Exercise to Prevent Cognitive Decline and Alzheimer’s disease: For Whom, When, What, and (most importantly) How Much?

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In several reviews, exercise was reported to be effective in reducing the risk for cognitive decline and dementia [1,2]. However, not all reviews concluded this. One recent review [3] stated that there was still insufficient evidence, as most studies were too small and had insufficient methodological information (intensity, duration) to enable appropriate evaluation. Here we discuss potential confounds or mediators that may explain these discrepancies.

We found that most observational studies showed at least some positive associations of exercise, but not always on the same cognitive tests [1]. Variance in studies was induced by inconsistent use of cognitive assessments (e.g. fluid intelligence compound scores vs Symbol Digit Modalities Test (SDMT) scores by itself); different assessments of fitness (objective vs. self reported hours of exercise engaged in); and different cut-offs for high/low exercise across studies. These limitations were echoed by others and recent reviews also illuminated potential confounds associated with both exercise and cognitive improvement, such as lifting of depression, as well as social and cognitive stimulation [4], and an increase in self efficacy (Stock, in press), which have usually not been taken along in analyses or adequately controlled for. Observational studies are limited in their ability to establish causality and many people could have stopped exercise because of other confounding morbidity, which may also affect cognitive function (e.g. vascular disease, see below). Randomised controlled trials (RCT) are better at establishing causality, but can also be affected by choice of measurements and population, suffer from baseline differences, regression to the mean and design of the control conditions (e.g. without social or cognitive stimulating aspects), as well as the above mentioned limitations of potential non-assessed confounds or mediators, such as mood.

In our earlier review of 26 RCT studies in community dwelling elderly without known dementia or cognitive impairment, which had been carried out up to 2009 [1], only 6 studies showed overall cognitive improvement, 13 some improvement and 7 none at all. The most consistent cognitive tests to be affected by exercise interventions in this group were simple tests, such as those of concentration and those using simple reaction times. Several earlier reviews suggested that more complex cognitive tests were most affected by exercise. However, our review finding was substantiated by those of the Cochrane meta-analyses [5], which is a gold standard medical review system. About half of RCT studies we had included in our review [1], which had used a simple test of concentration and working memory (Digit Span) found that it displayed significant positive results of exercise, but the other half of studies using this test (n=5) had not found any improvement. Of the complex information processing tests previously thought to be most sensitive to exercise, 21 tests (including the Stroop 4x, Symbol Digit Modalities test (SDMT) 4x, CRT 3x, memory search 2x, and abstract reasoning) showed no effects of exercise, versus only 10 tests of complex information processing that did (including the Stroop 1x, verbal Fluency 3x, and Digit Span backwards 2x, and CRT 2x, and 2 other complex tests). This suggests a 50% chance of finding an exercise effect on a simple concentration test, versus only a 32% chance of finding this when using complex cognitive tests. A recent meta-analyses [6] reported no greater effect for any specific cognitive domain (investigating Complex or Choice Reaction Times (CRT), executive or memory function tests) when extended cognitive test practice (n=25 studies) was compared to aerobic exercise (n=17 studies), although better study quality was associated with larger effect sizes. After both interventions, effect sizes seemed larger on executive function tests than on memory or CRT tests echoing earlier reviews. However, as the authors reflected, outcomes studied may have not fitted within the domain or combined several domains. Learning effects are clearly greater on executive function tests and without adequate control, it is difficult to establish whether exercise promotes implicit learning (how to do the test) over and above that of exposure to the test per se. However, other reviews showed that studies which had controlled for session number and psychosocial exposure by including an assumed non active intervention (e.g. using stretching and/or balancing exercises) did show additional cognitive effects of aerobic and/or strength training over and above participating in control (i.e. practice) sessions [1,2].

Our review [1] suggested that aerobic exercise of sufficient intensity which had been assessed objectively showed the best results in improving cognition in community dwelling elderly. However, again only half of the studies that reported an increase in VO2 measures found a positive effect on cognition. On the other hand, all studies which reported an improvement in muscle strength found that this type of exercise improved cognition. Resistance and strength exercise was thus thought to contribute positively to brain function, either by itself or in combination with aerobic exercise. However, flexibility, balancing and stretching exercise by itself (such as yoga) did not show overall positive effects on improving cognition. In recent reviews it is often seen to be used as a control treatment for this reason.

While intensity of exercise was important, a higher frequency of exercise did not necessarily induce more cognitive improvement [1]. Effects were seen already after only 4 [2] to 8 weeks [1], but adherence in many studies to exercise regimes was low, possibly contributing to null findings in some studies [1]. A recent study performed in our laboratory with sedentary older participants (40-65 years old) showed that resistance exercise (30 min 3x week for 12 weeks using resistance bands at home) had high adherence (90%) and improved memory (episodic and semantic memory using a word list recall and a verbal fluency test, respectively) when compared to yoga exercises of a similar...
duration in an order balanced cross over design. Other tests (of complex speeded information processing, such as the TMT and SDMT) were not improved by exercise. Effects in our study were particularly apparent in middle-aged women [7]. Others mention an optimum of 30 min 5 times a week of moderate aerobic intensity and resistance training twice a week conform Department of Health guidelines [2,8] (see also DH online guidelines 2011), with for those over 65 years of age, sessions lasting at least 10 min.

However, a trade-off between adherence and intensity needs to be made to promote long term sustainability of behavior. Carry-over effects with those in control conditions or cross over conditions carrying on with exercise and/or engaging with other activities (walking, gardening) need to be controlled for in future studies through objective assessment of strength and endurance. In our study, grip and leg strength did not mediate the improvement in cognition [7].

We also reviewed prospective studies investigating risk of dementia which was found to be reduced in those who exercise in 9 of 13 studies [1]. However, there was a wide variety in whether effects were mainly shown for particular dementia subtypes (vascular or Alzheimer’s disease) or all types of dementia without a clear consensus. The studies not finding effects had mainly used exercise self reports which have limited validity and again various definitions for exercise and high/low activity were included. Consistent with the greater effects of exercise on cognition in women in our recent intervention study [7], three observational prospective studies found the risk for dementia with exercise to be more reduced in women, although one study did not find a gender difference [1].

The randomized controlled four studies we reviewed [1] that had investigated exercise in participants with cognitive impairment or dementia also showed that those two which had included mainly women had the best results. One study reported that walking (30 min 3x per week for 6 weeks) improved complex information processing (executive function) in older women with cognitive impairment [9]. Another study that had included mainly women with dementia used mixed strength and aerobic exercises (once a week, which increased from 15 min to 45 min/week at 60% VO2max after 12 months) and showed effects on global cognitive function already after 6 months, which were further enhanced at 12 months [10]. In the latter study stretching, use of weights and aerobic components (staircase exercise etc.) were combined. The other two studies found no effects, but both intensity and adherence were thought to be possibly too low to induce improved cognitive performance [1]. However, in a recent review which had included more recent RCTs from 2008 to 2011, (aerobic) walking, but also movement or chair training exercises were shown to improve memory in 5 - and executive function in 4 - of 8 studies. In this recent review, all 8 studies showed some effects on cognition, which may reflect better procedures used in the studies, or, alternatively, inadequate search strategy or publication bias. Three studies of this review (not included in our review) had included participants with (subjective) memory impairment or dementia and in one of these studies women again had better executive function after aerobic exercise than men [2].

Findings of strongest effects of exercise on cognition in older women are intriguing. In pooled analyses of several mainly European countries the risk for Alzheimer’s disease (AD, the most common form of dementia) was found to be doubled for women [11,12]. This may be the case because women tend to live longer than men and age is a major risk factor for dementia. While AD is only seen in very few elderly around 65 years of age, the risk doubles with every 5 years of age onwards [12]. One in three babies born in the UK today is estimated to live to 100 years and many of these eventually will be afflicted with dementia. With an aging population worldwide, AD is a growing problem with high human and economic costs [13]. In the U.K., there were an estimated 800,000 suffers costing society almost $30 billion in 2010, and two thirds of these were women [14]. Data from 2011 ONS statistics show that currently in the U.K. dementia is the third leading cause of mortality in women (and the 8th in men) after ischemic heart disease and cerebrovascular disease. Dying of dementia related causes in women increased by 14% between 2004 and 2009 alone (Figure 1).

Many of the risk factors for AD overlap with those for cerebro- and cardiovascular disease, such as smoking, high blood pressure, total cholesterol, and obesity in midlife [16,17]. The link between midlife vascular disease and later AD may explain the gender difference in AD prevalence [17]. Women present with vascular disease on average 7-10 years later than men [18]. In past cohorts, possibly because of differences in lifestyle (smoking, work related stress), more men than women would have died because of circulatory disease before they could reach an old enough age to develop AD and VaD (Figure 1). However, survival rates for men after vascular incidents (stroke, myocardial infarct) have shown a steady improvement over the past decades. On the other hand, in 2007 more women died of vascular disease than men, reversing the trend that existed only 10 years earlier [18]. This relationship between vascular disease and AD may also explain why in many American cohorts, with a high incidence of obesity in both men and women, gender differences in AD are no longer found [19].

Central obesity and associated silent killers (high blood pressure and high cholesterol) is associated with a culture of unhealthy diets, work related stress, smoking and sedentary lifestyles [17]. The risk for both AD and vascular disease could be reduced in those who exercise possibly because it reduces these risk factors, such as stress, abdominal obesity, high blood pressure and high total cholesterol and triglycerides and it may encourage smoking cessation [8,17]. Meta analyses show that when women present with acute coronary disease (ACD), they are more likely to suffer from hypertension, high cholesterol, and diabetes, while men are more likely to smoke [18].

The question is whether these are true gender related differences in risk factors or whether - when assessed by self report rather than objective assessment- reflect women being more aware of suffering from these morbidities and already receiving medical treatment for these. If women really have a higher load of these vascular risk factors, they may respond better to exercise better than men because exercise...
would benefit those with a high vascular risk most substantially. However, women also have an increased tendency to seek screening and treatment earlier for these conditions, which may also be why they present a decade later with ACD [18]. An alternative explanation for the gender difference in response to exercise is that women adhere more to the exercise treatment regimen than men, in line with their overall more health promoting behavior.

Another explanation for the increased risk in women for dementia and cardiovascular disease after menopause could be the dramatic reduction of levels of sex steroids associated with menopause [20]. Sex steroids affect most of the mechanisms associated with protection of the brain and vascular system and could thus reduce dementia risk for [20]. While estrogen in older women is perhaps less effective and could even increase risk for dementia and vascular disease [20], androgens may be an alternative therapy. Short term aerobic and resistance exercise can increase androgen levels in women and men, but this may depend on exercise type, training regimen, age and other factors [21,22]. For instance, long term intense training regimes can also be associated with lower androgen levels [21] and there may thus be optimum levels of training to confer the best benefits. These could mimic the optimum levels of testosterone found in both older women and men to be associated with optimal cognitive function [23].

In conclusion, these gender related exercise results suggest that while exercise may help to prevent dementia, exercise of sufficient intensity (at least once to 3-5x per week for 30 min, walking and/or using weights and resistance bands) can also help improve global cognitive function even in those who already have dementia. This suggests that reduction of vascular risk factors in midlife is not the only pathway in prevention of cognitive decline. Perhaps mediation of androgen effects on the brain and vascular systems and/or the direct effect of exercise in improving oxygenation and neuro- genesis of the hippocampus and other parts of the brain associated with exercise of sufficient intensity [1,8] can explain improved cognitive function in those with dementia. Whether resistance exercise by itself is sufficient to improve cognition and whether psychosocial improvements and/or testosterone elevation mediate this association should be further investigated.

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