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Efficacy of exercise for functional outcomes in older persons with dementia

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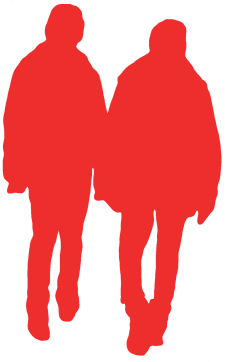
Chapter 1

General introduction



Aging and dementia

The world population is growing older. Between 2010 and 2015, the global life expectancy has risen by 5.5 years, mainly due to improvements in child survival rates in developing regions. Today, the global average life expectancy is ~74 years for women and ~70 years for men. In developed regions, the life expectancy for women and men approaches or exceeds 80 years [1].

In 2010 it was estimated that there were 524 million old adults (≥65 years). This number is expected to triple by 2050 [2]. Considering that old age is the most important risk factor for dementia, it is expected that by 2050 the number of older persons with dementia (PwD) will triple to 150 million worldwide [3]. Dementia is a syndrome that is characterized by progressive neurodegeneration that surpasses normal age-related decline. PwD progressively lose cognitive and physical abilities [3,4] and become increasingly dependent upon formal and informal care. Dementia may have various causes, and it must be noted that at least 50% of PwD show signs of multiple dementia pathologies [5]. Alzheimer's Disease (AD) accounts for 60-80% of all dementia cases [6]. AD is characterized by deposits of Amyloid β (Aβ) plaques and neurofibrillary tangles. Vascular Dementia (VaD), i.e., dementia resulting from extensive damage to brain blood vessels appears in ~40% of PwD [6]. Dementia with Lewy Bodies (LBD), characterized by neuronal abnormalities in Alpha-synuclein protein, is recognized as the third most common cause for dementia, accounting for another >10% of dementia cases [6].

It is estimated that 1/3 of dementia cases are attributable to a combination of nine modifiable risk factors: low education in early life; hypertension, obesity and hearing loss in midlife; and smoking, depression, physical inactivity, social isolation and diabetes in later life [7]. The most important biological risk factor for dementia (AD in particular) is the Apolipoprotein ε4 (ApoE4) allele. ApoE4 is directly linked to AD through impaired lipoprotein metabolism [8], which is associated with immunoreactive accumulations of Aβ and tau pathology and subsequent declines in neurocognitive health [9,10]. Compared with ApoE2 and/or E3 carriers, ApoE4 heterozygotes are three times more likely to develop AD and ApoE4 homozygotes are eight times more likely to develop AD [9].

The economic burden of dementia is high. Costs for prevention, diagnosis, symptom treatment, informal care and environmental adaptations for PwD increasingly accumulate with time. In 2018, the global cost of dementia exceeded $1 trillion [3]. Considering the high societal and economic burden of dementia it is of great importance that treatments are

developed. Pharmacological treatments are still insufficient in producing clinically relevant effects [11] and frequently cause side effects such as gastrointestinal issues and vertigo [12]. Non-pharmacological treatments for dementia may pose fewer side-effects and include exercise, music therapy, cognitive stimulation, social stimulation and sensory enrichment. Amongst these, exercise may be the preferred choice as it is consistently associated with better physical and mental health outcomes in older populations [13] conform the philosophy 'Exercise is medicine'.

Physical activity in old adults with and without dementia

The American College of Sports Medicine (ACSM) defines physical activity (PA) as 'any bodily movement produced by skeletal muscles that results in energy expenditure above resting levels' [14]. Exercise is defined as 'PA that is planned, structured, and repetitive and that has as a final or intermediate objective the improvement or maintenance of physical fitness'. In other words, exercise is PA that is specifically intended to improve fitness.

The WHO [13] advises all old adults to perform ≥150 minutes of moderate-intensity aerobic PA and/or ≥75 minutes of vigorous-intensity aerobic PA, in bouts of ≥10 minutes, every week. Whole-body muscle strengthening exercises should be done at least two days per week. Especially old adults with mobility impairments are advised to perform balance exercises on ≥3 days of the week. For old adults with poor physical health, even low amounts of PA are beneficial. However, a review of PA levels in old adults from six continents reported that only 20-60% of old adults met the recommended amounts of PA [15]. PwD are even less active as compared to their healthy peers. Van Alphen and colleagues [16] showed that community-dwelling PwD are ~22% less active than cognitively healthy peers. Institutionalized PwD even spend ~72% of their day sitting. Low levels of PA are associated with poor health, increased risk of mortality and hospitalization and increased risk of cognitive impairment [17]. Increasing PA may ameliorate poor health in PwD.

Exercise and functional outcomes in old adults with and without dementia

In healthy old adults, aerobic and strength exercise are associated with improvements in physical function such as endurance, mobility, gait speed, muscle strength and balance [18-21]. Multimodal exercise, i.e., a combination of aerobic, strength, and coordination training has the highest efficacy for physical function. Likewise, the beneficial effects of exercise on the

aforementioned physical functions are apparent in PwD with multimodal exercise having the highest efficacy (see [22] for a review). Furthermore, multimodal exercise may be preferable over aerobic-only exercise for Activities of Daily Life (ADL) in PwD [23].

Exercise-induced improvements in physical function may facilitate cognitive function through increases in brain plasticity and activation [24-26]. In 1999, Arthur Kramer and colleagues were among the first to show a positive effect of exercise on executive processes in a sample of 124 healthy but sedentary old adults [27]. Since then there has been a growing body of evidence that aerobic, anaerobic and multimodal exercise is related to better cognitive function in healthy old adults, with multimodal exercise having the highest efficacy for cognitive function (see [28] for a meta-analysis). In PwD, the effects of exercise on cognition are inconclusive [29-33]. A combination of alternating aerobic and strength exercise appears to be the most beneficial for physical and cognitive function [23,30] perhaps because 1) aerobic exercise is facilitated through strength increases especially in the lower limbs and 2) the neuromotor stimulus is higher in combined exercise compared with aerobic- only training due to compensatory mechanisms. However, it is unknown whether such a combination is also effective in PwD in earlier stages of dementia. Furthermore, it is unknown whether this combination of alternating aerobic and strength training is effective when performed for a longer period of time. Last, it is uncertain whether the beneficial effects of exercise in PwD last after detraining.

Several underlying neurobiological mechanisms may play a role in the neuroprotective effects of exercise. In animals and healthy old adults, exercise is related to dose-dependent increases in growth factors (insulin-like growth factor type I (IGF1), brain derived neurotrophic factor (BDNF), vascular endothelial growth factor (VEGF)), increases in neurotransmitters (noradrenalin, serotonin, dopamine) and decreases in inflammatory markers (homocysteine [34,35]). These neurobiological changes are related to changes in brain structure and connectivity [36-39] in areas important for healthy cognitive function e.g. frontal and temporal areas. Whether this is also true for PwD is yet to be determined by future studies. Figure 1 models the relationships between exercise and physical and cognitive function in PwD. This model is adapted from Bossers [40].

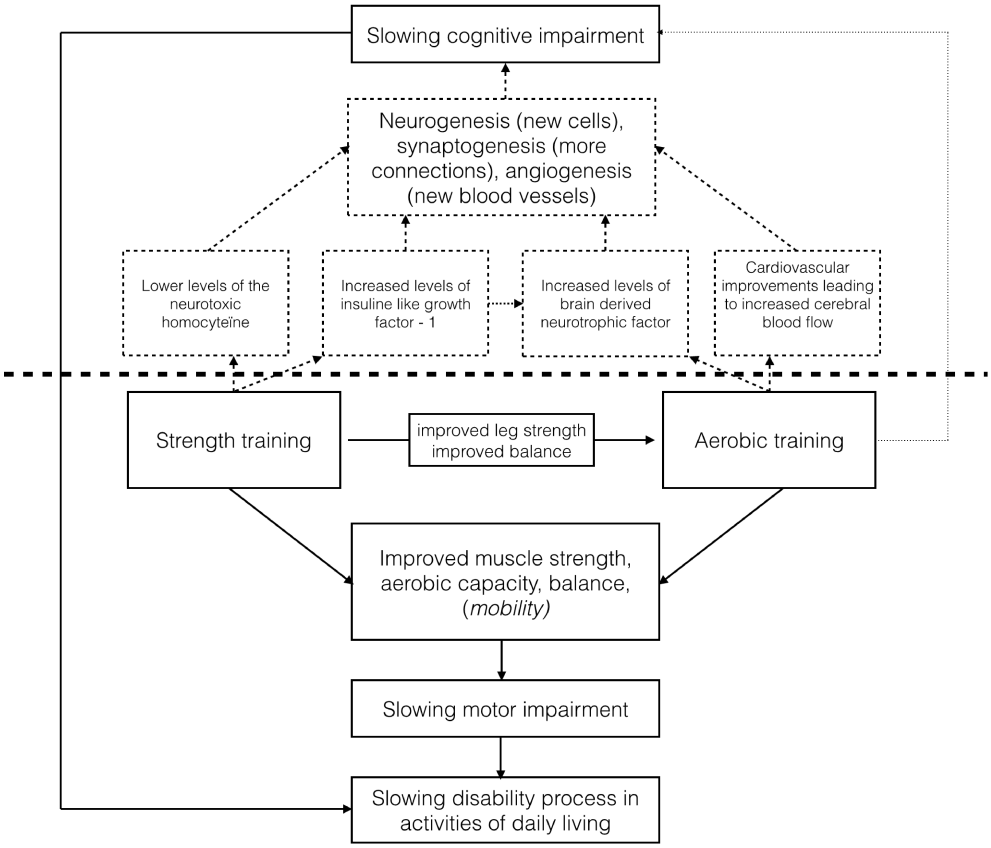


Figure 1. Relationships between exercise, physical function and cognition in PwD. Continuous lines represent evidence-based relationships whereas dotted lines represent hypothesized relationships.

Moderators and confounders of exercise effects on physical and cognitive function in PwD

As previously outlined, the evidence for the efficacy of exercise for functional outcomes in PwD is inconclusive. Furthermore, there is insufficient evidence to determine the variables that may act as moderators and confounders of exercise effects on physical and cognitive function in PwD. Such data are needed to optimize exercise programs for PwD and implement

exercise efficiently in daily health care. Previous reviews and meta-analyses in healthy old adults have identified several potential moderators and confounders. The effects of exercise on executive processes may be more pronounced in older women vs. men [41] and in older vs. younger seniors [42]. In addition, the effects of exercise on cognitive function in old adults may be moderated by genes and dietary factors [43]. In PwD, the effects of exercise on physical and cognitive function appear to be independent of sex, age and dementia subtype, although it is uncertain whether the effects of exercise are moderated by disease severity [22,32,33,44]. There is little or inconclusive evidence on several other potential moderators and confounders of exercise effects in PwD. Use of medications with anticholinergic and/or sedative properties ('inappropriate medications') as measured by the Drug Burden Index (DBI) is associated with lower physical and cognitive function in healthy old adults [45-48]. Whether this is true also for PwD is unknown. Data on the associations between DBI and physical and cognitive function in PwD is needed to determine whether the effects of exercise on physical and cognitive function are potentially confounded by anticholinergic and sedative drug burden. In addition to drug burden, exercise type and dose-parameters (program duration, session duration, frequency and intensity) may moderate the magnitude of exercise effects on physical and cognitive function in PwD. However, the dose-response relationships between exercise with physical and cognitive function in PwD are poorly understood. Especially exercise intensity may be an important moderator of exercise effects because higher exercise intensity is associated with better physical fitness (i.e., VO2max) and health outcomes [49-52] that may fuel exercise effects on physical and cognitive function. Studies in which exercise intensities are compared among randomized PwD are needed to investigate exercise intensity as potential moderator in PwD. No such studies have been performed thus far. Last, preliminary evidence has identified ApoE4-carriership to be a potential moderator of exercise effects on functional outcomes in old adults with and without dementia [43,53]. However, it is uncertain whether ApoE4 carriers as compared to non-carriers show greater or fewer benefits from exercise on physical and cognitive function [53-56]. Furthermore, there is a scarcity of randomized studies that investigate the strength and direction of this hypothesized moderation in PwD specifically.

The effects of exercise on physical and cognitive function in PwD and potential moderators and confounders can only be adequately assessed with performance-based tests that are feasible, valid and reliable in PwD. The reliability of six motor tests for endurance, gait speed, balance, strength and functional mobility was previously found to be good to excellent in PwD,

although the reliability was lower for lower-functioning individuals [57]. Unfortunately, apart from global cognitive batteries, there is limited data on the psychometric properties of many cognitive tests in PwD. Furthermore, cognitive tests that are frequently used in healthy old adults may not be feasible, reliable and valid in PwD. This may be especially true for the STROOP task. The STROOP task measures selective attention and inhibitory control [58]. The STROOP task may be difficult for PwD because PwD may experience color confusion [59] and difficulties with verbal communication [60]. Furthermore, PwD may find the STROOP task instructions difficult to comprehend. The Flanker task could be a suitable non-verbal alternative for the STROOP task in PwD. The Flanker task requires the ability to inhibit nonrelevant competing responses to a nonverbal target stimulus [61]. The Flanker task may be a suitable alternative to the STROOP task in PwD because the Flanker task does not rely upon verbal responses and the use of colors. However, the psychometric properties of the Flanker task in PwD are yet to be evaluated.

Objectives and outline of this thesis

The main objective of this thesis is to examine the efficacy of alternating aerobic and lower-limb strength exercise vs. control activities for physical and cognitive function in a sample of older persons with mild-to-moderate all-cause dementia. The secondary objective of this thesis is to examine potential moderators and confounders of exercise effects in PwD. In this thesis we will focus on anticholinergic and sedative drug burden, exercise type, dose-parameters (program duration, session duration, frequency and intensity) and ApoE4-carriership. The last objective of this thesis is to examine the suitability of a Flanker task as a measure of inhibitory control in PwD.

Chapter 2 describes the results of a cross-sectional analysis into the associations between anticholinergic and sedative drug burden with physical and cognition function in 140 nursing home PwD. **Chapter 3** describes the results of a systematic review and meta-analysis into the effects of exercise on cognitive function in old adults with and without cognitive impairments. We investigated cognitive status (healthy vs. cognitively impaired), exercise type (aerobic vs. anaerobic vs. multimodal vs. psychomotor) and dose-parameters (program duration, session duration, frequency and intensity) as potential moderators of exercise effects on cognition. **Chapter 4** describes the feasibility and results of a 24-week randomized controlled trial (RCT) in 69 PwD visiting daycare or residing in residential care facilities. The primary outcomes were physical and cognitive functions measured with performance-based tests. We used a

two-arm exercise vs. control design, with the exercises being performed at a low (weeks 1-12) vs. high (weeks 13-24) intensity to investigate exercise intensity as potential moderator of exercise effects. ApoE4-status was determined post-intervention as potential moderator of exercise effects. **Chapter 5** describes the results of a pilot study into the psychometric properties (feasibility, validity and tests-retest reliability) of a computerized Flanker task in 22 PwD. Finally, **Chapter 6** summarizes and discusses the main findings of this thesis. Additionally, Chapter 6 offers suggestions for the implementation of exercise in dementia health care practice.

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