Smoking, acute mountain sickness and altitude acclimatisation: a cohort study

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ABSTRACT
Rationale The relationship between cigarette smoking and acute mountain sickness (AMS) is not clear.
Objective To assess AMS risk and altitude acclimation in relation to smoking.
Methods 200 healthy non-smokers and 182 cigarette smokers were recruited from Han lowland workers. These were men without prior altitude exposure, matched for age, health status and occupation, who were transported to an altitude of 4525 masl.
Measurements AMS, smoking habits, arterial saturation (SpO2), haemoglobin (Hb), lung function and mean pulmonary artery pressure (PAPm) were assessed upon arrival and after 3 and 6 months.
Main results Compared with non-smokers, smokers had a lower incidence of AMS and lower AMS scores than non-smokers upon arrival; higher Hb and PAPm associated with lower SpO2 at 3 and 6 months at altitude; and lower forced expiratory volume in 1 s and maximal voluntary ventilation at 3 and 6 months.
Conclusions Smoking slightly decreases the risk of AMS but impairs long-term altitude acclimatisation and lung function during a prolonged stay at high altitude.

INTRODUCTION
In China in 2010, 53% of men and 28% overall smoked tobacco.1  Apart from its general health risks, smoking may influence altitude hypoxia tolerance. According to some it aggravates hypoxaemia and hence increases the risk for acute mountain sickness (AMS) (Hultgren, p.469),2  but mountaineers find that smoking decreases AMS risk.3  However, sound epidemiological data on the effect of smoking on risk and disease course of AMS are lacking. During the construction of the Qinghai–Tibet railroad from 2001 to 2005, >78,000 lowland workers ascended to work and live at altitude. Since 34% of the employed Han male workforce smoked tobacco, this presented a unique occasion to directly investigate the effects of smoking on AMS risk. We therefore recruited construction workers ascending from low altitude to work and live at the highest construction sites at an average altitude of 4552 masl. We measured AMS incidence and progression, and acclimatisation in smokers and non-smokers.

METHODS
Three hospitals participated (4779 masl, barometric pressure (Pb) ~417 mm Hg; 4505 masl, Pb ~440 mm Hg; 4292 masl, Pb ~447 mm Hg). The highest work site was at 4905 masl. The study was approved by the China National Science Foundation and the Qinghai High Altitude Medical Research Institute Committee on Human Research. In 2008, a first group of 4653 workers was recruited. All prospective workers filled out a questionnaire providing information on age, sex, ethnicity, occupation, place of birth, altitude exposure, personal and family medical history, smoking and drinking behaviour. Subjects were interviewed and underwent a physical exam. Subjects in good health and physical condition were offered a job. The subjects went a physical exam. Subjects in good health and family medical history, smoking and drinking behaviour. Subjects were interviewed and underwent a physical exam. Subjects in good health and family medical history, smoking and drinking behaviour. Subjects were interviewed and underwent a physical exam. Subjects in good health and family medical history, smoking and drinking behaviour.

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Arterial oxygen saturation ($\text{SpO}_2$, finger oximetry, Ohmeda, Louisville, CO, USA) was measured in a seated position after 30 min of rest. Mean pulmonary artery pressure (PAPm) was estimated by Doppler. With a 3.5 MHz transducer (HP-Sonos 1000 or 1500, Palo-Alto, CA, USA) data were obtained from the parasternal short-axis or apical position, the subject lying in slight left oblique rotation. Recordings were stored on videotape for post hoc analysis by two independent cardiologists, unaware of smoking or altitude status. PAPm was estimated using the Kitabatake formula. In our institute correlation with directly measured pressure during right-heart catheterisation is high ($R^2=0.90$). PAPm $\geq 25$ mm Hg was considered pulmonary hypertension. Vital capacity (VC), forced expiratory volume in 1 s (FEV$_1$), forced expiratory flow between 25% and 75% of vital capacity (FEF$_{25-75}$%) and 20 s maximal voluntary ventilation (MVV) were measured with a portable spirometer (COSMED, Italy). Haemoglobin (Hb) was measured on venous blood (Au-400, Olympus, Shinjuku, Tokyo, Japan). Measurements were done at low altitude, upon arrival (first hour, except PAPm, next day, and lung function, upon arrival and after 3 days), and again after 1 week, 3 months and 6 months.

AMS was assessed with Lake Louise Scoring (LLS), which consists of self-reported assessment of symptoms (headache, dizziness/light-headedness, fatigue, gastrointestinal upset (anorexia–nausea–vomiting) and difficulty sleeping), each scored from 0 to 3 (nil, mild, moderate, severe). It was completed from SMO (17 vs 6 cases, $\chi^2=4.56$, $p=0.038$). On arrival, SMO still had lower scores than CON (1.4 vs 6.0, $p=0.005$). There was no altitude effect, packs/day smoked remained similar to low-altitude smoking ($p>0.05$).

### Results

#### Subjects

Four smokers withdrew before ascent and 14 were lost to follow-up at altitude for non-medical reasons; all non-smokers completed the study. We obtained data from 182 smokers (SMO, age $38\pm7$ years, range 25–54 years) and 200 non-smokers (CON, $38\pm6$ years, 24–56 years).

#### Smoking

The SMO group comprised 18% mild, 45% moderate and 37% heavy smokers. Smoking habit was 23% short-term, 35% medium term and 42% long term. At high altitude, packs/day smoked remained similar to low-altitude smoking ($p>0.05$).

#### Acute mountain sickness

AMS incidence in SMO was lower than in CON (LLS $\geq 3$: 45% vs 56%, $\chi^2=4.57$, $p=0.039$; LLS $\geq 4$: 39% vs 51%, $\chi^2=5.53$, $p=0.013$; LLS $\geq 5$: 3.4% vs 8.5%, $\chi^2=4.56$, $p=0.038$). Five per cent of subjects with LLS $\geq 5$ were hospitalised, more from CON than from SMO (17 vs 6 cases, $\chi^2=4.56$, $p=0.038$). On arrival, SMO had a lower LLS score than CON ($1.6\pm0.6$ vs $1.8\pm0.7$, $p=0.004$). SMO with LLS $\geq 3$ had lower scores than CON ($3.8\pm0.5$ vs $4.0\pm0.6$, $p<0.001$). At 1 week SMO still had lower scores than CON ($1.4\pm0.8$ vs $1.6\pm0.5$, $p=0.005$). There was no altitude or pulmonary oedema. SpO$_2$ correlated negatively with LLS score (CON: $R=−0.192$, $p=0.005$; SMO: $R=−0.174$, $p=0.019$; no difference between groups, $p=0.095$). PAPm analysis was used to estimate AMS risk for smoking versus control and to examine relationships between individual variables and presence of AMS. Multiple logistic regression analysis was performed to test for the effects of independent variables and identify the main effects. Significant risk factors were entered into forward regression using the likelihood ratio test. The dichotomous dependent variable was AMS ($0=$ no AMS, $1=$ AMS, LLS cutoff score $\geq 4$). Independent variables were SpO$_2$, Hb, PAPm, VC, FEV$_1$, FEF$_{25-75}$% and MVV. SpO$_2$ was recoded into $0=$ at least 90%, $1=$ 86–89% and $2=$ up to 85%. Hb concentration was recoded into $0=$ up to 16 g/dl and $1=$ greater than 16 g/dl. PAPm was recoded into $0=$ up to 20 mm Hg and $1=$ greater than 20 mm Hg. VC, FEV$_1$, FEF$_{25-75}$% and MVV was recoded as $0=$ normal low altitude value and $1=$ abnormal, that is, increased or decreased by $\geq 2$ SD from the low altitude value. Smoking behaviour was coded as $0=$ no smoking, $1=$ less than 1 pack/day, $2=$ about 1 pack/day and $3$ = more than 1 pack/day. Smoking history was coded as $0$ = no smoking, $1$ = short-term, $2$ = medium-term and $3$ = long-term smoking.

### Table 1

<table>
<thead>
<tr>
<th>Symptoms and signs of acute mountain sickness in non-smokers at 4525 masl</th>
<th>0 (%)</th>
<th>1 (%)</th>
<th>2 (%)</th>
<th>3 (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>46 (23)</td>
<td>70 (35)</td>
<td>56 (28)</td>
<td>28 (14)</td>
<td>154 (77)</td>
</tr>
<tr>
<td>Dizziness or light-headedness</td>
<td>158 (79)</td>
<td>22 (11)</td>
<td>12 (6)</td>
<td>8 (4)</td>
<td>42 (21)</td>
</tr>
<tr>
<td>Weakness or fatigue</td>
<td>87 (43)</td>
<td>68 (34)</td>
<td>42 (21)</td>
<td>3 (2)</td>
<td>113 (57)</td>
</tr>
<tr>
<td>Anorexia, nausea or vomiting</td>
<td>102 (51)</td>
<td>52 (26)</td>
<td>46 (18)</td>
<td>10 (5)</td>
<td>98 (49)</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>58 (29)</td>
<td>72 (36)</td>
<td>58 (29)</td>
<td>12 (6)</td>
<td>142 (71)</td>
</tr>
<tr>
<td>Reduction in activity</td>
<td>112 (56)</td>
<td>71 (36)</td>
<td>17 (9)</td>
<td>0</td>
<td>88 (44)</td>
</tr>
<tr>
<td>Change in mental status</td>
<td>196 (98)</td>
<td>3 (1.5)</td>
<td>1 (0.5)</td>
<td>0</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Ataxia</td>
<td>194 (97)</td>
<td>6 (3)</td>
<td>0</td>
<td>6 (3)</td>
<td>106 (53)</td>
</tr>
<tr>
<td>Peripheral oedema</td>
<td>172 (86)</td>
<td>21 (11)</td>
<td>7 (3)</td>
<td>0</td>
<td>28 (14)</td>
</tr>
</tbody>
</table>

Comparison between control group and smoking group for headache, $\chi^2=4.66$, $p=0.031$; for anorexia, nausea or vomiting, $\chi^2=3.85$, $p=0.049$; for difficulty sleeping $\chi^2=13.51$, $p<0.001$; for all other symptoms differences were non-significant. Total: the sum of scores $>0$.
correlated negatively with LLS score (CON: $R=−0.147$, $p=0.004$; SMO: $R=−0.156$, $p=0.048$; no difference between groups $p=0.075$). There were no significant correlations with other variables. SMO suffered less from headache, anorexia—nausea—vomiting or sleep disturbances than CON but reported similar frequency and intensity for the other LLS symptoms (tables 1 and 2). Average peak scores for separate AMS symptoms differed significantly for headache, anorexia—nausea—vomiting and difficulty sleeping (table 3).

**Lung function**

On arrival at 4525 masl VC tended to be lower in both groups (table 4). On day 3 the mean decrease was 4% and 6% in SMO and CON respectively. VC had normalised after 3 and 6 months in CON, but not in SMO. FEV1 and FEF25-75% were increased in CON and SMO upon arrival. They remained higher in SMO, whereas they decreased in SMO over time. A similar pattern was observed for MVV.

**Oxygen saturation**

Low-altitude SpO2 values were similar (CON: 97±7%, SMO: 97±6%, $p=0.816$). Upon arrival, SpO2 was lower (CON: 83±6%, SMO: 83±5%, $p=0.001$ vs low altitude, no difference between groups, $p=0.164$). With time spent at altitude, SMO developed a lower SpO2 than CON (3 months: 85±5% vs 86±6%, $p=0.004$; 6 months: 85±6% vs 86±6%, $p=0.002$, table 5). This difference was due to improvement of SpO2 in CON by 3.8% and 4.1% after 3 and 6 months respectively, whereas SMO SpO2 only increased by 2.8% and 2.5% at 3 and 6 months respectively ($p=0.035$ and $p=0.002$).

**Haemoglobin concentration**

Initially both groups had similar Hb (low altitude, SMO: 15.6±2.1 g/dl, CON: 15.5±1.4 g/dl, $p=0.164$; on arrival, SMO: 16.0±1.8 g/dl, CON: 15.8±1.6 g/dl, $p=0.189$). After 3 months the groups differed (SMO: 16.2±1.8 g/dl, CON: 15.8±1.5 g/dl, $p=0.021$). This difference was more marked after 6 months (SMO: 17.4±1.6 g/dl, CON: 16.2±1.5 g/dl, $p<0.001$, see table 5). Hb increased with packs/day (R=0.22, $p=0.005$) and years of smoking (R=0.23, $p<0.001$). At 6 months, Hb was higher in heavy and long-term smokers (17.2±2.1 g/dl and 18.1±2.3 g/dl respectively) than in mild and moderate smokers (crude OR 1.1, 95% CI 1.01 to 1.26, $p=0.035$) as well as short-term or medium-term smokers (crude OR 1.1, 95% CI 1.17 to 1.87, $p=0.011$, see table 6).

**Pulmonary artery pressure**

At low altitude PAPm was similar (SMO: 15.6±3.1 mm Hg, CON: 15.1±2.8 mm Hg, $p=0.101$). Both groups increased PAPm upon arrival and SMO had higher PAPm than CON (17.5±4.5 mm Hg vs 16.2±3.6 mm Hg, $p=0.005$). Over time PAPm increased further (3 months, SMO: 22.4±4.4 mm Hg, CON: 21.5±3.8 mm Hg, $p=0.005$; 6 months, SMO: 23.1±4.8 mm Hg, CON: 21.7±4.1 mm Hg, $p=0.023$, table 6). PAPm correlated with packs/day ($R=0.17$, $p=0.008$) and years smoking ($R=0.19$, $p=0.005$). At 6 months, PAPm in heavy and long-term smokers was 24.2±5.2 mm Hg and 24.0±5.7 mm Hg respectively, significantly higher than that of mild or moderate smokers (crude OR 1.2, 95% CI 1.05 to 1.68, $p=0.048$) and short-term and medium-term smokers (crude OR 1.2, 95% CI 1.01 to 1.71, $p=0.031$, see table 5). SpO2 correlated positively with PAPm in CON ($R=0.158$, $p=0.019$) and negatively in SMO ($R=−0.163$, $p=0.023$).

**DISCUSSION**

**Acute mountain sickness**

We found an 11–12% (20–24% relative) lower incidence of AMS for LLS cut-off scores ≥3 and ≥4 respectively in smokers compared with non-smokers. This contrasts with studies on AMS risk in tourists and climbers, but confirms a tendency found in a prospective cohort study (crude OR 0.66, 95% CI 0.41 to 1.07, $p=0.09$). Hultgren (p. 469) hypothesised that smokers would have more AMS and have problems aclimatising because

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**Table 3** Mean (±SD) peak scores of Lake Louise Scoring symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>CON</th>
<th>SMO</th>
<th>$p$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>1.33</td>
<td>0.56</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Dizziness or light-headedness</td>
<td>0.35</td>
<td>0.30</td>
<td>0.192</td>
</tr>
<tr>
<td>Weakness or fatigue</td>
<td>0.88</td>
<td>0.28</td>
<td>0.755</td>
</tr>
<tr>
<td>Anorexia, nausea or vomiting</td>
<td>0.77</td>
<td>0.42</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>1.48</td>
<td>0.45</td>
<td>$&lt;0.001$</td>
</tr>
</tbody>
</table>

CON, control group; SMO, smoking group.

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**Table 4** Pulmonary function for SMO versus CON

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low altitude</th>
<th>After arrival</th>
<th>Day 3</th>
<th>3 months</th>
<th>6 months</th>
<th>$P^*$</th>
<th>$P^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>VC (l)</td>
<td>SMO 4.48±0.46</td>
<td>SMO 4.38±0.63</td>
<td>SMO 4.24±0.60</td>
<td>SMO 4.12±0.62</td>
<td>SMO 4.10±0.38</td>
<td>0.046</td>
<td>0.110</td>
</tr>
<tr>
<td></td>
<td>CON 4.54±0.44</td>
<td>CON 4.43±0.45</td>
<td>CON 4.12±0.63</td>
<td>CON 4.52±0.32*</td>
<td>CON 4.50±0.26†</td>
<td>0.013</td>
<td>0.027</td>
</tr>
<tr>
<td>FEV1 (l)</td>
<td>SMO 3.92±0.82</td>
<td>SMO 3.98±0.74</td>
<td>SMO 4.02±0.84</td>
<td>SMO 3.96±0.78</td>
<td>SMO 3.82±0.74</td>
<td>0.321</td>
<td>0.164</td>
</tr>
<tr>
<td></td>
<td>CON 4.10±0.48</td>
<td>CON 4.21±0.51</td>
<td>CON 4.18±0.62</td>
<td>CON 4.28±0.46‡</td>
<td>CON 4.22±0.50§</td>
<td>0.388</td>
<td>0.465</td>
</tr>
<tr>
<td>FEF25-75% (litres/s)</td>
<td>SMO 4.08±1.05</td>
<td>SMO 4.01±0.85</td>
<td>SMO 4.06±1.06</td>
<td>SMO 4.02±1.12</td>
<td>SMO 3.92±0.92</td>
<td>0.465</td>
<td>0.044</td>
</tr>
<tr>
<td></td>
<td>CON 4.16±0.85</td>
<td>CON 4.24±0.66</td>
<td>CON 4.28±0.72</td>
<td>CON 4.81±0.83§</td>
<td>CON 4.93±0.67¶</td>
<td>0.006</td>
<td>0.048</td>
</tr>
<tr>
<td>MVV (litres/min)</td>
<td>SMO 108.0±4.5</td>
<td>SMO 110.2±4.4</td>
<td>SMO 111.6±4.8</td>
<td>SMO 106.3±5.2</td>
<td>SMO 107.4±5.3</td>
<td>0.035</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>CON 111.3±5.2</td>
<td>CON 115.5±5.6*</td>
<td>CON 111.4±6.8*</td>
<td>CON 118.3±3.8**</td>
<td>CON 117.8±4.5*</td>
<td>0.002</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD. *P*: ANOVA for repeated measures within each group separately. **P**: ANOVA—probabilities between groups (G), and interaction (I). Group comparisons: *SMO versus CON, $p=0.001$; †SMO versus CON, $p=0.001$; ‡SMO versus CON, $p=0.048$ and $p=0.036$; §SMO versus CON, $p=0.048$; ¶SMO versus CON, $p=0.021$; **SMO versus CON, $p=0.001$.

Because of technical problems only a subset of subjects had pulmonary function tests: at low altitude 40 (SMO) and 42 (CON), after arrival 36 (SMO) and 28 (CON), at 3 days 36 (SMO) and 28 (CON), at 3 months 32 (SMO) and 34 (CON) and at 6 months 28 (SMO) and 25 (CON). The measurements reported concern the same subjects over time. SMO, smoking group; CON, control group; VC, vital capacity; FEV1, forced expiratory volume in 1 s; FEF25-75% forced expiratory flow between 25% and 75% of vital capacity; MVV, maximal voluntary ventilation.
of aggravated hypoxaemia through diminished blood oxygen-carrying capacity from carboxyhaemoglobin (COHb), decreased oxygen uptake due to the respiratory effects of smoking, and impaired peripheral oxygen extraction. One study reported that a combination of smoking and alcohol impeded altitude acclimatisation to 3200 masl in lowland workers, but did not report AMS.

**Headache, gastrointestinal upset and sleep disturbance**

Differences in AMS incidence and severity were small but statistically highly significant. Of limited clinical relevance they are of interest for AMS pathophysiology. Smokers had less hypoxia in the presence of narrowed CO2 reserve and induce increased PAPm, which was expected since hypoxia impairs NO bioavailability and lowers NO levels. We speculate that decreased NO levels protected smokers somewhat from headache and gastrointestinal upset.

Smokers reported fewer sleep problems. Altitude exposure induces a periodic breathing pattern. The oscillations result from high ventilatory sensitivity to carbon dioxide (CO2) and hypoxia in the presence of narrowed CO2 reserve and induce frequent arousals from sleep. Nicotine, NO and carbon monoxide (CO) influence the regulation of breathing. We speculate that smokers slept better because of less breathing instability through higher nicotine and CO, and lower NO levels.

**Pulmonary arterial pressure**

Smokers tended to have higher PAPm at low altitude, which is expected since smoking increases PAP. At altitude, both groups had increased PAPm, which was expected since hypoxia increases PAPm.

Suggesting a dose–response effect. Increased PAP at altitude is associated with high altitude pulmonary oedema (HAPE). People prone to HAPE exhale less NO. PAP can be lowered by inhaling NO, and increasing NO with tadalafil prevents HAPE. Since smoking impairs NO bioavailability and lowers exhaled NO levels, we explain our findings of higher PAPm in smokers in part from decreased NO bioavailability in the pulmonary circulation.

**Saturations**

Increased SpO2 with time in non-smokers reflects ventilatory acclimatisation to altitude. At low arterial oxygen pressure (PaO2) peripheral chemoreceptor activation induces hyperventilation. The sensitivity of this pathway increases with time.

Smokers showed less increase in SpO2 at 3 and 6 months. This suggests that smoking hampers ventilatory acclimatisation to high altitude and may predispose smokers to developing HAPE.
Smoking causes polycythaemia. The tendency for higher Hb in smokers at low altitude became significant at 3 and 6 months at altitude. This increased blood oxygen carrying capacity, correcting for decreased saturation, as previously reported.26 Smoking-induced and hypoxia-induced erythropoiesis increased Hb more in smokers, placing them at higher risk of developing chronic mountain sickness if they remained at altitude for years.23 24 The reduced ventilatory drive results from less sensitivity of central chemoreceptors for CO2 and of peripheral chemoreceptors for hypoxia, and leads to polycythaemia.25 Since smoking is a risk factor for this syndrome,24 we speculate that smokers showed reduced ventilatory acclimatisation from reduced chemoreceptor sensitivity.

Most oximeters, including ours, interpret carboxyhaemoglobin as O2 saturation of Hb (HbO2) and thus indicate an erroneously high SpO2 in smokers.25 Since at altitude alveolar oxygen pressure (PaO2) and PaO2 decrease while alveolar carbon dioxide pressure (PaCO2) remains similar (assuming CO exposure from smoking invariable), competition between CO and O2 increases COHb.26 Since increased COHb in smokers displaces HbO2 dissociation curve leftward, smokers likely had lower PaO2, in line with reduced peripheral chemoreceptor sensitivity in smokers. Brewer et al26 indeed found lower PaO2 in smokers at 3100 masl than in non-smokers (53.4±5.8 mm Hg vs 58.6±4.2 mm Hg).

Smoking and health

Presenting ‘positive’ effects of smoking is uncomfortable; smoking must be strongly discouraged. We do not recommend smoking to prevent AMS. First, we did not study the effects in non-smokers but investigated habitual smokers. Second, smoking represents risk for others because of secondhand smoke.35 Third, altitude is accompanied by cold exposure and smoking increases the risk of frostbite.34 Fourth, smoking decreases exercise capacity.35 Fifth, smoking represents risk for others because of secondhand smoke.35 And finally, the effect on AMS risk and severity was small. Gradual ascent and sufficient time for acclimatisation are best for AMS prevention.9

CONCLUSION

We found that non-acclimatised smokers are at slightly reduced risk for AMS at altitude but acclimatised less well. We do not recommend smoking as a preventive measure for AMS but highlight the effects of smoking on NO metabolism and the
potential roles for CO, nicotine or other active compounds found in cigarette smoke in adaptation to altitude.

DISCLOSURE
Since it is well documented that the tobacco industry has been manipulating science, scientists and the general public for decades, the authors declare that none of them has or has ever had any ties to the tobacco industry and that this study is independent from any financial or other influence from the tobacco industry.

Contributors TYW conceived the study, analysed the data and participated in writing; SQD, JLL, JHU, ZCC, RCD, JJJZ and QD collected and analysed data; BK participated in data analysis, the interpretation of the results and writing the final manuscript.

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Competing interests None.

Ethics approval China National Science Foundation (NNSF) and the Qinghai High Altitude Medical Research Institute Committee on Human Research.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Any interested scholars can ask the corresponding author for an access to the original data.

REFERENCES