Quantifying the effects of acute hypoxic exposure on exercise performance and capacity: A systematic review and meta-regression

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Running head: Acute hypoxia and exercise performance: meta-regression

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Abstract

Objective: To quantify the effects of acute hypoxic exposure on exercise capacity and performance, which includes continuous and intermittent forms of exercise.

Design: A systematic review was conducted with a three-level mixed effects meta-regression. The ratio of means method was used to evaluate main effects and moderators providing practical interpretations with percentage change.

Data Sources: A systemic search was performed using 3 databases (Google scholar, PubMed and SPORTDiscus).

Eligibility criteria for selecting studies: Inclusion was restricted to investigations that assessed exercise performance (time trials, sprint, and intermittent exercise tests) and capacity (time to exhaustion test (TTE)) with acute hypoxic (< 24 hrs) exposure and a normoxic comparator.

Results: Eighty-two outcomes from 53 studies (N = 798) were included in this review. The results show an overall reduction in exercise performance/capacity -17.8 ± 3.9% (95% CI -22.8% to -11.0%), which was significantly moderated by -6.5 ± 0.9% per 1000 m altitude elevation (95% CI -8.2% to -4.8%) and oxygen saturation (-2.0 ± 0.4% 95% CI -2.9% to -1.2%). Time trial (-16.2 ± 4.3%; 95% CI -22.9% to -9%) and TTE (-44.5 ± 6.9%; 95% CI -51.3% to -36.7%) elicited a negative effect, whilst indicating a quadratic relationship between hypoxic magnitude and both TTE and TT performance. Furthermore, exercise < 2-min exhibited no ergolytic effect from acute hypoxia.

Summary/ Conclusion: This review highlights the ergolytic effect of acute hypoxic exposure; which is curvilinear for TTE and TT performance with increasing hypoxic levels, but short-duration intermittent and sprint exercise seem to be unaffected.

Key words: altitude, intermittent hypoxic training, extreme environments, environmental physiology.

1 **Introduction**

2 Sojourns to terrestrial high altitudes have grown in popularity in recent years, with the World Health

3 Organisation reporting that approximately 35 million people visit terrains greater than 3000 m every

4 year. Furthermore, there is a greater prevalence of altitude and hypoxic training camps amongst elite

5 athletes in preparation for major competition. This has necessitated a greater understanding on the effect

6 of altitude on exercise performance. A predominant environmental stressor for human physiology at

7 altitude is the lower partial pressure of oxygen with progressive elevations. As such, the recent

8 commercialisation of hypoxic simulation chambers and portable devices has increased the accessibility

9 to acute hypoxic training strategies for recreational athletes and individuals predisposed to health issues.

10 Intermittent hypoxic training (IHT) is one ergogenic training strategy commonly used; whereby isolated

11 acute hypoxic training bouts are interspersed within a training programme. These acute training bouts,

12 however, present a substantially negative impact on exercise capacity (Wehrlin & Hallén, 2006) and

13 performance (Clark et al., 2007; Goods, Dawson, Landers, Gore, & Peeling, 2014). Therefore,

14 quantifying the negative effect of hypoxia is important to inform exercise prescription and performance

15 management during IHT training and other forms of acute hypoxic exercise.

16 The magnitude of acute hypoxia's ergolytic effect is dependent on the type of exercise and the duration

17 (Wyatt, 2014). Indeed, mean power output during 5 min time trial (TT) reduces by 7% every 1000 m

18 (Clark et al., 2007) and exercise capacity is reported to decline by 9.4% in the first 500 m with a greater

19 14.3% per 1,000 m thereafter (Wehrlin & Hallén, 2006). However, mean power output and work

20 completed during repeated sprint exercise (RSE) is only impaired from hypoxic conditions equivalent

21 to 4000 m (Bowtell, Cooke, Turner, Mileva, & Sumners, 2014; Goods et al., 2014). This difference in

22 effect may be attributed to the shorter duration of activity during RSE tests; given the suggestion that

23 high intensity exercise lasting less than 2 min is largely unaffected by hypoxia (Wyatt, 2014).

24 Furthermore, acute hypoxia is shown to enhance the relative anaerobic energy contribution and

25 concurrently lower the relative and absolute aerobic contribution (Horscroft & Murray, 2014; Scott,

26 Goods, & Slattery, 2016). Therefore, the magnitude of decline is likely to be dependent on the

27 bioenergetic demand of the exercise bout, which is determined by duration and the required intensity.

28 Despite current evidence from experimental investigations, a pooled effect from all available evidence

29 will offer a more generalisable understanding of the effect of acute hypoxia on exercise performance.

30 The influence of acute hypoxia during exercise is subject to large inter-individual variability, with

31 training status (Macinnis, Nugent, Macleod, & Lohse, 2015) and an individual's ability to maintain

32 oxyhaemoglobin saturation (SaO2) during exercise (Chapman, Stager, Tanner, Stray-Gundersen, &

33 Levine, 2011) cited as primary reasons for this variability. Indeed, a meta-analysis identified that the

34 reduction of maximal rate of oxygen consumption (VO_{2max}) under acute hypoxia was greater in those

35 that possessed a superior VO_{2max} (Macinnis et al., 2015). Thereby, suggesting that athletes of a higher

36 training status may be subject to a greater decrement in performance compared to their untrained

37 counterparts. While, susceptibility to SaO_2 reductions is reported to be a more robust predictor of

38 exercise performance under hypoxia, given the preservation of SaO_2 during exercise is linked to the

39 improved maintenance of 3000 m running performance under acute moderate hypoxic conditions

40 (Chapman et al., 2011). Therefore, reducing peripheral oxygen delivery to active musculature, as

41 inferred through a lower SaO_2, is a hypothesised to be a primary moderator of exercise performance

42 within acute hypoxic conditions.

43 The purpose of this study was to perform a systematic review and meta-regression to quantify the effect

44 of varying magnitudes of hypoxia on exercise capacity and performance. Performance was further

45 subdivided into continuous (TT), intermittent and sprint (Wingate test) exercise sub-groups; and each

46 group assessed against the moderators of elevation equivalent to the hypoxic magnitude tested, SaO_2

47 reduction during exercise and training status. Furthermore, the ergolytic effect of hypoxia was assessed

48 against exercise of different durations.

49 **Method**

50 This meta-analysis followed the principles outlined in the Preferred Reporting Items for Systematic

51 Reviews and Meta-analyses (PRISMA) guidelines.

52 **Eligibility criteria**

The research question was formulated using PICO method (Population, Intervention, Comparison and Outcomes) and used to inform the eligibility criteria of selected studies. The *population* of the review were healthy male and females ($\geq$ 18 yrs old), including healthy to highly trained individuals. Samples that included acclimatised or altitude natives were excluded from the review. The *intervention* involved the assessment of exercise outcomes equivalent to sea level and an exposure to an acute hypoxic stress for less than 24 hrs prior to the assessment of performance. This timeframe was selected as a large degree of acclimatisation in exercise performance has been observed following 24 hrs of exposure (Wyatt, 2014). Investigations that utilised normobaric and hypobaric hypoxic exposures were included in this review. However, only laboratory simulations were included as equivalent power outputs elicit faster velocities at high terrestrial altitudes compared to sea level due to the lower air density, therefore mitigating performance decrements associated with the diminished O_2 availability (Garvican-Lewis et al., 2015). The *comparisons* for this review were randomised controlled trials that involved a sea level exercise trial. Where a sea level trial was not performed (i.e. at 0 m elevation or a fractional inspired oxygen (FiO_2) equal to 21%) the difference between the lowest hypoxic exposure and experimental hypoxic exposure was used for analysis. The FiO_2 used during experimental trials were converted to the equivalent altitude elevation for analysis, however all outcomes are interpreted as the effect of acute hypoxia only. If room air was used as the sea level trial, the elevation of the testing laboratory was checked to ensure the correct elevation was tested. The *outcomes* included in this review involved exercise performance and exercise capacity. Exercise performance was defined as activities that were self-paced continuous (e.g. TT) or intermittent tasks, while exercise capacity referred to tests that required individuals to work to a point of volitional exhaustion at an established controlled intensity.

Search strategy and study selection

A literature search was conducted to identify all relevant original investigations that assessed the influence of acute hypoxic exposure on exercise performance, capacity and physiological thresholds of intensity. This involved two investigators (S.K.D and L.A.G) independently inputting key search terms into three scientific data bases (Google Scholar, PubMed and SPORTDiscus). The search terms were combined to include a term referring to the environmental conditions ('altitude' 'hypoxia', and

80 'fractional inspired oxygen') with exercise performance ('time trial (TT)' repeated sprint exercise

81 (RSE)', 'anaerobic exercise', 'Wingate' and 'sprint performance') or exercise capacity ('time to

82 exhaustion (TTE)', 'exercise capacity'); with all searches restricted to the article titles. The articles were

83 then all reviewed for relevance, which was assessed by the title, with all remaining articles downloaded

84 for further screening and assessment against the eligibility criteria of this review. The reference lists of

85 all retrieved articles and of relevant review articles were also screened for additional eligible articles.

86 The abstracts of all studies were subsequently reviewed to narrow the pool the studies reviewed in full.

87 This list of eligible studies obtained independently were then compared and amalgamated for data

88 extraction. The last search was undertaken in April 2017.

89 **Data collection process**

90 The data from all eligible studies were extracted into a standardised excel template (S.K.D) and checked

91 for accuracy (L.A.G). The extracted data included author name, year, sample characteristics, VO_{2max},

92 type of hypoxic exposure, arterial oxyhaemoglobin saturation (including SaO2 obtained from blood

93 samples, and SpO2 obtained via pulse oximetry), exercise test description. Furthermore, the mean data

94 and standard deviation (SD) of control and experimental conditions were extracted, in addition to an

95 exact p value or a value that indicated the variance in the intervention effect (e.g. 95% confidence

96 intervals or SD of mean difference). Instances where mean ± SD were displayed in figures only, a graph

97 digitiser software was used to extract the data (Digitize, Germany). This extraction was performed

98 independently by two researchers (S.K.D and L.A.G) and compared for consensus, where this was not

99 apparent a third researcher (D.R.B) performed the extraction for agreement.

100 Data were primarily extracted as mean power output (or velocity) or total work done from the TT and

101 intermittent exercise protocols, while exercise duration was extracted for all exercise capacity tests.

102 Authors of studies where required data were missing or outcomes were not reported appropriately for

103 this review were contacted for further information. Where performance data was not reported in mean

104 power output or work done, but rather test completion time, the available datum was converted into

105 mean power (Carr, Hopkins, & Gore, 2011). Investigations that included multiple exercise tests and

106　varying magnitudes of hypoxia and experimental data from independent groups were extracted as

107　separate outcomes.

108　Data were categorised into sub-groups based on exercise type and duration of exercise bout. The

109　exercise subgroups reflected the outcomes outlined in the eligibility criteria: TT performance,

110　intermittent exercise, TTE and sprint tests. Exercise was also categorised into three time based sub-

111　groups (< 2 mins, 2 – 10 min and > 10 mins) as the ergolytic effect of hypoxia is proposed to be

112　dependent on duration (Wyatt, 2014). The first category was chosen as exercise below 2 min is

113　suggested to be unaffected by acute hypoxia (Wyatt, 2014); whereas the category between 2-10 min

114　was chosen to include the range of exercises that are likely to require an anaerobic energy contribution

115　(Duffield, Dawson, & Goodman, 2005). Exercise beyond 10 min is included in this review to represent

116　exercise intensities that predominantly require an aerobic energy contribution. Intermittent exercise,

117　which involved controlled repetitions of work and recovery, were categorised on the total duration of

118　high intensity activity periods. Furthermore, outcomes were categorised by training status with a sea

119　level $VO_{2max} \geq 55$ ml·kg^{-1}·min^{-1} classified as trained and < 55 ml·kg^{-1}·min^{-1} as healthy untrained (De

120　Pauw et al., 2013). Where VO_{2max} was not reported, articles were not included in analysis to maintain

121　objectivity.

122　**Quality and bias assessment**

123　The overall quality of evidence for each outcome was determined by S.K.D and L.A.G independently,

124　using the Grades of Recommendation, Assessment, Development and Evaluation Working Group

125　(GRADE) approach. The GRADE protocol offers a systematic method to evaluate the quality of

126　research whilst considering methodological limitation, consistency of outcomes, reporting or

127　publication bias and indirectness of evidence. Furthermore, to increase specificity to the current

128　research question three discipline specific factors were considered under the category methodological

129　limitation: 1) the control of prior altitude/hypoxic exposure to reduce any confounding effects of

130　acclimatisation; 2) standardisation of dietary intake prior to experimental trials; and 3) familiarisation

131　to exercise trials. In addition to the traditional quality control criteria to limit bias: 1) blinding of

132　participants; 2) blinding of researcher; 3) blinding outcome assessment; and 4) complete outcome data.

133　However, the indirectness of evidence was not considered in this review, due to inclusion criteria

134　requiring the assessment of exercise performance directly; while a traditional funnel plot was not used

135　to assess publication bias due to the natural negative skew expected in the data, given the strong

136　physiological basis that exercise performance will not be enhanced under acute hypoxia.

137　**Data analysis**

138　The ratio of means (ROM) method was used to establish pooled effects and variances of hypoxic

139　interventions. This method allows outcomes of different units to be pooled and compared, whilst also

140　allowing for easy interpretation for practitioners, athletes, and coaches because outcomes can be

141　expressed as a percentage change. The natural logarithm of each ROM (equation 1) and its variance

142　(equation 2) were calculated using the mean values of sea level ($\bar{x}_c$) and hypoxia ($\bar{x}_T$), their respective

143　standard deviations (SD), number of participants (N) and a correction (r) between sea level and hypoxic

144　trial performance:

145　$$\log(RoM) = [\log \frac{\bar{\bar{x}}_T}{\bar{x}_c}]$$ 　　　　　　　[Equation 1]

146　$$Var[log(RoM)] = \frac{(\text{SD}_C)^2}{N_c \bar{x}^2_c} + \frac{(\text{SD}_T)^2}{N_T \bar{x}^2_T} + \frac{2r\text{SD}_C\text{SD}_T}{\bar{x}_c \bar{x}_T \sqrt{N_c N_T}}$$ 　　[Equation 2]

147　The calculation of the variance of ROM requires knowledge of the correlation (r) between sea level and

148　hypoxic trial outcomes, which is not commonly reported. Estimates from individual studies were

149　obtained using reported t statistics as follows (equation 3):

150　$$r = \frac{(SD_c)^2 + (SD_T)^2 - t^{-2}N(\bar{x}_T - \bar{x}_c)^2}{2\text{SD}_C\text{SD}_T}$$ 　　　[Equation 3]

151　Appropriate information was only available for 23 studies; therefore, a pooled single estimate of the

152　correlation r was calculated from the available data using the Meta package in r (R Foundation for

153　Statistical Computing, Vienna Austria). The pooled correlation value (r = 0.78, 95% confidence

154　interval: 0.62 to 0.87) was then applied to all studies. Sensitivity analyses using correlation values of r

155　= 0.68 and r = 0.88 were also carried out to validate the primary model.

156   A three-level mixed effects meta-regression was used to analyse ROMs and variances whilst accounting

157   for dependencies in the data set. The three levels can be described by regression equations at the sample

158   (level 1), outcome (level 2) and study (level 3) level (Van den Noortgate, López-López, Marín-

159   Martínez, & Sánchez-Meca, 2013). The fixed effects categorical moderators included exercise type

160   (TT, intermittent, TTE and Sprint), exercise duration (< 2 min, 2-10 min and > 10 min) and training

161   status (trained vs. healthy). The overall and interaction effects with altitude elevation in km equivalent

162   to the FiO_2 exposure and end exercise mean difference in SaO_2 between normoxic and hypoxic

163   conditions were also evaluated as continuous moderators. Furthermore, given the reported non-linear

164   relationship between acute hypoxia and VO_{2max} (Macinnis et al., 2015) and critical power (Townsend,

165   Nichols, Skiba, Racinais, & Périard, 2017), the review also assessed curvilinear effects of altitude

166   elevation using quadratic models. Regression analyses were constrained to a zero intercept to enhance

167   external validity. Pooled effects on the logarithmic scale were subsequently back transformed and

168   multiplied by 100 to provide percentage change of effects. A normal distribution was assumed for log-

169   transformed effects and therefore 95% confidence intervals were obtained from $\pm 1.96 \times$ standard error

170   and back transformed. All outcomes are reported as percentage effect estimate $\pm$ standard error and the

171   corresponding 95% confidence intervals, unless otherwise stated. All analysis was performed using the

172   metaphor package in R (R Foundation for Statistical Computing, Vienna Austria). Statistical significant

173   was assessed through 95% confidence intervals, with estimates that cross the zero-boundary interpreted

174   as non-significant.

175   **Results**

176   **Study characteristics**

177   Fifty-three studies met the inclusion criteria set for this review (Table 1), which provided effect statistics

178   for 82 outcomes within 798 participants and ranged from 500-5700 m altitude (mean $\pm$ SD: 3000 $\pm$

179   1300 m). These studies were categorised into an exercise modality and an exercise duration category

180   for analysis. Training status was explicitly reported in 47 outcomes, with 33 cohorts classified as trained

181   against 14 cohorts classified as untrained healthy participants; whilst SaO_2 was available in 54 outcomes

182 (13.2% ± 7.2%). Only five studies were performed utilising hypobaric hypoxia and therefore the type

183 of hypoxic exposure was not considered as a moderator in this study.

Quality assessment

185 Under the GRADE research quality assessment, the overall quality is rated high due to the inclusion of

186 only randomised control trials in this review and the limited evidence to warrant the downgrading of

187 quality. Methodological limitations and bias in the included articles, were assessed against pre-

188 determined criteria, with the percentage of studies demonstrating each criterion as follows: (1) the

189 control of prior altitude/hypoxic exposure: 47%; (2) standardisation of dietary intake: 62%; (3)

190 familiarisation to exercise trials: 87%; (4) blinding of participants: 43%; (5) blinding of researcher:

191 23%; (6) blinding outcome assessment: 0%; and (7) complete outcome data: 42%.

Overall effect

193 The intercept only three-level mixed effects model identified a negative 17.1 ± 3.7% (95% CI -22.8%

194 to -11%) effect on all categories of exercise capacity and performance with 20.8%, 62.5% and 16.7%

195 of the variance explained by the sample, between study and between outcome variance, respectively.

196 The outcomes from the sensitivity analysis found no substantive difference in effect or variance between

197 models using $r = 0.67$, $r = 0.87$ and $r = 0.77$ correlation values. Acute hypoxic exposure was calculated

198 to have a significant moderating effect that equates to a 6.5% reduction for every 1000 m elevated (-6.5

199 ± 0.9%; 95% CI -8.2% to -4.8%). No evidence was obtained for a non-linear effect of altitude on the

200 overall dataset. Similarly, for a 1% reduction in SaO_2 a significant negative 2.0 ± 0.4% (95% CI -2.9%

201 to -1.2%) effect was reported.

Moderating effects of exercise types

203 Exercise type was found to have a moderating effect on exercise performance under acute hypoxic

204 conditions (Figure 1), with TT performance and TTE tests experiencing a significant -16.2 ± 4.3% (95%

205 CI -22.9% to -9.0%) and -44.5 ± 6.9% (95% CI -51.3% to -36.7%) change. However, the overall effect

206 on intermittent exercise (-5.6 ± 4.8% ;95% CI -13.9% to 3.5%) and sprint performance (-2.9 ± 8.0; 95%

207 CI -16.5% to 12.8%) were non-significant. Moreover, interaction effects were reported between

208   exercise type and magnitude of altitude elevation. Additionally, altitude^2 moderator improved model fit

209   compared to the linear model when exercise type was included ($\chi_{(10)}$ = 8.0; p = 0.005), indicating a

210   curvilinear effect of acute hypoxia. The exercise type category was subsequently reduced to TT and

211   TTE sub-groups to determine the interaction effects with linear and quadratic effects of altitude

212   elevation (Table 2), which are depicted in Figure 2. The magnitude of SaO_2 decline was also determined

213   to have the largest moderating effect on TTE exercise compared to the three other exercise types, with

214   a -4.5 ± 0.5% (95% CI -5.4% to -3.6%) for every 1% reduction in SaO_2. A lower -1.3 ± 0.4% (95% CI

215   -2.1% to -0.5%) moderating effect for every 1% reduction in SaO_2 was also evident on TT performance.

216 **Moderating effects of exercise duration**

217   Acute hypoxia had no effect on exercise of < 2 min duration (-6.3 ± 5.6%; 95% CI -16.1% to -3.8%),

218   however exercise between 2-10 min and > 10 min had a significant -18.0 ± 6.0% (95% CI -25.8% to -

219   8.2%) and -26.8 ± 5.5% (95% CI -33.2% to -18.2%) effect, respectively. A similar interaction effect

220   with altitude was also found for exercise between 2 to 10 min and > 10 min, with a negative -13.6 ±

221   2.4% (95% CI -17.8% to 9.7%) and -18.2 ± 2.1% (95% CI -21.5% to -14.8%) per 1000 m, respectively.

222   A similar moderating effect of SaO_2 was noted for the 2-10 min category at -2.4 ± 0.7% (95% CI -3.8%

223   to -1.0%) and over 10 min category at -2.8 ± 0.6% (95% CI -3.9% to -1.6%) for every 1% reduction in

224   SaO_2.

225 **Moderating effect of training status**

226   Trained and healthy individuals were found to have a pooled -21.8 ± 6.8% effect (95% CI -31.2% to -

227   11.1%) and -29.5 ± 9.6% (95% CI -41.1% to -15.5%) decline in performance with acute hypoxia,

228   respectively. Given the variance in the range of altitude elevations and greater mean elevation in the

229   healthy cohort, further analysis that controlled for altitude found a non-significant effect between sub-

230   groups. There was however, a difference in the moderating effect of SaO_2 between the sub-groups, with

231   a significant moderating effect for every 1% reduction in SaO_2 apparent in trained (-2.8 ± 0.5%; 95%

232   CI -3.8% to -1.7%) but not in untrained healthy participants (-2.0 ± 1.6%; 95% CI -5.1% to 1.1%).

233 **Further analysis**

234   Owing to the large proportion of outcomes in the intermittent exercise group also classified as < 2 min

235   (17 of the 23), the main effect in the intermittent sub-group may have been skewed. Therefore, further

236   analysis to determine the pooled effect on intermittent exercise bouts > 2 min were performed. An

237   overall pooled estimate of -4.7 ± 1.3% (95% CI -7.2% to -2.2%) was observed, however acute hypoxia

238   elevation was not found to be a significant moderator of intermittent exercise over 2 min (95% CI -

239   7.7% to 3.1%).

240   **Discussion**

241   This is the first meta-analysis to study the effects of acute hypoxic exposure on exercise capacity and

242   performance; and assess the effect against moderators of altitude elevation based on FiO_2 tested, SaO_2,

243   training status, exercise duration and type of exercise. This review is the first to show the curvilinear

244   relationship between exercise and acute hypoxic exposure during TT and TTE exercise tests, and

245   exercise activity > 2 min. In contrast, no ergolytic effect was found during intermittent exercise and

246   sprint tests; and exercise < 2 min. When exercise < 2 min were removed from the analysis of intermittent

247   exercise, a significant negative effect was seen, suggesting prolonged intermittent exercise is impaired

248   under acute hypoxic conditions. Training status was demonstrated to be a significant moderator, with

249   trained and healthy individuals exhibiting a similar negative effect. While reductions in SaO_2 displayed

250   a negative moderating effect in the overall model, however these effects were more pronounced within

251   trained participants. Together, these results highlight the magnitude dependent moderating effects of

252   acute hypoxia, while also showing potential factors that are likely to influence exercise performance at

253   acute hypoxia.

254   The curvilinear relationship between exercise and hypoxic exposure is described by a quadratic model.

255   This is equivalent to the meta-analytic model previously used to describe the relationship with VO_{2max}

256   (Macinnis et al., 2015). Furthermore, critical power (CP), a suggested marker of maximal sustainable

257   aerobic power, has been fitted to a higher order cubic model to show the negative relationship within

258   nine trained cyclists (Townsend et al., 2017). Nonetheless, this is the first study to describe a curvilinear

259   relationship during TT performance and TTE tests, given previous experimental studies have reported

260   a linear 7.0% reduction in TT performance per 1000 m (Clark et al., 2007) and TTE decline linearly by

261   14.5% per 1000 m up to a moderate 3000 m elevation (Wehrlin & Hallén, 2006). When comparing the

262   quadratic models of the current dataset at a hypoxic exposure equivalent to 3000 m. TTE and TT

263   performance can be predicted fall by 47.7% and 17.7%, respectively, whereas previous research would

264   suggest a 43.5% reduction in TTE and 21.0% reduction in TT performance. The small but important

265   difference in the magnitude of decline and the curvilinear model is likely to be explained by the greater

266   range of acute hypoxic magnitudes, equivalent 500 m to 5700 m elevation, in the present model, which

267   includes severe hypoxic exposures, whereas previous experimental work only assessed low and

268   moderate altitudes (< 3000 m) (Clark et al., 2007; Wehrlin & Hallén, 2006). Indeed, earlier articles that

269   also reported a curvilinear relationship, also included severe hypoxic exposures (Macinnis et al., 2015;

270   Townsend et al., 2017), which suggests alternative fatiguing mechanisms may be operating. Current

271   evidence alludes to an exacerbated central fatigue action through diminished group III/IV afferent

272   feedback with exposure to severe hypoxic conditions, whereas the central motor output is unchanged

273   from sea level at moderate hypoxic exposures (Amann, Romer, Subudhi, Pegelow, & Dempsey, 2007).

274   This diminished central motor output may, in part, explain the exponential decline in performance

275   observed with greater elevation.

276   The magnitude of the impairment with acute hypoxia is dependent on the type and duration of exercise,

277   with TT performance and TTE tests found to elicit ergolytic effects, while sprint and intermittent tests

278   found to be largely unchanged from sea level. This effect may be explained by the duration of exercise

279   within these sub-groups, given sprint exercise and the repeated sprint exercise (RSE) within the

280   intermittent group formed the < 2 min sub-group. Indeed, experimental studies assessing the various

281   magnitudes of hypoxia on RSE have only reported performance decrements above 4000 m (Bowtell et

282   al., 2014; Goods et al., 2014). However, the current model did not show this due to the assessment of

283   performance against a continuous hypoxic moderator rather than at 1000 m categorical intervals used

284   in experimental studies. Nonetheless, sprint and RSE performance, which is equivalent for the < 2 min

285   duration category, are sustained with acute hypoxia; an effect that can be explained through greater

286   reliance on anaerobic energy sources, which provides the greatest contribution to RSE and sprint

287   performance (Scott et al., 2016). The separation of exercise activity less than 2 min in the intermittent

288   sub-group did however, suggest prolonged intermittent exercise is impaired under acute hypoxia, which

289   may explain the decrement in physical output during team sports competition at altitude (Aldous et al.,

290   2016). However, the moderating effect of acute hypoxia were not evident, which may be attributed to

291   the lack of available outcomes; therefore, further research should aim to assess effects of several

292   incremental magnitudes of acute hypoxia on prolonged intermittent performance.

293   The lack of effect during short duration (< 2 min) exercise bouts is also reflected in previous research

294   assessing the impact of altitude on track athletes (Hamlin, Hopkins and Hoolings, 2015) and may also

295   be mechanistically explained when viewed through the two parameter CP concept (Simpson et al. 2015;

296   Sherman et al., 2016; Townsend et al., 2017). When analysing track performances of major international

297   competitions at varying degrees of altitude, Hamlin et al., (2015) reported track sprint events (100-400

298   m) did not exhibit a negative effect associated with hypoxia, but rather, a performance improvement

299   due to the reduced aerodynamic resistance caused by the lower barometric pressure present at terrestrial

300   altitudes. Whereas, longer track events (800 -10000 m) that require a larger relative aerobic energetic

301   contribution exhibit a performance decrement at elevations $\leq$ 150 m. As such, demonstrating the

302   outcomes of this meta-analysis are also reflected during athletic competition. Further to this, with

303   hypoxic exposures, critical power exhibits a substantial decline in performance corresponding to the

304   performance impairment noted during longer TT and TTE exercise that requires a greater aerobic

305   contribution. Whereas, W', the ability to perform work above CP is unchanged under moderate hypoxic

306   conditions (Simpson et al. 2015; Sherman et al., 2016; Townsend et al., 2017). Traditionally, W' is

307   purported to represent the anaerobic work capacity and as such, the lack of change reported during

308   exercise < 2 min in the current study may be explained through the two parameter CP model.

309   There is evidence to suggest an individual variability in exercise response to acute hypoxic exposure,

310   which is predominantly accounted by superiorly trained individuals exhibiting the largest decrement

311   in VO_{2max} (Macinnis et al., 2015) under acute hypoxic conditions, given their inability to maintain SaO_2

312   during exercise compared to untrained individuals (Chapman et al., 2011). Chapman et al., (2011)

313   further identified that individuals that exhibited the greatest reductions in SaO_2 during a 3000 m running

314   performance, experienced a greater impairment in running performance. In the current study,

performance decrements between healthy and trained cohorts could not be differentiated when controlling for differing hypoxic exposures. However, the moderating effects of SaO_2 were more evident within trained individuals with a significant $2.8 \pm 0.5\%$ fall in performance for every 1% reduction in SaO_2, while no significant moderating effect was noted in healthy individuals. This is however, presented with a caveat as fewer outcomes were included in the healthy cohort sub-group, which may have contributed to the null findings. Nonetheless, SaO_2 was demonstrated to have an overall moderating effect, which was most evident during TTE tests and TT performance.

In this review, the effects of the type of hypoxic exposure (i.e. normobaric vs hypobaric) could not be evaluated due to the lack of available data. Research has suggested the different physiological response to exercise between normobaria and hypobaria (Coppel, Hennis, Gilbert-Kawai, & Grocott, 2015); while it is important to highlight the reduced air density at terrestrial altitude, result in fast velocities at equivalent power outputs (Garvican-Lewis et al., 2015), therefore the results of this study are not directly applicable to field based performance. Nonetheless, this review quantifies the non-linear relationship between acute hypoxia and both TTE and TT performance, whilst also highlighting the lack of effect during Sprint and RSE. Additional, noteworthy limitations to this study are apparent in the interpretation of the effect of SaO_2 and training status moderators. End exercise SaO_2 was used in the current study as opposed to mean SaO_2 due the much greater frequency in measurement of the former. The use of mean SaO_2 would take in to account the different rates of change in oxygen saturation during exercise and within exercise SaO_2 may have implications for pacing, therefore further experimental research should consider this effect. In the present study, training status was defined with a cut off in mean VO_{2max} to maintain objectivity of physiological fitness, however, this categorical approach is limited, in that, participant cohorts may not be homogenous with VO_{2max} of individuals ranging above and below the cut off. The moderating effects of VO_{2max} should therefore be interpreted with this caveat. Nonetheless, this review offers a useful practical interpretation for practitioners, coaches and athletes when planning training during a range of acute hypoxic levels. Furthermore, this review highlights the importance of mitigating the reduction of SaO_2 to maintain exercise performance

341   under acute hypoxia, particularly within trained cohorts who are suggested to experience a larger

342   moderating effect of SaO_2.

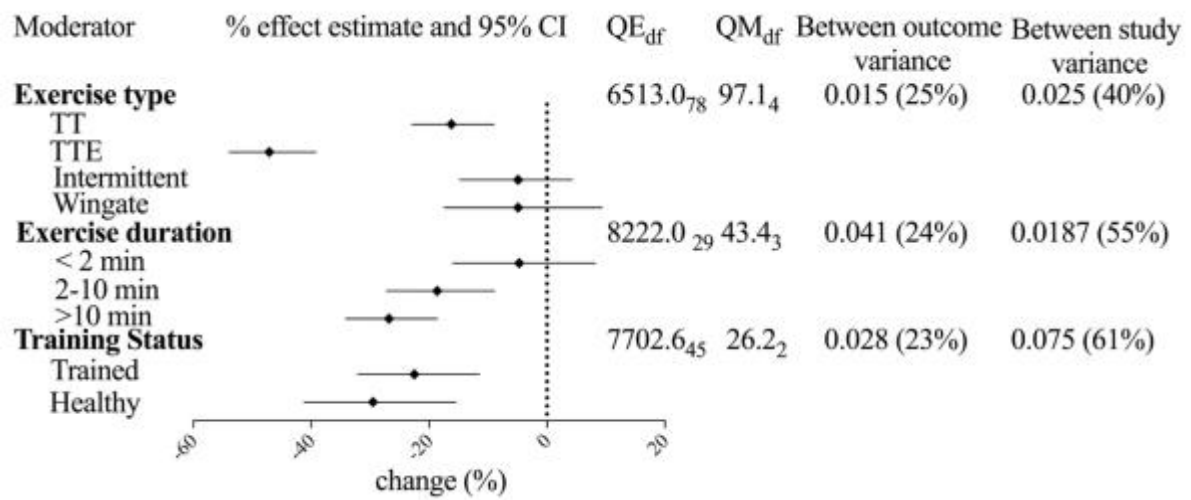| Moderator	% effect estimate and 95% CI	QE_{df}	QM_{df}	Between outcome variance	Between study variance
Exercise type		6513.0_{78}	97.1_4	0.015 (25%)	0.025 (40%)
TT					
TTE					
Intermittent					
Wingate					
Exercise duration		8222.0_{29}	43.4_3	0.041 (24%)	0.0187 (55%)
< 2 min					
2-10 min					
>10 min					
Training Status		7702.6_{45}	26.2_2	0.028 (23%)	0.075 (61%)
Trained					
Healthy					

change (%)

Figure 1. Results from categorical moderator analysis.
QE_{df}: residual heterogeneity test statistic; QM_{df}: omnibus moderator test statistic.
Between outcome and study variance are accompanied by a percentage showing the proportion of total variance in the model that they account for.
Confidence intervals crossing the zero-boundary show non-significant effects.
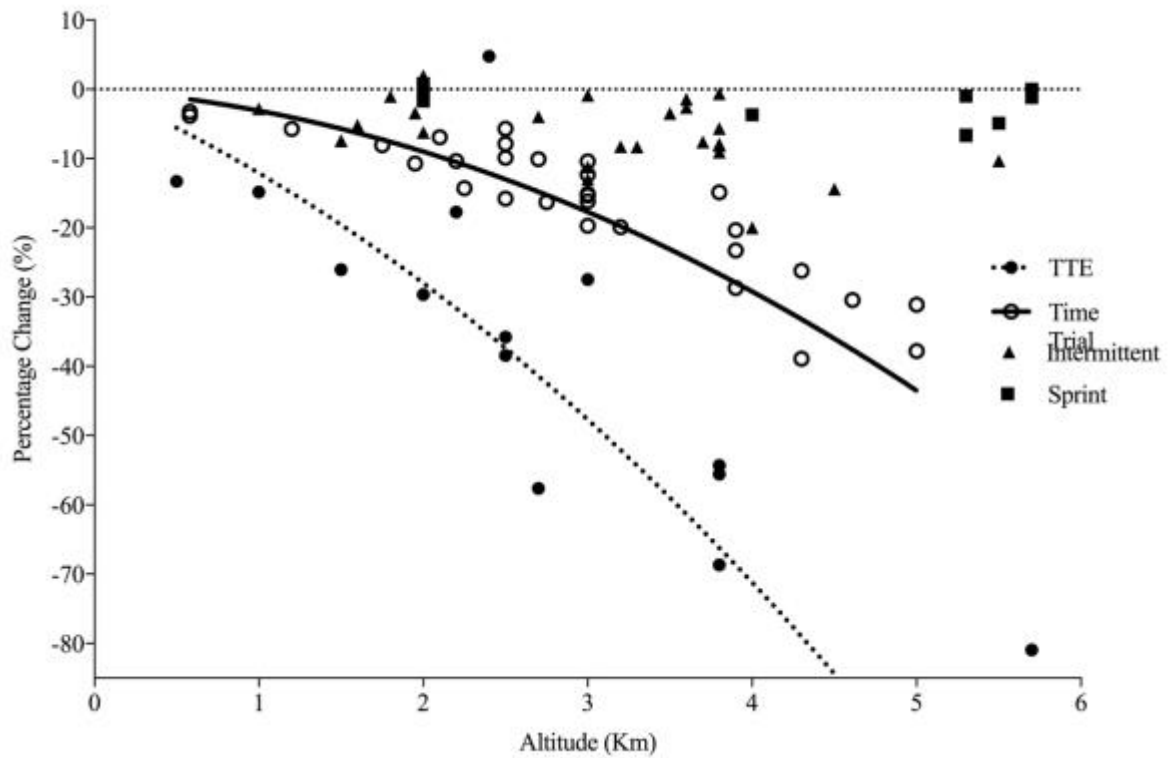
Figure 2. A scatterplot showing the outcomes included this meta–analysis categorised by exercise type, with quadratic regression lines shown for TTE and TT performance. Wingate, intermittent and TT performance are shown as a percentage change in mean power output, while TTE as a percentage change in exercise tolerance duration.

Table 1. Summary table of all outcomes by exercise type included in this review with effect and standard error of outcomes in this meta-analytic model.

Author	Participants [VO$_{2peak}$] (ml·kg^{-1}·min^{-1})	SaO$_2$ (%)	Altitude elevation (NH or HH)	Exercise duration category	Exercise protocol	Effect (%) (95% CI)
Exercise performance – Continuous TT exercise						
Amann et al., 2000	8 [63.0 ± 1.3]	14.0	2700 m (NH)	2	5 km TT	-10.4 (-12.2 to -7.7)
Beidleman et al., 2014	6 [49.5 ± 5.0]	17.6	4300 m (NH)	3	Time to complete 72 J work	-25.9 (-31.6 to -19.7)
	6 [47.5 ± 4.3]	19.5	4300 m (HH)	3		-38.7 (-41.7 to -35.6)
Bourdillon, Fan, & Kayser, 2014	13	30.0	5000 m (NH)	3	15 km TT	-30.9 (-33 to -29.5)
Bourdillon et al., 2015	12	28.3	5000 m (NH)	3	15 km TT	-37.5 (-44.6 to -30.2)
Castellani et al., 2010	7 [44.1 ± 4.9]	20.0	3000 m (HH)	3	Total Work done during a 30 min TT	-12.2 (-19.7 to -3.9)
Clark et al., 2007	10 [67.7 ± 1.3]	4.0	1200 m (HH)	2	Total Work done during a 5 min TT	-5.8 (-10.4 to -1.0)
		13.0	2200 m (HH)			-10.4 (-14.8 to -5.8)
		12.0	3200 m (HH)			-19.7 (-23.7 to -15.6)
Dahlstrom et al., 2013	8 [52 ± 7.3]		2750 m (NH)	3	20 km TT	-16.5 (-18.1 to -13.9)
Deb et al., 2017	11 [59.2 ± 6.8]	10.5	3000 m (NH)	2	Total Work done during 3 min	-10.4 (-15.6 to -5.8)
Fan et al., 2013	10 [63.3 ± 6.6]	30.0	4600 m (NH)	3	15 km TT	-30.2 (-32.3 to -28.1)
Foss, 2015	10 [66.5 ± 5.2]	3.90	2500 m (NH)	3	20 km TT	-9.5 (-15.6 to -3.9)
Gore et al., 1997	10 [72.3 ± 2]	1.8	580 m (HH)	2	Total Work done during a 5 min TT	-3 (-3.9 to -2.0)
	10 [60.8 ± 2]	3.4	580 m (HH)			-3.9 (-4.9 to -3.0)
Jacobs et al., 2011	20 [56.5 ± 1.2]	21.0	3900 m (NH)	2	6 km TT	-20.5 (-21.3 to -18.9)
	15 [45.3 ± 1]	18.0		3		-28.8 (-29.5 to -28.1)
Koelwyn et al., 2013	11 (58.3 ± 2.8)	10.8	1950 m (NH)	3	10 km TT	-10.4 (-13.1 to -7.7)
Kressler et al., 2011		5.0	2100 m (NH)	3	15 km TT	-6.8 (-8.6 to -4.9)

	21 [11 males: 55 ± 1.3] 10 females: [42.8 ± 0.6]	17.0	3900 m (NH)			-22.9 (-25.2 to -21.3)
MacLeod et al., 2015	11 [67.5 ± 5.8]	9.0	2500 m (NH)	3	10 km TT	-15.6 (-18.9 to -13.1)
Salazar-Martínez et al., 2017	16 [46.4 ± 8.7]		2500 m (NH)	2	Total Work done during a 10 min TT	-5.8 (-11.3 to 1.0)
Simpson et al., 2015	12 [41.6 ± 6.3]		3800 m (NH)	2	Total Work done during 3 min	-14.8 (-18.9 to -10.4)
Périard & Racinais, 2016	12 [59.5 ± 3.8]	13	3000 m (NH)	3	Time to complete 75 J work	-19.7 (-23.0 to -16.5)
Peltonen et al., 1995	6		2250 m (NH)	2	2.5 km rowing TT	-13.9 (-17.3 to -11.3)
Puype et al., 2013	10 [55.1 ± 2.5] 9 [53.3 ± 3.5] 10 [55.1 ± 1.7]		3000 m (NH) 3000 m (NH) 3000 m (NH)	2	Total Work done during a 10 min TT	-14.8 (-17.3 to -13.1) -15.6 (-16.5 to -14.8) -16.5 (-18.9 to -13.9)
Shearman et al., 2015	11 [61.5 ± 5.7]	11.4	2500 m (NH)	2	Total Work done during 3 min	-7.7 (-12.2 to -3.9)
Weavil et al., 2015	7 [61.5 ± 1.4]	9	1750 m (NH)	2	5 km TT	-7.7 (-11.3 to -4.9)

Exercise performance – Intermittent exercise

Aldous et al., 2016	12 [57.0 ± 2.0]		1000 m (NH)	3	90 min intermittent soccer performance test	-2.9 (-3.9 to -1.0)
Billaut & Buchheit, 2013	14		3800 m (NH)	1	10 x 10 sec sprints with 30 s rest	-7.6 (-13 to -2.9)
Billaut et al., 2013	10		3300 m (NH)	1	3 sets 5 x 5 s sprints with 25 s passive recovery	-8.6 (-18.1 to 2.0)
Bowtell et al., 2014	9	20.7 26.2 13.6	2700 m (NH) 3200 m (NH) 3800 m (NH)	1	10 X 6 sec sprints with 30 a rest	-3.9 (-8.6 to 1.0) -8.6 (-12.2 to -3.9) -8.6 (-13 to -5.8)

Study	N [age]		Altitude (m)		Protocol	Effect (95% CI)
		18.1	4500 m (NH)			-14.8 (-18.1 to -10.4)
Brosnan et al., 2000	8 [61.0 ± 4.0]		1500 m (NH)	3	3 x max work in 10 min with 5 min active recovery (< 100w)	-7.7 (-13.1 to -3.9)
				2	3 sets 6 x 15 s sprints with 45 s recovery (< 100 w). 3 min recovery between sets	-7.7 (-10.4 to -2.0)
Girard et al., 2015	13	8.1	1800 m (NH))	1	8 x 5 s sprint with 25 s passive recovery	-1 (-2.9 to 1.0)
		15	3600 m (NH)			-1 (-5.8 to 3.0)
Girard et al., 2016	6		3600 m (NH)	1	5 x 5 s sprint with 25 s passive recovery	-3 (-4.9 to -1.0)
Goods et al., 2014	10	5.4	2000 m (NH)	1	3 sets 9 x 4 sec max sprints non-motorised treadmill	-5.8 (-9.5 to -3.0)
		10.9	3000 m (NH)			-11.3 (13.9 to -7.7)
		20.2	4000 m (NH)			-19.7 (-22.9 to -17.3)
Goods et al., 2016	9					-10.4 (-16.5 to -3.9)
Kon et al., 2015	7		2000 m (NH)	2	4 x 30 s all out sprint with 4 min passive recovery	1.0 (0 to 2.0)
			3500 m (NH)			-3.9 (-4.9 to -2)
Morrison, McLellan, & Minahan, 2015	10		3800 m (NH)	1	4 sets of 4 x 4 sec sprints	-1.0 (-3.0 to 2.0)
Lovell, McLellan, & Minahan, 2015)	7		3800 m (NH)	1	10 x 26 sec sprint with 24 sec recovery	-5.8 (-11.3 to 0)
Smith & Billaut, 2010	13	12.1	3700 m (NH)	1	10 x 10 s sprint with 30 sec passive recovery	-7.7 (-10.3 to -4.9)
Smith & Billaut, 2012	10 male	12.5	3700 m (NH)	1	10 x 10 s sprint with 30 sec passive recovery	-7.7 (-13.1 to -3)
	10 female	14.7				-6.8 (-29.5 to -18.1)
Sweeting et al., 2017	7 [59.5 ± 5.1]		2000 m (NH)	3	26.4 min repeated sprint protocol	2.0 (-6.7 to 11.6)
			3000 m (NH)			-13.1 (-23.7 to -1.0)
Turner et al., 2014	9 [40.1 ± 4.6]	5	1600 m (NH)	3	80 min cycling intermittent sprint protocol	-4.9 (-13 to 3.0)
Witmer, 2011	14 [44.8 ± 8.0]	1.2	3000 m (NH)	1	10 X 6 sec sprints with 30 sec rest	-1.0 (-3.0 to 1.0)
Zinner et al., 2015	10 [72 ± 7.2]		2000 m (NH)	2	3 x 3 min 'all-out' double poling	-3.0 (-8.6 to 3.0)

Anaerobic exercise – Sprint

Calbet et al., 2015	11 [50.7 ± 4.0]		5300 m (NH)	1	30 s Wingate	-7.7 (-10.4 to -3.0)
Calbet et al., 2003	5 [62.0 ± 2.0] 5 [72.0 ± 1.0]		5300 m (NH)	1	30 s Wingate	-1.0 (-3.0 to 1.0) -6.7 (-9.5 to -3.9)
McLellan et al., 1990	12	15.7 13.7	5700 m (NH)	1	30 s Wingate 45 s Wingate	0 (-2.0 to 2.0) -1.0 (-3.0 to 1.0)
Morales-Alamo et al., 2012	10		5500 m (NH)	1	30 s Wingate	-4.9 (-9.5 to -1.0)
Ogura et al., 2006	7		2000 m (NH) 4000 m (NH)	1	40 s Wingate	0 (-5.8 to -5.1) -3.9 (-8.6 to 2.0)
Oguri et al., 2008	9 [62.5 ± 4.1] 9 [49.9 ± 5.2]	8 6	2000 m (NH)	1	30 s Wingate	1.0 (-5.8 to 7.3) -2.0 (-6.8 to 3.0)

Exercise capacity – time to exhaustion tests

Amann et al., 2007	8 [67.2 ± 2.5]	12 27	2700 m (NH) 5700 m (NH)	2	81.4% normoxic W_{peak}	-57.7 (-60.1 to -55.1) -81.0 (-82.1 to -79.6)
Billat et al., 2003	8 [57.3 ± 3.3]	13	3400 (NH)	2	Velocity at VO_{2max}	5.1 (-7.7 to 19.7)
Flinn, Herbert, Graham, & Siegler, 2014	12 [53.5 ± 10.0]	2.7	3000 m (NH)	2	Intermittent 30 s work at 120% W_{peak} and 30 s recovery at 30% W_{peak}	-27.4 (-33.6 to -20.5)
Girard & Racinais, 2014	11	8	2500 m (NH)	3	66% normoxic VO_{2peak}	-38.1 (-48.3 to -26.7)
Goodall et al. 2014	9 [61.1 ± 4.6]	17.4	3800 m (NH)	2	60% of the difference between the VT1 and $\dot{V}O_{2max}$	-55.5 (-62.1 to -47.8)
Heubert, Quaresima, Laffite, Koralsztein, & Billat, 2005	9	15	2200 m (NH)	2	90% Maximal aerobic power	-18.1 (-20.5 to -14.8)

Kelly et al., 2014	13 [58.3 ± 6.3]	14	3800 m (NH)	3	75% of the difference between the VT1 and VO$_{2max}$	-54.2 (-58.9 to -48.8)
Romer et al., 2007	9 [56.5 ± 2.7]	17	3800 m (NH)	3	92 ± 1% of W$_{peak}$	-68.7 (-70.2 to -67.0)
Wehrlin & Hallén, 2006	8 [66.0 ± 1.6]	2.8	500 m (HH)	2	107% VO$_{2peak}$	-13.1 (-16.5 to -9.5)
		4.8	1000 m (HH)			-14.8 (-17.3 to -12.2)
		7.2	1500 m (HH)			-25.9 (-28.8 to -22.9)
		9.8	2000 m (HH)			-29.5 (-31.6 to -27.4)
		12.4	2500 m (HH)			-35.6 (-37.5 to -34.3)

NH: normobaric hypoxia; HH: hypobaric hypoxia.

Exercise duration categories are numerically defined as: (1) < 2min; (2) 2-10 min; and (3) > 10 min.

Table 2. Linear and quadratic interaction between altitude and subgroups within exercise type, with an illustrative example of percentage effect on performance at 3000 m

Exercise Category	Model	Altitude	Altitude^2	Example performance effect at 3000 m
TT	Linear	-6.4 ± 0.4%*		-58.0%
	Quadratic	-1.7 ± 3.5%	-1.4 ± 0.3% *	-47.7%
TTE	Linear	-19.6 ± 2.0% *		-19.2%
	Quadratic	-10.2 ± 2.6% *	-1.9 ± 0.4% *	-17.7%

*Represents a statistically significant interaction determined through 95% confidence intervals
Data reported as mean ± standard error.
Intercept for all models are constrained to zero.

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