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META-ANALYSIS

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Effectiveness of hypoxic versus normoxic exercise on cardiovascular function in people without cardiovascular diseases: A systematic review and meta-analysis

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Abstract

Background: Exercise is a well-known strategy for the prevention and treatment of cardiovascular diseases; however, the potential additional benefits of hypoxic exercise on cardiovascular function in comparison to normoxic exercise are still unknown. This study aimed to synthesize the hypoxic exercise protocols of application and to comparatively determine the effects of hypoxic versus normoxic exercise on cardiovascular function (i.e. haemoglobin concentrations, arterial oxygen saturation %, maximal heart rate, blood pressure at rest and blood lactate levels) in people without cardiovascular diseases.

Methods: We systematically searched five databases, from inception to September 2023, and selected randomized controlled trials (RCTs) comparing the effects of chronic hypoxic exercise versus normoxic exercise on cardiovascular function in people without cardiovascular diseases. A random effects meta-analysis with

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both the Dersimonian-Laird and the Hartung-Knapp-Sidik-Jonkman methods was conducted to estimate the pooled standardized mean differences (SMDs) and their 95% confidence intervals (95% CIs) of the hypoxic exercise effectiveness on each of the included outcomes related to cardiovascular function. We performed meta-regression models—considering total sample size, age, BMI, length of intervention and FiO_2 percentages—to determine their influence on the estimated effect. Subgroup analyses based on age, gender, type of exercise and health status of participants were conducted.

Results: A total of 31 RCTs involving 910 individuals were included. None of the pooled SMDs comparing hypoxic versus normoxic exercise were statistically significant. Subgroup analyses were only significant for lactate in people under 30 years of age and healthy and/or athletic individuals (.59; 95% CI .11, 1.06).

Conclusions: Our data suggest that there were no additive benefits of performing hypoxic exercise on the cardiovascular function parameters explored for up to 7 weeks when compared to normoxic exercise in people without cardiovascular disease, except for a moderate increase in blood lactate levels in young healthy and/or athletic individuals.

KEYWORDS

cardiovascular, exercise, hypoxia, normoxic, physical activity

1 | BACKGROUND

Regular physical activity (PA) is widely established as a cornerstone in the prevention of cardiovascular disease (CVD)[1] and CVD-related mortality.[2] An increase in PA levels is noted among the first-line strategies to reduce CVD risk and burden,[3] conferring additional benefits such as reduced all-cause mortality.[4] Indeed, the World Health Organization has strongly recommended regular PA for all adults, highlighting further benefits on CVD risk[5] in a dose-dependent manner,[6,7] such as those reported in endothelial function, blood lipid profile, inflammatory processes, and thrombosis.[8]

Hypoxic exposure and hypoxic exercise have emerged as novel preventive and therapeutic approaches to reduce CVD risk.[9] Hypoxic exposure or intermittent hypoxia refers to the periodic and alternating cycles of hypoxia and normoxia, a phenomenon that induces significant and transitory reduction of arterial oxygen saturation (SaO_2) during both resting and exercise conditions.[10] Both modalities can stimulate specific biological signal cascades that promote physiological adaptations[11] and acute responses on human metabolism (i.e. appetite suppression, increased metabolic rate and serotonin level, decreased leptin levels) which in turn affect the cardiovascular system (e.g. increased resting and maximal heart rate [HRmax], increased peripheral vasodilatation, normalized blood pressure [BP]).[12] Moreover, hypoxic exercise could provide additional benefits on skeletal muscle capillarization and vascular dilator function, thus improving vascular health,[13] and being helpful for people with CVDs or at risk.[14,15] The physiological mechanisms underlying these benefits are related to the hypoxia-inducible factors (HIFs) pathway.

The HIFs (i.e. HIF-1 and HIF-2) are key transcription factors that control the hypoxia-induced genes, which regulate the cellular response to reduced levels of oxygen.[16] Specifically, HIF-1, which includes the subunits HIF-1 alpha and HIF-1 beta, is involved in the cascade of adaptations to hypoxic exercise able to exert positive effects on angiogenesis,[17,18] and resting BP.[19] During intermittent hypoxia, HIF-1 is responsible for cardiac protection and for the coordinated induction of multiple angiogenic factors related to the vascular response.[20] Importantly, when physical exercise is performed under hypoxic conditions, an increase in blood flow to the involved muscles is produced, aiming to compensate for the reduced arterial O_2 content and to maintain relatively constant O_2 delivery to the active muscle (i.e. 'compensatory vasodilatation')[21]; this phenomenon implies a subsequent reduction in BP that may be larger than that produced by exercise alone. Furthermore, hypoxic exercise could induce specific muscular adaptations including an increased (i) oxidative enzyme activity, (ii) mitochondrial density, (iii) capillary-to-fibre ratio and (iv) fibre cross-sectional area,[22] all of which are modulated via the HIF-1 alpha signalling cascade, which is not activated to the same extent in normoxic training or by passive hypoxic exposure.[15] Additionally, hypoxic conditions exacerbate the intensity of the exercise which in turn induces a peak peripheral lactate during and post-exercise that may confer several benefits on mitochondrial biogenesis in skeletal muscle,[23,24] and initiates a signalling cascade that leads to increased expression of vascular endothelial growth factor A, a protein that promotes cerebral angiogenesis.[25] Furthermore, lactate has been related to enhanced cardiac function, with increased left ventricular ejection.[26]

In this context, a systematic review concluded that chronic exposure to intermittent hypoxia—hyperoxia seems to be a promising non-pharmacological strategy not only to enhance physical performance but also to reduce blood glucose levels and BP in older patients with metabolic, CVD or cognitive impairment.[11] However, despite the promising benefits of hypoxic exercise on increasing lipid metabolism in the short term or vascular health and autonomic balance,[27] it is still relatively unknown whether hypoxic exercise may confer additional benefits compared to normoxic exercise on cardiovascular function. Moreover, controversial findings have been reported in some trials so far.[28–32]

Thus, a systematic review to synthesize and a meta-analysis to determine the effects of prolonged hypoxic exercise (>3 weeks) compared to normoxic exercise on cardiovascular function seem to be necessary to draw a solid conclusion and to help clinicians in decision-making when considering hypoxic exercise as a preventive or therapeutic intervention for cardiovascular health. Therefore, the aim of the present review was twofold: (i) to synthesize the current protocols of application, and (ii) to comparatively determine the effects of hypoxic versus normoxic exercise on cardiovascular function measures (Haemoglobin [Hb] concentrations, SaO2%, HRmax, BP at rest and blood lactate levels) in the adult population.

2 | METHODS

The Cochrane Collaboration Handbook[33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[34] guided the present study. The protocol was registered in the PROSPERO database (CRD42022342165).

2.1 | Data sources and searches

Two reviewers (RF-R and SR-G) independently searched the MEDLINE (via PubMed), Cochrane Library, Embase (via Scopus), Web of Science (WoS) and SportDiscus (via EBSCOhost) databases, from inception to September 2023. Databases were reviewed to identify randomized clinical trials (RCTs) aimed at determining the effectiveness of hypoxic exercise on cardiovascular function in adults. No language restrictions were applied. The Mendeley desktop find and merge duplicates tool was used to search for duplicates, and a third reviewer peer-reviewed the search process (VM-V). Further details of the search strategy employed for each database are available in Table S1.

2.2 | Study selection

The search criteria according to the PICOs strategy were as follows: (i) Participants: adults (18 y and older); (ii) Intervention: hypoxic exercise; (iii) Comparison: normoxic exercise; (iv) Outcomes/results: parameters of cardiovascular function such as Hb concentrations, SaO_2%, HRmax, BP at rest and maximal blood lactate levels; and (v) Study design: RCTs. The exclusion criteria were as follows: studies that combined hypoxic exercise with other interventions such as heat combined with hypoxic training vs. room temperature combined with normoxic exercise or training combined with sleeping at altitude. We also excluded those studies assessing the acute effect of a single hypoxic training session. The inter-rater agreement between authors for the independent study selection process had a kappa coefficient of −.04 ($p = .71$).

2.3 | Data extraction

Two authors (RF-R and AT-C) independently extracted the following information from each study included: (1) first author name and publication year; (2) country; (3) sample characteristics (i.e. sample size, percentage of females, health status or PA level, mean for age, and body mass index (BMI)); (4) intervention characteristics (i.e. hypoxic training regime, length, and frequency of the intervention); and (5) outcomes: parameters of cardiovascular function. Pre-post intervention data at rest or after a maximal exercise test were extracted for all included studies. In some of them,[35–38] data were obtained from graphs by reading them after adapting scales on the value axes using the Microsoft PowerPoint software. The inter-rater agreement between authors had a kappa coefficient of −.05 ($p = .79$). A third researcher (SR-G) independently appraised the accuracy of the extracted information.

2.4 | Risk of bias assessment and GRADE report

Two researchers (RF-R and AT-C) independently assessed the risk of bias of the included studies using the

Cochrane Collaboration's tool for assessing risk of bias (RoB2).[39] Any disagreement was resolved by consensus or by discussion with a third reviewer (VM-V). The RoB2 tool evaluates the risk of bias according to five domains: (i) randomization process, (ii) deviations from intended interventions, (iii) missing outcome data, (iv) measurement of the outcome and (v) selection of the reported result. Overall bias was scored as (i) 'low risk of bias' if the study was classified as 'low risk' in all domains, (ii) 'some concerns' if at least one domain was scored as 'some concerns' and (iii) 'high risk' if there was at least one domain rated as 'high risk' or several domains as 'some concerns' that affect the validity of the results.

The 'Grades of Recommendations, Assessment, Development, and Evaluation' (GRADE) tool was used to determine the certainty of the evidence of the present systematic review.[40] Each outcome was rated as having high-, moderate, low- or very low-quality evidence based on the design of the studies, risk of bias, inconsistency, indirect evidence, imprecision and publication bias. Accordingly, the score was downgraded one when serious risk of bias, as well as when inconsistency ($I^2 > 50\%$), indirect evidence, imprecision (wide confidence intervals) and publication bias were reported.

2.5 | Data synthesis

Random effect models were used to estimate the pooled standardized mean differences (SMDs) and their 95% confidence intervals (95% CIs) of the effectiveness of hypoxic exercise on each of the included outcomes related to cardiovascular function (i.e. $SaO_2\%$, Hb concentrations, HRmax, BP at rest and maximal blood lactate levels).[41] We only conducted a meta-analysis when at least five studies reported the estimated effect for the same outcome.[42] When outcomes were assessed at resting or through a maximal test, both measurements were registered considering their clinical interest; however, we only analysed data at resting or after a maximal test when studies reported the outcome mostly in this way; concretely, it occurred with BP that was mostly reported at resting, or blood lactate levels that were mostly reported after a maximal test. We only analysed the effect of hypoxic intervention versus the same training regime under normoxia, but not versus the control condition (e.g. non-exercise, waitlist).

According to the Cochrane Handbook recommendations, we extracted the pre-post mean, standard deviation (SD) and sample size of each arm trial. For those studies that did not report these data, we collected the mean difference and SE or SD of the change. For RCTs with a crossover design, we followed the conservative approach proposed by the Cochrane Handbook; thus, we took all measurements from intervention and control periods and analysed them as if the study's design had been a parallel-group trial. When studies applied more than one test for reporting an outcome, a combined estimate of them was calculated. Moreover, when studies were inversely scaled (i.e. lower values indicating worse outcomes), the mean in each group was multiplied by −1.

Statistical heterogeneity between studies was examined using the I^2 statistic. I^2 values of 0%–40% were assumed to indicate 'not important' heterogeneity, 30%–60% represented 'moderate' heterogeneity, 50%–90% represented 'substantial' heterogeneity and 75%–100% represented 'considerable' heterogeneity. We accordingly considered their corresponding p-values and 95% CIs.[43] To assess the robustness of summary estimates and to detect whether any single study accounts for a large proportion of heterogeneity, sensitivity analyses were performed, and influence graphs were generated by removing the included studies one by one from the analyses. Likewise, other subgroup analyses were conducted (i.e. by age [<30 y vs. ≥30 y], gender [males vs. mixed gender or females], health status [healthy and/or athletes vs. individuals with comorbidities and/or sedentariness] and exercise modality) when data were available. In the case of few studies for the subgroups, a sensitivity analysis was conducted to determine whether these variables showed an influence on our estimates. Meta-regression models—considering total sample size, age, BMI, length of the intervention and FiO_2 percentages—were conducted to determine their influence on the estimated effect. As suggested during the peer-review process, random-effects models were estimated with robust variance estimation using the Hartung-Knapp-Sidik-Jonkman, which provide more robust variance estimates in the meta-analyses and the meta-regression models.[44–46] Finally, we evaluated publication bias through visual inspection of funnel plots and Egger's regression asymmetry test to assess small study effects.[47] All statistical analyses were performed using StataSE v. 15 (StataCorp, College Station, TX, USA).

3 | RESULTS

3.1 | Literature search

A total of 8452 studies were identified through the systematic searches, of which 4113 duplicated records were removed (Figure 1). Finally, after the full-text review of the 91 studies assessed for eligibility, 31 studies were included in the systematic review and 29 provided data for

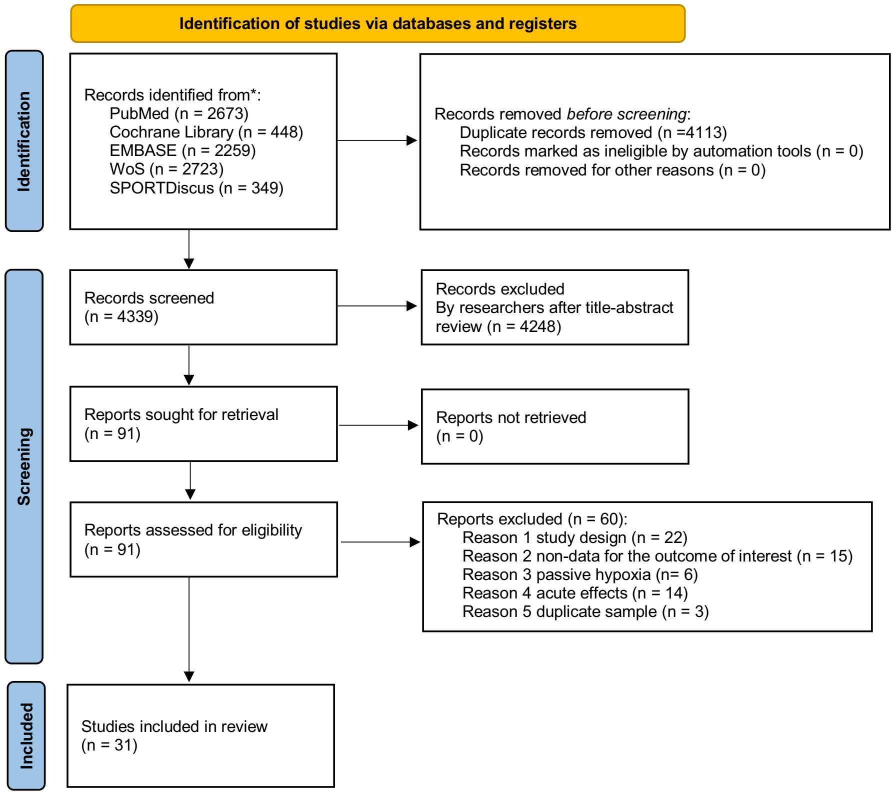

FIGURE 1 Flow diagram of studies through the review (PRISMA 2020).

the meta-analysis.[32,35–38,48–71] The reasons for exclusion after the full-text reading are available in Table S2.

3.2 | Study characteristics

The main characteristics of the included studies are available in Table 1. All of them were RCTs—two presenting a crossover design[38,58] —and were published between 2000 and 2023. The country of origin of the studies was heterogeneous: (i) seven were conducted in Germany,[32,49,51,53,56,57,59] (ii) three in Poland,[35,64,65] in Spain[38,52,69] and in Taiwan,[61,62,71] (iii) two in Australia,[54,67] France,[66,70] and the UK,[37,50] and (iv) one each in Brazil,[72] Thailand,[48] Korea,[55] Wales,[68] Netherlands,[60] Slovenia[36] and China.[63] The total number of participants included among the studies ranged from 12 to 73. A total of 910 participants were considered for the final analysis, of which 209 were sedentary and 156 were athletes or well/moderately trained participants (although the PA level was not usually reported); the remaining participants were categorized as obesity/overweight status ($n = 359$) according to their BMI ($\geq 25\,kg/m^2$). There was a fraction of participants who presented comorbidities at baseline such as type 1 diabetes (1.9%),[64] metabolic syndrome (2.8%),[56] sleep apnoea syndrome (3.2%)[52] and COVID-19 convalescents[72]; otherwise, they were categorized as 'healthy' Most studies were conducted only in males, except for 11 studies that included both males and females[32,49,51,53,54,57,59,60,67,70] and two that included only females[55,69]; another did not report gender.[72] The age range for the included participants was between 18.4 and 81.1 years old.

3.3 | Intervention

The hypoxic training protocols varied across the included studies, with most studies conducting hypoxic training at normobaric conditions (Table 2). The fraction of inspired oxygen (FiO_2) during training ranged from 12.0% to 17.2%, although some studies used 80%–85% of SaO_2%[59] or 3000 m above the sea[38] as hypoxic conditions. Additionally, the number of sessions per week ranged from 2 to 5 sessions/week (3 sessions/week was the most usual frequency used), the session duration ranged from 30 to 90 min (60 min was the most usual session volume), and the intervention length ranged between 2 and 32 weeks (mean: 6.7 weeks).

3.4 | Cardiovascular function parameters

Most studies assessed the effect of hypoxic training on SaO_2%,[35,37,50,61,70,72] blood lactate levels[32,38,49,50,56,63,66,68,70,72] and HR[35,37,38,48–52,56,57,59–62,64,70–72] through maximal tests. In contrast, systolic blood pressure (SBP), diastolic blood pressure (DBP)[32,51,53–56,66–70] and Hb[56,60,61,63–65] were usually assessed at rest. Other

TABLE 1 Characteristics of the included studies through the review.

Study characteristic			Population characteristics			Intervention characteristics			Outcome
Authors, Year	Country	Sample size (female's %)	Health status	Mean age (y) M ± SD or range	BMI (kg/m^2)	Length (weeks)	Frequency (times/week)	Hypoxic training regime (Modality: type of ergometer/exercise, volume of session, intensity, FiO2 or equivalent)	CVD function
Allsopp et al. 2020	Australia	20 (40%)	Healthy	64 ± .8	23.9 ± .8	8	2	Resistance training: whole body exercise/60 min/70% 1RM/14.4%	SaO2%, BP
Álvarez-Herms et al. 2016	Spain	12 (0%)	Sub-elite athletes	22 ± 4.7	NR	4	3	Resistance training: circuit strength/80–120 min/↑load intensity and altering work/rest ratio/3000 m above the sea	Hb, HRmax, lactate
Bailey et al. 2000	Wales	32 (0%)	Healthy	22 ± 3.0	NR	4	3	Cycling/20–30 min/70%–85% HRmax/16% FiO_2	BP, lactate
Camacho-Cardenosa et al. 2018	Spain	86 (100%)	OW/OB	NR	29 ± 5.2	12	3	INT and RS training groups: cycle ergometer/INT: 24–42 min; RS: 16–27 min/INT:3 min 90%-3 min 55%–65% W max; RS:3 min 130%-3 min 55%–65% W max/17.2% FiO_2	BP
Chacaroun et al. 2020	France	23 (17.4%)	OW/OB	54	31.5	8	3	Braked cycle ergometer/45 min/75% HRmax/13% FiO_2	SaO2%, HRmax, BP, lactate
Chen et al. 2018	Taiwan	30 (0%)	Sedentary	22	22.5	4	5	Cycle ergometer/30 min/50% W max/15% FiO_2	HRmax
Chinapong et al. 2021	Thailand	14 (0%)	Healthy	20 ± 1.7	NR	6	4	Resistance training: rowing/50 min/80%–90% HR anaerobic threshold/14.5% FiO_2	HRmax
Chobanyan-Jürgens et al. 2019	Germany	29 (48.3%)	Sedentary	62 ± 6.0	28.5	8	3	Cycling/30–40 min/60%–70% peak oxygen uptake/15% FiO_2	HRmax, lactate
Czuba et al. 2019	Poland	14 (0%)	Well-trained biathletes	20.7	NR	3	3	Running bouts: treadmill/60–70 min/bouts at 100% WR_{LT} hyp/WR_{LT}/16.6% FiO_2	SaO2%, HRmax
Debevec et al. 2010	Slovenia	18 (0%)	Healthy	21.1	22.9	4	5	Cycle ergometer/70 min/50% HR at hypoxic peak power/12% FiO_2	Hb, SaO2%, HRmax
Galvin et al. 2013	UK	30 (0%)	Healthy athletes	18.4 ± 1.5	NR	4	3	RS training: treadmill/10 × 6 s, 30s recovery intervals/maximum sprint/13% FiO_2	SaO2%, HRmax, lactate
Gatterer et al. 2015	Germany	32 (68.8%)	OB	51.4	37.3	32	2	Cycle ergometer, treadmill, or cross trainer 90 min/65%–75% HRmax (HR was increased by 10 beats/min when treadmill or cross trainer was used)/14% FiO_2	HRmax, BP
Ghaith et al. 2022	France	31 (25.8%)	OW/OB	51.5	32	8	3	Cycle ergometer, 2 min warm-up and 2 min cool down at 30%W max; HIIT from 16 to 32 bouts of 30–45 s (100%Wpeak) with 30s-1min of passive recovery/12% FiO_2	BP, lactate

TABLE 1 (Continued)

Study characteristic			Population characteristics			Intervention characteristics			Outcome
Authors, Year	Country	Sample size (female's %)	Health status	Mean age (y) M ± SD or range	BMI (kg/m^2)	Length (weeks)	Frequency (times/week)	Hypoxic training regime (Modality: type of ergometer/exercise, volume of session, intensity, FiO2 or equivalent)	CVD function
González-Muniesa et al. 2015	Spain	26 (0%)	OB with sleep apnoea syndrome	25–50	34.1	13	2	Aerobic+strength training: stationary bicycle+lifting 4 kg weights/60 min/NR intensity for aerobic exercise/first 2 weeks at 16% FiO_2, the rest at 13.7–14.8% FiO_2	HRmax, BP
Haufe et al. 2008	Germany	20 (0%)	Healthy	28.6	24.6	4	3	Treadmill/40 min /HR = 3 mmol L^{-1} lactate value in the F_IO_2 specific incremental test/15% FiO_2	HRmax, BP, lactate
Hein et al. 2020	Germany	29 (48%)	OW	62 ± 6	28.5 ± .5	8	3	Cycle ergometer/40 min/ first 4 weeks at 60% VO_2peak and 4 weeks at 70% VO_2 peak/15% FiO_2	BP
Hobbins et al. 2021	Australia	16 (43.8%)	OW/OB	36.6	32.5	2	4	INT: treadmill/60 min/15 × 2'walking at a RPE of 14 on the 6–20 Borg scale; rest = 2′/13% FiO_2	BP
Hollis et al. 2014	UK	18 (0%)	Highly trained	19.8	NR	8	2	Treadmill/40 min/30 m heavy intensity core phase = lactate turn point speed/16% FiO_2	SaO2%, HRmax
Jung et al. 2020	Korea	32 (100%)	OB	47.5 ± 7.5	25.8	12	3	Pilates/50 min/intensity NR/14.5% FiO_2	BP
Klug et al. 2018	Germany	23 (0%)	Metabolic syndrome	56.3	34.8	6	3	Treadmill/60 min/60%VO_2max/15% FiO_2	Hb, HRmax, BP, lactate
Peinado Costa et al. 2022	Brazil	43 (NR%)	Post-COVID-19	30–69	NR	8	3	Cycle ergometer/5 min warm-up and 3 min cool down, 3–6 sets of 5 min at 90–110% HR, 2.5 min passive recovery/ 13.5% FiO_2	SaO2%, HRmax, lactate
Pramsohler et al. 2017	Germany	40 (57.5%)	Healthy	81.1	25.5	3	NR	7 treadmill training sessions/30 min/80%VO_2peak/15.2% FiO_2	HRmax
Shi et al. 2013	Japan	14 (0%)	Healthy	27.4 ± 2.6	23.1 ± 1.0	4	3	Treadmill/50 min/60%HRmax/15.4% FiO_2	BP
Teleglów et al. 2022	Poland	14 (0%)	Elite athletes	21.8	24.2	3	3	Ergometer/60-70 min/80%–90% of the lactate threshold power/16% FiO_2	Hb
Torpel et al. 2020	Germany	73 (31.5%)	Healthy	24.3 young/68 older	23.8 young/27.3 older	5	4	Resistance training: machine based-resistance exercises/60 min training program phase/25%–40% 1RM/SaO_2 80%–85%	Hb, HRmax
Truijens et al. 2003	Netherlands	16 (62.5%)	Well-trained swimmers	28.9	NR	5	3	Anaerobic training: in a pool/10 bouts of 30s, rest 15 s, 5 bouts 1 min, rest 30s and 5 bouts 30s, rest 15 s; 2 min rest between sets/high intensity/15.3% FiO_2	Hb, HRmax

(Continues)

TABLE 1 (Continued)

Study characteristic			Population characteristics			Intervention characteristics			Outcome
Authors, Year	**Country**	**Sample size (female's %)**	**Health status**	**Mean age (y) M ± SD or range**	**BMI (kg/m^2)**	**Length (weeks)**	**Frequency (times/week)**	**Hypoxic training regime (Modality: type of ergometer/exercise, volume of session, intensity, FiO2 or equivalent)**	**CVD function**
Wang et al. 2010	Taiwan	36 (0%)	Sedentary	22.2	22.8	4	5	Cycle ergometer/30 min/1.hypoxic-relative exercise (50% HRmax reserve); 2.hypoxic-absolute exercise (50% W max)/15% FiO_2	Hb, SaO2%, HRmax
Wang et al. 2014	Taiwan	40 (0%)	Sedentary	21.7	22.3	5	5	Cycle ergometer/30 min/60%VO2max/15% FiO_2	HRmax
Wang et al. 2018	China	38 (0%)	Healthy	22.6	NR	4	2	RS training: cycle ergometer/3 sets of 5 × 10s all-out sprints/7.5% body mass loading with the highest revolutions per minute/14.5%–14.2%FiO_2	Hb, lactate
Wiesner et al. 2010	Germany	45 (60%)	OW/OB sedentary population	42 ± 7.1	30.2 ± 3.6	4	3	Treadmill/ 60 min/ 65% VO_2max/15%FiO_2	BP, lactate
Wrobel et al. 2021	Poland	16 (0%)	T1D	37	27.7	6	2	Aerobic+ resistance training: treadmill+ resistance exercise/75 min/aerobic: 10 sets of 1 min at 50%–70% HRmax; resistance:10 reps at 50% 1RM/15.4% FiO_2	Hb, HRmax

Abbreviations: BMI, body mass index; BP, blood pressure; CVD, cardiovascular; FiO2, fraction of inspired oxygen; Hb, haemoglobin; HRmax, maximal heart rate; kg, kilogram; min, minutes; NR, not reported; OB, obese; OW, overweight; INT, interval training; 1RM, one repetition maximum; RPE, rating of perceived exertion; reps, repetitions; RS, repeated-spring; s, seconds; SaO_2, arterial oxygen saturation; SIT, sprint interval training; T1D, type 1 diabetes; UK, United Kingdom; VO_2max, maximal oxygen consumption; W max, maximal work rate; WR_{LT} hyp/WR_{LT}, workload at lactate threshold determined in hypoxia and normoxia.

TABLE 2 Overview of the general variables for the application of hypoxic training interventions.

Variable	Application for the hypoxic intervention[a]
Hypoxic conditions (normobaric or hypobaric)	Most studies were conducting exercise on normobaric conditions (88.4%) with only two studies at hypobaric conditions (Álvarez-Herms et al. 2016; and Jung et. al 2020; and one study do not report the hypoxic condition [Trujiens et al. 2003]
Intensity of the hypoxia: level of hypoxemia, typically reported as fraction of inspired oxygen (FiO_2) and less frequently as oxygen saturation of the blood (SaO_2) or as training above the sea level	FiO_2: 12.2% and 17.2% (most frequently 15%)
Duration of the hypoxic session	From 20 to 120 min (most frequently 60 min/session)
Number of hypoxic sessions per week	From 2 to 5 sessions/week (most frequently 3 sessions/week)
Hypoxic intervention length	From 2 and 32 weeks (mean: 6.8 weeks)
Type of exercise and intensity in training in hypoxic interventions	Resistance, anaerobic or aerobic training (most frequently aerobic training with workloads between 50%–80% VO_2max or HRmax)

Abbreviations: FiO_2, fraction of inspired oxygen; HRmax, maximal heart rate; SaO_2, oxygen saturation; VO_2max, maximal oxygen consumption.

[a]It should be noted that the variables shown are those mainly reported for hypoxia training interventions and may serve as a reference for future studies in this field. However, at present, no specific recommendations on the most appropriate dose to improve cardiovascular risk in the adult population can be given as there is insufficient evidence to determine solid conclusions.

cardiovascular function parameters (i.e. maximal oxygen consumption, haematocrit, arterial stiffness or vascular endothelial function) were not sufficiently reported.

3.5 | Meta-analysis

There were no significant differences in the changes observed after hypoxic exercise vs. normoxic exercise in the explored cardiovascular function parameters; thus, no added benefits of hypoxic exercise. Concretely, we obtained .11 (95% CI: −.15 to .36; $I^2=0\%$; $n=9$ studies) for Hb concentrations (Figure 2), .00 (95% CI: −.27 to .27; $I^2=0\%$; $n=7$ studies) for $SaO_2\%$ (Figure 2), −.10 (95% CI: −.25 to .06; $I^2=0\%$; $n=18$ studies) for HRmax (Figure 3), −.01 (95% CI: −.21 to .20; $I^2=0\%$; $n=13$ studies) for SBP at rest (Figure 4), −.05 (95% CI: −.25 to .16; $I^2=0\%$; $n=13$ studies) for DBP at rest (Figure 4) and .27 (95% CI: −.01 to .54; $I^2=27\%$; $n=9$ studies) for maximal blood lactate levels (Figure 5). Robust variance estimation for random effects meta-analyses did not show any differences compared to our original estimates: .11 (95% CI: −.13 to .34; $I^2=0\%$; $n=9$ studies) for Hb concentrations, .00 (95% CI: −.29 to .29; $I^2=0\%$; $n=7$ studies) for SaO2%, −.10 (95% CI: −.22 to .02; $I^2=0\%$; $n=18$ studies) for HRmax, −.01 (95% CI: −.18 to .17; $I^2=0\%$; $n=13$ studies) for SBP at rest, −.05 (95% CI: −.27 to .18; $I^2=0\%$; $n=13$ studies) for DBP at rest and .27 (95% CI: −.06 to .34; $I^2=27\%$; $n=9$ studies) for maximal blood lactate levels.

3.6 | Subgroup and sensitivity analyses, meta-regression models, and publication bias

The subgroup analyses performed according to age, gender, health status, and exercise modality are available in Table 3. There was a significant difference in blood lactate levels when comparing hypoxic vs. normoxic exercise in people under 30 y old and healthy/athlete individuals (.59; 95% CI .11, 1.06) in favour of hypoxic exercise.

The sensitivity analyses indicated that, in general, there was no change in the direction or significance of the overall effect of hypoxic training on the analysed outcomes when any of the included studies were omitted or when only considering those applying hypoxia at normobaric

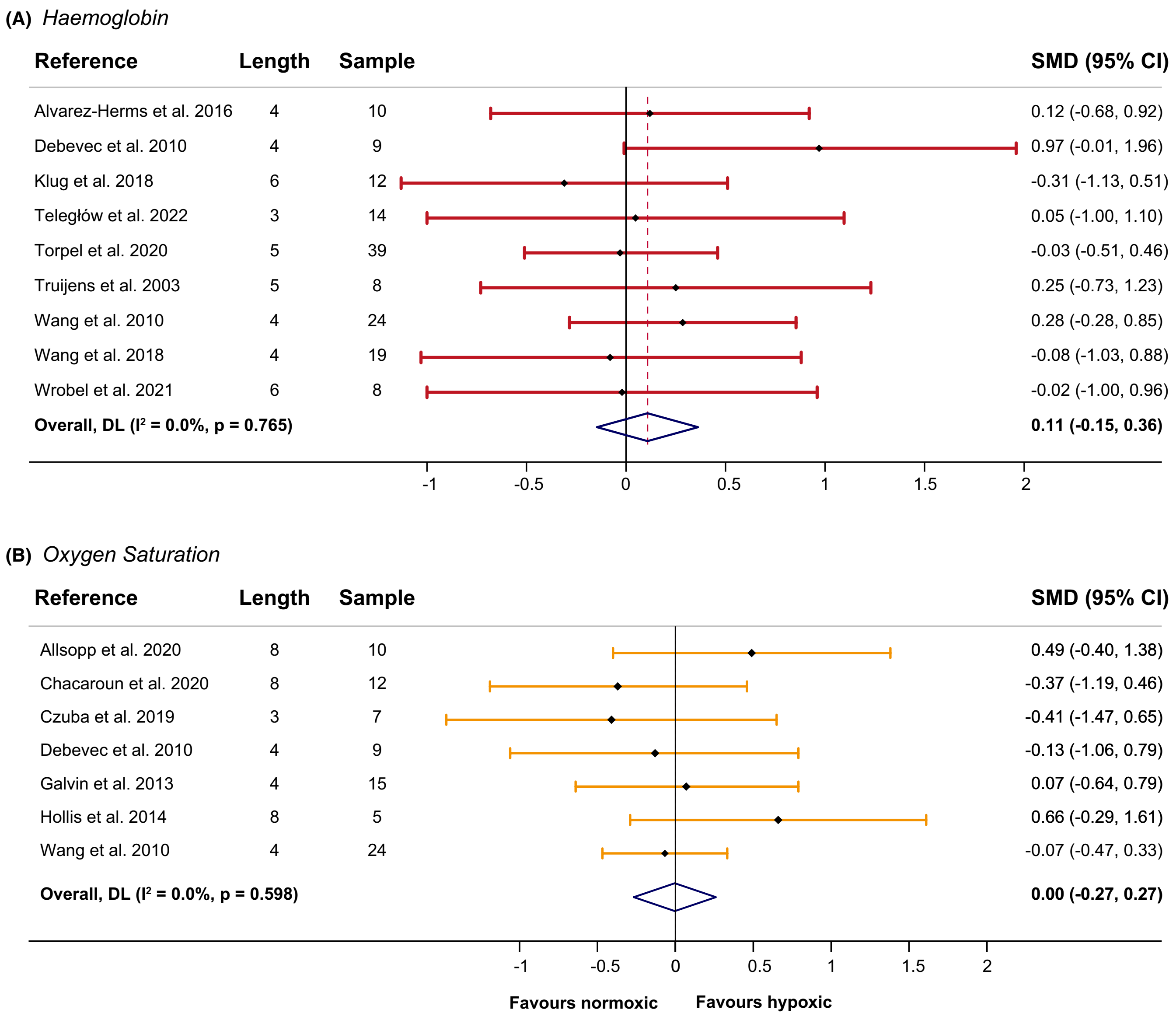

FIGURE 2 Meta-analysis of the standardized mean difference for the effect of hypoxic exercise versus normoxic exercise on haemoglobin and oxygen saturation. SMDs: Pooled standardized mean differences through a random effects model and their 95% confidence intervals (95% CIs).

conditions. The global effect estimator of hypoxic exercise also remained nonsignificant on blood lactate levels when any of the included studies were removed, except for those published by Chobanyan-Jürgens et al.,[49] Klug et al.[56] and Wang et al. 2018[63] (Table S3). Meta-regression models revealed no significant role of age, body mass index, length of intervention (weeks), total sample size and different hypoxic exposure levels on the effects of hypoxic training on the cardiovascular function parameters analysed (Table S4A). Meta-regression models with robust variance estimation showed statistically significant differences on Hb for age (coef: −.02; $p = .05$), BMI (coef: −.06; $p = .03$) and FiO_2 percentages (coef: −.23; $p = .02$); on DBP for age (coef: .02; $p = .04$), and on blood lactate levels for weight (coef: −.02; $p = .03$) (Table S4B). Finally, publication bias was detected in HRmax ($p > .05$) (Table S5 and Figure S1).

3.7 | Risk of bias assessment and GRADE report

The overall risk of bias assessment showed that 19 out of 31 studies (61.3%) presented some concerns, and 12 out of 31 (38.7%) were classified as low risk. Further details according to the score of each item for the risk of bias are available in Figure S2.

The overall certainty of evidence was set as 'low or very low' with not importance, mainly due to serious indirectness and imprecision. Further details related to the

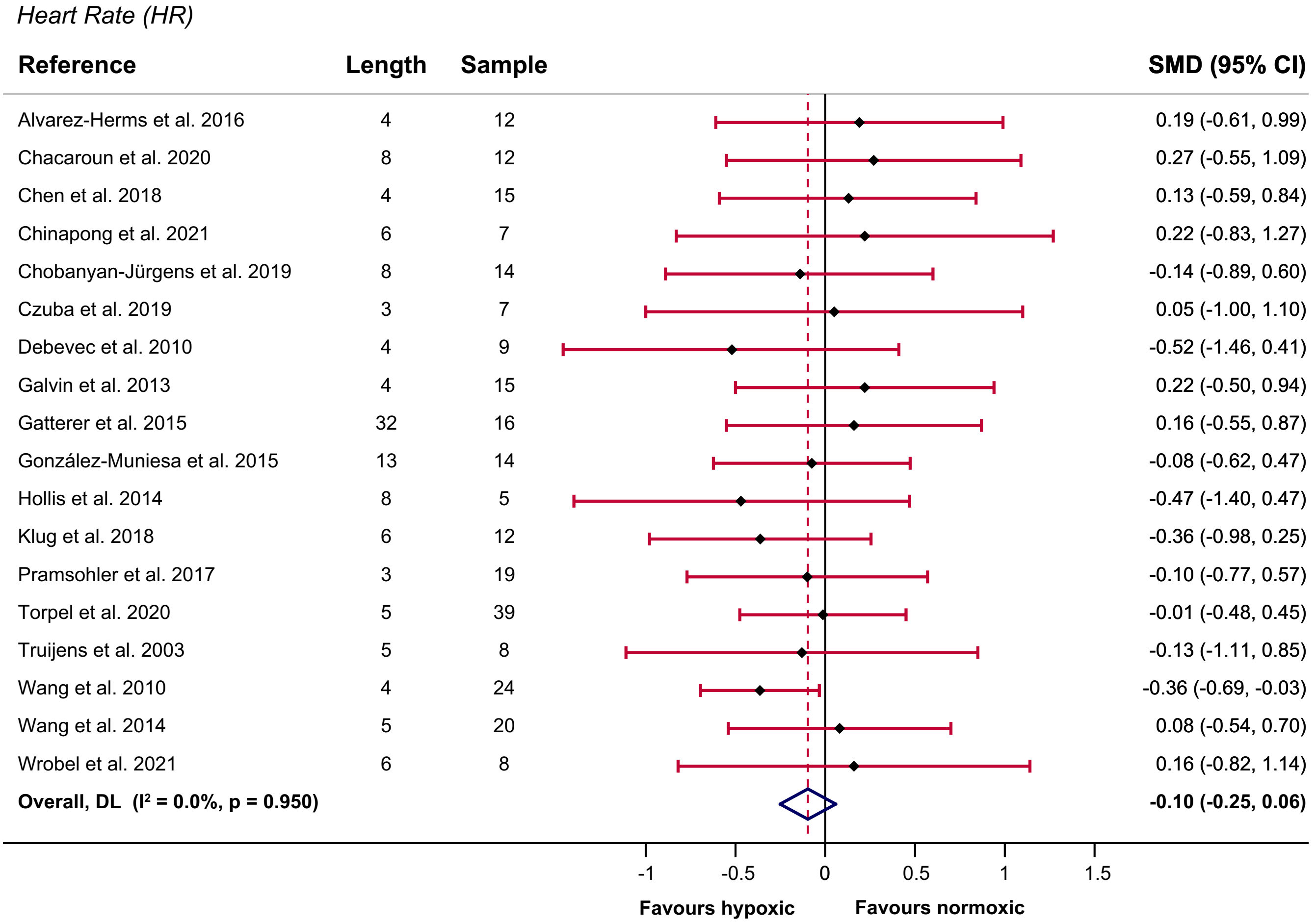

FIGURE 3 Meta-analysis of the standardized mean difference for the effect of hypoxic exercise versus normoxic exercise on heart rate. SMDs: Pooled standardized mean differences through a random-effects model and their 95% confidence intervals (95% CIs).

summary of findings are available in the Table S6. No relevant change was observed in the sensitivity analyses.

4 | DISCUSSION

This review was aimed at synthesizing and determining the effects of chronic hypoxic exercise versus normoxic exercise on some cardiovascular functions in people without cardiovascular disease. Our data suggest that hypoxic exercise does not confer additional benefits on cardiovascular function parameters (i.e. Hb concentrations at rest, SaO_2%, HRmax, BP at rest and maximal blood lactate levels) when compared to normoxic exercise in people without cardiovascular disease. Subgroup analyses considering age and health status showed a significant increase in maximal blood lactate levels in young healthy individuals and/or athletes under 30 years compared to adults ≥30 years with comorbidities and/or sedentariness. Our results were consistent and persisted when exploring potential confounding variables such as gender, BMI or length of the intervention. According to our systematic review, the most prescribed protocol of hypoxic training was based on the following characteristics: (i) FiO_2: 15%, (ii) time and frequency: 60 min and 3 sessions per week, (iii) length: 6 weeks.

Our findings indicated that hypoxic exercise does not lead to higher benefits on the explored cardiovascular function parameters when compared to normoxic exercise in people without cardiovascular disease. These findings do not concur with the results from a previous review which reported significant improvements in skeletal muscle capillarization and vasodilation function after hypoxic exercise.[13] Although our review is focused on different cardiovascular parameters, the study by Montero et al. had a smaller sample size (n = 331 individuals from 21 controlled studies) and included nonrandomized trials—factors that could increase the heterogeneity—, which could explain the discrepancy with the present results (n = 910 individuals from 31 RCTs). Further, as previously reported in a meta-analysis,[73] the cardiovascular adaptation and benefits may be significantly influenced by the length of the hypoxic exercise intervention, with arterial stiffness only improving in long-term interventions (i.e. ≥12 weeks). A comparison of the main methodological differences between our

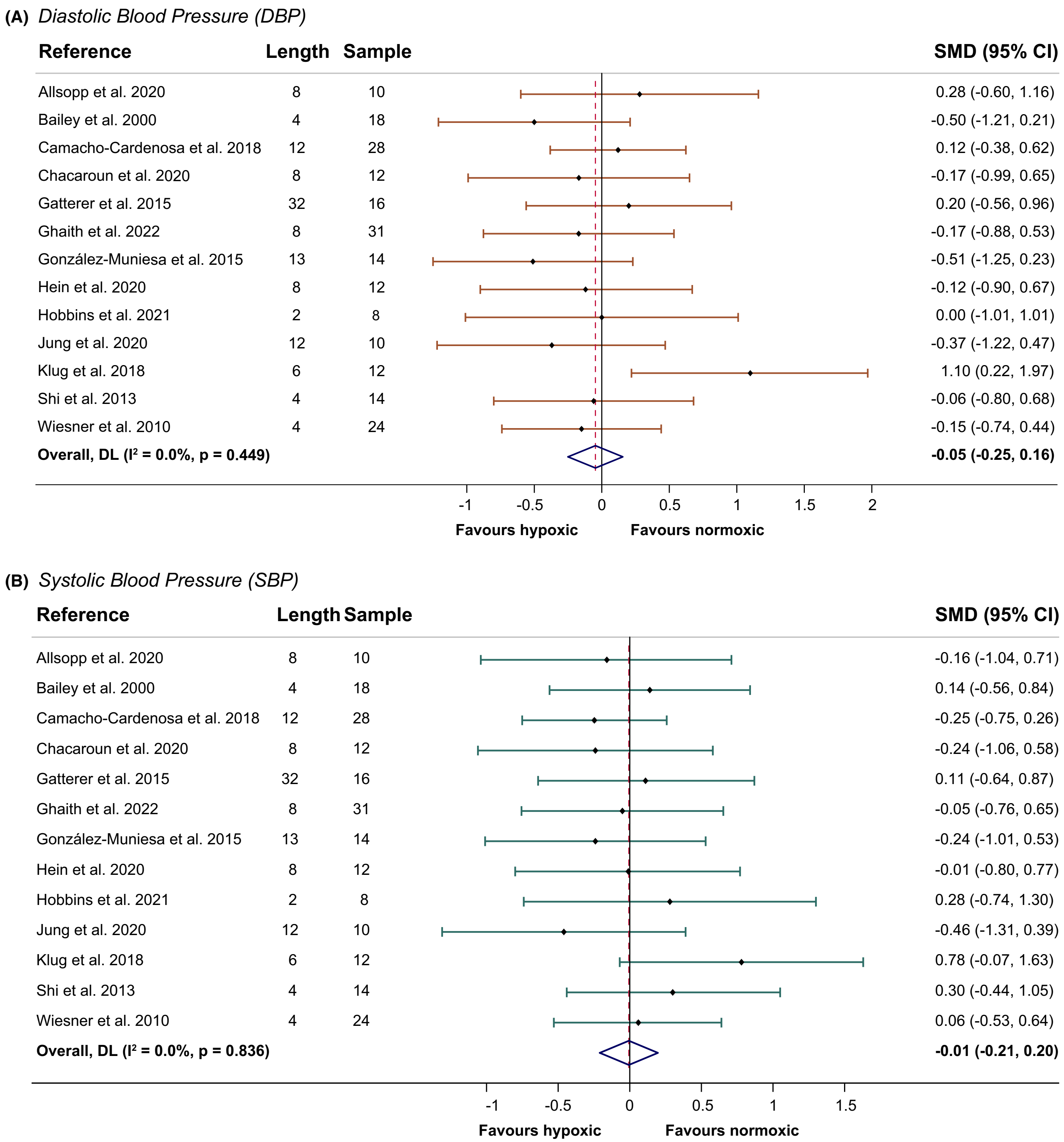

FIGURE 4 Meta-analysis of the standardized mean difference for the effect of hypoxic exercise versus normoxic exercise on systolic and diastolic blood pressure. SMDs: Pooled standardized mean differences through a random effects model and their 95% confidence intervals (95% CIs).

meta-analysis and those completed previously is shown in Table S7. Briefly, our meta-analysis included only individuals without cardiovascular disease, whereas Montero et al.[73] recruited prehypertensive individuals and considered longer duration of the interventions (13.5 weeks). Furthermore, Montero and Lundby et al. 2016 included similar population and intervention characteristics, but they were focused on skeletal muscle capillarization and vascular dilator function, showing statistically significant differences after hypoxic exercise that should be considered.[13] The average length of our included studies was 6.7 weeks, with only 4 out 31 studies with a duration of ≥12 weeks,[51,52,55,69] precisely those which showed some significant improvements on DBP, flow-mediated dilatation,

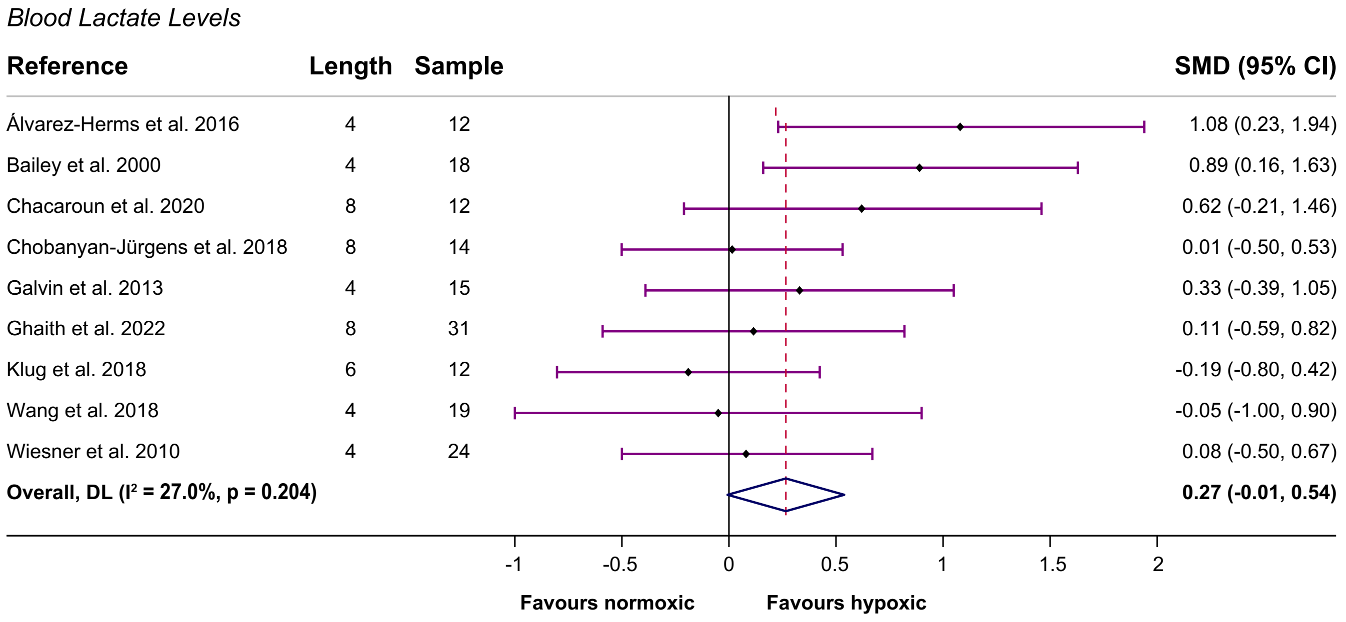

FIGURE 5 Meta-analysis of the standardized mean difference for the effect of hypoxic exercise versus normoxic exercise on blood lactate levels. SMDs: Pooled standardized mean differences through a random effects model and their 95% confidence intervals (95% CIs).

erythrocyte deformability and aggregation,[55] time to exertion,[52] SBP[51] and abdominal fat.[69] Particularly, the vascular adaptation that appears to be enhanced after hypoxic training may be related to the 'compensatory' increase in blood flow to the exercising muscle. Nevertheless, the specific mechanisms underlying these benefits remain to be elucidated. The increase in skeletal muscle capillarization could be potentially due to enhanced angiogenesis capacity. Finally, the training level of participants could play a key role in the adaptations and additional benefits of hypoxic exercise.[13] Therefore, further long-term RCTs should be conducted, including a complete picture of cardiovascular parameters. Moreover, they should clarify whether a hypoxic exercise intervention may provide additional benefits when compared to normoxic training.

The specific protocol of the hypoxic exercise programs may also have an impact on cardiovascular adaptations and responses. For instance, when exercise was performed at moderate hypoxic levels (i.e. ~1500–3000 m), BP was maintained or improved.[74] Conversely, high hypoxic levels (i.e. >5000 m) significantly increased BP.[74] Furthermore, exercise training under mild intermittent hypoxic conditions (i.e. 2000 m simulated altitude) resulted in more efficient stimuli for reducing arterial stiffness and inducing a vascular functional adaptation response (i.e. increased flow-mediated dilation) compared to similar normoxic training.[75] Therefore, this fact should be considered as a potential modulator of the hypoxic exercise-related effects on cardiovascular health. Despite this, our meta-regression models based on the hypoxic intensity (% FiO_2) did not influence our results. Nevertheless, hypoxic intensity should be further explored considering safe doses as higher intensities might be related to greater changes in the cardiovascular parameters explored in our review. Additionally, the type of exercise (resistance vs. endurance) may impact CV responses. Our main analysis combined resistance and endurance training, but these exercise modalities possess different targeted effects and may impact cardiovascular function differently; this could be a limitation. However, our subgroup analyses based on exercise modalities did not find any significant difference (except for increased blood lactate levels after resistance exercise modality). Despite this, we should be cautious due to the scarcity of studies included in our review that conducted resistance training under hypoxic conditions. For instance, some authors support that resistance training under hypoxia may induce muscle changes and physiological adaptations that would improve anaerobic performance by increasing muscle buffering capacity and glycolytic enzyme activity.[76,77] Otherwise, endurance training under hypoxia increases aerobic capacity by promoting ventilation, lung diffusion capacity or capillary oxygen saturation.[35,78] Training intensity emerges as a crucial factor, with the lactate threshold intensity being a practical option for improving aerobic and anaerobic performance. Nevertheless, intensity, duration, number and frequency of hypoxia bouts ('hypoxia dose') are important variables for hypoxic training interventions that may elicit beneficial or detrimental adaptive responses depending on the population studied. Harmonization of hypoxic training protocols and systematic assessments are essential to draw more solid conclusions on this topic.

TABLE 3 Subgroup analyses of hypoxic exercise by age, gender or health status.

	Age		Gender		Health Status	
	<30 years old	**≥30 years old**	**Males**	**Mixed**	**Healthy/ athletes**	**Comorbidities/ sedentariness**
Haemoglobin						
n	6	3	7	2	6	3
SMD (95% CI)	.26 (−.08, .60)	−.09 (−.47, .29)	.15 (−.16, .46)	.03 (−.41, .46)	.13 (−.19, .45)	.07 (−.35, .49)
Sat O2						
n	5	2	5	2	5	2
SMD (95% CI)	−.01 (−.30, .29)	.04 (−.80, .89)	−.01 (−.30, .29)	.04 (−.80, .89)	.15 (−.24, .55)	−.12 (−.49, .24)
HR						
n	10	8	11	6	7	10
SMD (95% CI)	−.14 (−.35, .07)	−.04 (−.27, .18)	−.14 (−.33, .04)	.00 (−.27, .28)	−.03 (−.30, .25)	−.13 (−.32, .06)
SBP						
n	3	10	3	9	2	11
SMD (95% CI)	.04 (−.40, .47)	−.02 (−.25, .21)	.08 (−.35, .50)	−.10 (−.34, .15)	.22 (−.30, .73)	−.05 (−.27, .17)
DBP						
n	3	10	3	9	2	11
SMD (95% CI)	−.31 (−.75, .13)	.03 (−.21, .26)	−.36 (−.78, .06)	−.03 (−.27, .21)	−.29 (−.80, .22)	−.001 (−.23, .22)
Blood lactate levels						
n	4	4	5	4	4	5
SMD (95% CI)	**.59 (.11, 1.06)**	.07 (−.21, .35)	.39 (−.10, .89)	.14 (−.17, .45)	**.59 (.11, 1.06)**	.07 (−.21, .35)

	Exercise modality				
	Resistance	**Aerobic**	**High intensity**	**Combined**	**Pilates**
Haemoglobin					
n	2	4	2	1	–
SMD (95% CI)	.01 (−.40 to .43)	.23 (−.24 to .69)	.08 (−.60 to .76)	−.02 (−1.00 to .96)	–
Sat O2					
n	1	4	2	–	–
SMD (95% CI)	.49 (−.40 to 1.38)	−.04 (−.35 to .20)	.00 (−.27 to .27)	–	–
HR					
n	3	10	3	2	–
SMD (95% CI)	.06 (−.31 to .44)	−.18 (−.38 to .02)	.09 (−.42 to .49)	−.02 (−.50 to .46)	–
SBP					
n	1	9	1	1	1
SMD (95% CI)	−.16 (−1.03 to .72)	.13 (−.12 to .38)	−.25 (−.75 to .26)	−.24 (−1.01 to .53)	−.46 (−1.31 to .39)
DBP					
n	1	9	1	1	1
SMD (95% CI)	.28 (−.60 to 1.16)	−.03 (−.30 to .24)	.12 (−.38 to .62)	−.51 (−1.25 to .23)	−.37 (−1.22 to .48)
Blood lactate levels					
n	1	6	2	–	–
SMD (95% CI)	**1.08 (.23 to 1.94)**	.19 (−.11 to .50)	.19 (−.38 to .77)	–	–

Note: SMD in bold: statistically significant.

Abbreviations: CI, Confidence interval; DBP, diastolic blood pressure; SaO_2, arterial oxygen saturation; SBP, systolic blood pressure; SMD, standardized mean difference.

Our results revealed the lack of age and gender influence in cardiovascular adaptations to hypoxia, and we were unable to explore the influence of ethnicity, a point that did not concur with previous studies.[79,80] According to ethnicity, it has been suggested that hypoxic exercise results in higher levels of arterial oxygen saturation in African–American versus Caucasian males after hypoxic exercise in arterial and cerebral oxygenation,[80] which might be explained by the decreased serum transferrin saturation in African–Americans. However, the social context associated with ethnicity (i.e. healthcare access, food security, family income or occupation) needs to be carefully considered, and these data were not available.[81] Moreover, implicit bias might play a role, since there were 598 African–American men and women and more than 12,000 age-matched white controls.[81] Conversely, when exploring age, we only observed a significant increase in maximal blood lactate levels for young adults (<30 years), but we should consider that they also had a healthy and/or athletic status. Accordingly, some authors have reported fewer cardiovascular adaptations and responses in older people after chronic hypoxic exposure.[82] In fact, those authors showed that hypoxic exercise resulted in a decreased cardiac response and lower maximal O_2 consumption, together with a decline in muscle mass and power with aging.[82] Furthermore, a greater exercise-induced desaturation in young and trained adults has been suggested when compared to older adults and less trained individuals.[82]

Previous studies have reported positive effects of hypoxic exercise interventions in people with chronic conditions[83–88]; therefore, the participant's health status should be a factor to take into consideration. For instance, notorious BP and HR benefits were pointed out in patients with clinical conditions—including individuals with coronary heart disease and chronic obstructive pulmonary disease[89] or hypertension[74]—compared with their healthy counterparts. Importantly, our data did not show significant differences between the health statuses for Hb concentrations at rest, SaO_2%, HRmax or BP at rest; however, a subgroup analysis indicated a moderately greater level of maximal blood lactate in healthy individuals and/or athletes compared to people with comorbidities and/or sedentariness. These controversial findings could be related to the ceiling effect of exercise interventions in healthy and highly trained participants, which suggests there is no 'room' for improvements when the outcomes are at optimal levels.[90]

It is worth noting that the moderate increase in maximal blood lactate levels in healthy individuals and athletes shown by our data could suggest an improved oxidative capacity of cells and mitochondrial function induced by chronic hypoxic exercise interventions.[91] Moreover, blood lactate is considered an exerkine with important metabolic functions, such as fuelling muscles and participating in the liver (Cori's cycle), together with effects on other tissues (e.g. central nervous system).[92,93] Moreover, hypertension status was responsible for attenuating the association between blood lactate levels and the risk of diabetes[94] and carotid atherosclerosis,[95] showing a higher resting blood lactate level in patients with carotid atherosclerosis independent of traditional cardiovascular risk factors. Therefore, lactate could play an important role in cardiovascular health and cardiometabolic risk.[96] However, we should be cautious regarding this point as greater blood lactate levels could be observed in cardiac patients when performing incremental exercise (sign of bad prognosis)[97] or highly trained individuals. Therefore, further long-term trials with standardized hypoxic training protocols are thus needed to explore the effects of hypoxic exercise on blood lactate levels and other exerkines to elucidate their potential role in cardiovascular, metabolic, immune and neurological health.

This review has limitations that should be noted. First, the heterogeneity among the included population as well as exercise protocols, mainly related to work rates, may explain some of the controversial results found. In fact, most studies were conducted in healthy, trained and young participants; therefore, the baseline levels of cardiovascular function-related parameters of such populations could make it difficult to show additional benefits of hypoxic exercise interventions ('ceiling effect'). Additionally, more sensitive cardiac function parameters should be evaluated in further trials such as left ventricular ejection fraction, stroke volume and cardiac output. Our findings should thus be taken cautiously when extrapolating to other specific populations (i.e. people with cardiovascular diseases). Second, the small sample size in the included RCTs (from 12 to 73 individuals) in addition to the short-term hypoxic exercise programs (<12 weeks for 27 out of 31 studies) could mask some potential long-term benefits of hypoxic exercise on cardiovascular function. Third, the certainty of the evidence was rated as low or very low. This was mainly explained by (i) the wide confidence intervals that include or are close to the null effect, (ii) the heterogeneity of the baseline characteristics of the participants included in the primary studies and (iii) the risk of bias. In particular, the randomization process (e.g. lack of information about the randomized allocation sequence and concerns about the concealment of the concealed allocation sequence until participants were assigned to interventions) and deviations from intended interventions (e.g. carers or people delivering the intervention were mostly aware of the assigned intervention) were sources of bias for the included trials. Despite this, our systematic review and meta-analysis provide a comprehensive synthesis of current evidence and did not exclude studies based on the quality assessment (a posteriori), and no trials were identified as having a high risk of bias. Fourth, the detrimental or beneficial adaptive responses of hypoxic training may depend mostly on the hypoxic dose, individual predisposition (population of study), physical activity, medication and type of exercise.[78] The ambiguity of the terminology used in hypoxic research and the lack of information in some studies regarding crucial variables (i.e. exposure type, frequency [single vs. repeated, acute vs. chronic], hypoxia intensity and duration, time of day and arousal state [wake/day vs. night/sleep], exercise protocols, carbon dioxide levels, population, physical activity and nutritional status and intention [pathophysiology vs. beneficial])[98] difficult to extrapolate solid conclusions about the sports and clinical applications of hypoxic training; thus, future research should take this carefully.

5 | CONCLUSION

In summary, the present data suggest that there are no additive benefits of performing exercise under hypoxic conditions on the cardiovascular function parameters explored (Hb concentrations, SaO_2%, HRmax, BP at rest and maximal blood lactate levels) when compared to normoxic exercise for up to a mean of 7 weeks in people without cardiovascular disease, except for a moderate increase in blood lactate levels in young healthy and/or athletic individuals. Thus, our findings could be useful to exercise physiologists, especially those working with athletes. Although hypoxic exercise could improve other cardiovascular and metabolic parameters related to CVDs, there is an urgent need for clinical trials with standardized hypoxic training protocols aimed at exploring the optimal dosing of hypoxia during training and whether hypoxic exercise may act through other pathways related to cardiovascular health in the long term in participants with chronic conditions and poor health status.

AUTHOR CONTRIBUTIONS

All authors have made substantial contributions to all of the following: (i) the conception and design of the study, acquisition of data, analysis and interpretation of data, (ii) drafting the article or revising it critically for important intellectual content, (iii) final approval of the version to be submitted.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding author upon reasonable request.

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