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Effects of 9 Weeks of High- or Moderate-Intensity Training on Cardiorespiratory Fitness, Inhibitory Control, and Plasma Brain-Derived Neurotrophic Factor in Danish Adolescents—A Randomized Controlled Trial

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ABSTRACT

Purpose: The primary aims of this study were to examine the effects of 9 weeks of aerobic training, comprising three 30-min sessions per week, on $\dot{V}O_{2max}$, inhibitory control, and plasma brain-derived neurotrophic factor (BDNF) levels among adolescents aged 16–19 years.

Methods: One hundred twenty-one untrained or recreationally active adolescents from a Danish high school were enrolled in the study, with 58 females (17.8 ± 0.8 years) and 27 males (18.0 ± 0.9 years) completing it. Participants were randomly divided into three groups performing aerobic training at either moderate-intensity (MIT: 60%–70% heart rate reserve [HRR]) or high-intensity (HIT: 80%–100% HRR) or a passive control group (CON) continuing their habitual lifestyle. Both the training groups exercised for 3 × 30 min per week for 9 weeks using a combination of cycling and running. Before and after the intervention period maximal oxygen uptake ($\dot{V}O_{2max}$) and the primary outcomes (inhibitory control measured by a modified flanker task, and resting plasma levels of BDNF) were evaluated.

Results: After the intervention period, the HIT group demonstrated a larger increase in $\dot{V}O_{2max}$ compared to both the CON and MIT groups, while no significant effects were observed on inhibitory control or plasma BDNF levels in any training group. However, compared to the CON group, the HIT group exhibited a tendency for greater improvement in the flanker interference score (accuracy), attributable to enhanced accuracy on the incongruent stimuli from pre to post.

Conclusion: Aerobic training in adolescents increased cardiorespiratory fitness in an intensity-dependent manner, but no clear effects were observed on neither inhibitory control nor resting plasma BDNF levels.

Clinical Trial Registration: ClinicalTrials.gov: NCT02075944.

1 | Introduction

Due to its numerous beneficial health effects, engagement in physical activity is recommended from childhood and throughout the later stages of life [1]. In adolescents, aerobic training has repeatedly been shown to be effective in improving cardiorespiratory fitness ($\dot{V}O_{2max}$) [2], and with high-intensity aerobic training shown to be more effective than moderate-intensity aerobic exercise in fostering adaptations in $\dot{V}O_{2max}$. Besides the attractive effects of aerobic exercise on $\dot{V}O_{2max}$, aerobic exercise has also proven beneficial with respect to cognitive performance [3], although the effect of exercise training and the intensity hereof on markers of cognitive performance is largely unknown in adolescents.

Concerning cognitive performance, a growing body of research indicates that aerobic training positively affects brain structure and function in healthy individuals [3–6]. In particular, executive functions (EFs) appear to be affected positively by both acute and chronic aerobic exercise [7]. EFs encompass goal-directed cognitive processes often associated with the frontal lobes and comprise cognitive flexibility ("shifting," i.e., transitioning between tasks and mental sets), working memory ("updating," i.e., retaining and manipulating information in mind), and inhibitory control ("inhibition," i.e., managing distractions and impulses) [8]. Well-developed EFs are found to be essential for school performance [9], vocation [10], and social behavior [9], and detailed knowledge about the effects of different physical training strategies on EFs are warranted. Adolescence is a period characterized by notable structural and functional brain development, particularly in regions linked to EFs, such as the prefrontal cortex [11]. Consequently, the development of EFs continues throughout adolescence and into early adulthood [11]. Therefore, the adolescent brain may be particularly responsive to interventions affecting EFs. Considering the vital role of EFs in various aspects of daily functioning and the increasing sedentary behavior among adolescents [12], knowledge about potential exercise-induced changes in EFs is highly pertinent for this age-group.

The majority of research examining the impact of aerobic training on aspects of EFs has been conducted in elderly individuals [3, 13] or children [5, 14], while there is a paucity of studies involving adolescents, that is, 10–19 years [15], underscoring the necessity for further research within this age-group [7, 16]. A study by Costigan and colleagues reported a small, insignificant effect of 8 weeks of high-intensity aerobic training on EFs in adolescents aged 14–16 years [17]. However, the training volume in the study was relatively low (i.e., 24–30 min per week) which may have been insufficient to induce improvements in EFs. In support of this notion, cardiorespiratory fitness was unaltered after the training period, suggesting that participants were subjected to a low training stimulus. Consequently, a definitive link between changes in cardiorespiratory fitness and EFs could not be established in that study [17], and remains to be elucidated in adolescents.

Several physiological mechanisms have been suggested to underlie potential effects of aerobic training on cognitive performance including enhanced regulation of cerebral blood flow [18], enhanced cerebral function, and changes in growth factors [19]. In addition, physical activity seems to enhance white matter integrity and activation of regions with importance for cognitive processes in children and adolescents [20]. A prolonged period of high-intensity interval training (HIT) has recently been shown to improve hippocampal metabolism among older adolescents with low cardiorespiratory fitness and interestingly, these improvements were associated with improvements in cardiorespiratory fitness and working memory [21]. Accordingly, training induced structural and functional adaptations are likely required to achieve observable changes in cognitive performance. Within the last decades, increased attention has been given to the growth factor protein brain-derived neurotrophic factor (BDNF). In rodents, exercise has been shown to increase BDNF levels in the brain, in association with improved cognitive performance [22]. Furthermore, the exercise-induced improvements in cognitive performance were blunted by inhibition of BDNF action [22]. In addition, studies in humans report that peripheral resting levels of BDNF may be increased following aerobic training [23, 24], potentially mediating improvements in cognitive performance [24]. However, inconsistencies within the literature exist. Moreover, studies have mainly been conducted in older adults and less is known about younger age groups. As such, research is needed to further elucidate details about the relation between aerobic exercise, peripheral BDNF, and cognitive performance in humans and particularly in younger age groups.

Therefore, the primary aim of the current study was to test the effects of 9 weeks of aerobic exercise on cardiorespiratory fitness, inhibitory control, and plasma BDNF in adolescents aged 16–19 years. The study included two types of training interventions: (1) continuous moderate-intensity aerobic training (MIT) and (2) HIT. The primary outcomes of the present trial were inhibitory control and plasma BDNF and based on the literature we hypothesized that an improved flanker task performance, a measure of inhibitory control, as well as higher levels of resting plasma BDNF would be accompanied by increased $\dot{V}O_{2max}$.

2 | Methods

The study was conducted as a 9-week parallel three-arm randomized controlled trial. Participants were randomly allocated to one of the three groups: (1) passive control with no intervention (CON group), (2) MIT group, or (3) high-intensity interval training (HIT group. Outcomes, including cognitive performance, $\dot{V}O_{2max}$, and plasma BDNF, were assessed before and after the intervention period.

2.1 | Participants

Participants were recruited from a local high school in Odense, Denmark. Four hundred seventy-five first and second year high school students (aged 16–19 years) were initially approached (Figure 1). Two hundred twenty-four students (~47%) expressed interest and were screened for eligibility by phone. Students were excluded if they (1) engaged in leisure time sport activities more than 8 h per week or

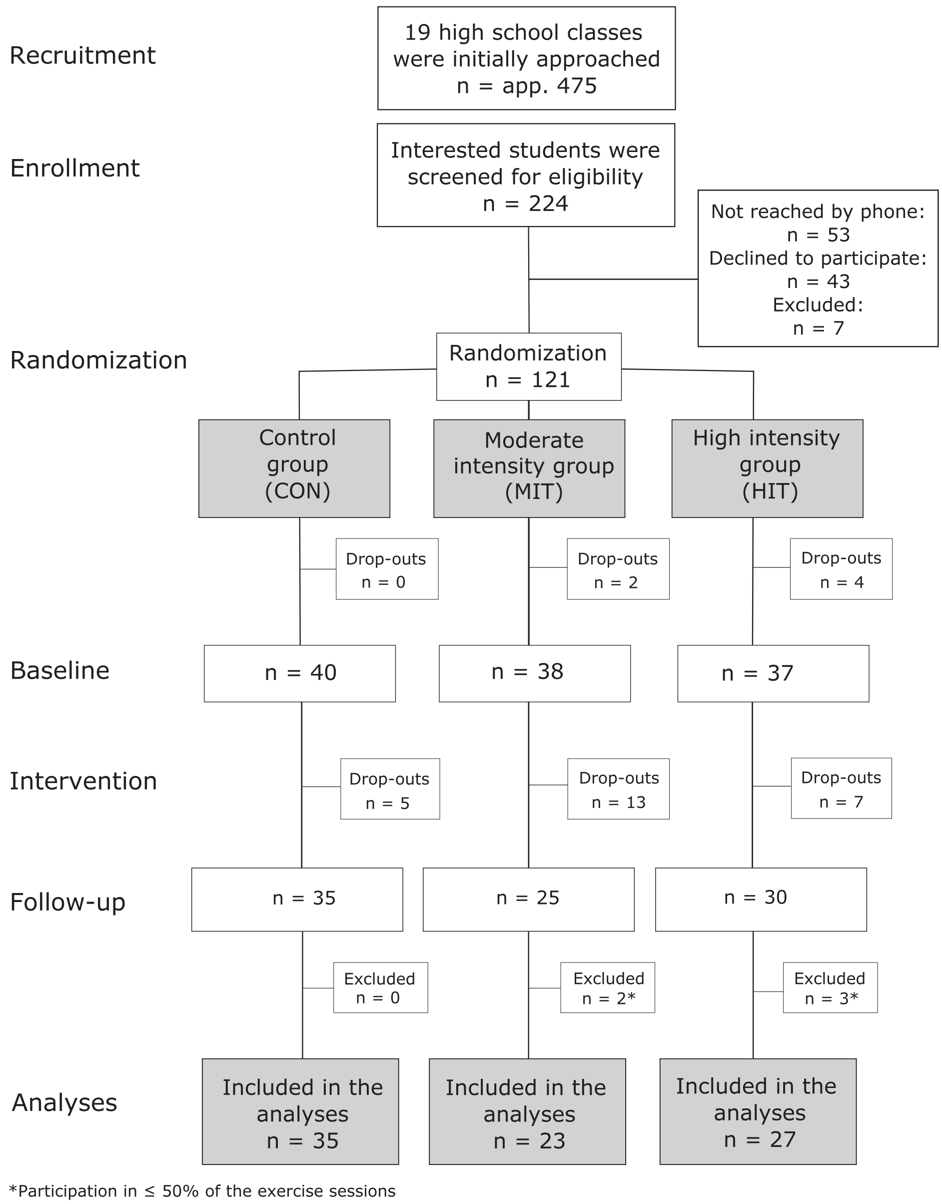

FIGURE 1 | The consort diagram illustrates the flow of participants through each stage of the study.

(2) had a physical condition (e.g., physical disability) which prevented them from performing aerobic training. Stratified by sex, a total of 121 students (~25%) were randomized in a 1:1:1 ratio to the passive CON group ($n=40$), the MIT group ($n=40$) or the HIT group ($n=41$). The randomization took place prior to the baseline measurements while participants received information about the randomization after the baseline measurements. Importantly, none of the participants were diagnosed with cognitive conditions. The team conducting the measurements operated under blinded conditions. In total, 30 participants either withdrew from the project or attended less than 50% of the training sessions and were therefore excluded from all analyses (Figure 1). The final sample included 85 participants with data available at baseline and post-intervention. All participants provided written informed consent and parental written consent was obtained for those younger than 18 years. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Regional Committees on Health Research Ethics for Southern Denmark (S-20130171).

2.2 | Procedure

Before and after the intervention period, outcome assessments were conducted during two visits at the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark, while one assessment session was completed at the high school (cognitive performance). The sequence of tests was the same for all participants and pre- and posttests were conducted at the same time of the day within individuals. At baseline, participants attended the university on average 3 weeks before the training intervention for extraction of fasting blood samples and anthropometric measurements (Figure 2). The second visit took place on average 6 days before the intervention period and included measurements of resting heart rate (HR_{rest})

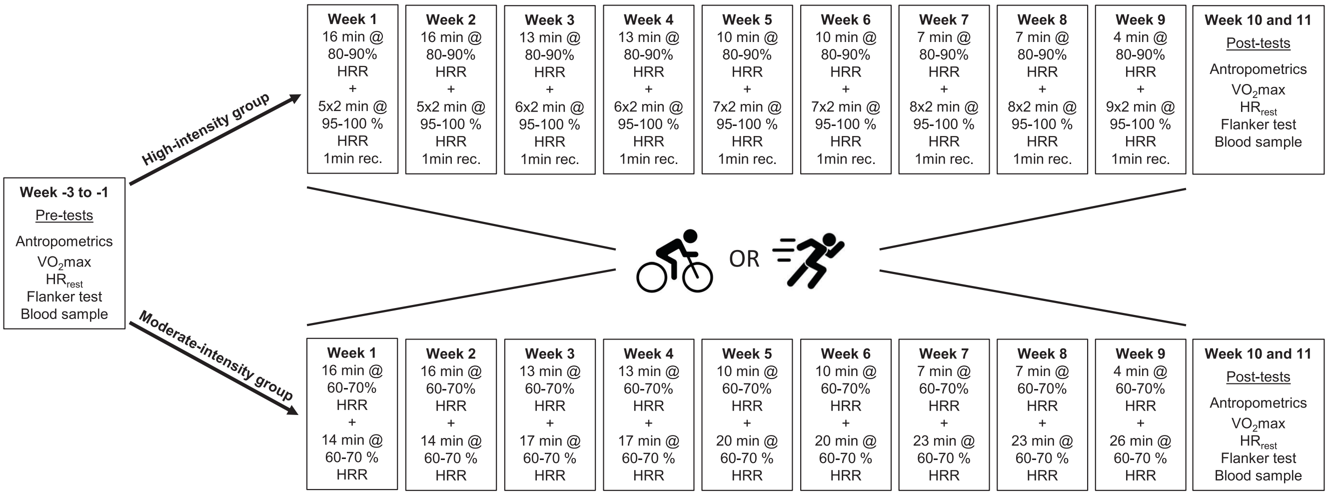

FIGURE 2 | Schematic study overview. Participants ($n=121$) were randomly assigned to a control group (CON) (not shown), a high-intensity training group (HIT) (top), or a moderate-intensity training group (MIT) (bottom). 1–2 weeks before and after the 9-week intervention period, participants attended the laboratory to conduct pre-tests and post-tests. Both the training groups exercised for 30 min (including recovery periods) three times per week. All sessions involving both cycling and running. In the HIT group, all sessions were initiated by continuous exercise at 80%–90% of HR reserve (HRR) (cycling or running) followed by 2-min intervals at 95%–100% HRR (opposite discipline of continuous exercise). Throughout the 9-week training period, the amount of continuous exercise was reduced every second week while the number of intervals was increased concomitantly. Each training session in the MIT group was divided into two parts with durations corresponding to those in the HIT group. By this design, a similar duration of cycling and running was performed between the training groups during the intervention period. HR_{rest} = resting heart rate, rec. = recovery, $\dot{V}O_{2max}$ = maximal oxygen uptake.

and a maximal cycling test to determine $\dot{V}O_{2max}$ and maximal heart rate (HR_{max}). Between the two visits at the university, cognitive assessments were conducted on average 11 days before the intervention period in standardized setting at the high school by trained staff studying Sport and Health at the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark. Post-intervention assessments were conducted on average 5 (fasting blood samples and anthropometrics), 7 (maximal cycling test, blood pressure, and HR_{rest}), and 14 days (cognitive assessments) after the end of the intervention period.

2.3 | Intervention

The 9-week training intervention period was conducted between March and May 2014. Participants trained three times per week, with all training sessions lasting 30 min in both the groups (Figure 2). All sessions were conducted in a school setting at the high school and consisted of both running and cycling at a prescribed and individually determined intensity based on individual heart rate reserve (HRR) calculated based on HR_{max} during the maximal cycling test at baseline and HR_{rest} (target HR (HR_{target}) = (HR_{max} − HR_{rest}) · target intensity + HR_{rest}). Most training sessions were supervised (~83%) by educated training instructors studying Sport and Health at the Department of Sports Science and Clinical Biomechanics, University of Southern Denmark. To ensure intervention fidelity, exercise intensity was objectively measured with heart rate telemetry (Polar RCX3, Polar Electro, Kempele, Finland). In addition, instructors visually inspected heart rate readings during cycling sessions to make sure that the target intensity was maintained. To increase adherence, sessions took place either in the morning before school or directly after school in a gym located at the high school (stationary cycling) or in areas surrounding the school (running). In both the groups, training was conducted as a mix of running and cycling, with an effort made to balance the modalities across the sessions. In the MIT group, training consisted of continuous aerobic exercise at a moderate intensity of 60%–70% HRR throughout the training period. The HIT group followed a HIT protocol (Figure 2). Specifically, participants in the HIT groups performed 16 min of continuous exercise (running or cycling) at a constant intensity of 80%–90% of HRR followed by five 2-min high-intensity intervals at 95%–100% of HRR during the initial 2 weeks. Intervals were interspersed by 1 min recovery. Every second week, one 2-minute interval was added, and the continuous exercise time was reduced concomitantly by 3 min to 13, 10, 7, and 4 min in the last weeks of the intervention (Figure 2). Participants in the CON group received no exercise intervention and were asked to maintain their usual physical activity routines and lifestyle.

2.4 | Measurements

2.4.1 | Cardiorespiratory Fitness

$\dot{V}O_{2max}$ was measured during a maximal exercise cycling test [25] using an electronically braked cycle ergometer (Monark Ergomedic 839, Vansbro, Sweden). The test started with a 5-min warm-up at 110 and 70 W load for males and females, respectively. The load was then increased by 40 W every 2 min until exhaustion. Participants were encouraged to maintain a cadence of 70–80 rpm and the test was terminated when a cadence of 30 rpm could not be maintained. $\dot{V}O_2$ was measured throughout the test using a mixing chamber system (AMIS 2001, Innovision, Odense, Denmark). Prior to each test, gas analyzers were calibrated using two known gases containing 20.91% and 14.96% O_2 and 0.00% and 4.97% CO_2, respectively. A 3-L syringe (Hans Rodolph, Shawnee, KA) was used to calibrate the flowmeter. $\dot{V}O_2$ was sampled every 10 s and averaged over 30 s periods. $\dot{V}O_{2max}$ was expressed as the highest $\dot{V}O_2$ (L·min^{-1}) over a 30-s period during the test [25]. Both the absolute (L·min^{-1}) and relative (mL·kg^{-1}·min^{-1}) values of $\dot{V}O_{2max}$ was used in the analyses. Heart rate data were sampled throughout the test with a Polar HR monitor (Polar RS800CX, Polar Electro, Kempele, Finland). HR_{max} was defined as the highest HR value registered during the cycling test. Blood lactate concentration was measured 2 min after termination of the test (YSI model 1500 Sport, YSI Inc., Yellow Springs, OH). Participants rated their perceived exhaustion (RPE) at the end of the test using a 20-point Borg scale. Tests were accepted as maximal if three out of the following four criteria were met: (1) RPE >15, (2) heart rate above 185 bpm, (3) blood lactate concentration >8 mmol/L, and/or (4) subjective approval by test administrator. Four participants (CON: $n=3$, HIT: $n=1$) only fulfilled two of the four criteria at baseline. At follow-up, eight participants fulfilled less than three criteria (CON: $n=5$, MIT: $n=2$, HIT: $n=1$). The evaluation of $\dot{V}O_{2max}$ was conducted after consumption of a habitual mixed diet.

2.4.2 | Inhibitory Control

Inhibitory control was measured by a modified Eriksen flanker task [26]. This task measures the ability to suppress distractors and attend to relevant information. Participants were asked to respond as quick and as accurate as possible with an index finger corresponding to the directionality (left or right) of a centrally positioned target arrow among an array of congruent (facing in the same direction >>>>>) or incongruent (facing the opposite direction >><>>) flanker arrows. Following 20 practice trials, participants completed two blocks of 100 experimental trials with equiprobable congruency. The stimuli were white arrows presented on a black background focally on a computer screen using E-Prime software (E-Prime v. 3.0, Psychology Software Tools Inc., Sharpsburg PA, USA). Presentation time was 100 ms, with 1000 ms response window and equiprobable, random interstimulus intervals (ISIs) of 1250, 1350, 1450, and 1550 ms. Outcome measures were mean reaction time (RT) and response accuracy (percent correct responses). Further, interference scores were calculated as the differences in RT and accuracy, respectively, for congruent and incongruent stimuli. A smaller interference score reflects an improved ability to inhibit distracting stimuli [26]. High test–retest reliability (ICC = 0.95) and convergent validity ($r=0.48$) have been observed using an abbreviated version of the task [27]. If accuracy on either congruent or incongruent stimuli fell below 50%, the test was deemed invalid and excluded from the analysis.

2.4.3 | Anthropometric Measurements

Body height was measured with a stadiometer (SECA, 22089 Hamburg, Germany) to the nearest 0.5 cm and body weight was assessed to the nearest 0.1 kg with an electronic scale (HEINE Optotechnik, D-82211 Herrsching, Germany) with participants wearing light clothing without shoes.

2.4.4 | Resting Heart Rate

For HR_{rest}, the participants were placed in a chair situated in a quiet room. A blood pressure cuff was attached to the right arm (Welch Allyn 767, Skaneateles Falls, NY, USA), and the participants were then asked to stay seated and relax for 12 min. After 12 min, resting heart rate was measured three times in a seated position with 1 min intervals between each measurement.

2.4.5 | Blood Samples

Blood samples were drawn after overnight fasting (i.e., minimum 8 h) from an antecubital vein. Blood samples for analysis of plasma BDNF were obtained in tubes containing ethylenediaminetetraacetic acid (EDTA) and immediately put on ice. Plasma samples were spun at 2500 g for 15 min at 4°C within 30 min of extraction [28]. After centrifugation, samples were transferred into Eppendorf tubes and stored at −80°C until analysis (~3 months for baseline as well as for follow-up samples). Samples were analyzed for total BDNF using an ELISA kits from R&D systems (R&D Systems, Inc., Minneapolis, MN, USA).

2.5 | Statistical Analyses

Differences between sexes in baseline characteristics were analyzed using unpaired *t*-tests for normally distributed variables and Wilcoxon rank-sum test for non-normally distributed variables. Between-group differences at baseline were tested using linear regression adjusted for sex. For non-normally distributed variables, between-group differences were examined using the Kruskal–Wallis rank test, while group differences in distribution of sex were tested using chi-squared test. Differences between the two exercise groups in mean %HRR during training was tested using *t*-test.

Effects of the interventions were analyzed using a per protocol approach where participants lost to follow-up ($n=25$) and participants who attended less than 50% of all exercise sessions ($n=5$) were excluded. Two-sample *t*-test, Wilcoxon rank-sum test, and chi-squared test were used to test baseline differences between participants included ($n=85$) and not included ($n=30$) in the per protocol analyses.

Within-group differences between pre- and post-values were examined using paired *t*-tests for normally distributed variables and Wilcoxon signed-rank test for non-normally distributed variables.

Intervention effects on flanker task performance were tested using multilevel mixed-effects linear regressions with individual as random effect and including a 3 (group: control, MIT and HIT) × 2 (congruency: congruent, incongruent) interaction separately for RT and accuracy to test whether the interventions had general or selective effects across stimuli requiring variable amount of inhibitory control. If a significant interaction term was observed, performance on congruent and incongruent stimuli were analyzed separately. If no group × congruency interaction was observed, this was reported. If a main effect for group was observed, the interaction term 'group × congruency' was removed and the analyses were conducted with accuracy and RT collapsed across stimuli type (i.e., congruent and incongruent), including "group" as independent variable and adjusting for "congruency."

The effects of the interventions on $\dot{V}O_{2max}$, $\dot{V}O_{2max}$ relative to body weight, HRrest, and flanker interference scores (RT and accuracy, respectively) were tested using linear regression. Model assumptions were checked by visual inspection of residual plots. In one case, plasma BDNF, the model assumptions were violated, and therefore, intervention effect on plasma BDNF were analyzed using the Kruskal–Wallis rank test. The flanker interference scores were calculated as the differences in RT and accuracy, respectively, for congruent and incongruent stimuli. A smaller interference score reflects an improved ability to inhibit distracting stimuli. All analyses were conducted including delta values generated by subtracting the pre-value from the post-value and adjusting for baseline values (with no adjustments made for BDNF analysis). Standardized effect sizes (ESs) were calculated by dividing the coefficient (difference from control) by the standard deviation of the residuals.

Associations between changes in VO_{2max} (both absolute and relative to body weight) and interference scores (for RT and accuracy, respectively) were tested using linear regression with robust standard errors, whereas associations between changes in VO_{2max} and plasma BDNF levels were tested using Spearman's correlation.

Stata 18.0 (StataCorp, College Station, Texas, USA) was used for all the analyses; an alpha level of 0.05 was assumed, except in regard to interaction terms; here the level of statistical significance was set to $p < 0.1$, as suggested by Twisk [29].

3 | Results

3.1 | Included and Excluded Participants

A total of 115 participants completed the baseline assessments and initiated the study (CON: 40 MIT: 38, HIT: 37) (Figure 1). Twenty-five participants (CON: 5, MIT: 13, HIT: 7) were lost to follow-up and five (MIT: 2, HIT: 3) participated in less than 50% of the training sessions and were excluded from all analyses. Included participants ($n = 85$, CON: 35, MIT: 23, HIT: 27) were comparable to those not included ($n = 30$, CON = 5, MIT = 15, HIT = 10) with respect to age, sex, $\dot{V}O_{2max}$, HR_{rest}, and BMI. Further, no differences were observed for either RT or accuracy for congruent or incongruent trials in the flanker task or plasma BDNF levels. Those included in the per protocol analyses had higher $\dot{V}O_{2max}$ relative to body weight compared to those not included.

In the analyses of flanker performance, two subjects were excluded due to response accuracy on incongruent trials below 50%. Further, one participant did not complete the flanker task at follow-up, resulting in a sample size of 82 in the analyses of flanker performance (CON: $n = 34$ MIT: $n = 23$ HIT: $n = 25$). Two participants did not complete the maximal cycling test at follow-up and were not included in the analyses of $\dot{V}O_{2max}$, resulting in a sample size of 83 in these analyses. Blood samples were not obtained from four participants (three declined blood sampling and one attended the laboratory in a non-fasted state). Moreover, BDNF values from one participant were excluded from the analyses including plasma BDNF due to methodological issues. Consequently, the sample size for plasma BDNF analyses was 80 (CON: $n = 34$, MIT: $n = 21$, HIT: $n = 25$).

3.2 | Baseline Characteristics

Detailed group- and sex-specific baseline characteristics of the participants included in the analyses are summarized in Table 1. Participants were on average 17.9 years old (SD = 0.8) with a greater proportion of females ($n = 58$, 68%). Males were taller and demonstrated higher absolute $\dot{V}O_{2max}$, $\dot{V}O_{2max}$ relative to body weight, and body weight compared to females ($p \leq 0.04$). No other differences were observed between the sexes at baseline ($p \geq 0.25$). No significant differences between groups in baseline values were observed for age, body weight, height, BMI, absolute $\dot{V}O_{2max}$, flanker performance, or BDNF ($p > 0.11$). However, at baseline, participants in the HIT group had higher $\dot{V}O_{2max}$ relative to body weight compared to the CON group (CON as reference, $\beta = 4.05\,mL\,O_2\,min^{-1}\,kg^{-1}$ 95% CI: 1.08; 7.01, $p = 0.008$). No differences in $\dot{V}O_{2max}$ relative to body weight were observed between the MIT group and CON group or between the MIT group and the HIT group at baseline.

The flanker task manipulation was successful as indicated by longer RT (median [IQR], congruent: 397 [371; 434], incongruent: 467 [430; 511], $z = -7.87$, $p < 0.001$) and lower accuracy (median [IQR], congruent: 99 [98:100], incongruent: 91.9 [85; 96.9], $z = 7.75$, $p < 0.001$) for incongruent trials compared to congruent trials across groups at baseline.

3.3 | Intervention Adherence and Heart Rate Data

Participants in the training groups (MIT and HIT) were offered a total of 27 training sessions. The median number of sessions attended were 24 (IQR = 6) in the MIT and 25 (IQR = 5) in the HIT group, respectively, and with no difference between groups ($p = 0.48$). The median length between the first and the last exercise session was 8.4 weeks in both the exercise groups (MIT: IQR = 0.14, HIT: IQR = 0.29). Valid HR data were obtained from ~64% of all sessions. The average %HRR during the training sessions varied between the two exercise groups ($p < 0.0001$) with a mean of 65.4% HRR (95% CI: 64.0; 66.8) in the MIT group and 82.6% HRR (95% CI: 80.7; 84.4) in the HIT group.

3.4 | Maximal Oxygen Uptake

During the intervention period, absolute $\dot{V}O_{2max}$ was increased in the HIT group (2793 ± 720 to $2935 \pm 735\,mL\,O_2\,min^{-1}$,

TABLE 1 | Subject characteristics.

	n	CON group		MIT group		HIT group		*p* value Group diff.	*p* value Sex diff.
n		35		23		27			
Sex (% females)	85	74.3		60.9		66.7		0.549	
Age (years)	85	17.9 ± 0.9		17.9 ± 0.8		17.8 ± 0.8		0.799	0.483
		Males	Females	Males	Females	Males	Females		
Height (cm)	85	174 ± 8	169 ± 7	178 ± 6	165 ± 8	178 ± 4	166 ± 5	0.549	<0.0001[a]
Body weight (kg) #	85	59.2 [57.7; 80.6]	63.6 [59.9; 72.0]	70.3 [60.6; 72.7]	59.2 [56.4; 63.9]	66.5 [63.9; 71.5]	58.0 [52.0; 64.0]	0.413	0.041[a]
BMI (kg m^{-2})#	85	19.9 [19.1; 22.6]	22.1 [20.4; 25.1]	20.6 [20.4; 23.8]	21.7 [19.9; 23.0]	20.9 [19.7; 21.8]	20.7 [19.0; 23.5]	0.271	0.257
$\dot{V}O_{2max}$ (L O_2 min^{-1}) #	83	3.23 [3.02; 3.39]	2.35 [2.12; 2.69]	3.47 [3.08; 3.56]	2.29 [1.99; 2.57]	3.67 [3.42; 3.98]	2.25 [2.10; 2.55]	0.560	0.0001[a]
$\dot{V}O_{2max}$ (mL O_2 min^{-1} kg^{-1})	83	48.3 ± 8.6	36.8 ± 4.8	49.9 ± 7.0	39.8 ± 5.4	54.0 ± 6.5	40.3 ± 4.2	0.028	<0.0001[a]

Note: Results are mean ± SD except for outcomes marked by # (median [IQR]).
Abbreviations: CON group, control group; HIT group, high-intensity training group; MIT group, moderate-intensity training group.
[a]Higher values in males compared to females.

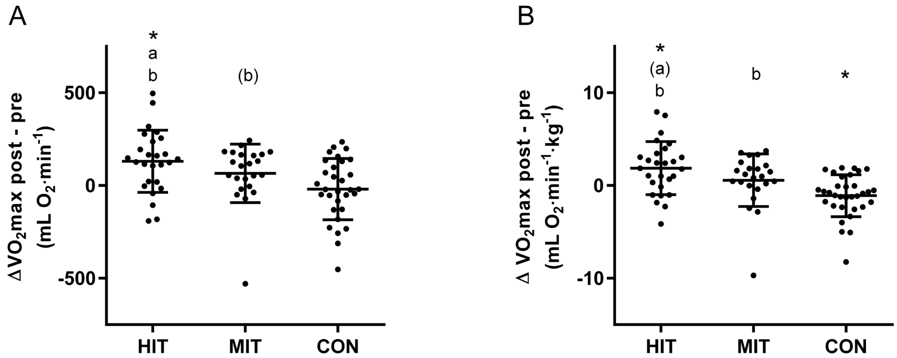

FIGURE 3 | Changes in absolute $\dot{V}O_{2max}$ (A) and $\dot{V}O_{2max}$ normalized to body weight (B) during the 9week intervention period in the high-intensity training group (HIT), the moderate-intensity training group (MIT), and the control group (CON). Changes are calculated as post–pre, meaning that positive results correspond to increased $\dot{V}O_{2max}$. Each dot represents one participant and horizontal lines and error bars are means and SD, respectively. *Change within group from pre to post, $p<0.05$. (a) Different from MIT, $p<0.05$. (b) Different from CON, $p<0.05$. (a) and (b) tendencies for differences compared to MIT and CON, respectively ($p=0.05$–0.1).

TABLE 2 | Flanker performance.

	CON group		MIT group		HIT group	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Reaction time (RT)						
Congruent (ms)	400 [372; 438]	397 [372; 433]	397 [368; 416]	408 [382; 419]*	392 [367; 434]	397 [374; 427]
Incongruent (ms)	478 [443; 515]	474 [437; 502]	455 [423; 497]	460 [441; 478]	466 [433; 518]	477 [436; 500]
Flanker (ms)	64 [54; 74]	68 [54; 78]	66 [50; 72]	60 [49; 67]	67 [59; 79]	66 [57; 80]
Accuracy						
Congruent (%)	99.0 [97.0; 100]	99.0 [98.0; 100]	99.0 [98.0; 100]	99.0 [98.0; 100]	99.0 [98.0; 100]	100.0 [99.0; 100]
Incongruent (%)	92.8 [80.8; 96.9]	90.5 [85.1; 97]	91.8 [87.1; 94.9]	93.9 [87.8; 97.0]	91.9 [85.0; 96.0]	92.9 [88.9; 97]*
Flanker (%-point)	6.5 [2.1; 15.2]	9.2 [2.1; 12.6]	8.1 [4.2; 10.1]	5.0 [2.9; 10.1]	7.1 [3.0; 13.1]	5.2 [2.0; 8.2]*

Note: Results are medians [IQR], $n=82$. Within-group differences between pre- and post-values were examined using Wilcoxon signed-rank test.
Abbreviations: CON group, control group; HIT group, high-intensity training group; MIT group, moderate-intensity training group.
*Significant change pre to post, $p<0.05$.

$p=0.0001$), but remained unchanged in the MIT group (2741 ± 646 to $2790\pm615\,mL\ O_2\,min^{-1}$, $p=0.153$) and the CON group (2566 ± 508 to $2545\pm502\,mL\ O_2\,min^{-1}$, $p=0.446$) (Figure 3A). In addition, $\dot{V}O_{2max}$ increased more in the HIT group than in the CON group ($+173\,mL\,min^{-1}$ [90; 256], $p<0.0001$, $ES=1.11$) and the MIT group ($96\,mL\,min^{-1}$ [6; 185], $p=0.038$), while the change in the MIT group tended to be larger than in the CON group ($+77\,mL\,min^{-1}$ [−9; 164] $p=0.079$, $ES=0.50$) (Figure 3A). Likewise, $\dot{V}O_{2max}$ relative to body weight was solely increased in the HIT group (44.9 ± 8.3 to $46.7\pm8.8\,mL\,O_2\,min^{-1}\ kg^{-1}$, $p=0.002$), whereas no change was observed in the MIT group (43.7 ± 7.8 to $44.3\pm7.5\,mL\,O_2\,min^{-1}\,kg^{-1}$, $p=0.345$) while a reduction was evident in the CON group (39.7 ± 8.0 to $38.6\pm7.8\,mL\,O_2\,min^{-1}\,kg^{-1}$, $p=0.009$) (Figure 3B). The increase in $\dot{V}O_{2max}$ normalized to body weight was greater in HIT vs. CON ($+3.21\,mL\,O_2\,min^{-1}\,kg^{-1}$ [1.81; 4.61], $p<0.0001$, $ES=1.25$) and MIT versus CON ($+1.86\,mL\,O_2\,min^{-1}\,kg^{-1}$ [0.41; 3.30], $p=0.013$, $ES=0.72$). Furthermore, a comparison of changes in HIT versus MIT revealed a tendency toward a larger increase in HIT ($+1.35\,mL\,O_2\,min^{-1}\,kg^{-1}$ [−0.13; 2.84], $p=0.073$).

Regarding resting HR, a reduction was observed in the HIT group (66 ± 10 to 62 ± 9 bpm, $p=0.005$), whereas no changes were observed in neither the MIT group (67 ± 10 to 68 ± 11 bpm, $p=0.956$) nor the CON group (66 ± 9 to 68 ± 10 bpm, $p=0.222$). Moreover, resting HR decreased more in HIT versus CON (−6 bpm [−11; −2], $p=0.004$, $ES=-0.79$) and HIT versus MIT (−5 bpm [−9; 0], $p=0.050$) whereas no differences were observed between MIT versus CON (−2 bpm [−6; 3], $p=0.447$, $ES=-0.21$).

3.4.1 | Flanker Performance

As indicated in Table 2, no changes within the three groups from baseline to follow-up were observed in the majority of flanker outcomes. However, the HIT group increased accuracy on incongruent stimuli ($p=0.015$) and demonstrated improved accuracy interference score at follow-up compared to baseline ($p=0.021$). Also, the MIT was slower on congruent stimuli at follow-up compared to baseline ($p=0.016$). In the analyses comparing differences in change in RT and accuracy, respectively, no significant group × congruency interactions were found ($p=0.222$ and $p=0.151$, respectively) and therefore, no further analyses were conducted. Moreover, no main effects of group were observed for either RT or accuracy across congruency ($p=0.156$ and $p=0.249$, respectively). Regarding the flanker interference scores, no significant differences in change between the groups were detected (Figure 4A,B). Nonetheless, the change observed in the HIT group tended to be greater than that in the CON group (−2.31 percentage points [−4.73; 0.11], $p=0.062$, $ES=-0.51$) (Figure 4B).

3.4.2 | Plasma Brain-Derived Neurotrophic Factor

No changes were observed in any of the three groups from baseline to follow-up, although there was a tendency towards an increase in the MIT group (median [IQR], HIT: 334 pg mL^{-1} [274;407] to 347 pg mL^{-1} [261;475], $p=0.731$; MIT: 292 pg mL^{-1} [266;345] to 373 pg mL^{-1} [314;471], $p=0.055$; CON: 304 pg mL^{-1} [261;392] to 300 pg mL^{-1} [205;468], $p=0.89$). Moreover, there were no differences in the changes of plasma BDNF levels during the intervention period between groups ($X^2=1.662$, $p=0.436$) (Figure 5).

3.5 | Associations Between Delta-Values Across Groups

Across groups, changes in absolute $\dot{V}O_{2max}$ were negatively associated with changes in the interference score for accuracy ($\beta=-0.195$, $r^2=0.04$, $p=0.036$), but not with changes in the interference score for RT ($\beta=0.001$, $p=0.986$) or changes in plasma BDNF levels ($\rho=0.018$, $p=0.876$). Furthermore, no correlations were observed between VO_{2max} relative to body weight and neither the interference score for accuracy ($\beta=-0.151$, $p=0.079$), the interference score for RT ($\beta=0.017$, $p=0.813$) nor plasma BDNF levels ($\rho=0.056$, $p=0.627$).

4 | Discussion

The main objectives of the present study were to investigate the effects of 9 weeks of aerobic training, involving three weekly 30-min sessions each, on $\dot{V}O_{2max}$, inhibitory control (i.e., flanker task performance), and plasma BDNF levels in adolescents aged 16–19 years. The results showed that the HIT group exhibited a larger increase in $\dot{V}O_{2max}$ compared to both the CON group and the MIT group. Additionally, there was a tendency for a larger increase in $\dot{V}O_{2max}$ in the MIT group compared to the CON group. Despite changes in $\dot{V}O_{2max}$, no effects of training were observed on inhibitory control, assessed by a modified flanker test, or plasma BDNF levels in any of the training groups. However, the HIT group displayed a tendency for a greater reduction in the flanker interference score (accuracy) compared to the CON group. In addition, the HIT group showed increased accuracy on the incongruent stimuli and decreased the flanker interference score (accuracy) after the training period.

4.1 | Adherence and Cardiorespiratory Fitness

Since the study was an efficacy study, per protocol analyses were conducted, including participants with a participation

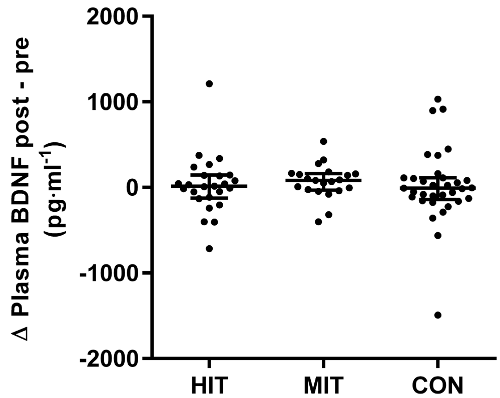

FIGURE 5 | Changes in plasma BDNF during the 9-week intervention period in the high-intensity training group (HIT), the moderate-intensity training group (MIT), and the control group (CON). Changes are calculated as post–pre, meaning that positive results correspond to increased levels of plasma BDNF. Each dot represents one participant and horizontal lines and error bars are medians and IQR, respectively. *Tendency towards change within group from pre to post ($p=0.05$).

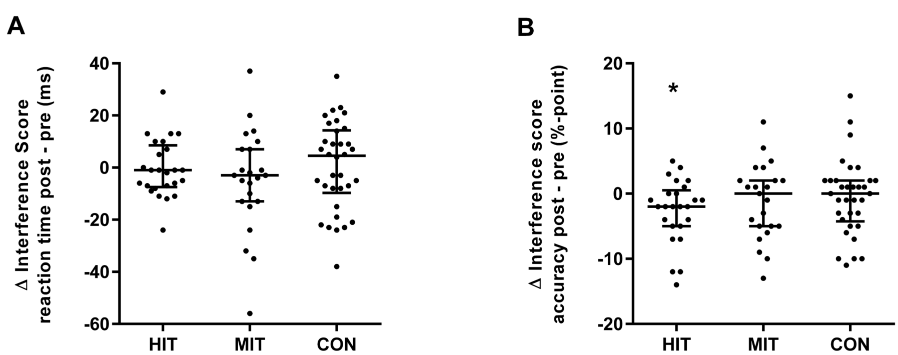

FIGURE 4 | Changes in the interference score for reaction time (RT) (A) and accuracy (B) during the 9-week intervention period in the high-intensity training group (HIT), the moderate-intensity training group (MIT), and the control group (CON). Changes are calculated as post–pre, meaning that negative results correspond to decreased interference score and improved performance. Each dot represents one participant and horizontal lines and error bars are means and SD, respectively. * Change within group from pre to post, $p<0.05$.

rate >50% (i.e., ≥14 training sessions). This criterion was chosen as our hypotheses connect cognitive improvements to increased aerobic fitness and since previous studies have reported positive effects (~8%–10% increase) of 12 training sessions of comparable intensity, duration, and frequency on $\dot{V}O_{2max}$ [30]. A significant increase in absolute $\dot{V}O_{2max}$ was observed in the HIT group (+5.1%), whereas it remained unchanged in the MIT and CON groups (+1.8% and −0.8%, respectively). Also, the HIT group exhibited a greater increase in $\dot{V}O_{2max}$ than the MIT group ($p = 0.038$), while this difference was borderline significant between training groups when $\dot{V}O_{2max}$ was normalized to body weight ($p = 0.073$). Nonetheless, both the training groups demonstrated greater increases in $\dot{V}O_{2max}$ in comparison to the CON group and as such, the interventions were successful in improving $\dot{V}O_{2max}$ in a nearly dose–response manner (Figure 3).

The change in $\dot{V}O_{2max}$ normalized to body weight in the HIT group compared to the CON group (i.e., +3.0 mL O_2 min^{-1} kg^{-1}, 95% CI: [1.3; 4.6]) was comparable to changes reported in a meta-analysis investigating the effect of HIT in adolescents (+2.6 mL O_2 min^{-1} kg^{-1}, 95% CI: [1.8; 3.3]) [31]. To further investigate potential mechanisms underlying changes in $\dot{V}O_{2max}$, resting HR was determined before and after the intervention period to indirectly estimate cardiovascular function. Since changes in absolute $\dot{V}O_{2max}$ were negatively associated with changes in resting HR ($r = 0.33$, $p = 0.003$) (i.e., larger increase in $\dot{V}O_{2max}$ associated with larger reduction in resting HR), we assume that changes in $\dot{V}O_{2max}$ were, at least partly, explained by central adaptations (e.g., increased blood volume, cardiac dimensions, and cardiac contractility), although peripheral adaptations may also have contributed (e.g., peripheral resistance, increased efficiency of muscle O_2 extraction) [32]. Although adaptations in the determinants of O_2 transport capacity were not examined in the present study, previous research has demonstrated that enhancements in $\dot{V}O_{2max}$ in response to high-intensity aerobic training can be attributed to an increased maximal stroke volume in 10- to 11-year-old children [33]. Accordingly, cardiac remodeling in response to endurance training in adolescents is manifested by increased atrial and ventricular dimensions, both strongly associated with $\dot{V}O_{2max}$ [34]. These findings align with findings in adults showing that high-intensity aerobic training compared to training at lower intensities enhances cardiac functions influencing $\dot{V}O_{2max}$ [35]. In this regard, increases in stroke volume following training interventions have been shown to occur in an intensity-dependent manner, with the largest response emerging by the highest exercise intensity (90%–95% HR_{max}) [36]. Our findings are in accordance with these findings, showing that resting HR was reduced in the HIT group but remained unchanged in the MIT and CON groups.

4.2 | Inhibitory Control

Although no selective effects of congruency (i.e., congruent or incongruent) were observed across groups, a trend towards a larger decrease in the interference score (accuracy) was observed in the HIT group compared to the CON group. Moreover, this decrease was accompanied by an increase in accuracy for incongruent trials but not congruent trials in the HIT group, while no changes were observed in the MIT group or the CON group. Together these results indicate that high-intensity training may potentially improve inhibitory control in older adolescents. Overall, previous studies have reported small positive effects of multiple bouts of aerobic training on EFs, including inhibitory control, in children and adolescents [5, 7, 16, 37], while also noting that the evidence is equivocal with a limited availability of high-quality studies. Existing reviews have often included a wide range of chronic exercise interventions commonly defined as physical activity involving multiple exercise sessions per week for at least 6 weeks. However, these interventions, when implemented in children and adolescents, have often comprised multiple components simultaneously (e.g., aerobic exercise and cognitive and/or motor challenges). Thus, knowledge about the effects of aerobic exercise on cognitive function per se in children and adolescents is lacking. A few studies have specifically examined the impact of high-intensity training on EFs in children and adolescents [37]. In a meta-analysis, Leahy and colleagues reported a small overall positive effect of HIT training on executive function in children and adolescents. However, this meta-analysis only included three studies involving older adolescents and the limited number and considerable heterogeneity among studies emphasize the necessity for additional high-quality research to confirm the findings.

A link between cardiorespiratory fitness and executive function has been suggested, although knowledge about this potential association is limited in older adolescents [17, 38]. Costigan and colleagues observed no effect of 8 weeks of HIT (8–10 min three times per week) on executive function in older adolescents (15.8 ± 0.6 years), despite a significant increase in cardiorespiratory fitness [17]. Likewise, Lubans and colleagues showed that 6 months of HIT, integrated within school hours (at least two sessions of 8–20 min per week), improved cardiorespiratory fitness in older adolescents (16 ± 0.43) with no enhancements in cognitive performance, including inhibitory control [38]. Although changes in $\dot{V}O_{2max}$ can be achieved by relatively low volumes of high-intensity training within untrained adolescents, such interventions might not cause a sufficient stimulus to induce detectable improvement in cognitive performance. Moreover, the studies by Costigan et al. and Lubans et al. used indirect estimations of cardiorespiratory fitness. As a result, it is likely that the observed changes in the shuttle run tests used to estimate cardiorespiratory fitness in the two studies were not solely explained by cardiorespiratory changes but also potential changes in running economy or peripheral adaptations (i.e., mitochondrial biogenesis). In the present study, $\dot{V}O_{2max}$ was measured directly, and in the group performing high-intensity training, we observed the largest increase in $\dot{V}O_{2max}$, which was accompanied by a borderline significant effect on the interference score (accuracy). Furthermore, in the longitudinal analyses with data collapsed across groups, an association between changes in absolute $\dot{V}O_{2max}$ and changes in interference scores for accuracy was observed, suggesting that improvements in inhibitory control may be related to increase in cardiorespiratory fitness. Of note however, changes in $\dot{V}O_{2max}$ only explained a small part (i.e., 4%) of the variation of changes in the interference score for accuracy. Nonetheless, it can be speculated that a larger load of high-intensity aerobic training (i.e., higher volume or intensity) could induce cognitive adaptations. However, this finding underscores the importance of considering additional factors, including other aspects of engaging in aerobic exercise (i.e., physiological and psychological), when aiming to enhance inhibitory control [4].

Future high-quality studies should clarify whether a larger aerobic training load and thereby larger increases in $\dot{V}O_{2max}$, will be accompanied by improvements in inhibitory control and/or other aspects of executive function. Moreover, additional research is needed to identify the most effective combination of intensity, duration, and type of activity to improve executive function in children and adolescents.

4.3 | Plasma BDNF Levels

Within the last decade, BDNF has gained extensive attention due to its potential role in coupling aerobic exercise and cognitive performance. In rodents, exercise training has been shown to increase BDNF levels in the brain, which has been associated with improved cognitive performance [22]. In humans, increased levels of peripheral levels of BDNF have been observed after both a single bout of exercise (acute) [39] and a prolonged training period (chronic) [23]. The increase after chronic exercise has further been linked to improved performance in tests of executive function, suggesting BDNF as a mediating factor [24].

Although a recent meta-analysis revealed a significant effect of aerobic training interventions on resting peripheral BDNF levels [23], inconsistencies exist within the literature. For example, Araya and colleagues reported increases in resting serum BDNF and platelet BDNF, but not plasma BDNF, after performing 30 min of moderate-intensity aerobic exercise three times a week for 10 weeks in overweight and obese individuals [40]. In contrast, Zoladz and colleagues found a significant increase in resting plasma BDNF levels following 5 weeks of moderate-intensity aerobic exercise in young healthy men [41]. Other studies have reported that resting peripheral levels of BDNF remain unchanged in response to training [23], which is in accordance with the present findings where no effects of the two training interventions were observed for plasma BDNF. Several methodological differences between the studies may account for some of the inconsistencies. These methodological differences include, but are not limited to, the biological medium in which BDNF is analyzed (i.e., serum or plasma), the time between collection and centrifugation of blood and centrifugation strategy (e.g., normal plasma vs. platelet-poor plasma) [28]. In particular, the biological medium in which BDNF is analyzed affects the levels of BDNF [42] and the biological relevance of serum BDNF and plasma BDNF may differ [28]. While BDNF measured in serum reflects the amount of BDNF released from platelets during clotting [42], BDNF measured in plasma may to a greater extent reflect freely circulating BDNF in plasma and thus the pool of BDNF being able to cross the blood–brain barrier [43]. In this regard, no standardized procedure for analysis of plasma BDNF has been applied in the literature and differences in the treatment of plasma samples may therefore, at least partly, explain differences in the plasma BDNF response to exercise training. We have previously demonstrated that BDNF measured in normal plasma vary greatly from BDNF measured in platelet-poor plasma, since normal plasma contains a large amount of platelets [28]. As such, it may be questioned whether relatively small increments in freely circulating BDNF is detectable in normal plasma due to the large influence of platelet-associated BDNF. However, even though platelet-poor plasma may be a more genuine measure of freely circulating BDNF in plasma and in the brain, exercise-induced changes may not appear in platelet-poor plasma [44]. In contrast, using a catheter inserted into the right internal jugular vein, Seifert and colleagues demonstrated an increased release of BDNF from the brain following 3 months of aerobic exercise [44], suggesting that alternative methods to quantify BDNF may be more applicable when focus is on changes in brain BDNF levels.

4.4 | Strengths and Limitations

An important strength of the present study is the randomized design and the quality of outcome measurement methods. Moreover, the majority of exercise sessions was supervised and monitored using heart rate telemetry, allowing a detailed evaluation of compliance to the exercise interventions. Despite a great effort to standardize the interventions regarding exercise setting, exercise type, exercise instructors, time a day, and so forth, differences between the two interventions, besides the exercise intensity may have influenced the results. Thus, the psychological aspects of engaging in the exercise interventions such as the extent to which the participants in the two groups were motivated to do the prescribed exercise may have been different between groups. Moreover, since habitual physical activity levels were not registered, we are unable to determine to what extent engagement in the training interventions increased the total PA levels of the participants. As such, participants in the exercise groups may have omitted participation in habitual physical activities. However, the increases in $\dot{V}O_{2max}$ in both the exercise groups indicate that the training load was increased above normal during the intervention period. In general, the included participants were relatively fit and cognitively well-functioning at baseline, potentially impacting their potential for improvement. The relatively high dropout rate, along with the difference in $\dot{V}O_{2max}$ relative to body weight between those included in the analysis and those excluded, could potentially introduce selection bias, thus impacting the external validity of the study. Moreover, it is important to note that the associational analyses between delta values were exploratory, and results should be interpreted with caution. Across groups, relatively small variations in delta values were observed, potentially impacting the sensitivity and reliability of these findings. Finally, due to the limited number of studies investigating the effects of aerobic exercise training on flanker performance in children and adolescents when the study was conducted, no priori power calculation was performed for the flanker outcome. As a result, we may lack power to detect differences in the flanker performance, increasing the risk of type II errors. Moreover, the observed borderline significant difference in accuracy interference score might be due to chance. However, the increase in accuracy for incongruent stimuli observed in the HIT group, support this finding.

5 | Conclusion

Nine weeks of aerobic training improved cardiorespiratory fitness in adolescents aged 16–19 years, but no significant effects were observed on inhibitory control or levels of plasma BDNF. However, a trend towards an effect of high-intensity training on inhibitory control was observed.

Knowledge about effects of aerobic training on EFs in older adolescents is limited, and the present randomized controlled trial presents novel observations within this area by showing that 9 weeks of high-intensity training increased $\dot{V}O_{2max}$ by 5.1% without a concomitant enhancement of flanker performance. However, we observed a tendency towards improved inhibitory control (i.e., decreased interference score in a flanker task) by high-intensity training and changes in $\dot{V}O_{2max}$ were associated with changes in interference score. Therefore, higher doses of high-intensity training may have the potential to increase EFs, and accordingly studies employing larger volumes of high-intensity training or longer intervention periods are warranted. In general, studies are needed to identify the impact of training intensity, duration, and type on changes in executive function among children and adolescents.

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Conflicts of Interest

The authors declare no conflicts of interest. The authors declare that the results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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