Introduction
1.1 Demographics of the aging population

Age is the number one risk factor for dementia. The increase in the number of patients with dementia will coincide with the worldwide aging of the population. More specifically, the number of patients with dementia, worldwide, will rise from 35.6 million in 2011 to 115.4 million in 2050 (World Health Organization 2012, Alzheimer’s Disease International 2009). In the Netherlands, the number of patients with dementia will double from 256,000 in 2013 to more than 560,000 in 2050 (Alzheimer Nederland 2013).

The clinical consequences of dementia are severe and involve various functional domains. Patients with dementia experience a great loss of cognitive function (e.g., memory and executive functions; Gaugler, Duval et al. 2007), physical performance (e.g., gait speed and functional mobility; Eggermont, Gavett et al. 2010, Ijmker, Lamoth 2012), independence (Iavarone, Milan et al. 2007), affect (Dai, He 2014), circadian rhythm (Eggermont, Knol et al. 2009, Dauvilliers 2007), and quality of life when the disease progresses. The impact of dementia on the quality of life of the patients is profound, but dementia also imposes other threats. Almost 70% of people with dementia live at home, which has a large impact on the informal caregivers. It is estimated that 90% of people who provide informal care, mostly spouses or children, are overloaded (Alzheimer Nederland 2013). In addition to the effect of dementia on the patients and their family, dementia also has a large impact on society due to (amongst others) the increasing impact on national health care costs (Alzheimer’s Disease International 2009, Wimo, Ballard et al. 2014). Consequently, in the following decades we have to deal with an increasing number of patients with dementia, which has a serious impact on the patients themselves, their direct environment and the society.

1.2 Modifiable risk factors for dementia

There is no cure for dementia (World Health Organization 2012). Treatments focus on the reduction of symptoms or on the prevention or delay of dementia onset. For the latter, knowledge regarding modifiable risk factors is necessary. However, according to the World Health Organization (WHO) even the identification of modifiable risk factors for dementia is still in its infancy (World Health Organization 2012). Nevertheless, the WHO proposes to focus on targets suggested by current evidence, such as diabetes, hypertension, midlife obesity, and physical inactivity (World Health Organization 2012).
Diabetes, hypertension and midlife obesity all have a negative impact on cardiovascular function, which can lead to cerebral hypoperfusion and consequently to brain damage (Qiu 2012). Interestingly, all these risk factors respond positively to physical activity.

### 1.3 Physical activity in cognitively healthy older adults

Aerobic exercise and resistance training has a beneficial effect on blood pressure (Pal, Radavelli-Bagatini et al. 2013). Aerobic exercise also has a positive effect on the prevention of adverse cardiovascular events (Pal, Radavelli-Bagatini et al. 2013). To decrease the level of obesity, the best outcomes are obtained through a combination of physical exercise and an energy-restricted diet (Miller, Fraser et al. 2013). Similarly, a diet in combination with aerobic and resistance exercise training lowered the risk for diabetes type 2 (Aguiar, Morgan et al. 2014). These findings suggest that physical activity can be used as one of the countermeasure to several of the known risk factors for dementia.

Physical inactivity is a risk factor for dementia (World Health Organization 2012, Scherder, Scherder et al. 2013, Volkers, de Kieviet et al. 2012). Epidemiological studies show that people with a sedentary lifestyle at the age of 50 have a higher risk to develop dementia (Rovio, Kareholt et al. 2005). Consequently, a more active lifestyle might prevent cognitive decline, the most apparent symptom of dementia (Rovio, Kareholt et al. 2005, Fratiglioni, Paillard-Borg et al. 2004). An active lifestyle is reflected in better physical performance. Cross-sectional studies show a positive relationship between different aspects of physical and cognitive performance in cognitively healthy older adults (Brown, Peiffer et al. 2012, Miller, Taler et al. 2012). For example, in cognitively healthy older adults associations between gait speed and aspects of executive functions are found (de Bruin, Schmidt 2010, Fitzpatrick, Buchanan et al. 2007, Holtzer, Wang et al. 2012, Liu-Ambrose, Davis et al. 2010, Martin, Blizzard et al. 2013, Mielke, Roberts et al. 2012, Watson, Rosano et al. 2010). Most of these studies, however, focus only on specific aspect of physical performance or cognitive performance and the used methodology varies across the different studies. Therefore, no clear overview about the relationship between physical and cognitive performance can be obtained (Miller, Taler et al. 2012).

Intervention studies (often involving sedentary but cognitively healthy older adults aged over 55; Hotting, Roder 2013) show significant improvements in executive functions after aerobic exercise (Voelcker-Rehage, Godde et al. 2011, Colcombe, Kramer et al. 2004),
memory (Scherder, Scherder et al. 2013, Stroth, Hille et al. 2009), and speed of processing (Moul, Goldman et al. 1995). Although aerobic exercise is often used as an intervention, it has been suggested that a combination of aerobic exercise and resistance training might be more beneficial for cognitive function (Colcombe, Kramer 2003, Bossers, Scherder et al. 2014). In sum, studies among cognitively healthy older adults strongly support the notion that physical exercise has a beneficial effect on cognitive performance (Hotting, Roder 2013) and may prevent or delay the onset of dementia.

1.4 Neurobiological pathways

Human and animal studies investigated the relationship between physical activity and cognitive performance. Both types of studies show that physical activity improves neuroplasticity. Neuroplasticity is the capacity of the brain to adapt to alterations in behavior, environment and neural processes by changing, amongst others, neural pathways, the level of neurotransmitters, and synapse density (Pascual-Leone, Freitas et al. 2011). Physical activity leads to an increase in brain derived neurotrophic factors (BDNF), and Insulin growth factor-1 (IGF-1; Hillman, Erickson et al. 2008). BDNF promotes, amongst others, cell survival, and synaptic plasticity (Kramer, Erickson 2007). The level of IGF-1 is important for neurogenesis, angiogenesis and neural plasticity (Hillman, Erickson et al. 2008, Cotman, Berchtold et al. 2007) and remain in the hippocampus only several days after exercise onset (Cotman, Berchtold et al. 2007). Increased levels of IGF-1 are detected within one hour after exercise (Cotman, Berchtold et al. 2007). It is argued that an increase in IGF-1 is crucial for exercise effects on hippocampal dependent learning and plasticity (Cotman, Berchtold et al. 2007). In addition, exercise results in an improved cerebral blood flow (Viboolvorakul, Patumraj 2014). These factors probably mediate the beneficial effects of physical activity on cognitive performance. Studies with human participants show that physically active older adults have a larger number of small cerebral vessels compared to less active older adults (Bullitt, Rahman et al. 2009). Physical exercise also increases the volume of the grey matter in the hippocampus (Colcombe, Erickson et al. 2006, Erickson, Voss et al. 2011) and frontal brain regions (Colcombe, Erickson et al. 2006).
1.5 Physical activity in older adults with dementia

The effects of physical activity on cognitive performance of older adults with dementia are investigated in a limited number of studies. However, the results are inconsistent (Ijmker, Lamoth 2012, Forbes, Forbes et al. 2008, van Uffelen, Chin A Paw et al. 2008, Thom, Clare 2011, Lucia, Ruiz 2011, Forbes, Thiessen et al. 2013, Bruce-Keller, Brouillette et al. 2012, Bruce-Keller, Brouillette et al. 2012, Eggermont, Swaab et al. 2009, McLaren, Lamantia et al. 2013, Snowden, Steinman et al. 2011). Van Uffelen and co-workers (2008) argued that the differences in type of intervention, intervention duration, study design, and outcome measures make it difficult to draw strong conclusions about the effects of physical activity on cognitive performance in people with dementia. Intervention studies that examine the cognitive effects of physical activity are time-consuming, expensive and require a lot of effort from participants. Results of more feasible cross-sectional studies can be used to optimize intervention studies. Information with respect to differences in associations between aspects of physical and cognitive performance and the influence of age and gender can be used to formulate specific hypotheses and to develop specific physical intervention strategies. Also, sensitive cognitive and physical outcome measures can be identified from cross-sectional studies.

As physical improvements precede cognitive improvements in intervention studies (Eggermont, Swaab et al. 2009), effective interventions to improve physical performance in people with dementia might be able to affect cognitive function as well. There is extensive evidence that physical activity positively influences physical function in people with dementia. However, to our knowledge, the literature has never been reviewed with the aim of identifying optimal settings with respect to the type of intervention, frequency, intensity and duration. A systematic review of the existing literature from this perspective will help to fill this gap in our understanding. In the various intervention and cross-sectional studies so far, a large number of different physical performance tests are used, despite the fact that the reliability of these measures has not yet been established in older adults with dementia. Therefore, there is a need to assess the reliability of frequently used physical performance tests in older adults with dementia, to assure a correct interpretation of the results found in cross-sectional and intervention studies.

In this thesis, we will investigate the effects on physical performance of different types of physical exercise interventions, we will analyze the reliability of frequently used physical performance measurements, and we will assess the association between physical and cognitive functions in older adults with and without dementia. Our aim is,
therefore, that the results of this dissertation will contribute to a better understanding of the relationship between physical and cognitive functioning in people with dementia, an increase in quality of future intervention studies, and ultimately to increase the quality of life of patients with dementia.

1.6 Outline of the present dissertation

This dissertation focuses on the association between physical performance and cognition in older adults with and without dementia.

Chapter 2 provides a systematic review of the existing literature on the effects of exercise on physical performance in older adults with dementia. In this chapter we investigate the characteristics of the most effective physical interventions to improve physical function in this group. More specifically, we are interested in the type of activity, duration and intensity leading to the strongest improvements in physical performance and the lowest number of drop-outs and intervention-related injuries. The aim of this chapter is to provide guidelines for physical interventions in older adults with dementia to improve physical function. These guidelines are important for two reasons. First, if people with dementia participate in effective physical activity interventions to improve physical function, they can benefit directly from their improved physical function as this contributes to a better performance of physical tasks of daily life and reduced dependence. Second, as an improvement in physical performance is necessary to expect an improvement in cognitive performance (Eggermont, Swaab et al. 2009), people with dementia may also benefit more from the cognitive effects of such physical activity interventions.

In Chapter 3 the reliability of frequently used physical performance tests for older adults with dementia are assessed. More specifically, the Six Meter Walk Test (Thomas, Hageman 2002), Timed Up and Go (Podsiadlo, Richardson 1991), Sit-to-Stand test (Rikli, Jones 2007, Jones, Rikli et al. 1999), Frailty and Injuries: Cooperative Studies of Intervention Techniques (Rossiter-Fornoff, Wolf et al. 1995), Grip Strength, and Figure of Eight (Johannson, Jarnlo 1991) are investigated. Measures of gait speed, balance, functional mobility, lower limb strength and grip strength are often used and important for physical functioning. However, to be able to interpret the results from cross-sectional or intervention studies correctly, the reliability of these measures should be determined in the target population of people with dementia.
Chapter 4 describes the association between physical and cognitive performance in healthy older adults. As studies with dementia patients are complex, due to the many possible confounding variables such as comorbidity, medication, cognitive impairment, and changes in mood, our first step in unraveling the relationship between physical and cognitive performance in older adults with dementia is to investigate this relationship in cognitively healthy older adults. Specifically, we are interested in which aspect of physical performance is the strongest predictor of cognitive performance, and if the association between physical and cognitive performance differs between (sub-)domains of cognitive performance. Despite the fact that various studies have assessed the association between physical and cognitive performance in healthy older adults, these studies were limited to specific aspects of physical and cognitive performance. To provide recommendations for intervention studies among older adults with dementia, we analyzed the association between physical and cognitive performance in older adults with a normal cognitive status using a large number of tests, while also taking into account the moderating effects of age and gender.

In contrast to Chapter 4, Chapters 5 and 6 focus on older adults with dementia. We investigate the association between gait speed, an important marker of mobility, and executive functions and memory in older adults with dementia in Chapter 5, and the relationship between grip strength and executive functions and memory in Chapter 6. We specifically selected gait speed and grip strength as physical measures, as these are often used, easy to administer, important for activities of daily living, and related to frailty (Vermeulen, Neyens et al. 2011, Heuberger 2011). More importantly, gait speed has been found to be associated with some aspects of executive functions in older adults with and without dementia (IJmker, Lamoth 2012). However, in Chapters 5 and 6, we include a broader range of executive functions and memory tests. The association between grip strength and cognitive performance has not been examined in older adults with dementia. We specifically investigate this association, as a large number of older adults with dementia are not capable of walking and can therefore not be included in most aerobic physical intervention programs. If an association exists between grip strength and cognitive performance, upper limb strength training might be an alternative way to improve cognitive performance.

Finally, Chapter 7 provides a summary and general discussion of the results of this dissertation. Besides discussing our findings in light of the existing literature, we also provide suggestions for further research and clinical implications.