SUMMARY
Vascular disease is a major health problem worldwide. Over the last decade the mortality associated with vascular disease had decreased. However, this has resulted in an increase in long-term morbidity such as cognitive impairment and dementia. The spectrum of cognitive deficits associated with vascular disease or vascular risk factors has recently been termed vascular cognitive impairment. In Chapter 1 an introduction to the pathophysiology, symptoms and treatment of vascular cognitive impairment is given.

With the expected increase in dementia prevalence, the prevention of cognitive decline and dementia is currently receiving much attention. In the general population, evidence suggests that higher levels of physical activity and maintaining physical fitness prevent cognitive decline and dementia. In patients with vascular disease, physical activity and exercise could therefore potentially have benefits on both the risk of vascular events and cognitive decline. The aim of this thesis was to investigate the effects of physical activity and exercise on secondary prevention and cognition in patients with vascular disease and to gain further insight into the mechanisms that mediate these effects.

Part I: Physical activity and fitness
In the first part of the thesis we investigated the association of physical activity and physical fitness with secondary prevention, cognition and different markers of vascular and brain aging. The amount of physical activity was assessed using questionnaires. We used cardiorespiratory fitness, which is the ability to engage in physical activities that rely on oxygen consumption as the primary source of energy, as the measure of physical fitness. In Chapter 2, we observed that in a cohort of almost 10,000 patients with vascular disease or vascular risk factors, higher levels of physical activity were associated with strongly reduced risk of new vascular events and all-cause mortality. We were particularly interested in this relation among patients with a history of stroke, as evidence is currently lacking. We found that a higher level of physical activity similarly reduced the risk of vascular events and all-cause mortality in patients with cerebrovascular disease, patients with coronary artery disease and across the other disease groups.

In the next two chapters, we investigated the associations of physical activity and fitness with cognition and brain structure in patients with vascular disease. In Chapter 3, we investigated the cross-sectional and prospective associations between physical activity and cognitive performance and measures of small vessel disease in a large cohort of patients with vascular disease. We observed that higher levels of physical activity did not have benefits on cognitive performance at baseline or on change in cognitive performance at follow-up. At baseline, a higher level of physical activity was associated with larger total brain volume, but not with other measures of small vessel disease. There were no associations between physical activity and a change in brain measures over time. In Chapter 4, we examined the association between cardiorespiratory fitness, cognition and brain structure in a small
Chapter 10

cohort of patients with a recent TIA or minor ischemic stroke. We observed that a higher level of cardiorespiratory fitness was associated with better cognitive performance, greater grey matter volume and greater integrity of the white matter. Grey matter volume partially mediated the association between fitness and memory performance. In contrary to cardiorespiratory fitness, physical activity was not associated with cognitive performance.

In Chapter 5, we examined the independent association of physical activity with characteristics of the carotid artery wall in patients with vascular disease or vascular risk factors. We showed that a higher level of leisure-time physical activity was associated with a lower risk of carotid artery stenosis and lower end-diastolic lumen diameter of the carotid artery. In addition, we found that patients with a light level of physical activity had a lower carotid stiffness than patients with no physical activity. Physical activity was inversely associated with common carotid intima media thickness only in patients with vascular disease, but not in patients with vascular risk factors. These results suggested that physical activity is important for vascular health, also in patients with vascular disease.

Part II: Physical exercise into practice

In the second part we described our practical experience with and preliminary findings of a trial investigating the effects of a physical exercise program on cognition in patients with a recent TIA or minor ischemic stroke. In Chapter 6, we described a pilot study of a randomised controlled trial that investigated the safety and feasibility of post-stroke care including an aerobic exercise program in patients with a recent TIA or minor ischemic stroke. Our results showed that this program was safe and feasible. We also found that a significant larger proportion of patients in the post-stroke care with exercise group reached the composite endpoint of optimal therapy, defined as the combination of prescribed antithrombotic therapy and achievement of both blood pressure (< 140/90 mmHg) and LDL-cholesterol (< 100 mg/dL) targets, in comparison with the post-stroke care without exercise group. The effect on achievement of LDL-cholesterol targets explained the difference for the greatest part. Chapter 7 covers the rationale, background and design of the MoveIT study, a two parallel group, single-centre, single-blinded, randomised controlled trial to investigate the effects of an aerobic exercise program on cognition in patients in the acute phase after TIA or minor ischemic stroke. In this study, we aimed to investigate the effects of a 12-week exercise program on cognition compared to usual care in 120 patients. In Chapter 8, we showed that patients with a recent TIA and minor
ischemic stroke have a poor cardiorespiratory fitness. In 88% of the participants the level of fitness was very poor, less than 20\(^{th}\) percentile of age and sex-related normative values. In the general population, values lower than the 20\(^{th}\) percentile of age and sex are associated with increased all-cause mortality. The main determinants of cardiorespiratory fitness were premorbid cardiovascular and pulmonary disease and vascular risk factors, but not stroke-related factors. This finding highlighted the importance of improving fitness not only in patients with a disabling stroke, but also in patients with a TIA or minor stroke.

In Chapter 9, the main findings of this thesis were discussed in broader context. The evidence for benefits of physical activity and fitness on secondary prevention, cognition and vascular and brain aging in patients with vascular disease were reviewed. Evidence suggests that physical activity and fitness have a strong benefit on the risk of vascular events, mortality and vascular aging in patients with vascular disease. Physical activity measured using questionnaires has a less consistent association with cognitive performance and brain aging. Questionnaires measure physical activity subjectively and this measure has a higher risk of misclassification due to recall bias and social desirability. Fitness, which is measured objectively and is principally determined by physical activity, may be a more reliable test to examine habitual exercise than self-reported physical activity.

In the second part, we reviewed studies investigating the effects of physical exercise programs on secondary prevention and cognition in TIA or stroke. Small randomised controlled trials have reported effects on vascular risk factors, vascular risk score and cognitive performance after an aerobic exercise program. Results of larger ongoing studies in TIA or minor ischemic stroke patients will hopefully provide more evidence for the effects on secondary prevention and cognition.

In the future, cohort studies using physical activity as determinant or outcome and randomised controlled trials using physical activity as outcome should consider the use of accelerometers to measure physical activity, because accelerometers provide a more objective measure of physical activity than questionnaires and are less costly and complex than the measurement of cardiorespiratory fitness. Future, randomised controlled trials investigating the benefits of physical exercise programs in patients with a TIA or stroke should consider the need of a supervised exercise test prior to starting an exercise program and should also include patients with a TIA as their physical fitness is also poor. Larger trials are needed to provide more evidence for the benefits of physical exercise programs on secondary prevention and cognition.