SUMMARY

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In recent years improvements in stroke care with intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) have led to improved clinical outcome by early opening of the occluded vessel to restore blood flow to the salvageable ischemic brain tissue that is not already infarcted. Besides this, recurrent stroke and vascular event rates have declined substantially over the last 5 decades. Despite these improvements in stroke care, secondary prevention to prevent recurrent cardiovascular event by reducing modifiable risk factors, remains important because of the increased risk of recurrent stroke and other cardiovascular events. Recurrent stroke increases the risk of long-term physical disability and dementia.

Although the improvements in stroke care have resulted in more patients with stroke leaving the hospital with improved functional independence in daily life, patients with transient ischemic attack (TIA) or minor stroke are often left with significant disabilities, including fatigue, cognitive impairment, depression and anxiety. In addition, most patients have low levels of cardiorespiratory fitness and often lead a sedentary lifestyle, which can lead to a decreased quality of life and an increased risk of a recurrent cardiovascular event. With this thesis, we aimed to contribute to the improvement of stroke care by investigating the effect of lifestyle interventions in the secondary prevention of recurrent cardiovascular events and by investigating the interaction of physical activity and exercise and its impact on fatigue, cognitive impairment, depression and anxiety after TIA or minor stroke in tertiary prevention. Tertiary prevention goes beyond secondary prevention measures to address the care of patients who have suffered a first TIA or minor stroke. Tertiary measures are aimed at the minimization of disability through patient rehabilitation, in order to reestablish partial or complete independence and improve quality of life.

The general introduction in **chapter 1** describes the aims of this thesis and how secondary prevention prevents recurrent cardiovascular events after TIA or stroke and how tertiary prevention reduces the impact of TIA or minor stroke. It also describes what the roles of physical activity, exercise and cardiorespiratory fitness are in primary, secondary and tertiary prevention.

In **chapter 2,** we describe the results of a systematic review and meta-analysis of lifestyle interventions (focusing on behaviorally modifiable risk factors with or without an exercise program) and whether they are effective in terms of (1) preventing recurrent cardiovascular events, (2) reducing mortality, and (3) improving modifiable risk factors associated with cardiovascular disease in patients after a TIA

or ischemic stroke. Twenty-two randomized controlled trials (RCT) were identified with a total of 2574 patients. Pooling showed a significant reduction (3.6 mm Hg) in systolic blood pressure by the lifestyle interventions applied, compared with usual care. No significant effect was found on cardiovascular events, mortality, diastolic blood pressure, or cholesterol levels. In the subgroup analyses, the trials with cardiovascular fitness interventions, trials with an intervention that lasted longer than 4 months, and interventions that used >3 behavior change techniques were more effective in reducing systolic blood pressure. We suggest that future high-quality RCTs investigating the effects of lifestyle interventions on preventing cardiovascular events, mortality, and modifiable risk factors should meet the following criteria: (1) complete description of all therapy related characteristics of the intervention (eg timing of the intervention, the intensity, the duration of the intervention, and the use of behavior change techniques) with the aim to improve replicability and comparability between studies. (2) the lifestyle intervention should preferably consist of > 8 contact moments, distributed over a treatment period of at least 4 months; (3) the lifestyle intervention should use > 3 behavior techniques; (4) the lifestyle intervention should include a guided cardiovascular fitness intervention with behavior change interventions, guidance on how to achieve and maintain an active lifestyle, in combination with guidance on medication adherence, smoking cessation, alcohol intake, and diet; (5) the use of a theoretical framework in developing lifestyle interventions.

In **chapter 3** we investigate the safety and feasibility of a post-stroke care program with an exercise intervention of 1 year, including a 8-weeks group exercise program and 3 times a 3-monthly follow-up after TIA or minor stroke. In the MotiveS & MoveIT trial 20 patients with a recent TIA or minor stroke without cardiac contraindications were randomly assigned to one of the two interventions; post-stroke care without exercise or post-stroke care with exercise. During this one-year post-stroke care program patients visited our outpatient clinic at 4 weeks, 3 months, 6 months and 9 months after the index event. The program consisted of a stepwise approach to lower blood pressure and LDL-cholesterol (LDL-c) levels with pharmacological therapy and an on motivational interviewing based counselling strategy. This counselling strategy aimed to motivate patients to attain a healthy and active lifestyle and optimize medication adherence. Patients in the intervention group participated in an 8-week exercise program. During this period patients had three one-hour exercise sessions a week supervised by two specialized physiotherapists. These sessions consisted of aerobic exercise and strength training. The exercise intensity was based on the maximal heart rate and the maximal power achieved during the maximal exercise test. During the program the exercise intensity was gradually increased. After the exercise program, patients were seen by a physiotherapist every 3 months in the outpatient-clinic to motivate them to maintain an active lifestyle. Patients were evaluated at baseline, 6 and 12 months. Eighteen patients completed the intervention. In none of the patients cardiopulmonary contraindications for the maximal exercise test and exercise program were found. No cardiovascular events occurred during the maximal exercise tests and exercise program. After one year, significantly more patients in the post-stroke care with exercise group achieved the composite endpoint of optimal medical therapy. We concluded that post-stroke care, including an exercise program, is safe and feasible in the acute phase after minor stroke or TIA and might be a way to increase effectiveness of secondary stroke prevention.

In **chapter 4**, we describe the rationale and design of the MoveIT trial, a randomized controlled trial of an exercise intervention after a TIA or minor stroke to prevent cognitive decline. In the MoveIT trial 120 adult patients with a TIA or minor stroke less than 1 month ago were randomly allocated to an exercise intervention consisting of a 12-week aerobic exercise program and regular follow-up visits to a specialized physiotherapist during the period of 1 year or to usual care. The primary goal of the MoveIT trial was to investigate the effect of an exercise intervention on cognition in patients after a TIA or minor stroke, compared with participation in usual care. The primary outcome was cognitive functioning measured with the Montreal Cognitive Assessment (MoCA) at 1 year. Secondary outcomes included neuropsychological tests, maximal exercise capacity, self-reported physical activity and measures of secondary prevention. Outcome measures were assessed at baseline, and at the 1-year and 2-year follow-up.

In **chapter 5,** we investigate the cardiorespiratory fitness in patients with a recent TIA or minor stroke and explored which determinants are associated with a lower fitness, using data from the baseline assessment of the MoveIT-study. Although it is clear that cardiorespiratory fitness is reduced in patients with stroke, it remains unclear whether it is also reduced in patients with TIA or minor stroke. In 113 patients with a recent TIA or minor ischemic stroke the peak oxygen consumption (VO2peak) was determined in a symptom-limited ramp exercise test. Physical activity level, vascular risk factors, history of vascular or pulmonary disease, and stroke characteristics were recorded at inclusion and related to the VO2peak. Mean VO2peak was 22 mL/kg/min, which is the fifth percentile of age- and sex-related normative values. Increasing age and female sex were associated with a lower VO2peak. Age- and sex-adjusted linear regression analyses showed that a history of cardiovascular disease and pulmonary disease was associated with a lower

VO2peak. In addition, a lower level of physical activity, hypertension, smoking, and overweight were associated with a lower VO2peak. History of stroke and stroke characteristics were not related to VO2peak. Our findings suggest that premorbid cardiovascular and pulmonary disease and vascular risk factors, but not necessarily TIA- or stroke-related factors, contribute to a reduced cardiorespiratory fitness.

In **chapter 6,** we describe the results of the MoveIT trial itself, a single-center, observer-blinded, randomized controlled trial to investigate the effect of an exercise intervention on global cognition. The intervention group of this trial participated in a 1-year exercise intervention consisting of a 12-week group exercise program, combined with three counselling visits to the physiotherapists over a 9-month period. The control group received standard care. The primary outcome was global cognitive functioning, assessed at one year, using the Montreal Cognitive Assessment (MoCA). Secondary outcomes included cardiorespiratory fitness, the cardiovascular profile, and attainment of secondary prevention targets, anxiety, depression and fatigue at one and two years. The experimental group consisted of 60 patients, while the control group consisted of 59 patients. The mean age was 64.3 years and 41% of patients were female. No between-group differences were found on global cognitive functioning or on secondary outcome measures at 1 and 2 years. The only significant between-group difference was found for fatigue, in favor of the experimental group, at 1 year. The neutral effect on cardiorespiratory fitness suggests that the effect of physical exercise training at this intensity was not sustained, probably due to the fact that the interval between the intervention and the time of MoCA assessment was too long. This may mean that a possible intervention effect on cognition and cardiorespiratory fitness in our trial may have disappeared due to an unsuccessful attempt to change patients' lifestyle during the intervention period from 1 year after the TIA or stroke. Future studies need to focus on optimizing rehabilitation strategies for this vulnerable group of patients.

In **chapter 7**, we describe the in-depth analysis of the MoveIT trial, in which we investigated the effect of an exercise intervention on cognitive functioning, compared with usual care, for up to 2 years. Cognition was measured with neuropsychological tests on three domains: 1) executive functioning, 2) attention-psychomotor speed and 3) memory. Linear mixed models were used for longitudinal data to determine the effect of the exercise intervention on cognitive functioning. We found that over the two years study period – and corrected for age, sex, and educational level – the intervention group on average improved significantly more in executive functioning than the control group. No significant intervention effects were found on either memory or attention-psychomotor speed. Our data suggest that a 1-year exercise intervention had a small, significant effect on executive functioning over time, compared to usual care. Based on our finding that an exercise program was able to improve executive functioning, we suggest that health care professionals could also recommend exercise to patients after a TIA or minor stroke to improve cognitive functioning. Since it is thought that stroke might affect executive functioning in particular, this type of intervention seems suitable. In addition, physical exercise has numerous other positive effects, such as less fatigue, a reduced risk of cardiovascular disease in general and a reduced risk of recurrent TIA or stroke, and death, with the advantage that it is inexpensive and has far fewer side effects than medication.

In **chapter 8,** we describe a cross-sectional association study to determine the association between poststroke fatigue and cardiorespiratory fitness in the 119 TIA and minor stroke patients included in the MoveIT trial, to find out whether this association was distorted by confounders. Poststroke fatigue was measured by the Fatigue Severity Scale (FSS) and cardiorespiratory fitness was quantified by maximal exercise capacity ($\dot{V}O_2$max). The FSS showed a significant association with $\dot{V}O_2$max, this association was confounded by anxiety and depression as measured by the subscales of the Hospital Anxiety and Depression Scale (HADS). After controlling for HADS scores on depression and anxiety, the univariate relationship between $\dot{V}O_2$max and FSS was no longer significant. These results suggest that the association between poststroke fatigue and cardiorespiratory fitness in patients with TIA or minor stroke is weak and significantly confounded by the factors of depression and anxiety. This study shows the importance of measuring depression and anxiety together with poststroke fatigue in patients with TIA and minor stroke to ensure that subtle impairments are detected and can be treated. This result also provides an indication that future randomized controlled trials and treatments should focus not only on improving poststroke fatigue and cardiorespiratory fitness, but also target depression and anxiety in patients with TIA and minor and major stroke.

In **chapter 9**, the main results of this thesis are discussed and recommendations for future research are given. The first part of the discussion focuses on the effect of lifestyle interventions to prevent cardiovascular events after TIA or stroke. Despite the recommendations in the recent American Heart Association (AHA)/American Stroke Association (ASA) guideline, a secondary prevention program is not an integral part of the care of patients with TIA or stroke in the Netherlands. Although it is possible that a program such as cardiac rehabilitation for secondary prevention, which is successful in patients with coronary heart disease, may also be effective in patients with TIA or stroke, more research is needed to investigate how to use a program such as cardiac rehabilitation in patients with TIA or stroke. There are three elements of cardiac rehabilitation that also can be used in patients with TIA or stroke. The first element is the multidisciplinary team that guides the rehabilitation, which should include neurologists, physiotherapists, nurse practitioners, rehabilitation physicians, general practitioners, psychologists and dieticians for patients with TIA or stroke. The second component of cardiac rehabilitation that could be used is detailed patient assessment, including assessment of co-morbidities, use of patient-reported outcome measures (PROMs) to measure fatigue, depression and anxiety, and identification of behavioral, medical, and non-modifiable risk factors. The third element is an early assessment of the patient's individual needs and prognosis, which is used to set personalized goals that are reviewed regularly.

The second part of the discussion is about the interaction of physical activity and exercise and its impact on fatigue, cognitive impairment, depression and anxiety after TIA or minor stroke in tertiary prevention. Management of physical (in)activity and exercise is important because patients with stroke are especially at risk for sedentary and prolonged sitting behaviors, and they should be encouraged to perform physical activity in a supervised and safe manner. Although we did not find a positive effect of our MoveIT intervention on our secondary outcome cardiorespiratory fitness, we did find that cardiorespiratory fitness was poor in patients in both the MoveIT and MotiveS & MoveIT studies. When cardiorespiratory fitness levels are low, physical activities may be either limited by fatigue or impossible to perform. Levels of cardiorespiratory fitness below those required to perform ADL may mean that ADL become impossible and this can lead to loss of independence. There is lack of knowledge about how and where to exercise and about the potential benefits of exercise in TIA and minor stroke. Despite the benefits described in systematic reviews and recommendations in guidelines, this lack of knowledge is possibly the reason why exercise interventions are not yet widely embedded into stroke care. With the results from the MoveIT trial, we think in future research, poststroke fatigue, cognitive impairment, depression, anxiety, physical activity and cardiorespiratory fitness are important factors to measure, in order to investigate how they interact and how this affects the improvement in modifiable risk factors in patient with TIA, minor and major stroke. If this interaction is clear, this knowledge, combined with the known barriers and facilitators of patients' favorable health behaviors, may help to develop and investigate the effectiveness of a personalized lifestyle intervention in a RCT to improve secondary and tertiary prevention in patients with TIA or minor stroke. Furthermore, although it remains unclear how poststroke fatigue, cognitive impairment, depression and anxiety influence each other, health care providers could measure these four determinants in patients with

TIA or stroke to ensure that subtle impairments are detected and can be treated. If these symptoms are not recognized, they are likely to result in a reduced effect of interventions, quality of life, influence patients' return to work and social activities and may affect behavior related to future stoke prevention. In conclusion, there is an urgent need in current stroke care to measure poststroke fatigue, cognitive impairment, depression, and anxiety, as well as to measure, stimulate and monitor physical activity and cardiorespiratory fitness in both patients with TIA and stroke.