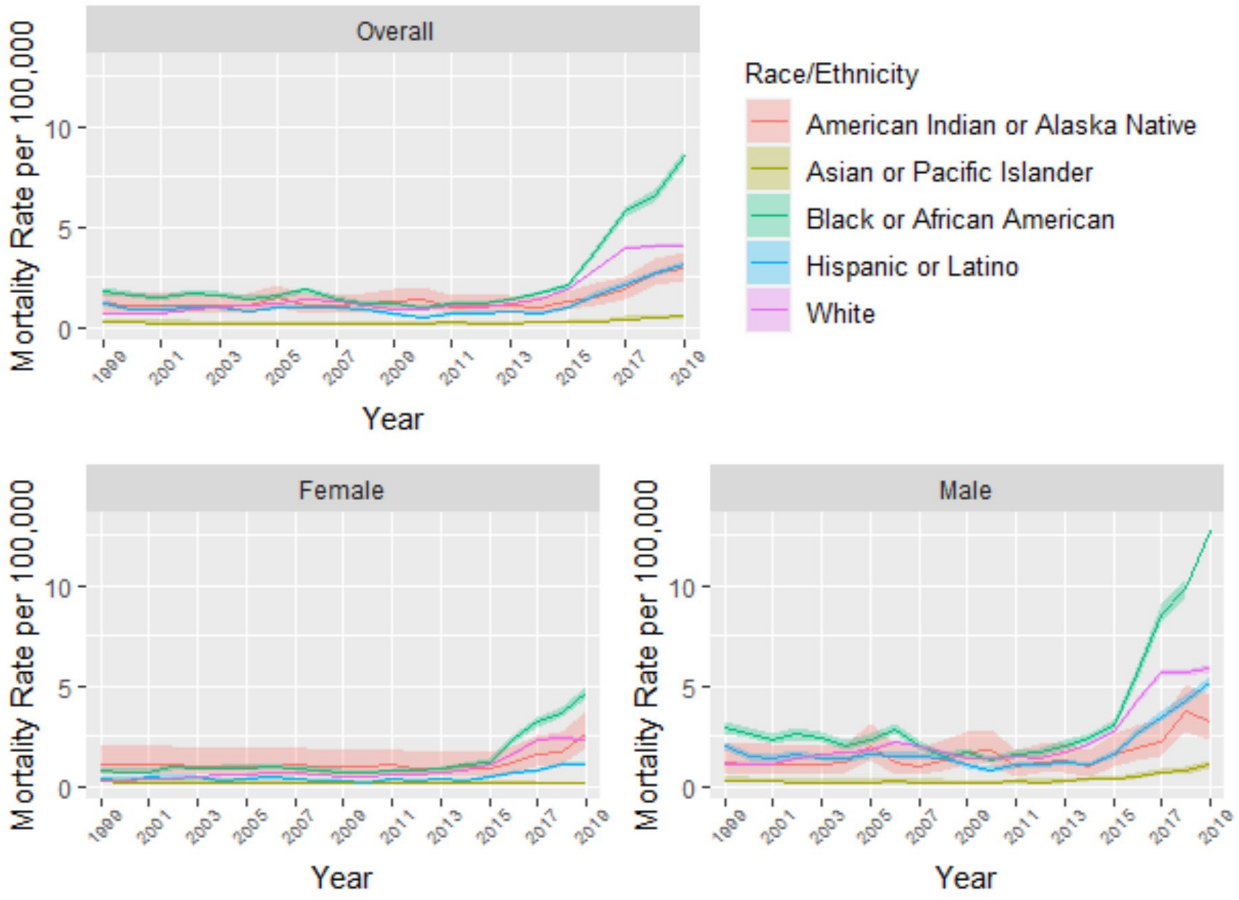

Figure 2c: Trends in opioid and cocaine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5)

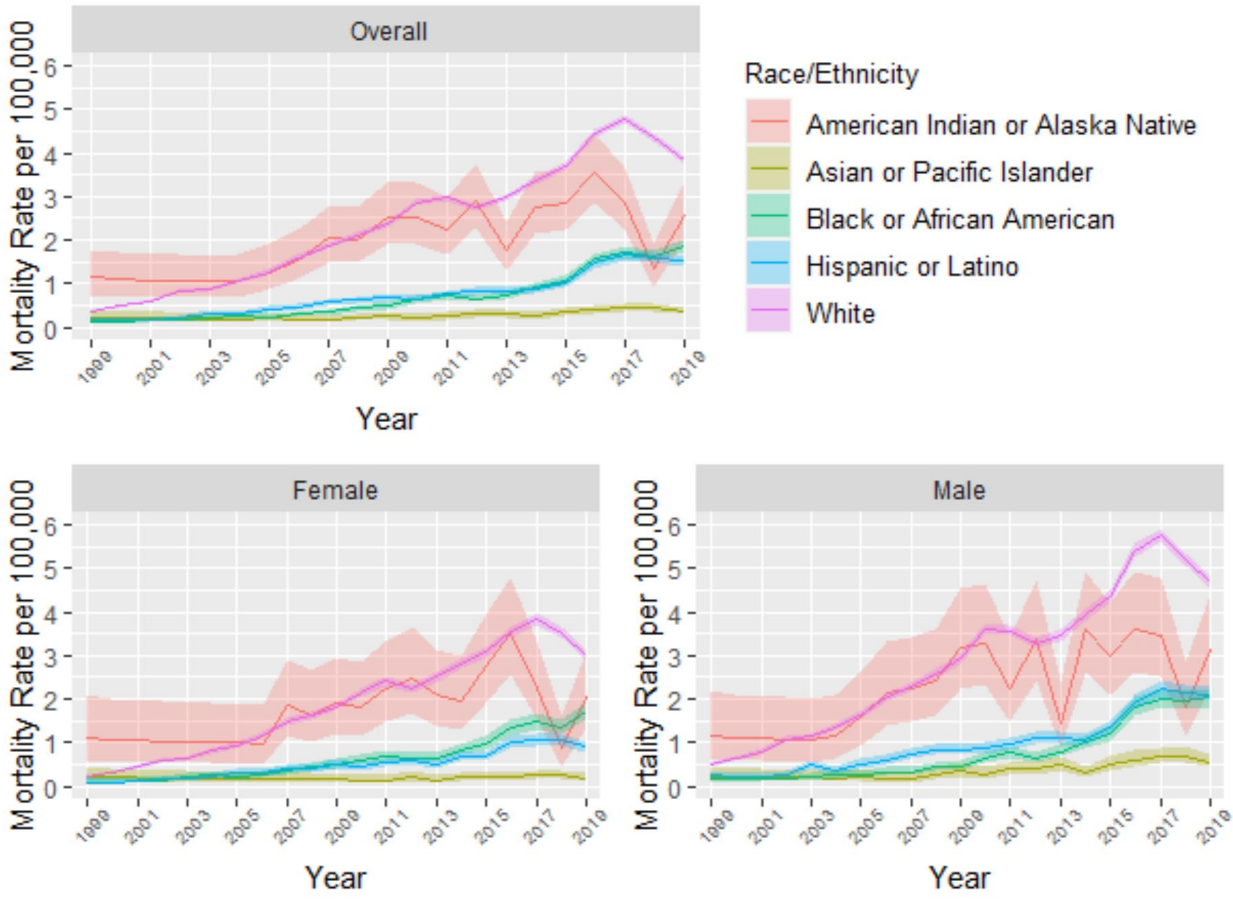

Figure 2d: Trends in opioid and benzodiazepine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4)

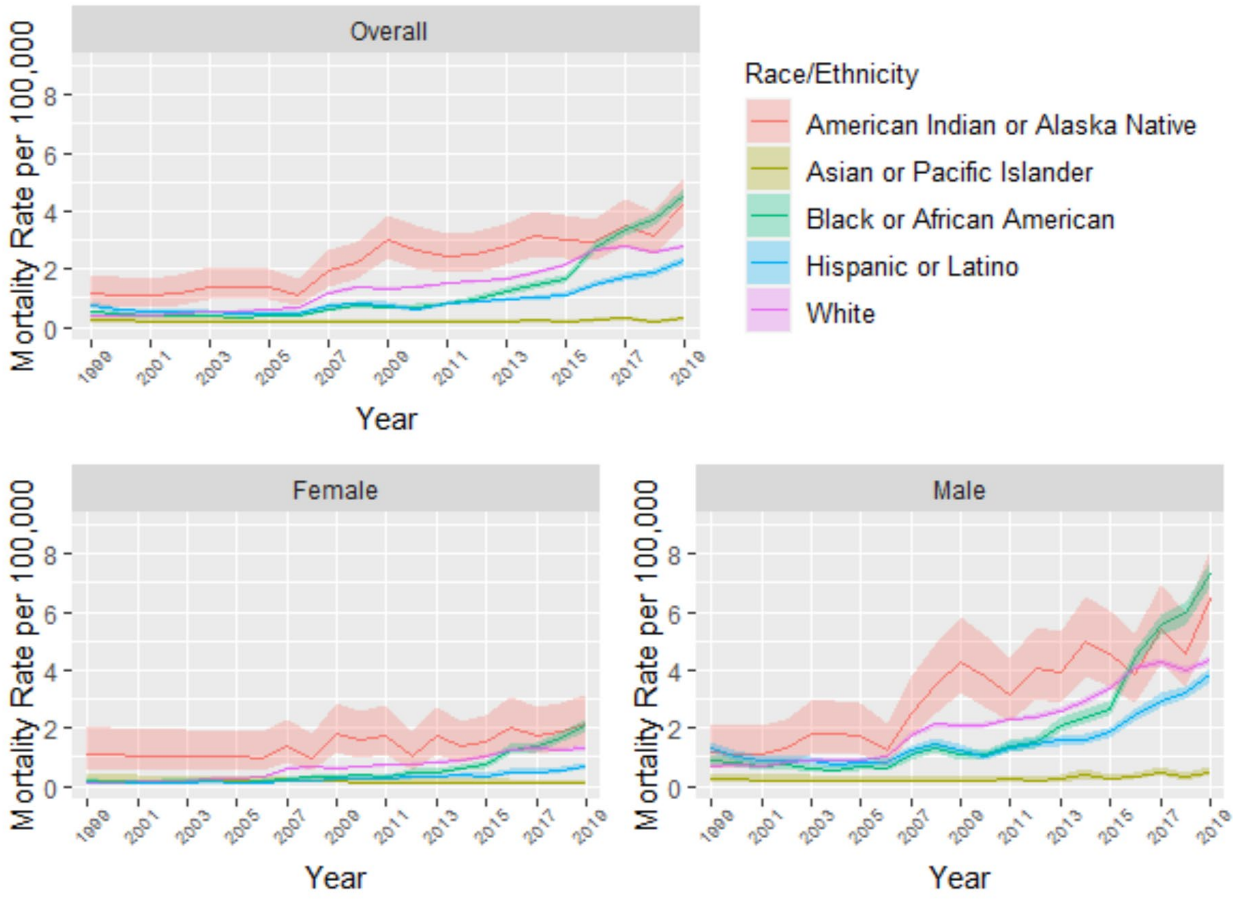

Figure 2e: Trends in opioid and alcohol[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Manuscript page 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Manuscript page 2
Methods			
Study design	4	Present key elements of study design early in the paper	Manuscript page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Manuscript page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Manuscript page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Manuscript page 3-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Manuscript page 3-5
Bias	9	Describe any efforts to address potential sources of bias	Manuscript page 4-5
Study size	10	Explain how the study size was arrived at	Manuscript page 3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Manuscript page 3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Manuscript page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Manuscript page 3-5
		(*c*) Explain how missing data were addressed	Manuscript page 4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Manuscript page 5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	All data captured on aggregate and each analysis scenario looked at different sub-population of patients within AIANs, eligibility criteria described in Manuscript page 3-5
		(b) Give reasons for non-participation at each stage	Manuscript page 3
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Manuscript page 4-7
		(b) Indicate number of participants with missing data for each variable of interest	Manuscript page 4
Outcome data	15*	Report numbers of outcome events or summary measures	Manuscript page 5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Manuscript page 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Manuscript page 7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	_
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Manuscript page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Manuscript page 7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Manuscript page 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Manuscript page 8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Manuscript page 8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	Manuscript page 11

applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Epidemiological trends in opioid-only and opioid/polysubstance–related death rates among American Indian/Alaska Native populations from 1999 – 2019: a retrospective longitudinal ecological study

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Abstract

Objectives: The rate of drug overdose deaths in the U.S. has more than tripled since the turn of the century, and rates are disproportionately high among the American Indian/Alaska Native (AI/AN) population. Little is known about the overall historical trends in AI/AN opioid-only and opioid/polysubstance–related mortality. This study will address this gap.

Design: This is a retrospective longitudinal ecological study.

Setting: U.S. death records from 1999 to 2019 using the Centers for Disease Control and Prevention (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER).

Participants: U.S. Non-Hispanic AI/AN people age 12 years and older.

Measures: The primary outcomes, identified via the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes, included overdose deaths due to (1) opioids only, opioids in combination with any other substance, all-opioid related overdoses; (2) combinations of opioids and alcohol, opioids and methamphetamine, opioids and cocaine, opioids and benzodiazepines; and (3) specific types of opioids.

Results: From 1999-2019, opioid-only mortality rates increased from 2.8 to 15.8 per 100,000 ($P<0.001$) for AI/AN women and 4.6 to 25.6 per 100,000 ($P<0.001$) for AI/AN men. All opioid-related mortality rates increased significantly ($P<0.001$) from 5.2 to 33.9 per 100,000 AI/AN persons, 3.9 to 26.1 for women, and 6.5 to 42.1 for men. AI/AN also exhibited significant increases in mortality rates due to opioids and alcohol, opioids and benzodiazepines, opioids and methamphetamine, and AI/AN men experienced substantial increases in mortality due to opioids and cocaine. Mortality rates by individual opioid types increased significantly over time for heroin, natural and semi-synthetic (prescription), and synthetic opioids (fentanyl/fentanyl analogs) other than methadone.

Conclusions: These findings highlight magnification over time in opioid-related deaths and may point to broader systemic factors that may disproportionately affect members of AI/AN communities and drive inequities.

Strengths and limitations of this study

- This is one of the first studies to consider the historical trends of opioid overdose mortality in the AI/AN population across the United States, with particular attention given to how co-use of opioids with certain substances contributes to drug overdose mortality in this population.
- This study offers stratified results by sex and compares mortality rates between NH AI/AN populations and other race/ethnicity groups to better identify sub-populations at risk of overdose death.
- This study provides insight into trends about opioid overdose mortality in the AI/AN population by specific opioid types, which can help guide harm reduction and public health prevention efforts for AI/AN communities.
- Due to data-use agreement requirements, subgroup data with small counts could not be disaggregated.
- Age-adjusted rates could not be obtained because they require larger sample sizes to avoid data suppression for small sample sizes.

Keywords: American Indian/Alaska Native; opioid use; opioid-related mortality, polysubstance use; epidemiology; trends

INTRODUCTION

Over the past two decades, the rate of drug overdose deaths in the United States (U.S.) has more than tripled.[1] This spike in overdoses, described as a public health crisis, has grown more destructive with time.[1,2] The American Indian(s)/Alaska Native(s) (AI/AN) population has been disproportionately affected by drug-related mortality. From 1999 to 2015, drug overdose mortality among metropolitan AI/AN populations increased from 7.1 per 100,000 to 22.1 per 100,000, representing a 261% change from 1999. [3] A magnified pattern was observed in non-metro AI/AN populations, whose overdose mortality rate climbed steeply from 3.9 per 100,000 in 1999 to 19.8 per 100,000 in 2015, representing a 519% increase. [3] Other groups also experienced rises in drug overdoses over this same period but at lower rates of change.[3]

Opioid overdose fatalities among AI/AN and non-Hispanic White populations both rose dramatically since 1999, surpassing national rates in all years since 2002. [4] While non-Hispanic White populations exhibit the highest rates since 2014, AI/AN populations demonstrate the second highest opioid overdose mortality across U.S. racial and ethnic groups. In 1999, the AI/AN opioid overdose mortality rate was 2.9 per 100,000 and had risen to 17.0 deaths per 100,000 by 2019.[4] Regional variations also exist in this trend among AI/AN populations. From 1999-2016, higher mortality rates from opioids among AI/AN were observed in states in the Pacific Northwest, and Great Lakes Region.[5] During 2013–2015, mortality rates among AI/AN populations in Washington state were 2.7 higher than rates among non-Hispanic White populations for all opioid-involved overdoses.[6]

The literature also points to variations in overdose rates from specific opioid types. Increases in overdose due to synthetic opioids, primarily driven by illicitly manufactured fentanyl, have contributed to the bulk of U.S. opioid-involved fatalities in recent years.[7,8] From

2017 to 2018, overdose death rates from synthetic opioids other than methadone among AI/AN populations increased from 6.5 per 100,000 to 7.3 per 100,000 deaths.[9] Compared to non-Hispanic Whites and non-Hispanic Blacks, AI/AN overdose rates from synthetic opioids were lower, but AI/AN rates were higher than Hispanic and Pacific Islander rates.[9] Additionally, while the U.S. has seen recent declines in heroin overdoses, decreases observed among AI/AN populations are modest compared to other racial and ethnic populations.[9]

Regarding polysubstance use, the literature suggests that people who use opioids often use other drugs concurrently, thereby creating drug interactions that can increase overdose risk.[10] The co-use of opioids with some other drugs may be of particular concern for AI/AN populations, as treatment admission data from the Treatment Episode Data Set (TEDS) demonstrated that among U.S. racial groups, AI/AN respondents consistently reported the highest rates of individuals entering treatment with concurrent use of methamphetamine and heroin each year from 2008 to 2017.[11]

The reasons for higher rates of drug overdose among Indigenous people are many but likely originate from a persistent legacy of colonialism, racism and intergenerational trauma.[12,13] This legacy is often complicated by current social, economic, and health disadvantages experienced by many AI/AN populations.[12-14] Taken together, these circumstances provide the ideal for increased risk of overdose.[12,15]

Although previous reports show AI/AN populations across the U.S. have experienced elevated rates of drug overdose deaths, the significance of historical trends in drug-related death rates among AI/AN populations remains unclear, especially regarding trends in deaths related to polysubstance use, which have risen dramatically in the general U.S. population in recent years. Deaths involving psychostimulants (e.g., cocaine, methamphetamine, MDMA, and prescription

stimulants) increased by over 30% between 2016 and 2017 across the U.S., and in 2017, over 70% of cocaine-involved overdose deaths and 50% of other psychostimulant-involved overdose deaths involved at least one opioid.[16] This study provides foundational knowledge on overdose deaths involving opioids among AI/AN populations by analyzing the historical patterns of opioid-only and opioid/polysubstance–related deaths.

METHODS

Settings

This is a retrospective longitudinal ecological study that uses serial cross-sectional data to analyze historical patterns of opioid-only and polysubstance-involved opioid overdose deaths among AI/AN populations. Specifically, this retrospective observational study used publicly available data from the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. Data on drug overdose deaths due to opioids and combinations of opioids with either alcohol, benzodiazepines, cocaine, or methamphetamine were obtained from the CDC WONDER's National Center for Health Statistics Mortality database (NCHS). This database contains county-level data comprising both mortality and population counts across all fifty United States and the District of Columbia. Mortality data were captured by either 1) being coded by states and provided to NCHS per the Vital Statistics Cooperative Program or 2) state registration offices providing copies of physical death certificates to the NCHS to be coded by the NCHS itself. Mortality information from individuals classified as nonresidents (i.e., nonresident aliens, citizens living abroad, residents of Puerto Rico, Guam, the Virgin Islands, other territories of the U.S.) as well as fetal deaths were excluded from capture. Population data were captured from the U.S. Census Bureau and comprise mid-year census, estimates of national, state, and county resident populations. Additional information such as time and place of

death, place of residence, age, sex, race, and ethnicity are also provided with the demographic data being captured on the death certificate for mortality data and by self-reporting for population data. The data spanned from 1999 to 2019, included all United States, all urbanization categories, all weekdays, all autopsy values, and all place of death categories. The population of interest was U.S. Non-Hispanic (N.H.) AI/AN of the age of 12 and older. Ethical approval was not required for this secondary analysis of publicly available aggregate county-level national data, in which no individual information would be identifiable.

Measures

All deaths were identified from the NCHS Mortality database by the underlying cause of death and multiple causes of death with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes. The outcomes of interest were separated into three scenarios: (1) overdose deaths relating to opioids alone (opioid-only), opioids in combination with any other substances (opioid/polysubstance), the sum of opioid-only and opioid/polysubstance cases (all-opioid related) (2) overdose deaths relating to opioids in combination with each of the other substance types and (3) overdose deaths separated by individual opioid types (heroin natural and semi-synthetic (prescription) opioids [e.g., oxycodone, hydrocodone], methadone, and synthetic opioids other than methadone[e.g., fentanyl, tramadol]). Opium(multiple cause code T40.0) and unknown opioids (T40.6) were not displayed alone because counts were too small. The specific substance-related overdose death types and corresponding ICD-10 codes are displayed by the outcome scenario below in List 1. While types of opioids are differentiated by these ICD codes, whether an opioid was prescribed or obtained via unregulated sources is not discernable using these data.

List 1: Substance-related overdose death types, and associated ICD-10 codes, by outcome scenario

	Underlying Cause of Death ICD-10	Multiple Cause of Death ICD-10[1]
Scenario 1		
Opioid-only	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6
Opioid/polysubstance	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9
All-opioid related[2]	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 OR (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5, T42.4, T43.6, T51.0, T51.1, T51.9)
Scenario 2		
Opioids and Methamphetamine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T43.6
Opioids and Cocaine	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T40.5
Opioids and Benzodiazepines	X40-44, X60-64, X85, Y10-Y14	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T42.4
Opioids and Alcohol	R78.0, X40-45, X60-65, X85, Y10-Y15	T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 AND T51.0, T51.1, T51.9
Scenario 3		
Heroin	X40-44, X60-64, X85, Y10-Y14	T40.1
Natural and semi-synthetic (prescription) opioids	X40-44, X60-64, X85, Y10-Y14	T40.2
Methadone	X40-44, X60-64, X85, Y10-Y14	T40.3
Synthetic opioids (other than methadone)	X40-44, X60-64, X85, Y10-Y14	T40.4

[1] Any of prescribed codes, if an "AND" is included then at least 1 from first code group AND 1 from other code group;
[2] Sum of opioid-only and opioid/polysubstance

For multiple causes of death codes, any qualifying code from the list of available codes was counted towards the outcome. In the case of opioids in combination with another substance, any qualifying code from the list of available opioid multiple causes of death codes (T40.0, T40.1, T40.2, T40.3, T40.4, T40.6) *and* any code from the other substance(s) list was counted towards the outcome. The count of deaths was divided by the population of interest and multiplied by 100,000 to provide a mortality rate per 100,000 NH AI/AN 12 years and older. Per the data use agreement of CDC WONDER, all counts 9, and lower were classified as 10. Trend analysis was stratified by age (15-24, 25-34, 35-44, 45+), sex (female, male), and race/ethnicity (NH AI/AN, NH Asian or Pacific Islander (API), NH Black, NH White, Hispanic/Latino).

Because age groupings were allowed only in 5 and 10-year increments, the age group was restricted to those 15 years and older instead of 12 years and older.

Statistical Analysis

Overdose death rates per 100,000 NH AI/AN population 12 and older, relating to the three outcome scenarios, were presented over time from 1999 to 2019. Figures and tables were constructed with 95% exact Poisson confidence intervals. To assess significant trends over time, non-parametric Jonckheere-Terpstra tests were performed for each substance type because rates exhibited non-normal distributions. All analysis results were presented overall and stratified by sex to identify sex-specific trends in the outcomes of interest. Supplementary figures were displayed for mortality rates due to opioids-only and due to opioids in combination with each other substance. Rates were stratified by age groups as well as by race/ethnicity. Racial comparisons were performed to assess how NH AI/AN rates compared to those of other racial groups.

All hypothesis tests were two-sided with a significance level of 5%. R version 3.6.1 (R Foundation for Statistical Computing) was used to perform all analyses.

Patient and public involvement

No patient was involved.

RESULTS

From 1999-2019 (Figure 1, Table 1), NH AI/AN opioid mortality rates increased significantly (all $P<0.001$) overall and for both women and men. All opioid-related mortality rates increased from 5.2 to 33.9 per 100,000 overall, 3.9 to 26.1 per 100,000 women, and 6.5 to 42.1 per 100,000 men. Opioid-only rates increased from 3.7 to 20.6 per 100,000 overall, 2.8 to 15.8 per 100,000 women, and 4.6 to 25.6 per 100,000 men. Opioid/polysubstance rates increased

from 1.5 to 13.3 per 100,000 overall, 1.1 to 10.3 per 100,000 women, and 1.9 to 16.5 per 100,000 men. Rates increased significantly even with total population counts of NH AI/AN increasing across 1999-2019 from 1,764,431 to 2,285,417 overall, from 902,815 to 1,173,309 for males, and from 861,616 to 1,112,108 for females.

Significant trends were also observed for mortality due to opioids in combination with other specific substances, with the exception of opioids and cocaine overall and among women (Figure 2, Table 2). Significantly increasing mortality rates were seen overall in NH AI/AN due to opioids and alcohol (rates per 100,000: 1.1 to 4.2, P<0.001), opioids and benzodiazepines (rates per 100,000: 1.1 to 2.6, P<0.001), and opioids and methamphetamine (rates per 100,000: 0.6 to 6.7, P=0.001). By sex, NH AI/AN men and women both exhibited significant increases in mortality rates due to opioids and alcohol (rates per 100,000 women: 1.1 to 2.1, P=0.01; rates per 100,000 men: 1.2 to 6.5, P<0.001), opioids and benzodiazepines (rates per 100,000 women: 1.1 to 2.0, P=0.01; rates per 100,000 men: 1.2 to 3.1, P<0.001), and opioids and methamphetamine (rates per 100,000 women: 1.1 to 6.2, P=0.02; rates per 100,000 men: 1.2 to 7.1, P=0.02). Only NH AI/AN men exhibited significantly increasing mortality rates due to opioids and cocaine (rates per 100,000 men: 1.2 to 3.2, P=0.02).

When looking deeper into individual opioid types (Figure 3, Table 3) there was a significant rise in natural and semi-synthetic (prescription) opioid death rates (rates per 100,000 overall: 1.4 to 5.1, P<0.001; rates per 100,000 women: 1.1 to 4.8, P<0.001; rates per 100,000 men: 1.6 to 5.4, P<0.001) and heroin (rates per 100,000 overall: 1.2 to 6.3, P<0.001; rates per 100,000 women: 1.1 to 4.9, P=0.056 [on the boundary of significance]; rates per 100,000 men 1.3 to 7.7, P<0.001). Death rates due to synthetic opioids (other than methadone) saw a drastic increase in recent years (2013 to 2019 rates per 100,000 overall: 1.5 to 12.5, P<0.001; 2013 to

2019 rates per 100,000 women: 1.5 to 8.6, P<0.001; 2013 to 2019 rates per 100,000 men: 1.5 to 16.5, P<0.001).

Supplemental analyses, by age groups, revealed that NH AI/AN ages 25-44 had higher opioid-only and opioid-combination mortality rates than those 15-24 and older than 44 (Supplemental Figures 1a and 1b). Overall and across both sexes, NH AI/AN populations generally exhibited opioid-only and opioid-combination mortality rates as high or higher than other races. Death rates across all years relating to opioids and methamphetamine remained consistently higher for NH AI/AN compared to all other races. However, in more recent years, NH White rates exceeded those of the NH AI/AN population, as seen in opioid-only and opioid-benzodiazepine mortality rates. NH Black men, additionally, saw higher opioid-only mortality rates than NH AI/AN men in recent years. Opioid and cocaine-related death rates among the NH Black population also exceeded rates of the NH AI/AN population overall and for men across most years and more recently for women. NH AI/AN exhibited higher opioid and alcohol mortality than other races, with N.H. Blacks showing slightly higher rates in recent years (Supplemental Figures 2a-2e).

DISCUSSION

This study provides a comprehensive historical overview of fatal drug overdose trends for NH AI/AN populations in the U.S., with particular attention to the role of opioids and combinations of opioids with alcohol, benzodiazepines, methamphetamine, and cocaine. We found that among NH AI/AN, mortality rates due to opioids have increased significantly over time. The trend of rising opioid-overdose mortality remains when data are stratified by sex and across age categories. Deaths due to polysubstance use involving opioids have also increased significantly over time among NH AI/AN populations. Among specific opioid types, heroin and

natural/semi-synthetic (prescription) opioid-related deaths have risen across the years, however, synthetic opioid-related deaths have spiked just in recent years alone. When comparing across U.S. racial and ethnic groups, NH AI/AN populations exhibit rising opioid-overdose mortality rates that have generally been higher than other groups, but in recent years NH AI/AN men's rates were below those of NH White and NH Black men, and NH AI/AN populations also display lower rates of death related to opioids and cocaine than NH Black populations. However, NH AI/AN populations exhibit higher mortality rates of opioid combinations with methamphetamine and alcohol than all other U.S. racial/ethnic groups.

In general, the increasing opioid overdose mortality from 1999-2019 among NH AI/AN populations observed in our analysis mirror the rising opioid overdose trends in the U.S. general population.[1,9,17] Similarly, deaths resulting from opioid combinations with other drugs among AI/AN populations follow an increasing trend that is supported by prior research.[16] The combination of opioids with other substances can be a potent inducer of drug overdose. Alcohol, opioids (heroin/morphine, tramadol, oxycodone, etc.), and benzodiazepines depress the central nervous system when used alone.[18,19] However, the combination of opioids with other substances may generate complex drug interactions associated with a heightened risk of fatal overdose.[10,20] Consequently, our results showed an escalation in mortality due to opioids in combination with methamphetamine and opioids in combination with alcohol from 1999 to 2019. Consistent with our findings, data from the CDC reported that roughly half of all psychostimulant deaths in 2017 also involved an opioid. Additionally, they observed a significant rise in deaths due to opioids in combination with psychostimulants from 2015 to 2017.[16] Aside from the elevated risk of overdose, the co-use of opioids with other substances has been shown to negatively impact treatment outcomes,[21] including lower rates of treatment retention.[22] Similarly, co-use of alcohol

with other substances has been associated with increased relapse rates.[23] Given the increased risk of overdose and poor treatment outcomes, it is essential that substance use treatment programs, interventions, and policies consider the complexities surrounding polysubstance, including identifying and addressing the root causes of such polysubstance use.

Regarding trends in specific opioid types fueling overdose mortality, our finding that AI/AN deaths resulting from synthetic opioids have increased sharply in recent years indicates AI/AN communities have experienced similar drivers of mortality as the general U.S. population. This group of opioids contains illicitly manufactured fentanyl, a highly potent synthetic opioid that can increase the risk of overdose and mortality in unregulated and unknown quantities.[24,25] While we cannot determine from these data whether the fentanyl involved in an overdose was prescribed or unregulated, current evidence points to increased illicit fentanyl poisoning in the U.S.[26,27], especially in combination with other drugs, as a key engine of drug poisoning deaths. Numerous analyses indicate a growing role for fentanyl in drug overdose deaths. A study consisting of toxicology data from 10 U.S. states showed that close to 60% of individuals who died of drug overdoses tested positive for fentanyl and fentanyl analogs in addition to cocaine, methamphetamine, and heroin.[28] Furthermore, overdose deaths resulting from fentanyl increased nearly 12 fold from 2013 to 2019.[8] Qualitative and mixed methods studies indicate that illicitly manufactured fentanyl, as opposed to prescription synthetic opioids, drive these trends.[29,30] Our results demonstrate the need for harm reduction interventions to mitigate the dangers of fentanyl, especially among individuals using unregulated drugs (e.g., naloxone training and safe drug supplies), along with improved access to evidence-based treatment programs that offer opioid agonist treatment.[31]

These findings highlight existing inequities in drug-related deaths and may point to broader systemic factors that disproportionately affect members of AI/AN communities. American Indians and Alaska Natives continue to encounter stressors that stem from diminished socioeconomic prospects, racism, and historical trauma from colonization. These stressors often contribute significantly to the heightened drug use and related overdoses in the AI/AN population.[13,15] Despite this disproportionate burden, indigenous communities continue to encounter significant challenges in treatment access, availablity[32], and quality.[33] A recent study using 2017 and 2018 data showed that only 22% of A.I./AN-serving treatment centers offer opioid agonists. Furthermore, they found that only 40% of AI/AN persons in specialty treatment receive medication-assisted treatment for opioid use disorder.[32] To mitigate the impact of drug overdoseon AI/AN communities, leverage points for intervention must look at the root causes and structural factors that shape substance use and addiction and seek to expand specialty treatment programs for AI/AN communities.

Furthermore, sex differences were apparent throughout our results. In our primary and supplemental analysis, male populations tended to experience higher rates and higher increases in drug overdose deaths than female populations. Sex differences observed in drug overdose studies are often characterized by higher rates in men.[34,35] However, historical trends are not uniform, and gaps between male and female populations have narrowed at specific periods during the drug overdose crisis and widened at other points.[35] Our observed results may reflect differential attitudes towards risk and varying social expectations for males and females in AI/AN communities and may suggest the need for targeted gender-sensitive interventions.

Finally, two essential observations in our study may shed light on the critical role of socioeconomic status in overdose deaths. In our supplemental analysis of opioid only deaths, we

found that individuals aged 35-44 carried the highest burden of death rates for most of the years from 1999-2010. Additionally, among this same age, overdose death rates spiked immediately following 2008. The period between 2008 and 2009 was defined by a worldwide economic crisis characterized by high unemployment rates.[36] Furthermore, most overdose deaths during the same period occurred among individuals who often bear the financial responsibility for their families (i.e., 35-44 age group). While additional studies will be needed to ascertain the relationship between the 2008 financial crises and the escalation in drug overdose deaths among AI/AN communities, our findings offer compelling insights into the importance of socioeconomic wellbeing in the context of substance use. Our findings should be considered within the constraints of certain important limitations. First, to capture as much AI/AN data as possible, age-adjusted results were not obtained because they required suppressing AI/AN-specific results. However, in comparing age-adjusted and raw rates, we found rates to be reasonably similar. Second, subgroup data with small counts were aggregated due to data-use agreement requirements. Third, due to the different demographic reporting techniques between the mortality data from death certificates (reported by surviving next of kin or funeral director observation)[37] and population data from the U.S. Census Bureau (self-reporting), inconsistencies could arise between the two groups, which could translate into biased mortality rates[38,39] across certain demographic groups (especially race and ethnicity). Fourth, deaths with specific demographics reported as "not stated" or unknown were not included in demographic-specific analyses.

On the other hand, our study has some unique strengths worth mentioning. First, this is one of the first studies to investigate AI/AN opioid overdose trends over time across the U.S., with emphasis on the drug overdose implications of the concurrent use of opioids with alcohol, benzodiazepines, cocaine, or methamphetamine contributes in this population. Second, by

stratifying our findings by sex and comparing mortality rates between NH AI/AN groups, our findings are mainly presented to better identify subpopulations at risk of overdose. Finally, our results highlight the historical trends of opioids overdose mortality among AI/AN populations by specific opioid types, including heroin, natural and semi-synthetic (prescription) opioids [e.g., oxycodone, hydrocodone], methadone, and synthetic opioids other than methadone [e.g., fentanyl, tramadol]). Providing these distinctions is essential for public health prevention and harm reduction strategies directed towards AI/AN communities.

CONCLUSIONS

Overall, our results suggest that AI/AN populations continue to face rising levels of overdose mortality due to the use of opioids alone and in combination with other substances, with rates as high or higher than all other racial/ethnic groups. AI/AN men and those aged 25-44 are especially impacted. While the type of opioid driving these trends has changed over the years, many underlying social factors that drive these patterns have not, including inequities in socioeconomic status, persistent effects of historical trauma, and inequities in healthcare access and treatment programs. Interventions for AI/AN populations with substance use disorders will be more impactful if they are comprehensive, culturally centered, and address social determinants of health, including socioeconomic factors and racial and ethnic discrimination.

Conflict of interest

The authors declare that there is no conflict of interest.

Ethics statements

Patient consent for publication

Not required.

Contributors

FQ, EFM, KLV, KE, and AD contributed to the concept and study design. BT, and FQ contributed to acquisition, curation and analysis of data. FQ, EFM, NAM, BT, and AD drafted the manuscript. JH and AHV worked on formatting tables, figures and references and provided edits to the final draft of the manuscript. All authors critically revised the manuscript for important intellectual content. All authors approved the final version of the manuscript.

Ethics Approval

This study does not involve human participants for using aggregated secondary data. No research ethics board approval was required since the data were publicly accessible.

Data Availablity statement

Data are publicly available at the CDC Wide-Ranging Online Data for Epidemiologic Research (CDC WONDER) database. Multiple Cause of Death 1999 - 2019. Available at: https://wonder.cdc.gov/wonder/help/mcd.html#. Accessed Dec 1, 2021.

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Table 1: Trends in opioid death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
All opioid-related	5.2 (4.2, 6.3)	5.0 (4.1, 6.1)	5.7 (4.6, 6.8)	6.8 (5.7, 8.0)	8.6 (7.3, 10.0)	10 (8.7, 11.5)	12.0 (10.5, 13.5)	11.5 (10.0, 13.0)	14.1 (12.5, 15.8)	16.0 (14.3, 17.8)	19.8 (17.9, 21.7)	17.3 (15.5, 19.1)	18.0 (16.2, 19.9)	20.0 (18.2, 22.0)	18.5 (16.8, 20.4)	21.5 (19.6, 23.4)	22.2 (20.3, 24.2)	25.6 (23.5, 27.7)	28.6 (26.4, 30.9)	25.8 (23.8, 28.0)	33.9 (31.5, 36.3)	<0.001
Opioid-only	3.7 (2.8, 4.6)	3.3 (2.5, 4.2)	4.2 (3.3, 5.2)	5.1 (4.1, 6.1)	6.4 (5.3, 7.5)	7.5 (6.3, 8.8)	8.2 (7.0, 9.5)	8.4 (7.2, 9.7)	9.6 (8.3, 11.0)	11.3 (9.9, 12.9)	13.5 (12.0, 15.2)	11.4 (10.0, 12.9)	12.2 (10.8, 13.8)	13.2 (11.7, 14.8)	12.7 (11.2, 14.2)	14.2 (12.6, 15.8)	14.3 (12.7, 15.9)	16.6 (15.0, 18.3)	18.2 (16.5, 20.0)	16.5 (14.8, 18.2)	20.6 (18.7, 22.5)	<0.001
Opioid/polysubstance	1.5 (1.0, 2.1)	1.7 (1.2, 2.3)	1.5 (1.0, 2.1)	1.7 (1.2, 2.3)	2.2 (1.6, 3.0)	2.5 (1.9, 3.3)	3.8 (2.9, 4.7)	3.1 (2.3, 3.9)	4.5 (3.6, 5.5)	4.7 (3.8, 5.6)	6.2 (5.2, 7.4)	5.9 (4.9, 6.9)	5.8 (4.8, 6.8)	6.8 (5.8, 8.0)	5.9 (4.9, 6.9)	7.3 (6.2, 8.5)	8.0 (6.8, 9.2)	9.0 (7.8, 10.2)	10.4 (9.1, 11.8)	9.4 (8.1, 10.7)	13.3 (11.8, 14.8)	<0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2199588	2222736	2243570	2265155	2285417	
Female																						
All opioid-related	3.9 (2.7, 5.3)	3.6 (2.5, 5.0)	5.2 (3.8, 6.7)	4.9 (3.6, 6.4)	6.4 (4.9, 8.1)	6.8 (5.3, 8.5)	9.6 (7.8, 11.6)	7.6 (6.0, 9.4)	12.9 (10.8, 15.2)	11.3 (9.4, 13.4)	13.1 (11, 15.4)	15.0 (12.8, 17.4)	15.7 (13.4, 18.1)	16.8 (14.4, 19.3)	16.7 (14.4, 19.2)	15.3 (13.1, 17.7)	16.7 (14.4, 19.1)	21.0 (18.4, 23.7)	22.1 (19.4, 24.9)	18.5 (16.1, 21.0)	26.1 (23.2, 29.1)	<0.001
Opioid-only	2.8 (1.8, 4.0)	2.2 (1.4, 3.3)	3.9 (2.7, 5.2)	3.8 (2.7, 5.2)	5.1 (3.8, 6.6)	5.2 (3.9, 6.7)	6.8 (5.3, 8.5)	5.9 (4.5, 7.4)	9.0 (7.3, 10.9)	8.6 (6.9, 10.5)	9.1 (7.4, 11)	10.6 (8.7, 12.6)	10.6 (8.7, 12.6)	11.7 (9.8, 13.9)	11.9 (9.9, 14)	10.5 (8.7, 12.5)	11.0 (9.1, 13)	13.8 (11.7, 16)	13.8 (11.8, 16.0)	12.0 (10.1, 14)	15.8 (13.6, 18.1)	<0.001
Opioid/polysubstance	1.1 (0.5, 1.9)	1.4 (0.7, 2.2)	1.3 (0.7, 2.1)	1.0 (0.5, 1.8)	1.3 (0.7, 2.1)	1.6 (0.9, 2.5)	2.8 (1.8, 3.9)	1.8 (1.0, 2.7)	3.9 (2.8, 5.2)	2.7 (1.8, 3.8)	4.0 (2.9, 5.3)	4.4 (3.3, 5.8)	5.1 (3.8, 6.5)	5.0 (3.8, 6.5)	4.8 (3.6, 6.2)	4.8 (3.6, 6.2)	5.7 (4.4, 7.1)	7.2 (5.7, 8.8)	8.3 (6.7, 10.0)	6.5 (5.2, 8.1)	10.3 (8.6, 12.2)	<0.001
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
All opioid-related	6.5 (4.9, 8.3)	6.5 (4.9, 8.3)	6.2 (4.7, 7.9)	8.8 (7.0, 10.8)	10.9 (8.9, 13.1)	13.4 (11.1, 15.8)	14.4 (12.1, 16.9)	15.5 (13.1, 18.1)	15.4 (13.0, 17.9)	20.9 (18.2, 23.9)	26.8 (23.7, 30.1)	19.7 (17.0, 22.5)	20.4 (17.8, 23.3)	23.5 (20.6, 26.5)	20.5 (17.9, 23.3)	27.9 (24.8, 31.2)	28.1 (25.0, 31.3)	30.4 (27.2, 33.7)	35.5 (32.1, 39.1)	33.6 (30.2, 37.1)	42.1 (38.4, 46.0)	<0.001
Opioid-only	4.6 (3.3, 6.2)	4.5 (3.2, 6.0)	4.5 (3.2, 6.0)	6.4 (4.9, 8.1)	7.7 (6.0, 9.6)	9.9 (8.0, 12)	9.7 (7.8, 11.7)	11.1 (9.1, 13.3)	10.2 (8.3, 12.3)	14.2 (12.0, 16.6)	18.2 (15.6, 20.9)	12.3 (10.2, 14.6)	14.0 (11.8, 16.4)	14.8 (12.5, 17.2)	13.5 (11.4, 15.9)	18.0 (15.5, 20.6)	17.7 (15.3, 20.3)	19.6 (17.0, 22.3)	22.8 (20.0, 25.7)	21.2 (18.6, 24.0)	25.6 (22.7, 28.7)	<0.001
Opioid/polysubstance	1.9 (1.1, 2.9)	2 (1.2, 3.0)	1.7 (0.9, 2.6)	2.4 (1.5, 3.5)	3.2 (2.2, 4.4)	3.5 (2.4, 4.8)	4.8 (3.5, 6.3)	4.4 (3.2, 5.8)	5.2 (3.9, 6.7)	6.7 (5.2, 8.5)	8.6 (6.9, 10.5)	7.3 (5.8, 9.1)	6.5 (5.0, 8.1)	8.7 (7.0, 10.6)	7.0 (5.5, 8.6)	9.9 (8.1, 11.9)	10.4 (8.5, 12.4)	10.8 (8.9, 12.8)	12.7 (10.7, 14.9)	12.3 (10.3, 14.5)	16.5 (14.2, 18.9)	<0.001
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072179	1083032	1092738	1102570	1112108	

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);
Opioid/polysubstance(underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T51.0, T51.1, T51.9);
All-opioid related: sum of "opioid-only" and "opioid/polysubstance"

[2] Non-parametric Jonckheere-Terpstra Test for trend

Table 2: Trends in opioid combination[1] death rates per 100,000 (95% CI) among US NH-AI/AN 12 and older by substance combination type

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Opioids and Alcohol	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.2 (0.7, 1.7)	1.4 (0.9, 2.0)	1.4 (0.9, 2.0)	1.4 (0.9, 1.9)	1.1 (0.7, 1.6)	1.9 (1.4, 2.6)	2.2 (1.6, 2.9)	3.0 (2.3, 3.8)	2.7 (2.0, 3.4)	2.4 (1.8, 3.1)	2.5 (1.9, 3.2)	2.8 (2.1, 3.5)	3.1 (2.4, 3.9)	3.0 (2.3, 3.8)	2.9 (2.3, 3.7)	3.5 (2.8, 4.3)	3.2 (2.5, 4.0)	4.2 (3.4, 5.1)	<0.001
Opioids and Benzodiazepines	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.3 (0.8, 1.8)	1.6 (1.1, 2.1)	2.0 (1.5, 2.7)	2.0 (1.4, 2.7)	2.5 (1.9, 3.3)	2.5 (1.9, 3.2)	2.2 (1.6, 2.9)	2.9 (2.2, 3.7)	1.8 (1.3, 2.4)	2.8 (2.1, 3.5)	2.9 (2.2, 3.6)	3.6 (2.8, 4.4)	2.9 (2.2, 3.6)	1.3 (0.9, 1.8)	2.6 (2.0, 3.3)	<0.001
Opioids and Cocaine	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.5 (1.0, 2.1)	1.1 (0.7, 1.5)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.3 (0.9, 1.9)	1.4 (0.9, 1.9)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.1 (0.7, 1.5)	1.0 (0.6, 1.4)	1.2 (0.8, 1.7)	1.5 (1.1, 2.1)	1.9 (1.3, 2.5)	2.7 (2.1, 3.4)	2.9 (2.3, 3.7)	0.14
Opioids and Methamphetamine	0.6 (0.3, 1.0)	-	1.1 (0.7, 1.6)	0.5 (0.3, 0.9)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	1.0 (0.6, 1.5)	0.5 (0.2, 0.8)	1.0 (0.6, 1.5)	1.1 (0.7, 1.6)	1.0 (0.6, 1.4)	1.0 (0.6, 1.4)	1.5 (1.0, 2.1)	1.5 (1.0, 2)	1.8 (1.3, 2.4)	2.3 (1.7, 3.1)	3.0 (2.3, 3.7)	4.6 (3.7, 5.5)	4.4 (3.6, 5.3)	6.7 (5.6, 7.7)	0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2199668	2222736	2243570	2265155	2285417	
Female																						
Opioids and Alcohol	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.4 (0.7, 2.2)	1.0 (0.5, 1.6)	1.8 (1.1, 2.7)	1.6 (0.9, 2.5)	1.8 (1.1, 2.6)	1.0 (0.5, 1.7)	1.7 (1.0, 2.6)	1.3 (0.8, 2.1)	1.5 (0.9, 2.3)	2.0 (1.3, 2.9)	1.7 (1.1, 2.6)	1.9 (1.2, 2.8)	2.1 (1.4, 3.0)	0.01
Opioids and Benzodiazepines	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.8 (1.1, 2.8)	1.6 (0.9, 2.5)	1.9 (1.2, 2.8)	1.8 (1.1, 2.7)	2.2 (1.4, 3.2)	2.5 (1.6, 3.5)	2.1 (1.3, 3.0)	2 (1.2, 2.9)	2.7 (1.9, 3.9)	3.5 (2.5, 4.7)	2.3 (1.5, 3.2)	0.9 (0.4, 1.5)	2.0 (1.3, 2.9)	0.01
Opioids and Cocaine	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.1 (0.5, 1.8)	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	1.0 (0.5, 1.7)	0.9 (0.4, 1.6)	0.9 (0.4, 1.5)	1.0 (0.5, 1.6)	0.9 (0.4, 1.6)	1.1 (0.6, 1.8)	1.6 (0.9, 2.4)	1.7 (1.1, 2.6)	2.6 (1.8, 3.7)	0.49
Opioids and Methamphetamine	-	-	1.1 (0.5, 1.8)	-	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	-	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.5, 1.6)	0.9 (0.4, 1.6)	1.4 (0.8, 2.2)	1.5 (0.9, 2.4)	1.3 (0.8, 2.1)	2.0 (1.3, 3.0)	2.1 (1.3, 3.0)	4.5 (3.4, 5.8)	3.4 (2.5, 4.6)	6.2 (4.9, 7.7)	0.02
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
Opioids and Alcohol	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.3 (0.7, 2.1)	1.8 (1.1, 2.8)	1.8 (1.0, 2.7)	1.8 (1, 2.7)	1.2 (0.6, 2.0)	2.5 (1.6, 3.6)	3.5 (2.5, 4.8)	4.3 (3.1, 5.7)	3.8 (2.7, 5.1)	3.1 (2.1, 4.3)	4.1 (2.9, 5.4)	3.9 (2.8, 5.2)	5.0 (3.7, 6.4)	4.6 (3.4, 5.9)	3.9 (2.8, 5.1)	5.4 (4.1, 6.9)	4.5 (3.4, 5.9)	6.5 (5.1, 8.1)	<0.001
Opioids and Benzodiazepines	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.2 (0.6, 1.9)	1.6 (0.9, 2.4)	2.2 (1.3, 3.2)	2.2 (1.4, 3.3)	2.4 (1.5, 3.5)	3.2 (2.2, 4.4)	3.3 (2.3, 4.5)	2.2 (1.4, 3.3)	3.4 (2.4, 4.6)	1.4 (0.8, 2.2)	3.6 (2.5, 4.8)	3.0 (2.0, 4.2)	3.6 (2.6, 4.8)	3.5 (2.5, 4.7)	1.8 (1.1, 2.7)	3.1 (2.2, 4.3)	<0.001
Opioids and Cocaine	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.2 (0.6, 1.9)	2.0 (1.2, 3.0)	1.1 (0.6, 1.9)	1.0.0 (0.5, 1.7)	1.3 (0.7, 2.1)	1.7 (1.0, 2.6)	1.8 (1.1, 2.7)	1.0 (0.5, 1.7)	1.2 (0.6, 1.9)	1.2 (0.7, 2.0)	0.9 (0.5, 1.6)	1.6 (0.9, 2.5)	1.9 (1.2, 2.9)	2.2 (1.4, 3.2)	3.7 (2.7, 4.9)	3.2 (2.3, 4.4)	0.02
Opioids and Methamphetamine	1.2 (0.6, 2.0)	-	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.8)	1 (0.5, 1.7)	1.0 (0.5, 1.7)	1.2 (0.6, 2.0)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.6 (1.0, 2.5)	1.4 (0.8, 2.2)	2.4 (1.5, 3.4)	2.6 (1.7, 3.9)	3.9 (2.8, 5.1)	4.7 (3.5, 6.0)	5.4 (4.2, 6.9)	7.1 (5.6, 8.8)	0.02
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072179	1083032	1092738	1102570	1112108	

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

[2] Non-parametri

Table 3: Trends in opioid death rates per 100,000 (95% CI) among US NH-AIAN 12 and older by individual opioid type[1]

	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	Trend p-value[2]
Overall																						
Heroin	1.2 (0.7, 1.8)	1.2 (0.8, 1.8)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.2 (0.8, 1.7)	1.1 (0.7, 1.6)	1.0 (0.6, 1.5)	1.1 (0.7, 1.5)	1.2 (0.8, 1.8)	1.2 (0.8, 1.8)	1.8 (1.2, 2.4)	1.4 (0.9, 1.9)	2.1 (1.5, 2.8)	2.2 (1.6, 2.8)	3.3 (2.5, 4.1)	4.4 (3.6, 5.3)	5.3 (4.4, 6.3)	5.9 (4.9, 6.9)	6.1 (5.1, 7.1)	5.9 (4.9, 6.9)	6.3 (5.3, 7.3)	<0.001
Methadone	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.2 (0.7, 1.7)	1.6 (1.1, 2.2)	2.5 (1.8, 3.2)	2.8 (2.1, 3.6)	3.0 (2.3, 3.8)	2.9 (2.2, 3.7)	3.7 (2.9, 4.6)	3.7 (2.9, 4.5)	3.4 (2.6, 4.2)	3.3 (2.6, 4.2)	2.6 (1.9, 3.3)	2.2 (1.6, 2.9)	1.6 (1.1, 2.1)	1.8 (1.3, 2.4)	1.7 (1.2, 2.2)	2.1 (1.5, 2.7)	1.2 (0.8, 1.7)	1.4 (1.0, 2.0)	0.70
Natural and semi-synthetic (prescription) opioids	1.4 (0.9, 2.0)	1.3 (0.8, 1.9)	1.8 (1.2, 2.4)	2.1 (1.5, 2.8)	2.4 (1.8, 3.1)	2.9 (2.2, 3.7)	3.1 (2.4, 3.9)	3.5 (2.7, 4.4)	4.2 (3.3, 5.1)	4.6 (3.7, 5.5)	6.3 (5.3, 7.5)	6.0 (5.0, 7.1)	5.6 (4.7, 6.7)	6.9 (5.8, 8.0)	6.7 (5.6, 7.8)	7.4 (6.3, 8.6)	6.8 (5.8, 8.0)	6.5 (5.5, 7.6)	6.6 (5.5, 7.7)	4.5 (3.7, 5.5)	5.1 (4.2, 6.0)	<0.001
Synthetic opioids (other than methadone)	1.1 (0.7, 1.7)	1.1 (0.7, 1.6)	1.1 (0.7, 1.6)	1.1 (0.6, 1.6)	1.0 (0.6, 1.5)	1.2 (0.8, 1.8)	1.3 (0.8, 1.8)	1.3 (0.9, 1.8)	1.1 (0.7, 1.7)	2.2 (1.6, 2.9)	2.8 (2.1, 3.5)	1.6 (1.1, 2.2)	1.5 (1.0, 2.1)	1.9 (1.4, 2.6)	1.5 (1.1, 2.1)	2.0 (1.5, 2.7)	2.3 (1.7, 3.0)	5.1 (4.2, 6.1)	7.6 (6.5, 8.8)	8.4 (7.3, 9.7)	12.5 (11.1, 14.0)	<0.001
Population count	1764431	1830341	1857916	1888990	1917057	1946151	1972126	1996129	2016480	2036583	2054468	2067226	2099967	2126296	2151271	2176524	2198688	2222736	2243570	2265155	2285417	
Female																						
Heroin	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.0 (0.5, 1.6)	0.9 (0.5, 1.6)	1.0 (0.5, 1.7)	1.7 (1.0, 2.5)	0.9 (0.4, 1.6)	1.8 (1.1, 2.7)	2.2 (1.4, 3.2)	2.8 (1.9, 3.9)	3.9 (2.8, 5.1)	4.2 (3.1, 5.4)	3.1 (2.2, 4.2)	4.9 (3.7, 6.2)	0.056
Methadone	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.2 (0.6, 2.0)	1.7 (1, 2.6)	1.6 (0.9, 2.5)	2.2 (1.4, 3.2)	2.3 (1.5, 3.4)	2.7 (1.8, 3.8)	3.0 (2.0, 4.1)	2.2 (1.4, 3.2)	3.5 (2.5, 4.7)	2.5 (1.7, 3.5)	2.6 (1.7, 3.6)	2.5 (1.7, 3.6)	0.9 (0.4, 1.5)	1.3 (0.7, 2.1)	1.4 (0.8, 2.2)	1.7 (1.1, 2.6)	1.4 (0.8, 2.1)	1.4 (0.8, 2.2)	0.32
Natural and semi-synthetic (prescription) opioids	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	2.0 (1.2, 3.0)	1.4 (0.8, 2.3)	2.3 (1.5, 3.4)	2.3 (1.5, 3.3)	2.6 (1.7, 3.7)	2.0 (1.2, 2.9)	4.6 (3.4, 6.1)	3.4 (2.3, 4.6)	5.0 (3.8, 6.5)	5.2 (3.9, 6.6)	5.6 (4.3, 7.1)	6.1 (4.7, 7.6)	6.7 (5.3, 8.3)	6.5 (5.1, 8.1)	5.7 (4.4, 7.1)	6.2 (4.9, 7.8)	6.0 (4.7, 7.5)	4.6 (3.4, 5.9)	4.8 (3.6, 6.1)	<0.001
Synthetic opioids (other than methadone)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.1 (0.5, 1.8)	1.0 (0.5, 1.8)	1.0 (0.5, 1.7)	1.0 (0.5, 1.7)	1.3 (0.7, 2.1)	1.3 (0.7, 2.1)	1.1 (0.5, 1.8)	2.0 (1.2, 3.0)	2.2 (1.4, 3.2)	2.0 (1.2, 2.9)	1.5 (0.8, 2.3)	2.1 (1.3, 3.1)	1.5 (0.9, 2.4)	1.5 (0.9, 2.3)	1.9 (1.2, 2.7)	3.9 (2.9, 5.2)	4.9 (3.7, 6.2)	5.3 (4.1, 6.7)	8.6 (7.0, 10.4)	<0.001
Population count	902815	935494	949825	965851	980999	995787	1009648	1022161	1033040	1043730	1053484	1060368	1076977	1090386	1102971	1115777	1127409	1139704	1150832	1162585	1173309	
Male																						
Heroin	1.3 (0.6, 2.1)	1.3 (0.7, 2.2)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.4 (0.7, 2.2)	1.3 (0.7, 2.1)	1.0 (0.5, 1.8)	1.1 (0.6, 1.9)	1.5 (0.9, 2.4)	1.5 (0.8, 2.4)	2.6 (1.7, 3.7)	1.7 (1.0, 2.6)	2.5 (1.7, 3.6)	3.5 (2.4, 4.7)	4.8 (3.5, 6.2)	6.7 (5.2, 8.3)	7.9 (6.3, 9.6)	8.0 (6.4, 9.8)	8.1 (6.5, 9.8)	8.8 (7.1, 10.6)	7.7 (6.2, 9.5)	<0.001
Methadone	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.5 (0.8, 2.4)	3.4 (2.3, 4.6)	3.4 (2.4, 4.7)	3.6 (2.5, 4.9)	3.1 (2.1, 4.2)	4.4 (3.2, 5.8)	5.2 (3.9, 6.7)	3.3 (2.3, 4.5)	4.2 (3.0, 5.5)	2.6 (1.7, 3.7)	1.9 (1.2, 2.8)	2.3 (1.4, 3.3)	2.3 (1.5, 3.3)	1.9 (1.2, 2.9)	2.5 (1.6, 3.5)	1.0 (0.5, 1.7)	1.4 (0.8, 2.2)	>0.99
Natural and semi-synthetic (prescription) opioids	1.6 (0.9, 2.6)	1.6 (0.9, 2.5)	1.5 (0.8, 2.4)	2.8 (1.8, 4.0)	2.5 (1.6, 3.6)	3.6 (2.5, 4.9)	3.6 (2.5, 4.9)	5.1 (3.8, 6.7)	3.7 (2.6, 4.9)	5.8 (4.4, 7.4)	7.7 (6.1, 9.5)	6.9 (5.3, 8.6)	5.7 (4.3, 7.2)	7.7 (6.1, 9.5)	6.7 (5.2, 8.3)	8.3 (6.7, 10.1)	8.4 (6.8, 9.9)	6.8 (5.4, 8.5)	7.1 (5.6, 8.8)	4.5 (3.4, 5.9)	5.4 (4.1, 6.8)	<0.001
Synthetic opioids (other than methadone)	1.2 (0.6, 2.0)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.9)	1.1 (0.5, 1.8)	1.5 (0.8, 2.3)	1.2 (0.6, 2.0)	1.3 (0.7, 2.2)	1.2 (0.6, 2.0)	2.4 (1.5, 3.5)	3.4 (2.4, 4.6)	1.2 (0.6, 2.0)	1.6 (0.9, 2.4)	1.7 (1.0, 2.6)	1.5 (0.9, 2.4)	2.5 (1.7, 3.6)	2.8 (1.9, 3.9)	6.3 (4.9, 7.9)	10.5 (8.7, 12.5)	11.7 (9.8, 13.8)	16.5 (14.2, 19.0)	<0.001
Population count	861616	894847	908091	923139	936058	950364	962478	973968	983440	992853	1000984	1006858	1022990	1035910	1048300	1060747	1072079	1083032	1092738	1102570	1112108	

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.1); Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.2); Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.3); Synthetic opioids other than methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.4);[2] Non-parametric Jonckheere-Terpstra Test for trend

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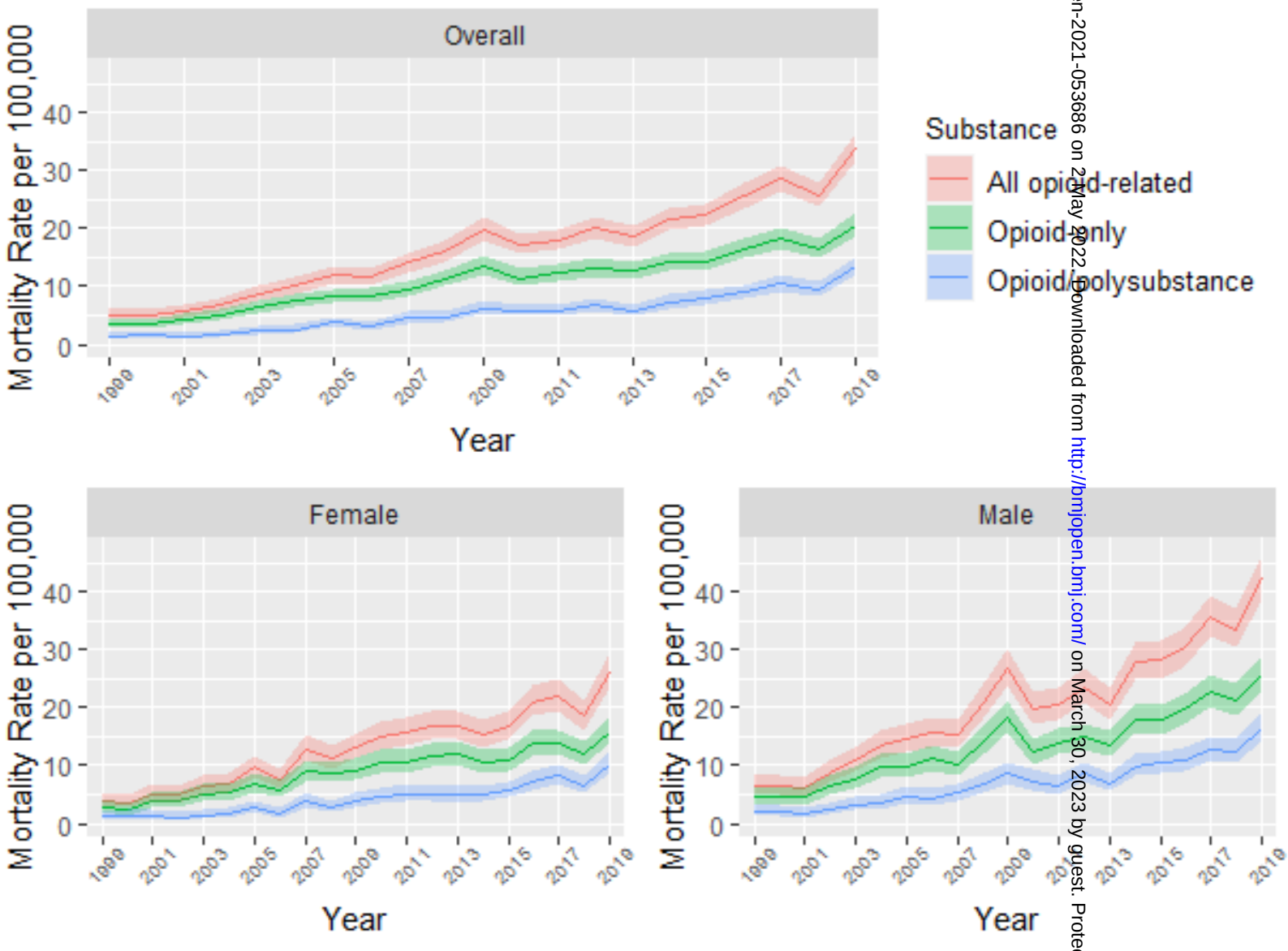

Figure 1: Trends in opioid death rates among US NH-AI/AN 12 and older by opioid-only (no other substances), opioid/polysubstance (opioids and at least one other substance), and all opioid-related cases (sum of opioid-only and opioid/polysubstance)

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6); Opioid/polysubstance (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5, T42.4, T43.6, T50.0, T51.1, T51.9); All-opioid related: sum of "opioid-only" and "opioid/polysubstance"

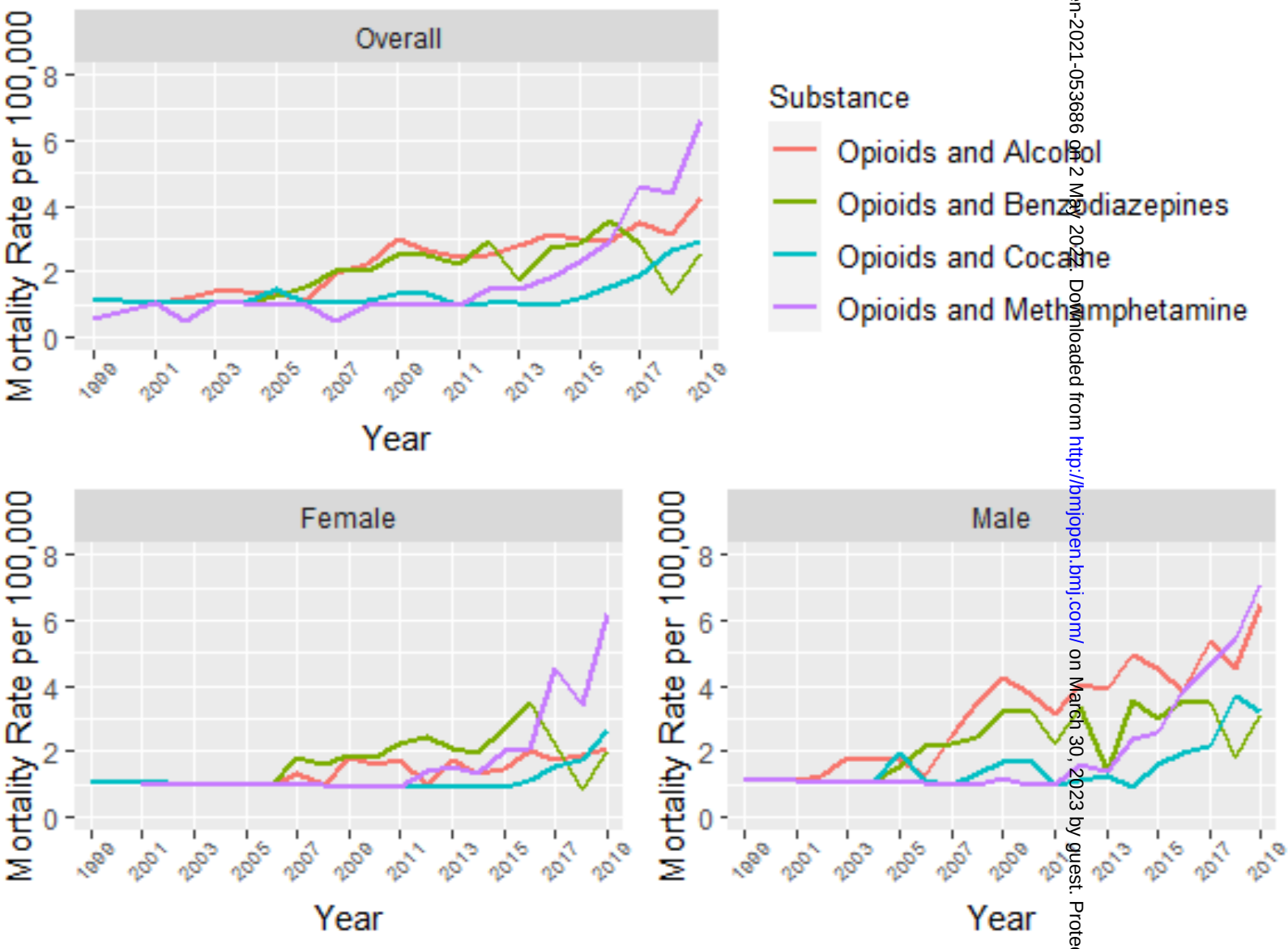

Figure 2: Trends in opioid combination[1] death rates among US NH-AI/AN 12 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9)

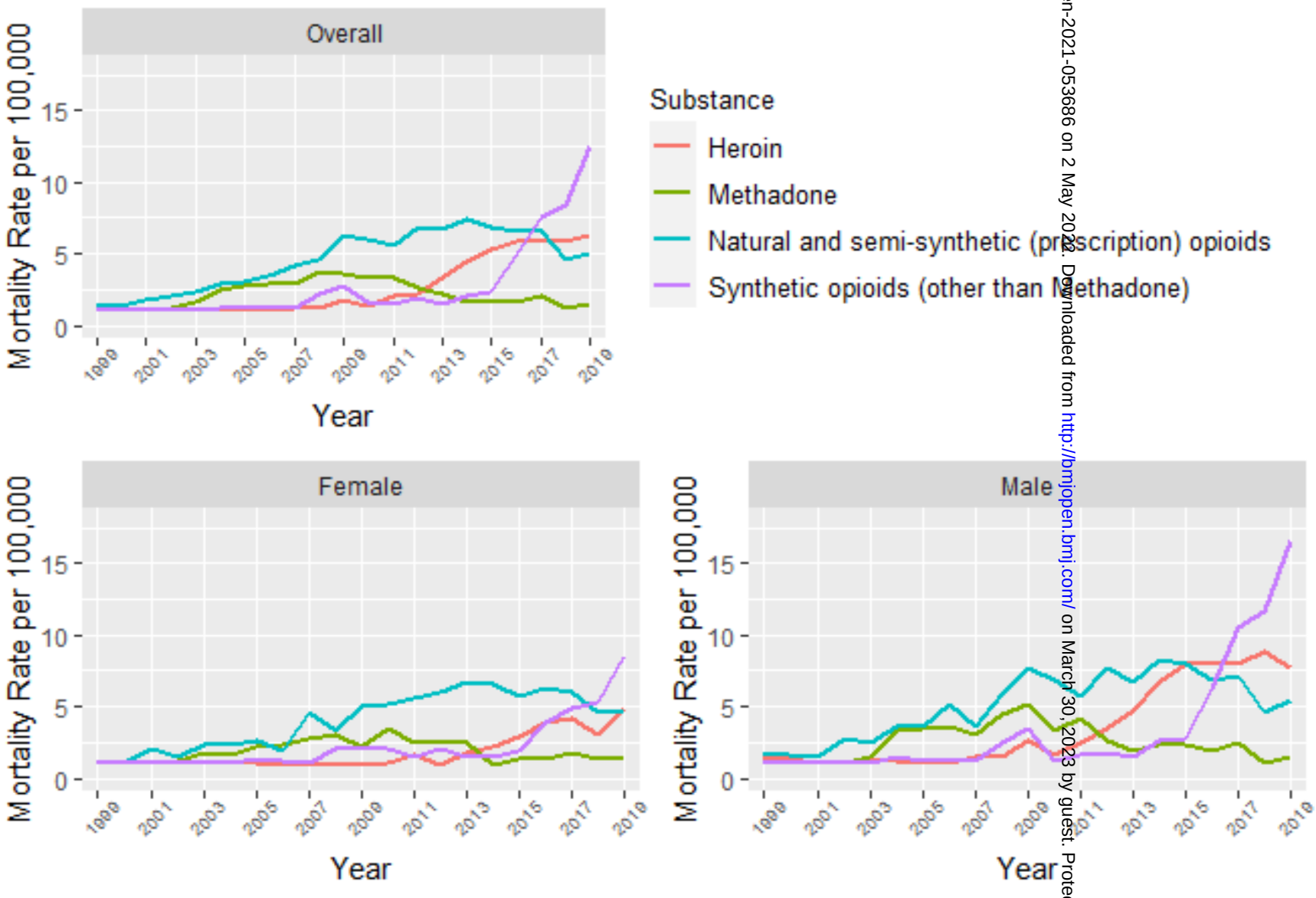

Figure 3: Trends in opioid death rates among US NH-AI/AN 12 and older by individual opioid types[1]

[1] Heroin (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.1);
Natural and semi-synthetic (prescription) opioids (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.2);
Methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.3);
Synthetic opioids other than methadone (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.4)

Supplement

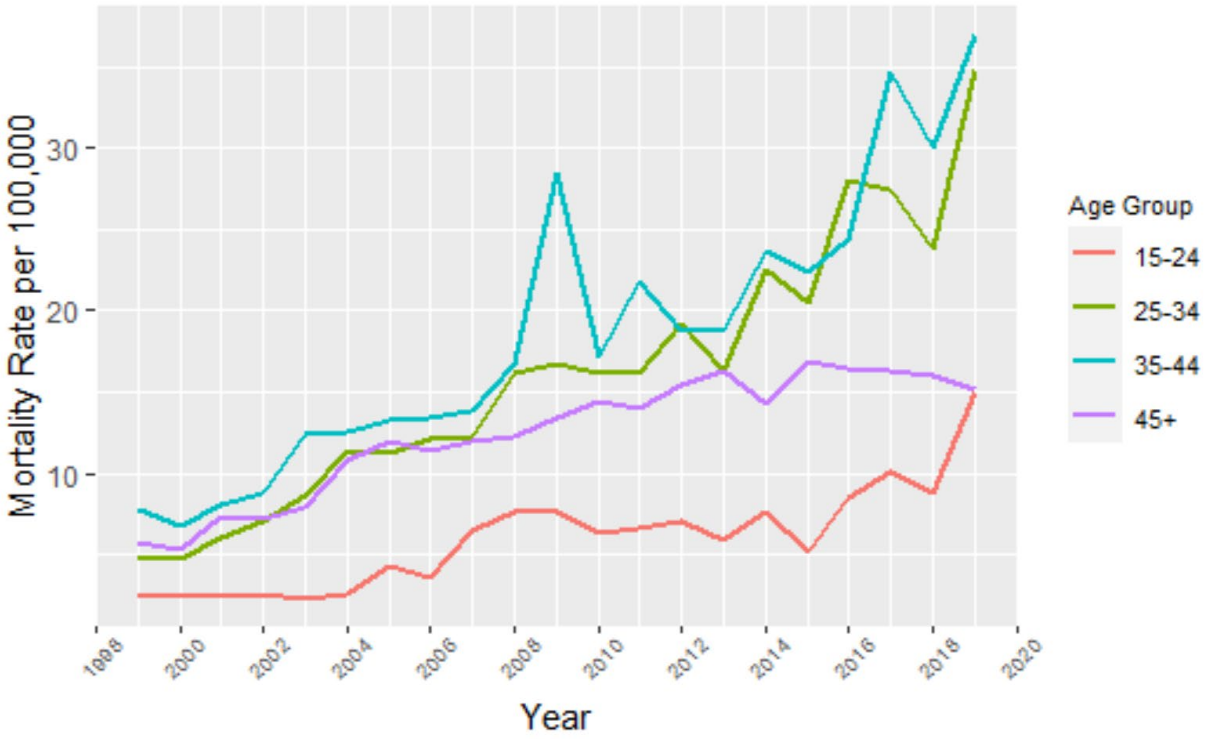

Figure 1a: Trends in opioid-only[1] death rates among US NH-AIAN 15 and older by age groups

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

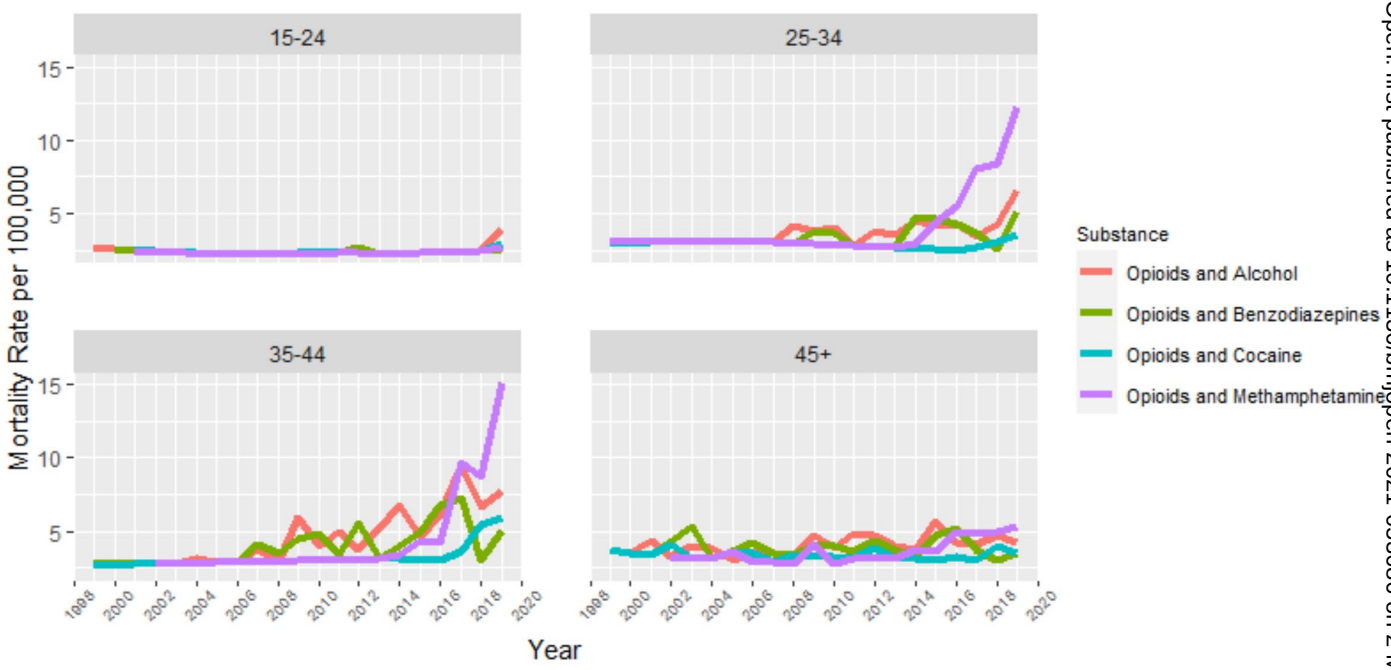

Figure 1b: Trends in opioid combination[1] death rates among US NH-AIAN age groups 15 and older by substance combination type

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);
Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5);
Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4);
Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9)

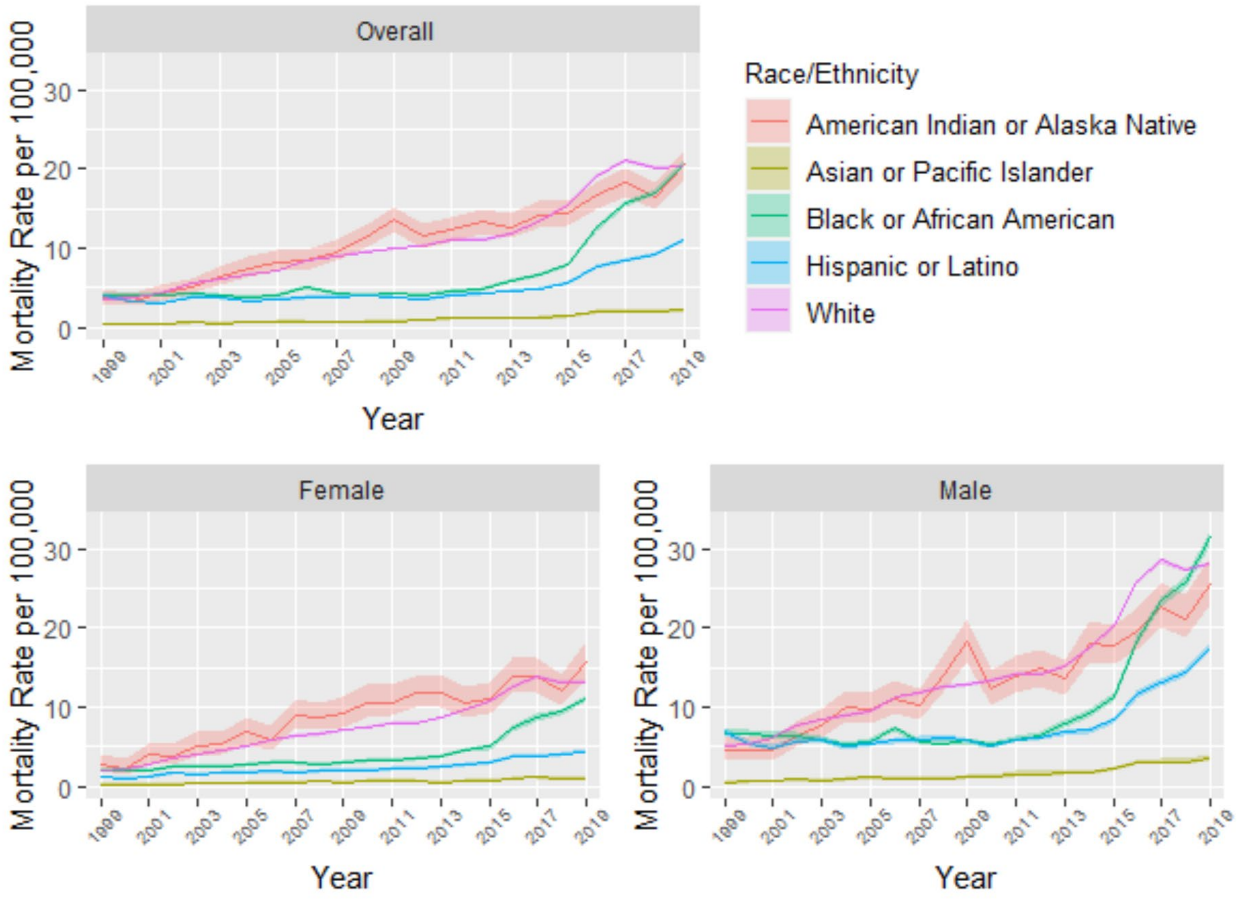

Figure 2a: Trends in opioid-only[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioid-only (underlying: X40-44, X60-64, X85, Y10-Y14; mutilple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6);

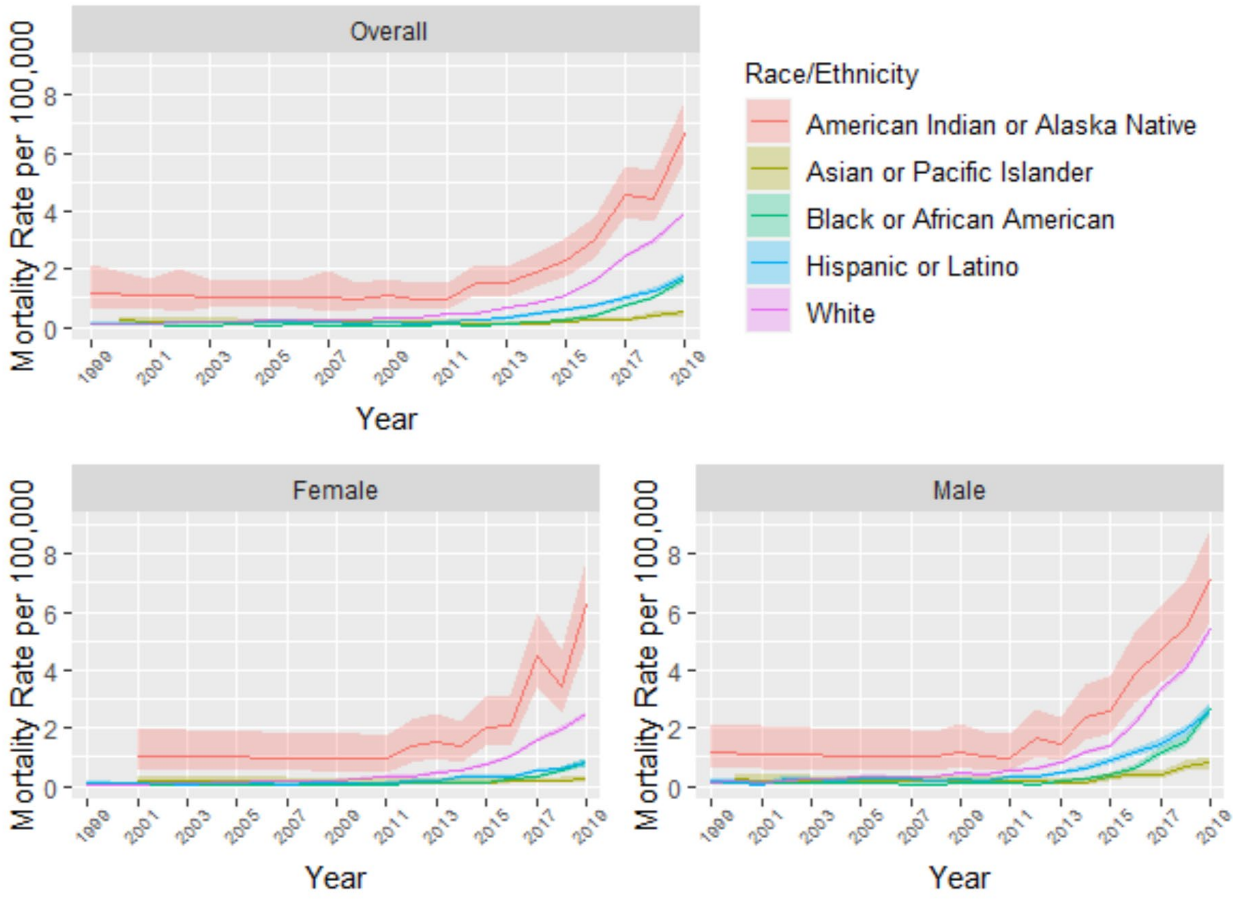

Figure 2b: Trends in opioid and methamphetamine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and methamphetamine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T43.6);

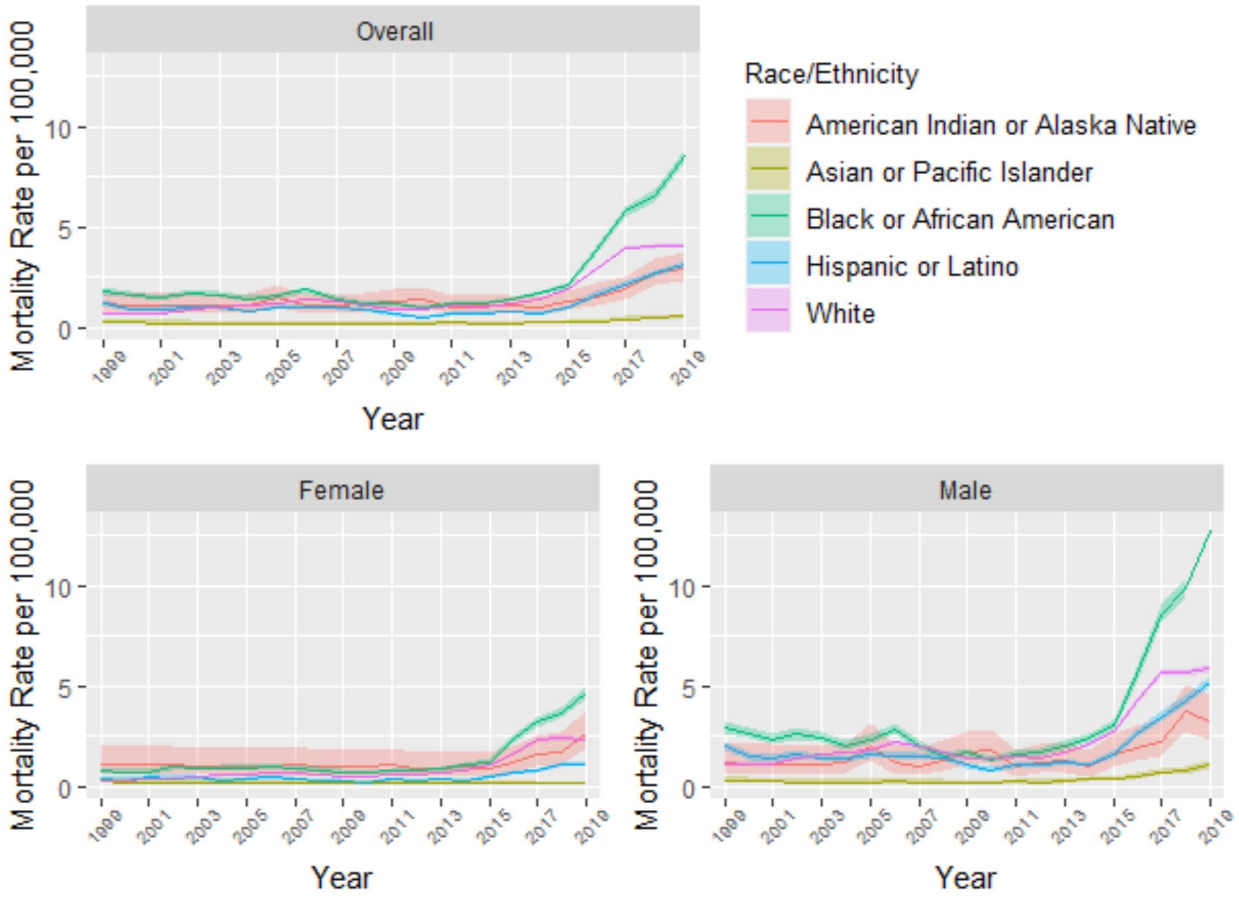

Figure 2c: Trends in opioid and cocaine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and cocaine (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T40.5)

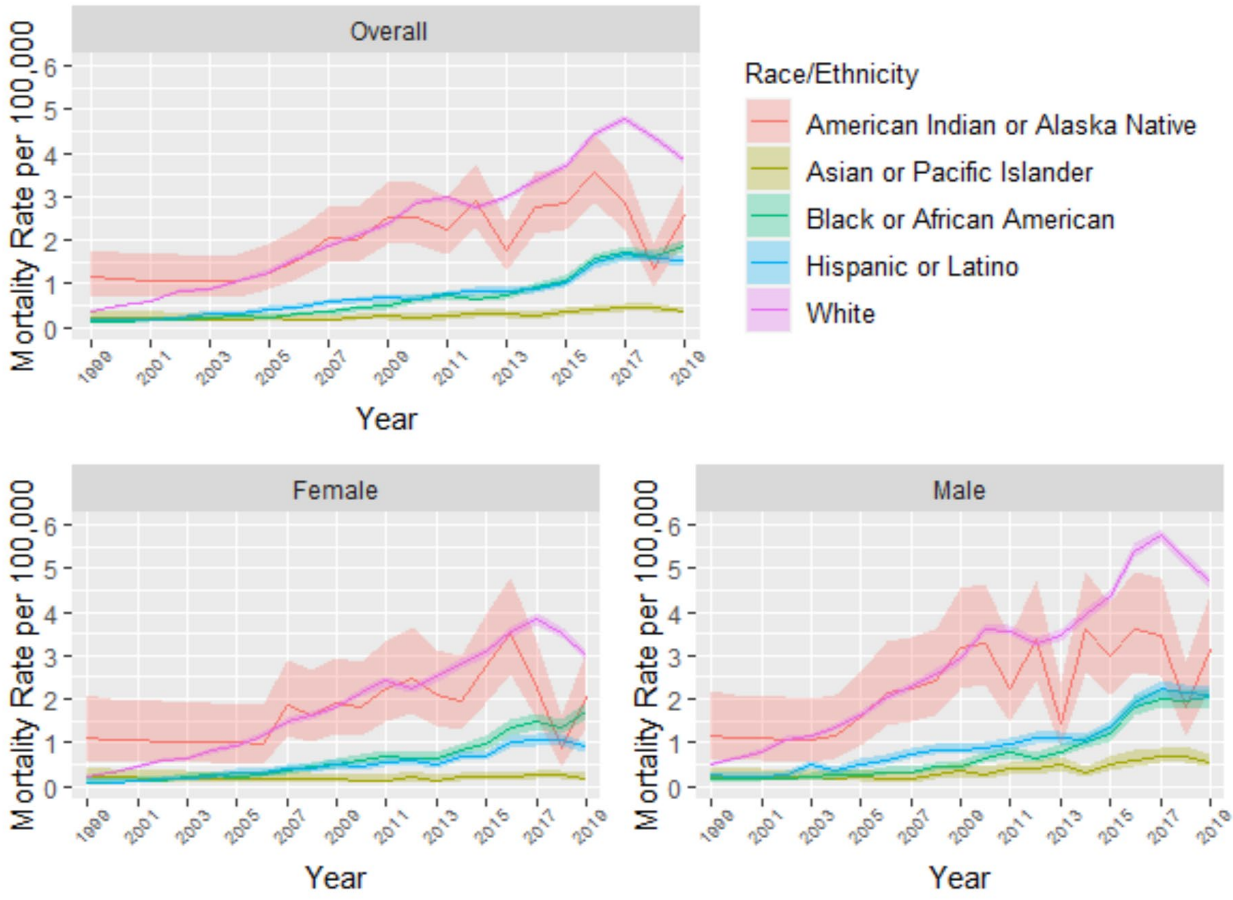

Figure 2d: Trends in opioid and benzodiazepine[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and benzodiazepines (underlying: X40-44, X60-64, X85, Y10-Y14; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T42.4)

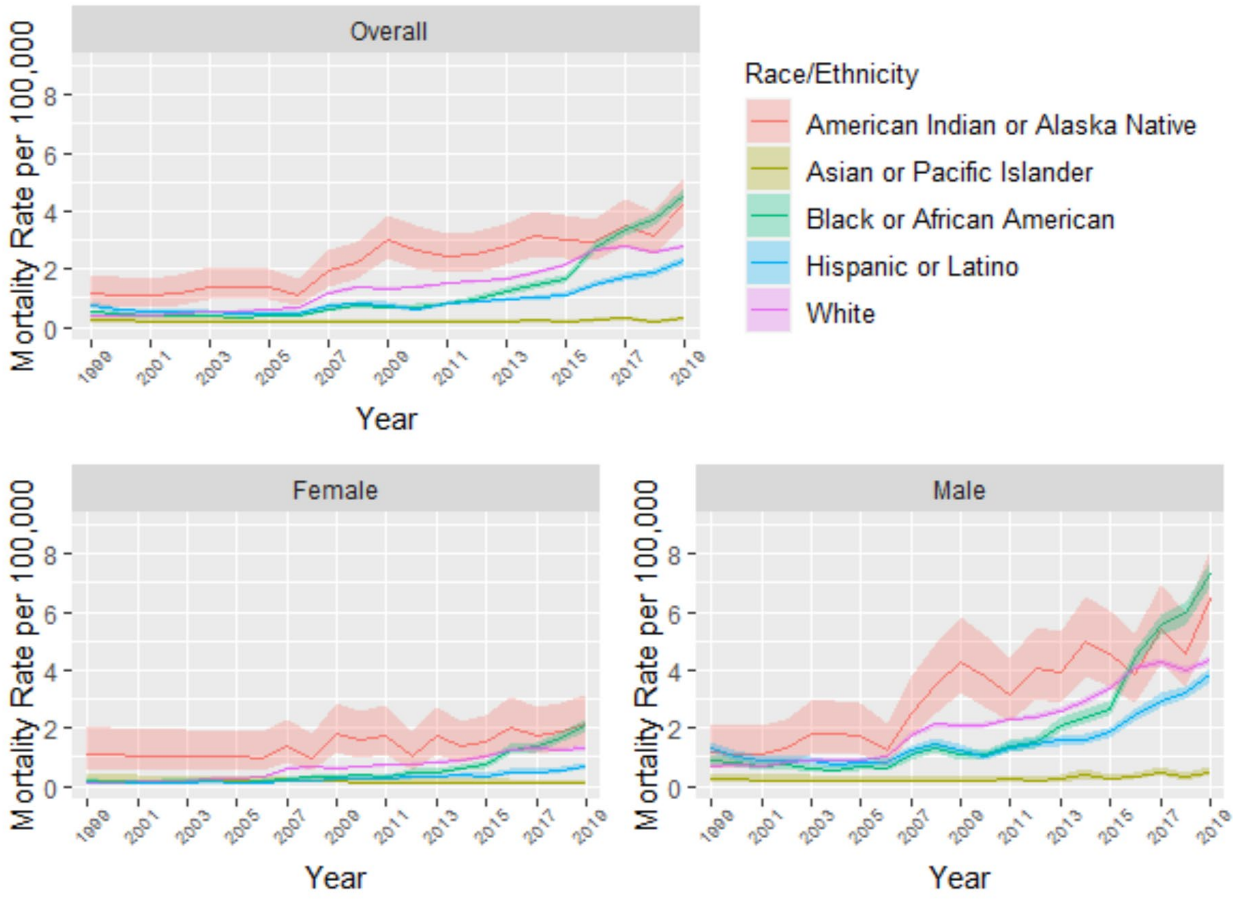

Figure 2e: Trends in opioid and alcohol[1] death rates among US men and women 12 and older by race and ethnicity

[1] Opioids and alcohol (underlying: R78.0, X40-45, X60-65, X85, Y10-Y15; multiple: T40.0, T40.1, T40.2, T40.3, T40.4, T40.6 and T51.0, T51.1, T51.9);

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Title and Abstract page
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract page
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Manuscript page 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Manuscript page 2
Methods			
Study design	4	Present key elements of study design early in the paper	Manuscript page 3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Manuscript page 3
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	Manuscript page 3
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Manuscript page 3-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Manuscript page 3-5
Bias	9	Describe any efforts to address potential sources of bias	Manuscript page 4-5
Study size	10	Explain how the study size was arrived at	Manuscript page 3
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Manuscript page 3-5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Manuscript page 5
		(*b*) Describe any methods used to examine subgroups and interactions	Manuscript page 3-5
		(*c*) Explain how missing data were addressed	Manuscript page 4
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	-
		(*e*) Describe any sensitivity analyses	Manuscript page 5
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	All data captured on aggregate and each analysis scenario looked at different sub-population of patients within AIANs, eligibility criteria described in Manuscript page 3-5
		(b) Give reasons for non-participation at each stage	Manuscript page 3
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Manuscript page 4-7
		(b) Indicate number of participants with missing data for each variable of interest	Manuscript page 4
Outcome data	15*	Report numbers of outcome events or summary measures	Manuscript page 5-6
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Manuscript page 5-6
		(*b*) Report category boundaries when continuous variables were categorized	Manuscript page 7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	_
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Manuscript page 7
Discussion			
Key results	18	Summarise key results with reference to study objectives	Manuscript page 7-8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Manuscript page 9-10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Manuscript page 8-10
Generalisability	21	Discuss the generalisability (external validity) of the study results	Manuscript page 8-10
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if	Manuscript page 11

applicable, for the original study on which the present article is based	

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.