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Moderate-to-vigorous group aerobic exercise versus group leisure activities for mild-to-moderate depression in adolescents: study protocol for a multicentre randomised controlled trial

Rebecca Mortazavi,[1,2] Maria Lalouni ,[3] Rebecca Grudin ,[3] Eva Serlachius,[1,3] Carl Johan Sundberg,[4,5] Jessica Norrbom,[4] Ingrid Larsson ,[6,7] Emma Haglund,[8,9] Andreas Ivarsson,[6,10] Fabian Lenhard,[11] Tina Cronqvist,[12] Kristina Ingemarsson,[2] Åsa Mårsell,[13] Olof Rask,[1] Håkan Jarbin [1,2]

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For numbered affiliations see end of article.

Correspondence to
Dr Håkan Jarbin;
hakan.jarbin@regionhalland.se

ABSTRACT

Introduction Depression is common, increasing among adolescents and carries risk of disability, lower educational achievements, cardiovascular disease, substance abuse, self-harm and suicide. The effects of evidence-based treatments with medication or psychotherapy are modest. Aerobic exercise is a promising intervention for adolescents with depression, but available studies are hampered by methodological shortcomings. This study aims to evaluate aerobic group exercise versus an active comparator of leisure group activities in adolescents from clinical services with mild-to-moderate depression.

Methods and analysis This study is a multicentre randomised controlled trial at four psychiatric clinics in Sweden. Participants (n=122) will be randomised 1:1 to group exercise delivered by exercise professionals and supported by mental health (MH) workers or leisure activities lead by the same MH workers for 1 hour three times a week for 12 weeks. Participants will be assessed at baseline, single blind after 13 weeks and 26 weeks and openly after 1 year. Participants randomised to the leisure group will be offered exercise in the open phase. The primary outcome is clinician-rated Children's Depression Rating Scale-Revised. Secondary outcomes are self-rated Quick Inventory of Depressive Symptomatology, self-rated functioning; clinician-rated improvement and functioning; objectively measured aerobic capacity, muscular strength, muscular endurance, body composition and presence or activity of selected biological markers of neuroprotection and neuroinflammation in blood samples. Further outcomes are cost-effectiveness and adolescents', parents' and coaches' experiences of the interventions and an exploration of how the adolescents' health and lifestyle are influenced by the interventions through qualitative interviews.

Ethics and dissemination The study is approved by the Swedish Ethical Review Authority (Ref. 2021-05307-01). Informed consent in writing will be provided from patients and parents of participants below 15 years of age. The results of this study will be communicated to the included participants and healthcare providers and also submitted for publication in peer-reviewed journals.

Trial registration number NCT05076214.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will address major shortcomings of previous studies such as weak comparators, recruitment from advertisement, diagnoses not based on criteria and lack of follow-up.
⇒ The multicentre setting across child psychiatric clinics will strengthen the generalisability of the study findings.
⇒ The study will provide data on the experiences of adolescents, parents and coaches.
⇒ Limitations include issues with respect to generalisability to standard and primary care settings, since group exercise with dedicated research teams in specialised services can be difficult to deliver in other contexts.

INTRODUCTION

Depression in adolescents is characterised by behavioural, cognitive and physical symptoms such as sadness, hopelessness and irritability during at least a 2-week period.[1] Depression affects 5%–11% of adolescents[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] Furthermore, depression in adolescents is a moderate risk factor for cardiovascular disease.[10] This risk 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 a first-line treatment option for depression in adolescence.[11] BPI involves psychoeducation, family participation and school support as well as activation with a focus on depression.[12 13] The effect sizes of evidence-based treatments with antidepressants or psychotherapy, such as cognitive behavioural therapy or interpersonal therapy, are modest.[14] Selective serotonin uptake inhibitors (SSRIs) have shown an effect on depression in children and adolescents, but the effect is often insufficient as 30%–40% of children fail to respond in standard SSRI trials.[15] Treatment resistance is common and data on augmentation or alternative treatments are very scarce.[16]

European Psychiatric Association guidance states that adults with depression can benefit from 2.5 hours of moderate-to-vigorous aerobic exercise per week.[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 has suggested an effect size 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 often deemed as low quality.[18 20–23] Available randomised controlled trials (RCTs) are heterogeneous with a diverse selection of participants, few comorbidities or no reports on comorbidity, diverse training intensity, diverse outcome measures and follow-up period.[24–28] There is a lack of studies evaluating the effect of exercise in a clinical psychiatric sample. Studies on clinical samples are required for generalisability to clinical settings.[17] Our open study 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 in this compromised clinical sample, substantial improvement after the 14-week intervention and further improvement after 1 year.[29]

Comorbidity in depression is common and up to half of clinical patients also suffer from two or more comorbidities, such as anxiety disorders or attention-deficit/hyperactivity disorder.[30] This is often not reported in existing studies[24 25 27] or excluded from them.[28] Long-term follow-up is virtually non-existent. Follow-up varied from none[27 28] to 1 month,[24] 6 months[25] or 1 year.[26] Studies beyond a 1-month follow-up had approximately 50% attrition and included in total only 58 participants in the long-term follow-up.[25 26]

One small study had controls receiving stretching exercises 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] Existing trials with control groups with no intervention do not mitigate confounders such as the benefit of having a regular routine, meeting with staff and being in a group with other adolescents. Group activities could be socially activating and an effective intervention in themselves in line with behavioural activation for depression.[31 32] Recent meta-analyses concluded that serious methodological limitations downgrade the evidence to low grade.[22 33] 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] while high risk of bias ratings for outcome and low numbers were also concerns in most meta-analyses restricted to participants diagnosed with depression, that is, not just depressive symptoms.[33]

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), interleukin6 (IL-6), kynurenic acid (KYNA), vascular endothelial growth factor, 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 in adolescents found that exercise can be a cost-effective intervention.[36]

The subjective approach with interviews describing how the intervention is perceived has shown acceptability for exercising not only in adults,[37 38] but also, in adolescents.[39] We found that group exercising brings adolescents joy of living through commitment, empowerment and participation.[40] Furthermore, we found at a 1-year follow-up, facilitators for continued exercise to be the companionship in training and achievement of exercise results such as getting more fit and less depressed. Parental support and encouragement to get to the gym were other facilitators. Identified barriers were symptoms of fatigue, social anxiety and lack of drive as well as lack of social support.[41] Other beneficial aspects of the programme were that the intervention was experienced as manageable, comprehensible and meaningful. This sense of coherence can further improve the outcome.[42]

To sum up, 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 and severe issues regarding recruitment, inappropriate controls, high risk of bias and absence of follow-up. More data on qualitative, cost-effectiveness and biomarker aspects are clearly warranted.

Objectives

The primary objective is to evaluate aerobic group exercise versus leisure group activities after 12 weeks of intervention on clinician-rated depression symptoms among outpatient adolescents with depression.

Secondary objectives are to evaluate clinician-rated global severity, improvement and function, patient-rated symptoms and function as well as aerobic capacity, muscular strength, muscular endurance, body composition and presence or activity of selected biological markers of neuroprotection and neuroinflammation in blood samples.

Further secondary objectives are to evaluate changes in symptoms and functioning in the intervention groups at 26 weeks and a long-term open follow-up at 1 year. We will also evaluate cost-effectiveness, changes in quality of life and adolescents', parents' and coaches' experiences of the intervention.

Methods and analysis

Study design

This multicentre RCT will include 122 adolescents at four psychiatric clinics in Sweden with mild-to-moderate depression randomised to 12 weeks of either aerobic group exercise or leisure group activities at a ratio of 1:1. The protocol is based on the Standard Protocol Items for Randomised Trials (SPIRIT).[43]

By using leisure activities in a group setting with the same leaders, time and duration for sessions as a control group, we control for the effect of social activation, interaction and attention.[31]

Evaluation appointments for diagnostic assessment and eligibility with a resident psychiatrist will take place at the clinics. 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 using the internet with patients and parents. Clinical interviews will be recorded video calls (qualitative interviews sound only).

Patient and public involvement

In our previous papers[40 41] and from interviews of participants from a pilot version of this study, we have elicited suggestions and advice on the exercise and leisure interventions. Otherwise, there is no further patient or public involvement planned.

Participants and recruitment

We will recruit patients in ongoing clinical care who have had at least three visits and thus are more likely to have received some basic psychosocial interventions. The patients will be identified through administrative systems. Eligible patients will be contacted by letter and phone. Consenting patients will be invited to an assessment by a resident child and adolescent psychiatrist with Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) and presence of inclusion and absence of exclusion criteria before baseline. The resident will receive training and discuss each interview with the principal investigator (PI).

Inclusion criteria:

- Adolescents aged 13–17 years with a Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-5) mild-to-moderate major depression.
- Have attended at least three clinical visits in order to have received some basic psychoeducational intervention for depression.
- Have not shown a clear response as assessed from clinical records.

Exclusion criteria:

- Eating disorder.
- High risk for suicide, which would necessitate adjustment of medication or psychotherapeutic interventions.
- Intellectual disability.
- Physical activity at least 150 min per week of moderate intensity or 75 min per week of high intensity.[44]
- Adjustment of antidepressant medication within 4 weeks or stimulants within 2 weeks.
- In need of interpreter.
- Social circumstances interfering with a regular exercise schedule.
- Concomitant psychotherapy.

Intervention

Randomisation 1:1 for each site to give equally sized groups and masking procedures will be conducted by an independent co-investigator. Sealed envelopes with randomisation numbers will be stored in a locked cabinet.

The investigators (RM and TC) conducting the baseline, 13-week and 26-week evaluations will be blind to treatment allocation. Rater training for outcome measure interviews has been performed in the pilot study and will be refreshed. Participants will be reminded at the start of each interview not to reveal their arm of allocation. The assessor will record whether the participants inadvertently revealed 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 26 weeks evaluation. At the 1 year open follow-up, all patients will have had the opportunity to exercise in the aerobic group format and the evaluation is unblinded. The clinical group leaders will participate in all sessions and will support the adolescents through reminders and reassurances before and during sessions to enhance adherence.

In case of medical emergency, participants will be encouraged to immediately seek appropriate healthcare and to inform the local study coordinator, who will follow-up the incident in collaboration with the PI.

Aerobic exercise:

The patients will participate in aerobic group exercise for 60 min three times a week for 12 weeks with continuous heart rate monitoring. The sessions will be supervised by a personal trainer. Sessions will start with a short (3–5 min) check-in on feelings, and recent events, that is, supportive listening but without interventions. Exercise begins with a warm up to increase heart rate including balance tasks and dynamic stretching for 10–15 min. Each week there

will be three types of sessions, one pure aerobic training, one strengthening exercises designed to also increase heart rate and one mixed session of both aerobics and strength. All major muscle groups will be used at each session. The interval training with have increased intensity over the course of sessions. At pure aerobic sessions, the intended intensity at session 1–18 will be at 80%–85% of maximum heart rate for about 21 min and at sessions 19–36 at 85%–90% for about 28 min (see online supplemental file 1).

Leisure activities:

The control group will receive leisure activity in a group setting for 1 hour three times a week for 12 weeks. Sessions will be held on the same weekdays, about at same hours and with same group leaders as the exercise group sessions. The sessions will start with a short (3–5 min) check-in on feelings and recent events, that is, supportive listening but without interventions, followed by non-heart rate increasing activities, such as playing games or cards (online supplemental file 2).

Data assessment

Clinical interviews will be performed by RM and TC through a recorded video call. Patients will fill out a web-based Quick Inventory of Depressive Symptomatology Adolescent version-17 self-report (QIDS-A_{17}-SR) and Outcome Rating Scale (ORS) every 2 weeks during the 12 weeks intervention period and monthly during the follow-up until 1 year. The web-based survey tool will send text message reminders at predetermined dates.[45] Qualitative individual interviews will be performed with a meaningful sample of the adolescents (n=20), parents (n=20) and coaches (n=8) from each group (intervention/exercise and control) evenly distributed across sites at week 13 and at 1 year. The study coordinator will check that the uploaded data has been completed every 2 weeks during interventions and monthly during follow-up and check to ensure that physical tests, blood sample collection and qualitative interviews have been completed at indicated points in time (figure 1 and table 1).

Methods for investigating effects

The *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 with items ranging from 1 to 5

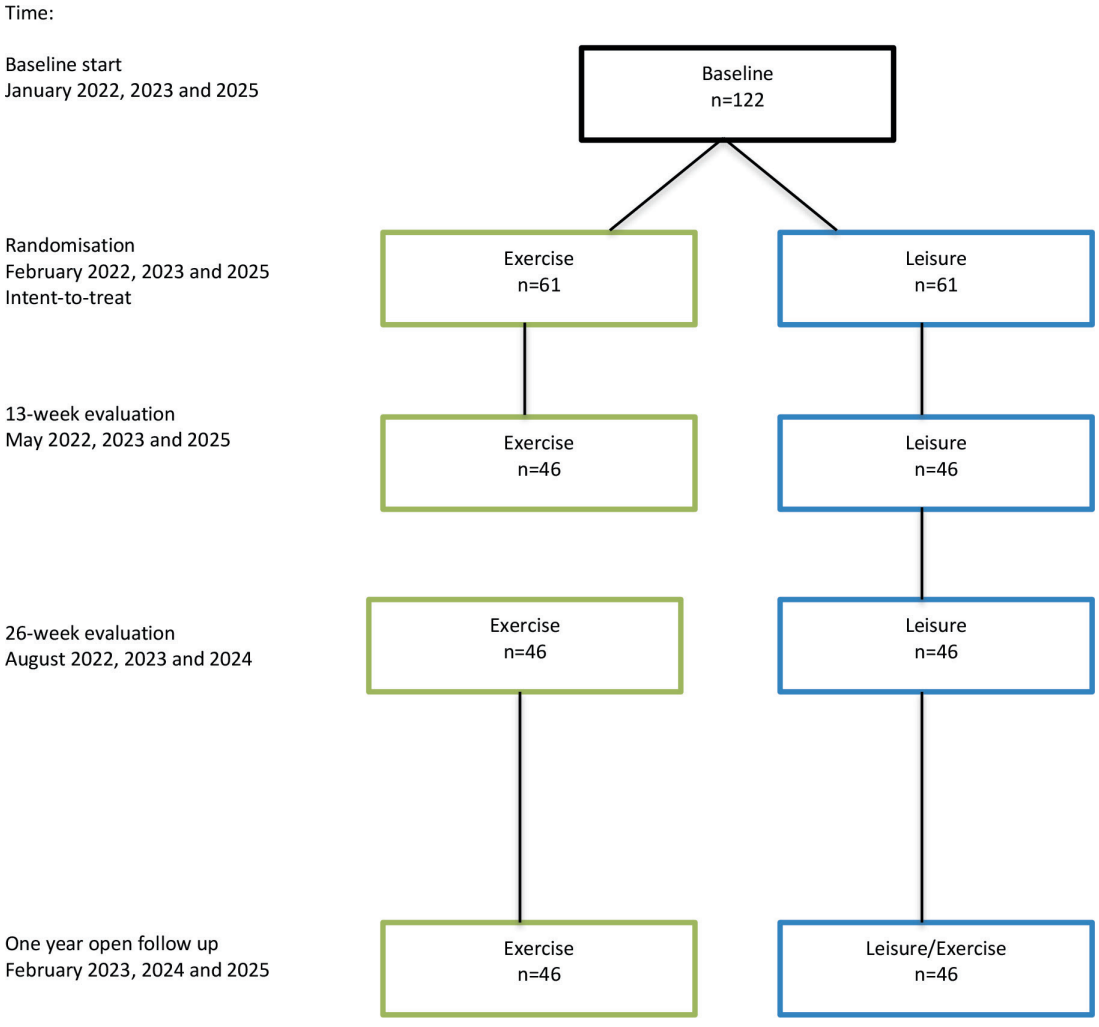

Figure 1 Time points for assessments in RCT and open phases. RCT, randomised controlled trial.

Table 1 Assessment points for each outcome measure

Assessment points: Outcomes:	Screening assessment	Baseline	Every other week during intervention and monthly up to 1 year	13-week evaluation	26-week evaluation	1-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
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 2 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

CDRS-R, Children's Depression Rating Scale-Revised ; C-GAS, Children Global Assessment Scale ; CGI, Clinical Global Impression; CHU9D, Child Health Utility 9 instrument ; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; ORS, Outcome Rating Scale ; QIDS-A_{17} -C, Quick Inventory of Depressive Symptomatology Adolescent version-17 clinician rating; QIDS-A_{17}- SR, Quick Inventory of Depressive Symptomatology Adolescent version-17 self-report .

or 1 to 7 with a total score of 17 to 113. A score of ≥40 indicates depression while a score of ≤28 is often used to define remission.[46] A raw summary score and T-score can only be obtained from interview with the child.[46] Response is defined as a reduction by half of the initial score on CDRS-R. Remission is defined as below 28 points on CDRS-R.

The *Clinical Global Impression (CGI*) 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 with 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'.[47]

The *Quick Inventory of Depressive Symptomatology—Adolescent version-17 (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 QIDS-A17-SR, for parent report and for clinician rating.[48]

The Children Global Assessment Scale is a clinician instrument for assessing psychiatric functioning on a scale from 1 (worst) to 100 (best) among persons aged 4–20 years.[49] Outpatients usually score from 40 to 60 while a score of 70 and above is regarded as normal functioning.

The ORS is a self-reported scale for assessing functioning in four domains covering individual, interpersonal, social and overall 'sense of well-being' aspects.[50] The scale provides a numerical value of functioning between 0 (worst) and 100 (best) on a Visual Analogue Scale.

The *Aerobic capacity* (VO_{2max}) will be measured according to Åstrand with a submaximal cycle ergometer test on an indoor bicycle.[51] Aerobic capacity will be presented relative to body weight and expressed as the total amount of oxygen metabolised per minute per kilogram of body weight (mL/kg/min).

The *Muscular strength* will be measured with an isometric mid-thigh pull strength test, 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.[52] 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[53]

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.[54] Each test will be performed twice and best performance or fastest time will be used for analysis.

The *body mass index (BMI)* is an index computed through the formula weight (kg)/height (m^2). Age corrected BMI for boys and girls according to the WHO will be presented with z-values adjusted for gender and age.[55]

The *Body composition* including body weight and a muscle-fat analysis measured with a Bioelectrical impedance analysis (BIA, InBody 770 USA, 2016). The BIA will be performed at least 2 hours after breakfast with the test person wearing only light clothing and with emptied bladder. The method has shown an acceptable validity and reliability.[56 57]

The *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. Thus, the estimated value could be the most accurate and also most ethical.

The *Blood sampling* in 10 mL EDTA and serum tubes will be frozen and stored by Region Halland, Sweden for subsequent analyses. The presence and activity of biological markers that have been suggested to be important for neuroprotection and neuroinflammation including Brain Derived Neurotrophic Factor (BDNF), C-reactive Proteins (CRP), Interleukin (IL)-6, Kynerunic Acid (KYNA)/3HK75, KYNA/Quinolinic Acid (QUIN)75, Kynerunic (KYN)-ACID75, Soluble Interleukin (SIL)-2 receptor, Tumor Necrosis Factor (TNF)-α, Insulin-like Growth Factor (IGF)-1 and their associated binding proteins will be analysed.

Child Health Utility instrument (CHU9D) is a generic preference-based measure of quality of life in children and adolescents designed specifically for use in an economic evaluation in healthcare.[58] It consists of nine dimensions rated on a 5-point Likert scale. Responses are converted to quality of life utilities ranging from 0 to 1 (implying perfect health). The Swedish version has shown good reliability and validity in adolescents.[59]

Methods for investigating cost-effectiveness

Cost-effectiveness will be assessed by Trimbos/iMTA questionnaire for costs associated with Psychiatric Illness—Child version (TiC-P). The *TiC-P* is used to measure consumption of healthcare, costs associated with illness and production loss among parents due to psychiatric problems in the child concerning the previous four weeks .[60] Healthcare costs cover aerobic and leisure sessions including hourly staff wages, time for preparation and travelling, telephone calls and administration. In the analysis from a societal perspective, other healthcare costs (other healthcare utilisation and medication use) as well as indirect costs (eg, informal care, productivity loss associated with school and work absenteeism) captured by the TiC-P will be included. 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.[61 62]

Two outcome measures will be used in the cost-effectiveness analysis,[1] remission status regarding clinical depression and[2] quality of life utilities measured with the CHU9D, in line with best practice standards in health economic analyses. Both outcomes will be used to calculate incremental cost-effectiveness ratios (ICERs) for cost-effectiveness and cost-utility, separately for each measure.

Methods for investigating subjective experiences

The *qualitative individual interviews* will be performed by an independent experienced researcher (IL) or trained and supervised research fellows (RM and RG). An open interview guide (online supplemental file 3) 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. The interviews will be digitally recorded and transcribed verbatim.

Statistical power

The statistical power calculation for this trial is based on data obtained from a pilot study conducted in early 2021.

For the pilot study the sample size was restricted to 14 participants due to COVID-19. Of the 14 participants, two dropped out due to COVID-19-related reasons and three dropped out due to other reasons/non-compliance. A total of nine participants completed the RCT phase and the week 13 assessments. Hence, we estimate that 9/12 (75%) of included patients will complete the RCT phase. This is in line with our 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 SD of 12.9-points (data on file). The power calculation, based on β=80% and α of 0.05, indicates that 92 patients are required. With an expected attrition of 25%, 122 participants are required at baseline.

Data analysis

All aspects of data management of the trial will comply with the General Data Protection Regulation. 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 available for the PI and the study coordinator. Notes will be made in the clinical records and data will be analysed with Statistical Package for the Social Sciences (SPSS) V.26.

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. Baseline scores for the participants with missing data will be compared with baseline scores for participants with completed data. Multiple imputation using the predictive mean matching approach will be used to replace missing values.[63] Data analysis will be conducted using linear mixed models to analyse change in outcome variables.[64 65] Time will be specified as a fixed effect parameter (consisting of baseline, week 13, week 26 and 1-year follow-up). Random effects parameters will be in intercept and linear slope terms. An unstructured covariance matrix will be used to account for patient correlation across time within the sample. Tests will be two-tailed, and α set to 0.05 to indicate statistical significance. Cohen's *f* will be used as effect size measure.

Cost analyses will be carried out in line with the Consolidated Health Economic Evaluation Reporting Standards checklist.[66] Differences between the groups will be analysed with regression analyses. As cost data tends to be right-skewed with a high occurrence of low values and few large values, regression analyses will be conducted using 1000 non-parametric bootstraps for estimation of valid confidence intervals (CIs).[67 68] The ratio of the differences in costs between the groups and the effects between the groups will be presented in incremental cost-effectiveness ratios (ICERs).[69] Cost-effectiveness planes will be presented, visualising the probability distribution of the bootstrapped cost and effect values. Sensitivity analyses will be carried out by inflation of staff costs, to test for the robustness of the analyses.[70]

Qualitative content analysis with an inductive approach will be used to analyse the interviews.[71 72] The qualitative content analysis will identify meaning units, condense and label them in order to group them into categories and finally interpret them in order to express the latent meaning of how the participants experience the intervention and how the intervention influences health and lifestyle.[72 73] Three researchers (IL, RG and RM) will independently analyse the text and discuss the interpretations with the research group.

ETHICS AND DISSEMINATION

The Swedish Ethical Review Authority has approved the study (ref. 2021-05307-01).

All patients and parents will be provided with oral and written information about the study (online supplemental file 4). Informed consent in writing will be provided from patients and parents to participants below 15 years of age by the local monitor after the diagnostic assessment (online supplemental file 5). Consent forms will be stored in a locked cabinet of the PI. Participants randomised to leisure activities will get the opportunity to exercise after 26 weeks, ensuring all participants are offered the active treatment. Self-report data will continuously be reviewed regarding increased suicidality and participants will, if indicated, be contacted for further assessment.

Participants are free to withdraw from the trial at any point, will not be requested to complete any further measures, but will be asked to provide non-obligatory feedback regarding their reason for withdrawal. Caregivers in the local Child and Adolescent Mental Health Service (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. Participants will continue, if indicated, to receive care from the local CAMHS. Outcome measures will not be analysed until the end of the trial period and will therefore not cause decisions to stop the research.

The results of this study will be communicated to the included participants and healthcare providers and submitted for publication in peer-reviewed journals.

DISCUSSION

Major shortcomings in available studies will be addressed. This multicentre RCT will provide evidence for the efficacy of aerobic group exercise versus an active comparator controlling for the effect of social interaction, attention and behavioural activation. Recruiting at secondary clinical services and after basic interventions is clinically sound. Furthermore, we perform a standard diagnostic assessment with K-SADS-PL, which is commonplace in pharmacological studies but not in exercise studies, in order to ensure a depression diagnosis and also to describe the extent of comorbidities to facilitate generalisation to clinical settings. Clinician-rated symptoms with CDRS-R was chosen as the primary outcome since the scale is well established and considered gold standard in studies on adolescent depression.[74] A single blinded outcome measure rated by a clinician will address the

high risk of bias in available studies on patients diagnosed with depression relying on self-reported outcome.[33]

There is currently no consensus on which level of exercise that is optimal. We have chosen a vigorous model with progression to higher intensity at one step after half of sessions. This is both in contrast to Carter *et al* who used preferred and considerably lower intensity[25] and to a recent study protocol aiming at both a steeper progression and more intense levels of exertion.[75] However, our level of exertion was acceptable and feasible to a similar cohort of adolescents from secondary mental health services in our previous study with an open design.[29]

To also assess the efficacy a period after end of active intervention, we intend to keep the blinding up to 26 weeks. However, there will be a long Swedish summer vacation from schools during the latter part of this period possibly diluting the results. We aim to evaluate an increasing benefit from exercise over time. Also, the sustainability of improvement up until 1 year after start of treatment (unblinded) will be evaluated. In our previous open study, the improvement continued. Longer-term results will make an important contribution to clinical decision-making. For ethical reasons, we refrain from keeping the groups separate after the 26 weeks. Also, the primary end point is at 13 weeks as changes in medication or other changes of treatment are more likely when the time frame is extended.

The qualitative studies provide an opportunity to explore adolescents', parents' and coaches' experiences of adolescents' participation in the intervention with both aerobic exercise and leisure group activities and how this influences their health and lifestyle. This will provide a deeper understanding of the effect from different perspectives and sites. Understanding what adolescents think, feel or do when participating in the intervention can make evidence-based interventions more effective, efficient, equitable and humane.[76]

There are some challenges with this study. Choosing leisure group activities with equal amounts of time and probably more social interaction with peers can be regarded as an active comparator rather than just an inactive control. A weakness of the study is the single blind procedure as participants will be aware of the presumed active treatment. We will address this dilemma with a strict adherence to the single blind design, but also with a treatment credibility scale in the early phase of each intervention. Another limitation is the generalisability, as group exercise with dedicated research teams in specialised services can be hard to deliver in standard care as well as in primary care settings.

This study will aim to answer the question of whether adolescents with depression should be offered aerobic exercise from healthcare providers as a treatment option.

Author affiliations
[1]Department of Clinical Sciences, Child and Adolescent Psychiatry, Lund University, Lund, Sweden
[2]Child and Adolescent Psychiatry, Region Halland, Halmstad, Sweden
[3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Region Stockholm, Sweden
[4]Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden
[5]Department of Learning, Informatics, Karolinska Institutet, Stockholm, Sweden
[6]Department of Health and Nursing, School of Health and Welfare, Halmstad University, Halmstad, Sweden
[7]Spenshult Research and Development Centre, Halmstad, Halland, Sweden
[8]The Rydberg Laboratory for Applied Sciences, Halmstad, Sweden
[9]Department of Health and Sport, School of Health and Sport, Halmstad University, Halmstad, Sweden
[10]Department of Sport Science and Physical Education, University of Agder, Kristiansand, Norway
[11]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden
[12]Psychiatry, Region Halland, Halmstad, Sweden
[13]PRIMA Barn- och Vuxenpsykiatri AB, Stockholm, Sweden

Twitter Rebecca Grudin @RebeccaGrudin and Fabian Lenhard @fabianlenhard

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ORCID iDs
Maria Lalouni http://orcid.org/0000-0002-6818-8156
Rebecca Grudin http://orcid.org/0000-0002-0284-0893
Ingrid Larsson http://orcid.org/0000-0002-4341-660X
Håkan Jarbin http://orcid.org/0000-0003-3533-453X

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Workout plan

Workout intervention plan for the physical activity intervention in "Randomised controlled trial of vigorous aerobic group exercise versus leisure group activities for mild to moderate depression in adolescents".

Training schedule

Mondays 15:30 – 16:35:	Strength focused training session
Wednesdays 15:30 – 16:35:	Aerobic focused training session
Thursdays 15:30 – 16:35:	Mixed training session

Reminders

Text messages (sms) are sent to all participants earlier the same day before group sessions. The messages can but need not be replied. The participants can text or call the group leader if they are hesitant to show up to the group session. The group leader will be available 15 minutes before session to make sure the group sessions start on time.

Check-in, 3-5 minutes

Check-in together where participants share how they are doing and some recent events.

Progression

The goal with every new week should be making every workout a little bit harder than the week before.

Strength sessions

- Week 1-6: 12-18 reps x 2 set per exercise and muscle
  30 s rest between exercises
- Week 7-12: 10-12 reps x 3 set per exercise and muscle
  20 s rest between exercises

Adding weight with gym equipment or changing body position in the exercises to succeed with the rep scheme and making it harder as the group develop their physical and mental ability.

Aerobic sessions

- Week 1-6: 75 seconds work time x 1 set per exercise
  30 seconds of rest between exercises
- Week 7-12: 50 seconds work time x 2 set per exercise
  20 seconds of rest between exercises

Mixed sessions

- Week 1-6: 35 s work time per exercise
  25 s rest between exercises
  x 2 rounds
- Week 7-12: 45 s work time per exercise
  15 s rest between exercises
  x 2 rounds

Strength session, 55 minutes

Warm-up: 11-15 minutes

- 5 minutes - Half of the group in conditioning machines, working from 65 % up to 80 % heart rate.
- 5 minutes – The other half doing easy dynamic mobility, led by the trainer. Focusing on ankle, knee, hip and the muscles that surround these joints.

Then, they switch places.

Strength in 6 different exercises: 22-30 minutes

- **Squat**

Starting with bodyweight and increasing weight with kettlebell, barbell or dumbbells as they get stronger.

- **Australian pull-up**

Adjust the feet in order to make the exercise easier/heavier.

- **Push-up**

Start on knees, with elevated hand position. Lowering the angle of the body and standing on feet as they get stronger.

- **Lunge (reverse)**

Alternating legs. Starting with bodyweight and increasing weight with kettlebell, barbell or dumbbells as they get stronger.

- **Calf raise**

Standing on a step board to get full range of motion. Starting with bodyweight and increasing weight with kettlebell or dumbbell as they get stronger.

- **Crunch including rotation**

Find the best version for the group. Suggesting crunch with upper body rotation to start with. Make it more challenging with adding legs in the motion.

Start at one exercise and work there for 60 seconds, rest 30 seconds and move on to the next exercise. Extra rest time between rounds.

Week 1-6:
- 12-18 reps x 2 set per exercise and muscle
- 60 second work time
- 30 s rest between exercises
- 60 s rest between rounds
- 2 rounds of extra core training

Week 7-12:
- 10-12 reps x 3 set per exercise and muscle
- 45 second work time
- 20 s rest between exercises
- 60 s rest between rounds
- 3 rounds of extra core training

Core training: 5-7 minutes

- **Side plank** with dynamic raise 30 seconds/side
  Starting with one knee on the floor and progress up to their feet as they get stronger.
- **Back extension** 45 seconds
  x 2-3 rounds with 30 second rest between rounds.

This part is done everybody at ones on their own mat.

Cool down: 5-10 minutes
Easy mobility led by the trainer. Focus on getting the heart rate down successively and to get a nice finish of this session.

Aerobic session – 55 minutes

Warm-up:

Balance: 5 – 7 minutes
- Training balance standing on one leg. Progress as the group evolves with more challenging moves at the same time. Balance training in combination with getting the whole body warm.

Jumping: 7 - 10 minutes
- Working on jumping: forward, backward, side, diagonal, up, down, one legged etc. Starting with jumping on floor level and progress with more challenging jumps as the group gets better.
- Combining the jumping with mobility focusing on the hip joint as active recovery.

Pre intervals: 6 minutes
- Cossack squat 20 s
- Jumping Jacks 10 s
- Bear crawl different directions 20 s
- High knees 10 s
- Rest 30 s

  1.5 minute rounds x 4

Interval aerobic training

12 stations: 18 – 26 minutes
- Rower (Concept 2 rower)
- Jump rope (Thick 400 g jump rope)
- Air bike (Xebex Air Bike)
- Rower (Concept 2 rower)
- Jump rope (Thick 400 g jump rope)
- Air bike (Xebex Air Bike)

- Step board side-jog (Standing over the board with the board between legs and jogging up and down)
- Half burpee walk over (Burpee without push-up and walking/jogging over a step board, facing the board and doing a new burpee)
- Running (Xebex Runner) /Trendmill /Shuttle run 10-15 m
- Bike (Concept 2 bike)
- Half burpee (Burpee without push-up)
- Shuttle run 10-15 m

Start at one exercise and work there for X seconds, rest X seconds and move on to the next exercise as a circuit. Extra rest time between rounds week 7-12.

Week 1-6:	75 s work time per exercise
	80-85 % of maximum heart rate
	30 s rest between exercises
	x 1 round
Week 7-12:	50 s work time per exercise
	85-90 % of maximum heart rate
	20 s rest between exercises
	x 2 rounds
	90 s rest between rounds

Cool down: 5-10 minutes

Easy mobility led by the trainer. Focus on getting the heart rate down successively and to get a nice finish of this session.

Mixed session 55 miuntes

Warm-up: 12 – 15 minutes

- Move through ankles, wrists, elbows, shoulders, knees, hips and the spine with some easy movement for 3-5 minutes.

- 2 minutes - Half of the group in conditioning machines, working from 65 % up to 80 % heart rate.
- 2 minutes – The other half of the group is led by the trainer, doing: Squats, jog on the spot, down-up dog, side plank, standing windmill for 20-30 s/exercise.

Then, they switch places. x 2 rounds (in total, 8 minutes of work)

Circuit interval training

12 different exercises: 26 minutes

- Walking lunges
- Push-up
- Russian twist
- Box step up/Box jump
- Plank walk out
- Sumo deadlift high pull with kettlebell

- Mountain climber
- Thruster with slamball
- Sideplank 5 s/side
- Burpee
- Step board jog
- Jumping pull-ups/Squat pullup

Start at one exercise and work there for X seconds, rest X seconds and move on to the next exercise as a circuit. Extra rest time between rounds.

Week 1-6:	35 s work time per exercise 25 s rest between exercises x 2 rounds 2 min rest between rounds
Week 7-12:	45 s work time per exercise 15 s rest between exercises x 2 rounds 90 s rest between rounds

Cool down: 5-10 minutes

Easy mobility led by the trainer. Focus on getting the heart rate down successively and to get a nice finish of this session.

Round off 2 minutes

A very short summary of today's session and coming exercises along with a refreshing drink e.g. smoothie.

Leisure plan

Leisure intervention plan for the leisure activity intervention in "Randomised controlled trial of vigorous aerobic group exercise versus leisure group activities for mild to moderate depression in adolescents".

Leisure schedules

Mondays 15:30 – 16:35
Wednesdays 15:30 – 16:35
Thursdays 15:30 – 16:35

Reminders

Text messages (sms) are sent to all participants earlier the same day before group sessions. The messages can but need not be replied. The participants can text or call the group leader if they are hesitant to show up to the group session. The group leader will be available 15 minutes before session to make sure the group sessions start on time.

Check-in, 3-5 minutes

Check-in together where participants share how they are doing and some recent events. Participants are prompted to suggest which game/activity to engage in and group leader makes the choice.

Snacks

The leader provides fruit, sandwich and juice after check-in.

Activities, 50 minutes

Games

Playing games in teams. For example card games, "Skippo", "Lenga", "Yatzy", " Ticket to ride".

Optional group activities

Painting or drawing together.

Round off, 5 minutes

Summing up together to end the group session. Participants share how they experienced the session. Group leader gives feedback and validates behaviours and emotional states but do not encourage behaviour change beyond group sessions.

Instructions to group leaders

Rational:

The group activity is intended to provide activities with peers and a supportive environment. Interventions that resemble cognitive behavioural therapy are to be avoided.

Do this:

- Ask the participants about how they are doing and how life is going
- Listen
- Validate feelings
- If someone gets sad – validate and listen, but don´t give advice or solutions
- Focus on the leisure activities for the session and choose topics associated to them

Don't do this:

- Do not encourage activities beyond sessions (no behavioural activation)
- Do not give advice on how to cope with depression
- Do not engage in problem solving
- Do not discuss treatment of depression but, if requested, give short answers about what might be helpful such as antidepressant medication, keep up daily routines with sleep, school and meals, be active, exercise and avoid alcohol and drugs.

Interview guides for qualitative analysis

in "Randomised controlled trial of vigorous aerobic group exercise versus leisure group activities for mild to moderate depression in adolescents".

1. Guide for interviewing participants

1. What is health for you?
    a. How do you perceive your health?
    b. What do you do to maintain / promote your health?
    c. How does exercise (or leisure activites) affect your health?
2. What does the term lifestyle mean to you?
    a. How would you describe your lifestyle?
    b. How do you feel your lifestyle affects your health?
3. How does the training (or leisure activites) affect
    a. Your lifestyle?
    b. Your habits?
    c. Your physical activity?
    d. Your diet / eating habits / cravings?
    e. Your sleep?
    f. Your fatigue?
    g. Your well-being?
    h. Your feelings of uneasiness?
    i. Your feelings of stress?
4. How do you estimate that your life at home is affected by the training (or the leisure activites)?
    a. Family
    b. Activity / rest

5. How do you estimate that the training (or the leisure activites) affects:
    a. Life at school?
    b. School results?
    c. Socializing with friends at school?
6. How do you estimate that your leisure time is affected by the training (or leisure the activites)?
    a. Leisure activities?
    b. Friends?
7. How do you estimate that the training (or the leisure activites) affects: *(Further in-depth questions based on the previous qualitative study)*
    a. Your commitment to different things?
        i. Your joy?
        ii. Your energy?
        iii. Your belief in the future?
    b. Your feeling of being in control of your life and your illness?
        i. Your self-confidence?
        ii. A security and a calm?
    c. Your sense of participation
        i. A balance in life?
        ii. A structure in everyday life?

Follow-up probes will be used to encourage the participants to provide more in-depth information by asking them: “Please tell me more” or “How do you mean?” or "What do you have in mind when you say ...?"

2. Guide for interviewing parents to participants in exercise group

1. What is health for your child?
2. What does exercise mean for your child?
3. Do you estimate that the training has led to any changes? How?
4. How do you estimate that group training has affected your child's depression?
5. How do you estimate that group training has affected your child's life at home?
6. How do you estimate that group training has affected studies for your child?
7. How do you estimate that your child's leisure time has been affected by group training?
8. What helped your child stick to the training?
9. What do you think has helped your child the most or been the best when it comes to group training?
10. How did your child experience the intensity of the training?
11. Do you estimate that the training in the training group has affected your child's self-confidence?
12. Do you estimate that the training in the training group has affected your child's balance in life?
13. Do you estimate that the training in the training group has affected your child's structure in everyday life?

3. Guide for interviewing parents to participants in leisure group

1. What is health for your child?
2. Do you estimate that the leisure group has led to any changes? How?
3. How do you estimate that group leisure activities has affected your child's depression?

4. How do you estimate that group leisure activities has affected your child's life at home?
5. How do you estimate that group leisure activities has affected studies for your child?
6. How do you estimate that your child's leisure time has been affected by group leisure activities?
7. What helped your child stick to the group?
8. What do you think has helped your child the most or been the best when it comes to group leisure activities?
9. Do you estimate that the training in the group leisure activities has affected your child's self-confidence?
10. Do you estimate that the group leisure activities has affected your child's balance in life?
11. Do you estimate that the group leisure activities has affected your child's structure in everyday life?

4. Guide for interviewing coaches to participants in exercise group

1. What is health for an adolescent with depression?
2. What does exercise mean for an adolescent with depression?
3. Do you estimate that the training has led to any changes? How?
4. How do you estimate that group training has affected participants depression?
5. How do you estimate that group training has affected participants life at home?
6. Did the participants explain how group training has affected their studies? How?
7. Did the participants explain how group training has affected their leisure time? How?
8. What helped participants stick to the training?

9. What do you think has helped the adolescents the most or been the best when it comes to group training?
10. How did the adolescents experience the intensity of the training?
11. Do you estimate that the training in the training group has affected the adolescents self-confidence?
12. Do you estimate that the training in the training group has affected the adolescents balance in life?
13. Do you estimate that the training in the training group has affected the adolescents structure in everyday life?

5. Guide for interviewing coaches to participants in leisure group

1. What is health for an adolescent with depression?
2. Do you estimate that the training has led to any changes? How?
3. How do you estimate that group leisure activities has affected participants depression?
4. How do you estimate that group leisure activities has affected participants life at home?
5. Did the participants explain how group leisure activities has affected their studies? How?
6. Did the participants explain how group leisure activities has affected their leisure time? How?

BÄSTA LIVSPLATSEN
Region Halland
Barn- och ungdomspsykiatriska kliniken

To patients ages 15 – 17 years

Consent to participate in "Randomised pilot study comparing physical exercise in groups with recreational activity in groups for adolescents with depression".

Consent refers to _____
(name, study code)

I have been able to explain and read the information about the study "Randomized pilot study where physical exercise in groups is compared with recreational activity in groups for adolescents with depression" and know that I can drop out of the study at any time and have my data removed and my blood tests discarded without having to give an explanation.

I agree to participate in the study¸ YES O
I agree that data about me is processed in the manner described in the research information¸ YES O
I agree that my samples are stored in a biobank in the way described in the research information¸ YES O
I agree that one of my parents will also be interviewed afterwards regarding my participation in the group activity YES O

_____ 202_-_ _-__

Patient _____
(signature)

Local study coordinator _____
(signature)

Adress: BUP, HSH, 30185 Halmstad **Besöksadress**: Fiskaregatan 8 **Tfn**: 035-13 17 61 **Fax**: 035-12 50 67
E-post: hakan.jarbin@regionhalland.se **Webb**: www.regionhalland.se **Org.nr**: 232100-0115

To guardians

Consent to participate in "Randomised pilot study comparing physical exercise in groups with recreational activity in groups for adolescents with depression".

Consent refers to _____
(name, study code)

I have read the attached information about the study "Randomised pilot study comparing physical exercise in groups with recreational activity in groups for adolescents with depression" and know that my child can cancel their participation at any time and have their data deleted and blood samples discarded without having to provide any explanation.

I agree that my child participates in the study¸ YES O
I agree that data about my child is processed in the way described in the research information¸ YES O
I agree that the samples of my child are stored in a biobank as described in the research information¸ YES O

Guardian(s) _____ _____
(signature) (signature)

_____ _____
(name printed) (name printed)

Local study coordinator _____
(signature)

_____
(name printed)

Adress: Region Halland, Box 517, 301 80 Halmstad . **Besöksadress**: Södra vägen 9 . **Tfn**: 035-13 48 00 . **Fax**: 035-13 54 44
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BÄSTA LIVSPLATSEN
Region Halland

Barn- och ungdomspsykiatriska kliniken

For you as a patient – research person information youth 13-14 years

Request to participate in the study "Randomised study comparing physical exercise in groups with recreational activity in groups for adolescents with depression"

Why do we want to do the study?

CAMHS now has a project in Halmstad, Stockholm, Kungsbacka and Lund with physical training or leisure activity in groups for young people with depression. We have already tried to treat young people who have been depressed for a long time with group training at a small gym. Most people got better in their depression but also contacts with friend and school improved. We don't know if it was the training itself or meeting and making something up with others that gave the effect. Now we want to compare the same physical training in groups with instead meeting in groups and playing games.

Who can participate?

Those who have been diagnosed with depression, do not yet exercise regularly and have not already gotten well or clearly better from the depression.

How does the study work?

The fact that the study is randomized means that you are drawn to either start working out in a group at the gym or to start meeting in groups to play games for twelve weeks. After the 12 weeks, those who have been drawn to play will have the opportunity to participate in the training in exactly the same way as the group that was originally drawn to training.

What happens before the group activities start?

If you're interested in participating, meet your local monitor (name here) to find out more. If you want to participate in the study, you will see a doctor for a simple medical examination, an assessment of depression and questions about other mental disorders, fill out a form about depression and provide a blood test. Then you get to test fitness and strength. The fitness is tested on a stationary exercise bike. You are allowed to cycle while your heart rate is measured, but the effort is moderate. You will also have to answer questions about depression and how it affects you via video calls on your mobile phone. That interview is being recorded. You then need to have a bankID installed on your phone or borrow your parent's phone with bankID for that moment.

Postadress: CAMHS, HSH, 30185 Halmstad **Besöksadress**: Vindrosvägen 4 **Tfn**: 035-13 17 61 **Fax**: 035-12 82 07
E-post: hakan.jarbin@regionhalland.se **Webb**: www.regionhalland.se **Org.nr**: 232100-0115

How does the treatment start?

After that, you will be drawn to either start with a playing group or with a training group. The training takes place at a small gym at Söndrumsvägen 29 at Rotorp and group leisure activities take place at CAMHS´ premises at Vindrosvägen 4 in Halmstad. (The correct location/address of the other centres is inserted). There will be three group trainings or group activities at 15:30 for 60 minutes each week for 12 weeks. The groups start in February 2022 and the last time is in May 2022. (Exact dates will be inserted and may differ slightly between centers). Groups will also start in February 2023 and the last time is in May 2023. During the training period, you get to meet your PT twice to talk about your training. Every other week, you are asked to fill in questions about depression during both the training and leisure period.

What happens after treatment?

After 12 weeks of training or leisure activity, your fitness and strength, blood sampling and interview via mobile phone for symptoms of depression are checked. Then you will also be interviewed via your mobile phone about how you have experienced the training or leisure activities.

After another 12 weeks, you will be interviewed again via mobile phone about symptoms of depression. If you first played games, you can then start training in a group.

One year after starting group activity in the study, your fitness and strength are checked, blood samples are taken and interviewed via mobile phone about symptoms of depression. Then you will also be interviewed via mobile phone about how you experienced the training and leisure activities.

How do parents participate?

Your parents may need to help so that you can get to physical tests, blood tests and doctor's appointments and to the training sessions or group of games. A parent will also be asked to fill in questions at the start of treatment, after 12 and 26 weeks and a year later. The questions are about whether they needed to be free because of your troubles for visits to CAMHS and how much you have been able to be at school. One of your parents is interviewed after the group activity and after a year about their view of what the activity has meant.

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Voluntarism

It is completely voluntary to participate and you can decline even if your parents want you to join. You can cancel at any time without affecting your treatment at CAMHS. You have the right to have all data and recorded interviews deleted as well as your blood samples discarded. You can also get other treatment, but during the training period you should not go to regular therapy sessions or change your medication yourself. If you get worse, you may see a doctor to get medication or other treatment.

What are the risks and benefits?

Physical tests and blood tests can be unpleasant. The training is done with a good PT so the risk of injury is small and the study is an opportunity to get started. If you continue to exercise after the study, you may not have to have another depression instead. Exercise also generally makes you healthier. It can also be good and counteract depression to make up stuff like games with others your age. If you feel significantly worse during the study, we will arrange for you to see a doctor quickly. You then tell the CAMHS employee who leads the group or asks your parents to do so. We can also see if your self-assessment has clearly deteriorated and then contact you and hear about the situation.

Data, sample management and privacy

The study includes filling out questionnaires before and after three months of group activity and one year later. You also fill out a questionnaire on your mobile every other week during the training/gaming period and every month for the rest of the year. Reminders come with automatic text messages. Everything we learn about you is treated with confidentiality. No outsider can access the answers so they can be connected to you. We store recorded interviews on a hard drive in a locked cabinet at CAMHS in Halmstad. The code key is available to monitor Henriette Nielsen and project manager Håkan Jarbin. The coded interview is printed by Secretary Anna Havner and then kept in a locked locker for ten years. These printouts are available to the research group, which will analyse the texts and encode the information based on a qualitative methodology. The group consists of Associate Professor Ingrid Larsson from Halmstad University and Doctoral Students Rebecca Mortazavi, CAMHS Halland and Rebecca Grudin, Karolinska Institutet. Blood samples stored pseudonymized (encoded) in a biobank in Region Halland to be investigated later for substances in the blood that may affect depression. You have the right to say no to the samples being saved. If you agree to the samples being saved, you have the right to later

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withdraw (undo) that consent. In this case, your samples will be discarded or de-identified. If you wish to regret consent, please contact Håkan Jarbin.

Region Halland is responsible for ensuring that your personal data is given the same protection as regular medical records. According to the EU Data Protection Regulation, you have the right to access the data about you handled in the study without paying, and if necessary to have any errors corrected. You can also request that information about you be deleted and that the processing of your personal data be restricted. If you would like to access the information, please contact Håkan Jarbin, CAMHS, Vindrosvägen 4, 30290 Halmstad, +46 (0)70-9162801 (secr) or via hakan.jarbin@regionhalland.se. Data Protection Officers can be reached at Region Halland, Operational Board Psychiatry 035-134800 or dataskydd@regionhalland.se. If you are dissatisfied with how your personal data is processed, you have the right to lodge a complaint with the Swedish Data Protection Authority, which is the supervisory authority. The application is approved by the Ethical Review Authority, the record number for the examination at the Ethical Review Authority is 2021 - 05307 - 01.

Compensation

You get an encouragement with a gift card of SEK 500 for each of the two occasions with interviews about the goal and about what you think about the group activity, physical tests and blood sampling that you do after the training period.

Halland, September 2021

Håkan Jarbin,
PhD, medical head and principal investigator
hakan.jarbin@regionhalland.se mobile phone 0706778006

For you as a patient – research person information youth 15-17 years

Request to participate in the study "Randomised study comparing physical exercise in groups with recreational activity in groups for adolescents with depression"

Why do we want to do the study?

CAMHS now has a project in Halmstad, Stockholm, Kungsbacka and Lund with physical training or leisure activity in groups for young people with depression. We have already tried to treat young people who have been depressed for a long time with group training at a small gym. Most people got better in their depression but also self-image, relationships and school results improved. We don't know if it was the training itself or meeting and making something up with others that gave the effect. Now we want to compare the same physical training in groups with instead meeting in groups and playing games.

Who can participate?
Those who have been diagnosed with depression, do not yet exercise regularly and have not already gotten well or clearly better from the depression.

How does the study work?

The fact that the study is randomised means that you are drawn to either start working out in a group at the gym or to start meeting in groups to play games for twelve weeks. After the 12 weeks, those who have been drawn to play will have the opportunity to participate in the training in exactly the same way as the group that was originally drawn to training.

What happens before the group activities start?

If you are interested in participating, you will meet the local monitor (name here) to find out more. If you want to participate in the study, you will see a doctor for a simple medical examination, an assessment of depression and questions about other mental disorders, fill out a form about depression and provide a blood test. Then you get to test fitness and strength. The fitness test is a so-called submaximal test on a stationary bike. You are allowed to cycle while your heart rate is measured, but the effort is moderate. You will also have to answer questions about depression and how it affects you via video calls on your

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mobile phone. That interview is being recorded. You then need to have a bankID installed on your phone or borrow your parent's phone with bankID for that moment.

How does the treatment start?

After that, you will be drawn to either start with a playing group or with a training group. The training takes place at a small gym at Söndrumsvägen 29 at Rotorp and group leisure activities take place at CAMHS's premises at Vindrosvägen 4 in Halmstad. (The correct location/address of the other centres is inserted after the contract is completed there). There will be three group activities at 3.30pm in 60 minutes each week for 12 weeks. The groups start in February 2022 and the last time is in May 2022. (Exact dates will be inserted and may differ slightly between centers) Groups will also start in February 2023 and the last time is in May 2023. During the training period, you get to meet your PT twice to talk about your training. Every other week, you are asked to fill in questions about depression during both the training and leisure period.

What happens after treatment?

After 12 weeks of training or leisure activity, your fitness and strength, blood sampling and interview via mobile phone are checked for symptoms of depression. Then you will also be interviewed via your mobile phone about how you have experienced the training or leisure activities. After another 12 weeks, you will be interviewed again via mobile phone about symptoms of depression.

If you first played games, you can then start training in a group.

One year after starting group activity in the study, your fitness and strength are checked, blood samples are taken and interviewed via mobile phone about symptoms of depression. Then you will also be interviewed via mobile phone about how you experienced the training and leisure activities. One year after starting group activity in the study, your fitness and strength are checked, blood samples are taken and interviewed via mobile phone about symptoms of depression. Then you will also be interviewed via mobile phone about how you experienced the training and leisure activities.

How do parents participate?

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Your parents may need to help so that you can get to physical tests, blood tests and doctor's appointments and to the training sessions or group of games. A parent will also be allowed to fill in questions at the start of treatment, after 12 and 26 weeks and a year later. The questions are about whether they needed to be free because of your troubles for visits to CAMHS and how much you have been able to be at school. One of your parents is interviewed after the group activity and after a year about their view of what the activity has meant.

Voluntarism

It is completely voluntary to participate and you can decline even if your parents want you to join. You can cancel at any time without affecting your treatment at CAMHS. You have the right to have all data and recorded interviews deleted as well as your blood samples discarded. You can also get other treatment, but during the training period you should not go to regular conversations or change your medication yourself. If you get worse, you may see a doctor to get medication or other treatment.

What are the risks and benefits?

Physical tests and blood tests can be unpleasant. The training is done with a good PT so the risk of injury is small and the study is a nice opportunity to get started. If your training continues after the study, you may not have to have another depression instead. Exercise also generally makes you healthier. It can also be good and counteract depression to come out and make up stuff like games with others your age. If you feel significantly worse during the study, we will arrange a quick medical assessment. You will then contact the CAMHS employee who is leading the group. We can also see if the self-assessment has clearly deteriorated and then contact you and hear about the situation.

Data, sample management and privacy

The study includes filling out questionnaires before and after three months of group activity and one year later. You also fill out a questionnaire on your mobile every other week during the training/gaming period and every month for the rest of the year. Reminders come with automatic text messages. Everything we learn about you is treated with confidentiality. No outsider can access the answers so they can be connected to you. We store recorded

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interviews on a hard drive in a locked cabinet at CAMHS in Halmstad. The code key is available to monitor Henriette Nielsen and prinicipal investigator Håkan Jarbin. The coded interview is typed by secretary Anna Havner and then kept in a locked locker for ten years. These printouts are available to the research group, which will analyse the texts and encode the information based on a qualitative methodology. The group consists of Associate Professor Ingrid Larsson from Halmstad University and Doctoral Students Rebecca Mortazavi, CAMHS Halland and Rebecca Grudin, Karolinska Institutet. The blood samples are stored pseudonymized (coded) at the biobank within Region Halland and later analyzed for biomarkers i.e. substances in the blood that can affect depression. You have the right to say no to the samples being saved. If you agree to the samples being saved, you have the right to later withdraw (undo) that consent. In this case, your samples will be discarded or de-identified. If you wish to regret consent, please contact Håkan Jarbin.

Region Halland is responsible for ensuring that your personal data is given the same protection as regular medical records. According to the EU Data Protection Regulation, you have the right to access the data about you handled in the study free of charge and, if necessary, to have any errors corrected. You can also request that data about you be deleted and that the processing of your personal data be restricted. If you want to access the data, please contact Håkan Jarbin, CAMHS, Vindrosvägen 4, 30290 Halmstad, 070-9162801 (secr) or via hakan.jarbin@regionhalland.se. Data Protection Officers can be reached at Region Halland, Operational Board Psychiatry 035-134800 or dataskydd@regionhalland.se. If you are dissatisfied with how your personal data is processed, you have the right to lodge a complaint with the Swedish Data Protection Authority, which is the supervisory authority.

The application is approved by the Ethical Review Authority, the record number for the examination at the Ethical Review Authority is 2021 - 05307 - 01.

Compensation

You get an encouragement with a gift card with SEK 500 for each of the two occasions with interviews about the goal and about what you think about the group activity, physical tests and blood sampling that you do after the training period.

Halland in September 2021

Håkan Jarbin,
PhD, medical head and principal investigator
hakan.jarbin@regionhalland.se mobile phone 0706778006

Adress: Region Halland, Box 517, 301 80 Halmstad . **Besöksadress**: Södra vägen 9 . **Tfn**: 035-13 48 00 . **Fax**: 035-13 54 44
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To guardians - research person information

Request to participate in the study "Randomized study comparing physical exercise in groups with recreational activity in groups for adolescents with depression"

Why do we want to carry out the study?

Within the framework of a multicenter study in Halmstad, Stockholm, Kungsbacka and Lund, physical training or leisure activity is offered in groups as a treatment for depression to young people 13-17 years of age. There is currently research to suggest that physical exercise has an effect comparable to conversational therapy or drug treatment. It is also known that social activation can be helpful in depression. We have conducted an open-label study in which 21 adolescents with persistent depression trained in groups. After treatment, depression but also self-image, relationships, school results and family life had improved, but we do not know if the social activity or exercise had an effect. In 2021, we also conducted a small pilot study where young people with depression either trained physically in groups or met to socialize and play games. With small improvements in the details of the study plan, we now want to take the next step and investigate whether physical exercise has an effect in addition to coming out and meeting other young people.

Target group

Participation in the study will be offered to young people who have been diagnosed with depression, do not yet exercise regularly and have not improved well or clearly after initial calls or other treatment at CAMHS.

How does the study work?

The fact that the study is randomised means that participants are drawn to either exercise in groups at a gym or to meet in groups to play games for twelve weeks. After the 12 weeks, those who were drawn for leisure activities will have the opportunity to participate in the physical training in exactly the same way as the group that was originally drawn to physical activity in a group. Those who were drawn for group training will not be offered extracurricular activities after completing training.

What happens before the group activities start?

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If your child is interested in participating, he/she and you will be invited to a meeting with the study's local monitor (name will be inserted later) for oral and written information about the study. Those who then agree to participate in the study then see a psychiatrist for an assessment of the diagnosis of depression and possibly other mental disorders. There will also be a simple medical examination and blood tests. The patient is allowed to fill out Self report questionnaires about symptoms. After that, there is the measurement of fitness and strength, blood sampling and an interview via mobile phone about the degree of symptoms of depression and how to manage to function in everyday life. That interview is being recorded. For security reasons, Region Halland's video calling platform Visiba care is used. Young people need to have bankID installed on their phone or to borrow a parent's phone with bankID.

How does the treatment start?

After that, you are drawn to either start with training or start with leisure activities. Both activities take place in groups with other adolescents with depression. For Halmstad, the training takes place at a small gym at Söndrumsvägen 29 at Rotorp and the leisure activity at CAMHS's premises at Vindrosvägen 4. (Location of other cities is added when contracts are signed). There will be three group trainings or group free time activities at 15:30 per week of 60 minutes with the first start February 2022 and then closure in May 2022 and starting February 2023 and then ending in May 2023 Each youth who trains will receive two individual conversations with PT for planning and monitoring the training. Forms about symptoms of depression and well-being are answered by youth via online link on the mobile phone every other week during both the training and leisure activity period.

What happens after treatment?

After 12 weeks of training or leisure activity, there is a renewed measurement of fitness and strength, blood sampling and interview via mobile phone about symptoms of depression. Then an interview of the youth is also conducted about how they have experienced the training or leisure activity. After another 12 weeks, a renewed interview takes place via mobile phone about symptoms of depression and questionnaires to parents about costs. Those who first had recreational activity in a group are then allowed to start with 12 weeks of training in a group and fill out forms about depression via mobile every two weeks.

How does the follow-up proceed up to one year after the start?

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Self report forms about symptoms of depression and well-being are answered by the youth on the mobile phone every month throughout the year. One year after the start, there is a renewed measurement of fitness, blood sampling and interview about depression and everyday function via mobile. Then a new interview of the youth will also be conducted about how they have experienced and been able to continue with the training.

How do parents participate?

Patients usually need support from parents to both get to and for the transport to the group activity on three occasions a week. Gradually, carpooling may be arranged for patients who have a similar itinerary to group activity. Parents need to participate in the diagnostic interview before the start of the study and be supportive so that the youth comes to the physical tests and blood tests. At the start of treatment, after 12 weeks, after 26 weeks and after one year via mobile phone, parents are offered to complete a questionnaire on health economics i.e. the presence of leave for the care of children, for visits to CAMHS and the current extent of schooling. Parents are offered to be interviewed via video link after group treatment and after one year about what group activity has meant and also to answer a survey question to what extent they have experienced any improvement in the well-being of their child.

Voluntarism

Participation is entirely voluntary. It is possible to discontinue group activities at any time without affecting other treatment. You also have the right to have all data and recorded interviews deleted and blood samples discarded. Patients have access to other treatment, but during the training period they should not go to regular conversations or change their medication themselves. Medication or adjusted medication may be offered in case of deterioration.

What are the risks?

There are few risks with the study. Measuring strength and fitness and blood sampling can cause slight discomfort at the moment. The training is done with close monitoring and thus little risk of injury. There are advantages to getting started with regular physical exercise under the supervision of a personal trainer. It increases the possibility of being free of depression. If exercise continues after the study, the risk of future episodes of depression may decrease. Exercise provides improved physical health. There are also advantages to

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participating in group leisure activities. Coming out and meeting other young people and participating in fun activities can counteract depression. If the patient should feel significantly worse during the course of the study, we will arrange a quick medical assessment. You then contact the CAMHS employee who leads the group. We can also see if the self-assessment has clearly deteriorated and then get in touch. During the course of the study, the usual patient insurance applies.

Data, sample management and privacy

The study includes filling out questionnaires before and after the group activity and one year after the start. Patients also complete a questionnaire every two weeks during the activity period and every month for the rest of the year. The questionnaires are filled in with a mobile phone and reminders come with automatic text messages. All data, such as social security numbers and questionnaire replies, are treated confidentially. Recorded interviews will be stored on a separate hard drive in a locked locker at the CAMHS clinic. The blood samples will be stored pseudonymized at the biobank within Region Halland (principal) within Halland Hospital, and later analyzed for inflammatory and neuroprotective biomarkers. You have the right to say no to the samples being saved. If you agree to the samples being saved, you have the right to later withdraw (undo) that consent. In this case, your child's samples will be discarded or de-identified. If you wish to regret consent, please contact Håkan Jarbin. The Ethical Review Authority has authorised the inclusion of the data collected in the study in a data-based research register. In the data register, the information is pseudonymized by a code, which is stored in a locked cabinet within CAMHS's premises at Vindrosvägen 4 in Halmstad. The code key is available to monitor Henriette Nielsen and project manager Håkan Jarbin. The coded interview is printed by Secretary Anna Havner and then kept in a locked locker for ten years. These printouts are available to the research group who will analyze the texts and encode the information based on a qualitative methodology. The group consists of Associate Professor Ingrid Larsson from Halmstad University and Doctoral Students Rebecca Mortazavi, CAMHS Halland and Rebecca Grudin, Karolinska Institutet. Thus, no outsider has the opportunity to access the answers in such a way that they can be linked to the person.

Region Halland is responsible for ensuring that personal data is given the same protection as ordinary medical records. According to the EU Data Protection Regulation, you have the right to access the data about your child handled in the study free of charge and, if necessary, to have any errors corrected. You can also request that data about your child be deleted and that the processing of your child's personal data be restricted. If you would like to access the

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information, please contact Håkan Jarbin, CAMHS, Vindrosvägen 4, 30290 Halmstad, +46 (0)70-9162801 (secr) or via hakan.jarbin@regionhalland.se. Data Protection Officers can be reached at Region Halland, Operational Board Psychiatry 035-134800 or dataskydd@regionhalland.se. If you are dissatisfied with how your child's personal data is processed, you have the right to lodge a complaint with the Swedish Data Protection Authority, which is the supervisory authority. The application is approved by the Ethical Review Authority, the record number for the examination at the Ethical Review Authority is 2021 - 05307 - 01.

Insurance and compensation

The usual patient insurance is valid for this study. There is no compensation for parents' or children's expenses for participation in the treatment, but the child receives an encouragement with a gift card of SEK 500 for each of the two occasions with physical tests, interview about symptoms and interview about how the group and the training have worked for them and blood sampling after the training period.

Halmstad in September 2021

Håkan Jarbin,
PhD, medical head and principal investigator
hakan.jarbin@regionhalland.se mobile phone 0706778006