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EXERCISE AS TREATMENT FOR DEPRESSION

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EXERCISE AS TREATMENT FOR DEPRESSION

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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ABSTRACT

Studies have reported that physical activity can be protective against developing depression and that exercise can be as effective as pharmacotherapy or psychotherapy in the treatment of depression. However less is known about the associations of sedentary behavior with depression, the optimal intensity of exercise for treating depression, especially in the long-term and whether prescribing exercise for depression will change the patterns of physical activity and sedentary behavior after the intervention is completed.

Data for this thesis derive from the Regassa study, a randomized controlled trial, which included three exercise groups at different intensity levels and a group that received Treatment As Usual (TAU). The participants were 18-67 years old with mild to moderate depression at baseline. The aim of Study I was to measure how physically active and sedentary people suffering from depression are and the association of physical activity and sedentary behavior with depression severity. Depression severity was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS). Accelerometer data was collected at baseline to assess physical activity and sedentary behavior (N=165). The aim of Study II was to determine the post- treatment (12 weeks) effect of three different exercise intensity groups (light, moderate and vigorous) on depression severity (MADRS) and compare with TAU (N=620). Study III used accelerometer data to determine whether the three exercise groups (N=68) had changed their physical activity and sedentary behavior patterns following the completion of the intervention. Study IV compared long-term effects (12 months) of the three exercise groups and TAU (N=620) on depression severity (MADRS).

The results showed that in this sample of depressed adults a large proportion of time was spent in sedentary pursuits and depression severity was associated with Light Physical Activity (LIPA) and number of sedentary bouts (Study I). Exercise, whether performed at light, moderate or vigorous intensity, was at least comparable with TAU, both in the short term (Study II) and long-term (Study IV) in reducing depression severity. Light intensity exercise was shown to have lower depression severity than TAU, both in the short (Study II) and long-term (Study IV). All exercise groups reduced sedentary and LIPA time though non-significantly following the conclusion of the intervention, but some detrimental effects were seen on sedentary patterns (fewer breaks and longer bouts) in the moderate group and a reduction of MVPA in the light and moderate groups (Study III).

The findings in this thesis show that the treatment potential is high and that exercise can be prescribed for depression at an intensity ranging from light to vigorous. Both short and long-term effects were comparable to TAU. The exercise intervention led to some positive changes in overall physical activity and sedentary behavior. However, some detrimental effects were seen, which could be further explored in future studies including a component for targeting sedentary behavior.

SAMMANFATTNING

Fysisk aktivitet kan minska risken för att utveckla depression och motion kan vara lika effektivt som farmakoterapi eller psykoterapi vid behandling av depression. Mindre är känt om associationen mellan stillasittande beteende och depression, och om vilken intensitet som ger effekter på depression, särskilt på lång sikt. Därtill saknas kunskap om hur fysisk aktivitet och stillasittande beteende förändras efter en behandlingsperiod med träning.

Data för denna avhandling härrör från Regassastudien, en randomiserad kontrollerad studie, som inkluderade tre grupper med träning i olika intensitetsnivåer och en grupp som fick sedvanlig behandling. Deltagarna var 18-67 år, och hade mild till måttlig depression vid baslinjen. Syftet med Studie I var att kontrollera nivån avfysisk aktivitet och stillasittande hos personer som led av depression och därtill att undersöka om fysisk aktivitet och stillasittande är associerat med depressionens svårighetsgrad. Svårighetsgraden mättes med Montgomery Åsberg Depression Rating Scale (MADRS). För att bedöma fysisk aktivitet och stillasittande beteende vid baslinjen användes accelerometrar (N = 165). Syftet med Studie II var att bestämma behandlingseffekterna (12 veckor) av tre olika intensitetsnivårena (lätt, måttlig och hög) på depressionens svårighetsgrad (MADRS) och jämföra med sedvanlig behandling (N = 620). I studie III användes accelerometerdata för att avgöra om deltagarna i de tre träningsgrupperna (N = 68) hade ändrat sin fysiska aktivitet och stillasittande beteende efter interventionen. Studie IV jämför långtidseffekter (12 månader) av de tre gruppernas träningsintensitet och sedvanlig behandling (N = 620) på depressionens svårighetsgrad (MADRS).

Resultaten visade att de som drabbats av depression tillbringade en stor del av tiden i stillasittande sysselsättningar och att endast ett fåtal uppfyllde rekommendationerna när det gäller fysisk aktivitet (Studie I). Depressionens svårighetsgrad var associerad med lätt fysisk aktivitet och antalet avbrott av stillasittande beteende (Studie I). Träning på låg, måttlig eller hög intensitet var jämförbart med sedvanlig behandling, när det gällde att minska depressionens svårighetsgrad både på kort (Studie II) och lång sikt (Studie IV). Låg intensitet visades ha en mindre effekt på svårighetsgraden än sedvanlig behandling, både på kort (Studie II) och lång sikt (Studie IV). Samtliga träningsgrupper minskade tid (icke-signifikant) i stillasittande och i lätt fysisk aktivitet efter behandlingen, men även några negativa effekter sågs. I gruppen med måttlig intensitet förändrades stillasittandemönster (färre avbrott och längre perioder) och i grupperna med låg och måttlig träningsintensitet sågs en minskning av måttlig till hög intensiv fysisk aktivitet (Studie III).

Resultaten i denna avhandling visar att behandlingspotentialen är hög och att motion kan förskrivas för depression med en intensitet som sträcker sig från låg till hög. Både de kort- och långsiktiga effekterna var minst jämförbara med sedvanlig behandling. Behandling med fysisk träning ledde till positiva förändringar i total fysisk aktivitet och förändringar i stillasittande beteende. Det fanns även negativa effekter som bör undersökas ytterligare och framtida studier bör innehålla en komponent för att minska stillasittande beteende.

LIST OF SCIENTIFIC PAPERS

I. Helgadottir B, Forsell Y, Ekblom Ö. Physical actitivity patterns of people affected by depressive and anxiety disorders as measured by accelerometers: A cross sectional study. PLoS One. 2015;10(1).
II. Helgadottir B, Hallgren M, Ekblom Ö, Forsell Y. Training fast or slow? Exercise for depression: A randomized controlled trial. Preventive Medicine. 2016; 8(91):123-131.
III. Helgadottir B, Owen N, Dunstan DW, Hallgren M, Ekblom Ö, Forsell Y. Changes in Physical Activity and Sedentary Behavior Associated with an Exercise Intervention in Depressed Adults. [Manuscript submitted]
IV. Helgadottir B, Forsell Y, Möller J, Hallgren M, Ekblom Ö. Long-term effects of exercise at different intensity levels on depression. [Manuscript]

CONTENTS

LIST OF ABBREVIATIONS

BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
ICBT	Internet-Based Cognitive Behavioral Therapy
ITT	Intention To Treat
LICF	Last Item Carried Forward
LIPA	Light Physical Activity
MADRS	Montgomery-Åsberg Depression Rating Scale
METs	Metabolic Equivalent Units
MHR	Max Heart Rate
MINI	Mini International Neuropsychiatric Interview
MVPA	Moderate-to-Vigorous Physical Activity
PHQ-9	Patient Health Questionnaire
RCT	Randomized Controlled Trial
TAU	Treatment As Usual
VEGF	Vascular Endothelial Growth Factor

1 INTRODUCTION

1.1 DEPRESSION

Depression is a serious public health problem, as it is the third leading burden of disease worldwide and the first in middle-and high-income countries (1). Studies from Western countries (United States and Europe) show that the lifetime prevalence of depression is around 13-16% (2, 3). Depression is a recurrent disorder in a majority of the cases (4).

Major depressive disorder is a mental disorder belonging to the group of mood disorders in the Diagnostic and Statistical Manual IV (DSM-IV-TR) (5). According to the definition it includes depressed or irritable mood, decreased interest or pleasure, change in weight or appetite, change in sleep patterns, change in activity, fatigue or loss of energy, guild/worthlessness, lack of concentration and suicidality. At least five out of nine symptoms need to be present nearly every day for a diagnosis of major depressive disorder. Furthermore the social, occupational or educational function of the patient needs to be impaired. Cut-offs are given for defining mild, moderate or severe depression. The Diagnostic and Statistical Manual V (DSM-V) uses a very similar definition of major depression as the previous version, though here the chapter on depressive disorder is separate from bipolar and related disorders (6).

The emotional burden of depression is high, both to those who suffer from it, family members and will have a considerable impact on the functioning of the depressed individual. The economic cost of depression to society includes both direct costs, such as treatment costs, and indirect such as loss to productivity due to morbidity and mortality. A Swedish study, combining both direct and indirect costs, showed an increase from 1.7 to 3.5 billion euros between 1997 and 2005 (7). While the direct costs were relatively stable over time the indirect costs increased, primarily sick leave and early retirement.

The epidemiology of depression shows that women are more likely to be affected and have a younger age of onset than men (8, 9). Depression prevalence is higher in the younger age groups but then decreases, reaching the lowest point in middle age at around 45 years of age, then increasing again and reaching its peak in adults 80 years or older (10). Obesity increases the risk of depression and being depressed will also increase the risk of developing depression (11). Abuse in childhood, whether physical abuse, sexual abuse or neglect, increases the risk of depression in adulthood (12). Stressful life events have also been shown to increase the risk of depression (13). Furthermore, some people are genetically more vulnerable to develop depression (14) and this can interact with stressful life events to increase the risk of depression (15). Other risk factors include low socioeconomic status, being single, divorced or widowed, and living in an urban area (16).

Almost two-thirds of those who suffer from depression have a comorbid anxiety disorder (2) and these persons are more prone to have poorer prognosis and more severe symptoms (17). Anxiety disorders have some of the same risk factors as depressive disorders and a similar

genetic profile (16, 18). Additionally, those who suffer from depression are at an increased risk for somatic disorders. It is now established that high levels of cardiovascular and metabolic disease are leading contributors to the premature mortality gap of approximately 15 years in those with depression compared to the general population (19). To further complicate matters, depressed patients are three times more likely than non-depressed patients to not comply with medical treatments prescribed by their physicians for other conditions(20).

1.1.1 Traditional depression treatments and the treatment gap

The most commonly prescribed treatment for depression is some form of psychotherapy or pharmacological treatment or a combination of the two (21). In Sweden, these are the most highly prioritized treatments by the National Board of Health and Welfare (Socialstyrelsen), though the emphasis varies a bit depending on the severity of depression (22). However there are problems with this approach as each treatment has some drawbacks. Compliance with pharmacological therapy is an issue as are the wide range of side effects associated with drug therapy, such as weight gain, insomnia, sexual problems and several others (23-26). Psychological therapy could include cognitive behavioral therapy (CBT) or supportive counselling, either in groups or individually. However waiting times for psychotherapy can be long due to lack of resources, the therapy itself expensive, the person and their therapist have to be fluent in the same language.

A troubling reality is that despite the availability of evidence-based treatment options, a large proportion of people affected by depression remain untreated. This is largely due to the fact that the affected persons do not seek care (27); one European study showed that 43% had not sought treatment and of those, 86% had not even considered doing so (9). The reasons for not seeking help from the health care system could be due to stigma, cost and availability of treatment (28). There is stigma attached to seeking assistance for mental health problems and ones perception of this societal stigma can be internalized as self-stigma which will affect ones attitude towards psychological treatment and the willingness to seek such treatment (29). Even when people do seek help, the care that is received is not always adequate as two-thirds of those seeking care do not receive sufficient treatment (9, 30).

Because of this treatment gap, various other treatments have been suggested as alternative or complimentary treatments for depression which might be free from stigma. Exercise is one of the more popular treatments considered by patients (31) and has received support from the literature(32) while physical activity has also been suggested as a protective factor against depression.

1.2 PHYSICAL ACTIVITY, EXERCISE AND SEDENTARY BEHAVIOUR

Before going further it is imperative to note the difference between physical activity and exercise as the two terms are often used synonymously in the literature. Caspersen and colleagues (1985) defined physical activity as "…any bodily movement produced by skeletal muscles that results in energy expenditure" (33, p126). As such it encompasses all forms of activity whether performed at work, during transportation, domestic activities such as

gardening or cleaning or during leisure time (34). Exercise however is defined as "…a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective of improvement or maintenance of physical fitness" (33, p126). Although many of the studies referenced further down used the term exercise rather than physical activity, the term did not always conform to this strict definition as transport physical activity could be included. The readers can hereafter assume that the terms exercise and physical activity refer to the definitions given above, unless otherwise stated, though the authors in the cited studies might have used a different term.

Furthermore there are some aspects of exercise that need to be defined. Dose consists of frequency, i.e. how many times per week, duration, i.e. how long does each session last, and intensity i.e. how strenuous the exercise is, for example expressed as percentage of maximal heart rate. Dose can be expressed by summarizing all of these variables or simply as the amount of energy expended expressed as Metabolic Equivalent Units (METs). Additionally each of the variables that comprise the dose can be explored separately.

The type of exercise can also vary and influence the response to treatment. For example, exercise can be aerobic or non-aerobic, elicit increases in skeletal muscle strength or not, be performed individually or in a group, be home-based or performed in supervised classes at a gym, and it can be outside or inside etc. Yoga is often considered separately from exercise even though it falls under the definition of exercise by Caspersen and colleagues (33). The issue with yoga is that, there are many different versions and opinions on how yoga should be practiced and depending on the variant it can include a strong mindfulness component. Mindfulness can be defined as self-regulated attention on immediate experience (35), which could have an effect on mood and depression independently of the effect of physical exertion.

Sedentary behavior has been defined as "…activities that do not increase energy expenditure substantially above the resting level" (36, p174), i.e. have an energy expenditure between 1.0-1.5 METs (36). The most common form of sedentary behavior is sitting, whether at work or during leisure time. It is important to note that it is not necessarily so that those that are sedentary are not also physically active. This phenomenon is called the "active couch potato", i.e. when a person spends most of their time in sedentary pursuits but is still physically active by example walking to work or exercising regularly (37).

There are many different ways of measuring physical activity and sedentary behavior. The two currently most popular and common methods are self-report questionnaires and accelerometers. Each option has pros and cons. Questionnaires are easy to administrate, low cost and present a minimal burden to participants but can be biased due to recall bias or because people tend to overestimate their physical activity due to social desirability bias (38). Accelerometers are small devices that estimate the acceleration forces due to movement. Accelerometers objectively measure a person's total physical activity and sedentary time, in a much more detailed way than is possible with questionnaires. However there is no information on the context and type of physical activity, the burden to the participant is high

and there are some activities that are difficult to capture with accelerometers such as bicycling.

1.3 PHYSICAL ACTIVITY AS A PROTECTIVE FACTOR FOR DEPRESSION

Changes in our lifestyle in modern times have led to a decrease in overall physical activity. According to a study from the United States this is mostly due to less activity at work, less activity in the home and less transport physical activity. At the same time, planned exercise has been rather stable or slightly increasing (39). A report based on surveys in 27 European countries showed that 60% say that they never or seldom exercise or play sports (40). However, other physical activity such as walking, bicycling, gardening etc. was much more common with 65% reporting engaging in such activities regularly or with some regularity.

The association between physical activity (usually defined as overall physical activity, exercise, or combined with other physical activity domains) and depression has long been of interest to researchers. Cross sectional evidence suggests that high levels of physical activity (overall or exercise) are associated with a lower prevalence of depression (41-45) but this does not clarify whether people have low physical activity because of their depression status or the depression is a result of low levels of physical activity. Longitudinal studies have consistently shown that high levels of physical activity are associated with a lower risk of depression (46, 47), though of course the patients might reduce their physical activity even further due to the onset of depression. A good example of longitudinal evidence for the association between physical activity and depression comes from the Alameda county study which had a longitudinal cohort with three waves of measurements (48). This allowed the researchers to demonstrate that not only were low levels of physical activity associated with a higher risk of depression at follow-up but also that the change in physical activity status contributed to the risk of depression. Compared to the reference group (high physical activity levels at both time points), those that changed from a high to a low physical activity status had an increased risk at the final follow-up, while those that changed from a low to high physical activity status had similar estimates as the reference group (48). This result was confirmed in another longitudinal study with four measurement points over six years, which showed that changes in physical activity were associated with changes in levels of depression severity (49). Additionally, healthy people who have been made to discontinue their regular aerobic exercise displayed an increase in depressive symptoms and fatigue in the following weeks (50)

There are however some who challenge this way of looking at the association between physical activity and depression. De Moor and colleagues (2008), used data from a twin study to propose that common genetic factors lead people to be physically active in their leisure time and are protective against developing depression (51). They suggested that exercise could still be used as treatment for depression though it should be supervised and part of a therapeutic program.

1.3.1 Sedentary behavior and depression

Recently the focus has shifted to include sedentary behavior as well as physical activity. Sedentary behavior has been on the rise (39) and has been shown to lead to an increased risk of poor health (52, 53) and mortality (54-56). As the association between sedentary behavior and poor health is independent of physical activity unless the levels of physical activity are very high (55), it would seem that unique physiological mechanisms are being triggered by sedentary behavior (37). Sedentary behavior has traditionally been measured with questionnaire, totaling up sitting time during working hours and leisure time or focusing on time spent watching TV. However, the advent of activity monitors such as accelerometers has paved the way for more nuanced analyses of the details of sedentary time, such as accumulated sedentary time and breaks in sedentary time. A cross sectional study using accelerometer data from the NHANES study found that sedentary time was associated with depression, especially in overweight and obese persons (42) and another study on overweight women showed that those that were sedentary less than eight hours a day (measured with accelerometers) had fewer depressive symptoms (57). Another cross sectional study found an association between TV viewing time and mental wellbeing (58). A recent review concluded, though based on rather limited evidence, that sedentary time increased the risk of depression (59). More research on the subject is needed (60)

1.4 EXERCISE AS TREATMENT FOR DEPRESSION

It logically follows that if being or becoming physically active can reduce the risk of depression then those already depressed might benefit from exercising. Numerous randomized controlled trials (RCTs) have demonstrated this and the evidence has been summarized in various reviews. A series of Cochrane reviews has shown that when compared to a control condition, such as waiting list or social activity, exercise has a small to moderate effect on depression (61-63). No differences were found when exercise was compared with traditional treatments i.e. pharmacotherapy or cognitive behavioral therapy (61-63). However these reviews have received some critique for their methodological choices as Ekkekakis (2015) demonstrated by showing that the choice of comparisons group could substantially influence the results (64). By reanalyzing the studies included in the meta-analysis but changing the categorization of comparisons group, the result is a much larger effect of exercise compared to no treatment than reported in the Cochrane reviews. However Ekkikakis found no significant differences when exercise in combination with other treatment was compared with the other treatment alone. Another review used meta-analysis to show that the effect of exercise on depression is in fact large as publication bias led to an underestimation of the effect in previous reviews (65).

The effect of exercise on depression, whether compared to a control group or active treatment has most frequently been reported as short term effects, i.e. the effects measured immediately after the intervention period has ended. Studies reporting long-term effects, i.e. measured at least 6 months or more after the end of the intervention period, are lacking. Systematic reviews suggest that the effects are not long-term (61, 66) or a small effect when exercise is

compared to waiting list or placebo (62). One study, found no differences between usual care and usual care plus an intervention to facilitate exercise, both in the short (4 months) and long-term (8 and 12 months) (67). Another study found no differences between exercise and antidepressant medication after 12 months of follow-up while exercising during the follow-up period was shown to predict higher remission rates in both groups (68).

Despite the evidence that exists showing exercise, whether by itself or in combination with other treatments, can be as effective as more traditional treatments, exercise is not commonly prescribed by physicians. In Sweden, exercise is not high on the list of recommended treatment for depression by the National Board of Health and Welfare (Socialstyrelsen) (22). However the county councils are free to adapt the guidelines and in some areas exercise might be more commonly suggested as treatment.

1.4.1 The optimal characteristics of exercise for depression

Although as discussed above exercise in general has been shown to be a viable treatment for depression, questions remain about type and dose.

1.4.1.1 Dose: Intensity, frequency and duration

An intervention of high intensity aerobic exercise (jogging) has been compared with low (walking) but no differences were found (69), while an intervention of high intensity strength training led to more reductions in depression than low intensity strength training (70). An RCT efficacy study by Dunn et al. (2005) compared an exercise dose equivalent to minimum physical activity recommendations (17.5-kcal/kg/week) with a lower dose (7.0-kcal/kg/week), performed either three of five times per week(71). The results showed that the higher dose produced larger effects but frequency had no significant effect. However the participants in this study were heavily supervised which may not be feasible in a community-based effectiveness trial. Another study found that exercise in combination with drug therapy yielded better results from a higher dose than a lower one (72). On the other hand a review by Rethorst, Wipfli & Landers (2009) concluded that there was no significant relationship between energy expenditure and changes in depression severity (73). The authors also found that larger effects seen for longer exercise bouts in clinical populations, but the opposite for depressed people from the general population. The same was also observed for the length of the interventions, with longer interventions being more effective in clinical populations while non-clinical populations had larger effects with shorter interventions (73). However, a meta-analysis of prescribed number of sessions using studies on people with depression, found moderate effects interventions with 0-12 sessions and ≥37 sessions while large effects were seen for 13-24 and 25-36 sessions (63).

1.4.1.2 Type of exercise

Various studies have explored the effects interventions of different types of exercise; the results suggest that there are no differences between aerobic and non-aerobic (74), but

supervised exercise yields better results than non-supervised (75). Several reviews have also reached the same conclusion (73, 76, 77).

Several systematic reviews have summarized the effect of yoga on depression. In general yoga seems to reduce depression, in both clinical and non-clinical samples but the studies included often suffer from methodological issues, such as small sample size, heterogeneity of the included studies, non-randomization and lack of blinding (78-81). A study comparing aerobic exercise with what the authors term "low impact exercise" (consisting of yoga, relaxation and stretching), showed no differences in depressive symptoms (82). A study on the opinions of those suffering from clinical depression on possible strategies for treating depression found that both exercise and yoga were rated as one of the most effective alternative strategies and both had been tried by a high proportion of the sample, though the scores were higher for exercise (31).

1.4.1.3 Summarizing doze and type

Different RCTs use different doses when they define their exercise treatment which makes comparisons problematic. Perraton, Kumar & Machotka (2010) attempted to tackle this issue by examining the characteristics of exercise in studies that had found a significant effect of exercise on depression. They concluded that exercise should be performed three times a week in 30 minutes aerobic exercise sessions at 60-80% of maximal heart rate for a minimum of 8 weeks (76). An update of this review by Stanton & Reaburn (2013) using the same methodology reported that supervised aerobic exercise at moderate or self-selected intensities, performed three times a week for at least nine weeks could be recommended (75). However neither of the two reviews included negative results and they are based mainly on studies that only had one exercise arm, not comparisons of two or more which would have facilitated comparisons of different types of characteristics.

To guide caregivers in prescribing physical activity and exercise, treatment options for various diagnoses have been put together by the Professional Associations for Physical Activity (Sweden) (83). Regarding depression the suggested dose is 3-5 sessions of aerobic exercise per week, for totaling at least 90 minutes at moderate to high intensity. Additionally, strength training should be performed 3 times a week.

1.5 ACUTE EFFECTS OF EXERCISE ON MOOD

Another related field of study is the immediate effect of exercise on mood, or affect. It has been shown that on average the positive effects of exercise on affect increase until the person is exercising at or above their ventilatory threshold, after which affect is negatively affected (84, 85). However when people are left free to choose the intensity of exercise they tend to disregard suggestions based on heart rate and choose an intensity that they feel is good (86). In fact, self-selected intensity is associated with more positive affect than an intensity that is imposed(85). A study on overweight women showed that imposing an intensity that lay 10% above what they had self-selected led to significant decline in affect (87). Interestingly, people tend to choose an exercise intensity that is within widely used physical activity

guidelines(86). The effects of exercise on affect are important to consider as this can predict physical activity patterns and adherence many months later as shown by Williams et al. 2008 (88). They sampled sedentary people who participated in a single exercise bout at baseline reported affect immediately afterwards and found that those reporting more positive affect had higher levels of physical activity at 6 and 12 months follow-up.

1.6 POSSIBLE MECHANISMS

Suggested explanations for the relationship between exercise and depression include both biological and psychological mechanisms. Most likely the effect of exercise on depression is due to a complex interaction between both biological and psychological mechanism.

1.6.1 Biological mechanisms

The hypothalamus-pituitary-adrenal axis might play a role in explaining the effect of exercise on depression. Although in the short term, exercise is a stressor and therefore increases the production of cortisol (the stress hormone), in the long-term the body adapts and can regulate its response to stress, i.e. it will be better equipped to deal with stress and therefore lead to decreased depression (89). A study on healthy individuals showed that exercise was protective against stress-related health issues (90). However, a recent meta-analysis in depressed people did not find this effect, though only two studies were included (91).

Endorphins have been shown to increase in plasma following exercise but it is difficult to determine whether this is an accurate reflection of what is happening in the brain (92). Similarly, there is an increase of brain neurotransmitters (serotonin, dopamine and norepinephrine) in plasma and urine following exercise (92). This relationship has been further examined in rats and has received some support (93).

It has been suggested that the effect of exercise on depression can be partly explained by improved sleep quality. Sleep disturbance is one of the most common symptoms of depression as the vast majority of patients are affected (94). In healthy adults, increased exercise has been shown to be associated with improvements in different aspects of sleep patterns (95, 96). A recent study has explored this effect in depressed persons and concluded that subjective reports of sleep disturbance decreased after the exercise treatment (97). Another recent study found that vigorous physical activity was associated with both improved sleep patterns and fewer depressive symptoms (43).

The neurogenesis hypothesis suggests that exercise could lead to the formation of new neurons in the brain (98). Exercise has been shown increase the levels of β-endorphins, Vascular Endothelial Growth Factor (VEGF) and Brain-Derived Neurotrophic Factor (BDNF) in animals which increase the proliferation of new cells in the hippocampus (β-endorphins) and support their survival (VEGF and BDNF) (98). Epigenetic research suggests that exercising increases the expression of the BDNF gene leading to an increased production of this protein (99). However a review of evidence in depressed human subjects showed no

effects in humans on VEGF and BDNF in response to exercise, though this was based on only a handful of studies (91).

Another hypothesis proposes that exercise can regulate the production of inflammatory cytokines, which have been shown to be dysregulated in depressed people (100). For example Interleukin-6 (IL-6) has been shown to be higher in those that have attempted suicide than in healthy controls (101). Regular physical activity has been shown, in healthy people to be related to lower levels of IL-6. However, a recent review of the evidence regarding depressed people concluded that there was currently no evidence to support this theory, neither for acute effects nor for chronic effects. But again there were not enough studies in humans to refute the theory (91).

1.6.2 Psychological mechanisms

Psychological mechanisms have also been suggested. The distraction hypothesis proposes that exercise might distract from worries and negative thoughts (102) though this effect might be limited (103). Another theory suggest that the effect of exercise on depression might be due to increased self-efficacy and sense of mastery, meaning that the depressed person feels more able do what is necessary to accomplish their goal (92), which has been shown to be a plausible explanation (103). Furthermore, interacting with others while exercise along with praise from friends and family and improved self-confidence could positively affect self-worth (104).

1.7 A BRIEF RATIONALE FOR THIS THESIS

Although there are plenty of published studies on the effects of exercise on depression and several systematic reviews have summarized this evidence, several key research questions remain unanswered . Frequently the authors of these reviews point out the lack of knowledge on the optimal dose, including intensity, of exercise and the long-term effects, especially at different intensity levels. Furthermore, we know little about how depressed individuals spend their time, i.e. the pattern of physical activity and sedentary behavior and how an exercise intervention might impact on these patterns. Such knowledge would contribute to improved clinical treatment of depression as well as inform public health authorities on appropriate guidelines.

2 AIMS

The overall aim of this thesis is to enhance knowledge regarding exercise as a treatment of mild to moderate depression as an easily applicable option to more traditional treatments.

Specific research questions:

- What is the habitual physical activity level and sedentary behavior patterns of people affected by mild to moderate depression, and is there an association with depression severity? (Study I)
- Is there a dose response effect of exercise performed at three different intensity levels on depression severity when measured after a 12 week intervention in depressed adults, and is the effect comparable to the effect of treatment as usual? (Study II)
- Do physical activity and sedentary behavior patterns of depressed adults change following a 12 week exercise intervention performed at light, moderate or vigorous intensity? If so, in what way? (Study III)
- What are the long-term effects of exercise performed at three different intensity levels on depression severity measured 12 months after the start of the intervention? How do the effects compare with treatment as usual? (Study IV)

3 MATERIALS AND METHODS

The data for this thesis arise from the Regassa study. The aim of Regassa was to explore possible new treatment options for mild to moderate depression that could be easily implemented in the whole of Sweden with the long-term goal of reducing sick leave. The two included novel treatments were Internet-Based Cognitive Behavioral Therapy (ICBT) and exercise and these were compared with Treatment As Usual (TAU) by primary care physicians. The focus of this thesis is on exercise so no data from the ICBT group was included.

3.1 STUDY DESIGN

The design of the Regassa study was a randomized controlled trial (RCT); the intervention lasted 12 weeks, and measurements were made at baseline, post-treatment (12 weeks) and at a follow-up 12 months after the start of the interventions (more information is available in Figure 1).

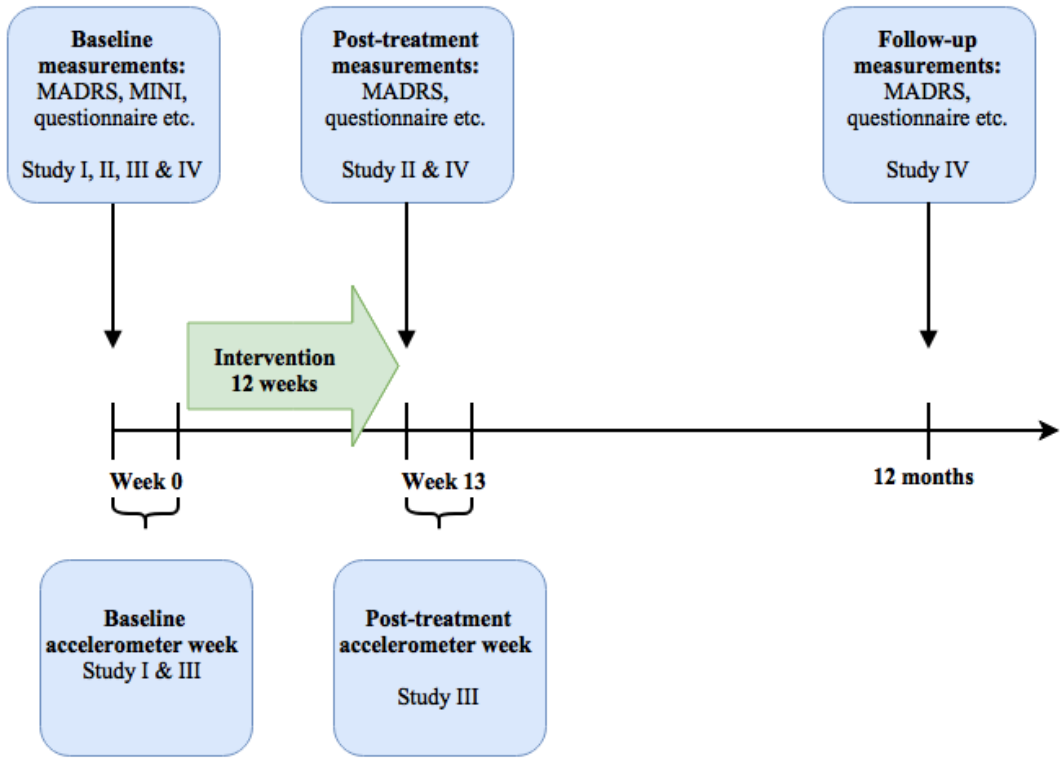

Figure 1 – Participant flow through the Regassa study

3.2 STAFF TRAINING

The nurses were trained by the principal investigator (a psychiatrist) before the start of the study to ensure that the interview procedures were consistent. Furthermore research assistants were trained by another member of the research team (a psychiatric nurse) in the entire examination procedure. The training took 1-2 days and included modules on the information that was to be given to the participants, how to obtain informed consent and how to instruct

participants on filling out questionnaires. The two staff members responsible for the training procedure were available to answer any questions for the duration of the trial.

3.3 RECRUITMENT OF PARTICIPANTS

Recruitment for the Regassa study began in February 2011 and concluded in January 2013. Participants were recruited through primary health care centers and advertisements in six Swedish county councils: Stockholm, Kronoberg, Blekinge, Region Skåne, Västra Götaland and Västmanland. Inclusion criteria were scoring ≥10 points on the Patient Health Questionnaire (PHQ-9)(105), being between 18 and 67 years of age and a basic understanding of Swedish as this was the language of all the materials used in the study. Participants were excluded if they had a primary diagnosis of alcohol or drug dependency, serious somatic disorders or required specialist psychiatric treatment. In all 945 were included in the trial, of those 310 participants were in the exercise arm and 310 participants were in the TAU arm. The participating physicians declined to keep records of those that were invited to participate in the study so the number and characteristics of these individuals is unknown.

3.4 RANDOMIZATION PROCEDURE

Following screening and baseline measurements (see below) the participants were randomized to one of the three main groups. The randomization was external (Karolinskas Trial Alliance) and computer generated and it was impossible to randomize a participant until they had completed all baseline measurements. The randomization was done in blocks of 36 to ensure an even distribution. After the randomization to one of the three main treatment groups, the participants in the exercise arm were further randomized to three exercise intensity groups: light exercise, moderate exercise and vigorous exercise (described further below). This led to a ratio of 3:3:1:1:1 for TAU, ICBT, light exercise, moderate exercise and vigorous exercise.

3.5 BASELINE MEASUREMENTS

The first interview with the potential participants was conducted by their primary care physicians, either face-to-face or through the telephone. The patients answered the PHQ-9, which is regularly used in primary care, and has shown good validity to detect depression (105, 106). Additionally the potential participants were evaluated with regards to other inclusion criteria (i.e. basic understanding of Swedish and correct age group) and exclusion criteria. Their physician also determined whether they had any serious somatic disorders which was judged as being the primary cause of depression and thus needed treatment (e.g. cancer) or could prevent them from participating in the exercise arm.

3.6 MEASURES OF DEPRESSION

After the initial interview by the physician all participants were interviewed at baseline (within a week) by research nurses using the Mini International Neuropsychiatric Interview (MINI) (107). The MINI is a short, structured clinical interview based on the DSM-IV. The purpose of the MINI was two-fold: 1) to exclude people who had passed the inclusion criteria

but who had a primary diagnosis of alcohol or drug dependency or required specialist psychiatric treatment due to for example suicidality or psychosis, and 2) to give a clinical diagnosis of depressive disorder, anxiety disorder or concomitant disorders, in the present thesis, this variable was used in Study I, II and IV.

Depression severity was measured by the Montgomery-Åsberg Depression Rating Scale (MADRS) (108). The scale has 10 items (apparent sadness, reported sadness, inner tension, reduced sleep, reduced appetite, concentration difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts) scoring from 0-6, with higher scores indicating more severe depression. Snaith and colleagues (1986) suggest cut-offs for the MADRS: 7-19 points for mild depression, 20-34 for moderate depression and 35-60 for sever depresion (109). MADRS was designed to be sensitive to change, has shown good sensitivity and validity (108, 110) and was completed face-to-face by the study personnel at baseline before treatment allocation. The baseline MADRS measurements were used in all studies.

Furthermore, for the duration of the intervention the participants received computerized follow-up telephone calls every third week that screened for extreme depression/suicidality(111) and protocols were in place to offer specialist help to those that screened positive.

3.7 OTHER INFORMATION GATHERED AT BASELINE

Additional participant information was gathered using a questionnaire at baseline. Height and weight was converted to Body Mass Index (BMI) using the formula kg/m^2. Standard BMI categories for overweight (25-29.9 kg/m^2) and obesity ($\geq$30 kg/m^2) were used but the BMI categories of underweight (<20 kg/m^2) and normal weight (20-24.9 kg/m^2) were analysed together as very few individuals belonged to the underweight category. Health status was assessed by counting the number of somatic conditions or disorders reported by the participants in the questionnaire, selected from a list of eleven possible areas of disorders that they had been treated for or received a diagnosis for by a physician. The eleven areas were: reduced mobility, rheumatologic disorders, back, shoulder or neck pain, headache; cardiovascular disease, including high blood pressure; neurological disease; diabetes or other metabolic disease, asthma or other lung conditions, ulcer and other chronic conditions of the digestive system and the liver, diseases in kidneys, urine tract or uterus; serious infection or injury, tumor; or other serious disease. Education was categorized as tertiary education ($\geq$2 years of university) or less; hazardous alcohol use was measured using the Alcohol Use Disorders Identification Test (AUDIT), where those that scored $\geq$8 were classified as hazardous drinkers (112). Leisure time physical activity habits were measured with a question with six response alternatives ranging from almost no physical activity to regular exercise at high intensity in the preceding year (113). We collapsed these alternatives into three categories: inactive, light exercisers, and moderate to vigorous exercisers. All the preceding variables were measured at baseline but in addition, the leisure time physical activity was also measured and used at the 12 month follow-up though here this question referred to the preceding three months. The follow-up physical activity question was only used in Study IV.

In addition to the information gathered in the questionnaire the participants were asked by the interviewing nurse to report their medication use at baseline. This information was then reviewed by a psychiatrist (YF). Approximately one-third of participants were taking anti-depressants (primarily selective serotonin reuptake inhibitors). The proportion of participants using other medications (e.g. contraceptives, statins, and thyroid drugs) during the trial was minimal. The question on medication use was repeated at the post-treatment measurement (12 weeks).

3.8 TREATMENT AS USUAL

Participants in TAU received standard treatment for depression administered and determined by their primary care physicians. In most instances, this involved brief general counselling sessions with the physician, and in some instances, cognitive behavioural therapy with a clinical psychologist

3.9 EXERCISE INTERVENTION

The three exercise groups were 1) light exercise consisting of classes incorporating yoga-based stretching and balance exercises, *(*mindfulness i.e. self-regulated attention on immediate experience (35) was not an active component of the yoga classes in this trial*)*; 2) moderate exercise consisting of an intermediate-level group aerobics class; and 3) vigorous exercise, consisting of a more strenuous group aerobics class. Members of the research team calibrated the classes by producing a series of sessions which were distinctly different, which were tested using indirect calorimetry and pulse watches. Heart rate data from these sessions was then compared with various classes at the gym, to identify classes of similar intensity. Participants were asked to join supervised pre-existing group classes (corresponding to their assigned intensity level) lasting approximately 60 minutes, three times per week for 12-weeks. Although specific exercise classes were recommended, the patients were permitted to participate in alternative exercise classes or self-directed activities such as walking that might be more convenient to them. They were however asked to keep these deviations from the protocol to a minimum. Importantly, these alternative options were of similar intensity and duration (e.g. walking instead of yoga). All exercise sessions were to be completed at a modern fitness centre chain with locations throughout Sweden. The staff at the fitness centers were informed about the study to ensure that the participants would be welcomed and given extra encouragement, especially at the beginning. To maximize adherence, membership was provided free to all exercise participants and they met with a member of the study personnel once per week to discuss their exercise progress, gather heart rate and accelerometer data (discussed below) and record attendance. The research personnel gave advice about exercise if requested, but were instructed not to discuss depressive symptoms as they did not have the necessary training as most were general nurses, personal trainers or physiotherapists.

3.9.1 How exercise intensity was measured

In addition to calibrating the classes before the start of the study, the intensity level was also checked by asking the participants to record their heart rate during their exercise sessions

using pulse watches. Two models were used: Polar RS400 and Activio BM-SWIEU. Information from the watches was downloaded once a week during the meetings with the study personnel. As some participants did not always wear the watches, or because of malfunction, the final registered number of exercise sessions was based on either the number of recorded sessions (78%), or in the absence of these data, the number of self-reported exercise sessions (22%).

The data for each session was compared with the calculated Max Heart Rate (MHR) for each participant (220 minus age). Three variables were calculated using the heart rate data: the average heart rate per session as a percentage of MHR, and the average number of minutes per session spent ≥60% and ≥80% of the calculated MHR.

3.10 DEPRESSION SEVERITY

The primary outcome in Studies II and IV was depression severity according to MADRS scores which was measured at post-treatment (12 weeks) and long-term follow-up (12 months). Personnel were blind to the participant's treatment group at the post-treatment and follow-up assessments. To maximize post-treatment and follow-up response rates, a mixture of face-to-face and telephone interviews were conducted and at follow-up, extra efforts were made to reach as many participants as possible as this was considered the study end point. There was also a web-based questionnaire available but MADRS was always done face-to-face or by telephone. The second item of the MADRS ("apparent sadness") was not scored in the telephone interviews; instead, item 1 (reported sadness) was imputed from the same time point. These two items were highly correlated ($r=0.568$, $p<0.001$). As there was some loss to follow-up for the MADRS post-treatment (23.5%) and follow-up (16.9%), the last item carried forward method (LICF) was used to be able to analyse the full sample (intention-to-treat analysis).

The post-treatment MADRS scores were used in Study II (main outcome) and Study IV (intermediate outcome), and the follow-up MADRS measurements were used in Study IV as the main outcome. In Study IV the MADRS was categorized into those that were defined as treatment responders at follow-up which was defined as a reduction of 50% from baseline (114).

3.11 OBJECTIVE MEASURMENT OF PHYSICAL ACTIVITY

3.11.1 Accelerometer protocol common to both Study I and Study III

Accelerometer data was used as an outcome in Study I and III, though in Study III the data was modeled as change from baseline to post-treatment. Accelerometers (ActiGraph GT3X+) were used to measure physical activity of the participants in the exercise arm. Participants were instructed to wear an accelerometer on the right hip, continuously throughout the waking part of the day, removing it only for bathing or swimming. Participants were asked to wear the accelerometer one week prior to the intervention (week 0), during the entire intervention (12 weeks), and one week after the intervention had finished (week 13). Actilife

version 6.4.3 was used for the processing and analyzing the accelerometer data. The accelerometers were initialized to give average data on movements in 60 second epochs. All the data was checked manually for spuriously high values (caused by electrical interference or malfunction of the accelerometer) and those days that showed evidence of this were removed (n=1). Only days with ≥600 minutes of wear time per day were included in the analyses (115). Non-wear periods were defined as ≥60 minutes of no activity (0 counts/minute), allowing for short bouts (≤2 minutes) of activity above this threshold. Cut-offs for categorizing activity counts were based on the suggestions by Freedson et al. (1998) (116); sedentary (<100 counts/min), light physical activity (LIPA, 100-1951 counts/min) and moderate-to-vigorous physical activity (MVPA, ≥1952 counts /min). Table 1 displays which activity measurements were used in each study and how they were summarized.

Table 1 – Definitions of accelerometer variables

Accelerometer variables (mean per day)	Cut-offs of activity counts	Minimum length (for bouts)	Used in study:
Counts per minute	N/A	N/A	Study I
Minutes sedentary	≤99 counts/min	N/A	Study I Study III*
Minutes in LIPA	100-1951 counts/min	N/A	Study I Study III*
Minutes in MVPA	≥1952 counts/min	N/A	Study I Study III*
≥20 min sedentary bouts	≤99 counts/min	≥20 min (no interruptions allowed)	Study I Study III
≥30 min sedentary bouts	≤99 counts/min	≥30 min (no interruptions allowed)	Study III
Number of sedentary bouts	≤99 counts/min	≥20 min (no interruptions allowed)	Study I
Sedentary interruptions	≥100	≥1 min interruption to sedentary time	Study III
Time in MVPA bouts	≥1952 counts/min	≥10 min (with 2 min interruption allowed)	Study I Study III
Number of MVPA bouts	≥1952 counts/min	≥10 min (with 2 min interruption allowed)	Study III

* In Study III these variables were adjusted for wear time by standardizing them to 16 hour days.

3.11.2 Accelerometer protocol in Study I

In Study I accelerometer data was used from the baseline week (week 0). This week occured before the start of the intervention; this was assured by comparing the dates of the accelerometer measurements with the date of the first attended exercise session for each participant. The accelerometer data was only used if the participants wore the accelerometer for four or more days, including at least one weekend day, which is a widely used method of representing a week of physical activity (115). Of the 308 participants[1], 165 fulfilled these requirements (53.6%).

[1] Study I included people aged 18-65 years as opposed to the other three studies which included people aged 18-67 years, hence the lower N in Study I.

Each person's total amount of physical activity was summed into average counts per minute. MVPA was summarized into bouts of activity which is a good way of estimating whether a person has met physical activity guidelines as it is recommended that physical activity be performed in bouts of at least 10 minutes (117). This was further explored categorizing those achieving ≥30 minutes of MVPA in ≥10 minute bouts on average on each day of the week or those that did not. We also compared those that fulfilled these requirements ≥5 days a week and those that did not. A maximum of two minutes of drop time was allowed, meaning that the counts during these MVPA bouts could drop below a 1952 counts/minute for a maximum of two minutes and still be counted as a MVPA bout.

Sedentary bouts were defined as <100 counts/min for a minimum of 20 minutes and were presented as number of sedentary bouts and total time in sedentary bouts. Each of the continuous accelerometer variables was calculated as the average for each person for the days that they wore the accelerometer.

3.11.3 Accelerometer protocol in Study III

Some changes were made to the protocol that was used in Study III compared to Study I. This was based on experiences from Study I, advice from new co-authors and that the sample in Study 3 was smaller due to insufficient follow-up data leading to less conservative criteria for number of days required.

A valid week was defined as at least one weekend and one weekday (115). Minutes spent in sedentary, LIPA and MVPA were standardized to 16 hour days to account for difference in wear times. Two variables represent accumulated sedentary time (<100 counts/min) in bouts of either ≥20 or ≥30 minutes (118), with no interruptions allowed. Number of sedentary interruptions was defined as an interruption in sedentary time that was ≥100 counts/min, lasting for at least 1 minute (119). Accumulated MVPA time was defined as bouts of ≥10 minutes of ≥1952 counts /min, with allowed interruptions of <1952 counts /min for two minutes. Number of MVPA bouts was also explored.

Study III used accelerometer data from baseline (week 0) and post-treatment (week 13). A few participants stopped exercising before the scheduled end of the intervention and did not hand in any accelerometer data for the post-intervention week (week 13). For these participants, we included their last observed accelerometer week if it occurred after they had stopped participating in the exercise intervention and had participated for at least 8 weeks. Approximately one-fifth had data from weeks 9-11, 66.2% from weeks 12-14 and 13.3% from later weeks due to delays in their intervention. No overlap between the accelerometer data and intervention period was permitted since the accelerometer observation had to occur pre- or post-intervention. This was possible as exact dates for when the exercise sessions occurred and when the accelerometer data was recorded were available.

Participants with valid pre- and post-intervention weeks and for whom other complete relevant data were available, were included in the study (n=68). The vast majority of the participants had at least 4 days of monitoring; 92.7% and 92.7% for the pre- and post-

intervention weeks, respectively. The large component of missing accelerometer data observed (from n=310 to n=68) was due to a missing pre-intervention week (n=104), incomplete pre-intervention week (n=34), missing post-intervention week (n=157), incomplete post-intervention week (n=63), and too few weeks between pre- and post-intervention (n=20).

3.12 STATISTICAL ANALYSES

As the data for this thesis is part of a larger study (120) no power calculations were performed specifically for each of the studies included; the power calculations for Regassa can be found in the protocol which is available online (http://www.regassa.se/sv/Om-Regassa/Protocol-REGASSA-studien/).

In all studies the distribution of categorical variables across groups was tested with Chi^2 tests. The distribution of continuous variables was tested with t-tests or ANOVA, depending on the number of groups.

In Study I, the relationships between each of the seven continuous accelerometer variables and diagnosis (MINI) were tested with one-way ANOVAs and the differences between categories were explored using the Bonferroni correction for multiple comparisons. The association of each of the continuous accelerometer variables to MADRS was explored using multiple linear regression models, controlling for sex, age, BMI, health status and MVPA. SAS version 9.3 was used for all the statistical analyses. Level of statistical significance was always set at α=0.05.

In Study II multiple linear regression models were used to calculate changes in mean MADRS scores from baseline to post-treatment with 95% Confidence Intervals (CI) and to test the post-treatment differences between groups. The MADRS was modelled as the difference between post-treatment and baseline scores. The analysis was stratified by gender, and a separate interaction analysis between gender and treatment group was performed by entering an interaction term into the model. Additionally, the effect of treatment group on depression severity was analysed using per protocol analysis, comparing compliers (≥12 exercise sessions) in each exercise group with the TAU group. Further sub-group analyses were performed, restricting to 1) those who answered MADRS at post-treatment, 2) those who received a depression diagnosis according to the MINI at baseline[2], 3) those who were inactive or lightly physically active at baseline , and 4) only those moderately or vigorously active at baseline. All models were adjusted for antidepressant use which was unequally distributed between groups (p=0.038). Significance was set at α=0.05 and all tests were two tailed. All analyses were performed using Stata 14.1 and the figures were created in draw.io and GraphPad Prism 6.

[2] Depression diagnosis according to the MINI was not an inclusion criterion, only a score of ≥10 on the PHQ-9 meaning that some people in the sample did not have a diagnosis of depression according to the MINI.

The analysis for the outcomes in Study III (standardized sedentary minutes, standardized light minutes, standardized MVPA minutes, time in sedentary bouts of ≥20 minutes, time in sedentary bouts of ≥30 minutes, number of sedentary interruptions, time in MVPA bouts of ≥10 minutes, and number of MVPA bouts) were performed using linear mixed models (in Stata: xtmixed) to account for the correlation between repeated measures of the same individuals over time. All models were adjusted for fixed effects of the group, pre-intervention values of the outcome, age, sex, BMI, number of weeks between pre- and post-intervention accelerometer measurements, and number of exercise sessions. All outcomes related to bouts and interruptions (time in sedentary bouts of ≥20 minutes, time in sedentary bouts of ≥30 minutes, number of sedentary interruptions, time in MVPA bouts of ≥10 minutes, and number of MVPA bouts) were additionally adjusted for wear time. Models did not display any problems with heteroscedasticity, nonlinearity, or non-normality. Results from all models were reported as marginal means with 95% confidence intervals. All analyses were done in Stata statistical software release 12.0 (Stata College Station, TX). Figures were created in draw.io and GraphPad Prism 6. Significance level was set at $p<0.05$ (two-tailed).

The main analyses in Study IV were performed using linear mixed models with time x group interactions to explore the differences in depression severity (MADRS continuous) at each time-point between the groups. To depict the main results in a figure we standardized the MADRS (mean of 0 and a standard deviation of 1) in the model which the figure is based on to bring the baseline MADRS to a completely equal starting point. Additionally we explored 'treatment response' (i.e. 50% score reduction) as the outcome using binary mixed models. Furthermore, the effect of treatment group on depression severity was analysed using per protocol analysis. The main analysis was also stratified by gender to see if the effect differed for men and women. Further sub-group analyses were performed, restricting to 1) those who received a depression diagnosis according to the MINI, 2) stratified by physical activity i.e. whether the participants reported being inactive or lightly physically active contrasted against those moderately or vigorously active at follow-up. All models were adjusted for treatment with antidepressants at baseline as this was unequally distributed across groups ($p=0.038$). Statistical significance was set at $\alpha=0.05$ and all tests were two tailed. All analyses were performed using Stata 14.1 and the figures were created in GraphPad Prism 6.

3.12.1 Ethical considerations

Before starting a randomized controlled trial, the state of knowledge should be in equipoise. This means that it should not be clear which treatment will be more effective so as to not expose people to treatment that is either known to be ineffective or withhold known effective treatment. Beforehand it was known that exercise could be as effective as medications or psychotherapy (62). What was not clear was at which level of intensity exercises should be performed to be most effective. It can therefore be concluded that the equipoise requirement was fulfilled. There should also be no unacceptable risk associated with exercise. Injury is the most common risk associated with exercising but this is minimal and the participants could

receive support and advice from study personnel regarding the exercise at least once a week and the exercise was performed under the supervision of experienced trainers.

All the participants received a pamphlet with a description of the Regassa study with all relevant information including contact information in case of questions, and signed an informed consent form. The form stated that participation was totally voluntary and that it could be stopped at any time without any explanation. Additionally the participant was asked to mark their acceptance or rejection of a) having their personal information collected and stored in a database and b) that their blood and/or saliva samples being stored at a KI biobank and being used for research regarding treatment or risk factors for mental ill health (not used in this thesis). This process should ensure that all the participants had the opportunity to understand what the study entailed and what they were agreeing to.

The people eligible to participate in the Regassa study can be viewed as a potentially vulnerable group and this was considered in the design of the study. The participants were screened for suicidal thoughts and serious psychiatric problems such as psychosis. If any such cases were found they were directed to appropriate care. Additionally there were follow-up telephone interviews every third week that screened for extreme depression/suicidality and those cases could be contacted with suggestions for more specialized care. The data was stored on secure servers and access was only granted to those involved in the data collection (each region had only access to its own region) and the researchers analyzing the data. None of the treatments offered added any unnecessary or additional stigma to the participants. The TAU is what they would have done anyway and the ICBT could be done at home. Exercise is what everybody should do and has therefore no special stigma attached to it and it can be argued that it makes people feel less like patients receiving treatment and more like societies image of what everybody should include in everyday life.

Table 2 – Brief overview of the four studies

Study	Study Design	Exposure	Outcome	N in main analysis	Statistical analysis
I	Cross sectional	MADRS at baseline	Physical activity and sedentary behavior at baseline	Exercise group=165	ANCOVA Linear regression
II	RCT	Group allocation	Change in MADRS from baseline to post-treatment (12 weeks), continuous	TAU=310 Light exercise=106 Moderate exercise=105 Vigorous exercise=99	Linear regression
III	RCT	Group allocation	Change in physical activity and sedentary behavior from baseline to post-treatment	Light exercise=21 Moderate exercise=25 Vigorous exercise=22	Linear mixed models
IV	RCT	Group allocation	MADRS at follow-up (12 months), continuous and 50% reduction from baseline	TAU=310 Light exercise=106 Moderate exercise=105 Vigorous exercise=99	Linear mixed models with group x time interaction

4 RESULTS

4.1 BASLINE CHARACTERISTICS AND TREATMENT RECEIVED

The overall sample in the exercise and TAU groups combined had a mean age of 42.6 years (SD=12.0), the majority were women (73.7%), and the majority were diagnosed with co-morbid depressive and anxiety disorders.

4.1.1 Treatment as usual

At the end of the study the participants in the TAU group reported what type of treatment they had received. The most common was some form of psychotherapy, including cognitive behavioural therapy (20.5%), followed by pharmacotherapy (10.0%), or a combination of those (11.5%). Approximately one-fourth reported receiving no treatment at all. On average, patients in the TAU group made 6.6 visits (SD: 7.4) to health or social care. *A*t baseline 21.6% of the TAU group were taking antidepressant while 51.8% reported antidepressant use at the end of the intervention.

4.1.2 Exercise groups

Most of the exercise sessions performed in the light group consisted of yoga (50.5%), or classes that mixed tai chi, pilates and yoga (18.8%). In the moderate group most of the sessions were the intended classes (66.5%), or similar aerobic activities (24.5%). In the vigorous group, 62.9% of the exercises completed were the recommended classes, and 25.9% were other types of aerobic activities. Because of this variation the heart rate data was used to confirm that the groups were exercising different intensity levels. The exercise groups were shown to be significantly different regarding intensity, both overall and between each other, when looking at average maximum heart rate (MHR) and time in ≥80% of MHR. The light group was significantly different from the moderate and vigorous groups regarding time in ≥60% of MHR, but the moderate and vigorous were not significantly different.

In the three exercise groups, 59.3% participated in at least one session, but only 32.3% attended 12 sessions. No significant differences were found between the different intensity groups regarding number of exercise sessions or proportion of compliers i.e. attending 12 sessions or more. Those attending 12 sessions or more were classified as compliers in Study II while in Study IV we added the requirement that these 12 or more sessions had to have belonged to the category of recommended classes, i.e. if a person in the moderate group attended a yoga class for example it did not count towards the 12 sessions. A cut-off of 12 sessions was chosen as this frequency of training is what might reasonably be expected of patients in this context.

4.2 TREATMENT POTENTIAL: BASELINE PHYSICAL ACTIVITY

The results showed that the participants spent time in sedentary pursuits on average 9.1 hours per day. On average 41.5 minutes were taken up by Moderate-to-Vigorous Physical Activity (MVPA) and about one-third fulfilled physical activity guidelines by performing MVPA in

10 minute bouts for at least 30 minutes per day, five times per week. There was a negative association between depression severity and Light Physical Activity (LIPA), with each one point increase in MADRS being associated with a two minute reduction in LIPA (Table 3). Depression severity was associated with number of sedentary bouts, the number of bouts increased with increasing severity of depression. Both relationships were independent of MVPA.

Table 3 – The association between MADRS (independent) and each physical activity variable (dependent) as depicted by multiple linear regression models**.**

	Model 1: MADRS, sex and age		**Model 2: MADRS, sex, age, BMI and health status**		**Model 3: MADRS, sex, age, BMI, health status and MVPA**	
	β	p	β	p	β	p
Counts per minute	-1.58	0.555	-0.72	0.785	N/A*	N/A
Sedentary (minutes)	0.66	0.552	0.57	0.610	1.07	0.296
LIPA (minutes)	**-2.19**	**0.011**	**-1.98**	**0.021**	**-2.21**	**0.008**
MVPA (minutes)	0.23	0.403	0.29	0.295	N/A	N/A
Time in sedentary bouts	1.89	0.119	1.76	0.152	2.20	0.061
Number of sedentary bouts	0.05	0.085	0.04	0.124	**0.06**	**0.041**
Time in activity bouts	0.32	0.106	0.36	0.069	N/A*	N/A

*Counts per minute and time in activity bouts were not adjusted for MVPA as they were too correlated r>0.7
Numbers in bold represent statistically significant results (p<0.05)

4.3 POST-TREATMENT EFFECTS

All the exercise groups had reduced their average MADRS scores, from moderate to mild at the post-treatment examination. As seen in Figure 2, all the exercise groups had significantly lower depression severity levels than the TAU. Although none of the exercise groups was significantly different from each other the light group had almost 2 points lower MADRS score at post-treatment than the moderate group (p=0.095).

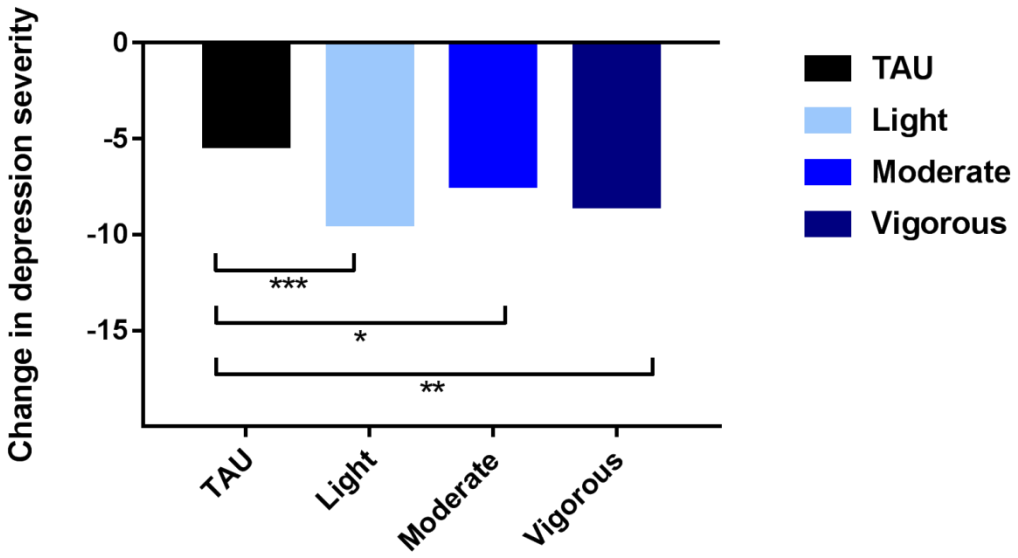

Figure 2 – Adjusted depression severity (MADRS scores) at baseline and post-treatment, with 95% confidence intervals (Sweden 2011-2013). Comparisons between groups:*p<0.05, **p<0.01, ***p<0.001

4.4 CHANGES IN PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

All exercise groups reduced their sedentary minutes and increased their LIPA minutes though these changes were not significant (Figure 3). The light group significantly reduced their MVPA minutes (Figure 3) and both the light and moderate groups significantly reduced the time spent in MVPA bouts (Figure 4). Additionally the light group significantly reduced the number of MVPA bouts and the moderate group significantly reduced the number of sedentary interruptions (Figure 5).

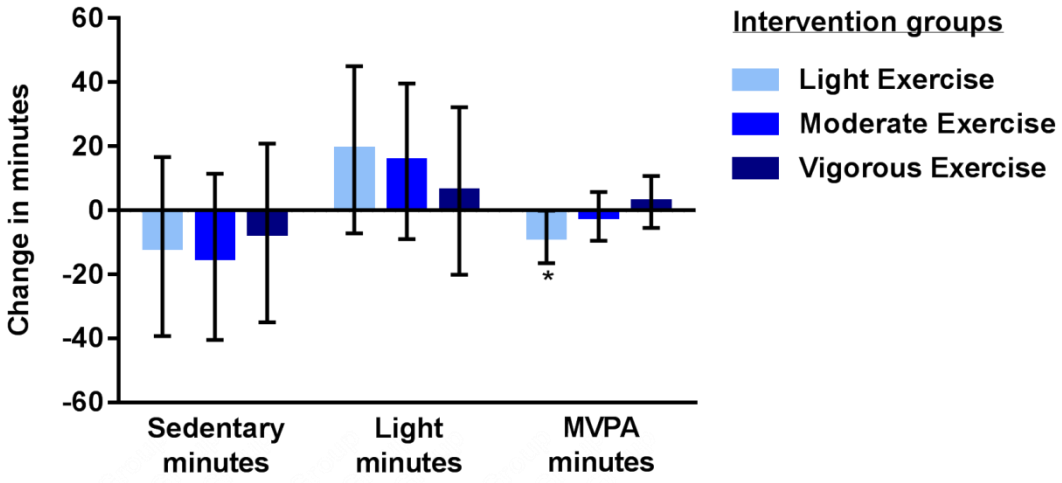

Figure 3 – Adjusted mean changes from pre-treatment to post-treatment in standardized minutes spent in sedentary, light and MVPA (*p<0.05)

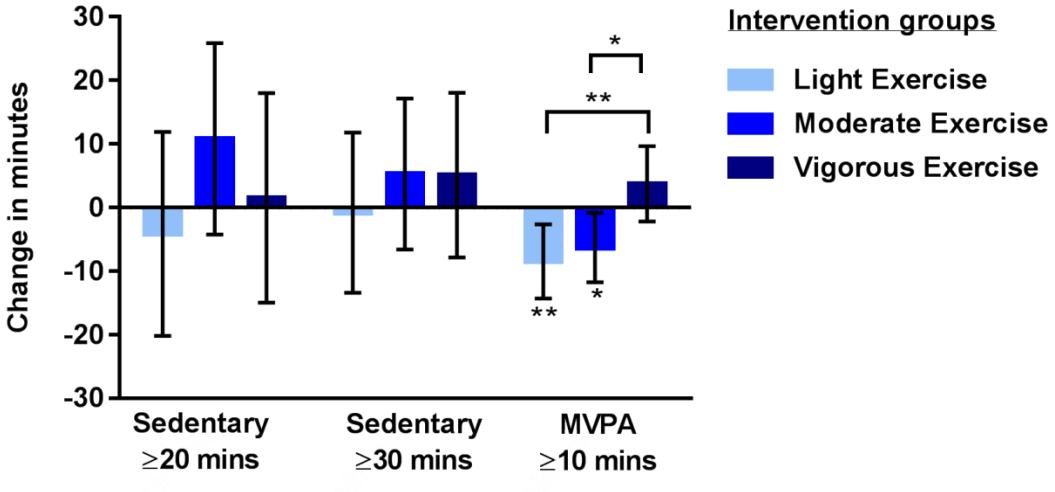

Figure 4 – Adjusted mean changes from pre-treatment to post-treatment in accumulated sedentary and MVPA bout time (*p<0.05, **p<0.01)

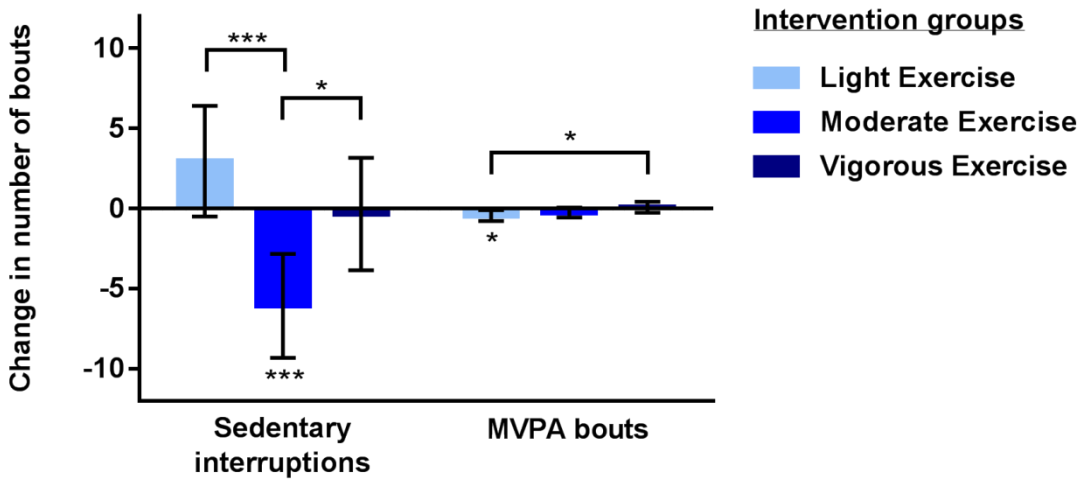

Figure 5 – Adjusted mean changes from pre-intervention to post-intervention in sedentary interruptions and MVPA bouts (*p<0.05, ***p<0.001)

4.5 LONG-TERM EFFECTS

At the follow-up, 12 months after the start of the intervention, the moderate and vigorous groups were comparable with TAU regarding depression severity, while the light group had significantly lower depression severity levels than TAU. Additionally, both the light and vigorous groups had lower depression severity than the moderate group at follow-up. Only the TAU and the vigorous groups reduced their depression severity between the post-treatment measurement and the follow-up. The effect in the light and moderate groups plateaued, neither decreasing nor increasing between post-treatment and follow-up.

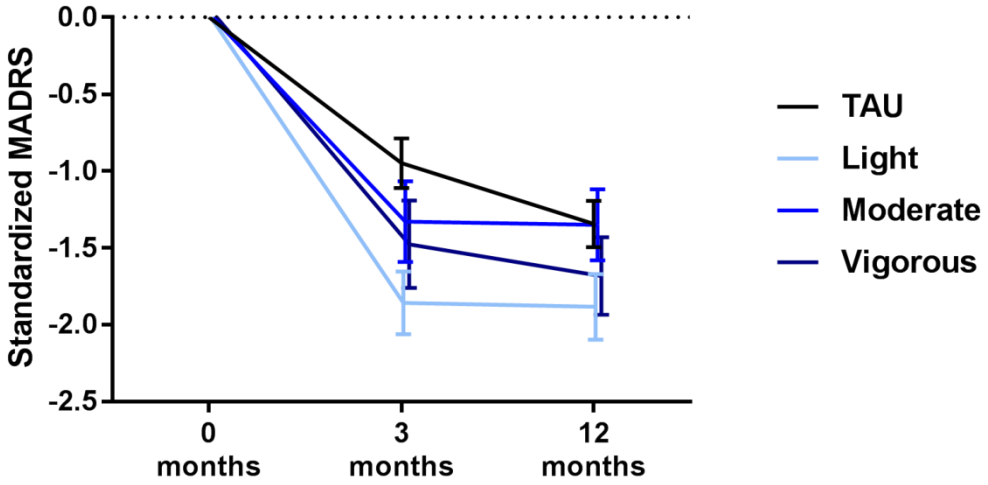

Figure 6 – Changes in standardized MADRS scores (depression severity) from baseline, to post-treatment (12 weeks), to follow-up (12 months)

5 DISCUSSION

5.1 SUMMARY OF MAIN FINDINGS

The overall aim of this thesis was to add to the existing knowledge regarding how exercise can be used as treatment for depression. Specifically to establish the baseline physical activity and sedentary behavior in people with mild to moderate depression and determine whether physical activity and sedentary behavior is related to depression severity. Morover, to establish if the intensity of exercise matters, both in the short and long-term. And finally to determine if an exercise intervention in depressed people will lead to a change in their overall physical activity and sedentary behavior.

The findings of this thesis demonstrate that the treatment potential of people suffering from mild to moderate depression is high, as they are largely sedentary and two-thirds do not fulfill physical activity guidelines. Both time in Light Physical Activity (LIPA) and number of sedentary bouts were associated with baseline depression severity. Exercise at intensities ranging from light to vigorous led to a larger decrease in depression severity levels compared to Treatment As Usual (TAU) immediately following the intervention but at the 12 months follow-up only light exercise resulted in significantly lower scores than TAU. Furthermore, both the light and vigorous groups had lower scores than the moderate group. Only the vigorous and TAU continued the decrease in depression severity between post-treatment and follow-up. Furthermore, although all exercise groups decreased their sedentary time and increased their LIPA, the changes were not significant. Some detrimental effects were observed on sedentary patterns in the moderate group, and both the light and moderate exercise had a negative impact on Moderate-to-Vigorous Physical Activity (MVPA).

5.2 EXERCISE COMPARED TO TRADITIONAL TREATMENTS

Exercise, alone or in combination with other treatments, has consistently been found to be comparable with traditional treatments of mild to moderate depression (61-63, 121), which is in line with the results from Study II and IV. Exercise has some clear advantages over the more established treatments though, such as being non-discriminatory towards persons with limited language skills and disabilities such as deafness, which would have barriers for participating in psychotherapy. A common problem with cognitive behavioral therapy is limiting resources resulting in long waiting time. This could be an explanation to why the TAU group responded “slower”, i.e. had higher depression severity levels than the exercise groups at post-treatment but showed a continued decrease at follow-up.

In addition to the positive effects on mental health, exercise has other important health benefits when performed at a moderate to vigorous intensity. Whilst suicide accounts for some of the premature deaths among people with depression, it is now established that high levels of cardiovascular and metabolic disease are leading contributors to the premature mortality gap of approximately 15 years in those with depression compared to the general population(19). It has also been shown that people who maintain their cardiorespiratory fitness across the lifespan have a reduced risk of experiencing a depressive episode(122), in

addition to other detrimental health outcomes, such as cardiovascular disease and diabetes(123, 124). These cardio-metabolic benefits are unlikely to be achieved through psychotherapy, anti-depressant use, or other treatments.

5.3 DIFFERENCES BETWEEN EXERCISE GROUPS

A priori one might expect a dose response to different intensity of exercise on depression but the findings of this thesis do not support that. The light and vigorous groups were comparable while there was a significantly slightly less pronounced effect of moderate exercise on depression severity at the 12 month follow-up. This could be due to different mechanisms being activated by different forms of exercise. Performing moderate or vigorous exercise could activate certain biological pathways (in combination with psychological ones) which are more likely to be activated when the strain on the body is higher. This idea is supported by the fact that the vigorous group had better, though non-significant, outcomes than the moderate, suggesting that a higher intensity elicits a larger effect. As frequency and duration were the same in all groups, the energy expenditure is automatically higher in the vigorous compared to the moderate group. A previous efficacy study also found that a higher dose of aerobic exercise leads to better depression outcomes (71). Light exercise might lead to an activation of mainly psychological pathways, though again most likely in combination with biological ones.

Consistent with general health guidelines, current Swedish recommendations suggest that exercise for depression be performed at a moderate to high intensity (measured as perceived intensity) (125). The results from the light group in the Regassa study, suggest that these recommendations can be expanded to also include lighter forms of exercise as high intensity does not seem to be necessary. This is further supported by a recent study in depressed people on acute effects of exercise at different intensity levels on depressed mood which found that all intensity levels yielded similar results (126).

Another way to look at the findings is to say it is a comparison of yoga, or similar types of exercise, with aerobic exercise. Yoga can take many forms with emphasis on different things and has been shown to have a positive effect on health. This is normally attributed to the mindfulness and focus on well-being that is often associated with yoga but the yoga included in this study had a minimal mindfulness component. Other types of classes were also performed by the light group such as pilates or a class that was a mixture of tai chi, pilates, yoga and stretching. All of these classes have in common a rather slow pace which would perhaps have led to an improvement in self-efficacy, a sense of mastery and increased body awareness, as the participants realized that they could complete the prescribed exercise. Yoga may be a particularly appealing form of exercise for those with a limited exercise participation history.

5.4 IMPACT ON PHYSICAL ACTIVITY AND SEDENTARY BEHAVIOR

At baseline there was an association between depressive symptoms and Light Physical Activity (LIPA) minutes which is in line with results from previous studies that had also

found associations between physical activity and depression severity (41, 42). Number of sedentary bouts was also associated with depression severity, which had not been explored before though there were some suggestions that sedentary time was associated with depression (59). Importantly, both associations were independent of Moderate-to-Vigorous Physical Activity (MVPA), i.e. even though a person exercises, the number of sedentary bouts and LIPA are still associated with depression severity.

The results from Study I suggested that the baseline activity levels of the sample was lower than in the general population and it was therefore of interest to explore whether this had changed after the intervention and to see if the groups differed in their response. The non-significant, though promising, changes seen in sedentary and LIPA minutes could be due to the fact that the aim of the intervention was not to impact overall activity or sedentary behavior. Two reviews have summarized the available evidence on the impact of interventions on sedentary behavior (127, 128). Though the approach differs in these reviews, they do agree that interventions focusing solely on sedentary behavior are most effective while there is some evidence for interventions combining different components, such as physical exercise, sedentary behavior and dietary advice. Smaller or no effects were seen for interventions that only aim to increase physical activity. Therefore it is perhaps not surprising that small non-significant effects on sedentary time were found in the Regassa study.

There were however some unfavorable changes to both MVPA and sedentary pattern in the light and moderate groups. The moderate group decreased the sedentary minutes but also decreased the number of sedentary breaks and (non-significantly) increased the time in sedentary bouts. This might at first glance appear contradictory, but it would seem that although the average sedentary time was lower, how it was spent was different, changing to longer bouts with fewer breaks. Additionally, both the light and the moderate group decreased the number of MVPA minutes. The reasons for these changes cannot be explained with the data at hand and further investigation is warranted. Perhaps the participants felt (consciously or not), that they had already done "enough" physical activity and were tired after the exercise. This could have led to feeling entitled to longer, less interrupted sedentary time during those times when they were sedentary or reducing MVPA by refraining from transport activity such as walking or bicycling to work. Further studies are needed, perhaps using diaries in combination with accelerometers or even qualitative interviews to explore what lies behind these behavioral changes. Reducing sedentary time and limiting longer bouts is extremely important in depressed population as they have a higher risk of metabolic and cardiovascular diseases(19), both of which have been linked to sedentary behavior(52, 53).

5.5 METHODOLOGICAL STRENGTHS AND LIMITATIONS

5.5.1 Study design

The Regassa study had a strong design as the randomized controlled trial (RCT) is considered to be the golden standard of intervention research due to the fact that the randomization of participants minimizes distortion by confounders. In a classic pharmacological RCT it is

possible to blind the participants to their assigned treatment using a placebo pill but in public health intervention research this is almost never possible. Therefore it is vital to adhere to blinding procedures in other parts of the study, which was done in the Regassa by measuring depression severity and other baseline variables before the randomization took place and the post-treatment and follow-up interviews were also done by personnel blinded to the participant's group allocation. The randomization itself was done by an independent organization (The Karolinska Trial Alliance) and through a computer program, making it impossible for the randomization to be manipulated. Another important aspect of an RCT is having a good control group, in the case of Regassa the control group was active and received treatment as usual. This was done to try to mimic what would have happened to the patients had they not been part of a study, as the it was left up to the primary care physicians to choose the appropriate treatment for their patients.

Another strength of the Regassa study was the large participant sample, to date one of the largest studies to explore exercise at different intensity levels and compare with TAU. As every effort was made to contact the participants post-treatment, and especially at follow-up, the response rate was quite high on the main outcome.

Study I used baseline data in a cross-sectional design and controlling for confounding was therefore an important consideration. Several possible confounders were considered based on the likelihood that they would affect the relationships of interest. Sex and age are commonly considered confounders and could certainly be associated with both physical activity and depression severity. High BMI and poor health status could also be seen as barriers to physical activity and have been associated with depression in previous studies (11). Finally, MVPA was included in the model as to be able to show that the associations found between sedentary behavior and light physical activity were independent of time spent being highly active.

Study II, III and IV utilized the randomization to minimize confounding. However, in Study II and IV the distribution of antidepressant use was uneven at baseline. Therefore it was included as a covariate in all analyses. Due to the small sample in Study III (discussed further below in sections: Statistical power, Selection bias and Accelerometer limitations) further adjusting was done to minimize the individual variation in each model in order to make the associations more robust. Importantly, choosing which confounders to test were based on a prior knowledge and theory.

5.5.2 Statistical power

Power calculations were done for the larger study, i.e. to detect differences between TAU, Internet-Based Cognitive Behavioral Therapy (ICBT), and exercise and it was determined that 930 people, 310 in each arm were needed (effect size=-0.3, 90% power, α=0.05 and drop-out rate=25%). However, no power calculations were done specifically for the studies included in this thesis. Study I might have detected significant differences between diagnoses if more people had been included while Study II and IV were sufficiently powered answer the

main research question of differences between groups and are considerably larger than previously published looking at similar research questions. Study III was not planned a priori but rather devised of as an attempt to explain the results of Study II. Some of the results of Study III, such as changes in sedentary and LIPA time would perhaps have been significant if more participants could have been included.

5.5.3 Bias due to non-response and non-adherence to accelerometer protocol

Participants in the Regassa study are different from the depressed population in general as they were more likely to be motivated to change and were accepting of the possibility to be randomized to exercise. However, as the goal of the Regassa study was to test the effectiveness of two primary care treatments for mild to moderate depression, consequently the results are meant to be generalizable to the population of depressed individuals consulting primary care for help. There were also some steps taken to maximize generalizability to primary care by recruiting participants from all over the country, both rural and urban areas.

As Study I only used baseline data, there were no problems with non-response to questionnaires and interviews. However, just over half of the sample wore their accelerometers and fulfilled the criteria for number of days needed, which led to the aforementioned power problems. Unfortunately, the TAU group was not asked to wear accelerometers which would have provided some interesting comparisons. Furthermore, those that were classified as non-wearers were younger and leaner (lower BMI) than wearers, which could have led to an underestimation of physical activity as they would have been more likely to be more active. On the other hand, questionnaire data addressing physical activity in the year leading up to the inclusion in the study did not depict any significant differences between wearers and non-wearers.

Study III used accelerometer data from the baseline week and the week following the end of the intervention. This led to a selective group of participants as they were older and attended more exercise sessions than the ones that did not have enough accelerometer data. Although it was not part of the intervention protocol to tell people to be more physically active, except for the instruction to exercise three times a week, it might be deduced by the participants that physical activity is beneficial to mental health and should be increased. As the people included in Study III, seemed to adhere better to the protocol than those not included in Study III due to insufficient accelerometer data it might also be assumed that they would be more likely to increase their overall physical activity, leading to an overestimation of the reduction of sedentary minutes and increase of LIPA. An attempt was made to minimize the impact of this by adjusting for age and number of exercise sessions attended.

The response rate to MADRS was high, 76.5% and 83.1% at post-treatment and follow-up, respectively. Study II and IV used Last Item Carried Forward (LICF) to carry out a full Intention To Treat (ITT) analysis on the whole sample according to their group allocation. LICF is a conservative method as it assumes that the participants didn’t improve from the

previous time-point and it yielded similar results as the ITT without LICF (i.e. only those that answered MADRS at post-treatment) in Study II.

5.5.4 Confirming exercise intensity

A key strength of the Regassa study was the use of heart rate data to confirm that the exercise groups differed on intensity. Although there were some technical problems and misunderstandings of how to use the pulse watches, data was collected representing almost 80% of all completed exercise sessions. The data showed clear heart rate differences between the groups allowing for meaningful comparisons to be made despite the real-world setting, which might have led to the assumption that people would just do whatever they pleased.

5.5.5 Non-compliance to exercise protocol

An issue in many exercise interventions is compliance especially in depressed populations as depressive symptoms have been shown to predict lower adherence (129). In Regassa, compliance to the exercise protocol was low; 40.7% attended no exercise sessions, though 32.3% attended 12 or more sessions which was chosen as a cut-off for acceptable attendance. On average the participants attended 8.6 sessions, though when restricted to those who attended at least one session, this rose to 14.5 sessions. The low compliance is comparable to what has been reported in comparable studies (130) and is common in this patient group and reflects the problems that would be associated with trying to implement such an intervention on a larger scale.

Despite the low compliance, exercise still had at least an equal effect to TAU. There are several possible explanations for this. First of all, that the effect of exercise is due to a combination of placebo and the fact that people with mild to moderate depression tend to get better over time. However it is unlikely that this explains all of the effect, as the exercise groups had at least an equal effect to TAU. Since the TAU group received evidence-based treatment this would imply that all the effect of that treatment was also due to placebo effects and the natural progression of depression. Furthermore there were some differences between the exercise groups, for example the light group had lower scores than the moderate group, at both time-points and the vigorous group was the only exercise group that continued to decrease depression severity between post-treatment and follow-up. Therefore it is probable that exercise generates specific effects that led to the further reduction of depression severity.

Another possible explanation is that the intervention led to a change in overall physical activity and sedentary behavior, meaning that the participants exercised more than they reported to the study staff and increased physical activity and decreased their sedentary behavior in their daily life. This was not entirely supported by the results of Study III as there was no significant change to sedentary minutes and LIPA minutes though the change was going in a positive direction. Furthermore, the accelerometer measurement came from people more likely to follow the protocol, and thus might not reflect the behavior of non-compliers, which might have changed their behaviors differently. Another issue with using the accelerometer data was that during the intervention period, the participants were told to

remove their accelerometers while attending the prescribed exercise sessions. The instructions for the last week of accelerometer data collection were to wear the accelerometer even during exercise but this might have been missed by some participants who might have followed the habit of always removing it. The per-protocol results from both Study II and IV showed a similar though stronger pattern as their respective main analysis suggesting that better compliance would have led to stronger results.

5.5.6 Type of exercise

The fact that the type of exercise was not consistent across groups, with one group performing yoga inspired exercises while the other two consisted of aerobic exercise, can be considered both a strength and a weakness. It did allow for comparison of exercise type, to confirm that the exercise sessions did not have to be aerobic and provided high quality evidence for the effect of yoga like exercising on depression which had previously been lacking. On the other hand, some might want to have a more "pure" comparison with all groups being aerobic but of different intensity. This was considered when the study was originally designed but it proved problematic to come up with low impact aerobic exercise that could be practiced under the same conditions as the other two groups, i.e. being offered by the fitness chain used in the study. This excluded walking as it is usually done outside and led by a trainer. This could have added a component of nature experiences. Pure stretching classes were not offered in the fitness center chain. A compromise was reached by using yoga classes, but it was also possible to attend similar classes consisting of pilates or tai chi. One can argue that any light intensity exercise invites the opportunity for more mindfulness as the focus is on the body in most exercise types and light intensity allows for the time to reflect on that.

5.5.7 Accelerometer limitations

Accelerometers represent a very convenient way of objectively collecting massive amounts of data on people's activity patterns but they are not without drawbacks. They do not accurately detect bicycling and swimming, though newer versions have started to come in water resistant versions. Therefore if the sample in Study III increased their swimming or bicycling it would not have been detected and led to an underestimation of the change in MVPA. This could especially have been a problem if the baseline week occurred in the winter while the post-treatment week occurred in the summer as bicycling and swimming are traditionally more common in the summer in Sweden.

There are also disagreements on many aspects of the protocol for using accelerometers in research. For example how many days are needed to accurately depict a week of physical activity? The literature does not agree on this and there is also the burden to the participants to consider. In Study I, the chosen cut-off was four days, with at least one of those a weekday. Three to five days has been suggested as an acceptable number of days for representing a week of activity for adults (131, 132) though others have found that seven days are needed to accurately measure sedentary behavior (133). In Study I four days represented

the acceptable balance of validity and maximizing the number of participants. Study III was underpowered which led to the decision to relax this criterion to having at least one weekday and one weekend day. However, most participants did fulfill the criterion used in Study I or 92.7%.

As the storage space in the accelerometer units has grown, it has become more popular to use smaller epochs to store the data. An epoch refers to the amount of data that is collected and then summarized. For example a common setting is using 60 second epochs, meaning that for each minute the activity is summarized and stored. Using smaller epochs such as 15 second epochs is more important in children than adults, as they tend to change their activity patterns quickly and frequently. In Regassa, epochs of 15 seconds were originally supposed to be used but by mistake a small part of the accelerometers was set to collect 60 second epochs, all of the data had to be changed to 60 second epochs as it is impossible to re-capture details that have already been averaged. It is difficult to say how this could have affected the measurements; it could have led to either an over- or underestimation of activity.

Although the cut-off for MVPA of 1972 counts per minute seems to be quite accepted the same cannot be said for the cut-off for sedentary time. A cut-off of a 100 counts is frequently used but is being challenged with a cut-offs of 150 or 200 which might be more valid (134)

Another important issue to consider is adjustment for wear time. It is generally accepted that a wear time of 10 hours is the minimum for representing a full day (135), but there might be variation in how long people chose to wear the accelerometers. Neglecting to adjust for wear time, as was done in Study I, could lead to a distortion of values as the non-wear time might more frequently occur during sedentary time, if for example the participants changes clothes after coming home, they might neglect to put the accelerometer on again. In Study III, wear time was adjusted for by standardizing the minutes spent in sedentary, LIPA and MVPA to 16 hour days. Of course the assumption here is that people spend their non-wear time in the same proportion in sedentary, LIPA and MVPA as they did during wear time.

An example of how important the different protocol decisions can be when working with accelerometers, a study by Hagströmer et al. (2007) showed that determining whether people have fulfilled physical activity recommendations is largely dependent on how an activity bout is defined(136). If 30 minutes of moderate-to-vigorous physical activity is defined as all MVPA accumulated throughout the day, the proportion of people in a sample from the general Swedish population that reach this goal is 57%. However when the 30 minutes have to be accumulated in bouts of at least 10 minutes, the proportion is 1%. In study I, an MVPA bout was defined as at least 30 minutes, collected in bouts of 10 minutes but as there was an allowance of 2 minutes of drop time (dropping below 1972 counts per minute) which might be rather generous and might have overestimated the proportion of people fulfilling public health recommendations. The question becomes whether any physiological (or psychological) effects can be expected when each bout is so short.

5.6 IMPLICATIONS OF FINDINGS

5.6.1 Public health policies

As people with mild to moderate depression do not always seek help from the health care system, it is important for there to be reliable sources of information for those that wish to use exercise as a self-help method for depression or in combination with other treatments. Updated guidelines from public health should include an emphasis on the importance of starting some type of exercise, be it at a low or high intensity. Awareness should be raised, perhaps through media campaigns or collaborations with the private sector which abounds with different apps meant to increase physical activity. An effort could be made for making exercise a more feasible option through changes to the environment or policies regarding flexibility at work for exercising. Additionally, the importance of exercising for reducing and preventing depression could be included in health education classes in schools. This would further strengthen the already established message of the importance of exercise not only for physical but also for mental health and that the exercise does not have to be of high intensity. Although not assessed in this study, previous research has shown that regular exercise is a highly effective way to reduce the substantial cardio-metabolic risks associated with depression (123, 124).

5.6.2 Clinical guidelines

The rationale for including three exercise arms in the Regassa study was to determine the optimal dose response. As it turned out, the exercise groups were at least equivalent to TAU, though each exercise group also had its drawbacks. The light group had decreased their depression severity more than the TAU group at both time points but they also had a decrease in MVPA minutes. The vigorous group had comparable results to the light group, usually lower but non-significantly so and was the only exercise group to continue decreasing depression severity between post-treatment and follow-up. However vigorous exercise might not be seen as feasible to all people and might even be too intimidating to contemplate by some. Therefore, based on the evidence at hand, exercise, by itself or in combination with other treatment can be advised. The patient should be allowed to choose the intensity him or herself, which is supported by a recent review (137) and evidence from studies on affect which suggest that people are happier with self-selected intensity and do tend to choose an intensity that falls within public health recommendations(86).

5.6.3 Future studies

An interesting and important area of study is how to increase compliance to exercise. As seen in the Regassa study compliance is a problem with many participants choosing not to attend even a single exercise session. Previously, it has been shown that depressed individuals have lower intentions of exercising than their healthy counterparts and those that do intend to exercise are less able to follow through with their intentions (138). Further exploration in this area is needed to increase compliance, perhaps through intervention studies to explore exactly what is the minimum support required for depressed individuals to maintain their exercise

program. The Regassa study provided the exercise participants with a "check in" meeting once a week but this would probably not be feasible in most settings. Some form of internet or mobile app support could be deployed instead, perhaps specifically geared towards this population, though this would of course needed to be rigorously tested.

Furthermore, it would be useful to be able to predict whether exercise will help a particular patient. A very recent study showed that affect following the first exercise session predicted treatment response and remission following a 12 week exercise intervention (139). However this study was exploratory and the results would need to be confirmed in the future, while also including other factors and interactions thereof.

More studies are also needed on sedentary behavior in depressed people and whether an intervention specifically designed for targeting sedentary behavior can lead to a reduction in depression. This could inform both public health authorities and clinicians on whether advice on changing sedentary behavior is needed in this population.

5.7 CONCLUSIONS

The data in this thesis comes from a large, community-based randomized controlled trial with stringent blinding procedures and an appropriate 'treatment as usual' comparison group. The important question of which exercise intensity is most effective in treating depression has been debated in the literature for decades. Moreover, few studies have examined the long-term effects of exercise on depressive symptoms and the effects of prescribed exercise on habitual physical activity and sedentary behavior are also poorly understood. This thesis contributes new, clinically relevant knowledge to several of these key research domains.

The findings show that people with mild to moderate depression are substantially more sedentary than the general population, indicating a significant treatment potential for exercise. The results also indicate that exercise can be prescribed for mild to moderate depression at a preferred intensity, ranging from light to vigorous. The effects of exercise on depression severity - both in the short and long-term - are at least comparable to treatment as usual by a physician; and in the case of light exercise, possibly better. The impact of exercise on physical activity and sedentary behavior in this study was complex, and further research is needed to better understand these inter-relationships. This is particularly important in the context of emerging research into the association between depression, physical activity and sedentary behavior. As suggested throughout this thesis, there is no mental health without physical health. In addition to improving the symptoms of depression, exercise also has the potential to reduce the significant cardio-metabolic risks associated with depression.

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