How does physical activity benefit people living with dementia? A systematic review to identify the potential mechanisms of action

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Jan Pringle, Ruth Jepson, Alison Dawson, Louise McCabe and Alison Bowes

Abstract

Purpose – *One limitation of research that assesses the effectiveness of physical activity interventions for people with dementia is that most do not describe the intervention in sufficient detail to ascertain a theoretical basis or mechanism of action that determines the effective components. This paper aims to identify studies which evaluate the mechanisms of action of physical activity interventions for people with dementia, to further inform effective intervention development.*

Design/methodology/approach – *Papers were screened for evidence of evaluation of specific forms of physical activity, using pre-defined inclusion criteria. Analysis was conducted to ascertain if mechanisms of action were corroborated by data within and between studies.*

Findings – *The authors identified 26 studies with a measured mechanism of action; these related to the effects of physical activity on either neurological structure or endocrinal markers, including hormones. Physical activity had potential to reduce hippocampal atrophy, increase neural recruitment, activate the noradrenergic system and improve anti-inflammatory responses. While individual studies were hampered by small sample sizes, the body of evidence indicated that physical activity may have potential to delay cognitive decline.*

Practical implications – *Mechanisms of action in relation to dementia and physical activity are likely to be multifaceted, and physical activity may be protective against progression in the early stages of cognitive decline. Physical activity may be of greatest benefit if incorporated into on-going lifestyle, rather than engaged in for short periods, and combined with social interaction.*

Originality/value – *This paper is unique in its focus on the mechanisms of action of physical activity interventions for people with dementia.*

Keywords *Systematic Review, Ageing, Physical activity, Dementia, Alzheimer's, Cognitive impairment or decline*

Paper type *Literature review*

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Background

Dementia, as a condition, is of global concern, with around 50 million people worldwide living with the disorder, and an estimated 10%–20% of cases being preventable (WHO, 2019). Physical activity is amongst the healthy lifestyle factors that may reduce the likelihood of developing dementia, or slow the progress of cognitive decline (Lewis *et al.*, 2020; WHO, 2019).

While the general benefits of physical activity are well documented (Reiner *et al.*, 2013), it has been estimated that around a quarter of adults are insufficiently active (WHO, 2019). Environmental factors, such as living in a safe neighbourhood with open spaces, can positively influence activity levels amongst healthy adults [National Institute for Heath and

Care Excellence (NICE), 2018]; however, for those with physical or mental impairments, keeping active may be more challenging (Bartlo and Klein, 2011). For example, people with conditions such as dementia may face particular difficulty due to the effects of the condition on memory, thought processes, behaviour and ability to perform everyday activities (Alzheimer's Society, 2015). Despite these challenges, studies of physical activity programmes for older adults suggest improved cognition (Colcombe and Kramer, 2003), increased independence (Mechling, 2008), and improved functional ability (Bowes *et al.*, 2013). If physical activity is undertaken in a group it can also increase social connection and reduce feelings of loneliness and isolation (Kim *et al.*, 2014).

Understanding the underlying or causal pathways that explain how such interventions produce their outcomes is an essential step towards informing further implementation (Moore *et al.*, 2014; gov.uk, 2018). One limitation of research that assesses the effectiveness of physical activity and behavioural change interventions is that most do not describe the intervention in sufficient detail to ascertain whether there is a theoretical basis, or underlying mechanism of action, to determine the effective (or ineffective) components (Bowes *et al.*, 2013). It is therefore difficult to replicate effective interventions, or identify the factors that contribute to effectiveness across interventions. Without such detail, researchers and practitioners aiming to develop and evaluate complex interventions may be unable to proceed with confidence (Bowes *et al.*, 2013).

A mechanism of action describes the manner in which a beneficial (therapeutic) agent or activity works, including the functional (biological, physiological or biochemical) processes within the body that produce a given response (Medical Dictionary, 2019). These responses have traditionally referred to medication (pharmacological) treatments. However, over the last couple of decades there has been increasing recognition that non-pharmaceutical interventions, in conjunction with improved understanding of the underlying condition, may produce better benefits; even in 2004 Douglas *et al.* emphasised that pharmacological treatments for dementia should be used as a second line approach and that non-pharmacological options should, in best practice, be pursued first.

We therefore sought to identify studies that might provide detail relating to mechanisms of action as the active or "operative" elements of physical activity interventions for people with dementia, via a systematic review. The focus was on human studies, rather than evidence that might have been derived from animal studies, due to our interest in informing practical interventions for people with dementia. Improved understanding of mechanisms of action can help to inform theories of change, and therefore more effective intervention development.

Methods

Approach

A systematic review was carried out to assess current evidence relating to the effects of physical activity for people with dementia, and identify studies detailing specific and well-defined mechanisms of actions.

Search terms and databases

Searches combined key words related to dementia with terms for exercise and physical activity, as used in our previously reported scoping study of physical activity for people with dementia (Bowes *et al.*, 2013). Key words and an example search string are shown in Table 1. The review sought to better understand mechanisms of action of interventions which require physical exertion. The language used to report and describe such interventions can vary between cultures and academic disciplines, for which reason, whilst acknowledging the distinction between the two, search terms were included to capture both "exercise" and "physical activity" and variants thereof.

Including terms around specific physical activities potentially allows consideration of mechanism of action at different levels of physical exertion.

The dementia-related search terms were purposely designed to capture studies of interventions aimed at people living with a range of dementias; the earlier scoping review found that studies used participant eligibility criteria ranging from diagnosis of specific dementias (e.g. Alzheimer's disease) to observed cognitive impairment suspected to be due to dementia. It is acknowledged that in practice there may be the co-existence of symptoms of multiple or mixed dementias at, or following, a dementia diagnosis. However, given the potential wide variation of symptoms and abilities, even between people with the same diagnosis or measured stage of their condition, it was felt important to examine and report on people with a broad range of cognitive impairment.

Individual searches were conducted using each exercise or activity-related term, with intra-database duplicates being removed. All study designs could be included, subject to meeting other inclusion criteria. An approach to study inclusion which does not privilege specific study designs can provide insight into the shape and volume of the "research landscape" in fields of enquiry where, due to ethical or practical challenges, fewer randomised or clinical controlled trials may take place. The approach has previously been employed successfully in reviews of a range of other topics (Bowes *et al.*, 2016; Dawson *et al.*, 2015; Rutherford *et al.*, 2019). The study design of included studies is identified and discussed in the findings section of this paper.

Publication dates up until August 2020 were included; databases accessed: Web of Knowledge (includes BIOSYS and Medline databases), CINAHL, ASSIA, Social Services Abstracts, Embase, PsycINFO, and the British Nursing Index.

Study selection

Papers were included if they described or evaluated a specific form of physical activity (rather than referring to physical activity in general), and identified a specific primary research study. In relation to outcomes, we aimed to identify if a mechanism of action had been suggested, and measured, in each study, therefore building on the evidence synthesis of exercise and dementia conducted by Lewis *et al.* (2020).

Inclusion and exclusion criteria for the review are summarised in Table 2.

With further regard to the inclusion/exclusion criteria, the term 'adults' referred to anyone over 18 years of age; no other lower age limit was set, to avoid excluding people with early onset conditions.

We were unable to include dissertations or theses, due to the typical length of such pieces of work. However, where shorter summaries of such work had been published, these were included, if the published work fulfilled all criteria for the review.

Applying the inclusion criteria

Results of individual searches were combined to produce a single dataset for each database. Within and between database duplicates were removed, titles and abstracts screened for relevance, followed by full text screening of remaining papers. Two members

Table 1 Search terms and example search string

Terms relating to dementia or cognitive impairment	*Exercise or activity-related terms*	*Example search string*
dement* Alzheimer* (Lewy* bod*)(cognit* impair*)	exercis*(physical activit*)swim*gym*walk*danc*yoga((tai chi) or (tai ji))stretch*sport*(physical train*)	TS=((dement* OR Alzheimer* OR "Lewy* bod*" OR "cognit* impair*") AND exercis*)

Table 2 Inclusion and exclusion criteria

Inclusion criteria	*Exclusion criteria*
Study design: specific primary research studies of any design, which include an intervention and outcome(s)English languagePopulation: adults (18yrs or older) with dementia or mild cognitive impairment, living independently or in a care environment; human studiesIntervention: defined, specific physical activity interventionsOutcomes: physiological, functional, psychological, or social outcomes that are attributable to physical activity interventionA stated and measured mechanism of action	Study design: study protocols without outcomes; commentary papers; dissertationsFull article not available or not in English languagePopulation: no dementia; congenital or traumatic cognitive impairment (e.g. brain injury); animal studies; populations under 18yrs of ageIntervention: no specific physical activity intervention; physical activity incidental to other factors/actions; risk or prevalence studies (as sole focus)Outcomes: no specific, separate, or identifiable effects of physical activity (e.g. multimodal studies where outcomes relating specifically to effect of physical activity are not reported)

of the review team blind screened papers during this process, with a third member of the review team acting as an arbitrator in cases of disagreement.

Data extraction and synthesis

Key information for studies was extracted into an evidence table, designed to capture essential data relating to participants, type of dementia, type, duration and frequency of physical activity, outcome measures, and suggested mechanism of action. Studies were examined to ascertain if the mechanism of action was corroborated by evidence, and findings/conclusions summarised (see Table 3 in results section).

Quality appraisal

Studies were appraised in relation to method, participant characteristics, selection bias, statistical power, outcome measures and validity of findings, using a mixed method appraisal tool (Pluye *et al.*, 2011).

Findings

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart (Figure 1) is used to summarise the literature review process and results (Moher *et al.*, 2009).

Following title and abstract, then full paper screening, 142 papers were found that discussed a potential mechanism of action; we further sought to identify whether the mechanism was directly measured. For example, a study might suggest that physical activity may improve neural plasticity without measuring any evidence of effect within the brain. Alternatively, another study might suggest improvements in brain neurotropic factors as a result of an exercise programme, and measure this through blood samples.

We identified 26 studies with a specified and measured mechanism of action. Details of these studies are given in Table 3.

General overview

The included studies were conducted in a wide range of countries: USA (8), Canada (3), Taiwan (3), Brazil (2), Iran (2), South Korea (2), Czech Republic (1), Denmark (1), Hong Kong (1), Pakistan (1), Portugal (1), Saudi Arabia (1). This indicates the global nature of interest, and the range of populations/ethnic groups that have been involved in research on this topic.

Table 3 Included studies with mechanism of action

Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
Allard2017USA	22 African Americans, mild CI > 55yrs, 13 intervention, 9 control	Aerobic exercise; 6 mths, 20–40 mins treadmill, 3x wkly, plus 45–60 mins walking 1x wkly. (control = stretch activities). Pilot RCT	Neuro protective effects, brain derived neurotrophic factor (BDNF) regulation; Apolipoprotein E (APOE) genotyping	Stretch and Aerobic groups showed mean increases in serum BDNF (stretch = 46.29%; and aerobic = 15.12%). Change in serum BDNF levels was significantly different between non-ε4 carriers and ε4 carriers (p= 0.012, U = 18.0). With adjustment for age, differences remained statistically significant (non- ε4 carriers = 27.2% versus ε4 carriers = −8.6%; p = 0.019)	Yes; Measures may showneuroprotectiveeffects of physical activity, more especiallyfor non-APOE gene carriers
Amjad2019Pakistan	44 participants (22 control), mild CI.Ages unclear	X-box 360 games; 6 wks, 25–30 mins, 5X wkly. Exercise (control); RCT	Effects on neurogenesis and neural plasticity; effects on EEG complexity	After 6 weeks intervention of games, delta (0.673 ± 0.029; p = 0.013), theta (0.129 ± 0.013; p = 0.002), beta2 waves (0.044 ± 0.009; p = 0.046), complexity of EEG (0.051 ± 0.042; p = 0.016), and MMSE (26.25 ± 0.347 vs. 23.722 ± 0.731; p = 0.003 improved significantly. These changes were not observed in the control group	Yes; short and longer durationX-box gaming showed benefits (complexity of EEG) for people with MCI
Anderson2017USA	27 participants, mild CI; average age 83.55yrs (SD 3.26)	Aerobic exercise, 6 mths, 2x wkly, 70 mins. Exact method not detailed	Insulin-like growth factor (IGF-I) stimulation may increase cognition after exercise	The Johnson-Neyman technique revealed a significant relationship between step test and MMSE when serum IGF-1 levels were above ($p < 0.05$; 70.4% of sample) but not at or below 73.96 ng/mL ($p \geq 0.05$; 29.6% of sample). The strength of this inverse relationship increased as serum IGF-1 levels increased	Mixed findings; greater aerobicendurance gains were associated withpoorer cognitive prognosis withelevated serum IGF-I levels
Baker2010USA	33 participants with mild CI, 55-85yrs; 22 intervention, 11 control	High intensity aerobic exercise;Stretching for control, 6mths, 4x wkly, 45–60 mins; RCT	Effects of exercise on inflammation and neurotrophic effects: BBNF, cortisol, insulin-like GF-1, beta-amyloids	For the aerobic group, plasma BDNF and cortisol were positively correlated (r = 0.51; p = 0.04). Plasma IGF-I increased in response to aerobic exercise for the men (p = 0.02). Cortisol levels increased for women in the control group during study period, but not for women in the aerobic group	Mixed findings; study supportsnon-pharmaceutical intervention inimproving executive controlprocesses; some gender differences,with older women benefiting more
Castellano2017Canada	10 people with mild AD, mean age 73yrs	Treadmill walking; 12 wks (6 wks progression; 6 wks at target level), 3x wkly, 15–40 mins. Increasing time/ intensity. Uncontrolled pilot study	Brain uptake of glucose; changes in glucose and ketone metabolism relating to neural activity; plasma insulin/ homocysteine levels	Brain uptake of acetoacetate was three-fold higher (0.6 ± 0.4 versus 0.2 ± 0.1 μmol/100 g/min; p = 0.01) after intervention. Plasma acetoacetate concentration and the blood-to-brain acetoacetate influx rate constant were also increased by 2–3-fold (all $p \leq 0.03$). Brain uptake of glucose was unchanged after walking (28.0 ± 0.1 μmol/100 g/min; p = 0.96)	Yes; aerobic training improved brainenergy metabolism by increasingketone uptake and utilization,while maintaining brain glucose uptake;no change in homocysteine levels

(*continued*)

Table 3

Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
Chirles2017USA	16 people with mild CI; 16 healthy elders aged 60-88yrs	12 week walking/aerobic exercise, 4x wkly, 30 mins (both groups); moderate intensity. Exact method not detailed	Effects on post cingulate cortex; fMRI neural recruitment mechanisms, leading to improved cognitive reserve	The MCI group exhibited increased correlations after the exercise intervention in ten regions. Clusters had peak voxels in the right midfrontal gyrus, superior frontal gyrus, postcentral gyrus, parahippocampal gyrus, and claustrum. Clusters were also found in the left inferior paretal lobe and bilateral precentral gyrus and culmen. No significant clusters demonstrating changes in connectivity across time were found in the healthy elders group	Yes; significant interaction in Rtparietal lobe observed; increasedconnectivity in 10 cerebral regions;exercise may enhance neural recruitmentmechanisms
Chupel2017Portugal	33 people with mild - moderate CI. > 60yrs; mean age 82.7yrs; 16 intervention, 17 control	Elastic band strength training – chair based; 28 wks, 2-3x wkly, 30–40 mins; control - usual care. Exact method not detailed	Reduces inflammatory response; improved anti-inflammatory cytokines concentration in blood samples	Cytokine concentration (IL-10) increased significantly in intervention group ($p = 0.02$; rpb = 0.4); no significant changes for control group. Strength training decreased leukocyte and lymphocyte counts and increased haemoglobin mean cell volume and concentration. MMSE score increased in strength training group but remained unchanged in the control group	Yes; resistance exercise improvesanti-inflammatory balance andphysical performance simultaneouslywith improved cognitive profile
Damirchi2018Iran	44 women with mild CI, 60-85yrs; 11 physical training, 11 mental training, 13 combined, 9 control	Walking and stretching programme, mental exercises (or combined); 8 wks, 3x wkly, 25 mins; control group activity not specified. RCT	Stimulation of BDNF serum levels and working memory impacts	Significant increase in working memory ($p = 0.012$) and BDNF ($p = 0.024$) in the mental training compared with the control group. Also the mental training group in comparison with the physical training group demonstrated better working memory ($p = 0.014$) and processing speed ($p = 0.024$).	Yes; BDNF and working memoryimprovements noted; mental training is a safe strategyto alleviate progression of MCI
El Kader & Al-Jiffri2016Saudi Arabia	40 people with AD. 65-75yrs; 20 intervention, 20 control	Treadmill aerobic exercise; 2 months, 3x wkly, 15–35 mins; control group had no training. RCT	Reduced systemic inflammation, via effects on tumour necrosis factor alpha TNF-α and interlukin-6 (IL-6)	There was a 25.2% and 19.4%, (significant) reduction in mean values of TNF-α and IL-6 respectively in the group who received aerobic exercise training; also increase in the mean values of SF-36 HRQL subscale scores. Results for control group were not significant	Yes; exercise intervention improved QoL,reduced systemic inflammation, andimproved well-being
Ho2018Hong Kong	204 people with very mild to mild dementia. ≥ to 65yrs	Dance (69), physical exercise (67) or control (68); 12 weeks, 2 hrs per week. Control – routine care. RCT	Activation of hippocampal areas, and networks associated with spatial memory; cortisol levels	The dance group showed significant decreases in depression, loneliness, and negative mood ($d = 0.33–0.42$, $p < 0.05$), and diurnal cortisol slope ($d = 0.30$, $p < 0.01$). The effects on daily functioning and cortisol slope remained at 1-year follow-up. The	Yes; dance therapy better thanexercise at reducing depressive symptoms,improving daily function,and diurnal cortisol levels

(*continued*)

Table 3

Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
				exercise group of matched intensity showed no significant effects on the outcomes	
Hong2017South Korea	22 people with mild CI; 25 healthy people; > 65yrs. Exercise/control in both groups	Resistance elastic band exercises; 12 weeks, 2x wkly, 60 mins. Control - current lifestyle. RCT	Neural activity;EEG pattern changes	After the 12-week exercise intervention, differences in a region that benefits from exercise were observed between the MCI exercise group in the relative theta power on left frontal electrode ($p< 0.05$) and relative alpha power ($p < 0.05$). In the control exercise group, changes were observed in the relative theta power on the left posterior electrodes ($p < 0.05$ and $p < 0.01$)	Yes; positive effects on EEG patterns,physical benefits, slight changesin cognitive functioning
Hsu2017Canada	21 people with mild vascular CI (10 intervention, 11 control); mean 71.5 yrs +/- 8.6 yrs	Aerobic training,6 months, 3x wkly, 60 mins.Control – usual care.RCT	Effects on white matter and neural lesion volume	Compared with control group, the aerobic training group significantly improved flanker task reaction time. Moreover, compared with the controls, the aerobic training group demonstrated reduced activation in the left lateral occipital cortex and right superior temporal gyrus. Reduced activity in these brain regions was significantly associated with faster flanker task performance at trial completion	Yes; improved neural efficiency ofassociated brain areas, from fMRI
Kim & Lee2018South Korea	18 women with mild dementia (9 intervention, 9 control); ≥ 65yrs; 79.22 yrs +/- 4.02	Whole body vibration exercise, 8 wks, 5x wkly . control group activity unclear. Pre/post test controlled study	Stimulation of neuromuscular system; EEG activation; brain metabolism changes and neurotransmitter secretion	Whole body vibration exercise intervention allows patients with dementia to participate in regular exercise; it significantly enhances the functional plasticity of the cerebral cortex, increases connectivity between the dendrites of neurons, and improves the functions of the central nervous system	Yes; improved EEG activationand cognitive function
Kohanpoor2017 x 2Iran	40 men with mild CI, 60-70yrs; exercise +/- lavender, lavender alone, or control (10 to each group)	Aerobic/running exercise program, with lavender essence therapy; 12 weeks, 3x wkly, 8–26 mins. Control – no exercise program, plus placebo. Pre/post test study	Anti-inflammatory effects (lavender essence); brain derived neurotrophic effects	BDNF levels of the exercise and exercise + lavender groups increased significantly compared to those of the other 2 groups ($p < 0.05$). In addition, the cognitive states of the 3 intervention groups increased significantly compared to that of the placebo group ($p < 0.05$)	Yes; intervention may decelerate orhalt progression of cognitive impairment,by reducing inflammatory factors

(*continued*)

Table 3

Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
Liu2020Taiwan	61 people with dementia completed the exercise programs, (50 men, 11 women). 66-95yrs; 85.7 +/- 6.9 years	Participants randomly assigned to either strength (n = 30) or aerobic training (n = 31) for a total of 4 weeks; 30mins, 5x wkly. Single blind RCT	Effects on plasma monocyte chemotactic protein-1 levels, insulin-like growth factor-1 levels, and serum brain-derived neurotrophic factor levels	Results were validated by multivariate regression	Yes; strength or aerobic trainingbrought significant benefits to participants;serum brain-derived neurotrophic factorwas additionally improvedthrough aerobic training
Morris2017USA	76 people with early AD (39 intervention, control 37), > 55yrs, mean 72.9yrs+/- 7.7	Physical activity intervention, 6 mths, 3–5 sessions wkly; 60–150 mins per wk. Control – stretching program. Pilot RCT	Delayed hippocampal atrophy (via MRI)	analysis, adjusting for age and CI, which showed improvement	Yes; secondary outcome analysis: benefitsin functional ability, CV function,memory and reduced hippocampalatrophy following intervention
Pedroso2018Brazil	31 people with AD; > 65yrs, mean 77,5 +/- 6.4. 14 intervention, 17 control	Physical exercise12 weeks, 3x wkly, 1 hr. Control - social activityExact method not detailed	EEG: effects on temporal, parietal lobes, or hippocampus; P300 latency (speed of information processing) and amplitude	in Barthel Index, MMSE, BDNF, and plasma MCP-1 after strength or aerobic training. The only outcome measure that was significantly influenced by difference in exercise mode was BDNF (p = 0.02)	Yes; intervention improvedreaction time, suggesting recoveryin cortical activity; however socialgroup may improveinformation processing
Rektorova2020Czech Republic	62 healthy seniors and people with mild CI, > 60 yrs with no major dementia or depression. Ages: 67.2 ± 6.7 (control); 68 ± 4.9 (intervention)	6 month intensive dance-exercise intervention (DI) (n = 31), 60 mins, 3x wkly; or life as usual (n = 31). RCT	Effects on cognition and brain structure via MRI, structural and diffusion tensor imaging (DTI), at baseline and after 6 months; changes in cortical thickness and DTI parameters derived from tract-based spatial statistics	No clear effect of intervention on memory, executive function, or depressive symptoms. However, secondary analyses revealed that change in cardiorespiratory fitness was positively correlated with change in memory performance and bilateral hippocampal volume. Effect size estimates and confidence intervals given to inform future studies	Yes; DI-induced improvement inexecutive function and increasedcortical thickness in thelateral occipito-temporal cortexwhich is engaged in activitiesimportant for motor learningand executing skilled movements

(*continued*)

Table 3

Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
Segal2012USA	23 people with mild CI, + 31 healthy older adults, 70yrs +/- 3yrs (both groups controlled)	Aerobic exercise (exercise bike, 2 day period, 6–14 minutes). Control – sedentary activities. RCT	Activation of noradrenergic system, and locus coreolus; effects on norepinephrine release (via salivary alpha-amylase levels)	Significant ($p < 0.05$) improvements in reduction of reaction time after exercise intervention (pre = 421.5 ms and post = 360.9 ms); also increase of P300 amplitude at central midline (pre = 5.9 μV and post = 6.9 μV) and parietal midline (pre = 4.7 μV and post = 5.7 μV). A decrease in the P300 latency at frontal midline (pre = 377 ms and post = 367 ms) observed in the social activity group after intervention	Yes; exercise that activatesnoradrenergic system maybenefit cognitive decline
Smith2013USA	35 participants; 17 with mild CI, plus 18 cognitively intact controls	12 wk supervised treadmill walking activity, medium intensity, 3-4x wkly, 30 mins. Both groups completed the activity. RCT	Exercise training leads to an increase in semantic memory-related activation, measured via fMRI	The whole-brain CT analysis showed significant cortical thickening in DI group, including inferior temporal,	Yes; exercise may improveneural efficiency during semanticmemory retrieval in MCI andcognitively intact older adults
Ten Brinke2015Canada	86 women with mild CI, 70-80yrs; 30 aerobic exercise, 28 resistance, 28 control	Aerobic activity +/- resistance training, 6 mths, 2x wkly, 60 mins. Controls did balance and tone training only. RCT	Effects on brain structure and function, hippocampal volume (MRI), special memory	fusiform and lateral occipital regions of the right hemisphere. Linear mixed-effects model showed significant interaction between time and group regarding the average cortical thickness ($b = 0.032$; $t(53) = 2.91$; $p = 0.005$)	Yes; aerobic training significantlyincreased hippocampal volume
Tsai2018Taiwan	66 participants with mild CI, 60-80yrs; 25 aerobic exercise, 21 strength/ resistance, 20 control	Aerobic (bike) activity or strength/resistance training, or control (non-exercise); 6 mths, 2x wkly, 40 mins. RCT	Neuro-regenerative effects on amyloid-B neuroprotective growth factors (exerkine factors, including BDNF via blood samples); EEG recordings	Exercise significantly ($p < 0.001$) elevated endogenous norepinephrine (salivary alpha-amylase) in both MCI patients and healthy controls. Additionally, exercise showed retrograde enhancement of memory in both MCI patients and controls	Yes; improved neuroprotectivegrowth factor changes andneurocognitive performancefor both aerobic and resistancetraining. Transient improvementsshown in the present workneed further long-term exerciseintervention studies

(*continued*)

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Lead authorYear of publicationLocation	*opulation*	*Intervention/Method*	*Suggested MoA*	*Results summary*	*MoAcorroborated by evidence? Findings/conclusions*
Tsai2019Taiwan	55 participants older adults with amnestic MCI (aMCI), 60-85yrs; aerobic exercise (AE) group (n = 19), resistance exercise (RE) group (n = 18), or a control group (n = 18)	Aerobic and resistance training, 3x weekly, 40 mins, for 16 weeks. Control group: 16 week stretching and balance exercises. RCT	Circulating neuroprotective growth factors (e.g., BDNF, IGF-1, VEGF, and FGF-2) and inflammatory cytokine (e.g., TNF-alpha, IL-1beta, IL-6, IL-8, and IL-15) levels at baseline and after either a 16-week aerobic or resistance exercise intervention program or a control period	Performance of a list-learning task significantly improved in the MCI participants. 11 brain regions activated during the semantic memory task showed a significant decrease in activation intensity following the intervention that was similar between groups (p-values ranged 0.048 to 0.0001)	Yes; aerobic and resistance exerciseeffective with regard to increasingneurotrophins, reducing someinflammatory cytokines,and facilitating neurocognitiveperformance
van der Kleij2018Denmark	51 participants with mild/moderate AD, 50-90yrs (68.5 +/- 7). Intervention 27, control 24	Moderate to high exercise, 16 wks, 3x wkly, 60 mins; control – usual care. RCT	Effects on cerebral blood flow (CBF), via MRI brain perfusion maps	Compared with control group, aerobic training significantly improved left, right, and total hippocampal volumes ($p \leq 0.03$). Increased left hippocampal volume was independently associated with reduced verbal memory and learning performance as indexed by loss after interference ($r = 0.42$, $p = 0.03$)	No; no effects on cerebralblood flow noted; authorsconcluded that 16 weeks ofexercise are not sufficient toproduce a consistent increase incerebral blood flow in arelatively small sample ofAlzheimer's patients.
Vital2016Brazil	30 participants with AD; 14 intervention, 16 control (social interaction)	Resistance training, 16 wks, 3x wkly, 60 mins. RCT	Effects on lipid profile and homocysteine levels	An acute bout of aerobic exercise significantly increased serum levels of BDNF and IGF-1 in elderly MCI individuals. Acute resistance exercise increased only serum IGF-1 levels. The exercise-induced elevated levels of these molecular markers returned almost to baseline levels about 20 min after acute exercise	No; no relationship foundbetween physical activityand metabolic variants

(*continued*)

Table 3

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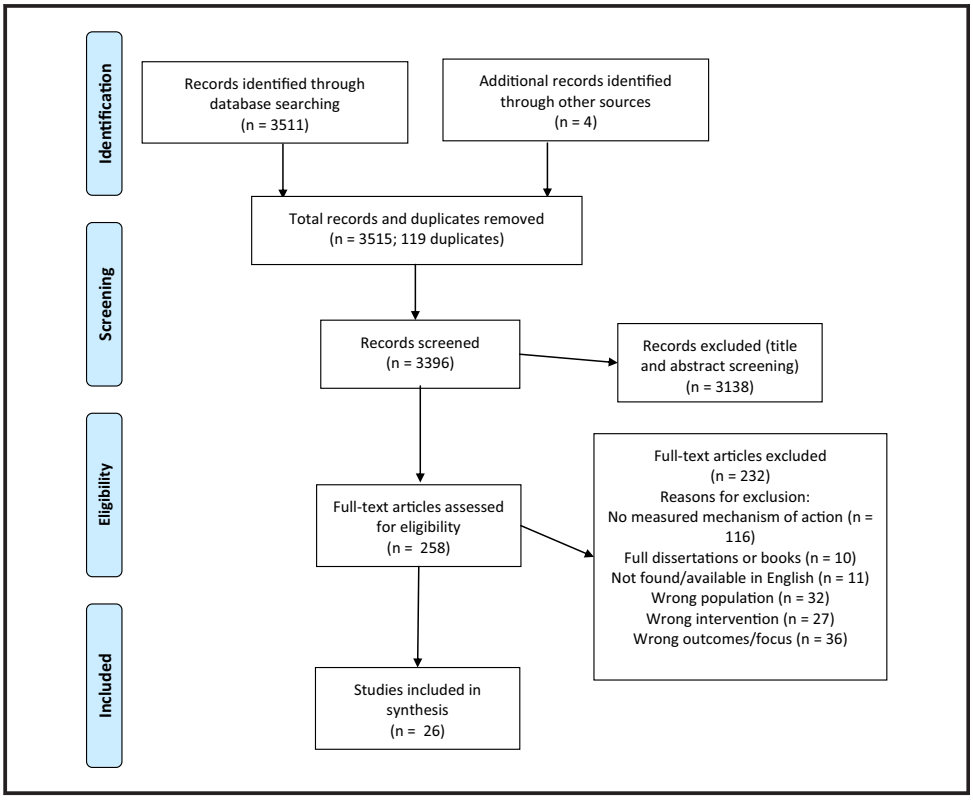
Yerokhin2012USA	13 participants with early stage dementia, mean age 79.3 yrs, range 60–95yrs; 9 normative older adult controls, 55–78yrs (mean 62.8)	Chair/standing exercises, with small weights, to strengthen muscles and improving balance (both groups); 45 minutes 3-5x per week for 10 weeks (able to be done if limited ability/ wheelchair bound). Pilot RCT		Neurophysiologicaleffects on frontal lobeasymmetry resulting from strengthening exercise; effects on resting EEG and activity-related ERP latency and amplitude	Peripheral serum BDNF level was significantly increased, and the levels of insulin, TNF-α, and IL-15 levels were significantly decreased in the AE group, whereas the RE group showed significantly increased IGF-1 levels and decreased IL-15 levels. The aerobic and resistance exercise modes likely employed divergent molecular mechanisms on neurocognitive facilitation
Yes; results revealedbeneficial effects of strengtheningexercise on verbal memory coupledwith EEG results indicatingincreased brain efficiency(frontal beta and delta powerasymmetries andN200 amplitude asymmetry)					

Figure 1 PRISMA Flow Diagram



Of the 26 studies, 16 were randomised controlled studies, three pilot RCTs, one other uncontrolled pilot study, and two pre/post-test studies; 4 studies did not detail an exact study method. All studies had been published within the past 10 years, with around 75% dating from 2017 onwards. This suggests a more recent focus and interest in the determination of mechanisms of action, and the operational elements of interventions.

Study participant numbers were generally small, with only eight studies recruiting over 50 participants (see Table 3 for further details). This perhaps reflects difficulties in conducting studies with, and recruiting, vulnerable groups of people (Economic and Social Research Council, 2019). With regard to diagnosis or degree of cognitive impairment, the majority of studies (n = 18) included participants with mild cognitive impairment. Six studies had participants with a diagnosis of Alzheimer's disease (mild to moderate), and two studies recruited participants with mild dementia.

Quality appraisal

Quality appraisal was hampered by lack of comparability of studies, and low statistical power due to small study numbers. In addition, differences such as disease stage and progression, intervention intensity and duration, and gender, all impacted on the ability to make direct comparisons between studies. However, inclusion criteria were well described in all studies, and outcome measures relevant; due to the nature of research and the participants, controlled trials were generally single-blind. Baseline characteristics between intervention and control groups were well described, but not comparable due to cognitive impairment being absent in some control subjects.

Mechanisms of action

In the included papers, measured mechanisms of action fell into two broad categories, determining:

1. structural or functional changes, measured either through brain imaging (e.g. MRI, fMRI) or EEG readings; and
2. levels of substances such as endocrines and hormones in blood or saliva samples

Structural and functional changes in the brain were reported in 11 studies, and the remaining studies reported on physiological mechanisms. Findings from these two broad categories, and their sub categories, are examined below.

While the focus was mainly on measuring elements within these two broad categories, there was only minor acknowledgement of the social benefits of taking part in a group activity, and any behavioural change mechanisms of action that may have resulted from the interventions. We were therefore unable to report in any depth on these elements, although a few pertinent points are made, as relevant.

Structural or functional measures

Hippocampal volume

Of the studies measuring structural changes, 3 examined hippocampal volume, using brain magnetic resonance imaging (MRI) techniques (Morris *et al.*, 2017; Ten Brinke *et al.*, 2015; Van der Kleij *et al.*, 2018). Morris reported benefits in functional ability, improved memory and reduced hippocampal atrophy (compared to control) following a 6 month physical activity programme for people with early Alzheimer's disease. Ten Brinke *et al.* (2015) reported significantly increased hippocampal volume (as opposed to reduced atrophy) following aerobic activity for a similar period of time. However, Van der Kleij et al (2018) found no consistent effects from a 16 week programme, and questioned whether this period of intervention time was sufficient to show a difference in a relatively small sample of 51 participants. Sample sizes in the other two studies were not much bigger, but Van der Kleij *et al.* did include participants with more moderate cognitive impairment, whereas participants in the other two studies had either mild or early changes only. All three studies had similar intervention types (aerobic activity of moderately to high intensity, 2–3 times a week) over a 4–6 month period.

Neural recruitment and activation

Studies by Chirles *et al.* (2017), Smith *et al.* (2013) and Hsu *et al.* (2017) used functional magnetic resonance imaging (fMRI) to measure changes in brain activation, with all 3 studies reporting improvements following their aerobic activity programmes for participants with mild cognitive impairment. Increased activity in 10 cerebral regions was reported by Chirles *et al.* (2017). Similar improvements in associated brain areas were reported by Hsu *et al.* (2017); in the study by Smith *et al.* (2013), a list-learning task significantly improved, and 11 brain regions showed increased activation during the memory task. Chirles *et al.* (2017) concluded that exercise may enhance neural recruitment mechanisms, and lead to improved cognitive reserve. Activity programmes lasted 3–6 months, were aerobic in nature, and sample sizes were small, with 10–17 intervention participants in these studies (see Table 3 for individual study details).

Neural connectivity

Neural connectivity effects were measured using electro-encephalogram (EEG) readings in 5 studies (Amjad *et al.*, 2019; Hong *et al.*, 2017; Kim and Lee, 2018; Pedroso *et al.*, 2018;

Yerokhin *et al.*, 2012). All studies reported improved EEG patterns/complexity, indicating improved neural connectivity; cognitive function was improved too, although improvements were only slight in the case of Hong *et al.* (2017). Again, intervention numbers were small (9–22). Intervention durations were shorter than other studies, ranging from 6–12 weeks, with less emphasis on intensity (e.g. X-box training (Amjad *et al.*, 2019), or whole body vibration (Kim and Lee, 2018).

In the study by Pedroso *et al.* (2018), while the physical activity intervention improved reaction time, the control group took part in a social activity, which also resulted in improved information processing. This was the only study that had a defined/explicit social activity for control participants, although other group activities (intervention or control) may have had an implicit social element.

Endocrine and hormonal measures

Cytokines

Several studies used measures of endocrine activity; these included cytokines (see definitions at the end of the paper) such as C-reactive protein, tumour necrosis factor-alpha, beta amyloid and interlukin-6. Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of the immune system; they regulate inflammation and haematopoiesis (formation of red blood cells). All these biomarkers can be associated with cognitive decline pathology in diseases such as Alzheimer's (Baker *et al.*, 2010). Studies that measured cytokines included Baker *et al.* (2010), Chupel *et al.* (2017), El-Kader and Al-Jiffri (2016), Liu *et al.* (2020), and Tsai *et al.*, 2019) all of which reported improved anti-inflammatory and cognitive results in the exercise intervention groups, although study numbers were small (intervention groups ≤ 31). However, exercise was seen as having potential as a beneficial non-pharmaceutical intervention for people with mild to moderate cognitive impairment.

In associated study measures, brain derived neurotrophic factor (BDNF) was also examined in seven studies (Allard *et al.*, 2017; Baker *et al.*, 2010; Damirchi *et al.*, 2018; Kohanpour *et al.* (2017); Liu *et al.*, 2020; Tsai *et al.*, 2018, 2019) . BDNF is the most prevalent growth factor in the central nervous system (CNS). It is essential for the development of the CNS, new cell production, and for neuronal plasticity (Autry and Monteggia, 2012). Benefits of exercise were shown (via BDNF levels) to be greater for differing groups in these studies: for example, the study by Allard *et al.* (2017) concluded that neuroprotective effects of physical activity were greater in those who were non-APOE gene carriers, whereas Baker *et al.* (2010) concluded that older women may benefit to a greater extent, according to BDNF levels. In comparison, the study by Damirchi *et al.* (2018) found that mental training or combined mental/physical training outperformed (via BDNF levels) physical training alone for older women with mild cognitive impairment; intensity and duration (8 weeks) in this latter study were lower than other studies examining similar interventions (for example, the Allard and Baker studies were both of 6 months duration). A 12 week intervention of exercise $\pm$ lavender extract exposure in the study by Kohanpour *et al.* (2017) showed increased BDNF levels and improved cognitive states in a sample of people with mild cognitive decline. There were no other immediately discernable differences in sample populations (e.g. ages, baseline cognitive levels etc.) to explain the differences found by these studies.

In terms of exercise type, all interventions in this subgroup examined aerobic-type activities; Tsai *et al.* (2018, 2019) compared aerobic and resistance-style exercise, and found both to be of benefit over 16–24 week periods, but concluded that longer term interventions are required to determine if benefits from either exercise type are sustained. The results from Liu *et al.* (2020) indicated that both strength and aerobic training programs over the course of 4 weeks can bring about significant benefits for patients with dementia in both their ADLs

and cognitive performance. Furthermore, the difference in results between the two modes of exercise was not significant.

Hormonal measures

Other markers of interest in the included studies included hormonal measures of Insulin-like growth factor (IGF-I), cortisol, and norepinephrine.

Insulin-like growth factor (IGF-I) is a peptide hormone that functions primarily to stimulate growth but that also possesses some ability to decrease blood glucose levels, having insulin-like actions in some tissues, though far less potent than insulin in decreasing blood glucose concentrations [Britannica Dictionary (science division), 2019]. IGF-I levels were measured in studies by Anderson *et al.* (2017), Baker *et al.* (2010), Liu *et al.* (2020), and Tsai *et al.* (2018, 2019). In these studies, results were mixed, with Tsai and colleagues reporting some acute exercise increases in IGF-I levels, but indicating that these increases might not be sustained following completion of the activity. Baker *et al.* (2010) found increases in IGF-I levels for men, but overall better cognitive outcomes for women with mild cognitive impairment. Liu et al (2020) reported that neither strength nor aerobic exercise had a significant effect on IGF-1 levels. In the study by Anderson *et al.* (2017) researchers found that contrary to the study expectations, greater exercise endurance was associated with poorer cognitive prognosis when serum IGF-I levels were above a certain level (73.96 ng/mL). They concluded that the higher IGF-I levels might indicate disease progression within their sample, potentially as a compensatory response, and therefore participants with higher IGF-I levels may be less likely to benefit from the intervention.

Cortisol is a steroid hormone, often called the "stress hormone" because of its connection to the stress response (Hormone.org, 2019). Studies by Baker *et al.* (2010) and Ho *et al.* (2018) examined cortisol levels, the former as plasma cortisol, the latter via salivary samples. Baker *et al.* (2010) reported stable rather than increasing cortisol levels in their aerobic exercise group (both sexes), rather than the increasing levels (for women only) in their control (stretching exercise) group. In their male (stretching) control participants cortisol levels dropped.

Ho *et al.* (2018) reported lower cortisol levels in both intervention types (dance therapy and physical exercise compared to control), with the dance therapy group showing greater improvements (i.e. lower cortisol levels) that were sustained over 1 year follow-up. Numbers in this study were higher than other studies, with interventions being undertaken by 137 participants, who had very mild or mild dementia.

Norepinephrine (also called noradrenaline or noradrenalin), acts as a hormone and neurotransmitter [Britannica Dictionary (science division), 2019], and was measured in the study by Segal *et al.* (2012) via salivary alpha-amylase biomarkers. This study concluded that exercise activates the noradrenergic system, which may, in turn, benefit cognitive decline in both those with and without existing cognitive decline (intervention and control subjects). The authors of this study concluded that the benefits of exercise may work through more than one mechanism. This certainly seems to be the case across the included studies, and this will be considered further in the discussion section.

All studies measuring hormonal markers had fairly high intensity physical activities. Differences in duration type and intensity will be discussed further below.

Discussion

Summary of findings and comparison with previous reviews

This review has concentrated on primary studies that directly measure and analyse the mechanisms of action of physical activity interventions for people with cognitive decline.

In the past, Douglas *et al.* (2004) stated that non-pharmacological options should be pursued as a first line of treatment for people with dementia. At that time, their review contained a small section on activity therapies (dance, sport, drama), but concluded that details outlining the mechanism of change underpinning such activity-based interventions was lacking (Douglas *et al.*, 2004).

A later review by Haeger *et al.* (2019) focussed on structural and functional changes following physical activity (measured via MRI), and concluded that the effects of exercise mainly impacted on brain structures sensitive to neurodegeneration. Our current review updates and builds on Haeger *et al.* by also examining changes in endocrine and hormonal measures; it demonstrates that progress has been made in recent years in terms of investigating mechanisms of action, but also indicates where further knowledge is still required.

As previously mentioned, there were very few references to the potential effects of socialising within activity (or control) groups, which may have additional memory-protective effects for older adults (Pan and Chee, 2019). Behavioural change mechanisms of action that may have resulted from the interventions were also not investigated in the included studies, but may have had an impact (Junge *et al.*, 2018). Within the overall body of evidence from the review, however, there was certainly sufficient cause for physical activity to be viewed as a potential means of delaying the progression of cognitive decline.

Disease progression

In the included papers, the level of existing cognitive impairment appeared to have an influence on the impact of interventions. For example, where the effects of interventions on cerebral blood flow were measured, participants with more advanced cognitive impairment benefited less, possibly due to existing lower blood perfusion (van der Kleij *et al.*, 2018). In addition, people with more advanced disease may also exhibit higher levels of substances such as IGF-I before participating in an intervention (Anderson *et al.*, 2017); this is thought to be due to IGF-I being produced in greater quantities during neurodegeneration progression, as a response to increasing IGF-I resistance (Anderson *et al.*, 2017). As a result, since it may be impossible to detect which study participants are deteriorating, and to what extent, cerebral blood flow and IGF-I levels may not give the most accurate indication of intervention effect. It would therefore seem advisable to determine as much information relating to cognitive ability and diagnoses as possible at the start of any study, to make any observed and measured changes easier to interpret.

Intervention type and duration

Within the interventions, there was a range of duration from intense aerobic activity, several times a week (Allard *et al.*, 2017; Baker *et al.*, 2010; Tsai *et al.*, 2019) to a single 2 day, short duration intervention (Segal *et al.*, 2012). Other interventions included X-box gaming (Amjad *et al.*, 2019), an "exergaming" intervention, which combines video gaming with physical activity while playing.

Some activities were of sufficient duration and intensity that only people who were already physically fit would have been able to participate (Ho *et al.*, 2018). However, interventions that were of shorter duration, and less intense, did not always appear to deliver the same benefits (Damirchi *et al.*, 2018; Vital *et al.*, 2016). These factors may explain the variable study results, since some of the study participants may not have had the necessary capability to participate to the same level, if at all. In addition, differing dementia sub-types, or clinical presentations, may render some participants better able to exercise than others. Overall, the evidence would tend to indicate that while physical activity can be beneficial for everyone, within their capabilities, being and remaining as active as possible throughout the

life-course is potentially a better means of delaying or averting cognitive loss than attempting to start activities once physical and mental abilities are already declining.

Activities for control participants ranged from "usual care" to balance and tone exercises (Ten Brinke *et al.*, 2015), stretching exercises (Allard *et al.*, 2017; Baker *et al.*, 2010), or exercise that was of same duration and intensity, but of a differing type (Ho *et al.*, 2018 compared dance-movement intervention, with a similar length/intensity exercise programme, and a routine care group). Rather than being sedentary, control groups were therefore often participating in another physical activity. As stated earlier, there may have been a social interaction element also involved in the intervention or control group activities, which was not acknowledged as a compounding and potentially beneficial factor.

With further regard to activity type, dance therapy was shown to outperform exercise at reducing depressive symptoms, and improving daily function (Ho *et al.*, 2018), which may reflect the additional elements included in dance activities, such as remembering steps, social engagement, and the effects of music (Merom *et al.*, 2016).

Gender

The studies in this review did indicate some differences in intervention effect between men and women. For example, the greater cognitive function results shown for women in the study by Baker *et al.* (2010) were attributed to improvements in glucose regulation, insulin sensitivity, and reduced cortisol levels. However, the women in this study were also more sedentary than the men at baseline, potentially making similar activity intervention effects more marked. While some differences in effect for each gender were noted in a few studies, there was no consistent message with regard to gender that could be drawn from the included studies.

Biomarker measures

There were a number of questions raised about biomarkers that may have impacted on findings. For example, although several studies used IGF-I levels as an outcome measure, higher IGF-I levels can indicate increasing disease progression, potentially as a compensatory response (Vardy *et al.*, 2007), and may not therefore be an accurate means of measuring intervention impact.

Cortisol was another biomarker that raised some interesting points. In short, increased cortisol levels can compromise brain resilience to stress, and potentially increase susceptibility to neurodegeneration (Baker *et al.*, 2010). However, the two studies that measured cortisol levels (Baker *et al.*, 2010 and Ho *et al.*, 2018) measured levels in different ways (the former as one day/time point plasma cortisol levels, the latter via single day salivary samples). Cortisol levels are not only subject to day-to-day variations, they are also elevated with age, a variable that is almost three times greater for women than men (Otte *et al.*, 2005). In addition, higher cortisol levels may be present where disease progression is more rapid (Csernansky *et al.*, 2006). These factors call into discussion the suitability of cortisol as an accurate outcome measure for ageing participants, particularly in relation to cognitive progression and gender.

With regard to BDNF, in humans it is only possible to measure circulating BDNF, which may not accurately reflect brain level changes (Tsai *et al.*, 2018), and make comparisons with the findings from animal studies problematic.

Homocysteine levels may also vary according to a wide range of factors, including exercise intensity, food consumption, and levels of vitamin B12 or folate (Vital *et al.*, 2016). Measuring and controlling for such factors would be very difficult, therefore the value of findings relating to homocysteine levels may be uncertain.

Choice of biomarker outcomes would therefore seem to need careful consideration.

Strengths and limitations

This review is unique in its focus on amalgamating evidence relating the mechanisms of action of physical activity for people with cognitive decline. Due to the diversity of variables such as intervention duration/intensity, participant characteristics and selected outcome measures, direct comparisons or meta-analyses were not feasible. However, the resulting descriptive analysis does serve to combine a key body of evidence from a range of diverse populations. While the included studies were limited by their small sample sizes, the challenges of conducting research that involves participants with cognitive decline should not be underestimated, and may necessitate reduced study numbers. However, the need to further our understanding of interventions that may be of benefit is vital, albeit within the perimeters that such research is bound to operate.

As with all systematic reviews, meticulously planned and conducted search and screening processes can still fail to capture all relevant evidence.

Conclusions

Taken as an overall body of evidence, this review has indicated the value of physical activity for people with cognitive decline. However, it seems clear that the mechanisms of action are still to be fully understood, and are likely to be multifaceted. Several areas worthy of further consideration were highlighted:

Clinical implications:

- In general, physical activity should be considered as protective against progression in the early stages of cognitive decline.
- Rather than short duration interventions, physical activity may be of greatest benefit if incorporated into on-going lifestyles.
- Physical activity combined with social interaction should be considered.
- Individual ability to participate in physical activity at the level required to promote mechanisms of action needs more consideration.

Research implications:

- Attention needs to be given to:
    - choice of biomarker, taking into consideration natural changes associated with disease progression;
    - levels of activity prior to intervention;
    - effect and type of control activity;
    - type and level of cognitive impairment;
    - type and level of intervention activity;
    - social mechanisms of action that may lead to benefits of taking part in activities; and
    - behavioural change mechanisms of action that may have resulted from the intervention.

Definitions

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of the immune system; they regulate inflammation and red blood cell production. They have an effect on the interactions between cells, and the behaviour of

cells. The cytokines includes the interleukins, lymphokines and cell signal molecules, such as tumour necrosis factor, and the interferons, which trigger inflammation and infection responses, and possible links to cognitive ability. (www.sinobiological.com)

Insulin-like growth factor (IGF) is a peptide hormone that functions primarily to stimulate growth, but that also possesses some ability to decrease blood glucose levels, having insulin-like actions in some tissues, although far less potent than insulin in decreasing blood glucose concentrations. (www.britannica.com/science)

Brain derived neurotrophic factor (BDNF) is a protein produced inside nerve cells. It is the most prevalent growth factor in the central nervous system (CNS). It is essential for the development of the CNS and for neuronal plasticity (Autry and Monteggia, 2012)

Cortisol is one of the steroid hormones and is made in the adrenal glands. It is often called the "stress hormone" because of its connection to the stress response; however, because most bodily cells have cortisol receptors, it affects many different functions in the body. Cortisol can help control blood sugar levels, regulate metabolism, help reduce inflammation, and assist with memory formulation (www.hormone.org/hormones-and-health)

Beta amyloid is derived from an amyloid precursor protein and is thought to be the primary component of plaque characteristic in Alzheimer's disease. It is also referred to as A-beta, amyloid beta, amyloid beta peptide, and amyloid beta protein (www.merriawebster.com)

Acetoacetate is associated with energy metabolism. It is produced in the liver and is released into the bloodstream as an energy source during periods of fasting, exercise, or as a result of type 1 diabetes mellitus. Heart muscle and renal cortex respond more to acetoacetate than to glucose. The brain uses acetoacetate when glucose levels are low due to fasting or diabetes (www.medical-dictionary.com)

C-reactive protein (CRP) is a substance produced by the liver in response to inflammation.

A high level of CRP in the blood is a marker of inflammation. High CRP levels can indicate inflammation in the arteries of the heart, or risk of a heart attack. However, the CRP test is an extremely nonspecific test, and CRP levels can be elevated in any inflammatory condition. (www.healthline.com)

Irisin has been dubbed the "exercise hormone; irisin is produced when humans work up a sweat, and is thought to hold promise as weight-loss treatment, with possible links to telomere lengthening and brain functioning (www.livescience.com).

Norepinephrine is also referend to as noradrenaline or noradrenalin, and is an organic chemical in the catecholamine family that functions in the brain and body as a hormone and neurotransmitter (www.britannica.com/science)

Homocysteine is an amino acid. Having elevated levels of homocysteine in the blood is associated with atherosclerosis and blood clots. It has been suggested that high levels of homocysteine are associated with poorer mental functioning, leading to investigations into the role of homocysteine in Alzheimer's disease (medical-dictionary.com).

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Further reading

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