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# Comparative efficacy of various hypoxic training paradigms on maximal oxygen consumption: A systematic review and network meta-analysis

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ABSTRACT

*Background:* Enhancement in maximal oxygen consumption ($VO_{2max}$) induced by hypoxic training is important for both athletes and non-athletes. However, the lack of comparison of multiple paradigms and the exploration of related modulating factors leads to the inability to recommend the optimal regimen in different situations. This study aimed to investigate the efficacy of seven common hypoxic training paradigms on $VO_{2max}$ and associated moderators.

*Methods:* Electronic (i.e., five databases) and manual searches were performed, and 42 studies involving 1246 healthy adults were included. Pairwise meta-analyses were conducted to compare different hypoxic training paradigms and hypoxic training and control conditions. The Bayesian network meta-analysis model was applied to calculate the standardised mean differences (SMDs) of pre–post $VO_{2max}$ alteration among hypoxic training paradigms in overall, athlete, and non-athlete populations, while meta-regression analyses were employed to explore the relationships between covariates and SMDs.

*Results:* All seven hypoxic training paradigms were effective to varying degrees, with SMDs ranging from 1.45 to 7.10. Intermittent hypoxia interval training (IHIT) had the highest probability of being the most efficient hypoxic training paradigm in the overall population and athlete subgroup (42%, 44%), whereas intermittent hypoxic training (IHT) was the most promising hypoxic training paradigm among non-athletes (66%). Meta-regression analysis revealed that saturation hours (coefficient, 0.004; $P = 0.038$; 95% CI [0.0002, 0.0085]) accounted for variations of $VO_{2max}$ improvement induced by IHT.

*Conclusion:* Efficient hypoxic training paradigms for $VO_{2max}$ gains differed between athletes and non-athletes, with IHIT ranking best for athletes and IHT for non-athletes. The practicability of saturation hours is confirmed with respect to dose–response issues in the future hypoxic training and associated scientific research.

*Registration:* This study was registered in the PROSPERO international prospective register of systematic reviews (CRD42022333548).

## 1. Introduction

Since the 1968 Mexico City Olympics, studies on hypoxic training have gradually emerged to promote sea-level exercise capacity and performance.[1,2] Adding a hypoxic stimulus to exercise may lower the mechanical load on the musculoskeletal system and maintain the cardiorespiratory stress to a level similar to that produced by higher exercise intensity in a normoxic environment.[3,4] Among the hypoxic training paradigms, the live high/train high (LHTH) paradigm was the first designed hypoxic training paradigm of living and training in the natural altitude environment (1500–4000 m).[5] Later on, the live high/train low (LHTL) paradigm was established to avoid the loss of exercise intensity and reduce the detrimental effects of chronic hypoxia when making use of altitude acclimatisation.[6] Within the last two decades, the invention of artificial hypoxic facilities promoted the development of live low/train high (LLTH) approaches, which offered people discrete and brief intervals of hypoxic exposure at rest (i.e., intermittent hypoxic exposure [IHE]) or during exercise sessions (e.g., intermittent

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hypoxic training [IHT], intermittent hypoxia interval training [IHIT], repeated sprint training in hypoxia [RSH], resistance training in hypoxia [RTH]).[7]

Hypoxic training has been proven to potentiate haematological capacity, central adaptations (i.e., ventilatory, haemodynamic, and neural adaptation), and peripheral adaptations (i.e., muscle buffering capacity, economy, and mechanical efficiency) in the healthy population.[8,9] Among the expected outcomes, the enhancement in the maximal oxygen consumption ($VO_{2max}$) is of great importance for both athlete and non-athlete populations. For athletes, $VO_{2max}$ is a primary determinant of cardiorespiratory fitness and endurance capacity, explaining 20–60% of the variation in exercise performance.[10,11] For non-athletes, a high $VO_{2max}$ serves as a robust indicator of general well-being and longevity.[12] The augmented $VO_{2max}$ is closely correlated with increased oxygen-carrying capacity in the blood,[13] improved cellular respiration efficiency,[14] enhanced cardiovascular and mental health,[15,16] heightened resistance to respiratory ailments,[17] and reduced likelihood of experiencing metabolic syndrome and mortality.[12,14] Compared to other conventional and efficacious forms of cardiorespiratory training, hypoxic training offers unique benefits for enhancing $VO_{2max}$. These advantages primarily manifest through rapid physiological adaptations,[18] heightened erythropoiesis (such as elevated production of erythropoietin and red blood cell count),[13] improved mitochondrial function,[14] and enhanced cardiovascular efficiency.[15] Additionally, hypoxic training allows for a more intense cardiovascular workout without necessarily increasing exercise intensity.[8] The aforementioned advantages render hypoxic training an attractive, time-efficient, and versatile alternative to conventional training methods to enhance $VO_{2max}$.[18]

The $VO_{2max}$ enhancement induced by hypoxic training is built on the premise that people can simultaneously benefit from altitude acclimatisation and exercise training.[5] Along with altitude acclimatisation, the elevated haemoconcentration resulting from plasma volume reduction and the increased red blood cell (RBC) mass caused by erythropoietin secretion work together in the facilitation of blood oxygen transport and utilisation, leading to the increase in $VO_{2max}$.[5,19] Besides, the increased capillarisation and oxidative capacity of working muscles also contribute to the $VO_{2max}$ enhancement.[20] Notably, the hypoxic training paradigms may differ in hypoxia-related mechanisms. The RBC mass is more likely to augment in sufficient residing altitude exposure like LHTH and LHTL,[21–23] whereas improved oxidative enzyme activity and mitochondrial function are commonly observed in the LLTH.[24] Previous related pairwise meta-analyses either evaluated the effectiveness of various hypoxic training paradigms in the $VO_{2max}$ enhancement in general[25] or focused on the single hypoxic training type,[26] which indicated the efficacy of hypoxic training but lack of comparison among multiple paradigms. This led to the inability to recommend the optimal hypoxic training scheme under different circumstances.

It is noteworthy that factors including personal characteristics (e.g., age, sex, body mass index [BMI], fitness level) and training protocols (e.g., dose and load) may influence the effect of hypoxic training paradigms on $VO_{2max}$ improvement.[27] Current evidence indicates that both men and women experience a 10% decline in $VO_{2max}$ per decade.[27] Age-related loss of $VO_{2max}$ appears to occur in a non-linear relationship with physical fitness declines,[27] including increased BMI and fat mass percentage.[28] This non-linear decline typically occurs in young adulthood among sedentary individuals and upon cessation of training among athletic individuals.[27] Exercise training may reduce this loss by up to 50% in young and middle-aged men, but not middle-aged and older women due to reduced estrogen levels.[27] Sex differences can also be reflected in respiratory and circulatory cost, neuroendocrine response, and metabolic adaptation during hypoxic training.[29,30] In addition, hypoxic dose (i.e., kilometre hours and saturation hours) and load are determinants of cardiometabolic stress and physiological response during hypoxic training, which may finally influence $VO_{2max}$ gains.[4,31,32]

As mentioned above, although a vast body of studies in this field have been conducted,[8,19,25,26] issues regarding how to recommend the optimal hypoxic training among multiple choices to promote $VO_{2max}$ improvement remain unclear. The varying training purposes and adaptations among populations (i.e., athlete and non-athlete) have not been given full consideration when evaluating $VO_{2max}$ gains from hypoxic training. Additional issues evaluating and comparing hypoxic training paradigms relate to heterogeneities in research design, including the participant characteristics and training protocol. These heterogeneities among studies may preclude determining the specificity and effectiveness of training paradigms to achieve similar $VO_{2max}$ gains in particular populations. Therefore, this systematic review and network meta-analysis aimed to 1) investigate and compare the efficacy of multiple hypoxic training paradigms (LHTH, LHTL, IHE, IHT, IHIT, RSH, RTH) in $VO_{2max}$ enhancement on overall, athlete, and non-athlete populations and to 2) assess the moderating effects of covariates related to participant and hypoxic training protocol in the relationship between hypoxic training and $VO_{2max}$ improvement.

## 2. Methods

The study was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Network Meta-Analyses statement (PRISMA-NMA).[33] The 27-item PRISMA-NMA checklist was used for critical appraisal when reporting (Appendix 1). The registration information (CRD42022333548) is available at https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=333548.

### 2.1. Data sources and searches

Two authors (ZK and QY) independently conducted the electronic search via five databases (PubMed, Web of Science, SPORTDiscus, ProQuest Central, and Cochrane Central Register of Controlled Trials) from their inception to March 2022, with arguments resolved by consensus (Appendix 2). We set up search alerts for the above-mentioned electronic databases up to March 2023. Manually, Google Scholar and the reference lists of related systematic reviews and/or meta-analyses published within the past three years were searched. Only peer-reviewed publications written in English were considered.

### 2.2. Study selection

The title and abstract were first screened by two independent authors (JN and QY) after removing duplications. When sufficient information could not be acquired in the abstract, the authors conducted a full-text evaluation. The lists of potential studies provided by two authors were compared, and disagreements were resolved by the involvement of a third expert (ZK).

The included studies needed to meet the following criteria: 1) Study design: randomised controlled trials or non-randomised controlled trials, with at least 10 participants in each trial arm to minimize the risk of publication risk. Besides most methodological practices of traditional pairwise meta-analysis, the Bayesian network meta-analysis has greater complexity due to multiple comparisons.[34] The effective sample size of network meta-analysis needs to provide the same degree and strength of evidence in both direct and indirect comparisons.[34,35] According to past practices and the results of Brook–Gelman–Rubin diagnosis in the present study, a minimum of 10 participants was required in each trial arm of network.[34–37] 2) Participants: healthy population aged 18 to 65.3) Interventions: any type of hypoxic training summarised in Table 1 from historical perspectives.[5,7,8,38–41] 4) Comparator: live low/train low (LLTL; live and exercise at sea level), live low/no train (LLNT; live at sea level without exercise), or another type of hypoxic training not applied in the experimental group. 5) Outcomes: $VO_{2max}$ directly assessed using devices prior to and after intervention. To increase the number of included studies, the experimental trial that evaluated the peak oxygen consumption ($VO_{2peak}$) rather than $VO_{2max}$ was also included. The reason is that the $VO_{2peak}$ is an acceptable estimate of $VO_{2max}$, and the

**Table 1**
Classification and definition of hypoxic training from historical perspectives.

| Type | | Definition |
|---|---|---|
| Live high-train high (LHTH) | | Hypoxic training requiring living and training at high altitude. |
| Live high-train low (LHTL) | | Hypoxic training requiring living at high altitude and training at low altitude. |
| Live low-train high (LLTH) | Intermittent hypoxic exposure (IHE) | Hypoxic training consisting of hypoxia exposure lasting seconds to hours with a return to normoxia or lower levels of hypoxia and repetition over days to weeks. |
| | Intermittent hypoxic training (IHT) | Hypoxic training with discontinuous use of hypoxia. |
| | Intermittent hypoxia interval training (IHIT) | Hypoxic training alternating hypoxia and normoxia during a single exercise session. |
| | Repeated sprint training in hypoxia (RSH) | Hypoxic training consisting of series of sprints with brief recovery periods ($\leq$60s) in hypoxia. |
| | Resistance training in hypoxia (RTH) | Hypoxic training combining resistance exercise and hypoxia for strength and muscle gains. |

criteria for reaching $VO_2$ at sea level may not be immutable with the elevation of altitude (e.g., the maximum heart rate decreases in hypoxia).[40] Hereafter, the term "$VO_{2max}$" is used uniformly. We excluded studies including 1) altitude natives; 2) less than one week of hypoxic training; 3) more than one type of hypoxic training; and/or 4) combination with another interventions (i.e., β-alanine supplementation). If more than one study used data from the same cohort, the study with the largest sample size was ultimately included.

### 2.3. Data extraction

Data extraction was undertaken by two independent authors (QS and QY), with the involvement of a third expert (ZK) when agreement could not be reached. The extracted data were compared by another author (JN), and a maximum of 5% inconsistency was allowed. When more than 5% inconsistency occurred in the extracted information, the data from relevant studies would be re-extracted. The following information was extracted from original studies: 1) study characteristics (author, publication year, country); 2) participant characteristics (participant type, sample size in each trial arm, sex, age, weight, height, BMI); 3) intervention (hypoxic training type, altitude level, saturation value, hypobaric/normobaric hypoxia, hypoxia mechanism, time per session, frequency, duration, exercise type, exercise intensity, supervision); 4) outcome ($VO_{2max}$ assessed prior to and after intervention). For each trial arm, the mean change of $VO_{2max}$ and corresponding standard deviation (SD) were directly recorded or calculated based on baseline and post-intervention values as follows (using an imputed correlation coefficient of 0.50):[42]

$$SD_{change} = \sqrt{SD^2_{baseline} + SD^2_{postintervention} - 2 * r * SD_{baseline} * SD_{postintervention}}$$

ImageJ, a Java-based image processing programme[43] (V.1.50i, https://imagej.nih.gov/ij/), was used for scientific image data extraction.[44–47]

### 2.4. Assessment of risk of bias and certainty of evidence

The Cochrane Collaboration's risk-of-bias tool (RoB version 2.0)[48] was applied for methodological evaluation in terms of randomisation process, deviations resulting from intended interventions, missing data and measurement of outcome, and selected reporting. The study was regarded as "low risk of bias" if all domains were rated "low risk", "some concerns" if any domain was rated "some concerns", and "high risk of bias" if there was at least one domain rated "high risk". The certainty of evidence was assessed by the Grading of Recommendation Assessment, Development and Evaluation (GRADE) approach.[49,50]

### 2.5. Data analysis

Pairwise meta-analyses using a random-effects modelling were conducted for direct comparisons among different hypoxic training types and comparisons between hypoxic training and control condition (LLTL and LLNT). A statistically significant difference was detected when the 95% confidence interval (95% CI) did not contain a null hypothesis value (zero).[51] The effect size was estimated by the standardised mean difference (SMD) (small: $<0.40$; moderate: 0.40–0.70; large: $>0.70$) of the change score.[52] The upper limits of $I^2$ index of 25%, 50%, and 75% were set to correspond to small, moderate, and high heterogeneity, respectively.[53,54] Sensitivity analyses were conducted to assess the estimates' robustness and identify the sources of heterogeneity, in which the primary analysis was repeated with altered dataset to determine whether excluding or including certain studies would have any effect on the outcome estimates.[55]

The Bayesian random effect of the network meta-analysis model was applied in the analysis of pre–post $VO_{2max}$ changes. The WinBUGS Bayesian analysis software (Bayesian inference Using Gibbs Sampling for Windows, V.1.4.3; Imperial College and MRC, UK) was used to fit the statistical model (BUGS codes available in Appendix 3).[56] Four Markov chains with 50,000 iterations were run simultaneously using non-informative prior distribution.[57] The first 10,000 iterations influenced by arbitrary initial were removed in each chain.[57] The values of interest were collected with a thinning interval of 10, and nearly 16,000 samples were acquired from all the chains.[57] The final convergence was assessed using Brook–Gelman–Rubin diagnosis, with the potential scale reduction factor close to 1 suggesting the approximate convergence was reached.[58] The rank probability for each intervention was calculated via the Surface Under the Cumulative Ranking (SUCRA) method,[59] with a higher SUCRA value indicating better ranking. The consistency between direct and indirect comparisons was tested by the node-splitting analysis.[57,60]

According to previous findings,[27–32] covariates including participant type (binary variable), age, gender ratio, BMI, hypoxic mechanism, kilometre hours, saturation hours, and hypoxic load may moderate the effect of hypoxic training on maximal oxygen consumption. Thus, subgroup analysis was performed to assess the efficacy of various hypoxic training paradigms for athlete and non-athlete participants. Univariate and multivariate network meta-regression analyses were designed to be conducted using State 15.0 (College Station, TX, USA: StataCorp LLC) to test the association between SMD and covariates like participants' age, sex ratio (males/females), BMI, hypoxic mechanism, kilometre hours ([metres/1000] * hours),[31] saturation hours ([98/saturation value in percent – 1] * hours * 100),[32] and hypoxic load ($SpO_2$,[61] the average percent of maximum heart rate divided by $SpO_2$ multiplied by time in minutes [avg %HRmax/$SpO_2$% × time in minutes][62]), if there were at least 10 studies in the comparison.[63,64] Identified predictors driven by a 95% CI from univariate regression were selected as multiple variables in the next multivariate regression analysis.[63,64] The rationale is that the 95% CI usually plays a central role in the interpretation of regression results and data-driven predictor selection is reasonable, necessary, and widely used in the prior determination of the model.[64] In the present study, the meta-regression analyses were simply conducted in the comparison of IHT and LLTL due to the limited number of included studies. There was simply one identified moderator (i.e., saturation hours) after univariate regression analysis, and thus further multivariate regression analysis was ultimately not conducted.

## 3. Results

### 3.1. Studies included and characteristics

Of the 51,516 studies retrieved from electronic databases and registers, 36,673 were retained after removing duplicates. After removing 36,517 irrelevant studies based on title and abstract, the full text of 156 studies was reviewed and evaluated for eligibility. Of these, 119 studies were excluded, with the main reasons listed in Appendix 4. After adding five studies identified from Google Scholar and citation searching,[65–69] a total of 42 studies were included in the current systematic review and network meta-analysis (Fig. 1 & Appendix 5).[6,44–47,65–101]

The characteristics of the included studies are shown in Appendix 6. There were 1246 healthy people participating in the included studies, with 732 athletes[6,44–46,65–70,72–76,80,82–85,88–90,93,95–97,100] and 514 non-athletes.[47,71,77–79,81,86,87,91,92,94,98,99,101] Reported baseline demographics consisted of age (mean: 24.05 years), weight (mean: 69.43 kg), height (mean: 173.04 cm), and BMI (mean: 22.69 kg/cm$^2$). Details of hypoxic training protocols are available in Appendix 7. Eight studies (104 participants) examined the efficacy of LHTH,[6,65,70,82,84,85,90,100] with six studies (68 participants) for LHTL,[6,66,67,72,93,95] nine studies (100 participants) for IHE,[68,74–77,79,81,91,92] 19 studies (216 participants) for IHT,[44–47,65,72,73,78–81,87,89,91–93,96,98,99] one study (11 participants) for IHIT,[73] six studies (91 participants) for RSH,[69,83,86,88,97,101] and one study (15 participants) for RTH[94] (Fig. 2).

### 3.2. Assessment of risk of bias and certainty of evidence

A total of 66.67% of the studies rated "some concerns" in the randomisation process of risk of bias assessment, while 33.33% were rated "high risk" (Fig. 3). All studies were rated high risk in the bias due to deviations from intended interventions (participants/research investigators were aware of the assigned intervention) and low risk in the selection of reported results. Most studies were rated some concerns in the missing outcome data (high risk: 11.90%; some concerns: 76.20%; low risk: 11.90%) and outcome measurement (high risk: 30.95%; some concerns: 57.14%; low risk: 11.91%). The certainty of evidence for the included studies was rated at low to moderate levels (Appendix 8).

### 3.3. Pairwise and network meta-analyses in the overall population

Thirty-two comparisons were made regarding $VO_{2max}$ improvement, involving 1246 participants of 42 studies (Fig. 2).[6,44–47,65–101] Both direct and indirect comparisons showed significant differences in six comparisons of IHE vs. LLNT (direct: SMD = 0.57, 95% CI [0.14, 1.01]; indirect: SMD = 1.45, 95% CI [0.33, 2.55]), IHT vs. LLNT (direct: SMD = 3.78, 95% CI [2.48, 5.09]; indirect: SMD = 6.94, 95% CI [5.83, 7.92]), LHTL vs. LLTL (direct: SMD = 0.71, 95% CI [0.04, 1.39]; indirect: SMD = 2.76, 95% CI [1.27, 4.20]), IHE vs. LLTL (direct: SMD = −0.95, 95% CI [−1.17, −0.20]; indirect: SMD = −2.50, 95% CI [−3.57, −1.31]), IHT vs. LLTL (direct: SMD = 0.73, 95% CI [0.41, 1.05]; indirect: SMD = 2.99; 95% CI [2.15, 3.82]), and IHT vs. IHE (direct: SMD = 3.09, 95% CI [2.05, 4.13]; indirect: SMD = 5.48, 95% CI [4.28, 6.56]) (Table 2 & Appendix 9). For pairwise meta-analyses, no significant differences were observed in the three comparisons of RSH vs. LLNT (SMD = 0.37, 95% CI [−0.05, 0.78]), LHTH vs. LLTL (SMD = 0.40, 95% CI [−0.05, 0.86]), and RSH vs. LLTL (SMD = 0.36, 95% CI [−0.11, 0.82]) (Appendix 9). Sensitivity analysis was conducted for the pairwise meta-analysis (LLNT vs. IHT) in which high heterogeneity existed (Appendix 9); the $I^2$ decreased from 81.80% to 75.00% after removing Chen et al., 2018.[92] and Lin et al., 2021.[99] The IHIT paradigm had the highest probability (42%) of being the best intervention in improving $VO_{2max}$, while IHT, LHTL, LHTH, and RSH ranked 2 to 5 (Fig. 2). A good consistency was shown between direct and indirect estimated comparisons, with all *P* values above 0.05 in node-splitting analysis.

### 3.4. Subgroup analysis (athlete subgroup vs. non-athlete subgroup)

For the athlete subgroup, 28 studies consisting of six hypoxic training

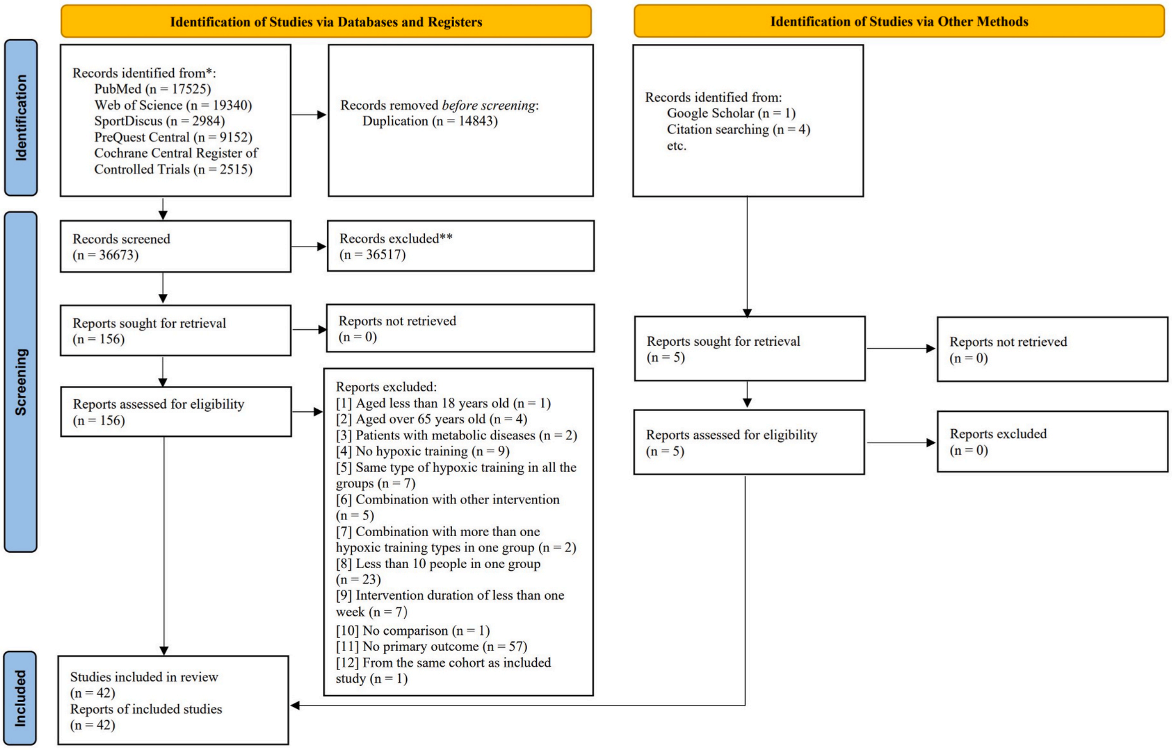

**Fig. 1.** PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

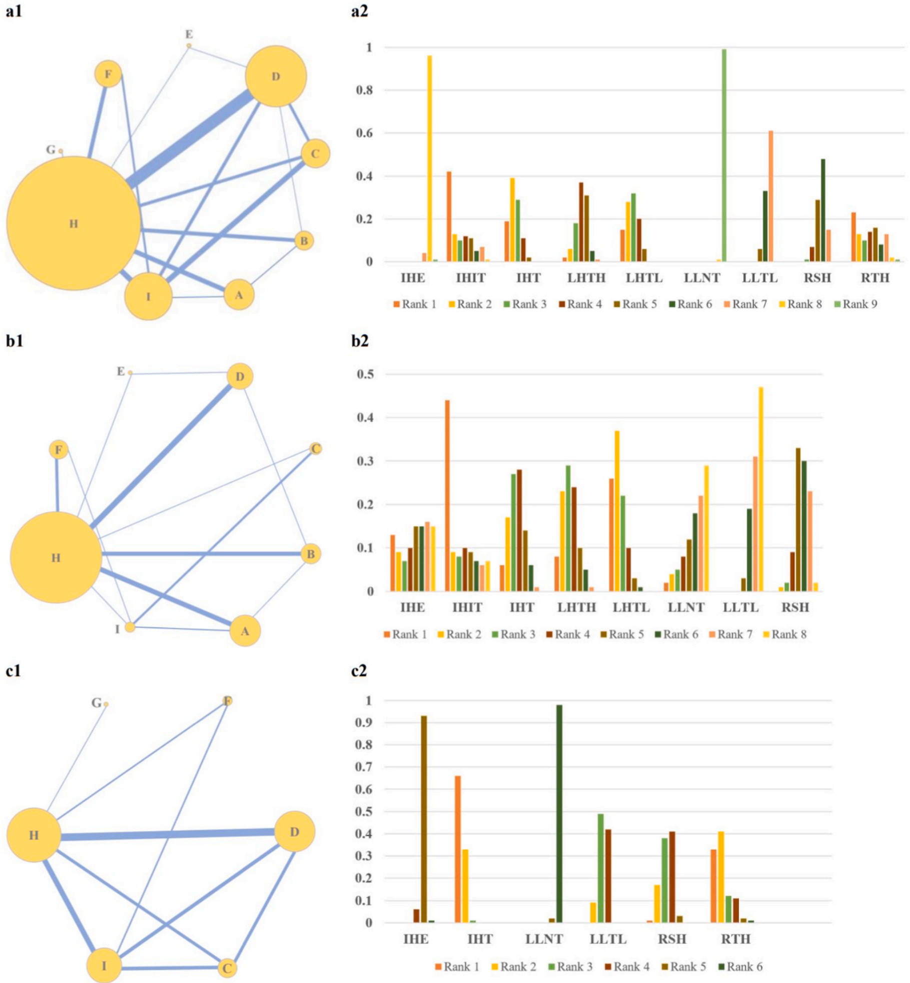

**Fig. 2.** Network meta-analysis maps and rank probability plots examining the efficacy of hypoxic training paradigms in maximum oxygen consumption (**Notes**. a1, network meta-analysis map of all included studies; b1, network meta-analysis map of athlete subgroup; b2, network meta-analysis map of non-athlete subgroup; a2, rank probability plot of all included studies; b2, rank probability plot of athlete subgroup; c2, rank probability plot of non-athlete subgroup [rank 1 is the best, rank last is the worst.]. A, LHTH; B, LHTL; C, IHE; D, IHT; E, IHIT; F, RSH; G, RTH; H, LLTL; I, LLNT.
In the network meta-analysis map of a1, b1, and c1, the node represented the intervention type and the line connected studies which were compared directly. Node size was weighted by the number of participants conducting certain intervention and the thickness of line was weighted by number of studies. For a2, b2, and c2, the y-axis value represented the likelihood of a specific hypoxic training paradigm ranking 1–8.)
**(Abbreviations.** LHTH, live high-train high; LHTL, live high-train low; IHE, intermittent hypoxic exposure; IHT, intermittent hypoxic training; IHIT, intermittent hypoxia interval training; RSH, repeated sprint training in hypoxia; RTH, resistance training in hypoxia; LLTL, live low-train low; LLNT, live low-no train.).

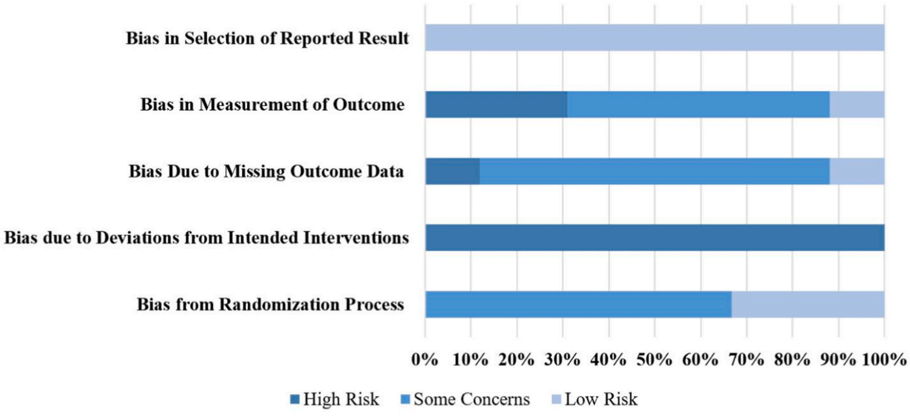

**Fig. 3.** Risk of bias assessment.

**Table 2**
Consistent model.

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **Consistent Model of all included studies** | | | | | | | | |
| **IHE** | 5.63 (0.92, 10.30) | 5.48 (4.28, 6.56) | 4.40 (2.29, 6.19) | 5.26 (3.33, 7.01) | −1.45 (−2.55, −0.33) | 2.50 (1.31, 3.57) | 3.07 (1.31, 4.66) | 4.61 (−0.13, 9.26) |
| −5.63 (−10.30, −0.92) | **IHIT** | −0.16 (−4.76, 4.44) | −1.24 (−6.14, 3.59) | −0.37 (−5.17, 4.35) | −7.10 (−11.74, −2.39) | −3.15 (−7.71, 1.42) | −2.56 (−7.32, 2.14) | −1.02 (−7.38, 5.55) |
| −5.48 (−6.56, −4.28) | 0.16 (−4.44, 4.76) | **IHT** | −1.08 (−2.94, 0.55) | −0.23 (−1.92, 1.38) | −6.94 (−7.92, −5.83) | −2.99 (−3.82, −2.15) | −2.41 (−3.95, −0.94) | −0.87 (−5.49, 3.77) |
| −4.40 (−6.19, −2.29) | 1.24 (−3.59, 6.14) | 1.08 (−0.55, 2.94) | **LHTH** | 0.85 (−0.94, 2.76) | −5.86 (−7.55, −3.85) | −1.91 (−3.36, −0.25) | −1.31 (−3.27, 0.74) | 0.21 (−4.48, 5.16) |
| −5.26 (−7.01, −3.33) | 0.37 (−4.35, 5.17) | 0.23 (−1.38, 1.92) | −0.85 (−2.76, 0.94) | **LHTL** | −6.71 (−8.38, −4.86) | −2.76 (−4.20, −1.27) | −2.19 (−4.15, −0.24) | −0.63 (−5.39, 4.23) |
| 1.45 (0.33, 2.55) | 7.10 (2.39, 11.74) | 6.94 (5.83, 7.92) | 5.86 (3.85, 7.55) | 6.71 (4.86, 8.38) | **LLNT** | 3.95 (2.89, 4.89) | 4.53 (2.86, 6.00) | 6.07 (1.37, 10.68) |
| −2.50 (−3.57, −1.31) | 3.15 (−1.42, 7.71) | 2.99 (2.15, 3.82) | 1.91 (0.25, 3.36) | 2.76 (1.27, 4.20) | −3.95 (−4.89, −2.89) | **LLTL** | 0.58 (−0.77, 1.85) | 2.10 (−2.44, 6.73) |
| −3.07 (−4.66, −1.31) | 2.56 (−2.14, 7.32) | 2.41 (0.94, 3.95) | 1.31 (−0.74, 3.27) | 2.19 (0.24, 4.15) | −4.53 (−6.00, −2.86) | −0.58 (−1.85, 0.77) | **RSH** | 1.55 (−3.21, 6.28) |
| −4.61 (−9.26, 0.13) | 1.02 (−5.55, 7.38) | 0.87 (−3.77, 5.49) | −0.21 (−5.16, 4.48) | 0.63 (−4.23, 5.39) | −6.07 (−10.68, −1.37) | −2.10 (−6.73, 2.44) | −1.55 (−6.28, 3.21) | **RTH** |
| **Consistent Model of Athlete Subgroup** | | | | | | | | |
| **IHE** | 1.64 (−4.18, 7.48) | 0.96 (−3.07, 4.98) | 1.16 (−2.80, 5.13) | 1.60 (−2.38, 5.53) | −0.84 (−4.07, 2.38) | −1.24 (−5.02, 2.48) | −0.25 (−4.16, 3.58) | |
| −1.64 (−7.48, 4.18) | **IHIT** | −0.64 (−4.99, 3.70) | −0.45 (−5.15, 3.94) | 0.00 (−4.47, 4.38) | −2.46 (−7.77, 3.10) | −2.89 (−7.29, 1.40) | −1.92 (−6.49, 2.47) | |
| −0.96 (−4.98, 3.07) | 0.64 (−3.70, 4.99) | **IHT** | 0.20 (−1.75, 1.90) | 0.64 (−1.12, 2.31) | −1.77 (−5.25, 1.76) | −2.26 (−3.53, −0.91) | −1.26 (−2.99, 0.42) | |
| −1.16 (−5.13, 2.80) | 0.45 (−3.94, 5.15) | −0.20 (−1.90, 1.75) | **LHTH** | 0.45 (−0.93, 2.01) | −1.95 (−5.27, 1.34) | −2.44 (−3.65, −0.94) | −1.47 (−3.04, 0.39) | |
| −1.60 (−5.53, 2.38) | −0.00 (−4.38, 4.47) | −0.64 (−2.31, 1.12) | −0.45 (−2.01, 0.93) | **LHTL** | −2.41 (−5.74, 0.89) | −2.90 (−4.07, −1.59) | −1.90 (−3.53, −0.22) | |
| 0.84 (−2.38, 4.07) | 2.46 (−3.10, 7.77) | 1.77 (−1.76, 5.25) | 1.95 (−1.34, 5.27) | 2.41 (−0.89, 5.74) | **LLNT** | −0.47 (−3.64, 2.71) | 0.49 (−2.73, 3.77) | |
| 1.24 (−2.48, 5.02) | 2.89 (−1.40, 7.29) | 2.26 (0.91, 3.53) | 2.44 (0.94, 3.65) | 2.90 (1.59, 4.07) | 0.47 (−2.71, 3.64) | **LLTL** | 1.01 (−0.22, 2.04) | |
| 0.25 (−3.58, 4.16) | 1.92 (−2.47, 6.49) | 1.26 (−0.42, 2.99) | 1.47 (−0.39, 3.04) | 1.90 (0.22, 3.53) | −0.49 (−3.77, 2.73) | −1.01 (−2.04, 0.22) | **RSH** | |
| **Consistent Model of Non-Athlete Subgroup** | | | | | | | | |
| **IHE** | 5.75 (4.42, 6.98) | −1.57 (−2.78, −0.27) | 2.60 (1.27, 3.87) | 2.65 (−0.22, 5.53) | 4.70 (−0.04, 9.41) | | | |
| −5.75 (−6.98, −4.42) | **IHT** | −7.31 (−8.44, −6.04) | −3.14 (−4.24, −2.02) | −3.10 (−5.87, −0.26) | −1.02 (−5.73, 3.70) | | | |
| 1.57 (0.27, 2.78) | 7.31 (6.04, 8.44) | **LLNT** | 4.16 (2.93, 5.30) | 4.21 (1.54, 6.87) | 6.27 (1.45, 10.97) | | | |
| −2.60 (−3.87, −1.27) | 3.14 (2.02, 4.24) | −4.16 (−5.30, −2.93) | **LLTL** | 0.05 (−2.60, 2.77) | 2.12 (−2.47, 6.69) | | | |
| −2.65 (−5.53, 0.22) | 3.10 (0.26, 5.87) | −4.21 (−6.87, −1.54) | −0.05 (−2.77, 2.60) | **RSH** | 2.05 (−3.25, 7.32) | | | |
| −4.70 (−9.41, 0.04) | 1.02 (−3.70, 5.73) | −6.27 (−10.97, −1.45) | −2.12 (−6.69, 2.47) | −2.05 (−7.32, 3.25) | **RTH** | | | |

Notes. LHTH, live high-train high; LHTL, live high-train low; IHE, intermittent hypoxic exposure; IHT, intermittent hypoxic training; IHIT, intermittent hypoxia interval training; RSH, repeated sprint training in hypoxia; RTH, resistance training in hypoxia; LLTL, live low-train low; LLNT, live low-no train.

paradigms (LHTH, LHTL, IHE, IHT, IHIT, RSH) were included in the analysis (Table 2 & Appendix 9).[6,44–46,65–70,72–76,80,82–85,88–90,93,95–97,100] The pairwise meta-analyses revealed a significant difference in the direct comparisons of LHTL vs. LLTL (SMD = 0.71, 95% CI [0.04, 1.39], $I^2 = 73.9\%$), IHT vs. LLTL (SMD = 0.43, 95% CI [0.14, 0.73], $I^2 = 0.0\%$), and RSH vs. LLTL (SMD = 0.76, 95% CI [0.29, 1.23], $I^2 = 13.7\%$) (Appendix 9). Sensitivity analysis was conducted in the comparison of LLTL and RSH where high heterogeneity existed (Appendix 9); the $I^2$ decreased from 76.00% to 13.70% after removing Faiss et al., 2013.[69] A significant difference in improving $VO_{2max}$ was also found in the indirect comparison of LHTH vs. LLTL (SMD = 2.44, 95% CI [0.94, 3.65]), LHTL vs. LLTL (SMD = 2.90, 95% CI [1.59, 4.07]), IHT vs. LLTL (SMD = 2.26, 95% CI [0.91, 3.53]), and LHTL vs. RSH (SMD = 1.90, 95% CI [0.22, 3.53]). The ranking of hypoxic training paradigms based on cumulative probability plots (Fig. 2) was as follows: IHIT, LHTL, LHTH, IHT, RSH, and IHE (from the best to the worst). No significant inconsistency was found between direct and indirect comparisons.

For the non-athlete subgroup, there were 14 studies including four hypoxic training paradigms (IHE, IHT, RSH, RTH) in the analysis (Table 2 & Appendix 9).[47,71,77–79,81,86,87,91,92,94,98,99,101] Pairwise meta-analysis revealed significant differences in the direct comparisons of IHE vs. LLNT (SMD = 0.82, 95% CI [0.19, 1.45], $I^2 = 65.2\%$), IHT vs. LLNT (SMD = 3.02, 95% CI [1.63, 4.40], $I^2 = 75\%$), RSH vs. LLNT (SMD = 0.54, 95% CI [0.03, 1.04], $I^2 = 0\%$), IHE vs. LLTL (SMD = −1.19, 95% CI [−1.99, −0.40], $I^2 = 70.8\%$), IHT vs. LLTL (SMD = 0.94, 95% CI [0.44, 1.44], $I^2 = 73.1\%$), and IHT vs. IHE (SMD = 3.09, 95% CI [2.05, 4.13], $I^2 = 68.1\%$). Sensitivity analyses were conducted in the comparison of LLNT and IHT (Appendix 9); the $I^2$ decreased from 81.80% to 75.00% after removing Chen et al., 2018.[92] and Lin et al., 2021.[99] Network meta-analysis revealed significant differences in the indirect comparisons of IHE vs. LLTL (SMD = −2.60, 95% CI [−3.87, −1.27]), IHT vs. LLTL (SMD = 3.14, 95% CI [2.02, 4.24]), IHE vs. IHT (SMD = −5.75, 95% CI [−6.98, −4.42]), and IHT vs. RSH (SMD = 3.10, 95% CI [0.26, 5.87]). IHT became the most promising hypoxic training paradigm, followed by RTH, RSH, and IHE (Fig. 2). There was no evidence of significant inconsistency.

### 3.5. Network meta-regression analysis

Due to the limited number of studies, the meta-regression analyses were simply conducted in the comparison of IHT and LLTL, with 431 participants from 18 studies (Table 3).[44–47,71,73,78–81,87,89,91–93,96,98,99] The covariates like participants' age ($p = 0.128$; 95% CI, −0.0607, 0.0076), sex ratio ($p = 0.145$; 95% CI, −0.2477, 1.6874), BMI ($p = 0.454$; 95% CI, −0.2430, 0.1086), hypoxic mechanism ($p = 0.068$; 95% CI, −0.0531, 1.4667), kilometre hours ($p = 0.261$; 95% CI, −0.0214, 0.0789), hypoxic load ($SpO_2$, $p = 0.060$; 95% CI, −0.1639, 0.0035), and hypoxic load (avg %HRmax/$SpO_2$% × time in minutes, $p = 0.431$; 95% CI, −0.0015, 0.0035) were not significant in explaining variations in $VO_{2max}$. Only saturation hours ($p = 0.038$; 95% CI, 0.0002, 0.0085; coefficient = 0.004) accounted for variation in $VO_{2max}$ in the univariate network meta-regression model.

## 4. Discussion

The present systematic review and network meta-analysis investigated the most prevalent hypoxic training paradigms for improving $VO_{2max}$ as well as the corresponding moderating factors. There were three important findings. Firstly, in the overall population, the seven hypoxic training paradigms (LHTH, LHTL, IHE, IHT, IHIT, RSH, RTH) mentioned in this study were all beneficial to $VO_{2max}$ improvement to varying degrees (SMDs: 1.45–7.10 [in comparison with LLNT]), with IHIT ranking best. Secondly, the ranking of efficient hypoxic training paradigms differentiated between athletes and non-athletes. The athletes were more likely to gain from IHIT, whereas the non-athletes responded better to IHT. Thirdly, the saturation hours positively predicted the $VO_{2max}$ improvement induced by IHT.

As revealed by network meta-analysis of 42 included studies, performing the hypoxic training approaches used in this study led to varying gains in $VO_{2max}$ in comparison with LLNT, with effect sizes ranging from 1.45 to 6.94. The present study included a total of seven hypoxic training approaches from the historical perspectives, which could be generally divided into three categories[5]: 1) LHTH, enhancing RBC count, haemoglobin (Hb) concentration, and haematocrit at the loss of absolute exercise intensity; 2) LHTL, combining the benefits of hypoxic acclimation (i.e., elevated RBC count and Hb concentration) and sea-level exercise (i.e., constant exercise intensity); and 3) LLTH (i.e., IHE, IHT, IHIT, RSH, RTH), increasing serum erythropoietin (EPO), RBC count, and muscle fibre structure and function.[5,25] The various hypoxic training paradigms, consisting of different exercise and hypoxic protocols, influenced the cardiorespiratory system via diverse mechanisms as above and thus resulted in distinct $VO_{2max}$ improvement. Moreover, it is important to note that the intervention effects of IHE were significantly inferior to those of LLTL (active control). IHE worked on cardiorespiratory function improvement by providing alternating exposures to hypoxia and normoxia, whereas LLTL enhanced the oxygen extraction capability and transport efficiency by exercise.[102] It seems that the stimulation of exercise exhibited greater promotion of cardiorespiratory fitness in comparison to pure hypoxic stimulation.

Based on the outcomes of subgroup analysis, IHIT was regarded as the most promising hypoxic training paradigm to ameliorate athletes' $VO_{2max}$, with the highest probability of 44% to rank best. IHIT, "IHE during interval training", was a combination of traditional hypoxic training paradigms (IHIT = IHT + IHE), which altered the hypoxic and normoxic periods during interval exercise.[103] Short-term IHE during interval training has been suggested to further foster EPO secretion and lower the heart rate.[104,105] Besides, compared with some LLTH approaches (IHT, RSH, and IHE), the athletes favoured the hypoxic training paradigms of living at high altitude (LHTL and LHTH). Additionally, the LHTL paradigm seems to be superior to LHTH in athletes' $VO_{2max}$ improvement according to ranking probabilities, even though the relative effect size was insignificant (LHTL vs. LHTH: SMD = 0.45, 95% CI [−0.93, 2.01]). This was partly consistent with previous pairwise meta-analysed effects of LHTH and LHTL on $VO_{2max}$ among sub-elite athletes, but not elite athletes.[106] Due to the limited number of studies including elite athletes, the present study did not conduct further analysis to explore the influences of athlete level, which remains to be solved in future network meta-analysis with a larger sample size.

In the non-athlete population, IHT had the highest probability (67%) of being the most efficient hypoxic training paradigm in the improvement of $VO_{2max}$. During IHT, the stresses from hypoxic exposure and exercise training worked together on the promotion of aerobic capacity and generated greater improvement in $VO_{2max}$ performance.[107] The increase in $VO_{2max}$ after IHT was caused by not only haematological adaptive mechanisms but also systemic and muscular adaptations (i.e., elevated musculoskeletal mitochondrial density, capillary-to-fibre ratio, and fibre cross-sectional area).[80,108–110] According to the network meta-analysis outcomes, both RSH and RTH showed more advantages in $VO_{2max}$ enhancement than LLNT (RSH: SMD = 4.21, 95% CI [1.54, 6.87]; RTH: SMD = 6.27, 95% CI [1.45, 10.97]), but not more than LLTL (RSH: SMD = 0.05, 95% CI [−2.60, 2.77]; RTH: SMD = 2.12, 95% CI [−2.47, 6.69]). It seems that the combination of hypoxia and repeated sprint training/resistance training did not bring extra benefits in significant $VO_{2max}$ improvement compared with pure exercise training.

To generate expected beneficial physiological responses, quantifying hypoxic dose and load has been regarded as one of the key issues in the application of hypoxic training. The "kilometre hours" model was first introduced to define hypoxic dose in the combination of altitude elevation and exposure duration.[31] Then, the "saturation hours" metric was proposed to take stimulus magnitude into consideration and defined hypoxic dose as the product of saturation value and sustained hours.[32] However, these metrics still remain and suppose the stage of theory assumption, let alone their practicability and priority to predict $VO_{2max}$ enhancement elicited by hypoxic training. The present study took both the "kilometre hours" and "saturation hours" into consideration when conducting the multivariate regression analysis. It is shown that the saturation hours, rather than kilometre hours, positively moderated the relationship between $VO_{2max}$ improvement and IHT. Based on the coefficient of 0.004, it indicates that one unit increase in saturation hour

**Table 3**
Outcome of meta-regression analysis.

| | Covariate | Coefficient | Standard Error | *P*-value | 95% confidence interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower Limit | Upper Limit |
| 1 | Participant's Age | −0.027 | 0.017 | 0.128 | −0.0607 | 0.0076 |
| 2 | Gender Ratio | 0.720 | 0.494 | 0.145 | −0.2477 | 1.6874 |
| 3 | Body Mass Index | −0.067 | 0.090 | 0.454 | −0.2430 | 0.1086 |
| 4 | Participant Type (athlete: 0; non-athlete:1) | 0.488 | 0.329 | 0.138 | −0.1565 | 1.1333 |
| 5 | Hypoxic Mechanism (hypobaric hypoxia: 0; normobaric hypoxia:1) | 0.707 | 0.388 | 0.068 | −0.0531 | 1.4667 |
| 6 | Kilometre Hours (km·h = [m/1000] *h) | 0.029 | 0.026 | 0.261 | −0.0214 | 0.0789 |
| 7 | Saturation Hours (%·h = [98/s - 1] *h * 100) | 0.004 | 0.002 | 0.038 | 0.0002 | 0.0085 |
| 8 | Hypoxic Load: (SpO2) | −0.080 | 0.043 | 0.060 | −0.1639 | 0.0035 |
| 9 | Hypoxic Load: (avg %HRmax/SpO2% × time in minutes) | 0.001 | 0.001 | 0.431 | −0.0015 | 0.0035 |

Notes. km, kilometre; h, hours; m, meters; s, arterial saturation value; SpO2, oxygen saturation; avg, average; HRmax, maximum heart rate.

corresponds to an $VO_{2max}$ enhancement of 0.004 units in effect size (SMD = difference in mean outcome between groups/SD of outcome among participants), when IHT was compared with LLTL (range of saturation hours: 56.82–337.50). A reason may be that the saturation hours have more advantages in handling the non-linear relationship between altitude elevation and saturation alteration and the large interpersonal variability in the physiological response, and considering the impacts of both internal and external stresses induced by hypoxic training.[32] The hypoxic load metric (hypoxic load = avg %HRmax/-$SpO_2$% × time in minutes), proposed by Wee et al.,[62] took both hypoxic and exercise stimuli into account to better describe the hypoxic load, but it failed to play a moderating role in the association between IHT and $VO_{2max}$ enhancement in the present study. A future study should further explore the indicator of exercise stimulus and the interaction between exercise and hypoxia in $VO_{2max}$ improvement.

The strengths of the present systematic review and network meta-analysis are worth mentioning. Firstly, this review included a large number of original studies (n = 42) with 1246 healthy participants to first compare the efficacy of up to seven common hypoxic training paradigms in $VO_{2max}$ improvement. Secondly, besides the network meta-analysis of all included studies, we particularly investigated the most and least promising hypoxic training paradigms for $VO_{2max}$ enhancement among targeted athlete and non-athlete populations. Thirdly, the outcomes of network meta-regression confirmed the practicability of saturation hours with respect to dose–response issues in the hypoxic training and associated scientific research.

However, there are also some limitations worthy of comment in this study. Firstly, the included studies of the current review were mostly rated low to moderate certainty of evidence due to risk of bias, inconsistency, and indirectness, which warrants readers to view the present results with caution. To minimize the adverse impacts of low evidence certainty, the set of LLNT in the current study enables more hypoxic training paradigms comparable, and the node-splitting analysis was used to test the consistency between direct and indirect evidences, with no inconsistency observed. Secondly, due to the limited number of included studies, the meta-regression analysis was conducted only for the IHT paradigm. The moderating roles of covariates in other hypoxic training paradigms need further analyses with more original research. Thirdly, the current meta-regression analysis testing the moderating role of saturation hours included studies targeting both athletes and non-athletes, and further stratified analyses for studies with athletes or non-athletes were hindered by insufficient data. It is suggested to retest the outcome of meta-regression analysis (i.e., saturation hours) for athletes/non-athletes when sufficient original studies are available. Fourthly, when calculating the effect sizes of hypoxic training in $VO_{2max}$ gains, the differences between sea-level and altitude criteria for establishing $VO_{2max}$ were not evaluated due to the lack of a unified measurement standard at altitude. The assessment method and criteria for reaching true $VO_{2max}$ at altitude await further research. Fifthly, exclusion of studies with fewer than 10 participants per group may limit our study's generalizability due to publication bias and issues of effective sample size and power in network meta-analysis. These factors may pose challenges in synthesizing all available evidence and investigating sources of between-study heterogeneity.

This systematic review and network meta-analysis indicates that the seven common hypoxic training paradigms (LHTH, LHTL, IHE, IHT, IHIT, RSH, and RTH) are effective to improve $VO_{2max}$ to varying degrees. In this regard, it remains unclear whether the combination of different hypoxic trainings would have an additive effect when compared with normoxic training. The present study simply included healthy adults; therefore, it is imperative to explore the ranking of multiple hypoxic trainings as well as the most efficient paradigm among other populations like clinical patients. In addition, the future meta-analysis targeted at athletes may elaborate on whether training status (e.g., training type and duration) influences the $VO_{2max}$ improvement resulting from hypoxic training. Furthermore, although the saturation hours were shown to be positively associated with $VO_{2max}$ improvement induced by IHT, the supposed superiority of saturation hours to predict the dose–response and efficiency of hypoxic training awaits further investigation.

## 5. Conclusion

The present study examined the effectiveness of multiple hypoxic training in $VO_{2max}$ improvement among healthy adults. The findings suggest to give priority to IHIT and IHT in terms of $VO_{2max}$ improvement in athletes and non-athletes, respectively, while other hypoxic training approaches can be used as alternatives to improve $VO_{2max}$ in particular circumstances. Additionally, our network meta-analysis results indicated a dose–response relationship between IHT and $VO_{2max}$ improvement, with saturation hours being an effective metric. The findings should be treated with caution due to potential risk of bias in at least one dimension of assessment and low to moderate certainty of evidence.

## Trial registration

This systematic review was registered in the PROSPERO international prospective register of systematic reviews (CRD42022333548).

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## Authors' contribution

ZK had full access to all of the data in the study and takes responsibility for both integrity and accuracy of the data analysis. Concept and design: ZK, QY, and JN; Data acquisition, analysis, or interpretation: ZK, QY, LZ, QS, and JN; Manuscript drafting: ZK and QY; Critical revision: ZK, LZ, RC, QS, and JN. Funding acquisition: ZK.

## Declaration of competing interest

The authors declare that there is no conflict of interest and the outcomes are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

## Conflict of interest/competing interest

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jesf.2023.09.001.

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