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REVIEW

Type of drug use and risky determinants associated with fatal overdose among people who use drugs: a meta-analysis

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ABSTRACT

Background: We assessed sociodemographic variables, risky determinants, and type of drug use associated with fatal overdose among people who use drugs (PWUD).

Methods: Studies in English published from January 1, 1985 to May 1, 2021, were searched on PubMed, Scopus, Cochrane, and Web of Science to identify studies on variables associated with fatal overdoses among PWUDs. After reviewing for study duplicates, the full-text of selected articles were assessed for eligibility using Population, Intervention, Comparator, Outcomes (PICO) criteria: (i) population: PWUD; (ii) intervention: fatal overdose in the past year; (iii) comparator: PWUD who had not fatal overdose; (iv) outcome: fatal overdose in the last year and (v) study type: cross-sectional, cohort, and case–control studies.

Results: Out of 13,821 articles, 25 studies met eligibility criteria. Our findings showed socio-demographic determinants (younger age, marital status, being homeless, being male,) risky determinants (poor mental health, experience non-fatal overdose and needle sharing), and type of drug use (cocaine disorder, benzodiazepines disorder, alcohol disorder, psychostimulant disorder, polysubstance disorders, and heroin dependence), were significantly associated with fatal overdose among PWUD.

Conclusions: The present study data indicated that numerous characteristics were correlated with overdose-induced mortality. Such characteristics are certainly interrelated; however, each factor could potentially be targeted for intervention. The most particular reason for death was practicing illicit drug use, including opioids (e.g., heroin).

Abbreviations: PWUD: People who use drug; CI: Confidence intervals; NOS: Newcastle-Ottawa Scale; OR: Odds ratio; PICO: Population, Intervention, Comparator, Outcomes; PRISMA: Protocols of Systematic Reviews and Meta-Analyses; PWIDs: People who inject drugs; WHO: World Health Organization

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Fatal overdose; cocaine disorder; benzodiazepines disorder; alcohol disorder; psychostimulant disorder

Introduction

In the United States, a major public health issue is considered to be drug-induced deaths (Rooney et al., 2018; Rossen et al., 2014). Furthermore, drug overdose accounted for more than 630,000 individuals from 1999 to 2016; of which, 55% of the cases concerned the use of opioids (Rooney et al., 2018). Drug-related overdose deaths could be prevented if they can be detected early (Walley et al., 2013). Preventive attempts such as harm reduction initiatives including "take home naloxone" (THN) programs and other overdose interventions may be successful to reduce overdose deaths (Walley et al., 2013).

The prevalence of deaths related to the overdose of opioid analgesics presented a 329% increase from 2000 to 2014 (Stewart et al., 2017). In the United States, the emergency rooms daily admit more than 1000 individuals with prescribed opioids use and about 115 of such cases lead to drug overdose-induced deaths (Stewart et al., 2017). In addition, the frequency of overdose-induced deaths due to prescribed and illicit opioids (e.g., heroin or illegally produced prescription drugs) increased up to 5 times from 1999 to 2016 (Davis et al., 2017). Scholars investigated the relationship between various health behaviors and the relevant outcomes concerning the influences of contextual and compositional characteristics (Jen et al., 2009). By definition, compositional characteristics consist of social and demographic features of the residents of a specific region (e.g., age, biological sex, ethnic/racial background, employment status, income level, etc.); however, contextual traits address a more extensive range of features of the region, i.e., beyond the compositional characteristics (e.g., population density, Thiel Index score, median household income, the frequency of population covered with health insurance, etc. Armah et al., 2015; Collins et al., 2017; Suzuki et al., 2012). A large body of literature highlighted the significance of contextual and compositional characteristics on individual health outcomes; however, these features were mainly considered as competing or mutually exclusive factors (Roux, 2016; Suzuki et al., 2012). Research studies are shifting from such

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a dichotomous aspect to the collective effects of compositional and contextual features on health outcomes (Armah et al., 2015; Cummins et al., 2007). Investigations addressing the potential collective association between contextual and compositional factors and fatal drug overdose worldwide are scarce; however, several studies were conducted to explore the effects of compositional or contextual factors on drug overdose deaths. Multiple compositional characteristics were identified to be correlated with overdose-induced deaths. For instance, one investigation reported higher odds of an unintentional fatal drug overdose in males, compared to females (Rooney et al., 2018); of them, more than 60% of the cases were related to opioids (including heroin) use (Gomes et al., 2018; Stewart et al., 2017). In addition, the frequency of opioid-induced deaths in the age groups of 15–24 years and 24–35 years were measured as 12% and 20%, respectively (Gomes et al., 2018; Stewart et al., 2017). Another predicting factor for drug use and overdose is suggested to be the mental health status of individuals. Prior research indicated greater odds of being prone to a fatal drug overdose among individuals encountering mental health issues, such as depression and anxiety (James Mcdonald et al., 2018). In this regard, opioids are of greater risks. This is because adult populations with diagnosed psychiatric conditions account for more than 50% of the total opioid prescriptions in the US, annually (Davis et al., 2017; Halbert et al., 2016). A considerable body of research literature classified drug use and overdose-related deaths in the class of contextual features. Accordingly, previous studies suggested a significant correlation between population density and the frequency of prescribing opioids, illicit drug use, and overdose deaths. Some studies also demonstrated that suburban residents are more prone to be strongly impacted by such issues, compared to the populations of the rural areas in metropolitan counties (Ghertner & Groves, 2018; Rossen et al., 2013).

The current systematic review and meta-analysis aimed to precisely detect the relationship between socio-demographic determinants (younger age, marital status, being homeless, being male,) risky determinants (poor mental health, experience non-fatal overdose and needle sharing), and type of drug use (cocaine disorder, benzodiazepines disorder, alcohol disorder, psychostimulant disorder, polysubstance disorders and heroin dependence), and fatal overdose in PWUD.

Methods

Search strategy and study selection

The present systematic review and meta-analysis study was implemented as per the instructions in Protocols of Systematic Reviews and Meta-Analyses (PRISMA; Bayani et al., 2020; Rezaei et al., 2020). The study selection process is illustrated in Figure 1.

The relevant studies were collected in accordance with the search strategy. We also included some other studies selected from the reference lists of the articles, i.e., published from January 1, 1985, to May 1, 2021.

In the study selection step, two independent researchers (A. B. and B.A.) individually reviewed the papers collected from the databases of PubMed, Scopus, Web of Science, and Cochrane (Table 1).

Only the English language papers were included in the present study. Furthermore, we employed some restrictions, such as time and geographic elements. The selected studies were reviewed twice in terms of abstract and relevance to the subject.

Inclusion criteria based on PICOS

Population: PWUD.

Intervention: fatal overdose in the past year

The Comparison Group: PWUD who had not any fatal overdose in the last year.

Outcomes: fatal overdose in the last year.

Study design: the cross-sectional, cohort, and case–control studies were included.

All the qualitative studies, secondary studies, systematic reviews and, meta-analysis studies, and also, non-English language papers were excluded from the present study.

Data extraction and study quality assessment

Two researchers (AB and BA) independently reviewed and evaluated the selected articles, as per a standardized data collection checklist.

Any disagreements between the two researchers were eliminated following consultation with the other research team members (EA and RM). Data extraction and management were performed in Microsoft Excel software. Two individual reviewers (author BA and AB) selected the studies in a two-phase monitoring procedure. Initially, the duplicated titles/abstracts (89% agreement) meeting the criteria 1–3 mentioned below were removed. Next, the articles' titles/abstracts were screened for full-text review based on the inclusion criteria of the study (96% agreement).

The required data were extracted from the selected articles. Accordingly, we documented the first author's surname, the date of publication, socio-demographic characteristics (younger age, gender, marital status, educational level); mental health status (depression/anxiety), the used drug type (the use of cocaine, benzodiazepines, alcohol, psychostimulants, & heroin dependence), as well as high-risk behaviors (methadone maintenance treatment, needle sharing, incarceration, & non-fatal overdose).

The Newcastle-Ottawa Scale (NOS; Stang, 2010) was implemented to examine the quality of the reviewed articles (Table 2).

In order to evaluate the quality of the included articles, the modified version of NOS was used respecting statistical quality, sample representativeness, and sample size assessments. The

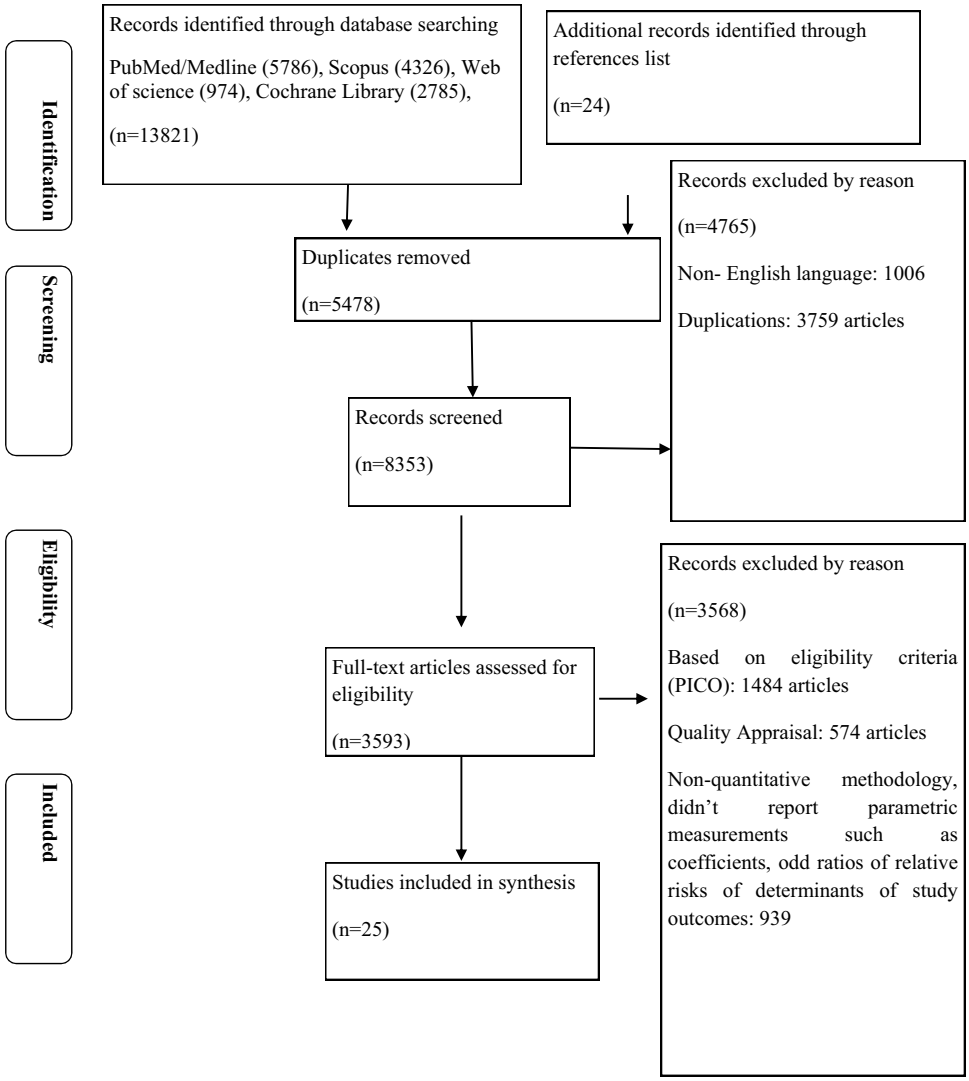

Figure 1. PRISMA flow diagram.

between-subject comparability was considered for the NOS with respect to the examination of the quality of individual studies.

Moreover, we applied the agreement beyond chance (unweighted kappa) to explore the consensus between the two authors (BA and AB) in the quality evaluation phase. The agreement levels of poor, slight, fair, moderate, substantial, and almost perfect were considered by the values 0, 01–0.02, 0.021–0.04, 0.041–0.06, 0.061–0.08, and 0.081–1.00, respectively (Landis & Koch, 1977).

Data synthesis and statistical analysis

The present systematic review and meta-analysis research was performed by generating pooled Odds Ratios (OR) and the 95% Confidence Intervals (CIs) for determining variables associated with drug overdose-induced deaths. The OR was computed by a 2 × 2 table, and an OR of <1 demonstrated a positive correlation between fatal overdose and the target characteristic. An OR of >1 (i.e., the statistical threshold for examining the correlation between the outcome and expositive variables) reflects a strong relationship between variables and vice versa. To evaluate the lack of correlation between studies, the Q test at $P < .05$ and I^2 statistics (with a cutoff point of ≥50%) were the most optimal choices. The 95%CI were considered for I^2; however, the negative scores were considered zero. To achieve the pooled estimation, the random-effects model was used, considering different sampling methods implemented in the studies. Begg's and Egger's publication bias method was used in graphical and statistical dimensions to identify any existing publication bias (Begg & Mazumdar, 1994; Egger et al., 1997). $P < .05$ was considered statistically significant. The relationships between high-risk behaviors were outlined using OR and 95%CI. Subsequently, the obtained data were illustrated in forest plots. The R 3.5.1 with the "meta" package was applied to perform the meta-analysis of the collected data.

Results

Study characteristics

Out of 13,821 articles identified, 25 studies were included (Altekruse et al., 2020; Bernstein et al., 2007; Binswanger et al., 2016; Bohnert et al., 2009; Burke et al., 2020; Caudarella et al., 2016; Daly et al., 2020; Davoli et al., 1993; Farrell &

Table 1. Search strategy.

	PubMed
#23	((((((((((((Death, Sudden, Cardiac[MeSH Terms]) OR (Heart Arrest[MeSH Terms])) OR (fatal overdose[Title/Abstract])) OR (Death[MeSH Terms])) OR (non-fatal overdose[Title/Abstract])) OR (Fetal Death[MeSH Terms])) OR (Myocardial Infarction[MeSH Terms])) OR (difficulties with breathing[Title/Abstract])) OR (convulsions[MeSH Terms])) OR (Seizures[MeSH Terms])) OR (inability to wake up[Title/Abstract])) OR (collapsing[Title/Abstract])) OR (blue skin color[Title/Abstract])) OR (Unconsciousness[MeSH Terms])) AND (((((((Opium Dependence [MeSH Terms]) OR (Morphine Dependence[MeSH Terms])) OR (Drug Users[MeSH Terms])) OR (Heroin[MeSH Terms])) OR (Heroin Dependence[MeSH Terms])) OR (Opioid-Related Disorders[MeSH Terms])) OR (Opiate Overdose[MeSH Terms]))
#22	((((((Opium Dependence[MeSH Terms]) OR (Morphine Dependence[MeSH Terms])) OR (Drug Users[MeSH Terms])) OR (Heroin[MeSH Terms])) OR (Heroin Dependence[MeSH Terms])) OR (Opioid-Related Disorders[MeSH Terms])) OR (Opiate Overdose[MeSH Terms])
#21	((((((((((((Death, Sudden, Cardiac[MeSH Terms]) OR (Heart Arrest[MeSH Terms])) OR (non-fatal overdose[Title/Abstract])) OR (non-fatal overdose[Title/Abstract])) OR (Death[MeSH Terms])) OR (Fetal Death[MeSH Terms])) OR (Myocardial Infarction[MeSH Terms])) OR (difficulties with breathing[Title/Abstract])) OR (convulsions[MeSH Terms])) OR (Seizures[MeSH Terms])) OR (inability to wake up[Title/Abstract])) OR (collapsing[Title/Abstract])) OR (blue skin color[Title/Abstract])) OR (Unconsciousness[MeSH Terms])
#20	Death, Sudden, Cardiac[MeSH Terms]
#19	Heart Arrest[MeSH Terms]
#18	non fatal overdose[Title/Abstract]
#17	Death[MeSH Terms]
#16	Fetal Death[MeSH Terms]
#15	Myocardial Infarction[MeSH Terms]
#14	difficulties with breathing[Title/Abstract]
#13	convulsions[MeSH Terms]
#12	Seizures[MeSH Terms]
#11	inability to wake up[Title/Abstract]
#10	collapsing[Title/Abstract]
#9	blue skin color[Title/Abstract]
#8	Unconsciousness[MeSH Terms]
#7	Opium Dependence[MeSH Terms]
#6	Morphine Dependence[MeSH Terms]
#5	Drug Users[MeSH Terms]
#4	Heroin[MeSH Terms]
#3	Heroin Dependence[MeSH Terms]
#2	Opioid-Related Disorders[MeSH Terms]
#1	Opiate Overdose[MeSH Terms]
	Scopus
#24	((TITLE-ABS-KEY (opiate AND overdose)) OR (TITLE-ABS-KEY (opioid-related AND disorders)) OR (TITLE-ABS-KEY (heroin AND dependence)) OR (TITLE-ABS-KEY (heroin)) OR (TITLE-ABS-KEY (drug AND users)) OR (TITLE-ABS-KEY (morphine AND dependence)) OR (TITLE-ABS-KEY (opium AND dependence))) AND ((TITLE-ABS-KEY (unconsciousness)) OR (TITLE-ABS-KEY (blue AND skin AND color)) OR (TITLE-ABS-KEY (collapsing)) OR (TITLE-ABS-KEY (inability AND to AND wake AND up)) OR (TITLE-ABS-KEY (seizures)) OR (TITLE-ABS-KEY (convulsions)) OR (TITLE-ABS-KEY (difficulties AND with AND breathing)) OR (TITLE-ABS-KEY (myocardial AND infarction)) OR (TITLE-ABS-KEY (fetal AND death)) OR (TITLE-ABS-KEY (death)) OR (TITLE-ABS-KEY (non AND fatal AND overdose)) OR (TITLE-ABS-KEY (heart AND arrest)) OR (TITLE-ABS-KEY (death, AND sudden, AND cardiac)))
4	(TITLE-ABS-KEY (unconsciousness)) OR (TITLE-ABS-KEY (blue AND skin AND color)) OR (TITLE-ABS-KEY (collapsing)) OR (TITLE-ABS-KEY (inability AND to AND wake AND up)) OR (TITLE-ABS-KEY (seizures)) OR (TITLE-ABS-KEY (convulsions)) OR (TITLE-ABS-KEY (difficulties AND with AND breathing)) OR (TITLE-ABS-KEY (myocardial AND infarction)) OR (TITLE-ABS-KEY (fetal AND death)) OR (TITLE-ABS-KEY (death)) OR (TITLE-ABS-KEY (non AND fatal AND overdose)) OR (TITLE-ABS-KEY (fatal AND overdose)) OR (TITLE-ABS-KEY (heart AND arrest)) OR (TITLE-ABS-KEY (death, AND sudden, AND cardiac))
#23	(TITLE-ABS-KEY (opiate AND overdose)) OR (TITLE-ABS-KEY (opioid-related AND disorders)) OR (TITLE-ABS-KEY (heroin AND dependence)) OR (TITLE-ABS-KEY (heroin)) OR (TITLE-ABS-KEY (drug AND users)) OR (TITLE-ABS-KEY (morphine AND dependence)) OR (TITLE-ABS-KEY (opium AND dependence))
#22	TITLE-ABS-KEY (death, AND sudden, AND cardiac)
#21	TITLE-ABS-KEY (heart AND arrest)
#20	TITLE-ABS-KEY (fatal AND overdose)
#19	TITLE-ABS-KEY (non AND fatal AND overdose)
#18	TITLE-ABS-KEY (death)
#17	TITLE-ABS-KEY (fetal AND death)
#16	TITLE-ABS-KEY (myocardial AND infarction)
#15	TITLE-ABS-KEY (difficulties AND with AND breathing)
#14	TITLE-ABS-KEY (convulsions)
#12	TITLE-ABS-KEY (seizures)
#11	TITLE-ABS-KEY (inability AND to AND wake AND up)
#10	TITLE-ABS-KEY (collapsing)
#9	TITLE-ABS-KEY (blue AND skin AND color)
#8	TITLE-ABS-KEY (unconsciousness)
#7	TITLE-ABS-KEY (opium AND dependence)
#6	TITLE-ABS-KEY (morphine AND dependence)
#5	TITLE-ABS-KEY (drug AND users)
#4	TITLE-ABS-KEY (heroin)
#3	TITLE-ABS-KEY (heroin AND dependence)
#2	TITLE-ABS-KEY (opioid-related AND disorders)
#1	TITLE-ABS-KEY (opiate AND overdose)
	web of knowledge
#1	TI = (Opioid- Related Disorders OR Heroin Dependence OR Heroin OR Drug Users OR Morphine Dependence OR Opium Dependence OR Opiate Overdose) *Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years*

(*Continued*)

Table 1. (Continued).

	PubMed
#2	TS = (Unconsciousness OR blue skin color OR collapsing OR inability to wake up OR Seizures OR Convulsants OR difficulties with breathing OR Myocardial Infarction OR Fetal Death OR Death OR fatal overdose OR non-fatal overdose OR Heart Arrest OR Death, Sudden, Cardiac) *Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = All years*
#3	#2 AND #1
	Cochrane
#1	MeSH descriptor: [Opioid-Related Disorders] explode all trees
#2	MeSH descriptor: [Heroin Dependence] explode all trees
#3	MeSH descriptor: [Heroin] explode all trees
#4	MeSH descriptor: [Drug Users] explode all trees
#5	MeSH descriptor: [Morphine Dependence] explode all trees
#6	MeSH descriptor: [Opium Dependence] explode all trees
#7	MeSH descriptor: [Opiate Overdose] explode all trees
#8	MeSH descriptor: [Unconsciousness] explode all trees
#9	(blue skin color):ti (Word variations have been searched)
#10	(collapsing):ti,ab,kw (Word variations have been searched)
#11	(inability to wake up):ti,ab,kw (Word variations have been searched)
#12	MeSH descriptor: [Seizures] explode all trees
#13	MeSH descriptor: [Convulsants] explode all trees
#14	(difficulties with breathing):ti,ab,kw (Word variations have been searched)
#15	MeSH descriptor: [Myocardial Infarction] explode all trees
#16	MeSH descriptor: [Fetal Death] explode all trees
#17	MeSH descriptor: [Death] explode all trees
#18	(fatal overdose):ti,ab,kw (Word variations have been searched)
#19	(non-fatal overdose):ti,ab,kw (Word variations have been searched)
#20	MeSH descriptor: [Heart Arrest] explode all trees
#21	MeSH descriptor: [Death, Sudden, Cardiac] explode all trees
#22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
#22	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22
#23	#22 AND #23

Table 2. Risk of bias assessment using Newcastle-Ottawa scale.

Study	Selection (***.)	Comparability (*)	Exposure/outcome (*..)	Method of assessment	Quality Assessment
Caudarella et al. (2016)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Kedia et al. (2020)	***.	*	*..	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
O'Driscoll et al. (2001)	*	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Satisfactory
Altekruse et al. (2020)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Burke et al. (2020)	**		*	Newcastle-Ottawa scale adapted for cross-sectional studies	Satisfactory
Daly et al. (2020)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Garg et al. (2017)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Hunter et al. (2018)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Krawczyk et al. (2020)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Ruhm (2017)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Gossop et al. (2002)	***			Newcastle-Ottawa scale adapted for cross-sectional studies	Satisfactory
Van Ameijden et al. (1999)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Binswanger et al. (2016)	***.	*	*..	Newcastle-Ottawa scale adapted for cohort studies	Very Good
Neira-León et al. (2011)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Ranapurwala et al. (2018)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Stoové et al. (2009)	***		*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Hall et al. (2008)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Bernstein et al. (2007)	*	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Satisfactory
Davoli et al. (1993)	*	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Satisfactory
Olfson et al. (2018)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good
Pizzicato et al. (2018)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Kelty & Hulse (2017)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Ødegård et al. (2007)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Bohnert et al. (2009)	***	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Very Good
Farrell and Marsden (2008)	**	*	*	Newcastle-Ottawa scale adapted for cross-sectional studies	Good

*: For cross-section studies.
·: For cohort studies.

Marsden, 2008; Garg et al., 2017; Gossop et al., 2002; Hall et al., 2008; Hunter et al., 2018; Kedia et al., 2020; Kelty & Hulse, 2017; Krawczyk et al., 2020; Neira-León et al., 2011; O'Driscoll et al., 2001; Ødegård et al., 2007; Olfson et al., 2018; Pizzicato et al., 2018; Ranapurwala et al., 2018; Ruhm, 2017; Stoové et al., 2009; Van Ameijden et al., 1999). Selected studies were from three WHO regions (16 from the America region [n = 2,536,402 participants], seven from the European region

[n = 122,542 participants] and two from the Western Pacific region [n = 8,398 participants]. The USA had the highest number of articles, with 15 studies (n = 2,533,804 participants).

Results of the meta-analysis

In Table 3, key characteristics of the included studies for variables associated with fatal overdose of patient with PWUD are presented. The characteristics of the 48 selected studies are presented in Table 3. The sample size ranged from 283 to 2,154,426 participants. Most studies were published between 1993 and 2020, and conducted in the USA. Eight cohort, and 47 cross-sectional studies were selected. Of the 25 studies, 10 were considered of high quality.

Sociodemographic variables associated with fatal overdose among PWUD

Results showed that there were associations between fatal overdose among PWUD and being age<30 years (OR = 1.61, 95%CI = 1.42–1.84. Those who were younger were 1.61 times more likely to report fatal overdose in the past 12 months (Table 4), as well as fatal overdose and being homeless (OR = 2.84, 95%CI = 2.1–3.84; Table 4). Associations between being male and fatal overdose among PWUD were found. These people were 1.48 times more likely to report fatal overdose during the past year (Table 4). Being unmarried was positively associated with fatal overdose, these being 3.34 more likely to have fatal overdose in the past 12 months (Table 4).

Risky determinants associated with fatal overdose among PWUD

Table 4 presents positive association between poor mental health and fatal overdose among PWUD. Participants who had suffers poor mental health were 1.84 times more likely to have had a fatal overdose in the past 12 months. Table 4 also presents positive association between experience non-fatal overdose and fatal overdose among PWUD. Those who had experienced a non-fatal overdose were 3.34 times more likely to have a fatal overdose in the past 12 months. Another finding was that positive association between needle sharing and fatal overdose among PWUD. PWID who had shared a syringe were 2.68 times more likely to report a fatal overdose in the past year (Table 4).

Type of drug use associated with fatal overdose among PWUD

Table 4 indicates the association between polysubstance disorders and fatal overdose among PWUD. Participants who have used polysubstances were 3.56 times more likely to report a fatal overdose during the past year (Table 4).

Participants who reported a psychostimulant disorder also were 2.71 times more likely to report a fatal overdose during the past year (Table 4). Additionally, results demonstrated that a correlation was demonstrated between alcohol and cannabis disorders and fatal overdose among PWUD. Those who had alcohol and cannabis disorders were 1.92 and 1.90 times more likely to have had a fatal overdose in the previous 12 months, than people who did not report such disorders (Table 4). A correlation between heroin

Table 3. Characteristics of non-fatal overdose among opiate users.

Author	participants	Sample Size	Year	Country	Study Design
Caudarella et al. (2016)	DU	2598	2016	Canada	Cross-section
Kedia et al. (2020)	IDU	22914	2020	USA	Cross-section
O'Driscoll et al. (2001)	IDU	2849	2001	USA	Cross-section
Altekruse et al. (2020)	DU	3800	2020	USA	Cross-section
Burke et al. (2020)	DU	2154426	2019	USA	Cohort
Daly et al. (2020)	DU	64195	2020	Ireland	Cross-section
Garg et al. (2017)	DU	150821	2017	USA	Cross-section
Hunter et al. (2018)	IDU	283	2018	USA	Cross-section
Krawczyk et al. (2020)	DU	963	2019	USA	Cohort
Ruhm (2017)	DU	16187	1990–2014	USA	Cohort
Gossop et al. (2002)	IDU	1075	2000	UK	Cross-section
Van Ameijden et al. (1999)	IDU	2809	1999	Netherland and USA	Cross-section
Binswanger et al. (2016)	DU	699	2017	USA	Cross-section
Neira-León et al. (2011)	IDU	991	2011	Spain	Cross-section
Ranapurwala et al. (2018)	DU	87124	2018	USA	Cohort
Stoové et al. (2009)	DU	4884	2009	Australia	Cohort
Hall et al. (2008)	DU	295	2008	USA	Cross-section
Bernstein et al. (2007)	DU	8774	2007	USA	Cross-section
Davoli et al. (1993)	IDU	4200	1993	Italy	Cohort
Olfson et al. (2018)	DU	1154	2018	USA	Cross-section
Pizzicato et al. (2018)	DU	82780	2018	USA	Cohort
Kelty & Hulse (2017)	DU	3515	2017	Australia	Cross-section
Ødegård et al. (2007)	DU	501	2006	Norway	Cohort
Bohnert et al. (2009)	DU	690	2008	USA	Cross-section
Farrell and Marsden (2008)	DU	48771	2007	Wales	Cross-section

Table 4. Pooled Odds ratio of variables associated with fatal overdose among PWUD.

Variables	Model	Number study	ORs, 95%CI	Degrees of freedom	P*	I^2
Being age< 30 years	Random	12.00	1.61, 95%CI(1.42–1.84)	11.00	0.01	0.95
Being male	Random	10.00	1.48, 95%CI(1.11–1.98)	9.00	0.01	0.96
Being homeless	Random	3.00	2.84, 95%CI(2.1–3.84)	2.00	0.84	0.00
Being unmarried	Random	6.00	3.34, 95%CI(2.82–3.97)	5.00	0.01	0.85
Experience non-fatal overdose	Random	5.00	3.34, 95%CI(2.68–4.16)	4.00	0.52	0.08
Poor mental health	Random	3.00	1.84, 95%CI (1.47– 2.31)	2.00	0.01	0.78
Needle sharing	Random	3.00	2.68, 95%CI(1.86–3.87)	2.00	0.75	0.00
Alcohol disorders	Random	4.00	1.92, 95%CI(1.02–3.63)	3.00	0.01	0.97
Polysubstance disorders	Random	3.00	3.56, 95%CI(2.36–5.38)	2.00	0.1	0.57
Cocaine disorders	Random	7.00	1.9, 95%CI(1.13–3.8)	6.00	0.01	0.88
Psychostimulant disorder	Random	3.00	2.71, 95%CI(2.01–3.65)	2.00	0.99	0.00
Benzodiazepines disorder	Random	5.00	2.74, 95%CI(1.67–4.5)	4.00	0.01	0.95
Heroin dependence	Random	6.00	1.68, 95%CI(1.36–2.07)	5.00	0.06	0.53

*P related to heterogeneity statistic

dependence, benzodiazepines disorder and fatal overdose among PWUD was also found. People with heroin dependence and benzodiazepines disorder were 1.68 and 2.74 times more likely to have had a fatal overdose in the previous 12 months, than people without such disorder (Table 4).

Publication bias

To identify the probable publication bias, the Egger's test and the graph were performed. The publication bias test indicates considerable bias based on Eggers test (coefficient = 3.66, *P* value < .001). Therefore, met-trim analysis was performed in order to remove the effect of publication bias on the pooled OR. The meta-trim analysis indicated that the pooled OR was 0.14 (95% CI, 0.11–0.25) in the random effect model.

Discussion

This meta-analysis aimed to explore variables associated with fatal overdose among PWUD. Generally, fatal overdose was associated with socio-demographic determinants (younger age, marital status, being homeless, being male), risky determinants (poor mental health, experienced a non-fatal overdose and needle sharing), and type of drug used (cocaine, benzodiazepines, alcohol, psychostimulants, polysubstances and heroin) among PWUD.

Chen et al. (2009) documented a more significant fatal poisoning potency, compared to other self-harm approaches for age. As a result, considering the association between enhanced rates of fatality and younger age is an essential prerequisite to prevent fatal overdose among the older populations. It is recommended that clinicians and physicians pay attention to many of the consumed drugs and the medication misuse indices among younger individuals. To guarantee the safety of the patients, medication prescription, especially of toxic drugs should be addressed prior to long-term use. In this approach, the therapeutic effects and associated risks must be weighed before prescription (Bedson et al., 2019).

In line with the data of the previous studies (Bartu et al., 2004; Brugal et al., 2005; Preti et al., 2002), the highest fatal overdose rates, as well as enhanced mortality risks, belonged to the male gender. A correlation was discovered between an enhanced risk of fatal overdose and older age, i.e., consistent with the findings of prior research. Despite a commonly held view, no association between younger, novice, or inexperienced use of heroin and a relevant fatal overdose was found. Instead, overdose-induced mortality is more prevalently observed in significantly experienced heroin users who are in their late twenties and early thirties (Bargagli et al., 2001; Gossop et al., 2002; Warner-Smith et al., 2001).

Studies neglected to explore the relationship between the risks of overdose-induced death and homelessness and there exists a research gap in this area. Severe types of drug use disorders elevate the risks of homelessness. Besides, risky routes of drug use might be considered as methods of coping with bio psychological stresses induced by homelessness (O'Driscoll et al., 2001).

The risk of opioid overdose death was greater among the divorced, separated, or widowed individuals, compared to the married subjects, supporting the previously reported correlation between marital status and fatal opioid-induced overdose (Day & Rosenthal, 2019; Martins et al., 2015). The determining characteristics behind such relationships remain undiscovered; however, such factors as biological, behavioral, and economic advantages of being married might promote health status in this group (Lo et al., 2016). Having a partner, like a spouse may restrict social isolation, or being alone might contribute to fatal opioid-related overdose (Lo et al., 2016). An opioid crisis in society could be prevented by interventions developed based on the significant correlation between enhanced interpersonal interactions and reduced risks of opioid use disorder.

As per the National Vital Statistics Reports, the frequency of cocaine-related overdose-induced deaths (regardless of intention) has risen by 62.5% from 1999 to 2005; however, the same rate concerning heroin was measured as a 2.4% increase (Bohnert et al., 2009). In the same period, cocaine was the most frequently reported substance (Bohnert et al., 2009). Further studies are required on cocaine and PWUD to explore the effects of providing training based on the previous investigations on necessary measures to manage overdose events.

Researchers identified an independent and strong relationship between overdose-induced fatality and using two non-injected substances, i.e., powdered cocaine and poppers (O'Driscoll et al., 2001). According to the literature, poly drug use is a critical contributing factor to death in PWUD; however, the focus of such investigations has been on the use of

alcohol and other sedative substances (e.g., barbiturates & benzodiazepines) as adjuncts to the injection of opiates (Darke & Zador, 1996; Van Haastrecht et al., 1996).

These findings are in line with those of previous research (Krawczyk et al., 2020). The studied subjects with a history of nonfatal overdose shaped the highest overdose-induced fatality rates, i.e., in agreement with the investigations suggesting overdose as a major predictor of fatal overdose in the future (Darke et al., 2011; Stoové et al., 2009). Additionally, A high-risk group for a fatal overdose encounters substantial variability (Brady et al., 2015; Caudarella et al., 2016).

Although fatal overdose cases are associated with the use of benzodiazepines such data were to some extent in line with those of previous studies (Geulayov et al., 2018). Some relevant investigations aimed at declining benzodiazepines-induced recurrence or fatal overdose are as follows. The research identified the relationship between benzodiazepine prescription and the risk of suicide in patients (Dodds, 2017), as well as decreasing the dose of benzodiazepine and suicide risk (Okumura & Nishi, 2017). Impactful benzodiazepine discontinuation steps consist of non-pharmacological interventions combined with dose-tapering; however, the positive effects of reduction measures on probable side effects in patients remain unclear and necessitates further research (Daly et al., 2020). A more effective and practical suggestion for patients with depression or other psychiatric conditions under treatment with potentially toxic medication could be screening and follow-up. Future investigations are recommended to explore the relationship between the frequency of benzodiazepine prescription adjunct to other potentially toxic drugs, like opioids, to prevent the elevated risk of relevant mortalities.

In line with the previous data, it was suggested that adjunct use of opioids, alcohol, and/or benzodiazepines are specific risk factors for fatal overdose. The research was performed among 555 drug users in the USA (Joe & Simpson, 1990), suggesting an association between elevated mortality risk and heavy alcohol use. According to the study conducted by Ruttenber and Luke (Ruttenber & Luke, 1984) as well as Risser and Schneider (Risser & Schneider, 1994), 30% and 56% of the overdose deaths in Austria were correlated with a single substance overdose and polysubstance use, respectively. Darke and Ross, (1999; Darke et al., 1996) conducted studies in Australia and demonstrated a significant relationship between polysubstance use, benzodiazepines use, and greater levels of alcohol use, and that fatal overdoses. In Scotland, Hammersley et al (Hammersley et al., 1995) reported polysubstance use of heroin, temazepam, diazepam, and alcohol were frequent in drug-related death cases. This finding was consistent with those of other researchers, outlining the prevalence of combined alcohol and drug use as well as polysubstance use among PWUD encountering non-fatal overdoses (Armoon, Bayani et al., 2021; Armoon, SoleimanvandiAzar et al., 2021; Noroozi et al., 2020). A direct respiratory is correlated with opioids use, adjunct to other substances (e.g., alcohol), leading to elevated relevant morbidity. The airways blockage induced by saliva, mucus, or vomit may also be considered as the secondary influencers of reduced respiratory capacity, causing death. As a result, the healthcare staff in charge are recommended to provide opioid users with explicit and comprehensive training on the respiratory depression-associated death risks, involved with polysubstance use. According to the literature, a significant proportion of NTORS clients practiced excessive alcohol use, raising concerns regarding the subsequent risks of such behaviors (Gossop et al., 2000). A negative impact of heavy alcohol drinking on the physical status of individuals with drug use disorders is the high prevalence of hepatitis C infection, which could be addressed as an independent risk factor for death in this population. Prior research specified heavy drinking as a serious risk factor in patients with chronic hepatitis C infection; even slight alcohol use was correlated with an elevated risk of viremia and hepatic fibrosis (Karimi et al., 2020).

Limitations of the study

In our study the most important limitation was the number of studies. The number of studies in each category (for example: depression or anxiety disorders, health insurance, other high-risk behaviors like injection of speedballs, frequency of drug use, cannabis use disorder, etc.) depends on whether they had reported in their studies. Second, most of the included studies were cross-sectional meaning causal and temporal relationships between risk behavior and fatal overdose are not possible. Thirdly, it was not possible to differentiate gender and therefore this analysis was not possible. Fourth, heterogeneity is part of the meta-analysis study and is inevitable and subject to limitations. In the present study, there were some limitations; including some articles that may be missing in this meta-analysis due to the following reasons (1) only two databases were considered for this study, (2) only English literature was searched, (3) unpublished literature was not considered.

Conclusions

The present study data indicated that numerous characteristics were correlated with overdose-induced mortality. Such characteristics are certainly interrelated; however, each factor could potentially be targeted for intervention. The most particular reason for death was practicing illicit drug use, including opioids (e.g., heroin). Previous studies highlighted the potential of opioid-induced overdose-prevention strategies, including the provision of take-home naloxone to the users (Mueller et al., 2015). However, the occurrence of overdoses by a sole drug is rare, and such cases are usually generated by polysubstance use. Healthcare providers to individuals with substance use as well as their clients with drug use disorders require further education concerning the risks associated with consuming a combination of substances, such as the use of illicit drugs adjunct to alcohol. The alcohol use disorder is highly frequent among numerous patients with drug use disorders, which complicate the treatment in this population (Gossop et al., 2000). Such data highlight the necessity of controlling heavy alcohol use disorder. Additionally, mental health issues encountered by this population may aggravate their mortality risks. In this respect, depression and anxiety disorders, as well as suicidal ideation, are greatly prevalent in individuals who use substances. As a result, substance treatment settings are recommended to encourage patients to receive additional

mental healthcare programs, if required. Environmental characteristics also impact the risk of death. One per 10 of the NTORS clients reported homelessness or lacking a constant accommodation at intake. Homelessness is correlated with an elevated risk of health conditions (e.g., HIV infection), as well as sexual abuse and violence (Morton et al., 2018; Walls & Bell, 2011). Our findings add to the available data by highlighting the correlation between enhanced risk of death and homelessness in subjects with drug use disorders. Thus, adequate measures must be taken to the provision of appropriate accommodation for this population. Policymakers and the related professionals are suggested to foster proactive approaches on drug use-induced fatality, rather than passively addressing it as a relevant risk in this area, not requiring special attention.

Future investigations are recommended to explore the effects of training concerning overdose and naloxone prescription, progressed transitional interventions, and healthcare services among substance users with comorbid mental health disorders, as well as alternative approaches to incarceration on mortality. In particular, the associated risk factors with post-release fatality consist of substance dependence and injection drug use, especially the use of opioids.

Ethics approval and consent to participate

This study was an analysis of preexisting literature and did not use human subjects.

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Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions

BA. Conceived the study. BA, LFM and LGN. collected all data. BA and RM analyzed and interpreted the data. B.A, drafted the manuscript. All authors commented on the drafts of the manuscript and approved the final copy of the paper for submission.

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