

Evolution of the Prevalence, Clinical Features and Risk Factors for Acute Mountain Sickness in the Qinghai-Tibet Plateau

Chen Zhang

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Chuan Liu

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Renzheng Chen

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Jie Yang

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Jingbin Ke

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Shizhu Bian

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Shiyong Yu

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Jihang Zhang

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Jie Yu

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Ying Zeng

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Xubin Gao

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Xiaohan Ding

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Yuanqi Yang

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Fangzhengyuan Yuan

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Chunyan He

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Yang Shen

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Hu Tan

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Xiaohui Zhao

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Jun Jin

Third Military Medical University Second Affiliated Hospital: Xinqiao Hospital

Lan Huang (✉ huanglan260@126.com)

The Second Affiliated Hospital, Third Medical University (Army Medical University)

<https://orcid.org/0000-0001-6200-2309>

Research

Keywords: high altitude, acute mountain sickness, risk factors, ascent protocol

Posted Date: July 13th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-663450/v1>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background Ascending to high altitude (HA) contribute to the development of acute mountain sickness (AMS). The prevalence, clinical features and relative risks for AMS may dynamically evolve but has not been described.

Methods A total of 1,629 healthy men aged from 16 to 45 years were enrolled. A fast ascent cohort (n=1283) ascended to 3700 m by airplane and further ascended to 4400 m by bus; a slow ascent cohort (n=346) ascended to 3450 m by bus and further ascended to 4100 m by bus. AMS was diagnosed by the Lake Louise Scoring (LLS) system.

Results As diagnosed by the old LLS and new LLS, the prevalence of AMS was 68.4% and 56.1% at 3700 m, respectively, which decreased to 21.4% and 14.3% after further ascending to 4400 m in the fast ascent cohort; the prevalence of AMS was 30.3% and 25.7% at 3450 m, which increased to 36.6% and 32.2% after further ascending to 4100 m in the slow ascent cohort. Moreover, AMS-related symptoms, such as headache, dizziness and fatigue, were the leading symptoms except at 4400 m in the fast ascent cohort. Fast ascent protocol was a risk factor during the initial ascent but became a protective factor after a further ascent to a higher altitude.

Conclusions Ascent protocol was the primary factor that affected the incidence of AMS and related symptoms. These findings imply a novel strategy for high altitude travels or work with a plan to ascend to a higher altitude.

Background

The number of sea level residents engaged in leisure, work or sports at high altitude (HA) is dramatically increasing. However, within the first few days after arrival at HA above 2500 m, 40–90% of unacclimated individuals may suffer from acute mountain sickness (AMS), depending on the altitude reached, the ascending rate, personal susceptibility, and degree of acclimatization [1]. If AMS is not treated appropriately, it may progress to life-threatening high-altitude pulmonary oedema (HAPE) or high-altitude cerebral oedema (HACE) [2]. Annually, AMS threatens the well-being and/or life of millions of sojourners and workers at HA, which subsequently hinders the development of social economy [3]. For these reasons, illuminating the prevalence, clinical features and relative risks for AMS is of great importance for the prediction, prevention and treatment of AMS.

The symptoms of AMS are usually non-specific but incapacitating and include headache, gastrointestinal (GI) upset, fatigue, dizziness, insomnia, and so on [4]. However, due to the poor association with the other symptoms of AMS, insomnia is no longer the defining symptom for AMS diagnosis by the Lake Louise Scoring (LLS) system, which was revised in 2018 [5]. Theoretically, compared with the old LLS, the prevalence of AMS diagnosed by the newly revised LLS will be less frequent. Nevertheless, the prevalence, clinical features and relative risks for AMS defined by the new LLS-AMS and the differences between the old and new versions are still unknown.

Identifying the risk factors for AMS is vital and challenging because of miscellaneous contributing factors. A previous study showed that the critical factors that influenced the risk of developing AMS were the altitude attained and the ascent rate. The prevalence of AMS increased with higher altitudes, and the risk of developing AMS was higher for fast ascents (faster than 400 m per day) than for slow ascents [6]. In addition, some demographic characteristics, such as age, sex, nationality, body mass index (BMI), and history of smoking have been evaluated and demonstrated to contribute to AMS. Additionally, some previous research revealed that the development of AMS declined when there were pre-acclimatization or prolonged acclimatization schedules [7]. Moreover, there is not always only a target altitude for individuals ascending to HA. Commonly, they may ascend to a higher altitude for various purposes after a short-term stay at an intermediate altitude. Therefore, the prevalence, clinical features and relative risks for AMS may dynamically evolve. However, this dynamic evolution has not been described to date.

For these reasons, the present study aimed to reveal the dynamics of the prevalence, clinical features and relative risks for AMS based on the old LLS and new LLS in a large population visiting above 3000 m with a fast or slow ascent protocol and further ascending to above 4000 m.

Methods

Study design and participants

The present study included two prospective cohorts at the Qinghai-Tibet Plateau in June-July 2012 and June-July 2013. A total 1629 healthy men who were born or permanently lived in the lowland (<500 m, above sea level, asl) were recruited in June 2012 (n=1283) and June 2013 (n=346). For all subjects enrolled, a comprehensive medical examination was performed before the expedition. Subjects with any clinical conditions that may exhibit HA-related symptoms were excluded, including known pulmonary diseases, cardiovascular diseases, any chronic cardiovascular therapy, haematologic diseases, liver and kidney dysfunction, malignant tumours, and so on. Subjects with psychiatric disorders that prevented the completion of the data collection and subjects with high-altitude cerebral oedema or high-altitude pulmonary oedema needing emergency treatment were also excluded.

Ascending procedures

For the 2012 cohort, named the “fast ascent cohort”, 1283 subjects successively ascended to HA from 500 m (Chengdu, Sichuan, China) to 3700 m (Lhasa, Tibet, China) by airplane in approximately 2 h. After staying for 7 days at 3700 m, they further ascended to 4400 m (Yangbanjin, Tibet, China) by bus. Among them, 387 subjects who did not further ascend to 4400 m and 138 subjects with incomplete questionnaires were excluded. Finally, the data from 757 subjects were collected after further ascending to 4400 m.

For the 2013 cohort, named the “slow ascent cohort”, 346 subjects successively ascended to 3450 m (Xinduqiao, Sichuan, China) from 400 m (Yanggongqiao, Chongqing, China) by bus within 4 days in a staged ascent mode. After staying for 3 days at 3450 m, they further ascended to 4100 m (Litang,

Sichuan, China) by bus. Among them, 21 subjects who refused to ascend further to 4100 m and 11 subjects with incomplete questionnaires were excluded. Finally, the data from 314 subjects were collected after the further ascent to 4100 m (Figure 1).

Data collection

For the 2012 cohort, data collection was performed on 15 June 2012 at SL and 18-24 h after arriving at 3700 m or 4400 m. For the 2013 cohort, data collection was performed on 19th June 2013 at SL and 18-24 h after arriving at 3450 m or 4100 m. Structured case report form questionnaires were used to record demographic information, including age, height, weight, smoking, nationality, educational level and history of HA exposure within 1 year. The BMI was calculated as weight (kg)/[height (m)]². Clinical symptoms were self-reported, including headache, dizziness, gastrointestinal upset, insomnia, fatigue, paraesthesia, constipation, dyspnoea, cough, chest distress, palpitation, tinnitus, dazzling, lethargy, and reduced activity.

Diagnosis of AMS

The incidence of AMS was identified by using the standard LLS as previously validated [8]. The severity of the AMS symptoms was scored from 0 (no discomfort) to 3 (severe discomfort) according to the participants' self-report. Participants were requested to complete the self-reported LLS before sleeping and after awakening, and the highest scores during the stay at HA were considered as the final LLS. In the present study, two criteria were used to define AMS: old LLS-AMS and new LLS-AMS. The latter was based on the old LLS-AMS without scoring the symptom of sleep disorders according to the newly revised diagnostic criterion [9]. Accordingly, subjects with LLS \geq 3 in the presence of headache were diagnosed with AMS.

Statistical Analysis

All the statistical analyses were conducted using SPSS 22.0 (IBM Corp., Armonk, NY, USA). Demographic characteristics, clinical symptoms and the incidence of AMS were presented as the mean \pm standard deviation or medians (25th–75th percentile) for continuous variables and compared using Student's t tests or the Mann–Whitney U test according to their normality following the Kolmogorov–Smirnov test. Categorical variables were expressed as counts and percentages and analysed using the χ^2 test or Fisher's exact test, as appropriate. For the risk factor analysis, univariate and multivariate logistic regression analysis were performed. Demographic parameters were adjusted in the multivariate analysis. Moreover, to reduce the effect of potential confounding factors in the present study, propensity score-matching was performed for rigorous adjustment for significant differences in the baseline characteristics. Statistical power was calculated by PASS software (version 11, NCSS, LLC, Kaysville, UT, USA), and more than 80% statistical power was achieved between subgroups using a two-sided alpha of 0.05. A two-sided p-value of <0.05 was considered statistically significant.

Ascending Procedures

For the 2012 cohort, named the “fast ascent cohort”, 1283 subjects successively ascended to HA from 500 m (Chengdu, Sichuan, China) to 3700 m (Lhasa, Tibet, China) by airplane in approximately 2 h. After staying for 7 days at 3700 m, they further ascended to 4400 m (Yangbanjin, Tibet, China) by bus. Among them, 387 subjects who did not further ascend to 4400 m and 138 subjects with incomplete questionnaires were excluded. Finally, the data from 757 subjects were collected after further ascending to 4400 m.

For the 2013 cohort, named the “slow ascent cohort”, 346 subjects successively ascended to 3450 m (Xinduqiao, Sichuan, China) from 400 m (Yanggongqiao, Chongqing, China) by bus within 4 days in a staged ascent mode. After staying for 3 days at 3450 m, they further ascended to 4100 m (Litang, Sichuan, China) by bus. Among them, 21 subjects who refused to ascend further to 4100 m and 11 subjects with incomplete questionnaires were excluded. Finally, the data from 314 subjects were collected after the further ascent to 4100 m (Fig. 1).

Results

Subject characteristics

The baseline demographic characteristics are shown in Table 1. Subjects in the fast ascent cohort were slightly older than those in the slow ascent cohort (23.5 ± 4.2 vs. 21.3 ± 3.1 years, $p < 0.001$), and the BMI of subjects in the fast ascent cohort was slightly higher than that in the slow ascent cohort (21.8 ± 2.2 vs. 21.2 ± 1.9 kg/m², $p < 0.001$), which was mainly attributed to their differences in body weight. Moreover, there were fewer previous smokers and Han subjects in the fast ascent cohort than in the slow ascent cohort. Additionally, higher education levels were found, and more individuals had a history of HA exposure in the fast ascent cohort than in the slow ascent cohort (S1 Table).

Incidence of clinical outcomes

When diagnosing AMS by the old LLS, 877 subjects (68.4%) in the fast ascent cohort developed AMS after the initial ascent to 3700 m, which decreased to 21.4% after further ascent to 4400 m, while 105 subjects (30.3%) in the slow ascent cohort developed AMS after the initial ascent to 3450 m, which increased to 36.6% after the further ascent to 4100 m. However, when diagnosing AMS by the new LLS, 720 subjects (56.1%) in the fast ascent cohort developed AMS after the initial ascent to 3700 m, which decreased to 14.3% after the further ascent to 4400 m, while 89 subjects (25.7%) in the slow ascent cohort developed AMS after the initial ascent to 3450 m, which increased to 32.2% after the further ascent to 4100 m (Table 1).

Among the 15 clinical symptoms that developed, headache (75.1%) was most common in the fast ascent cohort after the initial ascent to 3700 m, followed by dizziness, fatigue, activity reduction, and insomnia (Figure 2. A). However, after the further ascent to 4400 m, activity reduction (42.4%) became the leading

symptom, followed by dizziness, fatigue, insomnia, dyspnoea and headache (Figure 2. B). Interestingly, dizziness (49.7%) was most common in the slow ascent cohort after the initial ascent to 3450 m, followed by headache, fatigue, activity reduction, and paraesthesia (Figure 2. C). However, the order of the first five clinical symptoms was not markedly changed after further ascent to 4100 m (Figure 2. D).

The results from the symptomatic analysis showed that the incidences of clinical symptoms including headache, dizziness, gastrointestinal upset, insomnia, fatigue, paraesthesia, dyspnoea, cough, chest distress, palpitation, dazzling, lethargy and activity reduction in subjects who quickly ascended to an intermediate altitude (3700 m) were higher than those who slowly ascended to an intermediate altitude (3450 m). However, after ascending to the higher altitude, the incidences of clinical symptoms, including headache, dizziness, fatigue, paraesthesia and tinnitus in the fast ascent cohort, were lower than those in the slow ascent cohort, except for insomnia. Additionally, in the fast ascent cohort, the incidences of almost all clinical symptoms were significantly decreased after further ascent to a higher altitude, except for constipation and tinnitus. Nevertheless, in the slow ascent cohort, the incidences of fatigue, dyspnoea, cough and activity reduction were even increased after further ascent to a higher altitude (Table 1).

Risk factors for the incidence of AMS

The results from logistic regression suggested that age was only associated with the incidence of AMS at 4400 m in the fast ascent cohort when the old LLS was used for AMS diagnosis. Moreover, in the fast ascent cohort, current smoking was a protective factor (OR: 0.74, 95% CI: 0.56 to 0.97) at 3700 m in the fast ascent cohort when the old LLS was used but became a risk factor (OR: 1.95, 95% CI: 1.10 to 3.45) at 4100 m in the slow ascent cohort when the new LLS was used. Additionally, the Chinese non-Han population always acted as a protective factor at 4400 m or 3450 m when the old LLS was used or at 4100 m when the new LLS was used (Table 2a and Table 2b).

The outcomes after propensity score-matching

The propensity score-matched subjects among the overall population, fast and slow ascent cohorts showed no significant differences in the baseline demographic characteristics (S2 Table). There were no significant changes in the prevalence of AMS and its clinical features under different ascent protocols or diagnostic criteria, as well as their evolutions after further ascent to higher altitudes after propensity score-matching compared with that before propensity score-matching (S3 Table, Figure 2. A'-D'). However, after propensity score-matching, the ascent protocol was the most important factor affecting the incidences of AMS and its related symptoms (S4 Table). Irrespective of whether the old or new LLS was used for AMS diagnosis, the fast ascent protocol was a risk factor during the initial ascent but became a protective factor after further ascent to a higher altitude in the univariate and multivariate logistic regression models. Furthermore, these associations and risk evolutions have also been found for the incidences of headache, dizziness and fatigue, but not for the incidences of gastrointestinal upset and insomnia (Table 3).

Discussion

The major findings of our present study were as follows: 1) In the fast ascent cohort, the prevalence of AMS was 68.4% and 56.1% at 3700 m, which decreased to 21.4% and 14.3% when further ascending to 4400 m, as diagnosed by the old LLS and new LLS, respectively; 2) In the slow ascent cohort, the prevalence of AMS was 30.3% and 25.7% at 3450 m, which increased to 36.6% and 32.2% when further ascending to 4100 m, as diagnosed by the old LLS and new LLS, respectively; 3) AMS-related symptoms such as headache, dizziness, and fatigue were the leading symptoms after the initial ascent to 3700 m or 3450 m and were still the main symptoms after further ascending to 4100 m in the slow ascent cohort but not to 4400 m in the fast ascent cohort; and 4) the ascent protocol was the primary factor that affected the incidence of AMS and related symptoms, showing that the slow ascent protocol was protective during the initial ascent but became a risk factor after further ascending to a higher altitude.

AMS is a common medical problem that affects the well-being of a large population. A recent systematic review summarized the published incidences of AMS from 53603 subjects, which demonstrated that the median AMS incidence was 60% in randomized trials, 51% in cohort studies, and 32% in cross-sectional studies. The results from the multivariate analysis suggested that the study design, mode of ascent, maximum altitude, population, and geographical location were significantly associated with the incidence of AMS [10]. Indeed, our present data on AMS prevalence were higher or lower than those of previous studies mainly in the population characteristics, mode of ascent, altitude reached and AMS definitions. Similar to our protocol, it had been reported that the incidence of AMS was 84% among tourists who ascended directly to 3740 m by airplane, whereas the incidence of AMS was 61% in subjects who ascended to the same altitude from < 3000 m by foot [11], which was consistent with our present results that subjects ascending to HA by plane reported more frequent AMS than with other protocols. Furthermore, previous results showed that the overall incidence of AMS was 53% after ascending to 4243 m altitude at Pheriche in the Himalayas of Nepal. It had also been reported that the prevalence of acute mountain sickness was 9% at 2850 m, 13% at 3050 m, and 34% at 3650 m [12]; the latter of the three values was comparable with our prevalence in the slow ascent cohort at 3450 m. Moreover, it had been demonstrated that the incidence of AMS was 59% of children trekking at 3952 m (Jade Mountain, Taiwan), which was consistent with our results that the most common AMS symptom was headache, followed by fatigue, sleep disorders, dizziness or lightheadedness and gastrointestinal upset [13].

After arriving at a new altitude above 2500 m in unacclimated individuals, AMS patients usually developed a group of nonspecific symptoms. Among these various symptoms, headache was the defining and indispensable symptom for AMS diagnosis [14]. After sequencing the 15 clinical symptoms reported in our present study, the main symptoms of AMS, including headache, dizziness and fatigue, remained as the cardinal symptoms after the initial ascent to 3700 m by plane or 3450 m by bus, which was consistent with previous results [15]. However, after further ascending to 4400 m in the fast ascent cohort, fatigue, headache and dizziness were no longer the leading symptoms, and their incidence was also lower than that in the slow ascent cohort after further ascending to 4100 m, which suggested that the fast ascent protocol might be more effective in attenuating the incidence of AMS-related symptoms

than the slow ascent protocol when subjects further ascended to a higher altitude after a short term of staying at the intermediate altitude. Additionally, activity reduction, which was not a symptom for AMS diagnosis, was another more frequent complaint. Consistently, a previous review claimed that individuals with AMS were frequently incapacitated [16]. Although insomnia had been excluded from the newly revised AMS diagnostic criteria, the incidence of insomnia was still prevalent, as previously described, and was more frequent in the fast ascent cohort than in the slow ascent cohort in our study.

Consistently, the incidence of AMS was highly correlated with the speed of ascent and age, but not sex or previous altitude experience [16]. A previous systematic review summarized that the fast ascent protocol had an OR of 4.69 (95% CI, 2.79–7.90), whereas a slow ascent protocol had an OR of 0.30 (95% CI, 0.20–0.44) for the incidence of AMS, which was highly consistent with our present results during the initial ascent to 3700 m or 3450 m by plane or by bus, respectively. In addition, compared with non-smokers, smokers showed a lower incidence of AMS, suggesting that smoking slightly lowers the risk of AMS but impairs long-term altitude acclimation during prolonged HA exposure [17], which was similar to our present findings that smoking was a protective factor for AMS in subjects who rapidly ascended to 3700 m, but increased the risk for AMS in a prolonged HA exposure in the slow ascent cohort at 4100 m. However, our data suggested that the associations of smoking and AMS were uncertain and depended on the ascent protocol, altitude attained and diagnostic criteria. Indeed, a previous meta-analysis also showed that there were no consistent results demonstrating that cigarette smoking acted as either a protective factor against or a risk factor for AMS [18].

It had been recommended that AMS could be prevented by ascending slowly at altitudes above 3000 m and taking a rest day every 3–4 days [19]. Such a protocol had been described as a “staged ascent”, which had been considered the best method for AMS prevention [16]. Indeed, our present data also demonstrated that the incidence of AMS was definitely lower in the slow ascent cohort than in the fast ascent cohort after their initial ascent to an intermediate altitude. A previous report showed that 2 days of staging at an intermediate altitude lowered the incidence of AMS compared with the direct ascent group [20]. However, such approaches did not reduce the incidence of AMS with a rapid ascent to higher altitudes [21]. Therefore, the results from studies aiming to identify the benefit of intermittent hypoxic exposures for AMS prevention were somewhat conflicting for subjects planning a further ascent to higher altitudes. In our present study, the results from the field study at HA indicated that there was no significant impact of the slow ascent protocol combined with 3 days of staging at an intermediate altitude on the incidence of AMS after a further ascent to above 4000 m. Interestingly, although the incidence of AMS was high in subjects after the fast ascent to the initial altitude by plane, the number of subjects suffering from AMS after a further ascent to a higher altitude was significantly lower than that of the initial ascent in the fast ascent cohort and that of a further ascent in the slow ascent cohort. These findings might imply a novel strategy for AMS prevention in individuals travelling to or working at HA when a further ascent to a higher altitude was needed.

Limitations

There were also several limitations. First, the enrolled participants were young, healthy men, and whether the established results can extend to other types of individuals or circumstances (such as women, older adults, children) is still unknown. Second, the effects of other modes of transport (such as the train) on the incidence of AMS under the present conditions are also unknown. Third, the classification of AMS was based on a self-report without an immediate medical control, which might lead to possible classification bias. Finally, due to the reality of the field study at HA, the target altitudes were not absolutely the same between the two cohorts. Theoretically, the incidence of AMS would be higher in subjects at higher target altitudes [22]; thus, our conclusions would be even more affirmative if the target altitudes of further ascent were the same in the two cohorts.

Conclusions

Our large cohort study showed the prevalence of AMS was 56.1% at 3700 m, which decreased to 14.3% after further ascending to 4400 m in the fast ascent cohort; and the prevalence of AMS was 25.7% at 3450 m, which increased to 32.2% after further ascending to 4100 m in the slow ascent cohort. The ascent protocol was the primary factor that affected the incidence of AMS and related symptoms, showing that a fast ascent protocol, which acted as a risk factor during the initial ascent, was converted into a protective factor after further ascending to a higher altitude. These findings imply a novel strategy for HA travels or work with a plan to further ascend to a higher altitude.

Abbreviations

HA: high altitude; AMS: acute mountain sickness; HAPE: high-altitude pulmonary oedema; HACE: high-altitude cerebral oedema; BMI: body mass index.

Declarations

Ethics statements and registration

This study was approved by the Clinical Research Ethics Board at the Army Medical University (Third Military Medical University No. 2012014) and was conducted in agreement with the Declaration of Helsinki. All subjects volunteered to participate in this study and gave written informed consent. This study was registered with the Chinese Clinical Trial Registration (No. ChiCTR-RCS-12002232, <http://www.chictr.org.cn>).

Consent for publication: Not applicable.

Availability of data and materials: The datasets generated for this study are available on request to the corresponding author.

Competing interests: None.

Funding: This work is supported by grants from the National Natural Science Foundation of China (Grant No: 81730054), Military Logistics Research Project, PLA (Grant No: BLJ18J007) and the Special Health Research Project, Ministry of Health of PR China (Grant No: 201002012).

Authors' contributions: Prof. Lan Huang are guarantors and contributes to the study design. Dr. Chuan Liu and Chen Zhang analyze the data and draft the manuscript. All authors contribute to the interpretation of the results and approve the final version of the manuscript.

Acknowledgments: The authors are grateful to all participants in this study for their support.

Disclosures

None.

References

1. Schneider M, Bernasch D, Weymann J, Holle R, Bartsch P: **Acute mountain sickness: influence of susceptibility, preexposure, and ascent rate.** *Medicine and science in sports and exercise* 2002, **34**(12):1886-1891.
2. Beidleman BA, Tighiouart H, Schmid CH, Fulco CS, Muza SR: **Predictive models of acute mountain sickness after rapid ascent to various altitudes.** *Medicine and science in sports and exercise* 2013, **45**(4):792-800.
3. Bärtsch P, Swenson ER: **Clinical practice: Acute high-altitude illnesses.** *The New England journal of medicine* 2013, **368**(24):2294-2302.
4. Wilson MH, Newman S, Imray CH: **The cerebral effects of ascent to high altitudes.** *The Lancet Neurology* 2009, **8**(2):175-191.
5. Imray C, Booth A, Wright A, Bradwell A: **Acute altitude illnesses.** *BMJ (Clinical research ed)* 2011, **343**:d4943.
6. Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, Baillie JK: **The 2018 Lake Louise Acute Mountain Sickness Score.** *High altitude medicine & biology* 2018, **19**(1):4-6.
7. Meier D, Collet TH, Locatelli I, Cornuz J, Kayser B, Simel DL, Sartori C: **Does This Patient Have Acute Mountain Sickness?: The Rational Clinical Examination Systematic Review.** *Jama* 2017, **318**(18):1810-1819.
8. Hsu TY, Weng YM, Chiu YH, Li WC, Chen PY, Wang SH, Huang KF, Kao WF, Chiu TF, Chen JC: **Rate of ascent and acute mountain sickness at high altitude.** *Clinical journal of sport medicine : official journal of the Canadian Academy of Sport Medicine* 2015, **25**(2):95-104.
9. Biondi-Zoccai G, Romagnoli E, Agostoni P, Capodanno D, Castagno D, D'Ascenzo F, Sangiorgi G, Modena MG: **Are propensity scores really superior to standard multivariable analysis?** *Contemporary clinical trials* 2011, **32**(5):731-740.

10. Waeber B, Kayser B, Dumont L, Lysakowski C, Tramèr MR, Elia N: **Impact of Study Design on Reported Incidences of Acute Mountain Sickness: A Systematic Review.** *High altitude medicine & biology* 2015, **16**(3):204-215.
11. Hackett PH, Rennie D, Levine HD: **The incidence, importance, and prophylaxis of acute mountain sickness.** *Lancet (London, England)* 1976, **2**(7996):1149-1155.
12. Maggiorini M, Bühler B, Walter M, Oelz O: **Prevalence of acute mountain sickness in the Swiss Alps.** *BMJ (Clinical research ed)* 1990, **301**(6756):853-855.
13. Chan CW, Lin YC, Chiu YH, Weng YM, Li WC, Lin YJ, Wang SH, Hsu TY, Huang KF, Chiu TF: **Incidence and risk factors associated with acute mountain sickness in children trekking on Jade Mountain, Taiwan.** *Journal of travel medicine* 2016, **23**(1).
14. Marmura MJ, Hernandez PB: **High-altitude headache.** *Current pain and headache reports* 2015, **19**(5):483.
15. Hackett PH, Roach RC: **High-altitude illness.** *The New England journal of medicine* 2001, **345**(2):107-114.
16. Sutton JR, Powles AC, Gray GW, Houston CS: **Insomnia, sedation, and high altitude cerebral oedema.** *Lancet (London, England)* 1979, **1**(8108):165.
17. Wu TY, Ding SQ, Liu JL, Jia JH, Chai ZC, Dai RC, Zhao JZ, Tang QD, Kayser B: **Smoking, acute mountain sickness and altitude acclimatisation: a cohort study.** *Thorax* 2012, **67**(10):914-919.
18. Vinnikov D, Blanc PD, Steinmaus C: **Is Smoking a Predictor for Acute Mountain Sickness? Findings From a Meta-Analysis.** *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016, **18**(6):1509-1516.
19. Luks AM, Swenson ER, Bärtsch P: **Acute high-altitude sickness.** *European respiratory review : an official journal of the European Respiratory Society* 2017, **26**(143).
20. Beidleman BA, Fulco CS, Glickman EL, Cymerman A, Kenefick RW, Cadarette BS, Andrew SP, Staab JE, Sils IV, Muza SR: **Acute Mountain Sickness is Reduced Following 2 Days of Staging During Subsequent Ascent to 4300 m.** *High altitude medicine & biology* 2018, **19**(4):329-338.
21. Schommer K, Wiesegart N, Menold E, Haas U, Lahr K, Buhl H, Bärtsch P, Dehnert C: **Training in normobaric hypoxia and its effects on acute mountain sickness after rapid ascent to 4559 m.** *High altitude medicine & biology* 2010, **11**(1):19-25.
22. Fulco CS, Muza SR, Beidleman BA, Demes R, Staab JE, Jones JE, Cymerman A: **Effect of repeated normobaric hypoxia exposures during sleep on acute mountain sickness, exercise performance, and sleep during exposure to terrestrial altitude.** *American journal of physiology Regulatory, integrative and comparative physiology* 2011, **300**(2):R428-436.

Tables

Table 1. Incidence of Clinical Outcomes According to the Different High Altitudes in the Fast or Slow Ascent Cohort

| | Fast Ascent Cohort | | Slow Ascent Cohort | | P1 | P2 | P3 | P4 |
|--------------------------|--------------------|------------------|--------------------|------------------|--------|--------|--------|--------|
| | 3700m (n=1283) | 4400m (n=757) | 3450m (n=346) | 4100m (n=314) | | | | |
| Old LLS-AMS | 877 (68.4%) | 162 (21.4%) | 105 (30.3%) | 115 (36.6%) | <0.001 | <0.001 | <0.001 | 0.088 |
| New LLS-AMS | 720 (56.1%) | 108 (14.3%) | 89 (25.7%) | 101 (32.2%) | <0.001 | <0.001 | <0.001 | 0.068 |
| Clinical symptoms | | | | | | | | |
| Headache | 963 (75.1%) | 171 (22.6%) | 149 (43.1%) | 158 (50.3%) | <0.001 | <0.001 | <0.001 | 0.062 |
| Dizziness | 918 (71.6%) | 167 (22.1%) | 172 (49.7%) | 164 (52.2%) | <0.001 | <0.001 | <0.001 | 0.518 |
| GI upset | 277 (21.6%) | 82 (10.8%) | 48 (13.9%) | 25 (8.0%) | 0.001 | 0.154 | <0.001 | 0.016 |
| Insomnia | 835 (65.1%) | 238 (31.4%) | 69 (19.9%) | 73 (23.3%) | <0.001 | 0.007 | <0.001 | 0.302 |
| Fatigue | 913 (71.2%) | 269 (35.5%) | 136 (39.3%) | 155 (49.4%) | <0.001 | <0.001 | <0.001 | 0.009 |
| Paraesthesia | 595 (46.4%) | 116 (15.3%) | 95 (27.5%) | 92 (29.3%) | <0.001 | <0.001 | <0.001 | 0.600 |
| Constipation | 167 (13.0%) | 72 (9.5%) | 47 (13.6%) | 41 (13.1%) | 0.782 | 0.085 | 0.017 | 0.842 |
| Dyspnea | 438 (34.1%) | 190 (25.1%) | 30 (8.7%) | 63 (20.1%) | <0.001 | 0.077 | <0.001 | <0.001 |
| Cough | 271 (21.1%) | 129 (17.0%) | 27 (7.8%) | 62 (19.8%) | <0.001 | 0.293 | 0.025 | <0.001 |
| Chest distress | 521 (40.6%) | 167 (22.1%) | 65 (18.8%) | 66 (21.0%) | <0.001 | 0.707 | <0.001 | 0.473 |
| Palpitation | 249 (19.4%) | 62 (8.2%) | 30 (8.7%) | 31 (9.9%) | <0.001 | 0.373 | <0.001 | 0.594 |
| Tinnitus | 323 (25.2%) | 58 (7.7%) | 70 (20.2%) | 50 (15.9%) | 0.056 | <0.001 | <0.001 | 0.152 |
| Dazzling | 218 (17.0%) | 63 (8.3%) | 30 (8.7%) | 34 (10.8%) | <0.001 | 0.193 | <0.001 | 0.350 |
| Lethargy | 345 (26.9%) | 99 (13.1%) | 49 (14.2%) | 41 (13.1%) | <0.001 | 0.993 | <0.001 | 0.680 |
| Activity reduction | 871 (67.9%) | 321 (42.4%) | 98 (28.3%) | 130 (41.4%) | <0.001 | 0.762 | <0.001 | <0.001 |

Values are n (%). P1 value for comparison between 3700m and 3450m. P2 value for comparison between 4400m and 4100m. P3 value for comparison between 3700m and 4400m. P4 value for comparison between 3460m and 4100m. GI upset = Gastrointestinal upset.

Table 2a. Risk Factors of Old LLS-AMS and New LLS-AMS at Different High Altitudes in the Fast Ascent Cohort after Univariate Analysis

| | 3700m | | 4400m | |
|---|--------------------|-------------------|--------------------|-------------------|
| | Old LLS-AMS | New LLS-AMS | Old LLS-AMS | New LLS-AMS |
| Age, years | 1.02 (0.99, 1.05) | 1.01 (0.99, 1.04) | 1.05 (1.00, 1.10)* | 1.02 (0.97, 1.08) |
| Height, cm | 0.99 (0.97, 1.02) | 0.99 (0.96, 1.01) | 0.98 (0.95, 1.02) | 1.00 (0.96, 1.05) |
| Weight, kg | 1.00 (0.99, 1.02) | 1.00 (0.99, 1.02) | 1.01 (0.99, 1.03) | 1.02 (0.99, 1.05) |
| BMI, kg.m⁻² | 1.03 (0.97, 1.09) | 1.02 (0.97, 1.07) | 1.06 (0.98, 1.15) | 1.09 (1.00, 1.20) |
| Smoking, n(%) | | | | |
| non | 1 | 1 | 1 | 1 |
| previous | 0.84 (0.58, 1.21) | 1.07 (0.76, 1.51) | 1.05 (0.60, 1.81) | 0.85 (0.45, 1.64) |
| current | 0.74 (0.56, 0.97)* | 0.85 (0.66, 1.10) | 1.18 (0.78, 1.79) | 1.01 (0.63, 1.63) |
| Nationality, n(%) | | | | |
| Han | 1 | 1 | 1 | 1 |
| non-Han | 0.72 (0.50, 1.04) | 0.79 (0.55, 1.13) | 0.51 (0.27, 0.96)* | 0.60 (0.29, 1.24) |
| Education, n(%) | | | | |
| university | 1 | 1 | 1 | 1 |
| high school | 1.09 (0.79, 1.50) | 1.08 (0.80, 1.46) | 1.15 (0.70, 1.88) | 1.15 (0.64, 2.05) |
| under high school | 0.80 (0.57, 1.13) | 0.77 (0.56, 1.07) | 0.94 (0.55, 1.62) | 0.98 (0.52, 1.87) |
| unknown | 0.71 (0.36, 1.37) | 0.62 (0.32, 1.17) | 1.40 (0.46, 4.24) | 1.74 (0.52, 5.87) |
| History of HA exposure within 1 year, n(%) | | | | |
| no | 1 | 1 | 1 | 1 |
| yes | 0.99 (0.72, 1.35) | 0.93 (0.69, 1.24) | 0.94 (0.60, 1.49) | 0.79 (0.45, 1.36) |
| unknown | 0.95 (0.73, 1.24) | 0.88 (0.68, 1.13) | 1.34 (0.90, 2.01) | 1.14 (0.71, 1.82) |

Values are β /OR (95%CI); * means p-value <0.05, and **means p-value <0.01. Other abbreviations as in Table 1 and Table 2.

Table 2b. Risk Factors of Old LLS-AMS and New LLS-AMS at Different High Altitudes in the Slow Ascent Cohort after Univariate Analysis

| | 3450m | | 4100m | |
|-------------------------------|--------------------|-------------------|-------------------|--------------------|
| | Old LLS-AMS | New LLS-AMS | Old LLS-AMS | New LLS-AMS |
| Age, years | 1.02 (0.95, 1.10) | 1.00 (0.92, 1.08) | 0.92 (0.84, 1.00) | 0.92 (0.85, 1.01) |
| Height, cm | 0.98 (0.93, 1.03) | 1.00 (0.95, 1.05) | 0.97 (0.92, 1.02) | 0.97 (0.92, 1.02) |
| Weight, kg | 0.98 (0.94, 1.01) | 0.98 (0.95, 1.02) | 0.98 (0.94, 1.01) | 0.97 (0.94, 1.01) |
| BMI, kg.m⁻² | 0.93 (0.82, 1.05) | 0.93 (0.82, 1.06) | 0.95 (0.84, 1.08) | 0.94 (0.83, 1.07) |
| Smoking, n(%) | | | | |
| non | 1 | 1 | 1 | 1 |
| previous | 1.04 (0.55, 1.99) | 1.15 (0.58, 2.27) | 1.00 (0.52, 1.95) | 1.42 (0.71, 2.84) |
| current | 1.04 (0.61, 1.77) | 1.13 (0.64, 1.99) | 1.48 (0.86, 2.53) | 1.95 (1.10, 3.45)* |
| Nationality, n(%) | | | | |
| Han | 1 | 1 | 1 | 1 |
| non-Han | 0.39 (0.17, 0.91)* | 0.51 (0.22, 1.18) | 0.50 (0.23, 1.05) | 0.38 (0.16, 0.89)* |
| Education, n(%) | | | | |
| university | 1 | 1 | 1 | 1 |
| high school | 1.00 (0.52, 1.94) | 1.07 (0.53, 2.17) | 1.22 (0.63, 2.36) | 1.45 (0.72, 2.92) |
| under high school | 0.84 (0.38, 1.85) | 0.89 (0.38, 2.06) | 1.06 (0.49, 2.28) | 1.55 (0.69, 3.47) |
| unknown | 1.20 (0.42, 3.40) | 1.31 (0.44, 3.89) | 0.71 (0.20, 2.55) | 0.71 (0.17, 2.93) |
| no | 1 | 1 | 1 | 1 |
| yes | 1.32 (0.65, 2.67) | 1.12 (0.53, 2.39) | 1.26 (0.55, 2.85) | 0.89 (0.37, 2.14) |
| unknown | 0.63 (0.29, 1.39) | 0.57 (0.24, 1.34) | 0.80 (0.39, 1.61) | 0.74 (0.35, 1.55) |

Values are β /OR (95%CI); * means p-value <0.05, and **means p-value <0.01. Other abbreviations as in Table 1 and Table 2.

Table 3. Main Clinical Outcomes in the Overall Propensity Score-Matched Cohort According to Different Plateau Ascent Protocols

| | Ascent to High Altitude | | Further Ascent to Higher Altitude | |
|--------------------|-------------------------|-------------------|-----------------------------------|-------------------|
| | Univariate | Multivariate | Univariate | Multivariate |
| Old LLS-AMS | 4.2 (2.9, 5.9) ** | 4.3 (3.0, 6.1) ** | 0.4 (0.3, 0.6) ** | 0.4 (0.2, 0.5) ** |
| New LLS-AMS | 3.0 (2.1, 4.3) ** | 3.0 (2.1, 4.4) ** | 0.3 (0.2, 0.5) ** | 0.3 (0.2, 0.5) ** |
| Headache | 3.4 (2.4, 4.9) ** | 3.5 (2.4, 5.1) ** | 0.3 (0.2, 0.4) ** | 0.3 (0.2, 0.4) ** |
| Dizziness | 2.3 (1.6, 3.2) ** | 2.3 (1.6, 3.2) ** | 0.2 (0.2, 0.4) ** | 0.2 (0.2, 0.3) ** |
| GI upset | 1.6 (1.0, 2.5) | 1.6 (1.0, 2.5) | 0.9 (0.5, 1.7) | 0.9 (0.5, 1.6) |
| Fatigue | 3.1 (2.2, 4.4) ** | 3.2 (2.2, 4.5) ** | 0.5 (0.4, 0.8) ** | 0.5 (0.4, 0.7) ** |
| Insomnia | 6.4 (4.4, 9.3) ** | 6.5 (4.4, 9.5) ** | 1.6 (1.1, 2.3) * | 1.6 (1.1, 2.4) * |

Values are β /OR (95%CI) p Value; * means p-value <0.05, and **means p-value <0.01; Other abbreviations as in Table 1 and Table 2. Multivariate analysis were adjusted for age, BMI, smoking, nationality, education and plateau history.

Figures

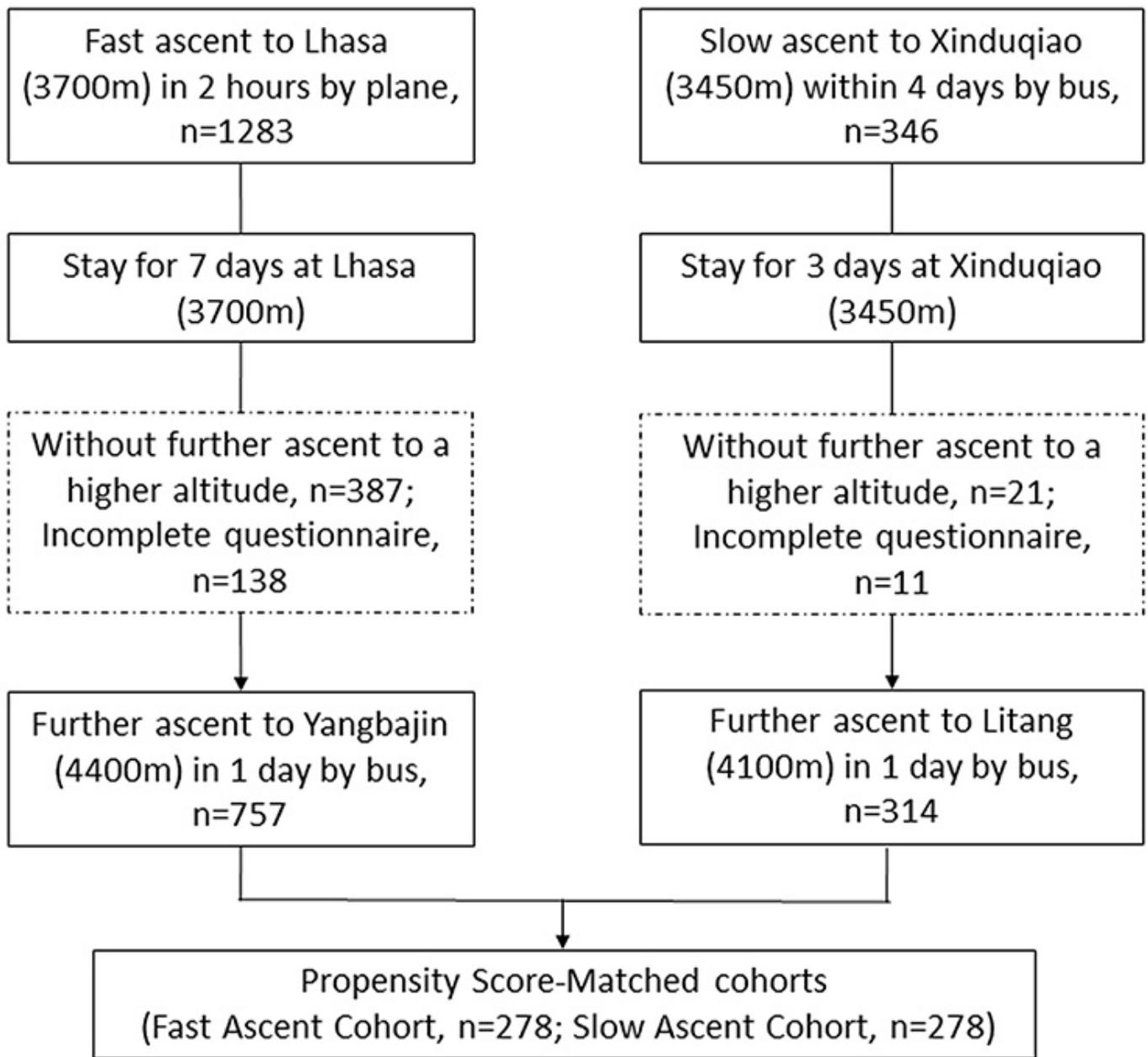


Figure 1

Study flow chart.

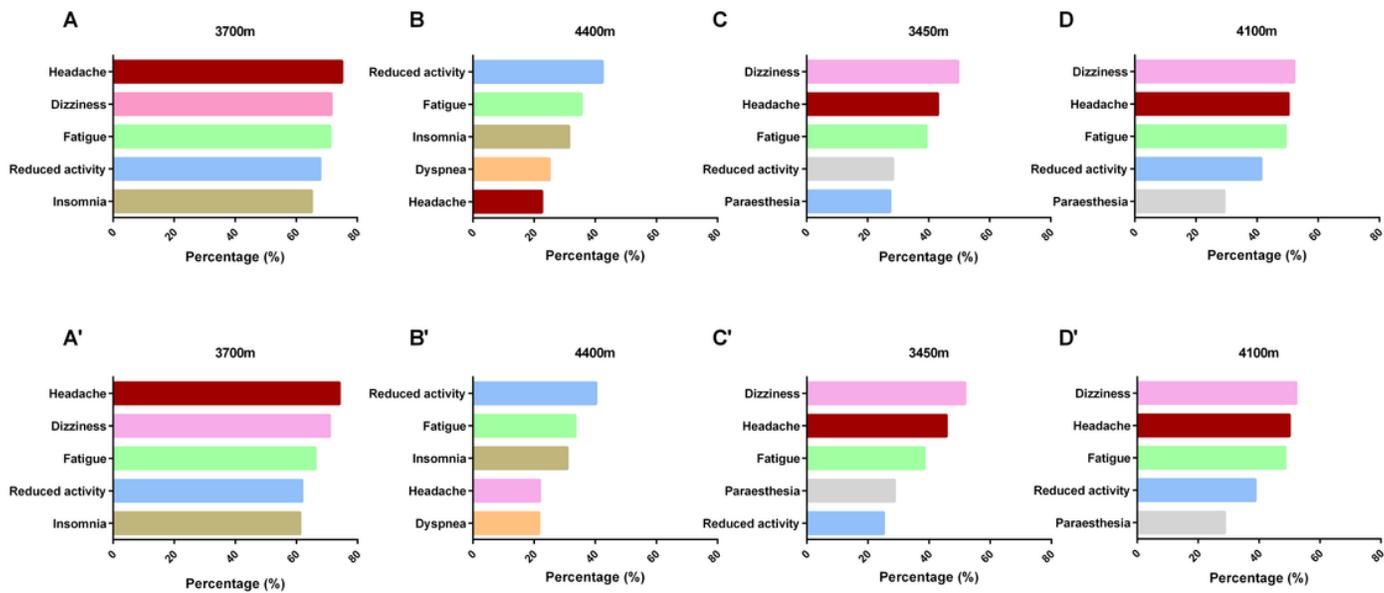


Figure 2

Evolution of the Clinical Symptoms According to the Different High Altitudes in the Entire and Propensity Score-Matched Cohorts. Figure (A-D) showed the ranking five clinical symptoms in the entire cohorts and Figure (A'-D') showed the ranking five clinical symptoms in the propensity score-matched cohort.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementaltables.doc](#)