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

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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

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*walk*danc*“yoga”((tai TS=((dement* OR Alzheimer* OR “Lewy” bod*” chi) or (tai ji))*stretch*sport*(physical train*)) | OR “cognit* impair*”) AND exercis*) |
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.

| Inclusion criteria                                      | Exclusion criteria                                      |
|--------------------------------------------------------|--------------------------------------------------------|
| Study design: specific primary research studies of any design, which include an intervention and outcome(s) | Study design: study protocols without outcomes; commentary papers; dissertations |
| English language | Full article not available or not in English language |
| Population: adults (18yrs or older) with dementia or mild cognitive impairment, living independently or in a care environment; human studies | Population: no dementia; congenital or traumatic cognitive impairment (e.g. brain injury); animal studies; populations under 18yrs of age |
| Intervention: defined, specific physical activity interventions | Intervention: no specific physical activity intervention; physical activity incidental to other factors/actions; risk or prevalence studies (as sole focus) |
| Outcomes: physiological, functional, psychological, or social outcomes that are attributable to physical activity intervention | 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) |
| Lead author/Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? Finding/conclusions |
|-------------------------------|----------|------------|---------------------|---------------|----------------|-----------------------------------------------|
| Allard 2017 USA               | USA      | 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 = 46.39%; 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 show neuroprotective effects of physical activity, more especially for non-APOE gene carriers |
| Amjad 2019 Pakistan           | Pakistan | 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 (0.67 ± 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 duration X-box gaming showed benefits (complexity of EEG) for people with MCI |
| Anderson 2017 USA             | USA      | 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 > 0.05; 29.6% of sample). The strength of this inverse relationship increased as serum IGF-1 levels increased | Mixed findings; greater aerobic endurance gains were associated with poorer cognitive processes with elevated serum IGF-1 levels |
| Baker 2010 USA                | USA      | 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-amyloid | For the aerobic group, plasma BDNF and cortisol were positively correlated (r = 0.51; p = 0.04). Plasma IGF-1 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 supports non-pharmacological intervention in improving executive control processes; some gender differences, with older women benefiting more |
| Casteliano 2017 Canada        | Canada   | 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 acetate was three-fold higher (0.6 ± 0.4 versus 0.2 ± 0.1 μmol/100 g/min; p = 0.011) after intervention. Plasma acetate concentration and the blood-to-brain acetate influx rate constant were also increased by 2-3-fold (all p < 0.03). Brain uptake of glucose was unchanged after walking (29.0 ± 0.1 μmol/100 g/min; p = 0.96) | Yes; aerobic training improved brain energy metabolism by increasing ketone uptake and utilization, while maintaining brain glucose uptake; no change in homocysteine levels | (continued) |
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? | Findings/conclusions |
|-------------|---------------------|----------|------------|---------------------|---------------|----------------|-----------------------------|---------------------|
| Chirles2017USA | 2017 USA | 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 parietal 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; increased connectivity in 10 cerebral regions; exercise may enhance neural recruitment mechanisms |
| Chupel2017Portugal | 2017 Portugal | 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 leucocyte 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 improves anti-inflammatory balance and physical performance simultaneously with improved cognitive profile |
| Damirchi2018Iran | 2018 Iran | 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 memory improvements noted; mental training is a safe strategy to alleviate progression of MCI |
| El Kader & Al-Jiffri2016Saudi Arabia | 2016 Saudi Arabia | 40 people with AD, 65-75yrs; 20 intervention, 20 control | Treadmill aerobic exercise; 2months, 3x wkly, 15-35 mins; control group had no training. RCT | Reduced systemic inflammation, via effects on tumour necrosis factor alpha TNF-α and interleukin-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. 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; exercise intervention improved QoL, reduced systemic inflammation, and improved well-being |
| Ho2018 Hong Kong | 2018 Hong Kong | 204 people with very mild to mild dementia; ≥ to 65yrs | Dance (69), physical exercise (67) or control (68); 12 weeks, 2hrs per week. Control – routine care. RCT | Activation of hippocampal areas, and networks associated with spatial memory; cortisol levels | (continued) |

(continued)
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? |
|-------------|---------------------|----------|------------|---------------------|---------------|----------------|-----------------------------|
| Hong | 2017 | South Korea | 22 people with mild CI; 25 healthy people; > 65 yrs. Exercise/control in both groups | Resistance elastic band exercises; 12 weeks, 2x wky, 60 mins. Control - current lifestyle. RCT | Neural activity, EEG pattern changes | exercise group of matched intensity showed no significant effects on the outcomes | Yes; positive effects on EEG patterns, physical benefits, slight changes in cognitive functioning |
| Hsu | 2017 | Canada | 21 people with mild vascular CI (10 intervention, 11 control); mean 71.5 yrs +/- 8.6 yrs | Aerobic training, 6 months, 3x wky, 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 of associated brain areas, from fMRI |
| Kim & Lee | 2018 | South Korea | 18 women with mild dementia (9 intervention, 9 control); > 65 yrs; 79.22 yrs +/- 4.02 | Whole body vibration exercise, 8 wks, 5x wky. 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. 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; improved EEG activation and cognitive function |
| Kohanpoor x 2 | 2017 | Iran | 40 men with mild CI, 60-70 yrs; exercise +/- lavender, lavender alone, or control (10 to each group) | Aerobic/running exercise program, with lavender essence therapy; 12 weeks, 3x wky, 8-26 mins. Control - no exercise program, plus placebo. Pre/post test study | Anti-inflammatory effects (lavender essence); brain derived neurotrophic effects | Yes; intervention may decelerate or halt progression of cognitive impairment by reducing inflammatory factors |

(continued)
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? | Findings/conclusions |
|-------------|---------------------|----------|------------|---------------------|---------------|----------------|-----------------------------|----------------------|
| Liu 2020    | Taiwan              | 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; 30 mins, 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 training brought significant benefits to participants; serum brain-derived neurotrophic factor was additionally improved through aerobic training |  |
| Morris 2017 | USA                 | 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: benefits in functional ability, CV function, memory and reduced hippocampalatrophy following intervention |  |
| Pedroso 2018| Brazil              | 31 people with AD; > 65yrs, mean 77.5 ± 7.7, 14 intervention, 17 control | Physical exercise 12 weeks, 3x wkly, 1 hr. Control - social activity Exact 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 improved reaction time, suggesting recovery in cortical activity; however social group may improve in information processing |  |
| Rektorova 2020 | Czech 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 in executive function and increased cortical thickness in the lateral occipito-temporal cortex which is engaged in activities important for motor learning and executing skilled movements |  |
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? |
|-------------|----------------------|----------|------------|---------------------|---------------|----------------|-----------------------------|
| Segal       | 2012 USA             | 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 \( \mu V \) and post = 6.9 \( \mu V \)) and parietal midline (pre = 4.7 \( \mu V \) and post = 5.7 \( \mu V \)). 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 activates noradrenergic system may benefit cognitive decline |
| Smith       | 2013 USA             | 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 D1 group, including inferior temporal, | Yes; exercise may improve neural efficiency during semantic memory retrieval in MCI and cognitively intact older adults |
| Ten Brinke  | 2015 Canada          | 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 (\( b = 0.032; t \text{ (53)} = 2.91; p = 0.005 \)) | Yes; aerobic training significantly increased hippocampal volume |
| Tsai        | 2018 Taiwan          | 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 (exercise 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 neuroprotective/growth factor changes and neurocognitive performance for both aerobic and resistance training. Transient improvement shown in the present work needs further long-term exercise intervention studies |
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | Findings/conclusions |
|-------------|---------------------|----------|------------|---------------------|--------------|-----------------|---------------------|
| Tsai 2019   | Taiwan              | 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 exercise effective with regard to increasing neurotrophins, reducing some inflammatory cytokines, and facilitating neurocognitive performance |
| van der Kleij 2018 | Denmark             | 51 participants with mild/moderate AD, 50-90yrs (68.5 +/-7). Intervention 27, control 24 | Moderate to high exercise, 16 wks, 3x/week, 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 < 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 cerebral blood flow noted; authors concluded that 16 weeks of exercise are not sufficient to produce a consistent increase in cerebral blood flow in a relatively small sample of Alzheimer’s patients |
| Vital 2016  | Brazil              | 30 participants with AD; 14 intervention, 16 control (social interaction) | Resistance training, 16 wks, 3x/week, 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 found between physical activity and metabolic variants |

(continued)
| Lead author | Year of publication | Location | Population | Intervention/Method | Suggested MoA | Results summary | MoA corroborated by evidence? Findings/conclusions |
|-------------|---------------------|----------|------------|---------------------|---------------|----------------|------------------------------------------------|
| Yerokhin    | 2012 USA            |          | 13 participants with early stage dementia, mean age 79.3 yrs, range 60–95 yrs; 9 normative older adult controls, 55–78 yrs (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 | Neurophysiologic effects on frontal lobe asymmetry 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 revealed beneficial effects of strengthening exercise on verbal memory coupled with EEG results indicating increased brain efficiency (frontal beta and delta power asymmetries and N200 amplitude asymmetry). |
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;
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 interleukin-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 ± 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](http://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](http://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](http://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](http://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](http://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](http://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](http://www.livescience.com)).

*Norepinephrine* is also refered 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](http://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](http://medical-dictionary.com)).

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**Further reading**

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Louise McCabe is a Senior Lecturer in Dementia Studies, University of Stirling, with expertise in qualitative research that engages with people with dementia and their families and focuses on the role and impact of care services.

Alison Bowes is a Professor in Sociology and Dean of the Faculty of Social Sciences, University of Stirling. She researches issues relating to supporting better ageing and better living with dementia, and has published widely in this area.