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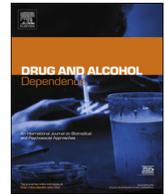
Full length article

Spatial analysis of drug poisoning deaths in the American west: A comparison study using profile regression to adjust for collinearity and spatial correlation

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ABSTRACT

Background: The USA has seen dramatic increases in drug poisoning deaths (DPD) recently. State-level rates have responded to federal and state initiatives, yet the counties with the highest rates are stable. Spatial analysis enables investigators to identify the highest risk counties and most important risk factors, although results are often confounded by spatial autocorrelation and multicollinearity.
Methods: Profile regression (PR) is an integrated method for cluster and regression analysis, which adjusts for spatial-autocorrelation and multi-collinearity.
Results: With PR, three clusters were identified in the Western USA with most of NM, NV and UT and several counties in AZ, CO, ID and WY being high-risk. Cluster analysis in a previous study only identified high-risk counties in northern CA, NM and NV. Elevation, suicide and LDS population were positively, and population density was negatively linked with DPD for PR and standard regression (SR) showing differences between the mountain west and coastal areas. Complex relationships between DPD and several variables were identified by PR which was not possible with SR.
Conclusions: Statistically principled methods like PR are needed for appropriate identification of the highest risk counties and important risk factors given the complex relationships with DPD. Funding for prevention, education and medical services should be targeted at rural, mountain communities in the west which have high %LDS and suicide rates. Counties with high %poverty and %Hispanic were also at high-risk. Individual-level studies are needed to confirm important risk factors in high-risk counties.

1. Introduction

Rates of drug poisoning death (DPD) have dramatically increased in the USA, with deaths due to opioids increasingly driving this trend (Scholl et al., 2018). Both heroin and prescription opioids (PO), have been implicated in these deaths (Ciccarone, 2017) and a well-documented route to addiction and abuse of Heroin has become through PO acting as a gateway drug (Cicero et al., 2014). Rates of DPD are generally high in the Western USA, with NM, NV, AZ and UT ranking second, fourth, sixth and eighth nationally in 2010. Federal grants have been awarded to some states to fund state initiatives such as greater use of the prescription drug monitoring program (PDMP), increased funding for substance abuse services, having a 'Good Samaritan' law and using the Naloxene protocol etc. (Trust for America's Health (TAH, 2013). Western states showed some response to such initiatives in the

2016 rankings (www.cdc.gov), although county-level rates (1999–2016) show consistent spatial patterns each year with the highest rates in certain Appalachian and Western US counties. Considerable geographic variation in opioid prescriptions, PO death and DPD has been documented nationally (McDonald et al., 2012; Paulozzi et al., 2014) and within individual states in the USA (Mair et al., 2018; Romeiser et al., 2019; Wagner et al., 2019) without clear understanding of the reasons for it. Understanding what drives the changes in DPD rates, and why there are differences among counties is important. Spatial studies can help to determine counties with a high risk of DPD and improve understanding of the factors involved.

Previous spatial analysis has been conducted investigating these issues, however, it has several limitations. Usually cluster and regression analysis are performed separately making links between clusters and risk factors hard to establish. Also, several risk factors tend to be

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correlated (multicollinearity) and spatial autocorrelation often exists in the data. Spatial autocorrelation can lead to underestimation of the variance of the regression coefficients and inflated R^2 values and multicollinearity causes inflation of the variances of regression estimates (Rogerson, 2001). In addition, relationships between variables are often complex and spatially non-stationary (Kerry et al., 2016). These issues restrict the ability of standard regression (SR) approaches to identify important risk factors.

This paper aims to address these issues through a re-analysis of DPD in the American west using profile regression (PR). It integrates cluster identification and regression, while accounting for multicollinearity and spatial autocorrelation (Liverani et al., 2016). PR has been used to investigate public health problems such as air pollution and respiratory hospital admission/death (Molitor et al., 2011; Coker et al., 2016; Liverani et al., 2016) and identification of areas with persistent excess risk of Malaria infection (Shekhar et al., 2017).

Using the same DPD and risk factor data, this study compares the findings of SR and cluster analysis (Kerry et al., 2016) with a single coherent PR analysis where spatial autocorrelation and multi-collinearity are accounted for. It is important to determine if results are markedly different between methods as this could affect what policies are implemented and where they are focused.

1.1. Literature review/conceptual model

A conceptual model to justify the choice of risk factor variables used in the analysis was developed from literature review. The main features of illicit and PO deaths, the two main causes of DPD, are discussed here but it is acknowledged that risk factors for particular drug groups are complex, inter-related and vary in space and time (Alexander et al., 2018). Compton et al. (2016) specifically investigated the complex relationship between non-medical PO use and heroin use.

1.1.1. Cultural variables

Traditionally, illicit drug use has been associated with poor, inner-city ethnic minority communities (Merrill et al., 2013). Whereas, studies of PO use have shown this to be primarily a white problem (Om, 2018) with fewer prescriptions made for ethnic minorities (Friedman et al., 2019; Santoro and Santoro, 2018) and greater proportions of non-medical PO use and death being reported among white students (Carter et al., 2019) and white mid-life adults (Ruhm, 2018), respectively. The two largest ethnic groups (%white and %Hispanic) in the west were investigated here.

The importance of religiosity in DPD has been shown with lower rates of illicit and non-illicit drug use documented among people who are religious (Drabble et al., 2016; Gallucci et al., 2018; Jorge et al., 2018) but there is little information on the use of prescribed medications among this group. As much of the western USA has high proportions of members of the Church of Jesus Christ of Latter-day Saints (LDS) (Fig. 1a) who have a strict health code relating to drug use (LDS Church, 2013), %LDS was used to investigate religiosity in this study (Table 1). Kerry et al. (2016) suggested that greater proportions of DPD in states with the highest LDS membership rates were from PO deaths rather than illicit drugs due to the demographics of those who died, a more naïve approach to PO use by those in UT and among those who do not smoke or drink (McNeely et al., 2014; Porucznik et al., 2011) and a well-documented pathway of legitimate prescriptions leading to addiction followed by use of illicit sources of PO and heroin (Rigg and Murphy., 2013).

The importance of family size and structure to DPD has been shown with greater prevalence among those living alone or without family support (Lanier et al., 2013; Reddy et al., 2014). This effect was investigated using average family size and family households (%).

1.1.2. Economic variables

Economic variables can determine timely access to physical and mental health care which could reduce DPD or increase the risk of PO prescription and abuse (Friedman et al., 2019). Health insurance is a key to cost-effective health-care in the USA, but 17% of those < 65 were uninsured in 2012 (CDC/NCHS, 2012). Medical insurance is usually provided by employers, so unemployment is a key variable. Also, even the insured pay a small percentage for each doctor visit (co-payment), so those in financial hardship may delay doctor visits, save old medications and self-medicate with prescription drugs obtained illicitly.

Rönkä et al. (2017) assessed social determinants of DPD and found statistically significant associations with unemployment and social disadvantage, but the strength of association varied with the type of DPD. Illicit drug use has been linked with economically depressed inner-city urban areas where unemployment, crime and delinquency rates are high (Johnson et al., 2013) and illicit drugs are readily available. In contrast, research shows that those with greater wealth are more likely to abuse PO prescribed by doctors while their poorer counterparts tend to obtain them from illicit sources (Cicero et al., 2012). Interestingly, however, Friedman et al. (2019) noted that PO prescriptions were highest in low-income white neighborhoods. Prescription opioid DPDs have been linked to rural areas which could be due to less infra-structure, uneven access to health care facilities and higher rates of PO prescribing in these areas (Paulozzi, 2012; Paulozzi et al., 2015; Rigg et al., 2018; Rose et al., 2018; Wagner et al., 2019) whereas illicit DPD have been linked to urban areas (Netherland and Hansen, 2016). To investigate the complex relations between DPD and economic factors: median household income, physician use delayed due to cost, poverty, unemployment and population density were used.

1.1.3. Environmental variable

Recent studies have found associations between high elevations and increased drug use (Fiedler et al., 2012; Kim et al., 2014), depression and suicide (Kim et al., 2011). The Appalachians and Western USA have some of the highest PO prescription rates in the USA (McDonald et al., 2012). Elevation is an important factor to investigate in the US Mountain West which is mostly > 1000 m elevation (Fig. 1b). Lower oxygen levels at high elevations deplete serotonin which increases the risk of depression and suicide, so self-medication with drugs and alcohol is common to temporarily raise serotonin (Brenner et al., 2011). Median county elevation was used to investigate this effect (Table 1).

1.1.4. Health and lifestyle variables

Illicit drug and PO users/abusers are more likely to smoke and abuse alcohol and other drugs (Cheng et al., 2013; Drabble et al., 2016; Johnson et al., 2013; Lanier et al., 2013) so smoking and binge drinking are included as variables in this study but are also strongly linked with the LDS faith in the American west.

Self-inflicted, intentional DPDs have obvious links with suicide (Donaldson et al., 2006) and premature death (years of potential life lost < 75 years) which are two important variables in this study (Table 1). Mental health problems (Austin et al., 2017; Cheng et al., 2013; Johnson et al., 2013), particularly depression (Subramanian and Stitzer, 2009) have been strongly associated with DPD, hence, the number of mentally unhealthy days in past 30 days and the depression rate among Medicare beneficiaries (those > 65 or disabled) were used in this study.

Pain and physical health problems have been linked to DPD as POs are often used to treat chronic pain and sometimes those experiencing long-term physical pain self-medicate from illicit drug sources (Cheng et al., 2013; Sehgal et al., 2012; Wang et al., 2012). This effect was investigated here using the number of physically unhealthy days in past 30 days.

State	UT	ID	WY	NV	AZ	HI	MT	AK	WA	OR	NM	CO	CA
% LDS	69	26	11	6.5	6.1	5.1	4.7	4.5	4	3.9	3.3	2.8	2.1
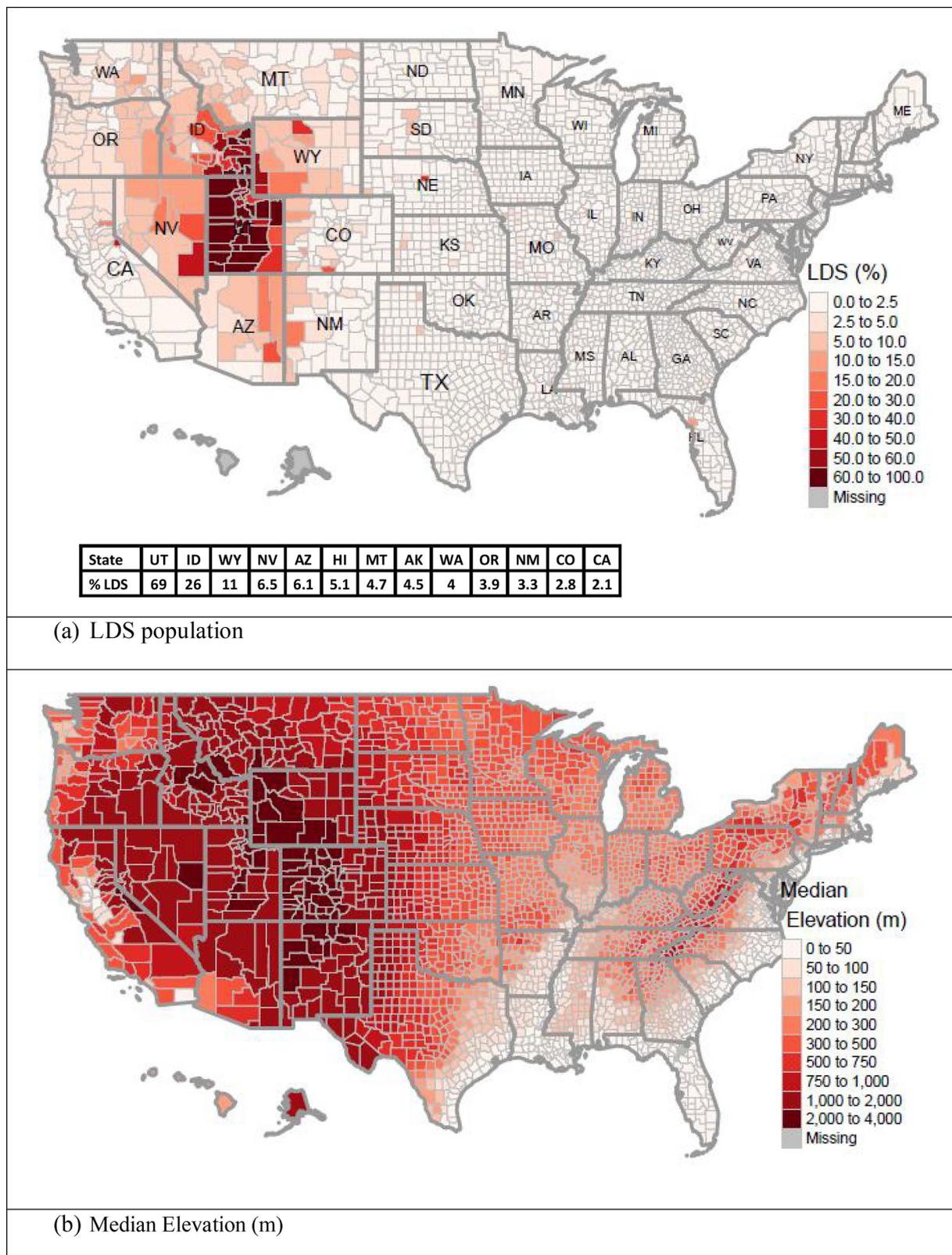
(a) LDS population

(b) Median Elevation (m)

Fig. 1. USA County Maps of (a) percentage of LDS population, (b) Median Elevation (m).

2. Methods

2.1. Data sources

For a direct comparison with the findings of Kerry et al. (2016) the same county-level DPD data for 2006–2010 were used (https://

healthdata.gov/) which come from Centers for Disease Control (CDC) annual reports from death certificates. Rates based on < 20 deaths were considered unreliable and considered as missing data. Kerry et al. (2016) used Poisson Kriging to populate the numerous data gaps in the American West and improve the reliability of rates for sparsely populated counties. The same approach was employed here (Fig. 2) to allow

Table 1
Variables used in analysis: period of recording, description and sources.

Variable	Years	Description	Source
Mortality Data			
Drug poisoning deaths (per 100,000)	2006-2010	Age-adjusted rates of accidental, intentional, and of undetermined poisoning by and exposure to various drugs illicit and non-illicit	https://healthdata.gov
Cultural variables			
Average family size	2000	Families have ≥2 members related by birth, marriage or adoption	http://www.census.gov
Family households (%)	2000	Family households have at least ≥2 people related by birth, marriage, or adoption living in same house	http://www.census.gov
LDS (per 1000)	2000	Adherents in congregations (baptized members plus their children)	http://www.theARDA.com
Race (% White, Hispanic)	2000	Percentages of people by race, White or Hispanic.	http://www.census.gov
Economic variables			
Median Household Income ($)	2010	Estimated by Census Bureau based on data for the SAIPE program	https://healthdata.gov
Physician use delayed due to cost (%)[§]	2004-2010	Estimates based on BRFSS survey question about physician use being delayed due to cost in the past year	https://healthdata.gov
Population density (per square mile)	2010	Number of persons divided by total land area	https://healthdata.gov
Poverty (%)[§]	2007	Estimated by Census Bureau based on data for the SAIPE program	https://healthdata.gov
Unemployment (%)	2008	LAUS data from the CPS, official measure of the labor force for the nation	https://healthdata.gov
Environmental variables			
Median Elevation (m)	2000	30 m SRTM elevation data (USGS) to calculate median elevation by county	http://www.usgs.gov
Health and lifestyle variables			
Binge drinking (%)§	2005-2011	Adults 18+ drinking > 5 drinks (men) or > 4 drinks (women) at one time. Estimates based on BRFSS survey question	https://healthdata.gov
Medicare beneficiaries with depression (%)[§]	2008	% of Medicare beneficiaries (adults 65+ and disabled) with depression	https://healthdata.gov
Mentally unhealthy days (past 30 days)	2005-2009	For adults 18+. Estimates based on BRFSS survey	https://healthdata.gov
Physically unhealthy days (past 30 days)	2005-2009	For adults 18+. Estimates based on BRFSS survey	https://healthdata.gov
Smoking (%)[§]	2003-2009	Estimates based on BRFSS survey	https://healthdata.gov
Suicide (per 100,000)[§]	2005-2011	Deaths from an act inflicted on oneself with intent to kill – intent determined by coroner	https://healthdata.gov
Years of potential life lost < 75 years[§]	2006-2008	Sum of life-years lost among persons dying before age 75 divided by persons under age 75	https://healthdata.gov

Behavioral Risk Factors Surveillance System (BRFSS) survey, estimates based on fewer than 50 cases are unreliable and removed.
SAIPE, Small Area Income and Poverty Estimates program; LAUS, Local Area Unemployment Statistics;
CPS, Current Population Survey; SRTM, Shuttle Radar Topography Mission; USGS, United States Geological Survey; NCHS, National Center for Health Statistics.
Years of potential life lost < 75 years puts more emphasis on causes of death that are more common at earlier ages, because persons dying at younger ages will have more years subtracted from age 75. Therefore it may underestimate the importance of chronic and other conditions occurring later in life.
[§] Rates are total (both genders, all races) and age-adjusted.

a direct comparison between studies. Further information on data sources and statistical methods is given in the supplementary material.

Table 1 summarizes the dataset used in this study. The rates were total (both genders and all races) and age-adjusted (Table 1). Risk factor data for the same time period as DPD were not always available, therefore, the most complete data and years/year ranges closest to the DPD data were selected.

Data on family structure and race were obtained from http://www.census.gov and most other health/lifestyle and socio-economic variables were obtained from https://www.healthdata.gov. Data for LDS membership were obtained from the association of religious data archives. County-level LDS membership from the 2000 survey were used in this study (Fig. 1a). Median county elevation was calculated from 30 m Shuttle Radar Topography Mission (SRTM) elevation data of the United States Geological Survey (USGS, http://www.usgs.gov, Fig. 1b).

2.2. Spatial profile regression

The joint effect of 18 risk factors (Table 1) on Poisson Kriged DPD risk is investigated using Bayesian PR with a Gaussian model. It uses covariate values to observe joint patterns within the data, to reduce the dimensionality of covariates (Coker et al., 2016). This allows investigation of the DPD risk in relation to the joint patterns of multiple risk factors, while accounting for their multicollinearity. To account for the spatially correlated structure in the Poisson Kriged DPD rates, a conditional autoregressive term (CAR) based on a distance-based neighbourhood of 270 km was included in the PR (Liverani et al., 2016).

The optimal number of clusters in PR is not based on ad-hoc rules but is determined by the data. This flexibility provides a mechanism to

incorporate cluster uncertainty into the modelling process, where the uncertainty in the assignment of each county to a cluster and the optimal number of clusters is incorporated (Molitor et al., 2011) through the Markov Chain Monte Carlo iteration and its post-processing (20,000 iterations and 100,000 burn-in period). All statistical analyses including Pearson correlation among covariates were conducted in R (v.3.3.2) (R Core Team, 2015). The PReMiuM package (v.3.1.4) (Liverani et al., 2015) was used for PR.

3. Results and discussion

The correlations among the 18 risk factors include moderate to strong positive and negative correlations between several health and lifestyle variables and among economic variables (Fig. 3). The reasons for most of these associations are somewhat self-evident, nevertheless, they illustrate that multicollinearity is an issue when SR is applied to this data.

3.1. Spatial clusters from profile regression and local Moran's I

For PR: western states (Fig. 4) with and without a CAR term, three clusters: high-, medium- and low-risk were identified (Fig. 5a). Fig. 5 shows the different relative risk of DPD for the three clusters in PR: western states. The box color shows if there are marked differences in DPD risk and every variable for each cluster. If the upper quantile of the simulated risk or a risk factor is below the global mean (black line), the box plot is considered low-risk (blue/light-grey) and if the lower quartile is above the global mean the cluster is considered high-risk (red/black). Boxes for clusters not meeting these criteria are green/dark-grey (medium-risk). Similarly, if there is overlap between two
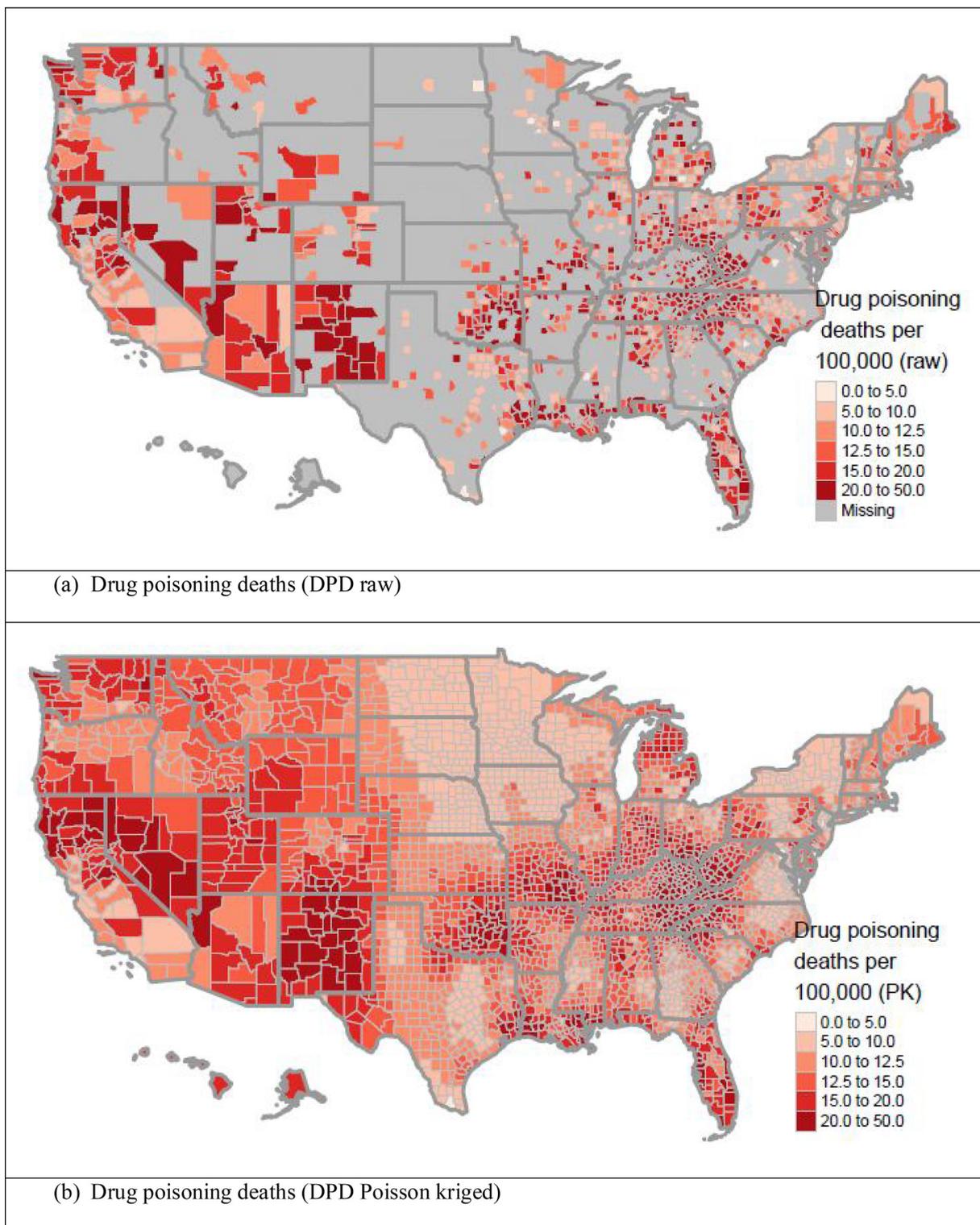
(a) Drug poisoning deaths (DPD raw)

(b) Drug poisoning deaths (DPD Poisson kriged)

Fig. 2. Rates of drug poisoning deaths (DPD) recorded by county for 2006–2010: (a) raw rates and (b) rates estimated by Poisson kriging.

boxes, both are green/dark-grey. Three of the 18 variables: Medicare beneficiaries with depression, physician use delayed due to cost and smoking were excluded for PR: western states due to overlap of boxes in a plot similar to Fig. 5 (not shown). These variables were excluded from PR due to multi-collinearity being accounted for and there being other variables in the study that are more closely linked with mental health, economics and lifestyle choices.

Fig. 4c and d show differences in the spatial configuration of clusters due to a CAR term. The clusters for the CAR model (Fig. 4d) were more

consistent with patterns in Fig. 4a so this was used for PR: western states. The average DPD rate for the west is slightly over 15 per 100,000 while rates for the low-risk, medium-risk and high-risk clusters shown in Fig. 4d are greater than 12.5, 14.5 and 18.5, respectively (Fig. 5a) with ~60, 240 and 110 counties in each cluster. The colors and lack of overlap of the boxes show that there are marked differences in DPD between clusters.

Kerry et al. (2016) used the univariate Local Moran's I to identify significant ($p < 0.05$) clusters of high and low DPD rates. Bivariate
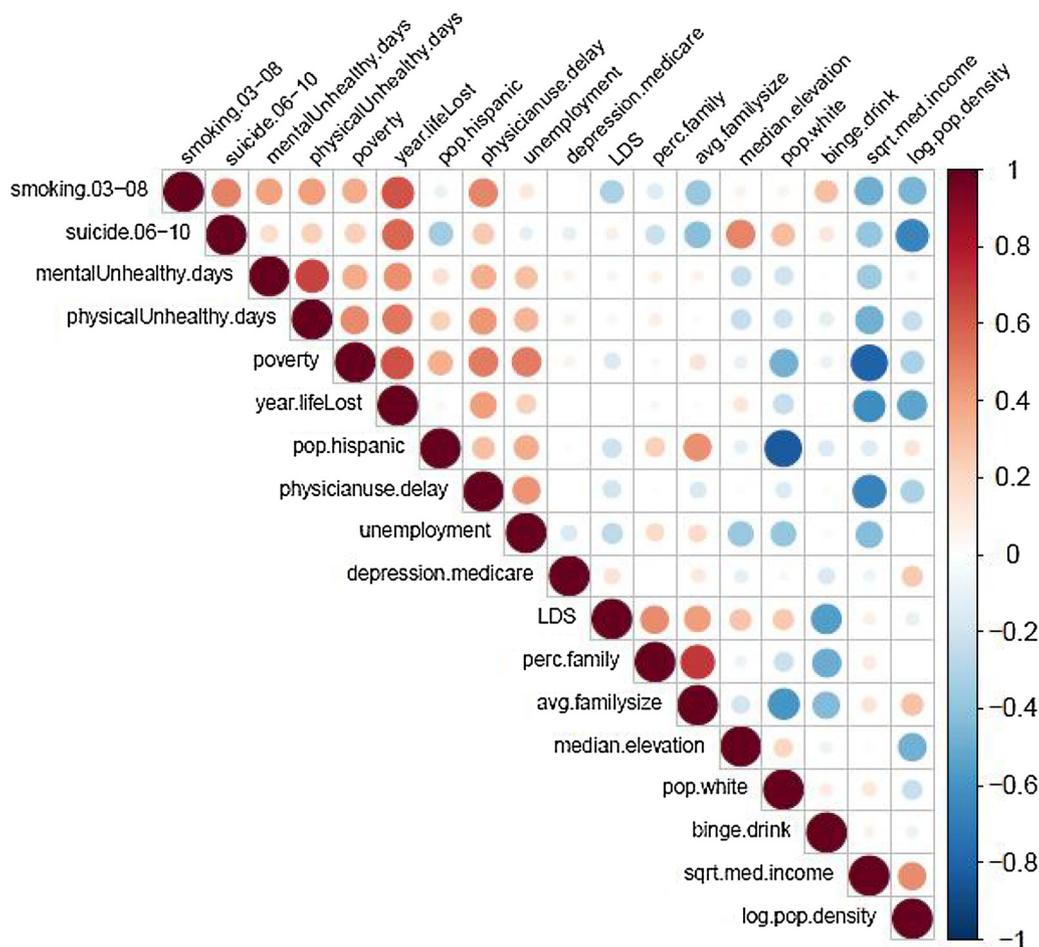
Fig. 3. Pearson correlations among risk factors (explanatory variables). The size of circle represents the magnitude of correlation coefficients. Red/light-grey is a positive correlation coefficient, and blue/dark-grey is negative. n = 3055 so correlation coefficients as low as 0.037 are significant at $p = 0.05$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Local Moran's I analysis was used to identify DPD rates that coincided with high or low rates of other risk factors, so only two variables could be considered at once. In contrast, PR identifies clusters based on all risk factors and DPD so it should more coherently identify the highest risk counties and their characteristics without several individual analyses. Counties identified as in the same cluster by PR have similar risk factor profiles and can therefore be treated the same for policy. Fig. 4d shows that PR: western states identified most of NM, NV and UT and several counties in AZ, CO, ID and WY as high-risk for DPD. In contrast, analysis in the previous study identified large clusters of high-risk counties in northern CA, NM and NV and one in UT. This difference in cluster identification when only DPD data are considered shows the merit of the integrated approach to cluster and regression analysis presented by PR.

Bivariate Local Moran's I in the earlier study, identified differences in the way risk factors were related to DPD in the coastal states and MT compared to the mountain states. This major difference between the mountain states (AZ, CO, ID, NM, NV, UT and WY) and the coastal states and MT was also identified by PR: western states, which is consistent with the literature that has identified the mountain west as particularly high-risk (Rigg et al., 2018). Fig. 4d identifies both urban and rural counties as high-risk suggesting that DPD is not just a rural problem in the mountain west (Rigg et al., 2018).

There are noticeable differences between states with the majority of NM, NV and UT counties being high-risk whereas only the heavily LDS counties in ID (Fig. 1a) are high-risk. AZ, CO and WY have large areas with medium-risk with abrupt changes to high-risk at state borders

(Fig. 4d). This suggests the importance of state drug and healthcare policies/funding. Kerry et al. (2016) compared the number of statewide strategies in place to curb DPD and found significantly more policies ($p = 0.01$) in place in states that voted Democrat in the 2012 general election (CA, CO, NV, NM, OR, WA) and the only states in the region to experience a decrease in DPD (WA, OR and NM) had the Naloxone protocol in place (Trust for America's Health (TAH, 2013). Different states also favor different drug rehabilitation approaches, despite marked differences in the success rates of different types of treatment (D'Onofrio et al., 2015). Jones et al. (2015) identify different provision rates of buprenorphine and methadone treatment between states and Sigmon (2014) notes regional differences in the willingness of clinicians to prescribe buprenorphine. The differences in DPD risk at state borders need further investigation to determine the most appropriate policy changes.

To further investigate the patterns in the high-risk western states, a PR was performed using the same 15 variables. Fig. 4e and 4f show the cluster maps from this PR without and with a CAR term, respectively. Fig. 4b shows spatial autocorrelation in DPDs so PR with the CAR term was used for PR: high-risk western states (Fig. 4f). Two clusters were identified with the largest rates clustered mostly in NM and NV. Three northern AZ counties were identified as high-risk while having markedly lower DPD rates than the rest of the cluster (Fig. 4b). Several counties in southern ID were also identified as high-risk for PR: western states (Fig. 4d). In both cases, these counties obviously had similar risk factor profiles to the other high-risk counties yet lower DPD rates. This could be considered a disadvantage of PR as DPD risk is over-estimated
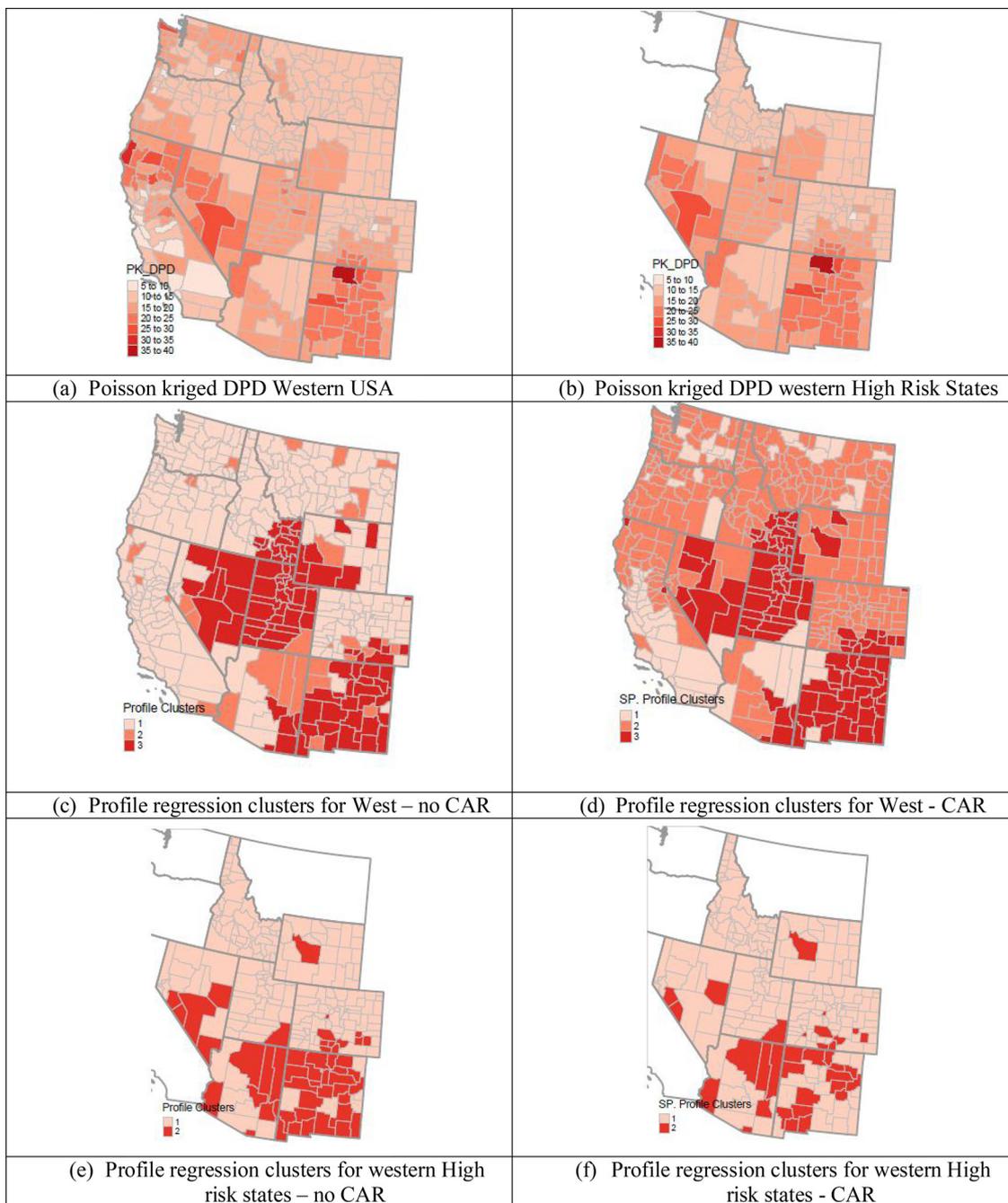
Fig. 4. Maps showing Poisson kriged DPD rates for (a) the western states and (b) high-risk western states. Location of profile regression clusters for western states with (c) no CAR term, (d) a CAR term, and high-risk western states with (e) no CAR term and (f) a CAR term.

and money and resources might be wasted on targeted policies in these counties. However, in PR, the likelihood is estimated based on risk factor profiles so it suggests that the chances of such counties being high-risk or low-risk is high suggesting that these counties could easily flip between clusters. The similar risk factor profiles of these counties to those that have high DPD rates lead to some useful questions. For example, why do these counties have similar risk factor profiles but different rates of DPD? What is different about these counties? Is there a time-lag? Will these counties develop high rates soon? If these questions can be answered policy insights may be possible from these marginal counties.

3.2. Risk factor profiles compared with standard regression

Column 3 of Table 2 gives a simplified summary of the expected relationships with DPD for each of the risk factors based on the conceptual model. Clearly some relationships differ in sign based on whether illicit drugs or PO are being investigated but the distinction between users of both types of drugs is often unclear as users of PO often end up misusing, then abusing illicit drugs (Rigg and Murphy, 2013) and complex relationships exist between these two main groups of DPD (Alexander et al., 2018). As DPD data include deaths from all types of drug, coefficients with the opposite sign in SR (column 4, Table 2) could lead to the conclusion that one type of drug abuse is prevalent when the coefficient sign could be due to multicollinearity, spatial autocorrelation or the existence of complex relationships
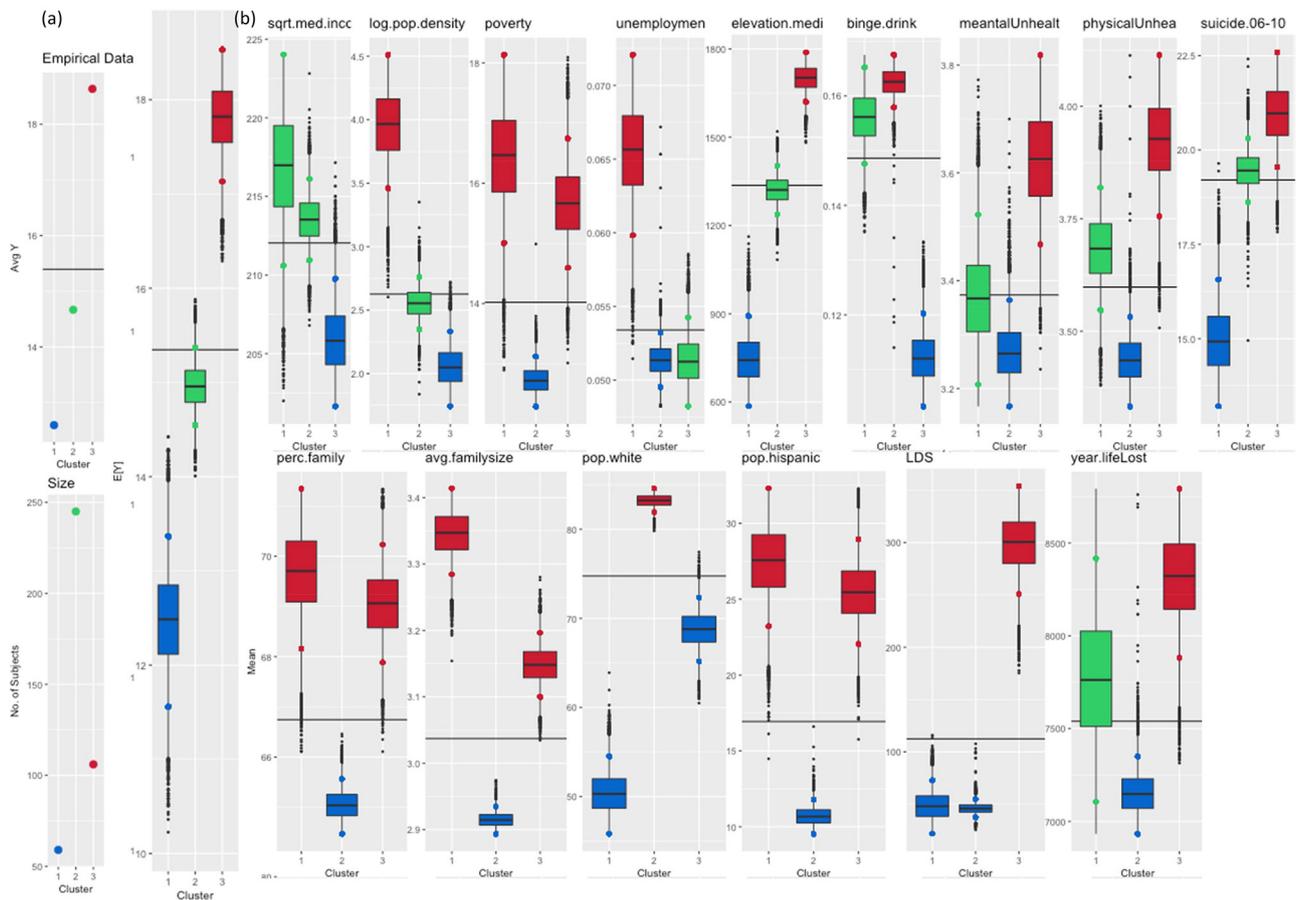
Fig. 5. Relative risk for low, medium and high risk clusters for DPD in the American West for (a) profile regression using 15 variables and a CAR term and (b) associated risk factor profiles. The color of boxes shows if there are marked differences in DPD risk and every variable for each cluster. If the upper quantile of the simulated risk (or a risk factor) is below the global mean (black line), the box plot is considered LR (blue/light-grey) and if the lower quartile is above the global mean the cluster is considered HR (red/black), otherwise boxes are green/dark-grey. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

between DPD and particular risk factors.

The SR results from the previous study are summarized in column 4 of Table 2 and columns 5 and 6 show abridged results for the risk factor profiles of PR: western states (Fig. 5) and PR: high-risk western states (Fig. 6), respectively. The type of relationship was determined by comparing the configuration of box plots for each risk factor to that for DPD. When the box plots varied similarly to DPD, namely, if, values of the risk factor for clusters increased as DPD risk of clusters increased, the relationship was considered positive. If the opposite pattern was observed, the relationship was negative. When all boxes were green, the relationship with DPD was considered not significant (NS) and the variable was excluded. Finally, when both low-risk and high-risk clusters of a risk factor had high (low) values but the medium-risk cluster had low (high) values, the relationship was designated mixed/non-linear.

3.2.1. Cultural risk factors

The conceptual model suggests negative relationships between % family households, average family size and %LDS and DPD (Table 2). For SR and PR: high-risk western states, average family size was not significant. This suggests that what is important for helping prevent DPD is not family size but being part of a family household. While % family households showed the expected negative relationship with DPD in SR and PR: high-risk western states, the relationship was mixed/non-linear for PR: western states for %family households and average family size. Fig. 5 shows that the high-risk and low-risk clusters both have large %family households and average family size compared to the

medium-risk cluster.

For PR: western states, %Hispanic and %White show mixed/non-linear relationships with DPD but the patterns are opposite for the two variables (Fig. 5). The %LDS shows a largely positive relationship with DPD which is unexpected (Table 2, Fig. 5). So PR: western states suggests that the high-risk counties have a large %LDS, %family households, average family size, %Hispanic and a low %White. In contrast, PR: high-risk western states showed the highest risk counties to have lower %family households, %White, %LDS and higher %Hispanic.

Some findings for cultural variables for PR: western states were contrary to existing literature from individual-level studies whereas PR: high-risk western states was more consistent with it. The latter showed negative relationships with %family households (Lanier et al., 2013; Reddy et al., 2014) and %LDS (Merrill et al., 2013) as in the literature. The different results for SR, PR: western states and PR: high-risk western states show the difficulty in making inferences about causality from population-level studies rather than individual-level studies. Nevertheless, they can identify the characteristics of the highest risk counties.

The positive association of DPD with LDS for SR and PR: western states suggests that in the west this relationship dominates at the population-level. The implications of this finding are that the naïve behavior observed with regard to PO in heavily LDS UT (Porucznik et al., 2011) leads to PO being a dominant pathway to addiction in heavily LDS areas. This suggests that greater education about POs is needed in heavily LDS counties. Second, individual-level studies emphasize the characteristics of those who die as not having family support, (Lanier

Table 2
Summary of results from Profile regression and standard regression (Kerry et al., 2016) for comparison.

Variable Group	Variables	Expected relationship given conceptual model	Standard Regression (western states)	Profile Regression (western states) 15 variables and CAR	Profile Regression (high-risk western states) 15 variables and CAR
Cultural	Average family size	Negative	NS	Mixed/non-linear	Positive (NS)
	Family households (%)	Negative	Negative	Mixed/non-linear	Negative
	LDS rate	Negative	Positive	Positive	Negative
	%Hispanic	Negative - PO Positive – illicit	Positive	Mixed/non-linear	Positive
	%White	Positive - PO	Positive	Mixed/non-linear	Negative
Economic	Median Household Income	Negative – illicit Positive – PO	NS	Negative	Negative
	Physician use delayed due to cost	Negative - illicit Positive - PO	NS	Excluded	Excluded
	Population density	Negative – PO Positive – illicit	Negative	Negative	Negative
	Poverty	Negative - PO Positive – illicit	Negative	Mixed/non-linear	Positive
	Unemployment	Negative – PO Positive –illicit	Positive	Negative	Positive
Environmental	Elevation	Positive	Positive	Positive	Positive (NS)
Health and Lifestyle	Binge drinking	Positive	Negative	Mixed/non-linear	Negative (NS)
	Medicare beneficiaries with depression	Positive	Positive	Excluded	Excluded
	Mentally unhealthy days (in past 30 days)	Positive	Positive	Mixed/non-linear	Positive
	Physically unhealthy days (in past 30 days)	Positive – particularly PO	NS	Mixed/non-linear	Positive
	Smoking	Positive	Positive	Excluded	Excluded
	Suicide	Positive	Positive	Positive	Positive (NS)
	Years of potential life lost < 75 years	Positive	Positive	Mixed/non-linear	Positive

NS = Not Significant.

et al., 2013; Reddy et al., 2014), but PR: western states identifies characteristics of communities where DPD are high. Taken together, this suggests that those without family support in heavily religious areas with large average family size may be overlooked and are particularly high-risk groups. Therefore, more safeguards are needed for those living alone who are prescribed PO or are illicit drug users in these counties. General policies that reduce social isolation should also increase the success rate of those participating in rehabilitation programs.

Given the relationships observed for PR: western states and PR: high-risk western states, the DPD problem could be summarized as widespread PO deaths with high-risk counties also having high rates of illicit DPD. This is perhaps due to the documented pathway of PO acting as a gateway drug (Cicero et al., 2014) and the complex relationship which now exists between those abusing PO and heroin (Compton et al., 2016). Finally, the high-risk clusters for both PR: western states and PR: high-risk western states have relatively high %Hispanic and low %White. This suggests either a dominant PO problem in heavily Hispanic counties with low income white communities (Friedman et al., 2019) or that the DPD problem in the west is largely a result of illicit drugs (Merrill et al., 2013). Also due to widespread poverty and associated lack of health insurance the Hispanic community may be more at risk from DPD through PO and heroin use from illicit sources and due to lack of access to treatment programs. Clearly, individual-level studies in the highest risk counties and states identified here are needed to confirm which of these suggestions are correct and to properly inform policy.

3.2.2. Economic risk factors

The simplified summary of the conceptual model (Table 2) shows opposite relationships prevalent for PO and illicit drugs. While these patterns have been observed, there is much overlap in the demographics of PO and illicit drug users in the contemporary drug market (Compton et al., 2016). Each type of regression found the risk factor

variable of 'physician use delayed due to cost' to be unimportant suggesting that it is long-term, rather than short-term economic difficulties, that are important to DPD. Indeed, the spatial patterns of the highest risk counties have been linked to social determinants of health (Novilla et al., 2011) and rural regions with traditional industries that are in decline and low-income levels. Dasgupta et al. (2018) note that such social and economic determinants of DPD are not easily fixed. This suggests that the temporally consistent spatial patterns at the county-level may be reflecting long-term patterns of social and economic disadvantage. For PR: western states, the dominant negative relationships with economic factors suggest that high-risk counties have low median household income, low population density and low unemployment.

Counties with low population density being high-risk is consistent with high rates of PO deaths in rural areas (Rigg et al., 2018; Rose et al., 2018; Wagner et al., 2019). PO are initially prescribed by a doctor, and perhaps with lack of frequent contact/monitoring of prescriptions in rural areas due to distance to medical facilities PO deaths becomes more frequent.

Low income communities with low unemployment being high-risk is consistent with previous findings where the highest rates of PO prescription were in low-income white communities (Friedman et al., 2019), yet to obtain a prescription individuals need some form of health insurance which usually comes with employment. The mixed/non-linear relationship with poverty for PR: western states shows high levels of poverty in the high-risk and low-risk clusters but for PR: high-risk western states, poverty and unemployment are both positively related to DPD as may be expected in areas with high rates of illicit DPD or with poorer PO abusers who tend to obtain them from illicit sources (Cicero et al., 2012).

The high %poverty, %unemployment and %Hispanics in the highest risk counties suggest that DPDs are strongly related to social determinants of health. The lack of health insurance among those employed in low income jobs could promote use of illicit sources of PO for pain management and also result in no access to drug rehabilitation
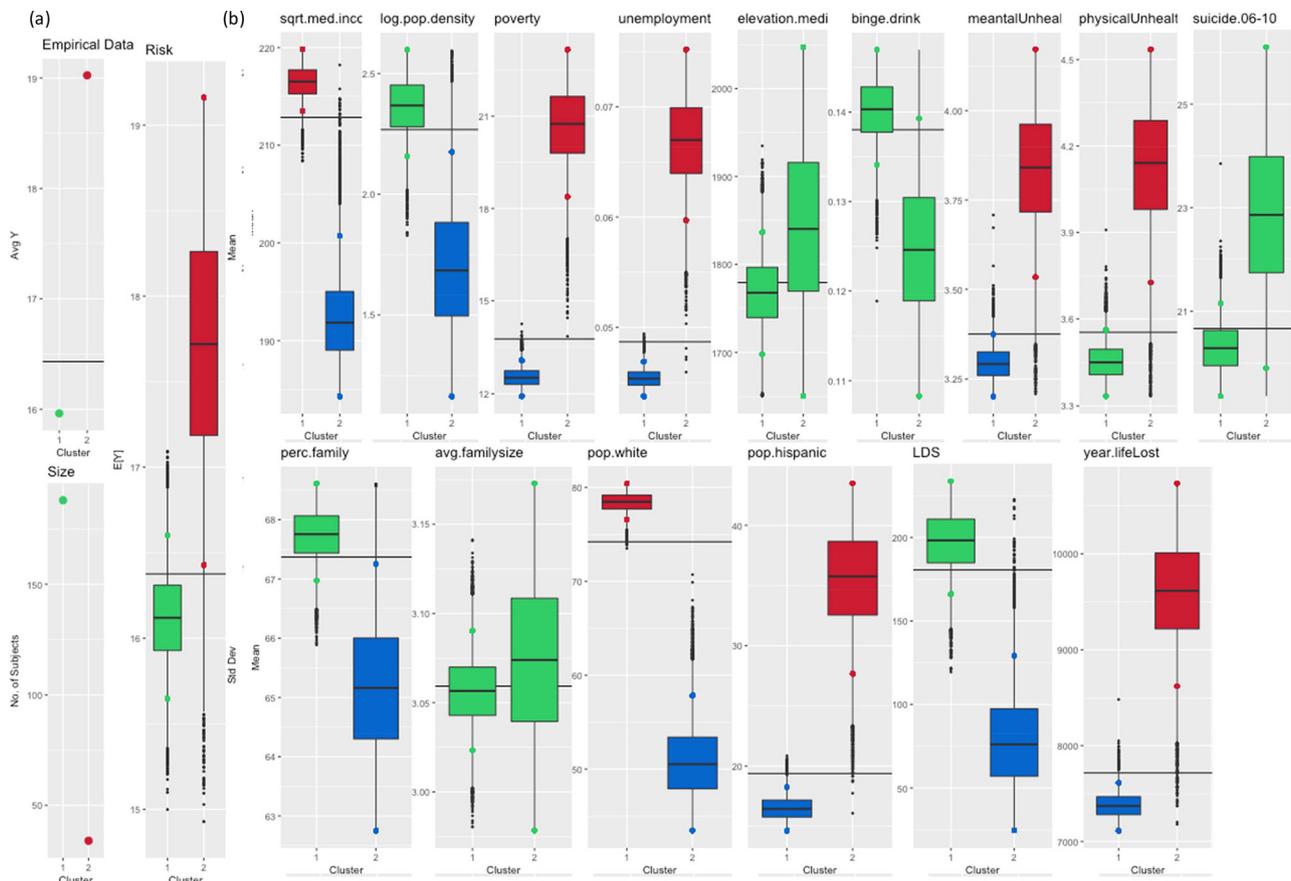
Fig. 6. Relative risk for low and high risk clusters for DPD in high risk states in the West for (a) profile regression using 15 variables and a CAR term and (b) associated risk factor profiles. The color of boxes shows if there are marked differences in DPD risk and every variable for each cluster. If the upper quantile of the simulated risk or a risk factor is below the global mean (black line), the box plot is considered LR (blue/light-grey) and if the lower quartile is above the global mean the cluster is considered HR (red/black), otherwise boxes are green/dark-grey. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

facilities. In addition, while the unemployed can access Medicaid, it was not until the 2010 Affordable Care Act (ACA), that it was mandatory for all health insurance providers, including Medicaid, to cover all basic aspects of drug and alcohol dependency recovery. Given the data used in this study the effect of this extended availability of rehabilitation treatment will not be seen. Also, not all facilities will accept Medicaid as a form of payment, and this might be a particular problem in rural areas where treatment facilities are few and far between. So, policies that increase access to treatment programs for those on Medicaid and without health insurance are needed.

3.2.3. Environmental risk factor

Elevation was positively related to DPD for SR, PR: western states and PR: high-risk western states which is consistent with the conceptual model that suggests that low oxygen at high elevation influences brain chemistry and makes depression, PO and illicit drug use and suicide more likely (Brenner et al., 2011). For PR: high-risk western states, however, the relationship was not strong (Fig. 6 - boxes green/dark-grey) suggesting that elevation thresholds exist. For health purposes, 2,100 m is considered high elevation as above this height, the saturation of oxyhemoglobin in the blood begins to decrease rapidly (Young and Reeves, 2002). Elevation has obvious links with several risk factors in this study such as population density and other economic variables, however, the strongest correlations (Fig. 3) were with suicide and population density, about 0.5 and -0.5, respectively. Given the link with population density, some of the issues raised with regard to rural areas could be particularly important in high elevation rural areas. The link with suicide suggests that mental health evaluations should be

mandatory when prescribing PO in high elevation counties.

3.2.4. Health and lifestyle risk factors

The conceptual model suggests a positive relationship is expected with DPD and each health and lifestyle variable (Table 2). However, suicide was the only one that showed positive relationships for SR, PR: western states and PR: high-risk western states. Positive associations with DPD were also found for SR and PR: high-risk western states for mentally unhealthy days, physically unhealthy days, and years of potential life lost < 75 years (Table 2).

Mental health (Cheng et al., 2013; Johnson et al., 2013; Webster et al., 2011), physical health (Lanier et al., 2013; Sehgal et al., 2012; Wang et al., 2012) and suicide (Donaldson et al., 2006) have been associated with high levels of DPD in general but lack of physical health has been associated slightly more with PO deaths (Cheng et al., 2013; Sehgal et al., 2012; Wang et al., 2012). Indeed, WHO (2017) state that it was the misguided extension of PO treatment to those in long-term pain in the 1990s that has been the dominant cause of the recent increase in DPD.

For PR: western states, the mixed/non-linear relationships between DPD and mentally unhealthy days, physically unhealthy days and years of potential life lost < 75 years show the high-risk DPD cluster associated with the highest values of mentally unhealthy days, physically unhealthy days and years of potential life lost < 75 years, yet the low-risk cluster has higher values of these variables than the medium-risk cluster. These complex relationships suggest that there are counties with high values of these variables and DPD where people are receiving PO treatment and becoming addicted and there are counties with high

values of these variables but low DPD where people are not receiving PO treatment. Spatial spikes in prescriptions throughout the west should be investigated to see if this is fueled by over-prescription or other socio-economic determinants of health discussed earlier. Also, the link between DPD and mentally unhealthy days suggests that mental health evaluations should accompany PO prescription.

Finally, binge drinking is a lifestyle variable that has been positively associated with illicit and PO use/abuse in individual-level studies (Cheng et al., 2013; Drabble et al., 2016; Johnson et al., 2013; Lanier et al., 2013) yet for PR: high-risk western states (Fig. 6) and SR (Table 2) it showed a negative relationship and a mixed/non-linear relationship for PR: western states (Fig. 5) with a dominant negative feature. This reflects the population characteristics with a large degree of abstinence from smoking and drinking in the high-risk western states associated with prevalence of the LDS faith (Fig. 1a). Evidence from previous individual-level studies in the area suggests that minorities in the population that are prone to substance abuse (Johnson et al., 2013; Lanier et al., 2013) are at high-risk of DPD and are being overlooked in heavily LDS counties. Any policies that could reduce the social isolation of these minorities in heavily LDS counties should help reduce DPD.

3.3. Limitations

The biggest limitation of the present study lies in the absence of separate data on PO deaths, illicit DPD and deaths from other prescription/over-the-counter medications. The latter are not explicitly considered in the conceptual model. The lack of separate data makes interpretation of regression outcomes difficult. The use of county-level DPD rates and covariates were required for spatial investigations at the regional scale but using such data assumes that population-level associations hold true at the individual-level (Loney and Nagelkerke, 2014) and one cannot determine causality without a controlled experiment. However, the design is appropriate for making geographical comparison and examining spatial patterns at the county-level (Coggon et al., 2003). It can help identify the highest risk counties where individual-level studies should be completed to confirm characteristics of the high-risk groups.

Some bias could result from the temporal mismatch between DPD and risk factor data, however, spatial patterns in relation to race and religion are somewhat stable over time with religious and Hispanic communities generally having larger families (Colby and Ortman, 2015; Lipka, 2015) even though average family size has decreased in all communities. The implications for DPD of state-level differences in healthcare policies and legislation/funding to combat drug problems were not explicitly considered here, but should be in future spatial studies.

4. Conclusions

This study demonstrated that spatial PR is effective in achieving two aims: identifying counties with high-risk of DPD and determining important characteristics of those counties. The analysis offers additional insights compared to SR and separate cluster analysis and shows that it is important to take into account multi-collinearity and spatial autocorrelation.

Elevation, suicide and population density showed consistent relationships with DPD across types of analysis showing that these are key variables to DPD in the west. Results showed that the coastal states behaved differently from the mountain states. The high-risk cluster for PR: western states was concentrated in NM, NV and UT with some abrupt changes at state borders suggesting that policies and funding differences between states influence DPDs. Variables that were excluded from PR analysis were clearly correlated with other economic and health and lifestyle variables so accounting for multi-collinearity helped more specifically identify the most important risk factors. The coherent cluster and regression procedure of PR should help public

health policies such as funding for prevention, education and medical services to be more focused to the characteristics of high-risk groups and where they are located spatially.

The PR: western states identified 3 types of cluster which allowed identification of non-stationary and complex relationships which is not possible with SR. The ability of PR to identify such complex relationships in the data is helpful for DPD where the characteristics of different drug users can be complex. While there was some conflicting evidence between this population-level and individual-level studies in the literature, this analysis was able to identify the characteristics of high-risk counties and further individual-level studies should be able to identify the individuals at high-risk within those counties.

The analysis of risk factor profiles along with existing literature suggests that high-risk counties for DPD in the west are rural, high elevation, low income/high poverty, heavily LDS and Hispanic counties with large %family households. Safeguarding policies for those living alone in such communities need to be implemented to reduce DPD as well as improving access to treatment facilities for those without health insurance or on Medicaid.

Contributors

The first and second authors conceived the need for the study. The first author gathered and pre-processed data as did the third author. The first author closely consulted with the second author who completed most of the data analysis. The first author wrote the majority of the first draft of the paper while the second author wrote a methodological section and the second and third authors provided editorial input to different drafts of the paper. The first author made most of the revisions required by reviewers and the second and third authors provided editorial input and approved the final version.

Declaration of Competing Interest

No conflict declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.107598.

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