Association between altitude, prescription opioid misuse, and fatal overdoses

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A B S T R A C T

Objective: Prescription opioid misuse and fatal overdoses have increased significantly over the last two decades. Living at altitude has been linked to greater reward benefits of other drugs of abuse, and living at altitude may also exacerbate the respiratory depression linked to opioid use. Therefore, we examined the relationships between living at altitude, and prescription opioid misuse and fatal overdoses.
Method: State-level past year rates of prescription opioid misuse were retrieved from the Substance Abuse and Mental Health Services Administration. County-level overdose data were extracted from the Centers for Disease Control and Prevention. Multiple linear regression models were fit to determine the relationship between average state elevation and state rates of opioid misuse. Logistic regression models were fit to determine the relationship between county elevation and county-level fatal opioid overdose prevalence.
Results: After controlling for state opioid prescribing rates and other confounders, we identified a significant positive association between mean state altitude and state-level opioid misuse rates for women, but not men. We also found a significant positive association between county-level altitude and prevalence of fatal opioid overdose.
Conclusions: Living at altitude is thus demographically associated with increasing rates of misuse of prescription opioids, as well as of cocaine and methamphetamine. Animal studies suggest that the hypobaric hypoxia exposure involved with living at altitude may disrupt brain neurochemistry, to increase reward benefits of drugs of abuse. This increased misuse of both stimulants and opioids may increase likelihood of overdose at altitude, with overdoses by opioid use also potentially facilitated by altitude-related hypoxia.

The widespread use and misuse of prescription opioids has become a significant issue in the United States in the past two decades. In the US, the amount of opioids prescribed tripled between 1999 and 2015 (Centers for Disease Control and Prevention, 2017a), and in 2015, enough opioids were dispensed to give every American adult a 3-week prescription (Centers for Disease Control and Prevention, 2017b). Furthermore, in 2015, around 97.5 million American adults (36.4%) were using prescription opioids and 12.5 million (4.7%) were misusing them (*Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health, 2017*). Between 1999 and 2015, fatal overdoses via prescription opioids increased by 397% to 17,133 deaths in 2015 (*Multiple Cause of Death 1999–2016 on CDC WONDER Online Database, 2017*). In addition, despite suggestions that opioid misuse may be stabilizing in the US since 2015 (*Key Substance Use and Mental Health Indicators in the United States: Results From the 2016 National Survey on Drug Use and Health, 2017*), emergency department visits related to opioid overdose increased significantly from 2016 to 2017, irrespective of other risk factors (Vivolo-Kantor et al., 2018). This high prevalence of opioid prescriptions has increased the focus on determining risk factors for susceptibility to opioid misuse and fatal opioid overdose.

Rates of opioid-related problems display significant differences based on sex and geographical location. In the US, women are prescribed opioids more often than men (Raofi & Schappert, 2006), but

men are more likely to misuse opioids and to overdose (Back, Payne, Simpson, & Brady, 2010; Hall et al., 2008; Jones, 2012). Rates of opioid prescriptions also vary significantly with geographical region in the US, with Southern regions having the highest opioid prescription rates (McDonald, Carlson, & Izrael, 2012). Rural-urban differences have been noted in substance abuse for years (Dombrowski, Crawford, Khan, & Tyler, 2016), and significant geographical variations have been documented in drug-related mortality rates across the US (Rigg, Monnat, & Chavez, 2018; Rossen, Khan, & Warner, 2013). Rural areas exhibit significantly higher opioid overdose rates than urban areas (Rigg & Monnat, 2015). However, rates of opioid-related medical visits and mortality vary significantly within the rural US, being high in predominantly rural states such as Maine, West Virginia and Kentucky, but amongst the lowest in rural states such as Iowa and Nebraska, suggesting that other crucial geographic and region-based socio-economic factors may be in play here (Keyes, Cerda, Brady, Havens, & Galea, 2014; Rigg et al., 2018). Efforts to understand geographical differences as they influence drug-related risks have been suggested to point to a range of "social ecological" factors underlying these differences (Dombrowski et al., 2016).

Another geographic factor which may play a role in prescription opioid misuse and overdose is living at altitude. Barometric pressure decreases with increasing altitude, causing a decrease in inspired oxygen (hypobaric hypoxia). In animal models, hypobaric hypoxia can significantly increase brain dopamine transmission (Akiyama et al., 1991; Parrot, Cottet-Emard, Sauvinet, Pequignot, & Denoroy, 2003; Ray et al., 2011), the neurotransmitter largely responsible for the rewarding and euphoric effects of drugs. An altitude-related increase in brain dopamine may explain the demographic association found previously between altitude of residence and increased use of cocaine (Fiedler, Kim, Kondo, & Renshaw, 2012) and methamphetamine (Kim, Kondo, Kim, & Renshaw, 2014). Although the mechanisms of dopamine release may differ amongst different drugs of abuse, in general, the more dopamine that is released through the reward pathway the greater the euphoria or "high" that is experienced by a drug user. Opioids are known to cause strong feelings of euphoria, and increased dopamine within reward pathways may enhance the rewarding properties of opioids, to reinforce misuse.

Opioid use is also associated with depression of respiratory function (Dahan, Aarts, & Smith, 2010). Although the exact mechanisms are still unclear, it is widely understood that mu (μ) opioid receptors of the brainstem play a significant role in opioid-induced respiratory depression. While typically negligible at lower doses, this can become hazardous when opioids are used in high doses or in conjunction with alcohol or drugs such as benzodiazepines, leading to dangerous and even fatal decreases in oxygen intake (White & Irvine, 1999).

Inspired oxygen levels decrease with increasing elevation beginning at roughly 2100 ft (Grover, Weil, & Reeves, 1986), with approximately 46 million Americans (14%) residing above this threshold (US Census Bureau, 2017). Living in regions of altitude is linked to multiple negative behavioral outcomes including depression (DelMastro et al., 2011; Gamboa, Caceda, & Arregui, 2011; Zaeh et al., 2016), anxiety (Ahmad & Hussain, 2017; Scholl et al., 2016), and suicidal behavior (Alameda-Palacios, Ruiz-Ramos, & Garcia-Robredo, 2015; Asirdizer et al., 2018; Brenner, Cheng, Clark, & Camargo Jr., 2011; Haws et al., 2009; Helbich, Bluml, Leitner, & Kapusta, 2013; Kim et al., 2011; Ortiz-Prado et al., 2017), and these effects are documented worldwide, irrespective of significant cultural differences and other risk factors. This suggests that living at even moderate altitudes can alter brain physiology and behavior, potentially due to hypobaric hypoxia. Although compensatory mechanisms, such as increased respiration, exist to acclimatize to higher altitudes (Pierson, 2000), studies indicate that these mechanisms do not completely adjust for the oxygen deficiency (Crapo, Jensen, Hegewald, & Tashkin, 1999). Since opioids may critically reduce levels of inspired oxygen, the hypoxia inherent in living at altitude may intensify respiratory deficits for opioid users, to increase the

likelihood of fatal overdose.

The relationship between altitude, oxygen intake, and brain dopamine levels suggest that prescription opioid misuse and overdose may increase with increasing altitude. Determining the relationship between these variables may elucidate which populations are especially vulnerable to opioid misuse and overdose. Using prescription opioid misuse and overdose data from national databases, we hypothesized that (Centers for Disease Control and Prevention, 2017a) misuse of opioids may be positively associated with altitude of residence, after adjusting for opioid prescription rates and health insurance coverage, and that (Centers for Disease Control and Prevention, 2017b) prevalence of fatal overdose by prescription opioids may be positively associated with altitude of residence, after adjusting for opioid prescription rates and county-urbanization classification.

1. Method

1.1. Past year misuse of prescription opioid pain relievers

Average state estimates for the prevalence rates of individuals that misused prescription opioids within the past year were obtained from the 2015–2016 National Survey of Drug Use and Health (NSDUH) conducted by the Substance Abuse and Mental Health Administration (SAMHSA) (*2016 National Survey on Drug Use and Health: Methodological Summary and Definitions*, 2017; *National Survey on Drug Use and Health*, 2017). The 2015–2016 NSDUH surveyed 190,106 civilian, non-institutionalized Americans aged 12 and older. Past year pain reliever misuse is defined by the NSDUH as "use of opioids such as hydrocodone (e.g., Vicodin®), oxycodone (e.g., OxyContin® and Percocet®), and morphine in any way not directed by a doctor, including use of someone else's prescription; use in greater amounts, more often, or longer than told; or use in any other way not directed by a doctor" (*Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health*, 2017). Data for this study were obtained for the overall population as well as by sex.

1.2. Misuse of prescription opioids covariates

The number of opioid prescriptions dispensed per 100 people for 2015–2016 were obtained from the CDC (Centers for Disease Control and Prevention, 2017d). These rates were subsequently averaged between the two years and included in the model as a potential confounder. State rates of health insurance coverage were retrieved from US Census Bureau (US Census Bureau, 2016). Coverage rates were averaged from both 2015–2016 for analyses. State-level rates of admission to treatment centers for opioid-related problems for 2015 were retrieved from the NSDUH Treatment Episode Data Set (TEDS). Treatment admission data used in this study included "admissions per 100,000 people 12 and older to treatment centers for 'non-heroin opiates/synthetics', including prescription opioids and other drugs with morphine-like effects. Nonprescription use of methadone is not included" (Treatment Episode Data Set (TEDS) 2005–2015, 2017).

To control for the potential impact of state-level differences in demographic composition on opioid misuse, male to female ratios and the median age of the population were obtained from the 2010 US Census (US Census Bureau, 2010). Median ages were subsequently standardized to z-scores for analyses.

1.3. Overdose data for prescription opioids

The number of prescription opioid overdose deaths from 2006 to 2016 was retrieved from the Centers for Disease Control and Prevention Wide-ranging Online Data for Epidemiologic Research system (CDC WONDER) Multiple Cause of Death database (*Multiple Cause of Death 1999–2016 on CDC WONDER Online Database*, 2017). CDC WONDER provides mortality data using the underlying cause of death and

subsequent contributing causes listed on official death certificates. States provide standardized underlying and contributing cause of death codes to the National Center of Health Statistics (NCHS) (Centers for Disease Control and Prevention & National Center for Health Statistics, 1999).

The number of prescription opioid overdose deaths between 2006 and 2016 were identified in CDC WONDER based on an underlying cause of death of "accidental" or "undetermined" intent (codes: X40–X44, Y10–Y14) that involved a contributing cause of "other opioids" or "methadone" (codes: T40.2, T40.3). Heroin, fentanyl, and other illicit opioid overdoses are not included within these codes. Overdose death data as well as population estimates of the underlying population were retrieved at the county-level for the overall population and by sex. Estimates of the annual populations were extrapolated by CDC WONDER from the 2000 and 2010 decennial census. Subpopulations in each county with < 10 deaths were suppressed to maintain confidentiality. Also, death rates based on counts of < 20 have a high relative standard error and are considered statistically unreliable by the CDC (*Multiple Cause of Death 1999–2016 on CDC WONDER Online Database,* 2017), therefore county populations with < 20 deaths were excluded from our analyses.

1.4. Opioid overdose covariates

To control for the potential impact of urbanization on opioid overdoses, county urbanization classifications were downloaded through CDC WONDER. CDC WONDER uses the 2013 Urban-Rural Classification Scheme for counties to assign one of six levels of urbanization (Ingram & Franco, 2014). County-level opioid prescribing rates between 2006 and 2016 were retrieved from the CDC (Centers for Disease Control and Prevention, 2017d) and averaged between years for analyses.

1.5. Average elevation

Average elevation for state and counties in the contiguous United States was calculated using the Shuttle Radar Topography Mission (SRTM) elevation dataset, developed by the National Aeronautics and Space Administration. The SRTM serves as a global digital topographic database of the earth with approximately 0.1 km spatial resolution providing mean elevations for each square kilometer of each county ($n = 3108$), and state ($n = 49$), including the District of Columbia (Shutte Radar Topography Mission (STRM) Dataset & USG, 2000). One county in Georgia and Montana, two counties in Virginia, and the states of Hawaii and Alaska are not included in the SRTM dataset and are therefore excluded from analysis.

Zonal statistics provided by ArcGIS/ArcInfo 9.3 (ESRI, Redlands, Calif.) and state/county outlines (National Atlas of the United States, 2001) were subsequently overlaid on to the elevation of each square kilometer provided by the SRTM to obtain mean county and state elevations in feet, as done previously in demographic studies related to altitude of residence (DelMastro et al., 2011; Fiedler et al., 2012; Huber, Coon, Kim, Renshaw, & Kondo, 2014).

1.6. Statistical analyses

Multiple linear regression analyses were conducted through the Statistical Package for the Social Sciences 25 (SPSS, Chicago, IL). The first model investigated the association between state altitude and rates of opioid misuse for the overall state population. A second model was subsequently fit and adjusted for average 2015–2016 opioid prescribing rates and health insurance coverage, individuals per 100,000 admitted to treatment facilities for prescription opioid-related problems, as well as state male-to-female ratios and standardized median ages. Admission to treatment facilities and health insurance coverage were considered cofounders since availability of medical care may influence rates of

opioid misuse (Han, Compton, Blanco, & Jones, 2018; SAMHSA, 2016).

Sex-stratified analyses were run to investigate potential sex-differences in rates of opioid misuse for males and females with respect to state elevation. The covariates included in these models were identical to the initial model, however excluded male to female ratios. Standardized ages also only included the corresponding sex for each analysis.

Logistic regression analyses were conducted through JMP software SAS 9.4 (SAS Institute Inc., Cary, NC). The logistic regression using the Williams method was used to accommodate overdispersion. Logistic regression models were fit to investigate the relationship between mean county altitude and county-level opioid death prevalence (further referred to as fatal overdose prevalence). Fatal overdose prevalence was calculated as a ratio of total deaths per county to county population estimates for the overall population and by sex.

The initial model investigated the relationship between mean county altitude and fatal overdose prevalence. This model was then adjusted to account for mean county opioid prescribing rates between 2006 and 2016, and county urbanization. The model was then stratified by sex to examine sex-specific associations between elevation and fatal overdose prevalence at the county-level. Fatal overdose prevalence odds ratios were reported for every 1000 ft elevation gain. Statistical significance for all analyses was defined at an alpha level of 0.05 (two-tailed).

2. Results

### 2.1. Prescription pain reliever misuse

The initial regression model for the total population did not detect a significant relationship between state-level prescription pain reliever misuse rate (adjusted $R^2 = 0.03$, $F(1, 48) = 2.568$, $p = 0.12$) and elevation ($\beta = 0.228$, $p = 0.12$). Following adjustment for state-level prescribing rates, health insurance coverage, opioid treatment center admissions, as well as state variability in age and sex-composition, the model (adjusted $R^2 = 0.086$, $F(6, 48) = 1.754$, $p = 0.132$), again did not detect a relationship between state elevation and rates of misuse ($\beta = 0.437$, $p = 0.06$) (Fig. 1a, Table 1).

For opioid misuse rates in men, the crude model (adjusted $R^2 = -0.017$, $F(1, 48) = 0.201$, $p = 0.66$) did not show any relationship between altitude and misuse ($\beta = 0.065$, $p = 0.66$). The adjusted model (adjusted $R^2 = 0.100$, $F(5, 48) = 2.067$, $p = 0.088$) also did not identify any relationship between elevation and opioid misuse in men ($\beta = 0.164$, $p = 0.28$) (Fig. 1b, Table 1).

However, for women, a significant association was noted between state altitude and opioid misuse rates. The crude model (adjusted $R^2 = 0.12$, $F(1, 48) = 7.23$, $p = 0.01$) found a significant positive association between state elevation and prevalence of prescription opioid misuse ($\beta = 0.365$, $p = 0.01$). Further, the adjusted model (adjusted $R^2 = 0.13$, $F(5, 48) = 2.4$, $p = 0.05$) continued to display a significant relationship between state elevation and increased rates of misuse ($\beta = 0.321$, $p = 0.04$) (Fig. 1c, Table 1). Fig. 2 documents rates of prescription opioid misuse by state, both in the total population (Fig. 2a) and by sex (Fig. 2b) with average state elevations noted (Fig. 2c). Table 1 presents a summary of the multiple regression models.

2.2. Prescription opioid overdose

Due to data unreliability and suppression, our sample for the overall logistic regression models was limited to 1116 counties out of 3108 counties nationwide. These counties however accounted for 92% of all fatal opioid overdoses from 2006 to 2016. In our male-specific model, 799 unique counties were analyzed accounting for 87% of the male overdoses over that period. The 600 counties within the female analyses accounted for 80% of all opioid overdoses for women from 2006 to 2016.
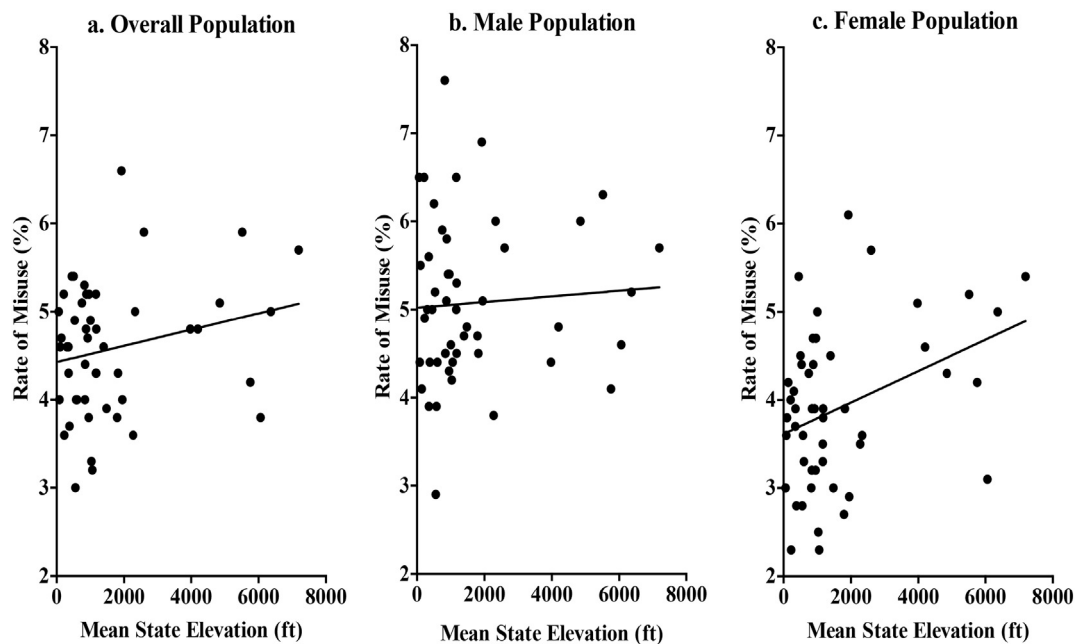
Fig. 1. Rates of prescription opioid misuse increase with mean state altitude in women, but not in men or the total US population. Prescription opioid misuse is plotted by mean state altitude for the (a) total population (adjusted $p = 0.06$), (b) male population and (adjusted $p = 0.28$) (c) female population, (adjusted $p = 0.04$) Data retrieved from the 2015–2016 NSDUH.

Table 1
Association between state-level misuse rates of prescription opioids and mean state altitude: multiple regression output.

Variables	Crude model		Adjusted model[a]	
	Standardized beta coefficient	P value	Standardized beta coefficient	P value
Overall population	0.228	0.12	0.437	0.06
Males	0.065	0.66	0.164	0.28
Females	0.365	0.01	0.321	0.04

Notes: Sex-stratified analyses did not account for state male-female ratios. Data from the 2015–2016 NSDUH.

[a] Adjusted for state opioid prescribing rates, rates of health insurance coverage, admissions to treatment centers for opioids, state standardized ages and sex-differences.

The initial crude model for the overall population detected a significant positive association between county altitude and prevalence of fatal overdoses (OR = 1.073 per 1000 ft, 95% CI [1.041, 1.105], $p < 0.001$), (Fig. 3a, Table 2). The relationship between county altitude and fatal overdose prevalence was robust following adjustment for average opioid prescribing rates and county urbanization classification (OR = 1.074 per 1000 ft, 95% CI [1.049, 1.098], $p < 0.001$).

Following stratification, county-level prevalence ratio odds were positively associated with increasing altitude in men (OR = 1.078 per 1000 ft, 95% CI [1.037, 1.12], $p < 0.001$), (Fig. 3b, Table 2). This relationship held true following adjustment (OR = 1.082 per 1000 ft, 95% CI [1.057, 1.108], $p < 0.001$). In women, a positive association was also found between increasing county elevation and prevalence of fatal opioid overdoses (OR = 1.102 per 1000 ft, 95% CI [1.058, 1.148], $p < 0.001$), (Fig. 3c, Table 2) and was robust to further adjustment (OR = 1.062 per 1000 ft, 95% CI [1.032, 1.092], $p < 0.001$). Table 2 represents a summary of the logistic regression models.

3. Discussion

These data reveal a positive relationship between altitude of residence and past year misuse of prescription opioids in women, but not in men or in the total population. Importantly, these findings hold true while accounting for state prescribing rates, health insurance coverage, and admissions to treatment centers for prescription opioids. We also find that county-level prevalence of fatal overdose by opioid use is positively associated with county altitude, in the whole population as well as in both men and women. This relationship remained significant while controlling for regional opioid prescribing rates, and urban or rural nature of residence. These data add to our previous findings of living at altitude as a risk factor for the misuse of cocaine and methamphetamine (Fiedler et al., 2012; Kim et al., 2014).

Activation of brain reward pathways play a large role in reinforcement of substance misuse behavior. Dopaminergic neurons of the mesolimbic pathway are considered an integral component of the reward pathway. Dopamine released from these neurons is largely responsible for the euphoric and reinforcing effects of many drugs, including opioids (Johnson & North, 1992; Nestler, 2005; Wise & Bozarth, 1985). While the mechanisms and interaction with dopamine may differ between drugs such as methamphetamine, cocaine, and opioids, all three of these drugs have been shown to increase dopamine release within the reward pathway (Wise & Bozarth, 1985). Opioids, for example, are believed to increase dopamine release by blocking gamma-aminobutyric acid (GABA)-mediated inhibition of dopaminergic neurons in the reward pathway (Johnson & North, 1992).

Our studies suggest that the hypobaric hypoxia experienced at altitude may alter the dopaminergic system to enhance drug-related reward and euphoria. Hypobaric hypoxia exposure at extreme high altitudes (20,000–25,000 ft) is shown to increase dopaminergic transmission in the rodent striatum (Akiyama et al., 1991; Parrot et al., 2003; Ray et al., 2011). In pilot studies, we find that housing at moderate altitudes (4500 ft. or 10,000 ft) significantly increases dopamine in the mesolimbic pathway in females. Dopamine increases in the prefrontal cortex, striatum and the ventral tegmental area of female rodents at moderate altitude, but not in males (Sheth, Ombach, Brown, Renshaw, & Kanekar, 2018). This is especially relevant as the relationship between elevated opioid misuse and altitude for women occurs within the moderate altitudes of residence in the US: cities such as Salt Lake City and Denver are at an altitude of 4500–5500 ft.

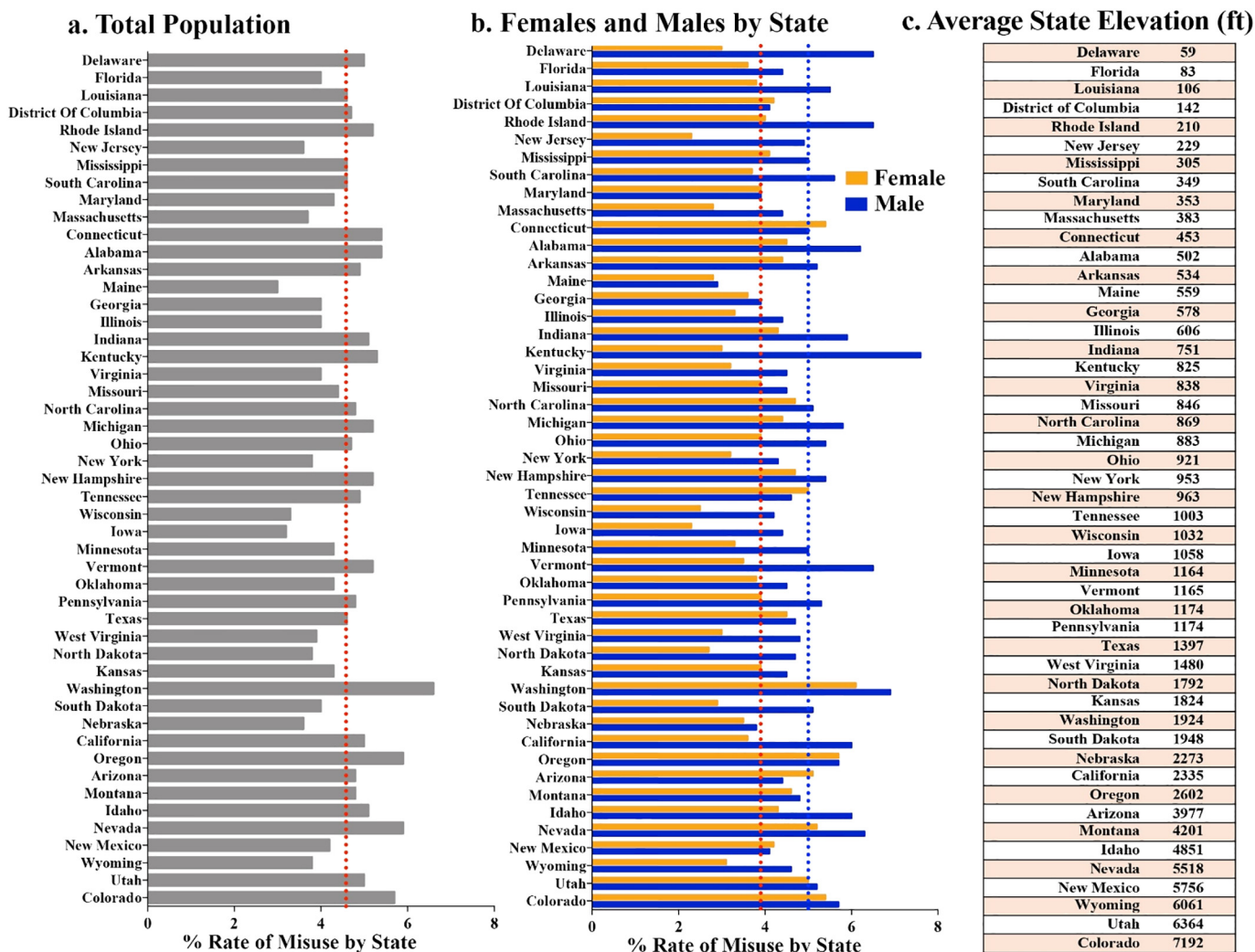These studies suggest that living at even moderate altitudes can be a

Fig. 2. State-level rates of prescription opioid misuse in the United States with respect to average state altitude.
States are ordered by mean altitude, from lowest state altitude (top) to highest state altitude (bottom). Vertical dotted lines represent average rates of prescription opioid misuse for the US population: Averages for the total population = 4.5%, female population = 3.9%, and male population = 5.1%. Data retrieved from the 2015–2016 NSDUH.

risk factor for the misuse of opioids, cocaine and methamphetamine (Fiedler et al., 2012; Kim et al., 2014). Fiedler and Kim did not differentiate between men and women in these studies. However, the sex-based differences noted in the current study are in line with previous animal model studies, which indicate that females may be more vulnerable to altitude-induced disruption of mood and substance misuse behavior (Kanekar et al., 2015; Kanekar et al., 2015; Sheth, Ombach, Olson, Renshaw, & Kanekar, 2018). Sex-based variations in substance abuse and addictive behaviors are widely documented in both humans and in animal models (Becker, 1999; Becker, 2016), potentially caused by sex-based differences in sociocultural and biological risk factors for addiction. Fundamental biological variations can occur as gender differences in the brain reward system, dopaminergic transmission and gonadal hormone impacts on brain neurotransmitters and the reward system (Becker, 1999; Becker, 2016). Sex-based differences have also been documented in behavioral response to stress, with females exhibiting greater vulnerability to the impact of hypoxic stress and neuroinflammation on mood and substance abuse (Bekhbat & Neigh, 2018). We are currently studying how housing at altitude affects reward benefits of methamphetamine use in an animal model (Han et al., 2018). The conditioned place preference (CPP) test is a widely validated measure for the rewarding and reinforcing properties of drugs (Karimi-Haghighi & Haghparast, 2018; Voigt, Riddle, & Napier, 2014).

We find that female rats housed at moderate altitudes exhibit higher methamphetamine preference in the CPP, vs. those housed at sea level, while males may not differ with altitude of housing (Kanekar, Bogdanova, Olson, Nizam, et al., 2015). These findings suggest that living at altitude (with chronic hypobaric hypoxia exposure) may enhance reward benefits of drugs of abuse, potentially with greater impact in women.

An altitude-related increase in rates of prescription opioid misuse would likely increase the impact of altitude on opioid overdoses (Silva, Schrager, Kecojevic, & Lankenau, 2013). However, unlike fatal overdose with other commonly abused drugs, such as methamphetamine and cocaine, opioid overdoses have characteristics that make them particularly vulnerable to being amplified at altitude. The potentially fatal stimulant characteristics of methamphetamine and cocaine are largely due to increased norepinephrine activity, which may cause seizures, hyperthermia, and cardiac arrest (Gay, 1932; O'Connor, Rusyniak, & Bruno, 2005; Zagnoni & Albano, 2002). In direct contrast, opioids *inhibit* norepinephrine release in the brain (Werling, McMahon, Portoghese, Takemori, & Cox, 1989), and target μ opioid receptors.

Mu opioid receptors are highly expressed in the brainstem's respiratory centers, and multiple lines of evidence suggest that activation of these receptors can cause respiratory depression. Upon administration of opioids, wild-type mice display typical respiratory depression,
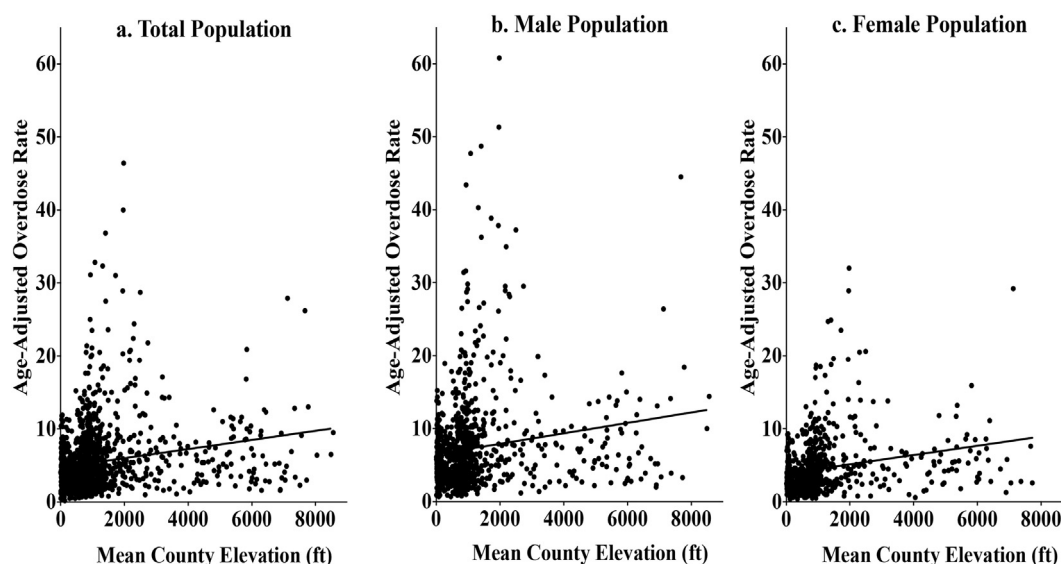
Fig. 3. Rates of fatal overdoses by prescription opioids increase with mean county altitude.
Fatal overdose rates are reported per 100,000 individuals. Overdoses include those of unintentional and undetermined intent between 2006 and 2016. Prevalence rates of fatal overdoses by prescription opioids increase with altitude for the (a) total population, as well as (b) male, and (c) female populations ($p < 0.001$ each). Data retrieved from the CDC WONDER database.

Table 2
Association between county-level elevation and fatal opioid overdose prevalence between 2006 and 2016: logistic regression output.

Variables	Crude model		Adjusted model[a]	
	Odds ratio [95% CI]	P value	Odds ratio [95% CI]	P value
Overall population	1.073 [1.041, 1.105]	< 0.001	1.074 [1.049, 1.098]	< 0.001
Males	1.078 [1.037, 1.120]	< 0.001	1.082 [1.057, 1.108]	< 0.001
Females	1.102 [1.058, 1.148]	< 0.001	1.062 [1.032, 1.092]	< 0.001

Notes: Odds ratios reported for every 1000 ft elevation gain. 95% CI = 95% confidence interval. Data retrieved from CDC WONDER.
[a] Adjusted for average county opioid prescribing rates between 2006 and 2016 and county urbanization classification.

while μ receptor-knockout mice do not display respiratory deficits (Romberg et al., 2003). Furthermore, opioid antagonists such as na-loxone (Narcan®) have the highest affinity for μ receptors, and significantly reduce or reverse opioid-induced respiratory depression (Open Chemistry Database, n.d.). Opioid binding of brainstem μ receptors thus inhibits respiratory function, to cause alterations in respiratory rhythm, tidal volume of breathing (amount of oxygen inhaled and carbon dioxide exhaled), and sensitivity to arterial oxygen and carbon dioxide levels (White & Irvine, 1999). If severe and not reversed with an opioid antagonist, these effects can ultimately lead to death.

Living at even moderate altitudes exposes people to significant levels of hypoxia. At sea level, inspired oxygen is equal to roughly 21%, but drops to 18% at an altitude of 4500 ft (Salt Lake City, Utah), a 12.3% decrease relative to sea level. Compensatory mechanisms attempt to maintain optimal oxygen levels in the body, yet healthy individuals residing in Salt Lake City were found to exhibit significantly lower arterial partial pressure of oxygen than individuals in two sea level cities (Crapo et al., 1999). Hypoxic stress likely increases in cities such as Denver, CO or Albuquerque, NM (at 5000–5500 ft), Park City, UT or Santa Fe, NM (at 7000 ft.), with a 15–20% decrease in inspired oxygen relative to sea level. Since opioid-related overdoses occur via respiratory inhibition, hypobaric hypoxia may exacerbate the respiratory effects of opioids, increasing the probability of overdose fatality. Consequently, the increased prevalence of fatal opioid overdoses at altitude may be directly linked to lower levels of oxygen inspired at altitude.

Limitations to the study: 1) Opioid misuse may not be related solely to euphoric effects, but with issues related to pain management.

Continued pain following the use of prescribed doses of opioids can also be a significant motivator for opioid misuse (*Prescription Drug Use and Misuse in the United States: Results from the 2015 National Survey on Drug Use and Health,* 2016); 2) Of particular importance, the risk for suicidal behavior is documented to increase with altitude of residence (Brenner et al., 2011; Haws et al., 2009; Kim et al., 2011). Women are more likely than men to attempt suicide through prescription medication (Tsirigotis, Gruszczynski, & Tsirigotis, 2011), so it is possible that the altitude-related increase in opioid misuse documented in women may also include attempts at suicide; 3) For the overdose analyses, we did not include overdose outcomes for every US county. This limits our ability to generalize these findings to all counties within the US, although each of our models accounted for 80% or more of fatal overdoses from prescription opioids between 2006 and 2016.

Despite these limitations, this study suggests that people living in regions at altitude may be more susceptible to opioid-related problems. As such, these regions may benefit by prioritizing non-opioid treatments for pain-related disorders, such as medical marijuana or mindfulness-based treatments. Reducing the misuse of opioids and opioid-related fatality should be a high priority regardless of geographic region. However, these data indicate that doctors and policy-makers in regions of altitude should be particularly aware of the potential for increased likelihood of opioid misuse and overdose when prescribing medications and proposing social policies that may impact the opioid crisis in America.

Conflict of interest

Dr. Renshaw has been funded by the NIH, VA, and USTAR, and received compensation as a consultant to Kyowa Hakko Kirin and Ridge Diagnostics. The other authors have no disclosures to declare. The views in this report are those of the authors and are not necessarily representative of the Veterans Affairs Health Systems.

Disclaimer

The findings and opinions reported here are those of the authors and do not necessarily represent those of the Veterans Health Administration or any other organization.

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