ORIGINAL RESEARCH

Smoking Increases the Risk of Acute Mountain Sickness

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Objective.—We aimed to ascertain risk factors for acute mountain sickness (AMS) in miners exposed to chronic intermittent high altitude conditions.

Methods.—All new hires (2009–2012) for mine employment (4000 m above sea level) were followed up for 12 months after first ascent. Demographics, physiologic data, and cigarette smoking were assessed at preemployment screening. Mine site clinic care for AMS defined incident events. Cox regression analysis estimated risk of AMS associated with smoking and selected covariates.

Results.—There were 46 AMS cases among 569 individuals during the first 12 months of employment. Adjusted for age, sex, and altitude of permanent residence, cigarettes smoked per day before hiring were prospectively associated with AMS (hazard ratio [HR], 1.9; 95% CI, 1.1 to 3.2 per 10 cigarettes smoked). This risk was higher in the subset of workers with less demanding physical work ($n = 336$; HR, 3.3; 95% CI, 1.7 to 6.3), whereas among those with more physically demanding jobs ($n = 233$), smoking was not associated with increased risk (HR, 0.6; 95% CI, 0.1 to 2.3).

Conclusions.—In workers newly hired to work at high altitude, smoking increases the likelihood of AMS, but this effect appears to be operative only among those with less physically demanding work duties.

Key words: smoking, high altitude, acute mountain sickness, mining, occupational

Introduction

Acute mountain sickness (AMS) is common, typically occurring among persons ascending to an altitude of at least 2500 m above sea level (MASL). Manifestations of AMS include headache (which can be incapacitating) and other neurological and cardiovascular signs and symptoms.¹ Although presenting over a range of severity, AMS potentially can progress to life-threatening complications, including high altitude pulmonary edema and high altitude cerebral edema.^{2,3}

Precisely because of these potentially severe complications, identifying the risk factors for AMS is important. Altitude, a well-established risk factor for AMS, is not amenable to modification. Other factors include a previous AMS event, rapidity of ascent, and lack of acclimatization.^{1,4} Among other potential risk factors, cigarette smoking is particularly important because it is modifiable. Previous findings in regard to smoking and AMS, however, have been quite variable, making this a confusing topic.^{4–17}

Relative to alpinists and trekkers, workers exposed to high altitude are an important but understudied risk group for AMS and its complications. Because working in on-site/off-site shifts at altitude does not allow for full acclimatization, AMS is likely to occur even after repeated ascents, leading to a cumulative elevated incidence of morbidity. Examining intermittently exposed subjects presents an important opportunity to study AMS in such a high-risk group, especially during the initial months of employment. In an earlier case-referent study of employees of a mining company working at an altitude of 4000 MASL, we observed that smoking was associated with increased odds of severe AMS (symptoms leading to compression chamber treatment).⁸ We wished to build on those findings by studying a nonoverlapping cohort from the same worksite, analyzing prospective risk factors for AMS, especially smoking, during the first year of employment.

Materials and Methods

In this cohort analysis of newly hired employees at a high altitude mining operation, we assessed the risk of AMS during the first 12 months of employment. The

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mine is located in the Tien Shan Mountains of Kyrgyzstan, with work sites at 3800 to 4500 MASL. Mining personnel commute on buses (journey of ≤ 8 hours) from residences either in the Issykul Lake plateau (1600 MASL) or in Bishkek and its environs (700 MASL) for 2-week on-site rotations (2 weeks on and 2 weeks off mine site).

All company employees undergo preplacement examinations. These include evaluations by 8 medical specialists or subspecialists along with relevant laboratory and ancillary testing. An electronic medical database includes these data as well as an oxygen saturation performed within the first hour of arrival at the mine site. The database also tracks any unscheduled walk-in visits to the mine site clinic, including mandatory entry of an associated diagnostic code. This includes 2 possible codes for symptoms consistent with altitude-related illness: "mountain sickness" and "acute mountain sickness." Although distinct options, in practice they are applied interchangeably and thus were collapsed into a single diagnostic entity of AMS for the purposes of this analysis. Typical symptoms that trigger the diagnosis of AMS being assigned are persistent headache (especially with a poor response to acetaminophen or ibuprofen), dizziness, shortness of breath, gastrointestinal complaints, sleep disturbance, and fatigue. In practice, systematic standard elicitation of complaints yielding a Lake Louise Score (LLS)—a diagnostic, symptom-based severity system for AMS¹⁸—was only initiated at the mine site after the period of this study. All workers have equal access to the on-site medical clinical while at the mine. Neither acetazolamide nor dexamethasone is used as a primary prevention among newly hired employees before a first AMS episode.

We constructed the study cohort by considering as potentially eligible all newly hired regular employees (trainee interns were not eligible) with preemployment screening obtained during the 4-year period between January 1, 2009 and December 31, 2012. Persons who were examined but not hired, including those who did not pass preemployment screening, were ineligible for cohort entry. We excluded otherwise eligible subjects who were employed to work at company locations other than the high altitude mine site and those who had no AMS event but did not complete 12 months of initial employment. Ultimately, 134 otherwise eligible subjects were excluded. There was no overlap between members of this cohort and the study population that we previously investigated in our earlier study of more severe AMS.⁸

Baseline preemployment screening data were used to derive demographics, place of permanent residence, and physical examination and testing data. The choice of

independent predictor variables of interest was informed by our previous analysis of more severe AMS as well as risks identified in other studies on AMS. Screening data included height and weight (yielding body mass index [BMI]), blood pressure, heart rate, hemoglobin, and pulmonary function testing (yielding forced expiratory volume in 1 second [FEV₁] and forced vital capacity [FVC];) (MicroLoop portable spirometer; CareFusion, Basingstoke, Hampshire, United Kingdom, performed to Kyrgyzstan guidelines).¹⁹ Oxygen saturation (Sao₂) obtained later at the mine site at first ascent was measured with standard equipment (ProPaq Encore monitor; Welch Allyn, Skaneateles Falls, NY).

We dichotomized new hires' occupations into those with less and more physically demanding job duties based on well-established job descriptions. The lower-demand jobs included all office staff (eg, engineers, interpreters, safety people, first aid and other clinical staffs, geologists, and secretaries); as well as security personnel, electricians, and all categories of drivers of heavy machinery (eg, haul truck drivers, passenger vehicles, and buses). We classified as high-demand jobs mechanics, drilling machine operators and related personnel; cleaners, mill operators, kitchen staff, warehousemen, blasters, underground operators, and riggers.

The cigarette smoking status of each mine employee at the time of preemployment was quantified in terms of self-reported current daily smoking (yes or no) and, for current smokers, smoking intensity in cigarettes smoked per day. Reported smoking intensity reflected that as recorded on a day of baseline examination. Data were not available on interval changes in smoking status intensity that may have occurred during follow-up. In addition, all those examined, regardless of smoking status, were further assessed with an exhaled carbon monoxide (CO) measurement using a portable breath CO analyzer (Smokerlyzer; Bedfont, Maidstone, Kent, United Kingdom). Based on the timing of examinations, the CO measurement is conducted at least 2 hours after the last cigarette smoked. We did not assess occupational secondhand tobacco smoke because company policy has banned smoking in all dormitories, common areas, and work sites. Dormitory heating and cooking is centralized without general exposure to combustion byproducts (eg, biomass fuels or individual cooking stoves).

Each employee was considered at risk for AMS for the entire first year of employment (365 days). During that period, we interrogated the medical database to identify any mine site visit coded for AMS, extracting the number of days elapsed after the first ascent to the mine until the first AMS event was recorded. Censoring observations at first AMS event or at the end of the first 365 days of employment (that is, considering subjects at

risk only until AMS or the end of the study period, whichever occurred first), we used time-to-event Cox regression analysis to estimate the risk of AMS associated with variables of study interest. These included 3 categories of variables: key demographics, potential physiological risk factors, and cigarette smoking. The key demographic covariables were age, sex, and lower vs higher altitude of permanent residence (that is, Bishkek vs Issykul). The physiologic predictors were obesity ($\text{BMI} \geq 30 \text{ kg/m}^2$), airflow obstruction ($\text{FEV}_1/\text{FVC} < 0.70$), heart rate, systolic and diastolic blood pressures, increased hemoglobin ($>180 \text{ g/L}$), and Sao_2 at first ascent. Smoking comprised the third group of risk factors, based on 3 measures: self-reported status (yes/no), number of cigarettes smoked daily, and exhaled CO. To assess temporal trends, we also tested year of enrollment as an independent AMS predictor. A set of additional analyses tested whether a lower hemoglobin cutoff point ($>170 \text{ g/L}$) or excluding the small number of below-weight subjects ($\text{BMI} < 18 \text{ kg/m}^2$) substantively affected study results. We tested each of the physiological variables in bivariate and then multivariate models adjusted for age, sex, and place of residence. Smoking was assessed in separate hierarchical models, one with demographics, a second adding the key physiological variables (except $\text{FEV}_1/\text{FVC} < 0.70$) identified as

associated with AMS in the initial analysis, and a third analysis also including $\text{FEV}_1/\text{FVC} < 0.70$. Smoking risk was further assessed stratifying by job demand and adjusting for key demographics. We retested the predictive model among those with less physical jobs including additional variables differing by physical activity: BMI, heart rate, and blood pressure. Cox regressions were run using the software package in NCSS 2007 (Kaysville, UT). The study protocol was approved by the Committee on Bioethics of the Kyrgyz State Medical Academy.

Results

We followed 569 individuals during 12 initial employment months (27,312 person-months of observation). There were 46 observed cases of AMS (8.1% cumulative incidence; 2.0 per 100 person-years). The majority of AMS events occurred in the first 6 months ($n = 33$; 71.7% of all cases). The highest incidence was in the initial month, gradually declining with time, albeit with a small respike in midyear. The median days elapsed until AMS was 124.

The study population (Table 1) was composed mainly of men (95%) aged in their mid-30s, most permanently residing at an intermediate altitude of 1600 MASL

Table 1. Baseline descriptive data for 569 newly hired employees by prospective occurrence of acute mountain sickness during the first 12 months of employment

Characteristics	AMS ($n = 46$)	No AMS ($n = 523$)	All ($n = 569$)
Demographics			
Male/female, n (%)	41/5 (89%/11%)	500/23 (96%/4%)	541/28 (95%/5%)
Lowland residents/Issykul residents n (%) ^a	11/35 (24%/76%)	77/446 (15%/85%)	88/481 (15%/85%)
Age, years, mean $\pm$ SD	33.9 $\pm$ 7.9	34.2 $\pm$ 7.6	34.1 $\pm$ 7.6
Smoking status			
Current cigarette smoking, n (%)	24 (52%)	229 (44%)	253 (44%)
Cigarettes per day, mean $\pm$ SD for smokers	9.5 $\pm$ 4.2	8.0 $\pm$ 4.2	8.1 $\pm$ 4.2
Median (25th-75th percentile)	10 (6.5; 11)	7 (5; 10)	8 (5; 10)
Exhaled CO, ppm, mean $\pm$ SD	8.4 $\pm$ 10.5	8.5 $\pm$ 7.8	8.6 $\pm$ 8.0
Physiological variables			
FEV_1/FVC %, mean $\pm$ SD	83.1 $\pm$ 7.8	80.5 $\pm$ 7.6	80.5 $\pm$ 7.6
$\text{FEV}_1/\text{FVC} < 0.70$, n (%)	6 (13%)	28 (5%)	34 (6%)
BMI, kg/m^2 , mean $\pm$ SD	25.6 $\pm$ 3.9	24.6 $\pm$ 3.6	24.7 $\pm$ 3.6
Obese, n (%)	5 (11%)	41 (8%)	46 (8%)
BP systolic, mm Hg, mean $\pm$ SD	117.8 $\pm$ 12.7	122.7 $\pm$ 11.8	122.7 $\pm$ 11.8
BP diastolic, mm Hg, mean $\pm$ SD	73.2 $\pm$ 7.9	77.1 $\pm$ 8.4	76.9 $\pm$ 8.4
Heart rate, beats/min, mean $\pm$ SD	74.6 $\pm$ 8.8	72.3 $\pm$ 9.1	72.4 $\pm$ 9.1
Hemoglobin, g/L, mean $\pm$ SD	162.2 $\pm$ 16.3	169.3 $\pm$ 16.9	169.0 $\pm$ 16.8
Hemoglobin $> 180 \text{ g/L}$, n (%)	8 (17%)	122 (23%)	130 (23%)
Sao_2 at first ascent, %, mean $\pm$ SD	89.7 $\pm$ 2.7	89.0 $\pm$ 2.8	89.0 $\pm$ 2.8

AMS, acute mountain sickness; BMI, body mass index; BP, blood pressure; CO, carbon monoxide; FEV_1 , forced expiratory flow in one second; FVC, forced vital capacity; Sao_2 , blood oxygen saturation.

^a Lowland is defined by residence at less than 1000 meters above sea level.

(Issykul). Current cigarette smoking was common (44% prevalence), but with only moderate current smoking intensity (on average, less than one half pack per day). Current smoking at baseline was reported somewhat more commonly among those who later experienced AMS, with slightly more cigarettes per day smoked in that group as well, although the levels of exhaled CO as a marker of smoking intensity were similar by later AMS status. At baseline, the number of smoked cigarettes per day had a moderate correlation with exhaled CO: $r = .55$. In this employed population, physiological indicators were typically within normal range. Less than 10% of the studied population manifested airway obstruction ($FEV_1/FVC < 0.70$). Most study participants were nonobese. Nearly 1 in 4 participants, however, had hemoglobin levels greater than 180 g/L; a more restrictive cutoff of greater than 190 g/L was achieved by 41 (7%). Hypoxemia at ascent was consistent with the partial pressure of oxygen at the altitude of measurement. Of recorded symptoms, headache was a complaint among 67% of the cases; dizziness in 17%; fatigue and gastrointestinal complaints in 15% each; and 4% (2 subjects only) reported breathlessness.

Using Cox regression analysis, we tested physiological covariates of study interest as risk factors for AMS within the first 12 months of observation. The associations between these variables are shown in Table 2, first in models adjusted only for age, sex, and place of residence, and then in full multivariate models that also included all of the physiological covariates shown. An FEV_1/FVC of less than 0.70 was the variable most strongly associated with AMS (hazard ratio [HR], 2.62; 95% CI, 1.08 to 6.35), although this association was somewhat weaker after inclusion of all the other covariates of interest (HR, 2.39; 95% CI, 0.97 to 5.84).

Both increased heart rate and lower diastolic blood pressure at baseline were weakly associated with AMS (Table 2). Obesity manifested a doubling in hazard ratio, although this association was not statistically significant in multivariate analysis. Reanalyzing this excluding 11 persons with low BMI ($< 18.5 \text{ kg/m}^2$) did not substantively impact this estimate (data not shown). Of note, neither lower SaO_2 nor hemoglobin of greater than 180 g/L were significantly associated with AMS (nor using a lower cutoff point of $> 170 \text{ g/L}$ hemoglobin; data not shown in Table). Calendar year of hire was not associated with risk of AMS (data not shown).

Smoking status defined by cigarettes smoked per day was associated with AMS (Table 3) after adjustment for age, sex, and place of residence, as well as after further adjustment for FEV_1/FVC less than 0.70 (model 2), and then further adjusted for heart rate, diastolic pressure, and obesity (model 3). Of note, the hazard ratio point estimate for the smoking intensity did not substantively change with inclusion of FEV_1/FVC less than 0.70 in the model. Although there was a parallel pattern of risk to that of smoking intensity when dichotomizing smoking as current or not, this latter association was not as strong the former. The association with exhaled CO measured at baseline, which would reflect cigarettes smoked in the hours before the screening examination, was not statistically associated with AMS risk in these models.

We wished to further examine the relationships between smoking and AMS, taking into account the physical demands of employment among the new hires. We dichotomized the workers into those with occupations with low ($n = 336$) vs high demand ($n = 233$). There was a disproportionate number of low-demand workers among the AMS group ($n = 31$; 67%) vs low-demand workers in the AMS-free group ($n = 305$; 58%;

Table 2. Baseline physiological variables and acute mountain sickness risk during the first 12 months of employment among 569 employees

Physiological variable	Model 1 ^a			Model 2 ^a		
	HR	95% CI	P value	HR	95% CI	P value
$FEV_1/FVC < 0.70$	2.62	1.08–6.35	.03	2.40	0.98–5.87	.06
SaO_2 at first ascent to 4000 m ^b	1.00	0.91–1.12	.86	1.01	0.91–1.13	.84
Heart rate ^b	1.03	1.00–1.06	.10	1.03	1.00–1.06	.07
Diastolic blood pressure ^b	0.97	0.95–1.01	.11	0.96	0.93–1.00	.05
Obesity	1.46	0.57–3.73	.43	2.19	0.81–5.91	.12
Hemoglobin $> 180 \text{ g/L}$	0.75	0.35–1.63	.47	0.77	0.35–1.67	.50

FEV_1 , forced expiratory flow in 1 second; FVC, forced vital capacity; HR, hazard ratio; SaO_2 , blood oxygen saturation.

^a Model 1 includes the variable listed in the row along with age, sex, and place of residence; model 2 includes age, sex, and place of residence and all of the other variables listed.

^b Hazard ratio for SaO_2 expressed per 10 ppm; hazard ratio for heart rate expressed per 10 beats/min; hazard ratio for blood pressure expressed per 10 mm Hg.

Table 3. Cigarette smoking-associated acute mountain sickness risk, first 12 months of employment

Variable	Model 1 ^b			Model 2 ^b			Model 3 ^b		
	HR	95% CI	P value	HR	95% CI	P value	HR	95% CI	P value
Current smoking	1.65	0.89–3.05	0.12	1.59	0.85–2.97	0.14	1.62	0.87–3.02	0.13
Cigarettes per day ^a	1.87	1.11–3.17	0.02	1.83	1.07–3.13	0.03	1.83	1.08–3.11	0.03
Exhaled CO ^a	1.16	0.82–1.66	0.40	1.11	0.78–1.56	0.57	1.12	0.79–1.58	0.52

CO, carbon monoxide; HR, hazard ratio.

^a Hazard ratio for cigarettes per day expressed per 10 cigarettes and for exhaled CO per 10 ppm.

^b Model 1 includes the individual variable listed along with age, sex, and place of residence; model 2 includes the individual variable listed along with age, sex, place of residence, and forced expiratory flow in 1 second/forced vital capacity (FEV₁/FVC) <70%; model 3 includes the individual variable listed along with heart rate, diastolic blood pressure, and obesity.

$P < .05$). To take potential risk modification into account, we reestimated the smoking-associated hazard ratio stratified by work demands and adjusted for age, sex, and altitude of residence (Table 4). Among those with low physical demands, the hazard ratio estimates for smoking intensity and current smoking were increased, whereas there was no association between those factors and AMS among those with more physically demanding jobs. There was also a parallel increase in hazard ratio associated with exhaled CO in the low-demand group, albeit a less-potent point estimate of risk and with wider confidence intervals (HR, 1.46; 95% CI, 0.98 to 2.17). Because the less physically active group manifested higher values for BMI, heart rate, and diastolic blood pressure, we retested the relationships in that stratum including those variables in the models. Cigarettes smoked per day were more strongly related to AMS (HR, 5.2; 95% CI, 1.6 to 17.4), as was current cigarette smoking (HR, 3.6; 95% CI, 0.93 to 13.9); the exhaled CO effect was somewhat attenuated (HR, 1.48; 95% CI, 0.66 to 2.9; data not in tables). We also reestimated the association between airflow obstruction and AMS in the low-demand stratum: the risk was potent (HR, 4.33; 95% CI, 1.67 to 11.23). Risk could not be estimated within the high-demand stratum because even though there were persons with airflow obstruction in

that group ($n = 12$), none manifested AMS in the first 12 months of employment.

Discussion

In this study of newly hired high-altitude miners, we identified cigarette smoking as a risk factor for incident AMS, with an exposure response manifested in cigarettes smoked per day. Of particular interest, the smoking-associated risk of AMS was present among the subset of newly hired workers who had less, rather than more, physically demanding job duties.

These findings for AMS, defined broadly to include a range of illness symptoms, are consistent with our previous analysis of more severe AMS (from the same mine site, but with a nonoverlapping cohort at risk).⁸ In that previous analysis, we also observed a cigarette smoking exposure response, both by self-report and based on exhaled CO. In the current analysis we took a number of demographic and physiologic covariates into account, the latter including BMI, hemoglobin, and SaO₂ at first ascent. Importantly, we also tested whether airflow obstruction contributed to the risk of AMS. Indeed, an FEV₁/FVC ratio of less than 0.70 was associated with a significantly elevated hazard ratio for AMS, but importantly, this airflow obstruction did

Table 4. Cigarette smoking and risk of acute mountain sickness stratified by job demands of occupation among 569 high altitude miners^a

Variable	Less physical (N = 336)			More physical (N = 233)		
	Risk	95% CI	P value	Risk	95% CI	P value
Cigarettes per day ^b	3.29	1.72–6.27	<0.01	0.57	0.14–2.30	0.43
Current smoking	2.39	1.09–5.23	0.03	0.74	0.22–2.48	0.62
Exhaled CO ^b	1.46	0.98–2.17	0.06	0.67	0.30–1.51	0.33

CO, carbon monoxide.

^a Models include the row variable listed along with age, sex, and place of residence.

^b Hazard ratio for cigarettes per day expressed per 10 cigarettes and for exhaled CO per 10 ppm.

not appear to be a mediator of the smoking-associated risk that we observed because it did not affect the smoking-associated hazard ratio. Put in other terms, both smoking and airflow obstruction appear to be risk factors for AMS, but the effect of one is not dependent on the other.

It is important to put this study in the context of the relevant literature on AMS in relation to smoking, which has been heterogeneous in its findings (Table 5). Of note, a range of exposure conditions, outcome definitions, and differing approaches to covariate adjustment complicate comparison among these studies. A group of studies has found smoking to be significantly protective against AMS, in particular some but not all investigations from China.^{5,12} One recent Chinese study of high altitude headache among employed men taken to altitude, however, not only observed a not significant smoking association, but also found that more-active work was significantly protective ($P < .05$).¹⁶

One key difference between our cohort and most of the subjects subsumed in Table 5 is that in our study the nature of the exposure was intermittent, that is, 2 weeks on and 2 weeks off site in rotation. This represents a strength of our study insofar as such intermittent exposure is typical of many occupational cohorts, especially in high altitude miners. This further underscores the importance of investigating high altitude effects in occupational groups, not only in mountaineers and trekkers.

LIMITATIONS

Our cohort was relatively small, even though it included all new hires during a 4-year period. Because of study numbers, we are limited in our ability to analyze specific strata of the cohort, for example, women or persons who are older at new hire. Because we could ascertain when the AMS event occurred, however, we were able to use a time-to-event analysis, thus increasing our power to observe the associations that we did. Moreover, given the 2-week cycles on site followed by descent to lower altitude, this group was repeatedly rechallenged during the 12 months of observation. Nonetheless, an even larger study might have allowed us to identify additional risk factors and especially to analyze AMS incidence within different strata of workers and to examine the potential risks of specific job duties. Also as noted, there were relatively few women in the cohort. Our choice of variables of study interest was informed by our previous analysis of AMS risk as well as being based on the findings of others.^{4,14,15} This mitigates against the potential pitfalls of multiple testing absent having an *a priori* set of risk factors chosen for study. This is

especially true of cigarette smoking, the focus of our study. Data on change in smoking status or intensity after baseline were not available for analysis. Because we studied time until first AMS event, however, any change in smoking status related to such illness would not have affected this analysis.

Other potential study limitations should also be considered. Exposure ascertainment should not have been biased by the presence or absence of AMS, since the independent variables were obtained before any AMS event. Our definition of AMS in this study allowed for heterogeneity in symptoms and was not restricted to more severe presentations defined with compression chamber treatment (the case definition in our previous study⁸) or a cutoff point in LLS (which was not available with reliability in this cohort and is widely used, albeit subject to revision²⁰). Such heterogeneity may have led to disease misclassification that, if present, should have biased to the null rather than account for any associations that we did observe. In addition, studying a wider spectrum of AMS can be viewed as a study strength because this is generalizable to the full clinical range of this syndrome, including factors such as sleep disturbance that are not currently included in the LLS.

Of note, ours is not a population that resides habitually at 4000 MASL, but rather one that works intermittently at this altitude. Although the work cycle of the labor force studied reflects a standard occupational factor especially in mining, one analytic limitation is our inability to assess AMS onset in terms of timing since ascent for any given 2-week work period. Moreover, workers arrive (and leave) in a staggered fashion every day; hence day of the week cannot serve as a surrogate for time since the most recent ascent. Our study, by being restricted to the initial 12 months of employment, cannot assess risk of AMS after longer-term employment with rotating shifts on- and off-site, and the risks identified may or may not be relevant to AMS among those with longer-term employment.²¹ Although we observed a fall-off in incidence even during the first 12 months, this does not establish the extent of acclimatization associated with intermittent high altitude exposure. Finally, there were certain risk factors that we were unable to take into account; for example, history of migraine headache (a risk factor for AMS in other studies)²² or rapidity of ascent (all of the workers studied travel up to the site in the same commuting arrangement).²³

IMPLICATIONS FOR PREVENTION

Our findings suggest several potential avenues for AMS risk-reduction among occupational cohorts. First and

Table 5. Smoking and AMS risk in selected relevant studies

<i>Source (reference)</i>	<i>N by smoking; cohort type</i>	<i>Altitude and location</i>	<i>AMS findings</i>	<i>Smoking effect</i>
Song et al, 2014 ⁵	506 smokers vs 436 nonsmokers; “volunteers”	Lhasa (3700 MASL)	AMS incidence: smokers, 56.6%; nonsmokers, 66.5%; (P < .05)	Protective
McDevitt et al, 2014 ⁶	332 participants; 11% smokers (≈ 37); trekkers	5400 MASL	AMS in smokers vs nonsmokers OR, 2.5; 95% CI, 1.1 to 5.6; P < .05)	Risk
Tang et al, 2014 ⁷	856 participants (smoking prevalence not provided); “volunteers”	Lhasa (3700 MASL)	AMS predictive model: smoking protective in univariate analysis (OR, 0.63; 95% CI, 0.46 to 0.87); NS adjusted for age	No association (protective trend)
Vinnikov et al, 2014 ⁸	17 smokers vs 28 nonsmokers; occupational cohort	Tien Shan (4000 MASL)	AMS (chamber treated) smokers vs nonsmokers, OR, 10.0; 95% CI, 1.5 to 67.4; P < .05)	Risk
Beidleman et al, 2013 ⁹	308 participants; 15.6% (≈ 48); military personnel	Pikes Peak and hypobaric chamber (1659–4501 MASL)	AMS predictive model: smoking not predictive (P value not provided)	No association
Bian et al, 2013 ¹⁰	Smokers 169 vs 624 nonsmokers; occupational (mixed)	Lhasa (3700 MASL)	Smokers 79% headache; nonsmokers 72%; AMS predictive model: smoking not predictive (P = .74)	No association (risk trend)
Richalet et al, 2012 ¹¹	Smokers 124 vs 1202 nonsmokers; mixed cohort, 75% trekkers/mountaineers; 14% occupational	Various sites; > 3500 MASL	AMS smokers vs nonsmokers (HR, 0.66; 95% CI, 0.41 to 1.1)	No association (protective trend)
Wu et al, 2012 ¹²	182 smokers vs 200 nonsmokers; occupational cohort	Qinghai-Tibet (4552 MASL)	AMS smokers, 45%; nonsmokers, 56% in nonsmokers (P < .05)	Protective
You et al, 2012 ¹³	138 smokers vs 176 nonsmokers; military personnel	West China (4300 MASL)	AMS smokers, 30.3%; nonsmokers, 52.3% (P < .05)	Protective
Meirer et al, 2010 ¹⁴	22 smokers vs 140 nonsmokers; mountaineers	European Alps (3454–3817 MASL)	AMS smokers, 13% ; nonsmokers, 27.8% (NS)	No association (protective trend)
Pesce et al, 2005 ¹⁵	917 participants; 9.1% smokers (≈ 83); mountaineers	Mt Aconcagua, Andes (6962 MASL)	AMS smokers vs nonsmokers (HR, 0.65; 95% CI, 0.3 to 1.3; NS)	No association (protective trend)
Gaillard et al, 2004 ¹⁶	619 participants; 15% smokers (≈ 93); trekkers	Annapurna, Nepal (5400 MASL)	AMS predictive model: smoking not predictive (P value not provided)	No association
Ziaee et al, 2003 ¹⁷	459 participants (smoking prevalence not provided); trekkers	Mt Damavand, Iran (4200- 5671 MASL)	AMS predictive model: smoking not predictive (P value not provided)	No association
Schneider et al, 2002 ⁴	128 smokers vs 699 nonsmokers; mountaineers	Capanna Margareta, European Alps (4559 MASL)	AMS smokers, 30%; nonsmokers, 28% (approximated from Figure; NS)	No association
Current study	253 smokers vs 314 nonsmokers; occupational	Tien Shan (4000 MASL)	AMS smokers vs nonsmokers (HR, 1.65; 95% CI, 0.89 to 3.05); per 10 cigarettes daily (HR, 1.87; 95% CI, 1.11 to 3.17)	Risk

AMS, acute mountain sickness; HR, hazard ratio; MASL, meters above sea level; NS, not significant; OR, odds ratio.

foremost, the association between smoking and AMS adds yet one more impetus for work-based smoking cessation efforts.^{24–26} Exposure to environmental

tobacco smoke at the workplace and mining camp, although not studied here for AMS, negatively affects respiratory health and this could play a role in AMS.²⁷

The association with airflow obstruction we observed suggests that spirometric surveillance may identify persons at greater risk of AMS and suggests a potential role for bronchodilator treatment, although this remains to be evaluated as a specific intervention to prevent AMS. Finally, the role of physically demanding work duties in AMS warrants further investigation. Although it may seem counterintuitive that relatively greater exertion decreases the risk of AMS, it could be that moderate exercise induces protective physiologic compensation or that physical deconditioning associated with less-demanding work increases a smoking effect. The smoking-associated risk seen in the lower physical activity group did not appear to be explained by confounding from BMI, heart rate, or blood pressure. What is clear is that occupationally associated AMS in this cohort of miners working at high altitude is common and that its prevention should be a focus of attention for occupational health providers.

Conclusions

Smoking is a distinct and potentially modifiable risk factor for AMS in workers employed for high altitude mines. Those in jobs with relatively less physical demands may be at greater risk of occupationally related AMS. Airflow obstruction is an independent predictor of AMS, suggesting that surveillance spirometry may identify persons at risk.

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