



Effects of High-Intensity Interval Training Protocols on Blood Lactate Levels and Cognition in Healthy Adults: Systematic Review and Meta-Regression

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Abstract

Background Some health benefits from high-intensity interval training (HIIT) are facilitated by peripheral blood lactate levels. However, the lactate response from HIIT is variable and dependent on protocol parameters.

Objectives We aimed to determine the HIIT protocol parameters that elicited peak lactate levels, and how these levels are associated with post-HIIT cognitive performance.

Study Design We conducted a systematic review with meta-regression.

Methods MEDLINE, Embase, CENTRAL, SPORTDiscus, and CINAHL + were searched from database inception to 8 April, 2022. Peer-reviewed primary research in healthy adults that determined lactate (mmol/L) and cognitive performance after one HIIT session was included. Mixed-effects meta-regressions determined the protocol parameters that elicited peak lactate levels, and linear regressions modelled the relationship between lactate levels and cognitive performance.

Results Study entries ($n = 226$) involving 2560 participants (mean age 24.1 ± 4.7 years) were included in the meta-regression. A low total work-interval volume (~ 5 min), recovery intervals that are about five times longer than work intervals, and a medium session volume (~ 15 min), elicited peak lactate levels, even when controlling for intensity, fitness (peak oxygen consumption) and blood measurement methods. Lactate levels immediately post-HIIT explained 14–17% of variance in Stroop interference condition at 30 min post-HIIT.

Conclusions A HIIT protocol that uses the above parameters (e.g., 8×30 -s maximal intensity with 90-s recovery) can elicit peak lactate, a molecule that is known to benefit the central nervous system and be involved in exercise training adaptations. This review reports the state of the science in regard to the lactate response following HIIT, which is relevant to those in the sports medicine field designing HIIT training programs.

Trial Registry Clinical Trial Registration: PROSPERO (CRD42020204400).

1 Background

High-intensity interval training (HIIT) involves repeated bouts of intense exercise (e.g., $\geq 80\%$ of peak or maximum heart rate) separated by intervals of recovery or rest [1]. Reviews have shown that HIIT improves cardiorespiratory fitness [2, 3], cardiac function [4], and even reduces abdominal fat [5]. Both HIIT and moderate-intensity continuous exercise have been shown to improve maximum oxygen capacity in young to middle-aged adults, with HIIT being slightly more effective [3] and more time efficient [6]. However, with numerous protocols studied to date, choosing the

right HIIT protocol may involve understanding the biomarkers that are produced by high-intensity exercise. High-intensity exercise such as HIIT requires energy (i.e., adenosine triphosphate [ATP]) contribution from anaerobic glycolysis in order to meet the high energy demands [7]. The ATP contribution from anaerobic glycolysis can be estimated by peripheral lactate [8], which is a blood biomarker that is upregulated post-HIIT [9].

Lactate was initially regarded as a by-product of glycolysis [10, 11]. Other roles of lactate are currently being studied, including its role as an energy substrate for skeletal muscles, the heart and neurons [12, 13]. The lactate shuttle theory suggests that the lactate produced by one cell (e.g., fast twitch-glycolytic muscle fibre) can be taken up by the

Key Points

This systematic review investigated the individual high-intensity interval training (HIIT) protocol parameters that elicited peak peripheral lactate.

A HIIT protocol using maximal intensity exercise that is between 1.5 and 5 min, (e.g., 8 × 30 s), with recovery intervals much longer than work intervals (e.g., 90-s recovery), for a total duration of 15 min, may elicit peak peripheral lactate levels

With further prospective research combining these parameters, researchers and exercise professionals can apply these parameters during exercise training to accelerate mitochondrial biogenesis in skeletal muscle, and potentially upregulate downstream targets such as brain-derived neurotrophic factor and vascular endothelial growth factor.

Our review identified four studies that reported a correlation between HIIT-induced lactate and inhibitory control; however, there remains insufficient evidence at this time to establish a conclusive association.

mitochondria of another cell (e.g., slow twitch-oxidative muscle fibre) through lactate receptors (i.e., monocarboxylate transporters), allowing lactate to be re-oxidised to pyruvate, and then participate in the Krebs cycle to provide energy [14]. The lactate produced by working skeletal muscle can also be consumed by the heart [15], liver and kidneys [16], and astrocytes and neurons [17–19]. Lactate has receptors other than monocarboxylate transporters, including hydroxycarboxylic acid receptor 1, which provides an example of how lactate serves as a signalling molecule. Hydroxycarboxylic acid receptor 1 is highly concentrated in the vessels supplying blood to the brain, and in intracerebral microvessels. Lactate binding to hydroxycarboxylic acid receptor 1 initiates a signaling cascade that leads to increased expression of vascular endothelial growth factor A, a protein that promotes cerebral angiogenesis [20]. Lactate has also been shown to promote brain-derived neurotrophic factor (BDNF), a protein that promotes neurogenesis, supporting learning and memory [21]. Furthermore, lactate has been found to support myelination [22, 23], be favored over glucose by neurons under high-energy demands [24], and support neuronal excitability and plasticity, which are important for newborn neuronal survival [25–27].

Achieving peak peripheral lactate during exercise may confer several benefits. Higher lactate levels (20 vs 10 mmol/L) signal greater expression of peroxisome proliferator activated-receptor γ coactivator-1 α [28]. Peroxisome proliferator activated-receptor γ coactivator-1 α is

considered the master regulator of mitochondrial biogenesis [29, 30] because it interacts with transcription factors (e.g., nuclear respiratory factors and cAMP response element-binding protein) to increase mitochondrial gene replication and transcription [31, 32]. In humans, inducing greater peripheral lactate accumulation during HIIT, via bicarbonate consumption, results in higher peroxisome proliferator activated-receptor γ coactivator-1 α expression [33]. In contrast, inhibiting lactate accumulation, via dichloroacetate consumption, attenuates these mitochondrial adaptations after long-term HIIT training [34]. These results suggest that higher lactate accumulation accelerates HIIT-induced mitochondrial biogenesis in skeletal muscle, which may be an important outcome for athletes. In addition, lactate induces the expression of brain plasticity genes (e.g., activity-regulated cytoskeletal gene, and early growth response 1 gene) in a concentration-dependent manner, with 20-mmol/L lactate levels being most effective [35]. Similar levels of lactate infusion (18 mmol/L) have been shown to reproduce specific brain exercise-related changes, such as increasing messenger ribonucleic acid expression of vascular endothelial growth factor A [36], a protein that promotes cerebral angiogenesis [37]. Lactate has also been shown to dose-dependently increase the expression and release of BDNF [38, 39], a protein that promotes neuronal survival [40].

The neuronal changes conferred by the exercise-induced peripheral lactate response may beget cognitive benefits. For example, acute bouts of HIIT have been shown to improve inhibitory control in humans, and lactate may play a role in facilitating these benefits [41, 42]. Hashimoto and colleagues [43, 44] found a dose-dependent relationship between HIIT-induced lactate levels and executive function, where higher peripheral lactate levels were associated with better inhibitory control performance. Exercise-induced lactate may supply neurons with the energy needed to achieve the enhanced dorsolateral prefrontal cortex neuronal activity that is associated with an improved interference control [45, 46]. In line with this, current studies demonstrate that high-intensity exercise increases the brain's utilisation of lactate in humans [18, 47]. Lactate may also improve executive function by acting as a signalling molecule. The exercise-induced lactate increases circulating BDNF, and BDNF is associated with improved inhibitory control performance [39]. Therefore, the effects of the exercise-induced peripheral lactate response may extend to cognition.

Lactate has been demonstrated to be one mediator of the benefits of exercise on the central nervous system [43, 48–51]. Given that HIIT elicits greater peripheral lactate accumulation than moderate continuous exercise [9], a HIIT protocol that elicits peak peripheral lactate may maximally confer the molecule's benefits on the nervous

system. The parameters of a HIIT protocol that influence peripheral lactate accumulation include work/recovery interval duration, intensity and session volume [1]. However, the optimal settings of these HIIT protocol parameters remain elusive, and have not yet been determined through a systematic review employing meta-analyses of the available evidence. This review aimed to ascertain the optimal individual HIIT protocol parameters for promoting peak peripheral lactate levels; secondarily, it aimed to ascertain how these levels may associate with post-HIIT cognitive performance. The ultimate impact of this line of research is to identify a HIIT protocol that would elicit a peak peripheral lactate response; such a protocol may facilitate cognitive improvements such as executive performance [21, 52] and memory (given lactate's connection to BDNF [53]). To this end, the current review posed two research questions: (1) individually, what is the work-interval duration, work-interval volume, session volume, and work-to-rest ratio that optimally increases peripheral lactate levels following HIIT in healthy adults? (2) What is the relationship, if any, between HIIT-induced peripheral lactate levels and post-exercise cognitive performance?

2 Methods

This review is registered with PROSPERO (CRD42020204400). The a priori methodology and search strategy for this review have been detailed in the published protocol [54], available [here](#). Briefly, using a search strategy approved by a health sciences librarian, we searched through MEDLINE, Embase, CENTRAL, SPORTDiscus and CINAHL+ using key terms such as “high-intensity interval training” and “lactates”. This paper was submitted a month after the last search date (8 April, 2022). We included studies with participants that were healthy and aged 18 years or older. Healthy participants were defined as individuals who are not described as having been hospitalised, or diagnosed with a disease/dysfunction and/or receiving medical treatment at the time of the study. The intervention of interest was HIIT, and the primary outcome was blood lactate levels (mmol/L) measured after one HIIT session. The secondary outcome was cognitive performance measured before and after one HIIT session. Mixed-effects meta-regressions were employed to analyse the effects of individual HIIT protocol parameters on peripheral lactate accumulation, while controlling for variables such as maximal intensity, blood measurement method and timing. Linear models were used to determine the relationship between post-HIIT Stroop Interference scores and peripheral lactate levels.

3 Results

3.1 Literature Search

Our search yielded 8636 records, from which 4884 (57%) unique records were screened. After screening titles, abstracts and full texts, data were extracted from 227 full texts (Fig. 1).

3.2 Description of Included Studies

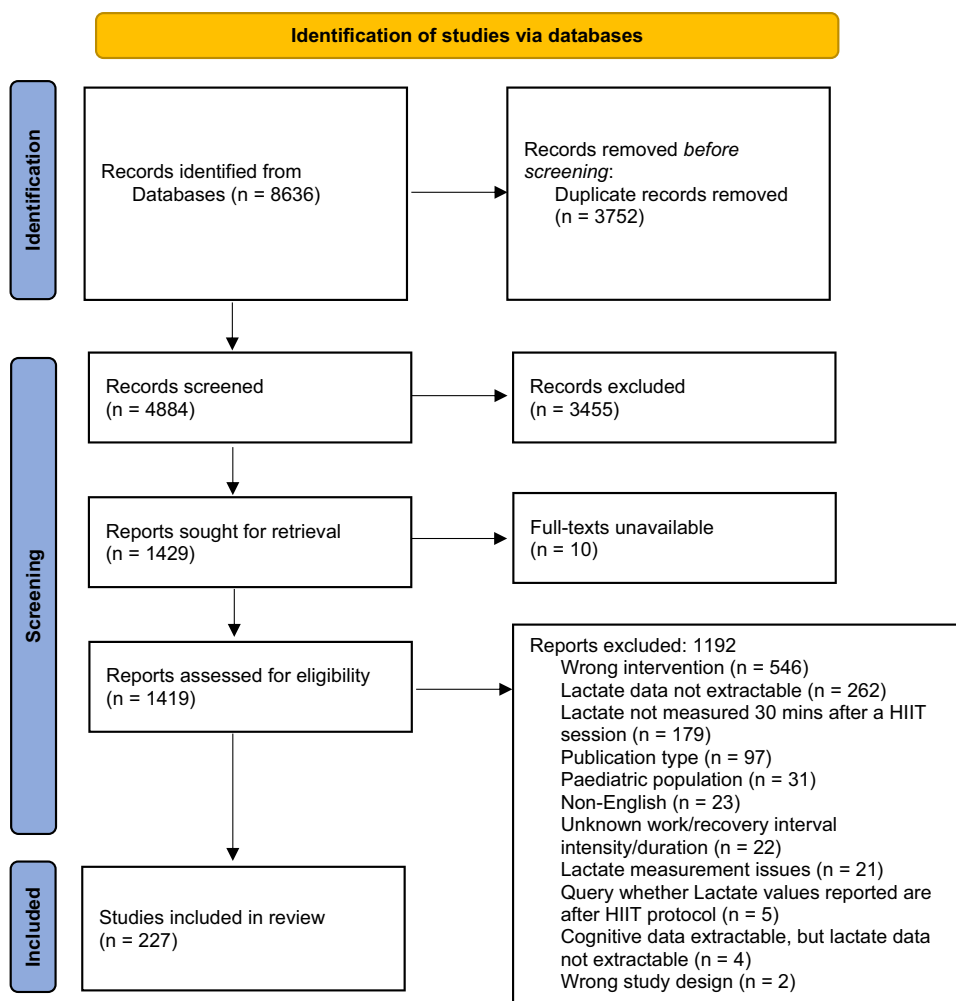
Two-hundred and twenty-seven studies (total $N = 2886$, with samples that ranged from 5 to 36 participants with an average age of 24.1 ± 4.5 years) were included in the final analysis. Some studies ($n = 24$) compared different subject groups (e.g., athletes vs sedentary populations; endurance vs sprint athletes; swimmers vs water polo players), and these were treated as separate study entries even though the data were extracted from the same paper. Thus, in total, there were 255 study entries: 226 single-arm and 29 multi-arm study entries. The 29 multi-arm study entries ($N = 326$; mean age 23.8 ± 2.9 years) compared the effects of different HIIT protocols within subjects. These multi-arm studies were analysed using network meta-analyses, and their descriptions are in Table S1 of the Electronic Supplementary Material (ESM). The ESM also includes network meta-analyses ranking tables for work-interval durations (Table S2), work-interval volume (Table S3), session volume (Table S4) and work-to-rest ratio (Table S5).

There were 226 study entries ($N = 2560$; mean age 24.0 ± 2.9 years; Table S6 of the ESM) that examined the effects of only one type of HIIT protocol, and were therefore analysed using a mixed-effects meta-regression. In these studies, 472/2560 (18%) participants were female, and the mean body mass was 73.3 ± 8.9 kg. The most frequently performed protocols combined a *low* session volume (i.e., total exercise duration was ≤ 5 min), with a *very low* work interval volume (i.e., actual time spent exercising was ≤ 1.5 min), a *small* work-interval duration (i.e., each work bout was ≤ 30 s) and a *medium* work-to-rest ratio (i.e., the ratio of work to rest bout was > 0.2 to ≤ 1.0). Most studies took place in Australia, Western Europe or North America.

3.3 Baseline Blood Lactate Levels of Participants

Baseline lactate data (mean 1.47 ± 0.67 mmol/L) were available for a subset of studies ($n = 103$), and were used as an outcome in a linear model, predicted by baseline fitness (i.e.,

Fig. 1 PRISMA flow diagram



VO₂ peak; mL·kg⁻¹·min⁻¹), body mass (kg) and method of blood draw (Table S7 of the ESM). This was done in order to determine homogeneity in baseline lactate values. Higher baseline fitness (i.e., VO₂ peak) and measuring blood lactate from the fingertip led to higher baseline lactate measurements. This model explained 34% of the variance in baseline blood lactate values. The small spread in the mean values (mean 1.47 ± 0.67 mmol/L) suggested that participants across these studies had similar baseline lactate values.

3.4 Effects of Interventions: Primary Research Question

Only data from the 226 single-arm study entries that were analysed using meta-regressions are discussed in the main text. Results from the 29 multi-arm study entries that were analysed using network meta-analyses can be found as ESM.

3.4.1 Work-Interval Duration Analyses

Work-interval duration categories were not a significant predictor of mean blood lactate levels (Figs. S1a and S1b of the ESM), when analysing maximal (n = 162) and sub-maximal (n = 64) intensity studies separately (p = 0.36 and p = 0.61, respectively). In the meta-regression analyses, work-interval duration was not a significant predictor of blood lactate when controlling for maximal intensity as a binary covariate (p = 0.65). The numerous intensity units used in the included studies precluded the use of precise exercise intensity values as a covariate in the regression models.

3.4.2 Work-Interval Volume Analyses

A low (> 1.5 to ≤ 5 min) work-interval volume led to significantly higher peripheral lactate (p < 0.01) when exercise intensity was maximal (Fig. 2). With sub-maximal intensity

(Figure S2 of the ESM), there were no significant differences between the work-interval volume categories ($p = 0.053$, $\eta^2 = 0.063$). Mixed-effects meta-regression analyses revealed that a *low* work-interval volume remained a significant positive predictor ($p = 0.0013$) even when controlling for other covariates such as maximal intensity, baseline fitness (i.e., peak oxygen consumption), blood measurement method and timing (Table 1).

3.4.3 Session Volume Analyses

A *medium* (> 5 to ≤ 15 min) session volume led to significantly higher mean blood lactate levels compared with a *low* (≤ 5 min; $p = 0.014$), but not a *high* session volume (> 15 min; $p = 0.22$), when the intensity was maximal (Fig. 3). However, when intensity was sub-maximal (Fig. S3 of the ESM), there were no significant differences between the session volume categories ($p = 0.5$). The mixed-effects meta-regression models revealed that a *medium* session volume remained a significant positive predictor ($p = 0.0355$) even when controlling for maximal intensity, baseline fitness (i.e., VO_2 peak), blood measurement method and timing (Table 2).

3.4.4 Work-to-Rest Ratio Analyses

As seen in Fig. 4, the Kruskal–Wallis test revealed that the work-to-rest ratio was a significant predictor ($p = 0.045$) of mean blood lactate levels at maximal intensity. However, the post-hoc Dunn’s test revealed no significant

differences ($p > 0.057$) between work-to-rest ratio categories when the p values were adjusted with the Benjamin Hochberg method. When intensity was sub-maximal (Fig. S4 of the ESM), a *low* (> 0.1 to ≤ 0.2) work-to-rest ratio led to significantly higher mean peripheral lactate levels compared to a *high* work-to-rest ratio (> 1). However, only two-submaximal intensity studies used a *low* work-to-rest ratio and this finding should be interpreted with caution. Mixed-effects meta-regression models revealed that a *low* (> 0.1 to ≤ 0.2) work-to-rest ratio remained a significant positive predictor ($p = 0.0043$) even after controlling for maximal intensity, baseline fitness (i.e., VO_2 peak), blood measurement method and timing (Table 3).

3.4.5 Additional Analyses

A dearth of studies in middle-aged and older adults precluded us from performing sub-group analyses by age, as only six studies included participants with a mean age of 35 years or older. Entering sex as a covariate with two levels (female individuals only, male individuals only) into the regression models revealed that sex was not a significant predictor of mean blood lactate. However, the low number of female-only studies ($n = 31$) may disqualify any firm conclusions regarding the effects of sex. Additionally, we assessed effects of HIIT modality, and found that running led to significantly lower blood lactate levels ($p = 0.0012$) compared with cycling, even after controlling for maximal intensity, baseline fitness (i.e., VO_2 peak), blood measurement method and timing (Table S8 of the ESM).

Fig. 2 Work interval volume violin boxplot—maximal intensity studies only. Note. Violin boxplot of blood lactate (mmol/L) with work interval volume as the categorical predictor using only maximal intensity studies. $N = 162$ studies. The red line represents average resting blood lactate value (1.47 ± 0.67 mmol/L) from 103 studies. The size of the circles is proportional to the sample size of each study

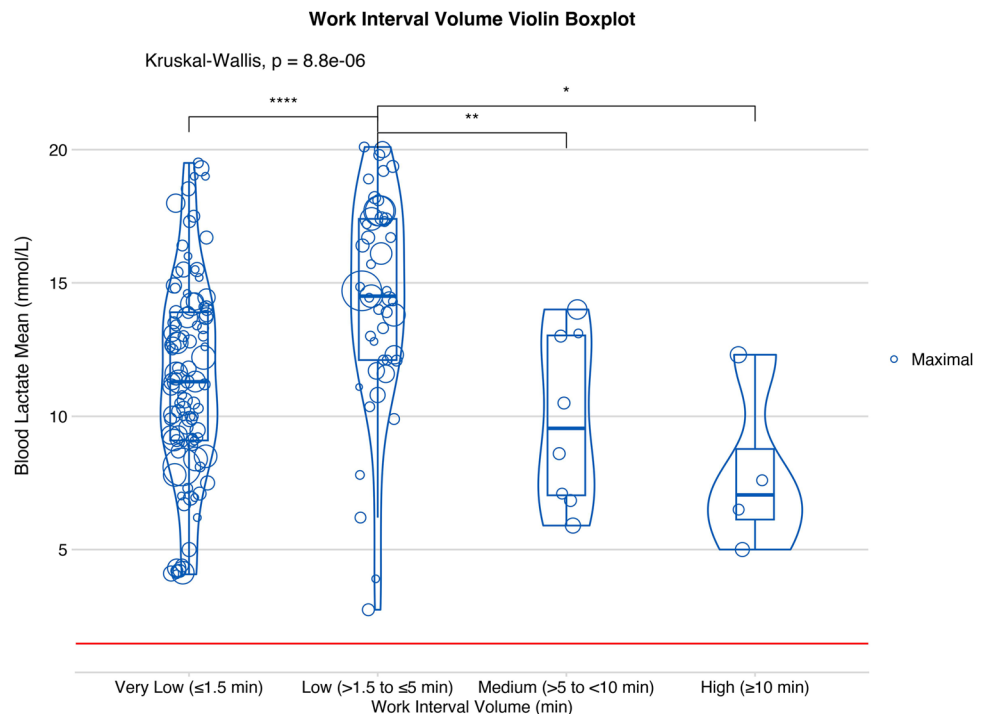


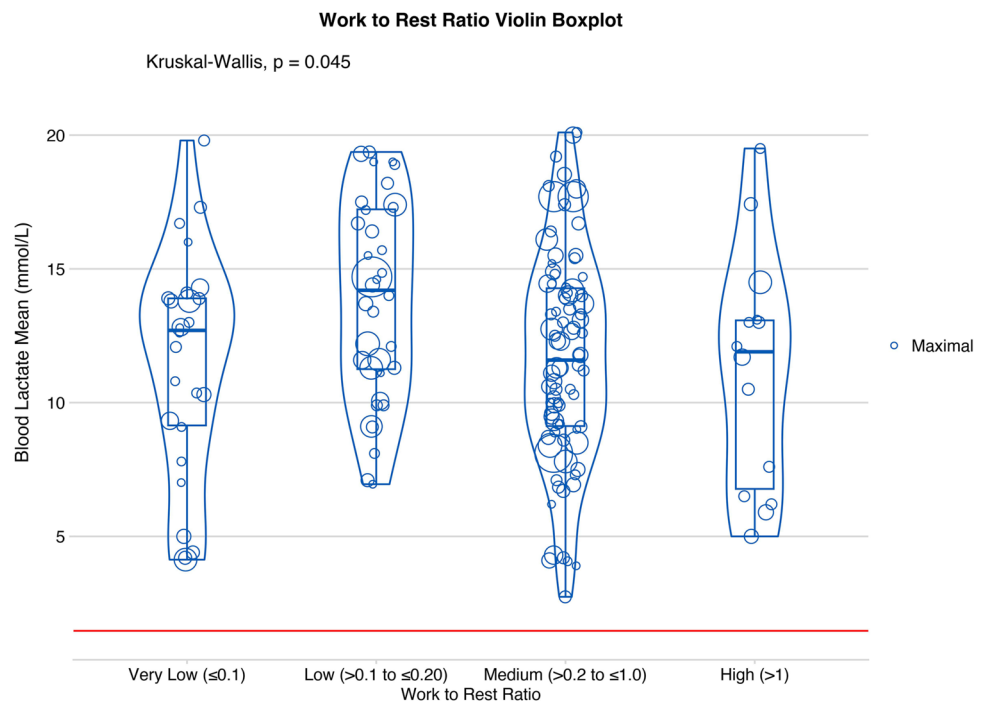
Table 2 Meta-regression model with session volume and other covariates

Session volume mixed-effects regression models		Model 1	Model 2	Model 3	Model 4
		$N=226$	$N=226$	$N=183$	$N=99$
		$R^2=0.0824$	$R^2=0.1604$	$R^2=0.2484$	$R^2=0.3937$
		β estimates			
Model variable estimates	(Constant)	11.9502***	11.6749***	10.0389***	6.538*
	Session volume				
	Medium (> 5 to ≤ 15 min)	2.0524**	2.0302**	2.324***	2.0774*
	High (> 15 min)	-0.7475	0.6169	0.7418	-0.1578
	Age	-0.0411	-0.0183	-0.0075	0.0554
	Work interval intensity (sub-maximal)		-2.9569***	-3.2291***	-3.427***
	BLa measurement timing (greater than 3 min)			1.145	1.7567*
	Method of blood draw				
	Fingertip prick			1.8119**	3.1247***
	From arm			1.0034	1.1576
	VO ₂ peak (mL/kg/min)				0.0352

β estimated coefficients of the model, BLa blood lactate, VO₂ peak peak oxygen consumption

Significant codes: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Fig. 4 Work-to-rest ratio violin boxplot—maximal Intensity studies only. Note. Meta Regression of blood lactate (mmol/L) with work-to-rest ratio as the only categorical predictor. $N=162$ studies. The red line represents average resting blood lactate value (1.47 ± 0.67 mmol/L) from 103 studies. The size the circles is proportional to the sample size of each study



3.5 Effect of Intervention: Secondary Research Question

Only four studies measured cognitive performance at pre- and post-HIIT in addition to blood lactate (Kujach et al. [39], Tsukamoto et al. [44, 49], Hashimoto et al. [43]). These studies only assessed the Stroop Color-Word Test performance, and thus only this cognitive measure could

be included in the analyses. Nevertheless, the Stroop interference condition task is considered a gold standard of attentional measures [55] and is a widely used measure of inhibitory control, which is a component of executive function [56]. The results from Tsukamoto et al. [44] and Hashimoto et al. [43] were analysed together as they used identical Stroop interference score units (Fig. 5 and Fig. S5 of the ESM). Tsukamoto et al. [49] (Fig. 6 and Fig. S6

Table 3 Meta-regression model with a work-to-rest ratio and other covariates

Work-to-rest ratio mixed-effects regression models		Model 1	Model 2	Model 3	Model 4
		<i>N</i> = 226	<i>N</i> = 226	<i>N</i> = 183	<i>N</i> = 99
		$R^2 = 0.1399$	$R^2 = 0.1828$	$R^2 = 0.2673$	$R^2 = 0.4476$
		<i>β</i> estimates			
Model variable estimates	(Constant)	12.8762***	12.0064***	9.8198***	3.6845
	Work-to-rest ratio				
	Low (> 0.1 to ≤ 0.20)	2.4438*	2.5244**	3.1658**	4.7734**
	Medium (> 0.2 to ≤ 1.0)	-0.3956	0.211	0.4705	2.0608
	High (> 1)	-2.4869**	-0.9597	0.2485	0.85
	Age	-0.0582	-0.0223	-0.0083	0.0593
	Work-interval intensity (sub-maximal)		-2.2219***	-2.6272***	-2.7371**
	BLa measurement timing (greater than 3 min)			1.374*	1.7997*
	Method of blood draw				
	Fingertip prick			1.8304**	2.7924***
	From arm			0.9525	0.679
	VO ₂ peak (mL/kg/min)				0.0527

B estimated coefficients of the model, *BLa* blood lactate, *VO₂ peak* peak oxygen consumption

Significant codes: **p* < 0.05; ***p* < 0.01; ****p* < 0.001

of the ESM) used the reverse-Stroop interference score ratio [(reaction time of incongruent task – reaction time of neutral task)/(reaction time of neutral task × 100)] and Kujach et al. [39] (Figs. S7a and S7b of the ESM) used interference execution time measured in milliseconds. All four studies found that Stroop interference performance improved after HIIT, as compared with pre-HIIT. Tsukamoto et al. [44, 49] and Hashimoto et al. [43] assessed Stroop interference score and measured blood lactate at multiple timepoints post-HIIT. In contrast, Kujach et al. [39] assessed blood lactate immediately post-HIIT, and Stroop interference execution time at 20 min post-HIIT. Using a series of sensitivity analyses for Tsukamoto et al. [44, 49] and Hashimoto et al. [43], linear regressions revealed that the strongest coefficient of determination was between blood lactate levels at 0 min post-HIIT and interference performance at 30 min post-HIIT (adjusted $R^2 = 0.14$, $r = -0.42$, $p = 0.039$ for Tsukamoto et al. [49]; adjusted $R^2 = 0.17$, $r = -0.45$, $p = 0.031$ for Tsukamoto et al. [44] and Hashimoto et al. [43]). However, for Kujach et al. [39], blood lactate at 0 min post-HIIT was not significantly associated with interference execution time at 20 min post-HIIT (adjusted $R^2 = -0.004$, $r = -0.22$, $p = 0.35$). Taken together, data from all four studies suggest that HIIT improves Stroop interference score and execution time, and that blood lactate levels immediately post-HIIT may predict 14–17% of the variance in Stroop interference score at 30 min post-HIIT. However, these

results are tentative given the low number of studies and should be interpreted cautiously.

3.6 Risk of Bias Assessment

Risk of bias in randomised studies was assessed using the Cochrane Risk of Bias Tool 2, where judgements can be “Low”, “High” or “Some Concerns” [57]. Risk of bias in non-randomised studies was assessed using the ROBINS-I Tool, where judgements can be “Critical”, “Low”, “Serious” or “Moderate” [58]. Of the 226 single-arm studies, two had a high risk of bias, two had a moderate risk, five had some concerns and 217 had a low risk of bias (Figs. S8a and S8b of the ESM). Including studies with only a low risk of bias in the analyses did not change any of the results.

4 Discussion

4.1 Recap of Objectives

The primary purpose of this review was to characterise a HIIT protocol that would elicit peak peripheral lactate levels because of this molecule’s many benefits on the nervous system, and on cognition [59]. Our secondary purpose was to better understand the relationship between

Fig. 5 Tsukamoto et al. [44] and Hashimoto et al. [43] Stroop interference (30 min post-HIIT) vs blood lactate (0 min post-HIIT). Note. All Stroop interference scores are from 30 min post-HIIT. All blood lactate values are from 0 min post-HIIT. Data combined from Tsukamoto et al. [44] and Hashimoto et al. [43]. $N=23$ subjects in total

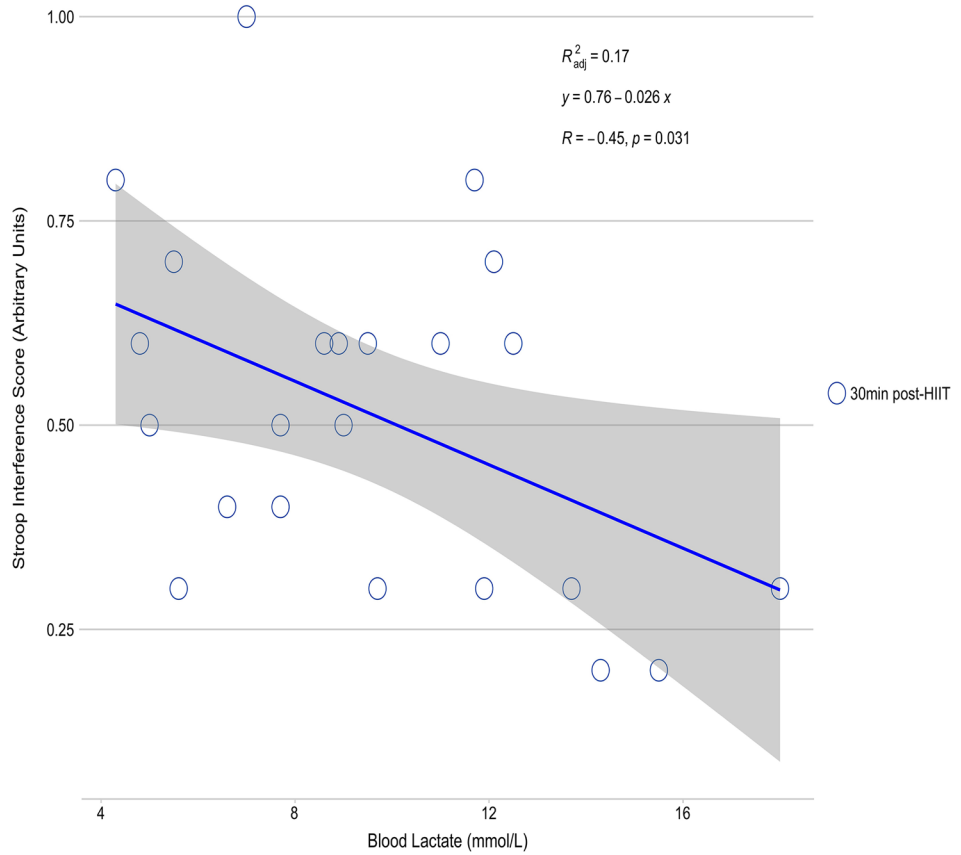
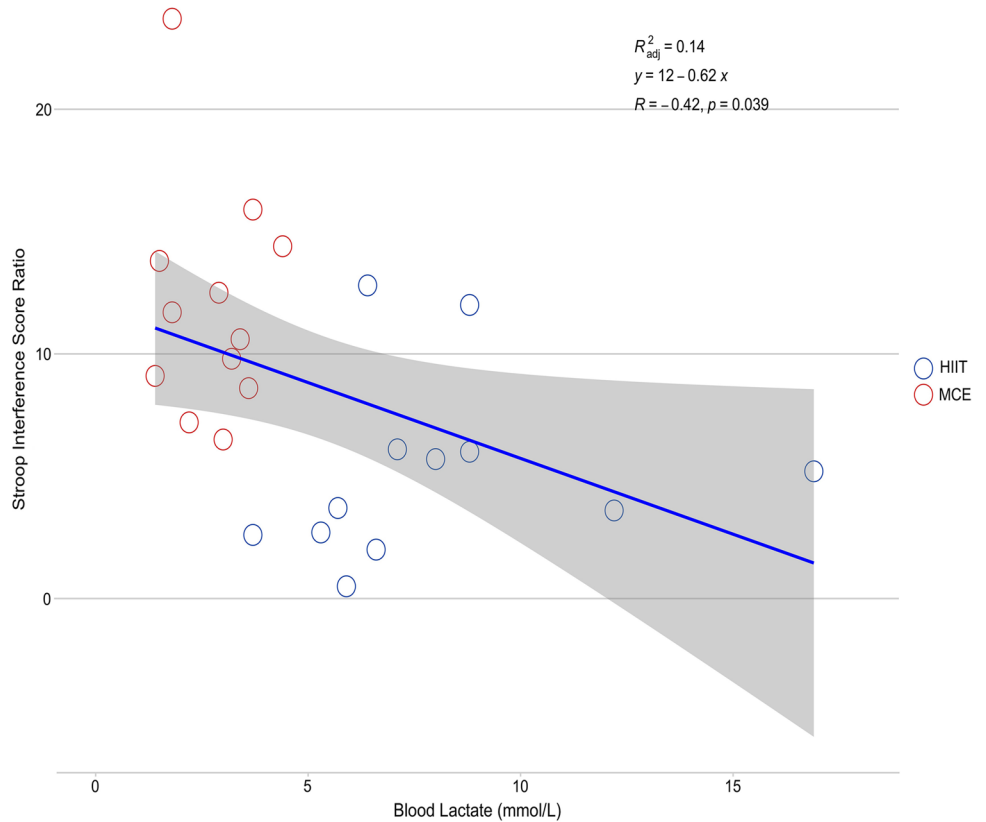


Fig. 6 Tsukamoto et al. [49]—Stroop interference (30 min post-exercise) vs BLa values (0 min post-exercise). Note: All Stroop interference values are from 30 min post-exercise. All blood lactate values are from 0 min post-exercise. $N=12$ subjects. MCE: moderate continuous exercise. Recreated with permission from Tsukamoto et al. [49]



HIIT-induced blood lactate levels and post-exercise cognitive performance in healthy adults.

5 Summary of Main Findings

With regard to research question 1, the mixed-effects meta-regressions suggested that the optimal individual protocol parameters, when the intensity was maximal, were:

1. *Low* work-interval volume (> 1.5 to ≤ 5 min);
2. *Medium* session volume (> 5 to ≤ 15 min);
3. Recovery intervals that are about five times longer than work intervals.

A HIIT protocol using the above parameters may allow anaerobic glycolysis to be the major ATP source during exercise. The ATP contribution from anaerobic glycolysis can be estimated by peripheral lactate accumulation [8]. In the studies ($n = 103$) that used a *very low* work-interval volume (≤ 1.5 min), the majority (90/103 studies; 87%) of the work-interval durations used were ≤ 20 s. During maximal exercise that lasts only 15–20 s, the phosphocreatine system supplies most of the ATP, and peak peripheral lactate levels are not expected as anaerobic glycolysis needs more time to be fully upregulated [60]. Thus, one potential explanation why *very low* work-interval volumes did not lead to peak peripheral lactate is because the phosphocreatine system, and not anaerobic glycolysis, was the major ATP contributor. In the studies ($n = 65$) using *medium* (> 5 and ≤ 10 min) and *high* (≥ 10 min) work-interval volumes, the majority (59/65 studies; 91%) of the work-interval durations were ≥ 60 s. When continuous exercise extends beyond 60 s, oxidative phosphorylation is the major ATP-generating pathway, which leads to less lactate accumulation as pyruvate would enter the Krebs cycle instead of being reduced to lactate [13, 61]. In the studies ($n = 58$) that used a *low* work-interval volume, the majority (41/58 studies; 71%) of the work-interval durations were between 30 and 60 s, and maximal continuous exercise lasting this long would rely mainly on anaerobic glycolysis, leading to a higher lactate accumulation [61]. Thus, a *low* work-interval volume at maximal intensity may rely more on anaerobic glycolysis rather than the phosphocreatine system or oxidative phosphorylation, which may explain why this category elicited peak peripheral lactate accumulation. In the studies ($n = 38$) that used a *low* work-to-rest ratio (> 0.1 to ≤ 0.20), the most frequent (23/38 studies; 61%) work-interval duration used was 30 s, and the majority (27/38 studies; 71%) of the recovery interval durations used were ≥ 120 s. Recovery intervals lasting this long

would allow more than 70% of the phosphocreatine system to replenish [62]. Replenishing the phosphocreatine system may help the individual to exercise at maximal intensity for each subsequent interval, and as our regression models have shown, exercising at maximal intensity is predictive of greater peripheral lactate accumulation.

With regard to research question 2, in Tsukamoto et al. [49], the HIIT group with greater blood lactate accumulation showed improved Stroop interference scores from pre- to post-HIIT, with improvements maintained up to 50 min post-HIIT (please note that the researchers did not measure post-50 min). In the moderate-intensity exercise group with lower blood lactate accumulation, however, the benefits only lasted 20 min post-exercise. These findings raise the hypothesis that *HIIT-induced improvements in interference control will last longer post-exercise when higher blood lactate levels are achieved immediately post-exercise*. In Tsukamoto et al. [49], Tsukamoto et al. [44] and Hashimoto et al. [43], we found a delayed relationship between Stroop interference score and blood lactate accumulation. A series of sensitivity analyses with linear models revealed that the strongest determination and correlation coefficients were found between lactate values immediately post-HIIT and Stroop interference scores from 30 min post-HIIT. Therefore, a second hypothesis raised is that *higher blood lactate levels immediately post-HIIT will be predictive of better Stroop interference scores at 30 min post-exercise*. The improved inhibitory control performance (e.g., Stroop interference) observed post-exercise may be metabolically costly, as it is associated with enhanced dorsolateral prefrontal cortex neuronal activity [46, 63, 64]. This increased neuronal activity costs ATP, which may be provided by lactate oxidation, as suggested by the astrocyte-to-neuron lactate shuttle hypothesis [65]. In this review, we have found preliminary evidence that increased peripheral lactate is associated with improved inhibitory control post-HIIT. This association may suggest that neurons use lactate to enhance neuronal activity. These results, however, cannot speak fully to the close relationship between post-exercise lactate changes and post-exercise inhibitory control performance, as only four studies were included in the analyses.

5.1 Immediate Applications

Lactate may be a key molecule that regulates the exercise-induced benefits on the brain [66], by promoting angiogenesis via vascular endothelial growth factor A [20], and neurogenesis via BDNF [53]. Healthy adults already engaging in HIIT may use our findings and adapt their protocol to maximally confer this molecule's benefits to the nervous system. In order to elicit peak peripheral lactate, one can

exercise maximally for a total duration of > 1.5 to ≤ 5 min, with recovery intervals about five times longer than the work intervals, for a total of 15 min. As shown by this review, one of the potential benefits of HIIT-induced lactate is improved interference control. Performing cognitively demanding tasks 10–50 min post-HIIT may be one way to take advantage of the HIIT-induced lactate levels. Our finding that peripheral lactate is increased by shorter rather than longer protocol durations, provided that intensity is maximal, is encouraging because a lack of time is a common exercise barrier [67–69].

A HIIT protocol that elicits peak peripheral lactate may also upregulate downstream targets such as BDNF. Schiffer and colleagues [48] have shown that lactate infusion at rest can result in increased circulation of BDNF in young adults. Based on animal studies, one mechanism may be that peripheral lactate is transported to the hippocampus, where it activates silent information regulator-1, which goes on to increase peroxisome proliferator activated-receptor γ coactivator-1 α and fibronectin type III domain-containing protein 5, which ultimately increases BDNF gene expression [53]. Increased BDNF from exercise is associated with neuroplasticity and activity-dependent plasticity in the hippocampus [70, 71]. Brain-derived neurotrophic factor has also been shown to induce activity-dependent myelination by affecting oligodendrocytes [72, 73], which contributes to long-term potentiation [74] and memory consolidation [75].

Exercise that elicits peak peripheral lactate levels may also have an impact on muscle mitochondrial density [76]. Animal studies have demonstrated that chronic lactate infusion enhances muscle mitochondrial biogenesis [77], and exercise-induced lactate mediates mitochondrial biogenesis in the hippocampus of healthy mice [78]. During exercise, muscle lactate levels would continually increase unless there is sufficient mitochondrial mass to shuttle the lactate produced from glycolysis towards the Krebs cycle [79]. This shuttling process may involve the mitochondrial lactate-oxidation complex [80, 81]. A greater volume density of mitochondria may lead to lower muscle/blood lactate build-up, even at higher rates of glycolysis, such as during higher intensity exercise [79, 82]. Mitochondrial density can increase in response to continued exercise training [83], leading to decreased peripheral lactate accumulation [79]. Greater mitochondrial content increases the muscles' reliance on fat oxidation and lowers the reliance on carbohydrate oxidation at a given intensity [84], thereby increasing the lactate threshold in individuals [85]. A higher lactate threshold (i.e., less blood lactate accumulation at a given intensity) may be interpreted as improved endurance capacity [86]. As lactate accumulation is a biomarker of metabolic strain [76], a corollary may be that when muscles are continually exposed to higher lactate levels during exercise training (i.e., a HIIT protocol that elicits peak peripheral

lactate), one training adaptation may be to increase mitochondrial biogenesis (i.e., increasing oxidative capacity) to handle future levels of high lactate build-up. The increased mitochondrial levels may then contribute towards a higher lactate threshold, which may promote aerobic fitness. Future trials in humans are needed to confirm whether the HIIT protocol parameters described in this review indeed elicit higher peripheral lactate levels that drive mitochondrial biogenesis, and improve the lactate threshold.

5.2 Limitations and Future Directions

The current review analysed the effects of individual protocol parameters on blood lactate. Future randomised controlled trials are needed to compare between different HIIT protocol parameter combinations. We offer two such example combinations that can be extrapolated from our findings to be tested in future research: (1) 8×30 s maximal intensity interspersed with 1 min 30 s of recovery and (2) 9×20 s maximal intensity interspersed with 1 min 20 s of recovery (Fig. 7). Both these protocols involve maximal intensity exercise time that is between 1.5 and 5 min, with recovery intervals much longer than work intervals, for a total of ~ 15 min. Future research is required to compare the changes in peripheral lactate levels and cognitive performance from these protocol combinations against other protocols commonly used in the literature, such as the Wisloff [87] protocol (4×4 min at 95% heart rate maximum, interspersed by a 3-min recovery at 70% heart rate maximum). Additional research is also required to determine whether total lactate production or peak lactate levels during exercise are more strongly associated with the benefits of lactate.

Maximal intensity was a significant covariate that increases blood lactate values. However, when prescribing high-intensity exercise, the difference between maximal and sub-maximal may not be easily identifiable as there was no consistent quantitative measure to determine

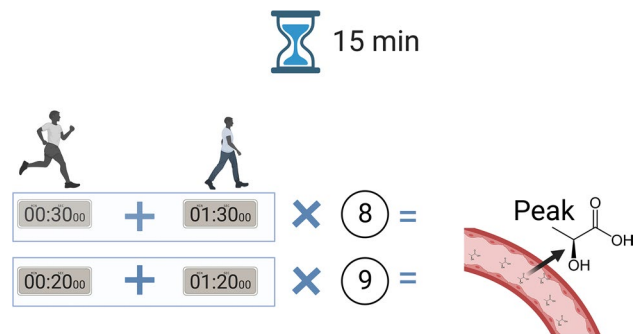


Fig. 7 Possible parameter combinations to be tested in future research. Note. These example protocols are derived by combining the optimal individual HIIT protocol parameters for increasing peripheral lactate levels

whether participants were truly and continuously exercising at maximal intensity. We encourage future research to report exercise intensity relative to the lactate threshold (estimated using a non-invasive gas exchange threshold during an incremental exercise test [76]) because this unit would provide a more homogenous exercise stimulus [88].

Regarding the second research question, only four studies provided data on both blood lactate and cognitive performance post-HIIT, preventing us from drawing any firm conclusions. Furthermore, all cognitive assessments were limited to the Stroop interference condition. Including additional tests that are highly sensitive to hippocampal function, such as high-interference memory performance (e.g., Mnemonic Similarity Task [89] or the Memory Image Completion test [90]), would be of value for future research. Lactate has shown to promote both hippocampal BDNF [53] and adult hippocampal neurogenesis [27]. Promoting hippocampal BDNF and neurogenesis is critically important for high-interference memory [91] because newborn neurons in the dentate gyrus are integrated to encode novel stimuli and reduce interference between highly similar stimuli [92, 93]. Furthermore, measuring brain activity during these cognitive assessments would determine whether higher lactate is associated with enhanced brain activation in the areas responsible for interference/inhibitory control, and high-interference memory performance.

Last, we encourage future research to consistently report on covariates such as method of blood draw, blood source, blood composition and the corresponding measurement timing of each reported blood lactate value (e.g., $10 \pm$ standard deviation mmol/L at 3 min post-HIIT). Some studies in this review did not report these covariates and therefore were excluded from the complex regression models.

6 Conclusions

Lactate is an important molecule that regulates neurogenesis and angiogenesis, supports myelination, and provides fuel for neurons under high-energy demands. This systematic review sought to find the optimal individual HIIT protocol parameters for inducing peak peripheral lactate levels. Just 5 min of actual exercise time, at maximal intensity, separated by recovery intervals that are about five times longer than work intervals, for a total of 15 min, appear to elicit peak peripheral lactate levels. Our findings from our second research question produced hypotheses regarding HIIT-induced blood lactate and cognitive performance. Future research is needed to test these hypotheses and to confirm our findings regarding the optimal HIIT protocol parameters. In the meantime, healthy adults may experience short-term cognitive benefits from this time-efficient HIIT protocol that uses shorter durations to elicit peak peripheral lactate levels.

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Declarations

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Author contributions NJ conceived the study, completed all statistical analyses and wrote the first manuscript draft. NJ and IS independently screened titles, abstracts, and full texts, and extracted data. BS reviewed all conflicts during screening, and provided valuable guidance during data extraction and analyses. IS, BS, SM, CT, PO and RG critically edited and revised the draft manuscript, and provided input throughout the review process. All authors read and approved the final manuscript.

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