Physical activity and health with focus on depression

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Project thesis at the Faculty of Medicine

UNIVERSITY OF OSLO

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Abstract

This project thesis studies the general effects of physical activity on the human body including the nervous system and the hormone systems. Furthermore the relationship between physical activity and depression is studied and if it is possible to treat depression with physical activity. A literature study has been conducted to answer the questions.

The relationship between physical activity and depression has been studied in a large number of studies. The thesis is mostly based on the results of recent systematic review articles. Searches for review articles were made in McMaster PLUS, PubMed and the Cochrane Library.

The results show that physical activity has several positive effects on the human body. Physical activity improves cognition, mood and physical capacity and reduces the risk for a number of diseases and premature death.

Regarding depression the present state of evidence indicate that systematic physical activity has a positive effect on depressed people comparable with other established treatment alternatives. The reasons behind the positive effect in reducing depression symptoms are not fully understood and include probably many different factors including physiological and neurobiological mechanisms. The effect might also partly be explained by a systematic, empathic attempt to help suffering patients.

Systematic physical activity is a cheap intervention alternative with few side effects. It is recommended as a means to increase the public health in general. This thesis has shown that regular physical activity also has a role in the treatment of depressed patients.

Preface

This project thesis is a part of my medical degree and I wanted to study something that interests me personally. I am a physical active man and have always liked to move my body and have been engaged in a lot of different sports, especially swimming. I have personally experienced the good effects physical activity has on the mood and wanted to investigate the reasons behind that. Furthermore psychiatry is a medical field that interests me a lot. Therefor I was interested in studying the relationship between depression and physical activity and if it is possible to treat depression through physical activity.

I would like to thank Professor Egil W. Martinsen for inspiring me and updating me with the latest knowledge in this field. I also would like to thank my supervisor Professor emeritus Dag Bruusgaard and my dad Professor Thorbjörn Laike for valuable comments, support and motivation throughout the work-process.

Nils Laike

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1 Introduction

It has long been known that physical activity has positive effects on the human body; this was already known at the ages of Hippocrates (Bahr, 2008). However the focus on this relationship has increased in recent times. One reason for this is that the modern society minimizes the need for physical activity in the daily life. A lot of people works today in offices with little need of daily motion and the modern transport system also decreases the daily physical activity. This has had devastating consequences regarding the public health in the developed world with increased problems related to overweight, diabetes and cardiovascular diseases (Bahr, 2008).

In the same time the psychiatric disease depression is the single most usual cause of lost healthy life-years in the Western world. In Sweden and Norway around 20% of the population is affected by depression sometime during their life (Martinsen et al, 2016).

Research has showed that physical activity and exercise can be used to prevent and to treat diseases. In fact there is evidence that support the theory that regular physical activity can have a positive effect on a number of different diseases including psychiatric diseases (Bahr, 2008).

2 Aim

The thesis is divided into two parts. The aim of the first part is to investigate and present the effects of physical activity on the human body including the nervous system and the hormone system. These systems are probably the most important to explain the effects of physical activity on depression.

The aim of the second part is to present the latest research regarding the relationship between physical activity and depression. This part will try to answer if it is possible to treat depression through regular physical activity.

3 Method

The study started out with an oral interview with Professor Egil W. Martinsen at the University of Oslo. He has an interest in the field of this thesis and has done a lot of research in the field himself. He is also the main-author of chapters about physical activity and depression in the Norwegian *Aktivitetshåndboken* (Bahr, 2008) and in the Swedish *Fysisk aktivitet i sjukdomsprevention och sjukdomsbehandling (FYSS).*

A literature study has been conducted to answer the questions in the two parts. In the first part the main sources of information have been a chapter in the *FYSS*-book (Henriksson & Sundberg, 2015) about the general effects of physical activity as well as the corresponding chapter in the English version of the *FYSS*-book namely *Physical Activity in the Prevention and Treatment of Disease* (Henriksson & Sundberg, 2010). These sources have been used to present the research regarding the general effects of physical activity on the human body.

To investigate the relationship between physical activity and depression a more extensive literature study has been done. This relationship has been studied in a large number of studies. To read all of these articles and to make a systematic review and meta-analysis is out of the scope of this thesis. Instead the thesis is mostly based on the results of recent systematic review articles.

Searches for review articles have been done in McMaster PLUS, PubMed and the Cochrane Library. Some of the most important keywords that were used during the search were "exercise", "physical activity" and "depression". In the Cochrane Library the systematic review "Exercise for depression" (Cooney et al, 2013) was found. This has been an important source of information. Three other systematic review articles have also been important sources of information, namely "Exercise as a treatment for depression: A meta-analysis" (Kvam et al, 2016), "Exercise as a treatment for depression: A meta-analysis adjusting for publication bias" (Schuch et al, 2016) and the epidemiological review article "Physical activity and sedentary behavior in people with major depressive disorder: A systematic review and meta-analysis" (Schuch et al, 2017). These publications are among the most important systematic reviews in the field and have been studied carefully.

Another important source of information is the chapter about physical activity and depression (Martinsen et al, 2016) in the Swedish *FYSS*-book updated in November 2016.

4 Physical activity and the human body

In this part the effects of physical activity on the human body will be presented as well as the definition of physical activity.

4.1 Definition of physical activity

Physical activity means all bodily movement resulting from the contraction of skeletal muscles and thereby resulting in increased energy expenditure (Henriksson & Sundberg, 2010, 2015). Exercise is defined according to American College of Sports Medicine (ACSM) as “planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness” (Cooney et al, 2013). Physical activity is thereby a definition that includes a wider range of activities than exercise. In this thesis the wider definition physical activity is used.

Physical activity can be performed in many different forms and with different intensity. Higher intensity means higher immediate impact on body functions. Depending on which type of metabolism that is dominant physical activity can be called either aerobic or anaerobic. There is one rule of thumb that states that if an activity can be performed more than two minutes the activity is aerobic (oxygen dependent). If it is possible to carry out the activity for two minutes but no longer the metabolism is approximately 50% aerobic and 50% anaerobic. If it is less than two minutes the anaerobic metabolism is dominant. The time interval is of course dependent on individual factors such as genetics. During high intensive physical activity the muscles work without sufficient oxygen supply and the dominant energy providing process is the anaerobic splitting of glucose and glycogen into the degradation product lactic acid. Strength training and running sprint are examples of activities where anaerobic processes are dominating while running a marathon is an example where aerobic processes dominates. During interval training, aerobic and anaerobic training is combined. Aerobic and anaerobic physical activity has different effects on the body. Regular aerobic activity stimulates the adaption of the heart and the aerobic system of the skeletal muscles. The capacity of the heart is increased and the mitochondrial volume in engaged muscle cells is increased. Anaerobic training does not have these effects. Instead, it leads to improved

conditions for greater lactic acid production and lactic acid tolerance (Henriksson & Sundberg, 2010, 2015).

4.2 General effects of physical activity on the human body

The human body is made for a life in motion and is still very similar to the body our ancestors had over 10 000 years ago. Our ancestors lived a completely different life compared to the modern life today and there was a need for physical activity and motion to survive. Therefore the human body evolved in symbiosis with the need of physical activity and is so to speak made to move (Henriksson & Sundberg, 2010).

When discussing effects of physical activity on the human body it is important to differentiate between immediate effects and long term effects on the human body. The immediate effects mean what is happening in the body during and after a single workout compared to a situation in rest while the long term effects mean what is happening to the body in the long time perspective (weeks or months) during regular physical activity and the differences compared to an untrained body. Some of the long term effects start already during the first workout while others take weeks or months before they are noticeable (Henriksson & Sundberg, 2010).

4.3 Immediate effects of physical activity

One single workout can have measurable effects on mood, cognition, blood pressure and blood glucose control (Henriksson & Sundberg, 2015).

Conscious body motions are planned, initiated and controlled by the primary motor cortex in the brain, from there nerves go through the brainstem and the spinal cord where motor neurons transmits signals through synapses to the skeletal muscle cells. This leads to the opening of ion channels and sodium ions goes into the cell and potassium ions leave the cell. This in turn leads to the spread of an action potential through the muscle cell membrane and the release of calcium ions to the cytoplasm. This activates the motor proteins actin and myosin that creates the contraction power and the motion. Energy in the form of adenosintrifosfat (ATP) is needed for this system to work. ATP forms through aerobe (oxygen

dependent) or anaerobe metabolism. During aerobic metabolism carbohydrates and fatty acids are metabolized. During anaerobic processes ATP forms together with lactate. When lactate is created, the pH falls in the muscle cells and in the blood. During the generation of ATP heat is also created, which leads to the increase of muscle- and body temperature. The oxygen consumption during aerobic physical activity, which is directly linked to the energy use in the body, rises from approximate 0,25 liter per minute at rest to about 1 liter per minute during a slow walk. During maximum physical activity the oxygen consumption rises to 2-7 liter per minute, about 10-25 times the resting rate (Henriksson & Sundberg, 2010, 2015).

During aerobic physical activity the pulse rises as well as the cardiac output, blood pressure and the body temperature. Furthermore the ventilation multiplies and the vascular resistance of the heart and the muscles decreases while the vascular resistance of the kidneys and the GI-tract increases. In this way the blood is directed to where it is needed, namely in the working tissues. During the workout lactic acid is formed and the secretion of hormones such as adrenaline, growth hormone and cortisol increases. After the workout the changed parameters goes back to normal but the glucose uptake remains at a higher level during 24-48 hours (Henriksson & Sundberg, 2010, 2015).

The performance of the body is dependent on many different factors such as gender, age, body size, genetics and of course how well trained the body is. The heart is usually considered the limiting factor during the first 5-15 minutes of maximum physical activity, it is limiting the maximum oxygen capacity. The longer the workout goes on the performance is limited by properties of the engaged skeletal muscle such as numbers of mitochondria, buffer capacity etc. During long term endurance activity the muscles storage of glycogen comprise an important limitation (Henriksson & Sundberg, 2010, 2015).

4.4 Long term effects of regular physical activity

As mentioned earlier regular physical activity has many effects on the human body in the long term perspective. During a single workout the skeletal muscles, the heart and the blood vessels are affected just to mention a few tissues. The immediate effects goes back to normal sometime after the workout is finished, but during repeated and regular physical activity processes start that changes, adapts and improves the tissues structure and function. Long

term regular physical activity improves cognition, physical capacity and reduces the risk for a number of diseases and premature death (Henriksson & Sundberg, 2015).

In this thesis, the long term effects of physical activity on some of the tissues will just be mentioned and the focus will be on the long term effects on the nervous system and the hormone system due to the supposed connection to depression. However the long term effects on the skeletal muscles and the heart will also be investigated.

4.5 Long term effects on the skeletal muscles

The skeletal muscles are very adaptable to training. Endurance training highly affects the function and the structure of the muscles, but the size is only affected a little bit whereas strength training can change the size a lot. The reason for this is the different kinds of muscle fibers. The so called slow-twitch fibers (type I) active during endurance training can only be somewhat larger while the fast-twitch type II-fibers active during strength training has more potential to grow. Type II-fibers can be divided into type IIa and IIx. Type IIa-fibers are also known as fast twitch oxidative muscle fibers which are oxygen-dependent and type IIx-fibers as fast twitch glycolytic which are not. Type I-fibers are characterized by low force and high endurance while type IIx are characterized by high force and low endurance. Type IIa are something in between type I and type IIx with high force and somewhat higher endurance than type IIx. During endurance training the proportion of type IIx decreases while the proportion of type IIa increases after one week (Sand et al, 2014).

Furthermore the number of mitochondria increases, the blood flow to the muscles improves and the glucose transporters in the skeletal muscle cells increases which improves the glucose uptake. Also the nutrients deposit in the muscle cells grows with increased storage of glycogen and fatty acids. After just a few weeks of training the carbohydrates are saved and fat is used to a greater extent to provide energy during a sub-maximal load level (Henriksson & Sundberg 2010, 2015).

4.6 Long term effects on the heart

Regular endurance training leads to an increase in the size of the left chamber of the heart and also of the wall thickness. The first change is concentric hypertrophy it means enlargement of the muscle mass around the chamber without an enlargement of the volume, thereafter also

the volume increases, so called excentric hypertrophy. When it comes to the right chamber it seems like the muscle mass and the volume increases in parallel. This improves the hearts stroke volume. The maximum heart rate frequency is lowered with some strokes per minute, therefor the increased heart minute volume is explained solely by the increased stroke volume (Henriksson & Sundberg, 2010, 2015).

4.7 Other long term effects

Other long term effects of regular physical activity on the human body includes decreased blood pressure, improved blood flow distribution, improved blood pressure regulation and other positive effects on the blood vessels. Furthermore, regular physical activity has positive effects on the composition of lipoproteins, on blood coagulation factors and platelet characteristics. In addition, the immune system is improved. Regular activity also affects the skeleton, the cartilages and the connective tissue in a positive way by building it stronger. Lungs are also affected by improved gas exchange as an example. Positive effects are also seen on the body composition with reduced adipose tissue and thereby reduced health risks connected to a large amount of adipose tissue. The decrease in fat weight is larger than the decrease in body weight and the body weight might not change at all due to increased muscle mass. Regular exercise also affects the GI-tract with higher gastric emptying rate and reduced risk of the formation of gall stone. Furthermore a well-trained person has better heat tolerance due to improved sweating function (Henriksson & Sundberg, 2010, 2015).

4.8 Important effects of physical activity regarding health

As mentioned above regular physical activity affects a large number of mechanisms in different tissues in the human body, which leads to positive effects regarding the health. Approximately half of the risk reduction in cardiovascular diseases connected to regular aerobic physical activity can be explained by impact of reduction of known risk factors such as reduced low grade inflammation (usually measured as the serum concentration of C-reactive protein (CRP)), reduced blood coagulation, blood pressure, lipids and body mass index (BMI). The reduced risk is also strongly linked to the increased sensitivity to insulin. Almost half of the risk reduction connected to regular physical activity and higher maximum

oxygen uptake cannot be explained by those factors but have to be explained by other today unknown factors (Henriksson & Sundberg, 2015).

4.9 Effects on the nervous system

The immediate effects of physical activity on the brain and the nervous system are among others increased blood flow, activity and metabolism in the areas of the brain that take care of motoractivity. However in the brain as a total there is no significant difference in these parameters. The concentration of glucose increases interstitially in the central nervous system and this is independent of the blood sugar concentration. During intense work out the brain uses lactate besides glucose as an energy substrate. Furthermore the release of a number of neurotransmitters in different parts of the brain are affected during physical activity, such as dopamine, serotonine and glutamate, some of which also play an important role during depression (Henriksson & Sundberg, 2010, 2015).

Regular physical activity affects several functions in the nervous system. Brain functions directly connected to the physical activity are improved, like coordination, reaction ability and balance. This improves the function ability which can contribute to the increased well-being that is connected to regular physical activity. Furthermore the cognitive ability is retained better, especially memory, planning and coordination of tasks. Moreover the sleeping quality is improved (Henriksson & Sundberg, 2010, 2015).

Animal tests have shown that growth factors with importance in the central nervous system are affected by physical activity. The hippocampus in the brain is also affected by physical activity with an increased number of growth factors, for example the occurrence of the growthfactor IGF-1 increases. Also the occurrence of noradrenaline in the brain increases. The hippocampus is important to memory formation. There are also studies that show that the formation of brain cells in animals who are allowed to run are increased with increased ability to learn for these animals. Other studies have showed that the formation of new vessels are increased in the cerebral cortex after regular physical activity. This can be significant to the supply of nutrients to this part of the brain (Henriksson & Sundberg, 2010, 2015).

4.10 Effects on the hormone systems

During a workout several hormone systems are activated and the plasma concentration of several hormones increases, such as adrenaline/noradrenaline, adrenocorticotrophic hormone (ACTH), cortisol, beta endorphin, growth hormone, renin, testosterone, thyroid hormone and several gastrointestinal hormones. The levels of insulin are decreased during the workout and the drop could be large while the levels of glucagon in arterial blood only are affected in a small degree. The levels of the catcholeamines adrenaline and noradrenaline are increased to a large degree and increases exponentially with increased workload. The most important cause to the rise in noradrenalin in plasma during physical activity is the activation of the sympathetic nerves. The increase in noradrenaline starts at a lower workload than the increase of adrenaline and the level of noradrenaline also increases more sharply when the workload and intensity increases. Furthermore the levels of noradrenalin in the blood often are increased for several hours after the end of the workout while the levels of adrenaline only are increased for a few minutes. During strenuous or prolonged exercise, these hormones can increase 10-20 times. During prolonged exercise the levels of beta endorphins increases, this could be of significance to well-being and blood pressure reduction in connection with workout (Henriksson & Sundberg, 2010, 2015).

The long-term effects of regular physical activity on the hormone systems are several. Decreased hormone responses at a given workload are observed among well-trained compared to untrained individuals. This applies to the increases in noradrenaline, adrenaline, growth hormone, ACTH and glucagon but also to the reduction in insulin. The most notable change is reduced hormone activation connected to the sympathetic nervous system. This change occurs already during the first two weeks of regular physical activity. It is unknown why it is like this and the activation of stress hormones connected to other stress stimuli is not reduced among people that work out regularly. Furthermore, well-trained people has an adrenal medulla with increased capacity to excrete adrenaline, a so called sports adrenal medulla. Moreover regular physical activity leads to lower insulin concentration in plasma, both basally and after sugar intake. The reason for this is reduced release of insulin from the islet of Langerhans in the pancreas but also an increased sensitivity to insulin in different tissues (Henriksson & Sundberg, 2010, 2015).

The hypothalamus-pituitary-adrenal (HPA) system, which is a system that is a messenger for different stress responses in the body, is affected by regular endurance training. The daily rhythm is shifted in a way that the morning peak comes earlier. Furthermore, the pituitary gland´s control hormone ACTH is increased. Even though increased ACTH can be seen as a stress state in the body the effector hormone in the HPA-axis, cortisol, is not changed in the resting state as a result of regular endurance training. This can be explained by that cortisol provides less effective feedback inhibition of the pituitary and possibly of the hypothalamus in well-trained bodies. This in turn leads to the increase in ACTH. The rise in ACTH can be one of several explanations to the disturbances seen in female athletes menstruations cycles and possible disturbances in male athletes reproductive system that may also exist, the later which is rarely discussed (Henriksson & Sundberg, 2010, 2015).

5 Physical activity and depression

5.1 Depression

In the daily life the word depression might be used just to describe a bad mood while a clinical depression is a psychiatric diagnosis and not just a bad mood. A variation of the mood is a normal part of the life but when the mood is depressed during a longer time (two weeks or more) and affects the sleeping, the appetite, joy of life, self-esteem and the possibility to work or study it is called a major depressive disorder (MDD). The diagnosis is decided by reported and observed symptoms (Martinsen et al, 2016). The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-V) has the following definition of a major depressive disorder:

"Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

Note: Do not include symptoms that are clearly attributable to another medical condition.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (Note: In children and adolescents, can be irritable mood.)

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (Note: In children, consider failure to make expected weight gain.)

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day.

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide."

Moreover the severity of the depression can be classified as mild (five or more symptoms with minor functional impairment), moderate (symptoms and functional impairment are between 'mild' and 'severe') and severe (most symptoms present and interfere with functioning, with or without psychotic symptoms) (Cooney et al, 2013). MADRS (Montgomery-Åsberg depression rating-scale) is used to rate and to follow up the depression, as well as BDI (Beck depression inventory) (Andersson et al, 2015).

Depression is common and is individually the most important reason to lost healthy years of life in the industrialized world. The diagnosis major depressive disorder is more than double as usual for women compared to men. In Sweden and Norway it is estimated that around 20% of the inhabitants are affected by depression sometime during their life, and at a certain point of time 4-10% of the grown up population in these countries fulfills the criteria for depression (Martinsen et al, 2016).

There is no easy explanation to why some people get depressed and some people do not. Negative stress factors increases the risk for depression but the vulnerability among individuals varies. Risk factors that can increase the vulnerability and the risk for depression includes separations, early psychological traumas, violations, fatigue and somatic diseases. A genetic disposition exists to a certain degree. Losses of different kinds as well as relation problems and diseases are usual trigger factors (Martinsen et al, 2016).

The pathophysiological factors behind depression is unclear. Sometime you can see a pathological raised activity in the HPA-axis during long-term depression. A normalization is seen at the end of the depression. Because antidepressant drugs improves the function of transmitter substances such as serotonin, noradrenaline and dopamine, one theory is that depression can be caused by disturbances in those systems. During depression a smaller

volume of hippocampus is seen where cortisol is believed to play an important role through decreased formation of new nerve cells (Martinsen et al, 2016).

Depression has a connection to low levels of the neuroprotective hormone brain derived neurotropic factor (BDNF). The hormone contributes probably to increased survival of nerve cells, increased growth and differentiation of new nerve cells and synapses, especially in the hippocampus, and is believed to reduce depression. Physical activity causes raised levels of BDNF in individuals with depression and anxiety (Martinsen et al, 2016).

5.1.1 Treatment of depression

Depression is usually treated with different forms of psychological therapy often in combination with pharmacological treatment with antidepressant drugs. Cognitive behavioral therapy (CBT) and Interpersonal therapy (IPT) have documented effect as well as modern antidepressant drugs (SSRI) (Martinsen et al, 2016). During mild forms of depression antidepressant drugs have limited effect and the effect is stronger in moderate and severe forms of depression. During severe forms of depression, especially depressions with psychotic symptoms antidepressant drugs are used in combination with antipsychotic drugs and in some cases in combination with electro chock therapy (ECT) (Martinsen et al, 2016). Light-therapy during winter-depression is widely used in Sweden and Norway but there are different opinions about the scientific evidence behind the treatment (Martinsen et al, 2016). There are also other alternative treatment options for depression such as acupuncture, family therapy, marital therapy and relaxation. Exercise is also considered to be an alternative treatment option of depression. The interest for alternative treatment options of depression is increasing (Cooney et al, 2013). Already today physical exercise is recommended during depression (Martinsen et al, 2016).

5.2 Research on physical activity and depression

5.2.1 Epidemiology

To begin with, a recent review article has studied how much depressed people engage in physical activity compared to healthy controls. The meta-analysis shows that adults with major depressive disorder (MDD) engage significant less time in physical activity and

significant more time in sedentary behavior. The definition of sedentary behavior is an energy expenditure <= 1.5 metabolic equivalents of task (METs). According to the article the relationship between physical activity and depression seems to be bidirectional. Depressed people are typically less active, whilst lower levels of physical activity increase the risk of depression. The article also mentions that sedentary behavior is independently associated with elevated levels of c-reactive protein (CRP) and metabolic syndrome and is directly related to short-term all-cause and cardio-metabolic disease related mortality. TV-viewing time is an important factor that has been associated with all-cause mortality including suicide. The article therefore concludes that seeking strategies to decrease sedentary behavior including TV-viewing time is required to reduce the elevated rates of cardio-metabolic disorders in the depressed population (Schuch et al, 2017). Even if it seems to be a relatively clear association between physical activity and depression this does not necessarily imply causality (Cooney et al, 2013).

5.2.2 Intervention studies

"Exercise for depression"

In the Cochrane review "Exercise for depression" (Cooney et al, 2013) the objective was to determine the effectiveness of exercise compared with no treatment for depression in adults and to determine the effectiveness of exercise compared to other interventions. Exercise is in the review defined according to the American college of sports medicine (ACSM) as "planned, structured and repetitive bodily movement done to improve or maintain one or more components of physical fitness". The review is an update of an earlier review first published in 2009. Searches for randomized controlled trials until 13 of July 2012 were made in databases. In the last review from 2009 also unpublished studies were found through contact with experts including authors of all included published studies. A new search for unpublished studies was not performed.

Furthermore, adult men and women in any setting (including inpatients) were included. Studies investigating post-partum depressions were excluded as well as studies that investigated the effect of exercise on anxiety, neurotic disorders and dysthymia. In total 39 trials fulfilled the inclusion criteria of which 37 provided data for meta-analyses. 33 trials provided aerobic exercise, of which 16 trials provided running. Two trials provided mixed

exercise i.e. endurance, muscle strengthening and stretching. The duration of the intervention ranged from 10 days to 16 weeks. Different depression measurement scales were used in the different trials. Beck Depression Inventory (BDI) scores were used in 12 studies and Hamilton Rating Scale for Depression (HAMD) scores were used for 13. A variety of other scales were also used.

Different kind of exercises was compared to different types of controls in the different studies. The analysis comparing exercise to a 'control' intervention including no intervention showed the following result:

- A moderate clinical effect in favour of exercise was found.
- Methodologically robust trials only show a smaller effect in favour of exercise.
- Eight trials found only a small effect in favour of exercise in long-term follow up data.

When exercise was compared to another form of active treatment where the aim was to improve mood the following results were seen:

- Exercise seems to be as effective as psychological treatments. This is however based on a few small trials.
- Exercise seems to be as effective as pharmacological treatments. Based on four trials.
- One trial found that exercise was superior to bright light therapy in reducing depression symptoms.

Subgroup analyses were also performed regarding type of exercise, intensity of exercise, duration and frequency of exercise, type of diagnosis and type of control. A large effect of exercise on depression was seen when exercise was compared to education and occupational therapy. There was no different in effect when exercise was compared with stretching, meditation or relaxation.

Regarding type of exercise aerobic exercise showed moderate clinical effect while mixed and strength exercise indicated larger effect but with wider confidence intervals. Regarding intensity moderate/vigorous showed the smallest effect size while vigorous and light/moderate showed the largest effect size. Regarding number of sessions fewer than 13

sessions showed a moderate effect while 25-36 sessions showed a large effect size, however more than 36 sessions only showed a moderate effect. The review only mentions the number of exercise sessions that gives the largest effect size on depression without mentioning the time-interval (during weeks or months).

Regarding attendance rates for exercise as an intervention there was some variation between studies which suggests that there might be factors that influence acceptability of exercise among participants according to the authors.

The authors have the following conclusion:

"Exercise is moderately more effective than a control intervention for reducing symptoms of depression, but analysis of methodologically robust trials only shows a smaller effect in favour of exercise. When compared to psychological or pharmacological therapies, exercise appears to be no more effective, though this conclusion is based on a few small trials".

"Exercise as a treatment for depression: A meta-analysis adjusting for publication bias"

Another updated systematic review and meta-analysis (Schuch et al, 2016) was published in the Journal of Psychiatric Research in 2016. The reason for this meta-analysis was to investigate one of the conclusions in the Cochrane-review, namely that studies with better methodological quality showed a smaller effect size of exercise on depression. The reason was also to investigate the wide range of effect sizes that earlier meta-analyses show, that might be influenced by both inclusion criteria and heterogeneity. 25 studies were included with in total 1487 adults with depression, of whom 757 and 730 were randomized to exercise and control conditions respectively.

The results from the meta-analysis show that physical activity has a large antidepressant effect when compared to non-active control conditions and can be used as a treatment of depression. It would require more than 1000 negative studies to nullify this result. The anti-depressant effect was higher for studies that included participants with major depressive disorder (MDD). Furthermore larger effect size was found for outpatients, in samples without other clinical co-morbidities. Aerobic as well as mixed exercise was associated with large effects across all studies. However in clinical samples only aerobic exercises had large and significant effects on depression, while mixed interventions had non-significant effects.

Supervised interventions had the largest effects. In opposite to the Cochrane-review this meta-analysis found out that trials with better study-design showed a larger effect size of exercise on depression. The effect size calculated confirms and strengthens the case that exercise is an evidence-based treatment for depression according to the authors of this review article.

The authors write the following in the abstract: "Our data strongly support the claim that exercise is an evidence-based treatment for depression".

"Exercise as a treatment for depression: A meta-analysis"

One earlier systematic review (Krogh et al, 2011) only includes studies where the participants had a clinical diagnosis of depression. In this review no benefit of exercise was found. With this in mind the authors of the review article "Exercise as a treatment for depression: A meta-analysis" in the Journal of Affective Disorders conducted a new meta-analysis (Kvam et al, 2016) where only studies on participants with a diagnosis of unipolar depression were included. According to the authors a new meta-analysis was needed.

The authors searched for articles published until November 2014. The effect size was computed with random effects models. The meta-analysis included a total of 23 randomized controlled trials (RCT) and in total 977 participants. The results showed that physical activity had a moderate to large effect on depression compared to control conditions. However at follow-up the effect was small and not significant. Compared to no intervention physical activity yielded a large and significant effect size and a moderate and significant effect when compared to usual care. There was no significant difference in the effect size when physical activity was compared to psychological treatments or antidepressant medication. Physical activity as an adjunct to antidepressants showed a moderate effect that trended toward significance. The authors concluded that physical activity is an effective intervention for depression.

6 Discussion

6.1 Summary of the results

6.1.1 Physical activity and the human body

Regarding physical activity and the human body research shows that there are several positive health effects including the hearth/vascular-system, the muscle/skeleton-system, the nervous system and the hormone systems. Physical activity improves cognition, mood and physical capacity and reduces the risk for a number of diseases and premature death (Henriksson & Sundberg, 2015).

6.1.2 Physical activity and depression

After studying the latest meta-analyses and review-articles in the field regarding physical activity and depression in adults it seems to be relatively clear that there is a connection between depression and physical activity. Intervention studies show that regular physical activity seems to have an anti-depressant effect. The effect size may be in the same range as psychological therapy or pharmacological treatment.

Furthermore the effect size of physical activity on depression seems to be in the same range as other treatment options for depression like mind-body activities such as yoga, qi-gong and tai chi.

When it comes to follow up after ended physical activity treatment of depression two of the meta-analyses studied in this thesis seem to agree that the anti-depressant effect is small. It seems like the anti-depressant effect of physical activity fades away when it is not performed regularly anymore.

The effect size tends to be largest for major depressive disorder and for outpatients without comorbidities. Furthermore supervised interventions seem to have larger effect than unsupervised, for example unsupervised physical activity on prescription schemes.

One of the latest meta-analysis (Kvam et al, 2016) in the field shows that also in a clinical setting there is a significant effect of physical activity.

Regarding what kind of physical activity (aerobic, strength or mixed) that has the largest effect size on depression the meta-analyses do not give a common answer. One favors strength and mixed exercise (Cooney et al, 2013) while another one favors aerobic exercise (Schuch et al, 2016). However both meta-analyses see an anti-depressant effect of aerobic exercise. Aerobic exercise is also the most common kind of intervention in the studies and has the largest sample size by far.

6.2 Methodological discussion

Even if regular physical activity seems to have a moderate effect on depression there are a lot of questions that remains and a lot of things to be discussed. One obvious thing that makes it more difficult to evaluate the effects of physical activity compared to for example pharmacological treatment is that it is not possible to double-blind a study regarding physical activity, the patient knows that he/she is performing the physical activity. Another big problem regarding meta-analyses is that the different research projects differ substantially regarding type, and duration of intervention as well as important differences in control groups.

Exclusion and inclusion of studies in meta-analyses is another important subject to discuss. Meta-analyses are not as objective as they may seem to be. The authors of the systematic review articles decide which criteria that should be used when choosing which studies to include and to exclude. In this way the authors can decide the criteria that include the articles that give them the result they want to show. In for example the Cochrane review (Cooney et al, 2013) also unpublished studies were included due to the fact that studies with positive results have higher possibility to be published, according to the authors. However unpublished studies may not have the same quality as the published one.

Another important issue to discuss is the fact that many patients with depression have other diseases as well, so called co-morbidities. These diseases can be both somatic and psychiatric and can make it problematic to attend in physical activity. Also the results indicate the largest effect of physical activity on depression on patients without co-morbidities. However patients with depression often have other psychiatric diseases in addition.

6.3 Discussion of the results

The thesis has described the most important effects of physical activity on the human body.

Intervention studies show that physical activity seems to have a positive effect in reducing depression symptoms. The question remains whether this effect is a result of the described physiological and neurobiological alterations. Physical activity may change endorphin and monoamine levels and may also reduce the levels of the stress hormone cortisol, all of these factors may improve mood. Exercise also stimulates the growth of new nerve cells and releases proteins known to improve health and survival of nerve cells namely brain-derived neurotrophic factor (BDNF) (Martinsen et al, 2016 & Cooney et al, 2013).

The immediate physiological effects of physical activity regarding the mood are more known than the long term effects. As presented in the thesis one single workout can have measurable effects on mood that can be physiological explained by for example increased levels of beta-endorphins. It is however more difficult to explain the long term physiological effects of physical activity on depression but as an example BDNF is believed to play an important role.

There are also plausible reasons why physical activity may improve the mood other than through physiology. One reason is that exercise might work as a diversion from negative thoughts and another reason is that the mastery of a new skill may increase the self-esteem. Low self-esteem is considered to be closely related to mental illness (Cooney et al, 2013). During exercise that involves social contact the social contact may contribute and be a part of the mechanism (Cooney et al, 2013). Other factors may influence the results such as the attention you get from the leader during supervised physical activity and the feeling of belonging to a group when you perform physical activity together with other persons.

However it is possible to take these factors into account for example if you compare a group performing physical activity with a group performing stretching. In the Cochrane review (Cooney et al, 2013) there was no different in effect of exercise when it was compared with stretching, meditation or relaxation, but this comparison included few studies. However according to Schuch et al (2016) techniques like meditation/mind-fullness and self-awareness are known to have an influence on depressive symptoms. This might indicate that the effect of physical activity on depression is partly explained by a systematic, empathic attempt to help suffering patients.

6.4 How to implement the results?

Even if the thesis has shown an effect of physical activity on depression one important question remains and that is how to implement the results. It might be difficult to motivate the depressed patient to attend in physical activity, and even undepressed people may have an aversion against physical activity. Hence systematic physical activity might be an alternative only for some patients. However there is a wide range of different kinds of physical activities and it should be possible to find one that suits the patient. For other patients other treatment options might be better alternatives, like mind-body activities such as meditation.

Motivation is important, but too much pressure might be counterproductive. Lacking ability to participate in systematic physical activity might be another burden for a depressed person.

7 Conclusions

- Physical activity has several positive health effects on the human body.
- Although research on the effect of physical activity on depression is complicated, the present state of evidence indicate that systematic physical activity has a positive effect on depressed people comparable with other established treatment alternatives.
- The effect-size is insecure and depends on several factors such as individual differences and type of physical activity.
- The reasons behind the positive effect in reducing depression symptoms are not fully understood and include probably many different factors including physiological and neurobiological mechanisms. The effect might also partly be explained by a systematic, empathic attempt to help suffering patients.
- Systematic physical activity is a cheap intervention alternative with few side effects. It is recommended as a means to increase the public health in general. This thesis has shown that regular physical activity also has a role in the treatment of depressed patients.

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