Study protocol

A randomised multicentre study comparing moderate-to-vigorous group aerobic exercise vs. group leisure activities for mild to moderate depression in adolescents

Long title of the trial:	A randomised multicentre study comparing moderate-to-vigorous group aerobic exercise vs. group leisure activities for mild to moderate depression in adolescents
Short title of the trial:	Aerobic versus leisure group for adolescents with depression
Date of protocol:	2025-03-16
Study protocol version:	2.0
Trial registration number:	ClinicalTrials.gov NCT05076214
Sites:	Child and adolescent psychiatric clinics ongoing in 1) Halmstad, 2) Varberg 3) Stockholm-Handen, 4) Stockholm-Järva Closed sites 5) Malmö 6) Kungsbacka
Principal investigator:	Håkan Jarbin

This version of the study protocol includes revisions to participating sites, clarifies statistical analyses, clarifies the first exclusion criteria, descirbes an additional ethical approval due to changes during the trial, and has been refined for improved clarity and coherence in the writing.

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1 Trial personnel

Principal Investigator (PI):	Håkan Jarbin, MD PhD Child and adolescent psychiatric clinic, Region Halland, Halmstad, Sweden Lund University, Faculty of Medicine, Department of Clinical Sciences Lund, Sweden. hakan.jarbin@regionhalland.se
Study coordinator:	Henriette Nielsen, assistant nurse Child and adolescent psychiatric clinic, Region Halland, Halmstad, Sweden
Site investigators	Halmstad: Håkan Jarbin, MD PhD Stockholm Handen and Järva: Åsa Mårsell, MD Varberg: Kristina Ingemarsson, MD Malmö: Olof Rask, MD PhD
Site coordinators	Halmstad: Henriette Nielsen, assistant nurse Stockholm Handen: Åsa Söderström, nurse Stockholm Järva: Sara Karlsson, social worker Varberg: Jessica Axheden, social worker Malmö: Alf Oredsson, assistant nurse Kungsbacka: Janina Olofsson, nurse
Senior advisor:	Eva Serlachius, professor, MD Professor, Department of Clinical Neuroscience, Lund University, Lund, Sweden.
Senior advisor:	Carl-Johan Sundberg, professor, MD Department of Physiology and Pharmacology Karolinska Institutet, Stockholm, Sweden
Senior advisor:	Maria Lalouni, psychologist post doctoral researcher Department of Clinical Neuroscience Karolinska Institutet, Stockholm, Sweden
Senior advisor:	Emma Haglund, PhD, associate professor Rydberg Laboratory for Applied Sciences, Halmstad University, Halmstad, Sweden Spenshult Research and Development Centre, Halmstad, Sweden
Senior advisor:	Charlotte Olsson, PhD, associate professor Center for Research on Welfare, Health and Sport (CVHI) Halmstad University, Halmstad, Sweden

Senior advisor:	Ingrid Larsson, RN, PhD, professor School of Health and Welfare, Department of Health and Nursing, Halmstad University, Halmstad, Sweden Spenshult Research and Development Centre, Halmstad, Sweden
Senior advisor:	Filipa Sampaio, researcher/health economist, PhD Department of Public Health and Caring Sciences Uppsala University, Uppsala, Sweden
Senior advisor:	Jessica Norrbom, PhD Department of Physiology and Pharmacology Karolinska Institutet, Stockholm, Sweden
Senior advisor:	Andreas Ivarsson, PhD, professor School of Health and Welfare, Department of Health and Sport, Halmstad University, Halmstad, Sweden Department of Sport Science and Physical Education, University of Agder, Kristiansand, Norway
Co-investigator:	Rebecca Mortazavi, MD, doctoral student Child and adolescent psychiatric clinic, Halmstad, Sweden
Co-investigator:	Tina Cronqvist, MD PhD Psychiatric clinic, Region Halland, Halmstad, Sweden
Co-investigator:	Rebecca Grudin, psychologist doctoral student Centre for Psychiatry Research, Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

2 Summary

Title:	A randomised multicentre study comparing moderate-to-vigorous group aerobic exercise vs. group leisure activities for mild to moderate depression in adolescents
Short title:	Aerobic group exercise for adolescents with depression
Objectives:	The aim is to evaluate aerobic group exercise versus leisure group activities in adolescents with mild to moderate depression. Primary outcome is Children's Depression Rating Scale – Revised (CDRS-R). Secondary outcomes are Clinical Global Impressions – Severity and Improvement scales (CGI), self-reported Quick Inventory of Depression Symptomatology (QIDS-A_{17}-SR), the self-reported Outcome Rating Scale (ORS), clinician rated Children Global Assessment Scale (C-GAS), aerobic capacity (VO_2max), muscular strength, body composition, Body Mass Index (BMI), presence or activity of selected biological markers of neuroprotection and neuroinflammation in blood samples

	and a cost evaluation rated by parents with Tic-P. Further objectives are to explore adolescents', parents' and coaches' experiences of the intervention as well as how the adolescents' health and lifestyle are influenced. A validation of QIDS- A_{17}-C and QIDS- A_{17}-SR versus CDRS-R will also be performed.
Type of trial:	Single-blind randomised controlled multicentre study
Trial design and methods:	Clinically referred adolescents with depression will be randomised to aerobic group exercise or leisure group activities for three times a week for 12 weeks. Participants will be assessed at baseline, 13 weeks post-randomisation, 26 weeks post-randomisation and at a one-year open follow-up.
Rationale for study:	There is increasing evidence for aerobic exercise as an intervention for depression in adolescents. However, studies have rarely included patients from clinical settings, lack an active control group and long-term outcome is not reported.
Participant time in trial:	Approximately 1 year (follow-up included).
Total trial duration:	The trial was extended to 4 years due to a slower inclusion rate than expected.
Planned trial sites:	Child and adolescent psychiatry clinics in Halmstad, Stockholm Handen, Kungsbacka, Malmö, Stockholm Järva and Varberg, Sweden.
Sample:	122 patients will be allocated to one of the two treatment arms at a ratio of 1:1. Patients allocated to group leisure activities will after 26 weeks get the opportunity to participate in an exercise group and their data at one year will be collected. Power was estimated based on data from a pilot RCT.
Brief eligibility criteria:	Eligible patients will be aged 13-17 years and diagnosed with a DSM-5 mild to moderate major depressive episode. Exclusion criteria are meeting criteria for an eating disorder, having high risk of suicide, intellectual disability, physical activity above recommended level, antidepressant medication adjusted within four weeks, chronic somatic illness precluding exercise, need of interpreter and social circumstances interfering with a regular exercise schedule. Full details are presented in section 5.5.
Statistical analyses:	Following an intention-to-treat (ITT) approach, data analysis will be conducted using linear mixed models (LMM) to analyze CDRS-R scores at the primary 13-week post-randomisation outcome. The model will adjust for baseline CDRS-R scores and include treatment group as a fixed effect, with a random intercept for each participant to account for individual variability. A two-sided 95% confidence interval will be used to assess the treatment effect, with statistical significance determined if the confidence interval does not include zero. Sensitivity analyses will include mutiple imputation and complete cases, as well as per protocol analyses. Secondary outcomes will be analysed using LMMs and ordinal mixed-effects models.

3. Introduction

Depression is characterised by behavioural, cognitive and physical symptoms such as feeling of sadness, hopelessness and irritability during at least a two week period (1). It is common in adolescence where 5-11% is affected (2, 3) and the prevalence is increasing, especially for girls (4, 5). Depression is a major cause of disability in adolescents worldwide (6, 7) and contributes to lower educational achievements (8), increased risks of substance abuse and suicide (9). Further, depression in adolescents is a moderate risk factor for cardiovascular disease, a risk that is mediated through inflammation, oxidative stress and autonomic nervous system dysfunction, generating high blood pressure, blood glucose and lipids (10). Sedentary behaviour is linked to depression in adolescents and increases risk for cardiovascular disease. Physical activity lowers cardiovascular risk by reducing body weight and improving blood pressure (10).

Brief psychosocial intervention (BPI) is recommended by the Swedish national board of health and welfare as the first hand treatment for depression in adolescence (11). BPI involves psychoeducation, family based and school support and activation with focus on depression (12, 13). The effect of evidence-based treatments with antidepressants or psychotherapy such as cognitive behavioural therapy (CBT) or interpersonal therapy (IPT) are modest (14). Selective serotonin uptake inhibitors (SSRIs) have shown effect on depression in children and adolescents, but the effect is often insufficient (15). Treatment resistance is common and data on augmentation or alternative treatments are very scarce (16).

The European Psychiatric Association guidance states that adults with depression can benefit from 2.5 hours per week of moderate to vigorous aerobic exercise (17). The effect is roughly equal to the effect of antidepressants or psychotherapy (17). A meta-analysis on exercise for youths aged 13-17 with depression showed an effect similar to the effect of SSRIs and psychotherapy (18, 19). Thus, aerobic exercise could be established as a treatment for depression in adolescents, but studies are heterogeneous and often of low quality (18, 20-23). Available randomised control trials (RCTs) are characterized by diverse selection of participants, few particpants with comorbidities, diverse training intensity, and diverse outcome measures and follow-up periods (24-28). Study populations have consisted of high school students screened for depression (28) or adolescents recruited from general practitioners, child and adolescent health services and school nurses (25) or partly recruited from advertisement (26). There is a lack of studies evaluating the effect of exercise in a clinical psychiatric sample of adolescents with depression. In an open study, we evaluated aerobic exercise in a representative sample of clinically referred adolescents with persistent major depression and significant comorbidity. We found good adherence to the vigorous exercise sessions also in a compromised clinical sample, substantial improvement after the 14-week intervention and further improvement after one year (29).

Comorbidity is the rule in depression and up to half of patients also suffer from two or more comorbidities (30) but comorbidities are often not reported in existing studies (24, 25, 27) or excluded (28), despite from one trial which included 1/3 of patients with comorbid ADHD (26) and one feasibility study including patients with ADHD and anxiety (31).

The exercise frequency varied from two[22] to three (24, 26-28) times a week for a period of six (25, 28) to twelve weeks (26, 31) with an intensity from 50% (25) to more than 70% (26, 27) of maximum heart rate. Outcome measures were self-report scales (24, 25, 31) or clinician interviews (26-28). Long term follow-up varied from none (27, 28) to one month (24), six months (25) or one-year (26) but often with low adherence (25).

One small study used a control group that received stretching in a group setting (26) while other studies had no active control group. The study with controls receiving stretching found reduced depressive symptoms in both the exercise and stretching group, with a more rapid and larger improvement in the exercise group (26). Group activities could be activating and an effective intervention in itself in line with behavioural activation for depression (32, 33). The most recent meta-analysis concluded that serious methodological limitations downgrade the evidence to low. The use of control groups without treatment was believed to exaggerate the effects of exercise and the lack of follow-ups to assess sustainability was another concern (22).

Several biomarkers have been suggested to be of importance for brain health and involved as mediators of the effect of exercise on brain health in humans. These factors include Brain Derived Neurotrophic Factor (BDNF), C-reactive protein (CRP), Interleukin 6 (IL-6), Kynurenic acid (KYNA), Vascular Endothelial Growth Factor (VEGF), Insulin-Like Growth Factors (IGFs) and their associated binding proteins. However, there is shortage of evidence when it comes to the effects of exercise on these biomarkers in the adolescent population (34, 35).

A single cost-effectiveness study found that exercise can be effective for adolescents with depression and also cost-effective according to the Children's Depressive Inventory-2 (CDI-2). Findings were hampered by attrition of more than half of participants for this analysis (36).

The subjective approach with interviews describing how the intervention is perceived have shown acceptability for exercising in adults (37, 38) and in adolescents (18). We found group exercising bringing adolescents joy of living through commitment, empowerment and participation (39). Further, we found—at a one-year follow-up—that facilitators for sustaining exercise to be the companionship in training and achievement of exercise results as getting more fit and less depressed as well as being supported and coached to get to the gym. Barriers were symptoms of fatigue, social anxiety and lack of drive and also lack of social support (40). Another beneficial aspect of the programme was the intervention being experienced as manageable, comprehensible and meaningful. This sense of coherence can further improve the outcome (41). The present qualitative data cannot disentangle the impact of group activity from the addition of aerobic exercise on the positive aspects of group physical activity.

The Children's Depression Rating Scale – Revised (CDRS-R) is the most commonly used outcome measure for research on adolescent depression (42). However, it is not available for routine clinical use. The self- and clinician-rated Quick Inventory of Depressive Symptomatology (QIDS-A_{17}) was developed for clinical use, is in line with the DSM and has versions for self (QIDS-A_{17}-SR), parent (QIDS-A_{17}-PR) and clinician (QIDS-A_{17}-C) ratings. QIDS-A_{17}-SR and QIDS-A_{17}-C were reliable in one convenient sample of child and adolescent psychiatric outpatients, while the QIDS-A_{17}-PR was less reliable. CDRS-R discriminated best at low and extremely high levels of depression, while QIDS-A_{17}-SR was more precise in discriminating at moderate levels of depression (43).

In summary, adolescent major depression is a significant health problem while available treatments have modest and often insufficient efficacy. Aerobic exercise seems to be a feasible and possibly effective option. However, available studies have several methodlogical limiations related to recruitment, inappropriate control groups and absence of follow-up. More data on subjective experiences of aerobic group exercise as an intervention for adolescent depression, efficacy, cost-effectiveness and biomarker aspects are clearly warranted.

4. Objectives

4.1 Primary objective

To evaluate aerobic group exercise versus leisure group activities 13 weeks post-randomisation on clinician rated depression symptoms among adolescents in child and adolescent outpatient care with mild to moderate depressive disorder by measuring changes on Children's Depression Rating Scale- Revised (CDRS-R).

4.2 Secondary objectives

First, we will examine the effects of group exercise versus leisure group activities on clinician rated Clinicial Global Impression – Severity (CGI–S) and Improvement scales (CGI-I) and function with Children Global Assessment Scale (C-GAS), self-rated depressive symptoms (QIDS-A_{17}-SR) and well-being with the Outcome Rating Scale (ORS), aerobic capacity measured by a submaximal aerobic capacity test, muscular strength measured by the isometric mid-thigh pull strength test, a hand grip strength test and muscular endurance by the one-leg sit-to-stand test, and body composition with a bioelectrical impedance analysis and presence or activity of selected biological markers of neuroprotection and neuroinflammation in blood samples.

Second, we will compare the intervention groups at 26 weeks post-randomisation, when the complimentary exercise intervention has not yet been offered to the leisure group, and also to compare them one year after randomisation compared to baseline measures for the entire sample.

Third, we will assess cost-effectiveness using data from the TIC-P questionnaire, trial-based resource use, and CHU9D-derived QALYs.

Fourth we will explore adolescents', parents' and coaches' experiences of the intervention as well as how the adolescents' health and lifestyle are influenced by the intervention through qualitative interviews.

Finally, we will validate the QIDS-A_{17}-C and QIDS-A_{17}-SR against CDRS-R.

5. Project description

5.1 Design

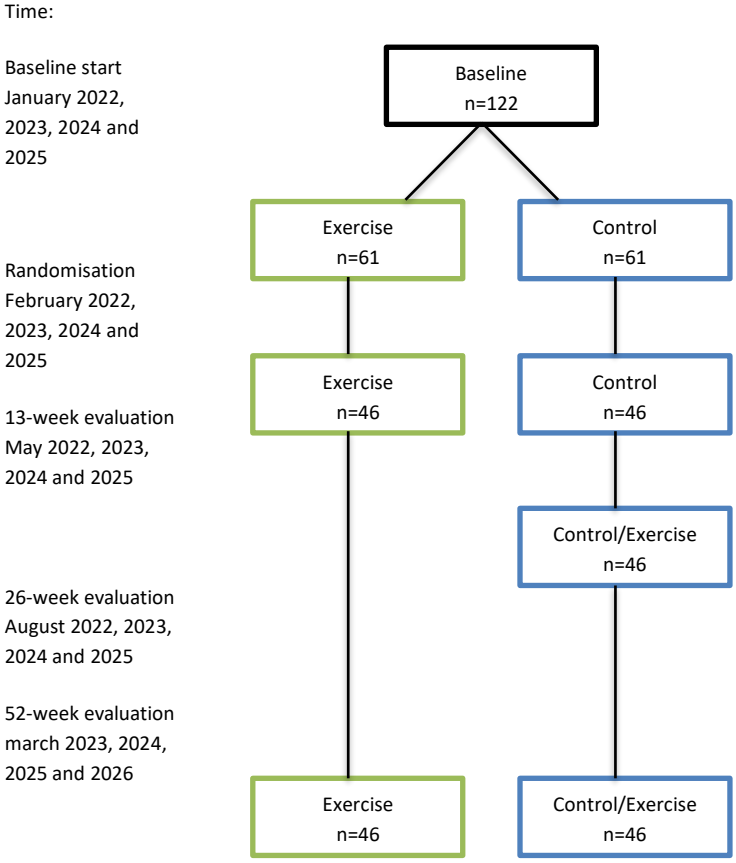
The study will be a multicentre randomised study that will include 122 adolescents who meet crtieria for ongoing mild to moderate depression after three or more visits including brief psychosocial interventions. The protocol is based on the Standard Protocol Items for Randomized Trials (SPIRIT) (44). Participants will be randomised to receive 12 weeks of either aerobic group exercise or leisure group activities at a ratio of 1:1. Previous studies on exercise and depression differ in exercise period from six (25, 28) to 12 weeks (26, 31) and a feasibility study (29) found a substantial improvement in depression symptoms after 14 weeks of aerobic exercise but significant improvement already after 7 weeks. We choose an intervention period of 12 weeks to be reasonably on the safe side. Adolescents allocated to leisure activities will get the opportunity to participate in aerobic exercise after the evaluation at 26 weeks. All patients will be evaluated at a one-year open follow-up.

5.2 Control group justification

By using leisure activities in a group setting with the same leaders and time for sessions as a control group, we control for the possible effect of social interaction, attention and behavioural activation (32).

5.3 Study setting

The study will be conducted at six child and adolescent psychiatric clinics in Sweden. Participants will be recruited from ongoing clinical patients diagnosed with depression. Evaluation appointments for eligibility with a resident psychiatrist will take place at the clinic. Exercise sessions will take place at a gym while leisure activities will be held at the clinics. Aerobic and strength tests will be performed at university facilities. Outcome variables will be assessed by communicating with patients and also with parents on smartphones. Research interviews will be recorded video calls, and self-rated measures will be collected electronically.



5.4 Power analysis

The statistical power calculation for this trial is based on data obtained from a pilot study conducted March through June 2021. For the pilot study, the initial sample size was 20, but due to challenges involving COVID-19 the final sample size was 14 participants. Of the 14 participants, four dropped out due to declining to participate and one was expelled. Two of the four who dropped out were due to COVID-related reasons. A toltal of nine participants completed the RCT phase and the assessments at week 13. Thus, for the sample size estimation, we calculated with a 25% study dropout rate. Hence, we estimate that 9/12 (75%) of included patients will complete the intervention and assessments at 13 weeks post-randomisation. This is also roughly in line with our previous open study (29). On the primary outcome measure (CDRS-R) there was a 7.5-point difference in favour of the exercise intervention with a standard deviation of 12.9-points (data on file). The power calculation, based on β =80% and alpha of 0.05, shows that 92 patients are required. With an expected attrition of 25% from consented participants, we will need to recruit 122 participants to enter the study at baseline.

5.5 Eligibility criteria

5.5.1 Inclusion criteria

- Adolescents aged 13-17 with a DSM-5 mild to moderate depression
- Who have received evaluation and some basic psychosocial interventions for at least 4 weeks (minimum three visits) without response, i.e. not achieved improvement by at least 50% as assessed from clinical records

5.5.2 Exclusion criteria

- Severe depression, i.e. exhibiting all DSM-5 symptoms and severe inability to function at school and with friends due to the depression. Thus, patients fulfilling most or all symptoms of depression but whose functional deterioration is primarily due to other disorders (like social anxiety disorder) are not considered as having severe depression and are thus eligible for the study
- Eating disorder
- High risk for suicide, which would necessitate adjustment of medication or psychotherapeutic interventions
- Intellectual disability
- Substance use disorder
- Actual physical activity the last four weeks meeting the level for sustained health by American College of Sports Medicine, i.e. at least 150 min per week of moderate intensity or 75 min per week of high intensity (45)
- Adjustment of antidepressant medication within the last four weeks or stimulants the last two weeks
- Chronic somatic illness precluding exercise
- In need of interpreter
- Social circumstances interfering with a regular exercise schedule
- Concomitant psychotherapy

5.6 Data collection

QIDS-A_{17}-SR and K-SADS-PL with the adolescent and parent will be conducted at the clinics before baseline. All diagnoses arrived at in the K-SADS-PL will be confirmed with the PI along with inclusion and exclusion criteria on videocall in conjunction with the interview before baseline assessments. CDRS-R, QIDS-A_{17}-C and CGAS at baseline, 13 weeks, 26 weeks (for controls that exercise after the initial 12 weeks) and one-year follow up assessment will be conducted through a recorded video call, using Zoom. In the pilot study, we successfully carried out and recorded video interviews. We chose to conduct the CDRS-R with the adolescent alone, since the raw summary score and T-score can only be obtained from interview with the child (46) and a previous study found good internal consistency for the CDRS-R conducted with adolescents and the total score was highly correlated with global severity from both patient and parent interviews (47). Two researchers (RM and TC) will perform all interviews and the same researcher will perform all interviews for each participant. Data from interviews will be entered into the web-based tool by the research investigator at the time of the interview. Patients will fill out a web-based questionnaire (ESmaker) with QIDS-A_{17}-SR and ORS every two weeks during the 12 weeks intervention period and monthly during the follow-up until one year. The web-based survey tool will send text message reminders at predetermined dates (48). Qualitative individual interviews will be performed with a purposeful sample of the adolescents (n=20), parents (n=20) and coaches (n=8 from each group (intervention/execise and control) evenly distributed across the various sites at 13 weeks, i.e. after the intervention and for adolescents and parents also at one year. The study coordinator will review the completeness of uploaded data every two weeks during interventions and monthly during follow-up. The study coordinator will monitor the completeness of physical tests, blood sample collection (through local monitors) and qualitative interviews (through research interviewers) at indicated points in time.

5.7 Measures

Clinician-rated measures will be entered into the web-based survey and a summary will be inserted in the medical record. The data are stored in Microsoft Excel and later transferred to Statistical Package for the Social

Sciences (SPSS) version 24. The self-report data will not be entered into the medical records but reviewed regarding increased suicidality.

CDRS-R

Children's Depression Rating Scale- Revised (CDRS-R) is the most widely used rating scale for assessing severity of depression and changes in depressive symptoms for clinical research trials in children and adolescents with depression. CDRS-R is a 17-item scale rated by clinical interviews with the child and parent, with items ranging from 1 to 5 or 1 to 7 with a total score of 17 to 113. A score of ≥40 indicates depression. A score of ≤28 is often used to define remission (47). A raw summary score and T-score can only be obtained from interview with the child (46).

K-SADS-PL

Kiddie-Schedule for Affective Disorders and Schizophrenia for School Aged Children – Present and Lifetime Version is a semi-structured diagnostic interview, widely used in research but also in clinical settings (49). The clinician integrates and judges information from patient and parent interviews, preferably held separately. It generates most psychiatric diagnoses (49) and has shown good inter-rater reliability (50) and good to excellent predictive validity (51). A DSM-5 version will be used and interviews will be performed in conjoint sessions albeit sensitive information (i.e. substance use, sexual assault and suicidality) will be gathered separately.

CGI

Clinical Global Impressions provides an overall clinician-determined summary measure of the patient's symptoms and functioning. The CGI consists of two measures; CGI-severity (CGI-S) evaluating severity of psychopathology from 1 to 7 and CGI-improvement (CGI-I) evaluating change from the initiation of treatment from 1 to 7. CGI-S answers the question "How mentally ill is the patient at this time?" based on symptoms, behaviour and functioning during the past 7 days, where 1=normal/not at all ill, 2=borderline mentally ill, 3=mildly ill, 4=moderately ill, 5=markedly ill, 6=severely ill and 7=among the most extremely ill patients. CGI-I answers the question "Compared to the patient's condition at admission to the project, this patient's condition is: 1=very much improved since the initiation of treatment, 2=much improved, 3=minimally improved, 4=no change from baseline, 5=minimally worse, 6=much worse and 7=very much worse since the initiation of treatment" (52).

QIDS-A_{17}

Quick Inventory of Depressive Symptomatology – Adolescent version (QIDS-A_{17}) covers the nine DSM-5 symptoms of depression rated on a scale from 0 (none) to 3 (highest) with a sum-range of 0-27. Mild depression corresponds to 6-10 points, moderate 11-15 points, severe 16-20 points and very severe 21 points and above. There are versions for self-report (QIDS-A_{17}-SR), for parent report (QIDS-A_{17}-PR) and for clinician rating (QIDS-A_{17}-C). Response is defined as a reduction by half of the initial score on QIDS-A_{17}-C. Remission is defined as below 6 points on QIDS-A_{17}-C (43). In this study, the self-report and clinician versions will be used.

Children Global Assessment Scale (C-GAS)

C-GAS is a clinician instrument for assessing psychiatric functioning on a scale from 1 (worst) to 100 (best) among persons aged 4-20 years (53). Outpatients usually score from 40 to 60 while a score of 70 and above is regarded as normal functioning.

The Outcome Rating Scale (ORS)

ORS is a self-reported scale for assessing functioning in four domains covering individual, interpersonal, social

and overall “sense of well-being” aspects (54). The scale provides a numerical value of functioning between 0 (worst) to 100 (best) on a visual analogue scale.

Aerobic capacity measure (VO_2max)

Aerobic capacity (VO_2max) will be measured according to Åstrand with a submaximal aerobic capacity test on an indoor bicycle (55). Aerobic capacity will be presented relative to body weight and expressed as the total amount of oxygen metabolized per minute per kilogram of body weight (mL/kg/min).

Muscular strength

Muscular strength will be measured with three different tests. For general muscle strength, an isometric mid-thigh pull strength test will be used, which is similar to a static sequence of a squat. The test person will be standing on a portable force plate (MuscleLab Force plate and software, Ergotest Innovation As, Stathelle, Norway) with a barbell in a rack placed between the test person's knee and hip in front. The instruction is to pull the bar vertically in an all-out effort (56). The test will measure vertical ground reaction force (Newton), and for the analysis relative values (body weight) will be used.

A hand dynamometer (KERN Sohn GmbH, Balingen, Germany) will measure the maximum grip strength (kg) as another indicator of general body strength (57).

Muscular endurance will be tested in the dominant leg with a 5 and 10 repeats one-leg sit-to-stand test. Seat height will be related to the test person's lower leg length (58). Each test will be performed twice and best performance or fastest time will be used for analysis.

Body Mass Index (BMI)

Body Mass Index (BMI) is an index computed through the formula weight (kg) / (height (m). Age corrected BMI for boys and girls according to the World Health (59) will be presented with z-values adjusted for gender and age.

Body composition

Body composition including body weight and a muscle-fat analysis will be measured with a Bioelectrical impedance analysis (BIA, InBody 770 USA, 2016). The BIA will be performed at least two hours after breakfast with the test person wearing only thin clothes, and with emptied bladder. The method has shown an acceptable validity and reliability (60, 61).

Maximum heart rate (HRmax)

HRmax will be calculated with the formula 220-age (years). In a pilot trial, patients experienced the maximum heart rate test on a stationary bike as dreadful and the test leader judged that most participants were not able to reach the maximum level due to their psychiatric state. For those reasons, the estimated value could be the most accurate and are certainly less painful for the participants.

Biological markers

Blood sampling in 10 ml EDTA and serum tubes will be conducted at about the same time of the day for each participant. Time points for blood draws are before the intervention (at baseline), at 24-72 hours after the last exercise at 13 weeks and at the 1-year follow-up. The samples will be frozen and stored for subsequent analysis.

The presence and activity of biological markers that have been suggested to be important for neuroprotection and neuroinflammation will be analysed. These factors include BDNF, CRP, IL-6, KYNA/3HK75, KYNA/QUIN75, KYN-ACID75, SIL-2 receptor, TNF-alpha, IGF-1 and their associated binding proteins.

Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness – Child version (TiC-P)
TiC-P is used to measure consumption of health care, costs associated with mental illness and production loss among parents due to psychiatric problems in the child concerning the previous four weeks. The TIC-P has been adapted for a child and adolescent population. Parental absence from work due to a sick child was included as well as informal care from parents (62, 63). It will be used for the health economy analysis (64). TiC-P will be administered to parents at baseline, 13 weeks, 26 weeks and at one year.

Child Health Utility 9D (CHU9D)

CHU9D is a generic preference based health related quality of life measure designed specifically for use in an economic evaluation of health care (65). It consists of nine dimensions/items with each item being rated on a five point Likert scale. Responses are converted into utility values ranging from 0, implying dead, to 1, implying perfect health. The Swedish version has shown good reliability and validity in adolescents (66).

Qualitative interview
The *qualitative individual interviews* will be performed by an independent experienced researcher (IL) or trained and supervised research fellows (RM and RG) utilizing a recorded video call facility or a phone call. The head interviewer is an experienced clinical nurse and qualitative researcher (IL) who can respect and give appropriate support during the interview if needed. An open interview guide (see attached file) with initial questions will be used to ensure similar data from all participants. The initial questions refer to the experiences of the exercise intervention and its impact on health and lifestyle from the adolescents', parents' and coaches' perspectives. Follow-up probes will be used to encourage the participants to provide more in-depth information by asking them: "Please tell me more", "How do you mean?" or "What do you have in mind when you say ...?" The interviews will be digitally recorded and transcribed verbatim.

6. Procedure

6.1 Screening and recruitment procedures

We will recruit patients from six child and adolescent psychiatric outpatient care diagnosed with depression and who have had at least three visits and thus most likely have received some basic psychosocial interventions. The patients will be identified through a scanning of the outpatient computer system or identified by staff. The patients will be assessed according to inclusion and exclusion criteria as described above. Eligible patients will be contacted by phone. Information will be offered verbally and in a leaflet. Patients consenting will be invited to a baseline assessment by a resident child and adolescent psychiatrist with K-SADS-PL and QIDS-A_{17}-SR and also inclusion and absence of exclusion criteria established before baseline. The resident will receive training by the PI and discuss each interview with the PI, who determines if criteria for inclusion and not exclusion are met. Previous and ongoing psychotropic medication, self harm and suicide attempts will be elicited.

6.2 Randomisation, enrolment and masking

Participants will be randomised at a ratio of 1:1 to aerobic group exercise or group leisure activities. Randomisation and masking procedures will be conducted in Halmstad but supervised by an independent

senior investigator in Stockholm (ML), not involved in the assessments for the study. Sealed envelopes with randomisation numbers will be stored in a locked cabinet. Randomization will occur among included participants at each site to give equally sized groups if full inclusion is not possible within the set time frame.

The investigators (RW and TC) conducting the baseline, 13-week and 26-week evaluations will be blind to treatment allocation. The outcome measures are identical for the two groups, ensuring that the assessors remain blind. Participants will be reminded at the start of each interview not to reveal their arm of allocation. To measure blinding integrity, the assessor will record whether the participating families inadvertently reveal their group allocation and this piece will be omitted from the recording ahead of coding by the alternate researcher The blinding will be broken after the trial's final participant has finished the evaluation after 26 weeks. At the one-year open follow-up, all patients have had the opportunity to exercise and the evaluation is unblinded.

In case of medical emergency, participants will be encouraged to immediately seek appropriate health care and to inform the local study coordinator, who can follow up the incident in collaboration with PI. This procedure ensures the blinding, since the outcome assessor is not involved.

6.3 Assessments

6.3.0 Rater training

Research investigators (RM and TC) have been trained on CDRS-R by an experienced user of CDRS-R including rating and discussing four recorded videos from interviews on depressed adolescents. QIDS-A_{17}-C, were also rated and discrepancies discussed. Rater training and interrater tests on video-recorded interviews were performed prior to the pilot study for the primary (CDRS-R) and the secondary (QIDS-A) assessment tools arriving at intraclass correlations ranging from 0.90 – 0.98 ($p<0.001$). Refresh interrater sessions will be performed ahead of the baseline evaluations.

6.3.1 Before baseline

- Screening assessment with K-SADS-PL.

6.3.2 Baseline

- Clinician video evaluation: CDRS-R, QIDS-A_{17}-C, CGI and C-GAS
  CDRS-R, QIDS-A_{17}-C and C-GAS will be conducted through a recorded video call, using Zoom by a researcher (RM or TC). The questionnaires will be performed in different order in every other participant. Inter-rater test will be performed between RM, TC and PI on ten CDRS-R, C-GAS and QIDS-A_{17}-C from baseline
- Self-reported web based by ES-maker: QIDS-A_{17}-SR, ORS and CHU9D
- Parent rated and web-based cost evaluation with Tic-P
- Anthropometric measures at site: height, weight, aerobic capacity, muscular strength and body composition
- Blood sampling

6.3.3 Recurrent evaluation

QIDS-A_{17}-SR and ORS will be filled in every other week using a web-based questionnaire.
The first recurrent evaluation, after two weeks of intervention, will include the credibility/expectancy questionnaire (67). We will also include questions on safety issues and possible side effects in line with section 9.3.

6.3.4 13 week evaluation

- Clinician video evaluation: CDRS-R, CGI and C-GAS
- Self-reported web-based by ES-maker: QIDS-A_{17}-SR, ORS and CHU9D
- Parent rated and web-based cost evaluation with Tic-P
- Qualitative interviews with adolescents, parents and coaches according to an interview guide
- Anthropometric measures at site: height, weight, aerobic capacity, muscular strength and body composition
- Blood sampling

6.3.5 26 week evaluation

- Clinician video evaluation: CDRS-R , CGI and C-GAS
- Self-reported web-based by ES-maker: QIDS-A_{17}-SR, ORS and CHU9D
- Parent rated and web-based cost evaluation with Tic-P

6.3.6 One-year open follow up

Patients will be assessed on a one-year follow-up the same month they made their baseline assessment to prevent bias for seasonal variations (68).

- Clinician video evaluation: CDRS-R, CGI and C-GAS
- Self-reported web-based by ES-maker: QIDS-A_{17}-SR, ORS and CHU9D
- Parent rated and web-based cost evaluation with Tic-P
- Qualitative interview with adolescents, parents and coaches according to the interview guide
- Anthropometric measures at site: height, weight, aerobic capacity, muscular strength and body composition
- Blood sampling

6.3.7 Assessment points for each outcome

ASSESSMENT POINTS: OUTCOMES:	**Screening assessment**	**Baseline**	**Every other week during treatment and every month after treatment to one year follow up**	**13 week evaluation**	**26 week evaluation**	**One-year follow up**
K-SADS PL (clinician-administered)	X					
CDRS-R		X		X	X	X
CGI		X		X	X	X
Demographic data (clinician-entered)	X					
QIDS-A_{17}-C		X				
QIDS-A_{17}-SR	X	X	X	X	X	X
C-GAS		X		X	X	X
ORS		X	X	X	X	X
Adverse event self-report		X	X	X		
The credibility/expectancy questionnaire			X (on the first evaluation after two weeks of intervention)			

Height		X		X		X
Weight		X		X		X
VO_2max submax test		X		X		X
Strength test		X		X		X
Body composition assessment		X		X		X
Blood samples		X		X		X
TIC-P		X		X	X	X
CHU9D		X		X	X	X
Qualitative interview				X		X

6.4 Treatment

6.4.1 Aerobic exercise

The patients will participate in aerobic group exercise for 60 minutes three times a week for 12 weeks with continuous heart rate monitoring. The sessions will be held in a small gym under supervision of a personal trainer with special training in medical issues. The exercise will be monitored with continuous heart rate registration.

The group training session will start with a short (5 minutes) check-in on feelings, recent events and difficulties and then begin with a warm-up to increase heart rate including balance tasks and dynamic stretching for 10-15 minutes. Every third session will be pure aerobic training, every third session will be strengthening exercises designed to also increase heart rate, and every third session will be a mixed session of both aerobic and strength exercises. All major muscle groups will be used at each session. Interval training with increased intensity over the course of sessions will be applied. The intended intensity is at pure aerobic sessions 1-18 at 80-85% for about 21 minutes and at sessions 19-36 at 85-90% for about 28 minutes (see supplemental file).

The clinical group leaders will participate in all sessions and will support the adolescents through reminders and reassurances before and during the sessions to enhance adherence.

6.4.2 Group sessions with leisure activities

The control group will receive leisure activity in a group setting for one hour three times a week for 12 weeks. The sessions will be held on the same weekdays and about the same hours as the exercise group sessions. The same group leaders as in the exercise sessions will participate in leisure sessions and will support the adolescents through reminders and reassurance before and during the sessions to enhance adherence. The sessions will start with a short (5 minutes) check-in on feelings, recent events and difficulties (i.e. supportive listening but not any interventions) followed by non-heart rate increasing activities, such as playing games or watching movies together.

6.5 End of trial

The trial will end when the final data from the one-year follow-up has been collected for the last patient.

6.5.1 Participant withdrawal from trial

Participants are free to withdraw from the trial at any point. After the withdrawal, participants will not be requested to complete any further measures, but will be asked to provide non-obligatory feedback regarding their reason for withdrawal. Once participants have withdrawn from the trial, it will not be possible to re-enter or resume treatment. Withdrawn patients will not be replaced in the trial. Caregivers in the local CAMHS will

be notified when the intervention is completed at week 13 or when the participant has withdrawn to evaluate the need for further treatment measures.

6.5.2 Discontinuation of trial

Outcome measures will not be analysed until the end of the trial period and will therefore not cause decisions to stop the research. Failure to recruit within the expected time frame could be a reason to extend the period of recruitment.

6.5.3 Concomitant interventions

Medication for the indication of depression is required to have been stable for the last four weeks prior to inclusion in the trial. Medications with stimulants or neuroleptics need to have been stable for the last two weeks. Additionally, the participants are encouraged (if possible according to his/her treating clinician) not to alter his/her medication or receive any psychological treatment until after the 13-week evaluation. Visits for safety evaluations, for school-planning and to issue parental child-sick leave are permitted.

7. Data management

7.1 Data collection and handling

All aspects of data management of the trial will comply with the General Data Protection Regulation (GDPR). Participant data will be anonymised with a code. A key for coding at each site will be sent to the study coordinator and stored in a locked cabinet. Thus, data in files will be pseudonymised and only the PI and study coordinator have access to the code key. Notes will be made in the clinical records of each participant.

8. Statistical analyses

Demographic data will be summarised using descriptive statistics. T-tests will be performed to investigate if missing data at the three follow up measures can be considered as missing at random (MAR). More specifically, baseline scores for the participants with missing data will be compared with baseline scores for participants with complete data on all outcome variables. Multiple imputation using the predictive mean matching approach will be used to replace missing values for CDRS-R, using data from the QIDS-A-17 self rating scales, baseline scores on the CDRS-R and relevant patient characteristics (e.g., age, sex) as input variables in the model. For more information about this approach see van Ginkle et al. (2020) (69). Data analysis will be conducted using linear mixed models (LME) to analyse change in outcome variables following the interventions (70, 71). Time will be specified as a fixed effect parameter. Random effects parameters are in intercept and linear slope terms. An unstructured covariance matrix will be used to account for within patient correlation across time. A two-sided 95% confidence interval will be used to assess the treatment effect, with statistical significance determined if the confidence interval does not include zero. Cohen's *f* will be used as the effect size measure for the statistical tests. The main analysis will be performed by an extern statistican, blind to randomisation.

8.1 Primary objective

The primary objective is to determine whether there is a significant group difference in change on the CDRS-R from baseline to 13 weeks post-randomisation. After conducting multiple imputation to address missing data, a linear mixed-effects model will be used to compare the groups, incorporating an interaction between group and time. The main analysis will follow the Intention to treat (ITT) principle, meaning that all randomised particpants are included. Sensitivity analyses will be conducted per protocol, meaning that only participants

who adhered to the intervention procdeures are included. In both groups, adherence to the intervention is defined as attending 50% or more of the sessions; for more information, see section 8.3.

8.2 Secondary objectives

We will further analyse CDRS-R, CGI, QIDS-A_{17}-SR, ORS, C-GAS, VO_2max, muscular strength, body composition and biological markers from baseline to 13 weeks in aerobic exercise versus leisure group activities using linear mixed effects models.

Furthermore we will also analyse CDRS-R, CGI, QIDS-A_{17}-SR, ORS, C-GAS at 26 weeks post randomisation using linear mixed effects models.

Naturalistic follow-up analyses will be conducted using data collected 1 year post-randomisation compared with baseline for CDRS-R, CGI, QIDS-A_{17}-SR, ORS, C-GAS, VO_2max, muscular strength, body composition and biological markers.

8.3 Definition of adherence

Sensitivity analyses will be performed per protocol, including only participants who adhered closely to the protocol. Adherence is defined as:

i. attending 50% or more of the intervention sessions
ii. not initiating any other treatment for depression during the intervention period
iii. no new onset of stimulants

We considered a 50% level of attendance, that is 18 sessions, as enough to have received sufficient sessions of exercise, since several studies had interventions totalling 12 (25) to 18 (72, 73) sessions. Further, a feasibility study (74) found a significant improvement in depressive symtoms already after 7 weeks of intervention.

Change of antidepressants is considered as an exclusion criteria within four weeks and stimulants within two weeks from baseline. However, during the trial, we noticed that some participants changed medications during the intervention even if it was not desirable. We considered a new onset of stimulant or antidepressant or increase of dosage of antidepressant during the RCT phase as a reason to be excluded from the sensitivity analyses. However, a decreased dosage of antidepressant or discontinuing an antidepressant or dose adjusments of stimulants were still considered as adhering to the protocol.

8.4 Economic evaluation

The economic evaluation will encompass **two analyses**: 1) a **cost-effectiveness analysis** using the outcome proportion **responders to treatment**; and 2) a **cost-utility analysis** using the outcome quality adjusted life years (**QALYs**). QALYs will be estimated using the scores from the CHU9D In the economic evaluation. CHU9D scores were transformed into Health Related Quality of Life scores by using English social tariffs generated from interviews with a sample of 300 adults from the UK general population, which assigns values to each health state described by the CHU9D (75). Individual HRQoL scores will be used to estimate QALYs over the complete period of the trial (from baseline to 1 year FU) using the area under the curve method (76).

We will compare costs and health outcomes between the intervention group and the control group. Costs will be collected from two different perspectives; a health care provider perspective, and a societal perspective. Costs within the health care provider perspective include the cost to run the interventions, namely: the cost for

the aerobic training sessions and the cost for the leisure activities including hourly staff wages, time for preparation and traveling, telephone calls, and administration. In the analysis from a societal perspective, other health care costs (other health care utilization and medication use), as well as social support, informal care and indirect costs (e.g., productivity loss associated with school and work absenteeism and presenteeism) captured by the TiC-P will be included in addition to the intervention costs.

Analyses will be carried out in line with standard health economic methods, following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. The within trial economic analysis will be conducted on an intention to treat (ITT) basis. Multiple imputation methods will be employed to account for missing data (77). Differences in QALYs and costs between the groups will be analysed using generalised linear models (GLM) to allow for the consideration of other distributions and functional forms to fit the cost and outcome data (78). Total costs will be analysed while controlling for baseline costs. Total QALYs will be analysed while controlling for baseline CHU9D utility values (79). Non-parametric bootstrapping with 5000 iterations will be carried out to deal with uncertainty around the cost and outcome data. Uncertainty around the incremental cost and outcome estimates will be represented on cost-effectiveness planes. A cost-effectiveness plane is a cloud of the 1000 bootstrapped incremental costs and effects across four quadrants, where each quadrant has a decision implication. Net monetary benefits at different thresholds of willingness to pay will be calculated and presented on cost effectiveness acceptability curves (CEAC). The CEAC captures decision uncertainty and shows the probability of the intervention being cost-effective at different cost-effectiveness thresholds (80). Sensitivity analyses will be carried out by inflation of staff costs, to test for the robustness of the analyses.

Data will be cleaned using Microsoft Excel and data analyses performed using Stata version 15.1.

8.5 Qualitative analysis

Qualitative content analysis with an inductive approach will be used to analyze the interviews (81, 82). The qualitative content analysis will identify meaning units, condense and label them in order to group them into categories and finally interpreted to express the latent meaning of how the adolescents , parents and coaches experience the intervention and how the intervention influences their health and lifestyle (81, 83). Two researchers (IL and RM) will independently analyse the text and discuss the interpretations with the research group.

8.6 Validation of QIDS-A_{17}-C against CDRS-R

A convergent validation of QIDS-A_{17}-C against CDRS-R will be performed using baseline measures. A validation of sensitivity to change for QIDS-A17-SR against CDRS-R will be performed using measures from baseline, 13 weeks, 26 weeks, and one year follow up.

9. Recording and reporting of adverse events and reactions

9.1 Definition of adverse events

Term	Definition
Serious Adverse Event (SAE)	Any unfortunate occurrence that: - results in death - is life-threatening - requires hospitalisation or prolongation of existing hospitalisation - results in persistent or significant disability or incapacity

	- is otherwise considered medically significant by the investigator

9.2 Expected adverse events

We have considered the following events as possible adverse events:

- Increased depressive symptoms
- Suicide attempt
- Increased stress due to time consuming sessions and transportation
- Injuries due to exercise

We also have to consider that psychological adverse events may also be symptoms of the underlying condition, i.e. depressive disorder, rather than the intervention itself.

9.3 Assessment of adverse events

A. Related events

The assessment of the relationship between adverse events and the administration of the treatment is a decision based on all available information. The final decision is taken by the PI. If the event is a result of the administration of any of the research procedures then it will be classified as related.

B. Expected events

If the event has been listed in the protocol (section 9.1) as an expected side effect of the intervention then the event will be classified as expected. If the event is not listed then it will be classified as unexpected.

9.4 Handling of adverse events

All adverse events will be noted by the trial coordinator in a specific log (including date, recorded clinical symptoms, and a brief description of the event). SAEs and SUSARs will be recorded in the trial coordinator's log. Appropriate action will be taken in the case of SAE and SUSAR, making sure the participant will get in contact with suitable health care services. Events will be considered as potentially treatment-related up to the 13 weeks evaluation and for the control group up to 26 weeks, where the reporting of adverse events will terminate.

9.5 Notification of serious breaches to GCP and/or the protocol

A "serious breach" is defined as a breach which is likely to a significant degree affect:

- the safety or physical or mental integrity of participants
  or
- the scientific value of the trial.

The PI will notify the Ethical Review Board in writing of any serious breach. Reports of serious breaches will contain when the breach occurred, the location, who was involved, the outcome and any information given to participants. An explanation regarding the cause of the serious breach will be given, and the Ethical Review Board will be informed of planned further actions.

10. Data sharing

We will not share trial data with external researchers.

11. Ethical considerations

The study is approved by the Swedish Ethical Review Authority (2021-05307-01).

All patients and parents will be provided with oral and written information about the study. Informed consent in writing will be provided from patients and parents to participants below 15 years of age.

Participants randomised to leisure activities will get the opportunity to receive the exercise intervention after 26 weeks, ensuring all participants are offered the active treatment.

We further made an amendment applicantion that was approved by the Swedish Ethical Review Authority (2024-04975-02), due to changes during the trial such as: adding new sites, postponed end of trial, added self rated instruments, increased compensation for participants, change of platform for video interviews, and, in some cases, including participants even when an existing care relation between the participant and a researcher was present.

12. Implications

Aerobic group exercise can, if shown to be effective, become a recommended treatment option for major depressive disorder in adolescents either alone or as an addition to present treatment options with cognitive behavioural therapy and antidepressants.

13. Finance for data collection

Resource/equipment	Extent	Costs	subtotal	Total
Principal investigator	2.5 years	5% of salary	168 000 SEK	
Co-investigators	Co-investigators rating interviews 6/day x 100 participants x 4/participant = 67 d/3mt		328 500 SEK	
	Data analysis 4 months		438 000 SEK	
Statistical support			50 000 SEK	
Study coordinator	2,5 years administrative work as trial coordinator	10% of salary 50000 /month	150 000 SEK	
Subtotal central cost				1 181 500 SEK
SITE/average 10 participants	12 cohorts are needed for the full sample Thus 3 rounds of interventions			
Site coordinator	6 months administrative work as trial coordinator for each round of interventions at a center (3 rounds x 4 centers)	20% of salary	60 000 SEK	480 000
Site Group leaders	Exercise intervention: 3 x 12 weeks and 5 hours/w = 120 hours = 3 weeks		Exercise group paid by the clinic	
	Leisure intervention 12 weeks x 5 hours/w = 60 hours = 1.5 weeks + planning 0.5 w = 2 weeks	2 w salary	40 000	
Site costs			105 657/round	
STAFF TOTAL COST				1 266 804 SEK
Exercise sessions	for 1 cohort 2 x 36 sessions. Paid by clinic?	4x156 000/round	624 000/round	1 872 000 SEK paid by clinic?
Room for leisure activities	Free at the clinical premises	-	-	
Heart rate monitors	Rent or purchade of Polar team pro system pulse sensors and central unit / cohort	10 000 SEK	10 000 SEK	60 000 SEK
Assessments of aerobic capacity, muscular strength and body composition	For 3 occasions/subject x 110 subjects (baseline 120, endpoint 90?)	1 500 SEK /subject		165 000 SEK

Travel expenses for body /fitness assesments			40 000 SEK	40 000 SEK
Blood analyses	Each subject sampling and 1 year storage 776 SEK (50 subjetcs from Halland) + 1250 (50 subjetcs from Malmö, Stockholm) Analyses of 100 subjects w blood from 3 points in time	101 300 SEK	60 000 SEK	435 000 SEK ???
ESmaker, SPSS	Free as clinical service has a subscription	-	-	
License for CDRS-R	300 interviews License fee (180 USD/100 interviews) Administrative fee /100 (USD 85)	5130 SEK 825 SEK	5955 SEK	5 955 SEK
Ethical Review Board	Application fee	15000 SEK	15 000	15 000 SEK
Patient gratification gift cards	Twice/subject for evaluation weeks (500)	1000 SEK/patient	100 000	100 000 SEK
Open Access	Publication Fees	25 000		100 000
TOTAL COSTS not trainer				3 184 884
TOTAL COST, also trainer				4 624 884

14. Publication plans

We plan to publish papers on:

- Evaluation of the effect of aerobic exercise versus leisure group activities for adolescents with depression 13 weeks and 26 weeks post-randomisation
- Evaluation of the effect of aerobic exercise for adolescents with depression at a one year follow up
- Qualitative evaluations of aerobic exercise and leisure group activities for adolescents with depression
- Validation of QIDS-A_{17}-C against CDRS-R at baseline and QIDS-A_{17}-SR against CDRS-R regarding sensitivity to change
- Evaluation of differential change in neuroinflammatory markers for intervention arms and for responders vs non-responders
- Cost-effectiveness analyses at 13 and 26 weeks, as well as one-year post-randomisation for the intervention groups

Papers will be submitted to scientific journals.

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