

# Physical activity for cognitive health: what advice can we give to older adults with subjective cognitive decline and mild cognitive impairment?

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Subjective cognitive decline (SCD) and mild cognitive impairment (MCI) are common conditions in older age and are associated with an increased risk of future cognitive decline and dementia. As there is currently no effective pharmacological treatment available for SCD and MCI, modifiable risk factors for cognitive decline and dementia have received increasing attention in the literature as a focus for clinical trials. Physical activity (PA) is one of the strongest protective lifestyle factors. This clinical review aims to highlight the accumulating evidence about the benefits of PA for SCD and MCI. Whilst there is agreement that at least 150 minutes of moderate aerobic PA per week in combination with additional resistance training is necessary to support brain health in people with SCD and MCI, future research is required to help inform specific advice on type of exercise, intensity, “dose” and effective strategies to encourage behavior change.

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## Introduction

This clinical research review aims to give an overview of current evidence whether and how physical activity (PA), as a protective lifestyle factor, might protect cognition in older adults who experience either subjective changes to their cognition (subjective cognitive decline; SCD) and/or objective changes (mild cognitive impairment; MCI). Based on the currently available knowledge, we were interested to determine what advice, based primarily on clinical trials, could be given in clinical settings to those groups of patients in relation to PA.

## Subjective cognitive decline and mild cognitive impairment in older age

SCD describes a condition where an older person expresses persistent concerns about their cognition with experiencing a subjective decline in comparison to their usual baseline cognitive abilities. Individuals with SCD, when assessed with neuropsychological measures, show intact performance for age, gender, and education—that is, their cognition is within normal limits. Various underlying causes can contribute to the experience of SCD, such as emerging neurodegenerative diseases or

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other dementia pathologies, cerebrovascular pathology, mental health or physical health problems, cognitive changes related to normal aging, personality traits, stressors, medication, and substance use, to name just a few.<sup>1</sup> Not surprisingly the prognosis of SCD varies depending on the underlying causes. Statistically there is a 1.5- to 3-fold increased risk that individuals with SCD will develop MCI or dementia at some stage in the future, but courses over time are often difficult to predict.<sup>2</sup> MCI differs from SCD in that objective cognitive impairment is present, but not to a level which would be required for a dementia diagnosis. For MCI, either the person themselves or someone who knows them well needs to have noticed cognitive decline, but activities of daily living are still preserved, except for minimal impairment in more complex activities of daily living.<sup>3</sup> There is still no undisputed inter-

national agreement about the exact criteria for both SCD and MCI for either research or clinical practice, which leads to various research criteria being used and makes comparison of research findings often challenging. For clinical practice, MCI could be considered as comparable to the World Health Organization (WHO) International Classification of Diseases (ICD-10) category of “Mild cognitive disorder.” In the Diagnostic and Statistical Manual of Mental Disorders (*DSM 5*) MCI may reflect a diagnosis of “mild neurocognitive disorder.”<sup>4,5</sup> However it falls even better under the term “cognitive impairment no dementia” (CIND) as CIND allows for multiple comorbidities contributing to the condition, which reflects better clinical reality.<sup>6</sup> MCI is often described as a transitional period between normal cognition and dementia, but this is more accurate for those cases where MCI occurs due to Alzheimer disease (AD) pathology, now often called “prodromal AD” or “MCI due to AD.”<sup>7</sup> Due to the heterogeneity of underlying causes, a stable presentation or even reverting back to normal cognition are also possible outcomes. Meta-analysis data suggest progression rates to dementia after 3 to 10 years’ follow-up differ depending on the sample, with progression rates in population-based studies of 22% and in clinical settings of 39%<sup>8</sup> compared with 1% to 3% in the normal population.<sup>8,9</sup> Due to the variety of criteria used for classification of SCD and MCI, exact prevalence rates are difficult to determine. A recent harmonization effort based on data from

### Physical activity is one of the strongest protective lifestyle factors

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geographical diverse cohorts lead to suggestions of a MCI prevalence rate for people of 60 and older of between 6% and 12%.<sup>10</sup> Accurate prevalence rates for SCD are difficult to determine due to the heterogeneity between studies in characterizing the condition.<sup>11</sup> The United States Center for Disease Control and Prevention (CDC) used a random digit dialed telephone survey across 49 States to assess SCD rates, and found 9.9% in adults aged 64 to 74, increasing to 14.3% in adults aged 75 years and older, experienced SCD.<sup>12</sup> Prevalence rates were higher in a recent Chinese study of 2689 participants, with SCD observed in 18.8% of adults aged 60 to 80 years.<sup>13</sup> Clearly, the prevalence of SCD is higher than of MCI, and both are more common than dementia. It is estimated that 47 million people live with dementia around the globe and that this number will increase to 47.7 million by 2030 and 131.5 million by 2050.<sup>14</sup> These estimated increases in prevalence rates reflect primarily the increases in population longevity seen around the world, but these estimates might need to be adjusted given a number of recent publications demonstrating lower incidence rates than expected.<sup>15</sup> The most common cause of dementia is AD, however there are many causes and the older a person is when developing dementia, the more likely that a mix of pathologies is responsible.<sup>16</sup> Whilst estimates of the economic cost of dementia are frequently reported, this is much less clear for SCD and MCI. Increased health care utilization and health care costs have been reported for people with SCD and MCI or those who are one year away from their dementia diagnosis.<sup>17-19</sup> As is the case for dementia, MCI is associated with lower levels of PA and an increased risk of balance and mobility problems as well as falls.<sup>20-23</sup>

With the current global knowledge base, effective dementia prevention is not yet a reality. Whilst this might change at some stage in the future, for example via advances in pharmacological research, in the meantime there is an increasing call to focus on potentially protective lifestyle factors to reduce the risk of cognitive decline and dementia in the aging population,<sup>24</sup> including in people with SCD and MCI. One of the strongest protective lifestyle factors is PA and it has been estimated that targeting physical inactivity could contribute to delaying or preventing a third of all dementia cases.<sup>16</sup>

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## Physical inactivity in older age

In many countries, the main contributors to the burden of morbidity and mortality are changing, with noncommunicable diseases (NCD), such as type 2 diabetes, cardiovascular, and neurodegenerative diseases, becoming more relevant compared with infectious diseases.<sup>25</sup> Physical inactivity is frequently a significant contributing component in the development of NCD and is currently estimated to be the fourth leading risk factor for global mortality.<sup>26</sup>

PA can be defined as “any movement by skeletal muscles that leads to energy expenditure.” Sub-groups of PA can be grouped under occupational, household, conditioning, and sports. Exercise in this context is targeted PA, which has the aim to improve or maintain physical fitness.<sup>27</sup> For this review we will focus on the subcategories of aerobic exercise and resistance training, as they have demonstrated cognitive benefits for these clinical groups.

Not surprisingly, older people are often more sedentary than younger adults. Recent systematic reviews demonstrated that sedentary lifestyle is associated with poorer cardiovascular and cognitive health and faster decline of cognitive performance.<sup>28,29</sup> However, the intensity of PA, especially when it comes to potential cognitive benefits, plays an important role. For example, whilst walking is one of the most popular ways for older adults to perform PA, many people reduce their walking speed with increasing age. A large Canadian longitudinal study with 2876 older adults aged 70 to 79 years reported recently that a slowing down of walking speed in individuals predicted future decline in PA and this finding was independent of baseline physical health. Furthermore, reduced walking speed in older age has been associated with an increased risk of future cognitive impairment and mortality.<sup>30,31</sup>

## Physical activity trials in subjective cognitive decline and mild cognitive impairment

Most clinical trials with aerobic PA interventions for participants with SCD or MCI have an intervention duration of 6 months with a few offering 12 months or longer.<sup>32-34</sup> Trials demonstrating significant benefits for cognition usually aimed for at least 150 minutes PA/week, but lower doses (120 and 90 minutes/week) were also reported.<sup>35,36</sup> The intervention intensity was either moderate or

vigorous which was frequently defined as a percentage of maximum heart rate, heart rate reserve, or oxygen uptake ( $VO_2$  max). Although still less commonly conducted, there are now trials with resistance training reporting cognitive benefits. Resistance training occurred at least twice a week over a 6-month intervention duration.<sup>35,37-39</sup>

Significant benefits for global cognition, for example measured with the Clinical Dementia Rating Scale (CDR), the Mini Mental State Examination Test (MMSE), or the Alzheimer’s Disease Assessment Scale-cognitive subscale (ADAS-Cog), have been reported in the majority of PA intervention trials,<sup>38-41</sup> with only a few negative exceptions.<sup>42,43</sup> These findings were confirmed in a recent meta-analysis of 11 randomized controlled trials (RCT) of aerobic PA in MCI.<sup>44</sup> Benefits in global cognition were also reported in trials employing multimodal intervention where aerobic PA and resistance training were combined,<sup>45-47</sup> or for specific exercises like tai chi<sup>48,49</sup> or handball.<sup>50</sup> Results for executive functions were more inconsistent, with reported benefits<sup>37,38,43,49,51</sup> but also frequent negative findings.<sup>32,40,41,48</sup> The same applied to memory functions, with positive<sup>35,37,40,45,48,49</sup> as well as negative<sup>32,33,37,39,41,51</sup> results. The previously mentioned meta-analysis by Zheng et al also reported small benefits for the memory domain.<sup>44</sup>

## Biomarker evidence

The last decade has seen a paradigm shift towards biomarker-based definitions of AD that have supported intervention and observational research in PA and other domains. The National Institute of Ageing and Alzheimer’s Association research framework (NIA-AA framework), first introduced in 2011, defines AD based on underlying pathology (eg,  $\beta$  amyloid deposition, pathologic tau, and neurodegeneration) rather than clinical consequences of the disease.<sup>52</sup> Jack and colleagues have further refined biomarker classification of AD by introducing the A/T/N classification scheme that provides a biomarker category agnostic to the temporal ordering of mechanisms underlying AD pathogenesis but characteristic of an individual’s current biomarker AD status across the three key AD biomarkers: “A” (Amyloid- $\beta$ ; PET or CSF), “T” (CSF phospho tau, or tau PET), and “N,” (biomarkers of neurodegeneration or neuronal injury, ie, [18F]-fluorodeoxyglucose-PET, structural MRI, or CSF total tau).<sup>53</sup> These

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biomarker paradigms enable research to examine effects of interventions such as PA on the underlying biological causes of AD dementia.

Whilst there is a wealth of publications exploring biomarker evidence to determine the underlying mechanisms how PA protects brain health in animal models and healthy people, much fewer papers have reported this in SCD and MCI. The most commonly used biomarker to date is structural and functional MRI. In a Canadian RCT with 86 female participants diagnosed with MCI, a 6-month resistance training intervention resulted in increased activation in three strategic cortical regions (right frontal pole, right occipital-fusiform gyrus, and right lingual gyrus) while performing an associative memory task.<sup>37</sup> In the Australian SMART trial with 100 participants with MCI, 6 months of progressive resistance training was associated with improved global cognition, a reduced progression of white matter lesions on MRI as well as positive gray matter changes in the posterior cingulate.<sup>39</sup> Finally, in a Canadian RCT with 70 older adults with mild vascular cognitive impairment a 6-month aerobic PA intervention improved global cognitive function measured with the ADAS-Cog, physical fitness measured with the 6-min walking test, and diastolic blood pressure compared with usual care with education, were observed.<sup>54</sup> In a substudy of this trial, employing functional MRI, reduced activation was reported in the PA group compared with the control group in the left lateral occipital cortex as well as the right superior temporal gyrus which indicates an improvement of neural efficiency.<sup>55</sup> These trial results are supported by cross-sectional evidence in MCI where PA was associated with greater hippocampal volume and fewer cerebrovascular pathology.<sup>56,57</sup> Other studies reported increases in brain derived neurotrophic factor (BDNF), reduction in inflammatory markers (TNF- $\alpha$  and IL-6), and improved insulin sensitivity or cortisol regulation.<sup>51,58-60</sup> Whilst these findings support interesting hypotheses about the underlying mechanisms how PA might impact on cognitive health in people with MCI, future replications of findings in larger studies are needed.

## Strategies for clinical advice

When aiming to suggest behavior change in a clinical setting in relation to lifestyle factors such as PA, it is

important to reflect on the potential enablers and barriers for behavior change in this specific population. Whilst there is a healthy body of literature when it comes to PA for older adults in general, much less is known in relation to SCD and MCI specifically. Individuals with SCD and MCI have been reported more frequently than healthy older adults of experiencing loss of self-confidence, reduced well-being, and increased perceived stress levels.<sup>33,61,62</sup> These findings suggest that many older adults with SCD and MCI might experience more barriers due to their more vulnerable mental health and potentially reduced resilience. There are examples in the literature where studies adapted motivational strategies used with people with dementia for individuals with MCI. These strategies included adapting the communication style when explaining the PA, providing written handouts, use of behavioral strategies, including pleasurable activities, involving a family member or friend in the activities, etc.<sup>42</sup> Other suggestions included, for example, individual tailoring of the PA program to adjust for cognitive impairment, incorporating more social interaction, carefully considering safety issues, allowing for longer learning periods with more feedback and the use of video recording and music, use of multimodal memory aids, increased interpersonal support with a focus on supervision, and encouragement. Qualitative research in the form of focus groups demonstrated that depending on the degree of the cognitive impairment as well as gender and personality, preference when considering PA could differ quite significantly.<sup>63</sup> The response to PA interventions may differ with gender, with men compared with women observed to achieve 14% higher adherence to a 6-month predominantly walking program<sup>64</sup> whereas in a structured lifestyle intervention women adhered better than men.<sup>49</sup> Liu-Ambrose et al highlighted in a recent review that in general, gender factors in PA are highly under-researched, and more specifically when exploring the efficacy of exercise in relation to biological sex.<sup>65</sup>

Most of the PA interventions to date have been supervised, group, or center-based<sup>66</sup> with few utilizing a home-based approach,<sup>34,40</sup> however the uptake and adherence to the PA has been good with similar results for both approaches. Lam et al noted from a systematic review of exercise training and physical function in individuals with cognitive impairment and dementia that not all studies report adverse events and in those that have

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**Recommendation 1:** Older adults who have MCI or SCD should participate in aerobic PA of moderate intensity for at least a total of 150 minutes/week, or vigorous intensity for at least a total of 90 minutes/week. This recommendation is in addition to incidental light intensity activities of daily living.

**Recommendation 2:** In addition to aerobic PA (as outlined in recommendation 1), older adults with MCI or SCD should engage in progressive resistance training (PRT) activities on at least 2 days per week. This is in addition to continuing incidental activities that help with strength.

**Recommendation 3:** Older adults with MCI or SCD should engage in activities that help to improve or maintain balance. This is particularly important, as older adults with MCI or SCD often have poorer balance and mobility as well as an increased falls risk, compared with older adults without MCI or SCD.

**Recommendation 4:** PA and exercise should be individually tailored, with consideration given to factors such as health problems, physical capacity and environment. Older adults with MCI or SCD are advised to consult with their health care professional for advice before undertaking PA and exercise.

**Box 1. PA guidelines recommendations for people with SCD and MCI. MCI, mild cognitive impairment; SCD, subjective cognitive decline.**

reported adverse events these are low in number and generally not related to participation in the PA program, concluding that overall participation in exercise training can be done safely.<sup>66</sup> If clinicians have concerns about their patient's lower body strength, mobility, lack of cardiovascular fitness or if they have identified patients who are at increased risk of falls then programs where expert supervision (for example exercise physiologists or physiotherapist) or fitness leaders trained in managing PA for seniors can be recommended. Center and group-based programs also have the advantage of providing social contact which can often be a potent motivating factor in encouraging participation. Home-based or independent exercise has other advantages for some such as convenience of time and place, low cost, and reduced transport issues. In order for PA to have an impact on brain health the PA needs to be of the amount, frequency, and intensity in line with the PA guidelines (*Box 1*) and patients need to be motivated firstly to initiate a PA program and maintain it in the long term. The patient should be encouraged to find an activity that they enjoy and have the physical capacity to perform, one that is accessible and they have the financial means to participate in, has a graded progression, allowing for short and long-term

goals and where they receive encouragement and regular feedback from significant others. The significant others can be family, friends, peers, other PA participants, PA trainers, and health professionals including clinicians.

The authors of this review recently contributed to an international and multidisciplinary effort to produce the first PA guidelines for people with SCD and MCI.<sup>67</sup> These guidelines reviewed the specific evidence on PA for people with SCD and MCI in the literature and adapted the existing Canadian Physical Activity Guidelines for Older Adults<sup>68</sup> according to the methodology outlined by the Guideline Adaptation Resource Toolkit (ADAPTE) and the Appraisal of Guidelines for Research Evaluation (AGREE II). This led to four recommendations (*Box 1*).

These guidelines were developed with the hope that clinicians of various backgrounds who engage with people with SCD and MCI might find them useful when trying to communicate the benefits of PA. A short lay version of the guidelines was specifically developed for the consumer and could function as a starting point to talk about the topic PA or as a reminder and motivator.

While there is now evidence that PA supports health in SCD and MCI, PA is only one component of a healthy lifestyle. A number of large multimodal intervention trials that include PA have been undertaken worldwide, including the worldwide FINGER network based on the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER trial; [www.fingers.com](http://www.fingers.com)), the French Multidomain Alzheimer Preventive Trial (MAPT), the Netherlands Prevention of Dementia by Intensive Vascular Care (preDIVA trial), the European Healthy Ageing Through Internet Counselling in the Elderly (HATICE), and the Australian Maintain Your Brain (MYB) study.<sup>69-71</sup> Such large-scale multi-modal intervention trials in populations at risk of dementia provide exciting opportunities to examine the utility of health lifestyle interventions that could be implemented at the population level to decrease dementia risk. However further research into strategies, particularly those employing behavioral change theories and practices to enhance the uptake and maintenance of PA in this target group, is needed for the potential of PA to have an impact on reducing the risk of cognitive decline and dementia is to be fully realized.



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## Conclusion

Whilst this area of research is still in its infancy, the accumulating evidence about the benefits of PA for SCD and MCI starts to appear in clinical recommendations and practice guidelines. Two examples are the clinical review in *JAMA* by Langa and Levine which gives dialogue examples on how to counsel patients with MCI on protective behaviors, such as exercise,<sup>72</sup> the other is the practice guideline update for MCI from the American Academy of Neurology, which suggests that, despite limited evidence, exercise is likely to provide benefit in MCI.<sup>73</sup> When advising patients with MCI on the protective lifestyle factors for brain health, might they benefit from a personalized medicine approach? Barha et al

promote, in their recent review paper, the need for personalizing exercise recommendations when it comes to brain health.<sup>74</sup> Many more research avenues need to be explored before we can be certain which type of exercise, at what level of intensity is best suited for each patient with MCI. However knowledge has advanced to a degree where some basic information on the cognitive benefits of PA can be communicated to patients with MCI in clinical settings and the recently released PA guidelines for people with SCD and MCI<sup>67</sup> should assist with this. ■

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