

MEDEX2015

Rossetti, Gabriella; Macdonald, Jamie; Smith, Matthew; Jackson, Anna; Callender, Nigel; Newcombe, Hannah K.; Storey, Heather; Willis, Sebastian; van den Beukel, Jojanneke; Woodward, Jonathan; Pollard, James; Wood, Benjamin; Newton, Victoria; Virian, Jana; Haswell, Owen; Oliver, Samuel

High Altitude Medicine and Biology

DOI:
[10.1089/ham.2016.0088](https://doi.org/10.1089/ham.2016.0088)

Published: 01/06/2017

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):

Rossetti, G., Macdonald, J., Smith, M., Jackson, A., Callender, N., Newcombe, H. K., Storey, H., Willis, S., van den Beukel, J., Woodward, J., Pollard, J., Wood, B., Newton, V., Virian, J., Haswell, O., & Oliver, S. (2017). MEDEX2015: Greater sea-level fitness is associated with lower sense of effort during Himalayan trekking without worse Acute Mountain Sickness. *High Altitude Medicine and Biology*, 18(2), 152-162. <https://doi.org/10.1089/ham.2016.0088>

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1 **This article was accepted in its current form to High Altitude Medicine & Biology on 11th**
2 **February 2017.**

3

4 **MEDEX2015: Greater sea-level fitness is associated with lower sense of effort during Himalayan trekking**
5 **without worse Acute Mountain Sickness**

6

7 **Running head:** Fitness, exercise and AMS at altitude

8

9

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29 **Abstract**

30 This study examined the complex relationships of fitness and hypoxic sensitivity with submaximal exercise
31 responses and Acute Mountain Sickness (AMS) at altitude. Determining these relationships is necessary before
32 fitness or hypoxic sensitivity tests can be recommended to appraise individuals' readiness for altitude. Forty-four
33 trekkers (26 men; 18 women; 20-67 years) completed a loaded walking test and a fitness questionnaire in normoxia
34 to measure and estimate sea-level maximal aerobic capacity ($\dot{V}O_{2max}$), respectively. Participants also completed a
35 hypoxic exercise test to determine hypoxic sensitivity (cardiac, ventilatory, and arterial oxygen saturation
36 responses to acute hypoxia, $FiO_2=0.112$). One month later all participants completed a three-week trek to 5085m
37 with the same ascent profile. On ascent to 5085m, ratings of perceived exertion (RPE_{ascent}), fatigue by Brunel
38 Mood Scale, and AMS were recorded daily. At 5085m, RPE during a fixed workload step test (RPE_{fixed}) and step
39 rate during perceptually-regulated exercise ($STEP_{RPE35}$) were recorded. Greater sea-level $\dot{V}O_{2max}$ was associated
40 with, and predicted, lower sense of effort (RPE_{ascent} $r=-0.43$; $p<0.001$; RPE_{fixed} ; $r=-0.69$; $p<0.001$) and higher step
41 rate ($STEP_{RPE35}$ $r=0.62$; $p<0.01$), but not worse AMS ($r=0.13$; $p=0.4$) or arterial oxygen desaturation ($r=0.07$;
42 $p=0.7$). Lower RPE_{ascent} was also associated with better mood, including less fatigue ($r=0.57$; $p<0.001$). Hypoxic
43 sensitivity was not associated with, and did not add to the prediction of submaximal exercise responses or AMS.
44 In conclusion, participants with greater sea-level fitness reported less effort during simulated and actual trekking
45 activities, had better mood (less fatigue), and chose a higher step rate during perceptually-regulated exercise, but
46 did not suffer from worse AMS or arterial oxygen desaturation. Simple sea-level fitness tests may be used to aid
47 preparation for high-altitude travel.

48

49

50 **Key words:** Maximal oxygen uptake, Exercise, Acute mountain sickness, Hypoxic ventilatory response,
51 Arterial oxygen saturation

52 Introduction

53 Many people travel to altitude for work and leisure including trekkers, military personnel, and miners
54 (Government of Nepal, 2013). As well as high-altitude illness, fatigue presents a major psychophysiological risk
55 factor for summit failure, injury, and fatality at altitude (Firth et al., 2008; Oliver et al., 2012). Recent
56 commentaries in this and other journals highlight the potential importance of adequate sea-level fitness to reduce
57 fatigue and therefore enhance altitude exercise performance, including trekking times and summit success
58 (Bärtsch & Swenson, 2013; Burtcher et al., 2015). However, the relationships between sea-level fitness,
59 submaximal exercise responses at altitude, and Acute Mountain Sickness (AMS) are complex (MacInnis et al.,
60 2015), and as yet unknown.

61
62 Numerous studies indicate that individuals with high sea-level maximal aerobic capacity ($\dot{V}O_{2max}$) have high
63 altitude $\dot{V}O_{2max}$ (Fulco et al., 1998). Yet there is evidence that the absolute loss of $\dot{V}O_{2max}$ in high-fit individuals
64 is greater at high altitude than their less-fit counterparts (Ferretti et al., 1997; Marconi et al., 2004; Mollard et al.,
65 2007). In fact, the decline in very high-fit individuals is so great at high altitude that their $\dot{V}O_{2max}$ is no different
66 *or even lower* than their less-fit counterparts (MacInnis et al., 2015). Furthermore it is often assumed that
67 individuals with high sea-level $\dot{V}O_{2max}$ have greater exercise performance. However, $\dot{V}O_{2max}$ is not the only
68 determinant of long-duration submaximal exercise responses, and other measures of fitness, such as fractional
69 utilization of $\dot{V}O_{2max}$ (e.g. ventilatory threshold) and economy, are potentially as important (Bassett & Howley,
70 2000; Coyle et al., 1988). For trekking activities, which are typically submaximal, sense of effort during exercise
71 (most often assessed by rating of perceived exertion; RPE) is also functionally important because it appraises the
72 individual's comfort level. Sense of effort is also an essential component of general fatigue (Enoka & Stuart,
73 1992). Despite the well-documented relationship between fitness and exercise performance at sea level, the
74 relationship between sea-level fitness and sense of effort during submaximal exercise at altitude is unclear.

75
76 Even if high sea-level fitness is associated with greater exercise capacity and reduced sense of effort, this may be
77 at the cost of exacerbating AMS. Indeed, regular endurance training has been identified as a risk factor for altitude
78 illness (Karinen et al., 2010; Richalet et al., 2012). A possible explanation for this is that fitter individuals
79 experience greater arterial desaturation with acute hypoxia even during submaximal exercise (Lhuissier et al.,
80 2012), which is likely a result of greater cardiac output (Richalet & Lhuissier, 2015), or an indirect effect of greater
81 oxygen extraction in the muscle (Van Thienen & Hespel, 2016). Alternatively, worse AMS may occur because

82 fitter individuals exercise at a greater intensity at altitude and/or gain altitude quicker. These arguments provide
83 possible reasons for the common anecdotal field observation of poorer than expected exercise performance and
84 AMS in high-fit persons at high altitude. Despite the anecdotes and plausible physiological responses, evidence
85 is lacking to explain the complex relationship between sea-level fitness, exercise, and AMS.

86

87 Some authors further advocate that hypoxic sensitivity is an important physiological factor determining altitude
88 exercise performance (Schoene et al., 1984) and illness risk (Richalet & Canouï-Poitaine, 2014). This has led to
89 the development of various resting and exercising hypoxic sensitivity tests to predict altitude exercise performance
90 and illness susceptibility (Lazio et al., 2010; Rathat et al., 1992). However these are not routinely implemented,
91 perhaps due to a lack of clinically relevant discrimination at an individual level (Bärtsch, 2014), or due to their
92 complexity and requirement for specialist equipment including a method to simulate a high-altitude environment.

93

94 In summary, the relationships of fitness and hypoxic sensitivity with sense of effort during submaximal exercise
95 and AMS at altitude are complex and unknown. Determining these relationships is necessary before fitness or
96 hypoxic sensitivity tests can be recommended to appraise individuals' readiness for altitude. Therefore, the first
97 aim of this study was to explain the relationship of sea-level fitness with submaximal exercise responses (sense
98 of effort during submaximal exercise and step rate during perceptually-regulated exercise) and AMS during
99 chronic altitude exposure. The second aim was to determine the utility of sea-level fitness (as assessed by $\dot{V}O_{2max}$,
100 ventilatory threshold, economy, and a simple questionnaire-based estimation of $\dot{V}O_{2max}$) and hypoxic exercise
101 testing to predict submaximal exercise responses and AMS at altitude. Finally we aimed to determine whether
102 physiological responses to hypoxia could explain the relationship between fitness and submaximal exercise
103 responses. To this end, we assessed sea-level fitness and acute physiological responses to hypoxia ($FiO_2 = 0.112$;
104 equivalent 5000 m) one month before a three-week trek to the Manaslu Circuit in the Nepal Himalaya. On the
105 trek, sense of effort during submaximal exercise was assessed during simulated and actual trekking activities and
106 physiological responses to chronic hypoxia were assessed at Base Camp (5058 m). AMS was assessed daily. We
107 hypothesized that high sea-level fitness would be associated with submaximal exercise responses (lower sense of
108 effort during submaximal exercise and higher step rate during perceptually-regulated exercise) at altitude, without
109 increased AMS. Second, we hypothesized that sea-level and hypoxic exercise tests would be significant predictors
110 of submaximal exercise responses. Third, we hypothesised that hypoxic exercise tests would be significant
111 predictors of AMS at altitude.

112 **Materials and Methods**

113 *Participants and study design*

114 Forty-four trekkers, 26 men and 18 women (mean (SD): age 39 (14) yr, body mass 69.0 (14.5) kg, height 172 (10)
115 cm) from the MEDEX Manaslu trek volunteered for this observational cohort study. All participants were
116 lowlanders, with an altitude of residence below 500 m. Forty-one participants (93%) had previously travelled to
117 high altitude (>1500 m), and of these 41 participants, 32 (78%) reported previous AMS, one (2%) had a history
118 of HACE, and none (0%) had a history of HAPE. Nine (20%) participants had a history of migraine (confirmed
119 by a physician), three (7%) were smokers, and average alcohol consumption was 81.0 (63.4) g·week⁻¹. Self-report
120 physical activity was assessed on a scale developed by Jackson and colleagues (1990), which ranged from 0 -
121 Avoids walking or exercise (e.g. always uses elevators, drives whenever possible instead of walking), to 7 - Runs
122 more than 10 miles per week or spends more than 3 hours per week in comparable physical activity. Self-report
123 physical activity ranged from 1-7, with mean of 5 (2), and $\dot{V}O_{2max}$, ranged from 29 to 62 with mean 45 (8) mL·min⁻¹·
124 kg⁻¹. The study received ethical approval from the North West Wales Research Ethics Committee and was
125 conducted in accordance with the Declaration of Helsinki 2008. All volunteers provided written informed consent.
126 Data were collected between February and April 2015. An overview of the study is depicted in Figure 1.

127

128 *Pre-trek experimental procedures*

129 One month before the trek participants completed assessments of sea-level fitness and hypoxic sensitivity.
130 Participants were asked to refrain from exhaustive exercise, caffeine and alcohol for twelve hours before all tests.
131
132 Sea-level fitness ($\dot{V}O_{2max}$, ventilatory threshold, and economy) was determined during a walking test to exhaustion
133 on a motorized treadmill (H-P-Cosmos, Sports & Medical GmbH; Nussdorf) with simultaneous gas analysis
134 (Cortex Metalyzer, Biophysik GmbH; Leipzig). Participants wore a weighted rucksack (15 kg for men and 12.5
135 kg for women). The test consisted of 5 km·h⁻¹ walking with a ramped increase in gradient from 5% to 25% over
136 18 minutes (1.11 %·min⁻¹), followed by a ramped increase in speed (0.67 km·h⁻¹·min⁻¹) thereafter. Rating of
137 perceived exertion (RPE) was recorded each minute of the test using the Borg CR100 (Borg & Borg, 2001).
138 $\dot{V}O_{2max}$ was identified by two or more of the following criteria (Pescatello et al., 2013): volitional fatigue, a plateau
139 in $\dot{V}O_2$ despite an increase in workload, respiratory exchange ratio ≥ 1.15 , heart rate $\geq 95\%$ age-predicted heart
140 rate maximum (220-age). $\dot{V}O_{2max}$ was also predicted using the equation provided in Matthews *et al.* (1999).

141 Ventilatory threshold was determined using the method outlined by Gaskill *et al.* (2001) and economy as $\dot{V}O_2$ (in
142 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$) at a gradient of 6%.

143

144 Hypoxic sensitivity was determined using a modified version of the Richalet test (Richalet et al., 2012; Canouï-
145 Poitrine et al., 2014), with the exercise modality changed from cycling on an ergometer to stepping in time to a
146 metronome, and the FiO_2 chosen to match the specific demands of the expedition. Participants completed fixed-
147 workload step tests in normoxia and hypoxia ($\text{FiO}_2 = 0.112$; 5000 m). Step tests were conducted in an
148 environmental chamber (Hypoxico Inc; NY), separated by 1.5 to 3 hours. Each step test included: 4 min 30 s of
149 seated rest and 4 min 30 s of exercise. During the exercise participants wore a 7 kg rucksack whilst stepping at 24
150 steps $\cdot\text{min}^{-1}$ on a 21 cm step. Ventilation ($\dot{V}E$) was determined by collection of expired gases (Douglas bag system,
151 Cranlea Ltd; Birmingham) for the final minute of exercise, and oxygen saturation (SpO_2) and heart rate were
152 measured by a pulse oximeter (9550 OnyxII, Nonin Medical Inc; Minnesota) and a heart rate monitor (RS800CX;
153 Polar UK; Warwick), and recorded in the final 30s of exercise. RPE was recorded in the final 30s for
154 familiarization.

155

156 Hypoxic sensitivity was determined using equations described previously (Canouï-Poitrine et al., 2014; Richalet
157 et al., 2012):

158 Desaturation during exercise: $\Delta\text{SpO}_{2e} (\%) = \text{SpO}_{2\text{EH}} - \text{SpO}_{2\text{EN}}$

159 Hypoxic cardiac response: $\text{HCR}_e (\text{bpm}\cdot\%^{-1}) = (\text{HR}_{\text{EH}} - \text{HR}_{\text{EN}}) / \Delta\text{SpO}_{2e}$

160 Hypoxic ventilatory response: $\text{HVR}_e (\text{L}\cdot\text{min}^{-1}\cdot\text{kg}^{-1}) = (\dot{V}E_{\text{EH}} - \dot{V}E_{\text{EN}}) / \Delta\text{SpO}_{2e} / \text{BM} \times 100$

161 Where SpO_2 , Oxygen saturation; HR, Heart rate; $\dot{V}E$, Minute ventilation ($\text{L}\cdot\text{min}$); EH, Exercise in hypoxia
162 (baseline); EN, Exercise in normoxia (baseline); BM, Body mass (kg).

163

164 *Trek experimental procedures*

165 Participants arrived in Kathmandu (1300 m) and were transported to Arughat (518 m) by bus to begin the trek.
166 The 44 participants travelled in five groups of mixed age, sex and sea-level fitness. Each group completed the
167 Manaslu trekking itinerary, and therefore the same altitude profile, an ascent profile that is typical of other high-
168 altitude treks (e.g. Dhaulagiri circuit). The ascent profile included four days trekking above 3000 m, with two
169 days of ~ 300 m ascent per day and two days with ~ 600 m ascent per day. They all completed the ascent to Base
170 Camp (5085m) in 15-17 days trekking. This variation in ascent was due to limited overnight accommodation at

171 some locations. Participants abstained from prophylactic medication and all other medications taken were
 172 recorded but not restricted.

173

174 Trekking Demands

175 On each day of the trek physical and physiological demands were assessed, but for the benefit of clarity only data
 176 from the final day of trekking on ascent to Base Camp are presented. To assess physical demands, after breakfast,
 177 body mass was assessed by weighing participants in base layers using mechanical scales (Salter Housewares,
 178 Kent; UK); loaded weight was assessed by weighing participants in full trekking attire including boots and
 179 rucksack; and external weight was calculated by subtracting the body mass from the loaded mass. Participants
 180 were able to walk at their chosen pace and the start and end times of each individual's trekking day was recorded.
 181 The trekking route was tracked using a global satellite positioning system (GPS; inReach SE, Delorme, Yarmouth;
 182 ME). Energy expenditure (EE) was then calculated using an equation validated previously (Pandolf et al., 1977).
 183 Relative trekking intensity for the ascent to Base Camp was calculated as:

$$184 \quad \text{Relative trekking intensity} = \text{RPE}_{\text{ascent}} / \text{EE} (\text{kJ}^{-1} \cdot \text{min}^{-1})$$

185 Where $\text{RPE}_{\text{ascent}}$, Session RPE (Fanchini et al., 2016) recorded 30 minutes after trekkers completed 6.3 km walking
 186 exercise from 4472 to 5085 m; EE, Energy expenditure (calculated from the equation provided in Pandolf et al.,
 187 1977).

188 To assess physiological demands, participants wore heart rate monitors (RS800CX, Polar, Warwick; UK)
 189 throughout the day's trek, and heart rate was averaged for the trekking session.

190

191 Sense of effort during submaximal exercise

192 To determine the relationship between sea-level fitness and sense of effort during submaximal exercise at altitude,
 193 we assessed sense of effort during submaximal exercise by recording RPE. RPE was recorded using the Borg
 194 CR100 (Borg & Borg, 2001) which asks participants to rate the intensity of the exercise sensation using numbers
 195 from 0-100+ and verbal descriptors (e.g. "moderate", equivalent to 25). Extensive evidence supports the use of
 196 RPE as a valid and appropriate method to record sense of effort and perceptual responses to exercise (Eston,
 197 2012). Sense of effort was determined from session RPE (Fanchini et al., 2016) recorded 30 minutes after trekkers
 198 completed 6.3 km walking exercise from 4472 to 5085 m ($\text{RPE}_{\text{ascent}}$). Session RPE has been validated as a
 199 quantitative measure of exercise load (Foster et al., 2001). Participants also completed the Brunel Mood Scale
 200 (BRUMS; Terry et al., 1999) on arrival at Base Camp to determine the psychological effects of the exercise,

201 including self-reported fatigue. To further determine sense of effort during submaximal exercise at altitude, all
 202 participants completed the fixed-workload step test the day after arriving at 5085 m (day 16-18 of the expedition),
 203 breathing altitude ambient air (549 (1) mbar) but otherwise using the same protocol as completed at sea level.
 204 Specifically, participants wore a 7 kg rucksack whilst stepping at 24 steps·min⁻¹ on a 21 cm step. The primary
 205 outcome variable for this test was RPE at 4 min 30 s of stepping (RPE_{fixed}). In addition, SpO₂, heart rate, and
 206 minute ventilation ($\dot{V}E$) were determined using methods as described for the sea-level step tests. Exercise
 207 ventilation reserve and ventilatory efficiency were calculated using equations adapted from Bernardi *et al.* (2006):

$$208 \quad \text{Exercise ventilation reserve (\%)} = ((\dot{V}E_{\text{max}} - \dot{V}E_{\text{alt}}) / \dot{V}E_{\text{max}}) \times 100$$

$$209 \quad \text{Ventilatory efficiency (\%·L}^{-1}\text{·min}^{-1}\text{)} = \text{SpO}_2 / \dot{V}E_{\text{alt}}$$

210 Where $\dot{V}E_{\text{max}}$, Maximal exercising ventilation from sea-level $\dot{V}O_{2\text{max}}$ test; $\dot{V}E_{\text{alt}}$, Exercising ventilation during
 211 fixed-workload step test at altitude; SpO₂, Oxygen saturation during fixed-workload step test at altitude.

212 Chronic change in heart rate was calculated as:

$$213 \quad \text{Chronic change in heart rate (bpm)} = \text{HR}_{\text{EN}} - \text{HR}_{\text{EA}}$$

214 Where HR_{EN}, Heart rate during fixed-workload exercise in normoxia (baseline); HR_{EA}, Heart rate during fixed-
 215 workload step test at altitude (Base Camp, 5085 m).

216
 217 Immediately after the fixed-workload step test, submaximal exercise capacity was determined by assessing step
 218 rate during perceptually-regulated exercise (STEP_{RPE35}). This perceptually-regulated step rate test provided
 219 assessment of exercise production at a relative workload. Clamping RPE to produce self-paced exercise in this
 220 manner is a validated tool for determining functional and endurance exercise capacity (Coquart, Tabben, Farooq,
 221 Tourny, & Eston, 2016; Eston, 2012). Each participant was asked to complete stepping exercise for four minutes
 222 at a step rate that was equivalent to an RPE of 35 (described on the RPE scale as “somewhat strong”). An RPE of
 223 35 was chosen because it has been previously reported as the typical sensed effort of mountain walkers and
 224 workers (Ainslie et al., 2002; Callender et al., 2012). During this exercise participants were free to alter their step
 225 rate. In the final minute step rate (STEP_{RPE35}), HR, and SpO₂ were recorded. For the purpose of familiarization,
 226 participants completed three practice trials (two in normoxia, one in acute hypoxia) that included familiarization
 227 with the CR100 scale and completing the entire stepping exercise. In a separate pilot study ($n = 6$), we showed
 228 that with three practice sessions this perceptually-regulated step rate test has good reliability, with intraclass
 229 correlation coefficient of 0.94, coefficient of variation of 2.4%, and limits of agreement bias and 95% confidence
 230 intervals (lower limit; upper limit) of 1.0 (-1.5; 3.5) steps·min⁻¹. The perceptually-regulated step rate test also has

231 good face validity, with trekkers and expedition leaders reporting that it was representative of their normal
232 trekking pace.

233

234 Both step tests were repeated two days later (on the third day at Base Camp), in a sub-sample of 21 participants.

235 The sub-sample was representative of whole study sample, with no difference in age, height, body mass, $\dot{V}O_{2max}$,
236 or sex ratio (all $p \geq 0.5$).

237

238 **Acute Mountain Sickness (AMS)**

239 Each morning on the trek, participants recorded AMS symptoms using the Lake Louise Score (LLS; Roach et al.,

240 1993) under the supervision of a researcher. From these symptoms clinically-defined AMS was identified when

241 the participant was higher than 2500 m, LLS total exceeded three or more, and headache with at least one other

242 symptom was present. An individual with AMS at any point over the expedition was classified as AMS susceptible

243 (AMS+); individuals without AMS over the expedition were classified as AMS resistant (AMS-). Percentage of

244 days with AMS and peak LLS were also calculated.

245

246 *Statistical analysis*

247 The primary independent variable of fitness was sea-level $\dot{V}O_{2max}$ (extensive exploratory analyses revealed no

248 additional benefit of the fitness variables ventilatory threshold or economy). The primary outcome variable of

249 sense of effort during submaximal exercise was RPE recorded during the fixed workload test performed at high

250 altitude (RPE_{fixed}).

251

252 To determine the relationships between sea-level fitness with i) submaximal exercise responses at altitude

253 (RPE_{fixed} , RPE_{ascent} , and $STEP_{RPE35}$); ii) acute physiological responses to hypoxia (HVRe, HCR_e, ΔSpO_2e); iii)

254 chronic physiological responses to hypoxia (exercise ventilation reserve, ventilatory efficiency, chronic change in

255 heart rate, and SpO_2 at altitude); iv) the percentage of trekking days with AMS, and peak AMS score, Pearson's

256 correlations were used. For all correlational analyses, the strength of a relationship was determined by the r value.

257

258 To determine whether hypoxic exercise testing significantly adds to sea-level fitness testing to predict sense of

259 effort during submaximal exercise at altitude and AMS, hierarchical regression was used and r^2 change was

260 reported. To determine the utility of $\dot{V}O_{2\max}$ and hypoxic sensitivity for predicting AMS susceptibility, Receiver
261 Operating Characteristic curves were calculated and comparison of area under the curves (AUC) was completed.

262

263 To investigate whether classical physiological responses to hypoxia mechanistically explain the relationship
264 between fitness and sense of effort during submaximal exercise at altitude, ventilatory and cardiac responses to
265 acute normobaric hypoxia (HVRe, HCR_e) and chronic high-altitude exposure (chronic change in heart rate,
266 exercise ventilation reserve, ventilatory efficiency), were investigated using a mediation analysis. Analysis was
267 completed using the SPSS macro PROCESS (Hayes, 2013) with 5000 bootstrap samples. An indirect effect
268 (evidence of a mechanistic explanation) was deemed significant if the upper and lower 95% Confidence Interval
269 limits of the size of the indirect path did not include zero.

270

271 A sample size estimation for the correlation between sea-level $\dot{V}O_{2\max}$ and RPE_{fixed} indicated that 37 participants
272 would be needed to produce a 90% chance of obtaining statistical significance at the 0.05 level for a minimum
273 important effect size of $r = 0.5$ (Bland, 2015).

274

275 Diagnostic accuracy analyses were completed using MedCalc version 15.8 (MedCalc Software, Ostend;
276 Belgium), all other analyses were completed using SPSS version 22 (IBM Corp, Armonk; NY). Statistical
277 significance was set at $p < 0.05$ for all analyses.

278 **Results**279 *Trekking demands*

280 Physiological and perceptual responses to the submaximal step tests are shown in Table 1. Physical, physiological
 281 and perceptual demands of the final day's trek into Base Camp are shown in Table 2. The trekkers took 262 (52)
 282 min to complete the 6.3 km trek with 613 m altitude gain from 4472 to 5085 m.

283

284 *Sea-level fitness and submaximal exercise responses at altitude*

285 Greater sea-level fitness was associated with lower sense of effort (RPE_{fixed} and RPE_{ascent}) and higher step rate
 286 ($STEP_{RPE35}$) at altitude (Figure 2). Ascent time to Base Camp was not related to fitness ($r = -0.11$; $p = 0.48$; Table
 287 2). Therefore, fitter persons ascended with less sensed effort (lower RPE) but a similar walking speed compared
 288 to their less-fit counterparts. Lower RPE_{ascent} was also associated with less negative mood (total mood disturbance;
 289 $r = 0.50$; $p = 0.001$), specifically less fatigue ($r = 0.57$; $p < 0.001$), tension ($r = 0.40$; $p = 0.01$), and confusion (r
 290 $= 0.35$; $p = 0.03$). Lower RPE_{ascent} was also associated with increased vigor, albeit weakly ($r = -0.28$; $p = 0.09$).
 291 Lower sense of effort and higher step rate in fitter individuals did not come at the cost of worse arterial oxygen
 292 saturation: sea-level $\dot{V}O_{2\text{max}}$ was not related to SpO_2 during the fixed-workload ($r = 0.07$; $p = 0.67$) or perceptually-
 293 regulated ($r = 0.16$; $p = 0.33$) step tests at altitude.

294

295 *Acute Mountain Sickness (AMS)*

296 Twenty-five participants (61%) had clinically-defined AMS at least once during the expedition. Of those with
 297 AMS, it lasted 4 (2) days. The highest incidence of AMS for a given day was 47%, occurring on day one at Base
 298 Camp (5085 m). AMS was not related to any sea-level assessment variables. None of sea-level fitness, hypoxic
 299 sensitivity or physiological responses to chronic hypoxia was related to AMS susceptibility, percentage of days
 300 with AMS, or peak LLS ($r = 0.05$ to 0.26 ; $p = 0.12$ to 0.91 ; Figure 5). AUC were all below 0.70, indicating poor
 301 diagnostic accuracy for all methods. Two (5%) participants took acetazolamide in the treatment of AMS for one
 302 and eight days each, while 30 (68%) participants took some form of analgesic medication, with 2.2 (1.9) days
 303 spent on analgesics across the whole sample. There was no relationship between fitness and number of days on
 304 acetazolamide ($r = -0.08$; $p = 0.60$) or analgesic medications ($r = 0.20$; $p = 0.22$).

305

306 *Acclimatization, sea-level fitness, and submaximal exercise responses at altitude*

307 In a sub-sample, the step tests were repeated on day three after participants' AMS symptoms had reduced (LLS
 308 decreased from 3.3 (2.5) to 2.1 (2.1); $p = 0.06$), and sense of effort during submaximal exercise had decreased
 309 across the sub-sample (RPE_{fixed} decreased from 57 (31) on day one to 44 (19) on day three; $p < 0.01$). Submaximal
 310 step rate during perceptually-regulated exercise increased ($STEP_{RPE35}$ increased from 26 (6) on day one to 28 (5)
 311 on day three; $p < 0.01$). These adaptive changes (representative of enhanced acclimatization) did not affect the
 312 relationship between fitness and submaximal exercise responses, which were consistent with those observed on
 313 day one. Greater sea-level fitness was associated with lower RPE_{fixed} on day three ($r = -0.75$; $p < 0.001$), and
 314 greater $STEP_{RPE35}$ on day three ($r = 0.70$; $p = 0.001$), and was not related to SpO_2 during the fixed-workload ($r =$
 315 0.26 ; $p = 0.28$). Greater sea-level fitness tended to be associated with greater SpO_2 during the perceptually-
 316 regulated step test ($r = 0.43$; $p = 0.058$), despite participants producing a higher absolute workload.

317

318 *Physiological Mechanisms*

319 Hypoxic sensitivity and submaximal exercise responses at altitude

320 Individuals with lower HVRe (Figure 3A) and higher HCRE (Figure 3B) had lower sense of effort compared to
 321 their counterparts. HVRe was positively related to RPE_{fixed} ($r = 0.38$; $p = 0.02$), and negatively related to $STEP_{RPE35}$
 322 ($r = -0.39$; $p = 0.02$). There was a weak negative relationship between HCRE and RPE_{fixed} , ($r = -0.31$; $p = 0.07$),
 323 but HCRE was not related to $STEP_{RPE35}$ ($r = 0.19$; $p = 0.26$). ΔSpO_2e was not related to any measure of sense of
 324 effort at altitude ($r = 0.23$ to 0.25 ; $p = 0.15$ to 0.17).

325

326 Physiological responses to chronic high altitude

327 Individuals with less ventilatory stress at altitude (Figure 3C) and a greater cardiac response to chronic high
 328 altitude (Figure 3D) had lower sense of effort compared to their counterparts. Greater exercise ventilation reserve
 329 was associated with lower RPE_{fixed} ($r = -0.61$; $p < 0.001$), and superior $STEP_{RPE35}$ ($r = 0.44$; $p = 0.01$). Greater
 330 ventilatory efficiency was associated with lower RPE_{fixed} ($r = -0.44$; $p = 0.01$), and superior $STEP_{RPE35}$ ($r = 0.44$;
 331 $p < 0.001$). A larger chronic change in heart rate was associated with lower RPE_{fixed} ($r = -0.49$; $p < 0.01$), and
 332 superior $STEP_{RPE35}$ ($r = 0.41$; $p = 0.01$).

333

334 Mediation Analysis

335 Cardiac parameters tended to explain (*negatively* mediate) the relationship between sea-level fitness and
 336 submaximal exercise sense of effort at altitude (Table 3). Hypoxic exercise ventilation reserve also tended to

337 explain (*positively* mediate) the relationship between sea-level fitness and submaximal exercise sense of effort at
338 altitude. In contrast, exercise ventilation reserve and ventilatory efficiency did not mediate the relationship
339 between sea-level fitness and sense of effort during submaximal exercise at altitude.

340

341 *Utility of variables to predict submaximal exercise responses at altitude*

342 Matthews and colleagues' equation (1999) was used to calculate a simple questionnaire-based estimation of
343 $\dot{V}O_{2\max}$. The predicted values were closely related to the measured values from the maximal exercise test ($r =$
344 0.80 ; $p < 0.001$). Furthermore, this simple fitness assessment negatively predicted sense of effort during
345 submaximal exercise at altitude (RPE_{fixed}), albeit the prediction was significantly improved with the addition of
346 laboratory-assessed $\dot{V}O_{2\max}$ (see table 4, *analysis 1*).

347

348 $\dot{V}O_{2\max}$ alone was sufficient to predict submaximal exercise responses at altitude, with hypoxic exercise testing
349 providing no additional benefit. Specifically, hypoxic sensitivity did not account for any additional variance than
350 laboratory $\dot{V}O_{2\max}$ when predicting sense of effort for RPE_{fixed} ($r^2\text{change} = 0.07$; $p = 0.22$; see table 4, *analysis 2*),
351 RPE_{ascent} ($r^2\text{change} = 0.05$; $p = 0.52$), or $STEP_{RPE35}$ ($r^2\text{change} = 0.06$; $p = 0.33$). In addition, hypoxic sensitivity
352 did not account for any additional variance than questionnaire-based estimation of $\dot{V}O_{2\max}$ when predicting
353 submaximal exercise responses for RPE_{fixed} ($r^2\text{change} = 0.09$; $p = 0.18$), RPE_{ascent} ($r^2\text{change} = 0.06$; $p = 0.48$), or
354 $STEP_{RPE35}$ ($r^2\text{change} = 0.09$; $p = 0.26$).

355 Discussion

356 The primary findings of this study were that greater sea-level fitness is associated with lower sense of effort and
357 higher step rate during perceptually-regulated exercise, but not worse AMS or arterial desaturation. We were able
358 to demonstrate that these relationships are robust, and are not affected by acclimatization. Consequently, simple
359 sea-level fitness tests predicted sense of effort during submaximal exercise at altitude, and no additional screening
360 information was gained from hypoxic sensitivity testing.

361

362 Greater sea-level fitness was associated with lower sense of effort during an arduous trekking day, lower sense of
363 effort during submaximal exercise, and a superior step rate during perceptually-regulated exercise (at the typical
364 chosen effort of mountain walkers and workers) at altitude. Importantly, lower sense of effort during trekking was
365 also associated with better mood, including less fatigue, tension and confusion. High fitness may therefore also
366 protect against the major risk factors of musculoskeletal pain (Jakobsen et al., 2015), injury (Burtscher et al.,
367 2015), and mortality (Firth et al., 2008), and enhance productivity in those travelling to altitude for work and
368 leisure. Lower sense of effort and better mood indicates trekkers more comfortably met the demands of the trek,
369 suggesting high fitness may also protect against summit failure and improve expedition enjoyment. Consequently,
370 this study provides the first empirical evidence that simple sea-level fitness assessments may be useful to aid
371 preparations for high-altitude travel. Further, it provides preliminary evidence to support the recommendation that
372 individuals should complete cardiorespiratory training to improve aerobic fitness before high-altitude travel
373 (Bärtsch & Swenson, 2013). Aerobic training can improve $\dot{V}O_{2max}$ by ~20%, although the response varies between
374 0-50%, depending on genetics, age, initial fitness, and the exact training type (Bacon et al., 2013; Bouchard et al.,
375 2011; Milanović et al., 2015). Aerobic fitness is therefore a factor that can be modified to the substantial benefit
376 of those that travel to altitude for work or leisure. As higher fitness was not associated with greater AMS or arterial
377 desaturation, we recommend increasing fitness as much as possible before altitude travel. But of course increased
378 fitness should not be used to ascend more quickly than current guidelines, which would increase altitude illness
379 risk.

380

381 The most useful variable to predict sense of effort during submaximal exercise at altitude was $\dot{V}O_{2max}$ as
382 determined by laboratory maximal exercise testing. Even sea-level fitness ($\dot{V}O_{2max}$) estimated by a short
383 questionnaire collecting simple demographic information also provided a strong prediction of sense of effort at
384 altitude. Since the addition of hypoxic sensitivity variables did not improve the prediction of sense of effort during

385 submaximal exercise at altitude, it must be concluded that technically demanding hypoxic exercise testing has no
386 additional benefit beyond simple fitness testing for screening individuals' readiness to perform at altitude. It must
387 be acknowledged that this study used a modified version of Richalet's proposed test. However research by
388 Richalet's group showed exercise intensity and FiO_2 do not affect HVR or HCR obtained from the test (Lhuissier
389 et al., 2012). Given the ease of administration (no arduous exercise or specialist equipment required), this simple
390 questionnaire-based assessment of sea-level fitness provides medical and outdoor practitioners with a useful tool
391 to help patients and clients prepare for altitude travel.

392
393 Importantly, lower sense of effort during submaximal exercise in fitter individuals did not come at the cost of
394 worse altitude illness. Increased sea-level fitness was not a risk factor for AMS at altitude when ascent rate and
395 trekking energy expenditure were similar in individuals. Additionally, in this study, all participants followed the
396 same ascent profile. In contrast, previous studies to show a positive relationship between fitness and AMS have
397 measured across multiple expeditions without accounting for differences in ascent rate (Karinen et al., 2010;
398 Richalet et al., 2012). This suggests that any observed relationship between fitness and AMS is likely an artefact
399 of behavioural differences. That is, fitter individuals likely ascend faster than their less-fit counterparts and it is
400 this increased ascent rate that is responsible for their increased AMS (Schneider et al., 2002).

401
402 Physiological responses provided some explanation for the lower sense of effort during submaximal exercise in
403 fitter individuals at altitude. Contrary to previous studies with acute hypoxic exposures, high-fit individuals had
404 similar or better SpO_2 than less-fit individuals during exercise tests completed at the high-altitude base camp on
405 day one and three, respectively. This was accompanied by an elevated heart rate response and a lower ventilatory
406 response to acute hypoxia and chronic altitude exposure. Thus, at steady state submaximal exercise (typical of
407 that required during trekking), the lung was able to accommodate the increased cardiac output without
408 compromising pulmonary gas exchange. It is not clear whether the lower ventilatory response in high-fit
409 individuals is due to decreased chemosensitivity or a more efficient ventilatory system, but whatever the cause
410 this response can be considered adaptive as it was associated with lower sense of effort during submaximal
411 exercise. In support of this interpretation, hyperventilation is associated with increased work of breathing and
412 dyspnea (Amann et al., 2007; Babb et al., 2008), which is a major determinant of RPE (Bernhardt et al., 2013).
413 Increased work of breathing is particularly detrimental at altitude as it elevates peripheral and central fatigue

414 (Ainslie & Ogoh, 2010; Amann, 2012) by reducing locomotor and cerebral blood flow that occur to maintain
415 respiratory muscle demands (Amann et al., 2007).

416

417 *Limitations*

418 This study included no altitude measure of maximal exercise capacity, such as $\dot{V}O_{2max}$, time to exhaustion, or time
419 trial tests. However, RPE during submaximal exercise is closely related to maximal exercise capacity (Eston,
420 2012; Coquart et al., 2014; Coquart et al., 2016). In addition, the assessment of maximal exercise capacity has
421 limited functional relevance to the assessment of trekking and other submaximal work and exercise commonly
422 performed at altitude. Due to their crucial role in fatigue (a major risk factor for mortality on high-altitude treks),
423 we believe sense of effort and perceptually-regulated exercise are the best methods available to assess trekking
424 exercise. This study provides preliminary evidence of the physiological mechanisms likely to explain the
425 relationship between sea-level fitness and sense of effort during submaximal exercise at altitude. Future studies
426 that experimentally manipulate fitness via training or other methods are required to confirm the importance of
427 cardiorespiratory adaptations for submaximal exercise and fatigue at high altitude.

428

429 **Conclusion**

430 Understanding the determinants of exercise and illness at altitude is important to better prepare those who travel
431 to high altitude (Puthon et al., 2015). This study indicates that greater sea-level fitness is related to lower sense of
432 effort during submaximal exercise at altitude and better mood (less fatigue, tension and confusion). Importantly,
433 the lower sense of effort during submaximal exercise in high-fit individuals did not come at the cost of worse
434 AMS or greater arterial oxygen destauration. This study provides the first empirical evidence to support recent
435 recommendations that people might complete sea-level aerobic fitness training before high-altitude travel (Bärtsch
436 & Swenson, 2013; Burtscher et al., 2015). Indeed, our data suggest low-fit persons may improve their trekking
437 experience by increasing sea level fitness because it is associated with less effort and better mood during trekking
438 at altiitude. The study also indicates that a sea-level fitness assessment could be used to aid preparation for high-
439 altitude travel by enabling better aerobic exercise prescription and identifying those people who might might
440 benefit most from the aerobic training. Given that fatigue and confusion are major risk factors for injury and
441 fatality at altitude, sea-level fitness assessment and exercise training should be considered as part of preparations
442 for high-altitude travel.

443

444 **Disclosure statement**

445 The authors of this article have no conflicts of interests to disclose.

446

447 **Acknowledgements**

448 MEDEX2015 research expedition comprised of many persons who without their help the study would not have
449 been possible. In particular, we would like to thank the expedition organizers and volunteers who participated in
450 this research, and also Kevin Williams, Jason Edwards, and Denzil Broadhurst for their technical assistance.

451

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- 563
- 564

Table 1. Physiological and perceptual responses to step tests.

	Fixed-workload step test			Perceptually-regulated step test		
		Acute	Chronic		Acute	Chronic
	Sea level	normobaric hypoxia	high altitude	Sea level ¹	normobaric hypoxia ¹	high altitude
RPE	20 (7)	30 (11)	46 (23)	35 ²	35 ²	35 ²
Step rate	24 ²	24 ²	24 ²	36 (7)	30 (5)	27 (6)
Heart rate (bpm)	116 (16)	143 (19)	132 (19)	145 (23)	157 (20)	135 (15)
SpO ₂ (%)	97 (3)	70 (5)	75 (5)	96 (5)	70 (4)	72 (4)
Ventilation (L/min)	33 (7)	47 (11)	40 (10)	-	-	-

N = 44. Values are mean (SD). ¹Conducted as familiarization trials, but data included here for completeness; ²By design, values are the same in all participants for this variable.

565

566

Table 2. Summary of trekking demands and relationship to sea level $\dot{V}O_{2max}$.

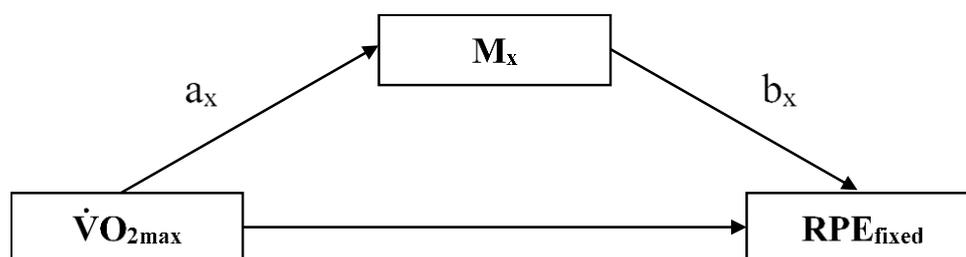
Trekking Variable	Ascent to Base Camp	Relationship to $\dot{V}O_{2max}$	
		r	p
Walking speed (km·h ⁻¹)	1.5 (0.3)	0.22	0.17
External load (kg)	11.1 (2.4)	0.15	0.37
Energy expenditure (kJ)	2298 (584)	-0.21	0.20
Heart rate (bpm)	126 (14)	-0.03	0.86
Session RPE	51 (20)	-0.43**	0.005
Relative exertion (RPE·kJ ⁻¹ ·min ⁻¹)	5.9 (2.6)	-0.35*	0.03

N = 44. Values are mean (SD). *p < 0.05; **p < 0.01.

567

568

569 **Table 3. Mediation analysis summary for acute normobaric hypoxia and chronic high altitude cardiac and**
 570 **ventilatory parameters.**



Variable (M_x)	a_x ($\dot{V}O_{2max} \rightarrow M_x$)	b_x ($M_x \rightarrow RPE_{fixed}$)	Indirect effect (ab_x)
<i>Acute normobaric hypoxia</i>			
HVRe	-0.27 (-0.58; 0.04)	0.21 (-0.07; 0.49)	-0.06 (-0.25; 0.01)
HCRE	0.37 (0.06; 0.69)*	-0.05 (-0.34; 0.23)	-0.02 (-0.18; 0.08)
<i>Chronic high altitude exposure</i>			
Exercise ventilation reserve	0.85 (0.60; 1.10)**	-0.29 (-0.72; 0.13)	-0.25 (-0.55; 0.33)
Ventilatory efficiency	0.59 (0.25; 0.93)**	-0.14 (-0.46; 0.18)	-0.08 (-0.28; 0.11)
Chronic change in heart rate	0.42 (0.12; 0.72)*	-0.23 (-0.51; 0.05)	-0.10 (-0.32; 0.00)

571 If a variable M_x explains (mediates) the relationship between $\dot{V}O_{2max}$ and RPE_{fixed} , the indirect effect (ab_x) should
 572 not span zero. The values suggest that HCRE and chronic change in heart rate tended or did significantly explain
 573 (*positively* mediate) the relationship between $\dot{V}O_{2max}$ and RPE_{fixed} . In contrast HVRe tended to explain (*negatively*
 574 mediate) the relationship between $\dot{V}O_{2max}$ and RPE_{fixed} . Values are standardized regression coefficients and 95%
 575 confidence intervals (lower limit; upper limit) for direct effects of $\dot{V}O_{2max}$ on mediators (a_x), direct effects of
 576 mediators on RPE_{fixed} (b_x), and indirect effects of $\dot{V}O_{2max}$ on RPE_{fixed} through mediators (ab_x). * $p < 0.05$; ** $p <$
 577 0.01.

578

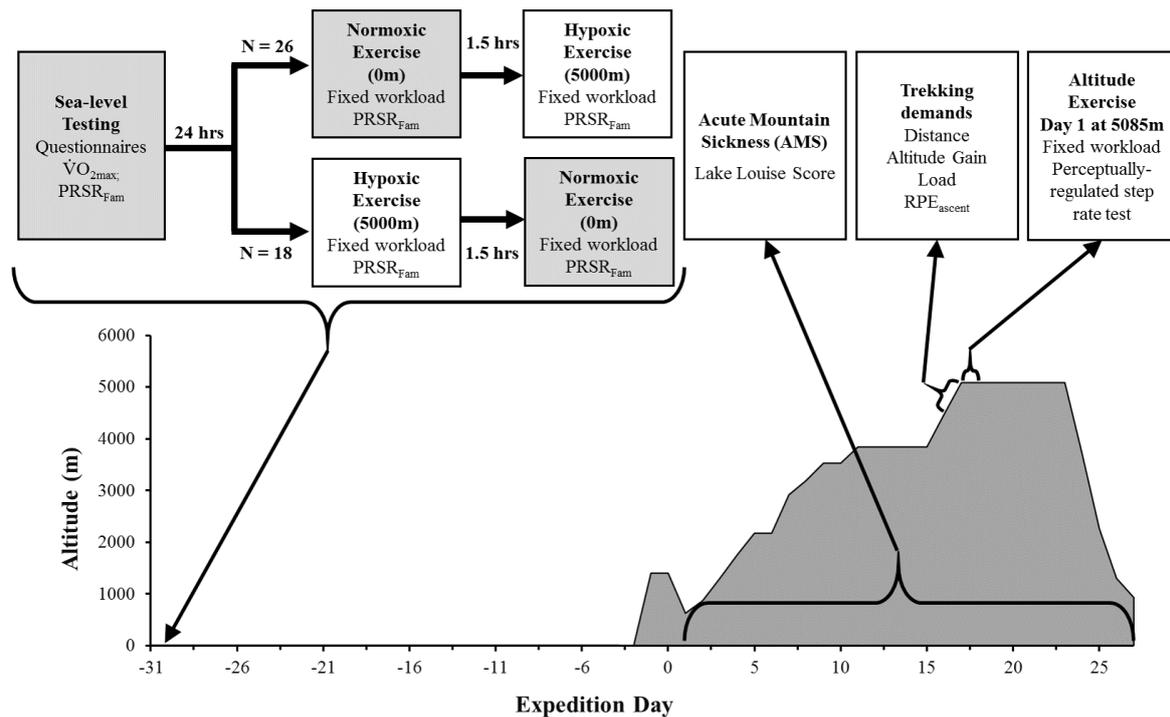
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580 **Table 4. Summary of hierarchical regression analyses for variables predicting sense of effort during**
 581 **submaximal exercise at altitude (RPE_{fixed}).**

Model	Variable	B	SE B	β	r^2	p	r^2 change	p for r^2 change
<i>Analysis 1</i>								
1	Questionnaire $\dot{V}O_{2max}$	-1.85	0.40	-0.62***	0.39	<0.001		
2	Questionnaire $\dot{V}O_{2max}$	-0.61	0.59	-0.21	0.47	<0.001		
	Laboratory $\dot{V}O_{2max}$	-1.49	0.56	-0.53*			0.11**	0.01
<i>Analysis 2</i>								
1	Laboratory $\dot{V}O_{2max}$	-1.91	0.35	-0.69***	0.47	<0.001		
2	Laboratory $\dot{V}O_{2max}$	-1.55	0.41	-0.56**	0.54	<0.001		
	HVRe	9.81	8.00	0.18			0.07	0.22
	HCRE	-8.80	7.64	-0.17				
	ΔSpO_2e	-0.67	0.57	-0.16				

582 In *analysis 1*, model 1 shows the utility of questionnaire-based estimation of $\dot{V}O_{2max}$, whilst model 2 shows the
 583 additional utility of laboratory-assessed $\dot{V}O_{2max}$ (note the significant r^2 in model 1 and r^2 change value in model
 584 2). In *analysis 2*, model 1 shows the utility of laboratory-assessed $\dot{V}O_{2max}$, whilst model 2 shows the lack of benefit
 585 of additional hypoxic exercise testing (note the significant r^2 in model 1 but insignificant r^2 change value in model
 586 2). B, unstandardized beta coefficient (the magnitude of the effect in raw units); SE B, standard error of B; β ,
 587 standardized beta coefficient (the magnitude of the effect in standardized units, allowing comparison between
 588 variables). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

589

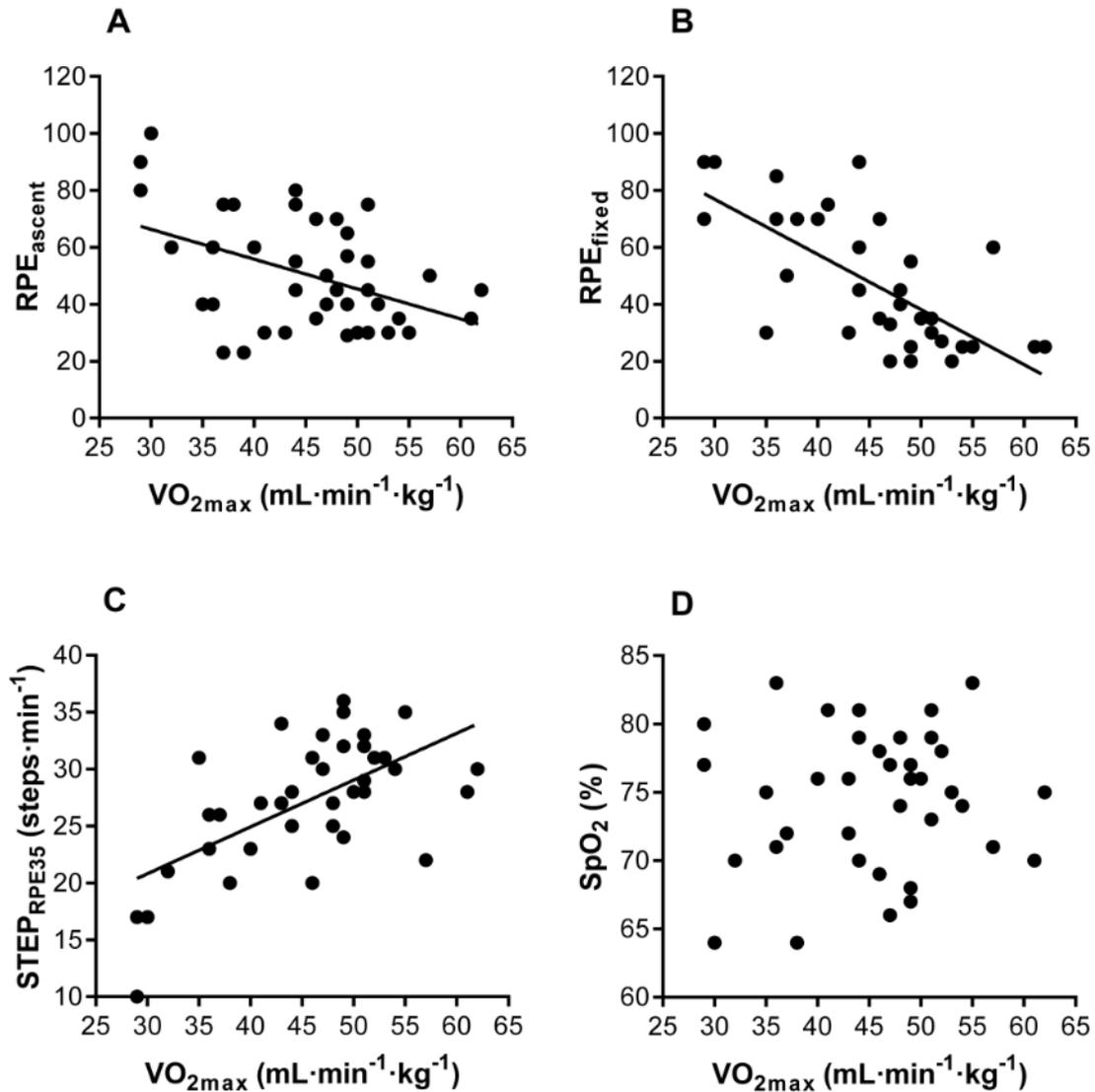


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591 **Figure 1.** Schematic representation of study protocol. Grey boxes indicate procedures undertaken in normoxia,592 white boxes indicate procedures undertaken in hypoxia. $PRSR_{Fam}$, Perceptually-regulated step rate test593 familiarization; LLS, Lake Louise Score; Load, External load for the trekking session (kg); RPE_{ascent} , Rating of

594 perceived exertion on ascent to Base Camp.

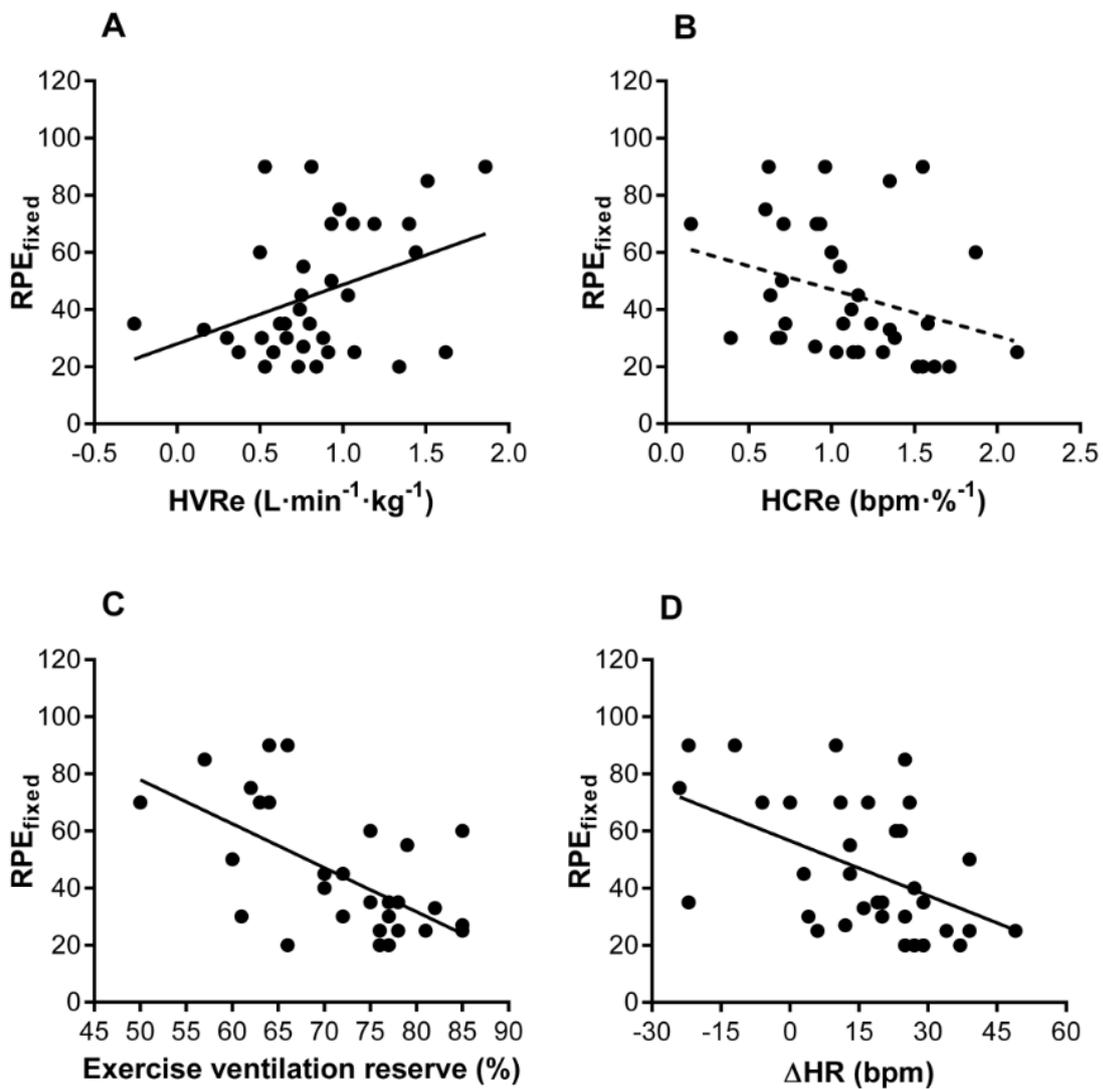
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597 **Figure 2.** Relationship between sea-level fitness ($\dot{V}O_{2max}$) and submaximal exercise at altitude. Greater sea-level598 fitness was associated with (A) reduced session RPE from ascent to Base Camp ($\text{RPE}_{\text{ascent}}$; $r = -0.43$; $p = 0.005$),599 (B) reduced RPE at a fixed workload ($\text{RPE}_{\text{fixed}}$; $r = -0.69$; $p < 0.001$), and (C) greater step rate during perceptually-600 regulated exercise ($\text{STEP}_{\text{RPE35}}$; $r = 0.62$; $p < 0.001$). Sea-level fitness was not related to (D) oxygen saturation601 during fixed-workload step test at altitude (SpO_2 ; $r = 0.07$; $p = 0.67$).

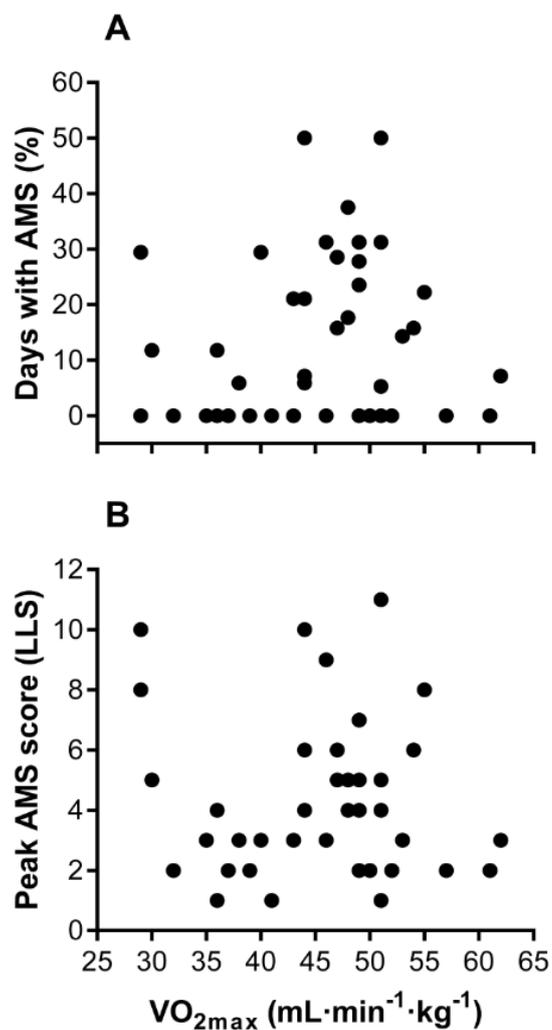
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604 **Figure 3.** Relationships between ventilatory and cardiac responses to acute and chronic high altitude with sense605 of effort at altitude (RPE_{fixed}). Reduced RPE_{fixed} was associated with (A) reduced hypoxic ventilatory response606 (HVRe; $r = 0.38$; $p = 0.02$), (B) elevated hypoxic cardiac response (HCR; $r = -0.31$; $p = 0.07$), (C) elevated607 exercise ventilation reserve at altitude ($r = -0.60$; $p < 0.001$), and (D) elevated chronic change in heart rate ($r = -$ 608 0.49 ; $p = 0.003$).

609



610
 611 **Figure 4.** Sea-level fitness ($\dot{V}O_{2max}$) was not related to (A) percent of trekking days with clinically-defined AMS
 612 ($r = 0.13$; $p = 0.41$), or (B) peak AMS score ($r = -0.05$; $p = 0.74$).
 613