ORIGINAL ARTICLE

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 acclimatisation 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 (SpO_2), 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 SpO_2 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.

Key messages

What is the key question?
- Are smokers really better off at altitude?

What is the bottom line?
- Smokers may be better off initially at altitude, but not in the long term.

Why read on?
- This study allows us to advise smokers on altitude exposure using solid epidemiological data and suggests new avenues for research on acute mountain sickness pathophysiology.

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 effects 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 cigarettes, 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 2003, a first group of 4683 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 were then asked to participate in a study on the health effects of altitude exposure. Subjects were kept unaware of the study objective, were not given information on smoking, received no incentives, were informed about procedures, knew they could withdraw at any time and gave signed consent. We sequentially recruited 200 lowland smoking and 200 non-smoking apparently healthy non-acclimatised male first-time ascenders, based on capacity. Three smokers and four non-smokers refused to participate. Groups had similar age, body mass index, working altitude and work (semi-mechanised, laying out tracks). Subjects travelled for 2 days by train to 2261 masl, stayed there for 2 days, and then travelled on for 12 h by train to 2808 masl where they stayed for 3 days. The final altitude was reached after a further 6–8 h bus ride.

A smoker was someone who smoked 10 or more cigarettes/day for >6 months. Non-smokers had never smoked; occasional smokers were excluded. Smoking was classified as mild (<1 pack/day, ie, 10–20 cigarettes/day), moderate (1 pack/day) or heavy (>1 pack/day). Smoking duration was short term (6 months to 2 years), medium term

(2–5 years), and long term (>5 years). There were only cigarette smokers.

Arterial oxygen saturation (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 ≥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),[4] 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 with three clinical signs (change in mental status (0–4), ataxia determined with heel-to-toe test (0–4), and peripheral oedema (0–2)). We used two cut-offs for AMS defining it as headache and a cumulative score ≥3 or ≥4. Severity of AMS was defined as mild for a score of 3–5 and severe for a score of 5 or more. AMS was assessed on the evening of arrival at 4525 masl and the following evenings, for 1 week.

Data were analysed with SAS version 8.1 and are presented as mean±SD. Significance was set at p<0.05. AMS incidence was calculated as cumulative case rate. Frequencies were compared by χ^2 test. Means were compared by t test. Pearson correlation was used for relationships between AMS scores and SpO_2, Hb, PAPm, and lung function measures. Lung function changes were analysed by two-way repeated measures analysis of variance, Tuckey's post hoc test and t test for group comparisons. Crude ORs with 95% CIs were calculated to quantify the association between smoking and AMS. Univariate logistic regression 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 ≥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 >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-tem, 2=medium-term and 3=long-term smoking.

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±7 years, range 25–54 years) and 200 non-smokers (CON, 38±6 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≥3: 45% vs 56%, χ^2=4.57, p=0.039; LLS≥4: 39% vs 51%, χ^2=5.53, p=0.013; LLS≥5: 3.4% vs 8.5%, χ^2=4.56, p=0.038). Five per cent of subjects with LLS≥5 were hospitalised, more from CON than from SMO (17 vs 6 cases, χ^2=4.56, p=0.038). On arrival, SMO had a lower LLS score than CON (1.6±0.6 vs 1.8±0.7, p=0.004). SMO with LLS≥3 had lower scores than CON (3.8±0.5 vs 4.0±0.6, p<0.001). At 1 week SMO still had lower scores than CON (1.4±0.8 vs 1.6±0.5, p=0.005). There was no altitude cerebral 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

Table 1 Symptoms and signs of acute mountain sickness in non-smokers at 4525 masl

	n (%)				
LLS symptom intensity	**0**	**1**	**2**	**3**	**Total**
Headache	46 (23)	70 (35)	56 (28)	28 (14)	154 (77)
Dizziness or light-headedness	158 (79)	22 (11)	12 (6)	8 (4)	42 (21)
Weakness or fatigue	87 (43)	68 (34)	42 (21)	3 (2)	113 (57)
Anorexia, nausea or vomiting	102 (51)	52 (26)	36 (18)	10 (5)	98 (49)
Difficulty sleeping	58 (29)	72 (36)	58 (29)	12 (6)	142 (71)
Reduction in activity	112 (56)	71 (36)	17 (9)	0	88 (44)
Change in mental status	196 (98)	3 (1.5)	1 (0.5)	0	4 (2)
Ataxia	194 (97)	6 (3)	0	0	6 (3)
Peripheral oedema	172 (86)	21 (11)	7 (3)	0	28 (14)

Comparison between control group and smoking group for headache, χ^2=4.66, p=0.031; for anorexia, nausea or vomiting, χ^2=3.85, p=0.049; for difficulty sleeping χ^2=13.517, p<0.001; for all other symptoms differences were non-significant. Total: the sum of scores >0.

Table 2 Symptoms and signs of acute mountain sickness in smokers at 4525 masl

	n (%)				
LLS symptom intensity	**0**	**1**	**2**	**3**	**Total**
Headache	104 (57)	42 (23)	22 (12)	14 (8)	78 (43)
Dizziness or light-headedness	144 (79)	22 (12)	13 (7)	3 (2)	38 (21)
Weakness or fatigue	81 (45)	50 (27)	42 (23)	6 (3)	101 (55)
Anorexia, nausea or vomiting	111 (61)	39 (21)	26 (14)	6 (3)	71 (39)
Difficulty sleeping	86 (47)	42 (23)	45 (25)	9 (5)	96 (53)
Reduction in activity	107 (59)	58 (32)	15 (8)	2 (1)	75 (41)
Change in mental status	180 (99)	2 (1)	0	0	2 (1)
Ataxia	178 (98)	4 (2)	0	0	4 (2)
Peripheral oedema	158 (87)	18 (10)	6 (3)	0	24 (13)

See table 1.

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

Symptom	CON	SMO	p Value
Headache	1.33±0.56	0.70±0.42	<0.001
Dizziness or light-headedness	0.35±0.30	0.31±0.18	0.192
Weakness or fatigue	0.88±0.26	0.89±0.28	0.755
Anorexia, nausea or vomiting	0.77±0.42	0.60±0.36	<0.001
Difficulty sleeping	1.48±0.45	0.95±0.38	<0.001

CON, control group; SMO, smoking group.

correlated negatively with LLS score (CON: R=−0.147, p=0.044; 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. FEV_1 and $FEF_{25-75\%}$ were increased in CON and SMO upon arrival. They remained higher in CON, whereas they decreased in SMO over time. A similar pattern was observed for MVV.

Oxygen saturation

Low-altitude SpO_2 values were similar (CON: 97±7%, SMO: 97±6%, p=0.816). Upon arrival, SpO_2 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 SpO_2 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 SpO_2 in CON by 3.8% and 4.1% after 3 and 6 months respectively, whereas SMO SpO_2 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: 15.8±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 1.11 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 1.1, 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). SpO_2 correlated positively with PAPm in CON (R=0.158, p=0.019) and negatively in SMO (R=−0.163, p=0.023).

Logistic regression

At altitude, subjects with SpO_2 ≤85% were 2.6 times more likely to have AMS than those with SpO_2 ≥90% (table 7). Hb, PAPm, and lung function variables did not show significant effects. Crude ORs of FEV_1, $FEF_{25-75\%}$ and MVV were similar to those of VC (not shown). Heavy smoking and medium-term or long-term smoking history decreased AMS risk (table 7). In multivariate logistic regression only SpO_2, smoking habits and smoking history had significant effects (table 8).

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,[5 6] but confirms a tendency found in a prospective cohort study (crude OR 0.66, 95% CI 0.41 to 1.07, p=0.09).[7] Hultgren[2] (p. 469) hypothesised that smokers would have more AMS and have problems acclimatising because

Table 4 Pulmonary function for SMO versus CON

Parameters	Low altitude	After arrival	Day 3	3 months	6 months	P[a]	P[b]
VC (l)	SMO 4.48±0.46	SMO 4.36±0.63	SMO 4.24±0.60	SMO 4.12±0.62	SMO 4.10±0.38	0.046	G: 0.110
	CON 4.54±0.44	CON 4.43±0.45	CON 4.12±0.63	CON 4.52±0.32*	CON 4.50±0.26†	0.013	I: 0.027
FEV_1 (l)	SMO 3.92±0.82	SMO 3.98±0.74	SMO 4.02±0.84	SMO 3.96±0.78	SMO 3.82±0.74	0.321	G: 0.164
	CON 4.10±0.48	CON 4.21±0.51	CON 4.18±0.62	CON 4.28±0.46‡	CON 4.22±0.50‡	0.388	I: 0.465
$FEF_{25-75\%}$ (litres/s)	SMO 4.08±1.05	SMO 4.01±0.85	SMO 4.06±1.06	SMO 4.02±1.12	SMO 3.92±0.92	0.465	G: 0.044
	CON 4.16±0.85	CON 4.24±0.66	CON 4.28±0.72	CON 4.81±0.63§	CON 4.93±0.67¶	0.006	I: 0.048
MVV (litres/min)	SMO 108.0±4.5	SMO 110.2±4.4	SMO 111.6±4.8	SMO 106.3±5.2	SMO 107.4±5.3	0.035	G: 0.002
	CON 111.3±5.2	CON 115.5±5.6**	CON 117.4±4.6**	CON 118.3±3.8**	CON 117.8±4.5**	0.002	I: 0.001

Data are presented as mean ± SD. P[a]: ANOVA for repeated measures within each group separately. P[b]: 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; FEV_1, forced expiratory volume in 1 s; FEF25-75% forced expiratory flow between 25% and 75% of vital capacity; MVV, maximal voluntary ventilation.

Table 5 Oxygen saturation, haemoglobin concentration and mean pulmonary artery pressure

	N	SpO_2 (%)	Hb (g/dl)	PAPm (mm Hg)
Low altitude				
SMO	182	96.5±6.4	15.8±2.1	15.6±3.1
CON	200	97.2±6.8	15.5±1.4	15.1±2.8
After arrival at altitude				
SMO	182	82.5±5.2	16.0±1.8	17.5±4.5
CON	200	83.2±5.8	15.8±1.6	16.2±3.6
After 3 months				
SMO	182	84.8±4.6*	16.2±1.8‡	22.4±4.4¶
CON	200	86.4±5.7	15.8±1.5	21.5±3.8
After 6 months				
SMO	182	84.6±6.3*	17.4±1.6§	23.1±4.8**
CON	200	86.6±5.7	16.2±1.5	21.7±4.1

Data are presented as mean±SD.
*SMO versus CON: p=0.004.
†SMO versus CON: p=0.001.
‡SMO versus CON: p=0.021.
§SMO versus CON: p<0.001.
¶SMO versus CON: p=0.044.
**SMO versus CON: p=0.004.
SMO, smoking group; CON, control group; Hb, haemoglobin concentration; PAPm, mean pulmonary artery pressure; SpO_2, arterial oxygen saturation.

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.[8]

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 headache, anorexia–nausea–vomiting and sleep disturbance. AMS headache may result from hypoxia-induced cerebral vasodilatation or its effectors, such as nitric oxide (NO), perhaps through activation of the trigeminovascular system[9] and cerebral venous hypertension.[10] At low altitude NO plays a role in tension type headache and NO prodrugs are associated with headache and nausea.[11] Nitroglycerin causes headache and exacerbates AMS[12] as does sildenafil.[13] Smoking impairs endothelial function, decreasing NO formation and increasing NO degradation[14] and smokers expire less NO.[15] 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.[16] The oscillations result from high ventilatory sensitivity to carbon dioxide (CO_2) and hypoxia in the presence of narrowed CO_2 reserve and induce frequent arousals from sleep. Nicotine, NO and carbon monoxide (CO) influence the regulation of breathing.[17 18] 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.[19] At altitude, both groups had increased PAPm, which was expected since hypoxia increases PAPm.[20] Smokers had higher PAPm, with a small significant difference between smokers and non-smokers at 3 and 6 months, which was more pronounced in heavy smokers, suggesting a dose–response effect. Increased PAP at altitude is associated with high altitude pulmonary oedema (HAPE).[21] People prone to HAPE exhale less NO. PAP can be lowered by inhaling NO, and increasing NO with tadalfil prevents HAPE.[21] Since smoking impairs NO bioavailability[14 19] and lowers exhaled NO levels[15] we explain our findings of higher PAPm in smokers in part from decreased NO bioavailability in the pulmonary circulation.

Table 6 Oxygen saturation, haemoglobin concentration and mean pulmonary artery pressure at 6 months and intensity/history of smoking

Smoking intensity/ smoking history	n	SpO_2	Hb (g/dl)	PAPm (mm Hg)
Mild	33	84.8±1.7	16.3±1.6	22.5±3.6
Moderate	82	84.2±2.2	16.5±1.7	22.8±4.4
Heavy	67	83.1±2.5*	17.2±2.1‡	24.2±5.2¶
Short term	41	85.2±2.4	16.6±1.6	22.1±3.5
Medium term	65	84.7±1.6	17.2±1.8	22.5±4.5
Long term	76	84.2±2.1†	18.1±2.3§	24.0±5.7**

Data are presented as mean±SD.
*Heavy levels of smoking versus moderate (p=0.002) and mild levels of smoking (p<0.001).
†Long-term smoking versus medium-term (p=0.009) and short-term smoking (p<0.001).
‡Heavy levels of smoking versus moderate (p=0.036) and mild levels of smoking (p<0.001).
§Long-term smoking versus medium-term (p=0.008) and short-term smoking (p<0.001).
¶Heavy levels of smoking versus moderate (p=0.048) and mild levels of smoking (p=0.040).
**Long-term smoking versus medium-term (p=0.057) and short-term smoking (p=0.044).
Hb, haemoglobin concentration; PAPm, mean pulmonary artery pressure; SpO_2, arterial oxygen saturation.

Saturation

Increased SpO_2 with time in non-smokers reflects ventilatory acclimatisation to altitude.[22] At low arterial oxygen pressure (PaO_2) peripheral chemoreceptor activation induces hyperventilation. The sensitivity of this pathway increases with time.[22] Smokers showed less increase in SpO_2 at 3 and 6 months. This suggests that smoking hampers ventilatory acclimatisation to

Table 7 Results of multiple univariate regression analysis (unadjusted) for the variables in the left column

Variables	AMS, n (%)	Crude OR (95% CI)	p Value
SpO_2 (%)			
≥90	32 (33)	1 (ref)	
86–89	65 (40)	0.986 (0.647 to 1.545)	0.069
≤85	76 (62)	2.630 (2.156 to 3.274)	<0.001
Hb (g/dl)			
≤16	142 (46)	1 (ref)	
>16	31 (42)	0.745 (0.504 to 0.762)	0.238
PAPm (mm Hg)			
≤20	164 (45)	1 (ref)	
>20	9 (45)	0.645 (0.446 to 0.672)	0.164
VC			
Normal	168 (46)	1 (ref)	
Less by ≥2 SD	5 (39)	0.211 (0.096 to 0.747)	0.770
Smoking			
No smoking	102 (51)	1 (ref)	
<1 pack/day	16 (49)	0.860 (0.674 to 0.901)	0.755
1 pack/day	30 (37)	0.786 (0.652 to 0.810)	0.035
>1 pack/day	25 (37)	0.627 (0.335 to 0.856)	0.039
Smoking history			
No smoking	102 (51)	1 (ref)	
Short term	17 (40)	0.864 (0.520 to 0.978)	0.465
Medium term	25 (39)	0.818 (0.465 to 1.075)	0.044
Long term	29 (38)	0.654 (0.358 to 0.861)	0.027

Table 8 Results of multiple logistic regression analysis (adjusted) with the variables in the left column retained in the final regression (all other variables not significant)

Variables	β	SE	Wald	Adjusted OR (95% CI)	p Value
SpO_2 ≤85%					
Non-smoking	−0.048	0.481	14.12	2.343 (2.121 to 2.895)	0.001
Smoking	−0.062	0.474	15.86	2.584 (1.984 to 3.365)	0.001
Smoking					
No smoking					
<1 pack/day	0.084	0.382	3.84	0.865 (0.583 to 1.014)	0.075
1 pack/day	−0.051	0.257	4.17	0.662 (0.424 to 0.898)	0.031
>1 pack/day	−0.056	0.236	4.28	0.646 (0.328 to 0.856)	0.020
Smoking history					
No smoking					
Short term	−0.086	0.408	3.86	0.748 (0.482 to 1.083)	0.057
Medium term	−0.068	0.252	4.04	0.674 (0.412 to 0.767)	0.027
Long term	−0.082	0.186	4.16	0.636 (0.318 to 0.825)	0.021

SpO_2, arterial oxygen saturation.

high altitude. Chemoreceptor function is modulated by NO and CO.[17] Nicotine increases peripheral chemoreflex sensitivity to reductions in arterial oxygen content in non-smokers but not in smokers.[18] In people who live at altitude all their lives, a decrease in ventilation may eventually develop.[23] The reduced ventilatory drive results from less sensitivity of central chemoreceptors for CO_2 and of peripheral chemoreceptors for hypoxia, and leads to polycythaemia.[23] 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 carboxyhaemoglogin as O_2 saturation of Hb (HbO_2) and thus indicate an erroneously high SpO_2 in smokers.[25] Since at altitude alveolar oxygen pressure (P_AO_2) and PaO_2 decrease while alveolar carbon dioxide pressure (P_ACO) remains similar (assuming CO exposure from smoking invariable), competition between CO and O_2 increases COHb.[26] Since increased COHb in smokers displaces the HbO_2 dissociation curve leftward, smokers likely had lower PaO_2, in line with reduced peripheral chemoreceptor sensitivity in smokers. Brewer *et al*[26] indeed found lower PaO_2 in smokers at 3100 masl than in non-smokers (53.4±5.8 mm Hg vs 58.6±4.2 mm Hg).

Smoking polycythaemia

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]

Lung function

VC tended to decrease upon arrival at altitude and normalised with time in non-smokers but not in smokers. Previous studies reported a decrease in VC during the first 12–24 h of altitude exposure.[27] This fall may be caused by increased pulmonary blood volume and mild interstitial oedema.[28] VC changes upon arrival were not related to SpO_2, but subjects with AMS had greater decreases in VC than those without (4.0±0.7 vs 4.2±0.5%, $p<0.002$).

Since air density decreases with altitude, increases in FEV_1 and $FEF_{25-75\%}$ were expected. But data in the literature are conflicting. FEV_1 was found to increase,[29] decrease[30] or remain unchanged at altitude.[31] After arrival at altitude, FEV_1 was slightly higher in smokers and non-smokers. This increase persisted over time in non-smokers but had decreased after 6 months in smokers, suggesting a decrease in lung function from smoking. $FEF_{25-75\%}$ was increased in non-smokers to 115% and 118% of low altitude values at 3 and 6 months, respectively. In smokers $FEF_{25-75\%}$ was similar to low altitude at 3 months and had decreased by 4% at 6 months. As expected, MVV increased in non-smokers and remained elevated at 3 months and 6 months. By contrast, MVV decreased throughout the altitude stay in smokers and overall smokers showed loss of lung function while at altitude.

Strengths and limitations

The main strength of our study is the inclusion of almost 200 smokers, allowing effects to be identified that were previously undiscovered. We did not measure exhaled levels of CO and NO, or blood gases or COHb levels, to relate these to AMS symptom scores. Sleep quality measured with actimetry, and quantification of the ventilatory response to hypoxia and hypercapnia might have provided further insight too. Since smoking was reported to reduce pain perception, we cannot fully exclude the fact that the perception of severity of symptoms of AMS was less in smokers compared with non-smokers.[32]

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 is strongly addictive and increases the risk of cardiorespiratory and other diseases, including cancer.[33] 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.[33] 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 acclimatise 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 present 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, JHJ, ZCC, RCD, JZZ and QDT collected and analysed data; BK participated in data analysis, interpretation of the results and writing the final manuscript.

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