

Can exercise prevent cognitive decline?

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Dr Sophie Behrman
BA BM BCh MRCPsych
CT3 in Psychiatry, Oxford Deanery, Oxford, UK

Professor Klaus P. Ebmeier
MD
Professor of Old Age Psychiatry,
University of Oxford, University Department of Psychiatry,
Warneford Hospital,
Oxford, UK



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AUTHORS

Dr Sophie Behrman
BA BM BCH MRCPsych
CT3 in Psychiatry, Oxford
Deanery, Oxford, UK

Professor Klaus P. Ebmeier

MD
Professor of Old Age
Psychiatry, University
of Oxford, University
Department of Psychiatry,
Warneford Hospital,
Oxford, UK



How effective is exercise for depression?

How does exercise affect cognitive function?

What type of exercise is suitable for older people?



THE NUMBER OF PEOPLE OVER 65 IS PREDICTED TO DOUBLE BETWEEN 2008 AND 2051,¹ ALTHOUGH THE

clinical impact of this may be attenuated by overall delayed ageing.² The presentation of major depressive disorder and memory loss is likely to become more frequent in primary care. As the tolerability of psycho-pharmacological agents decreases with age, exercise may be particularly helpful as a possible treatment or at least a stabiliser of mood and cognitive function in older age.

DEPRESSION

Exercise has been most commonly evaluated for the treatment of depression. Unfortunately, studies are often poorly designed, with methodological difficulties in blinding, controlling for past exercise habits, and design flaws, such as failure to do an intention to treat analysis.

Some use control conditions of limited validity (e.g. 'relaxation' or 'meditation', both of which have been shown to have modest antidepressant properties)^{3,4} or confound results by only recruiting participants who enjoy

(or at least tolerate) exercise. There appears to be a bias towards positive results in poor quality studies, whereas meta-analyses of well designed studies are less convincing.

In the most recent Cochrane review, only three trials with adequate allocation concealment, intention to treat analysis and blinded outcome assessment were identified, showing overall a moderate, but non-significant, effect size. The effect of exercise was not significantly different from that of cognitive therapy.⁵ Similar results have been confirmed in a subsequent

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SYMPOSIUM CARE OF THE ELDERLY

EXERCISE AND MENTAL HEALTH

meta-analysis.⁶ A later meta-analysis of five trials with long-term follow-up (i.e. outcomes measured beyond the end of the intervention) suggested no long-term benefit of exercise in depression.⁷ A further meta-analysis considering all age groups, and including more recent studies, found that the efficacy of exercise in the treatment of depression was influenced by age and severity of symptoms.⁸

Studies of individuals over 60 years showed a higher efficacy than in individuals below 60 years. Studies of patients with moderate and mild depressive symptoms showed a lower effect than those restricted to patients with mild depressive symptoms.⁸

No clear guidance about type of exercise or recommended intensity

can be derived from current research; most tend to follow similar protocols (i.e. 30-60 minutes of moderate-intensity activities three times a week).

‘Exercise has been shown to improve executive function acutely in adults of all ages’

Allowing participants to choose their own intensity of exercise appears to have positive results in middle-aged women,⁹ and this needs to be examined in the elderly, who are more likely to be

limited by physical comorbidity.

Exercise interventions designed primarily for treatment of physical conditions in the elderly do appear to confer psychological benefits as well, with reduction in depressive symptoms over the course of treatment.¹⁰ However, a cluster randomised controlled trial offering exercise programmes and staff training to care homes did not find any change in depressive symptoms in residents offered the intervention.¹¹ This may be because the exercise was indiscriminately offered at a low intensity, and the sample would have included a number of participants with cognitive impairment and only a minority with depression.

Perhaps targeting exercise interventions to those who are more

Table 1

Potential mechanisms for the effects of exercise on depression

	Theory	Comments
Biological	Inflammation may disrupt synthesis, reuptake and metabolism of neurotransmitters, affect the HPA axis, and inhibit neurogenesis ¹²	● Depression is associated with increased levels of inflammatory cytokines. Exercise has been shown to have anti-inflammatory effects in subjects who are not depressed ● In the TREAD study^{12,13} of depressed subjects with partial response to SSRIs, higher baseline TNF alpha levels were associated with a greater decrease in depressive symptoms over the period of exercise ($P < 0.0001$). There was a significant correlation between changes in IL-1 levels and depressive symptoms ($P < 0.04$). High TNF alpha may differentially predict better outcomes with exercise, as opposed to antidepressant medications for which high TNF alpha is linked to poor response ● Exercise may be a more effective treatment for depression associated with other comorbid inflammatory conditions, such as the metabolic syndrome, diabetes, arthritis etc
	Neurogenesis	Evidence exists, largely from rat studies, that exercise mediates neurogenesis, possibly by increasing levels of beta endorphins, vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and serotonin. ¹⁴ More recent evidence in humans suggests that the effect of exercise on depression is <i>not</i> mediated by BDNF ¹⁵
	Serotonin	Lipolysis with exercise may alter the distribution of tryptophan, a precursor for serotonin. ¹⁶ Reduction in plasma serotonin is seen with antidepressants and with exercise ¹⁷
Psychological	HPA axis	Depression is associated with high basal levels of cortisol. Exercise has been shown to reduce levels of cortisol in people with depression ¹⁸
	Cerebral blood flow and glucose metabolism	EEG changes in depressed elderly patients have been correlated with cerebral blood flow and glucose metabolism. Exercise reverses such EEG changes, ¹⁹ possibly by increasing cerebral blood flow
	Self-esteem	Mastery of a new skill ⁵ and positive feedback from others ⁷ may increase feelings of self-esteem and therefore improve mood
	Distraction	Exercise may distract participants from persistent negative thoughts
	Motivation from, and therapeutic relationship with, instructor	Support from a trained instructor using motivational and psychosocial techniques improved adherence to an exercise programme in middle-aged women ⁹
	Behavioural activation	CBT for depression typically includes a ‘behavioural activation’ component: participants schedule activities, and in completing these activities have a sense of achievement, an improvement in mood, and an increased likelihood of engaging in further activities
Social	Social contact	It is not clear if the effects of exercise are mediated by participation in group activity, or if solitary exercise has similar effects

physically able and with clearly abnormal depression scores would generate more positive results.

Mechanisms

The mechanisms by which exercise may alleviate depression are poorly understood, and are likely to be multifactorial. Some current hypotheses are summarised in table 1, opposite.

Clinical implications

Despite the heterogeneity of studies and the moderate effect sizes, it is important to recognise that the effects of exercise on reducing depressive symptoms are not dissimilar to the effects of traditional treatments, i.e. antidepressant drugs and cognitive behaviour therapy.⁵ Exercise may be a useful low-tech intervention for people with mild to moderate depression, who can be motivated to engage with a programme of exercise. In particular, exercise may be helpful in the elderly and in patients who have had insufficient response to, or are intolerant of, pharmacotherapy.

'The effects of exercise on depressive symptoms are not dissimilar to the effects of antidepressant drugs and CBT'

Only 30% of Western populations engage in significant amounts of exercise on a weekly basis,²⁰ participation in physical activity tends to decrease with age, and symptoms

of depression include lack of motivation and lack of energy.

Few elderly patients with depression may be able to increase their physical activity sufficiently to have a noticeable effect on their symptoms.

The question remains, therefore, whether exercise is a feasible treatment for most elderly people with depression. Further research is needed into the most beneficial treatment programme and intensity of exercise, but the recommendations of one meta-analysis⁸ seem sufficiently similar to the current WHO recommendations for moderate-intensity exercise in the elderly, for this to be used as a guide, see box 1, below.²¹

COGNITIVE DECLINE

Until very recently, reviews and guidelines arrived at the conclusion that physical activity programmes for persons with dementia provided insufficient or inconsistent evidence of efficacy.^{22, 23} However, a Cochrane review, published in December 2013,²⁴ found, after assimilating new evidence, that exercise has a moderate effect on the ability of people with dementia to perform activities of daily living (six studies, 289 participants, SMD 0.68, (95% CI:0.08-1.27) and may improve cognitive function (eight trials, 329 participants, SMD 0.55 (95% CI:0.02-1.09).

However, the confidence of these conclusions is diminished by the substantial statistical heterogeneity between trials. This means that either the outcome of exercise is not reliable, or there are as yet unknown factors that affect outcome, in a way that none of the exercise regimens can be recommended with confidence. No significant effect of exercise on depression or 'challenging behaviour' in people with dementia could be identified.

An older Cochrane review considering the effects of physical

activity on cognitive function in older people without a diagnosis found some evidence that aerobic exercise, which improved cardiorespiratory fitness, had some benefits on specific aspects of cognitive function. However, most comparisons did not yield significant results.²⁵ A recent cohort study (also published in December 2013) of 2,235 men and spanning 30 years²⁶ provides evidence that exercise at baseline (ages 45-59) is a predictor of less cognitive impairment odds ratio (OR) 0.64, $P < 0.04$ and dementia at follow-up OR 0.41, $P < 0.005$.

'The group who had to learn the dance routine outperformed the controls on other cognitive function tasks'

However, a meta-analysis of exercise interventions in participants, who had mild cognitive impairment found no evidence that exercise improves cognition in this population,²⁷ suggesting either that in epidemiological studies cognition and exercise can be confounded by cohort effects ('participants with good outcomes also exercise a lot'), or that for exercise to confer any protective benefit on cognition it must be undertaken at a younger age, i.e. before the onset of cognitive decline.

As was the case for depression, there are few studies considering the type of exercise that is most beneficial for cognition. A small trial randomised elderly participants to two dance programmes of equal physical intensity, one of which required memorisation of a specific sequential dance routine, the other used the same movements but in stereotypical homogeneous blocks.

The group who had to learn the dance routine outperformed the controls on other cognitive function tasks.²⁸ It is possible that dance routines or other exercise regimens requiring some cognitive input (short-term memory, executive function) may confer additional benefit to cognitive function.

Box 1

WHO recommendations for physical activity in adults aged 65 years and above (for physical and mental wellbeing)

- At least 150 minutes of moderate-intensity aerobic physical activity each week OR 75 minutes of vigorous-intensity aerobic physical activity each week OR an equivalent combination of the above
- For additional health benefits, these recommendations should be doubled
- Aerobic exercise should be performed in bouts of at least 10 minutes duration
- Adults of this age group with poor mobility should perform physical activity to enhance balance and prevent falls on 3 or more days per week
- If unable to accomplish the above, adults of this age group should be as physically active as their abilities and conditions allow

key points

SELECTED BY

Dr Peter Saul

GP, Wrexham and Associate GP Dean for North Wales

As the tolerability of psychopharmacological agents decreases with age, exercise may be particularly helpful as a possible treatment or stabiliser of mood and cognitive function in older age. Exercise has been most commonly evaluated for the treatment of depression.

In the most recent Cochrane review the effect of exercise on depression was not significantly different from that of cognitive therapy. Studies of individuals over 60 years showed a higher efficacy than in individuals below 60 years. Studies of patients with moderate and mild depressive symptoms showed a lower effect than those restricted to patients with mild depressive symptoms.

Exercise interventions designed primarily for treatment of physical conditions in the elderly do appear to confer psychological benefits as well, with reduction in depressive symptoms over the course of treatment.

Depression is associated with increased levels of inflammatory cytokines. Exercise has been shown to have anti-inflammatory effects in subjects who are not depressed. Mastery of a new skill and positive feedback from others may increase feelings of self-esteem and therefore improve mood. Exercise may distract participants from persistent negative thoughts.

The effects of exercise on reducing depressive symptoms are not dissimilar to the effects of antidepressant drugs and cognitive behaviour therapy. Exercise may be a useful low-tech intervention for people with mild to moderate depression. In particular, exercise may be helpful in the elderly and in patients who have had insufficient response to, or are intolerant of, pharmacotherapy.

The WHO recommendations in adults aged 65 and above for physical and mental wellbeing are: at least 150 minutes of moderate-intensity aerobic physical activity or 75 minutes vigorous-intensity aerobic activity each week. Aerobic exercise should be performed in bouts of at least 10 minutes.

Exercise has been shown to improve executive function acutely in adults of all ages. It is possible that dance routines or other exercise regimens requiring some cognitive input may confer additional benefit to cognitive function.

Good management of the metabolic syndrome and cardiovascular risk factors, e.g. with aerobic exercise, is likely to reduce the future risk of Alzheimer's disease. Linked to this, it is thought that the respiratory component of aerobic exercise alone may protect the brain from chronic hypoxic and ischaemic changes and therefore improve cognitive function. Exercise has a moderate effect on the ability of people with dementia to perform activities of daily living and may improve cognitive function. It is likely that midlife exercise may also have an impact on later cognitive function.

Table 2

The benefits of exercise on mental wellbeing and cognitive function

	Effect of intervention
Exercise for depression	Overall moderate, but non-significant, effect size. The effect of exercise on depression could not be differentiated from that of cognitive therapy ⁵ No long-term benefit of exercise in depression on outcomes measured beyond the end of the intervention ⁷
Physical activity, enhanced fitness and cognitive decline	Aerobic exercise, which improved cardiorespiratory fitness, had some benefits on specific aspects of cognitive function in older people without known cognitive impairment ²⁵ In participants who had mild cognitive impairment no evidence was found that exercise improves cognition in this population ²⁷ Exercise has a moderate effect on the ability of people with dementia to perform activities of daily living and may improve cognitive function ²⁴ Exercise in mid-life (45-59) is associated with reduced risk of cognitive impairment and dementia in later life (naturalistic study) ²⁶

Mechanism

As is the case for the link between exercise and depression, possible mechanisms linking exercise and cognitive function and dementia are not clearly established. Ageing brains have been shown to be capable of neuroplasticity,²⁹ although the mechanism is not clear. In particular, grey matter changes in the hippocampus have been seen following a course of aerobic exercise, but not after stretching exercises as a control intervention.³⁰

'The respiratory component of aerobic exercise may protect the brain from chronic hypoxic and ischaemic changes and improve cognitive function'

In this study, the effect was thought to be mediated by increased brain-derived neurotrophic factor (BDNF), which promotes dendritic branching and therefore increases hippocampal

volume; this hypothesis and suggestions of other contributing growth factors (IGF-1, VEGF) have been described in detail elsewhere.³¹

Improvements in cardiovascular health with exercise may have an impact on cognitive function in at least two ways. A link between physical fitness, cerebral perfusion and cognitive function has been established.³²

Exercise has been shown to improve executive function acutely in adults of all ages, although the mechanism behind this is not clear. Although blood flow in the middle cerebral artery (a proxy for perfusion) was strongly related to cognition at rest, these measures became uncoupled during exercise.³³

Second, the metabolic syndrome appears to increase the risk of Alzheimer's disease,³⁴ and it is thought that insulin moderates beta-amyloid and therefore insulin resistance leads to aggregation of beta-amyloid plaques. Good management of the metabolic syndrome and cardiovascular risk factors, e.g. with aerobic exercise, is likely to reduce the future risk of Alzheimer's disease.

Linked to this, it is thought that the respiratory component of aerobic exercise alone may protect the brain from chronic hypoxic and ischaemic changes and therefore improve cognitive function.³⁵

Other suggestions are that the effect is due to the cognitive stimulation function of the exercise

and the increased social contact the intervention provides; it may also be that improvements in mood lead in turn to improvements in memory, although the recent Cochrane review found no effect of exercise on depressive symptoms in people with dementia.²⁴

‘Exercise in mid-life (45-59) is associated with reduced risk of cognitive impairment and dementia in later life’

Clinical implications

There is mounting evidence to suggest that exercise improves activities of daily living in patients with dementia and it is likely that midlife exercise may also have an impact on later cognitive function, see table 2, opposite.

Until there is evidence for more specific protocols or interventions, it would be prudent to advise patients to adhere to the WHO recommendations for physical activity appropriate for their age group see box 1, p19.

The Cochrane review²⁴ did not discover any adverse events from exercise in any of the trials reviewed, making it a very low risk intervention for cognitive function, with likely benefits in a number of other physical and psychological domains.

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Useful information

Age UK
www.ageuk.org.uk

Depression Alliance
www.depressionalliance.org

Alzheimer's Society
www.alzheimers.org.uk

Living well with dementia: A national dementia strategy (2011)
www.dh.gov.uk/health/2011/07/dementia-strategy

Royal College of Psychiatrists
www.rcpsych.ac.uk

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