Association between physiological responses after exercise at low altitude and acute mountain sickness upon ascent is sex-dependent

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Abstract

Background: Acute mountain sickness (AMS) is the mildest form of acute altitude illnesses, and consists of nonspecific symptoms when unacclimatized persons ascend to elevation of $\geq 2500$ m. Risk factors of AMS include: the altitude, individual susceptibility, ascending rate and degree of pre-acclimatization. In the current study, we examined whether physiological response at low altitude could predict the development of AMS.

Methods: A total of 111 healthy adult healthy volunteers participated in this trial; and 99 (67 men and 32 women) completed the entire study protocol. Subjects were asked to complete a 9-min exercise program using a mechanically braked bicycle ergometer at low altitude (500 m). Heart rate, blood pressure (BP) and pulse oxygen saturation (SpO2) were recorded prior to and during the last minute of exercise. The ascent from 500 m to 4100 m was completed in 2 days. AMS was defined as $\geq 3$ points in a 4-item Lake Louise Score, with at least one point from headache within 6–8 h after the ascent.

Results: Among the 99 assessable subjects, 47 (23 men and 24 women) developed AMS at 4100 m. In comparison to the subjects without AMS, those who developed AMS had lower proportion of men (48.9% vs. 84.6%, $P < 0.001$), height (168.4 ± 5.9 vs. 171.3 ± 6.1 cm, $P = 0.019$), weight (62.0 ± 10.0 vs. 66.7 ± 8.6 kg, $P = 0.014$) and proportion of smokers (23.4% vs. 51.9%, $P = 0.004$). Multivariate regression analysis revealed the following independent risks for AMS: female sex (odds ratio (OR) = 6.32, $P < 0.001$), SpO2 change upon exercise at low altitude (OR = 0.63, $P = 0.002$) and systolic BP change after the ascent (OR = 0.96, $P = 0.029$). Women had larger reduction in SpO2 after the ascent, higher AMS percentage and absolute AMS score. Larger reduction of SpO2 after exercise was associated with both AMS incidence ($P = 0.001$) and AMS score ($P < 0.001$) in men but not in women.

Conclusions: Larger SpO2 reduction after exercise at low altitude was an independent risk for AMS upon ascent. Such an association was more robust in men than in women.

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Background

Acute mountain sickness (AMS) is the mildest form of acute altitude illnesses that typically occur in unacclimatized persons upon ascent to elevation at ≥2500 m. AMS consists of a series of non-specific symptoms, including headache, dizziness, lightheadedness, gastrointestinal symptoms and fatigue [1, 2]. Over 50% of individuals develop AMS when ascending to elevation at ≥6000 m [3]. In most cases, AMS spontaneously resolve after a few days at high altitude, but may progress to fatal high-altitude cerebral edema (HACE) [4].

Known risk factors for AMS include ascending speed, arrival elevation and individual susceptibility [3]. People who live at sea level for generations and those with a history of AMS or migraine are also reported to be at high risk for developing AMS [5]. Age, sex, smoking status and obesity have been associated with AMS in some but not all studies [5–9]. For example, younger subjects were found to be more susceptible to AMS [5, 8]. Gonggalanzi et al. [6] also found that age below 55 years was an independent AMS risk factor, but smoking reduced the risk of AMS. In a study by Meier et al. [7], younger age (< 50 years) was an AMS risk factor but smoking was not associated with AMS. Sex discrepancy, but again with controversial results. Lower susceptibility has been reported in men by some studies [10–12], whereas other studies reported either no difference or increased susceptibility in men [13–15].

Upon ascending to high altitude, a number of physiological responses are activated to adapt to decreased arterial oxygen saturation (SaO2). Sympathetic autonomic system is activated, with resulting vasoconstriction and increased blood pressure (BP) and heart rate (HR) [16]. Previous studies suggested that SpO2 reduction and physiological response after exercise at high altitude could be useful in assessing the degree of acclimatization to high altitude [17, 18]. More specifically, SpO2 reduction after exercise prior to ascending has been shown to be a risk factor for severe high-altitude illness (HAI) that included severe AMS, HACE and high-altitude pulmonary edema [8]. However, another study indicated that association between SpO2 and AMS is not strongly altitude-independent during the first 7 days of trekking [19]. Another important caveat that adds to the complexity of the controversy is the physiological and functional differences between men and women [20, 21].

In the current prospective cohort study, we examined reduction of SpO2 as well as HR and BP changes upon exercise in a group of healthy volunteers prior to ascending from 500 to 4100 m. Characteristics of those who developed AMS vs not were compared. Multivariate analysis was used to determine whether exercise-induced responses at low altitude prior to ascent could be used to predict AMS and whether such an association is sex-dependent.

Methods

Design and participants

We performed this prospective cohort study on the Qinghai-Tibet plateau in June 2019. A total of 111 unrelated healthy Chinese Han volunteers born and permanently lived in low altitude (≤500 m) without travelling to high-altitude areas (≥2500 m) in the past 6 months were approached. Exclusion criteria included: a history of AMS, migraine, cardiopulmonary diseases, neurological diseases, psychiatric disorders that prevented the completion of data collection, cerebral vascular diseases, cancer, or liver or kidney dysfunction, long-term use of any medications. Body mass index (BMI) was calculated as body weight in kg divided by square height in meter.

Exercise program

The testing was conducted prior to the ascent at 500 m. Exercise testing was conducted using a mechanically braked bicycle ergometer (Ergoline 900EL, Ergoline Company, Germany) [22]. The session consisted of a 3-min warm-up period with no resistance, a 3-min initial exercise phase at 25-W workload and a 3-min maintenance exercise phase with 50-W workload. HR, BP and SpO2 were recorded during the last minute of the session. BP and HR were recorded using an electronic sphygmomanometer (Omron HEM-6200, Japan). SpO2 values was determined using a pulse oximeter (Nonin ONYX OR9500, USA). The average of 3 measures was used in data analysis.

Assessment of AMS

Subjects ascended from 500 m to 4100 m in 2 days. AMS was assessed using the latest Lake Louise questionnaire [1] at 6–8 h after arriving at 4100 m. Participant completed a 4-item questionnaire with the assistance of an experienced doctor. The items included headache, dizziness or lightheadedness, gastrointestinal symptoms and fatigue. The score for each item ranged from 0 to 3: 0 for no, 1 for mild, 2 for moderate, and 3 for severe. AMS was defined as the total scores at ≥3 points, with at least one point from headache.

Keywords: High altitude, Exercise testing, Sex differences, Acute mountain sickness, Individual susceptibility
Statistical analysis
Statistical analyses were performed using SPSS 24.0 (Chicago, USA). Continuous variables are expressed as the mean ± standard deviation (SD), and group comparison was conducted using Student’s t-test or Welch’s test. Categorical variables are expressed as n (%) and compared using the chi-square test or Fisher’s exact test. Univariate logistic regression analysis was performed to evaluate the odds ratio (OR) with a 95% confidence interval (CI) for the factors associated with AMS. Then, multivariate logistic regression analysis was conducted of the potential risk factors (P < 0.1 for enter, and P < 0.05 for stay). Linear regression was applied to assess the correlation between the changes in physiological parameters after exercise and AMS score. A two-sided P < 0.05 was considered statistically significant.

Results

Subjects with vs without AMS
A total of 111 healthy adult subjects were invited to participate: 2 refused to participate, 3 did not adhere to the pre-planned ascent plan, 2 developed severe HAI during the ascending process and were immediately transferred to low-altitude areas for emergency medical interventions, and 5 had incomplete data. Among the 99 subjects in the final data analysis, 47 developed AMS (Fig. 1). Age did not differ significantly between the subjects who developed AMS (26.0 ± 7.7 years) vs without AMS (27.6 ± 8.8 years) (Table 1). The AMS group had higher proportion of women (51.1% vs. 15.4%, P < 0.001), lower height (168.4 ± 5.9 vs. 171.3 ± 6.1 cm, P = 0.019), weight (62.0 ± 10.0 vs. 66.7 ± 8.6 kg, P = 0.014) and percentage of smokers (23.4% vs. 51.9%, P = 0.004). SpO2 at rest at low altitude was higher in the AMS group (97.5% ± 1.2% vs. 96.8% ± 1.4%, P = 0.017). SpO2 reduction at the end of the 9-min exercise session at low altitude was larger in the AMS group (−0.6% ± 1.7% vs. 0.4% ± 1.7%; P = 0.004). The AMS group also had lower systolic BP (118.2 ± 11.8 vs. 126.0 ± 16.3) mmHg, P = 0.008) as well as smaller change in systolic BP (1.0 ± 15.0 vs. 8.7 ± 15.0 mmHg, P = 0.013) upon arrival at 4100 m.

Factors associated with AMS
In the univariate analysis that included all subjects, female sex (OR = 5.74, 95% CI 2.23–14.78, P < 0.001) and higher SpO2 at rest at 500 m (OR = 1.47, 95% CI 1.06–2.03, P = 0.021) were associated with increased risk of AMS. Greater height (OR = 0.92, 95% CI 0.86–0.99, P = 0.023), heavier weight (OR = 0.95, 95% CI 0.90–0.99, P = 0.016), smoking (OR = 0.28, 95% CI 0.12–0.67, P = 0.004) and greater change in SBP after arriving at 4100 m (OR = 0.97, 95% CI 0.94–0.99, P = 0.016) were associated with decreased incidence of AMS. Multivariate regression that included all subjects identified the following risks for AMS: female sex (P < 0.001), greater SpO2 reduction after exercise at 500 m (P = 0.002) and smaller change in SBP after arriving at 4100 m (P = 0.029) (Table 2).
Table 1 Baseline characteristics, exercise testing results, and measures upon arriving at 4100 m

| Index | Total (n = 99) | AMS (n = 47) | Non-AMS (n = 52) | P-value |
|-------|---------------|--------------|------------------|---------|
| Baseline characteristics | | | | |
| Age (year, x ± s) | 26.9 ± 8.3 | 26.0 ± 7.7 | 27.6 ± 8.8 | 0.358 |
| Men [n(%)] | 67 (67.7) | 23 (48.9) | 44 (84.6) | <0.001 |
| Women [n(%)] | 32 (32.3) | 24 (51.1) | 8 (15.4) | <0.001 |
| Height (cm, x ± s) | 170.0 ± 6.1 | 168.4 ± 5.9 | 171.3 ± 6.1 | 0.019 |
| Weight (kg, x ± s) | 64.5 ± 9.5 | 62.0 ± 10.0 | 66.7 ± 8.6 | 0.014 |
| BMI (kg/m², x ± s) | 22.3 ± 2.5 | 21.8 ± 2.7 | 22.7 ± 2.2 | 0.070 |
| Smoker [n(%)] | 38 (38.4) | 11 (23.4) | 27 (51.9) | 0.004 |
| HR at rest (beats/min, x ± s) | 73.2 ± 11.2 | 74.5 ± 10.9 | 71.9 ± 11.5 | 0.257 |
| SpO₂ at rest (%) | 97.1 ± 1.3 | 97.5 ± 1.2 | 96.8 ± 1.4 | 0.017 |
| SBP at rest (mmHg, x ± s) | 117.3 ± 12.1 | 117.2 ± 12.6 | 117.4 ± 11.8 | 0.937 |
| DBP at rest (mmHg, x ± s) | 73.5 ± 11.4 | 73.8 ± 12.3 | 73.4 ± 10.6 | 0.858 |
| After exercise testing | | | | |
| SpO₂ after exercise (%) | 97.1 ± 1.2 | 96.9 ± 1.3 | 97.2 ± 1.1 | 0.130 |
| ΔSpO₂ (%) | −0.1 ± 1.8 | −0.6 ± 1.7 | 0.4 ± 1.7 | 0.004 |
| After arriving at 4100 m | | | | |
| SBP at HA (mmHg, x ± s) | 122.3 ± 14.8 | 118.2 ± 11.8 | 126.0 ± 16.3 | 0.008 |
| ΔSBP (mmHg, x ± s) | 50 ± 15.4 | 10 ± 15.0 | 8.7 ± 15.0 | 0.013 |

AMS Acute mountain sickness, BMI Body mass index, HR Heart rate, SpO₂ Pulse oxygen saturation, SBP Systolic blood pressure, DBP Diastolic blood pressure, Δe Change after exercise testing (from the pre-exercise level), Δh Change after arriving at 4100 m (from the 500-m level)

Table 2 Regression analyses of the risk for AMS in the entire cohort

| Variable | Univariate analysis | | Multivariate analysis | |
|----------|---------------------|---|----------------------|---|
| | OR (95% CI) | P-value | OR (95% CI) | P-value |
| Age | 0.98 (0.93–1.03) | 0.361 | Not entered | |
| Female sex | 5.74 (2.23–14.78) | <0.001 | 6.32 (2.25–17.74) | <0.001 |
| Height | 0.92 (0.86–0.99) | 0.023 | | |
| Weight | 0.95 (0.90–0.99) | 0.016 | | |
| Smoking | 0.28 (0.12–0.67) | 0.004 | | |
| HR at rest | 1.02 (0.99–1.06) | 0.255 | Not entered | |
| SpO₂ at rest | 1.47 (1.06–2.03) | 0.021 | | |
| SBP at rest | 1.00 (0.97–1.03) | 0.936 | Not entered | |
| DBP at rest | 1.00 (0.97–1.04) | 0.856 | Not entered | |
| ΔeHR | 0.98 (0.95–1.01) | 0.231 | Not entered | |
| ΔeSpO₂ | 0.82 (0.67–1.03) | 0.091 | 0.63 (0.47–0.84) | 0.002 |
| ΔhSBP | 1.00 (0.97–1.02) | 0.778 | Not entered | |
| ΔhDBP | 1.00 (0.97–1.03) | 0.982 | Not entered | |
| ΔhHR | 1.00 (0.97–1.03) | 0.893 | Not entered | |
| ΔhSpO₂ | 0.97 (0.88–1.07) | 0.525 | Not entered | |
| ΔhSBP | 0.97 (0.94–0.99) | 0.016 | 0.96 (0.93–1.00) | 0.029 |
| ΔhDBP | 0.97 (0.94–1.00) | 0.059 | | |

Δ Odds ratio, 95% CI 95% confidence intervals, AMS Acute mountain sickness, BMI Body mass index, HR Heart rate, SpO₂ Pulse oxygen saturation, SBP Systolic blood pressure, DBP Diastolic blood pressure, Δe Change after exercise testing, Δh Change after arriving at 4100 m

Sex discrepancy

Table 3 shows basic characteristics, exercise testing results and measures after arriving at 4100 m in men vs women. In comparison to men, the women were younger (23.3 ± 3.7 vs. 28.5 ± 9.3 years, P < 0.001), shorter (165.0 ± 4.1 vs. 172.5 ± 5.2 cm, P < 0.001), and lighter (55.0 ± 2.0 vs. 68.2 ± 7.9 kg, P < 0.001), had lower BMI (20.5 ± 1.9 vs. 23.1 ± 2.2 kg/m², P < 0.001), lower SBP at rest (113.9 ± 11.5 vs. 126.3 ± 14.6 mmHg, P < 0.011), and SpO₂ at rest at 500 m (97.6 ± 1.2% vs. 96.9 ± 1.4%, P = 0.016). After exercise testing, women had lower SBP (118.1 ± 11.7 vs. 126.5 ± 14.4 mmHg, P = 0.001) and higher SpO₂ (97.6 ± 0.8% vs. 96.8 ± 1.3%, P < 0.001). Upon arriving at 4100 m, women had lower SBP (113.9 ± 11.5 vs. 126.3 ± 14.6 mmHg, P < 0.001), lower SpO₂ (85.9 ± 4.3% vs. 87.8 ± 3.5%, P = 0.034) and greater SpO₂ reduction (−11.6 ± 4.2% vs. −9.1 ± 3.9%, P = 0.005).

The rate of AMS and relevant symptoms in men vs women

In comparison to men, women had higher rate of AMS (75.0% vs. 34.3%, P < 0.001), average AMS score (3.4 ± 2.0 vs. 1.9 ± 1.4, P < 0.001). The rate of dizziness, gastrointestinal symptoms and fatigue were also higher in women than in men (71.9% vs. 43.3%, P = 0.010, 37.5% vs. 11.9%, P = 0.006; 90.6% vs. 58.2%, P = 0.001; respectively, Table 4).
Factors associated with AMS in men vs women

In the analysis that included only women, AMS was associated with $\Delta$SpO$_2$ upon arriving at 4100 m (adjusted OR = 1.47, 95% CI 1.01 to 2.12, $P = 0.042$), and not any other factors (Table 5). In the analysis that included only men, AMS was associated with $\Delta$SpO$_2$ after exercise testing at 500 m (adjusted OR = 0.56, 95% CI 0.39 to 0.79, $P = 0.001$).

Association of AMS score with SpO$_2$ reduction after exercise at 500 m

In the linear regression analysis, AMS score was associated with $\Delta$SpO$_2$ after exercise testing at 500 m in men ($r = -0.408$, $P < 0.001$) but not in women ($r = 0.264$, $P = 0.144$) (Fig. 2).

Discussion

The results from the current study showed higher AMS rate in women than in men. The female sex and greater SpO$_2$ reduction after exercise at low altitude prior to the ascent were independently associated with increased risk of AMS. Interestingly, SpO$_2$ reduction at low altitude was associated with the risk of AMS and higher AMS score in men but not in women.

Incidence of AMS

Previous studies have estimated that 10–70% of travelers will experience various degrees of AMS when ascending to elevation of ≥2500 m [6]. At 4500–5500 m, the incidence of AMS in unacclimatized persons has been estimated at 50–85% [5]. In army recruits ascending from

Table 3 Baseline characteristics, exercise testing results and measures after arriving at 4100 m: men vs women

| Index | Women (n = 32) | Men (n = 67) | P-value |
|-------|---------------|--------------|---------|
| Baseline characteristics | | | |
| Age (year, x ± s) | 23.3 ± 3.7 | 28.5 ± 9.3 | < 0.001 |
| Height (cm, x ± s) | 165.0 ± 4.1 | 172.5 ± 5.2 | < 0.001 |
| Weight (kg, x ± s) | 55.4 ± 5.3 | 68.8 ± 7.9 | < 0.001 |
| BMI (kg/m$^2$, x ± s) | 20.5 ± 1.9 | 23.1 ± 2.2 | < 0.001 |
| Smoker [n(%)] | 1 (3.1) | 37 (55.2) | < 0.001 |
| HR at rest (beats/min, x ± s) | 75.3 ± 10.3 | 72.2 ± 11.6 | 0.195 |
| SpO$_2$ at rest (%, x ± s) | 97.6 ± 1.2 | 96.9 ± 1.4 | 0.016 |
| SBP at rest (mmHg, x ± s) | 112.7 ± 11.9 | 119.4 ± 11.7 | 0.011 |
| DBP at rest (mmHg, x ± s) | 72.1 ± 9.5 | 74.3 ± 12.2 | 0.374 |
| After exercise testing | | | |
| SpO$_2$ after exercise (%, x ± s) | 97.6 ± 0.8 | 96.8 ± 1.3 | < 0.001 |
| SBP after exercise (mmHg, x ± s) | 118.1 ± 11.7 | 126.5 ± 11.4 | 0.001 |
| $\Delta$SpO$_2$ (%, x ± s) | 0.0 ± 1.3 | −0.1 ± 1.9 | 0.791 |
| $\Delta$SBP (mmHg, x ± s) | 5.3 ± 17.1 | 7.1 ± 12.6 | 0.575 |
| Upon arriving at 4100 m | | | |
| SpO$_2$ (%, x ± s) | 85.9 ± 4.3 | 87.8 ± 3.5 | 0.034 |
| SBP (mmHg, x ± s) | 1139 ± 11.5 | 1263 ± 14.6 | < 0.001 |
| $\Delta$SpO$_2$ (%, x ± s) | −11.6 ± 4.2 | −9.1 ± 3.9 | 0.005 |
| $\Delta$SBP (mmHg, x ± s) | 1.2 ± 14.6 | 6.9 ± 15.5 | 0.080 |

AMS Acute mountain sickness, BMI Body mass index, HR Heart rate, SpO$_2$ Pulse oxygen saturation, SBP Systolic blood pressure, DBP Diastolic blood pressure, $\Delta$e Change after exercise testing, $\Delta$h Change after arriving at 4100 m

Table 4 The rate of AMS and symptoms in men vs women

| Index | Women (n = 32) | Men (n = 67) | P-value |
|-------|---------------|--------------|---------|
| AMS [n(%)] | 24 (75.0) | 23 (34.3) | < 0.001 |
| AMS score (x ± s) | 3.4 ± 2.0 | 1.9 ± 1.4 | < 0.001 |
| Headache [n(%)] | 25 (78.1) | 42 (62.7) | 0.169 |
| Dizziness [n(%)] | 23 (71.9) | 29 (43.3) | 0.010 |
| Gastrointestinal symptoms [n(%)] | 12 (37.5) | 8 (11.9) | 0.006 |
| Fatigue [n(%)] | 29 (90.6) | 39 (58.2) | 0.001 |

AMS Acute mountain sickness

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Table 5: Regression analyses in men vs. women

| Variable | Unadjusted analysis | Adjusted analysis |
|----------|---------------------|------------------|
|          | OR (95% CI) | P-value | OR (95% CI) | P-value |
| **Women** |          |      |          |      |
| HR at rest | 1.02 (0.98–1.07) | 0.310 | 1.02 (0.97–1.07) | 0.362 |
| SpO2 at rest | 1.10 (0.59–2.05) | 0.758 | 0.98 (0.47–2.01) | 0.946 |
| SBP at rest | 0.98 (0.93–1.03) | 0.348 | 0.98 (0.91–1.04) | 0.442 |
| DBP at rest | 0.96 (0.90–1.03) | 0.270 | 0.96 (0.89–1.03) | 0.268 |
| ΔhHR | 1.00 (0.95–1.06) | 0.959 | 1.00 (0.93–1.07) | 0.938 |
| ΔhSpO2 | 1.21 (0.96–1.53) | 0.114 | 1.47 (1.01–2.12) | 0.042 |
| ΔhSBP | 0.95 (0.88–1.02) | 0.132 | 0.94 (0.87–1.02) | 0.150 |
| ΔhDBP | 0.96 (0.90–1.02) | 0.197 | 0.95 (0.87–1.04) | 0.302 |
| **Men** |          |      |          |      |
| HR at rest | 1.02 (0.98–1.07) | 0.310 | 1.02 (0.97–1.07) | 0.362 |
| SpO2 at rest | 1.45 (0.95–2.20) | 0.083 | 1.47 (0.95–2.28) | 0.086 |
| SBP at rest | 1.01 (0.96–1.05) | 0.795 | 1.00 (0.96–1.05) | 0.924 |
| DBP at rest | 1.02 (0.97–1.06) | 0.484 | 1.01 (0.97–1.06) | 0.593 |
| ΔhHR | 0.96 (0.91–1.01) | 0.090 | 0.96 (0.91–1.01) | 0.100 |
| ΔhSpO2 | 0.57 (0.40–0.80) | 0.001 | 0.56 (0.39–0.79) | 0.001 |
| ΔhSBP | 1.02 (0.97–1.06) | 0.477 | 1.02 (0.97–1.06) | 0.444 |
| ΔhDBP | 1.01 (0.97–1.04) | 0.748 | 1.01 (0.97–1.04) | 0.792 |
| ΔhHR | 1.00 (0.96–1.04) | 0.969 | 1.01 (0.97–1.05) | 0.822 |
| ΔhSpO2 | 0.97 (0.85–1.10) | 0.617 | 0.98 (0.86–1.13) | 0.785 |
| ΔhSBP | 0.99 (0.94–1.01) | 0.172 | 0.97 (0.94–1.01) | 0.123 |
| ΔhDBP | 0.98 (0.94–1.02) | 0.260 | 0.98 (0.94–1.02) | 0.290 |

Adjusted analysis Adjusted for age, height, weight, and smoking status. AMS Acute mountain sickness, HR Heart rate, SpO2 Pulse oxygen saturation, SBP Systolic blood pressure, DBP Diastolic blood pressure, Δh Change after exercise testing.

Higher incidence of AMS in women may be explained by the effects of hormones. First, testosterone possess potent erythropoiesis action [29]. High serum testosterone and hemoglobin levels are conducive to improvements in oxygen transport, normal cellular function and thus lower susceptibility to AMS. Second, 17 beta-estradiol could reduce the operating point for osmoregulation of arginine vasopressin and contribute to fluid retention [30]. Seventeen beta-estradiol could also up-regulate the expression of vascular endothelial growth factor (VEGF), which in turn promotes endothelial cellular proliferation, angiogenesis and vascular permeability [31]. Fluid retention and increased permeability of the vascular endothelium compromise the blood-brain barrier and promote brain tissue swelling and intracranial hypertension [32].

**Predictive value of exercise testing**

Under hypoxia, the sympathetic system is activated to ensure a sufficient oxygen supply. Heart rate variability (HRV) is a common indicator that reflects the balance of cardiac autonomic nervous function between the sympathetic system and the parasympathetic system. HRV has been found to be associated with AMS risk; however, the assessment of HRV requires 12-lead electrocardiogram; more importantly, the prediction value was limited [33]. A more convenient indicator is needed for the general population under field conditions. A previous study suggested that decreased SpO2 at rest increases the likelihood of AMS upon ascent to high altitude [34]. Fluid accumulation in the pulmonary vasculature and/or inflammatory reactions in the peripheral airways may reduce pulmonary gas exchange under hypoxic conditions. This may further decrease SaO2 and cause hypoxia-induced illness. Exercise testing under hypobaric conditions in laboratory could identify subjects who will develop severe HAI upon ascent.

is similar to a study by Boos CJ in which 69.2% of women developed AMS [25]. The Boos study also suggested that anxiety at low altitude is an independent predictor of AMS upon ascent, and women tend to have higher level of anxiety. The fact that anxiety levels are higher in younger adults and women may partly explain the difference in AMS susceptibility between women and men [26]. However, Pesce et al. failed to show a difference in the rate of AMS between men and women [27]. Wagner et al. [15] even found higher risk of AMS in men. These inconsistent findings may be attributed to the ethnic and age differences, different levels of anxiety, history of high altitude exposure, experience with hiking, and prophylactic use of pharmacological agents. In addition, Gatterer et al. [28] found that resting cortisol levels at sea level are associated with fluid balance and AMS risk after ascent, suggesting the involvement of autonomic nervous and endocrine system.
in some but not all studies [35, 36]. Also, such method is apparently not suitable as a screening test to identify subjects susceptible for the less severe AMS in the general population [13].

In the current study, SpO2 change after arriving at 4100 m was positively correlated with AMS in women. In addition to the effects of hormones, the regulation of the respiratory system and changes in physiological parameters also play important roles in the development of AMS. Relatively smaller tidal volume and higher breathing frequency in women could conceivably lead to increased strain on respiratory muscles under hypoxia and exercise conditions. Women are also more susceptible to hypoxemia, which may explain why the higher incidence of AMS in women observed in the current study as well as in previous studies [37]. We also showed an association between SpO2 change after exercise testing at low altitude with AMS risk in the entire cohort, and more so in men. ΔeSpO2 after exercise testing at low altitude was also positively correlated with AMS score in the men, suggesting that ΔeSpO2 after mild exercise could be a useful tool to predict AMS. Subjects with higher maximal oxygen consumption (VO2max) values perform better at endurance exercise. VO2max has been shown to be strongly associated with red cell volume and hemoglobin concentration [38]. Higher VO2max, red cell volume and hemoglobin concentration as the result of testosterone stimulation may partly explain the low incidence of AMS in men. When subjects exercised at equal intensity, the oxygen consumption in men was more remarkable, and exercise-induced desaturation could predict AMS risk. However, this did not translate into an increased incidence of AMS in men.

Consistent with a meta-analysis study about smoking and AMS [39], we found a lower percentage of smokers in the AMS group. Smokers have higher basal carbon monoxide (CO) [40], which in turn decrease cerebral blood flow velocities, and thus decreased risk of high altitude headache and AMS [41]. CO could occupy the binding sites of hemoglobin and decrease the oxygen content in the circulating blood [42]. These mechanisms may explain why smokers are less susceptible to AMS in the current study. In a previous study by Wu et al. [43], smoking was also a protective factor against AMS during acute hypoxia exposure. Such a finding by no means advocate smoking, since smoking could impair long-term acclimatization in addition to causing a variety of serious health problems.

Other factors related to AMS
Age has been inversely associated with AMS in some [44], but not all studies [45]. Trekkers younger than 60 years are twice as likely to develop AMS [46], possibly due to less experience and more rapid ascent. The ratio of cranial cerebrospinal fluid to brain volume increases with age, and may serve as a compensatory adaptation to limit the effect of brain swelling and ultimately decreased susceptibility to AMS. Also, respiratory responses to hypoxia and blood oxygenation increase with age in men, and lung diffusion limitation was less prominent in older people [44]. These findings may help to explain the wide difference in exercise-induced desaturation under hypoxic conditions across age groups.

Ge et al. [47] found higher AMS score and lower SaO2 in obese subjects. Such a phenomenon may be partly related to greater SpO2 reduction during the night at high altitude. In the current study, BMI was lower in the AMS group. In addition to BMI, however, other factors (e.g., waist, body fat and body composition) may also affect the development of AMS. As a result, BMI should not be considered in isolation. For example, the female
sex was strongly associated with increased AMS risk. Whether and how AMS susceptibility in women is connected to lower weight and BMI in women requires further studies.

Limitations
The present study does have limitations. First, participating subjects were mostly young despite of a wide range (19–59 years). Whether the findings could be extrapolated to older population remains unknown. Second, we used a single elevation and single ascending rate. The findings need to be validated in studies with different protocols. Third, the sample size of women was relatively small (n = 32). More importantly, men and women were not well matched by age and BMI. Lastly, the intensity of exercise was mild. SpO₂ reduction after exercise testing therefore is relatively small. Exercise programs with higher intensity might be more sensitive to identify persons at risk to develop AMS.

Conclusion
AMS is common if the ascent to 4100 m is completed within 2 days. AMS is more common and severe in women than in men. SpO₂ reduction at low altitude could be used to predict AMS upon ascent in men but not in women, indicating major sex differences.

Abbreviations
AMS: Acute mountain sickness; BMI: Body mass index; CI: Confidence intervals; CO₂: Carbon monoxide; DBP: Diastolic blood pressure; HACE: High-altitude cerebral edema; HAI: High-altitude illness; HIF: Hypoxia inducible factor; HR: Heart rate; OR: Odds ratio; SaO₂: Arterial oxygen saturation; SBP: Systolic blood pressure; SpO₂: Pulse oxygen saturation; VO₂max: Maximal oxygen consumption; Δh: Change after arriving at 4100 m

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Authors’ contributions
LH, CL and JHZ conceived and designed the experiments. YS, YQY, FZYY, LH, CL and JHZ performed field experiments and collected data both at sea level and in Lhasa. YQY performed the statistical analyses, created the tables and figures, and wrote the results section. YS analyzed the data, interpreted the results and wrote the initial manuscript. CL, JJ, HT, JY and LH critically reviewed and modified the manuscript. All authors approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
All procedures in this study were approved by the Clinical Research Ethics Board of Army Medical University (identification code, 201907501; approved 15 July, 2019). All subjects were informed of the study purpose and procedure in detail and volunteered to participate in this study. Written informed consent was obtained from all subjects prior to the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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