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General discussion
The general objective of this thesis was to explore the effects of physical activity, fitness and exercise on secondary prevention and cognition in patients with vascular disease and to gain further insight through which mechanisms these possible effects are mediated. In this chapter, the main findings of the studies in this thesis and its implications and future directions for further research are discussed. In the first part, the evidence for benefits of physical activity and fitness on secondary prevention, cognition and vascular and brain aging in patients with vascular disease is reviewed. In the second part, our practical experience of and preliminary findings of physical exercise programs in patients with a recent TIA or minor stroke is reviewed. Moreover, the results of completed studies and ongoing studies investigating the effects of physical exercise programs on secondary prevention and cognition in TIA or stroke are discussed. Finally, future perspectives for studies investigating benefits of physical activity and physical exercise programs in patients with TIA or stroke are discussed.

**PHYSICAL ACTIVITY AND FITNESS**

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure. (WHO website) A range of methods can be used to assess physical activity, including subjective measures such as questionnaires, systematic observation and more objective measures such as accelerometers. Each method has its own strengths and limitations. Questionnaires are an inexpensive tool and easily applicable to larger study populations. However, the results can be biased by the recall of patients and social desirability. Accelerometers supply a more objective measure of physical activity, although not every type of physical activity is adequately measured and participants can be tempted to temporally increase the amount of physical activity, especially during short acquisition periods.

Physical fitness is defined as a set of attributes that people have or achieve and relates to the ability to perform physical activity. Cardiorespiratory fitness (CRF), muscular strength, muscular endurance, flexibility and body composition are considered the five most important components of health related fitness and have a strong relationship with good health. In this chapter we will use CRF as the marker of physical fitness. CRF is defined as the ability to engage in physical activities that rely on oxygen consumption as the primary source of energy and is best indicated by the maximal oxygen consumption measured in a maximal exercise test. In patients with vascular or pulmonary disease, the criteria of the VO2max are usually not reached and therefore the VO2peak, the peak oxygen consumption, is commonly used to describe the CRF in this population.
Secondary prevention
In healthy people and in patients with coronary artery disease (CAD), a higher level of physical activity is associated with a lower risk of vascular events and mortality. Evidence for patients with other manifestations of vascular disease is currently lacking. In the SMART study, a prospective cohort study of patients with various manifestations of vascular disease, such as CAD, cerebrovascular disease, peripheral artery disease (PAD) or an aneurysm of the abdominal aorta (AAA), or vascular risk factors, we found that a light to moderate level of physical activity was already associated with a reduced risk of vascular events and mortality (Chapter 2). In addition, the risk reductions associated with physical activity were similar across all disease groups including patients with cerebrovascular disease. Moreover, in patients with multiple manifestations of vascular disease, a patient population at a particularly high risk of recurrent vascular events and mortality, physical activity had similar benefits. These results indicate that even in patients with severe vascular disease, the effects of physical activity are not overruled by the presence of other vascular risk factors. Therefore, all patients with vascular disease should be encouraged to perform regular physical activity.

In primary prevention, CRF is associated with a lower mortality and lower risk of vascular events. In patients with vascular disease less evidence exists. Prior to an elective operation for AAA, a lower CRF was associated with a higher mortality. These same associations have been observed in patients with CAD and PAD.

Evidence suggests that CRF is a stronger predictor of mortality and vascular events than physical activity and that CRF is possibly a better marker of habitual physical activity than physical activity assessed with questionnaires. Physical activity is the principal determinant of CRF, although there is a genetic component. A possible explanation for this stronger association is that the CRF is measured objectively and physical activity is often assessed by self-report, which inevitably leads to misclassification.

Cognition
In healthy people, physical activity has been associated with a decreased risk for dementia and cognitive decline. The population attributable risk of Alzheimer dementia for physical inactivity was estimated at 13%, which means that nearly 4.3 million of cases worldwide are potentially attributable to physical inactivity. Patients with vascular disease or vascular risk factors are at a higher risk of cognitive decline and dementia. In Chapter 3, we investigated the association between self-reported physical activity and cognition and cognitive decline in patients with vascular disease. In contrast to another study in women with vascular disease or multiple vascular risk factors, we found no association between physical activity and cognition at baseline and cognitive decline. A possible explanation for our findings could be that in comparison with other studies, our study included participants who were relatively young and had relatively intact cognitive functioning.
Maintaining CRF may also prevent cognitive decline. In patients with CAD, a higher CRF was associated with better executive functioning. In Chapter 4, we investigated the association of CRF and self-reported physical activity with cognitive performance in 84 patients with a recent TIA or minor ischemic stroke. Interestingly, a higher CRF, but not a higher level of physical activity was associated with a better cognitive performance. One other study in healthy older adults showed similar findings. As we described earlier for secondary prevention, CRF may also be a more reliable test to evaluate the association between cognition and habitual exercise than self-reported physical activity. This may also be an explanation for the absence of an association with physical activity in studies using questionnaires, as the risk of misclassification is higher.

Vascular and brain aging

Characteristics of the carotid artery wall such as carotid intima media thickness (CIMT), carotid artery stenosis (CAS), end-diastolic lumen diameter and stiffness are markers of vascular aging. In the general population, most studies found associations of a higher level of physical activity or a higher CRF with a lower carotid or aortic stiffness, lower CIMT, and less progression of CIMT. In Chapter 5, we investigated the independent associations of physical activity with characteristics of the carotid artery wall in the SMART cohort of patients with vascular disease or risk factors. We observed that a higher level of leisure-time physical activity was associated with a lower risk of CAS 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 CIMT only in patients with vascular disease, but not in patients with vascular risk factors. These results suggest that in patients with vascular disease the benefits of physical activity on the carotid artery wall are stronger than in patients with vascular risk factors. A similar result has been reported on the association of CRF with CIMT. Our results suggest that physical activity is important for vascular health directly and also through vascular risk factors and therefore support recommendations to increase physical activity, especially in patients with vascular disease.

Brain volume and white matter hyperintensity (WMH) volumes are markers of brain aging. In the general population, benefits of physical activity and CRF have been observed on total brain and grey matter volume. Associations with vascular brain lesions, such as WMH, have shown conflicting results. In Chapter 3, we found that in patients with vascular disease a higher level of physical activity was related to a larger total brain volume, but not to WMH volume. In Chapter 4, we found that in patients with a recent TIA or minor ischemic stroke a higher CRF was associated with greater grey matter volume and greater integrity of the white matter. One other study in patients with small vessel disease found an association between physical activity and WMH volume and white matter integrity. These cross-sectional results suggest that physical activity and maintaining a
higher level of fitness may be beneficial for structural brain changes, but a causal relation cannot be determined.

In Chapter 3, we observed no associations of physical activity with change in brain structures over time. However, a recent study using an accelerometer to measure physical activity found that a 5-year white matter and grey matter change was associated with less physical activity at follow-up. The results in Chapter 3 could indicate that physical activity measured with a questionnaire is not sensitive enough to detect subtle associations or that physical activity is not protective in patients with vascular disease as other risk factors for brain changes overrule the effect of physical activity.

PHYSICAL EXERCISE IN TIA OR STROKE

Patients with a TIA or stroke are at risk for recurrent vascular events and carry a higher risk for cognitive impairment and dementia. The risk of recurrence is particularly high early after the event. The long-term annual risk of myocardial infarction and non-stroke vascular death is a stable 2% per year, a percentage that is usually considered a high absolute cardiovascular risk. After stroke, dementia develops in 10% of patients and cognitive impairment occurs in up to 20–90% of patients, depending on the used criteria. Cognitive impairment is not limited to patients with a major stroke, but may also occur in patients after TIA or minor stroke. Increasing CRF and physical activity with an exercise program may both reduce the risk of recurrent vascular events and reduce the risk of cognitive impairment. In patients after CAD, a cardiac rehabilitation program that also includes aerobic exercise is associated with a significant reduction in mortality. In healthy elderly individuals, there is evidence that a physical exercise program is associated with an improvement in cognitive performance, although a recent Cochrane review failed to confirm these findings. A physical exercise program has not been implemented for patients with a TIA or minor stroke as yet.

In Chapter 6, we describe a pilot study of a randomised controlled trial (RCT) initiated in 2010 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. The main conclusions were that this program was safe and feasible. We also observed 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.

In patients with a disabling stroke, CRF is reduced, both in the subacute and the chronic phase after stroke. In Chapter 8, we report the CRF of patients after a recent TIA and
minor ischemic stroke. In these patients, the mean VO2peak was 22 ml/kg/min, which is the 5th percentile of age and sex related normative values. These values may have clinical impact as 12% had a value less than 15 ml/kg/min, the accepted minimal value necessary for independent living. In addition, values below 21 ml/kg/min have been associated with an increased mortality among patients with CAD and in the general population, values lower than the 20th percentile of age and sex are also associated with increased all-cause mortality. The main determinants of this poor CRF were premorbid cardiovascular and pulmonary disease and vascular risk factors, but not stroke-related factors. The poor CRF in patients with TIA or minor stroke indicate that it is important to improve CRF not only in patients with a disabling stroke, but also in patients with a TIA or minor stroke. Therefore, trials investigating physical exercise programs should also include patients with TIA or minor stroke.

Secondary prevention

Until now, only small RCTs have been performed that investigated the effect of an exercise program on secondary prevention. One small RCT in 70 patients with a recent minor stroke found a lower risk of recurrent vascular events after a lifestyle intervention of 24 weeks including an exercise program compared to the control group; there were 12 vascular events in the control group versus 1 in the intervention group. However, due to the small sample size, unbalanced groups as explanation for this result cannot be excluded. Other RCTs looked at cardiovascular disease risk score, markers of vascular aging or cardiovascular risk factors, because these studies were not large enough to investigate the effect of physical exercise on mortality and vascular events. Most RCTs found an improvement in cardiovascular risk score after an exercise program and one RCT found a decrease in carotid stiffness after an exercise program. A recent Cochrane review also examined the evidence for cardiovascular risk factor modification of exercise programs in patients with a stroke and found no effect on blood pressure and BMI, and only benefits on glucose metabolism and triglycerides in one RCT. However, this Cochrane review excluded studies with patients with TIA or studies with other interventions than an exercise program.

In our pilot RCT of 20 patients with a recent TIA or minor ischemic stroke, we found an effect on LDL-cholesterol levels, but not on blood pressure or BMI (Chapter 6). In line with our findings, RCTs including patients with a recent TIA or stroke generally found benefits on cholesterol levels, but not on BMI. Findings on blood pressure have been conflicting, three RCTs did not find an effect, whereas two other RCTs did find an effect on systolic or diastolic blood pressure. A recent meta-analysis of lifestyle interventions after TIA or stroke found a significant reduction in systolic blood pressure after cardiovascular fitness intervention and a combined intervention. Three larger RCTs with more than 200 patients are currently being conducted (NCT00536562). These trials will include patients with a TIA or minor stroke and have
a cardiovascular disease risk score or vascular risk factors as primary outcome measure. These trials will hopefully provide more evidence for the effects of exercise programs on secondary prevention in TIA and stroke.

**Cognition**

Only a few small RCTs investigating the effect of aerobic exercise on cognition have been completed and published and all have been performed in patients with chronic stroke.\(^{68-70}\) A recent Cochrane review reported that currently no conclusions about the effect of fitness training interventions on cognitive function in TIA or stroke can be drawn.\(^{62}\) Three small RCTs not included in the Cochrane review due to co-interventions or later publication date found benefits on global cognition,\(^{70}\) executive functioning\(^{68}\) and motor learning\(^{69}\) after an exercise program.

Three trials examined the possible mechanisms for benefits on cognition by measuring cerebral perfusion and upregulation of neuroprotective, neurotrophic factors.\(^{70-72}\) An improvement of cerebral blood flow measured with vasomotor reactivity\(^{71}\) and an increase in medial temporal lobe tissue blood flow was found after an exercise program,\(^{70}\) although the reported increase in the last study was not significantly different between the exercise and control group.\(^{70}\) Effects on neuroprotective, neurotrophic factors such as brain-derived neurotrophic factor (BDNF) have only been investigated in one non-randomised trial in patients with stroke, which found an increase in BDNF after an exercise program compared to the control group.\(^{72}\)

In conclusion, as only a few small RCTs have been conducted, there is currently insufficient evidence for the possible benefits of physical exercise programs on cognition and brain structure. Two larger RCTs with cognition as primary outcome measure (Chapter 7, NCT01916486) are currently being conducted. In Chapter 7 we describe the study protocol of the MoveIT study. In this study of 120 patients with a recent TIA or minor ischemic stroke, we will investigate the effects of a 12-week exercise program on cognition compared to usual care. The other ongoing RCT will investigate the efficacy of aerobic exercise training or a complex mental and social activities program for improving cognitive function in older adults with chronic stroke, compared with a program with stretch and relaxation techniques (control group) (NCT01916486). In addition, several ongoing, larger RCTs, which have disability, functional capacity, vascular risk factors or feasibility as primary outcome also have cognition as a secondary outcome measure.\(^{66,73,74}\) (NCT02272426, NCT00536562)
FUTURE PERSPECTIVES
Measurement of physical activity

In Chapter 3 we observed no association between self-reported physical activity and cognition and in Chapter 4 we did find an association between CRF and cognitive performance, but not with physical activity assessed with a questionnaire. Questionnaires measure physical activity subjectively and this measure has a higher risk of misclassification due to recall bias and social desirability. This could be a possible explanation for the inconsistent results regarding the association between physical activity and cognition, but also a possible explanation for a negative results in trials that use the amount of physical activity as outcome. The CRF, which is principally determined by physical activity, may be a more reliable test to examine habitual exercise than self-reported physical activity. However, CRF is not only determined by physical activity, but also by genetic factors and underlying health status and the cost and complexity of CRF measurements make it less suitable for larger cohort studies.

Motion sensors such as accelerometers can measure body motion and are a more objective measure of physical activity than questionnaires and less costly and complex than CRF. In addition, accelerometers can also objectively measure sedentary time. In the general population and in patients with vascular disease, sedentary time is a risk factor for vascular events and mortality, independent of the amount of physical activity. In addition, in studies using physical activity levels assessed with questionnaires, high levels of moderate intensity physical activity seemed to eliminate the increased mortality risk associated with prolonged sedentary time.

The estimate of physical activity and sedentary time measured with questionnaires and accelerometers has been compared. Questionnaires overestimated time in moderate to vigorous intensity physical activity and underestimated sedentary time in comparison to accelerometers. In addition, questionnaires did not always correctly classify inactive people, and showed a low agreement with the accelerometer derived physical activity. Relationships between sedentary time and moderate to vigorous intensity physical activity, and vascular risk factors, that are found with accelerometers, are not always revealed when using questionnaires. Questionnaires may underestimate the strength of some relationships.

Therefore, future cohort studies using physical activity as determinant or outcome and RCTs using physical activity as outcome should consider the use of accelerometers to measure physical activity. Larger cohort studies are beginning to use accelerometers to...
measure physical activity\textsuperscript{82} and data on the associations between objective physical activity and vascular events and mortality are now starting to emerge.\textsuperscript{83} As accelerometers provide an objective measure of physical activity intensity and sedentary time, these data can be used to determine the independent risk associated with prolonged sedentary time and the intensity and volume of physical activity required for risk reduction. These data can be used to improve the recommendations that health care providers can give patients concerning physical activity. In addition, future cohort studies should also examine this in different patient populations to investigate whether these recommendations can be applied generally or tailored recommendations should be offered, for example to patients with TIA or stroke.

Accelerometers have also been used to assess the associations between cognition and physical activity and these studies found a consistent benefit on cognition,\textsuperscript{18,84,85} whereas the studies using questionnaires have found conflicting results (Chapter 3).\textsuperscript{23,86,87} In future studies, associations between physical activity measured with accelerometers and questionnaires, and cognitive performance should be compared to elucidate whether conflicting results are caused by the used method to assess physical activity or whether the associations differ depending on the study population.

Exercise and secondary prevention after TIA and stroke

Circumstantial evidence supports the benefits of physical activity and exercise in patients after a TIA or stroke. Physical activity has similar benefits on mortality and vascular events in patients with cerebrovascular disease as in patients with CAD (Chapter 2). In patients with a TIA or stroke, one small study investigating a lifestyle program including aerobic exercise found a lower risk of recurrent events and most studies found effects on vascular risk factors.\textsuperscript{57} However, traditional risk factors do not explain the whole benefit of physical exercise on secondary prevention (Chapter 2). Physical activity also has direct effects on the artery wall (Chapter 5). In future studies it is therefore recommended to also assess markers of vascular aging, because traditional vascular risk factors do not describe the whole health benefit.

Future RCTs should consider several aspects. We found a prevalence of CAD in 18\% of our study population of patients with a recent TIA or minor ischemic stroke (Chapter 8), this finding confirms previous studies reporting a high prevalence of CAD.\textsuperscript{88} Therefore, these patients should be regarded as a high-risk population and future studies should consider the need of a supervised exercise test prior to starting an exercise program. Secondly, patients with a TIA should also be included in studies investigating exercise interventions, as they also have a poor cardiorespiratory fitness (Chapter 8). Thirdly, it is important to start with this intervention as early as possible, as there is evidence that those who start earlier demonstrate greater improvement and patients who started the program later had poorer attendance.\textsuperscript{89,90} Finally, larger trials in patients with TIA or stroke
are needed to examine the benefits of exercise programs and hopefully they provide the evidence for the implementation of an exercise program for patients with a TIA or stroke worldwide, following the standardized incorporation of exercise in a cardiac rehabilitation in CAD patients.

**Exercise and cognition after TIA and stroke**

Although there is substantial evidence linking more physical activity and higher CRF to less cognitive impairment and dementia, the benefits of an exercise program on cognition in the healthy population have not been proven.\(^5\) In patients with TIA or stroke, a population at risk for cognitive decline and dementia, an exercise program might have more profound benefits as the amount of physical activity is generally reduced and CRF is poor (Chapter 8). The results of small, randomised trials are promising.\(^6\)-\(^7\) The results of larger RCTs such as the MoveIT trial will hopefully provide more direction.
Chapter 9

REFERENCES


General discussion


General discussion


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Summary
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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
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 20th percentile of age and sex-related normative values. In the general population, values lower than the 20th 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.
Nederlandse samenvatting
NEDERLANDSE SAMENVATTING


Vanwege de verwachte toename van dementie krijgt de preventie van cognitieve achteruitgang en dementie op dit moment veel aandacht. Onderzoeksresultaten afkomstig uit de algemene bevolking suggereren dat meer fysieke activiteit en het handhaven van de fysieke conditie cognitieve achteruitgang en dementie kunnen voorkomen. Fysieke activiteit en training zouden daarom patiënten met hart- en vaatziekten kunnen beschermen tegen het risico op nieuwe vasculaire incidenten en tegen cognitieve achteruitgang. Het hoofdonderwerp van dit proefschrift is het effect van fysieke activiteit en training op het voorkomen van cognitieve achteruitgang en de kwaliteit van secundaire preventie bij patiënten met hart- en vaatziekten. Tevens willen we meer inzicht krijgen in de mechanismen die deze effecten mediëren.

Deel I: Fysieke activiteit en conditie

In het eerste deel van dit proefschrift hebben we de associatie van fysieke activiteit en conditie met secundaire preventie, cognitie en verschillende markers van vaat- en hersenveroudering onderzocht. De mate van fysieke activiteit werd gemeten met behulp van een vragenlijst. Als maat voor fysieke conditie hebben we cardiorespiratoire conditie gebruikt. Dit is het vermogen om deel te nemen aan fysieke activiteit waarbij gebruik wordt gemaakt van zuurstofconsumptie als belangrijkste bron van energie.

In hoofdstuk 2 vonden we dat in een cohort van bijna 10.000 patiënten met hart- en vaatziekten of vasculaire risicofactoren, meer fysieke activiteit was geassocieerd met een sterk verminderd risico op nieuwe vasculaire incidenten en overlijden. We waren voornamelijk geïnteresseerd in de resultaten van patiënten met een herseninfarct of hersenbloeding in de voorgeschiedenis, aangezien het bewijs voor deze groep patiënten momenteel ontbreekt. We vonden bij deze groep patiënten een vrijwel vergelijkbare verlaging van het risico op vasculaire incidenten en overlijden als bij patiënten met coronair hartziekten. Ditzelfde geldt ook voor patiënten met andere hart- en vaatziekten.

In de twee volgende hoofdstukken onderzochten we de associatie van fysieke activiteit en conditie met cognitie en hersenstructuur bij patiënten met hart- en vaatziekten. In hoofdstuk 3 keken we naar de cross-sectionele en prospectieve associatie tussen fysieke activiteit en cognitief functioneren enerzijds en MRI-markers van microvasculaire schade anderzijds. We deden dit in een groot cohort van patiënten met hart- en vaatziekten.
en vonden geen relatie tussen fysiologische activiteit en cognitief functioneren aan het begin van de studie en tussen fysiologische activiteit en verandering in cognitief functioneren bij follow-up. Meer fysiologische activiteit was geassocieerd met een groter hersenvolume aan het begin van de studie, maar niet met andere MRI-markers van microvasculaire schade. We vonden geen associatie tussen fysiologische activiteit en verandering in hersenvolume bij follow-up. In hoofdstuk 4 hebben we de associatie tussen cardiorespiratoire conditie, cognitie en structuur van de hersenen in een klein cohort van patiënten met een recente TIA of licht herseninfarct onderzocht. We vonden dat een betere cardiorespiratoire conditie geassocieerd was met beter cognitief functioneren, een groter volume van de grijze stof en betere integriteit van de witte stof. De relatie tussen conditie en geheugen werd gedeeltelijk gemediëerd door volume van de grijze stof. In tegenstelling tot cardiorespiratoire conditie was fysiologische activiteit niet geassocieerd met de mate van cognitief functioneren.

In hoofdstuk 5 onderzochten we de onafhankelijke associatie van fysiologische activiteit met karakteristieken van de carotiswand bij patiënten met hart- en vaatziekten of vasculaire risicofactoren. Intima media dikte, stenose graad, stijfheid en diastolische diameter zijn belangrijke maten van vasculaire gezondheid en toegenomen waarden zijn geassocieerd met een verhoogd risico op vasculaire incidenten en overlijden. We toonden aan dat meer fysiologische activiteit geassocieerd was met een lager risico op carotisstenose en lagere eind-diastolische lumen diameter van de carotiden. We vonden ook dat weinig fysiek actieve patiënten minder stijfheid van de carotiden hadden dan fysiek inactieve patiënten. In tegenstelling tot patiënten met alleen vasculaire risicofactoren, was bij patiënten met hart- en vaatziekten meer fysiologische activiteit geassocieerd met een lagere intima-media-dikte van de carotiden. Deze resultaten suggereren dat fysiologische activiteit belangrijk is voor vasculaire gezondheid, ook bij patiënten met hart- en vaatziekten.

**Deel II: Fysieke training in de praktijk**

In het tweede gedeelte van dit proefschrift beschrijven we onze eigen ervaring en voorlopige bevindingen van een studie, die de effecten van een trainingsprogramma op cognitief functioneren bij patiënten met een recente TIA of een licht herseninfarct onderzocht. In hoofdstuk 6 beschrijven we een pilotstudie van een gerandomiseerd, gecontroleerd onderzoek dat de veiligheid en haalbaarheid van een nazorgprogramma in combinatie met een aeroob trainingsprogramma bij patiënten met een recente TIA of licht herseninfarct onderzocht. Onze resultaten lieten zien dat het programma veilig en haalbaar was. Ook vonden we dat in vergelijking met de groep zonder trainingsprogramma, een significant groter deel van de patiënten in de nazorggroep met een trainingsprogramma het samengestelde eindpunt van optimale behandeling bereikte. Dit eindpunt was gedefinieerd als de combinatie van antitrombotische therapie en het behalen van bloeddruk (< 140/90 mmHg) en LDL-cholesterol (< 2,5 mmol/l) doelen. Het effect op het behalen van LDL-cholesterol doelen verklaarde het grootste gedeelte van
Nederlandse samenvatting

het gevonden verschil. **Hoofdstuk 7** beschrijft de onderbouwing, achtergrond en opzet van de MoveIT studie. Dit is een monocenter, éénzijdig geblindeerde, gerandomiseerde, gecontroleerde studie om de effecten van een aeroob trainingsprogramma op cognitie te onderzoeken bij patiënten in de acute fase na een TIA of licht herseninfarct. In deze studie willen we 120 patiënten inclueren om het effect van een 12-weken durend trainingsprogramma in vergelijking met gebruikelijke zorg te onderzoeken. In **hoofdstuk 8** hebben we aangetoond dat patiënten met een recente TIA of een licht herseninfarct een slechte cardiorespiratoire conditie hebben. In 88% van de deelnemers was de conditie slecht, minder dan het 20ste percentiel van leeftijd en geslacht-gerelateerde normatieve waarden. In de algemene bevolking zijn waarden lager dan het 20ste percentiel geassocieerd met een toegenomen risico op overlijden. De belangrijkste determinanten van cardiorespiratoire conditie waren premorbide hart- en vaatziekten, longaandoeningen en vasculaire risicofactoren, maar niet herseninfarct-gerelateerde factoren. Deze bevindingen laten het belang van het verbeteren van conditie zien, niet alleen bij patiënten met een herseninfarct, maar bij ook bij patiënten met een TIA of licht herseninfarct.

In **hoofdstuk 9** beschrijven we de belangrijkste bevindingen van dit proefschrift en plaatsen we deze in een breder kader. Het bewijs van de positieve effecten van fysieke activiteit en conditie op secundaire preventie, cognitie en vaat- en hersenveroudering bij patiënten met hart- en vaatziekten wordt besproken. Onderzoek suggereert dat fysieke activiteit en conditie het risico op vasculaire incidenten, overlijden en vaatveroudering in patiënten met hart- en vaatziekten sterk verminderd. Fysieke activiteit, gemeten met behulp van vragenlijsten, heeft een minder consistentie associatie met cognitief functioneren en hersenveroudering. Vragenlijsten meten fysieke activiteit subjectief en er is daardoor een groot risico op misclassificatie, o.a. door herinneringsbias en sociaal wenselijke antwoorden. Conditie wordt objectief gemeten en wordt voor het grootste gedeelte bepaald door fysieke activiteit. Het meten van conditie kan daarom een betrouwbaardere test zijn om gebruikelijke hoeveelheid fysieke activiteit te onderzoeken dan zelf-gerapporteerde fysieke activiteit.

In het tweede gedeelte bespraken we studies die de effecten van trainingsprogramma’s op secundaire preventie en cognitie bij patiënten met een TIA of herseninfarct hebben onderzocht. Kleine gerandomiseerde, gecontroleerde studies lieten effecten zien op vasculaire risicofactoren, vasculaire risicoscores en cognitief functioneren na een aeroob trainingsprogramma. De resultaten van grotere, lopende studies bij patiënten met een TIA of licht herseninfarct zullen hopelijk meer bewijs leveren voor de effecten op secundaire preventie en cognitie.

Toekomstige cohortstudies, die fysieke activiteit gebruiken als determinant of uitkomst, of gerandomiseerde, gecontroleerde studies die fysieke activiteit gebruiken als uitkomst, moeten overwegen accelerometers te gebruiken om de hoeveelheid fysieke
activiteit te meten. Accelerometers geven namelijk een meer objectieve maat van fysieke activiteit dan vragenlijsten en zijn minder kostbaar en complex dan het meten van de cardiorespiratoire conditie. Toekomstige, gerandomiseerde, gecontroleerde studies die de effecten van trainingsprogramma’s bij patiënten met een TIA of herseninfarct onderzoeken, moeten overwegen om een gesuperviseerde inspanningstest te doen voordat een trainingsprogramma wordt gestart, vooral vanwege de prevalentie van cardiale comorbiditeit. Ook zouden patiënten met een TIA geïncludeerd moeten worden aangezien hun conditie ook slecht is. Grotere studies zijn nodig om meer bewijs te kunnen leveren voor de effecten van trainingsprogramma’s op secundaire preventie en cognitie.
Acknowledgements
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SMART study

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CURRICULUM VITAE

Myrthe Boss was born on the 5th of June 1981 in Hoorn, the Netherlands. She attended secondary school at Christelijk Lyceum in Zeist from which she graduated in 1999 (cum laude). She studied Medicine at the University Utrecht (1999–2005).

After working a year as a resident Neurology not in training in the University Medical Center Utrecht, she started her residencies in Neurology at the Sint Lucas Andreas Hospital, Amsterdam (prof.dr. H.C. Weinstein). During her residency, she started her research on the effects of physical exercise on cognition after TIA and minor ischemic stroke in the Sint Lucas Andreas Hospital, supervised by dr. R.M. Van den Berg-Vos and prof. dr. H.C. Weinstein. From 2012 the research was extended to the University Medical Center Utrecht to investigate the effects of physical activity in a cohort of patients with vascular disease, supervised by prof. dr. L.J. Kappelle and dr. M.I. Geerlings. In February 2013, Myrthe finished her training as neurologist and she consecutively worked as a neurologist in the Alzheimer Center of the VU Medical Center, University Medical Center Utrecht and Maasstad Hospital, Roterdam. Since February 2017 she works in the Gelderse Vallei Hospital, Ede.

She is married to William Wiedeman Moyano with whom she has two daughters: Elisa (2013) and Anna (2016).
LIST OF PUBLICATIONS

This Thesis


Other Publications

Neurologische verschijnselen van een insulinoom

Vasculaire cognitieve beperking
H.M. Boss, R.M. van den Berg-Vos, P. Scheltens, H.C. Weinstein

Hoofdstuk 42 Cerebrovasculaire afwijkingen.
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Serum inflammatory mediators correlate with disease activity in electrical status epilepticus in sleep (ESES) syndrome.