Journal of
THERMAL BIOLOGY

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PII: S0306-4565(24)00011-1

DOI: https://doi.org/10.1016/j.jtherbio.2024.103793

Reference: TB 103793

To appear in: *Journal of Thermal Biology*

Received Date: 18 June 2023

Revised Date: 3 January 2024

Accepted Date: 12 January 2024

Please cite this article as: Willmott, A.G.B., Diment, A.G., Chung, H.C., James, C.A., Maxwell, N.S., Roberts, J.D., Gibson, O.R., Cross-adaptation from heat stress to hypoxia: A systematic review and exploratory meta-analysis, *Journal of Thermal Biology* (2024), doi: https://doi.org/10.1016/j.jtherbio.2024.103793.

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Statements and Declarations:

Competing Interests and Funding: The authors declare no competing interests and no sources of funding were used for this research.

Acknowledgments: The authors would like to thank Para-Monte, the Adam Savory Altitude Awareness Charity, Eastbourne, East Sussex (https://www.para-monte.org/) for their charitable support that has underpinned our hypoxic research.

1.0 Abstract

Cross-adaptation (CA) refers to the successful induction of physiological adaptation under one environmental stressor (e.g., heat), to enable subsequent benefit in another (e.g., hypoxia). This systematic review and exploratory meta-analysis investigated the effect of heat acclimation (HA) on physiological, perceptual and physical performance outcome measures during rest, and submaximal and maximal intensity exercise in hypoxia.

Database searches in Scopus and MEDLINE were performed. Studies were included when they met the Population, Intervention, Comparison, and Outcome criteria, were of English-language, peer-reviewed, full-text original articles, using human participants. Risk of bias and study quality were assessed using the COnsensus based Standards for the selection of health status Measurement INstruments checklist.

Nine studies were included, totalling 79 participants (100% recreationally trained males). The most common method of HA included fixed-intensity exercise comprising 9±3 sessions, 89±24-min in duration and occurred within 39±2°C and 32±13% relative humidity. CA induced a *moderate*, beneficial effect on physiological measures at rest (oxygen saturation: g=0.60) and during submaximal exercise (heart rate: g=-0.65, core temperature: g=-0.68 and skin temperature: g=-0.72). A *small* effect was found for ventilation (g=0.24) and performance measures (peak power: g=0.32 and time trial time: g=-0.43) during maximal intensity exercise. No effect was observed for perceptual outcome measures.

CA may be appropriate for individuals, such as occupational or military workers, whose access to altitude exposure prior to undertaking submaximal activity in hypoxic conditions is restricted. Methodological variances exist within the current literature, and females and well-trained individuals have yet to be investigated. Future research should focus on these cohorts and explore the mechanistic underpinnings of CA.

Key Points:

- Cross-adaptation refers to the process where individuals adapt to one environmental stressor, such as heat stress, but then demonstrate improved response to another environmental stressor, such as altitude exposure.
- Following repeated exercise sessions in heat stress, termed heat acclimation, humans demonstrate physiological adaptations, such as improved oxygen saturation at rest and reduced heart rate and core temperature during submaximal exercise in hypoxic/altitude conditions.

- Cross-adaptation offers individuals, such as occupational and military workers, a time efficient alternative to traditional hypoxic training interventions, to adapt for submaximal activity at altitude.

2.0 Introduction

Cross-adaptation (CA) refers to the successful induction of adaptation in an organism under one environmental stressor (such as heat or cold stress, or altitude exposure), with said adaptation demonstrating subsequent tolerance or physiological advantage to another environmental stressor (1). In the last decade, human CA has become an area of increased research interest given a historic paucity of data characterising human responses to combinations of exercise stimuli and/or environmental stressors (2). Three types of CA have been identified (3): first, that adaptation to one stimulus provides tolerance to another (e.g., passive heat adaptation improves systemic physiological responses in hypoxia); second, that adaptation to two combined stimuli (e.g., exercise and heat) provide enhanced tolerance to a third stressor (e.g., rest or exercise in hypoxia), and; third, that adaptation to one stressor offers a level of advanced adaptation to another (e.g., heat adaptation enhances training quality at altitude). Of these paradigms, the first and second construct are the most widely examined (1, 4–8), with a paucity of evidence addressing the third (1, 9).

CA is considered independent of ‘combined adaptation’, which utilises multiple environmental stressors simultaneously within an intervention (e.g., heat or cold and hypoxia) to induce specific adaptations for benefit in single/dual stressor situations (e.g., exercise-heat stress, cold-hypoxic stress) (3, 10, 11). Regardless of the approach, combined adaptation subtly differs from CA, where one environmental stressor (with or without exercise) is used to induce adaptation in another environmental stressor. In combined adaptation, two or more environmental stressors are united (with or without exercise) to induce adaptation in another context. Readers are directed towards original experimental work to understand the efficacy of this approach (10–14). Similarly, consideration of the use of heat stimuli for enhancing normoxic (sea-level) performance is not considered within this article but has been addressed elsewhere (15).

CA strategies have several proposed applications that are relevant for human performance and/or mitigation of illness. These are apparent when logistical barriers prevent optimal, stressor-specific protocols being implemented. For example, the CA concept may reduce or remove the need for extensive preparation of individuals who must perform optimally in unfamiliar environments. Specifically, heat adaptations can be induced following repeated consecutive or non-consecutive exposures (e.g., 60-90-min) within 4-14 days (16), whereas hypoxic adaptations typically require more sustained exposures (e.g., several hours per day) over a number of weeks (17). In this regard, a recent narrative review has postulated the benefits of CA for athletes and military personnel performing in hypoxia (6). Occupational workers, including the military, may benefit from greater flexibility when preparing for rapid deployment to unfamiliar, combined stressor and/or changeable environments. Individuals undertaking sojourns to environmental extremes may also experience combined and/or changeable environmental stressors and would likely benefit from a more generic or broad adaptation. Finally, clinical/health applications of CA have been identified, with organ specific benefits reported (e.g., improved cardiac mechanics and metabolic performance during ischemia and reperfusion) (8, 18–21). Human CA has been considered at cellular, physiological, perceptual and performance levels, with experimental studies examining CA between heat and hypoxia (22–32), hypoxia and heat (14, 33), heat and cold (34), and cold and hypoxia (35). Readers are directed towards a sample of specific literature examining heat (9, 36, 37), cold (38–40) and altitude adaptations (30–35) for outcomes in these specific environments. At the current time, interactions between heat and hypoxia are the most widely considered, with demonstrable effects at rest and low/moderate exercise intensities, but equivocal outcomes at maximal/performance intensities (1, 6).

A number of narrative reviews have considered CA (1, 4–7, 47–49), where authors are largely in agreement with the conceptual benefits, however, empirical review studies examining the proposed mechanisms were lacking at the time of writing. The CA field has developed in the last decade, such that a systematic review and meta-analysis now appears warranted to determine a) whether the field warrants further investigation in general; b) the specific direction(s) any future research should follow; and if available, c) create evidence-based recommendations for the implementation of CA strategies. Given that to-date, the predominant experimental focus has considered the benefits of heat adaptation (via HA) for subsequent hypoxic exposure, the aim of this systematic review and meta-analysis was to comprehensively examine the interaction between these stressors at physiological, perceptual and performance levels. The exploratory meta-analysis may also overcome the limitation of a relatively low sample size found within previous experimental studies. Furthermore, where possible, we seek to infer the specific resting and/or exercise intensity related applications where CA may have the greatest efficacy to guide future application and research. Based upon a recent narrative review (6), it is hypothesised that heat into hypoxic CA will enhance aerobic performance when the exercise is undertaken in acute hypoxia.

3.0 Methods

3.1 Search strategy

This review was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (50). A search strategy was formulated, consisting of main syntax features medical subject headings (MeSH): 1) “hypoxia” OR “hypoxic” OR “hypobaric” OR “normobaric”; OR "cross acclimation" OR "cross tolerance" OR "cross adaptation" OR "altitude training"; AND 2) "heat acclimatization" OR "heat acclimation" AND "heat adaptation" OR "thermoregulation"; AND 3) “exercise” OR “performance”; AND 4) “human”. The study selection process was conducted independently, in two stages, by two authors. Searches were performed across two main databases, SCOPUS and PubMed. Other sources included reference lists of the selected studies. Multiple searches were conducted to ensure no relevant studies were omitted. Searches occurred between 1st March 2022 and 1st September 2023. Whilst CA was most completely defined in 2019 (3), there were no limitations for the selected search dates, as we wanted to include all relevant literature on this topic.

3.2 Selection Criteria

A Population, Intervention, Comparator and Outcome model (PICO) was created to assess the studies suitability, with those that did not meet the following criteria being excluded (51). Population: a) stated as healthy, physically active humans (male or female), b) adults aged ≥18 years; Intervention: c) a minimum duration of 3-days’ active or passive HA within ≥30°C; Comparator: d) change in outcome measure between the pre- and post-HA hypoxic (>1500 m [i.e., FiO_2: <0.18]) test data at rest, or during submaximal and/or maximal exercise (via screening, tolerance, sensitivity and/or performance tests); and Outcome: e) cardiovascular (heart rate [HR], stroke volume [SV], cardiac output [$\dot{Q}$], peripheral capillary oxygen [O_2] saturation [SpO_2]), f) respiratory (ventilation [$\dot{V}_E$], breathing rate [BR], rate of O_2 uptake [$\dot{V}O_2$]), (g) metabolic (respiratory exchange ratio [RER]), h) thermoregulatory (core temperature [T_{core}], skin temperature [T_{skin}], i) performance (aerobic capacity, as defined by maximal or peak oxygen uptake [$\dot{V}O_{2max/peak}$], time trial [TT] time/work completed, peak power [PP]), and, j) perceptual (rating of perceived exertion [RPE], Lake Louise Questionnaire [LLQ] scores). Only full-text articles in English were included into this review. Opinion statements, reviews, books, thesis’, conference papers and surveys were excluded.

3.3 Risk of Bias and Quality Assessment

A COnsensus-based Standards for the selection of health status Measurement INstruments (COSMIN) checklist was implemented to assess the transparency and the Risk of Bias (RoB) of the included studies, by measuring study quality (52). The COSMIN RoB tool was used as it provides a valid, transparent and systematic assessment of the methodological quality of studies and the reliability and measurement error of outcome measures (51). This COSMIN checklist was scored separately by two authors. Each COSMIN item for all categories were scored from 4-1 (4 = '*Very good'*, 3 = '*Adequate'*, 2 = '*Doubtful'*, 1 = '*Inadequate'* and '*N/A*' = no score). Any disagreement between authors were resolved using the mean score. The COSMIN '*worst score'* approach was set for all items at ≥ 3.0, to meet the acceptable requirement of study quality and inclusion (53). Studies that scored lower than the total threshold were excluded. Intraclass correlation coefficient ([ICC] with 95% upper, lower confidence intervals [CIs]) were used to assess the reliability between authors' rating scores, with correlation thresholds interpretated as: 0.0-0.1 = '*Trivial'*, 0.1-0.3 = '*Small'*, 0.3-0.5 = '*Moderate'*, 0.5-0.7 = '*Large'*, 0.7-0.9 = '*Very large'*, and 0.9-1.0 = '*Nearly perfect'* (54). To evaluate the heterogeneity among the studies, I^2 test was implemented, with values of 0-40% = '*Might not be important'*, 30-60% = '*Moderate'*, 50-90% = '*Substantial'*, and 75-100% = '*Considerable'* (53). Further, Egger funnel plot was used to identify asymmetry, with Egger's regression test set to $p \leq 0.05$ (54). If asymmetry was found, re-analysis occurred following "leave-one-out method", until studies that caused asymmetry were identified and subsequently removed from meta-analysis. I^2 data was also independently used to examine if leave-one-out analysis were required and was deemed necessary when I^2 demonstrated '*Considerable'* (75-100%) heterogeneity. This was appropriate where symmetry was observed, yet high I^2 data were found.

3.4 Data Extraction

Relevant data from intervention (and control if available) groups at baseline, and at pre- and post-HA intervention time points in hypoxia/altitude were extracted from each study. Data included the number of participants, mean, standard deviation (SD), p values, and 95% CIs (if available). Study data were manually extracted and entered into a custom Excel spreadsheet (Microsoft, USA). This was completed by two authors independently and cross-checked by a third author. If any data were not available, authors were contacted in the first instance. Upon request, if the data were not provided, the data were excluded from analysis. Mean and SD data were both collected for each outcome measure. Data extraction were separated into three sections: 1) participant characteristics (number of participants, sex, aerobic capacity, age, height, mass); 2) HA interventions (method, number of sessions, duration, ambient temperature [T_{amb}], relative humidity [RH], activity) and hypoxic tests (hypoxic conditions [elevation, pressure, partial pressure of inspired O_2 [PiO_2], FiO_2, O_2 %] duration, intensity, modality, test, normobaric hypoxia [NH], hypobaric hypoxia [HH], T_{amb}, RH) and; 3) physiological, perceptual and performance data (as discussed in the PICO outcome measures above). The extracted data were then entered into the meta-analysis software (Meta-Essentials 1.4 [Microsoft Excel, USA]) and separated into rest, submaximal and maximal sections, as per the study design and/or methods. Resting data were categorised where studies specifically stated a rest period with a duration of ≥2-min prior to, or during hypoxic testing protocols. Submaximal data were categorised as an exercise intensity ≤90% of aerobic capacity for a duration of ≥1-min. Maximal data were categorised as any performance test (e.g., TT), aerobic capacity test, and/or an exercise intensity >90%. Data were extracted from the maximal part of the test or at test termination, as stated by the individual study. A minimum of two studies were required to have reported the same variable outcome for comparison and inclusion within the meta-analysis (55). To ensure consistency, absolute $\dot{V}O_{2max/peak}$ were reported (i.e., $mL.min^{-1}$ or $L.min^{-1}$), with the closest reported mean body mass (i.e., pre- or post-intervention kg) used to determine relative $\dot{V}O_{2max/peak}$ ($mL.kg^{-1}min^{-1}$) when this data was not available. The standard deviation (SD) was proportionally inferred (28). Likewise, for TT scores, seconds were computed into minutes where applicable.

3.5 Statistical Analysis

Descriptive data are reported as mean ± SD. All scores were converted from absolute to relative individual specific scores where possible. The pre-to-post intervention mean ± SD data from each study were used to calculate standardised mean differences (SMD), from which Hedges' g effect sizes (ES), combined ES (CES), and 95% CIs are provided. Data pertaining to the pre-to-post difference, mean difference and weighted mean difference are also provided. Meta-Essentials spreadsheet 1.4 (Microsoft Excel, USA) was used to perform the meta-analysis, produce forest and Egger's funnel plots, and undertake statistical analyses, with alpha set at $p<0.05$ (55). Study weightings for all forest plots were also calculated using Meta-essentials code. Where 95% CIs crossed the 'no effect' line at zero, the pre-to-post intervention SMD were not considered statistically significant (56). A random effects model was implemented, with heterogeneity across studies assessed using I^2 test. Continuous data were pooled and SMD (Hedges' g ES/CES) calculated to show the size and effect of the HA intervention, with interpretations for Hedges' g ES/CES as: <0.19 = '*Trivial*', 0.20-0.49 '*Small*', 0.50-0.79 = '*Moderate*' and ≥0.80 = '*Large*' (57). For descriptive purposes only, where studies had >1 trial (e.g., multiple $\dot{V}O_{2max}$ tests in different environmental conditions within White et al. (28) and Salgado et al. (27), and/or multiple exercise intensities within a single trial (e.g., 10-min at 40% then 10-min at 65% $\dot{V}O_{2peak}$ within Gibson et al. (31), individual trial data are provided in the Tables. Where multiple data were extracted from the same study using the same participants (albeit from different trials, conditions and/or exercise intensities), data were combined to create a single pair-wise comparison (as per Section 16.5.4 *Cochrane Handbook for Systematic Reviews of Interventions* (58)). This avoided *unit-of-analysis* error during statistical analysis (e.g., double counting), which can affect the accuracy of results (57). Sample size, mean and SD were adjusted to reflect the combination of data (as per Section

7.7.3.8 and formulas provided in Table 7.7.a (58)). Where adjusted analysis occurred, the reported mean ± SD data are still provided in Tables, however, only combined data were used for statistical analyses. If only 1 study were found that included multiple data sets of the same outcome variable, they were excluded from statistical analysis (55) and used for descriptive purposes only. I^2 and Egger regression test data for all outcome measures were initially screened, with specific individual study data being excluded from statistical analyses for rest SpO_2 (Table 4) and submaximal HR and T_{skin} (Table 5). Submaximal BR and LLQ (Table 5), and maximal RER and BR data (Table 6) were also excluded from statistical analysis due to these data pertaining to 1 study only.

4.0 Results

4.1 Search results, RoB and heterogeneity overview:

Average COSMIN scores for 10 identified research studies were: 3.2 ± 0.7 (range: 1.6-3.9), with a mean difference between authors of 0.0 ± 0.3. COSMIN RoB assessment excluded 1 study (59) from a full review and subsequent analysis, due to a score of <3 (mean 1.6), reflecting a low sample size (n = 4 males) and a lack of experimental control during HA prescription. The COSMIN score for the remaining 9 studies was 3.4 ± 0.3. An ICC of 0.73 (95% CI: 0.30, 0.91) was found between authors' rating scores. RoB assessment for the remaining studies demonstrated an acceptable, low risk of bias, based on thresholds set by the COSMIN tool for the methodological quality and transparency of the research.

Figure 1 illustrates the stages of the selection criteria in accordance with the PRISMA guidelines (50, 53), which resulted in 9 research studies being included in this review and meta-analysis.

Add Figure. 1 A PRISMA flow diagram outlining the systematic review identification, screening, inclusion and exclusion process (COSMIN: COnsensus-based Standards for the selection of health status Measurement INstruments, HA: heat acclimation).

4.2 Participant characteristics and testing designs

The CA research included a total of 79 participants (9 ± 2 participants per study [range: 7-13]), of which, 100% were male. Participant characteristics from each study are presented in Table 1. A summary of the HA protocols are presented in Table 2. The most common method of HA was fixed-intensity (number of studies [n] = 7), followed by isothermic (n = 2). Overall, HA consisted of 9 ± 3 sessions (range: 3-12 sessions) with a duration of 89 ± 24-min per session (range: 60-120-min) and occurred within 39 ± 2°C (range: 35-40°C) and 32 ± 13% RH (range:

20-56%). The most common modality of exercise stimuli was cycling (n = 7), followed by treadmill walking/running (n = 2). Of the cycling fixed-intensity studies (n = 5), the exercise intensity equated to 52 ± 3% of aerobic capacity (range: 50-55%). The treadmill-based fixed-intensity studies (n = 2) utilised the same absolute exercise intensities of 5 $km.hr^{-1}$ and 2% incline. The isothermic studies (n = 2) both targeted the maintenance of a T_{core} of ≥38.5°C, achieving this via cycling at 65% $\dot{V}O_{2peak}$ (31) or 50% PP (25) from normoxic data, until the target T_{core} was reached. Thereafter the target T_{core} was typically maintained using intermittent periods of exercise.

A summary of the hypoxic test protocols are presented in Table 3. Resting measures were assessed prior to submaximal trials beginning (n = 4 [range: 2-15-min prior]), as part of the submaximal test (n = 1 [10-min]) or during a long-term exposure (n = 1 [1-hr and 23-hrs within a 30-hr exposure]). Eight studies included submaximal tests. Gibson et al. (31) utilised 2 incremental exercise intensities within a single test (40% and 65% $\dot{V}O_{2peak}$), whilst Salgado et al. (29) included 2 different tests in alternate hypoxic conditions (elevation: 1600 m and 4350 m, PiO_2: 123 and 86 mmHg), totalling 9 overall submaximal tests pre-to-post HA. All tests were undertaken on a cycle ergometer at an intensity corresponding to 58 ± 14% $\dot{V}O_{2peak}$ (range: 40-80%) for 37 ± 10-min (range: 30-60-min). Six tests were conducted in NH, the remaining 3 tests were conducted within HH. Four studies included $\dot{V}O_{2max}$ tests in hypoxic conditions (2860 ± 1399 m [range elevation: 1600-4350 m and PiO_2: 123-86 mmHg]). Two of these studies included multiple tests in different conditions (both: 1600 m and 4350 m), totalling 6 $\dot{V}O_{2max}$ tests pre-to-post HA. Five of the 6 tests were undertaken on a cycle ergometer, with the other conducted on a treadmill. Four tests were conducted in HH, with the remaining 2 within NH. Of the 3 self-selected cycle TT tests, 2 were assessed for time to complete 16.0 km and 16.1 km, whereas the other was assessed for the amount of work completed in 15-min.

Add Table 1

Add Table 2

Add Table 3

4.3 The effect of HA on physiological, perceptual and performance measures in hypoxia

Summary data for all available resting, submaximal and maximal outcome measures can be found in Figure 2 (including: intensity, mean difference, weighted mean difference, SMD [CES ± 95% lower, upper CIs]). All available resting, submaximal and maximal data for the physiological, perceptual and performance outcome measures from each study's hypoxic tests pre-to-post HA are displayed within Tables 4, 5 and 6, respectively (including: conditions, mean ± SD, difference, SMD [ES ± 95% lower, upper CIs], weighting, I^2 and p values). Where data are not provided for either resting, submaximal and/or maximal intensities, this reflects a lack of available data from a minimum of two studies. Publication bias assessments using Egger's test and I^2 criteria revealed all individually grouped resting, submaximal and maximal outcome measures to be <40% (*Might not be important*), aside from submaximal RER (43.3%) and SpO_2 (55.7%).

4.4 The effect of HA on cardiovascular measures in hypoxia:

HA had a *moderate* effect on reducing submaximal HR (g = -0.65 [-1.11, -0.20], n = 6), however, only a *trivial* effect was found for resting HR (g = -0.12 [-0.58, 0.35], n = 3) and HR max in hypoxia (g = -0.10 [-0.56, 0.37], n = 4). HA had a *small* effect on improving submaximal $\dot{Q}$ (g = -0.21 [-0.24, -0.19], n = 2) and SV in hypoxia (g = 0.21 [-0.93, 1.35], n = 2). HA had a *moderate effect* on improving resting SpO_2 (g = 0.60 [-0.07, 1.27], n = 2) and a *small* effect on submaximal SpO_2 in hypoxia (g = 0.29 [-0.22, 0.80], n = 5). No effect was found for SpO_2 during maximal exercise (g = 0.01 [-0.10, 0.12], n = 2).

4.5 The effect of HA on respiratory and metabolic measures in hypoxia:

HA had a *trivial* effect on increasing resting $\dot{V}_E$ (g = 0.14 [-0.32, 0.61], n = 3) and lowering submaximal $\dot{V}_E$ in hypoxia (g = -0.08 [-0.57, 0.41], n = 4). A small effect was found for maximal $\dot{V}_E$ (g = 0.24 [-0.40, 0.87], n = 2). HA also had a *trivial* effect on increasing resting (g = 0.17 [0.04, 0.29], n = 2) and maximal $\dot{V}O_2$ in hypoxia (g = 0.08 [-0.18, 0.35], n = 3), and lowering submaximal $\dot{V}O_2$ (g = -0.12 [-0.33, 0.10], n = 4). *Trivial* effects were observed for submaximal RER (g = -0.11 [-0.90, 0.68], n = 3).

4.6 The effect of HA on thermoregulatory measures in hypoxia:

HA had a *small* effect on reducing T_{core} at rest (g = -0.40 [-3.39, 2.60], n = 2) and a *moderate* effect for reducing T_{core} during submaximal exercise in hypoxia (g = -0.68 [-0.85, -0.51], n = 4). A *moderate* effect was also observed for T_{skin} during submaximal exercise following HA (g = -0.72 [-4.47, 3.03], n = 2).

4.7 The effect of HA on perceptual measures in hypoxia:

HA had a *small* effect on reducing submaximal RPE (g = -0.29 [-0.86, 0.28], n = 4), but no effect on maximal RPE in hypoxia (g = 0.00 [0.00, 0.00], n = 2).

4.8 The effect of HA on performance measures in hypoxia:

HA had a *small* effect on PP (g = 0.32 [-0.98, 1.61], n = 2) and TT performance time in hypoxia following HA (g = -0.43 [-2.27, 1.42], n = 2).

Add Table 4

Add Table 5

Add Table 6

Add Figure 2. Exploratory meta-analysis data across rest, submaximal and maximal outcome measures.

5.0 Discussion

The primary aim of this systematic review and exploratory meta-analysis was to investigate the process of CA through the understanding of HA effectiveness on physiological, perceptual and performance responses in hypoxia. This analysis also sought to improve the understanding of resting and/or exercise applications in which CA between heat and hypoxia may have the greatest efficacy. The systematic review identified nine eligible CA research studies, including 79 male participants, and examined numerous dependent variables (cardiovascular, respiratory, thermoregulatory, perceptual and performance) across resting conditions and, submaximal and maximal exercise intensities. We found a *moderate*, beneficial effect of HA increasing SpO_2 at rest and reducing HR, T_{core} and T_{skin} during submaximal exercise in recreationally trained males in hypoxic conditions. However, during maximal exercise conditions only small and trivial effects were found in hypoxia following HA. The absence of benefit in maximal exercise conditions opposes our initial hypothesis that heat into hypoxic CA would enhance aerobic performance when the exercise is undertaken in acute hypoxia. Finally, whilst beneficial effects were found for a number of variables, it is important to recognise the statistical significance (or lack of) of some of these outcome measures, therefore some caution is advised when interpreting these data. Accordingly, p values and a statement as to whether data crossed the 'no effect' line has been added to our illustrations (Figure 2 and 3).

5.1 Analysis of CA interventions

Participants within the CA research studies displayed comparable characteristics to those found in a recent systematic review of direct HA literature (current data *vs.* Tyler et al. (60) for aerobic capacity: 52 *vs.* 50 $mL.kg^{-1}.min^{-1}$ and age: 24 *vs.* 26 years). However, all participants in the current review were male (100% *vs.* 93% in Tyler et al. (60)). The HA methods prescribed within these studies were also comparable to existing literature. For example, a similar number of sessions (9 *vs.* 9), session duration (89 *vs.* 105-min) and ambient conditions (39 *vs.* 40°C, 32 *vs.* 40% RH) (60). The majority of protocols were 'medium-term' HA (MTHA: 8-14 days), with only one including 'short-term' HA (STHA: ≤7 days - Lee et al. (22)). The most common method of HA was fixed-intensity, followed by isothermic. These data reaffirm fixed-intensity exercise as the most common method of HA (60) and MTHA as the preferred duration of HA (9, 61, 62). However, no research has investigated emerging passive approaches for CA purposes (63), e.g., hot water immersion. Nonetheless, Table 2 displays distinct differences in prescribed HA methods (e.g., number of sessions, dose and HA activity). It is also prudent to highlight the disparities in hypoxic test protocols in Table 3 (e.g., duration, activity, intensity, altitude conditions [elevation and pressure]), where heat adaptations were evaluated across resting conditions and, submaximal and maximal exercise intensities. Therefore, caution is advised when interpreting the effectiveness of CA, as the magnitude of adaptations are likely influenced by methodological differences in both HA and hypoxic test protocols. In light of this, recommendations for future research are considered after the review of meta-analysis data and practical recommendations for CA application.

5.2 The effect of HA on physiological measures at rest and during submaximal exercise in hypoxia:

There were *moderate,* beneficial effects of HA increasing resting SpO_2 and reducing mean HR, T_{core} and T_{skin} during submaximal exercise in hypoxia. These improvements are comparable to literature which has demonstrated beneficial effects of HA on reducing physiological strain during subsequent exercise in heat stress (60). The significant reduction in mean HR during submaximal exercise in hypoxia is likely attributed to PV expansion following HA, which has been shown to increase by 4-15% (61). Within the studies included in this review, PV expansion was identified following HA, with mean changes ranging from ~2-15% (+4.6% (22), +15% (31), +4% (24), +1.9% (28), +8.3% (30), +3.7% (25), +8.4% (29)). In addition to a relationship with reduced HR (64), PV expansion also supports a multitude of other physiological improvements via increased cardiovascular stability (e.g., SV, $\dot{Q}$ and SpO_2) (65, 66). However, only *small* effect sizes were found for these outcome measures during submaximal exercise following HA. Indeed, as hypoxia decreases PV (67), future work may investigate how long HA-induced PV expansion is retained for during subsequent hypoxic exposure. Significant increases in SpO_2 have been reported during submaximal exercise in the CA literature (+1.5% (32), +1.6-3.0% (31), +2.0% (24)) and have been proposed as a response to a leftward shift in the oxyhaemoglobin dissociation curve due to beneficial T_{core} reductions. Whilst T_{core} reductions may enhance the O_2 saturation of haemoglobin (for a given partial pressure of O_2), it's unlikely T_{skin} reductions would provide a physiological benefit aside of a wider, or maintained core-to-skin temperature gradient. Despite the evidence of T_{core} and T_{skin} reductions during submaximal exercise, only *small* beneficial improvements ($p>0.05$) were found in SpO_2 following HA, likely due to variable changes observed across studies (Table 5), suggesting the change is more complex than a temperature-dependent response. Indeed, at high-altitude environments, cold stress is likely to be present alongside hypoxia, whereby, HA may improve cold tolerance (via increased vasodilatory responses (34)). However, further research is required within cross-stress investigations. The benefits for SpO_2 are more apparent at rest, where a *moderate* effect occurred, however, not every study observed an improvement (Table 4). This likely explains the positive and negative CIs for SpO_2 in Figure 2. Together with T_{core}, there appears limited potential benefits in the resting domain. Nonetheless, it is evident that repeated exercise-heat stress (i.e., HA), decreases physiological strain (comprising cardiovascular and thermoregulatory function improvements) during acute submaximal exercise at altitude.

Only *trivial* effects of HA on $\dot{V}O_2$ were found during submaximal exercise, indicating limited changes to gross mechanical economy (GME) in hypoxia. The limited effects are likely explained by minor changes in submaximal $\dot{V}O_2$ following isothermic (31) and fixed-intensity HA (24) in normobaric hypoxia (FiO_2: 12%, ~4400 m and FiO_2: 14%, ~3000 m, respectively) and following fixed-intensity HA in hypobaric conditions (1600 m and 4350 m (27)). In contrast, significant reductions in submaximal exercise $\dot{V}O_2$ were reported following fixed-intensity HA, at 2- and 24-hrs within a hypobaric hypoxia trial (-2.4% in $\dot{V}O_2$ (29)), as well as following isothermic HA within normobaric hypoxia (-3.9% in $\dot{V}O_2$ (25)). It should also be noted that a reduction in submaximal exercise $\dot{V}O_2$ following HA is not a universal finding and thus ambiguity may persist [70]. Due to limited studies providing mechanistic interpretations, biological reasons for this disparity remain unclear. Non-significant, t*rivial*-to-*small* effects of HA were also found for $\dot{V}_E$ and RER across resting and exercise conditions. As such, based upon available data it appears HA has little to no benefit on respiratory and metabolic parameters during acute rest and exercise in hypoxia.

5.3 The effect of HA on performance measures and determinants of performance in hypoxia:

There were also limited improvements in maximal aerobic capacity, PP and TT performance when undertaken in hypoxia following HA (Figure 2). Whilst difficult to delineate why benefits to performance were not observed, and aside of the notable limited studies on performance included (Table 3), the lack of improvements coincided with limited effects of HA on $\dot{V}_E$, HR_{max} and SpO_2 (i.e., factors that may improve $\dot{V}O_{2max}$) during maximal exercise (Figure 2). These findings contrast emerging evidence where improvements in maximal performances are observed in normoxic conditions following HA (15). S*mall* beneficial effects in PP were found following HA (Salgado et al. (27): +11 W [+3.2%, p = 0.04], Sotiridis et al. (25): +12 W [+4.9%, p = 0.14]). However, it is unclear from our analysis which physiological mechanism(s) contributed to these PP improvements and no comparisons can be made as control groups were not included. Sotiridis et al. (25) have previously suggested that an increased GME may mediate PP improvements. Nonetheless, despite suggestions that CA is beneficial for hypoxic performance (6), experimental work across different environmental conditions indicates HA may have greater benefits on PP in thermoneutral normoxia (+6 W [+8.2%]) and heat alone (+41 W [+13.4%]) rather than hypoxia. This observation aligns with a wider body of previous literature (11, 68–70). Cycling TT performances were shown to significantly improve in normobaric (24) but not hypobaric hypoxia (28) following HA (CES: g = -0.43). Lee et al. (24) report a +4.8% improvement during a 16.1 km TT in ~3000 m ($p = 0.05$), whereas, White et al. (28) observed a non-significant improvement of 28-seconds during a 16.0 km TT in 4350 m ($p = 0.07$). Adaptations following HA including, glycogen sparing, and metabolic efficiency were considered as contributing factors to explain the improved TT performance at 3000 m (24), whilst in the absence of PV-mediated improvements to $\dot{V}O_{2max}$, White et al. (28) speculated that reduced metabolic stress and/or cellular adaptations may improve TT performance at 4350 m. However, such outcome measures in these studies were not directly assessed. Furthermore, whilst data were not included in our analysis due to the study being the only one of its type, it should be noted Salgado et al. (29) also report no improvements in the total work during a 15-min TT at 2-hrs (106.3 ± 23.8 *vs.* 101.4 ± 23.0 kJ) and 24-hrs (107.3 ± 23.4 *vs.* 106.3 ± 20.8 kJ) within hypobaric hypoxia (3500 m) following 8 days of HA, despite an 8% PV expansion.

Given the current inconclusive data and *trivial*-to-*small* effects found for aerobic capacity, PP and TT time, it appears the ergogenic efficacy of HA to enhance maximal/performance intensity responses in hypoxia is minimal. Reflecting the lack of uniformity in CA methodologies, future research focus may consider the relevance of CA in this context or investigate other setting-specific performance measures.

5.4 The effect of HA on perceptual measures in hypoxia:

There were *small* effects, albeit non-significant, of HA reducing RPE during submaximal exercise. This may be a result of a lower physiological strain (via reductions in HR and T_{core}). Whilst LLQ data were excluded from analysis due to it being from only 1 experimental study, Gibson et al. (31) found no significant improvements in the symptoms of acute mountain sickness (AMS), suggesting perceptual improvements did not match the adapted physiological responses, perhaps due to the short altitude exposure duration (31). Additional AMS data were also not included within this review due to differences in questionnaire type (LLQ vs Environmental Symptoms Questionnaire [ESQ]). Nonetheless, Salgado et al. (29) reported 23% of participants who presented AMS symptoms prior to HA, subsequently reduced their incidence of AMS during a 30-hour exposure to hypobaric hypoxia following HA. As such, further research is warranted to assess if and how, HA may reduce the incidence of AMS developing in both acute and chronic durations of hypoxia.

5.5 Limitations:

We highlight key limitations within current CA research including: 1) the quality of included studies; 2) reporting bias and 2), the relative infancy of CA. While every effort was taken to ensure the included studies were of sufficient quality and RoB were minimised using COSMIN, this does not remove it completely. Issues within the presented studies are linked to the stage of CA research development and nature of this exploratory analysis, as demonstrated by a lack of control groups, small sample size and disparity between methods. Consequently, the limited number of studies and/or participants included within the analysis likely led to the CIs for the SMD within the forest plot crossing the no effect line (56). We highlight the uncommon, and in some instances sub-optimal methods used during HA interventions, specifically a low number of sessions undertaken, which likely reduced the magnitude of outcome improvements in hypoxia (i.e., 3-days or 180-min of HA (22)). However, this study's inclusion within the review and analysis was maintained to avoid bias. Furthermore, there remains a challenge to blind participants to heat and hypoxia. While significant under-representation of females is commonplace within exercise science and sports medicine (71, 72), CA research is completely void of female participants, and lacks research that investigates well-trained populations, and across the age span.

The authors acknowledge limitations within their own exploratory analyses of the relevant CA literature. Such as separating data from a single trial into two data sets (Gibson et al. (31), for 40% and 65% intensities, Salgado et al. (29) for 2- and 24-hr time points), although to account for this, these data were combined for statistical analysis (as per Cochrane Handbook for Systematic Reviews of Interventions Section 7.7.3.8). We also acknowledge the differences in prescription methods when assessing the effectiveness of HA within post-intervention normobaric and hypobaric hypoxia trials (Table 3), as well as differing methods and equipment (e.g., inspired hypoxic gas *vs.* hypobaric chamber), which may affect results (73). Whilst specific pressure differences are unclear, physiological responses (e.g., $\dot{V}_E$) to hypobaria may be affected by lessened O_2 diffusion (via increased hypoxic-pulmonary vasoconstriction) (73). Therefore, some caution is advised if translating adaptations following HA in normobaric to hypobaric hypoxia. We must also recognise discrepancies in the range of hypoxic conditions assessed (e.g., elevation and duration) and therefore the breadth of practical application. There are differences in participants' habitual acclimatisation between studies, as some participants were sea-level residents less-familiar and less-exposed to altitude (24, 31), others resided at low altitude (~1600 m) for 6 months prior to testing (27, 28). Though some studies have quantified cellular (e.g., heat shock protein) responses to CA, the varied methods used to determine changes in this marker within heat-altitude research (e.g., intracellular *vs.* extracellular response, mRNA *vs*. protein) (22, 24, 31, 74–78), and varied timepoints makes comparison ineffective at the current time. Finally, whilst the field of CA is emerging and ~10 studies have been conducted, our review and analysis complement recent narrative literature (1, 6) and provide insights into relevant future research directions which is vital for the progression and development of CA research.

5.6 Recommendations for future research:

Whilst the authors provide an overview of CA research, we highlight the fact that there is little consensus for optimal HA methods, nor hypoxic tolerance tests, making interpretation and comparisons between studies problematic. Therefore, future studies assessing CA should consider a standardised tolerance, screening or sensitivity test that allows for the assessment of physiological and perceptual measures at rest, and during submaximal and maximal exercise intensities. A need for future work in hypobaric hypoxia is required for applying CA into terrestrial altitude, as barometric pressure may have an independent effect and evoke a greater physiological strain, increase health risk and performance impairment compared to normobaric hypoxia (79). A consistent approach to exercise HA may also aid with determining the efficacy of CA, however given the growing appreciation of HA using passive interventions (e.g., post-exercise sauna or hot water immersion) (9), that offer useability benefits (e.g., lessened training load, accessible facilities, and lower costs), this modality as a tool for CA requires investigation. Work in this regard might also consider 'over-dressing' participants (59, 80) to induce heat adaptation. Controlling for routine training is also warranted during experimental interventions, as White et al. (28) suggest a lack of PV expansion was due to participants' continuing their habitual training. The effect of CA on females is unknown, since all participants within this review were male. Although more female-focussed HA investigations are emerging, research must examine the effectiveness of HA on subsequent hypoxic exposure in females, with consideration of recent guidance for research in females (81). This is important given sex differences are apparent in the time-course of heat adaptations (76, 82, 83) and females may experience an increased prevalence of AMS (84). There is also a lack of information with regards to athletic/well-trained and clinical populations, as the current sample population appear to be recreationally trained (performance level 2 (85)), healthy males. Furthermore, there was a lack of research that assessed symptoms of altitude illness, or AMS (whether via LLQ or ESQ). Therefore, future investigations should utilise these perpetual measures to further our understanding on how adapting to heat stress, may or may not support reductions in AMS prevalence, as shown following hypoxia acclimation, which can provide protection from illnesses associated with rapid ascent to high altitude (4). Finally, mechanisms supporting CA remain hypothetical, with work required to elucidate the role of body temperature, cardiovascular response, and other systemic adaptations. In summary, future studies must investigate the extent to which CA may enhance physical performance more comprehensively, and further our understanding of the mechanistic pathways across a range of population groups.

5.7 Practical recommendations:

CA demonstrates the potential to reduce physiological strain whilst exercising at a submaximal intensity in hypoxia with *small* to *moderate* effects observed within recreationally trained, healthy males (Figure 3). However, it appears resting and maximal exercise intensity improvements are currently limited following HA. Cross-adaptation may be a more cost effective, geographically convenient and time efficient method, than hypoxic training (e.g., 3-12 days *vs.* >3 weeks, respectively), when the ability to acclimate to hypoxia is logistically and financially challenging. Implementation of CA, via exercise-heat stress, could therefore be considered an accessible intervention to reduce submaximal physiological strain prior to rapid deployment to altitude locations.

Add Figure 3. A summary of the exploratory meta-analysis' cross-adaptation (CA) responses from heat acclimation to hypoxic exposure.

6.0 Perspectives and Significance:

This is the first systematic review and exploratory meta-analysis to investigate the effects of heat adaptation on physiological, perceptual and performance outcomes in hypoxia. Our findings suggest that HA may elicit a *moderate*, beneficial effect on reducing physiological strain at rest (attenuated decreases in SpO_2) and during submaximal exercise in hypoxic conditions (lower HR, $T_{core,}$ T_{skin}) for recreationally trained males. However, generally *small* and *trivial* effects were found during resting conditions and at maximal exercise intensities in hypoxia following HA. Females and well-trained individuals are not present within current CA literature and thus require future research. Consideration should also be given to assessing alternate methods of repeated heat stress and standardising prescription protocols for both HA and hypoxic tolerance tests.

7.0 Figure Captions

Figure. 1. *A PRISMA flow diagram outlining the systematic review identification, screening, inclusion and exclusion process (COSMIN: COnsensus-based Standards for the selection of health status Measurement INstruments, HA: heat acclimation).*

Figure. 2. *Exploratory meta-analysis data across rest, submaximal and maximal outcome measures.*

Figure. 3. *A summary of the exploratory meta-analysis' cross-adaptation (CA) responses from heat acclimation to hypoxic exposure.*

8.0 Table Titles

Table 1. Participant characteristics from the included CA research studies.

Table 2. Heat acclimation methods implemented in the included CA research studies.

Table 3. Hypoxic test methods implemented in the included CA research studies.

Table 4. Resting data observations from the included CA research studies.

Table 5. Submaximal data observations from the included CA research studies.

Table 6. Maximal data observations from the included CA research studies.

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Table 1. Participant characteristics from the included CA research studies.

Study	HA group						Control group					
	n	Sex	Aerobic capacity (mL.kg^{-1}·min^{-1} or L.min^{-1})	Age (years)	Height (m)	Body mass (kg)	*n*	Sex	Aerobic capacity (mL.kg^{-1}·min^{-1} or L.min^{-1})	Age (years)	Height (m)	Body mass (kg)
Heled et al. [32]	8	Male	57.0 ± 3.7*	23 ± 3	-	-	-	-	-	-	-	-
Lee et al. [22]	8	Male	46.2 ± 10.0$^{\#}$ (3.50 ± 0.08)$^{¥}$	21 ± 3	1.80 ± 0.10	75.7 ± 8.2	8	Male	46.3 ± 8.0$^{\#}$ (3.47 ± 0.08)$^{¥}$	20 ± 1	1.80 ± 0.10	76.0 ± 10.0
Gibson et al. [31]	8	Male	4.32 ± 0.68$^{\#}$ 58.5 ± 12.5$^{\#}$	23 ± 4	1.82 ± 0.06	74.6 ± 7.9	8	Male	4.22 ± 0.62$^{\#}$ 56.6 ± 6.9$^{\#}$	26 ± 5	1.79 ± 0.07	74.6 ± 4.8
Lee et al. [24]	7	Male	50.7 ± 4.7$^{\#}$ (3.64 ± 0.04)$^{¥}$	25 ± 6	1.78 ± 0.08	71.7 ± 9.2	7	Male	51.4 ± 10.0$^{\#}$ (3.73 ± 0.11)$^{¥}$	22 ± 3	1.74 ± 0.08	72.5 ± 11.4
White et al. [28]	8	Male	4.20 ± 0.54* (~55 ± 7)$^{¥}$	28 ± 6	1.78 ± 0.08	75.7 ± 8.4	-	-	-	-	-	-
Lee and Thake [30]	7	Male	50.7 ± 4.7$^{\#}$ (3.64 ± 0.04)$^{¥}$	25 ± 6	1.78 ± 0.08	71.7 ± 9.2	7	Male	51.4 ± 10.0$^{\#}$ (3.73 ± 0.11)$^{¥}$	22 ± 3	1.74 ± 0.08	72.5 ± 11.4
Salgado et al. [27]	8	Male	4.19 ± 0.54$^{\#}$ (~55 ± 7)$^{¥}$	28 ± 6	1.78 ± 0.08	75.7 ± 8.4	-	-	-	-	-	-
Sotiridis et al. [25]	12	Male	4.12 ± 0.41 54.7 ± 5.7$^{\#}$	22 ± 3	-	-	-	-	-	-	-	-
Salgado et al. [29]	13	Male	3.19 ± 0.43$^{\#}$ (~43 ± 6)$^{¥}$	21 ± 3	1.73 ± 0.08	75.1 ± 12.2	13	Male	3.19 ± 0.43$^{\#}$ (~43 ± 6)$^{¥}$	21 ± 3	1.73 ± 0.08	75.1 ± 12.2
Weighted mean ± SD	**9 ± 2**	**-**	**51.9 ± 5.2**	**24 ± 3**	**1.78 ± 0.03**	**74.5 ± 1.6**	**8 ± 2**	**-**	**48.9 ± 5.0**	**22 ± 2**	**176 ± 0.03**	**74.3 ± 1.3**

Note: reported $^{*}\dot{V}O_{2max}$ or $^{\#}\dot{V}O_{2peak}$ within the study and $^{¥}$calculated data from reported body mass is shown within brackets (either ml.kg^{-1}.min^{-1} or L.min^{-1}), SD: standard deviation.

Table 2. Heat acclimation methods implemented in the included CA research studies.

Study	Method	Sessions (n)	Session duration (min)	T_{amb} (˚C)	RH (%)	Modality	HA activity
Heled et al. [32]	Fixed-intensity	12	120	40	40	Treadmill walking	5 km.hr^{-1}, 2% incline (~30% $\dot{V}O_{2max}$)
Lee et al. [22]	Fixed-intensity	3	60	40	20	Cycling	50% $\dot{V}O_{2peak}$
Gibson et al. [31]	Isothermic	10	90	40	41	Cycling	65% $\dot{V}O_{2peak}$ until target T_{core} of 38.5°C
Lee et al. [24]	Fixed-intensity	10	60	40	25	Cycling	50% $\dot{V}O_{2peak}$
White et al. [28]	Fixed-intensity	10	110 (50, 10 rest, 50)	40	20	Cycling	75 W below VT (~55% $\dot{V}O_{2max}$)
Lee and Thake [30]	Fixed-intensity	10	60	40	25	Cycling	50% $\dot{V}O_{2peak}$ (136 ± 16 W)
Salgado et al. [27]	Fixed-intensity	10	110 (50, 10 rest, 50)	40	20	Cycling	75 W below VT (~55% $\dot{V}O_{2max}$ [171 ± 44 W])
Sotiridis et al. [25]	Isothermic	10	90	35	56	Cycling	50% PP until target T_{core} of 38.5°C
Salgado et al. [29]	Fixed-intensity	8	120	40	40	Treadmill walking	5 km.hr^{-1}, 2% incline

Note: VT = ventilatory threshold, PP = peak power, T_{amb} = ambient temperature, RH = relative humidity.

Table 3. Hypoxic test methods implemented in the included CA research studies.

Study	Approx. Elevation (m)	NH / HH (pressure [mmHg])	FiO_2	PiO_2 (mmHg)	Duration	Intensity	Modality	Protocol	T_{amb} (˚C)	RH (%)
Heled et al. [32]	~2400	NH	0.16	~114	To volitional exhaustion	5 $km.hr^{-1}$ (3-min), then 7 $km.hr^{-1}$, then 1 $km.hr^{-1}$ every 3-min	Walking Running	OBLA to $\dot{V}O_{2max}$	-	-
Lee et al. [22]	~3000	NH inspired gas	0.14	~100	75-min	Rest (15-min) then 50% $\dot{V}O_{2peak}$ (60-min)	Rest and Cycling	Stress Test: Rest and Submaximal	-	-
Gibson et al. [31]	~4390	NH	0.12	~86	30-min	Rest (10-min), then 40% (10-min) and 65% (10-min) of normoxic $\dot{V}O_{2peak}$	Rest and Cycling	Rest and Submaximal	18	40
Lee et al. [24]	~3000	NH inspired gas	0.14	~100	55-min	Rest (15-min) then 50% normoxic $\dot{V}O_{2peak}$ (40-min)	Rest and Cycling	Stress Test: Rest and Submaximal	-	-
	~3000	NH inspired gas	0.14	~100	16.1 km	Self-selected	Cycling	TT (time)	-	-
White et al. [28]	1600	HH (633)	-	~123	To volitional exhaustion	70 W (1-min), then 35 $W.min^{-1}$	Cycling	$\dot{V}O_{2max}$	-	-
	4350	HH (455)	-	~86	To volitional exhaustion	70 W (1-min), then 35 $W.min^{-1}$	Cycling	$\dot{V}O_{2max}$	-	-
	4350	HH (455)	-	~86	16.0 km	Sell-selected	Cycling	TT (time)		
	1600	HH (633)	-	~123	45-min	55% $\dot{V}O_{2max}$	Cycling	Stress Test: Submaximal	40	20
Lee and Thake [30]	~3000	NH inspired gas	0.14	~100	55-min	Rest (15-min) then 50% normoxic $\dot{V}O_{2peak}$ (40-min: 136 ± 16 W)	Rest	Stress Test: Rest and Submaximal	-	-
Salgado et al. [27]	1600	HH (633)	-	~123	To volitional exhaustion	70 W (1-min), then 35 $W.min^{-1}$	Cycling	$\dot{V}O_{2peak}$	-	-
	4350	HH (455)	-	~86	To volitional exhaustion	70 W (1-min), then 35 $W.min^{-1}$	Cycling	$\dot{V}O_{2peak}$	-	-
	1600	HH (633)	-	~123	30-min	Self-selected (10-min), then ~70% power @ VT-75 W (10-min: 120 ± 30 W), then ~80% power @ VT-75 W (10-min: 137 ± 35 W). Power @ VT-75 W = 171 ± 44 W	Cycling	Stress Test: Submaximal	21	-
	4350	HH (455)	-	~86	30-min	Self-selected (10-min), then ~70% power @ VT-75 W, (10-min: 95 ± 23 W), then ~80% power @ VT-75 W (10-min: 108 ± 26 W).	Cycling	Stress Test: Submaximal	21	-

						Power @ VT-75W = 133 ± 32 W				
Sotiridis et al. [25]	~3600	NH inspired gas	0.13	~93	30-min	Rest (2-min), warm up at 90 W (2-min) then 40% of normoxic PP (30-min)	Cycling	Stress Test: Rest and Submaximal	23	50.5
	~3600	NH inspired gas	0.13	~93	To volitional exhaustion	100 W (2-min), then 20 W.min^{-1}	Cycling	$\dot{V}O_{2peak}$	23	50.5
Salgado et al. [29]	3500	HH (495)	-	~94	30-min	~50% normoxic $\dot{V}O_{2peak}$ (30-min)	Cycling	Stress Test: Submaximal	20	20
	3500	HH (495)	-	~94	15-min	Self-selected	Cycling	TT (work completed)	20	20
	3500	HH (495)	-	~94	30-hrs	Long-term exposure	Rest and Cycling	Long-term exposure: rest and Submaximal	20	20

Note: OBLA = onset of blood lactate accumulation, VT = ventilatory threshold, VT-75 W = ventilatory threshold subtracted by 75 watts, PP = peak power, TT = time trial, NH = normobaric hypoxia, HH = hypobaric hypoxia, FiO_2 = fraction of inspired of oxygen, PiO_2 = partial pressure of inspired oxygen (equation: FiO_2 x [barometric pressure – saturated vapour pressure of H_2O]), T_{amb} = ambient temperature, RH = relative humidity.

Table 4. Resting data observations from the included CA research studies.

Measure	Study	*n*	Conditions	Pre-HA		Post-HA		Difference	SMD (Hedges' g)	95% CIs		Weight (%)
				Mean	SD	Mean	SD			Lower	Upper	
HR (b.min^{-1}) (I^2 = 0.0%, P = 0.28)	***Salgado et al. [29]**	13	3500 m [23-hrs]	87	13	89	11	+2	0.15	-0.41	0.72	-
		13	3500 m [1-hr]	72	10	70	9	-2	-0.20	-0.76	0.37	-
									0.00	-0.39	0.39	58.9
	Lee et al. [24]	7	3000 m	82	16	79	11	-3	-0.18	-0.97	0.60	20.6
	Gibson et al. [31]	8	4390 m	65	8	61	10	-4	-0.38	-1.14	0.38	20.5
SpO$_2$ (%) (I^2 = 0.0%, P < 0.001)	**Lee et al. [24]**	7	3000 m	89.0	3.0	91.0	2.0	+2.0	0.66	-0.23	1.55	46.2
	Gibson et al. [31]	8	4390 m	79.8	3.6	82.0	3.3	+2.2	0.55	-0.24	1.35	53.9
	#Salgado et al. [29]	13	3500 m [23-hrs]	88.0	4.0	89.0	3.0	+1.0	0.26	-0.31	0.84	-
		13	3500 m [1-hr]	87.0	7.0	87.0	4.0	0.0	0.00	-0.56	0.56	-
$\dot{V}_E$ (L.min^{-1}) (I^2 = 0.0%, P = 0.19)	***Salgado et al. [29]**	13	3500 m [1-hr]	12.2	2.1	12.9	2.4	+0.7	0.29	-0.29	0.86	-
		13	3500 m [23-hrs]	13.4	2.3	13.9	2.2	+0.5	0.21	-0.36	0.78	-
									0.25	-0.15	0.64	57.1
	Lee et al. [24]	7	3000 m	16.0	2.5	16.5	2.7	+0.5	0.16	-0.62	0.95	20.7
	Gibson et al. [31]	8	4390 m	10.5	2.3	10.2	1.4	-0.3	-0.14	-0.87	0.59	22.3
$\dot{V}O_2$ (L.min^{-1}) (I^2 = 0.0%, P < 0.001)	**Lee et al. [24]**	7	3000 m	0.36	0.06	0.38	0.12	+0.02	0.18	-0.61	0.96	48.2
	Gibson et al. [31]	8	4390 m	0.34	0.06	0.35	0.05	+0.01	0.16	-0.57	0.89	51.8
T_{core} (°C) (I^2 = 15.3%, P = 0.09)	**Lee et al. [24]**	7	3000 m	37.11	0.20	37.08	0.15	-0.03	-0.14	-0.93	0.64	46.5
	Sotiridis et al. [25]	12	3600 m	37.40	0.30	37.20	0.30	-0.20	-0.62	-1.26	0.03	53.5

Note: * represents combined group data for further statistical analyses. # represents data that was combined but removed from further statistical analysis due to Egger regression asymmetry (p<0.05).

Table 5. Submaximal data observations from the included CA research studies.

Measure	Study	*n*	Conditions / Intensity	Pre-HA Mean	Pre-HA SD	Post-HA Mean	Post-HA SD	Difference	SMD (Hedges' g)	95% CIs Lower	95% CIs Upper	Weight (%)
HR (b.min^{-1}) (I^2 = 27.1%, P < 0.001)	**#Salgado et al. [29]**	13	3500 m 50% $\dot{V}O_{2peak}$ [24-hrs][a]	160	13	158	9	-2	-0.17	-0.73	0.40	-
		13	3500 m 50% $\dot{V}O_{2peak}$ [2-hrs][a]	151	13	148	10	-3	-0.24	-0.81	0.33	-
	***Lee et al. [22]**	8	3000 m 50% $\dot{V}O_{2peak}$[a]	159	20	150	14	-9	-0.45	-1.23	0.32	-
		8	3000 m 50% $\dot{V}O_{2peak}$[b]	165	20	156	12	-9	-0.47	-1.25	0.30	-
									-0.50	-1.04	0.03	26.6
	***Gibson et al. [31]**	8	4390 m 65% $\dot{V}O_{2peak}$ [a]	168	14	158	13	-10	-0.64	-1.46	0.18	-
		8	4390 m 40% $\dot{V}O_{2peak}$ [a]	132	13	122	12	-10	-0.69	-1.53	0.14	-
									-0.33	-0.84	0.19	27.9
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$ [a]	140	14	131	9	-9	-0.64	-1.53	0.24	15.9
	White et al. [28]	8	1600 m 55% $\dot{V}O_{2peak}$[c]	166	16	148	19	-18	-0.89	-1.79	0.01	14.7
	Sotiridis et al. [25]	12	3600 m 40% PP[a]	153	8	143	6	-10	-1.30	-2.13	-0.48	14.9
$\dot{Q}$ (L.min^{-1}) (I^2 = 0.0%, P < 0.001)	**Lee et al. [24]**	7	3000 m 50% $\dot{V}O_{2peak}$[a]	13.8	1.3	13.5	1.1	-0.3	-0.21	-1.00	0.58	41.2%
	Sotiridis et al. [25]	12	3600 m 40% PP[a]	17.9	3.4	17.2	2.6	-0.7	-0.21	-0.81	0.38	58.8%
SV (mL) (I^2 = 0.0%, P = 0.02)	**Lee et al. [24]**	7	3000 m 50% $\dot{V}O_{2peak}$[a]	99	10	103	11	+4	0.32	-0.49	1.13	39.8%
	Sotiridis et al. [25]	12	3600 m 40% PP[a]	117	23	120	17	+3	0.14	-0.45	0.73	60.2%
SpO_2 (%) (I^2 = 55.7%, P = 0.11)	***Gibson et al. [31]**	8	4390 m 65% $\dot{V}O_{2peak}$[a]	73.4	3.0	76.4	3.1	+3.0	0.85	-0.03	1.74	-
		8	4390 m 40% $\dot{V}O_{2peak}$[a]	74.3	4.9	75.9	3.3	+1.6	0.33	-0.42	1.09	-
									0.61	0.05	1.16	21.4
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$[a]	83.0	3.0	85.0	2.0	+2.0	0.66	-0.23	1.55	15.2
	Heled et al. [32]	8	2400 m 7 km.hr^{-1}[a]	86.5	2.0	88.0	2.0	+1.5	0.65	-0.17	1.47	16.0
	***Salgado et al. [29]**	13	3500 m 50% $\dot{V}O_{2peak}$ [2-hrs][a]	84.0	3.0	84.0	3.0	0.0	0.00	-0.56	0.56	-
		13	3500 m 50% $\dot{V}O_{2peak}$ [24-hrs][a]	84.0	3.0	84.0	3.0	0.0	0.00	-0.56	0.56	-
									0.00	-0.39	0.39	26.6
	Sotiridis et al. [25]	12	3600 m 40% PP[a]	78.4	4.2	77.4	4.9	-1.0	-0.20	-0.80	0.39	20.7
$\dot{V}_E$ (L.min^{-1})	***Salgado et al. [29]**	13	3500 m 50% $\dot{V}O_{2peak}$ [2-hrs][a]	53.7	5.6	55.9	5.9	+2.2	0.36	-0.23	0.94	-

(I^2 = 36.9%, P = 0.59)		13	3500 m 50% $\dot{V}O_{2peak}$ [24-hrs]^{a}	56.1	5.0	56.9	5.7	+0.8	0.14	-0.43	0.70	-
								+1.5	0.26	-0.14	0.66	33.8
	***Gibson et al. [31]**	8	4390 m 40% $\dot{V}O_{2peak}$	54.0	12.5	50.7	10.5	-3.3	-0.25	-0.99	0.49	-
		8	4390 m 65% $\dot{V}O_{2peak}$ ^{a}	116.1	27.4	108.7	17.6	-7.4	-0.28	-1.02	0.47	-
								-5.3	-0.11	-0.61	0.40	27.0
	Sotiridis et al. [25]	12	3600 m 40% PP^{a}	66.9	10.5	63.2	10.1	-3.7	-0.33	-0.94	0.27	22.4
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$^{a}	60.8	5.0	58.8	3.2	-2.0	-0.40	-1.22	0.42	33.8
	***Gibson et al. [31]**	8	4390 m 65% $\dot{V}O_{2peak}$^{a}	2.85	0.45	2.85	0.28	0.00	0.00	-0.73	0.73	-
		8	4390 m 40% $\dot{V}O_{2peak}$^{a}	1.82	0.32	1.78	0.25	-0.04	-0.12	-0.85	0.61	-
								-0.02	-0.02	-0.53	0.48	26.1
$\dot{V}O_2$ (L.min^{-1})	**Lee et al. [24]**	7	3000 m 50% $\dot{V}O_{2peak}$^{a}	1.60	0.10	1.60	0.14	0.00	0.00	-0.78	0.78	14.5
(I^2 = 0.0%, P = 0.08)	***Salgado et al. [29]**	13	3500 m 50% VO_{2peak} [24-hrs]^{a}	1.63	0.23	1.60	0.26	-0.03	-0.11	-0.68	0.45	-
		13	3500 m 50% VO_{2peak} [2-hrs]^{a}	1.63	0.24	1.59	0.26	-0.04	-0.15	-0.71	0.42	-
								-0.03	-0.12	-0.51	0.27	40.2
	Sotiridis et al. [25]	12	3600 m 40% PP^{a}	2.31	0.27	2.22	0.25	-0.10	-0.34	-0.94	0.27	19.3
	***Salgado et al. [29]**	13	3500 m 50% $\dot{V}O_{2peak}$ [2-hrs]^{a}	0.94	0.10	0.96	0.10	0.0	0.19	-0.38	0.75	-
		13	3500 m 50% $\dot{V}O_{2peak}$[24-hrs]^{a}	0.91	0.11	0.93	0.10	0.0	0.18	-0.39	0.74	-
RER									0.18	-0.21	0.58	43.1
(I^2 = 43.3%, P = 0.56)	***Gibson et al. [31]**	8	4390 m 40% $\dot{V}O_{2peak}$^{a}	0.94	0.07	0.92	0.08	0.0	-0.23	-0.97	0.51	-
		8	4390 m 65% $\dot{V}O_{2peak}$^{a}	1.06	0.08	1.01	0.08	-0.1	-0.54	-1.34	0.25	-
									-0.27	-0.78	0.24	34.4
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$^{a}	0.98	0.06	0.95	0.06	0.0	-0.42	-1.25	0.40	22.5
BR (breaths.min^{-1})	**Gibson et al. [31]**	8	4390 m 40% $\dot{V}O_{2peak}$^{a}	25	4	25	2	0	-	-	-	-
		8	4390 m 65% $\dot{V}O_{2peak}$^{a}	40	5	39	4	-1	-	-	-	-
	***Lee et al. [24]**	8	3000 m 50% $\dot{V}O_{2peak}$^{a}	37.80	0.40	37.60	0.30	-0.20	-0.49	-1.27	0.29	-
		8	3000 m 50% $\dot{V}O_{2peak}$^{b}	38.10	0.40	37.80	0.30	-0.30	-0.74	-1.58	0.11	-
T_{core} (°C)									-0.61	-1.17	-0.06	36.6
(I^2 = 0.0%, P < 0.001)	**Sotiridis et al. [25]**	12	3600 m 40% PP^{a}	37.40	0.30	37.20	0.30	-0.20	-0.62	-1.26	0.03	28.5
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$^{a}	37.55	0.18	37.40	0.14	-0.15	-0.78	-1.71	0.15	17.1
	White et al. [28]	8	1600 m 55% $\dot{V}O_{2peak}$^{c}	38.80	0.50	38.40	0.30	-0.40	-0.84	-1.72	0.04	17.8
T_{skin} (°C)	**^Lee et al. [22]**	8	3000 m 50% $\dot{V}O_{2peak}$*	32.40	0.50	33.30	1.10	+0.9	0.91	0.01	1.82	-

(I^2 = 32.1%, P = 0.01)		8	3000 m 50% $\dot{V}O_{2peak}$$^{¥}$	33.10	0.80	33.70	1.30	+0.6	0.48	-0.30	1.26	-
	Sotiridis et al. [25]	12	3600 m 40% PP^{a}	34.20	0.80	33.80	0.70	-0.4	-0.49	-1.12	0.14	62.0
	White et al. [28]	8	1600 m 55% $\dot{V}O_{2peak}$^{c}	37.70	0.30	37.10	0.60	-0.6	-1.10	-2.07	-0.12	38.0
LLQ	**Gibson et al. [31]**	8	4390 m 40% $\dot{V}O_{2peak}$^{a}	0.1	0.4	0.1	0.4	0.0	-	-	-	-
		8	4390 m 65% $\dot{V}O_{2peak}$^{a}	0.8	1.2	0.1	0.4	-0.7	-	-	-	-
RPE (I^2 = 37.6%, P = 0.10)	***Gibson et al. [31]**	8	4390 m 40% $\dot{V}O_{2peak}$^{a}	9.4	1.9	10.1	1.6	+0.7	0.35	-0.41	1.10	-
		8	4390 m 65% $\dot{V}O_{2peak}$^{a}	16.4	2.2	15.8	1.3	-0.6	-0.29	-1.03	0.46	-
									0.02	-0.48	0.52	29.6
	***Salgado et al. [29]**	13	3500 m 50% $\dot{V}O_{2peak}$ [2-hrs]^{a}	14.0	3.0	14.0	3.0	0.0	0.00	-0.56	0.56	-
		13	3500 m 50% $\dot{V}O_{2peak}$ [24-hrs]^{a}	15.0	2.0	14.0	3.0	-1.0	-0.36	-0.95	0.22	-
									-0.18	-0.57	0.22	36.6
	Lee et al. [24]	7	3000 m 50% $\dot{V}O_{2peak}$^{a}	12.0	2.0	11.0	1.0	-1.0	-0.53	-1.38	0.32	17.9
	White et al. [28]	8	1600 m 55% $\dot{V}O_{2peak}$^{c}	15.0	2.0	13.0	2.0	-2.0	-0.87	-1.76	0.02	15.9

Note: LLQ and BR data from multiple trials were excluded from statistical analysis as data is from only 1 study, ^{a} represents mean data, ^{b} represents peak data, ^{c} represents end data, * represents combined group data for further statistical analyses, $^{\#}$ represents data that was combined but removed from further statistical analysis due to Egger regression asymmetry ($p<0.05$) and ^ represents data that was combined but removed from further statistical analysis due to high I^2 (Considerable heterogeneity [75-100%]).

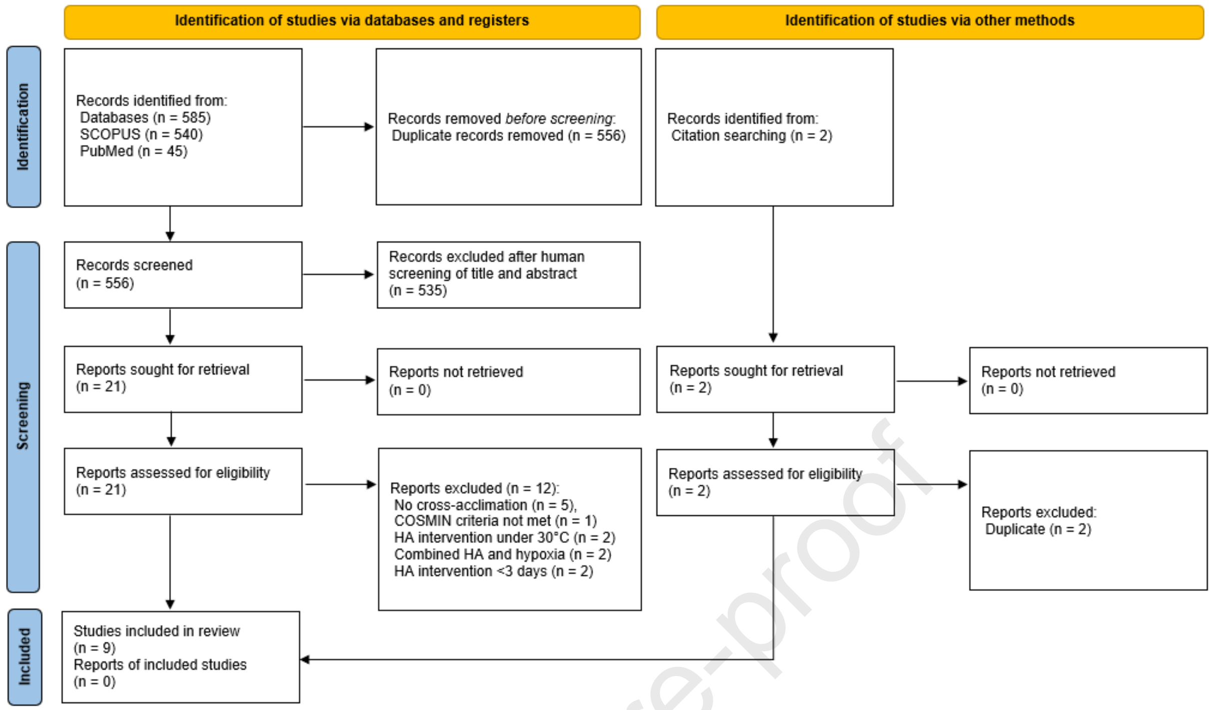
Table 6. Maximal and performance data observations from the included CA research studies.

Measure	Study	*n*	Conditions / Intensity	Pre-HA		Post-HA		Difference	SMD (Hedges' g)	95% CIs		Weight (%)
				Mean	SD	Mean	SD			Lower	Upper	
HR (b.min^{-1}) (I^2 = 29.9%, P = 0.51)	***White et al. [28]**	8	1600 m $\dot{V}O_{2max}$	173	13	177	6	4	0.34	-0.41	1.10	-
		8	4350 m $\dot{V}O_{2max}$	170	12	170	9	0	0.00	-0.73	0.73	-
		8	1600 m 16.0 km TT	172	8	172	5	0	0.00	-0.73	0.73	-
									0.10	-0.31	0.51	32.0
	Lee et al. [24]	7	3000 m 16.1 km TT	164	11	166	13	2	0.14	-0.64	0.92	16.0
	***Salgado et al. [29]**	13	3500 m 15-min TT [24-hrs]	165	12	164	12	-1	-0.08	-0.64	0.49	-
		13	3500 m 15-min TT [2-hrs]	154	14	152	12	-2	-0.14	-0.71	0.42	-
									-0.13	-0.52	0.26	33.4
	Sotiridis et al. [25]	12	3600 m $\dot{V}O_{2peak}$	187	8	182	8	-5	-0.58	-1.22	0.06	18.6
SpO_2 (%) (I^2 = 0.0%, P = 0.34)	***White et al. [28]**	8	4350 m $\dot{V}O_{2max}$	75.6	3.8	75.9	3.7	0.3	0.07	-0.66	0.80	-
		8	1600 m $\dot{V}O_{2max}$	90.4	2.4	90.6	4.4	0.2	0.05	-0.68	0.78	-
		8	1600 m 16.0 km TT	76.4	3.3	76.5	2.6	0.1	0.03	-0.70	0.76	-
									0.02	-0.39	0.43	48.1
	***Salgado et al. [29]**	13	3500 m 15-min TT [2-hrs]	83.0	4.0	83.0	3.0	0.0	0.00	-0.56	0.56	-
		13	3500 m 15-min TT [24-hrs]	84.0	3.0	84.0	3.0	0.0	0.00	-0.56	0.56	-
									0.00	-0.39	0.39	51.9
$\dot{V}_E$ (L.min^{-1}) (I^2 = 0.0%, P < 0.001)	**Sotiridis et al. [25]**	12	3600 m $\dot{V}O_{2peak}$	169	28	177	22	8	0.29	-0.31	0.89	43.3
	***White et al. [28]**	8	1600 m $\dot{V}O_{2max}$	171	30	176	25	5	0.16	-0.57	0.89	-
		8	4350 m $\dot{V}O_{2max}$	175	33	181	32	6	0.16	-0.57	0.89	-
									0.19	-0.32	0.70	56.7
RER	**White et al. [28]**	8	4350 m $\dot{V}O_{2max}$	1.22	0.06	1.23	0.04	0.01	-	-	-	-
		8	1600 m $\dot{V}O_{2max}$	1.23	0.06	1.21	0.04	-0.02	-	-	-	-
BR (breaths.min^{-1})	**White et al. [28]**	8	4350 m $\dot{V}O_{2max}$	55.2	12.1	56.7	10.9	1.5	-	-	-	-
		8	1600 m $\dot{V}O_{2max}$	54.1	12.3	54.6	8.3	0.5	-	-	-	-

RPE (I^2 = 0.00%, P = n/a)	***White et al. [28]**	8	1600 m $\dot{V}O_{2max}$	17.5	1.7	18.4	1.2	0.9	0.53	-0.26	1.32	-
		8	1600 m 16.0 km TT	18.8	1.3	18.4	1.3	-0.4	-0.27	-1.01	0.48	-
		8	4350 m $\dot{V}O_{2max}$	18.5	1.1	17.9	1.1	-0.6	-0.47	-1.25	0.30	-
									0.00	-0.41	0.41	48.2
	***Salgado et al. [29]**	13	3500 m 15-min TT [2-hrs]	17.0	2.0	17.0	2.0	0.0	0.00	-0.56	0.56	-
		13	3500 m 15-min TT [24-hrs]	17.0	2.0	17.0	2.0	0.0	0.00	-0.56	0.56	-
									0.00	-0.39	0.39	51.8
$\dot{V}O_2$ (mL.kg^{-1}.min^{-1}) (I^2 = 0.0%, P = 0.17)	**Sotiridis et al. [25]**	12	3600 m $\dot{V}O_{2peak}$	44.0	4.3	44.9	3.6	0.9	0.21	-0.38	0.80	32.5
	***White et al. [28]**	8	4350 m $\dot{V}O_{2max}$	46.1	4.7	47.1	5.6	1.0	0.18	-0.55	0.92	-
		8	1600 m $\dot{V}O_{2max}$	55.4	7.2	54.8	5.9	-0.7	-0.09	-0.82	0.64	-
									0.02	-0.48	0.52	42.4
	Heled et al. [32]	8	2400 m $\dot{V}O_{2peak}$	57.0	3.7	57.1	2.9	0.1	0.03	-0.70	0.76	25.1
PP (W) (I^2 = 0.0%, P = 0.002)	**Sotiridis et al. [25]**	12	3600 m $\dot{V}O_{2peak}$	282	28	294	26	12	0.41	-0.20	1.02	55.4
	Salgado et al. [27]	8	1600-4350 m $\dot{V}O_{2peak}$	342	50	353	43	11	0.20	-0.53	0.94	44.6
TT (min) (I^2 = 0.0%, P = 0.003)	**White et al. [28]**	8	4350 m 16.0 km TT	29.2	1.4	28.7	1.2	-0.5	-0.30	-1.04	0.45	55.8
	Lee et al. [24]	7	3000 m 16.1 km TT	42.7	2.9	40.7	2.8	-2.0	-0.59	-1.46	0.28	44.2

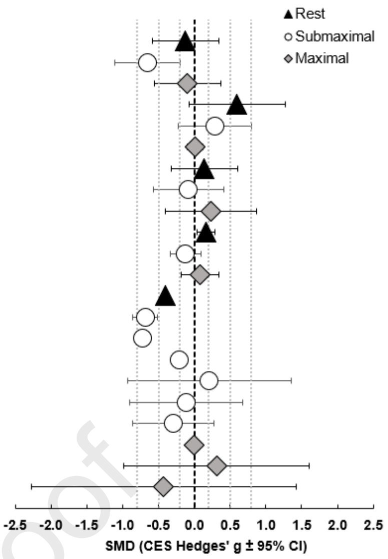
Note: RER and BR data from multiple trials were excluded from statistical analysis as data is from only 1 study, * represents combined group data for further statistical analyses.

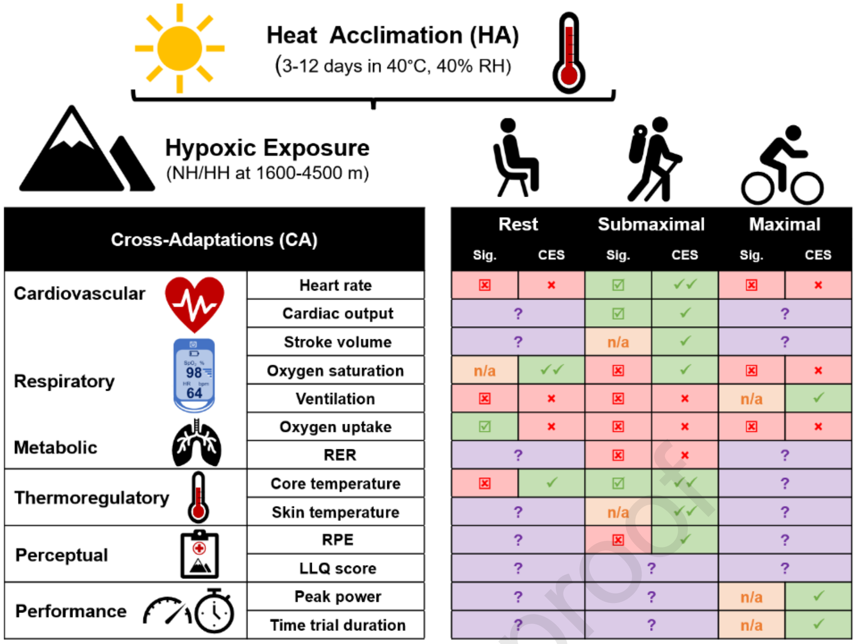
PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources



Measure	Intensity	Mean Difference	Weighted Mean Difference	SMD (CES Hedges' g)	95% CIs		P-value
					Lower	Upper	
HR (b.min^{-1})	Rest	-2	-1	-0.12	-0.58	0.35	0.28
	Submaximal	-10	-11	-0.65	-1.11	-0.20	<0.001*
	Maximal	-1	-1	-0.10	-0.56	0.37	0.51
SpO$_2$ (%)	Rest	+2.0	+2.0	0.60	-0.07	1.27	<0.001
	Submaximal	+1	+1	0.29	-0.22	0.80	0.11
	Maximal	+0.1	+0.1	0.01	-0.10	0.12	0.34
$\dot{V}_E$ (L.min^{-1})	Rest	+0.3	+0.4	0.14	-0.32	0.61	0.19
	Submaximal	-2.4	-1.7	-0.08	-0.57	0.41	0.59
	Maximal	+7.0	+6.9	0.24	-0.40	0.87	<0.001
$\dot{V}O_2$ (L.min^{-1})	Rest	+0.02	+0.01	0.17	0.04	0.29	<0.001*
	Submaximal	-0.04	-0.04	-0.12	-0.33	0.10	0.08
$\dot{V}O_2$ (mL.kg^{-1}.min^{-1})	Maximal	+0.4	+0.4	0.08	-0.18	0.35	0.17
T$_{core}$ (°C)	Rest	-0.11	-0.14	-0.40	-3.39	2.60	0.09
	Submaximal	-0.25	-0.25	-0.68	-0.86	-0.51	<0.001*
T$_{skin}$ (°C)	Submaximal	-0.50	-0.48	-0.72	-4.47	3.03	0.01
$\dot{Q}$ (L.min^{-1})	Submaximal	-0.5	-0.6	-0.21	-0.24	-0.19	<0.001*
SV (mL)	Submaximal	+4	+3	0.21	-0.93	1.35	0.02
RER (A.U.)	Submaximal	-0.01	0.00	-0.11	-0.90	0.68	0.56
RPE (A.U.)	Submaximal	-0.9	-0.6	-0.29	-0.86	0.28	0.10
	Maximal	0.0	0.0	0.00	0.00	0.00	-
PP (W)	Maximal	+12	+12	0.32	-0.98	1.61	0.00
TT (min)	Maximal	-1.2	-1.2	-0.43	-2.27	1.42	0.00

Note: CI data removed for rest T$_{core}$ and submaximal T$_{skin}$ for figure clarity. * represents data that doesn not cross the 'no effect' line.





Cross-Adaptations (CA)		Rest Sig.	Rest CES	Submaximal Sig.	Submaximal CES	Maximal Sig.	Maximal CES
Cardiovascular	Heart rate	☒	×	☑	✓✓	☒	×
	Cardiac output	?		☑	✓	?	
	Stroke volume	?		n/a	✓	?	
Respiratory	Oxygen saturation	n/a	✓✓	☒	✓	☒	×
	Ventilation	☒	×	☒	×	n/a	✓
Metabolic	Oxygen uptake	☑	×	☒	×	☒	×
	RER	?		☒	×	?	
Thermoregulatory	Core temperature	☒	✓	☑	✓✓	?	
	Skin temperature	?		n/a	✓✓	?	
Perceptual	RPE	?		☒	✓	?	
	LLQ score	?		?		?	
Performance	Peak power	?		?		n/a	✓
	Time trial duration	?		?		n/a	✓

Combined effect size ([CES] Hedges' g): × = <0.19 (*Trivial*), ✓ = 0.20-0.49 (*Small*), ✓✓ = 0.50-0.79 (*Moderate*) and ✓✓✓ = ≥0.80 (*Large*).
Significance (Sig.): ☑ = significant ($p<0.05$), ☒ = non-significant ($p>0.05$), n/a = non-significant (confidence intervals cross line of no effect), ? = insufficient data.
Note: RH = relative humidity, NH = normobaric hypoxia, HH = hypobaric hypoxia, RER = respiratory exchange ratio, RPE = rating of perceived exertion, LLQ = Lake Louise Questionnaire.

Highlights:

- Cross-adaptation refers to the process where individuals adapt to one environmental stressor, such as heat stress, but then demonstrate improved response to another environmental stressor, such as altitude exposure.
- Following repeated exercise sessions in heat stress, termed heat acclimation, humans demonstrate physiological adaptations, such as improved oxygen saturation at rest and reduced heart rate and core temperature during submaximal exercise in hypoxic/altitude conditions.
- Cross-adaptation offers individuals, such as occupational and military workers, a time efficient alternative to traditional hypoxic training interventions, to adapt for submaximal activity at altitude.

Funding Sources: none

Declarations of interest: none