

THE UNIVERSITY OF CAPE TOWN

SWEATING AWAY DEPRESSION?

THE IMPACT OF INTENSIVE EXERCISE ON DEPRESSION

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**SWEATING AWAY DEPRESSION?
THE IMPACT OF INTENSIVE EXERICSE ON DEPRESSION**

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DEDICATION

TO MY PARENTS, THANK YOU FOR SUPPORTING ME AND ENCOURAGING ME
TO FOLLOW MY DREAMS.

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I would like to thank my supervisors for all their help and guidance during my time at ESSM. Thank you Dr. Laurie Rauch for your guidance and knowledge. Also, thank you to Dr. Ross Balchin for meeting with me every week during data collection and for encouraging me to push through. A special thanks to Dr. Dee Blackhurst for analyzing all the blood samples. Last but not least, I want to thank all the staff and students at ESSM for making my stay in Cape Town worthwhile and for their words of encouragement when it seemed like there was no end in sight. I am thankful for the friendships I have gained throughout this process and will look back fondly on my experience obtaining my Masters at UCT.

TABLE OF CONTENTS

LIST OF TABLES	VIII
1.) Baseline characteristics	VIII
2.) Depression questionnaire scores	VIII
3.) Results of column statistics for measurement of serum β -endorphin concentrations within the three experimental groups, before and after exercise.....	38
4.) Results of individual changes within the three experimental groups, before and after exercise.....	VIII
5.) Results of pooled data and other statistical analyses for measurement of serum β -endorphin concentrations for all three groups.....	40
LIST OF FIGURES	VIII
1.) HAM-D and MADRS scores for participants who dropped out of the study	VIII
2.) Severity of depression for those who dropped out of the study	VIII
3.) Average heart rate per exercise session for each group over six weeks	VIII
4.) Average heart rates for all three groups	VIII
5.) Average heart rate per participant	VIII
6.) Box and whiskers indicating the initial and final HAM-D scores for all three exercising groups.....	VIII
7.) Overall results and severity of depression at the end of 6 weeks.....	VIII
8.) MADRS scores.....	VIII
9.) β -endorphin levels for Moderate-and High-intensity groups.....	37
ABSTRACT	IX
1. LITERATURE REVIEW	- 1 -
2. AIMS AND HYPOTHESES	- 20 -
3. METHODOLOGY	- 20 -
3.1 PARTICIPANTS.....	- 20 -
3.1.1 EXCLUSION CRITERIA.....	- 21 -
3.2 MATERIALS.....	- 22 -
3.2.1 <i>The Hamilton Rating Scale for Depression</i>	- 22 -
3.2.2 <i>Montgomery Åsberg Depression Rating Scale</i>	- 22 -
3.2.3 <i>Heart Rate Monitor</i>	- 23 -
3.2.4 <i>DVDs</i>	- 23 -
3.2.5 <i>Lode Bike</i>	- 23 -

3.2.6 BORG scale.....	- 23 -
3.2.7 Peak Sustained Power Output (PSPO) test	- 24 -
3.2.8 Beta Endorphin Analysis.....	- 24 -
3.3 DESIGN.....	- 28 -
-	
3.4 DATA ANALYSIS.....	- 25 -
3.4.1 B-endorphin analysis	- 25 -
3.5 PROCEDURE.....	- 26 -
4. RESULTS	- 28 -
4.1 Participant drop out	- 28 -
4.2 EXPERIMENTAL PARTICIPANTS: Heart Rate ranges	- 30 -
4.3 Psychological data	- 33 -
4.4 B-endorphin.....	- 36 -
5. DISCUSSION.....	- 39 -
5.1 Depression scores.....	- 28 -
5.2 β -endorphins.....	- 28 -
5.3 Frequency.....	- 28 -
6. LIMITATIONS.....	- 47 -
7. CONCLUSION.....	- 48 -
7. REFERENCES	- 49 -
8. APPENDICES	- 52 -
Appendix A: MDI.....	- 52 -
Appendix B: Hamilton Rating Scale of Depression (HAM-D)	- 55 -
Appendix C: Montgomery Åsberg Depression Rating Scale (MADRS)	- 56 -
Appendix D: Health and History Questionnaire	- 57 -
Appendix E: Consent form	- 62 -

LIST OF TABLES

- 1.) Baseline characteristics
- 2.) Depression questionnaire scores
- 3.) Results of column statistics for measurement of serum β -endorphin concentrations within the three experimental groups, before and after exercise
- 4.) Results of individual changes within the three experimental groups, before and after exercise
- 5.) Results of pooled data and other statistical analyses for measurement of serum β -endorphin concentrations for all three groups

LIST OF FIGURES

- 1.) HAM-D and MADRS scores for participants who dropped out of the study
- 2.) Severity of depression for those who dropped out of the study
- 3.) Average heart rate per exercise session for each group over six weeks
- 4.) Average heart rates for all three groups
- 5.) Average heart rate per participant
- 6.) Box and whiskers indicating the initial and final HAM-D scores for all three exercising groups
- 7.) Overall results and severity of depression at the end of 6 weeks
- 8.) MADRS scores
- 9.) β -endorphin levels for Moderate- and High-intensity groups

ABSTRACT

In periods of prolonged stress and pain from strenuous exercise, the body produces chemicals called endorphins that help it endure pain. These natural analgesics are presumably only released when the level of pain intensity is at least moderately high. The PANIC/separation distress system is built on the same pathways as the physical pain system, and is responsible for the ‘mental pain’ (feelings of panic anxiety, loss and sorrow) that is associated with the loss of an attachment object, or separation from it. Given this overlap, it is reasonable to expect that endorphin release can affect depressive symptoms in a positive way. There is existing evidence that exercise has a beneficial effect on depressive symptoms, yet the underlying physiological mechanism has yet to be properly determined. The purpose of this three-armed prospective randomized control pilot study was therefore to try to establish this mechanism by investigating whether intensive exercise can improve the symptoms of moderate depression as a result of demonstrable increases in plasma β -endorphins. It has previously been established that exercise-induced β -endorphin release correlates positively with the intensity of the exercise.

There were two central hypotheses for this study. The first was that the mechanism behind the improvements seen in depressive symptoms due to exercise is the same mechanism that is responsible for the established analgesic effect of exercise, namely endorphin release. The second hypothesis was that only high-intensity exercise (i.e. greater than 70% of heart rate reserve) will be sufficient to produce a guaranteed endorphin release, whereas moderate-intensity exercise (just under 50% of the heart rate reserve) and very low intensive exercise would not be sufficient to release endorphins, and would therefore not result in an improvement in depressive symptoms. The main aim was therefore to investigate whether intensive exercise (greater than 70% of heart rate reserve) improves moderate depression, and if so, whether this correlates with a demonstrable increase in β -endorphins. This study therefore wished to determine which of low, moderate or high intensity exercise alleviates the symptoms of depression. It also intended to determine whether an increase in β -endorphins correlates to an improvement in the participants’ depression levels, and whether greater β -endorphin release occurs during high-intensity exercise compared to low- and moderate intensity exercise.

Male participants (n = 33) with *moderate* levels of depression were randomly assigned to one of three experimental groups of varying exercise intensities: High-intensity (> 160 beats

per min (bpm)), Moderate intensity (140bpm), and a low-intensity control group (under 120bpm). All participants underwent a six-week exercise program that involved participation for three days per week, for one hour per day (i.e. 18 sessions in total). Once weekly, the Hamilton Rating Scale for Depression (HAM-D) and the Montgomery Åsberg Depression Rating Scale (MADRS) were administered to each participant. The participants in the High- and Moderate-intensity exercise groups each had 5ml of blood drawn, once per week, before and after exercise, in order to measure their β -endorphin levels, and to track any changes in these levels over time. The participants in the Control group had blood samples taken twice – once at the start of the study (a baseline measure), before and after exercise, and once on completion of the study, before and after exercise.

The results indicate that both Moderate- and High-intensity exercise improved the participants' depression levels, while the Control group also showed some improvement, but not to the same extent as the other two groups. A significant difference ($p < 0.0001$) was found when comparing the initial and final HAM-D scores between all three groups. The participants' MADRS scores also improved between all three exercising groups. A significant difference ($p = 0.0182$) was found when comparing the initial scores within each of the three groups to their final MADRS scores. No significant difference was found in the serum β -endorphin levels when comparing the Moderate- with the High-intensity group. The differences between the baseline and post-exercise serum β -endorphin measurements were also not significantly different for both the Moderate- and High-intensity groups ($p = 0.953$ and $p = 0.992$ respectively), while the Control's pre- to post levels decreased significantly ($p < 0.017$). A significant difference between the Control-, Moderate-, and High-intensity groups ($p < 0.022$) was found when comparing the three groups' serum β -endorphin concentrations after they engaged in exercise.

Overall, the results of this pilot study go against the hypothesis that only High-intensity exercise would improve symptoms of moderate depression, as both high- and moderate-intensity exercise had a clear positive impact on depression scores. However, consistent with this hypothesis, very-low intensity exercise did not seem to have as beneficial an effect. The mechanism underlying the benefit of exercise on the symptoms of depression cannot be conclusively confirmed given the overall β -endorphin results. A larger sample size and more accurate analysis methods of β -endorphin levels are required in order to test these tentative findings more rigorously.

1. LITERATURE REVIEW

Depression is a very prevalent mental disorder that affects 340 million people globally and is projected to become the leading cause of disability, and the second leading contributor to the global burden of disease (GBD) by the year 2020 (Dinas et al., 2011). Depression can have a detrimental effect on a sufferer's health, mental well-being, activities of daily living, and self-worth. Depression can affect each person at least once in their lives, and it is a mental disorder that most do not want to confess to having. A combination of environmental, genetic, biological and psychological factors can give rise to depression; for example, the loss of a loved one, stress from work or losing a job, trauma, a difficult relationship, or moving to a new location, can all trigger a depressive episode.

Most doctors or psychiatrists will look to anti-depressive therapy in the form of drugs, psychotherapy, support groups, or lifestyle/behavioural modification in order to help patients diagnosed with depression symptoms. Admitting to suffering from depression can be difficult and embarrassing. Most people do not seek help, or receive inadequate treatment; Stein (2005) estimates that a mere quarter to one half of patients with depression in the United States receive adequate care. Moreover, many people with depression avail themselves of complementary and alternative therapies, which perhaps speaks to their dissatisfaction with, or inadequate access to, conventional treatments (Stein, 2005). Not all treatments work for everyone, and it might take a depression sufferer numerous attempts at trying different treatments in order to help alleviate his/her symptoms. This may cause anguish, and can potentially lead to doubt over the treatments, thereby resulting in discontinuation and remission.

There is existing evidence that exercise has a beneficial effect on depressive symptoms. However, the physiological basis of the antidepressant effect of exercise has not been fully investigated. Whilst key research needs to be undertaken in order to investigate the mechanisms responsible for this relationship, the fact remains that physical activity is good for physical and mental health, and therefore beneficial for overall well-being (Blake, 2012). There are a lot of factors to consider. Everyone responds differently to exercise: some love it and some hate it. Motivation is key to living an active lifestyle and for some finding the time or motivation to exercise is difficult. Furthermore, is 30 minutes of physical activity per day,

five times per week enough to make an impact? Even though numerous studies suggest that exercise is beneficial in alleviating the symptoms of depression, it is still unclear how much, how frequent, how intense this exercise should be, and what kind of exercise is best. In periods of prolonged stress and pain from strenuous exercise, the body produces chemicals called endorphins that help the individual endure pain. However, it is understood that these natural ‘painkillers’ are only released once exercise intensity has reached moderate to high levels.

To date, there have been few clinical-control trials looking at exercise and its effects on depression. Most, if not all, studies find that exercise is an effective treatment and is comparable to antidepressant therapy. However, it is still unclear which mode, frequency or intensity of exercise is most effective, and the physiological mechanism underlying exercise’s antidepressant effect has yet to be established. There are very few studies that have looked at different intensities of exercise to alleviate depression. The relationship between exercise and endorphins is another area that has been inadequately studied.

What is depression?

Depression refers to a wide range of mental health problems characterized by the absence of a positive affect (a loss of interest and enjoyment in ordinary things and experiences), low mood, and a range of associated emotional, cognitive, physical and behavioural symptoms (NICE, 2007). Individuals suffering from depression show signs of decreased energy and low levels of physical activity, and a lack of motivation and interest towards hobbies or tasks that they once enjoyed — which may lead to feelings of guilt, decreased appetite or sleep, low self-worth, and low levels of mood. These symptoms may become chronic when they carry on for months, which can even lead to disability or suicide in extreme cases.

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) categorizes major depressive disorder (MDD) as a clinical syndrome characterized by depressive mood or loss of interest in activities, which last for two weeks or more, and which are accompanied by at least four additional features involving emotional, physiological, or cognitive symptoms; for example, sleep disturbances, changes in eating habits, fatigue, suicidal thoughts, reduced ability to concentrate (DSM-V, American Psychiatric Association,

2013) (Josefsson, Lindwall, & Archer, 2013). Depression is a common and important cause of morbidity and mortality worldwide.

Treating depression

There are many forms of treatment for depression, the most popular being antidepressants and psychotherapy. Even though numerous treatment options are available, not all therapies work for everyone. Most depression sufferers will try one form of treatment and, if it is not successful, will then be reluctant to try another. Antidepressant therapy in the form of drugs such as paroxetine (Paxil), fluoxetine (Prozac), sertraline (Zoloft), fluvoxamine (Luvox), and citalopram (Celexa) may have many side effects. Acute side effects include: upset stomach, nausea, headache, fatigue, dry mouth, and nervousness. Some of the more chronic side effects include: sleep disturbances, increased risk of cardiovascular disease, sexual dysfunction, weight gain, and insomnia. Furthermore, adherence to antidepressant medications is often poor, and patients frequently discontinue their antidepressant therapy prematurely. It has been suggested that approximately 50% of psychiatric patients and 50% of primary care patients, are non-adherent when assessed 6-months after the initiation of treatment (Blake, 2012).

There are many different forms of psychological treatment, including cognitive behavioural therapy (CBT); behaviour therapy (BT); interpersonal psychotherapy (IPT); problem-solving therapy (PST); counselling, short-term psychodynamic psychotherapy; and couple-focused therapies (NICE, 2007). There has been increasing interest in the potential role of alternative therapies for the management of depression, such as music therapy, light therapy, acupuncture, family therapy, marital therapy, relaxation, and exercise (Mead et al., 2009). However, with all of these treatment options available, why is the burden of depression increasing each year? Of the 130 cases of depression (including mild cases) per 1000 population (Great Britain), only 80 will consult their GP. The most common reasons given for reluctance to contact the family doctor were: did not think anyone could help (28%); a problem one should be able to cope with (28%); did not think it was necessary to contact a doctor (17%); thought the problem would get better by itself (15%); too embarrassed to discuss it with anyone (13%); afraid of the consequences (e.g. treatment, tests, hospitalisation, being sectioned - 10%) (Meltzer et al., 2003).

Evidence shows that pharmacotherapy is only effective in about one third of depressed patients, and some only have a partial response to treatment, thereby prompting the need to

identify other forms of treatment. Exercise is becoming more popular for treating depression, and can be used in conjunction with other treatments. There are a number of possible theoretical reasons as to why exercise may improve depression (Mead et al., 2009). Physical exercise has also received a significant amount of attention with regard to stress reduction and improving mood (Hamer et al., 2012). Physical activity, including exercise, is a relatively inexpensive and non-harmful lifestyle intervention, which lacks the side-effects of medication and does not require the introspective ability required for most psychotherapies (Kruisdijk et al, 2012).

Benefits of exercise and physical activity

Regular physical activity is associated with better mental health and wellbeing (Hammer et al., 2012). The benefits of engaging in regular physical activity include an increased work capacity (U.S Department of Health and Human Services, 1996); decreased body fat and increased lean body tissue (Sidney et al., 1977); increased bone density (Smith et al., 1976); and lower ratings of coronary heart disease (CHD) (Paffenbarger et al., 1978), diabetes mellitus, hypertension (Tipon et al., 1991) and cancer (Lee et al., 1991). Regular physical activity and exercise can also assist in improving one's mood and motivation (Ntoumanis et al., 1999), as well as enhance their quality of life, improve one's capacity for work and recreation, and alter one's rate of decline in functional status (Shephard et al., 1999).

The Healthy People 2020 Physical Activity Objective PA-2.1 (U.S Department of Health and Human Services, 2011) highlights the need for *every adult to engage in moderate aerobic physical activity for at least 150 min per week or 75 min of vigorous aerobic physical activity per week or an equivalent combination*. With depression having such a high prevalence, affecting 340 million people globally, it is projected to become the leading cause of disability, and the second leading contributor to the global burden of disease by the year 2020 (Dinas et al., 2011). In looking at exercise as a means to cure or lessen the symptoms of depression, there is sufficient evidence showing that exercise is an effective mechanism. Goodwin et al. (2003) examined 5877 individuals aged 15-54 years and showed that those who were more physically active reported lower levels of depression than non-active individuals. Paffenbarger and colleagues conducted a classic study in 1994. They examined the questionnaires of 31 000 Harvard College graduates in 1962, 1966, 1977 and 1988 and found that physically active individuals reports lower depression levels than their physically inactive peers.

Dinas et al. (2011) found that exercise and being physically active have beneficial results on depressive symptoms and are comparable to those of anti-depressive therapy. Blumenthal et al. (2012) looked at a combination of the medication sertraline and exercise and how effective this was in alleviating depressive symptoms. These authors found that a combination of both was more effective in reducing depressive symptoms compared to placebo in patients with coronary heart disease. Rimer et al. (1996) and Jodefsson et al. (2013) found that exercise seemed to improve depressive symptoms when compared to a control and no treatment condition in people diagnosed with depression. Dunn et al. (2005) looked at different doses of exercise and found that a dose consistent with ACSM's daily-recommended amount of physical activity per week (i.e. 30 minutes of an aerobic activity five days per week, or vigorous activity for a minimum of 20 minutes, three days per week) was sufficient in reducing depressive symptoms. Mead et al (2009) found that the effect of exercise was not significantly different to that of cognitive therapy, which means that individuals suffering from depression might be able to either partake in exercise to alleviate depression, or do cognitive therapy, given that they seem to yield similar results. Kruisdijk et al. (2012) also found that exercise as a remedy for depression can be used as a standalone intervention or as an add-on intervention. Moses et al. (1989) took sedentary individuals and assigned them to four exercise conditions, with their findings being that psychological benefits were seen with the moderate exercise condition, but not with the high exercise or attention-placebo conditions. Krogh et al. (2011) found a short-term benefit for exercise as a remedy for depression in clinically depressed patients.

Exercise as a means to alleviate depression

Encouraging evidence has shown that exercise and physical activity have beneficial effects on symptoms of depression that are often comparable to those of antidepressant treatments (Dinas et al., 2011). Engaging in regular exercise does not carry a stigma, is relatively low in cost, and can be done outside standard medical settings. In addition, exercise may be a more acceptable treatment for some (e.g. pregnant women and adolescents) because of its relative safety and lack of side effects compared to antidepressant drug treatments (Dunn et al., 2002). Prescribing exercise to treat depression is still a fairly new concept, and knowing how much exercise is required, and what duration is necessary, are issues that still require further investigation. In general, exercise is good for overall well-being and fitness, as prescribed by the American College of Sports Science (ACSM) — i.e. 30 minutes of an aerobic activity

five days per week, or vigorous activity for a minimum of 20 minutes three days per week (ACSM's guide for Exercise Testing and Prescription, 8th edition, p.8). To date, research is showing that exercise and physical activity can be used as therapeutic means for acute and chronic depression in the general population, as well as in hypertensive and cardiovascular disease patients (Dinas et al., 2011). Exercise also increases a person's feeling of well-being and is an effective therapy for many chronic diseases in older adults. If one searches for studies using the key words *depression*, *exercise*, and *physical activity*, one will find hundreds of articles that support exercise as a means to cure depression, or to minimize its symptoms.

The burden of depression

The GBD study highlights how mild to moderate MDD ranks second behind ischemic heart disease for years of life lost due to premature death or disability (Dunn et al., 2005). Depression has serious effects on a person's health and can lead to heart disease and even death if left untreated. Ferrari et al. (2013) looked at the burden that depression has on health and they found depressive disorders were a leading cause of disease burden in the 1990 and 2000 GBD studies. The GBD initiative, which aims to provide data that can be used to improve public-health policy and the knowledge that depressive disorders are a leading cause of disease burden worldwide, has helped to prioritize depressive disorders in global public-health agendas. Researchers collected data from published articles on the prevalence, incidence, remission rates, and burden of MDD and dysthymia (sub-clinical depression) and on the excess deaths caused by these disorders. Major depressive disorder was also a contributor of burden and added to the prevalence of suicide and ischemic heart disease. These findings emphasize the importance of making depressive disorders a public-health priority and implementing cost-effective interventions to reduce its burden (Ferrari et al., 2013).

Depression often co-occurs with other chronic diseases and can worsen their associated health outcome. Prevalence values for four chronic physical diseases — angina, arthritis, asthma, and diabetes — were also estimated using algorithms derived via a Diagnostic Item Probability Study (Moussavi et al., 2007). These data came from 245 404 participants from 60 countries, and from all regions of the world. The authors found that a significant percentage of respondents with any one of the chronic physical conditions also had depression. For respondents with diabetes, at the worldwide level, 9.3% (7.3–11.3) also had

depression; 10.7% (9.1–12.3) with arthritis also had depression; 15.0% (12.9–17.2) with angina; and the respondents with asthma had the highest prevalence of depression at 18.1% (15.9–20.3). For the 7.1% (6.6–7.6) of respondents who had comorbidity of two or more chronic physical conditions, nearly a quarter (23%) also had depression in addition to their existing comorbid conditions. Thus, the prevalence of depression in individuals with chronic diseases is significantly higher (3.2%, $p < 0.0001$) than in individuals without such conditions (Moussavi et al., 2007). By examining these results, it is clear that depression had the largest effect on worsening mean health scores when compared to other chronic conditions. If a participant had one or more chronic diseases coupled with depression, then s/he had the worst health scores overall. These results indicate the urgency needed in addressing depression as a public-health priority in order to reduce disease burden and disability, and to improve the overall health of populations (Moussavi et al., 2007).

Depression also plays a detrimental role in cardiovascular disease (CVD). The relationship between depression and CVD is bidirectional: just as depression increases the risk for CVD, so too the development of CVD increases the risk for depression (Rozanski, 2012). To the knowledge of Blumenthal and co-workers, no randomized clinical trial has examined the effects of exercise on depression in patients with CVD. Therefore, these authors assessed the efficacy of exercise and antidepressant medication in reducing depressive symptoms and improving cardiovascular biomarkers in depressed patients with coronary heart disease (Blumenthal et al., 2012). In their UPBEAT (Understanding the Prognostic Benefits of Exercise and Antidepressant Therapy) study, 100 outpatients with coronary heart disease and elevated depressive symptoms were randomized to either 4 months of aerobic exercise (3 times/week), the drug sertraline (50-200 mg/day), or a placebo. Other assessments of cardiovascular biomarkers were made, including heart rate variability, endothelial function, baroreflex sensitivity, inflammation, and platelet function. This study found that after 16 weeks, all groups showed improvement based on Hamilton Rating Scale for Depression scores. Their participants in both the aerobic exercise (mean -7.5; 95% confidence interval: -9.8 to -5.0) and the sertraline (mean -6.1; 95% confidence interval: -8.4 to -3.9) groups achieved larger reductions in depressive symptoms compared with those receiving the placebo (mean -4.5; 95% confidence interval: -7.6 to -1.5; $p = 0.034$). Exercise and sertraline were equally effective at reducing depressive symptoms ($p = 0.607$). Exercise and medication tended to result in greater improvements in heart rate variability compared with placebo ($p = 0.052$); and exercise tended to result in greater improvements in heart rate variability

compared with sertraline ($p = 0.093$) (Blumenthal et al., 2012). In conclusion, this study found that both the exercise and sertraline groups had greater reductions in depressive symptoms compared to the placebo group. Exercise is seen to have cardiopulmonary benefits and was effective in lowering depressive symptoms. These findings add to the growing body of research suggesting that exercise may be a viable alternative to traditional psychopharmacological treatments of depression.

The effect of exercise and physical activity on depression

Based on the currently available evidence, it is clear that exercise and physical activity have beneficial effects on depression symptoms that are comparable to those of antidepressant treatments. Dinas et al. (2011) reviewed the published evidence covering topics such as the link between β -endorphins and exercise; exercise, physical activity and depression; exercise and physical activity as treatments for depression; the properties of exercise stimuli; intervention programs; and the efficacy of exercise and physical activity for treating depression in diseased individuals. These authors found that exercise of sufficient intensity and duration increased circulating β -endorphin levels, which positively affected mood. However, they concluded that the mechanism by which β -endorphins decrease depressive symptoms is incomplete. With regard to exercise and physical activity, Dinas et al. found an inverse linear relationship: an increase in exercise frequency reveals lower reported levels of depression and similarly, decreased activity shows higher levels of depression. Looking at exercise and physical activity as treatment for depression, the authors found that aerobic exercise programs were more successful than placebo and pharmacological treatments in reducing the symptoms of depression. For the properties of exercise stimulus, they found that the duration of exercise interventions is not clearly related to outcome, but the more intense the exercise regime, the larger the improvements in mood seem to be. If aerobic and resistance training is combined, then they have a stronger effect than aerobic and flexibility training.

Supervised programs also show promising effects, whereas participants in unsupervised programs do not have the encouragement to continue, and consequently lose the interest to complete the program. On the topic of exercise and physical activity for treating depression in diseased individuals, Dinas et al. (2011) found exercise to be beneficial for patients who were recovering from heart attacks in improving their depressive symptoms, but these benefits for cardiovascular mortality/morbidity may be independent of their effects on

depression. The authors highlight that more research needs to be done given the methodological limitations of the existing research, which preclude a clear identification of the optimum exercise properties for treating depression, while the risk and cost effectiveness associated with relevant interventions remain unknown (Dinas et al., 2011). Overall, these authors found that the evidence presented suggested that exercise and physical activity have beneficial effects on depression symptoms that are comparable to those of antidepressant treatments.

Mead and co-workers (2009) did a review on exercise in relation to depression in order to examine its effectiveness in the treatment of depression. For this review, twenty-eight trials fulfilled their inclusion criteria, of which 25 provided data for meta-analyses. These authors state that depression is commonly treated with antidepressants or psychological therapies, or a combination of both. However, a Cochrane review (Moncrieff, 2003) found only small differences between antidepressant medications and active placebos. Furthermore, antidepressants may have adverse side effects, adherence can be poor, and there is a lag time between one starting antidepressants and improvements in mood. Psychological treatments are generally free from side effects, but some people may not wish to attend psychotherapy because of perceived stigma (Mead et al., 2009). Overall, this review revealed that methodological factors, in particular intention-to-treat analyses and blinding of outcome assessors, influenced the effect size and the significance of these effects. Hence, further trials that are methodologically robust are required in order to determine more accurately, the effect of exercise on depression. The authors also found that the effect of exercise was not significantly different from that of cognitive therapy.

One paragraph in the above-mentioned review that is interesting and relevant to the present study is where the authors looked at data regarding the intensity of exercise. Here, they found that high-intensity exercise was more effective than low-intensity exercise, and the same applied for resistance training (Singh, 2005). The authors also found that mood correlated with fitness (Blumenthal, 1999; Pinchasov, 2000; Martinsen, 1985; Singh, 2005). They suggest additional subgroup analyses that look at supervised versus unsupervised training, indoor versus outdoor training, and individual versus group training. There is also a need for studies that are larger in terms of sample size in order for the effect size to have statistical significance.

A less recent review by Rimer and co-workers (1996) sought to determine the effectiveness of exercise in the treatment of depression by looking at thirty-two trials (1858 participants) that fulfilled their inclusion criteria, of which 30 provided data for meta-analyses. In six trials that compared exercise with cognitive behavioural therapy (152 participants), the effect of exercise was not significantly different from that of cognitive therapy. The authors concluded that exercise seemed to improve depressive symptoms in people with a diagnosis of depression when compared with no treatment or control intervention; however, since analyses of methodologically robust trials show a much smaller effect in favour of exercise, some caution is required when interpreting these results (Rimer et al., 1996).

Another meta-analysis and systematic review by Josefsson et al. (2013) looked at physical exercise interventions in depressive disorders in order to determine the efficacy of: (i) exercise in reducing symptoms of depression compared with no treatment; (ii) placebo conditions; and (iii) usual care among clinically defined depressed adults (Josefsson et al., 2013). Here, the authors looked at 89 studies, of which 15 passed the inclusion criteria and 13 presented adequate information for calculating effect size. The results of the meta-analysis showed adequate evidence that physical exercise reduces depression, and showed a significantly large overall effect favouring exercise intervention. However, the authors also state that it is not possible to determine exactly how effective exercise is in reducing depression symptoms in clinical and nonclinical depressed populations respectively.

Krogh et al. (2011) have also conducted a systemic review and meta-analysis that examined the effect of exercise in clinically depressed adults. These authors identified thirteen trials that fulfilled their inclusion criteria, of which eight had adequate allocation concealment, six with blinded outcome, and five used intention-to-treat analyses. Findings indicated that there was an inverse association between duration of intervention and the magnitude of the association of exercise with depression ($P=.002$). Pooled analysis of five trials with long-term follow-up (i.e. that examined outcomes beyond the end of the intervention) suggested no long-term benefit (SMD, $-.1$; 95% CI, $-.28$ to $.06$). Only three studies were assessed as high quality (adequately concealed random allocation, blinded outcome assessment, and intention-to-treat analysis). When the results from these studies were pooled, the estimated beneficial effect of exercise was more modest (SMD, $-.09$; 95% CI, $-.17$ to $.00$) than the pooled result for all 13 studies, with no strong evidence of benefit (Krogh et al., 2011). From

their results, these authors concluded that exercise may have a small short-term effect on depression, but it cannot yet be recommended as a treatment for clinical depression.

Exercise is, of course, not the only solution to the growing problem of depression worldwide, and it will not be appropriate for all depressed people. On the other hand, this limitation applies to all traditional treatments; that is to say, medication and psychotherapy are also not suitable for everyone (Josefsson et al., 2013).

The overall conclusion that is reached by most authors is that good quality research needs to be conducted on clinical populations, with allowance for adequate follow up. According to Mead and Rimer, there is also a need for studies that are higher in methodological quality; that is, studies involving adequate allocation concealment, blinding, and intention-to-treat analyses. Research that is of poor methodological quality can lead to inaccurate or skewed effect sizes.

Dose response of exercise as treatment for depression

Based on the knowledge that exercise is an effective antidepressant treatment, the question is: what ‘dosage’ is required to be most beneficial? There are various dose-response questions that persist with respect to depression and exercise, which include: ‘Is there a minimal dose that is required to produce benefits?’ and ‘Is there a maximal threshold?’. The present study will offer substantial evidence towards addressing these questions, but further research is still required in order to enable public-health guidelines for the mental health benefits of exercise to be established (Dunn et al., 2002).

The Depression Outcomes Study of Exercise (DOSE) by Dunn et al. (2002) involved a randomized clinical trial to determine whether exercise is an efficacious treatment for mild to moderate MDD in adults aged between 20 and 45 years. This study was conducted between 1998 and 2001, analyzed in 2002 and 2003, and published in 2005. It had two major objectives: (i) “to determine the efficacy of aerobic exercise as a sole treatment of mild to moderate depression, and (ii) to determine the dose-relationship between different amounts and frequencies of aerobic exercise with the reduction of depressive symptoms.” This study involved a 2x2 factorial design, with an exercise placebo as the control group. The two exercise factors manipulated were total weekly energy expenditure per kilogram of body weight (7 kcal/kg/week and 17.5 kcal/kg/week), and frequency of exercise (3 days/week or 5

days/week). Therefore, for a 70-kg person, the total weekly energy expenditure would be 490 kcal/week if s/he received the 7 kcal/kg/week dose, or 1225 kcal if s/he received the 17.5 kcal/kg/week dose. The total energy expenditure was then divided among the three days or the five days for the dose of exercise per session. Eighty men and women who were diagnosed with a Structured Clinical Interview for Depression, and who had mild (HRSD 12-16) to moderate (HRSD 17-25) MDD, were randomized to one of five of the groups above as follows: 7.0 kcal/ kg/week in 3 days/week; 7.0 kcal/kg/week in 5 days/week; 17.5 kcal/kg/week in 3 days/week; 17.5 kcal/kg/week in 5 days/week; or 3 days/week of stretching and flexibility exercises for 15 to 20 minutes per session. The participants had their symptoms of depression measured once per week by a “blinded” clinician.

The primary outcome measure for this study was the change in the HRSD₁₇ (Hamilton Rating Scale of Depression 17-item) score from baseline to 12 weeks. The secondary outcomes were response (50% reduction in symptoms) and remission (HRSD₁₇ score of ≤ 7). The secondary outcome measures were the Inventory of Depressive Symptoms (clinician and self-report), the HRSD scores at 24 weeks, cardiorespiratory fitness, self-efficacy, and quality of life. The findings showed that the main effect of energy expenditure in reducing HRSD₁₇ scores at 12 weeks was significant. Adjusted mean HRSD₁₇ scores at 12 weeks were reduced 47% from baseline for Public Health Dose (PHD), compared with 30% for Low Dose (LD) and 29% for control. There was no main effect of exercise frequency at 12 weeks. The authors concluded that aerobic exercise at a dose consistent with public health recommendations is an effective treatment for MDD of mild to moderate severity. A lower dose is comparable to placebo effect (Dunn et al., 2005). This study shows a specific dose of aerobic exercise that can be administered in the treatment for depressive symptoms, and this dose that is needed is equivalent to the consensus public health recommendations. The only drawback is that the authors did not blind their participants to their treatment assignments. Consequently, as participants become aware that they were in the placebo group, they were more eager to drop out.

This study by Dunn et al. can be used as a benchmark for other studies on the topic of exercise as a method of alleviating depressive symptoms. It shows that exercise at different energy expenditures and frequencies is efficacious in the treatment of depression; however, further research needs to be done in order to establish proper guidelines regarding the benefits that exercise has on mental health.

Association between physical activity and mental disorders

Goodwin (2003) examined the association between physical activity and mental disorders among adults in the United States. Multiple logistic regression analyses were used to compare the prevalence of mental disorders among those who did and did not report regular physical activity. This was done using data from the National Comorbidity Survey (n = 8098), a nationally representative sample of adults ages 15–54 in the United States. Slightly more than one-half of adults reported regular physical activity (60.3%). Regular physical activity was associated with a significantly decreased prevalence of current major depression and anxiety disorders, but was not significantly associated with other affective disorders, substance use, or psychotic disorders. The association between regular physical activity and lower prevalence of current major depression (OR = 0.75 (0.6, 0.94)), panic attacks (OR = 0.73 (0.56, 0.96)), social phobia (OR = 0.65 (0.53, 0.8)), specific phobia (OR = 0.78 (0.63, 0.97)), and agoraphobia (OR = 0.64 (0.43, 0.94)) persisted after adjusting for differences in sociodemographic characteristics, self-reported physical disorders, and comorbid mental disorders. Self-reported frequency of physical activity also showed a dose–response relation with current mental disorders. In conclusion, these data document a negative association between regular physical activity and depression and anxiety disorders among adults in the U.S. population (Goodwin, 2003). This study did not have a clear definition of what they consider to be “regular” physical activity and this might have caused confusion with regard to the frequency with which the participants reported engaging in exercise.

Treating depression and depression-like behaviour with physical activity

Physical activity (PA) is increasingly investigated as a preventative, early intervention and treatment option for depression. Interest in investigating PA may have risen for a number of reasons, including that the burden of depression is increasing, so novel therapeutic and preventative options were required. In looking at a review of studies, Eyre et al. (2013) found the investigation of the neuroimmune effects of PA on depression and depression-like behaviour is a rapidly developing and important field. This paper summarizes the most recent findings in the field, and proposes a model in which PA enhances the beneficial effects of the neuroimmune system and reduces the detrimental effects of the neuroimmune system. Physical activity appears to increase the following factors: interleukin (IL)-10, IL-6 (acutely), macrophage migration inhibitory factor, central nervous system-specific autoreactive CD4+T cells, M2 microglia, quiescent astro- cytes, CX3CL1, and insulin-like growth factor-1. On the

other hand, PA appears to reduce detrimental neuroimmune factors such as: Th1/Th2 balance, pro-inflammatory cytokines, C-reactive protein, M1 microglia, and reactive astrocytes. The beneficial effects of PA are likely to occur centrally and peripherally (e.g. inflammatory markers in visceral fat reduction) (Eyre et al., 2013).

Hamer and colleagues (2012) reviewed 13 prospective cohort epidemiological studies examining the association between physical activity and risk of future depression. The sample sized was 73 487 participants, with three cohorts consisting of women only, three of men only, and the remaining seven of mixed gender. Participants were healthy and not clinically depressed at the baseline assessment, and physical activity levels were assessed through self-reported measures. Depression was measured using a variety of methods, including a physician diagnosis and the administration of different validated psychometric tools, such as the Centre of Epidemiologic Studies of Depression Scale. The follow-up period ranged from two to 25 years. The study found that the pooled odds ratio (OR) of depression in the physically active participants compared with the sedentary participants was 0.78 (95% CI, 0.71-0.86, $P < 0.001$). This finding suggests that the active participants had a 22% reduced risk of developing depressive symptoms. Another interesting finding was that the effects of physical activity appeared to be stronger in women (OR=0.81, 0.66-0.99, $P = 0.045$), since women generally report more psychological distress and depression than men do. In conclusion, PA seems to be independently associated with the risk of becoming depressed, and regular exercise is associated with higher positive mood and lower negative mood symptoms (Hamer et al., 2012).

Hamer et al. (2012) also examined the association between depressive symptoms and inflammatory risk markers. The link between both mood and exercise with inflammatory pathways led them to hypothesize that better mental wellbeing experienced by regular exercisers might be partly explained by an underlying neurotransmitter mechanism. If a person experiences alterations in neurotransmitter function that involve serotonin, norepinephrine, and dopamine, then this induces depression. "Exercise is thought to alter serotonin metabolism, release endogenous opioids, and increase central noradrenergic neurotransmission which may all contribute to antidepressant and anxiolytic effects" (Hamer et al., 2012). A third section in this paper looked at the exercise withdrawal paradigm. The authors hypothesized that mood disturbances caused by withdrawal from regular exercise might act as a mild inflammatory stimulus. In asking habitual exercisers to withdraw from

their regular training for two weeks, this study found significantly higher inflammatory responses to mental stress compared to those with low or no mood disturbance. The study also found that participants in the highest category of mood disturbance demonstrated the greatest inflammatory response to mental stress. Overall, this paper shows that exercise can play a big role in improving mental health and wellbeing, either due to the inflammatory response, the exercise paradigm, or due to being more physically active. The only negative aspect of this research is the fact that the participants did self-reported physical activity levels for the epidemiology study. This may not be as accurate as, for example, an accelerometer might have been given since each participant may have had a different understanding of how fit s/he thought s/he was.

β -endorphin is 31 amino acids long that is the result of processing the precursor proopiomelanocortin (POMC), and is classed as an endogenous opioid peptide neurotransmitter. β -endorphin is contained in neurons in both the central and peripheral nervous system. β -endorphin is an agonist of opioid receptors, which gives it analgesic properties — the body produces this peptide to numb or dull pain (<http://www.mdbioproducts.com/products/elisas/%CE%B2-endorphin-elisa>).

Øktedalen et al. (2001) looked at the influence of physical and mental training on plasma β -endorphin level and pain perception following intensive physical exercise. The study aimed to investigate a possible correlation between increase in circulating blood levels of β -endorphin and decrease in pain perception after short-term intensive physical exercise. The authors also wanted to explore whether plasma β -endorphin levels and pain perception were influenced by regular physical training or mental training, and to examine whether there were differences in response between trained and untrained subjects. The intervention period lasted six months, which involved twenty physically trained males who did regular physical endurance training. Of the twenty participants, eleven were randomized to perform additional mental training (ACEM meditation) on a daily basis. Nine untrained males were in the control group and were investigated only at baseline. Each participant had his VO_{2max} measured during treadmill exercise, and pain perception was measured using an ischemic pain test both before and after the VO_{2max} test. Blood samples for β -endorphin levels were taken both before and after the tests. Findings showed that there was no statistically significant difference in VO_{2max} among the two groups of trained subjects, either before or after the intervention period (before: median 56.0 (range 43.7–66.1) ml $kg^{-1} min^{-1}$ in the

meditation group; 57.5 (range 43.7–75.9) ml kg⁻¹ min⁻¹ in the exercise control group; after: 56.2 (range 42.8–65.5) ml kg⁻¹ min⁻¹ in the meditation group; 58.1 (range 46.3–73.1) ml kg⁻¹ min⁻¹ in the exercise control group). The untrained control group showed a median VO_{2max} of 44.1 (range 39.3–53.2) ml kg⁻¹ min⁻¹, which was smaller than for the trained groups ($p < 0.05$).

For the endorphin levels, the plasma level in the above-mentioned study decreased from 13.6 nmol l⁻¹ to the level of 7.2 nmol l⁻¹ ($p = 0.005$) after an intervention period of six months involving regular physical training. Practicing meditation regularly for six months did not influence the basal plasma level of β -endorphin and there was no significant difference in basal endorphin level between the trained and the untrained subjects. Short-term meditation of 30 min duration did not alter the plasma level (before: 5.8 nmol l⁻¹ \pm 0.6; after: 5.4 nmol l⁻¹ \pm 0.5). The level was no different from the basal level measured after six months of intervention. The VO_{2 max} test caused a two-fold increase in plasma level ($p < 0.001$) that remained elevated for the first five minutes after the exercise. There was no significant difference in exercise-induced response between the trained and the untrained subjects. Neither six months of regular physical training, nor six months of regular mental training had any effect on the exercise-induced β -endorphin response.

For pain perception, there was no significant change in pain assessment between the trained and untrained subjects. Intensive physical exercise (VO_{2 max} test) reduced the pain perception significantly ($p < 0.001$), as well as the time course ($p < 0.01$), but the post-exercise analgesic effect was not different between the trained and the untrained subjects. The plasma level of β -endorphins was only highly increased after short-term intensive physical exercise. Other exercise studies indicate that the release of β -endorphins is dependent more on the relative than the absolute amount of exercise, and that exercise intensities of at least 70 percent of VO_{2 max} must be reached before the plasma level of β -endorphins increases (Øktedalen et al., 2001). In conclusion, regular mental training had no impact on circulatory β -endorphin levels or on pain perception, and regular physical training increased pain tolerance. This study relates to the present study with respect to examining the basal β -endorphin concentrations. As Øktedalen et al. (2001) stated, for the release of β -endorphins to occur, at least 70 percent of VO_{2 max} test must be reached. This is very difficult to achieve with people who do not

exercise regularly and their baseline will be very low, meaning that they will have to push themselves very hard in order to achieve an increased release of β -endorphins.

The effect of running therapy on depression

Kruisdijk et al. (2012) published a proposal to examine the effectiveness of exercise therapy on depression through running (RT) and Nordic walking (NW). In addition, the participants will also receive usual care (i.e. antidepressant medication and/or cognitive and/or interpersonal therapy). The authors hypothesize that in conjunction with usual care, adding exercise therapy will result in a larger reduction in depressive symptoms. Participants will be randomized into one of two groups: a control group who receive usual care and a treatment program consisting of pharmacotherapy and/or sociotherapy, psychotherapy, psycho-education and indicated nonverbal therapies; and an intervention group who will be allowed to exercise at low intensity as part of their daily program. The intervention group will receive six months of supervised exercise therapy for one hour per week and were instructed to train unsupervised for one hour per week (a combination of about 40 exercise sessions).

Those in the intervention group will be invited to take part in RT or NW for 30 minutes continuously (at 60% of max heart rate). If these participants are not comfortable, or are unable to run due to medical contra-indications or muscular-skeletal problems, then they will do the NW protocol. The study will use the HRSD to determine severity of depression and eligibility includes a score of ≥ 4 . Other health measurements, such as cardiovascular fitness using a sub maximal cycling test and biometric information will be gathered, and blood samples will be collected for metabolic parameters. Co-morbidity with pain, anxiety and personality traits will also be examined, as will quality of life and cost-effectiveness (Kruisdijk, 2012). Although testing still needs to be done, the authors inferred that exercise as a treatment for depression can be used as a stand-alone intervention, or as an add-on intervention. This protocol can be used as an example, and it will be interesting to see the results. Kruisdijk et al. also state that this is the first high quality large trial examining the effectiveness of exercise as an add-on treatment for depression in adult patients in specialized mental-health care.

The effect of different exercise intensities on mood and mental well-being

Moses et al. (1989) studied the effects of exercise training on mental well-being in the normal population. This study compared the effects of two aerobic training programmes of different

intensities on mood and mental well-being with those of a credible attention-placebo condition. The study took sedentary adult volunteers and assigned them to one of four conditions: high exercise, moderate exercise, attention-placebo, and a waiting list. Training was done over a 10-week period, and consisted of one supervised and three unsupervised sessions per week for each condition. The high exercise group fulfilled the recommendations of the American College of Sports Science (ACSM), which requires exercise on three to five days per week, with 15 to 60 minutes of continuous aerobic activity at 60 to 90% of HRmax. The participants took part in a walk-jog programme for continuous exercise of 30 min at an intensity to elevate HR to 70-75% of HRmax. The moderate exercise group also fulfilled ACSM's recommendations, and their sessions consisted of 20 minutes of continuous walking or jogging at an intensity sufficient to elevate HR to 60% of HRmax. The attention-placebo group performed strength, mobility and flexibility exercises for each of their sessions and also carried out slow, intermittent exercise for at least 30 minutes at an intensity of less than 50% of HRmax. Later, the subjects in the waiting list group were offered the moderate exercise programme.

This above-mentioned study found that positive psychological responses were reported by the subjects in the moderate exercise group, but not by those in the high exercise or attention-placebo groups. This finding was not confined to a single outcome measure, but was observed in a number of ratings of mood and perceived coping ability. The authors state that it is possible that the participants in the high exercise condition found the training too demanding, and that the rigour of the schedule mitigated against any improvements in well-being. The moderate exercise condition may have been more enjoyable, permitting the participants to achieve goals of physical activity that had previously seemed beyond them, without exerting undue effort (Moses & Edwards, 1989). These findings are relevant to the present study. The authors showed that moderate intensity exercise is a better prescription compared to the higher intensity exercise. Participants in the high-intensity group might have felt anxious about having to perform at such a demanding intensity, and this may have caused them to feel worse if they could not perform or meet the expectations required of them. Moderate intensity exercise coincides with ACSM's recommendations, thus the participants in this group probably did not feel pressured to perform at an intensity that was too demanding, and they might have been more relaxed and able to meet the requirements.

The PANIC/separation-distress system as the ‘missing mechanism’

There are considered to be four ‘basic-emotion command systems’ in the human brain, namely the SEEKING-, FEAR-, RAGE- and the PANIC/separation-distress system (Panksepp, 1998). The PANIC/separation-distress system is built over the physical pain pathway in the brain, with the anterior cingulate gyrus as its core (Solms & Turnbull, 2002). Stimulation of the PANIC system has even been known to produce a full clinical depression (Solms & Turnbull, 2002). The psychological pain that is felt when separation from an attachment figure occurs is caused by a withdrawal of endogenous opioids (of which endorphins are one type). Therefore, the young animal or human experiences ‘mental pain’ upon separation and because this feels bad, learns not to let it happen again (a clear evolutionary benefit). Separation distress results in two distinct behaviours. Firstly, the animal calls out to be found by its caregiver, which is known as the 'protest phase'. Secondly, if the caregiver does not return, then after a while the animal withdraws and waits to be found, which is known as the 'despair phase' (Panksepp, 1998). This despair phase behaviour is characterized by withdrawal and hiding away from the world, which looks exactly like the behavior seen in depression (Solms & Turnbull, 2002).

Rationale

In periods of prolonged stress and pain from strenuous exercise the body produces chemicals called endorphins that help it endure the pain. From an evolutionary point of view this system presumably evolved to enable escape from dangerous situations despite one being injured. These natural analgesics are only released when the level of pain intensity is at least moderately high. The PANIC (separation-distress) system (which seems deeply involved in the genesis and maintenance of depression) is built on the same pathways as the pain system. The term ‘mental pain’ in the context of feelings of loss is arguably justified in the light of this relationship between the physical pain and social loss systems. It is therefore reasonable to expect that endorphin release can also affect depressive symptoms in a positive way, as it does physical pain.

The available research shows that exercise helps to alleviate depression. Exercise helps lessen the effects of depression and also improves mental well-being, mood and health in general. The literature suggests that exercise in conjunction with antidepressants has the greatest effect on ameliorating depressive symptoms. Thus far, following the guidelines for daily-recommended energy expenditure (i.e. 30 minutes of an aerobic activity five days per week,

or vigorous activity for a minimum of 20 minutes three days per week) seems to be the best prescription for overall health and mental well-being. However, the physiological basis (the precise mechanism) of the antidepressant effect of exercise has not been fully delineated. The exact duration and intensity of exercise required in order to produce a guaranteed β -endorphin release, and to improve the symptoms of depression, is also still not clear.

2. AIMS AND HYPOTHESES

There were two central hypotheses for this study. The first was that the mechanism behind the improvements seen in depressive symptoms due to exercise is the same mechanism that is responsible for the established analgesic effect of exercise, namely endorphin release. The second hypothesis was that only high-intensity exercise (i.e. greater than 70% of heart rate reserve) will be sufficient to produce a guaranteed endorphin release, whereas moderate-intensity exercise (less than 50% of the heart rate reserve) and very low-intensity exercise would not be sufficient to release endorphins, and would therefore not result in an improvement in depressive symptoms. The main aim was therefore to investigate whether intensive exercise improves moderate depression, and if so, whether this correlates with a demonstrable increase in β -endorphins.

This study therefore had the following objectives:

- To determine which of low, moderate or high intensity exercise best alleviate the symptoms of depression.
- To determine whether an increase in β -endorphins correlates to an improvement in participants' depression.
- To determine whether greater β -endorphin release occurs during high-intensity exercise compared to low- and moderate intensity exercise.

3. METHODOLOGY

3.1 PARTICIPANTS

This study focused exclusively on individuals with *moderate* depression, which was determined using an online version of the Major Depression Inventory (MDI) (see Appendix A for the questionnaire and scoring criteria), and was then later confirmed by an interview with a psychologist using the Hamilton Rating Scale of Depression (HAM-D) (see Appendix B). The sample comprised 33 males between the ages of 18 and 42, all of whom were

students or staff from the University of Cape Town (UCT). Following the screening process, the suitable participants were randomly assigned to one of three exercise/experimental groups: High-intensity exercise, Moderate-intensity exercise, or a Control group (very low intensity exercise). A total of 21 participants completed the entire six weeks of the exercise intervention, and twelve participants (36%) dropped out of the study at some point. From the 21 participants who finished the study, the High-intensity group consisted of six participants, while there were 10 participants in Moderate-intensity group, and five participants in the Control group (see Table 1 for baseline characteristics). Among the randomized participants, the mean age was 24 years. The 12 participants who dropped out all did so because of their demanding schedules; six were in the Control group, two in the Moderate-intensity group and four in the High-intensity group.

Table 1: Baseline characteristics				
Characteristics (Mean)	Moderate intensity (n=10)	High intensity (n=6)	Control (n=5)	All groups (n=21)
Age, years	22	26	25	23.8
BMI, kg/m ²	24.7	24.6	33.6	26.8

3.1.1 EXCLUSION CRITERIA

Females were excluded from this study due to the menstrual cycle. One important methodological barrier appears to be that women using hormonal contraception must be considered as a separate group for purposes of analysis (Becker, JB, et al. 2005). Any individual who had a prior high-intensity exercise routine (i.e. 70% of his heart rate reserve, for more than three times per week) was excluded from the study. Any individual whose mood was evaluated to be either below, or above, the level of moderate depression was also excluded, as was anyone who was already on any form of antidepressant therapy/medication. Finally, individuals who had any medical condition (such as coronary heart disease, pulmonary disease, metabolic disease, or hypertension, etc.) that put them at risk when doing exercise were also excluded (see Appendix E).

3.2 MATERIALS

The following materials were used as part of this study:

3.2.1 *The Hamilton Rating Scale for Depression*

This widely used, diagnostically proven and effective multiple-choice scale was used as an external assessment of the severity of depressive symptoms. The Hamilton Rating Scale for Depression (HAM-D or HRSD) is required to be administered by a clinician, who interviews the participant and then judges the severity of his/her symptoms for each of the 21 items, producing a total score (only the first 17 items count towards the total score). Some of the items have five possible answers, while others have three. For example, *Item 1* is titled: ‘Depressed Mood’ (sadness, hopeless, helpless, worthless), and has the following score allocations: = ‘Absent’; = ‘These feeling states indicated only on questioning’; 2 = These feeling states spontaneously reported verbally’; = Communicates feeling states non-verbally — i.e. through facial expression, posture, voice, and tendency to weep’; 4 = Patient reports VIRTUALLY ONLY these feeling states in his spontaneous and non-verbal communication’. The HAM-D cut-off scores for the different severities of depression are as follows: 0-7 = Normal, 8-13 = Mild, 14-18 = Moderate, and 19-22 = Severe (Hamilton, 1960). The HAM-D is designed to be administered to individuals who have already been identified as depressed, with the higher the score, the more severe the depression. This questionnaire rates the overall severity of the symptoms that are observed in depression, such as low mood, insomnia, agitation, anxiety and weight loss, and is currently one of the most commonly used scales for rating depression in medical research.

3.2.2 *Montgomery Åsberg Depression Rating Scale* (see Appendix C)

The Montgomery-Åsberg Depression Rating Scale (MADRS) contains ten-items, and is primarily designed to measure the severity of depressive episodes. The MADRS is also intended to be a supplementary questionnaire for the HAM-D — there is a high degree of correlation between scores for the two scales — as it is more sensitive to the changes in level of depression than the HAM-D (Montgomery & Åsberg, 1979; Heo, Murphy, & Meyers, 2007). The items on the scale require the clinician examiner to decide, based on interviewing the subject, whether his/her response lies on the scale criteria of the MADRS (i.e. a score of 0, 2, 4 or 6) or between these scores (i.e. a score of 1, 3 or 5) and then to score the response accordingly. The MADRS score range for normal/symptom absent is 0 to 6, while *Mild*

depression is a total score of 7 to 19, *Moderate* depression a score of 20 to 34, and *Severe* depression is a score of >34. Each MADRS item is assessed in terms of the participant's state over the past week (Montgomery & Asberg, 1979).

3.2.3 Heart Rate Monitor

A *Suunto t6d* watch with a chest strap was used in this pilot study. The *Suunto t6d* heart rate monitor was chosen because of its extensive data logging capabilities. This monitor records heart rates every 3/100 of a second, which can then be viewed on a graph using the *Training Manager* program. The monitor also records maximum and minimum heart rates (HR) and gives an average of both these parameters after each workout.

3.2.4 DVDs

Two different television series were offered to the participants so that they could choose to watch one of them whilst exercising. Here, each participant watched his desired series while he cycled in the lab. Each participant cycled individually. This approach allowed the participants to watch a show in order to eliminate possible boredom that they otherwise might have experienced while in the lab for a full hour.

3.2.5 Lode Bike

For the planned exercise, the participants cycled on a *Lode Excalibur Sport Ergometer* (Groningen Netherlands; V1.52, 1991). This indoor, stationary bicycle was used because the resistance in Watts (W) could be externally controlled in order to keep the participants within the specific HR zones, as were predetermined for each of the three experimental groups.

3.2.6 BORG scale

The BORG scale is a Rating of Perceived Exertion (RPE) scale. The BORG starts at a score of six and ends at a score of 20, with six being very, very light exertion and 20 being maximum exertion. This scale was used as an indication of how hard the participants felt they were working while they were exercising. In this way, the author could tell whether the participant was exerting himself too much, or too little, thereby allowing for the set workload to be maintained.

3.2.7 Peak Sustained Power Output (PSPO) test

The Peak Sustained Power Output test (PSPO) method of calculating (using the Karvonen formula) maximum heart rate (HR) was preferred because it is more accurate than using the ‘22 minus the participant’s age’ approach (Robergs, 2002). Given that there are many other equations in the literature that can be used to determine maximum HR, it was felt that a cycling-based test was more valid and accurate than the calculation method. An accurate maximum HR was required in order to calculate the exact parameters of the HR training zones in which the participants would be exercising.

3.2.8 β -endorphin Analysis

The first type of kit used to measure the β -endorphin concentrations in the samples was a *CUSABIO ELISA KIT* (catalogue number CSB-E 682 h; human β -endorphin, β -EP ELISA kit) ordered from *Biocom Biotech*. This kit produced faulty results and a second, more accurate kit by *MD Bioproducts* was used. This second human β -endorphin kit produced by *MD Bioproducts* is an “Enzyme-linked immunosorbent assay” (ELISA) designed to detect a specific peptide and its relative peptides based on the principle of “competitive” enzyme immunoassay. The assay protocol was followed as per the manufacturer’s instructions (MD Bioproducts division of MD Biosciences, Inc., North America) for the quantitative determination of β -endorphins in human serum and plasma samples. The certificate of analysis states: sensitivity (0.14 ng/mL), precision (Intra-assay variation <10%, inter-assay variation <15%), range (0-100 ng/mL), linear range (0.14-2.3 ng/mL), positive control (Rehydrate Positive Control (0.4~0.7ng/mL) with 200 μ L assay buffer, add in duplicates, 50 μ L Standard, Controls and Samples. Blood samples of 3ml were collected into the gold Vacutaner tubes, which contain Z Serum Sep Clot Activator.

3.3 DESIGN

This was a three-armed prospective randomized control pilot study. Each participant was randomly assigned to one of three exercise groups — achieved by drawing a number which correlated to what group he was placed in. All the participants underwent a six-week exercise program involving participation three days per week, for one hour per day (i.e. 18 sessions in total). This program took place under supervision at the UCT/MRC Research Unit for Exercise Science and Sports Medicine (ESSM) at the Sports Science Institute of South Africa (SSISA) in Newlands, Cape Town. The High-intensity exercise group exercised on a Lode cycle-ergometer at an intensity of 70 to 75 percent of their HR reserve. The Moderate-

intensity exercise group also exercised on the Lode cycle-ergometer at an intensity of 45 to 50 percent of their HR reserve, while members of the Control group were required to keep their HRs below 120 beats per minute by walking and/or doing very light cycling during their exercise session.

Once weekly, the HAM-D and the MADRS interview-based depression questionnaires were administered to each participant by a psychologist. Finally, the participants in the High- and Moderate-intensity groups each had 5ml of blood drawn, once per week, both before and after exercise in order to measure circulating β -endorphin levels and to track any changes in these levels over time. The participants in the Control group only had blood samples taken twice – once at the start of the study (a baseline measure), both before and after exercise, and once on completion of the study, both before and after exercise.

3.4 DATA ANALYSIS

The GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego California USA, (www.graphpad.com)) was used for statistical analyses. Non-parametric one-way ANOVAs with Kruskal-Wallis and Mann-Whitney tests were performed to calculate: (i) differences in the HAM-D scores and in the MADRS scores, (ii) circulating β -endorphin levels, and (iii) the differences in the heart rates of all three groups' participants.

3.4.1 β -endorphin analysis

The first type of kit used to measure the β -endorphin concentrations in the samples was a *CUSABIO ELISA KIT* (catalogue number CSB-E 682 h; human β -endorphin, β -EP ELISA kit) ordered from *Biocom Biotech*, which arrived at the Chemical Pathology Division at the University of Cape Town. Several attempts were made to measure the concentration of β -endorphins in approximately 14 serum samples that had been stored between a few days and six months. On each occasion, even though the standards supplied in the kit gave anticipated values, the samples were unable to be measured due to the absorbance values being too low to read — even lower than the kit buffer. The company concluded that their kit was not suitable for the samples being tested (the authors suppose that this meant the samples had concentrations of β -endorphins below the detection limit of the kit).

A second kit, manufactured by *MD Bioproducts* (catalogue number M056011) was then used with a greater sensitivity (15.6-10000pg/mL) than the *Cusabio* kit. Serum samples tested

using the first kit from *MD Bioproducts* confirmed that this particular ELISA kit was able to measure β -endorphin concentrations in the stored serum samples. Unfortunately, the time delay after placing the order with Bioco Biotech was several months. This meant that the samples were stored for longer than the kit's validity (stable for one month at -70°C). In total, of the approximately 212 samples, 128 were finally tested using the MD Bioproducts ELISA kit (five controls' samples, six participants' from the Moderate intensity group, and four participants' from the High-intensity group: each pre-and post-exercise).

3.5 PROCEDURE

Advertising for this study was done both through the University of Cape Town's *Monday Monthly* newspaper and via emails sent to all students on the University database.

Participants were recruited using an online MDI questionnaire. The suitability of the potential participants who were identified as moderately depressed using the MDI, was then confirmed by a follow-up interview with a psychologist using the HAM-D — conducted in order to further verify this level of depression. Any individuals who were identified as being too depressed (severe or major depression) were contacted and offered support. Any potential participant with suicidal ideation and/or psychotic thoughts was also excluded from the study and help was immediately offered to them. Following the interview, the suitable participants were contacted in order to start their exercise sessions. At their first session, all participants completed a Health History Questionnaire (See Appendix D) and the study's Consent Form (see Appendix E). Each participant's height and weight were then recorded, and a 5ml blood sample was taken before he started his exercise session. Blood rested in the tube for 30 minutes after it was collected, and was then centrifuged at 3000 revolutions per minute (RPM) for 15 minutes. The plasma was extracted and kept at -80°C until it was analyzed. Blood samples were collected at the UCT/MRC Research Unit for Exercise Science and Sports Medicine (ESSM) at the Sports Science Institute of South Africa (SSISA) from December 2012 to March 2014. In total, 212 samples were collected and stored at -80°C , first at ESSM, and then later at UCT's Division of Chemical Pathology for analysis.

Both the High- and the Moderate-exercise groups then did a Peak Sustained Power Output (PSPO) test in order to determine their maximum HR in order for the subsequent exercise intensity parameters to be calculated. For this test, the participants each wore a heart rate monitor and performed a light five-minute warm-up on the Lode cycle-ergometer. This test was performed at a starting work rate of 2.0W/kg body mass, after which the load was

increased incrementally by 20 Watts each minute until the participant could not sustain a cadence greater than 70 RPM. The maximum HR was the highest recorded value at any time during the test. If a participant was unable to complete the PSPO test, then the measure of 220 minus their age was instead used to calculate his maximum HR. After the PSPO test was completed, the participants each did their one-hour of cycling in the ESSM lab individually within their predetermined HR zones. HR for the entire session was recorded with a heart rate monitor, while RPE was recorded using the BORG scale. The HR reserve for individuals in the high intensity group was calculated as follows: $(\text{maximum HR} - \text{resting heart rate}) \times 70\% + \text{resting heart rate}$. The HR reserve for individuals assigned to the moderate intensity group was calculated as follows: $[(\text{maximum HR} - \text{resting heart rate}) \times \% + \text{resting heart rate}]$. The participants were required to cycle at their HR reserve ± 5 beats per minute.

4. RESULTS

4.1 Participant drop out

Three of the 12 participants who dropped out did so after only one session, while the other nine completed at least 3 sessions, which allowed for a baseline HAM-D score and an additional (final) HAM-D and MADRS score before they dropped out (see Table 2).

Table 2: Depression questionnaire scores in the 21 participants who completes all 18 sessions					
Group	n	HAM-D initial score Mean & (SD)	HAM-D final score Mean & (SD)	MADRS initial score Mean & (SD)	MADRS final score Mean&(SD)
High intensity	6	15.5 (1.5)	4.2 (4.5)	12 (3.7)	5.3 (5.7)
Moderate intensity	10	16.2 (1.4)	5.7 (4.2)	14 (4.3)	8.1 (6.4)
Control	5	17.4 (1.3)	9.8 (4.7)	19 (9.2)	13.4 (6.5)
Depression scores of drop out participants who completed at least 3 sessions					
High Intensity	3	17 (2.4)	8.7 (8.1)	15 (4.5)	10.3 (8.5)
Moderate intensity	1	18	16	18	18
Control	5	17 (1.1)	13.8 (1.8)	19 (2.7)	17 (3.4)
HAM-D code: 0-7 = Normal, 8-13 = Mild, 14-18 = Moderate, 19-22 = Severe					
MADRS code: 0-6 = Normal, 7-19 = Mild, 20-34 = Moderate, >34 = Severe					

The details of those participants who completed more than a week of the exercise protocol before dropping were as follows (Figure 1). In the Control group, two participants completed one week (HAM-D score indicated they stayed moderately depressed), two completed one and a half weeks (one went from moderate to mild depression and the other stayed at a moderate level), one did two and a half weeks (stayed moderately depressed) before dropping out of the study. There was only one Moderate-intensity group participant who completed

one week before dropping out (he stayed at a Moderate level of depression). In the High-intensity group, one participant completed four weeks and had no indication of depression at the time of dropping out. Two more participants in the High-intensity group only completed one week, and one of these went from moderate to mild depression before he dropped out. The severity of depression of the participants who dropped out is shown in Figure 2. All those who dropped out informed the author through writing that they wished to drop out of the study due to time constraints.

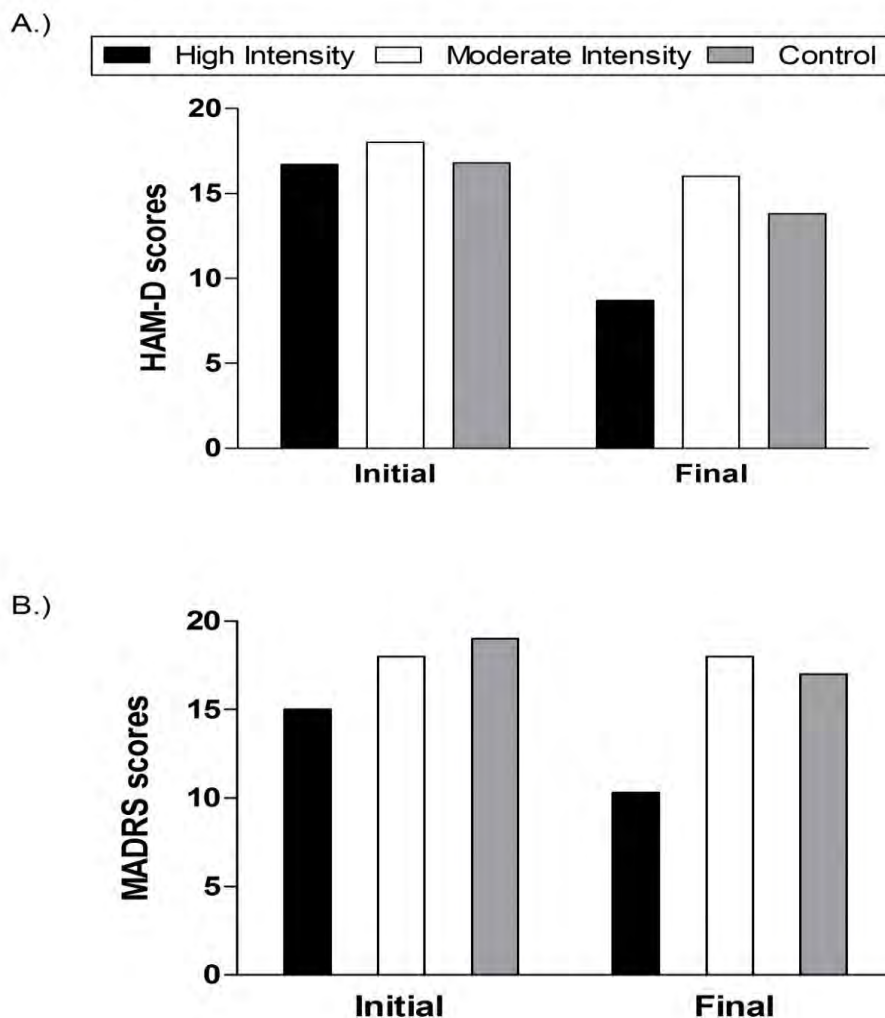


Figure 1. HAM-D and MADRS scores for participants who dropped.
 A.) Shows, for all three groups, the average initial and final HAM-D scores for the participants who dropped out of the study. B.) shows the average initial and final score of the MADRS before dropping out.

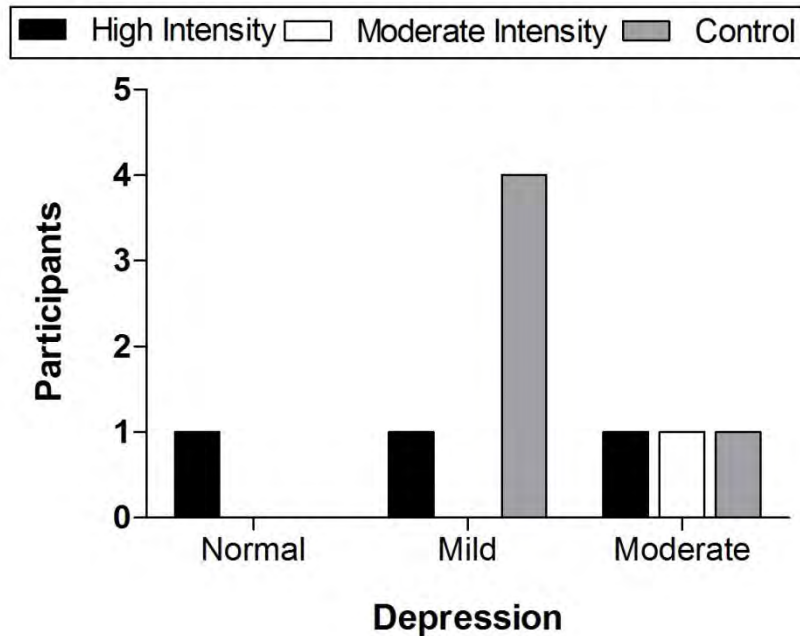


Figure 2. **Severity of depression for participants who dropped out of the study.** The overall results and severity of depression after completing at least one week of the study (based on the HAM-D from the initial to final scores).

4.2 EXPERIMENTAL PARTICIPANTS: Heart Rate ranges

The heart-rate range for the High-intensity group was 70 to 75% of their HR reserve. All six participants exercised within this range or close to it. These participants cycled at intensities of between 100-180 Watts, and their PRE was between 13 and 19 on the Borg scale. The ten Moderate-intensity group participants had to exercise at 45 to 50% of HR reserve. These participants cycled at intensities between 80-100 Watts on the Lode cycle-ergometer, while their RPE was between 7 and 12 on the Borg scale. The five Control group participants engaged in very light exercise by cycling on the Lode cycle-ergometer at 60 Watts at 50-60 RPM, and/or by walking on an indoor walking track (\pm 70m in circumference). These Control group participants were instructed not to exceed 120 beats per minute (bpm) while they exercised, and their average heart rate for each session did not exceed 120 bpm (with the exception of two participants whose average heart rates were 124 bpm and 122 bpm, respectively). However, this did not cause these two participants to cross over into the moderate-intensity range. Figure 3 shows the average heart rate ranges for each session. The High-intensity group had the highest heart rates between 150-160 bpm. The Moderate-

intensity group was in the middle with heart rates between 130-140 bpm, while the Control group had the lowest heart rates at 120 bpm and under.

When analyzed, the three experimental groups' average heart rates per exercise session throughout the six weeks of exercise were significantly different. When comparing individual sessions, there were no significant differences between the Moderate- and Control groups during sessions 1, 2, 8, 9, and 17, but for the other sessions (3-7, 10-16, and 18) there was a significant difference between these two groups. There was a significant difference between the High-intensity- and Control groups over all 18 sessions (see Figure 3). Overall, the participants were able to exercise in their prescribed intensities for the majority of the sessions, and all three experimental groups were significantly different in terms of their heart rate ranges ($p = <0.0001$) due to the different exercise intensities (see Figure 4). Figure 5 shows the average heart rate over all 18 sessions for each participant.

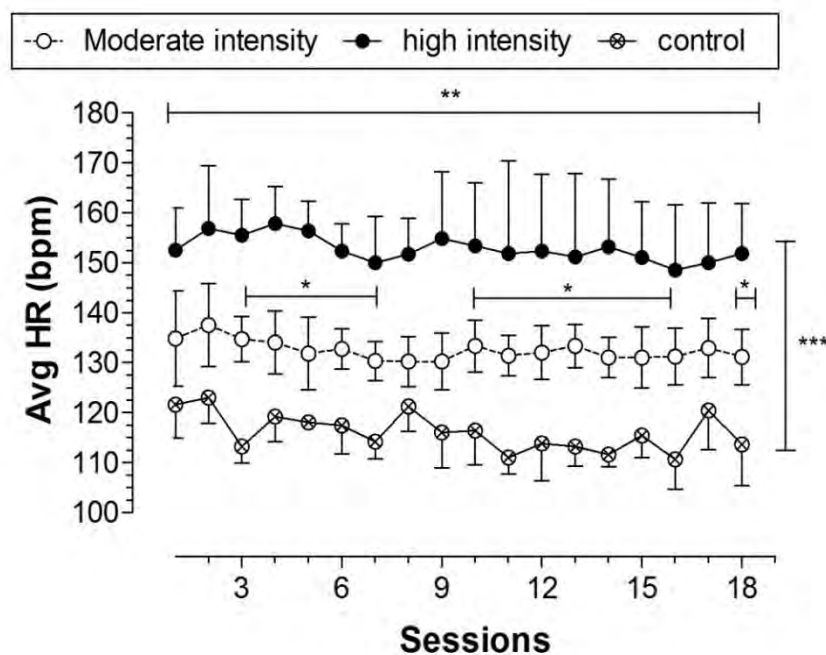
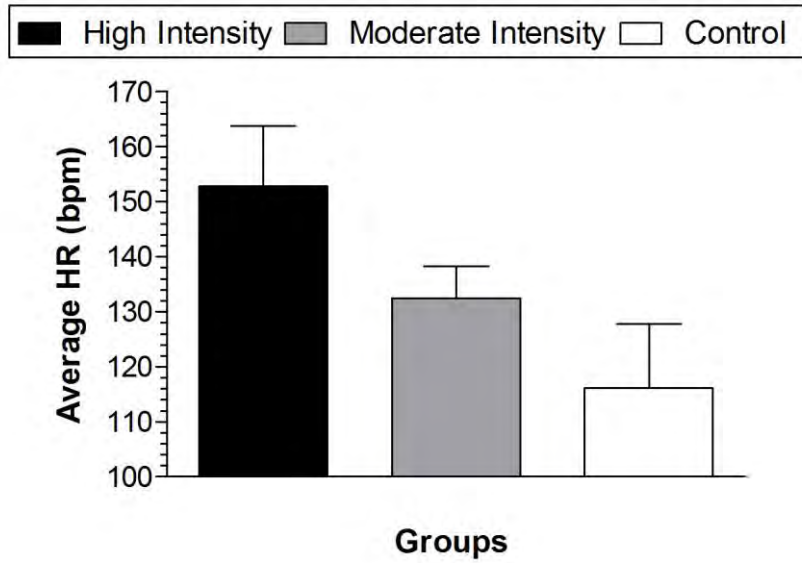


Figure 3. Average heart rate per exercise session for each group over six weeks (18 sessions). *Sessions significantly different between Moderate- and Control groups. **Significant difference between the High-intensity- and the Control group for all 18 sessions ($p = <0.0001$). *** All three groups' average HRs were significantly different ($p = .$) .



Figur4.Average heart rates.

Shows the average heart rates for all three exercising groups. The High-intensity group had an average HR of 153 bpm. The Moderate-intensity group's average HR was 132 bpm and the Control group's was 116 bpm. There was a significant difference between all three groups based on the average heart rates achieved in all 18 sessions, $p = <0.0001$. No SD values are reported since we used non parametric statistics.

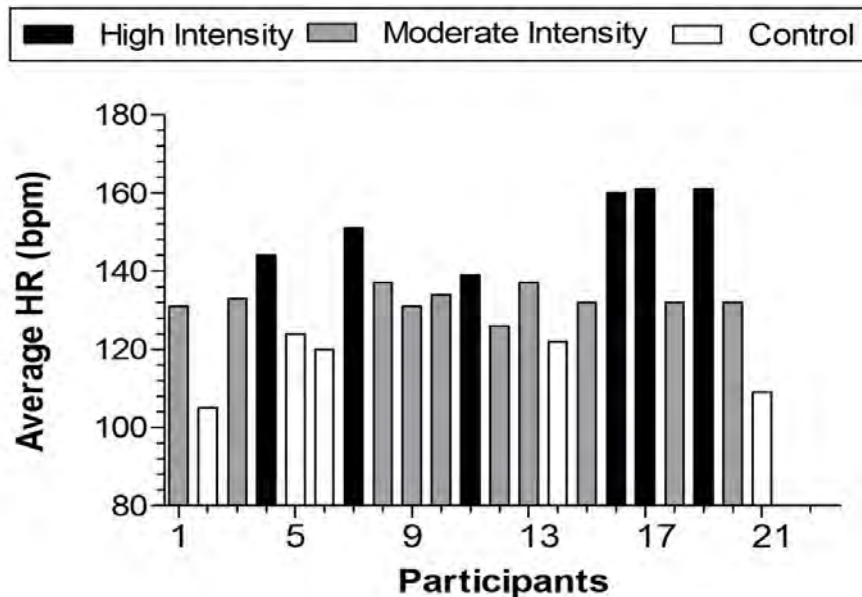


Figure 5. Average heart rate per participant for all three groups over 6 weeks (18 sessions).

4.3 Psychological data

The HAM-D and the MADRS were completed through an interview by all participants, once weekly, for a total of six times (see Table 2). The High- and Moderate-intensity groups showed greater improvement in their depression scores over the six-week exercise intervention. All participants were moderately depressed at the start of the study. Figure 6 shows a box and whiskers diagram displaying all three groups' HAM-D scores prior to starting the exercise intervention, as well as posts the exercise intervention after six weeks. Both the Moderate- and High-intensity groups showed improvement in their HAM-D scores, while the Control group also improved, but not as much as the other two groups. There was no significant difference when comparing all three groups' initial HAM-D scores ($p = 0.0789$) with each other, or when comparing their final HAM-D scores ($p = 0.0974$). However, there was a significant difference ($p = < 0.0001$) when comparing the initial scores for each group to their final HAM-D scores. In examining the individual groups' HAM-D scores, there is a significant difference ($p = 0.0048$) for the High-intensity group when comparing their initial and final scores. The Moderate-intensity group also showed a significant difference between their initial and final HAM-D scores ($p = 0.0002$). The same trend was apparent for the Control group, although not quite as significant as for the other two groups ($p = 0.0160$).

Figure 7 shows how the High-intensity group ($n=6$) had five participants with no depression, and one participant with mild depression after the 18-session intervention. The Moderate-intensity group ($n=10$) had six participants with no depression, and four participants had mild depression after the 18-session intervention. The Control group ($n=5$) had one participant stay at moderate depression (i.e. no change), one with no depression, and three participants with mild depression after the 18-session intervention. In all three experimental groups, none of the participants increased from moderate to severe or major depression. These findings show that all three interventions were effective, to some extent at least, for all but one participant.

The MADRS was also used to measure the severity of depression in each participant, with the results for this questionnaire displayed in Figure 8. There was no significant difference when comparing all three groups' initial MADRS scores ($p = .26$), or when comparing their final MADRS scores ($p = 0.1596$). However, there was a significant difference ($p = 0.0182$) when comparing the initial scores within each group to the final MADRS scores. The High- and Moderate-intensity groups showed a significant difference between their initial and final scores ($p = 0.0450$) and ($p = 0.0340$) respectively. The Control group did not show a

significant difference between their initial and final scores ($p = 0.3443$). When comparing the final MADRS scores between the High-and Moderate-intensity groups there was not a significant difference ($p = 0.4139$), nor was there when comparing the final scores between the High-intensity and Control groups ($p = 0.0988$).

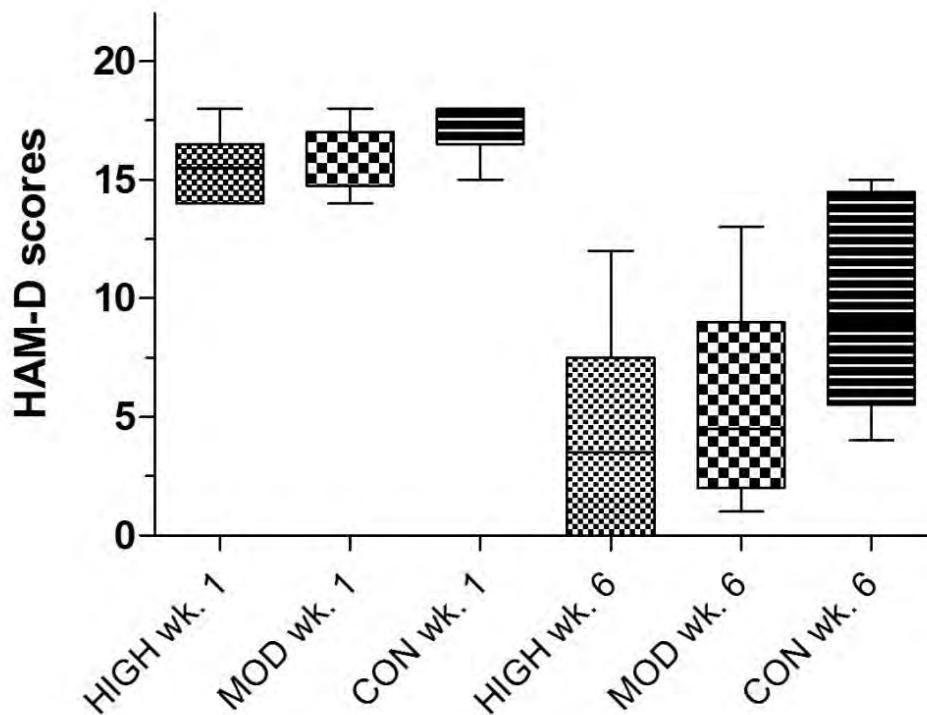


Figure 6. **Box and whiskers indicating the initial and final HAM-D scores for all three exercising groups.** The High-intensity group's average HAM-D scores improved from 15.5 to 4.2. The Moderate-intensity group's average scores improved from 6.2 to 6.7. The Control group improved from 17.4 to 9.8 in their average HAM-D scores. All three experimental groups showed an improvement in their HAM-D scores, and there was a significant difference between the initial and final scores ($p = <0.0001$).

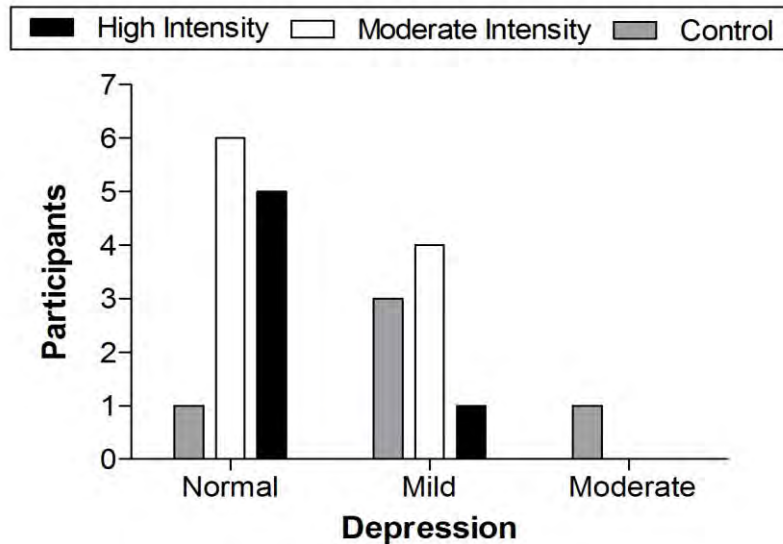


Figure 7. **Overall results and severity of depression at the end of 6 weeks.** Overall results for the HAM-D after six weeks of exercise at various intensities. The High-intensity group had five participants improve from a moderate level of depression to no depression, and one participant improved from a moderate to a mild level of depression. The Moderate-intensity group had six participants improve from a moderate level of depression to no depression, and four improve from a moderate to mild level of depression. In the Control group, one participant improved from a moderate level of depression to no depression, while three participants improved from a moderate to mild level of depression, and one participant showed no change (i.e. he stayed at the moderate level of depression).

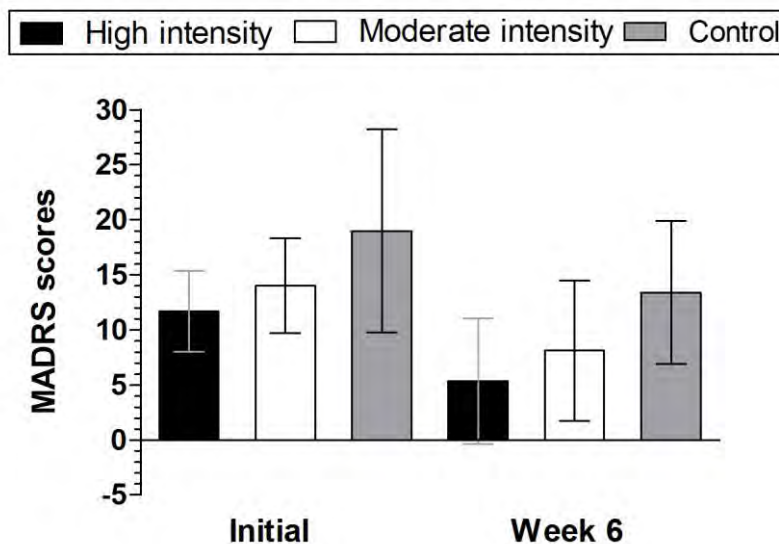


Figure 8. **MADRS scores.**

Shows the initial and final MADRS scores, which indicates the severity of depression. Both the Moderate- and High-intensity groups showed lower scores than the control group did, with the High-intensity group having the lowest (the lowest level of depression). All three groups showed a statistically significant difference between their initial and final scores ($p = 0.0182$). No SD values are reported since we used non parametric statistics.

4.4 β -endorphin

Figure 9A shows the mean circulating β -endorphin levels for each week between the Moderate- and High-intensity groups. Figure 9B shows the relationship between the individual heart rate achieved and the serum β -endorphins concentrations obtained in any particular session (once per week, for six weeks) for both the Moderate- and the High-intensity groups – here, no clear relationship was found.

There was a significant difference ($p = 0.0222$) in the post-exercise concentrations of β -endorphin (see Table 3) amongst the Control, Moderate- and High-intensity groups. When comparing the post exercise β -endorphin values of the Control group to the Moderate-intensity group, a significant difference of $p = 0.0173$ was found. On the other hand, when comparing the post exercise β -endorphin values of the Control to the High-intensity group, there was no significant difference ($p = 0.0856$). Since the β -endorphin levels in the Control group decreased throughout the six-week intervention, unlike the other two groups whose β -endorphins did not decrease, it could be concluded that low-intensity exercise does not yield an endorphin release.

Each of the Control group participants (with the exception of one participant for one visit) showed a significant decrease in their β -endorphin concentrations after exercise (Table 4), whereas there were an almost equal number of increased and decreased values for those within the Moderate-intensity exercise group (see Table 4). The High-intensity group participants showed a slightly greater number of decreased values for β -endorphin concentrations over all their sessions. The mean values after exercise for both the Moderate- and High-intensity groups were not significantly different to their baseline values (see Table 5). The differences between the baseline and post-exercise measurements were also not significantly different for both the Moderate- and High-intensity groups ($p = 0.953$ and $p = 0.992$, respectively).

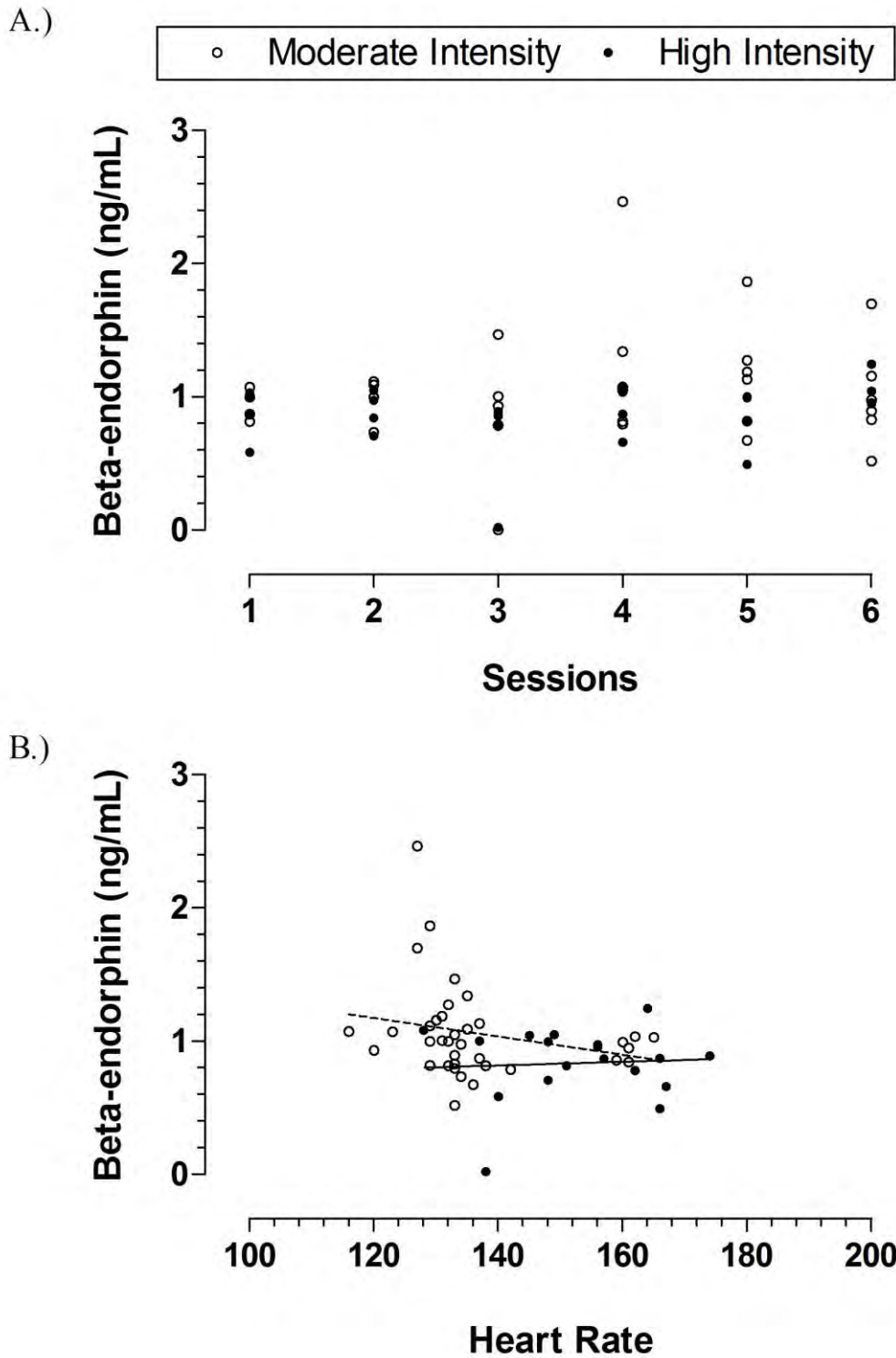


Figure 9. **Beta-endorphin levels for Moderate- and High-intensity groups.**

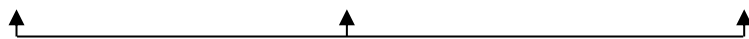
A.) Shows the β -endorphin levels for the Moderate- and High-intensity groups each week.

B.) Shows that there was no relationship between the heart rate and the β -endorphin levels for both the Moderate- and High-intensity groups, indicated with linear regression lines.

	CON PRE	CON POST	MOD PRE	MOD POST	HIGH PRE	HIGH POST
Number of values	8	8	30	30	24	24
Minimum	0.6400	0.2520	0.5350	0.5180	0.6340	0.4930
25% Percentile	0.7823	0.4910	0.8315	0.8163	0.8333	0.8220
Median	1.103	0.7320	1.039	1.001	0.9205	0.9530
75% Percentile	1.661	0.9480	1.145	1.164	1.027	1.028
Maximum	1.866	1.272	2.241	2.465	1.148	1.245
Mean	1.196	0.7370	1.087	1.082	0.9190	0.9059
Std. Deviation	0.4530	0.3187	0.4080	0.3878	0.1278	0.1709
Std. Error	0.1602	0.1127	0.07449	0.07080	0.02609	0.03489
Lower 95% CI of mean	0.8175	0.4706	0.9346	0.9367	0.8650	0.8337
Upper 95% CI of mean	1.575	1.003	1.239	1.226	0.9729	0.9781
Sum	9.570	5.896	32.61	32.45	22.06	21.74



P = 0.159



P = 0.022*

Table 3. Results of column statistics for measurement of serum β -endorphin concentrations within the three experimental groups, before and after exercise. Non-parametric ANOVA (Kruskal-Wallis) statistics when analyzing all three groups' pre-exercise measures showed $p = 0.159$, while the post-exercise measures showed a significant difference of $p = 0.022$. When comparing the MOD- versus the CON group, $p = 0.0173$, while when comparing the HIGH- versus the CON group, $p = 0.0856$. When comparing the MOD- versus the HIGH group, $p = 0.0896$.

CON PRE	CON POST	changeCTL	MOD PRE	MOD POST	changeMOD	HIGH PRE	HIGH POST	changeHIGH
0.741	0.470	0.271	1.047	1.074	-0.027	0.843	1.030	-0.187
0.640	0.252	0.388	1.031	1.091	-0.060	0.767	0.843	-0.076
1.495	0.954	0.541	1.153	1.071	0.082	0.792	0.857	-0.065
1.175	0.741	0.434	1.018	1.273	-0.255	0.830	1.035	-0.205
1.866	1.272	0.594	0.996	1.156	-0.160	1.012	0.993	0.019
1.716	0.723	0.993	2.241	2.465	-0.224	0.877	0.950	-0.073
1.031	0.554	0.477	2.212	1.865	0.347	0.928	0.995	-0.067
0.906	0.930	-0.024	1.998	1.699	0.299	0.857	0.974	-0.117
			0.809	0.788	0.021	0.913	0.780	0.133
			0.781	0.797	-0.016	0.807	0.659	0.148
			0.710	0.674	0.036	0.734	0.493	0.241
			0.535	0.518	0.017	0.964	1.245	-0.281
			1.098	0.814	0.284	0.976	0.867	0.109
			0.593	0.736	-0.143	1.051	1.050	0.001
			1.223	0.933	0.290	0.881	0.889	-0.008
			0.854	0.814	0.040	0.862	0.872	-0.010
			0.793	0.817	-0.024	0.930	0.815	0.115
			0.849	0.894	-0.045	0.967	0.956	0.011
			0.839	0.871	-0.032	0.634	0.586	0.048
			0.783	1.115	-0.332	1.148	0.706	0.442
			1.223	1.467	-0.244	1.128	1.021	0.107
			1.303	1.339	-0.036	1.088	1.083	0.005
			1.135	1.188	-0.053	1.032	1.000	0.032
			0.944	0.976	-0.032	1.034	1.043	-0.009
			1.096	1.048	0.048			
			1.064	0.999	0.065			
			1.142	1.003	0.139			
			1.132	0.999	0.133			
			1.141	1.132	0.009			
			0.864	0.830	0.034			



P = 0.0010

Dunn Post Hoc-test:

CON vs LOW P <0.05**

CON vs HIGH P <0.05**

Table 4. **Results of individual changes within the three experimental groups, before and after exercise.** A positive value indicates a decrease. Non-parametric ANOVA (Kruskal-Wallis) statistics when comparing the changes in all three groups were $p = 0.0010$. A Dunn Post Hoc-test comparing the Control- versus the Moderate-intensity group, $p < 0.05$, and the Control- versus the High-intensity group, $p = < 0.05$.

CON	CON	MOD	MOD	HIGH	HIGH
pre mean	post mean	pre mean	post mean	pre mean	post mean
0.691	0.361	1.049	1.133	0.854	0.951
1.495	0.954	2.150	2.010	0.867	0.858
1.521	1.007	0.709	0.694	0.945	0.908
1.716	0.723	0.902	0.835	1.011	0.907
0.969	0.742	1.038	1.159		
		1.073	1.002		







 	 	 
P = 0.017 paired-t	P = 0.734 paired-t	P = 0.772 paired-t

Table 5. Results of pooled data and other statistical analyses for measurement of serum β -endorphin concentrations for all three groups. A Paired-t test indicates there was a significant difference when comparing the Control groups' mean pre-and post-exercise values $p=0.017$. Both the Moderate-and High-intensity groups' mean pre-and post-exercise values were not significant, $p=0.734$ and $p=0.772$.

5. DISCUSSION

All the participants exercised within their assigned heart rate ranges throughout the six weeks of the study. All three of the experimental groups were significantly different in terms of their average heart rates achieved per session ($p = < 0.05$). This indicates that there was no overlap between the experimental groups, and that the participants exercised within their required heart rate ranges (70%, 50%, or $< 30\%$ of HR reserve). This also indicates that it is possible to implement a structured exercise routine for individuals with depression who are generally unfit.

Due to the fact that there were a number of sessions (1,2,8, 9 and 17) where there were no significant difference between the Moderate- and Control groups' heart-rate ranges, it can be inferred that for their first and second sessions, the participants might not have known what to expect and they may have been nervous, which therefore might have caused them to over-perform. As the weeks went on, the participants seemed to become more comfortable with the study's procedure and routine, so they performed within the parameters of the prescribed heart-rate intensities. It is not clear why there was no significant difference between the Moderate- and Control groups in sessions 8, 9 and 17. Perhaps this was because there were two participants in the Control group who failed to maintain a low heart rate (not exceeding 120 bpm) during a number of their sessions.

Some of the participants (potentially those in all three groups) may have experienced training adaptations. Throughout the study, the workloads at which the High- and Moderate-intensity groups were cycling had to be increased in order to maintain the heart-rate range that they were prescribed. As the participants became more familiar with the training, and their bodies adapted to the workload, the workloads had to be increased in order for their heart rates to remain within the specified range. Although most of the participants were inactive prior to starting the study, it can be assumed that most experienced changes or adaptations in physiological function in response to the repeated series of exercise intervention. Typically, most untrained individuals can expect between a 10% to 30% improvement in VO_2 peak and work capacity following an eight-to-12 week period of training (American College of Sports Medicine, 2011). Although the present study did not measure VO_2 max, this would have been a more accurate measure of assessing whether the participants underwent any exercise adaptations or fitness gains.

5.1 Depression scores

In order to determine which exercise intensity/intensities alleviated the symptoms of depression, all the participants completed a HAM-D and MADRS questionnaire on a weekly basis. Overall, the participants' HAM-D scores after six weeks of exercise were reduced 77% from baseline for the High- intensity group, significantly more than the Moderate-intensity group (65%) and the Control group (44%). The MADRS scores also improved after six weeks of exercise. The High-intensity group's MADRS scores reduced 8% from baseline and the Moderate-intensity group showed an improvement of 43% and the Control group 24%.

Based on the HAM-D and MADRS scores, the High-intensity group showed the greatest improvement, with a reduction of 77% over the six-week period, which was significantly better than the Control group. This indicated that the participants in the High-intensity group experienced a better response to the high-intensity exercise, which in turn increased their mood states. However, all of the experimental groups showed improvement in their HAM-D scores at the end of the six weeks. This finding goes against the study's hypothesis that only the High-intensity group participants would improve their level of depression. Given that some of the Control's also showed some small improvement in their level of depression, it has to be concluded that other variables were also responsible for the improvements seen, such as a positive psychological boost experienced from participating in an exercise programme perceived as resulting in self-improvement, and the possibility of spontaneous recovery in some of the participants. In order to avoid the possibility of social support influencing treatment response, all the participants exercised in a lab by themselves, supervised only by the project leader. Every Friday, the study's psychologist interviewed the participants and completed the HAM-D with them. It is thus possible that the attention that the participants received from the psychologist each week may have had a minor therapeutic effect (although this would not have favoured any of the three experimental groups in particular). Finally, given that lack of motivation and lethargy characterize depression, having a structured exercise program for six weeks may have also counteracted these characteristics to some extent. Motivation was important, especially during the first week of the study, which presumably acted as a trial period for the participants, making or breaking their drive to

continue. When sessions were missed, the participant was contacted immediately to ensure that he was okay, and was then encouraged to try to make it to his next appointment.

These above-mentioned findings also answer the question of which exercise intensities were able to alleviate the symptoms of depression, and it is clear that overall both high- and moderate-intensity exercise produced meaningful improvements in depressive symptoms (evident through the reductions in the HAM-D and MADRS scores). Low-intensity exercise (<30% HR reserve) also showed improvements, but not as greatly as for the high- and moderate-intensities. All of the High-intensity groups' participants improved in their HAM-D scores as well as their MADRS scores. Within the Moderate-intensity group, all the participants' HAM-D scores improved, and all but one of the participants' MADRS scores improved. This one participant's MADRS score was initially 6 and at the end of the six weeks it worsened to 20. This indicated that his level of depression increased. The Control participants HAM-D scores all also improved, as did their MADRS scores (with the exception of one participant, who's score went from a 22 to 2). The fact that overall the individuals in the High-intensity group improved relatively more in terms of their level of depression (when observing where they had improved to by the end of the six weeks) needs to be seen in relation to the study's β -endorphin results (see below). Given the small sample size of this pilot study, and the fact that the experimental groups were not even in size, these results must be viewed tentatively, and it would be interesting to see whether a larger sample size would yield different results between the High- and Moderate-intensity groups with regard to their improvements in level of depression.

The reduction in level of depression displayed in the present study is comparable to the results of Dunn and co-workers (2005), which showed that the high-energy expenditure dose (consistent with public health recommendations) was effective in reducing depressive symptoms (47% from baseline measurement) over a 12-week treatment period. Although those randomized into the low energy expenditure dose did experience some reduction in depression over the 12-week period (30% from baseline measurement), they did not respond significantly better than the control condition (29% from baseline measurement) (Dunn et al., 2005). In younger adults, a previous investigation examined whether daily activity and the tendency to participate in exercise were associated with mood states in a student cohort. The results showed that mood tended to be higher on the day an individual exercised, and that daily activity and exercise overall are strongly linked with mood states. In line with these

findings, a recent study showed that exercise significantly improves mood states in non-exercisers, recreational exercisers, as well as marathon runners (Dinas et al., 2011).

Therefore, consistent with the literature, the results of this pilot study indicate how all three exercise groups showed improvement in their HAM-D and MADRS scores at the end of the six-week intervention, with the High-intensity group demonstrating the greatest improvement overall.

5.2 β -endorphins

It was predicted that a β -endorphin release would only occur during high-intensity exercise, and not with low- and moderate-intensity exercise. This hypothesis was disproven in that there was no significant difference found between the baseline and post-exercise serum β -endorphin levels in the High-intensity group ($p = 0.992$). No difference was found in the Moderate-intensity exercise group either ($p = 0.953$). There were an almost equal number of increased and decreased values for those in the Moderate-intensity group (with only two participants exhibiting an increase at almost every visit). Surprisingly, the High-intensity group showed a slightly greater number of decreased values for β -endorphin concentration at all the visits (with only one subject showing an increase at every session, save for one). The mean values after exercise for both the Moderate- and the High-intensity groups were not significantly different to the baseline values. The finding of a significant difference in post-exercise concentration of β -endorphin amongst the Controls, and the Moderate- and High-intensity groups (with a $p < 0.02$ for the Controls versus the Low-intensity group) is probably not meaningful in the context of this study's small sample size. Interestingly, each of the Control group participants (with the exception of one during one of his sessions) showed a significant decrease in β -endorphin concentrations following exercise. The Control group's values of absolute change (even though they decreased after exercise) were greater than the changes for the Moderate- and the High-intensity groups' values.

These above-mentioned β -endorphin results are surprising, inconsistent and inconclusive. However, these unpredicted results can most likely be explained by the problems encountered with the ELISA kits and the various reasons (see the 'Limitations' section below) why they were unable to detect possible increases meaningfully. Despite these findings, inferences can still be made regarding the release of endorphins in relation to the intensity of exercise and the possibility for improvements in depressed mood, as the High-intensity group clearly experienced the greatest overall improvement in their depression levels, so it may be that

elevated brain endorphin levels could account for this trend even though conclusive elevations could not be demonstrated in the circulation due to the limitations of the testing methods. In addition, the Control group's circulating β -endorphin levels did not improve throughout the study (but rather decreased), indicating that exercising at <30% of maximum heart rate is not enough to produce a β -endorphin release.

Other exercise-based studies indicate that the release of β -endorphins is dependent more on the relative, than the absolute, amount of exercise, and that exercise intensities of at least 70 percent of VO_{2max} must be reached before the plasma level of β -endorphin increases (Øktedalen et al., 2001). In comparison, there were no differences in serum β -endorphin levels in the present study's Moderate- and High-intensity groups. It appears as though there was a slight increase in the Moderate-intensity group's serum β -endorphin levels in the middle of the intervention versus those of the High-intensity group, but not enough to be significant (see Figure 9). It is not clear why there was no significantly higher increase in β -endorphins in the High-intensity group compared to the Moderate-intensity group, other than surmising that is this due to the problem of having to measure β -endorphins through the blood. There is also the possibility that the participants in the High-intensity group felt pressured to perform at such a vigorous intensity and that it was too demanding, and this may therefore have caused angst among them, although this was not reported by any of the participants when interviewed on a weekly basis.

A review by Goldfarb and co-workers (1997) suggests that exercise-induced β -endorphin alterations in the circulation are related to the type of exercise and the special populations tested, and may differ in individuals with health problems. Some of the possible mechanisms that may induce β -endorphin changes in blood circulation include analgesia, lactate or base excess, and metabolic factors. Based on the type of exercise, different mechanisms may be involved in the regulation of β -endorphin release during exercise (Goldfarb et al., 1997). Measuring circulating β -endorphins may be more difficult than perceived due to other metabolic and mechanistic factors not known. According to Schwarz and colleagues, intense endurance exercise performed at lactate steady-state leads to an increase in β -endorphins only beyond an exercise duration of approximately one hour, so that during endurance training in leisure-time sports or healthy sporting activities, no increase in β -endorphins is generally expected. However, in long-lasting endurance exercise (such as long-distance running) an

increase in endogenous opioids, and concomitant endorphinergic effects (such as changes in mood state), can be assumed (Schwarz & Kindermann, 1992).

Another study by Schwarz & Kindermann (1990) concluded that exercise involving anaerobic components increases β -endorphin and lactate levels more profoundly. It is also possible that a longer intervention of eight to 12 weeks may have yielded more favourable results. However, a systemic review by Krogh and co-workers (2011) examined the effectiveness of exercise in adults with clinical depression and found that within the 13 trials that fulfilled their inclusion criteria, there was evidence that those with a shorter intervention (less than 10 weeks) had a stronger beneficial effect than those trials in which the duration of the intervention was longer (Krogh et al., 2011). There is a large amount of literature that supports the belief that physical exercise has on increasing circulating β -endorphin levels, but there is also controversial evidence; for instance, in a study done on eight healthy volunteers who had to exercise for one hour, no elevation of circulating β -endorphin levels was reached after 20 or 60 minutes (Elias et al., 1986). The same authors observed an elevation in circulating β -endorphins in exercise-trained participants, but these raised levels returned to normal 60 minutes after physical activity (Elias et al., 1989). A study conducted by Langenfeld et al. (1987) found no increase in β -endorphin levels after exercise (bicycle ergometer and treadmill) testing at 60% VO₂ max. Consistent with this finding, Rahkila et al. (1988) observed that endorphin-secretion into the circulating is stimulated only by relatively strenuous physical activity.

5.3 Frequency of exercise

There has not been much research on the effect that exercise frequency has on lowering depression scores. It would seem that the more frequently someone exercises, the greater the improvement in his/her depression might be. Dunn and co-workers (2005) found that there was no significant difference in treatment response between participants who exercised for three days per week relative to those who exercised for five days per week. In conclusion, high energy expenditure dose (consistent with public health recommendations for energy expenditure) is recommended for remission of major depressive disorder in previously sedentary adults, regardless of the number of days of exercise per week (Dunn, et al., 2005). All the participants in the present study followed the protocol, which required them to come in for testing three times per week. On some occasions, a participant might have been ill and

missed a session or two, but overall they were eager to continue as soon as possible in order to meet the required total of 18 completed sessions.

6. LIMITATIONS

This pilot study's small sample size, and its uneven group sizes with respect to those who completed, limit the ability to comprehensively determine whether there might have been a greater difference noticed between the Moderate-and High intensity-groups' improvements in depressed mood. Despite this, from a qualitative perspective, consistent and meaningful differences were nonetheless found between the High- and Moderate-intensity groups. In any event, it would have been logistically very difficult to derive a larger sample size given the time that it takes to put one participant through the six-week programme, and the restrictions on the number of individuals that can be seen per week due to the limited amount of the equipment that is required, the fact that the participants exercised individually, and the amount of man-hours required to see each participant. Future studies must bear these logistical restrictions in mind.

The extent to which the study's volunteer participants are representative of the general population of depressed individuals is also somewhat uncertain, although these were individuals who were in the main not seeking treatment actively for their depression prior to enrolling in this study, and their motivation levels were found to be low during the study, so it is unlikely that they were unrepresentative in this regard.

This study also had a number of problems concerning the measurement of the participants' β -endorphin levels, which potentially led to the strange and inconclusive results that were observed. In order to measure these levels, blood/serum samples were used. It is known in the literature that measuring serum β -endorphins levels is problematic, and it is not clear how effective this method is, nor how accurate it is in terms of representing the total amount of centrally circulating endorphins (i.e. those in the brain) (Schwarz & Kindermann, 1992) (Meyer & Schwarz, 1975). A more accurate means of measuring β -endorphins would be to measure levels in the brain, however this is not possible during exercise. We also encountered problems with the first kit type that was used to analyze the β -endorphins in the first ten participants. Another potential limitation might be the time the samples were kept in the freezer before analysis. It would have been best to test the samples on a monthly basis, and it

could be speculated that the samples were kept in freezers too long before being analyzed due to the waiting period between ordering new kits. However, various logistical realities make getting around these problems very difficult in reality for any study. These realities include: (i) the delays caused between ordering and receiving kits; (ii) the need to experiment with various kits first to ensure that they are effective in detecting β -endorphin; and the limited time one has to use the kit before it expires versus the amount of time it takes to collect enough blood samples to analyze. It is unclear how one would avoid these logistical realities.

Encouragement was also given to the participants to continue with exercise after they completed the study, but it is not known whether they took this advice. These findings are consistent with and extend previous studies by showing a specific association between (aerobic) exercise within the range of $>50\%$ of HR reserve and decreased prevalence of depressive symptoms.

7. CONCLUSION

This study's central hypothesis was disproved in that both High- and Moderate-intensity exercise were shown to have a positive impact on alleviating the symptoms of moderate depression, whereas it was initially believed that only high-intensity exercise would be sufficient to produce a β -endorphin release. The exercise intensity that is sufficient in alleviating depression appears to be in the range between moderate (50% of heart rate reserve) and high ($>70\%$ heart rate reserve) intensity, while lower-intensity exercise does not appear to be as effective. This study therefore supports the literature in showing that exercise is useful for the treatment of depression. However, β -endorphin values did not increase in a significant manner during exercise in the High- and Moderate-intensity groups. Given the problems encountered with the ELISA analysis kits, the acknowledged difficulty with measuring β -endorphins in the blood, and the lack of significant differences with respect to the Moderate- and High-intensity groups' serum β -endorphin levels, this study cannot conclusively prove the hypothesis regarding the mechanism underlying the benefit of exercise on the symptoms of depression; namely, involvement of the PANIC/separation-distress system.

Future studies are required to replicate these findings in a larger sample (> 45 participants) and to address the problems associated with measuring serum β -endorphin levels.

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8. APPENDICES

Appendix A: MDI



Psychiatric Research Unit
Hillerød

Major Depression Inventory (MDI)

The following questions ask about how you have been feeling over the past two weeks. Please put a tick in the box which is closest to how you have been feeling.

How much of the time ...		All the time	Most of the time	Slightly more than half the time	Slightly less than half the time	Some of the time	At no time
1	Have you felt low in spirits or sad?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2	Have you lost interest in your daily activities?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3	Have you felt lacking in energy and strength?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4	Have you felt less self-confident?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5	Have you had a bad conscience or feelings of guilt?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6	Have you felt that life wasn't worth living?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
7	Have you had difficulty in concentrating, e.g. when reading the newspaper or watching television?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8a	Have you felt very restless?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
8b	Have you felt subdued or slowed down?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
9	Have you had trouble sleeping at night?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10a	Have you suffered from reduced appetite?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
10b	Have you suffered from increased appetite?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>Total score</i>						<input type="checkbox"/>	<input type="checkbox"/>



Major Depression Inventory (MDI): Scoring Key

At the top, the diagnostic demarcation line is indicated and at the bottom, the total scores of the 10 items are summed up.

How much of the time ...		Diagnostic demarcation line						
		All the time	Most of the time	Slightly more than half the time	Slightly less than half the time	Some of the time	At no time	
Highest score for DSM-IV major depression	1	Have you felt low in spirits or sad?	5	4	3	2	1	0
	2	Have you lost interest in your daily activities?	5	4	3	2	1	0
	3	Have you felt lacking in energy and strength?	5	4	3	2	1	0
	4	Have you felt less self-confident?	5	4	3	2	1	0
	5	Have you had a bad conscience or feelings of guilt?	5	4	3	2	1	0
	6	Have you felt that life wasn't worth living?	5	4	3	2	1	0
	7	Have you had difficulty in concentrating, e.g. when reading the newspaper or watching television?	5	4	3	2	1	0
Highest score	8a	Have you felt very restless?	5	4	3	2	1	0
	8b	Have you felt subdued or slowed down?	5	4	3	2	1	0
	9	Have you had trouble sleeping at night?	5	4	3	2	1	0
Highest score	10a	Have you suffered from reduced appetite?	5	4	3	2	1	0
	10b	Have you suffered from increased appetite?	5	4	3	2	1	0

Total Score (item 1 - 10) : = ___ + ___ + ___ + ___ + ___ =

DSM-IV diagnosis _____



Major Depression Inventory (MDI): Scoring Instruction

A: As a diagnostic instrument for DSM-IV major depression

The diagnostic demarcation line indicates at which point a symptom is severe enough to be used in the DSM-IV algorithm of major depression. Thus, the first three symptoms should have been present at least "most of the time" during the past two weeks, while the other symptoms should have been present "more than half" of the period. For symptoms 4 and 5, only the highest score should be used, as the DSM-IV contains only 9 of the 10 MDI symptoms and as symptoms 4 and 5 belong to the same category in DSM-IV. For symptoms 8 and 10, only the one of the two alternatives (a or b) with the highest score is considered.

Major depression is diagnosed if 5 or more of the 9 symptoms (items 4 and 5 combined) have been present in the past two weeks and if symptom 1 or symptom 2 are included in these 5 symptoms.

Reference:

Bech P, Rasmussen N-A, Olsen LR, Noerholm V, Abildgaard W. The sensitivity and specificity of the Major Depression Inventory, using the Present State Examination as the index of diagnostic validity. *J Affect Disord* 2001; 66: 159-164

B: As a depression rating scale

As a severity measure, the MDI score ranges from 0 to 50, since each of the 10 items can be scored from 0 (at no time) to 5 (all the time). Again, for items 8 and 10, alternative a or b with the highest score is considered.

Mild depression	MDI total score of 20 to 24
Moderate depression	MDI total score of 25 to 29
Severe depression	MDI total score of 30 or more

Reference:

Olsen LR, Jensen DV, Noerholm V, Martiny K, Bech P. The internal and external validity of the Major Depression Inventory in measuring severity of depressive states. *Psychol Med* 2003; 33, 351-356

Appendix B: Hamilton Rating Scale of Depression (HAM-D)

THE HAMILTON RATING SCALE FOR DEPRESSION

(to be administered by a health care professional)

Patient's Name _____

Date of Assessment _____

To rate the severity of depression in patients who are already diagnosed as depressed, administer this questionnaire. The higher the score, the more severe the depression.

For each item, write the correct number on the line next to the item. (Only one response per item)

1. **DEPRESSED MOOD** (Sadness, hopeless, helpless, worthless)

- 0= Absent
 1= These feeling states indicated only on questioning
 2= These feeling states spontaneously reported verbally
 3= Communicates feeling states non-verbally—i.e., through facial expression, posture, voice, and tendency to weep
 4= Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

2. **FEELINGS OF GUILT**

- 0= Absent
 1= Self reproach; feels he has let people down
 2= Ideas of guilt or rumination over past errors or sinful deeds
 3= Present illness is a punishment. Delusions of guilt
 4= Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. **SUICIDE**

- 0= Absent
 1= Feels life is not worth living
 2= Wishes he were dead or any thoughts of possible death to self
 3= Suicidal ideas or gesture
 4= Attempts at suicide (any serious attempt rates 4)

4. **INSOMNIA EARLY**

- 0= No difficulty falling asleep
 1= Complains of occasional difficulty falling asleep—i.e., more than 1/2 hour
 2= Complains of nightly difficulty falling asleep

5. **INSOMNIA MIDDLE**

- 0= No difficulty
 1= Patient complains of being restless and disturbed during the night
 2= Waking during the night—any getting out of bed rates 2 (except for purposes of voiding)

6. **INSOMNIA LATE**

- 0= No difficulty
 1= Waking in early hours of the morning but goes back to sleep
 2= Unable to fall asleep again if he gets out of bed

7. **WORK AND ACTIVITIES**

- 0= No difficulty
 1= Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
 2= Loss of interest in activity, hobbies or work—either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
 3= Decrease in actual time spent in activities or decrease in productivity
 4= Stopped working because of present illness

8. **RETARDATION: PSYCHOMOTOR** (Slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

- 0= Normal speech and thought
 1= Slight retardation at interview
 2= Obvious retardation at interview
 3= Interview difficult
 4= Complete stupor

9. **AGITATION**

- 0= None
 1= Fidgetiness
 2= Playing with hands, hair, etc.
 3= Moving about, can't sit still
 4= Hand wringing, nail biting, hairpulling, biting of lips

10. **ANXIETY (PSYCHOLOGICAL)**

- 0= No difficulty
 1= Subjective tension and irritability
 2= Worrying about minor matters
 3= Apprehensive attitude apparent in face or speech
 4= Fears expressed without questioning

11. **ANXIETY SOMATIC:** Physiological concomitants of anxiety; i.e., effects of autonomic overactivity, "butterflies," indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency. Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

- 0= Absent
 1= Mild
 2= Moderate
 3= Severe
 4= Incapacitating

12. **SOMATIC SYMPTOMS (GASTROINTESTINAL)**

- 0= None
 1= Loss of appetite but eating without encouragement from others. Food intake about normal
 2= Difficulty eating without urging from others. Marked reduction of appetite and food intake

13. **SOMATIC SYMPTOMS GENERAL**

- 0= None
 1= Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
 2= Any clear-cut symptom rates 2

14. **GENITAL SYMPTOMS** (Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances)

- 0= Absent
 1= Mild
 2= Severe

15. **HYPOCHONDRIASIS**

- 0= Not present
 1= Self-absorption (bodily)
 2= Preoccupation with health
 3= Frequent complaints, requests for help, etc.
 4= Hypochondriacal delusions

16. **LOSS OF WEIGHT**

- A. When rating by history:
 0= No weight loss
 1= Probably weight loss associated with present illness
 2= Definite (according to patient) weight loss
 3= Not assessed

17. **INSIGHT**

- 0= Acknowledges being depressed and ill
 1= Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
 2= Denies being ill at all

18. **DIURNAL VARIATION**

- A. Note whether symptoms are worse in morning or evening; if NO diurnal variation, mark none
 0= No variation
 1= Worse in A.M.
 2= Worse in P.M.
 B. When present, mark the severity of the variation. Mark "None" if NO variation
 0= None
 1= Mild
 2= Severe

19. **DEPERSONALIZATION AND DEREALIZATION** (Such as: Feelings of unreality; Nihilistic ideas)

- 0= Absent
 1= Mild
 2= Moderate
 3= Severe
 4= Incapacitating

20. **PARANOID SYMPTOMS**

- 0= None
 1= Suspicious
 2= Ideas of reference
 3= Delusions of reference and persecution

21. **OBSESSIVE AND COMPULSIVE SYMPTOMS**

- 0= Absent
 1= Mild
 2= Severe

Total Score _____

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Appendix C: Montgomery Åsberg Depression Rating Scale (MADRS)

Name: _____ Date: _____

Montgomery-Åsberg Depression Scale (MADRS)

Instructions: The ratings should be based on a clinical interview moving from broadly phrased questions about symptoms to more detailed ones which allow a precise rating of severity. The rater must decide whether the rating lies on the defined scale steps (0, 2, 4, 6) or between them (1, 3, 5). It is important to remember that it is only rare occasions that a depressed patient is encountered who cannot be rated on the items in the scale. If definite answers cannot be elicited from the patients, all relevant clues as well as information from other sources should be used as a basis for the rating in line with customary clinical practice. This scale may be used for any time interval between ratings, be it weekly or otherwise, but this must be recorded.

1. **Apparent Sadness**

Representing despondency, gloom and despair, (more than just ordinary transient low spirits) reflected in speech, facial expression, and posture. Rate on depth and inability to brighten up.

- 0 No sadness
- 1
- 2 Looks dispirited but does brighten up without difficulty.
- 3
- 4 Appears sad and unhappy most of the time.
- 5
- 6 Looks miserable all the time. Extremely despondent.

2. **Reported Sadness**

Representing reports of depressed mood, regardless of whether it is reflected in appearance or not. Includes low spirits, despondency or feeling of being beyond help without hope. Rate according to intensity, duration and the extent to which the mood is reported to be influenced by events.

- 0 Occasional sadness in keeping with the circumstances.
- 1
- 2 Sad or low but brightens up without difficulty.
- 3
- 4 Pervasive feelings of sadness or gloominess. The mood is still influenced by external circumstances.
- 5
- 6 Continuous or unvarying sadness, misery or despondency.

3. **Inner Tension**

Representing feelings of ill-defined discomfort, edginess, inner turmoil mounting to either panic, dread or anguish. Rate according to intensity, frequency, duration and the extent of reassurance called for.

- 0 Placid. Only reflecting inner tension.
- 1
- 2 Occasional feelings of edginess and ill-defined discomfort.
- 3
- 4 Continuous feelings of inner tension or intermittent panic which the patient can only master with some difficulty.
- 5
- 6 Unrelenting dread or anguish. Overwhelming panic.

4. **Reduced Sleep**

Representing the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well.

- 0 Sleeps as usual.
- 1
- 2 Slight difficulty dropping off to sleep or slightly reduced light or fitful sleep.
- 3
- 4 Sleep reduced or broken by at least two hours.
- 5
- 6 Less than two or three hours sleep.

5. **Reduced Appetite**

Representing the feeling of loss of appetite compared with when well. Rate by loss of desire for food or the need to force oneself to eat.

- 0 Normal or increased appetite.
- 1
- 2 Slightly reduced appetite.
- 3
- 4 No appetite. Food is tasteless.
- 5
- 6 Needs persuasion to eat.

6. **Concentration Difficulties**

Representing difficulties in collecting one's thoughts mounting to incapacitating lack of concentration. Rate according to intensity, frequency, and degree of incapacity produced.

- 0 No difficulties in concentrating.
- 1
- 2 Occasional difficulties in collecting one's thoughts.
- 3
- 4 Difficulties in concentrating and sustaining thought which reduces ability to read or hold a conversation.
- 5
- 6 Unable to read or converse without great initiative.

7. **Lassitude**

Representing a difficulty getting started or slowness initiating and performing everyday activities.

- 0 Hardly no difficulty in getting started. No sluggishness.
- 1
- 2 Difficulties in starting activities.
- 3
- 4 Difficulties in starting simple routine activities which are carried out with effort.
- 5
- 6 Complete lassitude. Unable to do anything without help.

8. **Inability to Feel**

Representing the subjective experience of reduced interest in the surroundings, or activities that normally give pleasure. The ability to react with adequate emotion to circumstances or people is reduced.

- 0 Normal interest in the surroundings and in other people.
- 1
- 2 Reduced ability to enjoy usual interest.
- 3
- 4 Loss of interest in surroundings. Loss of feelings for friends and acquaintances.
- 5
- 6 The experience of being emotionally paralyzed, inability to feel anger, grief or pleasure and a complete or even painful failure to feel for close relatives and friends.

9. **Pessimistic Thoughts**

Representing thoughts of guilt. Inferiority, self-reproach, sinfulness, remorse and ruin.

- 0 No pessimistic thoughts.
- 1
- 2 Fluctuating ideas of failure, self-reproach or self-depreciation.
- 3
- 4 Persistent self-accusations, or definite but still rational ideas of guilt or sin. Increasingly pessimistic about the future.
- 5
- 6 Delusions of ruin, remorse or unredeemable sin. Self-accusations which are absurd and unshakable.

10. **Suicidal Thoughts**

Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.

- 0 Enjoys life or takes it as it comes.
- 1
- 2 Weary of life. Only fleeting suicidal thoughts.
- 3
- 4 Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intention.
- 5
- 6 Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

Total Score: _____

Appendix D: Health and History Questionnaire



SWEATING AWAY DEPRESSION?

THE IMPACT OF INTENSIVE EXERCISE ON DEPRESSION

HEALTH SCREENING QUESTIONNAIRE

PERSONAL DETAILS

GENERAL -

Name: _____

Surname: _____

Date of birth: _____ Age: _____

Gender: _____

Postal address: _____

Code: _____

Email address: _____

Phone number: (w) _____ (h) _____

Cell phone: _____

Weight: _____ (kg)

Height: _____ (cm)

BMI: _____

Body fat: _____ (%)

Blood pressure: _____ (mm Hg)

LIFESTYLE HABITS -

Occupation/Degree (and level) registered for: _____

Do you smoke? (number per day): _____

Have you ever smoked? (number per day): _____

What is your typical alcohol consumption? (units/day): _____

Do you use recreational drugs? (type/amount/frequency): _____

Have you ever used them? (type/amount/frequency): _____



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MEDICAL HISTORY

Are you aware of, have you ever suffered from, or have you been diagnosed as being at risk of circulatory or peripheral vascular disease , or coronary artery disease due to factors such as high blood cholesterol , a family member with heart disease , cigarette smoking , lack of physical activity , hypertension (high blood pressure), or being overweight ?	yes	no
<i>If yes, please specify which factor(s) and/or disease, and provide details:</i>		
Have you <u>previously</u> suffered from, or have you ever been diagnosed with a heart or blood vessel condition, such as a heart attack , angina (chest pain), cardiac failure , cardiac arrhythmia (abnormal heart beat), rheumatic fever , heart murmur or an inherited heart defect ?	yes	no
Have you ever undergone a coronary artery bypass operation , angioplasty , cardiac transplant , or have to make use of a pacemaker ?	yes	no
<i>If yes, please specify which condition(s), and provide details:</i>		
Do you <u>currently</u> experience any symptom(s) of a heart or blood vessel condition, such as swollen ankles , abnormal shortness of breath (with exercise), palpitations , chest pain , pain (or discomfort) in the neck , jaw or arms at rest or during exercise, frequent dizziness or fainting spells , and/or calf pain when walking/running?	yes	no
<i>If yes, please specify which symptom(s), and provide details:</i>		
Do you currently suffer from any metabolic or hormonal disease or condition, such as diabetes mellitus (insulin-dependent or non-insulin-dependent), thyroid gland disorders , hypoglycaemia (low blood sugar), hyperglycaemia (high blood sugar), heat intolerance , malignant hyperthermia , or an underlying metabolic muscle abnormality ?	yes	no
Have you ever suffered from any abnormal thermoregulatory response <i>specifically to exercise</i> , such as heat illness , rhabdomyolysis , renal failure or exercise-induced heatstroke ?	yes	no
<i>If yes, please specify which disease and/or condition, and provide details:</i>		
Do you suffer from any respiratory (lung) disease or symptom(s), such as asthma , emphysema , tuberculosis , wheezing , coughing , postnasal drip , hay fever , or repeated flu-like illness ?	yes	no
<i>If yes, please specify which disease and/or symptom(s), and provide details:</i>		
Do you suffer from any allergies, or have a history of allergic reactions to medication , plant material and/or animal material ?	yes	no
<i>If yes, please specify which allergy, and provide details:</i>		
Do you suffer from any gastrointestinal disease or symptom(s), such as heartburn , nausea , vomiting , abdominal pain , weight loss or gain (> 5kg) , a change in bowel habits , chronic	yes	no

diarrhea, blood in the stools, or have a past history of liver or gallbladder disease ?		
Have you ever undergone gastrointestinal (GI) tract surgery , or have been diagnosed with a known or suspected obstructive disease of the GI tract , an inadequate gag reflex , reflexion of the oesophagus , or polyps in the colon , or have a hypermotility disorder of the GI tract ?	yes	no
<i>If yes, please specify which disease and/or symptom(s), and provide details:</i>		
Do you suffer from any disease or symptom(s) of the central nervous system, such as a past history of stroke or transient ischaemic attack (a transient episode of neurologic dysfunction caused by loss of blood flow), frequent headaches , epilepsy , depression , anxiety attacks , muscle weakness , nerve tingling , loss of sensation , or blackouts/fainting ?	yes	no
<i>If yes, please specify which disease and/or symptom(s), and provide details:</i>		
Do you suffer from any disease or symptom(s) of the kidney or bladder, such as a past history of kidney or bladder disease , blood in the urine , loin pain , kidney stones , frequent urination , or burning during urination?	yes	no
<i>If yes, please specify which disease and/or symptom(s), and provide details:</i>		
Do you suffer from any disease of the blood or immune system, such as anaemia , recurrent infections , HIV/AIDS , leukemia , or are you using any immunosuppressive medication(s) ?	yes	no
<i>If yes, please specify which disease, and provide details:</i>		
Do you suffer from any growths or cancer , or have a history of cancer ?	yes	no
<i>If yes, please specify which type of cancer, and provide details:</i>		
Do you have a history of sudden death in your family, under the age of 60 years?	yes	no
Do you suffer from chronic fatigue syndrome ?	yes	no
Do you suffer from arthritis , gout , neck- , back- or joint pain , or any other musculoskeletal disorder ?	yes	no
<i>If yes, please provide details:</i>		
Do you suffer from any <i>other</i> medical condition(s), or experience any other significant symptoms which you are concerned about?	yes	no
<i>If yes, please provide details:</i>		

MEDICATION AND SUPPLEMENT USE

What **medication**, if any, are you **currently** using (acute and/or chronic)

Name of medication and duration of use:

What **dietary supplements/ vitamins**, if any, are you **currently** using?

Name of supplement and duration of use:

TRAINING HISTORY

Have you ever suffered from muscle cramping (painful, spontaneous, sustained spasms of a muscle) during or immediately (within 6 hours) after an activity?	yes	no
Do you <u>currently</u> , or have you suffered from any symptom(s) of an injury (muscles, tendons, bones, ligaments or joints) within the <u>past 12 months</u> ? (ONLY symptoms of an injury that was severe enough to interfere with exercise, or which required treatment, such as medication or intervention from a medical professional.)	yes	no

If **yes**, please specify which symptom(s) and injury, and provide details:

CRITERIA: Training needs to be LESS than three times per week, and LESS than 1 hour sessions

In the past **three months** -

How much time would you spend on average exercising or being active, per day?

Please provide details: _____ hours/day

How many days do you train, or are you involved in any form of activity, per week?

Please provide details: _____ days/wk

How many hours do you train on average, or are you involved in any form of activity, per week?

Please provide details: _____ hours/wk

Appendix E: Consent form

Participant Information Sheet

Sweating away depression? The impact of intensive exercise on depression

- You are invited to participate in a neuropsychological study conducted by the University of Cape Town (UCT) Psychology Department in collaboration with the Exercise Science & Sports Medicine (ESSM) division at the Sports Science Institute of South Africa. Please read this information sheet carefully and do not hesitate to ask the researcher for any additional information.
- The overall purpose of this study is to investigate the influence of 3 different exercise protocols on depressive symptoms. You will be required to attend three 60-minute exercise sessions per week, for six weeks (i.e. 18 sessions in total).
- If you are placed in Groups 1 or 2, you will be required to complete two Peak Sustained Power Output (PSPO) test on a cycle ergometer to assess your maximum heart rate, which entails cycling progressively harder until fatigue, generally around 6-8 minutes. You will have a small amount of blood taken once per week (i.e. on only one day of the week), both before and after the exercise. You will also be asked to complete three questionnaires once weekly. Two of these questionnaires measures depressive symptoms via external assessment. The other questionnaire is a self-report measure of personality and emotions. Finally, a medical doctor will examine you before you exercise to ensure that you are physically able to do so.
- You are not eligible to participate in this study if you already have an exercise routine that exceeds a three-times weekly load of at least one hour, at an intensity of 70% of your Maximum Heart Rate.
- You are not eligible to participate in this study if you are already being treated for depression either with therapy or antidepressant medication.
- There are no anticipated risks involved in this research, but if you should experience any form of psychological or physical distress please be aware that you can inform the researcher/doctor immediately. Psychological support will be offered to you should you want it through either the University of Cape Town's Student Wellness Service — Student Counseling Services (Tel: 021 650 1017 / 1020), or alternatively, you can also consult your GP or a private psychologist.
- It is up to you to decide whether or not you take part. If you decide to take part, you will be given this information sheet to keep and also asked to sign a separate consent form. If you decide to participate, you are still free to withdraw from the study at any time, without having to give a reason.
- You will be reimbursed for the petrol/transport costs incurred in getting to the Sports Science Institute to participate in the study. If you are unable to get there yourself, an alternative transport arrangement can be organized.
- The confidentiality of your data and your identity will be protected. All data collected will be suitably anonymous, securely stored, and made accessible only to the researcher.
- This research will be carried out by researchers from UCT and ESSM, and is funded by the Institute for the Study of Affective Neuroscience (ISAN).

- This study has been reviewed by the UCT Psychology Department's Ethics Committee and the UCT Health Sciences Faculty Human Ethics Research Committee (HREC).
- If you have any questions regarding this study, or concerns regarding the manner in which the study was conducted, or would like to be informed of the results when the study is completed, please feel free to contact the principal researcher.

Address/contact details for communications (Co-investigator):

Dr Ross Balchin

Tel. 083 3731495

Email: rm.balchin@uct.ac.za

Professor Marc Blockman

Chair of Human Research Ethics Committee

[For any questions concerning your
rights and wellbeing as a participant]

Ph. (021) 406 6496

CONSENT FORM

**TITLE OF PROJECT: *Sweating Away Depression?*
*The impact of intensive exercise on depression***

*Please cross out
as necessary*

Have you read the Participant Information Sheets? YES/NO

Have you had an opportunity to ask questions and discuss the study? YES/NO

Have you received satisfactory answers to all your questions? YES/NO

Have you received enough information about the study? YES/NO

Who have you spoken to? Dr/Mr/Mrs/Ms/Prof.

Do you understand that you are free to withdraw from the study:

-at any time

-without having to give a reason for withdrawing

-and without affecting your future treatment? YES/NO

Do you consent to the unattributed and confidential use of the data collected for scientific purposes? YES/NO

Signed

Date:

(NAME IN BLOCK LETTERS)