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Longitudinal changes in co-involved drugs, comorbidities, and demographics of methamphetamine-related deaths in Los Angeles County

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ABSTRACT

Introduction: We conducted a population-based observational study of all medical examiner cases in Los Angeles County from January 2012 through June 2021 in which methamphetamine was listed as a cause of or contributing factor to death (n = 6125). We aimed to characterize demographics, comorbidities, and co-involved substances in methamphetamine-related deaths longitudinally in Los Angeles County, California.

Methods: We used detailed death record data to manually classify fatalities by involvement of each organ system, opioids, alcohol, cocaine, other drugs or medications, and external/traumatic causes. Primary outcomes included: the number of methamphetamine-involved deaths, demographics of decedents, percentage of methamphetamine deaths also involving other drugs, and percentage of methamphetamine deaths involving different organ systems. We performed Mann Kendall tests of trends to identify statistically significant longitudinal changes.

Results: During the study period, the percentage of methamphetamine-related deaths involving opioids significantly increased from 16 % in 2012 to 54 % in 2021 ($p < 0.001$). Concurrently, the percentage involving cardiovascular causes significantly decreased from 47 % to 26 % ($p < 0.05$). Methamphetamine-related deaths in LAC increasingly affected people experiencing homelessness, for whom the percentage tripled from 13 % in 2012 to 35 % in 2021. The share of decedents under 40 years old increased from 33 % to 41 %. The percentage of Black or African American decedents increased over five-fold from 3 % to 17 %.

Conclusions: Methamphetamine-related deaths involving opioids more than tripled in Los Angeles County from 2012 to 2021, reflecting the drug supply's shift to illicit fentanyl. More than a quarter involved cardiovascular causes. These findings have implications for treatment and prevention, including scaling up contingency management, distributing naloxone to people who primarily use stimulants, and including cardiovascular care alongside these interventions directly targeted to reduce harms of methamphetamine use.

1. Introduction

Methamphetamine use and related deaths have increased in the United States in recent years, reaching unprecedented levels (Ciccarone, 2021; Ciccarone & Shoptaw, 2022; Han, Cotto, et al., 2021). Unlike opioid overdoses, whose mechanism is respiratory depression, methamphetamine fatalities typically involve a variety of organ systems and comorbidities (Darke, Duflou, & Kaye, 2017; Darke, Kaye, & Duflou, 2017; Turner et al., 2018). Acutely, methamphetamine use produces a catecholamine surge that rapidly increases heart rate and blood pressure (Reddy, Ng, Oh, Moady, & Elkayam, 2020). Although methamphetamine and other stimulants can cause fatal arrhythmias or other complications in people without underlying cardiovascular disease, fatal complications are more likely in older individuals with existing diseases. For people who use methamphetamine regularly, the hyperadrenergic state creates an imbalance in the vasoregulatory system resulting in hypertension, cardiac fibrosis, and cardiotoxicity (Kevil et al., 2019). As a result of chronic use and concomitant cardiovascular remodeling,

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individuals have decreased physiologic reserve and are more susceptible to succumb to cardiomyopathy, ischemic heart disease, and/or pulmonary hypertension (Kevil et al., 2019).

Nationally, deaths involving methamphetamine with and without opioids have increased in recent years (Han, Compton, Jones, Einstein, & Volkow, 2021). Fentanyl has increasingly been detected in urine drug screens positive for methamphetamine (LaRue et al., 2019), and evidence exists of increasing intentional co-use of methamphetamine with heroin or fentanyl (i.e., goofballing) (Glick, Klein, Tinsley, & Golden, 2021; Palamar et al., 2022). Some seizure data suggest an increasingly contaminated or comingled supply (Park et al., 2021).

The available literature suggests key treatment and prevention gaps for people who die from methamphetamine overdose, particularly when opioids are involved. A study of approximately 1380 Veterans Health Administration patients who died from a methamphetamine overdose between 2012 and 2018 found that compared to veterans who died from methamphetamine overdose without opioids, those who died from overdose involving both methamphetamine and opioids were less likely to have been diagnosed with a stimulant use disorder (Coughlin et al., 2022). The same study found that <30 % of veterans who died from a stimulant overdose (methamphetamine or cocaine) had received any substance use disorder treatment in the year prior to their death.

Despite the increase in deaths involving opioids and methamphetamine, and the well-documented cardiovascular conditions that arise from or are exacerbated by methamphetamine use, research has not examined the way these factors may interplay at a population level. A better understanding of trends in co-involved substances and organ systems in methamphetamine-related deaths can inform prevention and treatment. The limited information describing comorbidities and detailed polysubstance involvement stems from limitations inherent to national mortality reporting systems. Nevertheless, detailed records from medical examiner and coroner data can provide granular details (Friedman et al., 2022; Shover et al., 2020; Shover, Falasinnu, Freedman, & Humphreys, 2021). We leveraged medical examiner data from Los Angeles County (LAC) to provide a detailed examination of changes in comorbidities, co-involved substances, and decedent demographics of deaths involving methamphetamine.

With a population of approximately 10 million, LAC had the highest number of overdose deaths (2133) of any United States county in 2020 (National Center for Health Statistics, 2022; U.S. Census Bureau, 2022). That year, according to national statistics released by the Centers for Disease Control and Prevention, overdose deaths involving psychostimulants with abuse potential, an International Classification of Diseases category dominated by methamphetamine, accounted for 49 % of all fatal overdoses in LAC compared to 25 % nationwide (Han, Compton, et al., 2021; National Center for Health Statistics, 2022). LAC is thus a highly relevant setting to examine the rising toll of methamphetamine-related deaths. In this retrospective observational study of all deaths referred to the LAC Department of the Medical Examiner and Coroner (DMEC) from January 2012 and June 2021, we sought to characterize changes in methamphetamine-related deaths over this period. Specifically, we aimed to analyze longitudinal trends in methamphetamine-related deaths in LAC from 2012 to 2021, including annual death toll, demographics, organ systems, and co-involved drugs.

2. Methods

We obtained demographic and cause of death data representing all death investigations in LAC from January 1, 2012, through June 30, 2021, from the LAC DMEC. The DMEC is required by state law to determine cause of death of all sudden, violent, or unusual deaths, as well as deaths in which the decedent had not been seen by a physician in the 20 days prior to death (Los Angeles County Medical Examiner and Coroner, 2018). This number includes all drug-related causes of death. These records include age, sex, a single variable for race and ethnicity, manner of death (i.e., accidental, homicide, natural, suicide, undetermined), up to four lines for cause of death, significant contributing factors, and injury description. Race was assessed and input by death investigators, with information from families when available. The medical examiner also indicates if a person is experiencing homelessness at time of death. We classified deaths as methamphetamine-related when "methamphetamine" was listed in the fields: cause of death (cause A–cause D), contributing factors, or description of injury. The study did not included cases in which methamphetamine was detected during toxicological testing but not listed in the death certificate fields. We then classified deaths by prespecified categories including organ system involvement (Hier & Pearson, 2019); involvement of opioids, alcohol, cocaine, other drugs or medications (any other drug or medication besides opioids, alcohol, or cocaine that was listed); neonatal death (in utero or <4 weeks); obesity; and external or traumatic causes (e.g., homicide, suicide, drowning, blunt trauma, vehicle accidents). The study categorized neonatal deaths separately because these made up a substantial category, including records of intrauterine fetal demise in which methamphetamine was a cause or contributing factor. We added the category "obesity" when it emerged as a recurrent standalone cause of death that did not indicate specific organ system involvement. Co-authors (CLS, RR, BC, AT, JAM) assigned each death to one or more categories with physician co-authors (RB, DGM) making a final decision in ambiguous cases (Hier & Pearson, 2019).

We employed a supervised coding model with sampled double-coding and calculated percent agreement. CLS checked the first 10 records that each of the other four coders categorized for accuracy before allowing the coder to continue. After all authors finished coding, we selected 200 records randomly to be double coded by CLS, 50 from each of the other four coders. For each attribute coded, the percent agreement was 97 % or higher with an overall percent agreement of 98.9 % across all attributes. Given this high level of agreement, the rest of the records were singly coded.

2.1. Statistical methods

For each year and demographic group, drug, and organ system, we calculated the number of methamphetamine-related deaths. The study did not assess statistical uncertainty for these estimates, as the data represent the total population of this jurisdiction. We used a Mann Kendall trend test to determine statistically significant trends over time for each set of deaths related to methamphetamine use (total number per year, and percentage of all methamphetamine-deaths for each category). In response to the findings on the shift in age, race, and homelessness status and causes of death over time, we conducted three additional analyses: 1) age differences by the most common co-involved drugs and organ systems, 2) differences in cause of death by homelessness status, 3) differences in cause of death by race. We performed these analyses in R version 4.1.1 and Stata version 17.0.

3. Results

The analysis included 6125 methamphetamine-involved deaths occurring between January 1, 2012, and June 30, 2021 (Table 1). The number of methamphetamine-involved deaths per year grew from 238 in 2012 to 1385 in 2020, the last year with complete data ($p < 0.001$). People experiencing homelessness comprised an increasing share of deaths from 13 % of all methamphetamine-related deaths in 2012 to 35 % in 2020 (see Fig. 1). Excluding neonatal deaths, the average age of decedents was 45.1 years (range 11 to 86). The racial composition of decedents changed during the study period with an increasing proportion of Black and decreasing proportions of white and Asian decedents (Fig. 2).

3.1. Methamphetamine-related deaths with and without other drugs

The proportion of methamphetamine-related deaths (14.8 %) that

Table 1
Characteristics and comorbidities of people with methamphetamine as cause of or contributing factor to death in Los Angeles County, California.

	Total		2012		2021 (Jan–Jun)		Mann–Kendall test of trend
	n	%	n	%	n	%	p-Value
Sex							
Male	4727	77 %	192	81 %	515	77 %	
Female	1389	23 %	45	19 %	155	23 %	0.47
Unknown	9	0 %	1	0 %	1	0 %	N/A
Age group							
>1 year	218	4 %	15	6 %	13	2 %	1.00
1–10 years	0	0 %	0	0 %	0	0 %	N/A
11–19 years	21	0 %	1	0 %	2	0 %	0.17
20–29 years	751	12 %	22	9 %	101	15 %	<0.01
30–39 years	1228	20 %	41	17 %	156	23 %	<0.01
40–49 years	1508	25 %	75	32 %	138	21 %	<0.01
50–59 years	1614	26 %	63	26 %	176	26 %	<0.01
60–69 years	690	11 %	19	8 %	78	12 %	<0.001
70–92 years	73	1 %	2	1 %	7	1 %	0.02
Race/ethnicity							
American Indian or Alaska native	24	0.4 %	2	1 %	2	0.3 %	N/A
Asian or Pacific Islander	219	4 %	12	5 %	14	2 %	0.02
Black	844	14 %	8	3 %	111	17 %	<0.01
White	2778	45 %	125	53 %	278	41 %	0.03
Hispanic or Latin American	2142	35 %	87	37 %	257	38 %	0.11
Other race or ethnicity	25	0.4 %	1	0.4 %	7	1 %	N/A
Unknown	93	2 %	3	1 %	2	0.3 %	N/A
Homeless/indigent	1753	29 %	32	13 %	237	35 %	<0.001
Opioids	2021	33 %	37	16 %	363	54 %	<0.001
Heroin	894	15 %	25	11 %	69	10 %	0.21
Fentanyl	1035	17 %	0	0 %	311	46 %	<0.001
Prescription opioids	295	5 %	12	5 %	20	3 %	0.21
Cocaine	442	7 %	11	5 %	56	8 %	<0.001
Alcohol	502	8 %	10	4 %	63	9 %	0.92
Other drugs or medications	393	6 %	6	3 %	72	11 %	<0.001
External causes (suicide, homicide, drowning, accident)	372	6 %	22	9 %	18	3 %	0.12
Obesity	214	3 %	9	4 %	21	3 %	0.18
Systems involved							
Cardiovascular	2331	38 %	113	47 %	172	26 %	0.05
Endocrine and metabolic	455	7 %	17	7 %	43	6 %	1.00
Ear, nose, throat	10	0.2 %	0	0 %	3	0 %	N/A
Eye	0	0 %	0	0 %	0	0 %	N/A
Gastrointestinal	419	7 %	17	7 %	23	3 %	0.03
Genito-urinary-breast	113	2 %	3	1 %	9	1 %	N/A
Haematological	72	1 %	4	2 %	2	0 %	N/A
Inflammatory or infectious	335	5 %	9	4 %	35	5 %	0.60
Integumentary	40	1 %	1	0 %	3	0 %	N/A
Musculoskeletal	23	0.4 %	0	0 %	2	0 %	N/A
Neoplasms	61	1 %	1	0 %	3	0 %	N/A
Neurological	390	6 %	15	6 %	29	4 %	0.18
Psychiatric	53	1 %	1	0 %	1	0 %	N/A
Respiratory	495	8 %	16	7 %	40	6 %	1.00
Number of substances							
Methamphetamine only	3513	57 %	184	77 %	252	38 %	<0.001
One other drug	1816	30 %	44	18 %	274	41 %	<0.001
Two or more other drugs	796	13 %	10	4 %	145	22 %	<0.001
Number of organ systems involved							
None (drugs only)	3047	50 %	102	43 %	435	65 %	<0.01
One organ system listed	1857	30 %	88	37 %	151	23 %	<0.01
Two or more organ systems listed	1221	20 %	48	20 %	85	13 %	0.05
Polysubstance and at least one organ system	990	16 %	24	10 %	99	15 %	
Total	6125	100 %	238	100 %	671	100 %	

1. Includes morphine, hydrocodone, oxycodone, methadone, tramadol, codeine, buprenorphine, oxymorphone, hydromorphone, meperidine.

did not list any organ systems or other drugs did not significantly change throughout the study period (p = 0.5); however, the proportion involving polysubstance use increased significantly. The percentage with concomitant opioid-involvement grew substantially, with most of the increase attributable to fentanyl and fentanyl analogs, as did the proportion involving cocaine and the proportion involving other non-opioid drugs or medications (Fig. 3).

3.2. Organ system involvement

Nearly half of methamphetamine-related deaths (n = 3045, 49.7 %) did not list any organ systems in cause of death. Thirty percent (n = 1859) listed one system, 14 % listed two, and about 6 % listed three or more. Across the analysis period, the most commonly involved organ systems were cardiovascular (38 %, n = 2331), respiratory (8 %, n = 495), endocrine and metabolic (7 %, n = 455), and gastrointestinal (7 %, n = 419). Cardiovascular system involvement significantly decreased from 47 % in 2012 to 26 % by 2021 (p < 0.05; Fig. 3). The percentage of deaths involving the gastrointestinal system also dropped, from 7 % in 2012 to 3 % in 2021 (p < 0.05). Other systems involvement was stable: the percentage of deaths involving each of the other systems varied by one percentage point at most comparing 2012 to 2021.

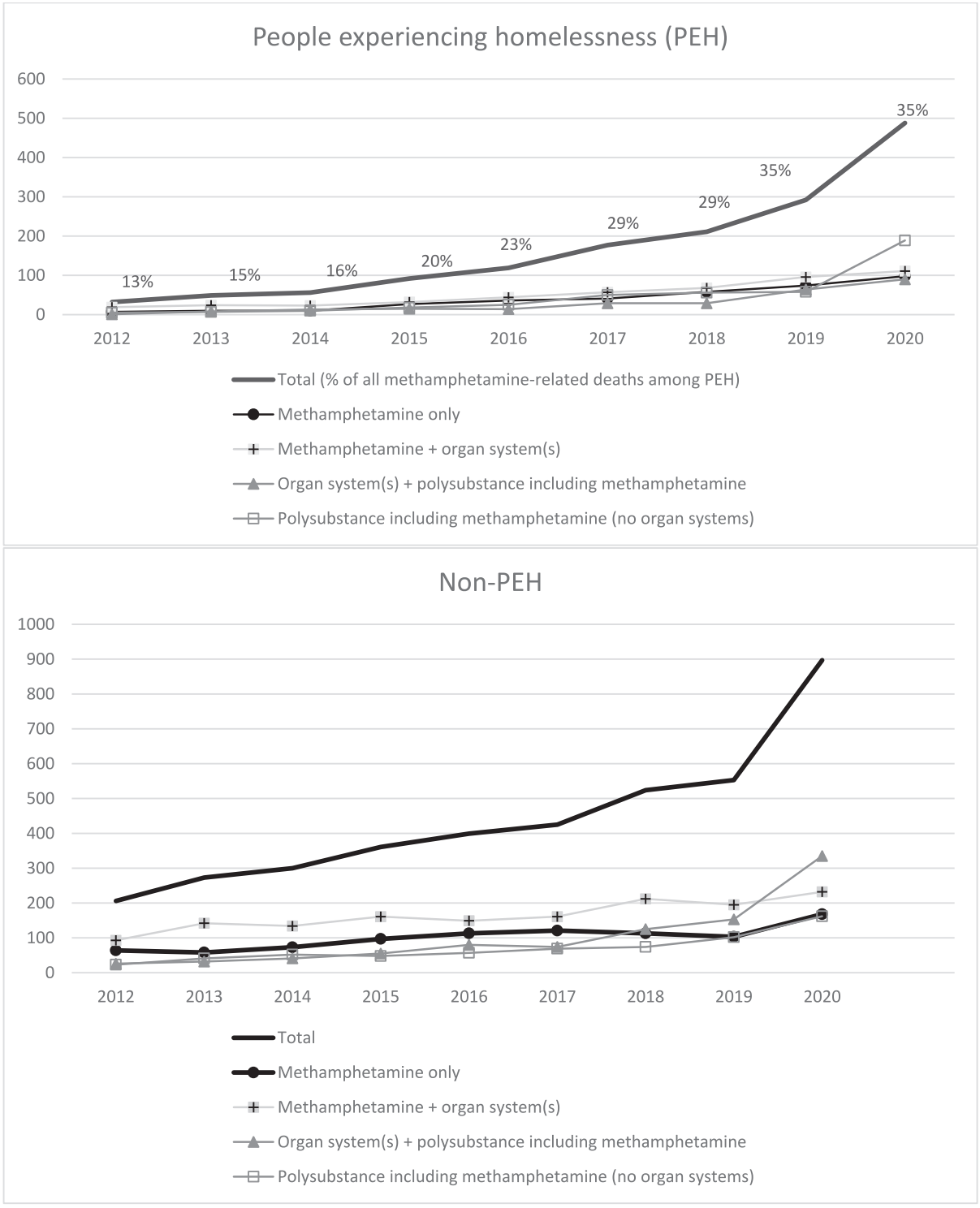


Fig. 1. Annual methamphetamine-related deaths, stratified by homelessness status, polysubstance, and organ system involvement, Los Angeles County, 2012–2020.

3.3. Age differences by cause of death

Deaths involving fentanyl occurred at younger ages (mean age 39.2), while those involving cardiovascular causes (48.5) or multiple organ systems (47.9) occurred at older ages. The mean age for deaths in which only methamphetamine was involved with no comorbidities or co-involved substances was 45.8 years. Mean age for deaths involving opioids but not fentanyl was 43.6 years. Mean age for deaths involving cocaine, alcohol, or other drugs did not substantially differ from the overall mean. The mean age for deaths involving both fentanyl and cardiovascular causes (n = 169) was 41.9 years.

4. Discussion

Methamphetamine deaths in Los Angeles County changed in several key ways from 2012 to 2021: 1) a large increase in the total number of deaths, 2) a dramatic increase in the percentage of deaths among people experiencing homelessness, younger individuals, and Black individuals,

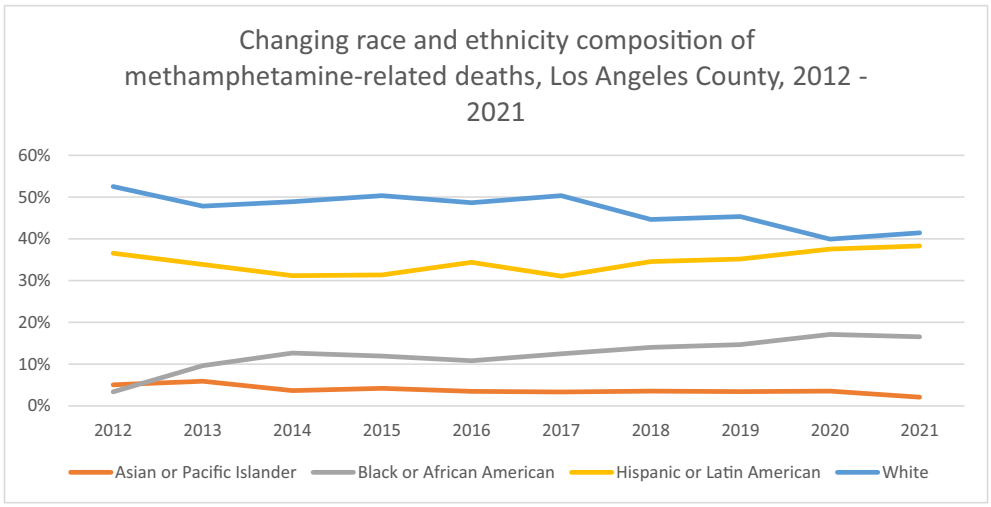


Fig. 2. Changing race and ethnicity composition of methamphetamine-related deaths, Los Angeles County, 2012–2021.

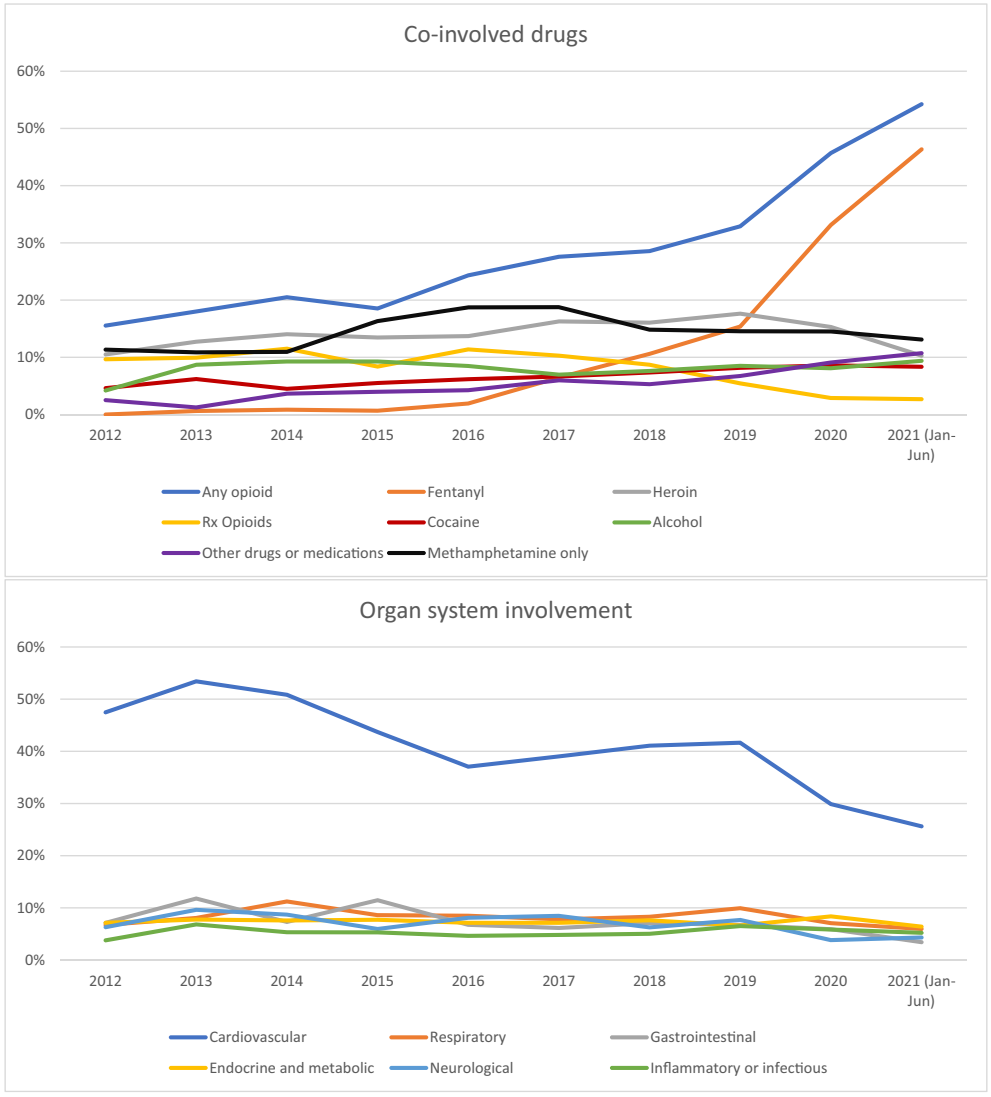


Fig. 3. Longitudinal change in percentage of methamphetamine-related deaths with co-involved causes, Los Angeles County, 2012–2021.

3) a shift to a majority involving concomitant opioids, and 4) a decrease in the percentage of deaths also involving cardiovascular causes. These findings demonstrate how the trajectories of stimulant use have changed in the era of highly potent synthetic opioids, with important implications for treatment and prevention.

At the beginning of the study period, cardiovascular causes accounted for a large percentage of methamphetamine-related deaths. Given that chronic physiological changes due to or exacerbated by methamphetamine use take time, mortality is skewed toward older individuals in the earlier portion of the data. However, in more recent years, the cardiovascular system has been implicated to a lesser degree, and an increase has occurred in the percentage of deaths among younger individuals. With the younger age of death, the sequelae of chronic methamphetamine use such as cardiomyopathy may not be apparent on autopsy. Moreover, the increase in concomitant opioid related deaths may account for this shift as individuals using methamphetamine with little or no opioid tolerance are being exposed to fentanyl earlier in their drug using careers and dying before the chronic changes of methamphetamine use can occur.

Our data had direct implications for treatment, harm reduction, and public health. The first is that given the considerable amount of opioid involved methamphetamine deaths, naloxone should be provided to everyone known to use methamphetamine. Though much naloxone provision occurs in the context of harm reduction services, this finding also means that clinicians treating patients who are known to use methamphetamine, regardless of what the reasons for treatment are, should provide or prescribe naloxone as they would to patients known to use opioids. On the other side, even as opioid involvement has increased, at this time a sizable minority of methamphetamine-related deaths do not involve opioids and involve cardiovascular complications. Modifiable risk factors for cardiovascular disease should be addressed (e.g., hypertension and cholesterol management) alongside directly preventing and treating methamphetamine use disorder (Reddy et al., 2020). Though currently no pharmacotherapies approved for treatment of methamphetamine use disorder exist, treatment with mirtazapine and a combination of long acting naltrexone with high dose bupropion demonstrated evidence for reductions in methamphetamine use (Coffin et al., 2020; Colfax et al., 2011; Trivedi et al., 2021). Contingency management is a nonpharmacologic option that has consistent effectiveness in treatment-seeking populations, including among people experiencing homelessness (Brown & DeFulio, 2020; Ciccarone & Shoptaw, 2022; Rawson et al., 2006; Reback et al., 2010). As of 2022, California initiated a pilot program to provide publicly funded coverage of contingency management, and if successful, wider dissemination should follow (California Department of Healthcare Services, 2021). Finally, harm reduction methods that have not yet been widely implemented in the United States, such as safe consumption sites, deserve consideration and real-world evaluation.

Changes in the demographics of people dying from methamphetamine-related causes deserve further study to inform prevention. The percentage of methamphetamine-related deaths occurring among Black individuals increased more than five-fold from 2012 to 2021, which is in line with findings that overdose deaths have disproportionately increased among Black and other people of color in recent years in California and nationally (Friedman, Hansen, et al., 2021; Friedman, Mann, et al., 2021). The fact that the share of methamphetamine-related deaths occurring among people experiencing homelessness tripled reveals a trend that would not be captured in national data, since housing status is not routinely captured or reported by the National Center for Health Statistics (National Center for Health Statistics, 2022).

Though the finding that people experiencing homelessness account for so large a share of Los Angeles' methamphetamine-related deaths is novel, it squares with previous studies of homelessness, mortality, and methamphetamine use. Homelessness is a known risk for premature mortality from a variety of specific causes, including overdose, cardiovascular disease, and infectious diseases (Brown et al., 2022; Chandra et al., 2022; Chang et al., 2022; Nicholas, Greenwell, Henwood, & Simon, 2021). Previous studies in Los Angeles have documented an association between homelessness and recent methamphetamine use (Anderson-Carpenter, Fletcher, Swendeman, & Reback, 2019), including among youth, where peer group methamphetamine use has been shown to be especially salient (Barman-Adhikari, Begun, Rice, Yoshioka-Maxwell, & Perez-Portillo, 2016; Zhao, Kim, Li, Hsiao, & Rice, 2018). Both nationally and in California, homelessness has also been found to be associated with seeking treatment for methamphetamine use disorder (Jones, Han, Seth, Baldwin, & Compton, 2023; Padwa, Bass, & Urada, 2022).

The changes in causes of methamphetamine-related deaths also indicate a change in the drug supply as fentanyl has permeated the drug supply throughout the western United States (Shover et al., 2020). While the co-occurring presence of methamphetamine and an opioid in a decedent do not distinguish between intentional and unintentional co-use, the rapid rise suggests a major change in the supply and use patterns. Seizure data and news accounts show increasing manufacture of synthetic drugs—namely, methamphetamine and fentanyl—in place of more space-intensive plant-derived drugs like heroin or cannabis (Associated Press, 2021; Palamar, Le, Carr, & Cottler, 2021). As the availability of both methamphetamine and synthetic opioids increases, understanding the product overlap is key, as is targeting opioid overdose prevention tools to people who may primarily use stimulants.

4.1. Limitations

This study relies on death certificate data as overdose surveillance, which introduces some limitations relevant to this study (Slavova et al., 2015). Prior to 2020, full autopsies were performed on suspected overdoses with rare exceptions. Particularly during the increased case load of the COVID-19 pandemic, detailed post-mortem examinations may have been less frequently performed in cases with signs of other causes of death (e.g., drugs and paraphernalia found at the scene), such that some causes only ascertainable on internal examination may be underestimated. The medical examiner's determination that a decedent was homeless was somewhat subjective. If individuals who appeared to be experiencing homelessness were misclassified, the percentage of homeless decedents was slightly overestimated; however, individuals who would meet the Housing and Urban Development definitions of homelessness (which includes individuals fleeing domestic violence and those at imminent risk of homelessness within 14 days) would likely also be misclassified as not homeless (US Department of Housing and Urban Development, 2019). Therefore, the direction and magnitude of this potential bias is unclear.

4.2. Conclusions

The shifting composition of the burden of methamphetamine-involved deaths represents a unique public health challenge. Methamphetamine-related deaths involving opioids more than tripled in Los Angeles County from 2012 to 2021, reflecting a shifting drug supply. The increasing presence of illicitly manufactured fentanyl and other synthetic opioids in the drug supply appears to drive mortality at a younger age for people who use methamphetamine, especially among Black individuals and people experiencing homelessness. These findings highlight the importance of prevention efforts focused on making naloxone widely available for primarily stimulant-using populations and the urgent need for more effective pharmacologic and non-pharmacologic modalities for treatment of methamphetamine use. Contingency management scale up is critically important. Other harm reduction strategies, such as safe consumption sites, may also play a role.

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CRediT authorship contribution statement

CLS: Conceptualization, supervised coding, led data analysis, wrote the first draft.

JRF: Contributed to data analysis and visualization, critically revised the manuscript.

RR: Data collection and coding, critically revised the manuscript.

RB: Clinical interpretation of coding and results, critically revised the manuscript.

BC: Data collection and coding, critically revised the manuscript.

AT: Data collection and coding, critically revised the manuscript.

JAM: Data collection and coding, critically revised the manuscript.

LW: Content-specialist interpretation of results, critically revised the manuscript.

JL: Contextualized findings related to Dept of Medical Examiner and Coroner, critically revised the manuscript.

DGM: Supervision, clinical interpretation of findings, drafted sections of manuscript, critically revised the manuscript.

All authors have read and approved the submitted manuscript.

Declaration of competing interest

None to declare.

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