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ORIGINAL RESEARCH

Altitude and risk of depression and anxiety: findings from the intern health study

Brent M. Kious[a], Amanda Bakian[a], Joan Zhao[b], Brian Mickey[a], Constance Guille[c], Perry Renshaw[a] and Srijan Sen[b]

[a]Department of Psychiatry, University of Utah, Salt Lake City, UT, USA; [b]Department of Psychiatry, University of Michigan, Ann Arbor, MI, USA; [c]Department of Psychiatry, Medical University of South Carolina, Charleston, SC, USA

ABSTRACT

Multiple studies suggest that the risks of depression and suicide increase with increasing altitude of residence, but no studies have assessed whether changing altitude changes these risks. To address this gap, this study used data from the Intern Health Study, which follows students from the end of medical school through the first year of residency, recording depression via the 9-item Patient Health Questionnaire (PHQ-9), anxiety via the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7), and multiple risk factors for these symptoms. Data from 3764 medical students representing 46 schools and 282 residencies were available. Odds ratios (OR) representing the effects of altitude on psychiatric symptoms were estimated using generalized linear models. After excluding participants with missing altitude data, 3731 medical students were analyzed. High altitude residence (> 900 m) was significantly associated with PHQ-9 total score (OR = 1.32, 95% CI = 1.001–1.75, $p < 0.05$), and PHQ-9 suicidal ideation (OR = 1.79, 95% CI = 1.08–0.02, $p = 0.02$). Moving from low to high altitude was significantly associated with PHQ-9 total score (OR = 1.47, 95% CI = 1.087–1.98, $p = 0.01$), GAD-7 total score (OR = 1.40, 95% CI = 1.0040–1.95, $p < 0.05$), and PHQ-9 suicidal ideation (OR = 1.10, 95% CI = 1.01–1.19, $p = 0.02$). The data suggest that moving from low to high altitude is associated with increasing symptoms of depression, anxiety, and suicidal ideation.

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Depression; anxiety; altitude; suicidal ideation

Introduction

Depression and anxiety are severe, recurrent psychiatric symptoms that affect millions of persons in the US and elsewhere (Kessler et al., 2005; Kessler, Chiu, Demler, Merikangas, & Walters, 2005). Both cause important decrements in personal and occupational functioning (Markkula et al., 2016; van der Voort et al., 2015), and contribute to suicide risk (Gamboa, Caceda, & Arregui, 2011; Joiner, Brown, & Wingate, 2005; Malone, Haas, Sweeney, & Mann, 1995). There is significant geographical variation in the rates of depression and suicide. Notably, the states encompassing the Rocky Mountains typically exhibit the nation's highest age-adjusted annual suicide rates. Wyoming, for example, had a suicide rate of 28.0 per 100,000 persons per year in 2015, compared to only 7.8 per 100,000 persons per year for New York (National Center for Health Statistics, 2017). Mountain states also have disproportionately high rates of depression. In 2007, the annual prevalence of major depressive episodes in Utah was 10.1%, compared to only 7.3% in South Dakota (Mark, Shern, Bagalman, & Cao, 2007). This increase in psychiatric risk in the Rocky Mountain states may be related, in part, to altitude. Several cross-sectional studies have identified a correlation between local altitude and the risk of depression and suicide, even after controlling for multiple confounding factors such as population density, rates of gun ownership, and average regional income (Brenner, Cheng, Clark, & Camargo, 2011; Brenner, Cheng, Muller, Clark, & Camargo, 2006; Cheng, Mendenhall, & Brenner, 2005; Haws et al., 2009; Huber, Coon, Kim, Renshaw, & Kondo, 2014; Kim et al., 2011). An analysis of the National Survey on Drug Use and Health (NSDUH) for 2004–2006 ($n = 203\ 870$) found that regional mean altitude was significantly correlated with the percentage of people having at least one major depressive episode in any of the study years ($r = 0.27$, $p < 0.0001$) (DelMastro

CONTACT Brent M. Kious brent.kious@hsc.utah.edu Department of Psychiatry, University of Utah, 501 Chipeta Way, Salt Lake City, UT, 84108, USA

et al., 2011). Similar associations have been observed in other countries, such as Spain (Alameda-Palacios, Ruiz-Ramos, & García-Robredo, 2015) and South Korea (Kim et al., 2014).

While these large, population-based studies have identified correlations between altitude of residence and the risks of depression and suicide, they cannot rule out the possibility that these correlations are due to unidentified differences, such as demographic, cultural, or socioeconomic differences, between persons who reside at high altitude and those who do not. One way to address this gap is to show that *changes* in a person's altitude of residence are linked to *changing* risks of depression, anxiety, and suicidality. To date, studies of this type are limited to small prospective cohorts (Bardwell, Ensign, & Mills, 2003; Nicolas et al., 2000) and case series (Fagenholz, Murray, Gutman, Findley, & Harris, 2007). To advance our understanding of the relationship between altitude and psychopathology, large-scale prospective studies are needed. The Intern Health Study is an ongoing, prospective, longitudinal NIH-supported study that has been assessing depression, anxiety, and suicidal ideation among training physicians as they move from medical school to residency. This transition represents a time when a large cohort of individuals will predictably change geographic locations and experience substantial psychiatric symptoms, as residency training is strongly associated with depression (Mata et al., 2015). Here, we utilize the intern model to assess psychiatric symptoms at baseline near the end of medical school as well as after subjects have moved to a new location for residency. Because previous studies (Brenner et al., 2011) had reported that the association between suicide rates and altitude increased dramatically at a threshold of between 2000–3000 ft (or 610–900 m), we chose an altitude of 900 m as marking a threshold between 'high' and 'low' altitude, and classified each participant's location at the end of medical school and during residency accordingly.

We examined the effect of moving between altitude categories (e.g. from low to high altitude) on our outcomes of interest in Intern Health Study participants. Our primary hypothesis was that moving from low to high altitude between medical school and residency would be positively associated with the severity of depressive symptoms, anxiety, and suicidal ideation. We also hypothesized that higher residency altitude itself would be positively associated with each outcome.

Methods

Subjects

The Intern Health Study (IHS) encompasses measurements of depressive symptoms and related data for physician interns from ~ 46 medical school locations and almost 300 residencies, across a variety of specialties (for more information about the Intern Health Study, see https://www.srijan-sen-lab.com/intern-health-study). The study examines depressive symptoms as measured by the 9-item Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001) and anxiety symptoms as measured by the 7-item Generalized Anxiety Disorder Questionnaire (GAD-7) (Spitzer, Kroenke, Williams, & Löwe, 2006) both at the end of medical school and quarterly during residency. The IHS also assesses baseline factors that have been found to predict psychopathology during residency as well as in-residency factors such as medical errors, sleep hours, work hours, and other life events that contribute to symptoms, and information about relevant demographic factors (Sen et al., 2010). Informed consent was obtained from all study participants and participation was voluntary. Overall, the 59% of subjects that chose to participate was slightly younger (1.4 years) and included a slightly higher percentage of women (3.8%), but otherwise did not differ significantly from non-participants. The study was approved by the University of Michigan Institutional Review Board.

Altitude measurements

Altitude exposure for each participant was inferred from the primary address of his or her medical school and residency program using Google Earth (Copyright © 2017, Google LLC, Mountain View, CA). For programs with multiple community sites, residency altitude was assumed to be the altitude of the main program location (i.e. of the central hospital or program office). Altitude (in metres) was treated as a continuous variable. We classified participants' medical school and residency altitudes as belonging to a 'high altitude' group if they were greater than or equal to 900 m above sea level, and as 'low altitude' otherwise, and then created a variable that classified residents based on whether each participant had stayed at low altitude, stayed at high altitude, moved from low to high altitude, or moved from high to low altitude at the start of internship. For this analysis, staying at low altitude was treated as the reference variable.

Statistical analysis

Statistical analyses were conducted with version 9.4 of the SAS System for Windows (Copyright © 2016, SAS Institute Inc., Cary, NC). A last observation carried forward approach was used to impute missing PHQ-9 and GAD-7 scores, as these were deemed to be not missing at random. PHQ-9 and GAD-7 scores were treated as ordinal values. We used PHQ-9 item #9 as our measure of suicidal ideation. This asks whether the respondent has experienced 'thoughts of being better off dead or hurting yourself' in the last 2 weeks; the item can be rated as 0 (not at all), 1 (several days), 2 (more than half the days), or 3 (nearly every day). For simplicity and because of low frequencies of subjects reporting suicidal ideation, this item was treated as a binary variable, such that any nonzero rating on this item was regarded as evidence of suicidal ideation.

The chained equation approach was used to conduct multiple imputations of missing covariate data using the MI procedure in SAS 9.4, as this data was assumed to be missing at random. Five copies of the original data set were created and five estimates of the missing data were made, resulting in five complete datasets available for this analysis. Separate models were fit for each of the five datasets containing imputed data. A series of generalized linear models using generalized estimating equations with multinomial distributions were fit to examine associations with PHQ-9 and GAD-7 scores. Models were fit using the cumulative logit link function for PHQ-9 and GAD-7 total scores and using the logit link function for the binary rating of suicidality.

For this study, statistical models were developed using covariates that we had previously demonstrated to be correlated with depression and anxiety in this cohort (Sen et al., 2010) and which we deemed likely to be correlated with altitude. These included age, sex, Caucasian race, PHQ-9 and GAD-7 total scores at the end of medical school (baseline measures), a personal history of depression, and average sleep over the week before each quarterly rating. Baseline depression and anxiety were included because we wanted to assess whether persons with greater psychiatric symptoms during medical school might be more likely to move to higher altitudes. We also assumed that sleep could be disrupted in those residing at higher altitudes (Nussbaumer-Ochsner, Ursprung, Siebenmann, Maggiorini, & Bloch, 2012). Other factors known to influence the risk of depression or anxiety in this cohort, such as neuroticism or early family environment (Sen et al., 2010), were excluded from our models because we assumed they did not correlate with altitude (indeed, this was confirmed in univariate analyses using generalized estimating equations; data not shown). Model output was combined and overall parameter estimates and standard errors were generated using the MIANALYZE procedure in SAS 9.4. An alpha of 0.05 was selected *a priori* for assessing statistical significance. The same approach was used for our secondary analyses, wherein we examined the effects of altitude considered as a continuous variable on each outcome, as well as the effect of change in altitude considered as a continuous variable.

Results

Subjects

A total of 6577 graduating medical students were offered study participation between the 2012–2015 academic years; 3764 (57.2%) provided both baseline and internship information. The initial dataset therefore included 3764 participants, who represented 46 participating medical schools and 282 residency locations. Of this set, 33 participants were excluded because altitude measurements for either the medical school location or residency location could not be determined, leaving a final sample of 3731. The sample was 51% male ($n = 1896$) (Table 1).

Altitude

Cohort characteristics are summarized in Table 1. The average medical school altitude was 171.1 ± 259.1 m and the average residency altitude was 185.7 ± 282.5 m, such that the average change in altitude between medical school and residency was small, at 17.2 ± 336.0 m. The maximum altitude of any site in the study was 1641.4 m. Only 127 participants (3.4%) attended residency at altitudes of at least 900 m, comprising 16 residency sites. The majority of participants (91.7%, $n = 3{,}420$) attended residency close to sea level, at altitudes less than 1000 ft (or ~300 m) (see Figure 1). The mean altitude for those attending residency at a low altitude location was 163.4 ± 217.1 m. The mean altitude for those attending residency at high altitude locations was much greater, at 1,046.3 ± 112.3 m. In total, 3529 (94.6%) participants stayed at low altitude, 20 (0.5%) stayed at high altitude, 75 (2.0%) moved from high altitude to low altitude, and 107 (2.9%) moved from low altitude to high altitude.

Table 1. Demographic and altitude characteristics of sample.

	n (%)
Sex	
M	1896 (51.1)
F	1815 (48.9)
Age	
≤ 25	78 (2.0)
26–30	2886 (77.4)
31–35	503 (13.4)
≥ 36	82 (2.2)
Specialty	
Internal Medicine	877 (24.7)
Surgery	332 (9.4)
Obstetrics/Gynaecology	234 (6.6)
Paediatrics	392 (11.0)
Psychiatry	157 (4.4)
Emergency Medicine	240 (6.8)
Family Medicine	67 (1.9)
Other	1251 (33.5)
Marital Status	
Single	2279 (61.4)
Engaged	430 (11.6)
Married	979 (26.3)
Separated	5 (0.1)
Divorced	25 (0.7)
Race/Ethnicity	
Caucasian	2367 (63.9)
African American	156 (4.2)
Hispanic/Latino	90 (2.4)
Asian	741 (20.0)
Native American	2 (0.1)
Pacific Islander	6 (0.2)
Other	238 (6.4)
Altitude	
Medical School Altitude, mean (SD), m	171.1 (259.1)
Residency Altitude, mean (SD), m	185.7 (282.5)
Change in Altitude, mean (SD), m	17.2 (336.0)
Low Residency Altitude (< 900 m)	3604 (96.6)
High Residency Altitude (≥ 900 m)	127 (3.4)
Staying at Low Altitude	3529 (94.6)
Staying at High Altitude	20 (0.5)
Moving from High to Low Altitude	75 (2.0)
Moving from Low to High Altitude	107 (2.9)
Altitude of low altitude residents, mean (SD), m	163.4 (217.1)
Altitude of high altitude residents, mean (SD), m	1046.3 (112.3)

Symptom severity

The mean PHQ-9 score increased from 2.7 ± 3.1 in the baseline period to 5.1 ± 4.5 during residency. The mean GAD-7 score increased from 2.8 ± 3.3 at baseline to 4.4 ± 4.3 during residency. At baseline, 125 participants (3.3%) had any suicidal ideation on PHQ-9 item #9, and 486 participants (12.9%) had at least one quarterly recording with any suicidal ideation on PHQ-9 item #9 (Table 2).

Multivariable analyses

Results of multivariable analyses using generalized estimating equations with repeated measures are summarized in Table 3. We found that, compared to low altitude, high altitude was significantly associated with PHQ-9 total score (OR = 1.32, 95% CI = 1.001–1.75, $p < 0.05$) and PHQ-9 suicidal ideation (OR = 1.79, 95% CI = 1.08–0.02, $p = 0.02$), although it was not statistically significantly associated with GAD-7 total score (OR = 1.27, 95% CI = 1.006–1.72, $p = 0.1$).

Compared to remaining at low altitude, moving from low to high altitude was, as hypothesized, significantly associated with each of PHQ-9 total score (OR = 1.47, 95% CI = 1.087–1.98, $p = 0.01$), GAD-7 total score (OR = 1.40, 95% CI = 1.0040–1.95, $p < 0.05$), and PHQ-9 suicidal ideation (OR = 1.10, 95% CI = 1.01–1.19, $p = 0.02$). In contrast, remaining at high altitude or moving from high altitude to low altitude were, compared to remaining at low altitude, not significantly associated with PHQ-9 total score, GAD-7 total score, or PHQ-9 suicidal ideation.

In our secondary analysis, numeric residency altitude was significantly associated with PHQ-9 total score (OR per 100 m = 1.021, 95% CI = 1.0020–1.040, $p = 0.03$) and with PHQ-9 suicidal ideation (OR per 100 m = 1.037, 95% CI = 1.0040–1.070, $p = 0.03$), although not with GAD-7 total score. Numeric *change* in altitude between medical school and residency was not significantly associated with PHQ-9 total score, GAD-7 total score, or PHQ-9 suicidal ideation. Results are shown in Table 4.

Discussion

The results presented here confirm our original hypothesis that moving from low altitude to high altitude (≥ 900 m) is significantly associated with symptoms of depression, anxiety, and suicidal ideation, compared to remaining at low altitude. Our study demonstrates, for the first time in a large cohort, that moving from low altitude to a high altitude (≥ 900 m) is associated with an increase in an individual's risk of depression, anxiety, and suicidal ideation. This suggests that observed population-level associations between altitude and suicide rates are not wholly mediated by unmeasured covariates, such as local socioeconomic factors.

Our study is also the first, to our knowledge, to demonstrate an association in a large cohort between anxiety and altitude, although this result is consistent with reports of new-onset anxiety disorders in persons travelling to high altitudes (Fagenholz et al., 2007) or living at simulated high altitude (Nicolas et al., 1999, 2000). The study also confirms previous findings that living at higher altitude itself is associated with increased psychiatric symptoms. Although we did not find a significant association between numeric change in altitude from medical school to residency and any psychiatric symptoms, this was

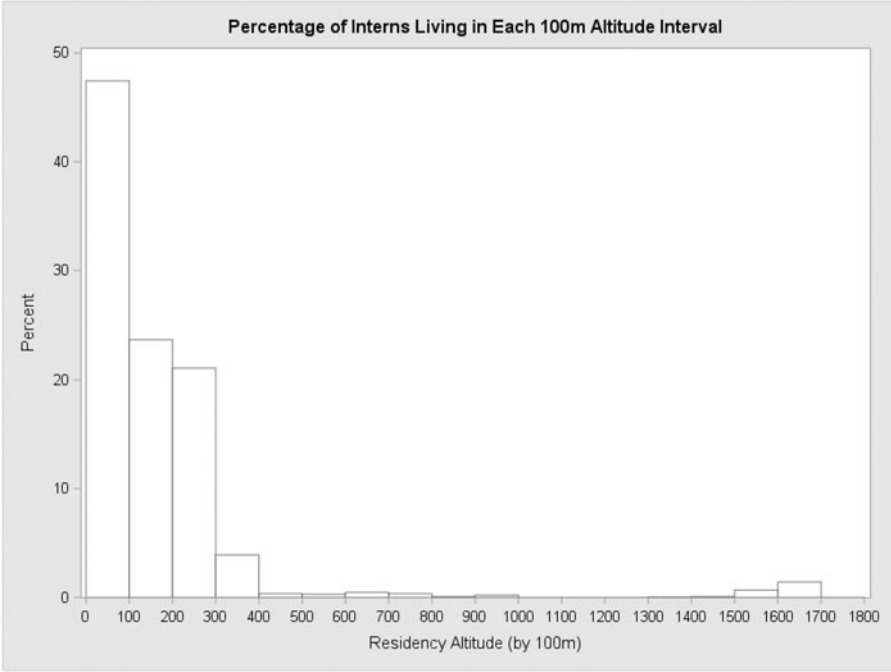

Figure 1. Distribution of residency altitudes among Intern Health Study participants in 100 m intervals above sea level.

Table 2. Baseline and average quarterly measures of symptom severity.

	Baseline	Quarterly	Cumulative Quarterly
PHQ-9 Score, mean (SD)	2.7 (3.1)	5.1 (4.5)	
GAD-7 Score, mean (SD)	2.8 (3.1)	4.4 (4.3)	
Any suicidal ideation (PHQ-9 item #9 positive), No. (%)	125 (3.3)		486 (12.9)

Table 3. Associations of altitude as a categorical variable and change in altitude as a categorical variable and depression, anxiety, and suicidality among participants in the Intern Health Study ($n = 3731$).

	PHQ-9 total score				GAD-7 total score				Any suicidal ideation (PHQ-9 item #9 > 0)			
Parameter	OR	95% CI		*p*	OR	95% CI		*p*	OR	95% CI		*p*
Altitude of residency as a categorical variable												
Low altitude (< 900 m)	ref.	—	—	—	ref.	—	—	—	ref.	—	—	—
High altitude (≥ 900 m)	*1.32*	*1.00*	*1.75*	*< 0.05*	1.27	1.06	1.72	0.1	*1.79*	*1.08*	*2.97*	*0.02*
Baseline depression	*7.48*	*5.58*	*10.0*	*< 0.0001*	*4.10*	*3.18*	*5.29*	*< 0.0001*	*5.08*	*3.57*	*7.22*	*< 0.0001*
Age	1.01	0.993	1.04	0.2	1.00	0.98	1.02	0.7	1.02	0.977	1.06	0.4
Sex (=F)	*1.48*	*1.32*	*1.65*	*< 0.0001*	*1.57*	*1.41*	*1.75*	*< 0.0001*	0.953	0.767	1.19	0.7
Caucasian race	0.993	0.890	1.11	0.9	*1.12*	*1.01*	*1.25*	*0.04*	*0.740*	*0.591*	*0.927*	*0.01*
Baseline anxiety	*3.80*	*2.83*	*5.10*	*< 0.0001*	*7.82*	*5.87*	*10.4*	*< 0.0001*	*2.89*	*1.98*	*4.21*	*< 0.0001*
Personal history of depression	*2.07*	*1.86*	*2.31*	*< 0.0001*	*1.95*	*1.75*	*2.17*	*< 0.0001*	*2.70*	*2.15*	*3.38*	*< 0.0001*
Average sleep in last week	*0.727*	*0.690*	*0.766*	*< 0.0001*	*0.787*	*0.748*	*0.828*	*< 0.0001*	*0.914*	*0.835*	*1.00*	*0.05*
Change in altitude between medical school and residency as a categorical variable												
Staying at low altitude	ref.	—	—	—	ref.	—	—	—	ref.	—	—	—
Staying at high altitude	0.840	0.459	1.54	0.6	0.887	0.478	1.64	0.7	0.947	0.852	1.05	0.3
Moving from high to low altitude	1.27	0.893	1.82	0.2	1.36	0.934	1.98	0.1	1.08	0.974	1.21	0.1
Moving from low to high altitude	*1.47*	*1.09*	*1.98*	*0.01*	*1.40*	*1.00*	*1.95*	*< 0.05*	*1.10*	*1.01*	*1.19*	*0.02*
Baseline depression	*7.53*	*5.62*	*10.1*	*< 0.0001*	*4.11*	*3.19*	*5.29*	*< 0.0001*	*1.54*	*1.36*	*1.75*	*< 0.0001*
Age	1.01	0.990	1.04	0.3	1.00	0.981	1.02	0.9	1.00	1.00	1.01	0.4
Sex (=F)	*1.48*	*1.32*	*1.65*	*< 0.0001*	*1.57*	*1.41*	*1.75*	*< 0.0001*	0.989	0.970	1.01	0.2
Caucasian race	0.986	0.885	1.10	0.8	*1.11*	*1.00*	*1.24*	*< 0.05*	*0.972*	*0.952*	*0.992*	*0.01*
Baseline anxiety	*3.74*	*2.79*	*5.02*	*< 0.0001*	*7.69*	*5.75*	*10.3*	*< 0.0001*	*1.24*	*1.12*	*1.37*	*< 0.0001*
Personal history of depression	*0.484*	*0.435*	*0.539*	*< 0.0001*	*0.516*	*0.465*	*0.573*	*< 0.0001*	*0.930*	*0.913*	*0.947*	*< 0.0001*
Average sleep in last week	*0.724*	*0.688*	*0.762*	*< 0.0001*	*0.784*	*0.746*	*0.824*	*< 0.0001*	*0.992*	*0.984*	*1.00*	*0.04*

Statistically significant associations ($p < 0.05$) are shown in italic text; 'ref.' indicates a reference value for the parameter.

Table 4. Associations of residency altitude and change in altitude and depression, anxiety, and suicidality among participants in the Intern Health Study ($n = 3{,}731$).

	PHQ-9 total score				GAD-7 total score				Any suicidal ideation (PHQ-9 item #9 > 0)			
Parameter	OR	95%CI		p	OR	95%CI		p	OR	95%CI		p
Models for residency altitude												
Residency altitude (per 100 m)	*1.02*	*1.00*	*1.040*	*0.03*	1.02	1.00	1.04	0.09	*1.04*	*1.00*	*1.07*	*0.03*
Baseline depression	*7.47*	*5.57*	*10.0*	*< 0.0001*	*4.09*	*3.17*	*5.28*	*< 0.0001*	*5.04*	*3.54*	*7.17*	*< 0.0001*
Age	1.01	0.992	1.04	0.2	1.00	0.984	1.02	0.7	1.02	0.978	1.06	0.4
Sex (=F)	*1.48*	*1.32*	*1.65*	*< 0.0001*	*1.57*	*1.41*	*1.76*	*< 0.0001*	0.957	0.770	1.19	0.7
Caucasian race	0.988	0.886	1.10	0.8	1.12	1.00	1.24	*< 0.05*	*0.733*	*0.586*	*0.92*	*0.01*
Baseline anxiety	*3.80*	*2.83*	*5.10*	*< 0.0001*	*7.82*	*5.87*	*10.4*	*< 0.0001*	*2.90*	*1.99*	*4.23*	*< 0.0001*
Personal history of depression	*2.07*	*1.86*	*2.31*	*< 0.0001*	*1.95*	*1.75*	*2.17*	*< 0.0001*	*2.69*	*2.15*	*3.37*	*< 0.0001*
Average sleep in last week	*0.726*	*0.689*	*0.765*	*< 0.0001*	*0.786*	*0.748*	*0.827*	*< 0.0001*	*0.913*	*0.834*	*1.00*	*0.05*
Models for change in altitude between medical school and residency												
Change in altitude (per 100 m)	1.01	1.00	1.026	0.1	1.00	0.990	1.02	0.4	1.02	0.986	1.06	0.2
Baseline depression	*7.41*	*5.53*	*9.93*	*< 0.0001*	*4.07*	*3.15*	*5.25*	*< 0.0001*	*4.99*	*3.51*	*7.09*	*< 0.0001*
Age	1.02	0.993	1.04	0.2	1.00	0.985	1.03	0.7	1.02	0.976	1.06	0.4
Sex (=F)	*1.48*	*1.32*	*1.65*	*< 0.0001*	*1.57*	*1.41*	*1.75*	*< 0.0001*	0.955	0.769	1.19	0.7
Caucasian race	1.00	0.892	1.11	0.9	*1.12*	*1.01*	*1.25*	*0.03*	*0.741*	*0.590*	*0.931*	*0.01*
Baseline anxiety	*3.84*	*2.86*	*5.15*	*< 0.0001*	*7.89*	*5.92*	*10.5*	*< 0.0001*	*2.95*	*2.03*	*4.29*	*< 0.0001*
Personal history of depression	*2.07*	*1.86*	*2.31*	*< 0.0001*	*1.95*	*1.75*	*2.17*	*< 0.0001*	*2.71*	*2.16*	*3.39*	*< 0.0001*
Average sleep in last week	*0.727*	*0.690*	*0.766*	*< 0.0001*	*0.787*	*0.749*	*0.828*	*< 0.0001*	*0.914*	*0.835*	*1.00*	*0.05*

Statistically significant associations ($p < 0.05$) are shown in italic text.

most likely due to limited study power, since most subjects clustered at low altitudes and the average change in altitude between medical school and residency was small.

There are multiple possible mechanisms linking the observed associations between altitude and depression, anxiety, and suicidal ideation. One hypothesis is that increased altitude of residence is associated with relative hypobaric hypoxia, which could alter brain activity in multiple ways. Brain oxygen availability is proportionate to arterial oxygen levels, which are in turn proportionate to the partial pressure of inspired oxygen (Lilienthal, Riley, Proemmel, & Franke, 1946). As barometric pressure decreases with decreasing altitude, inspired oxygen levels decrease (Rahn & Otis, 1949). Travelling from sea level to high altitude is associated with acute relative hypoxia, which is then attenuated by multiple compensatory processes (Peacock, 1998; Rahn & Otis, 1949). Even so, persons who reside chronically at high altitude continue to exhibit relative hypoxia compared to those who reside at sea level (Crapo, Jensen, Hegewald, & Tashkin, 1999).

At least two different pathways could mediate a relationship between relative hypoxia and psychiatric symptoms. First, it has been hypothesized that hypoxia could produce reductions in serotonin production, which could in turn promote depression and anxiety (Young, 2013). Serotonin synthesis is exquisitely dependent on oxygen availability, as the rate-limiting step of serotonin synthesis, the conversion of tryptophan to 5-hydroxytryptophan by tryptophan hydroxylase, requires molecular oxygen (Katz, 1980, 1981). Accordingly, relative hypoxia tends to decrease serotonin synthesis in animal models, which is often associated with depression-like behaviour (Bogdanova et al., 2014; Kumar, 2011; Olson, Vidruk, McCrimmon, & Dempsey, 1983; Prioux-Guyonneau, Mocaer-Cretet, Redjimi-Hafsi, & Jacquot, 1982; Radha, Venkitasubramanian, & Viswanathan, 1976; Ray et al., 2011). Chronic hypoxia in humans living at high altitude could, therefore, produce depression by reducing the efficiency of serotonin synthesis.

Similarly, relative hypoxia could lead to alterations in brain bioenergetics, which could also contribute to depression. Multiple magnetic resonance spectroscopy studies have suggested that persons with depression exhibit alterations in markers of brain energy metabolism, such as levels of adenosine triphosphate (Ågren & Niklasson, 1988; Iosifescu et al., 2008; Kondo et al., 2016; Mathur et al., 1999; Shi et al., 2012). Similar alterations have been demonstrated in animal models after exposure to hypoxia or simulated high altitude (Jain, Prasad, Singh, & Kohli, 2015; Muthuraju & Pati, 2014; Raman et al., 2005). Moreover, healthy persons residing at high altitude (~1400 m, in Salt Lake City, UT) exhibit significant differences in brain pH and inorganic phosphate levels compared to those residing at sea level (in Belmont, MA) (Shi et al., 2014). In summary, then, persons residing chronically at high altitude may have relative impairments in cerebral bioenergetics secondary to hypoxia, which contribute to depressive symptoms.

Despite its strengths, our study does have several limitations. Although our cohort is relatively large, clustering of residency locations near sea-level, with

only 3.4% of medical residents living at high altitude, may have limited the power of the study to detect an effect of change in altitude on our outcomes. It is also possible that confounding factors which were not reported in the original dataset, such as religious affiliation, could moderate the apparent associations between altitude measures and psychiatric symptoms. Finally, it should be noted that PHQ-9 item #9 may be relatively insensitive compared to other measures of suicidal ideation, such as the Columbia Suicide Severity Rating Scale (Posner et al., 2011).

Most importantly, our models did not adjust for the effect of residency programme and programme location *per se*. Residency programme (i.e. the particular hospital, hospital system, or university hosting the residency) is obviously correlated with altitude, and would also be expected to strongly predict resident morale because of variability in academic climate, work load, and other systemic factors. It was, however, impossible to control for programme identity because of the large number of programmes involved in the study and because of heterogeneity in the reporting of programme names. It should also be noted that relatively few cities accounted for the bulk of persons living at high altitude (only two cities, Denver and Salt Lake City, accounted for 73 of the 127 residents living above 900 m, for instance). This means that other local factors associated with altitude that were not measured in this study, such as cost of living or local racial or ethnic diversity, could contribute to the associations observed. Finally, we assumed that the altitude of the central office or main hospital for each listed residency program represented the altitude to which participants were exposed; for persons who have their domicile at a large distance from the programme's main hospital, or for residency programmes with multiple, widely dispersed training sites, this assumption may not accurately reflect the average altitude to which each participant was exposed, although we would expect the discrepancies due to these factors to be small.

Despite these limitations, this study is the first to our knowledge to provide evidence from a large cohort suggesting that moving from low altitude to high altitude contributes to increased risk of depression, anxiety, and suicidal ideation. This suggests that reported associations between altitude and suicide rates are not solely due to baseline differences in populations residing at different altitudes. This in turn provides additional motivation for studies assessing the mechanisms that could mediate the connections between altitude and psychiatric symptoms, such as the effects of hypobaric hypoxia on serotonin synthesis, brain bioenergetics, or other pathways. Future lines of investigation could include studies of genetic or physiologic predictors that mediate the contribution of altitude to anxiety and depression, such as neuroimaging studies of serotonin production or brain metabolism, as well as clinical trial of interventions targeting the hypothesized mechanisms through which hypobaric hypoxia contributes to depression.

Disclosure statement

On behalf of all authors, the corresponding author reports that there are no conflicts of interest to declare.

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ORCID

Brent M. Kious https://orcid.org/0000-0003-3477-5659
Amanda Bakian https://orcid.org/0000-0001-6805-1160
Brian Mickey https://orcid.org/0000-0002-7847-7680
Constance Guille http://orcid.org/0000-0001-6004-3027

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