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SYSTEMATIC REVIEW

A Critical Systematic Review of Current Evidence on the Effects of Physical Exercise on Whole/Regional Grey Matter Brain Volume in Populations at Risk of Neurodegeneration

Lars G. Hvid[1] · Dylan L. Harwood[1] · Simon F. Eskildsen[2] · Ulrik Dalgas[1]

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Abstract

Background Despite the intriguing potential of physical exercise being able to preserve or even restore brain volume (grey matter volume in particular)—a tissue essential for both cognitive and physical function—no reviews have so far synthesized the existing knowledge from randomized controlled trials investigating exercise-induced changes of the brain's grey matter volume in populations at risk of neurodegeneration. Our objective was to critically review the existing evidence regarding this topic.

Methods A systematic search was carried out in MEDLINE and EMBASE databases primo April 2020, to identify randomized controlled trials evaluating the effects of aerobic training, resistance training or concurrent training on brain grey volume changes (by MRI) in adult clinical or healthy elderly populations.

Results A total of 20 articles (from 19 RCTs) evaluating 3–12 months of aerobic, resistance, or concurrent training were identified and included, involving a total of 1662 participants (populations: healthy older adults, older adults with mild cognitive impairment or Alzheimer's disease, adults with schizophrenia or multiple sclerosis or major depression). While few studies indicated a positive effect—although modest—of physical exercise on certain regions of brain grey matter volume, the majority of study findings were neutral (i.e., no effects/small effect sizes) and quite divergent across populations. Meta-analyses showed that different exercise modalities failed to elicit any substantial effects on whole brain grey volume and hippocampus volume, although with rather large confidence interval width (i.e., variability).

Conclusion Altogether, the current evidence on the effects of physical exercise on whole/regional grey matter brain volume appear sparse and inconclusive, and does not support that physical exercise is as potent as previously proposed when it comes to affecting brain grey matter volume.

Key Points

Few summarized 'effects of exercise' data exist on populations at risk of brain atrophy.

Grey matter brain volume is not increased and/or preserved following 3–12 months of aerobic training or resistance training.

Current evidence overall appear sparse and inconclusive.

Current evidence does not support that physical exercise is as potent as previously proposed.

Lars G. Hvid and Dylan L. Harwood are the joint first authors.

✉ Lars G. Hvid
lhvid@ph.au.dk

[1] Exercise Biology, Department of Public Health, Aarhus University, Aarhus, Denmark

[2] Center of Functionally Integrative Neuroscience, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

1 Introduction

Neurodegeneration is a main contributor to brain atrophy [1] and is viewed as a hallmark of aging along with several neurological and psychiatric disorders (e.g., multiple sclerosis, Alzheimer's dementia, depression, schizophrenia). Brain atrophy is even being used as a measure of disease progression in some neurological disorders [2, 3]. Moreover, cognitive and physical impairments are most often associated with, and to some extent mediated by, whole/regional brain atrophy (grey matter volume in particular [4]) in aging [5, 6] as well as in neurological and psychiatric disorders [7–12]. Preventing brain atrophy could, therefore, likely extend the time to neurological reserve depletion, under the assumption that other qualitative measures are influenced, ultimately decreasing or postponing symptoms (e.g., cognitive and physical impairments) and subsequently improving quality of life.

While accelerated brain atrophy predominantly occurs late in life, i.e., starting around 50 years of age with the rate of atrophy differing between specific brain regions [13, 14], it is detectable much earlier (around 30–40 years of age) in patients with multiple sclerosis [15], schizophrenia [10, 16], and depression [11]. Regardless of when brain atrophy sets in, it is likely exacerbated by low levels of physical activity, as indicated by associations between fitness level and brain volume [17]. Strategies focusing on increasing spontaneous and structured (particularly moderate-to-high intensity) physical activities, might, therefore, attenuate brain atrophy as also proposed in recent guidelines for physical activity [18]. Indeed, an increasing number of studies have shown that structured moderate-to-high intensity physical activity (i.e., exercise) has a preservative or even restoring effect on whole/regional brain grey matter volume [19–21]. Regional brain volumes are of particularly interest, as cognitive and physical functions appear to be better correlated to such regions than to whole brain volume [7, 8]. The latter notion suggests that the primary focus should be on regional changes rather than on whole brain changes, when investigating whether exercise-induced changes in brain matter are appropriate for reducing symptoms and/or mediating disease or aging processes.

When trying to understand the effects of different exercise modalities, a common approach is to investigate resistance and aerobic training as these modalities constitute the two extremes of physical exercise. Yet, the combination of resistance and aerobic training (termed concurrent training) has also been investigated. To expand our understanding of the effects of different exercise modalities on whole and regional brain volumes, a literature review summarizing exercise interventions that include resistance, aerobic and concurrent training in individuals at risk of neurodegeneration seem warranted. While a number of reviews investigating the effects of exercise on brain morphology already exist [22–26], most of them appear to have interpreted their findings narratively (i.e., often positively skewed) and rarely summarized their findings quantitatively. The former is a common challenge when interpreting systematic reviews [27]. One exception is the systematic review and meta-analysis by Firth and colleagues focusing on the effects of controlled aerobic exercise interventions on hippocampus volume, reporting an increase in left hippocampus yet not in right and total hippocampus [23]. Another example is the broad scoping review by Batouli and Saba [22] enrolling both observational and interventional results, compromising the external validity and limiting conclusions on causal relationships between exercise and preservation of brain volume. Nonetheless, Batouli and colleagues concluded that at least 80% of grey matter is modifiable by physical activity. While this statement is intriguing—thus supporting physical exercise as being highly potent in terms of eliciting positive changes in grey matter brain volume—the substantial number of included cross-sectional studies limit conclusions in relation to exercise interventions [28]. This adds justification to a review that only enroll interventional studies with well-described interventions. Thus, the scope of the present review is to quantitatively summarize evidence from randomized controlled trials evaluating the effects of moderate-to-high intensity resistance training, aerobic training or concurrent training on whole and regional brain grey matter in adult populations known to undergo neurodegeneration.

2 Methods

2.1 Literature Sources and Search Strategy

The present review was carried out in accordance with the PRISMA guidelines. Literature searches were performed in PubMed (search strategy: ((”Exercise”[Mesh]) AND”Brain”[Mesh]) AND “Magnetic Resonance Imaging”Mesh]) and Embase (search strategy: 'exercise'/exp AND 'brain'/exp AND 'nuclear magnetic resonance imaging'/exp AND ([article]/lim OR [article in press]/lim) AND [english]/lim AND [embase]/lim). The search was performed primo April 2020.

2.2 Inclusion Criteria

The criteria for inclusion in the present review were the following: (1) studies had to be randomized controlled studies, (2) one of the intervention arms had to consist of

moderate-to-high intensity aerobic training, resistance training or a combination of the two (i.e., concurrent training) (see below for specific definitions), (3) study participants had to be either healthy older people (mean age ≥ 65 years) or adult patients (mean age ≥ 18 years) having pathological conditions known to cause progressive neurodegeneration, (4) outcomes had to include grey whole and/or regional brain volumetric outcomes assessed pre- and post-intervention by magnetic resonance imaging, and (5) articles had to be written in English. LGH and DLH screened and extracted papers.

Aerobic training was defined as activities aiming to increase cardiovascular fitness, with an intensity ultimately progressing to a minimum of 60% of heart rate max (HRmax) or reserve (HRreserve) (or if the equivalent was met by other intensity outcomes). Resistance training was defined as activities aiming to increase muscular strength (predominantly of the larger muscle groups), with an intensity ultimately progressing to a minimum of 12 repetition maximum (i.e., an external loading/resistance that can be moved no more than 12 times by use of voluntary force exertion, corresponding to ≥ 70% of 1RM).

2.3 Quality Assessment

The quality of the studies was assessed using the TESTEX rating scale (Table 2), an assessment tool specific for exercise studies that addresses both methodological and reporting criteria [29]. The scale includes 12 criteria with some criteria given more than one possible point, allowing a maximum score of 15 points (5 points for study quality, 10 points for study reporting; higher scores are better). As there are presently no validated cutoff score for the TESTEX rating scale [29], the median score across all studies were used to categorize studies as either high quality (TESTEX score at or above median) or as low-to-moderate quality (TESTEX score below median). LGH and DLH performed the TESTEX scoring, with UD being consulted in cases with disagreement.

2.4 Data Extraction and Analysis

The following data were extracted from the identified studies; training modality (including session type), session duration, intended training frequency, number of participants, population group, intervention duration, along with grey matter volume method and between-group (time × group) outcomes. The extracted data were sectionalized by the between-group change in whole and/or regional brain volume. Random effects meta-analyses comprising data on whole brain grey volume and hippocampus—the two most examined outcomes—were conducted using *Meta-Essentials version 1.5* designed for Excel [30] (Fig. 2a–f). Intervention effect sizes (ES) (between-group differences) for whole/regional brain grey matter volumes at post-treatment (mean of right and left regional volumes) were calculated using Hedges' g statistic, along with 95% confidence intervals (CIs) around the estimated effect-size. Of note, two studies [20, 21] did not provide sufficient information to establish ES for their respective outcomes. ES were interpreted according to Cohen's proposed guidelines as follows: small = 0.2, medium = 0.5, and large = 0.8 [23, 31]. Statistical heterogeneity was quantified using Higgins' I^2 statistic, and was interpreted as follows: heterogeneity: > 50%, no or limited heterogeneity: < 50% [23]. In addition, ES was calculated and presented for all whole/regional brain grey matter outcome measures, not just whole brain grey volume and hippocampus despite the numerous number of studies examining these two specific outcomes. These ES were furthermore used to create a 'brain map' visualizing brain regions being examined in the identified exercise studies (Fig. 3). If ≥ 2 studies were examined for a specific brain region, the *Meta-Essentials version 1.5* designed for Excel were used to calculate weighted ES (corresponding to random effects meta-analyses, as performed for whole brain grey volume and hippocampus). ES are displayed according to color coding ranging from ES = − 0.4 (red) to ES = 0.4 (blue). The different brain regions were segmented as a 2D atlas using the statistical software R (package: *ggseg*) [32], and were colored according to the ES (see Table 3).

3 Results

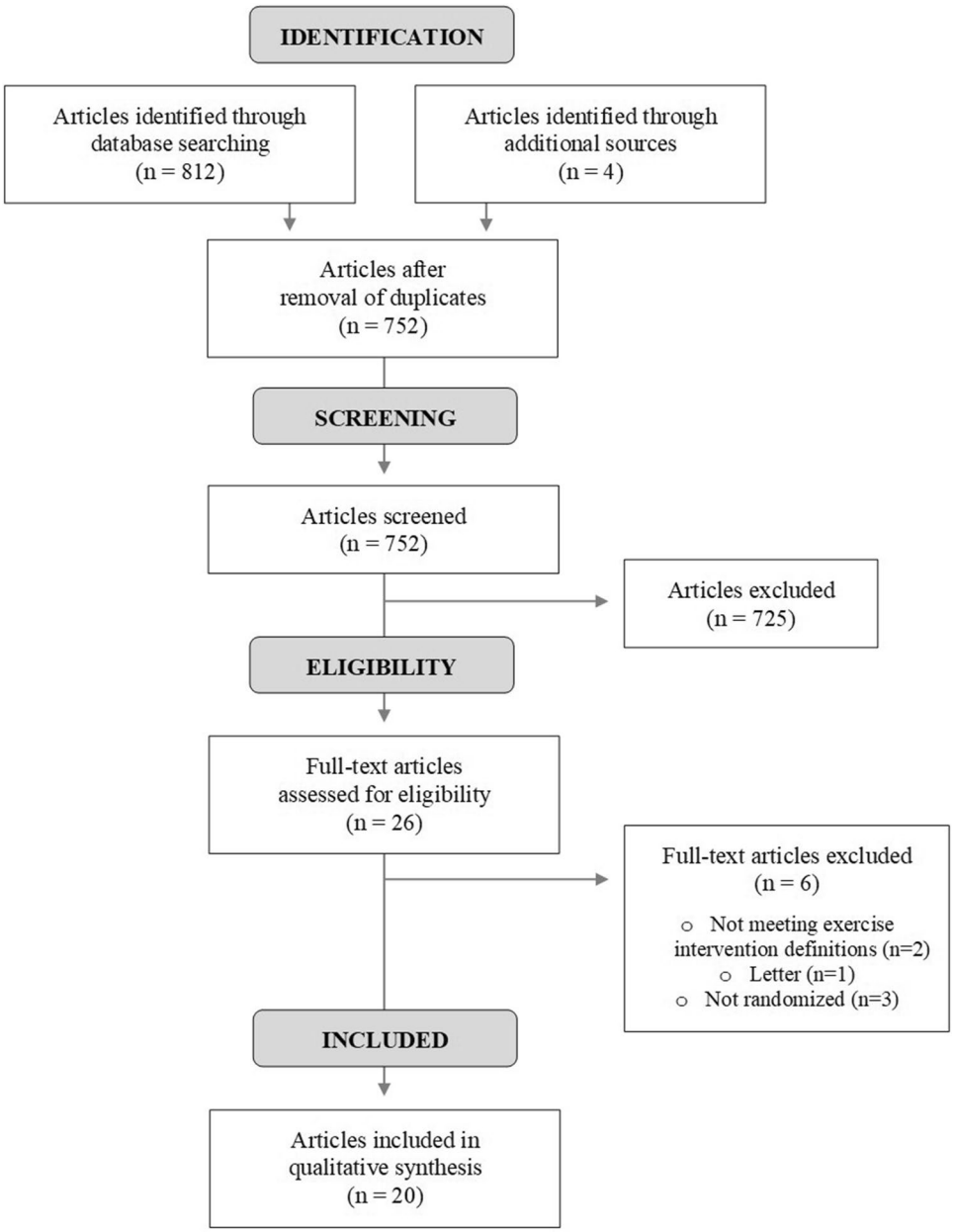
3.1 Literature Search

A total of 812 articles were found through searches performed in Embase and Pubmed databases, along with 4 articles found in references of the identified database articles. After removal of duplicates, articles were screened by title and abstract leaving 26 articles where full-texts were closely read. Of these, 6 articles were excluded leaving 20 articles (from 19 RCTs) fulfilling the inclusion criteria (Fig. 1).

3.2 Study Characteristics

The extracted data are presented in Table 1, grouped according to training modality and populations, and subsequently listed in alphabetical order. These 20 articles evaluating 3–12 months of aerobic training ($N = 14$ studies), resistance training ($N = 4$ studies), aerobic training and resistance training separately ($n = 1$ study), or concurrent training ($N = 1$ study), involved a total of 1662 participants. Number of study participants ranged from $n = 24$ to $n = 322$. Populations associated with neurodegeneration included healthy older adults ($N = 10$ studies), older

Fig. 1 Study flowchart



adults with mild cognitive impairment ($N = 3$ studies), schizophrenia ($N = 2$ studies), multiple sclerosis ($N = 3$ studies), older adults with Alzheimer's disease ($N = 1$ studies), and major depression ($N = 1$ studies).

Based on the median TESTEX score = 10 (range 5–14) (Table 2), 11 out of 20 studies were categorized as high-quality studies (i.e., with TESTEX scores being 10 or higher). The TESTEX criteria items with the lowest scores were Item 2 ("randomization" 9/20 possible points), Item 7 ("intention-to-treat analyses" 9/20 possible points), and Item 10 ("activity monitoring in control" 2/20 possible points).

3.3 Effects on Grey Matter Brain Volume

3.3.1 Whole Brain Grey Volume

See Table 3 for an overview of study findings. Aerobic training was reported to increase whole brain grey matter volume in older healthy adults ($n = 59$, 3 sessions/week, 24 weeks, ES not computable [19]), yet not in patients with schizophrenia ($n = 24$, 3 sessions/week, 24 weeks, ES = 0.27 [33]), multiple sclerosis (n = 42, 3 sessions/week, 12 weeks, ES = 0.16 [34]; $n = 86$, 2 sessions/week, 24 weeks, ES = − 0.04 [35]), or Alzheimer's disease ($n = 76$, 3–5 sessions/week,

Table 1 Summary of studies evaluating MRI outcomes following exercise interventions

Study	Participants Population Numbers (m/f %) Age in years (range)	Intervention	Type of AT or RT Session duration (min) Intensity Frequency (sessions/week) Duration (months)	MRI primary outcome[A] (yes/no/not mentioned) Intervention elicited physiological adaptations[B] (yes/no/not mentioned)	Grey matter volume outcome(s) (group × time interaction)
Colcombe et al. [19][a]	Healthy older $n = 59$ (45/55%) Age: 66.2 (60–79)	1. AT 2. Stretching	AT: not specified (session type: unknown) Session duration: 60 min Intensity: 40 → 70% HR_{res} Frequency: 3 sessions/week Duration: 6 months	Primary outcome: not mentioned Physiological adaptations: yes	Method: automated voxel-based morphometric (point-by-point) Whole brain[C] Supplementary motor area[C] Middle frontal gyrus bilaterally[C] Dorsolateral region of the right inferior frontal gyrus[C] Posterior aspect of the middle frontal gyrus[C] Dorsal anterior cingulate cortex[C] Dorsal aspect of the left superior temporal lobe[C]
Erickson et al. [20]	Healthy older $n = 120$ (33/67%) Age: 66.6 ± 5.6	1. AT 2. Stretching	AT: walking (session type: unknown) Session duration: 10 → 40 min Intensity: 50 → 75% HR_{res} Frequency: 3 sessions/week Duration: 12 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('FMRIB' tool) Hippocampus[C] Caudate nucleus Thalamus
Jonasson et al. [41]	Healthy older $n = 60$ (44/56%) Age: 68.7 ± 2.7 (64–78)	1. AT 2. Stretching	AT: walking, cycling, cross-trainer (session type: unknown) Session duration: 30 → 60 min Intensity: 40 → 80% HR_{max} Frequency: 3 sessions/week Duration: 6 months	Primary outcome: not mentioned Physiological adaptations: yes	Method: manual ('Freesurfer') Hippocampus Dorsolateral prefrontal cortex Ventrolateral prefrontal cortex Anterior cingulate cortex
Kleemeyer et al. [40]	Healthy older $n = 52$ (38/62%) Age: 66 ± 4.4 (59–74)	1. AT high intensity 2. AT low intensity	AT: cycling in both high and low (session type: group) Session duration: 30 → 60 min Intensity: 80% HR_{at} (+ anaerobic sprints in AT high) Frequency: 2 → 3 sessions/week Duration: 6 months	Primary outcome: not mentioned Physiological adaptations: no	Method: automated ('Freesurfer') Hippocampus
Maass et al. [39]	Healthy older $n = 40$ (45/55%) Age: 68.4 ± 4.3 (60–77)	1. AT 2. Stretching	AT: walking (session type: unknown) Session duration: 40 min Intensity: 65 → 80% HR_{max} Frequency: 3 sessions/week Duration: 3 months	Primary outcome: not mentioned Physiological adaptations: yes	Method: manual ('MRIcron') Hippocampus

Table 1 (continued)

Study	Participants Population Numbers (m/f %) Age in years (range)	Intervention	Type of AT or RT Session duration (min) Intensity Frequency (sessions/week) Duration (months)	MRI primary outcome[A] (yes/no/not mentioned) Intervention elicited physiological adaptations[B] (yes/no/not mentioned)	Grey matter volume outcome(s) (group × time interaction)
Nagamatsu et al. [49]	Healthy older $n = 101$ (31.7/68.3%) Age: 66.4 ± 5.8	1. AT 2. Balance	AT: walking (session type: group) Session duration: 60 min Intensity: 40 → 80% HR_{res} Frequency: 3 sessions/week Duration: 12 months	Primary outcome: no Physiological adaptations: not mentioned	Method: automated ('FIRST') Caudate nucleus Left putamen[C]/right putamen Pallidum
Niemann et al. [42] Niemann et al. 2014b [48]	Healthy older $n = 92$ (30/70%) Age: 68.5 ± 3.6 (62–79)	1. AT 2. Coordination 3. Active control	AT: nordic walking (session type: group) Session duration: 45–60 min Intensity: not specified, yet around HR_{at} Frequency: 3 sessions/week Duration: 12 months	Primary outcome: not mentioned Physiological adaptations: yes	Method: manual ('Analyze 10.0') Hippocampus Caudate nucleus Putamen Pallidum
Tarumi et al. [44][b]	MCI (amnestic) $n = 70$ (39/61%) Age: 64.7 ± 6.3 (55–80)	1. AT 2. Stretching and toning	AT: walking (session type: unknown) Session duration: 25–40 min Intensity: 75 → 90% HR_{max} Frequency: 3–5 sessions/week Duration: 12 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('Freesurfer') Hippocampus
Ten Brinke et al. [43]	MCI $n = 86$ (0/100%) Age: (70–80)	1. AT 2. RT 3. Balance and toning	AT: walking (session type: unknown) Session duration: 60 min Intensity: 40 → 80% HR_{res} Frequency: 2 sessions/week Duration: 6 months RT: machines, free-weights Exercises: 10 (major muscle groups) Session duration: 60 min Intensity: 2 sets, 6–8 reps at 7RM Frequency: 2 sessions/week Duration: 6 months	Primary outcome: no Physiological adaptations: not mentioned	Method: manual ('FIRST') Hippocampus[C] (AT) Hippocampus (RT)
Pajonk et al. [33]	Schizophrenia $n = 24$ (100/0%) Age: 35.2 ± 9.4	1. AT 2. Table football	AT: cycling (session type: unknown) Session duration: 30 min Intensity: 75% HR_{at} Frequency: 3 sessions/week Duration: 3 months	Primary outcome: no Physiological adaptations: no	Method: manual ('Analyze 10.0' and 'SPM99') Whole brain Hippocampus[C]

Table 1 (continued)

Study	Participants Population Numbers (m/f %) Age in years (range)	Intervention	Type of AT or RT Session duration (min) Intensity Frequency (sessions/week) Duration (months)	MRI primary outcome[A] (yes/no/not mentioned) Intervention elicited physiological adaptations[B] (yes/no/not mentioned)	Grey matter volume outcome(s) (group × time interaction)
Feys et al. [34][c]	Multiple Sclerosis $n = 42$ (10/90%) Age: 40.5 ± 8.5	1. AT 2. Waitlist control	AT: walking → running (session type: group + individual) Session duration: 60 → 30 min Intensity: not specified Frequency: 3 sessions/week Duration: 3 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('FMRIB' tool) Whole brain Hippocampus Caudate nucleus Putamen Left pallidum[C]/right Pallidum Thalamus
Langeskov-Christensen et al. [35]	Multiple sclerosis $n = 86$ (40/60%) Age: 44.8 ± 9.4 (18–65)	1. AT 2. Waitlist control	AT: cycling, rowing, cross-trainer (session type: group + individual) Session duration: 30 → 60 min Intensity: 65 → 95% HR_{max} Frequency: 2 sessions/week Duration: 6 months	Primary outcome: yes Physiological adaptations: yes	Method: automated ('FMRIB' tool) Whole brain Hippocampus Caudate nucleus Putamen Pallidum Thalamus
Krogh et al. [45]	Major depression $n = 79$ (33/67%) Age: 41.3 ± 12.1	1. AT 2. Stretching	AT: cycling (session type: unknown) Session duration: 45 min Intensity: 80% HR_{res} Frequency: 3 sessions/week Duration: 3 months	Primary outcome: no Physiological adaptations: yes	Method: manual (MATLAB's 'RIP') Hippocampus
Morris et al. [36]	Alzheimer's disease $n = 76$ (49/51%) Age: 72.9 ± 7.7	1. AT 2. Stretching	AT: not specified (session type: unknown) Session duration: 45 min (150 min/week) Intensity: 40 → 75% HR_{res} Frequency: 3–5 sessions/week Duration: 6 months	Primary outcome: no Physiological adaptations: no	Method: manual (MATLAB's 'VBM8 toolbox') Whole brain Hippocampus

Table 1 (continued)

Study	Participants Population Numbers (m/f %) Age in years (range)	Intervention	Type of AT or RT Session duration (min) Intensity Frequency (sessions/week) Duration (months)	MRI primary outcome[A] (yes/no/not mentioned) Intervention elicited physiological adaptations[B] (yes/no/not mentioned)	Grey matter volume outcome(s) (group × time interaction)
Best et al. [37]	Healthy older $n = 155$ (0/100%) Age: 69.6 ± 3.9	1. RT 1 × weekly 2. RT 2 × weekly 3. Balance	RT: machines, free-weights, whole-body (session type: unknown) Exercises: 3 and more (unspecified) (major muscle groups) Session duration: 60 min Intensity: 2 sets, 6–8 reps at 7RM Frequency: 1 or 2 sessions/week Duration: 12 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('FIRST') Whole brain Hippocampus
Gylling et al. [46]	Healthy/chronically diseased older $n = 322$ (39/61%) Age: 66.0 ± 2.5	1. RT high intensity 2. Habitual physical activity	RT: machines, free-weights (session type: group) Exercises: 9 (major muscle groups) Session duration: not specified Intensity: 3 sets, 6–12 reps at 7–12RM Frequency: 3 sessions/week Duration: 12 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('Freesurfer') Hippocampus
Suo et al. [47]	MCI $n = 100$ (32/68%) Age: 70.1 ± 6.7 (55–87)	1. RT + CCT 2. RT + SHAM CTT 3. CCT + SHAM RT 4. SHAM RT + SHAM CCT	RT: machines (session type: unknown) Exercises: 5–6 (major muscle groups) Session duration: not specified Intensity: 3 sets, 8 reps Frequency: 3 sessions/week Duration: 6 months	Primary outcome: no Physiological adaptations: not mentioned	Method: automated ('FMRIB' tool) Hippocampus Posterior cingulate cortex[C]
Kjolhede et al. [21][d]	Multiple Sclerosis $n = 35$ (77/23%) Age: 43.2 ± 8.1	1. RT 2. Waitlist control	RT: machines (session type: unknown) Exercises: 6 (major muscle groups) Session duration: not specified Intensity: 3–5 sets, 6–12 reps at 6–15RM Frequency: 2 sessions/week Duration: 6 months	Primary outcome: no Physiological adaptations: yes	Method: manual ('Analyze 10.0' and 'FMRIB' tool) Whole brain Anterior cingulate gyrus[C] Temporal pole[C] Orbital sulcus[C] Inferior temporal Sulcus[C]

Table 1 (continued)

Study	Participants Population Numbers (m/f %) Age in years (range)	Intervention	Type of AT or RT Session duration (min) Intensity Frequency (sessions/week) Duration (months)	MRI primary outcome[A] (yes/no/not mentioned) Intervention elicited physiological adaptations[B] (yes/no/not mentioned)	Grey matter volume outcome(s) (group × time interaction)
Scheewe et al. [38]	Schizophrenia $n = 63$ (81/19%) Age: 29.6 ± 7.6	1. CT 2. Occupational therapy	AT: cycling, rowing, cross-trainer, walking/running (session type: unknown) Session duration: 40 min Intensity: 45 → 75% HR_{res} Frequency: 2 sessions/week Duration: 6 months RT: machines Exercises: 6 (major muscle groups) Session duration: 20 min Intensity: 3 sets, 10–15 reps at 10–15RM Frequency: 2 sessions/week Duration: 6 months	Primary outcome: no Physiological adaptations: yes	Method: automated ('FMRIB' tool) Whole brain Hippocampus

AT aerobic training, *RT* resistance training, *CT* concurrent training, *CCT* computerized cognitive training

[A]Study designed to examine MRI as primary outcome (i.e., by use of power calculation)

[B]Comprise physiological adaptations, i.e., in muscle strength (with RT) or aerobic capacity (with AT)

[C]Significant between-group change (i.e., group × time interaction). a: examined all brain regions, yet presenting positive findings only. b: presenting significant between-group changes in hippocampus in amyloid-positive MCI participants. c: also examined amygdala and accumbens presenting no changes with exercise. d: examined 74 brain regions, yet presenting positive findings only (4 regions)

Table 2 TESTEX study quality assessment

Study		Study quality						Study reporting								Total
		1	2	3	4	5	Sub-total	6	7	8	9	10	11	12	Sub-total	
Aerobic training																
Colcombe et al. [19]	(O)	1	0	0	0	1	2	2	0	1	0	0	1	1	5	7
Erickson et al. [20]	(O)	1	0	1	1	0	3	1	0	1	1	0	1	1	5	8
Jonasson et al. [41]	(O)	1	0	1	1	0	3	3	0	1	1	0	1	1	7	10
Kleemeyer et al. [40]	(O)	1	0	0	1	0	2	3	0	1	1	0	1	1	7	9
Maass et al. [39]	(O)	1	0	1	0	0	2	2	1	1	1	1	1	1	8	10
Nagamatsu et al. [49]	(O)	1	0	0	0	1	2	0	0	2	1	0	1	1	5	7
Niemann et al. [42]	(O)	1	0	0	0	1	2	0	0	1	1	0	1	1	4	6
Niemann et al. [48]	(O)	1	0	0	0	0	1	0	0	1	1	0	1	1	4	5
Tamuri et al. [44]	(MCI)	1	1	1	1	1	5	1	1	2	1	0	1	1	7	12
Ten Brinke et al. [43]	(MCI)	1	1	1	1	1	5	2	1	2	1	0	1	1	8	13
Pajonk et al. [33]	(Sch)	1	0	1	1	1	4	2	0	1	1	0	0	1	5	9
Feys et al. [34]	(MS)	1	0	1	0	0	2	2	1	2	1	0	1	0	7	9
Langeskov-Christensen et al. [35]	(MS)	1	1	1	1	1	5	2	1	2	1	0	1	1	8	13
Krogh et al. [45]	(D)	1	1	1	1	1	5	1	1	1	1	0	1	1	6	11
Morris et al. [36]	(Alz)	1	1	1	1	1	5	3	0	2	1	0	1	1	8	13
Resistance training																
Best et al. [37]	(O)	1	1	1	1	1	5	3	1	2	1	0	1	1	9	14
Gylling et al. [46]	(O)	1	1	1	1	1	5	2	1	2	1	1	1	1	9	14
Suo et al. [47]	(MCI)	1	1	1	0	1	4	2	1	2	1	0	0	1	7	11
Ten Brinke et al. [43][a]	(MCI)	1	1	1	1	1	5	2	1	2	1	0	1	1	8	13
Kjolhede et al. [21]	(MS)	1	0	1	1	1	4	1	0	1	1	0	1	1	5	9
Concurrent training																
Scheewe et al. [38]	(Sch)	1	1	1	1	1	5	2	0	1	1	0	1	1	6	11
Total (across sub-scores)		20	9	15	13	14		34	9	29	19	2	18	19		Median = 10

Study quality: 1, eligibility criteria specified; 2, randomization specified; 3, allocation concealment; 4, groups similar at baseline; 5, blinding of assessors. Study reporting: 6, outcome measures assessed in 85% of patients; 7, intention-to-treat analysis; 8, between-group statistical comparisons reported; 9, point measures and measures of variability for all reported outcome measures; 10, activity monitoring in control group; 11, relative exercise intensity remained constant; 12, exercise volume and energy expenditure. The abbreviations shown in brackets denote the specific populations at risk of neurodegeneration (O: older healthy adults, MCI: older adults with mild cognitive impairment, Sch: adults with schizophrenia, MS: adults with multiple sclerosis, D: adults with depression, Alz: older adults with Alzheimer's disease).

[a]Same study as evaluated under aerobic training, yet here with resistance training as the exercise modality (the scoring under resistance training are not included in the total score)

26 weeks, ES = − 0.36 [36]). For resistance training, whole brain grey matter remained unaffected in older healthy adults (n = 155, 1–2 sessions/week, 52 weeks, ES = − 0.50 [37]) and in patients with multiple sclerosis (although a trend towards a preservative effect was reported) (n = 35, 2 sessions/week, 24 weeks, ES = 0.71 [21]). For concurrent training, whole brain grey matter remained unaffected in patients with Schizophrenia (n = 63, 2 sessions/week, 24 weeks, ES = − 0.13 [38]).

The meta-analyses showed no effects on whole brain grey volume following all exercise modalities (N = 7 studies, ES = − 0.07 [− 0.42:0.28], I^2 = 39%), aerobic training separately (N = 4 studies, ES = − 0.08 [− 0.43:0.27], I^2 = 0%) as well as resistance training separately (N = 2 studies, ES = 0.07 [− 7.58:7.71], I^2 = 87%) (Fig. 2a–c). Across all exercise modalities, low-to-moderate quality studies were in favor of exercise (N = 3 studies, ES = 0.39 [− 0.37:1.15], I^2 = 0%; ES not including Colcombe et al. 2006 that were also in favor of exercise), whereas high-quality studies were not (N = 4 studies, ES = − 0.26 [− 0.60:0.08], I^2 = 0%). Following all exercise modalities within the separate study populations, no effects on whole brain grey volume were observed in older healthy adults (N = 1 study, ES = − 0.50, mentioned above) or in patients with schizophrenia (N = 2 studies, ES = 0.01 [− 2.40:2.41], I^2 = 0%), multiple sclerosis (N = 3 studies, ES = 0.19 [− 0.73:1.12], I^2 = 33%), or Alzheimer's disease (N = 1 study, ES = − 0.36, mentioned above).

Table 3 Summary of study findings in whole/regional grey matter brain volume across different exercise modalities

Study		Whole brain grey volume	Deep grey structures					Frontal lobe							Cingulate cortex			Temporal lobe		
			Hippocampus	Caudate nucleus	Putamen	Globus pallidus/ pallidum	Thalamus	Supplementary motor area	Middle frontal gyrus bilaterally	Dorsolateral right inferior frontal gyrus	Posterior middle frontal gyrus	dlPFC	vlPFC	Orbital sulcus	Dorsal anterior cingulate cortex	ACC	PCC	Dorsal left superior temporal lobe	Temporal pole	Inferior temporal sulcus
Aerobic training																				
Colcombe et al. [19][a]	(O)	S (ES n.c.)						S (ES n.c.)	S (ES n.c.)	S (ES n.c.)	S (ES n.c.)				S (ES n.c.)			S (ES n.c.)		
Erickson et al. [20]	(O)		S (ES 0.26)	NS (ES 0.06)			NS (ES −0.07)													
Jonasson et al. [41]	(O)		NS (ES −0.31)									NS (ES −0.17)	NS (ES −0.33)			NS (ES 0.00)				
Kleemeyer et al. [40]	(O)		NS (ES −0.32)																	
Maass et al. [39]	(O)		NS (ES −0.03)																	
Nagamatsu et al. [49]	(O)			NS (ES 0.16)	S (ES 0.49)	NS (ES 0.07)														
Niemann et al. [42]	(O)			NS (ES −0.70)	NS (ES −0.32)	NS (ES −0.34)														
Niemann et al. [48]	(O)		NS (ES 0.26)																	
Tarumi et al. [44][b]	(MCI)		NS (ES 0.35)																	
Ten Brinke et al. [43]	(MCI)		S (ES 0.74)																	
Pajonk et al. [33]	(Sch)	NS (ES 0.27)	S (ES 0.24)																	
Feys et al. [34][c]	(MS)	NS (ES 0.16)	NS (ES −0.36)	NS (ES 0.13)	NS (ES −0.31)	S_L (ES −0.32)	NS (ES −0.30)													
Langeskov-Christensen et al. [35]	(MS)	NS (ES −0.04)	NS (ES 0.00)	NS (ES −0.28)	NS (ES −0.02)	NS (ES −0.09)	NS (ES −0.06)													

Table 3 (continued)

Study		Whole brain grey volume	Deep grey structures					Frontal lobe							Cingulate cortex			Temporal lobe		
			Hippocampus	Caudate nucleus	Putamen	Globus pallidus/ pallidum	Thalamus	Supplementary motor area	Middle frontal gyrus bilaterally	Dorsolateral right inferior frontal gyrus	Posterior middle frontal gyrus	dlPFC	vlPFC	Orbital sulcus	Dorsal anterior cingulate cortex	ACC	PCC	Dorsal left superior temporal lobe	Temporal pole	Inferior temporal sulcus
Krogh et al. [45]	(D)		NS (ES −0.08)																	
Morris et al. [36]	(Alz)	NS (ES −0.30)	NS (ES 0.25)																	
Resistance training																				
Best et al. [37]	(O)	NS (ES −0.50)	NS (ES 0.57)																	
Gylling et al. [46]	(O)		NS (ES −0.20)																	
Suo et al. [47]	(MCI)		NS (ES −0.31)														S (ES 0.40)			
Ten Brinke et al. [43][A]	(MCI)		NS (ES −0.32)																	
Kjolhede et al. [21][d]	(MS)	NS (ES 0.71)												S (ES n.c)		S (ES n.c)			S (ES n.c)	S (ES n.c)
Concurrent training																				
Scheewe et al. [38]	(Sch)	NS (ES −0.13)	NS (ES −0.09)																	
Significant/ total studies	1/8		3/17	0/5	1/4	1/4	0/3	1/1	1/1	1/1	1/1	0/1	0/1	1/1	1/1	1/2	1/1	1/1	1/1	1/1

The last row show the number of studies reporting significant between-group change in whole/regional grey matter brain volume across all exercise modalities, in relation to the total number of studies examining this. S: significant exercise-induced between-group change (i.e., group x time interaction), S_L: significant exercise-induced between-group change in left region only (but also examined and non-significant in the right region), NS: no significant exercise-induced between-group change. Effect sizes (Hedge's g) are shown in brackets, with the exception of the studies Colcombe et al. 2006 [19] and Kjolhede et al. 2018 [21] as effect sizes were not computable (n.c.) based on the available data. The abbreviations shown in brackets denote the specific populations at risk of neurodegeneration (O: older healthy adults, MCI: older adults with mild cognitive impairment, Sch: adults with schizophrenia, MS: adults with multiple sclerosis, D: adults with depression, Alz: older adults with Alzheimer's disease). dlPFC: dorsolateral prefrontal cortex, vlPFC: ventrolateral prefrontal cortex, ACC: anterior cingulate cortex, PCC: posterior cingulate cortex. a: Examined all brain regions, yet presenting positive findings only. b: Presenting significant between-group changes in hippocampus in amyloid-positive MCI participants. c: Also examined amygdala and accumbens presenting no changes with exercise. d: Examined 74 brain regions, yet presenting positive findings only (4 regions)

[A]Same study as evaluated under aerobic training, yet here with resistance training as the exercise modality

3.3.2 Deep Grey Structures—Hippocampus

Aerobic training was reported to increase the hippocampus in one study involving older healthy adults ($n = 120$, 3 sessions/week, 52 weeks, ES = 0.26 [20]), while it remained unaffected in four other studies ($n = 40$, 3 sessions/week, 12 weeks, ES = − 0.03 [39]; $n = 52$, 2 sessions/week, 26 weeks, ES = − 0.32 [40]; $n = 60$, 3 sessions/week, 26 weeks, ES = − 0.31 [41]; $n = 92$, 3 sessions/week, 52 week, ES = 0.26 [42]). In older adults with mild cognitive impairment, one study reported aerobic training to have a preservative effect on the hippocampus ($n = 86$, 2 sessions/week, 26 weeks, ES = 0.74 [43]) while it had no effect in another study ($n = 70$, 3–5 sessions/week, 52 weeks, ES = 0.35 [44]). Aerobic training was reported to increase the hippocampus in one study involving patients with schizophrenia ($n = 24$, 3 sessions/week, 12 weeks, ES = 0.24 [33]), while it remained unaffected in patients with multiple sclerosis ($n = 42$, 3 sessions/week, 12 weeks, ES = − 0.36 [34]; $n = 86$, 2 sessions/week, 24 weeks, ES = 0.00 [35]), major depression ($n = 79$, 3 sessions/week, 12 weeks, ES = − 0.08 [45]), and Alzheimer's disease ($n = 76$, 150 min/week, 26 weeks, ES = 0.25 [36]). For resistance training, the hippocampus remained unaffected in older healthy adults ($n = 155$, 1–2 sessions/week, 52 weeks, ES = 0.57 [37]; $n = 332$, 3 sessions/week, 52 weeks, ES = − 0.20 [46]) and in older adults with mild cognitive impairment ($n = 100$, 3 sessions/week, 26 weeks, ES = − 0.31 [47]; $n = 86$, 2 sessions/week, 26 weeks, ES = − 0.32 [43]). For concurrent training, the hippocampus also remained unaffected in patients with schizophrenia ($n = 63$, 2 sessions/week, 26 weeks, ES = − 0.09 [38]).

The meta-analyses showed no effects on hippocampus volume following all exercise modalities ($N = 17$ studies, ES = 0.10 [− 0.16:0.36], $I^2 = 61\%$) and aerobic training separately ($N = 12$ studies, ES = 0.06 [− 0.12:0.23], $I^2 = 2\%$), yet a small non-significant effect following resistance training ($N = 4$ studies, ES = 0.39 [− 1.27:2.05], $I^2 = 90\%$) (Fig. 2d–f). Across all exercise modalities, neither low-to-moderate quality studies ($N = 5$, ES = 0.04 [− 0.35:0.43, $I^2 = 70\%$] nor high-quality studies appeared to be in favor of exercise (N = 12, ES = 0.14 [− 0.22:0.51], $I^2 = 0\%$). Following all exercise modalities within the separate study populations, no effects on hippocampus were observed in older healthy adults ($N = 9$ studies, ES = − 0.09 [− 0.30:0.12], $I^2 = 13\%$), in older adults with mild cognitive impairment ($N = 4$ studies, ES = 0.81 [− 0.56:2.19], $I^2 = 79\%$), or in patients with schizophrenia ($N = 2$ studies, ES = 0.02 [− 1.97:2.02], $I^2 = 0\%$), multiple sclerosis ($N = 2$ studies, ES = − 0.09 [− 2.10:1.92], $I^2 = 0\%$), or Alzheimer's disease ($N = 1$ study, ES = 0.25, mentioned above).

3.3.3 Deep Grey Structures—Other Regions

In older adults, three studies reported aerobic training to have no effect on the caudate nucleus ($n = 92$, 3 sessions/week, 52 weeks, ES = − 0.70 [48]; $n = 120$, 3 sessions/week, 52 weeks, ES = 0.06 [20]; n = 101, 3 sessions/week, 52 weeks, ES = 0.16 [49], one study reported aerobic training to superiorly preserve the left putamen ($n = 101$, 3 sessions/week, 52 weeks, ES = 0.49) [49] while another did not ($n = 92$, 3 sessions/week, 52 weeks, ES = − 0.32) [48], two studies found no effect on the pallidum ($n = 101$, 3 sessions/week, 52 weeks, ES = 0.07 [49]; $n = 92$, 3 sessions/week, 52 weeks, ES = − 0.34 [48]), and one study found no effect on the thalamus ($n = 120$, 3 sessions/week, 52 weeks, ES = − 0.07) [20]. In persons with multiple sclerosis, one study reported aerobic training to increase the left pallidum volume yet without effect on the right pallidum, caudate nucleus, putamen, or thalamus ($n = 42$, 3 sessions/week, 12 weeks, overall ES ≈ − 0.20) [34], and another found no effect on the caudate nucleus, putamen, pallidum, or thalamus $n = 86$, 2 sessions/week, 24 weeks, ES = 0.00 [35]).

3.3.4 Frontal Lobe

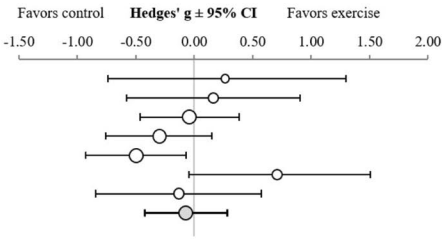
In older adults, one study reported aerobic training to increase the supplementary motor area, middle frontal gyrus bilaterally, dorsolateral region of the right inferior frontal gyrus, and the posterior aspect of the middle frontal gyrus ($n = 59$, 3 sessions/week, 26 weeks, ES not computable) [19], while another study found no effect on the dorso- and ventrolateral prefrontal cortex ($n = 60$, 3 sessions/week, 26 weeks, overall ES ≈ − 0.25) [41]. In persons with multiple sclerosis, resistance training was reported to preserve the orbital sulcus ($n = 35$, 2 sessions/week, 26 weeks, ES not computable) [21].

3.3.5 Cingulate Cortex

In older adults, one study reported aerobic training to increase the posterior cingulate ($n = 59$, 3 sessions/week, 26 weeks, ES not computable) [19] and one study showed no effect on the anterior cingulate ($n = 60$, 3 sessions/week, 26 weeks, ES = 0.00) [41]. In persons with multiple sclerosis, one study reported resistance training to preserve the anterior cingulate gyrus ($n = 35$, 2 sessions/week, 26 weeks, ES not computable) [21]. In older adults with mild cognitive impairment, one study reported resistance training to preserve the posterior cingulate ($n = 100$, 3 sessions/week, 26 weeks, ES = 0.40) [47].

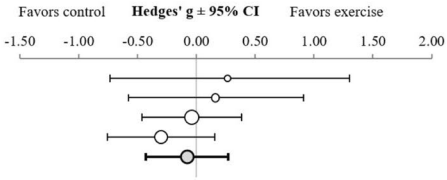
a Aerobic + Resistance + Concurrent training — Whole brain greay matter

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Aerobic	1	Pajonk et al. 2010 (Sch) [33]	0.27	-0.74	1.30	7.2%
	2	Feys et al. 2017 (MS) [34]	0.16	-0.58	0.91	11.0%
	3	Langeskov-Christensen et al. 2020 (MS) [35]	-0.04	-0.47	0.38	20.4%
	4	Morris et al. 2017 (Alz) [36]	-0.30	-0.76	0.15	19.2%
Resistance	5	Best et al. 2015 (O) [37]	-0.50	-0.93	-0.07	20.3%
	6	Kjolhede et al. 2018 (MS) [21]	0.71	-0.04	1.51	10.3%
Concurrent	7	Scheewe et al. 2013 (Sch) [38]	-0.13	-0.84	0.58	11.6%
		All	**-0.07**	**-0.42**	**0.28**	



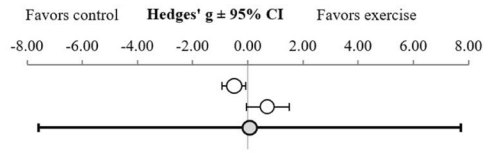
b Aerobic training — Whole brain grey matter

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Aerobic	1	Pajonk et al. 2010 (Sch) [33]	0.27	-0.74	1.30	8.3%
	2	Feys et al. 2017 (MS) [34]	0.16	-0.58	0.91	14.4%
	3	Langeskov-Christensen et al. 2020 (MS) [35]	-0.04	-0.47	0.38	41.2%
	4	Morris et al. 2017 (Alz) [36]	-0.30	-0.76	0.15	36.1%
		All	**-0.08**	**-0.43**	**0.27**	



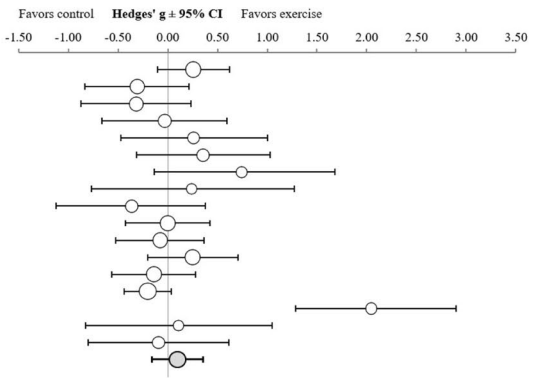
c Resistance training — Whole brain grey matter

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Resistance	1	Best et al. 2015 (O) [37]	-0.50	-0.93	-0.07	53.3%
	2	Kjolhede et al. 2018 (MS) [21]	0.71	-0.04	1.51	46.7%
		All	**0.07**	**-7.58**	**7.71**	



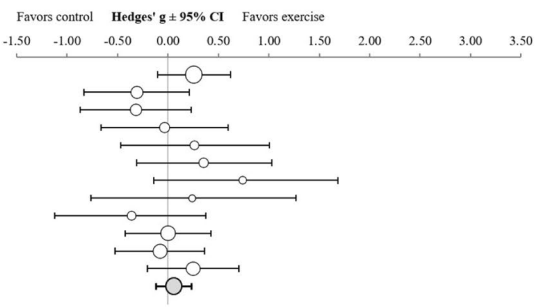
d Aerobic + Resistance + Concurrent training — Hippocampus

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Aerobic	1	Erickson et al. 2011 (O) [20]	0.26	-0.10	0.62	8.1%
	2	Jonasson et al. 2017 (O) [41]	-0.31	-0.83	0.21	6.5%
	3	Kleemeyer et al. 2016 (O) [40]	-0.32	-0.87	0.23	6.2%
	4	Maass et al. 2015 (O) [39]	-0.03	-0.66	0.60	5.6%
	5	Niemann et al. 2014a (O) [42]	0.26	-0.47	1.01	4.8%
	6	Tamuri et al. 2019 (MCI) [44]	0.35	-0.31	1.03	5.2%
	7	Ten Brinke et al. 2015 (MCI) [43]	0.74	-0.14	1.68	3.8%
	8	Pajonk et al. 2010 (Sch) [33]	0.24	-0.77	1.27	3.4%
	9	Feys et al. 2017 (MS) [34]	-0.36	-1.12	0.37	4.7%
	10	Langeskov-Christensen et al. 2020 (MS) [35]	0.00	-0.43	0.43	7.5%
	11	Krogh et al. 2014 (D) [45]	-0.08	-0.52	0.37	7.3%
	12	Morris et al. 2017 (Alz) [36]	0.25	-0.20	0.71	7.1%
Resistance	13	Best et al. 2015 (O) [37]	-0.14	-0.56	0.28	7.5%
	14	Gylling et al. 2020 (O) [46]	-0.20	-0.44	0.03	9.4%
	15	Suo et al. 2016 (MCI) [47]	2.05	1.28	2.90	4.3%
	16	Ten brinke et al. 2015 (MCI) [43]	0.11	-0.82	1.05	3.7%
Concurrent	17	Scheewe et al. 2013 (Sch) [38]	-0.09	-0.80	0.62	5.0%
		All	**0.10**	**-0.16**	**0.36**	



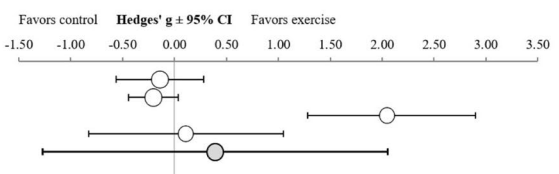
e Aerobic training — Hippocampus

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Aerobic	1	Erickson et al. 2011 (O) [20]	0.26	-0.10	0.62	18.0%
	2	Jonasson et al. 2017 (O) [41]	-0.31	-0.83	0.21	9.0%
	3	Kleemeyer et al. 2016 (O) [40]	-0.32	-0.87	0.23	8.1%
	4	Maass et al. 2015 (O) [39]	-0.03	-0.66	0.60	6.4%
	5	Niemann et al. 2014a (O) [42]	0.26	-0.47	1.01	4.8%
	6	Tamuri et al. 2019 (MCI) [44]	0.35	-0.31	1.03	5.7%
	7	Ten Brinke et al. 2015 (MCI) [43]	0.74	-0.14	1.68	3.3%
	8	Pajonk et al. 2010 (Sch) [33]	0.24	-0.77	1.27	2.8%
	9	Feys et al. 2017 (MS) [34]	-0.36	-1.12	0.37	4.7%
	10	Langeskov-Christensen et al. 2020 (MS) [35]	0.00	-0.43	0.43	13.3%
	11	Krogh et al. 2014 (D) [45]	-0.08	-0.52	0.37	12.2%
	12	Morris et al. 2017 (Alz) [36]	0.25	-0.20	0.71	11.7%
		All	**0.06**	**-0.12**	**0.23**	



f Resistance training — Hippocampus

		Study name	Hedges' g	CI Lower limit	CI Upper limit	Weight
Resistance	1	Best et al. 2015 (O) [37]	-0.14	-0.56	0.28	27.2%
	2	Gylling et al. 2020 (O) [46]	-0.20	-0.44	0.03	28.7%
	3	Suo et al. 2016 (MCI) [47]	2.05	1.28	2.90	22.7%
	4	Ten brinke et al. 2015 (MCI) [43]	0.11	-0.82	1.05	21.4%
		All	**0.39**	**-1.27**	**2.05**	



◂**Fig. 2** Effects of effects of exercise on whole and regional brain grey matter, displayed as forest plots. **a** Effects of aerobic, resistance, and concurrent training on whole brain grey matter; $I^2 = 39\%$. **b** Effects of aerobic training on whole brain grey matter; $I^2 = 0\%$. **c** Effects of resistance training on whole brain grey matter; $I^2 = 87\%$. **d** Effects of aerobic, resistance, and concurrent training on hippocampus; $I^2 = 61\%$. **e** Effects of aerobic training on hippocampus; $I^2 = 2\%$. **f** Effects of resistance training on hippocampus; $I^2 = 90\%$. The abbreviations shown in brackets denote the specific populations at risk of neurodegeneration (*O* older healthy adults, MCI: older adults with mild cognitive impairment, *Sch* adults with schizophrenia, MS: adults with multiple sclerosis, *D* adults with depression, *Alz* older adults with Alzheimer's disease)

3.3.6 Temporal Lobe

In older adults, one study reported aerobic training to increase the volume of the dorsal aspect of the left superior temporal lobe ($n = 59$, 3 sessions/week, 26 weeks, ES not computable) [19]. In patients with multiple sclerosis, resistance training was found to preserve the temporal pole and the inferior temporal sulcus ($n = 35$, 2 sessions/week, 26 weeks, ES not computable) [21].

4 Discussion

The present study quantitatively summarizes and critically reviews the effects of structured physical activity (i.e., progressive moderate-to-high intensity aerobic, resistance, or concurrent training) on brain grey matter volume in individuals at risk of neurodegeneration, based solely on data from randomized controlled trials. The identified studies (19 RCTs, 20 articles, $n = 1662$ participants) were generally heterogeneous, particularly in relation to the six different populations and to the diverging exercise programs. Only few of these studies report findings supporting that exercise has the potential to preserve and/or expand brain volumes, and markedly less pronounced than what was concluded in a previous review enrolling both interventional and cross-sectional data [22]. Specifically, only 1 of 8 studies (approximately 13%) elicited positive effects on whole brain grey matter volume and only 3 of 14 studies (approximately 18%) found effects on hippocampus. Moreover, our random effects meta-analyses showed that the different exercise modalities (combined or separately) failed to elicit any substantial effects on the two most commonly assessed outcomes: whole brain grey volume and hippocampus volume (Fig. 2a–f). In addition, the effect sizes do not support any substantial effects in any of the remaining regions (Table 3). In our 'brain maps' (Fig. 3), we have attempted to summarize/visualize the different aspects outlined above. Such information could be useful for the design of future studies.

While the initial interpretation of our study findings do not support that physical exercise elicit adaptations in whole/regional grey matter brain volume, this conclusion is tempered by three aspects. First, when considering the aim of the identified studies (i.e., to preserve or restore brain volume), the 3–12-month duration of the exercise interventions (4 studies lasted 12 months, 8 studies lasted 6 months, 4 studies lasted 3 months) appear insufficient for a general neuroprotective effect to occur across the grey matter (see "Limitations" for further information). In fact, we should perhaps have expected that short lasting physical exercise (3–12 months) would not elicit substantial effects on grey matter whole/regional brain volume. Second, the majority of the identified studies were likely underpowered (i.e., having too few study participants) (see "Limitations" for further information). Three, only whole brain grey matter and hippocampus volumes were consistently examined across all study populations and exercise modalities, whereas evidence appeared to be lacking for other regions of brain grey matter. In addition, when the identified study findings were not pooled across the populations at risk of neurodegeneration and across the different exercise modalities, evidence appeared to be lacking (except perhaps for healthy older adults and aerobic exercise, respectively). Altogether, it seems prudent to conclude that the summarized current evidence on the effects of physical exercise on grey matter brain volume are sparse and inconclusive, and should be interpreted with caution.

Whole brain grey matter volume is well known to be associated with cognitive and physical function [5, 6, 8–11] and in certain clinical populations also with disease progression [2, 3, 8, 12]. Preservation/restoration of whole/regional brain grey matter volume thus seems as an important target of medical treatment and (if proven efficient) physical rehabilitation. However, the present data do not strongly support that aerobic, resistance, or concurrent exercise can elicit positive adaptations in whole brain grey matter, as only one study found a positive effect (Table 2). This was verified by performing quantitative analyses, i.e., showing that neither all exercise modalities combined (meta-analysis: $N = 7$ studies, ES = −0.07), aerobic training (meta-analysis: $N = 4$ studies, ES = −0.08), resistance training (meta-analysis: $N = 2$ studies, ES = 0.07, heterogeneity between studies), nor concurrent training ($N = 1$ study, ES = −0.13) elicited positive adaptations in whole brain grey matter. In addition, neither all exercise modalities combined (meta-analysis: $N = 17$ studies, ES = 0.10, heterogeneity between studies), aerobic training (meta-analysis: $N = 12$ studies, ES = 0.06), resistance training ($N = 4$ studies, ES = 0.39, heterogeneity between studies), nor concurrent training ($N = 1$ study, ES = −0.09) elicited positive adaptations in hippocampus volume. Whether studies were categorized as low-to-moderate or high quality (according to the TESTEX score) did not appear to affect the present whole/regional brain grey matter outcomes. The present findings are thus in overall

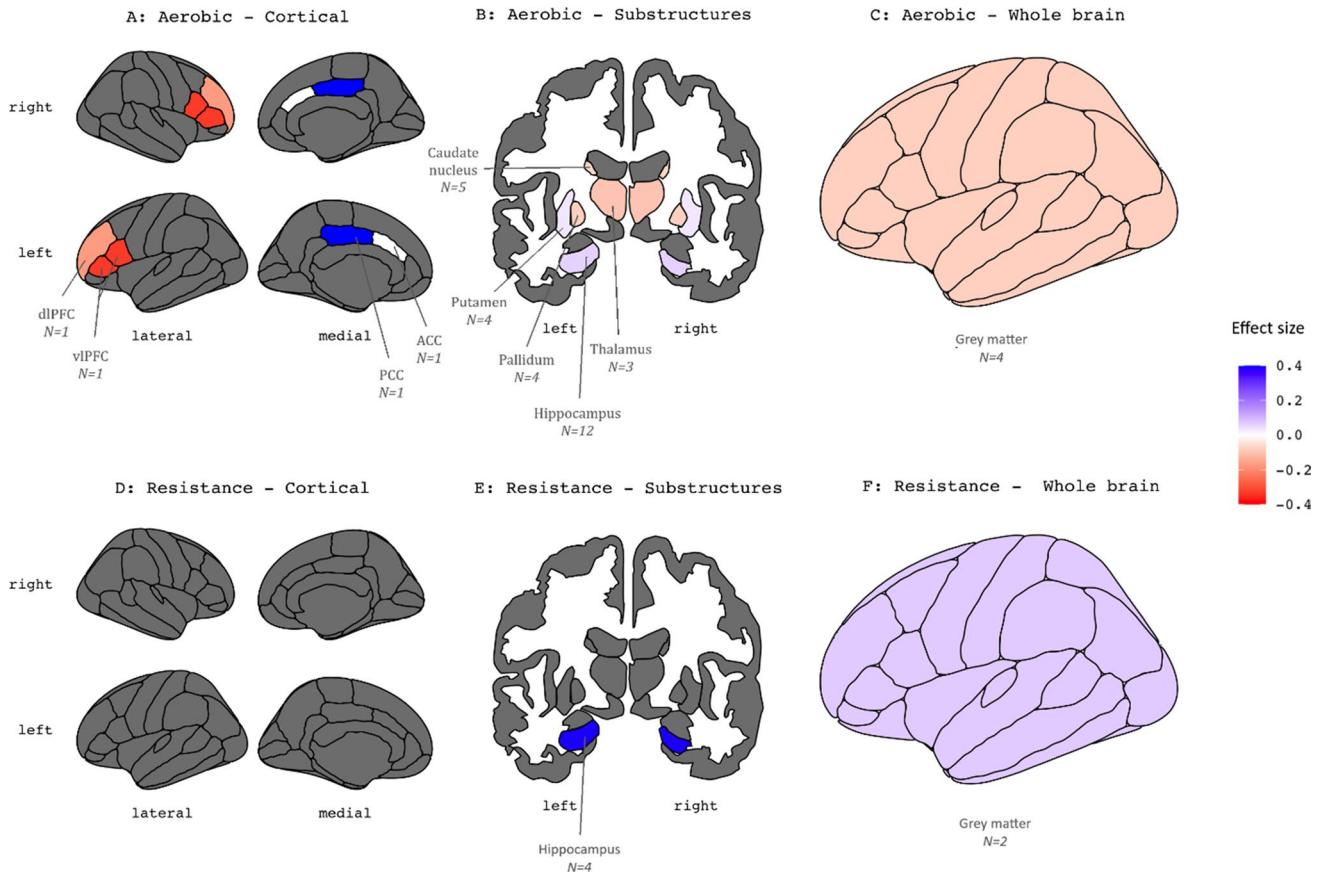


Fig. 3 'Brain maps' visualizing current evidence on the effects of physical exercise on whole/regional grey matter brain across populations at risk of neurodegeneration (i.e., healthy older adults, older adults with mild cognitive impairment or Alzheimer's disease, adults with schizophrenia or multiple sclerosis or major depression). Between-group changes induced by aerobic training (**a** cortical regions, while findings are based on left and right side combined, both sides are displayed; **b** substructures, while findings are based on left and right side combined, both sides are displayed; **c** whole brain) and resistance training (**d** cortical regions, no study findings identified; **e** substructures, while findings are based on left and right side combined, both sides are displayed; **f** whole brain) are shown as effect sizes. Dark grey denote regions that have not been examined or where data have not been reported. See Tables 1 and 2 for specific study details (e.g., study population), significant/non-significant findings, and effect sizes. *dlPFC* dorsolateral prefrontal cortex, *vlPFC* ventrolateral prefrontal cortex, *ACC* anterior cingulate cortex, *PCC* posterior cingulate cortex

agreement with previous systematic reviews [23, 25], but must be interpreted in light of the small number of resistance and concurrent training studies, the heterogeneity between resistance training studies, and the obvious difficulties in comparing the effects of exercise across different populations. To exemplify, Colcombe and colleagues reported positive effects on whole brain grey volume in healthy older individuals (age ≈ 66 years, aerobic fitness ≈ 23 ml O_2/kg/min, cognitive status (Mini-Mental State Examination, MMSE) score ≈ 29) undergoing 6 months of aerobic training [19]. In contrast, Morris and colleagues carried out a comparable aerobic training program yet in older Alzheimer's disease patients (age ≈ 72 years, aerobic fitness ≈ 34 ml O_2/kg/min, cognitive status (MMSE) score ≈ 25), and did not observe any positive effects [36]. Could it be that Alzheimer's disease—along with other neurological and psychiatric disorders—comprise features that blunt exercise-induced brain volume adaptations? At present, it is unclear if findings from healthy (aging) populations can be transferred to clinical populations and vice versa. Importantly, we also acknowledge the advantage of comparing the effects of exercise across similar populations, particularly when number of participants, exercise modality, duration, etc. are quite comparable. Although few of the identified studies allow this comparison, both Colcombe and colleagues [19] and Jonasson and colleagues [41] investigated the effects of 6-month aerobic training (3 sessions per week, 30–60 min sessions, 40–80% HRmax) in healthy older adults (66–68 years old, aerobic fitness 20–23 ml O_2/kg/min, MMSE score ≥ 29). While both studies observed comparable significant increases in VO_2-max (corresponding to intervention-versus-control effects of + 11 and + 9%, respectively, i.e., the physiological 'active ingredient' argued to be mediating the neuroprotective effects), Colcombe and

colleagues found aerobic training to significantly increase the volume of multiple brain regions, whereas Jonasson and colleagues found no effects. At present, we do not have an answer to help explain these contrasting findings.

While the link between exercise-induced improvements in brain grey matter volume and cognitive or physical function is highly complex, improvements in cognitive and/or physical function constitutes main outcomes. Some of the included studies did address this for cognitive function, although revealing some unexpected observations. The study by Erickson and colleagues which is one of the largest studies in the field (older individuals, $n = 120$, 12 months of aerobic training, 3 sessions per week) [20], has often been cited for reporting an association between increases in hippocampus volume and improvement in cognitive function (spatial memory test) in the aerobic exercise group. While we do not dispute this observation, it may not entirely be caused by the intervention per se, as the active control group (= stretching) experienced decreases in hippocampus volume (significantly different from the aerobic exercise group) while at the same time having an improvement in cognitive function (spatial memory test, comparable to the aerobic exercise group). As another example, Ten Brinke et al. [43] found that increases in hippocampus volume was associated with a reduction in cognitive function (sub-elements of verbal memory and learning) following aerobic training. Altogether, it is noteworthy that increasing brain volume does not always lead to concomitant increases in cognitive outcomes as mentioned above.

The physiological mechanisms explaining how aerobic and resistance (and concurrent) training affect the brain are still not fully understood, although a number of mechanisms are consistently being put forward. First, both aerobic and resistance training have been argued to increase the levels of brain-derived neurotrophic factors (BDNF) and other neurotrophic factors (e.g., insulin like growth factor 1, nerve growth factor, neurotrophin-3 and -4/5 [50, 51]) within the central nervous system. This is believed to occur either directly due to neuronal activity [52] or indirectly through elevated myokines (e.g., cathepsin B, PGC1-alpha, irisin) within the skeletal muscles, which subsequently via the blood is transported to the cerebrospinal fluid and the brain, where it increases the BDNF levels) [53]. BDNF have been shown to impose a quite marked stimuli on the central nervous system, i.e., by facilitating gliogenesis [54], neurogenesis [55], synaptogenesis [56], and angiogenesis [57]. However, existing evidence (systematic reviews, meta-analyses) from human studies comprising different populations are rather weak and equivocal, with some stating that aerobic training but not resistance training can improve chronic circulating BDNF levels [58, 59] and others vice versa [60]. Moreover, most of these BDNF studies miss to report whether any neuroprotective effects had taken place, alongside changes in BDNF. An exception is the study by Erickson and colleagues, reporting a weak yet significant association between changes in chronic BDNF levels and hippocampus volume following 12 months of aerobic training in older individuals [20]. Another exception is produced by our group, as we failed to observe an association between changes in acute or chronic BDNF levels and whole brain grey volume (trend) or cortical thickness in multiple sclerosis patients [21, 61]. The highly divergent data on circulating BDNF levels may partly stem from methodological issues, which are seldom similar across studies. Indeed, recent studies have reported handling of blood samples (clotting time and centrifugation strategy) [62] and available blood sample kits that vary in precision, sensitivity, and detection range [63], markedly influences the magnitude and direction of changes of circulating BDNF levels. Second, exercise has long been argued to elicit positive effects on cytokines (anti-inflammatory and pro-inflammatory markers). Intriguingly, this should attenuate neuroinflammation which is a central feature of neurodegeneration in all the identified populations [64–66]. However, as with BDNF, the existing evidence (systematic reviews, meta-analyses) from human studies across different populations are quite weak and equivocal [67–70], with interleukin-6 being the most robust candidate [67, 69]. In MS, attenuation of neuroinflammation are specifically targeted and achieved by disease-modifying drugs [4]. An interesting consequence of such treatment is the occurrence of 'pseudoatrophy' (albeit preferentially of white brain matter), argued to reflect an accelerated brain atrophy due to the resolution of inflammation and edema independent of any changes in brain tissue structures [71, 72]. If physical exercise do in fact attenuate neuroinflammation as proposed, and not just in MS but generally [64–66], the occurrence of 'pseudoatrophy' could thus mask any positive effects on regional/whole brain volume. While we can only speculate whether this occurred or not, future studies should address this conundrum. Third, exercise—aerobic training in particular—has been shown to increase cerebral blood flow along with mitochondrial biogenesis. This optimizes energy metabolism, delivery of circulating signaling factors such as BDNF, and removal of metabolic waste products. Exercise can thus counteract hypometabolism which is believed to precede cognitive impairment [73] and plausible also brain atrophy.

4.1 Limitations

The evidence based on the identified studies of the present review has a number of limitations that should be kept in mind when interpreting the results, and that should be taken into account when designing future studies. First, existing RCTs are few and heterogeneous making direct comparisons across studies/study populations difficult, which is also

why the meta-analyses outputs of the present study should be interpreted with caution. However, whole/regional grey matter brain volume did not appear to adapt differently in any of the separate study populations following physical exercise. Second, when considering the aim of the studies (to preserve or restore brain volume) the durations of the studies were generally short (4 studies lasted 12 months, 8 studies lasted 6 months, 4 studies lasted 3 months). Along with others [41], we would argue that such durations of exercise interventions are less likely to provide sufficient time for a general neuroprotective effect to occur across the grey matter. In support of this notion, when patients with relapsing–remitting multiple sclerosis receive disease-modifying treatment, marked neuroprotective effects on (grey matter) brain volume appear to require a treatment period of 24 months or more [4, 74, 75]. This emphasizes that changes in brain (grey matter) volume is a slowly occurring process. In correspondence, recent meta-analyses of RCTs investigating exercise and cognition argue that the duration of such interventions should last longer than 6–12 months [76–78]. Third, the identified studies build their study rationales on the expectation that aerobic, resistance, or concurrent training will elicit physiological adaptations, which will subsequently mediate the neuroprotective effects (i.e., preserve or restore grey matter brain volume). Surprisingly, 3 studies did not observe significant improvements in aerobic fitness following aerobic training [33, 36, 40] and 3 other studies did not report physiological adaptations in the main targeted systems [43, 47, 49], suggesting somewhat failed or inefficient exercise interventions (Table 1). This clearly weakens the evidence that links exercise-induced physiological adaptations to changes in grey matter brain volume (and further on to changes in cognitive/physical function). Fourth, and perhaps the most critical, the majority of studies appeared underpowered and only one of the included studies investigated whole/regional brain grey matter volume as their primary outcome [35] (Table 1). Of the remaining seven studies investigating whole brain volume following exercise, six [21, 33, 34, 36–38] included the change in whole brain grey matter as a secondary outcome, while one [19] did not specify whether it was a primary or secondary outcome. By assuming that any expectations of observing positive findings in the identified 3–12 month exercise studies would elicit small effect sizes (i.e., recollecting that brain (grey matter) is a slowly adapting tissue), a much larger number of study participants should have been included [31] compared to what was actually included. A closer examination of the presented meta-analyses (e.g., the width of the confidence intervals), furthermore reveal that some of the exercise-induced effects were measured rather imprecisely for the result to be interpreted with confidence (except perhaps for whole brain grey matter and hippocampus across all populations and exercise modalities). Fifth, some studies were selective when reporting their findings, i.e., by mentioning that numerous outcomes had been examined yet only reporting those that turned out to be positive [19, 21]. While there may be pragmatic reasons for this, it is an obvious problem if only the positive outcomes are reported. Hence, the dark grey regions illustrated in Fig. 3 does not necessarily represent brain regions that have not previously been examined. Finally, the present review itself was limited by the fact that we only examined grey matter brain volume. Within the last decade, more emphasis has been put on exercise-induced effects on white matter brain volume (which together with grey matter brain volume makes up *brain morphology*), and importantly also on *brain function* through methods such as functional MRI, EEG, and TMS [26, 79].

4.2 Clinical Implications

As emphasized in the sections above, the clinical implications for the effects of exercise on grey matter brain volume in populations known to undergo neurodegeneration are debatable. The evidence generated from the present systematic review appear sparse and inconclusive, and does not unequivocally support that physical exercise is as potent as previously proposed, when it comes to eliciting positive changes in brain grey matter volume. The latter is likely due to the absence of large, long-term (exercise durations ≥ 1 year), high-quality studies designed specifically to examine the effects of physical exercise on whole/regional grey matter brain volume. Moreover, future studies examining exercise-induced effects on brain volume should perform parallel assessments of cognitive and physical function, as well as quality of life, to further our general understanding of the link between adaptations in brain volume and these important clinical outcomes. Despite the sparse and inconclusive evidence provided in the present review—that may even moderate recent guidelines for physical activity proposing that brain atrophy can be reduced [18]—it still seems reasonable to recommend exercise as a potential means for brain (functional) preservation in populations known to undergo neurodegeneration. Indeed, physical exercise appear to be a safe, low-cost, multi-beneficial, almost entirely absent of side effects, and easily accessible intervention, which includes numerous other health benefits (e.g., on physical function, cardiorespiratory function, neuromuscular function). This justify our continuous strong support of physical exercise as an integral part of counteracting aging along with several neurological and psychiatric disorders.

5 Conclusion

Across heterogeneous neurodegenerative populations, few studies report findings that support a preservative or even restoring effect of 3–12-month physical exercise on certain regions of brain grey matter, with changes overall being

modest and inconsistent. Moreover, meta-analyses showed that different exercise modalities failed to elicit any substantial effects on whole brain grey volume and hippocampus volume, with rather large confidence interval width (i.e., variability). Altogether, the current evidence on the effects of physical exercise on whole/regional grey matter brain volume appear sparse and inconclusive. Future well-designed studies are necessary to determine if exercise can be utilized for moderating effects on brain grey matter volume in populations at risk of neurodegeneration.

Author Contributions LGH, DLH, SFE, and UD contributed to the conception of the study and to the development of the search strategy. LGH and DLH conducted the systematic search and completed the acquisition of data. LGH and DLH performed the data analysis. LGH took the lead in writing the manuscript. All the authors discussed the results and contributed to the final manuscript.

Availability of Data and Materials Data are available from the authors upon reasonable request.

Declarations

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