Summary of the results and general discussion
7.1 Purpose of this dissertation

In this dissertation we aimed to provide more insight into the association between physical performance and cognition in older adults with and without dementia. We started with determining (via a literature review) the best way to improve physical performance in older adults with dementia (Chapter 2). In the next chapter (Chapter 3), we analyzed the reliability of physical performance tests in this group. Given the complexity of our target group of older adults with dementia, the goal of Chapter 4 was to analyze the association between physical performance and cognitive performance in cognitively healthy older adults. In this chapter, a broad range of physical and cognitive tests were included to investigate if the association between physical and cognitive performance were similar across different cognitive and physical domains, or if they were different. In addition, the moderating effect of age and gender on these associations was investigated. Finally, in Chapters 5 and 6, we returned to our target group and assessed the association between gait speed (Chapter 5), grip strength (Chapter 6) and cognitive performance. In the following, we will give a short overview of each individual chapter, followed by a general discussion. We end with the limitations, future directions and clinical implications.

7.2 Summary of the main findings

In Chapter 2 we showed that physical performance can be improved in older adults with dementia. Most importantly, none of the studies investigated in Chapter 2 reported adverse effects by a physical activity intervention. Improvements in (different aspects of) physical performance were most likely when interventions combined different types of training, such as endurance, balance, strength, and mobility training. Furthermore, the intervention should be at least of moderate intensity. In general, the longer the intervention is, the larger the effects on physical performance are. Our recommendation is that interventions should last at least three months, with three sessions per week of 45 to 60 minutes per session. However, based on our results we hypothesize that longer is probably better and physical exercise should therefore be an important aspect of regular care.

In Chapter 3 we assessed the reliability of six commonly used physical performance tests: Six Meter Walk Test, Timed Up and Go, FICSIT-4, Figure of Eight, Grip Strength, and the modified Sit-To-Stand test. We found that each of the six physical performance
tests could be used to analyze differences between groups. Unfortunately, these six measures were not sensitive enough to interpret individual differences.

In Chapter 4 we analyzed the relationship between individual aspects of physical and cognitive performance in cognitive healthy older adults. Chapter 4 revealed that walking abilities (i.e. a combination of gait speed and endurance), balance, and strength were significant predictors of cognitive performance in that group. We only identified a general relationship and not a more specific relationship between physical and cognitive performance (i.e. the effects of walking ability, balance, and strength on cognitive performance were not significantly different for different aspects of cognitive performance). In addition, we found a gender effect, indicating that balance and walking ability were stronger predictors of cognitive performance for men than for women.

In contrast to Chapter 4, Chapters 5 and 6 focused again on older adults with dementia together with a control group of healthy older adults. In Chapter 5, we found that the predicting effect of gait speed on cognitive performance did not significantly differ between older adults with and without dementia. In addition, the predicting effect of gait speed did also not significantly differ between the cognitive domain (i.e. memory, set-shifting, and planning). These findings indicate that gait speed might be an indicator of overall cognitive performance.

Chapter 6 focused on the predicting effect of grip strength on cognitive performance in older adults with dementia and without dementia. In contrast to the results of Chapter 5, we found that the predicting effect of grip strength on cognitive performance differed between older adults with and without dementia. Moreover, the predicting effect of grip strength differed significantly between the cognitive domains (i.e. memory, set-shifting, planning, and fluency). In older adults with dementia grip strength was only associated with fluency and working memory. In contrast, for our control group of cognitive healthy older adults, grip strength was a significant predictor of all executive functions. These results indicate that grip strength is more selectively associated with aspects of cognitive performance than gait speed.

Overall, our results show the complexity of the association between physical and cognitive performance. Physical performance can be improved by exercise, but the effects of a physical performance improvement on cognitive performance are difficult to predict. Our results show that gender and age should be taken into account when analyzing the association between physical and cognitive performance. Furthermore, our findings indicate that for some aspects of physical performance and cognitive performance the
association might differ between cognitively healthy controls and older adults with dementia.

7.3 General discussion

Exercise training in older adults with dementia

There is a large debate in the Dutch society about the future of geriatric health care. It is argued, mostly for financial reasons, that older adults should live independently as long as possible and fewer older adults should live in residential care and. Physical exercise may contribute to this societal development.

In our review in Chapter 2, we demonstrated that physical exercise led to improvements in physical performance in community dwelling as well as nursing home patients with different stages of dementia. Our reliability study showed that physical performance can indeed be reliable measured at the group level. A recent and excellent Finnish study strengthens our results. In the study of Pitkälä and colleagues (2013) an intensive and long-term home-based exercise program slowed down the decline in physical performance in home-dwelling older adults with dementia. Consequently, it is important that physical exercise is stimulated in older adults with and without dementia. The question arises whether this is possible in a cost effective way. Although physical interventions are time consuming and costly, Pitkälä and co-workers (2013) showed that an intensive physical exercise program was more cost-effective and cheaper than regular care. They calculated the costs for health and social services used by both the patient and their caregivers, while also taking into account the adverse health effects of spousal caregiving (Hirsch 2013). In addition, further cost reduction might be possible when the exercise is guided by informal care (Vreugdenhil, Cannell et al. 2012). Positive effects on physical performance are also reported after a four-month community based exercise program, where informal caregivers supervised daily exercises and walking (Vreugdenhil, Cannell et al. 2012). The authors argued that these improvements were not only beneficial for the patient, but also for their informal caregivers observing the improvements (Vreugdenhil, Cannell et al. 2012). Despite the positive effects of exercise (McLaren, Lamantia et al. 2013), the number of people who conform to the Dutch physical activity guidelines decreases when people get older (Buchman, Wilson et al. 2014). The Dutch physical activity guidelines are in line with the international standard (Haskell 2007; Kemper et al., 2000; Ooijendijk
et al., 2007; WHO global recommendations on physical activity and health, 2010) and state that older adults should have at least half an hour of moderate intensity exercise for a minimum of 5, but preferably 7 days a week. For sedentary older adults with or without a handicap every additional exercise (irrespective of intensity, frequency and type) compared to their normal activity patterns is meaningful. In addition, the guideline recommends strengthening exercises twice per week. Our review in Chapter 2 indeed shows that interventions should consist of multiple components, such as aerobic training and strength training. In contrast with the physical activity guidelines, the conclusion of our review was that physical activity should be performed three times a week for 45 to 60 minutes per sessions, which is a lower frequency and longer duration than recommended by the Dutch physical activity guidelines. The dose-response relationship in our review showed a preference for programs with a higher exercise frequency (three times per week versus once or twice per week), and this suggests that for older adults with dementia an exercise frequency of 5 to 7 times per week may be even more beneficial than a program using an exercise frequency of 3 times per week. However, this should be confirmed in further research.

Based on the discussion above we recommend that for every older adult in a nursing home their individual treatment plan should include goals for physical activity. To facilitate this, the level of physical activity of older adults, especially when they have dementia, should be closely monitored. The type of activity should be specified (including at least aerobic and strengthening exercises), as well as the frequency and duration (at least three times per week for 30 minutes).

**Physical performance and cognitive performance**

Section 7.3.1 focused on the positive effects of physical exercise on physical performance. In this section, we focus on the relationship between physical performance and cognitive performance. The results presented in Chapters 4, 5 and 6 provide evidence for a positive association between physical and cognitive performance in older adults with and without dementia. Our results show that in cognitive healthy older adults (mean age of 74) lower limb strength, walking ability and balance are significant predictors of cognitive performance (Chapter 4). For balance and walking ability this association is stronger for men than for women. In a group of older adults with and without dementia who are almost a decade older (mean age of 83) this gender effect disappeared. Gait speed (Chapter 5) and grip strength (Chapter 6) were significant predictors of (some aspects of) cognitive performance.
performance in older adults with and without dementia. Consequently, gait speed and grip strength are not only important indicators of physical functioning (Legrand, Adriaensen et al. 2013, Seino, Yabushita et al. 2013), they also seem to reflect some aspects of cognitive performance (Chapter 5 and 6) and the state of the neuronal system (Murray, Senjem et al. 2010).

Our cross-sectional studies in Chapter 5 and 6 indicated that the association between physical and cognitive performance differs at various levels: the specific content of the physical exercise program, cognitive status as well as age and gender of the participant, and the cognitive domain that is targeted. Consequently, future intervention studies need to take into account these aspects.

When only focusing on the effects of aerobic activity (walking) on cognition, the results across different studies show an ambiguous pattern (see Scherder, Scherder et al. 2013). The results of our studies (Chapters 4, 5 and 6) indicate that gait speed, endurance, balance, lower limb strength, and grip strength are associated with cognition. As it has been argued that cognitive improvements are mediated by physical improvements (Eggermont, Swaab et al. 2009), we hypothesize that direct stimulation of the multiple physical components related to cognition will improve cognitive performance. Considering the specificity principle of training, aerobic activity only may be not sufficient. Next to aerobic activity, lower limb strength training should be included as lower limb strength is related to cognitive performance and it is important for gait speed and balance (Holviala, Kraemer et al. 2012). Given the relationship between balance and grip strength on cognitive performance (Chapters 4 and 6), inclusion of specific balance exercises and grip strength training may help to optimize the cognitive benefits of physical exercise as well.

Our findings suggest that the content of effective interventions depends partly on the cognitive status of the participants. The association between gait speed and different aspects of cognitive function is rather similar (i.e. not significantly different) in older adults with and without dementia. Therefore, the inclusion of lower limb strength exercises in interventions may be suitable for all older adults. In contrast, grip strength is specifically associated with aspects of executive functions in older adults with dementia. Dementia is associated with physical decline (McLaren, Lamantia et al. 2013) which may hamper lower limb and walking exercises. For the physically more impaired older adults with dementia, improving grip strength by upper limb strength training may be a suitable alternative – if intervention studies (which unfortunately have not yet been conducted; Cadore, Moneo et al. 2014) identify that there is a causal relationship between the two. While several
studies focused on lower limb strength, an improvement in this area does not transfer to grip strength (Hauer, Schwenk et al. 2012). Given the importance of grip strength for activities of daily living (Collard, Comijs et al. 2013, Langlois, Norton et al. 1999), frailty (Vermeulen, Neyens et al. 2011), and its association with cognitive performance (Chapter 6), we recommend the inclusion of grip strength training in intervention protocols for older adults with dementia.

All intervention studies need to take age and gender into account. The effect of gender on the association between physical and cognitive performance was observed in a group of relatively young older adults (mean age of 74, Chapter 4), but not in an older group (mean age of 83, Chapter 5 and 6). In the younger group the association was stronger in men, but in the older group this gender difference disappeared. Gender and age differences of physical and cognitive performance have been observed previously with stronger effects for females and younger participants (Colcombe, Kramer 2003). These gender differences are probably caused by differences in brain morphology (Rubia, Hyde et al. 2010, Baker, Frank et al. 2010). These findings show that the analyses of data from cross-sectional, longitudinal, and intervention studies need to control for age and gender effects. Based on our findings, gender-specific interventions may be necessary for relatively young older adults. For example, the inclusion of balance exercises might be more beneficial for men than for women.

Our results do not confirm nor reject the hypothesis that specific cognitive domains are linked with specific physical domains. In cognitively healthy older adults, we did not find evidence that the effect of various measures of physical performance varied across cognitive domains. In older adults with and without dementia we assessed two different measures of physical performance. Whereas gait speed did not reveal any specificity regarding cognitive domains, grip strength clearly showed a distinctive association with different aspects of cognitive performance. Future intervention studies are necessary to provide a decisive answer.

While we tested older adults with and without dementia in nursing homes, our results may be useful for other populations of older adults as well. The majority of admissions in hospitals are older adults, and when leaving the hospital they may suffer from the “post hospital syndrome” (Krumholz 2013). The post hospital syndrome is a state of deconditioning, physically as well as mentally which occurs after hospitalization (Krumholz 2013). Deconditioning might be expected, knowing that, on average, patients spend 20 out of 24 hours lying in bed even though most patients were able to walk...
Another study showed that especially the physical subscales of the Functional Independence Measure are associated with readmission to the hospital (Hoyer, Needham et al. 2014). Given our results, hospital staff should encourage patients to initiate more physical activity during their time in the hospital in order to prevent a decline in physical and cognitive functioning.

In sum, staying physically active seems not a choice, but a necessity. In addition, when general practitioners or geriatric specialists encounter an older adult suffering from physical decline (e.g., in muscle strength or gait speed) they should not forget to focus on their cognitive performance as well. Furthermore, they should stimulate the older adult to start exercising when they are sedentary, and encourage them to keep doing so when they are still physically active.

7.4 Limitations

The studies described in this dissertation have some general limitations. First, the reliability of some of the cognitive performance measures used in this thesis was not investigated in older adults with dementia. However, in a recent review most cognitive tests we used were recommended as the best choice (Bossers, van der Woude et al. 2012). Second, we used a cross-sectional design in Chapters 4, 5 and 6, and therefore no causation between physical exercise and improvements in cognitive performance may be presumed. Third, we did not differentiate between Alzheimer's disease, vascular dementia or other types of dementia. Differentiation was not possible as many of our participants did not have an explicit diagnosis and the majority of older adults with dementia have a mixed pathology (Jellinger, Attems 2010). Finally, the patients with dementia in our studies were living in a nursing home and were capable of walking. As only one-third of the patients with dementia lives in a nursing home, the generalizability of our results to outpatients and to institutionalized immobile patients with dementia should be investigated.
7.5 Clinical implications

- Older adults with dementia in a nursing home should at least exercise 3 days per week, with moderate intensity for 45 to 60 minutes.
- In nursing homes, physical exercise should be one of the items in the individual treatment plans of patients with dementia.
- A recent policy in the Netherlands is that older persons have to stay at home as long as possible. Consequently, interventions should focus on cognitive functions and physical performance, since these functions are crucial for independent functioning. Physical exercise is such an intervention.
- Physical interventions that aim to improve physical and cognitive performance of older adults should integrate aerobic exercise, and the training of lower limb strength, balance, and grip strength.

7.6 Future directions for research

- More studies are needed to understand the complex relationship between different aspects of physical and cognitive performance. It is important that the effect of age and gender on the association between physical performance and cognitive performance is fully understood. For example, are different interventions necessary for men and women?
- Additional studies are needed to analyze the influence of dementia on the association between physical and cognitive performance. For grip strength, but not for gait speed, we identified a significantly different association between older adults with and without dementia. For other measures of physical performance, except for gait speed, this has not been analyzed.
- Future intervention studies need to analyze the specificity of the physical exercise intervention on the targeted cognitive domains.
- The effect of the type of dementia (e.g., vascular dementia, Alzheimer’s disease) on the association between physical and cognitive performance needs to be assessed.
- Future studies on the effects of exercise on cognition should always control for age and gender in their analyses.
• Future studies should investigate home-based physical activity programs (which can be supervised by spouses or other caregivers) that focus on improving physical performance and stabilizing or improving cognitive performance.
• Future intervention studies should focus on the dose-response relationship in older adults with dementia. Does an intervention of five times a week lead to larger gains than an intervention of three times a week?
• The effects of upper limb strength training on cognitive performance in older adults with dementia are not known and should be investigated.
• Future intervention studies that aim to improve cognitive performance with physical exercise should include interventions combining aerobic exercises, strength training, and balance exercises.
Chapter 7
Summary of the Results and General Discussion