Altitude and Breathing during Sleep in Healthy Persons and Sleep Disordered Patients: A Systematic Review

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Abstract

Objetive The aim of this systematic review is to analyze the recent scientific evidence of the clinical effects of altitude on breathing during sleep in healthy persons and sleep disordered patients.

Material and Methods A search was carried out in PubMed and Scopus looking for articles published between January 1, 2010 and December 31, 2021, in English and Spanish, with the following search terms: "sleep disorders breathing and altitude". Investigations in adults and carried out at an altitude of 2000 meters above mean sea level (MAMSL) or higher were included. The correlation between altitude, apnea hypopnea index (AHI) and mean SpO2 during sleep was calculated.

Results 18 articles of the 112 identified were included. A good correlation was found between altitude and AHI (Rs = 0.66 P = 0.001), at the expense of an increase in the central apnea index. Altitude is inversely proportional to oxygenation during sleep (Rs = −0.93 P = 0.001), and an increase in the desaturation index was observed (3% and 4%). On the treatment of respiratory disorders of sleeping at altitude, oxygen is better than servoventilation to correct oxygenation during sleep in healthy subjects and acetazolamide controlled respiratory events and oxygenation during sleep in patients with obstructive sleep apnea under treatment with CPAP.

Conclusions Altitude increases AHI and decreases oxygenation during sleep; oxygen and acetazolamide could be an effective treatment for sleep-disordered breathing at altitude above 2000 MAMSL.

Keywords
- altitude
- sleep apnea, obstructive
- sleep apnea, central
- hypoxia
- sleep apnea syndromes

Introduction

Around 140 million people reside at high altitudes over 2,500 meters above mean sea level (MAMSL), but an even greater number may live at moderate altitudes of 2,000 to 2,500 MAMSL, and some 35 million people travel to sites at these elevations each year for work or leisure activities.[1] A significant percentage of these populations live in Latin American countries like Bolivia, Colombia, Ecuador, Mexico, and Peru.

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Because altitude is inversely proportional to barometric pressure, it reduces the partial pressure of inspired oxygen (PIO_2); as a result, ascending to high elevations generates a decrease in partial pressure of arterial oxygen (PaO_2), reduces arterial oxygen saturation (SaO_2), and causes ventilatory changes due to acclimatization characterized by increase in minute ventilation and respiratory alkalosis[2,3]; these changes are especially important during sleep.[4]

Sleep-related breathing disorders (SRBDs) comprise a heterogeneous group of conditions characterized by respiratory disturbances that occur or worsen during sleep.[5] The main SRBD associated with ascent to moderate/high altitudes is the central sleep apnea syndrome,[6] but exposure to altitude could also aggravate a preexisting disorder such as obstructive sleep apnea syndrome (OSAS), the latter being the most common worldwide affecting around one billion people and with prevalences that are on the rise.[7,8] The aim of this systematic review is to analyze the recent scientific evidence of the clinical effects of altitude on breathing during sleep in healthy persons and sleep disordered patients.

Material and Methods

A literature search was carried out in the PubMed and Scopus databases to identify articles published between January 1, 2010, and December 31, 2021, using the following search terms: *sleep disorders breathing and altitude*. Filters ensured that research in English and Spanish would be identified. Two independent reviewers (JLCA and SRC) analyzed all the information gathered, beginning with the titles and abstracts of all potentially eligible articles as a preliminary screening. A list of full-text articles was then organized. Subsequently, both reviewers read the complete texts of all those articles to apply the inclusion/exclusion criteria. Both observational and interventions studies were included as long as they were (i) carried out at altitudes of 2,000 MAMSL or higher, (ii) involved adults aged 18 years or older, and (iii) utilized objective measurements of breathing during sleep. Review articles, conference abstracts, comments, and editorials were excluded. The quality of the information was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) model[9]; articles with very low quality of evidence were eliminated of the final analysis, and disagreements were resolved by consensus. In the final step, one author (SRC) extracted the data, and the second author (JLCA) reviewed it.

The data extracted focused on the following: the apnea hypopnea index (AHI), the central apnea index (CAI), the obstructive apnea index (OAI), the oxygen desaturation index (ODI), mean saturation during sleep (mean SpO_2), and minimum saturation during sleep (minimum SpO_2). The information was organized in three categories: the effect of altitude on the apnea hypopnea index (AHI); the effect of altitude on oxygenation during sleep; and the treatment of sleep-related breathing disorders at moderate and high altitudes. To evaluate the association between altitude and breathing alterations during sleep, a correlation was performed among altitude, the AHI, and mean SpO_2; due to skewness of data (evaluated with the Shapiro-Wilk test), the Spearman Rho test was used. All correlation analyses were run in the Stata 15 for MAC (StataCorp., LLC, College Station, TX, USA) program. Correlation plots were constructed using the Stata 15 for MAC program and edited in Microsoft PowerPoint (Microsoft Corp., Redmond, WA, USA).

Results

Some of the results of this research were presented previously as an abstract. Of the 112 articles identified in the initial search, 74 were eliminated after analyzing and discussing the title and abstract, leaving 38 to be evaluated by reading the full text. Of those 38 studies, 20 were eliminated due to very low quality of evidence, so the final selection included 18 articles (►**Figure 1**).[10–27] Fifteen reports were based on real ascents to high or moderate elevations, while the other 3 presented studies of simulated altitudes. The data analyzed involved a total of 530 subjects and presented the results of 1,291 sleep studies. According to GRADE, the information evaluated was of moderate-to-low quality (►**Table 1**).

Effect of Altitude on the Apnea Hypopnea Index

A total of 14 studies evaluated the effect of altitude on the AHI: 9 with healthy individuals, 1 with patients with chronic obstructive pulmonary disease (COPD), and 4 with patients suffering from OSAS (►**Table 2**). A directly proportional relation was determined between altitude and AHI (Rs x2009;= 0.66, $P = 0.001$) (►**Figure 2**). This increase in AHI was secondary to an increase in the CAI, but it is important to note that in the studies by Pagel et al. (2011), Nussbaumer-Ochsner et al. (2012), and Ulrich et al. (2014), based on OSAS patients, the increase in the CAI did not exceed the proportion of 50% of total AHI; therefore, the most important disorder in this group of patients was found to be of the obstructive type.

The effect of altitude on the AHI may diminish over time; this would explain why the AHI decreased on the second night after the ascent, as in the report by Latshang et al. (2013) and Frost et al. (2021) on healthy individuals; however, this was not corroborated by Lombardi et al. (2013) and Bird et al. (2021) (in a rapid ascent to an altitude of 3,800 MAMSL) in their study of healthy individuals, or by Nussbaumer-Ochsner et al. (2010) in their work with OSAS patients. Lombardi et al. (2013) conducted an additional assessment on the 10th night after an ascent to 5,400 MAMSL, but only made comparisons between biological sexes.

Effect of Altitude on Oxygenation During Sleep

We identified 16 articles with information on the impact of altitude on oxygenation during sleep: 11 in healthy persons, 1 in patients with COPD, and 4 in patients with OSAS (►**Table 3**). Altitude is inversely proportional to oxygenation during sleep, the correlation between altitude and the mean SpO_2 during sleep presented an $Rs = -0.93$ and a $p = 0.001$ (►**Figure 3**). In addition, an increase in ODI (3% and 4%) and a decrease in the minimum SpO_2 were observed (►**Table 3**).

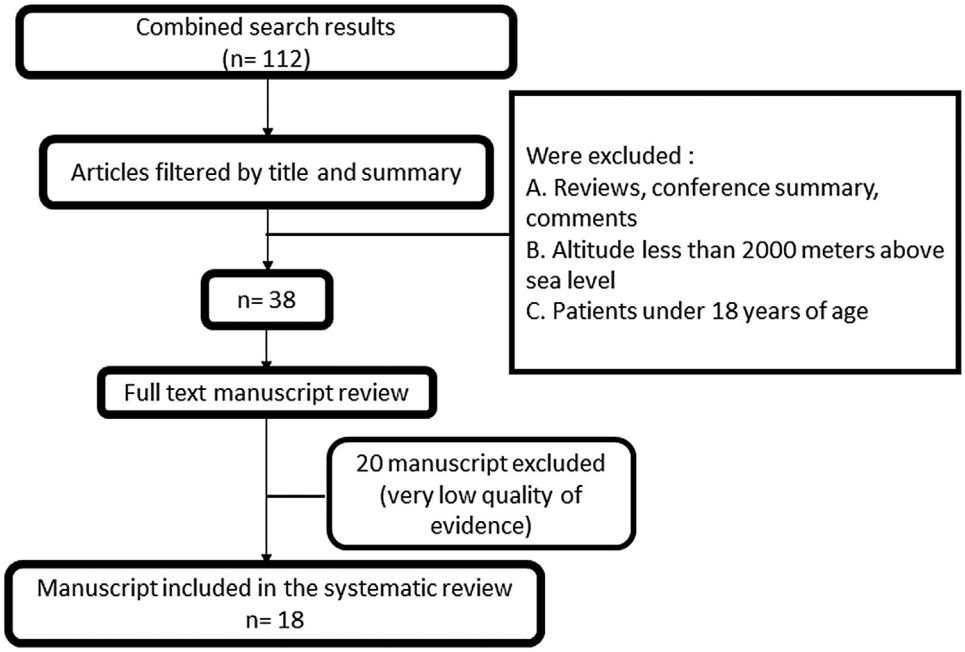

Fig. 1 Flowchart of the article selection and evaluation process.

Table 1 Quality of the evidence according to the GRADE system.

		Items that lower the quality					Items that raise quality					
Manuscripts	**Year**	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**Quality**	**Type of investigation**
Bloch et al.[10]	2010				1						Moderate	Randomized
Nussbaumer-Ochsner et al.[11]	2010			1	1						Low	Randomized
Pagel et al.[12]	2011				1						Low	Observational
Latshang et al.[13]	2012	1									Low	Randomized
Nussbaumer-Ochsner et al.[14]	2012				1						Moderate	Randomized
Latshang et al.[15]	2013			1							Moderate	Randomized
Lombardi et al.[16]	2013	1			1						Low	Observational
Ulrich et al.[17]	2014			1	1						Low	Randomized
Shogilev et al.[18]	2015	1			1						Low	Observational
Heinzer et al.[19,*]	2016			1	1						Moderate	Randomized
Steier et al.[20]	2017	1			1						Low	Observational
Pramsohler et al.[21,*]	2017		1		1						Low	Randomized
Orr et al.[22]	2018	1				1					Low	Randomized
Pramsohler et al.[23,*]	2019	1			1	1					Low	Randomized
Tan et al.[24]	2020				1						Moderate	Randomized
Frost et al.[25]	2021	1			1						Low	Observational
Ju et al.[26]	2021	1			1						Low	Observational
Bird et al.[27]	2021	1		1	1						Moderate	Observational

GRADE ITEMS: A = Limitations in the design and execution of the study, B = Inconsistency of results, C = Uncertainty that the evidence is direct, D = Imprecision, E = Publication or notification bias, F = Association strength, G = Very strong association, H = Existence of the dose-response gradient, I = Evidence that all possible confounders could have reduced the observed effect.
*Studies conducted with simulated altitude.

Table 2 Effect of altitude on the apnea hypopnea index.

Manuscripts	Altitude MAMSL	n	AHI h^{-1} mean/median ± SD/IR		CAI h^{-1} mean/ median ± SD/IR	OAI h^{-1} mean/ median ± SD/IR	Evaluation method
Healthy persons							
Bloch et al., 2010[10]	490 (basal)	34	4.0 (1.2–9.7)		NR	NR	**RP**
	4,497	32	71.9 (37.2–96.2)*		NR	NR	
	5,533	29	114.1 (81.1–130.3)*		NR	NR	
	6,265	24	142.6 (120.4–154.2)*		NR	NR	
	6,865	24	132.3 (103.3–157.4)*		NR	NR	
Latshang et al., 2013[15]	490 (Basal)	51	4.6 (2.3–7.9)		2.0 (1.2–3.7)	1.3 (0.3–4.6)	**PSG**
	2,590 (1st night)		13.1 (6.7–32.1)*		8.9 (5.0–25.8)*	1.8 (0.7–3.8)	
	2,590 (2nd night)		8.0 (4.4–23.1)*^		5.8 (2.8–13.1)*^	1.6 (0.7–3.4)	
Lombardi et al., 2013[16]			M	F			
	Sea level (basal)	37	0.03 ± 0.11	0.14 ± 0.21	NR	NR	**RP**
	3,400	36	2.4 ± 2.8*	40.3 ± 33.0*&	NR	NR	
	5,400 (1st/2nd night)	24	41.1 ± 44*	87.5 ± 35.7*&	NR	NR	
	5,400 (10th night)	28	84.7 ± 22.5*	97.0 ± 30.3*&	NR	NR	
Heinzer et al., 2016[19,#]	485 (NN, basal)	13	8.2 (3.9–8.8)		NR	NR	**PSG**
	3,450 (NH)		11.4 (5.0–65.4)*		NR	NR	
	3,450 (HH)		20.5 (15.8–57.4)*		NR	NR	
Pramsohler et al., 2017[21,#]	5,500	11	143.1 (24.6–168)		NR	NR	**PSG**
Pramsohler et al., 2019[23,#]	3,500 (basal)	11	37.96		NR	NR	**PSG**
	4,500		68.55*		NR	NR	
	5,500		93.44*		NR	NR	
Frost et al., 2021[25]	340 (basal)	15	4.3 (4.5)		0.5 (0.6)	0.5 (1.1)	**RP**
	3,800 (1st night)		35.3 (28.7)*		14.0 (17.1)	0.3 (0.8)	
	3,800 (2nd night)		16.0 (21.1)		7.6 (15.2)	0.1 (0.2)	
	3,800 (3rd night)		7.3 (5.3)		0.8 (0.8)	0.1 (0.2)	
Ju et al., 2021[26]	154 (basal)	10	1.4 (0.8–3.0)		NR	NR	**RP**
	2,761		10.3 (5.7–15.4)*		NR	NR	
Bird et al., 2021[27]	Rapid ascent						**RP**
	1,130 (basal)	21	3.4 ± 3.5		NR	NR	
	3,800 (2nd night)	20	12.3 ± 14.5*		NR	NR	
	3,800 (9th night)	20	24.6 ± 23.7*		NR	NR	
	Incremental ascent						
	1,130/1,400 (basal)	21	3.7 ± 4.1		NR	NR	
	3440 (2nd/3th night)	19	10.8 ± 11.8		NR	NR	
	4240 (6/7th night)	14	26.7 ± 17.8*		NR	NR	
	5160 (9/10th night)	15	39.2 ± 32.6*		NR	NR	
Patients with chronic obstructive pulmonary disease							
Tan et al., 2020[24]	490 (basal)	32	22.0 ± 15.8		1.6 ± 1.9	20.4 ± 15.2	**PSG**
	2048		44.0 ± 35.8*		32.4 ± 32.3*	11.6 ± 13.2*	
Patients with obstructive sleep apnea syndrome							
Nussbaumer-Ochsner et al., 2010[11]	490 (basal)	40	51.2 (31.7–74.4)		2.4 (0.4–8.8)	21.0 (16.4–24.9)	**PSG**
	2590 (1st night)		90.0 (64.2–103.2)*		51.3 (32.8–75.5)*	32.0 (3.3–54.6)	
	2,590 (2nd night)		88.6 (62.4–108.4)*		49.4 (22.6–57.8)*	25.2 (6.5–58.8)	
Pagel et al., 2011[12]	2,165	142	46.7 ± 26.8		15.8	30.9	**PSG**
Nussbaumer-Ochsner et al., 2012[14]	490 (basal)	45	51.2 (42.4– 72.2)		1.6 (0.5– 3.2)	49.4 (41.4– 67.6)	**PSG**
	2590		86.2 (67.2–103.1)*		23.4 (14.0–44.5)*	55.5 (34–75.0)	

Table 2 (*Continued*).

Manuscripts	Altitude MAMSL	n	AHI h^{-1} mean/median ± SD/IR	CAI h^{-1} mean/ median ± SD/IR	OAI h^{-1} mean/ median ± SD/IR	Evaluation method
Ulrich et al., 2014[17]	490 (Basal)	18	57.3 (46.5–67.3)	0.8 (0.2–1.8)	49.6 (42.2–62.2)	PSG
	2,590		86.5 (70–117)	30.7 (21.2–48.2)*	61.3 (33.9–75.0)	

Abbreviations: AHI, apnea hypopnea index, CAI, central apnea index, COPD, chronic obstructive pulmonary disease, F, female, h-1, events per hour, HH, hypobaric hypoxia, IR, interquartile range, M, male, MAMSL, meters above sea level, NH, normobaric hypoxia, NN, normobaric normoxia, NR, not reported, OAI, obstructive apnea index, PSG, polysomnography, RP, respiratory polygraphy, SD, standard deviation.
*$p < 0.05$ vs. Basal.
^$p < 0.05$ vs 1st night.
&$p < 0.05$ males vs females.
#Studies conducted with simulated altitude.

The work by Lombardi et al. (2013) stands out in this regard because it reported differences between biological sexes, which showed that altitude had a greater impact on men than women; also important is the study by Heinzer et al. (2016), who found differences between normobaric hypoxemia and hypobaric hypoxemia; and the work by Bird et al. (2021), which describes changes in respiration with 2 different patterns of ascent (rapid and incremental). (►**Table 3**).

Treatment of Sleep-Related Breathing Disorders at High-to-Moderate Altitudes

Only two publications were identified for this aspect of our review; one involving healthy individuals, the second OSAS patients. Orr et al. (2018) analyzed a group of healthy individuals who ascended to 3,800 MAMSL; they found that oxygen therapy was more effective at reducing the ODI 3% and increasing mean SpO_2 than adaptive servoventilation. Latshang et al. (2012), meanwhile, working with a group of OSAS patients who were receiving CPAP treatment, reported that this therapy plus acetazolamide decreased the AHI by reducing the number of central events and improving oxygenation during sleep, compared to CPAP therapy plus placebo (►**Table 4**).

Discussion

This systematic review identified recent and updated evidence obtained from observational and intervention studies regarding the effects of altitude on breathing during sleep in healthy persons, patients with COPD and OSAS and possible solutions to SRDB at altitude. People who travel to high altitudes often report symptoms that include low sleep quality, insomnia, and frequent awakenings with a sensation of suffocation secondary to alterations in breathing. Although idiosyncratic reactions may occur at altitudes above 1,500 MAMSL, periodic breathing and central apneas secondary to altitude typically appear with variable severity at elevations over 2,000 MAMSL, while at altitudes above 4,000 MAMSL, these disorders will be present in practically all individuals.[28] The decrease in barometric pressure secondary to altitude and the hypoxia that this produces generate a process of ventilatory acclimatization characterized by a progressive increase in ventilation (hyperventilation) until a partial restoration of PaO_2 is achieved with a concomitant decrease in $PaCO_2$.[4,29] The precise mechanisms that control this process of acclimatization are not well understood because a large number of influencing factors may be involved, including: the sensitivity of central and

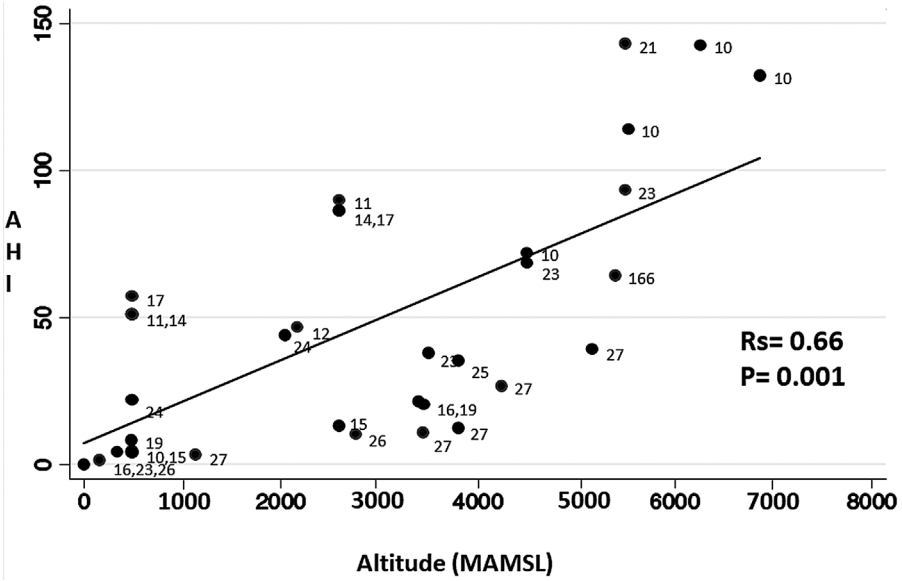

Fig. 2 The directly proportional association (measured by Rho Spearman) between altitude in meters above mean sea level (MAMSL) and the apnea hypopnea index (AHI) in events per hour of sleep is presented.

Table 3 Effect of altitude on oxygenation during sleep.

Manuscripts	Altitude MAMSL	n	ODI 3% h^{-1} mean/median ± SD/IR		ODI 4% h^{-1} mean/ median ± SD/IR	Mean $SpO_{2\%}$ mean/median ± SD/IR		Minimun $SpO_{2\%}$ mean/median ± SD/IR		Evaluation method
Healthy individuals										
Bloch et al., 2010[10]	490 (Basal)	34	NR		NR	NR		95 (94–96)		RP
	4,497	32	NR		NR	NR		80 (78–82)		
	5,533	29	NR		NR	NR		70 (68–72)		
	6,265	24	NR		NR	NR		62(60–66)		
	6,865	24	NR		NR	NR		60(55–63)		
Latshang et al., 2013[15]	490 (Basal)	51	0.3 (0.0–1.1)		NR	96 (95–96)		NR		PSG
	2,590 (1° night)		8.1 (3.3–30.9)*		NR	90 (89–91)*		NR		
	2,590 (2° night)		5.4 (2.5–14.8)*		NR	91 (90–92)*		NR		
Lombardi et al., 2013[16]			M	F		M	F	M	F	
	Sea level (basal)	37	0.1 ± 0.2	0.1 ± 0.2	NR	97.4 ± 0.9	97.3 ± 0.8	92.9 ± 1.5	93.0 ± 1.0	RP
	3,400	36	8.6 ± 5.7	37.9 ± 25.8	NR	84.9 ± 3.0	82.1 ± 3.8*	75.5 ± 4.2	73.7 ± 5.1*	
	5,400 (1^{st}/2^{nd} night)	24	55.8 ± 29.6	79.9 ± 25.6*	NR	72.5 ± 4.9	73.1 ± 4.2*	61.8 ± 6.2	62.2 ± 4.7*	
	5,400 (10^{th} night)	28	45.3 ± 34	84.7 ± 22.4*	NR	78 ± 2.3	76.5 ± 2.9*	68.7 ± 3.8	66.1 ± 6.0*	
Shogilev et al., 2015[18]	760 (basal)	4	NR		NR	95.6		NR		PR
	2,670		NR		NR	91		NR		
	3,200		NR		NR	88.4		NR		
	3,540		NR		NR	87.2		NR		
Heinzer et al., 2016[19,#]	485 (NN, basal)	13	4.4 (2.2–4.8)		0.9 (0.5–1.2)	95.5 ± 0.9		92.0 ± 1.5		PSG
	3,450 (NH)		22.7 (13.1–73.8)*		9.1 (5.7–59.2)*	83.6 ± 1.9*		74.7 ± 7.0*		
	3,450 (HH)		47.6 (22.1–82.2)*		29.2 (8.8–57.1)*	81.2 ± 3.1*		72.6 ± 4.2*		
Steier et al., 2017[20]	Sea level (basal)	4	NR		0.8 ± 0.4	97.5 ± 1.3		95.3 ± 1.7		PSG
	3,380		NR		22.0 ± 7.2	84.8 ± 0.5		68.1 ± 8.6		
	4,370		NR		61.4 ± 26.9	81.0 ± 4.1		67.4 ± 7.6		
	5,570	1	NR		144.9	68.5		50.4		
Pramsohler et al., 2017[21,#]	5,500	11	NR		NR	65.6 ± 3.7		NR		PSG
Pramsohler et al., 2019[23,#]	3,500 (basal)	11	NR		NR	NR		66.0 ± 10.7		PSG
	4,500		NR		NR	NR		56.8 ± 9.8*		
	5,500		NR		NR	NR		55.6 ± 4.03*		

Table 3 (*Continued*).

Manuscripts	Altitude MAMSL	n	ODI 3% h^{-1} mean/median ± SD/IR	ODI 4% h^{-1} mean/ median ± SD/IR	Mean $SpO_{2\%}$ mean/median ± SD/IR	Minimun $SpO_{2\%}$ mean/median ± SD/IR	Evaluation method
Frost et al., 2021[25]	340 (basal)	15	3.1 (3.3)	NR	94.7 (0.9)	85.8 (4.4)	RP
	3,800 (1st night)		34.3 (22.6)*	NR	77.0 (2.4)*	65.3 (6.2)*	
	3,800 (2nd night)		19.5 (22.9)	NR	77.6 (2.9)	68.0 (6.4)	
	3,800 (3rd night)		7.2 (6.1)	NR	78.5 (1.6)	70.7 (3.6)	
Ju et al., 2021[26]	154 (basal)	10	NR	NR	95.7 (95.1–96.2)	NR	RP
	2,761		NR	NR	86.9 (84.7–88.9)	NR	
Bird et al., 2021[27]	Rapid ascent		Rapid ascent		Rapid ascent	Rapid ascent	
	1,130 (basal)	21	6.8 ± 5.3	NR	93.7 ± 2.1	86.0 ± 5.1	RP
	3,800 (2nd night)	20	26.1 ± 18.1*	NR	81.1 ± 3.6*	71.2 ± 6.2*	
	3,800 (9th night)	20	38.8 ± 26.7*	NR	84.0 ± 2.3*	74.3 ± 6.1*	
	Incremental ascent		Incremental ascent		Incremental ascent	Incremental ascent	
	1,130/1,400 (basal)	21	9.8 ± 7.8	NR	94.3 ± 1.6	87.1 ± 3.7	
	3,440 (2nd/3rd night)	19	28.5 ± 15.3*	NR	84.8 ± 5.5*	75.4 ± 6.7*	
	4,240 (6/7th night)	14	43.7 ± 21.7*	NR	81.6 ± 3.1*	70.6 ± 5.0*	
	5,160 (9/10th night)	15	54.4 ± 24.8*	NR	73.5 ± 4.2*	63.7 ± 6.6*	
Patients with chronic obstructive pulmonary disease							
Tan et al., 2020[24]	490 (basal)	32	0.8 ± 1.3	NR	92 ± 2	NR	PSG
	2,048		4.2 ± 5.6*	NR	86 ± 3*	NR	
Patients with obstructive sleep apnea syndrome							
Nussbaumer-Ochsner et al., 2010[11]	490 (basal)	40	37.3 (14.6 - 52.7)	NR	94 (93–95)	NR	PSG
	2,590 (1st night)		80.6 (52.4–103.4)	NR	86 (84–89)	NR	
	2,590 (2nd night)		71.5 (43.4–98.6)	NR	87(84–89)	NR	
Pagel et al., 2011[12]	1,421 (basal)	150	NR	NR	NR	73.5 ± 11.3	PSG
	2,165	142	NR	NR	NR	74.2 ± 9.6	
Nussbaumer-Ochsner et al., 2012[14]	490 (basal)	45	NR	NR	93 (92–94)	NR	PSG
	2590		NR	NR	85 (83–88)*	NR	
Ulrich et al., 2014[17]	490 (basal)	18	NR	NR	93 (92–94)	NR	PSG
	2,590		NR	NR	86 (84–87)*	NR	

Abbreviations: F, female, h-1, events per hour, HH, hypobaric hypoxia, IR, interquartile range, M, male, MAMSL, meters above mean sea level, NH, normobaric hypoxia, NN= normobaric normoxia, NR, not reported, ODI, oxygen desaturation index, PSG, polysomnography, RP, respiratory polygraphy, SD, standard deviation, SpO_2, pulse oximetry.
*$p < 0.05$ vs. basal.
#Studies conducted with simulated altitude.

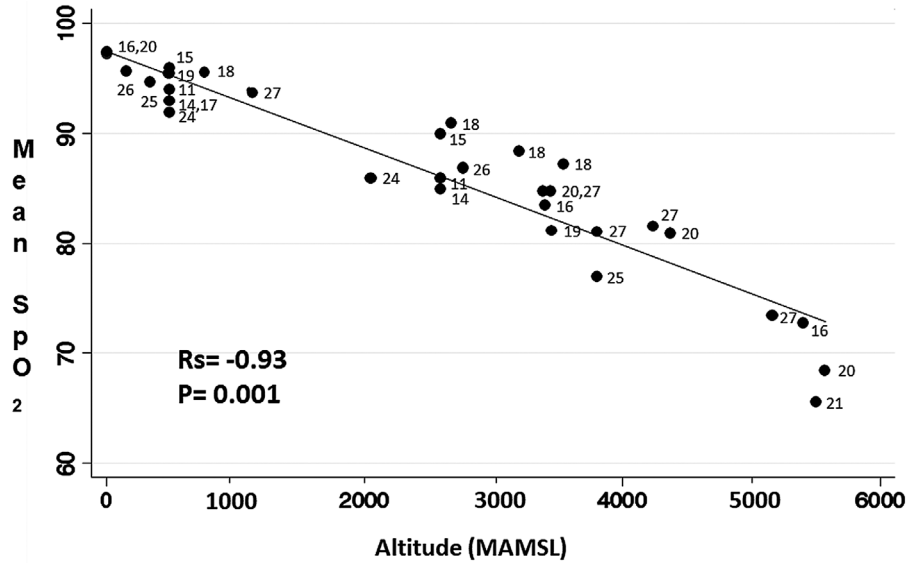

Fig. 3 The inversely proportional association (measured by Rho Spearman) between altitude in meters above mean sea level (MAMSL) and average SpO2 during sleep (expressed as a percentage) is presented.

peripheral chemoreceptors, cerebral blood flow, pulmonary artery pressure, the micro/macro architecture of sleep, and the complex interaction among these parameters.[4]

Altitude was found to have a directly proportional relation to AHI; in both healthy persons and COPD patients. This increase in AHI was secondary to an increase in the number of central apneas; thus, hyperventilation secondary to ventilatory acclimatization intensifies over time and after 10 minutes of sleep tidal volume oscillates at increasing magnitudes, decreasing $PaCO_2$ even more; this alters loop gain, reaches the apneic threshold, and causes central apneas.[30] The results of OSAS patients show that while they had a considerable number of central apneas, the most important disorders affecting them were of the obstructive type, indicating that obstructive and central events are interrelated in this group of patients in such a way that central apneas could represent ventilatory instability secondary to altitude, and this instability could foster obstructive events.[31,32]

It is important to note that in two investigations, a decrease in AHI was reported on subsequent nights compared to the first; although completing the ventilatory acclimatization process may take weeks, most of it is accomplished between days 1 and 2 of the ascent, so this phenomenon may be the reason behind this change[33–35]; However, this finding was not consistent, so different altitude acclimatization phenotypes could be present among individuals.

Altitude was also associated with hypoxemia during sleep, as indicated by several markers: mean SpO_2, minimum SpO_2, and ODI. Though the decline in the PIO_2 secondary to the decrease in barometric pressure due to altitude alone might explain this phenomenon, the most important generating mechanism involves the ventilatory oscillations secondary to both central and obstructive respiratory events.

Given this correlation among altitude, apneas, and hypoxia, the most obvious form of treatment would consist simply in descending to lower altitudes, but this is not always possible. Although the information available for analysis is scarce, it appears that measures which stabilize ventilation by modifying respiratory control are more effective than positive pressure devices that function by directly regulating ventilation during sleep. Thus, increasing FIO_2 and thereby raising SaO_2 gradually decreases both hyperventilation and $PaCO_2$.[36] Acetazolamide is known to inhibit central apneas by 50 to 80% by generating metabolic acidosis, stimulating ventilation, and favoring CO_2 retention,[37,38] and it is important to keep in mind that positive pressure devices can have a double antagonistic effect, which could decrease their effectiveness in eliminating respiratory events at higher altitudes. While they could increase ventilation and decrease $PaCO_2$ even more, they might also increase functional residual capacity, thereby increasing PaO_2.[4] Unfortunately, the evidence available to date is so limited that we are unable to determine the ideal treatment for respiratory disorders associated with sleeping at high altitudes. Finally, we must evaluate the possibility that central apneas with periodic respiration could act as a compensatory mechanism rather than a pathological process, since this type of respiration reduces demand for O_2 by the respiratory muscles.[39]

Other significant considerations are that most of the data analyzed was generated at high altitudes using healthy individuals, and that few studies have been carried out at moderate altitudes. It may be, however, that moderate altitudes have little clinical significance for healthy individuals; for example, Hernández-Zenteno et al. (2002) reported the results of a polysomnographic study of asymptomatic subjects conducted at 2,240 MAMSL, with the mean SpO_2 of those individuals being $93 \pm 2\%$, the minimum SpO_2 was 86 ± 6, and the ODI 3% was $10 \pm 22\,h^{-1}$.[40] Ascending to moderate altitudes, however, could have a greater impact on patients who have some chronic respiratory disorder, such as diffuse interstitial lung disease or chronic obstructive pulmonary disease (COPD), in which more severe hypoxemia during sleep has been reported.[41,42]

Table 4 Treatment of sleep-related breathing disorders at high-to-moderate altitudes.

Manuscripts	Altitude MAMSL	Treatment	n	AHI h-1 median (IR)	CAI h^{-1} median (IR)	OAI h^{-1} median (IR)	ODI 3% h^{-1} mean ± SD	mean $SpO_{2\%}$ mean ± DE	TP cmH2O median (IR)	Evaluation method
Healthy individuals										
Orr et al., 2018[22]	3,800	ASV vs No Tx	16	NR	NR	NR	10.7 ± 2.9 vs 17.1 ± 4.2	81 ± 1 vs. 79 ± 1[&]	NR	PSG
		O2 vs No Tx	15	NR	NR	NR	0.5 ± 0.2 vs 16.5 ± 4.5[&]	96 ± 0 vs. 79 ± 1[&]	NR	
		ASV vs O2	15	NR	NR	NR	8.8 ± 1.9 vs 0.5 ± 0.2[&]	80 ± 1 vs. 97 ± 0[&]	NR	
Patients with obstructive sleep apnea syndrome										
Latshang et al., 2012[13]	490 (basal)	CPAP	25	6.6 (4.5–11.4)	1.6 (0.5–4.3)	3.5 (1.6–6.6)	1.3 (0.5–2.5)	95 (94–96)	8.4 (7.5–10.9)	PSG
	2,590	CPAP + placebo	12	19.3 (9.3–29.0)[*]	12.6 (5.6–23.0)[*]	3.5 (1.6–7.9)	16.2 (9.2–27.3)[*]	89 (87–91)[*]	10.0 (8.9–13.2)[*]	
		CPAP + acetazolamide	13	6.8 (3.5–10.1)[^]	4.0 (1.2–7.6)[^]	2.3 (1.0–5.5)[*^]	6.4 (2.6–11.9)[*^]	91 (90–92)[*^]	8.9 (7.1–10.8)[^]	

Abbreviations: AHI, apnea hypopnea index, ASV, adaptive servo ventilation, CAI, central apnea index, CPAP, continuous positive airway pressure, h^{-1}, events per hour, IR, interquartile range, MAMSL, meters above mean sea level, OAI, obstructive apnea index, ODI, oxygen desaturation index, PSG, polysomnography, RP, respiratory polygraphy, TP, therapeutic pressure, Tx, treatment.
[*] $p < 0.05$ vs. CPAP 490 m.
[^] $p < 0.05$ vs. CPAP + placebo.
[&] $p < 0.05$.

Several limitations must be mentioned regarding interpretations of the data presented. First, several different study designs were included. Second, follow-up times were short. Third, distinct parameters were applied to classify respiratory events. Fourth, most of the data was generated with acute exposure to altitude during rapid ascent so a comparison with incremental ascent and/or high-altitude residents was not possible. Fifth, various reports did not employ the gold standard. Sixth, the information was reported in a very heterogeneous way, which made it difficult to group it into categories. Finally, because central hypopneas are difficult to identify by simplified monitoring, their frequency may has been underestimated. The strengths of this review, in contrast, include the substantial number of sleep studies and subjects involved, and the extensive evaluations conducted at a broad range of altitudes (from sea level to 6,865 MAMSL). The latter aspect made it possible to establish a dose-response gradient among altitude, respiratory events, and oxygenation during sleep. According to the GRADE scale, the quality of the evidence was moderate-to-low, but it is important to recognize that a parameter like exposure to altitude is difficult to randomize or study using blind approaches. For this reason, an assessment scale like GRADE, which favors information obtained from controlled clinical trials, tends to systematically indicate low scores.

Clearly, future research should include larger study populations with more patients who have preexisting sleep-related breathing disorders. They must also strive to produce evidence of higher quality and to assess such potential confounders as acclimatization, biological sex, and the acid-base balance.

Conclusion

Altitude increases the AHI at the expense of central events while decreasing oxygenation during sleep. In patients with OSAS, altitude aggravates the preexisting sleep-related breathing disorder. Administering oxygen to healthy persons and acetazolamide with CPAP to OSAS patients could prove to be more effective forms of treatment than adaptive servo-ventilation devices.

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Conflict of Interests

The authors have no conflict of interest to declare.

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