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Review

The effect of physical activity on cognitive function in patients with dementia: A meta-analysis of randomized control trials

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ABSTRACT

Non-pharmacological therapies, such as physical activity interventions, are an appealing alternative or add-on to current pharmacological treatment of cognitive symptoms in patients with dementia. In this meta-analysis, we investigated the effect of physical activity interventions on cognitive function in dementia patients, by synthesizing data from 802 patients included in 18 randomized control trials that applied a physical activity intervention with cognitive function as an outcome measure. Post-intervention standardized mean difference (SMD) scores were computed for each study, and combined into pooled effect sizes using random effects meta-analysis. The primary analysis yielded a positive overall effect of physical activity interventions on cognitive function (SMD[95% confidence interval] = 0.42[0.23;0.62], $p < .01$). Secondary analyses revealed that physical activity interventions were equally beneficial in patients with Alzheimer's disease (AD, SMD = 0.38[0.09;0.66], $p < .01$) and in patients with AD or a non-AD dementia diagnosis (SMD = 0.47[0.14;0.80], $p < .01$). Combined (i.e. aerobic and non-aerobic) exercise interventions (SMD = 0.59[0.32;0.86], $p < .01$) and aerobic-only exercise interventions (SMD = 0.41[0.05;0.76], $p < .05$) had a positive effect on cognition, while this association was absent for non-aerobic exercise interventions (SMD = -0.10[−0.38;0.19], $p = .51$). Finally, we found that interventions offered at both high frequency (SMD = 0.33[0.03;0.63], $p < .05$) and at low frequency (SMD = 0.64[0.39;0.89], $p < .01$) had a positive effect on cognitive function. This meta-analysis suggests that physical activity interventions positively influence cognitive function in patients with dementia. This beneficial effect was independent of the clinical diagnosis and the frequency of the intervention, and was driven by interventions that included aerobic exercise.

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Contents

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1. Introduction

Dementia is a clinical syndrome characterized by cognitive decline, motor deficits and/or behavioral problems, causing a decline in daily functioning (Scott and Barrett, 2007). Various neuropathologies can underlie dementia syndromes but the most prevalent cause is Alzheimer's disease (AD), accounting for 60–70% of the cases (Reitz et al., 2011). Other types of dementia include vascular dementia, dementia with Lewy bodies and frontotemporal dementia. Advancing age is the main risk factor for most sporadic forms of dementia, and with the ever increasingly aging population worldwide the prevalence of dementia is expected to nearly double from 35.6 million cases in 2010 to 65.7 million in 2030 (Prince et al., 2013). This expected increase will have profound social and financial consequences, and dementia has therefore been denoted a public health priority by the World Health Organization (Wortmann, 2012).

Currently, no disease modifying drugs for dementia are available and pharmacological treatment is limited to therapies that alleviate the symptoms. However, these treatments are not efficacious in all patients and may introduce undesirable side-effects (Galimberti and Scarpini, 2010). Non-pharmacological interventions, such as physical activity interventions (Deslandes et al., 2009; Hooghiemstra et al., 2012; Kirk-Sanchez and McGough, 2014; Sofi et al., 2011), are therefore appealing alternatives or add-ons. Epidemiological studies have shown that increased lifetime engagement in physical activities reduces the risk of dementia-onset in cognitively normal elderly persons (Abbott et al., 2004; Buchman et al., 2012; Chang et al., 2010; Hamer and Chida, 2009; Larson et al., 2006; Laurin et al., 2001; Podewils et al., 2005; Rovio et al., 2005; Scarmeas et al., 2009; Taaffe et al., 2008; Yaffe et al., 2001). Experimental animal studies have identified several molecular mechanisms such as enhancement of neurotrophin levels (Adlard et al., 2005; Berchtold et al., 2005, 2002; Gómez-Pinilla et al., 2007; Macias et al., 2007; Radak et al., 2010; Swain et al., 2003; Vaynman et al., 2003), neurogenesis (Kronenberg et al., 2006; Sahay et al., 2011; Van Praag et al., 2005, 2000, 1999) and vascularization (Black et al., 1990; Ding et al., 2004; Isaacs et al., 1992; Kleim et al., 2002; Swain et al., 2003) that may explain this beneficial effect. Moreover, physical activity may even reduce aggregation of pathogenic proteins (Adlard et al., 2005; Belarbi et al., 2011; Leem et al., 2009 Yuede et al., 2009), mediate neuroinflammation (Belarbi et al., 2011) and inhibit neuronal dysfunction (Um et al., 2011).

Physical activity thus seems to enhance brain vitality and several studies have investigated whether physical activity interventions are sufficient to slow down cognitive decline once the clinical diagnosis of dementia has been established. Results have been mixed, however, as some studies indeed showed a positive effect of physical activity interventions (Farina et al., 2014; Hess et al., 2014; Heyn et al., 2004; Scherder et al., 2014), while others did not (Forbes et al., 2015; Littbrand et al., 2011; Öhman et al., 2014). In the current study, we performed a meta-analysis of randomized controlled trials that investigated the effect of physical activity on cognitive function in patients with dementia. Secondary objectives of this meta-analysis were to assess whether the effect of physical activity on cognitive function was (1) comparable across different types of dementia, (2) dependent on aerobic and/or non-aerobic exercise, and (3) affected by the frequency of the intervention.

2. Methods

2.1. Study selection procedure

We searched the Pubmed/MEDLINE, Web of knowledge/science, Science Direct and ALOIS databases for eligible studies published between January 1st 1960 and May 1st 2015. We used the following (combination of) search terms: "physical activity", "exercise(s)", "(cardiovascular) fitness", "(an/non-) aerobic", "danc(e/ing)", "walk(ing)", "train(ing)", "yoga", "Tai Chi", "strength", "Alzheimer('s)", "dementia", "cognition", "cognitive" and "MMSE". We included only peer-reviewed articles (written in English) with a randomized control trial (RCT) design. Patients diagnosed with any type of dementia were included, except for dementia syndromes presenting with prominent motor features (e.g. Parkinson's disease dementia or Huntington's disease), as this may affect the ability to partake in a physical activity intervention. Experimental patient groups were required to undergo an intervention solely focusing on physical activity, thus studies assessing multi-modal interventions (e.g. occupational therapy or cognitive exercises in addition to physical activity) were not taken into account. During the intervention period, patients in the control group were not allowed to receive any form of physical activity therapy other than that provided in standard care. Other types of therapies, such as therapies aimed at social interaction, were allowed. Only studies providing post-intervention cognitive outcome measures, either in the article or upon request, were included in this meta-analysis.

2.2. Interventions, controls and outcome measures

The physical activity interventions were categorized into three groups: aerobic-only, non-aerobic and combined (i.e. aerobic and non-aerobic). Categorization was performed independently by two authors (C.G. and A.M.H.) using the intervention specifics provided in the primary articles and those provided by corresponding authors. Based on World Health Organization recommendations (World Health Organization, 2010), a cut-off at 150 min of physical activity per week was used to distinguish between high and

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