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# BMJ Open

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

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3 **Place, Poverty, and Prescriptions: Using Area Deprivation Index to Assess Opioid Use and**  
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5 **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

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

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## Introduction

The drug epidemic has incurred great personal, societal, and economic costs,<sup>1</sup> driven, in part, by the widespread availability and use of prescription opioids.<sup>2</sup> In 2016, there were over 200 million dispensed opioid prescriptions,<sup>3</sup> approximately 32,445 prescription opioid-related deaths,<sup>4</sup> and more than 63,600 drug-poisoning deaths<sup>5</sup> 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.<sup>6</sup> 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.<sup>7 8</sup>

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.<sup>9 10</sup> Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.<sup>7 11</sup> 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,<sup>12</sup> 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,



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3 which is likely caused by a multitude of factors, affects all members of society, and is fueled by  
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5 both prescription and illicit drugs.  
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10 A variety of policies and public health campaigns have been implemented in an effort to curb the  
11 epidemic of opioid overdoses and other drug-related morbidity and mortality, including the  
12 introduction of state prescription drug monitoring programs and the 2016 Centers for Disease  
13 Control and Prevention (CDC) opioid-prescribing guidelines.<sup>2</sup> Though most of the focus has  
14 been on opioids, other non-opioid prescription and illicit drugs, such as heroin and fentanyl, have  
15 also contributed to the increase in drug-poisoning deaths<sup>13</sup> over the past two decades. Thus, the  
16 two outcomes – opioid prescribing and drug-poisoning mortality – should be tracked in parallel  
17 to assess the impact of limiting opioid use on overall drug mortality. Historically, areas with  
18 higher opioid prescription rates also experienced higher drug-related mortality,<sup>12</sup> but recent  
19 intensive policy and public health efforts aimed at reducing opioid prescribing may have  
20 inadvertently created a divergence between opioid prescribing and drug-poisoning mortality,  
21 particularly in areas where opioid use may be low, but mortality due to non-opioids remains  
22 high. There is therefore a need for a contemporary population-level evaluation of current trends  
23 in opioid prescribing practices and drug-related mortality to identify populations at greatest risk  
24 of harm from opioid and non-opioid misuse.  
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47 The area deprivation index (ADI) is a validated composite measure of social determinants of  
48 health that can be used to quantify socioeconomic disadvantage for granular census-based  
49 regions.<sup>14</sup> The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty,  
50 education, housing, and employment.<sup>15</sup> County-level indicators of economic disadvantage reflect  
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3 general resource availability, safety, education quality, employment opportunity, and social  
4 support,<sup>16</sup> all of which contribute to physical, emotional, and financial health of communities and  
5 their residents. Despite the potential individual and public health implications of area-level  
6 deprivation for a wide range of clinical and public health outcomes, composite area-based  
7 measures have not been widely used to inform healthcare policy or clinical practice due to  
8 previously inaccessible national geospatial data.<sup>14</sup> In this study, we address a pressing public  
9 health need and pursue a critical knowledge gap by examining the relationships between county-  
10 level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in  
11 the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-  
12 level deprivation, this work contributes to the evidence base for informing clinical, public health,  
13 and policy interventions targeted at highest-need areas and populations.  
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## 30 **Methods**

### 31 **Study Design**

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

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3 All U.S. counties with opioid prescription and drug-poisoning mortality data available each year  
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5 between 2012 and 2017 were included in the study sample. Counties without data for all six  
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7 years of the study were excluded from the sample.  
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### 10 11 12 Patient Involvement

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14 No patients or members of the public were directly involved in the design, conduct, reporting, or  
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16 dissemination plans of the research.  
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### 19 20 21 ADI Derivation

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23 County demographic information necessary for ADI derivation was ascertained from 2012-2016  
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25 and 2013-2017 5-year ACS estimates.<sup>17</sup> The ADI was derived using 17 county-level indicators  
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27 and calculated separately each year for each U.S. county, as deprivation indices may change over  
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29 time (Table S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the  
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31 Census Application Programming Interface (API) to obtain data from the ACS.<sup>18</sup> The ACS is an  
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33 annual survey conducted by the U.S. Census Bureau which randomly samples housing units and  
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35 provides population-level estimates representative of the non-institutionalized U.S. population.<sup>17</sup>  
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37 In-depth survey methodology is available from the Census Bureau.<sup>17</sup>  
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### 44 45 Outcomes

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47 IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1,  
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49 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by  
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51 approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e.,  
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53 prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or  
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3 cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.;  
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5 information on drugs filled by mail order pharmacies is unavailable.<sup>3</sup>  
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10 Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual  
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12 rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a  
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14 county per 100 residents as estimated by the ACS.<sup>3</sup> Opioids, identified using National Drug  
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16 Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone,  
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18 morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone  
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20 dispensed through maintenance therapy programs was not included.  
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26 CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality  
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28 rates between January 1, 2012 and December 31, 2017; these data were available for each year  
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30 for 3,133 counties (Figure 2). Hierarchical Bayesian methods with spatial and temporal random  
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32 effects generated adjusted county-level drug-poisoning mortality rates per 100,000 residents.<sup>19</sup>  
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34 Drug-poisoning deaths were classified on the basis of International Classification of Diseases,  
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36 Tenth Revision (ICD-10) codes and included deaths with unintentional (X40–X44), suicide  
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38 (X60–X64), homicide (X85), and undetermined intent (Y10–Y14).<sup>5</sup>  
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### 45 **Role of the Funding Source**

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47 The funding sources for this study had no role in study design, data collection, data analysis, data  
48  
49 interpretation, or writing of the report. The corresponding author had full access to all data in the  
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51 study and final responsibility for the decision to submit for publication.  
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### Statistical Analysis

We calculated modified ADI scores, using the Singh method,<sup>15</sup> for all 3,142 counties in the U.S. using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach<sup>15 20 21</sup> 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.<sup>7 9-12</sup> 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

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3 smaller decrease in prescription rate. Although the absolute opioid prescription rate decrement  
4 was largest in ADI Q5, the proportion of the decrease was similar across all ADI quintiles.  
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### 10 **Drug-Poisoning Mortality across Quintiles of ADI and over Time**

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12 In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning  
13 mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62];  $p < 0.001$ ) between 2012 and  
14 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-  
15 poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28,  
16 1.44];  $p < 0.001$ ) (Table 1). However, the association between ADI and drug-poisoning mortality  
17 was not linear. Instead, the increase in drug-poisoning mortality with rising deprivation reached a  
18 threshold between Q2 and Q3. The adjusted rates of drug-poisoning mortality were similar  
19 between counties in ADI Q1 and Q2 (40% least deprived counties), and significantly lower than  
20 counties in ADI Q3 to Q5 (60% most deprived counties) (Figure S1).  
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### 35 **Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality**

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

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3 Social determinants of health underlie many causes of the ongoing epidemic and need to be  
4 considered to when developing and implementing interventions seeking to address it. In this  
5 study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated  
6 with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may  
7 be a powerful tool for identifying areas of greatest need as well as informing and contextualizing  
8 future public health and policy interventions. We also found that while opioid prescriptions  
9 decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them,  
10 persistent disparities in both prescription opioid use and drug-poisoning mortality remain.  
11 Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-  
12 related mortality than less deprived counties. Moreover, despite reductions in opioid  
13 prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and  
14 2017, reinforcing the growing impact of drugs obtained outside of the health care system and  
15 missed opportunities to tailor and target interventions to those at highest risk for harm. By  
16 considering contextual factors and developing customized approaches using area-level  
17 indicators, harm reduction strategies could yield a more sustainable and meaningful impact for  
18 the communities they serve.

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



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

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11 Although opioid prescribing rates declined over time, rates of drug-poisoning mortality rose  
12 steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too, was  
13 consistently higher in the most deprived counties. We also observed a threshold effect of ADI on  
14 drug-poisoning mortality, with 60% of most deprived counties experiencing significantly higher  
15 drug-poisoning mortality rates than the remaining 40% of counties. This finding underscores the  
16 complexity of the opioid and drug use epidemic. First, current opioid prescribing rates are not the  
17 sole driver of drug-poisoning mortality, as mortality has continued to rise while prescription rates  
18 have declined. Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates  
19 of addiction due to overprescribing, all play an important role in drug-related deaths.<sup>2 28</sup> Second,  
20 high rates of drug-poisoning mortality result not only from greater availability of drugs, but also  
21 from greater probability of death with drug use. People living in deprived areas often have  
22 inadequate access to substance use disorder treatment and medications<sup>29-33</sup> and limited access to  
23 healthcare,<sup>34</sup> resulting from failure to expand Medicaid coverage, inadequate reimbursement for  
24 treatment,<sup>23 35</sup> and variation in types of providers able to prescribe and manage treatment.<sup>36</sup>  
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26 Third, as a result of structural violence and barriers, individuals living in deprived communities  
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3 may be less likely to seek medical treatment due to stigma and criminalization leading to higher  
4 rates of drug-poisoning mortality.<sup>37</sup> Reducing mortality will therefore require a wide range of  
5 interventions in addition to limiting opioid prescribing, including improving availability of and  
6 access to nonopioid pain management, social services, mental health, and substance use  
7 treatment.  
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17 Consistent with prior literature, we found that higher proportions of male residents within a  
18 county were protective against both opioid prescriptions<sup>7 38</sup> and drug-poisoning mortality.<sup>39</sup>

19 Women are more likely than men to be prescribed opioid medications and to be co-prescribed  
20 other medications that increase overdose risk;<sup>39-41</sup> women are also less likely to enter substance  
21 use disorder treatment programs.<sup>42</sup> Counties with fewer men may also reflect larger systemic  
22 issues such as higher incarceration rates among males.<sup>37</sup> Incarceration not only interferes with  
23 the ability to seek substance abuse treatment, but is strongly associated with family disruption,  
24 unemployment, neighborhood decline, chronic economic hardship, and importantly, increased  
25 mortality from drug-use disorders.<sup>37</sup>  
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40 Our study has several key strengths, making it relevant and actionable to public health  
41 professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses  
42 highlighted the importance of understanding county resources and economic conditions that may  
43 affect both use of and mortality related to opioids and other drugs. We also identified the degree  
44 of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to  
45 curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and  
46 accounting for changes in demographics and ADI quintiles over time using yearly demographic  
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3 estimates and census indicators from ACS, which has not been done to date. This is also the first  
4 study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying  
5 it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid  
6 prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless,  
7 our findings are limited by potential reverse causality bias and the inability to identify causal  
8 relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not  
9 capture all prescription opioids; methadone dispensed through maintenance therapy programs  
10 and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly,  
11 given the use of ACS survey data, our study is susceptible to non-response and imputation bias.  
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26 Addressing the drug crisis requires multifaceted interventions that address the wide range of  
27 biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving  
28 problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing  
29 are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.<sup>2</sup>  
30 Our work demonstrates the need to consider local factors when developing interventions related  
31 to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed  
32 by indicators such as ADI to identify areas that may benefit from additional monitoring, specific  
33 resources, and tailored interventions.  
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## Acknowledgements

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

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26 **Competing Interests:** All authors have completed the ICMJE uniform disclosure form at  
27 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: Dr. Jeffery's spouse owns shares in Vireo  
28 Health.

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33 **Ethical Approval:** Not required.

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**Data Sharing:** All data are publicly available. Statistical code and datasets are available from  
the corresponding author at [kurani.shaheen@mayo.edu](mailto: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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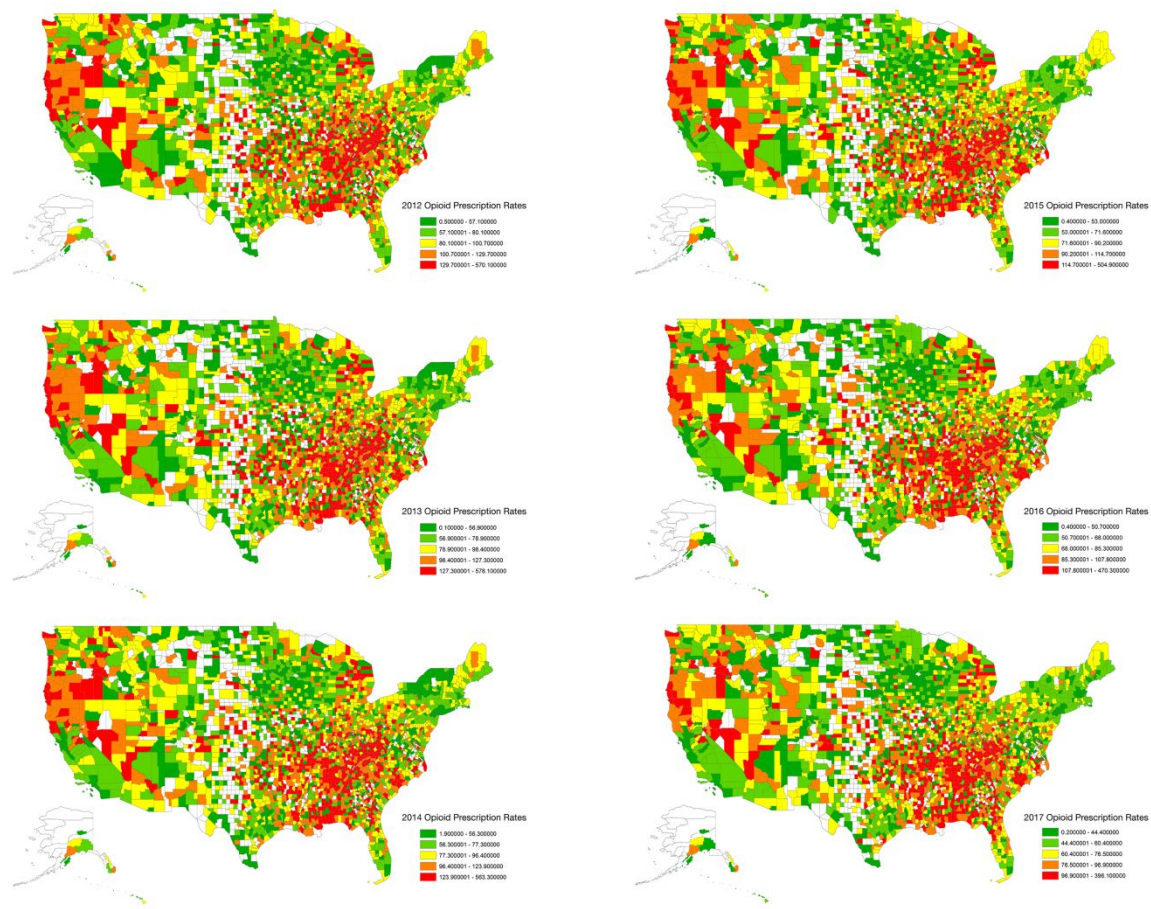
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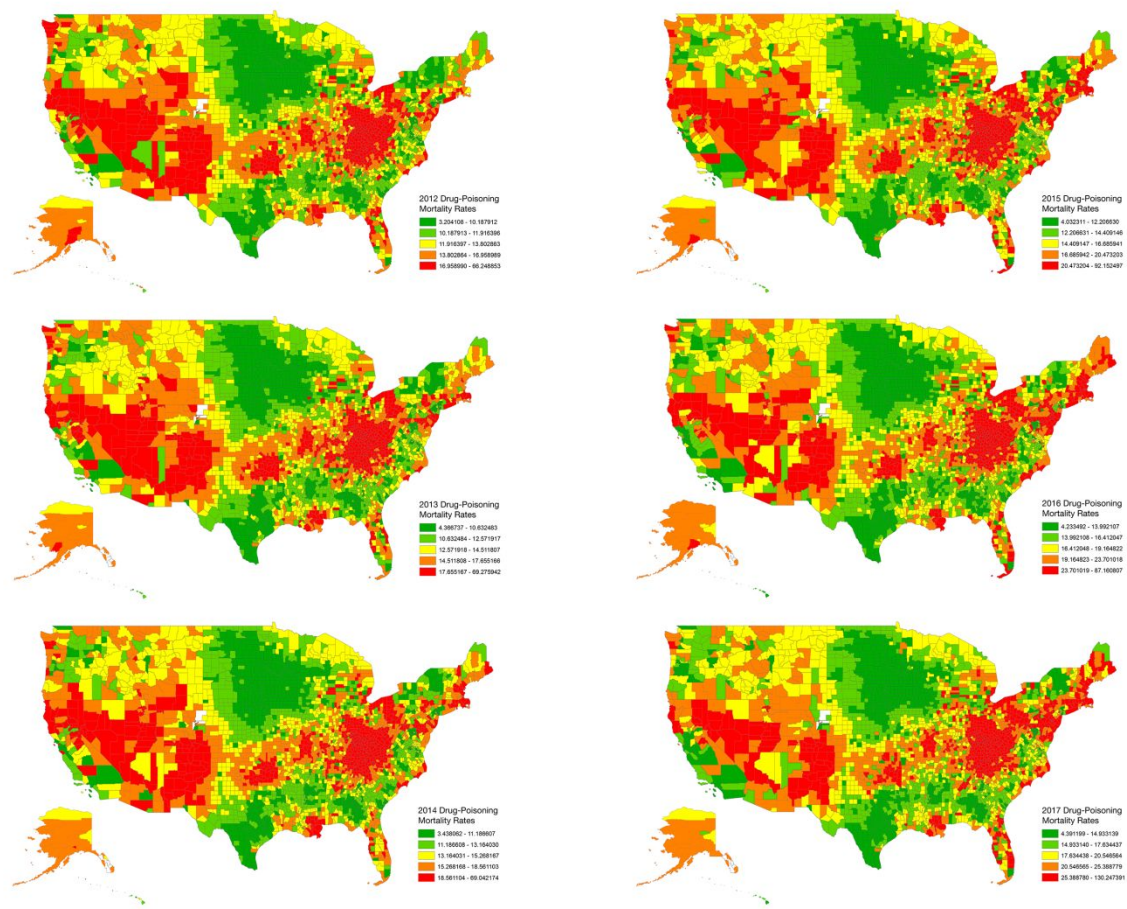
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**Figure 1. Opioid prescription rates across U.S. counties from 2012-2017.**  
 2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.



**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.

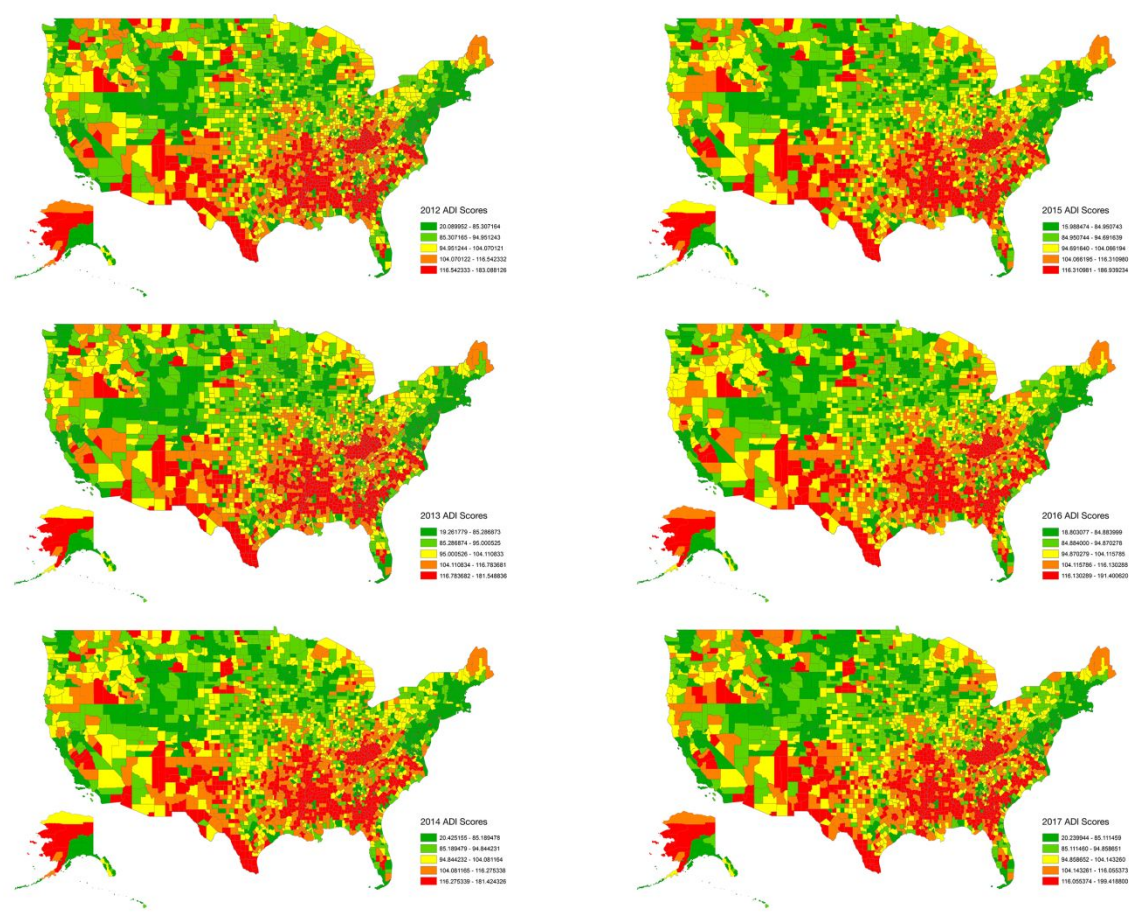
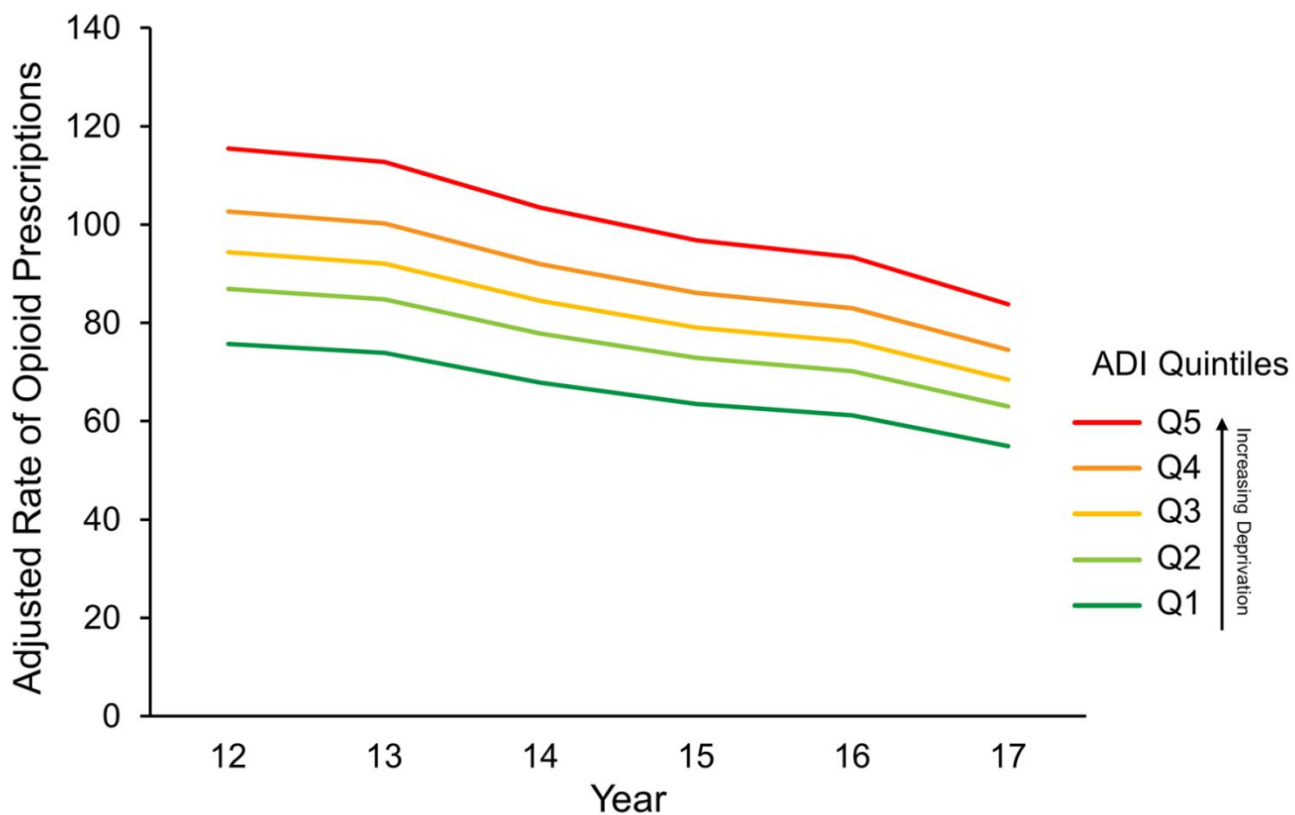


Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017.

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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.97	0.96	0.97	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.05	1.04	1.07	<0.001
<b>Age, percentage</b>				
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

<b>Employed persons ≥16 in white collar occupation</b>	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
<b>Civilian labor force unemployed (aged ≥16)</b>	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
<b>Population aged ≥25 with &lt;9yr education</b>	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
<b>Population aged ≥25 with at least a high school education</b>	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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.94	0.94	0.95	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.04	1.03	1.06	<0.001
<b>Age, percentage</b>				
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)



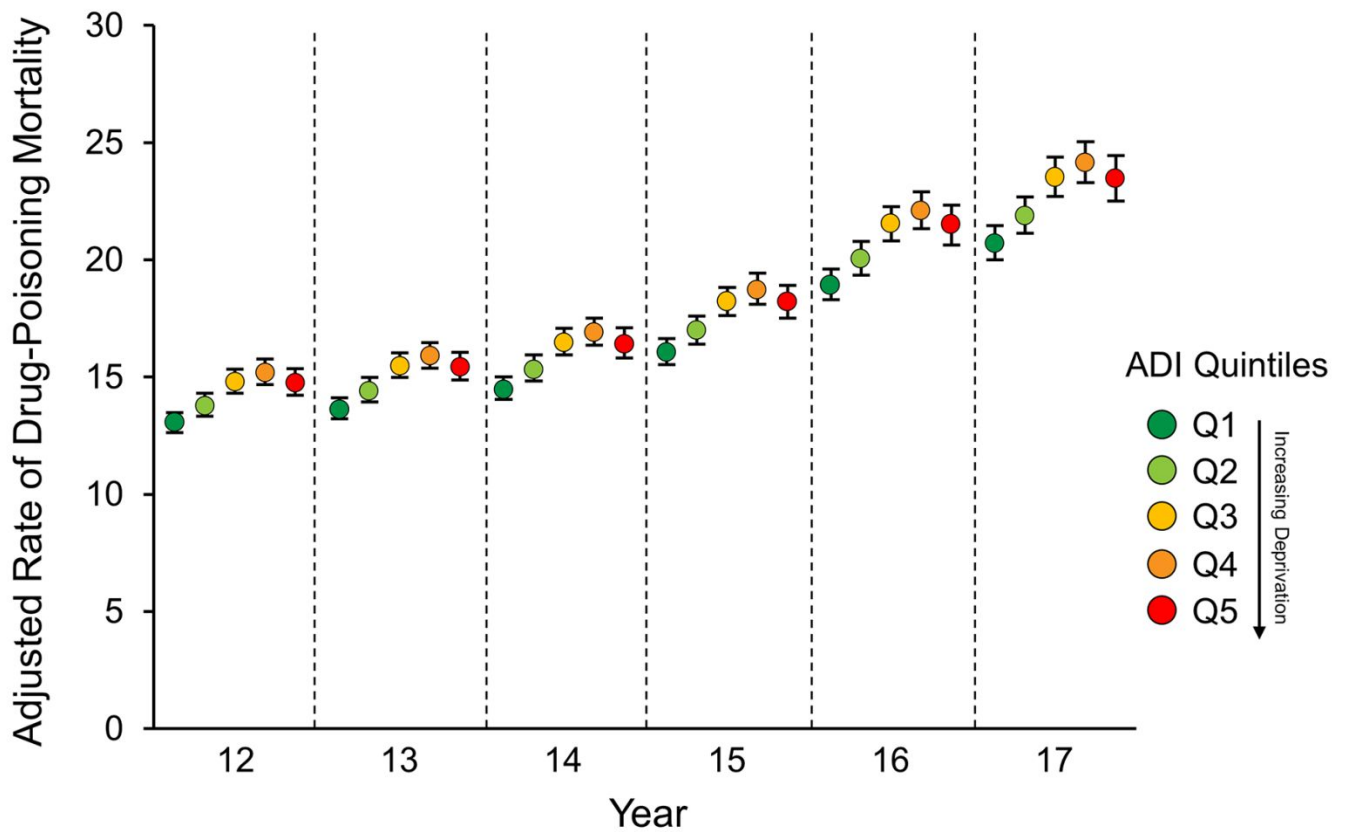


Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

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>.

For peer review only

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	--
<b>Results</b>			
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

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2	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
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6			(b) Report category boundaries when continuous variables were categorized
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9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
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11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
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14	<b>Discussion</b>		
15	Key results	18	Summarise key results with reference to study objectives
16			11-
17			12
18	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
19			14-
20			15
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22			11-
23			15
24	Generalisability	21	Discuss the generalisability (external validity) of the study results
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26			
27	<b>Other information</b>		
28	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
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\*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](http://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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3 **Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index**  
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5 **to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017**  
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7

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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



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2  
3 Counties with greater area-level deprivation have higher rates of filled opioid prescriptions and  
4  
5 drug-poisoning mortality. Although opioid prescription rates declined across all ADI quintiles,  
6  
7 rates of drug-poisoning mortality continued to rise proportionately in each ADI quintile. This  
8  
9 underscores the need for individualized and targeted interventions that consider the deprivation of  
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11 communities where people live.  
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For peer review only

### 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,<sup>1</sup> driven, in part, by the widespread availability and use of prescription opioids.<sup>2</sup> In 2017, there were over 191 million dispensed opioid prescriptions,<sup>3</sup> approximately 47,600 opioid-related deaths,<sup>4</sup> and 70,237 drug-poisoning deaths<sup>4</sup> 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.<sup>5</sup> 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.<sup>6,7</sup>

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.<sup>8,9</sup> Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.<sup>6,10</sup> 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,<sup>11</sup> 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,

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2  
3 which is likely caused by a multitude of factors, affects all members of society, and is fueled by  
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5 both prescription and illicit drugs.  
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10 A variety of policies and public health campaigns have been implemented in an effort to curb the  
11 epidemic of opioid overdoses and other drug-related morbidity and mortality, including the  
12 introduction of state prescription drug monitoring programs and the 2016 Centers for Disease  
13 Control and Prevention (CDC) opioid-prescribing guidelines.<sup>2</sup> Though most of the focus has  
14 been on prescription opioids, other non-opioid prescription and illicit drugs, such as heroin and  
15 fentanyl, have also contributed to the increase in drug-poisoning deaths<sup>12</sup> over the past two  
16 decades. Thus, the two outcomes – opioid prescribing and drug-poisoning mortality – should be  
17 tracked in parallel to assess the impact of limiting opioid use on overall drug mortality.  
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20 Historically, areas with higher opioid prescription rates also experienced higher drug-related  
21 mortality,<sup>11</sup> but recent intensive policy and public health efforts aimed at reducing opioid  
22 prescribing may have inadvertently created a divergence between opioid prescribing and drug-  
23 poisoning mortality, particularly in areas where opioid use may be low, but mortality due to non-  
24 opioids remains high. There is therefore a need for a contemporary population-level evaluation  
25 of current trends in opioid prescribing practices and drug-related mortality to identify  
26 populations at greatest risk of harm from opioid and non-opioid misuse.  
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47 The area deprivation index (ADI) is a validated composite measure of social determinants of  
48 health that can be used to quantify socioeconomic disadvantage for granular census-based  
49 regions.<sup>13</sup> The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty,  
50 education, housing, and employment.<sup>14</sup> County-level indicators of economic disadvantage reflect  
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3 general resource availability, safety, education quality, employment opportunity, and social  
4 support,<sup>15</sup> all of which contribute to physical, emotional, and financial health of communities and  
5 their residents. Despite the potential individual and public health implications of area-level  
6 deprivation for a wide range of clinical and public health outcomes, composite area-based  
7 measures have not been widely used to inform healthcare policy or clinical practice due to  
8 previously inaccessible national geospatial data.<sup>13</sup> In this study, we address a pressing public  
9 health need and pursue a critical knowledge gap by examining the relationships between county-  
10 level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in  
11 the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-  
12 level deprivation, this work contributes to the evidence base for informing clinical, public health,  
13 and policy interventions targeted at highest-need areas and populations.  
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## 30 **Methods**

### 31 **Study Design**

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

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3 All U.S. counties with opioid prescription and drug-poisoning mortality data available each year  
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5 between 2012 and 2017 were included in the study sample. Counties without data for all six  
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7 years of the study were excluded from the sample.  
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### 10 11 12 Patient Involvement

13  
14 No patients or members of the public were directly involved in the design, conduct, reporting, or  
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16 dissemination plans of the research.  
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### 20 21 22 American Community Survey Estimates

23  
24 County demographic information necessary for ADI derivation was ascertained from 2012-2016  
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26 and 2013-2017 5-year ACS estimates; the 5-year estimates are single year estimates based on 60  
27  
28 months of data.<sup>17</sup> The ADI was derived using 17 county-level indicators and calculated  
29  
30 separately each year for each U.S. county, as deprivation indices may change over time (Table  
31  
32 S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the Census  
33  
34 Application Programming Interface (API) to obtain data from the ACS.<sup>18</sup> The ACS is an annual  
35  
36 survey conducted by the U.S. Census Bureau which randomly samples housing units and  
37  
38 provides population-level estimates representative of the non-institutionalized U.S. population.<sup>17</sup>  
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40 In-depth survey methodology is available from the Census Bureau.<sup>17</sup>  
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### 47 48 49 Outcomes

50  
51 IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1,  
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53 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by  
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55 approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e.,  
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3 prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or  
4 cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.;  
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6 information on drugs filled by mail order pharmacies is unavailable.<sup>3</sup>  
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12 Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual  
13 rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a  
14 county per 100 residents as estimated by the ACS.<sup>3</sup> Opioids, identified using National Drug  
15 Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone,  
16 morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone  
17 dispensed through maintenance therapy programs was not included.  
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28 The CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality  
29 rates between January 1, 2012 and December 31, 2017; these data were available for each year  
30 for 3,133 counties (Figure 2). The CDC performs hierarchical Bayesian methods with spatial and  
31 temporal random effects to generate adjusted county-level drug-poisoning mortality rates per  
32 100,000 residents.<sup>19</sup> Drug-poisoning deaths related to opioid and non-opioid drugs were  
33 classified on the basis of International Classification of Diseases, Tenth Revision (ICD-10) codes  
34 and included deaths with unintentional (X40–X44), suicide (X60–X64), homicide (X85), and  
35 undetermined intent (Y10–Y14).<sup>16</sup>  
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### 49 **Role of the Funding Source**

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3 The funding sources for this study had no role in study design, data collection, data analysis, data  
4 interpretation, or writing of the report. The corresponding author had full access to all data in the  
5 study and final responsibility for the decision to submit for publication.  
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## 10 11 12 ADI Derivation

13  
14 We calculated modified ADI scores, using the Singh method,<sup>14</sup> for all 3,142 counties in the U.S.  
15 using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach  
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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.

## 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **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



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3 county-level estimates for age, percent white, percent male, and year. The specific independent  
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5 variables were chosen based on previous literature suggesting an area-level association between  
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7 those demographic indicators and greater opioid use or drug mortality.<sup>6 8-11</sup> Predicted margins for  
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9 adjusted prescription rates and drug-poisoning mortality were assessed by ADI quintile across all  
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11 years.<sup>22</sup>  
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17 Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata 15.1  
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19 (StataCorp LLC, College Station, TX). Opioid prescription rates, drug-poisoning mortality, and  
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21 ADI at the county-level were visually represented with geographic information system (GIS)  
22  
23 maps created in ArcMap 10.7 using Census TIGER/Line shapefiles.  
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## 28 **Results**

### 29 **Association of Area-Level Deprivation with Opioid Prescription Rates**

30  
31 Opioid prescription rates were significantly higher among counties in the highest ADI quintile  
32  
33 (Q5: most deprived) compared to those in the lowest quintile. The risk of filling an opioid  
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35 prescription was 72% higher in ADI Q5 than Q1 (IRR, 1.72; 95% CI [1.63, 1.82];  $p < 0.001$ )  
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37 (Table S2).  
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45 Overall, rates of filled opioid prescriptions declined over time, from 96.6 per 100 people in 2012  
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47 to 72.2 per 100 people in 2017. Analogously, the percentage and total number of counties with  
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49 more than 1 opioid prescription per resident steadily declined over time: 40.3% (n=1093) in  
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51 2012, 38.6% (n=1047) in 2013, 36.9% (n=1001) in 2014, 31.5% (n=855) in 2015, 26.7%  
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53 (n=723) in 2016, and 17.6% (n=477) in 2017.  
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5 Rates of opioid prescriptions appear to decrease between 2012 and 2017 within each ADI  
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7 quintile (Figure 4). The adjusted prescription rate for counties in the most deprived ADI quintile  
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9 (Q5) decreased from 115.9 prescriptions per 100 people in 2012 to 86.6 in 2017 (IRR 0.75, 95%  
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11 CI [0.73, 0.76];  $p < 0.001$ ) (Table S2). Adjusted rates calculated from the predicted margins  
12  
13 suggest that each successively less deprived ADI quintile displayed a smaller decrease in  
14  
15 prescription rate. Although the absolute opioid prescription rate decrement was largest in ADI  
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17 Q5, the proportion of the decrease was similar across all ADI quintiles.  
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#### 24 **Association of Area-Level Deprivation with Drug-Poisoning Mortality**

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26 In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning  
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28 mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62];  $p < 0.001$ ) between 2012 and  
29  
30 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-  
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32 poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28,  
33  
34 1.44];  $p < 0.001$ ) (Table 1). The association between ADI and drug-poisoning mortality appeared  
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36 to be linear with rising deprivation resulting in higher rates of drug-poisoning mortality (Figure  
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38 S1).  
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#### 45 **Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality**

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47 As shown in Figures 1-3, there were consistent and strongly demarcated spatial differences in  
48  
49 both outcomes across ADI quintiles. The highest opioid prescription rates were seen in counties  
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51 in southern states and Appalachia. Southwestern U.S. and Appalachia also saw high drug-  
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3 poisoning mortality. There were no major visual geospatial changes in the patterns of  
4 deprivation, opioid prescriptions, or drug-poisoning mortality during the study period.  
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## 10 **Discussion**

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12 Social determinants of health underlie many causes of the ongoing epidemic and need to be  
13 considered to when developing and implementing interventions seeking to address it. In this  
14 study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated  
15 with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may  
16 be a powerful tool for identifying areas of greatest need as well as informing and contextualizing  
17 future public health and policy interventions. We also found that while opioid prescriptions  
18 decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them,  
19 persistent disparities in both prescription opioid use and drug-poisoning mortality remain.  
20 Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-  
21 related mortality than less deprived counties. Moreover, despite reductions in opioid  
22 prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and  
23 2017, reinforcing the growing impact of drugs obtained outside of the health care system and  
24 missed opportunities to tailor and target interventions to those at highest risk for harm. By  
25 considering contextual factors and developing customized approaches using area-level  
26 indicators, harm reduction strategies could yield a more sustainable and meaningful impact for  
27 the communities they serve.  
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51 A number of state and federal programs have been introduced over the past decade to increase  
52 public awareness, decrease access to prescription opioids, improve opioid use disorder treatment,  
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3 and expand access to naloxone for overdose reversal.<sup>23</sup> The interventions targeting opioid  
4 prescribing (i.e. state controlled substance monitoring programs) likely contributed to the decline  
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6 in rates of opioid prescriptions between 2012 and 2017, but did not rectify the disparities  
7  
8 associated with drug-poisoning deaths. Persistent disparities in opioid prescription rates may be  
9  
10 attributed higher prevalence of comorbidities and disability in deprived areas,<sup>24</sup> difficulty  
11  
12 accessing medication for opioid use disorder,<sup>25</sup> and a different experience of pain in the setting of  
13  
14 lower health literacy<sup>26</sup> and socioeconomic distress. Further efforts should focus on identifying  
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16 alternative pain management strategies that are effective, affordable, and accessible to all who  
17  
18 need them, irrespective of where they live. At present, access to and reimbursement for non-  
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20 pharmacologic pain management modalities remains limited,<sup>27</sup> which may further exacerbate  
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22 disparities in opioid use and misuse among disadvantaged U.S. adults.  
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31 Although opioid prescribing rates declined over time, rates of drug-poisoning mortality appeared  
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33 to rise steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too,  
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35 was higher in the most deprived counties. This finding underscores the complexity of the opioid  
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37 and drug use epidemic. First, current opioid prescribing rates are not the sole driver of drug-  
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39 poisoning mortality, as mortality has continued to rise while prescription rates have declined.  
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41 Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates of addiction  
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43 due to overprescribing, all play an important role in drug-related deaths.<sup>2 28</sup> Second, high rates of  
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45 drug-poisoning mortality result not only from greater availability of drugs, but also from greater  
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47 probability of death with drug use. People living in deprived areas often have inadequate access  
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49 to substance use disorder treatment and medications<sup>29-33</sup> and limited access to healthcare,<sup>34</sup>  
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52 resulting from failure to expand Medicaid coverage, inadequate reimbursement for treatment,<sup>35 36</sup>  
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3 and variation in types of providers able to prescribe and manage treatment.<sup>37</sup> Third, as a result of  
4 structural violence and barriers, individuals living in deprived communities may be less likely to  
5 seek medical treatment due to stigma and criminalization leading to higher rates of drug-  
6 poisoning mortality.<sup>38</sup> Reducing mortality will therefore require a wide range of interventions in  
7 addition to limiting opioid prescribing, including improving availability of and access to  
8 nonopioid pain management, social services, mental health, and substance use treatment.  
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11 Consistent with prior literature, we found that higher proportions of male residents within a  
12 county were protective against both opioid prescriptions<sup>6 39</sup> and drug-poisoning mortality.<sup>40</sup>  
13  
14 Women are more likely than men to be prescribed opioid medications and to be co-prescribed  
15 other medications that increase overdose risk;<sup>40-42</sup> women are also less likely to enter substance  
16 use disorder treatment programs.<sup>43</sup> Counties with fewer men may also reflect larger systemic  
17 issues such as higher incarceration rates among males.<sup>38</sup> Incarceration not only interferes with  
18 the ability to seek substance abuse treatment, but is strongly associated with family disruption,  
19 unemployment, neighborhood decline, chronic economic hardship, and importantly, increased  
20 mortality from drug-use disorders.<sup>38</sup>  
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42 Our study has several key strengths, making it relevant and actionable to public health  
43 professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses  
44 highlighted the importance of understanding county resources and economic conditions that may  
45 affect both use of and mortality related to opioids and other drugs. We also identified the degree  
46 of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to  
47 curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and  
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3 accounting for changes in demographics and ADI quintiles over time using yearly demographic  
4 estimates and census indicators from ACS, which has not been done to date. This is also the first  
5 study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying  
6 it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid  
7 prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless,  
8 our findings are limited by potential reverse causality bias and the inability to identify causal  
9 relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not  
10 capture all prescription opioids; methadone dispensed through maintenance therapy programs  
11 and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly,  
12 given the use of ACS survey data, our study is susceptible to non-response and imputation bias.  
13 However, our study had less than 1% of missing data for each year and fewer than 80 variable  
14 observations were imputed in total. Thus, the potential for imputation bias is very low.  
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33 Addressing the drug crisis requires multifaceted interventions that address the wide range of  
34 biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving  
35 problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing  
36 are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.<sup>2</sup>  
37 Our work demonstrates the need to consider local factors when developing interventions related  
38 to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed  
39 by indicators such as ADI to identify areas that may benefit from additional monitoring, specific  
40 resources, and tailored interventions.  
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14 **Contributors:** SK and NS conceived and designed the study; SK and JI acquired data; SK, RM,  
15 SC, LR analyzed/interpreted the data; NS, MJ, JI, and RG supervised data analysis. All authors  
16 refined the various versions of the full paper and approved the final manuscript. The  
17 corresponding author attests that all listed authors meet authorship criteria and that no others  
18 meeting the criteria have been omitted. SK and ND are the guarantors.

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26 **Competing Interests:** All authors have completed the ICMJE uniform disclosure form at  
27 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: Dr. Jeffery's spouse owns shares in Vireo  
28 Health.

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33 **Ethical Approval:** Not required.

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**Data Sharing:** All data are publicly available. Statistical code and datasets are available from  
the corresponding author at [kurani.shaheen@mayo.edu](mailto: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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.97	0.96	0.97	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.05	1.04	1.07	<0.001
<b>Age, percentage</b>				
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)

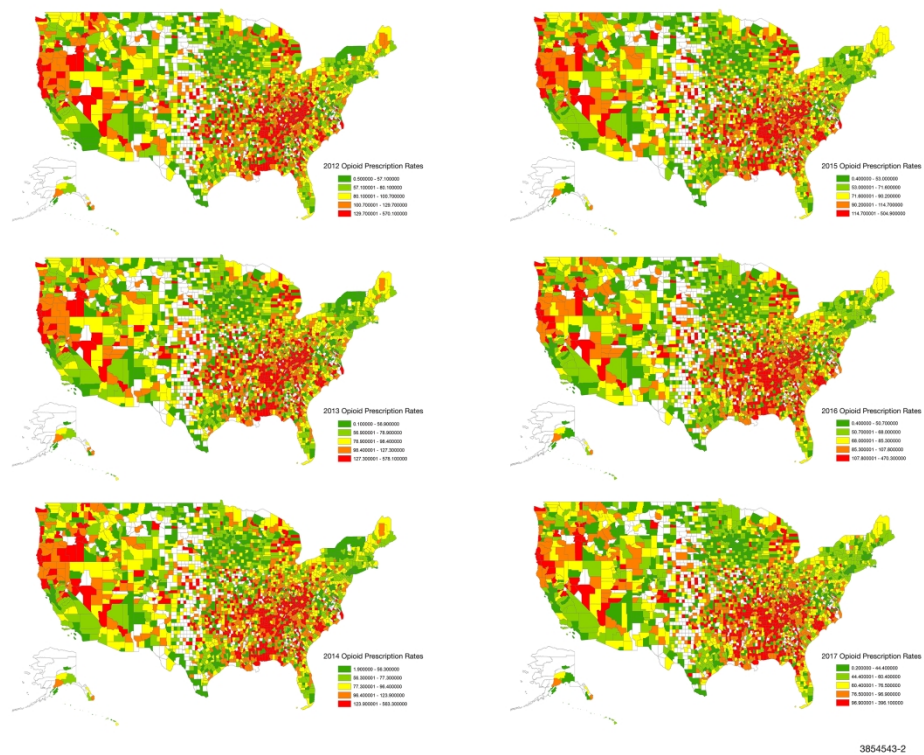


Figure 1. Opioid prescription rates across U.S. counties from 2012-2017. 2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

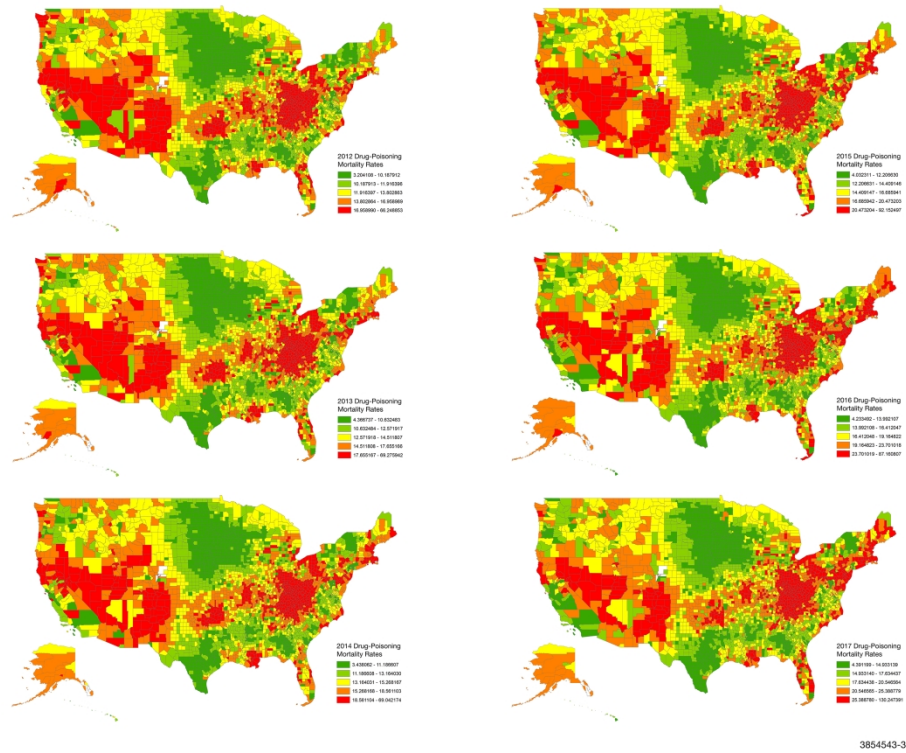


Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017. 3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

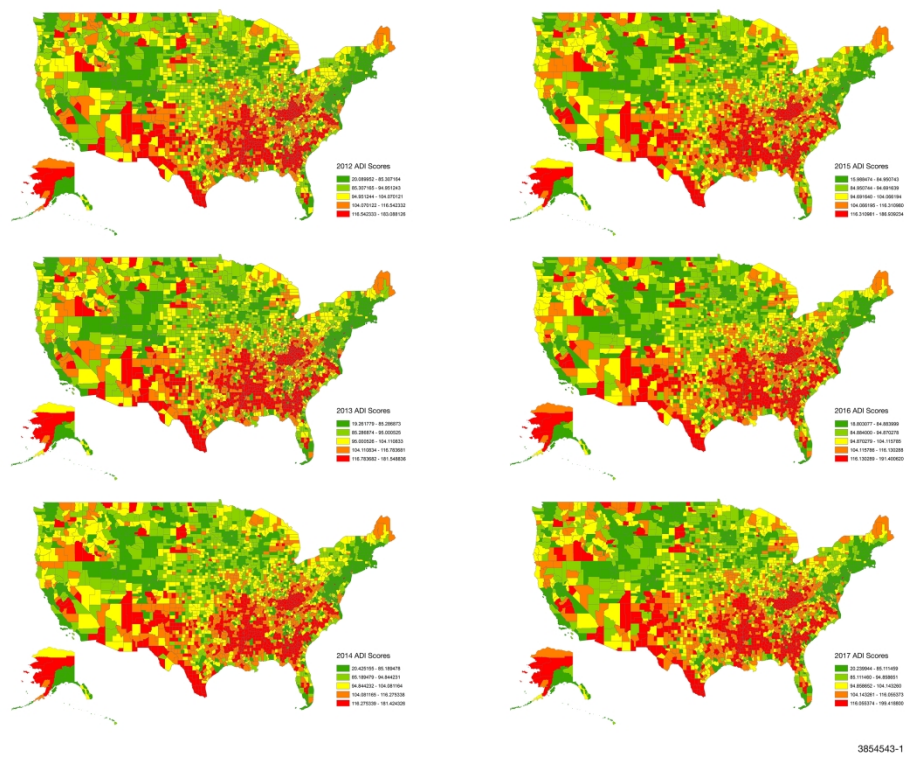


Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017. ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

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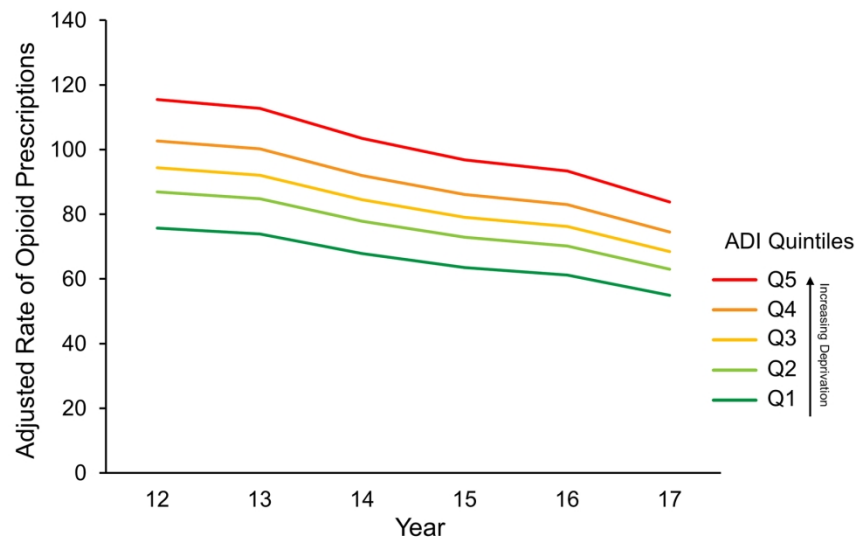


Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017. Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.

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## 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

<b>Employed persons <math>\geq 16</math> in white collar occupation</b>	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
<b>Civilian labor force unemployed (aged <math>\geq 16</math>)</b>	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
<b>Population aged <math>\geq 25</math> with <math>&lt; 9</math>yr education</b>	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
<b>Population aged <math>\geq 25</math> with at least a high school education</b>	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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.94	0.94	0.95	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.04	1.03	1.06	<0.001
<b>Age, percentage</b>				
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)

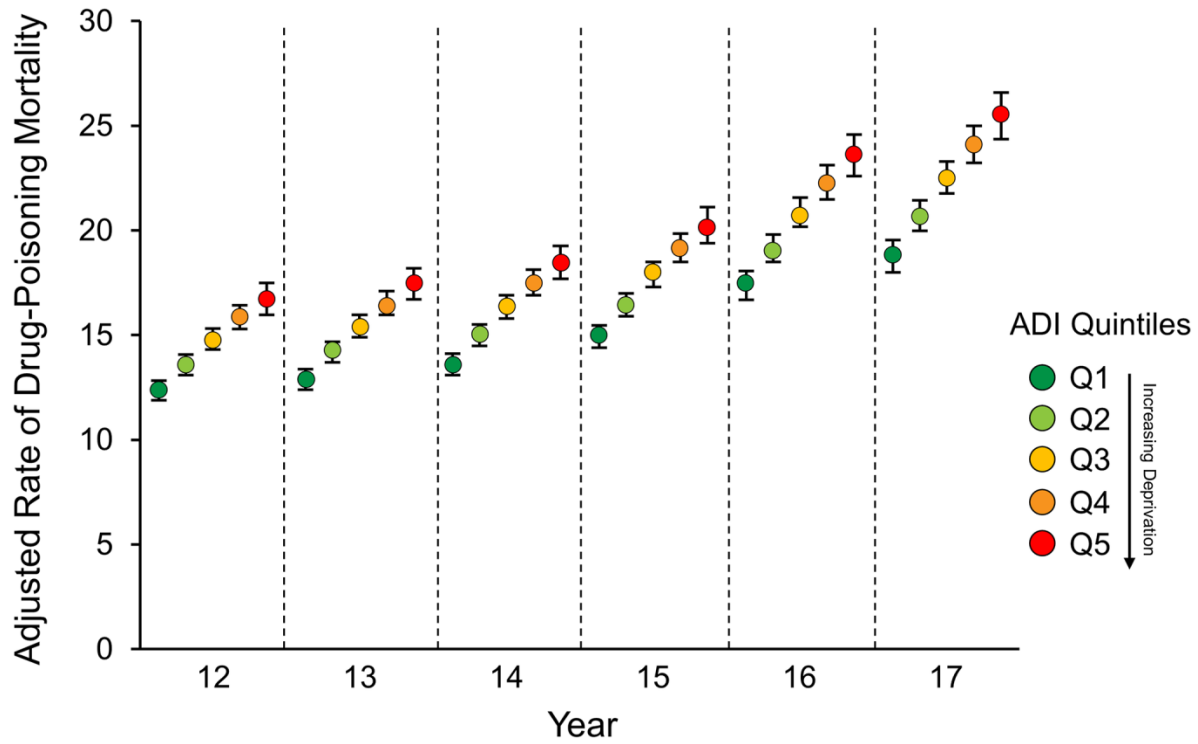


Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

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>.

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	--
<b>Results</b>			
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

1			
2	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
3			10-
4			11
5			
6			(b) Report category boundaries when continuous variables were categorized
7			10
8			
9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
10			--
11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
12			--
13			
14	<b>Discussion</b>		
15	Key results	18	Summarise key results with reference to study objectives
16			11-
17			12
18	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
19			14-
20			15
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22			11-
23			15
24	Generalisability	21	Discuss the generalisability (external validity) of the study results
25			15
26			
27	<b>Other information</b>		
28	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
29			16
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\*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](http://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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3 **Place, Poverty, and Prescriptions: A Cross-Sectional Study Using Area Deprivation Index**  
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5 **to Assess Opioid Use and Drug-Poisoning Mortality in the U.S. from 2012-2017**  
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7

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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

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2  
3 Counties with greater area-level deprivation have higher rates of filled opioid prescriptions and  
4 drug-poisoning mortality. Although opioid prescription rates declined across all ADI quintiles,  
5 rates of drug-poisoning mortality continued to rise proportionately in each ADI quintile. This  
6  
7 underscores the need for individualized and targeted interventions that consider the deprivation of  
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9 communities where people live.  
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### 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

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## Introduction

The drug epidemic has incurred great personal, societal, and economic costs,<sup>1</sup> driven, in part, by the widespread availability and use of prescription opioids.<sup>2</sup> In 2017, there were over 191 million dispensed opioid prescriptions,<sup>3</sup> approximately 47,600 opioid-related deaths,<sup>4</sup> and 70,237 drug-poisoning deaths<sup>4</sup> 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.<sup>5</sup> 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.<sup>6,7</sup>

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.<sup>8,9</sup> Other studies noted the greatest rise in drug-poisoning and overall mortality in areas where rurality intersects economic distress.<sup>6,10</sup> 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,<sup>11</sup> 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,

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2  
3 which is likely caused by a multitude of factors, affects all members of society, and is fueled by  
4  
5 both prescription and illicit drugs.  
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10 A variety of policies and public health campaigns have been implemented in an effort to curb the  
11 epidemic of opioid overdoses and other drug-related morbidity and mortality, including the  
12 introduction of state prescription drug monitoring programs and the 2016 Centers for Disease  
13 Control and Prevention (CDC) opioid-prescribing guidelines.<sup>2</sup> Though most of the focus has  
14 been on prescription opioids, other non-opioid prescription and illicit drugs, such as heroin and  
15 fentanyl, have also contributed to the increase in drug-poisoning deaths<sup>12</sup> over the past two  
16 decades. Thus, the two outcomes – opioid prescribing and drug-poisoning mortality – should be  
17 tracked in parallel to assess the impact of limiting opioid use on overall drug mortality.  
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20 Historically, areas with higher opioid prescription rates also experienced higher drug-related  
21 mortality,<sup>11</sup> but recent intensive policy and public health efforts aimed at reducing opioid  
22 prescribing may have inadvertently created a divergence between opioid prescribing and drug-  
23 poisoning mortality, particularly in areas where opioid use may be low, but mortality due to non-  
24 opioids remains high. There is therefore a need for a contemporary population-level evaluation  
25 of current trends in opioid prescribing practices and drug-related mortality to identify  
26 populations at greatest risk of harm from opioid and non-opioid misuse.  
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47 The area deprivation index (ADI) is a validated composite measure of social determinants of  
48 health that can be used to quantify socioeconomic disadvantage for granular census-based  
49 regions.<sup>13</sup> The ADI is comprised of 17 U.S. census indicators spanning four domains – poverty,  
50 education, housing, and employment.<sup>14</sup> County-level indicators of economic disadvantage reflect  
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3 general resource availability, safety, education quality, employment opportunity, and social  
4 support,<sup>15</sup> all of which contribute to physical, emotional, and financial health of communities and  
5 their residents. Despite the potential individual and public health implications of area-level  
6 deprivation for a wide range of clinical and public health outcomes, composite area-based  
7 measures have not been widely used to inform healthcare policy or clinical practice due to  
8 previously inaccessible national geospatial data.<sup>13</sup> In this study, we address a pressing public  
9 health need and pursue a critical knowledge gap by examining the relationships between county-  
10 level area deprivation and patterns of both opioid prescriptions and drug-poisoning mortality in  
11 the U.S. between 2012 and 2017. By examining the drug epidemic through the lens of county-  
12 level deprivation, this work contributes to the evidence base for informing clinical, public health,  
13 and policy interventions targeted at highest-need areas and populations.  
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## 30 **Methods**

### 31 **Study Design**

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



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3 All U.S. counties with opioid prescription and drug-poisoning mortality data available each year  
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5 between 2012 and 2017 were included in the study sample. Counties without data for all six  
6  
7 years of the study were excluded from the sample.  
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### 10 11 12 Patient Involvement

13  
14 No patients or members of the public were directly involved in the design, conduct, reporting, or  
15  
16 dissemination plans of the research.  
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### 20 21 22 American Community Survey Estimates

23  
24 County demographic information necessary for ADI derivation was ascertained from 2012-2016  
25  
26 and 2013-2017 5-year ACS estimates; the 5-year estimates are single year estimates based on 60  
27  
28 months of data.<sup>17</sup> The ADI was derived using 17 county-level indicators and calculated  
29  
30 separately each year for each U.S. county, as deprivation indices may change over time (Table  
31  
32 S1). The *acs* R package (v2.1.3 Haber Glenn, 2018) was used to connect to the Census  
33  
34 Application Programming Interface (API) to obtain data from the ACS.<sup>18</sup> The ACS is an annual  
35  
36 survey conducted by the U.S. Census Bureau which randomly samples housing units and  
37  
38 provides population-level estimates representative of the non-institutionalized U.S. population.<sup>17</sup>  
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40 In-depth survey methodology is available from the Census Bureau.<sup>17</sup>  
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### 47 48 49 Outcomes

50  
51 IQVIA Xponent data were used to obtain county-level opioid prescription rates from January 1,  
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53 2012 to December 31, 2017. The Xponent database includes all prescriptions issued by  
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55 approximately 50,000 retail pharmacies across the U.S. irrespective of insurance coverage (i.e.,  
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3 prescriptions are captured whether paid for with commercial insurance, Medicaid, Medicare, or  
4 cash). Sampled pharmacies dispense nearly 90% of all retail prescriptions in the U.S.;  
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6 information on drugs filled by mail order pharmacies is unavailable.<sup>3</sup>  
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11  
12 Opioid prescription data from 2012-2017 was available for 2,712 counties (Figure 1). The annual  
13 rate of opioid prescriptions was calculated as the total number of prescriptions dispensed in a  
14 county per 100 residents as estimated by the ACS.<sup>3</sup> Opioids, identified using National Drug  
15 Codes, included: buprenorphine, codeine, fentanyl, hydrocodone, hydromorphone, methadone,  
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17 morphine, oxycodone, oxymorphone, propoxyphene, tapentadol, and tramadol. Methadone  
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19 dispensed through maintenance therapy programs was not included.  
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28 The CDC National Center for Health Statistics data were used to obtain drug-poisoning mortality  
29 rates between January 1, 2012 and December 31, 2017; these data were available for each year  
30 for 3,133 counties (Figure 2). The CDC performs hierarchical Bayesian methods with spatial and  
31 temporal random effects to generate adjusted county-level drug-poisoning mortality rates per  
32 100,000 residents.<sup>19</sup> Drug-poisoning deaths related to opioid and non-opioid drugs were  
33 classified on the basis of International Classification of Diseases, Tenth Revision (ICD-10) codes  
34 and included deaths with unintentional (X40–X44), suicide (X60–X64), homicide (X85), and  
35 undetermined intent (Y10–Y14).<sup>16</sup>  
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### 49 **Role of the Funding Source**

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3 The funding sources for this study had no role in study design, data collection, data analysis, data  
4 interpretation, or writing of the report. The corresponding author had full access to all data in the  
5 study and final responsibility for the decision to submit for publication.  
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## 10 11 12 ADI Derivation

13  
14 We calculated modified ADI scores, using the Singh method,<sup>14</sup> for all 3,142 counties in the U.S.  
15 using 5-year ACS estimates (Figure 3). Variables were selected using a factor analysis approach  
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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.

## 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 **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

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3 quintile, percent county-level estimates for age, percent white, percent male, and year. The  
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5 specific independent variables were chosen based on previous literature suggesting an area-level  
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7 association between those demographic indicators and greater opioid use or drug mortality.<sup>6-11</sup>  
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9 Predicted margins for adjusted prescription rates and drug-poisoning mortality were assessed by  
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11 ADI quintile across all years.<sup>22</sup>  
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17 Analyses were conducted using SAS v9.4 (SAS Institute Inc., Cary, NC) and Stata 15.1  
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19 (StataCorp LLC, College Station, TX). Opioid prescription rates, drug-poisoning mortality, and  
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21 ADI at the county-level were visually represented with geographic information system (GIS)  
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23 maps created in ArcMap 10.7 using Census TIGER/Line shapefiles.  
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## 28 **Results**

### 29 **Association of Area-Level Deprivation with Opioid Prescription Rates**

30  
31 Opioid prescription rates were significantly higher among counties in the highest ADI quintile  
32  
33 (Q5: most deprived) compared to those in the lowest quintile. The risk of filling an opioid  
34  
35 prescription was 72% higher in ADI Q5 than Q1 (IRR, 1.72; 95% CI [1.63, 1.82];  $p < 0.001$ )  
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37 (Table S2).  
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45 Overall, rates of filled opioid prescriptions declined over time, from 96.6 per 100 people in 2012  
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47 to 72.2 per 100 people in 2017. Analogously, the percentage and total number of counties with  
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49 more than 1 opioid prescription per resident steadily declined over time: 40.3% (n=1093) in  
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51 2012, 38.6% (n=1047) in 2013, 36.9% (n=1001) in 2014, 31.5% (n=855) in 2015, 26.7%  
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53 (n=723) in 2016, and 17.6% (n=477) in 2017.  
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5 Rates of opioid prescriptions appear to decrease between 2012 and 2017 within each ADI  
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7 quintile (Figure 4). The adjusted prescription rate for counties in the most deprived ADI quintile  
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9 (Q5) decreased from 115.9 prescriptions per 100 people in 2012 to 86.6 in 2017 (IRR 0.75, 95%  
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11 CI [0.73, 0.76];  $p < 0.001$ ) (Table S2). Adjusted rates calculated from the predicted margins  
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13 suggest that each successively less deprived ADI quintile displayed a smaller decrease in  
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15 prescription rate. Although the absolute opioid prescription rate decrement was largest in ADI  
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17 Q5, the proportion of the decrease was similar across all ADI quintiles.  
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#### 24 **Association of Area-Level Deprivation with Drug-Poisoning Mortality**

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26 In contrast to the decline in opioid prescription rates over time, the rates of drug-poisoning  
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28 mortality rose steadily by 59% (IRR 1.59; 95% CI [1.56, 1.62];  $p < 0.001$ ) between 2012 and  
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30 2017 (Table 1) and increased incrementally with higher ADI (greater deprivation). Drug-  
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32 poisoning mortality risk was 36% higher in ADI Q5 than Q1 counties (IRR, 1.36; 95% CI [1.28,  
33  
34 1.44];  $p < 0.001$ ) (Table 1). The association between ADI and drug-poisoning mortality appeared  
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36 to be linear with rising deprivation resulting in higher rates of drug-poisoning mortality (Figure  
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38 S1).  
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#### 44 **Geospatial Variation in ADI, Opioid Prescriptions, and Drug-Poisoning Mortality**

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46 As shown in Figures 1-3, there were consistent and strongly demarcated spatial differences in  
47  
48 both outcomes across ADI quintiles. The highest opioid prescription rates were seen in counties  
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50 in southern states and Appalachia. Southwestern U.S. and Appalachia also saw high drug-  
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3 poisoning mortality. There were no major visual geospatial changes in the patterns of  
4 deprivation, opioid prescriptions, or drug-poisoning mortality during the study period.  
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## 10 **Discussion**

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12 Social determinants of health underlie many causes of the ongoing epidemic and need to be  
13 considered to when developing and implementing interventions seeking to address it. In this  
14 study, we demonstrated that area-level deprivation, as measured by ADI, is strongly associated  
15 with geospatial variation in opioid prescriptions and drug-poisoning mortality, and as such, may  
16 be a powerful tool for identifying areas of greatest need as well as informing and contextualizing  
17 future public health and policy interventions. We also found that while opioid prescriptions  
18 decreased over time, likely driven by the multifaceted policy and practice efforts to reduce them,  
19 persistent disparities in both prescription opioid use and drug-poisoning mortality remain.  
20 Deprived counties continue to have significantly higher rates of opioid prescriptions and drug-  
21 related mortality than less deprived counties. Moreover, despite reductions in opioid  
22 prescriptions, rates of drug-poisoning mortality have continued to increase between 2012 and  
23 2017, reinforcing the growing impact of drugs obtained outside of the health care system and  
24 missed opportunities to tailor and target interventions to those at highest risk for harm. By  
25 considering contextual factors and developing customized approaches using area-level  
26 indicators, harm reduction strategies could yield a more sustainable and meaningful impact for  
27 the communities they serve.  
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51 A number of state and federal programs have been introduced over the past decade to increase  
52 public awareness, decrease access to prescription opioids, improve opioid use disorder treatment,  
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3 and expand access to naloxone for overdose reversal.<sup>23</sup> The interventions targeting opioid  
4 prescribing (i.e. state controlled substance monitoring programs) likely contributed to the decline  
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6 in rates of opioid prescriptions between 2012 and 2017, but did not rectify the disparities  
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8 associated with drug-poisoning deaths. Persistent disparities in opioid prescription rates may be  
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10 attributed higher prevalence of comorbidities and disability in deprived areas,<sup>24</sup> difficulty  
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12 accessing medication for opioid use disorder,<sup>25</sup> and a different experience of pain in the setting of  
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14 lower health literacy<sup>26</sup> and socioeconomic distress. Further efforts should focus on identifying  
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16 alternative pain management strategies that are effective, affordable, and accessible to all who  
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18 need them, irrespective of where they live. At present, access to and reimbursement for non-  
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20 pharmacologic pain management modalities remains limited,<sup>27</sup> which may further exacerbate  
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22 disparities in opioid use and misuse among disadvantaged U.S. adults.  
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31 Although opioid prescribing rates declined over time, rates of drug-poisoning mortality appeared  
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33 to rise steadily between 2012 and 2017. While this increase affected all ADI quintiles, it, too,  
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35 was higher in the most deprived counties. This finding underscores the complexity of the opioid  
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37 and drug use epidemic. First, current opioid prescribing rates are not the sole driver of drug-  
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39 poisoning mortality, as mortality has continued to rise while prescription rates have declined.  
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41 Illegally obtained opioids, non-opioid prescription and illicit drugs, and high rates of addiction  
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43 due to overprescribing, all play an important role in drug-related deaths.<sup>2 28</sup> Second, high rates of  
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45 drug-poisoning mortality result not only from greater availability of drugs, but also from greater  
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47 probability of death with drug use. People living in deprived areas often have inadequate access  
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49 to substance use disorder treatment and medications<sup>29-33</sup> and limited access to healthcare,<sup>34</sup>  
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54 resulting from failure to expand Medicaid coverage, inadequate reimbursement for treatment,<sup>35 36</sup>  
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3 and variation in types of providers able to prescribe and manage treatment.<sup>37</sup> Third, as a result of  
4 structural violence and barriers, individuals living in deprived communities may be less likely to  
5 seek medical treatment due to stigma and criminalization leading to higher rates of drug-  
6 poisoning mortality.<sup>38</sup> Reducing mortality will therefore require a wide range of interventions in  
7 addition to limiting opioid prescribing, including improving availability of and access to  
8 nonopioid pain management, social services, mental health, and substance use treatment.  
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11 Consistent with prior literature, we found that higher proportions of male residents within a  
12 county were protective against both opioid prescriptions<sup>6 39</sup> and drug-poisoning mortality.<sup>40</sup>  
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14 Women are more likely than men to be prescribed opioid medications and to be co-prescribed  
15 other medications that increase overdose risk;<sup>40-42</sup> women are also less likely to enter substance  
16 use disorder treatment programs.<sup>43</sup> Counties with fewer men may also reflect larger systemic  
17 issues such as higher incarceration rates among males.<sup>38</sup> Incarceration not only interferes with  
18 the ability to seek substance abuse treatment, but is strongly associated with family disruption,  
19 unemployment, neighborhood decline, chronic economic hardship, and importantly, increased  
20 mortality from drug-use disorders.<sup>38</sup>  
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42 Our study has several key strengths, making it relevant and actionable to public health  
43 professionals, policy makers, payers, and health systems. By leveraging ADI, our analyses  
44 highlighted the importance of understanding county resources and economic conditions that may  
45 affect both use of and mortality related to opioids and other drugs. We also identified the degree  
46 of deprivation associated with increased drug-poisoning mortality in spite of extensive efforts to  
47 curb opioid use/misuse. We improved on earlier ADI studies by modifying the ADI and  
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3 accounting for changes in demographics and ADI quintiles over time using yearly demographic  
4 estimates and census indicators from ACS, which has not been done to date. This is also the first  
5 study to examine disparities in the opioid and non-opioid drug epidemic using ADI and applying  
6 it to most recent CDC mortality data, allowing us to explore contemporary trends in opioid  
7 prescription and drug-poisoning mortality rates at a granular level across the U.S. Nevertheless,  
8 our findings are limited by potential reverse causality bias and the inability to identify causal  
9 relationships between ADI, opioid prescription rates, and drug-poisoning death. We also did not  
10 capture all prescription opioids; methadone dispensed through maintenance therapy programs  
11 and medications dispensed by mail-order pharmacies and hospitals were not included. Lastly, the  
12 standard errors may be impacted by potential spatial autocorrelation and uncertainty in the  
13 modeled outcome rates.  
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31 Addressing the drug crisis requires multifaceted interventions that address the wide range of  
32 biomedical, psychosocial, and socioeconomic factors contributing to this complex and evolving  
33 problem. Recent analyses have shown that current efforts aimed at decreasing opioid prescribing  
34 are not sufficient and may slow, but not meaningfully reverse, the rise in drug-poisoning deaths.<sup>2</sup>  
35 Our work demonstrates the need to consider local factors when developing interventions related  
36 to opioid and non-opioid use. Policies should avoid a one-size-fits-all approach and be informed  
37 by indicators such as ADI to identify areas that may benefit from additional monitoring, specific  
38 resources, and tailored interventions.  
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15 SC, LR analyzed/interpreted the data; NS, MJ, JI, and RG supervised data analysis. All authors  
16 refined the various versions of the full paper and approved the final manuscript. The  
17 corresponding author attests that all listed authors meet authorship criteria and that no others  
18 meeting the criteria have been omitted. SK and ND are the guarantors.

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26 **Competing Interests:** All authors have completed the ICMJE uniform disclosure form at  
27 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: Dr. Jeffery's spouse owns shares in Vireo  
28 Health.

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33 **Ethical Approval:** Not required.

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**Data Sharing:** All data are publicly available. Statistical code and datasets are available from  
the corresponding author at [kurani.shaheen@mayo.edu](mailto: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.

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3 **Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017.**  
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5 3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.  
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**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.

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3 **Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017.**  
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5 Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.  
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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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.97	0.96	0.97	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.05	1.04	1.07	<0.001
<b>Age, percentage</b>				
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)

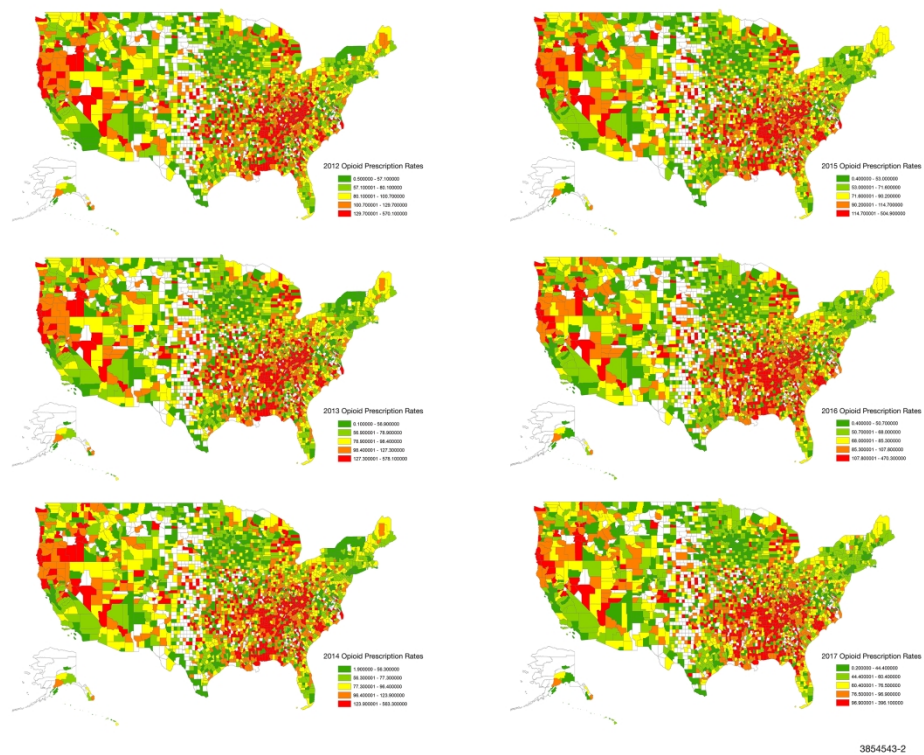


Figure 1. Opioid prescription rates across U.S. counties from 2012-2017. 2,712 of 3,142 U.S. counties with available opioid prescribing data are shown. All rates are expressed per 100 people.

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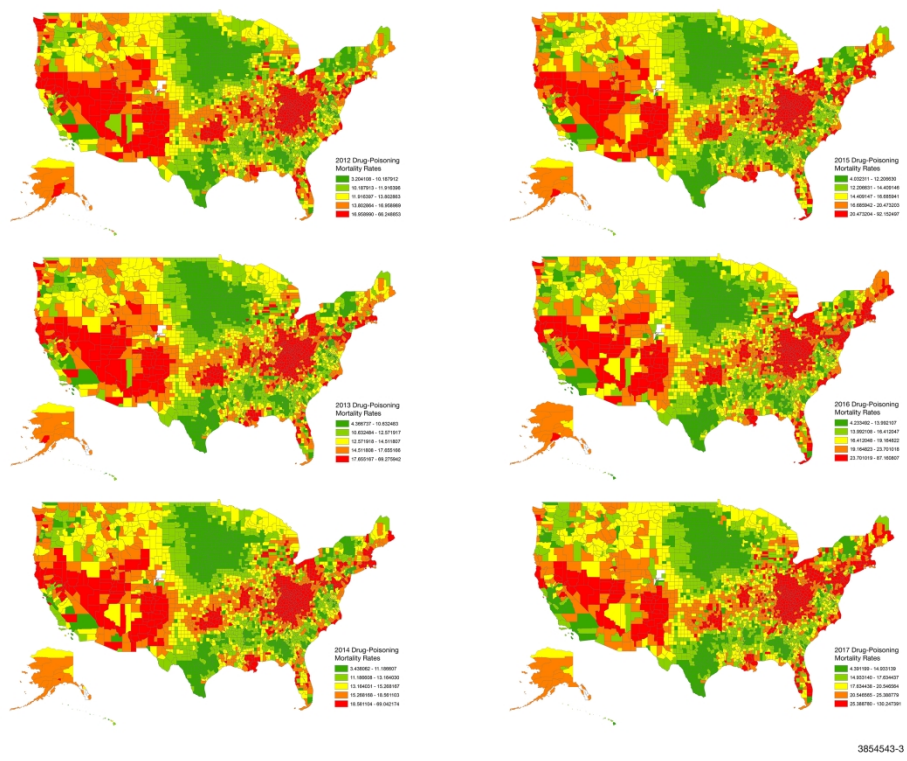


Figure 2. Drug-poisoning mortality rates across U.S. counties from 2012-2017. 3,133 of 3,142 U.S. counties with available mortality data are shown. All rates are expressed per 100,000 people.

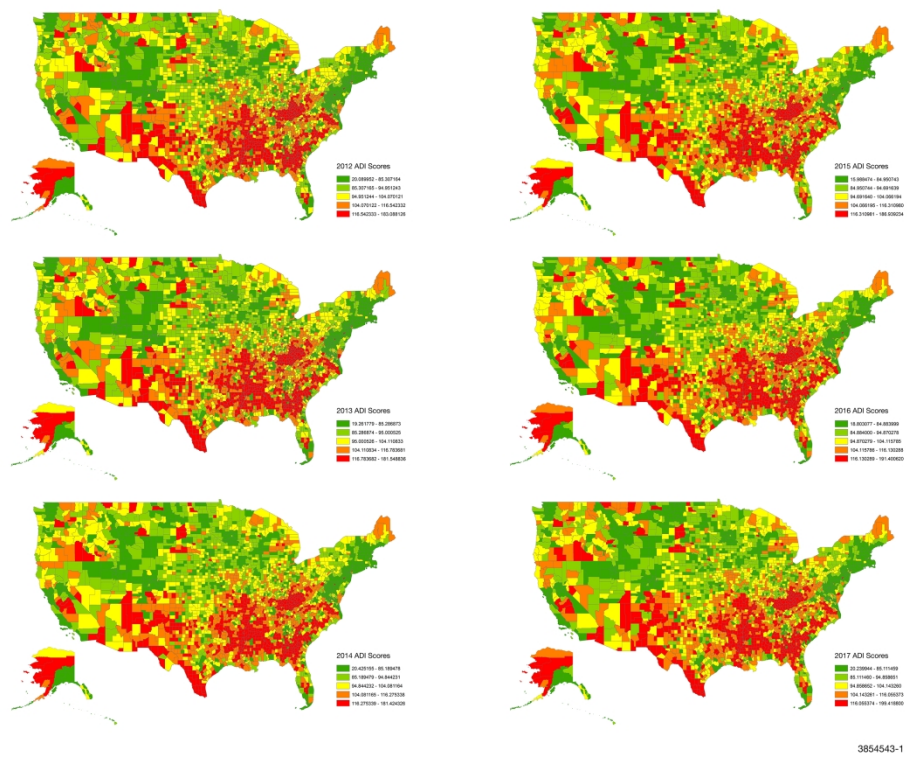


Figure 3. Area Deprivation Index quintiles presented for all 3,142 U.S. counties from 2012-2017. ADI was calculated using 5-year ACS estimates and all U.S. counties were included.

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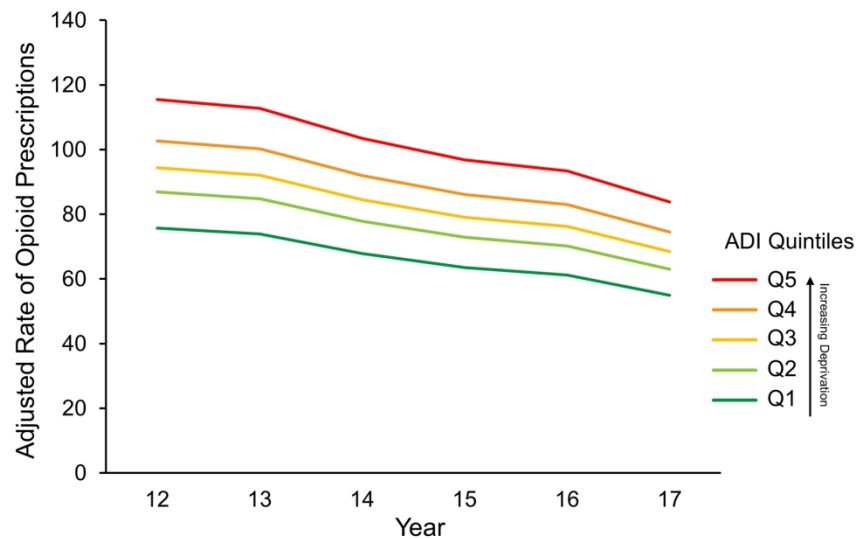


Figure 4. Adjusted rates of opioid prescriptions by ADI quintile from 2012-2017. Rates calculated from predicted margins adjusted for year, age, race, and sex were calculated per 100 people.

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



<b>Employed persons <math>\geq 16</math> in white collar occupation</b>	C24010	-0.01983	-0.02211	-0.0239	-0.02224	-0.02079	-0.01947
<b>Civilian labor force unemployed (aged <math>\geq 16</math>)</b>	B23025	0.02676	0.02071	0.02081	0.02157	0.0228	0.02451
<b>Population aged <math>\geq 25</math> with <math>&lt; 9</math>yr education</b>	B15003	0.01503	0.016	0.01088	0.00766	0.00431	0.01132
<b>Population aged <math>\geq 25</math> with at least a high school education</b>	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
<b>Year</b>				
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
<b>Area Deprivation Index, quintile</b>				
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
<b>Sex, percentage</b>				
Male	0.94	0.94	0.95	<0.001
<b>Race/ethnicity, percentage*</b>				
White	1.04	1.03	1.06	<0.001
<b>Age, percentage</b>				
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)

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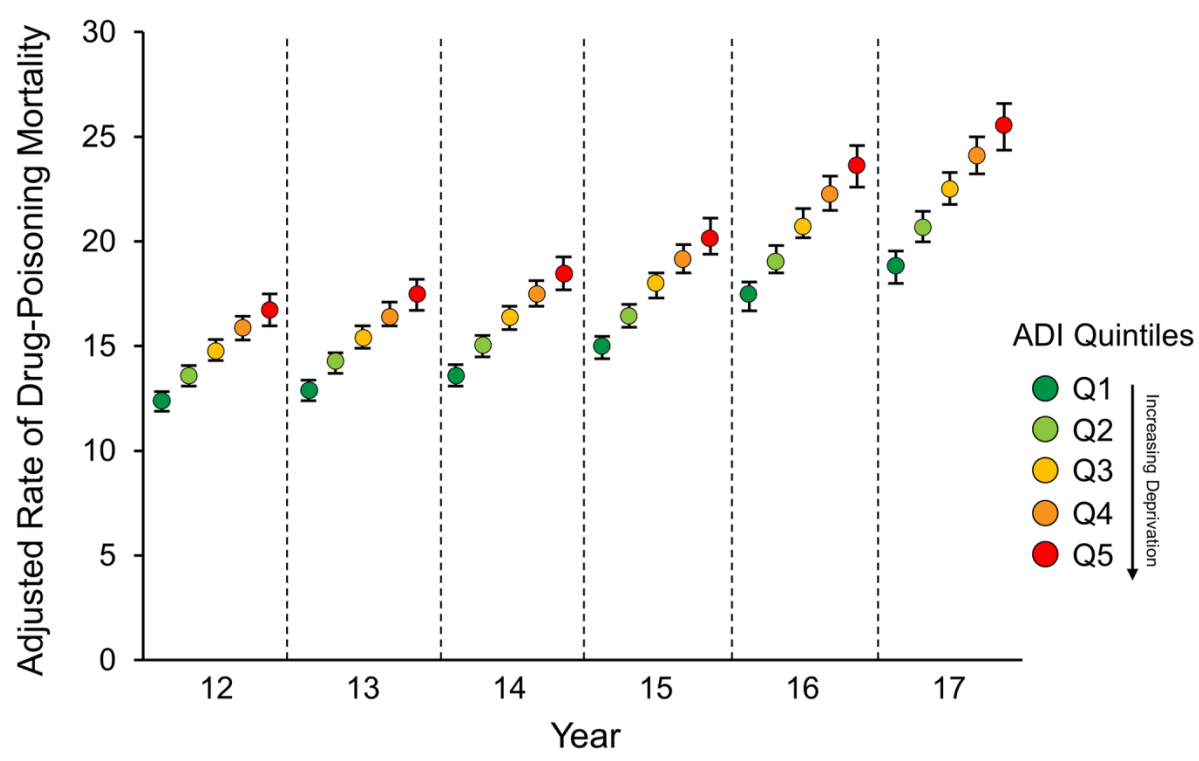


Figure S1. Adjusted rates of drug-poisoning mortality by ADI quintile from 2012-2017.

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>.

For peer review only

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

	Item No	Recommendation	Page No
<b>Title and abstract</b>	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
<b>Introduction</b>			
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
<b>Methods</b>			
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	--
<b>Results</b>			
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

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2	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
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6			(b) Report category boundaries when continuous variables were categorized
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9			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
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11	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
12			--
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14	<b>Discussion</b>		
15	Key results	18	Summarise key results with reference to study objectives
16			11-
17			12
18	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
19			14-
20			15
21	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
22			11-
23			15
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25	Generalisability	21	Discuss the generalisability (external validity) of the study results
26			15
27	<b>Other information</b>		
28	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
29			16
30			
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\*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](http://www.strobe-statement.org).