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

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.

Introduction

Sojourns to terrestrial high altitudes have grown in popularity in recent years, with the World Health Organisation reporting that approximately 35 million people visit terrains greater than 3000 m every year. Furthermore, there is a greater prevalence of altitude and hypoxic training camps amongst elite athletes in preparation for major competition. This has necessitated a greater understanding on the effect of altitude on exercise performance. A predominant environmental stressor for human physiology at altitude is the lower partial pressure of oxygen with progressive elevations. As such, the recent commercialisation of hypoxic simulation chambers and portable devices has increased the accessibility to acute hypoxic training strategies for recreational athletes and individuals predisposed to health issues. Intermittent hypoxic training (IHT) is one ergogenic training strategy commonly used; whereby isolated acute hypoxic training bouts are interspersed within a training programme. These acute training bouts, however, present a substantially negative impact on exercise capacity (Wehrlin & Hallén, 2006) and performance (Clark et al., 2007; Goods, Dawson, Landers, Gore, & Peeling, 2014). Therefore, quantifying the negative effect of hypoxia is important to inform exercise prescription and performance management during IHT training and other forms of acute hypoxic exercise.

The magnitude of acute hypoxia's ergolytic effect is dependent on the type of exercise and the duration (Wyatt, 2014). Indeed, mean power output during 5 min time trial (TT) reduces by 7% every 1000 m (Clark et al., 2007) and exercise capacity is reported to decline by 9.4% in the first 500 m with a greater 14.3% per 1,000 m thereafter (Wehrlin & Hallén, 2006). However, mean power output and work completed during repeated sprint exercise (RSE) is only impaired from hypoxic conditions equivalent to 4000 m (Bowtell, Cooke, Turner, Mileva, & Sumners, 2014; Goods et al., 2014). This difference in effect may be attributed to the shorter duration of activity during RSE tests; given the suggestion that high intensity exercise lasting less than 2 min is largely unaffected by hypoxia (Wyatt, 2014). Furthermore, acute hypoxia is shown to enhance the relative anaerobic energy contribution and concurrently lower the relative and absolute aerobic contribution (Horscroft & Murray, 2014; Scott, Goods, & Slattery, 2016). Therefore, the magnitude of decline is likely to be dependent on the bioenergetic demand of the exercise bout, which is determined by duration and the required intensity.

Despite current evidence from experimental investigations, a pooled effect from all available evidence will offer a more generalisable understanding of the effect of acute hypoxia on exercise performance.

The influence of acute hypoxia during exercise is subject to large inter-individual variability, with training status (Macinnis, Nugent, Macleod, & Lohse, 2015) and an individual's ability to maintain oxyhaemoglobin saturation (SaO2) during exercise (Chapman, Stager, Tanner, Stray-Gundersen, & Levine, 2011) cited as primary reasons for this variability. Indeed, a meta-analysis identified that the reduction of maximal rate of oxygen consumption (VO_{2max}) under acute hypoxia was greater in those that possessed a superior VO_{2max} (Macinnis et al., 2015). Thereby, suggesting that athletes of a higher training status may be subject to a greater decrement in performance compared to their untrained counterparts. While, susceptibility to SaO_2 reductions is reported to be a more robust predictor of exercise performance under hypoxia, given the preservation of SaO_2 during exercise is linked to the improved maintenance of 3000 m running performance under acute moderate hypoxic conditions (Chapman et al., 2011). Therefore, reducing peripheral oxygen delivery to active musculature, as inferred through a lower SaO_2, is a hypothesised to be a primary moderator of exercise performance within acute hypoxic conditions.

The purpose of this study was to perform a systematic review and meta-regression to quantify the effect of varying magnitudes of hypoxia on exercise capacity and performance. Performance was further subdivided into continuous (TT), intermittent and sprint (Wingate test) exercise sub-groups; and each group assessed against the moderators of elevation equivalent to the hypoxic magnitude tested, SaO_2 reduction during exercise and training status. Furthermore, the ergolytic effect of hypoxia was assessed against exercise of different durations.

Method

This meta-analysis followed the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.

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 (≥ 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

varying magnitudes of hypoxia and experimental data from independent groups were extracted as separate outcomes.

Data were categorised into sub-groups based on exercise type and duration of exercise bout. The exercise subgroups reflected the outcomes outlined in the eligibility criteria: TT performance, intermittent exercise, TTE and sprint tests. Exercise was also categorised into three time based sub-groups (< 2 mins, 2 – 10 min and > 10 mins) as the ergolytic effect of hypoxia is proposed to be dependent on duration (Wyatt, 2014). The first category was chosen as exercise below 2 min is suggested to be unaffected by acute hypoxia (Wyatt, 2014); whereas the category between 2-10 min was chosen to include the range of exercises that are likely to require an anaerobic energy contribution (Duffield, Dawson, & Goodman, 2005). Exercise beyond 10 min is included in this review to represent exercise intensities that predominantly require an aerobic energy contribution. Intermittent exercise, which involved controlled repetitions of work and recovery, were categorised on the total duration of high intensity activity periods. Furthermore, outcomes were categorised by training status with a sea level $VO_{2max} \geq 55$ ml·kg^{-1}·min^{-1} classified as trained and < 55 ml·kg^{-1}·min^{-1} as healthy untrained (De Pauw et al., 2013). Where VO_{2max} was not reported, articles were not included in analysis to maintain objectivity.

Quality and bias assessment

The overall quality of evidence for each outcome was determined by S.K.D and L.A.G independently, using the Grades of Recommendation, Assessment, Development and Evaluation Working Group (GRADE) approach. The GRADE protocol offers a systematic method to evaluate the quality of research whilst considering methodological limitation, consistency of outcomes, reporting or publication bias and indirectness of evidence. Furthermore, to increase specificity to the current research question three discipline specific factors were considered under the category methodological limitation: 1) the control of prior altitude/hypoxic exposure to reduce any confounding effects of acclimatisation; 2) standardisation of dietary intake prior to experimental trials; and 3) familiarisation to exercise trials. In addition to the traditional quality control criteria to limit bias: 1) blinding of participants; 2) blinding of researcher; 3) blinding outcome assessment; and 4) complete outcome data.

However, the indirectness of evidence was not considered in this review, due to inclusion criteria requiring the assessment of exercise performance directly; while a traditional funnel plot was not used to assess publication bias due to the natural negative skew expected in the data, given the strong physiological basis that exercise performance will not be enhanced under acute hypoxia.

Data analysis

The ratio of means (ROM) method was used to establish pooled effects and variances of hypoxic interventions. This method allows outcomes of different units to be pooled and compared, whilst also allowing for easy interpretation for practitioners, athletes, and coaches because outcomes can be expressed as a percentage change. The natural logarithm of each ROM (equation 1) and its variance (equation 2) were calculated using the mean values of sea level ($\bar{x}_c$) and hypoxia ($\bar{x}_T$), their respective standard deviations (SD), number of participants (N) and a correction (r) between sea level and hypoxic trial performance:

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

$$Var[log(RoM)] = \frac{(SD_C)^2}{N_c \bar{x}^2_c} + \frac{(SD_T)^2}{N_T \bar{x}^2_T} + \frac{2rSD_C SD_T}{\bar{x}_c \bar{x}_T \sqrt{N_c N_T}} \quad \text{[Equation 2]}$$

The calculation of the variance of ROM requires knowledge of the correlation (r) between sea level and hypoxic trial outcomes, which is not commonly reported. Estimates from individual studies were obtained using reported t statistics as follows (equation 3):

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

Appropriate information was only available for 23 studies; therefore, a pooled single estimate of the correlation r was calculated from the available data using the Meta package in r (R Foundation for Statistical Computing, Vienna Austria). The pooled correlation value (r = 0.78, 95% confidence interval: 0.62 to 0.87) was then applied to all studies. Sensitivity analyses using correlation values of r = 0.68 and r = 0.88 were also carried out to validate the primary model.

A three-level mixed effects meta-regression was used to analyse ROMs and variances whilst accounting for dependencies in the data set. The three levels can be described by regression equations at the sample (level 1), outcome (level 2) and study (level 3) level (Van den Noortgate, López-López, Marín-Martínez, & Sánchez-Meca, 2013). The fixed effects categorical moderators included exercise type (TT, intermittent, TTE and Sprint), exercise duration (< 2 min, 2-10 min and > 10 min) and training status (trained vs. healthy). The overall and interaction effects with altitude elevation in km equivalent to the FiO_2 exposure and end exercise mean difference in SaO_2 between normoxic and hypoxic conditions were also evaluated as continuous moderators. Furthermore, given the reported non-linear relationship between acute hypoxia and VO_{2max} (Macinnis et al., 2015) and critical power (Townsend, Nichols, Skiba, Racinais, & Périard, 2017), the review also assessed curvilinear effects of altitude elevation using quadratic models. Regression analyses were constrained to a zero intercept to enhance external validity. Pooled effects on the logarithmic scale were subsequently back transformed and multiplied by 100 to provide percentage change of effects. A normal distribution was assumed for log-transformed effects and therefore 95% confidence intervals were obtained from ± 1.96 × standard error and back transformed. All outcomes are reported as percentage effect estimate ± standard error and the corresponding 95% confidence intervals, unless otherwise stated. All analysis was performed using the metaphor package in R (R Foundation for Statistical Computing, Vienna Austria). Statistical significant was assessed through 95% confidence intervals, with estimates that cross the zero-boundary interpreted as non-significant.

Results

Study characteristics

Fifty-three studies met the inclusion criteria set for this review (Table 1), which provided effect statistics for 82 outcomes within 798 participants and ranged from 500-5700 m altitude (mean ± SD: 3000 ± 1300 m). These studies were categorised into an exercise modality and an exercise duration category for analysis. Training status was explicitly reported in 47 outcomes, with 33 cohorts classified as trained against 14 cohorts classified as untrained healthy participants; whilst SaO_2 was available in 54 outcomes

(13.2% ± 7.2%). Only five studies were performed utilising hypobaric hypoxia and therefore the type of hypoxic exposure was not considered as a moderator in this study.

Quality assessment

Under the GRADE research quality assessment, the overall quality is rated high due to the inclusion of only randomised control trials in this review and the limited evidence to warrant the downgrading of quality. Methodological limitations and bias in the included articles, were assessed against pre-determined criteria, with the percentage of studies demonstrating each criterion as follows: (1) the control of prior altitude/hypoxic exposure: 47%; (2) standardisation of dietary intake: 62%; (3) familiarisation to exercise trials: 87%; (4) blinding of participants: 43%; (5) blinding of researcher: 23%; (6) blinding outcome assessment: 0%; and (7) complete outcome data: 42%.

Overall effect

The intercept only three-level mixed effects model identified a negative 17.1 ± 3.7% (95% CI -22.8% to -11%) effect on all categories of exercise capacity and performance with 20.8%, 62.5% and 16.7% of the variance explained by the sample, between study and between outcome variance, respectively. The outcomes from the sensitivity analysis found no substantive difference in effect or variance between models using r = 0.67, r = 0.87 and r = 0.77 correlation values. Acute hypoxic exposure was calculated to have a significant moderating effect that equates to a 6.5% reduction for every 1000 m elevated (-6.5 ± 0.9%; 95% CI -8.2% to -4.8%). No evidence was obtained for a non-linear effect of altitude on the overall dataset. Similarly, for a 1% reduction in SaO_2 a significant negative 2.0 ± 0.4% (95% CI -2.9% to -1.2%) effect was reported.

Moderating effects of exercise types

Exercise type was found to have a moderating effect on exercise performance under acute hypoxic conditions (Figure 1), with TT performance and TTE tests experiencing a significant -16.2 ± 4.3% (95% CI -22.9% to -9.0%) and -44.5 ± 6.9% (95% CI -51.3% to -36.7%) change. However, the overall effect on intermittent exercise (-5.6 ± 4.8% ;95% CI -13.9% to 3.5%) and sprint performance (-2.9 ± 8.0; 95% CI -16.5% to 12.8%) were non-significant. Moreover, interaction effects were reported between

exercise type and magnitude of altitude elevation. Additionally, altitude^2 moderator improved model fit compared to the linear model when exercise type was included ($\chi_{(10)}$ = 8.0; p = 0.005), indicating a curvilinear effect of acute hypoxia. The exercise type category was subsequently reduced to TT and TTE sub-groups to determine the interaction effects with linear and quadratic effects of altitude elevation (Table 2), which are depicted in Figure 2. The magnitude of SaO_2 decline was also determined to have the largest moderating effect on TTE exercise compared to the three other exercise types, with 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 -2.1% to -0.5%) moderating effect for every 1% reduction in SaO_2 was also evident on TT performance.

Moderating effects of exercise duration

Acute hypoxia had no effect on exercise of < 2 min duration (-6.3 ± 5.6%; 95% CI -16.1% to -3.8%), however exercise between 2-10 min and > 10 min had a significant -18.0 ± 6.0% (95% CI -25.8% to -8.2%) and -26.8 ± 5.5% (95% CI -33.2% to -18.2%) effect, respectively. A similar interaction effect with altitude was also found for exercise between 2 to 10 min and > 10 min, with a negative -13.6 ± 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. A similar moderating effect of SaO_2 was noted for the 2-10 min category at -2.4 ± 0.7% (95% CI -3.8% 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 SaO_2.

Moderating effect of training status

Trained and healthy individuals were found to have a pooled -21.8 ± 6.8% effect (95% CI -31.2% to -11.1%) and -29.5 ± 9.6% (95% CI -41.1% to -15.5%) decline in performance with acute hypoxia, respectively. Given the variance in the range of altitude elevations and greater mean elevation in the healthy cohort, further analysis that controlled for altitude found a non-significant effect between sub-groups. There was however, a difference in the moderating effect of SaO_2 between the sub-groups, with a significant moderating effect for every 1% reduction in SaO_2 apparent in trained (-2.8 ± 0.5%; 95% CI -3.8% to -1.7%) but not in untrained healthy participants (-2.0 ± 1.6%; 95% CI -5.1% to 1.1%).

Further analysis

Owing to the large proportion of outcomes in the intermittent exercise group also classified as < 2 min (17 of the 23), the main effect in the intermittent sub-group may have been skewed. Therefore, further analysis to determine the pooled effect on intermittent exercise bouts > 2 min were performed. An overall pooled estimate of -4.7 ± 1.3% (95% CI -7.2% to -2.2%) was observed, however acute hypoxia elevation was not found to be a significant moderator of intermittent exercise over 2 min (95% CI -7.7% to 3.1%).

Discussion

This is the first meta-analysis to study the effects of acute hypoxic exposure on exercise capacity and performance; and assess the effect against moderators of altitude elevation based on FiO_2 tested, SaO_2, training status, exercise duration and type of exercise. This review is the first to show the curvilinear relationship between exercise and acute hypoxic exposure during TT and TTE exercise tests, and exercise activity > 2 min. In contrast, no ergolytic effect was found during intermittent exercise and sprint tests; and exercise < 2 min. When exercise < 2 min were removed from the analysis of intermittent exercise, a significant negative effect was seen, suggesting prolonged intermittent exercise is impaired under acute hypoxic conditions. Training status was demonstrated to be a significant moderator, with trained and healthy individuals exhibiting a similar negative effect. While reductions in SaO_2 displayed a negative moderating effect in the overall model, however these effects were more pronounced within trained participants. Together, these results highlight the magnitude dependent moderating effects of acute hypoxia, while also showing potential factors that are likely to influence exercise performance at acute hypoxia.

The curvilinear relationship between exercise and hypoxic exposure is described by a quadratic model. This is equivalent to the meta-analytic model previously used to describe the relationship with VO_{2max} (Macinnis et al., 2015). Furthermore, critical power (CP), a suggested marker of maximal sustainable aerobic power, has been fitted to a higher order cubic model to show the negative relationship within nine trained cyclists (Townsend et al., 2017). Nonetheless, this is the first study to describe a curvilinear relationship during TT performance and TTE tests, given previous experimental studies have reported a linear 7.0% reduction in TT performance per 1000 m (Clark et al., 2007) and TTE decline linearly by

14.5% per 1000 m up to a moderate 3000 m elevation (Wehrlin & Hallén, 2006). When comparing the quadratic models of the current dataset at a hypoxic exposure equivalent to 3000 m. TTE and TT performance can be predicted fall by 47.7% and 17.7%, respectively, whereas previous research would suggest a 43.5% reduction in TTE and 21.0% reduction in TT performance. The small but important difference in the magnitude of decline and the curvilinear model is likely to be explained by the greater range of acute hypoxic magnitudes, equivalent 500 m to 5700 m elevation, in the present model, which includes severe hypoxic exposures, whereas previous experimental work only assessed low and moderate altitudes (< 3000 m) (Clark et al., 2007; Wehrlin & Hallén, 2006). Indeed, earlier articles that also reported a curvilinear relationship, also included severe hypoxic exposures (Macinnis et al., 2015; Townsend et al., 2017), which suggests alternative fatiguing mechanisms may be operating. Current evidence alludes to an exacerbated central fatigue action through diminished group III/IV afferent feedback with exposure to severe hypoxic conditions, whereas the central motor output is unchanged from sea level at moderate hypoxic exposures (Amann, Romer, Subudhi, Pegelow, & Dempsey, 2007). This diminished central motor output may, in part, explain the exponential decline in performance observed with greater elevation.

The magnitude of the impairment with acute hypoxia is dependent on the type and duration of exercise, with TT performance and TTE tests found to elicit ergolytic effects, while sprint and intermittent tests found to be largely unchanged from sea level. This effect may be explained by the duration of exercise within these sub-groups, given sprint exercise and the repeated sprint exercise (RSE) within the intermittent group formed the < 2 min sub-group. Indeed, experimental studies assessing the various magnitudes of hypoxia on RSE have only reported performance decrements above 4000 m (Bowtell et al., 2014; Goods et al., 2014). However, the current model did not show this due to the assessment of performance against a continuous hypoxic moderator rather than at 1000 m categorical intervals used in experimental studies. Nonetheless, sprint and RSE performance, which is equivalent for the < 2 min duration category, are sustained with acute hypoxia; an effect that can be explained through greater reliance on anaerobic energy sources, which provides the greatest contribution to RSE and sprint performance (Scott et al., 2016). The separation of exercise activity less than 2 min in the intermittent

sub-group did however, suggest prolonged intermittent exercise is impaired under acute hypoxia, which may explain the decrement in physical output during team sports competition at altitude (Aldous et al., 2016). However, the moderating effect of acute hypoxia were not evident, which may be attributed to the lack of available outcomes; therefore, further research should aim to assess effects of several incremental magnitudes of acute hypoxia on prolonged intermittent performance.

The lack of effect during short duration (< 2 min) exercise bouts is also reflected in previous research assessing the impact of altitude on track athletes (Hamlin, Hopkins and Hoolings, 2015) and may also be mechanistically explained when viewed through the two parameter CP concept (Simpson et al. 2015; Sherman et al., 2016; Townsend et al., 2017). When analysing track performances of major international competitions at varying degrees of altitude, Hamlin et al., (2015) reported track sprint events (100-400 m) did not exhibit a negative effect associated with hypoxia, but rather, a performance improvement due to the reduced aerodynamic resistance caused by the lower barometric pressure present at terrestrial altitudes. Whereas, longer track events (800 -10000 m) that require a larger relative aerobic energetic contribution exhibit a performance decrement at elevations ≤ 150 m. As such, demonstrating the outcomes of this meta-analysis are also reflected during athletic competition. Further to this, with hypoxic exposures, critical power exhibits a substantial decline in performance corresponding to the performance impairment noted during longer TT and TTE exercise that requires a greater aerobic contribution. Whereas, W', the ability to perform work above CP is unchanged under moderate hypoxic conditions (Simpson et al. 2015; Sherman et al., 2016; Townsend et al., 2017). Traditionally, W' is purported to represent the anaerobic work capacity and as such, the lack of change reported during exercise < 2 min in the current study may be explained through the two parameter CP model.

There is evidence to suggest an individual variability in exercise response to acute hypoxic exposure, which is predominantly accounted by superiorly trained individuals exhibiting the largest decrement in VO_{2max} (Macinnis et al., 2015) under acute hypoxic conditions, given their inability to maintain SaO_2 during exercise compared to untrained individuals (Chapman et al., 2011). Chapman et al., (2011) further identified that individuals that exhibited the greatest reductions in SaO_2 during a 3000 m running performance, experienced a greater impairment in running performance. In the current study,

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

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

under acute hypoxia, particularly within trained cohorts who are suggested to experience a larger moderating effect of SaO_2.

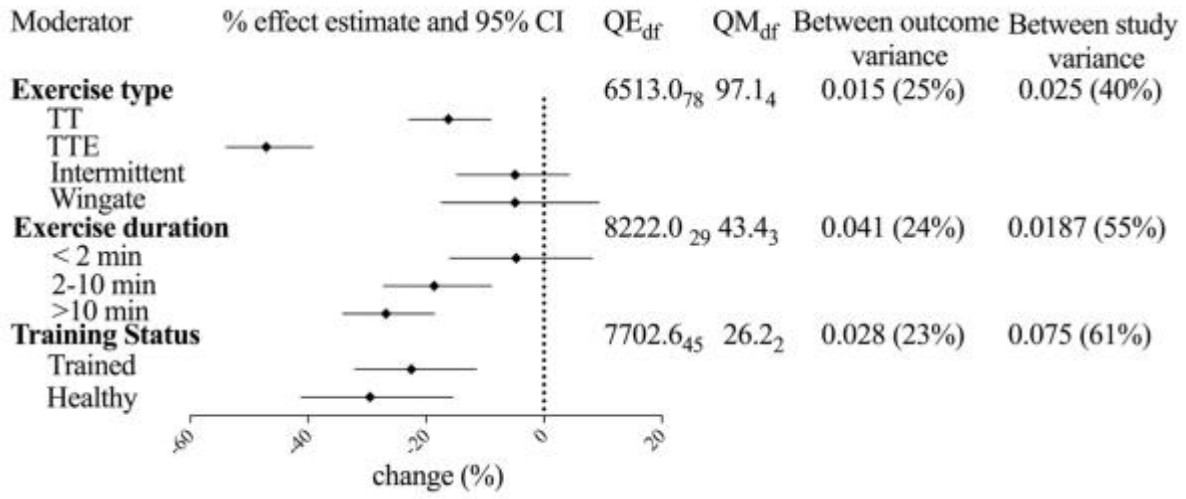

Figure 1. Results from categorical moderator analysis.
QE_{df}: residual heterogeneity test statistic; QM_{df}: omnibus moderator test statistic.
Between outcome and study variance are accompanied by a percentage showing the proportion of total variance in the model that they account for.
Confidence intervals crossing the zero-boundary show non-significant effects.

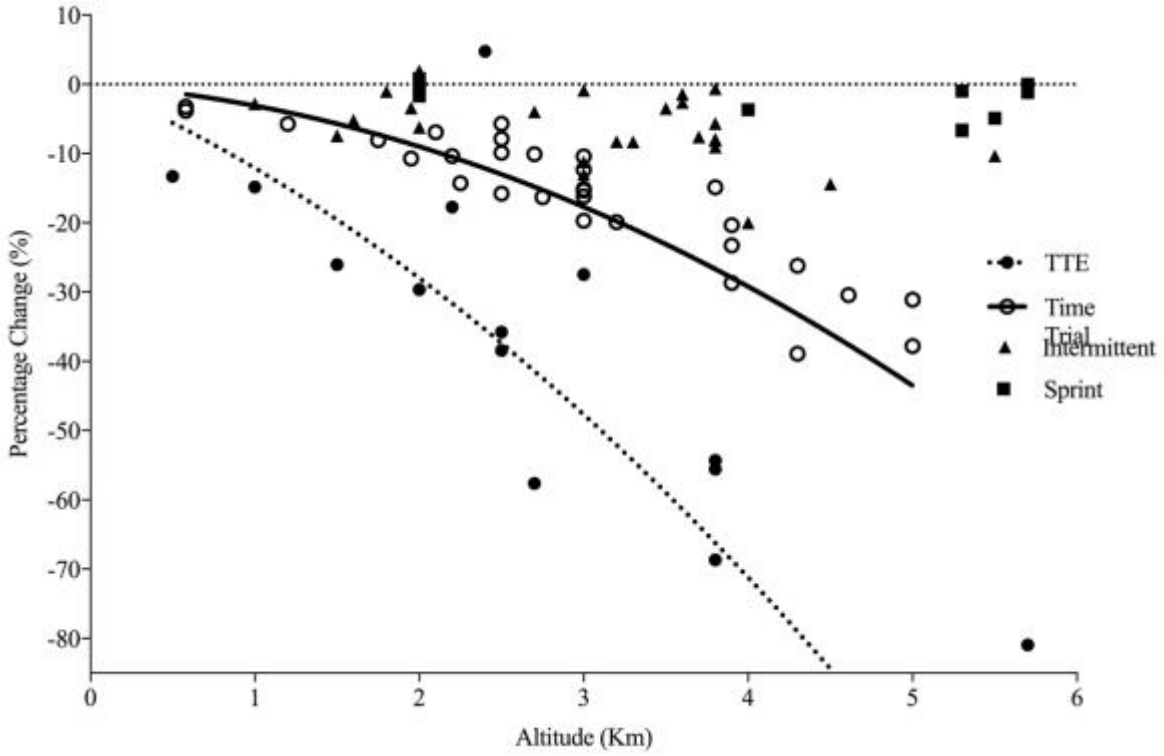

Figure 2. A scatterplot showing the outcomes included this meta–analysis categorised by exercise type, with quadratic regression lines shown for TTE and TT performance. Wingate, intermittent and TT performance are shown as a percentage change in mean power output, while TTE as a percentage change in 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}] ($ml \cdot kg^{-1} \cdot min^{-1}$)	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]		3000 m (NH)	2	Total Work done during a 10 min TT	-14.8 (-17.3 to -13.1)
	9 [53.3 ± 3.5]		3000 m (NH)			-15.6 (-16.5 to -14.8)
	10 [55.1 ± 1.7]		3000 m (NH)			-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	2700 m (NH)	1	10 X 6 sec sprints with 30 a rest	-3.9 (-8.6 to 1.0)
		26.2	3200 m (NH)			-8.6 (-12.2 to -3.9)
		13.6	3800 m (NH)			-8.6 (-13 to -5.8)

		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 $\dot{V}O_{2max}$	-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.

1. Aldous, J. W. F., Chrismas, B. C. R., Akubat, I., Dascombe, B., Abt, G., & Taylor, L. (2016). Hot and Hypoxic Environments Inhibit Simulated Soccer Performance and Exacerbate Performance Decrements When Combined. *Frontiers in Physiology*, *6*, 421. https://doi.org/10.3389/fphys.2015.00421
2. Amann, M., Eldridge, M. W., Lovering, A. T., Stickland, M. K., Pegelow, D. F., & Dempsey, J. A. (2006). Arterial oxygenation influences central motor output and exercise performance via effects on peripheral locomotor muscle fatigue in humans. *The Journal of Physiology*, *575*(Pt 3), 937–52. https://doi.org/10.1113/jphysiol.2006.113936
3. Amann, M., Romer, L. M., Subudhi, A. W., Pegelow, D. F., & Dempsey, J. A. (2007). Severity of arterial hypoxaemia affects the relative contributions of peripheral muscle fatigue to exercise performance in healthy humans. *The Journal of Physiology*, *581*(Pt 1), 389–403. https://doi.org/10.1113/jphysiol.2007.129700
4. Beidleman, B. A., Fulco, C. S., Staab, J. E., Andrew, S. P., & Muza, S. R. (2014). Cycling performance decrement is greater in hypobaric versus normobaric hypoxia. *Extreme Physiology & Medicine*, *3*, 8. https://doi.org/10.1186/2046-7648-3-8
5. Billat, V. L., Lepretre, P. M., Heubert, R. P., Koralsztein, J. P., & Gazeau, F. P. (2003). Influence of acute moderate hypoxia on time to exhaustion at vVO2max in unacclimatized runners. *International Journal of Sports Medicine*, *24*(1), 9–14. https://doi.org/10.1055/s-2003-37251
6. Billaut, F., & Buchheit, M. (2013). Repeated-sprint performance and vastus lateralis oxygenation: Effect of limited O_2 availability. *Scandinavian Journal of Medicine & Science in Sports*, *23*(3), e185–e193. https://doi.org/10.1111/sms.12052
7. Billaut, F., Kerris, J. P., Rodriguez, R. F., Martin, D. T., Gore, C. J., & Bishop, D. J. (2013). Interaction of Central and Peripheral Factors during Repeated Sprints at Different Levels of Arterial O2 Saturation. *PLoS ONE*, *8*(10), e77297. https://doi.org/10.1371/journal.pone.0077297
8. Bourdillon, N., Fan, J.-L., & Kayser, B. (2014). Cerebral oxygenation during the Richalet hypoxia sensitivity test and cycling time-trial performance in severe hypoxia. *European Journal of Applied Physiology*, *114*(5), 1037–48. https://doi.org/10.1007/s00421-014-2835-8
9. Bourdillon, N., Fan, J.-L., Uva, B., Müller, H., Meyer, P., & Kayser, B. (2015). Effect of oral nitrate supplementation on pulmonary hemodynamics during exercise and time trial performance in normoxia and hypoxia: a randomized controlled trial. *Frontiers in Physiology*, *6*, 288. https://doi.org/10.3389/fphys.2015.00288
10. Bowtell, J. L., Cooke, K., Turner, R., Mileva, K. N., & Sumners, D. P. (2014). Acute physiological and performance responses to repeated sprints in varying degrees of hypoxia. *Journal of Science and Medicine in Sport*, *17*(4), 399–403.

https://doi.org/10.1016/j.jsams.2013.05.016

11. Brosnan, M. J., Martin, D. T., Hahn, A. G., Gore, C. J., & Hawley, J. A. (2000). Impaired interval exercise responses in elite female cyclists at moderate simulated altitude. *Journal of Applied Physiology (Bethesda, Md. : 1985)*, *89*(5), 1819–24.
12. Calbet, J. A. L., De Paz, J. A., Garatachea, N., Cabeza de Vaca, S., & Chavarren, J. (2003). Anaerobic energy provision does not limit Wingate exercise performance in endurance-trained cyclists. *Journal of Applied Physiology*, *94*(2), 668–676. https://doi.org/10.1152/japplphysiol.00128.2002
13. Calbet, J. A. L., Losa-Reyna, J., Torres-Peralta, R., Rasmussen, P., Ponce-González, J. G., Sheel, A. W., … Lundby, C. (2015). Limitations to oxygen transport and utilization during sprint exercise in humans: evidence for a functional reserve in muscle O2 diffusing capacity. *The Journal of Physiology*, *593*(20), 4649–64. https://doi.org/10.1113/JP270408
14. Carr, A. J., Hopkins, W. G., & Gore, C. J. (2011). Effects of acute alkalosis and acidosis on performance: a meta-analysis. *Sports Medicine (Auckland, N.Z.)*, *41*(10), 801–14. https://doi.org/10.2165/11591440-000000000-00000
15. Castellani, J. W., Muza, S. R., Cheuvront, S. N., Sils, I. V., Fulco, C. S., Kenefick, R. W., … Sawka, M. N. (2010). Effect of hypohydration and altitude exposure on aerobic exercise performance and acute mountain sickness. *Journal of Applied Physiology*, *109*(6), 1792–1800. https://doi.org/10.1152/japplphysiol.00517.2010
16. Chapman, R. F., Stager, J. M., Tanner, D. A., Stray-Gundersen, J., & Levine, B. D. (2011). Impairment of 3000-m run time at altitude is influenced by arterial oxyhemoglobin saturation. *Medicine and Science in Sports and Exercise*, *43*(9), 1649–56. https://doi.org/10.1249/MSS.0b013e318211bf45
17. Clark, S. A., Bourdon, P. C., Schmidt, W., Singh, B., Cable, G., Onus, K. J., … Aughey, R. J. (2007). The effect of acute simulated moderate altitude on power, performance and pacing strategies in well-trained cyclists. *European Journal of Applied Physiology*, *102*(1), 45–55. https://doi.org/10.1007/s00421-007-0554-0
18. Coppel, J., Hennis, P., Gilbert-Kawai, E., & Grocott, M. P. (2015). The physiological effects of hypobaric hypoxia versus normobaric hypoxia: a systematic review of crossover trials. *Extreme Physiology & Medicine*, *4*(1), 2. https://doi.org/10.1186/s13728-014-0021-6
19. Dahlstrom, B. K., Duff, W. R. D., Poloskei, S., Schaerz, S., Len, T. K., & Neary, J. P. (2013). Neuromuscular changes following simulated high-intensity cycling performance in moderate hypoxia. *Journal of Exercise Science & Fitness*, *11*(2), 78–84. https://doi.org/10.1016/j.jesf.2013.10.001
20. Lovell, D., McLellan, C., & Minahan, C. (2015). Performance and Metabolic Responses of Highly-Trained Team-Sport Athletes during Repeated Sprinting in Hypoxia. *Journal of Athletic Enhancement*, *4*(2). https://doi.org/10.4172/2324-9080.1000190

21. De Pauw, K., Roelands, B., Cheung, S. S., de Geus, B., Rietjens, G., & Meeusen, R. (2013). Guidelines to classify subject groups in sport-science research. *International Journal of Sports Physiology and Performance*, *8*(2), 111–22.
22. Deb, S. K., Gough, L. A., Sparks, S. A., & McNaughton, L. R. (2017). Determinants of curvature constant (W') of the power duration relationship under normoxia and hypoxia: the effect of pre-exercise alkalosis. *European Journal of Applied Physiology*, *117*(5), 901–912. https://doi.org/10.1007/s00421-017-3574-4
23. Duffield, R., Dawson, B., & Goodman, C. (2005). Energy system contribution to 1500- and 3000-metre track running. *Journal of Sports Sciences*, *23*(10), 993–1002. https://doi.org/10.1080/02640410400021963
24. Fan, J.-L., Bourdillon, N., & Kayser, B. (2013). Effect of end-tidal CO2 clamping on cerebrovascular function, oxygenation, and performance during 15-km time trial cycling in severe normobaric hypoxia: the role of cerebral O2 delivery. *Physiological Reports*, *1*(3), e00066. https://doi.org/10.1002/phy2.66
25. Flinn, S., Herbert, K., Graham, K., & Siegler, J. C. (2014). Differential effect of metabolic alkalosis and hypoxia on high-intensity cycling performance. *Journal of Strength and Conditioning Research / National Strength & Conditioning Association*, *28*(10), 2852–8. https://doi.org/10.1519/JSC.0000000000000489
26. Foss, J. (2015). Short Term Arrival Strategies For Endurance Exercise Performance At Moderate Altitude. [dissertation]. Indianna University.
27. Garvican-Lewis, L. A., Clark, B., Martin, D. T., Schumacher, Y. O., McDonald, W., Stephens, B., … Menaspà, P. (2015). Impact of Altitude on Power Output during Cycling Stage Racing. *PLOS ONE*, *10*(12), e0143028. https://doi.org/10.1371/journal.pone.0143028
28. Girard, O., Brocherie, F., Morin, J.-B., & Millet, G. P. (2015). Neuro-mechanical determinants of repeated treadmill sprints - Usefulness of an "hypoxic to normoxic recovery" approach. *Frontiers in Physiology*, *6*, 260. https://doi.org/10.3389/fphys.2015.00260
29. Girard, O., Brocherie, F., Morin, J.-B., & Millet, G. P. (2016). Running mechanical alterations during repeated treadmill sprints in hot *versus* hypoxic environments. A pilot study. *Journal of Sports Sciences*, *34*(12), 1190–1198. https://doi.org/10.1080/02640414.2015.1101482
30. Girard, O., & Racinais, S. (2014). Combining heat stress and moderate hypoxia reduces cycling time to exhaustion without modifying neuromuscular fatigue characteristics. *European Journal of Applied Physiology*, *114*(7), 1521–32. https://doi.org/10.1007/s00421-014-2883-0
31. Goodall, S., Twomey, R., & Amann, M. (2014). Acute and chronic hypoxia: implications for cerebral function and exercise tolerance. *Fatigue : Biomedicine, Health & Behavior*, *2*(2), 73–92. https://doi.org/10.1080/21641846.2014.909963

32. Goods, P. S. R., Dawson, B., Landers, G. J., Gore, C. J., Croft, K., & Peeling, P. (2016). Effect of repeat-sprint training in hypoxia on post-exercise interleukin-6 and F_2 -isoprostanes. *European Journal of Sport Science*, *16*(8), 1047–1054. https://doi.org/10.1080/17461391.2015.1123776
33. Goods, P. S. R., Dawson, B. T., Landers, G. J., Gore, C. J., & Peeling, P. (2014). Effect of Different Simulated Altitudes on Repeat-Sprint Performance in Team-Sport Athletes. *International Journal of Sports Physiology and Performance*, *9*(5), 857–862. https://doi.org/10.1123/ijspp.2013-0423
34. Gore, C. J., Little, S. C., Hahn, A. G., Scroop, G. C., Norton, K. I., Bourdon, P. C., … Emonson, D. L. (1997). Reduced performance of male and female athletes at 580 m altitude. *European Journal of Applied Physiology and Occupational Physiology*, *75*(2), 136–43. https://doi.org/10.1007/s004210050138
35. Hamlin, M.J., Hopkins, W.G., & Hollings, S.C. (2015) Effects of altitude on performance of elite track-and-field athletes. *Int J Sports Physiol Perform*. 10(7), 881 -887. https://doi: 10.1123/ijspp.2014-0261
36. Heubert, R. A. P., Quaresima, V., Laffite, L. P., Koralsztein, J. P., & Billat, V. L. (2005). Acute Moderate Hypoxia Affects the Oxygen Desaturation and the Performance but not the Oxygen Uptake Response. *International Journal of Sports Medicine*, *26*(7), 542–551. https://doi.org/10.1055/s-2004-821329
37. Horscroft, J. A., & Murray, A. J. (2014). Skeletal muscle energy metabolism in environmental hypoxia: climbing towards consensus. *Extreme Physiology & Medicine*, *3*(1), 19. https://doi.org/10.1186/2046-7648-3-19
38. Jacobs, K. A., Kressler, J., Stoutenberg, M., Roos, B. A., & Friedlander, A. L. (2011). Sildenafil Has Little Influence on Cardiovascular Hemodynamics or 6-km Time Trial Performance in Trained Men and Women at Simulated High Altitude. *High Altitude Medicine & Biology*, *12*(3), 215–222. https://doi.org/10.1089/ham.2011.0011
39. Kelly, J., Vanhatalo, A., Bailey, S. J., Wylie, L. J., Tucker, C., List, S., … Jones, A. M. (2014). Dietary nitrate supplementation: effects on plasma nitrite and pulmonary O2 uptake dynamics during exercise in hypoxia and normoxia. *AJP: Regulatory, Integrative and Comparative Physiology*, *307*(7), R920–R930. https://doi.org/10.1152/ajpregu.00068.2014
40. Koelwyn, G. J., Wong, L. E., Kennedy, M. D., & Eves, N. D. (2013). The effect of hypoxia and exercise on heart rate variability, immune response, and orthostatic stress. *Scandinavian Journal of Medicine & Science in Sports*, *23*(1), e1–e8. https://doi.org/10.1111/sms.12003
41. Kon, M., Nakagaki, K., Ebi, Y., Nishiyama, T., & Russell, A. P. (2015). Hormonal and metabolic responses to repeated cycling sprints under different hypoxic conditions. *Growth Hormone & IGF Research*, *25*(3), 121–126. https://doi.org/10.1016/j.ghir.2015.03.002
42. Kressler, J., Stoutenberg, M., Roos, B. A., Friedlander, A. L., Perry, A. C., Signorile, J. F., &

Jacobs, K. A. (2011). Sildenafil does not improve steady state cardiovascular hemodynamics, peak power, or 15-km time trial cycling performance at simulated moderate or high altitudes in men and women. *European Journal of Applied Physiology*, *111*(12), 3031–3040. https://doi.org/10.1007/s00421-011-1930-3

43. Macinnis, M. J., Nugent, S. F., Macleod, K. E., & Lohse, K. R. (2015). Methods to Estimate V˙O2max upon Acute Hypoxia Exposure. *Medicine & Science in Sports & Exercise*, *47*(9), 1869–1876. https://doi.org/10.1249/MSS.0000000000000628
44. MacLeod, K. E., Nugent, S. F., Barr, S. I., Koehle, M. S., Sporer, B. C., & MacInnis, M. J. (2015). Acute Beetroot Juice Supplementation Does Not Improve Cycling Performance in Normoxia or Moderate Hypoxia. *International Journal of Sport Nutrition and Exercise Metabolism*, *25*(4), 359–66. https://doi.org/10.1123/ijsnem.2014-0129
45. McLellan, T. M., Kavanagh, M. F., & Jacobs, I. (1990). The effect of hypoxia on performance during 30 s or 45 s of supramaximal exercise. *European Journal of Applied Physiology and Occupational Physiology*, *60*(2), 155–61.
46. Morales-Alamo, D., Ponce-González, J. G., Guadalupe-Grau, A., Rodríguez-García, L., Santana, A., Cusso, M. R., … Calbet, J. A. L. (2012). Increased oxidative stress and anaerobic energy release, but blunted Thr172-AMPKα phosphorylation, in response to sprint exercise in severe acute hypoxia in humans. *Journal of Applied Physiology*, *113*(6).
47. Morrison, J., McLellan, C., & Minahan, C. (2015). A Clustered Repeated-Sprint Running Protocol for Team-Sport Athletes Performed in Normobaric Hypoxia. *Journal of Sports Science & Medicine*, *14*(4), 857–63.
48. Ogura, Y., Katamoto, S., Uchimaru, J., Takahashi, K., & Naito, H. (2006). Effects of low and high levels of moderate hypoxia on anaerobic energy release during supramaximal cycle exercise. *European Journal of Applied Physiology*, *98*(1), 41–7. https://doi.org/10.1007/s00421-006-0214-9
49. Oguri, K., Fujimoto, H., Sugimori, H., Miyamoto, K., Tachi, T., Nagasaki, S., … Matsuoka, T. (2008). Pronounced muscle deoxygenation during supramaximal exercise under simulated hypoxia in sprint athletes. *Journal of Sports Science & Medicine*, *7*(4), 512–9.
50. Peltonen, J. E., Rantamäki, J., Niittymäki, S. P., Sweins, K., Viitasalo, J. T., & Rusko, H. K. (1995). Effects of oxygen fraction in inspired air on rowing performance. *Medicine and Science in Sports and Exercise*, *27*(4), 573–9.
51. Périard, J. D., & Racinais, S. (2016). Performance and Pacing during Cycle Exercise in Hyperthermic and Hypoxic Conditions. *Medicine & Science in Sports & Exercise*, *48*(5), 845–853. https://doi.org/10.1249/MSS.0000000000000839
52. Puype, J., Van Proeyen, K., Raymackers, J.-M., Deldicque, L., & Hespel, P. (2013). Sprint Interval Training in Hypoxia Stimulates Glycolytic Enzyme Activity. *Medicine & Science in Sports & Exercise*, *45*(11), 2166–2174. https://doi.org/10.1249/MSS.0b013e31829734ae

53. Romer, L. M., Haverkamp, H. C., Amann, M., Lovering, A. T., Pegelow, D. F., & Dempsey, J. A. (2007). Effect of acute severe hypoxia on peripheral fatigue and endurance capacity in healthy humans. *American Journal of Physiology. Regulatory, Integrative and Comparative Physiology*, *292*(1), R598-606. https://doi.org/10.1152/ajpregu.00269.2006
54. Salazar-Martínez, E., Gatterer, H., Burtscher, M., Naranjo Orellana, J., & Santalla, A. (2017). Influence of Inspiratory Muscle Training on Ventilatory Efficiency and Cycling Performance in Normoxia and Hypoxia. *Frontiers in Physiology*, *8*, 133. https://doi.org/10.3389/fphys.2017.00133
55. Scott, B. R., Goods, P. S. R., & Slattery, K. M. (2016). High-Intensity Exercise in Hypoxia: Is Increased Reliance on Anaerobic Metabolism Important? *Frontiers in Physiology*, *7*, 637. https://doi.org/10.3389/fphys.2016.00637
56. Shearman, S., Dwyer, D., Skiba, P., & Townsend, N. (2015). Modeling Intermittent Cycling Performance in Hypoxia Using the Critical Power Concept. *Medicine and Science in Sports and Exercise*. https://doi.org/10.1249/MSS.0000000000000794
57. Simpson, L. P., Jones, A. M., Skiba, P. F., Vanhatalo, A., & Wilkerson, D. (2015). Influence of hypoxia on the power-duration relationship during high-intensity exercise. *International Journal of Sports Medicine*, *36*(2), 113–9. https://doi.org/10.1055/s-0034-1389943
58. Smith, K. J., & Billaut, F. (2010). Influence of cerebral and muscle oxygenation on repeated-sprint ability. *European Journal of Applied Physiology*, *109*(5), 989–999. https://doi.org/10.1007/s00421-010-1444-4
59. Smith, K. J., & Billaut, F. (2012). Tissue oxygenation in men and women during repeated-sprint exercise. *International Journal of Sports Physiology and Performance*, *7*(1), 59–67.
60. Sweeting, A. J., Billaut, F., Varley, M. C., Rodriguez, R. F., Hopkins, W. G., & Aughey, R. J. (2017). Variations in Hypoxia Impairs Muscle Oxygenation and Performance during Simulated Team-Sport Running. *Frontiers in Physiology*, *8*, 80. https://doi.org/10.3389/fphys.2017.00080
61. Townsend, N. E., Nichols, D. S., Skiba, P. F., Racinais, S., & Périard, J. D. (2017). Prediction of Critical Power and W' in Hypoxia: Application to Work-Balance Modelling. *Frontiers in Physiology*, *8*, 180. https://doi.org/10.3389/fphys.2017.00180
62. Turner, G., Gibson, O. R., & Maxwell, N. S. (2014). Simulated moderate hypoxia reduces intermittent sprint performance in games players. *The Journal of Sports Medicine and Physical Fitness*, *54*(5), 566–74.
63. Van den Noortgate, W., López-López, J. A., Marín-Martínez, F., & Sánchez-Meca, J. (2013). Three-level meta-analysis of dependent effect sizes. *Behavior Research Methods*, *45*(2), 576–594. https://doi.org/10.3758/s13428-012-0261-6
64. Weavil, J. C., Duke, J. W., Stickford, J. L., Stager, J. M., Chapman, R. F., & Mickleborough, T. D. (2015). Endurance exercise performance in acute hypoxia is influenced by expiratory

flow limitation. *European Journal of Applied Physiology*, *115*(8), 1653–1663. https://doi.org/10.1007/s00421-015-3145-5

65. Wehrlin, J. P., & Hallén, J. (2006). Linear decrease in .VO2max and performance with increasing altitude in endurance athletes. *European Journal of Applied Physiology*, *96*(4), 404–12. https://doi.org/10.1007/s00421-005-0081-9
66. Witmer, C. A. (2011). *Effects of acute exposure to moderate hypoxia during different phases of repeated-sprint cycling on fatigue and anaerobic power reserve :[Dissertations*. Temple University .
67. Wyatt, F. (2014). Journal of Exercise Physiologyonline Editor-in-Chief JEPonline Physiological Responses to Altitude: A Brief Review, *17*(1).
68. Zinner, C., Hauser, A., Born, D.-P., Wehrlin, J. P., Holmberg, H.-C., & Sperlich, B. (2015). Influence of Hypoxic Interval Training and Hyperoxic Recovery on Muscle Activation and Oxygenation in Connection with Double-Poling Exercise. *PLOS ONE*, *10*(10), e0140616. https://doi.org/10.1371/journal.pone.0140616