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Hypoxia-related risk factors for death by suicide in a national clinical sample

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ABSTRACT

The relationship between three markers of chronic hypoxia (altitude, smoking and chronic obstructive pulmonary disease (COPD)) and suicide risk has not been well-studied. We conducted a population-based cohort study evaluating the association between chronic hypoxia and suicide risk. Patients entered the cohort in their first year with a documented healthcare encounter and remained in the cohort until their death or the end of the study period. Generalized estimating equation (GEE) methodology was used to assess the association between suicide and three risk markers of chronic hypoxia. Findings were summarized using odds ratio (OR) and 95% confidence intervals (CI). Among the 9,620,944 patients in the cohort, there were 22,403 suicide deaths. There was a statistically significant progression of suicide risk as altitude rose in increments of 1000 m (OR: 1.22). There was a strong association between the number of hypoxic conditions and the odds of suicide. Patients with three markers of chronic hypoxia was nearly four times more likely to die by suicide than patients with no markers (OR: 3.96). Chronic hypoxia is a risk factor for suicide and having multiple indicators of hypoxia confers a greater risk for suicide, indicating a dose-response relationship.

1. Introduction

Available research suggests that several markers of chronic hypoxia, such as living at high altitude, current smoking status, and diagnosis of chronic obstructive pulmonary disease (COPD), may be associated with increased risk of death by suicide (Young, 2013b). It is hypothesized that chronic hypoxia may contribute to suicide risk through the role of oxygen in serotonin synthesis (Young, 2013b). The body requires near optimal blood oxygen levels in order to produce serotonin from its amino acid precursor, tryptophan (Diksic and Young, 2001; Katz, 1980, 1981; Nishikawa et al., 2005; Young, 2013b). Experimental manipulations to lower tryptophan in human have been shown to lower mood as well as increase irritability and aggression in some patients (McCloskey et al., 2009; Young and Leyton, 2002). Low basal levels of serotonin metabolites in cerebrospinal fluid are also known to be associated with an increased risk for suicidal behavior and death by suicide (Asberg, 1997; Mann, 2003; Moberg et al., 2011). Furthermore, biochemists have proposed several mechanisms linking altitude to suicide, including the disrupted synthesis of multiple neurotransmitters, such as serotonin (decreased levels are linked to development of depression) and dopamine (increased levels lead to increased impulsivity) (Trouvin et al., 1986), and an increased global suppression of cerebral metabolism (energy production) (Kious et al., 2018). For example, in a recent trial of depressed patients living at moderately high altitude, Kious et al. found that augmenting selective serotonin reuptake inhibitors with dietary supplementation of both tryptophan (to increase serotonin production) and creatine (to increase cerebral energy production) improved symptoms of depression (Kious et al., 2017).

While there is some evidence to support that altitude may lead to increased suicide risk (Kious et al., 2018), no study has explored all three markers of chronic hypoxia (high altitude, smoking status, and COPD) or their relationship to risk of death by suicide in individual patients. The highest resolution studies of the relationship between altitude and suicide risk have examined altitude only at the county level, precluding adjustment for individual-level confounders (Reno et al., 2017). Two studies have looked at suicide risk in deceased

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individuals living at high altitude, but neither study included non-deceased individuals living at similar elevations or with similar risk factors (Betz et al., 2011; Huber et al., 2014). Furthermore, concurrent assessment of individuals' smoking and COPD status has not been combined with altitude in any study.

To address these gaps in the literature, we conducted a population-based, retrospective cohort study using national administrative data from the Veterans Affairs (VA) health system. We hypothesized that individuals with risk factors associated with chronic hypoxia (i.e., living at high altitude, current smokers, or COPD diagnosis) are at increased risk for death by suicide, and there may be an additive effect from having multiple risks factors. Clarifying the relationship between these three markers at the individual level may uncover opportunities to further study ways in which treatment and healthcare services can modify that risk.

2. Methods

We conducted a population-based, retrospective cohort study using national administrative data from the United States Veterans Affairs (VA) health system. Patients entered the cohort in their first year with a documented VA healthcare encounter and remained in the cohort until their death or the end of study period. Patients were eligible for study inclusion if they were enrolled in the Veterans Health Administration (VA beneficiaries), were over 18 years of age and accessed VA healthcare services at any time during the study period. We did not exclude any patients with partial or missing data. We collected information on hypoxia-related risk factors of interest for each person-year that an individual contributed to the dataset.

2.1. Data sources

We used the VA Corporate Data Warehouse (CDW) to develop a cohort of all individuals who accessed any healthcare services at a Veterans Affairs facility (VA users) between fiscal years (FY) 2005 and 2014. We collected vital status and cause of death information from the VA/Department of Defense (VA/DoD) Suicide Data Repository (SDR) (Center of Excellence for Suicide Prevention). The VA/DoD SDR was created in conjunction with the Center for Disease Control and Prevention (CDC) and the National Death Index (NDI), and includes mortality data on Veterans residing in the 50 U.S. states and the District of Columbia.

We used the National Elevation Dataset to determine the altitude of each patient's residence ZIP Code centroid, which was updated each calendar year throughout the study period (United States Geologic Survey, 2009). To determine smoking status, we used the tobacco screening administered to all VA users, which is a valid indicator of current, former, and never smoking status (Calhoun et al., 2017). Lastly, we determined COPD status using the International Classification of Diseases Version 9 (ICD-9) codes (World Health Organization, 2011). After the first indication, we carried the COPD diagnoses through to all subsequent person-years. We took this approach because we expected that after a diagnosis of COPD, the patient would have the illness until death.

2.2. Analytical approach

The unit of analysis is a person year, with each observation containing updated covariate and hypoxia status as well as an indicator for suicide in the year as the dependent variable. We applied generalized estimating equation (GEE) methodology with an exchangeable correlation structure to the logistic model to account for repeated measures for individuals. Since the outcome (suicide) was known from 10/1/2004 to 9/20/2014 but the units of observation were calendar years, we down-weighted observations from years 2004 and 2014. Using a GEE model, we could assess the association between suicide and each of the hypoxic conditions of interest (high altitude, COPD, and smoking status). We treated elevation as a categorical variable, defining high altitude as living at ≥ 1500 m (Paralikar and Paralikar, 2010), and as a continuous variable so we could determine if there was a linear relationship with increasing elevation. We calculated this progression of suicide risk at increasing increments of 1000 m in altitude." We also assessed whether there was an additive effect from having multiple hypoxic conditions, ranging from the presence of no conditions to the presence of all 3 conditions. We adjusted all models for age and age squared, gender, race, ethnicity, rurality, and VA use in each year.

It is worth noting that we encountered missing or incomplete data for a proportion of patients. Specifically, routine screening for smoking occurred at a low frequency in the early years of our study but improved markedly after 2008. We accounted for missing or incomplete data on smoking status in the following manner. First, we added tobacco use disorder to supplement the survey data on smoking status (Bohnert et al., 2013). Second, we used longitudinal information from each individual (or diagnosis if available) to impute years missing. Finally, we ran two sensitivity analyses. In the first, missing values are assumed to be non-smoking years; in the second, missing values are assumed to be a level of exposure. We also compared the characteristics of people with missing smoking status to those with known smoking status. We performed all analyses using SAS version 9.4 (Carey, NC). We reported both raw (univariate) and adjusted odds ratios (OR) as well as the associated 95% confidence interval (CI). We considered a p value < 0.05 and a confidence interval that did not cross one to be statistically significant.

2.3. Ethical considerations

The Veteran's Institutional Review Board of Northern New England (VINNE) and the Research and Development Committee, White River Junction Veterans Affairs Medical Center (WRJ VAMC) approved this project after full committee review.

3. Results

We identified 8 million VA beneficiaries in FY 2005. Of these 8 million beneficiaries, 54% (4,401,286) accessed VA care in FY 2005 and entered the study cohort. The size of the cohort continued to rise over time as more beneficiaries accessed VA care. Ultimately, a total of 9,620,944 patients were included in the study cohort. Among these individuals, there were 2,165,210 deaths, of which 22,403 were deaths by suicide. **Table 1** describes key characteristics of the included sample. The majority of patients were male (93.8%, $n = 9,024,445$) and the mean age of the study population was 58.2 years (SD: 17.1). Furthermore, 85.9% (8,261,366) of patients resided at < 500 m and most patients lived in an urban setting (73.9%, $n = 7,109,878$). Approximately 13.6% of patients received a diagnosis of COPD during the course of the study.

As shown in **Table 2**, patients who had at least one of the three hypoxia-related conditions had a significantly increased odds of suicide, even after adjusting for confounding. For example, patients who were current smokers had a nearly two times greater odds of dying by suicide compared with never smokers. Conversely, the odds of suicide among former smokers had a lower risk of suicide than never smokers, suggesting that these individuals may experience other factors in addition to quitting smoking that may help to reduce their suicide risk (OR: 0.74, 95%CI: 0.70, 0.77). While patients who lived at elevations above sea-level were at significant increased risk for suicide (OR [high altitude]: 1.36, 95%CI: 1.23, 1.40), there was not a significant difference in odds of suicide between elevation cutoff points (i.e., 500–999 m vs. 1000–1499 m vs. ≥ 1500 m). Yet, when we treated altitude as a continuous measure, there was a significant progression of risk for suicide as elevation rose by increments of 1000 m (OR: 1.22, 95%CI: 1.18, 1.26, $p < 0.0001$).

Table 1
Baseline characteristics of the study population (N = 9,620,944)*.

Demographic characteristics	
Male, % (*n*)	93.8 (9,024,445)
Age, Mean (SD)	58.2 (17.1)
Race	
White, % (*n*)	70.9 (6,820,905)
Black, % (*n*)	13.7 (1,315,184)
Hispanic, % (*n*)	5.0 (478,124)
Other/unknown, % (*n*)	15.4 (1,484,855)
Geographic indicator	
−100 – 499 m (Sea level), % (*n*)	85.9 (8,261,366)
500–999 m, % (*n*)	5.8 (555,624)
1000–1499 m, % (*n*)	3.2 (303,191)
1500+ m (High altitude), % (*n*)	3.1 (299,335)
Missing	2.1 (201,428)
Population density of home address	
Isolated small rural, % (*n*)	5.7 (548,394)
Small rural, % (*n*)	6.7 (6,446,032)
Large rural, % (*n*)	12.3 (1,183,376)
Urban, % (*n*)	73.9 (7,109,878)
Missing, % (*n*)	1.5 (144,314)
Health indicators	
Smoking status	
Never, % (*n*)	18.8 (1,808,078)
Former, % (*n*)	36.2 (3,481,698)
Current, % (*n*)	32.0 (3,078,464)
Missing, % (*n*)	13.0 (1,252,704)
Chronic obstructive pulmonary disease**	
No, % (*n*)	86.4 (8,312,942)
Yes, % (*n*)	13.6 (1,308,448)

N = Number, % = percent, SD = Standard Deviation.
* Demographic characteristics and health indicators reflect baseline information that was available for patients in the first year of study enrollment.
** Includes patients diagnosed with COPD at any point during the study.

Table 3 shows that there was a strong association between the number of hypoxic conditions and the odds of death by suicide. In fact, the odds of suicide appeared to increase as patients acquired more hypoxic conditions. For example, the odds of suicide among patients who had all three hypoxic conditions was nearly four times that of patients who did not have any of these hypoxic conditions (OR: 3.96, 95%CI: 3.47, 4.52). We also observed that there was not much association between smoking and COPD with 56% of patients with COPD being current smokers and 32% of patients without COPD being current smokers. Finally, when we dropped one or the other variable in our model, we found that the effect remained although the parameter estimates changed slightly.

The sensitivity analyses that treated missing smoking status as non-smokers or coded missing smoking status as a separate level did not substantively change our findings: current smokers still had much higher risk than never-smokers. We found that the demographic characteristics (i.e., age, % female, % urban, % black, and % Hispanic) of patients with missing smoking status was similar to those with smoking information. However, we did observe that patients with missing smoking status were less likely to access VA services in the current year and had similar rates of diagnosed COPD as non-smokers. The COPD finding may be an artifact of these patient's lower level of VA use since disease identification came solely from diagnoses coded during VA visits.

4. Discussion

To the best of our knowledge, this is the largest study to examine the relationship between several markers of chronic hypoxia and death by suicide. Our study is also the first study to combine altitude with patient-level health status markers of chronic hypoxia. This work confirms prior literature suggesting that markers of chronic hypoxia including high altitude, smoking and COPD are risk factors for suicide. These findings hold true even after adjusting for patient-level confounders. Furthermore, our study suggests that there is a dose-response relationship between these various hypoxic conditions and suicide risk. In fact, patients who have all three of these hypoxic conditions are nearly four times more likely to die by suicide than patients who do not have any of these markers of hypoxia.

We are unable to directly compare our findings with those of prior studies because no prior studies have combined altitude with patient-level markers of chronic hypoxia. Yet, similar to previous studies, we found that living at a higher elevations was associated with increased risk for suicide (Kious et al., 2018). Brenner et al. (2011) for example, reported that age-adjusted suicide rates strongly correlated with altitude ($r = 0.50, p < 0.001$). In a study of suicide risk and altitude across 18 U.S. states, Betz et al. also reported a significant difference in unadjusted suicide rates between high-altitude, middle-altitude and low altitude states (17.7 vs 11.9 vs 5.7 per 100,000, respectively) (Betz et al., 2011). However, Betz et al. raised concerns that their results may have been subject to ecological fallacy because subjects differed significantly with respect to important confounders (e.g., race, rural residence) (Betz et al., 2011). Unlike Betz et al., we found that elevation was associated with a significant risk for suicide, even after adjusting for age, gender, race, ethnicity, and rural residence. We decided not to adjust for zip income or poverty because we felt that veterans might not be that influenced by area level factors. Finally, similar to (Brenner et al., 2011) we found that suicide risk began to emerge at elevations over 500 m. This finding is surprising because there is no physiological reason to suspect hypoxia at these elevations

Table 2
Contribution of geographic, health behavior, and health status indicators of hypoxia to risk of death by suicide among VA users, fiscal years 2005–2014.

Hypoxic condition	Suicides	PYR	Suicides 100,000 PYR	OR (95%CI)*	Adjusted OR** (95%CI)
Altitude					
−100–499 m (Sea level)	18,529	58,256,591	31.8	Reference	Reference
500–999 m	1718	4,018,692	42.8	1.35 (1.28, 1.42)	1.23 (1.17, 1.29)
1000–1499 m	996	2,177,751	45.7	1.43 (1.34, 1.53)	1.31 (1.23, 1.40)
1500 + m (High altitude)	974	2,052,200	47.5	1.49 (1.39, 1.59)	1.36 (1.27, 1.45)
Smoking***					
Never	4099	14,997,359	27.3	Reference	Reference
Former	4597	22,060,351	20.8	0.76 (0.73, 0.80)	0.74 (0.70, 0.77)
Current	10,633	21,969,568	48.4	1.76 (1.70, 1.83)	1.88 (1.81, 1.95)
COPD					
No	18,743	59,117,128	31.7	Reference	Reference
Yes	3660	7,942,583	46.1	1.45 (1.40, 1.50)	1.52 (1.46, 1.57)

CI = confidence interval; COPD = chronic obstructive pulmonary disease; m = meters; OR = odds ratio; PYR = person years at risk.
* model is univariate association between suicide and hypoxic conditions.
** Adjusted for demographic variables (i.e. age, gender, race, ethnicity, rurality, and VA use in each person year of risk).
*** Analysis is limited to patients for whom smoking status was available in the current year.

Table 3
Number of hypoxic conditions and the risk of suicide among VA users, fiscal years 2005–2014.

	Suicides	PYR	Suicides 100,000 PYR	OR (95%CI)*	Adjusted** OR (95%CI)
Number of hypoxic conditions¥***					
No conditions	6662	34,341,150	19.4	Reference	Reference
One condition	8783	23,470,105	37.4	1.93 (1.87, 1.99)	2.01 (1.95, 2.08)
Two conditions	2777	5,575,949	49.8	2.57 (2.46, 2.68)	2.62 (2.50, 2.74)
Three conditions	223	279,789	79.8	4.12 (3.62, 4.70)	3.96 (3.47, 4.52)

CI = confidence interval; OR = odds ratio; PYR = person years at risk.
* model is univariate association between suicide and hypoxic conditions.
** Adjusted for demographic variables (i.e., age, gender, race, ethnicity, rurality, and VA use in each person year of risk.
*** Maximum number of conditions including living at high altitude, having a diagnosis of COPD and being a current smoker.
¥ Excludes patients with missing smoking status.

(Brenner et al., 2011; Reno et al., 2017).

No studies have evaluated the combined effect of altitude, smoking, and COPD on suicide risk and only a few studies have separately explored the association between suicide risk and COPD (Chung et al., 2014; Fleehart et al., 2015; Goodwin, 2011; Strid et al., 2014). Yet, our results are consistent with available evidence. For example, Chung et al. evaluated patients with COPD and found that the Global Initiative for COPD (GOLD) stages III and IV were associated with increased suicide risk as compared to the general population (suicide attempts - unadjusted OR 2.83, 95%CI: 1.03–7.75; adjusted OR 2.94, 95%CI: 1.03–8.31) (Chung et al., 2014). Furthermore, fairly similar to our results, Strid et al. reported an increased risk of suicide among patients hospitalized for COPD, even after adjusting for confounders (OR 2.0, 95%CI: 1.8–2.2) (Strid et al., 2014). Other studies have also proposed that smoking is a risk factor for suicidal behavior, as suggested by our findings as well. For example, in a large meta-analysis of 63 studies with over 8 million participants, Poorolajal et al. found that compared to non-smokers, the relative risk of suicide in current smokers was 1.83 (95%CI: 1.64–2.02) (Poorolajal and Darvishi, 2016). This result is similar to our study (Adjusted OR: 1.88, 95%CI: 1.81–1.96).

Our study has several strengths. First, our study was conducted in a large integrated healthcare system and contained over 9 million participants. Second, unlike prior studies of altitude and suicide risk, we were able to include patient-level data such as demographic history, medical history and specific geographic location of residence. A limitation of prior studies has included a reliance on state or county-level, rather than patient-level, data (Reno et al., 2017). Third, to the best of our knowledge, this is the first study to examine the effects of three markers of chronic hypoxia on suicide risk and evaluate how these risks were modified when multiple factors were present.

Our study has limitations. First, while we were able to demonstrate an association between suicide and three markers of chronic hypoxia, we were unable to confirm these findings using direct measurement of oxygen levels. Second, studies have used varying elevation strata and data sources to evaluate the effect of changes in elevation on suicide risk. This limits comparison across studies. We selected a moderate, but conservative estimate of ≥ 1500 m to define "high altitude" because there is evidence that physiological symptoms of hypoxia begin to emerge at this elevation (Paralikar and Paralikar, 2010). We did not observe a significant difference in suicide risk across elevation cutoffs greater than 500 m (i.e., 500–999 m, 1000–1499 m and ≥ 1500 m). However, we did demonstrate a linear relationship between altitude and suicide risk when elevation was increased in increments of 1000 m. Third, our study was unable to account for individual biological factors that may influence acclimatization to living at higher elevation. Degree of acclimatization, duration of time spent living at higher altitude and transition periods may factor into suicide risk. Fourth, we did not adjust for other potential confounders such as access to firearms and psychosocial variables. It is important that future studies of similar scale to ours measure the influence of these factors. Fifth, we did not examine the association between other markers of hypoxia and suicide risk. For example, there is modest evidence to suggest an association between asthma and suicidal behavior (Kuo et al., 2010). Sixth, we did not adjust for mental illness because mental illness may, in fact, be a link in the causal pathway between hypoxia and suicide. For example, depression may be caused by markers of chronic hypoxia (Luger et al., 2014; Tsai et al., 2013); therefore, controlling for depression may decrease the strength of the hypoxia-suicide relationship. Seventh, we were unable to assess the quantity of tobacco used daily or the number of years people smoked. Thus, we could not evaluate a dose response effect for tobacco exposure, account for the differential effects of years of smoking, amount of smoking, and pack-years on the association between suicide and smoking. Our study was also subject to other limitations including missing data for some markers of interest, the potential for measurement bias and a lack of biological markers to verify the oxygenation status of individuals during the course of the follow-up. To mitigate these risks, we used standardized methods to define variables of interest and obtained patient-level elevation measurements. Finally, smoking is generally associated with lower socioeconomic status and other comorbidities and both COPD and smoking can reduce quality of life. As such, the increased risk we found for these factors could be caused by lower quality of life as opposed to hypoxia.

4.1. Conclusions

Chronic hypoxic conditions including high altitude, smoking, and COPD are important risk factors for suicide. Notably, patients who have more than one of these conditions are at even greater risk for suicide than those patients with one or no risk factors. Our findings present possible levers for suicide prevention across the health system. Patients with these risk factors may not only require closer follow-up, but may also benefit from specialized treatments. For example, if chronic hypoxia contributes to suicide risk through disruptions in serotonin metabolism, patients with depression living at high altitude may be non-responsive to serotonergic antidepressants, and thus, require alternative antidepressant agents, such as noradrenergic antidepressants. (Young, 2013a) Future studies are needed that rely on ecologic and experimental methods to ascertain effective, targeted interventions that can decrease suicide risk in patients with exposure to chronic hypoxia.

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