Chapter 9

SUMMARY AND GENERAL DISCUSSION

The focus of the present thesis was on the effects of different types of physical activity on cognition, mood, and the rest-activity rhythm of older nursing home residents with dementia. One aim of the present thesis was to evaluate the existing literature on this topic. Accordingly, one review was included that describes intervention studies that offer a program consisting of physical activity to patients with Alzheimer’s disease (AD) and used cognitive outcome measures. The second review displays the studies on the impact of physical intervention programs on mood, sleep, and functional ability in older people with dementia. Also the potential reduction in caregiver burden as a result of the physical intervention is highlighted. In the clinical section of the thesis, the relationship between level of activity and the rest-activity rhythm and cognitive functioning was determined in older ambulatory nursing home residents with dementia.

The main focus of the clinical section was on the effects of several physical activity interventions on cognition offered to older nursing home residents with dementia. With respect to a common activity in older people, walking, it was investigated whether this type of activity is of sufficient intensity to improve aerobic fitness. A walking intervention was then applied to determine whether this activity could actually generate a positive effect on cognition in a group of older nursing home residents with dementia. The effects of two other interventions involving physical activities were examined as well: interventions regarding the performance of hand motor activity and the observation of hand motor activity. First a summary of all chapters is given, then a general discussion.

SUMMARY

REVIEW SECTION

Chapter 2 reviews studies that focused on the effects of a physical activity intervention on cognition. The few available studies regarding exercise in older people with dementia reveal a positive effect on cognition, probably due to enhanced cerebral perfusion, mediated via an increase in endothelium-derived nitric oxide levels. However, due to dysregulation of nitric oxide in AD and to increased blood supply to other organs than the brain, exercise may not be beneficial for cognition in those people with dementia in which cardiovascular risk factors are present. Positive effects of exercise on cognition were reported in seven of the reviewed studies, including three that excluded and two that included patients with cardiovascular risk factors. These findings suggest that cardiovascular risk factors may mitigate the beneficial effects of exercise on cognition in cognitively impaired people, but the risks are not sufficiently known for this group. When prescribing physical activity programs to people with dementia, they should first undergo careful physical examination, particularly in order to exclude cardiovascular risk factors.

In Chapter 3 studies are reviewed that investigated the effects of planned physical activity programs on disruptive behavior that lead to increased caregiver burden. Since caregiver burden is associated with rates of institutionalization, it is interesting to evaluate the indirect effects of physical activity programs on the caregiver. Studies that examined the effects of a physical activity intervention on mood, sleep, and functional ability in people with dementia were explored. A literature search revealed a total of 27 studies, which were evaluated on their methodological quality.
Results show that in order to benefit mood, the most effective type of physical activity was walking. Studies that examined the effects on mood during the physical activity consistently reported that the physical activity was enjoyed. After a physical activity intervention that was frequently applied, the quality of sleep improved, i.e. the participants slept longer and had reduced awakenings during the night. The positive effects of physical activity on functional ability were restricted to long-term exercise interventions. These improvements in mood, sleep quality, and functional ability of the persons with dementia may reduce the burden of the caregiver.

**Clinical section**

Chapter 4 highlights the positive association between level of physical activity, the rest-activity rhythm, and cognitive functioning. Nursing home residents with dementia suffer from cognitive decline and often show rest-activity disturbances. They show varying levels of daily physical activity, despite being able to walk. In this chapter it was investigated whether the level of daily physical activity differed between similar ambulatory nursing home residents with dementia, and whether the level of physical activity was associated with both the rest-activity rhythm and the cognitive functioning. Nursing home staff was consulted to categorize the residents as being ‘active’ or ‘sedentary’. Actigraphy data revealed that the people that were considered ‘active’ had a significantly better rest-activity rhythm compared with the sedentary subgroup and there were some indications that they showed better cognitive functioning. An intriguing finding of this study was that no direct relationships were found between the level of daytime physical activity and cognition in either group. The main conclusion of the study was that differences are still found between the level of physical activity, the rest-activity rhythm, and the level of cognitive functioning in older people with moderately advanced dementia living on psychogeriatric wards, but that the precise relationship between those parameters remains unclear.

In Chapter 5, the exact level of energy expenditure was determined of people older than 75 years of age while they were walking with their rollator. In healthy older people, improved aerobic fitness has proven to generate a positive effect on cognition. Many older people however, particularly in a nursing home, make use of a rollator during walking. In order to examine whether walking with a rollator is of sufficient intensity to improve aerobic fitness, energy expenditure was determined in 15 older people who walked on a treadmill with their rollator. It was concluded that for older people, self-paced walking with a rollator is an activity of moderate to high level of intensity. This intensity of physical activity can be sufficient to improve aerobic fitness.

Chapter 6 investigated whether a walking intervention applied to older nursing home residents with moderate dementia can improve cognition. Ninety-seven participants were randomly divided to the experimental condition (walking) or the control condition (social visits). Interventions were applied for 30 minutes, 5 days a week, during 6 weeks. Neuropsychological tests were administered and the Apolipoprotein epsilon (ApoE) genotype was determined. Data-analyses did not show beneficial effects of the walking intervention on cognition and the ApoE4 genotype did not appear to influence treatment outcome. It is argued that the lack of a positive effect could be the result of the many cardiovascular conditions that were present in the study population. Cardiovascular disease may reduce cardiac output, which in turn, may preclude an increase in cerebral perfusion as a result of walking.

Chapter 7 evaluated the effects of a hand motor activity intervention on cognition, mood, and the rest-activity rhythm in 61 older nursing home residents with dementia. This type of activity does not require participants to be able to walk. The
nursing home residents participated in either a hand movement program (experimental condition) or a read aloud program (control condition) for 30 minutes, 5 days a week, during 6 weeks. After the intervention, the total group of older people in the experimental condition did not show an improvement in cognition, mood, or the rest-activity rhythm. However, the participants that showed a high attendance of the hand motor activity intervention revealed improved mood.

In Chapter 8 it is described that besides the execution of motor activity, also the observation of hand motor activity may stimulate neural function. Since in older people the ability to engage in physical activity is often limited it was investigated whether observation of motor activity, i.e. hand motor activity exerted a positive impact on cognition in older nursing home residents with dementia. Forty-four older people with dementia observed videos that showed hand movements (experimental condition) or videos that showed a documentary without hand movements (control condition) for 30 minutes, 5 days a week. Results indicate that overall cognition did not improve after 6 weeks, but there were indications that certain cognitive functions did respond better to the intervention than others.

**GENERAL DISCUSSION**

**IMPLICATIONS OF THE PRESENT STUDY**

The intervention studies in the present thesis focused on physical activities of different levels of intensity. Results show that the walking intervention, the type of intervention with the largest intensity, did not reveal a significant effect on cognition. A milder type of physical activity, hand motor activity, did not improve cognition either, but the people that frequently attended the intervention did reveal an improved mood. The activity without actual motor activity, the observation of hand motor activity, showed some evidence of improved cognitive functions. It is important to realize that the present study populations all consisted of older nursing home residents with moderately advanced dementia. For that reason, large effects of the physical activity interventions were not expected and the effects that were found, e.g. on mood, were hence encouraging. Possible explanations for the present findings and suggestions for future research are given below. Firstly, it is highlighted that physical activity may play a particularly important role in the prevention of cognitive decline.

**PHYSICAL ACTIVITY AS A PREVENTION STRATEGY**

Based on epidemiological studies, a positive relationship between physical activity and cognition exists across the life span. As early as during the preschool period, children (age 3.5 - 7 years) that participate in sports activities have revealed better motor and cognitive functioning (Krombholz, 2006). In concordance with these findings, children born with meningomyelocele (i.e. herniation of meningeal and spinal cord tissue through a bony defect in the vertebral column) that were ambulatory with or without a walking aid, outperformed children with the same condition that were not able to walk, with regard to their performance IQ (Rendeli et al., 2002). Engaging in physical activity early in life may also benefit cognition later in life. More specifically, it was shown that retrospectively determined participation in high intensity physical activity between the ages of 15 - 25 years, was positively associated with information processing speed in older men (Dik, Deeg, Visser, & Jonker, 2003). It is argued that neural plasticity early in life may set the level for later use and maintenance of brain function (Rosenzweig & Bennett, 1996). In a cross-sectional study examining younger (mean age 25.5 years) and older (49.6 years) community-dwelling individuals, frequency of participation in
high intensity physical activity was positively related with information processing speed in both younger and older groups (Hillman et al., 2006). It is noteworthy however that performance during task conditions that required interference control, i.e. executive function, was significantly associated with physical activity in the older individuals, whereas in the younger individuals it was not (Hillman et al., 2006). These data suggest that although regular physical activity may be associated with better cognitive function across the life span, physical activity appears to have a larger impact on cognition during the later stages of life (Hillman et al., 2006).

Several recent studies have provided support for the inverse relationship between physical activity and the risk for cognitive decline and dementia. In one prospective cohort study, in which participants were evaluated with a time-interval of 5 years, the performance of physical activity of a high intensity was shown to reduce the risk of cognitive impairment (Laurin, Verreault, Lindsay, MacPherson, & Rockwood, 2001). These findings were particularly observed in women. A 10-year follow-up study that included older men revealed that longer and more intense participation in physical activity was associated with less cognitive decline (Van Gelder et al., 2004). In another study, participants were tested at midlife and again after a mean time-interval of 21 years (Rovio et al., 2005). People who participated at baseline in leisure-time physical activity twice a week or more were classified as ‘active’ people; those who were active less than two times a week were categorized as ‘sedentary’ people. Results show that an active lifestyle is associated with a considerable reduction in the risk for AD. However, not all epidemiological studies show a positive relationship between physical activity and cognition (Wilson et al., 2002; Sturman et al., 2005). One explanation may be that increased levels of physical activity may not generate a positive effect on all cognitive function domains, but this effect may be more selective. More specifically, although greater cardiorespiratory fitness is associated with less cognitive decline across various cognitive measures, particularly measures for executive function seem to respond the most (Barnes, Yaffe, Satariano, & Tager, 2003).

Although knowledge on the positive association between physical activity and cognition is still emerging, the positive relationship between physical activity and the cardiovascular system can be considered conventional wisdom (Kavanagh, 2001). Engaging in physical activity is associated with a better cardiovascular condition, i.e. reduced blood pressure, and a decreased risk of both arteriosclerosis as well as diabetes mellitus, among others (Bassuk & Manson, 2003). Physical activity is also associated with a lower risk for dementia, which may be partly due to the beneficial effects on the cardiovascular condition (Anstey & Christensen, 2000). In order to delay cognitive decline, it is recommended to stay physically active during a large part of the life span. However, in all cases, physical activity should be kept within the physiological range (Swaab, 1991). In addition, the present thesis argues that special attention should be paid to co-morbidities such as cardiovascular disease. In general, physical activity is known to benefit the cardiovascular condition and hence cognition, but in some cases of serious cardiovascular disease, this beneficial effect may be diminished (see chapter 2).

Cardiovascular Disease
It is highlighted in the present thesis, that cardiovascular risk factors and cardiovascular disease may play a negative role in the effects of cognition in dementia. It is speculated that the lack of profit on cognition from the current walking intervention in older nursing home residents with dementia may be attributed to the high prevalence of cardiovascular disease in this population. This suggestion may be explained as follows. Older people with dementia, irrespective of major subtype of dementia, show a
decrease in cerebral perfusion (Mito et al., 2005; Shimizu et al., 2005). Cardiovascular
disease, e.g. atrial fibrillation and hypertension, can reduce cardiac output (De Leeuw
et al., 2000; Sowers & Farrow, 1996). In addition, cardiovascular disease that is
treated with medication, e.g. beta-blockers, reduces cardiac output even more, espe-
cially in older people (Everly, Heaton, & Cluxton, 2004). The blood flow to organs is
determined by the cardiac output. Particularly in patients with an impaired cardiac
output, an increased distribution of blood supply to muscles during physical activity
may deprive other organs of blood (Ide, Pott, Van Lieshout, & Secher, 1998). There-
fore, reduced cardiac output can result in a decrease in cerebral perfusion during
exercise (Ide et al., 1998). Indeed, patients with cardiovascular disease, i.e. valvular
dysfunction, and atrial fibrillation, who engaged in physical activity revealed a reduc-
tion of cerebral blood flow (Koike et al., 2004; Ide, Horn, & Secher., 1999). Since
cerebral perfusion, cerebral metabolism and cognition are tightly linked (Iadecola,
2004), the possible lack of increase in cerebral perfusion as a result of the walking
intervention of the present thesis may have attenuated a beneficial effect on cognition.

Another reason for a limited effect of a physical activity intervention on cogni-
tion may be a reduced ability to participate in the intervention. To what extent
someone can engage in a physical activity intervention may be dependent on the
presence of disturbances in motor function.

**MOTOR DISTURBANCES**

A number of studies reveal disturbances of motor activity, e.g. gait disturbances, in
older people, which include a decrease in step length and gait velocity, a widened
base, a decrease in balance and reduced lower limb strength (Menz, Lord, & Fitz-
patrick, 2003). Some disturbances in gait seem to depend on the level of cognitive
function (Scherder et al., 2007). More specifically, compared with healthy older
people, patients with Mild Cognitive Impairment (MCI) show even lower levels of
balance and less coordination in the lower extremities (Franssen, Souren, Torossian, &
Reisberg, 1999). In AD patients, more gait disturbances have been reported compared
with healthy controls, and the gait disturbances are more pronounced in AD patients in
a more advanced stage of dementia (Goldman, Baty, Buckles, Sahrmann, & Morris,
1999; Scherder et al., 2007). Besides disturbances of motor activity that may hamper
the participation in a walking intervention, motor disturbances in older people have
also been reported regarding hand motor function: hand movements of older persons
are slower, less accurate and less automated than those of younger persons (Mergl,
Tigges, Schröter, Möller, & Hegerl, 1999). In MCI patients, it is found that hand move-
ments are less automated than those of healthy older people, especially when the task
is more complex (Schröter et al., 2003). MCI patients also show disturbances in fine
motor function, but not in gross motor function (Kluger et al., 1997), whereas AD
patients show both disturbances in fine motor function, as well as in gross motor
function (Kluger et al., 1997). These disturbances in motor activity may have had an
impact on to what degree the older nursing home residents with dementia could have
engaged in the walking and the hand motor activity interventions.

Response to a physical activity intervention of any sort on cognition may also be
dependent on the ApoE genotype. Both in pharmacological intervention studies as well
as in epidemiological studies concerning physical activity, the presence of the ApoE4
allele has shown a moderating effect.
APOE genotype

In studies examining the effects of pharmacological interventions, i.e. cholinesterase-inhibitors on cognition, ApoE genotype may moderate treatment effect; however results have not been consistent. Tacrine and Donepezil have proven to benefit cognition either in ApoE4 carriers or in ApoE4 non-carriers only (Almkvist et al., 2001; Farlow et al., 1998; Bizzarro et al., 2005), but some other studies show no influence of the presence of the ApoE4 allele (Rigaud et al., 2000; Rigaud et al., 2002). Studies that examined effects of Rivastigmine treatment in relation to ApoE4 genotype have consistently found no influence of the ApoE4 genotype (Farlow, Lane, Kudaravalli, & He, 2004; Visser, Scheltens, Pelgrim, Verhey, 2005; Blesa et al., 2006). Therefore, the role of the presence of the ApoE4 allele in treatment outcome remains a controversial issue. Also with regard to the influence of the ApoE4 allele on the relationship between physical activity and cognition, results have not been straightforward. One study revealed that the presence of the ApoE4 allele precludes beneficial effects of physical activity on cognition (Podewils et al., 2005). The authors suggest that any potential positive effect associated with physical activity is not enough to overcome the effect of ApoE4 alleles. Support for this hypothesis comes from studies in which ApoE4 carriers did not acquire the same benefits as non-carriers from physical activity concerning blood pressure and lipid patterns (Hagberg, Ferrell, Dengel, & Wilund, 1999; St-Amand et al., 1999). Podewils and colleagues (2005) suggest that beneficial effects of physical activity on cognition are limited to ApoE4 non-carriers. In contrast, other studies showed a positive relationship between physical activity and cognition only in ApoE4 carriers (Schuit, Feskens, Launer, & Kromhout, 2001; Rovio et al., 2005; Etnier et al., 2007). More specifically, two studies showed a positive relationship between self-reported physical activity and cognition in ApoE4 carriers whereas this relationship was less pronounced (Rovio et al., 2005) or even absent (Schuit et al., 2001) in ApoE4 non-carriers. Some argue that individuals carrying an ApoE4 allele have less effective neural protection and repair mechanisms (Mahley & Rall, 2000), and may therefore rely more on lifestyle-related factors to protect them against dementia (Rovio et al., 2005). Recently, a study revealed that aerobic fitness (VO_{2peak}) is positively associated with cognition only in people that carry 2 ApoE4 alleles (Etnier et al., 2007). These results can be explained by the cognitive reserve hypothesis: the individuals at the highest risk for AD (i.e. ApoE4 homozygotes, with the smallest cognitive reserve) reveal the greatest benefit from aerobic fitness (which may increase cognitive reserve) (Etnier et al., 2007).

However, the abovementioned epidemiological studies examining the relationship between ApoE4, physical activity and cognition generally included younger participants, varying from 10 years younger (Podewils et al., 2005; Schuit et al., 2001), 15 years younger (Rovio et al., 2005), to almost 25 years younger (Etnier et al., 2007). Therefore, particularly the results of the latter study can not be generalized to the present population without serious contemplation. The lack of influence of the ApoE4 genotype may indeed be attributed to the advanced age of participants, as it seems that the ApoE4 loses its influence in people of higher ages (Juva et al., 2000). Nonetheless, in future intervention research, the possible influence of the ApoE4 genotype should be taken into consideration.

One may also speculate about other reasons for the lack of improved general cognition in the 3 intervention studies. It is therefore important to take a close look at the study design.
STUDY DESIGN

In the present thesis, it was aimed to determine the effects of three interventions on a large range of cognitive functions, among which episodic memory, memory for faces, inhibition, word fluency and working memory in older people with moderately advanced dementia. Although memory could be assessed reliably in most participants, executive functions were more difficult to assess. In particular both computerized tests, i.e. the Stop Signal test (Logan & Cowan, 1984) and the ANT test (Fan, McCandliss, Sommer, Raz, & Posner, 2002), could not be performed in a substantial portion of participants. Reasons for not properly performing the tests by the current population of older people with moderate dementia included difficulty in remembering the instructions, being too slow to react within the given response interval, motor impairments, and not being able to sufficiently distinguish stimuli on the screen, among others. It is known that people with dementia can fail an executive function test for other reasons than executive dysfunction, e.g. impairment of memory (Thompson, Stopford, Snowden, & Neary, 2005).

In the present thesis, level of depression has been determined by using the Geriatric Depression Scale (GDS) (Yesavage et al., 1982). This questionnaire is widely used in older people and people with cognitive impairment and dementia (Orsitto et al., 2007; Riccio, Solinas, Astara, & Mantovani, 2007). Nevertheless, it has been argued that it is not the most appropriate questionnaire to assess symptoms of depression in dementia (Körner et al., 2006). However, they also state that results of the GDS remain satisfactory, and they conclude that the GDS can still be used in the population of older people with dementia (Körner et al., 2006). Assessing symptoms of depression in dementia is challenging, considering the overlap between the symptoms of depression and the symptoms of dementia, among which loss of interest, reduced energy level, difficulty concentrating, and apathy (Hoogendijk, 1998). In studies diagnosing the presence of depression in people with dementia, this may however be a larger problem than it has been in the present intervention studies, since in the latter studies participants were mainly compared within groups, and served as their own controls. Nonetheless, it is recommended in future studies to use an instrument specifically designed for people with dementia, e.g. the Cornell Scale for Depression in Dementia (Alexopoulos, Abrams, Young, & Shamoian, 1988).

It is also important to take a close look at the physical activity interventions that were offered and to determine whether some interventions could be improved in future studies. Firstly, apart from walking or hand motor activity by itself, it could be considered to include other activities. In a review of physical activity intervention studies in older people, it was shown that the combination of aerobic and anaerobic activities, e.g. training of muscle strength, generated the largest effect (Colcombe & Kramer, 2003). Besides the type of activity, the duration of the intervention may be extended. On the other hand, this may not be desirable concerning the age and frailty of the current study population. A consequence of long-term trials is the higher loss to follow-up, which may undermine the value of these trials (Burns & O’Brien, 2006). Besides, also short-term trials of pharmacotherapy have been sufficient to demonstrate cognitive benefits (Burns & O’Brien, 2006). Which type of intervention, i.e. length, intensity, duration, frequency may lead to the most favorable outcome on cognition requires further clarification. Whereas some argue that interventions with a duration of longer than 6 months will generate the most benefit (Colcombe & Kramer, 2003), others even refute the assumption that an increase of physical fitness itself is required to generate a positive effect on cognition (Etnier, Nowell, Landers, & Sibley, 2006).
Therefore, more research including for instance different types of activities, a longer treatment period, and a younger study population could shed more light on the moderators of the effects of physical activity on cognition.

**Compensatory strategies**

When it concerns physical activity interventions in older people, there are some factors that should be taken into account. Firstly, older participants in physical activity studies differ considerably in their motivation and effort, and thus study outcome may also vary between participants (Spirduso & Cronin, 2001). Secondly, lack of a significant benefit of a physical activity intervention in older people may be explained by a compensatory reduction in overall physical activity. Older people have displayed this technique when participating in exercise training programs (Westerterp, 2000). More specifically, a physical activity index (formed by dividing the total energy expenditure by the resting energy expenditure) in older people did not seem to increase during an exercise training program (Westerterp, 2000). An explanation could be that older people compensate for exercise training by reducing their spontaneous activity during the day (Morio et al., 1998). These findings were confirmed by another study in which participation of older people in an exercise training program did result in increased physical fitness but that the total physical activity level of the participants remained unchanged (Meijer, Westerterp, & Verstappen, 1999).

In the intervention studies of the present thesis, it is unknown to what degree compensation for the activities in the interventions occurred. There is no information available in the literature whether this also happens during interventions that do not involve walking. In future physical activity intervention studies, regardless of the type of physical activity, a possible compensation for the intervention should be taken into account. Finally, to optimize the effects of a physical activity intervention, one may use an intervention that is presumed to stimulate neural activity on the one hand, but this could be accompanied by specific training of cognitive function on the other hand.

**Training**

In the current thesis, the physical activity interventions did not turn out to be adequate to significantly benefit overall cognition or cognitive domains in particular. Despite the lack of brain imaging recordings it is likely that the interventions did activate brain areas. Merely activating brain areas may however not be enough to actually improve or maintain cognitive functioning in this group of older nursing home residents. It is argued that cognitive functions may have to be actively trained. Support for this notion stems from animal experimental studies examining treatment possibilities for neurodegenerative disorders, e.g. Parkinson’s disease. The replacement of lost cells and circuit reconstruction in a neurodegenerative animal model by means of grafting may not be sufficient for restoration of function (Döbrössy & Dunnett, 2001). Brain functioning can be improved by increased neurotrophins, dendritic arborisation and synaptic density, but by itself this may not be enough to recover cognitive function (Döbrössy & Dunnett, 2001). Although physical activity may improve brain functioning (Churchill et al., 2002; Neeper, Gómez-Pinilla, Choi, & Cotman, 1995), functional recovery may require specific training, i.e. cognitive rehabilitation. This suggestion is reinforced by pharmacological intervention studies in dementia. Pharmacotherapy alone has shown modest effects on cognition, and cognitive training alone does not seem to benefit cognition in dementia to a similar degree (Burns & O’Brien, 2006). Nonetheless, it has appeared that pharmacological treatment combined with cognitive training enhances treatment effect compared with pharmacotherapy alone (Bottino et al., 2005; Requena et al., 2004). Notably, regarding the type of cognitive training that should be offered,
training activities that are specifically needed in daily life activities (ADL) (procedural memory) are more effective in improving cognition and ADL than stimulating ‘residual’ cognitive functions (Farina et al., 2002). Physical activity may reinforce brain function; cognitive training could restore the patterns of behavior that were impaired by the neurodegenerative disease. A possible synergistic effect of a physical activity intervention combined with cognitive therapy is definitely worthy of a future randomized clinical trial.

**FUTURE DIRECTIONS**

Functional imaging studies examining the effects of physical activity on cognition in older people are emerging (Colcombe et al., 2004; Colcombe et al., 2006). Those studies revealed that aerobically trained older people show increased brain volume (Colcombe et al., 2006) and increased activation of the prefrontal, parietal and anterior cingulate cortices during an inhibition task (Colcombe et al., 2004). The exact influence of physical activity on brain function in dementia is precarious. Further elucidation of this issue requires brain imaging studies in dementia.

The precise role of concomitant cardiovascular disease in the effects of physical activity on cognition in older people with dementia is to be determined. In future physical intervention studies regarding people of an advanced age, particularly cardiovascular conditions, such as high blood pressure, should be closely monitored, to prevent unwanted side-effects. Screening for cardiac disease before older people enter a physical activity program has been suggested earlier (Lautenschlager, Almeida, Flicker, & Janca, 2004). As the prevalence of cardiovascular disease increases with advancing age (Priebe, 2000) and a possible aim in the future would be to avoid the high cardiovascular burden present in the current population, focus may be on people with dementia of a younger age, for instance people with a pre-senile onset of dementia.

The role of gender should also be taken into account. The studies in the current thesis mainly focused on older women, since they account for the majority of the older institutionalized population with dementia. There may have been gender differences in treatment outcome, but this could not be established due to the small number of male participants. With regard to the association between physical activity and cognition, differences have been reported between men and women. More specifically, a positive association between level of physical activity and information processing speed has been reported in men, not in women (Dik et al., 2003). Also, incidence of cardiovascular disease is higher in men than in women (Li, Engström, Hedblad, & Janzon, 2006), but this was not the case in the current studies, since this difference reduces with advancing age (Li et al., 2006). In order to examine gender as a possible moderator in the response to a physical activity intervention it is again argued that one could focus on ‘younger’ older participants.

**CONCLUSIONS AND CLINICAL IMPLICATIONS**

The present thesis has reviewed studies that report a positive relationship between level of physical activity and cognition, mood, and the rest-activity rhythm. Unfortunately, randomized controlled intervention studies in older people with dementia are scarce and the intervention studies that do exist are usually not characterized by a rigorous methodological design.

For older people, self-paced walking with a rollator turned out to be an activity of moderate to high level of intensity, which is an intensity that can be sufficient to improve aerobic fitness. Nonetheless, a walking intervention in the present thesis did not exert a beneficial effect on the cognitive functioning in older nursing home resi-
dents with moderately advanced dementia. A possible explanation for the lack of benefit on cognition involves the serious cardiovascular co-morbidity that was present in the study population. People with cardiovascular disease may have a reduced cardiac output. It is speculated that the blood supply may have been to the organs involved in the motor activity (e.g. legs) instead of to the brain, causing the cerebral perfusion to diminish. If people of an advanced age participate in a physical activity program, they should be closely monitored. In addition, gait disturbances are frequently present in older people with dementia and, regarding the possible cardiovascular co-morbidity, the present thesis invites for the development of tailor-made physical activity interventions with individualized risk-benefit considerations.

In view of the frailty of the present population, other types of activities were used as an intervention in the present thesis. Performing hand movements is reported to activate several brain areas. The group of older nursing home residents with dementia that frequently participated in the hand motor activity intervention showed improved mood. The observation of hand motor activity did not improve cognitive domains significantly, but there were indications for a positive effect on more specific cognitive functions. Both types of activities, i.e. execution and observation of hand motor activity, are relatively easy to apply in the nursing home setting. The current findings therefore seem encouraging.