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Review

County-level predictors of US drug overdose mortality: A systematic review

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ABSTRACT

Background: This systematic review summarized published literature on county-level predictors of drug overdose mortality in the United States (US).

Methods: Peer-reviewed studies and doctoral dissertations published in English between 1990 and July 19, 2022 were identified from PubMed, Web of Science, ProQuest Dissertations & Theses, PsycINFO, CINAHL, and EconLit. Eligible studies examined at least one county-level predictor of drug overdose mortality in US counties. Two reviewers independently completed screening, quality assessment (with an adapted National Institutes of Health Quality Assessment Tool), and data extraction. Results were qualitatively summarized and grouped by predictor categories.

Results: Of 56 studies included, 42.9% were subnational, and 53.6% were limited to opioid overdose. In multiple studies, measures related to opioid prescribing, illness/disability, economic distress, mining employment, incarceration, family distress, and single-parent families were positively associated with drug overdose mortality outcomes, while measures related to cannabis dispensaries, substance use treatment, social capital, and family households were negatively associated with drug overdose mortality outcomes. Both positive and negative associations were documented for smoking, uninsurance, healthcare professional shortage status, physicians per capita, unemployment, income, poverty, educational attainment, racial composition, and rurality. Findings within studies also differed by subpopulation (by race/ethnicity, gender, age, or rurality) and the type of drugs involved in overdose.

Conclusions: The findings of this review provide relatively mixed evidence regarding many county-level predictors of overdose mortality, several of which also vary between subpopulations, supporting the importance of additional research to elucidate pathways through which the county context may shape risk of fatal overdose.

1. Introduction

Drug overdose deaths have increased four-fold in the United States (US) since 1999 (Centers for Disease Control and Prevention, 2021), exacting a staggering economic and societal burden (Florence et al., 2021; Gomes et al., 2018). Although the escalation in overdose deaths has impacted all regions across the US, researchers have documented wide geographic variations in rates of drug overdose mortality (Rossen et al., 2014). For example, age-adjusted drug overdose mortality rates in 2019 ranged from 4.8 deaths per 100,000 residents in Hidalgo County, Texas to 120.1 deaths per 100,000 residents in Scioto County, Ohio (Centers for Disease Control and Prevention, 2022).

Numerous studies have examined potential underlying causes of this geographic variation in US drug overdose mortality (Langabeer et al., 2020; Monnat, 2018, 2019; Monnat et al., 2019), yet such studies vary in methodology, measures, and specific outcomes examined. The present systematic review aims to synthesize the knowledge base regarding county-level factors associated with drug overdose mortality across the

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US. The review's focus on counties, as opposed to broader geographic levels (e.g., states), is informed by the substantial extent of within-state variation in drug overdose mortality rates. The county represents the smallest geographic unit available in national mortality data (Centers for Disease Control and Prevention, 2022); various subnational studies have examined drug overdose mortality at more granular levels (e.g., neighborhoods, cities/towns, or zip code tabulation areas; Cerdá et al., 2013; Green et al., 2011; Hester et al., 2012), yet data at these levels are not routinely available for the entire US.

Literature reviews related to fatal or non-fatal drug overdoses have been published on a variety of topics, including (but not limited to) prevalence and trends (Martins et al., 2015), risk factors for overdose in general or specific subpopulations (Armoon et al., 2021a, 2021b; Brady et al., 2017; Flam-Ross et al., 2022; Larney et al., 2020; Lyons et al., 2019; Mital et al., 2020; Van Draanen et al., 2020, 2021), and interventions for overdose prevention (Bahji and Bajaj, 2018; Ma et al., 2019; McDonald and Strang, 2016; Mercer et al., 2021; Potier et al., 2014). Most of these reviews have focused on research about drug overdose at the *individual* level (Armoon et al., 2021a, 2021b; Brady et al., 2017; Flam-Ross et al., 2022; Larney et al., 2020; Ma et al., 2019; Mital et al., 2020; Van Draanen et al., 2021), while others have included research at the state level (Beaudoin et al., 2016) or multiple levels (Van Draanen et al., 2020). The present systematic review, in contrast, focuses exclusively on county-level predictors of drug-related mortality, as factors at levels beyond the individual represent opportunities for interventions with broader reach and impact (Frieden, 2010).

2. Methods

This systematic review was based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), as detailed subsequently. (The review was not registered, and no protocol was published.) Eligible studies modeled at least one county-level indicator as a predictor or correlate of county-level rates of drug overdose mortality. We included studies that examined drug overdose mortality overall, as well as those that focused on deaths attributed to a specific drug type (e.g., opioids). Although the focus of the review was drug *overdose* mortality, we also included studies that used the broader designation of "drug-induced" ("drug-related") mortality, as drug overdoses account for approximately 95% of the deaths in this category (Centers for Disease Control and Prevention, 2022). However, studies that combined drug overdose deaths with chronic substance-related causes of death, such as alcoholic liver disease, were not eligible for inclusion. We included studies examining accidental/unintentional drug overdoses, considering that the majority (88%) of drug overdose deaths in the US are classified as accidental/unintentional (Centers for Disease Control and Prevention, 2022). Additionally, due to uncertainty in the classification of overdose intent (Rockett et al., 2018), we also included studies that combined accidental/unintentional drug overdoses with intentional drug overdoses or drug overdoses of undetermined intent.

Studies were eligible for inclusion if the setting comprised counties in the US, whether the entire US or a specific area within the US, with a population of either the overall resident population or a specific subgroup (e.g., certain age range or racial/ethnic group). Peer-reviewed articles and doctoral dissertations were eligible for inclusion, while master theses, non-peer-reviewed conference papers, and gray literature were excluded. In cases in which both a doctoral dissertation and its corresponding peer-reviewed publications met criteria for inclusion, the peer-reviewed publications were included while the doctoral dissertation was excluded, in order to avoid duplication. Only articles published in English were included. Considering that the contemporary US "opioid crisis" began in the 1990s (Centers for Disease Control and Prevention, 2021), articles were included if published after 1990 (and prior to the final literature search date of July 19, 2022).

2.1. Search Strategy

Studies were retrieved on September 23, 2020 and July 19, 2022 from six electronic databases (PubMed, Web of Science, ProQuest Dissertations & Theses, PsycINFO, CINAHL, and EconLit). The search terms used for each database are provided in Supplemental Table 1 and summarized as: (county or counties) and (overdos* or death* or mortalit* or fatal* or poisoning or decedent* or died) and (drug* or opioid* or opiat* or heroin or fentanyl or cocaine or methamphetamine* or stimulant* or psychostimulant* or benzodiazepine*).

Citations retrieved from all databases were consolidated in EndNote™ and uploaded in the Covidence software, where duplicate entries were automatically removed. Additionally, citations from the reference lists of studies which met inclusion criteria in the first search (retrieved via the online Citationchaser tool; Haddaway et al., 2022) were also uploaded in Covidence for screening. Two reviewers (M.C. and P.O., S.A.O., A.S., or A.C.M.) independently evaluated each title/abstract to exclude any publications unrelated to the review topic. Any discrepancies were resolved with the input of a third independent reviewer (Y.K. or S.O.). Finally, two reviewers (M.C. and S.O. or A.C.M.) independently completed a full text review to determine whether each study met inclusion criteria, with discrepancies again resolved by a third independent reviewer (Y.K.). For the title/abstract screening, the mean Cohen's Kappa across pairs of reviewers was 0.54, suggesting "moderate" agreement (Landis and Koch, 1977, p. 165). For the full text review, the mean Cohen's Kappa across two pairs of reviewers was 0.93, suggesting "almost perfect" agreement (Landis and Koch, 1977, p. 165).

2.2. Data extraction and quality assessment

Two authors (M.C. and S.O. or A.C.M.) independently completed a quality assessment and data extraction form for each study. Any discrepancies in responses were resolved via discussion. The data extraction form, available in Supplemental Table 2, included information on the study's population, sample size, outcome measures, predictors, covariates, years, data sources, missing data, analytical plan, and results.

Considering that the review included studies examining a wide variety of predictors and several different types of drug-related mortality outcomes, we focused on extracting data regarding the direction of statistically significant associations between county-level predictors and drug-related mortality, without reporting measures of the strength of these associations. For studies that examined both county-level and non-county-level (such as state-level) predictors, we extracted findings regarding the county-level predictors only. We focused on reporting results regarding associations with variables modeled as *predictors*, rather than also reporting associations with variables modeled as *controls/covariates*, in consideration of the risk of the "Table 2 Fallacy" (Westreich and Greenland, 2013). We provided result summaries for each study in table format and additionally qualitatively synthesized findings in diagrams based on predictor categories (health-related, economic or social factors, and demographic or geographic characteristics).

The quality assessment form used in the review is provided in Supplemental Table 3 and was adapted from the National Institutes of Health (NIH) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Institutes of Health, 2021). The NIH Quality Assessment Tool has been previously used in systematic reviews of opioid overdose (Van Draanen et al., 2020, 2021) and was modified for the current review in order to accommodate studies at the county level. For example, questions regarding sample recruitment, blinded exposure status, participation rate, and loss to follow-up were not applicable to county-level analyses and were therefore eliminated.

In addition to the questions included in the quality assessment form, we also extracted data regarding a unique data quality concern for studies examining drug-specific overdose mortality at the county level. Researchers from the Centers for Disease Control and Prevention have highlighted the need for caution when examining opioid overdose mortality rates at the county level, in light of dramatic differences between counties in the completeness of drug identification and reporting on death certificates (Jones et al., 2019). Therefore, we extracted data on whether each study included analyses with drug-specific outcomes (e.g., opioid overdose deaths), which are subject to underreporting. For studies examining drug-specific outcomes, we also extracted data on whether (and how) authors reported addressing underclassification of drug type, such as by using imputation procedures (Boslett et al., 2020; Ruhm, 2018) or adding analyses for drug overdoses as an overall category.

3. Results

3.1. Identified studies

As depicted in Fig. 1, title/abstract screening was completed for 5659 studies; 5501 records were excluded after title/abstract review, primarily due to research areas unrelated to the systematic review topic (e.g., motor vehicle fatalities, cancer mortality, drug-resistant tuberculosis). Of the remaining 158 studies included in the full-text screening, 102 were excluded, rendering a final sample of 56 studies. Examples of studies that did not meet the inclusion criteria are available in Supplemental Table 4. Of the 56 studies included in the review, all were published in peer-reviewed journals, with the exception of three doctoral dissertations (Hall, 2022; Sun, 2021; Suriaga, 2021). All studies were published between 2013 and 2022, with 91% published between 2018 and 2022.

3.2. Study characteristics

Table 1 provides information regarding the population, setting, sample size, and excluded/ missing data for each study included in the review, while Table 2 details the outcome measures, predictors, covariates, and statistical methods reported. As presented in Table 1, seventeen studies in the review (Blake-Gonzalez et al., 2021; Cordes, 2018; Gunn et al., 2018; Haley et al., 2019; Hall, 2022; Henry et al., 2021; Jones et al., 2020; Kline et al., 2019; Lister et al., 2020; Marotta et al., 2019; Romeiser et al., 2019; Rowe et al., 2022; Sauber-Schatz et al., 2013; Sawyer et al., 2021; Suriaga, 2021; Valentini and Jayawardhana, 2019; Whitley et al., 2022) were limited to one particular state, while seven other studies were limited to a specific region such as

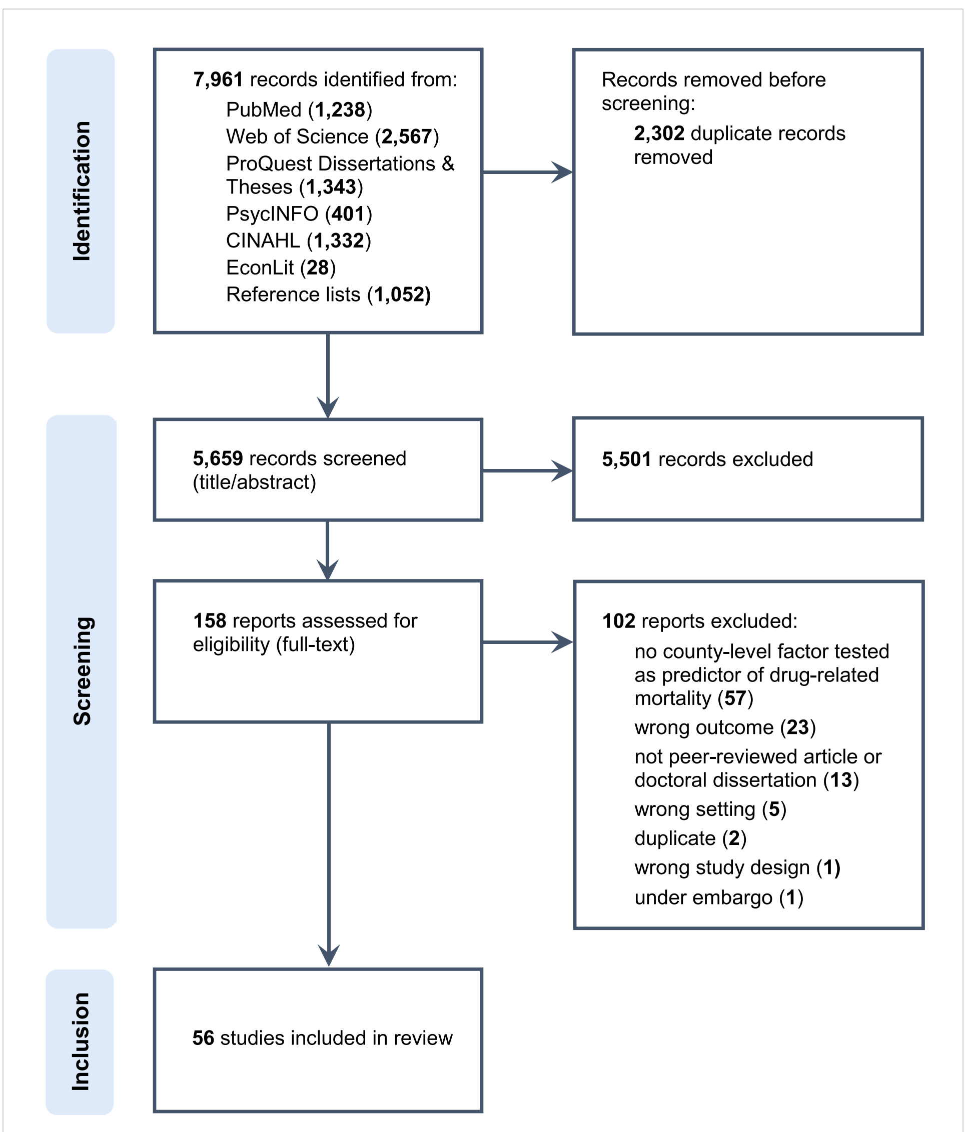

Fig. 1. PRISMA diagram for study identification, screening, and inclusion.

Table 1
Information on population/subpopulations, counties, and missing data for the 56 articles included in the systematic review.

Author (year)	Population/Subpopulation (s) Included	Area Included	N Counties or County-Years	Excluded or Missing Data
Betz and Jones (2018)	resident population overall and by gender and race	US; overall and metro/nonmetro	26,337 nonmetro and 13,649 metro county-year observations	n.s.
Blake-Gonzalez et al. (2021)	resident population	VA	84 county-equivalents	counties w/ missing outcome data excluded
Bradford and Bradford (2020)	resident population	US except AK, AR, ND, SD; overall and urban/suburban/rural	32,269 county-years of observation	AK, AR, ND, SD excluded due to missing data on predictor
Bruch et al. (2021)	resident population	US-Mexico border	21 counties; 43 in secondary analyses	n.s.
Congdon (2020)	resident population	US; overall and by geographic division	3141 counties	overdose rates for counties w/ less than 10 deaths missing, predicted values modeled
Cordes (2018)	resident population	NC	n.s.	n.s.
Dean and Kimmel (2019)	resident population	US	820 counties	excluded counties with suppressed mortality data; imputed in sensitivity analyses
Frankenfeld and Leslie (2019)	resident population overall and by race	US	2067 counties overall; 3142 in imputed dataset; smaller N for race-specific analysis	multiple imputation used for the 34% of counties with 10 or fewer deaths
Gabriel et al. (2021)	Non-Hispanic White population	AL, AR, FL, GA, LA, MS, NC, SC, TN	738 counties	excluded counties missing covariate or outcome data
Griffith et al. (2021)	resident population	US	26,970 county-years	two counties excluded; multiple imputation for missing values on the outcome; linear interpolation for missing values on covariates
Grigoras et al. (2018)	resident population	US	832 counties for opioid mortality analysis; lower N for specific opioids	excluded counties w/ suppressed mortality data
Gunn et al. (2018)	resident population	NC	100 counties	n.s.
Hadland et al. (2019)	resident population	US	9398 county-years	multiple imputation for 6–13% of counties missing prescribing rates
Haley et al. (2019)	resident population	NY	62 counties	n.s.
Hall (2022)	resident population	TX	91 counties	counties without mortality data available excluded
Henry et al. (2021)	resident population	CA	58 counties	n.s.
Hollingsworth et al. (2017)	resident population overall and by race	US	3138 counties; lower for race analyses	n.s
Hsu and Kovacs (2021)	resident population ages 21+	23 states w/ legal cannabis dispensaries, plus DC	812 counties in main analyses	n.s.
Jones et al. (2020)	resident population	NC	n.s.	excluded unspecified number of counties w/ unavailable data
Kelly et al. (2021)	children under 12 years old	US	3140 counties	excluded two smallest counties
Kerry et al. (2016)	resident population	US overall, West, and UT	n.s.	Poisson kriging used for counties with missing data on the outcome
Kerry et al. (2019)	resident population	Western US overall and "high risk" western states	n.s.	Poisson kriging used for counties with missing data on the outcome
Kline et al. (2019)	resident population	OH	88 counties	unspecified for mortality analysis
Kurani et al. (2020)	resident population	US	3133 counties	single imputation for unspecified number of counties missing predictor data
Langabeer et al. (2020)	resident population	US	1058 counties	excluded counties with less than 10 deaths
Lee et al. (2019)	resident population	US	n.s.	n.s.
Lin et al. (2020)	resident population overall and by age category, sex, race, and educational attainment	US	3132 counties	data on one covariate missing for 7 counties across 2 years
Lister et al. (2020)	resident population	MI	83 counties	n.s.
Marotta et al. (2019)	resident population	NY	62 counties	n.s.
Monnat (2018)	resident population	US	3106 counties	multiple imputation for 623 counties (20%) with suppressed mortality data
Monnat (2019)	Non-Hispanic White population	48 contiguous states and DC; overall and for urban and rural statuses	3047 counties	excluded Broomfield County and counties with fewer than 1000 NH White adults; multiple imputation used for 295 counties (9.7%) missing opioid prescribing data
Monnat et al. (2019)	resident population	US- 48 contiguous states and DC	3079 counties	multiple imputation for 6–13% of counties missing prescribing data
Nosrati et al. (2019)	resident population	US	2640 counties	AK, CT, DE, HI, RI, VT excluded due to no local jail system; 77 counties (including all in VA) excluded due to changing county boundaries over time; ~15% of observations excluded due to data quality concerns on predictor
Ombach et al. (2019)	resident population overall and by sex	US- contiguous states	1116 counties; fewer for sex-specific analyses	counties with fewer than 20 prescription opioid overdose deaths excluded
Pierce and Schott (2020)	resident population overall and by age category, race, and sex	US	3122 counties	n.s.

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Table 1 (*continued*)

Author (year)	Population/Subpopulation (s) Included	Area Included	N Counties or County-Years	Excluded or Missing Data
Rangachari et al. (2022)	resident population	US	554 counties	counties without outcome data available excluded
Romeiser et al. (2019)	resident population	NY	n.s.	excluded one county w/ missing data on predictor
Rowe et al. (2022)	resident population	CA	58 counties	n.s.
Rudolph et al. (2020)	resident population overall and by sex and race/ ethnicity	US except AK; only counties w/ unemployment above 4.9% or labor-force nonparticipation above 33%	2659 counties in labor force analysis; 1701 counties in unemployment analysis; fewer for subgroup-specific analyses	for unemployment analysis, excluded counties w/ < =4.9% unemployed adults; for labor force analysis, excluded counties with < =33% adults out of labor force; for subgroup analyses, excluded counties w/ < 5000 residents in subgroup
Ruhm (2019)	resident population overall and by sex, race, education level, and age group	US	3098 counties	29 counties excluded due to missing data on predictors/covariates; education missing for ~5% of death certificates
Sauber-Schatz et al. (2013)	resident population	FL	67 counties	n.s.
Sawyer et al. (2021)	resident population	IN	92 counties	n.s.
Smith (2020)	adults only, overall and by sex and race (NH White)	US- continental states except CA	48,799 county-years	CA excluded due to dispensaries open prior to study period
Sun (2021)	resident population	US- contiguous states; overall and by urban/rural status	3107 counties	linear interpolation or multiple imputation used for missing data on outcome and predictor/ covariates
Suriaga (2021)	older adults (ages 65+)	FL, overall and by metro and nonmetropolitan status	67 counties	0–0.004% missing data reported
Swensen (2015)	resident population overall and by age category, race, and sex	US- contiguous states; overall, urban and rural, and by income tercile	2408 counties	excluded counties without at least one treatment facility
Tacheva and Ivanov (2021)	resident population	US	2891 counties	missing outcome data addressed using interval regression with missing (suppressed) values in lowest interval
Valentini and Jayawardhana (2019)	resident population	GA	159 counties	n.s.
Venkataramani et al. (2020)	ages 18–65 only, overall and by age category, sex, and race	counties in 30 commuting zones with top quintile of manufacturing workers, mostly in South/ Midwest	112 counties	n.s.
Whitley et al. (2022)	resident population	OH	19 counties	n.s.
Wu and Evangelist (2022)	ages 25–54, overall and by race, sex, and age	US	3137 counties	n.s.
Yang et al. (2021)	resident population	US	2648 counties	excluded counties w/ missing values on predictors
Zemore et al. (2022)	resident population	US-Mexico border states (CA, NM, AZ, TX)	360 counties	counties with fewer than 10 deaths excluded
Zhu et al. (2022)	resident population	US overall and by rural/urban status	3034 counties	108 counties excluded due to missing data on predictors; Poisson-gamma model used for estimating missing values on outcome variable
Zoorob and Salemi (2017)	resident population	US	3104 counties	31 counties (1%) excluded due to missing data on the predictor
Zoorob (2018)	resident population	US	9106 county-years	12 county-years missing mortality data and one county-year missing demographic data

Abbreviations. AK, Alaska; AL, Alabama; AR, Arkansas; AZ, Arizona; CA, California; CT, Connecticut; DC, District of Columbia; DE, Delaware; FL, Florida; GA, Georgia; HI, Hawaii; IN, Indiana; LA, Louisiana; MI, Michigan; MS, Mississippi; N, number; NC, North Carolina; ND, North Dakota; NH, New Hampshire; NM, New Mexico; n.s., not specified; NY, New York; OH, Ohio; RI, Rhode Island; SD, South Dakota; TN, Tennessee; TX, Texas; US, United States; UT, Utah; VT, Vermont; VA, Virginia; w/, with.

the US-Mexico border (Bruch et al., 2021; Zemore et al., 2022), the western US (Kerry et al., 2019), southern states (Gabriel et al., 2021), or areas that met a specific characteristic (i.e., manufacturing share [Venkataramani et al., 2020]; unemployment or labor-force nonparticipation rates [Rudolph et al., 2020]; or legalized cannabis dispensaries [Hsu and Kovacs, 2021]); the other 32 studies focused on the US overall. Two studies (Gabriel et al., 2021; Monnat, 2019) examined overdose mortality in the Non-Hispanic White population only, and six studies (Hsu and Kovacs, 2021; Kelly et al., 2021; Smith, 2020; Suriaga, 2021; Venkataramani et al., 2020; Wu and Evangelist, 2022) were limited to specific age ranges; all other studies included the overall resident population.

As presented in Table 2, more than half of the studies (53.6%) were limited to overdose deaths involving opioids, in main analyses (Betz and Jones, 2018; Cordes, 2018; Dean and Kimmel, 2019; Gabriel et al., 2021; Griffith et al., 2021; Grigoras et al., 2018; Gunn et al., 2018; Hadland et al., 2019; Haley et al., 2019; Hall, 2022; Henry et al., 2021; Hsu and Kovacs, 2021; Jones et al., 2020; Kline et al., 2019; Langabeer et al., 2020; Lee et al., 2019; Lister et al., 2020; Ombach et al., 2019; Rangachari et al., 2022; Romeiser et al., 2019; Rowe et al., 2022; Sawyer et al., 2021; Smith, 2020; Sun, 2021; Suriaga, 2021; Tacheva and Ivanov, 2021; Venkataramani et al., 2020; Wu and Evangelist, 2022; Yang et al., 2021; Zhu et al., 2022), while one study examined overdoses involving a variety of specific drug types, including stimulants (Bradford and Bradford, 2020), and the remaining studies included drug overdose deaths overall (involving any drug, with or without additional analyses for specific drugs). Variables modeled as predictors included measures related to *health* (e.g., opioid prescribing, other substance use,

Table 2
Information on measures and statistical analyses reported by the 56 articles included in the systematic review.

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
Betz and Jones (2018)	opioid overdose deaths of any intent	1999–2014	employment and wage growth in different industries	total employment; population; income; poverty	regression using Bartik instrument
Blake-Gonzalez et al. (2021)	drug overdose deaths	2008–2017	opioid prescribing; market share of 5 largest pharmacy suppliers; income; unemployment; mining employment; % with disability; % insured; population density; % high school or more; mean work commute; incarceration; % white	none	semi-log period, fixed effects estimating equation
Bradford and Bradford (2020)	poisoning deaths involving: any opioid; prescription opioids; heroin; synthetic opioids; cocaine; stimulants with abuse potential; benzodiazepines; antidepressants; alcohol	2004–2016	eviction rate	income; % in poverty; unemployment; % male; % aged 20–64; % Caucasian; rurality; % uninsured; # of doctors per population; electronic PDMP (state level)	linear model with county fixed effects using a control function (2SRI)
Bruch et al. (2021)	drug overdose deaths	1990–2017	border wall construction	race/ethnicity, sex, and age composition; urbanization	semiparametric OLS difference-in-difference with county and year fixed effects
Congdon (2020)	drug overdose deaths of any intent	2015–2017	unemployment rate; unemployment rate change; Index of Concentration at Extremes (income inequality); social capital; urban-rural status; racial segregation; [opioid prescribing and fentanyl exposure measured at state level]	none	Bayesian Poisson-lognormal regression
Cordes (2018)	opioid involved overdose deaths, unintentional or intentional, involving: any opioid; heroin; methadone; synthetic opioids; semi-synthetic opioids; prescription opioids	1999–2015	median age; racial/ethnic composition; urban-rural status; poverty rate; unemployment rate; % with disability; uninsurance rate; educational attainment; per capita income	none	OLS regression
Dean and Kimmel (2019)	opioid-related overdose deaths of any intent, involving any type of opioid	1999–2015	trade-related job losses	population; income; racial demographics; population density; state-level labor union density; opioid prescription rates; number of physicians certified to prescribe buprenorphine; unemployment, mass layoffs unrelated to trade; presence of fentanyl	OLS regression
Frankenfeld and Leslie (2019)	drug overdose deaths of any intent	2010–2015	residential segregation measures; % poverty; % unemployed; income; % no high school; % disabled; % single-parent; % racial/ethnic minority; % speak English less than well; % multiunit structures; % mobile homes; % crowding; % no vehicle; % group quarters; % uninsured	% ages 65+ ; % less than 18 years old (also modeled as predictors)	negative binomial regression
Gabriel et al. (2021)	opioid overdose of any intent	2009–2018	% of 1860 population enslaved; number of lynchings (1865–1950); presence of active KKK chapter (1964–1966)	all covariates from 1860: population; % farms smaller than 5- acres; land holding inequity; farm value per acre; acres of improved farmland; % of free Black residents	censored, Bayesian multilevel negative binomial regression
Griffith et al. (2021)	opioid-related deaths	2006–2013	per capita oxycodone/ hydrocodone pill shipment volume	sex, age, and racial composition; cancer mortality rate; income; unemployment; % with 4+ years of college; MDs per population; specialist MDs per population; nurse practitioner prescribing authority; inpatient days per capita; outpatient visits per capita; % uninsured; % on Medicare; % dual-eligible (Medicare & Medicaid); number of hospices; short-term general hospital beds; short-term non-general hospital beds; long-term hospital beds; hospital-based	adjusted linear regression model with county-level fixed effects, weighted by county population

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Table 2 (*continued*)

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
				nursing home beds; early Medicaid expansion (state-level)	
Grigoras et al. (2018)	opioid-involved overdose deaths	2010–2014 pooled	opioid prescription rate to Medicare enrollees; % in poverty; racial composition; % male; age composition; population density; number of Medicare-enrolled opioid prescriber physicians per population	none	multivariable linear regression with spatial regression analyses
Gunn et al. (2018)	unintentional poisoning deaths involving: opioids; heroin	1999–2016	rurality; opioid prescriptions; HIDTA designation	none	logistic regression with random county effects
Hadland et al. (2019)	prescription opioid-related overdose deaths of any intent	Aug 1, 2014-December 31, 2016	pharmaceutical marketing of opioids to physicians; opioid prescribing rates	% male; mean age; main race/ethnicity; unemployment; income; poverty; % without education beyond high school; Gini index for income inequality; metropolitan status	negative binomial regression; mediation analysis
Haley et al. (2019)	opioid-related deaths	2012–2014	geographic access to: 1. FQHCs; 2. opioid treatment programs; 3. Buprenorphine providers	racial composition; % below poverty level; % without high school diploma	spatial error model regression
Hall (2022)	opioid overdose deaths	2020	presence of telemedicine; number of telemedicine service points	none	independent samples t-test and simple linear regression
Henry et al. (2021)	opioid overdose deaths of any intent: overall and for prescription opioids	2011–2018	presence of opioid safety coalition; initiative support of coalition	presence of substance use disorder treatment center "hub," number of "spokes" in treatment center "hub" per population	interrupted time series; mixed effects negative binomial regression with random intercepts for county and an order 1 autoregressive correlation structure
Hollingsworth et al. (2017)	drug overdose deaths of any intent, involving: any drug; and opioids	1999–2014	unemployment rate	not used in models with county and year fixed effects	regression models with county and year fixed effects
Hsu and Kovacs (2021)	opioid overdose deaths of any intent, overall and involving: prescription opioids; heroin; and synthetic opioids	2015–2018	number of cannabis dispensaries: overall, and medical and recreational dispensaries specifically	legalization of recreational cannabis sales; naloxone access laws; pain management laws; pharmacist patient identification laws; population size; unemployment; disability; income; % white; % bachelor's degree; % male; yearly GDP	panel regression
Jones et al. (2020)	unintentional opioid-related deaths	2010–2012; 2015–2017	per capita: opioid pills; buprenorphine prescriptions; EMS naloxone administrations; certified peer support specialists	none	Pearson product moment correlations
Kelly et al. (2021)	psychoactive drug overdose deaths of any intent	1999–2016	metropolitan status; unemployment; poverty; income; % with a Bachelor's degree; % foreign-born; % female-headed households; % Black; % Hispanic; state-level per-capita spending on education, public welfare, hospitals, and health; state-level PDMPs, Expanded Naloxone Access, Good Samaritan Laws, pain clinic prescribing restrictions, Medical Marijuana Laws	none	multilevel linear regression models
Kerry et al. (2016)	drug poisoning deaths of any intent	2006–2010	income; delayed physician use due to cost; population density; poverty; unemployment; median elevation; binge drinking; depression in Medicare enrollees; mentally unhealthy days; physically unhealthy days; smoking prevalence; suicide; average family size; % families; % Hispanic; % White; Latter-day Saints rate; YPLL	none	multiple linear regression and geographically weighted regression, including only variables strongly correlated with the outcome
Kerry et al. (2019)	drug poisoning deaths of any intent	2006–2010	average family size; % family households; Latter-day Saints rate; % White; % Hispanic; income; delayed physician use due to cost; population density; poverty; unemployment; elevation; binge drinking; depression in Medicare enrollees; mentally unhealthy	none	spatial profile regression

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Table 2 (*continued*)

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
			days; physically unhealthy days; smoking; suicide, YPLL		
Kline et al. (2019)	opioid poisoning deaths	2013–2015	health professional shortage area; disability rate; unemployment; % white; median age; % with Bachelor's degree; % single female households	none	Bayesian Poisson regression models
Kurani et al. (2020)	Bayesian smoothed drug poisoning mortality rates for overdoses of any intent, any drug	2012–2017	Area Deprivation Index (includes 17 measures related to poverty, education, housing, and employment)	age composition, % White, % male, year	negative binomial regression
Langabeer et al. (2020)	opioid-involved overdose deaths of accidental or undetermined intent	2016–2017	tobacco use rate; food insecurity rate; HIV prevalence; adult uninsurance rate; unemployment rate; % rural; % ages 65+ ; % NH White; % female	none	multivariate linear regression models with variables with a significant correlation to the outcome; stepwise backward selection
Lee et al. (2019)	opioid-related overdose deaths of any intent, any opioid	2016	opioid-related industry payments to providers	none	Spearman rank correlation
Lin et al. (2020)	drug overdose deaths of any intent, involving: any drug; any opioid; and not involving opioids	2003–2014	healthcare intensity index (ratio of local versus average national healthcare utilization rates)	% female; % racial/ethnic minority; % age; education; % foreign-born; % female-headed households; hospital beds and physicians per 1000 population; state PDMPs; medical/ recreational marijuana legalization; rural-urban continuum code; income; unemployment; poverty	regression with state and year fixed effects (linear models and dose-response models with quintiles)
Lister et al. (2020)	opioid overdose deaths of any intent, involving any opioid	2013–2017	urban/rural classification	none	Mann-Whitney U tests
Marotta et al. (2019)	drug overdose deaths of any intent involving: any drug; any opioid; heroin; opioid pain relievers; methadone; synthetic opioids	2013–2015	prescriptions for opioid analgesics; racial/ethnic composition	median income	spatial regression modeling
Monnat (2018)	drug-related deaths (drug poisoning of any intent, drug-induced disease, drugs in the blood, mental/ behavioral disorders due to drugs)	2006–2015	indices and measures regarding: economic distress; housing distress; industry classification; family distress; residents living in different county five years earlier; social capital; healthcare environment	metropolitan status; racial composition; age composition; % military/veterans	generalized spatial two-stage least squares autoregressive models
Monnat (2019)	drug-related deaths	2014–2016	metropolitan status; economic distress index; family distress index; persistent population loss; industry classification; opioid prescriptions; opioid prescribing in neighboring counties; [exposure to fentanyl (state-level)]	age composition; racial composition; % military/ veterans	linear random effects regression models
Monnat et al. (2019)	drug-related deaths; opioid deaths; heroin deaths; prescription opioid deaths; synthetic opioids deaths; multiple cause (2+ opioids) deaths	2002–2004; 2014–2016	racial and age composition; % veterans; % moved into county in last 5 years; population density; nonmetropolitan status; % not working; % no 4-year college degree; ratio of federal to county median household income; poverty rate; public assistance rate; Thiel's L [income inequality]; Gini coefficient [income inequality]; % separated or divorced; % single-parent families; % vacant housing units; % renter-occupied housing units; occupational composition; industry composition; opioid prescribing	% NH White; % age 65+ ; population density (also modeled as predictors)	multilevel negative binomial regression
Nosrati et al. (2019)	drug use disorder-related deaths	1983–2014	jail and prison admission rates; median household income	violent crime rate; racial/ethnic composition; opioid prescription rate; all-cause mortality rate	two-way fixed-effects panel regression
Ombach et al. (2019)	prescription opioid overdose deaths of accidental or undetermined intent	2006–2016	mean elevation	urban-rural classification; opioid prescribing rates	logistic regression using Williams method
	drug overdose deaths	1990–2013			difference-in-difference

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Table 2 (*continued*)

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
Pierce and Schott (2020)			trade liberalization (exposure to Permanent Normal Trade Relations)	average US import normal trade relations tariff for county-produced goods; average exposure to phasing out of global Multi-Fiber Arrangement; average changes in Chinese import tariffs/ domestic production subsidies; income; % without college degree; % veteran; % foreign-born; manufacturing job share	
Rangachari et al. (2022)	opioid use deaths	2009–2018	% female; median age; % Black; % White; % Hispanic; % Asian; % with bachelor's degree; median income; % in poverty; % unemployed; % institutionalized; % veterans; % in armed forces; number of FQHCs; number of rural health clinics; number of households; % of occupied housing units rented; % of housing units that are mobile homes	none	regression analysis with county, year, and state-by-year fixed effects
Romeiser et al. (2019)	prescription opioid overdose deaths of any intent	2013–2015	opioid prescriptions	none	Poisson regression
Rowe et al. (2022)	opioid-related deaths of any intent	2010–2018	buprenorphine NP/PA waiver capacity; buprenorphine MD/DO-275 waiver capacity	buprenorphine prescribing capacity rate; unemployment; % insured; non-buprenorphine opioid prescription rate; proportion of opioid-related deaths involving fentanyl	Poisson regression models with county and quarter level fixed effects
Rudolph et al. (2020)	drug overdose deaths of any intent	2015	unemployment rate; labor-force nonparticipation rate; relative unemployment rate (ratio of rate in subgroup vs. rate in overall county); relative labor-force nonparticipation rate (ratio of rate in subgroup vs. rate in overall county)	% of county population in the racial/ethnic sub-group; % of population in gender subgroup; % ages 0–19; % ages > 64 years; ratio of % 0–19 in subgroup to % 0–19 in overall population; ratio of % > 64-year in subgroup to % > 64 in overall percentage; drug overdose deaths in 2000 and 2009	longitudinal-g computation; negative binomial regression
Ruhm (2019)	drug poisoning deaths of any intent, involving: any drug; opioid analgesics; illicit opioids (heroin and synthetic opioids)	1999–2015	unemployment rate; poverty rate; median household income; median home prices; exposure to imports	% female; racial composition; age composition; % with some college; % female-headed households; % foreign-born; number of hospital beds; number of physicians per 1000; rural-urban continuum; PDMP (state-level); medical and recreational cannabis legalization (state-level)	fixed effects regression models
Sauber-Schatz et al. (2013)	drug-caused deaths; opioid-caused deaths; oxycodone-caused deaths	2009	pain clinics; opioid pills distributed to pharmacies/ physicians; oxycodone pills distributed to pharmacies/ physicians	age composition; racial composition; % male	negative binomial regression
Sawyer et al. (2021)	opioid-involved overdose deaths	2017	opioid-related emergency department visits; opioid-related arrests; chronic HCV cases; opioid prescriptions; median income	% female-led households; unemployment; Gini index; % without high school diploma; % with disability; % NH Black; opioid use disorder services rate; % internet access	bivariate negative binomial regression models
Smith (2020)	prescription opioid overdose deaths of any intent	1999–2014	existence of medical marijuana dispensary	% age; % White; % male; unemployment, average weekly wages; PDMP (state-level)	difference-in-difference
Sun (2021)	opioid overdose mortality of any intent: overall and for prescription opioids, heroin, and synthetic opioids	2005–2018	rurality (index of relative rurality)	% ages 15–24; % ages 65+ ; % male; % White; % Black; % Hispanic; % with high school degree or higher; % in agriculture, forestry, fishing and hunting, mining, construction, and manufacturing; % divorced/separated; % with disability; diabetes prevalence; poverty; unemployment;	spatial panel regression, two-way fixed effects models

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Table 2 (*continued*)

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
				uninsurance; % with Medicaid; % veterans; % receiving public assistance; social capital index; number of active MDs, nurse practitioners, physician assistants, dentists, chiropractors; number of pain management doctors, surgeons, sports medicine doctors, oncologists	
Suriaga (2021)	opioid-related deaths of any intent	2014–2018	metro status; median income; % high school and higher; racial composition	none	generalized linear model
Swensen (2015)	drug-induced poisoning deaths	1999–2008	number of substance abuse treatment facilities	unemployment rate; firm births; per-capita income; racial composition; age composition	weighted regression models with county and year fixed effects
Tacheva and Ivanov (2021)	opioid overdose deaths of any intent	2014–2016	score for county: openness; conscientiousness; extroversion; agreeableness; and neuroticism, as assessed via linguistic analysis of Twitter posts	YPLL; low birth weight rate; % BMI> =30; access to healthy foods; % no leisure physical activity; % access to places for physical activity; % driving deaths with alcohol; STD rate; teen birth rate; uninsurance; discharges for ambulatory care sensitive conditions in Medicare enrollees; diabetic Medicare enrollees receiving HbA1c test; female Medicare enrollees with mammogram in two years; % postsecondary education; unemployment; child poverty; % children in single-parent households; % households with overcrowding, high costs, no kitchen, or no plumbing; % driving alone to work; % car commutes > 30 min; words in aggregated tweets	panel interval regression models with control function
Valentini and Jayawardhana (2019)	drug overdose deaths due to any drug except alcohol, and opioid overdose deaths	1999–2015	rural/non-rural status	age composition; racial composition; % male; income; poverty; unemployment; % uninsured; primary care physicians per 1000 population	multivariate linear regression
Venkataramani et al. (2020)	opioid overdose deaths of any intent; in secondary analyses, drug overdoses overall, prescription opioids, and “illicit opioids” (opium and heroin)	1999–2016	auto assembly plant closures	none in main analysis	difference-in-difference, regression models with county and year fixed effects
Whitley et al. (2022)	drug overdose deaths of all intents	2013–2020	urine drug test positivity for: heroin; other opioids (natural/ semisynthetic); synthetic opioids; cocaine; and methamphetamine	none	Poisson regression models, county fixed effects
Wu and Evangelist (2022)	opioid overdose deaths of any intent	1999–2012	mass layoff rate; non-layoff unemployment rate	state-level maximum unemployment insurance benefit; GDP; income; poverty; population; unemployment; unemployment insurance weekly wage; SNAP recipients; TANF recipients; Medicaid enrollees; state earned income tax credit rate; minimum wage	difference-in-difference
Yang et al. (2021)	opioid-related deaths of any intent	2015–2017	unemployment rate; social capital index; social isolation index; smoking prevalence	% White; % Black; % male; median age; dependency ratio; % uninsured; MDs per capita; opioid prescribing rate; net migration rate; affluence index; metropolitan status	path analysis
Zemore et al. (2022)	drug-related mortality	2008–2017	on- versus off- border county designation	age/ gender / racial composition; education; poverty; employment rate; urbanicity; HIDTA status	spatial lag models
Zhu et al. (2022)	opioid overdose mortality of any intent	2014–2018 (pooled)	population size; population density; % Hispanic; % Black; % Asian; % Native Hawaiian or Other	none	generalized additive models with a thin plate spline term of spatial coordinates

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Table 2 (*continued*)

Author (year)	Outcome Measure	Years for Outcome Measure	County-Level Predictors	Controls/Covariates	Analysis
			Pacific Islander; % other race; % two or more races; % male; % 25–64; % 65+ ; % high school; % some college or higher; income; % unemployed; physicians per population; healthcare professional shortage area score		
Zoorob and Salemi (2017)	smoothed rates of drug overdose mortality (any intent, any drug) classified as low, moderate, and high	1999–2014	social capital index (based on civic associations/non-profits, voting rate, Census response rate, and non-profit organizations)	income; poverty; racial/ethnic composition; rurality; specialized substance use treatment centers per capita; opioid prescriptions for Medicare enrollees; year	multinomial logistic regression
Zoorob (2018)	smoothed rates of drug overdose mortality (any intent/ drug); low, medium, high, very high	2013–2015	percentage of all Medicare Part D claims that are for opioids and benzodiazepines	income; poverty; education; race/ethnicity; urban-rural index	multinomial logistic regression

Abbreviations. 2SRI, Two-stage Residual Inclusion; BMI, Body Mass Index; EMS, Emergency Medical Services; FQHC, Federally Qualifying Health Center; GDP, Gross Domestic Product; HIDTA, High Intensity Drug Trafficking Area; HCV, hepatitis C virus; HIV, Human Immunodeficiency Virus; KKK, Ku Klux Klan; MD, Medical Doctor; NP, Nurse Practitioner; OLS, Ordinary Least Squares; PA, Physician Assistant; PDMP, Prescription Drug Monitoring Program; SNAP, Supplemental Nutrition Assistance Program; TANF, Temporary Assistance for Needy Families; YPLL, Years of Potential Life Lost

healthcare systems and access, and health indicators), *economic factors* (e.g., economic health, employment, industries, income and poverty, housing), *social factors* (e.g., social capital, education, religion, family), and *demographic or geographic characteristics* (e.g., racial/ethnic, sex, and age composition, rurality, elevation). While some studies focused on a single predictor (e.g., Ombach et al., 2019; Romeiser et al., 2019; Valentini and Jayawardhana, 2019), others included 30 or more predictors (Frankenfeld and Leslie, 2019; Monnat et al., 2019). Studies also varied widely in the number and type of controls/covariates included in analyses, ranging from no controls/covariates (e.g., Hall, 2022; Jones et al., 2020; Lee et al., 2019; Lister et al., 2020), to more than 20 controls/covariates (e.g., Sun, 2021; Tacheva and Ivanov, 2021).

3.3. Quality Assessment

Results of the quality assessment are provided in Supplemental Table 5. All studies included a clearly defined research question, population, exposure, and outcome. While 89.3% of studies provided sample size information/justification, lower proportions mentioned adjusting for specific controls/covariates (62.5%) or evidenced temporal precedence (41.1%).

Supplemental Table 6 summarizes information about the extent to which included studies addressed the specific risk of bias due to underreporting of drug types on death certificates (Jones et al., 2019). Of the 56 studies in the review, 38 (67.9%) included analyses with overdose outcomes related to specific drug types, which are subject to underreporting. Among these 38 studies examining specific drug involvement in overdose deaths, five studies (Hollingsworth et al., 2017; Lin et al., 2020; Ruhm, 2019; Smith, 2020; Wu and Evangelist, 2022) reported using imputation to correct for opioid underreporting, while two other studies mentioned other corrections (e.g., additionally examining deaths without opioids reported [Monnat et al., 2019] or adding supplemental analyses with drug overdoses overall [Venkataramani et al., 2020]).

3.4. Results from the Included Studies

Table 3 summarizes main findings from each study, while Figs. 2–4 provide an overview of the directions of significant associations between county-level predictors and drug overdose mortality outcomes. Health-related predictors are depicted in Fig. 2, economic and social predictors in Fig. 3, and demographic and geographic predictors in Fig. 4. In each figure, the + symbol signifies a significant positive association between the listed predictor and the drug overdose mortality outcome examined in the particular study, while the – symbol signifies a significant negative association, and the + /- symbol is used when both significant positive and negative associations were reported in the study across different models or different subpopulations. Most of these associations are conditional on other variables included in the regression model (Table 2 presents the variables included in each study's statistical analysis/analyses). Nearly all frequentist approaches reported statistically significant associations with a threshold of $p < 0.05$, while Bayesian approaches reported significant associations via 90% (e.g., Gabriel et al., 2021) or 95% intervals (e.g., Congdon, 2020).

With respect to health-related predictors (Fig. 2), various indicators of poor physical/mental *health* (disability rate, hepatitis C virus cases, prevalence of human immunodeficiency virus, physically unhealthy days, mentally unhealthy days, depression in Medicare beneficiaries, suicide rate, and years of potential life lost; Cordes, 2018; Frankenfeld and Leslie, 2019; Kerry et al., 2016, 2019; Langabeer et al., 2020; Sawyer et al., 2021) were positively associated with drug overdose mortality outcomes. Associations between *substance use*-related indicators (e.g., smoking; Kerry et al., 2016; Langabeer et al., 2020; Yang et al., 2021) and drug overdose mortality outcomes were mixed, however. Measures related to *opioid prescribing* (whether opioid prescribing rates, pill shipments, pain clinics, or opioid marketing/ industry payments; Blake-Gonzalez et al., 2021; Griffith et al., 2021; Grigoras et al., 2018; Gunn et al., 2018; Hadland et al., 2019; Lee et al., 2019; Marotta et al., 2019; Monnat, 2019; Monnat et al., 2019; Sauber-Schatz et al., 2013; Sawyer et al., 2021) were consistently positively associated with drug overdose mortality outcomes, with one exception (Romeiser et al., 2019). Findings regarding *healthcare systems and access* were inconsistent; for example, uninsurance rates were negatively associated with drug overdose mortality outcomes in two studies (Langabeer et al., 2020; Blake-Gonzalez et al., 2021) while both positive and negative findings were reported in another study (Frankenfeld and Leslie, 2019). Although mixed results were observed regarding the healthcare system in general (e.g., healthcare professional shortage area, physicians per capita; Grigoras et al., 2018; Kline et al., 2019; Zhu et al., 2022), measures related to substance use disorder treatment access were more consistently associated with lower drug overdose mortality outcomes (Haley et al., 2019; Jones et al., 2020; Swensen, 2015).

As presented in Fig. 3, associations between economic indicators and drug overdose mortality outcomes were relatively mixed. Although economic distress and economic decline were positively associated with drug-related mortality (Monnat, 2018, 2019; Ruhm, 2019), Ruhm

Table 3
Findings regarding associations between county-level predictors and drug-related mortality outcomes, as reported by the 56 articles included in the systematic review.

Author (year)	Main Findings
Betz and Jones (2018)	Associations between employment growth or wage growth and opioid overdose mortality vary by tier of industry, gender, race, and metro/nonmetro counties. Negative associations between lower-tier industry employment growth or wage growth and opioid overdose mortality; positive association between top-tier industry employment growth and opioid overdose mortality.
Blake-Gonzalez et al. (2021)	In Virginia: opioid prescribing rate, mining employment share, % insured, incarceration rate, mean commute time, and unemployment rate positively associated with drug overdose mortality; market share of five largest pharmacies, median income, and population density negatively associated with drug overdose mortality.
Bradford and Bradford (2020)	Positive association between eviction rate and substance-related mortality (for all opioids, prescription opioids, synthetic opioids, heroin, benzodiazepines, and alcohol poisoning) in all counties; these positive associations were also observed in urban counties (except for prescription opioids), but not consistently observed in suburban or rural counties.
Bruch et al. (2021)	Nonsignificant association between border wall construction and drug overdose mortality.
Congdon (2020)	Association with drug overdose mortality was: positive for unemployment rate, unemployment rate growth, and racial segregation; negative for Index of Concentration at Extremes (income inequality), social capital, and rurality. In analyses by geographic division: income inequality and rurality were negatively associated with drug overdose mortality across all divisions, while the significance of associations between drug mortality and unemployment, social capital, or segregation varied between geographic divisions.
Cordes (2018)	In North Carolina: Association with prescription opioid mortality was: negative for percent Black and percent Hispanic, positive for percent disability. Association with heroin mortality was: negative for rurality and positive for percent with college education.
Dean and Kimmel (2019)	Positive association between trade-related job loss and opioid-related mortality; association strengthened when fentanyl is present in the county's heroin supply.
Frankenfeld and Leslie (2019)	Overall, positive associations between overdose mortality rates and multiple residential segregation measures, as well as % unemployed, income, % without high school diploma, % civilian disabled, % single-parent household, % without a vehicle. Overall, negative associations between overdose mortality and: % in poverty, % racial/ethnic minority, % speaking English less than well, % multiunit structures, % mobile home housing, % group quarters, and % crowded housing. Association with uninsurance rate varied (positive/ negative) based on model. Associations with overdose mortality differed by race/ethnicity (unemployment positive for White, negative for Hispanic; income positive for Black, negative for Hispanic; percent crowded housing positive for Black; percent uninsured null for White, negative for Black and Hispanic). Association between racial diversity and overdose mortality was null for White population and negative for Hispanic and Black populations.
Gabriel et al. (2021)	In the southern states examined: proportion enslaved (in 1860) was negatively associated with contemporary opioid mortality in the Non-Hispanic White population.
Griffith et al. (2021)	Positive association between per capita oxycodone/ hydrocodone pill shipment volume and opioid-related deaths.
Grigoras et al. (2018)	Positive associations between opioid overdose mortality and: rates of opioids prescribed (overall and by emergency medicine, family medicine, internal medicine, physician assistants), poverty rate, and White population share; negative association for number of opioid prescribing physicians per population.
Gunn et al. (2018)	In North Carolina: Positive association between opioid prescriptions per capita and unintentional opioid mortality; negative association between rurality and unintentional heroin mortality.
Hadland et al. (2019)	Positive association between all three measures of pharmaceutical industry opioid marketing and prescription opioid overdose mortality; prescribing rates partially mediated this relationship.
Haley et al. (2019)	In New York state: Negative associations between opioid mortality rates and geographic access to a) opioid treatment programs and b) Federally Qualified Health Centers. Negative significant association between buprenorphine provider concentration and opioid mortality in 2014 but not 2012.
Hall (2022)	In Texas: no significant association between the presence of telemedicine, or number of telemedicine service points, and opioid overdose mortality.
Henry et al. (2021)	In California: presence of a county opioid safety coalition was negatively associated with opioid overdose mortality and prescription opioid overdose mortality.
Hollingsworth et al. (2017)	Positive association between unemployment rate and opioid-related deaths or drug-related deaths in overall population and White population. In Black population, negative association between unemployment rate and opioid deaths.
Hsu and Kovacs (2021)	In population ages 21+ within states with legalized cannabis dispensaries: the number of cannabis dispensaries (and the number of medical dispensaries specifically) was negatively associated with overdose deaths due to any opioid, prescription opioids, heroin, or synthetic opioids. For recreational dispensaries specifically, negative associations with overdose mortality were statistically significant for opioids overall and synthetic opioids, but not prescription opioids or heroin.
Jones et al. (2020)	In North Carolina: opioid-related mortality positively associated with change in number of EMS naloxone administrations and negatively associated with change in buprenorphine prescription rates.
Kelly et al. (2021)	Proportion of female-headed households negatively associated with pediatric (children under age 12) overdose mortality.
Kerry et al. (2016)	In US overall: positive associations between drug poisoning death rate and: median household income; delaying use of physician due to cost; unemployment; elevation; depression in Medicare beneficiaries; mentally unhealthy days; physically unhealthy days; suicide rate; percent White; and years of potential life lost; negative associations with binge drinking, smoking, and average family size. In Western US: positive associations between drug poisoning death and: depression in Medicare beneficiaries; mentally unhealthy days; years of potential life lost; percent Hispanic; and Latter-Day Saints rate; negative for population density; poverty rate; and percent family households. In Utah: positive associations between drug poisoning death and: population density; unemployment; and years of potential life lost; negative for binge drinking and suicide rate.
Kerry et al. (2019)	In all western states: positive associations between drug overdose mortality and Latter-Day Saints rate, elevation, and suicide rate; negative associations with median household income, population density, and unemployment. In "high-risk" western states: positive association between drug overdose mortality and percent Hispanic, poverty, unemployment, mentally unhealthy days, physically unhealthy days, years of potential life lost; negative associations with percent family households, Latter-Day Saints rate, percent White, median household income, population density.
Kline et al. (2019)	In Ohio: Association with opioid poisoning mortality was: positive for percent of single-female households;

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Table 3 (*continued*)

Author (year)	Main Findings
	and negative for location in a Health Professional Shortage Area.
Kurani et al. (2020)	Positive association between Area Deprivation Index quintile and drug poisoning mortality.
Langabeer et al. (2020)	Positive associations between opioid mortality and tobacco use, HIV prevalence, percent rural, percent NH White, and percent female; negative associations between opioid mortality and food insecurity rate and uninsurance rate.
Lee et al. (2019)	Positive association between opioid-related industry payments and opioid-related mortality.
Lin et al. (2020)	Positive association between healthcare intensity and opioid-involved mortality in the overall population, as well as both sexes, all educational levels, ages 20–44 and 45–64, White and Black (but not Hispanic or other races); no association with non-opioid overdose mortality.
Lister et al. (2020)	In Michigan: Urban (vs. rural) counties had higher opioid overdose death rates.
Marotta et al. (2019)	In New York state: Positive association between opioid prescriptions and overdose mortality from any opioid, opioid pain relievers, and synthetic opioids. Positive association between percent Black and heroin overdose mortality.
Monnat (2018)	Association with drug-related mortality was: positive for economic distress, rental stress, labor market dependence on mining, and family distress; negative for labor market dependence on public sector, proportion of residents living in other counties five years prior, and number of religious establishments.
Monnat (2019)	Positive associations between NH White drug-related mortality rate and economic distress, family distress, mining and service industry, persistent population loss, and opioid prescribing rates; negative association with rurality (vs. large metro status) and manufacturing or public sector economic dependence. Some associations differed across urban-rural continuum or nonmetro labor markets.
Monnat et al. (2019)	Positive association with drug-related mortality for percent NH White, percent 65+ , population density, percent not working, percent with no 4-year college; ratio of federal to county median household income, poverty percent, public assistance percent, Gini coefficient, percent separated/divorced, percent single-parent family, percent vacant housing units, opioid prescribing rate, occupational percent in personal services, and industry percent in health, retail/personal services/food/accommodations, mining, and public administration. Negative association with drug-related mortality for percent NH Black, percent moved into county in last 5 years, occupational percent in executive/managerial or farming/fishing/forestry, and industry percent in agriculture/fishing/forestry, business/professional, finance/insurance/real estate, manufacturing, wholesale trade.
Nosrati et al. (2019)	Positive association between jail and prison admission rates and drug use disorder mortality rates; negative association between household income and drug use disorder mortality.
Ombach et al. (2019)	Positive association between mean elevation and prescription opioid overdose mortality, in overall population and male and female populations.
Pierce and Schott (2020)	Positive association between exposure to Permanent Normal Trade Relations and drug overdose mortality rate in the overall and White populations (both males and females) but not for any other races.
Rangachari et al. (2022)	Negative association between opioid use mortality and: median age; percent Hispanic; median income; and percent veterans.
Romeiser et al. (2019)	In New York state: negative association (described by authors as “small” and “essentially null”) between opioid prescription rate and prescription opioid mortality.
Rowe et al. (2022)	In California: no significant associations between NP/PA or MD/DO-275 buprenorphine waiver capacity and opioid-related mortality.
Rudolph et al. (2020)	Generally positive associations between overall and relative unemployment rates and drug overdose mortality both in the short and long term for males across racial/ethnic groups. For overall and relative labor-force nonparticipation rates, associations with drug overdose mortality differed by gender, race/ethnicity, and short/long term timeframe.
Ruhm (2019)	Positive associations between economic decline measures and overdose deaths due to all drugs, opioid analgesics, or illicit opioids were substantially attenuated or became non-significant after adjusting for covariates.
Sauber-Schatz et al. (2013)	In Florida: Positive association between rates of opioid or oxycodone pills distributed and overdose deaths due to any drugs, opioids, or oxycodone. Positive association between pain clinic rate density rate and oxycodone overdose deaths only in the unadjusted model but not adjusted model.
Sawyer et al. (2021)	In Indiana: opioid-related emergency department visit rate, opioid-related arrest rate, opioid prescription rate, and chronic HCV cases positively associated with opioid-involved overdose deaths (in bivariate models).
Smith (2020)	Negative association between opening of a medical marijuana dispensary and prescription opioid-related deaths- for adults overall and for males, females, and NH White males.
Sun (2021)	Index of relative rurality was negatively associated with opioid-related mortality (for all opioids, prescription opioids, heroin, and synthetic opioids) in the US overall. Index of relative rurality was positively associated with opioid-related mortality in urban counties; no significant relationship in rural counties.
Suriaga (2021)	In Florida: % with high school degree or higher positively associated with opioid death rate in older adults (ages 65+).
Swensen (2015)	Negative association between substance use disorder treatment facilities and drug-induced mortality rate, for facilities overall and for outpatient facilities; Negative associations with number of facilities observed across ages 10+ , all racial groups, male and female populations and in large urban and medium/small urban (but not rural) and medium and high income (but not low income) counties.
Tacheva and Ivanov (2021)	Positive associations between opioid overdose mortality and county Twitter-based scores of: conscientiousness, extraversion, and neuroticism.
Valentini and Jayawardhana (2019)	In Georgia: Negative association between rurality (vs. urban) and drug overdose mortality rate.
Venkataramani et al. (2020)	Positive association between automotive assembly plant closures and opioid overdose mortality in overall population and in NH White men ages 18–34 and 35–65 and NH White women ages 18–34.
Whitley et al. (2022)	In Ohio: positive bivariate associations between drug overdose mortality rates and urine test positivity rates for cocaine, synthetic opioids, and methamphetamine; negative bivariate associations between drug overdose mortality rates and urine test positivity rates for heroin and other (natural/semisynthetic) opioids. (Associations for methamphetamine and heroin nonsignificant in model that included positivity rates for all other drugs.)
Wu and Evangelist (2022)	Nonsignificant association between (a) mass layoff rate or (b) non-layoff unemployment rate and opioid-related mortality. However, state-level unemployment insurance benefit level moderated the association, for the overall population (ages 25–54) and for men, women, White individuals, ages 25–34, and 45–54.
Yang et al. (2021)	Unemployment was positively associated with opioid-related mortality. In path analysis, smoking was positively associated with opioid-related mortality; social capital was negatively associated with opioid-related mortality. Social capital, social isolation, and smoking were all significant mediators of the association between unemployment and opioid-related mortality.
Zemore et al. (2022)	

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Table 3 (*continued*)

Author (year)	Main Findings
	In US-Mexico border states: county on-border (vs. non-border) status was not significantly associated with drug-related mortality in bivariate model but significantly negatively associated with drug-related mortality when adjusting for covariates.
Zhu et al. (2022)	In both rural and urban counties: opioid overdose mortality rates positively associated with % two or more races and % ages 25–64; negatively associated with % Black, % male, and median income. In urban counties only: positively associated with unemployment rate and physicians per capita. In rural counties only: positively associated with healthcare professional shortage area score.
Zoorob and Salemi (2017)	Negative association between social capital measure and drug overdose mortality rates
Zoorob (2018)	Positive association between percent of Medicare Part D claims for benzodiazepines (or opioids) and drug overdose mortality, with interaction between benzodiazepine and opioid claim percentages

Abbreviations: EMS, Emergency Medical Services; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NH, Non-Hispanic; MD/DO, Medical Doctor/ Doctor of Osteopathic Medicine; NP/PA, Nurse Practitioner/ Physician Assistant; US, United States.

(2019) noted that positive associations with economic decline measures were substantially attenuated or non-significant after adjusting for confounding factors. Associations between unemployment rates and drug overdose mortality outcomes varied between and within studies and subpopulations, with three studies reporting both positive and negative associations (Frankenfeld and Leslie, 2019; Hollingsworth et al., 2017; Kerry et al., 2019) and eight studies reporting positive associations (Blake-Gonzalez et al., 2021; Congdon, 2020; Kerry et al., 2016; Monnat et al., 2019; Ruhm, 2019; Rudolph et al., 2020; Yang et al., 2021; and Zhu et al., 2022), including one study concluding that the association was mediated by social capital, social isolation, and smoking (Yang et al., 2021). While mining employment share (Blake-Gonzalez et al., 2021; Monnat, 2018, 2019; Monnat et al., 2019) and specific large-scale job losses (Dean and Kimmel, 2019; Venkataramani et al., 2020) were consistently associated with higher overdose mortality outcomes, associations between overdose mortality and other economic indicators were more nuanced; for example, lower-tier industry employment/wage growth was negatively associated with opioid mortality, yet top-tier industry employment growth was positively associated with opioid mortality (Betz and Jones, 2018), and associations between overdose mortality and overall or relative labor-force nonparticipation rates varied by time-frame, gender, and race/ethnicity (Rudolph et al., 2020).

Associations between measures of income/poverty and overdose mortality were also mixed. Six studies (Blake-Gonzalez et al., 2021;

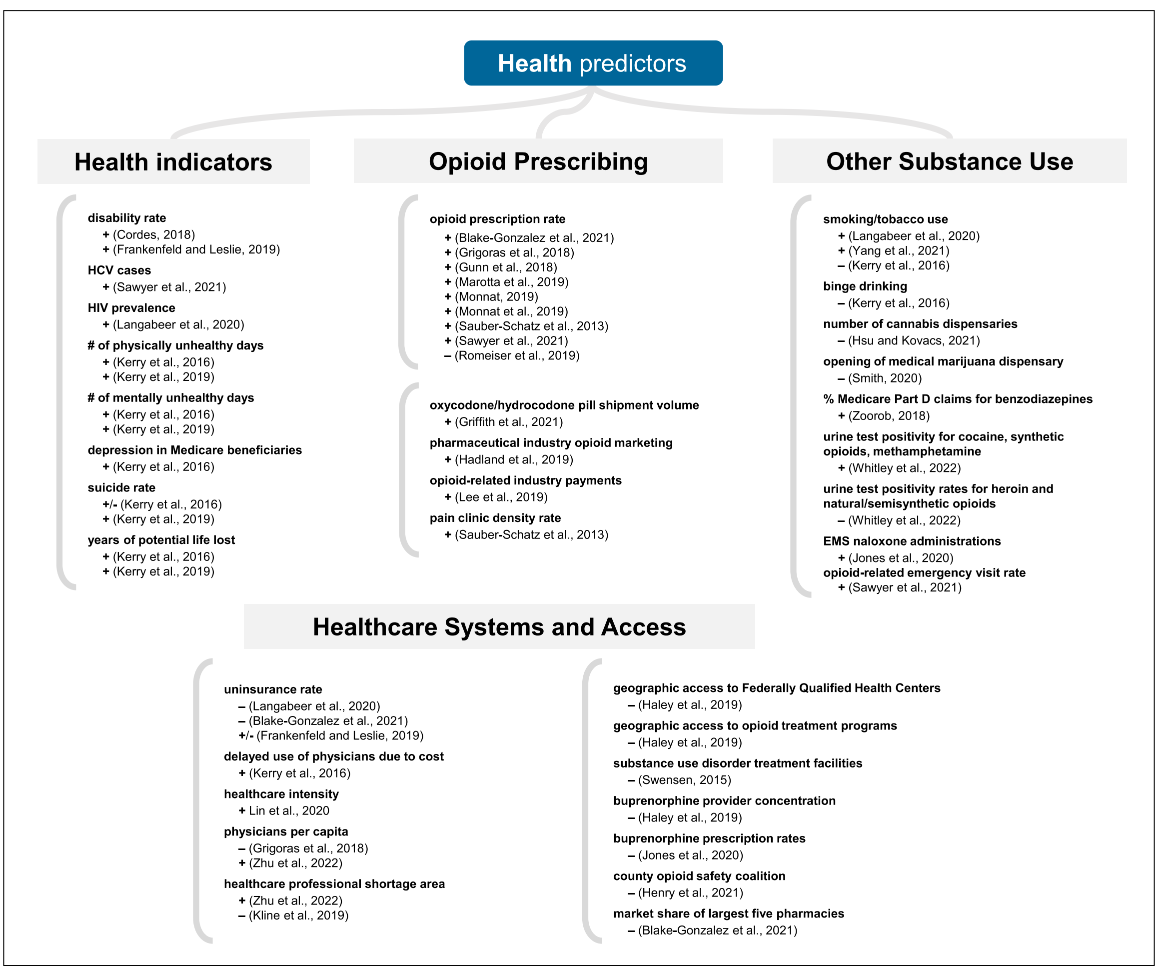

Fig. 2. Health-related county-level predictors of drug overdose mortality outcomes. Notes: The + symbol indicates a statistically significant positive association reported between the specified predictor and the overdose mortality outcome examined in the particular study, the - symbol indicates a statistically significant negative association, and + /- signifies that both significant positive and negative associations were documented in the study (in different analyses or subpopulations). While some associations are bivariate, others are conditional on the controls or covariates included in the statistical models. *Abbreviations*: HCV, hepatitis C virus; HIV, human immunodeficiency virus; EMS, Emergency Medical Services.

Fig. 3. Economic and social county-level predictors of drug overdose mortality outcomes. Notes: The + symbol indicates a statistically significant positive association reported between the specified predictor and the overdose mortality outcome examined in the particular study, the - symbol indicates a statistically significant negative association, and + /- signifies that both significant positive and negative associations were documented in the study (in different analyses or subpopulations). While some associations are bivariate, others are conditional on the controls or covariates included in the statistical models.

Kerry et al., 2019; Nosrati et al., 2019; Rangachari et al., 2022; Ruhm, 2019; Zhu et al., 2022) reported negative associations between income measures and overdose mortality outcomes, while one study (Kerry et al., 2016) reported a positive association and another study reported both positive and negative associations (differing based on racial/ethnic group; Frankenfeld and Leslie, 2019). Similarly, the poverty rate was positively associated with overdose mortality outcomes in four studies (Grigoras et al., 2018; Kerry et al., 2019; Monnat et al., 2019; Ruhm, 2019) yet negatively associated in two other studies (Frankenfeld and Leslie, 2019; Kerry et al., 2016). With respect to social characteristics, higher social capital (Congdon, 2020; Yang et al., 2021; Zoorob and Salemi, 2017) and proportions of family households (Kerry et al., 2016, 2019) were consistently associated with lower overdose mortality outcomes, while higher rates of incarceration (Blake-Gonzalez et al., 2021; Nosrati et al., 2019), family distress (Monnat, 2018, 2019), and single-parent families were associated with higher overdose mortality rates.

Finally, Fig. 4 depicts associations between overdose mortality

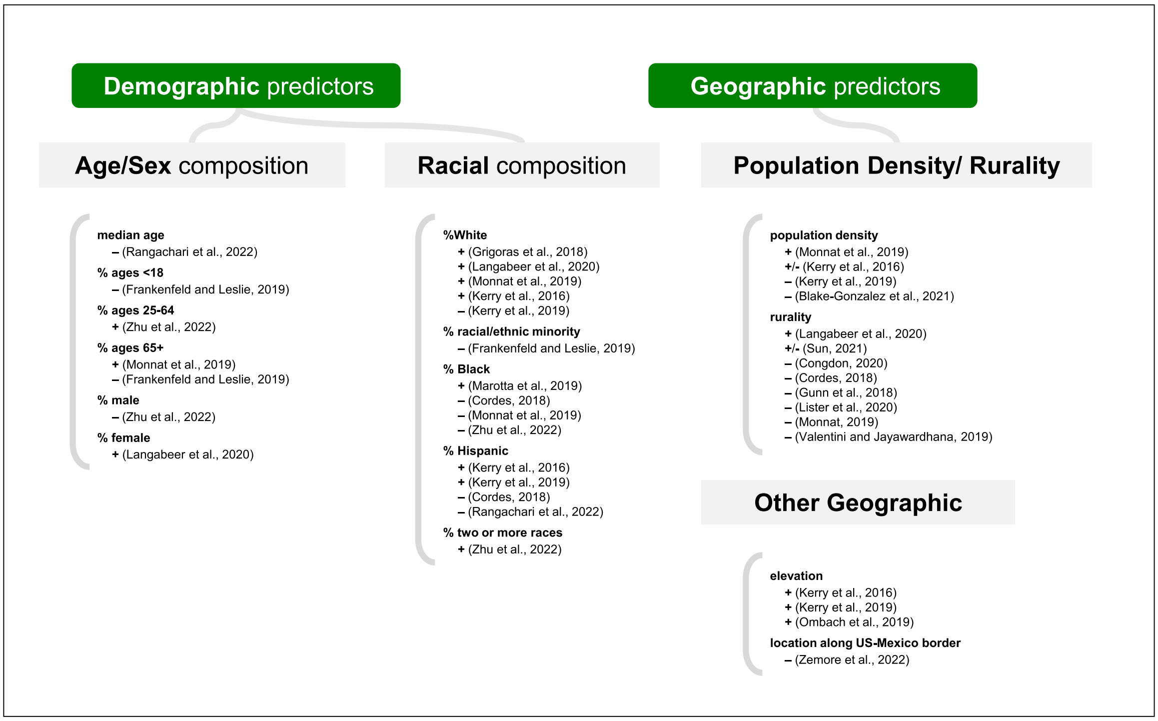

Fig. 4. Demographic and geographic county-level predictors of drug overdose mortality outcomes. Notes: The + symbol indicates a statistically significant positive association reported between the specified predictor and the overdose mortality outcome examined in the particular study, the - symbol indicates a statistically significant negative association, and + /- signifies that both significant positive and negative associations were documented in the study (in different analyses or subpopulations). While some associations are bivariate, others are conditional on the controls or covariates included in the statistical models.

outcomes and demographic or geographic predictors. The associations between racial composition and overdose mortality outcomes varied between studies. Associations between population density or rurality and overdose mortality outcomes were also mixed; population density was negatively associated with drug overdose mortality in two studies (Blake-Gonzalez et al., 2021; Kerry et al., 2019), positively associated in another study (Monnat et al., 2019), and both positively and negatively associated in different geographic areas within another study (Kerry et al., 2016). Rurality was associated with reduced overdose mortality outcomes in six studies (Congdon, 2020; Cordes, 2018; Gunn et al., 2018; Lister et al., 2020; Monnat, 2019; Valentini and Jayawardhana, 2019) yet associated with increased drug overdose mortality in another study (Langabeer et al., 2020), and the index of relative rurality was negatively associated with opioid-related mortality in the US overall while positively associated with opioid-related mortality in urban counties (Sun, 2021).

4. Discussion

This systematic review qualitatively synthesized associations between US county-level predictors and drug overdose mortality outcomes across 56 published studies. County-level variation in drug overdose mortality appears to represent a relatively recent yet quickly expanding topic of research; although our systematic review search included publications beginning in 1990, no publications prior to 2013 met criteria for inclusion, and 91.1% of included studies had been published between 2018 and July 2022, with 80.4% of studies published between 2019 and July 2022. The recent growth in this research topic may potentially reflect the increasing severity of the drug overdose crisis (Hedegaard et al., 2021), the public availability of county-level overdose mortality data across multiple online platforms (e.g., Centers for Disease Control and Prevention, 2022; Robert Wood Johnson Foundation, 2022), and recent, prominent conceptualizations of the social and economic roots of the overdose crisis and "deaths of despair" (e.g., Case and Deaton, 2017; Dasgupta et al., 2018).

Across studies in this systematic review, measures related to *opioid prescribing* (Blake-Gonzalez et al., 2021; Griffith et al., 2021; Grigoras et al., 2018; Gunn et al., 2018; Hadland et al., 2019; Lee et al., 2019; Marotta et al., 2019; Monnat, 2019; Monnat et al., 2019; Sauber-Schatz et al., 2013; Sawyer et al., 2021), *disability/illness* (Cordes, 2018; Frankenfeld and Leslie, 2019; Kerry et al., 2016, 2019; Langabeer et al., 2020; Sawyer et al., 2021), *economic distress* (Monnat, 2018, 2019), *mining* employment (Blake-Gonzalez et al., 2021; Monnat, 2018, 2019; Monnat et al., 2019), *incarceration* (Blake-Gonzalez et al., 2021; Nosrati et al., 2019), *family distress* (Monnat, 2018, 2019), and proportions of *single-parent families* (Frankenfeld and Leslie, 2019; Monnat et al., 2019) were generally consistently associated with increased drug overdose mortality outcomes across multiple studies. In contrast, measures related to *cannabis dispensaries* (Hsu and Kovacs, 2021; Smith, 2020), *substance use treatment* (Haley et al., 2019; Jones et al., 2020; Swensen, 2015), *social capital* (Congdon, 2020; Yang et al., 2021; Zoorob and Salemi, 2017), and proportions of *family households* (Kerry et al., 2016, 2019) were generally consistently associated with lower drug overdose mortality outcomes across multiple studies. Results regarding smoking/tobacco use, uninsurance, healthcare professional shortage status, physicians per capita, unemployment, income, poverty, education, racial composition, and rurality were less consistent, with both positive and negative associations documented. Findings in this systematic review were relatively less consistent than those reported in a recent systematic review of associations between socioeconomic marginalization and overdose at the individual level (Van Draanen et al., 2020).

The variation in results across studies in the review may plausibly be rooted in differences in study time periods, settings, measures, and methodology. First, the specific years of data and geographic areas examined may influence study findings, considering that the overdose crisis has varied widely across years and regions, both in terms of severity and the drug types frequently implicated in overdose deaths (Hedegaard et al., 2019, 2021). Second, predictor and outcome measures varied considerably across the studies included in the review. For instance, some studies examined drug overdose deaths involving any type of drugs, while other studies focused on overdose deaths attributed to specific drugs. Individual studies that examined multiple overdose outcomes (each involving a different type of drug) often yielded divergent results depending on drug type; for example, healthcare intensity was associated with opioid-involved mortality yet not with non-opioid drug mortality (Lin et al., 2020). As such, some of the variation in the results of studies included in the systematic review may be rooted in the variation in types of drug overdoses examined. Furthermore, studies examining overdose deaths involving specific drugs (e.g., opioids, heroin) may be subject to the bias introduced by county-level variation in the extent to which specific drugs are identified and recorded on death certificates (Jones et al., 2019), while this specific source of bias does not apply to studies examining drug overdose deaths overall. Finally, varying results across studies in this systematic review may also stem from the different methodologies employed, such as panel data versus cross sectional analyses, one year of data versus several years pooled, and inclusion of spatial and/or time lags. Study variation in addressing missing data (e.g., listwise deletion versus imputation) may also contribute to the mixed findings, considering that even within a single study, results differed between analyses using complete cases only and analyses with an imputed sample (e.g., Frankenfeld and Leslie, 2019). Furthermore, the number and type of covariates included in models varied widely across studies, and even within individual studies, results were sensitive to the inclusion of particular covariates (Ruhm, 2019; Sauber-Schatz et al., 2013; Whitley et al., 2022; Yang et al., 2021; Zemore et al., 2022). The potential relevance of which controls/covariates are modeled is underscored by analyses indicating that confounding factors nearly fully accounted for associations between economic decline proxies and overdose deaths due to various drug types (Ruhm, 2019) and that the association between unemployment and opioid-related mortality became non-significant after adjusting for social capital (Yang et al., 2021).

Beyond methodological differences, mixed findings between and within studies may also reflect the complex, often mediated and moderated pathways and multidirectional associations between health-related, social, economic, and demographic factors and overdose mortality outcomes. For instance, healthcare access may be accompanied both by increased access to prescription opioid pain relievers (which may increase overdose risk) and increased access to treatment for substance use disorders (which may reduce overdose risk; Kravitz-Wirtz et al., 2020). Findings from this systematic review also emphasize subpopulation variation in county-level risk factors for drug overdose mortality. Predictors of drug-related mortality differed in urban versus rural counties (Bradford and Bradford, 2020; Monnat, 2019; Swensen, 2015; Zhu et al., 2022), low versus medium/high income counties (Swensen, 2015), men versus women (Rudolph et al., 2020), and individuals of different age ranges (Lin et al., 2020). Variation between racial/ethnic groups was also observed for associations between drug mortality outcomes and employment or wage growth (Betz and Jones, 2018), unemployment (Hollingsworth et al., 2017; Frankenfeld and Leslie, 2019), labor force non-participation (Rudolph et al., 2020), per capita income, racial and unemployment diversity, percentage of crowded housing (Frankenfeld and Leslie, 2019), healthcare intensity (Lin et al., 2020), and trade policies (Pierce and Schott, 2020). Prior literature has suggested that racial/ethnic groups differ in terms of individual-level risk factors for substance use-related outcomes (Cano and Gelpí-Acosta, 2022; Shih et al., 2010; Stone et al., 2012), yet it is unclear if, or how, such individual-level factors or processes may translate into differences observed at the county level. When considering why associations between certain predictors and drug overdose mortality vary by racial/ethnic group, it may also be relevant to note that analyses often model predictors measured for the overall county population while the outcome is measured within one specific racial group, even though, when considering an example such as median income, the median income in any given county overall may not necessarily reflect the median income within a racial/ethnic minority subpopulation in that county.

4.1. Limitations

Studies included in this systematic review are subject to limitations such as geographic variation in the completeness of drug reporting on death certificates (Boslett et al., 2020; Jones et al., 2019), missing data for counties with suppressed mortality data, and limited evidence of conceptual frameworks guiding variable selection; moreover, temporal precedence, sensitivity analyses, corrections for multiple testing, and methods accounting for spatial autocorrelation were not consistently implemented across all studies.

In this systematic review, the measure of agreement between screeners was only “moderate” for the first stage of screening (title/abstract screening), yet this moderate level of initial agreement was addressed by the use of a third independent reviewer to screen all titles/abstracts with discrepancies in votes; near perfect agreement between reviewers was observed at the full text review stage. Although the present review included studies published through July 19 2022, all but two studies (Hall, 2022; Whitley et al., 2022) used mortality data solely from years prior to 2020; as such, it is unclear to what extent findings from the review may apply to county-level drug overdose mortality in the era of COVID-19.

The wide variety of predictors in the included studies precluded a meta-analysis of the estimates; therefore, this systematic review focused on identifying significant county-level predictors of drug-related mortality without examining the strength of these associations. We extracted data solely regarding associations identified by study authors as statistically significant; therefore, the findings reported were subject to the arguably arbitrary (Wasserstein et al., 2019), albeit conventional, cut-off points selected by study authors for p values or credible intervals. The effect sizes of most findings were relatively modest, and a determination of whether findings should be considered clinically significant, as opposed to only statistically significant, was outside the review scope. Finally, due to the study’s focus on county-level predictors, evidence regarding policies at the state-level (e.g., Prescription Drug Monitoring Programs, Medicaid expansion, cannabis legalization) was outside of the review scope, as was evidence regarding “deaths of despair” beyond drug overdoses (i.e., alcohol poisoning, suicide, or alcoholic liver disease).

4.2. Implications

The studies included in this systematic review examined a wide range of potential predictors of drug overdose mortality, yet predictors related to illicitly-manufactured fentanyl exposure were examined notably less frequently than predictors related to prescription opioid pain relievers. Of the 56 studies in the review, only two included a county-level measure related to fentanyl exposure (as a moderator in Dean and Kimmel, 2019; as a control in Rowe et al., 2022), and two other studies modeled fentanyl exposure at the state-level (Congdon, 2020; Monnat, 2019). Deaths involving synthetic opioids such as fentanyl have surpassed deaths involving prescription opioid pain relievers since 2016 (Hedegaard et al., 2021); as such, future research may benefit from including measures related to the presence of illicitly-manufactured fentanyl in the drug supply, which varies regionally (Hedegaard et al., 2019). Furthermore, as the US overdose crisis has continued to evolve, stimulants such as methamphetamine and cocaine have been increasingly involved in overdose deaths, often in combination with opioids (Hoots et al., 2020); considering that only one study in the review (Bradford and Bradford, 2020) reported examining psychostimulant-involved and cocaine-involved mortality, and only one study examined a stimulant-specific predictor (Whitley et al., 2022), county-level measures related to stimulants may also represent a relevant future research direction.

Future research may also benefit from increased utilization of the imputation procedures researchers have developed to correct for the underreporting of opioid involvement on death certificates (Boslett et al., 2020; Ruhm, 2018), as only five studies in this review (Hollingsworth, 2017; Lin, 2020; Ruhm, 2019; Smith, 2020; Wu and Evangelist, 2022) specifically reported employing such imputation procedures even though 38 studies examined drug-specific outcomes that are subject to underreporting limitations. In consideration of the inconsistencies in results reflected in this review, future researchers may wish to build on the example of studies that utilized multiple model specifications and sensitivity analyses to evaluate robustness of findings (e.g., Hollingsworth et al., 2017; Swensen, 2015; Ruhm, 2019), as well as moderation analyses to determine the extent to which findings apply across different subpopulations (Frankenfeld and Leslie, 2019; Hollingsworth et al., 2017; Lin et al., 2020; Monnat, 2019; Rudolph et al., 2020; Smith, 2020; Venkataramani et al., 2020; Wu and Evangelist, 2022; Zhu et al., 2022) or vary by state-level policies (Wu and Evangelist, 2022). Finally, mediators and potential pathways for associations represent a promising step in expanding the knowledge base on county-level predictors of drug overdose mortality, as mediation analyses were utilized in relatively few (e.g., Hadland et al., 2019; Yang et al., 2021) of the 56 studies included in this systematic review.

5. Conclusion

Researchers diverge in the extent to which they attribute the US overdose crisis to supply-side factors versus demand-related measures such as socioeconomic vulnerabilities (Ciccarone, 2019; Dasgupta et al., 2018; Fischer et al., 2020; Ruhm, 2019). Based on the studies included in this review, both county-level supply- and demand-related measures are associated with overdose mortality rates, although county-level demand-related predictors have been examined more frequently, and with a greater variety of indicators, than county-level supply-side factors. This observation regarding *county-level* measures contrasts with the conclusions of a narrative review of primarily *state-level* policies (Maclean et al., 2022) which documented more published quasi-experimental studies of health impacts from supply-side policies (e.g., prescription drug monitoring programs, pain clinic management laws) than demand-side policies (e.g., doctor shopping laws, cannabis legalization). The findings of the present systematic review provide relatively mixed evidence regarding many county-level predictors of overdose mortality, several of which also vary between subpopulations. As such, findings support the need for additional research to elucidate the pathways by which the county context shapes residents' risk of fatal overdose, in order to translate data into contextual interventions to reverse the rising rates of overdose deaths across the US.

CRediT authorship contribution statement

Manuel Cano: Conceptualization, Investigation, Data curation, Writing – original draft. **Sehun Oh:** Conceptualization, Investigation, Writing – review & editing. **Preston Osborn:** Investigation, Data curation. **Samson Olowolaju:** Investigation, Data curation. **Armando Sanchez:** Investigation, Data curation, **Yeonwoo Kim:** Conceptualization, Methodology, Writing – review & editing. **Alberto Cano Moreno:** Investigation, Data curation.

Role of funding source

Nothing declared.

Conflict of interest

No conflict declared.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109714.

References

Armoon, B., Bayani, A., Griffiths, M.D., Bayat, A.H., Mohammadi, R., Fattah Moghaddam, L., Ahounbar, E., 2021a. Prevalence and high-risk behaviors associated with non-fatal overdose among people who use illicit opioids: a systematic review and meta-analysis. J. Subst. Use 1–16. https://doi.org/10.1080/14659891.2021.1978112.

Armoon, B., SoleimanvandiAzar, N., Rostami, M., Higgs, P., Bayani, A., Bayat, A.H., Fattah Moghaddam, L., 2021b. Drug type and risk behaviors associated with non-fatal overdose among people who use drugs: a systematic review and meta-analysis. J. Addict. Dis. 40, 114–125. https://doi.org/10.1080/10550887.2021.1950262.

Bahji, A., Bajaj, N., 2018. Opioids on trial: a systematic review of interventions for the treatment and prevention of opioid overdose. Can. J. Addict. 9, 26–33. https://doi.org/10.1097/CXA.0000000000000013.

Beaudoin, F.L., Banerjee, G.N., Mello, M.J., 2016. State-level and system-level opioid prescribing policies: the impact on provider practices and overdose deaths, a systematic review. J. Opioid Manag. 12, 109–118. https://doi.org/10.5055/jom.2016.0322.

Betz, M.R., Jones, L.E., 2018. Wage and employment growth in America's drug epidemic: is all growth created equal? Am. J. Agric. Econ. 100, 1357–1374. https://doi.org/10.1093/ajae/aay069.

Blake-Gonzalez, B., Cebula, R.J., Koch, J.V., 2021. Drug-overdose death rates: the economic misery explanation and its alternatives. Appl. Econ. 53, 730–741. https://doi.org/10.1080/00036846.2020.1813248.

Boslett, A.J., Denham, A., Hill, E.L., 2020. Using contributing causes of death improves prediction of opioid involvement in unclassified drug overdoses in US death records. Addiction 115, 1308–1317. https://doi.org/10.1111/add.14943.

Bradford, A.C., Bradford, W.D., 2020. The effect of evictions on accidental drug and alcohol mortality. Health Serv. Res. 55, 9–17. https://doi.org/10.1111/1475-6773.

Brady, J.E., Giglio, R., Keyes, K.M., DiMaggio, C., Li, G., 2017. Risk markers for fatal and non-fatal prescription drug overdose: a meta-analysis. Inj. Epidemiol. 4, 1–24. https://doi.org/10.1186/s40621-017-0118-7.

Bruch, J.D., Barin, O., Venkataramani, A.S., Song, Z., 2021. Mortality before and after border wall construction along the US-Mexico border, 1990-2017. Am. J. Public Health 111, 1636–1644. https://doi.org/10.2105/AJPH.2021.306329.

Cano, M., Gelpí-Acosta, C., 2022. Variation in US drug overdose mortality within and between Hispanic/Latine subgroups: a disaggregation of national data. SSM Ment. Health 12, 100095. https://doi.org/10.1016/j.ssmmh.2022.100095.

Case, A., Deaton, A., 2017. Mortality and morbidity in the 21st century. Brook. Pap. Econ. Act. 2017, 397–476. https://doi.org/10.1353/eca.2017.0005.

Centers for Disease Control and Prevention, 2021. Drug overdose: Understanding the epidemic. Accessed 26 January 2022. ⟨https://www.cdc.gov/drugoverdose/epidemic/index.html⟩.

Centers for Disease Control and Prevention, 2022. National Center for Health Statistics Mortality Data on CDC WONDER. Accessed 26 January 2022. ⟨https://wonder.cdc.gov/mcd.html⟩.

Cerdá, M., Ransome, Y., Keyes, K.M., Koenen, K.C., Tracy, M., Tardiff, K.J., Vlahov, D., Galea, S., 2013. Prescription opioid mortality trends in New York City, 1990-2006: examining the emergence of an epidemic. Drug Alcohol Depend. 132, 53–62. https://doi.org/10.1016/j.drugalcdep.2012.12.027.

Ciccarone, D., 2019. The tripe wave epidemic: supply and demand drivers of the US opioid overdose crisis. Int. J. Drug Policy 71, 183–188. https://doi.org/10.1016/j.drugpo.2019.01.010.

Congdon, P., 2020. Geographical aspects of recent trends in drug-related deaths, with a focus on intra-national contextual variation. Int. J. Environ. Res. Public Health 17, 8081. https://doi.org/10.3390/ijerph17218081.

Cordes, J., 2018. Spatial trends in opioid overdose mortality in North Carolina: 1999–2015. Southeast. Geogr. 58, 193–211.

Dasgupta, N., Beletsky, L., Ciccarone, D., 2018. Opioid crisis: no easy fix to its social and economic determinants. Am. J. Public Health 108, 182–186. https://doi.org/10.2105/AJPH.2017.304187.

Dean, A., Kimmel, S., 2019. Free trade and opioid overdose death in the United States. SSM Popul. Health 8, 100409. https://doi.org/10.1016/j.ssmph.2019.100409.

Fischer, B., Pang, M., Jones, W., 2020. The opioid mortality epidemic in North America: do we understand the supply side dynamics of this unprecedented crisis. Subst. Abus. Treat. Prev. Policy 15. https://doi.org/10.1186/s13011-020-0256-8.

Flam-Ross, J.M., Lown, J., Patil, P., White, L.F., Wang, J., Perry, A., Barocas, J.A., 2022. Factors associated with opioid-involved overdose among previously incarcerated people in the US: a community engaged narrative review. Int. J. Drug Policy 100, 103534. https://doi.org/10.1016/j.drugpo.2021.103534.

Florence, C., Luo, F., Rice, K., 2021. The economic burden of opioid use disorder and fatal opioid overdose in the United States, 2017. Drug Alcohol Depend. 218, 108350 https://doi.org/10.1016/j.drugalcdep.2020.108350.

Frankenfeld, C.L., Leslie, T.F., 2019. County-level socioeconomic factors and residential racial, Hispanic, poverty, and unemployment segregation associated with drug overdose deaths in the United States, 2013-2017. Ann. Epidemiol. 35, 12–19. https://doi.org/10.1016/j.annepidem.2019.04.009.

Frieden, T.R., 2010. A framework for public health action: the health impact pyramid. Am. J. Public Health 100, 590–595. https://doi.org/10.2105/AJPH.2009.185652.

Gabriel, R., Esposito, M., Ward, G., Lee, H., Hicken, M.T., Cunningham, D., 2021. White health benefits of histories of enslavement: the case of opioid deaths. Ann. Am. Acad. Political Soc. Sci. 694, 142–156. https://doi.org/10.1177/00027162211009.

Gomes, T., Tadrous, M., Mamdani, M.M., Paterson, J.M., Juurlink, D.N., 2018. The burden of opioid-related mortality in the United States. e180217-e180217 JAMA Netw. Open. 1. https://doi.org/10.1001/jamanetworkopen.2018.0217.

Green, T.C., Grau, L.E., Carver, H.W., Kinzly, M., Heimer, R., 2011. Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997–2007. Drug Alcohol Depend. 115, 221–228.

Griffith, K.N., Feyman, Y., Auty, S.G., Crable, E.L., Levengood, T.W., 2021. Implications of county-level variation in U.S. opioid distribution. Drug Alcohol Depend. 219, 108501 https://doi.org/10.1016/j.drugalcdep.2020.108501.

Grigoras, C.A., Karanika, S., Velmahos, E., Alevizakos, M., Flokas, M.E., Kaspiris-Rousellis, C., Evaggelidis, I.N., Artelaris, P., Siettos, C.I., Mylonakis, E., 2018. Correlation of opioid mortality with prescriptions and social determinants: a cross-sectional study of Medicare enrollees. Drugs 78, 111–121. https://doi.org/10.1007/s40265-017-0846-6.

Gunn, A.H., Bartlett, B., Feng, G., Gayed, M., Kanter, K., Onuoha, E., Thornton, M., Muzyk, A., Schramm-Sapyta, N., 2018. Running the numbers: county level dynamics of heroin mortality in North Carolina. N. C. Med. J. 79, 195–200. https://doi.org/10.18043/ncm.79.3.195.

Haddaway, N.R., Grainger, M.J., Gray, C.T., 2022. Citationchaser: A tool for transparent and efficient forward and backward citation chasing in systematic searching. Res. Synth. Methods. https://doi.org/10.1002/jrsm.1563.

Hadland, S.E., Rivera-Aguirre, A., Marshall, B., Cerdá, M., 2019. Association of pharmaceutical industry marketing of opioid products with mortality from opioid-related overdoses. JAMA Netw. Open. 2, e186007 https://doi.org/10.1001/jamanetworkopen.2018.6007.

Haley, S.J., Maroko, A.R., Wyka, K., Baker, M.R., 2019. The association between county-level safety net treatment access and opioid hospitalizations and mortality in New York. J. Subst. Abus. Treat. 100, 52–58. https://doi.org/10.1016/j.jsat.2019.02.004.

Hall, C., 2022. The impact of telemedicine availability on fatal opioid overdose rates in Texas. 2020. ProQuest Diss. Theses, 29166336.

Hedegaard, H., Miniño, A.M., Spencer, M.R., Warner, M., 2021. Drug overdose deaths in the United States, 1999–2020. NCHS Data Brief, no 428. National Center for Health Statistics, Hyattsville, MD. https://doi.org/10.15620/cdc:112340.

Hedegaard, H., Bastian, B.A., Trinidad, J.P., Spencer, M., Warner, M., 2019. Regional differences in the drugs most frequently involved in drug overdose deaths: United States. 2017. Natl. Vital.-. Stat. Rep. 68, 1–15.

Henry, S.G., Shev, A.B., Crow, D., Stewart, S.L., Wintermute, G.J., Fenlon, C., Wirtz, S.J., 2021. Impacts of prescription drug monitoring program policy changes and county opioid safety coalitions on prescribing and overdose outcomes in California, 2015-2018. Prev. Med. 153, 106861 https://doi.org/10.1016/j.ypmed.2021.106861.

Hester, L., Shi, X., Morden, N., 2012. Characterizing the geographic variation and risk factors of fatal prescription opioid poisoning in New Hampshire, 2003–2007. Ann. Gis. 18, 99–108.

Hollingsworth, A., Ruhm, C.J., Simon, K., 2017. Macroeconomic conditions and opioid abuse. J. Health Econ. 56, 222–233. https://doi.org/10.1016/j.jhealeco.2017.07.009.

Hoots, B., Vivolo-Kantor, A., Seth, P., 2020. The rise in non-fatal and fatal overdoses involving stimulants with and without opioids in the United States. Addiction 115, 946–958. https://doi.org/10.1111/add.14878.

Hsu, G., Kovacs, B., 2021. Association between county level cannabis dispensary counts and opioid related mortality rates in the United States: panel data study. BMJ 372, m4957. https://doi.org/10.1136/bmj.m4957.

Jones, C.M., Warner, M., Hedegaard, H., Compton, W., 2019. Data quality considerations when using county-level opioid overdose death rates to inform policy and practice. Drug Alcohol Depend. 204, 107549 https://doi.org/10.1016/j.drugalcdep.2019.107549.

Jones, K., Luo, H., Mansfield, C.J., Imai, S., 2020. Tracking trends in the opioid epidemic in North Carolina: early results from the Opioid Action Plan metrics. N. C. Med. J. 81, 355–362. https://doi.org/10.18043/ncm.81.6.355.

Kelly, B.C., Vuolo, M., Frizzel, L.C., 2021. Pediatric drug overdose mortality: contextual and policy effects for children under 12 years. Pediatr. Res. 90, 1258–1265. https://doi.org/10.1038/s41390-021-01567-7.

Kerry, R., Yoo, E., Ingram, B., 2019. Spatial analysis of drug poisoning deaths in the American west: a comparison study using profile regression to adjust for collinearity and spatial correlation. Drug Alcohol Depend. 204, 107598 https://doi.org/10.1016/j.drugalcdep.2019.107598.

Kerry, R., Goovaerts, P., Vowles, M., Ingram, B., 2016. Spatial analysis of drug poisoning deaths in the American West, particularly Utah. Int. J. Drug Policy 33, 44–55. https://doi.org/10.1016/j.drugpo.2016.05.004.

Kline, D., Hepler, S., Bonny, A., McKnight, E., 2019. A joint spatial model of opioid-associated deaths and treatment admissions in Ohio. Ann. Epidemiol. 33, 19–23. https://doi.org/10.1016/j.annepidem.2019.02.004.

Kravitz-Wirtz, N., Davis, C.S., Ponicki, W.R., Rivera-Aguirre, A., Marshall, B., Martins, S.S., Cerdá, M., 2020. Association of Medicaid expansion with opioid overdose mortality in the United States. JAMA Netw. Open. 3, e1919066 https://doi.org/10.1001/jamanetworkopen.2019.19066.

Kurani, S., McCoy, R.G., Inselman, J., Jeffery, M.M., Chawla, S., Finney Rutten, L.J., Giblon, R., Shah, N.D., 2020. Place, poverty and prescriptions: a cross-sectional study using Area Deprivation Index to assess opioid use and drug-poisoning mortality in the USA from 2012 to 2017. BMJ Open 10, e035376. https://doi.org/10.1136/bmjopen-2019-035376.

Landis, J.R., Koch, G.G., 1977. The measurement of observer agreement for categorical data. Biometrics 33, 159–174.

Langabeer, J.R., Chambers, K.A., Cardenas-Turanzas, M., Champagne-Langabeer, T., 2020. County-level factors underlying opioid mortality in the United States. Subst. Abus. 43, 76–82. https://doi.org/10.1080/08897077.2020.1740379.

Larney, S., Peacock, A., Tran, L.T., Stockings, E., Santomauro, D., Santo Jr, T., Degenhardt, L., 2020. All-cause and overdose mortality risk among people prescribed opioids: a systematic review and meta-analysis. Pain. Med 21, 3700–3711. https://doi.org/10.1093/pm/pnaa214.

Lee, A.J., Bandari, J., Macleod, L.C., Davies, B.J., Jacobs, B.L., 2019. Concentration of opioid-related industry payments in opioid crisis areas. J. Gen. Intern. Med. 34, 187–189. https://doi.org/10.1007/s11606-018-4700-7.

Lin, D., Liu, S., Ruhm, C.J., 2020. Opioid deaths and local healthcare intensity: a longitudinal analysis of the U.S. population, 2003-2014. Am. J. Prev. Med. 58, 50–58. https://doi.org/10.1016/j.amepre.2019.09.008.

Lister, J.J., Ellis, J.D., Yoon, M., 2020. Opioid prescribing and opioid-overdose deaths in Michigan: urban-rural comparisons and changes across 2013-2017. Addict. Behav. Rep. 11, 100234 https://doi.org/10.1016/j.abrep.2019.100234.

Lyons, R.M., Yule, A.M., Schiff, D., Bagley, S.M., Wilens, T.E., 2019. Risk factors for drug overdose in young people: a systematic review of the literature. J. Child Adolesc. Psychopharmacol. 29, 487–497. https://doi.org/10.1089/cap.2019.0013.

Ma, J., Bao, Y.P., Wang, R.J., Su, M.F., Liu, M.X., Li, J.Q., Degenhardt, L., Farrell, M., Blow, F.C., Ilgen, M., Shi, J., Lu, L., 2019. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol. Psychiatry 24, 1868–1883. https://doi.org/10.1038/s41380-018-0094-5.

Maclean, J.C., Mallatt, J., Ruhm, C.J., Simon, K.I., 2022. The opioid crisis, health, healthcare, and crime: a review of quasi-experimental economic studies. NBER Working Paper Series. 〈https://www.nber.org/systefm/files/working_papers/w29983/w29983.pdf〉.

Marotta, P.L., Hunt, T., Gilbert, L., Wu, E., Goddard-Eckrich, D., El-Bassel, N., 2019. Assessing spatial relationships between prescription drugs, race, and overdose in New York State from 2013 to 2015. J. Psychoact. Drugs 51, 360–370. https://doi.org/10.1080/02791072.2019.1599472.

Martins, S.S., Sampson, L., Cerdá, M., Galea, S., 2015. Worldwide prevalence and trends in unintentional drug overdose: a systematic review of the literature. Am. J. Public Health 105, e29–e49. https://doi.org/10.2105/AJPH.2015.302843.

McDonald, R., Strang, J., 2016. Are take-home naloxone programmes effective? Systematic review utilizing application of the Bradford Hill criteria. Addiction 111, 1177–1187. https://doi.org/10.1111/add.13326.

Mercer, F., Miler, J.A., Pauly, B., Carver, H., Hnízdilová, K., Foster, R., Parkes, T., 2021. Peer support and overdose prevention responses: a systematic 'state-of-the-art' review. Int. J. Environ. Res. Public Health 18, 12073. https://doi.org/10.3390/ijerph182212073.

Mital, S., Wolff, J., Carroll, J.J., 2020. The relationship between incarceration history and overdose in North America: a scoping review of the evidence. Drug Alcohol Depend. 213, 108088 https://doi.org/10.1016/j.drugalcdep.2020.108088.

Monnat, S.M., 2018. Factors associated with county-level differences in U.S. drug-related mortality rates. Am. J. Prev. Med 54, 611–619. https://doi.org/10.1016/j.amepre.2018.01.040.

Monnat, S.M., 2019. The contributions of socioeconomic and opioid supply factors to US drug mortality rates: urban-rural and within-rural differences. J. Rural Stud. 68, 319–335. https://doi.org/10.1016/j.jrurstud.2018.12.004.

Monnat, S.M., Peters, D.J., Berg, M.T., Hochstetler, A., 2019. Using census data to understand county-level differences in overall drug mortality and opioid-related mortality by opioid type. Am. J. Public Health 109, 1084–1091. https://doi.org/10.2105/AJPH.2019.305136.

National Institutes of Health. 2021. Study quality assessment tools. Accessed 16 January 2021. 〈https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools〉.

Nosrati, E., Kang-Brown, J., Ash, M., McKee, M., Marmot, M., King, L.P., 2019. Economic decline, incarceration, and mortality from drug use disorders in the USA between 1983 and 2014: an observational analysis. Lancet Public Health 4, e326–e333. https://doi.org/10.1016/S2468-2667(19)30104-5.

Ombach, H.J., Scholl, L.S., Bakian, A.V., Renshaw, K.T., Sung, Y.H., Renshaw, P.F., Kanekar, S., 2019. Association between altitude, prescription opioid misuse, and fatal overdoses. Addict. Behav. Rep. 9, 100167 https://doi.org/10.1016/j.abrep.2019.100167.

Pierce, J.R., Schott, P.K., 2020. Trade liberalization and mortality: evidence from US counties. Am. Econ. Rev. Insights 2, 47–64. https://doi.org/10.1257/aeri.20180396.

Potier, C., Laprévote, V., Dubois-Arber, F., Cottencin, O., Rolland, B., 2014. Supervised injection services: what has been demonstrated? A systematic literature review. Drug Alcohol Depend. 145, 48–68. https://doi.org/10.1016/j.drugalcdep.2014.10.012.

Rangachari, P., Govindarajan, A., Mehta, R., Seehusen, D., Rethemeyer, R.K., 2022. The relationship between Social Determinants of Health (SDoH) and death from cardiovascular disease or opioid use in counties across the United States (2009–2018). https://doi.org/10.1186/s12889–022-12653–8.

Robert Wood Johnson Foundation, 2022. County health rankings database. RWJ/University of Wisconsin Population Health Institute. 〈https://www.countyhealthrankings.org/explore-health-rankings/use-data〉.

Rockett, I.R.H., Caine, E.D., Connery, H.S., D'Onofrio, G., Gunnell, D.J., Miller, T.R., Nolte, K.B., Kaplan, M.S., Kapusta, N.D., Lilly, C.L., Nelson, L.W., Putnam, S.L., Stack, S., Varnik, P., Webster, L.R., Jia, H., 2018. Discerning suicide in drug intoxication deaths: paucity and primary of suicide notes and psychiatric history. PLoS One 13, e0190200. https://doi.org/10.1371/journal.pone.0190200.

Romeiser, J.L., Labriola, J., Meliker, J.R., 2019. Geographic patterns of prescription opioids and opioid overdose deaths in New York State, 2013-2015. Drug Alcohol Depend. 195, 94–100. https://doi.org/10.1016/j.drugalcdep.2018.11.027.

Rossen, L.M., Khan, D., Warner, M., 2014. Hot spots in mortality from drug poisoning in the United States, 2007–2009. Health Place 26, 14–20. https://doi.org/10.1016/j.healthplace.2013.11.005.
Rowe, C.L., Ahern, J., Hubbard, A., Coffin, P.O., 2022. Evaluating buprenorphine prescribing and opioid-related health outcomes following the expansion the buprenorphine waiver program. J. Subst. Abus. Treat. 132, 108452 https://doi.org/10.1016/j.jsat.2021.108452.
Rudolph, K.E., Kinnard, E.N., Aguirre, A.R., Goin, D.E., Feelemyer, J., Fink, D., Cerda, M., 2020. The relative economy and drug overdose deaths. Epidemiology 31, 551–558. https://doi.org/10.1097/EDE.0000000000001199.
Ruhm, C.J., 2018. Corrected US opioid-involved drug poisoning deaths and mortality rates, 1999–2015. Addiction 113, 1339–1344. https://doi.org/10.1111/add.14144.
Ruhm, C.J., 2019. Drivers of the fatal drug epidemic. J. Health Econ. 64, 25–42. https://doi.org/10.1016/j.jhealeco.2019.01.001.
Sauber-Schatz, E.K., Mack, K.A., Diekman, S.T., Paulozzi, L.J., 2013. Associations between pain clinic density and distributions of opioid pain relievers, drug-related deaths, hospitalizations, emergency department visits, and neonatal abstinence syndrome in Florida. Drug Alcohol Depend. 133, 161–166. https://doi.org/10.1016/j.drugalcdep.2013.05.017.
Sawyer, J.L., Shrestha, S., Pustz, J.C., Gottleib, R., Nichols, D., Van Handel, M., Lingwall, C., Stopka, T.J., 2021. Characterizing opioid-involved overdose risk in local communities: an opioid overdose vulnerability assessment across Indiana, 2017. Prev. Med. Rep. 24, 101538 https://doi.org/10.1016/j.pmedr.2021.101538.
Shih, R.A., Miles, J.N.V., Tucker, J.S., Zhou, A.J., D'Amico, E.J., 2010. Racial/ethnic differences in adolescent substance use: mediation by individual, family, and school factors. J. Stud. Alcohol Drugs 71, 640–651. https://doi.org/10.15288/jsad.2010.71.640.
Smith, R.A., 2020. The effects of medical marijuana dispensaries on adverse opioid outcomes. Econ. Inq. 58, 569–588. https://doi.org/10.1111/ecin.12825.
Stone, A.L., Becker, L.G., Huber, A.M., Catalano, R.F., 2012. Review of risk and protective factors of substance use and problem use in emerging adulthood. Addict. Behav. 37, 747–775. https://doi.org/10.1016/j.addbeh.2012.02.014.
Sun, F., 2021. Rurality and the opioid crisis in U.S. counties: a spatiotemporal investigation. Dissertation Abstracts International, AAI28648480.
Suriaga, A., 2021. The social determinants of opioid-related deaths in older adults. Dissertation Abstracts International, AAI28412583.
Swensen, I.D., 2015. Substance-abuse treatment and mortality. J. Public Econ. 122, 13–30. https://doi.org/10.1016/j.jpubeco.2014.12.008.
Tacheva, Z., Ivanov, A., 2021. Exploring the association between the "Big Five" personality traits and fatal opioid overdose: county-level empirical analysis. JMIR Ment. Health 8, e24939. https://doi.org/10.2196/24939.
Valentini, C.A., Jayawardhana, J., 2019. Drug overdose deaths in Georgia: impact of rural versus non-rural counties. J. Pharm. Health Serv. Res. 10, 341–346. https://doi.org/10.1111/jphs.12296.
Van Draanen, J., Tsang, C., Mitra, S., Karamouzian, M., Richardson, L., 2020. Socioeconomic marginalization and opioid-related overdose: a systematic review. Drug Alcohol Depend. 214, 108127 https://doi.org/10.1016/j.drugalcdep.2020.108127.
Van Draanen, J., Tsang, C., Mitra, S., Phuong, V., Murakami, A., Karamouzian, M., Richardson, L., 2021. Mental disorder and opioid overdose: a systematic review. Soc. Psychiatry Psychiatr. Epidemiol. 57, 647–671. https://doi.org/10.1007/s00127-021-02199-2.
Venkataramani, A.S., Bair, E.F., O'Brien, R.L., Tsai, A.C., 2020. Association between automotive assembly plant closures and opioid overdose mortality in the United States: a difference-in-differences analysis. JAMA Intern. Med. 180, 254–262. https://doi.org/10.1001/jamainternmed.2019.5686.
Wasserstein, R.L., Schirm, A.L., Lazar, N.A., 2019. Moving to a world beyond "p<0.05." Am. Statistician 73, 1–19. https://doi.org/10.1080/00031305.2019.1583913.
Westreich, D., Greenland, S., 2013. The Table 2 fallacy: presenting and interpreting confounder and modifier coefficients. Am. J. Epidemiol. 177, 292–298. https://doi.org/10.1093/aje/kws412.
Whitley, P., LaRue, L., Fernandez, S.A., Passik, S.D., Dawson, E., Jackson, R.D., 2022. Analysis of urine drug test results from substance use disorder treatment practices and overdose mortality rates, 2013-2020. JAMA Netw. Open. 5, e2215425 https://doi.org/10.1001/jamanetworkopen.2022.15425.
Wu, P., Evangelist, M., 2022. Unemployment insurance and opioid overdose mortality in the United States. Demography 59, 485–509. https://doi.org/10.1215/00703370-9772414.
Yang, T.C., Kim, S., Matthews, S.A., 2021. Unemployment and opioid-related mortality rates in US counties: investigating social capital and social isolation-smoking pathways. Soc. Probl. https://doi.org/10.1093/socpro/spab053.
Zemore, S.E., Li, L., Bensley, K., Karriker-Jaffe, K.J., Cherpitel, C., 2022. Alcohol- and drug-related mortality among adults within and outside the U.S.-Mexico border region. J. Stud. Alcohol Drugs 83, 175–184. https://doi.org/10.15288/jsad.2022.83.175.
Zhu, Y., Fei, Z., Mooney, L.J., Huang, K., Hser, Y., 2022. Social determinants of mortality of COVID-19 and opioid overdose in American rural and urban counties. J. Addict. Med. 16, e52–e55. https://doi.org/10.1097/ADM.0000000000000834.
Zoorob, M.J., 2018. Polydrug epidemiology: benzodiazepine prescribing and the drug overdose epidemic in the United States. Pharmacoepidemiol. Drug Saf. 27, 541–549. https://doi.org/10.1002/pds.4417.
Zoorob, M.J., Salemi, J.L., 2017. Bowling alone, dying together: the role of social capital in mitigating the drug overdose epidemic in the United States. Drug Alcohol Depend. 173, 1–9. https://doi.org/10.1016/j.drugalcdep.2016.12.011.