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Original research

Effects of a school-based physical activity program on retinal microcirculation and cognitive function in adolescents

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ABSTRACT

Objectives: To investigate the effect of combined aerobic and coordinative exercise on retinal microcirculation and its association with changes in cognitive performance in healthy adolescents.
Design: Using cluster-randomization (on class-level), 36 participants were allocated to an exercise group (EX) performing a 20-min aerobic and coordinative exercise session on each school day over a period of 8 weeks or a control group, which was encouraged to have social interactions (CON).
Method: Prior to and following the intervention period, central retinal arteriolar (CRAE) and venular diameters (CRVE) were assessed by use of a static vessel analyzer. Additionally, a computer-based version of the Stroop Color-Word task was administered to assess inhibitory control.
Results: The statistical analysis revealed that EX compared to CON showed higher CRAE at post-test, when pre-test values were accounted for, $F(1,32) = 4.92$, $p = 0.036$, $\eta^2 = 0.130$. In contrast, no such effect was reported for CRVE. With regard to cognitive performance, a greater reduction of reaction time on the Stroop task was observed in EX relative to CON, $F(1,30) = 8.58$, $p = 0.006$, $\eta^2 = 0.222$. The increase in CRAE was significantly correlated with a decrease of reaction time on trials demanding inhibitory control, even after adjusting for covariates, $r(31) = -0.438$, $p = 0.011$.
Conclusions: A structured exercise program leads to a widening of retinal arteriolar diameters, which is associated with improvements in inhibitory control. Consequently, daily exercise sessions performed during the school break-time can be recommended for promoting both cardiovascular and cognitive health in adolescents.

Practical implications

- Combined aerobic and coordinative exercise leads to a widening of retinal arteriolar diameters, thus improving retinal microvascular health in adolescents.
- Alterations of retinal arteriolar diameters are associated with benefits in cognitive performance and inhibitory control in particular.
- Implementing a structured exercise program into the school day may prove to be a economic approach for the elicitation of cardiovascular and cognitive health benefits.

1. Introduction

The aetiology of cardiovascular disease is based on the development of atherosclerosis and arterial remodeling in large and small arteries. The retinal microcirculation is part of the cerebrovascular bed and subclinical retinal microvascular alterations have received growing attention as a valid biomarker of cardiovascular morbidity and mortality.[1–3] Cardiovascular health during childhood plays a crucial role for the prevention of cardiovascular disease in later life.[4] The need for primary prevention in childhood is emphasized by the high prevalence of cardiovascular risk factors, such as overweight, high blood pressure and physical inactivity, among children and adolescents in developed countries.[5] Assessment of retinal vessel diameters in pediatric populations is clinically relevant, can be performed non-invasively and without mydriasis.[1] In previous studies with children, elevated blood pressure and high body mass index have predominantly been associated with retinal arteriolar narrowing.[6] Higher physical activity and fitness have been found to be related to favorable retinal vessel diameters as indexed by wider retinal arteriolar[7,8] and arteriolar to venular ratio in

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children.[9] These cross-sectional findings provide a first indication that physical activity may alter retinal vessel diameters. However, exercise interventions targeting improvement of physical activity are required to assess causal effects on this health-related outcome in early life.

Retinal and cerebral small vessels are closely related as they share a similar embryological origin as well as important structural and functional characteristics, for example the blood-brain barrier.[10] A review of the literature suggests that there is a relationship between retinal microvascular alterations and decrements in cognitive function, with stronger associations found in middle-aged relative to older adults.[11] However, it should be noted that the reviewed studies were limited to adult populations and mainly included patients with vascular disease and those at risk. To rule out that the relationship between microcirculation and cognitive function is solely due to similar effects of vascular disease on both parameters, findings in healthy populations are necessary. In this respect, a study in middle-aged adults showed that participants with wider retinal venular diameters performed worse on a wide variety of cognitive tests.[12] Similar results were obtained in healthy children and those born preterm as higher-order cognitive functions were positively correlated with retinal arteriolar diameters as well as the arteriolar-to-venular diameter ratio.[13] These findings suggest that the brain's vascular network contributes to cognitive function.

Similar to retinal microcirculation,[7,8] behavioral performance on (more complex) cognitive tasks has been found to be correlated with physical activity in children.[14] Causal evidence for this relationship is provided by meta-analytical findings showing that exercise programs aimed at increasing daily physical activity elicit benefits for both executive functions (i.e. top-down guidance of behavior towards a specific goal) and less complex cognitive domains in children and adolescents.[15] Subgroup analyses further revealed that exercise implemented in the school curriculum led to greater improvements in comparison to other settings. Experimental studies employing such an ecological approach have almost consistently found beneficial effects for the inhibitory aspect of executive function,[16–18] which relates to the ability to resist distractions and to suppress unwanted thoughts, feelings and/or actions.[19] Recalling that the retinal vessels allow insights into the state of the brain's vascular network, the examination of exercise-induced effects on both retinal microcirculation and inhibitory control may broaden our understanding of mechanisms underlying cognitive benefits. In general, the potential of retinal vessel imaging for investigating cardiovascular health and cognitive function has rarely been utilized in sports medicine, as previous studies (A) only used cross-sectional designs, (B) were mainly limited to older age groups, and (C) allowed no conclusions on the contribution of changes in microcirculation to cognitive benefits.

The main purpose of the present study was to examine the effects of a combined aerobic and coordinative exercise program on retinal vessel diameters in adolescents. The investigation of the effects of the exercise program on inhibitory control and their association with changes in retinal microcirculation were secondary aims. Based on cross-sectional evidence, we expected that children in the exercise compared to the control group would show wider retinal arteriolar diameters[7,8] and increased inhibitory control[16–18] following the intervention period. Additionally, we hypothesized that an increase in retinal arteriolar diameters would be correlated with improvements in inhibitory control.[13]

2. Methods

A total of 13 female and 23 male students were recruited from a local private school. Participants aged 12–15 years with right hand dominance and corrected-to or normal vision were deemed eligible. Exclusion criteria were attendance of special education services related to attentional disorders, color blindness, being under pharmacological treatment for any mental disorder, and/or any injuries or diseases that impose an increased health risk during exercise performance. During an information event, the legal guardians of the participants received information on the testing procedures and associated risks. Afterwards, the participants and their legal guardians provided written assent and consent, respectively. The study protocol was reviewed and approved by the local ethics committee. Research was conducted according to the ethical standards outlined in the Declaration of Helsinki.

As participants were recruited class-wise (4 classes in total), cluster-randomization was used to allocate them to the exercise group ($n = 20$) or a wait-list control group ($n = 16$). Over a period of 8 weeks, the exercise group engaged in a physical activity program implemented during recess after lunch. At pretest, anthropometric data was collected and all participants completed the Strengths and Difficulties Questionnaire (SDQ). Prior to and following the intervention period, retinal vessel diameters and blood pressure were assessed. Additionally, participants completed a computer-based Stroop task. The laboratory assessments were performed between 08:00 and 11:30 a.m. and with one participant at a time. Following the intervention period, all tests were repeated at the same time of the day. Participants were instructed to have their last meal 2 h prior to testing and to avoid engagement in physical activity.

The intervention consisted of 20-min exercise sessions performed on 5 days a week over 8 weeks. The exercise sessions were scheduled 5–10 min after lunch and supervised by two trained instructors. Aiming for a high compliance, the exercise program was composed of playful and age-appropriate forms of combined aerobic and coordinative exercise. These exercises were at least moderately-intense and at the same time, they required the maintenance of a high degree of body coordination and adaptation to changing task demands. Exercise programs with such demands have been shown to be most promising for the elicitation of benefits for inhibitory control.[15] Typical exercises included in the intervention were variations of ball games, relay games and playing tag. Exercise intensity was monitored during 5 sessions using RS-400 (Polar, Finland) devices. In each of these sessions, heart rate was recorded (due to constraints in time) in 5 participants only. The control group was encouraged to have conversations with their classmates while the exercise group performed the exercise sessions. As the exercise program involved team games, this approach was chosen to ensure that group differences in cognitive function do not result from a greater degree of social interaction. Following the 20-min session, all participants continued with their regular school lessons. After completion of the post-tests, the control group had the opportunity to engage in the exercise program.

Retinal arteriolar and venular diameters were assessed using a static vessel analyser (SVA-T, Imedos Systems UG, Germany) with an integrated fundus camera and an advanced image processing unit. SVA is a highly reproducible, computer-based, semi-automated tool with an intraclass correlation of about 0.90–0.95 and coefficient of variation of about 2% in children.[9] The analysis was consistent with the standardized procedure explained in a previous study.[8] Three valid photographs from the right and left eye were taken at an angle of 45° with the optic disc at the center. Retinal vessels were identified in an area of 0.5–1 disc diameter away from the margin of the optic disc (Vesselmap 2, Visualis, Imedos Systems UG). One single experienced examiner differentiated retinal arterioles and venules in the ring zone. Central retinal arteriolar (CRAE) and venular equivalents (CRVE) were calculated using the Parr-Hubbard formula.[20]

For the assessment of inhibitory control, participants completed a modified version of the Stroop task. The task was administered with E-Prime 2.0 (PST, USA) and used conflicting color words as stimuli. Whereas color words appeared in the same color of ink on compatible trials (e.g. "yellow" printed in yellow), they were presented in a different color of ink on incompatible trials (e.g. "yellow" printed in blue). During the task, participants were required to indicate the color ink of the color word by pressing a button on a serial response box. Compatible and incompatible trials appeared with equal probability. On each trial, the stimulus was presented for 200 ms and responses were collected within 1500 ms after its onset. Trials were separated by an inter-stimulus interval lasting 1500–2000 ms (random variation). Feedback on responses was only presented in practice trials. The task comprised a practice block with 20 trials and 4 test blocks with 36 trials each. Following each block, there was a 30-s recovery phase. For statistical analyses, the average reaction time on response-correct trials and accuracy on incompatible trials were extracted.

Statistical analysis of collected data was performed with SPSS 25.0 (IBM Statistics, USA). Prior to main comparisons, Gaussian distribution of the data and homogeneity of variances were checked using the Shapiro–Wilk and Levene tests (see supplement), respectively. Anthropometric data, blood pressure and psychopathology were compared between groups using one-way ANOVA. Subsequently, zero-order correlations between psychopathology, body mass index, blood pressure, age, gender and the dependent variables were examined. Variables showing at least a moderate ($r = 0.30$) or a significant correlation ($p \leq 0.05$) with the outcomes were entered as covariates in main comparisons. The effects of the exercise intervention on retinal vessel diameters and inhibitory control were examined by applying an ANCOVA with group as between-subjects factor on post-test values, while controlling for pre-test values. Moreover, the association between pre-to-post-test changes in retinal vessel diameters and Stroop task performance was assessed by calculating the Pearson correlation coefficient on difference scores. In case covariates other than pre-test values had to be included for main comparisons, partial correlations controlling for these covariates were calculated in the next step. The level of significance was set to $p \leq 0.05$ and a η^2 of 0.010,0.060 and 0.138 corresponded to small, moderate and large effects, respectively.[21]

3. Results

Complete data was available from 35 participants as one student terminated the study prematurely due to personal reasons. The exercise group performed 78.6 ± 11.3% of the scheduled exercise sessions and the mean heart rate during exercise was 134.6 ± 9.4 beats/min. With regard to baseline assessments, there were no group differences in age, height, body mass index and psychopathology (Table 1). Zero-order correlations revealed a significant relationship between gender and post-test reaction time, $r(33) = 0.34$, $p = 0.043$, and a moderate association between age and post-test CRAE that approached significance, $r(33) = 0.30$, $p = 0.081$.

Table 1
Participants' anthropometric data, blood pressure and psychopathology at baseline (means and standard error).

	EX (N = 19)		CON (N = 16)		ANOVA	
	M	*SE*	*M*	*SE*	*F*	*p*
Age in y	12.5	0.2	12.4	0.2	0.14	0.715
Height in cm	154.8	1.7	158.8	1.8	2.55	0.120
BMI in kg/m2	18.2	0.5	19.7	0.9	2.57	0.118
Systolic BP in mmHg	117.1	1.4	116.9	2.2	0.02	0.968
Diastolic BP in mmHg	74.1	1.4	74.3	1.4	0.13	0.909
SDQ score	12.4	0.8	11.8	1.0	0.18	0.675

EX = exercise group; CON = control group; BMI = body mass index; BP = blood pressure; SDQ = Strengths and Difficulties Questionnaire.

Investigating retinal vessel diameters, the ANCOVA revealed that the exercise compared the control group showed higher CRAE at post-test (adj. $M_{DIFF} = 3.4$; $SE = 1.5$), $F(1,32) = 4.92$, $p = 0.036$, $\eta^2 = 0.130$, when controlled for pre-test values (Fig. 1). This main effect of group remained significant even after adjusting for the participants' age, $F(1,31) = 4.92$, $p = 0.034$, $\eta^2 = 0.137$. In contrast, no such effect was observed for post-test CRVE (adj. $M_{DIFF} = 0.8$; $SE = 1.8$), $F(1,32) = 0.27$, $p = 0.608$, $\eta^2 = 0.008$.

With regard to inhibitory control, lower post-test reaction time on incongruent trials was found in the exercise compared to the control group (adj. $M_{DIFF} = 70.6$; $SE = 20.8$), when pre-test values were accounted for (Fig. 2), $F(1,30) = 11.53$, $p = 0.002$, $\eta^2 = 0.265$. Including sex as additional covariate, the group difference in reaction time on incongruent trials remained significant, $F(1,30) = 8.58$, $p = 0.006$, $\eta^2 = 0.222$. For accuracy at post-test, the ANCOVA revealed no main effect of group (adj. $M_{DIFF} < 0.1$; $SE < 0.1$), $F(1,30) = 0.13$, $p = 0.718$, $\eta^2 = 0.004$.

Based on the examination of correlations, change scores (post-pre) of reaction time on incompatible trials and CRAE were associated, $r(33) = -0.427$, $p = 0.010$. This relationship was also found when partial correlations, controlling for sex and age, were calculated, $r(31) = -0.438$, $p = 0.011$. Pre- to post-test changes in CRVE showed no correlation with changes in behavioral performance on the Stroop task, $r(33) \leq -0.14$, $p \geq 0.428$.

4. Discussion

In comparison to social interaction, the combined aerobic and coordinative exercise program implemented in the school break-time elicited alterations of retinal vessel diameters in healthy adolescents. Given that previous research in this age group was limited to cross-sectional studies,[7–9] the moderate pre- to post-test increase in CRAE observed in the exercise group is a novel finding.

So far, a few cross-sectional studies have examined the association of physical activity and fitness with retinal vessel diameters. Their findings indicated that physical activity is linked with wider retinal arterioles, whereas sedentary behavior shows an association with wider venules.[8] A previous study further showed a

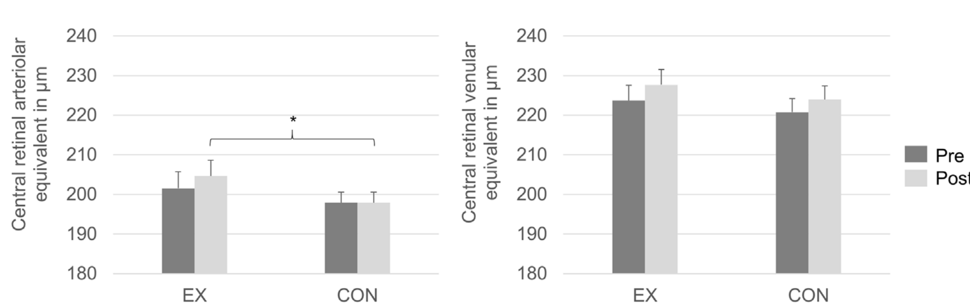

Fig. 1. Central retinal arteriolar and venular equivalent (means and standard error) displayed for the exercise (EX) and control (CON) groups at both pre- and post-test. *Note*: *indicates a significant difference in post-test values between groups, when adjusted for baseline values (ANCOVA).

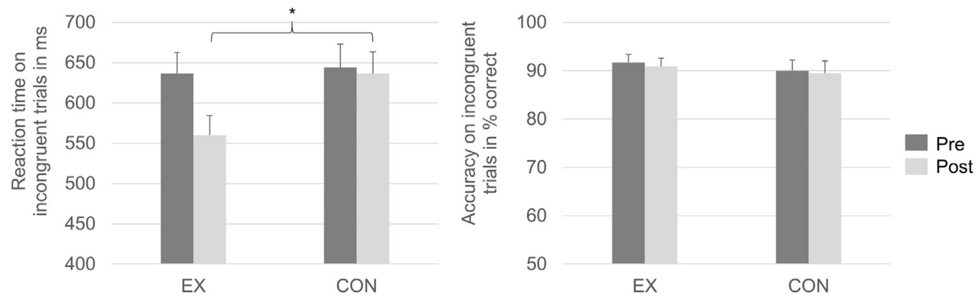

Fig. 2. Behavioural performance on the Stroop task (means and standard error) displayed for the exercise (EX) and control (CON) groups at both pre- and post-test. *Note*: *indicates a significant difference in post-test values between groups, when adjusted for baseline values (ANCOVA).

relationship between cardiorespiratory fitness and the arteriolar-to-venular ratio.[9] The effects of the combined aerobic and coordinative exercise intervention point in a similar direction as after adjusting for pre-test scores, greater post-test CRAE was found in the exercise compared to the control group. In contrast, the change of CRVE was not significantly different between groups. This is in conflict with the association found between retinal venular narrowing and physical activity in older adults,[1] but a difference in the prevalence of systemic cardiovascular disease between children and older adults might account for this discrepancy. The exercise-induced effect on CRAE has an important clinical implication, since wider retinal arterioles are associated with reduced cardiovascular risk among both children and adults.[6,22] The present findings are in line with a previous study showing a favorable alteration of retinal vessel diameters in lean and obese adults following 10 weeks of aerobic exercise training.[23] It should be noted, however, that widening of the arterioles was limited to obese participants, which indicates a normalization of the retinal arteriolar diameters. In contrast, the present findings suggest that a combined aerobic and coordinative exercise program further reduces the cardiovascular risk beyond the normal range. Given that a previous study reported a decrease of CRAE by 0.38 μm per unit increase in body mass index,[8] the adjusted mean difference of 3.4 μm between the exercise and control group at post-test indicates a meaningful change. Consequently, early prevention strategies promoting physical activity, sport and exercise behaviour may have the potential to counteract the development of small vessel disease in childhood and later in life.

Along with favorable changes in retinal vessel diameters, the exercise group showed large improvements in behavioral performance. These cognitive benefits were indexed by decreased reaction time on incongruent trials at a comparable accuracy, so that a simple speed-accuracy trade-off can be ruled out. Exercise-induced enhancements of inhibitory control have already been reported in previous studies, which also implemented an exercise program into the school day.[17,18] However, it should be noted that in the present study, large improvements on inhibitory control were found after a shorter intervention period (8 vs. at least 20 weeks). This finding is of high practical relevance, given that inhibitory control assessed from Stroop-like tasks has been found to predict academic performance.[24]

Despite accumulating evidence for cognitive benefits following a period of exercise training,[15] findings on the underlying mechanisms are still limited.[25] A review based on neurophysiological evidence suggests that improved allocation of attentional resources and conflict monitoring contribute to cognitive enhancements following a period of exercise training.[26] The present findings provide some novel insights on the potential role of the microcirculation as an additional pathway, because participants with a greater widening of the retinal arteriolar diameters also showed a more pronounced speeding of reaction time. Consequently, these results expand previous cross-sectional evidence showing a similar association between retinal vessels and some aspects of higher-order cognitive function in children.[13] However, the direction of the effect cannot be inferred from correlations of changes. Previous studies with healthy adults suggest that the oxygenation of the prefrontal cortex is linked with aerobic fitness[27] and that the cerebral blood flow mediates the effect of regular exercise on inhibitory control.[28] Moreover, a review has shown that cognitive abilities generally depend on the supply of oxygen and nutrients through the brain's dense network of vessels.[29] These findings provide an indication that exercise-induced improvements of the brain's vascular network may have contributed to higher cognitive performance, so that the effect is not anticipated to point in the opposite direction.

Some limitations need to be addressed. First, the sample size was relatively small. However, the study was part of a project in which sample size was calculated based on another outcome,[30] and it should be noted that there were no effect sizes available for exercise-induced changes in microcirculation among children and adolescents. Second, the training heart rates should be interpreted with caution as it was monitored only in small portion of the exercise group. Thus, it cannot be ruled out that the exercise intensity was lower or higher than moderate. As physical activity levels were not recorded over the intervention period, there is also a risk that increased physical activity following the school day has contributed to the observed effects. Third, there was no assessment of aerobic and muscular fitness, so that it remains unclear if an improvement in this variable is a precondition for the elicitation of microvascular benefits. Additionally, no conclusions can be drawn on whether aerobic exercise, coordinative exercise or the combination of both were driving the changes found in retinal vessel diameters and inhibitory control. Fourth, exercise-induced effects were not controlled for potential moderators, such as intelligence, socioeconomic status and pubertal status. However, inter-individual variance in intelligence and socioeconomic status was assumed to be low as all participants were taught on a high educational level at a private school. This specific sample characteristics limit the generalizability of the findings. Lastly, it cannot be ruled out that changes in retinal vessel diameters are associated with improvements in general rather than domain-specific cognitive abilities.

5. Conclusion

A structured aerobic and coordinative exercise program implemented in the school recess leads to a widening of the retinal arteriolar diameters, indicating a favorable change of microvascular health in adolescents. Beyond the cardiovascular benefits, this change is associated with an improvement of inhibitory control. Consequently, daily exercise sessions are encouraged to elicit further vascular and cognitive benefits in healthy adolescents.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jsams.2018.11.029.

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