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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

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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

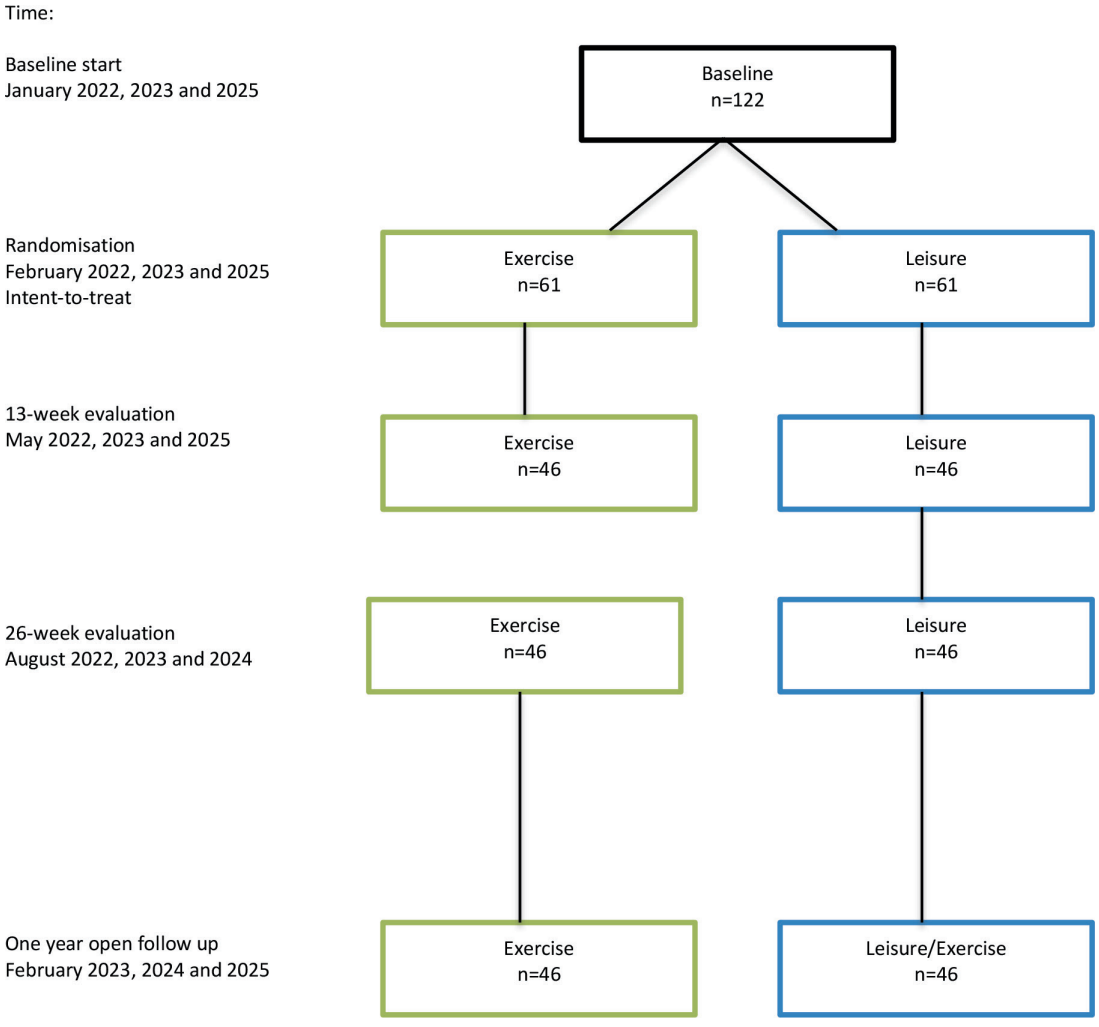

Figure 1 Time points for assessments in RCT and open phases. RCT, randomised controlled trial.

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.

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