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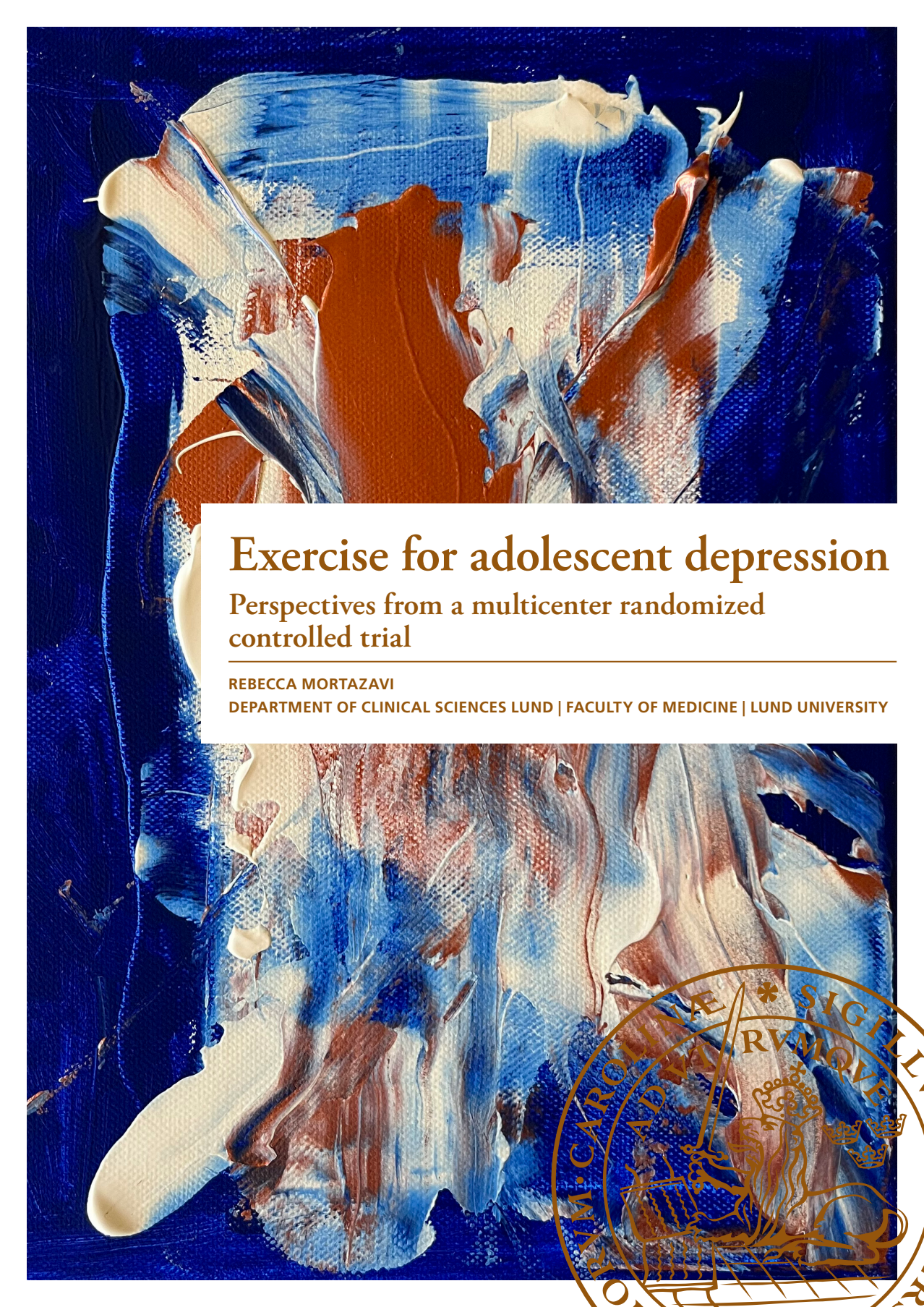
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Exercise for adolescent depression

Perspectives from a multicenter randomized controlled trial

REBECCA MORTAZAVI

DEPARTMENT OF CLINICAL SCIENCES LUND | FACULTY OF MEDICINE | LUND UNIVERSITY



Exercise for adolescent depression

Exercise for adolescent depression

Perspectives from a multicenter randomized controlled trial

Rebecca Mortazavi



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DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 2nd of October at 09.00 in Fullriggaren, Hallands Sjukhus, Halmstad.

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Title and subtitle: Exercise for adolescent depression – Perspectives from a multicenter randomized controlled trial

Abstract:

Background

Depression is common among adolescents, and available treatments with antidepressants and psychological treatments have small to moderate effects. Moreover, approximately one third of adolescents with depression do not respond to current treatments, highlighting the need for new treatment options. Exercise is recommended as a treatment for depression in adults and early studies show promising results also for adolescents, but the quality of the evidence is weak due to methodological limitations. The aim of this thesis is to compare group-based aerobic exercise with group-based leisure activities for adolescents with mild to moderate depression in a randomized controlled trial (RCT), using a sample recruited from regular child and adolescent mental health services. The thesis also includes qualitative studies of adolescents', parents', and healthcare professionals' experiences of the exercise intervention and analyses of how adolescents with depression understand health.

Methods

The thesis includes four studies. Studies I-II were based on the multicenter RCT. Study I presented the study protocol and Study II evaluated whether exercise was superior to leisure activities for adolescent depression. Study III included participants from a pilot study and used a qualitative latent content analysis to describe adolescents', parents', and healthcare professionals' experiences of the group exercise intervention. Study IV included participants from the pilot study and the multicenter RCT and used a phenomenographic approach to explore how adolescents with depression understand health.

Results

Group exercise (n=62) was not superior to group leisure activities (n=63) on the primary depression severity outcome, or any secondary outcomes. Among adolescents with $\geq 50\%$ attendance and no changes in antidepressant medications (n=75, 60%), the exercise group improved more in aerobic capacity. In post-hoc analyses, adolescents in the exercise group were also more often classified as responders and improved more on the core depression symptoms of irritability and sadness. Adolescents, parents, and healthcare professionals experienced group exercise for adolescent depression as promoting empowerment and engagement in everyday life. Adolescents' conceptualizations of health could be summarized into four metaphors: establishing sound routines, connecting to others, managing depression symptoms, and attaining inner drive.

Conclusion

Exercise was not more effective than leisure activities for adolescents with depression, although there were some indications of beneficial effects among those who adhered to the intervention. Exercise was experienced as promoting empowerment and engagement in everyday life and contributing to sound routines and connection to others, which were also described as important aspects of health among adolescents living with depression.

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Exercise for adolescent depression

Perspectives from a multicenter randomized controlled trial

Rebecca Mortazavi



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To Simon

Table of Contents

Abstract	10
List of papers	11
Sammanfattning på svenska	12
Overview of papers	15
Abbreviations	16
Introduction	19
Background	21
Depression	21
Treatments for adolescent depression	24
Health	27
Physical activity	28
Physical activity as a treatment for depression	30
Potential mechanisms of physical activity on depression	33
Rationale for the thesis	37
Aims	39
Methods	41
Randomized controlled trial (RCT) (Paper I-II)	41
Study design	41
Recruitment and participants	41
Intervention	42
Assessments	42
Outcome measures	45
Statistics	45
Qualitative content analysis approach (Paper III)	46
Recruitment, participants and intervention	47
Data collection	47
Data analysis	47
Phenomenographic approach (Paper IV)	48
Recruitment, participants and intervention	48

Data collection.....	48
Data analysis.....	49
Ethical considerations	49
Use of Artificial Intelligence (AI)	50
Results.....	51
Results in numbers - RCT (Papers I-II).....	51
Main findings.....	51
Post-hoc analyses.....	52
Harms	53
Qualitative experiences of exercise for depression (Paper III)	53
Main findings.....	53
Qualitative understanding of health among adolescents with depression (Paper IV).....	55
Main findings.....	55
Discussion	57
Is exercise effective for adolescent depression? (Paper I-II).....	57
Exercise was not superior to leisure activities.....	57
Both intervention groups improved over time.....	59
Exercise compared to available treatments for depression.....	60
Strengths and limitations of the RCT	61
Does exercise bring added values to depressed adolescents? (Paper III).....	63
Do we measure the right thing? (Paper IV).....	64
Strengths and limitations – qualitative studies (Paper III-IV)	66
Advantages and disadvantages with exercise as a treatment.....	67
Conclusion	69
Planned additional research within the project.....	69
Recommendations for future research.....	70
Acknowledgements	71
References	73

Abstract

Background: Depression is common among adolescents, and available treatments with antidepressants and psychological treatments have small to moderate effects. Moreover, approximately one third of adolescents with depression do not respond to current treatments, highlighting the need for new treatment options. Exercise is recommended as a treatment for depression in adults and early studies show promising results also for adolescents, but the quality of the evidence is weak due to methodological limitations. The aim of this thesis is to compare group-based aerobic exercise with group-based leisure activities for adolescents with mild to moderate depression in a randomized controlled trial (RCT), using a sample recruited from regular child and adolescent mental health services. The thesis also includes qualitative studies of adolescents', parents', and healthcare professionals' experiences of the exercise intervention and analyses of how adolescents with depression understand health.

Methods: The thesis includes four studies. Studies I-II were based on the multicenter RCT. Study I presented the study protocol and Study II evaluated whether exercise was superior to leisure activities for adolescent depression. Study III included participants from a pilot study and used a qualitative latent content analysis to describe adolescents', parents', and healthcare professionals' experiences of the group exercise intervention. Study IV included participants from the pilot study and the multicenter RCT and used a phenomenographic approach to explore how adolescents with depression understand health.

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Conclusion: Exercise was not more effective than leisure activities for adolescents with depression, although there were some indications of beneficial effects among those who adhered to the intervention. Exercise was experienced as promoting empowerment and engagement in everyday life and contributing to sound routines and connection to others, which were also described as important aspects of health among adolescents living with depression.

List of papers

Paper I

Mortazavi R, Lalouni M, Grudin R, Serlachius E, Sundberg CJ, Norrbom J, Larsson I, Haglund E, Ivarsson A, Lenhard F, Cronqvist T, Ingemarsson K, Mårzell Å, Rask O, Jarbin H. 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. *BMJ Open*. 2022 Jul 12;12(7):e060159.

Paper II

Mortazavi R, Cronqvist T, Mårzell Å, Ingemarsson K, Rask O, Ivarsson A, Serlachius E, Cervin M, Lalouni M, Jarbin H. Exercise versus leisure activities for adolescents with depression: a multicentre randomised controlled trial. *Submitted*.

Paper III

Mortazavi R, Grudin R, Jarbin H, Larsson I. Empowered and engaged: Group exercise for adolescent depression - perspectives from adolescents, parents and healthcare professionals. *SAGE Open Med*. 2024 Feb 3;12:20503121231225340.

Paper IV

Danielsson K, Ahlborg M, **Mortazavi R**, Jarbin H, Larsson I. Depression in adolescence and the understanding of health-A phenomenographic study. *PLoS One*. 2025 Jan 27;20(1):e0318061.

Sammanfattning på svenska

Bakgrund

Depression är ett tillstånd som är karakteriserat av ett ihållande sänkt stämningsläge, minskad lust för vardagliga aktiviteter (anhedoni), eller hos barn och ungdomar en ihållande irritabilitet som varar i minst två veckor. Depression följs av andra symptom så som minskad energi, förändrad aptit, sömnsvårigheter, koncentrationssvårigheter, känslor av värdelöshet, psykomotorisk oro eller långsamhet, eller tankar på döden. Depression är vanligt i tonåren och flickor är mer drabbade än pojkar. Dagens behandlingar mot depression i form av antidepressiva läkemedel eller psykoterapi har begränsad effekt och upp till en tredjedel av ungdomar med depression svarar inte på behandlingen. Det finns därför ett behov av nya behandlingar och träning har visat sig vara ett alternativ och är rekommenderat som behandling för lindrig till medelsvår depression hos vuxna. Studier visar på att träning också kan vara effektivt mot depression hos ungdomar, men dessa studier har metodbrister som gör att resultaten har hög risk för bias och att det därmed är för tidigt att rekommendera träning som behandling.

Syfte

Syftet med denna avhandling är att jämföra aerob gruppträning med lugna gruppaktiviteter för ungdomar med lindrig till medelsvår depression genom en randomiserad kontrollerad studie med ett kliniskt urval av deltagare. Avhandlingen innehåller också kvalitativa studier om hur ungdomar med depression, deras föräldrar och personal inom barn och ungdomspsykiatri (BUP) upplevde träningsinterventionen, samt hur ungdomar med depression uppfattar hälsa.

Metod

Avhandlingen innehåller fyra studier. Studie I och II baserar sig på en multicenter randomiserad kontrollerad studie. Studie I består av studieprotokollet för studien. Studie II jämför aerob gruppträning med lugna gruppaktiviteter för 125 ungdomar med depression i åldern 13-17 år. Studie III är en kvalitativ studie med deltagare från en pilotstudie, som föregick multicenterstudien, där vi använde en kvalitativ innehållsanalys för att utforska ungdomars, föräldrars och BUP-personals upplevelser av träning som behandling mot ungdomsdepression. Studie IV är en kvalitativ studie med deltagare från både pilotstudien och multicenterstudien, där vi genom en deskriptiv kvalitativ design utforskade på vilka olika sätt hälsa kan upplevas för ungdomar med depression.

Resultat

Träning i grupp var inte mer effektivt än lugna aktiviteter i grupp avseende förbättring i depressionsgrad för ungdomar med lindrig till medelsvår depression i ett kliniskt urval. Träning var inte heller mer effektivt för sekundära mått så som

depressionens svårighetsgrad, förbättringsgrad, funktionsnivå, självskattade depressionssymptom eller självskattat välmående. I en analys på de deltagare som deltog i minst hälften av sessionerna och hade stabil antidepressiv medicinering, förbättrades träningsgruppen mer vad gäller kondition. De förbättrades också mer avseende nedstämdhet och irritabilitet och de svarade oftare på behandlingen i post-hoc analyser. Kvalitativa analyser visade att ungdomar, föräldrar och BUP-personal upplevde att träning i grupp främjade egenmakt och engagemang i vardagen. Ungdomarna upplevde sin hälsa på olika sätt, vilket tolkades i fyra metaforer: att etablera sunda rutiner, att knyta an till andra, att hantera depressionssymtom och att uppnå inre drivkraft.

Slutsatser

Träning i grupp var inte mer effektivt än lugna aktiviteter i grupp för ungdomar med lindrig till medelsvår depression, men bland de som hade högre närvaro svarade ungdomar i träningsgruppen oftare på behandlingen och deras nedstämdhet och irritabilitet minskade. Träning främjade egenmakt och engagemang i vardagen och bidrog till sunda rutiner och kontakt med andra, vilket beskrivs som viktiga aspekter av hälsa bland ungdomar som lever med depression.

Overview of papers

Table 1. Overview of papers

Paper I	
Aim	Rationale for the study
Methods	Rationale for methods used in the multicenter RCT on exercise versus leisure activities for adolescents with depression
Data source	-
Main findings	-
Paper II	
Aim	Determine if exercise is more effective than leisure activities for adolescents with depression
Methods	RCT
Data source	Multicenter RCT, n=125
Main findings	No statistically significant between-group differences were observed for the primary outcome (CDRS-R) or any secondary outcomes in the intention to treat analysis. In the per protocol analysis for adolescents who attended $\geq 50\%$ of sessions and with no new or increased dosage of antidepressants (n=75), the exercise group improved more in aerobic capacity, were more often classified as treatment responders and improved more on items sadness and irritability in post hoc analyses.
Paper III	
Aim	Explore experiences from adolescents, parents, and healthcare professionals from an exercise intervention for adolescents with depression
Methods	Latent qualitative content analysis
Data source	Pilot RCT, n=19
Main findings	Exercise for adolescent depression promotes empowerment and engagement in everyday life: 1) Exercise alleviates depressive symptoms, 2) Exercise contributes to balance in life, 3) Exercise promotes self-esteem
Paper IV	
Aim	Explore how adolescents with depression understand health
Methods	Descriptive qualitative design with a phenomenographic approach
Data source	Pilot RCT + Multicenter RCT (cohort 1), n=33
Main findings	Metaphors describing the understanding of health: 1) Establishing sound routines, 2) Connecting to others, 3) Managing depression symptoms, 4) Attaining inner drive

Abbreviations

5-HT	5-hydroxytryptamine (Serotonin)
ADHD	Attention-Deficit/Hyperactivity Disorder
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
BPI	Brief Psychosocial Intervention
CAMHS	Child and Adolescent Mental Health Services
CBT	Cognitive Behavioral Therapy
CDRS-R	Children's Depression Rating Scale-Revised
C-GAS	Children's Global Assessment Scale
CGI-I	Clinical Global Impression-Improvement
CGI-S	Clinical Global Impression-Severity
CRP	C-reactive Protein
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECT	Electroconvulsive Therapy
GABA	Gamma-aminobutyric acid
HP	Healthcare Professional
HPA-axis	Hypothalamic Pituitary Adrenal-Axis
HRmax	Maximum Heart Rate
HRV	Heart Rate Variability
IGF-1	Insulin-like Growth Factor 1
IL-1	Interleukin-1
IL-6	Interleukin-6
IPT	Interpersonal Therapy
ITT	Intention To Treat
K-SADS-PL	Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version
KYNA	Kynurenic Acid
LMM	Linear Mixed-effect Models

MDD	Major Depressive Disorder
NEQ	Negative Effects Questionnaire
NICE	National Institute for Health and Care Excellence
NMDA	N-methyl-D-aspartate
NNT	Number Needed to Treat
ORS	Outcome Rating Scale
PP	Per Protocol
PTSD	Post-Traumatic Stress Disorder
QIDS-A ₁₇ -SR	Quick Inventory of Depressive Symptomatology Adolescent version-17 Self Report
RCT	Randomized Controlled Trial
SAE	Serious Adverse Event
sIL-2R	Soluble Interleukin-2 Receptor
SMD	Standardized Mean Difference
SSRI	Selective Serotonin Reuptake Inhibitor
TMS	Transcranial Magnetic Stimulation
TNF- α	Tumor Necrosis Factor-Alpha
VEGF	Vascular Endothelial Growth Factor
VO ₂ max	Maximal Volume of Oxygen Uptake
WHO	World Health Organization

Introduction

Depression is common among adolescents and the prevalence is increasing, especially among girls.^{1,2} Adolescent depression is characterized by persistent symptoms of sadness, irritability, or diminished interest or pleasure.³ Depression is a leading cause of disease burden among adolescents worldwide⁴ and can lead to educational impairments,⁵ substance misuse, self-harm,⁶ and suicide.⁵ It is also a risk factor for early cardiovascular disease and atherosclerosis.⁷

Available evidence-based treatments for adolescents with depression, such as psychological treatments or antidepressants, have modest effects.^{8,9} One third of adolescents with depression will not benefit from standard treatments¹⁰ and novel treatments are needed.

Physical activity improves mental health in adults¹¹ and is recommended as a standalone treatment for mild to moderate depression in adults.^{12,13} Available studies on physical activity for adolescent depression have several methodological limitations and physical activity is not yet recommended as a treatment for adolescent depression due to insufficient evidence.¹³⁻¹⁵

The aim of this thesis is to compare group-based aerobic exercise with group-based leisure activities for adolescents with mild to moderate depression in a randomized controlled trial with a clinical sample recruited from routine care. By comparing exercise with an active control group in a population with mild to moderate depression and substantial comorbidity, it will contribute to the understanding of whether aerobic exercise is effective for adolescent depression in a child and adolescent mental health outpatient setting. The thesis will also evaluate perspectives on health and depression and experiences from participating in the exercise intervention.

Background

Depression

Clinical presentation

Depression varies in degrees of symptoms and impairment and is sometimes described as a spectrum; from normal fluctuations of low mood, to subthreshold depression (not meeting criteria for a diagnosis), to major depressive disorder (MDD).¹⁶ MDD is characterized by at least one of the core symptoms of sadness (or irritability for children and adolescents) or diminished interest or pleasure (anhedonia), along with associated symptoms (Table 2). Five or more symptoms need to be fulfilled during a period of at least two weeks together with either clinically significant distress and/or a loss of functioning to meet criteria for an MDD.³ The severity can be graded into mild, moderate or severe MDD, based on number of criteria, severity of symptoms and degree of functional impairment.³ Furthermore, the Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 add specifiers such as depression with anxious distress, with melancholic features, and with seasonal pattern.³

Table 2. Abbreviated diagnostic criteria for MDD according to DSM-5.³

Diagnostic criteria for MDD	
A.	Five or more of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. 1. Depressed mood (or irritable mood in children and adolescents) 2. Diminished interest or pleasure (anhedonia) 3. Change in appetite or weight 4. Insomnia or hypersomnia 5. Psychomotor agitation or retardation 6. Fatigue or loss of energy 7. Feelings of worthlessness or inappropriate guilt 8. Diminished ability to think or concentrate 9. Recurrent thoughts on death
B.	The symptoms cause clinical distress or impairment of functioning
C.	The episode is not attributable to the psychological effects of a substance or another medical condition.
D.	Not better explained by psychotic disorders
E.	There has never been a manic or hypomanic episode

Epidemiology

Depression affects people across all ages. The prevalence is about 1% among children under the age of 13, with no difference between genders.¹⁷ Depression becomes substantially more common in adolescents, with a 12-month prevalence of around 11%, and girls are more affected than boys.^{2,16} Adolescence is commonly defined as the period between 10 and 19 years of age.¹⁸ However, this thesis will focus on adolescents aged 13-17, reflecting the age range of study participants.

The prevalence of depressive symptoms¹⁹ and diagnosed depression among adolescents has increased in the past decades and especially among girls.^{1,2,16} The one year prevalence of depression increased from about 8% to 11-15%,^{1,2} while not all studies identify an increase.²⁰ It is unclear whether an increase is due to sociocultural changes or improved identification.¹⁵ Depressive symptoms continued to increase in both children, adolescents^{21,22} and adults²³ during the Covid-19 pandemic. Recent prevalence rates indicate that 7-15% of adolescents experiences depression each year^{1,2,24,25} and 20% before adulthood.^{10,26}

Symptom presentation and etiology

MDD is more common among adolescents with a family history of depression¹⁶ and is thought to be caused by both genetic and environmental factors.²⁶ The onset of a depression can be triggered by stressors such as bullying, conflicts, and other stressful life events.^{16,26}

Besides depression being more common in girls than boys after puberty, it is also more common among older adolescents and among those with lower socioeconomic status, those with special educational needs, and those suffering from chronic health problems.¹⁶

Depression is a heterogeneous condition and may be viewed as a construct involving changes in mood, behavior and physiological parameters.²⁷ Depression in childhood is more heterogeneous than adult depression.²⁶ Since MDD is a diagnosis based on a combination of diagnostic criteria, it allows for different combinations of symptoms and presentations. Over one thousand unique symptom profiles were identified from a large depression study.²⁸ The agreement between two clinicians on a depression diagnosis is lower than for other diagnoses, implying the difficulty of capturing the condition.²⁹ Heterogeneity in symptoms and in etiological aspects indicate that treatment response might also be heterogeneous.³⁰ It is suggested that for some, biological vulnerability due to family history is the main vulnerability leading to depression, while it is mainly environmental factors that triggers depression in others.³⁰ Proposed pathophysiological mechanisms include involvement of biomarkers such as brain-derived neurotrophic factor (BDNF),³¹ serotonin,³² and low grade inflammation.³³ Presently, there are no definite depression subcategories, but studies on molecules, neuroimaging and new treatments are adding knowledge to the research field.

‘All happiness is alike, but each pain is painful in its own way’

Haruki Murakami, 1Q84, 2012

(A rephrased interpretation of Leo Tolstoy’s Anna Karenina)

Comorbidities

Adolescents with MDD often suffer from other psychiatric conditions, and about half meet criteria for two or more comorbidities.²⁶ The most common comorbidities are anxiety disorders, attention-deficit/hyperactivity disorder (ADHD), behavior disorders, and substance use disorders.^{5,26} Comorbidities are more common in severe MDD and is associated with poorer long-term outcome and more severe impairment.⁵

Burden and course

Depressive disorders are a main cause of morbidity and disease burden in adolescents world-wide.^{4,34} Beyond the psychological suffering, depression is also associated with impaired educational achievements,^{5,26} increased risk of self-harm,⁶ alcohol, and drug use.^{16,26} Depression is also a major risk factor for suicide among adolescents^{5,16,35} and suicide is one of the most common causes of adolescent death.^{10,35} Depression also affects the physical health of adolescents and is a risk factor for development of atherosclerosis,⁷ early cardiovascular disease,^{7,16} and obesity.¹⁶ Onset of depression in adolescence is associated with persistence into adulthood and a larger degree of severity,¹⁰ such as a chronic course,²⁶ recurrent depressions later in life,^{16,26} and a higher risk of bipolar disorder.^{16,26}

About one third of adolescents with depression will not improve in spite of adequate treatment trials with antidepressants and psychotherapy, sometimes referred to as treatment resistant depression.¹⁰ An even larger proportion achieve only a partial response, meaning they remain depressed despite some improvement after treatment.^{36,37} Thus, there is a clear need for new treatment options for adolescent depression.¹⁵

Lived experiences of depression

Experiences from living with depression in adolescence are identified from qualitative studies, with themes involving feelings of misery, anger, a bleak view of life, isolation, and with a negative impact on education.³⁸ A qualitative systematic review identified adolescents experiencing depression as social disconnection, overwhelming distress, altered sense of self, low mood, negative outlook, anger, fear, and fatigue.³⁹ Another study described adolescents struggling to make sense of their situation.⁴⁰ Notable is that many studies identified lived experiences such as anger and isolation that are not diagnostic criteria for depression, and further emphasize the complexity of capturing the heterogeneity of depression.^{38,39,41}

Treatments for adolescent depression

The recommended psychological and pharmacological treatments for adolescent depression have, unfortunately, only modest effects. The evidence mainly relies on four large studies: the Treatment of Adolescents with Depression Study (TADS)³⁶ and the Treatment of Resistant Depression In Adolescents (TORDIA)³⁷, both conducted in the United States, and the Adolescent Depression Antidepressants and Psychotherapy Trial (ADAPT),⁴² and the Improving Mood with Psychoanalytic and Cognitive Therapies (IMPACT),⁴³ conducted in the United Kingdom.

For mild MDD in adolescents, international guidelines often recommend a stepped-care approach, with initial supportive interventions,^{15,44} followed by psychological treatment if needed.⁴⁴ For moderate to severe MDD, psychological treatment, in the form of cognitive behavioral therapy (CBT) or interpersonal therapy (IPT), and/or antidepressants are recommended.^{15,26,44} The British NICE guideline recommends psychological treatment with CBT or IPT for four to six weeks followed by antidepressants, primarily fluoxetine, if there is insufficient clinical improvement or if depression remains moderate to severe,⁴⁴ while the guideline from American Academy of Child and Adolescent Psychiatry states that psychological treatment with CBT or IPT, or fluoxetine can be used in no specific order.¹⁵

Psychological treatments

CBT includes behavioral activation and cognitive restructuring. Behavioral activation aims to increase engagement in meaningful and rewarding activities and reduce withdrawal and avoidance, with the long-term goal of improving mood and daily functioning. Cognitive restructuring is a process in which the therapist helps the patient become aware of negative cognitive distortions and the patient learns to identify, challenge, and modify negative thoughts.¹⁵

In IPT, interpersonal relationships are the primary focus and are thought to contribute to the onset or maintenance of the depression. The goals of IPT are to increase social support, reduce interpersonal stress, improve processing of emotions, and strengthen social functioning.¹⁵

Psychotherapies generally have small effect sizes for adolescent depression compared to control conditions.^{9,45} Meta-analyses suggest effect sizes ranging from SMD 0.05 to 0.41 for CBT versus controls.⁴⁶⁻⁴⁸ In the landmark TADS study, CBT was not superior to pill placebo.³⁶

Comparative evidence suggests that CBT and IPT are among the better-supported psychotherapies for adolescent depression, but there is no clear evidence that one is consistently superior to the other. In one network meta-analysis, IPT showed a larger estimated effect than CBT when each was compared with psychological control conditions,⁴⁸ although this should not be interpreted as evidence of superiority in

direct comparison. Other studies and meta-analyses have not found consistent differences between CBT and IPT.^{45,49} This uncertainty is also reflected in the large UK IMPACT trial, where CBT and short-term psychoanalytic psychotherapy were not superior to a brief psychosocial intervention among adolescents treated in specialist services.⁴³ Overall, psychological therapies can be helpful, but a substantial proportion of adolescents with depression do not respond; one meta-analysis estimated that more than 60% of youth receiving psychological treatment did not meet criteria for treatment response.⁵⁰

Qualitative studies with adolescents receiving CBT have emphasized the importance of the relationship with the therapist, adapting CBT to the adolescent's specific difficulties, using check-ins during therapy, and considering how depressive symptoms can affect the therapeutic process.⁵¹ The importance of the therapeutic relationship has also been highlighted in other qualitative studies on CBT for adolescent depression.^{52,53} One of these studies also showed that attending and engaging in CBT sessions may be challenging for some adolescents.⁵²

Pharmacological treatments

The pharmacological treatment with antidepressants for adolescent depression consists mainly of selective serotonin reuptake inhibitors (SSRIs).^{14,54} Fluoxetine has shown most consistent effects^{48,55} and is the preferred antidepressant for moderate to severe MDD today.^{14,15,44,54} Serotonin, also known as 5-hydroxytryptamine (5-HT), is important in regulation of fear and stress,¹⁵ and involved in the pathophysiology and treatment of mood disorders.⁵⁶ The proposed mechanism of an SSRI is to inhibit the pre-synaptic reuptake of serotonin in the brain, which increases the levels of serotonin in the synaptic cleft between two neurons.^{15,56} Increased levels of serotonin lead to downregulation (reduced number of receptors) or desensitization (reduced sensitivity) of serotonin autoreceptors (5-HT_{1A}).^{15,56} The 5-HT_{1A} autoreceptors responds to serotonin by inhibiting the firing of serotonergic neurons.⁵⁷ Thus, the downregulation and desensitization of these autoreceptors is thought to increase the firing of serotonergic neurons and serotonin release with an increased serotonergic signaling.^{15,57} These adaptive changes take time and may explain the delayed clinical effect.^{15,56} Besides downregulation of serotonin receptors, SSRIs also increase synthesis of neurotrophic factors such as BDNF.⁵⁶ It is still unknown how SSRI affects the developing brain and much of what we know are based on adult studies.⁵⁸ One downside with SSRIs is potential serious side effects, such as agitation, hypomania, increased suicidal thoughts, suicidal behavior, and the serotonin syndrome.¹⁵ SSRIs are also believed to reduce growth in children and adolescents, especially during puberty.^{59,60}

Antidepressants have small to moderate effect sizes ranging from SMD 0.12 to 0.51^{8,48,55,61} compared to placebo for the treatment of adolescent depression. The combination of antidepressants and psychological treatment is often recommended,^{13,15,44,62} but it is still unclear whether combination treatment is

superior to antidepressants or psychological treatment alone.^{36,42,62,63} For adult depression, a network meta-analysis found that combination therapy was more effective than either treatment alone.⁶⁴ However, for adolescents, a Cochrane review found no significant differences between antidepressants, psychological treatment, or their combination,⁶² while another large meta-analysis found that the combination of CBT and fluoxetine was more effective than CBT alone, but not compared to fluoxetine alone.⁴⁸ TADS found combination therapy superior to either treatment (CBT and SSRI) alone.³⁶ However, the ADAPT study, recruiting more severely depressed adolescents, did not reveal any benefit of adding CBT to SSRI,⁴² in line with another RCT finding no further effect of combining SSRI and CBT.⁶⁵ Thus, currently, there is no clear consensus on whether the combination of antidepressants and psychological treatment is superior to either treatment alone.

In qualitative studies, adolescents have described several negative connotations of SSRIs such as ‘perceived threat to autonomy’, ‘a sign of severity’, ‘a support, not a solution’, and ‘an ongoing process of trial and error’.⁶⁶ Adolescents also describe that SSRI was not a quick fix, but could give tools to improve mental health, that the net outcomes of symptoms needs to be weighed against side-effects, that taking SSRI confers a social stigma, and is a proof of a mental disorder.⁵⁸ Adults have described emotional blunting, reduction of both positive and negative emotions, feeling less like oneself, and having difficulties to stop treatment.^{67,68}

Swedish guidelines

In Sweden, the recommended treatment for adolescent depression starts with a brief psychosocial intervention (BPI), regardless of depression severity.^{13,14,60} BPI includes giving the family information about the depression diagnosis and a rationale for how difficulties arose and are maintained.⁶⁰ BPI also focuses on increasing the patient’s level of activity, emphasizing routines for eating and sleeping. Furthermore, BPI addresses family and school stress, such as relationship issues, too high demands in school, or bullying.^{13,43,60}

For mild to moderate MDD, BPI continues for four to eight weeks.^{14,60} If BPI is not sufficient, treatment continues with CBT or IPT for mild MDD.^{13,14,60} For moderate MDD, if BPI is not sufficient, it is recommended to proceed with antidepressants and/or CBT or IPT.^{13,60} For severe MDD, BPI is recommended for only two weeks, followed by antidepressants if BPI is not sufficient.¹⁴

Other treatments for depression

Electroconvulsive therapy (ECT) should be considered for adolescents with severe MDD and psychotic symptoms, catatonia or treatment resistance.^{10,13,26,44,60} ECT aims to rapidly reduce depressive symptoms in this severe condition.¹³ Through ECT, an electric current is used to induce a brief and controlled epileptic seizure.⁶⁹ The treatment is given under general anesthesia⁶⁹ and often in series three times a week for up to four weeks.^{70,71} The seizure starts localized near electrode sites,

progresses to a generalized seizure, and terminates by inhibition from cerebellum, and is thought to reset the corticolimbic dysfunction seen in depression.⁶⁹ The precise mechanism is still unknown, but higher inflammatory markers such as TNF- α and IL-6 before ECT predict a better outcome⁷² and BDNF increases after ECT.^{69,73} There are no randomized controlled trials (RCTs) on ECT for adolescent depression,¹⁰ and recommendations are based on observational studies or RCTs of adult depression,¹³ where the short term effect of ECT is large compared to simulated ECT.⁷¹

Repetitive transcranial magnetic stimulation (TMS) is approved for treatment-resistant depression in adults.^{10,13} Through TMS, cortical neurons are stimulated with magnetic pulses⁷⁴ which gives an electrical stimulation but with lower amplitudes than ECT and no seizures.⁷³ This is suggested to modulate cortical gamma-aminobutyric acid (GABA)-ergic and glutamatergic imbalances. However, much is still unknown regarding the mechanism and biomarkers involved.⁷⁴ Today, there are mostly open trials on TMS for adolescent MDD.⁷⁴⁻⁷⁶ One larger RCT on TMS for treatment resistant MDD in adolescents did not show any difference between active TMS or sham TMS.⁷⁷ TMS is not yet included in the Swedish guidelines for adolescent MDD, but recently approved in the U.S.⁷⁸

Ketamine is a novel pharmacological alternative that is well supported in adults^{10,13} but recently also in adolescents and recommended on par with ECT for more severe presentations.⁶⁰ Ketamine is an N-methyl-D-aspartate (NMDA)-receptor antagonist that is proposed to be rapid acting for depression.⁷⁹ Besides inhibiting NMDA-receptors, ketamine is also thought to be involved in several other pathways through GABA, serotonin, dopamine, opioid, and cholinergic receptors,⁸⁰ as well as involved in synaptic plasticity including BDNF.⁷⁹ Ketamine is given as an intravenous infusion or in the form of esketamine intranasally.¹⁰ Esketamine intranasally is not yet recommended in Swedish guidelines and partially due to the risk of sensitization to abuse and its limited evidence.^{13,14,60}

Health

World Health Organization (WHO) defines health as a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.⁸¹ In qualitative studies, adolescents describe that, for them, health consists of physical, mental, and psychosocial aspects, and the importance of these domains have differed between studies.⁸²⁻⁸⁴ Adolescents also describe physical health as exercising regularly, eating healthy, and avoiding risk factors such as obesity, alcohol, tobacco, and substance use,^{82,83} and mental health as avoiding stress,^{82,83} having a high self-esteem,⁸³ and a positive thinking.⁸³ Psychosocial aspects of health according to adolescents include the importance of engaging in activities^{83,85} and a

social belonging.^{83,85} Girls describe social relationships as more important than boys do.⁸³

Physical activity

Physical activity is defined as any bodily movement produced by skeletal muscle that requires energy.^{86,87} Exercise is a subset of physical activity, and defined as planned, structured, and repetitive with the aim to improve or maintain physical fitness.⁸⁷ Aerobic exercise, also called endurance exercise or cardio exercise, is the rhythmical movement of the large muscle groups in the body, such as walking, running, bicycling, or swimming.⁸⁸ Aerobic exercise leads to increased heart rate.⁸⁸ The intensity of exercise is often divided into light, moderate, or vigorous, based on the amount of energy required (Figure 1). Percentage of maximum heart rate (HRmax) ranges from 50-63% for light intensity, 64-76% for moderate intensity, and 77-93% for vigorous intensity.⁸⁹ A light intensity activity is for example walking slowly, while power walking is at moderate, and running at vigorous intensity.⁸⁸ Muscle-strengthening exercise, also called resistance training or weightlifting, is when the muscles work or hold against a weight.⁸⁸

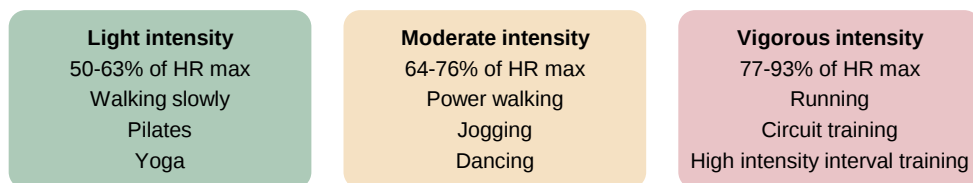


Figure 1. Overview of exercise intensities, with examples of activities at each intensity level.

Cardiorespiratory fitness, also known as aerobic capacity, is defined as the capacity of the body's circulatory and respiratory systems to supply oxygen to the skeletal muscle mitochondria for energy production during physical activity. Aerobic capacity is defined as maximal oxygen uptake (VO_2max), which refers to the maximal oxygen flux through the lungs, transported by the circulation to the mitochondria in the exercising muscle. The gold standard for measuring aerobic capacity is through measuring respiratory gases during a cardiopulmonary maximal exercise test. The maximal test requires lab facilities and is very demanding for the

participant. A more feasible proxy is estimation of aerobic capacity (VO_2max) through a submaximal exercise test.⁹⁰

Heart rate variability (HRV) refers to the changes in interval between heart beats, which is a sign of the heart's autonomic function through the interaction between cardiac sympathetic and parasympathetic activity.⁹¹ HRV is a sign of current health status and low HRV is associated with increased risk of mortality in adults.^{91,92}

WHO and U.S. physical activity guidelines recommend 60 minutes of moderate- to vigorous- intensity activity daily for adolescents.^{86,88} Adults are recommended at least 150 minutes per week of moderate intensity activity or 75 minutes per week of vigorous intensity activity.^{86,88} Global data shows that up to 81% of boys and girls aged 11-17 years do not meet recommendations of physical activity, and that girls are more inactive than boys.¹¹ Only half of boys and a third of girls are reported to have healthy cardiorespiratory fitness.⁹⁰ Studies are also showing a decline in VO_2max among adolescents over the last decades.^{90,93}

Health risks with sedentary behavior and screen time

Sedentary behavior is defined as any waking behavior with a low level of energy expenditure while sitting or lying. Sedentary behavior occurs not only in leisure time but also occupationally and at school. Children and adults spend over 7 hours per day being sedentary. Sedentary behavior appears to have health risks and increases risk of mortality among adults.⁸⁸ For adolescents, sedentary behavior has been associated with both depression and lower psychological wellbeing, such as poorer life satisfaction and lower happiness.⁹⁴

Recreational screen time is time spent with screens without educational purpose.³⁴ Adolescents today interact with screens in various ways and the relation between social media and mental well-being show mixed results.⁹⁵⁻⁹⁸ Recreational screen time is associated with less physical activity and sleeping problems.³⁴ Some evidence support that screen time is associated with depressive symptoms,⁹⁹ and that time spent on social media is associated with higher risk for depression among adolescents.¹⁰⁰⁻¹⁰² Other studies claim that it is premature to conclude a relation between time spent on social media and mental health.^{95,96} Being physically active seems to decrease the vulnerability of depressive symptoms from a high level of screen time.¹⁰³ Furthermore, high level of screen time is associated with poorer fitness and cardiovascular health, overweight, and obesity.^{99,104} The American Academy of Pediatrics do not set any time limit for screen time in their guideline, but argue the importance of considering the quality of interactions with digital media.¹⁰⁵ The Public Health Agency of Sweden recommend a time limit of 2-3 hours screen time daily for adolescents,¹⁰⁶ and recently recommended to avoid smartphones before age 13.¹⁰⁷ More research is warranted on both quantity and quality of screen time and its influence on well-being in adolescents.¹⁰⁸

Health benefits from physical activity

Physical activity entails several health benefits for adolescents as well as for adults. Immediately after physical activity, benefits include reduced blood pressure, improved sleep, increased insulin sensitivity, improved cognitive function, reduced anxiety and stress, and enhanced mood.^{88,109} After weeks or months of regular physical activity, benefits can be observed through improved cardiorespiratory health, muscular strength, bone health, a sustained reduction of blood pressure, and lower risk of obesity.^{34,88} Cardiorespiratory health is improved from exercise as indicated by increases in VO_2max and HRV.^{90,110-112} Physical activity improve aerobic capacity through improved oxygen transport and increased cardiac output, secondary to increased blood volume, myocardial contractility, and angiogenesis. There is a small to moderate association between exercise and VO_2max in adolescents, but also a possible genetic component to VO_2max according to adult studies.⁹⁰

Physical activity levels are associated with mental health in adolescents. Sport participation in childhood and adolescence is correlated with better self-esteem, a sense of belonging, and less anxiety and depressive symptoms.¹¹³ Current levels of physical activity are also negatively associated with depression¹¹⁴, and the most active adolescents have a lower risk for depression in early adulthood.¹¹⁵ Moreover, cardiorespiratory fitness (i.e. aerobic capacity) is associated with better academic achievement and mental wellbeing.⁹⁰

Physical activity as a treatment for depression

Physical activity as a treatment for depression in adults

Physical activity provides improvement in depression symptoms on par with those of antidepressants and psychological treatment for adult depression¹² and is recommended for adults with mild to moderate MDD.^{12,13} Meta-analyses on exercise for adult depression reveal moderate effect sizes, including Hedge's g values (a small-sample corrected SMD estimate) from 0.62¹¹⁶ to 0.79¹¹⁷, and an SMD of 0.66.¹¹⁸

However, effect sizes for exercise for depression among adults are based on studies with high risk of bias, for example, lack of masked outcome assessors and risk of publication bias.¹¹⁸ When restricting the analysis to studies with low risk of bias, the effect size decreases to an SMD 0.11.¹¹⁸ Risk of bias was regarded as substantial with a strict method from Cochrane¹¹⁸ while another meta-analysis did not find a substantial risk of bias.¹¹⁷

A large network meta-analysis found a dose response relationship, where the effects of exercise were proportional to the exercise intensity.¹¹⁶ The guidance from the

European Psychiatric Association states that exercise at a moderate to vigorous intensity gave larger effect sizes than light intensity exercise for MDD.¹² In contrast, one study found no difference between low, moderate, or high intensity, indicating that even a low intensity exercise is beneficial for depression.¹¹⁹

Exercise supervised by exercise professionals have larger effect than exercise delivered by mental health staff, and is recommended for reaching optimal outcomes and to reduce dropouts.¹² Similarly, supervised exercise achieved higher adherence compared to unsupervised exercise in a study on adults with medical conditions, but not MDD.¹²⁰ A study on sedentary adults found that personalized exercise prescription based on HRV was as effective as group training led by a personal trainer.¹²¹

An umbrella review examining the association between physical activity, MDD and HRV found that HRV, a measure for cardiac fitness, was lower in individuals with MDD compared to non-MDD individuals.¹¹² Further, physical activity seemed to improve HRV in individuals with MDD, in addition to also reducing depressive symptoms.¹¹² An association between improved VO₂max and reduced depression severity has also been described.¹²²

To summarize, primarily supervised physical activity is recommended for adults with depression¹³, with effect on par with antidepressants and psychotherapy,¹² but the effect is smaller in studies with low risk of bias.¹¹⁸

Physical activity as a treatment for depression in adolescents

Meta-analyses on exercise for adolescents with depression¹²³⁻¹³¹ indicate small to large, but mostly moderate, effect sizes, ranging from SMD 0.41¹²⁹ to 1.14.¹²⁷ Thus, exercise is suggested to have an effect size comparable to, or larger than, current treatments with SSRIs⁸ or psychological treatment,⁹ for which meta-analyses report SMDs of 0.12-0.51^{8,48,55,61} and 0.05-0.41,⁴⁶⁻⁴⁸ respectively. However, treatment guidelines have graded the evidence for exercise as low because of methodological limitations and have not yet recommended physical activity as a treatment for depression.^{13,15} A newer guideline states that children or young persons with depression should be given advice about exercise on a regular basis⁴⁴ and such advices are also included in the Swedish BPI approach to adolescent depression.⁶⁰

As stated above, the certainty of the existing evidence is low due to methodological weaknesses, which risk overestimating effect sizes and reducing generalizability. First, among seven RCTs with clinical participants,¹³²⁻¹³⁸ two studies lack an active control group, one study compared exercise to treatment as usual,¹³³ and another to no treatment.¹³⁶ One study had exercise as add on to CBT and SSRIs given to the control group.¹³⁷ Active control groups have included group stretching exercises,¹³⁴ board games,¹³⁵ and social relaxation,¹³⁸ or other physical activities, but with less sessions than the exercise intervention.¹³² Studies comparing exercise to passive controls, such as waitlist or treatment as usual, can examine an effect on depression

but does not distinguish specific effects of exercise from other factors such as attention, group participation, and expectancy. Use of weak control conditions risk overestimating the effect of exercise and the selection of comparator is important when designing intervention trials.¹³⁹

Second, outcome measures have often been collected through self-reported depressive symptoms,^{132,133,135-137} with only two studies using clinical interviews with masked assessors.^{134,138} The use of unblinded assessors or self-reports risk overestimation of the results.

Third, sample sizes have often been small, with existing trials including between 27 and 87 participants,^{132-136,138} except from a Chinese study with 138 participants.¹³⁷

Fourth, some RCTs do not describe comorbidities,^{132,133,137} or have only included participants with few comorbidities.^{134,136,138} Psychiatric comorbidity is common among adolescents with depression,²⁶ and not describing comorbidity patterns in trial samples hampers the understanding of the study population and limits the generalizability of the findings to other populations. Moreover, samples with few comorbidities might overestimate the effect of exercise due to increased attendance compared to Child and Adolescent Mental Health Services (CAMHS) samples.

Fifth, some studies do not describe any diagnostic verification.^{132,135,138} While some studies have confirmed depression diagnoses using clinical interviews,^{134,136,137} one study relied on self-reported depression scales.¹³³ Other RCTs include non-clinical participants with depression¹⁴⁰⁻¹⁴⁴ or even participants with only depressive symptoms or subthreshold depression.¹⁴⁵⁻¹⁴⁸ Again, including participants where a diagnosis of depression is not confirmed hampers the generalizability of the results to clinical settings.

Because studies on clinically representative samples are lacking, it is difficult to generalize current findings on exercise to patients in a routine CAMHS setting, where comorbidity is common and severity often higher, potentially affecting both treatment response and adherence. An open feasibility study of an aerobic exercise intervention with moderate to vigorous intensity for adolescents with depression and extensive comorbidity in CAMHS found the intervention to be feasible.¹⁴⁹ Depression symptoms were alleviated after the intervention and further improvements were seen at the one-year follow-up. Aerobic capacity improved during the intervention but did not differ between baseline and one-year follow-up.¹⁴⁹ A three-armed RCT of inpatients with MDD compared medication and exercise to medication and TMS or medication alone and found that adjunctive treatment with either exercise or TMS significantly reduced depressive symptoms compared to medication alone. No differences were seen between the exercise and TMS conditions.¹⁵⁰

Dose-response analyses between exercise and depression among adolescents usually favors 40-50 minutes of exercise, three times a week for 12 weeks.¹²⁹ A U-

shaped curve has also been observed,¹⁵¹ indicating that too low or high doses of exercise were less beneficial than a moderate dose.

Qualitative studies on exercise for depression among adolescents illustrate several beneficial experiences. Exercise contributed to joy of living through commitment and empowerment.¹⁵² Group exercise was experienced as manageable, comprehensible, and meaningful.¹⁵³ Also a preferred (low) intensity exercise brought improved mood, enjoyment, and achievement.¹⁵⁴ Continued exercise one year after start was facilitated by increased self-esteem, by having companionship, by reaching exercise results, and by having a supportive environment, while barriers to continue exercising were disease burden and a lack of support.¹⁵⁵

Potential mechanisms of physical activity on depression

Potential biological mechanisms

The mechanisms behind the effects of physical activity on depression is incompletely understood and often extrapolated from animal studies.^{31,156,157} Some hypotheses link the effects of physical activity on the brain to biomarkers of neuroinflammation (Figure 2).¹⁵⁸ There is a suggested alternation in levels of biomarkers that is associated with physical activity and depression, but also a possibility of stressful events leading to epigenetic modifications that alter the expression of genes encoding for some of the proposed biomarkers.¹⁵⁸ In the future, biomarkers related to depression may help verify depression diagnoses, predict treatment response, guide treatment selection, and monitor treatment effects.

Serotonin (5-HT) is a neurotransmitter possibly involved in the underlying mechanisms of the positive effects of exercise on depression. Levels of serotonin are thought to be lower in neuronal circuits in individuals with depression¹⁵⁸ and serotonin is a target for the most common antidepressants.⁵⁶ Serotonin is known to increase neurogenesis (i.e. the growth of new neurons in the adult brain) and adult cellular proliferation, which is the process when a cell grows and divides itself into two daughter cells.³² Other neurotransmitters such as dopamine and norepinephrine have also been proposed to be related to depression, illustrated by the findings that different antidepressants act through increasing the levels of these neurotransmitters in the synaptic cleft.¹⁵⁸ Exercise can release serotonin in the brain, increase the sensitivity of serotonin-receptors,¹⁵⁷ and increase serotonergic fibers in the brain in older adults.¹⁵⁶

The kynurenine pathway is the way through which most of tryptophan is catabolized. Tryptophan is an amino acid known as a precursor in the biosynthesis of serotonin.¹⁵⁹ The kynurenine pathway catabolizes tryptophan into different neuroactive kynurenines, linked to both inflammation and depression.^{159,160} The imbalance between neurotoxic and neuroprotective metabolites of this pathway is

suggested to play a role in the development of depression.¹⁶¹ ECT, ketamine, and exercise alter kynurenine metabolism, suggesting kynurenine metabolites to be a possible mechanism behind and/or a marker for treatment response.¹⁶⁰

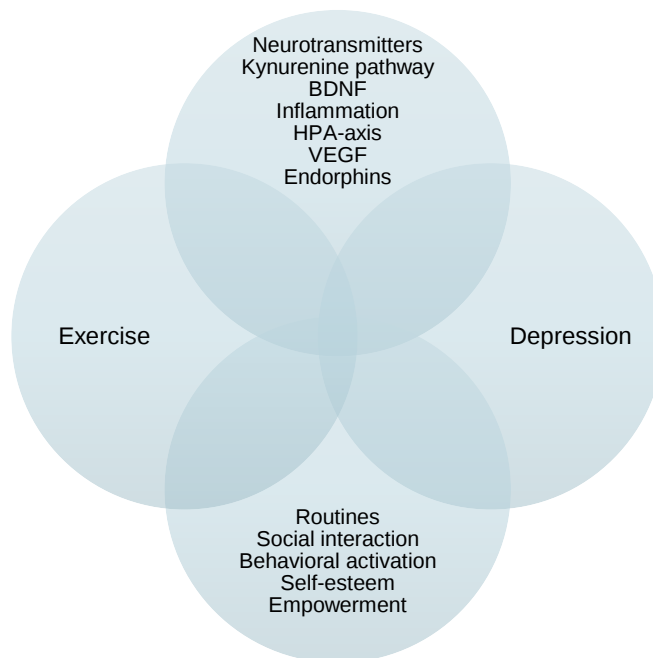


Figure 2. Mechanisms possibly involved in the relationship between physical activity and depression.

BDNF is a neuropeptide involved in synaptic development, which is the formation of connections between neurons. BDNF is also involved in the plasticity of the brain, i.e. the brain's adaptation to change,³¹ and is thought to promote cell survival.¹⁵⁶ Decreased levels of BDNF is associated with depression in adults.¹⁵⁶ However, there is less evidence for an association between BDNF and depressive symptoms in children and adolescents.¹⁵⁸ BDNF is suggested to be involved in antidepressant mechanisms,³¹ and one proposed mechanism is through the upregulation of BDNF synthesis.¹⁵⁸ Depression is also associated with smaller hippocampal volumes.¹⁵⁶ Hippocampus is an area in the brain involved in emotional processing and stress regulation, often affected in people with depression.³³ Decreased levels of BDNF is also linked to hippocampal atrophy.¹⁵⁶ Antidepressants seems to increase BDNF^{31,156,158} and to reverse the hippocampal atrophy seen in depression.¹⁵⁶ ECT is suggested to increase levels of BDNF.⁷³ Likewise, the antidepressant effect of ketamine is associated with a rapid increase of BDNF.^{79,80}

Exercise also increases hippocampal size and seems to increase levels of BDNF and reduce depression.^{32,156,157}

One theory behind development of depression is low-grade inflammation.^{158,162,163} Adults with depression have been shown to have increased levels of pro-inflammatory markers, such as interleukin-6 (IL-6), interleukin-1 (IL-1), tumor necrosis factor alpha (TNF- α), C-reactive proteins (CRP),³³ and soluble interleukin-2 receptor (sIL-2R).¹⁶⁴ Insulin-like growth factor 1 (IGF-1) is a hormone involved in neuroprotective processes.¹⁶⁵ Proinflammatory cytokines regulate endocrine systems in a bi-directional way and imbalances in this regulation may be a factor for development of depression.¹⁶⁶ For adolescents with depression, only increased levels of IL-6 and CRP have been observed.^{158,162} Inflammation is also suggested to dysregulate BDNF.¹⁵⁸ Increased levels of inflammatory markers have been suggested to predict a poorer response to SSRIs among both children, adolescents, and adults.¹⁵⁸ Interestingly, anti-inflammatory medications have been shown to decrease depressive symptoms,³³ and there is an association between nonsteroidal anti-inflammatory drug use and lower incidence of suicide in females.¹⁶⁷ Exercise can reduce inflammation in the body and lower the levels of inflammatory factors such as IL-6 and CRP,³³ and increase levels of IGF-1, which is thought to have an anti-inflammatory effect.¹⁶⁵ This anti-inflammatory effect may also be a mechanism through which exercise alleviate depressive symptoms.^{33,163}

Dysregulation of the hypothalamic-pituitary-adrenal (HPA)-axis is another suggested explanation of the pathophysiology of adult depression.¹⁵⁸ Depression in adults can lead to stress-induced hyperactivity of the HPA-axis and high levels of cortisol.¹⁵⁸ Association between HPA-axis dysregulation and depression is also seen among adolescents.^{168,169} It has been suggested that stress in early life affect the HPA-axis and increases the risk of depression.¹⁵⁸ Acute effects of exercise elevates cortisol levels, while over a long-term, regular exercise lowers baseline resting cortisol levels, possibly by enhancing HPA-axis function with a more rhythmic secretion of cortisol.^{170,171} Thus, changes in the regulation of the HPA-axis is a possible explanation of the antidepressant effect from exercise.¹⁶³

Vascular endothelial growth factor (VEGF) is a protein that stimulates the formation of blood vessels. VEGF is also known to increase neurogenesis, which is the growth of new neurons in the adult brain. It is suggested that decreased neurogenesis in adults is linked to depression.³² Increased signalling of VEGF in the hippocampus is a suggested mechanism behind the effect of ECT on depression.⁷³ Exercise is known to improve cerebral blood flow, probably through angiogenesis, the formation of blood vessels.³³ Exercise leads to increased levels of VEGF.^{32,33,130}

Endorphins are endogenous opioids, thus produced by the body itself, and similar to exogenous opioids such as heroin and morphine. Endorphins are involved in various processes in the body, such as mood, pain, motivation, and addiction.¹⁵⁷ Beta (β)-endorphins is one type of endorphin that is seen to influence neurogenesis³² and

to have an antidepressant effect.¹⁵⁷ Endogenous endorphins are released during exercise and enhances mood and relieves pain.¹⁵⁷

Potential psychological mechanisms

Beyond the possible linkage between exercise and reduced depressive symptoms on a biological level, there are also several psychological mechanisms suggested to play important roles (Figure 2). Participating in exercise sessions regularly may have a direct effect on depressive symptoms, through establishing routines, meeting group leaders and other adolescents, similar to behavioral activation¹³ in CBT for depression. Behavioral activation has an effect on depression¹⁷² and aims to engage the patient in rewarding activities that reduce withdrawal and avoidance.¹⁵ Group exercise leads to social interactions and support which in itself may be beneficial for people with depression.^{13,33} Several studies suggest that exercise leads to increased self-esteem, which may also have an effect on depressive symptoms.^{33,152,153} Exercise is also proposed to enhance self-efficacy, the belief that one can achieve a task,^{13,33} and empowerment¹⁵², the perception of personal control and a proactive approach to life,¹⁷³ both of which may help reduce depressive symptoms.

Rationale for the thesis

There is a clear need for new treatment options for adolescent depression. Exercise is recommended for adults with depression and may have an effect also for adolescent depression, but because the certainty of the evidence remains low, it is not yet recommended.^{13,15} The rationale for this thesis is to address methodological weaknesses in the existing evidence by conducting an RCT comparing exercise to a structurally matched active control condition with the same amount of sessions and social contact, with the goal to evaluate the specific effect of exercise for adolescent depression. We will also use masked assessors for evaluating outcomes, a large sample, recruit participants from specialized services with common comorbidities, and use interview-confirmed depression diagnoses to secure the quality of the study, and to increase generalizability to CAMHS settings. The thesis will further address lived experiences by adding qualitative aspects of adolescents', parents', and healthcare professionals' (HPs') experiences of the exercise intervention and analyses of how adolescents with depression understand health.

Aims

The overall aim of this thesis was to compare group-based aerobic exercise with group-based leisure activities for adolescents with mild to moderate depression using an RCT and a sample recruited in a naturalistic clinical setting. The thesis further included qualitative studies on the experiences of adolescents, parents, and HPs after an exercise intervention, along with how adolescents with depression understand health more broadly.

Paper I: The aim was to describe the rationale for the multicenter RCT.

Paper II: The aim was to compare changes in clinician-rated symptoms of depression, global improvement and functioning as well as self-reported symptoms and well-being after 12 weeks of moderate to vigorous group aerobic exercise versus group leisure activities at 13 weeks and 26 weeks post-randomization.

Paper III: The aim was to explore the experiences of adolescents, parents, and HPs of how a group exercise intervention affected adolescents with depression.

Paper IV: The aim was to explore different ways of understanding health among adolescents with mild to moderate depression.

Methods

Randomized controlled trial (RCT) (Paper I-II)

Study design

Papers I-II were based on a multicenter RCT including 125 adolescents diagnosed with mild to moderate depression from different CAMHS in Sweden between 2022 and 2025, with Paper I being a protocol paper outlining the study rationale and design. Prior to the multicenter RCT, we conducted a pilot RCT (n=14) in 2021 with an identical design.

The aim of the RCT was to compare 12 weeks of group-based aerobic exercise with 12 weeks of group-based leisure activities as an active control condition for adolescents with mild to moderate depression from a routine clinical sample.

Recruitment and participants

Participants were recruited from CAMHS and identified from administrative systems. Those who consented were assessed with Kiddie Schedule for Affective Disorders and Schizophrenia Present and Lifetime Version (K-SADS-PL) and inclusion and exclusion criteria were reviewed before baseline. Inclusion and exclusion criteria are presented below.

Inclusion Criteria

- Adolescents aged 13-17 with mild to moderate depression according to DSM-5
- Having attended at least three clinical visits
- Not showed clear response assessed from clinical records, that is at least 50% of depressive symptoms remaining

Exclusion Criteria

- Eating disorder
- High risk of suicide
- Intellectual disability
- Physical activity on a level of at least 150 min per week of moderate intensity or 75 min per week of high intensity
- Adjustment of antidepressant medication within 4 weeks or stimulants within 2 weeks from baseline measures
- In need of interpreter
- Social circumstances interfering with a regular exercise schedule
- Concomitant psychotherapy
- Somatic illness precluding exercise
- Substance misuse

Intervention

Patients were randomized 1:1 to group-based exercise or group-based leisure activities, each delivered as 60-minute sessions three times a week for 12 weeks.

The exercise sessions were supervised by a personal trainer and supported by HPs from CAMHS. Sessions started with a short check-in on current emotional state and recent significant events. HPs were allowed to listen and validate feelings but not to give any interventions. Each week there were three types of sessions: one pure aerobic session, one session with strengthening exercises also designed to increase heart rate, and one mixed session. Exercise intensity increased progressively and aimed for a heart rate at a moderate to vigorous level, corresponding to 80-85 % of maximum heart rate for the first half and 85-90% for the last half of the 36 sessions.

The leisure group activities were led by the same HPs from CAMHS on the same days and hours as the group exercise. The sessions started with a similar check-in, followed by having a snack, playing games and cards, painting, or watching a movie together in a group. These activities were designed to avoid elevating heart rate.

Assessments

Two psychiatrists conducted video interviews at baseline, week 13, and 26 using the Children's Depressive Rating Scale-Revised (CDRS-R), the Children's Global Assessment Scale (C-GAS) and the Clinical Global Impression – Severity (CGI-S), and – Improvement (CGI-I) scales (Figure 3). The outcome assessors were masked to treatment allocation. Participants could not be masked due to the nature of the intervention.

The participants also filled out web-based questionnaires, including the Quick Inventory of Depressive Symptomatology Adolescent Version-17 Self-Report (QIDS-A₁₇-SR), and the Outcome Rating Scale (ORS) every 2 weeks from baseline to week 12 and then monthly to week 26.

Aerobic capacity (VO₂max) was assessed through a submaximal aerobic test at baseline and at week 13.

Participants also completed additional physical tests and provided blood samples, and parents completed forms related to cost-effectiveness; these data are not included in this thesis. An additional follow-up was conducted at week 52, but outside the scope of this thesis.

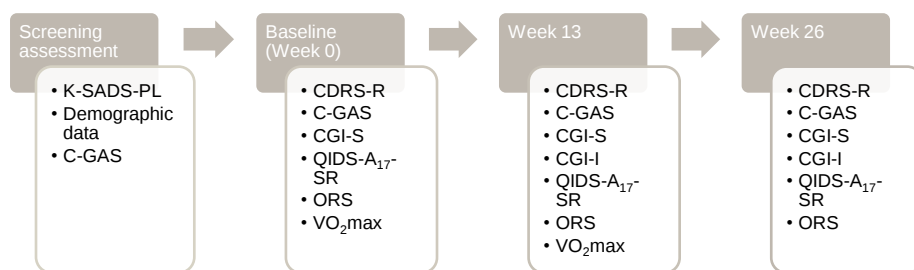


Figure 3. Assessment points for outcome measures

QIDS-A₁₇-SR and ORS were also assessed every two weeks during the intervention and monthly from weeks 13 to 26.

Children's Depression Rating Scale-Revised (CDRS-R)

The CDRS-R is a commonly used interview for assessing depressive symptoms in children and adolescents in clinical research. The interview has 17 items ranging from 1 to 5 or 1 to 7, giving a total score from 17 to 113, which are rated by interviewee the child or adolescent.¹⁷⁴ A score of ≥ 40 indicates depression while a score of ≤ 28 indicates remission or a non-clinical level of depressive symptoms.¹⁷⁵ Response is typically defined in depression studies as a reduction of at least 50% from the baseline score.¹⁷⁶ CDRS-R has shown good psychometric properties for adolescents with depression in American¹⁷⁵, European¹⁷⁷ and Asian^{178,179} populations. However, no validation has been conducted in a Swedish or Scandinavian population.

Children Global Assessment Scale (C-GAS)

The C-GAS is an instrument for clinician-assessed general functioning during the last month on a scale from 1 (worst) to 100 (best) among persons aged 4-20 years.¹⁸⁰ A Scandinavian review of C-GAS describes satisfactory evidence for convergent, discriminant, and predictive validity, as well as for interrater reliability.¹⁸¹

Clinical Global Impression (CGI)

The CGI is an overall clinical measure of the patient's symptoms and functioning. CGI consists of two measures, CGI-severity (CGI-S) and CGI-improvement (CGI-I). The CGI-S assesses the patient's severity of psychopathology from 1 to 7, using the following prompt: 'How mentally ill is the patient at this time?' based on symptoms, behavior 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. The CGI-I assesses the change from the start of treatment to the assessment point from 1 to 7, using the following prompt: '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'.¹⁸² Response is typically defined as a CGI-I score ≤ 2 , i.e. much or very much improved.³⁶ There is a relationship between CGI-I scores and changes on CDRS-R and QIDS-A₁₇-SR.¹⁷⁶

Quick Inventory of Depressive Symptomatology- Adolescent version-17 Self Report (QIDS-A₁₇-SR)

The QIDS-A₁₇-SR is a self-report assessment with items that covers the nine DSM-5 symptoms of depression. The answers of the items are rated on a scale from 0 (none) to 3 (highest) with a total score of 0-27. Mild depression corresponds to a score of 6-10, moderate 11-15, severe 16-20, and very severe 21 and above.¹⁸³ QIDS-A₁₇-SR has high internal consistency and a discriminant diagnostic validity for measuring depression in adolescents.¹⁸⁴ However, there is no validation of the instrument in a Swedish setting.

Outcome Rating Scale (ORS)

The ORS is a self-reported visual analog scale assessing functioning in four domains: individual, interpersonal, social, and overall 'sense of well-being' aspects. The scale is numerical from 0 (worst) to 100 (best).¹⁸⁵ ORS is feasible since it is very brief but has also shown good internal consistency and moderate concurrent validity in adults and adolescents.¹⁸⁵⁻¹⁸⁷ There is no known validation in a Swedish population.

Aerobic capacity (VO₂max)

The aerobic capacity was measured with a submaximal cycle ergometer test on an indoor bicycle according to the Åstrand test.¹⁸⁸ The aerobic capacity was expressed as maximal oxygen uptake (VO₂max), that is, the total amount of oxygen metabolized per minute per kilogram of body weight (mL/kg/min). VO₂max is higher among boys than girls and increases with age in youths.⁹⁰ Reference values for VO₂max based on a Swedish cohort aged 14-16 years indicate mean 41.6 mL/kg/min (SD ±8.5) for boys and mean 38.1 mL/kg/min (SD ±7.7) for girls.¹⁸⁹ The values are in line with estimations from a Canadian cohort aged 13-17 years.⁹³ Suggested cut-offs for cardiorespiratory fitness are based on gender and age, and for 15 year old boys 43 mL/kg/min and for girls 34 mL/kg/min.¹⁹⁰ Not meeting these cut-offs were associated with higher odds for high cardiometabolic risk and unhealthy weight status.¹⁹⁰ Instead it is sometimes referred to percentiles for age and gender where the lowest 5th percentile can be considered as pathological, and <20th percentile as very poor, and 20-40th percentile as poor cardiorespiratory fitness.¹⁹¹

Maximal exercise testing which requires a high motivation was deemed too difficult to use in this population, as also identified by a previous study which showed that the Åstrand submaximal test to be more feasible for adults with MDD.¹⁹² The Åstrand test has been evaluated in children with a strong correlation among girls and a moderate correlation among boys compared to the maximal exercise test.⁹⁰

Outcome measures

The primary outcome measure was CDRS-R at 13 weeks post-randomization with intention-to-treat (ITT) analysis, meaning that all randomized participants were included in the analysis.

Secondary outcomes with ITT analysis were CDRS-R at week 26, C-GAS, CGI-S, CGI-I, QIDS-A₁₇-SR, and ORS at week 13 and 26, and VO₂max at week 13 only. Further secondary outcomes included per protocol (PP) analyses on participants with adherence of ≥50% of sessions and stable antidepressants regarding all outcomes above.

Post hoc analyses included response rates, numbers needed to treat (NNT) for response, and analyses of items capturing the core depressive symptoms of sadness, irritability, and anhedonia, according to CDRS-R and QIDS-A₁₇-SR at week 13 and 26 with ITT and PP analyses.

Statistics

The statistical power calculation for the multicenter RCT was based on data from the pilot study conducted in 2021. This study showed a 7.5-point difference on

CDRS-R favoring the exercise intervention (SD 12.9 points). The power calculation, based on $\beta=80\%$ and $\alpha=0.05$, indicated that 92 patients were required to complete the RCT phase until week 13 for the primary outcome. Due to an expected dropout rate (from the pilot study) of 25%, a total of 122 participants were needed to be recruited to the multicenter RCT, making this one of the largest RCTs on exercise for adolescent depression to date. The study was preregistered on ClinicalTrials.gov (2021-09-30, NCT05076214), and the RCT study protocol paper reported all prespecified primary and secondary outcomes in accordance with the registration. Any post hoc analyses were clearly identified as such.

For paper II, we used descriptive statistics to summarize demographic data. We used linear mixed-effect models (LMM) to analyze change in outcome variables following the interventions at week 13 and 26. Time was specified as a fixed effect parameter (assessment points at baseline, week 13, and week 26). Random effect parameters were in intercept and linear slope terms. Tests were two-tailed, and α set to 0.05 to indicate statistical significance. Cohen's f were used as effect size measure of the interaction (time*group), where 0.1 indicated small, 0.25 medium and 0.4 large effect sizes.¹⁹³ Cohen's d were used to estimate effect sizes within a group over time, where 0.2 indicated small, 0.5 medium, and 0.8 large effect sizes.¹⁹⁴ Mann Whitney U-test was used to determine differences in CGI-I between groups, since the value in itself describes a change over time.

ITT analyses were performed using all 125 randomized participants. PP analyses were performed on participants adhering to the protocol, defined as attending $\geq 50\%$ of sessions and with no increased dosage or change of antidepressant medication during the intervention. PP analyses included 75 (60%) participants at week 13 (38 in the exercise group and 37 in the leisure group) and 58 (46%) participants at week 26 (31 in the exercise group and 27 in the leisure group). Although we achieved the planned recruitment target, fewer than expected adhered to the intervention, resulting in a smaller PP sample and reduced statistical power.

Response rates were calculated based on reduction of $\geq 50\%$ on total CDRS-R or CGI-I ≤ 2 , or both, at week 13 and 26 respectively. Remission was defined as a CDRS-R score of ≤ 28 .

Qualitative content analysis approach (Paper III)

In Paper III, we used a latent qualitative content analysis with an inductive approach to explore adolescents', parents', and HPs' experiences of a group exercise intervention for adolescents with depression.

This method was chosen because it allowed us to analyze the participants' experiences of the exercise intervention not just on a manifest level, but also to

explore the underlying (latent) meaning. Since qualitative research on exercise interventions for depression is still limited, we chose an inductive approach, allowing for exploring participants' experiences and capturing new insights.

Recruitment, participants and intervention

Participants were recruited from the pilot RCT, conducted prior to the multicenter RCT. Participants were identified from administrative systems except for three participants who were recommended by staff at the local CAMHS. Inclusion and exclusion criteria were identical to those in the multicenter RCT. In total, 14 adolescents were randomized in the pilot study, but five dropped out. The nine adolescents who completed the intervention, their parents and the two HPs were invited by phone to qualitative interviews about their experiences. Nine adolescents, eight parents, and the two HPs chose to participate, resulting in 19 qualitative interviews.

Data collection

Qualitative interviews were performed by two researchers: one experienced qualitative researcher and one clinical psychologist and PhD student. Participants were interviewed individually, except for one adolescent who wanted her mother to be present. The five adolescents randomized to group exercise were interviewed after the 12-week intervention. The four adolescents randomized to leisure activities performed exercise after week 26 or had participated in an open trial with identical group exercise before. Two of them were interviewed directly after the exercise intervention but two had exercised about 6 or 12 months earlier. All parents and HPs were interviewed mostly 5 months after the exercise session due to a pending ethical approval for interviewing also parents and HPs.

A semi-structured interview guide (provided as a supplement to Paper I) was used during the interviews to explore adolescents', parents', and HPs' experiences of the exercise intervention. For example, adolescents were asked 'Has exercise led to any changes? How?' Parents and HPs were asked, for example: 'How do you perceive that group exercise has affected your child's/the participants' depression?'

Data analysis

The data analysis followed Graneheim and Lundman's steps for latent qualitative content analysis.¹⁹⁵ The transcripts were read through, and parts associated with the aim, that is, exploring adolescents', parents', and HPs' experiences of the impact of group exercise on adolescents with depression, were identified as meaning units. We identified 508 meaning units that were labelled with codes, briefly describing

their content. Codes were grouped into nine sub-categories based on their similarities and differences at a manifest level. The nine sub-categories were grouped into three main categories, and the latent meaning of the content was abstracted into an overarching theme.

Phenomenographic approach (Paper IV)

In Paper IV, we used a descriptive qualitative design with a phenomenographic approach to describe qualitatively different ways in which adolescents with depression understand health.

A descriptive design was used to provide insight into a phenomenon and to describe participants' conceptions of health.¹⁹⁶ A phenomenographic approach was chosen to describe variation in how individuals understand or conceptualize a phenomenon, with the focus placed on variation in conceptions of health within the group rather than on individual conceptions as such.¹⁹⁷ This method enabled us to describe qualitatively different ways in which adolescents with depression understand health, without using predefined theories.

Recruitment, participants and intervention

Participants were recruited from the pilot study and from the first cohort of the multicenter RCT, resulting in a sample of 33 adolescents diagnosed with depression who had participated in either the group-based exercise or the group-based leisure activities intervention for 12 weeks.

Data collection

Data were collected through qualitative interviews performed by one experienced qualitative researcher and two clinical psychologists. We used the same semi-structured interview guide as in Paper III, but with a focus on questions regarding health and conceptualizations of health. Questions used were for example; 'What is health for you?', 'How do you perceive your health?', 'What do you do to maintain/promote your health?', and 'How does exercise (or leisure activities) affect your health?'

Data analysis

The data analysis followed the steps for phenomenographic analysis described by Larsson and Holmström.¹⁹⁸ The interviews were first read repeatedly to gain familiarity with the material. Meaning units related to adolescents' conceptions of health were then identified and descriptions of each adolescent's dominant way of understanding health were formulated, and similarities and differences between these descriptions were compared. Based on this comparison, categories were constructed to represent qualitatively different ways of understanding health. Each category was then assigned a metaphor to symbolize how health was understood by adolescents with depression. Finally, the relationships between the categories were described as an outcome space.

Ethical considerations

The study obtained ethical approval from the Swedish Ethical Review Authority; for the pilot study with no. 2020-03364 and an amendment application due to extension of qualitative interviews to also include parents and HPs with no. 2021-04029, and for the multicenter RCT with no. 2021-05307-01, and amendment application due to minor changes (such as new study sites, postponed end-date, and added self-rating scales) with no. 2024-04975-02.

All adolescents and caregivers were provided with oral and written information about the study. Informed consent in writing was collected from adolescents aged 15 and above and caregivers of participants below 15 years of age for the RCT. For the qualitative study (Paper III), written informed consent was obtained also from caregivers and HPs for their participation in the study.

Participants were free to withdraw from the study at any time. The local CAMHS were notified when the intervention was completed at week 13 or when the participant had withdrawn from the study, to make sure they got further care if needed.

Ethical reflection

An ethical dilemma with a superiority RCT is that one treatment often is hypothesized to be more effective than the other. Thus, it may be considered ethically questionable to keep participants randomized to a control group instead of the supposed effective intervention. To compensate, we offered all participants randomized to the leisure group to participate in an identical exercise intervention after week 26. However, the leisure group was not thought to be completely ineffective, like a waitlist control, since it was designed as an active control group. Participants in the leisure group met other adolescents three times per week and

socialized, resembling aspects of behavioral activation and therefore potentially reducing depressive symptoms.

Another ethical difficulty with the study design is that concomitant psychological treatment and change of medication were exclusion criteria for participation. This may lead to some adolescents opting to end their psychological treatment or avoid changes in medications prior to inclusion. Likewise, randomization to the leisure group might be less helpful than continuing evidence-based standard care. However, the adolescents filled in self-rated symptoms of depression regularly and had short check-ins about mood at each group session, and distinctly worsened mood or increased suicidality were noticed and assessed by the Principal Investigator for further actions. Participants were also free to withdraw from the study at any time.

A third ethical dilemma regarding research on adolescent depression is that even though participation is voluntary, it is possible that participants feel pressure or expectations from their parents to participate. However, they were free to withdraw from the trial at any time and the participant information clearly stated that participation was entirely voluntary and that they did not have to participate even if their parents wanted them to.

Use of Artificial Intelligence (AI)

During the preparation of this thesis, I used generative AI tools (Copilot, ChatGPT) for limited language support, including checking grammar, punctuation, and abbreviations, and improving wording and flow of individual sentences. All outputs were critically reviewed, and I take full responsibility for the content of the thesis.

Results

Results in numbers - RCT (Papers I-II)

Main findings

The multicenter RCT on group-based exercise versus group-based leisure activities resulted in a final sample of 125 adolescents with mild to moderate depression recruited from routine CAMHS. Participants had a mean age of 15.2 years (SD=1.28), 102 (82%) were girls, with a depression duration of a mean of 21.8 months (SD=18.7), and 48 (38%) had at least one previous depressive episode. More than half (59%) had ongoing antidepressant medication and about a third (30%) had a history of two or more antidepressants despite still being depressed, often defined as treatment resistance.¹⁰ Most participants had other psychiatric comorbidities such as anxiety disorders (63%), ADHD (58%), and Post-Traumatic Stress Disorder (PTSD) (8%).

After randomization, 62 participants were allocated to exercise and 63 participants to leisure activities. Attendance was mean 52% (18.8 sessions) in the exercise group and 55% (19.6 sessions) in the leisure activities group. Equally, 63% of participants from both groups attended at least 50% of sessions, and 60% did neither change or increase dosage of antidepressants and were included in the PP analyses.

The primary outcome, change in CDRS-R, at week 13 did not differ significantly between groups in the ITT analysis ($p=0.348$, Cohen's $f=0.085$, 95% CI: 0-0.261) (Figure 4). However, both groups improved over time between baseline and week 13; with a 12.45 point decrease in mean CDRS-R score for the exercise group ($p<0.001$, Cohen's $d=0.92$) and a 10.12 point decrease ($p<0.001$, Cohen's $d=0.73$) in the leisure group.

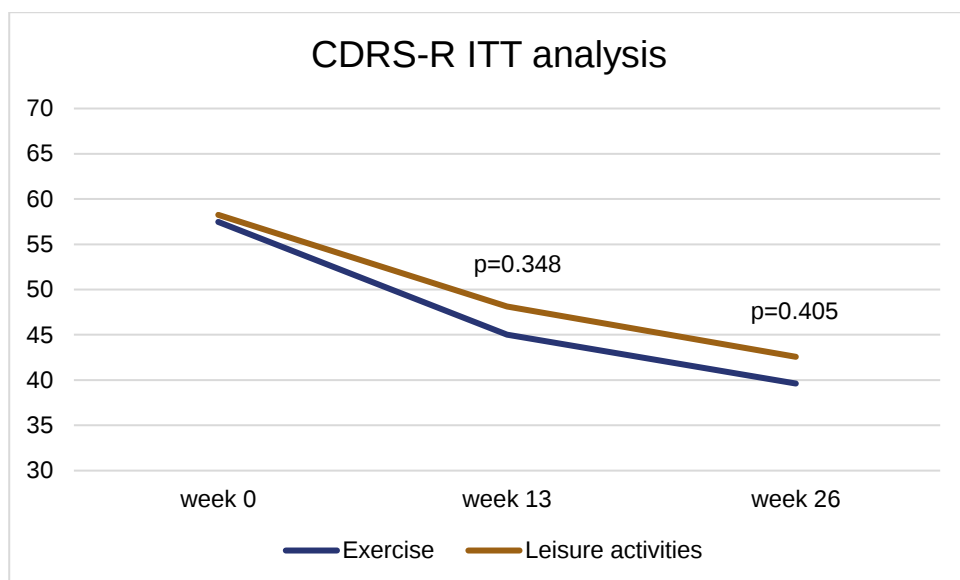


Figure 4. Linear mixed model graph illustrating change in CDRS-R for the ITT analysis

For the secondary outcomes, aerobic capacity ($VO_2\text{max}$) was significantly improved in the exercise group compared to the leisure group at week 13 in the PP analysis ($p=0.026$), but not in the ITT analysis ($p=0.118$). No other secondary outcomes (CGI-S, CGI-I, C-GAS, QIDS-A₁₇-SR and ORS) were significant at either week 13 or 26 in the ITT or PP analyses.

Post-hoc analyses

Response rates according to a $\geq 50\%$ reduction of CDRS-R and CGI-I ≤ 2 at week 13 in the ITT analysis were 25.8% for the exercise group and 14.3% for the leisure group ($p=0.107$), giving a number needed to treat (NNT) of 9. Response rates at week 26 in the ITT analysis were 43.5% in the exercise group and 33.3% in the leisure group ($p=0.240$), with an NNT of 10.

In the PP analysis, response rates at week 13 were 28.9% in the exercise group, which was significantly higher than the leisure group's 10.8% ($p<0.05$) with an NNT of 6. The PP analysis showed a response rate at week 26 of 32.3% in the exercise group and 11.1% in the leisure group, which was not significantly different ($p=0.054$), with an NNT of 5.

Remission rates were low, 8.1% and 9.5% in the exercise and leisure group, respectively, at week 13 in the ITT analysis, and did not differ between groups ($p=0.773$).

When analyzing core depressive symptoms, significant results emerged for the item irritability according to CDRS-R at week 13 in the ITT analysis ($p=0.017$) and according to QIDS-A₁₇-SR at week 13 in the PP analysis ($p=0.025$) in favor of the exercise group. Sadness according to CDRS-R was significantly improved in the exercise group compared to the leisure group in the PP analysis at week 13 ($p=0.038$) and week 26 ($p=0.046$), but not according to QIDS-A₁₇-SR. There were no significant differences between groups on the item anhedonia on CDRS-R or QIDS-A₁₇-SR.

Harms

Adverse events were assessed from three different sources during the intervention period: the HPs' attendance lists, self-reported harms, and through questions on self-harm and suicide from clinician interviews.

Fatigue ($p=0.003$), muscle/joint pain ($p<0.001$), fever ($p=0.045$), menstruation/menstruation pain ($p=0.030$), and stress about sessions ($p=0.027$) were more common in the exercise group compared to the leisure group. The exercise group reported less increased thoughts about self-harm ($p=0.039$) and about suicide ($p=0.026$). Suicide attempt was considered as a severe adverse event (SAE), and 5 were identified in the exercise group and 6 in the leisure group according to self-reports, and did not differ between groups ($p=0.797$), neither did non-suicidal self-injury.

Qualitative experiences of exercise for depression (Paper III)

Main findings

Adolescents', parents', and HPs' experiences of the exercise intervention were abstracted into an overarching theme: group exercise for adolescent depression promotes empowerment and engagement in everyday life. The theme was based on three main categories: exercise alleviates depressive symptoms, exercise contributes to balance in life, and exercise promotes self-esteem (Table 3).

Table 3. Overarching theme, categories, and subcategories exploring adolescents', parents', and healthcare professionals' experiences from exercise for adolescent depression.

Group exercise for adolescent depression promotes empowerment and engagement in everyday life	
Categories:	Sub-categories:
Exercise alleviates depressive symptoms	Physical symptoms Emotional symptoms Cognitive symptoms
Exercise contributes to balance in life	Daily routines Sociability School performance Leisure activities
Exercise promotes self-esteem	Sense of accomplishment New attitude to bodily health

Adapted from Mortazavi et al. Empowered and engaged: Group exercise for adolescent depression – perspectives from adolescents, parents and healthcare professionals. SAGE Open Med. 2024 Feb 3;12:20503121231225340. Licenced under [CC BY](#). Layout modified.

Alleviation of depressive symptoms was experienced through changes in physical, emotional, and cognitive symptoms. Participants described improved strength and energy, but also fatigue. Some participants experienced less sadness and irritability, while others felt more stress from the interventions and the schedule coinciding with school. Cognitive symptoms were improved for some through better memory and concentration, according to parents and adolescents, but not mentioned by HPs.

Exercise was reported to contribute to balance in life by daily routines, sociability, school performance, and leisure activities. The impact on balance in life could be both positive and negative. Some adolescents experienced better routines for eating and sleeping, while others had more difficulties falling asleep after exercise. Adolescents, parents, and HPs agreed that the exercise schedule brought structure to everyday life. Some adolescents found it easier to be social after participating in the group exercise intervention. Parents and HPs described how the adolescents supported each other in the group. There were both positive and negative impacts on school performance; some experienced better attendance while others reported more stress about school because of the exercise schedule. Some reported improved leisure time and more commitment in leisure activities after participating in the exercise intervention.

For some, the exercise intervention improved self-esteem through a sense of accomplishment after managing to participate in an exercise intervention and by gaining a new attitude towards bodily health. Adolescents and parents described improved confidence and self-acceptance, while HPs noticed adolescents developing improved self-esteem. Adolescents were more motivated to continue taking care of their bodies and maintaining exercise after the intervention. The

findings also showed variation, as not all participants described improvements from exercising.

Qualitative understanding of health among adolescents with depression (Paper IV)

Main findings

Adolescents with depression described health in different ways, which were represented by four metaphors: establishing sound routines, connecting to others, managing depression symptoms, and attaining an inner drive (Figure 5).

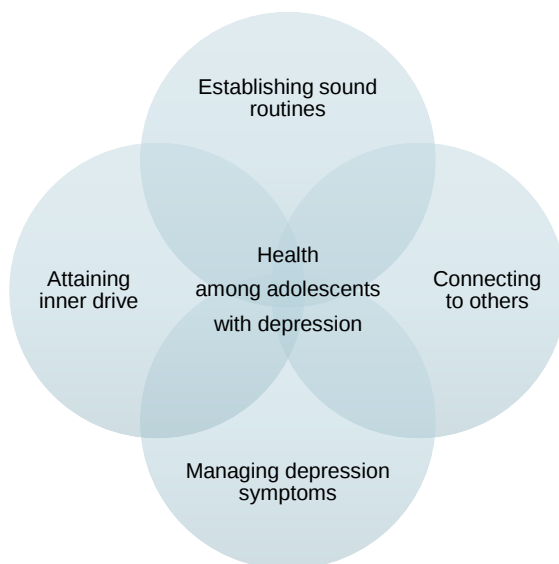


Figure 5. The outcome space for the understanding of health among adolescents with depression. Adapted from Danielsson et al. Depression in adolescence and the understanding of health-A phenomenographic study. PLoS One. 2025 Jan 27;20(1):e0318061. Licenced under [CC-BY 4.0](#). Colors and layout modified.

Establishing sound routines concerned the ability to manage everyday life. Health was understood as having routines and balance related to diet, sleep, physical activity, and distracting activities.

Connecting to others concerned access to social resources. Adolescents described social support and connection to others as important for health, including supportive

family members or friends who understood their situation. Social competence was also described as an aspect of health.

Managing depressive symptoms concerned control over mental illness. Health was understood as finding treatments and strategies to get rid of depressive symptoms and to gain control of depression. Adolescents also described both physical and mental well-being as important for health.

Attaining inner drive concerned experiencing joy in everyday life and included a sense of meaning, purpose, and self-worth. This could involve having a dream or goal, or finding joy and meaning in leisure activities or relationships. Motivation and energy were also considered important for health, and were often something the adolescents were lacking during a depressive episode.

The outcome space illustrated the relations between these four metaphors, describing how they together represented adolescents' understanding of health. They were understood as parts of a whole without being hierarchically ordered. Health could be understood in different ways, and not all adolescents described all four understandings. The four understandings could also support and depend on each other in different ways.

Discussion

Is exercise effective for adolescent depression? (Paper I-II)

Exercise was not superior to leisure activities

Group-based exercise was not superior to group-based leisure activities for adolescent depression severity in this multicenter RCT, although both groups improved over time during the 12-week interventions. Post hoc findings revealed greater improvement on irritability for the exercise group and for sadness, with the latter only being significant in PP analyses. Aerobic capacity was significantly improved and the response rate was higher in the exercise group compared to the leisure group at week 13 in PP analyses.

Our result differs from previous RCTs in the field, who indicate that exercise is superior to control groups for adolescent depression.¹³²⁻¹³⁸ Previous meta-analyses¹²³⁻¹³¹ suggests small to large, but often moderate effect sizes, ranging from 0.41¹²⁹ to 1.14,¹²⁷ compared to our Cohen's $f = 0.085$, corresponding to an effect size approaching the threshold for a small effect with a SMD of -0.17.

The discrepancy regarding the effect size compared to other studies may be due to several reasons. Previous RCTs have methodological limitations which can explain their larger effect sizes for exercise. First, few studies compare exercise to an active control group that receives the identical amount of sessions and social contact, as in our study.^{134,135,138} Other studies compared exercise to treatment as usual¹³³ or no treatment.¹³⁶ Comparing exercise to treatment as usual or wait-list control probably enhances the effect size because these comparator conditions are associated with less improvement. Further, without a structurally matched comparator, it is difficult to distinguish the specific effect of exercise from non-specific factors such as behavioral activation, attention, social interaction, and expectancy. The selection of comparator is important when designing a trial, for being able to answer the research question.¹³⁹

Second, most studies lack blinded outcome assessors and use self-reported symptoms,^{132,133,135-137} possibly overestimating the effect of exercise and making the results more uncertain.

Third, previous studies have often included small sample sizes^{132-136,138} and not all have included clinical participants.¹⁴⁰⁻¹⁴⁸ From studies including clinical participants,¹³²⁻¹³⁸ only some use clinical interviews to confirm the depression diagnosis.^{134,136,137} We recruited clinically referred adolescents with mild to moderate depression and substantial comorbidities, in routine CAMHS, while prior studies often lack detailed information about the study sample, making comparisons difficult. However, our sample is in line with that in the TADS study³⁶ regarding depression severity at baseline, but with longer depression durations and higher frequency of comorbidities. Scores on depression severity, functioning and self-rated depression measures may be influenced by the substantial comorbidities in our sample, thereby limiting participants' improvement and reducing the likelihood of achieving remission. Moreover, our sample being more severely affected may have contributed to the generally low adherence to the interventions. Despite our large sample size compared to previous studies, the RCT might have been underpowered. The exercise group improved slightly more in numerical terms, but the difference was not statistically significant according to most outcomes. The numerical differences were generally larger in the per protocol analyses, indicating that the study might be underpowered to detect smaller effect sizes. Our power calculation was based on the pilot study, to detect an improvement of a mean of 7 CDRS-R points in favor of the exercise group after 12 weeks of intervention. The multicenter RCT produced smaller between group differences of 2.33 points in the ITT analysis and 3.74 points in the PP analysis. The power calculation was thus not based on finding such small between-group differences and would have required a larger number of participants to do so. It is also unclear whether such a small between-group difference is clinically meaningful. However, this difference is similar to the 3.23 points difference between SSRI and placebo in TADS³⁶ and the 2.84 points in a network meta-analysis⁵⁴ that today's depression treatment guidelines are largely based upon.^{15,44}

Fourth, the challenge with scales being less sensitive to change in a cohort with comorbidities is recognized in previous studies on depression.^{199,200} Another sign of a harder-to-treat sample than in previous studies is the rather small improvement in our active control group, which is even smaller than in the TADS placebo group.³⁶ Many (59%) of our participants had already tried at least one antidepressant, which is similar to the TORDIA study that included adolescents not responding to an SSRI.³⁷ In TORDIA, as in our study, there were no difference between groups regarding change in the CDRS-R or self-rated depression symptoms, but a difference was found for response, which was defined equally as in our study using a CGI-I ≤ 2 and at least a 50% reduction on the CDRS-R.³⁷

Fifth, since many (59%) of participants already had antidepressants, the exercise intervention became more of an add-on treatment to treatment resistant MDD, and could be a reason for the small effect. This phenomenon is recognized from adults

with depression, where lower remission rates are seen when more treatment steps have been tried.²⁰¹

It should be noted that the reported mean differences and effect sizes between exercise and leisure activities represent average treatment effects, and some individuals may experience substantially greater improvement. Thus, it is important to further understand for whom exercise is most suitable. Despite no significant differences on overall depressive symptoms, exercise still led to higher response rates among adherent participants and a larger improvement in sadness and irritability compared to leisure activities. The improvement in core depressive symptoms could indicate an antidepressant effect that is partially masked on broader depression scales by high levels of comorbidity. For example, having ADHD and anxiety may not allow for changes on some items on the depression scales. Similarly, adult studies on SSRIs for depression without effects on total depression scales, found significant results when restricting the analysis to the single item of depressed mood.¹⁹⁹

Both intervention groups improved over time

Both intervention groups improved over time, with a 12.45-point improvement in the exercise group and a 10.12-point improvement in the leisure group in the ITT analysis from baseline to 13 weeks. This is a rather small improvement compared to other RCTs on adolescent depression, both in the exercise trial using CDRS-R¹³⁴ and studies on antidepressants and psychological treatment.^{36,37} The small improvement may be due to the burdened sample, as discussed above.

Improvement in both groups could be partly due to behavioral activation from meeting other adolescents regularly. Behavioral activation aims to increase engagement in meaningful and rewarding activities and to reduce withdrawal and avoidance, with the long-term goal of improving mood and daily functioning.¹⁵ Thus, meeting others and establishing new friendships through both interventions may be a mediator, especially for adolescents with prior difficulties with peers or experiences of bullying. The leisure group possibly received more social interaction from conversations and interaction than the exercise group, which may influence the results and lead to an underestimation of the effect of exercise.

The small improvement in both intervention groups in this more burdened sample could also be due to the seasonal variation in sunlight in Sweden. When including participants in March with a follow up in May and August, there might be a seasonal variation in mood that influence depression severity.²⁰² Seasonal variations in mood may also exist due to comorbidity with ADHD. The long summer break from schools may affect the follow up in August and seasonal variations in ADHD show lower symptoms in August, which probably influences the depression rating scales as well.²⁰³ However, the modest improvement observed in both groups over time

suggest a higher degree of chronicity in our sample and likely a reduced influence of seasonal variation.

Another possible explanation for both groups improving over time is regression to the mean, which is a statistical phenomenon where high scorings tend to naturally move closer to the group's mean during repeated assessments. This phenomena could look like an treatment effect, but is rather a spontaneous improvement.²⁰⁴ However, the smaller improvement over time compared to previous depression studies makes regression to the mean a less likely major factor for improvement, but can still contribute.

Furthermore, a placebo effect, that is the expectancy of improvement and the context of the interventions, could explain both groups improving over time. Placebo effects are common in psychiatry studies,²⁰⁵ especially in depression studies,²⁰⁶ and among adolescents with depression.^{60,61} Placebo response rates in studies on adolescent depression are as large as 30-60%.²⁶ Well-designed psychotherapeutic placebo control groups with identical number and duration of sessions is nearly as effective as an active psychotherapeutic treatment.²⁰⁷ Our active control group with leisure activities improved about half of the pill placebo group in TADS according to change in CDRS-R, which contradicts a large placebo-response in our study.³⁶ However, we cannot rule out that the numerically smaller improvement in the leisure activities group could be a possible placebo effect.

Exercise compared to available treatments for depression

According to depression scores

The difference in symptom improvement between the groups was, 2.33 points (not statistically significant) on the CDRS-R for the ITT sample, and 3.74 points (not statistically significant) for the PP sample, at week 13 in favor for the exercise group. These differences are in line with the 2.46⁶¹ and 2.84⁵⁴ point differences between antidepressants and placebo in psychopharmacological meta-analyses on adolescent depression, and the 3.23³⁶ point difference in TADS. When comparing psychological treatments to placebo, CBT did not improve significantly more than placebo in TADS.³⁶ In a clinical practice guideline¹⁵ (based on a systematic review)²⁰⁸ CBT was shown to be superior to waitlist but the evidence was insufficient when comparing to active control or pill placebo. Other meta-analyses include a mix of active and passive controls and do not report changes in depression scores.^{9,45,46,48}

According to effect sizes

Effect sizes of available treatments for adolescent depression are overall small to moderate. Effect sizes for antidepressants range from SMD 0.12 to 0.51,^{8,48,55,61} and

for psychological treatment from SMD 0.05 to 0.41, compared to control conditions.^{9,45-48} As described earlier, there is no consensus whether the combination of psychological treatment with antidepressants are superior to either treatment alone. However, combination of antidepressants and CBT versus placebo enhances effect sizes to SMD 0.73⁴⁸ and Hedge's g 0.98,³⁶ according to some studies. Our study approaches a small effect size corresponding to an SMD of 0.17, which is within the range of effects typically observed for adolescent depression. Previous meta-analyses on exercise for depression arrived at mostly moderate^{123-126,128-130} but sometimes large^{127,131} effect sizes, with SMD between 0.41¹²⁹ to 1.14.¹²⁷ Effect sizes are influenced by the choice of comparator for the active treatment.²⁰⁹ Using passive controls (such as waitlist) often yield larger effect sizes than active controls (such as placebo).²⁰⁹ Pharmacological studies with active controls often use pill placebo, while psychological treatment studies can be an arm in these studies or use waitlist or psychological controls.^{9,36,48,61} The larger effect sizes in previous exercise trials are probably partially due to the use of passive controls,^{133,136} or active controls with fewer sessions.¹³² The effect size may further be larger if participants did not use medication at baseline as in our study. According to studies on adults with depression, when more treatment steps are required, remission rates decrease.²⁰¹

According to number needed to treat (NNT)

Response rates for participants who adhered to at least 50% of sessions were 28.9% in the exercise group and 10.8% in the leisure group ($p < 0.05$) at week 13, with an NNT of 6. At week 26, the NNT decreased to 5, but with borderline significance between groups, still suggesting a potential trend. Previous studies on antidepressants have shown NNTs ranging from 4³⁶ to 10.^{26,210} A meta-analysis on psychological treatments for children and adolescents with depression presented an NNT of 6.2 for response compared to control conditions⁵⁰, while TADS arrived at an NNT of 12 for CBT alone.³⁶ NNTs in studies on adolescent depression are typically influenced by high placebo responses.²⁶ Taken together, the effect of exercise in our study is largely in line with recommended treatments for depression regarding NNT for response. However, still 71% did not respond from exercise in our trial in the PP analysis at week 13. TADS had higher response rates, but based on CGI-I 1-2 alone. Using only the CGI-I criterion, our study had a response rate of 50 %, which is in line with TADS, where 60.6% responded to SSRI and 43.2% to CBT.³⁶

Strengths and limitations of the RCT

Our multicenter RCT address several limitations from earlier studies on exercise for adolescent depression. First, we used an active control group with the same number of sessions and social interaction, enabling us to distinguish the specific effect of exercise from other factors associated with participating in a group intervention,

which is in line with recommendations for selection of comparators in behavioral intervention trials.¹³⁹ Second, we used outcome assessors who were masked to treatment allocation. Third, we used DSM-5 diagnoses verified through clinician-administered interviews. Fourth, we recruited a consecutive clinical cohort with common comorbidities from routine CAMHS, strengthening representativeness to clinical practice. Finally, a strength is the reporting of harms and SAEs that is uncommon in prior exercise trials for adolescent depression.

However, our results should be interpreted in the light of several limitations. First, although our sample was larger than those of previous exercise trials, it was still underpowered to detect small between-group differences. The low attendance rates compared to other exercise trials further aggravates this issue, with only 60% of participants meeting criteria for being included in the PP analysis. Previous RCTs on clinical patients had attendance ranging from 70-77%,^{133,134,136,138} but several studies have not reported attendance rates.^{132,135,137} The lower attendance in our study is possibly due to the more burdened sample, as discussed above. The exercise sessions aimed for a vigorous intensity level, which possibly were too high for this sample, which may have reduced attendance further. Using a more personalized exercise program, with lower intensities when needed, could potentially have enhanced attendance with maintained antidepressant effect.¹¹⁹ The baseline mean CDRS-R score dropped about 1.4 points and C-GAS increased about 1.3 points for the exercise group from the ITT analysis when compared to the PP analysis, which may indicate that more depressed adolescents had difficulties attending the exercise sessions.

A second limitation when recruiting a consecutive cohort from CAMHS with mild to moderate depression is that we ended with a rather chronic sample who had not responded to ongoing clinical care. The sample thus corresponds to a mix of initial treatment for depression as in TADS³⁶ and patients who already tried at least one antidepressant as in TORDIA.³⁷ This is a strength in that the cohort is representative to the CAMHS setting, but improvement from exercise might be larger in a less affected sample or as an initial treatment.²⁰¹

A third limitation is the use of depression scales such as CDRS-R and QIDS-A₁₇-SR in this burdened sample, since the total score probably is influenced by comorbidities and thus not as sensitive to change from interventions for depression.^{199,200}

Fourth, depression is heterogeneous²⁸ and especially with onset in childhood.²⁶ Combinations of symptoms can vary and exercise may be beneficial for participants with certain symptom presentations. It is therefore important to further investigate which participants respond to exercise.

A fifth limitation is that even though we verified depression diagnoses through K-SADS-PL interviews, it can sometimes be difficult to differentiate treatment resistant depression from emotionally unstable personality disorder, since K-SADS-

PL does not contain supplements for personality disorders.²¹¹ The inclusion of adolescents with traits of personality disorders might decrease the effect seen from exercise on depression, since it is known that personality difficulties predict a poorer outcome with shorter time to recurrence of depression.²¹²

Does exercise bring added values to depressed adolescents? (Paper III)

"Not everything that can be counted counts, and not everything that counts can be counted"

William Bruce Cameron, 1963

Not every improvement can be measured by numbers. By combining quantitative measures with qualitative studies, it enables us to grasp important experiences not shown from instruments measuring depression severity. The qualitative study on adolescents', parents', and HPs' experiences from the exercise intervention for adolescent depression showed us that exercise promoted empowerment and engagement in everyday life through alleviated depressive symptoms, balance in life, and promoted self-esteem.

This study brings new insights from adding interviews with parents and HPs. The results are in agreement with previous qualitative studies on exercise for adolescent depression, showing the importance of daily structure,¹⁵²⁻¹⁵⁴ improved mood,^{152,154} and self-esteem.¹⁵²⁻¹⁵⁵

The structure and improved balance in everyday life from a regular exercise schedule resembles the behavioral activation part of CBT, known as an effective treatment for adolescent depression.^{9,213} Behavioral activation is the part of CBT where the engagement in activities, and especially social activities, aims to improve mood over time.²¹³ Thus, by regularly engaging in exercise together with others, the adolescent may gain an effect on their depressive mood despite the possible effect of the heart rate increasing activity itself. This may also be a part of the explanation of why the control group improved over time in the RCT, however with a small improvement compared to other depression studies.³⁶

Some adolescents experienced improved mood and alleviated depressive symptoms. The qualitative methodology does not allow us to grasp if this is by the exercise intervention itself or through mediating factors such as the activation. Others experienced stress and fatigue from the exercise. Even for an adolescent without depression, exercising three hours a week is probably demanding and further so in our study sample. The exercise intervention is unlikely to benefit all adolescents equally and may require a certain level of functioning to attend sessions regularly.

Future studies are important for investigating for which severity of depression or level of functioning exercise is most suitable and manageable.

Participating in the exercise intervention also promoted self-esteem through a sense of accomplishment and a new attitude towards bodily health. Adolescents felt proud for managing to participate in the exercise intervention. They became more aware of exercise as a way to take care of their bodies and got more motivated to exercise. This is an interesting additional value that came up from the qualitative interviews that the other instruments in the RCT did not reveal. The increased self-esteem and moreover the empowerment and gaining of confidence to control one's life and health may be important when it comes to continuing exercise regularly and possibly keeping the depression in remission.

Exercising in a group is probably adding values compared to exercising alone at a gym or at home. First, the group setting was experienced to give a sense of support and togetherness, which may also have encouraged continued attendance. Second, meeting others also contributes to behavioral activation as mentioned above. Guidelines on depression treatments in adults recommend leader led exercise for mild to moderate depression.^{12,13} Supervised exercise sessions results in lower drop out,¹² and thus may contribute to a more regular exercise schedule. Leader-led sessions may further enable participants to attain higher exercise intensities.

Adolescents today report higher levels of loneliness than in previous years.²¹⁴ Loneliness is correlated to negative affect²¹⁴ and increases risk for depression.²¹⁵ Thus, the group interventions in our study may be important also for bringing adolescents together. This is highlighted by the participants themselves through improved sociability and the support they experienced from the group.

Do we measure the right thing? (Paper IV)

Depression trials primary measures depressive symptoms through self-rated depression scales or clinician interviews.^{174,176,183} CDRS-R is the most widely used instrument,²¹⁶ and is based on the Hamilton Depression Rating Scale,¹⁷⁵ while the items on QIDS-A₁₇-SR directly correspond to the DSM-5 criteria for depression.¹⁸³ However, some adolescents suffer from treatment-resistant depression with long durations and no improvement from available treatments. In our sample, participants in general had long durations of depression, many with recurrent episodes, and without substantial improvement from previous treatments. Maybe reaching remission is not the initial goal, but finding relief from what is burdening them the most. In order to grasp what is most essential for those adolescents, it is important to understand how adolescents suffering from depression understand health.

When adolescents with depression expressed what health is, they described the importance of establishing sound routines, connecting to others, managing depressive symptoms, and attaining inner drive. Quantitative depression scales mainly capture symptom-related aspects of health, while the adolescents' descriptions also included routines, social connection, meaning, motivation, and joy.

The importance of routines was also expressed in the study exploring experiences of the exercise intervention, as well as in a study on parents' view on health for adolescents with depression.²¹⁷ Exercise could be a way to establish sound routines, and was also experienced to improve eating and sleep habits according to some adolescents. Scheduled sessions, not particularly exercise, but maybe also leisure activities, could act as a way to establish better daily routines.

Social isolation,^{38,218} social exclusion,²¹⁹ or disconnection³⁹ are associated with adolescent depressive symptoms, and could explain why some adolescents find connecting to others as an important aspect of health. Social exclusion or bullying can also contribute to the development of depression.¹ Regardless of whether social withdrawal is a vulnerability leading to depression or a consequence of the depression, the importance of connecting to others are highlighted by adolescents living with depression. Connecting to others could be achieved by the increased sociability from group exercise or other group activities. Social support can also be enhanced through interventions in other settings, such as sport activities, school interventions, or other group leisure activities. The social aspect was not explicitly analyzed in the RCT, but since adolescents highlighted its importance, future analyses could consider the CDRS-R item 'social withdrawal'.

Both routines and social aspects are aspects that are unlikely to be directly influenced by treatment with antidepressants, but were perceived as important for health according to depressed adolescents.

Attaining an inner drive is an aspect of health seeming to come from within, described as a feeling of joy, motivation, and a sense of meaning or purpose. Feelings of joy and engagement in meaningful activities was also experienced by parents as important for health among adolescents with depression.²¹⁷ Adolescents without depression also highlight meaningfulness as an aspect of health.²²⁰ This aspect is difficult to capture with commonly used depression rating scales, but the lack of motivation and joy may be recognized as anhedonia. Anhedonia is a core criterion of depression, also known as diminished interest or pleasure.³ The absence of anhedonia may allow for feelings of joy and meaningfulness, described as important for health according to adolescents with depression.

Strengths and limitations – qualitative studies (Paper III-IV)

Trustworthiness is a way of describing the quality of qualitative studies, where concepts commonly used in quantitative research, such as validity, reliability, and generalizability are not always directly applicable.¹⁹⁵ Trustworthiness can be described through the concepts of credibility, dependability, confirmability, and transferability.²²¹

Credibility indicates how well the data reflect the focus of the research and whether the findings are grounded in the data.^{195,222} It is influenced by the selection and number of participants for obtaining a rich variation of experiences,¹⁹⁵ sometimes referred to as saturation.²²³ Credibility was strengthened in both studies by using a purposive sampling and sufficient numbers of participants (n=19 and n=33) with variation in age, gender, and depression severity, to ensure a rich data with a variety of aspects, and thus reaching saturation.

Dependability is the aspect focusing on data acquisition and stability of findings over time.¹⁹⁵ Dependability can be influenced by the researchers' pre-understanding, when it comes to interviewing and interpretation of data into codes and categories.²²¹ Dependability was strengthened by the use of individual interviews, via phone or video calls, using an interview guide while allowing for open-ended follow-up questions. However, using digital tools for interviews might limit the quality of the contact between the participant and the interviewer compared to interviews in person. We used two and three interviewers respectively in each study, which both can enhance dependability by increasing variation in the interviews, but might also be considered as a limitation because it can reduce consistency through interviews with differences in interviewer style and interaction between interviewer and participant.

Confirmability describes how well the findings can be confirmed by other researchers, and is enhanced by a neutral interpretation of data.²²² Credibility and confirmability were strengthened through discussions of data within the research groups, consisting of researchers with different backgrounds and experiences. Participants were not asked to read the transcripts for correcting possible misunderstandings, which is a weakness.

Transferability describes how well the findings can be transferred to other settings or groups, and is enhanced by a clear description of the study sample and context.¹⁹⁵ One limitation in paper III is that participants were recruited from a single site in the forthcoming multicenter study, possibly influencing the transferability to other settings or sociodemographic contexts. However, the findings are probably transferable to other CAMHS in Sweden. A further limitation in study IV is that participants were interviewed after randomly having participated in an exercise or leisure activities intervention, possibly influencing their view on health. In the end, it is up to the reader to judge the trustworthiness of a study, based on the methodological decisions and descriptions.¹⁹⁶

Advantages and disadvantages with exercise as a treatment

Despite the effect from exercise as described above, a further advantage is the few serious adverse events recorded, which overall did not differ significantly between exercise and leisure activities. Exercise seems to have mild harms, such as fatigue, muscle/joint pain, fever, and menstrual pain, when comparing to antidepressants with potential harms including agitation, activation, hypomania and increased suicidality.²⁶ In our study exercise even seemed to have a protective effect on thoughts on self-harm and thoughts on suicide, compared to the leisure activities. Furthermore, exercise is known to contribute to cardiorespiratory health, muscular strength, bone health, and a healthier weight.^{34,88} Additional physical tests have been conducted in our project, but not yet analyzed and are not part of this thesis. Exercising in a group seem to promote empowerment, self-esteem, and contribute to balance in life among adolescents with depression. Balance in life was experienced through features such as daily routines, which is further described as an essential aspect of health according to adolescents living with depression. Group interventions such as group exercise bring adolescents together and counteracts isolation, recognized as a common issue when living with depression.^{38,39,41}

A disadvantage with exercise as a treatment is mainly the difficulty attending to sessions regularly, which is a consequence of a rather demanding treatment. For adolescents living with depression and maybe suffering from fatigue, it is easy to imagine difficulties adhering to exercise sessions three times a week compared to taking an antidepressant. Adolescents with depression describe psychological treatment as challenging when it comes to engaging in sessions and completing homework, possibly a similarity with exercise in that it requires more effort.⁵² Barriers for maintaining exercise from a previous qualitative study described factors as disease burden due to fatigue, social anxiety, a lack of drive, and a lack of a supportive environment.¹⁵⁵ Exercise might be more suitable for milder depressions or for adolescents with higher motivation or a certain level of functioning, enabling exercising more regularly. Motivational factors are known to influence the effect of exercise,²²⁴ indicating the importance of involving adolescents when choosing treatment.

Conclusion

Exercise was not superior to a structurally matched active control condition with leisure activities according to depression severity in a clinical sample of adolescents with mild to moderate depression participating in a 12 week intervention three times a week. Both intervention groups improved over time. The multicenter RCT addressed several methodological limitations from previous studies on exercise for adolescent depression, indicating that larger effect sizes from previous meta-analyses might reflect comparisons with weaker and passive controls and unblinded outcome measures. However, the not statistically significant effect size from exercise in our study is in line with the effects of recommended treatments with antidepressants and psychological treatments for adolescents with depression.

Among participants with attendance to at least half of the sessions and no change of antidepressants, the exercise group responded more often and improved in aerobic capacity, as well as on the core depressive symptoms irritability and sadness.

Exercise had few serious adverse events and mild harms. Exercise promoted empowerment and engagement in everyday life, and contributed to sound routines, and connection to others, described as important aspects of health among adolescents living with depression.

Planned additional research within the project

We are planning to conduct a prediction study where, based on baseline variables, we want to evaluate who benefited the most from exercise as a treatment for depression in this sample of clinical patients with MDD. We further want to assess how exercise compared to leisure activities affects various physiological parameters, including muscular strength, body mass index, and body composition. We also plan to assess the effect of exercise on biomarkers from blood sampling. Additionally, we want to evaluate cost-effectiveness comparing the two interventions. Lastly, we will conduct a one-year follow up study, after the randomization is broken, and where all participants have been offered to participate in an exercise intervention.

Recommendations for future research

Depression is a heterogeneous condition and exercise is possibly more effective for some individuals than others. Future research is needed to better understand which subgroups benefit most from exercise. Promising avenues include examining exercise at a primary care level with adolescents with less comorbidities and higher levels of functioning, as well as exploring whether exercise is more effective for those with poor aerobic capacity, elevated inflammatory markers, or higher level of motivation that may support adherence.

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References

1. Daly M. Prevalence of Depression Among Adolescents in the U.S. From 2009 to 2019: Analysis of Trends by Sex, Race/Ethnicity, and Income. *J Adolesc Health*. Mar 2022;70(3):496-499. doi:10.1016/j.jadohealth.2021.08.026
2. Mojtabai R, Olfson M, Han B. National Trends in the Prevalence and Treatment of Depression in Adolescents and Young Adults. *Pediatrics*. 2016;Dec(6)(138):e20161878. doi:10.1542/peds.2016-1878
3. American Psychiatric Association A. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, Text Revision (DSM-5-TR)*. American Psychiatric Association; 2022.
4. GBD Mental Disorders Collaborators. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Psychiatry*. Feb 2022;9(2):137-150. doi:10.1016/S2215-0366(21)00395-3
5. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet*. Mar 17 2012;379(9820):1056-67. doi:10.1016/S0140-6736(11)60871-4
6. Hawton K, Saunders K, Topiwala A, Haw C. Psychiatric disorders in patients presenting to hospital following self-harm: a systematic review. *J Affect Disord*. Dec 2013;151(3):821-30. doi:10.1016/j.jad.2013.08.020
7. Goldstein BI, Carnethon MR, Matthews KA, et al. Major Depressive Disorder and Bipolar Disorder Predispose Youth to Accelerated Atherosclerosis and Early Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. Sep 8 2015;132(10):965-86. doi:10.1161/CIR.0000000000000229
8. Locher C, Koechlin H, Zion SR, et al. Efficacy and Safety of Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, and Placebo for Common Psychiatric Disorders Among Children and Adolescents: A Systematic Review and Meta-analysis. *JAMA Psychiatry*. Oct 1 2017;74(10):1011-1020. doi:10.1001/jamapsychiatry.2017.2432
9. Weisz JR, Kuppens S, Ng MY, et al. What five decades of research tells us about the effects of youth psychological therapy: A multilevel meta-analysis and implications for science and practice. *Am Psychol*. Feb-Mar 2017;72(2):79-117. doi:10.1037/a0040360
10. Dwyer JB, Stringaris A, Brent DA, Bloch MH. Annual Research Review: Defining and treating pediatric treatment-resistant depression. *J Child Psychol Psychiatry*. Mar 2020;61(3):312-332. doi:10.1111/jcpp.13202

11. World Health Organization. *Global status report on physical activity 2022*. 2022. <https://www.who.int/publications/i/item/9789240059153>
12. Stubbs B, Vancampfort D, Hallgren M, et al. EPA guidance on physical activity as a treatment for severe mental illness: a meta-review of the evidence and Position Statement from the European Psychiatric Association (EPA), supported by the International Organization of Physical Therapists in Mental Health (IOPTMH). *Eur Psychiatry*. Oct 2018;54:124-144. doi:10.1016/j.eurpsy.2018.07.004
13. National Board of Health and Welfare. *Nationella riktlinjer för vård vid depression och ångestsyndrom*. 2021. <https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/nationella-riktlinjer/2021-4-7339.pdf>
14. Svenska föreningen för barn- och ungdomspsykiatri. *SFBUP Riktlinje depression 2024*. 2024. <https://slf.se/sfbup/app/uploads/2024/03/riktlinje-depression-webb.pdf>
15. Walter HJ, Abright AR, Bukstein OG, et al. Clinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Major and Persistent Depressive Disorders. *J Am Acad Child Adolesc Psychiatry*. May 2023;62(5):479-502. doi:10.1016/j.jaac.2022.10.001
16. Thapar A, Eyre O, Patel V, Brent D. Depression in young people. *Lancet*. Aug 20 2022;400(10352):617-631. doi:10.1016/S0140-6736(22)01012-1
17. Spoelma MJ, Sicouri GL, Francis DA, Songco AD, Daniel EK, Hudson JL. Estimated Prevalence of Depressive Disorders in Children From 2004 to 2019: A Systematic Review and Meta-Analysis. *JAMA Pediatr*. Oct 1 2023;177(10):1017-1027. doi:10.1001/jamapediatrics.2023.3221
18. Sawyer S, Azzopardi P, Wickremarathne D, Patton G. The age of adolescence. *The Lancet Child & Adolescent Health*. 2018;2:223-228.
19. Lu B, Lin L, Su X. Global burden of depression or depressive symptoms in children and adolescents: A systematic review and meta-analysis. *J Affect Disord*. 2024 Jun(354)(1):553-562. doi:10.1016/j.jad.2024.03.074
20. Wiens K, Williams JV, Lavorato DH, et al. Is the prevalence of major depression increasing in the Canadian adolescent population? Assessing trends from 2000 to 2014. *J Affect Disord*. 2017 Mar(210)(1):22-26. doi:10.1016/j.jad.2016.11.018
21. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global Prevalence of Depressive and Anxiety Symptoms in Children and Adolescents During COVID-19: A Meta-analysis. *JAMA Pediatr*. Nov 1 2021;175(11):1142-1150. doi:10.1001/jamapediatrics.2021.2482
22. Madigan S, Racine N, Vaillancourt T, et al. Changes in Depression and Anxiety Among Children and Adolescents From Before to During the COVID-19 Pandemic: A Systematic Review and Meta-analysis. *JAMA Pediatr*. Jun 1 2023;177(6):567-581. doi:10.1001/jamapediatrics.2023.0846
23. COVID-19 Mental Disorders Collaborators. Global prevalence and burden of depressive and anxiety disorders in 204 countries and territories in 2020 due to the COVID-19 pandemic. *Lancet*. Nov 6 2021;398(10312):1700-1712. doi:10.1016/S0140-6736(21)02143-7

24. Ormel J, Raven D, van Oort F, et al. Mental health in Dutch adolescents: a TRAILS report on prevalence, severity, age of onset, continuity and co-morbidity of DSM disorders. *Psychol Med*. Jan 2015;45(2):345-60. doi:10.1017/S0033291714001469
25. Shorey S, Ng ED, Wong CHJ. Global prevalence of depression and elevated depressive symptoms among adolescents: A systematic review and meta-analysis. *Br J Clin Psychol*. Jun 2022;61(2):287-305. doi:10.1111/bjc.12333
26. Birmaher B, Brent D. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Depressive Disorders. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2007;46(11):1503-1526. doi:10.1097/chi.0b013e318145ae1c
27. Keyes KM, Gary D, O'Malley PM, Hamilton A, Schulenberg J. Recent increases in depressive symptoms among US adolescents: trends from 1991 to 2018. *Soc Psychiatry Psychiatr Epidemiol*. Aug 2019;54(8):987-996. doi:10.1007/s00127-019-01697-8
28. Fried EI, Nesse RM. Depression is not a consistent syndrome: An investigation of unique symptom patterns in the STAR*D study. *J Affect Disord*. 2015;Feb(172)(1):96-102. doi:10.1016/j.jad.2014.10.010
29. Regier DA, Narrow WE, Clarke DE, et al. DSM-5 field trials in the United States and Canada, Part II: test-retest reliability of selected categorical diagnoses. *Am J Psychiatry*. 2013 Jan(1)(170):59-70.
30. Stringaris A. Editorial: What is depression? *J Child Psychol Psychiatry*. Dec 2017;58(12):1287-1289. doi:10.1111/jcpp.12844
31. Wang CS, Kavalali ET, Monteggia LM. BDNF signaling in context: From synaptic regulation to psychiatric disorders. *Cell*. Jan 6 2022;185(1):62-76. doi:10.1016/j.cell.2021.12.003
32. Ernst C, Olson A, Pinel J, Lam R, Christie B. Antidepressant effects of exercise: evidence for an adult-neurogenesis hypothesis? *J Psychiatry Neurosci*. 2006;Mar;31(2):84-92.
33. Kandola A, Ashdown-Franks G, Hendrikse J, Sabiston CM, Stubbs B. Physical activity and depression: Towards understanding the antidepressant mechanisms of physical activity. *Neurosci Biobehav Rev*. Dec 2019;107:525-539. doi:10.1016/j.neubiorev.2019.09.040
34. World Health Organization. *Global Accelerated Action for the Health of Adolescents (AA-HA!): guidance to support country implementation, second edition*. 2023. <https://www.who.int/publications/i/item/9789240081765>
35. Grossberg A, Rice T. Depression and Suicidal Behavior in Adolescents. *Med Clin North Am*. Jan 2023;107(1):169-182. doi:10.1016/j.mcna.2022.04.005
36. March J, Silva S, Petrycky S, et al. Fluoxetine, cognitive-behavioral therapy, and their combination for adolescents with depression: Treatment for Adolescents With Depression Study (TADS) randomized controlled trial. *JAMA*. Aug 18 2004;292(7):807-20. doi:10.1001/jama.292.7.807

37. Brent D, Emslie G, Clarke G, et al. Switching to Another SSRI or to Venlafaxine With or Without Cognitive Behavioral Therapy for Adolescents With SSRI Resistant Depression: The TORDIA Randomized Controlled Trial. *JAMA*. 2008;Feb 27(8)(299):901-913. *JAMA*. 2019 Nov 5;322(17):1718. doi: 10.1001/jama.2019.16240. doi:10.1001/jama.299.8.901.
38. Midgley N, Parkinson S, Holmes J, Stapley E, Eatough V, Target M. Beyond a diagnosis: The experience of depression among clinically-referred adolescents. *J Adolesc*. Oct 2015;44:269-79. doi:10.1016/j.adolescence.2015.08.007
39. Twivy E, Kirkham M, Cooper M. The lived experience of adolescent depression: A systematic review and meta-aggregation. *Clin Psychol Psychother*. Jul-Aug 2023;30(4):754-766. doi:10.1002/cpp.2834
40. McCann TV, Lubman DI, Clark E. The experience of young people with depression: a qualitative study. *J Psychiatr Ment Health Nurs*. May 2012;19(4):334-40. doi:10.1111/j.1365-2850.2011.01783.x
41. Viduani A, Arenas DL, Benetti S, Wahid SS, Kohrt BA, Kieling C. Systematic Review and Meta-Synthesis: How Is Depression Experienced by Adolescents? A Synthesis of the Qualitative Literature. *J Am Acad Child Adolesc Psychiatry*. Oct 2024;63(10):970-990. doi:10.1016/j.jaac.2023.11.013
42. Goodyer IM, Dubicka B, Wilkinson P, et al. A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial. *Health Technol Assess*. 2008;May;12(14):iii-iv, ix-60. doi:10.3310/hta12140.
43. Goodyer IM, Reynolds S, Barrett B, et al. Cognitive-behavioural therapy and short-term psychoanalytic psychotherapy versus brief psychosocial intervention in adolescents with unipolar major depression (IMPACT): a multicentre, pragmatic, observer-blind, randomised controlled trial. *Health Technol Assess*. Mar 2017;21(12):1-94. doi:10.3310/hta21120
44. The National Institute for Health and Care Excellence (NICE). *Depression in children and young people: identification and management*. Vol. NG134. 2025. www.nice.org.uk/guidance/ng134
45. Weisz JR, McCarty CA, Valeri SM. Effects of psychotherapy for depression in children and adolescents: a meta-analysis. *Psychol Bull*. 2006;Jan(1)(132):132-49. doi:10.1037/0033-2909.132.1.132
46. Keles S, Idsoe T. A meta-analysis of group Cognitive Behavioral Therapy (CBT) interventions for adolescents with depression. *J Adolesc*. Aug 2018;67:129-139. doi:10.1016/j.adolescence.2018.05.011
47. Oud M, de Winter L, Vermeulen-Smit E, et al. Effectiveness of CBT for children and adolescents with depression: A systematic review and meta-regression analysis. *Eur Psychiatry*. Apr 2019;57:33-45. doi:10.1016/j.eurpsy.2018.12.008
48. Zhou X, Teng T, Zhang Y, et al. Comparative efficacy and acceptability of antidepressants, psychotherapies, and their combination for acute treatment of children and adolescents with depressive disorder: a systematic review and network meta-analysis. *Lancet Psychiatry*. Jul 2020;7(7):581-601. doi:10.1016/S2215-0366(20)30137-1

49. Rosselló J, Bernal G. The efficacy of cognitive-behavioral and interpersonal treatments for depression in Puerto Rican adolescents. *Journal of Consulting and Clinical Psychology*. 1999;67(5):734–745.
50. Cuijpers P, Karyotaki E, Ciharova M, et al. The effects of psychological treatments of depression in children and adolescents on response, reliable change, and deterioration: a systematic review and meta-analysis. *Eur Child Adolesc Psychiatry*. Jan 2023;32(1):177-192. doi:10.1007/s00787-021-01884-6
51. Ferguson N, Rice S, Gleeson J, Davey CG, Hetrick SE. The experience of young people receiving cognitive behavioural therapy for major depression: A qualitative study. *Early Interv Psychiatry*. Jan 2023;17(1):47-56. doi:10.1111/eip.13290
52. Herring GT, Loades ME, Higson-Sweeney N, Hards E, Reynolds S, Midgley N. The experience of cognitive behavioural therapy in depressed adolescents who are fatigued. *Psychol Psychother*. Mar 2022;95(1):234-255. doi:10.1111/papt.12365
53. Wilmots E, Midgley N, Thackeray L, Reynolds S, Loades M. The therapeutic relationship in Cognitive Behaviour Therapy with depressed adolescents: A qualitative study of good-outcome cases. *Psychol Psychother*. Jun 2020;93(2):276-291. doi:10.1111/papt.12232
54. Hetrick SE, McKenzie JE, Bailey AP, et al. New generation antidepressants for depression in children and adolescents: a network meta-analysis. *Cochrane Database Syst Rev*. May 24 2021;5(5):CD013674. doi:10.1002/14651858.CD013674.pub2
55. Cipriani A, Zhou X, Del Giovane C, et al. Comparative efficacy and tolerability of antidepressants for major depressive disorder in children and adolescents: a network meta-analysis. *Lancet*. Aug 27 2016;388(10047):881-90. doi:10.1016/S0140-6736(16)30385-3
56. Stahl SM. *Stahl's Essential Psychopharmacology Fourth Edition*. Cambridge University Press; 2013.
57. Gray NA, Milak MS, DeLorenzo C, et al. Antidepressant treatment reduces serotonin-1A autoreceptor binding in major depressive disorder. *Biol Psychiatry*. Jul 1 2013;74(1):26-31. doi:10.1016/j.biopsych.2012.11.012
58. Murphy SE, Capitao LP, Giles SLC, Cowen PJ, Stringaris A, Harmer CJ. The knowns and unknowns of SSRI treatment in young people with depression and anxiety: efficacy, predictors, and mechanisms of action. *Lancet Psychiatry*. Sep 2021;8(9):824-835. doi:10.1016/S2215-0366(21)00154-1
59. Calarge CA, Mills JA, Karaviti L, Teixeira AL, Zemel BS, Garcia JM. Selective Serotonin Reuptake Inhibitors Reduce Longitudinal Growth in Risperidone-Treated Boys. *J Pediatr*. Oct 2018;201:245-251. doi:10.1016/j.jpeds.2018.05.040
60. Läkemedelsverket. *Behandlingsrekommendation: Depression och ångest*. Vol. november 2025. 2025. www.lakemedelsverket.se/depression-angest
61. Feeney A, Hock RS, Fava M, Hernandez Ortiz JM, Iovieno N, Papakostas GI. Antidepressants in children and adolescents with major depressive disorder and the influence of placebo response: A meta-analysis. *J Affect Disord*. May 15 2022;305:55-64. doi:10.1016/j.jad.2022.02.074

62. Cox GR, Callahan P, Churchill R, et al. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. *Cochrane Database Syst Rev*. Nov 30 2014;2014(11):CD008324. doi:10.1002/14651858.CD008324.pub3
63. Melvin GA, Tonge BJ, King NJ, Heyne D, Gordon MS, Klimkeit E. A comparison of cognitive-behavioral therapy, sertraline, and their combination for adolescent depression. *J Am Acad Child Adolesc Psychiatry*. Oct 2006;45(10):1151-1161. doi:10.1097/01.chi.0000233157.21925.71
64. Cuijpers P, Noma H, Karyotaki E, Vinkers CH, Cipriani A, Furukawa TA. A network meta-analysis of the effects of psychotherapies, pharmacotherapies and their combination in the treatment of adult depression. *World Psychiatry*. 2020 Feb(1)(19):92-107. doi:10.1002/wps.20701
65. Davey CG, Chanen AM, Hetrick SE, et al. The addition of fluoxetine to cognitive behavioural therapy for youth depression (YoDA-C): a randomised, double-blind, placebo-controlled, multicentre clinical trial. *Lancet Psychiatry*. Sep 2019;6(9):735-744. doi:10.1016/S2215-0366(19)30215-9
66. Maroun RA, Thackeray LA, Midgley N. Meaning and medication: a thematic analysis of depressed adolescents' views and experiences of SSRI antidepressants alongside psychological therapies. *BMC Psychiatry*. Nov 28 2018;18(1):374. doi:10.1186/s12888-018-1961-y
67. Price J, Cole V, Goodwin GM. Emotional side-effects of selective serotonin reuptake inhibitors: qualitative study. *Br J Psychiatry*. Sep 2009;195(3):211-7. doi:10.1192/bjp.bp.108.051110
68. Gibson K, Cartwright C, Read J. 'In my life antidepressants have been...': a qualitative analysis of users' diverse experiences with antidepressants. *BMC Psychiatry*. May 11 2016;16:135. doi:10.1186/s12888-016-0844-3
69. Leaver AM, Espinoza R, Wade B, Narr KL. Parsing the Network Mechanisms of Electroconvulsive Therapy. *Biol Psychiatry*. 2022;Aug 1(3)(92):193-203. doi:10.1016/j.biopsych.2021.11.016.
70. Rask O, Nordenskjöld A, Johansson BA, Movahed Rad P. Electroconvulsive therapy in children and adolescents: results from a population-based study utilising the Swedish National Quality Register. *Eur Child Adolesc Psychiatry*. 2023 Dec(12)(32):2649-2656. doi:10.1007/s00787-022-02123-2
71. UK ECT Review Group. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. Mar 8 2003;361(9360):799-808. doi:10.1016/S0140-6736(03)12705-5
72. Dellink A, Vanderhaegen G, Coppens V, et al. Inflammatory markers associated with electroconvulsive therapy response in patients with depression: A meta-analysis *Neurosci Biobehav Rev*. 2025;Mar(106060)(170)doi:10.1016/j.neubiorev.2025.106060
73. Deng ZD, Robins PL, Regenold W, Rohde P, Dannhauer M, Lisanby SH. How electroconvulsive therapy works in the treatment of depression: is it the seizure, the electricity, or both? *Neuropsychopharmacology*. Jan 2024;49(1):150-162. doi:10.1038/s41386-023-01677-2

74. Croarkin PE, MacMaster FP. Transcranial Magnetic Stimulation for Adolescent Depression. *Child Adolesc Psychiatr Clin N Am*. Jan 2019;28(1):33-43. doi:10.1016/j.chc.2018.07.003
75. Donaldson AE, Gordon MS, Melvin GA, Barton DA, Fitzgerald PB. Addressing the needs of adolescents with treatment resistant depressive disorders: a systematic review of rTMS. *Brain Stimul*. Jan-Feb 2014;7(1):7-12. doi:10.1016/j.brs.2013.09.012
76. Wall CA, Croarkin PE, Maroney-Smith MJ, et al. Magnetic Resonance Imaging-Guided, Open-Label, High-Frequency Repetitive Transcranial Magnetic Stimulation for Adolescents with Major Depressive Disorder. *J Child Adolesc Psychopharmacol*. Sep 2016;26(7):582-9. doi:10.1089/cap.2015.0217
77. Croarkin PE, Elmaadawi AZ, Aaronson ST, et al. Left prefrontal transcranial magnetic stimulation for treatment-resistant depression in adolescents: a double-blind, randomized, sham-controlled trial. *Neuropsychopharmacology*. Jan 2021;46(2):462-469. doi:10.1038/s41386-020-00829-y
78. Srivastava AV, Nemeroff CB, O'Sullivan SJ. TMS in adolescent depression: A milestone FDA clearance. *Mol Psychiatry*. Feb 10 2026;doi:10.1038/s41380-026-03455-0
79. Zanos P, Gould TD. Mechanisms of ketamine action as an antidepressant. *Mol Psychiatry*. Apr 2018;23(4):801-811. doi:10.1038/mp.2017.255
80. Jelen LA, Stone JM. Ketamine for depression. *Int Rev Psychiatry*. May 2021;33(3):207-228. doi:10.1080/09540261.2020.1854194
81. World Health Organization. Basic documents: forty-ninth edition. 2020;
82. Ott MA, Rosenberger JG, McBride KR, Woodcox SG. How do adolescents view health? Implications for state health policy. *J Adolesc Health*. Apr 2011;48(4):398-403. doi:10.1016/j.jadohealth.2010.07.019
83. Singletary JH, Bartle CL, Sviryzdenka N, Suter-Giorgini NM, Cashmore AM, Dogra N. Young people's perceptions of mental and physical health in the context of general wellbeing. *Health Education Journal*. 2015;74(3):257-269.
84. Parvizi S, Hamzehgardeshi Z. Adolescents' view of health concept and its risk factors: a literature review. *Int J Adolesc Med Health*. 2014;26(3):351-9. doi:10.1515/ijamh-2013-0311
85. Borraccino A, Pera R, Lemma P. "What being healthy means to me": A qualitative analysis uncovering the core categories of adolescents' perception of health. *PLoS One*. 2019;14(6):e0218727.
86. World Health Organization. *Global action plan on physical activity 2018–2030: more active people for a healthier world*. 2018.
87. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research *Public Health Rep*. 1985;Mar-Apr(2)(100):126-31.
88. U.S. Department of Health and Human Services. *Physical Activity Guidelines for Americans 2th edition*. 2018.

89. Canning KL, Brown RE, Jamnik VK, Salmon A, Ardern CI, Kuk JL. Individuals underestimate moderate and vigorous intensity physical activity. *PLoS One*. 2014;9(5):e97927. doi:10.1371/journal.pone.0097927
90. Raghuveer G, Hartz J, Lubans DR, et al. Cardiorespiratory Fitness in Youth: An Important Marker of Health: A Scientific Statement From the American Heart Association. *Circulation*. Aug 18 2020;142(7):e101-e118. doi:10.1161/CIR.0000000000000866
91. Rennie KL, Hemingway H, Kumari M, Brunner E, Malik M, Marmot M. Effects of moderate and vigorous physical activity on heart rate variability in a British study of civil servants. *Am J Epidemiol*. Jul 15 2003;158(2):135-43. doi:10.1093/aje/kwg120
92. May R, McBerty V, Zaky A, Gianotti M. Vigorous physical activity predicts higher heart rate variability among younger adults. *J Physiol Anthropol*. Jun 14 2017;36(1):24. doi:10.1186/s40101-017-0140-z
93. Leone M, Levesque P, Bourget-Gaudreault S, et al. Secular trends of cardiorespiratory fitness in children and adolescents over a 35-year period: Chronicle of a predicted foretold. *Front Public Health*. 2022;10:1056484. doi:10.3389/fpubh.2022.1056484
94. Rodriguez-Ayllon M, Cadenas-Sanchez C, Estevez-Lopez F, et al. Role of Physical Activity and Sedentary Behavior in the Mental Health of Preschoolers, Children and Adolescents: A Systematic Review and Meta-Analysis. *Sports Med*. Sep 2019;49(9):1383-1410. doi:10.1007/s40279-019-01099-5
95. Jaycox LH, Murphy ER, Zehr JL, Pearson JL, Avenevoli S. Social Media and Suicide Risk in Youth. *JAMA Netw Open*. Oct 1 2024;7(10):e2441499. doi:10.1001/jamanetworkopen.2024.41499
96. Ferguson CJ, Kaye LK, Branley-Bell D, Markey P. There is no evidence that time spent on social media is correlated with adolescent mental health problems: Findings from a meta-analysis. *Professional Psychology: Research and Practice*. 2025;56(1):73–83. doi:<https://doi.org/10.1037/pro0000589>
97. Li L, Zhang Q, Zhu L, et al. Screen time and depression risk: A meta-analysis of cohort studies. *Front Psychiatry*. 2022;13:1058572. doi:10.3389/fpsyt.2022.1058572
98. Twenge JM, Martin GN, Campbell WK. Decreases in psychological well-being among American adolescents after 2012 and links to screen time during the rise of smartphone technology. *Emotion*. Sep 2018;18(6):765-780. doi:10.1037/emo0000403
99. Folkhälsomyndigheten. *Forskningssammanställning om digital medieanvändning och psykisk, fysisk och sexuell hälsa samt levnadsvanor bland barn och unga*. 2024. <https://www.folkhalsomyndigheten.se/contentassets/e7ca33c8783a4bfc86a4b431f950b8ea/forskningssammanstallning-digital-medieanvandning-psykisk-fysisk-sexuell-halsa-levnadsvanor-barn-unga.pdf>
100. Liu M, Kamper-DeMarco KE, Zhang J, Xiao J, Dong D, Xue P. Time Spent on Social Media and Risk of Depression in Adolescents: A Dose-Response Meta-Analysis. *Int J Environ Res Public Health*. Apr 24 2022;19(9)doi:10.3390/ijerph19095164

101. Santos RMS, Mendes CG, Sen Bressani GY, et al. The associations between screen time and mental health in adolescents: a systematic review. *BMC Psychol.* Apr 20 2023;11(1):127. doi:10.1186/s40359-023-01166-7
102. Nagata JM, Otmar CD, Shim J, et al. Social Media Use and Depressive Symptoms During Early Adolescence. *JAMA Netw Open.* May 1 2025;8(5):e2511704. doi:10.1001/jamanetworkopen.2025.11704
103. Folkhälsomyndigheten. *Rekommendationer för barns och ungas digitala medieanvändning.* 2024.
<https://www.folkhalsomyndigheten.se/contentassets/201463a976054dde8ad7aa8a47861c0a/rekommendationer-digitala-medier-barns-ungas-medieanvandning.pdf>
104. WHO Guidelines on Physical Activity and Sedentary Behaviour (2020).
105. American Academy of Pediatrics. Screen Time Guidelines. Updated 2025. Accessed 2026-07-07, 2026. <https://www.aap.org/en/patient-care/media-and-children/center-of-excellence-on-social-media-and-youth-mental-health/qa-portal/qa-portal-library/qa-portal-library-questions/screen-time-guidelines/?srsltid=AfmBOoq9Peht17PhCPnodDGGeBb5sHYdOuX7eunCpSzO7MywQOE-fw5h>
106. Folkhälsomyndigheten. Råd om skärmar för ungdomar 13–18 år – information till föräldrar. Updated 2026-03-17. Accessed 2026-04-22,
<https://www.folkhalsomyndigheten.se/publikationer-och-material/publikationsarkiv/r/rad-om-skarmar-for-ungdomar-13-18-ar-information-till-foraldrar/>
107. Folkhälsomyndigheten. Rekommendation om när barn tidigast bör få en egen smart telefon. 26th june, 2026. Updated 11th june 2026. Accessed 2026-06-26,
<https://www.folkhalsomyndigheten.se/vara-amnesomraden/digitala-medier-och-halsa/rekommendation-13-ar-for-smart-telefon/>
108. van Sluijs EMF, Ekelund U, Crochemore-Silva I, et al. Physical activity behaviours in adolescence: current evidence and opportunities for intervention. *Lancet.* Jul 31 2021;398(10298):429-442. doi:10.1016/S0140-6736(21)01259-9
109. Basso JC, Suzuki WA. The Effects of Acute Exercise on Mood, Cognition, Neurophysiology, and Neurochemical Pathways: A Review. *Brain Plast.* Mar 28 2017;2(2):127-152. doi:10.3233/BPL-160040
110. Gormley SE, Swain DP, High R, et al. Effect of intensity of aerobic training on VO2max. *Med Sci Sports Exerc.* Jul 2008;40(7):1336-43. doi:10.1249/MSS.0b013e31816c4839
111. Chen H, Xu J, Xie H, Huang Y, Shen X, Xu F. Effects of physical activity on heart rate variability in children and adolescents: a systematic review and meta-analysis. *Cien Saude Colet.* May 2022;27(5):1827-1842. doi:10.1590/1413-8123202275.10402021
112. Kreppke JN, Brupbacher G, Rupf K, et al. Association Between Physical Activity, Heart Rate Variability and Major Depressive Disorders: An Umbrella Review. *Sports Med.* Mar 2026;56(3):703-723. doi:10.1007/s40279-025-02365-5

113. Wade L, Eime R, Pankowiak A, et al. The impact of sports participation on psychological health and social outcomes in children and adolescents: a systematic review and update to the "Mental Health through Sport" conceptual model. *Syst Rev*. Mar 11 2026;doi:10.1186/s13643-026-03104-1
114. Zhang X, Cao T, Zhang W, Xie L, Nie Y, Dai Y. A network analysis of the relationship between active health behaviors and mental health in adolescents. *BMC Psychol*. Feb 6 2026;14(1)doi:10.1186/s40359-026-04080-w
115. Knowles C, Paradis KF, Breslin G, Shannon S, Carlin A. Physical activity in childhood and adolescence and future depressive symptoms: an 11-year prospective cohort study. *Eur J Public Health*. Oct 10 2023;33(5):878-883. doi:10.1093/eurpub/ckad122
116. Noetel M, Sanders T, Gallardo-Gomez D, et al. Effect of exercise for depression: systematic review and network meta-analysis of randomised controlled trials. *BMJ*. Feb 14 2024;384:e075847. doi:10.1136/bmj-2023-075847
117. Morres ID, Hatzigeorgiadis A, Stathi A, et al. Aerobic exercise for adult patients with major depressive disorder in mental health services: A systematic review and meta-analysis. *Depress Anxiety*. Jan 2019;36(1):39-53. doi:10.1002/da.22842
118. Krogh J, Hjorthøj C, Speyer H, Gluud C, Nordentoft M. Exercise for patients with major depression: a systematic review with meta-analysis and trial sequential analysis. *BMJ Open*. 2017;7(9)doi:10.1136/bmjopen-2016-014820
119. Meyer JD, Koltyn KF, Stegner AJ, Kim JS, Cook DB. Influence of Exercise Intensity for Improving Depressed Mood in Depression: A Dose-Response Study. *Behav Ther*. 2016 Jul(4)(47):527-37. doi:10.1016/j.beth.2016.04.003
120. Santos A, Braaten K, MacPherson M, et al. Rates of compliance and adherence to high-intensity interval training: a systematic review and Meta-analyses. *Int J Behav Nutr Phys Act*. Nov 21 2023;20(1):134. doi:10.1186/s12966-023-01535-w
121. Casanova-Lizon A, Manresa-Rocamora A, Sarabia JM, et al. Impact of heart rate variability-based exercise prescription: self-guided by technology and trainer-guided exercise in sedentary adults. *Front Sports Act Living*. 2025;7:1578478. doi:10.3389/fspor.2025.1578478
122. Rahman MH, B; Hallgren, M; Forsell, Y; Stubbs, B; Vancampfort, D; Ekblom, Ö. Cardiorespiratory fitness and response to exercise treatment in depression. *BJPsych Open*. 2018 Aug 14(5)(4):346-351. doi:10.1192/bjo.2018.45
123. Carter T, Morres ID, Meade O, Callaghan P. The Effect of Exercise on Depressive Symptoms in Adolescents: A Systematic Review and Meta-Analysis. *J Am Acad Child Adolesc Psychiatry*. Jul 2016;55(7):580-90. doi:10.1016/j.jaac.2016.04.016
124. Axelsdottir B, Biedilae S, Sagatun A, Nordheim LV, Larun L. Review: Exercise for depression in children and adolescents - a systematic review and meta-analysis. *Child Adolesc Ment Health*. Nov 2021;26(4):347-356. doi:10.1111/camh.12438
125. Oberste M, Medele M, Javelle F, et al. Physical Activity for the Treatment of Adolescent Depression: A Systematic Review and Meta-Analysis. *Front Physiol*. 2020;11:185. doi:10.3389/fphys.2020.00185

126. Radovic S, Gordon MS, Melvin GA. Should we recommend exercise to adolescents with depressive symptoms? A meta-analysis. *J Paediatr Child Health*. Mar 2017;53(3):214-220. doi:10.1111/jpc.13426
127. Yan H, Chen R, Chen D, Li C. Effectiveness of exercise intervention on children and adolescents with depression: a systematic review and meta-analysis of randomized controlled trial. *Front Psychiatry*. 2025;16:1699554. doi:10.3389/fpsy.2025.1699554
128. Singh B, Bennett H, Miatke A, et al. Systematic Umbrella Review and Meta-Meta-Analysis: Effectiveness of Physical Activity in Improving Depression and Anxiety in Children and Adolescents. *J Am Acad Child Adolesc Psychiatry*. Apr 14 2025;doi:10.1016/j.jaac.2025.04.007
129. Li J, Zhou X, Huang Z, Shao T. Effect of exercise intervention on depression in children and adolescents: a systematic review and network meta-analysis. *BMC Public Health*. Oct 4 2023;23(1):1918. doi:10.1186/s12889-023-16824-z
130. Wang X, Cai ZD, Jiang WT, Fang YY, Sun WX, Wang X. Systematic review and meta-analysis of the effects of exercise on depression in adolescents. *Child Adolesc Psychiatry Ment Health*. Feb 28 2022;16(1):16. doi:10.1186/s13034-022-00453-2
131. Zhang Y, Li G, Liu C, Guan J, Zhang Y, Shi Z. Comparing the efficacy of different types of exercise for the treatment and prevention of depression in youths: a systematic review and network meta-analysis. *Front Psychiatry*. 2023;14:1199510. doi:10.3389/fpsy.2023.1199510
132. Brown SW, Welsh MC, Labbé EE. Aerobic exercise in the psychological treatment of adolescents. *Percept Mot Skills* 1992;(74):555–60.
133. Carter T, Guo B, Turner D, et al. Preferred intensity exercise for adolescents receiving treatment for depression: a pragmatic randomised controlled trial. *BMC Psychiatry*. 2015;15(1)doi:10.1186/s12888-015-0638-z
134. Hughes CW, Barnes S, Barnes C, Defina LF, Nakonezny P, Emslie GJ. Depressed Adolescents Treated with Exercise (DATE): A pilot randomized controlled trial to test feasibility and establish preliminary effect sizes. *Ment Health Phys Act*. Jun 2013;6(2)doi:10.1016/j.mhpa.2013.06.006
135. Kanner KD. High versus low-intensity exercise as part of an inpatient treatment program for childhood and adolescent depression. *Diss Abstr Int*. 1990;(51):4053.
136. Wunram HL, Hamacher S, Hellmich M, et al. Whole body vibration added to treatment as usual is effective in adolescents with depression: a partly randomized, three-armed clinical trial in inpatients. *Eur Child Adolesc Psychiatry*. May 2018;27(5):645-662. doi:10.1007/s00787-017-1071-2
137. Zhang J, Li S, Ji W. Exercise intervention improves the quality of life, anxiety, and depression of adolescent depression patients. *Int J Clin Exp Med*. 2021;14(2):1292-1300.
138. Philippot A, Dubois V, Lambrechts K, et al. Impact of physical exercise on depression and anxiety in adolescent inpatients: A randomized controlled trial. *J Affect Disord*. Mar 15 2022;301:145-153. doi:10.1016/j.jad.2022.01.011

139. Freedland KE, King AC, Ambrosius WT, et al. The selection of comparators for randomized controlled trials of health-related behavioral interventions: recommendations of an NIH expert panel. *J Clin Epidemiol.* Jun 2019;110:74-81. doi:10.1016/j.jclinepi.2019.02.011
140. Dabidy Roshan V, Pourasghar M, Mohammadian Z. The Efficacy of Intermittent Walking in Water on the Rate of MHPG Sulfate and the Severity of Depression. *Iran J Psychiatry Behav Sci.* 2011;5(2):26-31.
141. Jeong YH, SC; Lee, MS; Park, MC; Kim, YK; Suh, CM. Dance movement therapy improves emotional responses and modulates neurohormones in adolescents with mild depression. *Int J Neurosci.* 2005;Dec;115(12):1711-20.
142. Moghaddam JBH, M; Salehian, M H; Shirmohammadzadeh, M Effect of Different Exercises on Reducing Male Students Depression *Annals of Biological Research.* 2012;3(3):1231-1235.
143. Mohammadi M. A Study and Comparison of the Effect of Team Sports (Soccer and Volleyball) and Individual Sports (Table Tennis and Badminton) on Depression among High School Students. *Australian Journal of Basic and Applied Sciences.* 2011;5(12):1005-1011.
144. Uebelacker LA, Wolff JC, Guo J, et al. Assessing feasibility and acceptability of yoga and group CBT for adolescents with depression: A pilot randomized clinical trial. *Clin Child Psychol Psychiatry.* Apr 2023;28(2):525-540. doi:10.1177/13591045221092885
145. Beffert JW. *Aerobic exercise as treatment of depressive symptoms in early adolescents.* University of Northern Colorado; 1993.
146. Gu Q, Zhao X, Lin L, Teo WP, Liu L, Yuan S. Effects of open-skill and closed-skill exercise on subthreshold depression in female adolescents: A randomized controlled trial. *Int J Clin Health Psychol.* Oct-Dec 2024;24(4):100512. doi:10.1016/j.ijchp.2024.100512
147. Lin K, Stubbs B, Zou W, et al. Aerobic exercise impacts the anterior cingulate cortex in adolescents with subthreshold mood syndromes: a randomized controlled trial study. *Transl Psychiatry.* May 18 2020;10(1):155. doi:10.1038/s41398-020-0840-8
148. Zhang J, Qin S, Zhou Y, Meng L, Su H, Zhao S. A randomized controlled trial of mindfulness-based Tai Chi Chuan for subthreshold depression adolescents. *Neuropsychiatr Dis Treat.* 2018;14:2313-2321. doi:10.2147/NDT.S173255
149. Jarbin H, Hoglund K, Skarphedinsson G, Bremander A. Aerobic exercise for adolescent outpatients with persistent major depression: Feasibility and acceptability of moderate to vigorous group exercise in a clinically referred sample. *Clin Child Psychol Psychiatry.* Oct 2021;26(4):954-967. doi:10.1177/13591045211000782
150. Tang Y, Jia Y, Li D, Li Q, Wang J, Fu Q. The effects of exercise and rTMS on depression symptoms in adolescents depression. *Front Psychol.* 2025;16:1496344. doi:10.3389/fpsyg.2025.1496344
151. Tian S, Che W, Liang Z, Qiu F, Yu Y, Wang X. The effects of exercise type and dose on depression in children and adolescents: A systematic review, network, and dose-response meta-analysis. *J Affect Disord.* Feb 1 2026;394(Pt B):120604. doi:10.1016/j.jad.2025.120604

152. Serrander M, Bremander A, Jarbin H, Larsson I. Joy of living through exercise - a qualitative study of clinically referred adolescents' experiences of moderate to vigorous exercise as treatment for depression. *Nord J Psychiatry*. Nov 2021;75(8):574-581. doi:10.1080/08039488.2021.1909128
153. Reinodt S, Haglund E, Bremander A, Jarbin H, Larsson I. Adolescents' Long-Term Experiences of Manageability, Comprehensibility, and Meaningfulness of a Group-Based Exercise Intervention for Depression. *Int J Environ Res Public Health*. Mar 2 2022;19(5)doi:10.3390/ijerph19052894
154. Carter T, Morres I, Repper J, Callaghan P. Exercise for adolescents with depression: valued aspects and perceived change. *J Psychiatr Ment Health Nurs*. Feb 2016;23(1):37-44. doi:10.1111/jpm.12261
155. Sunesson E, Haglund E, Bremander A, Jarbin H, Larsson I. Adolescents' Experiences of Facilitators for and Barriers to Maintaining Exercise 12 Months after a Group-Based Intervention for Depression. *Int J Environ Res Public Health*. May 19 2021;18(10)doi:10.3390/ijerph18105427
156. Erickson KI, Miller DL, Roecklein KA. The aging hippocampus: interactions between exercise, depression, and BDNF. *Neuroscientist*. Feb 2012;18(1):82-97. doi:10.1177/1073858410397054
157. Alizadeh Pahlavani H. Possible role of exercise therapy on depression: Effector neurotransmitters as key players. *Behav Brain Res*. Feb 29 2024;459:114791. doi:10.1016/j.bbr.2023.114791
158. Zwolinska W, Dmistrz-Weglarz M, Slopian A. Biomarkers in Child and Adolescent Depression. *Child Psychiatry Hum Dev*. Feb 2023;54(1):266-281. doi:10.1007/s10578-021-01246-y
159. Davis I, Liu A. What is the tryptophan kynurenine pathway and why is it important to neurotherapeutics? *Expert Rev Neurother*. 2015;15(7):719-21. doi:10.1586/14737175.2015.1049999
160. Savitz J. The kynurenine pathway: a finger in every pie. *Mol Psychiatry*. Jan 2020;25(1):131-147. doi:10.1038/s41380-019-0414-4
161. Nikkheslat N, Zajkowska Z, Legido-Quigley C, et al. Sex-Specific Alterations of the Kynurenine Pathway in Association With Risk for and Remission of Depression in Adolescence. *Biol Psychiatry*. Oct 1 2025;98(7):549-557. doi:10.1016/j.biopsych.2024.11.020
162. Colasanto M, Madigan S, Korczak DJ. Depression and inflammation among children and adolescents: A meta-analysis. *J Affect Disord*. Dec 1 2020;277:940-948. doi:10.1016/j.jad.2020.09.025
163. Ignacio ZM, da Silva RS, Plissari ME, Quevedo J, Reus GZ. Physical Exercise and Neuroinflammation in Major Depressive Disorder. *Mol Neurobiol*. Dec 2019;56(12):8323-8335. doi:10.1007/s12035-019-01670-1
164. Euteneuer F, Schwarz MJ, Dannehl K, Hartung A, Westermann S, Rief W. Increased soluble interleukin-2 receptor levels are related to somatic but not to cognitive-affective features in major depression. *Brain Behav Immun*. 2012 Nov(8)(26):1244-8. doi:10.1016/j.bbi.2012.06.007

165. Eyre H, Baune BT. Neuroimmunological effects of physical exercise in depression. *Brain Behav Immun*. Feb 2012;26(2):251-66. doi:10.1016/j.bbi.2011.09.015
166. O'Connor JC, McCusker RH, Strle K, Johnson RW, Dantzer R, Kelley KW. Regulation of IGF-I function by proinflammatory cytokines: at the interface of immunology and endocrinology. *Cell Immunol* 2008 Mar-Apr(1-2)(252):91-110. doi:10.1016/j.cellimm.2007.09.010
167. Andersson P, Lundberg J, Jarbin H, Jokinen J, Desai Bostrom AE. Inverse association of anti-inflammatory prescription fills and suicide-related mortality in young adults: Evidence from a nationwide study of Swedish regions, 2006-2021. *Brain Behav Immun Health*. Aug 2023;31:100665. doi:10.1016/j.bbih.2023.100665
168. Lopez-Duran NL, Kovacs M, George CJ. Hypothalamic-pituitary-adrenal axis dysregulation in depressed children and adolescents: a meta-analysis. *Psychoneuroendocrinology*. Oct 2009;34(9):1272-83. doi:10.1016/j.psyneuen.2009.03.016
169. Zajkowska Z, Gullett N, Walsh A, et al. Cortisol and development of depression in adolescence and young adulthood - a systematic review and meta-analysis. *Psychoneuroendocrinology*. Feb 2022;136:105625. doi:10.1016/j.psyneuen.2021.105625
170. Du H, Dong D, Huang H. Aerobic exercise for depression symptoms in adolescents: a systematic review and dose-response meta-analysis. *BMC Public Health*. Feb 5 2026;26(1)doi:10.1186/s12889-026-26504-3
171. Budde H, Wegner M, Ahrens C, et al. Effects of Acute Coordinative vs. Endurance Exercise on Cortisol Concentration in Healthy Women and Men *Sports Med Open*. 2025;Jun 10(1)(11):72. doi:10.1186/s40798-025-00884-z
172. Sturmey P. Behavioral Activation Is an Evidence-Based Treatment for Depression *Behavior Modification*. 2009;33(6):818-829. doi:<https://doi.org/10.1177/0145445509350094>
173. Zimmerman MA. Psychological empowerment: issues and illustrations. *Am J Community Psychol*. Oct 1995;23(5):581-99. doi:10.1007/BF02506983
174. Poznanski EO, Mokros HB. *Children's depression rating scale, revised (CDRS-R) manual*. Western Psychological Services; 1996.
175. Mayes TL, Bernstein IH, Haley CL, Kennard BD, Emslie GJ. Psychometric Properties of the Children's Depression Rating Scale-Revised in Adolescents. *Journal of Child and Adolescent Psychopharmacology*. 2010;20(6):513-516. doi:10.1089/cap.2010.0063
176. Zhang CY, Voort JLV, Yuruk D, et al. A Characterization of the Clinical Global Impression Scale Thresholds in the Treatment of Adolescent Depression Across Multiple Rating Scales. *J Child Adolesc Psychopharmacol*. Jun 2022;32(5):278-287. doi:10.1089/cap.2021.0111
177. Keller F GJ, Ernst M, Spröber N, Fegert JM, Kölch M. Children's Depression Rating Scale-Revised (CDRS-R): development of a German version and psychometric properties in a clinical sample. *Z Kinder Jugendpsychiatr Psychother*. 2011;May(3)(39):179-85. doi:10.1024/1422-4917/a000090

178. Huang Y, Li X, Li J, et al. Reliability and Validity of the Chinese Version of the Children's Depression Rating Scale-Revised (CDRS-R). *Healthcare (Basel)*. Mar 2025;13(7):doi:10.3390/healthcare13070734
179. Kim KM NS, Choi JW, Jung AH, Hong SB, Kim JW, Kim SY, Kim E, Kim JW. Psychometric Properties and Factor Structures of the Korean Version of Children's Depression Rating Scale-Revised. *J Child Adolesc Psychopharmacol*. 2018;May(4)(28):285-292. doi:10.1089/cap.2016.0183
180. Shaffer D, Gould MS, Brasic J, et al. A children's global assessment scale (CGAS). *Arch Gen Psychiatry*. Nov 1983;40(11):1228-31. doi:10.1001/archpsyc.1983.01790100074010
181. Jozefiak T, Hanssen-Bauer K, Bjelland I. Måleegenskaper ved den norske versjonen av Children's Global Assessment Scale (CGAS). *PsykTestBarn*. 2018;8(1):1-16. doi:10.21337/0058
182. Busner J, Targum SD. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*. 2007;Jul(7)(4):28-37.
183. Bernstein IH, Rush AJ, Trivedi MH, et al. Psychometric properties of the Quick Inventory of Depressive Symptomatology in adolescents. *Int J Methods Psychiatr Res*. Dec 2010;19(4):185-94. doi:10.1002/mpr.321
184. Haley CL, Kennard BD, Morris DW, et al. The Quick Inventory of Depressive Symptomatology, Adolescent Version (QIDS-A17): A Psychometric Evaluation. *Neuropsychiatr Dis Treat*. 2023 May(19)(2):1085-1102. doi:10.2147/NDT.S400591
185. Miller S, Duncan B, Brown J, Sparks J, Claud D. The Outcome Rating Scale: A Preliminary Study of the Reliability, Validity, and Feasibility of a Brief Visual Analog Measure *Journal of Brief Therapy*. 2003;2(Spring/Summer)
186. Bringhurst MDL, Watson CW, Miller SD, Duncan BL. The Reliability and Validity of the Outcome Rating Scale: A Replication Study of a Brief Clinical Measure. *Journal of Brief Therapy*. 2006;5(1)
187. Duncan BL, Sparks JA, Miller SD, Bohanske RT, Claud DA. Giving Youth a Voice: A Preliminary Study of the Reliability and Validity of a Brief Outcome Measure for Children, Adolescents, and Caretakers. *Journal of Brief Therapy*. 2006;5(2)
188. Åstrand I. Aerobic work capacity in men and women with special reference to age. *Acta Physiol Scand Suppl*. 1960;49:1-92.
189. Berndtsson G, Mattsson E, Marcus C, Larsson UE. Age and gender differences in VO2max in Swedish obese children and adolescents. *Acta Paediatr*. 2007 Apr(4)(96):567-71. doi:10.1111/j.1651-2227.2007.00139.x
190. Lee EY, Barnes JD, Lang JJ, Silva DAS, Tomkinson GR, Tremblay MS. Testing validity of FitnessGram in two samples of US adolescents (12-15 years) *J Exerc Sci Fit*. 2020 Sep(3)(18):129-135. doi:10.1016/j.jesf.2020.04.002
191. Ortega FB, Artero EG, Ruiz JR, et al. Physical fitness levels among European adolescents: the HELENA study. *Br J Sports Med*. 2011 Jan(1)(45):20-9. doi:10.1136/bjsm.2009.062679
192. Gerber M, Schilling T, Ludyga S, et al. Validity and feasibility of four standardized aerobic fitness tests in patients with depression: A cross-sectional study. *J Psychiatr Res*. Jan 2025;181:116-125. doi:10.1016/j.jpsychires.2024.11.019

193. Cohen J. A power primer. *Psychol Bull.* 1992 Jul(1)(112):155-9. doi:10.1037//0033-2909.112.1.155
194. Leppink J, O'Sullivan P, Winston K. Effect size - large, medium, and small. *Perspect Med Educ* 2016 Dec(6)(5):347-349. doi:10.1007/s40037-016-0308-y
195. Graneheim UH, Lundman B. Qualitative content analysis in nursing research: concepts, procedures and measures to achieve trustworthiness. *Nurse Educ Today.* Feb 2004;24(2):105-12. doi:10.1016/j.nedt.2003.10.001
196. Doyle L, McCabe C, Keogh B, Brady A, McCann M. An overview of the qualitative descriptive design within nursing research. *J Res Nurs.* Aug 2020;25(5):443-455. doi:10.1177/1744987119880234
197. Marton F, Booth S. *Learning and Awareness.* Lawrence Erlbaum Associates, Publishers; 1997.
198. Larsson J, Holmström I. Phenomenographic or phenomenological analysis: does it matter? Examples from a study on anaesthesiologists' work. *International Journal of Qualitative Studies on Health and Well-being.* 2007;2(1):55-64.
199. Hieronymus F, Emilsson JF, Nilsson S, Eriksson E. Consistent superiority of selective serotonin reuptake inhibitors over placebo in reducing depressed mood in patients with major depression. *Mol Psychiatry.* Apr 2016;21(4):523-30. doi:10.1038/mp.2015.53
200. Lisinski A, Hieronymus F, Naslund J, Nilsson S, Eriksson E. Item-based analysis of the effects of duloxetine in depression: a patient-level post hoc study. *Neuropsychopharmacology.* Feb 2020;45(3):553-560. doi:10.1038/s41386-019-0523-4
201. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry.* 2006 Nov(11)(163):1905-17. doi:10.1176/ajp.2006.163.11.1905
202. Jack RH, Joseph RM, Hollis C, et al. Seasonal trends in antidepressant prescribing, depression, anxiety and self-harm in adolescents and young adults: an open cohort study using English primary care data. *BMJ Ment Health.* Oct 2023;26(1)doi:10.1136/bmjment-2023-300855
203. Kovalenko PA, Hoven CW, Wicks J, Moore RE, Mandell DJ, Liu H. Seasonal variations in internalizing, externalizing, and substance use disorders in youth. *Psychiatry Res.* 2000;May 15(2)(94):103-19. doi:10.1016/s0165-1781(00)00140-2
204. Hengartner MP. Is there a genuine placebo effect in acute depression treatments? A reassessment of regression to the mean and spontaneous remission *BMJ Evid Based Med.* 2020 Apr(2)(25):46-48. doi:10.1136/bmjebm-2019-111161
205. Weimer K, Colloca L, Enck P. Placebo effects in psychiatry: mediators and moderators. *Lancet Psychiatry.* Mar 2015;2(3):246-57. doi:10.1016/S2215-0366(14)00092-3
206. Jones BDM, Razza LB, Weissman CR, et al. Magnitude of the Placebo Response Across Treatment Modalities Used for Treatment-Resistant Depression in Adults: A Systematic Review and Meta-analysis. *JAMA Netw Open.* Sep 1 2021;4(9):e2125531. doi:10.1001/jamanetworkopen.2021.25531

207. Baskin TW, Tierney SC, Minami T, Wampold BE. Establishing specificity in psychotherapy: a meta-analysis of structural equivalence of placebo controls. *J Consult Clin Psychol*. 2003;Dec(6)(71):973-9. doi:10.1037/0022-006X.71.6.973
208. Viswanathan M, Kennedy SM, McKeeman J, et al. *Treatment of Depression in Children and Adolescents: A Systematic Review [Internet]*. Rockville (MD): Agency for Healthcare Research and Quality (US); 2020.
209. Wadhwa M, Cook TD. The Set of Assumptions Randomized Control Trials Make and Their Implications for the Role of Such Experiments in Evidence-Based Child and Adolescent Development Research *New Dir Child Adolesc Dev*. 2019;Sep(167):17-37. doi:10.1002/cad.20313
210. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. *JAMA*. 2007;Apr 18(297(15)):1683-96. doi:10.1001/jama.297.15.1683
211. Kaufman J, Birmaher B, Brent D, et al. Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL): initial reliability and validity data. *J Am Acad Child Adolesc Psychiatry*. 1997;Jul(7)(36):980-8. doi:10.1097/00004583-199707000-00021
212. Karlsson L, Kiviruusu O, Miettunen J, et al. One-year course and predictors of outcome of adolescent depression: a case-control study in Finland. *J Clin Psychiatry*. 2008 May(5)(69):844-53. doi:10.4088/jcp.v69n0519
213. Smarason O, Skarphedinsson G, Storch EA. Cognitive Behavioral Therapy for Anxiety and Depression in Children and Adolescents. *Psychiatr Clin North Am*. Jun 2024;47(2):311-323. doi:10.1016/j.psc.2024.02.002
214. Twenge JM, Haidt J, Blake AB, McAllister C, Lemon H, Le Roy A. Worldwide increases in adolescent loneliness. *J Adolesc*. Dec 2021;93:257-269. doi:10.1016/j.adolescence.2021.06.006
215. Loades ME, Chatburn E, Higson-Sweeney N, et al. Rapid Systematic Review: The Impact of Social Isolation and Loneliness on the Mental Health of Children and Adolescents in the Context of COVID-19. *J Am Acad Child Adolesc Psychiatry*. Nov 2020;59(11):1218-1239 e3. doi:10.1016/j.jaac.2020.05.009
216. Jain S, Carmody TJ, Trivedi MH, et al. A psychometric evaluation of the CDRS and MADRS in assessing depressive symptoms in children *J Am Acad Child Adolesc Psychiatry*. 2007;Sep(9)(46):1204-1212. doi:10.1097/chi.0b013e3180cc2575
217. Persson S, Haglund E, Mortazavi R, Jarbin H, Larsson I. Parents' Perceptions of What Health Means for Adolescents with Depression-A Qualitative Study. *Children (Basel)*. Sep 21 2025;12(9)doi:10.3390/children12091267
218. Christiansen J, Qualter P, Friis K, et al. Associations of loneliness and social isolation with physical and mental health among adolescents and young adults. *Perspect Public Health*. Jul 2021;141(4):226-236. doi:10.1177/17579139211016077
219. Reicher H, Matischek-Jauk M. Depressive adolescents at risk of social exclusion: The potentials of social-emotional learning in schools. *Improving Schools*. 2019;22(1):43-54.

220. Johansson A, Brunnberg E, Eriksson C. Adolescent girls' and boys' perceptions of mental health. *Journal of Youth Studies*. 2007;10(183–202)(2)
221. Graneheim UH, Lindgren BM, Lundman B. Methodological challenges in qualitative content analysis: A discussion paper. *Nurse Educ Today*. Sep 2017;56:29-34. doi:10.1016/j.nedt.2017.06.002
222. Korstjens I, Moser A. Series: Practical guidance to qualitative research. Part 4: Trustworthiness and publishing. *Eur J Gen Pract*. Dec 2018;24(1):120-124. doi:10.1080/13814788.2017.1375092
223. Malterud K, Siersma VD, Guassora AD. Sample Size in Qualitative Interview Studies: Guided by Information Power. *Qual Health Res*. Nov 2016;26(13):1753-1760. doi:10.1177/1049732315617444
224. Wunram HL, Hamacher S, Oberste M, et al. Influence of motivational placebo-related factors on the effects of exercise treatment in depressive adolescents. *Eur Child Adolesc Psychiatry*. Jul 2022;31(7):1-14. doi:10.1007/s00787-021-01742-5

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