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Are Nocturnal Breathing, Sleep, and Cognitive Performance Impaired at Moderate Altitude (1,630-2,590 m)?

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Study Objectives: Newcomers at high altitude (> 3,000 m) experience periodic breathing, sleep disturbances, and impaired cognitive performance. Whether similar adverse effects occur at lower elevations is uncertain, although numerous lowlanders travel to moderate altitude for professional or recreational activities. We evaluated the hypothesis that nocturnal breathing, sleep, and cognitive performance of lowlanders are impaired at moderate altitude.

Design: Randomized crossover trial.

Setting: University hospital at 490 m, Swiss mountain villages at 1,630 m and 2,590 m.

Participants: Fifty-one healthy men, median (quartiles) age 24 y (20-28 y), living below 800 m.

Interventions: Studies at Zurich (490 m) and during 4 consecutive days at 1,630 m and 2,590 m, respectively, 2 days each. The order of altitude exposure was randomized. Polysomnography, psychomotor vigilance tests (PVT), the number back test, several other tests of cognitive performance, and questionnaires were evaluated.

Measurements and Results: The median (quartiles) apnea-hypopnea index at 490 m was 4.6/h (2.3; 7.9), values at 1,630 and 2,590 m, day 1 and 2, respectively, were 7.0/h (4.1; 12.6), 5.4/h (3.5; 10.5), 13.1/h (6.7; 32.1), and 8.0/h (4.4; 23.1); corresponding values of mean nocturnal oxygen saturation were 96% (95; 96), 94% (93; 95), 94% (93; 95), 90% (89; 91), 91% (90; 92), $P < 0.05$ versus 490 m, all instances. Slow wave sleep on the first night at 2,590 m was 21% (18; 25) versus 24% (20; 27) at 490 m ($P < 0.05$). Psychomotor vigilance and various other measures of cognitive performance did not change significantly.

Conclusions: Healthy men acutely exposed during 4 days to hypoxemia at 1,630 m and 2,590 m reveal a considerable amount of periodic breathing and sleep disturbances. However, no significant effects on psychomotor reaction speed or cognitive performance were observed.

Clinical Trials Registration: Clinicaltrials.gov: NCT01130948.

Keywords: Altitude, healthy, hypoxia, sleep apnea, vigilance

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INTRODUCTION

Uncontrolled observations suggest that sleep in unacclimatized newcomers to high altitude (> 3,000 m) is unrefreshing and disturbed by high-altitude periodic breathing related to an enhanced loop gain of respiratory control.[1,2] Manifestations of altitude-related illness include headache and malaise, and potential direct adverse effects of hypoxia may additionally affect sleep quality.[3-7] Some studies have also suggested impairments in cognitive performance and mood at simulated or real altitude > 3,000 m.[8,9] Although climbing to such elevations is generally performed by only a few well-trained subjects, the number of persons who travel to settlements and tourist destinations at more moderate altitudes of 1,000 to 3,000 m is high.[10] According to the World Tourism Organization, mountain tourism accounts for 15-20% of worldwide tourism, i.e., it involved 147.5 to 196.6 million people in 2011.[11,12] Nevertheless, it has not been conclusively studied whether healthy mountain travelers experience nocturnal breathing and sleep disturbances already at moderate altitude (< 3,000 m) and whether this is associated with cognitive impairments during daytime. Recently, we observed that patients with untreated obstructive sleep apnea syndrome living at an altitude below 800 m revealed a major exacerbation of sleep apnea, pronounced hypoxemia, and impaired driving simulator performance during a stay in the mountains at altitudes of 1,860 m and 2,590 m.[13,14] If similarly striking effects would occur even in healthy individuals without preexisting breathing disorder, this would have major implications for a large number of travelers to moderate altitude as well as for flight passengers and air crew[15,16] in terms of impairment of subjective well-being, and performance during professional activities and sports. Therefore, the purpose of the current study was to perform a randomized trial evaluating the hypothesis that acute exposure to hypobaric hypoxia at moderate altitude during 4 days is associated with periodic breathing, sleep disturbances, and impaired psychomotor and cognitive function during daytime.

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METHODS

Study Design and Setting

This randomized crossover trial evaluating effects of moderate altitude on breathing, sleep, and psychomotor performance was carried out from July 2010 to October 2010. Baseline evaluations were performed during 1 day at the University Hospital of Zurich (490 m, 1,608 ft, barometric pressure [PB] 719 Torr,

baseline), altitude studies were performed during 4 days in Swiss alpine villages, 2 days at Davos Wolfgang (1,630 m, 5,348 ft, PB 630 Torr) and 2 days at Davos Jakobshorn (2,590 m, 8,497 ft, PB 562 Torr). At all locations, sleep studies and daytime evaluations were performed in quiet single rooms.

Participants

Healthy men living below an altitude of 800 m, 18 to 70 y old, with a body mass index of 18-30 kg/m^2 were invited to participate. Smokers, persons who regularly consumed alcohol, used drugs, or were on regular medication, or those with previous intolerance of moderate altitude (< 3,000 m) were not admitted. The study was approved by the Cantonal Ethics Committee, and subjects gave written informed consent. Trial registration: ClinicalTrials.gov NCT01130948.

Randomization and Interventions

Participants were randomized to four groups with permuted sequences of altitude exposure according to a balanced block design: group A: 490 m/1630 m/1630 m/2590 m/2590 m; B: 490 m/2590 m/2590 m/1630 m/1630 m; C: 1630 m/1630 m/2590 m/2590 m/490 m; and D: 2590 m/2590 m/1630 m/1630 m/490 m. Randomization was performed by allowing subjects register for one of the available study time slots according to preference and availability without being aware of the corresponding altitude exposure sequence. Subjects were instructed to sleep regularly for > 7 h per night in the week preceding the study. Compliance with this requirement was verified by actigraphy. Participants traveled by train between Zurich and Davos Wolfgang and by cable car between the Davos train station and Davos Jakobshorn. The trial ended as planned. Subjects were busy most of the day with various tests and they remained within the range of the hotel area except for transfers as part of the protocol. They had to avoid strenuous exercise. Napping was not allowed; this was regularly checked by the investigators. Three meals were served per day on a regular schedule. Caffeinated drinks were not allowed.

Measurements and Outcomes

Sleep Studies

Polysomnography was performed from 23:00 to 06:00 (Alice 5, Philips Respironics AG, Zofingen, Switzerland) as previously described.[13] Recordings included electroencephalogram, electro-oculogram, submental and bilateral anterior tibial electromyogram, pulse oximetry, capnography of expired air, calibrated respiratory inductive plethysmography, nasal prong pressure recordings,[17] and bilateral diaphragmatic surface electromyogram.[18] Sleep stages and arousals,[19] respiratory events, and breathing pattern characteristics[20] were determined as described previously[7,21,22] by investigators blinded to the clinical data and study location. Apneas/hypopneas were defined as a reduction in the inductive plethysmographic sum signal or the nasal pressure swings to < 50% of the preceding 2 min baseline during ≥ 10 s. Transient reductions in breathing amplitude to < 50% baseline for 5-10 s were also scored as apneas/hypopneas if they occurred as part of a periodic breathing pattern with central apneas/hypopneas for > 3 consecutive cycles.[7,21,22] The apnea-hypopnea index and the oxygen desaturation index (ODI, > 3% dips) were computed as number of events per hour of sleep.

Vigilance, Psychomotor and Cognitive Performance

Tests were performed between 10:00-12:00. Assessments included the psychomotor vigilance test (PVT),[23] the divided attention steering simulator (DASS),[24] the 1-, 2-, and 3-number back task[25] and the trail making test A.[26]

Clinical Examination and Questionnaires

After waking up in the morning, acute mountain sickness (AMS) was assessed by the Environmental Symptoms Questionnaire cerebral score (AMSc)[27] with values > 0.7 considered clinically relevant AMS.[28] Subjective sleep quality was rated on a visual analog scale, 100 mm in length, marked "extremely bad" at 0 mm, and "excellent" at 100 mm. Subjective insomnia was evaluated by asking subjects to estimate the time spent awake during the previous night.[7,21] Sleepiness was assessed by the Karolinska Sleepiness Scale, which evaluates the current tendency to fall asleep on a scale ranging from 1 (very awake) to 9 (very tired).[29] The midsleep time corrected for any sleep debt was determined as a measure of the individual chronotype by computing the midpoint between self-reported sleep onset and awakening on free days and work days, respectively, over the past few weeks.[30]

Lung Function Assessment

Lung function assessment included spirometry, sniff nasal pressure, and single breath carbon monoxide diffusing capacity.[31,32]

Outcomes and Sample Size Estimation

Primary outcomes were the apnea-hypopnea index (AHI) and the PVT response speed (reciprocal value of the response time).[23] Secondary outcomes were variables reflecting the breathing pattern, sleep structure, and other measures of vigilance and cognitive performance. Minimally important differences in the AHI and in the PVT response speed were assumed as 10/h (standard deviation [SD] 20/h)[14] and 0.125 1/s (SD 0.25),[23] respectively. To achieve a power of 80%, with a two-sided significance level of 0.05 and a dropout rate of 5%, the required sample size was estimated to be 50.

Data Analysis and Statistics

Data distribution was evaluated by Shapiro-Wilks statistics. Because most outcome variables were not normally distributed, all data are summarized as medians (quartiles). Occasional missing values were replaced by the corresponding median value of the group. The effects of altitude and time at any altitude were evaluated by Friedman analysis of variance (ANOVA) followed by Wilcoxon matched pairs tests if P ANOVA was significant.

Generalized least-squares regression and ordered logistic regression analyses were used to assess effects of altitude on the AHI, and measures of sleep, vigilance, and psychomotor performance while controlling for various potential confounders. Outcomes were mathematically transformed to obtain a normal distribution or, if this was not feasible, they were divided into quintiles. Predictor variables for which univariable analysis

indicated an association with a probability of $P < 0.2$ were entered into a subsequent multivariable model.

Statistical significance was assumed at $P < 0.05$ applying a Bonferroni correction as appropriate. Further details of the methods and of the statistical analysis are provided in the supplemental material.

RESULTS

Subjects

Of 190 screened subjects, 51 healthy men met the inclusion criteria and were randomized (see patient flow, Figure 1). Their median age was 24 y (quartiles 20 to 28), body mass index 23.0 kg/m^2 (quartiles 21.0 to 24.8), and Epworth Sleepiness Scale score 7 (quartiles 4 to 9, maximal value 10). Their self-reported median bedtime and wake time on work days were 22:45 (22:00 to 23:00) and 07:00 (06:30 to 07:45) with an estimated sleep duration of 8.0 h (7.5 to 8.3); bedtime on free days was 01:00 (00:30 to 03:00), wake time was 09:00 (09:00 to 10:00), and estimated sleep duration was 9.0 h (8.0 to 9.5). The midsleep time was 04:30 (03:58 to 05:11). Actigraphy confirmed a minimal duration of nocturnal rest time > 7 h in all participants and a median rest time of 7.8 h (quartiles 7.4 to 8.4) in the week before the study.

Sleep Studies

Results of sleep studies are summarized in Table 1. Compared to values recorded at an altitude of 490 m, the nocturnal oxygen saturation was significantly reduced at 1,630 m and at 2,590 m in an altitude-dependent manner (Figure 2A). Although the median AHI was normal at an altitude of 490 m, its values were increased significantly at 1,630 m and even more at 2,590 m. This was predominantly related to the emergence of central apnea-hypopnea. There was a considerable interindividual variability of the oxygen saturation and of the AHI with individual maximal AHI of 25.4/h at an altitude of 490 m, of 39.5/h at 1,630 m, and of 100.8/h at 2,590 m (Figure 2C). Compared to the first night at an altitude of 2,590 m, the oxygen saturation was higher and the total and central AHI were lower in the second night at 2,590 m, suggesting some acclimatization. Mean inspiratory flow (tidal volume/inspiratory time), a measure of ventilatory drive[33] increased at altitude due to an increase in both tidal volume and breath rate. Correspondingly, end tidal carbon dioxide tension ($PetCO_2$), the surrogate of the arterial PCO_2, decreased with increasing altitude.

Sleep stage-specific analysis revealed an increase in the central AHI during nonrapid eye movement (NREM) sleep at 1,630 m and 2,590 m and during rapid eye movement (REM) sleep at 2,590 m compared to 490 m (supplemental material, Table S1). Oxygen saturation was reduced to a similar degree in NREM and REM sleep. Mean inspiratory flow and minute ventilation were increased during NREM sleep at altitudes of 1,630 m and 2,590 m, and this was associated with a reduction in $PetCO_2$.

To investigate the determinants of the AHI at altitudes of 1,630 m and 2,590 m, generalized least-squares regression analysis was performed. Apart from altitude, variables derived from polysomnography (mean nocturnal oxygen saturation, end-tidal PCO_2), the forced vital capacity (FVC), the number

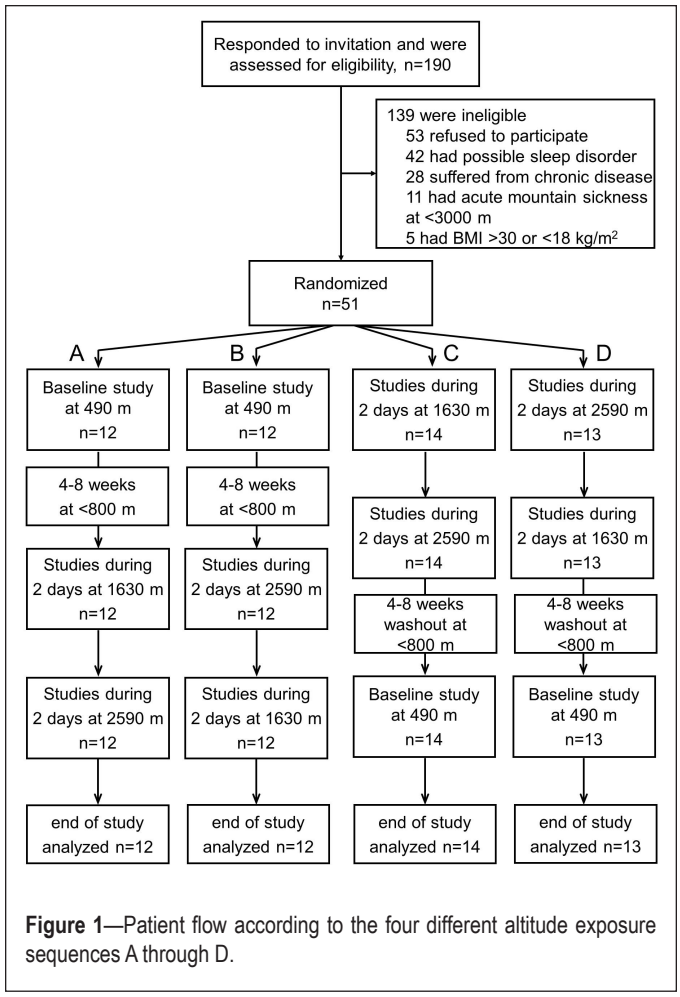

Figure 1—Patient flow according to the four different altitude exposure sequences A through D.

of days spent at altitude, altitude exposure sequence, and baseline characteristics (age, body mass index, AHI, and nocturnal oxygen saturation at an altitude of 490 m) were entered into the analysis. The results confirmed a positive association of the AHI with altitude, and a negative association of the AHI with the number of days at altitude (Table 2). In addition, the AHI at an altitude of 490 m was a significant positive predictor of the AHI at altitude whereas the body mass index was not. To illustrate the increase in AHI with increasing altitude and age, the regression model (Table 2) was used to predict the AHI at the three altitudes for three distinct ages (the 10th, the 50th, and the 90th percentile of the age distribution of all subjects, i.e., 20 y, 24 y, and 38 y) (Table 3). An exploratory analysis restricted to a more homogeneous group of 43 younger subjects (20-29 y of age) did not reveal results that differed principally from those obtained in all 51 subjects in terms of the major outcomes, mean nocturnal oxygen saturation, and AHI (data not shown).

Sleep continuity was high at all altitudes as reflected in a high sleep efficiency, a short time in wakefulness after sleep onset, and a low arousal index (Table 1). Compared to values at an altitude of 490 m there were slight but statistically significant changes in sleep structure, resulting in a reduction in slow wave sleep (NREM stages 3 and 4) at an altitude of 2,590 m (Figure 2D), and an increase in REM sleep in the second night at altitudes of 1,630 m and 2,590 m, respectively (Table 1). The altitude-related sleep disturbances were further

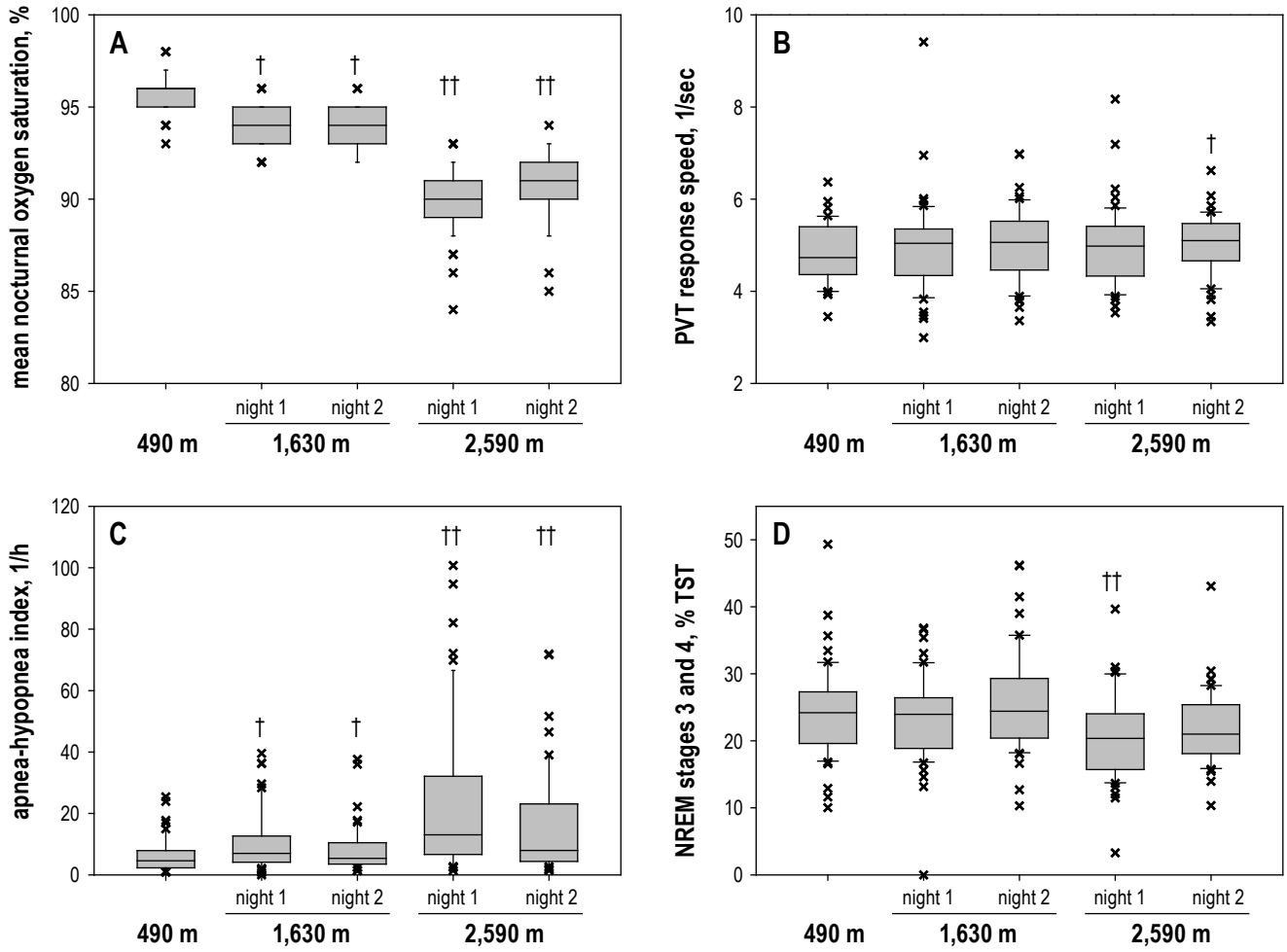

Figure 2—The mean nocturnal oxygen saturation **(A)**, psychomotor vigilance test response speed **(B)**, apnea-hypopnea index **(C)**, and slow wave sleep (**D**, nonrapid eye movement sleep stages 3 and 4 in % of total sleep time) at the different altitudes. Horizontal lines, boxes, and whiskers represent the median, quartiles, and the 10th and 90th percentiles, respectively; individual values beyond this range are displayed by an **x**. † indicates $P < 0.05$ versus 490 m, †† indicates $P < 0.05$ versus 490 m and 1,630 m, respectively.

corroborated by significant independent effects of altitude on slow wave sleep and on the arousal index in multiple regression analyses, respectively (supplemental material, Tables S2 and S3). Consistent with the minimal and statistically nonsignificant changes in wakefulness after sleep onset and in sleep efficiency, regression analyses did not suggest any independent effect of altitude on these outcomes (supplemental material, Tables S4 and S5). Although age was a significant independent predictor of some of the sleep variables, the body mass index and the midsleep time were not (supplemental material, Tables S2-S5).

Daytime Evaluation

Daytime evaluations are summarized in Table 4. There were no consistent changes in the outcomes of the PVT (Figure 2B), the divided attention steering simulator test, the number back test and the trail making test at altitudes of 1,630 m and 2,590 m compared to baseline values at an altitude of 490 m. To evaluate whether any potential effect of altitude on tests of vigilance and psychomotor performance was masked by confounding effects of time (i.e., including learning or acclimatization effects), the sequence of altitude exposure or disturbances of breathing and sleep in the previous night multivariable regression analyses were performed. These analyses did not reveal any independent effect of altitude exposure on outcomes when controlled for covariables (supplemental material, Tables S6-S9).

According to the questionnaires, subjects did not think that they had spent more time awake during nights at altitudes of 1,630 m and 2,590 m compared to 490 m (Table 4). They rated their sleep quality as slightly better on the second night at altitudes of 1,630 m and 2,590 m compared to 490 m. Subjects were not particularly sleepy as assessed by the Karolinska Sleepiness Scale and their rating remained unchanged during the study. None of the subjects suffered from symptoms of acute mountain sickness (Table 4, AMSc questionnaire) such as lost appetite, headaches, or faintness as evidenced by a median score of the corresponding items of 0 (quartiles 0, 0) with item scores ranging from 0 = ”not at all” to 5 = ”extreme”.

Spirometry revealed a decrease in FVC by 4% predicted and an increase in the ratio of the forced expiratory volume in 1 sec to vital capacity (FEV1/FVC) at an altitude of 2,590 m, whereas the nasal sniff pressure and diffusing capacity were unchanged compared to an altitude of 490 m (supplemental material, Table S10).

Table 1—Sleep studies

	490 m	1,630 m		2,590 m		P Friedman ANOVA
		1st night	2nd night	1st night	2nd night	
AHI, total, 1/h	4.6 (2.3;7.9)	7.0 (4.1;12.6)[a]	5.4 (3.5;10.5)[a]	13.1 (6.7;32.1)[a,b,c]	8.0 (4.4;23.1)[a,b,c,d]	< 0.001
AHI obstructive, 1/h	1.3 (0.3;4.6)	1.8 (0.6;4.4)	2.7 (1.5;5.2)	1.8 (0.7;3.8)	1.6 (0.7;3.4)	0.010
AHI central, 1/h	2.0 (1.2;3.7)	4.6 (2.3;7.9)[a]	2.8 (1.7;5.1)[a,b]	8.9 (5.0;25.8)[a,b,c]	5.8 (2.8;13.1)[a,b,c,d]	< 0.001
ODI (> 3%), 1/h	0.3 (0.0;1.1)	1.6 (0.5;3.8)[a]	1.8 (0.5;3.8)[a]	8.1 (3.3;30.9)[a,b,c]	5.4 (2.5;14.8)[a,b,c,d]	< 0.001
Mean nocturnal SpO_2, %	96 (95;96)	94 (93;95)[a]	94 (93;95)[a]	90 (89;91)[a,b,c]	91 (90;92)[a,b,c,d]	< 0.001
Time SpO_2 < 90%, %	0 (0;0)	0 (0;0)[a]	0 (0;0)	36 (9;70)[a,b,c]	16 (2;40)[a,b,c,d]	< 0.001
Mean inspiratory flow (Vt/Ti), L/s	0.16 (0.13;0.18)	0.17 (0.14;0.20)	0.16 (0.12;0.19)	0.18 (0.14;0.24)[a]	0.17 (0.14;0.20)	0.046
Minute ventilation, L/min	3.95 (3.14;4.49)	4.23 (3.74;4.91)	3.95 (3.20;5.54)	4.06 (3.52;6.48)[a]	4.47 (3.81;5.18)[a,b]	0.006
Tidal volume, L	0.24 (0.21;0.29)	0.27 (0.22;0.33)	0.27 (0.21;0.34)	0.28 (0.22;0.40)[a]	0.29 (0.24;0.34)[a]	0.015
Breath rate, 1/min	15 (14;16)	15 (14;17)	15 (14;17)	16 (14;18)[c]	16 (14;18)[a,b,c]	< 0.001
End-tidal PCO_2, mm Hg	41 (39;44)	38 (37;40)[a]	39 (37;40)[a]	37 (34;38)[a,b,c]	36 (34;37)[a,b,c]	< 0.001
Heart rate, 1/min	56 (50;61)	56 (51;61)	56 (51;60)	60 (55;65)[a,b,c]	61 (56;65)[a,b,c]	< 0.001
Total sleep time, min	399 (386;412)	400 (372;411)	408 (400;414)[a,b]	402 (384;410)[c]	405 (388;413)	0.011
Sleep latency, min	13 (8;21)	12 (7;16)	10 (7;12)[a,b]	9 (7;13)[a]	9 (7;12)[a]	< 0.001
Sleep efficiency, %	97 (95;100)	98 (91;99)	99 (98;100)	98 (94;99)	98 (96;99)	0.077
WASO, min	11 (3;22)	12 (4;39)	7 (3;11)	11 (4;25)	9 (3;22)	0.096
NREM 1+2, %	56 (51;63)	55 (49;61)[c]	50 (42;53)[a,b]	58 (52;64)[c]	55 (51;62)[c]	< 0.001
NREM 3+4, %	24 (20;27)	24 (19;26)	24 (20;29)	20 (16;24)[a,b,c]	21 (18;25)[c]	< 0.001
REM, %	19 (15;24)	22 (18;26)	26 (21;29)[a,b]	20 (18;25)[c]	22 (19;26)[a,c]	< 0.001
Arousal index, 1/h	8.3 (6.1;9.6)	6.5 (5.3;9.3)	6.8(5.5;8.3)	7.7 (6.1;9.7)[c]	7.7 (6.1;10.9)	0.005

Medians (quartiles), n = 51. AHI, apnea-hypopnea index; ANOVA, analysis of variance; NREM, nonrapid eye movement; REM, rapid eye movement; SpO_2, oxygen saturation; ODI, oxygen desaturation index; WASO, wakefulness after sleep onset. [a]P < 0.05 versus 490 m, [b]P < 0.05 versus 1,630 m day 1, [c]P < 0.05 versus 1,630 m day 2. [d]P < 0.05 versus 2,590 m, day 1.

Table 2—Generalized least square regression analysis of the effect of altitude exposure on the apnea-hypopnea index

	Univariable analysis			Multivariable model		
Dependent variable Log10 (AHI)	**Coefficient**	**95% CI**	**P**	**Coefficient**	**95% CI**	**P**
Altitude						
1,630 m versus 490 m	0.160	0.077 to 0.243	< 0.001	0.200	0.039 to 0.362	0.015
2,590 m versus 490 m	0.396	0.290 to 0.502	< 0.001	0.337	0.001 to 0.674	0.049
Mean nocturnal oxygen saturation, %	-0.064	-0.082 to -0.047	< 0.001	-0.019	-0.074 to 0.036	0.493
$PetCO_2$, mm Hg	-0.031	-0.043 to -0.020	< 0.001	-0.010	-0.022 to 0.003	0.123
FVC, % predicted	-0.001	-0.008 to 0.006	0.719			
Number of days at altitude						
2nd versus 1st day	-0.167	-0.252 to -0.081	< 0.001	-0.163	-0.258 to -0.068	0.001
3rd versus 1st day	-0.092	-0.224 to 0.039	0.169	-0.099	-0.214 to 0.015	0.089
4th versus 1st day	-0.154	-0.278 to -0.030	0.015	-0.151	-0.268 to -0.033	0.012
Altitude exposure sequence	-0.026	-0.111 to 0.059	0.542			
Age	0.016	0.010 to 0.023	< 0.001	0.005	-0.005 to 0.015	0.344
Body mass index, kg/m^2	0.026	-0.013 to 0.066	0.184			
AHI at 490 m	0.041	0.029 to 0.052	< 0.001	0.037	0.025 to 0.048	< 0.001
Mean nocturnal oxygen saturation at 490 m	-0.076	-0.147 to -0.004	0.038	-0.016	-0.089 to 0.056	0.663

n = 255 observations (51 participants) at 490, 1,630, and 2,590 m. Results are presented for the logarithmically (log 10) transformed apnea-hypopnea index (AHI) as dependent variable. Independent variables with P < 0.2 in the univariable analysis were included in the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. CI, confidence interval; FVC, forced vital capacity; $PetCO_2$, mean nocturnal transcutaneous PCO_2.

Table 3—Apnea-hypopnea indices predicted for men of different age by a regression model

Predicted AHI at specified age, 1/h	490 m	1,630 m		2,590 m		P regression
		1st night	2nd night	1st night	2nd night	
Age 20 y (10th percentile)	5.2 (3.3 to 8.0)	8.2 (6.1 to 11.0)	5.6 (4.3 to 7.4)	8.9 (6.0 to 13.3)	7.9 (5.5 to 11.4)	< 0.001
Age 24 y (50th percentile)	5.4 (3.6 to 8.2)	8.6 (6.6 to 11.2)	5.9 (4.6 to 7.6)	9.3 (6.4 to 13.6)	8.3 (5.9 to 11.6)	< 0.001
Age 38 y (90th percentile)	6.3 (3.9 to 10.3)	10.0 (6.8 to 14.8)	6.9 (4.6 to 10.5)	10.9 (6.9 to 17.3)	9.7 (6.3 to 14.9)	< 0.001

The predicted apnea-hypopnea indices (AHI) with their 95% confidence intervals were computed based on the regression model presented in Table 2 for men of three different ages ascending from an altitude of 490 m to altitudes of 1,630 m and 2,590 m.

Table 4—Daytime evaluation

	490 m	1,630 m		2,590 m		P Friedman ANOVA
		1st day	2nd day	1st day	2nd day	
Vigilance and cognitive performance						
PVT response speed (1/RT), 1/s	4.7 (4.4;5.4)	5.0 (4.3;5.3)	5.1 (4.5;5.5)	5.0 (4.3;5.4)	5.1 (4.7;5.5)[a]	0.015
PVT number of lapses	1 (0;4)	2 (0;3)	1 (0;3)	1 (0;3)	1 (0;3)	0.069
DASS, reaction time, s	1.9 (1.5;2.3)	2.1 (1.6;2.6)	2.1 (1.6;2.6)	1.9 (1.5;2.4)	1.8 (1.4;2.6)	0.389
DASS, tracking error, arbitrary units	0.30 (0.21;0.39)	0.27 (0.22;0.40)	0.29 (0.20;0.35)[a]	0.26 (0.20;0.35)	0.24 (0.19;0.30)[a,b,c,d]	< 0.001
1-, 2-, 3- number back mean reaction time of correct answers, ms	637 (554;793)	674 (594;828)	635 (554;713)[b]	674 (579;769)	628 (550;734)	0.019
1-, 2-, 3- number back correct answers, %	92 (89;95)	93 (90;96)[a]	93 (90;95)[a]	93 (90;95)	93 (91;95)	0.031
Trail making test, s	52.4 (43.8;58.9)	48.1 (42.5;58.5)	46.5 (40.7;55.5)[a,b]	51.2 (43.5;58.4)	48.0 (40.8;55.5)[a,d]	0.003
Questionnaire evaluation						
Estimated night-time spent awake, min	20 (10;40)	20 (10;30)	10 (5;20)[a,b]	20 (10;50)[c]	15 (5;30)[c]	< 0.001
Sleep quality, Visual analog score	6.2 (4.0;7.5)	6.0 (4.3;7.5)	7.1 (6.0;8.2)[a,b]	5.5 (3.8;7.0)[c]	6.3 (5.1;7.9)[a]	0.006
Karolinska Sleepiness Scale score[e]	3 (2;4)	3 (3;5)	3 (3;5)	3 (3;5)	3 (3;4)	0.192
Acute mountain sickness score (AMSc)	0.00 (0.00;0.10)	0.00 (0.00;0.09)	0.00 (0.00;0.00)	0.00 (0.00;0.00)	0.00 (0.00;0.00)	0.194

Medians (quartiles), n = 51. ANOVA, analysis of variance; DASS, divided attention steering simulator; PVT, psychomotor vigilance test. [a]P < 0.05 versus 490 m, [b]P < 0.05 versus 1,630 m day 1, [c]P < 0.05 versus 1,630 m day 2, [d]P < 0.05 versus 2,590 m, day 1. [e]Subjective sleepiness rated from 1 (very awake) to 9 (very tired).

DISCUSSION

Our randomized crossover trial in a relatively large cohort of healthy young men living near sea level reveals a considerable and individually highly variable amount of sleep related periodic breathing associated with mild hypoxemia during acute exposure to altitudes of 1,630 m and 2,590 m for a total of 4 days. Mild alterations in sleep structure and in subjective sleep quality were also noted. Performances in a battery of cognitive and psychomotor vigilance tests were not consistently changed. These novel results are important because they are pertinent to a large number of persons traveling to moderate altitudes worldwide.

There are few published reports on sleep, breathing, and daytime performance at moderate altitude, and studies are heterogeneous including only small groups of subjects. Mizuno and coworkers[34] did not observe significant changes in the AHI and in sleep structure in five healthy men undergoing polysomnography in a hypobaric chamber at sea level and at simulated altitudes of 1,500 m and 3,000 m, possibly related to an inadequate sample size. Muhm and coworkers[15] performed a randomized, double-blind crossover study in 20 healthy men undergoing simulated air travel in a hypobaric chamber for 14 h including an 8-h night rest. At the altitude equivalent of 2,438 m, nocturnal oxygen saturation fell to 86% and the AHI increased to 13/h, similar to values at 2,590 m in the current study. No changes in sleep structure and in neurobehavioral tests performed in the following morning at the same altitude equivalent were noted.[15] Field studies and simulations in unacclimatized subjects sleeping at greater altitudes (> 4,000 m)[7,8,35,36] or in trekkers ascending gradually up to an altitude of 5,050 m[6] suggest alterations in sleep structure with a reduction in sleep efficiency, deep sleep, and an increase in arousals in association with a low oxygen saturation and periodic breathing. Evaluation of cognitive and psychomotor performance at high altitude (> 3,500 m) has revealed conflicting results, with some studies suggesting an impairment in cognitive performance, attention, and mood [8,37] whereas others show no consistent changes.[38-40] This may relate to the lack of randomization of the order of altitude exposure and small sample size in certain studies.

Our study extends the cited observations in several ways. The strength of the current randomized trial includes its robust design and blinded data analysis, the realistic field setting at two different moderate altitudes that are relevant for a large number of travelers to destinations worldwide and the statistical power due to the inclusion of a large number of participants. Our data demonstrate that the mild hypoxemia at altitudes of 1,630 m

and 2,590 m was sufficient to induce periodic breathing with very high numbers of central apneas/hypopneas in certain individuals (i.e., an AHI up to 39.5/h at 1,630 m, and up to 100.8/h at 2,590 m, Figure 2C). The elevations in the AHI at altitudes of 1,630 m and 2,590 m were associated with an altitude-dependent decrease in oxygen saturation, an increase in mean inspiratory flow (the measure of ventilatory drive) and minute ventilation, and a decrease in $PetCO_2$. This finding is consistent with respiratory control theory, suggesting that breathing is destabilized by hypoxic stimulation of ventilation, a high sensitivity to CO_2 and hypoxia along with a reduced CO_2 reserve.[41] Multivariable regression analysis revealed that the AHI at 490 m was a significant predictor of the AHI at altitudes of 1,630 m and 2,590 m (Table 2), suggesting that the propensity for unstable control of breathing was present in certain subjects already at low altitude. This would be in line with the major increase in the AHI observed in the same altitude setting in patients with preexisting obstructive sleep apnea syndrome.[13,14] The increase in oxygen saturation in the second day at an altitude of 2,590 m associated with a decrease in the AHI as well as the negative correlation of the AHI with the number of days spent at altitudes of 1,630 m and 2,590 m (Table 2) indicates that acclimatization took place. Although AHI decreased over the course of the 4 days at moderate altitude, observations at much higher altitudes (3,750 m to 6,850 m) revealed a persistent increase in periodic breathing over the course of 2 weeks.[22]

The trends of changes in sleep structure after ascent to an altitude of 2,590 m were similar in terms of reduction in slow wave sleep, but less pronounced compared to the changes we observed recently at 4,559 m.[7] In contrast to the findings at higher altitude the sleep efficiency and measures of sleep continuity (arousal index and wakefulness after sleep onset) were not significantly affected at altitudes of 1,630 m and 2,590 m (Table 1).

The modest sleep disturbances, mild hypoxemia, and the nocturnal periodic breathing did not result in measurable impairments of vigilance, cognitive, and psychomotor performance at altitudes of 1,630 m and 2,590 m, although an extensive battery of tests evaluating different aspects of reaction, divided attention, cognitive performance, and memory was used. Our study was powered to detect a reduction in PVT reaction speed of less than 0.125/s, a change reported to occur after restricting sleep to 4 h for 1 night.[23] These results are reassuring as larger effects of acute exposure to moderate altitude on the PVT reaction speed did not occur in our subjects as a group. However, we cannot exclude that individual susceptible subjects might experience subtle alterations in neurophysiological and psychomotor function not detected by our tests, although still relevant in the daily activities of mountain travelers, drivers, air crew, and in other settings. Multivariable regression analyses indicated an improvement in tests of vigilance, and cognitive and psychomotor performance with each additional day at altitude. This might have been related to learning, acclimatization, or both (supplemental material, Tables S6-S9). However, no correlation of any of these outcomes with the AHI or nocturnal oxygen saturation was found. We therefore do not have evidence that altitude-induced breathing disturbances caused cognitive impairments. In addition to elucidating the effects of altitude, our study provides a valuable set of normative data for the battery of cognitive and psychomotor performance tests that were applied to a large cohort of healthy subjects at low altitude.

Questionnaire evaluations revealed no symptoms of acute mountain sickness, including no aspects of fatigue or excessive sleepiness at altitudes of 1,630 m and 2,590 m compared to 490 m, and neither the subjective sleep quality nor the estimated time spent awake at night were altered in participants of the current study during their altitude sojourn (Table 4). In contrast, patients with obstructive sleep apnea perceived having spent more time awake at an altitude of 2,590 m than at 490 m, possibly related to their severe hypoxemia and breathing and sleep disturbances.[13] Our study was performed in healthy young men during 4 days at moderate altitude. Whether similar or more pronounced changes occur in older persons, in women, or in patients with a preexisting respiratory or cardiovascular condition requires further study. Although our findings do not suggest an interaction of altitude effects with the chronotype we cannot exclude that altitude exposure is associated with alterations of the circadian rhythm.[42,43]

In conclusion, the current randomized trial performed in a large cohort of healthy men provides robust evidence that nocturnal breathing and sleep are disturbed in the first 4 nights after ascent to an altitude of 1,630 m and 2,590 m. The amount of periodic breathing is highly variable and predicted in part by the AHI at low altitude. The finding that measures of vigilance and cognitive and psychomotor performance were not altered to a measurable degree is particularly relevant for the large number of persons traveling to moderate altitudes worldwide as well as for air crew. Nevertheless, susceptible persons, the elderly, or patients with obstructive sleep apnea syndrome and other preexisting breathing disorders might still experience adverse effects of moderate altitude.

DISCLOSURE STATEMENT

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SUPPLEMENTAL MATERIAL

SUPPLEMENTAL METHODS

Monitoring of Ventilation During Sleep

Apneas/hypopneas were detected by nasal prong pressure recordings and by calibrated respiratory inductive plethysmography (RIP).[1] RIP was calibrated in the evening as previously described.[2,3] After a qualitative diagnostic calibration, a fixed volume calibration was performed by letting subjects rebreathe into a bag of 800-mL volume.[4] Accuracy of volume calibration was verified in the morning after sleep studies by rebreathing into the 800- mL bag. If tidal volume deviated by > 20% from this volume, the variables depending on this calibration were omitted from analysis. Additional respiratory monitoring included diaphragmatic surface electromyogram,[5] capnography of expired air,[6] and pulse oximetry.

Breath-by-breath measurement of breathing pattern characteristics (breath rate, tidal volume, minute ventilation, and mean inspiratory flow) and of end-tidal carbon dioxide tension were assessed with dedicated software (EDP V4.2, Non-invasive Monitoring Systems, Miami Beach, FL) as described previously.[2] Apneas/hypopneas were defined as a reduction of the inductive plethysmographic sum signal or the nasal pressure swings to < 50% of the preceding 2 min baseline during ≥ 10 s. Transient reductions in breathing amplitude to < 50% baseline for 5-10 s were also scored as apneas/hypopneas if they occurred as part of a periodic breathing pattern with hyperventilation alternating with central apneas/hypopneas for at least three consecutive cycles.[3] Obstructive apneas/hypopneas were identified by rib cage and abdominal asynchrony and persistent or increasing diaphragmatic electromyographic (EMG) activity.[6] Central apneas/hypopneas were identified by absent rib cage-abdominal asynchrony, no signs of inspiratory flow limitations (no flattening of nasal pressure contour), and reduced or absent diaphragmatic EMG activity. Mixed apneas/hypopneas that showed some characteristics suggesting upper airway obstruction were classified as obstructive events. The apnea-hypopnea index and the oxygen desaturation index (ODI, > 3% dips) were computed as the number of events per hour of sleep.

Table S1—Sleep stage-specific oxygen saturation and ventilation

	490 m	1,630 m		2,590 m		P Friedman ANOVA
		1st night	2nd night	1st night	2nd night	
Obstructive AHI NREM, 1/h	0.5 (0.0;2.8)[e]	0.6 (0.0;1.8)[e]	1.0 (0.4;2.2)[e]	0.9 (0.0;2.2)[e]	0.5 (0.0;2.2)[e]	0.510
Obstructive AHI REM, 1/h	4.1 (0.0;9.8)	5.8 (1.0;11.0)	5.3 (2.9;12.5)	4.4 (1.8;11.0)	4.8 (2.1;7.6)	0.154
Central AHI NREM, 1/h	2.1 (0.9;3.6)	5.1 (2.0;8.5)[a]	2.9 (1.6;5.5)[a,b]	9.3 (4.7;31.6)[a,b,c,e]	5.4 (2.9;13.3)[a,b,c,d,e]	< 0.001
Central AHI REM, 1/h	1.8 (0.8;4.5)	3.5 (1.4;6.9)	2.3 (1.2;4.4)	6.9 (3.6;13.2)[a,c]	3.6 (1.7;9.1)[a,c]	< 0.001
SpO_2 during wakefulness, %	96 (96;97)	94 (94;95)[a]	95 (94;95)[a]	91 (90;92)[a,b,c]	92 (91;93)[a,b,c,d]	< 0.001
SpO_2 during NREM, %	96 (95;96)[e]	94 (93;94)[a,e]	94 (93;94)[a,e]	90 (89;91)[a,b,c]	91 (90;92)[a,b,c,d]	< 0.001
SpO_2 during REM, %	96 (96;97)	94 (93;95)[a]	94 (94;95)[a]	90 (88;91)[a,b,c]	91 (90;92)[a,b,c,d]	< 0.001
Vt/Ti awake	0.22 (0.18;0.26)	0.24 (0.21;0.33)	0.24 (0.19;0.31)	0.22 (0.18;0.37)	0.25 (0.19;0.35)	0.297
Vt/Ti NREM	0.15 (0.12;0.19)	0.16 (0.14;0.20)	0.16 (0.12;0.20)	0.18 (0.14;0.25)[a]	0.18 (0.14;0.21)[a]	0.012
Vt/Ti REM	0.16 (0.13;0.19)	0.18 (0.14;0.22)	0.17 (0.13;0.21)	0.16 (0.13;0.24)	0.18 (0.14;0.22)	0.343
V`E awake, L/min	6.03 (4.50;6.57)	5.87 (5.41;7.01)	5.98 (4.92;7.67)	5.58 (4.55;8.13)	5.81 (4.79;7.77)	0.902
V`E NREM, L/min	3.88 (3.02;4.75)[e]	4.11 (3.64;4.65)[e]	3.71 (3.07;5.27)[e]	3.96 (3.46;6.32)[a,e]	4.32 (3.75;5.06)[a,b,e]	< 0.002
V`E REM, L/min	4.52 (3.64;5.49)	4.91 (4.22;6.00)	4.87 (3.64;6.16)	4.62 (3.84;6.68)	4.84 (3.99;5.66)	0.240
Vt awake, L	0.31 (0.28;0.44)	0.38 (0.34;0.44)	0.35 (0.25;0.43)	0.35 (0.29;0.48)	0.35 (0.28;0.46)	0.383
Vt NREM, L	0.24 (0.20;0.29)[e]	0.26 (0.22;0.32)[e]	0.26 (0.19;0.33)[e]	0.28 (0.22;0.42)[a]	0.29 (0.23;0.34)[a]	0.012
Vt REM, L	0.27 (0.25;0.35)	0.30 (0.24;0.37)	0.30 (0.22;0.40)	0.30 (0.24;0.39)	0.29 (0.24;0.35)	0.797
Breath rate awake, 1/min	16 (15;19)	16 (15;18)	17 (15;19)	16 (15;18)	17 (15;18)	0.395
Breath rate NREM, 1/min	15 (14;17)[e]	15 (14;17)[e]	15 (14;17)[e]	15 (14;17)[c,e]	16 (14;17)[a,b,c,e]	< 0.001
Breath rate REM, 1/min	16 (14;17)	16 (15;19)	16 (14;18)	16 (15;18)[a,c]	17 (15;18)[a,c]	< 0.001
$PetCO_2$, awake, mm Hg	40 (37;42)	37 (35;39)[a]	37 (35;39)[a]	36 (34;38)[a]	35 (34;37)[a,b,c]	< 0.001
$PetCO_2$, NREM, mm Hg	41 (39;44)[e]	39 (37;41)[a,e]	39 (37;40)[a,e]	37 (34;39)[a,b,c,e]	36 (35;37)[a,b,c,e]	< 0.001
$PetCO_2$, REM, mm Hg	41 (39;43)	38 (35;40)[a]	38 (37;40)[a]	37 (33;38)[a,c]	36 (34;37)[a,b,c]	< 0.001
Heart rate, 1/min	56 (50;61)	56 (51;61)	56 (51;60)	60 (55;65)[a,b,c]	61 (56;65)[a,b,c]	< 0.001
Premature beats, entire night, 1/h	2.7 (0.3;10.2)	3.0 (0.7;11.7)	3.3 (1.1;11.8)	1.7 (0.6;8.4)	2.0 (0.4;14.3)	0.101

Data are medians (quartiles), n = 51. AHI, apnea-hypopnea index; NREM, nonrapid eye movement; $PetCO_2$, end tidal carbon dioxide tension; REM, rapid eye movement; SpO_2, oxygen saturation; V`E, minute ventilation, Vt, tidal volume. [a]P < 0.05 versus 490 m; [b]P < 0.05 versus 1,630 m day 1; [c]P < 0.05 versus 1,630 m day 2; [d]P < 0.05 versus 2,590 m day 1; [e]P < 0.05 versus rapid eye movement (REM).

Table S2—Logistic regression analysis of the effect of altitude exposure on slow wave sleep

Dependent variable quintiles of slow wave sleep	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	0.079	-0.338 to 0.496	0.711	-0.978	-1.980 to 0.024	0.056
2,590 m versus 490 m	-0.798	-1.328 to -0.268	0.003	-2.644	-4.693 to -0.594	0.011
Mean nocturnal oxygen saturation, %	0.134	0.049 to 0.220	0.002	-0.249	-0.575 to 0.076	0.133
AHI, 1/h	-0.041	-0.072 to -0.010	0.009	-0.026	-0.053 to -0.002	0.067
Number of days at altitude						
2nd versus 1st day	0.945	0.442 to 1.447	< 0.001	1.060	0.476 to 1.644	< 0.001
3rd versus 1st day	0.389	-0.110 to 0.889	0.126	0.578	0.018 to 1.138	0.043
4th versus 1st day	0.737	0.206 to 1.267	0.006	0.916	0.292 to 1.540	0.004
Altitude exposure sequence	0.067	-0.292 to 0.426	0.715			
Age	-0.073	-0.119 to -0.027	0.002	-0.076	-0.129 to -0.024	0.004
Body mass index, kg*m^{-2}	-0.066	-0.207 to 0.075	0.358			
Midsleep time, h	0.223	-0.174 to 0.620	0.271			

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for quintiles of slow wave sleep as dependent variable. Independent variables with P < 0.2 in the univariable analysis were included into the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

Table S3—Logistic regression analysis of the effect of altitude exposure on the arousal index

Dependent variable quintiles of arousal index, 1/h	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	-0.676	-1.141 to -0.212	0.004	-0.835	-1.667 to -0.003	0.049
2,590 m versus 490 m	-0.054	-0.463 to 0.355	0.796	-0.815	-2.564 to 0.935	0.361
Mean nocturnal oxygen saturation, %	-0.085	-0.164 to -0.007	0.034	-0.068	-0.331 to 0.196	0.614
AHI, 1/h	0.044	0.016 to -0.072	0.002	0.040	0.008 to 0.073	0.015
Number of days at altitude						
2nd versus 1st day	-0.943	-0.599 to 0.411	0.714	0.222	-0.354 to 0.798	0.450
3rd versus 1st day	-0.631	-1.208 to -0.054	0.032	-0.493	-1.08 to 0.093	0.099
4th versus 1st day	-0.346	-0.976 to 0.283	0.281	-0.074	-0.763 to 0.616	0.834
Altitude exposure sequence	-0.031	-0.343 to 0.281	0.846			
Age	0.045	0.014 to 0.076	0.004	0.022	-0.019 to 0.063	0.291
Body mass index, kg*m^{-2}	0.060	-0.087 to 0.207	0.425			
Midsleep time, h	0.005	-0.360 to 0.369	0.980			

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for quintiles of arousal index per hour as dependent variable. Independent variables with P < 0.2 in the univariable analysis were included into the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

Data Analysis and Statistics

The normality of distribution of outcomes was evaluated by the Shapiro-Wilks statistic.[7] This revealed that the majority of outcome variables were not normally distributed. Therefore, all data are summarized by medians and quartiles. Data were grouped according to altitude, and overall effects were evaluated by Friedman analysis of variance (ANOVA). If ANOVA revealed a significant overall effect, planned *post hoc* analyses were performed using Wilcoxon matched-pairs tests.

Regression analyses were used to separately assess the effect of altitude (1,630 m and 2,590 m versus 490 m) on major outcomes while controlling for several potential confounders. For certain variables, a normal distribution was achieved by the following transformation: logarithm (log 10) or 1/square root. The transformed variables revealing a normal distribution were entered into univariable and multivariable random effects generalized least-squares regression analyses. If an outcome variable was not normally distributed and mathematical transformation to a normal distribution could not be achieved,

Table S4—Logistic regression analysis of the effect of altitude exposure on wake after sleep onset

Dependent variable quintiles of wakefulness after sleep onset	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	-0.172	-0.686 to 0.343	0.513	0.619	-0.236 to 1.474	0.156
2,590 m versus 490 m	0.123	-0.320 to 0.566	0.585	0.878	-0.677 to 2.432	0.268
Mean nocturnal oxygen saturation, %	-0.084	-0.168 to 0.001	0.052	-0.025	-0.266 to 0.215	0.836
AHI, 1/h	0.019	0.001 to 0.037	0.038	-0.002	-0.017 to 0.014	0.846
Number of days at altitude						
2nd versus 1st day	-0.966	-1.512 to -0.420	0.001	-1.079	-1.758 to -0.400	0.002
3rd versus 1st day	-1.050	-1.668 to -0.432	0.001	-1.174	-1.885 to -0.463	0.001
4th versus 1st day	-1.108	-1.644 to -0.573	< 0.001	-1.182	-1.864 to -0.500	0.001
Altitude exposure sequence	-0.029	-0.377 to 0.320	0.872			
Age	0.082	0.042 to 0.121	< 0.001	0.078	0.035 to 0.121	< 0.001
Body mass index, kg*m^{-2}	0.143	0.031 to 0.255	0.012	0.066	-0.053 to 0.184	0.276
Midsleep time	-0.164	-0.549 to 0.221	0.404			

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for quintiles of wake after sleep onset as dependent variable. Independent variables with P < 0.2 in the univariable analysis and altitude, the parameter of the main hypothesis were included into the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

Table S5—Logistic regression analysis of the effect of altitude exposure on sleep efficiency

Dependent variable quintiles of sleep efficiency	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	0.199	-0.314 to 0.712	0.447	-0.610	-1.512 to 0.293	0.186
2,590 m versus 490 m	-0.132	-0.624 to 0.360	0.599	-0.872	-2.414 to 0.669	0.267
Mean nocturnal oxygen saturation, %	0.091	-0.001 to 0.184	0.052	0.023	-0.239 to 0.285	0.864
AHI, 1/h	-0.021	-0.037 to -0.005	0.009	-0.002	-0.017 to 0.013	0.791
Number of days at altitude						
2nd versus 1st day	1.161	0.539 to 1.783	< 0.001	1.208	0.482 to 1.934	0.001
3rd versus 1st day	1.017	0.377 to 1.656	0.002	1.106	0.373 to 1.839	0.003
4th versus 1st day	1.234	0.605 to 1.863	< 0.001	1.280	0.538 to 2.022	0.001
Altitude exposure sequence	0.001	-0.324 to 0.326	0.996			
Age	-0.073	-0.104 to -0.043	< 0.001	-0.068	-0.101 to -0.036	< 0.001
Body mass index, kg*m^{-2}	-0.135	-0.235 to -0.034	0.009	-0.066	-0.171 to 0.040	0.225
Midsleep time, h	0.174	-0.165 to 0.513	0.315			

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for quintiles of sleep efficiency as dependent variable. Independent variables with P < 0.2 in the univariable analysis and altitude, the parameter of the main hypothesis were included into the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

quintiles of that variable were entered as the dependent variable into univariable and multivariable ordered logistic regression analyses using robust standard errors. All predictor variables for which univariable analysis indicated an association with a probability of P < 0.2 were entered into a subsequent multivariable model.

In a first regression analysis, potential predictors of the AHI were evaluated. The dependent variable was the apnea-hypopnea index (AHI; log 10 transformed); the independent variables (predictors) were altitude (490 m = 1, 1,630 m = 2, 2,590 m = 3), mean nocturnal oxygen saturation, end-tidal PCO_2 (the surrogate of the arterial PCO_2), forced vital capacity (FVC), number of days at altitude (1 to 4), altitude exposure sequence (A to D, see Figure 1), age, AHI at 490 m, and mean nocturnal oxygen saturation at an altitude of 490 m.

Additional regression analyses were performed to evaluate the predictors of variables reflecting sleep structure (slow wave sleep; arousal index; sleep efficiency; wakefulness after sleep onset), and of performance in tests of vigilance and psychomotor performance. Dependent variables were: PVT response

Table S6—Logistic regression analysis of the effect of altitude exposure on psychomotor vigilance test

Dependent variable quintiles of PVT response speed (1/reaction time)	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	0.330	-0.130 to 0.790	0.159	-0.100	-0.607 to 0.407	0.699
2,590 m versus 490 m	0.317	-0.061 to 0.695	0.100	-0.066	-0.539 to 0.407	0.784
Mean nocturnal oxygen saturation, %	0.001	-0.080 to 0.082	0.979			
Slow wave sleep, min	0.012	0.000 to 0.024	0.049	0.009	-0.003 to 0.021	0.151
AHI, 1/h	-0.000	-0.021 to 0.020	0.981			
Number of days at altitude						
2nd versus 1st day	0.449	0.149 to 0.748	0.003	0.332	-0.063 to 0.728	0.099
3rd versus 1st day	0.731	0.332 to 1.130	< 0.001	0.725	0.302 to 1.148	0.001
4th versus 1st day	0.867	0.529 to 1.204	< 0.001	0.782	0.404 to 1.160	< 0.001
Altitude exposure sequence	0.157	-0.232 to 0.546	0.429			
Age	-0.035	-0.082 to 0.131	0.155	-0.026	-0.078 to 0.025	0.317

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for quintiles of the PVT response speed as dependent variable. Independent variables with P < 0.2 in the univariable analysis are included into the multivariable analysis. The multivariable model is adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. CI, confidence interval; PVT, psychomotor vigilance test; AHI, apnea-hypopnea index.

Table S7—Generalized least square regression analysis of the effect of altitude exposure on driving simulator performance

Dependent variable Log10 (tracking error)	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	-0.037	-0.075 to 0.001	0.057	0.018	-0.031 to 0.067	0.466
2,590 m versus 490 m	-0.071	-0.106 to -0.036	< 0.001	-0.029	-0.115 to 0.057	0.507
Mean nocturnal oxygen saturation, %	0.007	0.002 to 0.012	0.006	-0.004	-0.015 to 0.008	0.502
Slow wave sleep, min	-0.000	-0.001 to 0.001	0.922			
AHI, 1/h	0.000	-0.001 to 0.002	0.619			
Number of days at altitude						
2nd versus 1st day	-0.058	-0.087 to -0.029	< 0.001	-0.055	-0.085 to -0.026	< 0.001
3rd versus 1st day	-0.088	-0.125 to -0.050	< 0.001	-0.085	-0.123 to -0.046	<0.001
4th versus 1st day	-0.118	-0.159 to -0.077	< 0.001	-0.114	-0.156 to -0.072	< 0.001
Altitude exposure sequence	-0.008	-0.040 to 0.024	0.633			
Age	0.002	-0.001 to 0.004	0.184	0.002	-0.001 to 0.004	0.253

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for the logarithmically (log 10) transformed tracking error (standard deviation of the mean deviation from the center line) as dependent variable. Independent variables with P < 0.2 in the univariable analysis are included in the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude were 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

speed (quintiles of the reciprocal value of reaction time), divided attention steering simulator tracking error (log 10 transformed SD of mean deviation from the center line), response time in the 1-, 2-, or 3-number back test (log 10 transformed), and time to complete the trail-making test (transformed by computing 1/ square root). The independent variables in these analyses were: altitude (490 m = 1, 1,630 m = 2, 2,590 m = 3), mean nocturnal oxygen saturation, slow wave sleep duration (time in nonrapid eye movement stages 3 and 4), the AHI, the number of days at altitude (1 to 4), altitude exposure sequence (A to D), age.

A probability of $P < 0.05$ applying a Bonferroni correction was considered statistically significant. Analyses were performed with Statistica V8.0, StatSoft, Tulsa, OK, USA, and Stata 11.1, StataCorp, College Station, TX, USA.

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Table S8—Generalized least-squares regression analysis of the effect of altitude exposure on the 1-, 2-, 3-number back test

Dependent variable Log10 (mean response time of all correct answers)	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficient	95% CI	P
Altitude						
1,630 m versus 490 m	-0.002	-0.027 to 0.023	0.886	0.035	0.006 to 0.064	0.017
2,590 m versus 490 m	-0.011	-0.034 to 0.011	0.316	0.020	-0.137 to 0.054	0.246
Mean nocturnal oxygen saturation, %	0.000	-0.003 to 0.003	0.995			
Slow wave sleep, min	-0.000	-0.001 to -0.000	0.007	-0.000	-0.000 to 0.000	0.124
AHI, 1/h	0.000	-0.000 to 0.001	0.169	0.000	-0.000 to 0.001	0.180
Number of days at altitude						
2nd versus 1st day	-0.032	-0.046 to -0.017	< 0.001	-0.026	-0.041 to -0.010	0.001
3rd versus 1st day	-0.059	-0.078 to -0.041	< 0.001	-0.057	-0.075 to -0.038	< 0.001
4th versus 1st day	-0.077	-0.095 to -0.058	< 0.001	-0.071	-0.090 to -0.053	< 0.001
Altitude exposure sequence	-0.017	-0.035 to 0.002	0.082	-0.017	-0.034 to 0.000	0.055
Age	0.003	0.001 to 0.004	0.002	0.002	0.001 to 0.004	0.002

n =255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for the logarithmically (log 10) transformed mean response time of all correct answers in the 1-, 2-, 3-number back test as dependent variable. Independent variables with P < 0.2 in the univariable analysis and altitude were included into the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude were 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

Table S9—Generalized least-squares regression analysis of the effect of altitude exposure on the trail making test

Dependent variable 1/(time to complete the trail making test)$^{0.5}$	Univariable analysis			Multivariable model		
	Coefficient	95% CI	P	Coefficent	95% CI	P
Altitude						
1,630 m versus 490 m	0.004	0.001 to 0.007	0.010	-0.002	-0.005 to 0.001	0.240
2,590 m versus 490 m	0.003	-0.000 to 0.006	0.058	-0.003	-0.006 to 0.001	0.177
Mean nocturnal oxygen saturation, %	-0.000	-0.001 to 0.000	0.918			
Slow wave sleep, min	0.000	0.000 to 0.000	0.006	0.000	-0.000 to 0.000	0.091
AHI, 1/h	-0.000	-0.000 to 0.000	0.231			
Number of days at altitude						
2nd versus 1st day	0.004	0.002 to 0.005	< 0.001	0.003	0.001 to 0.005	< 0.001
3rd versus 1st day	0.009	0.007 to 0.011	< 0.001	0.009	0.007 to 0.011	< 0.001
4th versus 1st day	0.012	0.010 to 0.014	< 0.001	0.011	0.009 to 0.013	< 0.001
Altitude exposure sequence	-0.001	-0.005 to 0.003	0.542			
Age	-0.001	-0.001 to -0.000	0.010	-0.001	-0.001 to -0.000	0.022

n = 255 observations at altitudes of 490 m, 1,630 m, and 2,590 m (51 participants). Results are presented for the reciprocal value of the square root transformed time to complete the trail making test as dependent variable. Independent variables with P < 0.2 in the univariable analysis were included in the multivariable analysis. The multivariable model was adjusted for all variables listed. Altitude levels were 1 = 490 m, 2 = 1,630 m, 3 = 2,590 m; the number of days at altitude was 1-4; altitude exposure sequences were A-D, see Figure 1. AHI, apnea-hypopnea index; CI, confidence interval.

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Table S10—Pulmonary function tests

	490 m	2,590 m		P Friedman ANOVA
		1st day	2nd day	
FVC, % predicted	107 (100;115)	105 (96;112)[a]	103 (98;113)[a]	< 0.001
FEV1, % predicted	103 (96;110)	104 (95;111)	103 (95;109)	0.668
FEV1/FVC, %	81 (76;85)	83 (78;87)[a]	82 (78;86)[a]	< 0.001
Sniff nasal pressure, cm H_2O	109 (92;129)	108 (87;121)	114 (94;129)	0.062
DLCO adj, % predicted	102 (94;110)	100 (93;107)	100 (91;106)	0.555

Medians (quartiles), n = 51. [a]P < 0.05 versus 490 m (Bonferroni correction by factor 3). No pulmonary function tests were performed at 1,630 m. ANOVA, analysis of variance; DLCO, single breath carbon monoxide diffusing capacity adjusted for barometric pressure; FEV1, forced expiratory volume in 1 sec; FVC, forced vital capacity.