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Original Article

Exercise under hypoxia on glucose tolerance in type 2 diabetes mellitus risk individuals: A systematic review and meta-analysis

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Abstract

Objectives: To analyze the impact of exercise under hypoxic exposure versus normoxic exposure on blood glucose level, insulin level, and insulin sensitivity in people at risk of Type 2 diabetes mellitus (T2DM). **Materials and Methods:** We systematically performed electronic searching on PubMed, Web of Science, ProQuest, and Scopus. Primary studies that met the inclusion criteria were analyzed using Revman 5.4.1. **Results:** Nine randomized controlled trials were included in this meta-analysis. We found that physical exercise under hypoxic exposure had no significant effect on improving blood glucose levels, insulin levels, and insulin sensitivity in the elderly and sedentary people compared to normoxic condition. However, physical exercise during hypoxic exposure had a significant effect on lowering blood glucose levels in overweight/obese individuals (pooled Standardized Mean Difference = 0.29; 95% confidence interval = 0.01–0.57; $P = 0.04$). **Conclusions:** Exercising under hypoxic exposure can be an alternative strategy for reducing blood glucose levels in overweight/obese people. Nevertheless, in other populations at risk of T2DM, exercising in hypoxic conditions gives similar results to normoxic conditions.

Keywords: *Exercise, Glucose tolerance, Hypoxic, Obesity, Type 2 diabetes mellitus*

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by high blood glucose levels that can be increasing mortality rate [1,2]. In 2021, estimated that there will be 537 million individuals (aged 20–79) globally with diabetes [3], with type 2 diabetes mellitus (T2DM) accounting for about 85% of cases [4] and type 1 diabetes mellitus (T1DM) accounting for only 5%–15% of cases [5]. Finding effective therapeutic approaches to treat diabetes is essential. However, concentrating on people with prediabetes or pursuing people at risk of developing DM (before prediabetes manifests) may become concerns to halt the onset of T2DM [6]. Sedentary lifestyle, being elderly, being overweight or obese, and having insulin resistance are some risk factors for T2DM [6,7]. Intriguingly, the prevalence of DM is lower at high altitudes compared to sea level [8]. In comparison to lowlanders, highlanders are known to have lower fasting blood glucose levels and improved glucose tolerance [9].

Altitudes are environments between 1500 and 5500 m (5000 and 18,000 feet) above the sea level [10]. Significant physiological changes will be induced by both short- and long-term exposure to an altitude environment [11]. The principal causes of these physiological changes are low atmospheric pressure and hypoxia, which result in reduced PO_2 levels [9]. The application of hypoxic exposure as a simulation of altitude to DM and those at risk for T2DM has been the focus of numerous studies in recent years. Hypoxic conditions are established artificially as a simulation of altitude by varying the barometric pressure (hypobaric hypoxic) or the percentage of fraction of inspired oxygen/F_iO_2 in the room or chamber (normobaric hypoxic) [11].

Physical exercise is known to reduce insulin resistance, since muscular contractions enhance membrane permeability, and allow glucose to enter cells [12]. Physical exercise at high altitudes will cause physiological adaptation responses that are more rapid and robust than at sea level, since hypoxic conditions will induce physiological stress similar to that of physical exercise and cause various physiological changes (acclimatization) [13]. Physical exercise at high altitude is known to promote glucose uptake by skeletal

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muscles through an insulin-independent mechanism, hence promoting the process of lowering blood glucose levels [10,14]. According to a recent narrative review, certain studies that examined the effects of hypoxia exposure on glucose metabolism and health status in individuals at risk for T2DM demonstrated advantages over normoxic training. Nonetheless, some other studies exhibited no significant difference [6]. Therefore, we aim to conduct a meta-analysis assessing the benefits of physical exercise under hypoxic exposure versus normoxic condition on glucose tolerance in people at risk of T2DM.

Materials and methods

Searching and selection strategies

This review article followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered in the International Prospective Register of Systematic Review (CRD42022362028). We performed an electronic database searching on PubMed, Web of Sciences, Proquest, and Scopus for articles up to September 2022. Our study was restricted to randomized controlled trials (RCTs) written in English and published since 2001. Articles other than RCTs, duplicated studies, incomplete data, and articles without full-text were excluded. MeSH terms, Boolean operators, asterisk (*), and automated tools offered by each database were all included in the search terms utilized [Table 1].

Inclusion and exclusion criteria

The previously determined eligibility criteria before conducting this systematic review were studies involving individuals at risk of T2DM, which fulfil one of the following criteria: body mass index (BMI) >25 kg/m^2, elderly (>45 years old), or physically inactive/sedentary (exercise <3 times/week). In addition, to ensure that the subjects were able to complete the exercise, studies involving subjects with good exercise tolerance were included, while studies involving subjects with cardiometabolic disease were excluded. Studies comparing physical exercise in altitude simulation performed under a hypoxic exposure to exercise conducted in a normoxic environment with any of the following outcomes: Blood glucose levels, insulin levels, or insulin sensitivity were included in this meta-analysis. Studies those published prior to 2001, not written in English, presenting incomplete data, not available in full-text and duplicates were excluded in this meta-analysis.

Data extraction

Data extraction was carried out by collecting the data and describing study characteristics (i.e., author, year of publication), sample characteristics (i.e., subject criteria used, age, and BMI), intervention characteristics (i.e., the dose of physical exercise and the dose of exposure to hypoxic/altitude simulation), and the outcomes (mean ± SD) from blood glucose levels, insulin levels, and insulin sensitivity [Table 2].

Assessment of bias and quality

Risk-of-bias tool for randomized trials (RoB 2) from Cochrane was used to analyze research bias in the RCT study design as a critical review to ensure the quality of the selected primary study articles. On this scale, five domains contain questions that covering randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result [15]. Only when at least ten studies have been included in the meta-analysis should tests for funnel plot asymmetry be applied [16]. Two reviewers (HSNR and AA) performed the searching, data extraction, and quality assessment. Any disagreement was solved by negotiation or a consensus meeting with the other two investigators (BP and CDKW).

Data analysis

A heterogeneity test was conducted to determine the analysis model. We performed fixed effect model for studies with low heterogeneity (I^2 < 50%), while random effect model was used for studies with high heterogeneity (I^2 > 50%) [17,18]. The study will examine the intervention's effects on blood glucose levels, insulin levels, and insulin sensitivity between hypoxic and normoxic group. Pre- and post-test (on hypoxic and normoxic groups) and sub-group analysis was also carried out regarding exercise intensity (moderate and high intensity), training load (constant and progressive), and study duration (4 weeks and >4 weeks of intervention) to determine the effect on each group. In addition, a sensitivity analysis was carried out by eliminating the study with higher risk of bias [18]. Pooled standardized mean difference (SMD) was used to compare the effect of the exercise, with the outcomes were also presented in forest plot. Pooled MD is not suitable for our case since pooled SMD is used when multiple studies utilize various instruments or units to measure the same outcome [19]. The effect size of this study is interpreted where the effect size is considered small = 0.2, moderate = 0.5, and large = 0.8 [20]. The statistical power will be calculated using the meta power calculator (available for free on https://jtiebel.

Table 1: Concept and keywords

Concept	Keywords
Related to hypoxic exposure/ altitude	(Hypoxi* OR Normoxi* OR Hypobari* OR Normobari* OR altitude OR "high altitude" OR "low oxygen" OR "decreased oxygen" OR "oxygen deficienc*") NOT (Apne* OR pregnanc* OR Obstructive)
Related to glucose tolerance	Diabetes OR Diabetic OR hyperglycemi* OR prediabet* OR "impaired glucose toleran*" OR "impaired fasting glucose" OR dysglycemia OR "blood glucose" OR "glucose leve*" OR "glucose toleran*" OR "glucose homeo*" OR "glucose metabolism" OR "glycemic index" OR "glycemic control" OR "insulin level" OR "insulin sensitivit*" OR "HOMA*" OR "insulin resistan*" OR sedentary OR overweight OR obes* OR elderly OR older
Related to physical exercise	"Physical Activit*" OR "Physical Exercis*" OR Exercis* OR Training OR "Physical Fitness"

Table 2: Characteristics of the included studies

Author (year)	Country	Study design	Subject	Age	BMI	Sample size		Intervention		
						HX	NX	Exercise type (intensity)	Frequency - duration	F_iO_2
Wiesner *et al*. (2010) [22]	Germany	RCT-single blind	Overweight - obesity, sedentary lifestyle	42±7.1	30.2±3.6	24	21	Treadmill (60 min/65% HRmax)	3 days/ weeks–4 weeks	F_iO_2: 15% (~2.740 m)
Morishima *et al*. (2014) [28]	Japan	RCT	Overweight man, sedentary lifestyle	33±2	25.6±0.8	9	11	Ergocycling (60 min/55% VO_2 max)	3 days/ weeks–4 weeks	F_iO_2: 15% (~2.500 m)
Gatterer *et al*. (2015) [23]	Austria	RCT-single blind	Obesity	52.4±7.9	36.3±40	16	16	Ergocycling/treadmill/cross training (90 min/65%–70% HRmax)	2 days/ weeks–8 months	F_iO_2: 14% (~3.500 m)
Camacho-Cardenosa *et al*. (2018) [27]	Spain	RCT-double blind	Overweight - obesity	INT: 43.14±7.67 IHT: 44.43±7.18	INT: 29.59±5.25 IHT: 30.03±6.37	IT: 13	IT: 13	HIIT: Ergocycling 3 min (90% Wmax) - followed by 3 min active recovery (55%–65% Wmax)	Progressive load: 24 min at first meeting, increased to 42 min at weeks 9–12	3 days/ weeks–12 weeks	F_iO_2: 17.2% (~1.500 m)
				RSN: 40.05±8.66 RSH: 37.40±10.3	RSN: 28.74±4.77 RSH: 27.71±4.55	RS: 18	RS: 15	Repeated-sprint: 30 s all-out (130% Wmax) followed by 3 min active recovery			
Shin *et al*. (2018) [29]	Japan	RCT	Normal - overweight men	HO: 445.6±20.9 NO: 46±20.5	HO: 26.8±2.3 NO: 27±3	OW: 8	OW: 9	Treadmill (50 min/60% HRmax)	3 days/ weeks–4 weeks	F_iO_2: 15.4% (~2.500 m)
				HN: 28.6±15.6 NN: 27.8±13	HN: 21.5±1.9 NN: 21.1±2	Normoxic: 12	Normoxic: 12			
Chobanyan-Jürgens *et al*. (2019) [24]	Germany	RCT-single blind	Elderly (55–75 years old), sedentary lifestyle	HX: 60.4±5.1 NX: 63.8±5.8	HX: 28.6±3 NX: 28.3±1.9	12	13	Ergocycling (30 min/60% VO_2 max)	Progressive Load: 40 min/70% VO_2 Max at 5–8 weeks	3 days/ weeks–8 weeks	F_iO_2: 15% (~2.750 m)
Chacaroun *et al*. (2020) [25]	France	RCT-single blind	Overweight/obesity, sedentary lifestyle	54±11	31.5±2.8	12	11	Ergocycling (45 min/75% of HRmax)		3 days/ weeks–8 weeks	F_iO_2: 13% (~3.700 m)
Jung *et al*. (2020) [30]	Korea	RCT	Obesity woman (34–60 years old)	47.5±7.5	Control: 25.2±2 NX: 25.1±3.3 HX: 27.1±4.3	12	10	Pilates (50–2 min/type - 25 types)		3 days/ weeks–12 weeks	F_iO_2: 14.5% (~3.000 m)
Kong *et al*. (2022) [26]	China	RCT-single blind	Sedentary woman	21.9±2.8	23±3.7	15	16	Ergocycling-interval sprint (80 repetition-6 s all out-9 s recovery)	Initial load: 1 kg–increase 0.5 kg until each participant reaches 5% body mass after 2 training sessions	3 days/ weeks–4 weeks	F_iO_2: 15% (~2.500 m)

HIIT: High-intensity interval training, INT: HIIT in normoxic, IHT: HIIT in hypoxic, RSN: Repeated sprint in normoxic, RSH: Repeated sprint in hypoxic, HO: Hypoxic-obesity, HN: Hypoxic-normal weight, NO: Normoxic obesity, NN: Normoxic normal, OW: Overweight, HX: Hypoxic, NX: Normoxic, RCT: Randomized controlled trial, BMI: Body mass index

shinyapps.io/MetaPowerCalculator/). A study is regarded adequately powered if it has a statistical power of 0.8 at a significance level of 0.05 [21].

Results

Searching and selection strategies

Our literature search yielded 4.257 studies from four selected databases. These studies were then filtered using automatic tools or filters that available in the respective databases, such as Publication year, document type (Article), language, and subject area (n = 2.176). The duplication check was carried out using the Mendeley desktop application. After deleting the duplicates (n = 709), the remaining 1.467 studies were quickly filtered by reading the titles and abstracts. After screened each full-text according to the previously formulated inclusion and exclusion criteria, finally, we had eight studies and put additional one study from Google Scholar as gray literature. The total study used as the primary study in this research was nine studies. This selection process is described in the PRISMA Flow 2020 diagram [Figure 1].

Assessment of bias and quality

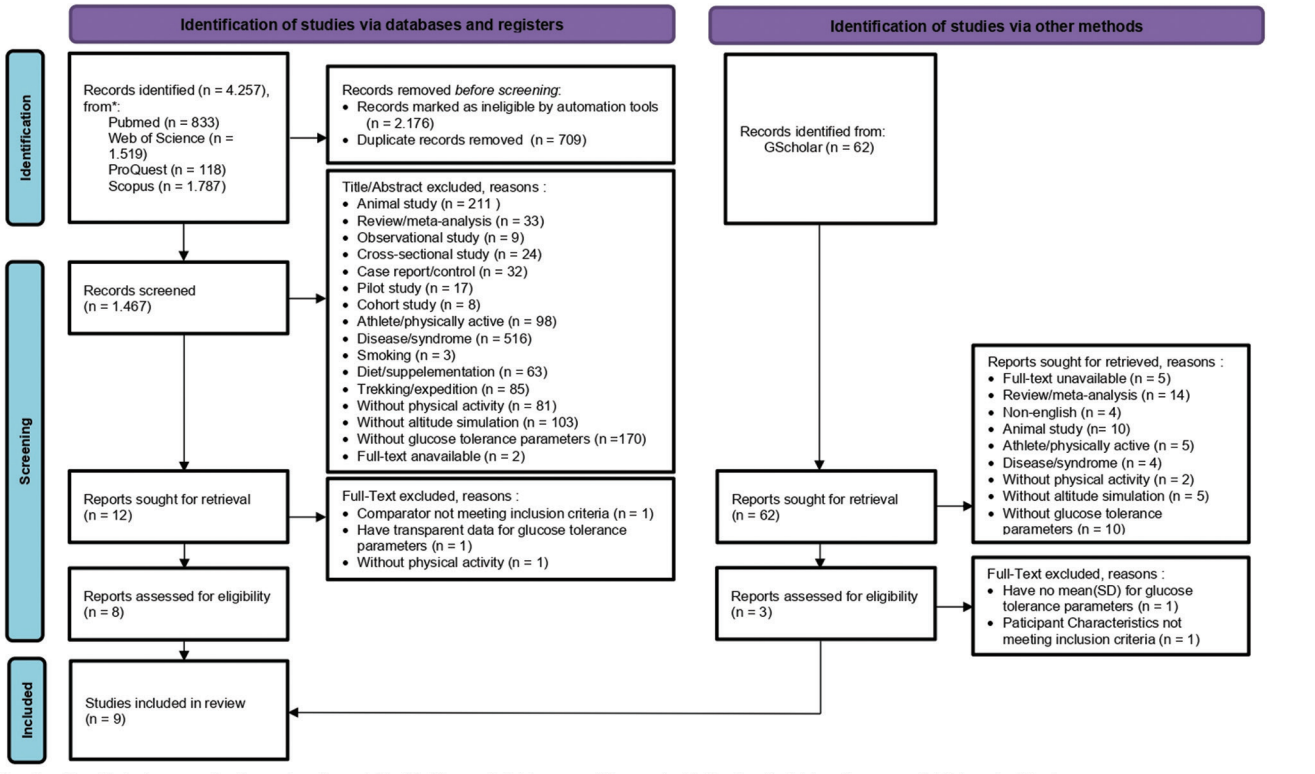
The results of bias analysis using RoB 2 on nine included studies showed that three studies had low risk and six studies had some concern of bias [Figure 2]. Sensitivity analysis was carried out by eliminating the study with higher of bias one by one and the results showed that there were no significant changes.

Data extraction

The overall study characteristics are summarized in Table 2. The included RCTs consisted of five studies using the single-blinding method [22-26], one study with double-blinding [27], and three studies in which the blinding methods were not described [28-30]. The total subjects from all nine studies were 274 people with either overweight obesity, elderly, or having sedentary activity [22-30]. The intervention given to all selected studies was a combination of physical exercise and exposure to hypoxic condition as a simulation of altitude by adjusting F_iO_2 levels.

Analysis of the effect of physical exercise under hypoxic exposure on blood glucose levels

The effect of physical exercise under hypoxic and normoxic conditions on lowering blood glucose levels in adults at risk for diabetes was compared from seven research [Supplementary Table 1]. In a fixed-effect model, the findings of analysis revealed no significant difference between the two groups, as indicated by pooled SMD = 0.10 (95% confidence interval [CI] = −0.15–0.36; P = 0.43) [Figure 3]. In order to conduct a more in-depth analysis, the effect of lowering blood glucose levels in individuals at risk for diabetes was further examined using the pre- and post-test model under hypoxic and normoxic conditions. However, the results of the effect analysis also showed that there was no significant difference between pre- and post-test analyses in both hypoxic (pooled SMD = 0.25; 95% CI = −0.01–0.51;



*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).
**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71
For more information, visit: http://www.prisma-statement.org/

Figure 1: Selection study using preferred reporting items for systematic reviews and meta-analyses flow 2020

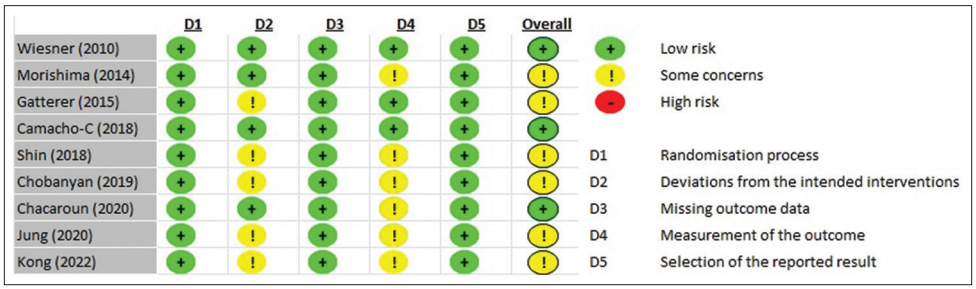


Figure 2: Risk-of-bias tool for randomized trials for bias assessment

P = 0.06) and normoxic condition (pooled SMD = 0.30; 95% CI = −0.20–0.80; P = 0.25) [Figure 4]. In addition, subgroup analyses were conducted regarding the dose of exercise, which included exercise intensity, training load, and project duration. However, all analyses also revealed no effect.

After including overweight-obese population only by eliminating one study with a BMI <25 kg/m^2 (normal weight) [26], different results were found [Figure 4]. Using the same model as previous by comparing the results of the pre- and post-test in the physical exercise group under hypoxic exposure, the results showed that physical exercise under hypoxic exposure had a low significant effect on reducing blood glucose levels compared to normoxic condition, as indicated by the pooled SMD value of 0.29 (CI = 0.01–0.57; P = 0.04) with the statistical power shows a value of 0.3124. The statistical with metapower calculator indicates the actual effect size derived when heterogeneity is considered. SMD can be translated back into a scale that is more familiar to doctors to make it more therapeutically meaningful, so in this study an experiment was carried out to convert the SMD value into natural units by choosing the standard deviation obtained from the largest experiment [31], which is 14.39. The overall mean difference was a reduction of fasting blood glucose by exercise under hypoxic of 0.29 (95% CI, 0.01–0.57) more than the reduction from exercise under normoxic. This is equivalent to a reduction in hypoxic exposure of 4.17 mg/dL. In several analyses related to blood glucose levels, one study carried out measurements twice (in the 3rd and 8th months) [23]. Furthermore, one study was carried out by two types of exercise (HIIT and Repeated Sprint) [27], so these two studies were mentioned repeatedly.

Analysis of the effect of physical exercise under hypoxic exposure on insulin levels

Five studies have evaluated the effect of elevating insulin levels in people at risk of T2DM by comparing the effects of exercise under hypoxic and normoxic exposure [Supplementary Table 2]. The findings of the heterogeneity test showed that this study had substantial variance (heterogeneous) as indicated by I^2 = 91%, thus the effect analysis was then carried out using random effect. The effect analysis results showed no significant effect between the two groups, as indicated by P = 0.60. A further investigation was also carried out about the effect of elevating insulin levels in individuals at risk of T2DM utilizing the pre- and post-test model under exposure to hypoxic and normoxic. The results of the effect analysis showed that there was no significant effect from the two [Figure 5].

Analysis of the effect of physical exercise under hypoxic exposure on insulin sensitivity

Five studies have investigated the effect of improving insulin sensitivity in people at risk of T2DM by comparing the effects of exercise under hypoxic and normoxic exposure [Supplementary Table 3]. The findings of the heterogeneity test showed that this study had high heterogeneity, as indicated by I^2 = 77%, thus we performed a random effect model. The effect analysis results showed no significant effect between the two groups, as demonstrated by P = 0.53 (CI = −01.01–0.52). An evaluation was also carried out about the effect of improving insulin sensitivity in people at risk of T2DM with the pre-and post-test model under exposure to hypoxic and normoxic. The results of the effect study similarly showed that there was no significant influence between the two groups [Figure 6].

Discussion

Several risk factors for T2DM are well known. Among them are being overweight-obese, having a sedentary lifestyle and being old [6]. Being overweight-obese is one of the main modifiable risk factors [32,33]. Nearly 90% of diabetes patients are previously obese [34]. The risk of diabetes and prediabetes increases with a significant BMI increasing in overweight-obese subjects [32]. An increase in the number of fatty acids, glycerol, hormones, pro-inflammatory cytokines, and other factors will cause disturbances in pancreatic β-cells, insulin sensitivity, and ultimately cause failure to control blood glucose levels [7,32]. Another risk is sedentary lifestyle, it defined as a sedentary physical activity by doing physical exercises <3 days/week which can cause progressive loss of β-cells, thereby reducing insulin sensitivity and impaired glucose tolerance [7]. The last is aging. A clear relationship has been found between the prevalence of diabetes and increasing age in individuals, as evidenced by the results of studies where a risk of <2% (16–34 years), 5.1% (35–54 years), 14.3% (55–74 years), and 16.5% (>75 years) [32]. Aging will increase chronic inflammation and disruption of lipid metabolism due to the accumulation of body fat, which leads to insulin resistance [7].

The incidence of T2DM has been found to have an inverse comparison with physical exercise [35]. It because the contractile activity of the muscles during exercise can induce signals to stimulate glucose uptake by insulin independent, it can also provide a synergistic effect when combined with insulin action on the disposal or utilization of blood

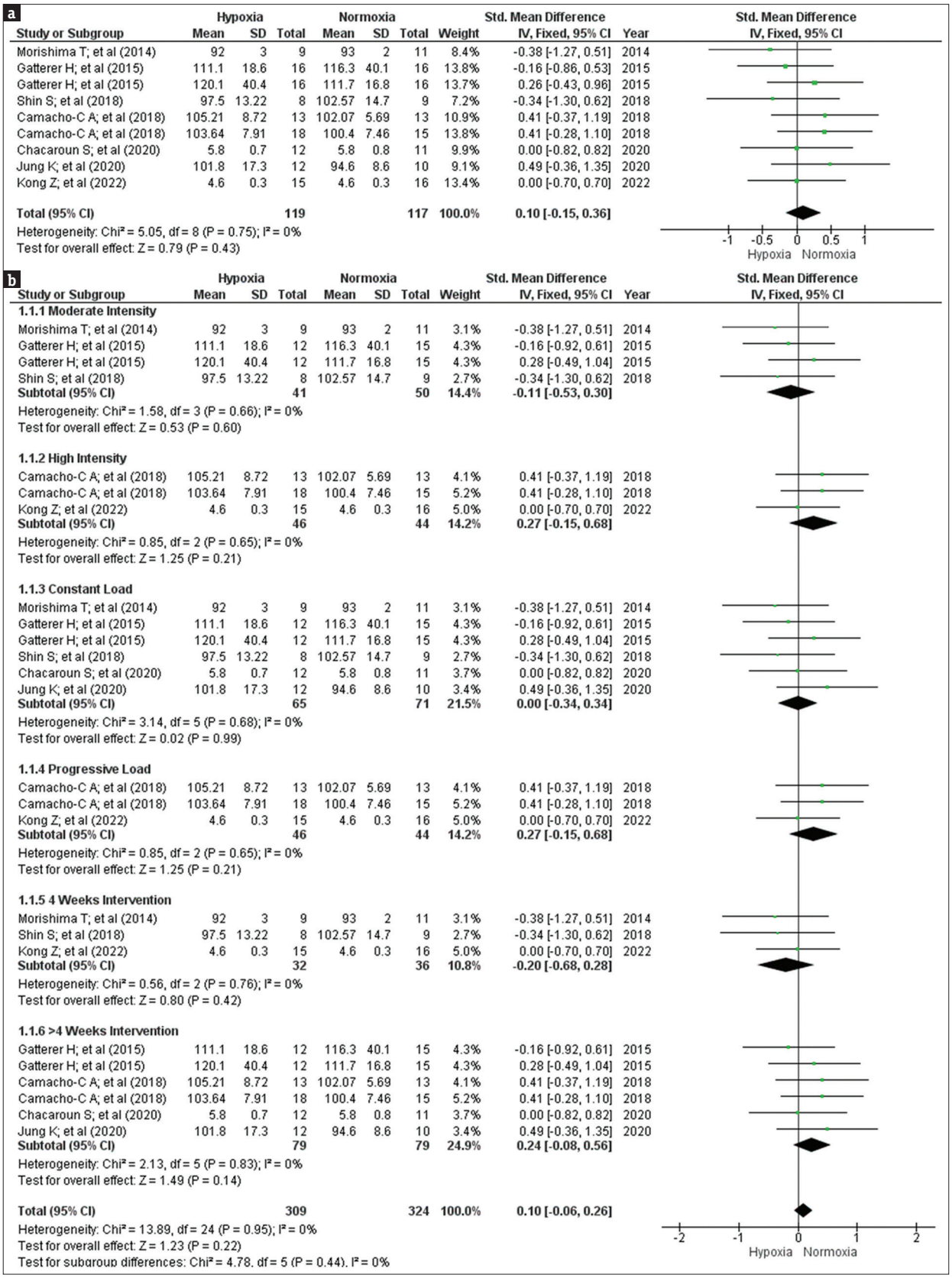


Figure 3: Forest plot of blood glucose levels analysis comparing exercise under hypoxia exposure versus normoxia. (a). Overall data (b). Subgroup analysis: Moderate intensity, high intenstity, constant load, progressive load, 4 weeks intervention, >4 weeks interventions

glucose [36]. Performing physical exercises at altitude have been widely used worldwide since the 1968 Olympics in Mexico and are famously done to increase endurance [13]. Physical training at altitude causes a physiological

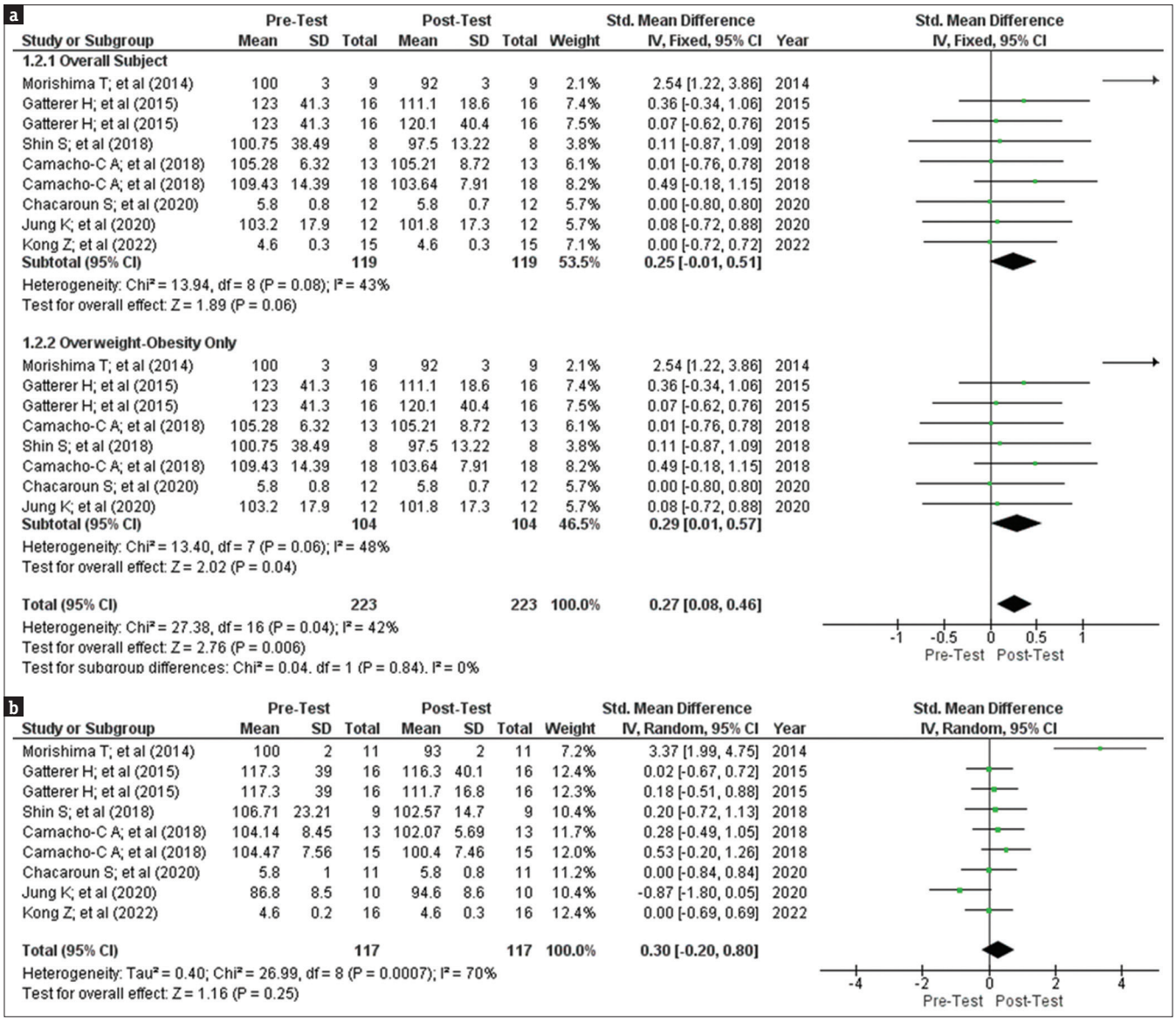


Figure 4: Forest plot of blood glucose levels analysis comparing pretest versus posttest of exercise under hypoxia exposure (a) All subject, (b) overweight-obese individuals only, (c) Analysis comparing pretest versus posttest of exercise under normoxia exposure

adaptation response faster and more significantly than at low altitude [13,37]. Exercising at altitude is also known to increase glucose uptake through an insulin-independent mechanism to the skeletal muscles that will further encourage the process of reducing blood glucose levels because both physical exercise and being in a hypoxic environment facilitate this [10,38].

To our knowledge, this is the first study that systematically investigates the effect of physical exercise under hypoxic compared to normoxic condition on glucose in people at risk of T2DM. The present meta-analysis revealed that physical exercise under exposure to hypoxia did not give a significant effect on improving blood glucose levels, insulin levels, and insulin sensitivity in elderly and sedentary people. However, physical exercise under exposure hypoxia has a low significant effect on reducing blood glucose levels in subjects with BMI >25 kg/m^2. The reason for the insignificant result was mentioned by possibly due to insufficient dose of intervention (either intensity, amount, or duration) to induce changes significantly [25,26]. Even though high-intensity exercise and hypoxic exposure have been carried out, this may still not be enough to cause a hypoxic condition for the subject [24]. This is because the regulation of the hypoxic environment simulation is carried out by adjusting the F_iO_2 level in the chamber or mask, while the hypoxic response in each individual can vary from one to another [25]. Therefore, compared to giving exposure to hypoxia by adjusting the F_iO_2 level in a mask or chamber, it would be better if a target of SpO_2 = 80% was used for each subject so that hypoxic conditions could be controlled precisely [26]. In addition, the various study characteristics may also affect the results of the analysis. Analysis of the time or duration of the study showed that training within 4 weeks and >4 weeks did not have a significant effect. Even yet, a shorter training regimen

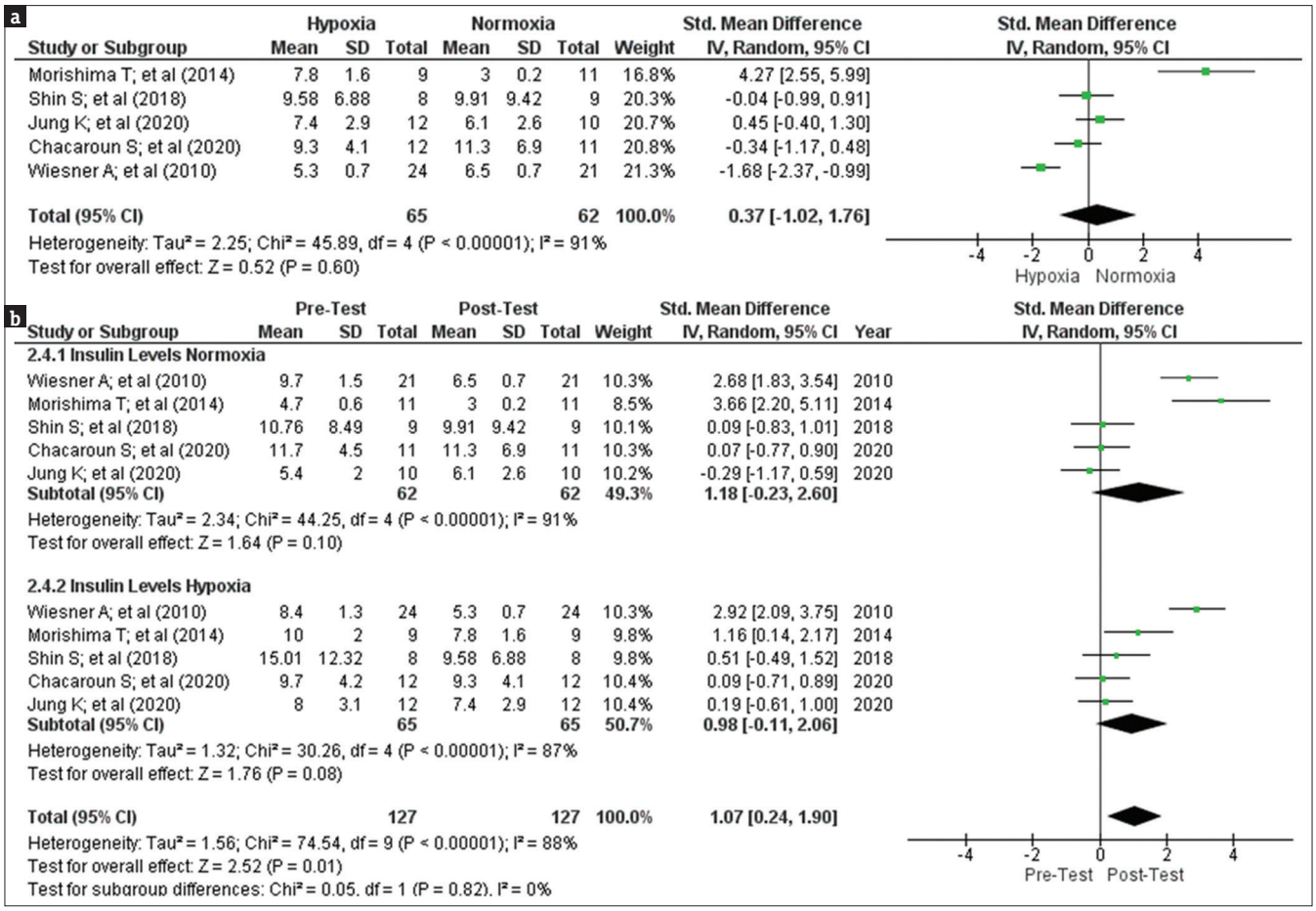


Figure 5: Forest plot of insulin levels analysis. (a) Analysis comparing exercise under hypoxia exposure versus normoxia, (b) Subgroup analysis comparing pre-test versus post-test of exercise under hypoxia and normoxia

might produce better outcomes. Exercises performed in normoxia and hypoxia as well as measurements taken in the 3rd and 8th months showed that the examination results in the 3rd month were better than those in the eighth [23]. This shows that endocrine adaptation has a limit after a specific amount of time, including glucoregulatory hormones and metabolites, thus it is best to avoid using the same intervention or stimulation beyond 3 months [23].

In the analysis of physical exercise under hypoxic exposure on decreasing blood glucose levels by comparing the pre- and post-test groups, different results were found after the subject's BMI criteria were specified to BMI >25 kg/m^2 (overweight-obese) by eliminating 1 study [26]. In general, obesity is associated to hypoxic condition [39]. Several potential reasons that cause hypoxic conditions in obesity, including: (1) Insufficient blood supply to adipose tissue [40]. In obese subjects, a decrease in blood flow to adipose tissue and muscle was found by around 30%–40% compared to nonobese subjects [41]. It is also known that capillary density is 44% lower and vascular endothelial growth factor is 58% lower, which indicates lower PO_2 levels in overweight and obese subjects compared to nonobese subjects [39,40], (2) obese subjects will experience adipose cell hyperplasia and hypertrophy [42]. The adipose tissue will increase while the oxygen diffusion capacity is limited to 150–200 μm only [39] and (3) increased oxygen demand by adipose cells and inflammatory cells [40].

As previously indicated, hypoxia is not always experienced by all subjects exposed to hypoxia because individual reactions differ [25,26]. This complex adaptation of hypoxic tendencies due to changes in oxygen concentrations in adipose tissue that are dependent on body fat may be responsible for the disparities in blood glucose levels between overweight and obese patients [26]. Overweight and obesity, as well as physical activity and exposure to hypoxia, limit oxygen supply. When oxygen supply and demand are imbalanced (need is greater than supply), a progressive transition from aerobic glycolysis to anaerobic glycolysis occurs in the mitochondria [43]. To sustain the current level of ATP production, anaerobic glycolysis will accelerate [44]. Despite producing less ATP than aerobic glycolysis, anaerobic glycolysis occurs 100 times more quickly [45]. This increase in glycolysis will result in a rise in glucose uptake and a subsequent decrease in blood glucose levels [46]. The combination of exposure to a hypoxic environment and exercise in people with obesity would have a good influence by normalizing glucose and lipid metabolism, boosting blood flow, and decreasing inflammation and fibrosis [43].

Based on the effect analysis results, a decrease in blood glucose levels was found. In contrast, insulin levels and

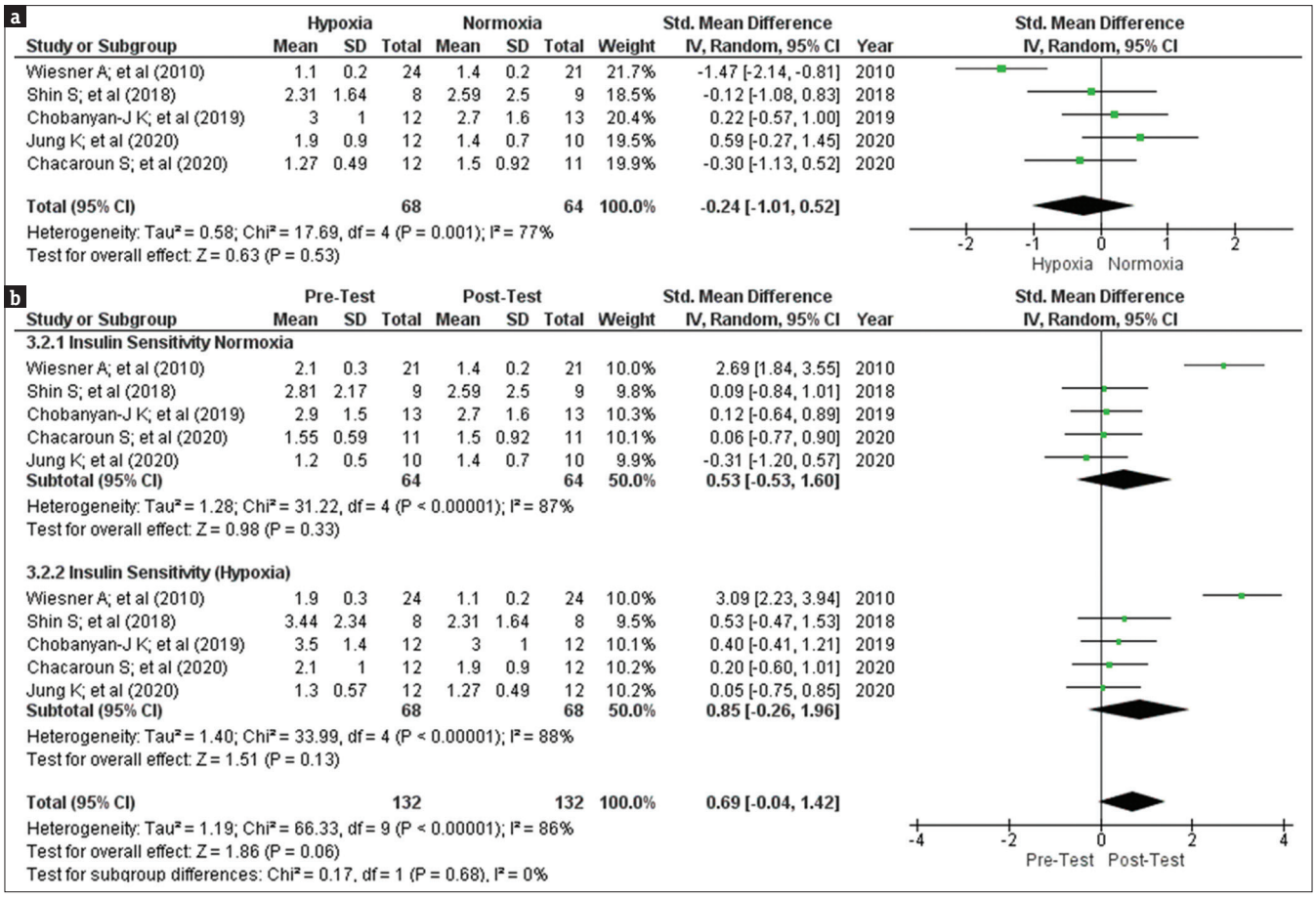


Figure 6: Forest plot of insulin sensitivity analysis. (a) Analysis comparing exercise under hypoxia exposure versus normoxia, (b) Subgroup analysis comparing pre-test versus post-test of exercise under hypoxia and normoxia

sensitivity parameters were not detected to have improved. This is due to hypoxic conditions, stimulating more blood glucose uptake with independent insulin [10,14]. It was previously known that insulin would stimulate GLUT-4 as a glucose co-transporter which causes an increase in glucoregulation so that blood glucose levels can decrease [47,48]. Insulin is also mentioned as anti-GSK3, which will activate glucose synthesis, leading to reduced blood glucose levels [49]. Nonetheless, hypoxic conditions and greater muscular contraction due to exercise can increase the adenosine monophosphate (AMP)/ATP ratio, resulting in the activation of AMPK (AMP-activated protein kinase) [50]. AMPK will then activate AS160 and induce an increase in GLUT-4 translocation, resulting in a decrease in glucose absorption and blood glucose levels [51-53]. It was also discovered that an increase in AMPK would phosphorylate GSK3 and render it inactive [54]. Glycogen synthase kinase-3 (GSK3) is reportedly one of the enzymes that regulate glycogen synthesis (GS) [55]. GSK3 inactivation has been demonstrated to have an anti-diabetic impact by stimulating GS so that glycogenesis increases and blood glucose levels decrease [49]. In addition to enhancing GS, it might also inhibit gluconeogenesis and effectively lowering blood glucose levels in rat models of T2DM [55]. Consequently, it is possible to reduce blood glucose levels without increasing insulin production.

Furthermore, several limitations may cause the results of the analysis of exercise under hypoxic exposure to be insignificant, such as due to the small number of studies that can be analyzed accompanied by a relatively few of subjects, such as in the moderate-intensity exercise subgroup (4 data from 3 studies), exercise with program duration 4 weeks (3 data from 3 studies), training with progressive loads (3 data from 3 studies). In addition, it is fascinating to conduct research in developing countries because the primary studies are carried out in developed countries.

Conclusions

Our meta-analysis found that physical exercise in a hypoxic condition did not significantly improve blood glucose levels, insulin levels, and insulin sensitivity in people at risk of developing T2DM compared to normoxic condition. However, but it had a benefits on reducing blood glucose level in subjects with BMI >25 kg/m^2. To better regulate hypoxic conditioning in each person, the stimulation of hypoxic must be conducted that is more concentrated on employing SpO_2 targets than on modifying F_iO_2 levels in chambers or masks. In order to fully comprehend the range of impacts and physiological pathways, further research is required on the type, amount, and features of exercise and hypoxia.

Data availability statement

All the data generated or analyzed during this study are included in this published article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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SUPPLEMENTARY MATERIAL

Supplementary Table 1: Summary of meta-analysis results on blood glucose levels

Outcome/subgroup	Number of study	Sample size	Statistical method	Effect estimate (pooled SMD with 95% CI and *P*)
Blood glucose levels (hypoxia - normoxia) [23,25-30]	7	236	Fixed effect (I^2)=0%	0.10 (−0.15–0.36; 0.43)
Blood glucose levels (pre- and post-test-hypoxia)	7	238	Fixed effect (I^2=43%	0.25 (−0.01–0.51; 0.06)
Blood glucose levels (pre- and post-test-normoxia)	7	234	Random effect (I^2)=70%	0.30 (−0.20–0.80; 0.25)
Subgroup				
Moderate intensity [23,28,29]	3	91	Fixed effect (I^2)=0%	−0.11 (0.53–0.30; 0.60)
High intensity [26,27]	2	90	Fixed effect (I^2)=0%	0.25 (−0.15–0.68; 0.21)
Constant load [23,25,28-30]	5	136	Fixed effect (I^2)=0%	0.0 (−0.34–0.34; 0.99)
Progressive load [26,27]	2	90	Fixed effect (I^2)=0%	0.25 (−0.15–0.68; 0.21)
4 weeks intervention [26,28,29]	3	68	Random effect (I^2)=0%	−0.20 (−0.68–0.28; 0.42)
>4 weeks intervention [23,25,27,30]	4	158	Fixed effect (I^2)=0%	0.24 (−0.08–0.56; 0.14)
Blood glucose levels (overweight/obesity - hypoxia) [23,25,27-30]	6	208	Fixed effect (I^2)=48%	0.29 (0.01–0.57; 0.04)*

*Significant at $P<0.05$.[18] SMD: Standardized mean difference, CI: Confidence interval

Supplementary Table 2: Summary of meta-analysis results on insulin levels

Outcome/subgroup	Number study	Sample size	Statistical method	Effect estimate (pooled SMD with 95% CI and *P*)
Insulin levels (hypoxia - normoxic) [22,25,28-30]	5	127	Random effect (I^2)=91%	0.37 (−1.02–1.76; *P*=0.60)
Insulin levels (pre- and post-test-hypoxia)	5	130	Random effect (I^2)=87%	0.98 (−0.11–2.06; *P*=0.08)
Insulin levels (pre- and post-test-normoxic)	5	124	Random effect (I^2)=91%	1.18 (−0.23–2.60; *P*=0.10)

SMD: Standardized mean difference, CI: Confdence interval

Supplementary Table 3: Summary of meta-analysis results on insulin sensitivity

Outcome/subgroup	Number of study	Sample size	Statistical method	Effect estimate (pooled SMD with 95% CI and *P*)
Insulin sensitivity (hypoxia - normoxia) [22,24,25,29,30]	5	132	Random effect (I^2)=77%	−0.24 (−01.01–0.52; 0.53)
Insulin sensitivity (pre- and post-test-hypoxia)	5	136	Random effect (I^2)=88%	0.85 (−0.26–1.96; 0.13)
Insulin sensitivity (pre-and post-test-normoxia)	5	128	Random effect (I^2)=87%	0.53 (−0.53–1.60; 0.33)

SMD: Standardized mean difference, CI: Confdence interval