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Human Kinetics
SCHOLARLY REVIEW

Effects of Physical Exercise Training on Cerebral Blood Flow Measurements: A Systematic Review of Human Intervention Studies

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The aim of this systematic review was to examine the effects of physical exercise training on cerebral blood flow (CBF), which is a physiological marker of cerebrovascular function. Relationships between training-induced effects on CBF with changes in cognitive performance were also discussed. A systematic search was performed up to July 2022. Forty-five intervention studies with experimental, quasi-experimental, or pre–post designs were included. Sixteen studies (median duration: 14 weeks) investigated effects of physical exercise training on CBF markers using magnetic resonance imaging, 20 studies (median duration: 14 weeks) used transcranial Doppler ultrasound, and eight studies (median duration: 8 weeks) used near-infrared spectroscopy. Studies using magnetic resonance imaging observed consistent increases in CBF in the anterior cingulate cortex and hippocampus, but not in whole-brain CBF. Effects on resting CBF—measured with transcranial Doppler ultrasound and near-infrared spectroscopy—were variable, while middle cerebral artery blood flow velocity increased in some studies following exercise or hypercapnic stimuli. Interestingly, concomitant changes in physical fitness and regional CBF were observed, while a relation between training-induced effects on CBF and cognitive performance was evident. In conclusion, exercise training improved cerebrovascular function because regional CBF was changed. Studies are however still needed to establish whether exercise-induced improvements in CBF are sustained over longer periods of time and underlie the observed beneficial effects on cognitive performance.

Keywords: cerebrovascular function, cognitive performance, physical fitness

It is well-known that human aging is associated with an increased risk to develop subjective cognitive decline, mild cognitive impairment and ultimately (vascular) dementia (Rabin et al., 2015; Wahl et al., 2019). Further, it is known that a healthy diet combined with exercise training may protect against cognitive impairment (Gorelick et al., 2011; Wahl et al., 2019). Underlying mechanisms are largely unknown, but lifestyle-induced beneficial effects on cerebral blood flow (CBF), which is an important physiological marker of cerebrovascular function in humans, and positively associated with cognitive performance (Gorelick et al., 2011; Hays et al., 2016; Joris et al., 2018; Wolters et al., 2017), are thought to play an important role. In fact, different dietary factors have already been identified that may beneficially affect CBF and cognitive performance (Joris et al., 2018). The acute regulation of CBF during exercise has already extensively been reviewed (Smith & Ainslie, 2017), while effects of exercise training on mechanisms maintaining CBF despite changes in blood pressure (i.e., cerebral autoregulation) have recently been summarized (Claassen et al., 2021). However, effects of physical exercise training on CBF measurements have not been systematically reviewed so far. Furthermore, longer term human intervention studies already showed that physical exercise training improves cognitive performance (Gates et al., 2013; Northey et al., 2017) potentially via changes in cerebrovascular function (Zimmerman et al., 2021).

Various techniques can be used to measure CBF, which makes it difficult to compare results between studies. The most frequently used imaging techniques are positron emission tomography (PET), magnetic resonance imaging (MRI), transcranial Doppler ultrasound, and near-infrared spectroscopy (NIRS) (Fantini et al., 2016; Tymko et al., 2018). In brief, CBF as quantified by PET is considered the gold standard and involves intravenous injection of a radioactive contrast agent that diffuses through the blood–brain barrier. However, only a limited number of studies have used PET due to radiation exposure, while repeated scans are frequently needed. Perfusion-weighted MRI requires the intravenous injection of a nondiffusible contrast agent, such as gadolinium. Another reliable noninvasive alternative is the MRI perfusion method arterial spin labeling (Xu et al., 2010), which relies on magnetically labeled water molecules from the blood flowing through the major arteries toward the brain. These scans result in a quantitative, three dimensional map of CBF providing information on the blood flow in a specific region, or the whole brain. Transcranial Doppler ultrasound is another technique that noninvasively measures blood flow velocity in the basal arteries of the brain (e.g., proximal anterior and posterior cerebral arteries). Finally, NIRS is an optical technique assessing the concentration of (de)oxygenated hemoglobin in the cerebral cortex superficially through the scalp, which provides an indirect measure of brain activity, particularly in the prefrontal cortex. The aim of this systematic review is to give a comprehensive overview of the effects of physical exercise training on CBF in humans as measured by MRI, transcranial Doppler ultrasound and NIRS. In addition, relationships between exercise-induced changes in (regional) CBF with physical fitness and cognitive performance will be discussed.

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Methods

Search Strategy

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) checklist was used to structure the systematic review. The online databases Medline (PubMed), EMBASE (Scopus), and CENTRAL (Cochrane Central Register of Controlled Trials) were searched up to July 2022 to identify relevant articles. The search terms consisted of “exercise [MeSH term]” AND “cerebrovascular circulation [MeSH term] OR cerebral oxygenation.” The complete search string for the different databases is presented in Supplementary Material (available online). All articles were imported into a reference manager (EndNote X9) and checked for duplicates. Remaining articles were imported into a systematic review manager (www.covidence.org).

Study Selection

Only original human intervention studies, that investigated the relationship between exercise training and CBF using experimental (randomized controlled trials [RCTs]) or non-RCTs, such as quasi-experimental and pre–post designs, were included. Conference papers, posters, and reviews were excluded. Articles describing the same intervention study in more than one paper were considered as one study. Only studies with an intervention period of at least 1 week were included. Studies combining exercise training with a dietary and/or cognitive cointervention were also included. Articles were independently assessed for eligibility by two of the authors (Kleinloog and Joris). When inconclusive, eligibility was discussed until consensus was reached. Finally, reference lists of the included articles and related reviews were also checked manually for relevant articles.

Data Collection

Information on the study design (experimental, quasi-experimental, or pre–post designs), intervention (i.e., type and length of exercise intervention, frequency and duration of training sessions, intensity, and modality), and study population (health status, age, body mass index [BMI], and gender) was extracted, and entered into a custom-made database. Data on CBF as assessed using MRI, transcranial Doppler ultrasound, and NIRS were also collected. Although studies were not required to assess physical fitness levels and cognitive performance (i.e., global cognition, psychomotor speed, verbal fluency, verbal and spatial memory, and executive function), information on these outcomes were included in the database, if reported. Finally, the revised Cochrane risk-of-bias (RoB) tool two was used to assess the RoB for the included studies (Sterne et al., 2019).

Results

Study Characteristics

The PRISMA flow diagram is shown in Figure 1. The initial search returned 4,403 articles. After removing duplicates, titles and abstracts of 3,949 articles were screened, and 477 articles were retrieved for review of the full texts. In the end, 48 articles met all the inclusion criteria. However, three intervention studies were described in seven articles (Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Aziz, Dobson, et al., 2016; Chapman et al., 2013, 2016, 2017; Tomoto, Liu, et al., 2021; Tomoto, Tarumi, et al., 2021). Finally, 45 original intervention studies were identified, of which 16 used MRI (10 of these studies used arterial spin labeling, two studies used gadolinium as a contrast

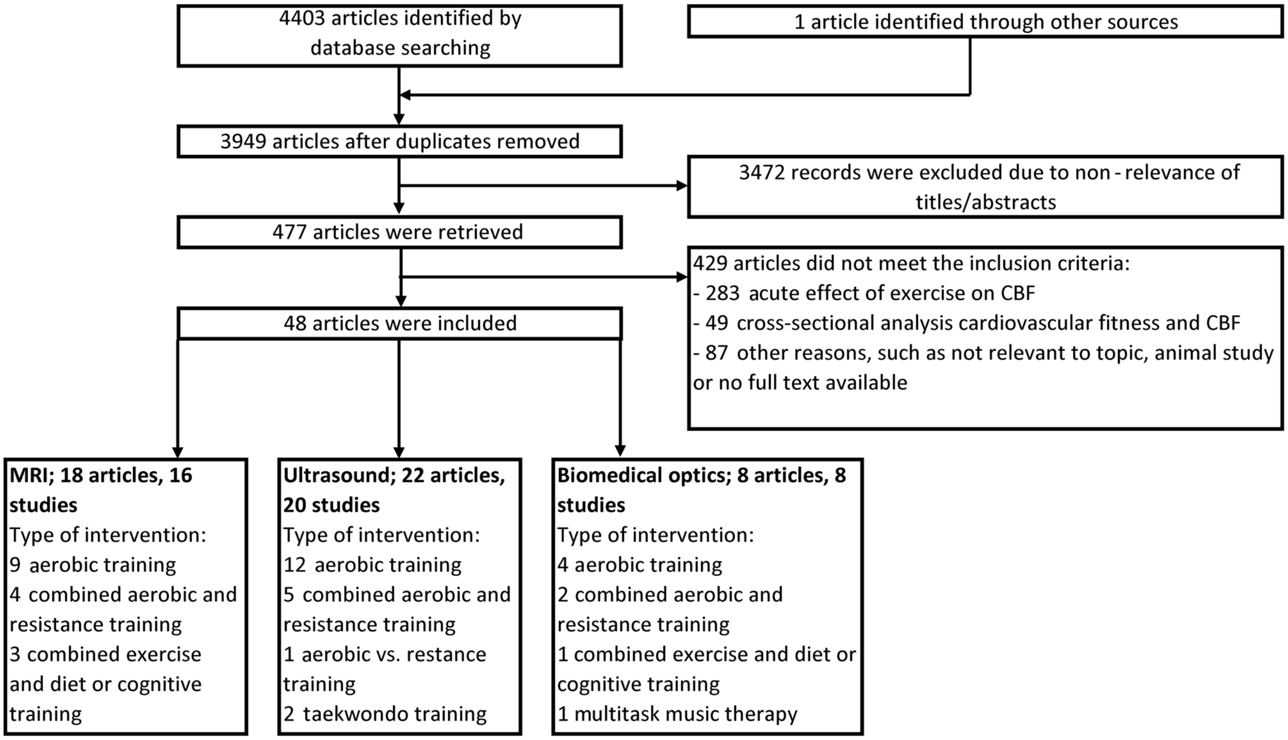

Figure 1 — Preferred Reporting Items for Systematic Reviews and Meta-Analysis flow diagram of each stage of study selection. CBF = cerebral blood flow; MRI = magnetic resonance imaging.

agent, and one study used PET), 20 transcranial Doppler ultrasound, and eight NIRS. Twenty-six RCTs were included (MRI: $n = 10$ [Chapman et al., 2013; Espeland et al., 2018; Kaiser et al., 2021; Kaufman et al., 2021; Kleinloog et al., 2019; Maass et al., 2015; Maffei et al., 2017; Moore et al., 2015; Small et al., 2006; van der Kleij et al., 2018]; transcranial Doppler ultrasound: $n = 12$ [Akazawa et al., 2012; Bailey, Cable, Aziz, Atkinson, et al., 2016; Cho & Roh, 2019; Green et al., 2021; Hata et al., 1998; Heli et al., 2013; Ivey et al., 2011; Lee et al., 2021; Miller et al., 2022; Northey et al., 2019; Thomas et al., 2021; Tomoto, Liu, et al., 2021]; and NIRS: $n = 4$ [Fu et al., 2013; Hamasaki et al., 2019; Tsai et al., 2016; Wang et al., 2010]) that involved a control group, which performed no exercise or performed activities not affecting fitness levels (e.g., yoga or stretching). The remaining 18 studies (MRI: $n = 6$ [Alfini et al., 2019; Anazodo et al., 2016; Burdette et al., 2010; Pereira et al., 2007; Robertson et al., 2017; Steventon et al., 2021]; transcranial Doppler ultrasound: $n = 8$ [Akazawa et al., 2018; Bailey, Cable, Miller, et al., 2016; Drapeau et al., 2019; Lake et al., 2022; Lewis et al., 2019; Murrell et al., 2013; Stanek et al., 2011; Tomoto et al., 2015]; and NIRS: $n = 4$ [Caen et al., 2019; Drigny et al., 2014; Pollock et al., 2020; Shimizu et al., 2018]) had a quasi-experimental design, as a (suitable) control group was missing. The RoB assessment showed some concerns for 15 (33%) studies, while a low RoB was observed for the remaining 30 (67%) studies (Table S1 in the Supplementary Material [available online]).

The type of intervention and the study population are detailed in Table 1 for MRI studies, in Table 2 for transcranial Doppler ultrasound studies and in Table 3 for NIRS studies. The exercise training arms included continuous exercise (MRI: $n = 8$ [Alfini et al., 2019; Burdette et al., 2010; Chapman et al., 2013; Kaiser et al., 2021; Kaufman et al., 2021; Kleinloog et al., 2019; Pereira et al., 2007; van der Kleij et al., 2018]; transcranial Doppler ultrasound: $n = 14$ [Akazawa et al., 2012, 2018; Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Miller, et al., 2016; Green et al., 2021; Hata et al., 1998; Ivey et al., 2011; Lake et al., 2022; Miller et al., 2022; Murrell et al., 2013; Northey et al., 2019; Stanek et al., 2011; Thomas et al., 2021; Tomoto, Liu, et al., 2021]; and NIRS: $n = 3$ [Fu et al., 2013; Tsai et al., 2016; Wang et al., 2010]) or high-intensity interval training (HIIT; MRI: $n = 1$ [Maass et al., 2015]; transcranial Doppler ultrasound: $n = 2$ [Drapeau et al., 2019; Northey et al., 2019]; and NIRS: $n = 3$ [Caen et al., 2019; Fu et al., 2013; Tsai et al., 2016]) or a combination of different types of exercise (MRI: $n = 7$ [Anazodo et al., 2016; Espeland et al., 2018; Maffei et al., 2017; Moore et al., 2015; Robertson et al., 2017; Small et al., 2006; Steventon et al., 2021]; transcranial Doppler ultrasound: $n = 3$ [Heli et al., 2013; Lewis et al., 2019; Tomoto et al., 2015]; and NIRS: $n = 3$ [Drigny et al., 2014; Hamasaki et al., 2019; Pollock et al., 2020]). The exercise protocol progressed in frequency, duration, and/or intensity in most studies. The progression was either standardized for the whole group or individualized for each participant. Studies controlled the intensity levels of aerobic exercise based on the heart rate reserve (HRR), maximum heart rate (HR_{max}), maximal power (P_{max}) or rating of perceived exertion (RPE). The intensity of resistance training was based on the one repetition maximum (1RM) and the number of repetitions. Finally, 41 out of 45 studies indicated that at least three sessions per week were supervised. In the remaining studies, one or two sessions per week were supervised (Heli et al., 2013; Robertson et al., 2017; Shimizu et al., 2018), and one study indicated that supervision was only provided during the first 6 months (Espeland et al., 2018).

Magnetic Resonance Imaging

The median for the intervention duration was 14 weeks (range: 1–541 weeks), and for the exercise the mean frequency duration was 3 days/week (range: 2–7 days/week) and 45 min (range: 20–60 min), respectively. The median sample size was 18 participants per study arm (range: 5–157). Study participants had a median age of 68 years (range: 23–81 years) and their median BMI was 26.7 kg/m^2 (range: 24.5–36.3 kg/m^2).

Transcranial Doppler Ultrasound

The median intervention duration was 14 weeks (range: 6–52 weeks) and the frequency of the exercise sessions was 3 days/week (range: 2–5 days/week). The median duration of these sessions was 45 min (range: 20–60 min). The median sample size per study arm was 11 (range: 4–203). The median age of included participants was 56 years (range: 11–69 years) and their median BMI was 25.3 kg/m^2 (range: 19.2–34.9 kg/m^2).

Near-Infrared Spectroscopy

The median duration of the interventions was 8 weeks (range: 4–16 weeks) and mean frequency of exercise sessions 3 days/week (range: 1–6 days/week). The median duration of exercise sessions was 30 min (range: 30–60 min). The median age of the subjects was 56 years (range: 21–75 years), and for the BMI 22.7 kg/m^2 (range: 21.0–29.7 kg/m^2).

Effects on CBF

Physical exercise training-induced effects on CBF as measured by MRI, transcranial Doppler ultrasound and NIRS are summarized in Table 4.

Magnetic Resonance Imaging

Two studies found increases in either whole-brain CBF (Espeland et al., 2018) or gray-matter CBF (Robertson et al., 2017), while in eight other studies no differences were observed (Anazodo et al., 2016; Chapman et al., 2013, 2016, 2017; Kaiser et al., 2021; Kleinloog et al., 2019; Maass et al., 2015; Moore et al., 2015; Steventon et al., 2021; van der Kleij et al., 2018). Studies that focused on differences in blood flow in brain lobes observed an increased CBF in the limbic (Espeland et al., 2018), occipital (Espeland et al., 2018), medial temporal (Moore et al., 2015), and parietal lobe (Robertson et al., 2017). Analyses of specific brain regions within the frontal lobe showed increases in CBF in the anterior cingulate gyrus (Alfini et al., 2019; Anazodo et al., 2016; Chapman et al., 2013; Kleinloog et al., 2019) and in the inferior frontal gyrus (Alfini et al., 2019), while CBF was decreased in the left dorsolateral prefrontal cortex (Small et al., 2006). CBF within specific regions of the medial temporal lobe were affected. Specifically, blood flow was increased in the dentate gyrus (Pereira et al., 2007) and hippocampus (Burdette et al., 2010; Kaufman et al., 2021; Pereira et al., 2007; Steventon et al., 2021). Although hippocampal CBF decreased within the exercise group in another study, but not compared with the control group (Maass et al., 2015). Positive associations were found between changes in hippocampal CBF with improvements in memory performance (Chapman et al., 2013; Kaufman et al., 2021; Maass et al., 2015). Finally, CBF increased in the parahippocampal (Maffei et al., 2017) and decreased in the temporal fusiform gyrus (Kleinloog et al., 2019), which are both located in the temporal lobe.

Table 1 Characteristics of the 16 Studies That Used Magnetic Resonance Imaging

Study	Health status	*N* (% female)	Age (years)	BMI (kg/m^2)	Type	Duration	Intervention effects	
							CBF	VO$_2$max
Aerobic exercise training								
Alfini et al. (2019)	Healthy	18 (82)	77 ± 7	N/A	CE	12 weeks (4×/week: 30 min)	Healthy: ↑ ACC	↑ 3%
	MCI	17 (60)	81 ± 6				MCI: ↓ ACC and inferior frontal gyrus	↑ 14%
Burdette et al. (2010)	Healthy	6 (50)	78 ± 5	27 ± 6	CE	16 weeks (4×/week: 40 min)	↑ Hippocampus	N/A
		5 (0)	74 ± 3	28 ± 2	SC			
Chapman et al. (2013, 2016, 2017)	Healthy	19 (74)	64 ± 4	26 ± 3	CE	12 weeks (3×/week: 60 min)	↑ ACC	↑ 4%
		18 (72)	64 ± 4	28 ± 5	CT			
		18 (56)	62 ± 3	26 ± 4	Control			
Kaiser et al. (2021)	Healthy	22 (50)	23 ± 3	24 ± 3	CE	12 weeks (3×/week: 45 min)	No effects	↑ 13%
		23 (57)	24 ± 3	24 ± 3	SC			
Kaufman et al. (2021)	Healthy	29 (58)	72 ± 5	N/A	CE	52 weeks (150 min/week)	↑ Hippocampus (APOE-e4 +)	↑ 10%
		15 (67)	73 ± 6		EC			
Kleinloog et al. (2019)	Healthy	17 (0)	67 ± 2	30 ± 4	CE	8 weeks (3×/week: 50 min)	↑ Frontal, ↓ Medial temporal	↑ 10%
					Control			
Maass et al. (2015)	Healthy	21 (52)	69 ± 5	25 ± 3	HIIT	12 weeks (3×/week: 30 min)	No effects	↑ 10%
		19 (58)	68 ± 4	25 ± 3	SC			
Pereira et al. (2007)	Healthy	11 (82)	33	N/A	CE	12 weeks (4×/week: 60 min)	↑ Hippocampus	↑ 13%
Van der Kleij et al. (2018)	AD	27 (37)	68 ± 7	N/A	CE	16 weeks (3×/week: 60 min)	No effects	↑ 8%
		24 (41)	69 ± 7		Control			
Combined aerobic and resistance exercise training								
Anazodo et al. (2016)	Healthy	17 (48)	59 ± 6	25 ± 3	CE + RT	24 weeks (3×/week: 30 min)	↑ ACC	↑ 5%
	CAD	21 (29)	59 ± 8	30 ± 5	Control			
Moore et al. (2015)	Poststroke	20 (10)	68 ± 8	26 ± 4	CE + RT	19 weeks (3×/week: 30 min)	↑ Medial temporal	↑ 17%
		20 (20)	70 ± 11	26 ± 4	Control			
Robertson et al. (2017)	Poststroke	8 (25)	67 ± 11	27 ± 11	CE + RT	24 weeks (5×/week: 20–60 min)	↑ Gray matter and parietal	↑ 20%
Steventon et al. (2021)	Healthy	15 (0)	30 ± 6	26 ± 3	CE + RT	1 week (5 × 25 min)	↑ Hippocampus	N/A
Combined exercise training and dietary interventions or CT								
Espeland et al. (2018)	T2D	157 (73)	58 ± 6	35 ± 0	HL	541 weeks (3×/week: 60 min)	↑ Whole-brain, limbic, and occipital	N/A
		153 (66)	59 ± 7	36 ± 0	EC			
Maffei et al. (2017)	MCI	53 (53)	74 ± 5	N/A	CE, RT + CT	28 weeks (3×/week: 60 min)	↑ Parahippocampal	N/A
		50 (45)	75 ± 4		Control			
Small et al. (2006)	Healthy	8 (63)	54 ± 12	N/A	HL	2 weeks (7×/week: 45 min)	↓ Dorsolateral prefrontal cortex	N/A

Note. ACC = anterior cingulate cortex; AD = Alzheimer's disease; APOE-e4 = apolipoprotein E; BMI = body mass index; CAD = corony artery disease; CBF = cerebral blood flow; CE = continuous exercise; CT = cognitive training; EC = educational control; HIIT, high-intensity interval training; HL = healthy lifestyle; MCI = mild cognitive impairment; RT = resistance training; SC = stretching control; T2D = Type 2 diabetes; VO$_2$max = maximum rate of oxygen consumption during incremental exercise; N/A = not applicable.

Transcranial Doppler Ultrasound

Four studies that used transcranial Doppler ultrasound to quantify resting CBF observed an increased middle cerebral artery (MCA) velocity (MCAv) (Akazawa et al., 2012; Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Miller, et al., 2016; Lake et al., 2022), while 12 studies observed no differences (Akazawa et al., 2018; Cho & Roh, 2019; Drapeau et al., 2019; Heli et al., 2013; Ivey et al., 2011; Lewis et al., 2019; Murrell et al., 2013; Northey et al., 2019; Stanek et al., 2011; Thomas et al., 2021; Tomoto et al., 2015). Although MCAv did not change, Stanek et al.

Table 2 Characteristics of the 20 Studies That Used Transcranial Doppler Ultrasound

Study	Health status	*N* (% female)	Age (years)	BMI (kg/m^2)	Type	Duration	Intervention effects	
							CBF	VO_2max
Aerobic exercise training								
Akazawa et al. (2012)	Healthy	10 (100)	60 ± 2	23	CE	8 weeks (3–5×/week: 45 min)	↑ MCAv, ↓ CVR, = PI	↑ 10%
		10 (100)	61 ± 2	21	Control			
Akazawa et al. (2018)	Healthy	10 (80)	62 ± 4	22	CE	12 weeks (5×/week: 30–45 min)	↓ PI (acute) = MCAv, CVR	↑ 21%
Bailey, Cable, Aziz, Atkinson, et al. (2016) and Bailey, Cable, Aziz, Dobson, et al. (2016)	Healthy	14 (100)	52 ± 4	29 ± 6	CE	16 weeks (3–5×/week: 30–45 min)	↑ MCAv = CVR	↑ 24%
		7 (100)	52 ± 6	28 ± 7	Control			
Bailey, Cable, Miller et al. (2016)	Athletes	9 (100)	26 ± 5	24 ± 4	CE	8 weeks (3×/week: 30 min)	↑ MCAv and CVC	↑ 5%
		9 (100)			WI			
Drapeau et al. (2019)	Athletes	8 (0)	26 ± 6	23	HIIT	6 weeks (3×/week: until exhaustion	No effects	↑ 6%
		9 (0)	28 ± 6	24				
Green et al. (2021)	Healthy	19 (74)	62 ± 7	28 ± 2	CE	24 weeks (3×/week: 15–60 min)	No effects	↑ 10%
		22 (73)	62 ± 6	29 ± 4	Water-CE			
		22 (73)	63 ± 9	27 ± 5	Control			
Hata et al. (1998)	Athletes	10 (100)	23 ± 1	19 ± 2	CE	52 weeks (3–5×/week: 50 min)	↓ OCA PI	N/A
		10 (100)	23 ± 2	21 ± 1	Control			
Ivey et al. (2011)	Poststroke	19 (42)	61 ± 8	28 ± 6	CE	24 weeks (3×/week: 40 min)	↓ MCAv, ↑ CVMR	↑ 24%
		19 (42)	62 ± 10	26 ± 5	Control			
Lake et al. (2022)	Healthy	203 (51)	66 ± 6	27 ± 4	CE	24 weeks (3–5×/week: 30 min)	↑ MCAv, ↓ CVR	↑ 8%
Miller et al. (2022)	Athletes	11 (27)	22 ± 5	22 ± 2	CE	8 weeks (3×/week: 50 min)	No effects	↑ 6%
		10 (20)	22 ± 5	23 ± 3	Cold-CE			
Murrell et al. (2013)	Healthy	10 (50)	23 ± 5	26 ± 3	CE	12 weeks (3×/week: 20–50 min)	No effects	↑ 10%
		10 (50)	53 ± 5	25 ± 3				↑ 5%
Northey et al. (2019)	Breast cancer survivors	5 (100)	68 ± 7	25	CE	12 weeks (3×/week: 20–30 min)	No effects	↑ 9%
		6 (100)	60 ± 8	25	HIIT			↑ 22%
		6 (100)	62 ± 8	28	Control			
Stanek et al. (2011)	CVD	42 (33)	68 ± 9	30 ± 6	CE	12 weeks (3×/week: 60 min)	No effects	N/A
Thomas et al. (2021)	Healthy	68 (62)	26 ± 5	27 ± 4	CE	12 weeks (3×/week: 60 min)	CE: No effects	↑ 9%
					RT		RI: ↓ MCAv and PI, ↑CVR	=
Tomoto, Liu, et al. (2021) and Tomoto, Tarumi, et al. (2021)	MCI	18 (44)	65 ± 6	27 ± 5	CE	52 weeks (3–5×/week: 20–40 min)	↑ CVMR, ↓ PI	N/A
		19 (47)	65 ± 7	27 ± 4	SC			
Combined aerobic and resistance exercise training								
Heli et al. (2013)	MetS	6 (100)	63 ± 10	31 ± 6	HIIT + RT	16 weeks (2×/week: 25–45 min)	No effects	↑11%
		4 (100)	56 ± 6	35 ± 6	EC			
Lewis et al. (2019)	Healthy	20 (50)	64 ± 5	26 ± 3	CE + HIIT	8 weeks (3×/week: 20–45 min)	No effects	↑ 17%
	COPD	23 (43)	69 ± 7	28 ± 3				↑ 9%
Tomoto et al. (2015)	Athletes	13 (46)	N/A	21 ± 8	CE + HIIT + RT	16 weeks (3×/week: 60–90 min)	No effects	↑ 3%

(continued)

Table 2 ***(continued)***

Study	Health status	*N* (% female)	Age (years)	BMI (kg/m^2)	Type	Duration	Intervention effects	
							CBF	VO_2max
Cho and Roh (2019)	Healthy	15 (40)	11 ± 1	21 ± 2	Taekwando	16 weeks (5×/week: 60 min)	No effects	↑ 3%
		15 (40)	11 ± 1	21 ± 4	Control			
Lee et al. (2021)	Healthy	12 (100)	56 ± 3	26 ± 2	Taekwando	16 weeks (5×/week: 60 min)	No effects	N/A
		12 (100)	58 ± 3	26 ± 2	Control			

Note. BMI = body mass index; CBF = cerebral blood flow; CE = continuous exercise; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; CVC = cerebrovascular conductance; CVMR = cerebral vasomotor reactivity; CVR = cerebrovascular resistance; dCA = dynamic cerebral autoregulation; EC = educational control; HIIT = high-intensity interval training; MetS = metabolic syndrome; MCAv = middle cerebral blood flow; MCI = mild cognitive impairment; N/A = not applicable; OCA = ophthalmic cerebral artery; PI = pulsatility index; RT = resistance training; SC = stretching control; VO_2max = maximum rate of oxygen consumption during incremental exercise; WI = water immersion.

Table 3 **Characteristics of the Eight Studies That Used Near-Infrared Spectroscopy**

Study	Health status	*N* (% female)	Age (years)	BMI (kg/m^2)	Type	Duration	Intervention effects	
							CBF	VO_2max
Aerobic exercise training								
Caen et al. (2019)	Athletes	11 (0)	22 ± 1	26	HIIT	6 weeks (3×/week: 49 min)	↑ HHb and totHb, ↓ O_2Hb and cTOI (exercise)	↑ 8%
Fu et al. (2013)	CVD	13 (38)	66 ± 2	25	CE	12 weeks (3×/week: 30 min)	↑ totHb, = O_2Hb and HHb (exercise)	↑ 9%
		14 (36)	68 ± 2	25	HIIT			↑ 31%
		13 (31)	68 ± 3	25	Control			
Tsai et al. (2016)	Healthy	20 (0)	22 ± 1	22 ± 1	CE	6 weeks (5×/week: 30 min)	↑ totHb, = HHb (HIIT, not CE)	↑ 12%
		20 (0)	22 ± 1	22 ± 1	HIIT			↑ 23%
		20 (0)	22 ± 1	23 ± 1	Control			
Wang et al. (2010)	Healthy	12 (0)	21 ± 1	23 ± 1	CE	4 weeks (5×/week: 30 min)	= totHb, O_2Hb, and HHb (exercise)	↑ 5%
		12 (0)	23 ± 1	24 ± 1	Control			
Combined aerobic and resistance exercise training								
Drigny et al. (2014)	Healthy	6 (N/A)	49 ± 8	30 ± 1	CE + HIIT + RT	16 weeks (5×/week: 20–60 min)	↑ HHb, = totHb and O_2Hb (exercise)	↑ 12%
Pollock et al. (2020)	Parkinson	12 (70)	66 ± 10	N/A	CE + RT	8 weeks (3×/week: 30 min)	No effects	N/A
Combined exercise training and dietary intervention								
Hamasaki et al. (2019)	Healthy	16 (N/A)	63 ± 4	22 ± 2	CE (PLA)	6 weeks (4–6×/week: 40–45 min)	↑ O_2Hb (cognitive task)	↑ 7%
		18 (N/A)	63 ± 6	22 ± 3	Control (PLA)			
Alternative exercise training								
Shimizu et al. (2018)	Healthy	30 (91)	73 ± 7	N/A	Multitask	12 weeks (1×/week: 60 min)	↑ O_2Hb (cognitive task)	N/A
		9 (82)	75 ± 4	N/A	Single-task			

Note. BMI = body mass index; CBF = cerebral blood flow; CE = continuous exercise; cTOI = tissue oxygenation index; CVD = cardiovascular disease; HHb = deoxygenated hemoglobin; HIIT = high-intensity interval training; N/A = not applicable; O_2Hb = oxygenated hemoglobin; PLA = placebo; RT = resistance training; totHb = total hemoglobin; VO_2max = maximum rate of oxygen consumption during incremental exercise.

(2011) reported training-induced increases in the anterior cerebral artery (ACA) velocity (ACAv). The cerebrovascular conductance (CVC), which is calculated as the MCAv divided by the mean arterial pressure, increased in one study (Bailey, Cable, Miller, et al., 2016), decreased in another study (Akazawa et al., 2012), and did not change in seven studies (Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Miller, et al., 2016; Cho & Roh, 2019; Drapeau et al., 2019; Green et al., 2021; Lake et al., 2022; Miller et al., 2022; Murrell et al., 2013). Seven studies that measured cerebrovascular resistance (CVR; mean arterial pressure divided by

Table 4 Summary of Exercise Training-Induced Effects on CBF as Measured With Magnetic Resonance Imaging, Transcranial Doppler Ultrasound, and Near-Infrared Spectroscopy

	Increased	Decreased	No difference	Not assessed
Magnetic resonance imaging (n = 16 studies)				
Whole-brain CBF	2	—	8	6
Regional CBF[a]	12	3	3	—
Transcranial Doppler ultrasound (n = 20 studies)				
MCA velocity	4	—	12	4
ACA velocity	1	—	—	19
CVC	1	1	7	11
CVR	—	2	6	12
PI MCA	—	—	7	13
PI ACA	—	—	1	19
PI OCA	—	1	—	19
PI MCA 30 min postexercise	—	1	—	19
dCA	2	—	2	16
CVMR	3	—	4	13
Near-infrared spectroscopy (n = 8 studies)				
During exercise				
totHb	3	—	3	2
O_2Hb	1	—	4	3
HHb	1	—	4	3
cTOI	1	—	—	7
During cognitive task				
O_2Hb	2	—	1	5

Note. ACA = anterior cerebral artery; CBF = cerebral blood flow; CVC = cerebrovascular conductance; CVMR = cerebral vasomotor reactivity in response to hypocapnia or hypercapnia; CVR = cerebrovascular resistance; dCA = dynamic cerebral autoregulation; HHb = deoxygenated hemoglobin; MCA = middle cerebral artery; OCA = ophthalmic cerebral artery; O_2Hb = oxygenated hemoglobin; PI = pulsatility index; totHb = total hemoglobin; cTOI = tissue oxygenation index.

[a] Studies investigated multiple regions and could have observed a regional increase, decrease and/or no difference. Additionally, time effects of multiple populations within one study were observed.

the MCAv) did not observe differences (Drapeau et al., 2019; Green et al., 2021; Ivey et al., 2011; Lewis et al., 2019; Miller et al., 2022; Murrell et al., 2013; Thomas et al., 2021; Tomoto, Tarumi, et al., 2021), whereas CVR decreased in two studies (Akazawa et al., 2018; Lake et al., 2022). Finally, a decreased pulsatility index (PI), calculated as the difference between peak systolic and end-diastolic flow velocities divided by the mean velocity, was observed of the ophthalmic cerebral artery (OCA) in one study (Hata et al., 1998). Seven studies measured the PI of the MCA (Akazawa et al., 2012, 2018; Cho & Roh, 2019; Lee et al., 2021; Stanek et al., 2011; Thomas et al., 2021; Tomoto et al., 2015) and ACA (Stanek et al., 2011), but no differences were observed. Exercise training reduced the PI of the MCA 30 min after an acute exercise trigger (Akazawa et al., 2018). Also, dynamic cerebral autoregulation of the MCA increased during exercise in two studies (Drapeau et al., 2019; Miller et al., 2022), but no changes were observed in another two studies (Green et al., 2021; Lewis et al., 2019). Cerebral vasomotor reactivity (CVMR) reflects changes in CBF in response to changes in blood carbon dioxide (Claassen et al., 2021). Three studies showed an increased CBF of the MCA in response to hypercapnia (Ivey et al., 2011; Murrell et al., 2013; Tomoto, Liu, et al., 2021), but the CVMR of the MCA did not significantly change following hypocapnia in four studies (Lewis et al., 2019; Miller et al., 2022; Northey et al., 2019). Furthermore, Tomoto, Tarumi, et al. (2021) have reported a positive association between changes in CVMR with improvements in letter fluency as assessed using the Delis-Kaplan Executive Function System battery.

Near-Infrared Spectroscopy

CBF as measurement by NIRS during physical exercise resulted in a training-induced increase in total hemoglobin (totHb) in three study groups with HIIT training (Caen et al., 2019; Fu et al., 2013; Tsai et al., 2016), while for two of these studies no differences in totHb were observed in the continuous exercise group (Fu et al., 2013; Tsai et al., 2016). Another study also did not observe changes in totHb following continuous exercise (Wang et al., 2010). Oxygenated hemoglobin (O_2Hb) increased in one study following HIIT training (Caen et al., 2019), whereas no changes were reported in four other studies (Drigny et al., 2014; Fu et al., 2013; Tsai et al., 2016; Wang et al., 2010). Only one study observed an increased deoxygenated hemoglobin (HHb) during combined aerobic and resistance exercise training (Drigny et al., 2014), but no significant differences were found in four studies (Caen et al., 2019; Fu et al., 2013; Tsai et al., 2016; Wang et al., 2010). The difference between O_2Hb and HHb that is defined as the cerebral tissue oxygenation index (cTOI) was increased during aerobic exercise in one study (Caen et al., 2019). Finally, totHb did not significantly change during cognitive tasks in one study (Pollock et al., 2020), while two other studies did observe an increased O_2Hb during either the Stroop task (Hamasaki et al., 2019) or a Frontal Assessment Battery (Shimizu et al., 2018) assessing both executive functioning.

Discussion

The aim of this systematic review was to give a comprehensive overview of physical exercise training-induced effects on CBF in humans as measured by MRI, transcranial Doppler ultrasound, and NIRS. In addition, relationships between these effects with observed changes in physical fitness and cognitive performance were examined.

Effects on CBF

Magnetic Resonance Imaging

Out of 10 studies, whole-brain CBF was increased in one extremely long study (541 weeks) with an intensive lifestyle intervention in T2D patients (Espeland et al., 2018) and gray-matter CBF in another study with participants that had suffered from a stroke 3 months before the start of the intervention (Robertson et al., 2017). In the latter study, however, a control group was missing and the effect observed may have been due to the natural recovery of CBF after a stroke and not by the exercise intervention per se (Salinet et al., 2014; Zhang et al., 2019). Thus, the evidence that exercise training affects whole-brain CBF is not convincing.

Regional changes in CBF were, to some extent, more consistent. In general, CBF was increased in the anterior cingulate cortex and hippocampus. However, exercise training also decreased blood flow within regions of the medial temporal lobe. The regional CBF pattern changes during aging. This pattern may also vary between different health conditions, such as in Type 2 diabetes (Cui et al., 2017), and may change during disease progression (Chen et al., 2011) that is, for example, observed during the development from cognitive healthy to mild cognitive impairment and Alzheimer's disease (Firbank et al., 2011; Sierra-Marcos, 2017). Furthermore, differences in participant characteristics, including the age range and baseline physical fitness levels, may have contributed to the observed differential regional CBF responses between the included studies. Moreover, physical exercise training was combined with a dietary and/or cognitive cointervention in three studies (Espeland et al., 2018; Maffei et al., 2017; Small et al., 2006). Although the effects of these studies cannot be attributed to only exercise training, the results of these studies are in line with those that included exercise training only. Alternatively, differences between studies may be directly related to MRI image acquisition or the statistical approach used. Obviously, the studies that acquired only CBF data of a predefined region may have missed potential changes in other brain regions (Alfini et al., 2019; Burdette et al., 2010; Maass et al., 2015; Maffei et al., 2017; Pereira et al., 2007; Small et al., 2006). In contrast, studies that imaged the entire brain may be more susceptible for partial volume effects due to larger voxel size. Another explanation for these differences may be the different statistical approaches that were used such as region of interest (Burdette et al., 2010; Chapman et al., 2013; Espeland et al., 2018; Kaiser et al., 2021; Kaufman et al., 2021; Maass et al., 2015; Maffei et al., 2017; Moore et al., 2015; Pereira et al., 2007; Steventon et al., 2021; van der Kleij et al., 2018), or voxel-wise analyses (Alfini et al., 2019; Anazodo et al., 2016; Chapman et al., 2013; Kleinloog et al., 2019; Small et al., 2006). The latter approach is more sensitive as it permits statistical inferences at voxel level after normalization to a reference atlas and is not limited to predefined brain regions (Astrakas & Argyropoulou, 2010). However, most studies analyzed data using custom-made programs, which makes it difficult to compare the different methodologies used between the included studies.

Transcranial Doppler Ultrasound

In healthy participants, exercise training did not consistently change parameters related to resting CBF measured with transcranial Doppler ultrasound. In fact, in some studies increases were observed (Akazawa et al., 2012; Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Miller, et al., 2016; Hata et al., 1998; Lake et al., 2022), while in other studies no changes were found (Akazawa et al., 2018; Cho & Roh, 2019; Drapeau et al., 2019; Lewis et al., 2019; Murrell et al., 2013; Thomas et al., 2021; Tomoto et al., 2015). In studies with patients (Heli et al., 2013; Ivey et al., 2011; Lewis et al., 2019; Northey et al., 2019; Tomoto, Liu, et al., 2021), CBF only increased in the study with CVD patients (Stanek et al., 2011). All studies, but one (Northey et al., 2019), with continuous exercise training protocols observed variable changes in at least one of the CBF parameters (Akazawa et al., 2012; Bailey, Cable, Aziz, Atkinson, et al., 2016; Chapman et al., 2013; Drigny et al., 2014; Hata et al., 1998; Stanek et al., 2011), while HIIT training was not effective (Drapeau et al., 2019; Heli et al., 2013; Northey et al., 2019; Tomoto et al., 2015). This could be explained by the longer duration of the continuous exercise sessions, which may be needed to affect resting CBF. It should be noted, however, that results were difficult to compare because different cerebral arteries were assessed, while a great variety of outcome parameters were reported.

Training affected cerebral autoregulation by increasing the CBF in response to different stimuli such as exercise (Akazawa et al., 2018; Drapeau et al., 2019; Miller et al., 2022; Murrell et al., 2013) and reactivity to hypercapnia (Ivey et al., 2011; Murrell et al., 2013; Tomoto, Liu, et al., 2021). Both stimuli may increase carbon dioxide levels in blood, thereby challenging the regulation of CBF. Only one study did not find changes in dCA during repeated squat stands after 5 min of supine rest (Lewis et al., 2019), while two other studies did observe effects in response to 10 min of standing rest (Drapeau et al., 2019) or a cycling trigger (Akazawa et al., 2018; Murrell et al., 2013). Possibly, carbon dioxide levels in the blood were not increased in the former study (Lewis et al., 2019), as CBF was not affected following a hypocapnic stimulus (Lewis et al., 2019; Miller et al., 2022; Murrell et al., 2013; Northey et al., 2019). A recent review concluded that exercise training has no major impact on cerebral autoregulation (Claassen et al., 2021). Their conclusion was however also based on cross-sectional studies, while some exercise trials that did observe an increased dCA were not considered (Drapeau et al., 2019; Miller et al., 2022). Furthermore, the present review included intervention studies that specifically showed an increased vasomotor reactivity in response to hypercapnia (Ivey et al., 2011; Murrell et al., 2013; Tomoto, Liu, et al., 2021).

Near-Infrared Spectroscopy

Results of the various studies using NIRS were more difficult to compare. In fact, CBF changes were measured during different experimental conditions or cognitive tasks, and at different time points during exercise triggers, while different outcome parameters were reported. This may explain why changes in CBF were variable, although the only two studies measuring CBF during cognitive tasks observed an increased O_2Hb signal (Hamasaki et al., 2019; Shimizu et al., 2018). Remarkably, studies with only a continuous exercise training protocol observed no changes when exercise (Fu et al., 2013; Tsai et al., 2016; Wang et al., 2010) or a cognitive task (Pollock et al., 2020) was used as a challenge, while incorporating HIIT training was an effective approach to increase totHb during exercise (Caen et al., 2019; Fu et al., 2013; Tsai et al., 2016). This suggests that HIIT training is more effective than continuous exercise to increase CBF during exercise which is in contrast to findings on CBF in studies using transcranial Doppler ultrasound. This may be due to the shorter duration of the continuous exercise training sessions in studies using NIRS (median: 30 min) as compared with transcranial Doppler ultrasound studies (median: 45 min). HIIT is well known for its cardiovascular health benefits, which are already evident after a shorter time period compared with continuous exercise (Su et al., 2019). The only study including older obese participants observed increased HHb during exercise (Drigny et al., 2014), which suggests that deoxygenation became more efficient. However, the sample size ($n = 6$) was probably too limited to draw any firm conclusions. Additionally, increased O_2Hb during exercise was only observed in already physically active men (Caen et al., 2019). However, whether training status affects the CBF response after training remains to be determined.

Physical Fitness and CBF

In most studies using MRI, increases in physical fitness levels were accompanied by a region-dependent increase or decrease in CBF (Alfini et al., 2019; Chapman et al., 2013; Kleinloog et al., 2019; Maass et al., 2015; Moore et al., 2015; Pereira et al., 2007; Robertson et al., 2017). Moreover, the increase in physical fitness was positively associated with changes in hippocampal CBF in two studies (Maass et al., 2015; Pereira et al., 2007) and whole-brain CBF in another study (Espeland et al., 2018). In one study with Alzheimer's patients, CBF did not change even though physical fitness was improved (van der Kleij et al., 2018). This may suggest that these patients were not responsive or that a stronger intervention is needed to observe any effects on CBF. In contrast, CBF increased in one study involving coronary artery disease patients, while physical fitness levels did not significantly change (Anazodo et al., 2016).

Similarly, concomitant improvements in physical fitness and the transcranial Doppler ultrasound parameters MCAv (Akazawa et al., 2012; Bailey, Cable, Aziz, Atkinson, et al., 2016; Bailey, Cable, Miller, et al., 2016; Lake et al., 2022; Robertson et al., 2017), ACAv (Stanek et al., 2011), CVC (Akazawa et al., 2012; Bailey, Cable, Miller, et al., 2016), or PI OCA (Hata et al., 1998) were observed. Interestingly, the change in physical fitness was positively related to improvements in CVMR in two studies (Green et al., 2021; Tomoto, Liu, et al., 2021). In another two studies, physical fitness and CBF did both not change (Heli et al., 2013; Tomoto et al., 2015). In chronic obstructive pulmonary disease (COPD) patients, exercise did not affect CBF although oxygen uptake increased (Lewis et al., 2019). Whether this indicates that a stronger intervention or a different protocol is needed to affect CBF in COPD patients warrants further study.

Exercise training interventions also concomitantly improved parameters measured with NIRS, as increases were reported in totHb (Caen et al., 2019; Fu et al., 2013; Tsai et al., 2016), O_2Hb (Caen et al., 2019; Shimizu et al., 2018), cTOI (Caen et al., 2019), and HHb (Drigny et al., 2014) during exercise and O_2Hb during a cognitive task (Hamasaki et al., 2019). Fu et al. (2013) also reported a positive association between the change in physical fitness and totHb. In contrast, physical fitness improved without changes in totHb, O_2Hb, and HHb during exercise in one study, but this study had the shortest intervention period and lasted only for 4 weeks (Wang et al., 2010).

Therefore, measuring physical fitness is recommended to determine the effectivity of the exercise training intervention, and has added value to understand effects of the exercise protocol on regional CBF as a marker of cerebrovascular function, which was also concluded by a recent systematic review performed by Chen et al. (2020).

CBF and Cognitive Performance

Changes in CBF may underlie the well-known improvements in cognitive performance after exercise training (Gates et al., 2013; Northey et al., 2017). In most studies (Alfini et al., 2019; Chapman et al., 2013; Kleinloog et al., 2019; Maass et al., 2015; Moore et al., 2015; Pereira et al., 2007; Small et al., 2006), we observed concomitant changes in regional CBF measured with MRI and cognitive performance. Specifically, CBF increased in the anterior cingulate cortex, while verbal fluency (Alfini et al., 2019) and memory (Alfini et al., 2019; Chapman et al., 2013), and executive function (Kleinloog et al., 2019) improved. Furthermore, positive associations were found for increases in hippocampal CBF and improvements in memory performance (Chapman et al., 2013; Kaufman et al., 2021; Maass et al., 2015). Both the anterior cingulate gyrus and the hippocampus are important brain areas known to be involved in cognitive processing (Grady, 2012; Stevens et al., 2011). An advantage of transcranial Doppler and NIRS above MRI is that CBF can be measured more easily at the same time when cognitive testing is performed. However, only a very limited number of the transcranial Doppler ultrasound and NIRS studies also measured cognitive performance. Improvements in verbal fluency and executive function were positively associated with enhanced CVMR and higher O_2Hb (Hamasaki et al., 2019; Thomas et al., 2021). Moreover, in one study using transcranial Doppler ultrasound concomitant changes in resting CBF and cognitive performance were observed (Stanek et al., 2011), while no changes were observed in two studies (Heli et al., 2013; Northey et al., 2019). In one study cognitive performance changed, but CBF did not (Cho & Roh, 2019). It is possible that the changes in resting CBF as measured in the basal arteries using transcranial Doppler ultrasound are too low when blood flow only changes in specific regions. Studies using NIRS observed an increased CBF during exercise (Drigny et al., 2014) and during a cognitive task (Shimizu et al., 2018) in combination with improved cognitive performance. In addition, in one study measuring totHb during exercise, both CBF and cognitive performance did not change (Pollock et al., 2020).

Strengths and Limitations

We have for the first time systemically reviewed the effects of physical exercise training interventions on regional CBF using different techniques. Overall, good quality of evidence was provided by the included studies, and the results of the studies showing some concerns did not alter our conclusions. The protocol was however not preregistered to international prospective register of systematic reviews. Another potential limitation is that the time between the last bout of exercise training and measurements differed between studies and was often not reported. Finally, no quantitative analyses could be performed due to heterogeneity in the CBF outcomes and outcome assessment methodologies.

Conclusion

Exercise training consistently increased CBF in the anterior cingulate cortex and within regions of the medial temporal lobe as measured with MRI, but changes in whole-brain CBF were less consistent. Moreover, effects of exercise training on resting CBF measured using transcranial Doppler ultrasound and NIRS were also variable. Exercise may increase MCAv in response to exercise or hypercapnic stimuli, but the number of studies is limited. Regulation of CBF is challenged during these measurements, as metabolic demands and carbon dioxide levels in blood are increased. Under these conditions, changes in CBF may become more apparent. Interestingly, concomitant changes in physical fitness and regional CBF were observed, while a relation between training-induced improvement in CBF and cognitive performance was also evident. In conclusion, exercise training improved cerebrovascular function because regional CBF was changed. Studies are however still needed to establish whether exercise-induced improvements in CBF are sustained over longer periods of time and underlie the observed beneficial effects on cognitive performance.

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