BRAIN IN MOTION:
COMBINED COGNITIVE AND PHYSICAL EXERCISE TRAINING IN PEOPLE WITH DEMENTIA

Esther Karssemeijer

DONDERS
SERIES

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Doctoral Thesis

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to be defended in public on Thursday, June 6, 2019
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by
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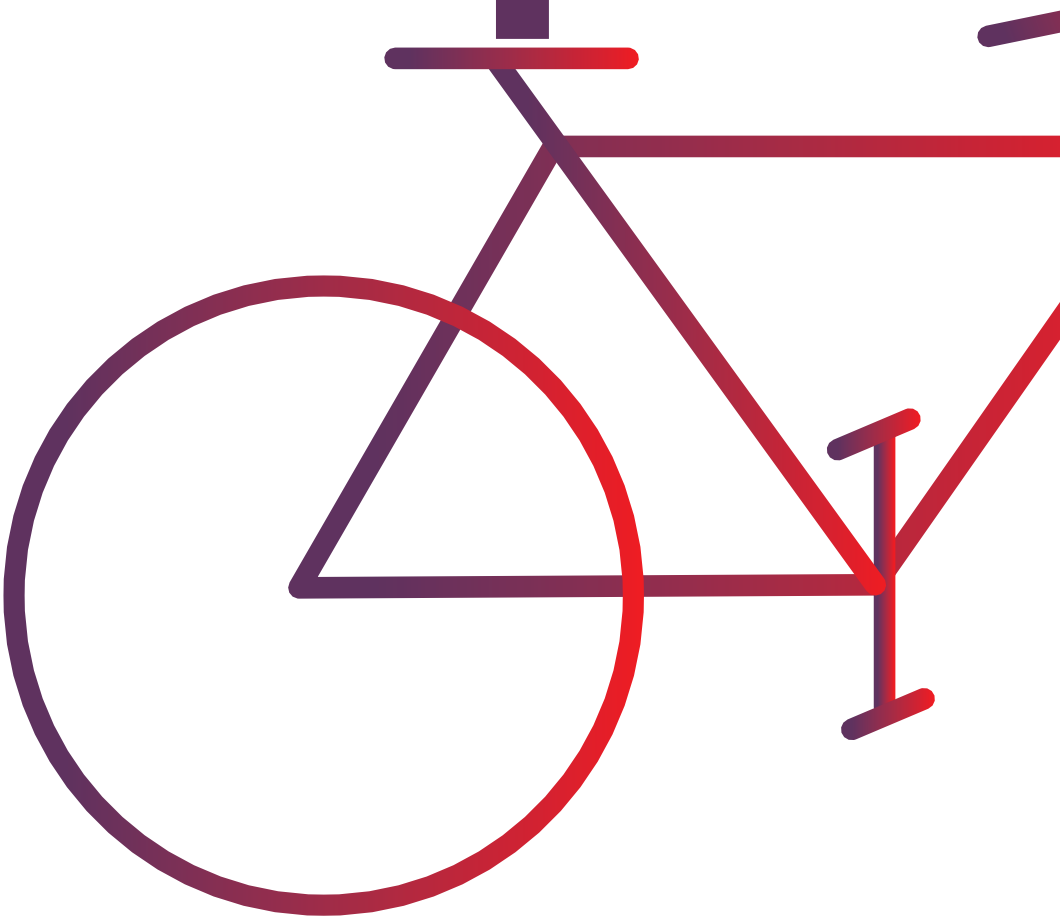

General Introduction

Dementia is a growing societal problem

High age is the main risk factor for developing dementia.[8] Currently in the Netherlands, one in four people (4,3 million people) is 60 years old or above and this number is expected to grow even further in the near future.[1] As a consequence, the prevalence and incidence of dementia increases.[2] Worldwide, approximately ten million new cases of dementia arise each year; a number which is expected to grow to approximately 131.5 million prevalent dementia cases in 2050.[2] Specific estimates for the Netherlands show 270,000 dementia cases in 2017 with a predicted increase to approximately 500,000 dementia cases in 2040.[3] These growing numbers will have a large societal (e.g. quality of life) and economical impact (e.g. healthcare costs).[2,4] Therefore, the World Health Organization (WHO) stresses to take global action against cognitive decline and dementia, encouraging governments worldwide to focus on prevention, disease-modifying therapies and improving health care service.[5]

Modifiable risk factors

Over one third of the dementia cases can be attributed to risk factors, such as hypertension, obesity, physical inactivity and smoking, which are known to positively respond to lifestyle interventions.[6] Multidomain interventions targeting modifiable lifestyle factors (i.e., physical activity, a change in diet, or vascular risk monitoring) may delay dementia onset.[7] Physical activity is recognized as a key component of a healthy lifestyle and is defined by the WHO as: "Any bodily movement produced by skeletal muscles that increases energy expenditure".[8] Furthermore, both physical activity and physical exercise (i.e., planned, structured, repetitive forms of physical activity)[9] are proposed to be important for the development and preservation of cognitive functions.[10-14] On the other end of the activity spectrum there is physical inactivity and sedentary behaviour, which are associated with chronic conditions (e.g. cardiovascular and metabolic diseases) and higher rates of negative health outcomes.[15-18] Despite the known health risks related to physical inactivity, many older people are inactive.[19] Specifically in the Netherlands, 29% of the people over 75 are categorized as 'inactive' (defined as no single day of the week being active over 30 minutes) and inactivity rates are even higher in individuals with dementia, compared to their cognitively unimpaired peers.[20,21]

Physical exercise as medicine to delay cognitive decline in dementia

Currently, there is no cure or effective disease-modifying drug to treat dementia.[22] Thus far, pharmacological therapies solely temporarily alleviate dementia symptoms, but fail to modify disease progression.[23,24] In light of the 'exercise is medicine' paradigm,[25] physical activity is suggested to be a non-pharmacological treatment that may slow disease progression in people with dementia.[34-36] Despite increased awareness of the importance of exercising, stimulating people with dementia to participate in physical activity remains challenging.[45] People with dementia may experience barriers such as problems with orientation, apathy, and a decrease of initiative and interest, that hamper physical activity participation.[26,27] Therefore,

it is important to develop an exercise method that is feasible and attractive for people with dementia, and helps them to overcome barriers for physical activity.

Underlying mechanisms of exercise on cognition

It is hypothesised that physical exercise leads to improved cognitive function, as it may promote hippocampal neurogenesis,[28] brain angiogenesis,[29] and synaptic plasticity,[30] elicited by an increased expression of neurothropic factors such as Brain Derived Neurothropic Factor (BDNF), Insulin Growth Factor 1 (IGF-1) and Vascular Endothelial Growth Factor (VEGF).[31] Earlier studies already showed that physical exercise may improve cognitive function in cognitively healthy older adults, with the largest gains on executive control processes, psychomotor speed and attention.[10-13,32] Physical exercise may also be beneficial in persons suffering from neurocognitive disorders such as dementia or mild cognitive impairment (MCI), however the evidence to date is less convincing.[33-36]

Motor-cognitive training

It has been proposed that combining physical exercise and cognitive training could evoke cognitive enhancement to a larger extent than physical exercise or cognitive training alone.[37-40] According to the "guided plasticity facilitation" framework (see Figure 1.1), a combination of physical and cognitive activities may have positive synergistic effects that emerge from (I) the "facilitation effects" of physical exercises, and (II) the "guidance effects" of cognitive exercises.[41] The "facilitation effect" of physical exercise triggers neurophysiological mechanisms, which may promote neuroplasticity.[41] A possible mechanism is the enhanced release of neurothropic factors (e.g. BDNF) which are associated with neurogenesis and synaptogenesis.[28,30,31] Cognitive stimulation may "guide" these neuroplastic processes by exerting a survival promoting effect on newborn neurons.[39,40] A combination of both, therefore, may result in greater benefits than either physical activity or cognitive stimulation alone.[39,40,41] As shown in Figure 1.1, motor and cognitive exercises can be combined in several ways: (1) sequential motor-cognitive training, where motor exercises and cognitive training are undertaken separately, and (2) simultaneous motor-cognitive training, where both motor and cognitive training are performed at the same time.[41,42] A recent review that compared sequential and simultaneous motor-cognitive training reported that simultaneous training significantly improved cognitive performance in various populations, while the results of sequential training regimes were inconclusive.[42] Therefore, simultaneous motor-cognitive training regimes seems most promising to foster cognitive performance, and innovative exergaming interventions may best realize this in a frail population with dementia.

Exergames

Exergaming is an innovative method that combines physical exercise and cognitive stimulation in a virtual environment.[43] Exergaming is a safe and attractive way to exercise that may stimulate people with dementia to be physically active and help them to overcome barriers to physical activity.[43] Research showed cognitive benefits of exergames in healthy older adults and in a clinical population of patients with Parkinson's disease, schizophrenia, multiple sclerosis and mild cognitive impairment (MCI), over and above physical exercise training alone.[44] In the current thesis, we will examine whether exergame training also has beneficial effects for people with mild-to-moderate stage dementia, irrespective of the aetiology of the dementia syndrome.

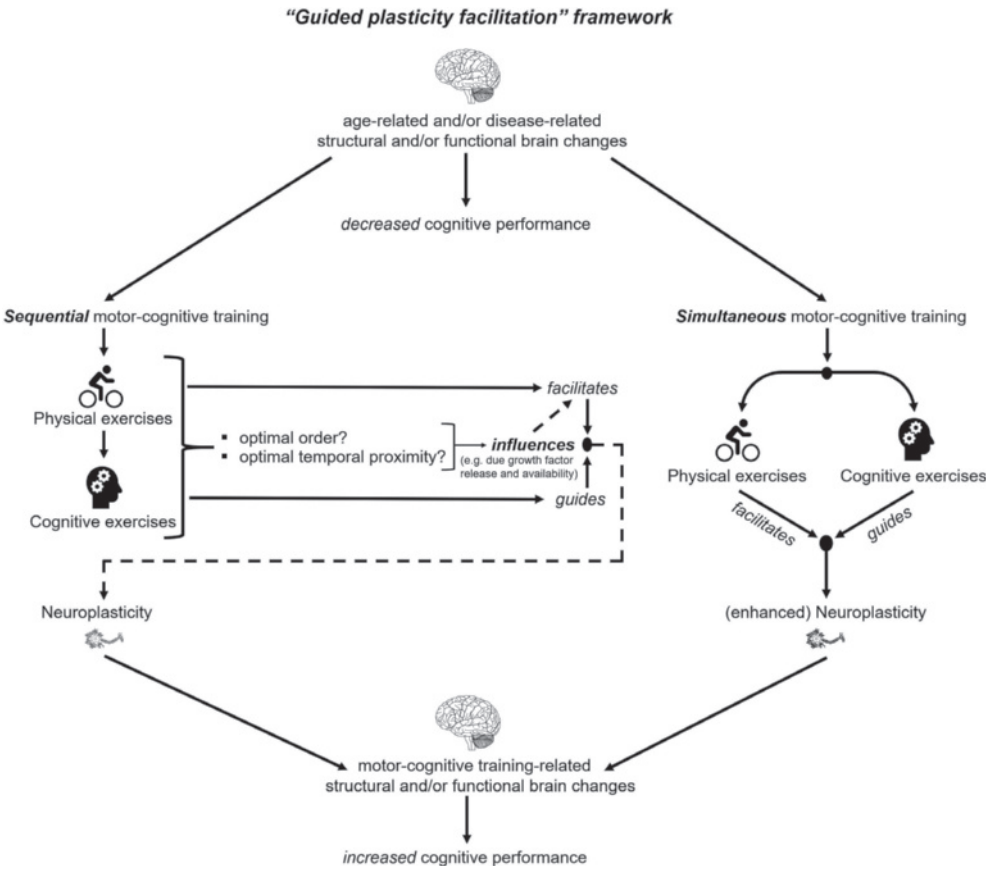

Figure 1.1 Schematic illustration of the "Guided plasticity facilitation" framework. Image from Herold et al.[41]

Aim of this thesis

The aim of this thesis is to present our study examining the role of physical exercise training with and without cognitive stimulation in reducing the rate of cognitive decline in people with dementia. In addition, the effects of training on frailty, physical functioning, levels of physical activity, and activities of daily living will be investigated. To do so, a randomized controlled trial (RCT) was designed in which people with dementia were randomized to a 12-week motor-cognitive exergame training, aerobic training or active control condition. We measured cognitive and physical functioning at baseline, after the 12-week intervention period and at 24-week follow-up. Frailty and activities of daily living were assessed at baseline and post-intervention. Our hypotheses are visualized in figure 1.2. We expect that both motor-cognitive training and aerobic training improve physical performance (see pathway A in figure 1.2). Furthermore, we hypothesize that both training regimes improve cognitive functioning, and that improved physical performance mediates improved cognitive function (see pathway B in figure 1.2).[11] In the motor-cognitive training group we expect an enhanced effect on cognitive performance (see pathway C in figure 1.2).[39,40,41] The improvements in physical performance and cognitive function may then translate into improved activities of daily living and reduced frailty (see pathway D in figure 1.2). Secondary aims of this thesis are to (1) study differences in activity levels between people with dementia and cognitively health older adults, (2) explore barriers, motivators, and facilitators for physical activity in people with dementia, and (3) review the literature to assess the cognitive benefits of combined motor-cognitive training in older adults with mild cognitive impairment or dementia.

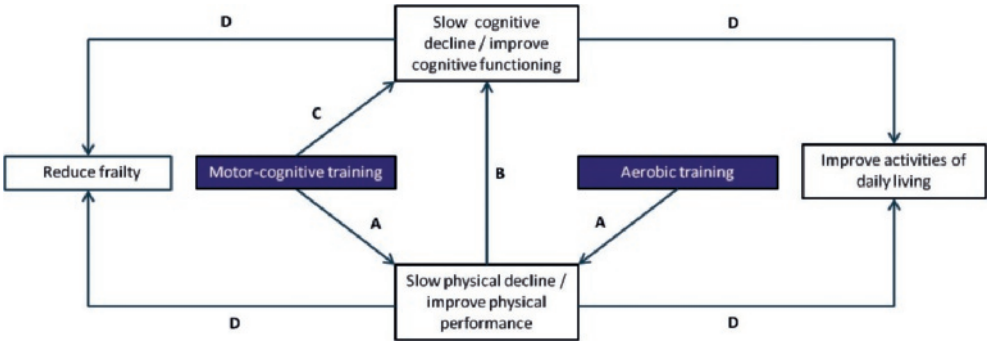

Figure 1.2. Hypothesised pathways on how motor-cognitive training and aerobic training elicit cognitive effects. We hypothesize that (A) combined motor-cognitive training and aerobic training improve physical performance, which (B) mediates the improvement in cognitive function. We expect that (C) the motor-cognitive training results in a greater effect on cognitive performance compared to aerobic training. We propose that (D) both changes in physical and cognitive performance mediate improved performance in activities of daily living and reduced frailty. Note: in reality, this model is not linear and many of the proposed pathways may be bidirectional. In the presented model we only included the pathways that were investigated in this thesis.

Content of this thesis

In **Chapter 2** physical activity and sedentary behaviour characteristics of ambulatory and community-dwelling people with dementia are compared to cognitively healthy age-, sex- and weight-matched controls. **Chapter 3** explores the barriers, motivators, and facilitators to promote physical activity participation of people with dementia. In **Chapter 4** results from a meta-analysis are presented that quantifies the effect of combined cognitive and physical interventions on cognitive function, activities of daily living, and mood, in older adults with MCI or dementia. **Chapter 5** describes the study design of an RCT. The following two chapters present the results of this RCT. In **Chapter 6** the results on the primary outcome measures of our RCT are presented. We investigated the effects of a 12-week exergame training and aerobic training on cognitive functioning, in people with dementia. We administered an elaborate neuropsychological examination consisting of four cognitive domains, with executive functioning as primary outcome measure. **Chapter 7** presents the results on the secondary outcome measures of our RCT. We investigated the efficacy of a 12-week exergame training and single aerobic training compared to an active control group, on physical performance measures and frailty. **Chapter 8** concludes with a summary of the main findings and a general discussion of the performed studies, their limitations, clinical implications and potential directions for future research.

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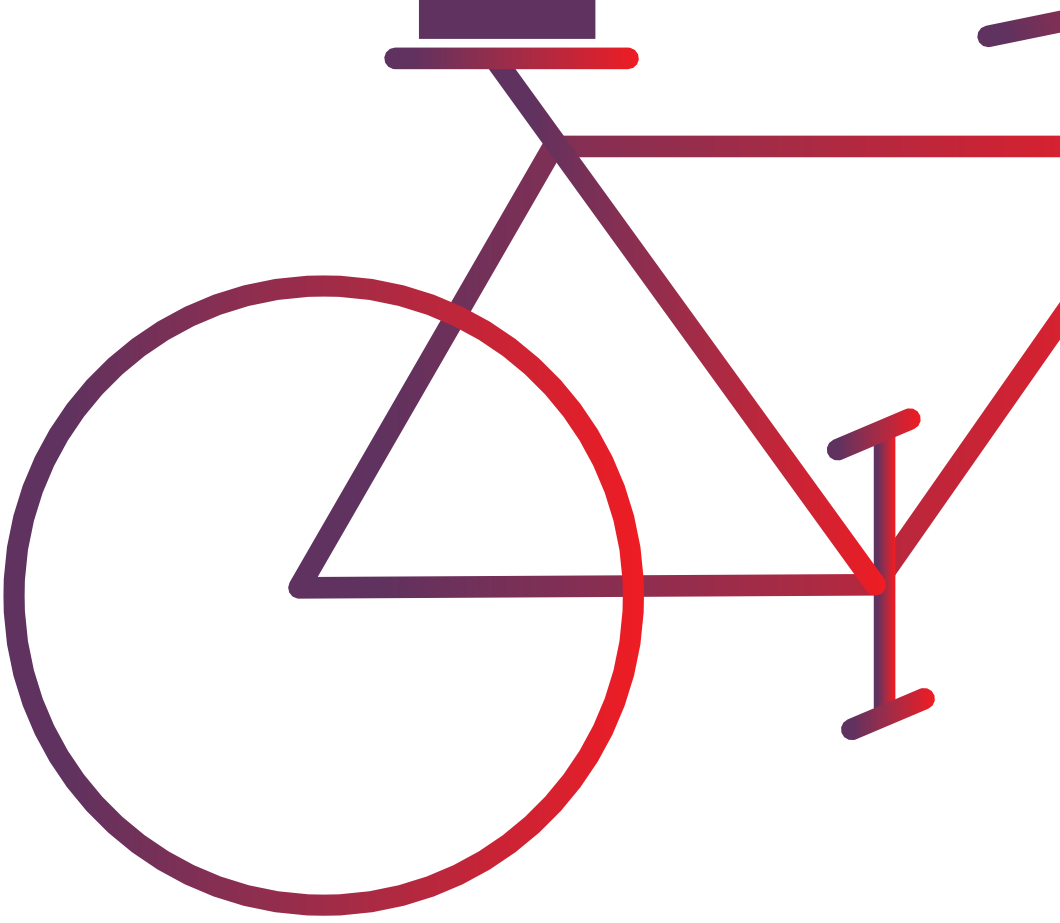

Dementia patients are more sedentary and less physically active than age- and sex-matched cognitively healthy older adults

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ABSTRACT

Aims

To examine physical activity and sedentary behaviour characteristics of ambulatory and community dwelling patients with dementia compared to cognitively healthy age-, sex- and weight-matched controls.

Methods

In this cross-sectional study we included community dwelling dementia patients (N=45, age=79.6±5.9 years, MMSE=22.8±3.2) and matched controls (N=49, age=80.0±7.7 years, MMSE=29.0±1.2). Participants wore a wrist accelerometer for seven days to assess sedentary time, sedentary bout duration and time spent in very light, light-to-moderate and moderate-to-vigorous physical activities.

Results

Relative sedentary time and sedentary bout duration was significantly higher in dementia patients compared to controls (median and interquartile range: *57% (49 - 68) vs. 55% (47 – 59) and 18.3 (16.4–21.1) minutes vs. 16.6 (15.3–18.4) minutes*, P=0.042 and P=0.008 respectively). In addition, dementia patients spent a lower percentage of their waking time in light-to-moderate and moderate-to-vigorous intensity physical activities (20% (15–23) *vs.* 22% (18–25) and 5% *(2–10) vs.* 10% (5–13), P=0.017 and P=0.001 respectively).

Conclusion

We revealed that dementia patients are more sedentary and perform less physical activity compared to cognitively healthy controls. This may have clinically important consequences, given the observation that sedentary behaviour and little physical activity independently predict all-cause mortality and morbidity.

INTRODUCTION

The incidence and prevalence of dementia is rising.[1] Pharmacological treatment to slow disease progression shows limited benefits on cognitive functioning.[2] Therefore, non-pharmaceutical therapies are needed to attenuate or slow cognitive decline. Engagement in moderate to vigorous physical activity (i.e. exercise) is one of the most important modifiable risk factors for dementia.[3] Moreover, exercise interventions have beneficial effects on cognitive function in older adults with dementia.[4] Interestingly, recent research showed that sedentary behaviour (activities requiring low levels of energy expenditure, e.g. sitting and lying), independent of performance of physical activity, is strongly related to negative health outcomes and mortality.[5,6] Moreover, sedentary behaviour is associated with lower cognitive performance,[7] which stresses the relevance to understand the prevalence and characteristics of sedentary behaviour in the context of dementia. Therefore, we aim to objectively determine physical activity and sedentary behaviour characteristics of community-dwelling dementia patients compared to cognitive healthy age-, sex- and weight-matched controls. Secondary, we will explore whether increasing age attenuates physical activity and sedentary behaviour in dementia.

MATERIALS AND METHODS

Participants and design

In this cross-sectional study persons with a dementia diagnosis, aged >60 years, that were ambulatory and community dwelling were included. Dementia diagnosis was based on comprehensive clinical assessment by a physician, typically including neuropsychological assessment and imaging. We used the mini-mental state examination (MMSE) to indicate severity of cognitive impairment.[8] Baseline measurements of a longitudinal trial examining the effects of exercise on cognitive functioning in dementia were used for the current study.[9] Cognitively healthy controls were age-, sex- and weight-matched to dementia patients and had no history of cognitive impairment (MMSE >24).[8] All participants were ambulatory and community-dwelling. The study protocol was approved by the local Medical Ethics Committee in accordance with the latest revision of the declaration of Helsinki. Written informed consent was obtained from all participants.

Physical activity monitoring

Directly after screening, physical activity and sedentary behaviour were assessed by the Philips Actiwatch 2, a wrist-worn accelerometer validated in middle-aged females.[10] The Philips Actiwatch 2 contains an acceleration-responsive piezoelectric sensor which measures wrist accelerations in three directions every 30 seconds. These wrist accelerations were translated into a number of counts that were used to estimate physical activity and sedentary behaviour.

The accelerometer was worn for seven days on the non-dominant wrist, to provide a reliable estimate of physical activity and sedentary behaviour.[11,12] All participants wore the actiwatch 24 hours per day. The accelerometer was waterproof and participants did not take if off during swimming or taking a shower. Therefore, non-wear time was not expected. Sleep intervals, including daytime naps, were filled in by the participants or their caregivers in a sleep diary.

Data analysis

Data was uploaded using the Philips Actiware 6 software. Data from the first day of testing were excluded from analysis to give participants the opportunity to familiarize with the device. Sleep intervals were manually set by the researcher using the Philips Actiware 6 software[13] and excluded by custom software written in MATLAB R2014b (MathWorks, USA). Hereby only the data of the waking hours remained. Participants were included if they provided at least six valid days (>10 h of waking data). Data was converted from counts per epoch into counts per minute (CPM). Cut-off points of 145 counts per minute (CPM), 145-274 CPM, 274-597 CPM and >597 CPM were used for sedentary behaviour, very light, light-to-moderate and moderate-to-vigorous physical activity respectively.[10] To account for individual differences in waking time, our primary analysis expressed activity levels as a percentage of total (awake) measuring time. Interruptions in sedentary behaviour were defined as spending one minute ≥145 CPM after 5 minutes <145 CPM. Prolonged sedentary behaviour was defined as spending 30 minutes <145 CPM without one minute above 145 CPM. Duration of average sedentary bout was defined by total time spent sedentary divided by number of interruptions in sedentary behaviour.

Statistical analysis

Statistical analyses were performed in IBM SPSS Statistics 20.0 (IBM SPSS; IBM Corp., Armonk, New York, USA). We performed a complete case analysis, including only those participants that wore the actiwatch for a minimum of 7 days. Chi^2-tests for categorical variables and independent samples t-tests for continuous variables were used to compare dementia patients and controls. Non-parametric tests were used for not normally distributed data (including physical activity and sedentary behaviour). To evaluate the impact of age, the same analyses were performed between participants aged <80 years and ≥80 years. All data are presented as median (interquartile range) unless stated otherwise. Level of significance was set at $P<0.05$.

RESULTS

45 dementia patients (mean±SD age=79.6±5.9 years, MMSE=22.8±3.2) and 49 controls (mean±SD age=80.0±7.7 years, MMSE=29.0±1.2) were included (Figure 2.1). Sex, BMI, walking aid use and number of comorbidities did not differ between groups (Table 2.1). MMSE was significantly lower in dementia patients (P<0.001), and dementia patients received significantly more home care (P<0.001). The majority of dementia patients and controls lived independently (93% and 98% respectively).

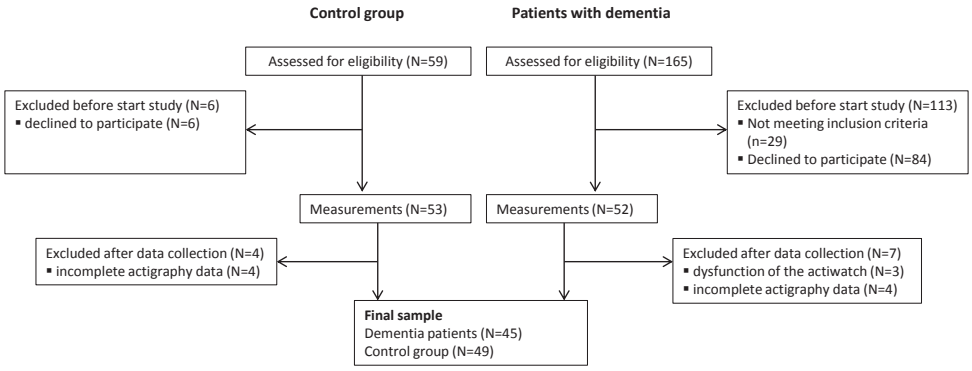

Figure. 2.1. Flowchart of participants

Total waking time tended to be lower in dementia patients compared to controls (mean±SD 14.9±1.3 h/day *vs.* 15.4±1.0 h/day, P=0.053, Table 2.2). Dementia patients had significantly lower activity counts and spent more hours in categories reflecting lower-intensity activity (Table 2.2). Relative sedentary time was significantly higher in dementia patients compared to controls (57% (49 - 68) vs. 55% (47 – 59), P=0.042, Table 2.2). In addition, dementia patients spent a lower percentage of their waking time in light-to-moderate and moderate-to-vigorous intensity physical activity (20% (15-23) *vs.* 22% (18-25) and 5% (2-10) *vs.* 10% (5-13), P=0.017 and P=0.001, respectively). Number of interruptions in sedentary behaviour and prolonged sedentary bouts did not differ. Duration of sedentary bouts was significantly longer in dementia patients compared to controls (18.3 (16.4-21.1) minutes vs. 16.6 (15.3-18.4) minutes, P=0.008, Table 2.2).

Table 2.1. Baseline characteristics

	Control (n=49)	Dementia (n=45)	P-value
Age (years), mean ± SD	80.0 ± 7.7	79.6 ± 5.9	0.744*
Females, n (%)	25 (51.0%)	22 (48.9%)	0.836†
Body Mass Index (kg/m²), mean ± SD	25.5 (4.0)	26.3 (5.0)	0.411*
Mini Mental State Examination‡, mean ± SD	29.0 ± 1.2	22.8 ± 3.2	**<0.001***
Number of walking aid users, n (%)	10 (20.4%)	16 (35.6%)	0.101†
Number of home-care receivers, n (%)	6 (12.2%)	24 (53.3%)	**<0.001**†
Number of comorbidities§, mean ± SD	2.7 ± 1.8	3.3 ± 1.9	0.150*
Residence, n (%)			0.629†
Independent, alone	18 (36.7%)	14 (31.1%)	
Independent, together	30 (61.2%)	28 (62.2%)	
Care home	1 (2.0%)	3 (6.7%)	
Nursing home	0	0	
Dementia type, n (%)			
Alzheimer's disease	n/a	25 (55.6%)	
Vascular dementia	n/a	2 (4.4%)	
Alzheimer's Disease/Vascular Dementia (%)	n/a	12 (26.7%)	
Dementia type not specified (%)	n/a	6 (13.3%)	

*Differences between groups were tested with independent samples t-test; †Differences between groups were tested with Chi-Square Test; ‡ Scores on the Mini-Mental State Examination (MMSE) range from 0 (severe impairment) to 30 (no impairment); §Comorbidites are scored using the Older Persons and Informal Caregivers Survey-Minimum Dataset (TOPICS-MDS) with a theoretical range of 0-17 and a higher score indicates more comorbidities.[14]

When comparing younger versus older subgroups, older participants showed more walking aid users. Whilst older controls showed significantly less physical activity and more sedentary behaviour compared to their younger peers, no such changes were present between dementia patients aged ≥80 years and aged <80 years (Figure 2.2). More specifically, younger controls had significantly higher activity counts, lower relative sedentary time, and spent more hours in categories reflecting light-to-moderate and moderate-to-vigorous intensity activity compared to older controls. Since no such differences were present between young and older dementia patients, differences in physical activity and sedentary behaviour characteristics between populations was most prominent in the younger groups (see Figure 2.2).

Table 2.2. Physical activity and sedentary behaviour characteristics

	Control (n=49)	Dementia (n=45)	P-value
Total waking time (h/day)	15.4 ± 1.0*	14.9 ± 1.3*	0.053†
Counts per minute	226 ± 61*	186 ± 76*	**0.005**†
Absolute values (h/day)			
Sedentary time	8.1 (7.2 – 9.2)	8.5 (7.2 – 10.0)	0.216
Very light intensity activity	2.2 (1.9 – 2.6)	2.3 (1.7 – 2.9)	0.748
Light-to-moderate intensity activity	3.5 (2.7 – 4.0)	2.7 (2.0 – 3.7)	**0.006**
Moderate-to-vigorous intensity activity	1.5 (0.8 – 2.0)	0.8 (0.4 – 1.5)	**0.001**
Relative values (% of total measuring time)			
% sedentary time	55 (47 – 59)	57 (49 – 68)	**0.042**
% very light intensity activity	15 (12 – 16)	16 (12 – 19)	0.284
% light-to-moderate intensity activity	22 (18 – 25)	20 (15 – 23)	**0.017**
% moderate-to-vigorous intensity activity	10 (5 – 13)	5 (2 – 10)	**0.001**
Sedentary behaviour characteristics			
Number of interruptions in sedentary behaviour (day^{-1})	28.2 (26.2 – 32.5)	27.2 (24.5 – 31.0)	0.195
Number of 30 minutes prolonged sedentary bouts (day^{-1})	2.0 (0.9 – 3.3)	2.3 (1.0 – 4.1)	0.227
Duration of average sedentary bout (minutes)	16.6 (15.3 – 18.4)	18.3 (16.4 –21.1)	**0.008**

Median and Interquartile range are presented unless reported otherwise. P-values represent Mann-Whitney U test; *Mean ± SD; †Differences between groups were tested with independent samples t-test

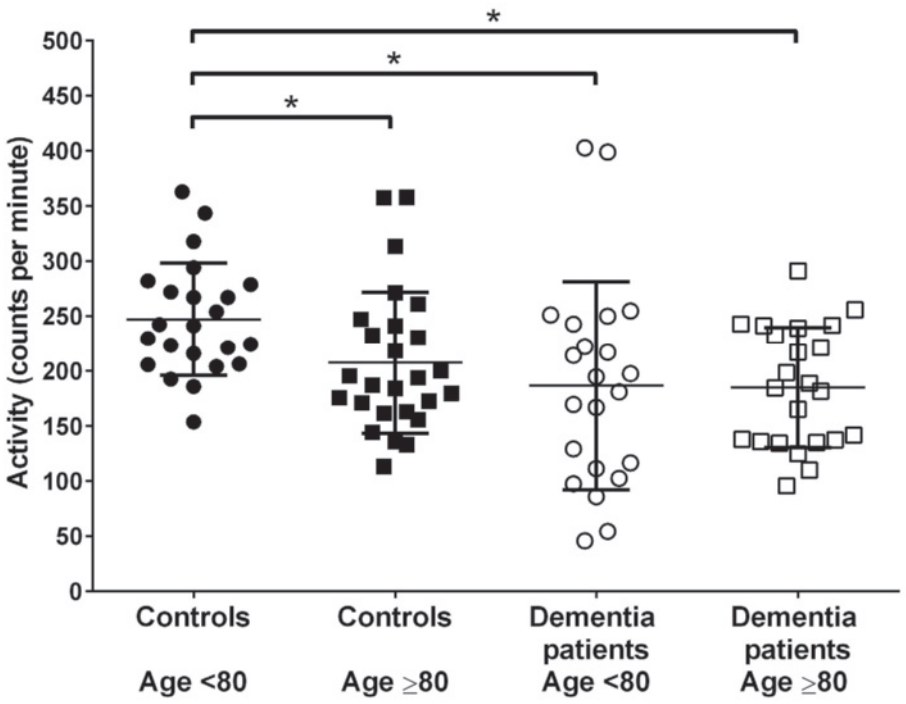

Figure 2.2. Activity levels of dementia patients and cognitively healthy controls in younger and older age groups. Mean activity score (counts per minute) grouped by age. Controls Age<80 (n=23), Controls Age ≥80 (n=26), Dementia patients Age <80 (n=22), Dementia patients Age ≥80 (n=23). Values represent median ± interquartile range. * Significant difference between: Controls Age <80 and Controls Age ≥80 P=0.044, Controls Age <80 and Dementia patients Age <80 P=0.004, Controls Age <80 and Dementia patients Age ≥ 80 P=0.002.

DISCUSSION

The aim of our study was to objectively investigate physical activity and sedentary behaviour characteristics of dementia patients compared to controls, and assess whether age affects this comparison. First, in our relatively large sample we found that dementia patients spent significantly more of their waking hours in a sedentary state and significantly less time in light-to-moderate and moderate-to-vigorous intensity activities. This may have clinically important consequences, given the observation of previous prospective studies that sedentary behaviour independently predicts all-cause mortality and morbidity.[5,15] Secondly, we found that older age was associated with a decline in physical activity and increase in sedentary behaviour in controls, whilst no such age-related changes were found in dementia patients. Consequently,

negligible differences in physical activity and sedentary behaviour characteristics were present when comparing older dementia patients and controls.

In line with observations from previous work,[16,17] our data confirm that community-dwelling dementia patients spend a large amount of time in sedentary behaviour and have low levels of physical activity. We add the novel finding that differences between dementia patients and controls remain when corrected for sleep time. Even though we used an accelerometer validated to measure physical activity and sedentary behaviour,[10] time spent in moderate-to-vigorous intensity activity seems unusually high in both groups.[18] We have compared our findings to other studies that assessed physical activity and sedentary behaviour in older adults with and without dementia, and we note that sedentary behaviour ranged from 6.7 to 10.7 hours between studies.[16,19,20] Moreover, percentage of elderly meeting physical activity guidelines (150min/week of moderate-to-vigorous physical activity) ranged from 27-69%.[18,21] Differences in sedentary behaviour and physical activity duration between studies might relate to the use of different types of accelerometers, given that the reported studies used hip-worn accelerometers, wrist-worn accelerometers or questionnaires to estimate physical activity and sedentary behaviour.[22] However, this does not invalidate our primary comparison between subjects with dementia and healthy peers. Moreover, this highlights the importance of including a control group to provide valid interpretation of the results.

Our observation raises the question if differences in physical activity and sedentary behaviour are simply a consequence of dementia. A decline in executive functioning (i.e. necessary for goal directed behaviour such as physical activity) could lead to apathy,[23] which is known to lower activity levels in Alzheimer's patients.[24] However, it is important to realize that lower physical activity and higher sedentary behaviour have already been reported in the preclinical stages of dementia[25] and in subjects with mild cognitive impairment.[26] This might suggest that differences in physical activity and sedentary behaviour are causally linked to progression from mild cognitive impairment to later stages of dementia. Future research is necessary to answer this question on cause or effect. Nevertheless, since higher physical activity and lower sedentary behaviour are associated with better cognitive performance,[7,26] benefits of interventions promoting physical activity and reducing sedentary behaviour should be investigated.

In response to our second research question, we found that older age was associated with a decline in physical activity and increase in sedentary behaviour in controls. This observation can partly be explained by deterioration of walking and mobility and increased disability with older age.[27] Interestingly, no further decline in physical activity and increase in sedentary behaviour were found in dementia patients, despite the age-related increased number of walking aid users. This striking result suggests that cognitive impairment in dementia has a great impact on physical activity and sedentary behaviour, and may be more important than the impact of

other factors such as deterioration of walking and mobility. An alternative explanation is that a (near) minimum level is achieved in the decline in levels of physical activity and sedentary behaviour in community-dwelling subjects.[18]

In addition to the duration of sedentary behaviour, previous work revealed that the frequency of breaking up sitting (and therefore duration of each sedentary bout) may have clinical relevance. Breaks in sedentary behaviour can prevent cardiovascular impairments[5] and plays a role in maintaining glycemic control, which may positively influence brain health.[28] Our study found that the average duration of a sedentary bout was higher in dementia patients compared to controls. This observation suggests that not only reducing sedentary time, but also preventing prolonged sedentary bouts by regularly breaking up sedentary behaviour, can be targeted as a lifestyle intervention.[29]

Limitations

Since we only included community-dwelling patients, our results cannot be generalized to institutionalised dementia patients. Furthermore, dementia patients in our study were enrolled in an exercise trial.[9] Therefore, this group may be more motivated to be physically active. Nonetheless, significant differences in physical activity characteristics were observed. Furthermore, physical activity characteristics were measured by wrist-worn accelerometry, which is associated with limited discriminative capacity between sedentary and very light intensity activities.[30] Consequently, differences between dementia patients and controls might even be more pronounced. Another limitation relates to our accelerometer, which has only been validated in a group of middle-aged females[10] and was unable to correct for potential presence of short (~1-min) periods of non-wear time. Nonetheless, we do not expect this will invalidate our findings of between-group differences in physical activity and sedentary behaviour. In addition, using wrist-worn accelerometry may explain the two outliers in the younger dementia patients (Figure 2.2), which could relate to restless arm movements. Whilst this may affect exploring individual differences in physical activity *versus* sedentary behaviour characteristics, significant differences remained present at group level. Furthermore, we did not discriminate between types of sedentary activities. Cognitively challenging sedentary activities, such as reading, might have a protective effect on cognition and are therefore less harmful than passive sedentary activities (e.g. television-viewing).[31] The final limitation is use of the MMSE as a cognitive screening instrument since this measure, especially in healthy highly educated older adults, has limited discriminative power to detect mild cognitive deficits.[32,33] It is important to indicate that diagnosis of dementia was not made using the MMSE, but included standard clinical procedures (including imaging if required).

Clinical relevance

Knowledge of physical activity characteristics across the entire activity spectrum in dementia is highly relevant given that physical activity is an important factor accelerating development and progression of dementia.[3,7] In addition, a high amount of sedentary behaviour and low amount of physical activity are associated with higher mortality and morbidity.[5,6] Even though we found relatively small differences in physical activity characteristics between dementia patients and controls, these may be highly relevant. For example, even very short breaks of light intensity activity (i.e. 2 minutes walking) can already prevent acute metabolic[34] and cardiovascular[5] impairments. This underlines the importance to develop interventions suitable for this vulnerable patient group to safely engage in light intensity activities. However, future research should first explore the role of physical activity and sedentary behaviour in the progression and prevention of dementia.

CONCLUSION

In the current study we objectively demonstrated that dementia patients spend significantly more of their waking hours in sedentary behaviour and spend less time in light-to-moderate and moderate-to-vigorous intensity physical activity. Moreover, we found that older age attenuated sedentary behaviour and physical activity in controls, whilst this age-related decline is absent in dementia patients. This means that patients with dementia (independent of age) lead a physically inactive lifestyle characterized with significant time spent sedentary. Taken together, these data improve our understanding of physical activity and sedentary behaviour characteristics in this highly relevant patient group and implies that targeting sedentary behaviour and physical activity may be relevant in dementia patients, especially at a younger age.

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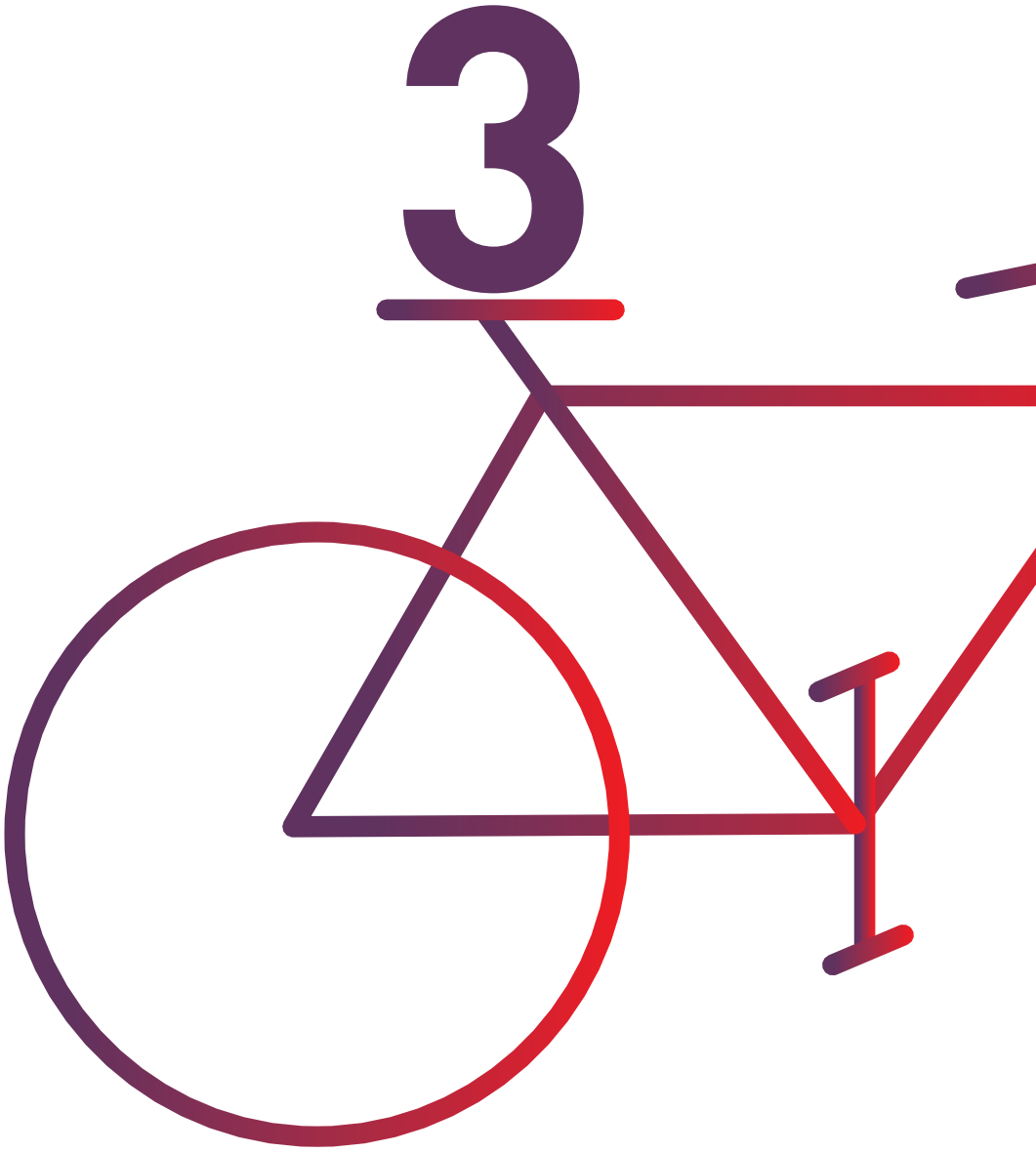
3

Ranking barriers, motivators, and facilitators to promote physical activity participation of persons with dementia: an explorative study

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ABSTRACT

Background and purpose

Community-dwelling persons with dementia are inactive most of the day. The purpose of this study was to rank the barriers, motivators, and facilitators that hamper or promote physical activity (PA) participation for persons with dementia. This could provide knowledge that can be used to design effective interventions to promote PA participation for persons with dementia.

Methods

Twenty community-dwelling persons with dementia (mean (SD) age = 79 (5.4) years; 25% female; mean (SD) Mini-Mental Status Examination score = 23 (3.5)), their informal caregivers (N = 20; mean (SD) age = 70 (11.5) years; 85% female), and an expert group of physiotherapists (N = 15; mean (SD) age = 41 (12.4) years; 73% female) were asked to rank preselected barriers, motivators, and facilitators of PA participation for persons with dementia. These statements were categorized at the intrapersonal, interpersonal, and community level.

Results and discussion

Persons with dementia and their informal caregivers selected only motivators and facilitators as being important for PA participation, with the motivator "beneficial health effects" considered the most important. The experts had a different perspective on PA participation; half of their ranked top 10 most important factors were barriers to PA participation for persons with dementia. This could be explained by the more critical role of a therapist, focusing on symptom control and treatment of disability; in this case, the elimination of barriers to maintain PA participation in their patients. Furthermore, all groups prioritised statements at the intrapersonal level.

Conclusions

The results of this study suggest a difference in perspective between the more optimistic view of persons with dementia and their informal caregivers and the more critical view of physiotherapy experts regarding the most important factors that influence PA participation. In addition, there was a strong focus on the individual characteristics that influence PA behaviour which warrant personalised interventions to promote PA in dementia.

INTRODUCTION

Older age is the strongest risk factor for developing dementia and, due to the ageing population, the number of older adults living with dementia is predicted to increase.[1,2] Over 9.9 million people are diagnosed with dementia each year, and the total number of persons with dementia is expected to reach 131.5 million by 2050, making prevention of dementia an international health, social, and economic priority.[3]

Dementia is characterized by progressive cognitive decline, motor deficits, behavioural problems, which complicate activities of daily living leading to higher care demands.[4-6] There is no cure or effective disease-modifying therapy for dementia.[7,8] Pharmacological treatment focuses on managing dementia-related symptoms, but its effectiveness is limited.[9] Therefore, recent research has focused on developing non-pharmacological interventions such as physical activity (PA) as alternative or add-on therapies to prevent dementia progression.[10]

PA levels decline progressively with age, and a stronger decline is observed in older adults with dementia compared to their peers without this disease.[4,11-13] Recent research showed that community-dwelling persons with dementia spent 66% of the day sedentary.[11] Besides, daily PA levels of community-dwelling persons with dementia were 21.6% lower than PA levels of healthy older adults.[11] PA may have beneficial effects on cognitive and physical abilities of persons with dementia,[14,15] which can lead to functional improvements and an increased quality of life.[16,17] It is therefore important to implement PA into the daily routines of persons with dementia.[4]

Different studies have identified barriers, motivators, and facilitators for persons with dementia to participate in PA.[4,15] Van Alphen et al.[4] identified 26 motivators, 35 barriers, and 21 facilitators, and classified them using the socio-ecological model. This model demonstrates that factors from a variety of levels could affect an individual's participation in PA; for example, factors from the intrapersonal level (health effects, individual preferences), interpersonal level (social support), and community level (organizational or environmental factors).[18-20] However, the relative importance of these factors in influencing PA in persons with dementia is still unknown, and such knowledge could elucidate why persons with dementia are physically active or inactive. This could lead to the development of more effective strategies to promote PA. Thus, the primary objective of our study is to rank the barriers, motivators, and facilitators influencing PA participation for persons with dementia, as judged by the patients themselves, their informal caregivers, and an expert group of physiotherapists.

METHODS

Study design

A qualitative design was used to rank the importance of factors for their influence on PA participation of persons with dementia. These factors were ranked by 3 different groups of participants; persons with dementia, informal caregivers, and an expert group of physiotherapists. All participants gave their oral and written informed consent prior to the study. The study protocol was approved by the Medical Ethical Committee of Radboud university medical center (Ref No: NL52581.091.15/2015-1857), and was conducted in compliance with the Declaration of Helsinki ethical standards.

Setting and participants

This study was executed from October to December 2016 in Nijmegen, the Netherlands. Persons with dementia, their informal caregivers (spouse, child, or other family member), and physiotherapists were included in the study. The persons with dementia participated in a larger trial, studying the effect of combined cognitive-aerobic training on cognitive function.[21] Inclusion criteria were: (1) a clinically confirmed diagnosis of dementia with a Mini Mental Status Examination (MMSE) score ≥ 17,[22] and (2) aged 60 years or above. Exclusion criteria were: (1) incapable of giving written informed consent; (2) a co-morbidity that limited exercising, including severe cardiovascular, musculoskeletal, or neurological diseases; (3) diagnosis of a depression, bipolar disorder, or psychotic disorder at the moment of inclusion; (4) drug or alcohol dependency; (5) exercising more than 5 times per week for at least 30 minutes at a moderate intensity; (6) wheelchair bound; and (7) severe hearing or visual problems that could not be corrected with the use of hearing aids/glasses. Figure 3.1 illustrates the flow of included participants. Twenty persons with dementia and their informal caregivers gave oral and written consent to participate in this study. Forty physiotherapists, who work with persons with dementia on a regular basis, were approached and 15 consented to participate (37.5%). Eight of these participating physiotherapists (53%) had a specialization in geriatrics. See Table 3.1 for the demographics of the 3 groups.

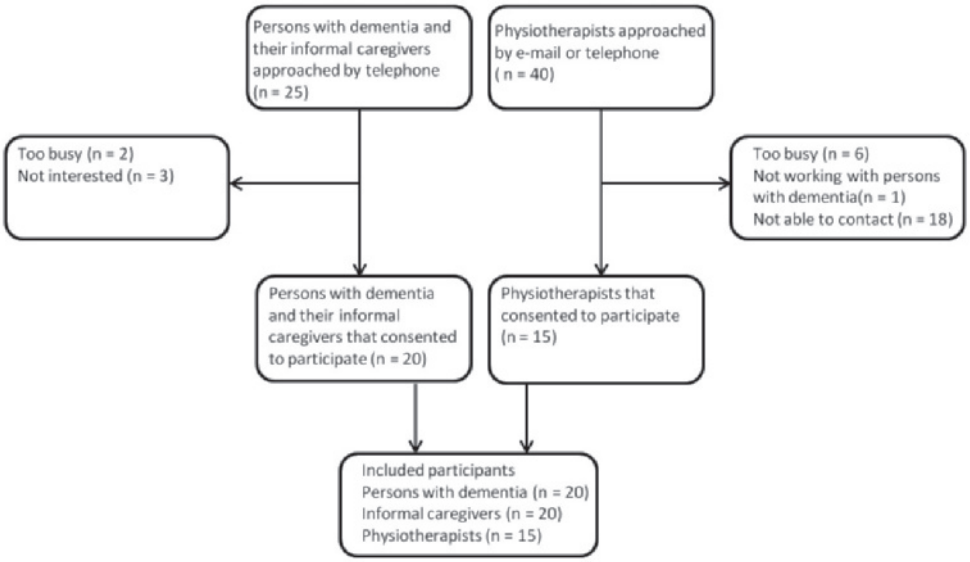

Figure 3.1. Flow diagram of the study's sample

Table 3.1. Baseline characteristics

Characteristics	Persons with dementia (N=20)	Informal caregivers (N=20)	Experts (N=15)
Age, y, mean (SD)	79 (5.4)	70 (11.5)	41 (12.4)
Gender, woman, n (%)	5 (25)	17 (85)	11 (73)
Education level, n (%)			
Primary school education or lower	2 (10)	1 (5)	0 (0)
Incomplete higher education	14 (70)	12 (60)	0 (0)
Higher education	4 (20)	7 (35)	15 (100)
MMSE, mean (SD)	23 (3.5)	n/a	n/a
Dementia type, n (%)			
Alzheimer	11 (55)	n/a	n/a
Vascular	1 (5)	n/a	n/a
Mixed	8 (40)	n/a	n/a
Functional Comorbidity Index[a], mean (SD)	2.3 (1.5)	n/a	n/a
Living situation, n (%)			
Independent	20 (100%)	n/a	n/a
Type of informal caregivers, n (%)			
Spouse	n/a	15 (75)	n/a
Child	n/a	3 (15)	n/a
Other family member	n/a	2 (10)	n/a

Abbreviations: n/a, not applicable; MMSE, Mini-Mental State Examination

[a] Theoretical range 0-18 and a higher score indicates more comorbidities.[23]

Statement set

Factors that influence PA participation of persons with dementia were formulated as statements, which were sorted by participants along a continuum to represent their opinion. The barriers, motivators, and facilitators identified by van Alphen et al.[4] were used to define the statements in this study, resulting in the inclusion of 51 statements. To ensure the statement set covered all relevant factors, additional data were collected by interviewing 7 persons with dementia and their informal caregivers (data not published), leading to the inclusion of 12 additional statements. This initial set of 63 statements was discussed within the research team (FK, EK, WB), after which 5 statements were rephrased and 10 statements were excluded to prevent overlap between statements and ensure completeness. This resulted in a final set of 53 statements. The statements were categorized into intrapersonal level, interpersonal level, and community level factors (see Appendix A for an overview of all statements).

Ranking methods

The statements were ranked using 2 different methods. The informal caregivers and experts employed a ranking method from the Q-methodology,[23] sorting the statements along a continuum to represent their opinion. The Q-method is shown to be reliable, and due to its qualitative aspects each individual's rank-ordered set of statements is considered a valid expression of their opinion.[23] A pilot study was performed with 3 participants to assess the feasibility of using this ranking method in persons with dementia. This method was found to be too complicated because participants became confused due to the higher number of statements that were presented to them. A simplified scoring method was used for this group consisting of a series of binary questions (disagree/not important or agree/important) with corresponding scores of 0 or 1.

Ranking method used by informal caregivers and experts

Participants were asked how important they thought the different statements on barriers, facilitators, and motivators were for influencing PA participation in persons with dementia, sorting the set of statements along a chosen continuum on a fixed grid that resembled a Likert scale. See Figure 3.2 for the sorting grid used for ranking by the informal caregivers and experts. The columns had different values, ranging from the 'not-important at all' column (-5) to the 'very important' column (+5). The rows were not assigned values and the shape of the sorting grid was determined by the expected opinions. We did not expect very strong opinions, so more space was available for statements in the centre with only limited space for statements at the ends. The participants were allowed to place statements outside of the sorting grid, if necessary, and they could make changes or replace statements during the sorting process. Scores given by the caregivers and experts were calculated and collated for each statement. See Appendix B for a more detailed explanation of this ranking method.

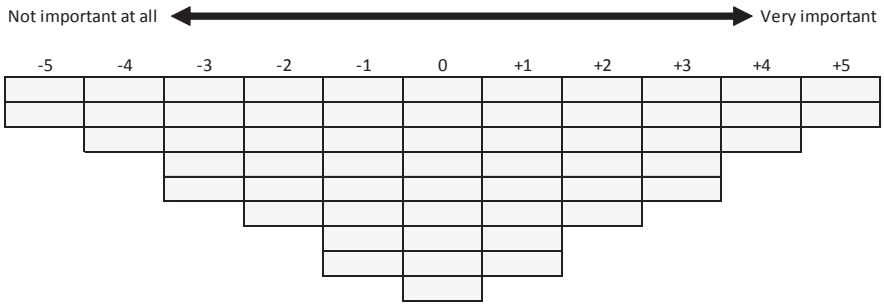

Figure 3.2. Representation of the grid used in the sorting procedure. Participants assigned all 53 statements to one of the places on the grid, representing how important each statement was for physical activity participation.

Ranking method used by persons with dementia

The statements were randomly presented to the persons with dementia in a maximum of 5 rounds. In every round, the participants were asked to agree or disagree with the presented statements. The participant was told that it was a matter of opinion, so there was no wrong or right answer. In the first round, every statement was read out loud, and the participant had to answer 'yes' or 'no', meaning that they agreed or disagreed with the statement being important for PA participation. The statements were placed on a 'yes' or 'no' pile. When there were difficulties understanding a statement or the participant could not decide, the statement was placed on a 'neutral'/'don't know' pile. These statements were treated the same as the statements on the 'no' pile. In the second round, all the statements on the 'yes' pile were again divided by the participants into 'very important' or 'less important' piles, using the same procedure as the first round. The question that was asked was: 'Is this very important to you, or just a little bit important?' If more than 10 statements were categorized as 'very important', the statements were subjected to another round of ranking by the participants until only 10 or fewer statements were classified as 'very important'. The number of rounds required varied between 3 and 5. For every round, the statement could receive a score of 0 (not important/disagree) or 1 (important/agree), and the final statement scores given by each participant were divided by the number of rounds taken to sort them. For example, if a participant took 4 rounds to reduce the number of statements, the scores were 0 for statements that did not move through the first round (0/0), 0.25 for statements that moved through the first round (1/4), 0.5 for statements that moved through the second round (2/4), 0.75 for statements that moved through the third round (3/4), and 1 for the statements that were considered 'very important' in the fourth and final round (4/4). This resulted in an ordinal scale with scores ranging from 0 to 1.

Data analysis

IBM SPSS Statistics 22 for Windows was used for data analysis. A ranking was created for each group. Median, interquartile range (IQR), minimum and maximum scores were calculated for each statement. Since use of the median results in a lower discriminative power for ranking the statements than use of the mean, we present the statements in order of the mean only if the median was exactly the same.

RESULTS

The 10 most important barriers, motivators, and facilitators ranked by each group are listed in Table 3.2. See Appendix C for the ranking of all statements. 'Beneficial health effects' was the most important motivator to engage in PA according to both the informal caregivers and the persons with dementia. Moreover, informal caregivers and persons with dementia selected only motivator and facilitator statements in their top 10. In contrast, the experts selected 5 barriers in their top 10: 'loss of initiative', 'suffering from pain', 'feeling tired', 'physical problems', and 'negative feelings'. In all groups, 'pleasant' and 'enjoyment' were selected as the 2 most important facilitators.

A majority of the 10 most important statements were classified as intrapersonal factors (see Figure 3.3). Six of the top 10 statements selected by informal caregivers were intrapersonal factors, whereas 8 of the top 10 from the experts and 9 of the top 10 selected by the persons with dementia were intrapersonal statements. The informal caregivers were the group that selected most community factors in their top 10: 'good weather', 'outdoors', and 'person leading the activity'. Both experts and informal caregivers selected 1 statement from the interpersonal level in their top 10: spouse support and support professional.

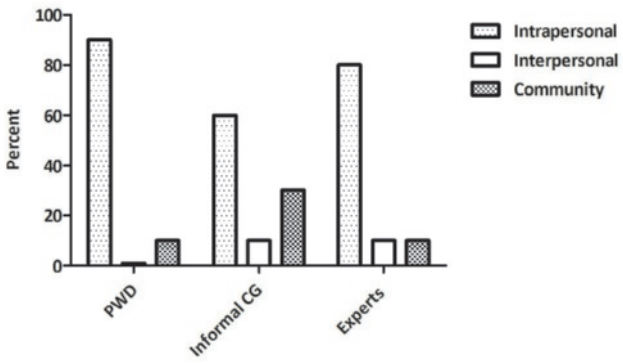

Figure 3.3. Percentage of statements in the top 10 that belong to the intrapersonal, interpersonal, and community level. Different groups are presented on the X-axis and the percentage on the Y-axis.
Abbrevations: PWD=Persons With Dementia; CG=Caregiver

Table 3.2. Ten most important barriers, motivators, and facilitators for PA participation according to persons with dementia, their informal caregivers, and physiotherapy experts

Ranking	Statement	Median	Interquartile range	Min	Max	Level[a]
		Persons with Dementia				
1	Beneficial health effects	1.0	1.0–1.0	0.5	1.0	Intrapersonal
2	Physical benefits	1.0	0.5–1.0	0.0	1.0	Intrapersonal
3	Retain flexibility	1.0	0.5–1.0	0.0	1.0	Intrapersonal
4	Outdoors	0.6	0.5–1.0	0.0	1.0	Community
5	Retain self–reliance	0.6	0.5–1.0	0.0	1.0	Intrapersonal
6	Enjoyment	0.5	0.4–1.0	0.0	1.0	Intrapersonal
7	Enjoyed physical activity in the past	0.5	0.5–0.9	0.0	1.0	Intrapersonal
8	Pleasant	0.5	0.5–1.0	0.0	1.0	Intrapersonal
9	Feel useful	0.5	0.3–1.0	0.0	1.0	Intrapersonal
10	Feel free	0.5	0.0–1.0	0.0	1.0	Intrapersonal
		Informal Caregivers				
1	Beneficial health effects	3.0	2.0–5.0	0	5	Intrapersonal
2	Physical benefits	2.5	1.0–4.0	-1	5	Intrapersonal
3	Person leading the activity	2.5	0.3–3.0	-3	5	Community
4	Enjoyment	2.0	1.0–3.0	-2	5	Intrapersonal
5	Good weather	2.0	1.3–3.0	-2	5	Community
6	Pleasant	2.0	1.0–3.8	-1	4	Intrapersonal
7	Outdoors	2.0	0.3–3.8	-2	5	Community
8	Retain flexibility	2.0	0.0–3.0	-3	5	Intrapersonal
9	Mental benefits	1.5	0.3–3.0	-1	5	Intrapersonal
10	Support professional	1.5	0.3–2.8	-5	5	Interpersonal
		Experts				
1	Loss of initiative	3.0	2.0–4.0	0	5	Intrapersonal
2	Pleasant	3.0	1.0–3.0	0	5	Intrapersonal
3	Retain self–reliance	3.0	1.0–5.0	-2	5	Intrapersonal
4	Suffering from pain	3.0	1.0–4.0	-1	5	Intrapersonal
5	Feel tired	3.0	1.0–5.0	-1	5	Intrapersonal
6	Enjoyment	3.0	1.0–3.0	-1	5	Intrapersonal
7	Dejected	3.0	1.0–3.0	-2	5	Intrapersonal
8	Physical problems	2.0	1.0–4.0	-3	5	Intrapersonal
9	Spouse support	2.0	0.0–4.0	-1	4	Interpersonal
10	Person leading the activity	2.0	1.0–3.0	0	4	Community

Abbreviations: PA, physical activity

[a] Statements are classified by the socio–ecological model, which demonstrates that factors at multiple levels could affect an individual's participation in PA, including intrapersonal factors, interpersonal factors, and community factors.[19]

The statements ranked lowest by the informal caregivers and experts are presented in Table 3.3. For persons with dementia there were 12 statements that never got through the first round. These statements were: 'transportation', 'unfamiliar', 'dejected', 'decreased energy levels', 'inactive', 'lack of trust', 'caregivers doubts about potential benefits', 'away from home', 'being dependent', 'time consuming', 'lack of understanding', and 'health problems of caregiver'. Both the persons with dementia and the informal caregivers ranked only barriers in their bottom 10, which represented the least important statements.

Table 3.3. Ten least Important barriers, motivators, and facilitators, according to informal caregivers and experts

Ranking	Statement	Median	Interquartile range	Min	Max	Level[a]
			Informal Caregivers			
44	Dependent	-1.5	-3.0–1.0	-5	4	Intrapersonal
45	Structural exercises	-1.5	-3.0–1.0	-4	0	Community
46	Feeling forced	-2.0	-3.0–0.0	-5	4	Intrapersonal
47	Lack of trust	-2.0	-2.8–0.0	-4	4	Intrapersonal
48	Reduces feelings of frustration	-2.0	-3.0–2.5	-4	4	Intrapersonal
49	Caregiver's doubts about potential benefits	-2.0	-3.8–-1.0	-5	0	Interpersonal
50	Inactive	-2.5	-4.0–-1.0	-5	2	Intrapersonal
51	Concerned about well–being	-2.5	-4.0–-1.0	-5	0	Intrapersonal
52	Burden on others	-3.0	-4.0–-1.0	-5	2	Interpersonal
53	Loss of freedom	-4.0	-5.0–-2.0	-5	0	Intrapersonal
			Experts			
44	Lack of understanding	-1.0	-3.0–0.0	-5	2	Intrapersonal
45	Knowledge	-1.0	-3.0–0.0	-5	1	Intrapersonal
46	Knowledge about memory problems	-2.0	-3.0–0.0	-4	2	Intrapersonal
47	Mental benefits	-2.0	-3.0–0.0	-4	2	Intrapersonal
48	Structural exercises	-2.0	-3.0–0.0	-5	1	Community
49	Reduces feelings of frustration	-2.0	-3.0–-1.0	-5	0	Intrapersonal
50	Concerned about well–being	-2.0	-3.0–-1.0	-5	1	Intrapersonal
51	Time consuming	-2.0	-4.0–-2.0	-5	0	Community
52	Caregiver has health problems	-3.0	-3.0–2.0	-5	5	Interpersonal
53	Loss of freedom	-4.0	-5.0–-2.0	-5	2	Intrapersonal

Abbreviations: PA, physical activity

[a] Statements are classified by the socio–ecological model, which demonstrates that factors at multiple levels could affect an individual's participation in PA, including intrapersonal factors, interpersonal factors, and community factors.[19]

DISCUSSION

The aim of this study was to rank barriers, motivators, and facilitators that hamper or promote PA participation for persons with dementia. Results of the current study may be used to increase the adherence rate of exercise prescriptions and interventions in persons with dementia. The 3 main findings of the current study are: (1) substantial differences in perspective exist between persons with dementia and their informal caregivers versus the expert physiotherapists regarding the factors that determine PA participation; (2) persons with dementia, caregivers, and experts all chose intrapersonal level factors as being important for promoting PA participation; and (3) the motivator "beneficial health effects" was the most important factor selected by persons with dementia and their informal caregivers. These 3 main findings will be discussed in more detail.

In the present study, the persons with dementia and their informal caregivers only selected motivators and facilitators as important factors for PA participation. Selecting positive and stimulating factors to maintain PA participation is in line with previous findings of Preston et al.[24] They showed that patients with early-stage dementia focus on positive characteristics that are largely unaffected by the disease. The researchers argued that, by doing so, patients maintain feelings of continuity and self-control.[24] In contrast, the physiotherapy experts in the current study chose a different perspective on PA participation; 5 of the 10 top-ranked items by professionals were barriers for PA participation. This may be explained by the more critical role of a therapist focusing on symptom control and treatment of disability, in this case by eliminating barriers to maintain PA participation in their patients. The transfer of knowledge on potential barriers and how to eliminate them from professionals to persons with dementia and their informal caregivers, may lead to higher PA participation in persons with dementia. On the other hand, a stronger focus on motivational aspects by professionals could positively influence PA behaviour.

We found that persons with dementia, informal caregivers, and professionals all considered intrapersonal factors to be most important for PA participation. Thirty statements (58%) in our study were characterized as intrapersonal, which comprised 77% of the top 10 ranked items. Thus, from the perspective of persons with dementia, informal caregivers, and professionals, PA participation may be strongly influenced by individual characteristics, suggesting the necessity of using a personalised approach synchronized with the individual needs of the patient. Research showed that personalised psychosocial interventions have positive effects on behavioural and psychological symptoms of dementia.[25] The effectiveness of personalised interventions to promote PA in persons with dementia is unknown; therefore, future research is warranted.

The motivator "beneficial health effects" was the priority choice of informal caregivers and persons with dementia. This finding is in line with a systematic review from Baert et al,[26] who showed that "health status" was the most commonly reported barrier and motivator for PA in older adults. In addition, the perceived health benefits were more salient in older adults compared to younger adults.[27] This indicates that emphasizing health benefits may be a decisive element for the promotion of PA.

Limitations

The generalizability of the results may be limited because only persons with dementia who had already participated in an exercise study were included.[21] Therefore, these participants could be more motivated to be physically active or could experience fewer barriers, leading to a sampling bias. Second, the reliability and validity of our simplified ranking method used in persons with dementia is unknown and requires future research. We did show that this method was feasible, as all persons with dementia were able to complete the process, and the procedure was efficient, safe, and low in cost. Third, we assigned no weightings to the individual factors that influence PA. Such weightings are needed to model how removing a barrier or adding a facilitator would affect PA behaviour of persons with dementia. Fourth, the distribution between men and women (75% male) in our sample does not reflect the known Western-world population of persons with dementia, the majority of whom are female (61%).[28] Since gender has an effect on the degree of PA, with older women generally being more sedentary and less active than older men,[29] this could have influenced our results. The final limitation is the questionable use of the MMSE as a cognitive screening instrument due to its potential failure to detect significant cognitive deficits.[22] A more recent and reliable measure such as the Montreal Cognitive Assessment (MOCA) may have been more appropriate.[30]

Practical implications

The results of this study suggest that the transfer of knowledge from professionals to persons with dementia and their informal caregivers regarding the elimination of potential barriers to PA may lead to higher participation levels. This dissemination of information could be implemented through personal intakes with healthcare professionals, organizing educational meetings, or publishing news items on this topic. In addition, since individual characteristics seem to most influence PA participation, personalised plans to promote PA behaviour should be developed and synchronized with each individual's needs. Future research should investigate the effect of these personalised interventions on PA participation for persons with dementia.

CONCLUSIONS

Differences in perspective may exist between the more optimistically oriented persons with dementia and informal caregivers and the more critically oriented physiotherapy experts concerning the most important factors influencing PA participation. Persons with dementia, focus mainly on positive characteristics that are unaffected by dementia, while professionals, focus on symptom control and treatment of disability. In addition, there is a strong focus on individual characteristics that influence PA behaviour, which warrant personalised interventions to promote PA in dementia.

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SUPPLEMENTARY MATERIAL

Appendix A. Overview of statements

Intrapersonal level statements

1. I want to be physically active, because it helps me to **retain my flexibility**.
2. I want to be physically active, because I have **knowledge about its potential benefits for my memory problems**.
3. I want to be physically active, because I **enjoyed physical activity in the past**.
4. I want to be physically active, because it has **beneficial health effects**.
5. I want to be physically active, because it makes me feel like **having a purpose.**
6. I want to be physically active, because I have **knowledge about the positive effects** of exercise.
7. I want to be physically active, because it makes me **feel free**.
8. I want to be physically active, because I **enjoy** it.
9. I want to be physically active, because it helps me **retain my self-reliance**.
10. I want to be physically active, because it helps me **retain my self-confidence**.
11. I want to be physically active, because it has **mental benefits**.
12. I want to be physically active, because it is **pleasant.**
13. I want to be physically active, because it has **physical benefits.**
14. I want to be physically active, because it **reduces feelings of frustration.**
15. I want to be physically active, because it helps making **new social contacts**.
16. I want to be physically active, because it **improves my mood.**
17. I want to be physically active, because it makes me **feel useful**.
18. I don't want to be physically active, because I am **unfamiliar** with the situation.
19. I don't want to be physically active, because I feel **dejected.**
20. I don't want to be physically active, because I have **loss of initiative**.
21. I don't want to be physically active, because I have **problems with my attention and memory**.
22. I don't want to be physically active, because I have **decreased energy levels**.
23. I don't want to be physically active, because I have been **inactive my entire life.**
24. I don't want to be physically active, because I have **loss of motivation**.
25. I don't want to be physically active, because I **feel forced.**
26. I don't want to be physically active, because of **physical problems**.
27. I don't want to be physically active, because I **suffer pain**.
28. I don't want to be physically active, because of **lack of trust**.
29. I don't want to be physically active, because I am **concerned about my well-being**.
30. I don't want to be physically active, because I **feel tired**.

Interpersonal level statements

1. I want to be physically active, because my **spouse supports me**.
2. I want to be physically active, because a **professional supports me**.
3. I want to be physically active, because **professionals said** it would be good for me.
4. I want to be physically active, because then I can be with other people with whom I can **identify**.
5. I don't want to be physically active, because my **caregiver has health problems**.
6. I don't want to be physically active, because I **do not know many other people.**
7. I don't want to be physically active, because my **caregiver has doubts about potential benefits**.
8. I don't want to be physically active, because I feel like I am a **burden on others**.
9. I don't want to be physically active, because I **don't want to depend on others.**
10. I don't want to be physically active, because of others people **lack of understanding.**

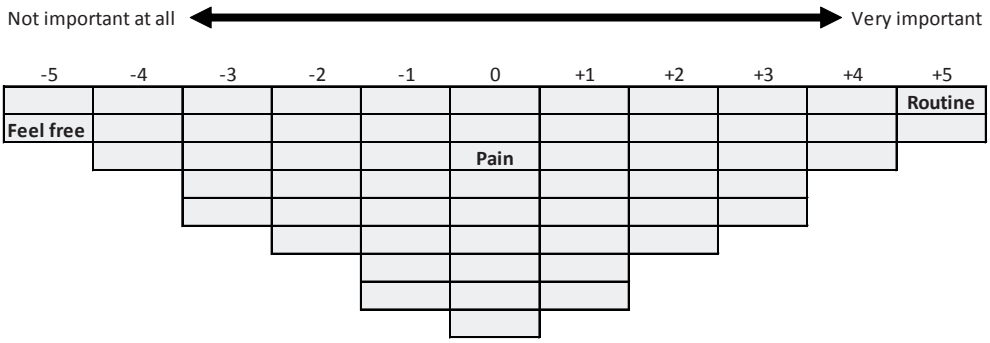
Community level statements

1. I want to be physically active, because I want to go **outdoors**.
2. I want to be physically active, because the **weather is good**.
3. I want to be physically active, because a **person is leading the activity**.
4. I want to be physically active, because it is **a routine**.
5. I want to be physically active, because the **environment is inviting**.
6. I don't want to be physically active, because I don't have any **transportation**.
7. I don't want to be physically active, because it is **time consuming**.
8. I don't want to be physically active, because I have **concerns regarding safety**.
9. I don't want to be physically active, because I am **afraid to get lost**.
10. I don't want to be physically active, because I **don't like structural exercises.**
11. I don't want to be physically active, because I **don't want to be away from home**.
12. I don't want to be physically active, because it makes me **lose my freedom.**
13. I don't want to be physically active, because the **weather is bad**.

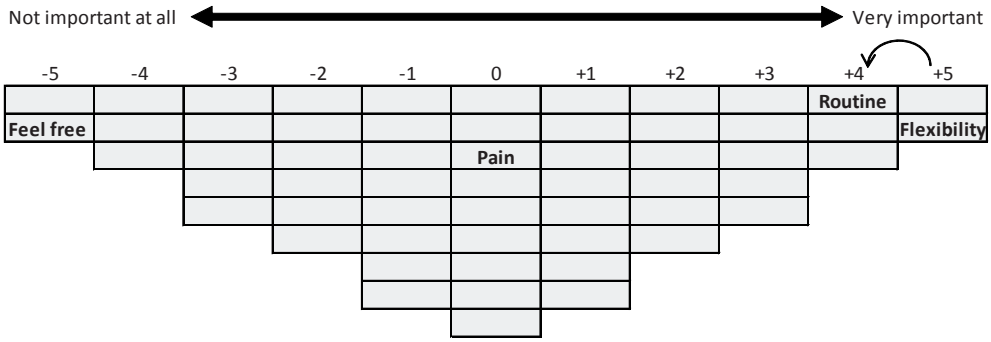
Appendix B. Ranking method used by informal caregivers and experts

Step 1. Fifty three statements on barriers, motivators, and facilitators for PA participation were presented to the participants.

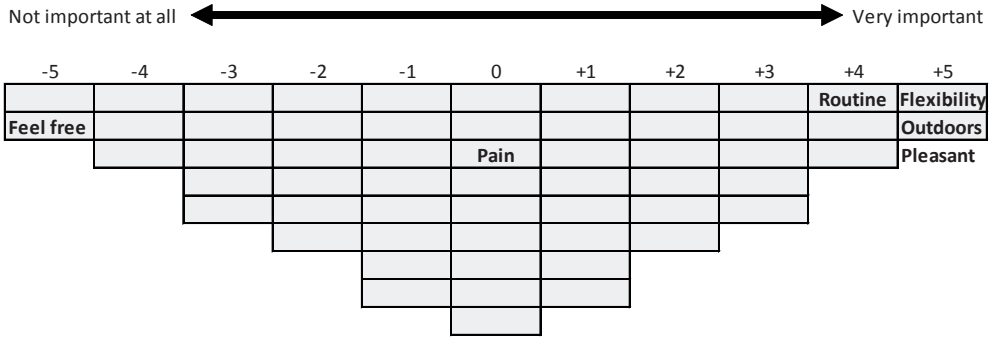
Step 2: Participants were instructed to sort the statements along a chosen continuum on a fixed grid. Participants assigned all 53 statements to one of the places on the grid, representing how important each statement was for PA participation. The columns have different values ranging from -5 (not important at all) to +5 (very important). The rows were not assigned values. For example, if the participant thought that an activity *being a routine* was an important motivator they placed this card in the last column. If the participant thought that *feeling free* was not important for PA participation they placed this card in the first column. If they did not have a strong opinion on the barrier *having pain* they placed this card in the centre.



Step 3: Participants were allowed to make changes or replace statements during this process. For example, if participants thought that the statement *retain flexibility* was more important than the statement *routine* they could replace this statement.



Step 4: The grid was just a format and participants were allowed to place statements outside the grid if necessary. For example, if they thought that the statements *retain flexibility, outdoors and pleasant* were equally important, they could place them all in the last column.



Step 5: After the participants placed all statements on the grid, statement scores were calculated. Each statement could receive a score of -5 (not important at all) to +5 (very important).

Appendix C. Ranking of persons with dementia, informal caregivers, and physiotherapy experts

Persons with Dementia

Ranking	Statement	Median	Interquartile range	Min	Max
1	Beneficial health effects	1.0	1.0-1.0	0.5	1.0
2	Physical benefits	1.0	0.5-1.0	0.0	1.0
3	Retain flexibility	1.0	0.5-1.0	0.0	1.0
4	Outdoors	0.6	0.5-1.0	0.0	1.0
5	Retain my self-reliance	0.6	0.5-1.0	0.0	1.0
6	Enjoyment	0.5	0.4-1.0	0.0	1.0
7	Enjoyed physical activity in the past	0.5	0.5-0.9	0.0	1.0
8	Pleasant	0.5	0.5-1.0	0.0	1.0
9	Feel useful	0.5	0.3-1.0	0.0	1.0
10	Feel free	0.5	0.0-1.0	0.0	1.0
11	Having a purpose	0.5	0.0-1.0	0.0	1.0
12	Mental benefits	0.5	0.0-1.0	0.0	1.0
13	Retain self-confidence	0.5	0.0-0.9	0.0	1.0
14	Improves mood	0.5	0.0-0.7	0.0	1.0
15	Good weather	0.5	0.0-0.9	0.0	1.0
16	Knowledge	0.5	0.0-0.6	0.0	1.0
17	Inviting environment	0.4	0.0-0.5	0.0	1.0
18	Knowledge about memory problems	0.3	0.0-0.7	0.0	1.0
19	New social contacts	0.3	0.0-0.6	0.0	1.0
20	Professional said	0.0	0.0-0.7	0.0	1.0
21	Support professional	0.0	0.0-0.5	0.0	1.0
22	Identify	0.0	0.0-0.5	0.0	1.0
23	Person leading the activity	0.0	0.0-0.5	0.0	1.0
24	Spouse support	0.0	0.0-0.5	0.0	1.0
25	Routine	0.0	0.0-0.5	0.0	1.0
26	Bad weather	0.0	0.0-0.0	0.0	1.0
28	Reduces feelings of frustration	0.0	0.0-0.0	0.0	1.0
29	Problems with attention and my memory	0.0	0.0-0.0	0.0	1.0
30	Feel forced	0.0	0.0-0.0	0.0	1.0
31	Physical problems	0.0	0.0-0.0	0.0	1.0
32	Loss of initiative	0.0	0.0-0.0	0.0	0.5
33	Feel tired	0.0	0.0-0.0	0.0	0.5
34	Loss of motivation	0.0	0.0-0.0	0.0	0.5
35	Suffering from pain	0.0	0.0-0.0	0.0	0.5
36	Concerned about my well-being	0.0	0.0-0.0	0.0	0.5
37	Know other people	0.0	0.0-0.0	0.0	0.5
38	Structural exercises	0.0	0.0-0.0	0.0	0.5
39	To get lost	0.0	0.0-0.0	0.0	0.3

26	Concerns regarding safety	0.0	0.0-0.0	0.0	0.3
40	Burden on others	0.0	0.0-0.0	0.0	0.3
41	Loss of freedom	0.0	0.0-0.0	0.0	0.3
42	Time consuming	0.0	0.0-0.0	0.0	0.0
43	Caregiver has health problems	0.0	0.0-0.0	0.0	0.0
44	Transportation	0.0	0.0-0.0	0.0	0.0
45	Unfamiliar	0.0	0.0-0.0	0.0	0.0
46	Dejected	0.0	0.0-0.0	0.0	0.0
47	Decreased energy levels	0.0	0.0-0.0	0.0	0.0
48	Inactive	0.0	0.0-0.0	0.0	0.0
49	Lack of trust	0.0	0.0-0.0	0.0	0.0
50	Doubts about potential benefits	0.0	0.0-0.0	0.0	0.0
51	Away from home	0.0	0.0-0.0	0.0	0.0
52	Dependent	0.0	0.0-0.0	0.0	0.0
53	Lack of understanding	0.0	0.0-0.0	0.0	0.0

Informal Caregivers

Ranking	Statement	Median	Interquartile range	Min	Max
1	Beneficial health effects	3.0	2.0-5.0	0	5
2	Physical benefits	2.5	1.0-4.0	-1	5
3	Person leading the activity	2.5	0.3-3.0	-3	5
4	Enjoyment	2.0	1.0-3.0	-2	5
5	Good weather	2.0	1.3-3.0	-2	5
6	Pleasant	2.0	1.0-3.8	-1	4
7	Outdoors	2.0	0.3-3.8	-2	5
8	Retain flexibility	2.0	0.0-3.0	-3	5
9	Mental benefits	1.5	0.3-3.0	-1	5
10	Support professional	1.5	0.3-2.8	-5	5
11	Routine	1.0	0.0-2.8	-1	5
12	Enjoyed physical activity in the past	1.0	0.0-2.8	-4	5
13	Having a purpose	1.0	-0.8-3.0	-3	4
14	Knowledge about memory problems	1.0	-0.8-2.0	-3	5
15	Feel free	1.0	0.0-2.8	-3	4
16	Bad weather	1.0	-0.8-3.0	-5	5
17	Feel useful	1.0	-0.8-2.8	-4	5
18	Spouse support	1.0	0.0-2.8	-3	4
19	Inviting environment	1.0	0.0-2.0	-2	3
20	Professional said	1.0	0.0-2.0	-5	3
21	Retain my self-reliance	1.0	-1.8-2.0	-3	4
22	Feel tired	1.0	-3.8-2.8	-5	4

23	Retain self-confidence	0.5	-1.0-1.8	-3	5
24	New social contacts	0.0	-1.0-3.0	-4	5
25	Loss of initiative	0.0	-0.8-3.0	-2	5
26	Knowledge	0.0	-0.8-2.0	-4	3
27	Improves mood	0.0	-2.0-2.0	-4	5
28	Transportation	0.0	-2.0-1.0	-5	4
29	Unfamiliar	0.0	-1.0-1.0	-4	5
30	To get lost	0.0	-2.0-2.8	-5	4
31	Decreased energy levels	-0.5	-1.8-1.5	-3	4
32	Dejected	-0.5	-2.0-1.0	-4	3
33	Physical problems	-0.5	-2.8-2.0	-5	4
34	Loss of motivation	-0.5	-2.0-1.0	-4	4
35	Identify	-0.5	-1.8-0.0	-5	2
36	Suffering from pain	-1.0	-2.8-2.0	-4	5
37	Know other people	-1.0	-2.8-0.0	-4	5
38	Problems with attention and my memory	-1.0	-2.0-0.0	-5	2
39	Concerns regarding safety	-1.0	-2.0-0.0	-5	2
40	Away from home	-1.0	-3.0- -1.0	-4	4
41	Caregiver has health problems	-1.0	-4.0-0.0	-5	2
42	Lack of understanding	-1.5	-3.0-0.0	-5	3
43	Time consuming	-1.5	-2.0-0.0	-5	2
44	Dependent	-1.5	-3.0-1.0	-5	4
45	Structural exercises	-1.5	-3.0-1.0	-4	0
46	Feel forced	-2.0	-3.0-0.0	-5	4
47	Lack of trust	-2.0	-2.8-0.0	-4	4
48	Reduces feelings of frustration	-2.0	-3.0-2.5	-4	4
49	Caregivers doubts about potential benefits	-2.0	-3.8--1.0	-5	0
50	Inactive	-2.5	-4.0--1.0	-5	2
51	Concerned about my well-being	-2.5	-4.0--1.0	-5	0
52	Burden on others	-3.0	-4.0--1.0	-5	2
53	Loss of freedom	-4.0	-5.0--2.0	-5	0

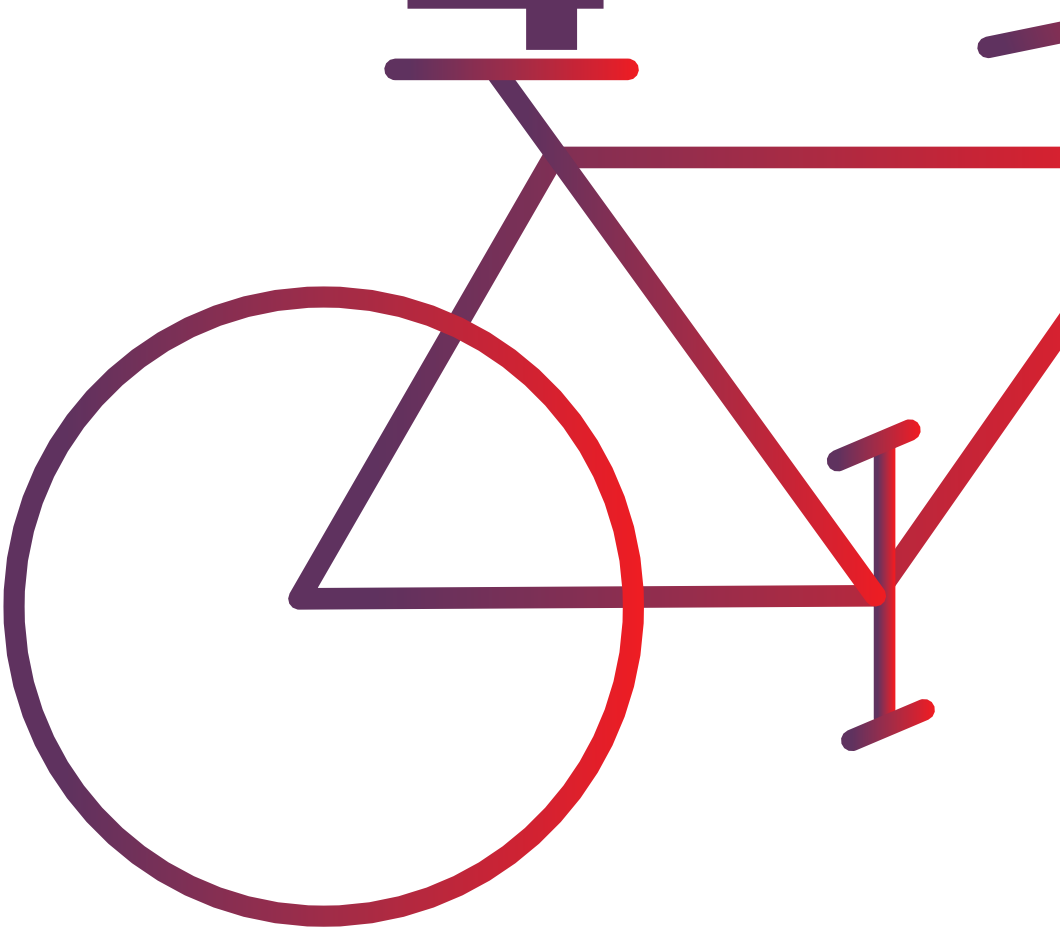
Experts

Ranking	Statement	Median	Interquartile range	Min	Max
1	Loss of initiative	3.0	2.0-4.0	0	5
2	Pleasant	3.0	1.0-3.0	0	5
3	Retain my self-reliance	3.0	1.0-5.0	-2	5

4	Suffering from pain	3.0	1.0-4.0	-1	5
5	Feel tired	3.0	1.0-5.0	-1	5
6	Enjoyment	3.0	1.0-3.0	-1	5
7	Dejected	3.0	1.0-3.0	-2	5
8	Physical problems	2.0	1.0-4.0	-3	5
9	Spouse support	2.0	0.0-4.0	-1	4
10	Person leading the activity	2.0	1.0-3.0	0	4
11	Loss of motivation	2.0	0.0-4.0	-3	5
12	Enjoyed physical activity in the past	2.0	1.0-3.0	-2	4
13	Decreased energy levels	2.0	0.0-3.0	-2	5
14	Inactive	2.0	0.0-3.0	-3	3
15	Beneficial health effects	1.0	0.0-1.0	-2	4
16	Support professional	1.0	1.0-3.0	-3	4
17	Concerns regarding safety	1.0	-1.0-3.0	-4	4
18	Professional said	1.0	0.0-1.0	-3	3
19	Physical benefits	1.0	0.0-1.0	-1	2
20	Routine	1.0	-1.0-2.0	-4	4
21	Inviting environment	1.0	-1.0-2.0	-3	4
22	Retain self-confidence	1.0	-1.0-1.0	-4	5
23	Feel forced	1.0	-2.0-2.0	-4	3
24	Outdoors	0.0	0.0-2.0	-1	5
25	Unfamiliar	0.0	-1.0-2.0	-3	4
26	Feel free	0.0	-1.0-1.0	-3	3
27	Lack of trust	0.0	-1.0-1.0	-4	5
28	Dependent	0.0	-1.0-2.0	-4	5
29	Feel useful	0.0	-1.0-2.0	-4	4
30	Know other people	0.0	-2.0-2.0	-4	4
31	Having a purpose	0.0	-2.0-2.0	-3	3
32	Doubts about potential benefits	0.0	-2.0-2.0	-5	3
33	Improves mood	0.0	-1.0-0.0	-3	1
34	New social contacts	0.0	-4.0-1.0	-5	3
35	Identify	0.0	-4.0-0.0	-5	1
36	Transportation	-1.0	-2.0-4.0	-4	5
37	Retain flexibility	-1.0	-2.0-2.0	-4	3
38	Problems with attention and my memory	-1.0	-2.0-1.0	-3	2
39	To get lost	-1.0	-2.0-1.0	-4	3
40	Burden on others	-1.0	-2.0-0.0	-4	3
41	Away from home	-1.0	-2.0-1.0	-3	1

42	Good weather	-1.0	-3.0-0.0	-4	3
43	Bad weather	-1.0	-2.0--1.0	-4	1
44	Lack of understanding	-1.0	-3.0-0.0	-5	2
45	Knowledge	-1.0	-3.0-0.0	-5	1
46	Knowledge about memory problems	-2.0	-3.0-0.0	-4	2
47	Mental benefits	-2.0	-3.0-0.0	-4	2
48	Structural exercises	-2.0	-3.0-0.0	-5	1
49	Reduces feelings of frustration	-2.0	-3.0--1.0	-5	0
50	Concerned about my well-being	-2.0	-3.0--1.0	-5	1
51	Time consuming	-2.0	-4.0--2.0	-5	0
52	Caregiver has health problems	-3.0	-3.0-2.0	-5	5
53	Loss of freedom	-4.0	-5.0--2.0	-5	2

4



Positive effects of combined cognitive and physical exercise training on cognitive function in older adults with mild cognitive impairment or dementia: A meta-analysis

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ABSTRACT

Combined cognitive and physical exercise interventions have potential to elicit cognitive benefits in older adults with mild cognitive impairment (MCI) or dementia. This meta-analysis aims to quantify the overall effect of these interventions on global cognitive functioning in older adults with MCI or dementia. Ten randomized controlled trials that applied a combined cognitive-physical intervention with cognitive function as an outcome measure were included. For each study effect sizes were computed (i.e., post-intervention standardized mean difference (SMD) scores) and pooled, using a random-effects meta-analysis. The primary analysis showed a small-to-medium positive effect of combined cognitive-physical interventions on global cognitive function in older adults with MCI or dementia (SMD [95% confidence interval] = 0.32 [0.17-0.47], $p < 0.00$). A combined intervention was equally beneficial in patients with dementia (SMD = 0.36 [0.12-0.60], $p < 0.00$) and MCI (SMD = 0.39 [0.15-0.63], $p < 0.05$). In addition, the analysis showed a moderate-to-large positive effect after combined cognitive-physical interventions for activities of daily living (ADL) (SMD = 0.65 [0.09-1.21], $p < 0.01$) and a small-to-medium positive effect for mood (SMD = 0.27 [0.04-0.50], $p < 0.01$). These functional benefits emphasize the clinical relevance of combined cognitive and physical training strategies.

INTRODUCTION

Due to the aging population, the number of people with mild cognitive impairment (MCI) or dementia is expected to grow.[1] Currently there are about ten million new cases of dementia each year, a number which will increase to approximately 131.5 million prevalent dementia cases in 2050.[2] These rapidly growing numbers will have a large societal impact, placing a high economic burden on health care.[2,3] Therefore, the World Health Organization (WHO) stresses to take global action against cognitive decline and dementia, encouraging governments worldwide to focus on prevention, disease-modifying therapies and improving health care service.[4]

Mild cognitive impairment (MCI) is the transitional phase between normal cognitive functioning and dementia, characterized by cognitive decline that is larger than expected considering a person's age and education, though without notably interference in daily-life activities.[5] The annual conversion rates from MCI to dementia ranges from 5 to 20%, depending on the sample studied and the follow-up duration.[6] Dementia is characterized by progressive and severe cognitive decline, motor deficits and/or behavioural problems causing a decline in activities of daily living (ADL).[7] A variety of neuropathololologies underlie dementia syndromes, with Alzheimer's disease being the most common cause in older adults, accounting for 60–80% of all dementia cases, followed by vascular dementia.[7] Thus far, pharmacological therapies solely alleviate dementia symptoms, but fail to modify disease progression.[8-10]

Recent meta-analyses show that physical exercise may help to preserve or even improve cognitive function in healthy older adults.[11-14] There is evidence that exercise increases the volumes of the prefrontal cortex[15] and the anterior hippocampus,[16,17] and may enhance neurogenesis[18] and angiogenesis.[19] Furthermore, exercise reduces cardiovascular risk factors.[20] In contrast, research on the effects of physical exercise in older adults with MCI or dementia are less abundant and vary in efficacy.[21-24] The large variability in exercise protocols, study populations and treatment compliance complicate interpretation of the results.[21,23,24]

Possibly, the neural and cognitive benefits elicited by physical activity can be enhanced by adding exposure to a cognitively challenging environment.[25-27] Experimental animal studies have shown that physical activity and environmental enrichment induce hippocampal neurogenesis via different pathways, and a combination results in greater benefits than either physical activity or an enriched environment alone.[26,27] In line, a meta-analysis of Zhu et al.[28] revealed significant benefits of combined cognitive and physical interventions, compared with both single exercise training and a control group, on overall cognitive function in healthy older adults. A qualitative review of Law et al.[29] shows some benefits of combined interventions in cognitively impaired populations, however the evidence was limited when the evaluation included comparison with active control groups. Moreover, conclusions drawn from this qualitative review were based on

reported levels of statistical significance without considering the magnitude of the observed effects. Therefore, a quantitative meta-analysis including the most recent studies is needed to clarify the efficacy of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia.

The primary objective of this meta-analysis is to quantify the overall effect of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia. Secondary objectives are to (1) assess the effect of combined cognitive and physical exercise interventions on the cognitive domains of memory and executive function/attention, (2) determine whether combined interventions positively influence activities of daily living (ADL) and (3) evaluate the efficacy of combined interventions on mood.

METHODS

The review was registered in the International prospective register of systematic reviews (PROSPERO, https://www.crd.york.ac.uk/PROSPERO/: CRD42016051342) and the work was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.[30]

Search strategy

In February 2017 systematic searches were conducted in the databases PUBMED, PsycINFO, Embase and Cochrane Library. This search was updated in May 2017. We used a combination of terms for cognitive impairment ("dementia" OR "cognitive impairment*" OR "Alzheimer"), AND cognitive/physical intervention terms ("exercise" OR "physical activity" OR "aerobic therapy*" OR "resistance training" OR "cognitive therapy" OR "memory training" OR "cognitive stimulation"), AND combined intervention terms ("multimodal" OR "combined" OR "cognitive-motor" OR "dual–task") (See Supplementary A for full search terms). To identify additional potentially relevant articles, the reference lists of the selected articles were screened.

Eligibility criteria and study selection

Studies were eligible if they met the following inclusion criteria: (1) inclusion of a sample of patients diagnosed with MCI or dementia not caused by traumatic brain injury or space-occupying lesion; (2) intervention consisting of a combined cognitive and physical training; (3) peer-reviewed articles with a randomized controlled trial (RCT) design including an active or passive control group and (4) reporting at least one measure for global cognitive function to calculate an effect size. Studies were excluded if they were: (1) prospective or retrospective cohort studies; (2) case reports; (3) conference abstracts or (4) not written in English. When articles reported an overlap in the sample of participants the article with the largest sample

was included. Two reviewers (E.K. and T.S.) screened the title/abstracts and subsequently full text articles separately. Disagreements were discussed with a third researcher (J.A.) and adjusted after reaching consensus.

Interventions and outcome measures

Only RCTs with a combined cognitive and physical exercise intervention group, that also included an active or passive control group, were included. If the RCTs consisted of two or more intervention groups (i.e., also single physical and single cognitive training), only data of the combined intervention and control group were used for analyses. Global cognitive function, evaluated with a global cognitive screening instrument, was used as the primary outcome measure. Secondary outcome measures were performance on the domains of memory and executive function/attention, ADL and mood. All outcome measures had to be administered at baseline and directly after the intervention period. Corresponding authors of eligible studies were contacted and asked to provide missing data in case of insufficient reporting of statistics.

Risk of bias assessment

The Cochrane Collaboration's tool[31] for assessing risk of bias was used as a measure of quality assessment. Risk of bias was reported in six domains; selection bias, performance bias, detection bias, attrition bias, reporting bias and other bias. Each bias domain was rated as low, high, or unclear. Two researchers (E.K. and T.S.) independently performed the risk of bias assessment. Differences in outcome were discussed with a third researcher (J.A.) until consensus was reached. A total risk of bias judgment was based on the assessment of all domains.

Statistical analysis

The statistical analysis was conducted using Comprehensive Meta-analysis (CMA) Version 2.0 (Englewood, NJ, USA, 2005). A random-effects meta-analysis was used to correct for variable effect sizes across the studies and because studies showed heterogeneity in the intervention methods (e.g. intervention type, duration, outcome measures).[32] The intervention effect was measured by the standardized mean difference (SMD) estimated as follows:[32]

$$SMD = \frac{\bar{X}_e - \bar{X}_c}{S_{within}}$$

$\bar{X}_e$ is the sample mean of the experimental group and $\bar{X}_c$ is the sample mean of the control group. S_{within} is the within group standard deviation, pooled across groups:

$$S_{within} = \sqrt{\frac{(n_e-1)\,S_e^2+(n_c-1)\,S_c^2}{n_e+n_c-2}}$$

where, S_e is the standard deviation of the experimental group, S_c is the standard deviation of the control group and n_e and n_c the numbers of participants in the experimental and control group. [32] Pooled-SMDs were computed for all three cognitive domains, ADL and mood, weighted for the sample size of the individual studies.[32] These pooled effect sizes were classified as small (0.2), moderate (0.5) and large (0.8) in accordance with convention.[33] If studies used more than one measure in a cognitive domain, an average effect size was computed to avoid one study over influencing the results.

A 95% confidence interval was used to determine the efficacy of combined interventions versus control on cognitive function, mood and ADL. In addition, Orwin's fail safe N was calculated for significant results to assess how many studies were needed in order to reduce the effect size to less than 0.1.[32]

The Q-statistic and I^2 index were calculated to report the level of heterogeneity. The Q-statistic is a measure of the true variance within studies. A significant Q-statistic indicates heterogeneity among studies. The I^2 index reflects the proportion of true heterogeneity in the observed variance and is calculated using the equation $\frac{Q-df}{Q}$ x 100%, where *df* symbolizes the degrees of freedom (=number of studies - 1). A I^2 value of 0% indicates no observed heterogeneity and larger values indicate increasing heterogeneity.[32]

Publication bias was assessed by visual inspection of funnel plots. These funnel plots display the relationship between sample size and effect size. In absence of publication bias, studies should be distributed symmetrically around the mean effect size in a funnel shape. Smaller studies with a relatively large variance scatter at the bottom and larger studies appear towards the top clustering around the mean effect size. Studies that fall outside the funnel shape have high risk of bias.[32]

RESULTS

Identification of studies

Figure 4.1 shows the flow diagram of the study selection. The initial search yielded 1687 articles (published between June 1976 and February 2017). Based on titles and abstracts 1597 papers were excluded. The remaining 90 articles were screened full text, leading to exclusion of 81 articles. An updated search in May 2017 identified one additional study.

Figure 4.2 shows the risk-of-bias profile for the ten included studies. The final judgment was low in six studies and unclear in four studies. The criterion of blinding of patients/personnel was disregarded for this total judgment, since this is not possible in combined intervention

studies. Risk of bias due to insufficient information regarding allocation concealment, random sequence generation and incomplete outcome data was our highest concern in the studies. Risk of bias data per study is provided in Supplementary Figure A and Table A.

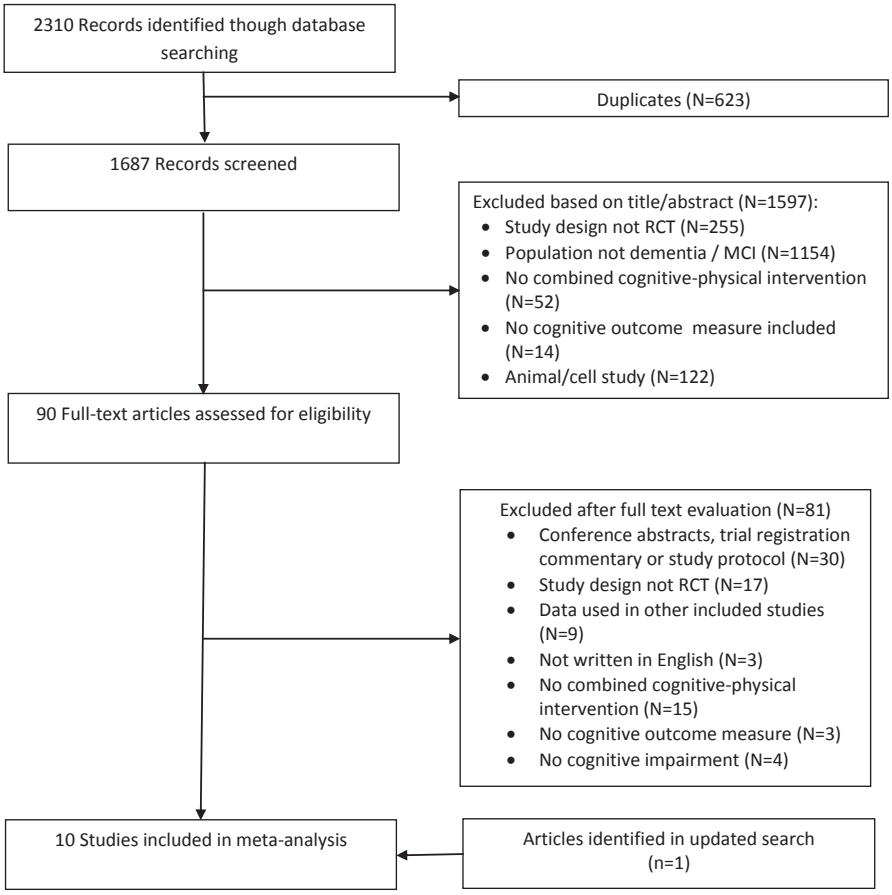

Figure. 4.1. Flowchart of study selection process

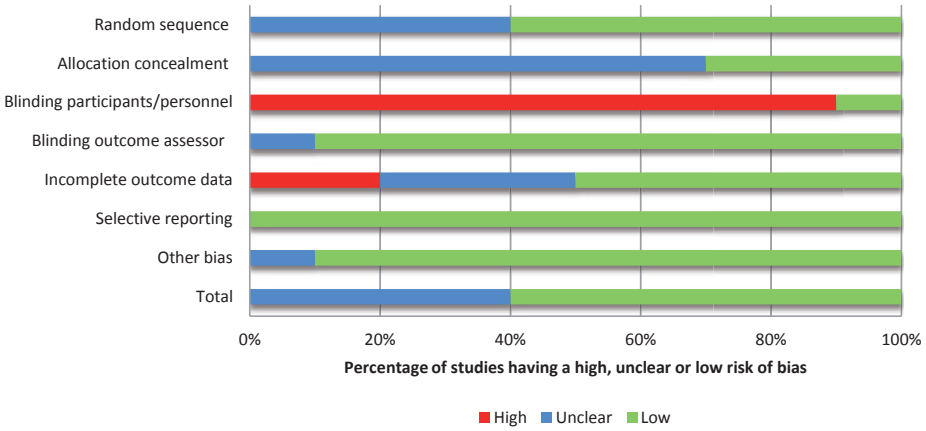

Figure 4.2. Risk of bias assessment per domain across studies, with domains of bias on the Y-axis and % of studies having a high, unclear or low risk of bias in each domain on the X-axis. The total score is the final author judgment of the total risk of bias.

Participant and study characteristics

Table 4.1 summarizes the characteristics of the included studies. Five RCTs included patients with dementia (N = 271),[34-38] three RCTs included patients with MCI (N = 267)[39-41] and two RCTs included both MCI and dementia patients (N = 204).[42,43] Global cognitive function data were available for 391 patients who participated in a combined cognitive-physical intervention and for 351 patients who participated as controls. The mean age of the total sample was 72.1 and 41% of the patients were men. All studies consisted of a combined cognitive-physical exercise intervention, with widely varying intervention components. In the majority of studies the mode of combination of the physical and cognitive intervention component was separate (7 studies). Intervention periods ranged between two to twelve months. The training frequency varied between two to six sessions per week and the duration per session varied between thirty to 120 minutes.

Table 4.2 gives an overview of the used outcome measures in the different studies. To measure global cognitive function four studies used the Mini-Mental State examination (MMSE,[44] three studies used the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog)[45] and three studies used both MMSE and ADAS-Cog. Measures of executive function and attention included Verbal Fluency (3 studies),[46,47] Symbol Digit Modalities Test (1 study),[47] WAIS-III Matrices and Similarities (1 study),[48,49] Digit Span Forward (1 study),[49] Corsi Span Forward (1 study),[50] Trail Making Test (1 study),[51] Raven Coloured Progressive Matrices (1 study),[50] Attentional matrices (1 study),[50] Copy of Rey-Osterrieth Complex Figure Test (1 study)[50] and

Table 4.1. Study characteristics

Study	Country	Sample					Combined Intervention Design								Control Group activity
		N (IG/CG)	Age (IG/CG)	% Male (IG/CG)	Diagnosis	Baseline MMSE (IG/CG)	Cognitive Intervention Component	Physical Exercise Component	Mode of Combination	Other Components	Setting	Frequency	Duration (weeks)	No. of sessions	
Burgener et al. (2008)	USA	43 (24/19)	77.9/76.0	54/53	Dementia	24.8/22.9	Cognitive exercises (focus on memory enhancement, verbal fluency, visual and spatial learning, verbal comprehension)	Taiji	Separate	Cognitive behavioural therapies, Support group	Mixed	CT: 90 min/ session, bi-weekly, PT: 60 min/ session, 3 x/wk	20	70	Attention-control educational programmes
Fiatarone Singh et al. (2014)	USA	54 (27/27)	-	-	MCI	27.0/27.0	Computer-based multimodal and multi-domain cognitive exercises	Progressive resistance training	Separate	No	Individual	100min/ session, 2-3 x/wk	26	65	Sham cognitive and sham exercise
Graessel et al. (2011)	Germany	96 (50/46)	84.5/85.7	12/22	Dementia	15.4/13.8	Cognitive tasks (not specified)	Motor exercises, e.g. bowling/ croquet	Separate	ADL, creative tasks, gardening	Group	120min/ session, 6 x/wk	52	312	Treatment as usual
Holthoff et al. (2015)	Germany	30 (15/15)	72.4/70.7	47/51	AD	22.1/22.0	Changes in direction (forward reverse) and type of training on movement trainer	Cycling on movement trainer	Dual-task	No	Individual	30min/ session, 3 x/wk	12	36	Care as usual
Ji Won Han et al. (2016)	Korea	120* (60/60)	75.6/76.8	31/44	MCI or dementia	22.6/23.0	Cognitive training, cognitive stimulation and reality orientation (not specified)	Physical Therapy	Separate	Music and reminiscence therapy	Group	180min/ session, 1 x/wk	8	8	Mock-therapy
Olazarán et al. (2004)	Spain	84 (44/40)	75.3/73.4	46/35	MCI or AD	17.3/17.4	Cognitive exercises (focus on memory, attention, executive functions, language, visuospatial abilities)	Psychomotor exercises	Separate	ADL training	Group	210min/ session, 2 x/wk	52	104	Psychosocial support

Train the Brain Consortium (2017)	Italy	113 (55/58)	74.0/74.9	47/55	MCI	25.4/25.9	Cognitive training programme (focus on attention, memory, orientation, lexical abilities)	Aerobic exercise	Separate	No	Group	CT: 120min/ session, 3x/wk. PT: 60min/ session, 3x/ wk	28	168	Care as usual
Santos et al. (2015)	Brazil	62 (46/16)	75.7/74.8	41/38	AD	23.0/23.3	Computer assisted cognitive training and cognitive stimulation (not specified)	Strength and balance training, walking	Separate	Occupational therapy, speech therapy, art therapy	Group	300min/ session, 2x/ wk	12	24	Care as usual
Suzuki et al. (2013)	Japan	100 (50/50)	74.8/75.8	50/52	MCI	26.8/26.3	Cognitive tasks during exercise (not specified)	Aerobic exercise, strength and balance training	Dual-task	No	Group	90min/ session, 2 x/wk	26	52	Education control group
Venturelli et al. (2016)	Italy	40 (20/20)	85.0/84.0	30/35	AD	-	Cognitive stimulation with reality orientation method	Walking at moderate intensity	Dual-task	No	Individual	60min/ session, 5 x/wk	12	60	Care as usual

Notes: IG=intervention group; CG=control-group; CT=cognitive training; PT=physical training; (-)=not data available; N=number of participants; AD=Alzheimer's disease; MCI=mild cognitive impairment; ADL=activities of daily living; *cross over design with 4 weeks wash-out period

Table 4.2. Outcome measures used in included studies

Article	Global cognitive function	Executive function & attention	Memory	ADL	Mood
Burgener et al. (2008)	MMSE	-	-	-	GDS
Fiatarone Singh et al. (2014)	ADAS-Cog	Verbal Fluency (COWAT and animal naming), Symbol Digit Modalities Test, WAIS-III Matrices and Similarities	WMS-III Auditory Logical Memory I and II, Benton Visual Retention Test-Revised 5th edition	Bayer ADL	-
Graessel et al. (2011)	ADAS-Cog	-	-	Erlangen ADL	-
Holthoff et al. (2015)	MMSE	Verbal Fluency, Reaction Time Ruler Test	-	ADCS ADL	-
Ji Won Han et al. (2016)	MMSE , ADAS-Cog	-	-	DAD-ADL	GDS
Train the Brain Consortium (2017)	ADAS-Cog	Digit Span Forward, Corsi Test Forward, Phonemic Verbal Fluency, Semantic Verbal Fluency, Trail Making Test, Attentional Matrices, Copy of Rey-Osterrieth Complex Figure Test, Raven Coloured Progressive Matrices	Rey Auditory Verbal Learning Task, Babcock Short Story, Rey-Osterrieth Complex Figure Test	-	-
Olazarán et al. (2004)	MMSE , ADAS-Cog	-	-	-	GDS
Santos et al. (2015)	MMSE	-	-	-	GDS
Suzuki et al. (2013)	MMSE, ADAS-Cog	-	WMS-III Logical Memory	-	-
Venturelli et al. (2016)	MMSE	-	-	-	-

Notes: (-)=no data available. MMSE=Mini-Mental State Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale; WAIS-III=Wechsler Adult Intelligence Scale; WMS-III=Wechsler Memory Scale Third Edition; COWAT=Controlled Oral Words Association Test; ADCS ADL=Alzheimer Disease Cooperative Study Activities of Daily Living; DAD-ADL=Disability Assessment for Dementia subscale Activities of Daily Living; DAD; E-ADL=Erlangen test of Activities of Daily Living; GDS=Geriatric Depression Scale

the Reaction Time Ruler Test (1 study).[52] Memory was assessed using the Logical Memory I and II subtests from the WMS-III (2 studies),[49] the Benton Visual Retention Test Fifth Edition (1 study),[53] Rey Auditory Verbal Learning Task (1 study),[50] Babcock Short Story test (1 study)[50] and Rey-Osterrieth Complex Figure Test (1 study.[50] Four studies included measures of ADL; The Bayer ADL,[54] Erlangen ADL,[55] Alzheimer Disease Cooperative Study (ADCS)[56] ADL and the Disability Assessment for dementia (DAD) ADL scale.[57] As a measure of mood the Geriatric Depression Scale (GDS)[58] was used in four studies.

Primary and secondary analyses

The primary analysis showed a positive small-to-medium effect of combined cognitive-physical exercise interventions on global cognitive function in older adults with MCI or dementia (SMD = 0.32 [0.17-0.47], p < 0.00, Fig. 4.3). There was no significant heterogeneity across the studies (Q=5.87, > 0.05, I^2 0%, Table 4.3). This effect remained for the subgroup analysis of dementia patients (SMD = 0.36 [0.12-0.60], p < 0.00, 5 studies) and MCI patients (SMD = 0.39 [0.15-0.63], p < 0.05, 3 studies), without significant heterogeneity. Visual inspection of the funnel plot did not reveal risk of publication bias (Fig. 4.4). Domain-specific analyses did not show any significant differences between the intervention and control groups for the domains executive function/attention (SMD = 0.38 [-0.21-0.97], p > 0.05, Table 4.3) and memory (SMD = 0.02 [–0.35-0.39], p > 0.05, Table 4.3). The domain executive function/attention showed significant heterogeneity across studies (Q = 7.15, p < 0.05, I^2 72%, Table 4.3).

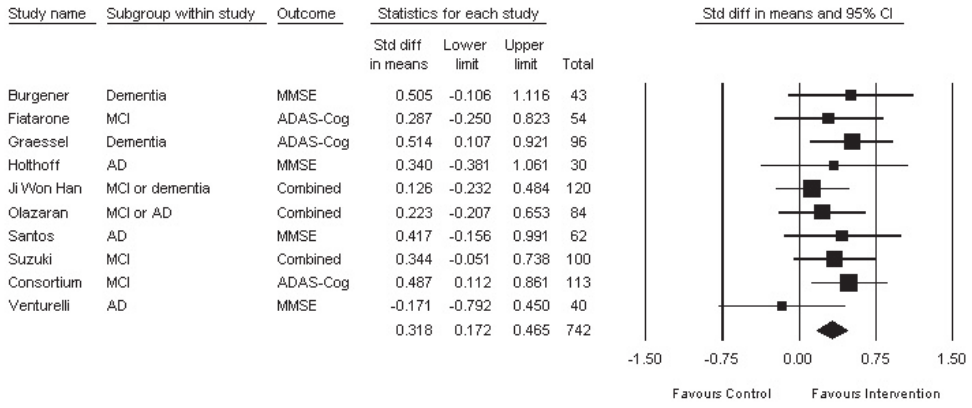

Figure 4.3. Forest plot for efficacy of combined cognitive-physical intervention compared to control group. A standardized difference in means > 0 favours intervention and < 0 favours the control arm. Box size represents study weighing. Diamond represents overall effect size and 95% confidence intervals. Notes: AD=Alzheimer's disease; MCI=mild cognitive impairment; MMSE=Mini-Mental State Examination; ADAS-Cog=Alzheimer's Disease Assessment Scale-Cognitive Subscale

Table 4.3. Mean weighted effect sizes, confidence interval and heterogeneity for primary and secondary outcome measures

		K	N	SMD	95% CI	Q	p (Q)	I^2	Fail-safe N
Cognitive domains	Global cognitive function	10	742	**0.32**	0.17-0.47	5.87	0.75	0.00	22
	Executive function/ attention	3	197	0.38	-0.21-0.97	7.15	0.03	72.04	-
	Memory	3	267	0.02	-0.35-0.39	4.56	0.10	56.18	-
Other outcome measures	ADL	4	302	**0.65**	0.09-1.21	15.28	0.00	80.37	15
	Mood	4	309	**0.27**	0.04-0.50	1.71	0.64	0.00	7

Notes: k=number of studies, N=number of patients, CI=confidence interval, Q=within domain heterogeneity, p(Q)= p-value for heterogeneity, I^2=percentage of heterogeneity due to true differences within studies, Fail-safe N=number of studies needed to nullify the effect, ADL=activities of daily living, $p<0.05$

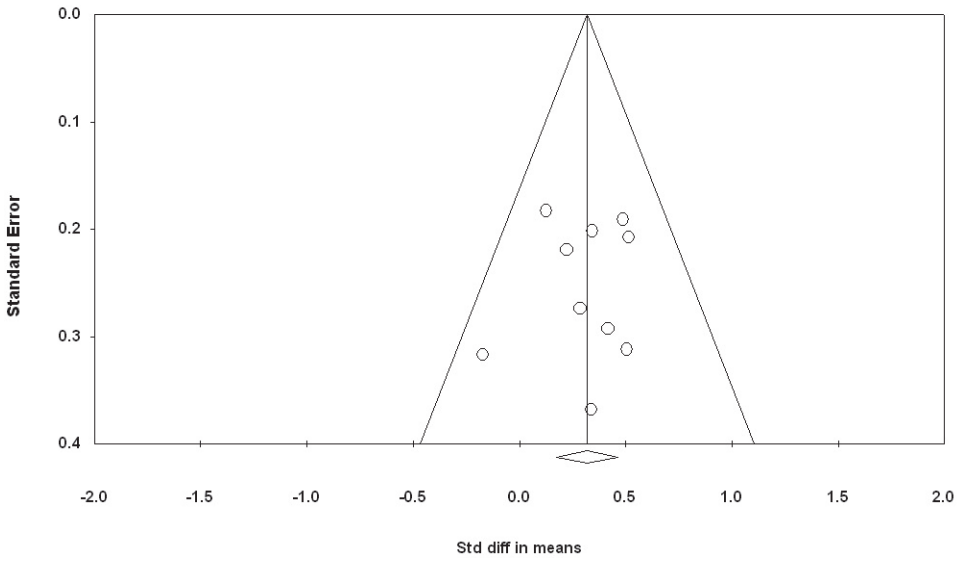

Figure 4.4. Funnel plot for global cognitive function showing the standardized difference in means (SMD) on the X-axis and the standard error on the Y-axis

Secondary analyses revealed a moderate-to-large positive effect of combined interventions on ADL (SMD = 0.65 [0.09-1.21], $p < 0.01$, 4 studies, Table 4.3) with significant heterogeneity across the studies (Q = 15.28, p = 0.00, I^2 = 80%, Table 4.3). Based on visual inspection of the funnel plot two studies were excluded for further analyses due to considerable risk of bias (Supplementary Figure B.1).[36,42] After removal of these studies, the effect size remained

moderate-to-large (SMD = 0.75 [0.42-1.08], p < 0.01) without heterogeneity (Q = 0.00, p = 0.97, I^2 = 0%). Furthermore, a small-to-medium overall effect of combined interventions on mood (SMD = 0.27 [0.04-0.50], p < 0.01,4 Table 4.3) was found, without significant heterogeneity (Q = 1.71, p = 0.64, I^2 0%, Table 4.3). The symmetrical funnel plot showed that there was no risk of publication bias (Supplementary Fig. B.2).

Orwin's fail-safe N was calculated only for the measures that showed significant differences between treatment and control. For global cognitive function, 22 studies would be required to reduce the observed effect to an effect size less than 0.1. For ADL and mood these were 15 and 7 studies respectively.

DISCUSSION

This meta-analysis examined the efficacy of combined cognitive and physical exercise interventions on global cognitive functioning in older adults with MCI or dementia. Secondary, the effects on memory, executive function/attention, ADL and mood were explored. Ten RCTs published between 2004 and 2017 were included in the meta-analysis.

The results of this meta-analysis emphasize the potential of combined cognitive and physical interventions to positively affect global cognitive function, ADL and mood in older adults with MCI or dementia. A positive small-to-medium effect of combined cognitive and physical exercise interventions on global cognitive function in older adults with MCI or dementia was found. In addition, the analysis showed a moderate-to-large effect of combined interventions on ADL and a small-to-medium effect on mood. These results may suggest a mediating effect of improved global cognitive function to improved function in ADL and mood, indicating the potential clinical relevance of combined interventions. Furthermore, the current results did not show a significant effect of combined interventions on the specific cognitive domains of executive function/attention and memory.

Interpretation of results and comparison with previous research

To the best of our knowledge, this is the first meta-analysis examining the effect of combined cognitive and physical exercise interventions on cognitive function in older adults with MCI or dementia. Law et al.[29] investigated the cognitive benefits of combined interventions in older adults with cognitive impairment in a systematic review. Five studies were included of which three studies showed significant improvements in global cognitive functions, memory, executive functions or attention. Importantly, only three out of five included studies were RCTs and two studies compared the results with an active control group.[29] This meta-analysis adds to the qualitative review of Law et al.[29] because only RCTs were included, and we were able to

quantify the magnitude of the overall effect, confirming the efficacy of combined interventions in MCI or dementia patients.

The current results are comparable with a recently published meta-analysis of Zhu et al.,[28] who reported a small-to-moderate positive effect on overall cognitive function after combined cognitive and physical interventions in healthy older adults (SMD = 0.29 [0.12-0.46]). In their study, domain specific analyses showed that combined interventions induced significant improvements with moderate effect sizes for global cognitive function and visuospatial ability, and small effects for memory, executive function and attention.[28] The domain specific effects are in contrast with our current data that did not show any significant effects in the domains executive function/attention and memory. However, our results should be interpreted with some caution, since the combined effect sizes were based on two studies only. Furthermore, the measures of cognition used varied across the studies that included cognitive tests, limiting its comparability. This stresses the need for further research on specific cognitive domains in order to draw definite conclusions.

A recent meta-analysis of Groot et al.[23] showed that physical exercise interventions – without a cognitive component – positively influence global cognitive function in patients with dementia. They found a small-to-medium positive overall effect of physical exercise interventions on global cognitive function (SMD = 0.42 [0.23-0.62]), which is comparable to the effect sizes observed in the current meta-analysis. Although no direct comparison can be made, these findings may question whether a combined intervention is indeed superior to a single physical intervention. In contrast, a meta-analysis of the Cochrane Library[21] reported that the effect of physical exercise on cognitive function in older adults with dementia could not be determined due to inconsistent results and low methodological quality of the studies. Moreover, Zhu et al.[28] found superiority of combined cognitive and physical exercise interventions compared with single physical exercise in healthy older adults, with a large effect size on global cognitive function (SMD = 0.87[0.31;1.44]). Assessing this possible additional benefit of combined interventions versus single physical exercise in older adults with dementia should be a focus of future research.

The moderate-to-large effect of combined interventions on ADL (SMD = 0.65 [0.09-1.21]) is in accordance with the efficacy of single physical exercise interventions on ADL found by Groot et al. [23] (SMD = 1.18 [0.57-1.79]) and the Cochrane Library (SMD = 0.68 [0.08-1.27]).[21] These changes in ADL may be mediated by improvement in motor and cognitive function.[59] ADL disability leads to increased dependency in daily life, which may result in a lower quality of life[60] and larger long-term care costs.[1] Interventions that slow decline in ADL function are therefore of high clinical relevance. In addition, three out of four studies only used proxy-reported ADL measures, which are, compared to performance-based ADL tests, less valid (e.g.

prone to social desirability bias) and less sensitive to detect change.[61,62] Future studies should therefore include both proxy- and performance-based ADL measures to study the effect of intervention on ADL. The current meta-analysis also showed a small-to-moderate positive effect of combined interventions on mood (SMD = 0.27[0.04;0.50]), suggesting that combined cognitive-physical interventions may be helpful in preventing or treating depressive symptoms. Depressive symptoms are key determinants for increased distress and therewith an important target for interventions.[63]

Strengths and limitations

A strength of this meta-analysis is that only studies with an RCT design were included for review analyses. Furthermore, we were able to obtain cognitive data from all eligible studies that were not reported in the primary paper by contacting the authors. Therefore, no RCTs were excluded due to missing data. There are also some limitations that need to be addressed when interpreting the current results. First, there is considerable heterogeneity in the included studies regarding the intervention characteristics (e.g. type of training, separate or dual-task, intervention period, frequency, duration). Therefore, the optimal intervention design for eliciting beneficial effects remains unclear. Second, due to the limited number of included studies (N = 10) it was statistically inappropriate to analyze the impact of different intervention components or to calculate the efficacy for different causes of neurodegeneration or disease severity using a moderator analysis.[64] However, moderation analyses are very useful in developing preventive strategies and designing appropriate interventions. Third, the majority of studies (N = 7) used the MMSE as a measure of global cognitive function. The MMSE was originally developed as a screening method for cognitive impairment and not as an outcome measure, since sensitivity to change over time is low.[65,66] This makes the MMSE an inappropriate outcome measure to assess the effect of interventions. Thus, another, more sensitive, method for measuring global cognition in MCI and dementia patients is needed. Fourth, in all included studies the adherence to the intervention and intensity of the physical exercise programme was not reported in detail, which could have influenced the study results. Also, data about adherence and intensity of intervention programmes are essential to gain insight in doses-response ratios. Finally, only studies reported in English were included in the current meta-analyses. This could have introduced language-bias, since this may not cover all potential eligible studies.

Implications for future research

To investigate the different intervention combinations, future research is warranted. We suggest using a multi-arm design, including a combined cognitive and physical training, single physical training, single cognitive training and a control group to distinguish the contribution of different components of the intervention. Also, additional studies are needed to explore the most effective training characteristics in combined interventions specifically aiming at duration,

frequency, intervention type and mode of combination. Furthermore, future research should focus on investigating physiological mechanisms that underlie the positive effect by including neuro-imaging measures and molecular markers as an outcome. Moreover, long-term effects of combined interventions should be studied to gain insight into possible maintenance effects. Zhu et al.[28] found that combined interventions had advantages over single training for long term maintenance in healthy older adults. It would be important to investigate whether this is also the case in older adults with MCI or dementia. Finally, the identification of individual predictors for a beneficial outcome is also important in order to personalise multi-modal interventions. To conclude, selecting appropriate outcome measurements is essential in future research. The use of a more comprehensive neuropsychological assessment is needed to assess which domains of cognitive function benefit most from a combined intervention.

CONCLUSION

Results of the present meta-analysis showed that combined cognitive and physical exercise interventions improve global cognitive function, ADL and mood in older adults with MCI or dementia. Studies show a large methodologically heterogeneity in intervention characteristics and the included study samples and thus, the current results should be interpreted with caution. Despite these methodological limitations the current meta-analysis illustrates the importance of combined interventions to help delay the progression of MCI or dementia. There is a need for future well-designed RCT's with a multi-arm design and long-term follow-up assessment to investigate the potential superiority of combined interventions over single interventions in older adults with MCI or dementia, including extensive neuropsychological assessments to gain more insight in the beneficial effects for the different domains.

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SUPPLEMENTARY MATERIAL

Supplementary A. Full search terms

Patient search terms

P: Cognitive function Disorders OR Mild Cognitive Impairment OR Dementia OR Cognitive impairment* OR Dementia* OR Alzheimer*

Intervention search terms

I1: search terms combined training

Combined Modality Therapy OR Multimodal OR Multi-modal OR Dual-task OR Dualtask OR Combine* OR Combination* OR Multicomponent OR Multi component

I2: search terms physical training

Exercise Therapy OR Exercise OR Exercise Movement Techniques OR Motor Activity OR Exercise OR Exercises OR Aerobic training OR Aerobe training OR Exercise training OR Physical training OR Endurance training OR Resistance training OR Aerobic intervention* OR Physical intervention* OR Endurance intervention* OR Resistance intervention* OR Aerobic therap* OR Physical therap*OR Endurance therap* OR Resistance therap* OR Physical activit* OR Motor activit*

I3: search terms cognitive training

Cognitive Therapy OR Cognitive therapy OR Cognitive therapies OR Cognitive function therapy OR Cognitive function therapies OR Cognitive intervention OR Cognitive interventions OR Cognitive function intervention OR Cognitive function interventions OR Memory training OR Cognitive stimulation* OR Cognitive training OR Cognitive function training OR Cognitive function task* OR Cognitive task* OR Mental training

I4: Umbrella terms

Exergame* OR Cognitive-motor OR Motor-cognitive Final Search: P AND ((I1 AND I2 AND I3) OR I4)

Supplementary Table A. Justification for risk of bias scores

Study	Cochrane risk of bias assessment checklist domain	Risk of bias assessment	Justification of assessment
Burgener et al. 2008	Random sequence generation	**Unclear**	Not reported
	Allocation concealment	**Unclear**	Not reported
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Unclear**	Not reported
	Incomplete outcome data	**Unclear**	Insufficient reporting of attrition/exclusions to permit judgment.
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Unclear**	Concerns about random sequence generation, allocation concealment, blinding of outcome assessors and incomplete outcome data
Fiatarone et al. 2014	Random sequence generation	**Low**	Computer-generated sequence used
	Allocation concealment	**Low**	Sealed envelopes used for allocation
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Low**	Low drop-out rates, no differences between groups
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Low**	No risk of bias observed
Graessel et al. 2011	Random sequence generation	**Low**	Computer generated randomization list used
	Allocation concealment	**Unclear**	Not reported
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Low**	Imputation of missing outcome data, intention to treat analysis. No differences in baseline characteristics between drop-outs and participants who completed the intervention
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Low**	Low on most domains, minor concerns regarding allocation concealment

Holthoff et al. 2015	Random sequence generation	**Unclear**	Insufficient information
	Allocation concealment	**Unclear**	Insufficient information
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Low**	All participants in intervention and control group completed post-intervention measurement, no missing data
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Low**	Minor concerns about random sequence generation and allocation concealment, low risk of bias in other domains
Ji Won Han et al. 2016	Random sequence generation	**Low**	Random code table used
	Allocation concealment	**Low**	Allocation sequence was produced independently and concealed
	Blinding of participants/personnel	**Low**	Patients and caregivers were blinded to intervention type
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Low**	Attrition rates reported per group, low drop out, intention to treat analysis
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Unclear**	Unclear whether a 4-week wash out period is enough
	Final author judgment	**Low**	There is a low risk of bias in most domains
Train the Brain Consortium et al. 2017	Random sequence generation	**Low**	Computer generated randomization sequence used
	Allocation concealment	**Unclear**	Insufficient information
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**High**	Imbalance in drop-out rates and therewith numbers for missing data across intervention groups
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Unclear**	Low on most domains, concerns regarding incomplete outcome data and allocation concealment
Olazarán et al. 2004	Random sequence generation	**Low**	Random number table used
	Allocation concealment	**Unclear**	Not reported
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Low**	Attrition rates and drop out reported, last observation carried forward for missing data
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Low**	There is a low risk of bias in most domains

Santos et al. 2015	Random sequence generation	**Unclear**	Not reported
	Allocation concealment	**Unclear**	Insufficient information
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**High**	Total drop-out reported but not per group (only for the intervention group), attrition rates unknown
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Unclear**	Concerns about random sequence generation, allocation concealment and incomplete outcome data.
Suzuki et al. 2013	Random sequence generation	**Low**	Random sampling in SPSS used
	Allocation concealment	**Low**	Researcher unrelated to the study performed randomization
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Unclear**	Missing outcome data not balanced in numbers across intervention groups, the effect and handling of missing data unknown
	Selective reporting	**Low**	All outcomes reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Low**	There is a low risk of bias in most domains
Venturelli et al. 2016	Random sequence generation	**Unclear**	Not reported
	Allocation concealment	**Unclear**	Not reported
	Blinding of participants/personnel	**High**	No blinding for group allocation
	Blinding of outcome assessment	**Low**	Outcome assessors blinded for group allocation
	Incomplete outcome data	**Unclear**	Insufficient reporting of attrition/exclusions to permit judgment.
	Selective reporting	**Low**	All outcomes are reported
	Other bias	**Low**	No other sources of potential bias observed
	Final author judgment	**Unclear**	Concerns about random sequence generation, allocation concealment and outcome data.

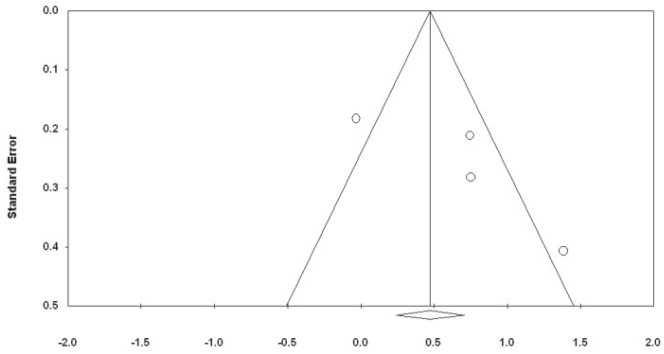
Supplementary Figure A. Risk of bias assessment per domain for each study

Study	Random sequence	Allocation concealment	Blinding participants/ personnel	Blinding outcome assessor	Incomplete outcome data	Selective reporting	Other bias	Total
Burgener et al. 2008	?	?	+	?	?	-	-	?
Fiatarone Singh et al. 2014	-	-	+	-	-	-	-	-
Graessel et al. 2011	-	?	+	-	-	-	-	-
Han et al. 2016	-	-	-	-	-	-	?	-
Holthoff et al.2015	?	?	+	-	-	-	-	-
Olazaran et al. 2004	-	?	+	-	-	-	-	-
Santos et al. 2015	?	?	+	-	+	-	-	?
Suzuki et al. 2013	-	-	+	-	?	-	-	-
Train the Brain Consortium et al. 2017	-	?	+	-	+	-	-	?
Venturelli et al. 2016	?	?	+	-	?	-	-	?

(-) = low risk of bias, (?)=unclear risk of bias, (+)=high risk of bias

Supplementary Figure B. Funnel plots of meta-analysis

1. Combined interventions on ADL



2. Combined interventions on mood

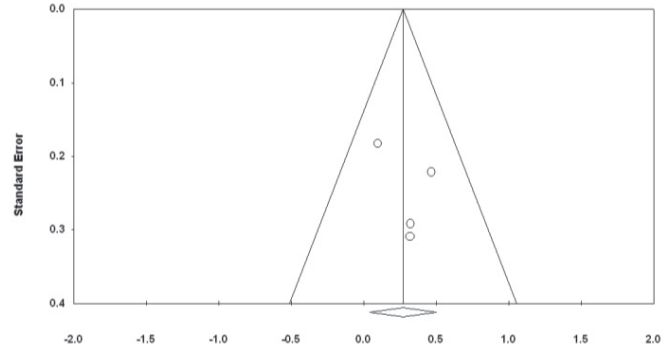


Figure. B. Funnel plots showing the standardized difference in means (SMD) on the X-axis and the standard error on the Y-axis

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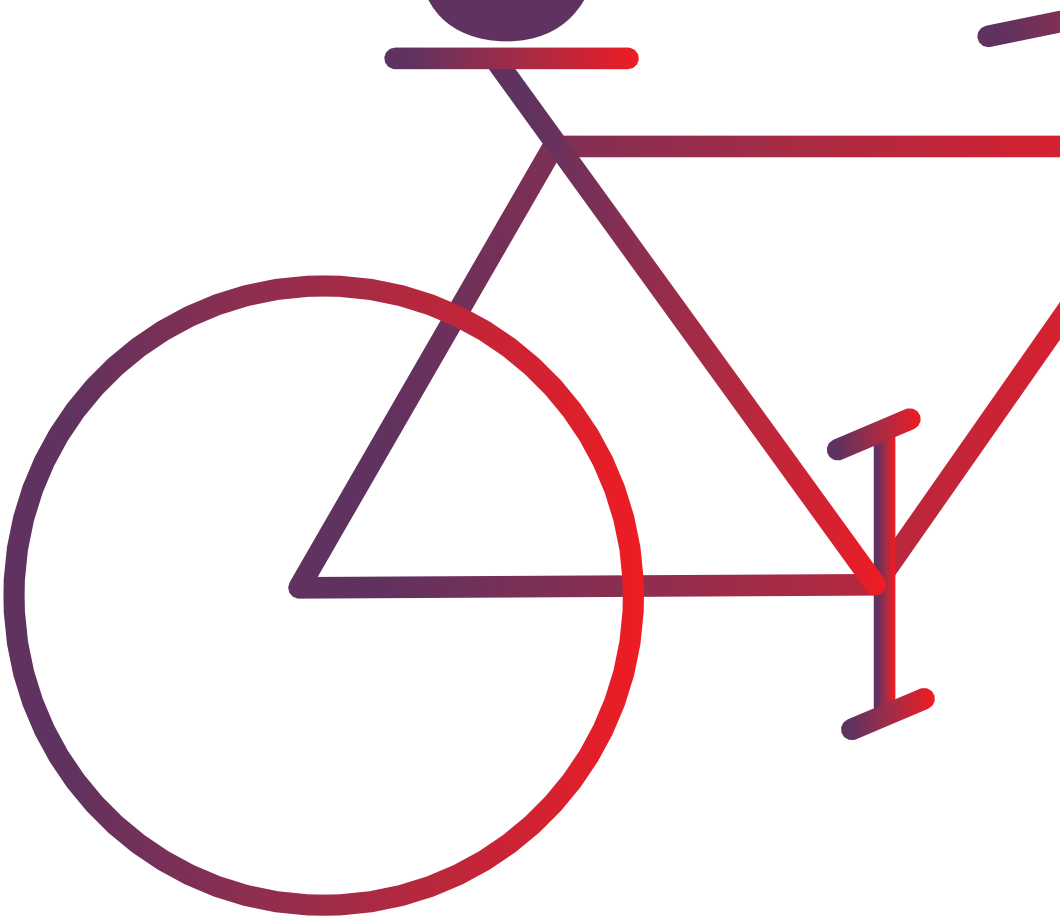

The effect of an interactive cycling training on cognitive functioning in older adults with mild dementia: study protocol for a randomised controlled trial

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ABSTRACT

Background

To date there is no cure or an effective disease-modifying drug to treat dementia. Available acetylcholine-esterase inhibiting drugs or memantine only produce small benefits on cognitive and behavioural functioning and their clinical relevance remains controversial. Combined cognitive-aerobic interventions are an appealing alternative or add-on to current pharmacological treatments. The primary aim of this study is to investigate the efficacy of a combined cognitive-aerobic training and a single aerobic training compared to an active control group in older adults with mild dementia. We expect to find a beneficial effect on executive functioning in both training regimes, compared to the control intervention, with the largest effect in the combined cognitive-aerobic group. Secondary, intervention effects on cognitive functioning in other domains, physical functioning, physical activity levels, activities of daily living, frailty and quality of life are studied.

Methods

The design is a single-blind, randomized controlled trial (RCT) with three groups: a combined cognitive-aerobic bicycle training (interactive cycling), a single aerobic bicycle training and a control intervention, which consists of stretching and toning exercises. Older adults with mild dementia follow a 12-week training programme consisting of three training sessions of 30–40 min per week. The primary study outcome is objective executive functioning measured with a neuropsychological assessment. Secondary measures are objective cognitive functioning in other domains, physical functioning, physical activity levels, activities of daily living, frailty, mood and quality of life. The three groups are compared at baseline, after 6 and 12 weeks of training, and at 24-week follow-up.

Discussion

This study will provide novel information on the effects of an interactive cycling training on executive function in older adults with mild dementia. Furthermore, since this study has both a combined cognitive-aerobic training and a single aerobic training group the effectiveness of the different components of the intervention can be identified. The results of this study may be used for physical and mental activity recommendations in older adults with dementia.

BACKGROUND

Dementia is a syndrome characterized by progressive cognitive decline, motor deficits and/or behavioural problems, which increasingly affect the ability to perform activities of daily living.[1] Alzheimer's disease (AD) is the most common cause of dementia accounting for approximately 60-80% of the dementia cases, followed by vascular dementia.[1] Older age is the strongest risk factor for dementia and due to the aging population the prevalence of dementia is increasing.[2] There are over 9.9 million new cases of dementia each year and the number of persons with dementia is expected to reach 131.50 million in 2050.[3] Currently, there is no cure or an effective disease-modifying drug to treat dementia.[4] Pharmacological treatment for AD and vascular dementia with acetylcholinesterase inhibitors (rivastigmine, galantamine, donepezil) or memantine produce small benefits on cognitive and behavioural functioning.[5,6] However, the clinical relevance of these pharmacological treatments is controversial and these drugs can cause adverse events (e.g. anorexia, gastrointestinal problems, insomnia) in this vulnerable patient group.[6] Therefore, we should focus on the development and implementation of non-pharmacological interventions as an alternative or add-on therapy. Physical activity seems to be an appealing option,[7,8] as increased lifetime engagement in physical activity reduces the risk of dementia[9] and recent research shows that older adults with dementia spend approximately two-third of the day being sedentary.[10]

Recent meta-analyses show positive effects of aerobic exercise interventions on cognitive function in cognitively healthy older adults, with the largest gains in executive-control processes.[11-14] Executive function refers to higher-order cognitive processes that controls basic, underlying cognitive functions for non-routine, purposeful, goal-directed behaviour and is linked to prefrontal-parietal network activity.[15] Several mechanisms have been identified that may explain this beneficial effect of aerobic exercise on cognitive function: (1) aerobic exercise in aging individuals may increase brain volume, in both grey and white matter, primarily located in the prefrontal and temporal cortices. These brain regions are important for executive control processes and episodic memory, respectively;[16,17] (2) aerobic exercise may increase the size of the anterior hippocampus, which may lead to improved memory performance;[18] (3) aerobic exercise may enhance neurogenesis in the dentate gyrus of the hippocampus;[19] (4) aerobic exercise may promote extensive cardiovascular changes in the peripheral and cerebral vasculature, such as enhanced angiogenesis[20] and (5) aerobic exercise promotes cardiovascular fitness and therefore reduces peripheral vascular risk factors.[21] Hence, aerobic exercise may have a positive effect on enhancing brain vitality and engagement in physical activity can reduce the risk of dementia-onset in healthy elderly.[9]

Several studies have investigated whether physical activity can slow the rate of cognitive decline in older adults with dementia. The results of these studies are mixed. A recently updated meta-

analysis of the Cochrane library[22] did not find evidence that physical activity slows cognitive decline in older adults with dementia. In contrast, a meta-analysis of Groot et al.[23] found a beneficial effect of physical activity on cognitive function. This positive effect was independent of the frequency of the intervention and driven by interventions that included aerobic exercise.[23] The opposing outcomes may be explained by the difference in the included studies. Groot et al. incorporated sixteen trials published up to 2015 in the analysis, while the Cochrane library incorporated nine trials and did not include studies after 2013.[22,23] Specifically, the most recent studies reviewed by Groot et al.[23] showed a beneficial effect of physical activity on cognition.[24-26] Moreover, both meta-analyses discuss the large variability in study population, exercise protocols and outcome measures that can complicate interpretation of the results.[22,23]

Studies suggest that the neural and cognitive benefits, elicited by physical activity, can be further enhanced if exposure occurs in the context of a cognitively challenging environment.[27-29] Experimental animal studies have shown that physical activity and environmental enrichment (a combination of complex inanimate and social stimulation)[30] differently affect hippocampal neurogenesis, with physical activity influencing the proliferation of neural precursor cells and enriched environment exerting a survival promoting effect on newborn neurons.[27,29] The findings of previous studies on cognitive effects of single physical training versus combined cognitive-physical training in healthy older adults are in favour of a combined intervention.[31,32] These combined interventions also seem to positively influence cognition in persons with dementia, with significant effects found on executive function, attention and processing speed.[33] These potential benefits of a combined cognitive-physical training need further investigation since the limited number and heterogeneity of the conducted studies.[33] Moreover, there is a lack of comparison with single physical training interventions to identify the effectiveness of the different components of the intervention. Thus, methodologically high-quality combined cognitive-physical training compared with single physical training studies are needed.

Earlier studies indicate that the gene Apolipoprotein E (APOE) may be involved as a moderator in the effects of physical activity on cognition.[34,35] APOE is a cholesterol carrier that supports lipid transport and is involved in brain injury repair.[36] The APOE gene is polymorphic with three major isoforms: ε2, ε3 and ε4.[37] Carrying the ε4 allele of APOE is the strongest genetic risk factor for developing AD and carrying the ε2 allele is protective.[2,38] Approximately 14% of the western population carries the ε4 allele and the estimated prevalence of APOE ε4 genotype amongst patients diagnosed with AD is 50%.[36,39] The risk of developing vascular dementia is also elevated in APOE ε4 carriers, although to a lesser extent.[40] The moderating role of APOE ε4 in the effect of physical activity on cognition is still unknown. Some epidemiological data suggest that physical activity is more protective in APOE ε4 carriers compared to non-carriers with respect to incidence of dementia;[21] cerebral amyloid deposition;[34] cognitive function;[35,41]cognitive decline[42] and memory-related brain activation.[35] Other studies, however,

suggest that physical activity is related to a lower incidence of dementia and higher level of cognitive functioning in APOE ε4 non-carriers.[43,44] In light of the 'exercise-is-medicine' paradigm, insight in APOE ε4 moderation may be relevant for the identification of people who will benefit most from physical activity and cognitive stimulation.

The proposed study will expand the scarce research on the cognitive effects of combined cognitive-aerobic training and single aerobic training in older adults with dementia. Furthermore, explorative data will be collected and analysed to study the moderating effect of APOE status on cognitive and physical function effects.

Objectives and hypothesis

The primary objective is to study the effect of a 12-week combined cognitive-aerobic bicycle training on executive functioning, compared to a single aerobic bicycle training and an active control group (i.e. stretching and toning), in community-dwelling older adults with mild dementia. We hypothesize that both training regimes will have a positive effect on executive function, compared to the control intervention, with the largest effect in the combined cognitive-aerobic group. Secondary objectives include investigating i) the effect of training on the cognitive domains of episodic memory, working memory and psychomotor speed, ii) the effect of the training regimes on physical functioning; iii) the effect of training on activities of daily living, mood, quality of life and frailty, and iv) whether the cognitive effects of training are modified by APOE ε4 carrier state.

METHODS

Design

This study is a single-blind, 12-week randomized controlled trial (RCT) with two experimental intervention groups and one active control group. The study design is illustrated in Fig. 5.1. Participants will be randomly allocated to one of the intervention groups or the active control group. Primary and secondary outcome measures are assessed at baseline and are repeated after the 12-week intervention period and at 24-weeks in a follow-up assessment. After 6 weeks there is an intermediate measurement consisting of the primary outcome measures. The study protocol has been approved by the Medical Ethical Committee of Radboud university medical center (Ref No: NL52581.091.15/2015-1857) and is registered at the Dutch trial register (http://www.trialregister.nl) with identification number NTR5581. The study is conducted in compliance with Declaration of Helsinki ethical standards.

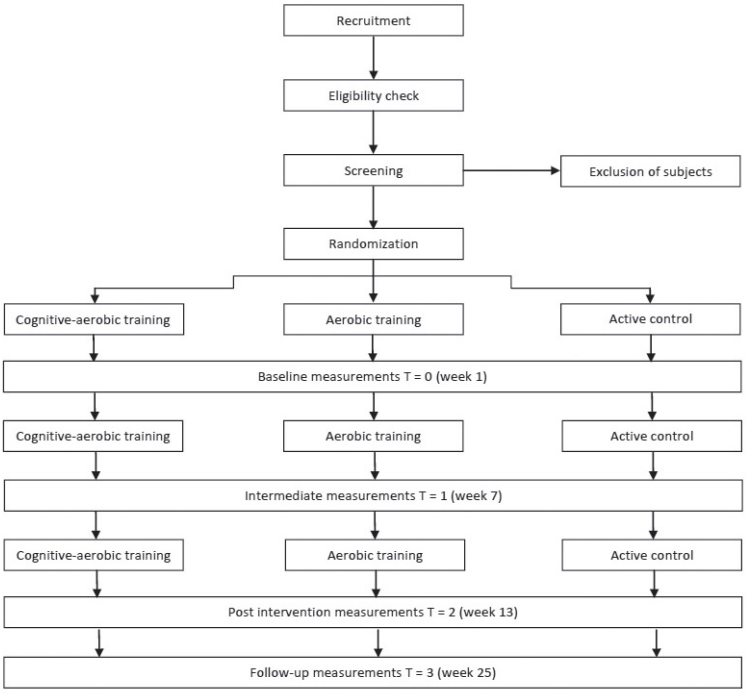

Figure 5.1. Flowchart of the study design

Patient sample and procedures

This study is conducted in community centres in the area of Nijmegen, the Netherlands. The study includes persons with a dementia diagnosis (vascular or Alzheimer or mixed type) aged 60 years and older. Exclusion criteria are: moderate or severe dementia defined by a Mini-Mental Status Examination (MMSE) score of < 17,[22] incapable to give written consent, comorbidities that limit physical activity (e.g. severe cardiovascular conditions, serious neurological or musculoskeletal problems), diagnosis of a major depression or other psychiatric disorder, drug or alcohol dependency, wheelchair bound and severe hearing or visual problems that cannot be corrected with the use of hearing aids/glasses. Furthermore, participants are excluded if they exercise more than five times per week, at least 30 min at a moderate intensity.[45]

Participants are recruited through the memory clinic of the Radboudumc Alzheimer Center. Potential eligible participants are notified by their physician about the study. Additionally, participants are recruited through day care centres for elderly with cognitive disorders, advertisement in the local newspapers, and word of mouth. All participants who are interested receive detailed information about the nature, purpose and duration of the study, as well as

possible objections, risks of participation and the possibility of withdrawal. The researcher contacts the participant to provide further information (if needed) and to invite them to participate. Subsequently, a screening visit is planned. Prior to the screening visit, written informed consent is obtained from the participants. During the screening visit, inclusion and exclusion criteria are assessed. If necessary, permission is asked by the researcher to access hospital files to further evaluate the in- and exclusion criteria. The inclusion period started in February 2016.

Interventions and control condition

The study includes two intervention groups, which are a combined cognitive-aerobic bicycle training (interactive cycling) and a single aerobic bicycle training group, and an active control condition (stretching and toning). All training groups receive 30–40 min of training, three times per week for 12 weeks. The training sessions are individually guided by well-trained research assistants. The trainer records the intensity and duration for each training session. In case of missed training sessions, the reason of absence is recorded. The training sessions are carried out at the participating community centres or day care centres in Nijmegen and the surrounding area.

Aerobic training

Aerobic training is performed on a stationary bike (Tunturi Go 50). Table 5.1 presents the progressions in intensity and duration during the training period, adapted from the American College of Sports Medicine (ACSM) Guidelines for Exercise Testing and Prescription.[46] Exercise intensity is prescribed using percentage of hearth rate reserve (HRR). Participants on medication that attenuates heart rate (e.g. beta-blockers) are prescribed exercise intensity using the Borg Rating of Perceived Exertion (RPE).[47] The RPE asks participants to rate their subjective feelings of exertion.[47] Heart rate is monitored with the Polar® A300 heart rate monitor. The possibility to increase exercise intensity and duration depends on the individual's physical ability. Duration, intensity and training load are monitored by a trained research assistant.

Table 5.1. Duration and intensity progression of aerobic training

Week	Duration (min)	Intensity (%HRR)	Intensity (RPE)
1&2	20	50-60	12-15
3&4	25	50-60	12-15
5&6	30	60-70	12-15
7-9	35	60-70	12-15
10-12	40	65-75	12-15

Interactive cycling training

The interactive cycling training is a combined cognitive-aerobic bicycle training developed by Fietslabyrint (www.fietslabyrint.nl). Additional file 1 shows the training set-up, in which the home-trainer is connected to a video screen. The aerobic training is identical to the training described above. Additionally, the participants are asked to follow a route through a digital environment presented on the video screen and simultaneously perform cognitive tasks that rely on executive functioning. There are different cognitive training levels and the difficulty of the cognitive tasks increases per level, to ensure that the training remains cognitively challenging. Additional file 2 describes the training tasks in further detail. At the end of each training session participants are provided with feedback on their scores on each task and the scores are registered in a diary. When the participants have a response time of less than 5 seconds and an error rate of less than 5%, they can proceed to the next level.

Stretching and toning active control group

Stretching and toning consists of relaxation and flexibility exercises with the same duration and frequency as the other training regimes. The exercises require minimal muscle strength and aerobic capacity and are easy to perform. The level of social engagement is similar to the intervention groups. In persons with dementia, social engagement may have a positive effect on cognitive function.[48] The stretching and toning group thus controls for this social effect. The flexibility exercises consist of upper and lower body exercises, including head rotation, shoulder rotation, shoulders up-down, arm rotation, arm and shoulder muscle strengthening, wrist rotations, flexion/extension fingers, rotation hip, stretching hip flexors and extensors, stretching knee flexors and extensors.

Outcome measures

Primary outcomes

The primary outcome measure of this study is objective executive function. Executive function is measured by four neuropsychological tasks, i.e. the short form of the Trail Making Test part B (numbers 1 to 7 and letters A to G);[49] the abbreviated 5-line Stroop Color Word Test;[50,51] Letter Fluency[52,53] and Rule Shift Cards Test[54] [see Additional file 3]. The tests are administered by trained research assistants before and after the training phase (T0 and T2) and at follow up (T3). Parallel versions are used for letter fluency to minimize learning effects at the second and third time point. All the tests, except for letter fluency, are also administered after 6 weeks (T1). The obtained scores are converted into z-scores based on the standard deviation and mean of the total sample at baseline. Subsequently an executive composite z-score is calculated by averaging the z-scores.

Secondary outcomes

Cognitive measurements

Episodic memory, working memory and psychomotor speed are assessed by neuropsychological assessment. Episodic memory is measured with the Location Learning Test – Revised,[55] working memory with the Digit Span subtest (forward and backward condition) from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III),[56] and the Spatial Span from the Wechsler Memory Scale – Third Edition (WMS-III),[57] and psychomotor speed is assessed using the Trail Making Test part A[49] and the reading and color-naming cards from the abbreviated Stroop Color-Word Test.[50] Additional file 3 describes the cognitive measurements and the scoring methods in more detail. The tests are administered at the same time points as executive function (T0, T2 and T3). A parallel version is used at T2 for the Location Learning Test to minimize learning effects. The obtained scores are converted into z-scores and a composite z-score is calculated for each domain.

Physical functioning

Physical functioning is measured with performance-based tests suitable for older people. Physical fitness is assessed with the Åstrand Bike Test,[58] mobility with the Timed Up & Go Test[59] and the 10-m Walk Test,[60] strength with the 5-times Chair Stand[61] and Handgrip Strength,[62] and balance is measured with the Frailty and Injuries Cooperative Studies of Intervention Techniques Subtest 4.[63] Additional file 4 describes the physical measurements in detail. The different motor domains, strength, physical fitness, balance and mobility, are assessed before and after the training phase (T0 and T2) and at follow-up (T3). At intermediate measurement (T1), only physical fitness and mobility are assessed.

Other secondary outcome measures

Level of physical activity is assessed objectively using an actigraphy device (Philips Actiwatch 2®) that participants wear for seven consecutive days and subjectively with the Physical Activity Scale for the Elderly.[64] The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS)[65] is administered to assess activities of daily living and mood. Quality of life is measured with the Dementia Quality of Life Instrument[66] and frailty by using the Evaluative Frailty Index for Physical Activity.[67] These outcome measures are assessed at pre-test (T0) and post-test (T2). Additional file 4 describes the measures in detail.

Moderator

After inclusion, saliva samples are taken with buccal swabs for APOE genotyping. Buccal samples are stored in –20 °C and analysed using real-time Polymerase Chain Reaction (PCR).[37] This results in different APOE gene phenotypes: three homozygous (ε2/ε2, ε3/ε3, ε4/ε4) and three heterozygous (ε2/ε3, ε2/ε4, ε3/ε4).[37]

Sample size

Sample size is determined using software package G*power.[68] The effect size (ES) is estimated based on a previous study on the cognitive effects of combined cognitive-aerobic training and single aerobic training using a similar intervention.[69] In this study a medium effect size ($d = 0.50$) was found for executive functioning after 3 months of training.[69] Therefore, assuming a power of 0.80, an alpha of 0.05 and an expected drop out of 15%, a medium effect size is detected with a total sample size of 171 participants.

Randomization, blinding, and treatment allocation

Participants are randomized after baseline assessments. The minimization technique[70] is used to minimize imbalance between the different groups for gender, severity of cognitive impairment, level of education, use of medication for AD and training location. Minimization is conducted by an independent statistician. Assessors of cognitive outcome measures are blinded to treatment allocation.

Statistical analysis

Socio-demographic and clinical characteristics at baseline are presented using descriptive statistics. If group differences are observed at baseline, those variables are included as covariates in further analyses. Alpha is set at 0.05 for all analyses. To assess the effect on the primary and secondary outcome measures, analysis of covariance (ANCOVA) is used with cognitive domain scores on the post-tests/intermediate tests as dependent variables, pre-test scores as covariates and group (interactive cycling, aerobic bicycle training, control) as between subject factor. In an explorative analysis the moderating effect of APOE ε4 is evaluated. All analyses are performed as intention-to-treat analysis, including all participants (irrespective of adherence to intervention). Additionally, analyses are rerun as per-protocol analysis. Missing data are substituted using multiple imputation method. Characteristic variables of the sample and cognitive and physical test scores at the different time points will be included in the imputation model. Each imputed dataset will be analysed, pooled and then reported.

DISCUSSION

Dementia is highly prevalent among older adults. To date no effective disease modifying treatment exists.[4] Combined cognitive-aerobic training seems to be a promising intervention to slow the rate of dementia related cognitive decline. However, up to now, there is insufficient evidence to support its effectiveness. To the best of our knowledge, our study is the first to evaluate the effect of a combined cognitive-aerobic bicycle training and a single aerobic bicycle training on executive functioning in older adults with mild dementia.

One of the major strengths of this study is the design with three groups. Most previous training studies compared a combined cognitive-aerobic training or a single aerobic training with a control group. This study includes both a combined cognitive-aerobic training and a single aerobic training. This gives us the opportunity to assess the differential effects between both training conditions and therewith identify the effectiveness of the different components of the intervention. Another strength is that the difficulty level of the cognitive component in the combined cognitive-aerobic training is adapted to the performance level of the participant. This insures that the training remains cognitively challenging.

A limitation of this study is the relatively short duration of the trial. Previous randomized controlled trials showing cognitive benefits of physical activity or combined cognitive-physical training in older adults with dementia, had intervention periods of 12 weeks or more.[7,33] We chose an intervention period of 12 weeks to increase the feasibility and adherence rate and minimize drop-out. Another limitation of this study is that the research population is very heterogeneous as older adults with different types of dementia (Alzheimer, vascular or mixed type) are included. This may affect the internal validity of the study. However, the heterogeneous population will increase the external validity of the results of this study to the community dwelling dementia population.

CONCLUSIONS

The results of this study will provide an important contribution to the existing body of knowledge on combined cognitive-aerobic interventions and single aerobic interventions in older adults with dementia. The results of this study can be important for physical and mental activity recommendations in older adults with dementia.

List of abbreviations

AD	Alzheimer 's disease
ACSM	American College of Sports Medicine
ANCOVA	Analysis of Covariance
APOE	Apolipoprotein E
HR	Heart Rate
HRR	Heart Rate Reserve
MMSE	Mini-Mental Status Examination
RCT	Randomised Controlled Trial
RPE	Rate of Perceived Exertion
TOPICS-MDS	The Older Persons and Informal Caregivers Survey Minimum DataSet
PCR	Polymerase Chain Reaction
WMS	Wechsler Memory Scale
WAIS	Wechsler Adult Intelligence Scale

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SUPPLEMENTARY MATERIAL

Additional file 1. Bicycle set-up

Additional file 2. Description of training levels

The training software consists of 7 levels, with an increasing difficulty. Each level contains of approximately 15 different cycling routes. An impression of the training software can be found at www.fietslabyrint.nl.

Level 1

In the first level participants cycle different routes through a digital environment. These routes contain no cognitive tasks.

Level 2

In the second level, balloons (blue, yellow, red) appear on the screen during cycling. When a blue or yellow balloon pops up, participants have to react by pushing on the blue or yellow button, respectively, attached to the steer. When a red balloon pops up participants have to inhibit their response. The balloons are large and remain on screen for ten seconds

Level 3

In the third level, participants have to indicate at each junction which direction to go to. This is not voluntarily and will be indicated on the screen by 'go left' or 'go right'.

Level 4

The fourth level is similar to level two. However, the balloons are smaller and stay on screen for only five seconds. Furthermore, air balloons can also appear on the screen. When an air balloon pops up, participants have to inhibit a response.

Level 5

The fifth level is a combination of level three and four. In this level both the balloons, air balloons and directions appear on the screen.

Level 6

The sixth level is similar to level four; only a set-shifting task element is added. When the participant hears a beep, the task is switched for the next button-press. The participant has to press the blue button if the yellow balloon appears and the yellow button if the blue balloon appears. After pressing the button, the old rules are applicable again.

Level 7

This final level is the most challenging level and contains both directions, balloons, air balloons and the set-shifting task.

Additional file 3. Neuropsychological tests by cognitive domain

Executive functioning

Trail Making Test - part B[49]

Participants are asked to connect numbers alternating with letters. Scores are time to completion in seconds. In this study, the short form is administered (numbers 1 to 7 and letters A to G).

Stroop Color-Word Test[50]

This test consists of three subtasks: 1) participants are asked to read names of colours (red, green, blue, yellow) printed in black (word-reading card); 2) Participants are asked to name the colour of printed coloured blocks in red, green, blue and yellow (colour-naming card); 3) Participants are presented with coloured words. The ink-colour in which the words are printed needs to be named and the automatic word-reading response needs to be inhibited (colour-word interference card). In this study, the abbreviated version (i.e., the first 5 lines of each card) is administered. Composite scores of accuracy and reaction time are calculated for the colour-word interference card and the colour-naming card. These speed-accuracy trade-off scores are calculated as follows: (100*accuracy) / reaction time.[51]

Letter Fluency[52,53]

This test consists of naming words starting with the same letter for 1 minute each. Participants have to name as many words as possible. Scores are the number of correct words. Three equivalent parallel versions will be used: 'D-A-T', 'K-O-M' and 'P-G-R'.

Rule Shift Cards Test[54]

Participants are asked to respond to a certain rule (part 1; say 'yes' if a red playing card is shown, say 'no' if a black playing card is presented). In part 2 the rule is changed (say 'yes' if the playing card has the same colour as the previous card, say 'no' if the colour is different) and participants have to adapt their responses, inhibiting their original response set. Scores are the errors made in part 2.

Working memory

Digit Span[71]

Sequences of digits (from two to nine digits), are read aloud by the examiner. In the forward condition, participants are instructed to repeat each series in the same order as presented, in the backward conditions, the digits sequences must be reproduced in reverse order. Outcome measure is the number of correctly reproduced items forward and backward. The test is discontinued if participants score zero on both trials of an item.

Spatial Span[57]

In this test 9 blocks are fixed on 9 locations on a board. The examiner taps sequences of blocks of increasing length. Participants must repeat the block sequences in the same order (forward condition) or reverse order (backward condition). Outcome measure is the number of correct items forward and backward. The test is discontinued if participants score zero on both trials of an item.

Memory

Location Learning Test - Revised[55]

The test consists of a 5×5 grid with 10 pictures of easy-to-name everyday objects placed at different locations in the grid. This grid is presented for 15 seconds and participants are subsequently asked to place the pictures on the correct locations in an empty 5×5 grid. Five learning trials are presented, followed by a delayed recall trial after 30 minutes. The total displacement score on the 5 learning trials is the immediate recall score; the displacement score on the delayed trial is the delayed recall score.

Psychomotor speed

Trail Making Test – part A[49]

Participants are asked to connect numbers in ascending order. Scores are time to completion in seconds. In this study, the short form is administered (numbers 1 to 14).

Stroop Color-Word Test[50]

This test is already described as a measure of executive functioning. Scores on the word-reading and colour-naming cards are measures of psychomotor speed.

Additional file 4. Secondary outcome measures

Physical functioning
Physical fitness
Åstrand Bike Test[58] This is a submaximal exercise test completed according to the Åstrand-Rhyming submaximal protocol. During the first two minutes of the test, resistance of the ergometer is increased until a steady state heart rate (HR) of approximately 70% of the estimated maximal HR is reached. Participants continue cycling for six minutes and each minute HR and RPE is recorded. The maximum oxygen uptake (VO_{2MAX}) is estimated using the average HR of minute 5 and 6 and the workload in the Åstrand nomogram.
Strength
5-Times Chair Stand[61] Participants are asked to stand-up and sit-down from a chair for five times. The test is performed two times and the fastest time to perform 5 repetitions is reported as a score.
Handgrip strength[62] Handgrip strength is measured using a hand held dynamometer. The dynamometer is set to read force in kilograms. Handgrip strength is measured three times, both left and right, and the highest score is reported.
Mobility
Timed Up & Go test[59] For this test subjects are asked to rise from a chair, walk three metre to an orange cone, walk around it and return in their chair. The test is performed two times and the mean time in seconds is used as a score.
10-metre Walk Test[60] This test measures walking speed. Participants are instructed to walk 10 metre at a comfortable pace in a straight line, passing a line set at 2 and 8 metre. The test is performed two times and the fastest time in seconds between 2 and 8 meters is used as score.
Balance
Frailty and Injuries Cooperative Studies of Intervention Techniques[63] This test measures static balance control. Participants are asked to perform four different stances and to hold every stance for 10 seconds. The stances are: (1) parallel stand, (2) semi-tandem, (3) tandem, and (4) single-leg without assistive device. The score ranges from 0 to 5 with a higher score indicating better performance.

Other outcome measures

Physical Activity Scale for the Elderly[64]
This is a questionnaire to assess level of physical activity. It consists of 12 questions regarding the frequency and duration of leisure activity (e.g. sports, jogging, swimming, strengthening and endurance exercise), household activity and work related activity. The total score is computed by multiplying either the time spent in each activity (hours per week) or participation (i.e. yes/no) in an activity, by empirically derived item weights and then summing overall activities.

The Older Persons and Informal Caregivers Survey Minimum DataSet (TOPICS-MDS[65]
Via this questionnaire data is collected on demographics, morbidity, quality of life, functional limitations, mental health, social functioning and health service utilization.

The Evaluative Frailty Index for Physical Activity[67]
This is an instrument to evaluate the effect of physical activity on frailty. The questionnaire consists of 50 items on physical functioning, psychological functioning, social functioning and health.

Dementia Quality of Life Instrument[66]
This is a quality of life instrument valid and feasible for patients with mild to moderate dementia. The domains self care, physical functioning, social functioning, mood, memory and orientation are assessed. Each theme has three response options ('no problems', 'some problems' or 'extreme problems').

6

The quest for synergy between physical exercise and cognitive stimulation via exergaming in people with dementia: a randomised controlled trial

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ABSTRACT

Background

Exercise is often proposed as a non-pharmacological intervention to delay cognitive decline in people with dementia, but evidence remains inconclusive. Previous studies suggest that combining physical exercise with cognitive stimulation may be more successful in this respect. Exergaming is a promising intervention in which physical exercise is combined with cognitively challenging tasks in a single session. The aim of this study was to investigate the effect of exergame training and aerobic training on cognitive functioning in older adults with dementia.

Methods

A three-armed randomised controlled trial (RCT) compared exergame training, aerobic training, and an active control intervention consisting of relaxation and flexibility exercises. Individuals with dementia were randomised and individually trained three times a week during 12 weeks. Cognitive functioning was measured at baseline, after the 12-week intervention period and at 24-week follow-up by neuropsychological assessment. The domains of executive function, episodic memory, working memory, and psychomotor speed were evaluated. Test scores were converted into standardised z-scores that were averaged per domain. Between-group differences were analysed with analysis of covariance.

Results

Data from 115 people with dementia (mean (SD) age = 79.2 (6.9) years; mean (SD) MMSE = 22.9 (3.4)) were analysed. There was a significant improvement on psychomotor speed in the aerobic and exergame groups compared to the active control group (mean difference domain score [95% CI] aerobic versus control: 0.370 [0.103–0.637], p=0.007; mean difference domain score [95% CI] exergame versus control: 0.326 [0.081–0.571], p=0.009). The effect size was moderate (partial η^2 = 0.102). No significant differences between the intervention and control groups were found on executive functioning, episodic memory, and working memory.

Conclusions

To our knowledge, this is the first RCT evaluating the effects of exergame training and aerobic training on cognitive functioning in people with dementia. We found that both exergame training and aerobic training improve psychomotor speed, compared to an active control group. This finding may be clinically relevant as psychomotor speed is an important predictor for functional decline. No effects were found on executive function, episodic memory, and working memory.

BACKGROUND

The increasing prevalence of dementia greatly impacts healthcare and society, stressing the need for global action.[1] Since there is no cure or effective disease-modifying drug to treat the most common types of dementia to date,[1] research should also focus on the development and implementation of non-pharmacological interventions as an alternative or add-on therapy.[2] Previous research has shown that physical exercise improves cognitive performance in older adults without dementia,[3] and that physical inactivity during midlife attributes to the risk of dementia.[4,5] However, research on cognitive effects of physical exercise in older adults with dementia has shown heterogeneous results.[6,7] It seems that physical exercise alone may not be enough for older adults with dementia to alter or slow down cognitive decline. Previous studies suggest that combining physical exercise with cognitive stimulation may be a more successful strategy.[8,9]

Animal studies have shown that physical exercise can prime the hippocampus to increase neurogenesis elicited by cognitive stimuli.[10,11] Furthermore, physical exercise combined with environmental enrichment positively affects hippocampal neurogenesis, possibly via separate pathways, with physical exercise influencing the proliferation of neural precursor cells and environmental enrichment fostering survival of newborn neurons.[10] In line with this, a meta-analysis[12] showed significant benefits of combined cognitive and physical interventions on cognitive function in healthy older adults. These beneficial effects significantly exceeded the effects of physical exercise training alone.[12] In addition, we recently performed a meta-analysis in older adults with mild cognitive impairment (MCI) or dementia which showed that combined cognitive and physical exercise interventions improve global cognitive performance.[13] Thus, these studies illustrate the potential of combined interventions in delaying disease progression in persons with MCI or dementia. However, the superiority of combined interventions over single physical exercise and the effects on different cognitive domains in individuals with dementia remain unknown. Hence, the aim of the current study is to investigate the effects of combined cognitive and physical exercise training on different cognitive domains in people with dementia.

Recent advances in technology present the opportunity to combine physical exercise with cognitively challenging tasks in a single session using exergames.[14] Exergaming is defined by "physical exercise interactively combined with cognitive stimulation in a virtual environment".[15] Exergame training is a physical-cognitive dual-task training, which requires the mental flexibility to switch between concurrent tasks. Mental flexibility is a core component of executive functioning, a set of higher-order cognitive processes also including cognitive inhibition, planning and problem-solving.[16] We, therefore, hypothesize that exergame training will specifically benefit executive functioning. Previous research already showed that

exergames improve global cognitive function in healthy older adults and in a clinical population of patients with Parkinson's disease, schizophrenia, multiple sclerosis and MCI, compared to physical exercise training alone.[17] Moreover, older adults were found to enjoy participation in exergames, which may facilitate long-term activity participation.[18] There is also preliminary evidence that exergames are a feasible and enjoyable intervention for people with dementia.[19,20] To our knowledge, no previous randomised controlled studies have investigated the effect of exergames on cognitive functioning, more specifically on executive functioning, in older adults with dementia.

Previous studies suggest that the gene apolipoprotein E (APOE) may be a moderator in the effects of exercise on cognition.[21,22] APOE is a cholesterol carrier and is important for lipid transport and injury repair in the brain.[23] There are three alleles of APOE: ε2, ε3 and ε4. Carrying the ε4 allele of APOE is a risk factor for Alzheimer's disease (AD) and carrying the ε2 allele is protective for AD.[1] Results from cohort-studies are contradictory, reporting both that physical exercise is protective for cognitive decline in APOE ε4 carriers[24,25] as well as lowering the risk of dementia in APOE ε4 non-carrier.[26] Insight in this moderating relationship may contribute to identify people who will benefit most from our exergame intervention.

The primary aim of the current study is to investigate the efficacy of a 12-week exergame training and aerobic training compared to a control group on executive functioning in older adults with dementia. We hypothesize that exergame training results in greater improvement on executive functioning than aerobic training. Secondary aims are: to assess the feasibility of exergames; to compare effects of exergame training with single aerobic training on the cognitive domains of psychomotor speed, episodic memory and working memory; to measure the follow-up effects of exergame training and aerobic training; and to determine whether the cognitive effects of training are modified by APOEε4 carrier state.

METHODS

Study design

The current study was a 12-week single-blind randomized controlled trial (RCT) with two experimental intervention groups and one active control group. Participants were included from January 2016 to September 2017. The Medical Ethics Committee of Radboud University Medical Center in Nijmegen, the Netherlands, approved the research protocol which was published previously.[27] The study was conducted in compliance with Declaration of Helsinki ethical standards. Participants all verbally agreed to participate in the study and gave written informed consent. The trial is registered at the Dutch trial register (http://www.trialregister.nl) with identification number NTR5581.

Participants and study procedures

Participants were approached via the memory clinic of Radboudumc Alzheimer Center, day care centres for older adults with cognitive disorders, advertisement in local newspapers and word of mouth. Eligibility criteria for inclusion were: clinically confirmed diagnosis of dementia following the DSM-IV criteria[28] (vascular, Alzheimer or mixed type) with a Mini Mental Status Examination (MMSE)[29] score of ≥ 17; aged 60 years or above; if using anti-dementia medication, a stable dose for at least three months before start of the trial; and being capable of giving informed consent.[30] Exclusion criteria were: co-morbidity that limited exercising, including severe cardiovascular, musculoskeletal or neurological disease; diagnosis of a depression, bipolar disorder or psychotic disorder at the moment of inclusion; current drug or alcohol dependency; exercising more than five times per week for at least 30 minutes at a moderate intensity; wheelchair bound; and severe hearing or visual problems that could not be corrected with the use of hearing aids/glasses. When participants were recruited by newspaper advertisement or word of mouth, we confirmed dementia diagnosis by investigating their medical record before planning a screening visit. The study was conducted in community centres in Nijmegen, the Netherlands. Participants were randomly assigned to one of the intervention groups or the control group by an independent statistician. The minimization method[31] was used to balance groups for gender, severity of cognitive impairment (MMSE ≥ 20 or < 20), use of medication for Alzheimer's disease, training location and level of education. The Dutch classification of education levels[32] was used to classify the educational attainment of participants as low (levels 1-3), average (levels 4-5), or high (levels 6-7).

Interventions

The study included three arms: exergame training, aerobic training and active control. Participants in each arm received three training sessions per week for 12 weeks. Training sessions were given on a one-on-one basis, and trained students or research assistants supervised the participants. Adherence to the intervention was calculated by dividing the number of sessions the participant followed through the total number of sessions that were offered.

The exergame training consisted of a combined cognitive-aerobic bicycle training developed by Bike Labyrinth (www.bikelabyrinth.com). The aerobic training component consisted of cycling on a stationary bike, 30-50 minutes per session. The aerobic exercise was tailored to an individual fitness level and health status, and aimed to achieve an intensity of 65%-75% of heart rate reserve after 12 weeks of training.[27] For participants on medication that attenuates heart rate (e.g. beta-blockers), the Borg Rating of Perceived Exertion (RPE)[33] was used to ensure that the intended training intensity was achieved. In addition, the stationary bike was connected to a video screen. Participants followed a route through a digital environment and simultaneously performed cognitive tasks targeting response inhibition, task switching and

processing speed. The exergame training consisted of seven different cognitive training levels. The difficulty of the cognitive tasks increased per level to ensure that the training remained cognitively challenging. In our protocol paper the exergame training and different training levels are described extensively.[27]

The single aerobic exercise group consisted of cycling on a stationary bike that was not connected to a video screen. The aerobic training was identical to the training described above. Participants in the active control group received a training that consisted of relaxation and flexibility exercises with a duration of 30 minutes and the same frequency as the training regimes of the intervention groups. The exercises required minimal muscle strength and aerobic capacity and were easy to perform. The level of social engagement was similar to the intervention groups.

Outcomes

Full assessments were carried out before (T0), after the 12-week training phase (T2), and 12 weeks thereafter at the 24-week follow-up (F1). Intermediate measurements were performed after six weeks of training (T1). Trained research assistants with a background in neuropsychology assessed cognitive performance using a test battery that was described previously,[27] and they were blinded to group allocation. The primary outcome measure was objective executive functioning, which was measured by four neuropsychological tasks that were averaged into one domain score: a short form of the Trail Making Test part B,[34] the abbreviated 5-line Stroop Color Word Test interference score,[35,36] Letter Fluency,[37,38] and the Rule Shift Cards Test.[39] All tests, except for letter fluency, were also administered after 6 weeks (T1). Secondarily, the following cognitive domains were assessed: episodic memory (Location Learning Test – Revised[40]), working memory (WAIS-III Digit Span[41] and WMS-III Spatial Span[42]), and psychomotor speed (short form of Trail Making Test part A[34] and the abbreviated Stroop Color Word Test parts I and II[35]). Only all psychomotor speed tests were also performed after 6 weeks (T1). Tests were categorised into cognitive domains a-priori using the conventional classification described by Lezak and colleagues.[43] In order to calculate domain scores, test scores were converted into z-scores based on the mean and standard deviation of the total sample at baseline.[44] Subsequently, these individual test z-scores were averaged per domain.

After inclusion, saliva samples were taken with buccal swabs for APOE genotyping. Samples were stored in -20°C and analysed using real-time Polymerase Chain Reaction (PCR).[45] This results in different APOE gene phenotypes: three homozygous (ε2/ ε2, ε3/ ε3, ε4/ε4) and three heterozygous (ε2/ε3, ε2/ ε4, ε3/ε4) [45].

Statistical analysis

Socio-demographic and clinical characteristics at baseline were presented using descriptive statistics. Feasibility measures (e.g. adherence to the exercise programme, measures of exercise intensity and rating of the exercise sessions) were compared between the groups with one-way analysis of variance (ANOVA) and independent-sample t-test.

To assess the effect of training on cognitive performance in each domain (i.e., executive function, episodic memory, working memory and psychomotor speed), analysis of covariance (ANCOVA) was done with post-training cognitive domain z-scores as dependent variables, baseline z-scores as covariates and group (exergame training, aerobic training and active control) as between subject factor. To specify significant group effects, Bonferroni corrected post-hoc tests were performed. To investigate follow-up effects of the intervention for each cognitive domain, we used mixed model ANCOVA. Variables included in the model were cognitive domain z-scores at T1 and FU as dependent variables, group as between-subject factors, time as within-subject factors, and the corresponding baseline measure as covariate. Additionally, a time*group interaction term was added as a fixed effect. To assess a moderating effect of APOE ε4, an interaction term between APOE ε4 and group was added separately as a predictor.

If a participant had missing data because he/she was cognitively incapable to perform a certain test, the worst possible score for this test was awarded. Afterwards the domain z-score was calculated. If there was missing data due to drop-out and the reason for missingness was at random, missing data was substituted using the multiple imputation method. Characteristic variables of the sample, cognitive domain scores at baseline and training group were included in the imputation model. The following imputation settings were used: automatic model setting, 15 iterations and 5 imputations. If a participant had missing data due to drop-out because of cognitive decline the criteria for missing at random was not fulfilled. Use of multiple imputation would in this case have been inappropriate as violation of the missing at random assumption biases the estimates.[46] We expected that the cognitive decline would be larger in these participants, than the mean decline in the entire group, as it was their reason for drop-out. We decided to use a single value imputation approach for these participants, in which we replaced the missing values by a single value, in our case the greatest decline in the group. To prevent imputing non-realistic values, the lowest possible score was used as a cut-off score. We performed additional sensitivity analyses to check whether this alternative method of dealing with missing data influenced our results.

All statistical analyses were performed as intention-to-treat analyses, including all participants irrespective of adherence to intervention. Additionally, we performed per-protocol analyses including only those participants that successfully completed the intervention period and all measurements. SPSS 22 was used for all analyses with alpha set at 0.05.

RESULTS

Patient flow and sample characteristics

In total, 307 participants were screened for eligibility and 121 participants eventually enrolled in the study. Six participants refused to participate during baseline measurements and the remaining 115 participants were randomized. Fourteen participants did not complete the 12-week intervention (12%). The number of dropouts did not differ significantly between the groups (P=0.930). The enrolment, allocation process and reasons for drop out are presented in Figure 6.1. Baseline characteristics for the randomised sample were well matched between the groups (Table 6.1). The included participants had a mean (SD) age of 79.9 years (6.5) and a mean (SD) MMSE score of 22.4 (3.2). There were no differences in age, MMSE score and Katz index between the different dementia types (see additional file 1).

Attendance, intensity, and safety

Table 6.2 presents the adherence per group; a trend was found towards higher adherence in the exergame group compared to the aerobic group (mean difference [95% CI]: 6.85 [-0.09–13.79], p=0.053). Participants rated both exercise interventions and the active control group highly (see Table 6.2). Training duration, training load, heart rate and rate of perceived exertion did not differ between both intervention groups. The mean training intensity was light in both intervention groups with an average of 41.8% (SD=13.3) and 43.5% (SD=18.2) of maximal heart rate in the exergame group and aerobic group respectively. For the exergame training the median [interquartile range] training level after 6 weeks was 5.0 [4.3-5.8], and after 12 weeks 5.5 [5.0-6.0]. After 6 weeks 25% of the participants reached level 6 or 7, and 50% level 5. After 12 weeks, 50% of the participants reached level 6 or 7, and 40% level 5. This demonstrates that there were no floor effects for the cognitive stimulation activity and around half of the participants was able to complete the highest levels, thus proving that the exergame training was feasible and that skill acquisition was present. No occurrence of serious adverse events (e.g. events leading to death, hospital admission or persistent disability) related to the exercise interventions were recorded.

Missing data

Missing data due to drop-out of participants was 0% at T0, 8.7% at T1, 9.6% at T2 and 17.5% at F1. Reasons for drop-out are described in Figure 6.1. In a total of six cases reason for drop-out was refused participation (5 out of 6 at follow-up measurements). Reason for refusal was cognitive decline, which led to caregivers' withdrawal of consent. As explained in the methods section, we used single value imputation for substituting missing data not at random, and performed additional sensitivity analyses to check whether this influenced our results. Data of the remaining 8 drop-outs was missing at random and was substituted using multiple-imputation, as explained in the methods section.

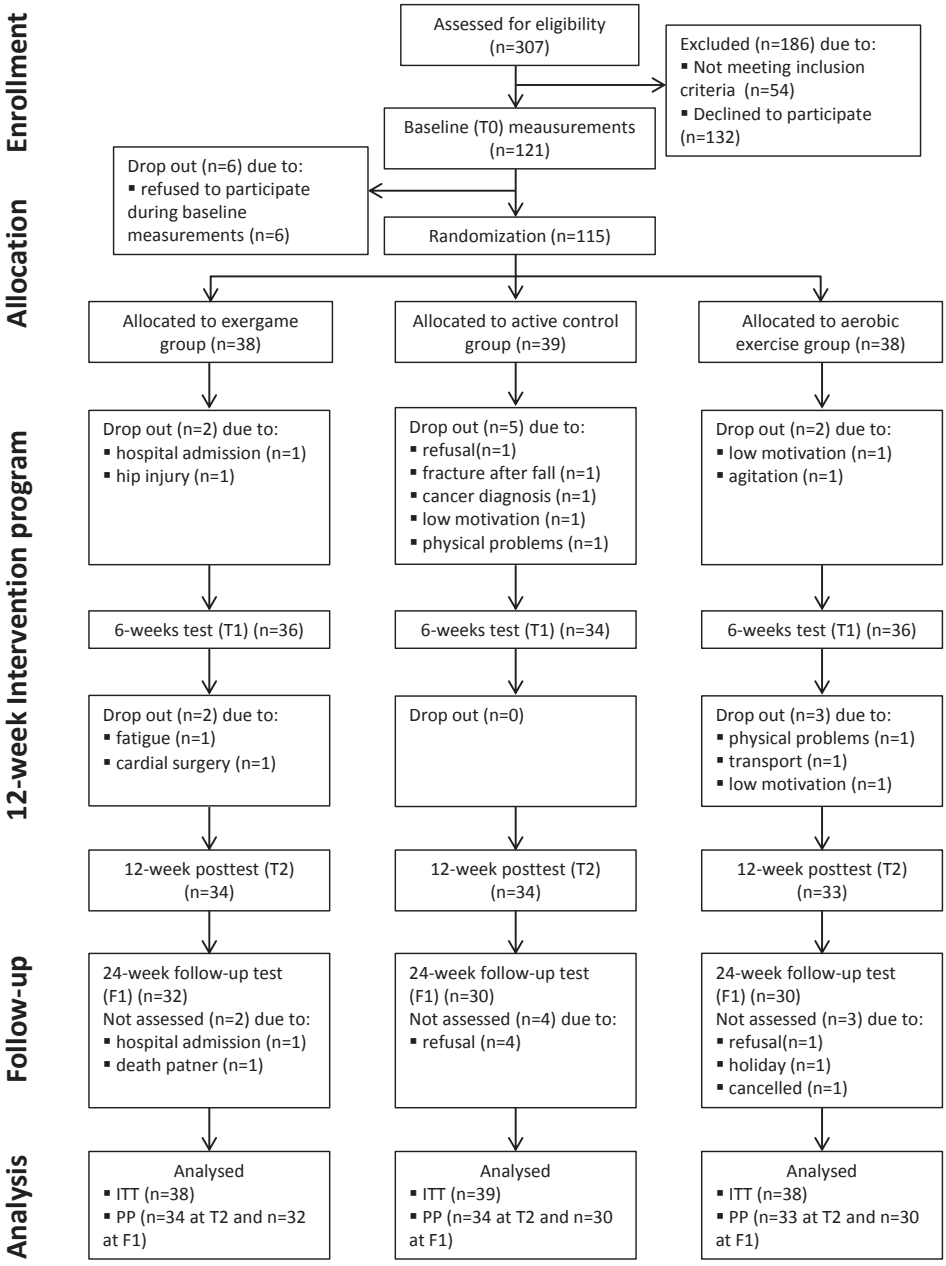

Figure 6.1. Flowchart of participants in study. Abbreviations: ITT, Intention to treat; PP, Per protocol

Table 6.1. Baseline characteristics of the study population

Variables	Exergame group (n=38)	Aerobic group (n=38)	Control group (n=39)
Age, years, mean (SD)	79.0 (6.9)	80.9 (6.1)	79.8 (6.5)
Men, n (%)	20 (52.6)	21 (55.3)	21 (53.8)
Educational level, n (%)			
Primary school education or lower	6 (15.8)	7 (18.4)	6 (15.4)
Secondary education or vocational training	23 (60.5)	22 (57.9)	22 (56.4)
Higher education	9 (23.7)	9 (23.7)	11 (28.2)
Mini Mental State Examination, mean (SD)[a]	22.9 (3.4)	22.5 (3.1)	21.9 (3.1)
Aetiology of dementia, n (%)			
Alzheimer's disease	22 (57.9)	16 (42.1)	21 (53.8)
Vascular dementia	4 (10.5)	4 (10.5)	3 (7.7)
Mixed dementia (Alzheimer/Vascular)	5 (13.2)	8 (21.1)	11 (28.2)
Not specified	7 (18.4)	10 (26.3)	4 (10.3)
APOE carrier state, n %)			
ε4/ ε4	1 (2.7)	5 (13.2)	3 (7.9)
ε3/ ε4	20 (54.1)	13 (34.2)	16 (42.1)
ε3/ ε3	15 (40.5)	16 (42.1)	16 (42.1)
ε3/ ε2	0	3 (7.9)	4 (7.9)
ε2/ ε4	1 (2.7)	1 (2.6)	0
ε2/ ε2	0	0	0
Duration since dementia diagnosis in months, mean (SD)	13.6 (19.9)	13.8 (12.3)	18.9 (22.4)
Functional Comorbidity Index[b], mean (SD)	2.5 (1.9)	2.4 (1.8)	2.2 (1.4)
Katz index[c], mean (SD)	5.2 (3.3)	4.5 (3.0)	5.1 (2.9)
Number of medication used, mean (SD)	4.9 (2.9)	5.9 (3.8)	6.1 (3.7)
Use of beta-blockers, n (%)	16 (42.1)	17 (44.7)	14 (35.9)
Dementia drugs, n (%)			
Rivastigmine	6 (15.8)	4 (10.5)	8 (20.5)
Donezepil	0	0	0
Galantamine	1 (2.6)	3 (7.9)	2 (5.1)
Memantine	0	1 (2.6)	0

[a] Scores on the Mini-Mental State Examination range from 0 (severe impairment to 30 (no impairment); [b] Theoretical range 0–18 and a higher score indicates more comorbidities; [c] Theoretical range 0–15 and a higher score indicates higher dependency in activities of daily living

Table 6.2. Training characteristics of the study population

Variables	Exergame group (n=38)	Aerobic group (n=38)	Control group (n=39)
Adherence rate, %, mean (SD)	87.3 (13.6)*	81.1 (13.7)*	85.4 (12.9)
Duration training session, min, mean (SD)	32.6 (6.0)	30.5 (8.7)	30[a]
Training load, watt, mean (SD)	53.7 (34.9)	51.2 (27.7)	Na
Resting heart rate, beats/min^{-1}, mean (SD)	79.4 (12.1)	77.9 (10.4)	Na
Heart rate during training, beats/min^{-1}, mean (SD)	105.5 (14.8)	103.9 (14.3)	Na
Heart rate difference, beats/min^{-1}, mean (SD)	26.1 (15.1)	26.0 (13.8)	Na
Training intensity[b], % of maximal heart rate, mean (SD)	41.8 (13.3)	43.5 (18.2)	Na
Rate of perceived exertion during training[c], mean (SD)	13.1 (1.2)	12.8 (1.9)	Na
Rating of training sessions[d], scale 1-5, Median [interquartile range]	5.0 [4.0-5.0]	5.0 [4.0-5.0]	5.0 [4.0-5.0]
Training level after 6 weeks[d], scale 1-7, Median [interquartile range]	5.0 [4.3-5.8]	Na	Na
Training level after 12 weeks[d], scale 1-7, Median [interquartile range]	5.5 [5.0-6.0]	Na	Na

Abbreviations: Na=not applicable, SD=standard deviation

Differences between groups were tested with one-way Analysis of Variance test (three groups) or independent-sample t-test (two groups), if data was normally distributed. For post-hoc comparisons Tukey HSD was performed. If data was not normally distributed, Kruskall Wallis test was performed.

[a] All training sessions lasted for 30 minutes, time has not been recorded; [b] Training intensity is only calculated for participants that do not use beta-blockers (n=21 and n=20 in the exergame and aerobic group respectively; [c] Theoretical range 6-20 where 6 indicates lowest intensity level and score 20 indicates highest intensity level; [d] Data not normally distributed therefore we present median and interquartile range

* A trend was found towards higher adherence in the exergame group compared to the aerobic group (mean difference [95% CI]: 6.85 [-0.09–13.79], p=0.053).

Intention-to-treat analysis

Figure 6.2 shows the performance on the four cognitive domains at each time point per treatment arm. No significant differences were found between the exergame group, aerobic group, and control group on executive functioning after 12-weeks of training. Since after 6 weeks (T1) letter fluency was not administered as an executive function test, we decided not to include T1 data in our analyses. Significant improvement on the secondary measure psychomotor speed was found for both the aerobic and the exergame group compared to the controls after 12 weeks of training (mean difference domain score [95%CI] aerobic versus control: 0.370 [0.103–0.637], p=0.007; mean difference domain score [95%CI] exergame versus control: 0.326 [0.081–0.571], p=0.009. The size of the effect was moderate (partial η^2 = 0.102). This effect was not present yet at the intermediate measurements after six weeks (see Figure 6.2). No significant differences were found between the groups on the secondary measures of episodic memory and working memory after the 12-week intervention period. An additional sensitivity analysis yielded similar results, which shows that our findings are robust. Follow-up analysis showed that the improvement in psychomotor speed was maintained for both the aerobic and the exergame group compared to the controls (mean difference domain score [95%CI] aerobic versus control: 0.453 [0.185–0.722]; mean difference domain score [95%CI] exergame versus control: 0.326 [0.070–0.604]. There was no significant difference between the exergame and aerobic group (mean difference domain score [95%CI] exergame versus aerobic: -0.116 [0.399– -0.398], p=0.399). We did not find any between-group differences in any of the of the other cognitive domains at follow-up. Sensitivity analysis pointed in the same direction with a maintenance effect in the aerobic group compared to controls (mean difference domain score [95%CI] aerobic versus control: 0.267 [0.048–0.486]), and no follow-up effect in any of the other cognitive domains. Moderator analysis showed that carrying APOE ε4 did not influence the relation between training and cognitive performance. Z-scores of the different cognitive domains per group and time point are presented in Additional file 2. Raw data of cognitive test scores are presented in Additional file 3.

Per-protocol analysis

In the per-protocol analyses, we excluded 14 participants who did not complete the 12-week intervention period. The remaining 101 participants were included in this analysis. The results of the per-protocol analyses were in line with the intention-to-treat analyses, with positive effects of exergame and aerobic training on psychomotor speed compared to controls (mean difference domain score [95%CI] aerobic versus control: 0.322 [0.038–0.607], p=0.021; mean difference domain score [95%CI] exergame versus control: 0.283 [0.002–0.563], p=0.047. As in the intention-to-treat analyses, no significant between-group differences were observed in the domains of executive function, memory, and working memory. At follow-up there were 9 additional drop-outs, which led to inclusion of 92 participants in the follow-up analysis. We found that there was a trend for maintained improvement in psychomotor speed at 24-week

follow-up in the aerobic group compared to the control group (mean difference domain score [95%CI] aerobic versus control: 0.267 [0.048–0.486], p=0.057). No significant intervention effects were observed in any of the other domains.

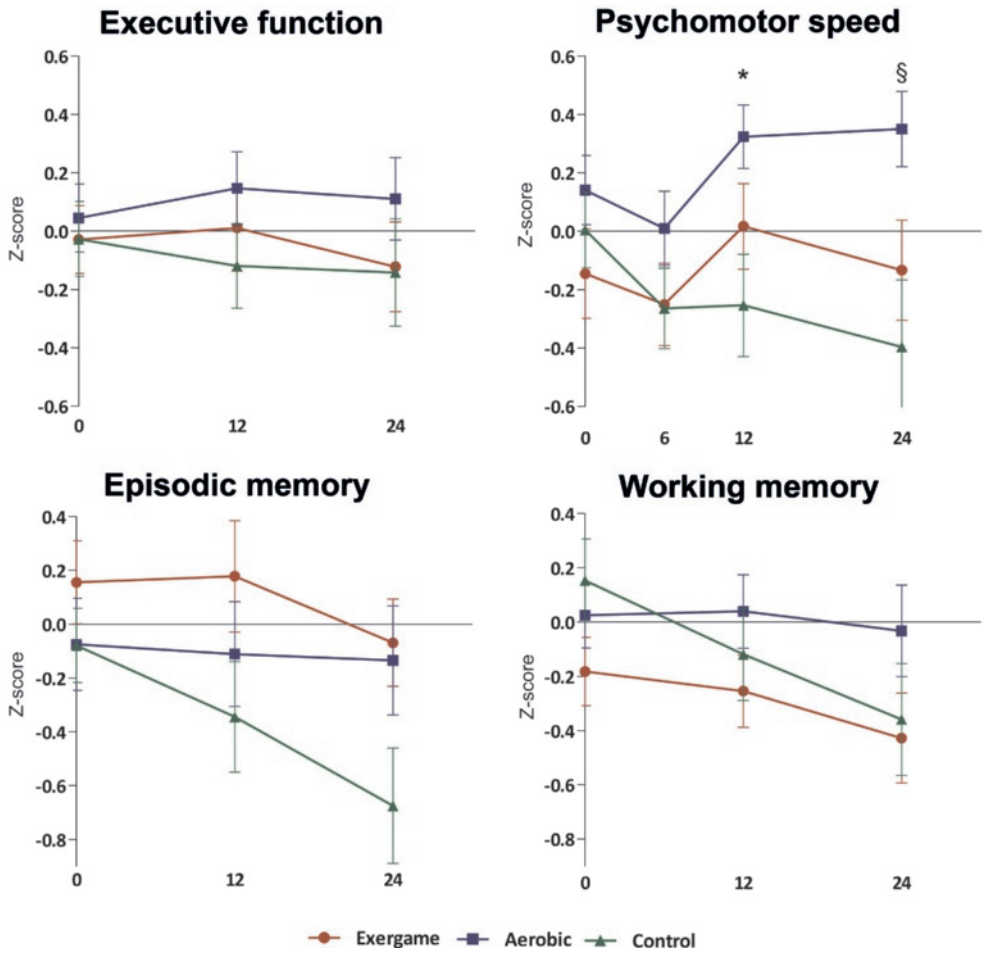

Figure 6.2. Mean z-scores and standard errors of the mean(SEM) at baseline, after 12 weeks and after 24 weeks for the domains of executive function, psychomotor speed, episodic memory and working memory. Arrows represent SEM; * significant effect (p<0.05) of exergame training and aerobic training on psychomotor speed compared to controls after 12 weeks; § maintenance effect (p<0.05) of aerobic and exergame training on psychomotor speed at 24-week follow-up.

DISCUSSION

To our knowledge this is the first randomized controlled trial that investigated the differential effect of exergaming versus aerobic training on cognitive functioning in people with dementia. We hypothesised that exergame training would result in greater improvement on executive functioning than single aerobic training. Although we did not find an effect of exergame training or aerobic exercise on executive function after 12 weeks, we found that psychomotor speed improved in both the exergame and the aerobic group compared to active controls. This effect was maintained at the 24-week follow-up. We did not find an effect of both intervention groups in the cognitive domains of episodic memory and working memory compared to the control group. Moderator analysis showed that APOE ε4 carriership did not influence the relation between training and cognitive function. Finally, we demonstrated that a newly developed exergame that comprises both physical and cognitive training elements is feasible for people with dementia.

Interpretation of results and comparison with previous research

Contrary to our hypothesis, the current results did not show a larger effect of exergame training compared to aerobic training on cognitive functioning. Comparable research on the differential effects of combined cognitive and physical training versus only cognitive or physical interventions in people with dementia is scarce. There is one previously published paper reporting that neither a 12-week combined cognitive-aerobic training nor aerobic training only improved global cognitive function in a smaller sample of 80 individuals with AD.[47] However, type of intervention and used outcome measures are incomparable to the current study. Research in individuals with MCI showed inconsistent findings regarding the cognitive benefits of combined interventions and its potential superiority compared to physical exercise or cognitive training alone.[48] In contrast, for older adults without cognitive impairment there is converging evidence that combined interventions (including exergames) are superior to physical or cognitive training alone,[48] with larger effect sizes for interventions that are performed simultaneously compared to sequential interventions.[12]

In healthy older adults, evidence for the efficacy of physical exercise and combined cognitive and physical interventions on executive functions,[12,49] memory,[12,49] working memory[12,50], and attention[51] have been well established. In our current study, both exergame and aerobic-only training did not positively affect executive functions, working memory or episodic memory. This seems partly in line with previous research. A meta-analysis performed by our group[13] demonstrated positive effects of combined interventions on global cognitive function in older adults with MCI or dementia, but no effects in the domains of executive function and memory. In contrast, a recently published RCT showed that both a mentally challenging exergame and a passive exergame improve executive functioning in people with MCI.[52] However, the more

challenging exergame only yielded significant effects after 6 months of training, while the passive exergame already produced gains after 3 months.[52] A possible explanation for this discrepancy is that participants in the mentally challenging exergame group needed more time to master the intervention, which may have delayed triggering the synergistic effects of the combined intervention.[52] This might also explain the negative findings in our study, since a mentally challenging exergame was used for a relative short intervention period of 12 weeks.

There is evidence that severity of neurocognitive disorder has a moderating impact on the cognitive effects of combined cognitive and physical training.[53] An increase in severity of neurocognitive disorder may lead to a decrease of the intervention effect.[53] This could be explained by a reduced structural brain capacity (e.g. reduced number of neurons and synapses) in participants with more severe neurocognitive disorder, which may lead to limited resources necessary for training-induced gains.[53] Therefore, it may be more difficult to induce cognitive benefits in people with dementia compared to those with MCI or healthy older adults. Moreover, the complexity to obtain valid neuropsychological outcomes that are sensitive to change in persons who already have severe cognitive deficits due to their dementia complicates the assessment of cognitive functioning in this group. It is particularly challenging to assess executive functions that include higher-order processes such as inhibitory control, mental flexibility and planning, which are already affected in early stages of the dementia.[54] Assessment of executive function in people with dementia may consequently result in floor effects or missing data, which makes it difficult to measure change over time.

In our study we found a moderate effect of exergame training and aerobic training on psychomotor speed after a 12-week training period in people with dementia. This effect was not yet present after 6 weeks of training. Firstly, this may imply that the improvement is due to the training and not due to non-specific treatment or practice effects. Secondly, this suggests that a longer training duration is necessary to improve psychomotor speed. Although still under debate, there is some evidence that physical exercise leads to improved cognitive function through promotion of hippocampal neurogenesis,[55] brain angiogenesis,[56] and synaptic plasticity[57] elicited by an increased expression of neurothropic factors.[58] In cognitively healthy older adults physical exercise interventions have the largest gains on executive control processes, psychomotor speed, and attention.[49,51,59,60] In people with dementia there is little research about the benefits for different cognitive domains. From a neurobiological perspective, however, we do not have an explanation for why exercise would only improve psychomotor speed, but not the other cognitive skills assessed. We hypothesize that only finding an effect on psychomotor speed, and not on executive functioning, is related to domain specific responsiveness of the selected outcome measures. Processing speed tests typically are continuous outcome measures without ceiling or floor effects that are highly sensitive,[61] which may explain its sensitivity to change even in a dementia sample. In contrast, tests that measured executive functioning

resulted in floor effects in our dementia sample, which made it difficult to measure change over time. Alternatively, one could also hypothesize that mood may be a mediating factor for improvement on speed measures, as previous research showed that exercise and exergame training can reduce depressive symptoms in healthy older adults. [63,64] The positive effect on psychomotor speed was consistent across the different neuropsychological tests used to measure psychomotor speed (short form of Trail Making Test part A and the abbreviated Stroop Color Word Test parts I and II), which shows the effect was robust and reliable. Its moderate effect size is slightly larger than to the small-to-moderate effect sizes commonly found in studied examining the effects of cholinesterase inhibitors on cognitive function.[62,65] Given that interventions to ameliorate cognitive decline of people with dementia are scarce, this effect size may be clinically relevant. Poor processing speed is a predictor of functional decline in basic and instrumental activities of daily living.[66] In addition, poor processing speed is reported to be a predictor for incident dementia[67] and was found to be associated with a shorter survival among older adults in Japan.[68] Furthermore, late-life cognitive decline is attributable to slower processing speed.[69] Thus, the reported improvement in processing speed may be clinically relevant.

The mean training intensity was light in both intervention groups with an average of 41.8% (SD=13.3) and 43.5% (SD=18.2) of maximal heart rate in the exergame group and aerobic group respectively. We expected that improved cardiorespiratory fitness would be a requirement to improve cognitive function,[51] and therefore we aimed to achieve a moderate exercise intensity (e.g. 65-75% of maximal heart rate) during the training sessions. However, the exercise training was tailored to an individual fitness level and health status and most participants were not able to achieve a moderate training intensity. The recently published Dementia and Physical Activity (DAPA) trial[70] showed that a moderate to high intensity aerobic and strength exercise training did not slow cognitive decline in people with mild to moderate dementia, and even worsened cognitive impairment in those that complied to the intervention, despite an improvement in physical fitness. It is therefore unlikely that the light training intensity in our study limited the beneficial effects of exercise on cognitive functioning.

Strengths and limitations

The strengths of our study include the inclusion of a relatively large sample of people with dementia, a high adherence rate, the use of a comprehensive neuropsychological assessment and follow-up measurement for long-term maintenance effects. However, some limitations need to be taken into account when interpreting our results. Firstly, only participants who were mobile and motivated enrolled in our study, which may limit external validity of the current findings. Secondly, participants were not blinded to allocation, which is an unavoidable limitation of exercise studies. Outcome assessors were masked for intervention allocation. Thirdly, although we used adapted versions of executive tests making administration in people

with dementia more feasible, a floor performance was still found in a number of individuals. This may have reduced the sensitivity to measure change over time, obscuring potential positive results. Fourthly, the intervention period was only 12 weeks, which may have been too short to show beneficial effects of exergames on executive functioning. Lastly, mood might be a potential mediating factor for the improvement on processing speed measures as previous research has shown that exergame training can reduce depressive symptoms in healthy older adults. Therefore, measures of mood should be included in future studies.

Clinical relevance and feasibility

Both exergame training and aerobic training improved psychomotor speed after 12-weeks, with a moderate effect size. This finding may be clinically relevant as psychomotor speed is an important predictor for functional decline. In our study, exergame training was not superior to aerobic training. However, there was a trend for higher adherence in the exergame group compared to the aerobic group. Additionally, trainers who individually guided the training sessions reported that it was easier to motivate participants in the exergame group and to increase duration of the training sessions. This was confirmed by our finding that no participants dropped out in the exergame group due to a low motivation (see Figure 6.1). Accordingly, exergaming seems to be an effective method to stimulate long-term physical activity participation in people with dementia.

Future directions

Future studies should examine whether certain individual characteristics (e.g. type of dementia) moderate the effect of physical activity on cognition. Insight into these individual differences is important because it can determine which people are most likely to benefit from physical activity. It can also help to personalise interventions, thereby stimulating physical activity. Moreover, additional studies are needed to explore the optimal intervention design and dose-response for eliciting beneficial cognitive effects in people with dementia. Future intervention trials should include measures of psychomotor speed as these can reliably and validly be assessed in people with dementia and are closely related to everyday activities. Furthermore, studies should also focus on investigating neurophysiological mechanisms that underlie the cognitive effects of exercise, for example by including neuro-imaging measures.

CONCLUSIONS

Exergaming is a feasible and highly appreciated exercise method to engage older adults with dementia in physical exercise, mixed with cognitive stimulation. Both exergame training and aerobic training can improve psychomotor speed, which may be clinically relevant as psychomotor speed is an important predictor for functional decline. Although no effects were found on executive function, episodic memory and working memory, the potential broad range of effects of exergames for older adults with dementia (e.g. physical functioning, quality of life, activities in daily living) should be studied in futures RCTs.

Abbreviations

AD: Alzheimer's disease
APOE: Apolipoprotein E
ITT: Intention to treat analysis
MCI: Mild cognitive impairment
MMSE: Mini Mental State Examination
PPA: Per protocol analysis
RCT: Randomised Controlled Trial

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SUPPLEMENTARY MATERIAL

Additional file 1. Baseline characteristics of the study population presented separately for the different types of dementia

Variables	Alzheimer's dementia (n=59)	Vascular dementia (n=11)	Mixed dementia (Alzheimer/Vascular) (n=24)	Not specified (N=21)
Age, years, mean (SD)	79.3 (6.9)	81.5 (5.1)	79.4 (5.5)	81.4 (7.0)
Men, n (%)	28 (47.5)	7 (63.6)	17 (70.8)	10 (47.6)
Educational level, n (%)				
Primary school education or lower	9 (15.3)	0 (0)	2 (8.3)	8 (38.1)
Secondary education or vocational training	35 (59.3)	6 (54.5)	17 (70.8)	9 (42.9)
Higher education	15 (25.4)	5 (45.5)	5 (20.8)	4 (19.0)
Mini Mental State Examination, mean (SD)[a]	21.8 (3.2)	23.7 (2.2)	23.1 (3.7)	22.8 (3.0)
APOE ε4 carrier, n (%)	30 (50.8)	4 (36.4)	14 (58.3)	12 (57.1)
Functional Comorbidity Index[b], mean (SD)	1.9 (1.7)	2.9 (1.1)	2. 4 (1.1)	3.4 (2.1)
Katz index[c], mean (SD)	4.5 (3.1)	5.4 (2.6)	5.5 (3.0)	5.5 (3.5)
Number of medication used, mean (SD)	4.5 (2.9)	6.1 (3.3)	7.8 (4.0)	5.9 (3.5)
Dementia drugs, n (%)	21 (35.6)	0 (0)	3 (12.5)	0 (0)
Intervention group				
Exergame group	22 (37.3)	4 (36.4)	5 (20.8)	7 (33.3)
Aerobic group	16 (27.1)	4 (36.4)	8 (33.3)	10 (47.6)
Control group	21 (35.6)	3 (27.3)	11 (45.8)	4 (19.0)

[a] Scores on the Mini-Mental State Examination range from 0 (severe impairment to 30 (no impairment); [b] Theoretical range 0–18 and a higher score indicates more comorbidities; [c] Theoretical range 0–15 and a higher score indicates higher dependency in activities of daily living

Additional file 2. Z-scores of the different cognitive domains per group and time point

	Exergame group (n=38)				Aerobic group (n=38)				Control group (n=39)				F test value (df), p-value	
	T0	T1	T2	F1	T0	T1	T2	F1	T0	T1	T2	F1	T0-T2	T2-F1
Executive function, mean z-score (SD)	-0.03 (0.71)	Na	0.01 (0.88)	-0.12 (0.88)	0.05 (0.72)	Na	0.15 (0.74)	0.11 (0.80)	-0.03 (0.80)	Na	-0.12 (0.87)	-0.14 (1.10)	F(2,115) = 1.095, p=0.338	F(2,103)=0.254, p=0.776
Psychomotor speed, mean z-score (SD)	-0.15 (0.94)	-0.25 (0.84)	0.02 (0.87)	-0.13 (0.98)	0.14 (0.73)	0.01 (0.75)	0.32 (0.64)	0.35 (0.73)	0.00 (0.81)	-0.26 (0.83)	-0.25 (1.04)	-0.39 (1.37)	F(2,115) = 5.772, p=**0.004***	F(2,103)=6.127, p=**0.003**§
Episodic memory, mean z-score (SD)	0.16 (0.95)	Na	0.18 (1.23)	-0.07 (0.93)	-0.08 (1.05)	Na	-0.11 (1.15)	-0.13 (1.15)	-0.08 (0.86)	Na	-0.34 (1.21)	-0.67 (1.29)	F(2,115) = 1.720, p=0.184	F(2,101)=2.151, p=0.122
Working memory, mean z-score (SD)	-0.18 (0.77)	Na	-0.25 (0.79)	-0.43 (0.95)	0.02 (0.73)	Na	0.04 (0.80)	-0.03 (0.95)	0.15 (0.95)	Na	-0.12 (1.02)	-0.36 (1.24)	F(2,115) =1.907, p=0.153	F (2,103)=2.963, p=0.056

Abbreviations: Na=not applicable

Values are presented as mean z-score (standard deviation). Differences between groups after the 12-week training period were tested with One-way Analysis of Covariance (ANCOVA). Follow-up effects were tested with mixed-model ANCOVA. P < 0.05; * Bonferroni post-hoc test showed a significant improvement for both the aerobic and the exergame group compared to controls after 12 weeks of training (Δ aerobic versus control: 0.370 [CI: 0.103–0.637], p=0.007; Δ exergame versus control: 0.326 (0.081–0.571), p=0.009; § improvement in psychomotor speed was maintained at 24-week follow-up (Δ aerobic versus control: 0.453 [CI: 0.185–0.722]; Δ exergame versus control: 0.337 [CI: 0.070–0.604]).

Additional file 3. Data of cognitive tests for each intervention group presented as mean (standard deviation)

		T0, pretest	T1, 6-week test	T2, 12-week posttest	F1, 24-week follow-up
Executive function					
Trail making test part B (sec)	Exergame group	166.6 (95.1)	147.1 (98.8)	160.7 (106.2)	178.1 (105.4)
	Aerobic group	155.6 (100.3)	157.6 (95.4)	124.9 (97.9)	141.1 (96.5)
	Control group	165.8 (101.5)	172.6 (114.6)	170.1 (106.8)	166.1 (105.1)
Stroop test speed-accuracy trade off scores	Exergame group	0.35 (0.17)	0.36 (0.18)	0.37 (0.18)	0.34 (0.18)
	Aerobic group	0.37 (0.18)	0.33 (0.15)	0.37 (0.18)	0.32 (0.15)
	Control group	0.32 (0.18)	0.33 (0.21)	0.31 (0.18)	0.29 (0.21)
Letter fluency	Exergame group	19.8 (8.9)	Na	20.9 (10.6)	20.9 (11.2)
	Aerobic group	20.2 (9.1)	Na	22.9 (9.5)	23.5 (12.9)
	Control group	22.0 (11.8)	Na	20.2 (12.0)	21.7 (15.1)
Rule shift cards test	Exergame group	7.8 (4.7)	8.6 (4.7)	8.3 (6.4)	9.2 (5.5)
	Aerobic group	7.8 (3.7)	8.7 (5.8)	8.3 (5.6)	7.6 (4.7)
	Control group	8.1 (5.1)	8.6 (5.7)	8.8 (6.2)	8.9 (6.7)
Psychomotor speed					
Trail making test part A (sec)	Exergame group	55.2 (51.2)	52.7 (42.6)	50.3 (42.0)	55.8 (54.0)
	Aerobic group	45.9 (45.0)	43.1 (42.0)	37.7 (26.9)	38.6 (40.2)
	Control group	48.2 (34.7)	52.4 (47.2)	63.6 (61.0)	68.5 (73.4)
Stroop test word-reading (sec)	Exergame group	41.4 (19.5)	37.4 (10.5)	37.3 (10.3)	41.1 (16.4)
	Aerobic group	37.3 (13.7)	36.7 (10.8)	33.8 (8.5)	35.7 (18.5)
	Control group	36.6 (12.7)	41.3 (19.5)	43.3 (22.6)	49.7 (33.4)
Stroop test color-naming (sec)	Exergame group	55.7 (25.6)	50.2 (16.3)	49.4 (17.9)	55.0 (26.1)
	Aerobic group	45.1 (13.4)	44.1 (14.0)	42.8 (9.9)	44.4 (22.8)
	Control group	52.9 (24.5)	54.0 (24.3)	56.7 (25.9)	61.4 (36.1)
Episodic memory					
Location learning test displacement score trial 1-5	Exergame group	91.0 (35.0)	Na	85.5 (41.7)	96.1 (34.1)
	Aerobic group	95.3 (35.3)	Na	96.6 (41.1)	97.5 (41.3)
	Control group	97.6 (32.0)	Na	107.1 (41.7)	118.8 (51.2)
Location learning test displacement score delayed recall	Exergame group	15.9 (8.5)	Na	16.9 (11.2)	18.5 (8.1)
	Aerobic group	18.8 (9.8)	Na	19.1 (9.9)	19.6 (10.5)
	Control group	18.3 (7.5)	Na	20.0 (10.9)	23.3 (10.8)
Working memory					
Digit span	Exergame group	10.2 (2.8)	Na	10.1 (2.9)	9.6 (3.3)
	Aerobic group	11.1 (2.8)	Na	10.8 (2.8)	11.0 (3.2)
	Control group	11.2 (3.9)	Na	10.8 (4.0)	9.8 (3.6)
Spatial span	Exergame group	8.6 (3.1)	Na	8.3 (3.6)	7.7 (3.8)
	Aerobic group	9.1 (3.1)	Na	9.5 (3.2)	9.4 (12.9)
	Control group	9.9 (3.6)	Na	8.7 (3.6)	9.3 (4.2)

Abbreviations: Na=not applicable

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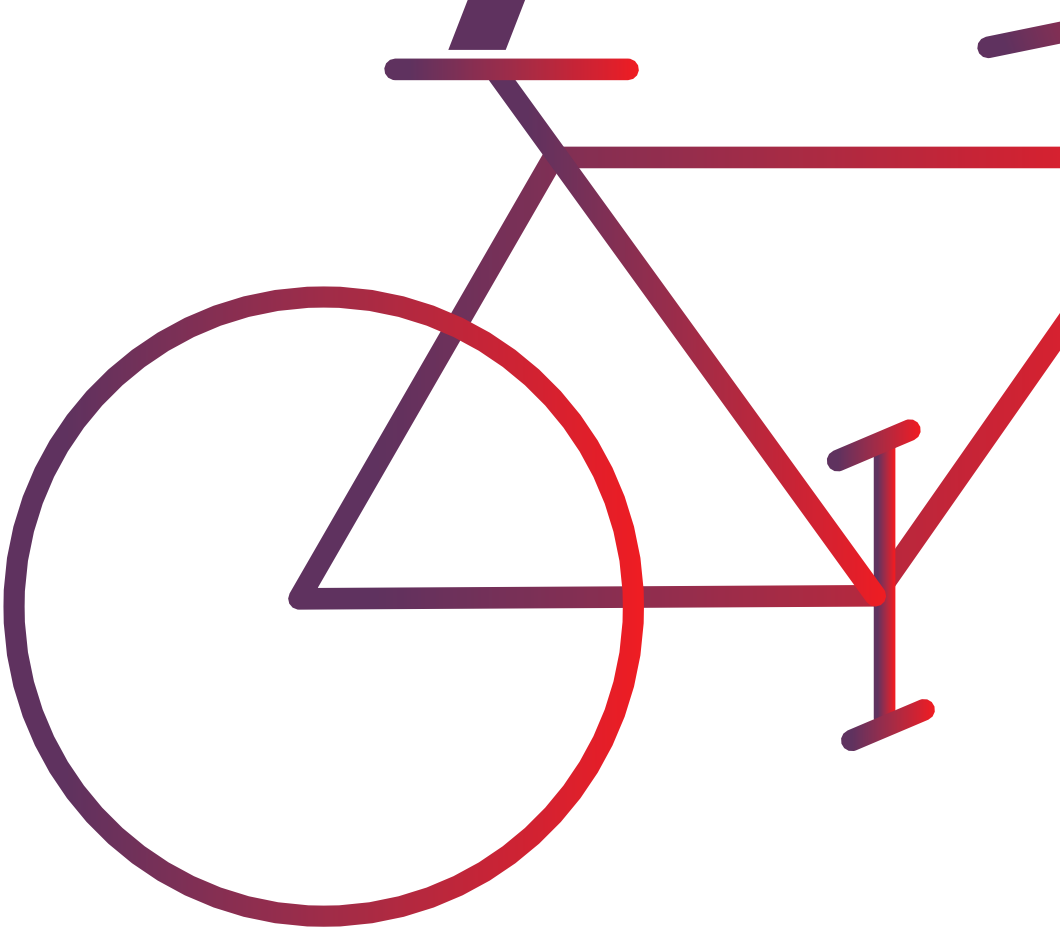

Exergaming as a physical exercise strategy reduces frailty in people with dementia: a randomised controlled trial

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ABSTRACT

Background

People with dementia are known to be physically frailer, more sedentary, and participate less in regular physical exercise compared to their healthy peers. Research has shown that physical activity interventions have potential to reduce the level of frailty in community-dwelling older adults, which suggests that frailty can be counteracted. Exergaming combines physical exercise with cognitive stimulation in a virtual environment. The aim of the current study was to investigate the efficacy of a 12-week exergame training and equally long aerobic training, both compared to an active control group, on frailty in people with mild-to-moderate dementia. In addition, the effects of exergame training on physical functioning, physical activity, and activities of daily living (ADL) were explored.

Methods

A three-armed randomized controlled trial compared exergame training, aerobic training, and an active control intervention consisting of relaxation and flexibility exercises. Individuals with dementia were randomized and individually trained three times a week during 12 weeks. The Evaluative Frailty Index for Physical activity (EFIP) was used to assess the level of frailty at baseline and after the 12-week intervention period. Physical functioning was assessed by performance-based tests, and level of physical activity and ADL were measured using questionnaires. Between-group differences were analysed with analysis of covariance.

Results

Data from 115 people with dementia (mean (SD) age = 79.2 (6.9) years; mean (SD) MMSE = 22.9 (3.4)) were analysed. The exergame group showed higher adherence compared to the aerobic group (87.3% versus 81.1%, p=0.053). A significant reduction on the EFIP was found in the exergame group (EG) compared to the active control group (CG) (mean difference [95%CI] EG versus CG: -0.034 [-0.062; -0.007], p=0.012), with a small-to-moderate effect size (partial η^2 = 0.055). No significant differences between the intervention and control groups were found on physical functioning, level of physical activity, and ADL.

Conclusions

This is the first study to show that a 12-week exergame intervention reduces the level of frailty in people with dementia. This is an important and promising result, since frailty is a powerful predictor of adverse health outcomes, and its reduction may have positive effects on health status. Moreover, exergaming resulted in high adherence rates of physical exercise, which makes it an effective strategy to engage people with dementia in physical activity.

BACKGROUND

People with dementia are known to be physically frailer than their healthy peers, with a reduction in lean mass and increased risk of sarcopenia.[1-4] Also, they are more sedentary and participate less in regular physical exercise,[1,5] which may accelerate the development of frailty and sarcopenia.[6] Research has shown that physical inactivity and sedentary behaviour are associated with negative health outcomes.[7,8] In turn, physical exercise may benefit physical functioning, cognition, daily functioning, and wellbeing in older people with dementia.[9-11] This underlines the clinical importance of promoting physical activity in this group. However, the effects of interventions depend highly on exercise adherence, which proved to be difficult in people with dementia.[12] Exergaming is an innovative and fun way of exercising and may, therefore, be a promising intervention to maintain sustained participation in physical activity in people with dementia.[13]

Exergaming combines physical exercise with cognitive stimulation in a virtual environment.[13] Research has shown that exergaming is a feasible and enjoyable intervention for people with dementia.[14,15] Up to now, only three randomised controlled trials have investigated the effectiveness of exergaming in people with dementia.[16-18] These studies showed some benefit of exergaming on balance[16] and dual-task performance.[18] Previously we demonstrated that a 12-week exergame training programme and an aerobic training programme both improved psychomotor speed in older adults with dementia.[19] The current study will further investigate the potential broader range of effects of exergames for people with dementia, including frailty.

Frailty is characterised by decreased reserves in multiple physiological systems and a reduced capacity to withstand stressors.[1] This results in increased vulnerability to adverse health outcomes and higher care demands.[1] Dementia and frailty are closely linked, as both are strongly associated with age and adverse health outcomes.[20-22] Furthermore, a higher level of frailty is related to a higher risk for developing dementia.[23] Research has shown that physical activity interventions have potential to reduce the level of frailty in community-dwelling older adults,[24] which suggests that frailty can be counteracted. There is also some evidence that multidomain interventions (i.e. including nutritional supplementation and cognitive training in addition to exercise) yield greater benefits than exercise training alone.[25] However, whether exercise or multidomain interventions also reduce the level of frailty in people with dementia is still unknown.

The aim of the current study was to investigate the feasibility and efficacy of a 12-week exergame training and an equally long aerobic training, both in comparison to an active control group, on frailty in people with mild-to-moderate dementia. In addition, the effects of exergame training on physical functioning, physical activity (PA), and activities of daily living (ADL) are

explored. We hypothesised that both exergaming and aerobic training reduce the level of frailty and improve physical performance, and that exergame training would yield greater benefits than aerobic training.

METHODS

Study design

The current study includes secondary outcomes from a previously published 12-week randomised controlled trial with the aim to investigate the effects of an exergame and an aerobic training on cognitive functioning in older adults with dementia.[19] The rationale and design of the study have been published previously.[26] Participants were included from January 2016 to September 2017. The study was approved by the Medical Ethics Committee of Radboud university medical center, Nijmegen, the Netherlands (Dutch Trial Register no.: NTR5581), and was conducted in compliance with Declaration of Helsinki ethical standards. Participants all verbally agreed to participate in the study and gave written informed consent.

Participants and study procedures

Participants were recruited via memory clinics, day care centres, advertisement in local newspapers and word of mouth. Eligibility criteria for inclusion were (1) a clinically confirmed diagnosis of dementia (vascular, Alzheimer or mixed type); (2) an MMSE score of ≥ 17 (8); (3) age ≥ 60 years, and (4) if using anti-dementia medication, a stable dose for at least three months before start of the trial. Exclusion criteria were (1) severe co-morbidity that hindered exercising (e.g. severe musculoskeletal, neurological, cardiovascular disease); (2) currently suffering from a depression, bipolar disorder or psychotic disorder; (3) current drug or alcohol dependency; (4) performing moderate intensity exercise for at least five times a week for 30 minutes; (5) wheelchair bound, and (6) severe hearing or visual problems that could not be corrected with the use of hearing aids/glasses. The study was conducted in community centres in Nijmegen, the Netherlands. Participants were randomly assigned to one of the intervention groups or a control group by an independent statistician. The minimisation method[27] was used to balance groups for gender, severity of cognitive impairment (MMSE ≥ 20 or < 20), use of anti-dementia medication, training location and level of education. The Dutch classification of education levels[28] was used to classify the educational attainment of participants as low (levels 1-3), average (levels 4-5), or high (levels 6-7).

Interventions

The study included two intervention groups (exergame training group (EG) and aerobic training group (AG)), and an active control group (CG). All participants received three training sessions per week for 12 weeks. The EG enrolled in a cognitive-aerobic bicycle training on a stationary

bike was connected to a video screen. The aerobic training component consisted of cycling for 30-50 minutes per session. The aerobic training component was tailored to an individual's fitness level and health status, and aimed to achieve an intensity of 65%-75% of heart rate reserve after 12 weeks of training.[26] For participants who used medication that attenuated heart rate (e.g. beta-blockers), the Borg Rating of Perceived Exertion (RPE)[29] was primarily used to ensure that the intended training intensity was achieved. The cognitive training component consisted of following a route through a digital environment while performing cognitive tasks targeting response inhibition, task switching and processing speed. There were seven different cognitive training levels and the difficulty of the cognitive tasks increased per training level to ensure that the training remained cognitively challenging. A detailed description of the cognitive training component and training levels has been published previously.[26]

The AG performed a cycling training on a stationary bike. This bike was not connected to a video screen. The aerobic training itself was identical to the training described above. Participants in the CG received a thirty-minutes-per-session training that consisted of relaxation and flexibility exercises. The exercises required minimal muscle strength and aerobic capacity and were easy to perform. The level of social engagement was similar to the intervention groups.

Trained students or research assistants gave training sessions on a one-to-one basis. All trainers completed a one-day course to ensure standardisation of the training intervention and recording of data. Subsequently, all trainers were monitored weekly during the entire training period.

Assessments

Full assessments were carried out before (T0) and after the 12-week training phase (T1). Measures of physical functioning and assessment of physical activity levels were also performed at 24-week follow-up (F1).

Assessment of frailty

The Evaluative Frailty Index for Physical activity (EFIP) was used to assess level of frailty.[30] This instrument is developed to evaluate the effect of physical activity on frailty, and previous research demonstrated its reliability and validity.[30] The questionnaire contained 50 items covering the physical domain, psychological domain, social domain, and general health status.[30] The EFIP was calculated for each individual based on the method of deficit accumulation, which expresses the level of frailty as the ratio of actual deficits to the total number of deficits considered.[31] This results in a frailty index with scores ranging from 0.00 to 1.00, with higher scores meaning frailer. The participants filled in the questionnaire themselves, with help of a research assistant. A majority of the questions in the domain general health status (9/16), and a minority of the questions in the physical domain (6/19), corresponded to The Older Persons

and Informal Caregivers Survey Minimum Dataset (TOPICS-MDS),[32] which was filled in by the informal caregiver, or with information from a participant's medical record. These questions only concerned factual information, and were therefore adopted from these other sources. At baseline, frailty was also assessed using the validated TOPICS-MDS frailty index that consists of 45 items containing six components: comorbidities, limitations in activities of daily living (ADL), limitations in instrumental activities of daily living (IADL), health-related quality of life, psychosocial health, and self-rated health.[33]

Assessment of physical functioning

Trained research assistants performed assessments of physical functioning. Physical fitness was measured using the 6-min Åstrand Cycle Ergometer test.[34] This is a submaximal exercise test which estimates the maximal oxygen uptake (VO_{2max}) based on workload and average heart rate during the last two minutes of the test.[34] A participant's heart rate should stabilize in the range of 110 to 170 beats/min in the last two minutes of cycling to be considered a valid test.[35,36] If a valid test was not achieved, data were handled as missing values.

Mobility was assessed with the Timed Up & Go Test (TUG)[37] and the ten-metre Walk Test (10MWT)[38]. The TUG Test measures the time it takes for a person to rise from a chair, walk three metres, turn, walk back to the chair and sit down. Participants were instructed to complete the test at their own pace.[37] The test was performed two times and the mean time in seconds was used. The 10MWT assesses gait speed. Participants were instructed to walk ten metres at a comfortable pace in a straight line, passing a line set at two and eight metres.[38] The test was performed two times and the fastest time in seconds between two and eight metres was noted. As an outcome measure, walking speed (metres per second) between two and eight metres was used.

The five-times Sit to Stand Test (FTSTS) assesses strength and endurance in the lower extremities by measuring the time needed to perform five repetitions of stands.[39] Balance was measured using the Frailty and Injuries Cooperative Studies of Intervention Techniques Subtest 4 (FICSIT-4).[40] Participants were asked to perform four different stances and to hold them for ten seconds: (1) parallel stand, (2) semi-tandem, (3) tandem, and (4) single-leg without assistive device. The score ranges from zero to five with a higher score indicating better performance.[40]

The Short Physical Performance Battery Test (SPPB) measured functional status and physical performance.[41] It is a composite measure assessing three components: (1) the ability to perform the parallel, tandem, and semi-tandem stance for up to ten seconds; (2) time to complete a six-metre walk; (3) time to rise from a chair five times. Scores are given based on the ability and time taken to complete the tasks, and range from zero to four for each task. This results

in a maximum score of 12 and a minimum score of zero, with higher scores indicating a higher level of functioning.[41]

Assessment of physical activity

The Physical Activity Scale for the Elderly (PASE) was used to assess level of physical activity at baseline (T0), after the 12-week intervention period (T1) and at 24-week follow-up (F1).[42] The PASE consists of 12 questions regarding the frequency and duration of leisure activity (e.g. sports, jogging, swimming, strengthening and endurance exercise), household activity and work-related activity. The total score is computed by multiplying either the time spent in each activity (hours per week) or participation (i.e., yes/no) in an activity, by empirically derived item weights and then summing overall activities. Total scores range from zero (no physical activity) to 700 (high levels of physical activity).[42] The informal caregiver filled in the PASE questionnaire.

Assessment of activities of daily living

Activities of daily living (ADL) and instrumental activities of daily living (IADL) were assessed using the Katz index, which is part of the TOPICS-MDS.[32] The informal caregiver filled in the TOPICS-MDS questionnaire before (T0) and after the intervention period (T1). Caregivers were asked if their loved one needed assistance performing 15 different activities. ADL activities included bathing, dressing, eating, toileting, use of incontinence products, and getting up from a chair (transferring). IADL activities included grooming, use of telephone, travelling, shopping, meal preparation, household tasks, taking medications, financial management, and walking. Answers were documented dichotomously (yes, assistance required, no assistance required). All 15-items were summed up resulting in a scale with scores ranging from zero to 15 limitations.[43]

Assessment of adherence

The attendance rate (in %) was defined as the total number of training sessions that were followed divided by the total number of training sessions that were offered to the participant.

Statistical analysis

Socio-demographic and clinical characteristics at baseline were presented using descriptive statistics. Feasibility measures (e.g. adherence to the exercise programme, measures of exercise intensity and rating of the exercise sessions) were compared between the groups with one-way analysis of variance (ANOVA) or independent-samples t-test for normally distributed data, and Kruskal-Wallis Test for not normally distributed data. The TOPICS and EFIP frailty index scores at baseline were correlated using Pearson's correlation coefficient (r).

Analysis of covariance (ANCOVA) was performed to assess the effect of 12 weeks of training on measures of frailty, physical functioning, level of physical activity, and ADL, with post-training

scores (T1) as dependent variables, baseline scores (T0) as covariates and group (exergame training, aerobic training and active control) as between subjects factor. In case of significant group effects, Bonferroni corrected post-hoc tests were performed to adjust for multiple comparisons. Partial eta squared (η^2) was used as a measure of effect size, and classified as small (0.01), moderate (0.09) or large (0.25) using the suggested benchmarks.[44,45] The multiple imputation method[46] was used to account for missing values at T0 and T1 (8.1% of the values missing; 2.3% at T0 and 12.4% at T1). Reasons for missing values were drop-out of participants or not returning the questionnaire. Therefore, we considered our missing data missing-at-random. Characteristic variables of the sample, baseline scores, and training group were included in the imputation model. The following imputation settings were used: automatic model setting, 15 iterations and five imputations.

To investigate follow-up effects of the intervention, we used mixed-model ANCOVA. Variables included in the model were test scores at T1 and FU as dependent variables, group as between-subject factors, time as within-subject factors, and the corresponding baseline measure as covariate. Additionally, a time × group interaction term was added as a fixed effect. Missing data at follow-up were not replaced using multiple imputation because of the mixed-model design which is rather robust for missing data.

Statistical analyses were performed as intention-to-treat analyses, including all participants irrespective of their intervention adherence. Additionally, per-protocol analyses were performed including only those participants that successfully completed the intervention period and all measurements. SPSS 22 was used with two-tailed significance set at 0.05.

RESULTS

Patient flow and baseline characteristics

In total, 307 participants were screened for eligibility, of which 121 participants enrolled in the study. Six participants refused to participate during baseline measurements and the remaining 115 participants were randomized. The dropout rate from allocation to post-intervention assessments at 12 weeks was 12% (N=14). This number did not differ significantly between the groups (11% in the EG, 13% in the AG and 13% in the CG, P=0.930). Figure 7.1 shows the enrolment, allocation process and reasons for dropout. Baseline characteristics for the randomised sample were well-matched between the groups (Table 7.1). Mean (SD) age of included participants was 79.9 years (6.5) with a mean (SD) MMSE score of 22.4 (3.2). Ninety-seven participants (85%) lived independently with or without a spouse.

Valid results of the Åstrand Cycle Ergometer test were available in 25 (22%) participants (eight in the EG, ten in the AG and seven in the CG). Reasons for not achieving the targeted heart rate of 110-170 BPM included limited physical capacity, joint pain or other comorbidities, which made it too hard to keep resistance for six minutes. Other reasons were the use of beta-blockers or other medication that prevented an increase in heart rate during exercise. As a consequence of the low number of valid Åstrand Cycle Ergometer results, we did not perform statistical analyses on this outcome measure.

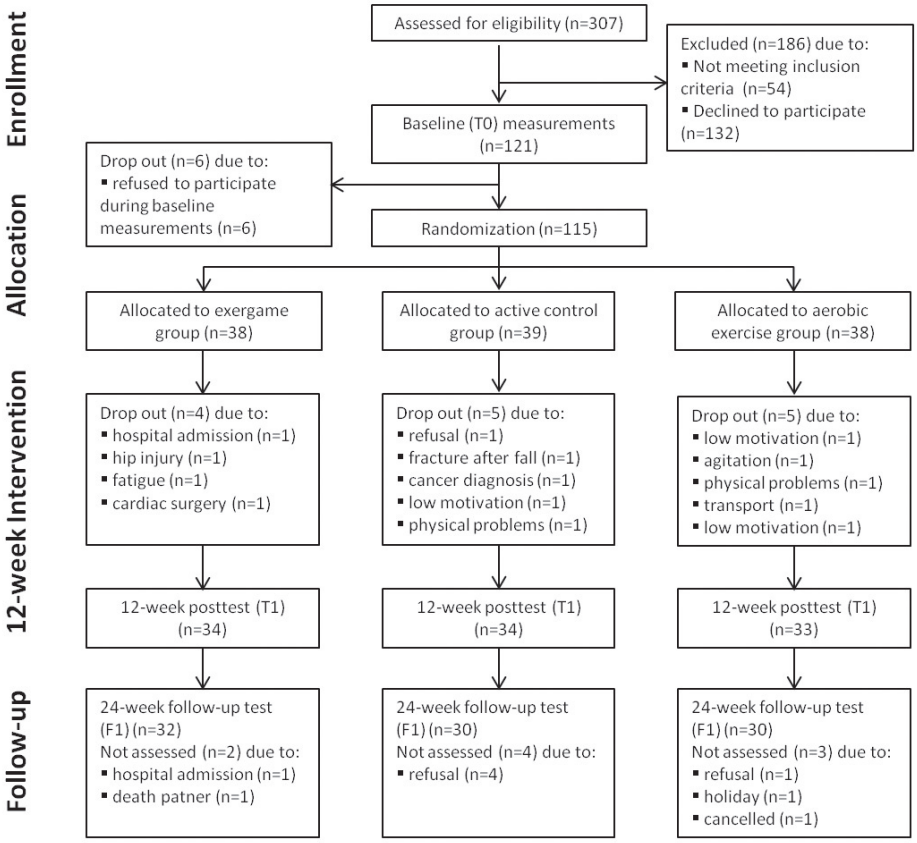

Figure 7.1. Flowchart of participants. Abbreviations: T1, 12-week assessment; F1, 24-week follow-up assessment

Table 7.1. Baseline characteristics of the study population

Variables	Exergame group (n=38)	Aerobic group (n=38)	Control group (n=39)
Age, years, mean (SD)	79.0 (6.9)	80.9 (6.1)	79.8 (6.5)
Men, n (%)	20 (52.6)	21 (55.3)	21 (53.8)
Educational level, n (%)			
Primary school education or lower	6 (15.8)	7 (18.4)	6 (15.4)
Secondary education or vocational training	23 (60.5)	22 (57.9)	22 (56.4)
Higher education	9 (23.7)	9 (23.7)	11 (28.2)
Mini Mental State Examination, mean (SD)[a]	22.9 (3.4)	22.5 (3.1)	21.9 (3.1)
Duration since dementia diagnosis in months, mean (SD)	13.6 (19.9)	13.8 (12.3)	18.9 (22.4)
Living situation, n (%)			
Independent, alone	13 (34.2)	12 (31.6)	9 (23.1)
Independent, with others (e.g. partner, children)	19 (50)	21 (55.3)	24 (61.5)
Care home	3 (7.9)	3 (7.9)	4 (10.3)
Nursing home	2 (5.3)	0	0
Comorbidities, n (%)			
Hypertension	10 (26.3)	16 (42.1)	12 (30.8)
Diabetes	8 (21.1)	10 (26.3)	4 (10.3)
Acute myocardial infarction	5 (13.2)	7 (18.4)	5 (12.8)
Cerebral infarction	8 (21.1)	8 (21.1)	8 (20.5)
Pulmonary disease	5 (13.2)	5 (13.2)	8 (20.5)
Medicine, n (%)			
Dementia drugs	7 (18.4)	8 (21.1)	10 (25.6)
Beta-blockers	16 (42.1)	17 (44.7)	14 (35.9)
BMI, kg/m^2, mean (SD)	26.4 (4.0)	25.4 (3.8)	26.0 (4.8)
Physical performance, mean (SD)			
Timed-up-and-go (sec)	14.0 (5.5)	14.7 (7.2)	14.7 (7.3)
10-m walk test (sec)	6.3 (2.7)	6.1 (1.5)	6.0 (1.8)
5-times-chair-stand (sec)	15.9 (5.7)	17.6 (7.7)	16.8 (5.3)
FICSIT-4[b], mean (SD)	3.6 (1.2)	3.5 (1.3)	3.5 (1.4)
PASE score[c], mean (SD)	74 (61)	72 (65)	53 (36)
Katz Index[d], mean (SD)	5.2 (3.3)	4.5 (3.0)	5.1 (2.9)
EFIP Frailty Index[e], mean (SD)	0.27 (0.12)	0.26 (0.13)	0.23 (0.09)
TOPICS Frailty Index[f], mean (SD)	0.31 (0.11)	0.30 (0.11)	0.28 (0.12)

[a] Scores on the Mini-Mental State Examination range from 0 (severe impairment) to 30 (no impairment); [b] FICSIT-4, frailty and Injuries Cooperative Studies of Intervention Techniques Subtest 4, scores ranging from 0-5; [c] PASE, physical activity scale for the elderly with higher scores indicating higher levels of physical activity; [d] Theoretical range 0–15 and a higher score indicates higher dependency in activities of daily living [e] EFIP, Evaluative Frailty Index for Physical Activity, scores ranging from 0.00 to 1.00 with higher scores meaning frailer; [f] TOPICS-MDS, The Older Persons and Informal Caregivers Survey Minimum Dataset, scores ranging from 0.00 to 1.00 with higher scores meaning frailer

Adherence, intensity, and safety

A non-significant trend was found towards higher adherence in the EG compared to the AG (mean difference [95% CI]: 6.85 [-0.09;13.79], p=0.053, see Table 7.2). Participants in the intervention groups and in the active control condition rated the training sessions positively (see Table 7.2). Training duration, training load, heart rate and rate of perceived exertion did not differ between both intervention groups. The mean training intensity was light in both intervention groups with an average of 41.8% (SD=13.3) and 43.5% (SD=18.2) of maximal heart rate in the EG and AG, respectively. No occurrence of serious adverse events (e.g. events leading to death, hospital admission or persistent disability) related to the exercise interventions were recorded.

Table 7.2. Training characteristics of the study population

Variables	Exergame group (n=38)	Aerobic group (n=38)	Control group (n=39)	Test statistic (df), p-value
Adherence rate, %, mean (SD)	87.3 (13.6)	81.1 (13.7)	85.4 (12.9)	F (2,112)=2.86 , p=0.061*
Duration training session, min, mean (SD)	32.6 (6.0)	30.5 (8.7)	30[a]	t(73)=0.91, p=0.363
Training load, watt, mean (SD)	53.7 (34.9)	51.2 (27.7)	Na	t(65)=0.23, p=0.748
Resting heart rate, beats/min^{-1}, mean (SD)	79.4 (12.1)	77.9 (10.4)	Na	t (67)=0.56, p=0.57
Heart rate during training, beats/min^{-1}, mean (SD)	105.5 (14.8)	103.9 (14.3)	Na	t(67)=0.46, p=0.644
Heart rate difference, beats/min^{-1}, mean (SD)	26.1 (15.1)	26.0 (13.8)	Na	t(67)=0.03, p=0.976
Training intensity[b], % of maximal heart rate, mean (SD)	41.8 (13.3)	43.5 (18.2)	Na	t(39)=-0.35, p=0.730
Rate of perceived exertion during training[c], mean (SD)	13.1 (1.2)	12.8 (1.9)	Na	t(67)=0.74, p=0.465
Rating of training sessions, scale 1-5, Median [interquartile range]	5.0 [4.0-5.0]	5.0 [4.0-5.0]	5.0 [4.0-5.0]	χ^2 (2)=0.43, p=0.805

Abbreviations: Na=not applicable, SD=standard deviation; differences between groups were tested with one-way Analysis of Variance test (three groups) or independent-samples t-test (two groups), if data was normally distributed. If data was not normally distributed, Kruskal Wallis test was performed. For post-hoc comparisons Tukey HSD was performed

[a] All training sessions lasted for 30 minutes, exact time has not been recorded; [b] Training intensity is only calculated for participants that do not use beta-blockers (n=21 and n=20 in the exergame and aerobic group respectively); [c] Theoretical range 6-20 where 6 indicates lowest intensity level and score 20 indicates highest intensity level; *A trend was found towards higher adherence in the exergame group compared to the aerobic group (mean difference [95% CI] 6.85 [-0.09–13.79], p=0.053)

Intention-to-treat analysis

All participants who were originally randomized to the intervention, irrespective of their adherence, were included in the intention-to-treat analysis. A significant reduction on the EFIP was found for the EG compared to the CG after 12 weeks of training (mean difference [95%CI] EG versus CG: -0.034 [-0.062; -0.007], p=0.012, see Figure 7.2). The size of the effect was small-to-moderate (partial $\eta^2 = 0.055$). The EFIP and TOPICS frailty index correlated highly (Pearson's r =0.76, p<0.001). In addition, a trend towards an improvement on the TUG was found for the EG compared to the CG after 12 weeks (mean difference [95%CI] EG versus CG: -1.659 [-3.450; 0.132], p=0.065), with a small effect size (partial $\eta^2 = 0.042$). There were neither significant between-group differences on our second measure of mobility (10MWT), on measures of strength (FTSTS), balance (FICSIT-4), nor on our global measure of functional status (SPPB). No significant differences were found between the groups on basic and instrumental ADL (Katz index) and level of physical activity (PASE). Follow-up analysis showed that the small effect on the TUG test and PASE was not maintained at 24-week follow-up. Test scores per group and time point are presented in Table 7.3.

Per-protocol analysis

In the per-protocol analyses, 14 participants were excluded because they did not complete the 12-week intervention period. The remaining 101 participants were included in this analysis. The results of the per-protocol analyses were partly in line with the intention-to-treat analyses, with a positive non-significant trend in the EG compared to the CG on the EFIP (mean difference domain score [95%CI] EG versus CG: -0.035 [-0.070; 0.001], p=0.059]. There was no clear trend on the TUG (Δ EG versus CG: -1.698 [CI -3.944;0.548], p=0.136). No between-group differences were observed on other measures of physical functioning and ADL. At follow-up, there were nine additional drop-outs, which led to inclusion of 92 participants in the follow-up analysis. We did not find any between group differences at follow-up.

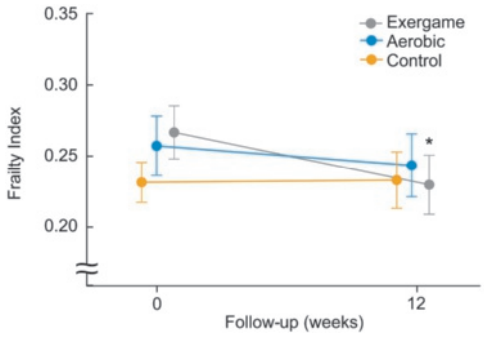

Figure 7.2. Mean z-scores and standard error of the mean (SEM) at baseline and after 12 weeks for the evaluative frailty index for physical activity (EFIP). Arrows represent SEM; * significant reduction (p<0.05) of frailty score in exergame group compared to controls after 12 weeks

Table 7.3. Test scores on the different outcome measures per time point

	Exergame group (n=38)			Aerobic group (n=38)			Control group (n=39)			F test value (df), p-value	
	T0	T1	F1	T0	T1	F1	T0	T1	F1	T0-T2	T2-F1
EFIP score	0.27 (0.12)	0.23 (0.12)	Na	0.26 (0.13)	0.24 (0.13)	Na	0.23 (0.09)	0.23 (0.12)	Na	F(2,115)=3.229, **p=0.043***	Na
10-meter-walk-test (m/s)	1.07 (0.34)	1.12 (0.37)	1.02 (0.33)	1.05 (0.27)	1.02 (0.30)	1.05 (0.41)	1.09 (0.33)	1.01 (0.31)	1.00 (0.30)	F(2,115)=2.290, p=0.106	F(2,102)=1.155, p=0.319
Timed up-and-go (s)	14.1 (8.0)	13.0 (4.2)	13.8 (5.5)	14.7 (7.2)	15.1 (6.6)	13.6 (5.3)	14.1 (5.5)	15.0 (7.5)	14.7 (7.3)	F(2,115)=2.799, p=0.065	F(2,109)=0.930, p=0.398
5 times-sit-to-stand (s)	17.3 (7.6)	14.7 (3.9)	15.9 (5.7)	17.6 (7.7)	16.3 (7.1)	16.0 (6.9)	16.8 (5.3)	16.3 (7.7)	17.9 (10.1)	F(2,115)=1.441, p=0.241	F(2,114)=1.471, p=0.234
FICSIT-4 score	3.6 (1.2)	3.8 (1.1)	3.8 (1.1)	3.5 (1.3)	3.4 (1.3)	3.6 (1.3)	3.5 (1.4)	3.7 (1.3)	3.7 (1.4)	F(2,115)=1.108, p=0.334	F(2,109)=1.018, p=0.365
SPPB score	8.9 (2.2)	9.5 (1.8)	9.3 (2.2)	9.2 (2.3)	9.2 (2.6)	9.3 (2.4)	8.8 (2.3)	9.2 (2.4)	9.0 (2.2)	F(2,115)=1.767, p=0.175	F(2,112)=1.7789, p=0.172
PASE score	66.5 (55.6)	78.6 (60.1)	65.5 (55.5)	74.2 (61.2)	89.4 (78.5)	72.4 (51.4)	52.9 (36.5)	55.1 (44.2)	54.2 (45.1)	F(2,115)=1.675, p=0.192	F(2,106)=1.362, p=0.260
Katz-index	5.2 (3.3)	4.9 (3.3)	Na	4.5 (3.0)	5.0 (3.4)	Na	5.0 (2.9)	5.8 (3.5)	Na	F(2,115)=2.166, p=0.119	Na

Abbreviations: Na=not applicable; EFIP, Evaluative Frailty Index for Physical Activity, scores ranging from 0.00 to 1.00 with higher scores meaning frailer; FICSIT-4, frailty and Injuries Cooperative Studies of Intervention Techniques Subtest 4, scores ranging from 0-5; PASE, physical activity scale for the elderly with higher scores indicating higher levels of physical activity; Katz index theoretical range 0–15 and a higher score indicates higher dependency in activities of daily living.

Values are presented as means ± SD. Differences between groups after the 12-week training period were tested with One-way Analysis of Covariance (ANCOVA). Follow-up effects were tested with mixed-model ANCOVA. P < 0.05; * Bonferroni post-hoc test showed a significant reduction in EFIP score in the exergame group compared to control group after 12 weeks of training (Δ exergame versus control: -0.034 [CI:-0.062 – -0.007], **p=0.012**.

DISCUSSION

This study is the first to show that a 12-week exergame intervention reduces the level of frailty in people with dementia. This is an important and promising result, since physical frailty is a powerful predictor for adverse health outcomes, and reducing frailty could have positive effects on health status.[1,2,4] Furthermore, we found a trend-level improvement on the Timed Up & Go Test in the exergame group compared to controls. No significant improvements were observed on other measures of physical functioning, level of physical activity and ADL.

Interpretation of results and comparison with previous research

A significant reduction on the frailty index was only measured in the exergame group after 12 weeks and not in the aerobic group. In the current study, frailty was scored using multiple dimensions, including the physical domain, psychological domain, social domain, and general health status.[30] The current exergame training protocol, in which physical exercise was combined with cognitive stimulation, may have potentially influenced multiple domains, whereas the aerobic training protocol may have only affected the physical domain in the frailly spectrum. This could explain why the total frailty score was not reduced in the aerobic group. Moreover, the adherence rate in the exergame group was higher compared to the aerobic group, suggesting a better clinical feasibility in light of programme compliance. Programme compliance may be a prerequisite for influencing frailty, and is an important outcome of this study as it is often challenging to realize high programme adherence to exercise interventions in people with dementia.[12]

It is unknown what the clinical value of the current 10% reduction in physical frailty score is. A previous study, that investigated the effect of a six month physical therapy strategy on frailty in community-dwelling older adults with mobility problems found a similar reduction on the EFIP between intervention and control group and, moreover, was cost-effective.[47] Since similar findings were found in an older patient group without dementia using a different training intervention, future research is needed to assess the dose-effect relation of training and to study cost-effectiveness of reduction in frailty in a dementia sample.

Contrary to our hypothesis, we found limited benefits of exergame and aerobic training on measures of physical functioning. Only in the exergame group we found a non-significant trend on the TUG test. Aerobic training, in contrast, did not lead to trend level changes on any of the measures of physical functioning, which is inconsistent with findings from previous research.[9,36] A recently published meta-analysis showed that physical exercise improves strength, balance, mobility, and endurance in people with dementia.[9] Illustrative was that positive motor function results were related to the specificity of the training programme.[9] For example, trials that

reported positive results on walking endurance included walking sessions, and trials that reported improvement in lower limb strength included lower limb strength training.[9] Our intervention consisted of aerobic bicycle training, with or without a cognitive dual-task. The used measures of physical functioning were not one-to-one related to the specific exercise used in the current intervention, which may explain that potential effects did not show.

In addition, previous research suggest that baseline physical fitness may influence training outcome, with poorer physical function being a determinant of better results after exercise training.[9] 85 percent of the participants included in the current study were community-dwelling. Compared to nursing-home residents, community-dwelling participants have better baseline physical functioning.[48] Therefore, there may have been less room for improvement in these participants and possible benefits of physical exercise training may be less pronounced.[9] This might explain our contrasting findings with the previous study of Bossers et al.,[49] which showed that a nine-week aerobic and strength-training programme improved walking endurance, muscle strength, and balance, in nursing home residents with dementia. Moreover, the tests used to measure physical functioning have shown to be reliable outcome measures in exercise intervention trials for older adults with mild to moderate dementia.[50] However, for most of these tests the standard error of measurement and minimal detectable change were large, which limits their sensitivity to detect changes over time.[51]

There was no increase in level of physical activity due to exercise training, which is largely in line with previous research.[52,53] There is only one study that reported improvement in physical activity levels after a three month resistance and functional training,[54] measured using the Physical Activity Questionnaire for the Elderly.[55] In the current study the Physical Activity Scale for the Elderly (PASE) was used to assess physical activity level.[42] Since questionnaires that assess physical activity level have shown limited reliability and validity,[56] results have to be interpreted with caution. Future studies should include objective measures of physical activity (i.e. accelerometry) to determine effects of exercise training.

Moreover, we found no improvement in ADL after a 12-week exergaming or aerobic training. A previous meta-analysis presented weak evidence supporting the use of exercise training for improving ADL measured using the Barthel index,[9] but the low quality of evidence and high heterogeneity across the included studies complicate interpretation of these results.[9] In the current study, the widely used 15-item Katz index was used to measure ADL and IADL performance. It should be noted though that despite being widely used, the discriminative ability of this index in a community-dwelling setting has been criticised,[43] stressing that our results need to be interpreted with caution.

Strengths and limitations

The relatively large sample size and high adherence rate in all intervention groups are strengths of the current study. However, some limitations should be taken into consideration. It is important to note that participants were not blinded to the intervention, which is an unavoidable limitation of exercise trials. However, due to practical and safety reasons, we were also not able to blind the outcome assessors, as they were research assistants and caregivers of the participants, both closely involved in organizing and administering the interventions. Furthermore, caregivers who completed a proxy-report for physical activity level and ADL might not always have been up-to date with patients' actual daily routines and activities, which may have biased the results. Another limitation is that only people with dementia who were mobile and motivated enrolled in the study, which limits generalizability of our results. Furthermore, the Åstrand Cycle Ergometer test was not a feasible measurement tool in the current sample and consequently resulted in high numbers of missing data and the absence of a good measure of physical fitness. In addition, reliability and validity of the EFIP as a measure of frailty has not yet been evaluated in dementia patients. To date, however, this is the only measure available for evaluating the effect of a physical activity intervention on frailty. The correlation between EFIP scores and the validated TOPICS-MDS frailty index[33] at baseline was strong, therefore EFIP scores appear valid in our dementia sample. We showed that the use of the EFIP was feasible, as all people with dementia were able to complete the process, and the procedure was efficient, safe, and low in cost.

Clinical relevance

The current 12-week exergame training resulted in high adherence rates and led to a reduction in frailty as measured on multiple dimensions. These are clinically important findings, as frailty is a powerful predictor of adverse health outcomes, and a reduction in frailty may have positive effects on health status. Moreover, this finding underlines the potential of gamified stimulating physical and cognitive activities in people with dementia. Future research should focus on defining criteria for clinically relevant changes of physical frailty and examine long-term exergame compliance.

CONCLUSIONS

Exergaming is a feasible, innovative and above all positively rated exercise method for people with dementia, thereby opening a low threshold opportunity to engage people with dementia in physical activity. The adherence rate in the exergame group was higher compared to the aerobic group, suggesting better clinical feasibility. Moreover, we found that a 12-week exergame intervention reduces level of frailty in a dementia sample. These beneficial effects of exergaming in people with in dementia warrant further innovation, implementation and evaluation of exergaming dementia health care.

Abbreviations

MMSE: Mini Mental State Examination
RCT: Randomised Controlled Trial
EFIP: Evaluative Frailty Index for Physical activity
TOPICS-MDS: The Older Persons and Informal Caregivers Survey Minimum Dataset
TUG: Timed Up & Go Test
10MWT: Ten-metre Walk Test
FTSTS: Five-times Sit to Stand Test
FICSIT-4: Frailty and Injuries Cooperative Studies of Intervention Techniques Subtest 4
SPPB: Short Physical Performance Battery
PASE: Physical Activity Scale for the Elderly
ADL: Activities of Daily Living
IADL: Instrumental Activities of Daily Living

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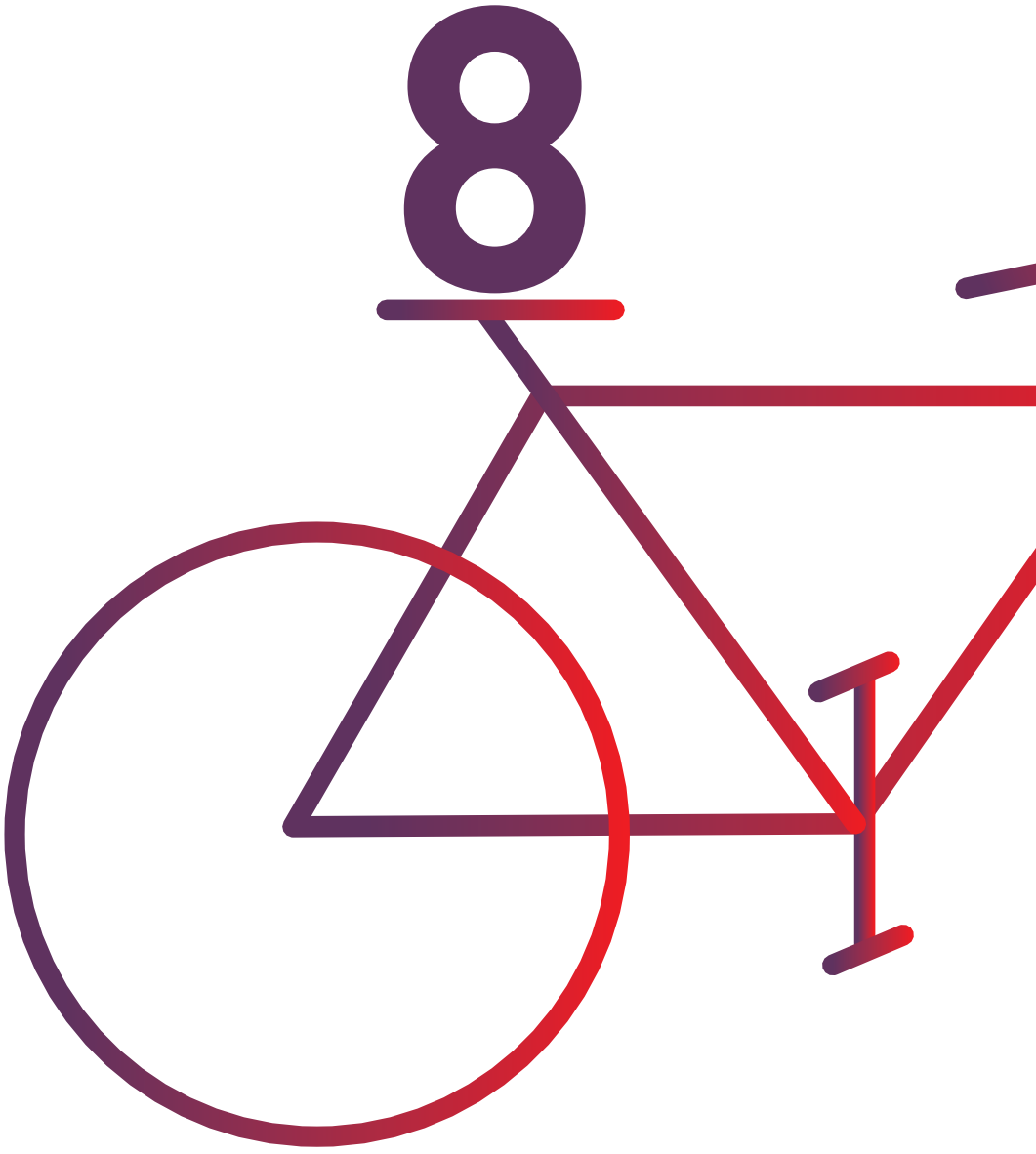
8

Summary and discussion

SUMMARY OF THE MAIN FINDINGS

The main objective of my thesis was to investigate the role of physical activity (PA), with or without cognitive stimulation, with the aim to reduce the rate of cognitive decline in people with dementia. Furthermore, the effects of training on frailty, physical functioning, level of PA, and activities of daily living (ADL) were examined. To put these results in perspective to clinical practice, we studied PA levels and sedentary behaviour in our sample of people with dementia. In addition, barriers, motivators, and facilitators that either hamper or promote PA participation of people with dementia were explored. This chapter starts with a summary of the main findings of the previous chapters. Subsequently, the results of the studies described in this thesis will be discussed. Methodological considerations of the studies, feasibility of exergame interventions and recommendations for future research will be addressed. In conclusion, clinical implications of the main findings will be discussed.

In **chapter 2** PA and sedentary behaviour characteristics of ambulatory and community-dwelling individuals with dementia were compared to cognitively healthy age-, sex- and weight-matched controls. A total of 45 people with dementia and 49 controls wore a wrist accelerometer for seven days to assess sedentary time, sedentary bout duration and time spent in very light, light-to-moderate and moderate-to-vigorous physical activities. Results showed that sedentary time and sedentary bout duration were significantly higher in the participants with dementia compared to controls. In addition, dementia patients spent a lower percentage of their waking time in light-to-moderate and moderate-to-vigorous intensity physical activities. This finding may have clinical relevance, given the observation that sedentary behaviour and little PA independently predict all-cause mortality and morbidity.

To gain more insight into the reasons why people with dementia are more sedentary and less physically active, the study in **chapter 3** was carried out. In this explorative study, community-dwelling people with dementia, their informal caregivers, and an expert group of physiotherapists ranked barriers, motivators, and facilitators that hamper or promote PA participation for people with dementia. Results revealed that people with dementia and their informal caregivers selected only motivators and facilitators as being important for PA participation, with the motivator *"beneficial health effects"* considered the most important. In contrast, the experts had a different perspective on PA participation; five out of the top-ten ranked items were barriers for PA participation. This could be explained by the more critical role of a therapist, focussing on symptom control and treatment of disability, in this case, the elimination of barriers to maintain PA participation in their patients. In addition, we found a strong focus on individual characteristics that influence PA behaviour, which warrants personalised interventions to promote PA in people with dementia.

The second part of the thesis studied the efficacy of exercise interventions in people with dementia. To start, **chapter 4** presents the results of a meta-analysis performed to quantify the overall effect of combined cognitive and physical exercise interventions on global cognitive function in older adults with Mild Cognitive Impairment (MCI) or dementia. Ten Randomised Controlled Trials (RCTs) were included that all applied a combined cognitive-physical intervention in older adults with MCI or dementia, and used cognitive functioning as an outcome measure. Primary analysis showed a small-to-medium positive effect of combined cognitive-physical interventions on global cognitive function. In addition, a moderate-to-large positive effect on ADL and a small-to-medium positive effect on mood were found. However, there was considerable heterogeneity in the included studies regarding the intervention characteristics (e.g. type of training, separate or dual-task, intervention period, frequency, duration) and used outcome measures that need to be considered. Results of this meta-analysis illustrate the importance of combined interventions to help delay the progression of MCI or dementia, though there is a need for future well-designed RCTs with a multi-arm design to investigate the potential superiority of combined interventions over single cognitive or physical interventions. Furthermore, future studies should include extensive neuropsychological assessments to gain more insight into the beneficial effects of combined motor-cognitive training for the different cognitive domains. In this context we developed an RCT. **Chapter 5** presents the study protocol of this RCT, and contains a detailed description of the rationale, design and methods. The primary objective was to study the effect of a 12-week combined motor-cognitive exergame training and aerobic training on cognitive functioning in older adults with dementia. The study design was a three-armed RCT with two experimental intervention groups (exergame and aerobic training) and one active control group (stretching and toning). People with dementia were randomised and individually trained three times a week over 12 weeks. Outcome measures were assessed at baseline, after the 12-week intervention period, and at 24-week follow-up. The primary outcome measure was objective executive function. Secondarily, the cognitive domains of episodic memory, working memory and psychomotor speed were evaluated. In addition, the effect of the different training regimes on frailty, physical functioning, level of PA and ADL were explored.

In **chapter 6** and **chapter 7** the results of this RCT are presented. **Chapter 6** investigated the effect of exergame training and aerobic training on cognitive functioning in older adults with dementia. In total, 115 participants enrolled in the study (mean (SD) age = 79.2 (6.9) years; mean (SD) MMSE = 22.9 (3.4)). Cognitive functioning was measured by neuropsychological assessment. Results showed no effect of exergame or aerobic training on the primary outcome measure of executive functioning after 12-weeks of training. Significant improvement on the secondary measure of psychomotor speed was found for both the aerobic and the exergame group compared to controls. Moreover, we showed that exergaming was a feasible and highly appreciated exercise method to engage older adults with dementia in physical exercise. The

aim of the study presented in **chapter 7** was to investigate the efficacy of a 12-week exergame training and an equally long aerobic training, both in comparison to an active control group, on frailty in people with dementia. In addition, the effects of training on physical functioning, level of PA, and ADL were explored. Results showed a significant reduction in level of frailty measured with the Evaluative Frailty Index for Physical Activity (EFIP) in the exergame group compared to controls. This is an important and promising result since frailty is a relevant predictor for adverse health outcomes. No significant differences between the intervention and control group were found on measures of physical functioning, level of PA, and ADL. In light of the above-mentioned, the general discussion focuses on conclusions that can be drawn from these findings, their clinical implications, and gives a glance towards future research.

General discussion

Taking the findings of the current thesis as a whole, two main conclusions can be formulated, which are: 1) people with dementia are more sedentary and participate less in PA compared to their cognitively healthy peers; 2) exergaming is a feasible, innovative and above all positively rated exercise method to engage people with dementia in physical exercise.

Conclusion 1 may have clinically important consequences, since sedentary behaviour and physical inactivity independently predict all-cause mortality and morbidity,[4-6] and are associated with lower cognitive performance.[7,8] Physical activity may have beneficial effects on cognitive and physical abilities of people with dementia,[2,9] which can lead to functional improvements.[9] Exercise-based therapy may therefore improve health status for people with dementia, however high adherence to the intervention is a prerequisite, which proved to be difficult.[10] Adherence to exercise interventions varies widely across studies and ranges from 33%[11] to 91%[12]. A combination of fixed factors (e.g. exercise history, ill health, education or environment) and modifiable factors (e.g. intervention design, support strategies) can influence adherence to exercise interventions.[13,14] Wide ranges of adherence support strategies (e.g. individual tailoring, goal setting, support to overcome exercise barriers, individual supervision) are being included in exercise interventions for people with MCI or dementia, but the evidence regarding their effectiveness is limited.[10] Results from the study presented in **chapter 3** showed that people with dementia, their informal caregivers, and professionals all considered intrapersonal factors to be most important for PA participation. Thus, a personalised approach should be considered an important adherence-support-strategy to promote PA.

An important note in light of conclusion 2 is that the fun and interactive aspects of exergaming led to more engagement in physical exercise, as confirmed by our finding that the exergame group showed higher adherence rates compared to the aerobic group (87.3 *versus* 81.1%, P=0.053). Additionally, trainers who individually guided training sessions reported that it was easier to motivate participants in the exergame group and to increase duration of the training

sessions. Consequently, exergaming seems to be an effective method to stimulate long-term PA participation in people with dementia. In addition, exergaming offers an enriched environment in which physical exercise and cognitive stimulation are combined, which has been proposed to improve brain functioning.[15,16] However, the current study in a heterogeneous sample of people with different types of dementia did not show evidence for an added value of exergaming over aerobic training with regards to improved cognition. To achieve additional cognitive benefits of exergaming, the intervention may need to be implemented earlier in the disease process (e.g. patients with mild-cognitive impairment) or as preventive method in healthy older adults.[17]

Box "Critical reflection"

In the past four years the literature in the field of exercise in dementia has increased rapidly. In March 2018, the BMJ published the Dementia And Physical Activity trial (DAPA).[1] Since this is the largest exercise study for people with dementia to date, findings from this paper will probably have a significant impact on the field. The DAPA trial included 494 community dwelling people with dementia mean (SD) age 77 (79) years, 61% men) who were randomized into a 4-month supervised exercise programme followed by an 8-month unsupervised exercise period (N=329) or a usual care control group (N=165). The primary outcome measure was score on the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) after 12 months, with higher scores indicating worse performance. After 12 months, there was a significantly larger increase in ADAS-Cog score in the exercise arm compared to the usual care arm. The authors conclude that a moderate-to-high intensity aerobic and strength training programme does not slow cognitive impairment in people with mild to moderate dementia, and might even worsen cognitive function. Although the results of previous studies on the effectiveness of exercise interventions are mixed [2,3], the DAPA study is, to the best of my knowledge, the first published trial that shows negative effects of exercise training on cognition among people with dementia. However, the trial suffers from a number of methodological concerns that lead us to question the results and overall conclusion of the DAPA trial. First of all, a 4-month supervised group-based exercise programme was conducted. Cognitive functioning was not evaluated directly after the intervention period, but only after 6 and 12 months. A gap of 8-months without any supervised exercise may have undermined the results of the 4-month intervention. Furthermore, the compliance of the supervised exercise training was low (67.7%) and no activity logs were collected during the 8-month unsupervised training period making adherence to this proportion of the programme unknown. In addition, there is no information on possibly compensatory behaviour after exercise (i.e. being more inactive during the rest of the day) that could counter the effects of the intervention. Also, the ADAS-Cog is potentially a less sensitive measure than a more extensive neuropsychological assessment. Given these methodological concerns, we believe that the main conclusions of the authors are unfounded. The DAPA trial shows us that there are a lot of methodological challenges we need to face

when conducting an exercise study in dementia, and a number of lessons can be learned from this study. A first lesson is that it is essential to carefully monitor exercise participation during but also after a supervised training period. This information is needed to draw conclusions about the effects of exercise. A second lesson is that group-based training may not be the best training regime to achieve a high adherence in people with dementia, as it is not possible to adapt the training to someone's ability. Individual training may also positively impact the level of confidence a participant has about being able to carry out the intervention. In our study, training sessions were given on a one-on-one basis and the adherence rate was much higher. A third lesson is that participants with mild-to-moderate dementia, especially those with lower MMSE scores, might not be able to adhere to an unsupervised exercise programme. Therefore, an unsupervised home-based exercise programme does not seem to be a feasible training method for this group. These lessons learned from the DAPA trial can be used for future studies or exercise prescription in dementia.

Theoretical considerations

In the introduction a model was presented that showed hypothesised pathways on how motor-cognitive training and aerobic training elicit cognitive effects (Figure 1.2). In this section an adjusted model based on the main findings of our study is introduced (Figure 8.1). Our study demonstrated that both an exergame and aerobic training improve psychomotor speed (see pathway C in figure 8.1). Contrary to the hypothesis, we were not able to provide evidence that exergaming was superior to aerobic training. Possible explanations for this finding may be the presence of (1) dual-task or switch cost (i.e. performance decrements in the motor task, the cognitive task, or in both tasks when two tasks are performed simultaneously)[18] and (2) prioritisation effects (i.e. prioritising either the motor or cognitive task) that can occur in simultaneous motor-cognitive training.[19] These effects vary individually and may have influenced results of the intervention. However, when the cognitive task is "incorporated" into the motor task (which can be observed in the exergame intervention) one would not expect prioritisation effects to occur.[19] In the current study, we found no differences in training characteristics (e.g. duration, intensity) between the aerobic and exergame group. Furthermore, we observed adequate skill acquisition on the cognitive task in the exergame group. Therefore, it is not likely that dual-task cost fully explains the lack of additive effect of exergaming. Other possible explanations are related to the used intervention and selected outcome measures. These will be discussed in the section methodological considerations.

Furthermore, we were not able to show that improvement in psychomotor speed is mediated by improvement in physical functioning as we had expected (see pathway A and B in Figure 8.1). No significant improvements were found on any of the measures of physical functioning (see pathway A in Figure 8.1). Based on previous research, possible neurobiological mechanisms

underlying improved cognitive function in response to exercise training include increased hippocampal neurogenesi,[20] brain angiogenesis,[21] and synaptic plasticity[22] elicited by an increased expression of neurothropic factors such as Brain Derived Neurothropic Factor (BDNF), Insulin Growth Factor 1 (IGF-1) and Vascular Endothelial Growth Factor (VEGF). In the studies presented in this thesis no data were collected with the specific aim to increase our understanding of these underlying mechanisms, such as blood markers (e.g. BDNF, IGF-1) or neuroimaging. As a result, we can only speculate on potential pathways. Gaining more insight in underlying mechanisms is a recommendation for future research.

In contrast to the hypothesis, ADL did not improve after a 12-week exergame or aerobic training (see pathway D in Figure 8.1). We found a decrease in frailty scores in the exergame group, but not in the aerobic group (see pathway E in Figure 8.1). This effect was not mediated by improvements in physical and cognitive performance. In this study, frailty was scored using multiple dimensions, including the physical domain, psychological domain, social domain, and general health status.[23] The current exergame training protocol, combining physical exercise with cognitive stimulation, may have potentially influenced multiple domains, whereas the aerobic training protocol may have solely affected the physical domain in the frailty spectrum. This could explain why the total frailty score was not reduced in the aerobic group.

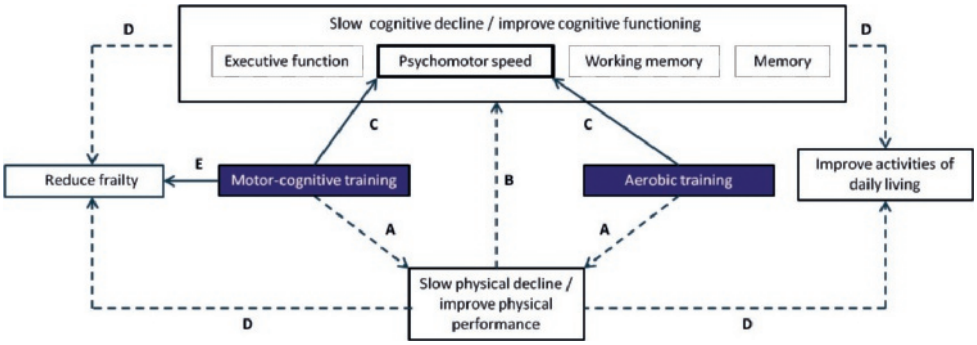

Figure 8.1. Adjusted model that was presented in Figure 1.2 in the introduction, illustrating the main findings of this thesis. A 12-week motor-cognitive (exergame) training and aerobic training improve psychomotor speed and this effect was not mediated by improved physical performance (A, B, C). Motor-cognitive training was not superior to aerobic training (C). Only motor-cognitive training reduced the level of frailty (E), which was not mediated by improved physical or cognitive performance (D). There were no improvements found on activities of daily living (D).

Methodological considerations

Outcome measures

Selection of appropriate outcome measurements in clinical trials is essential. In the current trial a comprehensive neuropsychological assessment was used, covering the domains of executive function, psychomotor speed, working memory and episodic memory, to evaluate which cognitive domains benefit most from the intervention. For most of the neuropsychological tests that we used, psychometric properties were good, but only available for cognitively unimpaired older people or specific patient groups (e.g. stroke patients, patients with Parkinson disease), and not for patients with dementia. This may impact the reliability and validity of the measurements in dementia patients. In a dementia sample, repeated assessments may be complicated to interpret due to fluctuations in cognitive functioning.[24] This, in turn, makes is difficult to assess the test-retest reliability in a dementia population and, consequently, the sensitivity of specific tests to measure change over time. Currently, the type of cognitive measures used varies widely across intervention studies which hampers comparability of outcomes of clinical trials and may partly explain the ambiguous results between studies.[25] Specifically, a majority of clinical trials studying the benefits of exercise or combined interventions in people with dementia included only a global measure of cognitive function, for example the MMSE, as their primary outcome measure.[2,16] These tests, developed as a screening method, are not sensitive to change over time, and suffer from other psychometric shortcomings.[26-28]

Although our sample included persons with a mild to moderate stage of dementia, a relatively large number of participants was not able to perform certain cognitive tests (up to one third). In particular neuropsychological tests that assessed higher-order executive functions such as mental flexibility and set shifting (Trail Making Test, Rule Shift Card Test) and response inhibition (Stroop Color Word Test) proved to be difficult. Even though care was taken to select tests or adapt existing tests for use in severely cognitively impaired individuals, participants did not always understand the instructions or could not complete the tests in the allocated time frame. This led to floor effects in some patients or resulted in missing data. This has especially affected our primary outcome measure, objective executive function. This outcome measure was selected since a decline in executive functioning is an important predictor for functional decline,[29] and in healthy older adults PA and combined motor-cognitive interventions have been found to benefit executive functions.[30,31] Executive function is an umbrella term and consists of various higher-order cognitive control processes.[32] Tests assessing executive functions are by definition more complex than for instance episodic memory tests, as instructions are related to specific higher-order rules, abstract reasoning or mental flexibility. Especially in a dementia sample, changes in executive function are difficult to assess, as executive function is already affected in an early stage of the disease. [33] This hampers the adherence and understanding of more abstract task instructions. Also, one could argue whether it is still possible to improve

executive functions in people with dementia – and measure such an improvement. It may be more meaningful to focus on cognitive functions that are still largely intact, such as alertness or processing speed. Poor processing speed is a predictor for functional decline in basic and instrumental activities of daily living,[34] and improvement in this domain may therefore be clinically relevant. Contrary to executive function, there were no floor effects for psychomotor speed tests and these tests showed to be responsive to measuring change over time. Focussing on functions that are still largely intact also seems more in line with the wish of the persons affected by dementia. Previous research shows that people with dementia tend to focus on positive characteristics that are largely unaffected by the disease, and by doing so maintaining feelings of continuity and self control.[35] This view has been confirmed by the findings of our qualitative study presented in **chapter 3** that showed that people with dementia only selected motivators and facilitators as being important for PA participation.

In light of the sections above, we advocate for the use of a more comprehensive neuropsychological assessment, carefully selecting outcomes that are feasible, reliable and valid in people with dementia. Ideally, consensus on a core-set of standard neuropsychological tests should be reached, which can be used in RCTs in people with dementia.

Intervention

The exergame intervention that was developed for our RCT consisted of seven cognitive training levels, which have been described in depth in our protocol paper **(chapter 5).** The difficulty of the cognitive tasks increased per level to ensure that the training remained cognitively challenging. The first two training levels focused on attention, in the third level response inhibition was introduced and in level six mental set-shifting was added. There were no floor effects for the cognitive stimulation activity and about half of the participants was able to complete the highest levels, thus proving that skill acquisition was present. This showed that the intervention was feasible in people with dementia. However, it remains unknown whether the intervention characteristics (e.g. content of motor-cognitive exergame, frequency and duration) were optimal to reach synergistic effects of combined motor-cognitive training. Previous studies showed that a 3-month virtual-reality bicycle training improved executive function compared to traditional exercise in cognitively healthy older adults and persons with MCI.[36,37] This suggests that an exergame intervention does not necessarily need to be cognitively challenging to reach synergistic effects. Therefore, our lack of effect is probably not related to the content of the exergame intervention.

Generalisability of the presented work is limited to a specific group of people with dementia. Only people with dementia who were mobile and motivated enough could enrol in our study. In addition, more than 85% of the participants was community dwelling and all had a minimum MMSE score of 17 (with a mean MMSE of 22.9; SD=3.4), excluding persons in the severe stage

of dementia. The exergame intervention may, however, also be applicable for a larger group. Due to the different cognitive training levels, and an increase in difficulty of the cognitive tasks per level, the intervention may also suit people with more severe stages of dementia who are institutionalised. In addition, the exergame intervention may also be suitable for people with dementia who are immobile or wheelchair-bound, since the home-trainer can be replaced by a motorised movement therapy device (MOTO med) in which participants remain in sitting position.

Feasibility of exergaming and aerobic training in people with dementia

In **chapter 6** we showed that it is feasible for older people with dementia to actively engage in an intensive 12-week exergame or aerobic training programme. Adherence of exergame training was higher than adherence to aerobic training. Moreover, experiences from the trainers who individually guided the training sessions reported that it was easier to motivate participants in the exergame group and to increase the duration of training sessions. In addition, none of the participants in the exergaming group dropped out due to low motivation, compared to two participants in the aerobic group and one participant in the control group. Taken together, exergaming seems to be an effective method to engage people with dementia in PA, and may therefore be an important strategy to stimulate long-term PA participation.

Previous research showed that interventions designed and delivered in a manner that gives people with dementia confidence about their ability to carry out the intervention (i.e. perceived behaviour control), promote engagement to the intervention and may facilitate sustained activity participation.[35,38] The exergame intervention seems to be suitable to do so, as the content of the intervention can be personalised based on someone's individual capacity. Therefore, people are able to carry out and master the intervention at their own level. This, in turn, is likely to positively influence engagement to the intervention and exercise adherence.

In the current study, training sessions were given on a one-on-one basis and were supervised by trained students or research assistants. An advantage of individual training regimes is that the training can be tailored to an individual fitness level and health status. Also, individual barriers for PA or behavioural problems can be taken into account. All of these elements contributed to a good quality trial with high adherence, low drop-out, no protocol deviations or occurrence of serious adverse events. In group-based training, it may be more difficult to ensure exercise quality per individual, because of the heterogeneity in patients and their ability. In addition, individual training sessions are a prerequisite to adequately monitor and motivate frail older adults.[39] Monitoring is important to prevent overload or injury, and to adapt the level of training if necessary. Therefore, an individual training approach seems to be preferred over a group-based approach in this frail patient group. Drawbacks of individual training regimes

are higher costs and a larger number of therapists that need to be trained. In some cases this barrier can be overcome by the use of trained (informal) caregivers.

The mean (SD) training intensity was light in both intervention groups with an average of 41.8% (SD=13.3) and 43.5% (SD=18.2) of the maximum heart rate in the exergame group and aerobic group respectively. We expected that improved cardiorespiratory fitness would be a requirement to improve cognitive function,[40] and therefore we aimed to achieve a moderate exercise intensity (e.g. 65-75% of maximal heart rate). However, most participants were not able to achieve a moderate training intensity in this intervention type because of comorbidities (e.g. musculoskeletal, cardiovascular or pulmonal disease) which made it impossible to increase resistance. In addition, it was hard to validly measure training intensity. 46 percent of the participants included in our study used beta-blockers or other medication that prevented an increase in heart rate during exercise. In those participants we primarily used the Borg Rating Scale of Perceived Exertion[41] as a method to measure exercise intensity. Previous research found low correlations between heart rate and reported perceived exertion in older adults with Alzheimer's disease.[42,43] Therefore, applying the Borg scale does not seem to be a valid method to monitor exercise response in people with dementia. This corresponded with personal experience, as trainers reported that a large number of participants did not understand the Borg scale or stopped cycling when they had to rate their perceived exertion. The burden of intensity measurements should not limit the participants in their exercise adherence. Therefore, we advocate focusing on exercise adherence instead of exercise intensity when implementing PA interventions in people with dementia.

Future research

In the presented studies, a heterogeneous sample of people with different types of dementia was included. Inclusion of participants with different types of dementia in our trial benefited the external validity of our results. However, it may have diminished the internal validity of the trial, as sub-analyses for different types of dementia were not possible because of the small sub-groups of dementia types. A proposed direction for future research is to study the cognitive benefits of exercise interventions for different dementia-types as this can provide us with information on who will benefit most from an intervention. We would expect, for example, that participants with a vascular component may benefit more from aerobic training as it improves vascular function and modifies key cardiometabolic risk factors.[44]

Our study focused on the efficacy of different exercise regimes and was not aimed at unravelling the underlying mechanisms that may be involved. In order to study underlying mechanisms, blood markers (e.g. BDNF, IGF-1) or neuro-imaging could be considered. However, including neuro-imaging measures in this vulnerable patient group places a high burden on participants and is therefore less desirable, also given the fact that severe atrophy is to be expected in

mild to moderate dementia patients, which hampers the analyses. Drawing blood to study growth factors could be of interest. However, given the frail patient group, we recommend to perform research on underlying neurobiological mechanisms earlier in the disease process (e.g. patients with mild-cognitive impairment) or in cognitively healthy older adults if possible.

Moreover, individual changes in cognitive performance, and investigating whether these changes are moderated by specific patient characteristics (e.g. dementia type, severity, APOE status) were not investigated. For future research it would be useful to focus on individual moderating effects as is in line with current perspective of personalised medicine, which emphasises a need for transition from a one-size fits all approach to tailored care. A method that could be used to identify individual progression is the Reliable Change Index (RCI), which determines if the difference between the pre-test and post-test score of an individual is statistically significant and thus shows whether the individual significantly improves or worsens during the intervention period.[45] In the future, such information may be used to deliver tailored exercise prescriptions to the individual.

Also, we did not investigate whether there was compensatory behaviour in the intervention groups (i.e. participants being more inactive during the rest of the day), that could counter the effects of the intervention. Future research should more carefully monitor PA levels of participants during the intervention period (outside of the intervention itself) by using an accelerometer. This makes it possible to rule out a possible rebound effect of the exercise intervention.

Lastly, exergaming has shown to be a feasible intervention for people with dementia, which benefits psychomotor speed and frailty. Possible benefits of exergaming on well-being, quality of life, mood and risk of falling need to be studied in future research.

Clinical implications

For practice

The findings of my thesis show that people with dementia are more sedentary and participate less in PA compared to their cognitively healthy peers. Moreover, results from the RCT highlight the potential of exergaming as an exercise method to engage people with dementia in PA. A small implementation step has already been made. Day-care centres have bought the five bicycle setups after the trial had ended. This demonstrates the willingness of these centres to offer PA on a regular basis, recognising the importance of stimulating PA among their clients. These bicycle setups contain the original software from bikelabyrinth (www.bikelabyrinth.com), without the different cognitive training levels developed for this trial. In addition, the original bicycle setups are already being used by many nursery homes as a way to stimulate PA

among residents. During our RCT, we experienced that certain components of the exergame intervention were particularly appreciated by the participants. For example, training levels in which participants had to respond to balloons appearing on the screen (level 2, 5, 6). Including these "fun" components may help to increase exercise adherence. Therefore, we recommend further developing these cognitive training levels for use in practice. To embed the intervention in local practice, collaboration and support from relevant stakeholders (e.g. physical therapists, community nurses, case managers, nursery homes, local authorities) is necessary. In order to achieve this, it is important to educate stakeholders on the importance of promoting PA in people with dementia and the opportunity of exergaming as a means to reach this goal. The knowledge provided in this thesis can help to substantiate this.

Furthermore, results from **chapter 3** indicate that large differences in perspective are present between people with dementia and their informal caregivers, compared to physiotherapy experts, concerning the most important factors influencing PA participation of people with dementia. The exchange of knowledge from professionals to persons with dementia and their informal caregivers may positively influence PA participation levels. For example, information on potential barriers for PA participation and how to eliminate them from physiotherapy experts to people with dementia and their informal caregivers, may lead to higher PA participation levels. In turn, a stronger focus on motivational aspects by experts could positively influence PA behaviour. Creating awareness on these differences in perspective among the professional group of geriatric physiotherapists is needed. This could be implemented through news items in their professional journal and website, or including it in the training programme for geriatric physiotherapists. In addition, findings from **chapter 3** showed that individual characteristics were found to most influence PA participation in people with dementia. This finding highlights the need for a personalised approach to promote PA behaviour in people with dementia.

For research

Experiences from our large randomized study described in **chapters 6** and **7** taught us that many challenges arise when conducting an exercise trial in people with dementia. Difficulties that we faced included the recruitment of patients, the logistics around executing the trial (e.g. transportation of participants, recruiting trainers, planning of training sessions and measurements), and the implementation of adequate tests for cognition, in particular for executive functioning. This taken together makes the execution of an exercise trial in people with dementia not only time-consuming, but it also requires a lot of manpower and finances to organise the logistics. Our RCT unfortunately did not include resources (e.g. trainers, time) to continue the training sessions after 12 weeks. A large number of participants (57%) regretted this, as they enjoyed the sessions and contact with the trainer, and because it became part of their weekly routine. Even a larger number of participants (87%) mentioned that they would have liked to continue exercising after the trial had ended. The involved health care

professionals (that is, case managers, physical therapists, supervisors of day-care centres) and informal caregivers were also disappointed that it was not possible to continue offering training sessions. This highlights the willingness of both people with dementia, health care professionals, and informal caregivers to further implement PA programmes in dementia care. Therefore, it is recommend to actively engage these groups in designing and executing future exercise studies. This offers the possibility for sustained PA participation and may facilitate implementation of the intervention in practice.

CONCLUSION

Physical exercise may be an effective strategy to improve speed of processing in people with dementia. It seems that the efficacy between exergame training compared to aerobic training does not differ. Thus, becoming physically active is an important prerequisite to success. Exergames may contribute in this matter. This thesis showed that exergaming is a feasible, innovative and potentially effective intervention in older adults with dementia. Moreover, exergaming is highly appreciated by the patient and often was considered more fun than exercise alone, thereby opening a low threshold opportunity to remain physically active for as long as possible.

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NEDERLANDSE SAMENVATTING

Inleiding

Dementie is een verzamelnaam voor een combinatie van symptomen waarbij sprake is van een geheugenstoornis, en één of meer andere stoornis(sen) in mentale functies zoals taal, gericht handelen, herkenning en uitvoerende functies (bijvoorbeeld planning). Deze stoornissen zijn dermate ernstig dat ze leiden tot een verminderd functioneren in het dagelijks leven. Een hoge leeftijd is de belangrijkste risicofactor voor het ontwikkelen van dementie. In de komende jaren zal het aantal ouderen fors toenemen. Daarom verwacht men een stijging van het aantal ouderen met dementie. Op dit moment zijn er in Nederland ongeveer 270.000 mensen met dementie. Naar verwachting zal dit aantal stijgen naar 500.000 in 2050. Deze forse stijging heeft een grote invloed op de zorg voor mensen met dementie en samenleving.

Wereldwijd wordt er veel onderzoek gedaan naar de oorzaken, mogelijke preventie en behandeling van dementie. Ondanks uitgebreid onderzoek is er voorlopig nog geen geneesmiddel om dementie te voorkomen of het ziekteproces te vertragen. Daarom is er ook aandacht voor behandelingen waarbij geen medicijnen gebruikt worden, de zogenaamde niet-farmacologische interventies, zoals beweegprogramma's of cognitieve trainingen. Uit onderzoek blijkt dat voldoende beweging het risico op cognitieve achteruitgang en dementie verlaagt bij cognitief gezonde ouderen en een positieve invloed heeft op cognitie. Minder sterke aanwijzingen zijn er voor een positief effect van beweging op de mentale (of cognitieve) functies bij ouderen met dementie. Gebaseerd op eerder onderzoek onder cognitief gezonde ouderen verwachten wij dat, ook bij ouderen met dementie, het combineren van beweging en cognitieve training zal leiden tot grotere verbeteringen van cognitieve functies dan enkel het aanbieden van bewegen. Een vernieuwende en speelse manier om beweging en cognitieve training te combineren is door gebruik te maken van beweeggames. Bij een beweeggame wordt fysieke inspanning interactief gecombineerd met een computerspel (game) in een virtuele omgeving. Eerder onderzoek heeft laten zien dat dergelijke beweeggames leiden tot verbeterde cognitieve functies in cognitief gezonde ouderen, ouderen met de ziekte van Parkinson, Multipele Sclerose, Schizofrenie en lichte cognitieve stoornissen. Of ze ook een positief effect hebben bij ouderen met dementie is nog onbekend.

Doel van het proefschrift

Dit proefschrift beschrijft een onderzoek naar het effect van een beweeginterventie, met of zonder cognitieve stimulatie, op het vertragen van de cognitieve achteruitgang van ouderen met dementie. Om beweging te combineren met cognitieve stimulatie wordt een beweeggame ingezet. Tevens worden de effecten van de beweegprogramma's op kwetsbaarheid, fysiek functioneren, fysieke activiteit en activiteiten van het dagelijks leven (ADL) onderzocht. Om deze resultaten in perspectief te plaatsen, is er voorafgaand aan deze studie onderzoek verricht naar het fysieke activiteitenniveau en zitgedrag in onze doelgroep. Aanvullend zijn barrières,

alsmede motiverende en faciliterende factoren onderzocht die invloed kunnen hebben op het beweeggedrag van ouderen met dementie.

Resultaten

Hoofdstuk 2 beschrijft de resultaten van het onderzoek naar beweeggedrag en zitgedrag van ouderen met dementie en hun leeftijdsgenoten zonder dementie. 45 ouderen met dementie en 49 cognitief gezonde ouderen droegen een week lang een activiteitenmonitor. De resultaten laten zien dat ouderen met dementie meer zitten en minder bewegen dan hun leeftijdsgenoten zonder dementie. Deze bevinding is klinisch relevant, aangezien fysieke inactiviteit een negatieve invloed heeft op de gezondheid en levensduur.

Om inzicht te krijgen in de redenen waarom ouderen met dementie meer zitten en minder bewegen dan hun leeftijdsgenoten zonder dementie werd de studie in **hoofdstuk 3** uitgevoerd. In deze studie hebben we 20 thuiswonende mensen met dementie, hun mantelzorgers en 15 fysiotherapeuten gevraagd welke factoren de grootste invloed hadden op het beweeggedrag van ouderen met dementie. Het ging hierbij om motiverende, belemmerende en faciliterende factoren. Alle betrokkenen moesten de 53 factoren rangschikken naar belangrijkheid. De lijst met factoren was gebaseerd op eerder onderzoek. Opvallend was dat de mensen met dementie en hun mantelzorgers de factoren anders rangschikten dan de fysiotherapeuten. De fysiotherapeuten noemden vijf belemmeringen in de top 10 van factoren met de meeste invloed op het beweeggedrag, bijvoorbeeld initiatiefverlies. De mensen met dementie en hun mantelzorgers hadden uitsluitend positieve factoren in hun top 10, zoals 'goed voor de gezondheid'. Deze uitkomst is niet onverwacht. Mensen met dementie richten zich liever op positieve zaken dan op verlies van functies. Fysiotherapeuten zijn in hun werk echter meer gericht op het wegnemen van belemmeringen, en noemen die daarom waarschijnlijk meer.

In het tweede deel van dit proefschrift is de effectiviteit van verschillende beweeginterventies bij ouderen met dementie onderzocht. In **hoofdstuk 4** presenteren we de resultaten van een meta-analyse naar het effect van gecombineerde cognitieve en fysieke interventies op cognitieve functies, stemming en ADL in ouderen met lichte cognitieve stoornissen of dementie. De resultaten van tien gerandomiseerde, gecontroleerde onderzoeken (RCT's) die het effect van een gecombineerde interventie vergeleken met een controlegroep werden samengevoegd. De voornaamste bevinding was dat er een klein, positief effect is van gecombineerde interventies op globaal cognitief functioneren. Er werd geen significante verbetering gevonden in het geheugen en de uitvoerende functies. Wel was er sprake van een verbetering van de stemming en van het dagelijks functioneren van deelnemers aan de gecombineerde interventies in vergelijking met een controlegroep. Deze resultaten benadrukken het belang van gecombineerde interventies om de progressie van lichte cognitieve stoornissen en dementie te vertragen. Echter, bij de interpretatie van de resultaten van de meta-analyse moet er wel rekening gehouden worden

met de verschillen tussen de afzonderlijke studies wat betreft de kenmerken van de training (bijvoorbeeld het type interventie, de duur en frequentie van de training en de duur van de interventieperiode) en de gebruikte uitkomstmaten. Toekomstig onderzoek is nodig om meer inzicht te krijgen in de voordelen van gecombineerde interventies voor de verschillende cognitieve domeinen. Tevens weten we nog niet of gecombineerde interventies een meerwaarde hebben boven enkel fysieke training bij ouderen met dementie. Om antwoord te kunnen geven op deze vragen hebben we zelf een RCT opgezet.

In **hoofdstuk 5** worden de rationale, de opzet en onderzoeksmethoden van het studieprotocol van deze RCT beschreven. Het doel van de RCT was om de effectiviteit van een 12 weken durende gecombineerde cognitieve en fysieke interventie te evalueren bij ouderen met dementie, en te vergelijken met enkel een fysieke interventie. We hebben hierbij gekeken naar de effecten op cognitieve functies, fysieke maten en het dagelijks functioneren. Als methode om bewegen en cognitieve training te combineren werd gebruik gemaakt van de beweeggame "Interactief Fietsen". Bij interactief fietsen fietsten deelnemers op een hometrainer die gekoppeld is aan een tv-scherm. Tijdens het fietsen volgden zij een route op het tv-scherm en voerden tegelijkertijd cognitieve taken uit. De tweede interventiegroep voerde enkel een fysieke training uit die bestond uit een fietstraining op een hometrainer. Daarnaast was er een actieve controlegroep; de deelnemers in deze groep voerden rek- en strekoefeningen uit. Door deze laatste groep kunnen we uitsluiten dat een waargenomen effect te danken is aan de aandacht die de deelnemers krijgen. Alle deelnemers aan de RCT trainden drie keer per week gedurende 12 weken en werden individueel begeleid gedurende de trainingsessies. De belangrijkste uitkomstmaat van de studie was de score op testen die executief functioneren (uitvoerende functies zoals planning en organisatie) meten. Daarnaast keken we naar de effecten op andere cognitieve domeinen: geheugen, werkgeheugen (het kortdurend vasthouden van informatie) en de snelheid van informatieverwerking. Tevens is het effect van de interventie op fysiek functioneren, fysieke activiteit, kwetsbaarheid en dagelijks functioneren onderzocht.

In **hoofdstuk 6** en **hoofdstuk 7** worden de resultaten van de RCT beschreven. **Hoofdstuk 6** richt zich op de effecten van de beweeginterventies op de verschillende cognitieve domeinen (executief functioneren, geheugen, werkgeheugen en snelheid van informatieverwerking). 115 ouderen met dementie (gemiddelde leeftijd 79 jaar) namen deel aan deze studie. Er werd geen effect gevonden van de beweeginterventies op onze belangrijkste uitkomstmaat, het executief functioneren. Na de interventieperiode van 12 weken lieten de deelnemers in de interactieve fietsgroep en de deelnemers in de fietsgroep wel een verbetering zien in de snelheid van informatieverwerking, vergeleken met de actieve controlegroep. We toonden tevens aan dat interactief fietsen een haalbare interventie is voor ouderen met dementie en bovendien positief wordt beoordeeld door deze doelgroep. De therapietrouw aan de interventie was zeer hoog (bijna 90%) en het aantal deelnemers dat uitviel was laag. Dat is bijzonder voor

deze populatie en maakt duidelijk dat interactief fietsen een geschikte methode is om ouderen met dementie te activeren. **Hoofdstuk 7** beschrijft de resultaten op de andere uitkomstmaten van de studie (fysiek functioneren, fysieke activiteit, kwetsbaarheid en dagelijks functioneren). Na 12 weken liet de interactieve fietsgroep een afname in kwetsbaarheid zien in vergelijking met de actieve controlegroep. Dit is een relevante bevinding aangezien kwetsbaarheid een belangrijke voorspeller is voor negatieve gezondheidsuitkomsten, zoals ziekenhuisopname en overlijden. Er is geen effect van de beweeginterventies aangetoond op fysiek functioneren, fysieke activiteit en het dagelijks functioneren.

Conclusies

Het laatste hoofdstuk van dit proefschrift, **hoofdstuk 8**, bestaat uit een samenvatting en algemene discussie. In dit hoofdstuk worden tevens de methodologische aspecten van het proefschrift besproken waarbij ook wordt ingegaan op de klinische relevantie van de bevindingen. Verder worden er aanbevelingen voor toekomstig onderzoek gepresenteerd.

Als alle bevindingen van het proefschrift worden samengevat kunnen er twee belangrijke conclusies worden getrokken: 1) mensen met dementie zitten meer en bewegen minder dan hun leeftijdsgenoten zonder dementie; 2) interactief fietsen is een haalbare, innovatieve en gewaardeerde methode om mensen met dementie te stimuleren meer te bewegen.

De eerste conclusie heeft klinisch-relevante consequenties, aangezien veel zitten en weinig bewegen een negatieve invloed heeft op de gezondheid en levensduur, en tevens samenhangen met verslechterde cognitieve functies. Bewegen heeft, daarentegen, een positief effect op fysieke functies van mensen met dementie en het heeft mogelijk ook een positief effect op cognitieve functies. Daardoor hebben mensen met dementie mogelijk baat bij beweeginterventies, waarbij een hoge therapietrouw wel een vereiste is. Eerder onderzoek heeft aangetoond dat dit vaak lastig te realiseren is in deze groep. De speelse interactieve aspecten van interactief fietsen leidden tot een hogere therapietrouw aan de interventie, in vergelijking tot de fietsgroep (87.3 *versus* 81.1%). Tevens werd door trainers die de trainingsessies begeleidden aangegeven dat het makkelijker was om de deelnemers in de beweeggame groep te motiveren voor de trainingsessies en om ze langer te laten trainen, dan in de andere groepen. Zodoende lijkt interactief fietsen een effectieve methode om mensen met dementie te stimuleren om op de lange termijn meer te bewegen. In onze studie vonden we dat zowel fietsen met als zonder interactieve component beide de snelheid van informatieverwerking verbeterden. De beweegcomponent van de interventie lijkt dus een belangrijke voorwaarde voor succes. Het inzetten van interactief fietsen kan hieraan bijdragen.

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ABOUT THE AUTHOR

Esther Karssemeijer was born on November 17th, 1987 in Breukelen, the Netherlands and grew up in Gouda, the Netherlands. After finishing higher education at de Goudse Waarden in 2006, she studied Medicine at Maastricht University. During her study she worked as a nursing assistant in home care. In the last year of her Master's phase, she focussed on Internal Medicine and Geriatrics. After graduation in September 2013 she worked for one year as a resident Internal Medicine at Haaglanden Medisch Centrum Bronovo in the Hague, the Netherlands. In January 2015, she started with her PhD at the department of Geriatric Medicine at Radboud university medical center in Nijmegen, the Netherlands. Under supervision of Professor Olde Rikkert (Geriatric Medicine) and Professsor Kessels (Medical Psychology) she performed the research described in this thesis. In addition to research, she was a secretary of the Donder's PhD council and helped organizing the department's quality lunch meetings. In April 2019, she started her specialisation in geriatrics. As a part of this, she is currently working as a resident Internal Medicine at Canisius Wilhelmina Ziekenhuis in Nijmegen, the Netherlands.

Esther Karssemeijer is geboren op 17 november 1987 in Breukelen en ze groeide op in Gouda. Na afronding van het atheneum aan de Goudse Waarden te Gouda, verhuisde ze naar Maastricht waar ze begon met de opleiding Geneeskunde aan de Universiteit van Maastricht. Tijdens de opleiding heeft ze bij de thuiszorg in Maastricht gewerkt. In het laatste jaar van haar Master Geneeskunde heeft ze zich gericht op de Interne Geneeskunde en Geriatrie. Na afronding van de opleiding Geneeskunde in September 2013 begon ze als arts-assistent op de afdeling Interne Geneeskunde van het Haaglanden Medisch Centrum Bronovo in Den Haag. In januari 2015 begon zij als promovenda op de afdeling Geriatrie van het Radboudumc in Nijmegen. Onder begeleiding van professor Olde Rikkert (Geriatrie) en professor Kessels (Medische psychologie) voerde zij het onderzoek uit dat geresulteerd heeft in dit proefschrift. Naast het onderzoek, was zij secretaris van de Donder's PhD council en was zij mede-organisator van de lunch bijeenkomsten op de afdeling rondom kwaliteit van onderzoek. In april 2019 startte zij de opleiding tot klinisch geriater, waarvoor ze begint met de vooropleiding Interne Geneeskunde in het Canisius Wilhelmina Ziekenhuis te Nijmegen.

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Logghe IHJ, **Karssemeijer EGA**, van Gennep M. Bewegingsstimulering en cognitieve training voor ouderen met dementie. Physios 2016;2(20-25).

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PORTFOLIO

Courses	
2015	Designing a PhD research project (Radboud University)
2015	Management voor promovendi (Radboud University)
2015	Introduction to data analysis (Erasmus summer school)
2015	How to write a medical scientific paper (Radboudumc)
2016	BROK course (PAO Heyendael)
2016	Opfriscursus statistiek voor promovendi (Radboud University)
2016	Scientific Integrity (Radboudumc Health Academy)
2017	Presenteren eigen onderzoek (Radboud University)
2017	Education in a nutshell (Radboud University)
2018	Scientific Writing (Radboud University)
2018	Advanced conversation in English (Radboud University)
2018	the Art of presenting Science (Radboud University)
Conference contributions	
2016	**Conference of the European Union Geriatric Medicine Society, France** Oral presentation: "Combined cognitive-physical interventions using exergames to prevent further cognitive decline in dementia"
2016	**TOPICS symposium, the Netherlands**
2018	**Alzheimer's Association International Conference, United States of America** Poster presentations: (1) "The quest for synergy between physical exercise and cognitive stimulation in dementia: a randomized controlled trial" (2) "Dementia patients are more sedentary and less physically active than cognitively healthy older adults"
2018	**Geriatriedagen, the Netherlands** Oral presentation: "Een gecombineerde cognitieve en fysieke training heeft een positief effect op het cognitief functioneren in ouderen met milde cognitieve stoornissen of dementie"
2018	**The Gerontological Society of America Annual Scientific Meeting, United States of America** Oral presentation: "The Cognitive Effects of Physical Exercise With or Without Cognitive Stimulation in Dementia: A Randomized Controlled Trial"
2019	**Geriatriedagen, the Netherlands** Oral presentation: "Het effect van een gecombineerde cognitieve en fysieke interventie op cognitief functioneren in dementie" Award winner Stimuleringsprijs jonge onderzoeker Geriatrie
Other activities	
2015-2017	**Secretary of the Donders PhD Council** Aim of the council is to facilitate day-to-day live of PhD candidates, among others by organizing PhD meetings
2016-2018	**Organize the departments quality lunch meetings** Discuss topics regarding quality of research, e.g. data-management, monitoring
2015-2018	**Peer reviewer for scientific journals**
2015-2018	**Supervise interns (bachelor and master) from Medicine, (applied) Psychology, Biomedical Sciences, Physiotherapy, Sport Health &Management**

RESEARCH DATAMANAGEMENT

The data obtained in this thesis are archived in accordance with the Findable, Accessible, Interoperable and Reusable principles (FAIR).[1] Raw data were stored in the online data management system Castor. All data stored in Castor are accessible by the principal investigator and the department's data manager. Processed data that were generated are stored on servers of the Radboudumc. To ensure general accessibility of the data, all filenames are documented according to the protocol of the department of Geriatrics. The study protocol of the studies described in **chapters 5, 6** and **7** were approved by the Medical Ethical Committee of Radboud University Medical Center, the Netherlands (Ref No. NL52581.091.15/2015–1857). The studies were performed in accordance with the latest revision of the declaration of Helsinki. Written informed consent was obtained from all participants. The datasets of the studies described in this thesis are available from the corresponding authors on reasonable request.

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Döpp, C.M.E. (2015). *Making the jump-The translation of research evidence into clinical occupational therapy practice.*

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Bakker, C. (2013). *Young onset dementia: care needs & service provision.*

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