



Review

Additive stress of normobaric hypoxic conditioning to improve body mass loss and cardiometabolic markers in individuals with overweight or obesity: A systematic review and meta-analysis



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ABSTRACT

We performed a systematic review and meta-analysis to determine if hypoxic conditioning, compared to similar training near sea level, maximizes body mass loss and further improves cardiometabolic markers in overweight and obese individuals. A systematic search of PubMed, Web of Science and the Cochrane Library databases (up to January 2019) was performed. This analysis included randomized controlled trials with humans with overweight or obesity assessing the effects of HC on body mass loss or cardiometabolic markers. A subgroup analysis was performed to examine if HC effects differed between individuals with overweight or obesity. 13 articles (336 participants) qualified for inclusion. HC significantly decreased body mass ($p = .01$), fat mass ($p = .04$), waist/hip ratio ($p < .001$), waist ($p < .001$), LDL ($p = .01$), diastolic ($p < .01$) and systolic blood pressure ($p < .01$) with these effects not being larger than equivalent normoxic interventions. There were trends towards higher triglycerides decrement ($p = .06$) and higher muscle mass gain in hypoxic ($p = .08$) compared with normoxic condition. Also, the two BMI categories displayed no difference in the magnitude of the responses. Compared to normoxic equivalent, HC provides greater reductions in triglycerides and greater muscle growth, while body mass changes are similar. In addition, HC responses were essentially similar between individuals with overweight or obesity.

1. Introduction

Obesity is the pandemic of the 21st century. It is characterized by excessive fat mass accumulation and chronic systemic inflammation, which likely predisposing individuals with obesity to metabolic diseases [1]. Obesity is generally defined as a body mass index (BMI) of 30 kg/m² and above, while overweight is defined as a BMI between 25 and 30 kg/m² [2]. Although it arises from a multifactorial etiology (e.g., genetics, lifestyle, socioeconomic status) [1] being obesity or overweight typically is caused by a positive energy balance, which results from an increased food intake, a decreased energy expenditure, or both [3]. Obesity is associated with increased risk of premature mortality and other comorbidities such as dyslipidemia, type 2 diabetes mellitus, hypertension, cancer, stroke and coronary heart diseases [4,5]. Carrying additional weight also produces excessive joint loads, eventually leading to the development of musculoskeletal pathologies (i.e. osteoarthritis) that in turn limit functional capabilities [6].

There is an urgent need for effective interventions to treat obesity. During the last decades, caloric restriction and exercise interventions have been primarily implemented as treatment for obesity [7]. Current exercise recommendations suggest that individuals with obesity should undertake 30–60 min of moderate-intensity physical activity on most, if not all, days of the week [8]. However, adherence to exercise often declines over time, and perhaps even more so in diseased populations [9]. This may lead to a plateau of body mass loss with a partial or total recovery of lost body mass only 6 months after the start of the nutrition and/or exercise interventions [9]. Today, it is imperative that innovative, non-pharmacological approaches are developed for individuals with overweight or obesity to match current exercise recommendations [5].

Several recent studies have used hypoxic exposure as a new therapeutic strategy to improve the symptoms of a range of cardiovascular, metabolic and pulmonary diseases including obesity [3,9,10]. Hypoxia is defined as a reduced O₂ supply to tissues caused by decreases in O₂

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saturation of arterial blood [11]. Hypoxic conditioning (HC) relates to passive (i.e., during rest) or active (i.e., during exercise) recurrent exposure to systemic (whole body) and/or local (tissue) hypoxia. By decreasing arterial O₂ availability, HC has the potential to further improve cardio-metabolic health, functional performance and well-being of individuals with chronic diseases and/or sustaining acute musculo-skeletal injuries [12]. HC that activates the hypoxia-inducible factor (HIF) may play an essential role in effective metabolism regulation (i.e. body mass maintenance, glucose homeostasis and liver metabolism) and thereby in the prevention of obesity [1]. Reportedly, passive and active hypoxia stimulate HIF-1 production [13], improving glucose intake and transport, glycolysis, lactate production to provide ATP [14] and oxygen transport and satiety [15] among others. Also, lipid metabolism can be further enhanced when exercise training is conducted in O₂-deprived environments [16]. However, other HC studies failed to demonstrate similar positive results on lipid metabolism [17] and body mass loss management [17,18]. Thus, there is conflicting evidence in relation to the effectiveness of HC as a tool to improve body mass loss and lipid oxidation in individuals with overweight or obesity.

To date, several studies have analyzed the effect of low intensity training (55–65% of maximum oxygen uptake (VO₂max)) [16,18–21] in hypoxia on body mass loss and cardiometabolic markers in individuals with overweight or obesity. Compared to normoxia, hypoxic training at low intensity in patients with obesity can induce higher increases in noradrenaline levels, peripheral vasodilatation, number of mitochondria, glycolytic enzyme activity, insulin sensitivity and/or reduction of leptin levels [9]. Other positive effects of HC have been observed on blood pressure [21] and metabolic markers such as triglycerides [22,23] or cholesterol [23], which were not found (or to a lower extent) with equivalent normoxic training. However, other studies did not find any additional effect of HC on blood pressure [16,24], triglycerides [17,20] or blood glucose [23,25]. To date, contradictory findings exist in the literature about the additional effect of low-intensity training HC on improvement of cardiometabolic markers.

During the past few years, new training paradigms under hypoxic conditions have been introduced. It is well established that high intensity training (HIT) in hypoxia can improve cardiorespiratory function (i.e. VO₂max) and performance (i.e. best and mean sprint during an repeat sprint ability test) [26] in athletic populations, while the usefulness of this training modality in patients as a tool to improve body mass loss and cardiometabolic markers is more recent [10,27]. Recent evidence suggests that HIT in hypoxia is more effective at increasing lean mass than normoxic exercise in women with overweight and obesity [28]. For instance, additional body mass loss and body fat reduction with also a concomitant increase in muscle mass have been reported after 12 weeks of HIT in hypoxia [10]. However, another HIT study [29] failed to report a positive change in body composition after a 5-wk training period. Contradictory findings exist regarding whether or not HC facilitates body mass loss compared to equivalent normoxic training.

Previous literature reviews (mainly narrative in nature) have critically discussed the potential of passive and active HC as a therapeutic intervention to loose body mass and improve health-related markers [3,5,9,30–32] in individuals with obesity. Limitations of this previous work include the analysis of the effect of HC on some other diseases (i.e. pulmonary and cardiovascular), inclusion of non-randomized controlled trials and an analysis period up to until 2017. Only in 2018, six additional randomized controlled trials [10,17,22,23,25,28] have been published that represent half of the total number of studies that were available until then. Remarkably, only one of these reviews is a systematic review [5], while it included both animals and humans (6 randomized controlled trials (RCT)) research. This 2017 systematic review that featured inconsistent findings for triglycerides and cholesterol markers. A potential limitation of a systematic review is that it does not include a data synthesis and statistical analysis to determine summary effect of the intervention on the outcomes measures. This

implies that the results obtained in the literature review by Hobbins et al [5] could be oversized without a specific statistical analysis that offers a more accurate and general picture of the HC effects on body composition and health markers. Taken as a whole, this clearly demonstrates the growing interest around HC potential and the need to conduct new analysis.

Previous studies found that body composition and physiological adaptations to training may differ between individuals with normo-weight, with overweight or with obesity [33]. For instance, a recently study [23] has shown a positive effect of low intensity training in hypoxia in overweight, but not normoweight, individuals on cardiometabolic markers such as triglycerides or high-density lipoprotein (HDL). To our knowledge, no meta-analysis study exists that specifically analyzed the influence of participant background on the magnitude of body mass loss and cardiometabolic health responses.

Therefore, our aim was to perform a systematic review and meta-analysis to determine if hypoxic conditioning, compared to similar training near sea level, maximizes body mass loss and further improves cardiometabolic markers in overweight and obese individuals.

2. Methods

2.1. Study design

The review was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42018117868). The methodological process was based on the recommendations formulated in the PRISMA declaration [34]. For the meta-analysis, only randomized controlled trials investigating the effects of normobaric HC on body mass loss and/or cardiometabolic markers were considered.

2.2. Data sources and search profile

A comprehensive literature search was performed using PubMed-Medline, Web of Science and the Cochrane Library from database inception up to January 2019. The database searches were performed independently by two authors (AP and DJRC) and the results obtained were the same. The flow diagram of the search process is shown in Fig. 1. The following combination of terms was used: “hypoxia” or “intermittent hypoxia” or “hypoxic training” or altitude training” or “passive hypoxic exposure”. The Boolean operator “AND” was used to combine these descriptors with: “obesity” or “overweight” or “weight loss”.

2.3. Selection criteria

The specific inclusion criteria were: [1] original studies with a randomized controlled design; [2] human experimentation; [3] participants with overweight (BMI > 25 kg/m²) or/and obesity (all obesity categories; BMI > 30 kg/m²); [4] studies examining the effect of passive or active normobaric HC intervention; [5] studies assessing at least body mass of tested participants; [6] studies published in English; and [7] chronic interventions with a minimal duration of two weeks. Research studies were excluded if they: [1] only focussed on sport performance outcomes; [2] included physically active participants who performed moderate-intensity aerobic physical activity for a minimum of 30 min/d on 5 d/week or vigorous-intensity aerobic activity for a minimum of 20 min/d on 3 d/wk.; [3] were clinical studies; [4] examined the effect of hypobaric hypoxia (terrestrial altitude and hypobaric hypoxia in a climatic chamber) or used other devices that do not reduce the FiO₂ (i.e. altitude training mask); [5] were reviews or assessed the effects of an acute intervention; and [6] were not an original investigation published in full.

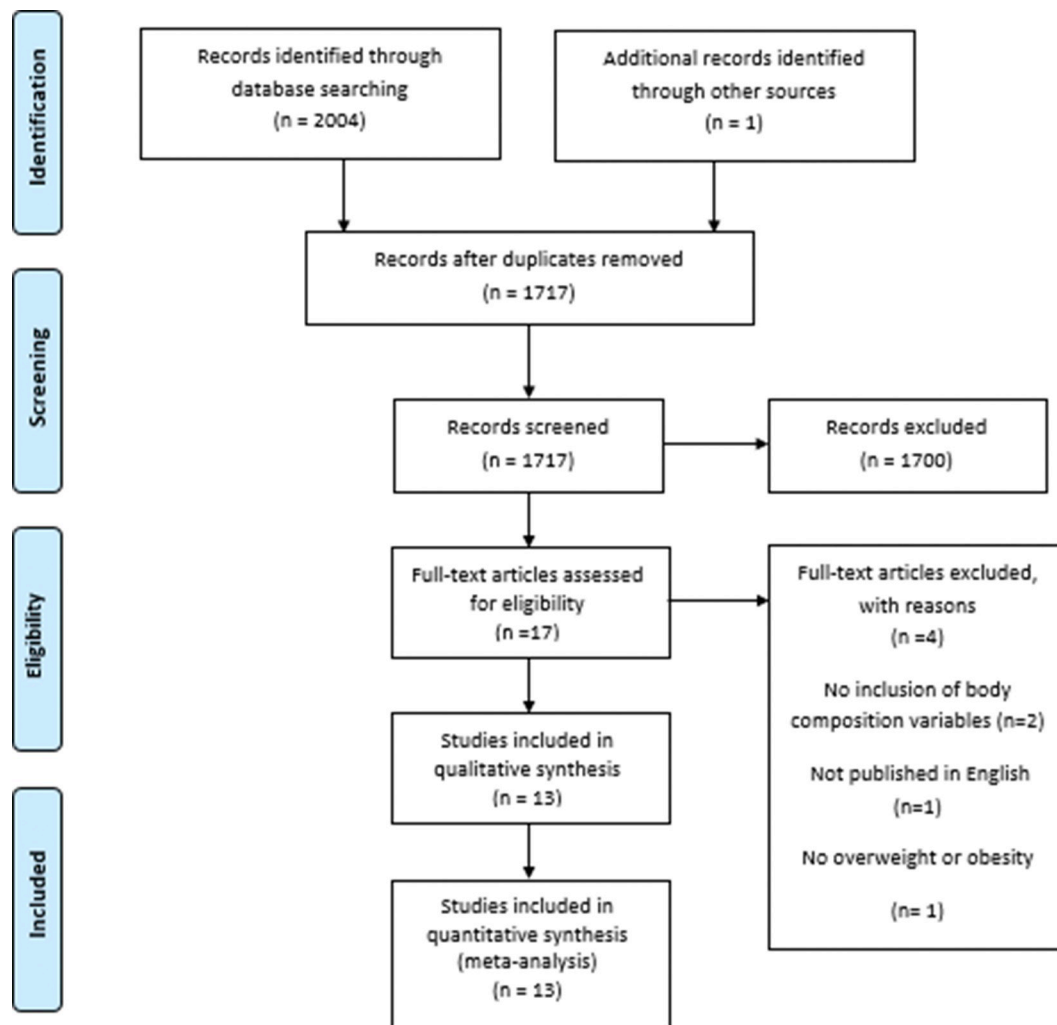


Fig. 1. Search process flow diagram.

2.4. Study selection and data extraction

Retrieved articles were reviewed independently by two authors (AP and DJRC) in order to select relevant articles. In addition to the literature search, references were scanned for further relevant articles and were included in our analysis if they met the inclusion criteria. Also, authors of selected studies were contacted for non-reported information. Two authors (AP and DJRC) independently extracted data from the included studies. The following information was extracted: authors of the paper, study design, number of participants included in each group, age, gender and BMI. Regarding the characteristics of the hypoxic intervention, the information extracted included: type of hypoxic exposure (passive, active or combination of both), protocol and training characteristics (volume, intensity, frequency, rest...), duration (number of weeks) and level of hypoxia.

2.5. Outcomes

The primary outcome was body mass loss. The secondary outcomes were: i) BMI; ii) waist circumference; iii) waist/hip (W/H) ratio; iv) muscle mass; v) fat mass; vi) Low-density lipoprotein (LDL); vii) HDL; viii) triglycerides; ix) blood glucose; x) systolic blood pressure (SBP); and xi) diastolic blood pressure (DBP).

2.6. Evaluation of the methodology of the studies selected

The methodological quality of the selected studies was assessed with the Cochrane risk-of-bias tool [35] that includes the following parameters: [1] random sequence generation (selection bias); [2] allocation concealment (selection bias); [3] blinding of participants and personnel (performance bias); [4] blinding of outcome assessment (detection bias); [5] incomplete outcome data (attrition bias); [6] selective reporting (reporting bias) and [7] other bias. For each study, each item was described as having either a low risk of bias, an unclear risk of bias or a high risk of bias. Risk of bias was assessed independently by two authors (JARA and DJRC) using the Cochrane risk-of-bias tool [35].

2.7. Data synthesis and statistical analysis

The meta-analysis and the statistical analysis were conducted using the Review Manager software (RevMan 5.2; Cochrane Collaboration, Oxford, UK). A random effects meta-analysis was conducted to determine the effect of HC on body composition (BMI, waist, W/H ratio, muscle mass, fat mass, and body mass) and cardiometabolic markers (LDL, HDL, triglycerides, blood glucose, SBP and DBP). The effects sizes of outcomes between hypoxic and normoxic conditioning as well as the differences between before and after training intervention were expressed as standard mean differences (SMD) and their 95% confidence intervals (CI). The threshold values for SMD were > 0.2 (small), > 0.6 (moderate), > 1.2 (large), and > 2.0 (very large). Also, the mean

Table 1
Main characteristics of included studies in the meta-analysis.

Study	Participants characteristics				Intervention		FiO ₂
	Participants	Age	Weight	BMI	Exposure type	Type of training	
Fernández-Menéndez et al. [17]	12 (F), 2 (M)	34.8 (4.7)	96.8 (9.5)	34.1 (2.6)	Active	Aerobic	14.5
	11 (F), 2 (M)	32.2 (8.4)	96.6 (9.6)	32.9 (2.7)	–	–	20.9
Kong et al. [21]	5(M), 5(F)	19.8 (2.2)	99 (19.5)	34.7 (5.3)	Active	Aerobic + strength	16.4/ 14.5
	5(M), 3(F)	22.3 (1.7)	103.4 (24.7)	33.8 (5.6)	–	–	21
Shin et al. [23]	8(M)	45.6 (20.9)	78.3 (8.4)	26.8 (2.3)	Active	Aerobic	14.5
	9 (M)	46.0 (20.5)	79.8 (11.0)	27.0 (3.0)	–	–	20.9
Netzer et al. [20]	2 (M), 8 (F)	50.1 (7.4)	89.8 (7.4)	33.4 (3.3)	Active	Aerobic	15
	2 (M), 8 (F)	45.5 (10.7)	91.5 (10.7)	32.8 (7.1)	–	–	20.1
Yang et al. [38]	8 (M), 8 (F)	14.3 (1.4)	93.0 (15.1)	32.9 (3.5)	Passive	Aerobic	14.7
	11 (M), 8 (F)	13.9 (0.9)	86.9 (12.8)	31.5 (3.3)	–	–	21
Wiesner et al. [16]	10 (M), 14 (F)	42.2 (0.2)	93.4 (2.6)	33.1 (0.3)	Active	Aerobic	15
	8 (M), 13 (F)	42.1 (1.7)	87.5 (3.6)	32.5 (0.8)	–	–	21
Camacho-Cardenosa et al. [10,28]	13 (F)	44.4 (7.2)	80.1 (18.9)	30.0 (6.4)	Active	Aerobic	17.2
	13 (F)	43.1 (7.7)	80.4 (16.3)	29.6 (5.2)	–	–	20.9
	18 (F)	37.4 (10.2)	73.7 (11.1)	27.7 (4.5)	Active	HIIT	17.2
	15 (F)	40.0 (8.7)	77.9 (11.3)	28.7 (4.8)	–	–	20.9
Kong et al. [29]	14 (F)	–	69.5 (5.8)	26.0 (2.4)	Active	HIIT	15
	15 (F)	–	68.2 (8.1)	25.7 (2.2)	–	–	21
Gatterer et al. [19]	12 (F), 4 (M)	50.3 (10.3)	105.5 (20.0)	37.9 (8.1)	Active + Passive	Aerobic	14
	10 (F), 6 (M)	52.4 (7.9)	103.2 (15.1)	36.3 (4.0)	–	–	21
De Groote et al. [22]	3 (M), 4 (F)	14.3 (1.1)	104.6 (13.6)	37.9 (8.1)	Active	Aerobic + Strength	15
	3 (M), 4 (F)	13.7 (1.39)	97.5 (25.9)	36.3 (4.0)	–	–	21

(continued on next page)

Table 1 (continued)

Study	Participants characteristics				Intervention		Protocol	Duration	FiO ₂
	Participants	Age	Weight	BMI	Exposure type	Type of training			
Morishima et al. [18]	9 (M)	30.0 (2.0)	74.4 (4.2)	25.6 (1.2)	Active	Aerobic	60 min cycling at 55% of the maximal oxygen uptake	4 wk. 3 d/wk. 60 min per S	15
	11 (M)	32.0 (3.0)	73.8 (4.0)	25.4 (0.9)	–				21
Klug et al. [25]	12 (M)	55.0 (2.1)	109.1 (5.2)	35.5 (1.4)	Active	Aerobic	60 min with 3 × 15 min of walking on a treadmill with 5 min of rest	6 wk. 3 d/wk. 60 min per S	15
	11 (M)	57.6 (2.2)	108.5 (3.0)	34.1 (0.9)					21

M: male; F: female; wk.: weeks; d: days; H: Hypoxia; N: Normoxia; FiO₂: inspired fraction of oxygen; kg: kilogram; HR: Hear rate; IRM: one-repetition maximum; *: Only for hypoxic group; HIIT: High intensity interval training; MAP: maximal aerobic power; Wmax: maximal power achieved during the last 3 min step complete during the incremental test; Mean (standard deviation).

difference (MD) was used when all the studies assessed the same outcome and measured it in the same way. Each difference of the means was weighed according to the inverse variance method [36].

The heterogeneity between the studies was evaluated through the I^2 statistic, and between-study variance using the tau-square (τ^2) [37]. I^2 values of 30–60% represented a moderate level of heterogeneity. A $p < .1$ value suggests the presence of substantial statistical heterogeneity. The publication bias was evaluated through an asymmetry test as estimated from a funnel plot. In addition, the Egger's test was used to assess publication bias. A $p < .05$ value was considered to be statistically significant. Finally, subgroup analyses were used to find the effects of the initial BMI (individuals with overweight versus individuals with obesity) of the individuals on the effectiveness of the HC. The cut-off value of the BMI variable was: individuals with overweight ($25 \text{ kg/m}^2 < \text{BMI} < 30 \text{ kg/m}^2$) and individuals with obesity ($\text{BMI} > 30 \text{ kg/m}^2$). The effects were expressed as SMD and MD and their 95% of confidence intervals.

3. Results

3.1. General characteristics of studies

The initial search identified 2004 articles from databases and 1 article from other sources. After excluding duplicate articles, 1717 article abstracts were screened. Thereafter, 1700 articles were excluded and 17 were screened as full-texts. Finally, 13 articles [10,16–23,25,28,29,38] that met the inclusion criteria were left, and these were selected for the meta-analysis (Fig. 1). The effects of HC (passive and active) on body mass loss were analyzed in 13 articles and 336 participants. The analysis of secondary outcomes is based on the following number of studies: BMI = 10; waist = 7; W/H = 5; muscle mass = 10; fat mass = 11; LDL = 8; HDL = 8; triglycerides = 11; blood glucose = 8; DBP = 7; SBP = 7. The number of participants analyzed in these secondary outcomes ranged between 66 and 166 participants. All selected studies were published between 2009 and 2018.

Table 1 provides an overview of the intervention and participants characteristics of the studies included in the quantitative analysis (meta-analysis). The age and BMI ranged from 13.7 to 52.4 years and 25.7 to 38.6 kg/m², respectively. The exercise program duration ranged from 3 to 34 weeks and from 2 to 12 sessions per week. Also, the FiO₂ applied in normoxic and hypoxic groups ranged from 20.0 to 20.9% and from 12.2 to 17.2%, respectively.

3.2. Risk-of-bias assessment

Risk-of-bias assessment is shown in Fig. 2. Overall, the risk of bias was 'high' in all studies due to lack of random sequence of participants, the allocation concealment and the blinding of participants and researchers to assigned training conditions. The regression test funnel plot asymmetry showed no significant heterogeneity for the following body composition outcomes: BMI ($Z = 0.600$, $p = .549$), muscle mass ($Z = 0.169$, $p = .866$), fat mass ($Z = 0.416$, $p = .677$) and body mass ($Z = 0.502$, $p = .615$). However, significant heterogeneity was observed in the following cardiometabolic outcomes: triglycerides ($Z = 4.504$, $p \leq .001$), LDL ($Z = 3.626$, $p \leq .001$) and HDL ($Z = 2.522$, $p = .012$) and blood glucose ($Z = 4.148$, $p < .001$).

3.3. Meta-analysis

3.3.1. Effects on body composition

Regarding body composition variables, a significant body mass loss was found in participants who trained under normoxic ($\text{MD} = -1.61$, 95% CI = -2.90 , -0.33 , $p = .01$; $I^2 = 0\%$, $p = .99$) and hypoxic ($\text{MD} = -1.42$, 95% CI = -2.76 , -0.09 , $p = .04$; $I^2 = 0\%$, $p = .98$) conditions. In addition, significant decreases in fat mass were found in participants who trained under hypoxia ($\text{SMD} = -0.26$, 95%

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Camacho-Cardenosa et al. (2018)	+	+	?	?	+	+	+
Camacho-Cardenosa et al. (2018)a	+	+	?	?	+	+	+
De Groote et al. (2018)	+	?	?	?	+	+	+
Fernández-Menéndez et al. (2018)	−	?	?	?	+	+	?
Gatterer et al. (2015)	−	+	+	?	+	+	?
Klug et al. (2018)	+	+	−	?	+	+	?
Kong et al. (2014)	−	−	?	?	+	+	?
Kong et al. (2017)	−	+	+	?	+	+	?
Morishima et al. (2014)	−	?	?	?	+	+	?
Netzer al. (2008)	+	?	?	?	+	+	?
Shin et al. (2018)	−	?	?	?	+	+	?
Wiesner et al. (2009)	+	+	?	?	+	+	?
Yang et al. (2018)	+	+	?	?	+	+	?

Fig. 2. Assessment of risk of bias in included randomized controlled trials.

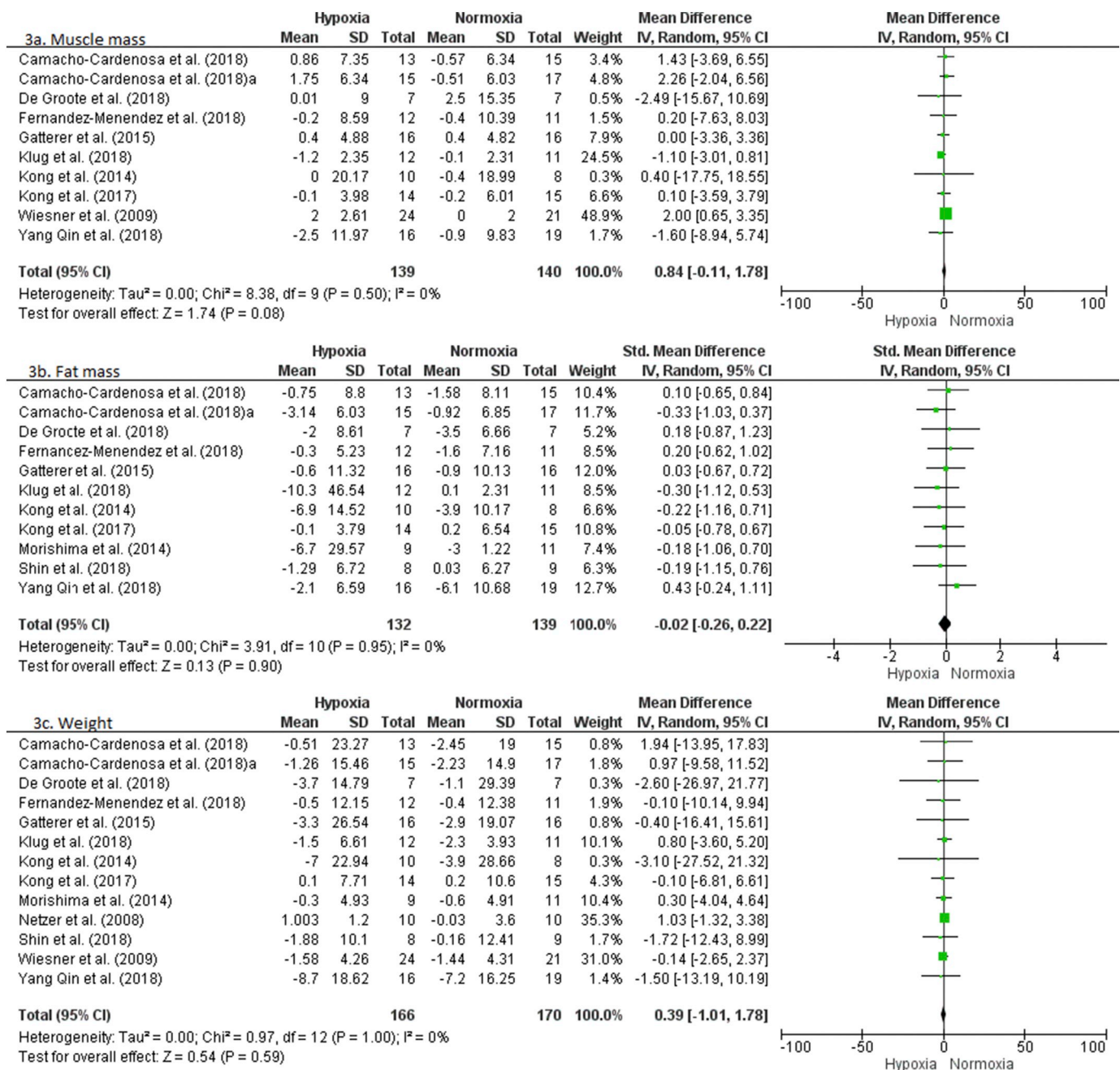


Fig. 3. Total effects of treatment on muscle mass (a), fat mass (b) and weight (c) hypoxic group vs. normoxic group.

CI = -0.50, -0.01, $p = .04$; $I^2 = 0\%$, $p = .99$) but not in normoxia. Also, BMI (MD = -0.54, 95% CI = -1.01, -0.07, $p = .03$; $I^2 = 0\%$, $p = .75$) decreased significantly in normoxic but not in hypoxic condition. Moreover, no significant post-training changes were observed on muscle mass in normoxic ($p = .86$) and hypoxic ($p = .47$) conditions. However, a trend towards higher muscle mass gain in hypoxic than in normoxic condition ($p = .08$) was observed. Furthermore, no significant differences between conditions were observed for fat mass ($p = .90$) and body mass changes ($p = .59$) (Fig. 3).

The W/H ratio decreased after both normoxic (MD = -0.02, 95% CI = -0.03, -0.01, $p = .003$; $I^2 = 0\%$, $p = .86$) and hypoxic (MD = -0.02, 95% CI = -0.04, -0.01, $p < .001$; $I^2 = 0\%$, $p = .76$) conditioning, yet with no statistical significant differences between conditions (Fig. 4a). Likewise, waist circumference decreased to the same extent in hypoxic (MD = -3.52, 95% CI = -4.75, -2.30, $p < .001$; $I^2 = 0\%$, $p = .86$) and normoxic (MD = -2.09, 95%

CI = -3.37, -0.81, $p = .001$; $I^2 = 0\%$, $p = .99$) conditions (Fig. 4b). BMI decreased significantly after training under normoxic (MD = -0.50, 95% CI = -0.98, -0.03, $p = .04$; $I^2 = 0\%$, $p = .73$) but not hypoxic condition (Fig. 4c).

3.3.2. Effect on cardiometabolic markers

A significant decrease in triglycerides was observed after training under hypoxic (SMD = -0.67, 95% CI = -1.02, -0.32, $p < .001$; $I^2 = 41\%$, $p = .09$) and normoxic (SMD = -0.57, 95% CI = -0.98, -0.15, $p = .008$; $I^2 = 61\%$, $p = .006$) conditions (Fig. 5a), also with a more favourable effect ($p = .06$; Chi² = 8.20, $p = .61$) due to hypoxia.

LDL decreased in normoxia (SMD = -0.46, 95% CI = -0.75, 0.17, $p = .002$; $I^2 = 0\%$, $p = .60$) and hypoxia (SMD = -0.51, 95% CI = -0.9, -0.12, $p = .01$; $I^2 = 41\%$, $p = .12$), with no difference between conditions (Fig. 5b). Compared to before, no significant HDL level differences occurred after training in either normoxic

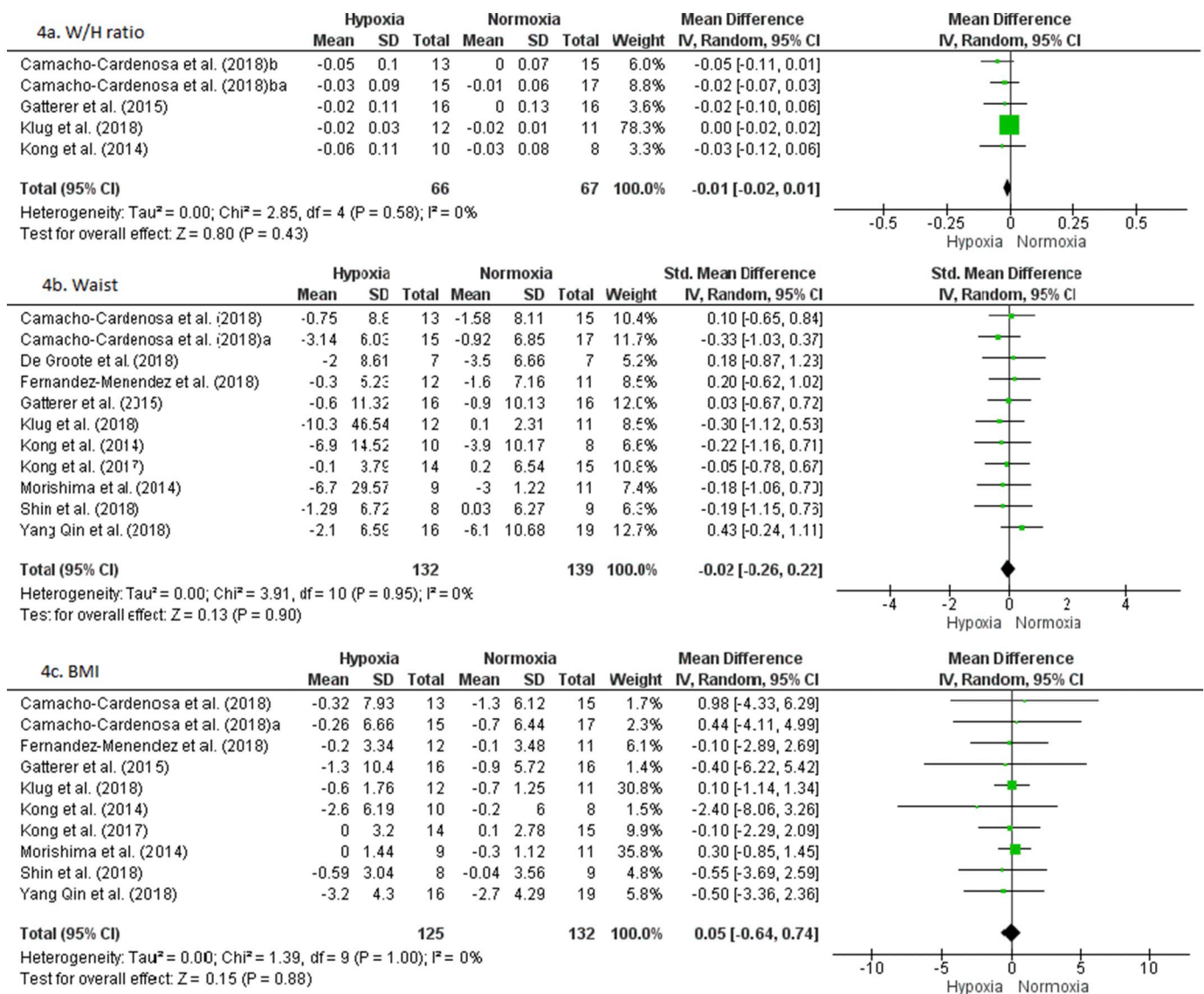


Fig. 4. Total effects of treatment on W/H ratio (a), waist (b) and BMI (c) hypoxic group vs. normoxic group.

(SMD = -0.14, 95% CI = -0.49, 0.21, $p = .42$; $I^2 = 28\%$, $p = .22$) or hypoxic (SMD = -0.20, 95% CI = -0.66, 0.26, $p = .40$; $I^2 = 55\%$, $p = .04$) conditions (Fig. 5c).

After training under hypoxic conditions, there was a trend towards lower blood glucose levels (SMD = -0.39, 95% CI = -0.79, 0.02, $p = .06$; $I^2 = 48\%$, $p = .06$), while no change were observed in normoxia (SMD = -0.38, 95% CI = -0.97, 0.21, $p = .21$; $I^2 = 77\%$, $p < .001$) (Fig. 5d).

DBP was lowered after training in normoxia (MD = -2.99, 95% CI = -5.52, -0.47, $p = .02$; $I^2 = 58\%$, $p = .03$) and hypoxia (MD = -2.67, 95% CI = -3.59, -1.76, $p < .01$; $I^2 = 0\%$, $p = .61$), yet with no significant differences between conditions (Fig. 6a). Similarly, SBP was similarly decreased after training in normoxia (MD = -6.08, 95% CI = -11.19, -0.97, $p = .02$; $I^2 = 76\%$, $p < .001$) and hypoxia (MD = -4.96, 95% CI = -7.90, -2.02, $p < .01$; $I^2 = 49\%$, $p = .07$) (Fig. 6b).

3.4. Sub-analysis

When a statistical comparison between individuals with overweight and obesity was performed, no significant differences were observed between conditions on fat mass (SMD = -0.01, 95% CI = -0.25,

0.23, $p = .29$; $I^2 = 0\%$, $p = .96$), body mass (MD = 0.01, 95% CI = -0.20, 0.23, $p = .86$; $I^2 = 0\%$, $p = 1.0$) and muscle mass (MD = 0.83, 95% CI = -0.1, 1.77, $p = .86$; $I^2 = 0\%$, $p = .49$).

4. Discussion

This systematic review with meta-analysis aimed to analyse the effect of HC as a means of further reducing body mass and improving cardiometabolic markers compared to similar training near sea-level. A secondary objective was also to examine if this intervention is more effective in overweight versus obese individuals. The major findings indicate that HC significantly reduces body mass, fat mass, W/H ratio, waist circumference and improve several cardiometabolic markers (triglycerides, LDL, HDL, SBP and DBP). However, only the magnitude of triglycerides decrease and muscle mass growth were greater in hypoxic than in normoxic condition. Moreover, the sub-analysis found no significant interaction for initial BMI level indicating that HC effects were similar in overweight and obese individuals.

4.1. Effect of HC on body composition

We observed a significant positive effect on body mass loss for both

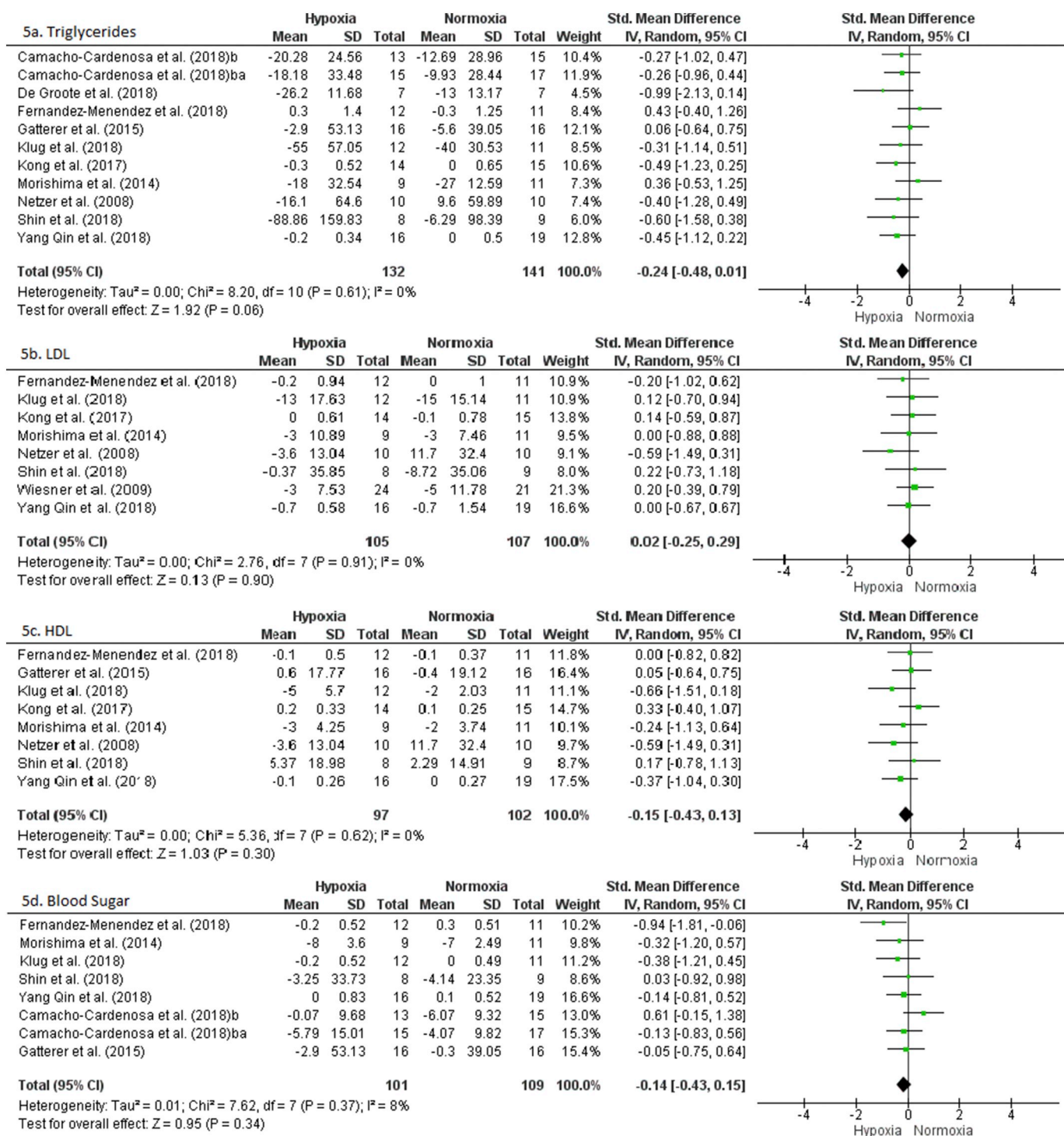


Fig. 5. Total effects of treatment on triglycerides (a), LDL (b), HDL (c) and blood glucose (d) hypoxic group vs. normoxic group.

hypoxic and normoxic conditioning, with also no significant differences between conditions ($MD = 0.39$, 95% CI -1.01 , 1.78). A close inspection of the literature highlights four separate studies (3 with active and 1 with passive HC) reporting significantly larger body mass loss in hypoxia versus normoxia [20,21,23,38], while three other studies using active HC displayed similar body mass losses in the two conditions [19,22,25]. One possible explanation for these discrepant findings may relate to the hypoxic dose during the session and the entire HC program. In general, studies reporting no body mass loss had HC session with shorter duration [28,29] (i.e. less than one hour) and/or had a lower total number of hours of hypoxic exposure during the program

(i.e. 9 [17] to 12 h [18]). Also, HC protocols that increase basal metabolic rate and energy expenditure likely benefit body mass loss in individuals with overweight and obesity [3]. Pending confirmatory research, this metabolic rate increment could result from an optimization of substrate utilization and mitochondrial oxidative capacity via signalling pathways that stimulate GLUT-4 transport [39]. This supports a view that prescribing HC with an appropriate dose may be relevant in individuals with overweight and obesity to lose more body mass.

Our meta-analysis showed a trend towards higher muscle mass gain in hypoxia versus normoxia ($Z = 1.74$; $p = .08$). Increased muscle growth is a positive adaptation in individuals with obesity who are

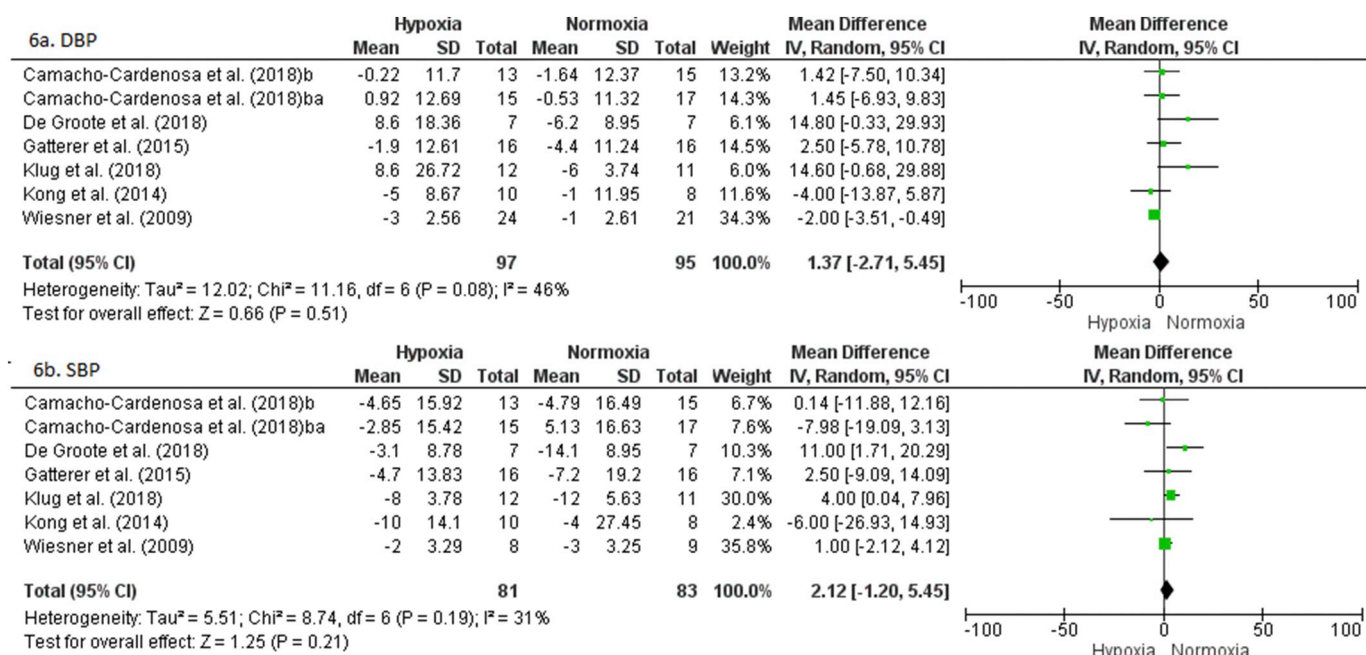


Fig. 6. Total effects of treatment on DBP (a) and SBP (b) hypoxic group vs. normoxic group.

commonly suffering from sarcopenia [40]. Regarding muscle mass, we report three separate studies displaying significant increases (2–4%) following active HC [10,16,28] or decreases (–1.5%) following passive [38] HC, while no changes occurred in normoxic condition. Another study also showed significant improvements in both normoxic and hypoxic conditions [22]. Disparate findings between studies could be due to alterations in the structure of the HC program (e.g., active or passive, intensity, FiO_2) performed. Specifically, passive HC seems to reduce muscle mass in the same terms as normoxia, while active HC would produce greater increases of muscle mass. Regarding active HC, only one study reported that four weeks of low intensity HC (65% of $\text{VO}_{2\text{max}}$) can improve fat-free mass (+2%) in hypoxia without changes in normoxic condition [16]. The most common type of exercise performed to increase muscle mass is resistance training. Reportedly, resistance training under hypoxia may lead to larger muscle gains than the same training in normoxia [41], primarily due to increases in metabolic stress and anaerobic glycolysis [41–43]. Other proposed mechanism involved in muscle growth are cellular swelling from metabolite accumulation in the cells and hypoxia-mediated increases in motor unit recruitment [41–44]. It is therefore possible that HIT may produce larger structural muscle adaptations by stimulating glucose-dependent metabolic pathways and consequently an acidic environment [45]. In fact, two of the studies with improved muscle mass [10,28] applied a HIT training of 12 weeks of duration at 17.2% FiO_2 increasing muscle mass by 2–4%. Taken as a whole, active HC at high-intensity may provide a small added benefit for muscular development over the same training performed in normoxia. An advantage of HC programs over normoxic training in patients who suffer from orthopaedic limitations is that this treatment may participate to reduce the risk of orthopaedic injury while also enhancing metabolic efficiency [28].

Previous studies reported that passive [38] or active [10,21,23,28] HC could significantly decrease fat mass. Using a meta-analytical analysis, our results showed a significant fat mass decrease in participants who trained under hypoxia but not in normoxia. This suggests a positive effect of active HC with a reduction of fat mass, which could possibly be attributed to higher post-exercise lipid oxidation [28]. In addition, a recent study [28] has shown an increase in fat oxidation at rest after 12 weeks of HIT in hypoxia, whereas an opposite trend was reported after the same training in normoxia. Thus, HIT in hypoxia likely

increases lipids metabolism at rest. In addition, BMI has been significantly reduced after passive [38] or active [10,21] HC programs. However, our results indicate that training with oxygen deprivation was not more effective than in normoxia to reduce fat mass or BMI. While BMI is frequently used to estimate the prevalence of obesity [46] it does not account for variation in body fat distribution and abdominal fat mass [47]. Arguably, measurements of waist circumference and W/H ratio would be more appropriate measures of both intra-abdominal fat mass and total fat [48].

We report the original observation that waist circumference and W/H ratio decreased significantly after HC and normoxia. Interestingly, two separate studies [16,23] with decreases in waist circumference in hypoxia but not in normoxic condition, implemented a low intensity aerobic training (60 min on a treadmill at 65% of $\text{VO}_{2\text{max}}$ at 14.5–15% of FiO_2). Another study [10] also demonstrated a significant decrease in waist circumference after training for 12 weeks using 30 s “all out” efforts performed at $\text{FiO}_2 = 17.2\%$. These findings, suggest a positive effect of combined hypoxia with HIT for reducing abdominal fat, which could be attributed to higher post-exercise lipid oxidation [28]. However, a rapid plateau in the aforementioned body composition adaptations can occur if the program fails to apply an unaltered stimulus (i.e., hypoxic level, exercise intensity/duration) [19]. Such scenario has previously been reported by both Camacho-Cardenosa et al. [10] and Gatterer et al. [19] who found similar improvements in body composition after completing either half (6 weeks and 3 months, respectively) or the entire (12 weeks and 8 months, respectively) conditioning program. Therefore, as for athletes, effective management of an HC program undoubtedly requires periodization strategies and readjusting regularly the training stimulus during the intervention.

In relation to the principle of initial value, a previous study [49] reported that the magnitude of body mass loss could largely be due to initial body composition. In support, those individuals with greater initial body fat and BMI values also were those who lost more body mass and fat after a combined exercise/diet intervention compared with those with a lower BMI [49]. In our review, overweight participants on average lost less body mass than individuals with obesity (–0.8 and –3.2 kg respectively) after HC. Similar results were obtained after low intensity HC comparing overweight vs normo-weight individuals [23]. However, the differences across the two BMI groups (individuals with obesity vs with overweight) observed in the present

review were small (no statistical differences). These results are in accordance with a previous review showing that initial BMI was not related to body mass loss during an intervention [50]. In this way, HC appears equally effective to body mass loss for individuals with overweight and obesity.

4.2. Effect of HC on cardiometabolic markers

Our study showed a higher no significant decrease of triglycerides after training under hypoxic than normoxic condition ($p = .06$). Three studies [10,23,38] found a larger decrease in this variable after HC than in normoxia. Interesting, the higher decrease was observed in Camacho-Cardeñosa's study [10]: i) -24.5% after 12 weeks of HIT in hypoxia using either 30-s “all out” efforts with 3 min of active recovery and ii) -27.5% after 12 weeks of training using 3 min at 90% of peak power with 3 min of active recovery both at 17.2% of FiO_2 . The interplay of mechanisms of HC which may improve some cardiometabolic markers such as triglycerides and cholesterol levels are still being elucidated. However, exercise protocols increasing post-exercise lipid oxidation also seem to decrease triglyceride levels [51]. Similarly, the mechanism by which HC reduces triglycerides levels likely include increased lipid oxidation through the transcription coactivator PGC1 α [14], which plays a key role in the regulation of muscle fatty acid oxidation [52]. Therefore, the use of high-intensity HC represents an effective method to increase post-exercise lipid oxidation and to reduce triglycerides values. In order to obtain a positive HC-related effects on lipid-related metabolic markers, interventions lasting at least 4 weeks would be required [5]. Our novel findings support this suggestion since the previous studies which demonstrated a significant improvement in triglycerides ranged between 4 [23,38] and 12 weeks [10,28] in duration.

Regarding cholesterol variables, our analysis showed significant decrease in LDL values after hypoxia and normoxia with no difference between conditions. In addition, our meta-analysis showed no significant increases in HDL after training in either normoxic or hypoxic conditions. Previous studies confirm that the increases in energy expenditure associated with aerobic intensity have been shown to positively influence in LDL and HDL [53]. In fact, only one low intensity HC study [25] reported a decrease in LDL, but similar changes were also observed after normoxic conditions. In addition, it has been reported that intense exercise is required to elicit reductions in LDL [54]. However, none of the HC studies using a high-intensity training program led to an improvement in HDL and LDL. Therefore, we conclude that active and passive HC may not promote any additional effect than the same normoxic program on both HDL and LDL levels.

Morishima et al. [18] found a significant decrease in glucose concentration after hypoxic (-8%) and normoxic (-7%) active training (60 min cycling at 55% of the maximal oxygen uptake at 15% of FiO_2). Although, no other study found a significant decrease in blood glucose after HC, our meta-analysis reports a trend towards lower glucose concentrations under hypoxic ($p = .06$) but not normoxic environments. These findings are in accordance with previous studies that reported a reduction of blood glucose [55] after passive or active HC in rats, suggesting that insulin signalling and glucose may have been up-regulated following HC [9]. Thus, compared to normoxia, HC may improve glycaemic control in individuals with overweight and obesity [9].

Regarding blood pressure, we report similar decreases in both SBP and DBP for hypoxic and normoxic conditioning. Previous studies applying active HC have shown significant improvements in SBP compared with active normoxic condition [21]. Kong et al. [21] found a significant decrease in SBP (7.6%) after 4 weeks of aerobic and strength training in hypoxia (14.5–16.4% of FiO_2) but no difference in the normoxic condition. These findings suggest that normoxic and HC have similar effectiveness to reduce blood pressure in individuals with obesity.

We found no differences in cardiometabolic markers after HC

according to the baseline BMI category when expressed as a percentage from baseline. Both, individuals with overweight and with obesity demonstrated similar magnitude of improvement in triglycerides, blood pressure, LDL, HDL and blood glucose after HC and normoxic condition. These findings are previously reported by some studies [56] which found that BMI category does not alter the benefit of body mass loss intervention on cardiometabolic markers if the results are expressed proportionally to the baseline.

4.3. Limitations, future research and practical applications

We acknowledge several limitations of this meta-analysis, which are related in part to the available RCTs and the divergent methodologies employed, including (i) the small number of studies; (ii) the number of studies using passive HC ($n = 1$); (iii) the different intensities, volume and training characteristics procedures applied in active HC studies; (iv) the lack of systematic information about the obesity related symptoms separating individuals with overweight and obesity; (v) the small number of studies using high-intensity training to obtain a more specific picture about the effect of this type of training in hypoxia on body composition and cardiometabolic markers; and (vi) the lack of longer studies to analyse the chronic effect of HC (only two studies had a program duration of > 8 weeks). In addition, we found that the available evidence has high risk of bias primarily due to low quality of available RCTs. Therefore, before a more comprehensive picture is depicted, further studies with a better quality design, analysing the effect of intervention of longer duration (< 8 weeks) and applying high-intensity HC programs are needed.

Previous studies [5] recommend the use of low intensity active HC at the commencement of the training program. During the first step of the treatment, according to the individual's characteristics, it is recommended that the HC program characteristics should include the following features: 4–6 weeks of 2–3 sessions of 60–90 min at 55–65% of VO_2max /60–70% of maximum heart rate at 13–14% of FiO_2 . To avoid a body mass loss plateau it is also necessary to implement a new training stimulus by using other types of training with increased exercise intensity. Specifically, HC should be designed to elicit higher post-exercise lipid oxidation to reduce fat mass and body mass and to increase metabolic stress under hypoxia to maximize muscle growth. Considering the findings from studies [10,28,29] which have demonstrated benefits for HC, high intensity training may produce these two responses. In doing so, HIT sessions should include a duration of 30–60 min per session, using intervals of 8–30 s all-out followed by 3 min of active recovery at 55–65% of peak power performed 3–4 times per week. HIT should be undertaken in moderate level hypoxia ($\text{FiO}_2 = 14\text{--}17.2\%$) though it is not known whether a dose-response relationship exists for the level of hypoxia on body mass loss. Finally, HIT sessions in hypoxia should be included progressively as a second step in the training program and always in combination with other sessions of aerobic training.

5. Conclusion

We conclude using a systematic review with meta-analysis that HC does result in significant reductions in body mass, fat mass, W/H ratio, waist circumference and in several cardiometabolic markers (triglycerides, LDL, HDL, SBP and DBP). However, only the magnitude of reductions in triglycerides and greater muscle growth was greater in hypoxic than in normoxic condition. In addition, the usefulness of HC was similar in individuals with overweight and obesity.

Potential conflicts of interest

None declared.

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