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Review

Does exercise have a protective effect on cognitive function under hypoxia? A systematic review with meta-analysis

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Abstract

Objective: This study aimed to examine (1) the independent effects of hypoxia on cognitive function and (2) the effects of exercise on cognition while under hypoxia.

Methods: Design: Systematic review with meta-analysis. Data sources: PubMed, Scopus, Web of Science, PsychInfo, and SPORTDiscus were searched. Eligibility criteria for selecting studies: randomized controlled trials and nonrandomized controlled studies that investigated the effects of chronic or acute exercise on cognition under hypoxia were considered (Aim 2), as were studies investigating the effects of hypoxia on cognition (Aim 1).

Results: In total, 18 studies met our inclusionary criteria for the systematic review, and 12 studies were meta-analyzed. Exposure to hypoxia impaired attentional ability (standardized mean difference (SMD = −0.4), executive function (SMD = −0.18), and memory function (SMD = −0.26) but not information processing (SMD = 0.27). Aggregated results indicated that performing exercise under a hypoxia setting had a significant effect on cognitive improvement (SMD = 0.3, 95%CI: 0.14 − 0.45, I^2 = 54%, $p < 0.001$). Various characteristics (e.g., age, cognitive task type, exercise type, exercise intensity, training type, and hypoxia level) moderated the effects of hypoxia and exercise on cognitive function.

Conclusions: Exercise during exposure to hypoxia improves cognitive function. This association appears to be moderated by individual and exercise/hypoxia-related characteristics.

Keywords: Cognition; Executive function; Exercise; Hypoxia; Memory

1. Introduction

Cognitive functions are brain-based skills that allow humans to carry out tasks at various levels of difficulty and that are critical in day-to-day life.[1,2] Notably, cognitive performance is possibly affected by environmental cues such as ambient temperature and altitude.[3,4] For instance, increasing altitude and the ensuing severity of hypoxia may attenuate oxygen delivery to the brain tissue. Such exponentially reduced oxygen fraction during inspiration may result in impairment of brain function and cognitive abilities, including executive function, attention, episodic memory, and information processing.[5−7] This occurrence may be detrimental for particular populations, including those in the armed forces, athletes, mountaineers, mountain rescuers, and other high-

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altitude residents who are repeatedly exposed to hypoxic conditions.[8−10]

Findings from several primary studies[11,12] and a previously published review[13] have indicated hypoxia-induced cognitive deficits. Regardless of cognitive task types (i.e., central executive *vs.* nonexecutive tasks) and hypoxic conditions (i.e., hypobaric *vs.* normobaric hypoxia), low partial pressure of oxygen (PaO_2) levels are strongly associated with greater reductions in cognitive function. In contrast, accumulating evidence suggests that hypoxia has no negative effects on cognitive function.[14−17] For instance, an experimental study by Lefferts et al.[9] showed that response accuracy on cognitive tasks was similar in normoxia compared to hypoxia in a mixed sample of young men and women. Sun et al.[18] reported that moderate hypoxia did not alter either reaction time or accuracy in sedentary young adults. Given the conflicting findings in previous studies, along with new publications on this topic, an updated systematic review is needed to evaluate and synthesize the current evidence on the effects of hypoxia on cognition.

Behavioral approaches such as exercise have previously been shown to enhance cognitive function and prevent neurocognitive disorders.[19−22] Notably, the majority of these previous studies investigating the cognitive benefits of exercise were conducted under normoxic conditions. Recent exploratory studies have suggested that moderate exercise has the potential to improve cognitive function during exposure to moderate or severe hypoxia,[3,10,16,23] whereas others have reported that cognitive function may be impaired if exercise occurred under hypoxic conditions.[8,24] In 2019, a narrative review qualitatively examined the combined effects of exercise and hypoxia on cognitive function, suggesting that these effects are determined largely by the interaction of moderators, such as exercise duration and intensity, hypoxia level and duration, and cognitive task type.[25]

Despite this recent narrative review,[25] current data investigating the quantitative effects of hypoxia on cognition and whether exercise modifies these effects are inconsistent, which may be due to differences in methodological and experimental conditions. Given the heterogeneity of these aforementioned results, further studies are required to test the moderator effects of experimental conditions on cognitive function in relation to hypoxia and exercise.[26,27] Therefore, to provide a comprehensive review of the extant research on this topic, the current meta-analysis addresses 2 primary aims. The first aim was to investigate the independent effects of hypoxia on cognitive function. The second aim was to examine the effects of exercise on cognition while under hypoxia. Given these aims, we further performed subgroup analyses to evaluate potential moderators of the direction and magnitude of the effect sizes. The potential moderators included key study characteristics (e.g., hypoxia protocol, exercise protocol, and specific cognitive task), and participant attributes (e.g., sex, age) were selected because they have been shown to affect cognitive function or influence the effects of exercise on cognitive function while under hypoxia.[20,25]

2. Methods

2.1. Protocol and registration

This study protocol was registered with PROSPERO and approved with registration number CRD42019145773.

2.2. Search strategy

To obtain adequate and efficient coverage of relevant literature, we used PubMed, Scopus, Web of Science, PsychInfo, and SPORTDiscus for the literature search. All documents were retrieved from inception to August 2019. Three groups of search terms were combined to locate studies: (1) "exercise" OR "training" OR "sport" OR "physical activity" OR "strength"; (2) "cognition" OR "cognitive function" OR "executive function" OR "cognitive flexibility" OR "cognitive task" OR "neuropsychological test" OR "perception" OR "reaction time" OR "memory" OR "mental" "processing" OR "inhibition"; and (3) "hypoxia" OR "hypobaric" OR "normobaric" OR "high altitude". Reference lists of selected studies were further investigated to avoid missing any relevant article. We performed this systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.3. Eligibility criteria

First, in this review we included only English-language studies published in peer-reviewed journals obtainable in full text. Second, given that this is the first systematic review of this topic, studies that investigated the effects of hypoxia on cognition or experimental studies of randomized controlled trials (RCT) and nonrandomized controlled studies (NRS) that investigated the effects of chronic or acute exercise on cognition under hypoxia were considered (Aim 2). Third, sufficient information (e.g., arterial oxygen saturation and/or altitude) had to be provided so that PaO_2 could be estimated. Fourth, at least 1 outcome measure of cognition had to be reported in order to be extracted for meta-analyses.

2.4. Collection of studies

All records from the searched databases were managed with an EndNote library. This literature-management tool helped to remove record duplications from the various searched databases. Based on the predetermined eligibility criteria, titles and abstracts of the remaining records were independently screened by 2 review authors in order to exclude ineligible studies. If a study met eligibility requirements, it received a full-text article assessment. If any disagreement occurred, a third review author was invited to achieve consensus through discussion.

2.5. Data extraction

We used a customized form for data extraction. Detailed information included the first author of the article and publication year, characteristics of participants (sample size and mean age/age range), study design, normoxia/hypoxia protocol,

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hypoxia-exercise temporality, exercise protocol, the instrument measuring and method of reporting the outcomes, and statistical analyses and results. To obtain pooled effect size of outcomes, we also extracted the following quantitative data: (1) mean and standard deviation (SD) of cognitive function between performing tasks under hypoxia and normoxia at rest and its corresponding sample size (Aim 1); (2) mean and SD of cognitive function between performing tasks under hypoxia during exercise and rest and its corresponding sample size (Aim 2); (3) mean and SD of pre-to-post difference, along with sample size of both experimental and control groups.

2.6. Methodological quality assessment

Two authors used the modified Downs and Black checklist to independently perform methodological quality assessment of both RCTs and non-RCTs.[28] This assessment consisted of 24 items across 4 domains (reporting, external validity, internal validity, and power), and scoring ranged from 0 to 25, with higher scores representing better methodological quality.

2.7. Classification of study aims

The study had 2 specific aims regarding the association between hypoxia and exercise on cognitive function. The first aim was to explore the effects of hypoxia on cognitive function by comparing cognitive performance between 2 groups, with 1 group performing the cognitive task during exposure to hypoxia and the other group completing the cognitive task during normoxia. The second aim was to examine the effects of exercise on cognitive function while under hypoxia by comparing cognitive performance between 2 groups, with 1 group performing the cognitive task and exercise under a hypoxic condition and the other group completing the cognitive task under hypoxia (no exercise).

2.8. Statistical analysis

Comprehensive Meta-Analysis software (Version 3.0; Biostat Inc., Englewood, NJ, USA) was used to calculate effect sizes (standardized mean difference (SMD)) representing the magnitude of the exercise intervention on cognition. SMD was considered as small (0.2−0.49), moderate (0.5−0.79), or large (≥0.8). Considering that the outcomes and unit of cognitive measures varied across the selected studies, the random-effects model was used along with a 95% confidence interval (CI). We used I-squared (I^2) to check heterogeneity, with 25%, 50%, and 75% reflecting small, medium, and large heterogeneity, respectively. Publication bias was assessed by the Egger's test, along with a visual funnel plot.

The heterogeneity of effect sizes (ESs) was assessed by Q statistics. Q statistics evaluate the null hypothesis that all individual ESs compute the same population ES. Statistically significant Q statistics indicate the existence of possible moderator variables.[29] The moderator analyses were conducted to test whether the above-mentioned moderators influenced the overall ESs.[20,25] Meta-regression was used for continuous variables (hypoxia duration, hypoxia level, hypoxia dose (determined by multiplying hypoxia duration by hypoxia level), and exercise duration) to quantify the relationship between the magnitude of the moderator and cognitive function,[30] whereas subgroup analyses were performed based on categorical variables, including sex, age (young adults = 20−24 years *vs.* older adults = 60 years and older), study design (RCT or non-RCT), exercise type, exercise intensity, exercise temporality, training type, and cognitive task type. We computed a mean ES and SE for each group, and then tested whether these mean ESs were significantly different from one another, a model that is analogous to a one-way random effects analysis of variance model.[31]

3. Results

Fig. 1 displays the flow chart for the literature search process. The computerized searches yielded 527 articles. Among the 527 articles, 161 were eliminated due to duplication, and 366 articles were screened. After initial screening of 366 titles and abstracts, 26 full-text articles were reviewed. Among these 26 articles, 8 were ineligible because they did not meet the inclusion criteria or did not provide sufficient data to calculate ESs. Therefore, in total, 18 studies met our inclusion criteria for the systematic review, and 12 studies were eligible for the quantitative meta-analysis.

3.1. Study characteristics

Detailed information on study characteristics is displayed in Table 1. Sample sizes ranged from 8 to 80 participants, with mean age varying from 20 to 92 years old.[32,33] Among the 18 studies, 6 (33%) were RCTs, and 12 (67%) were NRSs. The hypoxia protocol varied, including, for example, hypoxia duration (e.g., ranging from 5 min to 180 min), hypoxia level (e.g., ranging from fraction of inspired oxygen (FIO_2) 10% to 18%), and hypoxia dose (e.g., ranging from 0.73 to 25.38 exercise duration (min) x hypoxia level (%)). The exercise protocol varied by exercise type (e.g., cycle ergometer, a full-body strength-endurance program, multimodal training program, and repeated sprint running), exercise intensity (e.g., light, moderate, and high), exercise duration (e.g., ranging from 5 min to 165 min), exercise temporality (e.g., exercise occurred during hypoxia or both before and during hypoxia), and training type (e.g., acute exercise (also referred to as a single bout of exercise) and chronic exercise (also referred to as a training)). Of the 18 studies, 12 (67%) employed acute exercise interventions and 6 (33%) employed chronic exercise interventions. Cognitive tasks were categorized into information processing, attention-based ability, executive function, memory, and reaction time. A listing of these tasks is presented in Table 2.

3.2. Study quality

Based on the modified Downs and Black checklist, the methodological quality of the included studies was robust (21.31 ± 1.49, mean ± SD), ranging from 19 to 24, with the total maximum score of 25. All studies were within 3 SD of

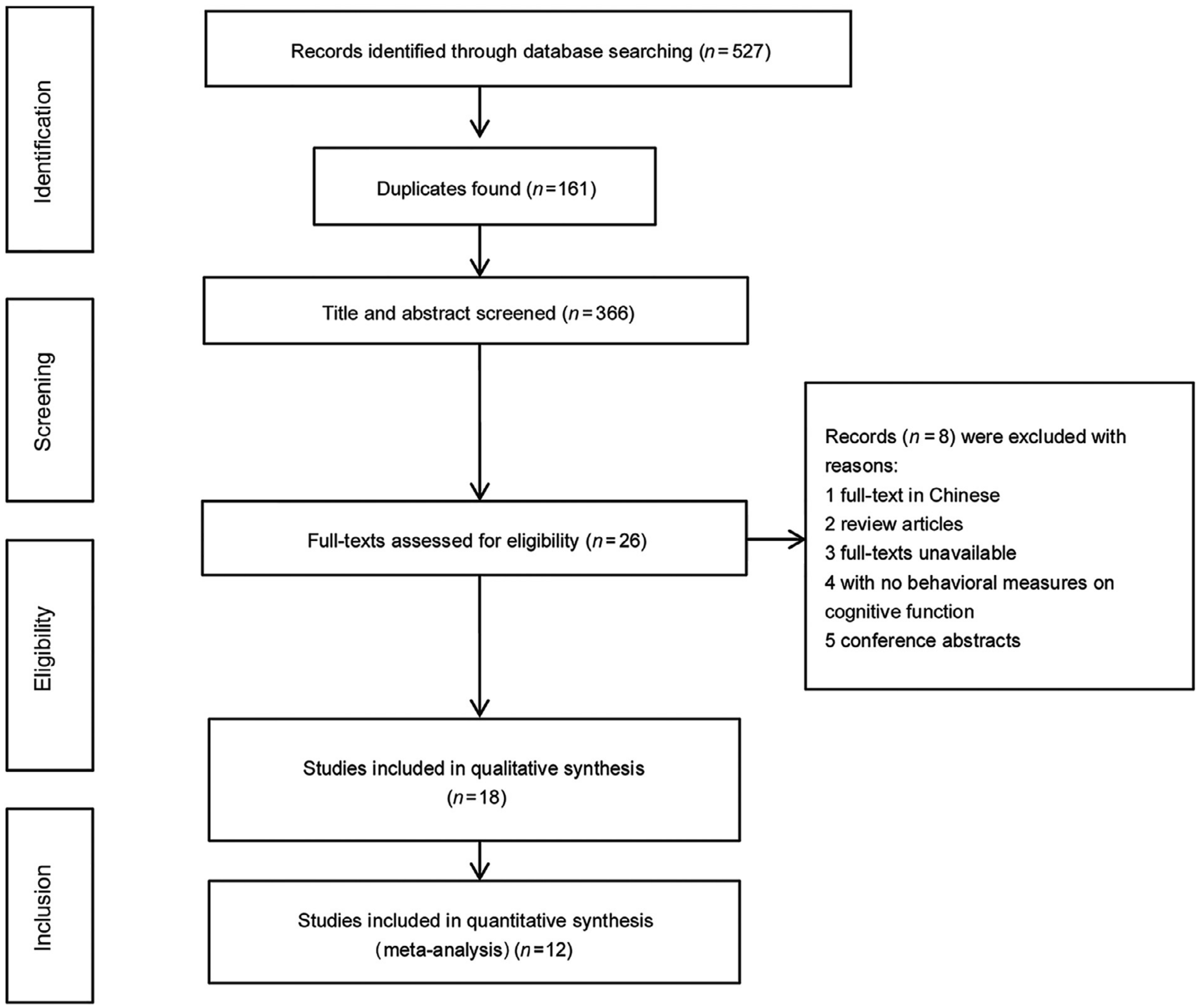

Fig. 1. Flow chart of literature search.

the mean scores and, thus, were included in the meta-analysis.[34]

3.3. Reasons for exclusions in each study screened by full text

Detailed reasons for the exclusion of participants in each study that received a full-text screening were extracted and are presented in Table 3. Examples included history of chronic diseases and physical problems during exercise or hypoxia, experience of smoking, medication use, cognitive disorders, exposured to hypoxia or high altitude within several months (3 months) prior to the study, and engagement in regular exercise training prior to the study.

3.4. Meta-analysis of effects on cognitive outcomes

Among these 12 studies, 31 ESs examining the effect of hypoxia on cognition were calculated. As illustrated in Fig. 2 (Aim 1), aggregated results indicated a non-statistically significant association between the presence of hypoxia and an overall lower cognition (SMD = −0.13, 95%CI: −0.28 to 0.01, I^2 = 45%, p = 0.075).

Among these 12 studies, 29 ESs examining the effect of exercise on cognition under hypoxia were calculated. As illustrated in Fig. 3 (Aim 2), the aggregated results indicated that performing exercise under a hypoxia setting has significant effects on cognitive improvement (SMD = 0.3, 95%CI: 0.14−0.45, I^2 = 54%, p < 0.001).

3.5. Moderator analyses

For Aim 1, in the subgroup analyses (Table 4), the effect of hypoxia on cognition was significantly moderated by sex (Q_b = 15.22, df = 2, p < 0.001) and cognitive task type (Q_b = 10.33, df = 3, p = 0.016) but not by other variables. Furthermore, males (SMD = −0.30, 95%CI: −0.48 to −0.11) suffered significant cognitive impairment when being exposed to hypoxia, as compared with females (SMD = 0.39, 95%CI: 0.09−0.69) and mixed sexes (SMD = 0.02, 95%CI: −0.19 to 0.22). Exposure to hypoxia impaired attentional ability (SMD = −0.40, 95%CI: −0.88 to 0.09), executive function (SMD = −0.18, 95%CI: −0.39 to 0.02), and memory function (SMD = −0.26, 95%CI: −0.55 to 0.04) but improved information processing (SMD = 0.27, 95%CI: 0.00−0.53). In the

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Table 1
Extraction table of the evaluated studies.

Study	Subject characteristics Age (mean ± SD or range)	Study design	Normoxia/Hypoxia protocol	Hypoxia-Exercise temporality	Exercise protocol	Cognitive function assessment	Results
Ando (2013)[3]	12 adult males 22.9 ± 1.5 years	Within-subject, Pre-post comparison	Performed cognitive tasks under either normoxia (20.9%) or normobaric hypoxia (18%, 15%) 25 min of hypoxia	Hypoxia/Normoxia both before and during exercise	5 min of cycle ergometer exercise at 20% peak VO_2max and 10 min of cycle ergometer exercise at 60% peak VO_2max / Acute exercise	GNG (Go /No-Go) task	GNG−RT (reaction time) Main effect EX: F (1,11) = 18.73, $p < 0.01$ Main effect HY: F (2,22) = 0.06, p = 0.94 EX * HY: F (1.41,15.53) = 0.06, p = 0.69 GNG − Accuracy Main effect EX: F (1,11) = 1.49, p = 0.25 Main effect HY: F (2,22) = 2.14, p = 0.14 EX * HY: N/A
Schega (2013)[32]	34 retired older adults 60−70 years	Between-subject, RCT, Pre-post comparison	The control group (CG) was supplied with a placebo air mixture and the experimental group (EG) was supplied with an IHT (intermittent hypoxia training) 10 min of hypoxia (10%)	Hypoxia/Normoxia during exercise	A full-body strength-endurance exercise program at 50% of maximum force/chronic exercise	d2 test: GZ (quantitative performance index; the rate at which participants mark off each d2 and the overall number of marked letters within the d2 test), SKL (concentration performance index; the standardized number of accurate answers minus confusion errors) and ZVT (Zahlen Verbindungs test)	GZ Main effect of EX: F (1,32) = 36.325, p = 0.00, η^2 = 0.532 Main effect HY: F (1,32) = 0.08, p = 0.78, η^2 = 0.002 EX * HY: F (1,32) = 4.59, p = 0.04, η^2 = 0.125 SKL Main effect EX: F (1,32) = 23.565, p = 0.00, η^2 = 0.424 Main effect HY: F (1,32) = 0.047, p = 0.831, η^2 = 0.001 EX * HY: F (1, 32) = 4.65, p = 0.034, η^2 = 0.127 ZVT Main effect EX: F (1,32) = 32.065, p = 0.00, η^2= 0.501 Main effect HY: F (1,32) = 1.906, p = 0.177, η^2 = 0.056 EX * HY: F (1,32) = 0.21, p = 0.649, η^2 = 0.007
Kim (2015)[8]	8 healthy adult males 41± 2 years	Within-subject, counterbalanced Pre-post comparison	In 1 of the experimental trials (HY, 12.5%), subjects remained resting in a seated position the entire 5 h; in the other experimental trial (HY + EX), subjects rested 2 h, cycled for 1 h, then rested the last 2 h.	Hypoxia/Normoxia both before and during exercise	1 h of a Lode cycle exercise (workload equivalent to 50% altitude-adjusted VO_{2max}) / Acute exercise	Trail Making Test A and B	Main effect Ex: N/A Main effect HY: N/A Ex * HY: N/A
Komiyama (2015)[16]	16 adult males 23.0 ± 2.3 years	Within-subject, Pre-post comparison	Performed cognitive tasks at rest and during exercise under normoxic and hypoxic conditions (15%) 45 min of hypoxia	Hypoxia/Normoxia both before and during exercise	30 min of cycle ergometer exercise until heart rate was 140 beats/min / Acute exercise	Spatial DR (Spatial delayed response), GNG task	Spatial DR − Accuracy Main effect EX: F (2, 30) = 1.34, p = 0.28, η^2 = 0.08 Main effect HY: F (1,15) = 0.81, p = 0.38, η^2 = 0.05 EX * HY: F (2, 30) = 1.69, p = 0.20, η^2 = 0.10 GNG − Accuracy Main effect EX: F (2, 30) = 2.79, p = 0.08, η^2 = 0.16 Main effect HY: F (1,15) = 2.5, p = 0.14, η^2 = 0.14 EX * HY: F (2, 30) = 1.13, p = 0.34, η^2 = 0.07 GNG − RT Main effect EX: F (2, 30) = 8.02, $p < 0.01$, η^2 = 0.35 Main effect HY: F (1,15) = 0.63, p = 0.44, η^2 = 0.04 EX * HY: F (2, 30) = 0.10, p = 0.91, η^2 = 0.006
Seo (2015)[45]	16 young healthy men 24 ± 4 years	Within-subject, counterbalanced, Pre-post comparison	Performed cognitive tasks at rest and during exercise under normoxic and hypoxic conditions (12.5%) 90-min of hypoxia	Hypoxia/Normoxia both before and during exercise	Two 15-min bouts of cycle ergometer exercise at 40% and 60% of adjusted VO_2max with 15-min recovery period between bouts/Acute exercise	GNG task, RMCPT (running memory continuous performance task)	GNG − RT Main effect EX: N/A Main effect HY: F = 1.8, p = 0.168 EX * HY: N/A GNG − Accuracy Main effect EX: N/A Main effect HY: F = 2.2, p = 0.098 EX * HY: N/A RMCPT − RT Main effect EX: 40% (p = 0.028), 60% (p = 0.009) Main effect HY: F = 3.4, p = 0.025 EX * HY: N/A

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Table 1 (Continued)

Study	Subject characteristics Age (mean ± SD or range)	Study design	Normoxia/Hypoxia protocol	Hypoxia-Exercise temporality	Exercise protocol	Cognitive function assessment	Results
							RMCPT - Accuracy Main effect EX: $p > 0.262$ Main effect HY: $F = 7.6, p \leq 0.001$ EX * HY: N/A RMCPT − Throughout score Main effect EX: 40% ($p = 0.023$), 60% ($p = 0.006$) Main effect HY: $F = 5.0, p = 0.005$ EX * HY: N/A
Dobashi (2016)[24]	8 healthy males 23.7 ± 2.1 years	Within-subject, counterbalanced, Pre-post comparison	Performed cognitive tasks before, during, and 60 min after exercise under normoxic and hypoxic conditions (14.1%) 180 min of hypoxia	Hypoxia/Normoxia both before and during exercise	Four 30-min bouts of cycle ergometer exercise at moderate intensity with a 15-min interval rest between each set / Acute exercise	CWST (color-word stroop task): Task 1 (reverse-Stroop control) Task 2 (reverse-Stroop interference) Task 3 (Stroop control) Task 4 (Stroop interference)	Task 1 − Number of Achievement Main effect EX: N/A Main effect HY: N/A EX * HY: F (3, 21) = 4.53, $p < 0.05$, $\eta^2 = 0.39$ Task 3 − Number of achievement Main effect EX: F (3, 14) = 4.09, $p < 0.05$, $\eta^2 = 0.37$ Main effect HY: F (3,21) = 0.24, $p > 0.05$, $\eta^2 = 0.03$ EX * HY: F (3, 21) = 2.97, $p > 0.05$, $\eta^2 = 0.30$ Task 2, 4 − Number of achievement Main effect EX: $p > 0.05$ Main effect HY: $p > 0.05$ EX * HY: $p > 0.05$ Task 1 − Number of correct response Main effect EX: N/A Main effect HY: N/A EX * HY: F (2, 14) = 5.63, $p < 0.05$, $\eta^2 = 0.45$ Task 3 − Number of correct response> Main effect EX: F (2, 14) = 3.2, $p > 0.05$, $\eta^2 = 0.31$ Main effect HY: F (1, 8) = 9.1, $p < 0.05$, $\eta^2 = 0.57$ EX * HY: F (2, 14) = 1.77, $p > 0.05$, $\eta^2 = 0.20$ Task 2, 4 − Number of correct response Main effect EX: $p > 0.05$ Main effect HY: $p > 0.05$ EX * HY: $p > 0.05$
Lefferts (2016)[9]	30 adults M = 15 22 ± 4 years W = 15 20 ± 3 years	Within-subject, Pre-post comparison	Performed cognitive tasks during exercise under normoxic and hypoxic conditions (12.5%) 120 min of hypoxia	Hypoxia/Normoxia both before and during exercise	25-min bouts of cycle ergometer exercise at moderate intensity/Acute exercise	Memory recognition, N-Back, Flanker tasks	Main effect EX: N/A Main effect HY: N/A EX * HY: N/A
33 older adults 60−75 years	Between-subject, RCT, Pre-post comparison	The CG breathed ambient air and the EG was supplied with IHT (10%) 120-min of hypoxia	Hypoxia/Normoxia both before and during exercise	30-min bouts of bicycle ergometer at moderate intensity/ Chronic exercise	Stroop test	Color task Main effect EX: N/A Main effect HY: $p = 0.004$ EX * HY: F (1,31) = 1.833, $p = 0.178$, $\eta^2 = 0.056$ Word-color-tasks Main effect EX: N/A Main effect HY: $p = 0.005$ EX * HY: F (1,30) = 1.506, $p = 0.23$, $\eta^2 = 0.048$	
Bayer (2017)[58]	33 older adults 60−75 years	Between-subject, RCT, Pre-post comparison	EG received multimodal training programs (MTP) and internal hypoxic−hyperoxic training (IHHT, 12%); CG received MTP during the IHHT. Both	Hypoxia/Normoxia during exercise	2 h of MTP (2−3 times/week, 14−15 trainings in 5−6 weeks) / Chronic exercise	DemTect (Dementia detection test), CDT (Clock-drawing test)	DemTect Main effect EX: 16.7% *vs.* −0.39%, $p < 0.001$ Main effect HY: N/A EX * HY: N/A CDT Main effect EX: 10.7% *vs.* −8%, $p = 0.031$

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Table 1 (Continued)

Study	Subject characteristics Age (mean ± SD or range)	Study design	Normoxia/Hypoxia protocol	Hypoxia-Exercise temporality	Exercise protocol	Cognitive function assessment	Results
			performed cognitive tasks before and after the training. 35 − 45 min of hypoxia				Main effect HY: N/A EX * HY: N/A
Bayer (2017)[59]	34 older adults 64−92 years	Between-subject, RCT, Pre-post comparison	EG received MTP and IHHT (10%−14%), and CG received MTP during the simulation of IHHT. Both performed cognitive tasks before and after the training. 30 − 40 min of hypoxia	Hypoxia/Normoxia during exercise	2 h of MTP (2−3 times/week, 12−15 trainings in 5−7 weeks) / Chronic exercise	DemTect, CDT	DemTect Main effect EX: 16.7% *vs.* −0.39%, $p < 0.001$ Main effect HY: N/A EX * HY: N/A CDT Main effect EX: 10.7% *vs.* −8%, $p = 0.031$ Main effect HY: N/A EX * HY: N/A
Komiyama (2017)[23]	13 adult males 21.5 years (mean)	Within-subject, Pre-post comparison	Performed cognitive tasks at rest and during exercise under either normoxic or hypoxic conditions (13%) 30 min of hypoxia	Hypoxia/Normoxia both before and during exercise	20 min of cycle ergometer exercise at moderate intensity/ Acute exercise	Spatial DR, GNG task	GNG−RT Main effect EX: F (1, 12) = 29.52, $p < 0.001$ Main effect HY: F (1,12) = 0.16, $p = 0.69$ EX * HY: N/A GNG −Accuracy Main effect EX: $p > 0.14$ Main effect HY: $p > 0.14$ EX * HY: N/A Spatial DR − Accuracy Main effect EX: $p > 0.14$ Main effect HY: $p > 0.14$ EX * HY: N/A
Seo (2017)[10]	15 healthy women 22 ± 2 years	Within-subject, counter-balanced, Pre-post comparison	Performed cognitive tasks at rest and during exercise under either normoxia or hypoxia (12.5%) 105 min of hypoxia	Hypoxia/Normoxia both before and during exercise	Two 15-min bouts of cycle ergometer exercise at 40% and 60% VO_{2max} with a 15-min recovery between bouts/ Acute exercise	RMCPT	Main effect EX: F (4, 56) = 2.6, $p = 0.047$, $\eta^2 = 0.2$ Main effect HY: N/A EX * HY: N/A
Stavres (2017)[60]	18 adults M = 9 22 ± 3 years W = 9 23 ± 2 years	Within-subject, counter-balanced, Pre-post comparison	Performed cognitive tasks at rest and during exercise under normoxic and hypoxic conditions (12.5%) 100 min of hypoxia	Hypoxia/Normoxia both before and during exercise	20 min of cycle ergometer exercise at moderate intensity/ Acute exercise	MATH (Mathematical performance), RMCPT	MATH Main effect EX: F(6, 102) = 3.67, $p = 0.002$ Main effect HY: N/A EX * HY: N/A RMCPT Main effect EX: F(6, 102) = 9.64, $p < 0.001$ Main effect HY: N/A EX * HY: N/A
Limmer (2018)[61]	80 adults M = 51, 25.5 ± 6.0 years W = 29 24.8 ± 5.9 years	Between-subject, Pre-post comparison	Group A: HYP + EX ($n = 15$) Group B: HYP ($n = 25$) Group C: EX ($n = 19$) Group D: NOR ($n = 21$)	Hypoxia/Normoxia during exercise	Group A: mountain climbing (7 days) Group B: rest in a hypoxic state Group C: ski hiking (7 days) Group D: rest in a normoxia state / Chronic exercise	FAIR-2	FAIR-2 Main effect EX: N/A Main effect HY: N/A EX * HY: N/A
Bayer (2019)[62]	34 older adults 64−92 years	Between-subject, RCT, Pre-post comparison	EG received MTP and IHHT (10%−14%), and CG received MTP during the simulation of IHHT. Both performed cognitive tasks before and after the training. 30−40 min of hypoxia	Hypoxia/Normoxia during exercise	30 min of MTP (2−3 times/week, 12 − 15 trainings in 5−7 weeks) / Chronic exercise	DemTect, CDT	Main effect EX: N/A Main effect HY: N/A EX * HY: N/A
Lei (2019)[17]	30 healthy inactive women 22.6 ± 3.2 years		Performed cognitive tasks at rest and during exercise		10-min bouts of cycle ergometer exercise at	Interference control task	Interference control task − RT Main effect EX: F (1,29) = 8.336, $p = 0.011$, $\eta^2_p = 0.203$

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Table 1 (Continued)

Study	Subject characteristics Age (mean ± SD or range)	Study design	Normoxia/Hypoxia protocol	Hypoxia-Exercise temporality	Exercise protocol	Cognitive function assessment	Results
		Within-subject, counterbalanced, Pre-post comparison	under normoxic and hypoxic conditions (12%) 20 min of hypoxia	Hypoxia/Normoxia both before and during exercise	moderate intensity / Acute exercise		Main effect HY: F (1,29) = 5.425, p = 0.043, $\eta^2_p = 0.134$ EX * HY: F (1,29) = 0.524, $p = 0.573$, $\eta^2_p = 0.011$ Interference control task − Accuracy Main effect EX: F (1,29) = 0.487, $p = 0.445$, $\eta^2_p = 0.02$ Main effect HY: F (1,29) = 0.777, $p = 0.796$, $\eta^2_p = 0.002$ EX * HY: F (1,29) = 0.03, $p = 0.798$, $\eta^2_p = 0.002$
Morrison (2019)[63]	11 amateur team-sport athletes 22.8 ± 3.6 years	Within-subject, counterbalanced, Pre-post comparison	Performed cognitive tasks before and after exercise under normoxic and hypoxic conditions (14.5%) 5 min of hypoxia	Hypoxia/Normoxia during exercise	A repeated sprint-running protocol (4 sets of 4, 4-s all-out sprints)/ Acute exercise	DET (detection task) IDN (identification task) OCL (one card learning task)	DET Main effect EX: N/A Main effect HY: N/A EX * HY: N/A IDN Main effect EX: N/A Main effect HY: N/A EX * HY: N/A OCL − RT Main effect EX: $F = 10.62$, $p = 0.01$, $\eta^2 = 0.52$ Main effect HY: $F = 0.3$, $p = 0.56$, $\eta^2 = 0.03$ EX * HY: $F = 0.29$, $p = 0.60$, $\eta^2 = 0.03$ OCL − Accuracy Main effect EX: N/A Main effect HY: $p = 0.20$ EX * HY: N/A
Sun (2019)[18]	20 inactive adults M = 10, W = 10 23.9 ± 2.5 years	Between-subject, RCT, Pre-post comparison	Performed cognitive tasks before and after exercise under normoxia and hypoxia (15.4%) 30-40 min of hypoxia	Hypoxia/Normoxia both before and during exercise	6 min of cycle ergometer exercise at high intensity (10 repetitions of 6 s with 30 s of recovery) / Acute exercise	GNG task	GNG − RT Main effect EX: $p = 0.204$, $\eta^2 = 0.083$ Main effect HY: $p = 0.782$, $\eta^2 = 0.004$ EX * HY: $p = 0.514$, $\eta^2 = 0.023$ GNG − Accuracy Main effect EX: $p = 0.001$, $\eta^2 = 0.467$ Main effect HY: $p = 0.972$, $\eta^{2\prime} = 0.001$ EX * HY: $p = 0.537$, $\eta^2 = 0.02$

Abbreviations: CDT = clock-drawing test; CWST = color-word stroop task; DemTect = dementia detection test; DET = detection task; EX = exercise; EX * HY = interaction effect between exercise and hypoxia; FAIR-2 = Frankfurt attention inventory-2; GNG = Go/No-Go; GZ = quantitative performance; HY = hypoxia; IHHT = interval hypoxic−hyperoxic training; IDN = identification task; M = male; MATH = mathematical; MTP = multimodal training programs; N/A = not assessed; NOR = normoxia; OCL = 1 card learning task; RCT = randomized controlled trial; RMCPT = running memory continuous performance task; performance index; SKL = concentration performance index; Spatial DR = spatial delayed response; VO_{2max} = maximum oxygen uptake; W = woman; ZVT = Zahlen Verbindungs test.

Table 2
Cognitive tasks and cognitive task categories.

Category	Task
Information processing	Color-word stroop task
Attention	d2 test (GZ, SKL)
	Frankfurt attention inventory-2
Executive function	Go/No-Go task
	Zahlen Verbindungs test
	Trail making test A and B
	Flanker task
	Mathematical performance
	Interference control task
Memory	Spatial delayed response
	Running memory continuous performance task
	Memory recognition
	N-back
	One cardlearning task
	Dementia detection test
	Clock-drawing test
Reaction time	Detection task
	Identificationtask

Abbreviations: GZ = quantitative performance index (quantitative performance index; the rate at which participants mark off each d2 and the overall number of marked letters within the d2 test); SKL = concentration performance index (concentration performance index; the standardized number of accurate answers minus confusion errors).

meta-regressions, the hypoxia-cognition associations did not differ by these hypoxia characteristics (hypoxia duration ($\beta = 0.002$, 95%CI: −0.001 to 0.005, $p = 0.19$), hypoxia level ($\beta = -0.03$, 95%CI: −0.11 to 0.05, $p = 0.42$), and hypoxia dose ($\beta = 0.01$, 95%CI: 0.00−0.03, $p = 0.25$)). Results of the meta-regressions are displayed in Fig. 4.

For Aim 2, in the subgroup analyses (Table 5), the effect of exercise on cognition under hypoxia was significantly moderated by age ($Q_b = 6.30$, $df = 1$, $p = 0.012$), cognitive task type ($Q_b = 9.34$, $df = 3$, $p = 0.025$), exercise type ($Q_b = 17.12$, $df = 3$, $p = 0.001$), exercise intensity ($Q_b = 3.98$, $df = 1$, $p = 0.046$), and training type ($Q_b = 6.30$, $df = 1$, $p = 0.012$). Furthermore, older adults (SMD = 0.51, 95%CI: 0.32−0.69) benefited more from exercise under hypoxia than did young adults (SMD = 0.16, 95%CI: −0.04 to 0.36). Exercising under hypoxia had the greatest (favorable) impact on attention (SMD = 0.78, 95%CI: 0.39−1.17) compared to information processing (SMD = 0.26, 95%CI 0.03−0.49), executive function (SMD = 0.07, 95%CI: −0.19 to 0.33), and memory (SMD = 0.38, 95%CI: 0.12−0.64). Full-body strength-endurance programs (SMD = 0.70, 95%CI: 0.39−1.01) were more effective than cycle ergometer (SMD = 0.23, 95%CI: 0.06−0.40), multimodal training program (SMD = 0.50, 95%CI: 0.14−0.85), and repeated sprint running (SMD = −0.71, 95%CI: −1.38 to −0.04) in improving cognitive function. Exercising at moderate intensity (SMD = 0.36, 95%CI: 0.22−0.50) had greater effects on cognitive improvement when compared to high-intensity exercise (SMD = −0.41, 95%CI: −1.16 to 0.34). Chronic exercise (SMD = 0.51, 95%CI: 0.32−0.69) was more effective than acute exercise (SMD = 0.16, 95%CI: −0.04 to 0.36) in enhancing cognitive function. In the meta-regressions, although no significant moderator effect was present for exercise duration ($\beta = 0.001$, 95%CI: −0.002 to 0.004, $p = 0.42$), hypoxia duration ($\beta = 0.001$, 95%CI: −0.002 to 0.004, $p = 0.68$), and hypoxia dose ($\beta = 0.001$, 95%CI: −0.02 to 0.02, $p = 0.96$), there was evidence of moderation effect for hypoxia level ($\beta = -0.12$, 95%CI: −0.19 to −0.06, $p < 0.001$), indicating that exercising while at greater hypoxia level was negatively associated with cognitive performance. Results of the meta-regressions are presented in Fig. 5.

3.6. Publication bias

Based on the funnel plot, the Egger test of regression intercept was not statistically significant in Aim 1 (intercept = −0.22, $p = 0.87$) or Aim 2 (intercept = −3.37, $p = 0.13$), indicating that there was no evidence of risk of bias across studies.

4. Discussion

4.1. Main study findings

This review included both RCTs and NRSs, with consideration of the following potential moderating variables: (1) the effects of hypoxia on cognitive function and (2) the effects of exercise under hypoxia on cognitive function. First, we found that hypoxia exposure impaired some but not all aspects of cognitive function. The effect of hypoxia on cognition was moderated by sex and cognitive task type. Second, exercising under hypoxia may have had small to medium positive effects on selected aspects of cognitive function. When being exposed to hypoxia, exercise-cognition association was moderated by age, cognitive task type, exercise type, exercise intensity, training type, and hypoxia level.

4.2. Comparisons with previous reviews

As indicated in recent narrative and meta-analytic reviews, cognitive function may be compromised during exposure to hypoxia.[13] In alignment with these previous reviews, our meta-analysis demonstrates that hypoxia had a selective effect on cognition, in that hypoxia enhanced information processing but impaired cognition-based attention, executive function, and memory. Even though this result supports the conclusions of other related studies, the magnitude of effect was smaller than in previous work. Notably, Taylor et al.[11] reported that hypoxia was more negatively associated with central executive tasks compared with nonexecutive tasks. This, however, is in contrast to the review by McMorris et al.,[13] which suggested that there are no significant hypoxia-induced differences between executive and nonexecutive tasks. Moreover, although the meta-analytic review by McMorris et al.[13] was for within-group studies, our work utilized both within- and between-group studies. These conflicting findings across the literature render challenges in the interpretation of our observations regarding Aim 1. If our findings are replicated and prove to be reliable effects, then future research should aim to evaluate the underlying reasons for hypoxia's having a unique effect on selective cognitions. Next, our main findings (Aim 2) demonstrate that exercise under hypoxia had a positive effect

Table 3
Exclusionary criteria table for each of the included studies.

Study	Exclusionary criteria
Ando (2013)[3]	Participants who were currently engaged in regular training. • Participants who had any history of cardiovascular, cerebrovascular, or respiratory disease.
Schega (2013)[32]	• Subjects who were physically active and did not pass a medical examination by a medical doctor.
Kim (2015)[8]	• Participants who had been exposed to normobaric hypoxia or altitudes over 2500 m within previous 2 months. • Participants who had any history of smoking or had signs of cardiovascular, metabolic, or respiratory disease. • Participants who had experienced syncope, anemia, or fainting during exercise.
Komiyama (2015)[16]	• Participants who had any history of cardiovascular, cerebrovascular, or respiratory diseases.
Seo (2015)[45]	• Subjects who reported presence or history of pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, skeletal muscle injury in the lower limbs, and metabolic syndrome. • Subjects who were exposed to normobaric hypoxia or an altitude above 2500 m within 2 months before study.
Dobashi (2016)[24]	• Participants who had any cardiovascular, cerebrovascular, or respiratory diseases. • Participants who had smoked, taken medications, or performed exercise training in the 6 months prior to study.
Lefferts (2016)[9]	• Participants who had experienced smoking, hypertension, diabetes mellitus, hyperlipidemia, pulmonary disease, renal disease, neurological disease, or peripheral artery disease.
Schega (2016)[33]	• Participants who had stayed in an altitude above 1800 m, as well as those who gave blood donations, in the past 2 months. • Participants who had chronic or acute renal, cardiovascular, metabolic, neuronal, or orthopaedic diseases.
Bayer (2017)[58]	• Individuals who were not able to move unaided or who had uncontrolled hypertension (systolic BP > 180 mmHg), chronic bronchopulmonary diseases, decompensated heart failure (NYHA, III-IV FC), previous intracerebral hemorrhages, or marked cognitive disorders (MMSE < 12 points).
Bayer (2017)[59]	• Subjects who were not able to walk without any staff assistance or suffered from severe dementia with a score of less than 12 points on the MMSE, uncontrolled hypertension (systolic BP > 180 mmHg and/or diastolic BP > 100 mmHg), COPD III−IV, decompensated heart failure (NYHA III−IV), or previous intracerebral bleeding.
Komiyama (2017)[23]	• Participants who had any history of cardiovascular, cerebrovascular, or respiratory disease.
Seo (2017)[10]	• Subjects who not were physically active and had any history of pulmonary disease, cardiovascular disease, postural orthostatic tachycardia syndrome, or skeletal muscle injury in the lower limbs. • Subjects who were exposed to hypoxia or an altitude above 2500 m (8202 feet) within 2 months prior to study.
Stavres (2017)[60]	• Subjects who had any history of any cardiac, metabolic, or respiratory disease; any musculoskeletal issues prohibiting exercise; or any previous adverse reaction to altitude exposure. • Subjects who had been at altitudes above 2500 m within 3 months prior to participating in study.
Limmer (2018)[61]	• Subjects who had previous experience with the Frankfurt attention inventory-2 (FAIR-2) test, altitude sojourns above 2000 m in the 4 weeks prior to the investigation, neurological disease, psychiatric illness, learning disabilities, alcohol or drug use, or any difficulty that could interfere with behavioral or cognitive testing.
Bayer (2019)[62]	• Patients of the Geriatric Day Clinic who did not suffer from any diseases.
Lei (2019)[17]	• Subjects who had not lived at an altitude below 1300 m. • Subjects who had previous experience with hypoxic training or prior engagement in any regular exercise. • Subjects who had experienced smoking and alcohol-drinking habits. • Subjects who had a self-reported regular menstrual cycle of 28−34 days in length. • Subjects who were taking any form of the contraceptive pill or other drugs.
Morrison (2019)[63]	• N /A
Sun (2019)[18]	• Subjects who had not lived at an altitude lower than 1000 m. • Subjects who had experience with hypoxic training and were currently engaged in any structured exercise. • Subjects who were smokers and had taken oral contraceptives or any medication during the past 6 months. • Subjects who had musculoskeletal problems.

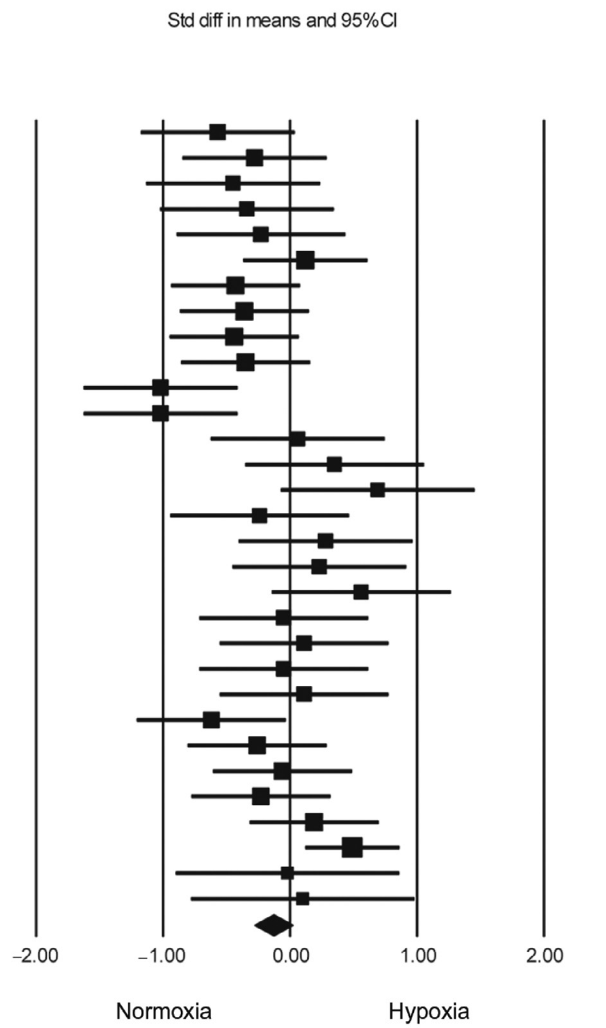
Abbreviations: BP = blood pressure; COPD = chronic obstructive pulmonary disease; MMSE = Mini-Mental State Examination; N/A = not available; NYHA, III-IV FC = New York Heart Association Functional Class III-IV.

on cognitive function, which extends a recently published narrative review on this topic.[25]

4.3. Possible explanation for study findings

Notably, for Aim 1, we found a significant sex-specific effect. That is, performing cognitive tasks under hypoxia was advantageous in improving cognitive function for females. This may, in part, be attributed to females' having relatively higher peripheral oxygen saturation (SpO_2) and estrogen hormones than males, which provide a greater resistance to hypoxia.[35−38] However, this neuroprotective effect of estrogen in response to hypoxia should be interpreted with caution, because few studies that investigated the hypoxia-cognition interaction for women during a specific timing of the menstrual cycles were included in this review. We also observed significant differences among cognitive task types. That is, hypoxia had a favorable effect on information processing as opposed to the observed impairment effect on attention, executive function, and memory. Such selected aspects of cognitive impairment are supported by a previous review suggesting that arterial PaO_2 is a strong predictor of reduced cognitive performance. If PaO_2 level is low (35−60 mmHg), increased cerebral blood flow may not compensate adequately for the lack of oxygen required to maintain cognitive ability. Ochi et al.[39] indicated that SpO_2 gradually decreases as the severity of

Study name	Statistics for each study			
	Std diff in means	Standard error	Lower limit	Upper limit
Ando (2013)[3] a	−0.570	0.310	−1.178	0.038
Ando (2013)[3] b	−0.280	0.290	−0.848	0.288
Schega (2013)[32] a	−0.450	0.350	−1.136	0.236
Schega (2013)[32] b	−0.340	0.350	−1.026	0.346
Schega (2013)[32] c	−0.230	0.340	−0.896	0.436
Komiyama (2015)[16] a	0.120	0.250	−0.370	0.610
Komiyama (2015)[16] b	−0.430	0.260	−0.940	0.080
Seo (2015)[45] a	−0.360	0.260	−0.870	0.150
Seo (2015)[45] b	−0.440	0.260	−0.950	0.070
Seo (2015)[45] c	−0.350	0.260	−0.860	0.160
Seo (2015)[45] d	−1.020	0.310	−1.628	−0.412
Seo (2015)[45] e	−1.020	0.310	−1.628	−0.412
Dobashi (2016)[24] a	0.060	0.350	−0.626	0.746
Dobashi (2016)[24] b	0.350	0.360	−0.356	1.056
Dobashi (2016)[24] c	0.690	0.390	−0.074	1.454
Dobashi (2016)[24] d	−0.240	0.360	−0.946	0.466
Schega (2016)[33] a	0.280	0.350	−0.406	0.966
Schega (2016)[33] b	0.230	0.350	−0.456	0.916
Schega (2016)[33] c	0.560	0.360	−0.146	1.266
Bayer (2017)[58] a	−0.050	0.340	−0.716	0.616
Bayer (2017)[58] b	0.110	0.340	−0.556	0.776
Bayer (2017)[59] a	−0.050	0.340	−0.716	0.616
Bayer (2017)[59] b	0.110	0.340	−0.556	0.776
Komiyama (2017)[23] a	−0.620	0.300	−1.208	−0.032
Komiyama (2017)[23] b	−0.260	0.280	−0.809	0.289
Komiyama (2017)[23] c	−0.060	0.280	−0.609	0.489
Komiyama (2017)[23] d	−0.230	0.280	−0.779	0.319
Seo (2017)[10]	0.190	0.260	−0.320	0.700
Lei (2019)[17]	0.490	0.190	0.118	0.862
Sun (2019)[18] a	−0.020	0.450	−0.902	0.862
Sun (2019)[18] b	0.100	0.450	−0.782	0.982
	−0.134	0.075	−0.281	0.014



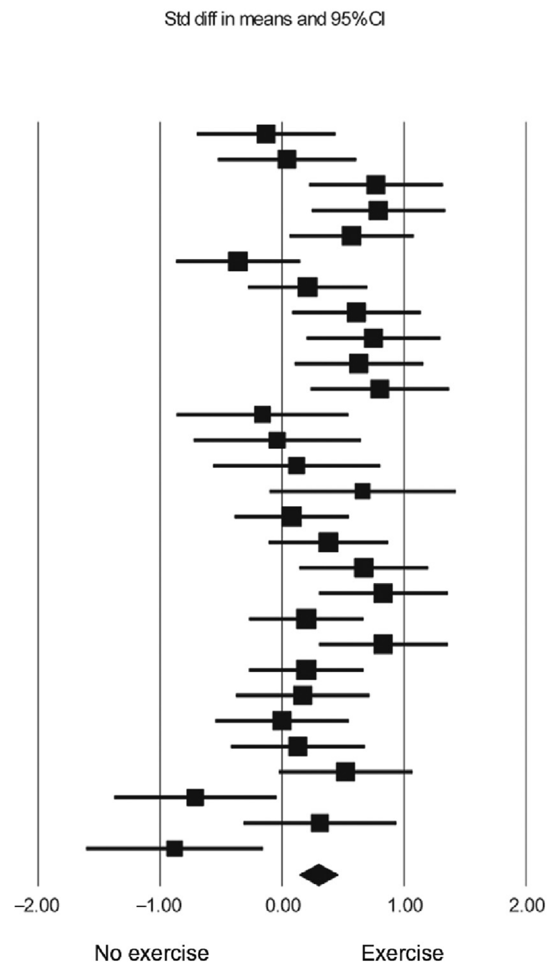
Meta Analysis

Fig. 2. Forest plot depicting the standardized mean difference effect sizes (hypoxia *vs.* normoxia) and 95%CI for Aim 1. Ando (2013): a = response time in Go/No-Go task; b = response accuracy in Go/No-Go task. Schega (2013): a = SKL in d2 test; b = GZ in d2 test; c = Zahlen Verbindungs test. Komiyama (2015): a = accuracy in spatial delayed response; b = response accuracy in Go/No-Go task. Seo (2015): a = response time in Go/No-Go task; b = response accuracy in Go/No-Go task; c = response time in running memory continuous performance task; d = response accuracy in running memory continuous performance task; e = total score in running memory continuous performance task. Dobashi (2016): a = Reverse-Stroop control task; b = Reverse-Stroop interference task; c = Stroop control task; d = Stroop interference task. Schega (2016): a = Word-task of the Stroop test; b = Color-task of the Stroop test; c = Word-color-task of the Stroop test. Bayer (2017)[58]: a = Dementia detection test; b = Clock-drawing test. Bayer (2017)[59]: a = Dementia detection test; b = Clock-drawing test. Komiyama (2017): a = accuracy in spatial delayed response; b = response accuracy on Go trial in the Go/No-Go task; c = response accuracy on No-Go trial in the Go/No-Go task; d = response time in Go/No-Go task. Seo (2017): total score in running memory continuous performance task. Lei (2019): response time in Go/No-Go task. Sun (2019): a = response time in Go/No-Go task; b = response accuracy in Go/No-Go task. CI = confidence interval; diff = difference; Std = standardized.

hypoxia increases, and low levels of SpO_2 may induce cerebral deoxygenation. Hence, it is plausible that hypoxia may be responsible for negative cognitive-related outcomes due to neurological and structural alterations of the brain tissue.[40]

Regarding Aim 2, we observed moderation effects for age, cognitive task type, exercise type and intensity, and hypoxia level. It is challenging to explain the moderation effects of age. If hypoxia has a greater negative effect on cognition for older adults (*vs.* younger adults), it is conceivable that exercise may help attenuate this effect in older adults. However, for our Aim 1, we did not observe an age-moderation effect. Our findings also demonstrate that attention tends to be more positively influenced by exercise during exposure to hypoxia than other cognitive task types (e.g., information-processing, executive function, and memory). Notably, however, all cognitions were enhanced with exercise. Although Chang et al.[20] observed that acute exercise under normoxia helped to improve executive function, there are few studies that investigate which types of

Study name	Std diff in means	Standard error	Lower limit	Upper limit
Ando (2013)[3] a	–0.130	0.290	–0.698	0.438
Ando (2013)[3] b	0.040	0.290	–0.528	0.608
Schega (2013)[32] a	0.770	0.280	0.221	1.319
Schega (2013)[32] b	0.790	0.280	0.241	1.339
Schega (2013)[32] c	0.570	0.260	0.060	1.080
Komiyama (2015)[16] a	–0.360	0.260	–0.870	0.150
Komiyama (2015)[16] b	0.210	0.250	–0.280	0.700
Seo (2015)[45] a	0.610	0.270	0.081	1.139
Seo (2015)[45] b	0.750	0.280	0.201	1.299
Seo (2015)[45] c	0.630	0.270	0.101	1.159
Seo (2015)[45] d	0.800	0.290	0.232	1.368
Dobashi (2016)[24] a	–0.160	0.360	–0.866	0.546
Dobashi (2016)[24] b	–0.040	0.350	–0.726	0.646
Dobashi (2016)[24] c	0.120	0.350	–0.566	0.806
Dobashi (2016)[24] d	0.660	0.390	–0.104	1.424
Schega (2016)[33] a	0.080	0.240	–0.390	0.550
Schega (2016)[33] b	0.380	0.250	–0.110	0.870
Schega (2016)[33] c	0.670	0.270	0.141	1.199
Bayer (2017)[58] a	0.830	0.270	0.301	1.359
Bayer (2017)[58] b	0.200	0.240	–0.270	0.670
Bayer (2017)[59] a	0.830	0.270	0.301	1.359
Bayer (2017)[59] b	0.200	0.240	–0.270	0.670
Komiyama (2017)[23] a	0.170	0.280	–0.379	0.719
Komiyama (2017)[23] b	0.000	0.280	–0.549	0.549
Komiyama (2017)[23] c	0.130	0.280	–0.419	0.679
Seo (2017)[10]	0.520	0.280	–0.029	1.069
Morrison (2019)[63]	–0.710	0.340	–1.376	–0.044
Sun (2019)[18] a	0.310	0.320	–0.317	0.937
Sun (2019)[18] b	–0.880	0.370	–1.605	–0.155
	0.295	0.078	0.142	0.448



Meta Analysis

Fig. 3. Forest plot depicting the standardized mean difference effect sizes (exercise *vs.* no exercise) and 95%CI for Aim 2. Ando (2013): a = response time in Go/No-Go task; b = response accuracy in Go/No-Go task. Schega (2013): a = SKL in d2 test; b = GZ in d2 test; c = Zahlen Verbindungs test. Komiyama (2015): a = accuracy in spatial delayed response; b = response accuracy in Go/No-Go task. Seo (2015): a = response time in running memory continuous performance; b = response time in running memory continuous performance; c = total score in running memory continuous performance task; d = Total score in running memory continuous performance task. Dobashi (2016): a = Reverse-Stroop control task; b = Reverse-Stroop interference task; c = Stroop control task; d = Stroop interference task. Schega (2016): a = Word-task of the Stroop test; b = Color-task of the Stroop test; c = Word-color-task of the Stroop test. Bayer (2017)[58]: a = Dementia detection test; b = Clock-drawing test. Bayer (2017)[59]: a = Dementia detection test; b = Clock-drawing test. Komiyama (2017): a = accuracy in spatial delayed response; b = response accuracy on Go trial in the Go/No-Go task; c = response accuracy on No-Go trial in the Go/No-Go task. Seo (2017): total score in running memory continuous performance task. Morrison (2019): accuracy in one card learning task. Sun (2019): a = response time in Go/No-Go task; b = response accuracy in Go/No-Go task. CI = confidence interval; diff = difference; Std = standardized.

cognitions are most sensitive to exercise in hypoxic conditions. Thus, this is an area in need of future research.

In addition, a notable finding was that full-body strength-endurance exercise had a greater impact on cognition improvement. This finding may be related to the cognitive enhancement effects of complex movement patterns, which we have detailed elsewhere.[41] Encouragingly, it is anticipated that more complicated movement patterns stimulate regional cerebral flow and cortical excitability, resulting in enhancing cognitive function;[42–44] thus, full-body strength-endurance exercise, consisting of aerobic exercise and strength training, may help to exert cognitive ability under hypoxia. Furthermore, we detected a significant difference in effect size for exercise intensity (moderate *vs.* high). Our findings indicated that moderate-intensity exercise under hypoxia increases cognitive function. This improvement effect is consistent with the moderation results from several previous studies.[17,18,45] Importantly, however, under normoxia, exercise intensity may differentially influence cognition-based reaction time and accuracy.[46] Future work should evaluate this under hypoxic conditions. However, when exposed to hypoxia, moderate-intensity exercise may increase cerebral blood flow and compensate for decreased SpO_2.[47,48] Indeed, exercising under moderate hypoxia favored cognitive benefits when compared

Table 4
Effect sizes by moderator variables in meta-analysis of variance for Aim 1.

Category	Effect size	SMD	95%CI	Q_b
Sex				15.22**
Male	17	−0.30**	−0.48 to −0.11	
Female	2	0.39*	0.09 to 0.69	
Mixed	12	0.02	−0.19 to 0.22	
Age				2.01
Young Adults	21	−0.20*	−0.39 to 0.00	
Older Adults	10	0.01	−0.20 to 0.23	
Cognitive task type				10.33*
Information processing	7	0.27	0.00 to 0.53	
Attention	2	−0.40	−0.88 to 0.09	
Executive function	12	−0.18	−0.39 to 0.02	
Memory	10	−0.26	−0.55 to 0.04	
Study design				2.38
RCT	12	0.02	−0.19 to 0.22	
NRS	19	−0.21*	−0.41 to -0.01	

* $p < 0.05$; ** $p < 0.01$.
Abbreviations: CI = confidence interval; NRS = non-randomized controlled studies; RCT = randomized controlled trials; SMD = standardized mean difference; Q_b = Cochran's Q statistics.

Table 5
Effect sizes by moderator variables in meta-analysis of variance for Aim 2.

Category	Effect size	SMD	95%CI	Q_b
Sex				2.96
Male	16	0.18	−0.03 to 0.38	
Female	1	0.52	−0.03 to 1.07	
Mixed	12	0.42**	0.19 to 0.65	
Age				6.30*
Young adults	19	0.16	−0.04 to 0.36	
Older adults	10	0.51**	0.32 to 0.69	
Cognitive task type				9.34*
Information processing	7	0.26*	0.03 to 0.49	
Attention	2	0.78**	0.39 to 1.17	
Executive function	8	0.07	−0.19 to 0.33	
Memory	12	0.38**	0.12 to 0.64	
Study design				1.98
RCT	12	0.42**	0.19 to 0.65	
NRS	17	0.20*	0.00 to 0.40	
Exercise type				17.12**
Cycle ergometer	21	0.23**	0.06 to 0.40	
A full-body strength-endurance program	3	0.70**	0.39 to 1.01	
Multimodal training program	4	0.50**	0.14 to 0.85	
Repeated sprint running	1	−0.71*	−1.38 to -0.04	
Exercise intensity				3.98*
Moderate	26	0.36**	0.22 to 0.50	
High	3	−0.41	−1.16 to 0.34	
Exercise temporality				1.43
During hypoxia	8	0.45**	0.13 to 0.78	
Both before and during hypoxia	21	0.23**	0.06 to 0.40	
Training type				6.30*
Acute exercise	19	0.16	−0.04 to 0.36	
Chronic exercise	10	0.51**	0.32 to 0.69	

* $p < 0.05$; ** $p < 0.01$.
Abbreviations: CI = confidence interval; NRS = non-randomized controlled studies; RCT = randomized controlled trials; SMD = standardized mean difference; Q_b = Cochran Q statistics.

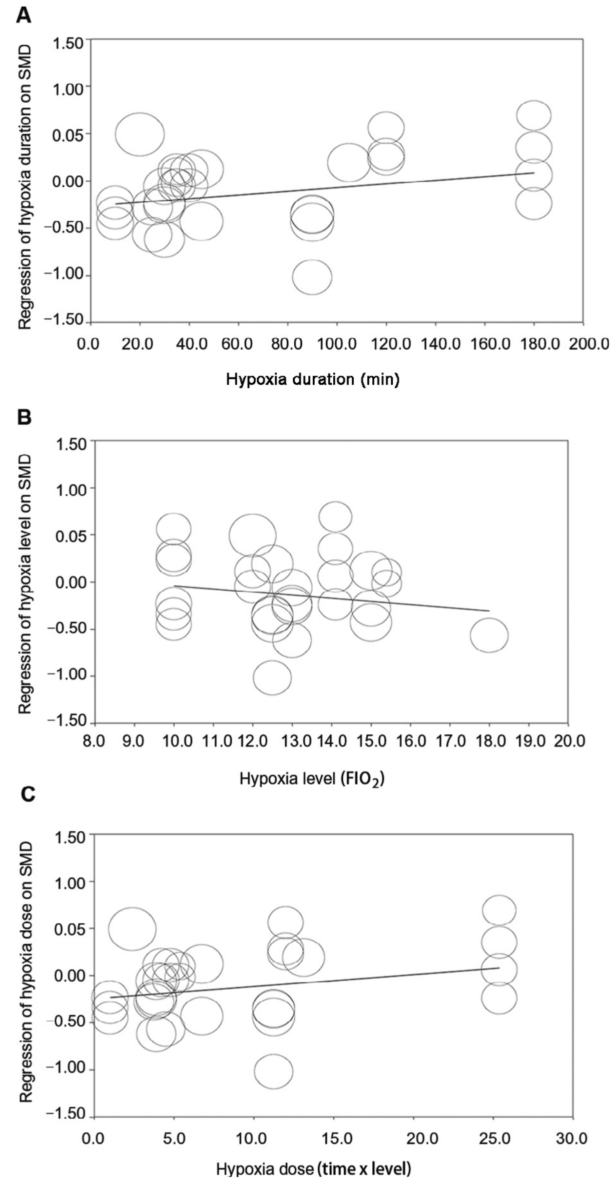


Fig. 4. Effect sizes by moderator variables in meta-regression for Aim 1. (A) Regression of hypoxia duration on SMD; (B) Regression of hypoxia level (FIO2) on SMD; (C) Regression of hypoxia dose on SMD). FIO_2 = fraction of inspired oxygen; SMD = standardized mean difference.

to severe hypoxia. This effect may be a result of the potential additive effects of exercise and moderate hypoxia on cognition. As fully discussed elsewhere,[18,49] moderate levels of hypoxia and exercise may enhance synaptic plasticity via an increased expression of brain-derived neurotrophic factor. The hypoxia- and exercise-induced upregulation of brain-derived neurotrophic factor can facilitate cerebral neural activation and neurogenesis and, therefore, lead to cognition improvements.[50] Last, chronic exercise had a more positive effect on cognition than acute exercise under hypoxia. This finding is consistent with previous work demonstrating that acute exercise under normoxia was not as beneficial in enhancing cognitive function when compared to chronic exercise.[51] This may be attributed partially to adaptations of physiological and neurological parameters induced by chronic exercise.[22,52,53] To

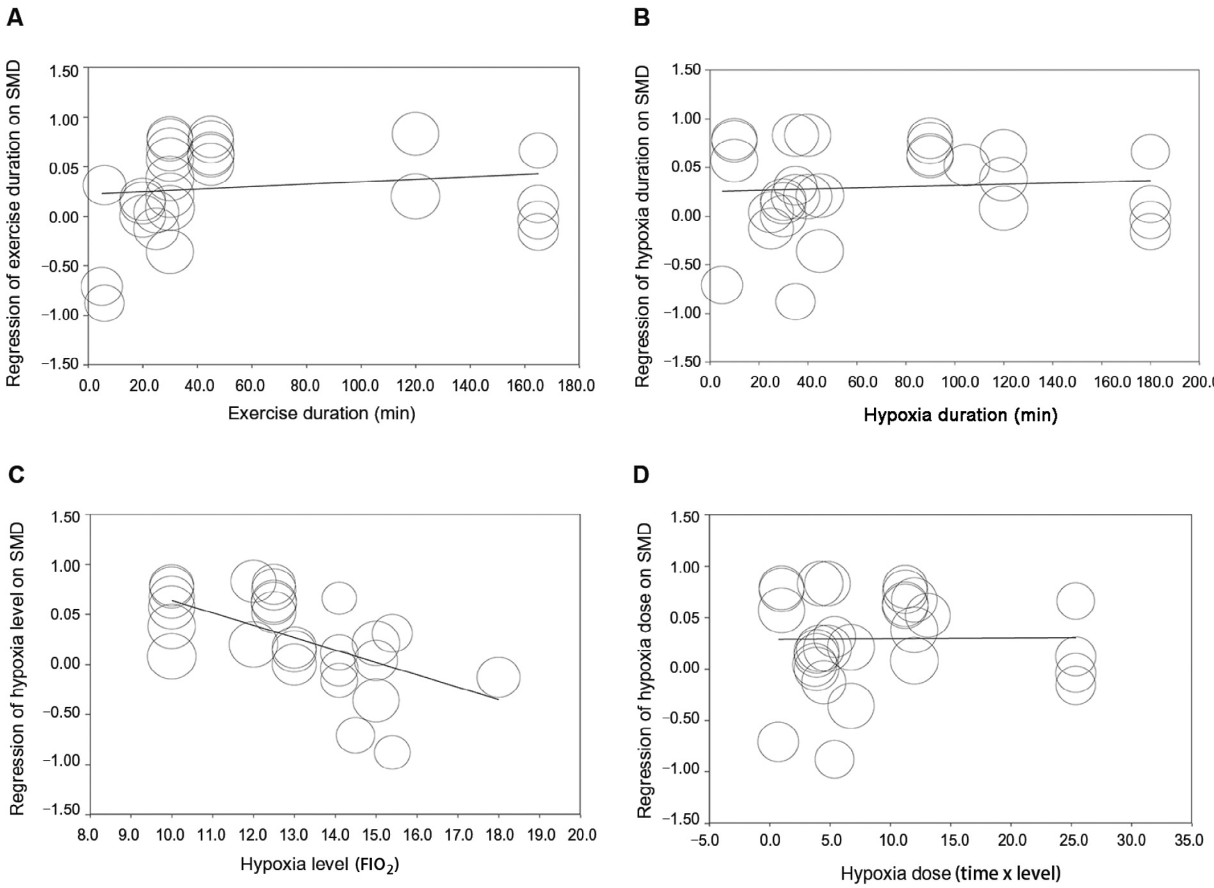


Fig. 5. Effect sizes by moderator variables in meta-regression for Aim 2. (A) Regression of exercise duration on SMD; (B) Regression of hypoxia duration on SMD; (C) Regression of hypoxia level (FIO_2) on SMD; (D) Regression of hypoxia dose on SMD. FIO_2 = fraction of inspired oxygen; SMD = standardized mean difference.

provide definitive conclusions, longitudinal studies of the effects of exercise training on cognition while under hypoxia are needed, because there are limited studies comparing how the length of training intervention affects cognition at different levels of hypoxia.

4.4. *Strengths and limitations*

This meta-analytic review has several strengths. First, this is the first meta-analytic review that investigated the combined effects of exercise and hypoxia on cognitive function. Second, we simultaneously demonstrated the independent effects of hypoxia on cognitive function and the interactive effects of exercise and hypoxia on cognitive function. Third, we tested a variety of moderating variables to determine the cause of heterogeneity, which provides a much clearer picture regarding the effects of exercise under hypoxia on cognitive function. Despite these strengths, there are several limitations in our study. First, several moderator effects should be interpreted with caution because small cell sizes in this review evaluated the relationship between exercise and cognition under hypoxia. Although there are limited cell sizes for moderators, the identification of potential moderators will help future work to demonstrate the complexity of these interactions. Second, timing of the cognitive task in relation to exercise (e.g., before, during, or after exercise) was not considered; thus, future studies should establish whether different cognitive assessment periods alter our observations. Third, training periods (e.g., short, medium, and long) should be included in further studies to determine the optimal training length for cognition improvement under hypoxia. Moreover, physiological parameters should be investigated to evaluate the underlying mechanisms of our observed effects. Fourth, although meta-analyses provide a rational way to summarize and quantitatively synthesize a large number of previous empirical studies, it is challenging to account for the unique design characteristics of individual experiments.[54,55] Therefore, the results may be biased by systematic confounding factors that correlate with effect size. For example, this problem may be applied to moderation analyses that include small numbers of studies and to between-study comparisons when we are actually interested in within-subject correlations.[56,57]

5. Conclusions

This meta-analysis demonstrates 2 important findings. First, cognitive function is impaired during hypoxia in resting conditions, particularly for executive function and memory. Second, exercise during exposure to hypoxia plays a key role in improving cognitive function. Various characteristics (e.g., exercise modality) are likely to moderate the relationship between exercise and cognition under hypoxia.

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Authors' contributions

While conducting this review, LZ played a role in conceiving, designing, overseeing data collection, and editing this paper; PDL played a role in conceiving, designing, and overseeing data collection/analysis and editing this manuscript; JJY played a role in collecting data and editing this manuscript; SR played in a role data collection/analysis; ZK, LY, MK, JL, HL, and LS played roles in editing this manuscript; and MJ played a role in analyzing the data and prepared the initial draft of the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Competing interests

The authors declare that they have no competing interests.

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