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Place, Poverty, and Prescriptions: Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality from 2012-2017

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Abstract

Objective

To identify the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality.

Design, Setting, and Participants

For this retrospective cross-sectional study, we used the IQVIA Xponent data to capture opioid prescriptions and CDC National Vital Statistics System to assess drug-poisoning mortality. The area deprivation index (ADI) is a composite measure of social determinants of health comprised of 17 U.S. census indicators, spanning four socioeconomic domains. For all U.S. counties with available opioid prescription (2,712 counties) and drug-poisoning mortality (3,133 counties) data between 2012 and 2017, we used negative binomial regression to examine the association between county-level ADI and rates of opioid prescriptions and drug-poisoning mortality adjusted for year, age, race, and sex.

Primary Outcome Measures

County-level opioid prescription fills and drug-poisoning mortality

Results

Between 2012-2017, overall rates of opioid prescriptions decreased from 96.6 to 72.2 per 100 people, while rates of drug-poisoning mortality increased from 14.3 to 22.8 per 100,000 people. Opioid prescription and drug-poisoning mortality rates were consistently higher with greater levels of deprivation. The risk of filling an opioid prescription was 72% higher, and the risk of drug-poisoning mortality was 36% higher, for most deprived compared to least deprived counties (both $p<0.001$).

Conclusions

Counties with greater area-level deprivation have higher rates of filled opioid prescriptions and drug-poisoning mortality. Although opioid prescription rates declined across all ADI quintiles, rates of drug-poisoning mortality continued to rise proportionately in each ADI quintile. This underscores the need for individualized and targeted interventions that consider the deprivation of communities where people live.

Strengths and Limitations of this Study

- The ADI was standardized to ensure that all variables were scaled equally prior to weighting
- The work accounted for changes in demographics and ADI quintiles over time using yearly demographic estimates and census indicators from ACS
- This study is limited by potential imputation and reverse casualty bias

Introduction

The drug epidemic has incurred great personal, societal, and economic costs,[1] driven, in part, by the widespread availability and use of prescription opioids.[2] In 2016, there were over 200 million dispensed opioid prescriptions,[3] approximately 32,445 prescription opioid-related deaths,[4] and more than 63,600 drug-poisoning deaths[5] in the U.S. Overdose deaths continue to be the leading cause of injury-associated mortality and, over the past decade, have exceeded traffic fatalities.[6] To date, the primary strategy for reducing drug-poisoning mortality has been limiting the inappropriate use of prescription opioids; yet, the relentless rise in drug-related mortality continued to contribute to the decline of life expectancy in the U.S. since 2015.[7 8]

Understanding factors associated with drug-related mortality, and identifying at-risk populations, is critical to developing and targeting interventions aimed to reduce it. While the drug epidemic has impacted all segments of society, recent studies identified young and middle-aged white men as populations disproportionately affected by drug-poisoning mortality.[9 10] Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.[7 11] Similarly, the association between county-level poverty and higher rates of opioid prescribing was previously demonstrated in a 2014 study of disabled Medicare and Medicaid beneficiaries,[12] though this was not examined in the general U.S. population or linked directly to drug-related mortality. Nevertheless, addressing this epidemic will require sophisticated policy and public health approaches that consider a breadth of fundamental social determinants of health and cannot be fully captured by singular constructs such as age, race, sex, or income. This is especially important for a complex and multifaceted public health problem such as the drug use epidemic,

which is likely caused by a multitude of factors, affects all members of society, and is fueled by both prescription and illicit drugs.

A variety of policies and public health campaigns have been implemented in an effort to curb the epidemic of opioid overdoses and other drug-related morbidity and mortality, including the introduction of state prescription drug monitoring programs and the 2016 Centers for Disease Control and Prevention (CDC) opioid-prescribing guidelines.[2] Though most of the focus has been on opioids, other non-opioid prescription and illicit drugs, such as heroin and fentanyl, have also contributed to the increase in drug-poisoning deaths[13] over the past two decades. Thus, the two outcomes – opioid prescribing and drug-poisoning mortality – should be tracked in parallel to assess the impact of limiting opioid use on overall drug mortality. Historically, areas with higher opioid prescription rates also experienced higher drug-related mortality,[12] but recent intensive policy and public health efforts aimed at reducing opioid prescribing may have inadvertently created a divergence between opioid prescribing and drug-poisoning mortality, particularly in areas where opioid use may be low, but mortality due to non-opioids remains high. There is therefore a need for a contemporary population-level evaluation of current trends in opioid prescribing practices and drug-related mortality to identify populations at greatest risk of harm from opioid and non-opioid misuse.

The area deprivation index (ADI) is a validated composite measure of social determinants of health that can be used to quantify socioeconomic disadvantage for granular census-based regions.[14] The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty, education, housing, and employment.[15] County-level indicators of economic disadvantage reflect

general resource availability, safety, education quality, employment opportunity, and social support,[16] all of which contribute to physical, emotional, and financial health of communities and their residents. Despite the potential individual and public health implications of area-level deprivation for a wide range of clinical and public health outcomes, composite area-based measures have not been widely used to inform healthcare policy or clinical practice due to previously inaccessible national geospatial data.[14] In this study, we address a pressing public health need and pursue a critical knowledge gap by examining the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-level deprivation, this work contributes to the evidence base for informing clinical, public health, and policy interventions targeted at highest-need areas and populations.

Methods

Study Design

We retrospectively analyzed county-level summary measures of opioid prescriptions, drug-poisoning mortality, and population demographics from 2012 to 2017 using the IQVIA Xponent prescription database,[3] CDC National Vital Statistics System data,[5] and American Community Survey (ACS) estimates,[17] respectively. These data are publicly available and contain no identifiable information; thus, this work was exempt from Institutional Review Board approval.

Study population

All U.S. counties with opioid prescription and drug-poisoning mortality data available each year between 2012 and 2017 were included in the study sample. Counties without data for all six years of the study were excluded from the sample.

Patient Involvement

No patients or members of the public were directly involved in the design, conduct, reporting, or dissemination plans of the research.

ADI Derivation

County demographic information necessary for ADI derivation was ascertained from 2012-2016 and 2013-2017 5-year ACS estimates.[17] The ADI was derived using 17 county-level indicators and calculated separately each year for each U.S. county, as deprivation indices may change over time (Table S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the Census Application Programming Interface (API) to obtain data from the ACS.[18] The ACS is an annual survey conducted by the U.S. Census Bureau which randomly samples housing units and provides population-level estimates representative of the non-institutionalized U.S. population.[17] In-depth survey methodology is available from the Census Bureau.[17]

Outcomes

IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1, 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e., prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or

cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.; information on drugs filled by mail order pharmacies is unavailable.[3]

Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a county per 100 residents as estimated by the ACS.[3] Opioids, identified using National Drug Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone dispensed through maintenance therapy programs was not included.

CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality rates between January 1, 2012 and December 31, 2017; these data were available for each year for 3,133 counties (Figure 2). Hierarchical Bayesian methods with spatial and temporal random effects generated adjusted county-level drug-poisoning mortality rates per 100,000 residents.[19] Drug-poisoning deaths were classified on the basis of International Classification of Diseases, Tenth Revision (ICD-10) codes and included deaths with unintentional (X40–X44), suicide (X60–X64), homicide (X85), and undetermined intent (Y10–Y14).[5]

Role of the Funding Source

The funding sources for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

Statistical Analysis

We calculated modified ADI scores, using the Singh method,[15] for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach [15 20 21] and missing values were substituted using single imputation. All variables were transformed to a rate per capita for the county. To improve upon published ADI methodologies and prevent distortion of ADI by larger continuous variables such as income, we standardized these proportions to a mean of 0 and standard deviation of 1, thereby ensuring that all variables in the modified ADI were scaled equally prior to weighting. Each variable was then multiplied by its respective weight obtained from the factor score coefficient (Table S1), and the 17 weighted measures were summed for each county to obtain the base score. Base scores were then standardized to a mean of 100 and standard deviation of 20. ADI was divided into quintiles for all analyses, with higher ADI values (quintile 5) representing greater deprivation.

We used negative binomial regression to examine the relationships between ADI and opioid prescription rates and drug-poisoning mortality from 2012 to 2017, controlling for over-dispersion of outcome estimates. We used Huber-White robust standard errors clustered at the county level to adjust standard errors for repeated county observations and variation. Independent variables in the models included ADI quintile, county-level estimates for age, percent white, percent male, and year. The specific independent variables were chosen based on previous literature suggesting an area-level association between those demographic indicators and greater opioid use or drug mortality.[7 9-12] Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all years.

Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata 15.1 (StataCorp LLC, College Station, TX). Opioid prescription rates, drug-poisoning mortality, and ADI at the county-level were visually represented with geographic information system (GIS) maps created in ArcMap 10.7 using Census TIGER/Line shapefiles.

Results

Opioid Prescription Rates across Quintiles of ADI and over Time

Opioid prescription rates were significantly higher among counties in the highest ADI quintile (Q5: most deprived) compared to those in the lowest quintile. The risk of filling an opioid prescription was 72% higher in ADI Q5 than Q1 (IRR, 1.72; 95% CI [1.63, 1.82]; p<0.001) (Table S2).

Overall, rates of filled opioid prescriptions declined over time, from 96.6 per 100 people in 2012 to 72.2 per 100 people in 2017. Analogously, the percentage and total number of counties with more than 1 opioid prescription per resident steadily declined over time: 40.3% (n=1093) in 2012, 38.6% (n=1047) in 2013, 36.9% (n=1001) in 2014, 31.5% (n=855) in 2015, 26.7% (n=723) in 2016, and 17.6% (n=477) in 2017.

Rates of opioid prescriptions decreased consistently between 2012 and 2017 within each ADI quintile (Figure 4). The adjusted prescription rate for counties in the most deprived ADI quintile (Q5) decreased from 115.9 prescriptions per 100 people in 2012 to 86.6 in 2017 (IRR 0.75, 95% CI [0.73, 0.76]; p<0.001) (Table S2). Each successively less deprived ADI quintile displayed a

smaller decrease in prescription rate. Although the absolute opioid prescription rate decrement was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles.

Drug-Poisoning Mortality across Quintiles of ADI and over Time

In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62]; p<0.001) between 2012 and 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28, 1.44]; p<0.001) (Table 1). However, the association between ADI and drug-poisoning mortality was not linear. Instead, the increase in drug-poisoning mortality with rising deprivation reached a threshold between Q2 and Q3. The adjusted rates of drug-poisoning mortality were similar between counties in ADI Q1 and Q2 (40% least deprived counties), and significantly lower than counties in ADI Q3 to Q5 (60% most deprived counties) (Figure S1).

Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality

As shown in Figures 1-3, there were consistent and strongly demarcated spatial differences in both outcomes across ADI quintiles. The highest opioid prescription rates were seen in counties in southern states and Appalachia. Southwestern U.S. and Appalachia also saw high drug-poisoning mortality. There were no major geospatial changes in the patterns of deprivation, opioid prescriptions, or drug-poisoning mortality during the study period.

Conclusions

Social determinants of health underlie many causes of the ongoing epidemic and need to be considered to when developing and implementing interventions seeking to address it. In this study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may be a powerful tool for identifying areas of greatest need as well as informing and contextualizing future public health and policy interventions. We also found that while opioid prescriptions decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them, persistent disparities in both prescription opioid use and drug-poisoning mortality remain. Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-related mortality than less deprived counties. Moreover, despite reductions in opioid prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and 2017, reinforcing the growing impact of drugs obtained outside of the health care system and missed opportunities to tailor and target interventions to those at highest risk for harm. By considering contextual factors and developing customized approaches using area-level indicators, harm reduction strategies could yield a more sustainable and meaningful impact for the communities they serve.

A number of state and federal programs have been introduced over the past decade to increase public awareness, decrease access to prescription opioids, improve opioid use disorder treatment, and expand access to naloxone for overdose reversal.[22] These interventions likely contributed to the decline in rates of opioid prescriptions between 2012 and 2017, but did not rectify the disparities that remain unchanged over time. Persistent disparities in opioid prescription rates may be attributed to greater availability of opioid prescribers in highly deprived counties,[23]

higher prevalence of comorbidities and disability in deprived areas,[24] difficulty accessing medication for opioid use disorder,[25] and a different experience of pain in the setting of lower health literacy[26] and socioeconomic distress. Further efforts should focus on identifying alternative pain management strategies that are effective, affordable, and accessible to all who need them, irrespective of where they live. At present, access to and reimbursement for non-pharmacologic pain management modalities remains limited,[27] which may further exacerbate disparities in opioid use and misuse among disadvantaged U.S. adults.

Although opioid prescribing rates declined over time, rates of drug-poisoning mortality rose steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too, was consistently higher in the most deprived counties. We also observed a threshold effect of ADI on drug-poisoning mortality, with 60% of most deprived counties experiencing significantly higher drug-poisoning mortality rates than the remaining 40% of counties. This finding underscores the complexity of the opioid and drug use epidemic. First, current opioid prescribing rates are not the sole driver of drug-poisoning mortality, as mortality has continued to rise while prescription rates have declined. Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates of addiction due to overprescribing, all play an important role in drug-related deaths.[2 28] Second, high rates of drug-poisoning mortality result not only from greater availability of drugs, but also from greater probability of death with drug use. People living in deprived areas often have inadequate access to substance use disorder treatment and medications[29-33] and limited access to healthcare,[34] resulting from failure to expand Medicaid coverage, inadequate reimbursement for treatment,[23 35] and variation in types of providers able to prescribe and manage treatment.[36] Third, as a result of structural violence and barriers, individuals living in deprived communities

may be less likely to seek medical treatment due to stigma and criminalization leading to higher rates of drug-poisoning mortality.[37] Reducing mortality will therefore require a wide range of interventions in addition to limiting opioid prescribing, including improving availability of and access to nonopioid pain management, social services, mental health, and substance use treatment.

Consistent with prior literature, we found that higher proportions of male residents within a county were protective against both opioid prescriptions[7 38] and drug-poisoning mortality.[39] Women are more likely than men to be prescribed opioid medications and to be co-prescribed other medications that increase overdose risk;[39-41] women are also less likely to enter substance use disorder treatment programs.[42] Counties with fewer men may also reflect larger systemic issues such as higher incarceration rates among males.[37] Incarceration not only interferes with the ability to seek substance abuse treatment, but is strongly associated with family disruption, unemployment, neighborhood decline, chronic economic hardship, and importantly, increased mortality from drug-use disorders.[37]

Our study has several key strengths, making it relevant and actionable to public health professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses highlighted the importance of understanding county resources and economic conditions that may affect both use of and mortality related to opioids and other drugs. We also identified the degree of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and accounting for changes in demographics and ADI quintiles over time using yearly demographic

estimates and census indicators from ACS, which has not been done to date. This is also the first study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless, our findings are limited by potential reverse causality bias and the inability to identify causal relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not capture all prescription opioids; methadone dispensed through maintenance therapy programs and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly, given the use of ACS survey data, our study is susceptible to non-response and imputation bias.

Addressing the drug crisis requires multifaceted interventions that address the wide range of biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.[2] Our work demonstrates the need to consider local factors when developing interventions related to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed by indicators such as ADI to identify areas that may benefit from additional monitoring, specific resources, and tailored interventions.

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Contributors: SK and NS conceived and designed the study; SK and JI acquired data; SK, RM, SC, LR analyzed/interpreted the data; NS, MJ, JI, and RG supervised data analysis. All authors refined the various versions of the full paper and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SK and ND are the guarantors.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr. Jeffery's spouse owns shares in Vireo Health.

Ethical Approval: Not required.

Data Sharing: All data are publicly available. Statistical code and datasets are available from the corresponding author at kurani.shaheen@mayo.edu or can be obtained from the following websites: https://www.census.gov/programs-surveys/acs; https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm; https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html

SK and NS affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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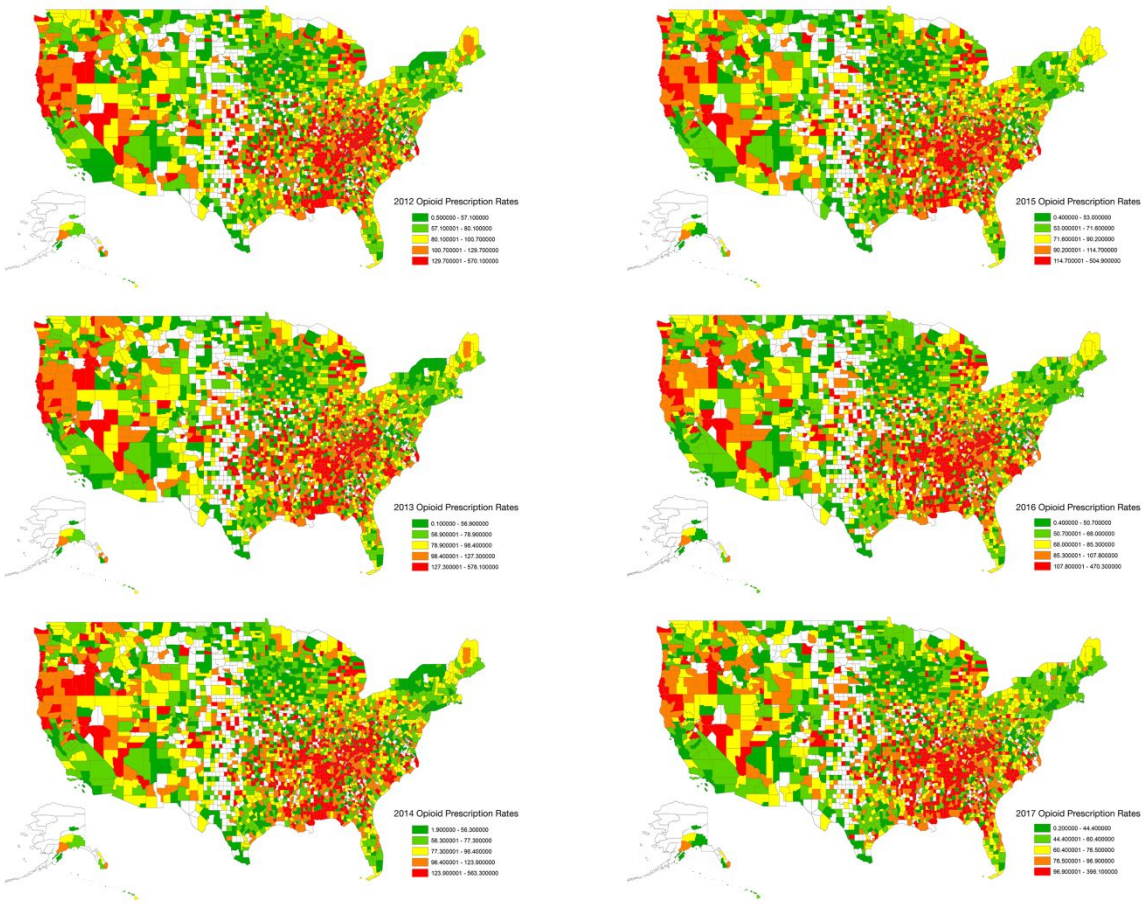

Figure 1. Opioid prescription rates across U.S. counties from 2012-2017.

2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

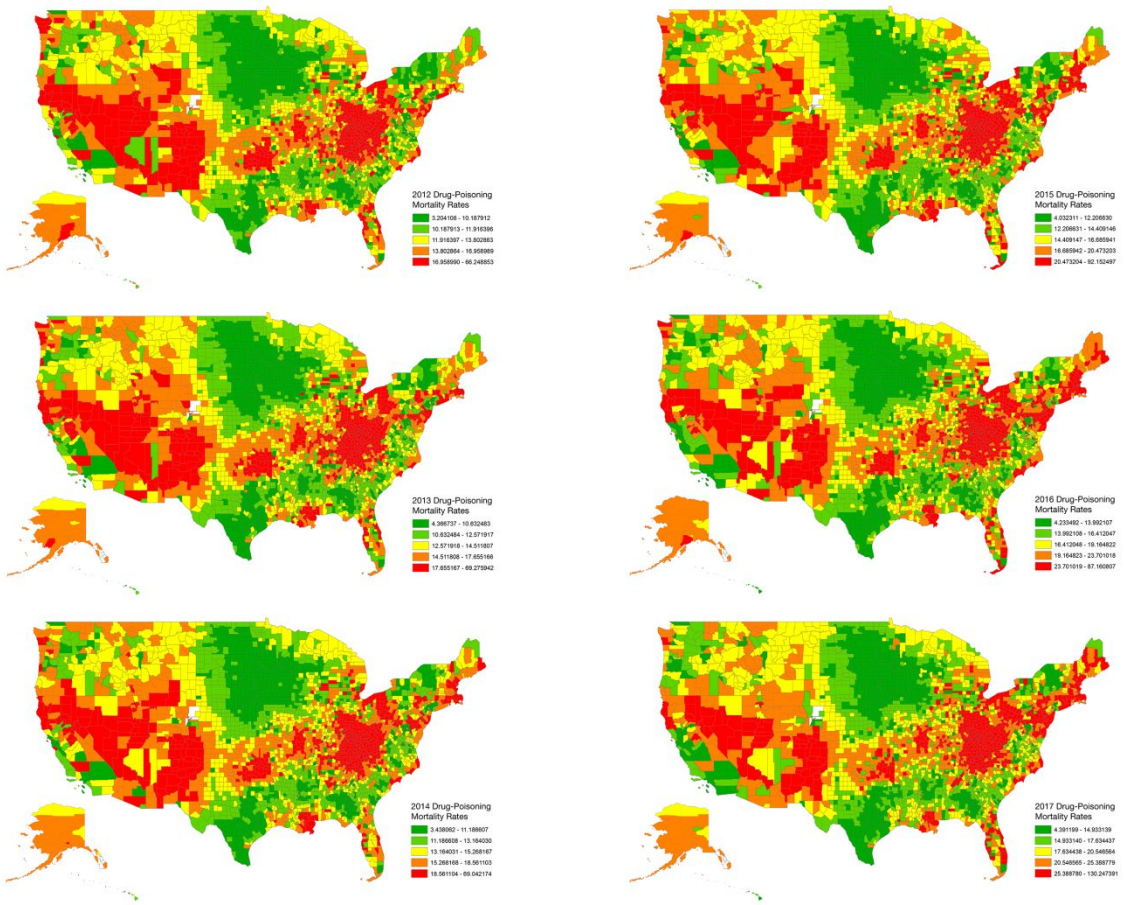

Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017.

3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

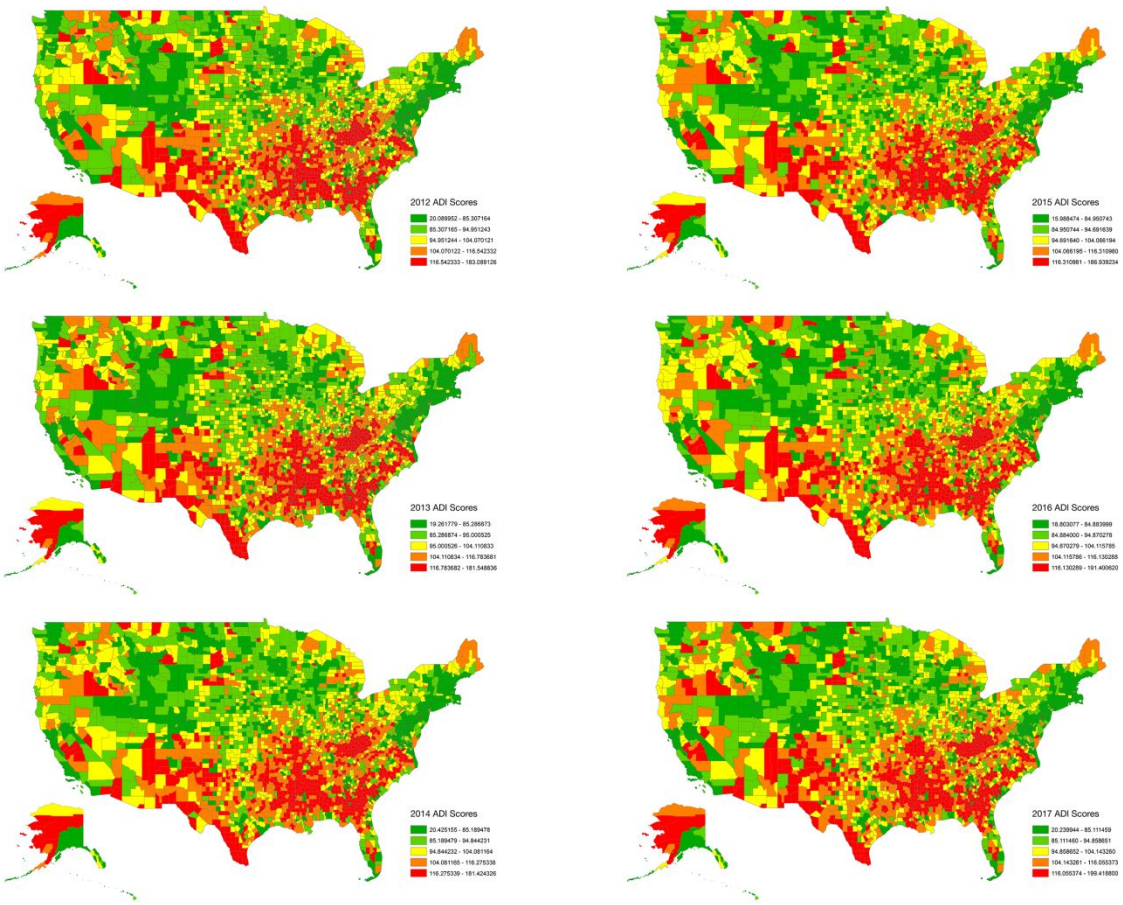

Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017.

ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

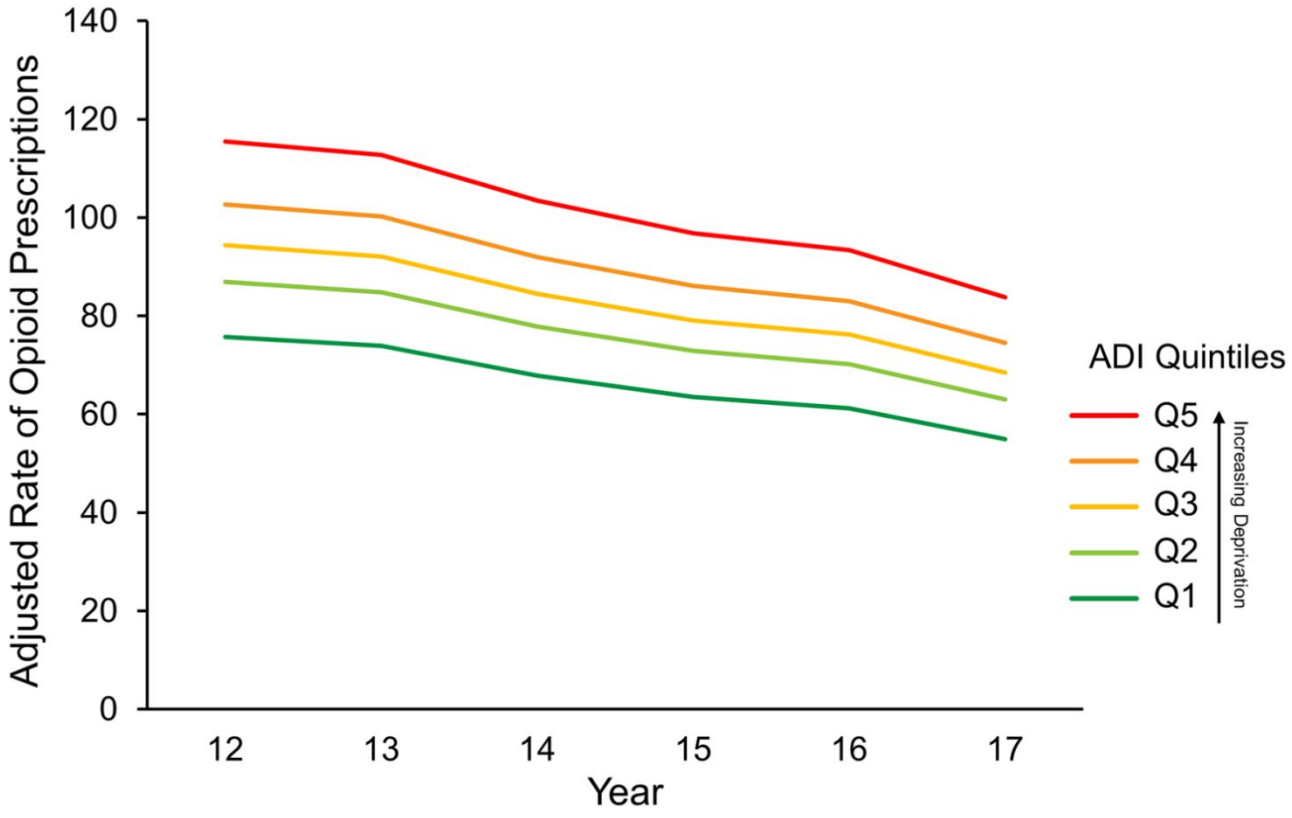

Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017.

Rates adjusted for ADI quintile, year, age, race, and sex were calculated per 100 people.

Table 1: Factors associated with drug-poisoning mortality in the U.S., 2012-2017. Negative binomial regression analysis examined the risk of higher rates of drug-poisoning mortality in 3,133 of 3,142 U.S. counties with available mortality data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		P-VALUE
Year				
2012	Ref.			
2013	1.05	1.04	1.05	<0.001
2014	1.11	1.10	1.12	<0.001
2015	1.23	1.22	1.25	<0.001
2016	1.45	1.43	1.48	<0.001
2017	1.59	1.56	1.62	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.10	1.04	1.16	<0.001
3	1.20	1.14	1.26	<0.001
4	1.28	1.22	1.35	<0.001
5	1.36	1.28	1.44	<0.001
Sex, percentage				
Male	0.97	0.96	0.97	<0.001
Race/ethnicity, percentage*				
White	1.05	1.04	1.07	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.03	<0.001
45-64 years	1.06	1.05	1.07	<0.001
≥65 years	1.01	1.00	1.01	0.04

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

Supplementary Figures and Tables

Table S1: American Community Survey census indicators, table references, and factor score coefficients from 2012-2017

US Census Indicator	2012-2017 ACS Table Reference, 5-year estimates	Factor Score Coefficient 2012	Factor Score Coefficient 2013	Factor Score Coefficient 2014	Factor Score Coefficient 2015	Factor Score Coefficient 2016	Factor Score Coefficient 2017
Median family income	B19013	-0.16638	-0.17221	-0.16295	-0.16102	-0.16087	-0.16993
Income disparity	B19001	0.07705	0.07615	0.08298	0.08417	0.08019	0.06799
Families below poverty level	B17010	0.11021	0.12182	0.12629	0.12707	0.12555	0.12298
% population below 150% poverty threshold	C17002	0.22177	0.21806	0.21815	0.22455	0.22914	0.23659
Single parent household with dependents <18	B23008	0.03544	0.03803	0.03658	0.03698	0.03817	0.04165
Households without a motor vehicle	B25044	0.0546	0.05144	0.05392	0.05365	0.05666	0.05646
Households without a telephone	B25043	0.01257	0.00894	0.00725	0.00648	0.00685	0.00892
Occupied housing units without complete plumbing	B25016	0.03533	0.03295	0.03167	0.03	0.02692	0.02963
Owner occupied housing units	B25003	-0.01012	-0.00841	-0.00915	-0.00855	-0.00888	-0.00733
Households with >1 person per room	B25014	0.02759	0.03006	0.02886	0.03246	0.03546	0.03747
Median monthly mortgage	B25088	-0.15057	-0.14344	-0.1461	-0.13736	-0.13578	-0.13004
Median gross rent	B25064	-0.05158	-0.05216	-0.05079	-0.05359	-0.05922	-0.06295
Median home value	B25077	-0.0649	-0.0689	-0.06525	-0.07038	-0.07345	-0.0749

Employed persons ≥16 in white collar occupation	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
Civilian labor force unemployed (aged ≥16)	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
Population aged ≥25 with <9yr education	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
Population aged ≥25 with at least a high school education	B15003	-0.23235	-0.22358	-0.22647	-0.22431	-0.22112	-0.21015

Table S2: Factors associated with opioid prescriptions in the U.S, 2012-2017

Negative binomial regression analysis examined the risk of higher rates of opioid prescriptions in 2,712 of 3,142 U.S. counties with available opioid prescribing data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		p-value
Year				
2012	Ref.			
2013	0.98	0.97	0.98	<0.001
2014	0.95	0.94	0.96	<0.001
2015	0.89	0.88	0.90	<0.001
2016	0.84	0.83	0.85	<0.001
2017	0.75	0.73	0.76	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.16	1.11	1.21	<0.001
3	1.38	1.32	1.44	<0.001
4	1.57	1.51	1.65	<0.001
5	1.72	1.63	1.82	<0.001
Sex, percentage				
Male	0.94	0.94	0.95	<0.001
Race/ethnicity, percentage*				
White	1.04	1.03	1.06	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.04	<0.001
45-64 years	1.02	1.01	1.03	<0.001
≥65 years	1.01	1.01	1.02	<0.001

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

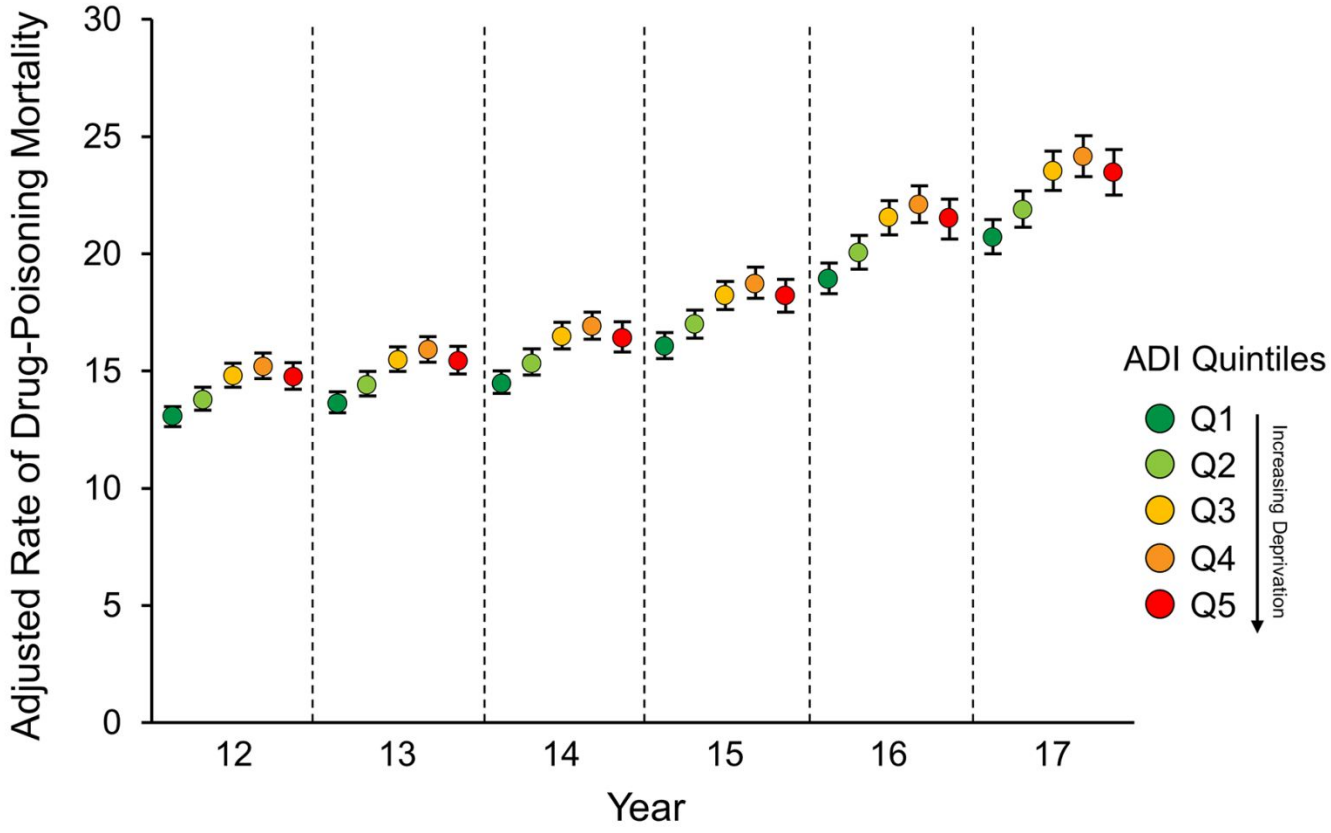

Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

Rates adjusted for ADI quintile, year, age, race, and sex were calculated per 100,000 people.

Supplementary Appendix

The county-level ADI scores used for this study could not be included in a single table. The interested reader can find them in a supplementary appendix online at https://www.mayo.edu/research/area-deprivation-index.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	14-15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	--
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	--
		(*e*) Describe any sensitivity analyses	--
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017

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Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017

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Abstract

Objective

To identify the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality.

Design, Setting, and Participants

For this retrospective cross-sectional study, we used the IQVIA Xponent data to capture opioid prescriptions and CDC National Vital Statistics System to assess drug-poisoning mortality. The area deprivation index (ADI) is a composite measure of social determinants of health comprised of 17 U.S. census indicators, spanning four socioeconomic domains. For all U.S. counties with available opioid prescription (2,712 counties) and drug-poisoning mortality (3,133 counties) data between 2012 and 2017, we used negative binomial regression to examine the association between quintiles of county-level ADI and rates of opioid prescriptions and drug-poisoning mortality adjusted for year, age, race, and sex.

Primary Outcome Measures

County-level opioid prescription fills and drug-poisoning mortality

Results

Between 2012-2017, overall rates of opioid prescriptions decreased from 96.6 to 72.2 per 100 people, while rates of drug-poisoning mortality increased from 14.3 to 22.8 per 100,000 people. Opioid prescription and drug-poisoning mortality rates were consistently higher with greater levels of deprivation. The risk of filling an opioid prescription was 72% higher, and the risk of drug-poisoning mortality was 36% higher, for most deprived compared to least deprived counties (both $p<0.001$).

Discussion

Counties with greater area-level deprivation have higher rates of filled opioid prescriptions and drug-poisoning mortality. Although opioid prescription rates declined across all ADI quintiles, rates of drug-poisoning mortality continued to rise proportionately in each ADI quintile. This underscores the need for individualized and targeted interventions that consider the deprivation of communities where people live.

Strengths and Limitations of this Study

- The ADI was standardized to ensure that all variables were scaled equally prior to weighting
- The work accounted for changes in demographics and ADI quintiles over time using yearly demographic estimates and census indicators from ACS
- This study is limited by potential imputation bias due to the use of survey data and reverse causality bias

Introduction

The drug epidemic has incurred great personal, societal, and economic costs,[1] driven, in part, by the widespread availability and use of prescription opioids.[2] In 2017, there were over 191 million dispensed opioid prescriptions,[3] approximately 47,600 opioid-related deaths,[4] and 70,237 drug-poisoning deaths[4] in the U.S. Overdose deaths continue to be the leading cause of injury-associated mortality and, over the past decade, have exceeded traffic fatalities.[5] To date, the primary strategy for reducing drug-poisoning mortality has been limiting the inappropriate use of prescription opioids; yet, the relentless rise in drug-related mortality continued to contribute to the decline of life expectancy in the U.S. since 2015.[6 7]

Understanding factors associated with drug-related mortality, and identifying at-risk populations, is critical to developing and targeting interventions aimed to reduce it. While the drug epidemic has impacted all segments of society, recent studies identified young and middle-aged white men as populations disproportionately affected by drug-poisoning mortality.[8 9] Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.[6 10] Similarly, the association between county-level poverty and higher rates of opioid prescribing was previously demonstrated in a 2014 study of disabled Medicare and Medicaid beneficiaries,[11] though this was not examined in the general U.S. population or linked directly to drug-related mortality. Nevertheless, addressing this epidemic will require sophisticated policy and public health approaches that consider a breadth of fundamental social determinants of health and cannot be fully captured by singular constructs such as age, race, sex, or income. This is especially important for a complex and multifaceted public health problem such as the drug use epidemic,

which is likely caused by a multitude of factors, affects all members of society, and is fueled by both prescription and illicit drugs.

A variety of policies and public health campaigns have been implemented in an effort to curb the epidemic of opioid overdoses and other drug-related morbidity and mortality, including the introduction of state prescription drug monitoring programs and the 2016 Centers for Disease Control and Prevention (CDC) opioid-prescribing guidelines.[2] Though most of the focus has been on prescription opioids, other non-opioid prescription and illicit drugs, such as heroin and fentanyl, have also contributed to the increase in drug-poisoning deaths[12] over the past two decades. Thus, the two outcomes – opioid prescribing and drug-poisoning mortality – should be tracked in parallel to assess the impact of limiting opioid use on overall drug mortality. Historically, areas with higher opioid prescription rates also experienced higher drug-related mortality,[11] but recent intensive policy and public health efforts aimed at reducing opioid prescribing may have inadvertently created a divergence between opioid prescribing and drug-poisoning mortality, particularly in areas where opioid use may be low, but mortality due to non-opioids remains high. There is therefore a need for a contemporary population-level evaluation of current trends in opioid prescribing practices and drug-related mortality to identify populations at greatest risk of harm from opioid and non-opioid misuse.

The area deprivation index (ADI) is a validated composite measure of social determinants of health that can be used to quantify socioeconomic disadvantage for granular census-based regions.[13] The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty, education, housing, and employment.[14] County-level indicators of economic disadvantage reflect

general resource availability, safety, education quality, employment opportunity, and social support,[15] all of which contribute to physical, emotional, and financial health of communities and their residents. Despite the potential individual and public health implications of area-level deprivation for a wide range of clinical and public health outcomes, composite area-based measures have not been widely used to inform healthcare policy or clinical practice due to previously inaccessible national geospatial data.[13] In this study, we address a pressing public health need and pursue a critical knowledge gap by examining the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-level deprivation, this work contributes to the evidence base for informing clinical, public health, and policy interventions targeted at highest-need areas and populations.

Methods

Study Design

We retrospectively analyzed county-level summary measures of opioid prescriptions, drug-poisoning mortality, and population demographics from 2012 to 2017 using the IQVIA Xponent prescription database,[3] CDC National Vital Statistics System data,[16] and American Community Survey (ACS) estimates,[17] respectively. These data are publicly available and contain no identifiable information; thus, this work was exempt from Institutional Review Board approval.

Study population

All U.S. counties with opioid prescription and drug-poisoning mortality data available each year between 2012 and 2017 were included in the study sample. Counties without data for all six years of the study were excluded from the sample.

Patient Involvement

No patients or members of the public were directly involved in the design, conduct, reporting, or dissemination plans of the research.

American Community Survey Estimates

County demographic information necessary for ADI derivation was ascertained from 2012-2016 and 2013-2017 5-year ACS estimates; the 5-year estimates are single year estimates based on 60 months of data.[17] The ADI was derived using 17 county-level indicators and calculated separately each year for each U.S. county, as deprivation indices may change over time (Table S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the Census Application Programming Interface (API) to obtain data from the ACS.[18] The ACS is an annual survey conducted by the U.S. Census Bureau which randomly samples housing units and provides population-level estimates representative of the non-institutionalized U.S. population.[17] In-depth survey methodology is available from the Census Bureau.[17]

Outcomes

IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1, 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e.,

prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.; information on drugs filled by mail order pharmacies is unavailable.[3]

Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a county per 100 residents as estimated by the ACS.[3] Opioids, identified using National Drug Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone dispensed through maintenance therapy programs was not included.

The CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality rates between January 1, 2012 and December 31, 2017; these data were available for each year for 3,133 counties (Figure 2). The CDC performs hierarchical Bayesian methods with spatial and temporal random effects to generate adjusted county-level drug-poisoning mortality rates per 100,000 residents.[19] Drug-poisoning deaths related to opioid and non-opioid drugs were classified on the basis of International Classification of Diseases, Tenth Revision (ICD-10) codes and included deaths with unintentional (X40–X44), suicide (X60–X64), homicide (X85), and undetermined intent (Y10–Y14).[16]

Role of the Funding Source

The funding sources for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

ADI Derivation

We calculated modified ADI scores, using the Singh method,[14] for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach [14 20 21] and missing values were substituted using single imputation. All variables were transformed to a rate per capita for the county. To improve upon published ADI methodologies and prevent distortion of ADI by larger continuous variables such as income, we standardized these proportions to a mean of 0 and standard deviation of 1, thereby ensuring that all variables in the modified ADI were scaled equally prior to weighting. Each variable was then multiplied by its respective weight obtained from the factor score coefficient (Table S1), and the 17 weighted measures were summed for each county to obtain the base score. Base scores were then standardized to a mean of 100 and standard deviation of 20. ADI was divided into quintiles for all analyses, with higher ADI values (quintile 5) representing greater deprivation.

Statistical Analysis

We used negative binomial regression to examine the relationships between ADI and opioid prescription rates and drug-poisoning mortality from 2012 to 2017, controlling for over-dispersion of outcome estimates and county population size. We used Huber-White robust standard errors clustered at the county level to adjust standard errors for repeated county observations and variation. Independent variables in the models included ADI quintile, percent

county-level estimates for age, percent white, percent male, and year. The specific independent variables were chosen based on previous literature suggesting an area-level association between those demographic indicators and greater opioid use or drug mortality.[6 8-11] Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all years.[22]

Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata 15.1 (StataCorp LLC, College Station, TX). Opioid prescription rates, drug-poisoning mortality, and ADI at the county-level were visually represented with geographic information system (GIS) maps created in ArcMap 10.7 using Census TIGER/Line shapefiles.

Results

Association of Area-Level Deprivation with Opioid Prescription Rates

Opioid prescription rates were significantly higher among counties in the highest ADI quintile (Q5: most deprived) compared to those in the lowest quintile. The risk of filling an opioid prescription was 72% higher in ADI Q5 than Q1 (IRR, 1.72; 95% CI [1.63, 1.82]; p<0.001) (Table S2).

Overall, rates of filled opioid prescriptions declined over time, from 96.6 per 100 people in 2012 to 72.2 per 100 people in 2017. Analogously, the percentage and total number of counties with more than 1 opioid prescription per resident steadily declined over time: 40.3% (n=1093) in 2012, 38.6% (n=1047) in 2013, 36.9% (n=1001) in 2014, 31.5% (n=855) in 2015, 26.7% (n=723) in 2016, and 17.6% (n=477) in 2017.

Rates of opioid prescriptions appear to decrease between 2012 and 2017 within each ADI quintile (Figure 4). The adjusted prescription rate for counties in the most deprived ADI quintile (Q5) decreased from 115.9 prescriptions per 100 people in 2012 to 86.6 in 2017 (IRR 0.75, 95% CI [0.73, 0.76]; p<0.001) (Table S2). Adjusted rates calculated from the predicted margins suggest that each successively less deprived ADI quintile displayed a smaller decrease in prescription rate. Although the absolute opioid prescription rate decrement was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles.

Association of Area-Level Deprivation with Drug-Poisoning Mortality

In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62]; p<0.001) between 2012 and 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28, 1.44]; p<0.001) (Table 1). The association between ADI and drug-poisoning mortality appeared to be linear with rising deprivation resulting in higher rates of drug-poisoning mortality (Figure S1).

Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality

As shown in Figures 1-3, there were consistent and strongly demarcated spatial differences in both outcomes across ADI quintiles. The highest opioid prescription rates were seen in counties in southern states and Appalachia. Southwestern U.S. and Appalachia also saw high drug-

poisoning mortality. There were no major visual geospatial changes in the patterns of deprivation, opioid prescriptions, or drug-poisoning mortality during the study period.

Discussion

Social determinants of health underlie many causes of the ongoing epidemic and need to be considered to when developing and implementing interventions seeking to address it. In this study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may be a powerful tool for identifying areas of greatest need as well as informing and contextualizing future public health and policy interventions. We also found that while opioid prescriptions decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them, persistent disparities in both prescription opioid use and drug-poisoning mortality remain. Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-related mortality than less deprived counties. Moreover, despite reductions in opioid prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and 2017, reinforcing the growing impact of drugs obtained outside of the health care system and missed opportunities to tailor and target interventions to those at highest risk for harm. By considering contextual factors and developing customized approaches using area-level indicators, harm reduction strategies could yield a more sustainable and meaningful impact for the communities they serve.

A number of state and federal programs have been introduced over the past decade to increase public awareness, decrease access to prescription opioids, improve opioid use disorder treatment,

and expand access to naloxone for overdose reversal.[23] The interventions targeting opioid prescribing (i.e. state controlled substance monitoring programs) likely contributed to the decline in rates of opioid prescriptions between 2012 and 2017, but did not rectify the disparities associated with drug-poisoning deaths. Persistent disparities in opioid prescription rates may be attributed higher prevalence of comorbidities and disability in deprived areas,[24] difficulty accessing medication for opioid use disorder,[25] and a different experience of pain in the setting of lower health literacy[26] and socioeconomic distress. Further efforts should focus on identifying alternative pain management strategies that are effective, affordable, and accessible to all who need them, irrespective of where they live. At present, access to and reimbursement for non-pharmacologic pain management modalities remains limited,[27] which may further exacerbate disparities in opioid use and misuse among disadvantaged U.S. adults.

Although opioid prescribing rates declined over time, rates of drug-poisoning mortality appeared to rise steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too, was higher in the most deprived counties. This finding underscores the complexity of the opioid and drug use epidemic. First, current opioid prescribing rates are not the sole driver of drug-poisoning mortality, as mortality has continued to rise while prescription rates have declined. Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates of addiction due to overprescribing, all play an important role in drug-related deaths.[2 28] Second, high rates of drug-poisoning mortality result not only from greater availability of drugs, but also from greater probability of death with drug use. People living in deprived areas often have inadequate access to substance use disorder treatment and medications[29-33] and limited access to healthcare,[34] resulting from failure to expand Medicaid coverage, inadequate reimbursement for treatment,[35 36]

and variation in types of providers able to prescribe and manage treatment.[37] Third, as a result of structural violence and barriers, individuals living in deprived communities may be less likely to seek medical treatment due to stigma and criminalization leading to higher rates of drug-poisoning mortality.[38] Reducing mortality will therefore require a wide range of interventions in addition to limiting opioid prescribing, including improving availability of and access to nonopioid pain management, social services, mental health, and substance use treatment.

Consistent with prior literature, we found that higher proportions of male residents within a county were protective against both opioid prescriptions[6 39] and drug-poisoning mortality.[40] Women are more likely than men to be prescribed opioid medications and to be co-prescribed other medications that increase overdose risk;[40-42] women are also less likely to enter substance use disorder treatment programs.[43] Counties with fewer men may also reflect larger systemic issues such as higher incarceration rates among males.[38] Incarceration not only interferes with the ability to seek substance abuse treatment, but is strongly associated with family disruption, unemployment, neighborhood decline, chronic economic hardship, and importantly, increased mortality from drug-use disorders.[38]

Our study has several key strengths, making it relevant and actionable to public health professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses highlighted the importance of understanding county resources and economic conditions that may affect both use of and mortality related to opioids and other drugs. We also identified the degree of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and

accounting for changes in demographics and ADI quintiles over time using yearly demographic estimates and census indicators from ACS, which has not been done to date. This is also the first study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless, our findings are limited by potential reverse causality bias and the inability to identify causal relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not capture all prescription opioids; methadone dispensed through maintenance therapy programs and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly, given the use of ACS survey data, our study is susceptible to non-response and imputation bias. However, our study had less than 1% of missing data for each year and fewer than 80 variable observations were imputed in total. Thus, the potential for imputation bias is very low.

Addressing the drug crisis requires multifaceted interventions that address the wide range of biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.[2] Our work demonstrates the need to consider local factors when developing interventions related to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed by indicators such as ADI to identify areas that may benefit from additional monitoring, specific resources, and tailored interventions.

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Contributors: SK and NS conceived and designed the study; SK and JI acquired data; SK, RM, SC, LR analyzed/interpreted the data; NS, MJ, JI, and RG supervised data analysis. All authors refined the various versions of the full paper and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SK and ND are the guarantors.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr. Jeffery's spouse owns shares in Vireo Health.

Ethical Approval: Not required.

Data Sharing: All data are publicly available. Statistical code and datasets are available from the corresponding author at kurani.shaheen@mayo.edu or can be obtained from the following websites: https://www.census.gov/programs-surveys/acs; https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm; https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html

SK and NS affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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Table 1: Factors associated with drug-poisoning mortality in the U.S., 2012-2017. Negative binomial regression analysis examined the risk of higher rates of drug-poisoning mortality in 3,133 of 3,142 U.S. counties with available mortality data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		P-VALUE
Year				
2012	Ref.			
2013	1.05	1.04	1.05	<0.001
2014	1.11	1.10	1.12	<0.001
2015	1.23	1.22	1.25	<0.001
2016	1.45	1.43	1.48	<0.001
2017	1.59	1.56	1.62	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.10	1.04	1.16	<0.001
3	1.20	1.14	1.26	<0.001
4	1.28	1.22	1.35	<0.001
5	1.36	1.28	1.44	<0.001
Sex, percentage				
Male	0.97	0.96	0.97	<0.001
Race/ethnicity, percentage*				
White	1.05	1.04	1.07	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.03	<0.001
45-64 years	1.06	1.05	1.07	<0.001
≥65 years	1.01	1.00	1.01	0.04

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

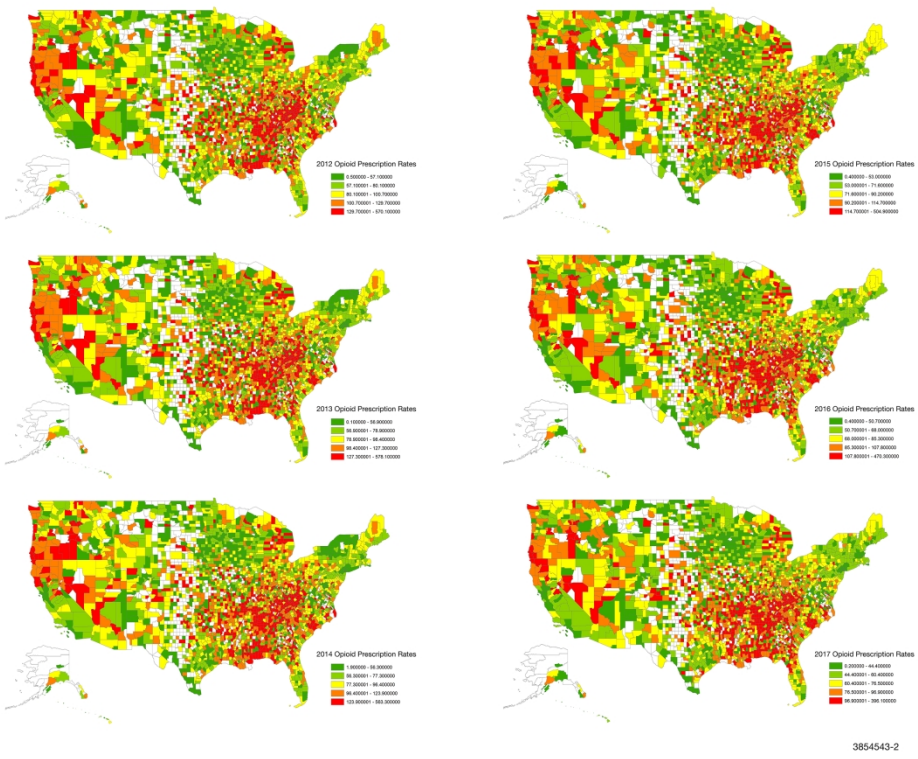

Figure 1. Opioid prescription rates across U.S. counties from 2012-2017.
2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

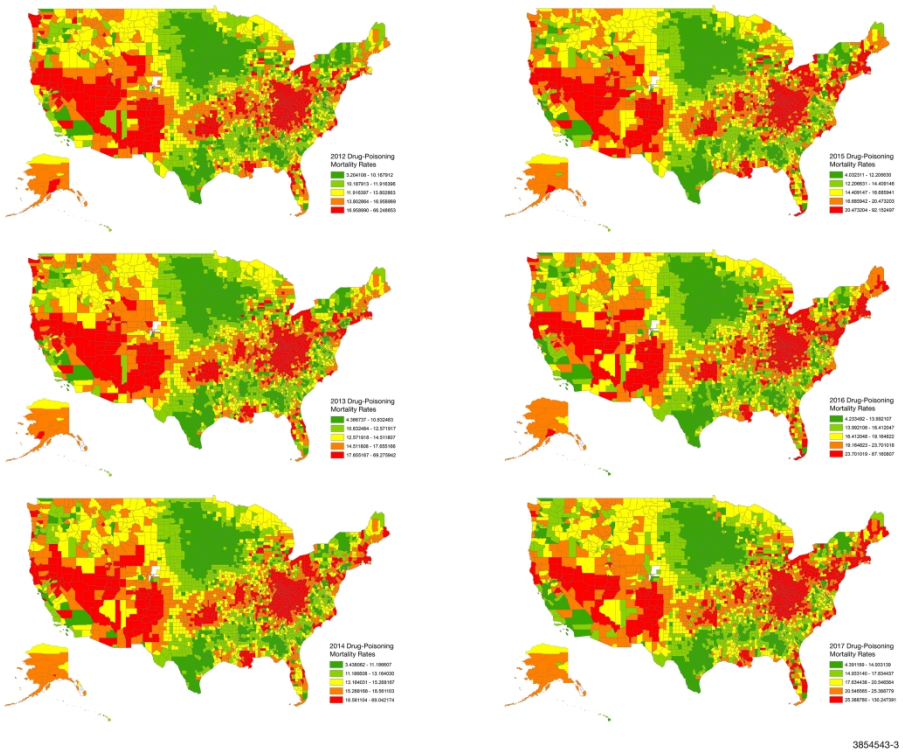

Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017.
3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

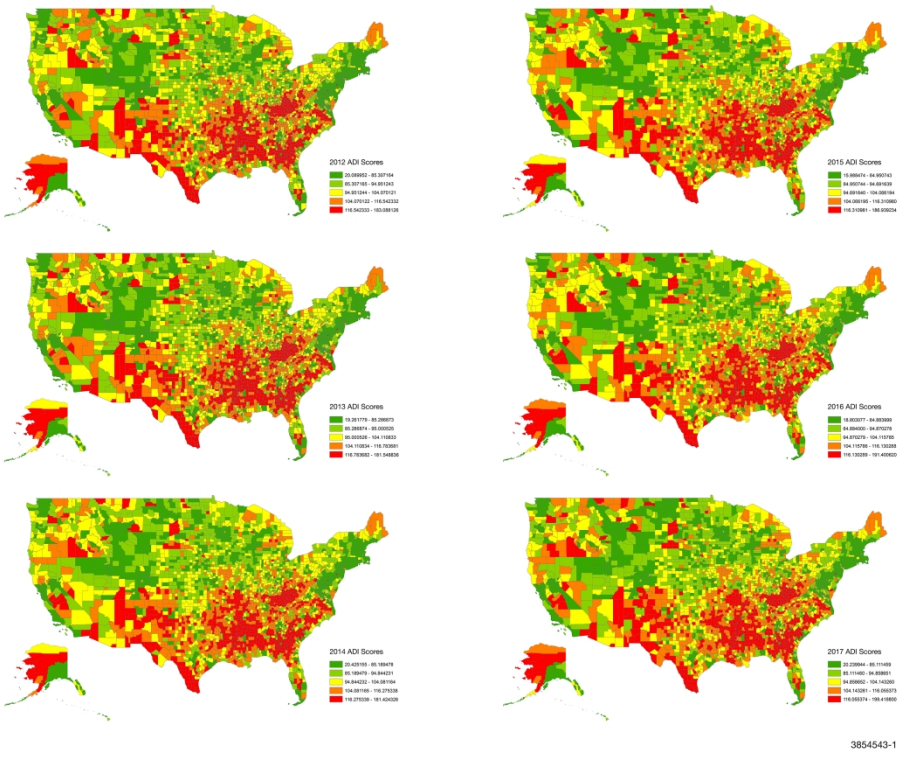

Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017. ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

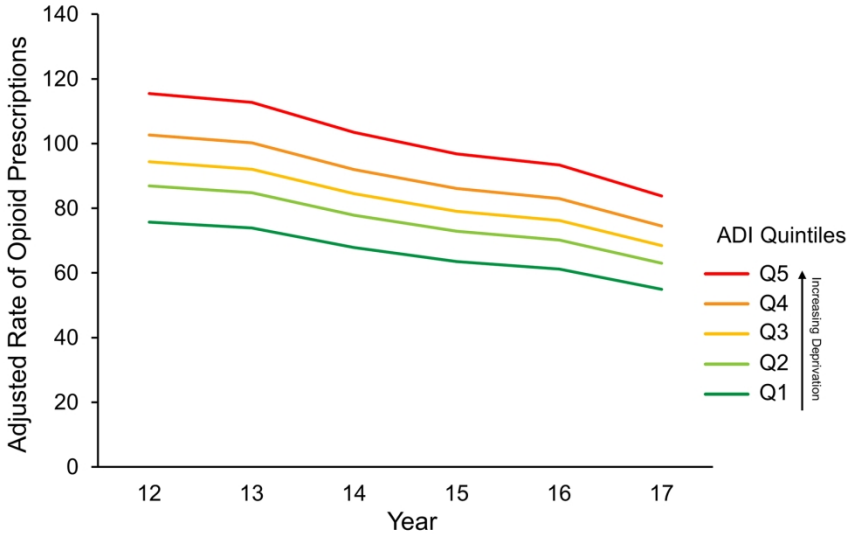

Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017.
Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.

177x133mm (300 x 300 DPI)

Supplementary Figures and Tables

Table S1: American Community Survey census indicators, table references, and factor score coefficients from 2012-2017

US Census Indicator	2012-2017 ACS Table Reference, 5-year estimates	Factor Score Coefficient 2012	Factor Score Coefficient 2013	Factor Score Coefficient 2014	Factor Score Coefficient 2015	Factor Score Coefficient 2016	Factor Score Coefficient 2017
Median family income	B19013	-0.16638	-0.17221	-0.16295	-0.16102	-0.16087	-0.16993
Income disparity	B19001	0.07705	0.07615	0.08298	0.08417	0.08019	0.06799
Families below poverty level	B17010	0.11021	0.12182	0.12629	0.12707	0.12555	0.12298
% population below 150% poverty threshold	C17002	0.22177	0.21806	0.21815	0.22455	0.22914	0.23659
Single parent household with dependents <18	B23008	0.03544	0.03803	0.03658	0.03698	0.03817	0.04165
Households without a motor vehicle	B25044	0.0546	0.05144	0.05392	0.05365	0.05666	0.05646
Households without a telephone	B25043	0.01257	0.00894	0.00725	0.00648	0.00685	0.00892
Occupied housing units without complete plumbing	B25016	0.03533	0.03295	0.03167	0.03	0.02692	0.02963
Owner occupied housing units	B25003	-0.01012	-0.00841	-0.00915	-0.00855	-0.00888	-0.00733
Households with >1 person per room	B25014	0.02759	0.03006	0.02886	0.03246	0.03546	0.03747
Median monthly mortgage	B25088	-0.15057	-0.14344	-0.1461	-0.13736	-0.13578	-0.13004
Median gross rent	B25064	-0.05158	-0.05216	-0.05079	-0.05359	-0.05922	-0.06295
Median home value	B25077	-0.0649	-0.0689	-0.06525	-0.07038	-0.07345	-0.0749

Employed persons ≥16 in white collar occupation	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
Civilian labor force unemployed (aged ≥16)	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
Population aged ≥25 with <9yr education	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
Population aged ≥25 with at least a high school education	B15003	-0.23235	-0.22358	-0.22647	-0.22431	-0.22112	-0.21015

Table S2: Factors associated with opioid prescriptions in the U.S, 2012-2017

Negative binomial regression analysis examined the risk of higher rates of opioid prescriptions in 2,712 of 3,142 U.S. counties with available opioid prescribing data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		p-value
Year				
2012	Ref.			
2013	0.98	0.97	0.98	<0.001
2014	0.95	0.94	0.96	<0.001
2015	0.89	0.88	0.90	<0.001
2016	0.84	0.83	0.85	<0.001
2017	0.75	0.73	0.76	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.16	1.11	1.21	<0.001
3	1.38	1.32	1.44	<0.001
4	1.57	1.51	1.65	<0.001
5	1.72	1.63	1.82	<0.001
Sex, percentage				
Male	0.94	0.94	0.95	<0.001
Race/ethnicity, percentage*				
White	1.04	1.03	1.06	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.04	<0.001
45-64 years	1.02	1.01	1.03	<0.001
≥65 years	1.01	1.01	1.02	<0.001

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

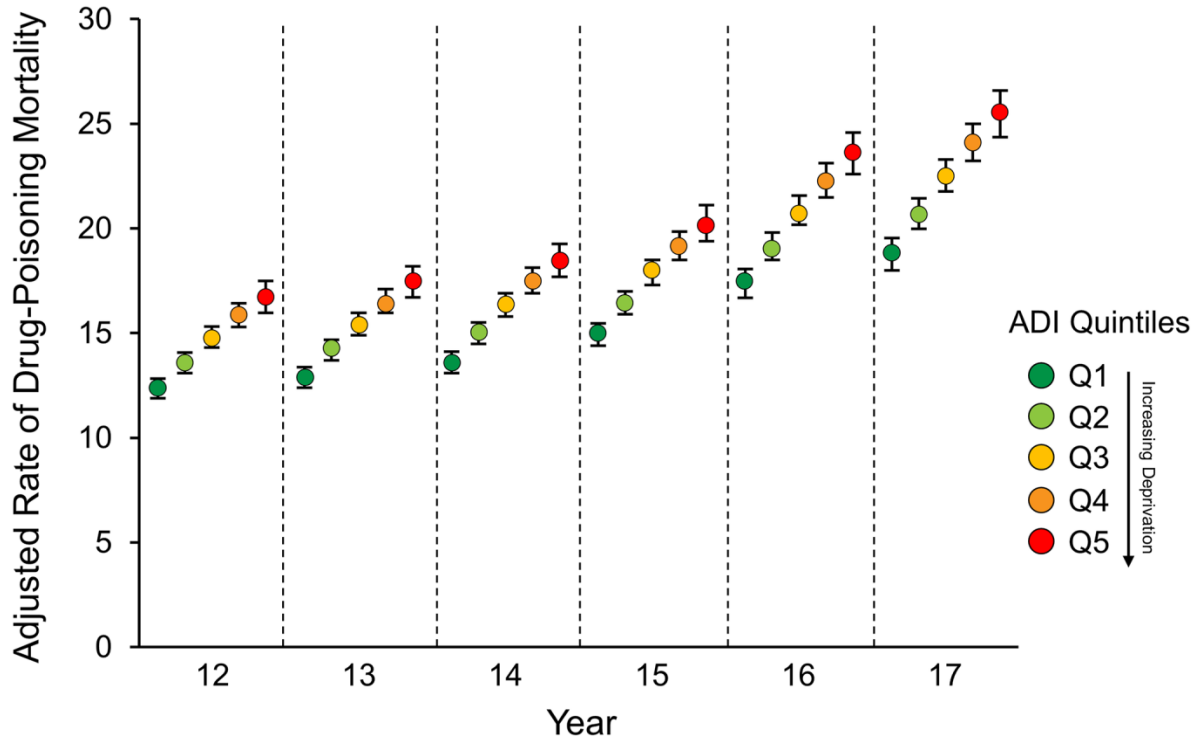

Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

Rates adjusted for year, age, race, and sex were calculated per 100,000 people.

Supplementary Appendix

The county-level ADI scores used for this study could not be included in a single table. The interested reader can information on how to request them online at https://www.mayo.edu/research/area-deprivation-index.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	14-15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	--
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	--
		(*e*) Describe any sensitivity analyses	--
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017

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Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017

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Abstract

Objective

To identify the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality.

Design, Setting, and Participants

For this retrospective cross-sectional study, we used the IQVIA Xponent data to capture opioid prescriptions and CDC National Vital Statistics System to assess drug-poisoning mortality. The area deprivation index (ADI) is a composite measure of social determinants of health comprised of 17 U.S. census indicators, spanning four socioeconomic domains. For all U.S. counties with available opioid prescription (2,712 counties) and drug-poisoning mortality (3,133 counties) data between 2012 and 2017, we used negative binomial regression to examine the association between quintiles of county-level ADI and rates of opioid prescriptions and drug-poisoning mortality adjusted for year, age, race, and sex.

Primary Outcome Measures

County-level opioid prescription fills and drug-poisoning mortality

Results

Between 2012-2017, overall rates of opioid prescriptions decreased from 96.6 to 72.2 per 100 people, while rates of drug-poisoning mortality increased from 14.3 to 22.8 per 100,000 people. Opioid prescription and drug-poisoning mortality rates were consistently higher with greater levels of deprivation. The risk of filling an opioid prescription was 72% higher, and the risk of drug-poisoning mortality was 36% higher, for most deprived compared to least deprived counties (both $p<0.001$).

Discussion

Counties with greater area-level deprivation have higher rates of filled opioid prescriptions and drug-poisoning mortality. Although opioid prescription rates declined across all ADI quintiles, rates of drug-poisoning mortality continued to rise proportionately in each ADI quintile. This underscores the need for individualized and targeted interventions that consider the deprivation of communities where people live.

Strengths and Limitations of this Study

- The ADI was standardized to ensure that all variables were scaled equally prior to weighting
- The work accounted for changes in demographics and ADI quintiles over time using yearly demographic estimates and census indicators from ACS
- This study is limited by potential reverse causality bias

Introduction

The drug epidemic has incurred great personal, societal, and economic costs,[1] driven, in part, by the widespread availability and use of prescription opioids.[2] In 2017, there were over 191 million dispensed opioid prescriptions,[3] approximately 47,600 opioid-related deaths,[4] and 70,237 drug-poisoning deaths[4] in the U.S. Overdose deaths continue to be the leading cause of injury-associated mortality and, over the past decade, have exceeded traffic fatalities.[5] To date, the primary strategy for reducing drug-poisoning mortality has been limiting the inappropriate use of prescription opioids; yet, the relentless rise in drug-related mortality continued to contribute to the decline of life expectancy in the U.S. since 2015.[6 7]

Understanding factors associated with drug-related mortality, and identifying at-risk populations, is critical to developing and targeting interventions aimed to reduce it. While the drug epidemic has impacted all segments of society, recent studies identified young and middle-aged white men as populations disproportionately affected by drug-poisoning mortality.[8 9] Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.[6 10] Similarly, the association between county-level poverty and higher rates of opioid prescribing was previously demonstrated in a 2014 study of disabled Medicare and Medicaid beneficiaries,[11] though this was not examined in the general U.S. population or linked directly to drug-related mortality. Nevertheless, addressing this epidemic will require sophisticated policy and public health approaches that consider a breadth of fundamental social determinants of health and cannot be fully captured by singular constructs such as age, race, sex, or income. This is especially important for a complex and multifaceted public health problem such as the drug use epidemic,

which is likely caused by a multitude of factors, affects all members of society, and is fueled by both prescription and illicit drugs.

A variety of policies and public health campaigns have been implemented in an effort to curb the epidemic of opioid overdoses and other drug-related morbidity and mortality, including the introduction of state prescription drug monitoring programs and the 2016 Centers for Disease Control and Prevention (CDC) opioid-prescribing guidelines.[2] Though most of the focus has been on prescription opioids, other non-opioid prescription and illicit drugs, such as heroin and fentanyl, have also contributed to the increase in drug-poisoning deaths[12] over the past two decades. Thus, the two outcomes – opioid prescribing and drug-poisoning mortality – should be tracked in parallel to assess the impact of limiting opioid use on overall drug mortality. Historically, areas with higher opioid prescription rates also experienced higher drug-related mortality,[11] but recent intensive policy and public health efforts aimed at reducing opioid prescribing may have inadvertently created a divergence between opioid prescribing and drug-poisoning mortality, particularly in areas where opioid use may be low, but mortality due to non-opioids remains high. There is therefore a need for a contemporary population-level evaluation of current trends in opioid prescribing practices and drug-related mortality to identify populations at greatest risk of harm from opioid and non-opioid misuse.

The area deprivation index (ADI) is a validated composite measure of social determinants of health that can be used to quantify socioeconomic disadvantage for granular census-based regions.[13] The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty, education, housing, and employment.[14] County-level indicators of economic disadvantage reflect

general resource availability, safety, education quality, employment opportunity, and social support,[15] all of which contribute to physical, emotional, and financial health of communities and their residents. Despite the potential individual and public health implications of area-level deprivation for a wide range of clinical and public health outcomes, composite area-based measures have not been widely used to inform healthcare policy or clinical practice due to previously inaccessible national geospatial data.[13] In this study, we address a pressing public health need and pursue a critical knowledge gap by examining the relationships between county-level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-level deprivation, this work contributes to the evidence base for informing clinical, public health, and policy interventions targeted at highest-need areas and populations.

Methods

Study Design

We retrospectively analyzed county-level summary measures of opioid prescriptions, drug-poisoning mortality, and population demographics from 2012 to 2017 using the IQVIA Xponent prescription database,[3] CDC National Vital Statistics System data,[16] and American Community Survey (ACS) estimates,[17] respectively. These data are publicly available and contain no identifiable information; thus, this work was exempt from Institutional Review Board approval.

Study population

All U.S. counties with opioid prescription and drug-poisoning mortality data available each year between 2012 and 2017 were included in the study sample. Counties without data for all six years of the study were excluded from the sample.

Patient Involvement

No patients or members of the public were directly involved in the design, conduct, reporting, or dissemination plans of the research.

American Community Survey Estimates

County demographic information necessary for ADI derivation was ascertained from 2012-2016 and 2013-2017 5-year ACS estimates; the 5-year estimates are single year estimates based on 60 months of data.[17] The ADI was derived using 17 county-level indicators and calculated separately each year for each U.S. county, as deprivation indices may change over time (Table S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the Census Application Programming Interface (API) to obtain data from the ACS.[18] The ACS is an annual survey conducted by the U.S. Census Bureau which randomly samples housing units and provides population-level estimates representative of the non-institutionalized U.S. population.[17] In-depth survey methodology is available from the Census Bureau.[17]

Outcomes

IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1, 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e.,

prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.; information on drugs filled by mail order pharmacies is unavailable.[3]

Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a county per 100 residents as estimated by the ACS.[3] Opioids, identified using National Drug Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone dispensed through maintenance therapy programs was not included.

The CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality rates between January 1, 2012 and December 31, 2017; these data were available for each year for 3,133 counties (Figure 2). The CDC performs hierarchical Bayesian methods with spatial and temporal random effects to generate adjusted county-level drug-poisoning mortality rates per 100,000 residents.[19] Drug-poisoning deaths related to opioid and non-opioid drugs were classified on the basis of International Classification of Diseases, Tenth Revision (ICD-10) codes and included deaths with unintentional (X40–X44), suicide (X60–X64), homicide (X85), and undetermined intent (Y10–Y14).[16]

Role of the Funding Source

The funding sources for this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and final responsibility for the decision to submit for publication.

ADI Derivation

We calculated modified ADI scores, using the Singh method,[14] for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach [14 20 21] and missing values were substituted using single imputation. All variables were transformed to a rate per capita for the county. To improve upon published ADI methodologies and prevent distortion of ADI by larger continuous variables such as income, we standardized these proportions to a mean of 0 and standard deviation of 1, thereby ensuring that all variables in the modified ADI were scaled equally prior to weighting. Each variable was then multiplied by its respective weight obtained from the factor score coefficient (Table S1), and the 17 weighted measures were summed for each county to obtain the base score. Base scores were then standardized to a mean of 100 and standard deviation of 20. ADI was divided into quintiles for all analyses, with higher ADI values (quintile 5) representing greater deprivation.

Statistical Analysis

We used negative binomial regression to examine the relationships between ADI and opioid prescription rates and drug-poisoning mortality from 2012 to 2017, controlling for over-dispersion of outcome estimates and county population size using an offset term. We used Huber-White robust standard errors clustered at the county level to adjust standard errors for repeated county observations and variation. Independent variables in the models included ADI

quintile, percent county-level estimates for age, percent white, percent male, and year. The specific independent variables were chosen based on previous literature suggesting an area-level association between those demographic indicators and greater opioid use or drug mortality.[6 8-11] Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all years.[22]

Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata 15.1 (StataCorp LLC, College Station, TX). Opioid prescription rates, drug-poisoning mortality, and ADI at the county-level were visually represented with geographic information system (GIS) maps created in ArcMap 10.7 using Census TIGER/Line shapefiles.

Results

Association of Area-Level Deprivation with Opioid Prescription Rates

Opioid prescription rates were significantly higher among counties in the highest ADI quintile (Q5: most deprived) compared to those in the lowest quintile. The risk of filling an opioid prescription was 72% higher in ADI Q5 than Q1 (IRR, 1.72; 95% CI [1.63, 1.82]; p<0.001) (Table S2).

Overall, rates of filled opioid prescriptions declined over time, from 96.6 per 100 people in 2012 to 72.2 per 100 people in 2017. Analogously, the percentage and total number of counties with more than 1 opioid prescription per resident steadily declined over time: 40.3% (n=1093) in 2012, 38.6% (n=1047) in 2013, 36.9% (n=1001) in 2014, 31.5% (n=855) in 2015, 26.7% (n=723) in 2016, and 17.6% (n=477) in 2017.

Rates of opioid prescriptions appear to decrease between 2012 and 2017 within each ADI quintile (Figure 4). The adjusted prescription rate for counties in the most deprived ADI quintile (Q5) decreased from 115.9 prescriptions per 100 people in 2012 to 86.6 in 2017 (IRR 0.75, 95% CI [0.73, 0.76]; p<0.001) (Table S2). Adjusted rates calculated from the predicted margins suggest that each successively less deprived ADI quintile displayed a smaller decrease in prescription rate. Although the absolute opioid prescription rate decrement was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles.

Association of Area-Level Deprivation with Drug-Poisoning Mortality

In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62]; p<0.001) between 2012 and 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28, 1.44]; p<0.001) (Table 1). The association between ADI and drug-poisoning mortality appeared to be linear with rising deprivation resulting in higher rates of drug-poisoning mortality (Figure S1).

Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality

As shown in Figures 1-3, there were consistent and strongly demarcated spatial differences in both outcomes across ADI quintiles. The highest opioid prescription rates were seen in counties in southern states and Appalachia. Southwestern U.S. and Appalachia also saw high drug-

poisoning mortality. There were no major visual geospatial changes in the patterns of deprivation, opioid prescriptions, or drug-poisoning mortality during the study period.

Discussion

Social determinants of health underlie many causes of the ongoing epidemic and need to be considered to when developing and implementing interventions seeking to address it. In this study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may be a powerful tool for identifying areas of greatest need as well as informing and contextualizing future public health and policy interventions. We also found that while opioid prescriptions decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them, persistent disparities in both prescription opioid use and drug-poisoning mortality remain. Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-related mortality than less deprived counties. Moreover, despite reductions in opioid prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and 2017, reinforcing the growing impact of drugs obtained outside of the health care system and missed opportunities to tailor and target interventions to those at highest risk for harm. By considering contextual factors and developing customized approaches using area-level indicators, harm reduction strategies could yield a more sustainable and meaningful impact for the communities they serve.

A number of state and federal programs have been introduced over the past decade to increase public awareness, decrease access to prescription opioids, improve opioid use disorder treatment,

and expand access to naloxone for overdose reversal.[23] The interventions targeting opioid prescribing (i.e. state controlled substance monitoring programs) likely contributed to the decline in rates of opioid prescriptions between 2012 and 2017, but did not rectify the disparities associated with drug-poisoning deaths. Persistent disparities in opioid prescription rates may be attributed higher prevalence of comorbidities and disability in deprived areas,[24] difficulty accessing medication for opioid use disorder,[25] and a different experience of pain in the setting of lower health literacy[26] and socioeconomic distress. Further efforts should focus on identifying alternative pain management strategies that are effective, affordable, and accessible to all who need them, irrespective of where they live. At present, access to and reimbursement for non-pharmacologic pain management modalities remains limited,[27] which may further exacerbate disparities in opioid use and misuse among disadvantaged U.S. adults.

Although opioid prescribing rates declined over time, rates of drug-poisoning mortality appeared to rise steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too, was higher in the most deprived counties. This finding underscores the complexity of the opioid and drug use epidemic. First, current opioid prescribing rates are not the sole driver of drug-poisoning mortality, as mortality has continued to rise while prescription rates have declined. Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates of addiction due to overprescribing, all play an important role in drug-related deaths.[2 28] Second, high rates of drug-poisoning mortality result not only from greater availability of drugs, but also from greater probability of death with drug use. People living in deprived areas often have inadequate access to substance use disorder treatment and medications[29-33] and limited access to healthcare,[34] resulting from failure to expand Medicaid coverage, inadequate reimbursement for treatment,[35 36]

and variation in types of providers able to prescribe and manage treatment.[37] Third, as a result of structural violence and barriers, individuals living in deprived communities may be less likely to seek medical treatment due to stigma and criminalization leading to higher rates of drug-poisoning mortality.[38] Reducing mortality will therefore require a wide range of interventions in addition to limiting opioid prescribing, including improving availability of and access to nonopioid pain management, social services, mental health, and substance use treatment.

Consistent with prior literature, we found that higher proportions of male residents within a county were protective against both opioid prescriptions[6 39] and drug-poisoning mortality.[40] Women are more likely than men to be prescribed opioid medications and to be co-prescribed other medications that increase overdose risk;[40-42] women are also less likely to enter substance use disorder treatment programs.[43] Counties with fewer men may also reflect larger systemic issues such as higher incarceration rates among males.[38] Incarceration not only interferes with the ability to seek substance abuse treatment, but is strongly associated with family disruption, unemployment, neighborhood decline, chronic economic hardship, and importantly, increased mortality from drug-use disorders.[38]

Our study has several key strengths, making it relevant and actionable to public health professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses highlighted the importance of understanding county resources and economic conditions that may affect both use of and mortality related to opioids and other drugs. We also identified the degree of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and

accounting for changes in demographics and ADI quintiles over time using yearly demographic estimates and census indicators from ACS, which has not been done to date. This is also the first study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless, our findings are limited by potential reverse causality bias and the inability to identify causal relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not capture all prescription opioids; methadone dispensed through maintenance therapy programs and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly, the standard errors may be impacted by potential spatial autocorrelation and uncertainty in the modeled outcome rates.

Addressing the drug crisis requires multifaceted interventions that address the wide range of biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.[2] Our work demonstrates the need to consider local factors when developing interventions related to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed by indicators such as ADI to identify areas that may benefit from additional monitoring, specific resources, and tailored interventions.

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Contributors: SK and NS conceived and designed the study; SK and JI acquired data; SK, RM, SC, LR analyzed/interpreted the data; NS, MJ, JI, and RG supervised data analysis. All authors refined the various versions of the full paper and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. SK and ND are the guarantors.

Competing Interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: Dr. Jeffery's spouse owns shares in Vireo Health.

Ethical Approval: Not required.

Data Sharing: All data are publicly available. Statistical code and datasets are available from the corresponding author at kurani.shaheen@mayo.edu or can be obtained from the following websites: https://www.census.gov/programs-surveys/acs; https://www.cdc.gov/nchs/data-visualization/drug-poisoning-mortality/index.htm; https://www.cdc.gov/drugoverdose/maps/rxcounty2017.html

SK and NS affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; no important aspects of the study have been omitted and any discrepancies from the study as planned have been explained.

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Figure 1. Opioid prescription rates across U.S. counties from 2012-2017.

2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017.

3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017.

ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017.

Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.

Table 1: Factors associated with drug-poisoning mortality in the U.S., 2012-2017. Negative binomial regression analysis examined the risk of higher rates of drug-poisoning mortality in 3,133 of 3,142 U.S. counties with available mortality data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		P-VALUE
Year				
2012	Ref.			
2013	1.05	1.04	1.05	<0.001
2014	1.11	1.10	1.12	<0.001
2015	1.23	1.22	1.25	<0.001
2016	1.45	1.43	1.48	<0.001
2017	1.59	1.56	1.62	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.10	1.04	1.16	<0.001
3	1.20	1.14	1.26	<0.001
4	1.28	1.22	1.35	<0.001
5	1.36	1.28	1.44	<0.001
Sex, percentage				
Male	0.97	0.96	0.97	<0.001
Race/ethnicity, percentage*				
White	1.05	1.04	1.07	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.03	<0.001
45-64 years	1.06	1.05	1.07	<0.001
≥65 years	1.01	1.00	1.01	0.04

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

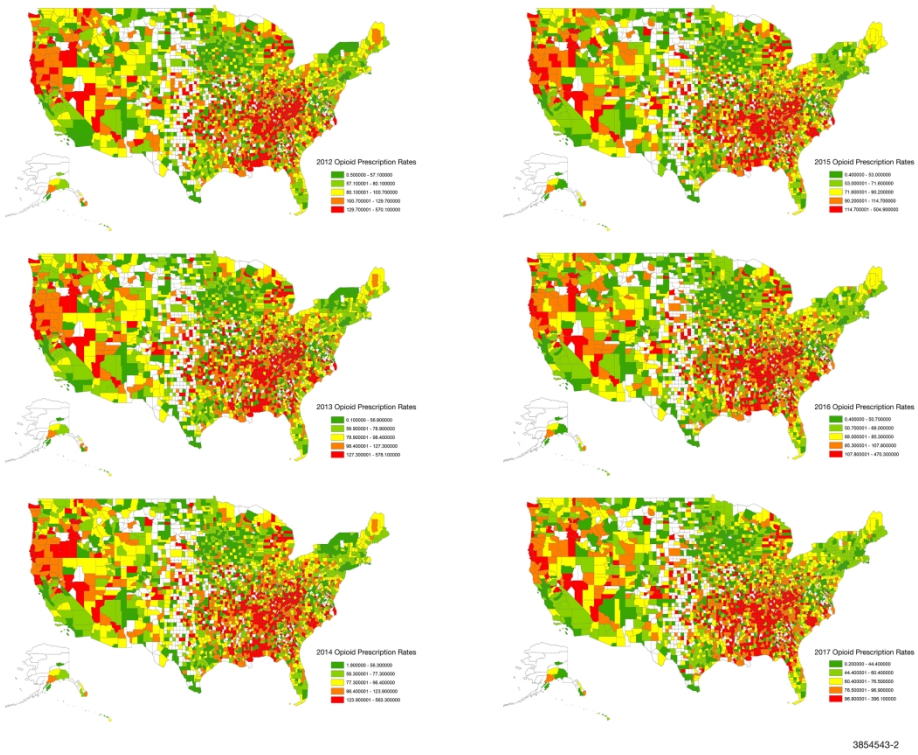

Figure 1. Opioid prescription rates across U.S. counties from 2012-2017.2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

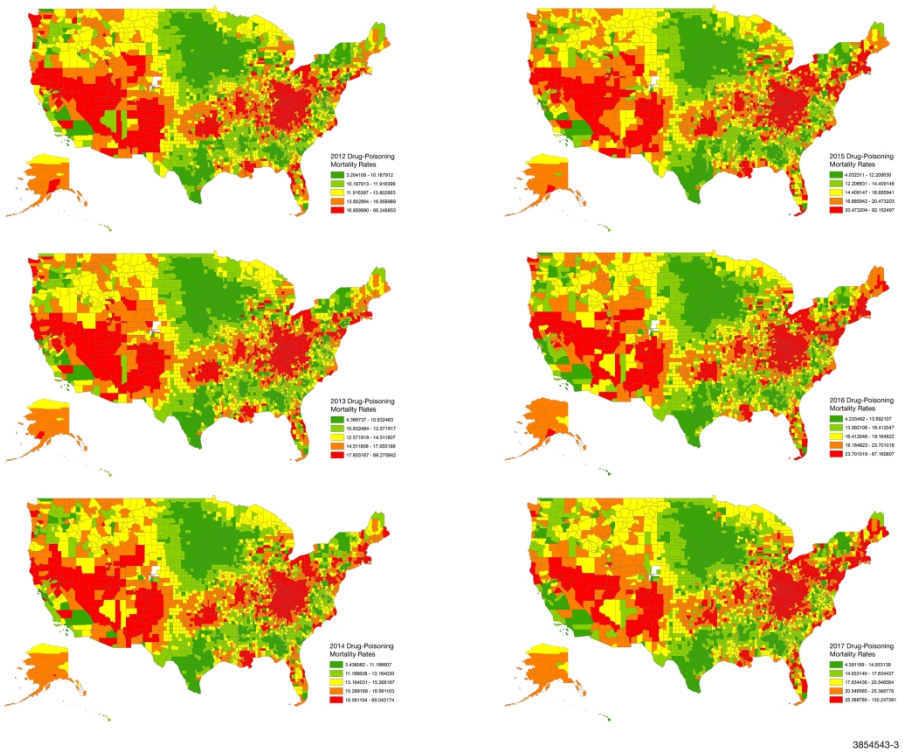

Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017.3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

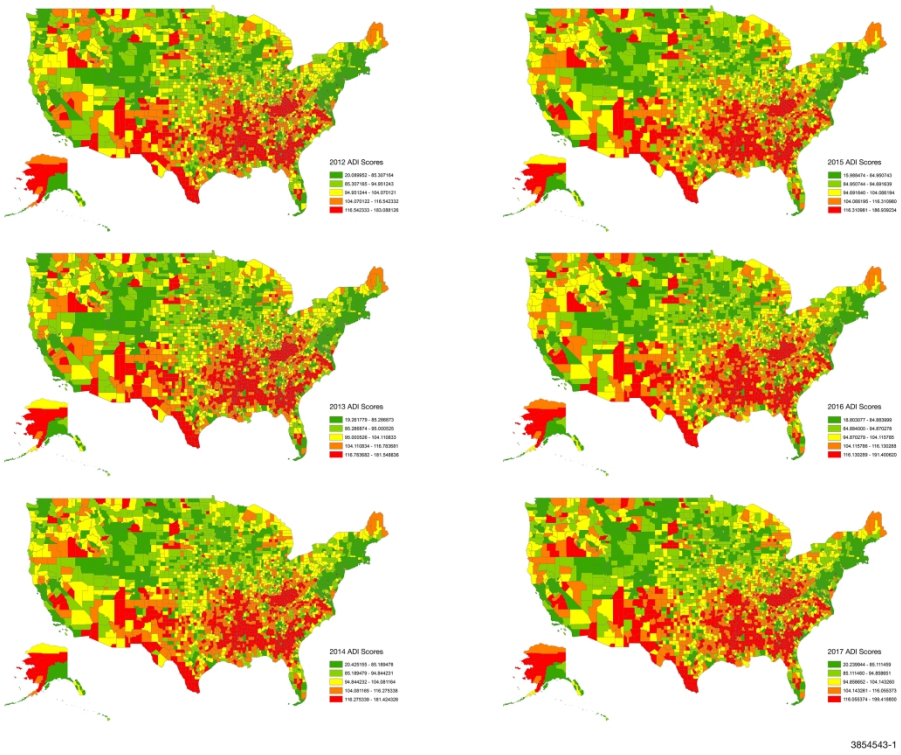

Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017.ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

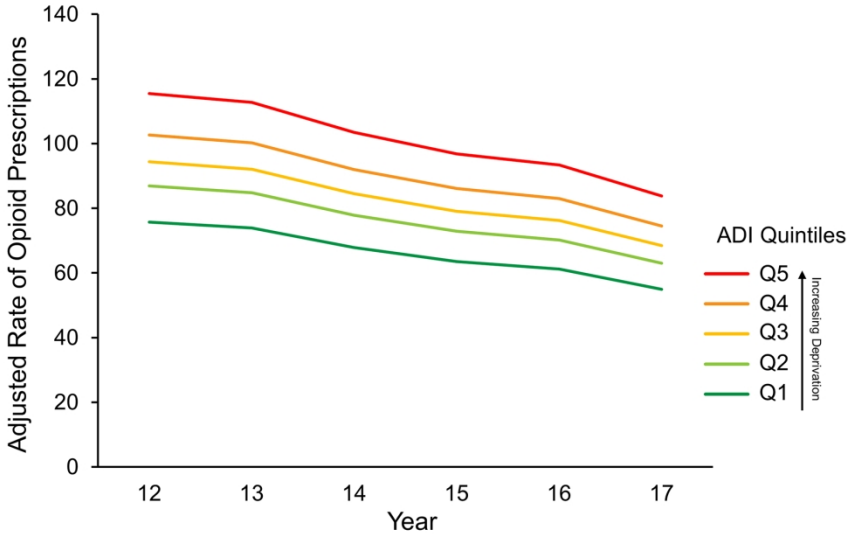

Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017. Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.

177x133mm (300 x 300 DPI)

Supplementary Figures and Tables

Table S1: American Community Survey census indicators, table references, and factor score coefficients from 2012-2017

US Census Indicator	2012-2017 ACS Table Reference, 5-year estimates	Factor Score Coefficient 2012	Factor Score Coefficient 2013	Factor Score Coefficient 2014	Factor Score Coefficient 2015	Factor Score Coefficient 2016	Factor Score Coefficient 2017
Median family income	B19013	-0.16638	-0.17221	-0.16295	-0.16102	-0.16087	-0.16993
Income disparity	B19001	0.07705	0.07615	0.08298	0.08417	0.08019	0.06799
Families below poverty level	B17010	0.11021	0.12182	0.12629	0.12707	0.12555	0.12298
% population below 150% poverty threshold	C17002	0.22177	0.21806	0.21815	0.22455	0.22914	0.23659
Single parent household with dependents <18	B23008	0.03544	0.03803	0.03658	0.03698	0.03817	0.04165
Households without a motor vehicle	B25044	0.0546	0.05144	0.05392	0.05365	0.05666	0.05646
Households without a telephone	B25043	0.01257	0.00894	0.00725	0.00648	0.00685	0.00892
Occupied housing units without complete plumbing	B25016	0.03533	0.03295	0.03167	0.03	0.02692	0.02963
Owner occupied housing units	B25003	-0.01012	-0.00841	-0.00915	-0.00855	-0.00888	-0.00733
Households with >1 person per room	B25014	0.02759	0.03006	0.02886	0.03246	0.03546	0.03747
Median monthly mortgage	B25088	-0.15057	-0.14344	-0.1461	-0.13736	-0.13578	-0.13004
Median gross rent	B25064	-0.05158	-0.05216	-0.05079	-0.05359	-0.05922	-0.06295
Median home value	B25077	-0.0649	-0.0689	-0.06525	-0.07038	-0.07345	-0.0749

Employed persons ≥16 in white collar occupation	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
Civilian labor force unemployed (aged ≥16)	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
Population aged ≥25 with <9yr education	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
Population aged ≥25 with at least a high school education	B15003	-0.23235	-0.22358	-0.22647	-0.22431	-0.22112	-0.21015

Table S2: Factors associated with opioid prescriptions in the U.S, 2012-2017

Negative binomial regression analysis examined the risk of higher rates of opioid prescriptions in 2,712 of 3,142 U.S. counties with available opioid prescribing data. Independent variables included year, ADI quintile, percent male, percent white, and age.

	IRR	95% CI		p-value
Year				
2012	Ref.			
2013	0.98	0.97	0.98	<0.001
2014	0.95	0.94	0.96	<0.001
2015	0.89	0.88	0.90	<0.001
2016	0.84	0.83	0.85	<0.001
2017	0.75	0.73	0.76	<0.001
Area Deprivation Index, quintile				
1	Ref.			
2	1.16	1.11	1.21	<0.001
3	1.38	1.32	1.44	<0.001
4	1.57	1.51	1.65	<0.001
5	1.72	1.63	1.82	<0.001
Sex, percentage				
Male	0.94	0.94	0.95	<0.001
Race/ethnicity, percentage*				
White	1.04	1.03	1.06	<0.001
Age, percentage				
18-44 years	1.03	1.02	1.04	<0.001
45-64 years	1.02	1.01	1.03	<0.001
≥65 years	1.01	1.01	1.02	<0.001

* Percent white variable was scaled by 10 in the model (i.e., per 10% change)

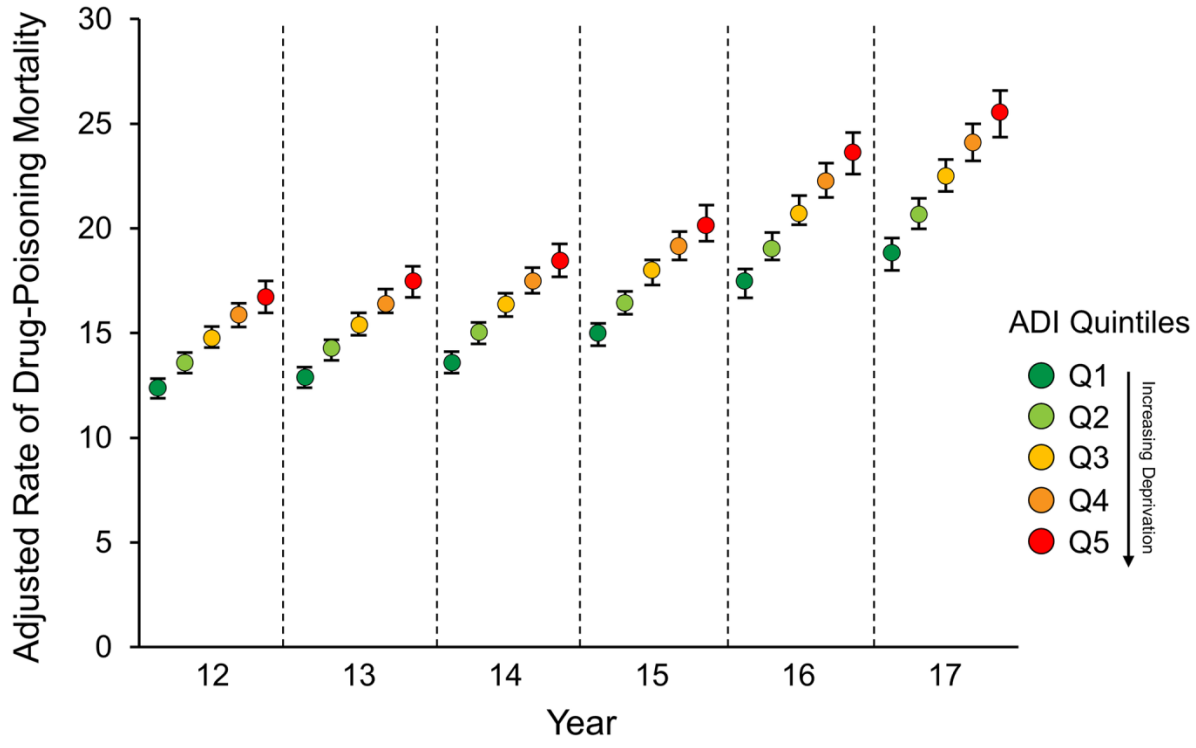

Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

Rates adjusted for year, age, race, and sex were calculated per 100,000 people.

Supplementary Appendix

The county-level ADI scores used for this study could not be included in a single table. The interested reader can information on how to request them online at https://www.mayo.edu/research/area-deprivation-index.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	14-15
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	--
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	--
		(*e*) Describe any sensitivity analyses	--
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	--
		(c) Consider use of a flow diagram	--
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	10-11
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	11

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-11
		(*b*) Report category boundaries when continuous variables were categorized	10
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	--
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	--
Discussion			
Key results	18	Summarise key results with reference to study objectives	11-12
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	14-15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	16

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.