BMJ open

# Physiological variables associated with the development of acute mountain sickness at the South Pole

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**To cite:** Harrison MF, Anderson PJ, Miller AD, *et al*. Physiological variables associated with the development of acute mountain sickness at the South Pole. *BMJ Open* 2013;**3**:e003064. doi:10.1136/bmjopen-2013-003064

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-003064).

Received 16 April 2013
Revised 11 June 2013
Accepted 17 June 2013

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## ABSTRACT

Exposure to altitudes >2500 m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition. Research has attempted to identify factors associated with developing AMS without controlling important factors related to the ascent or collecting a comprehensive set of variables.

**Objectives:** The Antarctic Study of Altitude Physiology (ASAP) investigated variables associated with the development of AMS in adults experiencing rapid passive transport to altitude by airplane.

**Design:** Our prospective observational trial collected data, including personal history, anthropometrics, vital signs, blood samples and pulmonary function, at sea level and at altitude. Statistical analysis utilised independent sample t tests to investigate between-group differences ($p<0.05$) and a forward, step-wise binary logisitic regression analysis was performed.

**Participants:** Of 248 eligible ASAP participants, those who did not use acetazolamide (N=98) were included in the present analysis.

**Primary outcome measures:** The diagnosis of AMS using the Lake Louise Symptom Score.

**Results:** Analysis of participants not using acetazolamide (n=90) found 30 participants developed AMS and 60 participants did not. Estimated plasma volume decreased significantly at altitude ($p=0.025$) in the AMS group as compared with the No AMS group while body weight did not change ($p=0.125$). Serum sodium ($p=0.045$) and low-density lipoprotein (LDL) ($p=0.049$) levels were higher in the No AMS group. A logistic regression analysis emphasised the contributions of LDL and eosinophil levels in the development of AMS.

**Conclusions:** These results suggest that the body water regulation and inflammation are key factors in AMS development when all other factors such as the level of physical exertion during ascent, the rate and magnitude of ascent and the use of acetazolamide are controlled.

## ARTICLE SUMMARY

### Article focus

- Incidence of acute mountain sickness among a population travelling rapidly to altitude.
- Broad data collection included numerous physiological variables at sea level and at altitude.

### Key messages

- Incidence of acute mountain sickness was associated with variables associated with total body water regulation.
- Incidence of acute mountain sickness was associated with variables associated with inflammation.

### Strengths and Limitations

- All participants in a large sample size travelled to altitude in an identical and rapid fashion and did not descend to sleep.
- Our sample size permitted the exclusion of participants who opted to utilise acetazolamide prophylactically.
- Our research oversight and ethics committee did not let us blind or regulate who opted to use acetazolamide. An individual's past experience with acute mountain sickness may have influenced their choice and introduced a bias.

## INTRODUCTION

Exposure to altitudes higher than 2500 m can result in acute mountain sickness (AMS), a mild and usually self-limiting condition that has been described as a 'nuisance' in that it halts progression to higher altitudes and has a negative impact on quality of life rather than posing a serious health risk.[1 2] The development of AMS is not clearly associated with any one particular factor in the currently available literature nor has a definitive aetiology of AMS been identified.[3–6] Rather many different factors such as age, gender, body habitus, physical fitness, tolerance of hypocapnia, rate of ascent, magnitude of ascent, recent prior ascents or simply individual susceptibility have been linked to increased risk of development of AMS but conflicting results are available related to the importance of each of these variables.[3 6–8]

However, the research methods employed in these studies may have influenced the variability in the reported results: many of these variables were collected by self-assessment (ie, physical fitness) or self-reporting (ie, medical history); the various destination altitudes and rates of ascent were not consistent; and the use of pharmaceutical prophylaxis (ie, acetazolamide) was not regulated.[9–11]

Using the Lake Louise Criteria, the diagnosis of AMS is based on recent travel to altitude and the presence of subjective symptoms including headache, fatigue/weakness, dizziness/lightheadedness, gastrointestinal disruption and sleep disturbances.[12] The subjective nature of the diagnosis likely compounds the difficulties in identifying factors to predict which individuals are at an increased risk. Furthermore, the benefit of predicting future cases of AMS based on an individual's history of previous AMS diagnoses is likely lost on the afflicted person—they would like to know ahead of their first ascent that they are at risk for AMS. This is especially true in cases, such as military endeavours or Antarctic assignments, where the rate of ascent cannot be slowed. It is with this in mind that a well-controlled data collection methodology would be beneficial to maximise the likelihood of firmly identifying predictive factors.

The Antarctic Study of Altitude Physiology (ASAP) studied participants in the United States Antarctic Program during austral summer months of 2005–2006 and 2006–2007. This project provided unique opportunities to observe a large and well-controlled population to assess which variables and factors, particularly at sea-level, were associated with AMS development in susceptible individuals. All participants underwent medical screening prior to deployment to Antarctica, were available to the research team during the first 7 days of their deployment and travelled from McMurdo Station (sea-level) to Amundsen-Scott South Pole Station (2835 m; physiological altitude of ~3200 m) via airplane in less than 4 h. The breadth of the data collected plus the controlled and uniform manner in which all individuals travelled to altitude provided an opportunity to evaluate which, if any, factors are related to the development of AMS.

## METHODS

### Participants

Acetazolamide was made available to all participants (N=248). However, for this presentation of results, only those who did not take acetazolamide (>n=98) were included in the initial analysis. Participants who did not complete all questionnaires, provide two blood samples or complete two pulmonary function tests (PFT) were omitted from the final analysis (N=8). The final analysis was performed using 90 participants.

### Procedure

Data were collected during two austral summer expeditions to Amundsen-Scott South Pole Station. Ethical approval was obtained from Mayo Clinic (Rochester, Minnesota, USA) and all participants provided written informed consent. Participants were included in the study if their duties at Amundsen-Scott South Pole Station exceeded 1 week in duration. During 2006–2007, data were only collected from those who had not been a participant during the 2005–2006 expedition. The data collection, the subsequent data analyses and dissemination of findings were performed in accordance with the STROBE principles.[13]

Following arrival at McMurdo Station, participants typically acclimatised to the ambient temperature and adjusted to the new timezone for ~2 weeks prior to departing for the Amundsen-Scott South Pole Station. Participants flew to the South Pole in an airplane that was pressurised after take-off but depressurised during the flight so that cabin pressure had equilibrated with ambient atmospheric pressure at the time of landing. During the acclimatisation period at sea level, participants underwent baseline testing and education related to high altitude illness. Acetazolamide was made available to any participant who wished to employ AMS prophylaxis even though this resulted in the exclusion of that individual's data from this manuscript's analysis. Baseline questionnaire collection included Lake Louise Symptom Score questionnaires as well as an additional symptom questionnaire pertaining to (1) dyspnoea (at rest and on exertion), (2) general health limitations, (3) mental status changes, (4) cough and (5) peripheral oedema. Further questionnaire data included information related to medical history and chronic medical conditions, current medication use, lifestyle assessment (ie, tobacco and alcohol use; exercise habits) and previous experience with altitude and/or Antarctic expeditions. Baseline anthropometric and physiological measurements included height, weight, heart rate, blood pressure, arterial oxygen saturation ($SaO_2$) and blood draw. Blood draws were performed after acclimatising to sea-level 1–2 days prior to departure to altitude. A repeat blood draw was performed on the third day after arrival to altitude. Blood samples were analysed for haemoglobin concentration and haematocrit; serum electrolyte and progesterone levels; circulating catecholamine levels; and thyroid, liver and kidney function. Changes in plasma volume were calculated using the Dill and Costill method.[14]

Participants completed the same questionnaire reporting AMS symptoms related to symptoms including the Lake Louise Symptom Score form on 9 separate occasions. Questionnaires were completed at baseline, on the plane to Amundsen-Scott South Pole Station, and daily for the first 7 days following arrival. The completion of the first questionnaire at the Amundsen-Scott South Pole Station occurred prior to sleep on the first night and each of the subsequent questionnaires was completed upon waking. An individual was determined to be suffering from AMS if their Lake Louise Symptom Score was ≥3 concurrent with a headache. Any individual who

reported a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the first 7 days at altitude was analysed with the AMS group. Individuals in the No AMS group did not report a Lake Louise Symptom Score that corresponded with a diagnosis of AMS at any time during the evaluation period.

### Statistical analysis

Visual inspection of all variables was performed to identify and remove any outliers (ie, data point >± 3 SD) from the data set on a case-by-case basis. Statistical analyses were performed with SPSS 20.0 (IBM Corporation, Armonk, New York, USA). Comparison of means was performed using independent samples t test for participants without AMS (LLSS≤2) (n=60) as compared to participants with AMS (LLSS≥3) (n=30). Significance was set as $p<0.05$. A forward, stepwise binary logistic regression analysis was also performed. All variables associated with the occurrence of AMS at $p<0.25$ in the initial analysis were then included in the generation of the final equation.[9] Employing participants who had been previously removed due to numerous missing data points (n=8) or for whom data points related to the regression equation generation were missing (n=21), the regression equation was applied to assess its reliability and validity in predicting the occurrence of AMS (n=29).

## RESULTS

Demographic and anthropometric data are presented in table 1. No significant differences were observed between groups. Data are presented as mean±SD. Haematological and laboratory results are included in tables 2 and 3 summarises the endocrine results; and table 4 presents the PFT results.

The forward, stepwise binary logistic regression initially included eight variables (chloride, aspartate aminotransferase (AST), low-density lipoprotein (LDL), eosinophils, red blood cell distribution width, leptin and epinephrine, $p<0.25$) for the generation of the model. Only participants for whom all eight variables were recorded and available were entered into the regression equation. For the AMS group, this resulted in n=19; for the No AMS group, this resulted in N=50. The logistic regression analysis generated a model that included LDL and eosinophils (eos) with a positive predictive value of 55.6%, a negative predictive value of 76.7%, a sensitivity of 26.3% and a specificity of 92%. The equation is provided below:

$$\text{Prob(AMS)} = (e^{1.593+(-0.037)(\text{LDL})+(0.433)(\text{eos})})(1+e^{1.593+(-0.037)(\text{LDL})+(0.433)(\text{eos})})^{-1}$$

At the outset, eight individuals were excluded from the analysis due to multiple missing data points (ie, did not present for repeat blood draw at altitude; did not complete intake questionnaire, etc). From the AMS group, 10 individuals were not included in the generation of the regression equation while 11 individuals were not included from the No AMS group. Of these 29 participants, 22 had data available with respect to their LDL and eosinophil levels and thus were used to verify the regression equation's accuracy. The model correctly categorised 57% of the participants.

**Table 1** Subject demographics and anthropometric data

| | No AMS (n=60) | AMS (n=30) |
|---|---|---|
| Sex (M, F) | 37M, 23F | 18M, 12F |
| Age (years) | 36.2±9.4 | 33.8±9.2 |
| Residence altitude (m) | 695.6±785.8 | 818.3±802.8 |
| Height (m) | 1.8±0.1 | 1.7±0.1 |
| Weight (kg) | | |
| Sea level | 78.3±14.8 | 70.2±15.4 |
| Altitude | 78.3±14.3 | 71.2±14.1 |
| Body mass index ($Wt/Ht^2$) | 26.1±4.1 | 24.1±2.5 |
| Heart rate (bpm) | | |
| Sea level | 73.3±12.2* | 67.4±10.0* |
| Altitude | 83.6±12.4 | 80.5±13.7 |
| *Blood pressure (seated)* | | |
| Systolic (mm Hg) | | |
| Sea level | 111.2±13.3* | 109.2±9.9* |
| Altitude | 106.1±12.7 | 101.1±12.6 |
| Diastolic (mm Hg) | | |
| Sea level | 70.3±10.4* | 67.0±9.2* |
| Altitude | 69.1±9.0 | 63.3±7.1 |
| *Oxygen saturation (%)* | | |
| Resting | | |
| Sea level | 97.7±1.2 | 97.5±0.9 |
| Altitude | 88.8±3.9 | 89.3±3.0 |
| Postbreath hold | | |
| Sea level | 93.5±4.7 | 94.9±3.3 |
| Altitude | 82.7±5.4 | 84.9±4.6 |
| Neck circumference (cm) | 35.9±3.5 | 35.4±3.2 |
| Waist circumference (cm) | 88.0±12.5 | 83.3±10.5 |
| Waist-to-hip ratio | 0.9±0.1 | 0.8±0.1 |

*Significant difference between the AMS and No AMS groups, $p<0.05$.

## DISCUSSION

Currently AMS is a clinical diagnosis based on subjective and self-reported measures. Reliably identifying objective variables that may differentiate those at risk for suffering AMS as compared with those at a decreased risk has eluded many investigators. Our study controlled many variables that are recognised as contributory to AMS development but which are not often well controlled; for example, the altitude at which individuals sleep or the means or rate by which individuals arrived at altitude.[3 8 15 16] In other studies, sleeping may have occurred at a lower altitude than the day's peak altitude and varied day by day, the rate of ascent may have differed by days and the level of exertion often differed from participant to participant. In our study, all

**Table 2** Electrolyte, blood chemistry and haematology results

| | No AMS (n=60) | AMS (n=30) |
|---|---|---|
| Sodium (mEq/L) | 139.4±1.6* | 138.5±1.8* |
| Potassium (mEq/L) | 4.2±0.3 | 4.2±0.4 |
| Chloride (mEq/L) | 102.1±3.0 | 101.9±1.7 |
| Calcium (mg/dL) | 9.6±0.4 | 9.6±0.3 |
| Alkaline phosphatase (U/L) | 62.7±16.4 | 66.5±16.1 |
| Transaminases | | |
| Alanine aminotransferase (ALT) (U/L) | 21.1±11.1 | 18.4±7.5 |
| Aspartate aminotrasnferase (AST) (U/L) | 20.9±5.2 | 20.8±5.6 |
| Leucocytes ($10^3/\mu L$) | 5.8±1.4 | 6.1±1.9 |
| Eosinophils ($10^3/\mu L$) | 1.9±1.6* | 2.7±2.0* |
| Erythrocytes ($10^3/\mu L$) | 4.7 ± 0.5 | 4.8±0.3 |
| Haemoglobin (g/dL) | 14.8±1.4 | 15.1±0.9 |
| Haematocrit (%) | 44.0±4.0 | 44.9±2.9 |
| Mean corpuscular volume ($\mu m^3$) | 92.9±4.0 | 93.8±3.8 |
| Mean corpuscular haemoglobin (pg/cell) | 31.3±1.2 | 31.5±0.9 |
| Mean corpuscular haemoglobin concentration (%) | 33.7±0.9 | 33.6±0.9 |
| Red blood cell distribution width (%) | 13.7±1.0 | 13.3±0.8 |
| Platelets ($10^3/\mu L$) | 237.6±53.2 | 255.9±52.3 |
| Estimated Δplasma volume (%) | −2.9±9.4* | −9.4±12.5* |
| Iron studies | | |
| Iron (μg/dL) | 113.9±31.8 | 119.5±42.0 |
| Iron sat (%) | 36.5±12.6 | 37.4±13.0 |
| Total iron binding capacity (μg/dL) | 325.0±47.5 | 322.1±37.4 |
| Unsaturated iron binding capacity (μg/dL) | 209.5±56.9 | 202.6±53.9 |
| Low-density lipoprotein (mg/dL) | 105.9±27.6* | 97.7±25.4* |
| High-density lipoprotein (mg/dL) | 60.2±15.8 | 65.3±17.4 |
| Very low-density lipoprotein (mg/dL) | 21.6±12.8 | 20.3±10.4 |
| Triglycerides (mg/dL) | 107.2±62.9 | 101.4±51.8 |

*Significant difference between the AMS and No AMS groups, p<0.05.

participants worked and slept at the same constant altitude and all participants travelled to altitude on a short duration flight (<4 h) with minimal exertion. These factors, if not controlled, can influence the development of AMS and confound results in attempting to identify physiological characteristics placing an individual at increased risk of developing AMS.

Our results support a number of hypotheses about causes of AMS that warrant discussion. An important caveat is the magnitude of the differences between the populations. While statistically significant and interesting in generating further hypotheses, these differences may be too slight to permit a clinical prediction of who will develop AMS at altitude. For example, the difference between a blood pressure of 111/70 mm Hg (AMS group) and 109/67 mm Hg (No AMS group) in any single individual on any given day is related to a number of factors (hydration, caffeine intake, etc) that would inevitably lead to intraindividual variability. But rather than considering this to be a weakness of our study, this more likely speaks of the subtle nature of AMS, an often mild and self-limiting condition described as a nuisance.[1 2]

Two of the subtle differences of interest are the serum sodium ($Na^+$) levels and LDL cholesterol levels. These values differed within the normal ranges in the AMS group ($Na^+$ 138.5 and LDL 97.7) as well as in the No AMS group ($Na^+$ 139.4 and LDL 105.9). Serum $Na^+$ has the largest influence on serum osmolarity, using the standard equation:

$$\text{Osmolarity} = 2 \times [Na^+] + [\text{Glucose}] \times 18^{-1} + [\text{Urea}] \times 2.8^{-1}$$

Increased serum $Na^+$ would decrease the flow of fluid from the intravascular space to the extravascular space, thereby decreasing cellular oedema. One of the hypothetical explanations for the occurrence of AMS suggests that tissue oedema, particularly in the cerebral tissue, is a contributing factor.[2 3 16] Similarly, LDL levels were significantly higher but still within the normal range in those who did not develop AMS as compared with those who did. In nephrotic syndrome, serum LDL concentration is inversely related to serum albumin concentration.[17–19] The rapid and dramatic increase in LDL in hypoalbuminaemic states focuses on the body's attempt to maintain an adequate oncotic pressure. While our participants were not hypoalbuminaemic by clinical assessment, the elevated LDL levels may have positively contributed to the prevention of AMS through increasing the oncotic pressures. Oncotic pressure, like serum

**Table 3** Endocrine and catecholamine results

| | No AMS (n=60) | AMS (n=30) |
|---|---|---|
| Progesterone (ng/Ml) | | |
| Sea level | 1.8±3.5 | 1.5±2.7 |
| Altitude | 1.4±2.6 | 1.2±1.8 |
| Erythropoietin (μIU/mL) | | |
| Sea level | 11.0±5.5 | 10.0±4.7 |
| Altitude | 31.7±20.1 | 24.3±9.0 |
| Leptin (ng/mL) | | |
| Sea level | 8.4±10.8 | 5.7±5.5 |
| Altitude | 6.9±6.1 | 5.1±4.4 |
| Angiotensin II (pg/mL) | | |
| Sea level | 7.6±5.7 | 11.5±21.2 |
| Altitude | 21.3±33.4 | 16.2±17.2 |
| Tumour necrosis factor-α (pg/mL) | | |
| Sea level | 1.3±0.6* | 1.4±0.7* |
| Altitude | 1.3±0.6 | 1.3±0.6 |
| Vascular endothelial growth factor (pg/mL) | | |
| Sea level | 42.4±22.7 | 43.5±26.1 |
| Altitude | 57.0±37.8* | 76.4±42.5* |
| Atrial natriuretic peptide (pg/mL) | | |
| Sea level | 434.6±263.8 | 562.5±289.0 |
| Altitude | 583.1±300.6 | 630.7±339.0 |
| Thyroid stimulating hormone (μIU/mL) | | |
| Sea level | 1.9±1.0 | 1.5±0.6 |
| Altitude | 2.2±1.3 | 1.9±0.8 |
| Norepinephrine (pg/mL) | | |
| Sea level | 402.4±165.9 | 357.9±108.8 |
| Altitude | 569.5±227.1 | 491.5±159.7 |
| Epinephrine (pg/mL) | | |
| Sea level | 42.0±76.1 | 29.2±20.9 |
| Altitude | 36.3±25.2 | 36.1±30.1 |
| Dopamine (pg/mL) | | |
| Sea level | 25.1±62.7 | 13.4±6.0 |
| Altitude | 24.4±16.6* | 16.2±14.8* |

*Significant difference between the AMS and No AMS groups, p<0.05.

osmolarity, is one of the means by which intravascular fluid (a component of the extracellular space) is kept within the vasculature in order to prevent oedema.

Furthering the possible link between fluid distribution between the body's compartments and AMS, a significant decrease in plasma volume at altitude was observed in the AMS group. As significant differences were not observed for participant weights between the sea level and altitude measurements for either group, it stands to reason that total body water remained relatively constant between the measurements. However, the AMS group saw a nearly 10% decrease in estimated plasma volume and this would suggest a fluid shift from the intravascular space to either the intracellular or the extracellular space. Previously, Loeppky *et al*[20] have reported fluid retention occurs during the initial exposure to simulated altitude and our results suggest this retained fluid does not remain in the vasculature. Hackett *et al*[21] have suggested abnormalities in handling body water as the common link between the two oedematous conditions, high altitude pulmonary oedema (HAPE) and high altitude cerebral oedema (HACE), representing the more serious forms of altitude-related illness. Research has shown that subclinical pulmonary oedema occurs among those with concomitant AMS.[22] This diagnosis in these individuals is made by the appearance of 'comet tails' on ultrasonography and offers a specific example of an extravascular fluid shift.

Three of the variables identified in our analysis are seemingly linked to each other and to hypothesised causes of AMS—vascular endothelial growth factor (VEGF), tumour necrosis factor-α (TNF-α) and eosinophils. VEGF levels at altitude were significantly elevated in the AMS group. VEGF's primary role is to promote the formation of new blood vessels and it increases in conditions that are associated with decreased oxygen supply to tissues.[23] However, VEGF has also been linked to increased vascular permeability that contributes to the development of oedema.[23 24] Serum eosinophil level was the other variable that was represented in the logistic regression model. While increased eosinophil levels are often associated with the immune response to a parasitic presence or a hypersensitive response such as asthma, they will also increase the serum concentration of VEGF.[24 25] At altitude, hypoxia prolongs the viability of

**Table 4** Pulmonary function results

| | No AMS (n=60) | AMS (n=30) |
|---|---|---|
| Forced vital capacity (FVC) (L) | | |
| Sea level | 5.0±1.0 | 5.1±1.0 |
| Altitude | 4.9±0.9 | 5.2±1.1 |
| Forced expiratory volume in 1 s ($FEV_1$) (L) | | |
| Sea level | 4.0±0.7 | 4.1±0.8 |
| Altitude | 4.1±0.7 | 4.1±0.9 |
| $FEV_1$/FVC (%) | | |
| Sea level | 81.2±5.8 | 79.4±5.8 |
| Altitude | 83.7±5.6* | 80.4±5.2* |
| Forced expiratory flow (FEF) (L/s) | | |
| 25% | | |
| Sea level | 7.8±2.0 | 7.2±2.2 |
| Altitude | 9.0±2.4 | 8.6±2.6 |
| 75% | | |
| Sea level | 1.8±0.6 | 1.8±0.8 |
| Altitude | 2.1±0.8 | 1.8±0.6 |
| Maximum | | |
| Sea level | 9.7±2.1 | 9.6±2.2 |
| Altitude | 10.8±2.1 | 10.7±2.6 |
| Expiratory reserve volume (ERV) (L) | | |
| Sea level | 1.3±0.5* | 1.7±0.6* |
| Altitude | 1.4±0.5* | 1.6±0.4* |

*Significant difference between the AMS and No AMS groups, p<0.05.

eosinophils while increasing the eosinophllic production of VEGF and other proinflammatory cytokines, prostaglandins and leukotrienes.[24 26] The serum concentration of a third inflammatory variable, TNF-α, was also higher in the AMS group (p=0.012). A cyclical link has been suggested between hypoxia and inflammation in the development of AMS—hypoxic tissue becomes inflamed, inflamed tissue becomes increasingly hypoxic and the magnitude of vascular leakage in response to the inflammatory response increases.[8 27] Anti-inflammatory medications such as dexamethasone and ibuprofen have demonstrated benefit in preventing and treating AMS and the more serious high-altitude oedemas.[2 16 28]

Our data and a review of the relevant literature would suggest a focus on maintaining intravascular volume while minimising inflammation. The statistically significant elevations of LDL, while still within the limits of a normal healthy adult range, suggests that even modest alterations in fluid dynamics may be protective at altitude. The positive association between AMS development and several inflammatory markers, when considered in light of the available literature that suggests either steroidal or non-steroidal anti-inflammatory medications can prevent the symptoms of AMS, is suggestive of means of prevention or treatment. Perhaps an effective solution may be as simple as a small bolus of colloid fluids (eg, albumin) in conjunction with a long-acting steroid (eg, dexamethasone).

Dopamine concentration was higher in the No AMS group and it can have a number of physiological effects depending on its levels. It can effect the body's vascular response (ie, dilation vs constriction, depending on amount administered) and urinary function.[20 21 29 30] Dopamine can also have stimulatory or inhibitory affects on many of the humoral immune cells depending on cell type and state (mature and activated vs immature and inactivated).[31 32] Some of these immunosuppressive characteristics are specific to the central nervous system itself and may support a hypothesis focused on the role of vasogenic oedema or inflammation as it pertains to AMS.[32]

The PFT results also serve to drive future work—the ratio of the forced expiratory volume over one second as compared with the forced vital capacity ($FEV_1$/FVC) differed significantly with the AMS group demonstrating a smaller ratio. The association between eosinophilia and asthma in allergic and non-allergic settings and the lack of association between asthma or chronic obstructive pulmonary disease with increased risk of AMS development deserve further investigation in light of our findings.[3 15 33] Perhaps PFT results in the low-normal range warrant further investigation in light of Jafarian *et al*'s[10] findings that an increased respiratory rate in the first hour at altitude predicts the development of severe AMS or in light of the report of subclinical pulmonary oedema in AMS sufferers.[22]

Finally, a strength and a caveat of our methodology requires addressing. The size of the present data set cx permitted the removal of individuals who opted to utilise acetazolamide as a prophylaxis against AMS. The National Science Foundation (NSF) provided oversight for this project and would not permit the regulation of acetazolamide such that two equal groups of users could be created nor would the NSF permit the use of a placebo among those individuals who wished to employ acetazolamide. This may have influenced our results as AMS is a subjective diagnosis based on self-reported

symptoms; however, many of our collected variables were objective measures (ie, electrolyte concentrations and haemotalogical variables) that are not controllable by the individual's thoughts or beliefs in treatment efficacy.

## CONCLUSION

Our results lend further strength to a number of the findings reported in previous investigations into the pathophysiology of AMS. Our results and comprehensive methodology also support a link between many of the previously reported findings. The regulation of body fluid to maintain intravascular volume and minimise oedema coupled with anti-inflammatory medication appears to be a promising avenue to consider for future work. Our findings of statistically significant results that would be difficult to detect clinically further suggests that the development of AMS is the result of minor derangements of normal.

**Correction notice** This article has been corrected since it was first published. The original version was published without taking into account the authors' corrections after typesetting. This version has incorporated the authors' corrections.

**Acknowledgements** We would like to thank the employees of the US Antarctic Program. This includes general science support, station management and cargo crew at South Pole, Crary Lab, medical team and transportation/shipping at both McMurdo and South Pole. We would also like to thank Dr Kenneth Beck, Jay O'Brien, Kent Bailey, and Josh Mueller for assistance with the many aspects of data collection and analysis. This study was supported by a grant from the National Science Foundation, B-179-M as well as funding through the Mayo Clinic Center for Translational Science Activity (CTSA), Clinical Research Unit, Grant Number 1 UL1 RR024150 from the National Center for Research Resources.

**Contributors** MFH was responsible for data analysis, manuscript preparation and submission. PJA, ADM, KAO, MLR and JBJ provided editorial comments and guidance during manuscript preparation and have reviewed the final document. BDJ supervised data analysis, provided editorial comments and guidance during manuscript preparation and has reviewed the final document.

**Funding** National Science Foundation (B-179-M) and Mayo Clinic Center for Translational Science Activity (CTSA), Clinical Research Unit, Grant Number 1 UL1 RR024150.

**Competing interests** None.

**Patient consent** Obtained.

**Ethics approval** Mayo Clinic IRB.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data sharing statement** No additional data are available.



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