Hypoxia and Cognitive Ability in Humans: A Systematic Review and Meta-Analysis

Abbreviated title: Hypoxia and Cognition

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ABSTRACT

This systematic and meta-analytical review examined how a reduction in oxygen availability to tissue (hypoxia) affects cognitive function. Hypoxia had a moderate-to-large detrimental effect on general cognitive ability and across domains, including memory, attention, executive function, processing speed, and psychomotor speed. Increased hypoxic severity was associated with greater declines in general cognitive ability and executive function, while longer duration of exposure was associated with greater declines in executive function and psychomotor speed. Participant age was a moderator for executive function and psychomotor speed, with older adults experiencing greater impairments. For executive function and psychomotor speed, the magnitude of these effects was less pronounced during intermittent and hypobaric exposures, potentially due to adaptive physiological mechanisms. While our models accounted for exposure characteristics and age of participants, substantial unexplained variance remained. These findings highlight hypoxia's impact on cognition and emphasize the need to investigate underlying neurophysiological mechanisms that may influence individual vulnerability.

INTRODUCTION

Overcoming reductions in oxygen availability to tissue (hypoxia) is a demanding physiological challenge requiring nervous, respiratory, renal, and cardiovascular adaptation. One of the earliest real-world accounts of cognitive impairment in a high-altitude setting comes from meteorologist James Glaisher and co-pilot Henry Coxwell during their 1862 hot air balloon ascent to 11,000 m above sea level. As altitude increased, Coxwell recounts losing motor control of his hands, while Glaisher lost visual acuity and eventually consciousness. Interestingly, the occurrence of these symptoms of "balloon sickness" intensified progressively during ascent. While anecdotal, this account suggests that hypoxia induces cognitive impairments that may depend on the duration and severity of exposure. Despite advances in our understanding of physiological adaptations to hypoxia, the impact of hypoxia on cognition remains unclear, particularly in relation to exposure severity and duration.

Cognition is a complex process, involving the integration of activity from multiple brain regions to interact and respond to a stimulus in the environment. Although valuable for understanding hypoxia's impact on cognition, real-world assessments in high-altitude environments cannot fully control for changes in barometric pressure and temperature. Considering this, laboratory-based assessments involving the manipulation of oxygen concentrations of inspired air (fraction of inspired oxygen; F_iO_2) allow for investigations of isolated hypoxic effects. In general, impairments in cognitive processes become evident from exposures equivalent to 2,500 to 3,000 m above sea level, but findings remain inconsistent, with hypoxia having a negligible-to-substantial impact on cognition [1, 2]. This inconsistency in findings may be due to the lack of standardization of tasks to assess cognitive processes, with multiple tasks assessing a cognitive process but with differing performance outcomes. Variation in the age of participants, severity, duration, and type (e.g., normobaric, hypobaric, intermittent) of exposure as well as intrinsic brain activity (e.g., periodic and aperiodic components of electroencephalographic [EEG] activity) may also contribute to inconsistent findings [3, 4].

Attentional tasks require the ability to sustain focus on a relevant stimulus while perceiving and appropriately ignoring irrelevant stimuli. Attention has been shown to be impaired in high-altitude exposures, with impairment increasing with the severity of exposure and attentional demand. Attentional performance is maintained at moderate altitudes (2,200 – 3,800 m above sea level) but reduced at extreme altitudes [5,800 m above sea level; 5, 6-8], in some cases persisting once returning to sea level [6]. Interestingly, attentional performance is more impacted by hypobaric exposures of hypoxia compared to normobaric exposures [8]. As attentional impairments are most evident during high-demand tasks [9], these findings suggest that attentional resources may be particularly vulnerable to hypoxia.

Tasks requiring retention and learning, such as those assessing memory-specific processes, have demonstrated similar results. Here, impairments in learning and retention of memory tasks can occur in high altitude and persist once returning to sea level [1 - 2 weeks post-summit; 10]. Studies on memory processing in pilots also demonstrate that increasing hypoxic severity and task complexity are associated with greater performance decrements [11, 12]. Alarmingly, individuals are

mostly unaware of such impairments while actively engaged in the task. Reductions in memory performance coincide with selective reductions in blood flow and delivery in the posterior cerebral artery, which is a primary supplier of oxygen to the hippocampus [8]. This suggests that the hippocampus may play an important role as the locus of hypoxia-induced memory impairment.

Complex tasks, such as performing two tasks simultaneously, place greater demands on executive functions to sustain goal-directed performance amid conflicting or distracting stimuli [13, 14]. In hypoxia, severe exposures have been shown to severely impact executive functions [15-18]. For example, when exposed to 30 – 60 minutes of acute hypoxia, participants exhibit greater reductions in performance during the naming (incongruent) component compared to the reading (congruent) component of the Stroop task [16-18]. Interestingly, increases in the Stroop interference effect are associated with decreasing peripheral blood oxygen saturation [S_pO_2; 18].

Task efficiency is also impacted by hypoxia and is related to the speed of processing and initiating a motor command [19], particularly when cognitive load is high [9, 20]. Hypoxia's impact on processing speed is also dependent on the type of stimulus being processed. Processing speed is reduced when presented with visual and auditory stimuli [9, 20, 21]. However, visual processing may be more impaired due to visual receptors inherently having a greater metabolic demand [22, 23] and involving a more diverse neural network [24]. Considering this, the type of cognitive task is an important factor when considering hypoxia's impact on speed of processing. Hypoxia also reduces an individual's ability to execute motor commands in response to a stimulus [25-28]. This is not surprising since exposure to hypoxia has regularly shown to reduce motor cortical and spinal output [29-32]. Psychomotor performance is reduced with increased reaction time during perceptual-motor tasks [25, 26, 33, 34]. However, this may be primarily due to reductions in processing speed [e.g., reduced visual sensitivity; 26, 33].

As human endeavours move into increasingly challenging environments, such as high altitude, a unique challenge is presented – how can complex cognitive processes operate with limited oxygen supply? Although 50 years of research [1, 2, 15, 35-39] has documented the impact hypoxia has on individual cognitive

processes, a comprehensive meta-analysis examining how factors such as severity, duration, type of exposure, participant age, and cognitive task type influence cognitive effects of hypoxia has not yet been conducted. In addition, previous systematic reviews have been limited by small study sizes [n = 7 - 18 included studies; 2, 35, 36], large variation in the time between onset of exposure and cognitive assessment [10 mins - 5 days; 35], the inclusion of concurrent exercise interventions [15], or a lack of meta-analytical approaches [1, 2, 36-39], all of which have hindered the standardization of hypoxic effects between studies [38].

Our systematic review and meta-analysis aims to provide a comprehensive synthesis of the impact hypoxia has on key cognitive domains including, memory, attention, executive function, processing speed, and psychomotor speed. In doing so, our review will: (1) provide an up-to-date assessment of the body of evidence, (2) address the question of how severity, duration, and type of exposure to hypoxia affects cognition compared to normal oxygen conditions in humans, and (3) what should be the focus of future research to better understand cognition in extreme environments.

RESULTS

Data Extraction

The two authors DJM and VRS agreed on 98.95% of the data items (*n* included= 38/857 data items, κ = .904) and disagreed on 1.05% (n= 9). From the disputed items, eight were ultimately included based on DJA's decision. In total, 46 data items were identified as being suitable for inclusion with measures consisting of author, year of publication, study design, intervention, sample characteristics, hypoxic duration and severity, outcomes, and main findings pertaining to cognitive processes (Table 1).

TABLE 1 HERE

Six data items were identified as having a substantial amount of risk of bias (Table 2). This risk was predominantly from Domain 1 (bias due to confounding effects), where studies either included a concomitant exercise protocol, did not include a control comparison condition (i.e., normoxia/sea level or low-lander

control), or had large participant age variability within the groups. Due to these potential risks of bias, these articles were not included in the meta-analyses.

TABLE 2 HERE

A Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow diagram provides a summary of the inclusion process (Figure 1). A reference list of excluded data items is presented in Supplementary Material 1.

FIGURE 1 HERE

For the general cognitive ability and domain-specific models, significant coefficients are reported in text. For full model results including non-significant coefficients, see Supplementary Material 2. While funnel plots suggest the potential influence of publication bias in model results, the coefficients were similar between the random-effects and *trimfill*-corrected models (Supplementary Material 2). Considering this, the original random-effects and multivariate models are reported below.

General Cognitive Ability

A random-effects meta-analysis was conducted to examine the impact of hypoxia on general cognitive ability independent of moderators (k = 151). The average effect size was moderate and negative (b = -.44, 95% CI = -.55, -.33), and statistically significant (z = -7.75, p < .0001; Figure 2) indicating that hypoxia has a moderate adverse effect on general cognitive ability independent of severity or duration of exposure and other moderators. Substantial heterogeneity was observed in effect sizes across studies (I^2 = 78.72%, p < .0001, τ^2 = 0.37, τ = 0.61, H^2 = 4.70), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

FIGURE 2 HERE

The multivariate model (k = 141) was a significant improvement over the reduced model (LRT = 40.70, p < .0001; full model: logLik = -172.28, AIC = 370.80, QE = 529.27; reduced model: logLik = -192.63, AIC = 389.34, QE = 661.83) indicating that the inclusion of the moderators explained more heterogeneity in the data, and a larger proportion of the variance (QM(7) = 29.19, p < .001).

Regarding the effects of each moderator, the severity of hypoxia was associated with greater impairment in general cognitive ability (b = 10.39, SE = 3.15, z = 3.30, p = .001, 95% CI = 4.22, 16.56).This result indicates that as the severity of hypoxia increases, so does the severity of impairment in general cognitive ability (Figure 3). The psychomotor speed domain was also a significant moderator with hypoxic impairment seen in general cognitive ability (b = -.48, SE = .12, z = -4.12, p < .0001, 95% CI = -.71, -.25), suggesting that psychomotor speed may be more adversely impacted by hypoxia compared to other cognitive domains. A moderate level of variance in effect sizes (σ^2 = 0.20, sqrt = .44) and a significant level of residual heterogeneity (QE(143) = 509.09, p < .0001) remained across studies, indicating that factors other than the included moderators contributed to the variance observed.

FIGURE 3 HERE

Attention

A random-effects meta-analysis was conducted to examine the impact of hypoxia on attention (k = 33). The average effect size was small and negative (b = -.25, 95% CI = -.43, -.06), and statistically significant (z = -2.61, p = .009; Figure 4) indicating that hypoxia has a small adverse effect on attention independent of severity or duration of exposure, and other moderators. Substantial heterogeneity was observed in effect sizes across studies (I^2 = 67.27%, p < .0001, τ^2 = 0.19, τ = 0.44, H^2 = 3.06), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

The inclusion of the multivariate model (k = 33) was not a significant improvement over the reduced model (LRT = 7.61, p = .18; full model: logLik = -23.28, AIC = 65.03, QE = 76.18; reduced model: logLik = -27.08, AIC = 58.56, QE = 98.19) indicating that the inclusion of the moderators did not explain more heterogeneity or a significant proportion of the variance in the data (QM(5) = 6.73, p = .24). A moderate level of variance in effect sizes (σ^2 = 0.14, sqrt = .37) and a significant level of residual heterogeneity (QE(27) = 76.18, p < .0001) remained across studies, indicating that factors other than the included moderators contributed to the variance observed.

Memory

A random-effects meta-analysis was conducted to examine the impact of hypoxia on the memory domain (k = 44). The average effect size was moderate and negative (b = -.33, 95% CI = -.54, -.13), and statistically significant (z = -3.17, p = .002; Figure 4), indicating that hypoxia has a moderate adverse effect on memory independent of severity or duration of exposure, and other moderators. Substantial heterogeneity was observed in effect sizes across studies (I^2 = 76.25%, p < .0001, τ^2 = 0.35, τ = 0.59, H^2 = 4.21), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

The inclusion of the multivariate model (k = 44) was a significant improvement over the reduced model (LRT = 38.79, p < .001; full model: logLik = -18.72, AIC = 88.86, QE = 57.45; reduced model: logLik = -38.11, AIC = 80.51, QE = 179.00) indicating that the inclusion of the moderators explained more heterogeneity and a significant proportion of the variance in the data (QM(14) = 30.16, p = .007).

Regarding the effects of each moderator, tasks that rely on episodic memory were significant (b = -2.54, SE = .93, z = -2.72, p = .007, 95% CI = -4.38, -.712), suggesting that episodic memory may be more adversely impacted by hypoxia compared to other memory tasks (e.g., working and associative memory). A moderate level of variance in effect sizes (σ^2 = 0.27, sqrt = .52) and a significant level of residual heterogeneity (QE(29) = 57.30, p = .001) remained across studies, indicating that factors other than the included moderators contributed to the variance observed.

Executive Function

A random-effects meta-analysis was conducted to examine the impact of hypoxia on the executive function domain (k = 43). The average effect size was large and negative (b = -.67, 95% CI = -.91, -.43), and statistically significant (z = -5.45, p < .0001; Figure 4) indicating that hypoxia has a large adverse effect on executive function independently of severity or duration of exposure, and other moderators. Substantial heterogeneity was observed in effect sizes across studies (I^2 = 84.64%, p < .0001, τ^2 = .53, τ = .73, H^2 = 6.51), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

The inclusion of the multivariate model (k =43) was a significant improvement over the reduced model (LRT = 109.26, p < .0001; full model: logLik = -8.55, AIC =

121.20, QE = 33.89; reduced model: logLik = -63.18, AIC = 130.66, QE = 236.87) indicating that the inclusion of the moderators explained more heterogeneity and a significant proportion of the variance in the data (QM(21) = 204.96, $p < .0001$).

Regarding the effects of each moderator, the severity of hypoxia was associated with greater impairment in executive function ($b = 11.81$, SE = 4.06, $z = 2.91$, $p = .004$, 95% CI = 3.86, 19.76; Figure 5), as well as longer durations of exposure ($b = -.18$, SE = .09, $z = -2.07$, $p = .038$, 95% CI = -.35, -.01), especially in normobaric exposures ($b = -.57$, SE = .29, $z = -1.97$, $p = .048$, 95% CI = -1.13, -.01). A range of executive function tasks were identified as being less impacted by hypoxia, including cognitive flexibility ($b = 1.88$, $p < .0001$), decision making ($b = 1.81$, $p < .001$), calculation error ($b = 3.13$, $p < .0001$), map orientation ($b = 1.90$, $p < .0001$), verbal fluency ($b = 2.69$, $p < .0001$), non-verbal fluency ($b = 2.25$, $p < .001$), proof reading ($b = 1.42$, $p = .041$), reasoning ($b = 1.98$, $p < .0001$), risk taking ($b = 1.79$, $p < .0001$), and spatial tracking ($b = 1.45$, $p < .0001$). Normobaric exposures of hypoxia had a greater impact on executive function compared to intermittent and hypobaric exposures ($b = -.57$, SE = .29, $z = -1.97$, $p = .048$, 95% CI = -1.13, -.01). Participant age was also a significant moderator ($b = -.06$, SE = .019, $z = -2.86$, $p = .004$, 95% CI = -.09, -.02), suggesting that hypoxia's effect on executive function increases with participant age. The estimated between-study variance was negligible ($\sigma^2 < 0.01$), and residual heterogeneity was not statistically significant (QE(21) = 31.91, p = .06), suggesting that effect sizes were highly consistent across studies, though unexplored factors may still contribute to some remaining variability.

Processing Speed

A random-effects meta-analysis was conducted to examine the impact of hypoxia on the processing speed domain ($k = 18$). The average effect size was moderate and negative ($b = -.30$, 95% CI = -.54, -.05), and statistically significant ($z = -2.37$, $p = .018$; Figure 4) indicating that hypoxia has a moderate adverse effect on processing speed independent of severity or duration of exposure, and other moderators. Substantial heterogeneity was observed in effect sizes across studies ($I^2 = 64.43\%$, $p < .0001$, $\tau^2 = 0.17$, $\tau = 0.42$, $H^2 = 2.81$), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

The inclusion of the multivariate model (k = 18) was a significant improvement over the reduced model (LRT = 112.24, $p < .0001$; full model: logLik = -12.87, AIC = 111.19, QE = 35.85; reduced model: logLik = -63.17, AIC = 129.65, QE = 243.87), indicating that the inclusion of the moderators did explain more heterogeneity in the data. However, the inclusion of the moderators did not explain a significant proportion of the variance (QM(6) = 0.62, p = .99). There was still a moderate level of variance in effect sizes across studies (σ^2 = .46, sqrt = .68), indicating that the other factors outside of the included moderators contribute to the variance seen in effect sizes.

Psychomotor Speed

A random-effects meta-analysis was conducted to examine the impact of hypoxia on the psychomotor domain (k = 11). The average effect size was large and negative (b = -.72, 95% CI = -1.10, -.33), and statistically significant (z = -3.61, $p <$ .001; Figure 4) indicating that hypoxia has a large negative effect on psychomotor speed independent of severity or duration of exposure, and other moderators. Substantial heterogeneity was observed in effect sizes across studies (I^2 = 76.59%, $p < .0001$, τ^2 = 0.31, τ = 0.56, H^2 = 4.27), suggesting that factors beyond the primary study variables contributed to the variability in effect sizes.

The inclusion of the multivariate model (k = 11) was not a significant improvement over the reduced model (LRT = .52, p = .97; full model: logLik = -8.13, AIC = 49.27, QE = 30.68; reduced model: logLik = -8.39, AIC = 22.29, QE = 45.86) indicating that the inclusion of the moderators did not explained more heterogeneity or a larger proportion of the variance in the data (QM(7) = 6.52, p = .48).

Regarding the effects of each moderator, duration of hypoxia was associated with greater impairment in psychomotor speed (b = -.17, SE = .07, z = -2.43, p = .015, 95% CI = -.30, -.03; Figure 5), indicating that the impact of hypoxia on psychomotor speed increases as the length of exposure increased. The type of hypoxic stimulus was also a significant moderator where effects were greater in hypobaric (b = -5.99, SE = 2.67, z = -2.25, p = .025, 95% CI = -11.22, -.76) and normobaric hypoxia (b = -8.51, SE = 3.79, z = -2.25, p = .025, 95% CI = -15.94, -1.09) compared to intermittent hypoxia. Participant age was a significant moderator (b = -.23, SE = .11, z = -2.02, p = .043, 95% CI = -.45, -.01), suggesting that

hypoxia's effect on psychomotor speed increases with participant age. A negligible level of variance in effect sizes across studies (σ^2 = .23, sqrt = .48) and a significant level of residual heterogeneity (QE(3) = 8.52, *p* = .036) remained, indicating that factors other than the included moderators contributed to the variance observed.

FIGURE 4 & 5 HERE

DISCUSSION

In this systematic and meta-analytical review, we provide robust evidence that hypoxia impairs general cognitive ability, alongside domain-specific functions including attention, memory, executive function, processing speed, and psychomotor speed. By including exposure severity, duration, type, participant age, and task characteristics, our models reveal that the impact of hypoxia on cognition is complex, not uniform, and dependent on the combination of moderating factors.

Hypoxia impairs both general and domain-specific cognitive function

We categorised general cognitive ability by pooling the performance of memory, attention, executive function, processing and psychomotor speed processes. We then constructed domains based on commonalities in cognitive tasks assessed in each study. Overall, hypoxia had a moderate negative effect on general cognitive ability, indicating that oxygen availability is integral for maintaining general cognitive function. However, not all cognitive domains had equal impairment. The psychomotor speed domain was more negatively impacted by hypoxia compared to other domains of the general cognitive ability model. This was also reflected in the domain-specific models, with psychomotor speed having the largest pooled negative effect of hypoxia.

Psychomotor speed reflects the efficiency of the sensorimotor system and is typically characterised by the speed at which one can efficiently elicit a motor response to a perceptual stimulus, resulting in voluntary movement [40]. Reductions in psychomotor processes typically begin from mild severities of hypoxia, primarily due to motor speed and accuracy reductions [37]. At moderate-to-severe altitudes (~4,000 m – 6,000 m above sea level), hypoxia has been shown to impair both perceptual and motor components of the sensorimotor system, including reduced

integration of sensory information [21, 41], decreased physiological tremor [42], diminished voluntary output from the motor cortex [31, 43], and lowered excitability of both cortical and spinal motoneurons [29, 30, 44]. However, whether reductions in psychomotor performance is due to reductions in processing speed or reaction time to initiate a motor response remains unclear. Given that processing speed was negatively affected in our model, but H-reflex and M-wave latencies (known markers of spinal and peripheral nerve conduction) typically remain unchanged under hypoxic conditions [45, 46], it is plausible that hypoxia has a stronger impact on speed of processing rather than speed of motor output.

More complex cognitive domains were impaired by hypoxia, such as attention, memory, and executive function. However, not all tasks within these domains were impaired to the same extent. Of all cognitive domains, attention was the least affected by hypoxia, even in models accounting for various moderators. This effect may be due to the limited characteristics of tasks used to assess attention. Here, most tasks (e.g., Stroop, go-no-go, and flanker task) focus on response inhibition, which may reflect only one aspect of attention.

In the memory domain, episodic memory was more impaired by hypoxia compared to working and associative memory. Episodic memory typically requires individuals to recall details about previous events such as recalling a set of words, events, or pictures [47]. Episodic memory has long been recognised to be dependent on the integrity of the hippocampus [48, 49], with hippocampal lesion studies demonstrating impairments in episodic memory but not visual pattern matching or schematic spatial knowledge [50-52]. The hippocampus is known to be particularly susceptible to hypoxia due to its high metabolic activity and dense synaptic connectivity [53-58]. Here, investigations into the impact hypoxia has on animal models provide insight into the potential underlying mechanisms responsible for the decrements seen in hippocampal function when exposed to hypoxia. Specifically, when exposed to transient continuous oxygen deprivation, the CA3-CA1 synapses and NMDA receptors of CA1 neurons of the rodent’s hippocampus exhibit long-term potentiation indicative of pathological hyperexcitability [59-63], disruptions to modulatory neurotransmitter activity [e.g., reduced ACh production; 64, 65], and altered firing of excitatory and inhibitory neurons [66]. These intrinsic neuronal adaptations have a detrimental impact on key cognitive processes. Indeed, exposure

to hypoxia is known to impair memory in mice when performing maze tasks [64, 67, 68] and passive avoidance tasks [69], which may recover after adaptation has occurred [70]. As episodic memory is reliant on CA1 and CA3 hippocampal neurons, it is unsurprising that memory, and particularly episodic memory, is susceptible to hypoxia-induced impairments.

Executive function was also negatively impacted by hypoxia, but more pronounced in some tasks than others. This likely reflects the heterogeneous nature of the tasks used to assess executive functions. For example, verbal fluency tasks involve language-based processes while non-verbal fluency relies on visuospatial skills, both of which are categorised as executive functions. Therefore, accounting for heterogeneity in tasks may help explain some of the variance remaining in the moderator model. Executive function tasks are strongly reliant on prefrontal cortical activity, which is sensitive to hypoxia [71]. However, tasks that were less affected included cognitive flexibility, verbal and non-verbal fluency, decision making, reasoning, risk taking, and map orientation performance. These less effected tasks may rely on more distributed neural networks outside of the prefrontal cortex, such as the parietal and temporal cortices [13, 14, 72]. Considering this, performance preservation in these tasks may reflect compensation from other cortical regions (less of a dependence on prefrontal cortical activity), rather than the resilience of executive function.

Type, severity, and duration modulate hypoxia's impact on cognition

The meta-analyses included studies performed in normobaric, hypobaric, and intermittent hypoxia. Variations in physiological adaptations across these types of exposure may account for some of the unexplained variance. For instance, when hypoxia is encountered in hypobaric environments, reductions in atmospheric pressure and temperature typically occur. This can alter respiratory, haematological, circulatory, and metabolic adaptations [73]. Similarly, intermittent exposure to hypoxia can produce a hormetic response [74]. This enhances pulmonary function, lowers blood pressure, mitigates inflammation, and increases cardiac vagal activity, leading to improved cognition, particularly in older populations [36, 74]. Further consideration needs to be given to other environmental factors outside of isolated hypoxic effects that could contribute to alterations in cognitive performance. For

example, cold stress can impact executive functioning and memory performance but is dependent on task complexity and attentional demand [2]. It is likely that adaptive processes that occur with hypobaric and intermittent exposures also mitigated hypoxia's impact on some cognitive domains.

Severity of hypoxia exposure was associated with lower performance in general cognitive ability and the executive function domain, whereby performance was reduced to a greater extent at more severe exposures. As physiological adaptations to hypoxia have an upper limit of mitigation [75], it is likely that at extreme altitudes impairment in cognitive function is unavoidable. However, as prolonged exposures to hypoxia result in more long-term adaptations [73, 76], paradoxically, remaining at a moderate level of altitude over a prolonged duration may also lessen the impact of hypoxia on some cognitive processes. This may explain why duration of exposure was associated with worse performance in the executive function, and psychomotor domains but not the general cognitive ability, nor attention, memory, and processing speed domains. Why severity and duration moderator effects were seen in some domains but not others remains unclear.

Limitations

While a substantial amount of variance was explained by the inclusion of domain or task, participant age, and severity, duration, and type of hypoxia, a moderate amount of unexplained variance remained for all models. At the task level, previous reviews have identified the challenge of comparing between tasks to assess a common cognitive process [38]. We aimed to account for this variance by assessing standardised effects while controlling for the weighting of each effect across the studies included. It is well known that aging is associated with cognitive decline in a range of cognitive processes [77, 78]. This was reflected in our meta-analyses as increasing participant age was associated with greater hypoxic impairment in executive function and psychomotor speed domains. Greater cognitive impairment in older individuals during hypoxia is likely due to reduced ability to effectively compensate for cognitive deficits, which are already associated with age-related cognitive decline [79]. For example, oxygen availability to active neural tissue is typically reduced by greater cerebrovascular resistance associated with aging, which reduces oxygen supply-demand and increases relative cognitive load [80].

Individual alpha peak frequency of the EEG is reflective of changes in cognitive load [81] and has been linked to variation in processing speed [81], memory [82], and attention [83]. Aperiodic activity, also referred to the level of 'neural noise' in the brain, has been linked to better cognitive performance in young and older populations [77, 84, 85]. Individuals who have greater exponents (reflective of reduced excitation:inhibition balance) and offsets (greater neural spiking) also exhibit better cognitive performance during processing speed [84], memory [86-88], and executive function [89] tasks. EEG research in hypoxia has, however, primarily focused on periodic activity [for review see 4]. Hypoxia has shown to left shift peak alpha frequency, indicated by a reduction in alpha power and an increase in theta power in canonical frequency bands [90] but see [91]. Hypobaric exposure to hypoxia reduces the exponent, reflective of a 'noisier' brain akin with non-pathological alterations in brain activity with age [3]. Considering this, future EEG research needs to focus on uncovering how hypoxia impacts aperiodic EEG activity and how this is associated with variation in hypoxia-induced reductions in cognitive performance.

Conclusion

We provide meta-analytical evidence that exposure to hypoxia has a moderate-to-large negative effect on general and domain-specific cognitive function. These effects are moderated by the severity or duration of exposure, depending on the cognitive task. Intermittent and hypobaric exposures of hypoxia may have a lower impact cognitive function due to protective adaptative physiological processes leading to increased hypoxia tolerability. Aging was associated with greater impairment in hypoxia in executive function and psychomotor speed. Although these findings align with the evidence of previous reviews indicating that hypoxia has a net negative effect on cognitive performance, a moderate level of unexplained variance remained due to moderating factors outside of those included in the meta-analysis. This variance may be explained by differences in underlying intrinsic brain activity that has previously been associated with performance differences in cognitive tasks. Considering this, future research should aim to uncover how these neural correlates change with hypoxic exposure.

METHOD

This systematic and meta-analytical review aligned with the 2020 PRISMA guidelines [92].

Eligibility Criteria

Eligibility criteria conformed to the population, intervention, comparator, outcome, setting, types (PICOST) framework. Data items included all relevant randomised-controlled trials, observational studies, longitudinal studies, cohort studies, case-control studies, before-after studies, and cross-sectional studies or surveys involving healthy humans exposed to either environmental (high altitude) or simulated (laboratory-based) hypoxia. Studies were included if they used normal oxygen, sea-level conditions, or low-landers as a comparator and measured outcomes related to memory, attention, executive function, processing speed, or psychomotor speed. Data items with hypoxic exposure due to pathology (e.g., chronic obstructive pulmonary disease), with interventions that were pharmaceutical or exercise-based, which did not have suitable comparators, or conducted in a hospital-based setting, were excluded from the review.

Data Sources & Search Strategy

The Evidence Research Accelerator [TERA; 93] suite was used to aid in the data source and search strategy, and data screening and selection process. The SearchRefiner tool [94] of TERA was used to aid in data sourcing and developing the search strategy. A literature search querying SCOPUS, PubMed, Medline, and Cochrane Library from inception to 6th January 2025 was performed. Search queries consisted of the terms “Hypoxia” or “Altitude”, or “Hypobaric”, and “Cognition” or “Attention” or “Memory” or “Executive Function” or “Processing Speed” or “Psychomotor Speed” with each of their combinations searched in each respective database. Thirteen seed PMIDs were used as “relevant citations” to aid in refining the literature search (Supplementary Material 1). In total, 858 data items were identified in the literature search. Using the Deduplicator tool [95] of TERA, one data item was identified as ‘likely being a duplicate’ and was removed [96], bringing the total number of data items to 857.

Selection & Data Collection Process

Authors DJM and VRS independently screened the citation search, title/abstract, full-texts, and trial registries for inclusion of data items against the inclusion and exclusion criteria. Any disagreements regarding data item inclusion were resolved by referring to the third author, DJA.

Risk of Bias

The ROBINS-I V2 assessment tool for non-randomised interventional studies was used to assess risk of bias within and between data items. Bias was assessed against seven domains: bias due to confounding (Domain 1), bias in the classification of interventions (Domain 2), bias in the selection of participants (Domain 3), bias due to deviation from intended intervention (Domain 4), bias due to missing data (Domain 5), bias arising from measurement of the outcome (Domain 6), bias in the selection of the reported result (Domain 7). For Domain 1, confounding factors consisted of participant-related, task-related, environment-related, and methodology-related factors (Table 3). Risk of bias assessments were performed by authors DJM and VRS. Any discrepancies between studies were evaluated by the third author, DJA. A list of data items identified as being of moderate–severe risk during the risk of bias assessment is presented in Table 2 (n = 6).

TABLE 3 HERE

Meta-analysis

Meta-analyses were performed in *R* (v 4.3.1) using the *metafor* package (v 4.8-0). A general cognitive ability construct was created, including all cognitive tasks, measured in the data items. Cognitive domain constructs for attention, memory, executive function, processing speed, and psychomotor speed were created from data items categorized in specified cognitive tasks (Table 4).

TABLE 4 HERE

Firstly, for the general cognitive ability and individual cognitive domains, a reduced model was calculated, which consisted of including study ID as a random-effect without including moderators. Following this, a full model was calculated by performing a multivariate mixed-effects model, which included moderators. Previous literature suggests that the impact of hypoxia on cognition may be dependent on the severity (F_iO_2 level) and duration (minutes of exposure) of the hypoxic stimulus.

Accordingly, severity and duration of hypoxia were included as moderators in the multivariate model. For studies comparing highlanders to lowlanders, we treated the highlanders' exposure duration as chronic and used the mean age of participants (in minutes) as a proxy for duration. Due to large variability in duration of exposure and skewness between studies, duration of exposure was log-transformed. Additionally, the type (normobaric hypoxia, hypoxia in barometric pressure equivalent to sea level; hypobaric hypoxia, hypoxia in barometric pressure lower than sea level; intermittent hypoxia, cyclic exposures to normobaric hypoxia typically in one minute intervals) of stimulus, cognitive domain for the cognitive ability model, cognitive task for the individual domain models, and participant age, were added as additional moderators to identify if the effects of hypoxia are type-, domain/task-, and age-specific. The reduced and full models were compared against each other using an ANOVA. In both models, Hedge's *g* (standardised mean difference) was calculated to quantify the effect size of each cognitive outcome measure, and 95% confidence intervals were used for variance in effect size.

Forest plots were used to visualise the relationships between effect sizes and the overall random effect. Funnel plots were used to inspect publication bias (Figure 6 and Supplementary Material 2). The *trimfill* function of the *metafor R* package was used to correct effect sizes for potential confounding of publication bias (Supplementary Material 2). Positive Hedge's *g* scores indicate better cognitive performance in hypoxic conditions, while negative Hedge's *g* scores indicate worse cognitive performance in hypoxic conditions. To visualise the relationship between hypoxia severity and cognitive ability decline, a meta-regression based on the multivariate mixed effects model was fit to a predicted dataset where severity was varied across its observed range derived from the 152 effect sizes. The duration of exposure and participant age were held constant as the average means in the general cognitive ability model (duration = 11 hours, participant age = 30 years).

FIGURE 6 HERE

DATA AVAILABILITY

Collated data and analysis code used in this manuscript can be found at https://github.com/MindSpaceLab/Hypoxia_Cognition_Review

COMPETING INTERESTS AND FUNDING

The authors declare that no competing interests exist, and no funding was obtained for this work.

AUTHOR CONTRIBUTIONS

Conceptualization: D.J.M., D.J.A, and V.R.S.; Data curation: D.J.M., D.J.A, and V.R.S.; Formal analysis: D.J.M., D.J.A, A.A.M., and V.R.S; Project administration: D.J.M.; Visualization: D.J.M.; Writing - original draft: D.J.M., D.J.A, A.A.M., and V.R.S.; Writing - review & editing: D.J.M., D.J.A, A.A.M., and V.R.S.

Table 1. Characteristics of included data items (n = 46).

Author & Year	Design	Intervention	Sample characteristics	Duration	Severity	Outcome measures	Main cognitive findings
Aebi et al., 2020 [97]	Non-randomised cross-over	NN, HH, NH, HN	16 healthy pilot trainees, 26 ± 4 yr	30 min	NN, HN = 440m HH, NH = 5500m	KLT KSS	↑ KLT error in NH & HH ↓Calculations in HH
Ando et al., 2023 [8]	Non-randomised cross-over	NN, HH	12 males, 23 ± 2 yr	7 hr	NN = 0.21 F_iO_2 HH = 0.12 F_iO_2	Go/No-Go Memory task accuracy	↓ Memory task accuracy in HH ↔ Go/No-Go RT & accuracy
Asmaro et al., 2013 [11]	Repeated measures within subject	NN, HH	35 aviation industry employees, 19-69 yr	30 min	NN = SL HH1 = 5335m HH2 = 7620m	ST DST Forward & Back TMT A & B	↓ Performance during ST and DST Forward & Backward, & TMT A&B in HH
Bailey et al., 2019 [98]	Cross-sectional observational	-	23 male highlander 17 male lowlanders	-	Highlanders = 3640m Lowlanders = 80m	RAVL RDF & RDB TMT A & B DSST GPDT	↓ RAVLT, RDB, RDF, TMT B, DSST, ST in highlanders compared to lowlanders
Bakhare v et al., 1981 [99]	Repeated measures within subject	LA, HA	7 young men	8 days	HA = 3400-3600m	Visual, short term, long term, operative, figurative, associative, involuntary, and auditory memory (RAVLT-like)	↓ Memory at day 2 Those of central Asia (highlanders) had less severe reductions compared to Pskov Region (lowlanders).
Blogg et al., 2006 [100]	RCT	NN, HH	13 subjects, 29.5 ± 6.4	10 min	21kPa, 15kPa, 10kPa P_iO_2	FCRT Mannequin test Finger-tapping test Medium-tapping test	↔ Psychomotor performance at 15kPa ↑ FCRT and medium-tapping test error at 10kPa. Although participants perceived being more focused
Bloomfield et al., 2023 [101]	RCT	NN, PCH, ICH	12 adults, 26 ± 6.2 yr	30 min	10% oxygen gas (5500m)	CNSVS test battery	↓ Neurocognitive index score, cognitive flexibility, complex attention, composite memory, and visual memory in PCH ↓ Neurocognitive index score, composite memory, psychomotor

							speed and ↑ RT in ICH
Bonnon et al., 1995 [102]	Comparative	NN, HH	6 subject experimental and unspecified control group	60 hr	4383m	Cognitive-motor task	↑ Cognitive-motor performance in control group ↔ Performance in experimental group comparable once at 60 hrs.
Bonnon et al., 1999 [103]	Comparative	NN, HH	7 subject experimental and unspecified control group	17 days	9 days at 3500-4400m, 8 days climbing 500m/day to 5400m	Cognitive motor task	↔ Difference between experimental and control group.
Bouquet et al., 1999 [28]	Comparative	NN, HH	8 male climbers, 24 – 37 yr 10 controls, 22 – 40 yr	31 days	Simulated climb to 8848m	Purdue pegboard, recognition task	↓ Purdue pegboard performance > 8000m ↓Recognition performance in from 5500m ↓Performance in complex task vs simpler task
Champod et al., 2013 [104]	Non-randomised cross-over	NN, IH	17 healthy males	6 hrs of 1min on/1 min off	-	*n*-back task	↑RT during spatial but not verbal n-back task in IH across all levels of difficulty
Chroboczek et al., 2023 [105]	Non-randomised cross-over	NN, NH	17 healthy males	15 min	NH = 0.13 F_iO_2	ST	↔ ST reading and naming interference
Crow et al., 1971 [106]	Repeated measures within subject	HH	86 medical students, 19 – 30 years. Organised into groups of 4 or 6	30 min	HH = 609m, 2438m, or 3656m	Required to memorize sequences of 6 digits at 1Hz (n-back-like task) to assess short-term memory	↔ error rate between conditions
Davis et al., 2015 [27]	Comparative	HH	132 residents into three groups based on altitude of residence (0-1500m, 1501-3000m, >3000m)	-	Testing occurred at 4860m	Go/no-go test score VFT Hand movement test	↔ VFT ↓ Go/no-go in >3000m group ↓ Correct hand movements in >3000m and 1500-3000m group compared to 1500m group
Falla et al.,	RCT	NN, HH	48 pre-hospital emergency service	30 min	NN = 200m HH = 3000m or 5000m	PVT BART	↓ PVT at 5000m compared to 200m, no difference in other test Participants

2024a [107]			personnel			DSST VAS	did not detect ↓ PVT on VAS
Falla et al., 2024b [108]	RCT	HH	36 pre-hospital emergency service personnel	30 min	Two trials at 4000m, one with supplement oxygen and one without (control)	PVT DSST *n*-back GPDT	↑ PVT with oxygen supplementation ↑ 0.37ms in PVT each % reduction in S_pO_2.
Gerard et al., 2000 [109]	Randomised cross-over	NH	23 healthy adults	2 hr	NH = 5000m with and without 6% O_2 enrichment	Story Memory TMT A&B DSST Finger Tapping Digit Vigilance GPDT PASA Matrix Reasoning KSS Probed Memory Recall PVT CPT CTT PERS VAS	↓ RT in all tasks with O_2 enrichment ↑ Hand-eye coordination, and mood with O_2 enrichment.
Guo et al., 2017 [110]	Observation	NN, HH	163 healthy adults	24 hr	HH = 3700m	RT Attention DSST DST Pursuit aiming	↔ Cognitive measures between those with headache and those without at HA
Hill et al., 2014 [111]	Comparative	LA, HA	229 in total: children (4-10 yr, LA = 44, HA = 52), adolescents (13-16 yr, LA = 23, HA = 25), young adults (25-40yr, LA = 20, HA = 20), older adults (>50 years, LA = 22, HA = 23)	-	LA = 500m HA = 3700m	Cognitive Drug Research battery	↓ Processing speed, attention in HA participants compared to LA.
Hohenauer et al., 2022 [112]	Randomised cross-over	NN, NH, HH	20 healthy participants, 27.6 yr	NH = 15 min HH1 = 1hr HH2 =	NN = 550m NH = .144 F_iO_2 HH = 2980m	ANAM	↔ RT, logical relations, math processing, switching, and *n* back tests in any condition

				24 hr			
Keeler et al., 2023 [113]	Repeated measures within subject	NN, NH	21 healthy adults, 27 ± 5 yr	90 min	NN = 0.206 F_iO_2 NH = 0.14 F_iO_2	Gridshot Capacity Multitracker	↔ no difference in any gamified task.
Koller et al., 1993 [114]	Comparative	NH	10 acclimatised mountaineers and 11 non-acclimatised controls	-	NH = 6000m	Attentiveness	↓ Attentiveness in lowlanders compared to highlanders >4000m
Latshang et al., 2013 [115]	Randomised cross-over	NN, HH	51 healthy men, 24 yr	2 days at each HH level	NN = 490m HH1 = 1630m HH2 = 2590m	PVT, DASS, *n*-back tasks	↔ All cognitive tasks across conditions.
Legg et al., 2016 [116]	Randomised cross-over	NN, HH	36 air force personnel	30 min	HH1 = 8000ft HH2 = 12000ft	ANAM	↔ All cognitive tasks across conditions
Malle et al., 2013 [12]	Comparative	NN, HH	28 pilots in HH and 29 control pilots	90 min	NN = SL HH = 10000m	PASA	↓ Working memory in HH group compared to NN
Merz et al., 2013 [117]	Comparative	NN, HH	32 mountaineers, separated into two groups summitting at different rates	-	NN = SL HH1 = 4497m HH2 = 5533m HH3 = 6265m	LB VFT RFFT CT	↔ All cognitive tasks across conditions
Niedermeier et al., 2017 [118]	RCT	NN, IH, HH	52 participants into a sham or IH pre-acclimatisation group	NN, IH = 1hr HH = 12 hr	NN = 0.2 F_iO_2 IH = 0.13 F_iO_2 HH = 0.13 F_iO_2	Game of Dice Task	↓ Risky decision making in HH for IH group compared to sham
Noble et al., 1993 [119]	Comparative	NN, NH	2 groups of 12 male subjects	30 min	NN = SL NH = 78% S_pO_2	TMT DSST LRT RT	↓ Performance of TMT and no learning effect in NH group compared to sham. ↑ RT
Parker et al., 2017 [120]	Comparative	NN, NH	10 orthopaedic surgeons into either NN or NH group	45 min	NN = SL NH = 0.14 F_iO_2	VWMC	↔ VWMC tasks across conditions
Pighin et al., 2014 [121]	Randomised cross-over	NN, NH	26 university students, 23 ± 6.8 yr	60 min	NN = 0.21 F_iO_2 NH = 0.14 F_iO_2	Decision-making task	↓ Loss aversion in NH compared to NN.

Quackenbush et al., 2016 [122]	Comparative	NN, HH	1 group performed VIHT 1 group performed sham	30 min	HH1 = 3048m HH2 = 3658m	ST SDMT DST	↑ ST and SDMT performance for VIHT group compared to sham
Ramirez-delaCruz et al., 2025 [123]	Randomised cross-over	NN, NH	19 participants, 23.7 ± 3.9 yr	45 min	NN = SL NH1=0.15 F_iO_2 NH2=0.13 F_iO_2 NH3=0.11 F_iO_2	Memory task, Go/No-go task (sustained attention), Ericksen Flanker test, BAT (anticipation), RT	↑ sustained attention at NH1, ↑ anticipation at NH1 & NH3, ↑ RT at NH3 ↔ no difference across conditions
Rice et al., 2019 [124]	Repeated measures within subject	NN, NH	60 aviation students	5 min/level	NN = SL NH1 = 2438m NH2 = 3658m NH3 = 4877m NH4 = 6096m	Visual Sequence Comparison X-Plane	↓ Visual Sequency Comparison & X-Plane performance in NH compared to NN
Schega et al., 2016 [125]	RCT	NN, IH	34 participants, 60 – 75 yr	90 min	IH = 90-85% S_pO_2	ST	↑ ST performance in IH group
Schega et al., 2013 [126]	RCT	NN, IH	34 participants, 60 – 75 yr	90 min	IH = 90-85% S_pO_2	ZVT	↑ ZVT performance in IH group
Schlaepfer et al., 1992 [127]	Repeated measures within subject	NN, HH, NH	10 healthy subjects	-	HH = 3450m NH = 0.145 F_iO_2	Read briefly displayed letters	↓ time needed to read letters in HH and NH
Shukitt-Hale et al., 1998 [128]	Repeated measures within subject	NN, HH	23 army personnel, 18-29 yr	4.5 hr	NN = 550m HH1 = 4200m HH2 = 4700m	Battery of cognitive tasks	↓ Performance in battery of cognitive tasks only after a few hours of exposure in a grade dependent fashion
Tesler et al., 2015 [129]	Randomised cross-over	NN, HH	26 participants, 26.9 yr	2 days	NN = 490m HH1 = 1630m HH2 = 2590m	Visio-motor learning task	↓ Sleep dependent memory performance in HH conditions
Thomas et al., 2007	Prospective	HH	11 subjects, 27 ± 1.5 yr	9 hr	HH1 = 7700ft HH2 = 10000ft HH3 = 13000ft	PVT *n*-back	↔ No difference in PVT & *n*-back

[130]							
Turner et al., 2015a [131]	Randomised match-paired	NN, NH	22 adults, 23 yr	50 min	NN = SL NH = 0.1 F_iO_2	CNS Vital Signs	↓ Performance in CNS Vital Signs
Turner et al., 2015b [132]	Randomised match-paired	NN, NH	15 adults, 21-55 yr	90 min	NN = SL NH = 0.1 F_iO_2	CNS Vital Signs	↓ Performance in CNS Vital Signs
van der Post et al., 2002 [133]	Randomised cross-over	NN, NH	12 healthy subjects	2 hr	NN = 97% S_pO_2 HH1 = 90% S_pO_2 HH2 = 80% S_pO_2	Memory task RT	↑ RT in HH2 compared to HH1 and NN. ↑ Cognitive performance in HH1 compared to NN and HH2
Van Dorp et al., 2007 [134]	RCT	NH	22 healthy subjects	45 min	Sham hypoxia = 103 mmHg $PetO_2$ without inspired CO_2 Isocapnic hypoxia = 40mmHg with 0.4 mmHg clamped CO_2 Poikilocapnic hypoxia = 40mmHg without CO_2	PVT and MAT-bat	↓ Performance in PVT and MAT-bat
Wu et al., 2023 [135]	RCT	NN HH	82 males 20.76 ± 1.6, into control or a RIPC group	6 days	HH = 3680m	WHO-NCTB	↑ Spatial memory and digit symbol performance in RIPC group compared to controls ↑ Spatial memory performance in RIPC group compared to RIPC at baseline
Yan et al., 2011a [136]	Comparative	NN HH	2 groups: 1 born at SL, the other in HA	-	-	*2*-back task	↔ Working memory performance
Yan et al., 2011b [137]	Comparative	NN HH	2 groups: 1 born at SL, the other in HA	-	-	Verbal working memory	↑RT in HA group ↓ Accuracy in HA group

Green arrows represent positive outcomes, yellow arrows represent no change in outcomes, red arrows represent negative outcomes. NN, normobaric normoxia; HH, hypobaric hypoxia; NH, normobaric hypoxia; HN, hypobaric normoxia; KLT, Konzentrations Leistungs Test-Revidierte Fassung; KSS, Karonlinska Sleepiness Scale; F_iO_2, fraction of inspired oxygen; RT, reaction time; RAVL, Rey Auditory Verbal Learning; RDF, Repetition of Digits Forward; RDB, Repetition of Digits Backwards test; TMT, Trail Making Test, DSST, Digit Symbol Substitution Test; ST, Stroop test; GPDT, grooved pegboard dexterity test; MoCA, Montreal Cognitive Assessment; BDI, Becks Depression Inventory; DST, Digit Span test; LA, low altitude; HA, high altitude; RCT, randomised control trial; P_iO_2, pressure of inspired oxygen; PCH, poikilocapnic hypoxia; ICH, isocapnic hypoxia; CNSVS, Central Nervous System Vital Signs; IH, intermittent hypoxia; VFT, verbal fluency test; BART, balloon analogue risk task; VAS, visual analogue scale; PASA, Paced Auditory Serial Addition; PVT, Psychomotor Vigilance Task; CPT, Calculation Performance Task; Compensatory Tracking Task; Performance Effort and Rating Scales; ANAM, Automated Neuropsychological Assessment Metrics; DASS, divided attention steering simulator; LB, line bisection test; RFFT, Ruff figural fluency test; CT, modified Pegboard test the Chess test; RBANS, The Repeatable Battery for the Assessment of Neuropsychological Status; WAIS-III, Wechsler Adult Intelligence Scale; RVP, Rapid Visual Information Processing test; OTS, One Touch Stockings of Cambridge; AMS, Acute Mountain Sickness; LRT, Letter Rotation Test; VWMC, verbal working memory capacity; VIHT, Voluntary Isocapnic Hyperventilation Training; SDMT, Symbol Digit Modalities Test; BAT, Bassin Anticipation Timer; MMSE, Mini Mental State Examination; ZVT, Number Combination Test; MAT-bat, Multi-Attribute Task battery; RIPC, remote ischemic precondition; WHO-NCTB, World Health Organization Neurobehavioral Core Test Battery; SL, sea level; FCRT, four choice reaction time.

Table 2. ROBINS-I-V2 risk of bias assessment for data items.

Data item	**Domain 1**	**Domain 2**	**Domain 3**	**Domain 4**	**Domain 5**	**Domain 6**	**Domain 7**	**Overall**
Chroboczek et al., 2023	Serious	Low	Low	Low	Moderate	Low	Moderate	Serious
Crow et al., 1971	Moderate	Moderate	Moderate	Low	Low	Low	Moderate	Moderate
Gerard et al., 2000	Serious	Low	Low	Low	Serious	Low	Moderate	Serious
Guo et al., 2017	Serious	Low	Moderate	Low	Low	Serious	Moderate	Serious
Quackenbush et al., 2016	Moderate	Serious	Moderate	Serious	Low	Low	Moderate	Serious
Van Dorp et al., 2007	Serious	Low	Low	Low	Low	Low	Moderate	Serious

Domain 1, Bias due to confounding; Domain 2, Bias in the selection of participants; Domain 3, Bias in the classification of interventions; Domain 4, Bias due to deviations from intended interventions; Domain 5, Bias due to missing data; Domain 6, Bias in the measurement of outcomes; Domain 7, Bias in the selection of the reported result.

Table 3. List of confounding factors taken into consideration of data items assessed against Domain 1 of the ROBINS-I V2.

Participant factors	**Task factors**	**Environmental factors**	**Methodological factors**
- Differences in baseline cognitive performance between conditions - Age variability - Physical fitness variability - Health conditions - Acclimatisation - Genetic factors	- Complexity of task - Familiarity to task	- Severity and duration of hypoxia - Simulation or environmental hypoxia - Temperature and pressure	- Sensitivity and reliability of tools used - Timing of assessments - Control groups used

Table 4. List of each cognitive domain construct and the associated cognitive tasks.

Cognitive Domain	**Cognitive task**	
Memory	• Working memory (score) • Learning and memory (score) • Short-term memory (score) • Associative memory (score) • Episodic memory (score)	• Long-term memory (score) • Involuntary memory (score) • Visual memory (score) • Verbal memory (score)
Attention	• Response inhibition (score)	
Processing speed	• Processing speed (milliseconds)	
Psychomotor speed	• Psychomotor speed (score) • Motor speed (score)	• Accuracy (score) • Fine-motor control (score)
Executive function	• Executive function (score) • Verbal fluency (score) • Non-verbal fluency (score) • Tower task (score) • Cognitive flexibility (score) • Coding (score) • Decision-making (score) • Visual acuity (score) • Reasoning (score)	• Risk-taking (score) • Addition (score) • Incorrect answers (score) • Neurocognitive index (score) • Pattern recognition (score) • Number comparison (score) • Proof-reading (score) • Spatial tracking (score) • Map compass (score)

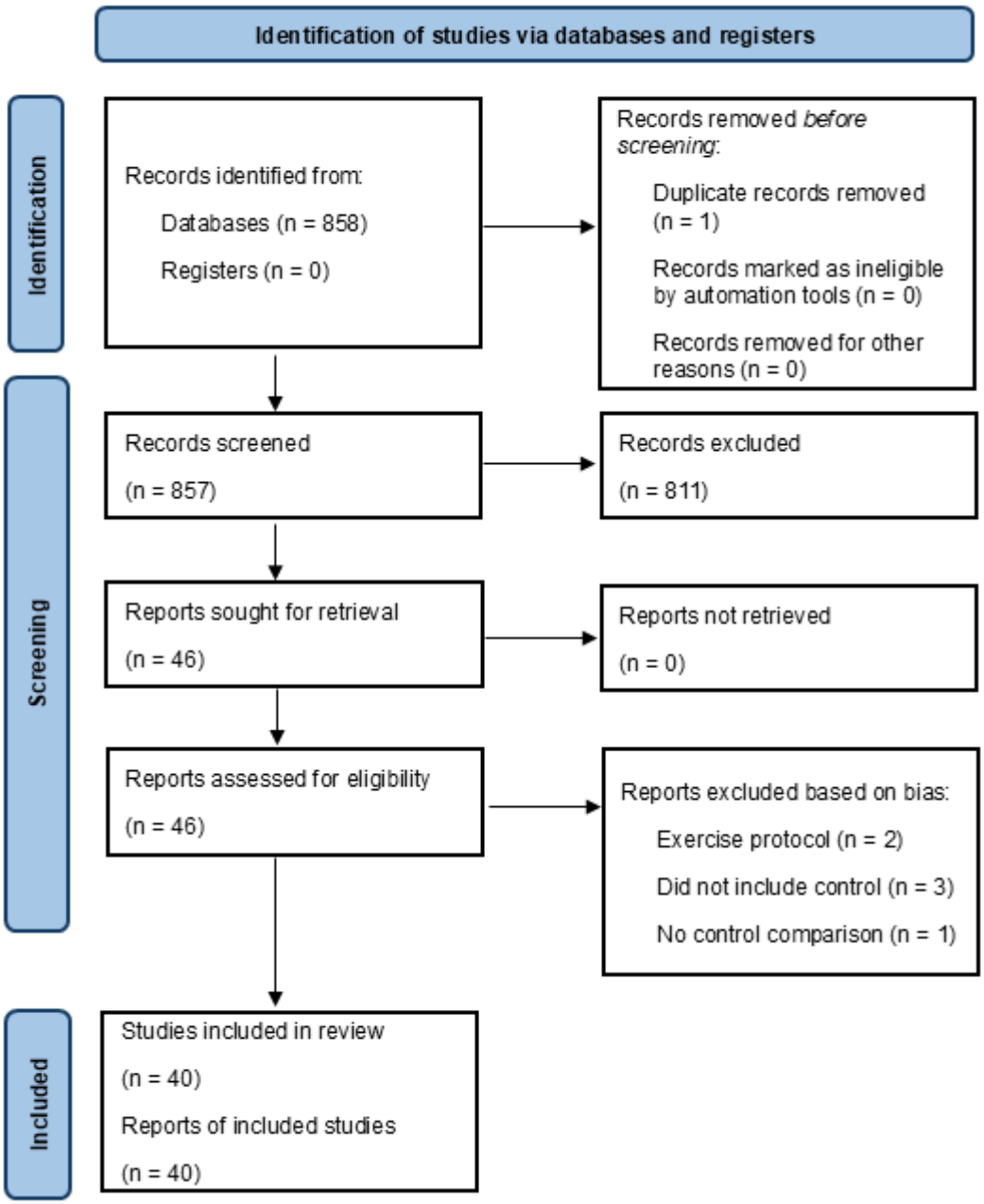
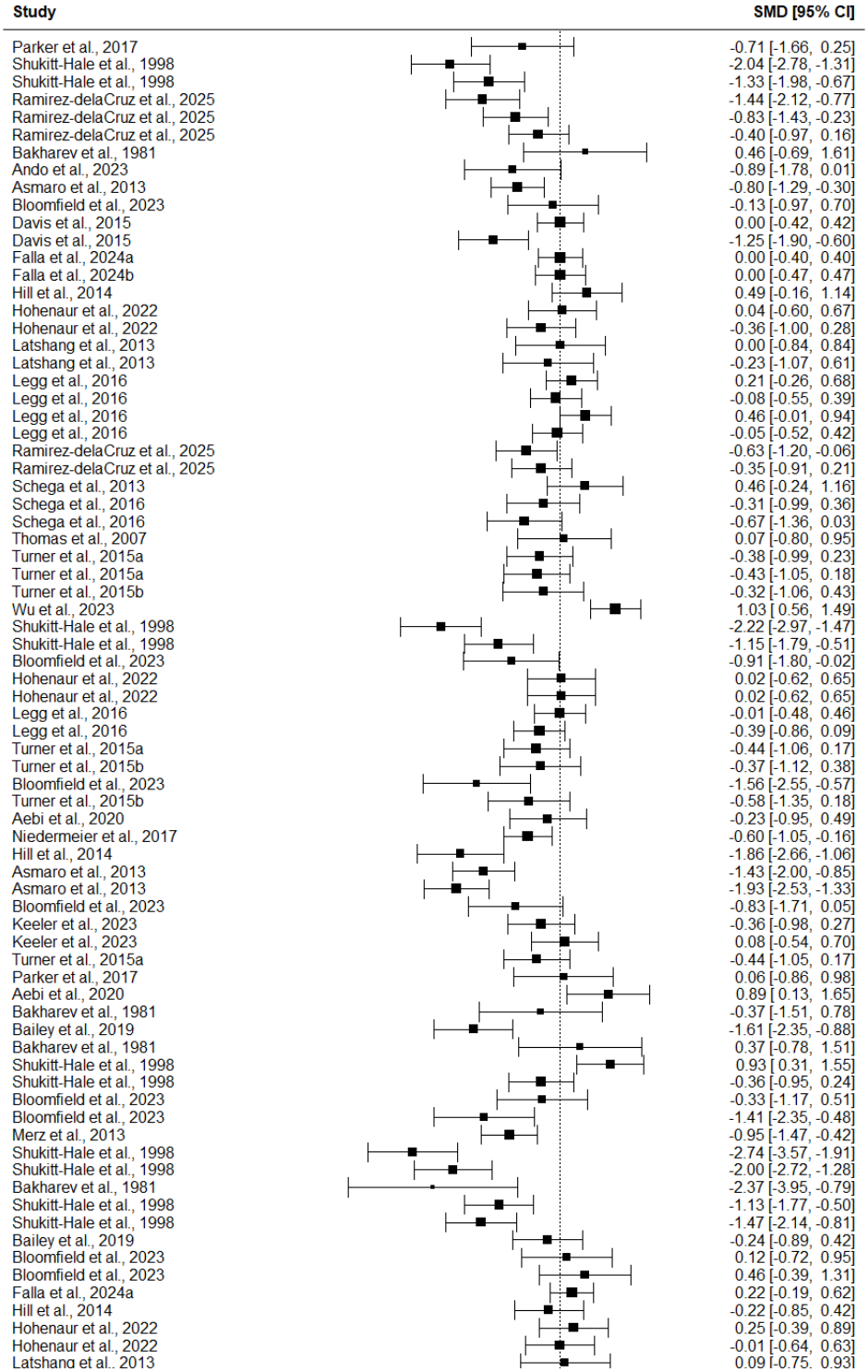


Figure 1. PRISMA flow diagram detailing the systematic inclusion and exclusion of data items. A total of 858 items were identified during the initial phase. One article was removed as a duplicate. The 857 articles were then screened based on titles and abstracts with 811 being excluded. From the forty-six data items assessed for eligibility, six were excluded due to risk of bias consisting of (e.g., concomitant exercise protocol, lack of control/ normoxia condition, and no control/normoxia statistical comparisons). Ultimately, forty data items were included for meta-analyses.

General Cognitive Ability



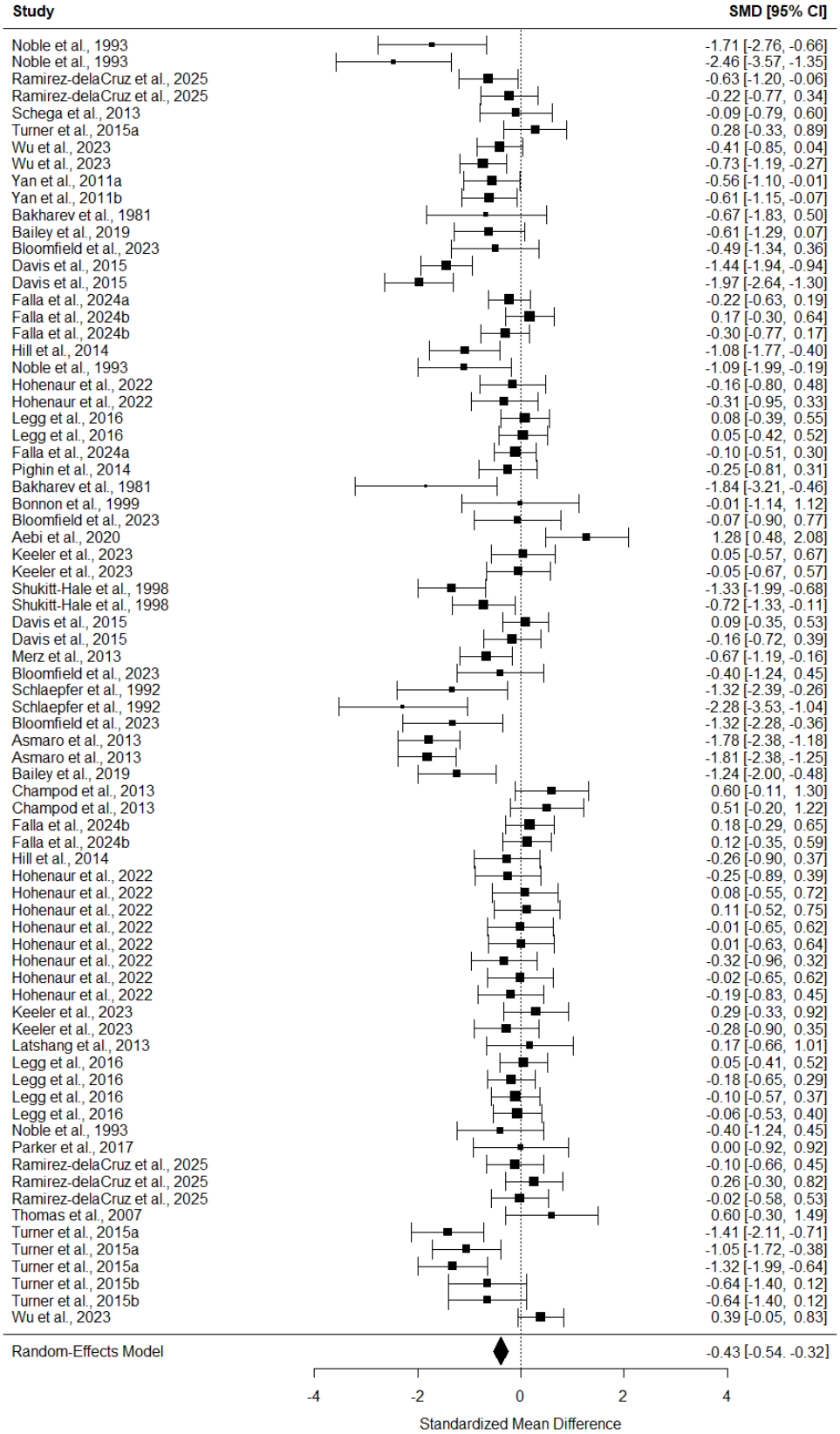


Figure 2. Forest plot for all 151 effect sizes with the grouped effect for the random-effects model categorising cognitive ability in hypoxia.

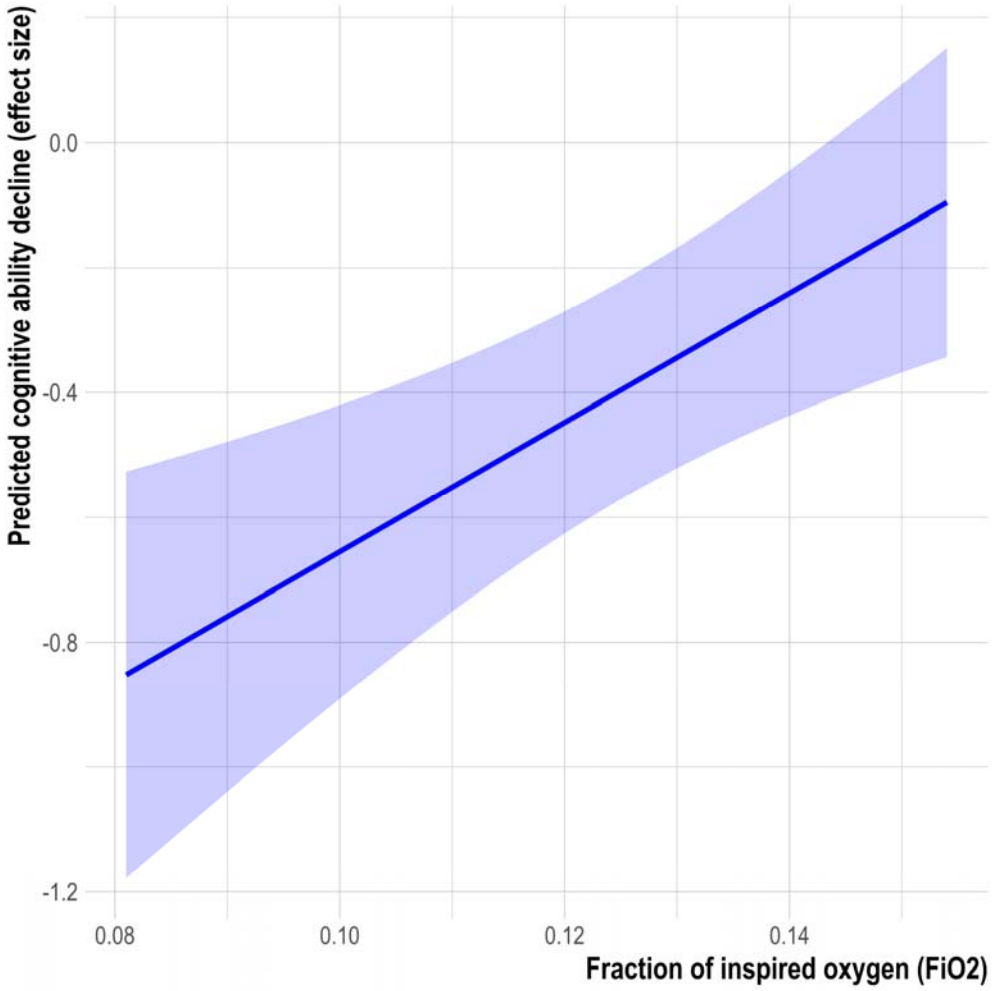
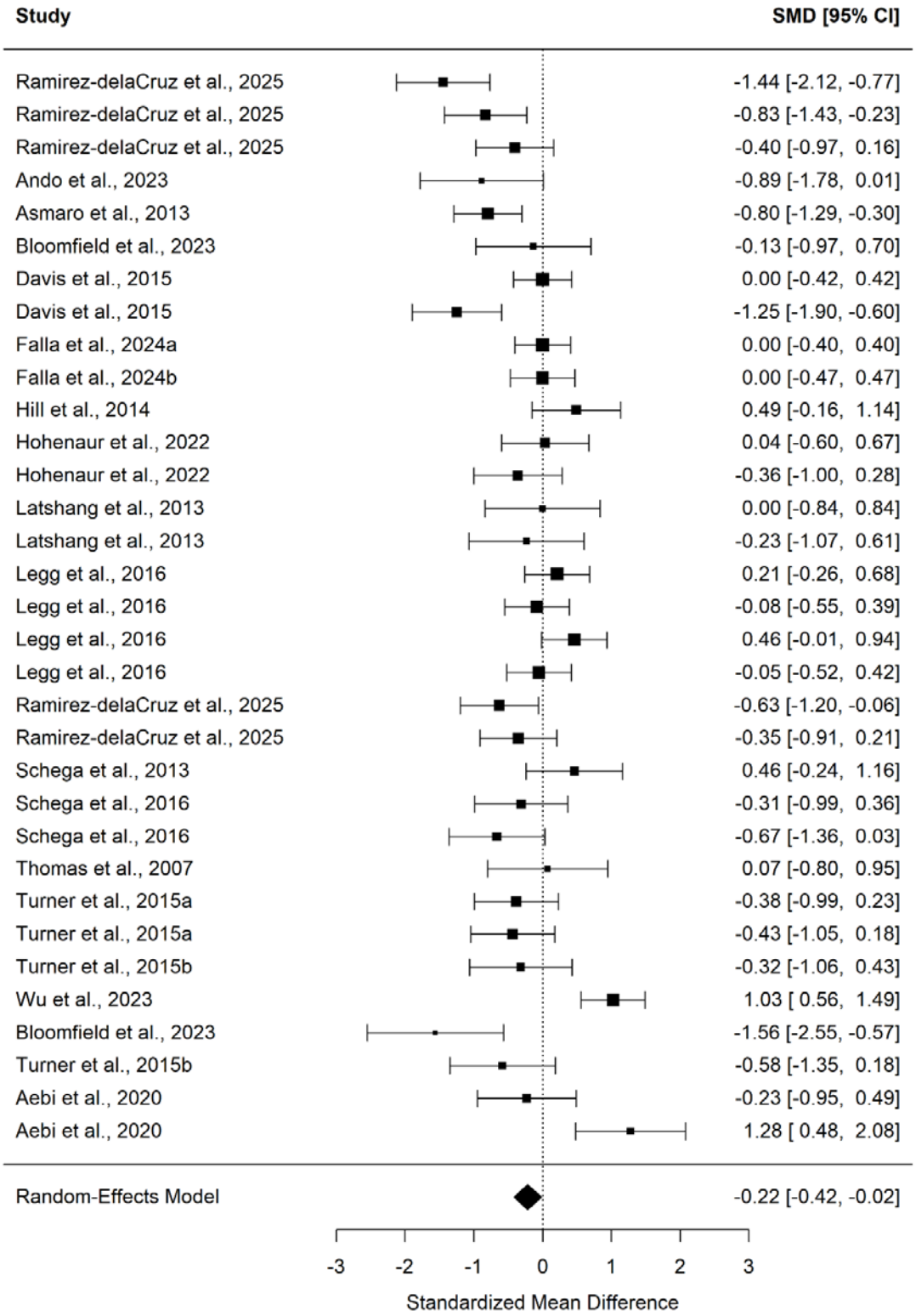


Figure 3. Predicted cognitive ability decline in hypoxia as a function of severity.

Attention


Study
SMD [95% CI]
Ramirez-delaCruz et al., 2025 -1.44 [-2.12, -0.77]
Ramirez-delaCruz et al., 2025 -0.83 [-1.43, -0.23]
Ramirez-delaCruz et al., 2025 -0.40 [-0.97, 0.16]
Ando et al., 2023 -0.89 [-1.78, 0.01]
Asmaro et al., 2013 -0.80 [-1.29, -0.30]
Bloomfield et al., 2023 -0.13 [-0.97, 0.70]
Davis et al., 2015 0.00 [-0.42, 0.42]
Davis et al., 2015 -1.25 [-1.90, -0.60]
Falla et al., 2024a 0.00 [-0.40, 0.40]
Falla et al., 2024b 0.00 [-0.47, 0.47]
Hill et al., 2014 0.49 [-0.16, 1.14]
Hohenaur et al., 2022 0.04 [-0.60, 0.67]
Hohenaur et al., 2022 -0.36 [-1.00, 0.28]
Latshang et al., 2013 0.00 [-0.84, 0.84]
Latshang et al., 2013 -0.23 [-1.07, 0.61]
Legg et al., 2016 0.21 [-0.26, 0.68]
Legg et al., 2016 -0.08 [-0.55, 0.39]
Legg et al., 2016 0.46 [-0.01, 0.94]
Legg et al., 2016 -0.05 [-0.52, 0.42]
Ramirez-delaCruz et al., 2025 -0.63 [-1.20, -0.06]
Ramirez-delaCruz et al., 2025 -0.35 [-0.91, 0.21]
Schega et al., 2013 0.46 [-0.24, 1.16]
Schega et al., 2016 -0.31 [-0.99, 0.36]
Schega et al., 2016 -0.67 [-1.36, 0.03]
Thomas et al., 2007 0.07 [-0.80, 0.95]
Turner et al., 2015a -0.38 [-0.99, 0.23]
Turner et al., 2015a -0.43 [-1.05, 0.18]
Turner et al., 2015b -0.32 [-1.06, 0.43]
Wu et al., 2023 1.03 [0.56, 1.49]
Bloomfield et al., 2023 -1.56 [-2.55, -0.57]
Turner et al., 2015b -0.58 [-1.35, 0.18]
Aebi et al., 2020 -0.23 [-0.95, 0.49]
Aebi et al., 2020 1.28 [0.48, 2.08]
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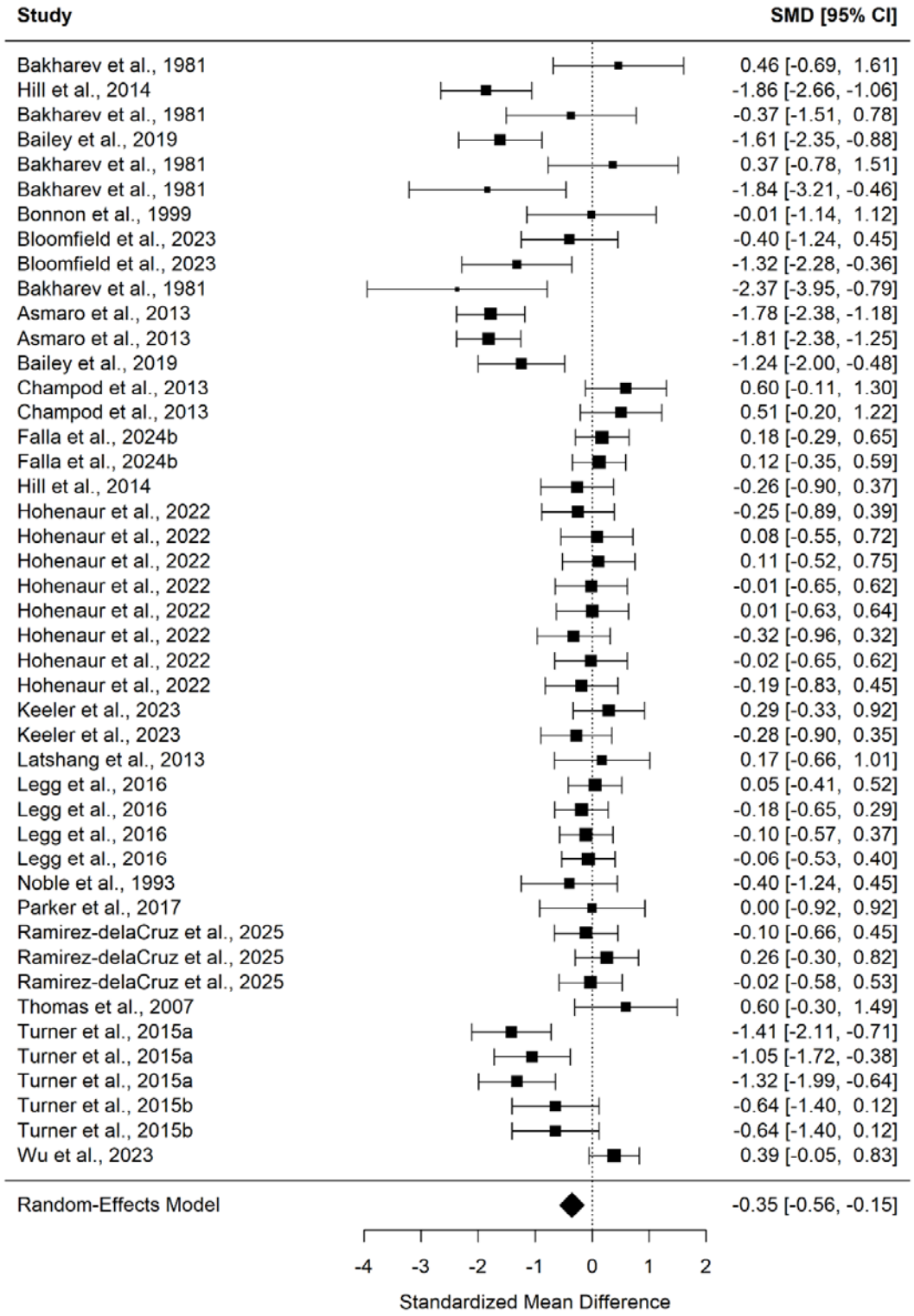
-3 -2 -1 0 1 2 3
Standardized Mean Difference

Memory


Study
SMD [95% CI]
Bakharev et al., 1981 0.46 [-0.69, 1.61]
Hill et al., 2014 -1.86 [-2.66, -1.06]
Bakharev et al., 1981 -0.37 [-1.51, 0.78]
Bailey et al., 2019 -1.61 [-2.35, -0.88]
Bakharev et al., 1981 0.37 [-0.78, 1.51]
Bakharev et al., 1981 -1.84 [-3.21, -0.46]
Bonnon et al., 1999 -0.01 [-1.14, 1.12]
Bloomfield et al., 2023 -0.40 [-1.24, 0.45]
Bloomfield et al., 2023 -1.32 [-2.28, -0.36]
Bakharev et al., 1981 -2.37 [-3.95, -0.79]
Asmaro et al., 2013 -1.78 [-2.38, -1.18]
Asmaro et al., 2013 -1.81 [-2.38, -1.25]
Bailey et al., 2019 -1.24 [-2.00, -0.48]
Champod et al., 2013 0.60 [-0.11, 1.30]
Champod et al., 2013 0.51 [-0.20, 1.22]
Falla et al., 2024b 0.18 [-0.29, 0.65]
Falla et al., 2024b 0.12 [-0.35, 0.59]
Hill et al., 2014 -0.26 [-0.90, 0.37]
Hohenaur et al., 2022 -0.25 [-0.89, 0.39]
Hohenaur et al., 2022 0.08 [-0.55, 0.72]
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Hohenaur et al., 2022 -0.01 [-0.65, 0.62]
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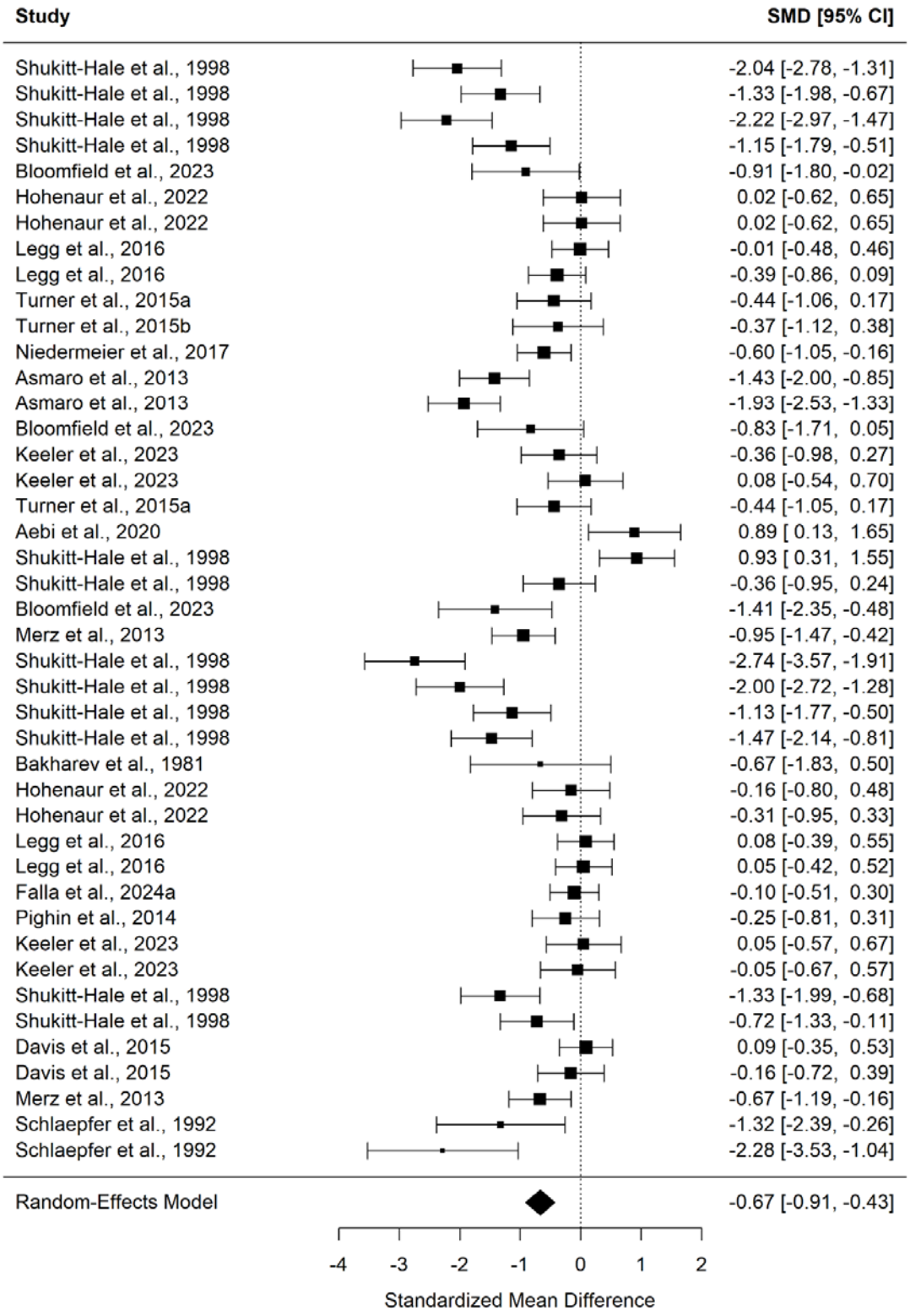
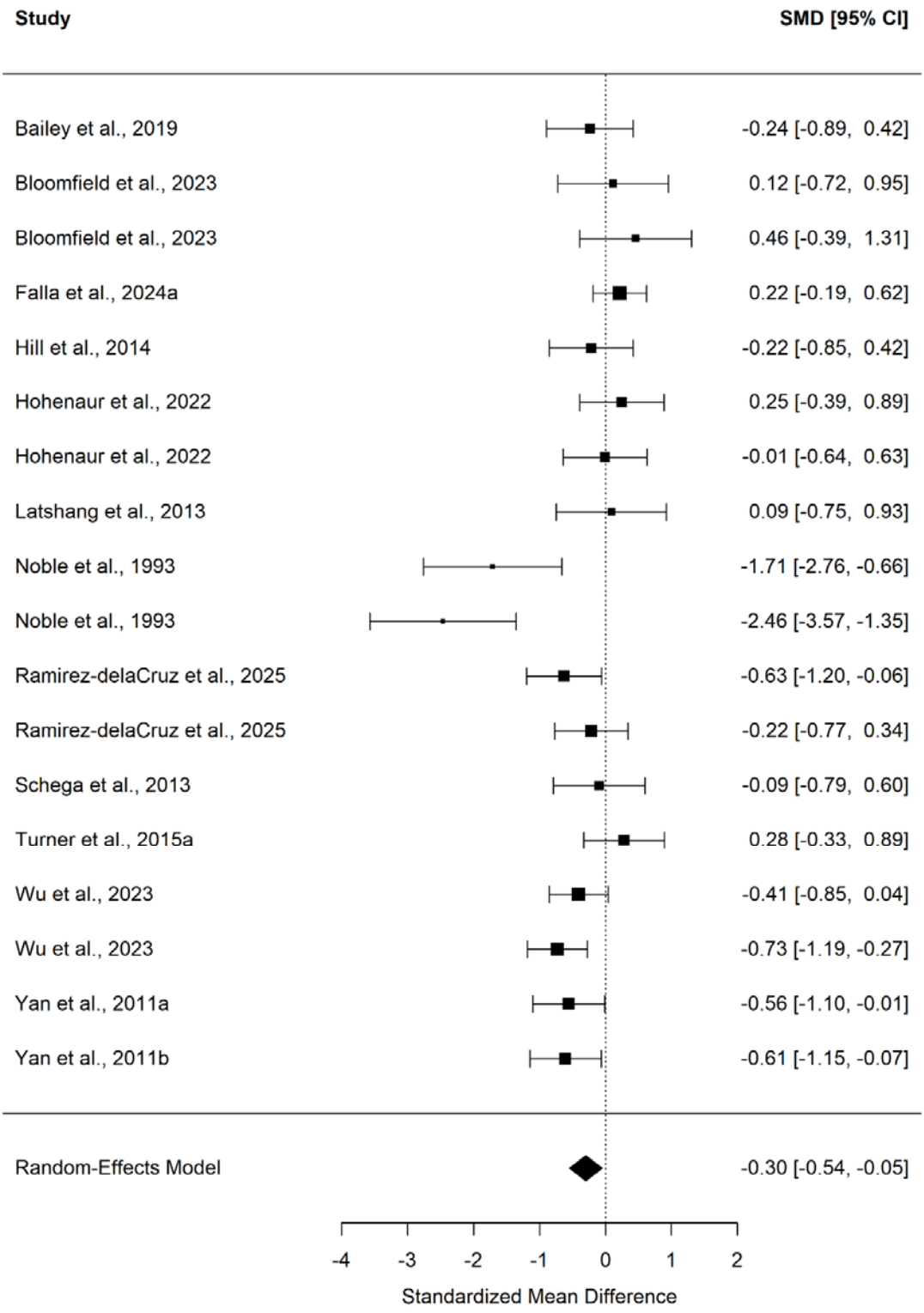
Hohenaur et al., 2022 -0.02 [-0.65, 0.62]
Hohenaur et al., 2022 -0.19 [-0.83, 0.45]
Keeler et al., 2023 0.29 [-0.33, 0.92]
Keeler et al., 2023 -0.28 [-0.90, 0.35]
Latshang et al., 2013 0.17 [-0.66, 1.01]
Legg et al., 2016 0.05 [-0.41, 0.52]
Legg et al., 2016 -0.18 [-0.65, 0.29]
Legg et al., 2016 -0.10 [-0.57, 0.37]
Legg et al., 2016 -0.06 [-0.53, 0.40]
Noble et al., 1993 -0.40 [-1.24, 0.45]
Parker et al., 2017 0.00 [-0.92, 0.92]
Ramirez-delaCruz et al., 2025 -0.10 [-0.66, 0.45]
Ramirez-delaCruz et al., 2025 0.26 [-0.30, 0.82]
Ramirez-delaCruz et al., 2025 -0.02 [-0.58, 0.53]
Thomas et al., 2007 0.60 [-0.30, 1.49]
Turner et al., 2015a -1.41 [-2.11, -0.71]
Turner et al., 2015a -1.05 [-1.72, -0.38]
Turner et al., 2015a -1.32 [-1.99, -0.64]
Turner et al., 2015b -0.64 [-1.40, 0.12]
Turner et al., 2015b -0.64 [-1.40, 0.12]
Wu et al., 2023 0.39 [-0.05, 0.83]
Random-Effects Model -0.35 [-0.56, -0.15]
-4 -3 -2 -1 0 1 2
Standardized Mean Difference

Executive Function



Processing Speed



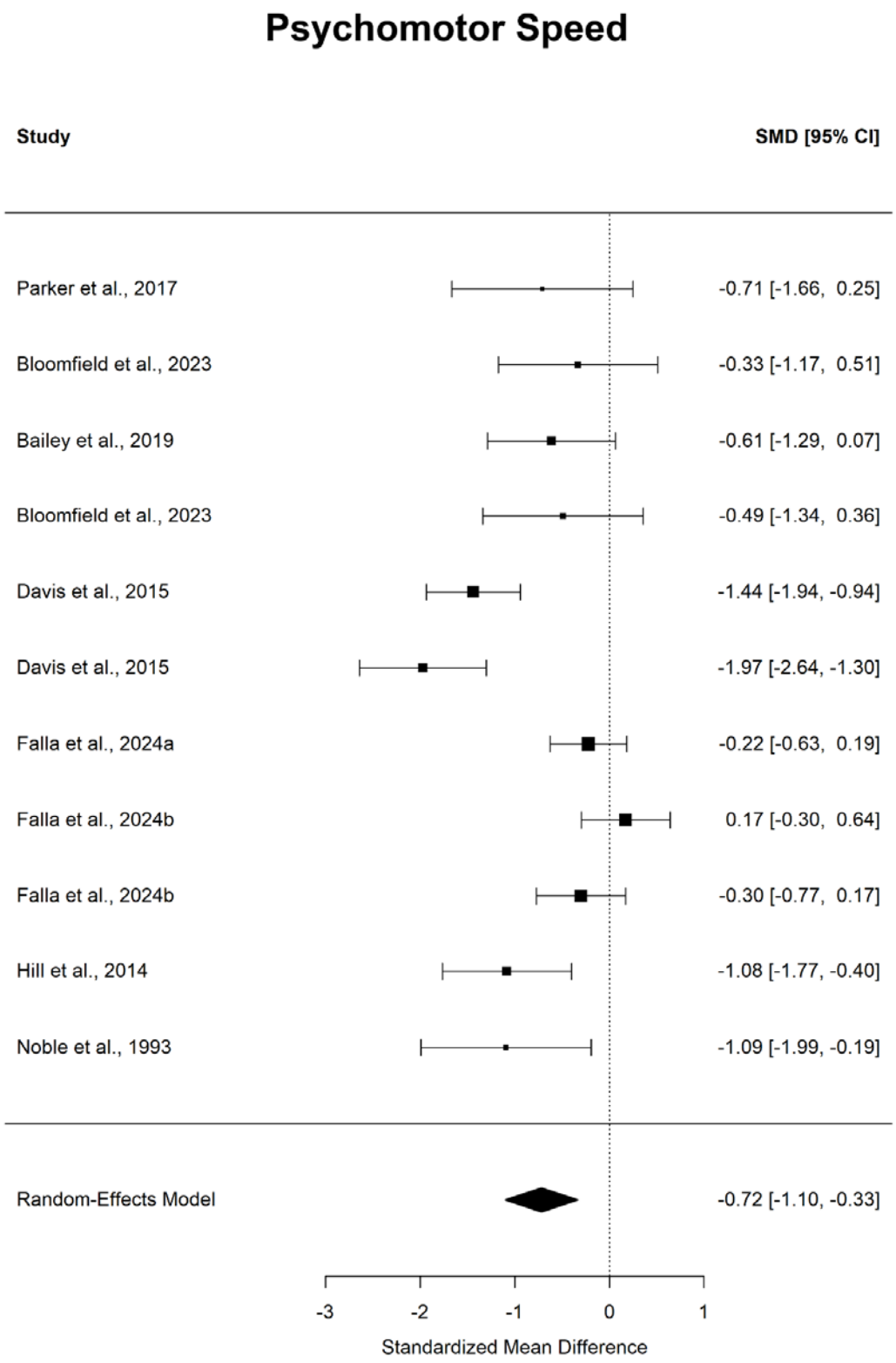


Figure 4. Forest plot for each cognitive domain for the random-effects model categorising hypoxia's domain-specific impact.

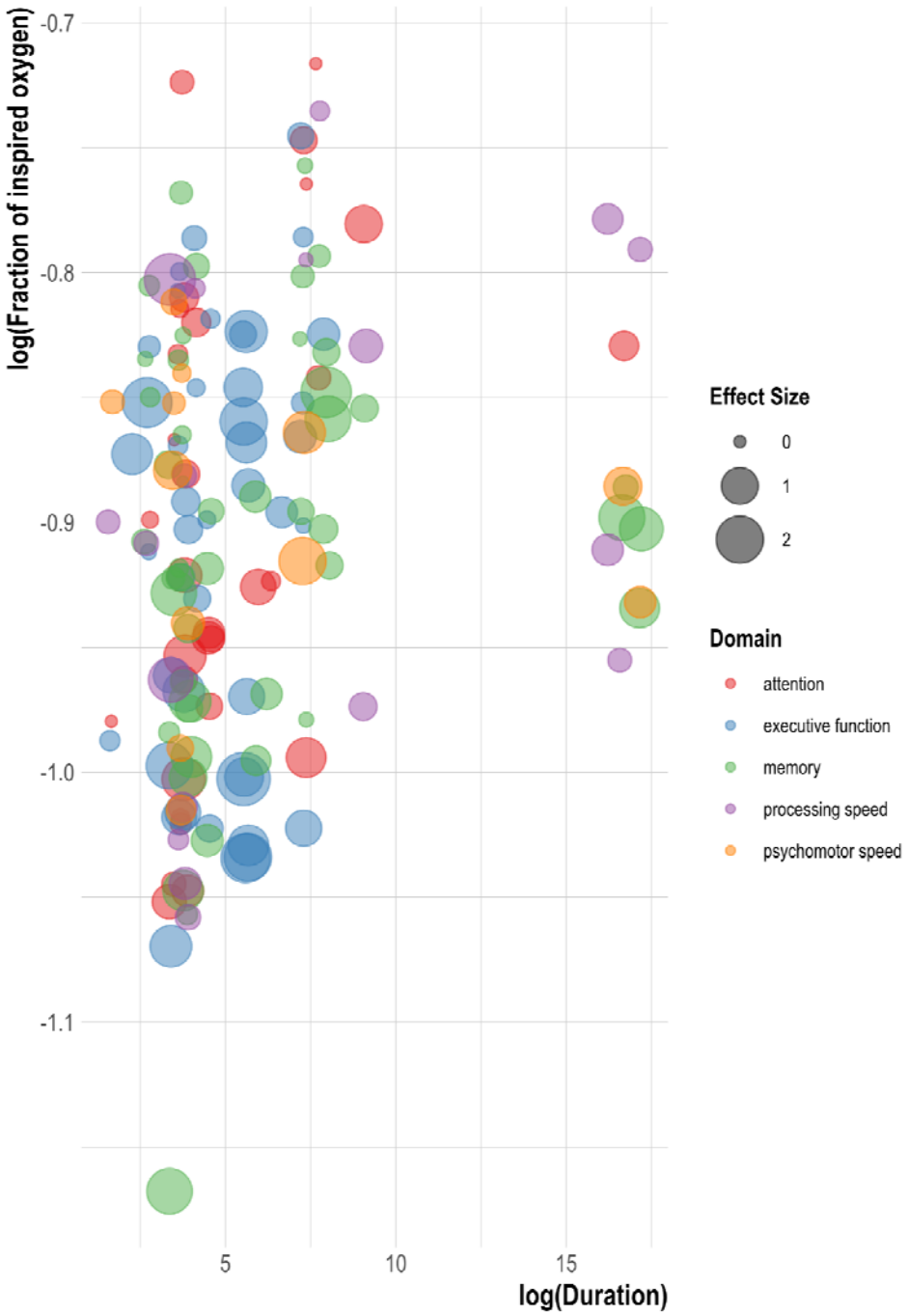


Figure 5. Bubble plot visualising the 151 effect sizes across all domains in relation to the severity and duration of hypoxia exposure. Notably, as fraction of inspired oxygen decreases effect of hypoxia increases for most cognitive domains.

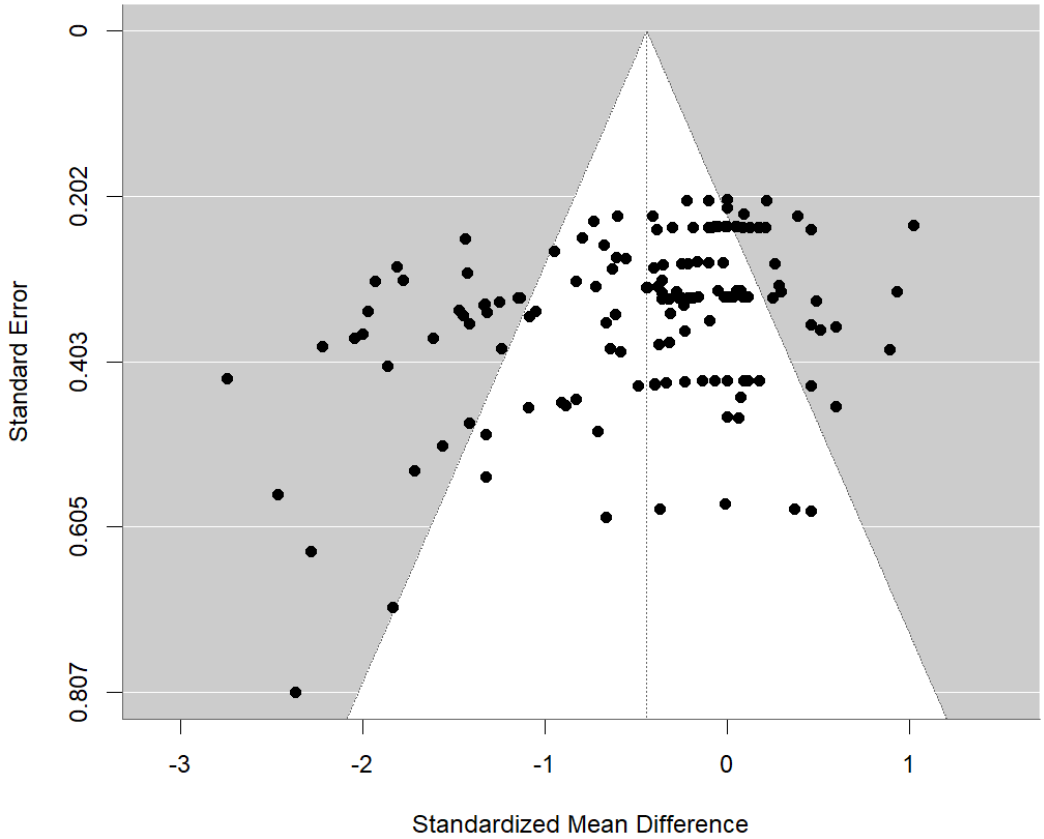


Figure 6. Funnel plot visualising the distribution of effect sizes included in the reduced model of the General Cognitive Ability Domain.

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