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Research paper

# Impact of physical exercise on depression and anxiety in adolescent inpatients: A randomized controlled trial

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Abbreviations
STAI
state-trait anxiety inventory
CDI
children depression inventory
HADS
hospital anxiety and depression scale
SDS
zung self-rating depression scale
BDI-13, beck depression inventory (13 items)
HAM-D
hamilton rating scale for depression
VO2max
maximal oxygen consumption

ABSTRACT

*Background:* Physical exercise therapy is of proven efficacy in the treatment of adults with depression, but corresponding evidence is lacking in depressed adolescent inpatients. The aim of this study was to document the effect of add-on treatment with structured physical exercise in a clinical population of adolescents hospitalized for depression and anxiety in a psychiatric hospital.
*Methods:* A group of 52 adolescent inpatients was randomly assigned to a physical exercise or control program three to four times per week over a six-week period (20 hours in total). The primary outcome was the Hospital Anxiety Depression Scale (HADS) for evaluation of depression and anxiety symptoms. Secondary outcomes were psychological self-assessments, diagnostic interviews, and physical examinations.
*Results:* Six participants were lost in each group, leaving 20 inpatients each in the intervention and control groups. A linear mixed model with F-test revealed a significant interaction in favor of physical exercise in reducing the mean depression score (HADS-D) by 3.8 points [95% (CI), range 1.8 to 5.7], compared to a mean reduction score of 0.7 [95% (CI), range -0,7 to 2.0] in the control group. No significant interaction was found for anxiety symptoms (HADS-A).
*Limitations:* The investigation was limited to the six-week hospital window and the small sample size prevented exploring differences in social characteristics.
*Conclusion:* Structured physical exercise add-on therapy integrated into the psychiatric hospitalization of adolescents has led to a reduction in their depressive symptoms, demonstrating its effectiveness in the care of adolescent inpatients with depression.

## 1. Introduction

"Depression is the leading cause of disability worldwide, and is a major contributor to the overall global burden of disease" (WHO (World Health Organization) 2020). Symptoms of depression and anxiety can first arise from childhood to adolescence with different severity levels, although not often leading to a clinical diagnosis. In fact, some 10% of adolescents experience subclinical depression (Bertha and Balazs, 2013), which is often associated with functional impairment and interference in their education, and may also be a precursor to a major depressive disorder in adulthood (Bertha and Balazs, 2013; Wesselhoeft et al., 2013). Furthermore, there is evidence for a causal association whereby anxiety precedes depression (Garber and Weersing, 2010), such that many young people with depressive symptoms suffer from

; HADS, Hospital Anxiety and Depression Scale; SDS, Zung Self-Rating Depression Scale; BDI-13, Beck Depression Inventory (13 items); CDI, Children Depression Inventory; STAI, State-Trait Anxiety Inventory; HAM-D, Hamilton-D: Hamilton Rating Scale for Depression; VO2MAX, Maximal Oxygen Consumption.

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comorbid anxiety. Early detection of depression and anxiety symptoms is crucial for timely initiation of treatment. The optimal treatment of depression and anxiety symptoms in young people should include complementary non-pharmaceutical options such as cognitive behavior and interpersonal therapies (Weersing, et al., 2017), and calls for attention to the risk of suicidality in adolescents treated with antidepressant medications (Stone et al., 2009).

There are many cohort studies or Randomized Controlled Trials (RCT) indicating that participation in physical activity or appropriate exercise programs is associated with a decrease in depressive symptoms among adults (Schuch et al., 2016) or adolescents (Bailey et al., 2018; Carter et al., 2016; Larun et al., 2006; Oberste et al., 2020; Radovic et al., 2017; Wegner et al., 2020). Previous studies with a RCT design have shown the positive effects of exercise on depression in adolescent outpatients (Carter et al., 2015; Hughes et al., 2013), some of which have been conducted in adolescents with severe depression (Dabidy et al., 2011). However, there are few data regarding the effect of exercise therapy as an add-on treatment in psychiatric units for adolescents (12-19 years old), which calls for additional studies (Carter et al., 2016; Radovic et al., 2017; Wegner et al., 2020). In the present study, we investigated the effect of structured physical exercise as an add-on treatment of depression and anxiety symptoms in a sample of teens hospitalized in a specialized psychiatric setting for youths. Psychiatric units for adolescents offer multidisciplinary residential care to young people suffering from severe psychological symptoms in a psychosocial crisis where outpatient care is not sufficient. In addition to this acute context, it has not yet been shown that implementing a structured physical exercise program in substantial and multidisciplinary psychiatric care can effectively better reduce psychological symptoms in a clinical sample of adolescents. We tested the hypothesis that a brief structured exercise program would result in a greater psychological improvement than a control program entailing social relaxation.

## 2. Methods

### 2.1. Design

We conducted a randomized controlled trial (RCT) to compare the effectiveness of a physical exercise intervention and a social relaxation activity for inpatients in a psychiatric hospital for adolescents. The two interventions entailed four sessions of 1 hour per week and lasting for five weeks to a total of twenty-hours of activity per program. For the complete Consolidated Standards of Reporting Trials (CONSORT) checklist, please see *Supporting Appendix S1*. This trial was registred as follows: Move and Feel Good, NCT02970825, https://clinicaltrials.gov/ct2/show/NCT02970825.

### 2.2. Participants

Participants were recruited on a voluntary basis in a psychiatric setting for adolescents in the AREA+ Epsylon ASBL ("Association Sans But Lucratif', "nonprofit organisation"), in Brussels, Belgium. All patients were receiving multidisciplinary care (psychiatrists, family and individual psychologists, social workers, artist monitor, nurses, educators, psychomotor therapist, physical education teachers, physiotherapists). After randomization, participants were included in only one intervention and they could not participate in the other arm. All participants could electively join other basic physical activities in addition to the research-related exercise and social-relaxation interventions. We could not refuse access to these activities for participants for ethical reasons. Participation in these activities was open, with free intensity, and not structured but supervised for security whereas the experimental structured physical exercise treatment was developed as an original add-on treatment. Information was recorded on their education level and school attendance and researchers were blinded to the participants' medication status until the end of the study. Written informed consent according to the Declaration of Helsinki and a medical history were required from the legal guardians of people aged less than 18 years of age, in addition to written consent from each participant.

### 2.3. Eligibility criteria

The inclusion criteria were that participants should be: participating in an official educational program before hospitalization; aged between 12 and 19 years; and willing to accept the principle of randomization; while having no neurological history (such as illness or head trauma), no schizophrenia or other psychosis, no uncorrected sensory disturbance preventing them from understanding of the instructions; and having no conduct disorders; and were being hospitalized for at least six weeks. The exclusion criteria were as follows: refusal to participate; Body Mass Index higher than P95 (meaning obesity with potential cardiovascular risk, with exception of specific cases with medical authorization); unstable diabetes; coagulation disorders (with exception of specific cases with medical authorization); severe and unstable asthma; history of heart defect or cardiovascular disease; any other medical conditions prohibiting sport or physical activity; behavioral disturbance and/or negative attitudes towards group activities. To identify whether the participants met all criteria, information was collected during a joint interview by a psychiatrist and a general practitioner.

### 2.4. Ethics approval

Ethics authorization was received from the ethics committee of the Faculty of Medicine of the Université catholique de Louvain and the local ethics committee of Epsylon ASBL (N°. CEHF-2016/17FEV/060-B403201627586).

### 2.5. Randomization and blinding

Before and after the interventions, the adolescents undertook psychological and physical tests. At baseline, the principal investigator, who was blind to the identity and characteristics of the participants, allocated them sequentially into one of two equivalent groups, using permuted block randomization with varying block size. A researcher not connected to the study team provided the group allocation by e-mail. During the intervention sessions, therapists and participants were unaware of the individual scores used for randomization. The outcome assessor was blind to the treatment group at the post-test time point (T2), because group allocation was unlabelled. Adolescents were instructed not to disclose their participation in physical activity or relaxation sessions during the HAM-D interview.

### 2.6. Interventions

In physical and control interventions we promoted a task-oriented and enjoyable environment, with highly varied interventions oriented towards the individuals' integrity and security, and with a learning component to encourage adaptive behaviors, healthy habits, and autonomous motivation to practice group activities. The wishes of the patients were taken into account to adapt the sessions so as to maintain compliance in the protocol. The heart rate was monitored in each participant with an individual POLAR FT2® heart rate monitor to measure the intensity of activity. The therapists were exercise professionals, physical health caregivers, physical education teachers and physiotherapists. They managed in alternation the same number of sessions in each group. Both interventions consisted of 20 sessions of 1 hour each (50 minutes activity + 10 minutes for gathering equipment, warm-up and cool-down), each administered three to four times a week for a duration of five to six weeks to complete the program (total = 20 hours).

### 2.7. Physical exercise intervention

The physical exercise intervention was conducted with moderate physical intensity and supervised by exercise specialists (Stubbs et al., 2018). The target heart rate during exercise was 40 to 59% of Heart Rate Reserve (HRR), which is an indicator of moderate intensity exercise (Kesaniemi et al., 2001). Each session started with a warm-up and ended with muscle stretching. Sessions entailed aerobic group games (basketball, ultimate frisbee, football, unihoc (floorball), volleyball, novel games (kinball, tchoukball) and muscular strengthening (using own body weight and weight machines). We also proposed racket sports (tennis, badminton, table tennis), biking sessions, and indoor wall climbing. On average, 80% of the sessions were focused on cardiovascular training with moderate physical intensity, and the remaining 20% devoted to muscle strengthening. The activities were led in a multisport gymnasium on the hospital premises, which included an indoor playing field, an outdoor synthetic field and a well-equipped fitness room.

### 2.8. Control intervention

A supervised social relaxation intervention was conducted without physical intensity (< 20% of HRR). The content of the 20 sessions of one hour each included group games, most of them performed while seated (interactive board games in teams, role-playing games), relaxation time with breathing control, guided do-it-yourself and craft activities using different materials (paper, wood, plastic, clay), as well as learning new skills (healthy and fun cookery classes). These activities occurred on an outdoor terrace and multipurpose rooms on the hospital premises.

### 2.9. Outcome measures

Details on outcome measures (description, reliability, severity thresholds) are provided *Supporting Appendix S1* in Data in brief for submission (Philippot et al., 2021).

### 2.10. Primary outcome

*The Hospital Anxiety & Depression Scale (HADS)* is a reliable and valid questionnaire (Zigmond and Snaith, 1983) for hospitalized populations, consisting of seven questions (rated 0, 1, 2 and 3) related to anxiety (subscale A) and seven others to depression (subscale D), thus providing two scores.

*Secondary outcomes: The Hamilton Depression Rating Scale (HAM-D)* is a semi-structured diagnostic interview evaluating depression (Hamilton, 1960) using the criteria of the Diagnostics and Statistics Manual (DSM), which was administered by a psychiatrist who was blind to the therapy group in this study. Self-assessment tools for depression included the *Child Depression Inventory (CDI)* (Smucker et al., 1986), *Beck's abbreviated Depression Inventory (BDI-13)* (Beck et al., 1988) and the *Zung Self-Assessment Depression Scale (SDS)* (Zung, 1965). Symptoms of anxiety were also assessed using the *State-Trait Anxiety Inventory (STAI)* consisting of two subscales, the STAI, form Y-A, which assesses the recent state and the STAI, form Y-B, which assesses the long-term trait anxiety (Knight et al., 1983).

A medical height gauge and a mechanical doctor's scale were used to measure the *Body Mass Index (BMI)*. An adapted version of the *Astrand-Rhyming Sub-Maximal Effort Test* (Swain et al., 2004) was used to estimate the maximal oxygen consumption ($VO_2$ max) using a bicycle ergometer. After each session in both interventions, the subjects noted in a personal folder using a ten cm Visual Analogue Scale (VAS) their *level of hedonia and fatigue*. They also reported their *mean and maximal heart rate* during the one-hour session as recorded on their individual POLAR FT2® heart rate monitor.

### 2.11. Sample size

A sample size was defined from a previous RCT, wherein the authors had used HADS to measure variance in depression scores, with physical exercise as treatment (Lopes et al., 2018). In order to detect a difference of -2.4 at the 5% significance level with a power of 82%, and assuming a standard deviation of 2.4 (corresponding to an effect size of 1), the sample size should be at least 18 participants per group. Assuming a dropout rate of 30%, we thus enrolled 52 participants.

### 2.12. Statistical analysis

We used a linear mixed model with F-test for differences between differences (T1-T2) to contrast the outcomes of the hospital-based interventions regarding the outcomes for psychological scores and physical fitness parameters. Randomization was used for allocating each adolescent to a group and aimed to avoid any confounding effect of a baseline variable on the outcome. A statistician (AR), blind to the intervention group and to the identity of the patients, carried out the statistical procedures using IBM SPSS Statistics 27.0 statistical software. Effects are reported with their 95% confidence interval (95%CI). A p-value lower than 0.05 was considered as significant.

## 3. Results

### 3.1. Study population

The recruitment period ran from February 2018 to June 2019. Among the 52 adolescents recruited in the pre-test phase, six participants in the social relaxation program and six in the physical exercise program dropped out during the five-week interventions (see Fig. 1 for details). The statistical analysis of pre- and post-test measures was thus restricted to the remaining 40 participants who stayed in the study. The mean age at assessment was 15.2 years (SD 1.50) with 13 girls and 7 boys in the control group and 15.5 years (SD 1.77), with 12 girls and 8 boys in the physical exercise group. For details of the study population, see Table 1.

### 3.2. Participation rate

The participants in the control group completed a mean of 18.1 (SD 2.2) sessions in 6.2 (SD 2.1) weeks, at a mean rate of 3.2 (SD 0.8) sessions/week. In the exercise group, participants completed mean of 18.4 (SD 2.1) sessions in 6.3 (SD 2.1) weeks, at a mean rate of 3.0 (SD 1.2) sessions/week. The mean attendance rates of the exercise (76%) and control group (79%) did not differ (p=0.53 unpaired two sample t-test of number of sessions). The mean duration of each active session were 51.2 (SD 6.7) minutes in the exercise group and 49.6 (SD 4.2) minutes in the control group (p=0.067, unpaired two sample t-test).

### 3.3. Primary and secondary outcome

A summary of the scores and the level of severity according to the pathological thresholds at baseline and after intervention are provided *in* Table 2. At baseline, the scores were similar in the two groups for all variables.

### 3.4. Primary outcome

In the depression component of HADS (HADS-D), the linear mixed model with F-test revealed a significant (group x change from baseline) interaction (p = 0.016) in favor of the exercise group (Table 3). After intervention, inpatients in the exercise group had a mean decline (before minus after intervention, i.e. T1-T2) of 3.8 points [95% Confidence Interval (CI), 1.8 to 5.7] in their HADS depression symptoms, progressing from a mean "probably pathological" score to a mean "non-

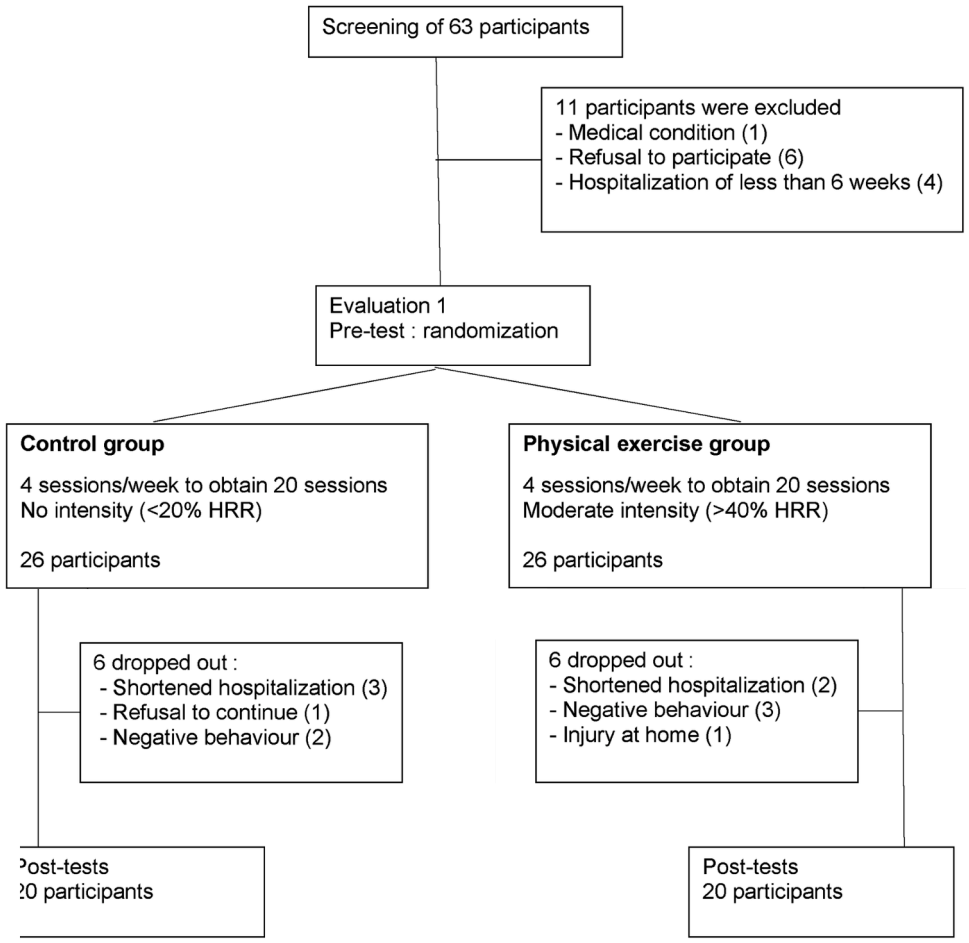


**Fig. 1.** Flow chart of study design: Among the 52 adolescents who were recruited and randomized, 12 participants were lost to follow-up (6 in each group for equivalent reasons), thus confining the statistical analysis of changes between T1 and T2 test measures was restricted to the 40 (n=20 per group) participants who completed the study. HRR: heart rate reserve, see text.

pathological" score. Inpatients in the control group had a mean decline (T1-T2) of 0.7 [95%(CI), -0.7 to 2.0] in their HADS depressive symptoms, thus remaining on average within the category of "probably pathological" score. In contrast, for the primary anxiety measure of the HADS (HADS-A), the linear mixed model with F-test showed no significant interaction (p>0.05) in T1-T2 score changes from b>etween groups (Table 3).

### 3.5. Secondary outcome

The mixed linear model with F-test revealed a significant group x change interaction (p-value = 0.020) in the evolution of the SDS score in favor of the exercise group (Table 3). After the interventions, the adolescents in the physical exercise group had a mean reduction of 0.11 [95% CI: 0.06 to 0.16] in their SDS scores, indicating an improvement from severe to moderate depression ranges, while the control group had a mean reduction of only 0.03 [95% CI: -0.02 to 0.07], indicating that they remained in the range for severe depression. There were no statistically significant treatment effects of intervention for any of the other secondary psychological outcomes.

A correlation analysis was performed to determine if a connection existed between the attendance rate and the reduction of depression in the exercise group. No significant result was found (all *p*-values > 0.05, Pearson correlation).

In both groups, the cardiovascular capacity at baseline, assessed by the $VO_2$ max indices in the modified Astrand-Rhyming sub-maximal effort test (Swain et al., 2004), corresponded to the 5th percentile based on normative values from 1,142,026 children and adolescents worldwide (Tomkinson et al., 2017). The linear mixed model with F-test performed on these $VO_2$max indices revealed a significant group x change interaction ($p = 0.024$) in favor of the physical exercise group (Table 3). The cardiovascular condition improved in the physical exercise group, as highlighted by a mean $VO_2$max index change (before minus after intervention, i.e T1-T2) of -3.32 [95% CI: -6.61 to -0.0], whereas in the control group the corresponding change in mean $VO_2$max index was 2.0 [95% CI: -0.9 to 5.0], indicating a decline in their physical condition (Table 3). In both groups there were two participants who did not perform the test for technical reasons or due to malaise on the day of physical testing. There was no group x change interaction in the evolution of BMI scores ($p > 0.05$). A summary of changes from baseline in the main fitness endpoints is presented in Fig. 2.

### 3.6. Level of hedonia and fatigue

The participants enjoyed the activities, as indicated by the mean baseline VAS hedonia index of 7.6 (SD 1.5) in the control group and 7.2 (SD 1.9) in the exercise group ($p = 0.45$, unpaired two sample t-test). The mean VAS tiredness index in the exercise group, which was 3.9 (SD 1.9) exceeded that in the control group, which was 1.9 (SD 1.8) ($p = 0.012$, unpaired two sample *t*-test). These rating were acquired at the end of each session in both interventions.

**Table 1**
Characteristics of the participants.

| | Control | | Physical exercise | |
|---|---|---|---|---|
| | ($n = 20$) | | ($n = 20$) | |
| **Age (years), mean ±SD** | 15.2 ± 1.5 | | 15.5 ± 1.8 | |
| **Gender, n (%)** | | | | |
| Male | 7 | 35% | 8 | 40% |
| Female | 13 | 65% | 12 | 60% |
| **Education level, n (%)** | | | | |
| ≤ 1st cycle | 8 | 40% | 7 | 35% |
| ≥ 2nd cycle | 11 | 55% | 12 | 60% |
| unknown (*) | 1 | 5% | 1 | 5% |
| school dropout ≥ 3 months | 11 | 55% | 11 | 55% |
| **Medications, n (%)** | | | | |
| No medication (**) | 4 | 20% | 5 | 25% |
| Antidepressants | 12 | 60% | 11 | 55% |
| Neuroleptics | 6 | 30% | 4 | 20% |
| Anxiolytics | 3 | 15% | 4 | 20% |
| Other (***) | 2 | 10% | 3 | 15% |
| **Co-morbidities, n (%)** | | | | |
| ADHD | 0 | 0% | 2 | 10% |
| Problems in eating behavior | 1 | 5% | 2 | 10% |
| History of substance abuse | | | | |
| *Cannabis* | 6 | 30% | 5 | 25% |
| *Alcohol* | 2 | 10% | 2 | 10% |
| Daily tobacco consumption | 10 | 50% | 10 | 50% |
| **History of self-endangering behavior, n (%)** | | | | |
| Self-harm/Fugue | 14 | 70% | 12 | 60% |
| Suicide attempt | 8 | 40% | 6 | 30% |

SD= Standard deviation; ADHD = Attention-Deficit Hyperactivity Disorder
(*) No details available.
Antidepressant drugs were Escitalopram, Fluoxetine, Mirtazapin, Duloxetin, Trazodone, or Sertraline. Neuroleptics were Olanzapine, Risperidone, Aripiprazole, Quetiapine or Clotiapine, prescribed for restlessness or insomnia. Anxiolytic drugs were Lormetazepam, Prazepam, Lorazepam or Diazepam.
(**) Shared decision between patient, parents/guardian, and psychiatrist according to American Psychological Association guideline for the treatment of depression (Association, 2019).
(***) Other medications included Melatonin, Valeriana, Lamotrigine at low dosage for anxiety or Hydroxyzine for allergy care; 6 subjects in control group and 6 subjects in exercise group took several medications.

## 4. Discussion

This is the first randomized, controlled trial aimed at evaluating the add-on effect of structured and supervised physical exercise in the treatment of adolescents hospitalized in a psychiatric unit for young people for treatment of clinical depression and anxiety. When compared to a control social relaxation program, the exercise intervention resulted in significantly reduced symptoms of depression after 6 weeks. Contrary to our initial expectations, both interventions showed similar benefits in reducing anxiety. At the baseline, both groups had severely low cardiovascular condition (5$^{th}$ percentile), which was significantly improved in the exercise group only.

### 4.1. Primary outcomes

The main clinical finding was a greater reduction of depression symptoms in the HADS-D scale in the group completing a structured and supervised physical exercise compared to control intervention. There are several potential explanations for this effect, as that the participants experienced a positive life experience, benefited from an improved therapeutic alliance, or had transference of physical fitness benefits to brain pathways underlying their improvements in mood.

Supervised group exercise, accompanied by increasing but realistic goals (gradually enjoying physical exercise, improving own performance, learning new sports), presented in a fun context, and encouraging enjoyable physical movements, associated positive peer interactions – i.e. positive life experience - could inherently improve self-esteem and feelings of self-efficacy, thus bringing a positive emotional response (Carter et al., 2015; Cid et al., 2019), while reducing social withdrawal, lack of motivation, and anhedonia.

Physical exercise therapy, administered at the initial phase of hospitalization for depression and anxiety, may be beneficial for the therapeutic alliance between adolescent inpatients and mental health care providers. This seems a particularly important factor in the present context, because it has already been shown that early therapeutic alliance with adolescents plays an essential role in psychotherapy, promoting early gains in depressive symptomatology (Labouliere et al., 2017), as has also been reported in adults (Zuroff and Blatt, 2006). However, in the context of this study, the promotion of the therapeutic alliance through the activities was not tested, and seems likely to have been similar in both groups, given their similar positive experiences.

Finally, structured physical exercise could also be beneficial for brain functions underlying affect and trait anxiety. Previous work has shown that regular physical activity in a general population of children and adolescents improves the performance of executive function and modifies the task-induced activation of involved brain areas such as the frontal cortex (Herting and Chu, 2017; Voss et al., 2011). Furthermore, hippocampal volume and memory performance are better in athletic participants compared to age-matched but sedentary participants (Chaddock et al., 2010). Since major depressive disorder in adolescents is associated with impaired executive function and mental ruminations (Belzung et al., 2015; Pan et al., 2020; Wagner et al., 2015), the hypothesis of a change in brain function should be tested in future functional imaging studies. By ascertaining the impact of physical exercise on brain structure and function in adolescents with mood disorders, a clearer causal mechanism might emerge to explain the pathway for reduction of depressive symptoms.

The longitudinal HADS-A scores showed a reduction in anxiety symptoms over time in both groups. Accordingly, we can infer that the participants benefited with respect to anxiolytic effect of the general psychiatric environment, but obtained no added value from physical exercise, or rather no benefit of sufficient effect size to attain significance. To date, there is also a lack of evidence for a reduction in symptoms of anxiety with exercise in young ambulatory patients (Carter et al., 2021; Das et al., 2016; Larun et al., 2006), in contrast to observations made in adults (Jayakody et al., 2014; LeBouthillier and Asmundson, 2017). In school settings, we previously reported that a low-to-moderate exercise program reduced anxiety symptoms to a greater extent compared to intensive exercise in a nonclinical sample of preadolescents (Philippot et al., 2019). Additional research should explore if tailored interventions can benefit outpatients and inpatients with clinical symptoms of anxiety.

### 4.2. Secondary outcomes

A better reduction in depressive symptoms on the SDS scale was observed in the physical exercise group compared to the social relaxation control group. Unlike the significant interaction obtained for depressive symptoms in SDS and HADS-D scales, statistical analysis revealed a comparable benefit of the two programs in the other depression tests scores, namely CDI, BDI, and HAM-D. These several tests are widely used in research to assess the severity of depression in ambulatory patients. The present trial was performed in hospitalized patients, who were already under multidisciplinary psychiatric care and, therefore should have been expected to benefit from treatment as usual. Our primary outcome, the HADS, is a brief test that focuses on anhedonia and assesses depression and anxiety in separate subcomponents, making it suitable for application in our adolescent inpatients. In addition, we note that the CDI was developed to enable longitudinal monitoring of depression at school, and therefore contains elements of school life, while 55% of the participants in the present study were no longer attending school daily before their hospitalization. Additionally, widely

**Table 2**
Psychological and physical assessements.

| | Baseline Control | | | Physical exercise | | | Post-test Control | | | Physical exercise | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Depression primary outcome** | | | | | | | | | | | | |
| HADS-D | | | | | | | | | | | | |
| Mean ±SD | 10.1 | ± | 4.1 | 10.2 | ± | 3.9 | 9.4 | ± | 4.5 | 6.5 | ± | 4.6 |
| Median (min-max) | 10 (4-19) | | | 10 (3-16) | | | 10 (3-18) | | | 7 (1-16) | | |
| Severity | | | | | | | | | | | | |
| no symptoms (0-7) | | | 6 | 7 | | | | | 9 | 11 | | |
| probably pathological (8-10) | | | 6 | 3 | | | | | 2 | 5 | | |
| considered clinical (> 10) | | | 8 | 10 | | | | | 9 | 4 | | |
| **Anxiety primary outcome** | | | | | | | | | | | | |
| HADS-A | | | | | | | | | | | | |
| Mean ±SD | 12.8 | ± | 3.2 | 13.0 | ± | 5.7 | 10.7 | ± | 5.5 | 11.3 | ± | 6.4 |
| Median (min-max) | 13 (6-18) | | | 14 (0-20) | | | 13 (1-18) | | | 13 (0-20) | | |
| Severity | | | | | | | | | | | | |
| no symptoms (≤7) | | | 1 | 3 | | | | | 8 | 8 | | |
| probably pathological (8-10) | | | 4 | 2 | | | | | 1 | 1 | | |
| considered clinical (> 10) | | | 15 | 15 | | | | | 11 | 11 | | |
| **Depression secondary outcomes** | | | | | | | | | | | | |
| HAM-D | | | | | | | | | | | | |
| Mean ±SD | 17.3 | ± | 6.9 | 15.9 | ± | 8.5 | 12.3 | ± | 8.4 | 9.9 | ± | 5.1 |
| Median (min-max) | 16 (6-28) | | | 15 (3-32) | | | 11 (1-34) | | | 9 (3-21) | | |
| Severity | | | | | | | | | | | | |
| no symptoms (0-7) | | | 2 | 5 | | | | | 6 | 7 | | |
| mild depression (8-16) | | | 9 | 6 | | | | | 9 | 10 | | |
| moderate depression (17-23) | | | 4 | 4 | | | | | 3 | 3 | | |
| severe depression (≥ 24) | | | 5 | 5 | | | | | 2 | 0 | | |
| CDI | | | | | | | | | | | | |
| Mean ±SD | 27.4 | ± | 10.4 | 25.2 | ± | 8.7 | 22.2 | ± | 9.5 | 19.4 | ± | 9.4 |
| Median (range) | 30 (7-42) | | | 27 (12-44) | | | 23 (7-37) | | | 18 (6-36) | | |
| Severity | | | | | | | | | | | | |
| Below cut-off (< 19) | | | 5 | 5 | | | | | 9 | 11 | | |
| Above cut-off (≥ 19) | | | 15 | 15 | | | | | 11 | 9 | | |
| BDI | | | | | | | | | | | | |
| Mean ±SD | 19.8 | ± | 9.5 | 19.1 | ± | 8.3 | 15.8 | ± | 9.3 | 12.1 | ± | 8.4 |
| Median (min-max) | 22 (3-34) | | | 19 (3-30) | | | 13 (0-31) | | | 10 (0-27) | | |
| Severity | | | | | | | | | | | | |
| Below cut-off (< 8) | | | 4 | 2 | | | | | 4 | 6 | | |
| Above cut-off (≥ 8) | | | 16 | 18 | | | | | 16 | 14 | | |
| SDS | | | | | | | | | | | | |
| Mean ±SD | 0.73 | ± | 0.12 | 0.73 | ± | 0.14 | 0.70 | ± | 0.12 | 0.62 | ± | 0.15 |
| Median (min-max) | 0.76 (.53-.96) | | | 0.75 (.48-.93) | | | 0.69 (.51-.93) | | | 0.64 (.31-.90) | | |
| Severity | | | | | | | | | | | | |
| no symptoms (0.25-0.49) | | | 0 | 1 | | | | | 0 | 3 | | |
| mild depression (0.50-0.59) | | | 3 | 3 | | | | | 5 | 6 | | |
| moderate depression (0.60-0.69) | | | 4 | 4 | | | | | 5 | 3 | | |
| severe depression (≥ 0.70) | | | 13 | 12 | | | | | 10 | 8 | | |
| **Anxiety secondary outcomes** | | | | | | | | | | | | |
| STAI A | | | | | | | | | | | | |
| Mean ±SD | 56.5 | ± | 10.3 | 53.3 | ± | 13.6 | 50.1 | ± | 15.4 | 47.1 | ± | 16.3 |
| Median (min-max) | 58 (38-78) | | | 57 (22-76) | | | 48 (24-72) | | | 49 (20-74) | | |
| Severity | | | | | | | | | | | | |
| Very low score (≤ 35) | | | 0 | 2 | | | | | 5 | 6 | | |
| Low score (36-45) | | | 4 | 4 | | | | | 3 | 3 | | |
| Average score (46-55) | | | 3 | 3 | | | | | 4 | 4 | | |
| High score (56-65) | | | 10 | 8 | | | | | 3 | 4 | | |
| Very high score (> 65) | | | 3 | 3 | | | | | 5 | 3 | | |
| STAI B | | | | | | | | | | | | |
| Mean ±SD | 64.2 | ± | 11.1 | 59 | ± | 14.6 | 58.8 | ± | 12.0 | 53.8 | ± | 14.0 |
| Median (min-max) | 66 (39-76) | | | 61 (23-76) | | | 56 (35-74) | | | 58 (22-75) | | |
| Severity | | | | | | | | | | | | |
| Very low score (≤ 35) | | | 0 | 2 | | | | | 1 | 2 | | |
| Low score (36-45) | | | 2 | 2 | | | | | 1 | 3 | | |
| Average score (46-55) | | | 2 | 1 | | | | | 8 | 4 | | |
| High score (56-65) | | | 6 | 9 | | | | | 1 | 7 | | |
| Very high score (> 65) | | | 10 | 6 | | | | | 9 | 4 | | |
| **Physical secondary outcomes** | | | | | | | | | | | | |
| BMI | | | | | | | | | | | | |
| Mean ±SD | 21.7 | ± | 4.0 | 25.0 | ± | 6.8 | 21.6 | ± | 3.7 | 24.8 | ± | 5.7 |
| Median (min-max) | 21 (16-30) | | | 22 (18-46) | | | 21 (16-30) | | | 23 (18-40) | | |
| VO2max | | | | | | | | | | | | |
| Mean ±SD | 25.5 | ± | 6.4 | 25.3 | ± | 8.3 | 23.8 | ± | 5.0 | 28.5 | ± | 8.8 |
| Median (min-max) | 26 (13-40) | | | 23 (13-48) | | | 23 (15-33) | | | 26 (19-52) | | |

At baseline the test scores were similar in the two groups. SD= Standard Deviation.

**Table 3**
results from linear mixed model with F test on differences between differences (T1-T2).

| | | Control | | | | | Physical exercise | | | | | Interaction F test |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | N | Mean | ±SEM | [95%CI, Lower to Upper] | | n | Mean | ±SEM | [95%CI, Lower to Upper] | | p-value |
| **Primary outcome** | | | | | | | | | | | | |
| *Depression symptoms* | HADS-D | 20 | 0.7 | ±0.7 | -0.7 | 2.0 | 20 | 3.8 | ±1.0 | 1.8 | 5.7 | **0.016** |
| *Anxiety symptoms* | HADS-A | 20 | 2.1 | ±1.0 | 0.1 | 4.1 | 20 | 2.0 | ±1.2 | -0.4 | 4.3 | 0.92 |
| **Secondary outcome** | | | | | | | | | | | | |
| *Depression symptoms* | SDS | 20 | 0.03 | ±0.0 | -0.02 | 0.07 | 20 | 0.11 | ±0.03 | 0.06 | 0.16 | **0.020** |
| | HAM-D | 20 | 5.1 | ±1.7 | 1.7 | 8.4 | 20 | 6.1 | ±1.4 | 3.3 | 8.8 | 0.65 |
| | CDI | 20 | 5.2 | ±1.8 | 1.8 | 8.6 | 20 | 5.9 | ±1.8 | 2.3 | 9.4 | 0.80 |
| | BDI | 20 | 4.1 | ±1.5 | 1.1 | 7.0 | 20 | 6.8 | ±1.4 | 4.0 | 9.6 | 0.20 |
| *Anxiety symptoms* | STAI A | 20 | 6.4 | ±3.2 | 0.1 | 12.7 | 20 | 6.2 | ±3.0 | 0.3 | 12.1 | 0.96 |
| | STAI B | 20 | 5.4 | ±2.1 | 1.3 | 9.5 | 20 | 5.3 | ±2.4 | 0.6 | 9.9 | 0.96 |
| *Physical condition* | $VO_2$max | 18 | 2.0 | ±1.5 | -0.9 | 5.0 | 18 | -3.3 | ±1.7 | -6.6 | 0.0 | **0.024** |
| | BMI | 20 | 0.1 | ±0.3 | -0.6 | 0.7 | 20 | 0.3 | ±0.4 | -0.5 | 1.0 | 0.68 |

SEM = Standard error of the mean.

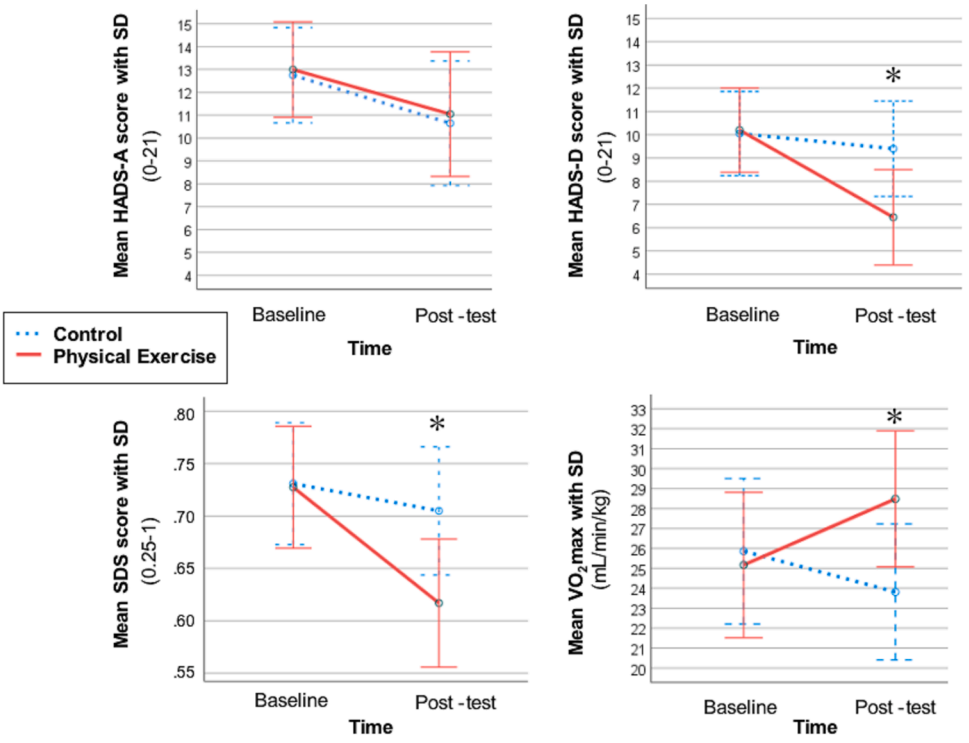


**Fig. 2.** Changes from baseline in main outcomes. From left to right and from top to bottom, the linear mixed model with F-test did not reveal a significant (group x change from baseline) interaction in the anxiety component of HADS (HADS-A) but revealed a significant interaction in favor of the exercise group in the depression component of HADS (HADS-D), in the evolution of the SDS score, and in the cardiovascular capacity assessed by the VO2max indices (see text). Error bars are SD, * $p<0.05$, interaction F-test.

used HAM-D scale for clinical research in adults includes somatic symptoms of depression as well as some symptoms of anxiety (Bagby et al., 2004) in the final score. The lack of group differences in these symptoms could therefore contribute to the lack of difference in the evolution of HAM-D scores in the present trial.

In the present study, the $VO_2$max indices, although still low after treatment, increased significantly in the exercise group, thus attaining the 10th percentile for girls (60% of the sample) (Tomkinson et al., 2017). At baseline, the mean $VO_2$max indices were well below the desirable threshold for cardio-respiratory condition (41.8 mL/min/kg in boys and 34.6 mL/min/kg in girls aged 15 years) to prevent the risk of cardiovascular disease later in life (Ruiz et al., 2016). Since depressive symptoms *per se* in otherwise healthy adolescents may influence later risk of cardiovascular disease (Olive et al., 2020), an adapted physical exercise program with endurance training should in any event be prescribed to adolescents with clinical depression because of the risk of sedentary lifestyle, irrespective of any benefits for present mood.

The study group completed 76% (exercise) or 79% (control) of the sessions offered over an average of 6 weeks to reach the goal of twenty sessions. This roughly matched the attendance rates in two RCTs of depressed adolescents involved in a previously investigated outpatient exercise program (79% observed for 12 weeks (Hughes et al., 2013) and 70% for 6 weeks (Carter et al., 2015)).

### 4.3. Strengths

A strong point of the study is that there haven not hitherto been any reports on RCTs in a psychiatric hospital setting documenting the physical and psychological/psychiatric effects of a structured, reassuring, and supervised exercise program. Thanks to the design of our RCT, we can attribute improvements in certain endpoints as main effects of the exercise program *per se*. At baseline, all psychological assessments corresponded to clinical thresholds of moderate to (mainly) severe depression and anxiety. There are relatively few reports of physical exercise interventions as an add-on treatment in patient groups with relatively severe mood disorder symptoms and nearly all were conducted in outpatients (Carter et al., 2015; Dabidy Roshan et al., 2011; Hughes et al., 2013). The positive effect of structured and supervised

exercise on depressed mood seen in the present study is in accordance with the conclusions of these previous studies, especially trials with clinical samples (Bailey et al., 2018; Carter et al., 2016; Radovic et al., 2017). Although noticeably smaller effect sizes were found in studies that used non-physical activity as control treatments compared to studies without control group (Oberste et al., 2020), here, we observed a significant benefit of physical exercise intervention as compared to a control intervention conducted in parallel. The good participation and enjoyment scores recorded using VAS at the end of each session indicated that the content of the sessions was equally attractive in both programs. This stands in contrast to conventional thinking that depressed adolescents would not adhere to an exercise program, which might generalize to more effective interventions based on present methods, as likewise recently suggested in the literature (Radovic et al., 2018). In addition, the very low mean aerobic score observed in our sample at baseline underscores the critical need to improve the physical condition of depressed adolescents who are at risk for future cardiovascular disease. Our structured, supervised, task-oriented exercise program in a fun setting could be easily implemented in gyms as part of a successful rehabilitation strategy to achieve this goal of improving physical condition of non-hospitalized depressed adolescents.

### 4.4. Limitations

It would have been preferable to record long-term effect of the intervention on mood symptom scores, but this approach was not possible due to the incomplete medical follow-up after six months. Therefore, we confined out investigation to the six week window of typical psychiatric hospitalization. Only 40 participants completed the whole study, which is not a sufficiently large sample to explore the effects of factors such as social and clinical characteristics of the participants, and the use of randomization precluded performing an analysis of any sub-group. The study dropout rate of 23% mainly reflected decisions of participants to shorten their hospital stay, or expulsion due to non-compliance with internal unit rules. The circumstances of hospitalization typically result in high rates of premature discontinuation (28 to 75%) in mental health research studies in adolescents (de Haan et al., 2013). We did not have information on prior physical activity from a physical activity questionnaire such as the SIMPAQ that is validated in adolescents (Rosenbaum et al., 2020). Furthermore, we note that physical activity is a regular part of multidisciplinary care at our hospital, thus being available to both study groups. On average, there was a low attendance of basic physical activities (open participation and unstructured sessions) at the rate of 1.2 session per week for the control group and 1.3 session per week for the exercise group and this was not sufficient to improve the VO2max score in the control group.

## 5. Conclusion

The results of our study indicate that a structured, group-based, and supervised exercise program imparts physical and psychological benefits in the treatment of young people admitted in a psychiatric hospital for depression and anxiety. Exercise appears to be an effective add-on intervention to antidepressants, thus being crucial for adolescents with depression, who are at chronicity of their mental disorder compounded by sedentary lifestyle. Further investigation regarding the role of training history, comorbidity, cognitive and social functioning on exercise programs in youth with mood disorders are urgently required.

## Author contributions

AP contributed to the study design, was involved in the two arms of the trial at all steps, contributed to the statistical analysis and wrote the first draft of the manuscript. VD was responsible of all medical procedures and logistical organization of the project in the Area+ hospital. AB supervised the diagnostic interviews and psychiatric care. KL and DG collected anamnestic data and contributed in the process of concealing identities of participants. KL, DG, UJ and WC were involved in the two arms of the trial. YB contributed to the study design, manuscript draft and gave advice in RCT procedure. AR made the statistical analysis and contributed to the manuscript draft. ADV made the study design, verified the exercise and control arms, made all scoring blindly, provided results on an anonymous basis, and wrote the manuscript. At the final step, all authors had access to the study data that support the publication.

Supplementary materials

Additional supporting information may be found online in the Supporting Information section at the end of the article:

~~Appendix S1. Details on outcome measures.~~

Appendix S1. CONSORT checklist.

## Declarations of Competing Interest

none

### *Data availability statement*

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2022.01.011.

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