Sex and Incidence of Acute Mountain Sickness

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Abstract

Acute Mountain Sickness (AMS) and its related illnesses, high altitude cerebral edema (HACE), and high altitude pulmonary edema (HAPE), affect many residents of lower elevations that travel to high altitude for pleasure or profession. This systematic review and meta-analysis aimed to assess the potential relationship between sex and incidence of AMS, hypothesizing that females will have a lesser incidence due to the respiratory stimulant effects of female sex hormone progesterone. Odds ratios were compiled into a forest plot and a summary estimate was calculated. Contrary to the hypothesis, females were found to be 1.48 times more likely to experience AMS symptoms compared to males (p<0.0001). It is concluded that there is an association between sex, specifically female sex, and incidence of AMS. Further research is suggested in assessing the relationship between sex and severity of AMS, as well as the relationship between female and male sex hormones and AMS, while taking into consideration specific hormone levels for each subject.

Introduction

Humans are equipped with a series of physiologic responses to cope with the hypoxic environment that exists at altitude. Decreased barometric pressure at altitude (roughly 70% of sea-level value at 3000m\textsuperscript{12}) results in decreased partial pressure of oxygen (PO\textsubscript{2}) in inspired air. Consequently, PO\textsubscript{2} is lowered at all steps of oxygen transport in the body. Peripheral chemoreceptors in the aortic and carotid bodies detect a decrease in arterial PO\textsubscript{2}, and the hypoxic ventilatory response (HVR) is initiated. To increase arterial PO\textsubscript{2}, and thus, the oxygen available for tissues, ventilation increases at the expense of carbon dioxide (CO\textsubscript{2}). This increase in CO\textsubscript{2} removal, combined with the bicarbonate store that exists as a buffer in tissues, results in alkalosis, or a more basic blood pH. The kidneys respond by excreting additional bicarbonate in the urine\textsuperscript{1}. 
The specific causes and physiologic mechanisms of AMS are still unclear. One potential mechanism involves a failure or delay of HVR, which could result in a buildup of CO\textsubscript{2} relative to O\textsubscript{2}, and an overall acidosis (decreased blood pH). Increased partial pressure of CO\textsubscript{2} (PCO\textsubscript{2}) may increase cerebral blood flow, and therefore, intracranial pressure\textsuperscript{1}. Several studies report that decreased ventilation is a significant risk factor for AMS\textsuperscript{2,3,4}. Further evidence for this theory lies in the success of acetazolamide, a pharmaceutical carbonic anhydrase inhibitor, in preventing AMS symptoms. It has been shown that acetazolamide increases ventilation, although the mechanism for this action remains uncertain\textsuperscript{5}.

The existence of pulmonary and cerebral edemas, or swelling caused by excess fluid in the lungs and brain, respectively, in response to altitude has researchers examining fluid balance as a potential mechanism for AMS\textsuperscript{6,7}. As previously mentioned, the compensatory mechanism for a respiratory-induced alkalosis is kidney-mediated excretion of bicarbonate in the urine. It is possible that retention of urine and bicarbonate, and the resulting alkalosis may have a cyclical effect on HVR by dampening its response\textsuperscript{6}.

AMS generally occurs above 2500m, when ascent rate exceeds an individual’s ability to acclimatize. It is characterized by headache and at least one other symptom, including gastrointestinal discomfort, fatigue, dizziness, or difficulty sleeping. It is the least severe, but most common, of the illnesses associated with altitude-related hypoxia, and frequently afflicts otherwise healthy people. According to one study conducted in Colorado, AMS affects 25% of the general population that travel to moderate altitudes\textsuperscript{8}. AMS is typically self-limiting and not life-threatening, but it can affect quality of experience and decrease productivity\textsuperscript{9}. Studies have shown that the AMS symptoms generally subside after several days of exposure, and that this acclimatization can have protective effects for future ascents for as long as 21 days later\textsuperscript{10}. The most effective treatment for AMS is acclimatization or
descent. Although a definitive link between AMS and the more severe illnesses of HACE and HAPE has yet to be found, continued rapid ascent increases risk of these potentially life-threatening conditions.

Individual susceptibility to AMS and other altitude illnesses varies greatly, and the reasons for this are not well understood. However, there are known risk factors, including history of altitude illness, original residence below 900m, and certain preexisting cardiopulmonary conditions. Ascent rate and time at altitude are major contributing factors to an individual’s susceptibility. Older people (age 50 and above) are less prone than younger individuals. Exercise at altitude is known to exacerbate symptoms. As with most things, the variability in susceptibility is likely due complex interactions between individual genetic factors and the environment, and relates to a person’s own ability to acclimatize.

Multiple studies have attempted to create a risk prediction score based on relevant variables by compiling self-reported data. Reviews have been conducted for rate of ascent and preventive drug use, but none so far have examined the relationship between sex and incidence of AMS.

**Physiological Rationale**

Because of the respiratory stimulant nature of the female sex hormone progesterone, it is hypothesized that females will have a lesser incidence of AMS. Two studies have shown that full-term pregnancy, a period of higher levels of circulating progesterone, increases resting ventilation and hypoxic and hypercapnic ventilatory responses. A follow-up study examined the specific effects of female sex hormones and metabolic rate on HVR in postmenopausal women, and found that progestin-only and combined progestin and estrogen accounted for 50% of the increase in HVR. Pre-travel clinics routinely discourage
women from taking oral contraceptives (OC) while traveling at altitude, because they reduce the amount of circulating progesterone. In one study\textsuperscript{20}, 85\% of OC users experienced AMS symptoms compared to 51\% of non-OC users (p=0.03) Furthermore, OC use was found to negate the preventive effects of acetazolamide use. This evidence supports the idea that the respiratory effects of progesterone might cause females to have a lesser incidence of AMS. These effects may be dependent on day of menstrual-cycle, as the levels of progesterone vary throughout the different phases of the cycle.

**Methods**

*Studies Included*

MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines were used for this systematic review and meta-analysis\textsuperscript{21}. Search began in August 2014 using the PubMed database. Keywords included *Acute Mountain Sickness, Risk or Prediction*, and *Gender or Sex*. Titles and abstracts were searched for relevant variables, and initial eliminations were made at this point. Eligible studies for the review met the following criteria: 1) dependent variable was incidence of acute mountain sickness; 2) contained both male and female subjects; 3) sample size of at least 100 people; 4) reported effect size in odds ratios including 95\% confidence intervals, or data that could be used to calculate odds ratios and confidence intervals; 5) used self-reported symptom questionnaires such as the Lake Louise Scoring System, Hackett’s Score, or the Environmental Symptoms Questionnaire III (as opposed to clinical assessment, see Appendix); 6) minimum altitude of study was 2500m (cutoff for AMS), while maximum was 5500m (cutoff for ‘extreme altitude’)\textsuperscript{12}; 7) must be able to be accessed for free through University of Colorado. Figure 1 depicts the method of locating eligible studies.
If article could not be accessed free-of-charge through the database or the University of Colorado Library, authors were contacted by the given email. If no response was received by 1 February 2015, the article was excluded from the study. Relevant cited studies within articles were included if they met the inclusion criteria and no follow-up study was found. All articles used were published in English (one non-English study was not included because it did not meet the inclusion criteria).

Figure 1. Flowchart describing method of finding eligible studies.
Assessment of Acute Mountain Sickness

Examples of the most common symptom quantification methods, including the Lake Louise Scoring System and Hackett’s Score, are included in the Appendix. The Environmental Symptoms Questionnaire Version III (ESQ-III) is the most burdensome to complete, and was developed to evaluate symptoms of military personnel when working in extreme conditions. It is not included in the Appendix, but it involves responding to 67 items and using item weight and an established divisor to determine factor score. ESQ-III can be used to assess respiratory AMS (AMS-R) and cerebral AMS (AMS-C)\(^2\). A shortened, online version of the ESQ-III has been developed and shown to be effective\(^2\). Hackett’s Score assesses symptoms both through a questionnaire and a physical examination by an experienced investigator\(^2\). The Lake Louise Scoring System was most favored by studies in this analysis. Its diagnostic criteria for AMS include a rise in altitude in the last 4 days, presence of a headache and at least one other symptom, a score of 3 or higher on the questionnaire. Lake Louise criteria for AMS, HACE and HAPE are also included in the Appendix. Comparisons of each method have yielded mixed results\(^2\), but in general, these three are accepted as the most relevant methods of assessing AMS symptoms.

Data Analysis

Table 1 shows relevant information for the studies analyzed. A few studies reported no significant relationship between sex and incidence of AMS\(^2\), or did not include usable data that showed this result\(^2\), or female sex was removed from the study entirely\(^2\). When their sample size is taken into consideration, these studies would have had a modest impact on the summary estimate, and so were excluded from the analysis. If effect size was not reported as an odds ratio, as in five of the studies\(^8,26,36,37,48\), this was calculated using a 2x2
<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Altitude of Study</th>
<th>Mean Age ± SD</th>
<th>Number of Subjects (Female)</th>
<th>Effect Size</th>
<th>Criteria</th>
<th>Covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canouï-Poitrine, et al., 2014</td>
<td>Sea level subjects with or without previous experience</td>
<td>&gt;4000m</td>
<td>45.8 ± 13.5 (with) 42.6 ± 15.1 (without)</td>
<td>537 (164) (with) 480 (214) (without)</td>
<td>OR</td>
<td>Hackett’s</td>
<td>History of SHAI, rate of ascent, history of migraine, location, age, sex, activity level, ventilatory and cardiac responses</td>
</tr>
<tr>
<td>McDevitt, et al., 2014</td>
<td>English-speaking subjects</td>
<td>5400m</td>
<td>35 ± 12</td>
<td>332 (169)</td>
<td>OR</td>
<td>Lake Louise, ESQ-III</td>
<td>Age, smoking status, BMI, AMS awareness</td>
</tr>
<tr>
<td>Santantonio, et al., 2014</td>
<td>Adults with pre-travel counseling</td>
<td>&gt;3500m</td>
<td>37 ± 16</td>
<td>162 (84)</td>
<td>OR</td>
<td>Hackett’s</td>
<td>Sex, age, BMI, data about ascent, trip organized by travel agency, medical history, and previous experience at high-altitude</td>
</tr>
<tr>
<td>Beidleman, et al., 2013</td>
<td>Unacclimatized men and women</td>
<td>Various</td>
<td>23.8 ± 5.4</td>
<td>308 (68)</td>
<td>OR</td>
<td>ESQ-III</td>
<td>Altitude, time at altitude, activity level, age, body mass index, race, sex, and smoking status</td>
</tr>
<tr>
<td>Richalet, et al., 2012</td>
<td>Altitude visitors using or not using acetazolamide</td>
<td>&gt;3500m</td>
<td>42.6 ± 12.8 (ACZ) 45.3 ± 14.1 (No ACZ)</td>
<td>409 (n/a) (ACZ) 917 (n/a) (No ACZ)</td>
<td>OR</td>
<td>Hackett’s</td>
<td>Ascent rate, history of migraine, ventilatory response to exercise at hypoxia, desaturation during exercise at hypoxia</td>
</tr>
<tr>
<td>Croughs, et al., 2011</td>
<td>Travelers who consulted a pre-travel clinic</td>
<td>&gt;2500m, median: 36, range: 17-76</td>
<td>744 (381)</td>
<td>Lake Louise</td>
<td>Previous AMS, age, gender, maximum overnight altitude, number of acclimatization nights, ascent rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bansyat, et al., 2010</td>
<td>Nepali pilgrims</td>
<td>4300m</td>
<td>33 ± 14</td>
<td>228 (62)</td>
<td>OR</td>
<td>Lake Louise</td>
<td>Age, sex, altitude acetazolamide use, alcohol during trip, smoking status,</td>
</tr>
<tr>
<td>Jackson, et al., 2010</td>
<td>Trekkers on Mt. Kilimanjaro</td>
<td>4370m</td>
<td>31 range: 18-71</td>
<td>189 (68)</td>
<td>Lake Louise</td>
<td>Ascent rate, acetazolamide use, rest day at 3700m, gastroenteritis, respiratory illness</td>
<td></td>
</tr>
<tr>
<td>Karinen, et al., 2008</td>
<td>Finnish trekkers on Mt. Kilimanjaro</td>
<td>Various</td>
<td>51 ± 10</td>
<td>112 (58)</td>
<td>Lake Louise</td>
<td>Age, BMI, smoking status, altitude experience, acetazolamide use, respiratory, cardiovascular and/or metabolic disease</td>
<td></td>
</tr>
<tr>
<td>Ziaee, et al., 2003</td>
<td>Iranian trekkers</td>
<td>2900m, 4200m</td>
<td>N/A</td>
<td>459 (148)</td>
<td>Lake Louise</td>
<td>Sex, age, height, weight, smoking status, weight of knapsack, time spent in shelter at 4200m</td>
<td></td>
</tr>
<tr>
<td>Honigman, et al., 1993</td>
<td>General tourist population</td>
<td>1920m-3000m</td>
<td>43.8 ± 11.8</td>
<td>3140 (981)</td>
<td>Custom Score</td>
<td>Residence &lt;3000m, previous AMS symptoms, age &lt;60 years, previous lung disease, poor or average physical condition</td>
<td></td>
</tr>
<tr>
<td>Kayser, et al., 1991</td>
<td>Western trekkers in Nepal</td>
<td>5400m</td>
<td>Men: 30.6 ± 7.6 Women: 30.1 ± 8.5</td>
<td>353 (160)</td>
<td>ESQ-III</td>
<td>Age, previous altitude experience, rate of ascent, smoking status, pre-trek training, oral contraceptives, number of trekkers in party, method of organization</td>
<td></td>
</tr>
</tbody>
</table>
contingency table\textsuperscript{39} and confidence intervals were generated using the calculated standard errors. For one study\textsuperscript{32}, incidence was found to be higher in men, so this odds ratio was inverted to obtain the female odds. Odds ratios with confidence intervals were compiled and a forest plot was created. Using the R meta package, fixed effect and random effects summary odds ratios were calculated, as well as test of heterogeneity (Q value).

Because each of the studies has been conducted by a different set of researchers, and the idea is to be able to generalize the effects to a wider population, a random effects model computation is more appropriate for this meta-analysis. A fixed effects model assumes the only variation between studies occurs by chance or error because the studies are functionally identical. In this meta-analysis, a fixed effect model would provide a summary estimate that overemphasizes the relative weight of each study according to sample size. The summary estimate in a random effects model computation is the mean of a distribution of effect sizes, which better represents the variation between the studies in this analysis. The difference between a fixed effect model and a random effects model can be seen in the standard error equations for the summary estimate for each model. For simplicity, these equations assume identical standard deviation and sample size for all studies. Note: $\sigma =$ standard deviation, $k =$ number of one-group studies, $n =$ sample size of each study, and $\tau =$ variance.

**Fixed Effect Model**

\[
SE_M = \sqrt{\frac{\sigma^2}{k \times n}}
\]

**Random Effects Model**

\[
SE_M = \sqrt{\frac{\sigma^2}{k \times n} + \frac{\tau^2}{k}}
\]
The standard error for a fixed effect model depends only on within-study variance. Standard error will approach zero when sample size is infinitely large. On the other hand, the random effects model equation has additional term, which represents between-study variance. Standard error in this case will only approach zero if the number of studies is infinitely large. For these reasons, the confidence intervals of the random effects model are usually wider than those of the fixed effect model.

The test of heterogeneity (Q value) assesses the variation between studies, and whether this variation is statistically significant or not. A Q that is greater than the degrees of freedom, coupled with a p value less than 0.05 (sometimes 0.10 is used), suggests significant heterogeneity. It is expected that random effects model computations will have greater heterogeneity than fixed effect model computations.

Results

A total of twelve studies, with 18 separate and relevant study groups, were included in this analysis. Figure 2 shows the organization of the data about two reference lines, one where the value of 1 crosses the x-axis (dotted), and one that goes through the random effects summary odds ratio (solid). The increasing weight of each study was depicted by increasingly darker shades of blue. Studies were listed from oldest published to newest, to show the progression of results as time went on. A consolidation around the summary estimate can be seen in the studies published later than 2012, a promising trend.
<table>
<thead>
<tr>
<th>Study</th>
<th>Relative Odds (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kayser, 1991</td>
<td>1.66 (1.07-2.58)</td>
</tr>
<tr>
<td>Honigman, et al., 1993</td>
<td>1.25 (1.06-1.49)</td>
</tr>
<tr>
<td>Ziaec, et al., 2003</td>
<td>0.81 (0.55-1.21)</td>
</tr>
<tr>
<td>Karinen, et al., 2008</td>
<td>1.33 (0.57-3.14)</td>
</tr>
<tr>
<td>Jackson, et al., 2010</td>
<td>0.73 (0.36-1.47)</td>
</tr>
<tr>
<td>Basnyat, et al., 2010</td>
<td>4.34 (1.83-10.7)</td>
</tr>
<tr>
<td>Croughs, et al., 2011</td>
<td>1.61 (1.13-2.31)</td>
</tr>
<tr>
<td>Richalet, et al., 2012 *</td>
<td>1.55 (1.01-2.37)</td>
</tr>
<tr>
<td>Richalet, et al., 2012 **</td>
<td>1.45 (0.86-2.45)</td>
</tr>
<tr>
<td>Beidleman, et al., 2013</td>
<td>0.61 (0.31-1.19)</td>
</tr>
<tr>
<td>Santantonio, et al., 2014</td>
<td>2.07 (1.05-4.05)</td>
</tr>
<tr>
<td>McDevitt, et al., 2014 ψ</td>
<td>2.28 (1.19-4.39)</td>
</tr>
<tr>
<td>McDevitt, et al., 2014 ψψ</td>
<td>1.58 (0.88-2.84)</td>
</tr>
<tr>
<td>McDevitt, et al., 2014 ψψψ</td>
<td>1.73 (1.04-2.88)</td>
</tr>
<tr>
<td>Canouï-Poitrine, et al., 2014 PE</td>
<td>1.73 (0.94-3.18)</td>
</tr>
<tr>
<td>Canouï-Poitrine, et al., 2014 Γε</td>
<td>1.51 (0.90-2.52)</td>
</tr>
<tr>
<td>Canouï-Poitrine, et al., 2014 Ψε</td>
<td>1.38 (0.75-2.54)</td>
</tr>
<tr>
<td>Canouï-Poitrine, et al., 2014 ΓΕ</td>
<td>1.60 (0.96-2.67)</td>
</tr>
</tbody>
</table>

**Fixed Effect Model**

**Random Effects Model**

*without acetazolamide
**with acetazolamide

Figure 2. Individual odds ratios and summary estimates of the association between female sex and incidence of AMS.
The fixed effect summary estimate was 1.394 (95% CI = 1.258-1.546) and the random effects summary estimate was 1.484 (95% CI = 1.248-1.680), both with p-values of less than 0.0001. However, as mentioned before, the random effects value is most relevant to this study. This indicates highly significant results, and an association between female sex and incidence of AMS. Statistical heterogeneity was assessed, and a Q value of 27.19 was found (df=17). However, the p-value for heterogeneity was 0.055, which does not meet the cut-off for significance, but does suggest moderate variation between studies, and reiterates the appropriateness of analyzing the random effects model summary estimate.

Three of the studies contained multiple subgroups within the study population. Canouï-Poitrine, et al., examined groups with and without previous experience, and within those groups, compared how clinical versus physio-clinical variables predicted risk of AMS. This study found that in females with previous experience, clinical variables were more predictive, whereas in females without previous experience, physio-clinical variables were more predictive of risk. The purpose was to develop an accurate scoring system based on clinical, physiological and environmental factors. Richalet, et al., only found a significant relationship between sex and incidence of AMS in females that did not take acetazolamide as a preventive measure. Acetazolamide use, perhaps, “levels the playing field” among individuals. McDevitt et al. separated groups according to their scores on the various questionnaires. Females that completed the ESQ-III showed greater odds of AMS than females that completed the Lake Louise Scoring System, which shows the variation between the diagnostic questionnaires that serves as a limitation for this meta-analysis.

Other studies included in the meta-analysis showed interesting findings. Santantonio, et al., found female sex to be the most powerful predictor of AMS. Basnyat, et al., reported an unusually high, but highly significant, odds ratio for females (4.340, 95% CI = 1.830-10.68,
This study also found a higher incidence of HACE and HAPE for females, which has not been the trend for other studies\textsuperscript{32,44,45}. It is an especially wide confidence interval, which weakens the result. However, the study reported a high incidence overall of AMS (68\%) and noted that they did not control for dehydration, which could have led to an overestimation of AMS symptoms. Also, the ascent was considered very rapid compared to most expeditions, which could have exacerbated AMS symptoms. Beidleman, et al., Jackson et al. and Ziaee et al., all reported higher incidence of AMS in males, though their results were not statistically significant. Beidleman, et al., on the other hand, did report significantly higher severity of AMS in males than females, a result discussed later in this study. Karinen, et al., noted that females are more likely to descend at presentation of AMS symptoms, which could imply that females experience more debilitating symptoms of AMS, or that females are less likely to push their own physical limits.

\textbf{Discussion}

This review suggests there is a relationship between sex and incidence of AMS, with greater incidence in females. This is contrary to the hypothesis, but highly unlikely due to chance alone (p<0.0001). In regards to mechanisms for this result, one study included in the review\textsuperscript{30} asked whether or not women tend to over-report symptoms. McDevitt et al. cited a study conducted in the U.K. that found no significant differences between men and women in their initial reporting of conditions\textsuperscript{31}.

The body responds to hypoxic environments in a number of ways; each of these responses presents a potential mechanism to explain why females tend to have a higher incidence of AMS. The time frame for each of these responses varies considerably, and some responses may not be as applicable to AMS, which occurs within hours of ascent to high
altitude. First to occur, as mentioned previously, is the body’s hypoxic ventilatory response (HVR), which acts to increase ventilation and $pO_2$. As discussed later, several studies have found that female sex hormones increase HVR, so this is not likely a mechanism by which females exhibit a higher incidence of AMS.

Second, the renal system responds to hypoxia by initiating diuresis and removal of bicarbonate\(^1\). In one study, those that eventually developed severe AMS displayed water retention within the first 3 hours of altitude exposure. Healthy subjects in the same study, by contrast, exhibited mild diuresis, or the excretion of urine\(^7\). The study surmises that this fast-acting effect is due to an early increase in anti-diuretic hormone (ADH), a hormone responsible for water reabsorption by the kidneys. Estrogens have been shown to lower the threshold for ADH, increasing fluid retention\(^{41}\). This provides a potential mechanism for the results of this study. Furthermore, Hackett finds that fluid retention could be a related to a failure of the HVR, and a cause for AMS symptoms\(^6\).

Third, the body exhibits a hematological response at altitude, a response often exploited by athletes training for endurance activities. Erythropoietin (EPO) concentrations spike within hours of ascent, which stimulate a gradual increase in hemoglobin over the course of days to weeks at altitude. This response helps maintain oxygen delivery to tissues in hypoxemia\(^1\). Testosterone is known to be an erythropoetic hormone\(^{42}\). It is possible that testosterone, a predominantly male sex hormone, gives males an advantage at altitude by increasing EPO levels. Perhaps EPO helps to initiate fluid loss that correlates with avoidance of AMS symptoms.

While the hypothesis was rejected, there may be hope for the idea that females are better equipped for high-altitude conditions. One study, noted previously, showed higher
severity, as opposed to incidence, of AMS in males compared to females. The females in the study, all premenopausal, demonstrated 29% lower severity (p=0.05) than men, which is consistent with one other study. These findings align with previous research, conducted at Colorado ski resorts, that suggests a greater susceptibility of males than females to HAPE, a more severe altitude illness. These studies surmise that this outcome could be due to increased ventilation in females, mediated by the female sex hormone, progesterone, a known respiratory stimulant.

After conducting this meta-analysis and becoming more familiar with the topic, it became clear that the studies included lacked crucial information to evaluate the hypothesis. None of the studies provided information about circulating progesterone levels in females, for example by reporting day of menstrual cycle, or oral contraceptive use. Only the mean age of female subjects can be used to guess whether or not the majority of subjects were pre- or post-menopausal, which not all studies provided. That progesterone levels vary significantly throughout the menstrual cycle and reproductive stage could be a confounding variable for this meta-analysis. Perhaps a majority of the females in were in the follicular phase of their cycle, or were post-menopausal, and thus had lower progesterone levels. However, if the inclusion criteria were updated to include female-specific information, there would not have been enough studies to conduct the analysis in the first place. These gaps in information are common in meta-analyses and limit the power of the conclusions than can be drawn.

**Limitations**

This study was limited in its scope due to the observational nature of the data used. As is possible with any meta-analysis, there were inherent differences in the conditions under
which the data was obtained in each study. For example, each study was conducted at slightly different altitudes, in different geographic locations, with subjects of different backgrounds and levels of expertise, and so forth. Each study adjusted data for its own important factors such as age, smoking status and previous experience, but these covariates were not consistent across all studies. Additionally, the subjective nature of diagnosing AMS is a limit to any study examining this illness. Symptoms, and thus incidence of AMS, are self-reported by subjects using questionnaires, rather than measured or obtained by more objective means. Much of the data is dependent on survey responses, which could lead to selection bias. Additionally, this study was limited to analyzing articles that could be accessed for free through the University of Colorado, or by other reasonable means. Finally, as mentioned earlier, information about progesterone levels was not included for the females in the studies used for meta-analysis.

**Recommendations for Further Research**

No causal relationship can be determined from this study because of its observational and non-interventional nature. Therefore, it would be beneficial to conduct a case-control study to verify a causal association between female sex and higher incidence of AMS. Additionally, research is needed to assess the link between the sex hormones and the physiological response to altitude, and to determine the mechanisms for associations that have already been established. This includes, but is not limited to, sex hormone and EPO role in the ventilatory response and fluid retention. Careful attention should be paid to female OC use and phase of menstrual cycle.
Conclusions

According to this study, there is a relationship between female sex and incidence of Acute Mountain Sickness, which is contrary to the hypothesis. There is a multitude of factors contributing to a person's development of altitude illnesses, and further research is needed in many aspects of this field.
References


## Appendix

### Figure 3. Lake Louise Criteria for Altitude Illness

#### Acute Mountain Sickness

In the setting of a recent gain in altitude, the presence of headache and at least one of the following symptoms:
- Gastrointestinal (anorexia, nausea or vomiting)
- Fatigue or weakness
- Dizziness or lightheadedness
- Difficulty sleeping

#### High Altitude Cerebral Edema

Can be considered "end stage" or severe AMS. In the setting of a recent gain in altitude, either:
- The presence of a change in mental status and/or ataxia in a person with AMS
- Or, the presence of both mental status changes and ataxia in a person without AMS

#### High Altitude Pulmonary Edema

In the setting of a recent gain in altitude, the presence of the following:

**Symptoms:** at least two of:
- Dyspnea at rest
- Cough
- Weakness or decreased exercise performance
- Chest tightness or congestion

**Signs:** at least two of:
- Crackles or wheezing in at least one lung field
- Central cyanosis
- Tachypnea
- Tachycardia

Lake Louise Score (LLS) for the diagnosis of Acute Mountain Sickness (AMS)

A diagnosis of AMS is based on:
1. A rise in altitude within the last 4 days
2. Presence of a headache

PLUS
3. Presence of at least one other symptom
4. A total score of 3 or more from the questions below

SELF-REPORT QUESTIONNAIRE
Add together the individual scores for each symptoms to get the total score.

<table>
<thead>
<tr>
<th>Headache</th>
<th>No headache</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild headache</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate headache</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe headache, incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal symptoms</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Poor appetite or nausea</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate nausea &amp;/or vomiting</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe nausea &amp;/or vomiting</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue &amp;/or weakness</td>
<td>Not tired or weak</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild fatigue/weakness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate fatigue/weakness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe fatigue/weakness</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness/lightheadedness</td>
<td>Not dizzy</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Mild dizziness</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Moderate dizziness</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Severe dizziness, incapacitating</td>
<td>3</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>Slept well as usual</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Did not sleep well as usual</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Woke many times, poor sleep</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Could not sleep at all</td>
<td>3</td>
</tr>
</tbody>
</table>

**TOTAL SCORE:**

Total score of:
- 3 to 5 = mild AMS
- 6 or more = severe AMS

Note: Do not ascend with AMS symptoms. Descend if symptoms are not improving or getting worse. Descend if symptoms of HACE or HAPE develop.

Table 2. Hackett Score for AMS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache relieved after a first degree analgesica</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
</tr>
<tr>
<td>Loss of appetite</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness, light-headedness</td>
<td>1</td>
</tr>
<tr>
<td>Headache not relieved after a first degree analgesic (paracetamol, ibuprofen or acetylsalicylic acid)</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Dyspnoea at rest</td>
<td>3</td>
</tr>
<tr>
<td>Unusual level of asthenia</td>
<td>3</td>
</tr>
<tr>
<td>Oliguria</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>18/18</td>
</tr>
</tbody>
</table>

Interpretation:
Total = 1–3: slight acute mountain sickness (AMS).
Total = 4–6: mild AMS.
Total >6: severe AMS.