

CHAPTER 8

Summary and general discussion

The main aims of this thesis were 1) to increase insight into the relationship between the level of physical activity and executive functioning (EF), to determine the rest-activity rhythm, emotional wellbeing, i.e. quality of life (QOL) and the level of depressive symptoms in patients with early-onset dementia (EOD), and 2) to investigate the potential effects of different exercise interventions on cognitive functioning, i.e. in particular EF, (instrumental) activities of daily living ((i)ADL), and QOL in patients with EOD. The main outcomes are summarized below.

Summary

CROSS-SECTIONAL STUDIES IN PATIENTS WITH EARLY-ONSET DEMENTIA

In **chapter 2**, the relationship between the level of physical activity and measures of EF was investigated. Physical activity was measured using a pedometer and a self-report questionnaire. A statistical trend for a positive relationship was found between category fluency, a measure of semantic memory and set-shifting, and mean steps per day (pedometer). No other relationships between measures of EF and measures of physical activity were found. The outcomes indicate an inconsistent relationship between EF and the level of physical activity in EOD.

In **chapter 3**, we studied parameters of the rest-activity rhythm, one of the circadian rhythms, and sleep parameters in patients with EOD. Also, it was explored which demographic, clinical, and lifestyle factors contributed to disturbances in the rest-activity rhythm. The results showed a trend towards a higher "Intradaily Variability" in patients with EOD compared to cognitively intact adults of the same age, which means that the rest-activity rhythm of patients with EOD was more fragmented within 24-h. Patients with EOD also spent more time in bed and needed more time to fall asleep than controls. Disturbances in the rest-activity rhythm were associated with a lower level of physical activity, the use of antidepressants, the use of medication

for neurological disorders of the central nervous system, and with being male. The finding that the level of physical activity is related to disturbances in the rest-activity rhythm is of particular interest for these young patients, because they are better capable to perform physical activity than elderly persons, and hence can adopt an active lifestyle more easily, which might benefit the rest-activity rhythm.

Finally, in **chapter 4** we studied the level of QOL and depression in patients with EOD; whether QOL was lower and depressive symptoms were more frequently present in patients with EOD compared to cognitively intact adults of the same age; and which demographic, clinical, and lifestyle factors contributed to QOL and depressive symptoms. Patients with EOD reported an overall “good” QOL, while controls reported “very good” QOL. Twenty-one percent of the patients with EOD and eight percent of the controls were depressed. QOL was lower and depressive symptoms were more frequently present in the EOD group compared to the control group. More depressive symptoms were associated with a more fragmented rest-activity rhythm. More depressive symptoms were associated with a lower QOL. These findings give an indication of emotional wellbeing in patients with EOD.

Taken together, the outcomes of the cross-sectional studies indicate that 1) the relationship between measures of EF and physical activity is inconsistent; 2) the level of physical activity is related to disturbances in the rest-activity rhythm, which are slightly more pronounced in patients with EOD compared to cognitively intact controls of the same age; 3) emotional wellbeing is reasonably good in the current EOD population and more depressive symptoms are related with a more fragmented rest-activity rhythm. These findings shed some light on relations between clinical and lifestyle factors in EOD, which may be further investigated in future research endeavors.

AN EXERCISE TRIAL IN PATIENTS WITH EARLY-ONSET DEMENTIA

First, in **chapter 5**, a theoretical framework was developed to estimate the value of exercise interventions in early-onset Alzheimer's disease (EOAD). A literature search was conducted on key words related to early-onset dementia, exercise, imaging, neurobiological mechanisms and cognitive reserve. Since literature results only included studies concerning early-onset *Alzheimer's disease*, this review focused on EOAD specifically, instead of EOD in general. The results of the review showed that brain regions, such as frontal and parietal regions, and neurobiological processes, such as neurogenesis and synaptogenesis, involved in the positive effects of exercise, are affected in EOAD, which provides theoretical support for exercise interventions in EOAD.

In **chapter 6**, we proposed the study protocol of the intervention trial. We aimed to recruit 150 patients with EOD divided over three intervention arms. After completion of the baseline measurements, patients living within a 50 kilometer radius of one of the rehabilitation centers were randomly assigned to either an *aerobic exercise program in a rehabilitation center* or to a *flexibility and relaxation program in a rehabilitation center*. These programs were applied three times a week during 3 months and were supervised by a physical therapist. Participants living outside the 50 kilometer radius were included in a *daily physical activity program at home using pedometers*. This program used exercise counseling to coach the participants. For all participants, measurements took place at baseline (entry of the study), after three months (end of the exercise program), and after six months (follow-up). Primary outcomes were cognitive functioning, (i)ADL, and QOL. Secondary outcomes included a variety of physical, cognitive, and rest-activity rhythm measures.

Conducting the exercise trial proved to be more problematic than thought beforehand. In **chapter 7** the specific challenges faced and the lessons learned were discussed. The main challenges were: recruiting enough patients with EOD; logistics around the rehabilitation centers; and assessment

of tests for cognitive functions, in particular tests for EF. Recommendations for future research are the consideration of busy lifestyles of young patients, i.e. making intervention programs flexible to match these lifestyles, and offer the programs as close to home as possible. Finally, we recommend considering implementation of alternative measurements besides classical EF tests.

Taken together, we were not able to meet one of our main research aims, i.e. to investigate the effect of different exercise interventions on cognitive functioning, (i)ADL, and QOL in patients with EOD. In the general discussion we reflect on our study and give suggestions for care and research with patients with EOD and for future exercise intervention studies. We will focus on QOL in EOD, research in EOD in general, and physical activity research in EOD.

General discussion

QUALITY OF LIFE IN EARLY-ONSET DEMENTIA

Although more and more studies focus on EOD, patients with EOD are still underrepresented in research. It is however important to include patients with EOD, because studies that focus on EOD could contribute to the development of specific care facilities. At this moment patients with EOD have to ultimately rely on care facilities that are in most cases developed for elderly people with dementia. There are hardly any care facilities and interventions available that take into account the specific characteristics and needs of patients with EOD.¹ This is unfortunate, since patients with EOD are a distinct group with age-specific needs.¹⁻³ One of the targets of our project was to include patients with EOD with a mild to moderate stage of dementia, who showed decline in the level of physical activity. However, the present study population with EOD consisted of patients who were willing to participate in an exercise intervention. The participating EOD patients may have better health and may be more active than EOD patients who were not willing to participate.⁴ In other words, we had a selected group of patients, limiting