Evaluating Health Impact at High Altitude in Antarctica and Effectiveness of Monitoring Oxygen Saturation

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ABSTRACT

Background The Japanese Antarctic Research Expedition (JARE) has been conducting research activities in inland Antarctica, which is extremely cold dryland covered with a thick ice sheet. This environment may cause a health disorder called acute mountain sickness (AMS). To improve the safety of expedition members, we evaluated the impact of extreme environmental conditions on human health and the effectiveness of monitoring of hypoxia for the early detection of AMS.

Methods In total, 9 members from JARE 59 were studied. Dome Fuji Station (Dome F), located 3,810 m above sea level (ASL), was the destination of the research party. We analyzed daily AMS scores (higher values correspond to more severe AMS-related symptoms), physiological findings, and percutaneous arterial blood oxygen saturation (SpO_2) during the inland activity. We also determined the factors related to AMS scores.

Results The average AMS score on arrival at Dome F was significantly higher than that at the departure point (560 m ASL). The average SpO_2 level was significantly lower than that at other points. The SpO_2 level correlated negatively with the AMS score in Spearman's rank correlation. Generalized estimating equations analysis showed that the AMS score was negatively associated with SpO_2 level and positively associated with age.

Conclusion Hypoxia is a contributory factor to AMS which we can easily assess by measuring the SpO_2 level with a pulse oximeter. SpO_2 monitoring is a potentially useful health management tool for members in inland Antarctic expeditions. In addition, our results are helpful for understanding physiological responses and health issues in extreme environments.

Key words Antarctic regions; altitude sickness; hypoxia; oximetry; cold temperature

Antarctica is covered with a thick ice sheet that reaches up to an average of 2,450 m above sea level (ASL). The average altitude of the Antarctic Continent is 2,300 m ASL, which is remarkably high compared with other continents. The average temperature is −10 ℃ along the Antarctic seaboard but decreases to –60 ℃ inland, with the lowest temperature dropping below –80 ℃. The extreme cold, dryness, and strong winds in Antarctica have created one of the most severe natural environments on Earth. Additionally, the air is rarefied at high altitude, precluding the success of any living creatures on inland Antarctica.

The Japanese Antarctic Research Expedition (JARE) has performed various observations at Syowa Station (69°00′S, 39°35′E, 29 m ASL), the Japanese Antarctic base, and the surrounding areas since 1956. The wintering team of JARE stays in Antarctica for 14 months, 10 months of which is spent in isolation with no means of leaving the station. Despite the lack of supplies from the outside world during this period, most wintering members maintain good health.[1, 2]

Dome Fuji Station (Dome F, 77°30′S, 37°30′E) was established on the second-highest summit of the East Antarctic ice sheet in 1995 to conduct deep ice-core drilling.[3, 4] Dome F is located 3,810 m ASL and 1,000 km distant from Syowa Station (Fig. 1). Since 1995, JARE has been also carrying out research activities under extreme environmental conditions at high altitude, which can lead to health disorders including acute mountain sickness (AMS).[5] Although no severe cases have been reported in JARE inland parties in the past, some members have complained of AMS-related
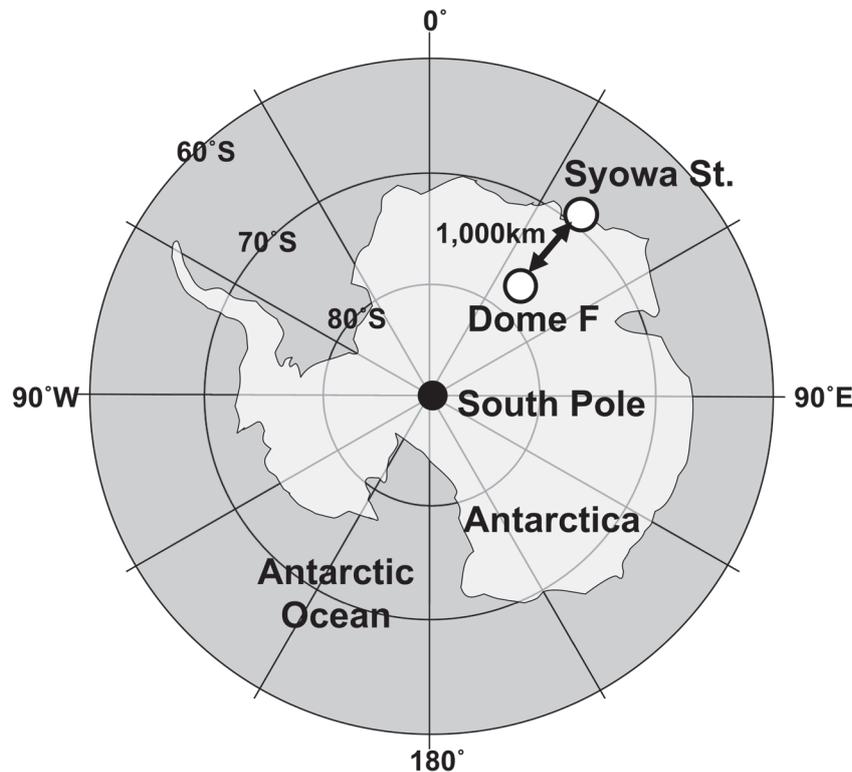
Fig. 1. Location map of Syowa Station (Syowa St.) and Dome Fuji Station (Dome F) in Antarctica.

symptoms during inland activity, such as headache, fatigue, breathlessness, and sleep disturbance. AMS is a lethal disease for which pre-symptomatic prevention is hugely important.[6] Some reports have mentioned the importance of hypoxemia as a predictive factor of AMS[7–9]; however, to date this has not been reported for inland Antarctica. With the goal of improving the safety of members during Antarctic expeditions, we evaluated the impact of extreme environmental conditions of the Antarctic inland on human health and effectiveness by monitoring of hypoxia for the early detection of AMS.

MATERIALS AND METHOD
Subjects
This study involved an inland Antarctic research party participating in the 59th JARE, which lasted from 2017 to 2019. The party comprised 10 healthy Japanese individuals including one woman; however, a male participant was excluded from the analysis because of missing data and self-administered acetazolamide of 38 days' duration to prevent mountain sickness.[6, 10] At the beginning of this study, the mean age of participants was 45.6 years (ranges 30–60 years); two members had previous experience of staying at Dome F. All subjects climbed Mt. Fuji (3,776 m ASL) in Japan as an advanced highland training in August 2017. Two participants had

a smoking habit.

The subjects split up and set off in five large snow vehicles measuring 3.5 × 7 m. The party left Syowa Station on November 8, 2017 (Day 1) and arrived at point S16 (69°02′S, 40°03′E, 560 m ASL), 16 km from Syowa Station, on the same day. After 6 days (Day 7), the party left S16 and took 27 days (until Day 33) to reach Dome F. During movement to or from Dome F, the subjects drove snow vehicles to cover about 40 km in 6 h and did outdoor work for short periods, 10–30 min, several times per day. The normal temperature inside the vehicles was about 20 °C during engine operation, but only –10°C to 0°C in the early morning because the engines had just been started up. During their stay at Dome F, the subjects were mainly engaged in construction and maintenance of the observation facilities for 8–10 h almost every day. During this study, participants mostly ate three regular balanced meals per day. Although caloric intake was not accurately determined, it was estimated that the daily intake from meals was 2000–3000 kcal depending on the individual. The party left Dome F on January 12, 2018 (Day 66) and arrived at point S16 on January 25, 2018 (Day 79) and stayed for 2 days. A timeline of this inland activity is shown in Fig. 2.
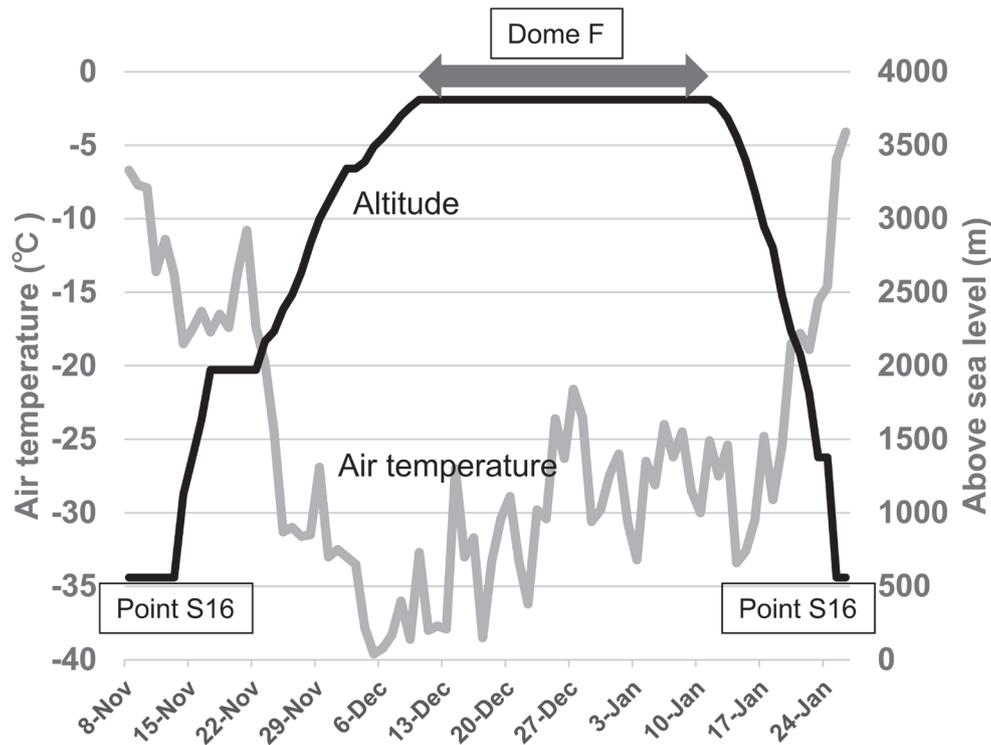
Fig. 2. A timeline of expedition details including height above sea level and air temperature. Dome F, Dome Fuji Station.

Basic health check

During the journey, all subjects had a medical checkup inside the snow vehicles during rest after getting up every morning. Percutaneous arterial blood oxygen saturation (SpO_2) was measured using a pulse oximeter (OXIM S-114, SEASTAR Corporation, Tokyo, Japan) for monitoring of hypoxia. We also measured systolic and diastolic blood pressure (HEM-6111, OMRON Corporation, Kyoto, Japan), pulse rate, body temperature, body weight (PS-130WH, KYOWA Manufacturing Co., Ltd., Osaka, Japan). We did not calibrate the body weight meter because the atmospheric pressure and latitude changes affect measurements under such conditions, though within an acceptable range (error of 1%). We made comparisons of average levels of each parameter over 2 days at the following time points: on arrival at S16 (days 1 and 2), Point A; on arrival at Dome F (days 34 and 35), Point B; departure from Dome F (days 65 and 66), Point C; and return to S16 (days 79 and 80), Point D.

High-altitude-related symptoms

High altitude related symptoms during the expedition were investigated based on the 1991 Lake Louise AMS score.[11] Symptoms of AMS in the evaluating consisted of headache (0, no headache; 1, mild headache; 2, moderate headache; 3, Sever headache, incapacitating), gastrointestinal symptoms (0, no gastrointestinal symptoms; 1, poor appetite or nausea; 2, moderate nausea or vomiting; 3, severe nausea and vomiting, incapacitating), fatigue and/or weakness (0, not tired or weak; 1, mild fatigue/weakness; 2, moderate fatigue/weakness; 3, severe fatigue/weakness, incapacitating), dizziness/lightheadedness (0, not dizzy; 1, mild dizziness; 2, moderate dizziness; 3, severe dizziness, incapacitating), and difficulty sleeping (0, slept as well as usual; 1, did not sleep as well as usual; 2 woke many times, poor night's sleep; 3, could not sleep at all).[11] Every symptom was assessed by each subject via self-check sheets. AMS score was taken as the sum of the points. In general, a total score of 3 to 5 indicates mild AMS and a score of 6 or more signifies severe AMS.

Statistical analysis

The comparison of average levels of each measurement item among Point A, B, C, and D was assessed by repeated-measures analysis of variance. The relationship between SpO_2 level and AMS score (including the severity of each symptom) was assessed using Spearman's rank correlation because the variables were not normally distributed. For the estimation of associated factors with AMS score, we used generalized

estimating equations (GEE), which is a good method for analysis of repeated measurements or other correlated observations, such as clustered data. Age, smoking status, and measurement items (SpO_2, body temperature, body weight, and systolic blood pressure) were selected as the independent variables, and all daily data were used for GEE. Pulse rate and diastolic blood pressure were excluded from GEE due to high variability and multicollinearity, respectively. All data analyses were performed using IBM SPSS Statistics Version 24 (IBM, Armonk, NY). $P < 0.05$ was considered statistically significant. Values are reported as mean ± standard error.

Ethics approval
This study was approved by the Medical Ethics Committee of the National Institute of Polar Research (NIPR), Japan (No. November-1-2017), Project Research no. KZ-32. We obtained informed consent from all research subjects.

RESULTS
Trends in daily average levels of SpO_2, body temperature, pulse rate, blood pressure, and body weight are shown in Fig. 3. The AMS trend including each symptom is presented in Fig. 4. Average levels of SpO_2, body temperature, pulse rate, blood pressure, body weight, and AMS score at each point are shown in Table 1. The average levels (± standard error) of SpO_2 at Points A to D was 97.9% ± 0.2%, 84.8% ± 1.4%, 87.9% ± 0.8%, and 97.8% ± 0.3%, respectively. The average SpO_2 levels at Point B was significantly lower than at any other points (Point A, $P < 0.001$; Point C, $P = 0.008$; Point D, $P < 0.001$). The average body temperature was 35.7°C ± 0.2°C, 35.8°C ± 0.1°C, 35.7°C ± 0.2°C, and 36.2°C ± 0.2°C at Points A to D, respectively. The average body temperature at Point D was significantly higher than at Point B ($P = 0.031$) and Point C ($P = 0.001$). The average pulse rate (per minute) at Points A to D was 76.6 ± 3.8, 78.7 ± 3.0, 85.2 ± 4.0, and 73.1 ± 3.7, respectively. The average pulse rate at Point C was significantly higher than at Point A ($P = 0.006$) and Point D ($P = 0.002$). The average systolic / diastolic blood pressure at Points A to D was 138.7 ± 6.5/89.1 ± 3.6 mmHg, 136.8 ± 5.5/96.7 ± 4.0 mmHg, 130.8 ± 5.0/91.8 ± 4.7 mmHg, and 132.2 ± 3.8/87.9 ± 4.0 mmHg, respectively. The average diastolic blood pressure at Point B was significantly higher than at Point A ($P = 0.048$) and Point D ($P = 0.003$). The average body weight in each point was 74.0 ± 3.2 kg, 70.6 ± 3.0 kg, 68.7 ± 2.7 kg, and 69.4 ± 2.9 kg, respectively. The average body weight at Points B, C, and D was significantly lighter than at Point A ($P = 0.002$, 0.001, and 0.003). and average body weight at Points C

was significantly lighter than at Point B ($P = 0.017$). The average AMS score at Points A to D was 0.33 ± 0.08, 0.50 ± 0.14, 0.33 ± 0.19, and 0.06 ± 0.06, respectively. The average AMS score at Point B was significantly higher than at Point D ($P = 0.021$) and the average AMS score at Point D was significantly lower than at Point A ($P = 0.013$).

The correlation coefficient (ρ) between SpO_2 level and AMS score including the severity of each symptom are shown in Table 2. SpO_2 level was negatively correlated with AMS score (ρ = –0.095, $P = 0.012$) and the severity of fatigue (ρ = –0.112, $P = 0.003$).

In GEE analysis (Table 3), AMS score was positively associated with age (standardizing coefficient, B = 0.010, $P < 0.001$) and negatively associated with the level of SpO_2 (B = –0.011, $P = 0.035$). There was no significant relationship between AMS score and smoking habit (B = 0.114, $P = 0.294$), systolic blood pressure (B = –0.005, $P = 0.070$), body temperature (B = 0.026, $P = 0.445$), and body weight (B = 0.010, $P = 0.051$).

DISCUSSION
No severe mountain sickness was found in any subjects, including the untargeted participants, so this inland operation was conducted safely. Hypoxemia is one of the predictive factors related to AMS,[7] and a hypoxic state can easily be confirmed by the levels of SpO_2 (a normal level is typically between 96 and 99%), as measured using a pulse oximeter. SpO_2 levels had a negative correlation with height above sea levels, and average level of SpO_2 after arriving at Dome F was 85.2%. Such low levels at low altitudes should raise suspicion of respiratory failure: for example, severe pneumonia or chronic obstructive pulmonary disease requiring oxygen inhalation. However, the high-altitude adaptation process reduces health risk and, in fact, no emergency cases except for one arrhythmia case have been reported among previous JARE inland parties or the current party. Usually, JARE inland parties travel at low speed in snow vehicles during their expedition and, consequently, the body can gradually become accustomed to high altitude. As we previously reported,[5] hematological acclimation responses are completed within several weeks and the resulting state of polycythemia is useful for oxygen transport. The activities of expeditions are bound by time constraints and tight schedules. Nevertheless, to prevent acute mountain sickness, it is desirable for members to ascend gradually when travelling to inland Antarctica. Additionally, members of JARE are rigorously selected using a strict medical checkup before leaving for Antarctica.[1, 2] These reasons may explain why no JARE members have developed

SpO₂

Body temperature

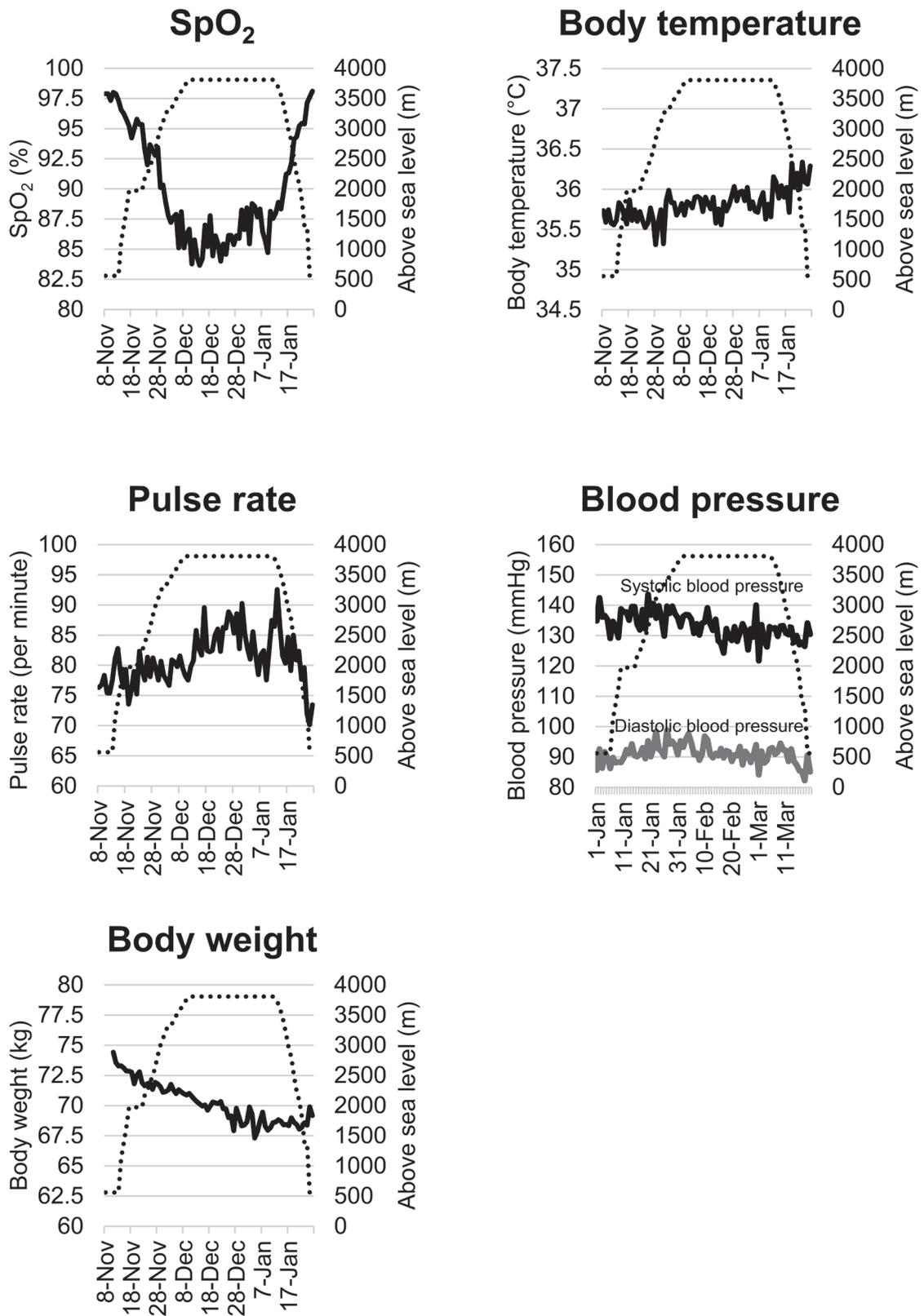## Pulse rate

Blood pressure

Body weight

Fig. 3. Percutaneous arterial blood oxygen saturation (SpO₂), body temperature, pulse rate, blood pressure, and body weight presented as daily values throughout the expedition. The dotted line represents height above sea level.
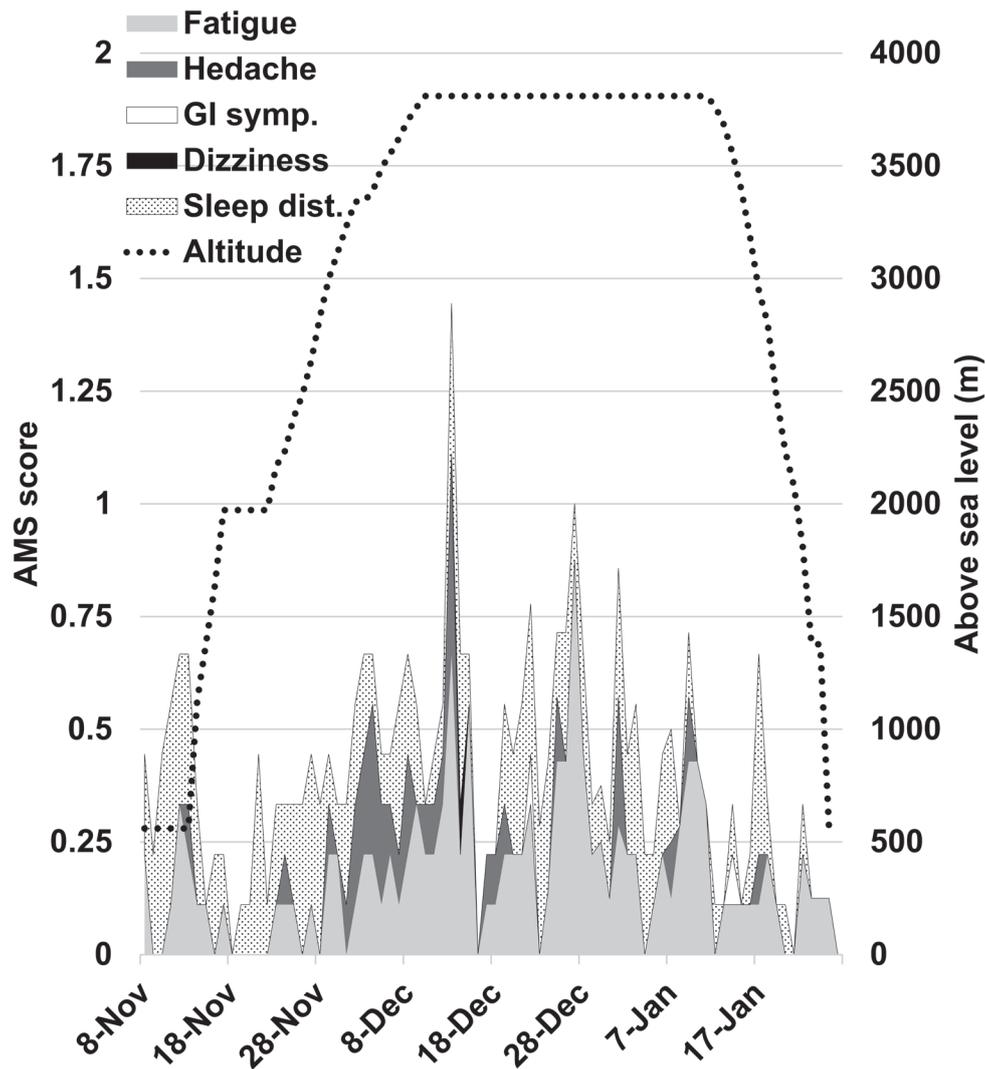
Fig. 4. Acute mountain sickness (AMS) score and scores of AMS-related symptoms, namely headache, gastrointestinal symptoms (GI symp.), fatigue, dizziness, sleep disturbance (sleep dist.), as daily values throughout the expedition. The dotted line represents height above sea level.

severe medical conditions.

In the present study, the SpO$_2$ level was negatively correlated with the AMS score. When considering each AMS-related symptom, we found a negative correlation between SpO$_2$ level and the severity of fatigue. Given that fatigue is a typical symptom arising from hypoxia, this result is understandable. The severity of headache, which is the most important symptom of early-stage AMS,[11] and other symptoms did not show any significant relationship with SpO$_2$ level. There are various possible reasons for these results. As previously mentioned, hypoxia can lead to polycythemia, which can itself cause headache, fatigue, and vertigo. In addition, sleep disturbances of subjects may be attributable to tremendous temperature differences (it is extremely

cold especially in the early morning) and/or tight spaces inside snow vehicles, besides the hypoxic environment. The sleep component, which was removed from the new AMS scoring system (the 2018 Lake Louise AMS score),[12] may not be important as a symptom of AMS. However, considering the overall AMS score, low levels of SpO$_2$ might be related to hypobaropathy. Mandolesi et al.[9] reported that AMS subjects present with more severe and prolonged oxygen desaturation than non-AMS subjects. One would thus expect that monitoring of hypoxia benefits the timely detection of AMS. Moreover, during the stay in Dome F, the SpO$_2$ level tent to increase and the average level of SpO$_2$ at Point C was significantly higher than at Point B, albeit at the same altitude. It is known that altitude acclimatization

Table 1. Clinical parameters at different determination points

	Point A	Point B	Point C	Point D
SpO_2 (%)	97.9 ± 0.2	84.8 ± 1.4	87.9 ± 0.8	97.8 ± 0.3
		$P < 0.001$	$P = 0.008$	$P < 0.001$
		$P < 0.001$		
			$P < 0.001$	
			$P = 0.799$	
Body temperature (℃)	35.7 ± 0.2	35.8 ± 0.1	35.7 ± 0.2	36.2 ± 0.2
		$P = 0.550$	$P = 0.647$	$P = 0.001$
		$P = 0.777$		
			$P = 0.031$	
			$P = 0.463$	
Pulse rate (per min)	76.6 ± 3.8	78.7 ± 3.0	85.2 ± 4.0	73.1 ± 3.7
		$P = 0.533$	$P = 0.053$	$P = 0.002$
		$P = 0.006$		
			$P = 0.174$	
			$P = 0.197$	
Systolic blood pressure (mmHg)	138.7 ± 6.5	136.8 ± 5.5	130.8 ± 5.0	132.2 ± 3.8
		$P = 0.653$	$P = 0.172$	$P = 0.644$
		$P=0.200$		
			$P = 0.180$	
			$P = 0.329$	
Diastolic blood pressusre (mmHg)	89.1 ± 3.6	96.7 ± 4.0	91.8 ± 4.7	87.9 ± 4.0
		$P = 0.048$	$P = 0.192$	$P = 0.229$
		$P = 0.192$		
			$P = 0.003$	
			$P = 0.801$	
Body weight (kg)	74.0 ± 3.2	70.6 ± 3.0	68.7 ± 2.7	69.4 ± 2.9
		$P = 0.002$	$P = 0.017$	$P = 0.149$
		$P = 0.001$		
			$P = 0.057$	
			$P=0.003$	
AMS score	0.33 ± 0.08	0.50 ± 0.14	0.33 ± 0.19	0.06 ± 0.06
		$P = 0.347$	$P = 0.397$	$P = 0.179$
		$P = 1.000$		
			$P = 0.021$	
			$P = 0.013$	

Point A: point S16 (day 1 and 2 at 560 m above sea level); Point B: the arrival at Dome Fuji Station (Dome F) (day 34 and 35 at 3,810 m above sea level); Point C: the departure from Dome F (day 65 and 66); Point D: the return to point S16 (day 79 and 80). AMS, acute mountain sickness; SpO_2, percutaneous arterial blood oxygen saturation.

Table 2. Correlation coefficients between percutaneous arterial blood oxygen saturation (SpO₂) value and acute mountain sickness (AMS) score and scores of AMS-related symptoms

	ρ	*P* value
Headache	−0.054	0.159
GI symptoms	−0.052	0.174
Fatigue	−0.112	0.003
Dizziness	−0.060	0.111
Sleep disturbance	−0.038	0.314
AMI score	−0.095	0.012

AMS, acute mountain sickness; GI, gastrointestinal; ρ, correlation coefficients.

improves respiratory function and gas exchange,[13] and the subjects seem to have adapted physiologically in this study.

A recent meta-analysis and a review point out that there is no association between age and the risk of AMS, and it is not clear whether age is a protective factor or a risk factor for AMS.[14, 15] However, ageing leads to changes in physical activity and functional fitness, and older members may become more susceptible to altitude-related illness. In the present study, AMS scores were positively associated with age despite a small sample number. Although most previous studies of age and AMS have targeted climbers and travelers,[14, 15] subjects of our study were JARE members who worked at various jobs such as scientific surveying, observation, and logistics. Moreover, the mean age of members in each JARE group, including inland parties, has increased year by year[2]: for example, the mean ages of inland expedition members in JARE40, JARE43, JARE46, and JARE59 were 33.7, 35.4, 43.0, and 45.4 (including the untargeted participant) years, respectively.[16] Currently, there is no age limit for selecting JARE members; nevertheless the effects of age may not be negligible in the near future.

Exposure to cold induces autonomic homeostatic responses for the maintenance of core body temperature, and cutaneous vasoconstriction and thermogenesis are the most important of these reactions.[17] It is well known that cold stimuli result in elevation of blood pressure and increased heart rate.[18] In the present study, the changes in blood pressure were significant but not compelling, perhaps because participants spent most of their time in snow vehicles or inside buildings where the air temperature was controlled. In fact, it was difficult to assess the effects of cold as each member was assigned a different task and had varying degrees of exposure. Nevertheless, subjects' pulse rate tended to increase until the end of stay in Dome F, possibly because of hypoxia.[19] The body temperature of participants tended to rise after arriving at Dome F and during the return trip from Dome F to S16, possibly because the outside air temperature tended to increase in the time interval from staying at Dome F to arrival at point S16. In addition, increased basal metabolism in the cold may be associated with elevated body temperature.[17] Although no major accidents have occurred as a result of the cold environment and stimuli, minor injuries and frostbite have been observed occasionally. It is known that acute cold stress impairs cognitive performance,[20] which may lead to accidents among members performing outdoor tasks in inland Antarctica.

Subjects' body weight continued to decrease during inland activity. The mechanisms leading to body weight changes are various and influenced by the individual adaptive response to hypoxia and cold, the level of physical activity, and the nutritional intake.[21] According to the food uptake standard of the ministry of Health, Welfare and Labor of Japan, the estimated energy requirement is 3,050 (2,300) kcal/day for a 30- to 49-year old male (female) with a high physical activity level and 2,800 (2,200) kcal/day for 50- to 69-year old counterparts.[22] In addition, higher calorie intake is

Table 3. Generalized estimating equations of factors associated with acute mountain sickness (AMS) score

	B	95% CI		*P* value
		Lower	Upper	
Age (years)	0.010	0.005	0.016	< 0.001
Smoking habit	0.114	−0.099	0.328	0.294
SpO₂	−0.011	−0.021	−0.001	0.035
Body temperature	0.026	−0.040	0.092	0.445
Systolic blood pressure	−0.005	−0.011	0.000	0.070
Bodyweight	0.010	−0.001	0.019	0.051

B, standardizing coefficient; CI, confidence interval.

required in cold environments because of promotion of energy metabolism.[20] In such extremely cold environments, dietary intake should be determined on the basis of activity and weight monitoring. At Syowa Station, the wintering team of each year makes a working rule such as working hours and days off for health promotion of 30 to 40 members similar to the work system in Japan,[1, 2] and every meal is provided to the wintering members by licensed chefs. Meanwhile, few nutritional or occupational hygiene approaches have been taken for the health care of Antarctic inland survey members in spite of the harsh working conditions. In contrast, the National Aeronautics and Space Administration (NASA) established the NASA Occupational medicine division in 1963 to provide health and safety management for astronauts and all supporting personnel.[23] Although the purpose, scale, and budget of NIPR, which conducts JARE, is quite different from NASA, they are alike in that they send out members with important missions to special environments. The health and safety of Antarctic inland expedition members must also be managed from the perspective of occupational medicine.

The limitations of our study include the difficulty of repeating the results in the same environment and situation because a JARE inland party is not always organized every year and the main purpose of the inland survey also differs each time. For this reason, analysis and assessment had to be performed with a small sample number of people and the effects of gender, pre-training, and smoking habits on symptoms could not be fully evaluated. Second, as we mentioned before, environmental factors affecting health were not the same for each subject because they had different tasks. Therefore, physical activity of each subject was not accurately evaluated. The amount of activity should be considered in more detail and, similarly, times of exposure to cold should be documented in detail. Third, we did not evaluate psychological stress among participants. Some health parameters, including symptoms, may be attributable to psychological stress arising from the isolated and extreme environment.[24] Moreover, it is reported that trait anxiety at low altitude was an independent predictor of severe AMS development at high altitude.[25] A simple psychological test may be necessary for the mental and physical health management of members, although this is a delicate and private matter.

Research and expeditions in Antarctica are very important for future projections of climate change[26]; thus, it is expected that detailed Antarctic inland surveys will continue. For this purpose, it is a prerequisite that the expedition members can work safely and healthily in Antarctica. Therefore, we need to continue collecting health-related data in such an extreme environment and share the results of the analysis not only with JARE, but also with Antarctic expedition teams from other countries. In addition, this kind of study will be helpful for better understanding of physiological responses and health issues in extreme environments.

The authors declare no conflict of interest.

REFERENCES

1 Otani S, Ohno G, Shimoeda N, Mikami H. Morbidity and health survey of wintering members in Japanese Antarctic research expedition. Int J Circumpolar Health. 2004;63(suppl 2):165-8. DOI: 10.3402/ijch.v63i0.17890, PMID: 15736644

2 Ikeda A, Ohno G, Otani S, Watanabe K, Imura S. Disease and injury statistics of Japanese Antarctic research expeditions during the wintering period: evaluation of 6837 cases in the 1st–56th parties – Antarctic health report in 1956–2016. Int J Circumpolar Health. 2019;78:1611327. DOI: 10.1080/22423982.2019.1611327, PMID: 31038401

3 Kawamura K, Parrenin F, Lisiecki L, Uemura R, Vimeux F, Severinghaus JP, et al. Northern Hemisphere forcing of climatic cycles in Antarctica over the past 360,000 years. Nature. 2007;448:912-6. DOI: 10.1038/nature06015, PMID: 17713531

4 Kawamura K, Abe-Ouchi A, Motoyama H, Ageta Y, Aoki S, Azuma N, et al.; Dome Fuji Ice Core Project Members. State dependence of climatic instability over the past 720,000 years from Antarctic ice cores and climate modeling. Sci Adv. 2017;3:e1600446. DOI: 10.1126/sciadv.1600446, PMID: 28246631

5 Otani S, Kusagaya H. Changes in Cytokines at Extreme Surroundings in Antarctica. Yonago Acta Med. 2003;46:29-34.

6 Jin J. Acute Mountain Sickness. JAMA. 2017;318:1840. DOI: 10.1001/jama.2017.16077, PMID: 29136446

7 Burtscher M, Szubski C, Faulhaber M. Prediction of the susceptibility to AMS in simulated altitude. Sleep Breath. 2008;12:103-8. DOI: 10.1007/s11325-007-0131-0, PMID: 18057977

8 Loeppky JA, Icenogle MV, Charlton GA, Conn CA, Maes D, Riboni K, et al. Hypoxemia and acute mountain sickness: which comes first? High Alt Med Biol. 2008;9:271-9. DOI: 10.1089/ham.2008.1035, PMID: 19115910

9 Mandolesi G, Avancini G, Bartesaghi M, Bernardi E, Pomidori L, Cogo A. Long-term monitoring of oxygen saturation at altitude can be useful in predicting the subsequent development of moderate-to-severe acute mountain sickness. Wilderness Environ Med. 2014;25:384-91. DOI: 10.1016/j.wem.2014.04.015, PMID: 25027753

10 Leaf DE, Goldfarb DS. Mechanisms of action of acetazolamide in the prophylaxis and treatment of acute mountain sickness. J Appl Physiol. 2007;102:1313-22. DOI: 10.1152/japplphysiol.01572.2005, PMID: 17023566

11 Roach RC, Bärtsch P, Hackett PH, Oelz O. The Lake Louise acute mountain sickness scoring system. In: Sutton JR, Houston CS, Coates G, eds. Hy poxia and molecular medicine. Burlington: Queen City Press; 1993. p. 272-4.

12 Roach RC, Hackett PH, Oelz O, Bärtsch P, Luks AM, MacInnis MJ, et al.; Lake Louise AMS Score Consensus Committee. The 2018 Lake Louise Acute Mountain Sickness Score. High Alt Med Biol. 2018;19:4-6. DOI: 10.1089/ham.2017.0164, PMID: 29583031

13 Bärtsch P, Saltin B. General introduction to altitude adaptation and mountain sickness. Scand J Med Sci Sports. 2008;18(suppl 1):1-10. DOI: 10.1111/j.1600-0838.2008.00827.x, PMID: 18665947

14 Gianfredi V, Albano L, Basnyat B, Ferrara P. Does age have an impact on acute mountain sickness? A systematic review. J Travel Med. 2020;taz104. DOI: 10.1093/jtm/taz104, PMID: 31897482

15 Wu Y, Zhang C, Chen Y, Luo YJ. Association between acute mountain sickness (AMS) and age: a meta-analysis. Mil Med Res. 2018;5:14. DOI: 10.1186/s40779-018-0161-x, PMID: 29747689

16 Otani S, Ohno G, Obinata K, Shimoeda N, Ohno H. Comparison of cardiorespiratory state between different approaches to a high altitude region in Antarctica. Japan Jounal of Mountain Medicine. 2006;26:87-90. Japanese.

17 Burtscher M, Gatterer H, Burtscher J, Mairbäurl H. Extreme Terrestrial Environments: Life in Thermal Stress and Hypoxia. A Narrative Review. Front Physiol. 2018;9:572. DOI: 10.3389/fphys.2018.00572, PMID: 29867589

18 Ikäheimo TM. Cardiovascular diseases, cold exposure and exercise. Temperature. 2018;5:123-46. DOI: 10.1080/23328940.2017.1414014, PMID: 30377633

19 Parati G, Agostoni P, Basnyat B, Bilo G, Brugger H, Coca A, et al. Clinical recommendations for high altitude exposure of individuals with pre-existing cardiovascular conditions. Eur Heart J. 2018;39:1546-54. DOI: 10.1093/eurheartj/ehx720, PMID: 29340578

20 Jones DM, Bailey SP, Roelands B, Buono MJ, Meeusen R. Cold acclimation and cognitive performance: A review. Auton Neurosci. 2017;208:36-42. DOI: 10.1016/j.autneu.2017.11.004, PMID: 29158117

21 Dünnwald T, Gatterer H, Faulhaber M, Arvandi M, Schobersberger W. Body Composition and Body Weight Changes at Different Altitude Levels: A Systematic Review and Meta-Analysis. Front Physiol. 2019;10:430. DOI: 10.3389/fphys.2019.00430, PMID: 31057421

22 Minister of Health. Labour and Welfare [Internet]. Tokyo: The Minister of Health, Labour and Welfare in accordance with Article 30-2 of the Health Promotion Act (Act No.103 of 2002). Overview of Dietary Reference Intakes for Japanese [updated 2014 March 28; cited 2020 March 26]. Available from: https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku/Overview.pdf

23 Moser R Jr. Occupational medicine's essential contributions to winning the race to the Moon. Occup Med (Chic Ill). 2019;69:308-10. DOI: 10.1093/occmed/kqz096, PMID: 31436817

24 Pattarini JM, Scarborough JR, Lee Sombito V, Parazynski SE. Primary Care in Extreme Environments: Medical Clinic Utilization at Antarctic Stations, 2013–2014. Wilderness Environ Med. 2016;27:69-77. DOI: 10.1016/j.wem.2015.11.010, PMID: 26948556

25 Boos CJ, Bass M, O'Hara JP, Vincent E, Mellor A, Sevier L, et al. The relationship between anxiety and acute mountain sickness. PLoS One. 2018;13:e0197147. DOI: 10.1371/journal.pone.0197147, PMID: 29927953

26 Convey P, Peck LS. Antarctic environmental change and biological responses. Sci Adv. 2019;5:eaaz0888. DOI: 10.1126/sciadv.aaz0888, PMID: 31807713