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Altitude is a Risk Factor for Completed Suicide in Bipolar Disorder

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Summary

Bipolar disorder (BD) is a severe brain disease that is associated with a significant risk for suicide. Recent studies indicate that altitude of residence significantly affects overall rate of completed suicide, and is associated with a higher incidence of depressive symptoms. Bipolar disorder has shown to be linked to mitochondrial dysfunction that may increase the severity of episodes. The present study used existing data sets to explore the hypothesis that altitude has a greater effect of suicide in BD, compared with other mental illnesses. The study utilized data extracted from the National Violent Death Reporting System (NVDRS), a surveillance system designed by the Centers for Disease Control and Prevention (CDC) National Center for Injury Prevention and Control (NCIPC). Data were available for 16 states for the years 2005–2008, representing a total of 35,725 completed suicides in 922 U.S. counties. Random coefficient and logistic regression models in the SAS PROC MIXED procedure were used to estimate the effect of altitude on decedent's mental health diagnosis. Altitude was a significant, independent predictor of the altitude at which suicides occurred ($F = 8.28$, p=0.004 and Wald chi-square=21.67, $p < 0.0001$). Least squares means of altitude, independent of other variables, indicated that individuals with BD committed suicide at the greatest mean altitude. Moreover, the mean altitude at which suicides occurred in BD was significantly higher than in decedents whose mental health diagnosis was major depressive disorder (MDD), schizophrenia, or anxiety disorder. Identifying diagnosis-specific risk factors such as altitude may aid suicide prevention efforts, and provide important information for improving the clinical management of BD.

Introduction/Background

Bipolar disorder (BD) is a severe and persistent mental illness affecting 4.4% of U.S. adults [1]. The risk of suicide for individuals with BD is approximately 60 times greater than that of the general population [2]. Fifteen to twenty percent of individuals with BD complete suicide and up to 40% report at least one suicide attempt during their lifetime [2]. The ratio of suicide attempts to completed suicides for the general population is 35:1, but for individuals with BD, the same ratio is 3:1 [2]. In fact, it is estimated that BD may account for one-quarter of all completed suicides [3]. Prior research has identified a number of psychosocial and medical predictors of suicide in BD, but the potential environmental risk factors are less well-studied in an epidemiological context. We speculate that altitude of resident may pose a heretofore unrecognized risk factor for completed suicide in BD, and present a secondary analysis of existing data in support of this hypothesis.

Regional variations in the rate of completed suicide across the U.S. have persisted throughout the past three decades. A consistent finding is that the states of the Intermountain West have elevated rates of suicide in the population [4, 5]. Cheng [4] found that suicide rates where higher in the Rocky Mountain states than in lowest altitude states from 1979 to 2006. Suicide rates were compared by state groups (top 5 states) for rurality, gun ownership, poverty, insurance, psychiatric availability and altitude. Additionally, the state group with the lowest psychiatrist availability, which includes states of low altitude (i.e., Alaska, Iowa, Mississippi, Arkansas, and Oklahoma), had lower suicide rates than the Intermountain West [4]. Recent studies have described an association between altitude and suicide rates at the state and county levels, both internationally and in the U.S. [4–7]. Controlling for gun ownership, rurality, age, and mental health providers, Kim et al. [6] noted a significant positive association between suicide rates and altitude. Additionally, Brenner and colleagues [8] reported a positive association between altitude and suicide in 2,584 counties in the U.S. despite the notable concomitant finding of a significant reduction in overall mortality with increasing altitude.

Others have studied the relationship between suicide and altitude and reported mixed results. Betz and colleagues [8] noted that individuals who committed suicide at high and low altitudes significantly differed with respect to race, ethnicity, rurality, use of firearms, and intoxication at the time of death. There were also dissimilarities in depressed mood, and recent financial, occupational, legal, or interpersonal problems. High altitude victims had higher rates of family or friends report depressed mood and having a crisis within the 2-week period before the suicide than low altitude victims [8]. Additionally, there were significant differences in personal, mental health, and suicide characteristics among altitude groups. In line with these findings, Delmastro and colleagues reported a positive correlation between altitude of residence and respondent's self-reported levels of psychological distress [9]. The mechanism by which altitude imposes this burden, however, remains to be identified.

The Hypothesis/Theory

Several biological theories may explain an altitude-suicide association. Dopamine and serotonin are neurotransmitters associated with pleasure, reward, and mood. Mood disorders have been linked with impaired neurotransmission of dopamine, serotonin, and norepinephrine [10]. Studies of hypobaric hypoxia have shown that exposure can cause an increase in brain dopamine and tyrosine hydroxylase [11] and a decrease in serotonin and tryptophan hydroxylase [12]. Decreased levels of serotonin and increased levels of dopamine and norepinephrine associated with hypoxia at higher altitudes may lead to increased irritability, depression, and suicide [13, 14].

Converging lines of evidence also indicate that mitochondrial dysfunction plays a role in the pathophysiology of BD and may influence the severity of episodes [15–17]. Research utilizing a range of methodologies has been used to characterize bipolar-related mitochondrial dysfunction [18–21]. Studies of patients with mitochondrial disease show that both adults [22, 23] and children [24, 25] have

elevated rates of depressive symptoms. Results from magnetic resonance spectroscopy (MRS) in individuals with BD have shown a decrease in the levels of intracellular pH and an increase in lactate, consistent with impaired cell energy metabolism [20].

Metabolic stress due to hypoxia may have important considerations for individuals with BD. Hypoxia due to reduced oxygen partial pressure at higher altitudes may further decrease mitochondrial function in individuals with BD [26–27]. For these individuals, metabolic changes associated with hypoxia may lead to depression, instability of mood, and increased risk of suicide [28]. Of note, those with BD are at highest risk for suicide during depressive and mixed episodes [2].

Evaluation of the Hypothesis

Based on observations of mitochondrial dysfunction in individuals with BD, the current study set out to examine the effects of altitude as a predictor of mental health diagnosis in suicide decedents in a national data set. We hypothesized that individuals diagnosed with BD living at higher altitudes would be at an increased risk for suicide when compared to individuals with other psychiatric disorders. This may occur if individuals with BD experience more significant mood episodes due to increased relative hypoxia at higher altitudes [29–31].

Empirical Data

This study utilized data extracted from the National Violent Death Reporting System (NVDRS), a surveillance system designed by the Centers for Disease Control and Prevention (CDC) National Center for Injury Prevention and Control (NCIPC) [32]. The system centrally aggregates information from the 16 states that collect violent death data and the contributions of the states' partners, which include agencies involved in law enforcement, vital records, medical examiners/coroners, and crime laboratories. The NVDRS includes data collection from the following states: Maryland, Massachusetts, New Jersey, Oregon, South Carolina, Virginia, Alaska, Colorado, Georgia, North Carolina, Oklahoma, Rhode Island, Wisconsin, California, Kentucky, New Mexico, and Utah. Data was available from 16 states for the time interval 2005–2008.

The NVDRS defines suicide as "death resulting from the intentional use of force against oneself" [32]. For each incident, the NVDRS collects information from numerous data sources. The primary data sources include death certificates, coroner/medical examiner records, toxicology reports, and police records. Other data sources include crime lab data, hospital data, and Bureau of Alcohol, Tobacco, Firearms, and Explosives (ATF) trace reports. The NVDRS collects demographic information, as well as information on mental health history. Mental health diagnoses of each individual that had committed suicide were noted, as assessed by a mental health practitioner. First and second mental health diagnoses were available for suicide decedents with the following classifications: Major Depressive Disorder (MDD), BD, schizophrenia, anxiety disorder, post-traumatic stress disorder, attention deficit disorder, eating disorder, obsessive-compulsive disorder, other, unknown, and not applicable [32].

For the purposes of this study, individuals were assigned a single mental health diagnosis of MDD, BD, schizophrenia, or anxiety disorder. In order to be assigned one of those mental health diagnoses, individuals had to have first or second mental health diagnoses by the NVDRS that were consistent with that classification. Due to the low frequency of individuals with mental health diagnoses of post-traumatic stress disorder, attention deficit disorder, eating disorder, obsessive-compulsive disorder or "other", those individuals were excluded from the study.

Furthermore, a diagnosis of BD or schizophrenia was given precedence over a diagnosis of MDD, and a diagnosis of BD was given precedence over MDD, regardless of whether it was the first or second diagnosis. For example, if an individual had a first diagnosis of MDD and a second diagnosis of BD,

they would be assigned a mental health diagnosis of BD. This coding decision results from the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) classifications of BD, MDD, and schizophrenia and the exclusionary criteria of each disorder [33].

According to the NVDRS, an individual classified with an "unknown" or "not applicable" mental health diagnosis may have had current treatment from a mental health provider, could have been currently depressed, or may have had current mental health problems according to others [32]. Sixty-four percent of suicide decedents in the NVDRS from 2005–2008 were classified with "other" or "not applicable" mental health diagnoses. Consequently, individuals classified as "unknown" may have actually had a mental health disorder that went undiagnosed, or was not detected during NVDRS data collection procedures. However, it is known that over 90% of suicides in all age groups in the U.S. and Europe are associated with mental or addictive illness [34]. Therefore, to avoid potential confounds and preserve face validity, individuals whose mental health diagnosis was coded in the database as "unknown" or "not applicable" were excluded from the analyses.

A total of 35,725 individuals residing in 922 counties were reported to have committed suicide from 2005–2008. Thirty-six percent of all individuals that completed suicide were classified as having a mental health diagnosis by the NVDRS. This left 12,861 individuals with a classification of a mental health diagnosis by the NVDRS in 809 counties. Table 1 lists the demographics of individuals with mental health diagnoses who committed suicide from 2005–2008.

Table 1

Demographic characteristics of individuals with mental health diagnoses who committed suicide from 2005–2008.

	Frequency
Gender	
Males	8,718
Females	4,143
Race	
Caucasian	11,912
African American	603
American Indian	104
Asian/Pacific Islander	208
Unknown/Other	34
Ethnicity	
Hispanic	442
Not Hispanic	12,393
Unknown	26
Age Groups	
0 – 9 Years	1
10 – 19 Years	496
20 – 29 Years	1,767
30 – 39 Years	2,156
40 – 49 Years	3,255
50 – 59 Years	2,829
60 – 69 Years	1,273
70 – 79 Years	694
80 – 89 Years	355
90 – 99 Years	32
Mental Health Diagnoses	
Major Depressive Disorder	9,713

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Average altitude for counties represented in the study was calculated using the Shuttle Radar Topography Mission (SRTM) altitude data [35]. Data used in the analysis are from a digital topographic global scale of the Earth created in February of 2000. Mean altitudes of U.S. counties allowed accurate calculations due to the 0.1 km spatial resolution of the SRTM dataset. The mean altitude of each county

(n=922) in the United States was calculated using zonal statistics of ArcGIS/ArcInfo 9.3 environment [35]. Digital altitude information for Alaska was not fully available in the STRM dataset, so county information for only 15 states was included in the analyses. County outlines from the National Atlas of the United States were used to obtain mean county altitudes in meters and the areas in square miles for each included county were evaluated based on the SRTM altitude data [36]. This method was previously used by Delmastro et al. [9] and Kim et al. [6] to calculate the altitudes for each U.S. county.

Data regarding the prevalence of household firearms were obtained from CDC's Behavioral Risk Factor Surveillance System (BRFSS) [37]. The BRFSS is the world's largest, on-going telephone health survey system, tracking health conditions and risk behaviors in the U.S. Data are collected monthly in all 50 states, the District of Columbia, Puerto Rico, the U.S. Virgin Islands, and Guam. Gun ownership data was collected from 201,881 respondents. Gun ownership data was only available on a state level and used for each county based on the state level.

Population density for each county was calculated based on county population from the CDC's Wide-ranging Online Data for Epidemiologic Research (WONDER) database [38]. County populations were from 2000 census reports.

Statistical analyses

Due to the high number of counties at sea level, only counties above 308.4 meters (1,000 ft.) were included in the analyses to account for this floor effect. This lower boundary was chosen based on findings by Brenner et al. [7] that increased suicide rates begin to occur at altitudes in the range from 2,000–2,999 feet. This restriction left 12,385 observations in 806 counties for analysis.

We used a random coefficient (RC) regression model approach [also known as a multilevel linear model) to account for the aggregation of some of the variables in the data [39]. This analysis was implemented using the PROC MIXED procedure in SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) which was used to estimate the effect on mental health diagnosis of the individual-level variables [gender, race, and ethnicity], and the aggregated variables (altitude, population density, and gun ownership) by including a categorical clustering level variable. Once significance was established using the PROC MIXED, we used least squares means to estimate mean altitude within mental health diagnostic category, adjusted for the effects of other associated variables. The mental health diagnostic variable included mental health diagnoses of BD, MDD, schizophrenia, and anxiety disorders. A second variable was computed where MDD, schizophrenia, and anxiety disorders were grouped to allow for a comparison of BD to the other diagnoses.

Results

Table 2 shows the *F* statistics and *p*-values for each predictor of mental health diagnosis in the RC regression model, and the estimated least squares mean altitude at which suicides occurred for each diagnosis. The effect of each variable is independent of the other effects in the model. The random effects portion of the model suggested that diagnoses do differ by county ($Z=1.75$, $p=0.04$), though the intraclass correlation (as measured by the variance due to clustering divided by the sum of the variance due to clustering) was low (0.009). The fixed effects results indicate a significant effect of altitude ($p=0.032$) and a marginal effect of gender ($p=0.07$).

Table 2

Results of Random Coefficient [RC] regression as implemented in SAS PROC MIXED.

Variable	F	p-value
Altitude	4.58	0.03
Gender	3.31	0.07
Race	0.41	0.80
Ethnicity	0.08	0.92
Population density	0.09	0.76
Gun ownership	0.37	0.54

Mental Health Diagnosis	Least Squares Means of Altitude [Meters]
Bipolar Disorder	1205.01
Major Depressive Disorder	1115.70
Anxiety	1180.70
Schizophrenia	1057.30

Note: A random effect of county was included to account for the fact that individuals within the 806 included counties share the same values on the group level variables [altitude, population density, gun ownership].

To explore these results further, we compared the overall fit of a model excluding altitude but with all other predictors, to a model including altitude, again with all other predictors. Without altitude, the fit as measured by the Akaike information criterion (AIC) [40], was 26,030.8. In this model, effects of gender and race were both significant (p=0.031 and p<0.0001, respectively). Including altitude (Table 2 results), significance only remained with altitude as noted above (p=0.03), and the AIC was 8,891.4, indicating the fit was significantly improved by inclusion of the altitude variable. Least squares means (LS means) of altitude for each mental health diagnosis, independent of other variables, shows that individuals diagnosed with BD committed suicide at the greatest mean altitude.

We used this same approach to test a more specific mental health diagnostic variable with individuals diagnosed with BD in one group, and individuals diagnosed with MDD or anxiety or schizophrenia in the in the other group. Table 3 presents the F statistics and p-values for each predictor in a RC model of this variable. The random effects portion of the model was now non-significant (Z=1.24, p=0.11), and the intraclass correlation was again low (0.005). These results suggest we could explore the data without taking into account clustering. Table 3 therefore includes fixed effects results from PROC MIXED, and also results from a logistic regression, not including the county variable. Regardless of the method used, the altitude at which suicides occurred was again significant (F = 8.28, p=0.004 from PROC MIXED, and Wald chi-square=21.67, p < 0.0001 from logistic regression). When looking at nested mixed models with and without altitude, as above, we found that the AIC went from 9,384.3 to 3,333.4, again showing a significant improvement in fit of the model by including altitude. Least

squares means of altitude for the two diagnostic groups shows the BD subjects at higher altitude.

Table 3

Results of Random Coefficient [RC]* and Logistic† regression with mental health recoded to contrast bipolar disorder vs. other diagnoses.

	RC Regression Model*		Logistic Regression Model†	
Variable	***F***	***p*-value**	**Wald chi-square**	***p*-value**
Altitude	8.28	0.004	21.67	<0.0001
Gender	18.57	<0.0001	53.73	<0.0001
Race	1.10	0.36	2.29	0.13
Ethnicity	2.31	0.10	1.47	0.23
Population density	5.56	0.02	1.13	0.29
Gun ownership	7.08	0.008	4.20	0.04

Mental Health Diagnosis	Least Squares Means of Altitude [Meters]
Bipolar Disorder	1204.83
Depression/Anxiety/Schizophrenia	1120.23

*Accounting for data clustering
†Not accounting for clustering

Consequences of the Hypothesis and Discussion

Among suicide decedents in the NVDRS, the altitude of residence is a significant predictor of individuals' mental health diagnosis. The hypothesis that altitude preferentially affects BD, compared with other serious mental illnesses, was confirmed. Table 2 and Table 3 display the higher altitude of residence for suicide decedents diagnosed with BD. These altitudes are in meters and show that individuals with BD completed suicide at significantly greater altitudes than individuals with mental health diagnoses of MDD, schizophrenia, or anxiety disorders.

One possible explanation for suicide in individuals with BD at higher county altitudes than other mental health disorders is related to the effect of hypoxia exposure on individuals with BD. Individuals with BD may be burdened with more symptoms living at higher altitudes due to mitochondrial dysfunction [2, 25, 28] or BD treatments may be comparatively less effective as altitude increases. Other individuals may be able to regulate mitochondrial functioning at higher altitudes more successfully; however, if individuals with BD have difficulty then their risk for suicide may be increased [28].

An alternative explanation for these results may be related to the association between lithium, altitude, and suicide rates. A recent study from 99 districts in Austria reported lower concentrations of lithium in

ground and drinking water at higher altitudes, which increased suicide mortality [41]. The therapeutic use of lithium is associated with lower rates of suicide; however the protective properties of lithium in drinking water are inconclusive. Further research is necessary with an international sample on a using a county level scale to better understand this relationship.

The altitude at which individuals with MDD complete suicide may not be as high as that of individuals with BD due to effective treatment with Selective Serotonin Reuptake Inhibitors (SSRIs), which increase levels of synaptic serotonin by inhibiting its reuptake into the pre-synaptic cell. It remains to be determined whether our results indicate that hypobaric hypoxia preferentially affects BD and increases the rate of completed suicide in that disease state, or if these findings are attributable to the diagnostic overlap between BD and MDD.

An unexpected finding was that the suicides of persons with a primary diagnosis of anxiety disorder occurred at an average altitude greater than that of suicides in MDD or schizophrenia. The results of animal studies by Einat et al. [42] and others [43, 44] provide support for the involvement of mitochondrial function in anxiety disorders. Very recent proteomic and metabolomic findings implicate a previously unrecognized role for mitochondria in modulating anxiety-related behaviors [43]. Furthermore, animal and human studies have identified the mitochondrial benzodiazepine receptor as a promising treatment target in anxiety disorders [44]. Taken together, data from this emerging area of inquiry is consistent with the underlying hypothesis that disorders involving mitochondrial function potentially have a more severe presentation, or may respond relatively poorly to treatment with increasing altitude.

These results suggest individuals with BD living in or traveling to counties at higher altitudes are at higher risk for suicide than individuals with MDD, schizophrenia, and anxiety disorders. The diagnostic specificity of this altitude risk association, if replicated, has important implications for treatment providers and individuals with BD living at higher altitudes. Studies designed to investigate the mechanism of altitude's effect on suicide for individuals with BD are necessary.

Strengths of this study include the use of NVDRS and GIS data to explore suicide rates for separate mental health disorders at a county level. Unfortunately, the NVDRS data has several limitations. First, only 15 of 50 states are represented in the study; however, many states in the intermountain west are included and the data was analyzed on a county level. Accuracy and completeness of proxy-driven information from the NVDRS may lead to misclassifications or underreporting. However, previous studies using information obtained from the NVDRS has shown that it was valid, reliable, and sufficient for analysis [45, 46]. The NVDRS dataset did not contain information about availability or access to mental health care services. However, previous studies have shown no association between availability of mental health providers, suicide rate, and altitude [4, 6]. These are all important variables to consider for future research, especially in examining county altitude and its effect on individual mental health disorders.

Conclusions

Suicide is unpredictable and often difficult to prevent; however, if risk factors are identified and individuals are properly assessed, there is a higher likelihood of intervening before it is too late. Individuals with BD have higher rates of suicide and higher rates of attempts than individuals without a mental illness [2]. Identifying the risk factors associated with suicide such as altitude of residence may lead to better suicide prevention efforts.

The present findings may be relevant for mental health providers, especially in light of the recent increase in diagnoses of BD [47, 48]. If altitude is a suicide risk factor for individuals with BD, this

would be an important consideration for providers in the areas of higher altitude [e.g., Colorado, Utah, New Mexico]. Further research will be needed to confirm the present findings and with more locations contributing to the NVDRS and continued data collection over time, the quality of this information will improve. Focusing on the availability of mental health providers and accessibility to mental health care will be particularly important for future research, as this aims at suicide prevention through informing public health policies and mental health providers. Finally, it will be important for future research to identify the mechanism by which altitude increases rates of suicide in BD.

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Footnotes

Conflict of Interest Statement

None

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