# Altitude-Induced Sleep Apnea Is Highly Dependent on Ethnic Background (Sherpa Vs. Tamang)

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préparée sous la direction du Professeur Raphael Heinzer
(avec la collaboration du Professeur Claudio Sartori)

et présentée à la Faculté de biologie et de médecine de
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DOCTEUR EN MEDECINE

par

Grégory Heiniger

Médecin diplômé de la Confédération Suisse
Originaire d'Affoltern im Emmental, Berne

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## Monsieur Grégory Heiniger

*intitulée*

***Altitude-Induced Sleep Apnea Is Highly Dependent on Ethnic Background (Sherpa Vs. Tamang)***

*Lausanne, le 29 septembre 2022*

*pour Le Doyen*
*de la Faculté de Biologie et de Médecine*

*Monsieur le Professeur John Prior*
*Vice-Directeur de l'Ecole doctorale*

# Altitude-Induced Sleep Apnea Is Highly Dependent on Ethnic Background (Sherpa Vs. Tamang)


**Contexte :**

L'altitude provoque une alcalose hypocapnique qui peut générer une apnée centrale lors du sommeil. Au Népal, deux groupes ethniques vivent à moyenne/haute altitude: Les Tamangs qui sont issus de populations tibéto-birmanes de basse altitude ainsi que les Sherpas qui descendent de Tibétains acclimatés à la haute altitude.

**Objectif de l'étude :**

Comparer la prévalence des apnées centrales en basse et en haute altitude entre des sujets Sherpas et Tamangs.

**Méthodes :**

Des enregistrements polygraphiques, incluant le débit d'air et la saturation en oxygène ont été effectués au Népal à des altitudes " basses " (2 030 m) et " hautes " (4 380 m). La ventilation au repos (VE) et le CO2 expiré mixte (FECO2) ont également été mesurés aux mêmes altitudes. Les différences dans l'index d'apnée-hypopnée (AHI), l'index de désaturation d'oxygène (ODI), et le pourcentage de respiration périodique nocturne (NPB) aux deux altitudes ont été comparées entre les ethnies.

**Mesures et principaux résultats :**

Vingt Sherpas et 20 Tamangs ont été inclus (hommes, âge médian [intervalle inter-quartile] : 24,5 [21,5-27,8] ans vs 26,0 [21,5-39,8] ans, indice de masse corporelle : 23,9 [22,1-26,1] kg/m2 contre 25,21 [20,6-27,6] kg/m2). Par rapport aux Tamangs, les Sherpas ont présenté une augmentation plus faible de l'IAH (+7,5 [2,6-17,2]/h contre +31,5 [18,2-57,3]/h, p<0,001), de l'IDO (+13,8 [5,5-28. 2]/h contre +42,0 [22,6-77,6]/h, p<0,001), et la proportion de NPB (+0,9 [0-3,5]% contre +12,8 [3,1-27,4]%, p < 0,001) de la basse à la haute altitude. La VE au repos était plus élevée chez les Sherpas que chez les Tamangs en basse altitude (8,45 [6,89-10,70] l/min contre 6,3 [4,9-8,3] l/min, p = 0,005) et en haute altitude (9,7 [8,5-11] l/min contre 8,74 [7,39-9,73] l/min, p = 0. 020), tandis que la diminution moyenne de l'écart-type de la FECO2 entre la basse et la haute altitude était plus importante chez les Tamangs que chez les Sherpas (-0,50%-0,44% vs. -0,80%-0,33%, p < 0,023).

**Conclusion :**

Les sujets d'origine Tamangs ont montré une augmentation des troubles respiratoires nocturne entre la basse et la haute altitude 3 fois plus importante que les sujets Sherpas qui sont génétiquement adaptés à l'altitude. Les sujets Sherpas ont une ventilation plus élevée et une baisse plus faible de la FECO2 lors du passage de la basse à la haute altitude. Ces données suggèrent que des différences génétiques dans le contrôle de la respiration pourraient être protectrices contre les apnées centrales.

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# Altitude-Induced Sleep Apnea Is Highly Dependent on Ethnic Background (Sherpa Vs. Tamang)

Grégory Heiniger,[1] Simon Walbaum,[2] Claudio Sartori,[2] Alban Lovis,[3] Marco Sazzini,[4,5] Andrew Wellman,[6] and Raphael Heinzer[1]



**Abstract**

Heiniger, Grégory, Simon Walbaum, Claudio Sartori, Alban Lovis, Marco Sazzini, Andrew Wellman, and Raphael Heinzer. Altitude-Induced Sleep Apnea Is Highly Dependent on Ethnic Background (Sherpa Vs. Tamang). *High Alt Med Biol*. 23:165–172, 2022.

***Rationale:*** High altitude-induced hypocapnic alkalosis generates central sleep apnea (CSA). In Nepal, two ethnic groups live at medium-to-high altitude: Tamangs originate from low-altitude Tibeto-Burman populations, whereas Sherpas descend from high-altitude Tibetans.

***Objective:*** To compare apnea severity at low and high altitude between Sherpas and Tamangs.

***Methods:*** Polygraphy recordings, including airflow and oxygen saturation, were performed in Nepal at ''low'' (2,030 m) and ''high'' (4,380 m) altitudes. Resting ventilation ($\dot{V}_E$) and mixed-exhaled $CO_2$ ($F_ECO_2$) were also measured at the same altitudes. Differences in apnea-hypopnea index (AHI), oxygen desaturation index (ODI), and % of nocturnal periodic breathing (NPB) at the two altitudes were compared between ethnicities.

***Measurements and Main Results:*** Twenty Sherpas and 20 Tamangs were included (males, median [interquartile range] age: 24.5 [21.5–27.8] years vs. 26.0 [21.5–39.8] years, body mass index: 23.9 [22.1–26.1] kg/m$^2$ vs. 25.21 [20.6–27.6] kg/m$^2$). Compared with Tamangs, Sherpas showed a lower increase in AHI (+7.5 [2.6–17.2]/h vs. +31.5 [18.2–57.3]/h, $p < 0.001$), ODI (+13.8 [5.5–28.2]/h vs. +42.0 [22.6–77.6]/h, $p < 0.001$), and NPB proportion (+0.9 [0–3.5]% vs. +12.8 [3.1–27.4]%, $p < 0.001$) from low to high altitude. Resting $\dot{V}_E$ was higher in Sherpas versus Tamangs at both low (8.45 [6.89–10.70] l/min vs. 6.3 [4.9–8.3] l/min, $p = 0.005$) and high (9.7 [8.5–11] l/min vs. 8.74 [7.39–9.73] l/min, $p = 0.020$) altitudes, whereas the mean ± standard deviation $F_ECO_2$ decrease between low and high altitude was greater in Tamangs versus Sherpas (–0.50% ± 0.44% vs. –0.80% ± 0.33%, $p < 0.023$).

***Conclusion:*** Overall, altitude-adapted Sherpas showed a 3.2-times smaller increase in sleep-disordered breathing between low and high altitude compared with Tamangs, and higher ventilation and a smaller drop in $F_ECO_2$ at high altitude. These data suggest that genetic differences in breathing control can be protective against CSA.

**Keywords:** altitude; central sleep apnea; genetic ancestry; loop gain; periodic breathing

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## Introduction

Altitude-induced hypoxia can have an impact on sleep, and especially on the nocturnal breathing pattern (Windsor and Rodway, 2012). Individuals with regular breathing during sleep at low altitude may develop periodic breathing with central sleep apnea (CSA) when sleeping at high altitude (Bloch *et al.*, 2010). Altitude-induced hypoxia increases respiratory drive, resulting in decreased arterial pressure of carbon dioxide ($CO_2$) and increases in the ventilatory response to variations in $CO_2$ levels (increased chemoreceptor sensitivity) (Weil, 2004; Burgess and Ainslie, 2016).

However, important individual variations in the propensity to develop periodic breathing at high altitude have been observed, with only about half of people affected at an altitude of 3,500 m (Lovis *et al.*, 2012). Thus, the altitude of onset and the severity of altitude-induced CSA vary markedly between individuals. This heterogeneity may be due to a genetic influence on breathing control adaptation to high altitude (Lahiri and Data, 1992; Kong *et al.*, 2015).

Nepal is populated by 126 ethnic groups (Nepal Go, Central Bureau of Statistics, 2011) each with a unique history and origin. Of these, the mountaineering Sherpas are certainly the most famous. Recently, genetic studies have traced the origin of Sherpas, showing that Tibetans and Sherpas share Tibeto-Burman ancestors who came from eastern Asia during the Neolithic and admixed with the autochthonous human groups that have colonized the Tibetan plateaus starting about 30,000–40,000 years ago (Cole *et al.*, 2017; Gnecchi-Ruscone *et al.*, 2017; Zhang *et al.*, 2018). In historic times, the Sherpas then left these plateaus to occupy the previously uninhabited Nepalese high-altitude valleys (Bhandari and Cavalleri, 2019).

The tremendous tolerance of Sherpas to hypoxia has been long studied (Gilbert-Kawai *et al.*, 2014) and some of the genetic determinants underlying their physiological adaptive traits have been identified (Beall *et al.*, 2010; Simonson *et al.*, 2010; Gnecchi-Ruscone *et al.*, 2018; Sazzini, 2019). This biological adaptation has also contributed to the legendary performances of the Sherpas as guides and carriers in high-altitude expeditions. Although men of Tamang ancestry are also regularly hired as high-altitude carriers, very few studies have focused on them (Law and Rodway, 2008). Descending from Tibeto-Burman ancestors closely related to those of the Sherpas, the Tamangs apparently had a different migratory journey (Gnecchi-Ruscone *et al.*, 2017). They bypassed the Himalayas from the east and joined Nepal from South Asia. There, they admixed with low-altitude populations of South Asian ancestry, which gives them a different genetic heritage from the Sherpas (Cole *et al.*, 2017; Gnecchi-Ruscone *et al.*, 2017).

The objective of the study was to determine whether there are differences in the occurrence of altitude-induced sleep apnea between the Sherpa and Tamang ethnic groups.

## Methods

### Study design

This open-label, prospective study was conducted in Nepal in October 2019. The study protocol was reviewed and accepted by the Nepalese Ethics Committee (number 730-2019). The trial was conducted in accordance with local laws/regulations, International Conference on Harmonisation-Good Clinical Practice (ICH-GCP), and the Declaration of Helsinki and its current revision. All participants provided written informed consent.

### Participants

Male subjects from two groups of Nepalese carriers, the Sherpas and the Tamangs, whose ancestors had belonged to the same ethnic group for at least three generations were eligible. Ancestry information was verified via their identity documents. Subjects with any known health condition potentially affecting nocturnal breathing were excluded. All subjects were smokers but were asked not to smoke for 24 hours before days on which measurements were taken.

### Protocol

Participants from both ethnic groups performed the same 6-day trek in Nepal (Fig. 1). This included spending 2 nights and 2 days of rest at 2,030 m (in Dunche, baseline measurements) followed by a first day of walking with a night at 2,200 m (in Thylo Syabru), and a second day of walking with a night at 3,280 m (in Shin Gompa). After the third day of trekking, the altitude camp at 4,380 m was reached (in Gosainkund). Subjects stayed two nights and an entire day at the altitude camp (4,380 m) where high-altitude evaluations were performed before they returned home.

### Measurements and assessments

Polygraphy. Subjects underwent one polygraphy recording at 2,030 m and another at 4,380 m. For logistical reasons, recordings at each altitude were split over the two nights spent at that altitude. Polygraphy was performed using ApneaLink™ Plus devices (ResMed, San Diego, CA, USA), which monitor pulse oximetry and nasal airflow (nasal pressure cannula) during the night.

Polygraphic recordings were interpreted manually using Noxturnal software (Noxmedical, Reykjavík, Iceland). The apnea-hypopnea index (AHI; events/h) was calculated with apneas defined as breathing cessation for ≥10 seconds and hypopneas defined as $a \geq 30\%$ decrease in the breathing signal followed by $a \geq 3\%$ desaturation. Given that many short apneas (<10 seconds) did not fulfil the American Academy of Sleep Medicine criteria for an apnea but generated significant oxygen desaturations (Fig. 2), we also calculated an ''atypical apnea-hypopnea index'' (A(at)HI) with apneas defined as breathing cessation for ≥5 seconds followed by ≥3% desaturation and the same hypopnea definition.

Other respiratory parameters determined were the oxygen desaturation index (ODI), defined as the number of oxygen desaturations of ≥3% per hour, and the proportion of the night (as a percentage) spent in periodic breathing characterized by trains of ≥3 cycles composed of an apnea (including atypical apnea)/hypopnea separated by a short period of ventilation.

Measurement of ventilation. Waking ventilation was assessed on the day of the baseline polygraphy recording at 2,030 m and again at 4,380 m. After sitting quietly for 20 minutes, ventilation ($\dot{V}_E$) and mixed expired $CO_2$ ($F_ECO_2$) were measured over a 5-minute period using a ''Pnoe'' device (Endo Medical, Palo Alto, USA). This device consists of a mask connected to flow sensor (MEMS Mass Air Flow

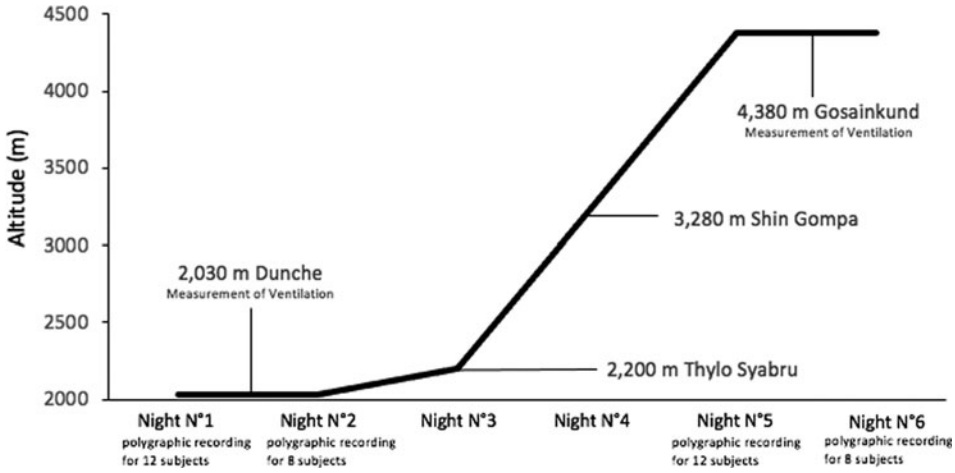


**FIG. 1.** Study protocol.



Meter) and a $CO_2$ sensor (nondispersive infrared absorption $CO_2$ sensor). Mean ventilation (L/min) and mean $F_ECO_2$ (%) over the full-test duration were calculated.

### *Statistical analysis*

The Kolmogorov–Smirnov test was used to assess data distribution. Non-normally distributed data are reported as medians [25th–75th percentile] (interquartile range [IQR]), whereas normally distributed data are reported as mean ± standard deviation (SD). Differences in all parameters between low and high altitude values were calculated and compared between the two ethnic groups using *t*-tests (normally distributed data) or Mann–Whitney tests (non-normally distributed data). A linear regression model was used to determine associations between altitude-induced variations in AHI and demographic or physiologic variables.

## Results

### *Participants*

Twenty individuals from each ethnic group were included in the study (total of 40 participants). Participants of Sherpa versus Tamang ethnicity had a similar age (median [IQR]: 24.5 [21.5–27.8] vs. 26.0 [21.5–39.8], $p = 0.363$), body weight (median [IQR]: 66.5 [60–71.5] kg vs. 63.5 [52.8–72.8] kg, $p = 0.715$), and body mass index (BMI) (median [IQR]: 23.91 [22.1–26.1] kg/m$^2$ vs. 25.2 [20.6–27.6] kg/m$^2$, $p = 0.534$), but Sherpa subjects were significantly taller than Tamang subjects (median [IQR]: 1.67 [1.62–1.70] m vs. 1.60 [1.57–1.67] m, $p = 0.015$).

All Sherpas and Tamangs were each born and raised in two different villages at altitude 1,500–1,980 m and 1,400–2,000 m, respectively. The majority of Sherpa subjects had spent the previous 3 months in their village or in Kathmandu

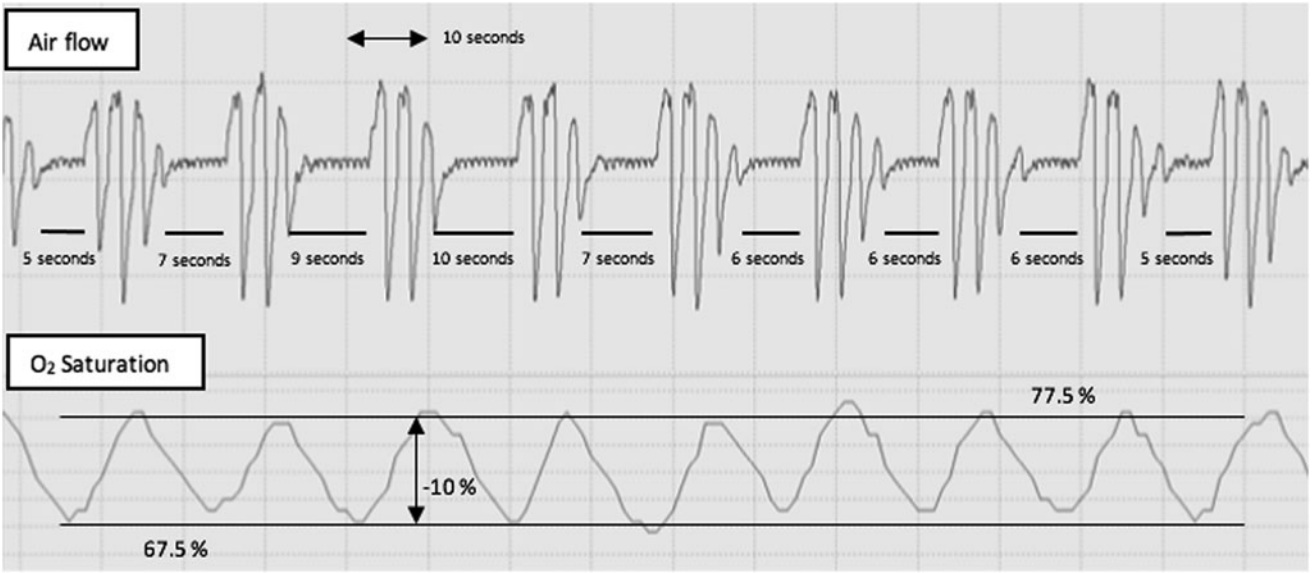


**FIG. 2.** Examples of typical and atypical apneas in a Tamang subject at 4,380 m. $O_2$, oxygen. A, atypical apneas; B, typical apnea.

(1,400 m). Three Sherpas had worked as carriers earlier in the season, but not within the 14 days before the study. All Tamang subjects had spent the previous 3 months in the same village. Due to illness, one Sherpa subject did not undergo baseline polygraphy at 2,030 m and one Tamang subject did not undergo polygraphy at 4,380 m.

### *Nocturnal breathing*

Sherpa subjects showed a significantly smaller increase in the AHI when sleeping at high altitude compared to low altitude (AHI difference) compared with Tamang subjects (median [IQR]: +7.5 [2.6–17.2]/h vs. +31.5 [18.2–57.3]/h, $p < 0.001$). At low altitude, there was no significant difference in AHI between Sherpa and Tamang subjects (median [IQR]: 6.8 [4.7–11.2]/h vs. 8.4 [4.95–14.57]/h, $p = 0.325$). At high altitude, the AHI was lower in Sherpas compared with Tamangs (median [IQR]: 18.8 [8.7–27.4]/h vs. 43.1 [23.0–73.1]/h, $p = 0.002$).

Inclusion of atypical apnea events (A(at)AHI) did not have any effect on the difference between ethnic groups at low altitude (median [IQR]: 6.8 [4.7–11.7]/h vs. 8.4 [5.0–14.8]/h, $p = 0.346$). However, at high altitude, the A(at)AHI was much lower in Sherpa versus Tamang subjects (median [IQR]: 19.95 [8.7–27.4]/h vs. 51.6 [24.1–87.6]/h, $p < 0.001$). The change in A(at)HI from low to high altitude was also much smaller in the Sherpa versus Tamang group (Fig. 3). Using a stepwise linear regression model, ethnic group showed the strongest association with altitude-induced AHI difference ($\beta$ 27.8, $p < 0.0001$). BMI ($\beta$ 2.6, $p = 0.021$) and age ($\beta$ 0.69, $p = 0.017$) were the only other significant independent predictors of altitude-induced AHI difference.

Similar to AHI, there was no difference between ethnic groups in the ODI at low altitude (median [IQR]: 7.3 [5.1–11.5]/h in the Sherpa group versus 9.9 [6.1–15.9]/h in the Tamang group, $p = 0.255$), while ODI at high altitude was significantly lower in Sherpa versus Tamang subjects (median [IQR]: 22.3 [12.9–39.3]/h vs. 57.4 [29.0–96.7]/h, $p = 0.003$). The change in ODI from low to high altitude was also much smaller in the Sherpa versus Tamang group (Fig. 3).

There was no significant difference between the two groups in the median [IQR] amplitude of oxygen desaturation at high altitude: (4.25 [3.9–4.77] % vs. 4.7 [4.2–6.5] %, $p = 0.052$) or in median [IQR] oxygen saturation during the whole night at high altitude: (Sherpa: 81.6 [79.3–82.6] % vs. Tamang: 79.3 [77.0–81.9] %, $p = 0.115$).

At low altitude, the episodes of nocturnal periodic breathing (NPB) were rare in both groups. In contrast, at high altitude, NPB was observed in both ethnic groups, but in lower proportion of the night in the Sherpa versus Tamang group (median [IQR]: 1.2 [0.0–4.4] % vs 12.8 [3.1–30.2] % of the night, $p < 0.001$). The difference in NPB between low and high altitudes was also much smaller in Sherpa subjects than in Tamang subjects (Fig. 3).

### *Ventilation during quiet wakefulness*

Ventilation at rest and tidal volume were higher in Sherpas compared with Tamangs at both low and high altitudes (Fig. 4). There was no significant difference between the two groups in the difference between low- and high-altitude ventilation.

At low altitude, Sherpa subjects had lower $F_ECO_2$ compared with Tamang subjects (mean ± SD: 3.36% ± 0.39% vs. 3.68% ± 0.3%, $p = 0.0057$). However, this difference was no longer evident at high altitude (mean ± SD: 2.85% ± 0.28% vs. 2.89% ± 0.26%, $p = 0.66$). The change in $F_ECO_2$ from low to high altitude was also significantly smaller in the Sherpa versus Tamang group (mean ± SD: –0.50% ± 0.44% vs –0.80% ± 0.33%, $p < 0.023$). There was no significant association between the decrease in $F_ECO_2$ and the increase in ventilation between low and high altitude.

## Discussion

To our knowledge, this is the first study to report a difference in altitude-induced sleep apnea between two closely related ethnic groups that differ only by the altitude at which their ancestors lived. Individuals of Tamang ethnicity showed an increase in AHI when ascending to high altitude

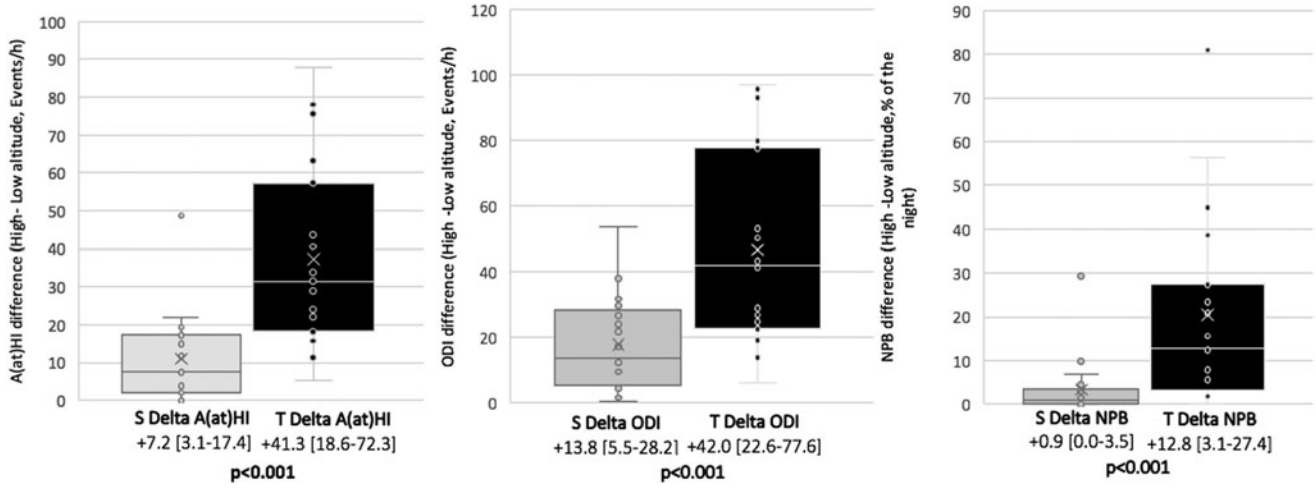


**FIG. 3.** Changes (delta) in nocturnal breathing parameters at high (4,380 m) versus low (2,030 m) altitudes in subjects of Sherpa (*grey boxes*) or Tamang (*black boxes*) ethnicity.. In the graphs, the *middle line* of each box shows the median, the *lower/upper lines* of each box show the first/third quartiles, the *cross* indicates the mean, and *circles* show individual data. A(at)HI, apnea (atypical apnea included)-hypopnea index; NBP, nocturnal breathing patter; ODI, oxygen desaturation index.

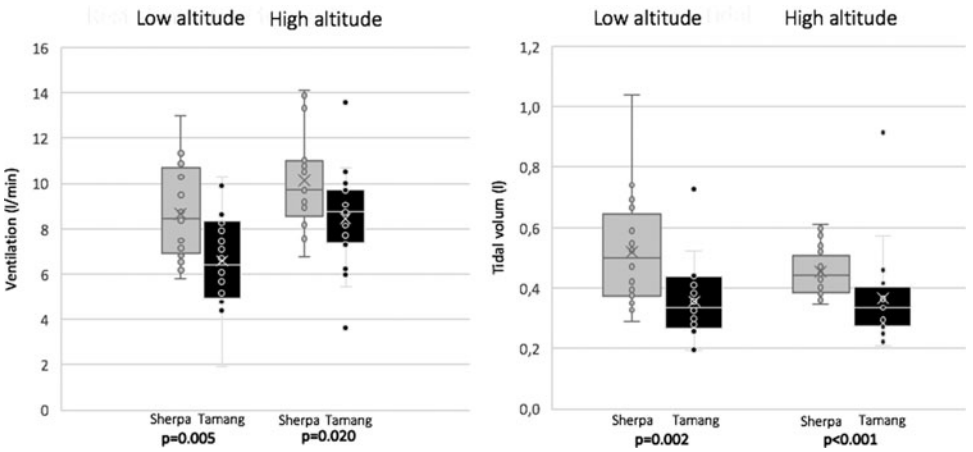


**FIG. 4.** Wake breathing characteristics at low and high altitudes in subjects of Sherpa (*grey boxes*) or Tamang (*black boxes*) ethnicity. In the graphs, the *middle line* of each box shows the median, the *lower/upper lines* of each box show the first/third quartiles, the *cross* indicates the mean, and *circles* show individual data.



that was more than three times higher than that seen individuals from altitude-adapted Sherpa ethnic group. Between-group differences in awake breathing patterns were also observed, with Sherpas having higher minute ventilation at low and high altitudes, and a smaller fall in $CO_2$ levels at high altitude.

Lahiri *et al.* (1983) and Lahiri and Data (1992) previously observed that Sherpa highlanders have a very low propensity to CSA at high altitude because none of their subjects showed any sustained periodic breathing with apnea during sleep at an altitude of 5,400 m. Another study on Himalayan populations compared native Tibetans to lowlander Hans living in Tibet and unexpectedly found no significant difference in AHI between these groups at an altitude of 3,800 m. However, the AHI values reported in that study were unusually low for this altitude ($4.19 \pm 2.48$/h vs. $4.31 \pm 2.83$/h in the Han and Tibetan groups, respectively), which may have attenuated a possible difference (Kong *et al.*, 2015).

At both low and high altitude, the Sherpa group showed significantly higher resting minute ventilation compared with the Tamang group. This difference is apparently due to a higher tidal volume in Sherpas. Similar differences were previously found between native Tibetans and Han people living in Tibet, with native Tibetans having larger chest circumference, total lung capacity, vital capacity, residual volume, and tidal volume compared with Hans of lowland Chinese origin (Sun *et al.*, 1990; Droma *et al.*, 1991; Chen *et al.*, 1997; Kapoor and Kapoor, 2005). This higher resting ventilation seems to be specific to Himalayan populations. In fact, Beall et al. (1997) showed that, compared with a high-altitude Andes population, Tibetans showed a greater resting ventilation and a larger tidal volume. This higher resting ventilation can also indicate higher respiratory drive in the Sherpa population.

However, the presence of differences in respiratory drive or hypoxic ventilatory response between these Himalayan populations and other populations are still debated (Gilbert-Kawai *et al.*, 2014). Looking at a Caucasian population for comparison, Nussbaumer-Ochsner *et al.* (2012) observed that European subjects had a higher propensity to develop CSA during the first night at 4,559 m ($n = 16$, AHI 60.9/h) compared with our observations in Sherpa and Tamang populations at a comparable altitude. In the Caucasian subjects, resting ventilation (6.3 l/min) and tidal volume (0.335 l) at 4,559 m were also lower compared with our Sherpa and Tamang subjects. Further study should compare nocturnal respiratory disorders between Caucasian and Himalayan populations by assessing the roles of respiratory drive and tidal volume in the loop gain.

In the current study, we also observed that the magnitude of $F_ECO_2$ drop when ascending to high altitude was greater in Tamangs compared with Sherpas. This may suggest differences in central $CO_2$ regulation between these populations. One previous study (Slessarev *et al.*, 2010) investigated ventilatory control in a high-altitude Himalayan population in Ladak. They compared the ventilatory response to $CO_2$ between 12 Himalayan residents and 21 unacclimated sea-level resident of European ancestry. Although the difference in acclimatization makes the results difficult to interpret, this study showed that the Himalayan highlanders had a decreased ventilatory response to increasing inhaled $CO_2$ compared with sea-levels residents.

This possible lower ventilatory response to $CO_2$ in Sherpas compared with Tamangs needs to be further investigated but could have an impact on their ''loop gain,'' (Younes *et al.*, 2001), which represents the propensity to develop periodic breathing.

Loop gain consists of a controller gain (ventilatory response to changes in $CO_2$ level), which may be lower in Sherpas, and a ''plant gain.'' Plant gain represents the change in $CO_2$ caused by a given change in ventilation. Steady state plant gain is the slope of the tangent line that touches the metabolic hyperbola at the ventilation point (Fig. 5). The metabolic hyperbola is a plot of the alveolar ventilation equation. A higher resting ventilation is associated with a flatter slope. Although we could not directly calculate their plant gain, we suspect that Sherpas may have a lower steady state plant gain (i.e., less change in partial pressure of carbon dioxide ($PCO_2$) for a given change in ventilation) because of the higher ventilation and estimated alveolar ventilation, making them less susceptible to periodic breathing.

Although previous studies suggested that the increase in ventilation caused by the change from a normoxic to a hypoxic environment did not have a protective effect on the

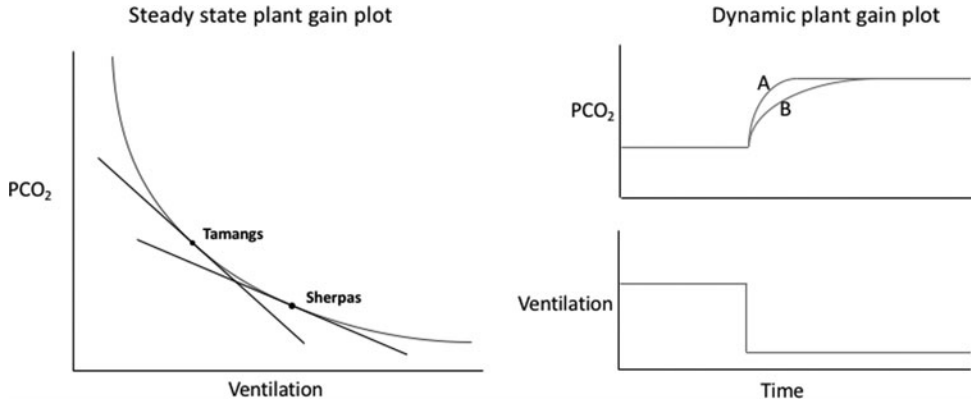


**FIG. 5.** Plant gain hypothesis. Steady state plant gain is the slope of the tangent line that touches the metabolic hyperbola at the ventilation point. A higher ventilation is associated with a smaller slope. Because Sherpas have a higher ventilation, they have a lower plant gain, that is, they will have less change in $PCO_2$ for a given change in ventilation, making them less susceptible to periodic breathing. In the ''steady state,'' the plant gains are the same in patients A and B, because they both ultimately reach the same delta $PCO_2$ for a given change in ventilation. Patient A just achieves it faster. The faster they reach the steady state $PCO_2$ level, the more likely they will achieve a larger delta $PCO_2$ when fast-cycling periodic breathing is occurring. $PCO_2$, partial pressure of carbon dioxide.



occurrence of CSA (Xie *et al.*, 2001), this does not apply to the present situation since Sherpas have a higher ventilation than Tamangs while both groups are in the same hypoxic conditions. To ensure that the metabolic curve is identical in Tamang and Sherpas, we calculated $CO_2$ production ($VCO_2$) in each group. In lowland and high altitude, we found no significant difference between the size-adjusted $VCO_2$ of each group (Lowland: Sherpa vs. Tamang mean [95% confident interval]: 0.253 [0.246–0.321] l/min vs. 0.283 [0.215–0.291] l/min, $p = 0.277$; High-altitude: Sherpa vs. Tamang mean [95% confident interval]: 0.277 [0.252–0.302] l/min vs. 0.254 [0.229–0.279] l/min, $p = 0.218$).

Another explanation for the observed findings could be a lower ''dynamic'' plant gain in Sherpas. Dynamic plant gain takes into account the rate of $CO_2$ changes caused by a given change in ventilation (Fig. 5). As shown on this figure, two subjects may both ultimately reach the same delta $PCO_2$ for a given change in ventilation, that is, they have the same steady state plant gain. However, one of the subjects reaches this $PCO_2$ more quickly, giving them a greater dynamic plant gain.

The faster the steady state $PCO_2$ level is reached, the larger the delta $PCO_2$ achieved when periodic breathing occurs, particularly if the cycle period is short, such as in high-altitude periodic breathing. Functional residual capacity (FRC) affects the dynamics of plant gain (Dempsey and Smith, 2004): the greater the FRC, the lower the dynamic plant gain. If, like Tibetans, Sherpas tend to have a large FRC (Sun *et al.*, 1990; Droma *et al.*, 1991; Chen *et al.*, 1997), we can speculate that they may have lower dynamic plant gain. Therefore, our data suggest that Sherpas may have a lower controller gain and a lower plant gain, which could explain their lower propensity to altitude-induced sleep apnea.

Finally, it is interesting to note that despite having a higher desaturation index (ODI), Tamangs showed similar nocturnal oxygen saturation to the Sherpas, suggesting that periodic breathing may not negatively affect mean oxygen saturation, as suggested by others (Levine *et al.*, 1995; Salvaggio *et al.*, 1998).

Our study has some limitations that need to be mentioned. Since the polygraphy recorders we used did not have chest motion detectors, it was not possible to distinguish between central and obstructive respiratory events. However, given that we compared the same subjects at low and high altitudes, and that obstructive events occurring at low altitude are mainly caused by anatomical characteristics, we expect that the rapid change in AHI observed between low- and high-altitude conditions was essentially due to altitude-induced respiratory events (Nussbaumer-Ochsner *et al.*, 2010). Second, as we did not perform a complete polysomnography, our recordings did not include electroencephalographic parameters.

Therefore, we could not assess total sleep time. If Sherpas had a longer wake time during the night compared to Tamangs, this could have artificially lowered the AHI. Moreover, our recordings do not allow evaluating the arousal thresholds. A lower arousal threshold in the Tamang could have contributed to the increased in sleep disordered breathing that was observed.

Third, polygraphy recordings were performed over 2 days at each altitude meaning that there could be a difference of acclimatization between subjects tested during the first night and those tested during the second night, but this bias is probably negligible because the same order of testing was used at both altitudes. Finally, the study population included only males, which limits the ability to generalize our results to females.

## Conclusion

High altitude-adapted Sherpas showed a significantly smaller increase in sleep-disordered breathing and a smaller fall in $CO_2$ level between low and high altitude compared with individuals from the Tamang ethnic group, whose ancestors lived at low altitude. This suggests that genetic specificities in breathing control could protect from altitude-induced sleep apnea and may represent a previously neglected adaptive trait evolved by Tibetan and Sherpa ancestors to cope with hypobaric hypoxia-related stresses.

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### Authors' Contributions

The hypothesis for this study was proposed by G.H. and R.H. They were assisted in the design and organization of the project by C.S., A.L., and S.W. G.H. and S.W. were in charge of the data acquisition in Nepal. Data analysis was performed by G.H. under the supervision of R.H. The interpretation of the results was done by G.H., R.H., C.S., A.L., and A.W. M.Z. supervised the writing of this article, including the historical and genetic differences between Tamangs and Sherpas.

### Data Availability Statement

All data collected can be made available to other research groups.

### Author Disclosure Statement

R.H. is member of the medical advisory board of Philips Nightbalance and Dreem and received speakers fees or honorarium of Resmed, Philips, Jazz, and Inspire. A.W. works as a consultant for Apnimed, Nox, Inspire, and Somnifix. He has received grants from Regeneron and Somnifix. He also has a financial interest in Apnimed Corp., a company developing pharmacologic therapies for sleep apnea. A.D.'s interests were reviewed and are managed by Brigham and Women's Hospital and Partners Health Care in accordance with their conflict of interest policies. All authors attest that they have no conflict of interest in relationship to this article.

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