Aspects of Acute Mountain Sickness among Travellers to Tibet

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SUMMARY

Background

Exposure to a high altitude hypoxic environment may lead to the development of Acute Mountain Sickness (AMS). Previous studies on AMS have primarily focused on physically fit climbers and soldiers in presumably good health. Over the past few decades, all types of people have visited high altitude places for different purposes. Nowadays, Lhasa, Tibet sees visits by a huge number of tourists from all over the world, other visitors like students from lowland China, as well as increasing number of Tibetans descending to lowlands and then re-ascending to high altitude after short or long periods of time. Little is known about AMS and the determinants of AMS among these groups.

Aims

The purpose of the study was to estimate the occurrences and determinants of AMS among ordinary tourists visiting Lhasa. An additional aim was to estimate the incidence of AMS, and address changes in arterial oxygen saturation (SaO_2) and heart rate (HR) in native Tibetans who reascend to Lhasa after a seven-year stay at low altitude, and in Han Chinese students who had previously not been at high altitude. The study also aimed to evaluate associations between AMS and resting SaO_2 and HR levels measured at low altitude and three consecutive days after ascent to high altitude among Han Chinese students who had previously not been at high altitude.

Methods

This thesis consists of one cross-sectional and two cohort studies. The cross-sectional study collected information from 2,385 tourists above the age of 15 years staying at selected hotels in Lhasa. The participants answered questions about the symptoms of AMS based on the Lake Louise Scoring System (LLSS) and potential contributing factors.
The second study followed 859 native Tibetan students who had been studying at seven randomly selected schools in lowland China for seven years. The students had finished their stay in the lowlands and questionnaire information about AMS-related symptoms, resting SaO_2 and HR were assessed before they left the lowlands and on the third day after their arrival in Lhasa. Comparisons were conducted with the population from the third study.

The third study followed 810 Han Chinese students, who had previously not been at high altitude, from the lowlands and three consecutive days after their ascent to high altitude Lhasa. The same date was collected with the same methods in both student studies. In addition, resting SaO_2 and HR were measured on the first and second day after an ascent to Lhasa among the Han Chinese students.

Results

A substantial amount of tourists (36.7 %) visiting Lhasa experience AMS, which often affected their activities. An age below 55 years (adjusted Prevalence Ratio (PR) 1.29, 95% CI 1.04–1.60), a poor or average health condition (adjusted PR 1.63, 95 % CI:1.38–1.93), and a rapid ascent to Lhasa (adjusted PR 1.17, 95 % CI:1.02–1.34) were independent AMS risk factors, while a pre-exposure to high altitude (adjusted PR 0.71, 95 % CI:0.60–0.84) and smoking (adjusted PR 0.75, 95 % CI:0.59–0.96) reduced the risk of AMS.

AMS occurred in only 1.2% (95% CI: 0.4% to 2.0%) of the Tibetan students re-ascending to high altitude by train after having lived seven years at low altitude, compared with 32.7% (95% CI: 28.0% to 37.3%) and 42.9% (95% CI: 38.0% to 47.7%) of the Han Chinese students of a similar age ascending to high altitude for the first time by train and by air, respectively.

Tibetan students had less changes in SaO_2 (-2.95 percentage points, 95% CI: -3.24% to -2.65%) and HR (10.89 beats per minute (bpm), 95% CI: 9.62 bpm to 12.16 bpm) at rest after three days at high altitude compared to Han Chinese students, although the same parameters did not differ between the two groups when measured at low altitude.

Among the Han Chinese students, there was an increasing risk of AMS by decreasing levels of SaO_2, both in the lowlands (risk ratio (RR): 1.16, 95% CI: 1.13-1.20) and on the first day in the highlands (RR: 1.19, 95%CI: 1.15-1.22) per a 1% reduction in SaO_2 level. HR and AMS were only weakly associated at any given point in time. ROC analysis revealed that the model of SaO_2 measurements in lowlands combined with the first day at altitude had the largest area under the curve (AUC) of 80.2%.

Conclusions

The results show that AMS is common among ordinary tourists and Han Chinese students travelling to Lhasa. Healthy Tibetans are mostly protected against AMS, even after a long period of living at low altitude. SaO_2, but not HR levels measured in both the lowlands and highlands were independently associated with the risk of developing AMS.

LIST OF PAPERS

Paper I - Gonggalanzi, Labasangzhu, Nafstad P, Stigum H, Wu T, Haldorsen OD, Ommundsen K and Bjertness E. Acute mountain sickness among tourists visiting the high-altitude city of Lhasa at 3658 m above sea level: a cross-sectional study. *Arch Public Health*. 2016 Jun 1;74:23. doi: 10.1186/s13690-016-0134-z. eCollection 2016.

Paper II - Gonggalanzi, Labasangzhu, Bjertness E, Wu T, Stigum H, Nafstad P. Acute Mountain Sickness, arterial oxygen saturation, and heart rate among Tibetan students who reascend to Lhasa after seven-years at low altitude: a prospective cohort study. Accepted for publication (BMJ Open).

Paper III - Gonggalanzi, Stigum H, Wu T, Bjertness E, Cui C, Nafstad P. Associations between arterial oxygen saturation, heart rate and acute mountain sickness in a population of 17-21 year old Han Chinese students traveling from low altitude to Lhasa at 3,658 m above sea level: a prospective cohort study. Submitted

ABBREVIATIONS

AMS	Acute Mountain Sickness
AMHAD	Acute Mild High Altitude Disease
BBB	Blood-Brain Barrier
BMI	Body Mass Index
bpm	beats per minute
CI	Confidence Interval
CNY	Chinese yuan ren min bi
CSF	Cerebrospinal Fluid
ESQ	Environmental Symptoms Questionnaire
HACE	High Altitude Cerebral Edema
HAMRQ	High Altitude Medical Research Questionnaire
HAPE	High Altitude Pulmonary Edema
HR	Heart Rate
HVR	Hypoxic Ventilatory Response
LLQ	Lake Louise Questionnaire
LLS	Lack Louise Score
LLSS	Lake Louise Scoring System
M	Metre (s)
OR	Odds Ratio
Po_2	Oxygen pressure
PR	Prevalence Ratio
PRC	People's Republic of China
RR	Risk Ratio
SaO_2	Arterial Oxygen Saturation
SPSS	Statistical Package for Social Sciences
TAR	Tibet Autonomous Region
TUMC	Tibet University Medical College

1 INTRODUCTION

1.1 Definition of Acute Mountain Sickness (AMS)

Acute Mountain Sickness (AMS) is an illness caused by acute exposure to a low partial pressure of oxygen at high altitude (1). It is usually presented by a combination of nonspecific symptoms, including headache, fatigue, dizziness, loss of appetite, nausea, vomiting and difficulty sleeping after arrival at high altitudes, but without any abnormal neurological presentation (2). The symptoms typically develop within six to 12 hours after ascent, and generally subside spontaneously within 24 hours after the start of high altitude exposure (2, 3). Most people usually become acclimatized during three-four days of hypoxia exposure, and the symptoms mentioned above may disappear (2, 3). In some serious cases, AMS may progress to life-threatening, high altitude cerebral edema (HACE), which is much less frequent than AMS, but potentially fatal (3). Since the pathophysiology of acute altitude illness is associated with the extravasation of fluid from the space in the brain, lungs and peripheral tissues, some studies found that AMS may also progress to high altitude pulmonary edema (HAPE).

1.2 Altitude and AMS

The high altitude environment consists of hypobaric hypoxia, dry air, low temperature and high cosmic radiation (2). Among them, hypoxia is the major challenge for people living at high altitude (2). As altitude increases, the available amount of oxygen to sustain body alertness decreases with the overall barometric pressure, although the relative percentage of oxygen in the air still contains 21% (4) (Table 1). It is difficult to define a distinct altitude cut off when hypoxia starts to be a substantial challenge to the human body, which might result in an increased risk of, for example, AMS, though for practical reasons, it can be useful to have rough guidelines.

- **High altitude** is 1,500 – 3,500 m above sea level (5), which is where the onset of the physiological effects of diminished inspiratory oxygen pressure (Po_2) starts. This includes decreased exercise performance and increased ventilation (1). Arterial oxygen transport may be slightly impaired and the arterial oxygen saturation (SaO_2) starts to fall, but generally stays above 90% (6). According to

West et al. (7), the lowest altitude at which individuals can develop AMS is as low as 2,000 m (7). At this altitude AMS starts to appear, but is rare, as the occurrence of AMS increases with increasing altitude after a rapid ascent to 2,000 m or more (8).

- **Very high altitude** - At 3,500 – 5,500 m above sea level, the maximum SaO_2 falls below 90% as the arterial Po_2 falls below 60 mmHg, and the occurrence of AMS becomes more common (9). Hypoxaemia may occur during sleep, exercise, and in the presence of some severe altitude illness, such as HACE or HAPE (6).
- **Extreme high altitude** - At 5,500 m above sea level or more (2), marked hypoxaemia, hypocapnia and alkalosis are all characteristic reactions (7). AMS occurs commonly in this range (6), and the progressive deterioration of physiologic function becomes more and more serious. As a result, no permanent human resident lives above 6,000 m (6).

The AMS symptoms typically start occurring within six to 12 hours after ascent, and sometimes even as early as within one hour (3, 10). The symptoms are most prominent after the first night spent at a given altitude, though often disappear over the next two or three days if there is no further increase in altitude (2). An ascent to higher altitude, after acclimatization at a lower altitude, may lead to a further attack of AMS (7). A descent and re-ascent within 10 days does not provoke symptoms, but a descent for more than 10 days renders the individual susceptible to AMS when re-ascending.

Table 1 Changes in barometric pressure and inspired Po_2 with altitude*

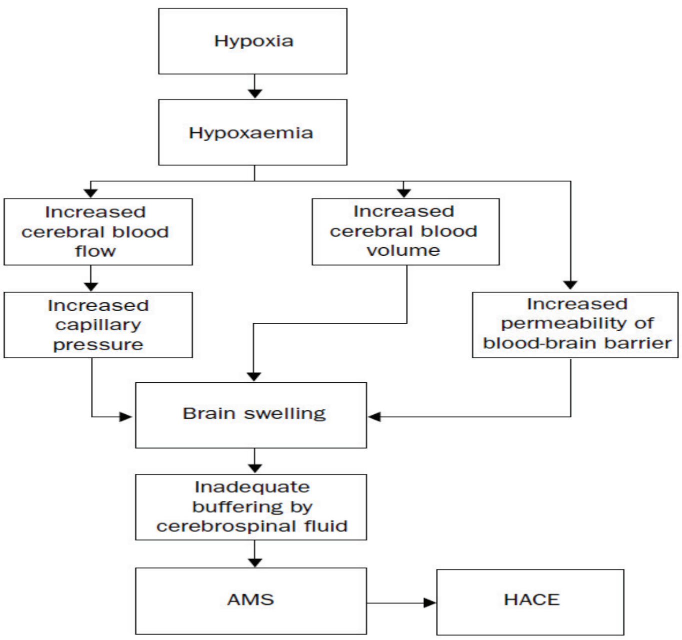
Metres	Feet	Barometric pressure (mmHg)	Inspired Po_2 (% of sea-level)
0	0	149	100%
1,000	3,281	132	89%
2,000	6,562	117	79%
3,000	9,843	103	69%
4,000	13,123	90	60%
5,000	16,404	78	52%
6,000	19,685	67	45%
7,000	22,966	58	39%
8,000	26,247	51	34%
9,000	29,528	42	28%

**Adapted from West JB, High Altitude Medicine and Physiology. 2007.(7).*

1.3 Pathophysiology of AMS

The pathophysiology of AMS is still unclear, although the symptoms and signs of AMS point to the central nervous system as the target organ for the illnesses (2). One current view is that AMS is an early stage of brain swelling, which is more apparent with HACE (2). The swelling is probably due to vasogenic mechanisms, in which brain blood flow, brain blood volume and permeability play a part (3). The essential factor responsible for this condition is hypoxia. Hackett and Roach (11-13) have proposed a pathophysiological model of AMS and HACE (3). According to this model, hypoxia causes hypoxaemia, which refers to a lowered oxygen level in the blood. Hypoxaemia elicits various hemodynamic and neuro-humoral reactions that lead to a rise in the cerebral blood flow, cerebral blood volume (13), and an increase in the vascular permeability of the blood-brain barrier (BBB) (Figure 1). These changes result in brain swelling and a raised intracranial pressure (13). In this model, AMS may occur in subjects who have an inadequate cerebrospinal capacity to buffer the brain swelling, as individuals with a larger ratio of cranial cerebrospinal fluid to brain volume compensate better for brain swelling through the displacement of cerebrospinal fluid, and hence decreased symptoms of AMS (14). This hypothesis may account for the individual susceptibility of AMS, but it still remains speculative (13).

Figure 1 Proposed pathophysiology of AMS and HACE*



**Adapted from Basnyat B, Murdoch DR. High-altitude illness 2003 (3).*

1.4 Assessment of AMS

There are currently no valid biomarkers for the diagnosis of AMS. An assessment of the presence and severity of AMS therefore depends on subjective reports of AMS-related symptoms and the possible quantification of clinical signs by a trained person with a good knowledge of altitude sickness (15-17).

1.4.1 Questionnaire tool for assessing AMS

Currently, two systems for assessing AMS are most commonly used: The Environmental Symptoms Questionnaire (ESQ) (18) and the Lake Louise Scoring System (LLSS) (19)

• Environmental Symptoms Questionnaire (ESQ)

The ESQ was developed in 1979 by Kobrick and Sampson for quantifying environmental stress in general (20), and is now in its third version (ESQ-Ш). This questionnaire has 67 questions, though only 11 are relevant for measuring AMS (Table 2) (18). The answers are graded on a six-point scale from zero (not present) to five (extremely severe) (18). A score called AMS-C (the C stands for cerebral symptoms) is used to calculate whether a person has AMS or not. The AMS-C score requires multiplying the scores by a respective factorial weight, which is then multiplied by five and divided by 25.95 (18). Generally speaking, an AMS-C score of ≥ 0.7 is a recommended criterion to identify subjects as having AMS (18). In addition, a shortened electronic version (ESQ-c) using only 11 questions has been shown to be equally effective as the full version of 67 questions in diagnosing AMS (21).

Table 2 AMS-related Questions of the ESQ-III questionnaire*

1.	I feel lightheaded	7.	I feel weak
2.	I have a headache	8.	I feel sick to my stomach (nauseous)
3.	I feel dizzy	9.	I lost my appetite
4.	I feel faint	10.	I feel sick
5.	My vision is dim	11.	I feel hung over
6.	My coordination is off		

** Source: Dellasanta P. et al., Comparing questionnaires for the assessment of acute mountain sickness. 2007(22).*

• Lake Louise Score System (LLSS)

In 1991, the Lake Louise Questionnaire (LLQ), a briefer and simpler questionnaire compared to previous questionnaires, was proposed at the International Hypoxia

Symposium held at Lake Louise in Alberta, Canada (19). The Lake Louise Score System (LLSS) has been found to be as sensitive as the ESQ in diagnosing persons with AMS, and in correctly identifying those without AMS (2). The LLSS consists of a self-assessment questionnaire, which may be used by itself or in combination with a clinical assessment and a functional score (Table 3) (19). The LLSS part of this scoring system is a five-item self-assessment questionnaire, which quantifies the presence of the most frequent symptoms of AMS (Table 3): headache, fatigue or weakness, gastrointestinal symptoms (loss of appetite, nausea or vomiting), dizziness and difficulty sleeping. Each answer uses a four-point scale from 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe) (19). A complete response will be a total score ranging from a minimum of zero to a maximum of 15 (19). A headache is considered to be a key symptom of AMS according to previous research (23). A total LLSS score of four or more, in addition to the presence of a headache, is considered to be sufficient to categorize persons suffering from AMS (24). The LLSS is validated against clinical assessment, and is now commonly used for diagnosing AMS (25).

There also exits various other criteria for diagnosing AMS by LLSS. Some define AMS as a condition that needs to be presented with a headache and a total LLSS score of 3 or greater (26, 27), while others define AMS as a Lack Louise Score (LLS) >2 (17). Currently, most researchers agree on using headache and a total LLSS score of 4 or greater for the diagnosis of AMS due to reports of a relatively good sensitivity and specificity (24, 28).

Table 3 Lake Louise Score (LLS) for the diagnosis of Acute Mountain Sickness (AMS)*

(a) AMS Self-Assessment. A headache and at least one other symptom and a total score of 4 or more are taken as a diagnosis of AMS. It is suggested that this part of the scoring system is to always be used and reported separately.		
a1. Headache	No headache	0
	Mild headache	1
	Moderate headache	2
	Severe headache, incapacitating	3
a2.Gastrointestinal symptoms	No gastrointestinal symptoms	0
	Poor appetite or nausea	1
	Moderate nausea or vomiting	2
	Severe nausea and vomiting, incapacitating	3
a3. Fatigue and/or weakness	Not tired or weak	0
	Mild fatigue/weakness	1
	Moderate fatigue/weakness	2
	Severe fatigue/weakness, incapacitating	3
a4.Dizziness/light headedness	Not dizzy	0
	Mild dizziness	1
	Moderate dizziness	2
	Severe dizziness, incapacitating	3
a5. Difficulty sleeping	Slept as well as usual	0
	Did not sleep as well as usual	1
	Woke many times, poor night's sleep	2
	Could not sleep at all	3
(b) Clinical Assessment. These questions are answered by a physician or other examiner.		
b1. Change in mental status	No change	0
	Lethargy/lassitude	1
	Disorientated/confused	2
	Stupor/semiconscious	3
	Coma	4
b2. Ataxia(heel/toe walking)	None	0
	Balancing manoeuvres	1
	Steps off the line	2
	Falls down	3
	Unable to stand	4
b3. Peripheral edema	None	0
	One location	1
	Two or more locations	2
(C) Functional Score. An optional question can be either checked by examiner or by a self-report assessment:		
Overall, if you had any of these symptoms, how did they affect your activities?	Not at all	0
	Mild reduction	1
	Moderate reduction	2
	Severe reduction (e.g. bedrest)	3

**Source: Thomas F. Hornbein al., High Altitude: An Exploration of Human Adaptation. 2001(2).*

There also exists other AMS scoring systems such as Hackett's Questionnaire (15) and the Chinese ad hoc "High Altitude Medical Research Questionnaire" (HAMRQ) (29).

• Hackett's Questionnaire

The "Hackett Questionnaire" was developed for the examinations that Hackett carried out in the 1970s with the aim of mapping AMS (15). It consists of a brief interview about headache, vomiting, nausea and dizziness. Besides this information, it includes a medical examination of respiratory rate, edema, lung and ataxia. The presence of AMS is based on combining the results of interview scores and medical examination together (15).

• The Chinese scoring system

The HAMRQ was developed by the Ad-Hoc Committee on High Altitude Illness of the Chinese Medical Association in 1995, with adjustments made at the next conference in 1996 (30). In the Chinese HAMRQ scoring system, "acute mild high altitude disease" (AMHAD) is equivalent to AMS (29). The diagnostic criteria and severity of AMS based on HAMRQ is shown in Table 4. Part (a) shows the questionnaire scoring system used to classify the disease based on the severity of symptoms, while part (b) shows the degree and grade based on the severity of the disease (30). For instance, mild AMS is defined as the presence of a headache or vomiting. If either of those symptoms is absent, a total score between 5 and 10 is required for the diagnosis of mild AMS, with one score assigned for each of the following symptoms: nausea, anorexia, diarrhea, dizziness/light-headedness, palpitation, shortness of breath, chest distress, constipation, dazzling/blurred vision, sleeplessness (insomnia), abdominal distension, cyanosis of the lips, lethargy and numbness of the extremities (29, 30).

Table 4 The Chinese diagnostic criteria and scoring system of Acute Mild High Altitude Disease (AMHAD) *

(a) Acute Mild High Altitude Disease (AMHAD) Scoring System			
Symptoms		Degree	Score
Headache			
	No headache, no suffering expression, no effect on daily activity.	±	1
	Mild headache with suffering expression; obvious improvement of headache after taking regular analgesic medicine; no effect on daily activity.	+	2
	Moderate headache with suffering expression; slight improvement of headache after taking regular analgesic medicine; daily activity is affected.	++	4
	Severe and unbearable headache; lie in bed and cannot get up; no effect of regular analgesic medication.	+++	7
Vomiting			
	Vomiting 1 to 2 times a day; vomit contains only intake food; obvious improvement with regular antivomit medication; no effect on daily activity.	+	2
	Vomiting 3 to 4 times a day; final vomit contains gastric juice; slight improvement with antivomit medication; daily activity is affected.	++	4
	Vomiting more than 5 times a day; must lie in bed and cannot get up; no improvement with regular antivomit medication.	+++	7
Others			
	Dizziness/light-headedness, nausea, palpitation, short breath, chest distress, dazzling/blurred vision, sleeplessness (insomnia), anorexia, abdominal distension, diarrhea, constipation, cyanosis of the lips, lethargy, and numbness of the extremities.	1 point each	

(b) Severity of Acute Mountain Sickness	
Severity	Scoring
Normal (±)	1 to 4
Mild (+)	Headache (+) or vomiting (+) or total score 5 to10
Moderate (++)	Headache (++) or vomiting (++) or total score 11 to 15
Severe (+++)	Headache (+++) or vomiting (+++) or total score >16

**Source: 1. West JB, English Translation of "Nomenclature, Classification, and Diagnostic Criteria of High Altitude Disease in China", 2010.(30); 2. Ren Y, Incidence of high altitude illnesses among unacclimatized persons who acutely ascended to Tibet, 2010. (29).*

1.4.2 Clinical signs which may be related to AMS

There are no clinical signs specific to AMS (2). This makes it more challenging to distinguish AMS from other causes of the same symptoms and signs (2). Changes in body temperature, SaO_2, heart rate (HR), rales or presence of peripheral edema have sometimes been found to be associated with AMS. Maggiorini et al. found a rise in body temperature of 0.5 °C in mild cases and 1.2 °C in severe cases of AMS (31), whereas Loppky et al. found a slight decrease in body temperature with symptoms of AMS (32). SaO_2 values are often lower in subjects with AMS, and in those who will subsequently develop AMS, than those without AMS (33-35). Resting HR has been reported to be higher in subjects with compared to subjects without AMS (36-38). However, the consistency in these observations is not obvious, as some studies did not find such associations (9, 37). The prevalence of rales has been reported to vary between 5% and 23% by different observers (17, 39, 40). Rales may occur in AMS cases (17), but also in non-AMS cases (39). This variability in observations suggests that pulmonary auscultation may be observer-dependent, and that there is no clear relationship between rale and AMS. Edema of the face, wrists and ankles were also found in 18% to 25% of trekkers (39) and mountaineers (17). Nonetheless, one-third of the peripheral edema occurred in non-AMS cases (39). It was also found that the incidence of peripheral edema did not increase with increasing altitude (17). As previously mentioned, AMS is not accompanied by abnormal neurological findings, but if unconsciousness or speech impairment appeared in AMS patient, it may be early signs of the progression from AMS to HACE, since it has been hypothesized both diseases share same pathophysiology, and AMS may appear in an early stage of HACE (2).

1.5 History of AMS

The existence of AMS or AMS-like conditions has been known for centuries (41). As early as 2,000 years ago (32 BC), a Chinese official reported about a place called “Little Headache Mountain” and another called “Great Headache Mountain”, where travellers experienced headache, vomiting and being feverish (2). A vivid description of symptoms of AMS was given in 1604 by Acosta when he was traveling in the Peruvian Andes (42), but the first modern account of AMS was reported by Ravenhill in 1913 (41). He was serving as a medical officer of a mining company in Chile at 4,700 m. The patients he observed were affected by the effect of the altitude (41). He distinguished between three types of illnesses related to acute exposure to high altitude to: ① the normal type, with headache, fatigue, vomiting and insomnia, ② the nervous type, which he thought was a "rare" divergence from the normal with decreased consciousness and ataxia, and ③ the cardiac type with severe dyspnea and rales, which he attributed to heart failure. Today, these three forms of illness correspond quite well with AMS, HACE and HAPE.

1.6 Epidemiology of AMS

1.6.1 Prevalence or incidence?

The terms and concepts of AMS "prevalence" or "incidence" are used interchangeably in AMS-related studies (43). Nevertheless, hardly any researchers discuss which expression is preferable in describing the occurrence of AMS.

Prevalence in epidemiology is the total number of a disease or condition that occurs in a given population during a specific time period (43). It includes cases who already have the disease or condition at the start of a study period, as well as those who acquire it during the time period. Prevalence is further specified into two types relevant for describing the occurrence of AMS according to the study's observation time: the point prevalence and the period prevalence (43). Point prevalence refers to the proportion of a specified population who has the disease or condition at a specific point in time, while period prevalence is the proportion of a specified population who has the disease or condition during a specified period of time (e.g. during a week, during a year or during life) (43).

Incidence is a measure of new cases of the disease or condition in a population over a given period of time (month, year, etc.). The expression incidence is often used, but incidence could be further presented as an incidence proportion or incidence rate (43). Incidence proportion is the proportion of new cases in a population who develops the condition of interest during a specified follow-up time (43). The incidence rate is measured as new cases per the unit time the individuals in the study are under observation.

The relationship between prevalence and incidence depends on the natural history of the conditions or disease being studied (43). For acute diseases like AMS, the incidence or incidence proportion and prevalence as used in this thesis become quite similar.

1.6.2 Occurrences of AMS

The available data shows that the occurrence of AMS seems to vary between 9% and 84% in different studies (17, 44-49). Studies have been carried out at different altitudes in high altitude areas in Europe, America, Asia, New Zealand and Africa (Table 5). It has been difficult to monitor time trends in AMS because of the lack of systematic and standardized criteria for how to measure AMS. However, it has been noted that over the last three decades the increasing awareness of AMS has led to a lower incidence of AMS (50). Nowadays people have started to travel much more than before, and going to altitude is no longer exclusively for climbers and soldiers as shown in Table 5 (3, 48, 50, 51). The consequences this has on AMS occurrence in the population of global travellers are still unclear.

It is generally accepted that the occurrence of AMS primarily depends upon the rate at which people ascend to altitude, the height of the altitude reached and individual susceptibility. For instances, trekkers in the Himalaya region of Nepal (52) appear to have a slower rate of ascent and a lower prevalence of AMS compared to those who have climbed Kilimanjaro, where conditions favour a more rapid ascent rate (53). In climbers ascending to very high altitudes, the differences of a few days in acclimatization can have a significant impact on the prevalence of AMS, the severity of symptoms and mountaineering success (54). Vardy et al. found that the prevalence of AMS among trekkers in Nepal ranged from 10% at 3,000–4,000 m, to 51% at 4,500–5,000 m (52), This is similar to what Maggiorini et al. reported among climbers in the Alps (from 9% at 2,850 m to 53% at 4,559 m) (17). The differences in the definitions of AMS limit the comparisons between studies. For example, it is difficult to compare the incidence of AMS among Chinese soldiers (57%) (29) travelling to 3,600 m by plane with tourists who flew to 3,740 m in Nepal (45), because the former study used the Chinese standard while the latter study used LLSS to diagnose AMS. Even studies that used the LLSS to estimate the presence of AMS have used different symptom cut-off points (17, 28). Since there are variations in scoring systems and cut-off points between previous studies (18, 19, 22, 55, 56), comparisons between studies should take all of these inequalities into account. These are some of the factors that make comparisons of AMS occurrence between studies difficult.

Table 5 The occurrence of acute mountain sickness (AMS) at main high altitude areas in the world

Location	Altitude (m)	Population	Ascent time	AMS occurrence (%)
Rocky Mountains, Colorado, USA (44)	1,920-2,957	Tourists	1-3 days	25
Swiss Alps (17)	2,850	Climbers	2-3 days	9
Swiss Alps (17)	3,050	Climbers	2-3 days	13
Swiss Alps (17)	3,650	Climbers	2-3 days	34
Swiss Alps (17)	4,559	Climbers	2-3 days	53
Nepal Himalaya (52)	3,000-5,500	Trekkers	10-13 days	23
Putre, Chile (57)	3,550	Soldiers	4 days	60
Nepal Himalaya	3,740	Tourists	2 days	84
Tibet, China (29)	3,600	Soldiers	14 days	57
Mt, Jade Taiwan (47)	3,952	Trekkers	1-2 days	28
Mt Rainier, USA (48)	4,394	Climbers	1-2 days	67-77
Tibet, China (58)	4,719	Tourists	1 day	42.3
Mt. Kilimanjaro, Tanzania (53)	5,895	Trekkers	6 days	75
Denali, Alaska, USA (48)	6,194	Climbers	3-7 days	30
Mt. Aconcagua, Argentina (59)	6,962	Climbers	5-10 days	39

1.6.3 Determinants of AMS

The occurrence of AMS mainly depends on the rate of ascent, the absolute altitude reached, individual susceptibility and previous acclimatization, while other factors like gender, age, general states of health and obesity have been found in some studies to be associated with the risk of developing AMS.

1.6.3.1 Altitude

Previous studies among climbers in Nepal (52) and the Alps (42), tourists in Colorado (44) and workers in Tibet (27) support the idea that the incidence of AMS increases with altitude. For example, the incidence of AMS was reported to be 10% for an ascent to between 3,000–4,000 m, 15% between 4,000–4,500 m, 51% between 4,500–5,000 m in the Nepali Himalayas (52), 6.9% at 2,200 m, 9.1% at 2,500 m, 17.4% at 2,800 m and 38.0% at 3,500 m in the Eastern Alps (28). Since hypoxia is the primary trigger for the development of AMS, it is not surprising to see that the incidence of AMS increases with altitude (Table 5).

1.6.3.2 Ascent rate

Murdoch and colleagues found the incidence of AMS to be 84% among tourists who flew directly to Shyangboche at an altitude of 3,740 m, and 61% among those who walked up from altitudes under 3000m to the same altitude (45). Hackett and Rennie found that at an altitude of 4,243 m at Pheriche Nepal, the trekkers who flew to the airstrip at Lukla at an altitude of 2,800 m, and then proceeded on foot to Pheriche had a higher incidence of AMS than those who travelled by land all the way from Kathmandu at 1,300 m (49% vs. 31%) (39). Different types of ascent rate clearly seem to have an effect on the development of AMS. A rapid ascent to high altitude was observed as a risk factor for the development and severity of AMS in several previous studies (3, 4, 52), as individuals need a sufficient amount of time to acclimatize to the hyperbaric hypoxic environment at high altitude (6, 8). A slow ascent rate and a graded ascent would be preferable for high altitude acclimatization and reducing the risk of AMS (60).

1.6.3.3 Previous experience at high altitude

Some studies reported that there is no relationship between previous exposure to high altitude and AMS (15, 39), whereas others indicate that a history of exposure to high altitude can offer some protective benefit against AMS (44, 59, 61, 62). For example, Richalet and colleagues found the symptoms of mild AMS and sleep disturbances were seen at every repetitive exposure to high altitude among Chilean miners (63), while Lyons and colleagues found a reduction in the incidence of AMS in a group of subjects who had previously been exposed to high altitude compared with a group without altitude exposure (64). Hultgren and colleagues found that climbers who visited the Himalayas annually had fewer symptoms and a better physical performance on later visits compared to what they experienced during their first visit (65).

1.6.3.4 Individual susceptibility of AMS

The individual susceptibility appears to be reproducible as indicated by the recurrence of AMS (1, 61). Not all studies have found in favour of this (15, 39). Studies indicate large variation in the individual's susceptibility to AMS (4, 50, 66). Wu et al. reported on AMS incidence among lowland construction workers who repeatedly spent seven-month periods at high altitude to work on the Qinghai-Tibet railroad each year from 2001 to 2005 (38). Some construction workers developed AMS more than twice while others were rarely or never affected, some had symptoms on the first day and others on day five to seven over the five-year follow-up (38). In spite of substantial research activity over more than 100 years, it is not clear which particular pathophysiological features are related to individual susceptibility to AMS (2).

1.6.3.5 Health condition

The impact of health condition on the development of AMS is unclear (2, 49). A finding from mountaineers in the Alps (67) and trekkers in Nepal (68) supported no relationship between fitness and the subsequent development of AMS. Cymerman and colleagues even reported an increased AMS prevalence in people with a greater baseline aerobic fitness (69). In contrast, other studies have shown that a good physical condition before entering a high altitude area increases a person's tolerance to altitude symptoms (8, 70). Conference attendees who reported themselves in poor physical condition were twice as likely to get AMS compared to those who considered themselves to be fit (44). Ri-Li and colleagues (71) found obese individuals to be more susceptible to AMS, probably because excess weight is more frequently associated with hypoventilation, sleep apnea and increased oxygen consumption (72). Additionally, some pre-existing illnesses such as heart failure, upper gastrointestinal tract bleeding and infection may be exacerbated by exposure to high altitude (61, 73, 74), but there is no evidence that the underlying diseases such as coronary artery disease, diabetes mellitus or asthma increase the risk of AMS following ascent, although it is probably prudent to avoid highly strenuous exercise (73). The advice for patients with lung disease depends on the severity of the disease, activity level and anticipated altitude.

1.6.3.6 Age

Previous studies have reported that older subjects do not appear to have an increased risk of AMS (52, 54). In fact, people older than 40–60 years tend to develop AMS less often than younger adults (15, 44, 75). These findings were confirmed in a group of visitors with a mean age of 69.8 years, who had an incidence of AMS of 16% at 2,500 m (75) compared to an incidence of 27% in a population with a mean age of 44 years at a similar altitude (76). In contrast, other studies found no influence of age on AMS (72). At the other end of the age spectrum, children and young adults (<40 years) appear to have a similar incidence and severity of AMS (77, 78). It has been reported that children between the age of 9-14 years who attended summer camp at 2,835 m (79) had a similar incidence (28%) of AMS to adults going to comparable altitudes (25%) (44).

1.6.3.7 Gender

Reports on the effect of gender on AMS have been mixed and inconclusive (10, 62). Many studies showed no difference in the development of AMS between males and females (15, 44). It has been reported that 51% of male trekkers climbing to Everest experienced AMS compared to 53% in female trekkers (15). Some studies found an increased susceptibility of AMS in women (68, 80). On the other hand, some studies found less AMS in women than in men (75, 81, 82). The reasons for these apparent differences in the prevalence of AMS groups are not clear.

1.6.3.8 Ethnicity

The term "high altitude acclimatization" refers to the process whereby lowlanders respond to changes in hypoxia in a short-term exposure to high altitude. These changes are seen as beneficial, as opposed to changes that result in illness (83). Compared to acclimatization among lowlanders occurring in a short-term physiological response to a hypoxia environment, the "high altitude adaptation" among highlanders is irreversible, including long-term physiological responses to high altitude hypobaric hypoxic environments of natural selection with heritable behavioural and genetic changes (83). Adaptation is defined by evolutionary biology as a feature of a function, structure or behaviour that enables humans to live and reproduce in a high altitude environment (83).

It is known that Tibetans have a better adaptation than any other ethnicities living at similar altitudes (83). It has been reported that Tibetan railway construction workers (27) and mountaineers (83) were resistant to AMS, and have a greater work capacity than other ethnicities. Sherpas, who are mainly of Tibetan origin in the Himalayas, are also renowned for reaching the summit of Everest on many occasions (83). The Sherpas appear completely free from AMS when moving from low to high altitudes (83). Other high altitude indigenous populations like the Ayamara and Quecha Indians have shown better adaptation than European/North American migrants in the high altitude area of the Andes, but data on AMS is lacking (84-86). These differences are likely to be affected by genetic components. However, no specific genetic differences have yet been identified for AMS.

1.6.3.9 Smoking

Many epidemiological studies of high altitude illness have limited data regarding the effects of smoking on the development of AMS (17, 24, 47). Wu et al. (87) found a 11%

decrease in the prevalence of AMS in smokers compared with nonsmokers. Another study by Song et al. (88) found that smokers had less AMS compared with non-smokers. In contrast, some studies on tourists (50) and climbers (61) did not find any relationship between AMS and smoking habits. Vinnikov and colleagues even reported that smoking increased the risk of AMS (89). Moreover, Lindgarde et al. reported that a combination of smoking and alcohol impeded altitude acclimatization, but they did not report the occurrence of AMS (90). However, smoking is generally considered harmful to one's health, and may reduce long-term adaptation to high altitude (87).

1.6.4 Arterial oxygen saturation, heart rate and AMS

Many studies have tried to look for ways to predict AMS by observing some physiological parameters such as hypoxic ventilatory response (HVR) (91, 92), end-expiratory Po_2 (93), gag reflex and a short breath-holding time (94). However, there is no consistent agreement on the usefulness of these tests (33). Since hypoxia is central for the development of AMS (Figure 1) (9, 33), and sympathetic activation is a primarily response to hypoxia (95, 96), it seems reasonable to monitor SaO_2 and HR for impending AMS. Even so, different studies focusing on correlations between SaO_2 and HR and AMS report inconsistent results (9, 33, 96, 97).

Oxygen is the basis of life activities, as each part of the human metabolism needs oxygen to function (98). Due to the reduced atmospheric pressure with increasing altitude, the partial pressure of inspired oxygen in the lungs, and therefore SaO_2, is reduced (98). The resulting lower SaO_2 level in tissue is regarded as a primary starting mechanism in the development of AMS in healthy persons (9, 99). A number of studies found a correlation between SaO_2 and AMS after an ascent to high altitude (9, 33, 35, 100). This was recently strengthened by a meta-analysis (101), but it was suggested that further studies of the SaO_2 as an indicator for AMS are required to confirm its efficacy and reproducibility. By contrast, other studies did not find any association between SaO_2 and AMS (37, 97). Thus far, previous studies have addressed this issue in selected populations like climbers, and most often after exposure to high altitude, while the relationship between AMS and SaO_2 measurements from before altitude exposure has seldom been addressed (Table 6). Several studies have shown an increased sympathetic activity and a reduction in parasympathetic activity during acute exposure to high altitude, which refers to an early response to a hypoxic environment (95, 102-104). This effect was also shown in a hypobaric chamber study at 5,000 m (105) and in mountaineers at 2,700 m and 3,700 m (106). HR reflects sympathetic and parasympathetic cardiac autonomic nervous system regulation (96). There is also some evidence that subjects with a high resting HR after arrival to high altitude more easily develop AMS (37, 38, 107), though other studies did not support this conclusion (9, 33). Table 6 shows the cautious conclusion between SaO_2, HR and AMS derived from overviews by Guo (101) and by Song (108).

Table 6 characteristics of the selected studies dealing with the SaO_2, HR and AMS susceptibility.

First author	Year	Maximum altitude (m)	Subjects	SaO_2 and AMS	HR and AMS
Roach (100)	1998	6,194	Climbers	Related	---
Burtscher (35)	2004	3,659	Mountaineers	Related	---
Saito (104)	2005	3,456	Trekkers	Not related	---
Tian (109)	2008	3,700	Healthy subjects	---	Related
Dyer (110)	2008	4,200	Healthy subjects	Not related	---
Fagenholz (111)	2009	4,240	Travellers	Related	Weak association
Koehlea (112)	2010	4,380	Patient population	Related	Not related
Huang (113)	2010	3,440	Healthy subjects	Not related	Related
Karinen (33)	2010	5,300	Climbers	Related	Not related
Johnson (114)	2010	3,800	Healthy subjects	Related	---
Chen (97)	2012	3,952	Trekkers	Not related	Not related
Wagner (115)	2012	5,640	Climbers	Not related	Not related
Major (116)	2012	5,200	Healthy subjects	Related	Related
Faulhaber (9)	2014	4,500	Healthy subjects	Related	Not related

1.7 Treatment of AMS

It often seems that a short rest and a stop of the ascent will significantly resolve mild AMS symptoms (3, 4). If the symptoms continue or get worse, supplemental oxygen and a descent is recommended (61). Moderate to severe symptoms may require symptomatic treatment with medication such as acetazolamide (trade name Diamox), dexamethasone and analgesics (5). Acetazolamide is the only medication approved by the US Food and Drug Administration (FDA) for preventing and ameliorating AMS, although there is still debate regarding the optimal dose (5). A reasonable prescription for prevention is 125 mg twice a day prior to ascent, and continuing for two days after arrival at a maximal altitude or until a descent is initiated; if the ascent is rapid, 250 mg twice a day may be more effective (5). In children, the recommended dose is 2.5 mg/kg every 12 hours with a maximum dose of 250 mg (117), while treatment for 48 hours is usually sufficient for the resolution of AMS symptoms (77). Acetazolamide is a sulfonamide drug, so patients with known allergies to sulfa should avoid acetazolamide (5). Dexamethasone is recommended only when a descent is impossible, and it is also effective as an emergency treatment for AMS with an initial dose of 4 –10 mg, followed by 4 mg every six hours (118-120). Acetaminophen and non-steroid anti-inflammatory drugs such as aspirin and ibuprofen are often effective in relieving the symptoms of headache and gastrointestinal upset associated with AMS (121, 122). Although some herbal supplements such as Ginkgo biloba, Coca leaf and Rhodiola species products are widely used to prevent AMS, most studies have not found any effect on these herbs exist (123-126). AMS patients must therefore be carefully monitored to avoid further progress to HACE or HAPE (5).

1.8 Prevention of AMS

The best way to prevent AMS is a slow ascent, which gives the body time to acclimatize to the hypoxic conditions (48). Doing only mild exercise for the first few hours after arrival at high altitude has also been suggested (48), as different people will acclimatize at different rates (48). The process of acclimatization to high altitude usually takes three–five days (48); therefore, acclimatizing for a few days at 2,500 m - 2,750 m before ascending to a higher altitude is ideal (127). A general recommendation about the speed of ascent is that after an ascent to 3,000 m, sleeping altitude should not be extended by more than 300 to 600 m per night, and one should take a rest day for every 1,000 m of ascent (48). A copious intake of water for hydration and nutritious food for energy has also been suggested (48). A history of previous AMS is considered as a indicator for repeated problems during subsequent exposure to similar altitudes at a similar ascent rate (5). Alcohol tends to cause dehydration and exacerbates AMS (48). Hence, it is recommended to avoid taking an alcoholic beverage in the first few hours after arrival at a high altitude (5). As previously mentioned, medication treatment may also be used as a prophylaxis against AMS.

1.9 AMS in Tibet

Several studies on AMS have been conducted in Tibet (29, 38, 58). For example, Wu et al. reported an AMS incidence of 31% in Han Chinese passengers travelling on the Qinghai-Tibet railroad (128). However, this study was only conducted during the travel and without any follow-up after arrival in Lhasa. A study on tourists conducted in 2008 at the Namtso Lake Tour Zone (4,718 m) reported that AMS occurred in 42.3% of 310 Han Chinese on a one-day trip to the lake (58). The study only included Han Chinese tourists during a one-day travel, though without the possibility to include sleeping disorder symptoms. So far, no AMS research has been conducted among ordinary tourists. Moreover, Ren et al. reported that the incidence of mild AMS in Han Chinese soldiers was 57.2% (29). Wu et al. reported that the overall incidence of AMS was 51% on initial exposure to high altitude among construction workers on the Qinghai-Tibet railway route (73). He also reported that due to altitude, health problems and other reasons, several workers withdrew from their position due to altitude-related health problems, and were replaced by new workers each year (38).

1.10 AMS and modernization

Over the past few decades, with a rapid economic development in many places around the world, the population ascending to the high altitude has changed and increased dramatically as new groups of individuals have started to travel to high altitudes. In Tibet, particularly with the completion of the Qinghai-Tibet Railroad in 2006, tourism from domestic China and abroad has increased remarkably (129, 130). Lhasa is the major destination for tourists from all over the world. Tourists who go there are no longer simply well-prepared physically fit climbers, workers and soldiers as previous studies indicate (24, 27, 29, 51). All types of individuals, including people of all ages and with different health conditions and levels of physical fitness, are visiting Lhasa for different purposes. Besides tourists, more and more lowland workers and students go to Tibet as well. In particular, there are a number of Han Chinese students who annually ascend to Tibet for continuing their education at Tibet University. Nearly half of them travel to Tibet by air, with most of the rest arriving by train. Using both a plane and train create a relatively rapid ascent, and

AMS-related illnesses may occur. The development of visitors has made AMS a public health concern in Tibet nowadays. At the same time, more and more Tibetans (highlanders) descend to the lowlands for entertainment, work and education for short or long periods of time and then reascend to Tibet. The changes in the population going high took place during a time when different forms of transportation have also changed, and the ascent to high altitude has become more rapid compared to the past when it was often done by foot or rather slow motor vehicles. Little is known about AMS among the new groups of travellers to high altitude Tibet. Furthermore, no study has actually addressed the acute reactions to altitude among groups like ordinary tourists, Han Chinese students and Tibetans re-ascending to high altitude after being exposed to low altitudes for a long time.

2 AIMS AND OBJECTIVES

The main aim of the current thesis is to investigate the occurrence and determinants of AMS among groups of travellers to Lhasa.

Specific objectives

- To investigate the occurrence and determinants of acute mountain sickness among ordinary tourists visiting the high altitude city of Lhasa at 3,658 m above sea level.

- To investigate the occurrence of acute mountain sickness and address the changes in SaO_2 and HR in native Tibetans who reascend to the high altitude city of Lhasa (3,658 m) after a seven-year stay at low altitude.

- To investigate the occurrence of acute mountain sickness and the association between AMS and resting SaO_2 and HR levels measured at low altitude and three consecutive days after ascent to high altitude in a population of students with no previous experience at high altitude.

3 MATERIALS AND METHODS

3.1 Study area

3. 1.1 General information about Tibet and Lhasa

Tibet is dubbed the “Roof of the World”, with an average elevation of more than 4,000 metres (131). Lhasa is the capital of the Tibet Autonomous Region (TAR), People’s Republic of China, situated at an elevation approximately 3,658 m above sea level. In the Tibetan language, Lhasa means the Holy Land or the Buddha Land. This ancient sprawling city was settled 1,300 years ago (132), and is the centre of Tibet’s economy, culture, politics, transport and religious activities. Lhasa has recently become the major destination for what one could call “ordinary” travellers, including all types of tourists, soldiers, workers and students.

3.1.2 Main connections with its surroundings

Historically, Tibet has been quite isolated, mainly because of its high altitude and remoteness, which is probably an important reason for why up to now there has been an aura of mysticism around the area. Pack animals were the primary mode of transportation in the old days, and travelling to Tibet was strenuous and took time. Today, travelling to Tibet has become much easier, and has become more and more comparable to travelling to other places, even if Tibet’s remoteness still makes it special. Today, one can travel to Tibet by plane, railway and car/bus.

3.1.2.1 By air

The fastest and most used transportation to Tibet is by plane. The Lhasa Gongga airport operates flights from several domestic cities, such as Chengdu (506 m), Chongqing (259 m), Beijing (32 m), Guangzhou (41 m), Shanghai (5 m), Xian (397 m), Xining (2260 m), Hangzhou (42 m), Changsha (45m), Nanjing (9 m), Tianjin (5 m), Shijiazhuang (81 m), Lanzhou (1517 m), Zhenzhou (110 m), Guiyang (1100 m), Kunming (1891 m), Fuzhou (84 m) and for international flights from Kathmandu, Nepal (1,300 m). All these flights take about two to three hours with a cabin pressure equivalent to 2,400 m from a lowland departure to the highland destination of Lhasa. The rapid ascent to Lhasa also opens for the possibility for more travellers to quickly continue to even higher altitudes with further challenges to high altitude acclimatization.

3.1.2.2 By train

The Qinghai-Tibet railway opened in 2006, and has become a popular way of travelling to Lhasa. Trains to Lhasa go from Xining to Glomud (10 hours, average altitude 2,906 m, range 2,261m-3,698 m) and from Glomud to Lhasa (14 hours, average altitude 4,251 m, range 2,808 m-5,072 m) (128). All train carriages are outfitted with an oxygen supply from a molecular sieve system. Even though the windows are sealed, the opening of doors at the intermediary railway stations will inevitably lead to some oxygen loss (128). This means that travelling by this route will result in more high altitude exposure than by plane, but the travel time is quite short.

3.1.2.3 By road

In modern time, travelling to Tibet by road has become an interesting option because it is an authentic way to explore Tibet, since it takes more time compared to both plane and train. It also means that it allows the body to acclimatize to high altitude. The two major highway routes to Tibet are:

- **Qinghai-Tibet Highway (Xining-Golmud-Lhasa)**: This road is approximately 2,000 km long, with an average altitude over 4,000 m that primarily follows the Qinghai-Tibet Railway. It is considered to be the safest and shortest highway to Tibet.
- **Sichuan-Tibet Highway (Chengdu-Lhasa):** The road begins in Chengdu in Sichuan and ends at Lhasa in Tibet, and is approximately 2,000 km long.

There are also several other possible road connections between Lhasa and its surroundings, including the spectacular Friendship Highway connecting Kathmandu Nepal with Lhasa Tibet.

3.1.3 Travellers in study area

3.1.3.1 Tourist in Tibet

Tibet has become a world-famous tourist destination. Lhasa is home to a great number of religious, cultural and historical sites, which makes it a huge magnet for numerous tourists from all over the world. In earlier times, climbers, trekkers and hikers comprised the majority of tourists coming to Tibet. Now this has changed. As mentioned before, with the improvement of transportation, visits by ordinary tourists have also increased dramatically. According to the National Bureau of Statistics of China, the number of tourists from domestic China and abroad to Tibet has increased remarkably, from 2.5 million in 2006 to more than 20 million visitors in 2015 (129). Tourism revenue accounted for over 28.19 billion Chinese yuan ren min bi (CNY) in Tibet in 2015 (129) (Table 7).

Table 7 Number of tourists, tourism income in Tibet from 2006 to 2015.

Year	Number of tourists in Tibet (millions)	Tourism revenue in Tibet (billions CNY*)
2006	2.51	2.77
2007	4.02	4.85
2008	2.24	2.25
2009	5.61	5.59
2010	6.85	7.14
2011	8.69	9.72
2012	10.58	12.64
2013	12.91	16.53
2014	15.53	20.43
2015	20.17	28.19

**CNY:Chinese yuan ren min bi*

3.1.3.2 Non-tourist visitors in Tibet

Over the past few decades, economic development, human boundaries and activities have gradually been extended between high altitude and low altitude. Many go to Tibet for business, and many workers and soldiers from inland China work in Tibet every year. Moreover, Tibet University has qualified as a part of "Universities of National 211 Project", and a number of students from inland China travel every autumn to Tibet for educational purposes.

3.1.3.3 Tibetans re-ascending to Tibet after a stay in the lowlands

Up until now Tibet has from several perspectives a lower economic and educational level compared to some of the other provinces or regions in the area. Therefore, many Tibetans have gone to lowland China to work or study. Workers' stays outside Tibet has until now usually been of a short duration, while students often stay in the lowland for relatively long time periods. There are several educational institutes in lowland China that train Tibetan students. The Tibetan student population who attended middle school in lowland China has provided a unique opportunity to study how Tibetans maintain their adaptation to high altitude. The number of Tibetans going to work or to study in lowland China is expected to increase in the future (132).

3.2 Study populations and study designs

This thesis is based on observations from three different study populations representing important groups of travellers to Lhasa Tibet: The general tourist population (tourist study) visiting Lhasa represented by a sample of ordinary tourists above 15 years visiting Lhasa, Tibetans re-ascending to Lhasa (Tibetan study) represented by a sample of 17-21 year old Tibetan students re-ascending to Lhasa after studying in the lowlands for seven years and the non-tourist visitors represented by a sample of 17-21 year old Han Chinese students (Han Chinese study) travelling to Lhasa to continue their education there. The first study has a cross-sectional design, while the other two have a cohort approach, following the populations from the lowlands and during their first days at altitude.

3.2.1 Tourist study

3.2.1.1 Sample size

We established the needed sample size based on prevalence from previous similar studies of AMS, reported to be 42.3% among tourists in the Namtso tour zone (58); the sample size in the tourists population was calculated according to the following formula:

$$N = \frac{t^2 P \times Q}{d^2}$$

N is the sample size; P is prevalence (Prevalence of AMS from the previous study); 1.96 is the Z score corresponding to the 95% level of confidence; Q=1-P, d is the allowance error of known prevalence:

t=1.96 P= 0.423 Q= 1-P= 0.577 d=0.1P

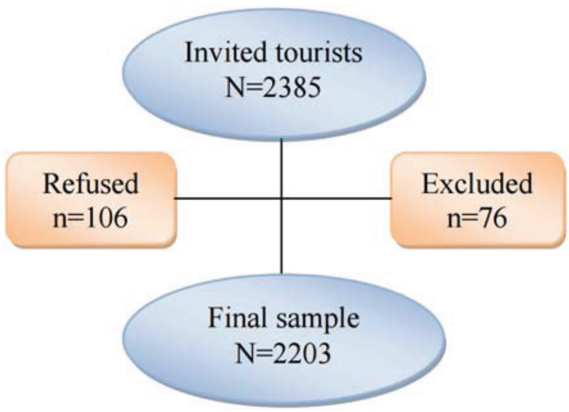
$$N = \frac{1.96^2 \times 0.423 \times (1-0.423)}{0.0423^2} = \frac{3.8416 \times 0.423 \times 0.577}{0.00179} \approx 524(\text{people})$$

Considering the non-response rate, and speculating that it would be 20%: 524 ×0.2≈ 105. Therefore, the present study sample size should preferably be increased to 629 tourists. We have included 2,203 tourists in the final data collection which also allowed for sub-group analyses.

3.2.1.2 Study population

The tourist study was conducted in Lhasa City. Nine hotels were randomly selected from a list of all hotels in Lhasa, which was provided by the local bureau of tourism. When the data collection was about to start, two of the hotels refused to participate. Thus, 2,385 tourists older than 15 years of age from seven randomly selected hotels were invited to participate between 2 June to 31 October 2010. Of the 2,385 invited tourists, 106 refused to participate and 76 were excluded due to incomplete questionnaire information, an age below 15 years or a non-tourist status, thereby leaving 2,203 (92.4 %) participants for the analyses.

Figure 2 The flow chart for the tourist study population



3.2.1.3 Inclusion criteria

- Tourists checked in at the selected hotels between 2 June and 31 October 2010 during periods when a select group of receptionists were working in the reception area.
- Age above 15 years.

3.2.1.4 Data collection

When arriving at the hotel, tourists were informed about the study and asked if they were willing to participate. Tourists received an anonymous questionnaire and instructions about how to fill in information and return the questionnaire to the receptionists before leaving the hotel. The procedure for returning the questionnaire depended on the duration of the tourist's stay in the hotel. This meant that the questionnaire should be returned on the third day after their arrival, or on the day when they checked out if they planned to stay two nights or less. Eight students from Tibet University Medical College (TUMC), and one to two receptionists from each of the selected hotels, assisted in the data collection. All of them were trained in how to distribute and collect questionnaires. A teacher from TUMC supervised them during the entire data collection period.

• Questionnaire information

An English and Chinese questionnaire based on the Lake Louise-AMS scoring system was developed. The English version of the AMS questions was identical to the one originally devised by the LLSS. We also used a Chinese version of the questionnaire based on the original LLSS questionnaire. Before the Chinese version of the questionnaire was used in the study, we translated the questions back into English, which coincided with the original English version.

The questionnaire consisted of eight main parts. Part I covered background information like gender, age, education, nationality, height, weight, and altitude of permanent residence, Part II information about travel schedule etc. and pre-exposure to high altitude. Part III consisted of the core questions regarding AMS (For details, see Table 3). If participants did not have any of the symptoms to report in Part III, they might skip Part IV and V, which included questions about the consequences if they experiences AMS-problems. Part VI included questions about the participants health status. Part VII about intake of prophylactic medicine etc., fluid, pain-relieving medication, and Part VIII questions about prior awareness of AMS and pre-experience of AMS symptoms.

Definition of AMS: As introduced early in the thesis, the definition of AMS (Table 3) is based on five basic symptoms, which include: headache, fatigue and/or weakness, gastrointestinal symptoms, dizziness/light headedness, difficulty in sleeping or insomnia. Each symptom was graded from 0 to 3 based on intensity levels of none, mild, moderate and severe symptoms, respectively. The diagnosis of AMS was defined as follows: 1) Presence of headache; 2) Presence of at least one other symptom (fatigue and/or weakness, gastrointestinal symptoms, dizziness/light headedness, difficulty sleeping), and 3) A total score of four or more.

3.2.2 Tibetan study

The Tibetan students' data collection was carried out in 2012. For a better understanding of high altitude adaptation among Tibetans, a population of well-matched Han Chinese students from the same lowland area going to Tibet University in 2014 to continue their education was used for comparison. The detail data collection procedure is presented later in the thesis (The Han Chinese Study).

The Tibetan students were recruited in seven cities in lowland China seven days before their departure to Lhasa and followed until the third day after their ascent to Lhasa. The seven lowland cities were: Nantong 5 m, Tianjin 5 m, Wuhan 23 m, Beijing 32 m, Yueyang 57 m, Shijiazhuang 81 m and Chengdu 506 m. The cities were chosen because they all had the educational institutions with Tibetan students planning to go home after finishing their seven years high school education, and with Han Chinese students graduating from high school and planning to go to Lhasa to continue their college education.

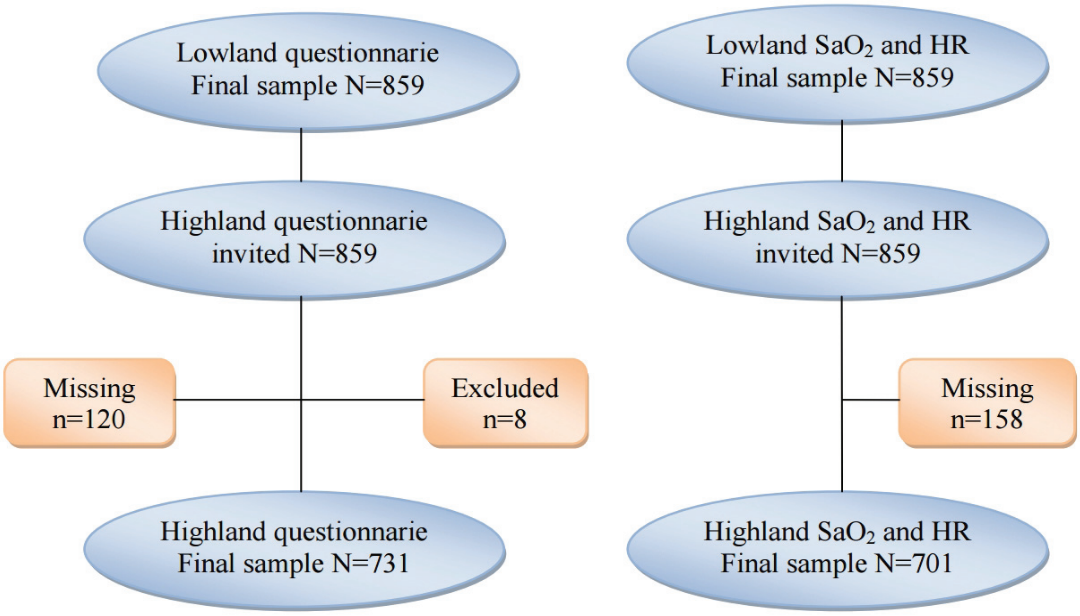
3.2.2.1 Sample size

Previous studies have reported that the occurrence of AMS was zero among Tibetan construction workers (38), train passengers (128) and mountaineers (83). Using the same formula as in the tourist study, speculating that the minimum occurrence of AMS among Tibetans was 5%, and applying the allowance error of 0.4, the sample size calculation results was 456, while if assuming the occurrence of AMS was 10%, the sample size calculation results were even smaller at 216. If considering that the non-response rate (assumption of a 5% AMS occurrence) was 20%, e.g. $456 \times 0.2 \approx 91$, the Tibetan study sample size should be increased to 547. The current Tibetan study has included 859 students in the final data collection, which was large enough to observe the AMS in Tibetan students. Compared to Tibetan students, all Han Chinese students (810) who were admitted to Tibet University and were from the same cities as Tibetan students were invited to participate in the Han Chinese study.

3.2.2.2 Study population

In total, 859 Native Tibetan students aged 17-21 from seven (out of 12) randomly selected high schools for Tibetans in lowland China were invited to participate in the study. The data collection took place from May to June 2012. Of the 859 eligible students, all students returned the questionnaires (lowland questionnaire) to fieldworkers, and had their SaO_2 and HR measured at their schools before leaving for high altitude. The same students were followed up three days after arrival at high altitude by collecting the same information as was collected in the lowlands. For unknown reasons, 120 students did not return the highland questionnaire and eight highland questionnaires were incompletely filled out, thereby leaving 731(85.1%) students with highland questionnaire information. Furthermore, 158 students did not attend the SaO_2 and HR measurements on the third day, leaving 701 students with high altitude SaO_2 and HR measurements (response rate 81.6%).

Figure 3 The flow chart for the Tibetan study population



3.2.2.3 Inclusion criteria

- Native Tibetan students staying in lowland China for seven years, and who were on lists from selected schools and about to graduate in 2012.

3.2.2.4 Data collection

The school leaders in the selected lowland schools were contacted in advance. The school leaders were informed about the purpose of the research, and assisted the fieldworkers in getting in touch with the eligible students. All eligible students were invited to participate in the study in the lowlands and again after arrival in Lhasa. The objectives of the study were given on the first page of the questionnaire, and the students were informed that the study was voluntary. All students returned questionnaires (lowland questionnaire) to fieldworkers, and took part in the measurements of SaO_2 and HR at their schools before their ascent to high altitude.

A new questionnaire (highland questionnaire) was handed out to the same students at the Lhasa railway station, since all of them went back to Tibet by train, which was organized by their school directors. All students were asked to meet at a designated place to have their SaO_2 and HR measured and to deliver the highland questionnaire to fieldworkers on the third day after arrival in Lhasa.

The same eight students and teacher as in the tourist study, in addition to two more teachers from TUMC, helped with the data collection.

• Questionnaire information

Two questionnaires in Chinese version based on the Lake Louise-AMS scoring system were used in the Tibetan study: one highland questionnaire and one lowland questionnaire. The highland questionnaire variables were the same as in the questionnaire used in the tourist study, except for an additional question about "have you been to Tibet before ?, if yes, followed by specify the times of visits". The purpose of the lowland questionnaire was to have information about baseline health conditions including information about AMS like symptoms before the students ascended to high altitude.

• Arterial oxygen saturation and heart rate

Both SaO_2 and HR were measured by finger pulse oximetry (Nellcor, NPB-40, California, USA). After a 15-minute rest period, the sensor was attached around the left index finger with the person in a sitting position. Resting SaO_2 and HR were obtained three times with 30-second intervals, and the average of the measurements was recorded for data analysis. The temperature was mostly between +5° and +20°C during the data collection period, and no smoking was permitted two hours before the measurements.

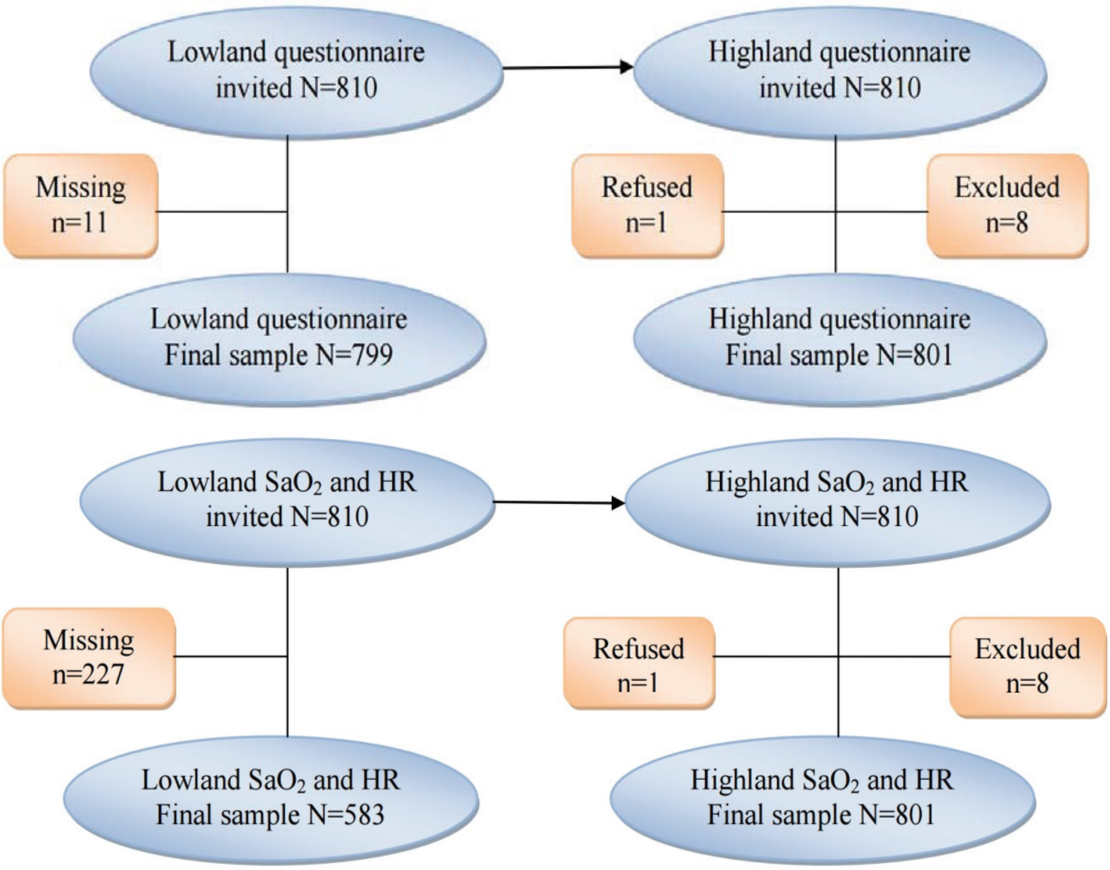
3.2.3 Han Chinese study

The Han Chinese students' study were carried out in the same seven cities in lowland China and Lhasa City as in the Tibetan students' study.

3.2.3.1 Study population

In total, 810 Han Chinese students aged 17-21 from the same lowland area where the Tibetan students had studied, and were going to study at Tibet University, were invited to participate in the study from August to September 2014. Of the 810 eligible students, 11 students did not return the lowland questionnaire because of misplacement (response rate 98.6%). For reasons unknown, 227 students did not attend the SaO_2 and HR measurements (response rate 72.0%) in the lowlands. After arriving in the highland, one student refused and eight were excluded because they had already been in Lhasa more than three days before the data collection started. Thus, a total of 801 students (response rate of 98.9%) participated in the measurements of SaO_2 and HR, and returned the highland questionnaire to the field workers.

Figure 4 The flow chart for the Han Chinese study population



3.2.3.2 Inclusion criteria

- Han Chinese students who were born and raised in the lowlands, without any former exposure to high altitude.
- Han Chinese students who came from the same lowland area where the Tibetan students had studied, and were going to study at Tibet University in 2014.

3.2.3.3 Data collection

All Han Chinese students who were admitted to study at Tibet University, and came from the same lowland area where the Tibetan students had studied, were sent lowland questionnaires via post before they ascended to Lhasa. A written consent form was given on the first page of the questionnaire, and the students were informed about the objectives of the research and that the participation was voluntary. They were asked to return the lowland questionnaire to fieldworkers when they registered at Tibet University. SaO_2 and HR measurements were carried out at a designated place in the seven lowland cities where the Tibetan students were studying. Upon arrival in Lhasa, the SaO_2 and HR were measured within one hour after arrival at the railway station or the airport. The same data collection procedures for the measurements of SaO_2 and HR were conducted on the second and third day. The students were asked to fill in highland questionnaires on the third day after arrival in Lhasa, and to return it to the field workers on the same day.
The same fieldworkers were responsible for the same data collection procedures as for the Tibetan students study.

• Questionnaire information

The same questionnaires were applied in the Han Chinese student study as in the Tibetan student study.

• Arterial oxygen saturation and heart rate

The same data collection procedure for the measurements of SaO_2 and HR were used as in the Tibetan student study.

3.3 Data management

All preparation work was done before the field work, which included the lay-out and printing of the questionnaires, preparation for the registration of questionnaire information and calibration of the equipment. All data was checked every day during the data collection, and entered into the Statistical Package for Social Science (SPSS IBM, Chicago, IL, USA) by the fieldworkers. The accuracy of the questionnaire information and the results of SaO_2 and HR were checked every day after the data collection, and all the data was copied in backup systems and stored in locked up systems.

3.4 Statistical analysis

The analyses of data were carried out using the SPSS (Statistical Package for Social Sciences, Version 22 and 24 for Windows. SPSS Inc. Chicago, USA).

Paper I:

Chi-square ($\chi 2$) tests were applied for comparing differences in prevalence between subgroups of the population, such as different countries (participants from Asia, Europe, America and Oceania) and users and none-users of prophylactic medicine.

A Log-Binomial Model was applied to analyse the relationship between AMS and selected risk factors, including gender, age, obesity, nationality, altitude of permanent residence, education, smoking, transportation, health condition, previous AMS symptoms, awareness of AMS, pre-exposure in the preceding three months, and the use of prophylactics.

Different approaches of analyses revealed similar results: analyses based on and including all determinants in the model, specific causal models for each of the variables and models that only included variables that were statistically significantly associated with AMS in the crude analyses. Only results from the first approach were reported in the first paper. Crude and adjusted prevalence ratios (PR) were computed with 95 % confidence intervals (Cl), whereas the level of statistical significance was set at $p < 0.05$.

Paper II:

The descriptive statistics were presented as frequencies and means with a standard deviation. Chi-square ($\chi 2$) tests were performed for comparing categorical variables by gender, smoking and incidence of AMS between native Tibetan and Han Chinese students by different types of transport. Student t-tests were used for comparing continuous variables by SaO_2 and HR between the Tibetan and Han Chinese students. One-way ANOVA was performed for comparing the differences in age, height, weight, BMI, SaO_2 and HR among Tibetans by train, Han Chinese by train and Han Chinese by air. A linear regression model was used to check the changes of SaO_2 and HR from low to high altitude.

SaO_2 and HR were treated as dependent variables, and altitude and ethnicity as explanatory variables. To explore interactions, an interaction term between altitude and ethnicity was added to the model. The level of statistical significance was set at $p < 0.05$.

Paper III:

Data was presented as a percentages with 95% Cl for categorical variables and mean with a range for continuous variables. The data was analysed, both in total and stratified by different transportation. Both the risk ratio (RR) and odds ratio (OR) were reported, as the dependent variable was common and also because many previous studies have presented an odds ratios. Logit-risk and Log-risk models were applied for analysing the independent effects of SaO_2 and HR on the incidence of AMS. OR and RR were computed with a 95% Cl, while linear regression was applied for analysing the correlations between SaO_2 and HR at different points in time. ROC curves (receiver operating characteristic curves) were used to evaluate SaO_2 and HR as diagnostic tests (to separate persons who developed AMS from those who did not develop AMS). To this, sensitivity and specificity were calculated for the selected cut-off points of SaO_2 and HR, and for combinations of SaO_2 and HR values. The level of statistical significance was set at $p < 0.05$.

3.5 Ethical considerations

For the tourist study, the study protocol was submitted to the Norwegian Regional Committee for Medical and Health Research Ethics, which found the study unnecessary to undergo evaluation since the collected information was considered to be anonymous. The Tibetan student and Han Chinese student studies were granted by the Medical Ethics Committee of Fu-kang Obstetrics & Gynecology, and Children's Hospital, Lhasa, Tibet, China, and approved by the Norwegian Regional Committees for Medical and Health Research Ethics. The study was supported by the National 973 Programme of China grants 2012CB518202. Information about the study procedure and consent form was given on the first page of the questionnaire. Participants were informed that they could refuse to participate in the study with no negative consequences. After quality controls, data was anonymized without any possibility of tracing the participants.

4 RESULTS

4.1 Paper I

Acute mountain sickness among tourists visiting the high-altitude city of Lhasa at 3658 m above sea level: a cross-sectional study

The prevalence of AMS was 36.7 % (95 % CI: 34.6%–38.7 %) among 2,203 ordinary tourists coming to Lhasa, and no HAPE and HACE were reported during the data collection period. There were no substantial differences in AMS prevalence among the participants from Asia, Europe, America and Oceania. Moreover, we did not find any contrast in the prevalence of AMS between the users and none-users of prophylactic medicine. Among the participants who developed AMS, 30.5 % reported that the onset of AMS symptoms started as early as on the journey to Lhasa, while in 47.6 % of participants the symptoms started within the first 12 h after arrival and in 21.9 % after 12 h. Furthermore, 21.0 % of the participants with AMS did not reduce their physical activity and 74.0 % had a moderate activity reduction, while 5.0 % chose to rest in bed because of their symptoms. In the fully adjusted model, the factors that remained statistically significantly associated with a higher risk of AMS were a poor or average health condition (adjusted PR 1.63, 95% CI: 1.38–1.93), an age below 55 years (adjusted PR 1.29, 95 % CI: 1.04–1.60) and a rapid ascent to Lhasa (adjusted PR 1.17, 95 % CI: 1.02–1.34), whereas smoking (adjusted PR 0.75, 95 % CI: 0.59–0.96) and pre-exposure to high altitude (adjusted PR 0.71, 95 % CI: 0.60–0.84) reduced the risk of AMS.

4.2 Paper II

Acute Mountain Sickness, arterial oxygen saturation, and heart rate among Tibetan students who reascend to Lhasa after seven years at low altitude: a prospective cohort study

Excluding students with AMS-like symptoms at baseline, new cases of AMS occurred in only 1.2% (95% CI: 0.4% to 2.0%) of the Tibetan students who came to Lhasa by train compared with 32.7% (95% CI: 28.0% to 37.3%) and 42.9% (95% CI: 38.0% to 47.7%) of the Han Chinese students who came to Lhasa by train and by air, respectively, within the third day after arrival in Lhasa. No HAPE and HACE were reported during the data collection period. For the nine Tibetan students categorized as having AMS, eight reported symptoms within 24 hours after arrival. For most of the Han Chinese students (81.7%) who were categorized as having AMS, the onset of symptoms occurred within the first 24 hours after arriving in Lhasa. There was no statistically significant differences between Tibetan and Han Chinese students regarding the overall means of SaO_2 (Tibetan vs. Han Chinese: 99.2% vs. 99.1% $P>0.05$) and HR (Tibetan vs. Han Chinese: 72.1% vs. 71.3% $P>0.05$) at low altitude. After arrival at high altitude, Tibetan students had less changes in SaO_2 (-2.95 percentage points, 95% CI: -3.24% to -2.65%) and HR (10.89 bpm, 95% CI: 9.62 bpm to 12.16 bpm) from low to high altitude compared to Han Chinese students.

4.3 Paper III

Associations between arterial oxygen saturation, heart rate and acute mountain sickness in a population of 17-21 year old Han Chinese students traveling from low altitude to Lhasa at 3,658 m above sea level: a prospective cohort study

The total incidence of AMS was 37.8% (95% CI:34.4% to 41.2%) among 810 Han Chinese students who came to Lhasa by both train and air after three days of exposure to high altitude. There was no statistically significant difference in the incidence of AMS during the first three days between the participants who took what they described as prophylactic medicine and those who did not ($p>0.05$). No HAPE and HACE were reported during the data collection period.

SaO_2 decreased and HR increased from lowland to highland measurements. The regression analyses revealed the risk of AMS increased by decreasing SaO_2 levels measured in both the lowlands (RR: 1.16, 95%CI: 1.13-1.20) and on the first day in the highlands (RR: 1.19, 95%CI: 1.15-1.22) per a 1% reduction in SaO_2 level. The stratified analysis by way of transportation also showed independent risks of both lowland and highland SaO_2 levels for the development of AMS. Other potential AMS risk factors such as sex, height, weight, use of prophylactics, health condition and diseases did not affect the results if they were added into the regression models. There were only weak associations between HR and risk of AMS at any point in time. ROC analyses revealed that the largest area under the curve (AUC) was at 80.2% when combining SaO_2 measurements from the lowlands and on the first day at the highlands.

5 DISCUSSION

The present thesis draws attention to AMS among three different populations of current travellers to Tibet. Previous studies have primarily focused on AMS in healthy and physically fit populations such as climbers and soldiers (18, 19, 22, 55, 56). Millions of travellers come to Tibet each year. Most of them are not climbers or soldiers, and many will experience AMS symptoms and struggle with acclimatization, which will spoil parts of their visit, and in some cases even lead to more severe health conditions. The findings in this thesis confirm that quite a few people will experience AMS or troublesome AMS-related symptoms, thus reducing the quality of their stay in Tibet. A reasonable assumption is that more attention to these problems could result in more awareness and better planning among travellers to high altitudes. However, there are several methodological issues that complicate the assessment of the burden of AMS among travellers.

5.1 Occurrences of AMS

As mentioned earlier, there has been no simple test for predicting or diagnosing AMS (15-17). For diagnosing AMS, one has had to rely on reports of symptoms that from experience are considered to be related to exposure to high altitude (15-17). Unfortunately, none of these symptoms are specific to AMS (2, 3). Several "tools" have been developed to help in diagnosing AMS (17, 44-49). For the purpose of estimating population-based prevalence or the incidence of AMS occurrence, the "tools" have to be simple and practical. In practice, it has mainly been questionnaire information about AMS-related symptoms that has been used to estimate AMS incidence or prevalence with the uncertainties that this may introduce to such estimates (5, 133). Several such questionnaires have been developed (2, 7, 8), including ESQ-Ш and LLSS (2, 8). Compared to ESQ-Ш, the LLSS self-assessment questionnaire is more effective for the assessment of AMS at high altitudes (25). Currently, the LLSS questionnaire is most often used (2, 25, 61, 134). It is reasonably simple for participants to answer and can be used as a self-administered questionnaire, which is convenient for the use in surveys (22, 135). Using the same questionnaire should increase the possibility to compare disease burden between studies. That is partially true, but there has been some disagreement between researchers about the number and severity of symptoms necessary for having AMS (17, 28, 61). This is illustrated by two surveys from the Alps, in which one reported AMS based on AMS defined as LLSS≥ 4, with headache (28), and the other with LLSS ≥ 3, both with or without headache (17). This thesis has used LLSS, and AMS was defined as LLS≥ 4, with headache (28). This practice has been used by most recent studies (24, 28) and LLSS was found to be the most suitable tool for our surveys. A potential weakness of LLSS is that one of the cardinal symptoms is sleep disturbance. If the questionnaire is used for assessing AMS for a time period not including a night, it will not be meaningful to ask about sleep disturbances. However, this was not a problem in any of our surveys, as the observation time always included at least a one night stay at high altitude. Hopefully new surveys could use the same methods to make it easier to investigate trends in AMS or to identify subgroups of the travelling population with special problems.

A further challenge for AMS surveys that complicates comparisons and studying the causes of AMS is self-selection. What is meant by self-selection is described in more detail under methodological considerations and in Paper I, but it points toward the fact that one can seldom be sure that it is a random sample of a population that decides to go to high altitude, and that this potential selection mechanism could be different in different populations and change over time. The tools for diagnosing AMS and the potential self-selection mechanism leave one in a situation in which conclusions should be drawn with caution. On the other hand, taking these factors into account, together with considering the differences in altitude where the surveys have been carried out and the ascent rate, the AMS prevalence reported among tourists in Paper I, and the incidence reported among Han Chinese students in Paper III, seems to be of a size comparable to other findings (44, 52, 66, 95, 102-104, 136, 137). The similarities between the results in Papers I and III with quite different populations could lead one to think that estimates of AMS are quite robust and not so dependent on which population is under study. Nonetheless, the evidence for such a conclusion is limited. To improve public health information about AMS, one should still search for differences between populations and groups of individuals, having variations in susceptibility to AMS and self-selection in mind. The heterogeneity in ascent rate, and lack of precise knowledge of ascent rate, is often a challenge in AMS surveys (3, 4, 52). In particular, the Han Chinese study has a quite unique methodology. All students were followed from low altitude until three days after arrival at the same high altitude. They had travelled to high altitude during the same period, and only used two well-defined travel routes. The routes were well known and defined, and the ascent rate for both routes was quite rapid. This excluded much heterogeneity. One could also argue that self-selection would be less of a problem since the Han Chinese students were all without any previous experience at altitude. Hence, there are several reasons to consider the AMS incidence as representative of young Han Chinese, given the described ascent rate and altitude reached. This could be something to compare other estimates of AMS against. The study also clearly demonstrated the impact of the ascent rate for AMS, as those arriving to Lhasa by plane had a higher incidence compared with those who came by train. This observation was also supported by the findings in Paper I.

The AMS incidence found in the Tibetan study supports that Tibetans keep their high altitude adaptation after a long absence from altitude exposure, and that this also includes a reduced risk of AMS. Even if they experienced some AMS-related symptoms, it seems that AMS was not a major concern.

Our findings support earlier research that AMS symptoms typically appear within the first 12 h, generally after the first overnight stay at high altitude (3, 48), and that most individuals acclimatize themselves during the initial three-four days at altitude. Using the cumulative incidence during the first three days in the Tibetan and Han Chinese studies helped us to catch AMS cases, both with early and late onset.

5.2 Determinants of AMS

As previously mentioned, the interpretation of the estimated associations between AMS and the potential determinants of AMS should be interpreted with care because of self-selection. Paper I has a cross-sectional design, which introduce an extra methodological challenge since exposure and outcome were measured at the same point in time (138, 139). Many studies of AMS risk factors have similar methodological challenges (43, 140).

Previous studies have reported that AMS occurrences depend on factors like altitude reach, ascent rate, pre-exposure to high altitude, individual susceptibility, age, gender, health condition, awareness, altitude of permanent residence and medication (3, 48, 50, 51). Ascent rate and altitude reached are the most universally accepted risk factors, and have already been partially discussed. Because all participants reached the same altitude, one cannot further explore the effects of altitude in any of the current populations, while the Han Chinese study and the tourist study demonstrated relationships in support of less AMS with a slower ascent rate. This suggests that travellers going to Tibet should be informed that a less rapid ascent from lowland areas would reduce their chances of experiencing troublesome AMS symptoms.

A beneficial effect of earlier exposure to altitude has also been reported (138, 139). But the residual benefit from prior exposure will be lost over a few days to weeks after a return to low altitude among lowlanders (138, 139). The Tibetan utility of pre-exposure has clearly been demonstrated and mentioned before. In principle, the study could not explore whether this is a genetic or pre-exposure effect. The Han Chinese study could not contribute to the knowledge about this since no student had been to high altitude. In the tourist study, there was evidence in support of such an effect, although self-selection should be kept in mind as a factor leading to uncertainty.

Two of the populations under study were young and mostly healthy students. The tourist study found that those who reported a poor or average health condition had a higher risk of developing AMS, which is in accordance with some earlier studies (8, 70), but in contrast with others (67, 68). On the other hand, the prevalence of AMS was similar between those with and without pre-existing illnesses, such as lung disease and cardio-vascular disease. The seeming inconsistency between health condition and disease could be explained by subjective reports and self-selection. Eight of nine Tibetan students with AMS reported having influenza shortly before leaving low altitude. This indicates that even in native highlanders acclimatization could be disturbed by current health problems like infections (61, 74, 100).

There are conflicting opinions about the effect of smoking (44, 68, 87-89). Smoking and AMS in the Tibetan and Han Chinese studies showed no ill effect, whereas smoking reduced the risk of AMS in the tourist study. The tourist findings are in accordance with studies conducted by Wu et al. (87) and Song et al. (88). A potential mechanism for this effect could be that smokers are habituated to a modest level of hypoxia, and the reduced NO levels in smokers may also protect them to a certain extent from AMS-related symptoms (87). In contrast, some have found that smoking increased the risk of AMS (89), Self-selection and other methodological issues such as biased reports of smoking should be considered before making conclusions about the effects of smoking.

Age is also an important issue, as more elderly people are taking up travelling to exotic destinations (44, 50, 127). Two of the studies were among young students only, while an age below 55 years was found to be a risk factor in the tourist study, which is in accordance with some previous studies (15, 44, 75). As shown in Figure 1, the higher cerebrospinal fluid (CSF) to brain volume might protect against AMS, since the displacement of CSF may act as an initial defence against an increase in cerebral pressure for any degree of cerebral edema (11-13). This mechanism may be related to the decreased risk of AMS in older people, since the ratio of CSF to brain volume is likely to be higher as a result of age-related cerebral atrophy (3). This could also be the reason for a varying individual susceptibility due to the different ratio of CSF to brain volume among individuals (3). However, the elderly will have more known and unknown chronic health conditions, so it is easy to think that the populations of the elderly are changing, and that more elderly with health problems will arrive at high altitude Tibet. It seems reasonable to consider them as a potential risk group that should be followed concerning AMS, even if there is yet no strong evidence for expecting higher risk in this group.
The impact of gender on AMS has thus far been inconclusive (10, 62). The current studies did not find any gender differences between individuals with or without AMS among tourists, Tibetan and Han Chinese students. The finding from the Han Chinese study is especially interesting because the participants had no former experience with high altitude exposure, thereby reducing the risk of self-selection.

The only universal medication for preventing and ameliorating AMS is acetazolamide, which was not used by any Han Chinese or Tibetan students. Only a small part of the tourists used acetazolamide, but there was no statistically significant difference in AMS by acetazolamide use among the tourists. This could probably be due to a low statistical power. Rhodiola is widely used to prevent AMS in Tibet (141, 142), even if there are no consistent agreements about its effect (123, 141, 143). One current study reported that Rhodiola was not effective in reducing the incidence or severity of AMS when compared with placebo and failed to show any prophylactic effects in humans (123). It is interesting that the analyses of the data from the current studies reveal no AMS effect from the drug, even if it was used by a substantial proportion of the participants in both the tourist study and Han Chinese study, hence leaving no support to the currently quite common preventive practice.

5.3 Arterial oxygen saturation, heart rate and AMS

A further aim of the thesis was to investigate associations between AMS and resting SaO_2- and HR levels measured at both low and high altitude. Associations between AMS and these parameters measured at altitude have some challenges in interpretation. At least in principle, associations could be interpreted as a result of both an AMS development and an initial reaction to high altitude that enhance the development of AMS. To decide whether outcome or exposure came first is difficult and a general problem when studying these relationships. For this reason, the first measurements of SaO_2 and HR in the Han Chinese study were carried out once the students arrived in Lhasa. The study had a quite unique possibility to collect data as soon as the participants arrived at the airport or train station because their travelling routes and schedules were known in detail. The first measurements reduced altitude exposure to a minimum compared to measuring these parameters after some time at altitude. Even so we had an interpretation challenge. We also had the possibility to measure these parameters shortly before leaving the lowlands without any high altitude exposure. In this case, the associations will have an obvious time relationship, and could be interpreted as a risks or predictors. Interestingly, the lowland level of SaO_2 independently increased the risk of AMS among the Han Chinese students even when adjusting for their high altitude levels. Still, there was also an independent effect of high altitude SaO_2. Because the first high altitude SaO_2 was measured before the collection of AMS symptoms, and before most of those who developed AMS probably had developed symptoms sufficient to classify them as having AMS, one could at least claim that SaO_2 was measured before AMS was diagnosed. The demonstrated associations were therefore interpreted as predictors for the development of AMS well aware of the challenging uncertainty about the true time relationship between high altitude SaO_2 levels and AMS. An approach with ROC curve analyses was also performed, which further supported the association between AMS and SaO_2, but did not resolve the time relationship questions.

The strength of the associations questions the usefulness of SaO_2 as a general diagnostic test or predictor, but persons with a large reduction clearly had an increased risk of experiencing AMS. However, the variance in SaO_2 levels in the lowlands was small, and many had an optimal SaO_2 level.

The SaO_2 and HR measurements provide further evidence of the differences in altitude reaction patterns between Tibetans and Han Chinese, as SaO_2 levels dropped and HR increased significantly more among the Han Chinese compared to Tibetans, thus providing further support for the idea of a unique physiological adaption among Tibetans. The finding of a weakening association between SaO_2 and AMS with the time spent at altitude seems reasonable, and could reflect a process of acclimatization with time at altitude (144-146).

5.4 Methodological considerations

Some methodological considerations are presented below, even if aspects of this have already been presented before in the discussion or in the papers.

5.4.1 Study design

This thesis comprises one cross-sectional study and two prospective cohort studies. Cross-sectional studies are used for measuring the prevalence of health and other parameters at a particular point in time, and is also known as prevalence studies (147). A cross-sectional design was used in the tourist study, in which we wanted to estimate the prevalence of AMS and AMS's relationship with potential risk factors, such as age, gender and nationality. The cross-sectional study is a suitable design for estimating prevalence but has limitations addressing the time direction of associations, which has already been mentioned. One could speculate whether this is less of a problem when studying an acute health condition like AMS, but as discussed earlier even a prospective cohort design will have challenges in the study of the relationship between SaO_2 and AMS.

The two other studies are prospective cohort studies. Here, one follows participants grouped according to their exposure levels to determine how this exposures affects the rates of a certain outcome (148). The cohort design was chosen because it has clear methodological advantages when it comes to the interpretation of association, and because the chance of certain sources of bias is reduced (43). Nevertheless, it is an observational design, and as mentioned there were still challenges related to the interpretation of findings. A challenge with prospective cohort studies is the losses to follow-up that also occurred in the Tibetan and Han Chinese student studies. However, conducting alternative analyses in subsamples of the populations strengthens the view that the experienced losses to follow-up did not substantially affect the main results.

5.4.2 Selection bias

Selection bias is the error caused by systematic differences in characteristics between participants selected for the study and those who did not participate (43, 147). Several mechanisms could cause selection bias, which could result in not only a biased estimate of disease occurrence, but also biased association measures (148).

Such a potential selection mechanism is inevitable in all epidemiological research, including in the current studies. For the student studies, we experienced high participation rates among those invited, thereby reducing the chance of that type of selection bias, and bias due to losses to follow-up as discussed in the paragraph above. Furthermore, the random recruitment of schools for data collection made it reasonable to expect that the chosen samples were representative of Tibetan students studying in lowland China, as well as Han Chinese students. When it comes to the tourist study, it is more complicated to claim representativity. First, it is difficult to define the tourist source population, and it seems reasonable to expect that the tourist population in Lhasa is not a static phenomenon but will continuously change. The aim was therefore to recruit a sample of tourists with a variation in background variables, and curry out the recruitment in a way that ensured that they were recruited as randomly as possible. Choosing to recruit more participants than necessary for a precise prevalence estimate opened for studying prevalences in subgroups and conducting comparisons between groups. A further reason for being modest about the idea of representativeness is that a tourist population is recruited from a population of potential tourists, which in principle could be expanded to the population of the world. Who decides to travel to high altitude is probably decided by a large number of conditions we do not know or have information about. If these conditions are related to individuals' risk of AMS, and to whether they decide to travel to altitude, this could affect relationships between AMS and exposure. In this thesis, this is called self-selection. One example could be that there are healthy older individuals who today travel to high altitudes, and that those staying at home have different risk of developing AMS than those who travel and that this can be different tomorrow. Surveys of AMS should therefore be interpreted in this perspective, as the tourist population could change; this presents an argument for new surveys of the tourist population and watching out for overall changes in prevalence, in addition to special groups of travellers with an increased risk. For the student populations, there are fewer reasons to believe that such self-selection is a problem.

5.4.3 Information bias

Information bias is a flaw in measuring exposure or outcome, which results in misclassification (149). Information bias could possibly occur in self-reporting questionnaires, and SaO_2, and HR measurements. To help reduce these possibilities, the same eight students and the same teacher who collected the data in the tourist study, together with two more teachers from TUMC, conducted the data collection in the student studies.

Recall bias is a type of information bias, and it is a major issue in studies that include self-reported data, especially in studies with a retrospective design (148). Recall bias is a potential issue for the current studies, since some participants may forget about their health problems. However, it is assumed that most people will remember which health problems they have experienced within a short time period, such as three days. Several other studies on AMS have also relied on this type of information being reasonably valid for even longer periods (2, 35, 150). Both Tibetan and Han Chinese students in the current studies had been contacted in lowland areas, and knew that they were going to take part in a study on AMS, which is a further argument against substantial recall bias.

5.4.4 Risk estimation

The use of prevalence and incidence in AMS studies has already been displayed in the introduction. Furthermore, the use of OR and RR for addressing associations between exposures and AMS have been presented in Paper III, including an argumentation for choosing RR if possible. The results of ROC curve analyses have been presented to supplement the regression analyses of the relationship among SaO_2, HR and AMS.

5.5 Future studies

AMS occurrences should be monitored among visitors to Tibet, preferably using a comparable methodology to be able to address time trends. Special interest should be given to ordinary tourists.

Studies could be conducted that strengthen the knowledge of how environmental factors are related to AMS. Still, there is much uncertainty and strong research designs are necessary.

Physiological parameters predicting AMS should be looked to, both for understanding the mechanism of AMS and for being able to give advices to people planning to go to high altitude or arriving at high altitude.

6 CONCLUSIONS

AMS is a common disease among tourists visiting the high altitude city of Lhasa Tibet. Poor or average health condition, an age below 55 years, a rapid ascent to Lhasa, no-smoking and no-pre-exposure to high altitude were all found to be associated with AMS among the studied tourists.

AMS is also a common disease among Han Chinese students previously not exposed to high altitude arriving in Lhasa Tibet and the occurrence of AMS is quite similar to what was experienced in the tourist population.

After a long stay at low altitude, Tibetan students clearly had a lower AMS incidence and less change in SaO_2 and HR when arriving in Lhasa, compared to Han Chinese students arriving in Lhasa who had previously not been exposed to high altitude. The contrast in reactions indicates that Tibetans keep their good adaptation to acute exposure to high altitude, even after a long-term stay at low altitude.

A reduced SaO_2 at both low and high altitude independently increased the risk of developing AMS.

SaO_2 levels as a diagnostic test for AMS seem to have their limitations.

Moreover, HR did not seem to be of substantial importance for the development of AMS.

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APPENDICES

APPENDIX I Tourist consent form

Help us to assess
Acute Mountain Sickness among tourists in Tibet

By filling in this short questionnaire, you will help us to providing better health services and advice to tourists in Tibet.

The project
Tibet University Medical College in cooperation with the Faculty of Medicine, University of Oslo, is currently running several projects related to High Altitude Sickness. In one of them, we elucidate special problems tourists may face when they arrive in high altitude areas like Tibet.

Deliver to the reception staff
Please deliver the questionnaire to the reception staff today, as soon as you have filled it in.

Even if you choose not to participate, could you please deliver the empty questionnaire back to the reception staff.

Please give the reason for why you do not want to participate:

The questionnaire
The questionnaire is distributed to all guests at selected hotels in Lhasa, and it is important that as many tourists as possible participate.

- If you do not have headache, poor appetite or any other of the symptoms asked for in this questionnaire, it is still very important for us that you participate in this questionnaire.
- If you are travelling with someone who is much affected by the high altitude, please help them to fill in this questionnaire.
- If you do not want to answer all questions, please leave them open.
- The participants must be 15 years old or older.

Thank you for your cooperation!
Sincerely,

Ouzhu Luobu
Professor
Dean, Tibet University Medical College, Lhasa, Tibet

Espen Bjertness
Professor, PhD
Faculty of Medicine, University of Oslo, Norway & Professor, Tibet University Medical College

APPENDIX II Tibetan and Han Chinese students consent form

Help us to assess
Acute Mountain Sickness among students in Tibet

By filling in this short questionnaire, you will contribute providing information for a better understanding of Acute Mountain Sickness.

The project
The research protocol of the 973 project, entitled: "Research on the acute acclimatization and long-term adaptation mechanism in a high altitude hypoxia environment - chronic hypoxia injury and long term adaptation mechanism in high altitude" is currently running several projects related to High Altitude Sickness. In one of them, we elucidate special problems young native Tibetan and Han Chinese students may face when they arrive in high altitude areas like Tibet.

The questionnaire
Two questionnaires based on the Lake Louise acute mountain sickness (AMS) Scoring System were developed and used in the data collection: one lowland questionnaire and one highland questionnaire.
Even if you choose not to participate, please deliver the empty questionnaire back to the fieldworkers.

Please give the reason for why you did not want to participate:

Deliver to the fieldworkers
Please deliver the lowland questionnaire once you have completed filling it in. Please deliver the highland questionnaire to the fieldworkers on the third day after you arrive in Lhasa.

- The study was granted by the Medical Ethics Committee of Fu-Kang Obstetrics & Gynecology, and the Children's Hospital, Lhasa, Tibet, China.

- Besides questionnaires, we are going to measure your Arterial Oxygen Saturation (SaO_2) and Heart Rate (HR) by finger pulse oximetry. Each of you has the right to refuse to participate at any time for any reason without any consequences. It is completely voluntary to participate in the current study, and all information about the participants will be handled confidentially.

- If you do not want to answer all the questions, please leave them blank.

- ______________________________

- Thank you for your cooperation!

- Contact information: Gonggalanzi, Tibet University Medical College. Tel: 0891 6811310 (office)
- Email: qeblanzi@hotmail.com

APPENDIX III QUESTIONNAIRE

(Questionnaire was in Tourist for 2010, Tibetan students for 2012 and Han Chinese students for 2014 studies)

Date of filling in questionnaire:
Please write the date and hour at which you filled in this questionnaire

____hour (24hr) ___year __month __day

Part I Background information

1. Age:____ years old

2. Gender: ☐ Male ☐ Female

3. How many years of schooling/education have you completed altogether?

_____________year/s

4. Nationality:_____________

5. Altitude of permanent residence/home city, *Please tick one of the alternatives*

☐ 2000 metres or higher (>6500 ft)
☐ Below 2000 metres (<6500 ft)

6. What is your weight? __ kg *or* __ pounds

7. What is your height? __ cm *or* __ feet __ inches

Part II Travelling schedule

8. Do you consider yourself to be a tourist on this present travel to Lhasa?

☐ Yes ☐ No

*If no, please specify*____________

9. When did you arrive Lhasa?

___hour (24hr) ___year __month __day

10. How and from where did you arrive Lhasa? *Please tick one of the alternatives*

☐ By air	From:
☐ By train	From:
☐ By car/bus	From:

11. How long have you been in Tibet before you arrived Lhasa? ____days

12. During the past 3 months, have you been to altitudes above 2000 m (6500 ft)?

☐ Yes ☐ No

If yes, please specify Altitude: _______ metres *or* _______ feet

How long:___________

13. Have you been to Tibet before?

☐ Yes ☐ No

*If yes, please specify how many times*_________

Part III Have you had any of the following symptoms?

14. Headache

☐ No headache
☐ Mild headache
☐ Moderate headache
☐ Severe headache, incapacitating

15. Gastrointestinal symptoms

☐ No gastrointestinal symptoms
☐ Poor appetite or nausea
☐ Moderate nausea or vomiting
☐ Severe nausea and vomiting, incapacitating

16. Fatigue and/or weakness

☐ Not tired or weak
☐ Mild fatigue/weakness
☐ Moderate fatigue/weakness
☐ Severe fatigue/weakness,incapacitating

17. Dizziness/light-headedness

☐ Not dizzy
☐ Mild dizziness
☐ Moderate dizziness
☐ Severe dizziness, incapacitating

18. Difficulty sleeping

☐ Slept as well as usual
☐ Did not sleep as well as usual
☐ Woke many times, poor night's sleep
☐ Could not sleep at all

If you did not have any of the symptoms in Part III, you may skip Part IV and Part V

Part IV Overall, if you had any of the symptoms in Part III...

19. How did they affect your activity? *Please tick one of the alternatives*

☐ No reduction in activity
☐ Mild reduction in activity
☐ Moderate reduction in activity
☐ Severe reduction in activity (e.g. bedrest)

20. When did they first begin?

☐ On the journey
☐ Less than 12 hours
☐ 12 to 24 hours
☐ 25 to 48 hours
☐ More than 48 hours

21. What do you think was the cause(s)? *Please tick all alternatives that apply*

☐ Food or water of bad quality
☐ The high altitude
☐ Other:_______________

Part V Treatment or help

22. Did you seek help or advice from anybody because of the symptoms?

☐ Yes ☐ No

If yes:
Please tick all alternatives that apply

☐ A doctor visited me
☐ A nurse visited me
☐ I went to the hospital
☐ I went to a local doctor
☐ I went to a local nurse
☐ Somebody else helped me, *please specify*:________________

23. Did you get the diagnose Acute Mountain Sickness from a doctor?

☐ Yes ☐ No ☐ I do not know

Part VI Health

24. How would you describe your present state of health, before this travel to Lhasa/Tibet?
Please tick one of the alternatives

☐ Poor
☐ Not very good
☐ Good
☐ Very good

25. Has a doctor diagnosed you for any of the following diseases/health problems?
Please tick all alternatives that apply

□ Diabetes mellitus
□ High blood pressure
□ Cardio-vascular disease
□ Emphysema/chronic obstructive bronchitis
□ Asthma
□ Other – *Please specify*________

26. Do you smoke? □ Yes □ No

27. If female, do you use contraceptive medicine or other estrogen containing medicine? (e.g. birth control or hormone substitution)?

□ Yes □ No

Part VII Intake of...

28. Did you take any medication aimed at preparing you for meeting the high altitude?

□ Yes □ No
If yes, was it:
□ Acetazolamid (ex. Diamox)
□ Steroids (ex. Dexametason)
□ Nifedipin (ex. Adalat)
□ Other *Please specify*__________

29. How much fluid (all fluids including soup) did you drink the 24 hours before and the first 24 hours after you arrived Lhasa?

	24 hours before Arriving Lhasa	24 hours after Arriving Lhasa
Less than normal	□	□
Normal	□	□
More than normal	□	□

30. Have you taken any pain-relieving medication during the first 48 hours after arriving Lhasa?

□ Yes □ No *If yes*, please specify___________

Part VIII Final questions

31. Before you arrived Tibet, were you aware of that a visit to high altitude may cause adverse health effects/health problems?

□ Yes □ No

If yes, how did you get this information?

Please tick all alternatives that apply

 Medical doctor
 Other health personnel
 Travel agency
 Friend/colleague/family
 Internet (www)
 Guidebooks
 Other: *Please specify*:_______________

32. After arriving Lhasa, have you been working out or done anything that increased your heart rate to a marked extent - such as running, steep hiking etc.?

 Yes No

33. Have you on earlier travels to high altitudes (above 2000 m / 6500 ft) experienced symptoms listed in part III in this questionnaire?

 Yes
 No
 Never been at high altitude

Thank you for participating!

APPENDIX Ⅳ

Measurements of arterial oxygen saturation (SaO_2) and heart rate (HR)

Participant No_____________

SaO_2 first time □.□□

SaO_2 second time □.□□

SaO_2 thrid time □.□□

HR first time □.□□

HR second time □.□□

HR thrid time □.□□

Investigator:_____________________

Date of test:_________/_________/2012

Date of test:_________/_________/2014

Paper I

Acute mountain sickness among tourists visiting the high-altitude city of Lhasa at 3658 m above sea level: a cross-sectional study

Gonggalanzi *et al. Archives of Public Health* (2016) 74:23
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RESEARCH Open Access

Acute mountain sickness among tourists visiting the high-altitude city of Lhasa at 3658 m above sea level: a cross-sectional study

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Abstract

Background: Traveling to Tibet implies a risk for developing acute mountain sickness (AMS), and the size of this problem is likely increasing due to the rising number of tourists. No previous study on AMS has been conducted among the general tourist population in Tibet. Thus, the aim of this study was to estimate the prevalence and determinants of AMS in a large tourist population visiting Lhasa.

Methods: A sample of 2385 tourists was recruited from seven randomly selected hotels in Lhasa between June and October 2010. Within three days of their first arrival, the participants filled in a questionnaire based on the Lake Louise Scoring System (LLSS) about AMS-related symptoms and potential contributing factors. AMS was defined as the presence of headache and a cumulative Lake Louise Score ≥4. After estimating the prevalence of AMS, a Log-Binomial Model was applied to analyse the relationship between AMS and selected risk factors.

Results: The prevalence of AMS was 36.7 % (95 % CI: 34.6–38.7 %) and was not dependent on tourists' country of origin. Among the participants who developed AMS, 47.6 % reported that they experienced symptoms within the first 12 h after arriving in Lhasa, and 79.0 % reported that they had to reduce their activity level. A poor or average health condition (adjusted PR 1.63, 95 % CI 1.38–1.93), an age below 55 years (adjusted PR 1.29, 95 % CI 1.04–1.60), a rapid ascent to Lhasa (adjusted PR 1.17, 95 % CI 1.02–1.34) were independent AMS risk factors, while smoking (adjusted PR 0.75, 95 % CI 0.59–0.96) and pre-exposure to high altitude (adjusted PR 0.71, 95 % CI 0.60–0.84) reduced the risk of AMS.

Conclusions: AMS is commonly experienced by tourists visiting Lhasa Tibet, and often affects their activities. The tourists' country of origin did not seem to affect their risk of AMS, and their age was inversely related to AMS. Subjects planning to visit a high-altitude area should be prepared for experiencing AMS-related problems, and consider preventive measures such as pre-exposure or a gradual ascent to high altitudes.

Keywords: Acute mountain sickness, Tourist, Tibet

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Background

Since the opening of the world's highest plateau railway (The Qinghai-Tibet Railway) to Lhasa in 2006, the number of tourists visiting Tibet has increased sharply from 2.5 million in 2006 to more than 15 million visitors in 2014 [1]. Tourism revenue accounted for over 20 % of the region's gross domestic product (GDP) in 2014 [1]. Tourists travelling to Tibet from low-altitude areas have the potential risk of developing acute mountain sickness (AMS) during the first few days due to exposure to hypobaric hypoxia environment at high altitude [2]. AMS is usually characterized by symptoms of headache, dizziness, vomiting, anorexia, fatigue and insomnia after arrival at high altitudes [3]. In some serious cases, AMS can progress to life-threatening high-altitude cerebral edema (HACE) or high-altitude pulmonary edema (HAPE) [4]. The prevalence of AMS after ascending to high altitude has been reported to vary between 9 and 84 % [5–9]. There are few places where large numbers of ordinary tourists can easily and rapidly reach altitudes as high as in Lhasa (3658 m above sea level). A recent study reported that 51 % of construction workers experienced AMS upon first-time exposure to high altitude on the Qinghai-Tibet railroad route [10]. In addition, 57 % of army recruits who travel from the lowlands to Lhasa by air developed AMS [11]. These studies were carried out in quite homogenous populations, primarily consisting of young participants in presumably good health, which is probably different from what one would expect to be the case among ordinary tourists visiting Lhasa nowadays. Data on AMS among ordinary tourists is scarce. More knowledge about AMS among tourists travelling to high altitude could be important for persons planning to go there, as well as for professionals taking care of them both before and after arrival at such altitudes. The present study aimed to estimate the prevalence of AMS and to identify the determinants for developing AMS in an adult population of ordinary tourists visiting Lhasa Tibet China.

Methods

Ethics

The Ministry of Health and the Tibet University Medical College in TAR approved the research. The study protocol was submitted to the Norwegian National Committee for Medical and Health Research Ethics, which found the study unnecessary to undergo evaluation since the collected information was considered anonymous. Information about the details of the study was given on the first page of the questionnaire. The potential participants were also informed that the study was voluntarily and anonymous, and that they could refuse to participate without any negative consequences.

Setting

The data collection was carried out in Lhasa, the capital city of the Tibet Autonomous Region (TAR). The elevation of Lhasa makes it one of the highest situated cities in the world [1]. Lhasa is a sacred city situated in the Himalayas and attractive for many types of tourists. There were 90 star-rated hotels and a few guest houses in Lhasa at the time of the data collection [12].

Study samples

Nine hotels were randomly selected to participate in the study from a list covering all hotels in Lhasa which was given by the local tourism bureau. The management of the hotels were informed about the study and asked if they were willing to participate. All hotels agreed to participate, but the managers of two of the hotels decided to withdraw from the study when the data collection started. Thus, in seven hotels, tourists older than 15 years of age were invited to participate in the present study between 2 June and 31 October 2010. Receptionists from the selected hotels were given instructions in how to inform participants about the study, all aspects of the data collection as well as how to act in case study participants were in need of support for AMS related problems. Tourists received a questionnaire and instructions about the criteria needed for participation (age >15 years; classified as a tourist), and how to fill in information and return the questionnaire before leaving the hotel, depending on the duration of their stay at the hotel. This meant that the questionnaire was to be returned to the receptionist the third night after their arrival, or on the day when they checked out if the tourists planned to stay two nights or less. In total, 2385 tourists were invited to participate during the data collection period and all returned the questionnaire. It turned out that 106 of the tourists refused to participate, and handed in their questionnaire without information. The lack of an understanding Chinese and English and limited time were the main reasons for refusing to participate. Furthermore, 76 participants were excluded due to incomplete questionnaire information, non-tourist status or an age below 15 years, leaving 2203 participants (92.4 %) for the analyses.

Variables

The questionnaire was tested in a pilot study in 2008, and a revised version was available for the current study in both Chinese and English. The questionnaire was designed to obtain data concerning age, gender, height, weight, altitude of permanent residence, nationality, education, type of transport to Lhasa (by plane, by train, by bus or by car), previous exposure to high altitude, prior history of high-altitude illness, the use of prophylactic medicine, smoking habits, awareness of altitude sickness and self-reported health condition. Body Mass Index (BMI) was calculated as body weight (kg) divided by height (m) squared. According to the World Health Organization (WHO), obesity was categorized by BMI ≥ 30.00.

AMS was assessed by the Lake Louise Score System (LLSS) [13], which is based on the most frequent symptoms considered important for AMS: headache, dizziness, gastrointestinal distress (loss of appetite, nausea, or vomiting), lassitude or fatigue and insomnia [14]. Each item is scored by the subject on a scale between 0 and 3 (0 = none, 1 = mild, 2 = moderate, 3 = severe). Single item scores are added up, with the total scores ranging from a minimum of 0 to a maximum of 15. Headaches have been recognized as a key symptom of AMS by previous researchers [15–17]. AMS was defined as the presence of a headache, at least one other symptom and a total LLS ≥4 [14].

Statistical analysis

The Log-Binomial Model was applied to analyse the relationship between AMS and selected risk factors. The crude and adjusted prevalence ratio (PR) was computed with 95 % confidence intervals (Cl), level of statistical significance was set at $p < 0.05$. The analyses were carried out using SPSS (Statistical Package for Social Sciences, Version 22 for Windows. SPSS Inc. Chicago, USA, 2010).

Results

Population characterization

The participants originated from 48 different countries. The largest group was from China (46.9 %), followed by the Netherlands (6.3 %), the US (5.8 %), Germany (4.8 %), France (3.7 %) and the United Kingdom (3.7 %). Population characteristics are given in Table 1, and there was an approximately equal representation of men and women, and the mean age was 37.2 ± 14.4 years (range 15–81 years). Most of the tourists were non-obese, lived at low altitudes, non-smokers and considered themselves to be in good health. Almost half of the participants took prophylactic medicine. Among them, 72.6 % took Rhodiola or other Chinese medicine, 25.3 % used acetazolamide or diamox and 2.1 % used steroids or nifedipin. More than one-third of the participants reported previous AMS symptoms, and 25.6 % had been exposed to high altitudes in the preceding three months. Some tourists reported to have diabetes mellitus ($n = 30$;1.4 %), high blood pressure ($n = 112$;5.3 %), cardio-vascular disease ($n = 25$;1.2 %) or lung diseases ($n = 90$;4.3 %).

Acute mountain sickness

A total of 808 (36.7 %, CI: 34.6–38.7 %) subjects reached the standard of AMS with headache and a total LLS ≥ 4. Table 1 also shows the prevalence of AMS in different subgroups of the population, as well as crude and adjusted prevalence ratios for the potential determinants of AMS. Different approaches of analyses yielded similar results: analyses based on including all determinants in the model, specific causal models for each of the variables and models that only included variables that were statistically significantly related to AMS in the crude analyses. Only results from the first approach are reported in the present study, and we did not find any substantial differences in AMS prevalence between Chinese and other nationalities. Further stratification into participants from Asia, Europe, America and Oceania did not show a substantial variation in AMS prevalence either. Moreover, we did not find contrasts in prevalences of AMS between users and none users of prophylactic medicine. That was also the case for subgroups of participants who used Rhodiola, acetazolamide, steroids and nifedipin (results not given). In the fully adjusted model, the factors that remained statistically significantly associated with a higher risk of AMS were a poor or average health condition, no pre-exposure to high altitude, an age below 55 years, being a non-smoker and arrival in Lhasa by air.

A total of 1808 participants (82.1 %) reported at least one of the recorded symptoms. Fatigue was the most frequently reported symptom, followed by headache, insomnia, dizziness and gastrointestinal symptoms (Fig. 1). The mean overall AMS scores were 3.34 ± 2.63. In subgroups among those both with and without AMS, the mean scores differed significantly ($p < 0.05$), 5.94 ± 1.92 and 1.68 ± 1.40, respectively. In 30.5 % of participants, the onset of AMS symptoms started as early as on the journey to Lhasa, while in 47.6 % of participants the symptoms started within the first 12 h after arrival and in 21.9 % after 12 h. Furthermore, 21.0 % of the participants with AMS did not reduce their physical activity and 74.0 % had a moderate activity reduction, while 5.0 % chose to rest in bed because of symptoms. A total of 282 participants reported to have sought help or advice for AMS. Among them, 150 (53.2 %) got help from their tour companions or local friends, 92 (32.6 %) went to local hospitals and 20 (7.1 %) received a visit by the local doctor. No cases of HACE or HAPE were reported among the participants during the three days follow up.

Discussion

AMS defined as LLS ≥ 4 with headache was reported by 36.7 % of the participants. Fatigue, headache and insomnia were the three most commonly reported AMS related symptoms (66.8, 60.4 and 56.3 %, respectively). Tourists who reported to not be in a good health condition, to have no pre-exposure at high altitude in the preceding three months, to be younger than 55 years of age, to be a non-smoker and to have

Table 1 Characteristics, prevalence and risk factors of acute mountain sickness among tourists above 15 years of age arriving in Lhasa, Tibet, China between June and October 2010

Characteristics	N	AMS+ N (%)	Crude PR (95 % CI)	Adjusted PR* (95 % CI)
Gender				
Female	1072	387 (36.1)	1	1
Male	1103	461 (41.8)	1.16 (1.04,1.29)	1.08 (0.94,1.23)
Age				
≥ 55 years	360	116 (32.2)	1	1
< 55 years	1796	722 (40.2)	1.25 (1.06,1.46)	1.29 (1.04,1.60)
Obesity				
No	2015	787 (39.1)	1	1
Yes	119	48 (40.3)	1.03 (0.82,1.29)	1.02 (0.76,1.37)
Nationality				
Chinese	1018	401 (39.4)	1	1
Other nationalities	1162	447 (38.5)	0.98 (0.88,1.09)	0.92 (0.78,1.08)
Altitude of permanent residence/home				
2000 m or higher (>6500 ft)	111	37 (33.3)	1	1
Below 2000 m (<6500 ft)	1994	784 (39.3)	1.18 (0.90,1.54)	1.06 (0.76,1.49)
Education				
College or higher	1766	701 (39.7)	1	1
High school or lower	361	130 (36.0)	1.10 (0.95,1.28)	1.11 (0.92,1.33)
Smoking				
No	1849	742 (40.1)	1	1
Yes	251	83 (33.1)	0.76 (0.63,0.92)	0.75 (0.59,0.96)
Transportation				
Not by air	1138	409 (35.9)	1	1
By air	1022	435 (42.6)	1.18 (1.07,1.32)	1.17 (1.02,1.34)
Health condition				
Good health	1904	710 (37.3)	1	1
Poor or average health	197	117 (59.4)	1.59 (1.40,1.81)	1.63 (1.38,1.93)
Previous AMS symptoms				
No	1011	361 (35.7)	1	1
Yes	590	221 (37.5)	1.05 (0.92,1.20)	1.10 (0.96,1.26)
Awareness of AMS				
No	248	92 (37.1)	1	1
Yes	1851	732 (39.5)	0.94 (0.79,1.11)	1.02 (0.83,1.27)
Pre-exposure in the preceding 3 months				
No	1609	695 (43.2)	1	1
Yes	552	148 (26.8)	0.62 (0.54,0.72)	0.71 (0.60,0.84)
Use of prophylactic				
No	1116	416 (37.3)	1	1
Yes	965	399 (41.3)	1.11 (1.00,1.24)	1.05 (0.92,1.20)

*Adjusted for all variables in the table

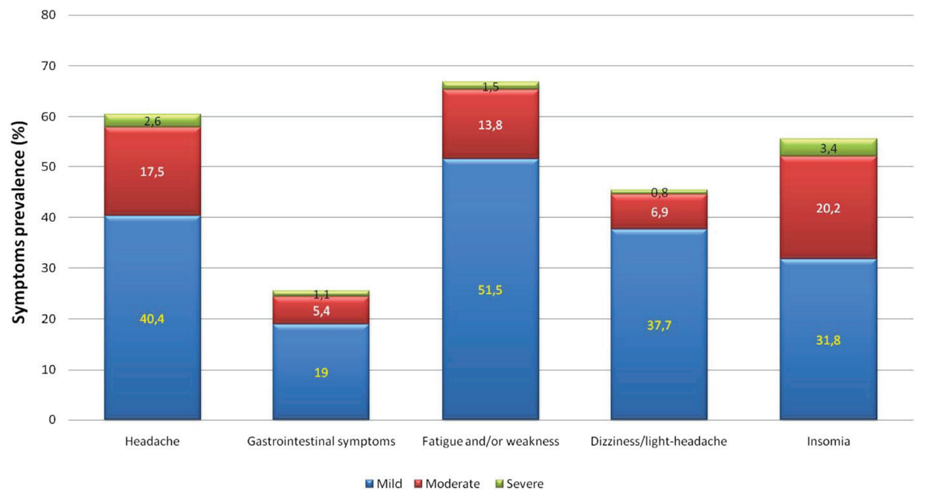

Fig. 1 Prevalence of symptoms of acute mountain sickness by severity among tourists above 15 years of age arriving in Lhasa, Tibet, China between June and October 2010

ascended to high altitude by air were at increased risk of experiencing AMS.

To the best of our knowledge, no other study has addressed the prevalence and risk factors of AMS in a large population of ordinary tourists arriving at an altitude as high as that in Lhasa. Characteristics of tourists visiting Lhasa will most likely change over time. We believe that the current study population resembled the typical recreational tourists to Tibet during the data collection period. The population showed a broad variation in characteristics that might influence their risk of developing AMS.

AMS was definitely a common problem among the study participants. Previous studies have reported both a higher and lower prevalence of AMS than our finding [6, 18–21]. Comparisons between studies are complicated by differences in population characteristics [20], altitude reached [6] and AMS definitions [18]. The current AMS prevalence is lower than what was reported in two other studies from Tibet, including one among tourists (42.3 %) visiting the Namtso Lake at 4718 m in Tibet [22] and one among construction workers (51 %) at Qinghai-Tibet altitudes up to 5000 m [23]. The higher altitude in these two studies could explain the higher prevalence of AMS compared to our study. The prevalence in our study was clearly higher than in a study carried out among tourists (28 %) in La Paz Bolivia at a similar altitude (3630 m) as that of Lhasa, even if we used a stricter definition of AMS [24]. However, that study consisted of only 32 participants, and AMS was measured immediately after arrival at high altitude. Several studies have been conducted among trekkers and mountaineers [8, 18, 20, 25, 26] with varying results. For example, one study showed a prevalence of 34 % in mountaineers in the Alps [8], which is quite comparable to our findings, while another study reported a prevalence of 10 % in trekkers in the Nepali Himalaya [18]. Overall, we believe that the prevalence found in this study is of an expected size compared with earlier studies if we attempt to take into account the differences in study populations, the altitude reached and the disease definition.

The unique culture and sacred places in Lhasa may motivate a variety of tourists to go there. Based on our observations, we cannot conclude that a population consisting of ordinary tourists has a substantially higher risk of AMS than more selected groups, even if there is reason to believe that such a population is less healthy and less physically fit compared to trekkers [11], mountaineers [25] and construction workers [10]. Our findings support the idea that AMS symptoms typically appear within the first 12 h after arrival at high altitude [3, 27, 28], and that people from different countries have a similar risk of developing AMS. In the present study, fatigue was the most frequently reported symptom of AMS, followed by headaches and sleep disorders. This is somewhat inconsistent with some earlier studies [16, 28, 29] that reported headaches and sleep disorders to be more common than fatigue. However, all these symptoms were common and most tourists have to expect some AMS-related symptoms and a reduction of activity during the first days, in addition to a few who would also prefer to stay in bed.

A lack of pre-exposure and rapid ascent to high altitude have been linked to AMS in previous studies [9, 11, 30–32]. For instance, Schneider and colleagues [32] reported that altitude exposure in the preceding two months reduces the risk of AMS. Hultgren and colleagues [33] found climbers who visited the Himalayas annually had fewer symptoms and improved their physical performance compared with the first time they visited. Our findings corroborate with this, and indicate some degree of physiological acclimatization and residual benefit from high-altitude exposure during the last three months. Living at high altitude has also been found to protect against AMS [6, 34]. Only a small proportion of the participants in our study lived at an altitude above 2000 m. Even if the AMS prevalence was low within this group, a low statistical power made it difficult to draw firm conclusions based on our findings. Several studies have shown an increased risk of AMS with a rapid ascent to high altitude [2, 3, 9]. Murdoch and colleagues found the prevalence of AMS to be 84 % among tourists who flew directly to Shyangboche at the altitude of 3740 m compared with 61 % among those who walked up from altitudes under 3000 m to the same altitude [9]. Our findings support this idea, as persons arriving by plane reported more frequent AMS than others. It is a possibility that the chosen transport to high altitude is related to a person's risk of developing AMS. We have attempted to address this by adjusting for an awareness of AMS and previous experience of AMS in the analyses. A further selection effect would probably lead to an underestimation of the effect of rapid ascent.

The impact of health conditions on the development of AMS is of importance for individual's decisions to travel to high altitude, though the answer to this question is unclear [6, 14, 31]. The prevalence of AMS was similar between those with and without diseases such as lung disease and cardio-vascular disease. This observation is in accordance with previous studies (18, 28, 29). On the other hand, we found that those who reported not being in good health had a higher risk of AMS. This seeming inconsistency could be explained by subjective reports of health condition by participants. Although smoking is generally considered harmful to health, studies have not always confirmed this [35, 36]. For example, Wu and colleagues [35] found that an 11 % decrease in the prevalence of AMS in smokers compared with non-smokers, whereas Song and colleagues [36] found that the prevalence of AMS was lower in smokers than in non-smokers. Our finding is in agreement with these studies. The potential explanation could be that smoking contributes to a reduction in nitric oxide (NO) [36], and it has been speculated that reduced NO levels may protect smokers from some AMS related symptoms [35]. However, this phenomenon would probably only last for a short period and perhaps reduce long-term adaptation to high altitude [35].

Reports on the effect of gender on AMS have been mixed and inconclusive [28, 37], as we did not find any indication of gender differences with AMS. Some previous studies conducted among Himalayan trekkers [38], conference attendees [6] and mountaineers [8] have reported that age was inversely correlated with AMS. Our findings corroborate with this. One theory [39] about the relationship between age and susceptibility to AMS is that there are age-dependent differences in intracranial and intraspinal cerebrospinal fluid capacity [40]. Old people with a larger ratio of cranial cerebrospinal fluid to brain volume results in them being better able to compensate for brain swelling by a displacement of cerebrospinal fluid, and are less likely to suffer from AMS than young people with a lower ratio [40].

Since there were only a few other accommodations or guest houses for tourists that were not on the tourist bureau's list, we have recruited participants from randomly selected hotels that represent the absolute majority of the places where tourists can stay in Lhasa. Most of the tourists who were invited to participate in the present study were willing to give the information that was asked for. We do not see strong reasons as to why AMS prevalence should be over- or underestimated in the study population. A more general problem with all such surveys is the potential selection mechanisms for the visiting populations, which could influence prevalence of AMS and associations between exposure and AMS. For example, it seems reasonable that people's decision not to go high could be affected by a previously bad experience with AMS. We believe that our finding of no negative effect of a former experience with AMS could have been caused by self-selection. Such selection processes could also affect other associations. It could be that people in old age, people who do not take prophylactic medicine, people with diseases, as well as smokers who decide to go high are a "healthy" part of that exposure group, and that such characteristics may change over time and between populations. Consistency in findings between different study populations with different characteristics would be of help. However, there are reasons for expecting differences between studies, so to draw general causal claims from these types of studies is therefore challenging. As a consequence, we believe that our findings reflect conditions and relations among tourists in Tibet recently, and if these findings corroborate well with results from similar studies carried out elsewhere, one could expand the interpretation of the findings.

Conclusion

AMS and AMS-related symptoms in tourists travelling to Lhasa are common, and tourists often need to reduce their activities during the first days of their stay. Symptoms typically start within the first 12 h after arriving. Associations between risk factors and AMS could be affected by self-selection in these types of studies. Age was inversely related to AMS, while country of origin, gender and reports of suffering from a chronic disease did not seem to be predictors of AMS. Subjects planning to visit high-altitude areas should be prepared for experiencing AMS-related problems, and consider preventive measures such as pre-exposure or gradual ascent to high altitudes.

Abbreviations

95 % CI: 95 % confidential interval; AMS: acute mountain sickness; BMI: body mass index; HACE: high-altitude cerebral edema; HAPE: high-altitude pulmonary edema; LLSS: Lake Louise Scoring System; PR: prevalence ratio; TAR: Tibet Autonomous Region.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

EB and LBSZ designed the study. LBSZ and colleagues collected the data. GGLZ analysed and drafted the manuscript. HS provided expert statistical advice. PN, EB and WTY provided professional advice and technical support. ØDH and KO did the pilot study. All authors read and approved the final version of the manuscript.

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Paper II

Acute Mountain Sickness, arterial oxygen saturation, and heart rate among Tibetan students who reascend to Lhasa after seven-years at low altitude: a prospective cohort study

Acute Mountain Sickness, arterial oxygen saturation, and heart rate among Tibetan students who reascend to Lhasa after seven years at low altitude: a prospective cohort study

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Key words: Acute Mountain Sickness, oxygen saturation, heart rate, Tibetan, reascend

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ABSTRACT

Objectives: The aim of the present study was to estimate the incidence of Acute Mountain Sickness (AMS), and address the changes in arterial oxygen saturation (SaO_2) and heart rate (HR) in native Tibetans who reascend to the high altitude city of Lhasa (3658 m) after a 7-year stay at low altitude.

Methods: We followed two cohorts of students aged 17 to 21 years (859 Native Tibetan and 801 Han Chinese), traveling from lowland China until three days after their arrival in highland city of Lhasa. Questionnaire information of the symptoms of AMS using the Lake Louise Scoring System (LLSS), resting SaO_2 and HR were assessed both before leaving the lowland and after arriving in Lhasa. Linear regression was performed to compare changes in SaO_2 and HR levels from low to high altitude in Tibetan and Han Chinese.

Results: New cases of AMS occurred in only 1.2% (95% CI: 0.4% to 2.0%) of the Tibetan students who came to Lhasa by train compared with 32.7% (95% CI: 28.0% to 37.3%) and 42.9% (95% CI: 38.0% to 47.7%) of the Han Chinese students who came to Lhasa by train and by air respectively. Tibetan students had less changes in SaO_2 (-2.95 percentage points, 95% CI: -3.24% to -2.65%) and HR (10.89 bpm, 95% CI: 9.62 bpm to 12.16 bpm) from low to high altitude compared to Han Chinese students, although measurements did not differ between the two groups when measured at low altitude.

Conclusions: Healthy Tibetans are mostly protected against AMS and primarily maintain their good adaptation to high altitude, even after a long period of stay at low altitude.

Strengths and limitations of this study

This is the first population-based study addressing the occurrence of Acute Mountain Sickness (AMS), and acute changes in arterial oxygen saturation (SaO_2) and heart rate (HR) levels in a large cohort of Tibetans who after living at low altitude for seven years returned to high altitude in Tibet at the same point in time.

The study was able to compare results among Native Tibetan students with similar results from a cohort of Han Chinese students well matched for characteristics like age, height, and weight travelling from the same lowland area to the same high altitude.

Only a few simple physiological parameters suitable for field studies were measured affecting the possibility to address the mechanism behind physiological adaptation in depth.

The data collection for the two cohorts took place in different years, but both studies were conducted in the warm season, and the same date collection procedure was used for both groups reducing the chance of bias caused by differences in environmental conditions and data collection methods.

There were some losses to follow up among the Tibetan students, but we did not find any differences in baseline characteristics between Tibetans lost or not lost to follow up reducing the chance of selection bias.

INTRODUCTION

Exposure to high altitude may lead to Acute Mountain Sickness (AMS), which usually manifests itself with nonspecific symptoms such as headache, dizziness, loss of appetite, nausea, vomiting, insomnia and fatigue.[1-5] Although AMS is generally benign and self-limiting, in some cases it may progress to more serious conditions like high-altitude cerebral edema (HACE).[1]

Studies of AMS among lowlanders have shown signs of some persistency of acclimatization which lead to reduction in the incidence and severity of AMS from prior high-altitude exposure,[6-9] and this residual acclimatization from prior exposure will be lost over a few days to weeks after a return to low altitude.[8 10-12] Since most high altitude natives live in high altitude, and usually only descend to low altitude for short periods, little information is available as to what extent and for how long a residual adaptation will persist. Findings from some previous studies among high-altitude natives of Bolivia[13] and Peru[5] indicate a reduction of adaptation when returning to high altitude after a short stay at low altitude. Among Tibetan highlanders, there are occasional reports of an AMS incidence of zero, usually upon ascending from a high to higher altitude or after only a short time stay at a low altitude.[9 14 15] However, the effect of exposure to low altitudes on AMS among Tibetans re-ascending to high altitudes is still unclear, especially after long stay at low altitudes.
The exact mechanism of AMS is unknown, but hypoxemia which refers to a lowered oxygen level in the blood is proposed as a principal cause of AMS,[16-20] making arterial oxygen saturation (SaO_2) an interesting measure for addressing acute acclimatization/adaptation to hypoxic exposure. Furthermore, a marked increase in peripheral sympathetic activity which can be reflected by heart rate (HR) has also been indicated as a consequence of highaltitude exposure.[21 22] Previous studies have mainly paid attention to comparisons of SaO_2 and HR between indigenous populations at specific altitudes.[4 9 14 23 24] As far as we know, no study has addressed acute changes of SaO_2 and HR after ascent from low to high altitudes among native highlanders.

Tibetan students who attended middle school in lowland China provided a unique opportunity to study AMS and changes in SaO_2 and HR among Tibetans re-ascending to high altitudes after long stay at low altitudes. A comparison of these parameters between native Tibetans and Han Chinese with matched characteristics may contribute to the understanding of high-altitude adaptation among Tibetans. Therefore, in the present study we have collected questionnaire information about AMS symptoms and measures of SaO_2 and HR in 17-21 year old Tibetan and Han Chinese students both at low and high altitude. The Tibetan students had been living at low altitude for seven years, while the Han Chinese students were born and raised at low altitude China and had never been to high altitude before. Data were collected shortly before both groups left lowland China, and when the same students arrived in Lhasa at 3,658 m. The aim of the present study was to investigate the incidence of AMS, and assess changes in SaO_2 and HR in a population of native Tibetan students returning to Lhasa after a seven-year stay at low altitude. We hypothesized that native Tibetans would have a lower risk of developing AMS and less changes in SaO_2 and HR after a long-term stay at low altitude areas compared with Han Chinese lowland residents.

MATERIALS AND METHODS

Setting

The data collections were carried out in seven different cities in lowland China seven days prior to departure and on the third day after the ascent to Lhasa. The seven lowland cities were: Beijing (32 metres above sea level (MASL)), Tianjin (5 MASL), Chengdu (506 MASL), Nantong (5 MASL), Wuhan (23 MASL), Yueyang (57 MASL) and Shijiazhuang (81 MASL). The cities were chosen because they all had educational institutions with Tibetan students planning to go home after ending their education, and with Han Chinese students planning to go to Lhasa to continue their education. Lhasa, the capital city of the Tibet Autonomous Region (TAR), People's Republic of China, is located at an elevation of 3,658 MASL, which makes it one of the highest situated cities in the world.

Study samples

We included two populations: Native Tibetan students who stayed in the lowland area for seven years, and Han Chinese students who were born and raised in the lowlands without any former exposure to high altitude.

Tibetan students: Seven out of a total of 12 middle schools for Tibetans in lowland China were randomly selected. All senior students from the selected schools who were about to graduate in June 2012 were invited to participate, with the data collection taking place from May to June 2012. Of the 859 eligible students, all students had their SaO_2 and HR measured, and returned completed self-assessment questionnaires (lowland questionnaire) to field workers at their schools before leaving for high altitude areas. The same students received a new questionnaire (highland questionnaire) at the Lhasa railway station, since all of them traveled to Tibet by train, which was organized by their school administrations. All students were asked to deliver the highland questionnaire to fieldworkers and measured the SaO_2 and HR on the third day after their arrival in Lhasa. For reasons unknown, 120 students did not return the highland questionnaire and eight questionnaires were incompletely filled out, leaving 731 (85.1%) highland questionnaires for the analysis. Moreover, 158 students did not attend the SaO_2 and HR measurements on the third day (response rate 81.6%).

Han Chinese students: The students came from the same lowland area where the Tibetan students had studied and were going to study at Tibet University. Data collection took place from August to September 2014. Of the 810 eligible students, all students received the lowland questionnaires via post before they ascended to Lhasa, and were asked to return it to fieldworkers when they registered at Tibet University. They were also asked to visit fieldworkers for measuring their SaO_2 and HR at the same place in the seven lowland cities as where the Tibetan students had their measurements taken before they ascended to Lhasa. For unknown reasons, 227 students did not attend the SaO_2 and HR measurements (response rate 72.0%). Moreover, 11 students did not return the lowland questionnaires because of misplacement (response rate 98.6%). Since all students live in campus during their study at Tibet University, we had the chance to follow the students and measure their SaO_2 and HR, and ask them to fill in the highland questionnaire on the third day after their arrival in Lhasa. One student refused, and eight were excluded because they had already been in Lhasa more than three days before the data collection took place. Thus, information from the highland questionnaire and measurements of SaO_2 and HR from 801 students were included in the analysis of high altitude information (response rate of 98.9%).

It takes about 2 hours with a cabin pressure equivalent to 2400 m by air from lowland China to Lhasa. Trains that go to Lhasa have only one route which is from Xining to Glomud (10 hours, average altitude 2906 m, range 2261m-3698 m) and from Glomud to Lhasa (14 hours, average altitude 4251 m, range 2808 m-5072 m).

A written consent form about the study was given on the first page of the questionnaire, and the participants were informed that they could withdraw from the study for any reason at any time without any negative consequences.

Questionnaire

Two questionnaires based on the Lake Louise-AMS scoring system were developed and used in the data collection: one lowland and one highland questionnaire. The lowland

questionnaires included questions on AMS-related symptoms, and the aim was to identify the basic health conditions and symptoms before the students ascended to high altitude.
In addition to including the same questions as in the lowland questionnaire, the highland questionnaire was designed to obtain data concerning gender, age, ethnicity, height, weight, type of transport to Lhasa, altitude of permanent residence, previous exposure to high altitude, self-reported health condition, history of high-altitude illness, use of prophylactic medicine, awareness of altitude sickness and smoking habits. Body Mass Index (BMI) was calculated as body weight (kg) divided by height (m) squared.

The AMS-related questions are based on a Chinese version of the original Lake Louise Score System (LLSS) questionnaire.[25] The Chinese version has been used in several earlier studies on AMS.[9 15 24 26 27] Before the questionnaire was used for the current study, we translated back the questions into English and it did not reveal any discrepancy with the original English version. The LLSS consists of a self-reported assessment of five AMS symptoms: headache, lassitude or fatigue, gastrointestinal distress (loss of appetite, nausea, or vomiting), dizziness and insomnia.[25] All symptoms were graded from 0 to 3, which was indicative of no, mild, moderate or severe symptoms respectively. A diagnosis of AMS was defined as the presence of headache, at least one of the other symptoms and a total LLS $\geqslant 4$.[28] The participants were also asked "when did the symptoms first begin?". The response options included "less than 12 hours" "12 hours to 24 hours" "25 hours to 48 hours" and "more than 48 hours after arrival".

Measurements of SaO_2 and HR

The arterial oxygen saturation (SaO_2) and heart rate (HR) were measured at low altitude and then again on the third day after arrival in Lhasa. SaO_2 and HR were measured by finger pulse oximetry (Nellcor, NPB-40, California, USA) with the probe placed on the index finger of the left hand in a sitting position after a 15-minute rest. Values were observed three times at 30-second intervals, and the mean of three readings was recorded for data analysis. Furthermore, all measurements were conducted by the same fieldworkers using the same equipment. No smoking was permitted within 2 hours before the measurements.

Statistical analysis

The descriptive statistics are presented as the frequencies and mean with a standard deviation (SD) for each variable. The Chi-square (χ^2) tests were performed for comparing categorical variables, and a Student t-test was used for comparing continuous variables. One-way analysis of variance (ANOVA) was performed for comparing the differences of SaO_2 and HR between Tibetan and Han Chinese students by different transportations. We used a linear regression model to check the changes from low altitude to high altitude of SaO_2 and HR for Tibetan and Han Chinese. We put SaO_2 and HR as dependent variables and altitude and ethnicity as explanatory variables, and added an interaction term between altitude and ethnicity. Associations were considered statistically significant at $p < 0.05$, and analyses were carried out using SPSS V.24 for Windows.

RESULTS

Population characterization

Table 1 shows that the population characteristics of native Tibetans and Han Chinese did not differ regarding sex, age, height, weight and BMI. However, Tibetans were more frequent smokers. Of the Tibetan students, 152 (17.7%) had visited Tibet once, 326 (38.0%) twice, 192 (22.4%) three times, 93 (10.8%) four times and 96 (11.2%) five times or more during their seven years of study in lowland China. Each visit lasted 30 days or less, except for one visit of two months after their graduation from junior middle school. None of the Tibetan students had been exposed to high altitude in the preceding three months before the baseline data collection. All Han Chinese students had permanent residence below 2,000 m, and had never been at high altitude before. Approximately half of them (49.3%) came to Lhasa by train and the rest by air.

Incidence of Acute Mountain Sickness

A total of nine Tibetan students (1.0%) had symptoms qualifying them as having AMS-like symptoms at baseline, while the corresponding number for the Han Chinese students was 12 (1.5%). Excluding students with AMS-like symptoms at baseline, a total of 9 (1.2%) Tibetan and 303 (37.8%) Han Chinese students developed AMS (headaches and an LLS ≥ 4) within the third day after arrival in Lhasa. Among the nine Tibetans free from AMS-like symptoms at baseline, and who developed AMS after arriving in Lhasa, eight (88.9%) reported having influenza and one sinusitis before they left for Lhasa. For the Han Chinese students who developed AMS, 7% reported influenza, 5% tonsillitis and 3% pollen allergy before their ascent to high altitude, whereas the rest did not report any diseases. For the nine Tibetan students that were categorized as having AMS eight reported symptom start within 24 hours after arrival. For most of the Han Chinese students (81.7%) who were categorized as having AMS, the onset of symptoms occurred within the first 24 hours after arriving in Lhasa. Table 2 compared the incidence of AMS, average SaO_2 and HR between Native Tibetan and Han

Chinese students. Han Chinese students were stratified into groups according to whether they traveled to Lhasa by plane or train. Before their ascent, there were no statistically significant differences between Tibetan and Han Chinese students regarding prevalence of AMS-like symptoms and means of HR. Both Tibetan students and Han Chinese students who came to Lhasa by train had higher SaO_2 than Han Chinese students by plane. However, there was no statistically significant differences between Tibetan and Han Chinese students regarding overall means of SaO_2 (Tibetan vs. Han Chinese: 99.2% vs. 99.1% $P>0.05$). On the third day after arrival in Lhasa, Han Chinese students who flew to Lhasa had a higher incidence of AMS compared with those who came to Lhasa by train ($P<0.05$). Both groups had a higher incidence of AMS, a lower SaO_2 and a higher HR compared with native Tibetans ($P<0.05$). The incidence of AMS and the means of SaO_2 and HR were not statistically significantly related to the number of visits to Tibet during the seven years of study in lowland China among Tibetan students (supplementary table1).

Some Tibetans were lost in the follow-up, and some Han Chinese students did not participate in parts of the data collection at baseline. Therefore we also compared the AMS incidence, SaO_2 and HR levels between Tibetan students and Han Chinese students with information from both the lowland and highland data collection. The results show similar contrasts between the population groups, as shown in Table 2 (results not presented). No HACE and HAPE were reported during the data collection time in both groups.

Symptoms of Acute Mountain Sickness

AMS-like symptoms were rare and of similar frequency in Tibetan and Han Chinese at low altitude, except that Han Chinese who came to Lhasa by air had more sleeping difficulties. After the ascent to high altitude, both the Han Chinese students arriving by train and by plane had statistically significant higher incidence of all the five AMS-related symptoms compared with the Tibetan students ($p<0.05$) (Table 3). A total of 452 Tibetan students (61.8%) and 682 Han Chinese students (85.1%) reported at least one AMS-related symptom. Headache was the most frequently reported symptom, followed by fatigue, dizziness, insomnia and gastrointestinal symptoms, both in Tibetans and Han Chinese (Table 3). The mean overall LLSS scores differed significantly with 1.31 ±1.46 among Tibetans compared with 3.15±2.56 and 3.96±2.76 among Han Chinese arriving by train or plane ($p<0.05$ respectively).

Resting SaO_2 and HR

There was no difference in SaO_2 and HR levels between Tibetan and Han Chinese students at low altitude (Table 2). After arrival at high altitude, Tibetan students had a significantly higher SaO_2 and lower HR compared with Han Chinese students. This was also the case when comparing Tibetan and Han Chinese students with and without AMS (Figure 1 and Figure 2). The SaO_2 was decreased in both Tibetan and Han Chinese students after arrival at high altitude. On average, the decrease was 8.1% in Tibetans (99.2% to 91.1%) and 11.1% in Han Chinese (99.1% to 88.0%). The HR among Tibetans on the third day after arrival at high altitude was similar to the values observed at low altitude (72.1 beats per minute (bpm) vs. 72.7 bpm), while on average the HR in Han Chinese increased by 11.5 bpm after arrival in Lhasa (71.3 bpm - 82.8 bpm). The changes in SaO_2 ($-11.2_{\text{by train}}$ vs. $-11.1_{\text{by air}}$, p=0.82) and HR ($10.3_{\text{by train}}$ vs. $12.5_{\text{by air}}$, p=0.07) were not statistically significantly different when comparing Han Chinese students arriving in Lhasa by train or plane. The linear regression model revealed that Tibetan students had less changes in SaO_2 (-2.95 percent points, 95% CI: -3.24% to -2.65%) and HR (10.89 bpm, 95% CI: 9.62 bpm to 12.16 bpm) from low to high altitude compared with Han Chinese. Participants with AMS also had a significantly lower average SaO_2 than those without AMS after arrival in Lhasa in both groups (Figure 1). The HR was significantly higher in AMS subjects than non-AMS subjects in Han Chinese, while for Tibetans, there was a similar but not statistically significant trend (Figure 2).

DISCUSSION

The Tibetan students clearly had a lower incidence of AMS and less AMS-related symptoms compared to the Han Chinese students. Furthermore, the Tibetans had significantly less changes in SaO_2 and HR levels than the Han Chinese students after a three-day stay at 3,658 m in Lhasa, even if they had similar levels before leaving lowland China.

The significantly lower incidence of AMS among Tibetan compared with Han Chinese students found in this study is not surprising, as it is well-known that native Tibetans have a better adaptation to high altitude than any other population.[1 24 29] Nonetheless, there are few population-based studies that have actually confirmed that Tibetans remain adapted to high altitude, and are protected against the development of AMS if high-altitude exposure is discontinued by stays at low altitude, especially after long-term stays. Some studies among train passengers,[15] construction workers[9] and mountaineers[30] have reported that Tibetans are completely free from AMS. However, these studies were conducted in selected populations moving from a high to higher altitude, or re-ascending to high altitude after a short stay at low altitude. To the best of our knowledge, this is the first population-based study addressing the occurrence of AMS, and the changes in SaO_2 and HR levels in Tibetans who lived at a low altitude for seven years and then returned to a high altitude.

We also had the possibility to compare our results to findings from a population of Han Chinese students with similar characteristics who had never been at high altitude before arriving in Lhasa. It appears that after a long-term stay at low altitude, Tibetans were clearly less susceptible to AMS than lowland Han Chinese, also when compared with subgroups of Han Chinese students who traveled by air or used the same mode of transportation as the Tibetans did, namely by train. Short visits to high altitude during a long-term stay at low altitude did not seem to influence the Tibetan's degree of adaptation. We could not claim that Tibetans were entirely immune against developing AMS, since AMS-related symptoms were reported by a substantial proportion of Tibetans. However, the incidence and severity of the symptoms were clearly lower in Tibetan than in Han Chinese students. Additionally, examining the data of the nine Tibetan students who developed AMS, we found that eight of them reported having influenza shortly before leaving low altitude. It has been suggested that normal acclimatization could be disturbed by respiratory infections.[31-33] In addition, such infections may also lead to AMS-like symptoms, and through that increase the potential for a misdiagnosis with AMS.[31] Overall, our findings support the idea that healthy Tibetans after a long-term stay at low altitude are primarily protected against the development of AMS when re-ascending to high altitude.

Tibetans also showed a different reaction to high altitude than Han Chinese students when it came to levels of SaO_2 and HR. Before their ascent, there were no signs of difference in these measurements between the two populations. After their arrival at high altitude, Tibetans had less change in SaO_2 and HR levels than Han Chinese, which may indicate a more favorable reaction to acute altitude exposure. Since hypoxia plays a key role in the development of AMS, measuring SaO_2 and HR has been suggested as simple indicators of adaptation/acclimatization to high altitudes and impending AMS.[33 34] This is motivated by the fact that lowered oxygen levels in the blood are clearly related to AMS at high altitude.[16 18] Likewise, individuals with a higher HR at rest have been reported to be at risk of developing AMS at high altitude.[9] It therefore seems reasonable to suggest that genetic factors involved in long-term adaptation to high altitude in Tibetans have contributed to our findings, even if we did not have the possibility to explore this. As opposed to acclimatization among Han Chinese, which occurs because of an immediate physiological response to a changing environment, the “high-altitude adaptation” among Tibetans has developed in long-term physiological responses to a high-altitude hypobaric hypoxic environment with heritable behavioral and genetic changes.[24] A study from second-generation Tibetan lowlanders[35] provides evidence of adaptation with regard to acute reaction to high altitude exposure. The study did not measure AMS, but Tibetans born and living in Kathmandu (1,300 m) exhibited a greater aerobic working capacity than Caucasian lowlanders when exposed to high altitude. This indicates that the adaptation to acute exposure to high altitude among Tibetans has not changed over one generation, and could be linked to unique adaptation genes.[35] Several recent genomic studies[14 36-38] in native Tibetan highlanders have revealed that some genes are associated with high-altitude adaptation. However, these genes have been related to chronic mountain sickness, and as far as we know, no direct evidence between these genes and AMS has been proposed.[38 39] Although it seems likely that genetics plays a role in the development of AMS, we cannot fully decide whether the observed differences between Tibetan and Han Chinese students can be explained by genetic background. It has been reported that lowlanders with a pre-exposure to high altitude may establish some degree of physiological adaptation, thus resulting in a reduction in the incidence and severity of AMS when they re-ascend to high altitude.[7-9] Hence, the previous length of stay in high altitude may also have contributed to the Tibetan students’ adaptation to high altitude. Taken together, both genetic and physiological factors may have contributed to a better adaptation to high altitude in the Tibetan than Han Chinese, also after a long-term stay at low altitude.

In the present study, some Tibetan students were lost to follow-up, and some Han Chinese students did not participate in parts of the data collection at baseline. If the subjects who did not complete the study had different characteristics compared with the total sample, the incidence of AMS could then be overestimated or underestimated. However, we did not find any low altitude differences in characteristics between the Tibetans lost or not lost to follow-up at altitude which we believe is an argument against expecting large difference in AMS among those lost and not lost to follow-up. For the Han Chinese the collected data were quite complete except for some missing information about baseline SaO_2 and HR which we do not believe have affected the main finding as these individuals were quite comparable to those with complete information. Therefore, we believe that our findings reflect AMS conditions and relations between Tibetan and Han Chinese students in general, as the samples were randomly selected. Some participants may forget about their health problems. However, we believe that most people will remember which health problems they have experienced during the last three days. Furthermore, in the present study, the participants had been informed about the purpose of the study and knew that they were going to answer to questions about AMS symptoms after arrival which is a further argument against substantial recall bias. The different ascent profiles may also have influenced AMS incidence in our study. Consequently, we also compared Tibetan with Han Chinese students who had arrived in Lhasa by train. The results still showed that Tibetans clearly had a lower incidence of AMS, a less changes in SaO_2 and HR levels than Han Chinese students. The two cohort studies took place in different years, but both studies were conducted in the warm season, and thus the effect of temperature on AMS, SaO_2 and HR were almost the same. Both the baseline measurements in Tibetan and Han Chinese were conducted one week before leaving low altitude. As a result, the influence of influenza on reported AMS symptoms at high altitude may have been different if baseline measures were registered just before the participants left. Practical reasons made this difficult, but the same data collection procedure for both groups should reduce the chance of biased comparisons between the groups. To obtain representative measurements, SaO_2 and HR were measured three times at 30-second intervals, and the same pulse oximeter was used throughout the data collection period by the same field workers.

CONCLUSION

The significantly lower incidence of AMS, less change in SaO_2 and HR levels in Tibetan than Han Chinese students favors the view that healthy Tibetans are mostly protected against AMS and maintain their good adaptation to high altitude, even after a long-term stay at low altitude. It is likely that both genetic and physiological factors contributed to this, but based on the available data this study could not address this issue further.

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Contributors PN, EB and GGLZ designed the study. GGLZ, LBSZ and colleagues collected the data. GGLZ analysed and drafted the manuscript. HS provided expert statistical advice. PN, EB and WTY provided professional advice and technical support. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Obtained

Ethics approval The study was granted by the Medical Ethics Committee of Fu-kang Obstetrics & Gynecology, and Children's Hospital, Lhasa, Tibet, China. The Norwegian Regional Committees for Medical and Health Research Ethics also approved the study.

Data sharing statement No additional data are available.

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Table 1.Population characteristics of 17-21-year-old native Tibetan and Han Chinese students in Lhasa

	Native Tibetan	Han Chinese	
	By train (n=859)	By train (n=395)	By air (n=406)
Male (%)	425 (49.5)	198 (50.1)	215 (53.0)
Age, years (SD)	18.89 (0.88)	18.94 (0.98)	18.96 (0.94)
Height, cm (SD)	167.20 (7.08)	166.99 (7.85)	167.62 (7.72)
Weight, Kg (SD)	59.88 (7.75)	60.15 (10.07)	60.34 (10.33)
BMI, Kg/m^2, (SD)	21.37 (1.98)	21.51 (2.82)	21.39 (2.76)
Smoking, yes (%)	140 (19.3)	28 (7.1) *	26 (6.4)$^{\Delta}$

Data are presented as frequencies (%) and means (SD). Data were analysed using χ^2 test for comparison of categorical variables, and One-way ANOVA for comparison of continuous variables.

* indicates p<0.05 native Tibetan vs. Han Chinese by train; $^{\Delta}$ indicates p<0.05 native Tibetan vs. Han Chinese by air.

Table 2. Incidence of acute mountain sickness (AMS) and means of arterial oxygen saturation (SaO_2) and heart rate (HR) with 95% CI in 17-21 year old native Tibetan and Han Chinese students

	Native Tibetan		Han Chinese			
	By train (n=859)		By train (n=395)		By air (n=406)	
Lowland						
AMS-like symptoms	0.011	(0.004,0.017)	0.015	(0.003,0.027)	0.015	(0.003,0.027)
SaO_2 (%)	99.2	(99.1,99.3)	99.2^{o}	(99.0,99.4)	98.9$^{\Delta}$	(98.7,99.1)
HR(bpm$^{\#}$)	72.1	(71.6,72.5)	71.6	(70.5,72.7)	71.1	(70.1,72.1)
Highland						
AMS	0.012*	(0.004,0.020)	0.327^{o}	(0.280,0.373)	0.429$^{\Delta}$	(0.380,0.477)
SaO_2 (%)	91.1*	(90.8,91.3)	88.1	(87.9,88.3)	87.9$^{\Delta}$	(87.6,88.1)
HR(bpm$^{\#}$)	72.7*	(72.1,73.2)	82.2	(81.2,83.2)	83.5$^{\Delta}$	(82.4,84.5)

$^{\#}$bpm: beats per minute; For Han Chinese students, the results are stratified according to the type of transportation from lowland China to Lhasa; * indicates $p<0.05$ native Tibetan vs. Han Chinese by train; $^{\Delta}$ indicates $p<0.05$ native Tibetan vs. Han Chinese by air, ^{O} indicates $p<0.05$ Han Chinese by train vs. Han Chinese by air.

Data were analysed using One-way ANOVA for comparison of the differences of SaO2 and HR between native Tibetan and Han Chinese by different transportation. Chi-square ($\chi 2$) test was performed for comparing incidence of AMS between native Tibetan and Han Chinese by different transportation.

Table 3. Incidence of Acute Mountain Sickness related symptoms in 17-21 year old native Tibetan and Han Chinese students after arrival in Lhasa

	Symptoms	Headache n (%)	Gastrointestinal symptoms n (%)	Fatigue n (%)	Dizziness n (%)	Difficulty sleeping n (%)
Tibetan by train	None	449(61.0)	683(93.1)	523(71.2)	599(81.4)	670(91.2)
	Mild	241(32.7)	42(5.7)	148(20.1)	119(16.2)	30(4.1)
	Moderate	44(6.0)	6(0.8)	45(6.1)	13(1.8)	23(3.1)
	Severe	2(0.3)	3(0.4)	19(2.6)	5(0.7)	12(1.6)
Han Chinese by train	None	178(45.1)	268(67.8)	183(46.3)	204(51.6)	239(60.5)
	Mild	166(42.0)	97(24.6)	137(34.7)	164(41.5)	85(21.5)
	Moderate	32(8.1)	19(4.8)	51(12.9)	24(6.1)	40(10.1)
	Severe	19(4.8)	11(2.8)	24(6.1)	3(0.8)	31(7.8)
Han Chinese by air	None	118(29.1)	251(61.8)	132(32.5)	148(36.5)	222(54.7)
	Mild	202(49.8)	114(28.1)	166(40.9)	205(50.5)	106(26.1)
	Moderate	69(17.0)	37(9.1)	78(19.2)	49(12.1)	50(12.3)
	Severe	17(4.2)	4(1.0)	30(7.4)	4(1.0)	28(6.9)

Data are presented as number with frequencies (%).

Figure 1. Mean of oxygen saturation (%) with 95% CI in AMS and non-AMS subjects on the third day after arrival in Lhasa by different ethnicity

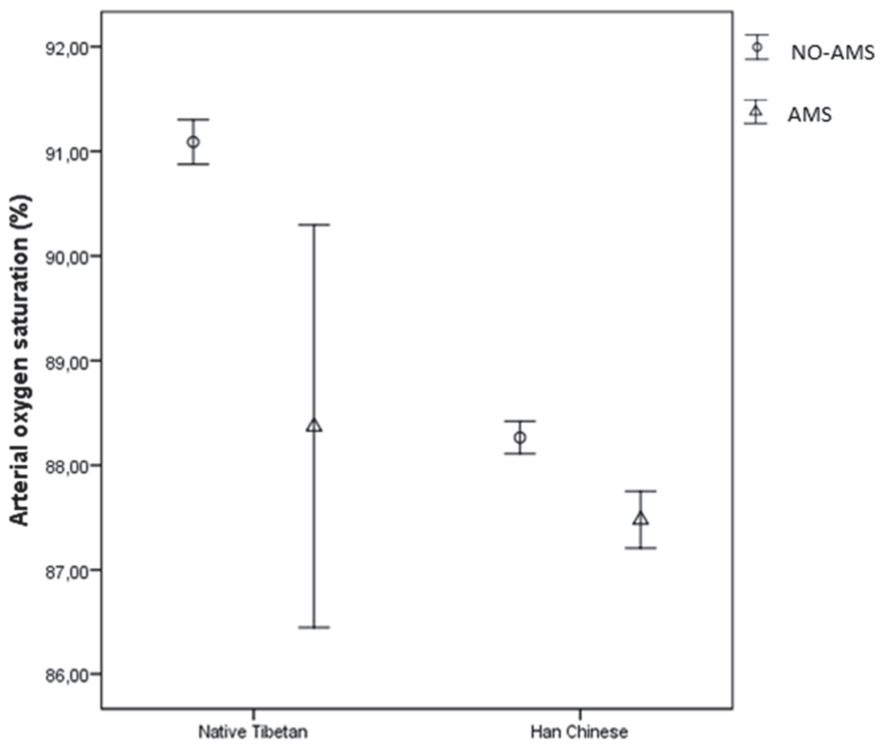
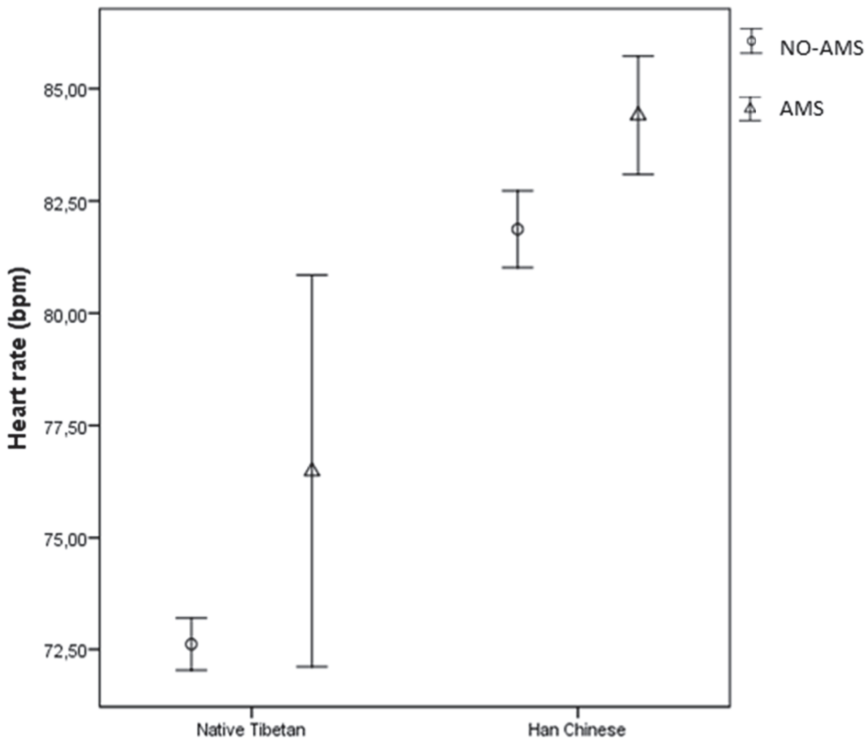


Figure 2. Mean of heart rate (bpm: beats per minute) with 95% CI in AMS and non-AMS subjects on the third day after arrival in Lhasa by different ethnicity



Supplementary table1. Incidence of acute mountain sickness (AMS) and means of arterial oxygen saturation (SaO_2) and heart rate (HR) with 95% CI in Tibetan students grouped according to number of visits to Tibet during their seven years of study in lowland China

Number of visits Tibet	Total number	AMS	P-value	SaO_2 %	P-value	HR bpm #	P-value
1	152	0.015(-0.006,0.035)		91.3(90.7,91.8)		72.1(71.1,73.0)	
2	326	0.011(-0.002,0.024)		90.9(90.5,91.2)		73.1(72.1,74.1)	
3	192	0.012(-0.005,0.028)	0.998	91.0(90.6,91.4)	0.602	73.0(71.6,74.4)	0.398
4	93	0.013(-0.013,0.040)		91.4(90.8,91.9)		72.8(71.0,74.6)	
≥5	96	0.014(-0.013,0.040)		91.2(90.4,91.9)		71.3(69.8,72.9)	

#bpm: beats per minute; One-way ANOVA was performed for comparing means of SaO_2 and HR between groups by number of visits to Tibet. Chi-square ($\chi2$) test was performed for comparing incidence of AMS between groups by number of visits to Tibet.

Paper III

Associations between arterial oxygen saturation, heart rate and acute mountain sickness in a population of 17-21 year old Han Chinese students traveling from low altitude to Lhasa at 3,658 m above sea level: a prospective cohort study