




# Characterizing Methamphetamine Use Among People Who Use Opioids: A Systematic Review

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## Abstract

Methamphetamine use is increasing among people who use opioids (PWUO); however, factors associated with methamphetamine use among PWUO have not been systematically examined. We searched five electronic databases, from inception to January 3<sup>rd</sup>, 2023, for primary studies that characterized methamphetamine use and its associated risk factors among PWUO. We screened 3801 unique studies and included 33 quantitative primary studies. Two reviewers independently screened, extracted data, and assessed the risk of bias. Findings were narratively summarized. Eleven studies reported increasing trends of methamphetamine use among PWUO in the US and Canada. Twenty-eight studies conducted in North America and Asia examined factors associated with methamphetamine use among PWUO. Methamphetamine use was associated with younger age, residing in rural areas, lower socioeconomic status, mental and physical illnesses, and engaging in risky sexual and drug use behaviours. To combat the expanding “twin epidemic” of opioid and methamphetamine use, scaling up harm reduction interventions, supporting low-threshold addiction care, and investing in therapeutic options for methamphetamine use disorder is warranted.

**Keywords** Methamphetamine · Opioids · Polysubstance use · Review

The drug overdose epidemic remains a significant public health challenge globally, with opioids being the leading cause of drug-related mortalities worldwide (UNODC, 2022). Approximately 61.3 million individuals were reported to have used opioids during the

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preceding year on a global scale in 2020 (UNODC, 2022). Meanwhile, methamphetamine continues to dominate the global supply of amphetamine-type stimulants, and its use has been increasing worldwide (Stoneberg et al., 2018; UNODC, 2022). Notably, recent studies have also reported a concerning trend of increasing methamphetamine use among people who use opioids (PWUO), leading to the emergence of a “twin epidemic” involving concurrent use of opioids and methamphetamine (Ellis et al., 2018; Jones et al., 2020a, b; Strickland et al., 2021; Twillman et al., 2020).

The drug overdose epidemic has a complex history, with drug use patterns varying significantly across different regions (Ciccarone, 2019; Dargan & Wood, 2012; Fischer et al., 2021; Ramachandram et al., 2020). In most settings in North America, the opioid epidemic has unfolded in three distinct waves. From 1999 to 2010, morbidity and mortality were primarily attributed to non-medical prescription opioid use. Between 2010 and 2013, the epidemic was mainly driven by heroin use. More recently, unregulated fentanyl, as well as other synthetic opioids, account for the majority of opioid-related morbidity and mortality (Ciccarone, 2019; Fischer et al., 2021; Karamouzian et al., 2022a). Furthermore, the increased production of methamphetamine in Mexico and subsequent transport into the United States and Canada has led to the high availability of the drug at relatively low prices, contributing to an elevated methamphetamine use prevalence in these countries (Brouwer et al., 2006; Onoka et al., 2020; Shukla et al., 2012). In East and South-East Asia, the transition from opium to heroin as the dominant opioid of use occurred gradually over several decades, and the emergence of fentanyl and other synthetic opioids has occurred more recently (Dargan & Wood, 2012; Ramachandram et al., 2020). Moreover, methamphetamine is widely available, and its use remains a significant public health concern across Asia (McKetin et al., 2008).

Given the rise in methamphetamine use and synthetic drugs contaminating the unregulated drug supply, the nature of the overdose epidemic is evolving and posing new urgent public health challenges (Palamar et al., 2022; Rhed et al., 2022; Taylor et al., 2021). Studies from various international settings have observed high and increasing methamphetamine use prevalence among PWUO (Des Jarlais et al., 2021; EMCDDA, 2021, 2022; Meacham et al., 2018a; Strickland et al., 2021; Wang et al., 2015). For example, a study using a nationally representative sample in the US found a significant surge in past-month methamphetamine use from 9.0% in 2015 to 44.0% in 2019 among individuals reporting past-month heroin use (Strickland et al., 2021). In Vietnam, data from a community-based survey of more than 2000 people who injected heroin suggested consistently high self-reported past-month methamphetamine use (over 40%) from 2016 to 2018 (Des Jarlais et al., 2021). Similarly, in a cohort of 1984 people who injected drugs in Vancouver, the prevalence of recent methamphetamine use significantly increased from 19% in 2006 to 36% in 2017 (Bach et al., 2020).

The combined use of opioids and methamphetamine is a substantial cause for concern, as it can result in serious health consequences, such as an increased risk of overdose, hospitalizations, and death (Al-Tayyib et al., 2017; Spencer et al., 2022; Strickland et al., 2021). The increasing use of methamphetamine has also complicated the opioid use disorders’ (OUD) treatment landscape (Chan et al., 2020; Cui et al., 2023; Frost et al., 2021). Studies have found that methamphetamine use among people receiving medications for OUD is associated with higher rates of treatment dropout and poorer treatment outcomes, including lower rates of abstinence and higher rates of relapse (Chan et al., 2020; Cui et al., 2023; Frost et al., 2021). Several qualitative studies have identified individual and structural reasons for the rise in methamphetamine use among PWUO (Baker et al., 2020; Corser et al., 2022; Daniulaityte et al., 2022; Esmaili et al., 2019; Hansen et al., 2021; Ivsins et al., 2022; Lopez et al., 2021; Palmer et al., 2020; Rhed et al., 2022; Silverstein et al., 2021; Steinberg

et al., 2022). Other reasons include the increased availability and purity of methamphetamine, as well as social and cultural factors, such as peer pressure and the acceptability of methamphetamine use within specific communities (Baker et al., 2020; Esmaili et al., 2019; Hansen et al., 2021; Steinberg et al., 2022).

The “twin epidemic” of methamphetamine and opioid use has created complex challenges for healthcare providers, communities, and policymakers worldwide. To effectively address the escalating risks associated with methamphetamine use among PWUO, it is crucial to have a comprehensive understanding of the individual and structural factors influencing this phenomenon (Park et al., 2020). However, the characteristics of methamphetamine use among PWUO have not been systematically summarized to draw essential insights. Therefore, this systematic review aims to comprehensively synthesize the available quantitative evidence characterizing methamphetamine use among PWUO. The objectives of this review are to characterize: 1) Methamphetamine use trends among PWUO; and 2) Individual and structural factors associated with methamphetamine use among PWUO. The insights from this review could contribute to the development of effective prevention, treatment, and harm reduction strategies targeting methamphetamine use among PWUO.

## Methods

### Databases and Search Strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Page et al., 2021), we conducted a comprehensive search for empirical peer-reviewed studies or gray literature on the use of methamphetamine among PWUO from inception to January 3<sup>rd</sup>, 2023, across several databases, including MEDLINE, PsycINFO, CINAHL, Embase, and the first 200 records of Google Scholar (Haddaway et al., 2015). Search terms were combined using appropriate Boolean operators. They included relevant subject heading terms and keywords for two primary search concepts, adjusted for use in each database: Opioid use (e.g., opioid OR opiate OR fentanyl OR heroin OR methadone OR buprenorphine OR hydromorphone) AND methamphetamine use (e.g., amphetamine OR methamphetamine). We additionally performed hand searches of the bibliographies of relevant published works, relevant conference proceedings, gray literature databases, and dissertations. Our search strategy was not restricted by publication date or language. A sample search strategy is included in Table S1. All inclusion criteria and analytical approaches were established *a priori* and documented in a PROSPERO protocol (Registration Number: CRD42022372905).

### Inclusion and Exclusion Criteria

Observational studies of any design (e.g., cross-sectional, cohort) and baseline data of experimental studies prior to interventions were considered for inclusion if they characterized methamphetamine use among PWUO. Additionally, the study population was limited to individuals who used opioids to a degree defined as “problematic” by the original study’s definition (Karamouzian et al., 2022a, b). This included: i) Individuals who used unregulated opioids, such as heroin and fentanyl; ii) Individuals who used prescription opioids for non-medical purposes; iii) Individuals who were diagnosed with OUD as defined

by the Diagnostic and Statistical Manual of Mental Disorders (DSM) or other validated diagnostic tools (American Psychiatric Association, 2013); or iv) Individuals who were seeking or receiving treatment for OUD. We also included studies with mixed populations of PWUO and people using other substances if they provided separate analyses for participants with PWUO. Studies were included if their study outcomes were any frequency and route of methamphetamine use or initiation during any time interval (e.g., lifetime, past year, past six months, past month, current). Studies were also included if they used latent class analysis to study factors associated with a latent methamphetamine and opioid use class compared to a latent opioid use-only class. Different studies using the same data source were included if they examined different methamphetamine outcomes or their associated covariates. Qualitative research, reviews, expert opinions, and studies that did not allow for the quantification of measures of associations were excluded.

## Screening Process

All records were imported into Covidence (Veritas Health Innovation, Melbourne) and de-duplicated. Two independent reviewers (ZC and AN) screened the titles and abstracts to ensure that each study met the criteria for inclusion in the review. Studies that met the inclusion criteria or were unclear were retained for full-text screening conducted by two independent reviewers (ZC and AN). When conflicts arose during the screening or data extraction process, ZC, AN, and a third co-author, MK, resolved them by consensus.

## Data Extraction

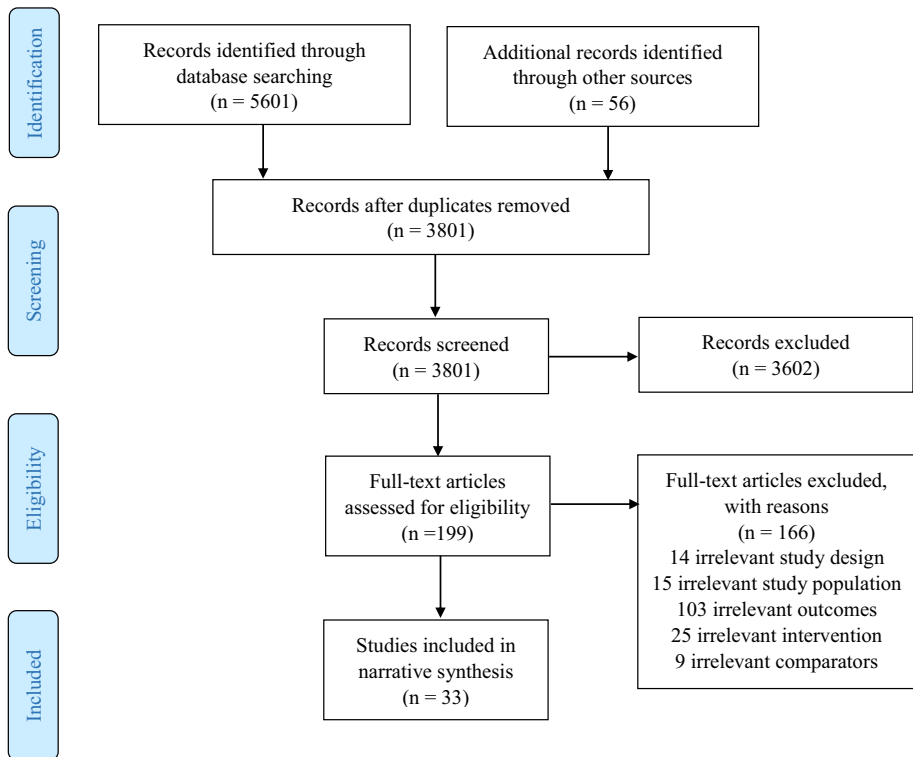
Data were extracted on study characteristics (e.g., study design, study date, location), participant characteristics (e.g., sample size, age, gender, ethnicity/race), outcome characteristics (e.g., ascertainment, definitions), and the main findings reported. Due to substantial variation in participants' characteristics, covariates (i.e., a range of individual and structural factors in the unadjusted or adjusted analyses), and outcome definitions (i.e., different frequencies and routes of methamphetamine use during varying time intervals), no meta-analysis was conducted. Study findings were summarized and presented narratively. The primary factors associated with methamphetamine use were identified and presented.

## Risk of Bias Assessment

We utilized a modified version of the Newcastle-Ottawa Quality Assessment Scale to independently assess the risk of bias in the studies included in our review. The tool employs multiple components to evaluate selection bias, comparability, and outcome assessment (Wells et al., 2000).

## Results

Our search strategy yielded 3801 unique records eligible for inclusion in this study. After screening the titles and abstracts, 199 were retained for full-text screening. Of those, a total of 33 studies met our inclusion criteria. Figure 1 provides a PRISMA flow diagram summarizing the article selection process and Table S2 provides the PRISMA checklist.



**Fig. 1** PRISMA flow diagram of the study screening process

## Study Overview

An overview of the included studies is presented in Table 1. All included studies were conducted over the period between 2000 and 2020. Most studies ( $n = 21$ ) were conducted in North America, with 16 in the US, three in Mexico, and two in Canada. A total of 9 studies were conducted in East Asia, with three in China, three in Malaysia, and three in Vietnam and three studies were conducted in West Asia (i.e., Iran).

Overall, 21 were cross-sectional, five were repeated cross-sectional, and seven were longitudinal cohort studies. Among the 33 studies, 12 characterized trends of methamphetamine use over time, and 28 studies examined various factors associated with methamphetamine use. Of the 28 studies, 16 conducted unadjusted comparisons, while the other 12 studies conducted multivariable models. Out of the total number of studies analyzed, 14 studies utilized convenience sampling recruitment in clinics, while eight studies employed a snowball or respondent-driven sampling strategy. Additionally, seven studies relied on surveillance data, while four studies utilized a nationally representative survey.

## Study Participants

Table 2 summarizes the characteristics of study participants in the included studies. All studies included a sub-population of PWUO, although the inclusion criteria of the

**Table 1** Overview of included studies in the systematic review of characterizing methamphetamine use among people who use opioids

First author (Publication year)	Location	Year	Data source	Study design	Sampling method	Quality
Choi et al. (2022)	US (National)	2012-2019	TEDS-A	Retrospective cohort study	Surveillance data	Very good
Smith et al. (2022)	US (National)	2019	NSDUH	Cross-sectional	Stratified multistage	Good
El Ibrahimy et al. (2022)	Oregon, US	2014-2017	TEDS-A linked with Medicaid	Cross-sectional	Surveillance data	Very good
Cui et al. (2022b)	Vancouver, BC, Canada	2005-2020	VIDUS & ACCESS	Prospective cohort study	Convenience/Snowball	Good
Cui et al. (2022a)	Vancouver, BC, Canada	2005-2020	VIDUS & ACCESS	Prospective cohort study	Convenience/Snowball	Good
Giang et al. (2022a)	Hai Phong, Vietnam	2019-2020	Drug use and infections in Vietnam survey	Prospective cohort study	Respondent-driven	Good
Giang et al. (2022b)	Hanoi, Vietnam	2018	A face-to-face paper-based survey in 17 MMT clinics	Cross-sectional	Convenience	Good
Havens et al. (2022)	Appalachian Kentucky, US	2008-2020	SNAP study	Prospective cohort study	Convenience	Good
Ellis et al. (2021)	US (National)	2012-2019	SKIP	Cross-sectional	Surveillance data	Good
Strickland et al. (2021)	US (National)	2015-2019	NSDUH	Repeated cross-sectional	Stratified multistage	Good
Glick et al. (2021)	Seattle and King County, Washington, US	2017 and 2019	Public Health-Seattle & King County syringe service programs	Repeated cross-sectional	Convenience	Good
Des Jarlais et al. (2021)	Hai Phong, Vietnam	2016-2018	A face-to-face interview on participants from three large community-based organizations	Repeated cross-sectional	Respondent-driven	Good
Twillman et al. (2020)	US (National)	2013-2019	Urine test results from urine specimens submitted for testing by health care professionals as part of routine care	Cross-sectional	Convenience	Very good

Table 1 (continued)

First author (Publication year)	Location	Year	Data source	Study design	Sampling method	Quality
Cicero et al. (2020)	US (National)	2011-2018	SKIP	Cross-sectional	Surveillance data	Very good
Shearer et al. (2020)	US (National)	2015-2018	NSDUH	Repeated cross-sectional	Stratified multistage	Good
Daniulaityte (2020)	Dayton area (Montgomery County), Ohio, US	2017-2018	Baseline for longitudinal structured interviews	Cross-sectional	Respondent driven	Good
Mamat et al. (2020)	Kuantan, Pahang, Malaysia	2018-2019	A semi-structured questionnaire among participants from nine primary health-care methadone clinics	Cross-sectional	Convenience	Fair
Singh et al. (2020)	Klang Valley, Malaysia	2018	A face-to-face survey among respondents from three primary and four private MMT sites	Cross-sectional	Snowball	Fair
Jones et al. (2020b)	US (National)	2008-2017	TEDS-A	Retrospective cohort study	Surveillance data	Very good
Strickland et al. (2019)	US (national)	2015-2017	NSDUH	Repeated cross-sectional	Stratified multistage	Good
Danesh & Noroozi (2019)	Golestan Province, Iran	2015	A questionnaire administered in 25 outpatient drug treatment clinics	Cross-sectional	Convenience	Good
Singh et al. (2019)	Kuantan, Pahang, Malaysia	2017	A face-to-face survey among respondents from five primary MMT program sites and two private MMT sites	Cross-sectional	Convenience	Fair
Ellis et al. (2018)	US (National)	2011-2017	SKIP	Cross-sectional	Surveillance data	Very good

**Table 1** (continued)

First author (Publication year)	Location	Year	Data source	Study design	Sampling method	Quality
Meacham et al. (2018a)	Tijuana, Baja California, Mexico	2011-2012	Baseline of a survey-based prospective cohort study	Cross-sectional	Convenience	Good
Meacham et al. (2018b)	Tijuana, Baja California, Mexico	2011-2012	Baseline of a survey-based prospective cohort study	Cross-sectional	Convenience	Good
Tavakoli et al. (2018)	Mashhad, Karaj, and Isfahan, Iran	2012	A questionnaire administered in 38 main methadone treatment services	Cross-sectional	Convenience	Fair
Alammehjerdi et al. (2017)	Tehran, Iran	2014-2015	A questionnaire administered in four large methadone treatment services	Cross-sectional	Convenience	Poor
Al-Tayyib et al. (2017)	Denver, Colorado, US	2015	The National HIV Behavioural Surveillance (NHBS) system established by the Centres for Disease Control and Prevention	Cross-sectional	Respondent driven	Good
Dong et al. (2017)	Hunan, China	2013-2014	Participants were recruited from public security systems, including compulsory or voluntary rehabilitation centres	Cross-sectional	Convenience	Fair
Meacham et al. (2015)	Tijuana, Baja California, Mexico	2006-2007	Baseline of a survey-based prospective cohort study	Cross-sectional	Respondent-driven	Good
Wang et al. (2015)	Dehong, Yunnan, China	2014	A structured questionnaire administered in five MMT clinics	Cross-sectional	Convenience	Good



**Table 1** (continued)

First author (Publication year)	Location	Year	Data source	Study design	Sampling method	Quality
Lin et al. (2013)	Taiwan, China	2005-2010	Medical records and registration data of addiction treatment outpatient clinics of three hospitals in the national MMT system were retrospectively reviewed	Retrospective cohort study	Surveillance data	Good
Back et al. (2011)	Colorado, Washington, Oregon, Connecticut, New York, Virginia, North Carolina, US	2003-2005	Baseline of a randomized controlled trial investigating the effectiveness of two buprenorphine tapering schedules	Cross-sectional	Convenience	Very Good

ACCESS: AIDS Care Cohort to evaluate Exposure to Survival Services study;

MMT: Methadone Maintenance Therapy;

NSDUH: National Survey on Drug Use and Health - an annual nationally representative survey;

SKIP: Survey of Key Informants' Patients - a Program run by Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System;

SNAP: Social Networks among Appalachian People;

TEDS-A: Treatment Episodes Data Set - Admissions;

VIDUS: Vancouver Injection Drug Users Study

**Table 2** Sample characteristics of included studies in the systematic review of characterizing methamphetamine use among people who use opioids

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Choi et al. (2022)	<i>Inclusion:</i> Treatment admissions involving heroin, where treatment centres received public funding, and patients aged 55 or older. <i>Exclusion:</i> NR	299,073 admissions	Age $\geq$ 55: 100%	Male: 74.5%	Non-Hispanic White: 27.5%
Smith et al. (2022)	<i>Inclusion:</i> Non-institutionalized US residents reporting lifetime heroin or non-medical prescription opioid use but no Kratom use, aged 12 or older. <i>Exclusion:</i> NR	NR	Age<26: 15.5%	Male: 54.7%	White: 71.0%
El Ibrahimy et al. (2022)	<i>Inclusion:</i> Patients with treatment admissions involving heroin, where the treatment centres received public funding. <i>Exclusion:</i> Patients with a missing Medicaid ID or more than a 90-day gap in Medicaid enrollment in each study year.	3,802	Age<40: 71.0%	Male: 48.7%	White: 68.6%
Cui et al. (2022b)	<i>Inclusion:</i> Study visits to when the participants were receiving OAT during the past six months prior to the interview date, where OAT includes methadone (94.6%), buprenorphine-naloxone, slow-release oral morphine, or injectable OAT, involving no past-6-month methamphetamine use at the immediately preceding study visits. <i>Exclusion:</i> NR	1,281 participants and 11,230 visits	Baseline median: 43	Male: 59.2%	White: 63.4%

**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Cui et al. (2022a)	<i>Inclusion:</i> Participants reporting at least weekly unregulated opioid use and/or receiving OAT in the past six months at baseline. <i>Exclusion:</i> The visits with no preceding visits within the past year	1,742 participants and 20,114 visits	Baseline median (Q1-Q3): 42 (34-48)	Male: 61.3%	White: 60.3%
Giang et al. (2022b)	<i>Inclusion:</i> People enrolled in one of the five largest MMT clinics in Hanoi at the time of the study, aged 18 or older. <i>Exclusion:</i> NR	427	Median (Q1-Q3) age: 39 (34-44)	Male at birth: 97%	NR
Giang et al. (2022a)	<i>Inclusion:</i> People actively injecting heroin with recent skin injection marks, urine test positive for heroin or methamphetamine, participating in both before- and after-survey, aged 18 or older. <i>Exclusion:</i> NR	780	Mean (SD): 44.1 (8.4)	Male: 93.8%	NR
Havens et al. (2022)	<i>Inclusion:</i> Community-dwelling residents of a rural county reporting past-30-day use of non-medical prescription opioids at baseline, of which 84.9% met DSM-IV criteria for opioid dependence. <i>Exclusion:</i> NR	498 participants and 3,474 observations	Baseline median (Q1-Q3): 31 (26-38)	Men: 54.3%	White: 94.2%
Ellis et al. (2021)	<i>Inclusion:</i> Clients newly entering substance use treatment programs with a primary diagnosis of OUD (DSM-IV or V), aged 18 or older. <i>Exclusion:</i> NR	12,025	Age < 35: 59.7%	Male: 50.3%	White: 75.6%

**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Strickland et al. (2021)	<i>Inclusion:</i> Non-institutionalized US residents reporting past-year heroin use, aged 12 years and older. <i>Exclusion:</i> NR	1,063	NR	NR	NR
Glick et al. (2021)	<i>Inclusion:</i> People who inject drugs whose primary drug of use was goofball or heroin, seeking harm reduction supplies or engaged in on-site substance use treatment <i>Exclusion:</i> NR	584	Age<40: 69.5%	Men: 63.1%	White: 75.5%
Des Jarlais et al. (2021)	<i>Inclusion:</i> Participants reporting recent injecting heroin with injection marks and urine test positive for heroin/morphine, residing in Hai Phong, aged 18 or older. <i>Exclusion:</i> NR	2,377; 2016: 1,383, 2017: 1,451, 2018: 1,445.	Mean (SD): 2016: 39.9 (9.0), 2017: 40.2 (9.0), 2018: 41.5 (8.8).	Male: 2016: 93.6%, 2017: 95.2%, 2018: 94.4%.	NR
Twillman et al. (2020)	<i>Inclusion:</i> Patients with urine test positive for fentanyl, from all 50 US states and multiple health care specialties. <i>Exclusion:</i> NR	26,463	Median (Q1-Q3): 45 (20-70)	Men: 51.2%	NR
Cicero et al. (2020)	<i>Inclusion:</i> Clients newly entering treatment program with OUD (DSM-IV or V). <i>Exclusion:</i> NR	15,741	Mean (SD): 33.5 (10.3)	Male: 53.9%	White: 79.1%
Shearer et al. (2020)	<i>Inclusion:</i> Non-institutionalized US residents reporting 4+ instances of prescription opioid misuse in past-month or any past-year heroin use, aged 18-64. <i>Exclusion:</i> NR	1,908	Age<35: 48.8%	Male: 60.5%	White: 72.7%

Table 2 (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Daniulaityte et al. (2020)	<i>Inclusion:</i> Individuals with P12M moderate to severe OUD (DSM-V) and self-reported P6M use of nonprescribed buprenorphine, aged 18 or older. <i>Exclusion:</i> NR	356	Mean (SD): 39.2 (9.6)	Male: 50.3%	Non-Hispanic White: 88.8%
Mamat et al. (2020)	<i>Inclusion:</i> Participants were stable and active MMT patients for $\geq 6$ weeks. <i>Exclusion:</i> Patients with clinical diagnoses with psychiatric illnesses, in the induction or re-induction phase, default or noncompliance to an MMT program.	237	Mean (SD): 37.7 (8.5)	Male: 97%	Malay: 96%
Singh et al. (2020)	<i>Inclusion:</i> Respondents self-reported as regular methadone users and ATS use in the P12M, aged 18 or older. Active methadone users who self-reported current methamphetamine use history. <i>Exclusion:</i> Respondents in an incoherent state of mind or reporting psychological problems.	231	Mean (SD): 45.4 (9.9)	Male: 96%	Malay: 84%
Jones et al. (2020b)	<i>Inclusion:</i> Treatment admissions where the primary substance of use was heroin, where treatment centres that received public funding, and patients aged 12 or older. <i>Exclusion:</i> NR	3,547,977 admissions; 2008: 186,711; 2017: 372,926.	NR	NR	NR

**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Strickland et al. (2019)	<i>Inclusion:</i> Non-institutionalized US residents reporting past-month heroin/prescription opioid use or past-year heroin/prescription opioid use disorder (DSM-IV), aged 12 years and older. <i>Exclusion:</i> NR	NR	NR	NR	NR
Danesh & Noroozi (2019)	<i>Inclusion:</i> Participants enrolled in opioid maintenance treatments, including methadone, buprenorphine, or opium tincture maintenance treatment for at least one month, providing a urine sample, aged 18 or older. <i>Exclusion:</i> NR	481	Mean (SD): 39.2 (11.1)	Male: 93.7%	NR
Singh et al. (2019)	<i>Inclusion:</i> Respondents self-reported as regular methadone users and ATS use in the P12M, aged 18 or older. <i>Exclusion:</i> Respondents who had a history of psychological problems.	237	Mean (SD): 37.7 (8.5)	Male: 97%	Malay: 96%
Ellis et al. (2018)	<i>Inclusion:</i> Clients newly entering substance abuse treatment program with a primary diagnosis of OUD (DSM-IV or V), aged 18 or older. <i>Exclusion:</i> NR	13,521	Age<35: 63.8%	Male: 52.3%	White: 79.7%

**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Meacham et al. (2018a)	<i>Inclusion:</i> People who have injected drugs in the past month confirmed by track mark (95% heroin injection), speaking Spanish or English, and residing in Tijuana with no plans to move for three years, aged 18 or older. <i>Exclusion:</i> NR	735	Mean (SD): 37.4 (8.9)	Male: 62%	NR
Meacham et al. (2018b)	<i>Inclusion:</i> People who have injected drugs in the past month confirmed by track mark (95% heroin injection), speaking Spanish or English, and residing in Tijuana with no plans to move for three years, aged 18 or older. <i>Exclusion:</i> NR	735	Median: 37	Male: 62%	NR
Tavakoli et al. (2018)	<i>Inclusion:</i> Females on methadone treatment services for at least three months, aged 18 or older. <i>Exclusion:</i> Females reporting drug withdrawal or severe intoxication at the time of interviewing.	570	Mean (SD): 34.8 (8.4)	Female: 100%	NR
Alammehjerdi (2017)	<i>Inclusion:</i> Women retained in methadone treatment for at least three months, reporting at least weekly methamphetamine use, defined as a score of at least 0.14 on the methamphetamine items of the Opiate Treatment Index. <i>Exclusion:</i> NR	120	Mean (SD): 38.8 (8.9)	Women: 100%	NR

**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Al-Tayyib et al. (2017)	<i>Inclusion:</i> People who have injected heroin in the past 12 months, have physical evidence of recent injection (fresh track marks) or have current knowledge of drug preparation, injection technique, and syringe description, aged 18 or older. <i>Exclusion:</i> NR	469	Age < 40: 53.9%	Male: 70.9%	Non-Hispanic White: 59.3%
Dong et al. (2017)	<i>Inclusion:</i> Males meeting heroin dependence criteria in the past month, mainly using methamphetamine or heroin, and not having used methamphetamine or heroin together in the year preceding admission, capable of effective communication, aged 18 or older. <i>Exclusion:</i> NR	945	Mean (SD): 33.0 (6.8)	Male: 100%	NR
Meacham et al. (2015)	<i>Inclusion:</i> At baseline, participants reporting past-30-day heroin injection, speaking Spanish or English, residing in Tijuana with no plans to move over the next 18 months, aged 18 or older. <i>Exclusion:</i> NR	1,025	Median: 36.6	Male: 85.5%	NR



**Table 2** (continued)

First author (Publication year)	Inclusion/exclusion criteria	Sample size	Age (years)	Sex/gender	Race/ethnicity
Wang et al. (2015)	<i>Inclusion:</i> Participants in five MMT clinics met the Chinese Classification of Mental Disorders version 3 criteria for opioid dependence, had no contraindications for taking methadone, registered as a resident in the local area where the clinic was located, and aged 20 or older. <i>Exclusion:</i> NR	2,121	Age 30-49: 69.0%	Male: 96.2%	Ethnic minorities: 58.3%
Lin et al. (2013)	<i>Inclusion:</i> Heroin users with opioid dependence (DSM-IV) who visited the addiction treatment outpatient clinics to receive MMT, with valid gender data. <i>Exclusion:</i> NR	1,892	Mean (SD): 38.0 (7.7)	Men: 86.0%	NR
Back et al. (2011)	<i>Inclusion:</i> Opioid-dependent (DSM-IV) individuals who reported gender <i>Exclusion:</i> NR	892	Mean (SD): 35.9 (10.3)	Men: 67%	Caucasian: 69%

DSM: Diagnostic and Statistical Manual of Mental Disorders;

NR: Not Reported; MMT: Methadone Maintenance Therapy;

OAT: Opioid Agonist Therapy; OUD: Opioid Use Disorder;

SD: Standard Deviation, Q1-Q3: 1<sup>st</sup> to 3<sup>rd</sup> quartile

studies varied greatly and included a wide range of participants, such as patients admitted to emergency departments with an OUD diagnosis, patients receiving methadone maintenance therapy (MMT), participants with positive urine tests for heroin, or participants who self-reported regular non-medical use of opioids.

Most studies ( $n = 30$ ) provided information on the age and sex/gender of their participants, with mean or median ages ranging from 30 to 45 years old. One study conducted in the US focused solely on treatment admissions for patients aged 55 years or older (Choi et al., 2022). The terms sex and gender were often confused; thus, we would not differentiate the term sex/gender when summarizing the findings. Of the 18 studies conducted in North America that reported on sex/gender, the proportion of men ranged from 48.7% to 85.5%. Among the 12 studies conducted in Asia that reported on sex/gender, two studies in Iran included only women, one study in China included only men, and nine included predominantly men (86% to 97%). Only 18 studies provided race/ethnicity information. Of the 14 studies conducted in the US, the proportion of White participants varied greatly, ranging from 20.4% to 94.2%. Three studies conducted in Malaysia were predominantly Malay (84% to 96%), while one study conducted in China reported that over half (58.3%) of the participants were ethnic minorities (i.e., ethnicities besides the dominant Han).

### Outcome Operationalization

The operationalization of methamphetamine use varied considerably among the included studies. Self-reported use was the most common measure ( $n = 25$ ). Several studies measured self-reported lifetime use ( $n = 2$ ), past-year use ( $n = 4$ ), past six-month use ( $n = 7$ ), past three-month use ( $n = 2$ ), past-month use ( $n = 8$ ), concurrent use ( $n = 1$ ), and methamphetamine dependence based on DSM-IV ( $n = 1$ ). Using self-reported substance use indicators, three studies also employed latent class analysis to classify participants into methamphetamine and/or opioid use classes. In addition, only five studies used urine drug testing to measure methamphetamine use, while four used reasons for hospital admissions related to methamphetamine use as outcome indicators. Moreover, three studies were explicitly conducted on individuals who used methamphetamine and reported outcomes included methamphetamine use severity, long duration of methamphetamine use (i.e., greater than five years), and methamphetamine initiation after treatment enrollment.

### The Trend of Methamphetamine Use Among PWUO

Table 3 summarizes the main findings from studies investigating methamphetamine use trends among PWUO. All 11 studies included in the analysis were conducted in the US and Canada. These studies consistently reported a significant upward trend in methamphetamine use across different periods from 2006 to 2020, pre-dating the COVID-19 pandemic. Notably, the rate of increase has been particularly rapid since approximately 2010. Five studies examined the trend of methamphetamine use among different subgroups. They found that the increase was notably higher in rural areas, in the Western region (i.e., the Mountain States, including Montana, Wyoming, Colorado, New Mexico, Idaho, Utah, Arizona and Nevada, as well as the Pacific States, including Washington, Oregon, California, Alaska and Hawaii), and among those with ongoing unregulated opioid use (e.g., fentanyl, heroin). Outside

**Table 3** Summary of studies characterizing trend of methamphetamine use among people who use opioids

First author Year	Country	Outcome definition	Main findings
Giang et al. (2022a)	Vietnam	Self-reported past-30-day methamphetamine use, urine test positive for methamphetamine	Change before vs. after: <ul style="list-style-type: none"> <li>➤ Past-30-day non-injecting methamphetamine use: 38.6% vs. 36.8%</li> <li>➤ Urine tested positive for methamphetamine 31.7% vs. 34.0%.</li> </ul>
Choi et al. (2022)	US	Treatment admissions involving methamphetamine use (higher hierarchy than cocaine use)	Treatment admissions involving methamphetamine increased from 1.6% in 2012 to 4.8% in 2019 <ul style="list-style-type: none"> <li>➤ 2019 vs. 2012 <b>relative risk ratio 5.94, 95% CI: 5.24-6.74.</b></li> </ul>
Cui et al. (2022b)	Canada	Self-reported methamphetamine initiation or re-initiation	Methamphetamine initiation or re-initiation rate increased from 2008 to 2019: 7.6 to 23.2 per 100 person-years <ul style="list-style-type: none"> <li>➤ <b>Rate ratio: 1.07, 95% CI 1.05-1.09 per year.</b></li> </ul>
Cui et al. (2022a)	Canada	Self-reported past-6-month methamphetamine use frequency: no use, less than monthly use, at least monthly but less than weekly use, at least weekly but less than daily use, and at least daily use	Past-6-month methamphetamine use prevalence increased from 2006 to 2020: <ul style="list-style-type: none"> <li>➤ In the absence of ongoing unregulated opioid use: Any use 9% to 21% in 2020; at least weekly use <b>2% to 15%</b>;</li> <li>➤ In the presence of ongoing unregulated opioid use: Any use 19% to 59% in 2020, at least weekly use <b>7% to 50%</b>.</li> </ul>
Havens et al. (2022)	US	Self-reported past-6-month methamphetamine use	Past-6-month methamphetamine use increased from November 2017 to March 2020: ➤ From <b>9.4% to 33.1%</b> .
Strickland et al. (2021)	US	Self-reported past-month /past-year methamphetamine use	Past-month methamphetamine use prevalence increased from 2015 to 2019: <ul style="list-style-type: none"> <li>➤ Among past-year heroin users: <b>8.2% to 34.2%</b>;</li> <li>➤ Among past-month heroin users: <b>9.0% to 44.0%</b>.</li> </ul> Past-year methamphetamine use prevalence increase from 2015 to 2019: <ul style="list-style-type: none"> <li>➤ Among past-year heroin users: <b>22.5% to 46.7%</b>;</li> <li>➤ Among past-month heroin users: <b>17.8% to 49.2%</b>.</li> </ul>
Ellis et al. (2021)	US	Self-reported past-month non-medical methamphetamine use	Past-month methamphetamine use prevalence increased from 2012 to 2019: <ul style="list-style-type: none"> <li>➤ Urban from <b>23.1% to 36.5%</b>; rural from <b>24.5% to 46.1%</b>.</li> </ul>
Cicero et al. (2020)	US	Self-reported past-month non-medical methamphetamine use	Past-month methamphetamine use prevalence increased from the second half of 2011 to the first half of 2018: <ul style="list-style-type: none"> <li>➤ 19.6% to 36.4% (<b>+85%</b>).</li> </ul>

**Table 3** (continued)

First author Year	Country	Outcome definition	Main findings
Twillman et al. (2020)	US	Urine test positive for methamphetamine	The positivity rates of co-occurring methamphetamine increased from 2013 to 2016 to 2019: ➤ <b>2.2% to 12.0% to 30.4%</b> .
Jones et al. (2020b)	US	Treatment admissions involving methamphetamine use	Percentages of heroin treatment admissions involving methamphetamine increased from 2008 to 2017: ➤ Overall: <b>2.1% in 2008 to 12.4% in 2017</b> ; ➤ By age group: 12-17 ( <b>3.7% to 27.8%</b> ), 18-24 ( <b>1.9% to 17.4%</b> ), 25-34 ( <b>2.5% to 15.0%</b> ), 35-44 ( <b>2.2% to 11.4%</b> ), 45-54 ( <b>1.9% to 6.6%</b> ), 55+ ( <b>1.3% to 4.5%</b> ); ➤ By gender: female ( <b>2.8% to 15.1%</b> ), male ( <b>1.7% to 10.8%</b> ); ➤ By race/ethnicity: White ( <b>2.7% to 13.8%</b> ), black ( <b>0.1% to 2.0%</b> ), American Indian or Alaska Native ( <b>9.0% to 37.4%</b> ), Hispanic ( <b>2.2% to 14.1%</b> ), Other ( <b>4.1% to 11.9%</b> ); ➤ By US census region: Northeast ( <b>0.2% to 1.7%</b> ), Midwest ( <b>0.8% to 12.1%</b> ), South ( <b>1.0% to 4.6%</b> ), West ( <b>11.2% to 43.3%</b> ).
Strickland et al. (2019)	US	Self-reported past-month methamphetamine use	Past-month methamphetamine use prevalence increased from 2015 to 2016 to 2017: ➤ Among past-month heroin users: <b>9.0% to 19.7% to 30.2%</b> ; ➤ Among past-year heroin use disorder: <b>6.2% to 15.4% to 19.1%</b> ; ➤ Among past-month prescription opioid users: <b>4.0% to 4.1% to 4.7%</b> ; ➤ Among past-year prescription opioid use disorder: <b>3.8% to 8.9% to 7.9%</b> .

**Table 3** (continued)

First author Year	Country	Outcome definition	Main findings
Ellis et al. (2018)	US	Self-reported past-month non-medical methamphetamine use	<ul style="list-style-type: none"> <li>➤ Past-month methamphetamine use prevalence increased from 2011 to 2017:</li> <li>➤ Overall: 18.8% to 34.2% (<b>+82.6%</b>);</li> <li>➤ Among those who only heroin but no prescription opioids in the past month (<b>+358.6%</b>);</li> <li>➤ By age group: 18-24 (<b>+34.3%</b>), 25-34 (<b>+38.8%</b>), 35-44 (<b>+35.6%</b>), 35-44 (<b>+120.5%</b>);</li> <li>➤ By gender: female (<b>+97.8%</b>), male (<b>+81.8%</b>);</li> <li>➤ By race: Whites (<b>+100.6%</b>), non-Whites (<b>+28.0%</b>);</li> <li>➤ By urbanicity: urban (<b>+123.0%</b>), suburban (<b>+9.8%</b>), rural (<b>+93.7%</b>);</li> <li>➤ By regionality: Northeast (<b>+109.8%</b>), South (<b>+25.6%</b>), Midwest (<b>+129.9%</b>), West (<b>+202.4%</b>).</li> </ul>

Bold font: Statistically significant increase with  $p$ -value < 0.05

the North American context, only one study in Vietnam assessed methamphetamine use longitudinally by looking at use among PWUO before and after COVID-19 but did not find any significant changes.

### **Factors Associated with Methamphetamine Use Among PWUO**

Table 4 presents the main findings of the studies that investigated factors associated with methamphetamine use among PWUO.

#### **Demographic Factors**

Of the 20 studies conducted among PWUO that examined the association between methamphetamine use and age, 14 found that younger age was associated with a higher prevalence of methamphetamine use. In contrast, one study reported methamphetamine use was more prevalent among those aged 26 years or older, and the remaining five studies reported no significant associations. Out of 20 studies that examined sex/gender among PWUO, ten found that methamphetamine use was more prevalent among women/females, while one study reported the opposite, and the remaining nine studies reported no significant differences. Race/ethnicity was primarily examined in the studies conducted in the US or Canada ( $n = 12$ ). Of those, eight studies found that methamphetamine use was more prevalent among White PWUO, while four reported no significant differences. Only one study in China examined the association between ethnicity and methamphetamine use and found that Dai minorities were more likely to use methamphetamine among participants in MMT clinics (Wang et al. 2015). Additionally, the associations between methamphetamine use and marital status or sexual orientation were only examined in a few studies. Two out of the seven studies examining marital status found methamphetamine use was associated with divorce, while one out of four studies examining sexual orientation found a significant association between methamphetamine use and self-identification as non-heterosexual.

#### **Socioeconomic Factors**

Several studies examined the association between methamphetamine use and socioeconomic status among PWUO, including employment, income level, education, housing status, rurality, and geographic location. Of 15 studies that examined the association between employment or income and methamphetamine use among PWUO, six found methamphetamine use was associated with unemployment or lower income. In comparison, two studies (one in Mexico and one in China) found the opposite, and the remaining seven reported non-significant associations. Among ten studies that examined the association between education and methamphetamine use, four found that PWUO with less than a high school education were more likely to use methamphetamine. Seven studies conducted in the US or Canada reported methamphetamine use among PWUO was associated with unstable housing status or homelessness, while four studies conducted elsewhere (two in Mexico and two in Iran) reported non-significant associations. In the US, several studies found that methamphetamine use prevalence among PWUO was higher in rural areas ( $n = 3$ ) or the Western region ( $n = 2$ ).

**Table 4** Summary of studies characterizing factors associated with methamphetamine use among people who use opioids

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Smith et al. (2022)	Self-reported lifetime methamphetamine use	Lifetime methamphetamine use: 26.8% (weighted)	<p>Lifetime methamphetamine use was associated with:</p> <ul style="list-style-type: none"> <li>➤ Age &lt; 26 <b>OR 0.32, 95% CI 0.25-0.39;</b></li> <li>➤ Female <b>OR 0.70, 95% CI 0.59-0.84;</b></li> <li>➤ Employed <b>OR 0.73, 95% CI 0.61-0.88;</b></li> <li>➤ Racial minority <b>OR 0.48, 95% CI 0.37-0.62;</b></li> <li>➤ PY mental health treatment <b>OR 1.30, 95% CI 1.06-1.58;</b></li> <li>➤ Perceived in recovery mental health <b>OR 1.28, 95% CI 1.02-1.61;</b></li> <li>➤ Ever inject drug use <b>OR 11.45, 95% CI 8.10-16.20;</b></li> <li>➤ PY opioid withdrawal <b>OR 1.56, 95% CI 1.03-2.36;</b></li> <li>➤ Felt needed substance use treatment <b>OR 2.59, 95% CI 1.56-4.30;</b></li> <li>➤ PY alcohol or drug treatment <b>OR 4.72, 95% CI 3.23-6.90;</b></li> <li>➤ Substance use disorder recovery <b>OR 3.93, 95% CI 3.02-5.11.</b></li> </ul>

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Choi et al. (2022)	Treatment admissions involving methamphetamine use (higher hierarchy than cocaine use)	Treatment admissions involving methamphetamine: 3.7%	<p>Compared to admissions involving heroin but no methamphetamine or cocaine, admissions involving methamphetamine was associated with:</p> <ul style="list-style-type: none"> <li>➤ Male gender <b>RRR 0.86, 95% CI 0.82-0.90</b>;</li> <li>➤ Compared to non-Hispanic White: non-Hispanic Black <b>RRR 0.14, 95% CI 0.12-0.15</b>, Hispanic <b>RRR 0.50, 95% CI 0.47-0.53</b>, or other race/ethnicity <b>RRR 0.74, 95% CI 0.68-0.81</b>;</li> <li>➤ Compared to never married: married <b>RRR 1.39, 95% CI 1.24-1.55</b>, or divorced/separated/widowed <b>RRR 1.54, 95% CI 1.42-1.68</b>;</li> <li>➤ Compared to &lt; high school education] high school/GED <b>RRR 0.85, 95% CI 0.81-0.90</b>, or Bachelor's degree or higher <b>RRR 0.82, 95% CI 0.73-0.91</b>;</li> <li>➤ Compared to not in labor force] working full- or part-time <b>RRR 0.90, 95% CI 0.83-0.97</b>;</li> <li>➤ Compared to independent living: living in a supervised setting <b>RRR 2.06, 95% CI 1.94-2.17</b>, or experiencing homelessness <b>RRR 1.46, 95% CI 1.37-1.55</b>;</li> <li>➤ Compared to Northeast region: Midwest <b>RRR 6.24, 95% CI 5.46-7.14</b>, South <b>RRR 2.39, 95% CI 2.07-2.75</b>, or West <b>RRR 54.53, 95% CI 48.42-61.42</b>;</li> <li>➤ First heroin use age &gt; 30 <b>RRR 1.53, 95% CI 1.46-1.60</b>;</li> <li>➤ Daily heroin use in past month <b>RRR 1.53, 95% CI 1.46-1.60</b>;</li> <li>➤ Current injection drug use <b>RRR 1.13, 95% CI 1.04-1.21</b>;</li> <li>➤ Compared to no prior treatment: having 2-4 times <b>RRR 1.10, 95% CI 1.04-1.17</b> or 5 + times <b>RRR 1.28, 95% CI 1.19-1.37</b> prior treatments;</li> <li>➤ Compared to never arrested: having one arrest <b>RRR 2.54, 95% CI 2.28-2.84</b> or 2+ arrests <b>RRR 1.63, 95% CI 1.32-2.00</b>;</li> <li>➤ Psychiatric problem <b>RRR 1.37, 95% CI 1.30-1.45</b>;</li> <li>➤ Alcohol involvement <b>RRR 0.39, 95% CI 0.36-0.42</b>;</li> <li>➤ Cannabis involvement <b>RRR 0.84, 95% CI 0.77-0.91</b>;</li> <li>➤ Prescription opioid involvement <b>RRR 0.33, 95% CI 0.30-0.37</b>;</li> <li>➤ Benzodiazepine involvement <b>RRR 0.39, 95% CI 0.33-0.47</b>.</li> </ul>



**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
El Ibrahimy et al. (2022)	Patients with both a heroin treatment admission and a methamphetamine treatment admission (whether concurrent or separate episodes) in the study time frame	Patients with both a heroin treatment admission and a methamphetamine treatment admission: 53%	<p>Patients with both heroin and methamphetamine admissions vs. patients with heroin admissions only:</p> <ul style="list-style-type: none"> <li>➤ Age under 40 <b>79% vs. 64%</b>;</li> <li>➤ Female <b>56% vs. 46%</b>;</li> <li>➤ White <b>72% vs. 65%</b>;</li> <li>➤ Alcohol misuse <b>43% vs. 35%</b>,</li> <li>➤ Depression <b>63% vs 54%</b>,</li> <li>➤ Psychoses <b>44% vs. 36%</b>;</li> <li>➤ Deficiency anemia <b>14% vs. 17%</b>;</li> <li>➤ Uncomplicated hypertension <b>22% vs. 27%</b>;</li> <li>➤ Inpatient encounters <b>41% vs. 32%</b>;</li> <li>➤ Outpatient encounters <b>98% vs. 97%</b>;</li> <li>➤ Residential encounters <b>42% vs. 16%</b>;</li> <li>➤ Receive MOUD <b>56% vs. 75%</b>,</li> <li>➤ Receive buprenorphine <b>28% vs 24%</b>;</li> <li>➤ Receive methadone treatment <b>40% vs. 63%</b>,</li> <li>➤ Receive extended-release naltrexone <b>0.9% vs. 0.3%</b>,</li> <li>➤ Average days on MOUD treatment <b>188 vs. 265</b>;</li> <li>➤ Average days on methadone treatment <b>111 vs. 190</b>.</li> </ul>
Cui et al. (2022b)	Self-reported methamphetamine initiation or reinitiation	<p>Methamphetamine initiation or re-initiation during study follow-up: 44.0%;</p> <p>of 953 methamphetamine initiation or re-initiation events: injection only: 51.1%, non-injection only 24.7%, both 14.9%, and goofball 9.3%.</p>	<p>Methamphetamine initiation or re-initiation rate was associated with:</p> <ul style="list-style-type: none"> <li>➤ Age <b>aRR 0.96, 95% CI 0.95-0.97</b>;</li> <li>➤ Unstable housing <b>aRR 1.28, 95% CI 1.11-1.49</b>;</li> <li>➤ Unprotected sex <b>aRR 1.28, 95% CI 1.09-1.50</b>;</li> <li>➤ History of methamphetamine use <b>aRR 3.66, 95% CI 3.04-4.40</b>;</li> <li>➤ P6M cocaine use <b>aRR 1.22, 95% CI 1.04-1.42</b>;</li> <li>➤ P6M prescription opioid use <b>aRR 1.18, 95% CI 1.01-1.38</b>;</li> <li>➤ P6M unregulated opioid use <b>aRR 1.45, 95% CI 1.25-1.68</b>.</li> </ul>

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Cui et al. (2022a)	Self-reported P6M methamphetamine use frequency: no use, less than monthly use, at least monthly but less than weekly use, at least weekly but less than daily use, and at least daily use	Methamphetamine use over the study period: 55.8%	Higher methamphetamine use frequency was associated with individuals who: [ref had not received OAT for at least one year] ➤ In the absence of ongoing unregulated opioid use: Recently discontinued OAT <b>aOR 0.47, 95% CI 0.27-0.79</b> , Newly initiated OAT <b>aOR 0.52, 95% CI 0.31-0.89</b> , Were retained on OAT <b>aOR 0.48, 95% CI 0.31-0.72</b> . ➤ In the presence of ongoing unregulated opioid use: Newly initiated OAT <b>aOR 1.24, 95% CI 1.02-1.51</b> . Methamphetamine use severity was associated with: ➤ Age: high vs. low <b>aOR 0.93, 95% CI 0.85-1.00</b> , moderate vs. low <b>aOR 0.96, 0.93-1.00</b> . ➤ Compared to Tay Ho clinic: Dong Dai: high vs. low <b>aOR 0.11, 95% CI 0.02-0.48</b> , moderate vs. low <b>aOR 0.35, 95% CI 0.14-0.87</b> ; Hai Ba Trung: high vs. low <b>aOR 0.03, 95% CI 0.00-0.18</b> , moderate vs. low <b>aOR 0.14, 95% CI 0.06-0.34</b> ; Hoang Mai: <b>high vs. low aOR 0.17, 95% CI 0.03-0.86</b> ; Nam Tu Liem: high vs. low <b>aOR 0.15, 95% CI 0.03-0.76</b> , high vs. moderate <b>aOR 0.25, 95% CI 0.06-0.96</b> . ➤ P3M heroin injection: high vs. low <b>aOR 4.05, 95% CI 1.30-12.55</b> , high vs. moderate <b>aOR 2.51, 95% CI 1.02-6.21</b> . ➤ years of heroin/opioid use: high vs. low <b>aOR 1.13, 95% CI 1.03-1.24</b> , moderate vs. low <b>aOR 1.06, 95% CI 1.01-1.11</b> . ➤ ACSA-craving: high vs. low <b>aOR 1.97, 95% CI 1.31-2.98</b> , high vs. moderate <b>aOR 1.72, 95% CI 1.33-2.22</b> .
Giang et al. (2022b)	Methamphetamine use severity: high vs. moderate vs. low	Methamphetamine use severity: high 8.7%; moderate 68.6%; low: 22.7%.	

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Havens et al. (2022)	Self-reported P6M methamphetamine use	Baseline P6M methamphetamine use: 9.4%	For all visits, P6M methamphetamine use was associated with: > Compared to baseline visit in 2008-2010: Latest visit <b>aOR 25.8, 95% CI 14.9-44.6</b> ; > Age <b>aOR 0.96, 95% CI 0.93-0.98</b> ; > Female <b>aOR 1.67, 95% CI 1.13-2.45</b> ; > History of methamphetamine use <b>aOR 3.07, 95% CI 2.06-4.57</b> ; > P6M non-medical prescription opioid use <b>aOR 2.52, 95% CI 1.61-3.97</b> ; > P6M benzodiazepine use <b>aOR 1.83, 95% CI 1.31-2.57</b> ; > P6M cocaine use <b>aOR 3.54, 95% CI 2.52-4.97</b> . For the latest visit, P6M methamphetamine use was associated with: > Age <b>aOR 0.96, 95% CI 0.93-0.99</b> ; > P6M non-medical prescription opioid use <b>aOR 1.89, 95% CI 1.13-3.15</b> ; > P6M heroin use <b>aOR 5.89, 95% CI 1.57-22.0</b> ; > P6M cocaine use <b>aOR 2.73, 95% CI 1.36-5.48</b> ; > P6M marijuana use <b>aOR 1.77, 95% CI 1.07-2.12</b> .
Strickland et al. (2021)	Self-reported PY methamphetamine use	NR	PY methamphetamine use was associated with: > White <b>aOR 2.15, 95% CI 1.25-3.69</b> , > rurality <b>aOR 2.31, 95% CI 1.08-4.95</b> , > PY injection drug use <b>aOR 1.85, 95% CI 1.23-2.77</b> ; > PY serious mental illness <b>aOR 2.12, 95% CI 1.32-3.42</b> ; > PY drug-specific treatment <b>aOR 0.61, 95% CI 0.39-0.98</b> .
Ellis et al. (2021)	Self-reported PM non-medical methamphetamine use	PM methamphetamine use: 32.3%	Any PM methamphetamine use vs. none: > Urban vs. rural <b>30.9% vs. 35.4%</b> .

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Glick et al. (2021)	Self-reported P3M main drug was goofball	P3M main drug was goofball: 20.5%	<p>P3M main drug was goofball vs heroin alone:</p> <ul style="list-style-type: none"> <li>➤ Age &lt; 40: <b>80.0% vs. 66.7%</b>,</li> <li>➤ Women <b>43.3% vs. 35.2%</b>,</li> <li>➤ Homeless or unstably housed <b>82.5% vs. 71.8%</b>,</li> <li>➤ Having private health insurance <b>2.5% vs. 9.5%</b>,</li> <li>➤ PY incarceration <b>56.7% vs. 41.0%</b>,</li> <li>➤ Daily injection <b>83.3% vs. 78.5%</b>,</li> <li>➤ Median number of injections per day <b>4 vs. 3</b>,</li> <li>➤ P3M syringe sharing <b>26.7% vs. 18.1%</b>,</li> <li>➤ P3M other equipment sharing <b>63.0% vs. 50.5%</b>,</li> <li>➤ Public injection <b>75.8% vs. 66.1%</b>,</li> <li>➤ P3M injected in femoral vein <b>20.0% vs. 15.3%</b>,</li> <li>➤ P3M injected in jugular vein <b>51.7% vs. 36.6%</b>,</li> <li>➤ Currently in methadone treatment <b>43.3% vs. 60.3%</b>,</li> <li>➤ P12M having endocarditis <b>5.9% vs. 2.2%</b>,</li> <li>➤ P12M witnessed opioid overdose <b>73.1% vs. 61.7%</b>,</li> <li>➤ P3M possessed naloxone <b>85.0% vs. 71.5%</b>.</li> </ul> <p>In 2016, 2017 and 2018 respectively, P30D methamphetamine use was associated with:</p> <ul style="list-style-type: none"> <li>➤ Age [20-24 vs. 55-59] 2016 <b>66.7% vs. 32.3%</b>, 2017 <b>54.0% vs. 42.0%</b>, 2018 <b>53.8% vs. 48.8%</b>;</li> <li>➤ Sex [female vs. male] 2016 OR 1.46, 95% CI 0.94-2.26, 2017 OR <b>1.83, 95% CI 1.13-2.97</b>, 2018 OR <b>1.84, 95% CI 1.17-2.90</b>;</li> <li>➤ HIV [negative vs. positive] 2016 OR <b>1.72, 95% CI 1.36-2.18</b>, 2017 OR <b>1.72, 95% CI 1.34-2.21</b>, 2018 OR <b>2.09, 95% CI 1.63-2.68</b>.</li> </ul>
Des Jarlais et al. (2021)	Self-reported P30D methamphetamine use	<p>P30D methamphetamine smoking: 2016: 46.6%; 2017: 41.9%; 2018: 43.7%.</p> <p>Urine tested positive for methamphetamine: 2016: 37.9%; 2017: 34.5%, 2018: 33.4%.</p>	

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Shearer et al. (2020)	Self-reported PY methamphetamine use	PY methamphetamine use: 18.5% (weighted)	<p>Any PY methamphetamine use vs not:</p> <ul style="list-style-type: none"> <li>➤ White <b>83.9% vs. 70.1%</b>,</li> <li>➤ Rurality <b>21.4% vs. 14.4%</b>,</li> <li>➤ Unstable housing <b>15.5% vs. 7.6%</b>,</li> <li>➤ Living below the federal poverty line <b>35.6% vs. 24.3%</b>,</li> <li>➤ PY heroin use <b>68.3% vs. 35.4%</b>,</li> <li>➤ Injection needle use <b>46.2% vs. 19.9%</b>,</li> <li>➤ Other unregulated drug use <b>87.7% vs. 75.9%</b>,</li> <li>➤ Treatment for unregulated drug use <b>27.8% vs. 17.1%</b>,</li> <li>➤ PM cigarette use <b>81.1% vs. 68.9%</b>,</li> <li>➤ PM marijuana use <b>55.9% vs. 44.6%</b>,</li> <li>➤ Alcohol abuse or dependence <b>31.2% vs. 23.0%</b>,</li> <li>➤ Have STI in the past year <b>9.6% vs. 6.2%</b>,</li> <li>➤ Hepatitis B or C <b>12.2% vs. 6.7%</b>,</li> <li>➤ Chronic obstructive pulmonary disease <b>12.9% vs. 6.3%</b>,</li> <li>➤ Severe mental illness <b>24.9% vs. 20.6%</b>.</li> </ul>

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Jones et al. (2020b)	Treatment admissions involving methamphetamine use	Treatment admissions involving methamphetamine use: 2.1% in 2008 to 12.4% in 2017; Among 533,394 primary heroin treatment admissions reporting methamphetamine use in 2017, usual route of methamphetamine use: 47.1% injecting, 46.0% smoking, 5.1% snorting and 1.8% oral/other.	Methamphetamine use at heroin treatment admission was associated with: <ul style="list-style-type: none"> <li>➤ Female: <b>aOR 1.44, 95% CI 1.31-1.59</b>;</li> <li>➤ Compared to age group 35-44: age 25-34 <b>aOR 1.18, 95% CI 1.04-1.35</b>;</li> <li>➤ Compared to non-Hispanic Whites: non-Hispanic American Indian/Alaska Native <b>aOR 2.73, 95% CI 1.08-6.89</b>;</li> <li>➤ Compared to Northeast: Midwest <b>aOR 7.68, 95% CI 3.09-19.09</b>, South <b>aOR 3.97, 95% CI 1.30-12.15</b>, West <b>aOR 47.36, 95% CI 27.61-81.23</b>;</li> <li>➤ Compared to full-time employment: part-time employment <b>aOR 1.15, 95% CI 1.02-1.29</b>, unemployment <b>aOR 1.63, 95% CI 1.44-1.85</b>, not in the labour force <b>aOR 1.59, 95% CI 1.34-1.88</b>;</li> <li>➤ Compared to independent living: dependent living <b>aOR 1.31, 95% CI 1.10-1.57</b>, homeless <b>aOR 1.66, 95% CI 1.45-1.89</b>;</li> <li>➤ Compared to individual/self-referral: treatment referral by health-care provider <b>aOR 1.25, 95% CI 1.04-1.49</b>, other community referral <b>aOR 1.33, 95% CI 1.07-1.67</b>, criminal justice referral <b>aOR 1.91, 95% CI 1.60-2.28</b>;</li> <li>➤ Heroin injection <b>aOR 1.71, 95% CI 1.47-1.98</b>;</li> <li>➤ *MOUD planned <b>aOR 0.65, 95% CI 0.50-0.84</b>;</li> <li>➤ Compared to 14 or less: age first use of heroin 15-17 <b>aOR 0.88, 95% CI 0.83-0.93</b>, 18-20 <b>aOR 0.87, 95% CI 0.80-0.94</b>, 21-24 <b>aOR 0.87, 95% CI 0.79-0.95</b>.</li> </ul>
Daniuliatyte et al. (2020)	Self-reported P6M methamphetamine use	P6M methamphetamine use: 55.6%; primary route: 57.6% injection, 25.3% smoke, 15.2% intranasal, 1.0% oral; Lifetime methamphetamine use: 79.8%; Lifetime methamphetamine injection: 55.3%.	P6M methamphetamine use was associated with: <ul style="list-style-type: none"> <li>➤ P6M homelessness <b>aOR 2.46, 95% CI 1.49-4.05</b>;</li> <li>➤ History of diverted pharmaceutical stimulant use <b>aOR 2.97, 95% CI 1.78-4.96</b>;</li> <li>➤ Injection as a primary mode of heroin/fentanyl administration <b>aOR 1.89, 95% CI 1.06-3.38</b>;</li> <li>➤ Prefer fentanyl than heroin <b>aOR 1.82, 95% CI 1.03-3.23</b>;</li> <li>➤ P6M days of use: marijuana <b>aOR 1.26, 95% CI 1.01-1.58</b>;</li> <li>➤ History of attending Vivitrol-based treatment <b>aOR 2.90, 95% CI 1.45-5.75</b>.</li> </ul>

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Singh et al. (2020)	Self-reported P30D/P7D methamphetamine use	P30D methamphetamine use: 34%; P7D methamphetamine use: 13%; Methamphetamine use initiation after MMT: 29%.	Clients who initiated methamphetamine after joining MMT program also had higher odds of using methamphetamine via the oral route in the last seven days ( <b>OR: 2.28; 1.05–4.95</b> ) and 30 days ( <b>OR: 2.49; 1.38–4.48</b> ).
Mamat et al. (2020)	Self-reported P12M/P90D/P30D methamphetamine use	P12M methamphetamine use: 75%; P90D methamphetamine use: 46%; P30D methamphetamine use: 44%; P30D route: 27% injected, 36% inhalation. Urine test positivity for methamphetamine 21%.	Methadone dose ≤50 vs. >50 mg/daily: ➤ P30D methamphetamine use 4.5% vs. 4.2%, OR 1.10, 95% CI 0.68–1.92; ➤ P90D methamphetamine use 49% vs. 44%, OR 1.21, 95% CI 0.72–2.02; ➤ P30D methamphetamine injection vs. chasing <b>52% vs. 36%</b> , OR <b>1.97, 95% CI 1.01–3.82</b> .
Danesh & Noroozi (2019)	Urine test positive for amphetamine/methamphetamine	Urine tested positive for amphetamine/methamphetamine 8.1% (92.6% methamphetamine)	Urine test positivity for amphetamine/methamphetamine was associated with: ➤ History of imprisonment <b>aOR 2.8, 95% CI 1.5–5.5</b> , ➤ Lifetime alcohol consumption <b>aOR 2.2, 95% CI 1.0–4.6</b> .
Singh et al. (2019)	Self-reported P30D methamphetamine use	P30D methamphetamine use: 64%; Route: 37% smoking, 27% injecting.	Private vs. public MMT: P30D methamphetamine use: <b>72% vs. 57%</b> ( <b>OR: 1.10, 95% CI 1.15–3.44</b> ); P30D methamphetamine injecting vs. smoking: 36% vs. 49% (OR: 0.60, 95% CI 0.30–1.10).

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Meacham et al. (2018a)	P6M heroin and methamphetamine injector class (high probabilities of injecting heroin, co-injection of heroin and methamphetamine; moderate probability of injecting methamphetamine); polydrug and polyroute users (high probabilities of injecting heroin, co-injecting heroin and methamphetamine, and smoking methamphetamine)	Heroin and methamphetamine injectors 37%; Polydrug and polyroute users 22%; Heroin and methamphetamine co-injection 56%; Methamphetamine smoking 41%; Methamphetamine injection 28%.	<ul style="list-style-type: none"> <li>Heroin and methamphetamine injectors were associated with:               <ul style="list-style-type: none"> <li>➤ Female <b>aOR 0.59, 95% CI 0.41-0.86</b>;</li> <li>➤ Ever in rehabilitation centre <b>aOR 1.62, 95% CI 1.14-2.28</b>;</li> <li>➤ Ever went to jail <b>aOR 1.62, 95% CI 1.09-2.41</b>;</li> <li>➤ Receptive syringe sharing <b>aOR 1.64, 95% CI 1.13-2.37</b>;</li> <li>➤ Cooker, cotton, water sharing <b>aOR 1.67, 95% CI 1.17-2.39</b>;</li> <li>➤ Great or urgent need for help <b>aOR 1.77, 95% CI 1.25-2.51</b>;</li> <li>➤ Polydrug and poly route users were associated with:                   <ul style="list-style-type: none"> <li>➤ Female <b>aOR 1.58, 95% CI 1.09-2.29</b>;</li> <li>➤ Age <b>aOR 0.97, 95% CI 0.95-0.99</b>;</li> <li>➤ ≥3500 pesos monthly income <b>aOR 1.65, 95% CI 1.10-2.46</b>;</li> <li>➤ Whole life in Tijuana <b>aOR 0.58, 95% CI 0.39-0.85</b>;</li> <li>➤ Ever received professional help <b>aOR 1.56, 95% CI 1.07-2.27</b>;</li> <li>➤ Ever on methadone <b>aOR 1.75, 95% CI 1.18-2.61</b>;</li> <li>➤ Ever in rehabilitation centre <b>aOR 1.72, 95% CI 1.19-2.49</b>;</li> <li>➤ Ever attended 12-step program <b>aOR 2.76, 95% CI 1.73-4.42</b>;</li> <li>➤ Ever went to jail <b>aOR 1.62, 95% CI 1.09-2.41</b>;</li> <li>➤ Receptive syringe sharing <b>aOR 3.61, 95% CI 2.26-5.77</b>;</li> <li>➤ Cooker, cotton, water sharing <b>aOR 3.81, 95% CI 2.45-5.94</b>;</li> <li>➤ Unprotected sex <b>aOR 2.19, 95% CI 1.48-3.25</b>;</li> <li>➤ Sex exchange <b>aOR 2.63, 95% CI 1.77-3.90</b>;</li> <li>➤ Drug use before sex <b>aOR 2.23, 95% CI 1.36-3.65</b>;</li> <li>➤ Overdose <b>aOR 2.03, 95% CI 1.12-3.67</b>;</li> <li>➤ Great or urgent need for help <b>aOR 1.35, 95% CI 0.94-1.95</b>.</li> </ul> </li> </ul> </li> </ul>
Meacham et al.(2018b)	P6M meth and heroin injecting class (100% daily heroin and meth co-injecting, 92% daily methamphetamine injecting)	Methamphetamine and heroin injecting class: 10%; Route: Co-injecting heroin and methamphetamine: 55.9%, injected methamphetamine alone: 28.4%, methamphetamine smoking: 41.4%.	<ul style="list-style-type: none"> <li>Meth and heroin injecting class was associated with:               <ul style="list-style-type: none"> <li>➤ Cooker, cotton and rinse water sharing <b>aOR 1.30, p-value 0.399</b>;</li> <li>➤ Drug use before or during sex <b>aOR 1.64, p-value 0.152</b>;</li> <li>➤ Years education <b>aOR 1.06, p-value 0.306</b>;</li> <li>➤ Age of first injection <b>aOR 0.98, p-value 0.433</b>;</li> <li>➤ Heroin first drug injected <b>aOR 0.73, p-value 0.397</b>;</li> <li>➤ Ever experienced forced sex <b>aOR 0.90, p-value 0.845</b>;</li> <li>➤ Hours on the street <b>aOR 1.03, p-value 0.239</b>;</li> <li>➤ Income over 2500 pesos per month <b>aOR 1.45, p-value 0.210</b>;</li> <li>➤ Any current need for help for drug use <b>aOR 3.19, p-value 0.081</b>.</li> </ul> </li> </ul>



**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Tavakoli et al. (2018)	Self-reported methamphetamine dependence (DSM-IV)	Methamphetamine dependence: 46.6%; Mean (SD) years of methamphetamine dependence: 5.0 (9.0); Main routes of methamphetamine administration: 78.2% smoking, 15.0% ingestion, 6.8% injection.	Methamphetamine dependence was associated with: <ul style="list-style-type: none"> <li>➤ Poor psychological well-being mean score <b>9.45 vs. 5.36</b>;</li> <li>➤ Social dysfunction mean score <b>24.65 vs. 19.54</b>.</li> </ul>
Al-Tayyib et al. (2017)	Self-reported P12M methamphetamine injection	P12M methamphetamine injection: 63.1% of those, 43.9% injecting separately with heroin at different times, 28.0% goofball, 24.0% doing both.	P12M methamphetamine injection vs. not: <ul style="list-style-type: none"> <li>➤ Age &lt; 40 <b>65.9% vs. 33.5%</b>,</li> <li>➤ Non-Hispanic White <b>67.6% vs. 45.1%</b>,</li> <li>➤ Currently homeless <b>77.0% vs. 46.8%</b>,</li> <li>➤ P30D network size of people who inject drugs &gt; 20 <b>60.8% vs. 39.3%</b>,</li> <li>➤ &gt; 10 years since first injection <b>48.0% vs. 71.7%</b>,</li> <li>➤ First injected drug was methamphetamine <b>29.7% vs. 6.4%</b>,</li> <li>➤ P12M more than daily IDU <b>79.7% vs. 61.9%</b>,</li> <li>➤ P12M reusing syringes more than once <b>63.9% vs. 56.7%</b>,</li> <li>➤ P12M syringe sharing <b>42.8% vs. 29.2%</b>,</li> <li>➤ P12M water, cookers, or cotton sharing <b>49.9% vs. 56.1%</b>,</li> <li>➤ P12M visited local syringe exchange <b>75.3% vs. 56.7%</b>,</li> <li>➤ P12M received a naloxone kit <b>42.2% vs. 30.1%</b>,</li> <li>➤ P12M held in a detention centre, jail, or prison for more than 24 hours <b>66.9% vs. 47.1%</b>,</li> <li>➤ P12M overdose <b>33.8% vs. 11.6%</b>.</li> </ul>
Alammehrjerdi et al. (2017)	>5 years of methamphetamine use	Long duration of methamphetamine use: 50.8%; Mean (SD) first methamphetamine use age: 25.5 (8.7).	>5 years of methamphetamine use were more likely to be engaged in high-risk sexual behaviours: mean Opiate Treatment Index score 6.6 vs. 5.0.

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Dong et al. (2017)	Meeting methamphetamine dependence criteria in the month preceding admission	Methamphetamine dependence: 26.1%	<ul style="list-style-type: none"> <li>males with vs. without methamphetamine dependence:               <ul style="list-style-type: none"> <li>➤ Mean age <b>32 vs. 33</b>,</li> <li>➤ <math>\geq 30k</math> PY income Chinese yuan <b>72.1% vs. 44.8%</b>,</li> <li>➤ PY main administration route was injection <b>85.4% vs. 19.8%</b>,</li> <li>➤ Duration of drug use <b>7.8 vs. 10.0</b>,</li> <li>➤ Family history of substance use <b>21.0% vs. 44.7%</b>,</li> <li>➤ Previous detoxification treatment <b>54.0% vs. 92.0%</b>,</li> <li>➤ Current independent psychotic disorder <b>8.1% vs. 0.7%</b>,</li> <li>➤ Current substance-induced psychotic disorder <b>31.6% vs. 0.6%</b>,</li> <li>➤ Lifetime independent psychotic disorder <b>11.3% vs. 0.9%</b>,</li> <li>➤ Lifetime substance-induced psychotic disorder <b>32.4% vs. 1.7%</b>,</li> <li>➤ Current substance-induced mood disorder <b>0.8 vs. 5.7%</b>,</li> <li>➤ Current alcohol use disorder <b>5.2% vs. 16.5%</b>,</li> <li>➤ Current sedative/hypnotic/anxiolytic use disorder <b>5.3% vs. 20.5%</b>,</li> <li>➤ Current hallucinogen abuse <b>9.3% vs. 1.4%</b>,</li> <li>➤ Lifetime hallucinogen abuse <b>38.5% vs. 9.0%</b>,</li> <li>➤ Lifetime cannabis abuse <b>8.1% vs. 0.7%</b>.</li> </ul> </li> </ul>
Meacham et al.(2015)	P6M methamphetamine use class (70% injection and 68% non-injection )	<p>Methamphetamine use class: 43.7%;</p> <p>P6M Methamphetamine prevalence: 33.7% injecting, 38.8% smoking or snorting.</p>	<ul style="list-style-type: none"> <li>Methamphetamine use class was associated with               <ul style="list-style-type: none"> <li>➤ Age <b>aOR 0.97, 95% CI 0.95-0.98</b>,</li> <li>➤ Female <b>aOR 1.81, 95% CI 1.31-2.49</b>,</li> <li>➤ Income <math>\geq 3,500</math> pesos/month <b>aOR 0.65, 95% CI 0.47-0.89</b>,</li> <li>➤ Drug use before sex <b>aOR 2.26, 95% CI 1.56-3.27</b>,</li> <li>➤ Receptive syringe sharing <b>aOR 2.63, 95% CI 2.17-3.18</b>.</li> </ul> </li> </ul>

**Table 4** (continued)

First author (Publication year)	Outcome definition	Outcome statistics	Main findings
Wang et al. (2015)	Urine test positive for methamphetamine (methamphetamine+); urine test positive for morphine was considered as using heroin (morphine+)	Morphine/methamphetamine: 67.5%; Morphine+/methamphetamine: 10.4%; Morphine-/methamphetamine+: 12.9%; Morphine+/methamphetamine+: 9.2%.	<p>Compared to those who with morphine-/methamphetamine- results, those with morphine-/methamphetamine+ results were associated with:</p> <ul style="list-style-type: none"> <li>➤ Compared to 50-79 years: aged 18-29 <b>aOR 2.00, 95% CI 1.09-3.57</b>;</li> <li>➤ Compared to Han: Dai minority <b>aOR 1.63, 95% CI 1.22-2.16</b>, or Jingpo ethnicity <b>aOR 0.47, 95% CI 0.25-0.86</b>;</li> <li>➤ Compared to MMT receipt for &lt;1 year: &gt;5 years <b>aOR 1.98, 95% CI 1.21-3.24</b>;</li> </ul> <p>Compared to MMT: methadone maintenance therapy; MOUD: medications for opioid use disorder;</p> <ul style="list-style-type: none"> <li>➤ : 31-60 ml <b>aOR 1.69, 95% CI 1.06-2.69</b>, 61-99 ml <b>aOR 1.86, 95% CI 1.15-3.02</b>, ≥ 100 ml <b>aOR 1.96, 95% CI 1.19-3.24</b>.</li> </ul> <p>Those with morphine+/methamphetamine+ results were associated with:</p> <ul style="list-style-type: none"> <li>➤ Compared to Han: Dai minority <b>aOR 1.50, 95% CI 1.04-2.14</b>;</li> <li>➤ Compared to never married: divorced <b>aOR 1.91, 95% CI 1.13-3.22</b>;</li> <li>➤ Have used drugs for &lt;10 years <b>aOR 1.54, 95% CI 1.09-2.13</b>;</li> <li>➤ Compared to MMT receipt for &lt;1 year: 1-5 years <b>aOR 0.60, 95% CI 0.40-0.88</b>, &gt;5 years <b>aOR 0.56, 95% CI 0.34-0.88</b>.</li> </ul>
Lin et al. (2013)	Self-reported lifetime/concurrent methamphetamine use	Lifetime methamphetamine use: 58.6%; Concurrent methamphetamine use at MMT entry: 7.0%.	<p>Women vs. men:</p> <ul style="list-style-type: none"> <li>➤ Lifetime methamphetamine substance use: <b>66.3% vs. 57.4%</b>;</li> <li>➤ Concurrent methamphetamine use while entering MMT: <b>15.5% vs. 5.6%</b>.</li> </ul>
Back et al. (2011)	Urine test positive for methamphetamine	Urine test positive for methamphetamine: 6%	<p>Urine test positive for methamphetamine:</p> <ul style="list-style-type: none"> <li>➤ Women vs. men <b>11% vs. 4%</b>.</li> </ul>

*Notes:* Bold font: Covariates with significant association with methamphetamine use.

aOR: adjust Odds Ratio; RRR: Relative Risk Ratio; aRR: adjusted Rate Ratio;

DSM: Diagnostic and Statistical Manual of Mental Disorders; IDU: Injection Drug Use;

MMT: Methadone Maintenance Therapy; MOUD: Medications for Opioid Use Disorder;

OAT: Opioid Agonist Therapy; OR: Odds Ratio; OUD: Opioid Use Disorder; P7D: Past-7-Day;

P30D: Past-30-Day; PM: Past-Month; P3M: Past-3-Month; P6M: Past-6-Month; P12M: Past-12-Month; PY: Past-Year

## Substance Use Behaviours

Of 14 studies examining injection drug use behaviours among PWUO, ten found that methamphetamine use was associated with injection drug use, and several studies also found it was associated with sharing or reusing syringes or other equipment. Furthermore, several studies found that recent methamphetamine use among PWUO was associated with a long history of drug use, history of methamphetamine use, recent non-medical stimulant use (e.g., cocaine) and/or opioid use (e.g., heroin). Most studies conducted among PWUO examining marijuana or alcohol reported positive associations between the use of methamphetamine and marijuana (4/6) or alcohol (5/8), while only one study reported methamphetamine use was negatively associated with marijuana or alcohol. Four studies examining the associations between the use of methamphetamine and benzodiazepines among PWUO reported inconclusive results. Recent methamphetamine use among PWUO was also associated with a previous or witnessed overdose.

## Risk Behaviours and Associated Activities

Out of nine studies examining associations between methamphetamine use and criminal activity among PWUO, seven found methamphetamine use was associated with drug dealing or a history of arrests or incarceration. Additionally, out of seven studies examining sexual behaviours among PWUO, five found methamphetamine use was associated with sex work involvement or engaging in high-risk sexual practices, such as having unprotected sex with casual partners, having multiple casual sex partners, or sexualized substance use.

## Mental and Physical Health Conditions

Overall, methamphetamine use among PWUO was associated with mental and physical health adversities; however, two studies examining self-rated health status reported non-significant findings. Nine out of ten studies examining mental health conditions among PWUO found methamphetamine use was associated with co-occurring mental illnesses, including anxiety, depression, and mood disorders. Regarding infectious diseases, ten studies conducted among PWUO were identified, of which two, conducted in Vietnam, found methamphetamine use was associated with HIV seropositivity and one study in the US found methamphetamine use was associated with hepatitis B/C seropositivity. Physical illnesses were often used as outcomes rather than covariates when assessing their relationship with methamphetamine use and thus rarely examined in studies that met our inclusion criteria. Only two studies included in our review examined respiratory and cardiovascular diseases, among which methamphetamine use was found to be associated with chronic obstructive pulmonary disease in one study and endocarditis in another.

## Participation in Drug Treatment and Harm Reduction Programs

In total, 14 studies conducted among PWUO examined the association between methamphetamine use and accessing drug treatment or harm reduction services. Among them, six studies found that PWUO who also use methamphetamine were more likely to have received drug treatment, with two studies indicating they were also more likely to feel the need for help, and one study reporting they were more likely to face barriers to treatment. In contrast, seven studies conducted among PWUO found that receiving drug treatment

was associated with lower methamphetamine use. Eleven studies specifically focused on MMT uptake. Of these, five studies found that lower levels of methamphetamine use were associated with participation in MMT, while three studies found that lower levels of methamphetamine use were associated with longer retention in MMT. The findings regarding the relationship between methadone dose and methamphetamine use were mixed across three studies. One study found that days missed on MMT were not significantly associated with methamphetamine use.

Additionally, three studies examined the association between methamphetamine use and receiving buprenorphine-based or naltrexone-based treatment. The findings were mixed, with one study showing a positive association between methamphetamine use and receiving buprenorphine-based treatment, another study showing a negative association between methamphetamine use and receiving naltrexone-based treatment, and a third study showing a positive association between methamphetamine use and ever-receiving naltrexone-based treatment. Moreover, some individual studies also found that methamphetamine use was linked to more inpatient/outpatient/residential treatment encounters and initiating methamphetamine after initiating treatment. Only two US-based studies specifically investigated harm reduction services, finding positive associations between methamphetamine use and accessing syringe exchange programs and possessing a naloxone kit.

### **Risk of Bias Assessment**

As presented in Table S3, most studies were of good quality regarding the risk of bias as evaluated by a modified version of the Newcastle Ottawa Quality Assessment Scale. Most studies had a sufficient sample size, had comparable participants, and were statistically sound; however, most suffered from measurement biases in their outcome and exposure ascertainment, primarily due to self-reported measurements.

### **Discussion**

We systematically reviewed 33 studies that characterized methamphetamine use among PWUO. Of those, 11 studies characterized an increasing trend of methamphetamine use in the US and Canada and 28 studies characterized factors associated with methamphetamine use among PWUO in North America and Asia. We found individuals who use methamphetamine to be more likely to be younger, reside in rural areas, have lower socioeconomic status, have mental and physical health conditions, and engage in risky behaviours that increase their risk for sexually transmitted infections and substance use-related harms. PWUO who use methamphetamine were also more likely to use unregulated opioids and have a history of other stimulant use practices. Notably, a longer duration of receiving medications for opioid use disorder (MOUD) was associated with lower levels of methamphetamine use.

This review is consistent with an increasing body of evidence highlighting the rise in the prevalence of methamphetamine use among PWUO in the US and Canada (Ellis et al., 2018; Jones et al., 2020a; Karamouzian et al., 2023). However, studies explicitly examining the trend of methamphetamine use among PWUO in settings outside of North America are limited, despite previous research conducted in Asia and Europe suggesting a rising trend in methamphetamine use among people who use drugs (Chomchai & Chomchai, 2015; Kwon & Han, 2018). Meanwhile, overdose fatalities involving both methamphetamine and

opioids have increased in recent years in both the US and Canada, underscoring the risks associated with polysubstance use (BC Coroners Service, 2020; National Institute on Drug Abuse, 2021). Our review also found that research studies conducted in various settings in North America and Asia have demonstrated an association between the use of methamphetamine and opioids. Qualitative studies found people either use methamphetamine with opioids (i.e., “goofball”) to achieve a rollercoaster high or use methamphetamine after opioids to help counteract the sedative effects of opioids (Daniulaityte et al., 2022; Hansen et al., 2021; Ivsins et al., 2022; Lopez et al., 2021; Palmer et al., 2020; Rhed et al., 2022; Silverstein et al., 2021; Steinberg et al., 2022). With the increasing presence of more potent synthetic opioids (e.g., fentanyl) in the unregulated drug supply (BC Coroners Service, 2020; Ellis et al., 2018; Hoopsick & Andrew Yockey, 2023; Karamouzian et al., 2018; National Institute on Drug Abuse, 2021), individuals may also use methamphetamine as an overdose prevention strategy and self-medicate with methamphetamine to alleviate opioid withdrawal symptoms (Baker et al., 2020; Hansen et al., 2021; Ivsins et al., 2022; Lopez et al., 2021; Palmer et al., 2020; Rhed et al., 2022; Silverstein et al., 2021; Steinberg et al., 2022). Methamphetamine might also improve work-life functioning or help individuals stay awake to avoid violence or robbery, particularly among those who are marginally housed (Korthuis et al., 2022).

Conversely, some studies examining combined methamphetamine and opioid use, with measurements including urine test results or fatality data, have captured cases of unintentional opioid exposure among people who use methamphetamine (Daniulaityte et al., 2019). Indeed, there are indications of increased opioid exposure, particularly fentanyl, due to the adulterated methamphetamine supply (Dai et al., 2022; Daniulaityte et al., 2023). For instance, a small-scale study in Montgomery County, Ohio, revealed that 71.9% of the 89 participants who reported past 30-day methamphetamine use tested positive for fentanyl (Daniulaityte et al., 2023). Another study in West Virginia, conducted between 2013 and 2018, found that opioids were detected in 64.7% of methamphetamine-related deaths (Dai et al., 2022). Moreover, in 2022 Canada, 78% of accidental apparent stimulant toxicity deaths involved an opioid (Government of Canada, 2022). Collectively, intentional and unintentional combined use of opioids and methamphetamine are concerning as they are associated with an increased risk of overdose compared to opioid or methamphetamine use alone (Karamouzian et al., 2022b).

In order to address the harms associated with polysubstance use involving methamphetamine among PWUO, it is crucial to ensure the ready availability of harm reduction supplies. Additionally, harm reduction facilities, including those with a specific focus on overdose prevention, should be easily accessible to PWUO. (Park et al., 2020). However, the availability of harm reduction programs and regulations varies widely by region and jurisdiction (Hammett et al., 2014). For example, naloxone — an opioid antagonist that can quickly reverse the effects of an opioid overdose (Davis & Carr, 2020) — can be obtained from pharmacies without a prescription in both US and Canada (Antoniou et al., 2021; Cohen et al., 2020; Hammett et al., 2014). However, naloxone is only available with a prescription in some other countries, including Mexico, Iran, and Malaysia, and is restricted in countries, such as China and Vietnam (Hammett et al., 2014; Mehrpour, 2019; Rostami et al., 2023; Vicknasingam et al., 2015). Canada, and more recently in a small number of settings in the US, have also implemented supervised consumption sites as a novel service design to meet the needs of people who use drugs (Kennedy et al., 2017; Kolla et al., 2020; Pauly et al., 2020; Wallace et al., 2019). Efforts should be directed towards expanding and widely implementing evidence-informed life-saving harm reduction programs globally.

These programs play a crucial role in addressing the escalating harms linked to the concurrent use of opioids and methamphetamine among PWUO.

Our review also noted that methamphetamine use is concentrated among structurally disadvantaged populations. In the US, the increase in methamphetamine use among PWUO is particularly significant in rural areas and Western regions (Compton et al., 2020; Ellis et al., 2018, 2021; Jones et al., 2020b). Qualitative studies conducted in the US have reported that the availability and affordability of methamphetamine may contribute to the appeal of methamphetamine as a coping mechanism for some PWUO (Hansen et al., 2021; Strickland et al., 2019). One reason for the increasing availability of methamphetamine use in Western regions may include its proximity to the primary methamphetamine production source in Mexico (Brouwer et al., 2006). The rural nature of many areas in Western regions may also contribute to the ease of methamphetamine production in clandestine labs (Donijan, 2013). Meanwhile, rural areas may have higher rates of economic stressors compared to urban areas, including unemployment or poverty (Keyes et al., 2014), which were both reported to be associated with higher rates of methamphetamine use in different settings (Danesh & Noroozi, 2019; Jones et al., 2020b; Shearer et al., 2020).

It is essential to note that social and economic inequities are also present in urban areas (Nijman & Wei 2020; Van Draanen et al., 2020). Unstable housing is generally more prevalent in urban areas, as cities tend to have higher housing costs and often have more housing resources for individuals experiencing homelessness (Sylvestre et al., 2018). People living on the street may use methamphetamine as a coping strategy to stay alert and avoid hazards (Fast et al., 2014; Mckenna, 2013). Nevertheless, as the use and possession of methamphetamine are illegal in most countries, methamphetamine use was found to be associated with criminal justice system involvement (Al-Tayyib et al., 2017; Choi et al., 2022; Cui et al., 2022b; Glick et al., 2021; Meacham et al., 2018b), which may further exacerbate social and structural discrimination (Redmond et al. 2020). Some countries (e.g., Canada, Uruguay, and Portugal) have taken steps to decriminalize non-violent drug offences among people who use drugs (Maynard & Jozaghi, 2021; Vale de Andrade & Carapinha, 2010; Von Hoffmann, 2016). In response to the rapidly increasing use of methamphetamine and the ongoing opioid toxicity epidemic, it is imperative to address the specific structural needs of residents in different regions. This includes initiatives, such as creating employment opportunities, promoting effective housing policies, and implementing evidence-based decriminalization strategies for people who use drugs (Austin & Boyd, 2021; Bardwell et al., 2017; Maynard & Jozaghi, 2021; Van Draanen et al. 2023).

Based on our findings, it became evident that methamphetamine use was more prevalent among younger PWUO. Additionally, increased methamphetamine use was associated with engaging in drug use or sexual behaviours that may pose a risk of transmitting infectious diseases. Younger people may be exposed to methamphetamine through peer pressure or social networks, as methamphetamine is sometimes marketed as a party drug and may be perceived as more socially acceptable among younger populations (Boshears et al., 2011; Russell et al., 2008). The pharmacological effects of methamphetamine work to decrease inhibition and increase sexual desire impulsivity, and increased engagement in unprotected sex with casual or multiple partners (Corsi & Booth, 2008; Fast et al., 2014; Forrest et al., 2010; Knight et al., 2019; Melendez-Torres et al., 2016; Pitpitan et al., 2018; Vearrier et al., 2012). This is particularly concerning for young PWUO who use methamphetamine, given the significant barriers to accessing MOUD among them (Pilarinos et al., 2022). Expanding and designing educational interventions and harm reduction messaging tailored towards youth, as well as tackling barriers to accessing MOUD among them could help inform them about the various

harms associated with concurrent use of opioids and methamphetamine and improve the treatment and health outcomes for them.

Several studies identified a high prevalence of methamphetamine injecting practices among PWUO (Cui et al., 2022b; Daniulaityte et al., 2020; Jones et al., 2020b; Meacham et al., 2015; Meacham et al., 2018a, b). More concerning is that methamphetamine use was found to be associated with sharing or reusing syringes (Al-Tayyib et al., 2017; Glick et al., 2021; Meacham et al., 2015, 2018a, b). However, the majority of studies included in our review did not find a significant association between methamphetamine use and infectious diseases, including sexually transmitted infections, HIV, or hepatitis B or C among PWUO. Only two studies conducted in Vietnam found an association between methamphetamine use and HIV seropositivity. In some resource-limited settings (e.g., Vietnam, China), the ambiguities and contradictions between laws and policy implementation by street police present challenges in promoting HIV prevention and harm reduction training among people who inject drugs (Jardine et al., 2012). A comprehensive prevention and harm reduction package, including facilitated access to sterile needles for people who inject drugs and engage in polysubstance use practices, is essential to ensure reduced injection-related harms, and expansion or re-emergence of HIV epidemics among them (Des Jarlais et al., 2016).

Among PWUO seeking or receiving MOUD, the findings of the reviewed studies were inconsistent across different settings, highlighting the complexities and challenges in providing effective treatment for OUD. On the one hand, several studies showed that participation in MOUD treatment, especially MMT, and longer duration of treatment were associated with reduced methamphetamine use (Cui et al., 2022a; El Ibrahimy et al., 2022; Glick et al., 2018; Jones et al., 2020b; Strickland et al., 2021). In alignment, a recently published systematic review suggested that people who use methamphetamine may have lower receipt of MOUD, retention in MOUD, and opioid abstinence during MOUD (Frost et al., 2021). On the other hand, some studies have reported increased methamphetamine use among individuals who have received MOUD, while they have also reported facing barriers to treatment or feeling the need for additional help. These findings suggest that there may be some unsatisfactory experiences with MOUD that contribute to increased methamphetamine use (Cui et al., 2022a; Meacham et al., 2018b; Smith et al., 2022). To improve the retention and outcomes of MOUD treatment, it is crucial to ensure timely access to MOUD (Husain et al., 2023; Leece et al., 2019; Pijl-Zieber et al., 2022; Wakeman & Rich, 2017) and provide patient-centred care that includes customized medication modalities and dosages (Buresh et al., 2022; Murthy, 2016). In the absence of effective medication treatment for methamphetamine use disorder, non-medical interventions, such as contingency management targeting methamphetamine use, can be incorporated with MOUD treatment, yet the long-term effectiveness of such non-medical interventions remains unclear (Brown & DeFulio, 2020). Therefore, there is a pressing need for pharmaceutical trials targeting patients with co-occurring methamphetamine and OUD to confront this uncontrolled overdose epidemic. Furthermore, this review also noted that compared to using opioids alone, the use of methamphetamine and opioids was associated with increased risks of mental (e.g., anxiety, depression, and mood disorders) and physical (e.g., cardiovascular and lung diseases) illnesses, and consequentially more treatment encounters. These encounters can be used as opportunities to connect individuals to appropriate care and treatment (e.g., concurrent mental health and substance use treatment).



## Limitations

Although our study was methodologically rigorous, there are some limitations to consider, primarily due to the methodological shortcomings of the individual studies included. First, all studies were conducted in North America and Asia, and all studies included in our review characterizing methamphetamine use trends prior to COVID-19 were conducted in the US and Canada. This may reflect the geographical popularity of methamphetamine in these regions, but it limits our findings' generalizability to other regions, such as Europe or South America, where methamphetamine use is also spreading (EMCDDA, 2022; Lewis et al., 2021). We came across studies conducted in Europe concerning related topics; however, they were excluded because they did not meet our eligibility criteria for reasons, such as not examining trends or factors associated with methamphetamine use among PWUO (Gabrovec, 2015), or not separating methamphetamine from other stimulant use (Makarenko et al., 2018). Second, the heterogeneity in our study population and outcome indicators, the varying sampling frameworks, and the assessment of participants' sociodemographic and behavioural characteristics made it challenging to make direct comparisons and estimate pooled effect measures. The extensive heterogeneity in participant characteristics across the original studies restricts the generalizability of our findings to the entire population of PWUO, including those who were not included in the settings described in our paper. Third, while COVID-19 was thought to significantly impact the unregulated drug supply market, only one study in Vietnam assessed changes in methamphetamine use among PWUO before and after the pandemic. Further research is needed to evaluate the impact of COVID-19 on methamphetamine and opioid use and their potential interactive contribution to the chronically high overdose fatalities. Fourth, many of our included studies relied on self-reported data, which may be subject to recall or social desirability bias. However, prior research has suggested that self-reported data is generally accurate among people who use drugs (Darke, 1998). Lastly, all our included studies were observational; thus, we cannot infer causation between the identified factors and methamphetamine use among PWUO. Specifically, more than half of our included studies conducted unadjusted analyses only, and the noted associations were subject to unadjusted, unmeasured, or unknown confounding. Also, the cross-sectional nature of many studies limits the ability to establish temporality. However, observational studies can provide important insights into real-world settings, particularly considering that a portion of the included studies used nationally representative samples. Nonetheless, most of the studies were robust, had a large sample size, and were of reasonable quality.

## Conclusion

Our systematic review provides a comprehensive overview of the increasing trend of methamphetamine use among PWUO and its associated individual and structural factors. Our findings emphasize that the prevailing focus on the opioid epidemic must be expanded to address the growing issue of methamphetamine use, and potentially other drugs, among PWUO. Future clinical trials should evaluate treatment effects in the context of concurrent methamphetamine and opioid use, and be further undertaken to identify effective candidate medications for stimulant replacement therapy. Policymakers should also consider further investments in structural remedies to address the vulnerabilities of PWUO. Findings

from our study call for the development of a holistic approach that considers prevention, intervention, and harm reduction strategies aimed at addressing the growing twin epidemic of methamphetamine and opioid use in North America and beyond.

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## Declarations

**Ethical Considerations** Not applicable given the secondary nature of the study.

**Informed Consent** Not applicable given the secondary nature of the study.

**Conflict of Interest** All authors declare that they have no conflict of interest.

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