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Social and economic determinants of drug overdose deaths: a systematic review of spatial relationships

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Abstract

Purpose—To synthesize the available evidence on the extent to which area-level socioeconomic conditions are associated with drug overdose deaths in the United States.

Methods—We performed a systematic review (in MEDLINE, EMBASE, PsychINFO, Web of Science, EconLit) for papers published prior to July 2022. Eligible studies quantitatively estimated the association between an area-level measure of socioeconomic conditions and drug overdose deaths in the US, and were published in English. We assessed study quality using the Effective Public Health Practice Project Quality Assessment Tool. The protocol was preregistered at Prospero (CRD42019121317).

Results—We identified 28 studies that estimated area-level effects of socioeconomic conditions on drug overdose deaths in the US. Studies were scored as having moderate to serious risk of bias attributed to both confounding and in analysis. Socioeconomic conditions and drug overdose death rates were moderately associated, and this was a consistent finding across a large number of measures and differences in study designs (e.g., cross-sectional versus longitudinal), years of data analyzed, and primary unit of analysis (e.g., ZIP code, county, state).

Conclusions—This review highlights the evidence for area-level socioeconomic conditions are an important factor underlying the geospatial distribution of drug overdose deaths in the US and the need to understand the mechanisms underlying these associations to inform future

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Author contributions

Fink, Keyes, Branas, Cerda, Gruenwald, and Hasin designed this study. Fink and Schleimer acquired and analyzed the data. Fink wrote the main manuscript text and prepared the tables and figures. All authors reviewed the manuscript.

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policy recommendations. The current evidence base suggests that, at least in the United States, employment, income, and poverty interventions may be effective targets for preventing drug overdose mortality rates.

Keywords

Drug overdose; Spatial epidemiology; Composition and contextual factors; Socioeconomic conditions

Introduction

Mortality resulting from drug use (generally referred to as “drug-related mortality” or “drug overdose deaths”) has risen exponentially since 1979 in the United States (U.S.) [1], reaching 91,799 deaths in 2020 [2]. Although the rising rates of drug overdose deaths have affected all groups and geographic regions across the U.S., differences in the geographic distribution of drug overdose deaths are well-documented. Prior research suggests that socioeconomic factors may partly explain these patterns [3–8]. Area-level socioeconomic conditions may well underly such spatial inequalities in drug overdose mortality rates across the U.S.

A substantial literature from health geography and social epidemiology has illustrated how the spatial variation in health and well-being broadly, and in drug-related morbidity and mortality specifically, reflect underlying fundamental differences across locations, including in the social, economic, and material conditions [9]. These differences across locations can affect drug use and drug-related harms through a variety of mechanisms. For example, particular environments (e.g., neighborhoods) increase the likelihood of exposure to trauma and adversity, such as experiences of discrimination and bias on the basis of race, sex, social class, or other social and physical characteristics. Previous studies have found that locations disproportionately affected by deindustrialization [10–13], those experiencing declines in their local economies [14], and those with higher poverty [15] and unemployment rates [16] have higher rates of drug use and drug overdose deaths than other locations. Theories of social exclusion and resource deprivation suggest that locations with poor socioeconomic conditions suffer from underdevelopment of social and institutional structures that increase opportunity and access to physical resources (e.g., housing, high-paying employment), which in turn reduces health directly through environmental exposures and indirectly through psychosocial mechanisms. For example, economic deprivation during periods of unemployment reduces access to material resources (e.g., food, housing) [17–20] and increases psychosocial stress [18, 19]. Although exposure to stress is ubiquitous, access to people and resources to mitigate that stress are more likely to be found in more affluent areas (e.g., influential social contact, job opportunities), which also have greater access to high-quality healthcare and addiction treatment to address new onset substance use disorders [21, 22].

Despite the considerable research being undertaken on this topic, there has been no formal, systematic, synthesis of the evidence exploring whether drug overdose mortality rates vary by area-level socioeconomic conditions. Although there are previous reviews that

have investigated the relationship between socioeconomic conditions and drug overdose mortality, these reviews lacked a systematic literature search [3–6], focused on individual-level characteristics rather than area-level contributors to overdose mortality rates [7, 8], excluded studies analyzing associations at the census tract, ZIP code, or state-level data [23], or pre-date the post-2013 rise of illicitly manufactured fentanyl in drug supplies and need to be updated [8]. As yet, there is no systematic review of the evidence exploring the relationship between area-level socioeconomic conditions and local drug overdose mortality rates. This is a critical gap that limits our ability to understand, predict, and intervene on the course of the current drug overdose crisis and any future epidemics. We therefore aimed to systematically review all quantitative research activities available on the area-level effects of socioeconomic conditions on drug overdose deaths in the U.S.

Methods

This systematic review follows the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [24]. The protocol for this review was developed and published to Prospero, an international prospective register of systematic reviews, in February 2018 (Registration number: CRD42019121317) and each step was pilot-tested to train and calibrate investigators. The protocol can be found in Online Resource 1.

We queried 5 on-line literature databases (MEDLINE, EMBASE, PsychINFO, Web of Science, EconLit). The search algorithms were applied to the indexed text of titles and abstracts of articles that investigated the spatial distribution of drug-related mortality or the association between area-level factors and drug-related mortality. Exact search terms can be found in Online Resource 2. No time restriction was imposed on searches, but articles were restricted to English language. ClinicalTrials.gov was searched for relevant completed and ongoing studies. Review articles and references from the selected studies were manually searched to identify additional papers. Dissertations, peer reviewed articles, and government reports were included. All resulting study titles and abstracts were exported to DistillerSR [25], a web interface for conducting the screening and data extraction phase of the review. Duplicate entries were removed. The search was conducted in January 2019 and was repeated in July 2022.

The first author (DSF) conducted the initial screening of all titles and abstracts for eligibility, and those considered relevant advanced to the full review. Two investigators (DSF, JPS) independently reviewed all full texts of selected articles to identify those that met the inclusion criteria. Agreement between the two investigators was required for exclusion of full texts. The two investigators agreed on 85% of the studies. For studies with discordant initial evaluations, the two investigators resolved all conflicts by discussion, determining whether each study fit the previously described inclusion criteria. In each stage of the study selection process, the order of studies was randomized to prevent bias due to review fatigue. We included studies that quantitatively estimated the association between area-level (e.g., Census tract, county, ZIP code, state) socioeconomic conditions on drug-related deaths in the U.S. and commentaries or opinion papers without empirical results were excluded. The study selection form can be found in Online Resource 3.

Study details were extracted by the first author using a customized data extraction form in DistillerSR (Online Supplement Document 3). These details included study design, study population (e.g., locations, years of data collection), the outcome (such as source of mortality data, definition of drug-related mortality, type of drugs included or excluded), the exposure (such as source of data, years of data included, definition of each measure), the primary unit of analysis (such as point or aggregated data, level of aggregation [e.g., ZIP code, county, state]), the analytical approach (such as model specification, handling of spatial and temporal autocorrelation, handling of potential confounding), and results (e.g., point estimates and standard deviations or confidence intervals, P values). The data extraction tool can be found in Online Resource 4.

We appraised risk of bias (ROB) in the included studies using the Effective Public Health Practice Project Quality Assessment Tool (EPHPP) [26]. This widely used tool, which has content and construct validity [26, 27], is used to evaluate the risk of bias in both randomized trials and observational studies. By answering questions provided by the EPHPP, ROB was assessed within five specific bias domains (selection bias, study design, confounders, data collection method, analysis, and overall bias), grading each domain as weak, moderate, or strong.

The heterogeneity of study populations, years, sources, and definitions of exposures and outcomes precluded formal meta-analysis. Instead, a systematic review was performed on all included studies to provide an overview of the results (see Table 1), including the effect sizes and mean differences with 95% confidence intervals (CI).

Results

Figure 1 depicts the literature search and selection process. The initial search yielded 1267 papers and another 17 were added from the updated (July 2022) search date (n = 1284). After removing 138 duplicates, 1146 unique papers were included in the initial screening stage, and 182 were selected for full-text review. Of these, 28 studies met inclusion criteria and were included in this systematic review.

Table 1 provides information on the population, level of aggregation, outcome, and risk of bias for each study included in the review. As presented in Table 1, 20 studies used longitudinal data [10–13, 16, 28–43], while two studies included data from a single year [44, 45] and five studies included data from two to four years [46–50]. The units of analysis ranged from the census tract, community district or neighborhood, county, and state; no studies analyzed ZIP code level data. More than half (n = 15) of the studies included overdose deaths involving any drug, 10 studies were limited to overdose deaths involving any opioid, while the remaining studies (n = 11) examined overdose deaths due to a specific type of opioid, including two that specifically examined prescription opioid deaths, three that included only illicit opioid deaths (i.e., heroin- or fentanyl-related deaths), and one that focused on fentanyl-related deaths specifically. Socioeconomic conditions were operationalized as either a single socioeconomic feature (single component of the economy, e.g., unemployment rate) or composite or index measures (combining multiple socioeconomic features). Variables used to model single socioeconomic features

included unemployment rate, median household income, poverty rate, income inequality, median home prices, industrial dependencies on specific job sectors (primarily mining and manufacturing), change in the share of employment due to manufacturing, trade-related job losses, proportion of residents receiving cash public assistance or Supplemental Security Income (SSI), minimum wage, and the earned income tax credit (Table 1). The seven studies using index measures created unique composite measures comprised of varying socioeconomic features [11, 12, 30, 32, 40, 47, 50]. No study used a validated index of area socioeconomic well-being, e.g., the Townsend index [51] or Human Development Index [52].

Risk of bias within studies

Results of the risk of bias assessment are summarized in Table 2 (additional information is provided in Online Resource 5). Moderate to serious concerns related to risk of bias were identified, and the performance of the literature on each domain in aggregate is presented visually in Fig. 2. Fifteen (54%) of the studies were determined to have a serious risk of bias due to confounding [12, 13, 16, 28, 29, 31, 34, 36, 43–45, 47–50]. Potential sources of confounding include compositional (e.g., race/ethnicity composition, age distribution, sex distribution) and contextual factors (e.g., urbanicity, economic and social conditions) and state-level drug policies (e.g., legalization of recreational or medical cannabis, prescription drug monitoring programs). Nine studies (32%) had moderate risk of bias due to missing data caused by CDC suppression of data for all county-years with fewer than 10 deaths. Twelve studies (43%) had moderate risk of bias from spatial or temporal autocorrelation in the data [12, 16, 29, 31–34, 37, 39, 41–44, 46, 48, 50]. Studies included in this review found moderate spatial autocorrelation clustering in drug-related mortality [11, 28, 29], unemployment [29], and employment-to-population ratio [29], the presence of spatial autocorrelations violates the assumption of independent observations upon which many standard statistical models assume, which will lead to loss of model precision and higher type I error rates.

Results from included studies

Employment—Findings regarding unemployment and drug overdose deaths were mixed, with six of the studies finding higher levels of unemployment associated with higher rates of drug overdose deaths [10, 16, 29, 34, 38, 39, 49], one study finding unemployment rates were negatively associated with drug overdose deaths [36], and one study finding no association [48]. Although most studies operationalized employment using county- or state-level unemployment rates, other studies used alternative employment metrics, including: employment-to-population ratio [29], employment growth rate [41], trade liberalization (i.e., county-level exposure to permanent normal trade relations to China [37]), trade-related job losses [10], and industry structure [11–13]. Three nationally representative studies reported the relationship between county industry structure (e.g., dependence on mining and manufacturing) and drug-related mortality [11–13]. For example, Monnat [11, 12] found greater dependence on mining and services was associated with higher rates of drug-related mortality, while greater dependence on manufacturing, public sector employment, and farming were associated with lower rates. Charles et al. [13] estimated the effect of change in the share of employment due to manufacturing on drug- and opioid-related

mortality using a shift-share instrument [53, 54] and found a 1% decline in manufacturing employment share of prime age workers between 2000 and 2016 was associated with a 0.05 per 1000 and 0.02 per 1000 increase in drug- and opioid-related deaths, respectively.

Income and poverty

Associations between measures of income and poverty with drug overdose deaths were also mixed: eight of the studies (67%) found that high-poverty/low-income areas were positively associated with higher rates of drug overdose deaths [10, 28–31, 36, 42, 43, 48], three studies (25%) reported a negative association [34, 35], and one study reported no association [38]. In a study of drug overdose deaths in San Francisco, area-level poverty was also found to affect the types of drug overdose that occurred within neighborhoods, with methadone and cocaine drug overdose deaths significantly more likely to occur in high-poverty areas and oxycodone and benzodiazepine drug overdose deaths more likely to occur in more affluent areas [43]. Although most studies operationalized income through either area-level poverty rate or median household income, two studies used housing quality (e.g., vacant or boarded up houses, housing dilapidation) [28, 30], finding that drug overdose deaths were higher in areas with more dilapidated and/or boarded up houses.

Income inequality

Three studies conducted over a period of 20 years using New York City mortality data consistently found that greater income inequality was associated with higher odds of drug overdose deaths. Compared with the midpoint of the most equitable income decile, Galea et al. [45] found that the unadjusted relative odds of death due to drug overdose in the 50th decile of inequality were 1.49 (95% CI = 1.13, 1.95) while, in neighborhoods in the 90th decile, the relative odds were 1.88 (95% CI = 1.22, 2.88); similar results were found comparing the midpoint of the lowest Gini decile to the 50th and 95th percentile [44]. Cerda et al. [28] found analgesic opioid and heroin deaths occurred in distinct types of neighborhoods, such that areas with higher median incomes experienced greater prescription opioid-related deaths, whereas areas with higher income inequality experienced greater heroin-related deaths.

Indices of multiple deprivations

Five studies of associations between indices of multiple deprivations and drug-related mortality consistently found that worse socioeconomic conditions were associated with higher levels of drug-related mortality [11, 30, 32, 47, 50]. Ruhm [32] presented results for several single socioeconomic features (i.e., poverty rate, median household income, median home price, unemployment rate), as well as the estimated percentage of the growth in drug-related mortality rates accounted for by a multiple index measure of all studied socioeconomic features. Although the single socioeconomic features were uniformly positively associated with drug-related mortality, such that counties experiencing relative economic deterioration had higher than average increases in drug-related mortality rates, the index estimate exceeded the coefficients for any single socioeconomic feature by 15% or more, suggesting the index measure captured a more complete picture of area socioeconomic conditions than any single indicator.

Social capital

Two of the studies included in our review examined the association between county-level social capital (i.e., networks of relationships among people who live and work within a community that enables the community to function effectively) and drug overdose deaths. Zoorob et al. [42] generated a county-level social capital index using the following four factors: (1) the density of civic associations and non-profit organizations in the county; (2) the percentage of county adults who voted in presidential elections; (3) the county's response rate to the census; and (4) the number of tax-exempt non-profit organizations in the county. Zoorob et al. [42] found a significant reduction in the odds of mortality with each increasing quintile of social capital, such that, compared to the lowest quintile, counties with the second through fifth quintiles experienced a 29%, 48%, 66%, and 87% decreased odds of high mortality, respectively. Similarly, Congdon [49] generated a county-level social capital index using (1) the percentage of voters who voted in presidential elections, (2) the county-level response rate to the Census Bureau's decennial census, and (3) the number of tax-exempt non-profit organizations, also finding that counties with high social capital had around half (IRR = 0.57; 95%CI = 0.38, 0.81) of the risk of drug deaths than those with low social capital.

Discussion

Findings from this review provide strong evidence that the socioeconomic conditions in geographically defined areas are linked to higher rates of drug overdose deaths. These findings were largely consistent despite considerable heterogeneity in methodology between studies. Notable findings included the wide variety of measures used to define the area-level units, study designs (e.g., cross-sectional versus longitudinal), years of data analyzed, and primary unit of analysis (e.g., ZIP code, county, state). Associations were more robust for drug overdose deaths in general, without restriction to a single type of drug, and opioid overdose deaths (i.e., deaths involving one or more type of opioid). Associations were less consistent for prescription opioid-related deaths and illicit opioid-related deaths specifically.

The consistency of results over heterogeneous methods and measures indicates that the effects of socioeconomic conditions on drug overdose deaths are robust to measurement and methodological variation. The literature linking socioeconomic conditions with drug overdose mortality aligns well with research linking poverty and unemployment to increased risk of illegal drug use [55] and overdose emergency department visits [16]. Previous research investigating the pathways through which local economic conditions may affect mental health have found that, while local stressors may exacerbate effects of individual-level stressors, local stress-buffering mechanisms (e.g., social capital, organizational resources) may enhance the effect of individual social support to protect against social isolation and improve mental health [56–59]. This suggests that designing or adapting neighborhoods to increase opportunities for social interaction and network development among neighbors may directly improve community health and help buffer against individual- and neighborhood-level stressors in socioeconomically deprived locations, which may in turn reduce drug overdose mortality rates. Future studies are needed to identify specific population and community characteristics that mark high-risk communities and

specific neighborhood spatial features (e.g., green space, community meeting spaces) that increase organizational and social supports for distressed individuals living in socioeconomically deprived locations. By identifying the factors that shape location vulnerability and resiliency, programs and policies can be developed to strengthen and empower communities to address existing vulnerabilities and facilitate future community capacities to mitigate future drug mortality.

Spatial inequalities in drug overdose deaths are likely attributed to more than local variations in socioeconomic conditions alone, but instead a result of multiple, complex factors, that interact in various ways to shape population health. For example, greater prescription opioid supply has been associated with higher rates of drug overdose deaths in the U.S. [32, 42, 60–63]. Between 1999 and 2009, the supply of prescription opioids increased dramatically and in parallel with rates of prescription opioid-related overdose death since the mid-1990s [64]. However, both opioid prescribing and prescription opioid-related mortality rates peaked in 2010, before trending slightly downward from 2011 through 2013 [65]. Despite these reductions, the overall rates of opioid-related mortality continued to rise in the US, driven by a 552% spike in deaths involving illicit opioids, i.e., heroin and illicitly manufactured fentanyl and its analogs [IMF] [1, 66]. However, prior research has found that socioeconomic conditions interact with prescription opioid supply, such that associations between prescription opioid supply and heroin overdose deaths are stronger in counties with less disadvantage and less income inequality [67]. Moreover, the fungibility between prescription opioids, heroin, and fentanyl suggests that focusing on supply side interventions to reduce access to pharmaceutically and illicitly manufactured opioids (e.g., heroin, fentanyl and its analogs) [68] may simply lead to a shift in the type of drug being used. Therefore, also identifying the demand-side factors that drive opioid use, such as socioeconomic conditions, is critical for both understanding the processes that generate drug overdose deaths and developing more productive interventions for reducing opioid-related harms. Finally, despite the growing role of fentanyl in the ongoing drug overdose crisis, only two studies in this review modeled the effects of socioeconomic conditions on fentanyl overdose deaths [10, 47]. Future research focused on this outcome is needed.

In this systematic review, the risk of bias assessment found serious risk of bias from confounding and moderate risk of bias from spatial autocorrelation in the data. First, many of the studies included in this review adjust for only a small set of potential confounding variables, with six of the studies not adjusting for any potential confounders [16, 28, 41, 44, 45, 50]. Future research should strengthen the knowledge base by applying more rigorous research designs. Although it is challenging to apply experimental approaches in place-based research, utilizing natural- or quasi-experimental design should be considered in future research. For example, four of the studies included in our review leveraged potentially exogenous sources of variation in the exposure to socioeconomic conditions to estimate their causal effect on drug-related mortality, including the timing of social service benefit issuance [46], changes in the minimum wage and the earned income tax credit (EITC) [33], passage of a U.S. Congress bill granting permanent normal trade relations (PNTR) to China, increasing trade and decreasing U.S.-based manufacturing [37], and an instrumental variable approach using Bartik-type variables [41]. Applying standard statistical approaches to adjust for potential confounding is unlikely to fully control for time-invariant and time-varying

differences between locations with high and low socioeconomic deprivation; novel study designs that exploit exogenous sources of variation to estimate the effect of socioeconomic conditions on drug overdose deaths are promising avenues for future research. Second, many studies included in our review were not analyzed using a statistical approach appropriate for spatially defined data. For example, despite some studies in this review finding substantial autocorrelation for values of prescription opioid supply [29], socioeconomic conditions [29], and rates of fatal drug poisonings [12, 29], few studies assessed spatial autocorrelation in the data and fewer still incorporated spatial dependencies into the models. Standard statistical regression models assume independence of observations. When spatial autocorrelation is present, the independence assumption in standard statistical regression models is violated, potentially causing bias and loss of efficiency [69–71]. Not taking into consideration the similarity of units across space and time could bias estimates in unknown direction, depending on the level of aggregation and autocorrelation among nearby units. Future studies should use spatial models that incorporate the spatial and the temporal structure of the data.

Review limitations

The protocol for this review was pre-registered and the methodology applied during this review was systematic. Although we required studies to be published in English, our review of references from the identified studies did not identify any non-English publications that met our eligibility criteria. Moreover, the wide search of five different databases and the review conducted by two independent investigators are likely to have identified all relevant articles. Nevertheless, whether the positive association between prescription opioid supply and socioeconomic conditions on drug-related mortality, reported by all studies included in this review, was due to the robustness of the effect or publication bias is unclear. However, methods to detect publication bias require a meta-analysis, and the heterogeneity of study populations, years, and exposures and outcomes precluded a formal meta-analysis. Lastly, as the focus on this review was on socioeconomic conditions, we excluded evidence on other potentially informative features of the local environment, such as features of the healthcare system and local drug markets, which fall outside the scope of this review. Nonetheless, much that fall outside the scope of this review may still be informative. For example, healthcare systems can play a key role in the access to prescription opioids and drug treatment services. As such, the relationship between local healthcare systems and drug overdose rates represents relevant topics for future systematic review.

Conclusions

This systematic review indicates evidence that locations with worse socio-economic conditions have higher rates of drug deaths. However, despite the consistency of findings, additional evidence from this review suggests that the associations between socioeconomic deprivation and drug deaths are complicated by many factors, including the duration and the timing of exposure, the accurate capture and operationalization of area-level socioeconomic deprivation, and the ecological nature of these data and analyses. Further evaluations are needed to identify salubrious organizational and social support characteristics and/or neighborhood and housing design features that may help buffer socioeconomically deprived

communities against future waves of drug-related morbidity and mortality. Future research like this could provide much needed insights into the causal mechanism(s) underlying the associations between socioeconomic conditions and drug overdose deaths to guide evidence-based policies and practices that address the ongoing public health crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest

Dr Hasin reported support from Syneos Health for an unrelated project. Dr Keyes reported personal fees from National Prescription Opioid Litigation related to expert witness work outside the submitted work. No other disclosures were reported.

Data availability

All data created to conduct this systematic review and supporting the results reported in this paper are included in Table 1 and the online resources.

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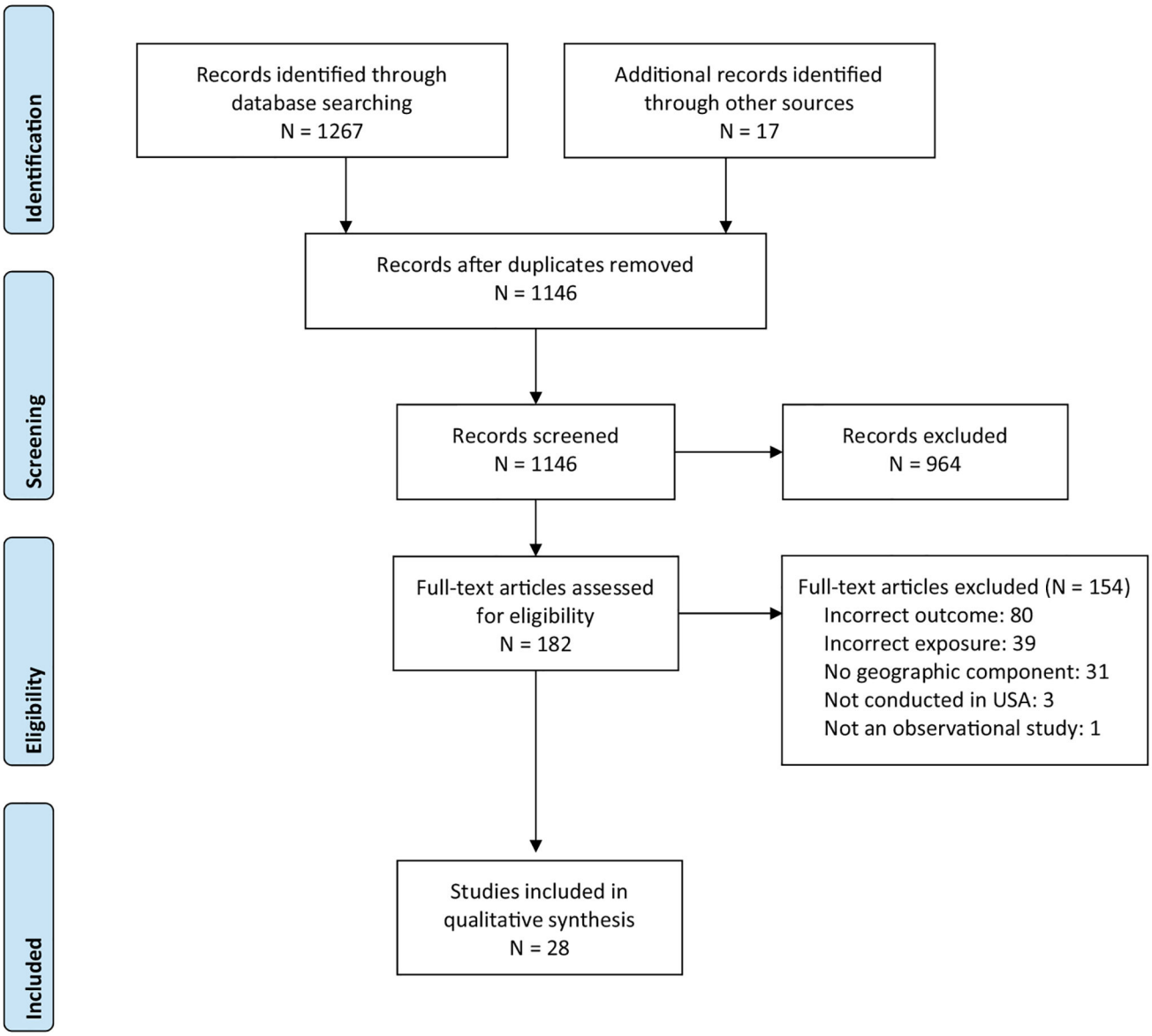

Fig. 1.

PRISM screening process. Flow diagram showing sequence by which studies were identified, screened, and reviewed

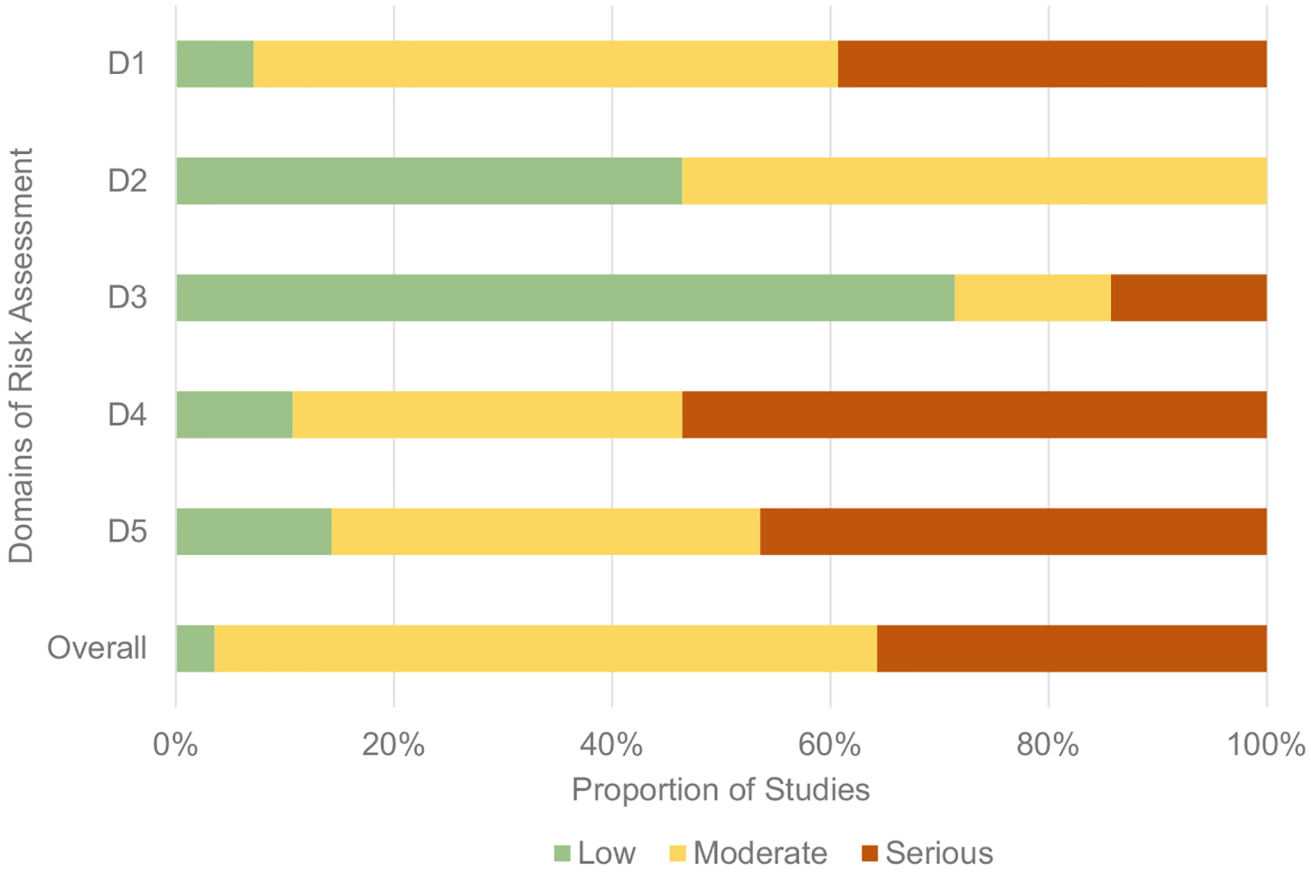

Fig. 2.

Aggregate risk of bias plot for included studies. Risk of bias was assessed within five specific bias domains: selection bias (D1), study design (D2), confounders (D3), data collection method (D4), analysis (D5), and overall bias, grading each domain as weak, moderate, or strong

Table 1

Studies included in the review with key measures explained

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results Socioeconomic conditions (*N* = 28)
Galea et al. [45]	Income inequality (1996)	Unintentional opioid analgesic deaths (UCD: X40-X44; MCOD: T40.0-T40.2)	New York, NY	Neighborhoods	Serious	**Income inequality (Gini coefficient)** Neighborhoods with greater income inequality had higher rates of fatal drug poisonings compared to neighborhoods with less income inequality. A threshold effect was found with rates of fatal drug poisonings increasing more rapidly above Gini coefficient 0.45 and below 39% of income earned by the lowest 70% of households
Nandi et al. [44]	Income inequality (1996)	Unintentional opioid analgesic deaths (UCD: X40-X44; MCOD: T40.0-T40.2)	New York, NY	Neighborhoods	Serious	**Income inequality (Gini coefficient)** 36% of the association between the distribution of income (Gini coefficient) and the rate of fatal drug poisonings was explained by the direct effect of income inequality on the rate of fatal drug poisonings (path coefficient = 0.21), with the remaining 64% of the association being indirect, mediated by environmental disorder, police activity, and quality of built environment
Hannon and Cuddy [30]	Poverty index[a]; Built environment (1991 to 1995)	Deaths from drug dependence (ICD-9 code: 304)	New York, NY	Census tracts	Moderate	**Poverty index** A 1 standard deviation increase in poverty index was associated with a 21.7% (95% CI = 13.4%, 30.5%) increase in deaths from drug dependence **Built environment** Drug dependence mortality was positively associated with boarded up houses ($b = 0.17$; SE = 0.05; $p < .0001$), and inversely associated with percent homeowners ($b = -0.007$; SE = 0.001; $p < .0001$)
Cerda et al. [28]	Income inequality; Family fragmentation; Housing dilapidation; Median household income (2000 to 2006)	Unintentional opioid analgesic deaths (UCD: X40-X44; MCOD: T40.0-T40.2)	New York, NY	Neighborhoods	Moderate	**Income inequality** Moderate spatial correlation with rates of fatal analgesic poisonings ($I = 0.17$; $P = 0.02$). Higher income inequality associated with lower odds of fatal analgesic vs. heroin overdose (OR = 0.74; 95% CI = 0.61, 0.91) **Family fragmentation** Moderate spatial correlation with rates of fatal analgesic poisonings ($I = 0.14$; $P = 0.04$). Higher level of family fragmentation associated with a lower odds of fatal analgesic vs. heroin overdose (OR = 0.65; 95% CI = 0.55, 0.78) **Housing dilapidation** Moderate spatial correlation with rates of fatal analgesic poisonings ($I = 0.18$; $P = 0.02$). Higher level of dilapidated housing structures was associated with 0.86 odds (95% CI = 0.70, 1.06) of fatal analgesic vs. heroin overdose **Median household income** Higher median income was associated with lower odds of dying from a fatal analgesic vs. heroin overdose (OR = 0.83; 95% CI = 0.71, 0.97)
Visconti et al. [43]	Poverty rate (1999 to 2014)	Opioid-related death (any illicit opiate or synthetic or semi-synthetic prescription opioid)	50 US states and Washington D.C	County	Serious	**Poverty rate** Deaths within areas below the poverty line were significantly more likely to involve methadone (53.2 vs. 25.0%) and cocaine (40.5 vs. 20.2%); deaths within areas above the poverty line were more likely to involve oxycodone (31.0 vs. 19.0%)

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results
Socioeconomic conditions (*N* = 28)						
Zoorob and Salemi [42]	Median household income; Poverty; Social capital (1999 to 2014)	Drug-related deaths (UCD: X40–44, X60–64, Y10-Y14)	50 US states and Washington D.C	County	Serious	**Median household income** Higher mortality was associated with low median household income (< $35,000 vs. ≥ 50,000, OR = 2.5; 95% CI = 2.0, 3.0) **Poverty** Increasing proportions of the county's population that live in poverty was associated with higher odds of drug overdose deaths (> 25% poverty vs. < 10% poverty, OR = 18.0; 95% CI = 13.6, 24.0) **Social capital** Each increasing quintile of social capital was associated with significant reductions in the odds of high vs. low drug overdose mortality; compared to the lowest quintile, counties with the second through fifth quintiles experienced a 29%, 48%, 66%, and 87% lower odds of high mortality, respectively
Hollingsworth et al. [16]	Unemployment rate (1999 to 2014)	Drug-related deaths (UCD: X40–44, X60–64, X85, Y10–14, Y35.2; MCOD: T40.1, T40.2–40.4)	50 US states and Washington D.C	County, State	Moderate	**Unemployment rate** County-level analysis: A 1% rise in county unemployment rate was associated with a 0.19 per 100,000 residents (SE = 0.05; $p < 0.001$) increase in opioid fatalities State-level analysis: A 1% rise in state unemployment rate was associated with a 0.35 per 100,000 residents (SE = 0.11; $p < 0.001$) increase in opioid fatalities
Marshall et al. [31]	Educational attainment; Poverty rate; Median household income (2010 to 2014)	Prescription-type opioid overdose; Illicit (heroin) opioid overdose; Mixed involvement (prescription and illicit use) opioid overdose	Orange County, CA	Census ZIP code tabulation area	Serious	**Educational attainment** Higher percent of residents 25 years or older with 4-year college degree associated with reductions in rates of prescription opioid-related overdose deaths **Poverty** Higher percent of residents below federal poverty level associated with higher rates of both prescription opioid- and heroin-related deaths **Median household income** Higher median household income associated with higher rates of both prescription opioid- and heroin-related deaths
Goedel et al. [46]	Public assistance (% of people receiving cash public assistance) (2014 to 2016)	Accidental drug poisoning death[b]	Rhode Island	State	Moderate	**Public assistance** Rates of drug poisoning deaths were higher at the beginning of the month than the end of the preceding month (OR = 1.17; 95% CI = 1.04, 1.38). Proportion of residents receiving cash public assistance or Supplemental Security Income were not associated with excess mortality; The proportion living in unaffordable housing was associated with mortality (OR = 1.42; 95% CI = 1.05, 1.91)
Charles et al. [13]	Change in the share of employment due to manufacturing (2012 to 2016)	Drug-related deaths (not explicitly defined); Opioid-related deaths (not explicitly defined)	45 US states	State	Serious	**Change in the share of employment due to manufacturing** A 1% decline in the manufacturing employment share of prime age workers between 2000 and 2016 was associated with a 0.04 per 1,000 and 0.02 per 1,000 increase in drug- and opioid-related deaths, respectively, between pooled 1999–2003 and pooled 2012–2016
Monnat [11]	Economic distress index[c]; Industrial dependence (2006 to 2015)	Drug-related mortality (UCD: X40–44, X60–64, Y10–14, drug-induced deaths, findings of drugs in the blood, mental and	48 contiguous US states and Washington D.C	County	Moderate	**Economic distress** A 1 SD increase in economic distress index was associated with a 6.4% (SE = 1.68; $p < 0.001$) increase in the drug-related mortality **Industrial dependence** Compared with diversified economies, mining dependent counties had a 13% (SE = 4.03; $p = 0.001$) higher average rate of drug-

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results
						Socioeconomic conditions (*N* = 28)
		behavioral disorders due to drugs; MCOD: N/A)				related mortality, public sector dependent (−11.8%; SE = 2.59; $p < 0.001$), manufacturing dependent (−3.53%; SE = 1.90; $p = 0.06$), and farming dependent (−6.62%; SE = 3.69; $p = 0.09$) counties were associated with lower rates
Ghertner and Groves [29]	Unemployment rate; Employment-to-population ratio; Poverty rate (2006 to 2016)	Drug-related mortality (UCD: X40–44, X60–64, X85, Y10–14; MCOD: N/A)	50 US states and Washington D.C	County	Moderate	**Unemployment rate** A 1% increase in county unemployment rate, employment-topopulation ratio, and poverty was associated with 4.6% (95% CI = 3.6%, 5.6%), 0.5% (95% CI = 0.3%, 0.7%), and 1.7% (95% CI = 1.3%, 2.1%) increase in drug-poisoning deaths, respectively
Ruhm [32]	Index of economic conditions[d] (1999 to 2015)	Drug-related deaths (UCD: X40–44 X60–64, X85, Y10–14, Y352); Prescription opioid-related deaths (MCOD: T40.2); Illicit opioid-related deaths (MCOD: T40.1, T40.4)	50 US states and Washington D.C	County, Nation	Low	**Index of economic conditions** A 1 standard deviation increase in index of economic conditions was associated with a 0.79 per 100,000 (SE = 0.44; $p < 0.1$) faster growth in overdose mortality and a 0.31 per 100,000 (SE = 0.17; $p < 0.1$) and −0.10 per 100,000 (SE = 0.31; $p > 0.1$) change in opioid analgesic and heroin death rates, respectively
Monnat [12]	Economic distress[e]; Industry structure (2014 to 2016)	Drug-related mortality (UCD: X40–44, X60–64, Y10–14, drug-induced deaths, findings of drugs in the blood, mental and behavioral disorders due to drugs; MCOD: N/A) Opioid-related mortality (MCOD: T40.0-T40.4, T40.6)	48 contiguous US states and Washington D.C	County	Moderate	**Economic distress index** A 1 standard deviation increase in economic distress in 2000 is associated with a 3.17 per 100,000 (95% CI = 1.68, 3.72) population increase in county-level drug mortality rates in 2014–2016 **County industry structure** County-level economic dependence on mining (3.23; 95% CI = 1.13, 5.33) and services (2.32; 95% CI = 0.85, 3.79) were associated with higher rates of drug-related mortality, and manufacturing (−1.26; 95% CI = −0.24, −2.28), public sector employment (−1.80; 95% CI = −0.45, −3.15), and farming (−1.81; 95% CI = −0.32, −3.30) were associated with lower rates
Nesoff et al. [47]	Neighborhood deprivation[f] (2014 to 2018)	Fentanyl or fentanyl analog poisoning death (deaths indicating fentanyl or fentanyl metabolite); non-fentanyl and polydrug fatal poisoning (drug poisoning involving opioids, stimulants, benzodiazepines)	Cook County, IL	None (geolocated)	Serious	**Neighborhood deprivation** Odds of fentanyl-involved drug poisoning increased 11.4% with each unit increase in neighborhood deprivation (95% CI = 1.07, 1.17)
Kerry et al. [36]	Median household income; Poverty rate; Unemployment rate (2006 to 2010)	Age-adjusted prescription opioid poisoning deaths of accidental, intentional, and of undetermined poisoning by exposure to prescription opioids (UCD: Unknown; MCOD: Unknown); Age-adjusted illicit opioid poisoning deaths of accidental, intentional, and of undetermined poisoning by exposure to illicit opioids (UCD: Unknown; MCOD: Unknown)	Deaths 11 Western US states	County	Moderate	**Descriptive:** Three clusters of high-risk areas were identified in the Western USA including most of New Mexico, Nevada, and Utah and several counties in Arizona, Colorado, Idaho, Wyoming **Median household income** High-risk counties had lower median household income (no statistics provided) **Unemployment rate** High-risk counties had lower unemployment rates (no statistics provided)

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results
Socioeconomic conditions (*N* = 28)						
Frankenfeld and Leslie [34]	Poverty rate; Unemployment rate; Median income; Built environment (1999 to 2015)	Drug-related mortality (UCD: X40–44, X60–64, X85, Y10–14; MCOD: N/A)	50 US states and Washington D.C	County	Serious	**Unemployment rate** County-level percent unemployment (1.14; 95% CI = 1.08, 1.20), percent without a vehicle in home (1.07; 95% CI = 1.03, 1.11), and residential segregation (1.35; 95% CI = 1.18, 1.54) are associated with higher rates of drug poisoning deaths **Poverty rate** County-level percent poverty (0.96; 95% CI = 0.93, 0.99), hosing that was mobile homes (0.97; 95% CI = 0.95, 0.98), housing that was group quarters (0.90; 95% CI = 0.97, 0.93), crowded housing (0.85; 95% CI = 0.89, 0.93) is associated with lower rates of drug poisoning deaths
Dean and Kimmel [10]	Trade-related job losses; income per capita; unemployment (1999 to 2015)	Opioid-related mortality (UCD: X40-X44, X60-X64, Y10–14; MCOD: T40.0-T40.4, T40.6) Fentanyl-related mortality (UCD: X40-X44, X60-X64, Y10–14; MCOD: T40.4)	50 US states and Washington D.C	County	Moderate	**Trade-related job loss** 1000 trade-related job losses were associated with a 2.7% (95% CI = 0.9%, 4.5%) increase in opioid-related overdose deaths. When fentanyl was present in the local heroin supply, 1000 trade-related job losses was associated with an 11.3% increase in opioid-related deaths **Income per capital** $1000 increase in income per capita was associated with −0.1% (95% CI = −0.3, 0.1) change in opioid-related deaths **Unemployment** A 1% increase in unemployment rate was associated with a 1.1% (95% CI = 0.5, 1.7%) increase in opioid-related deaths
Chichester et al. [48]	Poverty; Educational attainment; Public assistance (2015 to 2018)	Accidental drug overdose deaths (cases of overdose in which acute toxicology from one or more substances was the primary cause of death)	Jefferson County, Alabama	Census tract	Serious	**Poverty** Fatal overdoses were significantly more likely to occur in higher poverty areas. Relative to other substances, stimulant overdose deaths were more likely to occur in neighborhoods with the highest poverty levels **Educational attainment** Fatal overdoses were more likely to occur in neighborhoods with low educational attainment. Low educational attainment was more common in neighborhoods where stimulant overdose deaths occurred as compared to other substances
Kedia et al. [35]	Poverty rate; Median household income; Percentage of population with health insurance (2007 to 2016)	Drug-related mortality (UCD: X40–44, X60–64, X85, Y10–14; MCOD: N/A)	50 US states and Washington D.C	Census tracts	Moderate	**Poverty rate** Negatively associated with the drug poisoning death hot spot tracts (0.90; 95% CI = 0.86, 0.95) **Median household income** Negatively associated with the drug poisoning death hot spot tracts (0.90; 95% CI = 0.86, 0.96) **Percent with health insurance** Negatively associated with the drug poisoning death hot spot tracts (0.66; 95% CI = 0.64, 0.69)
Dow et al. [33]	Minimum wage and the earned income tax credit (EITC) (1999 to 2015)	Undefined	46 US states, Washington, D.C	State	Moderate	**Minimum wage and earned income tax credit (EITC)** No association was found between minimum wage nor EITC and drug deaths overall nor stratified by education, gender, race/ethnicity
Pierce and Schott [37]	County-level exposure to permanent normal trade relations (PNTR)	Drug overdoses (National Center for Health Statistics [NCHS] codes 31,700 and 35,300 for years 1990–1998	3,122 counties (unknown number of US states)	County	Moderate	**Permanent normal trade relations (PNTR)** An interquartile shift in exposure to PNTR was associated with a relative increase in drug overdose mortality of 2–3 deaths per

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results Socioeconomic conditions (*N* = 28)
	to China. (1990 to 2013)	and codes 420 and 443 for years 1999–2013)				100,000 population. This association were present primarily among working-age Whites
Betz and Jones [41]	County employment and wage growth; Bartik instrument (2001 to 2014)	Opioid-related death (UCD: X40–44, X60–64, X85, Y10–14; MCOD: T40.0-T40.4, T50.7, Y45.0, F11.0-F11.9)	50 US states	County	Moderate	**Employment growth rate** Employment growth rates were not associated with county opioid overdose rates in nonmetro or metro counties. Variation in middle-tier (−0.13; $p < 0.05$) and bottom tier (−0.20; $p < 0.05$) employment growth rates was associated with lower opioid overdose deaths in nonmetro and metro counties, respectively **Wage growth rate** Variation in bottom-tier (−0.23; $p < 0.05$) and middle-tier (−0.66; $p < 0.01$) wage growth rates was associated with lower opioid overdose deaths in nonmetro and metro counties, respectively
Johnson and Shreve [40]	Structural disadvantage[g] (2007 to 2017)	Fatal drug overdose deaths (no definition)	Philadelphia, Pennsylvania	ZIP code	Moderate	**Structural disadvantage** Each unit increase in disadvantage was associated with a 51% increase in mortality (IRR = 1.51) **Social control** Each unit increase in the arrest rate was associated with a 16% increase in overdose mortality (IRR = 1.16) **Built environment** Each unit increase in the build environment scale was associated with a 22% increase in mortality (IRR = 1.22)
Rudolph et al. [39]	Unemployment rate; Labor force nonparticipation rate (2000 to 2015)	Drug-related mortality (UCD: X40–44, X60–64, X85, Y10–14; MCOD: N/A)	49 U.S. states	County	Moderate	**Unemployment** Overall and relative unemployment rates were associated with increases in overdose deaths in both the short- and long-term for men, only over the long-term for Black and White women, and not associated with overdose for Hispanic/Latina women **Labor force nonparticipation** Nonparticipation rates were associated with greater overdose deaths in the long-term for White adults, but associated with decreased overdose deaths for Black and Hispanic/Latino adults in the short-term and with decreased overdose deaths for Black adults in the long-term
Congdon [49]	Unemployment rate; Index of concentration at extremes; Social capital; Racial/ethnic segregation; Gini index (2015 to 2017)	Drug-related deaths (ICD-10 codes: X40-X44, X60-X64, X85, and Y10-Y14)	49 US states	County	Moderate	**Unemployment rate** Counties with high unemployment have higher risk of drug overdose deaths (IRR = 1.39; 95%CI = 1.07, 1.81) **Index of concentration at extremes** Counties with high percentage of households with incomes over $150,000 and/or low percentages of households with incomes under $15,000 had lower risk of drug overdose deaths (IRR = 0.56; 95%CI = 0.50, 0.66) **Social capital** Counties with high social capital had around half the risk of drug deaths than those with low social capital (IRR = 0.57; 95%C = 0.38, 0.81) **Racial segregation** Counties with high racial segregation had higher risk of drug deaths (IRR = 1.43; 95%C = 1.29, 1.59)
Zhu et al. [38]	Unemployment rate; Median household income (2014 to 2018)	Opioid-related death (UCD: X40–44, X60–64, Y10–14; MCOD: T40.0-T40.4, T40.6)	South Carolina	County	Low	**Unemployment rate** Higher unemployment rate was associated with higher rates of opioid overdose mortality in urban, but not rural counties

Study	Exposure(Study Years)	Outcome	States/focus of study	Area of interest	ROB	Summary exposure(s) and results
Socioeconomic conditions (*N* = 28)						
						Median household income Counties with higher median household income associated with lower opioid overdose rates in both urban and rural counties
Rushovich et al. [50]	Neighborhood economic hardship level[h] (2015 to 2017)	Opioid-related overdose deaths (deaths that were listed as “opiate”, “opioid”, or “morphine” poisoning	Cook County, Illinois	Neighborhood	Serious	**Economic hardship** The highest rates of opioid-related deaths occurred in neighborhoods with high economic hardship (36.9 per 100,000 population) compared to medium- (20.5) and low-hardship (12.3) neighborhoods

UCD underlying cause of death, *MCOD* multiple cause of death, *SD* standard deviation, *SE* Standard error, *CI* confidence interval, *ROB* risk of bias

[a] Poverty index defined by poverty rate, median family income, % of households receiving public assistance income, unemployment rate

[b] Accidental drug poisoning death defined as OSME-confirmed accidental drug-related overdose deaths…involved illicit or “street” drugs and/or pharmaceutical drugs (prescription or over-the-counter”

[c] Economic distress index defined using % aged 25–54 in poverty, % aged 25–54 unemployed/not in labor force, aged 21–64 with disability, aged ≥ 25 with less than a college degree, households with supplemental security income or public assistance income, income inequality, aged 18–64 without health insurance

[d] Index of economic conditions defined using unemployment and poverty rates, median household incomes and home prices, exposure to imports

[e] Economic distress measure created using % in poverty, ratio of state-to-county median household income, % of households receiving public assistance income, % age ≥ 25 without a college degree, % unemployed or not in the labor force, % with a work disability

[f] Neighborhood deprivation index created using % of adults age ≥ 25 with a college degree, owner-occupied housing, households below poverty line, female-headed households with children

[g] Structural disadvantage included % single female-headed household with children < 18 years, owner-occupied households, residents with at least a college degree, residents living in poverty

[h] Neighborhood economic hardship level included unemployment, dependency, education, per capita income, crowded housing, and poverty

Table 2

Summary of risk of bias assessments for included studies

First author	Bias in selection of participants	Bias due to missing data	Bias in data collection methods	Bias due to confounding	Bias in analyses	Overall bias
Galea [45]	Moderate	Moderate	Low	Serious	Serious	Serious
Hannon [30]	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Nandi [44]	Moderate	Moderate	Moderate	Serious	Serious	Serious
Cerda [28]	Moderate	Moderate	Low	Serious	Moderate	Moderate
Visconti [43]	Moderate	Low	Low	Serious	Serious	Serious
Zoorob [42]	Low	Moderate	Serious	Moderate	Serious	Serious
Hollingsworth [16]	Low	Low	Low	Serious	Serious	Moderate
Marshal [31]	Serious	Low	Low	Serious	Moderate	Serious
Goedel [46]	Moderate	Low	Low	Moderate	Moderate	Moderate
Charles [13]	Moderate	Low	Serious	Serious	Serious	Serious
Monnat [11]	Moderate	Moderate	Low	Moderate	Low	Moderate
Ghertner [29]	Low	Low	Low	Serious	Serious	Moderate
Betz [41]	Low	Low	Low	Moderate	Serious	Moderate
Monnat [12]	Moderate	Moderate	Serious	Serious	Moderate	Moderate
Kerry [36]	Moderate	Moderate	Low	Serious	Moderate	Moderate
Frankenfeld [34]	Low	Moderate	Low	Serious	Serious	Serious
Dow [33]	Low	Moderate	Low	Low	Moderate	Moderate
Ruhm [32]	Low	Low	Moderate	Low	Moderate	Moderate
Nesoff [47]	Moderate	Moderate	Low	Serious	Serious	Serious
Dean [10]	Low	Moderate	Low	Moderate	Moderate	Moderate
Chichester [48]	Moderate	Low	Low	Serious	Serious	Serious
Congdon [49]	Low	Low	Low	Serious	Moderate	Moderate
Kedia [35]	Moderate	Moderate	Low	Moderate	Serious	Moderate
Pierce [37]	Low	Low	Serious	Low	Moderate	Moderate
Rudolph [39]	Low	Low	Low	Moderate	Moderate	Moderate
Johnson [40]	Moderate	Low	Moderate	Moderate	Low	Moderate
Rushovich [50]	Moderate	Moderate	Low	Serious	Serious	Serious

First author	Bias in selection of participants	Bias due to missing data	Bias in data collection methods	Bias due to confounding	Bias in analyses	Overall bias
Zhu [38]	Low	Moderate	Low	Moderate	Low	Low

The color red indicates high risk of bias, yellow indicates moderate risk of bias, and green indicates low risk of bias