Physical (in)activity and cognition in cognitively impaired older people

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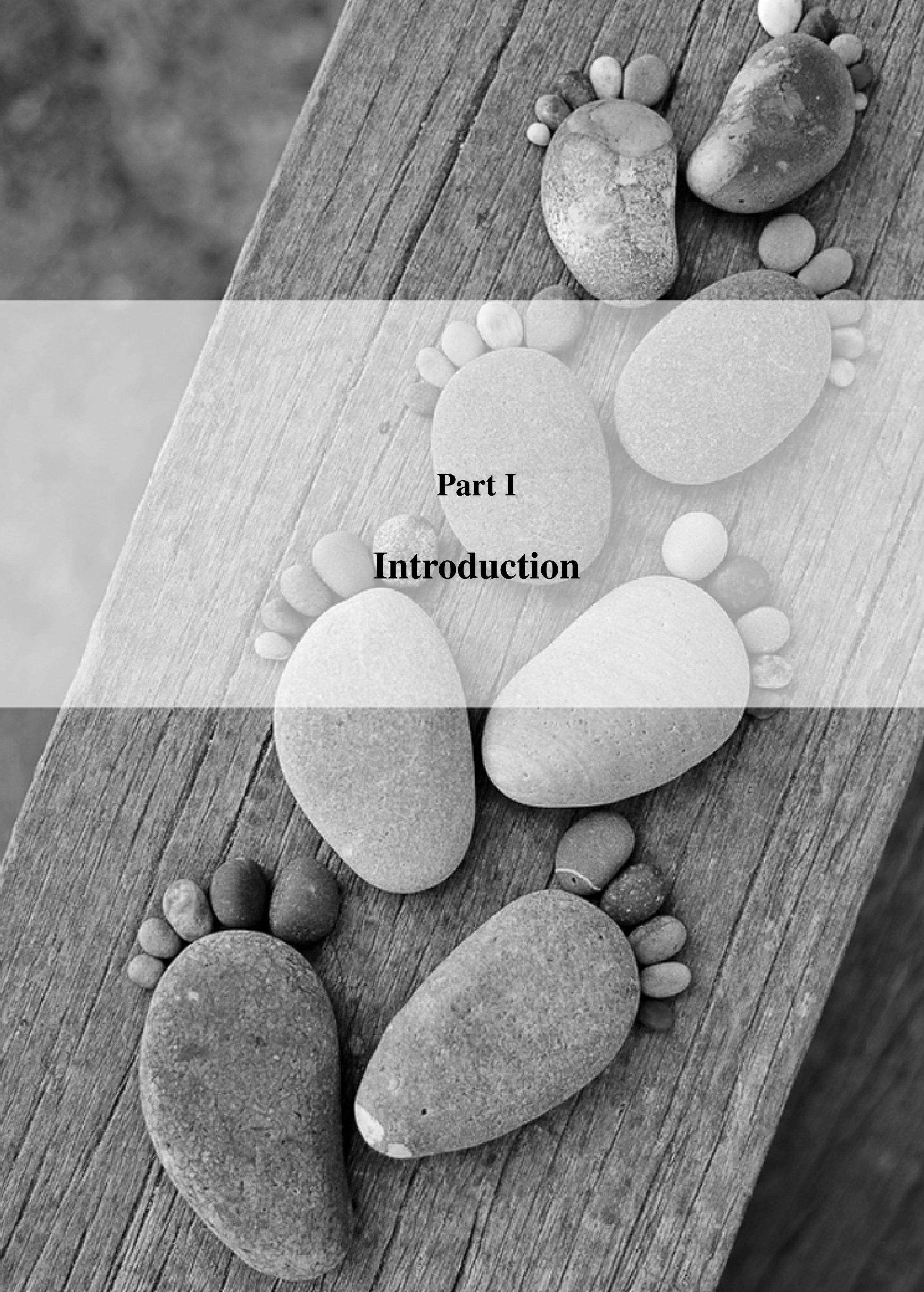


Part I

Introduction

CHAPTER 1

GENERAL INTRODUCTION

THE average lifespan of the world population is rising and it is expected that the number of older people (> 65 years) will even have doubled by 2030 in some countries[1]. Although a longer lifespan may co-occur with a further development of wisdom[2] and spirituality[3], old age is widely associated with a decline in cognitive and physical performance, such as memory and muscle strength, respectively[4,5]. Aging is also the number one risk factor for the development of dementia[6], and therefore the number of people suffering from dementia is predicted to increase rapidly in the next decades[7]. Since there is no cure for dementia so far, we should focus on the modifiable risk factors, such as physical activity, to reduce the expected number of people with dementia[8].

A high level of physical activity during life might decline the risk of dementia due to an increase in cognitive brain reserve[9], the capacity of the brain to manage pathology or age-related changes in the brain and thereby minimizing cognitive decline[10]. Growing evidence from animal and human experimental research shows that physical activity can increase the functional and structural capacity of the brain due to its positive effects on physiological processes of the brain, among which: 1) *angiogenesis*, a physiological process that reflects the growth of new blood vessels from pre-existing vessels[9,11]; 2) *neurotrophins*[9,11], i.e., proteins that increase neuronal survival, such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF)[12–14]; and 3) *neurogenesis*[9,11,13], i.e., the process by which new neurons are generated. It is suggested that these physiological responses to physical activity may restore or prevent the decrease in brain volume associated with normal aging[15]. Since brain volume is related to cognition[16], the above studies suggest a relation between physical activity and cognitive functioning[17]. Indeed, epidemiological studies show a positive relationship between physical activity and cognition[18–21].

Since physical activity also increases *physical performance*, e.g., muscle strength[22,23], gait speed, functional mobility and balance[23,24], it is not surprising that there is a positive relationship between physical performance and cognition in older people[25]. More specifically, older people with better physical performance levels, such as mobility[26–28], balance[29,30], strength[27,31–33] and aerobic fitness[17] have better cognitive functions, e.g., global cognition. Moreover, similar to physical activity, better physical performance, such as balance[29] and strength[33–35], decrease the risk of dementia as well[36,37]. It is even suggested that executive functions (EF), e.g., inhibition, scheduling, planning and working memory, as opposed to global cognition or memory, is particularly important for mobility performances, such as balance, gait[38] and the ability to perform activities of daily living (ADL)[39,40]. This suggestion was supported by a positive relationship between walking speed, a gait parameter, and EF in a combined group of elderly with and without mild dementia[41]. Walking speed in older people is mediated by the strength of lower limb muscles, such as the knee extensor musculus quadriceps[42].

Muscle strength provides greater physiologic and functional reserves that may protect against mortality[43–45]. Poor muscle strength is an indicator for vulnerability and frailty at old age[45,46] and increases the risk of falling[47–49]. As a consequence of falls, people often have to be transferred to acute care[50]. Moreover, preserving LLMS may be considered a very important determinant of functional independence in the elderly[51]. It is important to note that the studies addressed above only show a *relationship* between physical activity, physical performance and cognition, not a *causal* relationship.

A causal relationship between physical activity and physical performance, such as LLMS, is observed at young and old age[52,53]. During aging, physical activity can reduce muscle strength decline[54]. A gradual increase in physical workload produces a time-dependent improvement of strength[54]. Therefore, when the intervention stops, studies show rapid loss of muscle strength[55,56]. To prevent a rapid loss in strength, physical activity should be part of daily life instead of a short intervention. In addition, daily physical activity is not only effective for strength, but also for cognitive functioning[57].

A causal relationship between physical activity and cognition is shown by intervention studies with children[58], adolescents[59], older cognitive healthy people[60] and persons with mild cognitive impairment (MCI)[61]. A meta-analysis including 18 randomized controlled trial intervention studies found a moderate effect size (Hedges' $g = 0.48$) for aerobic exercise on cognitive function in older people without dementia aged 55–80 years[62]. Aerobic exercise refers to activities that improve oxygen consumption by the body through the purposeful, rhythmic use of large muscle groups for an extended period of time[63]. Although exercise effects were observed in a variety of cognitive processes, e.g., visuo-spatial processes, the effect was largest for EF[62,64–66].

Results on the effects of exercise on cognition in people with dementia are equivocal[67–70]. Two reviews argued that the lack of a beneficial cognitive effect was due to interventions that mainly consisted of strength-, balance- and/or flexibility-based exercises, while aerobic exercises, such as walking, improve cognitive functioning[68,70]. The other reviews indicate that the evidence is not sufficient to draw firm conclusions about the effectiveness of physical activity interventions on cognition in dementia[67,69]. Insufficient evidence may be due to for example, lack of methodology, differences in type of intervention, durations and outcome measures[67–70].

Since physical activity, together with socialization[71], is part of an enriched environment, it is not surprising that living in an enriched environment is beneficial for cognitive functioning, i.e., learning and memory[72,73]. The opposite effect of an impoverished environment on cognition is however less known, while the effect of physical inactivity and loneliness should not be underestimated: physical inactivity is a much stronger associate of functional limitations than chronic diseases[74] and for each 1–point higher level of loneliness on a 5–item scale, physical performances decline 40% more rapid[75]. Unfortunately, aging is negatively related to physical activity and socialization[76,77]. Not many older people meet the recommended level of at least 30 minutes of daily moderate intensity aerobic exercise[78]. In addition, a major concern is that people with cognitive impairment are at higher risk to have low levels of physical activity. Indeed, passivity is common among residents in nursing homes[79,80], but often not acknowledged as a noteworthy behaviour[81].

A lack of physical activity stimulation in nursing homes is unfortunate, because in older people physical activity has not only proven to be beneficial for physical functioning and cognition, but also for depression[82], anxiety[83], rest–activity rhythm[84], quality of life (QoL)[85,86], and ADL[87,88]. In addition, physical activity may have a positive effect on pain and agitation, two frequently observed symptoms in people with dementia[89,90]. Therefore, regular habitual physical activity should be stimulated in older people with or without dementia as part of daily living. In addition, it is recommended to perform a combination of endurance, strength, balance and flexibility exercises at moderate intensity[24,78], but exercises performed by older people, such as chair exercises, are only assumed to be of moderate intensity[91]. Similarly, self–paced walking with a rollator is known to be of moderate intensity for older people[92].

These issues concerning low levels of physical activity in older people with or without cognitive impairment indicate that there is possibly a lot to gain in this population when physical activity levels increase. Physical activity levels in older people with varying levels of cognitive impairment form the basis for this thesis, which has a special focus on the effect of low and high levels of physical activity in daily life on physical and cognitive functioning in people with mild to severe cognitive impairment.

1.1 Outline of the present thesis

This thesis is divided into two parts, i.e., a review section, and a clinical section with focus on cognitively healthy older people (**chapter 2** and **8**), older people with and without dementia (**chapter 3**), older people with mild to severe cognitive impairment (**chapter 5, 6** and **7**), and on dementia only (**chapter 4**). Three chapters focus on the possible effect of physical activity on: 1) LLMS (**chapter 2**) 2) agitation and pain (**chapter 4**); 3) cognition (**chapter 7**) and 4) various health aspects (**chapter 5**). The remaining chapters focus on the relation between an impoverished environment and cognition (**chapter 3**), the relation between physical performance and cognition (**chapter 6**) and finally, the intensity of chair-assisted exercises (**chapter 8**).

1.1.1 Review Section

In **chapter 2** a meta-analysis of literature on HPA and LLMS is performed. The main goal is to examine the relationship between HPA throughout life and LLMS above age 50. A differentiation between past and present levels of HPA is made, as well as the effect of age, gender and type of HPA, i.e., habitual physical activities that are especially focused on strength, endurance, or the remaining activities.

Chapter 3 focuses on studies that examined the effect of an impoverished environment on cognition in older animals and in older persons with and without dementia. An impoverished environment includes physical inactivity and loneliness, or even worse, passivity and isolation. Animal experimental studies will be discussed first, followed by clinical studies including older people living in institutions and in society both with and without dementia.

Chapter 4 addresses the question whether physical activity might influence pain and agitation in people with dementia. Physical activity has a positive effect on the inhibitory function of the brain and therefore, physical activity might also inhibit pain and inappropriate behaviour, such as agitation.

1.1.2 Clinical Section

Chapter 5 describes the protocol of a long-term randomized controlled, single blind study with ambulatory older people with cognitive impairment, who are regular visitors of daily care or living in a home for the elderly or nursing home in the Netherlands. The daily walking intervention and dependent variables on various health aspects are described, even as potential moderating variables, such as body mass index (BMI) and medication use.

Chapter 6 focuses on the predictive value of physical performances, such as strength, aerobic fitness, mobility and balance, on cognitive functioning, i.e., episodic memory and working memory.

In **chapter 7** the effect of regular walks on cognitive domains will be analysed with multilevel modelling. The results of this study will provide insight into the (different) effects of the performed walks on EF and memory in people with varying levels of cognitive impairment.

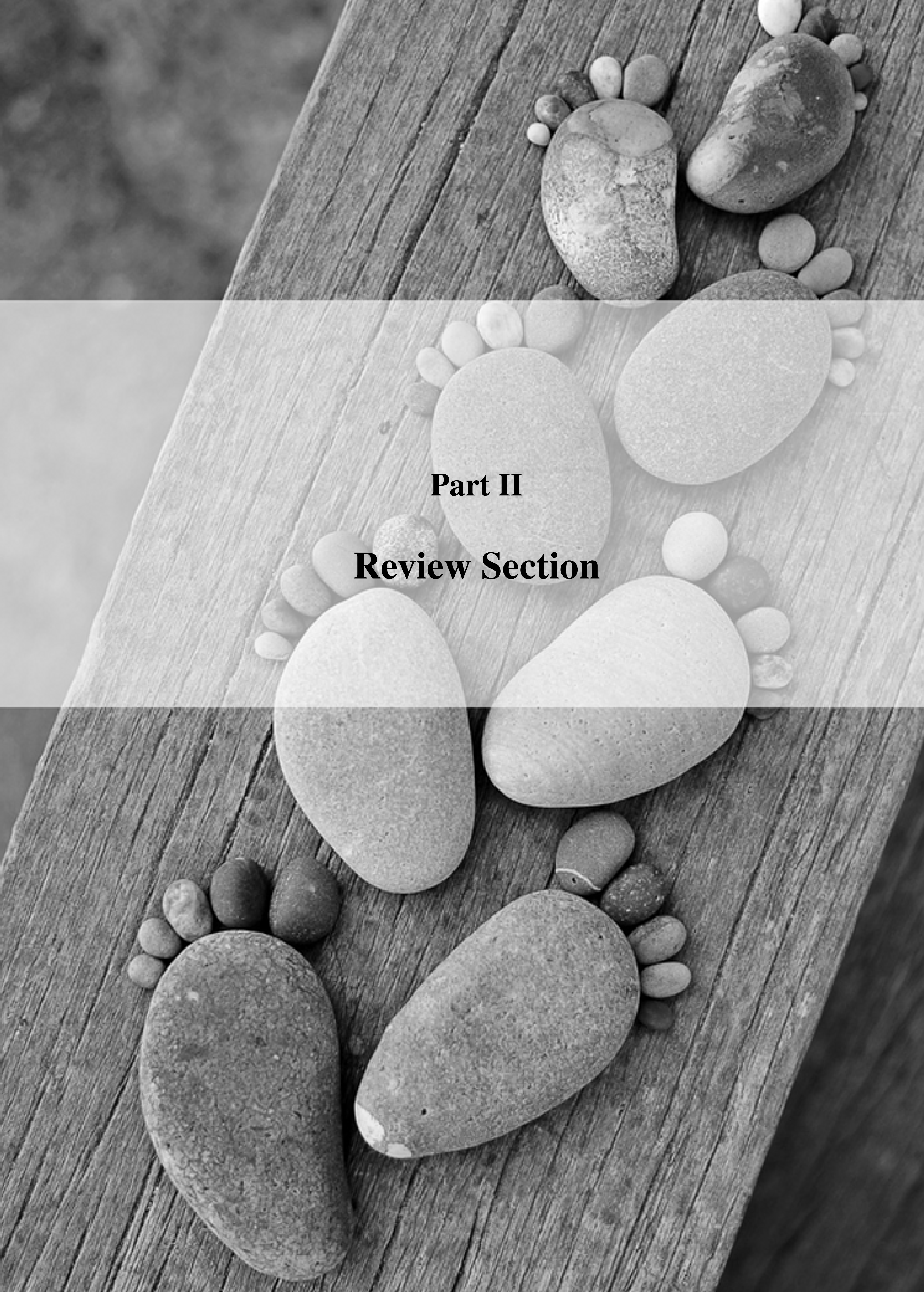
Chapter 8 deals with the intensity of chair-assisted exercises in older cognitive healthy people varying from independent living to home care residents.

1.1.3 General discussion

Chapter 9 contains the general discussion of the current thesis. The major aim is to discuss the implications of the previous chapters and to provide suggestions for future research, overall conclusions and recommendations.

Part II

Review Section



CHAPTER 2

LOWER LIMB MUSCLE STRENGTH: WHY SEDENTARY LIFE SHOULD NEVER START? A REVIEW

Abstract. Aging coincides with a decline in lower limb muscle strength (LLMS). Preserving LLMS may be considered a very important determinant of functional independence in the elderly. To maintain LLMS the question arises whether habitual physical activitys (HPAs) can prevent a decline in LLMS. This review aims to determine the relationship between HPAs throughout life and LLMS above age 50. Using relevant databases and keywords, 70 studies that met the inclusion criteria were reviewed and where possible, a meta-analysis was performed. The main findings are:

1. The present level of HPA is positively related to LLMS;
2. HPAs in the past have little effect on present LLMS;
3. HPAs involving endurance have less influence on LLMS compared to HPAs involving strength;
4. People with a stable habitually physically active life are able to delay a decline in LLMS.

In conclusion, to obtain a high amount of LLMS during aging, it is important to achieve and maintain a high level of HPA with mainly muscle-strengthening activities. [1]

2.1 Introduction

THE average lifespan of the world population is rising and it is expected that the number of older people ($>$ 65 years) will even have doubled by 2030 in some countries[1]. Although a longer lifespan may co-occur with a further development of wisdom[2] and spirituality[3], old age is widely associated with declines in physical functioning and muscle strength[5,93].

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[1] Volkers, K.M. et al., 2012. Lower limb muscle strength (LLMS): Why sedentary life should never start? A review. *Archives of Gerontology and Geriatrics*, 54(3):399-414.

Muscle strength has been reported to reach peak values between age 25 and 35, is maintained or is slightly lower between age 40 and 49 and then declines after age 50[94,95]. Muscle strength provides greater physiologic and functional reserves that may even protect against mortality[43–45]. Poor muscle strength is an indicator for vulnerability and frailty at old age[45,46] and increases the risk of falling[47–49]. As a consequence of falls, people often have to be transferred to acute care[50]. Moreover, preserving LLMS may be considered a very important determinant of functional independence in the elderly[96].

At a young age, LLMS can be positively influenced by physical activity[52]. It should be noted that different exercises have different effects on muscles. Strength exercises mainly increase muscle mass (for muscle strength), while endurance exercise mainly increase mitochondrial concentration (for muscle endurance)[97]. Even older people who participate in a temporary intervention program are still able to increase their LLMS[53] and can reduce muscle strength decline during aging[54]. A gradual increase in workload produces a time-dependent improvement of strength[54]. Therefore, when the intervention stops, studies show rapid loss of muscle strength[55,56]. Unfortunately, these temporary interventions do not provide much information about how actual levels of HPA observed in older people affect decline in strength. Delayed declines in LLMS caused by HPAs could occur in two different ways. First, it might be due to a build-up of ‘muscle reserve’ resulting from HPAs performed in the past; comparable to what has been suggested for cognition[98,99]. Second, irrespective of HPAs in the past, only the present level of HPA could delay the decline in strength; comparable to what has been suggested for maximal oxygen uptake ($\dot{V}o_2$max)[100]. $\dot{V}o_2$max is a measure for maximal aerobic capacity[101] that can decline rapidly when people cease their present physical activities[102]. The actual impact of HPAs on LLMS above age 50 and whether HPAs in the past or present could delay a decline in LLMS has never been reviewed. The aim of this systematic review and meta-analysis is to clarify the relationship between HPAs and LLMS above age 50. The following questions will be addressed:

1. Do present HPAs have a positive influence on LLMS?
2. Can HPAs in the past and present delay a decline in LLMS?
3. Are the results influenced by age, gender and type of HPA, i.e., sport physical activities that are especially focused on strength (for example sprinting, weight lifting), on endurance (for example marathon running) or the remaining HPAs (for example gymnastics, work and household activities)?

2.2 Methods

2.2.1 Search strategy

We conducted a systematic literature search of MEDLINE, EMBASE, PsycINFO and Cochrane library on March 1st 2010 in order to identify studies addressing the amount of LLMS (decline) in people whose HPA level is known. The search terms were divided into four groups: ‘muscle status’ (i.e., muscle strength or power), ‘lower limb muscles’, ‘aging’ and ‘physical activity’. The search terms included controlled terms, i.e., Mesh, emtree and thesaurus, but also text words. Studies contained at least one term of all four groups. The detailed search strategy can be obtained from the first author. The search resulted in 1679 articles in MEDLINE, 6374 articles in EMBASE, 121 articles in PsycINFO and 421 articles in Cochrane library. The bibliographic details of all retrieved articles ($n = 8595$) were stored in a Reference Manager file. First, the overlapping articles that were identified in the literature search of various database searches were included only once. This resulted in a total of 7797 articles. Second, two of the researchers independently reviewed all 7797 titles, after which abstracts of all studies with relevant titles were reviewed separately. At this initial screening stage, articles were deemed to be relevant if the study measured strength of lower limb muscles and level of HPA in healthy older people. The full text of any article that either investigator assessed as possibly relevant was obtained ($n = 178$). Both researchers independently assessed these 178 studies using the selection criteria. Disagreements were resolved by consensus and when consensus could not be reached, a third reviewer was consulted. We contacted authors for additional data if necessary. In total 70 articles (with 31 articles in the meta-analysis) were included in this review.

2.2.2 Criteria for selecting studies

The following criteria were used to select studies for inclusion in this review:

1. The study was published in an English or Dutch language journal;
2. The study measured both LLMS (knee extension, knee flexion, leg extension, hip abduction, hip adduction, ankle dorsiflexion and ankle plantar flexion) and the HPA level in people;
3. A comparison was made between strength and the level of HPA;
4. The study included people with a mean age of 50 or older, reporting population characteristics including gender and age.

The following exclusion criteria were used to focus only on healthy people and HPAs:

1. Studies with patients during hospitalization or patients with (chronic) diseases;
2. Studies with an exercise intervention.

2.2.3 Nomenclature

Studies differ in terms of LLMS measurement. Static muscle strength is the ability to generate force without movement. It is comparable to isometric muscle strength, i.e., fiber length remains constant in the presence of a force greater than the muscle is capable of counteracting[46]. In other words, the limb is not moving while strength is provided. Isometric muscle strength includes force in Newton (N) and torque in Newton meter (N·m)[103]. Dynamic muscle strength is the ability to generate force during movement of the limb. It includes isokinetic muscle strength, i.e., fibers are shortened or lengthened while the limb moves at fixed velocity[46] in Newton meter per second (N·m/s)[104] and kinetic muscle strength and power, i.e., fibers are shortened or lengthened while the limb moves at non-constant velocity in N·m/s, centimeters (cm) jumping height[105], or time needed to perform chair stands[106].

HPA includes occupational and leisure time physical activity[107]. Occupational physical activity includes physical activities at work[108]. Leisure time physical activity includes all physical activities performed during leisure time and can be subdivided into sport physical activity and other leisure time physical activities like brisk walking and gardening[109–111]. Sport physical activity includes all sports club activities (including exercise)[112]. These HPA domains are not the most important aspects, but are a marker of the type of activity. Theoretically, it is the total level and type of activity (strength vs. endurance or other) that influences muscle strength, but many included studies did not provide enough detailed information to determine the total level of HPA.

2.2.4 Nature of the evidence

There are three different types of study design. First there are cross-sectional studies where people were divided into groups based upon HPA level and the focus is on between subject differences in LLMS associated with HPA level. Second, there are cross-sectional studies that used a measure of HPA and provided a correlation coefficient between HPA level and LLMS. Finally, there are longitudinal studies where the focus is on within subject changes in LLMS over time and to what extent HPA level at baseline and follow-up affects this change. Studies were included in a meta-analysis only if they assessed knee extensor strength in Newton. Studies without a measure of knee extensor strength (in Newton) were qualitatively reviewed to examine whether the results supported the results of the meta-analysis of studies with a comparable design.

2.2.5 Statistical analysis

The meta-analysis was performed using the software Comprehensive Meta-analysis version 2.2[113] and SPSS version 14.0. To ensure stability of the outcomes, the meta-analysis was limited to strength variables reported by at least 4 different studies, which was the case for knee (and leg) extension muscle strength measured in Newton. An overall effect size for each dependent variable was computed by weighting each study's effect size by the study's sample size. To answer the first question, a combined effect size d[114] was determined for both the cross-sectional difference in knee extension strength between a HPA and a sedentary group and the correlation between HPAs and knee extension strength. To answer the second question, effect sizes were measured for the decline in knee extension strength within 3 groups, i.e., a group with a stable high or a stable sedentary level of HPA and a group of people with a decreasing level of HPA. In order to determine if age, gender and type of HPA affected the results, the Pearson correlation coefficient was calculated between age at (baseline) assessment and the studies' effect size and Q test statistics for gender and type of HPA on combined effect sizes were assessed. For the interpretation of the correlation coefficients and effect sizes, Cohen's[114] guidelines were used. To test heterogeneity of the effect sizes, a Q test was conducted[115].

To study the possibility of publication bias, we used linear regression methods proposed by Egger et al.[116] to investigate the degree of funnel plot asymmetry (1–sided p) and an additional fail safe N was calculated[117], measuring the necessary number of studies to nullify the overall effect. Furthermore, we investigated the correlation between sample sizes and effect sizes for each dependent variable. The fact that significant results in small samples tend to be easier to publish in comparison with non-significant results in small samples, would become evident by way of a significant negative correlation between sample size and effect size. Significance testing was 2-sided and set at $p < 0.05$.

2.3 Results

Table 2.1 (page 23) shows an overview of longitudinal studies and Table 2.2 (page 25) of cross-sectional studies that measured LLMS in people of 50 years and older in relation to their level of HPA. All studies are sorted in alphabetic order by first author.

2.3.1 Do present HPAs have a positive influence on LLMS?

Cross-sectional differences

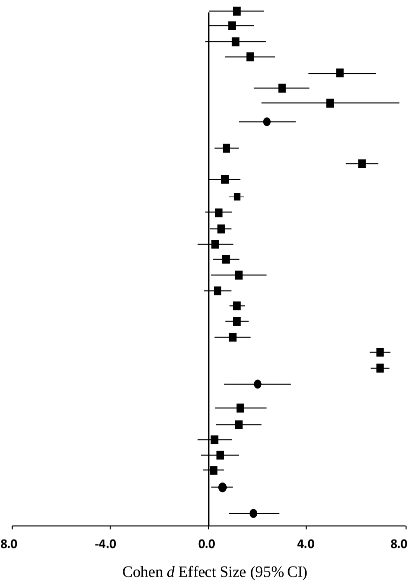
Eighteen studies measured and reported the amount of knee extension strength (in Newton) in 1475 habitually physically active and 1379 sedentary people[107,118–131]. Overall knee extension strength was higher in habitually physically active people compared to sedentary people, with a combined effect size of $d = 1.89$ (95% CI = $0.95 - 2.83$; $p < 0.001$) (Figure 2.1 on page 17). Data were heterogeneously distributed indicating that findings were not consistent among studies ($Q(26) = 1814.50$, $p < 0.001$). Found effect size did not differ between studies measuring HPAs during the whole of a person's lifetime[107,118,119,123,125,128,129,131], and those only measuring the HPAs during the last year(s) of life ($Q(1) = 0.29$, $p = 0.59$)[120–122,124,126,127,130,132,133]. There was no evidence for publication bias, as Egger's degree of funnel plot asymmetry was not significant ($p = 0.32$), fail safe N was 6669 and studies with higher sample sizes showed higher effect sizes ($r = 0.69$, $p < 0.001$).

Reviewing comparable literature with other LLMS measurements, 24 studies support the significant difference in LLMS, irrespective of measuring HPAs during an entire lifespan[111,123,131,134–139], or during the last year(s) of life[121,122,124,130,133,140,141,141–149]. In contrast, one study showed no difference in knee extension and flexion strength between people with high and people with low levels of occupational physical activity[150].

Correlation studies

Nine studies assessed a correlation between HPAs and knee extension strength (in Newton) in 1315 people[107,109,119,133,143,145,151–153]. Overall, there was a significant positive effect of $d = 0.25$ (95% CI = $0.20 - 0.30$; $p < 0.001$) and data were homogeneously distributed ($Q(13) = 19.67$, $p = 0.10$) (Figure 2.2 on page 18). There was a non-significant degree of funnel plot asymmetry ($p = 0.26$), fail safe N was 231 and a negative non-significant relation between effect size and sample size ($r = -0.33$, $p = 0.10$), together indicating no evidence of publication bias. Reviewing comparable literature with other LLMS and power measurements, 18 studies support this positive correlation[106,109,110,124,145,151–163]. Only one study showed a contrasting result with a negative correlation between occupational physical activities and knee extension strength[164].

HPA	Study	Age	Gender	Effect size (95% CI)	*p*
Strength	Aagaard et al., 2007	74	m	1.17 (0.07 - 2.27)	0.04
	Dreyer et al., 2006	65	m	0.99 (0.08 - 1.89)	0.03
	Leong et al., 1999	71	m	1.11 (-0.12 - 2.35)	0.08
	Pearson et al., 2002	54	m	1.71 (0.69 - 2.74)	0.00
	Pearson et al., 2002	64	m	5.35 (3.87 - 6.83)	0.00
	Pearson et al., 2002	74	m	3.01 (1.88 - 4.13)	0.00
	Pearson et al., 2002	84	m	4.99 (2.18 - 7.79)	0.00
	Combined Effect Size Strength			*2.41 (1.26 - 3.55)*	*0.00*
Other	Brooke- Wavel et al., 2008	68	w	0.74 (0.27 - 1.22)	0.00
	Hunter et al., 2001	53	w	6.27 (5.62 - 6.92)	0.00
	Laroche et al., 2007	71	w	0.67 (0.03 - 1.31)	0.04
	McCrory et al.,2009	74	m,w	1.28 (0.95 - 1.62)	0.00
	Rantanen et al., 1992	55	w	0.44 (-0.12 - 0.99)	0.12
	Rantanen et al., 1993	74	w	0.53 (0.11 - 0.95)	0.01
	Rantanen et al., 1997 [a]	75	m	0.30 (-0.42 - 1.01)	0.42
	Rantanen et al., 1997 [a]	75	w	0.73 (0.20 - 1.26)	0.01
	Rantanen et al., 1998 [a]	80	m	1.25 (0.12 - 2.37)	0.03
	Rantanen et al., 1998 [a]	80	w	0.39 (-0.18 - 0.96)	0.18
	Ringsberg et al., 2001	71	w	1.18 (0.87 - 1.50)	0.00
	Ringsberg et al., 2001	80	w	1.17 (0.70 - 1.64)	0.00
	Sipila et al., 1994	74	w	1.00 (0.27 - 1.73)	0.01
	Visser et al., 2005	73	w	7.00 (6.59 - 7.41)	0.00
	Visser et al., 2005	74	m	7.00 (6.62 - 7.38)	0.00
	Combined Effect Size Other			*2.00 (0.65 - 3.35)*	*0.00*
Endurance	Aagaard et al., 2007	72	m	1.33 (0.28 - 2.38)	0.01
	Dreyer et al., 2006	67	m	1.26 (0.34 - 2.17)	0.01
	Harridge et al., 1997	79	m	0.26 (-0.42 - 0.95)	0.45
	Karamanidis et al., 2006	64	m	0.49 (-0.28 - 1.25)	0.22
	Tarpenning et al., 2006	56	w	0.21 (-0.21 - 0.64)	0.33
	Combined Effect Size Endurance			*0.57 (0.14 - 1.00)*	*0.01*
Total Combined Effect Size				*1.89 (0.95 - 2.83)*	*0.00*

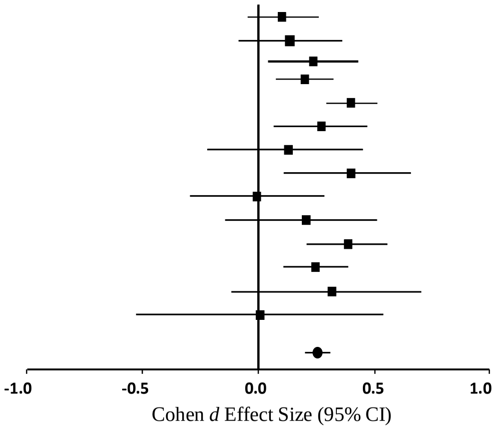


Notes: CI = Confidence Interval; HPA = Habitual Physical Activity; m = men; w = women

[a] Longitudinal study (other studies are cross-sectional)

Figure 2.1: Effect sizes for the cross-sectional differences in knee extension strength between a HPA group and sedentary group.

HPA	Study	Age	Gender	Effect size (95% CI)	p
OPA	Andrews et al., 1996	64	m,w	0.11 (-0.05 - 0.26)	0.17
HPA	Aoyagi et al., 2009	73	m	0.15 (-0.08 - 0.36)	0.20
HPA	Aoyagi et al., 2009	72	w	0.25 (0.05 - 0.43)	0.02
LPA	Bohannon et al., 1997	20-79	m,w	0.20 (0.08 - 0.33)	0.00
LPA	Hunter et al., 2001	53	w	0.41 (0.29 - 0.52)	0.00
HPA	Low Choy et al., 2007	55	w	0.28 (0.07 - 0.47)	0.01
HPA	Neder et al., 1999	20-80	m	0.13 (-0.22 - 0.45)	0.47
HPA	Neder et al., 1999	20-80	w	0.42 (0.11 - 0.66)	0.01
OPA	Rantanen et al., 1993	74	w	-0.01 (-0.29 - 0.28)	0.97
OPA	Rantanen et al., 1993	75	w	0.21 (-0.14 - 0.51)	0.24
HPA	Rantanen et al., 1997 [a]	75	m	0.40 (0.21 - 0.55)	0.00
HPA	Rantanen et al., 1997 [a]	75	w	0.25 (0.11 - 0.39)	0.00
SPA	Sipila et al., 1994	74	w	0.36 (-0.11 - 0.70)	0.13
Sed	Sipila et al., 1994	74	w	0.01 (-0.53 - 0.54)	0.98
Total Combined Effect Size				*0.25 (0.20 - 0.30)*	*0.00*



Notes: CI = Confidence Interval, HPA = habitual physical Activity, LPA = leisure physical activity, m = men, OPA = occupational physical activity, Sed = sedentary with only walking activities, SPA = sport physical activity, w = women

[a] longitudinal study (other studies are cross-sectional)

Figure 2.2: Effect sizes for the correlation between HPA and knee extension strength.

2.3.2 Can HPAs in the past and present delay a decline in LLMS?

Active people vs. sedentary people vs. people who decrease their HPA level

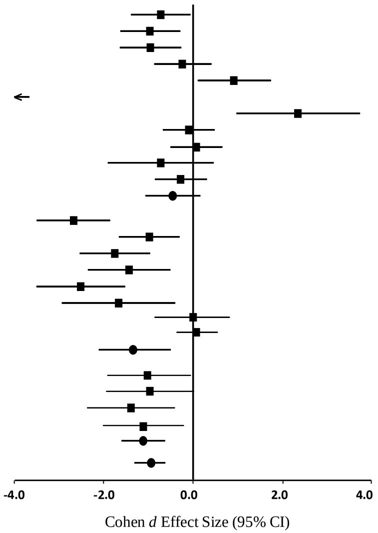
People ($n = 195$) with a stable HPA level show a small, but non-significant decline in knee extension strength within 5 − 11 years, as indicated by the combined effect size of -0.46 (95% CI = -1.07 − 0.14; $p = 0.13$) (Figure 2.3 on page 21). In contrast, sedentary people ($n = 146$) or people who decrease their level of HPA ($n = 40$) show a significant decline in knee extension strength within respectively 5 − 11 years (d = -1.35; 95% CI = -2.14 − -0.55; $p = 0.001$) and 10 days − 13 years (d = -1.12; 95% CI = -1.59 − -0.65; $p < 0.001$) (Figure 2.3 on page 21). The HPA and sedentary groups were heterogeneously distributed and the group of people with a decreasing level of HPA was homogeneously distributed $Q(10) = 74.41$, $p < 0.001$; $Q(7) = 58.37$, $p < 0.001$; $Q(3) = 0.47$, $p = 0.93$, respectively, indicating that findings among HPA and sedentary groups should be interpreted with caution. Between these three groups, the HPA group showed a slower decline (trend) in knee extension strength compared to the sedentary group ($Q(1) = 3.02$, $p = 0.08$) and the group of people with a decreasing level of HPA ($Q(1) = 2.82$, $p = 0.09$). The sedentary group and the group of people with a decreasing level of HPA showed comparable declines in knee extension strength ($Q(1) = 0.23$, $p = 0.63$). The degree of funnel plot asymmetry for the HPA group, the sedentary group and the group of people with a decreasing level of HPA was $p = 0.27$; $p = 0.03$; $p = 0.36$ respectively, fail safe N was 28; 147; 19 respectively, and the correlation between effect size and sample size was r = -0.07, $p = 0.83$; $r = 0.31$, $p = 0.45$; r = -0.31, $p = 0.70$, respectively. This indicates a possibility for publication bias in the sedentary group and the group of people with a decreasing level of HPA and the necessity to interpret these outcomes cautiously.

Reviewing comparable literature with other LLMS measurements, most studies support results from the meta-analysis. Studies support the result that habitually physically active people show no decline[165,166] and that they can delay[167,168] a decline in LLMS compared to a sedentary group[169]. Eight longitudinal studies support a significant decline in LLMS for people with a decreasing level of HPA[56,111,145,170–173], with one study showing a decline only for knee extension strength, but not for knee flexion strength over 9 years[171]. In contrast with results from the meta-analysis, one longitudinal study could not support a decline in knee extension strength for sedentary people within 6 years[111] and three studies suggest that the decline in LLMS is faster in a group of people with a decreasing level of HPA than the decline in a sedentary group[111,145]; people who decrease their level of HPA end up with an amount of LLMS that is comparable to that of sedentary people[174].

Dynamic LLMS and power seems to be more vulnerable to aging than static LLMS for two reasons. First, no decline in static knee extension strength within $6-8$ years was observed in habitually physically active people[111,175], while dynamic LLMS and power showed a significant decline within $6-10$ years[111,172]. Second, some studies with both static and dynamic strength measurements show that the decline in dynamic strength is higher than the decline in static strength[123,140,176] and that dynamic power declines even faster than dynamic strength[123,135,176]. No exploratory analysis could be done between the decline in static and dynamic strength measurements due to the fact that there were only two longitudinal studies which provided the amount of dynamic strength in Newton and the level of HPA[171,177].

HPAs in the past (before age 40) are not relevant for the amount of LLMS[141,164,174,178] at the age of 60 or older. Therefore, men with an equal level of HPA in the last year, have comparable knee extension strength[141] and leg extension power[179] irrespective of the age at which they took on their active lifestyles (i.e., before age 35, after age 40 or 50). This finding is supported by a non-significant negative relation between the effect size of the eighteen cross-sectional studies, measuring the difference in knee extension strength between habitually physically active people and sedentary people and the amount of years that the 1475 habitually physically active people are already active ($r =$ -0.13, $p =$ 0.53).

HPA	Study	Age	Gender	FU	Effect size (95% CI)	*p*
Active	Bohannon et al., 1997	54	w	11.0	-0.73 (-1.38 - -0.08)	0.03
	Bohannon et al., 1997	55	m	11.4	-0.97 (-1.63 - -0.31)	0.00
	Bohannon et al., 1997	65	w	8.3	-0.96 (-1.63 - -0.29)	0.01
	Bohannon et al., 1997	66	m	6.8	-0.24 (-0.87 - 0.39)	0.45
	Pearson et al., 2002	54	m	10.0	0.91 (0.11 - 1.72)	0.03
	Pearson et al., 2002	64	m	10.0	-5.21 (-6.74 - -3.68)	0.00
	Pearson et al., 2002	74	m	10.0	2.34 (0.97 - 3.71)	0.00
	Rantanen et al., 1997 [a]	75	m	5.0	-0.11 (-0.67 - 0.46)	0.71
	Rantanen et al., 1997 [a]	75	w	5.0	0.06 (-0.50 - 0.63)	0.83
	Rantanen et al., 1998 [a]	80	m	5.0	-0.74 (-1.90 - 0.44)	0.22
	Rantanen et al., 1998 [a]	80	w	5.0	-0.28 (-0.85 - 0.29)	0.33
	Combined Effect Size Active				*-0.46 (-1.07 - 0.14)*	*0.13*
Sedentary	Al-Abdulwahab et al., 1999	59	m	5.0	-2.69 (-3.50 - -1.87)	0.00
	Al-Abdulwahab et al., 1999	64	m	8.0	-0.99 (-1.65 - -0.32)	0.00
	Al-Abdulwahab et al., 1999	72	m	9.0	-1.76 (-2.53 - -0.99)	0.00
	Pearson et al., 2002	53	m	11.0	-1.44 (-2.35 - -0.53)	0.00
	Pearson et al., 2002	64	m	11.0	-2.52 (-3.50 - -1.55)	0.00
	Pearson et al., 2002	75	m	9.0	-1.68 (-2.93 - -0.42)	0.01
	Rantanen et al., 1997 [a]	75	m	5.0	-0.03 (-0.87 - 0.80)	0.94
	Rantanen et al., 1997 [a]	75	w	5.0	0.08 (-0.37 - 0.54)	0.73
	Combined Effect Size Sedentary				*-1.35 (-2.14 - -0.55)*	*0.00*
Decrease	Connelly et al., 1997 [a]	82	w	1.0	-0.99 (-1.92 - -0.06)	0.04
	Frontera et al., 2000 [a]	65	m,w	13.0	-0.97 (-1.95 - 0.00)	0.05
	Frontera et al., 2008 [a]	71	m,w	9.0	-1.40 (-2.38 - -0.42)	0.01
	Kortebein et al., 2008 [a]	67	m,w	0.03	-1.12 (-2.02 - -0.22)	0.02
	Combined Effect Size Decrease				*-1.12 (-1.59 - -0.65)*	*0.00*
Total Combined Effect Size					*-0.96 (-1.29 - -0.62)*	*0.00*



Notes: Age = age at baseline (years); CI = Confidence Interval; FU = follow-up measurement (years); HPA = habitual physical activity between baseline and follow-up measurement; m = men; w = women

[a] Longitudinal study (other studies are cross-sectional)

Figure 2.3: Effect sizes for the decline in knee extension strength of people with a stable active, stable sedentary or a decreasing level of HPA.

2.3.3 Are the results influenced by age, gender and type of HPA?

Age

The mean age of participants showed a non-significant negative correlation with effect sizes for both cross-sectional differences ($n = 27$ studies) ($r =$ -0.11, $p = 0.61$) and correlation studies ($n = 14$ studies) ($r =$ -0.25, $p = 0.43$) and a non-significant positive correlation with effect size of muscle strength decline ($n = 23$ studies) ($r = 0.23$, $p = 0.30$). This indicates that there is no evidence of an age effect for all outcomes.

Gender

Exploratory analysis did not show any significant difference between fourteen studies with only men ($n = 627$) and twelve studies with only women ($n = 753$) for cross-sectional differences in knee extension strength between HPA and sedentary groups ($Q(1) = 0.16$, $p = 0.69$). Due to the fact that only two correlation studies with men were available; no exploratory analysis for gender was done for correlation studies. The rate of decline in knee extension strength was slightly slower in six studies with only women ($n = 134$) ($d =$ -0.40; 95% CI = -0.79 − -0.01; $p = 0.04$) than fourteen studies with only men ($n = 217$) ($d =$ -1.04; 95% CI = -1.74 − -0.35; $p = 0.003$), but this difference was not significant ($Q(1) = 2.51$, $p = 0.11$). This indicates that there is no evidence of a gender effect for both outcomes.

Table 2.1: Summary of the included longitudinal studies.

Study	Age^{a}	HPA level^{b}	Subjects^{c}	Strength^{d}	Results
Aniansson et al. (1983)[140]	$70 \rightarrow 75$	Activity only known within last year before measurement: →**B**: moderate activities →**S**: mainly sitting activities	men 19 wn 21	KE KF Dyn, isom (N·m), isok (N·m)	→**B** men more isok KE KF strength than →**S** men† Higher rate of isok KE strength decline than isom strength decline*
Aniansson et al. (1992)[170]	$69 \rightarrow 73$ $69 \rightarrow 80$	**A**→**A** walked or participated in moderate activities $\geq 4h/w$ **A**→**B** walked or participated in moderate activities $\geq 4h/w$, but reduced this level within first 4 years	men 9	KE Dyn, isom (N·m), isok (N·m)	Decline in KE strength in 4 and 11 years*
Connelly and Vandervoort (1997)[56]	$82 \rightarrow 83$ $81 \rightarrow 83$	**A**→**S** participated 3 times/week in resistance exercise program, but reduced this level to short walks and sitting activities	wn 10 wn 4	KE Dyn, isom (N·m), isok (kg)	Decline in KE strength in 1 and 2 years*
Frontera et al. (2000)[171]	$65 \rightarrow 77$	**B**→**S** 834 ± 1409 kcal/w and strength training $\rightarrow 578 \pm 489$kcal/w	men 9	$KEKF$ Dyn, isok (N·m)	Decline in $KEKF$ strength in 12 years*
Frontera et al. (2008)[180]	$71 \rightarrow 80$	**A**→**B** 2919 ± 1631 kcal/w $\rightarrow$ 2261 ± 1620kcal/w	men 5 wn 7	$KEKF$ Dyn, isok (N·m, N·m/cm^2)	Decline in KE strength in 9 years*** No decline in KF strength in 9 years
Greig et al. (1993)[175]	$74 \rightarrow 82$	Activity based on Grimby scale $(1-6)$: **A**→**A** $3-5 \rightarrow 3-5$ **A**→**S** nm $\rightarrow 2$ $(n = 1)$	men 4 wn 10	KE Dyn, isom (N)	No decline in KE strength in 8 years
Hughes et al.(2001)[172]	$62 \rightarrow 72$	Activity within last year before both measurements: **A**: ≥ 500 kcal/w **AS**: ≥ 500 kcal/w with at least 40 weeks strength exercises **S**: < 500 kcal/w	men 52 wn 68	$KEKF$ CybexII, isok (N·m)	Decline in $KEKF$ strength in 10 years*** Older people show higher rate of strength decline‡

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Kortebein et al. (2008)[173]	67 → 67	**A→S** healthy participants completed 10 continuous days of bed rest at a clinical research center	men 5 wn 6	*KEKF* Dyn, isom (N), isok (W) *LEpower* sc (W)	Decline in *KEKF* strength and *LEpower* in 10 days*
Rantanen et al. (1997)[145]	75 → 80	Activity based on Grimby scale (1 – 6): **A→A** 4 – 6 → 3 – 6 **S→A** 1 – 3 → 3 – 6 **A→S** 4 – 6 → 1 – 2 **S→S** 1 – 3 → 1 – 2	men 35 wn 110	*KE* Dyn, isom (N)	No decline in *KE* strength in 5 years *KE* strength was related to activity level in men ($r = 0.40$) and wn ($r = 0.25$)*** **A→A** more *KE* strength than **S→S****
Rantanen and Heikkinen (1998)[121]	80 → 85	Activity based on Grimby scale (1 – 6): **A→A** men 4 – 6 → 4 – 6 **A→A** wn 3 – 6 → 3 – 6 **Others**	men 15 wn 59	*KE* Dyn, isom (N)	Decline in *KE* strength in 5 years in wn** **A→A** men more *KE* strength than **Others** men* Baseline *KE* strength negatively related to % change in strength in 5 years* No difference in rate of strength decline between **A→A** and **Others**
Uusi-Rasi et al. (2006)[111]	62 → 68	**A→A** gymnasts for 34 ± 10 years at least 2x/week and current leisure time activity is 275 ± 149 hours/year **A→S** gymnasts active at baseline, but not at follow-up **S→S** referents and current leisure time activity is 182 ± 129 hours/year	wn 217	*KE* Dyn, isom (kg) *LE* STS, SOS, kin (N/kg) *LEpower* JH, kin (cm)	**A→A** more *KE* strength and *LEpower* than **S→S**‡ **A→A** more *LE* strength than **S→S*** No decline in *KE* strength in **A→A**, **S→S** Decline in *LEpower* in **A→A**, **S→S*** No difference in rate of *KE* and *LEpower* decline between **A→A** and **S→S** **A→S** showed higher rate of *KE* strength and *LEpower* decline than **A→A**‡

Notes: **A** = active; **AS** = active involving strength; **B** = semi-active; cm = centimeters; dyn = dynamometer; h = hours; isok = isokinetic; isom = isometric; JH = jumping height; kcal = kilocalories; *KE* = knee extension; *KF* = knee flexion; kg = kilogram; kin = kinetic; *LE* = leg extension; m = meters; N = Newton; **S** = sedentary; sc = stair climbing; SOS = step-on-stair test; STS = sit-to-stand; w = week; W = Watt; wn = women; y = years

[a] Age at baseline → age at follow-up (years) [b] HPA level at baseline → HPA level at follow-up [c] Gender and number of participants [d] Strength measurement

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ † $p < 0.10$ ‡ p value not mentioned

Table 2.2: Summary of included cross-sectional studies.

Study	Age[a]	HPA level[b]	Subjects[c]	Strength[d]	Results
Aagaard et al. (2007)[128]	71 – 74	Activity based on last 50 years: **AE**: 3 – 4 x/w running/cycling **AS**: 2 – 3 x/w track and field athletics **S**: no regular activity	men 24	*KE* Dyn, isom (N·m/kg)	**AE** and **AS** have more *KE* strength than **S*** No difference in *KE* strength between **AE** and **AS**
Al-Abdulwahab (1999)[181]	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79 80 – 89	**S**: none were engaged in active sports for more than 2 h/w	men 160	*KE* Dyn, isom (N)	*KE* strength starts decreasing between age group 20 – 29 and 30 – 39‡
Alway et al. (1996)[144]	25 62	Activity based on last 10 years: **AE**: 2 runners, 3 tri-athletes, 1 cyclist training 7 h/w **S**: no regular physical training	men 24	*PF* Dyn, isom (N·m, N·m/cm^2, N·m/cm^3), isok (N·m, N·m/cm^2, N·m/cm^3)	No difference in absolute (N·m) *PF* strength between **AE** and **S** **AE** more *PF* strength per cm^2 or cm^3 plantar flexor muscles than **S*** Age group 25 more *PF* strength than age group 62*
Amara et al. (2003)[160]	55 – 86	Total amount of METs/d in the last year before measurement	men 188 wn 205	*PF* Dyn, isom (N, N·m/cm^2)	Activity positively related to *PF* strength*
Andrews et al. (1996)[109]	50 – 59 60 – 69 70 – 79	Activity based on median activity during life (4-point scale): **OA**: ocupational activity **LA**: leisure activity	men 77 wn 79	*KE KF AD HAb* Dyn, isom (N)	Some relations between **OA** and strength ($r = 0.03 - 0.26$ not specified)* Some relations between **LA** and strength ($r = 0.13 - 0.22$ not specified)*

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Aniansson et al. (1980)[164]	70	Occupational activity after age 40: **O1**: mostly sitting jobs **O2**: walking around jobs **O3**: walking/climbing and lifting jobs **O4**: heavy physical jobs **LA**: leisure activity before age 40 (not further specified)	men 40 wn 32	*KE* Dyn, isom (N·m), isok (N·m)	No relation between *KE* strength and **LA** Inverse relation between isom *KE* strength and **O**ccupational activity in men (no analysis could be done in wn)* Wn show *KE* strength decline at younger age than men‡
Aoyagi and Katsuta (1990)[141]	60 – 68	At time of measurement comparable occupational activity: **A26**: active since < age 35 **A45**: active since age 40 – 49 **A56**: active since age 50 – 59 **B**: moderate active, no systematic training	men 39	*KE* Dyn, isom (N·m), isok (N·m)	**A26** and **A45** have more isom *KE* strength than **B*** **A26** and **A56** have more isok *KE* strength than **B*** No difference between **A26**, **A45** and **A56** in *KE* strength
Aoyagi et al. (2009)[143]	65 – 84	Activity based on 'number of steps' and 'duration of activities' of >3METs within last year (mean): **A1**: >7000 steps/d **A2**: >19 min/d activities of >3METs **S1**: <6500 steps/d **S2**: <14 min/d activities >3METs	men 76 wn 94	*KE* Dyn, isom (N·m/kg)	*KE* strength positively related to activity **1** and **2** in wn* **A1** more *KE* strength than **S1*** **A2** more *KE* strength than **S2***
Asaka et al. (2009)[147]	63 – 74	**A**: rowers, 2 – 3 x/w for 8 years **S**: untrained, ≤ 2 x/w exercise	men 34	*LE power* Dyn, kin (W,W/cm^2)	**A** have 43% more *LE power* than **S*****
Bischoff et al. (2001)[178]	80 – 89	Self reported sport activities before age 40	men 38 wn 96	*KE KF* Pull gauge, isom (kg)	Sport activities before age 40 had no influence on *KE KF* strength
Bohannon (1997)[151]	20 – 29 30 – 39 40 – 49 50 – 59 60 – 69 70 – 79	Activity based on median activity during life: **OA**: ocupational activity **LA**: leisure activity	men 106 wn 125	*AD KE HAb* Dyn, isom (N)	*KE* strength decline within age group 40 – 49‡ *KE* (NDom leg) strength positively related to **LA***** No relation between **OA** and *AD KE HAb* strength

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Borges (1989)[150]	20 – 70	Occupational activity last 5 years: **O1**: mostly sitting jobs (no systematic exercise) **O4**: heavy physical jobs (no systematic exercise)	men 139 wn 141	*KE KF* Dyn, isom (N·m), isok (N·m)	No difference in *KE KF* strength between **O4** and **O1**
Boussuge et al. (2006)[162]	57 – 74	Activity measured by QUANTAP (does not consider the frequency and intensity of different activity sessions): Habitual activity in the past Leisure activity in the past Current habitual activity Current leisure activity	wn 23	*LE power* Cycle Ergometer, kin (W, N, W/kg, N/kg) JH, kin (cm, cm·kg)	No relation between *LE power* and habitual or leisure activity
Brooke-Wavell and Cooling (2009)[130]	60 – 75	Leisure physical activity: **A**: >3 h/w (bowlers) **S**: <3 h/w	wn 74	*KE* A framed chair, isom (N)	**A** more *KE* strength than **S***
Buford et al. (2010)[139]	55 – 75	**A**: >15 h/month sport activities (mean is 6.2 ± 0.8 h/w for 23 ± 3 years) **S**: light walking for daily activity	men 27	*KE(power)* Dyn, isok (N·m, N·m/kg, W)	**A** more *KE* strength than **S*** No difference in *KE power* between **A** and **S**
Casale et al. (2003)[166]	20 – 40 41 – 59 60 – 85	All subjects were (inter)national skiers: **LA** based on a regular week did not differ between age groups	men 37	*AD* Transducer, isom (kg)	No difference in *AD* strength between age groups
Dreyer et al. (2006)[125]	60 – 74	Activity based on last 30 years: **AS**: chronic endurance and resistance training, 5 d/w, 39 km/w running; currently at least 1 year 1x/w resistance training **AE**: chronic endurance training, 5 d/w, 46 km/w running **S**: Community dwelling	men 32	*LE power* Leg press, kin (N, N/kg) Bassey power rig, kin (W, W/kg)	No difference in *LE power* per kg leg lean mass between activity groups **AS** more *LE* strength than **S*** **AS** and **AE** more *LE* strength per kg leg lean mass than **S***

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Era et al. (1992)[155]	31 – 35 51 – 55 71 – 75	**LA**: leisure activity: **3 groups**: low, average, high **OA**: occupation activity: **3 groups**: manual workers, lower white collar workers, higher white collar workers **G**: gymnastics: **2 groups**: <1x/w, ≥1x/w	men 350	*KE* Dyn, isom (Nkg/m^2)	**LA** positively related to *KE* strength in age groups 31 – 35 and 51 – 55* No relation between **OA** and *KE* strength No difference in *KE* strength between **G** groups
Gauchard et al. (2003)[174]	≥ 60	**A**→**A**: more than 40 years active without interruption and still active **S**→**A**: sedentary for at least 4 years but now active **A**→**S**: active during youth and definitely stopped at least 30 years ago **S**→**S**: were never active during life	men 12 wn 28	*KE*(*power*) *KF*(*power*) *AD*(*power*) *PF*(*power*) Dyn, isok (N·m, W)	→**A** more *KE KF AD PF* strength and *KE KF power* than →**S*** No difference in strength and power between **A**→**A** and **S**→**A** No difference in strength and power between **S**→**S** and **A**→**S**
Gerdhem et al. (2003)[161]	75	Present activity level based on questionnaire Jonsson (scale 1 – 8)	wn 938	*KE KF* Dyn, isom (W)	Activity positively related to *KE* ($r = 0.30$) and *KF* ($r = 0.24$) strength***
Grassi et al. (1991)[135]	17 – 26 40 – 49 50 – 59 60 – 69 > 70	All athletes were still active for 1 – 2 h/d for 3 – 5 d/w: **AE**: endurance athletes **AP**: power athletes **S**: sedentary	men 151	*LE power* JH, kin (W, W/kg, W/l)	**AP** more *LE power* than **AE** and **S** until age 70* Linear decline in absolute *LE power* and *LE power* per kg body mass with increasing age‡
Harridge et al. (1997)[120]	21 – 35 70–100	**AE**: Life-long running and at time of measurement walking/running most d/w for at least 1 hour **B**: recreational active **S**: no regular activity	men 46	*KE PF* Dyn, isom (N/kg, N·m/kg)	No difference in *KE* and *PF* strength between **AE** and **S** *KE* and *PF* strength declined with age* **B** 21 – 35 more *KE* and *PF* strength than all in 70 – 100 age group*
Hunter et al. (2000;2001)[13	20 – 89	Leisure activity based on last two weeks on 6-point scale: **A**: ≥mean activity rating within 5-y age groups **S**: <mean activity rating within 5-y age groups	wn 217	*KE PF* Steel-framed chair, isom (N, N·m, N·m/kg)	Leisure activity positively related to *KE* and *PF* strength*** **A** more *KE* strength than **S*****

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Karamanidis and Arampatzis (2005; 2006)[126,182]	$21-32$ $60-69$	**AE**: last 10 years at least 3x/w running and competition **S**: no sport activity except at school	men 49	*KE PF* Dyn, isom (N·m/kg, N/kg)	No difference in *KE* and *PF* strength between **AE** and **S** Age group $21-32$ more *KE* and *PF* strength than $60-69^{*}$ No age × activity interaction in *KE* and *PF* strength
Kent-braun and Ng (1999)[169]	32 72	Habitual physical activity within 1 week: All subjects had low levels of physical activity (maximal 2x/w exercise)	men 22 wn 18	*AD* Transducer, isom (N, N/cm^2)	Old men less *AD* strength than young men* No difference in *AD* strength between old and young wn
Kettunen (1999)[179]	$45-68$	Participants were (inter)national sporters between 1920 and 1965 and had comparable activity level in last year before measurement: **AE**: runners **AI**: interval (soccer)players **AS**: weight lifters **B**: shooters	men 117	*LE power* JH, kin (cm)	**AS** highest JH, **B** the lowest (without osteoarthritis)* No difference in JH between activity groups with osteoarthritis *LE power* positively related to hours in team-sport training during last 12 months and lifetime participation in power training**
Klitgaard et al. (1990)[142]	$68-70$	Active men trained for last 12-17 years 3x/w and were sedentary before: **S→A**: swimmers **S→AE**: runners **S→AS**: strength trained **S→S**: sedentary	men 26	*KE* Flywheel, isom (N·m)	**S→AS** more *KE* strength than **S→S** and **S→A*** No difference in *KE* strength between **S→AE**, **S→A**, and **S→S** No difference in *KE* strength between **S→AS**, **S→AE** and a young control group (age 28)
Korhonen et al. (2006)[138]	$18-33$ $40-49$ $50-59$ $60-69$ $70-84$	**AS**: sprinters with (inter)national succes during life **S**: habitual activity of low intensity	men 91	*KE* Dyn, isom (N) *LE power* JH, kin (cm)	**AS** more *KE* strength and *LE power* than **S**‡

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Korhonen et al. (2009)[176]	17 – 33 40 – 49 50 – 59 60 – 69 70 – 82	All participants were good (inter)national sprinters: **A**→**B**: a decrease in training hours and sessions/w with increasing age	men 58	*LE*^{1} Dyn, isom (N) *LE*^{2} Smith machine, isok (kg) *LEpower* JH, kin (cm)	Overall decline in *LE* strength and *LEpower* with increasing age* *LE*^{1} strength declined 8% per decade *LE*^{2} strength declined 9% per decade *LEpower* declined 11% per decade
Kostka et al. (1997)[156]	66 – 82	Mean habitual activity (**HA**) of last week Mean leisure activity (**LA**) of last week	wn 29	*KEpower* Ergometer, kin (W/kg)	*KEpower* positively related to **HA** ($r = 0.51$) and **LA** ($r = 0.58$)**
Kostka et al. (2000)[110,159]	65 – 84	Activity based on 1 typical week: 1) Mean habitual daily energy expediture (**MHDEE**) 2) Leisure time sports activity (**LA**)	men 25 wn 29	*LEpower* Dyn, kin (W/kg)	No relation between *LEpower* and **MHDEE** or **LA** in men No relation between *LEpower* per kg quadriceps muscle and **MHDEE** or **LA** in wn *LEpower* per kg body mass positively related to **LA** ($r = 0.41$) in wn* *LEpower* per kg body mass positively related to **MHDEE** ($r = 0.35$) in wn†
Kuh et al. (2005)[106]	53	Leisure activity based on last 4 weeks: **A**: moderately active (≥5 exercises) **B**: mildly active (1-4 exercises) **S**: not active (0 exercises)	men 1357 wn 1400	*LE* 10 chair stands, kin (s)	**A** was faster than **B**, and **B** was faster than **S*****
Kuta et al. (1970)[134]	60 – 69 70 – 79	Activity based on at least 15 years: **A**: intense physical contest sports **B**: regular recreational sports activities **S**: never trained	men 132	*KE KF* Cable tensiometer, isom (kg)	**A** and **B** of age 60 – 69 had more *KE KF* strength than **S** of age 60 – 69* **A** of age 70 – 79 had more *KE* strength than **S** of age 70 – 79*
Laroche et al. (2007)[129]	65 – 84	Activity after age 50: **A**: active in competitions: >41 METs·h/w **S**: no regular activity: <41 METs·h/w	wn 40	*KE* Dyn, isom (N·m/kg)	**A** had 15% more *KE* strength than **S***
Leong et al. (1999)[132]	65 – 80	Activity based on at least 5 years: **AS**: weight lifters (until time of measurement in strength training) **S**: age-matched controls	men 12	*KE* Force transducer, isom (N)	**AS** had more *KE* strength than **S***

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Lindström et al. (2009)[148]	$30-69$	Leisure activity within last year: **LA1**: gym(nastics), aerobics **LA2**: nordic walking, swimming **LA3**: gardening, household activities **‘S’**: sedentary people, but also active people of another **LA** group	wn 316	$LE\,power$ One-leg squat, kin	**LA1** had more $LE\,power$ than **‘S’**** **LA2** had more $LE\,power$ than **‘S’**† No difference in $LE\,power$ between **LA3** and **‘S’**
Low Choy et al. (2007)[153]	$20-39$ $40-49$ $50-59$ $60-69$ $70-79$	Habitual physical activity (scale 1-6) No further information provided	wn 320	KE HAb HAd Spring-gauge, isom (N·m)	Activity positively related to KE strength** Activity positively related to HAb HAd strength* Decline in KE strength in age group $60-69^{*}$ Decline in KE HAb HAd strength in age group $70-79^{**}$ Activity declined with increasing age‡
McCrory et al. (2009)[131]	$65-93$	Athletes of the National Senior Games: **A**: runners, cyclists, swimmers **S**: controls (ranging from sedentary to active)	men 103 wn 64	KE KF Chair, isom (N·m/kg)	**A** had more KE KF strength than **S*****
Miyatake et al. (2009)[149]	$20-69$	Activity based on last 3 months: **A**: minimum of 2x/w at least 30 min/session **S**: less active than **A**	men 3018 wn 6881	KE Dyn, isom (kg, kg/kg)	**A** had more KE strength than **S***
Neder et al. (1999)[152]	$20-39$ $40-59$ $60-80$	**HA**: habitual physical activity of last two weeks, including occupation, sport and leisure activity **S**: non-trained (most people score <8 on Baecke scale (1982))	men 34 wn 37	KE Dyn, isok (N·m)	No relation between KE strength and **HA** in men Positive relation ($r = 0.42$) between KE strength and **HA** in wn**
Pearson et al. (2002)[123]	$40-89$	**AS**: elite master olympic weightlifters **S**: untrained	men 108	KE Dyn, isom (N) $LE\,power$ Dyn, kin (W, W/kg, W/cm^3)	**AS** had more KE strength and $LE\,power$ than **S*** Rate of KE strength and $LE\,power$ decline comparable between **AS** and **S**

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Pollock et al. (1997)[167]	60 – 69 70 – 78 79 – 89 90 – 92	All men were track athletes 20 years ago and more than 90% still trained frequently at an intensity of 60-85% HRmax reserve	men 21	*LE* Leg press machine, kin (kg)	*LE* strength declined at age 90 – 92*
Rantanen et al. (1992)[118]	50 – 60	**A University**: physical education teachers **A Vocational**: gymnastics **S University**: other teachers **S Vocational**: random control group	wn 112	*KE* Dyn, isom (N)	**A** had more *KE* strength than **S***** **University** had more *KE* strength than **Vocational***
Rantanen et al. (1993)[107]	66 – 85	**A**: a mean of 50 years habitual activity and 70% still active for at least 3x/w **S**: no regular activity The history of heavy or sedentary manual **work** within each group	wn 94	*KE* Dyn, isom (N)	**A** had more *KE* strength than **S*** No relation between **work** history and *KE* strength in **A** and **S**
Rantanen et al. (1999)[157]	>65	Activity based on last 1-2 weeks: **A**: moderately active **B**: minimally active **S**: extremely inactive	wn 755	*KE* Dyn, isom (kg)	Positive relation between activity and *KE* strength*
Ringsberg et al. (2001)[122]	65 – 75 76 – 89	**A**: active for last 20 years at least 1 h/w **S**: random controls from urban (**U**) and rural (**R**) community	wn 357	*KE KF* Cybex II (**A** and **SU**), transducer (**SR**), isom (N·m)	**A** had more *KE KF* strength than **SU*** No difference in *KE KF* strength between **A** and **SR**
Sandler et al. (1991)[154]	25 – 34 35 – 44 45 – 54 >55	Amount of calories expended per week in ADL, walking, climbing stairs and sports	wn 620	*PF HAb* Custom-made devices, isom (kg, kg/kg)	Positive relation between activity and *PF HAb* strength**
Scott et al. (2009)[163]	50 – 79	Amount of ambulatory activity measured with a pedometer during 5-7 consecutive days	men 481 wn 501	*LE* Dyn, isom (kg, kg/kg)	Positive relation between ambulatory activity and *LE* strength in wn* Positive relation between ambulatory activity and *LE* strength in men†

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Sipila et al. (1991)[136]	70 – 81	Activity based on last 5 years: **AS**: weight lifters and throwers **A**: sprinters and jumpers **AE**: long distance runners, orienteer's and cross-country skiers **S**: moderate active	men 139	*KE* Dyn, isom (N, N/kg) *LE power* JH, kin (cm)	**AS**, **A**, **AE** had more *KE* strength than **S*** **AS**, **A** had more *KE* strength than **AE*** **AS**, **A**, **AE** had more *KE* strength per kg lean body mass than **S**** **A** had more *KE* strength per kg lean body mass than **AE**** **AS**, **A**, **AE** had more *LE power* than **S***** **A** had more *LE power* than **AS**, **AE***
Sipila and Suominen (1994)[119]	66 – 85	Activity based on last 15 – 74 years: **A**: athletes participating in various sports (7 h/w training within last year) **S**: a random sample with mainly walking activities	wn 36	*KE* Dyn, isom (N, N·m, N/kg, N·m/kg, N/cm^2)	**A** had more *KE* strength than **S*** **A** had more *KE* strength per kg body mass than **S**** No difference in *KE* strength per cm^2 quadriceps muscle between **A** and **S**
Slade et al. (2002)[183]	60 – 85	**AS**: participating in strength training $\geq$ 2 d/w for $\geq$ 12 w, and habitual active for 3 d/w **A**: 3 d/w habitual activities for at least 25 min/d	men 18 wn 17	*LE power* Cycle ergometer, kin (W, W/l, W/kg) *LE* Double leg press, kin (kg)	**AS** had more *LE* strength and *LE power* per l lean thigh volume than **A*** No difference in *LE power* per kg fat free mass between **A** and **AS**
Tarpenning et al. (2004)[168]	40 – 49 50 – 59 60 – 69 70 – 79 80 – 89	**AE**: master athletes for at least 5 years and now running at least 15 km/w and at least 1x/y in organized running competition	men 107	*KE* Dyn, isok (N·m/kg)	No difference in *KE* strength between age groups 40 – 49, 50 – 59, 60 – 69 *KE* strength decreased in age group 70 – 79 and 80 – 89*
Tarpenning et al. (2006)[127]	40 – 49 50 – 59 60 – 69	**AE**: master athletes for at least 5 years and now running at least 15 km/w **S**: run less than 1 mile/w or spend less than 30 min/w in activity	wn 94	*KE* Dyn, isok (N·m, N·m/kg)	No difference in *KE* strength between **AE** and **S** **AE** less *KE* strength per kg lean body mass than **S*** *KE* strength declined with age* No decline in *KE* strength per kg lean body mass

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Visser et al. (2005)[124]	70 – 79	Activity based on last 7 days: **A**: $\geq$1000 kcal/w physical activity **B**: <1000 kcal/w physical activity and $\geq$2719 kcal/w total activity **S**: <1000 kcal/w physical activity and <2719 kcal/w total activity Walking on last 7 days: **Frequent walkers**: $\geq$400 kcal/w **Occasional walkers**: <400 kcal/w **Never walkers**: 0 kcal/w	men 1443 wn 1544	*KE* Dyn, isok (N·m)	Physical activity positively related to *KE* strength*** **A** and **B** had more *KE* strength than **S***** No relation between walking and *KE* strength in men and wn
Xu et al. (2008)[146]	>60	$\mathbf{A}_1$: minimal 4 year only regular Tai Chi exercise $\mathbf{A}_2$: minimal 4 year regular jogging and other exercise, but no Tai Chi **S**: minimal 5 year no regular exercise	men 36 wn 25	*KE KF AD PF* Dyn, isok (N·m/kg)	$\mathbf{A}_2$ had more *KE KF* strength than **S*** No difference in *KE KF* strength between $\mathbf{A}_1$ and $\mathbf{A}_2$ $\mathbf{A}_{1+2}$ had more *AD* strength than **S***
Yoshiga et al. (2002)[137]	65 – 66	Activity based on at least 40 year: **A**: rowing more than 2x/w **S**: untrained (not further specified)	men 30	*KEpower* Dyn, isok (W)	**A** had more *KEpower* than **S***

Notes: **A** = active; *AD* = ankle dorsiflexion; ADL = activities of daily living; **AE** = active involving endurance; **AI**: active involving interval; **AP** = active involving power; **AS**: active involving strength; **B** = semi-active; cm: centimeters; d: days; dyn: dynamometer; h = hours; *HAb* = hip abduction; *HAd* = hip adduction; HRmax = maximal heart rate; isok = isokinetic; isom = isometric; JH = jumping height; kcal = kilocalories; *KE* = knee extension; *KF* = knee flexion; kg = kilogram; kin = kinetic; km = kilometers; l = liters; **LA** = leisure activity; *LE* = leg extension; METs = metabolic equivalent of tasks; min = minutes; N = Newton; NDom = non-dominant; N·m = Newton meter; *PF* = plantar flexion; **S** = sedentary; s = seconds; w = week; W = Watt (N·m/s); wn = women; y = years

[a] Age range of groups in years [b] HPA groups: habitual physical activity level of each group [c] Gender and number of participants [d] Strength measurement

* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$ † $p < 0.10$ ‡ p value not mentioned

Type of HPA

When we divide habitually physically active people in three different groups based on characteristics of their HPAs, effect size is the highest for 68 people who participate in HPAs that are mainly focused on strength ($d = 2.41$; 95% CI = $1.26 - 3.55$; $p < 0.001$), followed by 1217 people who participate in other (no specific) HPAs ($d = 2.00$; 95% CI = $0.65 - 3.35$; $p < 0.01$) and 117 people who participate in HPAs that are mainly focused on endurance ($d = 0.46$; 95% CI = $0.16 - 0.75$; $p < 0.01$) (Figure 2.1 on page 17). Data of people participating in strength activities and other (no specific) HPAs were heterogeneously distributed ($Q(6) = 36.33$, $p < 0.001$ and $Q(14) = 1646.39$, $p < 0.001$, respectively) and data of people participating in endurance activities were homogeneously distributed ($Q(4) = 7.17$, $p = 0.13$). The group with endurance activities had a significant lower effect size compared to the groups with strength and other (no specific) HPAs ($Q(1) = 8.64$, $p = 0.003$ and $Q(1) = 3.88$, $p = 0.05$, respectively). The difference in effect size between the group with strength activities and other (no specific) HPAs was not significant ($Q(1) = 0.20$, $p = 0.65$), although it should be interpreted with caution, because both groups were heterogeneously distributed. For strength activities, other (no specific) HPAs and endurance activities the degree of funnel plot asymmetry was $p = 0.05$; $p = 0.29$; $p = 0.03$ respectively, fail safe N was 157; 4196; 13 respectively and the relation between effect size and sample size was $r = 0.25$, $p = 0.59$; $r = 0.69$, $p < 0.001$; $r = -0.64$, $p = 0.25$, respectively. In terms of endurance activities, this indicates that there is possible evidence for publication bias and the necessity to interpret outcomes cautiously, there is some evidence for publication bias in strength activities and no evidence for publication bias in other (no specific) HPAs. Exploratory analysis between types of HPA was not possible for correlation studies and studies measuring the decline in knee extension strength due to a small amount of studies with different types of HPA.

Reviewing comparable literature with other LLMS measurements, one study supports the result from the meta-analysis that a group with endurance activities has less LLMS and power than a group with strength activities[136]. In contrast with results from the meta-analysis, six studies found no significant difference in LLMS between people participating in endurance activities and sedentary people[120,126,135,142,144,182]. In one study, a group with mainly strength activities had significantly more LLMS and power than a group with other (no specific) HPAs[183].

2.4 Discussion

2.4.1 Do present HPAs have a positive influence on LLMS?

Habitually physically active people have more LLMS than sedentary people with an effect size of $d = 1.89$, as indicated by 18 different studies with 1475 habitually physically active and 1379 sedentary people in the meta-analysis and 23 studies in the review. It should be noted that in the meta-analysis various groups (age or gender) in one study were separately analyzed which might have caused less variance in the results. Although detailed information is lacking, we argue that the heterogeneity of effect in Figure 2.1 (on page 17) is due to the differences in intensity of the HPA level, mainly in the active groups, because there is less variance in intensity level in the sedentary groups. Higher levels of physical activity are associated with higher levels of LLMS in a continuous dose-response manner. The higher effect sizes are caused by vigorous sport physical activities and exercise performed most days of the week (like weight lifting, or burning 8642 kcal per week, which is for a person of 70 kg body weight comparable to climbing hills with 42 lb load for almost 2 hours every day[184]). Medium effect sizes are observed in moderate physical activities for (at least) 4 hours per week (domestic work such as dusting, making beds, ordinary gardening) or vigorous physical activities for (at least) 2 hours per week (activities causing breathlessness and sweating). Low effect sizes are observed in moderate physical activities for maximal 3 hours per week or when people perform only cardiovascular endurance sport activities (running nonstop for at least 15 km or 1 hour a day, regardless of the amount of days per week). The correlation between HPAs and LLMS showed an effect size of $d = 0.25$ as indicated by 9 studies with 1315 people in the meta-analysis and 18 studies in the review. Only two studies showed no relation between occupational physical activity and LLMS[150,164], possibly because people who perform highly physical activities at work tend to engage in less physical activities during leisure time; literature for adults shows that leisure-time activity levels tend to increase over time, while occupational physical activity decreases over time[185].

2.4.2 Can HPAs in the past and present delay a decline in LLMS?

Results from this meta-analysis indicate that people who maintain a high level of HPA show no decline in static knee extension strength within $5-11$ years ($p = 0.13$). This result is supported by two other longitudinal studies[111,175]. There is evidence that dynamic LLMS declines faster than static LLMS in habitually physically active people[123,176,186], but the exact rate of dynamic LLMS decline is not known. One explanation might be that dynamic muscle strength performance does not solely depend on strength, but also on range of joint motion and prolonged reaction time[161], both of which are vulnerable to aging[187,188].

In contrast to active people, sedentary people show a significant decline in static knee extension strength within 5 – 11 years ($d = -1.35$) although findings were wide-ranging. One longitudinal study showed no support for this significant decline[111]. An explanation for this contrasting result is that, in the latter study, the sedentary group engaged in HPAs for 3.5 hours per week; the sedentary groups in all other studies were active for less than 2 hours per week. In combination with the result that sedentary people have less knee extension strength than habitually physically active people, a decline in LLMS means that sedentary people are exposed to a higher risk of severe functional impairment[51,189].

People who decrease their level of HPA show a significant decline in knee extension strength within 10 days to 12 years ($d = -1.12$). This result was consistent among studies in the meta-analysis and was supported by six longitudinal studies in the review[56,111,170–173] and one cross-sectional study[176]. The majority of the studies show that knee flexion strength declines in a similar way as knee extension strength[171–173], except for one study[180].

The respective declines in LLMS in these three groups (a HPA group, a sedentary group and a group of people who decrease their HPA) did not differ significantly from one another in the meta-analysis. The length of follow-up could not explain the heterogeneity in Figure 2.3 on page 21, but it should be noted that in the group of people who decrease their HPA, half of the studies measured a decline in knee extension over a much shorter period (10 days and 1 year) compared to the other studies that showed a decline in knee extension strength in the habitually physically active group and the sedentary group (5 – 13 years). A comparable decline in strength within a shorter period would suggest a faster decline in strength. Three other studies in this review support a faster decline in LLMS in the group of people who decrease their HPA compared to the habitually physically active group and the sedentary group[111,145,174]. Together with the result that HPAs before the age of 40 seem to have little effect on LLMS and power after the age of 60, this finding implies that physical activity in distant history (e.g., 10 years ago) is less beneficial for present LLMS than more recent physical activity (e.g., only 1 year ago). This indicates that a high level of HPA in the present is a prerequisite for maintaining high levels of LLMS.

Overall, LLMS declines when people cease their HPAs. Unfortunately, most people show a decline in level of HPA during aging[190,191], especially after retirement[192] or when people move into a nursing home[193]. These people have an increased risk of becoming disabled, because both lower physical activity level and declined muscle strength are significant predictors of disability[157]. Therefore, older people should be encouraged to participate regularly in HPAs to delay the decline in LLMS and the associated negative effects on, for example, health and cognition.

2.4.3 Are the results influenced by age, gender and type of HPA?

Age does not seem to influence the relation between present HPAs and knee extension strength. At all ages, HPAs can increase LLMS. This result is comparable to a review showing that older people of all ages are able to increase LLMS by strength training[194]. At all ages, the loss of knee extension strength seems to be the same in this meta-analysis. However, because most people decrease their level of HPA as they grow older, it is more likely that older people lose more strength, but this might be caused mainly by a decreasing level of HPA.

Men and women do not seem to differ in the relation between HPAs and LLMS in this meta-analysis; the difference in knee extension strength between habitually active people and sedentary people was not different for men and women ($p = 0.69$). In line with other studies[164,195], the rate of decline in knee extension strength was slightly, but not significantly, slower for women (d = -0.40) than for men (d = -1.04).

Various types of HPA have a positive influence on knee extension strength, as indicated by significant effect sizes for people who perform HPAs that are mainly focused on strength, on other (no specific) HPAs, or mainly on endurance ($d = 2.41$, $d = 2.05$, $d = 0.46$ respectively). However, the influence of habitual endurance activities on knee extension strength was significantly lower than that of habitual strength activities. A possible explanation is that endurance activities mainly increase the aerobic capacity of the involved muscles (muscular endurance) and not muscle mass specifically[196,197]. Muscle mass is positively related to strength[198] and can be increased by (strength) activities of sufficient intensity and duration[196]. It should be noted that endurance activities are important for aerobic capacity[196], cognition, especially for executive functions[17,199] and it lowers the risk of mobility limitations[124] and dementia[200]. Muscle tissue is highly plastic that responds to the type and intensity of day to day demands.

2.4.4 Limitations

The present meta-analysis and review have several limitations. First, the type of strength measurement differs throughout most of the studies, which may contribute to variations found in the various studies[181]. However, the correlations between various strength and power measurements are high[162,201,202]. Furthermore, some categories show a limited number of studies involving LLMS measurements, for example for men or women of different ages. More research is necessary to determine the difference in decline in LLMS between people with different types of HPA. In addition, more longitudinal studies covering a longer period are necessary, because cross-sectional studies can underestimate the changes with age compared to a longitudinal design, as seen with upper limb strength[203].

2.5 Conclusions

In conclusion, to obtain a high amount of LLMS during aging, it is important to achieve and maintain a high level of HPA with mainly muscle-strengthening activities throughout a person's lifetime, performing moderate physical activities for (at least) 4 hours per week or vigorous physical activities for (at least) 2 hours per week. Future research should now focus on how age affects the ability and level of HPA, because during normal aging people decline their HPA level.

CHAPTER 3

IMPOVERISHED ENVIRONMENT, COGNITION, AGING AND DEMENTIA

Abstract. Animals living in an impoverished environment, i.e., without the possibility of physical and social activity, perform worse on cognitive tests compared to animals in an enriched environment. The same cognitive difference is also observed in humans. However, it is not clear whether this difference is caused by a decrease in cognition due to an impoverished environment or an increase due to an enriched environment. This review discusses the impact of an impoverished environment on cognition in animal experimental studies and human experimental studies with community-dwelling and institutionalized older people. Results show that the cognitive functioning of old rats is more affected by an impoverished environment than young rats. Similarly, sedentary and lonely people (impoverished environment) have worse cognitive functioning and show a faster cognitive decline than physically and socially active people. Institutionalization further aggravates cognitive decline, probably due to the impoverished environment of nursing homes. In institutions, residents spend an unnecessary and excessive amount of time in bed; out of bed they show mainly sedentary or completely passive behaviour. In conclusion, older people, especially those that have been institutionalized, have poor levels of physical and social activity, which in turn has a negative impact on cognitive functioning. [1]

3.1 Introduction

EPIDEMIOLOGICAL studies show a positive relationship between physical activity and cognition[18]. More specifically, a high level of physical activity during life is related to lower rates of dementia and might even protect against dementia[204,205]. Correspondingly, a low level of physical activity during life is related to higher rates of dementia and might increase the risk of developing dementia[18,204,205]. A mechanism underlying these findings is that a low level of physical activity is related to a smaller volume of

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[1] Volkers, K.M. and Scherder, E.J.A., 2011. Impoverished environment, cognition, aging and dementia. *Reviews in the Neurosciences*, 22(3):259-266.

the hippocampus[206], an area in the medial temporal lobe that is involved in long-term memory and spatial navigation[207]. It is important to note that these studies only show a 'relationship' between physical activity and cognition, not a 'causal' relationship.

A causal relationship, i.e., an effect of physical activity on cognition, is shown by intervention studies with children[58], adolescents[59], older cognitive healthy people[60], persons with mild cognitive impairment[61] and older persons with Alzheimer's disease (AD)[208]. Results of the studies with older people show that particularly executive functions such as inhibition, scheduling, planning and working memory respond positively to an increase in physical activity[17,62,64,66]. One of the brain areas that plays a crucial role in executive functions is the prefrontal cortex (PFC)[209]. Indeed, the PFC reacts positively to physical activity[210]. Physical activity is part of an enriched environment, together with socialization[71]. It is known that an enriched environment induces a variety of neurophysiological changes, e.g., neurogenesis[211]. Living in an enriched environment could also improve cognition, i.e., learning and memory[72,73].

Considering the positive effect of an enriched environment on cognition, the question arises whether an impoverished environment will worsen cognitive functions. This question is of clinical relevance, as passivity is common among residents in nursing homes[80,212], but often not acknowledged as a noteworthy behaviour[213].

Therefore, the goal of the present review is to address studies that examined the effect of an impoverished environment on cognition in older animals and in older persons with and without dementia. An impoverished environment includes physical inactivity and loneliness, or even worse, passivity and isolation. Animal experimental studies will be discussed first, followed by clinical studies including older people living in society and in institutions both with and without dementia.

3.2 Animal experimental studies

There is ample evidence that animals living in an impoverished environment perform worse on cognitive tests compared to those living in an enriched environment[214–222]. However, these results do not indicate whether these differences are caused by a decrease in cognition due to the impoverished environment or by an increase due to the enriched environment. Therefore, within the scope of the present review, we will address studies that compared an impoverished environment with a 'standard' environment.

3.2.1 Physical inactivity

A first interesting finding is that old rats are more influenced by environmental conditions compared to young or mature rats[73,223]. Especially in impoverished environments, i.e., environments without possibilities to be physically active (e.g., due to immobilization) and without social interaction, aged rats are more affected than young rats[73]. In this one available study, old rats living in an impoverished environment for 92 days showed a decline in learning and memory compared to rats in a standard environment[73]. A mechanism underlying this finding might be that an impoverished environment contributes to a reduced density of metabotropic glutamate receptors in the PFC which results in impaired working memory[221,224]. Interestingly, the cognitive impairments observed after three months of impoverished environment in old rats were reversible[73]. When old rats were transferred from an impoverished to an enriched environment for an additional three months, their cognitive performance improved with 32%[73]. An opposite transfer, from a standard to an impoverished environment, caused a cognitive decline of 74%[73]. Rats with the worst cognitive performances were housed in an impoverished environment for six consecutive months[73].

3.2.2 Isolation

As mentioned above, an environment restricting physical activity has a negative influence on cognition. It is, however, suggested that loneliness, another aspect of an impoverished environment, has an even higher negative impact on cognition[225]. Already in an early period in life, isolation causes memory problems[226], attention deficits[227], disruption of inhibitory control in attentional selection[228], reduction in information processing[220] and deficits in learning[229,230], e.g., rule learning[231] or reversal learning[217,231]. Reversal learning requires the inhibition of previously learned responses which has been associated with prefrontal-corticostriatal functioning[232]. Also, in adult male mice, isolation for 60 days causes a decrease and delay in their learning performances[233], possibly due to changes in dopamine metabolism in the PFC[234]. Old isolated rats had more learning problems compared to social rats after 70 days[223].

It is suggested that brain damaged animals are more sensitive to the effects of their environment than normal animals[235]. This implies that brain damaged animals suffer a greater disadvantage from impoverished environments than normal animals. If this also applies to humans, the environment is especially important for people with brain damage, e.g., dementia and stroke.

3.3 Human experimental studies

3.3.1 Community-dwelling

Many studies with healthy older people describe ‘successful aging’, but cognitive components of successful aging are in the minority compared to physical functioning[236]. Factors, i.e., genetics, (neuro)biological, emotional/psychological, and social/environmental determinants, associated with a positive effect on cognitive functioning have already been reviewed[236]. Research describing the opposite is, however, scarce; e.g. to what extent does impoverished environment contribute to unsuccessful cognitive aging.

Physical inactivity

From 39% to 95% of US adults from 65 years and older and 100% of European adults of at least 70 years of age do not meet the recommendations for physical activity levels[237–239] (see Table 3.1 on page 45). Overall, the daily minutes in, e.g., moderate activity is frequently obtained, but activity session durations are often too short to meet the criteria[240]. For example, a small sample of older Australian people (71 years old) spent a total of 429 min/day upright, including 298 minutes standing and 130 minutes walking[80]. However, they had a median session of 8 minutes, and 75% of the sessions were shorter than 17 minutes. None of them participated in more than two episodes per week of moderate intensity physical activity[80]. Out of 15 participants, one was extremely sedentary and was not upright for even 15 min/day at all, which was not due to health problems[80]. The level of activity of European people seems even worse; almost half of them did not perform any session of 10 minutes of moderate physical activity[237]. Another study with younger American participants (57 years) showed a median of 32 minutes of moderate physical activity per day[241]. However, the sessions of physical activity that lasted at least 10 minutes contained only 4.6 minutes of moderate intensity[241]. Overall, older people spend more time on sedentary to low-intensity activities, e.g., lying, sitting, standing (< 3 metabolic equivalent units (METs), i.e., a value to rate energy expenditure of activities compared to rest[242]) instead of moderate- and high-intensity activities than younger adults[237,243–245]. After age 70 years, people spend more than 66% (> 9 hour) of their waking hours in sedentary behaviour[243]. This sedentary behaviour increases in a linear trend with age[243], as also seen in the mean number of daily steps people between age 70 and 75 years make (5661 steps/day) compared to people older than 80 years (3410 steps/day)[246]. Both of these groups do not achieve the recommended 7500 steps a day which corresponds to approximately 30 minutes of moderate physical activity[247].

The studies addressed above used objective measurements with accelerometers. The subjective amount of physical activity would probably be higher, because (older) people often indicate higher levels of physical activity than indicated by objective measurements[239,241,248]. In addition, the prevalence of sedentary people assessed by questionnaires varies from 14% to 41%[249], which emphasizes the limitations of self-reported physical activity habits[250,251].

Table 3.1: Physical activity recommendations for adults.

- ≥ 30 min of moderate-intensity for 5 days/week in one continuous session or more sessions of at least 10 minutes[238,268].
    - Lower or higher intensity activities increase or decrease the duration and frequency, respectively. A combination of different intensity activities is possible.
- $\geq 2\times$/week strengthening & flexibility exercises for older adults[268].
    - Strengthening: $8-10$ exercises, $10-15$ repetitions per exercise.
    - Flexibility: at least 10 minutes.

Sedentary people not only have lower cognitive performances compared to people who perform physical activities, they also show a faster decline in cognitive performance[72,252–261]. Most studies show that a sedentary midlife or youth is associated with a faster cognitive decline and higher risk of dementia[98,204,257,262,263], but not all studies show this association[264]. Perhaps in this study the intensity of the physical activity was too low; a lower intensity and frequency of physical activities lacks association with cognition[265]. A meta-analysis showed that sedentary people can enhance their cognitive functioning, especially executive functions, by exercise training[62] which indicates that these people are not performing at their highest cognitive level with a sedentary lifestyle. The opposite direction has also been observed: people who decrease the intensity of their physical activities show a faster cognitive decline compared to those who have a stable intensity level[266,267].

Loneliness

Frail older people in the society spend more than 50% of their days alone[269]. More loneliness, i.e., less social networks and social engagement, is related to low cognitive performances and a faster cognitive decline in older people with or without cognitive impairment[99,232,270–274], especially concerning executive functioning[232]. Another review did not report such firm conclusions due to low quality of evidence; this review missed evidence due to high demands for inclusion[260]. Social activities during midlife are also related to a reduced dementia risk[275]. Community-dwelling older people with dementia report that their needs for social interaction and participation in activities are largely unmet[276]. Those with higher age, lower Mini-Mental State Examination (MMSE) scores, and living alone have greater levels of unmet needs[276]. These aspects result unfortunately in a higher risk of moving into a nursing home which is an even more impoverished environment, which will be addressed in the next section.

3.3.2 Institutionalized

Physical inactivity

By 1966 it was already observed that continued hospitalization has a negative effect on cognition in elderly residents[277]. Others also observed that cognitive functioning of old people in various institutional settings is worse than the cognitive functioning of the community-dwelling aged[278,279]. Even when these groups are carefully matched on different variables such as age, intelligence and health, most residents show an impaired function in frontal and medial temporal lobe brain regions compared to their counterparts in the community[279]. These brain regions play an important role in executive functioning and memory[209,280]. Animal experimental studies (see above) suggest that this might be due to the impoverished nature of nursing homes.

A nursing home can reflect a passive environment; in one study, more than 30% of the residents reported a decrease in physical activity during their stay in a nursing home, despite their largely positive attitude towards physical exercise[193]. As a result, ambulatory residents sit down for long periods[281] and they spend daily only 137 minutes upright, including 94 minutes standing and 43 minutes walking[80]. These walking activities were split into several sessions with a median duration of 4 minutes, and as a result these residents rarely spend 30 minutes continuously upright, and some (4 out of 16) did not stay upright for more than 10l minutes per day[80]. Other studies confirm that residents show primarily sedentary behaviour[282–284]. Most studies show that especially residents with dementia rarely do anything[285–287]; when they are not in bed during the daytime they sleep 30% of the time[288]. By contrast, one study observed more participation in activities in residents with mild to moderate dementia compared to those without dementia, possibly due to their required engagement in rehabilitation[282]. These residents spend most of their activity time in therapeutic activities[289], but this amount becomes less when they have severe dementia[282,286,289,290].

In nursing homes, an extreme form of physical inactivity is physical restraint. Physical restraints are often used to immobilize residents[291,292] with the consequence that these people are sitting or lying down for 94% of the day[281]. Persons who are physically restrained are not able to explore their environment, have less personal interaction and are dependent on others for their daily routines, such as going to the toilet. Impoverished environment by use of physical restraint (with or without the combination of neuroleptic use) is associated with cognitive decline[293–295], more than those who are not restrained[294,296]. It should be noted that not all nursing homes use physical restraints often[297,298]. It is striking that some unrestrained residents are even less active than residents who are immobilized by physical restraints[281].

Many residents take psychoactive drugs that causes sedation[286,299], but also environmental restrictions might explain the low levels of physical activity[300]. The engagement in activities of residents is among others dependent on the availability and quality of the activity programs[282]. Concerning the amount and type of activities, nursing homes do not respond to the (individual) needs of their residents, especially not to those with sleep disturbances who exhibit excessive sleepiness during the day[284,301]. In addition, nursing homes underestimate the abilities of these residents resulting in unchallenging activities[284]. For example, in one study 20% of the residents received occasional activities such as singing or cooking and 12% received daily activities, but these activities were considered inappropriate based on the level of functioning or the individual's interest[290]. There is a tendency that staff overemphasizes the deficits in residents with dementia and that they fail to recognize and stimulate the abilities residents still have[302]. However, when independence is promoted, residents with moderate to severe dementia can achieve more than is typically observed during daily interactions[303].

Residents not only have low activity levels when they are out of bed, they also spend an excessive time in bed while not being ill[288,304,305]. For example, between 7:00 and 19:00 o'clock, $8 - 18\%$ of the residents in 15 different Californian nursing homes spend almost 10 hours in bed[305]. In total, most of the residents were more than 17 hours per day in bed[305]. In another study, the time in bed differed from 1.7 to 4.6 hours (mean is 3.2 hours) between 08:00 and 17:00 o'clock according to direct observations[288].

Loneliness

Institutions are often an impoverished environment, not only due to the very low levels of physical activity; the amount of social isolation is also higher compared to community-dwelling elderly[306]. When people move into a nursing home, they experience difficulty maintaining their social relationships with friends[307,308] and new friendships with other residents remain scarce and superficial[309]. More than half of the residents with or without dementia experience loneliness[310,311]. High frequencies of social contact with family and friends from outside the institution is important to reduce residents feelings of loneliness[308,309].

3.3.3 Other institutions

Not only nursing homes show impoverished environments, but also acute care stroke units. In one study, 58 patients were observed for two weeks during their stay in a stroke unit directly after the stroke[312]. Stroke severity ranged from mild to severe, but only nine patients were restricted to bed, due to among other things unstable blood pressure, reduced consciousness and infection. The non restricted people spent 49% of the time in bed. Patients with more severe strokes spent more time in bed than patients with mild stroke. In addition, for more than 60% of the day the patients were alone, and $15 - 24\%$ of the time family or friends were the only people present. Therapists spent only 5% of the time with the patient and most of this time was in or beside the bed. There were limited opportunities to move away from the bedside, which becomes clear in the high proportion of time patients spent in their rooms, i.e., almost 90%. These low levels of physical activity did not change within two weeks.

3.4 Barriers to improve physical activity and loneliness in nursing homes

There is a lot of variation in the quality of care nursing homes give. Some nursing homes try to improve this quality together with residents[313]. Low quality is often caused by poor pay, shortage of qualified workers and high rates of staff turnover[314]. However, in the care of physical activity and loneliness most nursing homes fall short in the 21st century despite the stimulation of physical activity since 1974[315]. The barriers to use non-pharmacological interventions include: more impaired residents compared to the 20th century and the inability of the staff to interact and reach out to the residents with dementia[213]. Successful use of non-pharmacological interventions requires staff with an appropriate education[213]. In future, technological advances, such as robots who serve as companions and assistants, are suspected to increase quality of life in the elderly[316].

3.5 Conclusions

1. Animals, especially old animals, living in an impoverished environment perform worse and show a faster decline in cognitive functioning compared to animals in a standard environment. This decline in cognitive functioning is, however, reversible after three months in a standard or enriched environment.
2. Sedentary and lonely people have worse cognitive functions and show a faster cognitive decline than physically and socially active people.
3. Most community-dwelling older people do not meet the recommended levels of physical activity.
4. Cognitive performances are worsened when people move into institutions due to their impoverished environments; residents spend an excessive time in bed, show mainly sedentary behaviour, and often have feelings of loneliness.
5. Physical restraints are associated with cognitive decline.

CHAPTER 4

PHYSICAL ACTIVITY FOR AGITATION AND PAIN IN DEMENTIA

Abstract. It is well known that a dysfunction of the prefrontal cortex (PFC) in dementia produces disinhibited behaviour, reflected in agitation/aggression. The role of the PFC in pain inhibition might be less known, but implies that frontal lesions in dementia may lead to an increase in pain experience. Hence, in patients with dementia, a dysfunction of the PFC may lead to a co-occurrence of agitated behaviour and pain. We argue that physical activity may decrease agitation and pain in dementia, by strengthening the inhibitory function of the PFC. [1]

4.1 Introduction

THERE is ample evidence for a serotonin and cholinergic-mediated top-down process in which lesions of the ventromedial and orbitofrontal PFC result in disinhibited, impulse aggression[317–319]. Support for such a process emerges from neuro-imaging studies, using for example positron emission tomography (PET) that show a relationship between aggression and PFC dysfunction, i.e., anterior frontal, orbitofrontal, and ventromedial[320]. In addition, low scores on tests for executive functions, functions in which the PFC is involved[321], appear to be related to aggressive behaviour. Lesions of the ventromedial and orbitofrontal cortex causing disinhibition, and consequently, agitation/aggression, may occur in neurodegenerative disorders such as dementia[318]. This issue will be addressed first. Subsequently, considering the role of the PFC in pain suppression, we will highlight that PFC lesions in dementia may not only cause agitation/aggression, but may also contribute to an increase in pain experience. Consequently, in dementia agitation/aggression could be related to pain, a topic that will be addressed next. Finally, we suggest that physical activity could have a beneficial influence on both agitation/aggression and pain experience by restoring the inhibitory function of the PFC.

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[1] Scherder, E.J.A. and Volkers, K.M., 2010. Physical activity for agitation and pain in dementia. *Journal of Pain Management*, 3(4):373-376.

4.2 Prefrontal cortex, disinhibition and agitation

A transgenic mouse model of Alzheimer's disease (AD) (amyloid precursor protein-Swedish mutation) showed a relationship between behavioural disinhibition and an increase in serotonin turnover in the PFC[322]. Agitated/aggressive patients with dementia, in particular those suffering from AD, showed neuropathology, i.e., hypoperfusion, reduced metabolism, atrophy, and cholinergic dysfunction, in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), and anterior temporal lobe[323–326]. In dementia, irrespective of its subtype, an association between a decreased volume in the ventromedial PFC and disinhibition has been confirmed[327]. In the behavioural variant of frontotemporal dementia and in frontotemporal lobar degeneration, disinhibition is related to atrophy of the DLPFC and orbitofrontal cortex[328,329].

4.3 Prefrontal cortex and pain suppression

In rats, morphine inhibits inhibitory GABAergic interneurons in the ventrolateral orbital frontal cortex, activating a descending cortico-subcortical system that suppresses pain at a spinal level, through the periaquaductal grey[330]. A top-down inhibitory influence of the PFC on ascending pain-transmitting pathways has also been suggested by human studies. For example, in healthy adults who received a heat stimulus at the forearm, the PET results show a negative correlation between activity in the DLPFC and activity in the connection between the midbrain, medial thalamus and ACC, an ascending connection that mediates nociceptive information to the brain[331,332]. Similar findings have been reported for cold-evoked pain[333]. Further support for such a top-down process emerges from a study with healthy adults in which transcranial magnetic stimulation (TMS) applied to the left PFC caused an increase in thermal pain threshold[334].

4.4 The relationship with dementia

Studies addressed so far, clearly indicate that lesions of the PFC may cause both disinhibition and agitation/aggression and an increase in pain experience in patients with dementia. The question arises whether these two symptoms indeed co-occur in dementia and whether a causal relationship exists between the presence of pain and agitation, i.e., does an increase in pain provoke agitation/aggression in patients with dementia?

4.4.1 Relationship between agitation and pain, where agitation could be a sign of pain in dementia

In one study, a significant proportion of the variance in discomfort of patients with moderate to severe dementia (14%) was explained by agitation[335]. These results suggest that the presence of a painful condition may profoundly contribute to the discomfort/agitation in patients with dementia[335]. According to these authors, agitation should not be considered as an exclusive consequence of the dementia itself.

The relationship between agitation and pain has also been observed in older patients visiting a day care centre[336]. In that study, pain was a significant predictor of verbally non-aggressive agitation. In patients with dementia who received end-of-life care in a hospice, less complaints of pain coincided with less prevalence of restlessness, sleep problems, agitation, and aggressiveness, compared to those who were not enrolled in a hospice[337].

4.4.2 Causal relationship between agitation and pain

A long-acting opioid (oxycodone, 10 mg every 12 hour, or 20 mg morphine a day for those with problems in swallowing pills), administered during 4 weeks, reduced the level of agitation only in the oldest patients (= 85 years of age) who were in an advanced stage of dementia. According to the authors, only older patients may still react positively to a low dose[338].

4.5 Effect of physical activity

Exercise of even a low intensity, implying mild cardiovascular involvement, may enhance prefrontal oxygenation[339]. In healthy older people, who initially had a reduced level of gait speed, functional near-infrared spectroscopy showed that the higher the intensity of walking, the higher the increase in heart rate, and the higher the oxygenated haemoglobin in the left PFC[340].

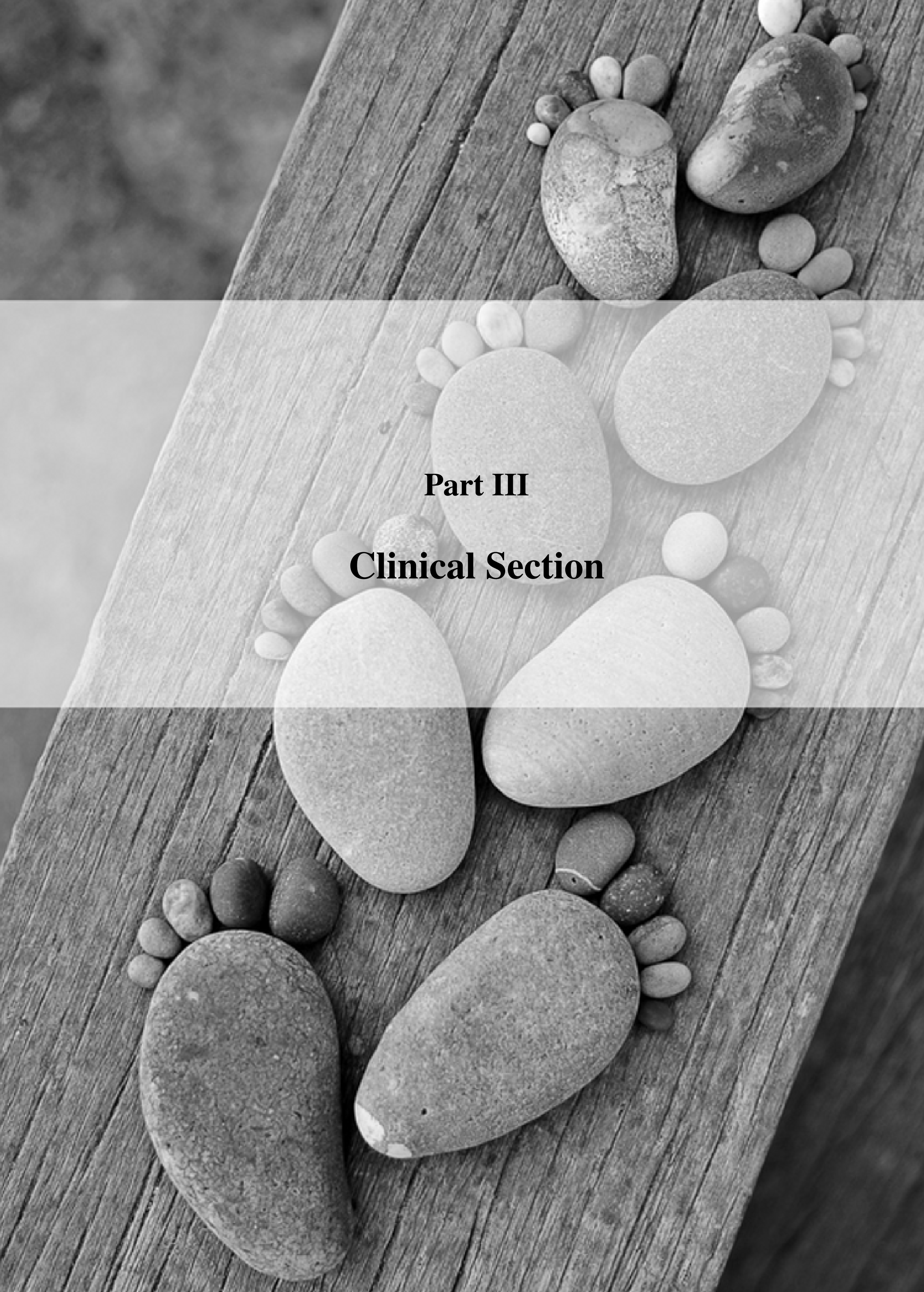
A direct effect of physical activity on inhibition has been observed in both young and older persons. Young healthy males who participated in twelve weeks of jogging showed a beneficial influence on the No-Go performance of a GO/No-Go task; this task appeals to subject's inhibitory capacity[341]. In older adults, a greater task-related activity, measured by functional magnetic resonance imaging (fMRI), was observed in among others the PFC, after an aerobic exercise program of six months[342]. The task used in this study was a flanker task with a congruent (<<<<<) and an incongruent (<<><<) condition. The subject is requested to indicate the direction of the central arrow; the incongruent condition appeals to the subject's inhibitory capacity.

It is important to note that physical activity is culture-dependent. Physical activity such as exercise is an important ingredient of leisure time and leisure time inactivity is characteristic for Latinos, more for women than for men[343].

Similarly, physical inactivity is common in midlife Korean immigrant women in the United States[344] and a majority of Turkish and Moroccan women are not actively involved in sports[345]. These findings imply that stimulating the PFC by exercise to reduce agitation and pain requires particular attention in patients with dementia from ethnic minority groups.

4.6 Conclusions

1. Lesions of the PFC may cause disinhibition and, consequently, agitation/aggression and pain in older persons with dementia.
2. The co-occurrence of agitated/aggressive behaviour and pain in dementia has been observed.
3. An increase in pain experience may further aggravate agitation/aggression.
4. Adequate pain treatment may decrease agitation/aggression in patients with dementia.
5. Physical activity may restore the inhibitory capacity of the PFC, reducing agitation/aggression and pain in patients with dementia.
6. Within the scope of stimulating the PFC by physical activity, particular attention should be paid to patients with dementia from ethnic minority groups who are not familiar with exercise.
7. Immobilizing patients with dementia may further enhance PFC degeneration, and consequently, produce more disinhibition, and thus agitation/aggression and pain.



Part III

Clinical Section

CHAPTER 5

THE EFFECT OF REGULAR WALKS ON VARIOUS HEALTH ASPECTS IN OLDER PEOPLE WITH DEMENTIA: PROTOCOL OF A RANDOMIZED-CONTROLLED TRIAL

Abstract.

Background: Physical activity has proven to be beneficial for physical functioning, cognition, depression, anxiety, rest-activity rhythm, quality of life (QoL), activities of daily living (ADL) and pain in older people. The aim of this study is to investigate the effect of walking regularly on physical functioning, the progressive cognitive decline, level of depression, anxiety, rest-activity rhythm, QoL, ADL and pain in older people with dementia.

Methods/design: This study is a longitudinal randomized controlled, single blind study. Ambulatory older people with dementia, who are regular visitors of daily care or living in a home for the elderly or nursing home in the Netherlands, will be randomly allocated to the experimental or control condition. Participants of the experimental group make supervised walks of 30 minutes a day, 5 days a week, as part of their daily nursing care. Participants of the control group will come together three times a week for tea or other sedentary activities to control for possible positive effects of social interaction. All dependent variables will be assessed at baseline and after 6 weeks, and 3, 6, 9, 12 and 18 months of intervention.

The dependent variables include neuropsychological tests to assess cognition, physical tests to determine physical functioning, questionnaires to assess ADL, QoL, level of depression and anxiety, actigraphy to assess rest-activity rhythm and pain scales to determine pain levels. Potential moderating variables at baseline are: socio-demographic characteristics, body mass index (BMI), subtype of dementia, Apolipoprotein E (ApoE) genotype, medication use and comorbidities.

Discussion: This study evaluates the effect of regular walking as a treatment for older people with dementia. The strength of this study is that 1)

it has a longitudinal design with multiple repeated measurements, 2) we assess many different health aspects, 3) the intervention is not performed by research staff, but by nursing staff which enables it to become a routine in usual care. Possible limitations of the study are that 1) only active minded institutions are willing to participate creating a selection bias, 2) the drop-out rate will be high in this population, 3) not all participants will be able to perform/understand all tests. [1]

Trial registration: NTR1482

5.1 Background

AGING may coincide with a decline in the level of physical activity[346]. This age-related decline in physical activity is often related to difficulties in physical performances, e.g., walking and getting out of a chair[192,347]. There is ample evidence that in cognitively intact older people living in the community or in long-term care, physical performance can be enhanced by physical activity interventions[194,348–353]. It is suggested that the intensity of the intervention is positively related to its effectiveness, i.e., a higher intensity produces a higher effect[354]. Nursing home residents are sometimes considered as too frail or too cognitively impaired to benefit from physical activity interventions, but cognitively impaired people seem to benefit from physical activity interventions just as much as cognitively intact people[350]. Furthermore, it has been suggested that frail dependent people only benefit from frequent individualised interventions, while less frail people already respond positively to traditional group interventions[355]. Other studies, including residents with and without cognitive impairment[350,353] or only people with cognitive impairment[67,68,88,354,356], confirmed that all residents can improve physical performances through physical activity, but evidence of high-quality studies is still limited or inconclusive.

The risk of dementia might be reduced by physical activity due to its positive effect on cognition[60,62,348,357–359], especially on executive functions (EF)[62,358]. When people already show a cognitive decline or suffer from dementia, which highly affects cognition due to neuropathology[360], results on the effects of exercise on cognition are equivocal[67,68]. An explanation for not finding a beneficial cognitive effect was that the interventions mainly consisted of strength-, balance- and/or flexibility-based exercises[68]. A recent meta-analysis indicated that the evidence is not sufficient for firm conclusions about the effectiveness of physical activity interventions on cognition in dementia[69]. The evidence that is available is promising since exercise has a large effect on cognition (Cohen's $d = 1.31$) and was observed as being significantly different from the control group (moderate effect: Cohen's $d = 0.56$ and 0.57)[88,361].

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[1] Volkers, K.M. and Scherder, E.J.A., 2011. The effect of regular walks on various health aspects in older people with dementia: protocol of a randomized-controlled trial. *BMC Geriatrics*, 11(1):38.

More research is warranted, because the available studies differ in exercise protocols, durations and outcome measures[68,69].

One of the risk factors for dementia is an increased level of anxiety and/or depression[362]. In healthy older people physical activity interventions can increase mental health, e.g., self-esteem, happiness and mood[348,363]. Looking explicitly at depression and anxiety, physical activity interventions can reduce the depressive symptoms within 3 months in older people with a depression[82] or anxiety after 3 weeks in people with a chronic physical condition, e.g., fibromyalgia[83]. Long-term effects of exercise on depressive symptoms and anxiety remain to be demonstrated in clinical trials[82,348]. Even though physical activity as a treatment for depression may be as effective as medication, it is currently under-used for this disorder despite having many additional health benefits, for example a reduced risk of heart disease, stroke, high blood pressure, some cancers, type 2 diabetes, osteoporosis and obesity[82]. This makes a physical activity treatment appropriate for older people with a combination of physical and mental health problems such as dementia[82]. In people with dementia evidence of helping with depression is limited[69,354], but the results of available studies are promising[67,68].

Together with a rising level of depression and cognitive impairment, the prevalence and frequency of sleep disorders in long term care residents is increasing[301]. More than half of the residents suffer from some kind of sleep disorder[301]. Night-time wakefulness can lead to increased daytime sleeping and vice versa[364]. Sleep disorders and a lack of activities negatively influence each other[301]. Long-term care residents spend extended periods of time in bed and are sedentary during the daytime, which contributes to abnormal circadian rhythms, i.e., rest-activity rhythm[364]. In older persons with or without dementia, a physical activity intervention seems to be effective[84,361,365–367] , especially in people with poor sleep at baseline[367]. These studies, however, are scarce since the majority of physical activity intervention studies are multidimensional, i.e., physical activity is combined with bright light or a decrease in noise at night[361,364,365,367]. Such a combination hampers the understanding of which intervention is (most) effective[368]. A disturbance in the rest-activity rhythm is one of the prominent clinical symptoms in people with dementia which should be recognized and enhanced, since it has a high impact on the QoL[365].

QoL is determined by many aspects in life, e.g., quality and quantity of sleep[369], cognitive functioning[369] and level of depressive symptoms[370]. Exercise programs can slow down the decline in QoL in older community dwelling people[85] and in a combined resident group of people with and without dementia[86]. However, for a group including only people with dementia the evidence for an effect on QoL due to physical activity is limited[67,69,354].

QoL is also affected when people with dementia lose the ability to cope with the physical ADL, e.g., eating, bathing, using the toilet, dressing, walking and continence[371]. Due to participation in a physical activity intervention, a combined resident group of people with and without dementia can prevent or reduce a decline in ADL compared to a control group[86,355]. In groups with only older people with dementia, there is some evidence that physical activity can improve the ability to cope with ADL[87,88], but there were not sufficient studies for a meta-analysis to conclude whether or not physical activity could be effective for ADL performance in people with dementia[67,69].

The risk to decline in ADL performance increases by approximately 20% for each (additional) painful part of the body, i.e., the neck, back, hands, hips, knees or feet[372]. In older people pain is often caused by the musculoskeletal condition of the joints[373]. In cognitively intact older people a dose-response relationship exists between the level of physical activity and pain; a higher physical activity level was related to less stiff and painful joints[373] and people experienced less pain during a cancer treatment when they performed more aerobic exercises, e.g., walking[374]. In addition, there is more evidence that pain can be reduced by stretching activities[375] or resistance training[376] and specifically (low) back pain by resistance, agility or stretching activities[376]. In contrast, a moderate-intensity endurance and strengthening program had no effect on pain in healthy elderly[375] and neither had a 12 weeks walking program in older people with dementia[377]. No other studies including people with dementia examined the effect of physical activity on pain even though this is necessary since pain is often under-diagnosed and under-treated in people with dementia[378,379].

Studies related to older people with (or without) dementia have not been able to reach a consensus on the types and intensity of the exercise, nor the frequency and duration of the intervention to be most effective and efficient[68]. This is due to the variety in outcome measures; one outcome measure can respond faster to a physical activity intervention than another outcome measure[68]. The effect on outcome measures is also dependent on the age of participants, the cognitive impairment and frailty level[68]. However, in both frail and non-frail older adults regular exercise is the only therapy found to consistently improve health aspects, e.g., physical function, cognitive performance and mood[348]. Most meta-analyses and reviews have concluded that longitudinal randomized controlled trials (RCTs) are of vital importance[60,67,68,348,352,353,355,358,359,380,381]. Especially people with more severe cognitive impairment should be included in future research[68]. As mentioned above, physical activity has proven to be beneficial to improve or slow down many health aspects in older people with dementia. The aim of the present study is therefore to investigate longitudinally the effect of regular walking on physical functioning, cognition, level of depression and anxiety, rest-activity rhythm, QoL, ADL and pain in older people with dementia.

5.2 Methods/design

5.2.1 Participants

Participants are older mobile people with dementia who are visiting day care or living in a home for the elderly or nursing home in the Netherlands. Inclusion criteria are 1) a diagnosis of dementia or presence of cognitive impairment that is reported in the medical status and 2) ambulatory with or without walking aid (walker or cane). Exclusion criteria are the presence of personality disorders, cerebral traumata, hydrocephalus, neoplasm, disturbances of consciousness and focal brain disorders.

5.2.2 Study design and randomization

This study is a RCT. Participants will be randomly divided into the intervention or control group. In order to preclude that the effects arise only from the intensified social contacts during intervention, the control group within a residency will come together three times a week for tea or other sedentary activities, e.g., watching television. The Medical Ethical Committee of VU university medical center approved the study. Oral and written informed consent will be obtained from all participants or their relevant relatives prior to their enrolment.

5.2.3 Intervention

The intervention consist of a daily 30 minute walk, 5 times a week under supervision of an assistant, e.g., medical staff, volunteers or family members. Depending on the participant, the assistant, the living area and the weather, the intervention can take place in the morning or afternoon, inside or outside, during midweek and/or weekends. Each day the participant has walked will be carefully noted, together with the time of day, duration and whether it was inside or outside.

5.2.4 Sample size

Sample size calculation was performed using the statistical power analysis program G*Power 3.1 [382] which has the possibility to perform power analyses for a repeated measures design with a between group variable. Based on two meta-analyses studying the effect of physical activity on cognition [88,361], the estimated effect size in this study is expected to be moderate to large (Cohen's $d = 0.32$). Using a type 1 error of 0.05, a power of 0.80, seven repeated measurements and 2 groups, a sample size of 70 in each group is required. Taking into account an attrition rate of 25%, 175 participants should be included in this study.

5.2.5 Recruitment

Participants for this study will be recruited via medical staff of aged care facilities. First, the medical staff will be informed about the goal and procedure of the study. Secondly, possible participants will be selected within subunits of the institutions by a team, including the researcher, medical staff and nurses. Third, an information letter with informed consent will be sent to the legal representatives of the participants, together with an invitation to attend an oral presentation. Fourth, once written consent is received, subunits make a schedule for assistants to accompany the regular walks of participants in the intervention group.

5.2.6 Procedure

The outcome variables are measured at baseline (pre-treatment: T0), after 6 weeks of intervention (post-treatment: T1) and after 3 (T2), 6 (T3), 9 (T4), 12 (T5) and 18 (T6) months of intervention. Trained experimenters, blinded to the intervention assignment, will administer the neuropsychological tests, physical tests and level of depression, anxiety and pain. The nursing staff fills in questionnaires to measure QoL, ADL and define the stage of dementia. The other variables are objective measurements.

5.2.7 Characteristics

Characteristics include *age, gender, subtype of dementia, type of living situation*, i.e., independently in society, in a home for the elderly or in a nursing home, as well as the following aspects:

Highest education level The highest education level will be determined on a seven-point scale with 1 = less than elementary school, 2 = 6 grades of elementary school, 3 = 7 or 8 grades of elementary school, 4 = 3 years of lower general secondary education, 5 = 4 years of lower general secondary education, 6 = pre-university education and higher vocational education, 7 = university and technical college[383].

BMI BMI is calculated as weight in kilograms divided by height in meters squared.

ApoE genotype ApoE type 4 allele (ApoE4) plays a major role in cerebral perfusion and metabolism and is a known risk factor for late onset Alzheimer's disease (AD)[384]. In addition, ApoE4 carriers show different effects on cognition as a result of some therapy than non-carriers[385,386]. In view of this possible moderating effect on treatment outcome, ApoE genotype of participants will be determined. Buccal swabs will be taken by making use of Catch-all™ collection swabs (Epicentre, Madison, Wisc., USA). First, participants must rinse their mouth thoroughly with water.

Then two swabs are taken from each participant, will be left to dry for approximately 30 minutes and are frozen until deoxyribonucleic acid (DNA) will be released from the swab by a rapid lysis technique[387] and the nucleotide sequence will be determined[388].

Stage of dementia To assess the stage of dementia of participants, the Dutch version of the global deterioration scale was used[389]. This classification scale indicates the severity of the dementia from pre-dementia stages (1 to 3) to profound (stage 7).

Comorbidity Comorbid conditions are extracted from the medical status and categorized based on the Dutch translation of the Long-Term Care Facility Resident Assessment Instrument (RAI), section I. This section (disease diagnoses) includes the following categories: 1) *endocrine/metabolic/nutritional*, i.e., diabetes mellitus, hyperthyroidism and hypothyroidism, 2) *heart/circulation*, i.e., arteriosclerotic heart disease, cardiac dysrhythmia, congestive heart failure, deep vein thrombosis, hypertension, hypotension, peripheral vascular disease and other cardiovascular disease, 3) *musculoskeletal*, i.e., arthritis, hip fracture, missing limb (e.g., amputation), osteoporosis and pathological bone fracture, 4) *neurological*, i.e., AD, aphasia, cerebral palsy, cerebrovascular accident, dementia other than AD, hemiplegic/hemiparesis, paraplegia, multiple sclerosis, Parkinson's disease, seizure disorder, transient ischemia attack, traumatic brain injury and quadriplegia, 5) *sensory*, i.e., cataracts, diabetic retinopathy, glaucoma and macular degeneration, 6) *psychiatric/mood*, i.e., anxiety disorder, depression, manic depression (bipolar disorder) and schizophrenia, 7) *pulmonary*, i.e., asthma and emphysema/chronic obstructive pulmonary disease, 8) *other*, i.e., allergies, anaemia, cancer and renal failure.

Medication Medication use is coded according to the Dutch Pharmacotherapeutic Compass and is ranged by the following groups: 1) sedatives, 2) antipsychotics, 3) antidepressants, 4) pychotropics (central nervous system (CNS)), 5) neurological (CNS), 6) anaesthetics and muscle relaxing, 7) blood, 8) cardiovascular, 9) gastrointestinal tract, 10) respiratory tract, 11) kidneys and urinary tract, 12) genital tract, 13) dermatology, 14) otolaryngology, 15) ophthalmologic, 16) infectious diseases, 17) hormones and bone metabolism, 18) corticosteroids nonsteroidal anti-inflammatory drugs (NSAID), 19) corticosteroids nonNSAID, 20) analgesics, antirheumatic drugs and gout agents, 21) vitamins and minerals, 22) malignancies, 23) infectious diseases, 24) various preparations, 25) dentistry, 26) opioids.

5.2.8 Assessment of physical functioning

For all tests of physical functioning, participants wear their regular footwear and are permitted to use their regular walking aid. As encouragement has been shown to improve performance[390], standardized encouragements will be provided regularly. All tasks are explained and demonstrated to the participants before testing. No practice trials are included. Participants perform the tests under continuous supervision of the researcher to prevent the participants forgetting what they have to do during the tests.

Blood pressure systolic blood pressure (SBP) and diastolic blood pressure (DBP) are measured on the left arm in millimeters of mercury (mmHg) with an ambulatory blood pressure monitoring device (model 90207, SpaceLabs Medical Inc., Redmond, Washington, USA) while participants are sitting quietly in a chair for at least 5 minutes[391]. This device is automated, lightweight, calibrated and validated[392]. Observers do not wear a white-coat to prevent higher blood pressure measurements due to a white-coat effect and multiple cuff bladders are used to measure blood pressure with a cuff bladder that encircles at least 80% of the arm[391]. In particular, blood pressure of participants with hypertension, i.e., a higher SBP than 160 mmHg and/or a higher DBP than 100 mmHg is expected to decrease during treatment[393]. The SBP and DBP reduction represents the clinical effectiveness of the treatment[394].

Six minute walk test The six minute walk test (6MWT) can be used reliably in the assessment of functional endurance ambulation in persons with acquired brain injury[395]. During the performance of the 6MWT, participants are instructed to cover as much distance as possible during 6 minutes with the opportunity to stop and rest if necessary[396]. Participants have to walk around a pre-measured, unobstructed 10 by 1 meter rectangular circuit having semi-circular ends with 0.5 meter radii marked out with plastic cones to prevent participants having to walk at sharp angles. One full round covers 26.3 meters walking. The total walking distance by each participant will be measured to the nearest meter. To estimate the effort of participants during the 6MWT the increase in heart rate will be determined (see heart rate)[397].

Heart rate Heart rate at rest is simultaneously measured with blood pressure. This blood pressure device (see blood pressure) also measures heart rate in beats per minute. In addition, heart rate is measured with a pulse oximeter (CMS 60C TFT color Pulse oximeter) before and directly after the 6MWT for 2 minutes. The faster the heart rate recovers within 1 minute after the 6MWT the healthier the heart; a slower heart rate recovery is associated with more severe coronary artery disease[398].

Oxygen saturation Arterial oxygen saturation is measured before and directly after the 6MWT to determine dyspnea[399]. This is measured with the same pulse oximeter as mentioned above, simultaneously with heart rate. Oxygen saturation is not measured during the 6MWT due to motion artefact which results in unacceptably high failure rates of the devices[396].

Ten meter timed walk Participants are requested to walk 10 meters at their own regular pace between 4 small traffic cones which are placed in the corners of a 10 by 1 meter rectangle. Their walk is filmed from behind by a digital video camera (Panasonic NV-GS330, Matsushita Electric Industrial Co., Ltd. Osaka, Japan) standing at least 8 meters behind the start on an 24.25 inch tripod (Vanguard MK-4). Time to walk 10 meters is measured by hand with a stopwatch to the nearest of 1/10 of a second and by video-analysis. By video-analysis also walking speed measured over 6 meters, i.e., without the 2 meters at start and 2 meters at finish to exclude starting hesitation and the slowing down at finish, step frequency, base width and step length will be analysed.

Figure of eight The figure of eight is an applicable and reliable dynamic functional balance measure of mobility for people with various degrees of physical disability[400,401] and geriatric patients[402]. The figure of eight test requires continuous turning during gait with an emphasis on accuracy (avoid oversteps), speed (timed task) and switching of motor patterns during the cross-over from the clockwise to the counter-clockwise loop. Participants are timed while walking in a figure-8 trajectory. The figure-8 trajectory is marked with white paint on a dark green rubber carpet, each loop having an outer diameter of 165 centimeters (cm) and a step width of 15 cm. The time to walk two complete eight figures is measured with a stopwatch. The onset time is based on the first detectable movement of the participant following a "Go!" command from the observer. Any step taken outside the white line is noted. The fastest attempt of two trials is recorded together with the corresponding oversteps. Speed (meter per second (m/s)) is 19.792 meter divided by the time in seconds.

Timed up and go The timed up and go (TUG) is a reliable and valid test for quantifying functional mobility that may also be useful in following clinical change over time[403]. To complete the TUG, participants are requested to rise from a standard chair (48 cm height, horizontal seat and armrests), walk 3 meters, turn around and return to a fully seated position in the chair again[404]. Each participant has two trials and the average time in seconds is the outcome of the TUG. Scores under 10 seconds are associated with individuals who are functionally independent in the frail elderly population[404].

Sit to stand The sit to stand (STS) is normally a reliable and valid indicator of lower body strength in adults over the age of 60 years[405]. However, in this study participants are allowed to use upper limbs to rise from the chair to test their rising performance that is closest to the clinical setting and to reduce a floor effect; a high percentage of older dependent elderly cannot rise from a chair with the arms crossed in front of the chest[406,407]. Participants are instructed to stand up and sit down in a standard chair as many times as possible within 30 seconds. The STS score is formed by the total number of performances with a sit-stand-sit performance counting as 1. Ending in a standing position is counted by a 0.5 point.

Frailty and injuries: cooperative studies of intervention techniques The frailty and injuries: cooperative studies of intervention techniques (FICSIT-4) is a test to measure static balance[408]. The participants have to maintain balance in 4 positions with increasing difficulty. Each position is demonstrated first and support is offered while participants position their feet. When participants are ready, the support will be released and timing begins. The timing stops when participants move their feet or grasp the researcher for support, or when 10 seconds have elapsed. Only when one stand is performed 10 seconds, the next, more difficult stand is performed. The first stand is with the feet together in parallel (side-by-side) position. Second is the semi-tandem position; the heel of one foot is placed to the side of the first toe of the other foot. The participant can choose which foot to place forward. Third is a tandem position; the heel of one foot directly in front of the toes of the other foot. The final stand is standing on one leg. The total summed seconds of all stands is the outcome score.

5.2.9 Assessment of cognition

Cognition will be assessed by the following neuropsychological tests:

Mini-Mental State Examination The Mini-Mental State Examination (MMSE) measures the global level of cognitive functioning[409]. Globally, a score between 25 to 30 indicates no dementia, between 15-24 mild dementia, between 5-14 moderate to severe dementia and between 0 to 4 profound dementia[410].

Eight words test The eight words test is a list learning test for people with memory problems[411]. In this test the examiner reads out eight words in a row, which is repeated five times. Every time the participant is asked to recall as many words as possible. The first outcome measure is the total number of correctly recalled words after the five trials (*immediate recall score*, maximal score = 40). After an interval of approximately 15 minutes the participant is asked to recall as many words as possible (*delayed recall score*, maximal score = 8). Subsequently, the examiner reads aloud 16 words among which 8 words presented before and 8 new words. The participant is asked to recognize the words from the list presented before (*recognition score*, maximal score = 16).

Rule shift cards The rule shift cards is a subtest of the Behavioural Assessment of the Dysexecutive Syndrome (BADS)[412]. This subtest purports mental flexibility and is one of the best qualifiers to discriminate people with perseverative tendency, i.e., an executive dysfunction, from healthy people[413]. Participants have to respond to stimuli (red or black playing cards) according to one of two rules that are presented consecutively. Performance is scored according to how successfully the respondent shifts from applying the first to the second rule[412].

Key search test The key search test is also a subtest of the BADS[412] and is used to measure how well the participant is able to prepare an efficient plan of action in the context of a routine event[413]. The patient is asked to imagine that a 100-millimeter (mm) square on an A4 size paper is a large field, in which they have lost their keys. They are asked to draw a line, beginning at a black dot, 50 mm below the square, to show the strategy they would use to search the field, to make absolutely certain that they would find their keys. The test evaluates a person's ability to monitor and evaluate their own performance, taking into account factors that are not explicitly stated in the instructions. Their search strategy score is based on a number of criteria, such as efficiency and effectiveness. The best strategy score is 15 and the worst score is 2.

Digit span (forward and backward) The digit span is a subtest from the Wechsler Memory Scale-Revised (WMS-R)[414]. In the digit span forward, increasingly long sequences of random numbers are orally presented at a rate of one digit per second to the participants, who have to repeat the sequence immediately after oral representation. In the digit span backward, participants have to repeat the sequence in reverse order. To do this, participants perform extra mental operations on the information that is being held in short term memory. While the backward condition is often hypothesized as tapping more into EF than the forward condition which should measure more short term memory, research has failed to demonstrate this result[415,416]. These studies suggest that both conditions tap into EF. Each condition ends when a participant fails to recall at least two strings of the same length or repeated an eight-digit sequence correctly. The minimal score for both conditions is 0 and the best score is 21.

Face recognition Face recognition is a subtest from the Rivermead Behavioral Memory Test (RBMT)[417] and measures visual, nonverbal long term memory. Two versions (C+D) are combined to prevent a ceiling effect. In this test the participant is shown 10 cards with faces one at a time for 5 seconds. After a short interval of approximately 2 minutes, the participant is shown 20 cards, including 10 shown before and 10 cards with new faces. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of faces correctly recognized minus the number of faces incorrectly recognized. The worst score is -20 and the best score is +20.

Picture recognition Picture recognition is also a subtest from the RBMT[417], which measures visual, verbal long term memory. Two versions (C+D) are combined to prevent a ceiling effect. The participant is shown each of the 20 cards with drawings of objects for 5 seconds. With each card, the participant is requested to name the object on the card. After a short interval of approximately 2 minutes, the participant is shown 40 cards, including 20 shown before and 20 cards with new objects. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of objects correctly recognized minus the objects that were incorrectly recognized. The lowest score is -40 and the maximal score is +40.

Category fluency test The category fluency test is a verbal fluency test which can be used to evaluate EF[418,419]. The participant is asked to name as many examples of a given category as possible, within 1 minute. This requires a strategic search mechanism to retrieve information from semantic memory[420]. This study uses the category 'animals' and 'professions'[421]. The outcome measure is the total number of animals and professions produced.

Visual memory span (forward and backward) The visual memory span is a subtest of the WMS-R[414]. The visual memory span stimuli consist of squares printed on a two dimensional card and requires the participant to repeat a number of tapping sequences that becomes longer with each trial. The visual memory span contains a forward and a backward sequence, similar to the digit span test. It was initially added to the WMS-R as a visual analogue digit span test. The forward condition is used as a measurement of attention and immediate visual memory, the backward condition is used as a measure of attention and visual working memory[414]. Scores range from 0 (worst) to 14 (best) in the forward condition and from 0 (worst) to 12 (best) in the backward condition.

Picture completion Picture completion is a subtest from the Groninger Intelligence Test (GIT)[422]. The GIT is a test of general intelligence that is used in the Netherlands for purposes comparable to the Wechsler Adult Intelligence Scale (WAIS). The picture completion subtest measures visual perception, specifically, alertness to visual detail[423]. Available literature suggests that this subtest may have utility as a measure of suboptimal effort, especially in less-educated participants and is a moderately effective measure of response bias[423]. Figures are not completely drawn and participants are instructed to describe the missing parts of pictured objects. The figures increase in difficulty. After 20 figures or after 5 false descriptions in a row, the subtest is finished. The best score is 20, representing 1 point for every correct description.

Stroop task The version of the Stroop task that is commonly used in the Netherlands[424] consists of three subtasks which the participant performs as quickly as possible; each test has a 45 second time limit. In the first subtask, participants are presented with four color words, i.e., red, green, blue and yellow, printed in black ink in ten rows with ten names each. The participant's task is to read as many color names in the right order. Second, the participant is presented with a similar paper, but this time with solid color patches (red, green, blue and yellow) that have to be named in the right order. In the final subtask the names of the colors are written in a different color ink than the meaning of the word (i.e., the word 'blue' written in red ink) and the participants again need to name the color of the ink, thus suppressing reading the word, which is a highly automatic reaction. This test has been found to correlate moderately well with other tests of response inhibition[425], which is an EF task[426]. The score on each card is the total correct mentioned colors within 45 seconds. The final score is the score on card 2 minus the score on card 3. A lower final score indicates a better performance of inhibition.

Digit symbol substitution test The digit symbol substitution test (DSST) is a subtest of the WAIS-Revised[414] and has been widely used as a measure of general information processing speed in studies of cognitive aging[427]. Test scores correlate with general intelligence, cognitive impairment, chronological age and activation in the frontal regions[428–431]. Participants are presented with a rectangular grid of numbers. For each of these numbers, participants are instructed to substitute the appropriate symbol according to a code that appears at the top of the page. The DSST score is recorded as the number of correct symbols drawn in 2 minutes.

5.2.10 Assessment of depression level and anxiety

The level of depression and anxiety will be assessed by the following questionnaires:

Geriatric depression scale The Dutch version[432] of the geriatric depression scale (GDS) is a 30-item questionnaire used to measure general mood[433]. The GDS is a reliable and valid self-rating depression screening scale for elderly populations[434]. The GDS questions are answered by 'yes' or 'no' depending on which response is most appropriate at the time of measurement, with 0 or 1 point for each answer. Higher scores indicate a higher level of depression.

Symptoms checklist 90 Two subscales from the Dutch version[435] of the symptoms checklist 90 (SCL-90), a 90-item self-report symptom inventory designed to reflect patterns of current psychological symptoms, will be used to measure depression and anxiety[436,437]. The depression and anxiety subscale includes 15 and 10 items respectively. Each item is rated on a 5-point likert scale, from 1 (not at all) to 5 (extremely). A higher score indicates more symptoms of depression or anxiety.

5.2.11 Assessment of rest-activity rhythm

Rest-activity data are collected by the use of an Actiwatch activity monitor (Cambridge Neurotechnology Ltd., Cambridge, Great Britain). Actiwatches are small activity monitors worn on the dominant wrist for several days. Three variables below are analysed.

Interdaily stability The interdaily stability (IS) serves as a measure to which extent the activity patterns of all included 24 hour periods resemble each other. IS is calculated as the ratio between the variance of the average 24 hours pattern around the mean and the overall variance[438]:

$$IS = \frac{n \sum_{h=1}^{p} (\bar{x}_h - \bar{x})^2}{p \sum_{i=1}^{n} (x_i - \bar{x})^2} \tag{5.1}$$

where n is the total number of data, p is the number of data per day (in this study, 24), $\bar{x}_h$ are the hourly means, $\bar{x}$ is the mean of all data, and x_i represents the individual data points. Higher values indicate a more stable rhythm between days.

Intradaily variability The intradaily variability (IV) quantifies how well the continuity of an arousal state (sleep / activity) is. Normal rest-activity patterns will show every 24 hours one major active period (day) and one major resting period (night) and therefore show a low IV. IV is calculated as the ratio of the mean squares of the difference between successive hours (first derivative) and the mean squares around the grand mean (overall variance)[438]:

$$IV = \frac{n \sum_{i=2}^{n} (x_i - x_{i-1})^2}{(n-1) \sum_{i=1}^{n} (x_i - \bar{x})^2} \tag{5.2}$$

Lower values indicate a better rest-activity pattern.

Relative amplitude The relative amplitude (RA) measures the relative difference in the 10 most active consecutive hours (M10) and the uninterrupted least active 5 hours period (L5) within the average 24 hours cycle[438].

$$RA = \frac{M10 - L5}{M10 + L5} \tag{5.3}$$

Because it is a relative measure, variance resulting from differences in sensitivity of actigraphs is reduced. Higher values indicate a larger difference between daytime activity and night time rest and therefore a better rhythm.

5.2.12 Assessment of quality of life

Qualidem The Qualidem is a reliable and valid 40-item questionnaire designed to determine QoL in institutionalized residents with dementia[439–441]. The questionnaire includes indicative and contra-indicative items that can be divided into 9 homogeneous subscales: 1) care relationship (7 items), 2) positive affect (6 items), 3) negative affect (3 items), 4) restless tense behaviour (3 items), 5) positive self-image (3 items), 6) social relations (6 items), 7) social isolation (3 items), 8) feeling at home (4 items), 9) having something to do (2 items). Three items are not included in a subscale (enjoys meals; does not want to eat; likes to lie down (in bed)). The items are printed in random order, so that items of a subscale are spread within the questionnaire. Each item has 4 possible responses; ‘never’, ‘rarely’, ‘sometimes’ and ‘often’. Each response is scored with 0 to 3 points, with higher scores per subscale indicating higher QoL. The questionnaire is completed by the nursing staff.

5.2.13 Assessment of activities of daily living

Katz index The Katz index is a 6-item measure of basic human activities of daily living: bathing, dressing, toileting, transfer, continence and feeding[442]. The scale is completed by the nursing staff and varies from complete independency (score 6) to maximum dependency (score 18).

5.2.14 Assessment of pain

Pain will be assessed by the following pain scales:

Coloured analogue scale The coloured analogue scale (CAS) will be used to determine both pain intensity and unpleasantness, i.e., affect[443]. The CAS includes 2 pain thermometers which are white at the bottom and red at the top to measure both aspects of pain. It was originally developed to measure pain in young children, but it has also been used in elderly with dementia[444]. The psychometric properties of CAS are comparable to those of visual analogue scales[443]. Participants are instructed to rate both the pain intensity and the unpleasantness of the pain from which they suffer at that moment. On the back of the thermometers a value is given to the pain aspects from 0 (no pain / no affect) to 10 (highest pain intensity / highest affect).

Faces pain scale The faces pain scale (FPS) is an instrument to assess the severity of pain on a scale with 7 faces, ranked in order of pain[445]. The participant's score corresponds to the scale number, ranging from 0 (neutral face) to 6 (extreme painful face). It was originally developed to measure pain in young children, but the FPS has also been used in elderly people with dementia[444].

5.2.15 Statistical analysis

Comparability between the intervention group and the control group will be assessed at baseline to check for differences between the groups on characteristics that may influence the results on the outcome variables. Scores on neuropsychological tests will be converted into z-scores and, according to factor analysis, summed up to form specific cognitive domains. A two-way repeated measurement design (T1−T6), with time as within group factor and group (intervention vs control) as between group variable, will be used to analyse the effect of the intervention on the outcome variables.

5.3 Discussion

This paper presents the design of a RCT, which aims to explore the longitudinal effect of regular walking on several health aspects of older people with dementia. The strength of this study is that 1) the intervention is not performed by the research staff, but by the nursing staff which enables it to become a routine in usual care, 2) we have a high number of repeated measurements, i.e., one baseline and 6 post measurements, 3) the various outcome variables enables us to analyse the development of different health aspects within 18 months.

Possible limitations of this study are that 1) only active minded institutions are willing to participate creating a selection bias, 2) there will be a (high) drop-out rate, for example due to death, 3) not all participants will be able to perform/understand all tests.

This method is appropriate to collect data on the effectiveness and feasibility of a walking program. It is also interesting to examine what aspects determine the compliance of the participants. Due to the aging and dementia process, it is not always necessary to increase in test score to find an effect of the intervention, but stabilizing cognitive and behavioural functioning in those who participate in the walking group would also be worthwhile.

CHAPTER 6

PHYSICAL PERFORMANCE PREDICT WORKING MEMORY IN OLDER PEOPLE WITH MILD TO SEVERE COGNITIVE IMPAIRMENT

Abstract.

Background: Physical performance and cognition are positively related in cognitively healthy people. The aim of this study was to examine whether physical performances can predict specific cognitive functioning in older people with mild to severe cognitive impairment.

Methods: This cross-sectional study included 134 people with a mild to severe cognitive impairment (mean age 82 years). Multiple linear regression was performed with the performances on mobility, strength, aerobic fitness and balance as predictors and working memory and episodic memory as dependent variables.

Results: Strength, aerobic fitness and balance are significant predictors of working memory, irrespective of the severity of the cognitive impairment. Physical performance does not predict episodic memory in older people with mild to severe cognitive impairment.

Conclusion: The relationship between physical performance and working memory necessitates the development of therapeutic strategies that are aimed at preventing a decline in physical performance in older people with mild to severe cognitive impairment. [1]

6.1 Introduction

In healthy older people a high level of physical activity coincides with a high level of cognitive performance, such as speed of information processing, attention[60] and executive control processes, e.g., working memory[446]. The results of those studies are in line with the finding that a high level of physical activity during life might decline the risk of dementia[447]. Since physical activity also increases *physical performance*, such as muscle strength[22,448], gait speed, functional mobility and balance[24,448], it is not surprising that

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[1] Volkers, K.M. and Scherder, E.J.A. Physical performance predict working memory in older people with mild to severe cognitive impairment. *Submitted*.

there is a positive relationship between physical performance and cognition in healthy older people [25]. More specifically, older people with better physical performance levels, e.g., mobility [27,28], balance [29,30], strength [27,32,33] and aerobic fitness [17] have better cognitive functions, such as cognitive flexibility or global cognition. Moreover, similar to physical activity, better physical performance, such as balance [29] and strength [33–35], also decrease the risk of dementia [36,37].

The studies mentioned above suggest a close relationship between physical performance and cognitive functioning in cognitive healthy older people. In older adults with amnestic mild cognitive impairment (aMCI) [26] or mild dementia [31], this relationship is further strengthened. In people with aMCI, gait speed and the performance on the timed up and go (TUG) are both associated with executive functions (EF) [26], which are higher cognitive functions, such as attention, planning and inhibition, supported by the prefrontal cortex (PFC) [209]. It is even suggested that particularly EF, as opposed to global cognition or memory, is important for mobility performances, such as balance, gait [38] and the ability to perform the activities of daily living (ADL) [39,40]. This suggestion was supported by a positive relationship between gait and EF in a combined group of cognitive healthy young elderly, and elderly with and without mild dementia [41].

Not only gait is affected in an early stage of dementia [31,449–452], but there is increasing evidence for a decline in lower-extremity functioning, e.g., walking speed [451,453], balance [450,452,454], fine and complex motor functioning [455,456], aerobic fitness [457] and limb coordination [452] already in an early stage of dementia. When people have dementia in a relatively early stage, balance stays an independent predictor of the progression in (further) global cognitive decline [458]. The studies above, which included people with dementia, show only a relation between physical performance and the stage or progression of the dementia, not with specific cognitive functions. In addition, these studies often include only specific types of dementia or only people in, for example, a mild stage of dementia.

The goal of the present study was to examine if physical performance (strength, balance, mobility, aerobic fitness) predict specific cognitive functions in people with mild to severe cognitive impairment. If this appears to be the case, therapeutic interventions specifically aimed at maintaining or improving one or more physical performances might be useful to slow down a decline or even to improve cognitive functioning in cognitively impaired older people.

6.2 Methods

The present cross-sectional study includes baseline data of a long-term randomized controlled trial (RCT) examining the effect of physical activity on, among others, physical performance and cognition (for details, see Volkers and Scherder, 2011[459]).

6.2.1 Participants

One hundred and thirty four participants (96 women), 82.2 ± 7.4 years old, with cognitive impairment participated in this study. The severity of the cognitive impairment was determined by the Mini-Mental State Examination (MMSE), a test to measure global cognitive functioning with scores ranging from 0 to 30[409] (mean MMSE was 15.4 ± 5.9). Eligibility criteria for study participation were the presence of cognitive impairment (MMSE < 25) and being ambulatory with or without walking aid (walker or cane). Exclusion criteria were the presence of personality disorders, cerebral traumata, hydrocephalus, neoplasm, disturbances of consciousness and focal brain disorders. Characteristics of participants are shown in Table 6.1 (page 75).

6.2.2 Level of depression

The level of depression was based on the summed standardized scores of geriatric depression scale (GDS) and symptoms checklist 90 (SCL-90) (Crohnbach's $\alpha = 0.91$).

GDS The Dutch version[432] of the GDS is a 30-item questionnaire used to measure general mood[433]. The GDS is a reliable and valid self-rating depression screening scale for elderly populations[434]. The GDS questions are answered by 'yes' or 'no' depending on which response is most appropriate at the time of measurement, with 0 or 1 point for each answer. Higher scores indicate a higher level of depression with a maximum score of 30.

SCL-90 One subscale from the Dutch version[435] of the SCL-90, a 90-item self-report symptom inventory designed to reflect patterns of current psychological symptoms, was used to measure depression[436,437]. The depression subscale includes 15 items. Each item is rated on a 5-point likert scale, from 1 (not at all) to 5 (extremely). A higher score indicates more symptoms of depression with a maximum score of 75.

6.2.3 Comorbid conditions

Comorbid conditions (see Table 6.1 on page 75) were extracted from the medical status and categorized based on the Dutch translation of the Resident Assessment Instrument (RAI), section I. This section (disease diagnoses) includes the following categories: 1) endocrine/metabolic/nutritional, 2) heart/circulation, 3) musculoskeletal, 4) neurological, 5) sensory, 6) psychiatric/mood, 7) pulmonary, 8) other. The total sum of 8 categories was used as a comorbidity score.

6.2.4 Medication use

Medication use is coded according to the Dutch Pharmacotherapeutic Compass and is ranged by the following groups: 1) sedatives, 2)antipsychotics, 3) antidepressants, 4) pychotropics (central nervous system (CNS)), 5) neurological (CNS), 6) anaesthetics and muscle relaxing, 7) blood, 8) cardiovascular, 9) gastrointestinal tract, 10) respiratory tract, 11) kidneys and urinary tract, 12) genital tract, 13) dermatology, 14) otolaryngology, 15) ophthalmologic, 16) infectious diseases, 17) hormones and bone metabolism, 18) corticosteroids nonsteroidal anti-inflammatory drugs (NSAID), 19) corticosteroids nonNSAID, 20) analgesics, antirheumatic drugs and gout agents, 21) vitamins and minerals, 22) malignancies, 23) infectious diseases, 24) various preparations, 25) dentistry, 26) opioids. The total number of categories was used as medication score.

6.2.5 Informed consent

The Medical Ethical Committee of VU university medical center approved the longitudinal study. Before the baseline measurement, participants or their caregivers provided written informed consent for the longitudinal study.

Table 6.1: Participant characteristics

	Total (*n*=134)		included analysis (*n*=87)		excluded analysis (*n*=47)		Test Statistic	
Demographics	mean	SD	mean	SD	mean	SD	t	*p*<
MMSE (0−30)	15.4	5.9	17.4	4.8	11.6	6.1	−5.66	0.01
age (years)	82.2	7.3	82.5	7.1	81.4	7.8	−0.84	0.41
education (1−7)	3.4	1.5	3.4	1.4	3.4	1.7	0.12	0.91
gender (% women)	71.6		75.9		63.8		$2.18^\dagger$	0.14
ApoE (% with allele 4)	41.3		39.8		44.7		$0.27^\dagger$	0.61
GDS (0−30)	7.2	5.5	7.1	5.7	8.5	3.7	0.85	0.40
SCL-90 (0−75)	21.1	6.5	21.0	6.6	21.4	5.1	0.17	0.87
BMI (kg/m^2)	26.9	4.4	27.2	4.3	26.3	4.5	−1.01	0.32
SBP (mmHg)	139.3	16.3	140.1	15.9	137.0	17.5	−0.86	0.40
DBP (mmHg)	73.8	12.6	74.4	12.8	72.2	12.2	−0.81	0.42
medication use (0-26)	4.7	2.5	4.6	2.5	5.0	2.4	0.81	0.43
Comorbidities (*% with disease*)								
endocrine/metabolic/nutritional	24.2		26.4		20.0		$0.67^\dagger$	0.42
heart/circulation	65.2		66.7		62.2		$0.26^\dagger$	0.62
musculoskeletal	37.9		41.4		31.1		$1.33^\dagger$	0.25
neurological	97.0		96.6		97.8		$0.15^\dagger$	0.70
sensory	24.2		26.4		20.2		$0.67^\dagger$	0.42
psychiatric/mood	24.2		25.3		22.2		$0.15^\dagger$	0.70
pulmonary	9.8		9.2		11.1		$0.12^\dagger$	0.73
other	30.3		29.9		31.1		$0.02^\dagger$	0.89

Notes: ApoE = Apolipoprotein E genotype (participants with at least one type 4 allele); BMI = Body Mass Index; DBP = diastolic blood pressure; GDS = Geriatric Depression Scale; MMSE = Mini-Mental State Examination; SBP = systolic blood pressure; SCL-90 = Symptoms Checklist 90. † = $\chi 2$ test.

6.2.6 Material

To assess physical performance and cognitive functioning the following tests were administered.

Assessment of physical performance

Mobility The mobility performance was computed by three physical tests, i.e., the ten meter timed walk, figure of eight and the TUG (Cronbach's $\alpha = 0.86$). For final mobility, the performance was multiplied by -1, with as result that higher scores indicate better mobility.

Ten meter timed walk Participants are requested to walk 10 meters at their own regular pace between 4 small traffic cones, which are placed in the corners of a 10 by 1 meter rectangle[460]. The time to walk 10 meters is measured by hand with a stopwatch to the nearest of 1/10 of a second.

Figure of eight The figure of eight is an applicable and reliable dynamic functional balance measure of mobility for people with various degrees of physical disability[400,401] and geriatric patients[402]. The figure of eight test requires continuous turning with an emphasis on accuracy (avoid oversteps), speed (timed task) and switching of motor patterns during the crossover from the clockwise to the counter-clockwise loop. Participants are timed while walking in a figure-8 trajectory. The figure-8 trajectory is marked with white paint on a dark green rubber carpet, each loop having an outer diameter of 165 centimeters (cm) and a step width of 15 cm. The time to walk two complete eight figures is measured with a stopwatch. The onset time is based on the first detectable movement of the participant following a "Go!" command from the observer. Any step taken outside the white line is noted. The fastest attempt of two trials is recorded together with the corresponding oversteps.

Timed up and go The TUG is a reliable and valid test for quantifying functional mobility that may also be useful in following clinical change over time[403]. To complete the TUG, participants are requested to rise from a standard chair (48 cm height, horizontal seat with armrests), walk 3 meters, turn around and return to a fully seated position in the chair again[404]. Each participant has two trials and the average time in seconds is the outcome of the TUG.

Strength

Sit to stand The sit to stand (STS) is normally a reliable and valid indicator of lower body strength in adults over the age of 60 years[405]. However, in this study participants are allowed to use upper limbs to rise from the chair to test their rising performance that is closest to the clinical setting and to reduce a floor effect; a high percentage of older dependent elderly cannot rise from a chair with the arms crossed in front of the chest[406,407]. Participants are instructed to stand up and sit down in a standard chair as many times as possible within 30 seconds. The STS score is formed by the total number of performances with a sit-stand-sit performance counting as 1. Ending in a standing position is counted by a 0.5 point.

Aerobic fitness

Six minute walk test The six minute walk test (6MWT) can be used reliably in the assessment of functional endurance ambulation in persons with acquired brain injury[395]. During the performance of the 6MWT, participants are instructed to cover as much distance as possible during 6 minutes with the opportunity to stop and rest if necessary[396]. Participants have to walk around a pre-measured, unobstructed 10 by 1 meter rectangular circuit having semi-circular ends with 0.5 meter radii marked out with plastic cones to prevent participants having to walk at sharp angles. One full round covers 26.3 meters walking. The total walking distance by each participant will be measured to the nearest meter.

Balance

Frailty and injuries: cooperative studies of intervention techniques The frailty and injuries: cooperative studies of intervention techniques (FICSIT-4) is a test to measure static balance[408]. The participants have to maintain balance in 4 positions with increasing difficulty. Each position is demonstrated first and support is offered while participants position their feet. When participants are ready, the support will be released and timing begins. The timing stops when participants move their feet or grasp the researcher for support, or when 10 seconds have elapsed. Only when one position is performed 10 seconds, the next, more difficult position is performed. The first position is with the feet together in parallel (side-by-side) position. Second is the semi-tandem position; the heel of one foot is placed to the side of the first toe of the other foot. The participant can choose which foot to place forward. Third is a tandem position; the heel of one foot directly in front of the toes of the other foot. The final position is standing on one leg. The total summed seconds of the performed positions is the outcome score.

Assessment of cognitive functioning

Besides the MMSE, 13 neuropsychological tests were administered, but 6 tests, i.e., digit span forward, visual memory span forward, rule shift cards, key search test, picture completion and the Stroop test (for details, see Volkers and

Scherder, 2011[459]) were not analysed in this study, because these tests could not be included in a specific cognitive domain.

Working memory The working memory domain was computed by five neuropsychological test scores, including the digit span backward, visual memory span backward, 2 category fluency tests and the digit symbol substitution test (DSST) (Cronbach's $\alpha = 0.82$).

Digit span backward The digit span is a subtest from the Wechsler Memory Scale-Revised (WMS-R)[414]. In the digit span backward, increasingly long sequences of random numbers are orally presented at a rate of one digit per second to the participants, who have to repeat the sequence in reverse order immediately after oral representation. This condition ends when a participant fails to recall at least two strings of the same length or repeated an eight-digit sequence correctly. The minimal score for this conditions is 0 and the best score is 21.

Visual memory span backward The visual memory span is a subtest of the WMS-R[414]. The visual memory span backward stimuli consist of squares printed on a two dimensional card and requires the participant to repeat a number of tapping sequences in reverse order, similar to the digit span backward. This test is used as a measure of visual working memory[414]. Scores range from 0 (worst) to 12 (best).

Category fluency test The category fluency test is a verbal fluency test which can be used to evaluate EF[418,419]. The participant is asked to name as many examples of a given category as possible, within 1 minute. This study uses the category 'animals' and 'professions'[421]. The outcome measure is the total number of animals and professions produced.

Digit symbol substitution test The DSST is a subtest of the Wechsler Adult Intelligence Scale (WAIS)-Revised[414]. Test scores correlate with general intelligence, cognitive impairment, chronological age and activation in the frontal regions[428–431]. Participants are presented with a rectangular grid of numbers. For each of these numbers, participants are instructed to substitute the appropriate symbol according to a code that appears at the top of the page. The DSST score is recorded as the number of correct symbols drawn in 2 minutes.

Episodic memory The episodic memory domain was computed by five neuropsychological test scores, i.e., three test scores of the eight words test, and face- and picture recognition (Cronbach's $\alpha = 0.75$).

Eight words test The eight words test is a list-learning test for people with memory problems[411]. In this test the examiner reads out eight words in a row, which is repeated five times. Every time the participant is asked to recall as many words as possible. The first outcome measure is the total number of correctly recalled words after the five trials (*immediate recall score*, maximal score = 40). After an interval of approximately 15 minutes the participant is asked to recall as many words as possible (*delayed recall score*, maximal score = 8). Subsequently, the examiner reads aloud 16 words among which 8 words presented before and 8 new words. The participant is asked to recognize the words from the list presented before (*recognition score*, maximal score = 16).

Face recognition Face recognition is a subtest from the Rivermead Behavioral Memory Test (RBMT)[417] and measures visual, nonverbal long term memory. Two versions (C+D) are combined to prevent a ceiling effect. In this test the participant is shown 10 cards with faces one at a time for 5 seconds. After a short interval of approximately 2 minutes, the participant is shown 20 cards, including 10 shown before and 10 cards with new faces. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of faces correctly recognized minus the number of faces incorrectly recognized. The worst score is -20 and the best score is +20.

Picture recognition Picture recognition is also a subtest from the RBMT[417], which measures visual, verbal long term memory. Two versions (C+D) are combined to prevent a ceiling effect. The participant is shown each of the 20 cards with drawings of objects for 5 seconds. With each card, the participant is requested to name the object on the card. After a short interval of approximately 2 minutes, the participant is shown 40 cards, including 20 shown before and 20 cards with new objects. The participant has to recognise whether the card was shown before or not. The outcome measure is the number of objects correctly recognized minus the objects that were incorrectly recognized. The lowest score is -40 and the maximal score is +40.

6.2.7 Data analysis

The data was analyzed using Statistical Package for the Social Sciences (SPSS) version 16.0 (SPSS, Inc., Chicago, IL). Scores on neuropsychological and physical tests were converted into z-scores and, according to factor analysis, summed up to define specific cognitive domains and physical performances. Hierarchical multiple regression analysis involved four steps. We tested the hypothesis that a physical performance (mobility, balance, strength or aerobic fitness) would be a significant predictor of cognitive functioning (working memory or episodic memory) (step 3) after controlling for age, education, depression, comorbidities, medication use (step 1) and cognitive impairment (MMSE) (step 2). The significance of the increment in the squared multiple correlation was tested when the physical performance was entered after the control variables. Furthermore, to analyse whether the physical performance as a predictor was different between people with mild and severe cognitive impairment, we added the interaction (MMSE × physical performance) to the model (step 4). To analyse whether the people who were excluded from the above mentioned regression analysis (due to missing values on depression, education and medication use) influenced the results, the same hierarchical regression analysis was performed without depression, education and medication use. A two-sided p value < 0.05 was considered statistically significant.

6.3 Results

The results of the hierarchical multiple regression analysis with working memory and episodic memory as dependent variables; age, education, depression, comorbidity, medications (step 1); MMSE (step 2); physical performance (step 3); and interaction between physical performance and MMSE (step 4) entered as predictors are shown in Table 6.2 (page 81). Out of 134 participants, 36 had no valid score on depression because they were too cognitively impaired (MMSE < 15), 5 participants had an unknown level of education, and medication use was unknown in 3 participants. This resulted in 94 participants with valid scores on variables included in step 1. Ten and 15 participants had no valid score on working memory and episodic memory, respectively, and 11 participants had missing values on physical performance (step 3 and 4), but most of these participants were already excluded in step 1. It should be mentioned that without depression, level of education and medication use in step 1, the items in step 3 and 4 remained comparable as described below with even higher explained variances ($5\% - 9\%$) of working memory.

6.3.1 Working memory

Balance, *strength* and *aerobic fitness* are all significant predictors of working memory ($p < 0.05$) after controlling for covariates (step 1) and the level of global cognition (step 2). Each performance explains $3 - 7\%$ of the total variance of working memory, irrespective of the level of cognitive impairment (interaction not significant).

6.3.2 Episodic memory

Mobility, *balance*, *strength* and *aerobic fitness* do not significantly predict episodic memory ($p \geq 0.05$) after controlling for covariates (step 1) and the level of global cognition (step 2) in older people with cognitive impairment.

Table 6.2: Results of multiple regression analysis

Dependent variable		Predictor	β	t	Cum R^2	Incr R^2
Working memory						
$n = 86$	step 1	age	−0.23	2.12^{*}		
		education	0.26	2.50^{*}		
		depression	−0.22	2.13^{*}		
		comorbidity	−0.04	0.29		
		medication	−0.13	1.10	0.17	0.17^{*}
	step 2	MMSE	0.61	7.01^{**}	0.49	0.32^{**}
	step 3	mobility	0.08	0.77	0.49	0.00
	step 4	MMSE*mobility	0.18	0.78	0.50	0.00
	step 3	balance	0.20	2.02^{*}	0.51	0.03^{*}
	step 4	MMSE*balance	0.15	0.39	0.52	0.00
	step 3	strength	0.31	3.43^{**}	0.56	0.07^{**}
	step 4	MMSE*strength	0.81	1.79	0.57	0.01
	step 3	fitness	0.21	2.02^{*}	0.51	0.03^{*}
	step 4	MMSE*fitness	0.46	1.22	0.52	0.01
Episodic memory						
$n = 87$	step 1	age	−0.29	2.60^{*}		
		education	0.19	1.82		
		depression	0.07	0.62		
		comorbidity	0.05	0.36		
		medication	0.06	0.46	0.12	0.12
	step 2	MMSE	0.58	6.20^{**}	0.40	0.29^{**}
	step 3	mobility	−0.05	0.45	0.40	0.00
	step 4	MMSE*mobility	−0.14	0.54	0.41	0.00
	step 3	balance	0.14	1.31	0.42	0.01
	step 4	MMSE*balance	−0.54	1.31	0.43	0.01
	step 3	strength	−0.07	0.72	0.41	0.00
	step 4	MMSE*strength	−0.40	0.76	0.41	0.00
	step 3	fitness	−0.00	0.02	0.40	0.00
	step 4	MMSE*fitness	−0.34	0.81	0.41	0.01

Notes: MMSE = Mini-Mental State Examination; $^{*}p < 0.05$; $^{**}p < 0.01$

6.4 Discussion

Although physical performances, such as strength and mobility, are assumed to be related to cognition, e.g., global cognition measured with 19 different neuropsychological tests[34], and EF[26,27], our findings show that in people with mild to severe cognitive impairment this is also true for working memory, but not for episodic memory. More specifically, the observed significant associations indicate that a better performance in *balance*, *strength* and *aerobic fitness* predict a better performance in working memory, irrespective of the level of cognitive impairment.

6.4.1 Working memory

Strength, *balance* and *aerobic fitness* are significant predictors of working memory, an aspect of EF[461], in people with a mild to severe cognitive impairment. This prediction is independent of the number of comorbidities, age, level of depression, education level and medication use. *Strength* (also measured with STS) as a predictor of working memory/attention, measured by the digit span forward and backward, was also observed in older cognitively healthy women[462]. In contrast, in a combined group of cognitively healthy older men and women, knee extension strength was not related to working memory[27]. However, in that study working memory was assessed by only one neuropsychological test, i.e., the digit span backward. In addition, knee extension strength was related to a lexical fluency test[27]. The latter test measures cognitive flexibility, which is in the current study included in the working memory domain by two category fluency tests[463]. In the current study the digit span backward and two category fluency tests were only three out of five neuropsychological tests of a strong domain ‘working memory’ (Cronbach’s $\alpha = 0.85$). Overall, all of the measured working memory and cognitive flexibility tests mentioned above appeal to EF[459], and therefore *strength* seems to predict EF, and not only working memory.

In the present study, *mobility* was not a significant predictor of working memory in people with a cognitive impairment. The same result has been observed in cognitively healthy older people; the 4 meter timed walk test was not related to the digit span test (score of digit span backward minus the score on the digit span forward) in older women[464], nor was the mobility performance (measured with performance-oriented mobility assessment (POMA)) related to the digit span backward in older men and women[27]. In contrast, the mobility performance of the latter study was associated with fluency, a cognitive performance that we included in working memory. However, their mobility performances (measured with the POMA) included not only gait and mobility, but also balance. Possibly balance caused the significant relation, since *balance* is also a significant predictor of working memory in the present study. *Balance* is dependent on the functioning of the fronto-cerebellar and fronto-striatal connections[31], connections between respectively, the cerebellum and the striatum and the frontal cortex, e.g., dorsolateral prefrontal cortex (DLPFC)[465–467]. Since the DLPFC is also involved in working memory[468], it is not surprising that in people with a cognitive impairment, balance is a significant predictor of working memory, because both performances appeal to the same neural circuits.

Aerobic fitness (measured with 6MWT) is a significant predictor of working memory in cognitively impaired older people. This was not observed in cognitively healthy older women[462]. However, the latter study measured a small number of participants ($n = 41$) and had a combined EF domain of working memory with attention. This combined domain was measured with the digit span backward, and with the digit span forward, which is different from the current study. A mechanism underlying the present finding might be that *aerobic fitness* is associated with white matter volume, even after controlling for age, gender, dementia severity, physical activity, and physical frailty[457]. White matter volume is positively related to working memory[62]. Indeed, executive control processes, such as working memory, show the largest benefits of improved fitness in older people[62]. Clinically, working memory is essential for storing information and therefore it is crucial for long-term memory and learning[469,470]. However, working memory is vulnerable during aging and dementia[471]. To reduce a decline in working memory, results of this study suggest that it is important to maintain good balance, strength and aerobic fitness. Indeed, in older people with mild Alzheimer's disease (AD), balance and coordination exercises seem to improve working memory in a pilot study[208].

6.4.2 Episodic memory

Mobility, *balance*, *strength* and *aerobic fitness* did not predict episodic memory in people with mild to severe cognitive impairment. These non-significant results are not very surprising, since motor performances are highly related to prefrontal cortex related cognitive functions, e.g., attention, EF and working memory, and less with hippocampal cognitive functions, e.g., episodic memory. Therefore *aerobic fitness* interventions show the highest effect sizes on cognitive functions in which the PFC plays an important role[62]. However, a higher effect size does not imply that aerobic fitness is only related to PFC related cognitive functions, and not with hippocampal related cognitive functions. Indeed, a comparable study in older people with mild cognitive impairment (MCI), have suggested that aerobic fitness may be the most important physical performance, besides strength, balance and mobility, that is related to the volume of the hippocampus[472]; this has been confirmed in another study in people with (very) mild AD[473]. Because hippocampal volume is positively related to episodic memory[474], these studies suggest that aerobic fitness and episodic memory are associated in people with MCI and (very) mild AD. However, participants of both studies were not only 8 years younger than participants of the current study (74 vs 82 years), they had less cognitive impairment as well, including also people with subjective cognitive impairment, with a mean MMSE of 27[472] or 26[473]; in the current study participants with a MMSE above 24 were excluded. With decreasing cognitive impairment, the hippocampus and PFC are both more affected[475,476]. However, to encode items in episodic memory, the anterior medial PFC is activated as well[477].

This suggests that, in people with decreasing cognitive impairment a high level of aerobic fitness, obtained by a high level of physical activity, has to improve the affected PFC first, before an improvement in episodic memory can be observed. Therefore, we argue that the relationship between aerobic fitness and working memory (or EF) is stronger than the relationship between aerobic fitness and (episodic) memory in people with cognitive impairment. Indeed, in people with a decline in both working memory and episodic memory as is the case in obese older people[478], aerobic fitness was related to EF, but not with memory[479]. In cognitively healthy people with a well-functioning PFC, the relationship between aerobic fitness and episodic memory is more often observed[206,480–482]. As far as the authors know, there are no other comparable studies assessing the relation between specific physical performance and episodic memory in older people with objective mild to severe cognitive impairment.

6.4.3 Passivity

Physical performances cannot only be improved by physical activities in cognitively healthy older people, but also in people with a cognitive impairment[350]. Since physical performances are important predictors for cognitive functioning, it is not surprising that cognitive functioning decreases faster in people with low levels of physical activity[348]. Regrettably, most older community-dwelling people do not meet the recommended level of physical activity[483], which is at least 30 minutes of moderate-intensity for 5 days per week in sessions of at least 10 minutes[238,268]. Cognitive functions decline even faster when people move into an institution, because of their low levels of physical activity[483]. Therefore, we need to consider the optimal timing and intensity of the physical activity, as well as the type of training, which should improve balance, strength and aerobic fitness.

6.4.4 Limitation

A limitation of the present study is its cross-sectional design, implying that one can only report associations instead of a causal relationship. Cross-sectional studies may therefore present similar[458,462], but also opposite findings, i.e., that attention predicts mobility[484], and that EF predicts functional performances, i.e., (instrumental) activities of daily living[39,184,485]. Longitudinal intervention studies are necessary to examine whether improvements in physical functioning also increase cognitive functioning, such as working memory and episodic memory.

6.4.5 Conclusion

In people with mild to severe cognitive impairment, the performances in balance, strength and aerobic fitness are significant predictors of working memory, but not of episodic memory. The association between physical performance and working memory necessitates the development of therapeutic strategies that are aimed at preventing a decline in physical performance in older people with mild to severe cognitive impairment. For the best strategies, we need to consider the optimal timing and intensity of the physical activity, as well as the type of training, which should improve balance, strength and aerobic fitness.

CHAPTER 7

THE EFFECT OF REGULAR WALKS ON COGNITION IN OLDER PEOPLE WITH MILD TO SEVERE COGNITIVE IMPAIRMENT; A LONG-TERM RANDOMIZED CONTROLLED TRIAL

Abstract.

Introduction: Physical activity has a positive effect on cognition, especially executive functions (EF), in healthy older people, but randomized controlled trials (RCTs) are scarce in people with mild to severe cognitive impairment. The goal of this study was to perform a long-term RCT examining the effect of 30 minute walks 5 days a week, as part of daily care, on cognition in a group of older people varying from mild cognitive impairment (MCI) to severe dementia.

Method: 148 participants with cognitive impairment (Mini-Mental State Examination (MMSE) < 25), a mean age of 82 years and a mean MMSE of 16, were randomly divided into a walking group ($n = 85$) and a control group ($n = 63$). Cognitive functioning was measured 7 times within 18 months of intervention with 12 neuropsychological tests. Intentionally, the intervention implied walking 5 days a week, 30 minutes a day during 18 months as part of usual care.

Results: Compliance with the intervention was poor: a mean of 36 ± 42 minutes per week was obtained, varying from 0 to 195 minutes per week, with a mean of 1.34 ± 1.45 times per week. The walks had only an effect on EF in people with MCI/mild dementia (MMSE ≥ 20).

Conclusion: From a cognitive point of view, physical activity should be applied as soon as possible in older people with MCI/mild dementia, preferable even before the onset of cognitive impairment. [1]

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[1] Volkers, K.M., Scheltens, P., and Scherder, E.J.A. The effect of regular walks on cognition in older people with mild to severe cognitive impairment; a long-term randomized controlled trial. *Submitted*.

7.1 Introduction

As the population of the world is aging, the number of older adults with dementia is estimated to increase[486] since age is the highest risk factor for one of the most prevalent subtypes of dementia, i.e., Alzheimer's disease (AD)[487]. Consequently, there is a growing interest in the development of interventions that will enhance cognitive functioning of older adults and reduce the risk for age-related neurodegenerative disorders, such as Alzheimer's disease. One of the interventions that seem to enhance cognitive functioning in older adults is physical activity[488]. The question arises how consistent the effects of physical activity on cognition in older persons with and without dementia are.

In older people without dementia, a meta-analysis including 18 randomized controlled trial intervention studies found a moderate effect size (Hedges' $g = 0.48$) for aerobic fitness training on cognitive function[62]. Although fitness effects were observed in a variety of cognitive processes in people without dementia, e.g., visuo-spatial processes, the effects were largest for executive-control processes, such as inhibition, planning, and working memory[62]. These processes are supported by the frontal brain regions and show negative changes with age[489]. Compared to the changes during aging, cognitive performances are more affected by increasing neuropathology in people with dementia[360].

Results on the effects of exercise on cognition in people with dementia are equivocal[68,92,359,447,490,491] and not sufficient to draw firm conclusions[67,492]. Two reviews argue that the lack of a beneficial cognitive effect is due to interventions that mainly consisted of strength-, balance- and/or flexibility-based exercises, while aerobic exercises, such as walking, improve cognitive functioning[68,359]. Others suggest that the high number of cardiovascular risk factors in people with dementia is an explanation for lack of a beneficial effect[92,493]. Insufficient evidence in studies including people with dementia may be due to for example, lack of methodology, differences in type of intervention, durations and outcome measures[67,68,359,492].

With the backdrop of the aforementioned reviews, others have suggested that long-term RCTs are warranted in older people with and without dementia[60,352,355,358,381]. Indeed, most interventions end after less than 10 weeks[66,494,495], 10–24 weeks[496–504], while a duration of at least 6 months is recommended[505]. In addition, students or researchers often carry out these interventions. When they leave the clinical setting, former usual care continues with the possible result that the improvements of the intervention disappear[506,507], unless it is a successful behavioural stimulation intervention[504,508]. This calls for a continuous physical activity program in institutions for older people with a cognitive impairment. Therefore, the goal of this study was to perform a RCT examining the effect of 30 minutes walks for 5 days a week, during 18 months, as part of daily care on cognition in a large group of older people with a mild to severe cognitive impairment. It is hypothesised that the walks would have a beneficial effect on cognitive functioning.

7.2 Methods

This study was a randomized controlled single-blind study within 17 different institutions, i.e., day care centers ($n = 4$), homes for the elderly ($n = 6$) or nursing homes ($n = 7$) within the Netherlands. It was part of a larger study that is described in more detail elsewhere[459].

7.2.1 Participants

All 148 participants with a cognitive impairment, defined by a (MMSE < 25), were randomly divided into a walking group ($n = 85$) or control group ($n = 63$). As it was expected that the intervention as part of usual daily care would be performed with variability, participants within a department were placed in a two to one ratio in the intervention and control group respectively, provided that the number of walking guides was sufficient within a department. Eighteen participants could not be included in the multilevel analysis to predict cognitive functioning, because they did not complete the minimal EF or memory tests once. The characteristics of the included participants of both walking and control group are shown in Table 7.1 (page 91). Exclusion criteria were the presence of personality disorders, cerebral traumata, hydrocephalus, neoplasm, disturbances of consciousness and focal brain disorders.

7.2.2 General characteristics

Global cognitive function Global cognitive functioning was measured with the MMSE[409].

Highest education level Education level was determined on a seven-point scale varying from less than elementary school (1) to university and technical college (7)[383].

Body mass index body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared.

Apolipoprotein E (ApoE) type 4 allele ApoE type 4 allele (ApoE4) is a known risk factor for late onset AD[384]. In addition, ApoE4 carriers show a higher effect on cognition as a result of physical activity interventions than non-carriers[509]. ApoE genotype of participants was determined by a rapid lysis technique[387].

Medication use Medication use was coded according to the Dutch Pharmacotherapeutic Compass and is ranged by 26 categories. The total number of medication categories was used as medication use covariate.

Comorbid conditions Comorbid conditions were extracted from the medical status and categorized based on the Dutch translation of the Long-Term Care Facility Resident Assessment Instrument (RAI), section I. This section (disease diagnoses) includes 43 subcategories within 8 main categories. The total number of subcategories was used as a comorbidity covariate.

Cardiovascular risk factors The total number of cardiovascular risk factors including diabetes, deep vein thrombosis, hypertension, arteriosclerotic heart disease, peripheral vascular disease, rheumatoid arthritis, cerebrovascular accident, transient ischemia attack and a BMI > 30 was used.

Ten meter timed walk The time to walk 10 meters at regular pace was recorded.

7.2.3 Assessment of mood

To measure the level of depression, the geriatric depression scale (GDS)[432] and symptoms checklist 90 (SCL-90)[435] were administered.

7.2.4 Procedure

Cognitive functioning of participants was measured 7 times, i.e., at baseline, and after 6 weeks, 3, 6, 9, 12 and 18 months of intervention. Trained experimenters, blinded to the intervention assignment, administered the neuropsychological tests and questionnaires to measure mood. The Medical Ethical Committee of VU University Medical Center approved this study. All participants or their relevant relatives prior to their enrolment gave oral and written informed consent.

7.2.5 Assessment of cognitive functioning

To assess aspects of cognitive functioning that are known for a positive response on physical activity[359], such as EF and memory, 12 neuropsychological tests were administered (for details, see Volkers and Scherder, 2011[459]). However, to strive for as much data-reduction as possible, 4 tests, i.e., rule shift cards[412], digit span forward[414], visual memory span forward[414] and picture completion[422] were not included in the data-analysis of this study, because these tests could not be included in a specific cognitive domain.

EF

The EF domain contained the following neuropsychological tests: key search[412], digit span backward[414], category fluency tests (animals and professions)[421], visual memory span backward[414], Stroop task (subtask 3)[424], and digit symbol substitution test (DSST)[414].

Table 7.1: Characteristics of participants within the walking and control group

	Walking group (n=75)		Control group (n=55)		Test Statistic	
Characteristics	mean	SD	mean	SD	t	$p<$
age (years)	82.0	7.2	82.3	7.8	0.16	0.88
education (1−7)	3.2	1.5	3.6	1.4	1.25	0.22
BMI (kg/m^2)	27.2	4.7	26.2	4.4	−1.14	0.26
MMSE (0−30)	15.3	5.0	17.1	6.1	1.78	0.08
RAI (0−43)	4.4	2.3	4.3	2.2	−0.33	0.75
Cardiovascular rf (0−9)	1.6	1.3	1.8	1.3	0.70	0.49
medication (0−26)	4.4	2.4	4.2	2.2	−0.53	0.60
10-meter (seconds)	16.5	9.5	17.5	9.6	0.59	0.56
mood (z-score baseline)	−0.06	0.85	0.10	1.09	0.80	0.43
EF (z-score baseline)	−0.14	0.69	0.06	0.66	1.59	0.12
memory (z-score baseline)	−0.19	0.60	0.01	0.76	1.62	0.11
					$\chi 2$	$p<$
gender (% women)	76.0		67.3		1.21	0.28
%ApoE	36.2		51.0		2.57	0.11
diagnosis:					4.34	0.37
%MCI	1.4		5.6			
%AD	50.0		50.0			
%VaD	13.5		18.5			
%AD + VaD	10.8		3.7			
%other	24.3		22.2			

Notes: AD = Alzheimer's Disease; %allele4 = participants with at least one type 4 allele; ApoE = Apolipoprotein E genotype; BMI = Body Mass Index; MCI = Mild Cognitive Impairment; MMSE = Mini-Mental State Examination; %other = people with other types of dementia than AD or VaD or people with unknown type of dementia; rf = risk factors; VaD = Vascular Dementia.

memory

The memory domain contained the following neuropsychological tests: Eight Words test (immediate recall score, delayed recall score and recognition score)[411], Face Recognition[417], and Picture Recognition[417].

7.2.6 Intervention

Intentionally, the intervention was to walk 5 days a week, 30 minutes a day during 18 months under supervision of a walking guide. This intervention was part of usual care and therefore guided by the staff, family or volunteers of the nursing home. The actual performed walks (of the intervention) were recorded for each participant. For each participant of the walking group, the mean amount of minutes walked (only the minutes walked by intervention) between two consecutive measurements was calculated. Since there were 7 measurements (T0-T6), each participant of the walking group had 6 walking periods, i.e., T0-T1 (1), T1-T2 (2), T2-T3 (3), T3-T4 (4), T4-T5 (5), T5-T6 (6), with for each period a mean score of minutes walked per week.

7.2.7 Data analysis

Participants who were included in the multilevel analysis were compared with the 18 participants who were excluded on characteristics with Mann–Whitney–U–tests and χ^2 tests. Descriptive statistics were calculated for participants in the intervention and control group and differences between the groups at baseline were analyzed by means of independent-samples t-tests and χ^2 tests. Scores on EF and memory tests were converted into z-scores and, after a factor analysis, the mean of these scores resulted in an EF domain and a memory domain. To reduce missing values, a mean score on the EF domain was accepted if participants had a valid score on at least 4 out of 7 tests. For memory at least 3 out of 5 tests had to have a valid score. Cronbach's α was 0.68 for EF and 0.67 for memory. Level of depression was based on the z-score of both questionnaires and resulted in a Cronbach's α of 0.89.

Whether the intervention (defined by groups or walks in minutes per week) had an effect on cognitive functioning, i.e., EF and memory, was investigated with multilevel modelling using the gamm4 and mgcv package for R[510]. Multilevel modelling is an extension of multiple regression for data with a hierarchical structure; in the present study all our participants (level 1) are nested in 17 different locations (level 2); these are our two random-effect factors. These random-effect factors are necessary to reduce systematic variation, i.e., random noise, and make a statement regarding the larger population.

To predict cognitive functioning in our study, we analysed 2 models for both EF and memory, with three predictors in addition to the two random-effect factors. The first model includes 'group' (intervention or control), 'time' (cumulative days of the measurements) and the interaction between 'group × time' to analyse the effect of the intention to treat. The second model includes the performed 'walks' in minutes per week, 'time' and the interaction 'walks × time' to analyse the effect of the performed walks. We performed the 2 models within the total group and within two subgroups of people with a MMSE $\geq$ 20 (MCI/mild dementia) or a MMSE $<$ 20 (moderate to severe cognitive impairment) since the effect of physical activity has mainly been observed in cognitively healthy people and people with MCI, while results in people with a moderate to severe cognitive impairment, i.e., dementia, are equivocal. Since the effect of physical activity on cognition is higher in people who are ApoE4 allele carriers than non-carriers and ApoE4 carriers are also at higher risk to show a cognitive decline, we performed the first models again and added ‘time × ApoE4’ and ‘group × ApoE4’, and in the second models we added ‘time × ApoE4’ and ‘walks × ApoE4’. Results of these interactions are only mentioned when significant ($p < 0.05$).

7.3 Results

7.3.1 Compliance with the intervention

Overall, participants of the walking group walked 1.34 ± 1.45 times per week with a mean of 36 ± 42 minutes per week per period, varying from 0 to 195 minutes per week. Only in 21% of the periods a mean of at least 30 minutes per walk was obtained. Participants with MCI/mild dementia walked as often as participants with moderate to severe cognitive impairment ($p > 0.05$).

7.3.2 Differences between groups

The 18 participants who could not be included in the models to predict cognition had a significant lower MMSE (median MMSE = 5, range $3 - 13$) at baseline than the participants who were included in the Model ($U = 4.29,\ p < 0.01$), but they did not differ in age, education, BMI, gender, ten meter timed walk, diagnosis, ApoE4 or group ($p > 0.05$).

Overall, the walking group did not differ from the control group on age, level of education, BMI, MMSE, number of comorbidities, medication use, gender, diagnosis, ApoE4 allele, cardiovascular risk factors, ten meter timed walk, EF or memory at baseline (see Table 7.1 on page 91). Most participants had at least one cardiovascular risk factor and this percentage was lower in people with MCI/mild dementia (78%) compared to people with moderate to severe cognitive impairment (84%) ($\chi^2 = 3.53, p = 0.06$). In addition, the number of cardiovascular risk factors was less in people with MCI/mild dementia (1.49) compared to people with a moderate to severe cognitive impairment (1.74) ($t = 2.27,\ p = 0.02$).

7.3.3 Models to predict cognition

Drop-out rate

The total number of observations in our original data set was 1036 (148 subjects with 7 measurements). However, at each measurement, not all participants fulfilled at least 50% of the neuropsychological tests of EF or memory. Therefore, our final data set consisted of 538 observations for EF, and 573 for memory. The drop-out rate was not different between the intervention and control group: within the intervention group, 70 (82%) participants had a mean of 4.43 measurements for EF, while the control group of 53 (84%) participants had 4.30 measurements. For memory, 75 (88%) participants of the intervention group performed 4.48 measurements, while 54 (86%) participants of the control group performed a mean of 4.39 measurements each. However, within the intervention group, a subgroup of people who did not walk (0 minutes per week) showed a higher drop-out rate; they performed only a mean of 1.49 and 1.51 measurements each for EF and memory, respectively.

Decline over time

Overall, ApoE4 carriers show a significant faster decline in EF and memory within 18 months than non-carriers within the total group ($t = 3.15,\ p < 0.01$; $t = 2.10,\ p = 0.02$ respectively) and within the MCI/mild dementia subgroup ($t = 1.81,\ p = 0.04$; $t = 1.80,\ p = 0.04$ respectively). The moderate to severe cognitive impairment subgroup shows a decline in EF and memory, irrespective of the ApoE4 carrier status.

Effect of intervention on cognition

The coefficients and associated statistics of the predictors for EF and memory are shown in Table 7.2 (page 95) and 7.3 (page 96), respectively. Not all participants were able to perform at least 50% of the EF or memory tests during repeated measurements. Therefore, the EF and memory models were based on 123 and 129 participants, respectively, with a mean of 4.4 measurements for each participant. In total, this amounts to 538 and 573 measurements for EF and memory, respectively. In both models of the total group and the subgroup with moderate to severe cognitive impairment, the intervention had no effect on EF or memory. However, within the MCI/mild dementia subgroup, the walks had a significant positive effect on EF, with an effect size of 0.36. This effect was somewhat higher in ApoE4 carriers since the interaction 'walks × ApoE4' showed a trend ($t = 1.52,\ p = 0.06$).

7.4 Discussion

This is the first study that assesses the effect of regular walks as part of daily care in older people with a wide range of cognitive functioning (mild to severe) over a longer period (18 months) with multiple measurements (7 measurements) and cognitive domains (EF and memory) measured with multiple neuropsychological tests.

7.4.1 Compliance with intervention

Unfortunately, the adherence to the program was poor. The current attendance rate (27%) was less than half of the rate in a one year walking program (63%)[70]. However, the latter walking program was only twice weekly, group-based, supervised by trained instructors, and included only people with MCI.

Table 7.2: Models to predict EF within 18 months in the total group, the subgroup of MCI/mild dementia (MMSE $\geq$ 20) and moderate to severe cognitive impairment (MMSE < 20)

Participants	Model	Fixed effects	Estimate	Std. Error	t-value
Total group	A	(Intercept)	-4.95×10^{-2}	1.15×10^{-1}	0.43
		group	-5.47×10^{-2}	1.23×10^{-1}	0.44
		time	-2.78×10^{-4}	1.22×10^{-4}	2.28^{*}
		group × time	-1.87×10^{-4}	1.57×10^{-4}	1.19
	B	(Intercept)	-9.78×10^{-2}	9.15×10^{-2}	1.07
		walks	6.93×10^{-4}	5.95×10^{-4}	1.17
		time	-3.47×10^{-4}	9.22×10^{-5}	3.76^{*}
		walks × time	-2.29×10^{-6}	3.13×10^{-6}	0.73
MMSE $\geq$ 20	A	(Intercept)	4.67×10^{-1}	1.21×10^{-1}	3.87
		group	5.17×10^{-3}	1.70×10^{-1}	0.03
		time	-1.46×10^{-4}	1.71×10^{-4}	0.86
		group × time	-1.74×10^{-5}	2.70×10^{-4}	0.06
	B	(Intercept)	4.34×10^{-1}	8.93×10^{-2}	4.86
		walks	2.61×10^{-3}	1.37×10^{-3}	1.91^{*}
		time	-8.08×10^{-5}	1.50×10^{-4}	0.54
		walks × time	-8.55×10^{-6}	6.72×10^{-6}	1.27
MMSE < 20	A	(Intercept)	-2.19×10^{-1}	1.07×10^{-1}	2.05
		group	1.84×10^{-2}	1.22×10^{-1}	0.15
		time	-2.42×10^{-4}	1.88×10^{-4}	1.29
		group × time	-3.06×10^{-4}	2.23×10^{-4}	1.37
	B	(Intercept)	-2.15×10^{-1}	7.61×10^{-2}	2.83
		walks	1.66×10^{-4}	7.11×10^{-4}	0.23
		time	-4.30×10^{-4}	1.25×10^{-4}	3.44^{*}
		walks × time	2.98×10^{-7}	3.87×10^{-6}	0.08

Notes: In the total group, model A is based on 538 observations in 123 participants, model B is based on 513 observations in 123 participants; in the subgroup MMSE $\geq$ 20, model A is based on 176 observations in 51 participants, model B is based on 170 observations in 51 participants; in the subgroup MMSE < 20, model A is based on 361 observations in 105 participants, model B is based on 342 observations in 105 participants. $^{*}p < 0.05$.

We expected that the intervention as part of usual care would be performed with variability during 18 months, but the intervention was performed less often than could be expected, considering the results of other studies[70,353,495,511].

Table 7.3: Models to predict memory within 18 months in the total group, the subgroup of MCI/mild dementia (MMSE $\geq$ 20) and moderate to severe cognitive impairment (MMSE < 20)

Participants	Model	Fixed effects	Estimate	Std. Error	t-value
Total group	A	(Intercept)	-1.21×10^{-1}	1.19×10^{-1}	1.02
		group	-2.54×10^{-2}	1.17×10^{-1}	0.22
		time	-2.38×10^{-4}	1.57×10^{-4}	1.52
		group × time	2.24×10^{-4}	2.02×10^{-4}	1.11
	B	(Intercept)	-1.63×10^{-1}	9.85×10^{-2}	1.66
		walks	8.94×10^{-4}	7.95×10^{-4}	1.13
		time	-1.04×10^{-4}	1.18×10^{-4}	0.88
		walks × time	2.04×10^{-7}	3.85×10^{-6}	0.05
MMSE $\geq$ 20	A	(Intercept)	5.42×10^{-1}	1.09×10^{-1}	4.96
		group	-2.43×10^{-1}	1.61×10^{-1}	1.51
		time	1.88×10^{-4}	2.35×10^{-4}	0.80
		group × time	2.50×10^{-4}	3.74×10^{-4}	0.67
	B	(Intercept)	4.12×10^{-1}	8.52×10^{-2}	4.84
		walks	3.70×10^{-4}	1.83×10^{-3}	0.20
		time	3.03×10^{-4}	2.10×10^{-4}	1.45
		walks × time	5.02×10^{-6}	9.50×10^{-6}	0.53
MMSE < 20	A	(Intercept)	-2.55×10^{-1}	1.11×10^{-1}	2.30
		group	5.51×10^{-3}	1.16×10^{-1}	0.05
		time	-4.39×10^{-4}	2.16×10^{-4}	2.03*
		group × time	3.20×10^{-4}	2.57×10^{-4}	1.25
	B	(Intercept)	-2.82×10^{-1}	8.31×10^{-2}	3.39
		walks	7.84×10^{-4}	8.65×10^{-4}	0.91
		time	-2.33×10^{-4}	1.42×10^{-4}	1.64
		walks × time	1.57×10^{-7}	4.24×10^{-6}	0.04

Notes: In the total group, model A is based on 538 observations in 123 participants, model B is based on 513 observations in 123 participants; in the subgroup MMSE $\geq$ 20, model A is based on 176 observations in 51 participants, model B is based on 170 observations in 51 participants; in the subgroup MMSE < 20, model A is based on 361 observations in 105 participants, model B is based on 342 observations in 105 participants. $^*p < 0.05$.

7.4.2 Differences between groups

The eighteen participants who were excluded from analysis were more cognitively impaired than the participants who were included in multilevel analysis. This is not surprising, because participants had to perform at least 50% of the EF and/or memory tests once to be included in the analysis. Especially EF tests demand a higher cognitive ability to understand the instructions of the tests than the memory tests as indicated by a lower number of people who were able to perform the EF tests than memory tests.

Despite that the randomization to assign participants to the intervention or control group was not performed with a computer generated randomization technique as recommended[492], it seems that this study has no allocation bias: the walking group did not differ from the control group on any of the known variables at baseline, i.e., age, level of education, BMI, MMSE, number of comorbidities, medication use, gender, diagnosis, ApoE4 allele, cardiovascular risk factors, level of depression, EF or memory.

7.4.3 Models to predict cognition

Although there was a decline in EF and memory over time, selective loss of the oldest and most cognitively impaired participants due to death or study withdrawal possibly resulted in a conservative estimate of true decline.

EF

This study supports previous findings of the benefits of physical activity on EF in older people with MCI/mild dementia; the more time people walk per week the better EF. This positive effect of physical activity on EF is supported by reviews and meta-analysis in people with MCI[359,447] or people without cognitive impairment[10,17,18,60,99,359,505,512–517], but should be interpreted with caution for two reasons; 1) no effect on EF was observed between the groups (intervention vs. control); 2) the level of physical activity besides the intervention is unknown. Possibly, people who performed the walks more often were also more active besides the intervention. This might have caused a bias in the results. We observed a faster cognitive decline in ApoE4 carriers, but a trend that ApoE4 carriers show a higher effect of walks on EF than non-carriers. This is in line with other studies showing that ApoE4 carriers are at higher risk for dementia or cognitive decline, but respond better to physical activity interventions to stimulate cognition[509,518].

Unfortunately, no effect of walking on EF was observed in people with moderate to severe cognitive impairment. Comparable studies are scarce; only one RCT showed that 6 weeks walking was not effective for EF in people with moderate dementia[495]. It has been observed more often that a walking intervention in a group with moderate to severe cognitive impairment is not effective, especially not in people with severe cognitive impairment[503]. Reviews in people with dementia showed that physical activity might have an effect on cognitive functioning, e.g., EF[88,367,447,490–492], but often (5 out of 8 studies) the physical activity interventions were combined with cognitive stimulation[490] or the effect size on cognition was combined with other outcome variables, such as physical functioning or behaviour[88], and it should be mentioned that most reviews included more studies with mild dementia than moderate to severe dementia. The current study did not combine the intervention, but used only regular walks as intervention, measured a control group and randomized participants into the groups, a methodology that other intervention studies including people with a mild to severe dementia missed[447,490,492].

Memory

Regular walks have no significant effect on memory in the current study. That memory benefits less from physical activity than EF is not a new finding[62], because physical activity has more effect on the prefrontal cortex (PFC), a brain area that is responsible for EF, than on the hippocampus, an important area for memory[64]. More recent reviews in older people without dementia or with mild dementia indicate that some studies show significant effects on memory, but not all[60,359,447]. In people with cognitive impairment, the hippocampus and PFC are both affected compared to cognitively healthy people[519,520]. However, to encode items in episodic memory, the anterior medial PFC is activated[477]. This suggests that, to find an improvement in episodic memory, an improvement in the anterior medial PFC might be a prerequisite when both areas are affected. Apparently, the improvement in both areas was not enough in the current study to observe an improvement in memory. To improve both areas, the physical activity should be of enough intensity[64]. It is possible that the current intervention was not performed with sufficient intensity, duration or frequency to find a significant effect on memory: people walked less than 2 times per week and many walks were less than 30 minutes which has less effect on cognition[62]. In addition, it is not known at what speed people walked or how many stops they made during the walks and therefore it is unknown whether they reached the mimimum intensity to have an impact on memory[521]. In addition, it is also known that more variation in physical activities might have more effect on memory[521]; the present intervention lacks variation. More comparable RCT studies are necessary to draw firm conclusions about the long-term effect of physical activity on EF and memory in older people with a wide range of cognitive impairment.

7.4.4 Limitations

Limitations of this study are the very low feasibility of the intervention. Since low levels of physical activity increase cognitive decline in institutionalized people[483], it is recommended to examine what factors increase the adherence to a physical activity intervention in institutionalised people with cognitive impairment. Otherwise, if the adherence remains low, the cost-benefit ratio is too high. Second, selective loss to follow-up measurements of the most impaired participants over time, risks underestimation of the true rates of decline and the effect of the intervention. We observed increasing drop out in later measurements. Such drop out can lead to a conservative estimate of our findings even though the dropout rate was comparable between the people with MCI/mild dementia and moderate to severe cognitive impairment, and between the control group and the intervention group. However, within the intervention group, most dropouts were people who did not walk. Possibly, the dropouts decline faster in cognitive functioning than the non-dropouts; some people who were aware of their cognitive decline refused the neuropsychological tests because it was too confronting, or they were not able to understand the neuropsychological tests anymore. Therefore, the decline in cognitive functioning might be underestimated due to dropouts. Since the people who did walk had less dropouts, the effect of walks on cognition is possibly underestimated as well. However, we tried to minimize this impact through the use of random mixed-effect models.

7.4.5 Conclusion

Taken together, implementation of five days a week supervised walking as part of daily care is not feasible in people with mild to severe cognitive impairment. The supervised walks that have been carried out seem to have a positive effect on EF in people with MCI/mild dementia who walked regularly, but had no effect on EF in people with moderate to severe cognitive impairment. Irrespective of the level of cognitive impairment, regular walks did not significantly improve memory. Clinically, it seems best to be physically active as soon as possible, preferably before the onset of cognitive impairment.

CHAPTER 8

THE INTENSITY OF CHAIR-ASSISTED EXERCISES IN OLDER COGNITIVE HEALTHY PEOPLE

Abstract.
Introduction: The American College of Sports Medicine prescribes regular performance of at least moderate intensity physical activity for healthy aging. This study examines whether one session of 30 minutes of chair-assisted exercises for elderly meets this intensity criterion.
Method: This cross-sectional study included 47 cognitive healthy volunteers (mean age 84 years). During the performance of 30 minutes chair-assisted exercises we determined oxygen uptake ($\dot{V}o_2$), carbon dioxide production ($\dot{V}co_2$), heart rate (HR) and rating of perceived exertion (RPE). These measures were expressed as a percentage of the estimated maximal oxygen uptake ($\dot{V}o_2$max), the estimated maximum heart rate (HRmax), and estimated as metabolic equivalent units (METs).
Results: Participants performed the chair-assisted exercises at 61.0% ± 14.7% of $\dot{V}o_2$max, 67.6% ± 11.3% of HRmax, 3.9 ± 0.9 METs, and 13.1 ± 2.1 RPE.
Conclusions: The intensity of these chair-assisted exercises is at least moderate for older people which is necessary for healthy aging. [1]

8.1 Introduction

REGULAR physical activity can help reduce age related cognitive decline and comorbidities such as cardiovascular disease[522]. A little physical activity is better for health than none, but for most health aspects, additional benefits occur when people increase the amount and/or intensity of physical activities[522]. The American College of Sports Medicine prescribes that all adults must regularly perform physical activity of at least moderate intensity for healthy aging[522]. Multiple measures are used in the literature

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[1] Volkers et al., 2012. The intensity of chair-assisted exercises in older cognitive healthy people. *Journal of Aging and Physical Activity* (accepted).

to determine the intensity level, i.e., percentage of $\dot{V}O_2$max (%$\dot{V}O_2$max), percentage of HRmax (%HRmax), energy expenditure, number of METs, or a subjective RPE. Each of these measures has a threshold which should be reached for (at least) moderate intensity. For example, an unfit person is exercising at moderate intensity when the following thresholds are gained: 40% of $\dot{V}O_2$max[523], 64% of HRmax, 2.0 METs (for people aged > 80 years), or 12 on the RPE scale[524]. These values could be considered thresholds; higher scores on these measures indicate a higher intensity level[523].

A widely applied type of physical activity for the oldest age group in for example long term care, is a group activity that is performed on and behind a chair (chair-assisted exercises) to guarantee safety[525], as older people may have balance problems[526]. Of many other daily activities the intensity is known[184], however, it is unclear whether chair-assisted exercises for older people is of (at least) moderate intensity, i.e., the recommended intensity level for healthy aging. Therefore, the goal of this study is to examine the level of physical intensity of 30 minutes of chair-assisted exercises, consisting of endurance, strength and balance exercises on and behind a chair.

8.2 Methods

8.2.1 Participants

This study sample consisted of 47 volunteers (17 men) varying from independent living ($n = 13$) to assisted-living ($n = 24$) and care home residents ($n = 10$). Mean age was 84.1 ± 5.6 years, mean systolic and diastolic blood pressure was 148 ± 24 mmHg and 77 ± 13 mmHg respectively, body mass index (BMI) was 25.3 ± 3.4 kg/m^2, and the level of global cognitive functioning was 27.0 ± 2.1 on the Mini-Mental State Examination (MMSE)[409] (see Table 8.1 on page 103). Participants were excluded from the study if they were younger than 70 years, not able to walk short distances with or without a walking aid or suffering from a cognitive impairment (MMSE < 23). Participants' medical history showed comorbidities that were representative of the general population of this age[527]. Fifteen participants used a β-blocker during their participation in this study, and three participants used other heart rate reducing medication (amiodaron, flecainide). The latter three participants were not included in either the non β-blocker users nor the β-blocker users. This study was approved by the Medical Ethical Committee of VU university medical center and all participants signed informed written consent.

8.2.2 Procedure

Participants performed one session of 30 minutes chair-assisted exercises (see Figure 8.1 (on page 107) once in our laboratory, with one or two participants at the same time. Before exercising, the participant had to place a soft mask over

Table 8.1: Participant characteristics

Characteristic	Mean	SD	*n*	Median	Range
Age (years)	84.1	5.7	47	84.0	71.0 - 96.0
MMSE score (0 - 30)	27.0	2.1	47	28.0	23.0 - 30.0
Diastolic blood pressure (mmHg)	77	13	46	76	47 - 120
Systolic blood pressure (mmHg)	148	24	46	148	97 - 217
BMI (kg/m^2)	25.3	3.4	47	25.4	17.0 - 32.5
Education level (1 - 7)	4.4	1.4	35	4.0	2.0 - 7.0

Notes: BMI = Body Mass Index; Education level is based on a 7 point scale in which 7 is the highest education and 1 the lowest; MMSE = Mini-Mental State Examination.

mouth and nose to measure oxygen consumption and carbon dioxide production and a Polar Vantage belt to measure the heart rate. People were able to get used to the mask and belt for approximately 5 minutes. Thereafter the exercises, of a special designed programme for older people started. These exercises were designed by a human movement scientist and were a combination of endurance, strength and balance exercises, since multicomponent interventions show the best improvements in functioning[24]. Two instructors demonstrated the exercises while motivating the participants. Participants performed the exercises at a level of intensity that was comfortable for them. While performing the chair-assisted exercises for 30 minutes, oxygen consumption, carbon dioxide production and heart rate were measured continuously. Directly after cessation of the exercises people had to rate their perceived intensity on a Borg's RPE scale[528].

8.2.3 Outcome variables

Oxygen consumption during the performance of 30 minutes chair-assisted exercises was determined by use of an Oxycon Alpha. The Oxycon Alpha is a valid and reliable on-line system for the measurement of parameters of respiration, at least at workloads up to 150 Watt[529]. This system consists of a soft mask to sample exhaled air every 5 seconds and measure the $\dot{V}o_2$, and carbon dioxide production $\dot{V}co_2$.

Oxygen uptake

The $\dot{V}o_2$ and $\dot{V}co_2$ measures fluctuated between the different exercises. The mean intensity of the 30 minutes session of chair-assisted exercises was calculated and expressed as mean $\dot{V}o_2$ (mL/min) and mean $\dot{V}o_2$ per kilogram of body weight (mL/min/kg). To estimate whether oxygen uptake was of at least moderate intensity, it was recalculated as a percentage of participants' estimated $\dot{V}o_2$max by the same method as a comparable study for people aged

55 to 86 years[527]. The $\dot{V}o_2$max regression equations for men were:

$$\dot{V}o_2max\ (L/min) = -0.034 \times age + 4.142 \tag{8.1}$$

or

$$\dot{V}o_2max\ (mL/min/kg) = -0.31 \times age + 44.23 \tag{8.2}$$

and for women:

$$\dot{V}o_2max\ (L/min) = -0.019 \times age + 2.528 \tag{8.3}$$

or

$$\dot{V}o_2max\ (mL/min/kg) = -0.25 \times age + 36.63 \tag{8.4}$$

Heart rate

HR was determined by use of a Polar Vantage belt. The HR fluctuated between the different exercises, but to determine the mean intensity of the complete 30 minutes of exercises, the mean HR over the 30 minutes was determined. To estimate whether this HR was of at least moderate intensity, it was recalculated as a percentage of participants' estimated HRmax which was estimated by:

$$HRmax\ (beats/minute) = 220 - age \tag{8.5}$$

The mean percentage of HRmax was determined for the whole group ($n = 44$, because HR measure failed in three participants) and for the group of non β –blocker users ($n = 26$), because β–blockers ($n = 15$) reduce HR[530].

Energy expenditure

Mean energy expenditure (J/s) was determined from the mean $\dot{V}o_2$ and $\dot{V}co_2$ measures by the formula:[531]

$$Energy\ expenditure\ (J/s) = \dot{V}o_2(L/s) \times (16{,}040 + \left(\frac{\dot{V}co_2}{\dot{V}o_2}\right) \times 4940) \tag{8.6}$$

Mean intensity of the activities was also expressed as an estimated number of METs; one MET is generally assumed to be 3.5 mL/min/kg[242], but due to the high age of participants this resting metabolic rate is probably overestimated[532]. Therefore the Harris–Benedict equation[533] was used to estimate the resting metabolic rate as recommended for this old group[532]; For men the resting metabolic rate in kilocalories per day is:

$$66.473 + 5.0033 \times height(cm) + 13.7516 \times weight(kg) - 6.755 \times age(yr) \tag{8.7}$$

and for women:

$$655.0955 + 1.8496 \times height(cm) + 9.5634 \times weight(kg) - 4.6756 \times age(yr) \tag{8.8}$$

To convert these kilocalories per day to ml/min/kg, the following formulas were used:

$$\frac{kcal/day}{1440} = kcal/min; \tag{8.9}$$

$$\frac{kcal/min}{5} = L/min; \tag{8.10}$$

$$\frac{L/min}{weight\ (kg) \times 1000} = ml/min/kg \tag{8.11}$$

Rating of perceived exertion

Borg's standard $6-20$ RPE scale was used to measure the participants' subjective level of perceived intensity[534].

8.2.4 Statistical analysis

All continuous variables were tested for normality by Kolmogorov–Smirnov statistics. Mean and standard deviations for the whole group were calculated for all variables with Statistical Package for the Social Sciences (SPSS) 17.0. These means were used to define at what intensity level the group is exercising. Differences in variables between β–blocker users and non β–blocker users, and men and women were analyzed with the Mann–Whitney–U–test. Differences between living situation, i.e., independent living, assisted-living or care home, was analyzed with a Kruskal–Wallis test. Spearman correlations between outcome variables were performed to indicate whether the different variables represent the same construct 'physical intensity'. To determine possible influencing characteristics on the performed intensity, Spearman correlations between characteristics (MMSE, age, education, BMI, blood pressure) and outcome variables were analyzed.

8.3 Results

All continuous variables were normally distributed for the whole group and for subsets of the group ($p > 0.05$), i.e., β-blocker users, non β-blocker users, independent living, assisted-living, and care home residents.

8.3.1 Oxygen uptake

Mean $\dot{V}O_2$ was 681 mL/min, and 10.0 mL/min/kg (see Table 8.2 on page 108). This is 66.0% and 61.0% of the estimated $\dot{V}O_2$max, respectively. The

$\%\dot{V}O_2max$ (L/min and mL/min/kg) was significantly higher for non β-blocker users than for β-blocker users ($U = 8.2,\ p < 0.01$ and $U = 5.0,\ p < 0.03$ respectively). There was no difference in $\%\dot{V}O_2max$ between men and women, or between people in different living situations ($p > 0.05$).

8.3.2 Heart rate

The whole group of participants reached a mean of 92 beats per minute which was estimated to be 67.6% HRmax. The non β-blocker users performed at a higher %HRmax than the β-blocker users ($U = 37.5,\ p < 0.01$). There was no difference in %HRmax between men and women, or between people in different living situations ($p > 0.05$).

8.3.3 Energy expenditure

Mean energy expenditure was 3.41 J/s/kg. Mean intensity was estimated to be 3.9 METs. The energy expenditure was not different between non β-blocker users and β-blocker users nor for men and women ($p > 0.05$). The number of METs was significantly higher for non β-blocker users than for β-blocker users ($U = 337.0,\ p < 0.01$). There was no difference in number of METs between men and women, or between people in different living situations ($p > 0.05$).

8.3.4 Rating of perceived exertion

Mean RPE score was 13.1 and RPE was neither different between non β-blocker users and β-blocker users, between men and women, or between people in different living situations ($p > 0.05$).

8.3.5 Correlations

All outcome variables based on objective measures $\%\dot{V}O_2max$ (L/min), $\%\dot{V}O_2max$ (ml/min/kg), energy expenditure (J/s/kg), %HRmax, METs showed significant positive correlations with each other in the whole group ($p < 0.05$) (see Table 8.3 on page 109). However, the subjective variable (RPE) was not related to any of the objective variables. In the group of β-blocker users only %HRmax was not related to any other variable.

Table 8.4 (page 109) shows that systolic blood pressure was positively related to $\%\dot{V}O_2max$ and number of METs. BMI was negatively related to $\%\dot{V}O_2max$ (ml/min/kg) and positively related to RPE.

10 minutes
Standing

30s Stepping while standing at same place♦
30s Rotate trunk (look over shoulder to the back)♦
30s Rotate each ankle: turn 7s left and 7s right♦
30s Rotate shoulders: turn 15s forward and 15s backward♦
30s Hula hoop movements: turn 15s left and 15s right♦
30s Standing on toes: fast up and down
30s Standing on toes: slow up (stay 3s up) and down
30s Standing on toes: fast up and down♦
90s Bring knee to chest: stay 3s in position and back:
 45s left leg and 45s right leg♦
90s Bring straight leg backwards up: stay 3s in position and
 back: 45s left leg and 45s right leg♦
90s Bend the knees: slowly down and up
 If possible: stay 3s in down position■

10 minutes
Sitting

50s Walk movements: with arms and legs♦
50s Sit-Stand-Sit♦
50s Bring straight leg up: slow up (stay 3s up) and down
 25s left leg and 25s right leg ♦
50s Walk movements: with arms and legs♦
50s Boxing: 25s left arm and 25s right arm♦
50s Bring knee to chest: stay 3s in position and back:
 25s left leg and 25s right leg♦
50s Stamp on floor: alternating left and right♦
50s Both legs lifting: slowly up (stay 1s up) and down♦
50s Sit-Stand-Sit♦
50s Walk movements: with arms and legs■

10 minutes
Standing

30s Standing on toes: fast up and down
30s Standing on toes: slow up (stay 3s up) and down
30s Standing on toes: fast up and down♦
90s Bring knee to chest: stay 3s in position and back:
 45s left leg and 45s right leg♦
90s Bring straight leg backwards up: stay 3s in position and back:
 45s left leg and 45s right leg♦
90s Bend the knees: slowly down and up
 If possible: stay 3s in down position♦
30s Stepping while standing at same place♦
30s Rotate trunk (look over shoulder to the back)♦
30s Rotate each ankle: turn 7s left and 7s right♦
30s Rotate shoulders: turn 15s forward and 15s backward♦
30s Hula hoop movements: turn 15s left and 15s right

Notes. ♦=10 seconds (s) rest until next exercise; ■ =15 s rest until next exercise

Figure 8.1: The chair aerobic exercises within 30 minutes

Table 8.2: All measured and their estimated outcome variables during 30 minutes of chair exercises

Measured variables						Estimated variables				
	Mean	SD	Median	Range	*n*		Mean	SD	Median	Range
$\dot{V}\mathrm{o}_2$ (mL/min)	681	196	674	312 - 1265	47	%$\dot{V}\mathrm{o}_2$max (mL/min)	66.0	16.5	66.9	30.3–115.8
β-blocker users			611	312 - 893	15	β-blocker users			54.6	30.3–77.7
non β-blocker users			688	462 - 1265	29	non β-blocker users			69.9	43.8–115.8
$\dot{V}\mathrm{o}_2$ (mL/min/kg)	10.0	2.5	9.8	5.2 - 15.7	47	%$\dot{V}\mathrm{o}_2$max (mL/min/kg)	61.0	14.7	62.2	32.9–87.8
β-blocker users			7.7	5.2 - 11.9	15	β-blocker users			50.3	32.9–67.7
non β-blocker users			10.5	6.2 - 15.7	29	non β-blocker users			65.4	35.9–87.8
HR (beats/min)	92	16	94	61 - 131	44	%HRmax (beats/min)	67.6	11.3	68.1	44.9–95.5
β-blocker users			83	62 - 101	15	β-blocker users			59.1	47.8–74.0
non β-blocker users			99	84 - 131	26	non β-blocker users			72.9	62.2–95.5
$\dot{V}\mathrm{co}_2$ (mL/min)	610	188	596	270 - 1150	47	METs	3.90	0.93	3.90	2.01–6.09
Energy exp (J/s/kg)	3.41	0.86	3.36	1.82 - 5.37	47	β-blocker users			3.01	2.01–4.68
RPE (6 - 20)	13.11	2.14	13	8 - 18	47	non β-blocker users			4.16	2.51–6.09

Notes: exp = expenditure; HR = heart rate; %HRmax = percentage of maximum heart rate; METs = metabolic equivalent unit; *n* = amount of participants (*n* is lower for heart rate data, because data of 3 participants was unreliable); RPE = Rating of Perceived Exertion; $\dot{V}\mathrm{co}_2$ = carbon dioxide production; $\dot{V}\mathrm{o}_2$ = oxygen uptake; %$\dot{V}\mathrm{o}_2$max = percentage of maximal oxygen uptake.

Table 8.3: Spearman’s ρ correlations between the outcome variables

	%$\dot{V}$o$_2$max (L/min)	%$\dot{V}$o$_2$max (mL/min/kg)	METs	Energy exp (J/s/kg)	RPE
%HRmax (beats/min)	0.51**	0.56**	0.53**	0.53**	−0.19
non β-blocker users	0.44*	0.68**	0.56**	0.64**	−0.12
β-blocker users	− 0.04	−0.10	−0.08	−0.04	−0.03
%$\dot{V}$o$_2$max (L/min)		0.84**	0.81**	0.75**	0.02
non β-blocker users		0.73**	0.69**	0.61**	0.14
β-blocker users		0.89**	0.92**	0.84**	0.00
%$\dot{V}$o$_2$max (mL/min/kg)			0.87**	0.88**	−0.12
non β-blocker users			0.81**	0.82**	−0.13
β-blocker users			0.95**	0.91**	0.00
METs				0.98**	−0.21
non β-blocker users				0.98**	−0.26
β-blocker users				0.94**	−0.01
Energy exp (J/s/kg)					−0.23

Notes: exp = expenditure; %HRmax = percentage of maximum heart rate; METs = metabolic equivalent unit; RPE = Rating of Perceived Exertion; %$\dot{V}$o$_2$max = percentage of maximal oxygen uptake. $^{*}p < 0.05$; $^{**}p < 0.01$

Table 8.4: Spearman’s ρ correlations between characteristics and outcome variables

	age	BMI	education	MMSE	DBP	SBP
%HRmax (beats/min)	0.07	−0.22	0.06	0.16	0.07	−0.04
non β-blocker users	0.06	−0.32	−0.04	0.34	0.20	0.10
β-blocker users	0.09	0.00	0.56	0.33	0.16	−0.19
%$\dot{V}$o$_2$max (L/min)	0.19	0.11	−0.19	−0.13	0.26	0.33*
non β-blocker users	0.15	0.35	−0.11	−0.08	0.12	0.26
β-blocker users	0.25	−0.01	−0.45	−0.06	0.36	0.27
%$\dot{V}$o$_2$max (mL/min/kg)	0.23	−0.30*	−0.26	−0.16	0.22	0.30*
non β-blocker users	0.20	−0.21	−0.12	0.02	0.12	0.29
β-blocker users	0.20	−0.28	−0.51	−0.19	0.27	0.14
METs	−0.07	−0.07	−0.08	0.01	0.21	0.30*
non β-blocker users	−0.21	0.04	0.09	0.15	0.08	0.26
β-blocker users	0.14	−0.08	−0.42	−0.05	0.32	0.28
Energy exp (J/s/kg)	−0.11	−0.20	−0.14	0.06	0.19	0.27
RPE	0.21	0.29*	−0.16	−0.22	0.06	−0.04

Notes: BMI = body mass index; DBP = diastolic blood pressure; exp = expenditure; %HRmax = percentage of maximum heart rate; METs = metabolic equivalent unit; MMSE = Mini-Mental State Examination; RPE = Rating of Perceived Exertion; SBP = systolic blood pressure; %$\dot{V}$o$_2$max = percentage of maximal oxygen uptake. $^{*}p < 0.05$

8.4 Discussion

The results suggest that older people perform chair-assisted exercises with an intensity that is above the moderate intensity threshold for all outcome variables ($\%\dot{V}\mathrm{o}_2$max, %HRmax, METs, RPE). The mean intensity performances of 66% $\dot{V}\mathrm{o}_2$max (L/min) and 61% $\dot{V}\mathrm{o}_2$max (ml/min/kg) are above the moderate intensity threshold of 40% $\dot{V}\mathrm{o}_2$max[523], regardless of using β–blockers or not. The mean of 68% HRmax is also above the threshold of 64% HRmax[78], but this threshold is not reached by people who use β-blockers (59% HRmax), because these medications are known to reduce heart rate[535]. The mean intensity of 3.9 METs was also above the threshold of 2.0 METs[78], regardless of using β–blockers or not. The mean of 13 on the subjective RPE scale was also above the threshold of 12[78], regardless of using β-blockers or not.

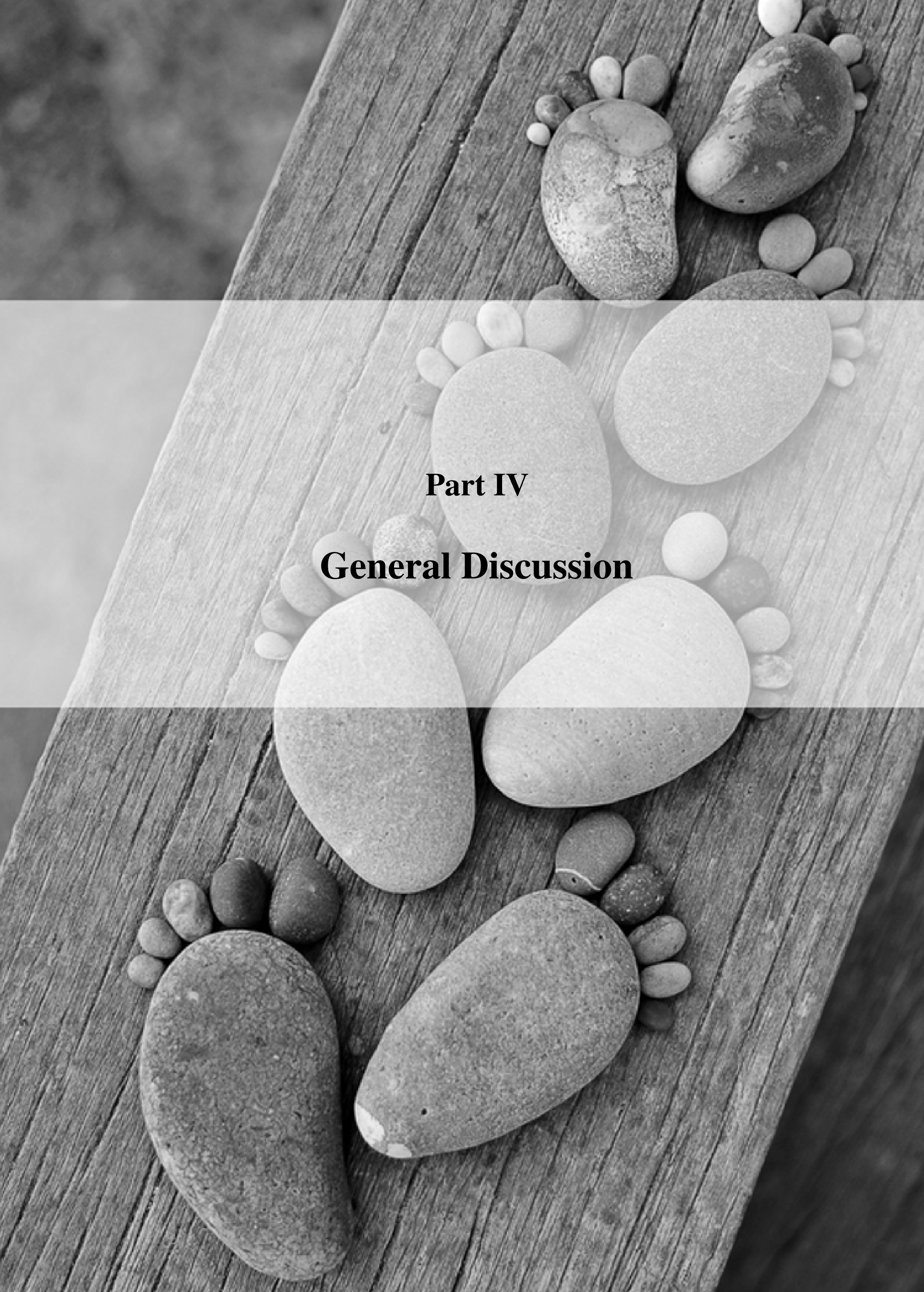
All outcome variables that are based on objective measures seem to assess the same construct 'physical intensity', because all objective measures are significantly correlated. Only in the group of β-blocker users HRmax was not related to any other variable, but this was expected since β-blockers reduce HR[535] and therefore the HR is influenced during the exercises within this group. In contrast, the subjective outcome variable (RPE) was not related to any of the objective outcome variables. This shows that people perceive the intensity not in the same way as the objective measures. Notably, it was difficult for participants to determine RPE for this programme, since some exercises (e.g., sit-stand-sit) were more intense than others (e.g., standing on toes). Also, participants continuously wore a soft mask during the exercises which may have caused a 'heavy feeling' in some people, which may have influenced their perceived intensity. In addition, depressed people are less able to accurately perceive exercise intensity[536]. In 30% of the participants depressive symptoms were assessed with the Geriatric Depression Scale[537] and Symptom Checklist-90[538]. Within this group, RPE score correlated significantly with depressive symptoms (Spearman's $\rho = 0.72, p < 0.01$) (data not shown); we therefore argue that depressive symptoms may have influenced RPE; more depressive symptomatology means higher perceived intensity.

The correlations between characteristics and the outcome variables show that BMI and systolic blood pressure are related to several outcome variables. People with a higher BMI have lower cardiorespiratory fitness levels[539] than people with a lower BMI which might cause them to perceive the exercises at higher intensity. However, people with a high BMI use a lower percentage of their $\dot{V}\mathrm{o}_2$max (ml/min/kg). This is probably caused by their high body weight; relative to their body weight people with high BMI use less oxygen per minute, while the absolute oxygen use is comparable as indicated by a non-significant relation between BMI and $\%\dot{V}\mathrm{o}_2$max when expressed in L/min. Finally, systolic blood pressure is positively related to $\%\dot{V}\mathrm{o}_2$max (in ml/min/kg and L/min) and number of METs. People with a high systolic blood pressure also have lower cardiorespiratory fitness levels[539]. Therefore, the exercises seem to be more intense for their body than for people with lower systolic blood pressure levels. In contrast to people with a high BMI, people with a high blood pressure do not perceive the exercises more intense than people with low blood pressure. This might be caused by their awareness; only 20% of the people with a high blood pressure are aware of this[540].

There are several limitations in this study. First, all variables are descriptive and are shown as a percentage of the estimated maximum ($\dot{V}o_2$max and HRmax) or as an estimation in METs. However, these percentages in $\dot{V}o_2$max and HRmax might be an underestimation due to the high proportion (32%) of people who use β-blockers. In a population with a lower percentage of β-blocker users, the $\dot{V}o_2$max and HRmax would probably be higher. These limitations however support the conclusion that these chair-assisted exercises are of at least moderate intensity. If possible, future research should determine $\dot{V}o_2$max and HRmax although this direct measurement is difficult in older people[541]. Second, this study has a small sample size. However, there is no reason to assume that the results cannot be generalized since all continuous outcome variables show a normal distribution. Third, all participants are measured only once, and therefore it is not known whether the intensity of these exercises remain comparable to the first time if performed more than once. Finally, this new programme contains different exercises for upper limbs, body and lower limbs, which are assumed to be endurance, strength and balance exercises. Whether this programme actually appeals to endurance, strength and balance has however not been examined. It is however more important that this program is of at least moderate intensity for healthy aging and that all exercises can be performed by multiple older people; with or without walking aid, with or without balance problems, with high or low fitness levels. Whether this programme can be performed in people with cognitive impairment (MMSE < 23) is unknown and has to be examined.

A variety of people, living independently, in assisted living communities or in a care home, participated in this research. These participants were chosen, to include a wide sample of cognitive healthy older people with expected higher and lower fitness levels, respectively. It is clinically relevant that this exercise programme can be performed by older people, with a sufficient intensity irrespective of their fitness level. The chair-assisted exercises of this study meet the intensity criterion for healthy aging[522]. The intensity of chair-assisted exercises is comparable to the intensity of walking in older people[527]. It is known that walking may increase cognition, in particular executive functions[65]. We suggest that chair-assisted exercises might be beneficial for cognition too, particularly for those who are not able to walk (long distances) anymore. Future research can examine the additional benefits of this programme on cognition, e.g., executive functioning, and physical functioning, e.g., strength and balance.

Besides the possible cognitive and physical benefits, this chair-assisted programme has practical benefits. First, chair-assisted exercises can be performed in a group with little risk of people disappearing from the instructor's field of view. Second, these exercises do not require the supervision of a person with a special education, e.g., a physiotherapist, since the exercises are simple. Therefore, it is expected that most caregivers are suitable to supervise the exercises, which makes the exercise programme very accessible. Third, it may be possible to instruct people by video, which allows them to exercise at home, since the exercises can be performed in every environment. Finally, the exercises involve different muscle groups, include a variety of exercises that are recommended for older people[522] and therefore appear a very suitable physical activity for this group.



Part IV

General Discussion

CHAPTER 9

GENERAL DISCUSSION

In this thesis issues concerning both low and high levels of physical activity in older people with and without cognitive impairment are discussed. These issues include the relationships and possible effects of physical activity on various health aspects, such as strength, pain and cognition. Suggestions for future research, overall conclusions and recommendations will be provided.

9.1 Impoverished environment

Most studies examine the positive effects of an enriched environment on cognitive functioning[542–547]. However, the negative impact of an impoverished environment, i.e, a sedentary and lonely lifestyle, remains underexposed. Therefore, we reviewed all studies comparing an impoverished environment with a normal environment to examine only the effect of an impoverished environment (**chapter 3**). The animal studies showed that even 3 months living in an impoverished environment can affect learning and memory in older animals. The exaggerated deficits of the older animals may be due to environmentally-induced changes in brain structure and function. As enriched environment enhances cognition due to stimulation of physiological processes, such as angiogenesis, neurotrophins, and neurogenesis, it follows that an impoverished environment could contribute to a failure of such neural mechanisms, reflected in impaired cognitive functioning[73]. Fortunately, the cognitive impairments in older animals were reversible indicating that the environmentally induced cognitive deficits of the animals in impoverished environments do not reflect permanent physiological changes. In other words, the brains of older animals are still plastic. However, especially in older people with brain damage, e.g., dementia, the plasticity of the brain decreases during aging[548].

In humans, the environment impoverishes with increasing age, especially when people move to a nursing home[306]. It has been suggested that moving to a nursing home has a negative impact on cognitive functioning, i.e., it enhances cognitive decline, and the risk for dementia[483]. In addition, when people develop a dementia, the cognitive decline accelerates even faster[549]. Therefore, nursing homes should enrich their environment by for example non pharmacological interventions, which requires staff who can interact and reach out to take initiative for the residents with a dementia[213], because initiation is vulnerable, particularly in dementia[550]. Sedentary behaviour and feelings of loneliness should be prevented in residents, and therefore physical restraints should not be used. To prevent sedentary behaviour is not only important for its negative influence on cognition, it also affects physical performance, such as strength[22].

9.2 Physical performance

A high level of physical activity not only concerns better physical performance, e.g., more lower limb muscle strength (LLMS), but coincides with a high level of cognitive performance as well[60], e.g., executive functions (EF)[446]. Therefore, it is not surprising that there is a positive relationship between LLMS and EF in healthy older women[462]. Not only strength, but also other types of physical performance, such as aerobic fitness and mobility, are related to global cognition and EF in healthy older people[25–27,34]. Results in **chapter 6** show that in people with mild to severe cognitive impairment this is also true for working memory.

In people with mild to severe cognitive impairment, the performance in balance, strength and aerobic fitness, but not in mobility predict the performance in working memory, irrespective of the level of cognitive impairment. That mobility was not related to working memory has been observed in older cognitively healthy people as well[27,464]. However, a mobility performance which includes not only gait/mobility, but also balance, is associated with fluency[27], a cognitive performance which was included in the working memory domain in **chapter 6**. Possibly balance caused the significant relation, since balance is also a significant predictor of working memory in people with mild to severe cognitive impairment. This result is not surprising, because both performances appeal to the same neural circuits: balance is dependent on the functioning of the fronto-cerebellar and fronto-striatal connections[31], connections between respectively, the cerebellum and the striatum and the frontal cortex, e.g., dorsolateral prefrontal cortex (DLPFC)[465–467] which is involved in working memory[468].

Strength was not only a predictor of working memory in people with mild to severe cognitive impairment (**chapter 6**); in cognitively healthy older people strength was a predictor of working memory/attention[462] and fluency[27], which was in **chapter 6** included in the working memory domain by two category fluency tests[463]. Overall, all of the neuropsychological tests measured in the studies above appeal to EF[459], and therefore strength seems to predict EF, and not only working memory. Aerobic fitness appeared to be a significant predictor of working memory in cognitively impaired older people (**chapter 6**). A mechanism underlying the finding that aerobic fitness is a significant predictor of working memory might be that aerobic fitness is associated with white matter volume, even after controlling for age, gender, dementia severity, physical activity, and physical frailty[457]. White matter volume is positively related to working memory[62]. Indeed, executive functioning, e.g., working memory, show the largest benefits of improved fitness in older people[62]. Clinically, working memory is essential for storing information and therefore it is crucial for long-term memory and learning[469,470]. However, working memory is vulnerable during aging and dementia[471]. To reduce a decline in working memory, results of this study suggest that it is important to maintain good balance, strength and aerobic fitness. Indeed, in a pilot study with older people with mild Alzheimer's disease (AD), balance and coordination exercises seem to improve working memory[208].

Mobility, balance, strength and aerobic fitness did not predict episodic memory in people with mild to severe cognitive impairment (**chapter 6**). These results are not surprising, since motor performances are highly related to prefrontal cortex (PFC) related cognitive functions, such as attention, EF and working memory, and less with hippocampal cognitive functions, e.g., episodic memory. Therefore aerobic fitness interventions show the highest effect sizes on cognitive functions in which the PFC plays an important role[62]. However, this large effect size, does not imply that aerobic fitness is not associated with cognitive functions in which the hippocampus is involved. Indeed, a comparable study in older people with mild cognitive impairment (MCI), have suggested that aerobic fitness may be the most important physical performance, besides strength, balance and mobility, that is related to the volume of the hippocampus[472]; this has been confirmed in another study in people with (very) mild AD[473]. Because hippocampal volume is positively related to episodic memory[474], these studies suggest that aerobic fitness and episodic memory are associated in people with MCI and (very) mild AD. However, participants of both studies were not only 8 years younger than participants of our study (**chapter 6**), they had less cognitive impairment as well, including also people with subjective cognitive impairment[472,473]. With increasing cognitive impairment, the hippocampus and PFC are both more affected[475,476]. However, to encode items for episodic memory, the anterior medial PFC is activated as well[477]. This suggests that, in people with decreasing cognitive impairment a high level of aerobic fitness, obtained by a high level of physical activity, has to improve the affected PFC first, before an improvement in episodic memory can be observed. Therefore, we argue that the relationship between aerobic fitness and working memory (or EF) is stronger than the relationship between aerobic fitness and (episodic) memory in people with cognitive impairment. Indeed, aerobic fitness was related to EF, but not to memory in people with a decline in both working memory and episodic memory[479] as is the case in obese older people[478]. In addition, **chapter 7** supports this argument in older people with MCI/mild dementia.

9.3 Effect of physical activity

9.3.1 Cognition

Chapter 7 supports previous findings of the benefits of physical activity on EF in older people with MCI/mild dementia; the more time people walk per week the better EF. This positive effect of physical activity on cognitive functioning, especially EF, is supported by reviews and meta-analysis in people with MCI[359,447] or people without cognitive impairment[10,17,18,60,99,359,505,512–517], but should be interpreted with caution for two reasons ; 1) no effect on EF was observed between the groups (intervention vs. control); 2) the level of physical activity besides the intervention is unknown. Possibly, people who performed the walks more often were also more active besides the intervention. This might have caused a bias in the results. We observed a faster cognitive decline in ApoE type 4 allele (ApoE4) carriers, but a trend that ApoE4 carriers show a higher effect of walks on EF than non-carriers. This is in line with other studies showing that ApoE4 carriers are at higher risk for dementia or cognitive decline, but respond better to physical activity interventions to stimulate cognition[509,518].

Unfortunately, no effect of walking on EF was observed in people with moderate to severe cognitive impairment. Comparable studies are scarce; only one randomized controlled trial (RCT) showed that 6 weeks walking was not effective for EF in people with moderate dementia[495]. It has been observed more often that a walking intervention in a group with moderate to severe cognitive impairment is not effective, especially in people with severe cognitive impairment[503]. Reviews in people with dementia showed that physical activity might have an effect on cognitive functioning, e.g., EF[63,69,88,367,447,490], but often (5 out of 8 studies) the physical activity intervention was combined with cognitive stimulation[490], or because of the lack of raw data, the effect size was not only based on cognition, but also on other outcome variables, such as physical functioning, strength or behaviour[88], and it should be mentioned that most reviews included more studies with mild dementia than moderate to severe dementia. Results of **chapter 7** were based on only regular walks in a RCT, a methodology that other intervention studies including people with a mild to severe dementia missed[69,447,490]. Overall, regular supervised walks have a positive effect on EF in people with MCI/mild dementia (Mini-Mental State Examination (MMSE) $20-24$), but has no effect on EF in people with moderate to severe cognitive impairment (MMSE < 20). Clinically, it seems best to be physically active as soon as possible when people have a cognitive impairment, preferably before the onset of cognitive impairment.

9.3.2 Agitation and pain

Since physical activity has a positive impact on the inhibitory capacity of the PFC, we discussed in **chapter 4** the possibility that physical activity might reduce agitation, aggression and pain in older people with a cognitive impairment, such as dementia. In people with dementia, the PFC is damaged and may cause disinhibition and consequently, agitation/aggression and an increase in pain experience[318,551]. The co-occurrence of agitated/aggressive behaviour and pain in dementia has been observed. Even an increase in pain experience may further aggravate agitation/aggression. Consequently, adequate pain treatment may decrease agitation/aggression in patients with dementia. In addition, immobilizing patients with dementia may further enhance PFC degeneration, and consequently, produce more disinhibition, and thus agitation/aggression and pain. Therefore, we should avoid physical restraints and psychoactive drugs that cause sedation[299,552].

9.3.3 Strength

A sedentary lifestyle is also related to a decline in physical performance, such as strength in the lower limbs, irrespective of age and gender, as reviewed in **chapter 2**. It was speculated that the heterogeneity of the effect of physical activity on LLMS was due to the differences in intensity of the habitual physical activity (HPA) level, mainly in the active groups, because there was less variance in intensity level in the sedentary groups. Higher levels of physical activity are associated with higher levels of LLMS in a continuous dose-response manner. In other words, vigorous physical activities and exercise performed most days of the week had more effect on LLMS than moderate physical activities for maximal 3 hours per week. In addition, the type of HPA influences its effect on LLMS; cardiovascular endurance activities have less effect on LLMS than strength activities. Endurance activities are mainly focused on the increase of the aerobic capacity of the involved muscles (muscular endurance) and not muscle mass specifically[196,197], while muscle mass is positively related to strength[553]. In addition, endurance activities have an effect on cognition, especially EF[17,199] and it lowers the risk of mobility limitations[124] and dementia[200].

The meta-analysis in **chapter 2** showed that people who maintain a high level of HPA show no decline in knee extension strength within $5-11$ years. In contrast, sedentary people showed a significant decline in knee extension strength within $5-11$ years. In combination with the result that sedentary people have less knee extension strength than habitually physically active people, a decline in LLMS means that sedentary people are exposed to a higher risk of severe functional impairment[96,189]. People who decrease their level of HPA show a significant decline in LLMS within 10 days to 12 years, which is probably a faster decline in strength compared to the habitually physically active group and the sedentary group[111,145,174]. In addition, it was observed that physical activity in distant history (e.g., 10 years ago) is less beneficial for present LLMS than more recent physical activity (e.g., only 1 year ago). This indicates that a high level of HPA in the present is a prerequisite for maintaining high levels of LLMS. Since declined muscle strength is a significant predictor of disability[157], people who decrease their HPA level have an increased risk of becoming disabled. Muscle tissue is highly plastic: it responds to the type and intensity of day to day demands. Therefore, older people should be encouraged to participate regularly in HPA to delay the decline in LLMS and the associated negative effects on, for example, health and cognition.

9.4 Regular walks

To encourage older people, especially those who have a high risk to live in an impoverished environment, such as older people with a cognitive impairment living in nursing homes, a walking protocol was described in **chapter 5**. Regular walks had to become part of daily living in older people with a cognitive impairment. Since long-term RCTs are scarce in older people with a cognitive impairment, this was part of the protocol. The strength of this study was 1) that the intervention was not performed by the research staff, but by the nursing staff which enabled it to become a routine in usual care, 2) it had a high number of repeated measurements, i.e., one baseline and 6 post measurements, 3) it assessed various outcome variables, such as cognition, physical performance, sleep-wake rhythm, depression, pain and quality of life. Results of other outcome variables besides cognition are not shown in this thesis, but will be analysed in the near future.

The compliance of this walking protocol was described shortly in **chapter 7**. Five days a week supervised walking as part of daily care was not feasible: only 8 out of 510 periods the intervention was performed as it was intended (150 minutes per week), while 120 periods the intervention was never performed (0 minutes per week). Eighteen from the 85 participants in the intervention group were not interested in regular walks and refused to walk frequently within the first few weeks. This was expected, because in a recent study, 7 out of 51 participants did not even continue a short duration program of 6 weeks with an intensity of five 30-minute walks per week[495]. Due to several other reasons such as bad weather, not enough time or people to supervise the walks, illness or changing staff, the intervention was not performed as intended. These findings show that it is difficult to perform regular supervised walks in daily care with older people with cognitive impairment.

Based on conversations with employees who were involved in this walking project, such as nurses and counsellors, some recommendations can be made for improving the implementation of structured daily walks in homes for the elderly or nursing homes. Firstly, the walking guides saw the intervention as a temporary ‘research’ project of 18 months, instead of the implementation of a new part of routine daily care. To improve compliance and to make the implementation successful it has been proven valuable to have one employee, e.g., the manager of the department, who is responsible for monitoring the implementation and who ensures that the walks really take place. A person within their own organisation who is responsible for the implementation, instead of an external researcher, strengthens the implementation as part of the organisation’s routine in daily care.

A second problem is that some participants were regularly not in the mood for a walk. In contrast, some participants liked to walk a lot and were even disappointed on the days that the walk had to be cancelled. The high variance in the minutes participants walked per week or the number of performed walks per week within the intervention group is visible in the large standard deviation. We recommend determining why people are not in the mood for a walk. If the participant does not like walking, we recommend performing other physical activities they like to do. However, it is possible that people have other reasons. For example, one woman was afraid that she would not be home by 4:30 pm, the time she had to be home when she was young. If the walking guide promised to be home before 4:15 pm the woman was enthusiastic. Possibly, peer modeling, as well as video and audio reinforcement can stimulate older people with dementia in their compliance to physical activity programs, as such a procedure appears to be effective in people with intellectual disabilities[554].

A final problem is that it was time-consuming to supervise the walks, often individually. Not only the 30 minutes walks, but also the time to prepare the participant to go for a walk takes time, for example by footwear that had to be changed into good walking shoes, participants who had to go to the bathroom first (and if the walking guide was a volunteer, (s)he had to call a nurse if the participant needed help), and putting on a coat first if they went outside. Although walks with the participants can take place during routine daily walks of the nurses, such as doing groceries, it takes more time to walk with a participant than alone. In addition, it is possible to put the right footwear already on in the morning and to let people go to the bathroom 15 minutes before the walk. However, activities for people with cognitive impairment cost time and money, because the activities need to be guided[555]. Therefore, activities that can be guided in a group are possibly easier to implement in daily living than individual guided activities.

9.5 Intensity

Since individually supervised walks are not feasible for 5 days a week, an alternative activity was requested by the institutions with two requests. First, the activity had to be performed in a group without losing people out of sight. Second, most care givers had to be able to guide the activity to make the exercise program accessible and easy to implement in daily care. In addition, we wanted an activity with exercises activating different muscle groups and a variety of exercises that are recommended for older people[522]. A widely applied type of physical activity for the oldest age group in long term care, is a group activity that is performed on and behind a chair (chair-assisted exercises) to guarantee safety[91], as older people may have balance problems[556]. Many other daily activities have a known intensity[184,242], however, it is unclear whether chair-assisted exercises for older people are of (at least) *moderate* intensity, i.e., the recommended intensity level for older people[522]. Therefore, we examined the level of physical intensity of 30 minutes of chair-assisted exercises, consisting of endurance, strength and balance exercises on and behind a chair (**chapter 8**).

The results suggest that older people perform chair-assisted exercises with an intensity that is above the moderate intensity threshold for all outcome variables (percentage of maximal oxygen uptake ($\dot{V}o_2$max), percentage of maximum heart rate (HRmax), metabolic equivalent units (METs), rating of perceived exertion (RPE)). All objective outcome variables were significantly related, indicating that all variables seem to assess the same construct 'physical intensity'. In contrast, the subjective outcome variable (RPE) was not related to any of the objective outcome variables. This shows that people perceive the intensity not in the same way as the objective measures. Notably, it was difficult for participants to determine RPE for this programme, since some exercises (e.g., sit-stand-sit) were more intense than others (e.g., standing on toes). Also, participants continuously wore a soft mask during the exercises which may have caused a 'heavy feeling' in some people, which might have influenced their perceived intensity. In addition, depressed people are less able to accurately perceive exercise intensity[536]. In 30% of the participants in **chapter 8** depressive symptoms were assessed with the geriatric depression scale (GDS)[537] and symptoms checklist 90 (SCL-90)[437]. Within this group, RPE score correlated significantly with depressive symptoms; we therefore argue that depressive symptoms may have influenced RPE; more depressive symptomatology means higher perceived intensity.

The correlations between characteristics and the outcome variables show that body mass index (BMI) and systolic blood pressure are related to several outcome variables. People with a higher BMI have lower cardiorespiratory fitness levels than people with a lower BMI[539] which might cause them to perceive the exercises at higher intensity. However, people with a high BMI use a lower percentage of their $\dot{V}o_2$max (ml/min/kg). This is probably caused by their high body weight; relative to their body weight people with high BMI use less oxygen per minute, while the absolute oxygen use is comparable as indicated by a non-significant relation between BMI and %$\dot{V}o_2$max when expressed in L/min. Finally, systolic blood pressure is positively related to %$\dot{V}o_2$max (in ml/min/kg and L/min) and number of METs. People with a high systolic blood pressure also have lower cardiorespiratory fitness levels[539].

Therefore, the exercises seem to be more intense for their body than for people with lower systolic blood pressure levels. In contrast to people with a high BMI, people with a high blood pressure do not perceive the exercises more intense than people with low blood pressure. This might be caused by their awareness; only 20% of the people with a high blood pressure are aware of this[540].

9.6 Recommendations

More research is warranted concerning aspects that motivate or demotivate sedentary people to adhere to recommended exercise. Motivating factors in older people can be the perceived prospects of staying independent, maintaining current health status, improving physical balance and improving the ability to walk[557]. Equally important is insight into the barriers to exercise, such as experienced reduction in health status, unpleasant experience(s) during previous exercise group sessions, and environmental factors, such as a lack of support, difficulties in the transportation to the exercise facilities or bad weather[557,558].

An impoverished environment should be prevented in older people with and without cognitive impairment. Therefore, it is suggested that older people derive the greatest benefits from continuing to live in stimulating environments where they can participate in known and successful activities[559]. With growing awareness of the benefits of stimulation and the hazards of stimulus-deprivation, it may be possible to incorporate environmental factors, such as enough space to exercise inside or nearby home, into programs aimed at enhancing cognitive function in people who have a cognitive impairment, or in people who are at increased risk to develop a cognitive impairment.

Furthermore, it is recommended to exercise in the afternoon[557] and to apply a variation in types of physical activity, influencing strength, endurance, and balance. We recommend that every day people should perform an activity that influences mainly one of these aspects, such as weight fitness for strength, cardio fitness or walking for endurance, and yoga for balance. It is however also possible to perform a combination in chair-assisted exercises. These exercises are of moderate intensity which can be performed by a variable group of older people (**chapter 8**). In addition, the chair-based exercises in **chapter 8** is a new program which contains different exercises for upper limbs, body and lower limbs, assumed to be endurance, strength and balance exercises. Whether this program actually appeals to endurance, strength and balance has not been examined. However, most importantly, this program is of at least moderate intensity for healthy aging and all exercises can be performed by multiple older people; with or without walking aid, with or without balance problems, and with high or low fitness levels. Whether this program can be performed in people with cognitive impairment (MMSE < 23) is unknown and has to be examined. The intensity of chair-assisted exercises is comparable to the intensity of walking in older people[527]. Because walking may increase cognition, in particular EF[17], we suggest that chair-assisted exercises might be beneficial for cognition too, particularly for those who are not able to walk (long distances) anymore. Future research can examine the additional benefits of this program on cognition, e.g., EF, and physical functioning, e.g., strength and balance.

Other populations, at risk for a sedentary lifestyle, such as people with intellectual disabilities, should be stimulated to become physically active as well. Almost 40% of older people with an intellectual disability are sedentary ($<$ 5000 steps a day)[560] and their fitness levels are similar or even worse than age groups 20 to 30 years older in the general population[561]. Such a sedentary lifestyle may have negative consequences for cognitive functioning and behaviour, such as aggression, which is a behaviour that often occurs in this population[562]. The effect of physical activity on cognition or aggressive behaviour has however not been studied in this population so far. Therefore, comparable research as described in **chapter 5**, should be performed in people with intellectual disabilities as well.

9.7 Heartfelt cry into the future

1. Force institutions to implement a daily physical activity program for those who are entering the nursing home; if an institution cannot meet this criterion, it has to face the financial restrictions.

2. Open a “hotline” where one can report if the institution does not take any initiative to maintain the activity level of the resident.

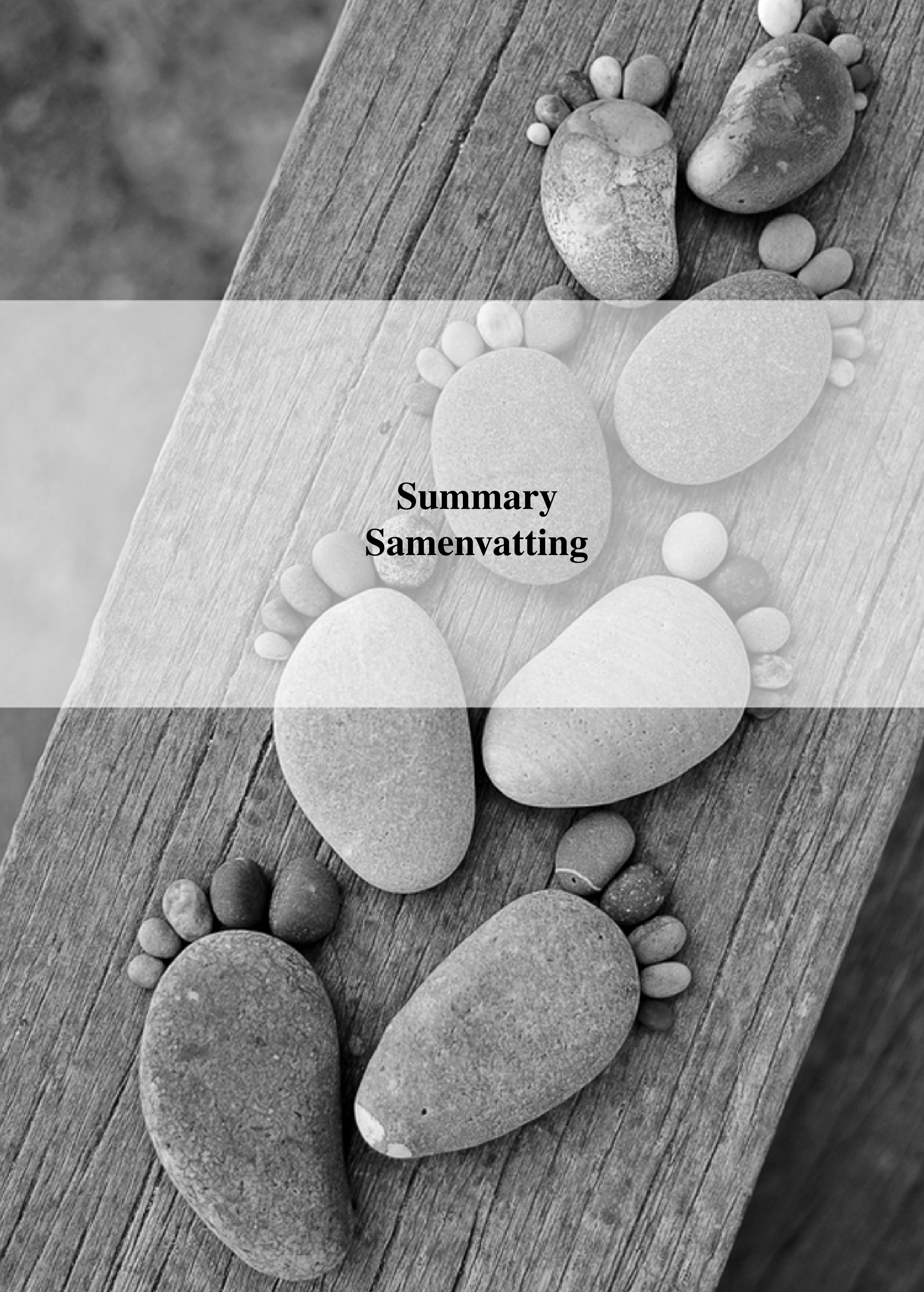
3. Compose the infrastructure of a department or nursing home in such a way that people have to walk to get coffee, tea, lunch or dinner.

4. Do not bring people to bed between 3 pm and 6 pm; this promotes passivity during daytime and restlessness/agitation at night.

5. Be physically active with the residents outside the institution, to obtain the beneficial effects of bright daylight, the sounds and smell of nature and traffic, and the sense of the wind.

6. Let residents climb stairs instead of using the elevator if people are still able to walk the stairs.

7. Forbid by law the use of physical restraints.



Summary

Samenvatting

Physical (in)activity and cognition in cognitively impaired older people

THIS dissertation focuses on the effect of different physical activity levels in daily life, e.g., usual care, in older people with and without cognitive impairment on various health aspects, such as strength, pain and cognition. This thesis was divided into two parts, i.e., a review section (chapter 2 – 4), and a clinical section (chapter 5 – 8).

Review section

Chapter 2 was a meta-analytic review to determine the relationship between habitual physical activity (HPA) throughout life and lower limb muscle strength (LLMS) above age 50. This relation is important for functional independence in the elderly, since LLMS, which declines during aging, may be considered a very important determinant of functional independence. The main findings were:

1. the present level of HPA is positively related to LLMS;
2. HPA in the past has little effect on present LLMS;
3. HPA involving endurance have less influence on LLMS compared to HPA involving strength;
4. people with a stable habitually physically active life are able to delay a decline in LLMS.

It was concluded that it is important to achieve and maintain a high level of HPA with mainly muscle-strengthening activities to obtain a high amount of LLMS during aging.

Chapter 3 reviews the impact of an impoverished environment, i.e., without the possibility of physical and social activity, on cognitive performances in animal experimental studies and human experimental studies with community-dwelling and institutionalized subjects. Animals living in an impoverished environment perform worse on cognitive tests compared to animals in an enriched environment. The same cognitive difference is also observed in humans. However, it is not clear whether this difference is caused by a decrease in cognition due to an impoverished environment or an increase due to an enriched environment. Therefore, an impoverished environment was only compared to a normal environment in this chapter. Results show that the cognitive functioning of old rats is more affected by an impoverished environment than young rats. Similarly, sedentary and lonely people (impoverished environment) have worse cognitive functioning and show a faster cognitive decline than physically and socially active people. Institutionalization further aggravates cognitive decline, probably due to the impoverished environment of nursing homes. In institutions, residents spend an unnecessary and excessive amount of time in bed; out of bed they show mainly sedentary or completely passive behaviour. The main conclusion of this review was that older people, institutionalized people especially, have poor levels of physical and social activity, which has a negative impact on cognitive functioning.

Chapter 4 evaluated the role of the prefrontal cortex (PFC) in agitation and pain in dementia. It is well known that a dysfunction of the PFC in dementia produces disinhibited behaviour, reflected in agitation/aggression. The role of the PFC in pain inhibition might be less known, but implies that frontal lesions in dementia may lead to an increase in pain experience. Hence, in patients with dementia, a dysfunction of the PFC may lead to a co-occurrence of agitated behaviour and pain. We argue that physical activity, which can stimulate the PFC, may decrease agitation and pain in dementia, by strengthening the inhibitory function of the PFC.

Clinical section

Chapter 5 is a study protocol of a long-term randomized controlled trial (RCT) in older people with cognitive impairment. The aim of this RCT single blind study was to investigate the effect of regular walks on physical functioning, the progressive cognitive decline, level of depression, anxiety, rest-activity rhythm, quality of life (QoL), activities of daily living (ADL) and pain in older people with cognitive impairment. Ambulatory older people with cognitive impairment, who were regular visitors of daily care or living in a home for the elderly or nursing home in the Netherlands, were randomly allocated to the experimental or control condition. Participants of the experimental group made supervised walks of 30 minutes a day, 5 days a week, as part of their daily nursing care. Participants of the control group came together three times a week for tea or other sedentary activities to control for possible positive effects of social interaction. All dependent variables were assessed at baseline and after 6 weeks, and 3, 6, 9, 12 and 18 months of intervention. The dependent variables included neuropsychological tests to assess cognition, physical tests to determine physical functioning, questionnaires to assess ADL, QoL, level of depression and anxiety, actigraphy to assess rest-activity rhythm and pain scales to determine pain levels. Potential moderating variables at baseline were: socio-demographic characteristics, body mass index (BMI), subtype of dementia, Apolipoprotein E (ApoE) genotype, medication use and comorbidities. This protocol was designed to evaluate the effect of regular walking as a treatment for older people with cognitive impairment. The strength of this protocol was that:

1. it had a longitudinal design with multiple repeated measurements;
2. different health aspects were assessed;
3. the intervention was not performed by research staff, but by nursing staff which enabled it to become a routine in usual care.

Possible limitations of the protocol were that:

1. only active minded institutions were willing to participate creating a selection bias;
2. the drop-out rate was expected to be high in this population;
3. not all participants were able to perform/understand all tests.

Chapter 6 examines whether physical performances can predict specific cognitive functioning in older people with mild to severe cognitive impairment. This cross-sectional study included 161 people with a mild to severe cognitive impairment (mean age 83 years). Multiple linear regression showed that strength, aerobic fitness and balance were significant predictors of working memory, irrespective of the severity of the cognitive impairment. With an increasing level of cognitive impairment (a lower Mini-Mental State Examination (MMSE)) balance became a significant predictor of episodic memory, as indicated by a significant interaction (MMSE × balance) as predictor. Therefore, clinicians need to realize that physical performances may be associated with cognitive functioning in people with mild to severe cognitive impairment. Therapeutic strategies to prevent a decline in physical performances might be useful for cognitive functioning in older people with mild to severe cognitive impairment.

Chapter 7 investigated whether 30 minute walks 5 days a week, as part of daily care, had a positive effect on cognition in a group of older people varying from mild cognitive impairment (MCI) to severe dementia (MMSE < 25). One hundred forty eight participants, with a mean age of 82 years and a mean MMSE of 16, were randomly divided into a walking ($n = 85$) and a control group ($n = 63$). Cognitive functioning was measured 7 times within 18 months of intervention with 12 neuropsychological tests. Intentionally, the intervention implied walking 5 days a week, 30 minutes a day during 18 months as part of usual care. However, results showed that the compliance with the intervention was poor: a mean of 36 ± 42 minutes per week was obtained, varying from 0 to 195 minutes per week, with a mean of 1.34 ± 1.45 times per week. The walks had a positive effect on executive functions (EF) in people with MCI/mild dementia (MMSE $\geq$ 20), but not on people with moderate to severe dementia (MMSE $<$ 20). The walks had no significant effect on memory. The main conclusion of this study, from a cognitive point of view, was that physical activity should be applied as soon as possible in older people with MCI/mild dementia, preferable even before the onset of cognitive impairment.

Chapter 8 determined the level of intensity of chair-assisted exercises in older people. Since it is not feasible to implement daily walking in usual care 5 days a week, chair-assisted exercises for older people were designed as alternative activity. Since walking is a moderate intensity activity, which is also the intensity that is prescribed by the public health guidelines for healthy aging, this study examined whether one session of 30 minutes of chair-assisted exercises met this intensity criterion. This cross-sectional study included 47 cognitive healthy volunteers (mean age 84 years). During the performance of 30 minutes chair-assisted exercises we determined oxygen uptake ($\dot{V}o_2$), carbon dioxide production ($\dot{V}co_2$), heart rate (HR) and rating of perceived exertion (RPE). These measures were expressed as a percentage of the estimated maximal oxygen uptake ($\dot{V}o_2$max), the estimated maximum heart rate (HRmax), and estimated as metabolic equivalent units (METs). Results showed that participants performed chair-assisted exercises at 61.0% ± 14.7% of $\dot{V}o_2$max, 67.6% ± 11.3% of HRmax, 3.9 ± 0.9 METs, and 13.1 ± 2.1 RPE. It was concluded that the intensity of these chair-assisted exercises was at least moderate for older people.

Overall, an impoverished environment should be prevented in older people with and without cognitive impairment. If possible, older people should perform different types of physical activities, influencing strength, endurance, and balance for most days of the week. More research is warranted concerning aspects that motivate or demotivate (barriers) sedentary people to adhere to these recommended physical activities.

Fysieke (in)activiteit en cognitie bij ouderen met een cognitieve stoornis

Dit proefschrift gaat over het effect dat (zeer) weinig tot (zeer) veel fysieke activiteiten die ouderen met en zonder cognitieve beperking in het dagelijkse leven uitvoeren heeft op verschillende gezondheidsaspecten, zoals kracht, pijn en cognitie. Dit proefschrift bestaat uit 2 delen waarvan het eerste deel bestaat uit literatuurstudies (hoofdstuk 2 – 4) en het tweede deel uit klinische studies (hoofdstuk 5 – 8).

Literatuurstudies

Hoofdstuk 2 is een meta-analyse (en review) over de relatie tussen de dagelijkse fysieke activiteiten gedurende het leven en de hoeveelheid beenkracht na je 50^e. Deze relatie is belangrijk voor het zelfstandig functioneren bij ouderen, omdat beenkracht, dat afneemt bij het ouder worden, gezien kan worden als een erg belangrijke determinant van het zelfstandig functioneren. De belangrijkste bevindingen van deze meta-analyse zijn:

1. het huidige niveau van de dagelijkse fysieke activiteiten laten een positieve relatie zien met de huidige hoeveelheid beenkracht;
2. de dagelijkse fysieke activiteiten die men in het (verre) verleden heeft uitgevoerd hebben weinig invloed op de huidige beenkracht.
3. de dagelijkse activiteiten die vooral een beroep doen op het uithoudingsvermogen hebben minder invloed op beenkracht dan de dagelijkse activiteiten die een beroep doen op spierkracht.
4. mensen die een stabiel fysiek actief leven leiden, verliezen pas op latere leeftijd aan beenkracht.

De conclusie van dit hoofdstuk is dat het belangrijk is om een fysiek actief leven te hebben en te behouden met voornamelijk activiteiten die je spieren versterken zodat je zo lang mogelijk je beenkracht op peil houdt bij het ouder worden.

Hoofdstuk 3 is een review over het effect van een verarmde omgeving, oftewel een omgeving zonder fysieke en sociale activiteiten, op het cognitief functioneren in dierexperimenteel onderzoek en experimentele studies bij mensen die zelfstandig in de gemeenschap of in instituten wonen. Dieren die in een verarmde omgeving leven presteren slechter op cognitieve testen in vergelijking met dieren in een verrijkte omgeving. Ditzelfde cognitieve verschil zien we ook bij mensen. Het is echter niet duidelijk of dit verschil wordt veroorzaakt door een toename in cognitie door een verrijkte omgeving of een afname van cognitie door een verarmde omgeving. Daarom is in dit hoofdstuk een verarmde omgeving alleen maar vergeleken met een normale omgeving. Resultaten laten zien dat het cognitief functioneren van oude ratten door een verarmde omgeving meer wordt aangedaan dan bij jonge ratten. Ook sedentaire en eenzame mensen (verarmde omgeving) functioneren cognitief slechter en laten een snellere cognitieve achteruitgang zien dan fysiek en sociaal actieve mensen. Institutionalisering verergert verdere cognitieve achteruitgang, waarschijnlijk als gevolg van de verarmde omgeving van verpleeghuizen. Het is in veel instellingen aangetoond dat bewoners een onnodige en buitensporige hoeveelheid tijd in bed doorbrengen. Indien bewoners uit bed zijn, tonen ze vooral zittend of volledig passief gedrag. De belangrijkste conclusie van dit onderzoek is dat de ouderen, vooral geïnstitutionaliseerde ouderen, weinig fysieke en sociale activiteiten hebben, wat een negatieve invloed heeft op het cognitief functioneren.

Hoofdstuk 4 evalueert de rol van de prefrontale cortex (PFC), het voorste deel van het brein, in agitatie en pijn bij dementie. Het is algemeen bekend dat het disfunctioneren van de PFC bij dementie ongeremd gedrag produceert. Dit ongeremde gedrag is te herkenbaar in agitatie/agressie. De rol van de PFC bij het remmen van pijn is minder bekend, maar dit suggereert dat frontale laesies bij dementie kunnen leiden tot een toename van de pijn ervaring. Een disfunctie van de PFC zou bij mensen met dementie dus kunnen leiden tot het gezamenlijk optreden van geagiteerd gedrag en pijn. Aangezien fysieke activiteiten de PFC kunnen stimuleren waardoor de remmende functie van de PFC wordt versterkt, is het ook mogelijk dat fysieke activiteiten agitatie en pijn bij dementie kunnen verminderen.

Klinische studies

Hoofdstuk 5 is een studie protocol van een 18 maanden durende gerandomiseerde, gecontroleerde studie bij ouderen met cognitieve stoornissen. Het doel van deze studie was om het effect van regelmatige wandelingen op fysiek functioneren, de cognitieve achteruitgang, de mate van depressie, angst, slaap-waakritme, kwaliteit van leven, activiteiten van het dagelijks leven (ADL) en pijn bij ouderen met cognitieve stoornissen te onderzoeken. Deelnemers van deze studie waren ambulante ouderen met cognitieve stoornissen, die regelmatig de dagbesteding bezochten of in een verzorgings- of verpleeghuis in Nederland woonden. Deze deelnemers werden willekeurig toegewezen aan de experimentele of controle groep. De deelnemers van de experimentele groep werden 5 dagen per week begeleid bij wandelingen van 30 minuten. Deze wandelingen werden een onderdeel van hun dagelijkse zorg. De deelnemers van de controlegroep kwamen 3 keer per week bij elkaar om een kopje thee te drinken of om een andere zittende activiteit te doen om zo te controleren voor mogelijke positieve effecten van sociale interactie tijdens de wandelingen. Alle afhankelijke variabelen werden gemeten bij aanvang en na 6 weken, en 3, 6, 9, 12 en 18 maanden van de interventie. De afhankelijke variabelen waren neuropsychologische testen om cognitie in kaart te brengen, fysieke testen om het fysiek functioneren te evalueren, vragenlijsten om ADL, kwaliteit van leven, de mate van depressie en angst weer te geven, actigrafie voor het slaap-waakritme en pijn schalen om het pijn niveau vast te stellen. Overige variabelen bij aanvang van de studie waren: sociaal demografische kenmerken, body mass index (BMI), subtype van de dementie, Apolipoprotein E (ApoE) genotype, medicijngebruik en ziektebeelden/aandoeningen. Dit protocol werd ontworpen om het effect van regelmatige wandelingen te evalueren als een behandeling voor ouderen met cognitieve stoornissen. De kracht van dit protocol was dat:

1. het een longitudinale opzet met meerdere herhaalde metingen had;
2. verschillende gezondheidsaspecten werden getest;
3. de interventie niet werd uitgevoerd door onderzoekers, maar door het verplegend personeel, waardoor het een onderdeel van de dagelijkse zorg werd, ook na het stoppen van het wetenschappelijke onderzoek.

Mogelijke beperkingen van het protocol waren dat:

1. alleen actief ingestelde instellingen bereid waren om deel te nemen aan dit onderzoek waardoor je mogelijk een een selectie bias hebt;
2. de uitval naar verwachting hoog zou zijn in deze populatie;
3. niet alle deelnemers in staat zouden zijn om alle testen uit te voeren of te begrijpen.

Hoofdstuk 6 onderzoekt of het fysiek functioneren cognitieve functies kan voorspellen bij oudere mensen met lichte tot ernstige cognitieve stoornissen. Deze cross-sectionele studie bestond uit 161 mensen met een lichte tot ernstig cognitieve stoornis (gemiddelde leeftijd 83 jaar). Meervoudige lineaire regressie toont aan dat kracht, aeroob uithoudingsvermogen en balans significante voorspellers zijn van het werkgeheugen, ongeacht de ernst van de cognitieve stoornis. Met een toenemende mate van cognitieve stoornis (een lagere Mini-Mental State Examination (MMSE)) wordt balans een significante voorspeller van het episodisch geheugen, zoals aangegeven door een significante interactie

(MMSE × balans) als voorspeller. Clinici moeten zich realiseren dat fysieke prestaties positief geassocieerd zijn met het cognitief functioneren bij mensen met een licht tot ernstig cognitieve stoornis. Therapeutische strategieën die erop gericht zijn om een achteruitgang in fysiek functioneren te voorkomen kunnen mogelijk dus ook nuttig zijn voor het cognitief functioneren bij oudere mensen met lichte tot ernstige cognitieve stoornis.

Hoofdstuk 7 onderzoekt of regelmatige dagelijkse wandelingen, als onderdeel van de dagelijkse zorg, een positief effect heeft op de cognitie in een groep van ouderen, variërend van een milde cognitieve beperking (MCI) tot ernstige dementie ($\text{MMSE} < 25$). Honderd achtenveertig deelnemers, met een gemiddelde leeftijd van 82 jaar en een gemiddelde MMSE van 16, werden willekeurig verdeeld in een wandel- ($n = 85$) en een controlegroep ($n = 63$). Cognitief functioneren werd 7 keer binnen 18 maanden gemeten met 12 neuropsychologische testen. Volgens het protocol zou de interventie groep 5 dagen per week, 30 minuten per dag gedurende 18 maanden als onderdeel van de dagelijkse zorg gaan wandelen. Echter, uit de resultaten blijkt dat de naleving van deze interventie slecht was: een gemiddelde van 36 ± 42 minuten per week werd er gewandeld, variërend van 0 tot 195 minuten per week, met een gemiddelde van $1,34 \pm 1,45$ keer per week. De wandelingen hadden wel een positief effect op de executieve functies (EF), oftewel hogere cognitieve functies zoals het werkgeheugen, bij mensen met een MCI/lichte dementie ($\text{MMSE} \geq 20$), maar niet op mensen met een matige tot ernstige dementie ($\text{MMSE} < 20$). De wandelingen hadden geen significant effect op het normale geheugen. De belangrijkste conclusie van deze studie, vanuit een cognitief oogpunt, is dat lichamelijke activiteit zo snel mogelijk moet worden gestimuleerd bij oudere mensen met MCI/milde dementie, bij voorkeur nog vóór het begin van de cognitieve stoornissen.

Hoofdstuk 8 beschrijft hoe intensief oefeningen op en rondom een stoel zijn bij oudere mensen. Zoals beschreven in hoofdstuk 7 is het niet haalbaar om elke dag te wandelen als onderdeel van de reguliere zorg gedurende 5 dagen per week. Oefeningen op en rondom een stoel voor oudere mensen zouden een goede alternatieve activiteit kunnen zijn aangezien deze activiteit ook in een groep uitgevoerd kan worden. Wandelen op eigen looptempo is een matig intensieve activiteit voor ouderen. Matig intensief is ook de (minimale) intensiteit die wordt voorgeschreven in de richtlijnen van de openbare gezondheidszorg om gezond ouder te worden. In deze studie is onderzocht of een sessie van 30 minuten met oefeningen op en rondom een stoel aan deze intensiteit voldoet bij ouderen. Deze cross-sectionele studie is uitgevoerd met 47 cognitief gezonde vrijwilligers (gemiddelde leeftijd 84 jaar). Tijdens de uitvoering van de oefeningen op en rondom een stoel gedurende 30 minuten hebben we de zuurstofopname ($\dot{V}\text{o}_2$), koolstofdioxide uitstoot ($\dot{V}\text{co}_2$), hartslag (HR) en de persoonlijk ervaren inspanning (RPE) gemeten. De uitkomsten van deze metingen zijn uitgedrukt als een percentage van de geschatte maximale zuurstofopname ($\dot{V}\text{o}_2\text{max}$), de geschatte maximale hartslag (HRmax) en als energieverbruik ten opzichte van het geschatte verbruik in rust, waarbij 1 metabolic equivalent unit (MET) gelijk is aan het energieverbruik in rust. De resultaten toonden aan dat deelnemers de oefeningen op en rondom de stoel uitvoerden op $61{,}0\% \pm 14{,}7\%$ van $\dot{V}\mathrm{o}_2$max, $67{,}6\% \pm 11{,}3\%$ van HRmax, $3{,}9 \pm 0{,}9$ METs en $13{,}1 \pm 2{,}1$ RPE. Hieruit kon geconcludeerd worden dat de intensiteit van deze oefeningen op en rondom de stoel op zijn minst matig intensief zijn voor oudere mensen.

Samengevat moet een verarmde omgeving voorkomen worden bij oudere mensen met en zonder cognitieve stoornissen. Indien mogelijk, zouden ouderen de meeste dagen van de week een mix van verschillende soorten fysieke activiteiten moeten beoefenen, zoals activiteiten die spierkracht en/of balans stimuleren, of activiteiten die een beroep doen op het uithoudingsvermogen. Meer onderzoek is gewenst met betrekking tot aspecten die sedentaire ouderen motiveren of demotiveren (barrières) om zich wel/niet te houden aan deze aanbevolen (hoeveelheid) fysieke activiteiten.

List of Acronyms

6MWT	six minute walk test
ACC	anterior cingulate cortex
AD	Alzheimer's disease
ADL	activities of daily living
aMCI	amnestic mild cognitive impairment
ApoE4	ApoE type 4 allele
ApoE	Apolipoprotein E
BADS	Behavioural Assessment of the Dysexecutive Syndrome
BDNF	brain-derived neurotrophic factor
BMI	body mass index
CAS	coloured analogue scale
CI	Confidence Interval
cm	centimeters
CNS	central nervous system
DBP	diastolic blood pressure
DLPFC	dorsolateral prefrontal cortex
DNA	deoxyribonucleic acid
DSST	digit symbol substitution test
EF	executive functions
FICSIT-4	frailty and injuries: cooperative studies of intervention techniques
fMRI	functional magnetic resonance imaging

FPS	faces pain scale
GDS	geriatric depression scale
GIT	Groninger Intelligence Test
HPA	habitual physical activity
HR	heart rate
HRmax	maximum heart rate
IS	interdaily stability
IV	intradaily variability
L5	uninterrupted least active 5 hours period
LLMS	lower limb muscle strength
M10	10 most active consecutive hours
MCI	mild cognitive impairment
MET	metabolic equivalent unit
mmHg	millimeters of mercury
mm	millimeter
MMSE	Mini-Mental State Examination
m/s	meter per second
NGF	nerve growth factor
NSAID	nonsteroidal anti-inflammatory drugs
PET	positron emission tomography
PFC	prefrontal cortex
POMA	performance-oriented mobility assessment
QoL	quality of life
RAI	Resident Assessment Instrument
RA	relative amplitude
RBMT	Rivermead Behavioral Memory Test
RCT	randomized controlled trial

RPE	rating of perceived exertion
SBP	systolic blood pressure
SCL-90	symptoms checklist 90
SPSS	Statistical Package for the Social Sciences
STS	sit to stand
TMS	transcranial magnetic stimulation
TUG	timed up and go
$\dot{V}\mathrm{co}_2$	carbon dioxide production
$\dot{V}\mathrm{o}_2$	oxygen uptake
$\dot{V}\mathrm{o}_2\mathrm{max}$	maximal oxygen uptake
WAIS	Wechsler Adult Intelligence Scale
WMS-R	Wechsler Memory Scale-Revised

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Publications

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2. Volkers, K.M. and Scherder, E.J.A. (2011). Impoverished environment, cognition, aging and dementia. *Reviews in the Neurosciences*, 22(3); 259-266 **(Chapter 3)**.

3. Scherder, E.J.A. and Volkers, K.M. (2010). Physical Activity for Agitation and Pain in Dementia. *Journal of Pain Management*, 3(4); 373-376 **(Chapter 4)**.

4. Volkers, K.M. and Scherder, E.J.A. (2011). The effect of regular walks on various health aspects in older people with dementia: protocol of a randomized-controlled trial. *BMC Geriatrics*, 11(1); 38 **(Chapter 5)**.

5. Volkers, K.M., van Dijk, T.C.W., Eggermont L.H., Hollander, A.P. and Scherder E.J.A. The intensity of chair-assisted exercises in older cognitive healthy people. *Journal of Aging and Physical Activity*, accepted **(Chapter 8)**.

6. Eggermont, L.H.P., Gavett, B.E., Volkers, K.M., Blankevoort, C.G., Scherder, E.J.A., Jefferson, A.L., Steinberg, E., Nair, A., Green, R.C. and Stern, R.A. (2010). Lower extremity function in normal cognitive aging, mild cognitive impairment, and Alzheimer's disease. *Archives of Physical Medicine and Rehabilitation*, 91(4); 584-588.

7. Scherder, E.J.A., Eggermont, L.H.P., Achterberg, W.P., Plooij, B., Volkers, K.M., Weijenberg, R.A.F., Hooghiemstra, A.M., Prick, A.J.C., Pieper, M.J.C., Blankevoort, C.G., Zwakhalen, S., Heuvelen, M.J.G. van, Hamers, J., Lobbezoo, F., Swaab, D. and Pot, A.M. (2009). Pain and Physical (in)activity in relation to cognition and behaviour in dementia. *Tijdschrift voor gerontologie en geriatrie*, 40(6); 270-278.

8. Hubbard, E.J., Santini, V., Blankevoort, C.G., Volkers, K.M., Barrup, M.S., Byerly, L., Chaisson, C., Jefferson, A.L., Kaplan, E., Green, R.C. and Stern, R.A. (2008). Clock drawing performance in cognitively normal elderly. *Archives of Clinical Neuropsychology*, 23(3); 295-327.

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1. Volkers, K.M. and Scherder, E.J.A. Physical performance predict working memory in older people with mild to severe cognitive impairment **(Chapter 6)**.

2. Volkers, K.M., Scheltens, P. and Scherder, E.J.A. The effect of regular walks on cognition in older people with mild to severe cognitive impairment; a long-term randomized controlled trial **(Chapter 7)**.

About the author

Karin Volkers was born on February 18, 1979 in Nijkerk. After high school, she had some difficult years with epileptic insults due to a brain tumor, which was removed in October 2001. In 2002, she started a 5-year study in Human Movement Sciences at the University of Groningen. After an internship at the Boston University Alzheimer's Disease Center, she graduated in 2007 with a specialization in aging and dementia. In January 2008 she started a PhD project on the effect of physical (in)activity on cognition in older people with mild to severe cognitive impairment at the VU University in Amsterdam. Currently, she is a post-doc researcher at the department of clinical neuropsychology of the VU University. Besides this post-doc, she is policy advisor and researcher at Stichting Philadelphia Zorg, a foundation for people with intellectual disabilities. Her goal is to contribute to the health of vulnerable people by increasing their physical activity level and to prove this with research.