Is Smoking a Predictor for Acute Mountain Sickness? Findings From a Meta-Analysis

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Abstract

Aim: Studies of the potential association between cigarette smoking and acute mountain sickness (AMS) have reached contradictory conclusions. Our aim was to perform a meta-analysis of studies across a range of populations to ascertain better the true relationship between cigarette smoking and AMS.

Materials and Methods: We used the PRISMA protocol to identify and screen eligible studies of smoking and AMS. Databases including Pubmed and Google Scholar were searched, using the terms “smoking” and “acute mountain sickness.” We conducted a meta-analysis of the selected studies in order to evaluate causal inference, evaluate potential biases, and investigate possible sources of heterogeneity across studies.

Results: We identified 3907 publications, of which 29 were eligible for inclusion by reporting smoking status and AMS. Of these, eight publications were excluded because they were duplicative or were lacking quantitative data. The 21 studies analyzed included 16,566 subjects. These fell into two groups: occupational/military (n = 8) or volunteers/trekkers/mixed (n = 13). Study heterogeneity was high (X2 = 55.5, P < .001). Smoking was not statistically associated with increased risk of AMS: pooled OR = 0.88 (95% CI = 0.74–1.05). Stratification yielded similar risk estimates among the occupational/military studies versus all others and studies at relatively higher and lower altitudes.

Conclusions: Overall, smoking was not statistically significantly associated with AMS: there is no consistent effect of cigarette smoking acting as either a protective factor against or a risk factor for AMS.

Implications: This is the first quantitative assessment of published studies on smoking and AMS, which shows smoking to be neither a risk, nor protective. Studies specifically focusing on smoking as a risk factor, should guide further research on this issue. Although all smokers should be strongly advised to quit, studies on risk factors for AMS focusing on other exposures could shed light on the full range of risks for AMS.

Introduction

Acute mountain sickness (AMS) frequently affects people ascending elevations higher than 2,500 meters above sea level and may even occur among susceptible persons at lower altitudes.1 It is a clinical syndrome, generally characterized by the presence of headache (cephalagia) combined with a number of other symptoms, predominantly neurologic.2 The Lake Louise Score is a standard measure used to define AMS,3 although other assessment tools have been used. Because cephalgia is the hallmark of AMS, this symptom following ascent to 2,500 meters above sea level is often presumed to be...
a manifestation of the syndrome, with or without formalized Lake Louise Score assessment.

The likelihood of AMS increases with greater altitude and more rapid ascent. Other risk factors have been considered in a number of epidemiologic investigations, with those analyzed including female sex, younger age, higher body mass index (BMI), and previous episodes of AMS. Findings have also been mixed in regard to some of these, for example, age. Cigarette smoking is another potential risk factor that has been considered in a number of AMS studies. In some of these, smoking-associated risk has been investigated on an a priori basis, driven by suspicion that baseline compromise in oxygen delivery or vascular tone might make AMS more likely. In other studies, smoking status is taken into account as a confounding variable whose potential role is not otherwise specified. The study of cigarette smoking in relation to AMS is further complicated by the heterogeneous attributes of the populations studied. Much of the AMS literature is based on cohorts or case series of mountaineers and other outdoor enthusiasts, among whom prevalence rates and intensity of smoking are relatively low. Other investigations, however, have studied working populations (eg, high altitude miners) or military personnel, among whom patterns of smoking, among other factors, are quite different.

Given such heterogeneity, it is not surprising that the association between smoking and AMS has been inconsistent across studies. Indeed, smoking has variously been found to be strongly protective against AMS or, conversely, a potent risk factor for development of the syndrome. For example, several studies have found that risk of AMS may be 40%–60% lower among smokers, a finding that may be driven by nicotine possibly acting as vasoactive component reducing mild headache intensity or even ablating it completely. Arguing against this proposed mechanism, smoking is known to compromise oxygen delivery and increase vascular tone, two physiologic effects that might make AMS more likely. Hence, the aim of this study was to conduct meta-analysis of available studies of smoking-associated risk for AMS and to do so across a range of populations as well as within more homogenous study subgroups. In so doing, we wished to ascertain whether smoking is or is not a risk factor for AMS and to identify possible sources of heterogeneity in the current literature. Our overall goal is to better inform interventions to reduce the incidence of this common, serious, and potentially preventable syndrome.

Methods

Search Strategy

We used PRISMA protocol for systematic reviews and meta-analyses. Two researchers (DV and CS) did the literature search and data abstraction independently. We searched four databases (PubMed, Embase, Google Scholar, and Web of Science) for all publications published through April 2015. We used the following search strategies: “smoking” AND “mountain sickness” in Embase; “smoking”[Mesh] AND “altitude sickness”[Mesh Terms] OR altitude sickness[Text Word] in PubMed; “smoking” AND “acute mountain sickness” in Google Scholar; and “smoking” AND “acute mountain sickness” in the Web of Science. Medical Subject Headings (MeSH) refers to the controlled vocabulary thesaurus used for indexing articles in PubMed. The search algorithm we employed is presented in Figure 1.

In total, there were 3907 publications identified through these searches. Duplicate citations, animal experimental studies, studies of children, investigations of chronic mountain sickness rather than AMS, conference presentations (eg, abstracts), conference proceedings, and limited case reports were classified as ineligible. From eligible studies, we further identified any additional relevant publications from among the reference citations. The search was carried out in April 2015.

Publications potentially eligible for inclusion (cross-sectional series, retrospective and prospective cohort investigations, and case-control studies) were read by two independent reviewers. Quantitative data on association of smoking and other risk factors with AMS were extracted from each eligible study.

Statistical Analysis

The effect measure in the selected epidemiological studies was the odds ratio (OR). We used the published OR and its associated 95 percent confidence interval (95% CI) or calculated the OR and 95% CI from published data providing the frequencies of smoking and AMS. Some studies provided only a qualitative estimate of the relationship of smoking to AMS without either a numerical estimate of the OR or the percentage of smokers in relation to AMS. In these cases, we contacted the lead author of any otherwise eligible publication and requested the relevant missing data (n = 6 papers included on this basis). Baseline data for each study included were
the logarithmically transformed OR with its corresponding standard error, which were then input to meta-analysis function of NCSS 9 software (Utah). Percent weights for each study as a contributor to the modeled estimates were calculated based on a weight of each study ($W_i$), which equaled 1/variance. Hence, studies with greater sample size and smaller standard error, contributor a greater weight to the analysis.

Because of substantial heterogeneity of studies in this analysis, we used a random effects modeling. This model assumes the samples come from populations with different effect sizes such that the true effect may vary substantially across studies. We computed a 95% CI around the mean effect size. Heterogeneity of variance of eligible studies was tested using overall $Q$ value and $I^2$ values. The $Q$ value is a measure of variance among the effect sizes, and a statistically significant ($P < .05$) sum of the squares of each effect size about the weighted mean ($Q$) indicates statistical heterogeneity. A potential problem with the random effects model is that is does not weight by study precision.\(^7\) In order to weight studies on precision, while still incorporating between-study variance, we used the fixed effects model to calculate summary relative risks, then adjusted their 95% CIs for heterogeneity using the method of Shore et al.\(^3\) Publication bias was evaluated using a funnel plot (which shows how many of the published studies had outlier results) and Begg’s and Egger’s tests that further assess the question of potential publication bias.\(^9,10\) Because we used grouped published data, this analysis was exempt from institutional review for research on human subjects.

## Results

In total, we identified 29 papers eligible for analysis. Six publications\(^11–16\) among this pool of eligible papers did not provide sufficient quantitative data estimates in the initial publication and the authors could not be reached or did not provide such data, although all six concluded that smoking was either not predictive of AMS or that smoking rates did not differ significantly in those with and without AMS. Of the 23 remaining publications, two\(^17\) represented initial reports from cohorts later analyzed and published in expanded form\(^18–19\) and thus were excluded. Study subject characteristics, attitudes of exposure, and the details of the study designs of the eight excluded papers are summarized in Table 1. In total, these excluded studies reported on 1859 subjects in four cross-sectional and four prospective cohorts.

Details of the 21 studies ultimately retained in the final analysis, including their ORs and contributory weights, are summarized in Table 2. These studies included data on 16,566 participants.\(^16–38\) Four studies were conducted among military personnel (two of these were not explicit on this point, but were from a Chinese military research group), four were occupational, and 13 were volunteers (one of these studies was mixed, including a minority [14%] of occupationally exposed participants). The publication dates for the studies ranged from 1991 to 2015, with 16 of the 21 appearing in 2006 or thereafter. The top three studies with the greatest contributory weight, Li et al.,\(^29\) Bian et al.,\(^32\) and MacInnis et al.\(^33\) (together accounting for 46.9% of weight), comprised only 4411 subjects (26.6% of the entire study population). One of these studies showed smoking-associated increased AMS risk, while the other two manifested a protective effect; all, however, were close to an OR = 1.0. The study with the smallest sample size contributed only 45 observations.\(^36\)

The smoking-associated ORs ranged from 0.23 to 10.0. When combined, the OR for smoking as predictor for AMS in a random effects model was 0.88 (95% CI = 0.74–1.05). The log transformed OR values for the individual studies and pooled estimate are shown in Figure 2. The pooled OR from a fixed effect model ($Q$-value 55.5; $P < .001$) using a Shore-adjusted 95% CI was similar: OR = 0.90 (95% CI = 0.77–1.06). We further analyzed the 21 included studies

### Table 1. Details of Otherwise Eligible Studies of Smoking and AMS Ultimately Excluded

<table>
<thead>
<tr>
<th>#</th>
<th>Source (reference)</th>
<th>Study design</th>
<th>Total subject N (% smokers)</th>
<th>Cohort type</th>
<th>Altitude and location</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anholm et al., 1979 (ref.(^11))</td>
<td>Cross-sectional</td>
<td>228 (NA)</td>
<td>Ski resort visitors</td>
<td>2835 MASL, Colorado, United States</td>
<td>No quantitative data provided. Smoking not associated with symptoms.</td>
</tr>
<tr>
<td>2</td>
<td>Richalet et al., 1988 (ref.(^17))</td>
<td>Prospective cohort</td>
<td>128 (27%)</td>
<td>Trekkers</td>
<td>6200–8848 MASL, Nepal</td>
<td>Subjects were included into a larger publication subsequently.(^14)</td>
</tr>
<tr>
<td>3</td>
<td>Roeggla et al., 1996 (ref.(^13))</td>
<td>Prospective cross-over</td>
<td>99 (23%)</td>
<td>Alpinists</td>
<td>2900 MASL, Austrian Alps</td>
<td>Smoking did not differ in alpinists with and without AMS.</td>
</tr>
<tr>
<td>4</td>
<td>Basnyat et al., 2000 (ref.(^13))</td>
<td>Cross-sectional</td>
<td>228 (27%)</td>
<td>Pilgrims</td>
<td>4300 MASL, Nepal</td>
<td>No quantitative data provided. &quot;Smoking did not enhance the risk of acquiring AMS&quot;.</td>
</tr>
<tr>
<td>5</td>
<td>Ziace et al., 2003 (ref.(^14))</td>
<td>Prospective cohort</td>
<td>459 (NA)</td>
<td>Trekkers</td>
<td>4200–5671 MASL, Iran</td>
<td>No quantitative data provided. Smoking not predictive.</td>
</tr>
<tr>
<td>6</td>
<td>Wu et al., 2010 (ref.(^15))</td>
<td>Cross-sectional</td>
<td>247 (13%)</td>
<td>Railroad Passengers</td>
<td>2900–4300 MASL, Qinghai–Tibet</td>
<td>Smoking was not associated with AMS.</td>
</tr>
<tr>
<td>7</td>
<td>Meirer et al., 2010 (ref.(^7))</td>
<td>Cross-sectional</td>
<td>162 (13%)</td>
<td>Mountaineers</td>
<td>3454–3817 MASL, European Alps</td>
<td>Subjects were included into a larger publication subsequently.(^19)</td>
</tr>
<tr>
<td>8</td>
<td>Beidlemann et al., 2013 (ref.(^16))</td>
<td>Prospective cohort</td>
<td>308 (16%)</td>
<td>Military personnel</td>
<td>1659–4501 MASL, Pikes Peak, United States and hypobaric chamber</td>
<td>No quantitative data provided. Smoking not predictive.</td>
</tr>
</tbody>
</table>

AMS = acute mountain sickness; MASL = meters above sea level.
<table>
<thead>
<tr>
<th>#</th>
<th>Source (reference)</th>
<th>Study design</th>
<th>Study, N</th>
<th>Cohort type</th>
<th>Location (altitude)</th>
<th>AMS findings</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kayser, 1991 (ref.20)</td>
<td>Cross-sectional</td>
<td>353</td>
<td>Trekkers</td>
<td>Nepal (5400 MASL)</td>
<td>OR = 0.81 (95% CI = 0.45–1.48)</td>
<td>2.5</td>
</tr>
<tr>
<td>2</td>
<td>Honigman et al., 1993 (ref.21)</td>
<td>Cross-sectional</td>
<td>3158</td>
<td>Conference participants</td>
<td>Colorado, United States (1900–2900 MASL)</td>
<td>OR = 0.98 (95% CI = 0.70–1.38)</td>
<td>7.7</td>
</tr>
<tr>
<td>3</td>
<td>Murdoch, 1995 (ref.22)</td>
<td>Cross-sectional</td>
<td>283</td>
<td>Mountaineers</td>
<td>Mount Everest Base Camp (5545 MASL)</td>
<td>OR = 1.26 (95% CI = 0.53–2.87)</td>
<td>1.3</td>
</tr>
<tr>
<td>4</td>
<td>Schneider et al., 2002 (ref.23)</td>
<td>Cross-sectional</td>
<td>806</td>
<td>Mountaineers</td>
<td>Capanna Margareta, European Alps (4559 MASL)</td>
<td>OR = 0.92 (95% CI = 0.60–1.41)</td>
<td>4.9</td>
</tr>
<tr>
<td>5</td>
<td>Gailland et al., 2004 (ref.24)</td>
<td>Cross-sectional</td>
<td>266</td>
<td>Trekkers</td>
<td>Nepal (5400 MASL)</td>
<td>OR = 1.30 (95% CI = 0.61–2.75)</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>Pesce et al., 2005 (ref.25)</td>
<td>Cross-sectional</td>
<td>917</td>
<td>Mountaineers</td>
<td>Mt Aconcagua, Andes (6962 MASL)</td>
<td>OR = 0.65 (95% CI = 0.3–1.3)</td>
<td>1.6</td>
</tr>
<tr>
<td>7</td>
<td>Wagner et al., 2006 (ref.26)</td>
<td>Cross-sectional</td>
<td>388</td>
<td>Trekkers</td>
<td>Mt Whitney, United States (4419 m)</td>
<td>OR = 0.44 (95% CI = 0.17–1.20)</td>
<td>0.9</td>
</tr>
<tr>
<td>8</td>
<td>Wagner et al., 2008 (ref.27)</td>
<td>Cross-sectional</td>
<td>886</td>
<td>Trekkers</td>
<td>Mt Whitney, United States (4419 m)</td>
<td>OR = 1.32 (95% CI = 0.75–2.32)</td>
<td>2.8</td>
</tr>
<tr>
<td>9</td>
<td>Jafarian et al., 2008 (ref.28)</td>
<td>Prospective cohort</td>
<td>90</td>
<td>Guests of high-altitude hotel</td>
<td>Tochal Mountain, Iran (3500 MASL)</td>
<td>OR = 0.65 (95% CI = 0.24–1.79)</td>
<td>0.9</td>
</tr>
<tr>
<td>10</td>
<td>Burtscher et al., 2011 (ref.29)</td>
<td>Prospective cohort</td>
<td>506</td>
<td>Trekkers</td>
<td>Eastern and Western Alps (2200–3817 MASL)</td>
<td>OR = 0.92 (95% CI = 0.54–1.85)</td>
<td>3.1</td>
</tr>
<tr>
<td>11</td>
<td>Yi et al., 2012 (ref.30)</td>
<td>Retrospective cohort</td>
<td>3727</td>
<td>Military personnel</td>
<td>Tibet–Qinghai Plateau (2900–4300 MASL)</td>
<td>OR = 1.21 (95% CI = 0.98–1.50)</td>
<td>19.5</td>
</tr>
<tr>
<td>12</td>
<td>Richalet et al., 2012 (ref.31)</td>
<td>Prospective cohort</td>
<td>1326</td>
<td>Mixed cohort, 75% trekkers/mountaineers; 14% occupational</td>
<td>Various sites, Europe (&gt;3500 MASL)</td>
<td>OR = 0.66 (95% CI = 0.41–1.1)</td>
<td>3.6</td>
</tr>
<tr>
<td>13</td>
<td>Wu et al., 2012 (ref.32)</td>
<td>Prospective cohort</td>
<td>382</td>
<td>Occupational cohort</td>
<td>Qinghai–Tibet (4352 MASL)</td>
<td>OR = 0.62 (95% CI = 0.41–0.92)</td>
<td>5.4</td>
</tr>
<tr>
<td>14</td>
<td>You et al., 2012 (ref.33)</td>
<td>Prospective cohort</td>
<td>314</td>
<td>Military personnel</td>
<td>Western China (4300 MASL)</td>
<td>OR = 0.40 (95% CI = 0.24–0.64)</td>
<td>3.7</td>
</tr>
<tr>
<td>15</td>
<td>Ban et al., 2013 (ref.34)</td>
<td>Prospective cohort</td>
<td>793</td>
<td>Occupational (mixed)</td>
<td>Tibet (3700 MASL)</td>
<td>OR = 0.97 (95% CI = 0.77–1.22)</td>
<td>16.7</td>
</tr>
<tr>
<td>16</td>
<td>MacNish et al., 2013 (ref.35)</td>
<td>Prospective cohort</td>
<td>491</td>
<td>Religious pilgrims</td>
<td>Nepal (4370 MASL)</td>
<td>OR = 0.79 (95% CI = 0.59–1.05)</td>
<td>10.7</td>
</tr>
<tr>
<td>17</td>
<td>McDevitt et al., 2014 (ref.36)</td>
<td>Cross-sectional</td>
<td>332</td>
<td>Trekkers</td>
<td>Nepal (5400 MASL)</td>
<td>OR = 2.5 (95% CI = 1.1; 5.6)</td>
<td>1.3</td>
</tr>
<tr>
<td>18</td>
<td>Tang et al., 2014 (ref.37)</td>
<td>Prospective cohort</td>
<td>856</td>
<td>Military</td>
<td>Tibet (3700 MASL)</td>
<td>OR = 0.63 (95% CI = 0.46–0.87)</td>
<td>8.7</td>
</tr>
<tr>
<td>19</td>
<td>Vinnikov et al., 2014 (ref.38)</td>
<td>Nested case-control</td>
<td>45</td>
<td>Occupational</td>
<td>Tien Shan, China (4000 MASL)</td>
<td>OR = 1.0 (95% CI = 1.5–67.4)</td>
<td>0.2</td>
</tr>
<tr>
<td>20</td>
<td>Ren et al., 2015 (ref.39)</td>
<td>Prospective cohort</td>
<td>80</td>
<td>Military</td>
<td>Tibet (4300 MASL)</td>
<td>OR = 0.23 (95% CI = 0.06–0.89)</td>
<td>0.5</td>
</tr>
<tr>
<td>21</td>
<td>Vinnikov et al., 2015 (ref.40)</td>
<td>Retrospective cohort</td>
<td>367</td>
<td>Occupational</td>
<td>Tien Shan, China (4000 MASL)</td>
<td>HR 1.65 (95% CI = 0.89–3.05)</td>
<td>2.3</td>
</tr>
</tbody>
</table>

AMS = acute mountain sickness; CI = confidence interval; MASL = meters above sea level; OR = odds ratio.

*Studies reporting only % of smokers in AMS group vs. % of smokers in non-AMS group. Crude ORs with 95% CI were calculated as part of this meta-analysis.

*This study reported high-altitude headache instead of AMS as an outcome.

*This study provided both crude and adjusted estimates for three categories (less than one pack a day; one pack a day and more than one pack a day). Data were combined in two categories: smokers vs. nonsmokers.
stratifying them by several different criteria (Table 3). When strati-
fied into two groups based on cohort types (military/occupational vs.
volunteers, trekkers or mixed), the former had a pooled OR = 0.83
(95% CI = 0.58–1.18), while the latter manifested an OR = 0.91
(95% CI = 0.77–1.08). Additional stratification of studies greater
than or equal to versus below the median altitude reported (4300
meters above sea level) observed a somewhat greater protective
effect at higher compared to lower altitude (pooled OR 0.80 vs.
0.97), although both had wide confidence intervals. Stratified by
study design (cross-sectional vs. prospective or case referent) or by
location (Asia vs. European/North American) did not reveal substan-
tial differences in the observed pooled risk estimates. No evidence
of publication bias was seen in all studies combined in Egger’s test
(bias coefficient = –0.181; P = .82), Begg’s test (P = .74), or in by an
inspection of a funnel plot of the results (Figure 3).

We also conducted sensitivity analysis by sequential exclusion
of each study from the overall analysis: the estimated OR did not
change substantively following any individual exclusion. The great-
est reduction (although not statistically significant) occurred when
McDevitt et al. study was excluded (retained pooled OR = 0.85;
95% CI = 0.71–1.01). In contrast, exclusion of the study by You
et al.43 increased the pooled OR to 0.92 (95% CI = 0.78–1.09).
When we calculated the pooled OR based on the four studies avail-
able that provided the results of multivariate risk modeling includ-
ing smoking,25,35,36,38 this was a weakly positive (11% increase) risk
factor for AMS with wide confidence intervals (OR = 1.13; 95%
CI = 0.53–2.41).

Discussion

In this meta-analysis including data from 21 studies, we did not
find definitive evidence that cigarette smoking neither consistently
imparted increased risk nor protected against AMS. Thus, although
were indeed statistically significant in either direction, this pooled
analysis failed to show a pattern from which chance variability could
be excluded as the likely explanation. Moreover, subgroup analyses
stratified by occupational or military cohorts versus volunteers or
avocational status showed a similar pattern of heterogeneous esti-
mates of risk. Limiting the studies to those at the higher versus lower
altitude also failed to establish any clear association between ciga-
rette smoking and the risk of AMS in either stratum. Other strati-
fied analyses were similarly nonrevealing. These data, taken together,
make it unlikely that smoking is a potent risk factor for AMS, just as
smoking is not likely to be strongly protective.

Clearly, delineating risk factors for AMS is critical to adequately
inform trekkers and other enthusiasts; assessing fitness for work
among occupational and military groups is no less important. Studies
of risk factors for AMS have traditionally focused on the attrib-
utes of the sojourn itself (rate of ascent, highest altitude reached).
Consistent with this, the studies we identified for analysis primarily
focused on risk factors other than cigarette smoking. Smoking, when
considered at all, typically was included as a potential confounder.
Because such studies were not designed to test cigarette smoking as
predictive of AMS, exposure ascertainment was not prioritized and
typically relied on self-report of dichotomized status (eg, smoker, yes
or no) without consideration of intensity (eg, cigarettes smoked per
day) or duration.

The marked heterogeneity among the studies included in this
meta-analysis likely reflects a variety of factors. Headache is a pri-
mary driver of AMS diagnosis. The pathophysiology of headache,
in turn, is complex. Vasconstriction is likely to be a contribu-
tor, especially at high altitude. This is relevant to cigarette smoke
because nicotine is known to affect the regulation of vascular tone.
Mechanistically, cigarette-smoke modulation of vascular tone might
explain either increased risk or protection or both, depending on
the timing and intensity of exposure. Heterogeneity in smoking-
AMS associations could arise from differing cumulative exposure to
Shore-adjusted Random effects Heterogeneity

Study design

Altitude

in many of the studies included in this meta-analysis and this mis-

with AMS.

sis actually used smoking verification methods, in both cases exhaled

be considered as an alternative. Only two studies in this meta-analy-

costly, exhaled carbon monoxide as a surrogate for exposure should

that measuring cotinine can be challenging in field studies as well as

pattern that may be particularly relevant to alpinists and trekkers

lier studies, Lake Louise Scoring system was not a widely accepted

smoking status shifts from daily smoking to occasional use, 42 a

estimated. 40,41 Moreover, the role of misclassification grows when

quantifying carbon monoxide in exhaled air. Such confirmation is

misclassification was also likely to have been present

of AMS. This should be a nondifferential misclassification of disease that would

be anticipated to bias toward the null, unless more severe diseases

were both less likely to be misclassified and differentially associated

with smoking. That association between AMS severity and smoking,

however, remains to be disproved. Most of the AMS in the stud-

ies included in this meta-analysis appears to be fairly mild, but we

did include one nested-case control study of illness severe enough to

have been treated with normobaric chamber compression.36 Of note,

that study observed a pronounced, smoking-associated elevated

AMS risk. Studies of smoking and high-altitude cerebral edema

(HACE), which may represent a more advanced central nervous sys-

tem response along a spectrum from AMS, as well as investigations

of smoking in relation to high-altitude pulmonary edema (HAPE)

may shed further light on this risk factor for adverse outcomes fol-

owing a shared environmental stimulus.

Selection bias is another potential limitation of most of the stud-

ies included. Analogous to healthy worker effect in occupational

cohorts, studies of volunteers and alpinists will be likely to select

physically fit young men, as would studies of military personnel.

Subjects in these studies also would be unlikely to have any seri-

ous medical conditions or chronic smoking-associated diseases. Our

analysis was also limited by having to rely on crude ORs instead

of adjusted ORs for most of the studies included. Unmeasured

confounders that varied systematically, therefore, also could have

contributed to heterogeneity in the observed associations. One can-

didate confounder might be athleticism, which could be a risk factor

for AMS, for example, through over-exertion at altitude, and con-

versely, negatively associated with cigarette smoking. Finally, most

of the studies included were cross-sectional, raising a potential issue

of temporality, although this should not be a contributor to the

observed heterogeneity in estimated risk.

In summary, this meta-analysis combining studies from around

the world, performed at various altitudes and including a variety of

participants, did not reveal a consistent and statistically significant

association between cigarette smoking and AMS. Given the marked

heterogeneity of the available studies, it is not surprising that no

convincing pattern emerged of a protective effect or of increased risk

Table 3. Stratification of Included Studies Into Four Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Fixed effects</th>
<th>Shore-adjusted</th>
<th>Random effects</th>
<th>Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>OR</td>
<td>CI₇</td>
<td>CIᵤ</td>
</tr>
<tr>
<td>Military/occupational</td>
<td>8</td>
<td>0.90</td>
<td>0.80</td>
<td>1.02</td>
</tr>
<tr>
<td>Voluntary</td>
<td>13</td>
<td>0.90</td>
<td>0.78</td>
<td>1.04</td>
</tr>
<tr>
<td>Higher</td>
<td>11</td>
<td>0.80</td>
<td>0.68</td>
<td>0.93</td>
</tr>
<tr>
<td>Lower</td>
<td>10</td>
<td>0.97</td>
<td>0.86</td>
<td>1.09</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>10</td>
<td>1.00</td>
<td>0.83</td>
<td>1.19</td>
</tr>
<tr>
<td>Prospective or case-control</td>
<td>11</td>
<td>0.87</td>
<td>0.78</td>
<td>0.97</td>
</tr>
<tr>
<td>Location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe/America</td>
<td>7</td>
<td>0.88</td>
<td>0.73</td>
<td>1.07</td>
</tr>
<tr>
<td>Asia</td>
<td>14</td>
<td>0.91</td>
<td>0.82</td>
<td>1.01</td>
</tr>
</tbody>
</table>

OR = odds ratio; CI₇ = lower confidence interval; CIᵤ = upper confidence interval.
of AMS attributable to cigarette smoking. It may only be possible to more definitely address smoking as a possible contributor for AMS through studies focusing on this question and rigorously quantifying both the exposure and outcome.

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Declaration of Interests
None declared.

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References


