Université Catholique de Louvain

Antidepressant and anxiolytic effects of physical exercise on youth mental health

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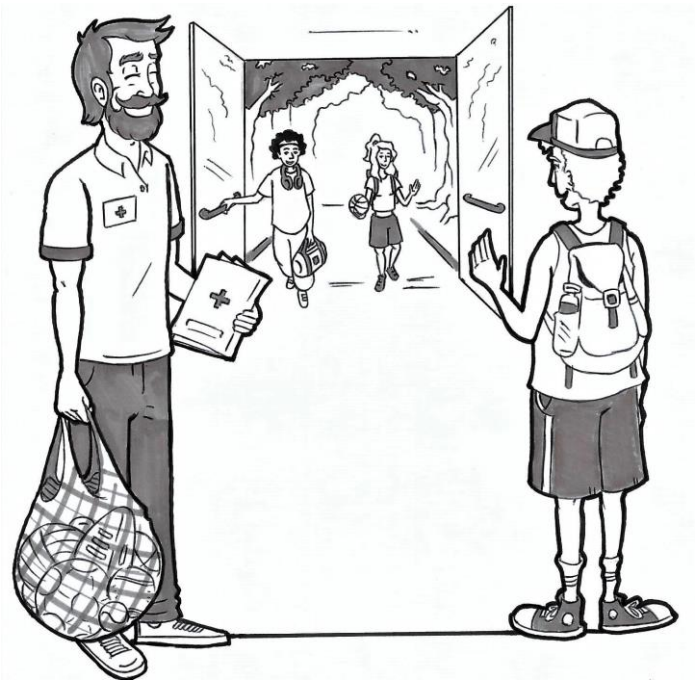

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List of abbreviations

COVID-19	Coronavirus Disease 2019
ACSM	American College of Sports Medicine
AOO	Age Of Onset
BDI	Beck Depression Index
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDI	Children Depression Index
CI	Confidence Interval
CVD	Cardio-Vascular Disease
CVR	Cardio-Vascular Risk
DASS-21	Depression, Anxiety and Stress Scale - 21
DSM-V	Diagnostic and Statistical Manual of Mental Disorders V
GAD	Generalized Anxiety Disorder
GAD-7	Generalized Anxiety Disorder-7
HADS	Hospital Anxiety Depression Scale
HAM-D	Hamilton Depression Rating Scale
HIFT	High-Intensity Functional Training
HIG	High-Intensity Group
HIIT	High-Intensity Interval Training
HIT	High-Intensity Training

HPA	Hypothalamic-Pituitary-Adrenal
HR	Heart Rate
LMIG	Low-to-Moderate Intensity Group
MDD	Major Depression Disorder
MET	Metabolic Equivalent Task
NICE	National Institute for Health and Care Excellence
PEDRO	Physiotherapy Evidence Database
RCT	Randomized Controlled Trial
RPE	Rate of Perceived Exertion
RT	Randomized Trial
SD	Standard Deviation
SDS	Zung Self-Rating Depression Scale
SEM	Standard Error Mean
SMD	Standard Mean Deviation
SSRIs	Selective Serotonin Reuptake Inhibitors
STAI	State Trait Anxiety Inventory
VO2Max	Maximal Oxygen Consumption
WHO	World Health Organisation

INTRODUCTION

Introduction

When the spread of Coronavirus Disease 2019 (COVID-19) threatened health systems, the strategy to contain this impact was to isolate the population through social distancing and restrictions, including cessation of non-essential activities, and limited access to schools and universities, known as the "lockdown". The various waves of the pandemic resulted in multiple lockdowns and then challenged the mental health of the population, especially among youth. The COVID-19 pandemic became a psychosocial crisis (1-3). As a traumatic event, the COVID-19 outbreak may have fostered a range of mental health problems in youth, likely due to social estrangement, school closures, and home quarantine that caused stress, anxiety, uncertainty, helplessness, and isolation (4). The incidence rate for depression and anxiety in Belgium doubled between 2018 and 2021 to reach 21% in the adult population and 34-38% in young people (5). Young people are in critical periods of development, especially neurologically. When they develop mental health problems and their psychological symptoms persist over time, they are more likely to develop psychiatric disorders in adulthood and experience multiple relapses throughout their lives (4, 6-8).

The pandemic has highlighted the psychological difficulties faced by youth, but it has also increased psychological prevalence and exacerbated mental distress among youth. Vulnerable groups with previous or current mental health difficulties are more likely to worsen their symptoms during a crisis. This pandemic has firstly revealed the critical need for mental health supports for children, adolescents and young adults and therefore in many situation the lack of means to help youth with depression and anxiety symptoms.

Depression and anxiety, major public health issues

Depression: a leading cause of disability worldwide

Depressive disorders in adulthood are the leading causes of disability worldwide and are a major contributor to the global burden of disease (Wordl Health Organisation 2022). Before the COVID crisis, an estimated 322 million people worldwide in 2015 suffered from depressive disorders (Figure 1), representing 4.4% of the global population, with a higher rate among women (5.1%) than men (3.6%) (Figure 2) (9, 10).

An episode of depression is different from the usual mood swings and short-lived emotional reactions to the challenges of everyday life. It can become a serious health problem, especially when it is recurrent and of moderate or severe intensity. A depressive episode lasts at least two weeks (11). The person could experience a depressed mood (e.g., feeling sad, hopeless, empty) or loss of pleasure or interest in all activities almost all day, nearly every day. Several other symptoms are also present, which may include insomnia or hypersomnia, poor concentration or indecisiveness, excessive feelings of guilt or low self-esteem, hopelessness about the future, psychomotor agitation, decrease or increase in appetite with weight gain or loss, feeling particularly tired or lacking in energy and thoughts of death or suicide ideation. In some cultural contexts, some people may express their affects more through somatic symptoms (eg, pain, fatigue, weakness) (11).

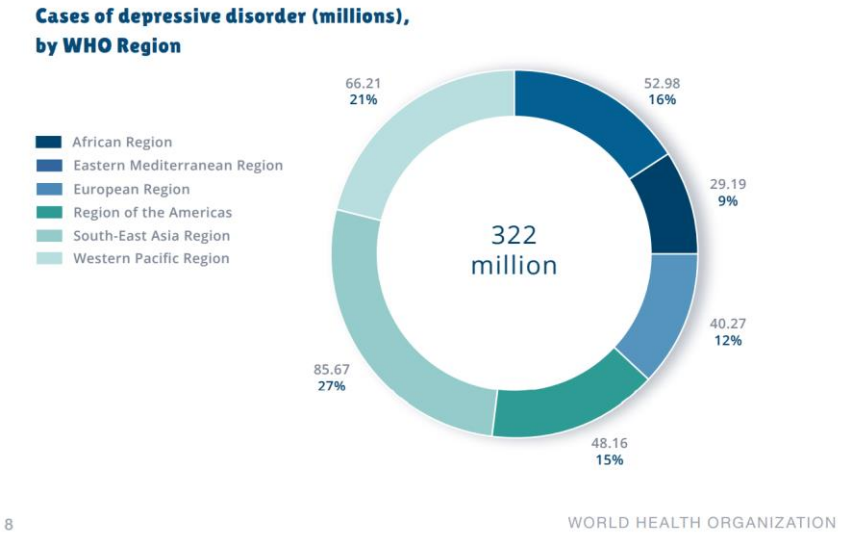

Figure 1 : cases of depressive disorder worldwide in 2015 (12) *Licence: CC BY-NC-SA*

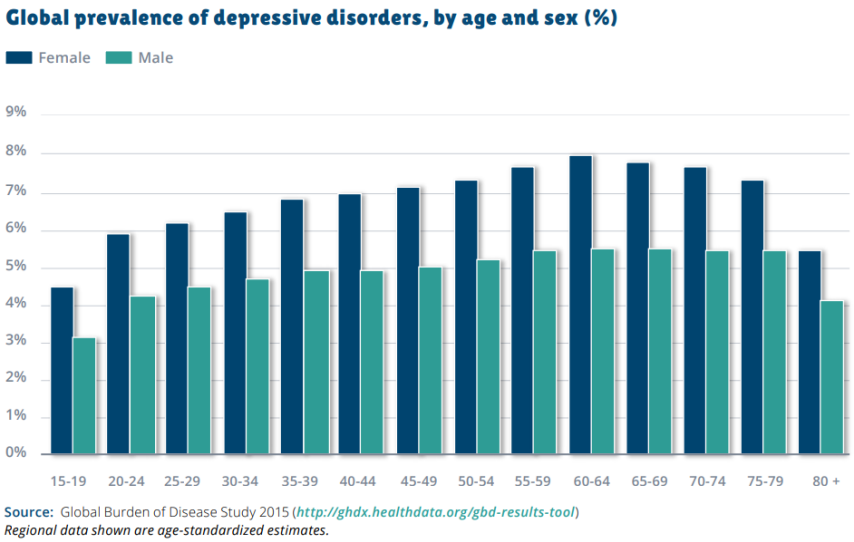

Figure 2 : Global prevalence across the world, by age and gender (12) *Licence: CC BY-NC-SA*

Depressive disorders are subdivided into different types that stand out following the duration, timing, or presumed aetiology. Diagnostic and Statistical Manual of Mental Disorders V (DSM-V) describe disruptive mood dysregulation disorder (specific to children and adolescents), major depressive disorder, persistent depressive disorder, premenstrual dysphoric disorder, substance/medication-induced depressive disorder, depressive disorder due to another medical condition, other specified depressive disorder, and unspecified depressive disorder. The standard features of all of these disorders are the presence of a sad, empty, or irritable mood, accompanied by somatic and cognitive changes that significantly affect the individual's capacity to function.

Major depressive disorder is the most representative and well-studied depressive disorder. One of the criteria for MDD is the presence of five (or more) symptoms, as described above, within a two-week period that represents a change from previous functioning. One of the symptoms is either a depressed mood or a loss of interest/pleasure. In European countries, the average lifetime prevalence of MDD was 11.32% (14.1% in Belgium) (13) and the average 12-month prevalence was 5.2% (5.0% in Belgium) (14). Based on data from 18 countries analyzed in one report (n = 89 037), the median reported age of onset of MDD was 25.7 years (29.4 years for Belgium) in high-income countries and 24.0 years in low- and middle-income countries. The 95% confidence intervals (CIs) indicated that, in all countries, the risk period for the emergence of depression spanned from the mid-teens to the early 40s (13). However, future research may indicate that the average onset may begin earlier and with a higher rate as a result of the COVID-19

pandemic. This is due to the fact that stressors from the psychosocial crisis and anti-contagion policies may have affected youth more severely (4, 6-8).

In young people

Depression is a common disorder that has been studied since ancient times. However, the first descriptions of children and adolescents suffering from depression were first documented in the literature 150 years ago. In 1907, the National Committee on Mental Hygiene emphasized that childhood is a key period for mental health and urged the development of initiatives in schools to identify the needs of troubled youth and to promote the social support available (15). It is only for some decades that psychopathology has become a reasonable study domain for young people. Age range standards are defined as follow: 10-24 years old for “young people” and 10-19 years old for “adolescents” (WHO 2022). The term "young adults" refers to individuals between the ages of 19-24 , who are entering adulthood, and the term "pre-adolescents" to children between the ages of 9-12, highlighting the enter in adolescence and puberty development (16). Almost 15% of adolescents experience at least one episode of major depressive disorder (17). When depression starts early, the symptoms tend to be more severe in later life (18, 19). In particular, MDD affects 3-5% of adolescents (20). DSM-V showed that adolescents may express psychological distress differently from adults (see Table 1) (11).

Table 1: Depressive Symptoms and exemples in Adolescents, inspired from DSM-V (11)

Signs and symptoms of Major Depressive Disorder	**Signs of Depression Frequenlty seen in youth**
Depressed mood most of the day	Irritable or crancky mood; preoccupation with song lyrics that suggest life is meaningless
Decreased interest/enjoyement in once-favorite activities	Loss of interest in sports, video games, and activities with friends
Significant weight loss/gain	Failure to gain weight as normally expected; anorexia or bulimia; frequent complaints of physical illness (eg, headache, stomach ache)
Insomnia or hypersomnia	Excessive late-night TV; refusal to wake for school in the morning
Psychomotor agitation/retardation	Talk of running away from home or efforts to do so
Fatigue or loss of energy	Persistent boredome
Low self-esteem; feelings of guilt	Oppositional and/or negative behavior
Decreased ability to concentrate; indecisive	Poor performance in school; frequent absences
Recurrent thought of deaths or suicidal ideation or behavior	Recurrent suicidal ideation or behaviour (threats of suicide, writing about death; giving away favorite toys or belongings)

Depression in children and adolescents is generally associated with social withdrawal, interpersonal problems, irritable mood, decreased school performance and attendance, functional impairment, and ultimately an

increased risk of suicide (11, 20). Some authors also suggest a new description: Very Early Onset Major Depressive Disorder (VEO MDD). The current DSM-based diagnostic criteria may not fully capture the presentation of depressive disorders in preadolescents (21).

Suicide is the second leading cause of death in 10–19 years old in Western countries (22, 23). Depression is the primary psychiatric disorder contributing to suicide, but anxiety, traumatic stress, psychotic disorders and other psychiatric disorders could also lead to suicide. Irritability appeared to be associated with a higher rate of suicide attempts. (24). It is therefore essential to detect the first symptoms of depression as early as possible, including at the start of adolescence, and to have adequate treatment to alleviate the symptoms. Scientific research and specialized care are absolutely necessary to achieve these goals.

Anxiety: a predictor of psychiatric disorders

The estimated number of people living with anxiety disorders is 264 million worldwide in 2015 (Figure 4), which equates to a rate of 3.6%. Like depressive disorders, anxiety disorders are more common in women 4.6% than in men 2.6% (Figure 5) (25) (WHO 2021).

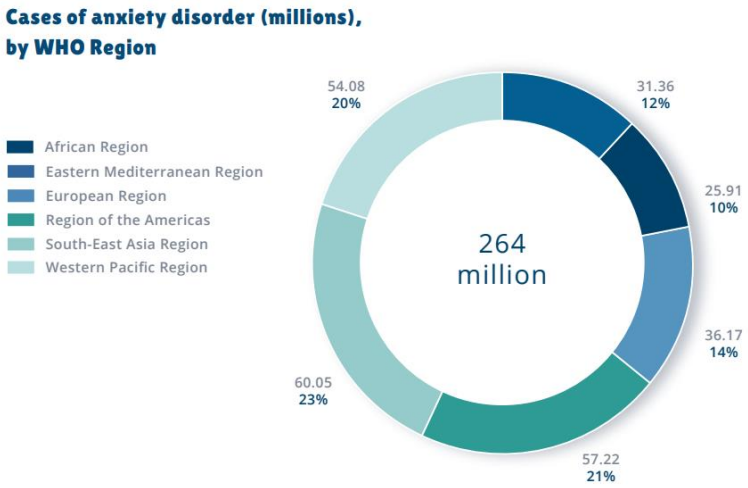

Figure 3 : cases of anxiety disorder worldwide (12) *Licence: CC BY-NC-SA*

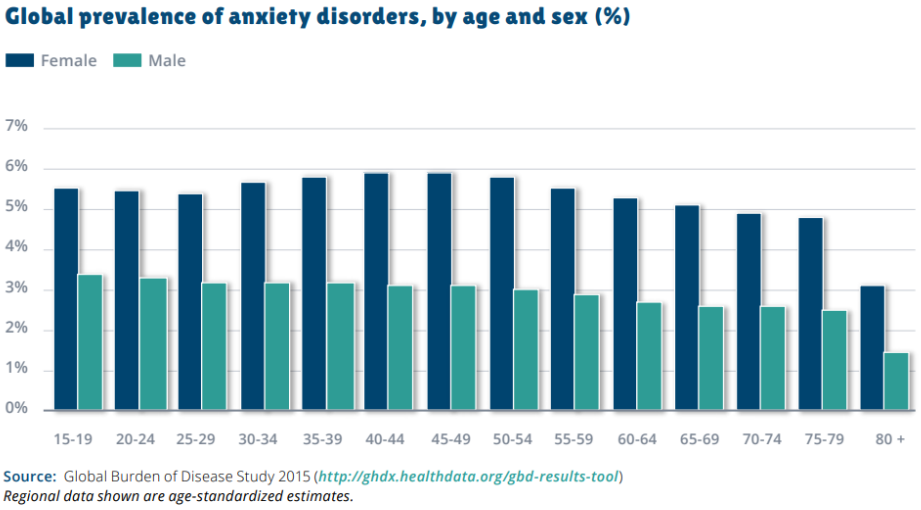

Figure 4 : Global prevalence of anxiety disorders across the world, by age and gender (12) *Licence: CC BY-NC-SA*

Introduction

Anxiety disorders include the disorders that share excessive fear and anxiety associated with behavioral problems. Anxiety can be thought of as an anticipation of future threats. Meanwhile, fear (or stress) is further defined as an emotional state when people are confronted with a potentially dangerous stimulus or an imminent real or perceived threat (11). "Two states overlap, but they also differ, with fear more often associated with surges of autonomic arousal necessary for fight or flight, thoughts of immediate danger, and escape. Anxiety disorder is often more associated with muscle tension and vigilance in preparation for future danger and cautious or avoidance behaviours" (11).

Anxiety disorders refer to mental disorders including generalized anxiety disorder, panic disorder, phobias, social anxiety disorder and post-traumatic stress disorder. Among the anxiety disorders, Generalized Anxiety Disorder (GAD) is one of the most prevalent mental disorders, associated with immense health care costs and a high disease burden. The key features of GAD are characterized by persistent and excessive worry (apprehension) about various routine activities and events, including work and school performance. The person has difficulty controlling his or her feelings of apprehension. In addition, the individual has at least three physical symptoms (one in children), including restlessness or feeling on edge, easy fatigue, difficulty concentrating or forgetfulness, irritability, muscle tension, and sleep disturbances. The anxiety or physical symptoms disrupt essential areas of the individual's functioning in a significant way and are not attributed to any other effect or medical condition (e.g., medications, hyperthyroidism) and other mental disorders (e.g., phobias, obsessions...). The preceding lines

are not intended to substantially define GAD but to illustrate its impact on the feelings and usual life of individuals.

In 15 high-quality and 3 low-quality epidemiological studies involving 48,214 participants, a systematic review examined the impact of subthreshold clinical anxiety on mental health over the life course. It was documented that mild or subthreshold symptoms could develop initiation and worsening of other mental illnesses, pain, and somatic disorders, resulting in severe impairment in daily life (26). Therefore, early detection and understand of this disorder seems essential to implement interventions.

In young people

During adolescence, risk factors for anxiety disorders could be shared with those of depression. These include gender (higher prevalence in girls), puberty onset, work or school performance pressure and childhood adversity. Adverse childhood experiences refer to all forms of physical/emotional neglects and sexual abuses that result in actual or potential harm to the young individual. It also includes experiences of peer rejection, housing instability, and family disruptions (eg, chronic mental or physical illness in the family, death, alcoholism) (27, 28). People with low socioeconomic status are more likely to experience financial and housing insecurity, as well as educational instability (28, 29). Social and financial constraints, inherent to a poorer environment, limit global access to health care and therefore to an appropriate medical follow-up (29), increasing the risk to develop anxiety and depression (28, 29).

Introduction

The prevalence rate of anxiety disorder ranges from 2.5 to 30% of children and adolescents, depending on the methods used to diagnose anxiety symptoms (30). According to the WHO epidemiological survey of students worldwide, prior to COVID-19, the 12-month prevalence of GAD was 16.7% (31). These rates were already high before COVID-19, they may have doubled after this crisis (4, 5, 32, 33), suggesting a growing and alarming issue for the mental health of young people.

Anxiety and depression are often related. Some authors described that depression disorder could be a reaction to long-standing untreated anxiety (34, 35). There is evidence of a causal association that anxiety may precede depression, so many young people with depressive symptoms would have co-occurring anxiety (36). A recent study recruited 113 subjects, comprising 62 females and 51 males, from 12 to 67 years old and including 80% of adults, with excessive anxiety and worry lasting more than 6 months, meeting the DSM-V criteria of GAD. The Age Of Onset (AOO) of their anxiety onset was identified as adolescence (77%). However, only 14% of the total sample presented and sought medical help during adolescence. Conversely, the occurrence of a major depressive episode was reported in 19% of subjects in adolescence and 81% in adulthood (with 41% occurrence after age 30) (34). Consistent with these findings, previous studies have demonstrated that the average age of development of generalized anxiety is 15.6 years, with 75% of cases occurring before the age of 20 (37). It also corroborated a previous meta-analysis of 8 studies that estimated that AOO for all anxiety disorders ranged from early adolescence to early adulthood (21.3 years (95% CI 17.46 to 25.07). This may vary by subtype of anxiety disorder, but separation anxiety disorder, specific phobia, and social phobia have an mean onset

before age 15 (38). However, it contrasted with DSM-V, which recorded a mean AOO at 30 years (11).

Physiopathology of depression and anxiety

The neurobiological causes and mechanisms involved in depression and anxiety are important and complex. Despite substantial research efforts over the past decade, the scientific community recognizes that the overall pathophysiology of these disorders remains imperfectly elucidated.

In 1960, after the development of new antidepressant drugs called Selective Serotonin Reuptake Inhibitors (SSRIs), an initial hypothesis supporting the role of underdeveloped monoamine neurotransmitters (serotonin, norepinephrine, dopamine) in explaining depression was put forward. The monoamines are responsible for communication in the brain and are associated with mental health (39). However, a recent systematic umbrella review found no convincing evidence of correlation between depression and depletion of serotonin concentration or activity. Most systematic studies included in this paper did not reveal serotonin level variations between depressed individuals and control groups. I This means that we cannot consider the pathophysiology of depression solely through the prism of serotonin and neurotransmitter depletion (40). Indeed, genetic and environmental factors, as well as interactions between the two, may result in maladaptive epigenetic mechanisms targeting stress response pathways, neurotransmitters (39), neuronal plasticity (41), neuroendocrine mechanisms (42), inflammation factors (43), and other behavior-related pathways that

have been found to be involved in mood disorders (44). For future research, scrutinizing these mechanisms could allow for better-targeted therapeutic interventions (45).

In the subsequent paragraphs, we describe some of the above-stated pathophysiological mechanisms involved in depression and anxiety.

Monoamine neurotransmitters

A dysfunction of neurotransmitters could cause several symptoms, as presented in Figure 5. For serotonin deficiency, there is: sadness, suicidal thoughts, aggressiveness, feelings of guilt, devaluation and appetite disorders; for dopamine deprivation: lack of motivation and social difficulties and finally for noradrenalin/noradrenaline depletion, reduced energy and alertness (39, 46). The author also described that glutamate deficiency could participate to psychomotor reduction, anhedonia, sleep disorders (39).

Neurotrophics factors

Brain regions are also affected by depression with alteration in cortical activity and volume in the prefrontal, limbic and anterior cingulate cortexes, the amygdala and, more consistently, the hippocampus which is an area involved in emotional processing and stress regulation (41). Reduction of neurogenesis with lower Brain-Derived Neurotrophic Factor (BDNF) rate may contribute to depression and cortical activity alteration (47). Indeed, BDNF is a major factor in activity-dependent neuronal plasticity in the brain,

regulating neuronal function and development (48), as the hippocampus (49) and amygdala (50).

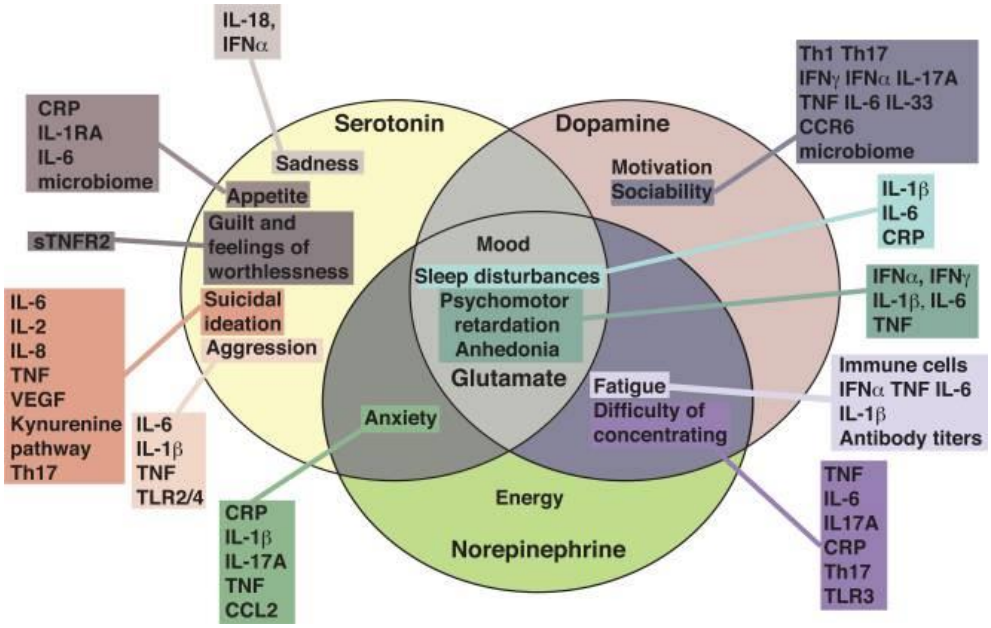

Figure 5: Symptoms of Depression Associated with Different Immunological Changes from Beurel et al., (39)

Legend Figure 5 : Symptoms of Depression Associated with different Neurotransmitters and Inflammatory/Immunological Changes. Monoamine neurotransmitters have been associated with various symptoms of depression as depicted in each oval. Some symptoms are dependent on multiple neurotransmitters, such as psychomotor retardation that is regulated by serotonin, dopamine, norepinephrine, and glutamate. Each box represents specific inflammatory/immunological changes (e.g., cytokines, immune cell, and others) that have been associated with each symptom.

Introduction

During adolescence, the strength of functional connectivity within the cognitive control network (e.g. dorsolateral prefrontal cortex, anterior cingulate cortex), engaged during executive function processes, increases with development (51). However, depreciations in brain connectivity and activation have been identified in young people with depression, demonstrating the existence of broad brain disturbances (52, 53) Indeed, neurocognitive impairments were reported in depressed children and adolescents, including deficits in inhibition capacity, sustained attention, verbal memory, planning and phonemic verbal fluency (54, 55). In a longitudinal sample, 151 participants aged 8 to 17 years with (n = 79) and without (n = 72) a history of childhood maltreatment were followed for two years. The authors observed greater resilience to depression development when young people were better able to regulate their emotions through recruitment of the frontoparietal network. This study supports the implementation of interventions targeting cognitive reappraisal and other cognitive emotion regulation strategies to prevent depression (56).

In anxiety disorders into adolescents and young adults, greater activation of the hippocampus (57, 58), left ventral striatum (59, 60) and less activity of the putamen (60) have been observed, reflecting their role in anticipating and processing potential threats (60). The hippocampus and striatum may be functionally connected regions involved in the development of anxiety disorders at this age. However, this is not a clear consensus. The mixed results may stem from differences in experimental design and study populations. Indeed, they may also reflect the complexity of anxiety disorders in youth with respect to psychosocial context and biological factors (61). Neuronal

activation could differ significantly depending on the event that produces the stress and the severity of the underlying anxiety level (58, 62).

Neuroendocrine mechanisms

The Hypothalamic-Pituitary-Adrenal (HPA) system mediates the physiological response to stress, including the secretion of glucocorticoids, a group of steroid hormones and mediators in the nervous and immune systems (63). The elevated concentrations of these hormones are observed during an acute adverse event. This higher level facilitates the consolidation of memories which will support behavioral adaptation and stress resilience (42). Chronic stress, particularly early in life, produces a dysfunction of the HPA and entails persistent elevated glucocorticoid hormones (43). In the context of a persistently high rate, it has been shown that secreted glucocorticoids during an adverse event will impair learning and memory processes (64). Prolonged stress and its impact on HPA, also results in decreased expression of a wide variety of genes, neuronal functions including BDNF circulation as well as increased expression of inflammatory cytokines (39, 63, 65, 66) ; Figure 5). Dysregulation of HPA appears to be implied in physical and psychiatric disorders, including depression and anxiety (65).

Inflammatory factors

Cytokines are produced by immune cells, and coordinate the activities of many cell types ultimately leading to both innate and adaptive immune responses, including microglia in the brain, which can have an impact on the

central nervous system. Cytokines have pro- or anti-inflammatory effects. A recent systematic review revealed that environmental stress factors such as the experience of childhood trauma (maltreatment, sexual abuse, violence) are associated to prolonged or excessive activity of pro-inflammatory cytokines (67, 68). This could disrupt neuronal functions, including alteration of neurotransmitter signalling, disruption of neurotransmitter synthesis, reuptake and release (39), seen Figure 5. In generalized anxiety disorders, a more pronounced proinflammatory response is associated with a reduced anti-inflammatory response, expressed by higher ratios of TNF-α/IL10, TNF-α/IL4, IFN-γ/IL10, and IFN-γ/IL4 compared to the healthy group (69). A meta-analysis yielded that pro-inflammatory cytokines are also higher in the blood of patients with MDD (70). However, the authors note the paucity of research examining biological and environmental stress risk factors for the development of psychiatric disorders in adolescence and young adulthood (68).

Future interventions inducing anti-inflammatory and neuroplasticity factors seem necessary and should therefore be investigated for the treatment of psychiatric disorders, including anxiety and depression (39, 47, 71).

Behavioral mechanism

Sleep problems could be a critical factor in developing GAD and MDD symptoms (72). In adolescence, Black et al., described the mechanisms underlying the relationship between insomnia, anxiety, and depression (73). The author reported biological (genetic, brain, cortisol, cytokine, memory, and sleep architecture dysregulation), psychological (cognitive/attention

biases and dysfunctional beliefs and attitudes about sleep) and social dimensions (reduced/impaired social interactions, unhelpful parenting behaviors, and family stress) (73).

Adequate mental health care for youth is not clear

Effective treatment for symptoms of depression and anxiety in youth is essential to prevent worsening of the course during development and to allow for a better prognosis in adulthood. Compared to adolescents, the research on adults is comprehensive, and the evidence for the effectiveness of mental health treatments could be outlined with a strong recommendation. Indeed, anxiety disorders should be treated with psychological therapy, pharmacotherapy or both in adulthood (74, 75). For the acute major depression disorder, the current standard treatment in adults is a combination of drugs and psychotherapy (WHO) (76, 77). Cognitive Behavioral Therapy (CBT) should be regarded as the psychotherapy with the highest level of evidence (74). In adults, to measure the impact of 21 antidepressants, Cipriani et al. revealed through a meta-analysis of 522 trials including 116,477 participants that all the antidepressants analyzed (agomelatine, amitriptyline, escitalopram, mirtazapine, paroxetine, venlafaxine, vortioxetine, fluoxetine, fluvoxamine, reboxetine, trazodone...) were more effective than placebo in MDD. This analysis was undertaken by excluding patients with resistant depression (76). In addition, antidepressant drug interventions may reduce levels of inflammation (IL-6, TNF, IL-10 and CCL2) (78), improve the functioning serotonin transmission by influencing glutamatergic,

serotoninergic, noradrenergic and histaminergic systems (46) and increase the expression and signalling of BDNF (47). The previous authors encouraged to develop other treatments to stack these effects.

In contrast to adults, American Psychological Association guidelines suggested only Fluoxetine in adolescents with with moderate-to-severe depression and mostly for indivuals who do not have access to psychotherapy (eg, in low-income and middle-income countries) (79) or have not responded to non-pharmacological interventions (11, 77, 80). This explained by sparse date and due to higher side than in adults (81), including the risk of suicidal thinking and behaviour (82), up to twice as much as placebo (83). In addition, youth participants at risk of suicide were often excluded from the trials, so we cannot be confident of the effects of these drugs on youth (84). To undertake an antidepressant drugs therapy in this age group, a shared decision must be taken between patient, parents/guardian, and psychiatrist for other drugs (77). In the clinical care of adolescents with major depressive disorder, guidelines recommend psychotherapy as the first-line interventions; especially CBT or interpersonal therapy (37, 77, 85, 86). Briefly, The National Institute for Health and Care Excellence (NICE) guidelines recommend to build a supportive and collaborative relationship with both the patient and the family or carers. NICE and literature describe that if CBT does not meet the clinical need, the following options could be considered: family psychotherapy, interpersonal psychotherapy for adolescents, psychodynamic therapy and brief psychosocial intervention. Brief psychosocial intervention includes psychoeducation (87), building health habits (diet, sleep and exercise practise), planning and scheduling valued activities, solicitation in school involvement and peer interaction (88). Treatments, such as exercise therapy,

cognitive training (87), mindfulness-based interventions, art therapy (88) have demonstrated encouraging results and appear to be acceptable in youth depression and anxiety (87). However, caution should be used before drawing conclusions because of the paucity of studies examining these effects, particularly in clinical populations and in psychiatric settings (88, 89).

Research indicated that future interventions promoting psychosocial aspects, anti-inflammatory effects, neuroendocrine changes, neuroplasticity with the improvement of cognitive and executive functions should be studied in the field of mental health, especially for their potential effects on depression and anxiety (39, 47, 56, 71, 87). These data therefore suggest the value of exploring complementary interventions, such as physical exercise, in the prevention and treatment of depression and anxiety.

Exercise medicine

For clarifications purpose, we defined the physical activity, exercise and different intensity terms used thorough the manuscript below from WHO guidelines on physical activity and sedentary behaviour, American College of Sports Medicine (ACSM).

-"**Physical activity** is any bodily movement produced by skeletal muscles that requires energy expenditure" (90). The minimal energy expenditure level for physical activity is from 1.0 to 1.5 Metabolic Equivalent Task (MET) (91).

-**“Exercise** is “physical activity that is planned, structured, and repetitive and has as a final or intermediate objective the improvement or maintenance of physical fitness” (90).

Intensity effort produced during a physical activity could vary between very light (<37% Maximal Oxygen Consumption (VO2Max)), light (37-45% VO2Max), moderate (46-63% VO2Max), vigorous/high (64-90% VO2Max) and near-maximal to maximal intensity (>90% V02Max) (92). Several tools and methods are used to monitor the aerobic physical activity intensity as the talk test, the cardiovascular monitor, subjective scale of perceived effort and motion sensor, as per the ACSM statement. Details on these measures are described in the appendix 1.

Engaging in regular physical activity in daily life is vital for the health (ACSM). Physical exercise could ensure improved thinking, learning, and judgment skills as well as healthy growth and development in youth (WHO 2020). Furthermore physical exercise has important physical health benefits by contributing to the prevention and management of diseases such as cardiovascular disease, (93), cancer (94-96) and diabetes (97). Despite these good health outcomes, more than 80% of the world's adolescent population is not sufficiently physically active (WHO 2020).

To illustrate the physiological impact of exercise medicine, we describe the impact of exercise through two mechanisms on body inflammation, one with adipokine and myokine, and the other with toll-like receptors. Adipokine is a cytokine produced by fat mass regulating the lipid and glucose metabolism and that have pro-inflammatory or anti-inflammatory activities (98). Disturbed metabolic homeostasis may imbalance pro-/anti-inflammatory

level, which may play a key role in the development of metabolic diseases, as illustrated in Figure 6 (99). Fat accumulation, as in obesity, secretes more pro-inflammatory adipokines, which could participate to the low grade inflammatory state. In response to muscular contractions, myocyte release myokines; cytokines inducing anti- and pro-inflammatory effect, as the myokine IL-6 (100). Long-term exercise may produce anti-inflammatory myokines in the skeletal muscle and counteract the unbalanced pro-/anti-inflammatory level, induced by overweight. Then these mechanisms may improve the chronic pro-inflammatory state as it could be observed in obesity and metabolic diseases (99, 101).

Another interesting benefit of exercise is its potential anti-inflammatory effect by reducing the expression and/or activation of pro-inflammatory receptors, particularly toll-like receptors (TLRs) (102). It could modulate the reduction of chronic inflammation in innate immune cells, which is one of the major inflammatory responses in obesity (97). Furthermore, it has even been suggested that individuals with high levels of cardiorespiratory fitness are likely to reduce chronic low-grade inflammation with downregulation of pro-inflammatory TLRs expression/activation (102) and produce several potent anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonist, and IL-6, and improve various immune markers (103).

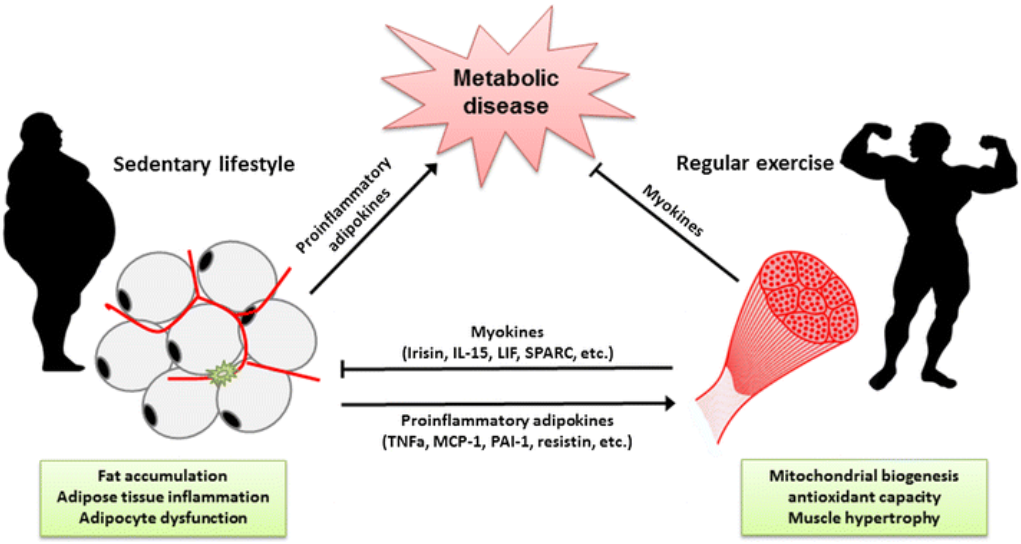

Figure 6: *Relationship between adipose tissue derived adipokines and skeletal muscle derived myokines. In the state of sedentary lifestyle, nutrient overload results in accumulation of fat and subsequent disturbance in adipocyte metabolism, which results in secretion of adipokines which are primarily proinflammatory cytokines. In contrast, contracting muscles in response to exercise secretes myokines, which are suggested to counteract the effects of proinflammatory adipokines. Therefore, the metabolic homeostasis is regulated by balance between adipokines and myokines, and are critical in development of metabolic diseases (99).*

From a neurodevelopmental perspective, exercise can trigger neuroplasticity and therefore improve an individual's ability to respond to new demands through behavior modifications (104). There is some evidence that aerobic exercise may enhance the neuroplastic response in the motor cortex (105), induced volumetric retention in the left hippocampus (106) and be a major source for the strenghtening of the BDNF-dependent executive functioning (107).

Exercise therapy is growing in mental health

Towards a valid recommendation in adults?

In **anxiety**, high physical activity versus low physical activity levels may prevent the development of anxiety in adults (108). Systematic reviews and meta-analyses revealed that exercise reduces anxiety symptoms in people with a current diagnosis of anxiety and/or stress-related disorders (109-112). Although authors have demonstrated these positive results, NICE guidelines for anxiety treatment only refer to physical exercise (oriented mostly to training) for its value in overall health. Its potential anxiolytic effect is not mentioned ~~to~~..

In **depression,** participation to regular physical activities may be one way to prevent depression emergence in adults (113, 114). Numerous cohort studies or RCTs (randomized controlled trials) indicate that physical exercise is associated with a decrease in depressive symptoms (112, 115-118) with positive changes in anedhonia, lack of motivation and energy (119). Consequently, NICE guidelines (in a recent report published in June 2022) introduced group exercise as a first line treatment for different levels of depression, including severe cases. This is in line with the American Psychological Association (APA) guidelines in adults, recommending exercise for the treatment of depressive disorders (77). The combined effect of exercise and other therapies, such as psychotherapy and pharmacotherapy, needs to be studied (120).

Introduction

For anxiety in adolescents, NICE and APA guidelines did not report the interest of exercise. For moderate and severe depression, NICE guidelines suggest the implementation of brief psychosocial interventions. One of its goals is to improve mental and physical health by targeting sleep, diet and exercise. Structured and supervised exercise is suggested with 3 sessions per week of moderate duration (45 minutes to 1 hour) for 10 to 12 weeks. However, it's not considered as a proper complementary treatment for depression in first line as in adults recommendations. While the evidence for exercise therapy in adult mental health has seemed to cross the line as a treatment to be considered in guidelines, exercise therapy has not yet moved up a notch in youth mental health care. We describe the scientific literature on this topic in the subsequent part.

Exercise has not moved up the notch in young people

In pre-adolescents (9-12 years)

A this age range, an exciting trial revealed that participation in moderate to vigorous physical activities predicted fewer symptoms of major depressive disorders in the following years (121). It corroborated with previous RCT demonstrating depression reduction after 12-week moderate-to-vigorous exercise program among 49 children aged 9 to 12 years (122). However, two systematic reviews synthesised the impact of exercise in preadolescents and found a moderate positive effect for depressive symptoms (k=5, Standard Mean Deviation (SMD) = -0.66, 95% Confidence Interval (CI) -1.25 to -0.08) (123) but not for anxiety symptoms (k=6, SMD= -0.48, 95% CI -0.97 to 0.01)

(124). The controlled trials that comprised these meta-research studies were generally of poor methodological quality and showed considerable heterogeneity in the samples studied, interventions, methods and outcome measures (123, 124). Evidence for antidepressant and anxiolytic effects by exercise in preadolescents remains weak in the literature. More substantial efforts are needed to evaluate the efficiency of exercise programs as prevention or treatment in this population.

In adolescents (10-19 years)

Studies over the past decade have provided additional and novel evidence on the impact of exercise on depression and anxiety in adolescents.

The anxiolytic effect of exercise was small in a recent meta-analysis (Hedges' g = -0.47, 95% CI = -0.71 to -0.24) (125). Still a lesser effect was found (k=8, 0.29, 95% CI -0.52, -0.06) when exercise interventions were compared with active controls (non-physical activity). In addition, the effect was not apparent in clinical samples. Overall, the studies were of low quality, and few trials explored the effect of exercise in a sample that exceeded the pathological threshold for anxiety. The author stated that the effectiveness of exercise as a treatment for clinical anxiety disorders remains unknown. Therefore, they requested caution with the findings regarding the lack of studies in the clinical population, particularly with regard to the dose-response relationship between level of intensity and severity of symptoms. Well-designed RCTs with youth should be a priority (125).

The anti-depressant effect was small in clinical and nonclinical samples (k=8, SMD -0.48, 95% CI -0.87, -0.10) in a meta-analysis targeting adolescents in

controlled studies (126). In depressed adolescents, very recent meta-researchs performed small antidepressant effect in a analysis, including non-randomized studies (k=9, Hedges' g = −0.47, 95% CI = −0.71 to −0.24) (127) and moderate in two others analysis with RCTs only (that comprises 7 trials in total) ; (k= 5, SMD = -0.57, 95% CI - 0.90, - 0.23, p < 0.01) (128) and (k=4, SMD = -0.59, 95% CI = -1.08 to -0.10, p = .02) (129). These promising results are mostly found in studies of better methodological quality (128-130). Exercise interventions appeared to be a complementary treatment for depression. However, these authors declare that this should confirm with larger clinical trials and in mental health settings with high-quality studies. Additionnaly, a smaller effect was observed when the control group was active than passive, revealing a real diminished impact of physical exercise (127). The forms of exercise intervention among adolescents should also be further enriched (128).

In young aduts (19-24 years)

Only one systematic review has been published on the anxiolytic effect of exercise in children and young people (125) and was described in the previous paragraph on adolescents.

A meta-analysis among adolescents and young adults including 16 RCTs and a total of 771 participants revealed a large effect of exercise on clinical and non-clinical depression symptoms compared to controls (SMD = -0.82, 95% CI = -1.02 to -0.61, p < 0.05, I2 = 38%). The effect remained robust in trials with clinical samples (k=5) and trials using active controls (k=7) (89).

In summary, further development is needed to identify the most efficient ways to explore the impact in clinical practice and how to implement exercise interventions in youth mental health services (131, 132). The characteristics of interventions to relieve symptoms of depression and anxiety also deserve to be studied, as the evidence is not yet clear.

Mechanisms of physical activity in mental health

As physical activity has been demonstrated to have major benefits for mental health, it seems important to explore its mechanisms. Both psychosocial and neurobiological factors could explain the protective and anti-depressant effects of physical activity on mental health in adults (Figure 7). **From a psychosocial perspective**, physical activity may exhibit positive results in physical self-perception, self-esteem, social support and self-efficacy (133, 134). The literature is existing for these components in healthy youth, so we do not describe here in more depth for adults. On the other hand, **from a neurobiological dimension**, physical activity might produce beneficial changes in neuroendocrine responses, oxidative stress, inflammation and cortical activity (112, 133, 135). A more substantial literature has been produced to understand these neurobiological effects of physical activity in adults compared to adolescents. We therefore expand on the neurobiological part in the following paragraphs.

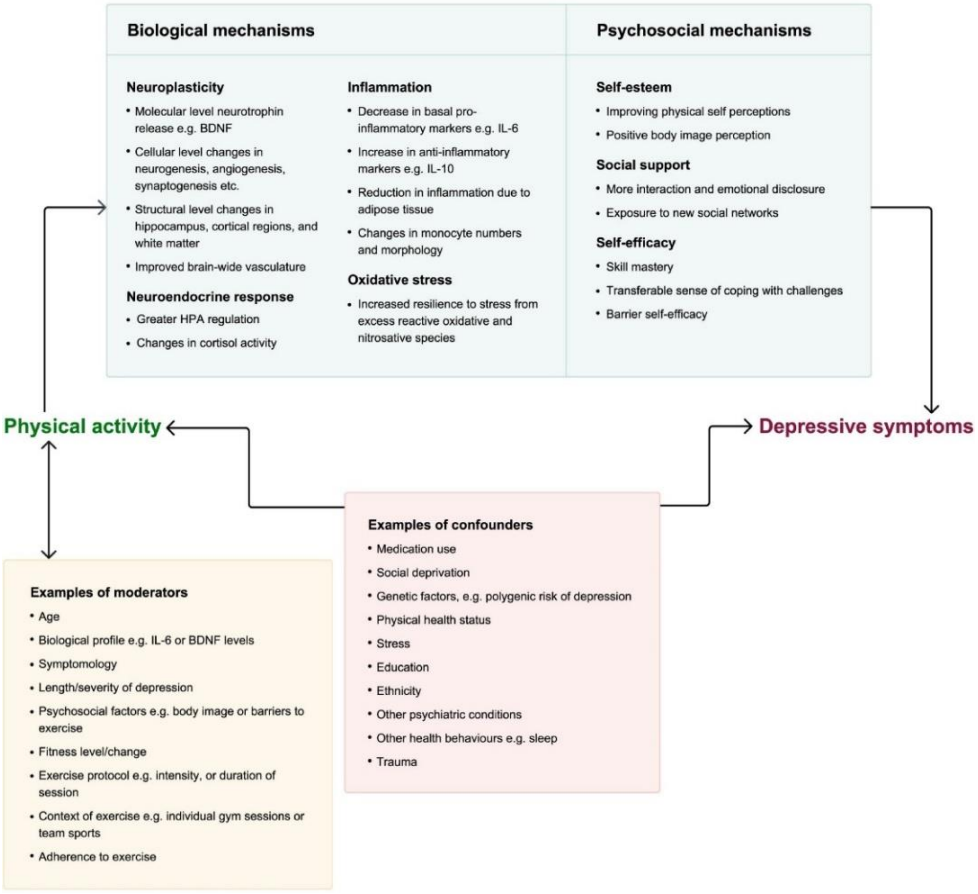

Figure 7: Mechanisms, moderators, and confounders of the relationship between physical activity and depressive symptoms from Kandola et., (133)

Neurobiological effect of exercise

There is evidence that exercise may induce some epigenetic mechanisms via BDNF expression delivering increased synaptic plasticity as well as cognitive and executive functions (136) which are precisely altered in depression. At the synapse level, Glutamate release, induced by exercise, stimulates NMDA-

R (N-methyl-D-aspartate receptor) and consequently Ca2+ influx into postsynaptic neurons. The increase in Ca2+ levels triggers a wave of molecular events allowing BDNF transcription (136). BDNF production through exercise could therefore constitute a target for future antidepressant approaches (47). In MDD adults, a meta-research collected 6 studies measuring BDNF in resting blood concentrations after chronic exercise intervention. Unexpectedly, the analysis demonstrated no significant increasing of BDNF levels (SMD = 0.43, 95% CI: −0.06–0.92, p = 0.09). However, due to the lack of studies in this area, authors reported that it's difficult to draw a definitive conclusion (137). Increased BDNF may not be present or in highly variable levels in all individuals, suggesting the importance of exploring predictors of response (64), particularly in patients with MDD who may prove resistant to antidepressant treatment (137).

Another mechanism induced by exercise is its effect on inflammation in central system (133). Chronic stress is related to HPA hyperactivity contributing to the pathophysiology of depression and anxiety (63). Animals, having performed exercise programs, have an attenuated glucocorticoid response to stressful stimuli and exhibit less anxious behavior in a novelty situation. Thus, physical activity may interact with HPA in attenuating the glucocorticoid response to stressful stimuli (112, 138).

Exercise may inhibit activation of inflammation in prefrontal cortex in rats (139). It could be explained by a better regulation of neuroendocrine responses via HPA (139), and potentially related to a reducing of neurotransmitters (133). Indeed, an increase in monoamine levels can be achieved by chronic exercise, but this has been reported in animal studies only (140). To our knowledge, this has not yet been studied in humans (112, 133).

Another anti-inflammatory effect by exercise has been observed in the skeletal muscle. Kynurenine metabolites regulate biological processes, including immune cell response and neuronal excitability. Kynurenine perturbation could participate in the immune activation, serotonergic deficiency and disturbed NMDA-R function, which has been associated with stress-induced depression (141). Ruas, J.L team demonstrated that kynurenine accumulation could be decreased by activation of skeletal muscle from exercise producing conversion of kynurenine to kynurenine acid, a metabolite unable to cross the blood-brain barrier. In animals, the reduction of kynurenine in blood during muscle contraction induced by exercise may protect the brain from stress-induced changes associated with depression (e.g., neuroinflammation) without the need to cross the blood-brain barrier. The effect of exercise on depression through modulation of the kynurenine pathway points to an important mechanism of inter-organ crosstalk (the communication by which one tissue can affect the metabolic pathways of a distant tissue) (142).

Compared to adults, there is a gap in the literature to understand the effects of exercise mechanisms in mental health for young individuals, particularly for the neurobiological mechanisms, which might be precisely age-dependent (139). Indeed, explanations highlighted for adults may not be transposed with certainty for adolescents due to (A) the social complex, neurobiological and somatic changes that take place during adolescence (143, 144), (B) the daily life and stress exposure influenced by the school and family environment as well as the socialisation with peers (27) and (C) the neurodevelopmental pathways still in development (6, 8). Therefore, caution is required in comparative studies across age ranges.

In mostly healthy children and adolescents (8-18 years old), Lubans et al., introduced a conceptual model (Figure 8) explaining the neurobiological, psychosocial and behavioural mechanisms of physical activity on cognition and mental health (145). The tested participants presented neither learning difficulties or cognitive deficits nor a diagnosis of developmental disorders. Based on their model and existing literature on young people, we describe each mechanism below.

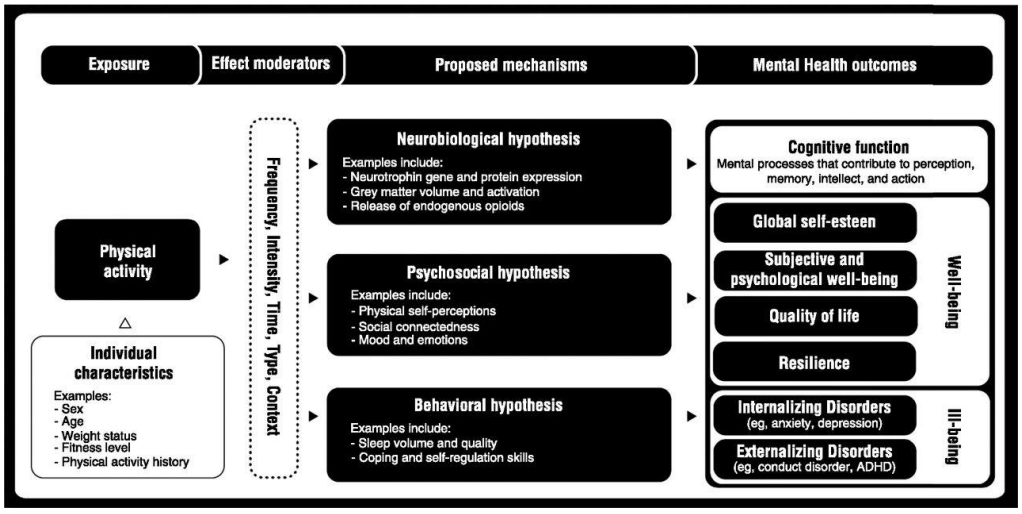

Figure 8: Conceptual model for the effects of physical activity on mental health outcomes in children and adolescents. Legend: ADHD, attention-defi cit/hyperactivity disorder (145)

Neurobiological effects

With 6 RCTs, in children aged 7-11 years only, Lubans et al., (145) reported that participation in physical activities improved neuropsychological tasks requiring inhibition, flexibility (146), planning (147) and better activation via

fMRI of the prefrontal cortex right anterior (148) while no results have been shown in cognitive control (149). These results are consistent with meta-researches conducted in youth (6-35 years) improving global executive functions after acute (150) and chronic exercise (151). A higher effect by long-term exercise was found for the accuracy of inhibition control in children and adolescents (152).

Obese children, who obtained poorer executive function scores, might improve them better than their normal-weight peers after physical exercise (153). Furthermore, better benefits for improving working memory, inhibitory control and cognitive flexibility (154) were also observed in sports programmes and extra-curricular physical activities than in school-integrated physical activities (151). In addition, neurobiological effects of exercise seemed also to be intensity-dependent (139). Thus, it appears that the baseline level of executive function and the characteristics of the physical activity may generate different responses in individuals. Given that executive functions predicted larger improvements in treatment for mental illness in adolescents (155) and more resilience in depression (56), targeting efficient interventions, such as exercise, to enhance executive functions may therefore have major implications.

Psychosocial mechanisms:

The conceptual model proposed by Lubans (Figure 8) suggested improvements through physical activity participation in self-physical perceptions, self-esteem, self-concept, quality of life, psychic well-being, emotional regulation, vitality and sense of self-efficacy (145).

Additionally, a poor score in (1) body satisfaction and image (i.e., internal perception of, attitude towards, and preoccupation with one's body size and shape), (2) physical competence (i.e., perception of one's own physical ability across different domains), and (3) instrumentality (i.e., tendency to approach the world with a self-determining, assertive attitude) is a predictor of depressive symptoms (156, 157). In young people, participation in physical activities and improving of their cardiovascular fitness are associated with better self-perception, increased perceived social acceptance and increased body satisfaction. If they are less worried about their appearances, they may feel less preoccupied with others' evaluation of their physiques (157, 158). Putting the data together, it hypothesized that these benefits the protective effect of exercise on the occurrence of depressive and anxiety symptoms (156-158).

Improving social support is also essential in mental health strategy care. A poorer social environment, frequently observed in depressed youth, may moderate the long-term effectiveness of the treatment (159). The inclusion of peer interactions such as in team sports may potentiate the reduction of the symptoms of depression and anxiety with an impact on social isolation, social relationship, and social anxiety (134). Supervision by mental health workers is essential to ensure a safe and motivational atmosphere as well as appropriate peer interactions (160).

These concepts are primarily investigated in non-clinical young populations at school and university. Yet, a substantial gap exists in this topic, and future research should confirm these observations in depressed young people.

Behavioural mechanisms :

Finally, in Lubans' model, only two studies were referenced for behavioral mechanisms. The authors were unable to document the impact of physical activity interventions on sleep and emotional regulation with strong evidence (145). Similarly a systematic review revealed mixed results that could not demonstrate a positive impact of exercise on sleep for healthy children and adolescents (161). However, it appears that physical inactivity (162) and increased sedentary behavior (163) may worsen sleep issues. Physical inactivity is an insufficient physical activity level to meet present physical activity recommendations (91). Sedentary behavior is any waking behaviour characterized by an energy expenditure of 1.5 METS or lower while sitting, reclining, or lying. It exists passive sedentary behaviour (e.g. taking a bath, watching TV, listening to music) and mentally active sedentary behaviour (e.g. knitting, sitting in a meeting, office work) (91). To our knowledge, there is no data showing effects of exercise on sleep quality in depressed youth. As meta-analyses have shown positive impact of exercise on sleep quality for adults with mental illnesses (164), it would be interesting to explore if a similar result could be observed with depressed adolescent .

What would be the best characteristics of exercise programs in young people ?

Intensity and frequency

A longitudinal study reported that higher sedentary behavior increased at the expense of total physical activity during adolescence, related to a higher risk of depressive symptoms (165). Others results have demonstrated that higher levels of physical activity intensity and frequency had more significant effects on preventing depressive symptoms, assessed primarily by self-reports or accelerometers (18).

Using systematic reviews of interventions from experimental trials, the authors suggested different dosages for reducing symptoms of depression through exercise. A first systematic review stated that low to moderate intensity three times a week for 6 to 12 weeks in a clinical setting should be efficient (126). But this suggestion was at odds with a second systematic review demonstrating that a low or high level of exercise intensity would be less effective than a moderate intensity in a sample of adolescents with clinical depression (130). This also contradicted other recent studies, which showed that moderate to vigorous intensity yielded better prevention results (89) and in treatment ($k = 9$, Hedges' $g = -0.68$, 95% CI = −0.94 to −0.42, $p \leq 0.001$, $T2 = 0.0$, $I2 = 0\%$) than the low intensity (166). Finally, the most recent meta-analysis in depressed adolescents suggested that moderate intensity is a better choice, supported by 5 RCTs (128).

The necessary duration of the program varied in multiple sessions, from a minimum of 6 weeks (167) or 8 weeks (89, 128). However, no statistical analysis was able to measure the most efficient duration and frequency (166).

In contrast to all of the previous authors' statements for depression, the authors were unable to hypothesize a dose-response relationship between exercise and anxiety symptoms decrease due to the limited number of studies and the lack of information provided on the protocols undertaken (125).

Content of session

Aerobic-based activities have been clearly shown to be efficient in reducing depression and anxiety in adults (115) and young people (89, 166, 168). Standard fitness programs on a cycloergometer or treadmill and programs embedded in games exhibited no difference in effectiveness in reducing depression after statistical analysis (166). Nevertheless, aerobic training with cognitive abilities might be promising for depression reduction. For example, dance has shown good improvement in neuroplasticity with complex movements recruiting different motor, somatosensory and cognitive areas among young people (169, 170). It remains unknown whether mixed intervention combining aerobic and anaerobic interventions could exhibit better results. Nonetheless, it appeared that mixed exercise could increase the natural antioxidant system capacity and stimulate neutrophic factors (171), inducing brain plasticity (172, 173).

In summary, the most appropriate intensity, frequency, duration and type of exercise programs for depressed and anxious youth (10-24 years) need to be explored. Dropout and adherence to exercise programs must also be

considered in order to examine an adequate response to exercise in mental health (174).

Aims of dissertation

Depression and anxiety in youth are major public health concerns and represent a real challenge for the medical community. This has become even more pronounced after the exacerbation of psychological distress seen during the COVID-19 crisis. Yet, there is a lack of evidence for an effective strategy to prevent and treat depression and anxiety in youth. This is a critical issue because ill-being which starts at an early age substantially disrupts daily life and is prone to persist or worsen in future adult life. Effective interventions to alleviate youth distress are therefore crucial. Physical exercise which has shown positive results on depression and anxiety symptoms in adults should be studied in youth (10-24 years).

The purpose of this dissertation is to investigate the antidepressant and anxiolytic effects of physical exercise on the mental health of youth. This will be fulfilled through 4 different chapters.

(1) In the chapter I, we will explore physical exercise programs that may reduce non-clinical and clinical depression in youth (10-24 years old). We will use a systematic review (Study 1) to establish the state of the most current evidence to conduct future antidepressant exercise interventions.

(2) In the chapter II, we will document the most appropriate exercise intensity to decrease symptoms of depression and anxiety in preadolescents (9-12 years old) attending school (Study 2). Thus, we will use a randomized trial to compare two different exercise programs in a non-clinical elementary school sample. In order to complement this second part, we will illustrate the potential effect of exercise on school well-being through the case of Andy, a young student who is a victim of bullying (Study 3).

(3) In the chapter III, we will present the results from the first randomised controlled trial comparing the effect of an add-on exercise program to a social relaxation program, integrated into substantial and pluri-disciplinary psychiatric care for adolescents (10-19 years) suffering from clinical symptoms of depression and anxiety. Dataset, participants characteristics and used instruments will be introduced (study 5).

(4) The lockdown induced by the COVID-19 pandemic severely damaged higher education students mental health. In this context, in the chapter IV, we will describe the results (study 6) from a randomised controlled trial comparing an online high-intensity functionnal training to a passive control group to reduce the psychological suffering of students impacted by the COVID-19 health crisis.

The expected impact of this dissertation is to evaluate whether exercise programs are efficient in preventing depression and anxiety and whether physical exercise therapy should be implemented as an essential part of mental health care in young people to treat depression and anxiety

CHAPTER I: Exercise and depression in young people

Study 1: Exercise programs for the prevention and treatment of depression symptoms in young people, aged 10-24 years: A systematic review

Manuscript in preparation

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Abstract

Background: We aimed to review the effectiveness of exercise interventions for treatment and prevention of depression in youth (10-24 years).

Methods: Pubmed, Sciencedirect, and Psycnet were searched from January 2005 to August 2021 for randomized studies evaluating exercise effects on depressive symptoms in youth compared to passive or active interventions. We assessed the reported antidepressant effects of exercise in clinical and non-clinical samples through qualitative analysis of the literature. Our analysis included the various characteristics of interventions and their efficiency in reducing depression symtoms. The PEDRO scale served to assess the quality of the trials.

Results: We identified 25 randomized studies, comprising 22 Randomised Controlled Trials (RCTs) and three randomised trials, together including 2180 adolescent or young adult participants. Based on 14 RTCs, exercise was effective in relieving moderate to severe depression symptoms compared with active or passive control interventions. Compilation of seven RTCs showed more limited effects on non-clinical symptoms. Moderate to vigorous intensity exercise consisting of 3 to 4 sessions per week for between 6 and 12 weeks appeared to reduce depression in youth. PEDRO scale results indicated medium quality for most of the studies, primarily due to difficulties in obtaining blindness of subjects, therapists, and evaluator, concealed assignation to a group, and intention-to-treat analysis.

Conclusion: Our systematic review revealed that exercise therapy can be an effective antidepressant treatment for youth with moderate to severe

depression scores. However, caution is warranted due to the medium quality of the available studies, and the frequent lack of crucial information about details of the study protocols. Higher quality studies with a comprehensive description of the sample and exercise protocols are necessary to substantiate fully the antidepressant efficacy of exercise in youth.

Introduction

Worldwide, more than 500 million people are currently experiencing depressive symptoms, and 5% of the world population suffers from Major Depression Disorder (MDD), a debilitating and recurrent condition. Indeed, depression is one of the leading causes of disability worldwide and is a major contributor to the global burden of disease (WHO 2021). An effective strategy to alleviate this worldwide burden could entail greater emphasis on prevention or treatment at first onset of symptoms, aiming to reduce the risk of a more severe course or recurrence (19) (175). The median age of onset of MDD is approximately 25.7 years in high-income countries, similar to the 24.0 years in low- and middle-income countries. However, 95% confidence intervals (CIs) indicate that the risk period for onset of MDD extends from the mid-teens to the early 40s (13). Recent circumstances of the COVID-19 pandemic may have lead to an earlier onset and higher rate of depressive symptoms. In particular, adolescents and young adults may be especially vulnerable to develop depressive disorders due to stressors related to the psychosocial crisis and contagion control policies arising during the pandemic (4, 6). Young people, defined by the WHO as those of age ranging

from 10 to 24 years, are in a critical period of neurological development, and are particularly vulnerable to develop psychiatric symptoms during the late stage of puberty, which is often associated with negative self-image and interpersonal stress (8) (WHO 2021). Onset of depression in young people may be followed by long-term alteration of neurobiological factors, including neurocognitive impairments (54, 55), elevated pro-inflammatory factors (39), blunted reward-related activity, cerebral white matter disruption, and brainwide disturbances (52), included altered volume of limbic regions involved in mood and motivation (67, 68). These elements may be a key role in the emergence of MDD as a persistent disorder (67, 68) with the increased risk of recurrence throughout life (4, 6).

Current thinking on the treatment of depression in youth favors psychotherapy, particularly cognitive behavioural or interpersonal therapy (34, 77, 85, 86, 176). Unlike the case in adults, pharmacotherapy is limited in the adolescence (10-19 years, following the WHO), with fluoxetine being considered the best option. Here, caution is warranted due to the lack of evidence of efficacy, and the potential risk of increased suicidal ideation after start of treatment (80, 84). Given this context and the early appearance of depression cases, complementary therapies should be investigated to reduce or prevent depression developpement in young people. Among current candidates for targeted therapy are inflammatory pathways, neurotrophic factors, and special support in the development of intra- and interpersonal relationships (39, 47, 71, 177). Exercise therapy could be an effect channel for intervention via its effects on physiological stress responses e.g., enhancing executive functions, and improving psychosocial components underlying depressive symptoms (53, 112, 133, 135, 152, 178) Furthermore,

aerobic physical exercise has shown efficiency in reducing depression levels in adults (114, 115, 178). American Psychological Association (APA) and National Institute for Health and Care Excellence (NICE) guidelines for treating depressive disorders have described physical exercise as complementary treatment to prescribe in adults (77). However, there is no corresponding recommendation for adolescents. Young adults, still in development (8) and in a critical period for the prevention of psychiatric disorders (4, 6), deserve also special emphasis (WHO 2021).

Several systematic reviews demonstrated the positive impact of exercise interventions in depressed adolescents and young adults (89, 126, 130, 167, 168). A systematic review, that collected data from four meta-analyses on people aged 5 to 20 years, found a moderate effect of exercise on depression reduction ($d = -0.50$) (168). However, it has been unclear whether physical activity might differ in reducing depression scores in young people with respect to (A) non-clinical symptoms, with scores falling below the cut-off score considered as pathological, and (B) clinical symptoms, of severity meeting the criteria for mild to severe levels of depression. One recent systematic review has considered this distinction in adolescents (13-17 years), which included RCTs along with non-peer reviewed reports (167). Another meta-research defined the targeted sample as aged 12-25 years but included only clinical symptoms (89). Furthermore, the anti-depressant efficacy of exercise for young people (aged 10–24, referring to the WHO definition) is not yet established across the spectrum from non-clinical and more severe symptoms. Few studies have examined the range of responses to symptom severity in the specific range of youth. In addition, there is still uncertainty about the nature and characteristics of physical exercise that are most

effecting in alleviating depression (167). In this systematic review, we aimed to compile and summarize studies on the effects of exercise interventions on depression in youth, placing special emphasis, first on the effect of exercise as non-clinical or clinical symptoms of depression and, second on the optimal characteristics of the therapeutic exercise regimens. We included on our review trials comparing exercise with a control group or another experimental program, thus aiming to identify the salient features of exercise interventions, particularly intensity-dosage effects in reducing depressive symptoms in youth. In order to assess the difference in impact between exercise programs, only randomized and baseline comparability studies were included. We searched for articles from 2005 due to Cochrane Collaboration systematic review that conducted with similar characteristics in previous years (124). We hypothesize this systematic review would indicate a positive benefit of exercise for prevention of depression in the general youth population and for treatment of clinically significant depressive symptoms.

Method

This systematic review was conducted in accordance with PRISMA Guidelines. A prospective protocol for the systematic review has been previously published in PROSPERO, an international prospective register of systematic reviews.

Search strategy

The included articles are indexed from January 2005 to August 2021 in bibliographic databases (*PubMed, ScienceDirect,* and *Psycnet*). MESH terms were mostly used with the Boolean operators “AND” and “OR”, as follows: S1. Teenagers AND depression AND "physical activity" ; S2. Teenagers AND depression AND "exercise program"; S3. Young AND prevention and treatment AND depression AND exercise; S4. Student AND depression AND "exercise program". The same search terms was used for all three databases. The filter “research article” was applied for *Sciencedirect*. Authors reviewed and approved the search terms and the strategies used to obtain the selected articles. In addition, relevant articles retrieved from references lists of recent meta-research or known to the authors were added manually.

Inclusion criteria

1. Mean age of participants was in the range 10-24 years old.
2. Inclusion of outcome measure of depressive symptoms as self-reports or diagnostic interview.
3. Evaluation of physical exercise on depression symptoms
4. Inclusion of a control or experimental comparison group. Exercise, psychological, or others interventions were eligible for comparison.
5. Only randomised studies were retrieved to compare exercise intervention to control or another experimental arm.
6. Data comparability between groups at baseline.
7. Published in the English language.
8. Published in a peer-reviewed journal
9. Published between January 2005 and August 2021.

Exclusion criteria

1. Exclusion of one-session exercise
2. Exclusion of trials comprising a single time of evaluation.
3. Lacking description of the exercise program.

Selection process

Two authors (RD and FM) collected the references in Endnote software to proceed with the article selection. Following the defined inclusion and exclusion criteria, we screened independently each step of article selection, proceeding from the title, to the abstract, and finally to the entire text. At the end of each step, any disagreements were resolved by discussion. Finally, any remaining inconsistencies between raters were resolved in consultation with a third author (AP). The full-text of the identified articles were then assessed for extraction of pertinent data.

Data collection process

Data from the selected articles were gathered by the three reviewers (AP, RD, FM) independently. Data regarding study design, setting, characteristics of the participants (sample size, gender, age, depression severity, comorbidity) and measures of depression were collected. Interventions were described in detail according to their content, intensity, duration, frequency, type of supervision (provider and mode of delivery), attendance rate, and drop out rate. If exercise intensity was not described, reviewers interpreted the intensity according to the updated compendium measuring the Metabolic

Equivalent of Task (MET) per hour (179). The statistical independent analysis was observed to detect differences between groups over time after intervention, along with any available follow-up data. In cases with missing data, we note that data were not reported.

Study risk of biais

The PEDro scale was developed by the Physiotherapy Evidence Database to determine the quality of clinical trials (180). Each trial selected for final analysis in this systematic review was given a total PEDro score, which ranges from 0 to 10. The first criteria, comprising identification of eligibility criteria, was not included in the final score. Scores are available on the website of Pedro Scale (https://pedro.org.au/). When the evaluation was not reported, the three authors provided independent analyses, and resolved any disagreements by discussion.

The 11 criteria of ther PEDRO scale were: 1. Eligibility criteria were specified; 2. Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated by the order in which treatments were received); 3. Allocation was concealed; 4. The groups were similar at baseline regarding the most important prognostic indicators; 5. There was blinding of all subjects; 6. There was blinding of all therapists who administered the therapy; 7. There was blinding of all assessors who measured at least one key outcome; 8. Measures of at least one key outcome were obtained from more than 85% of the subjects initially allocated to groups; 9. All subjects for whom outcome measures were available received the treatment or control (intention-to-treat); 10. The results of between-group statistical comparisons were reported for at least one key outcome; 11. The

study provided both point measures and measures of variability for at least one key outcome.

Results

Study selection

The details of the screening with detailed justifications are reported in Figure 1, which displays the flowchart of the study selection. The search terms entered into the various databases yielded 6296 articles. After excluding 366 duplicates, a total of 5,930 titles were screened. Following the title/abstract screen, the remained 269 references, of which25 were selected for full reading. A further 19 articles were selected from other sources, including the authors' reading of the current literature. This brought to 44 the total number of articles to be analysed in detail. After reading these texts in their entirety, twenty-five articles were identified as meeting all the criteria for our systematic literature review.

Type and quality study

Descriptive data concerning design are reported in Table 1. Of the 25 studies included in the analysis, 22 were randomised controlled trials (RCTs) and there were randomised studyies (RTs). One of RCTs has two sub-studies: an online RCT, and a laboratory RCT (181). Two of the RCTs were of cross-over design (182, 183). The three RTs did not have control groups, but only compared between two exercise interventions (170, 184, 185). We included the study of Wunram et al. (170) as an a RT because its control group was not

randomised, even though the authors did compare two different randomised exercise interventions on depression.

We used the PEDRO scale to evaluate quality of the design of exercise therapy studies, using the The 11 items listed above and stated in Table 1. A PEDRO score from 0 to 3 is considered poor, 4 - 5 average, 6 - 8 good, and 9- 10 excellent (186). Of the 25 articles, 3 obtained a low score, 15 an average score, and 7 a good score. No studies achieved the criterion 6 of blinded therapists, only one met criteron 5 of blinded participants (187), and only three satisfied the criterion 7 of blinded assessors (188-190). Finally, only a maximum of eight studies met the criterion 3, concealed allocation, criterion 8, describing that 85% of participants have completed the key outcome and criterion 9, the provision of intention-to-treat.

Figure 1: Prisma Flow-chart

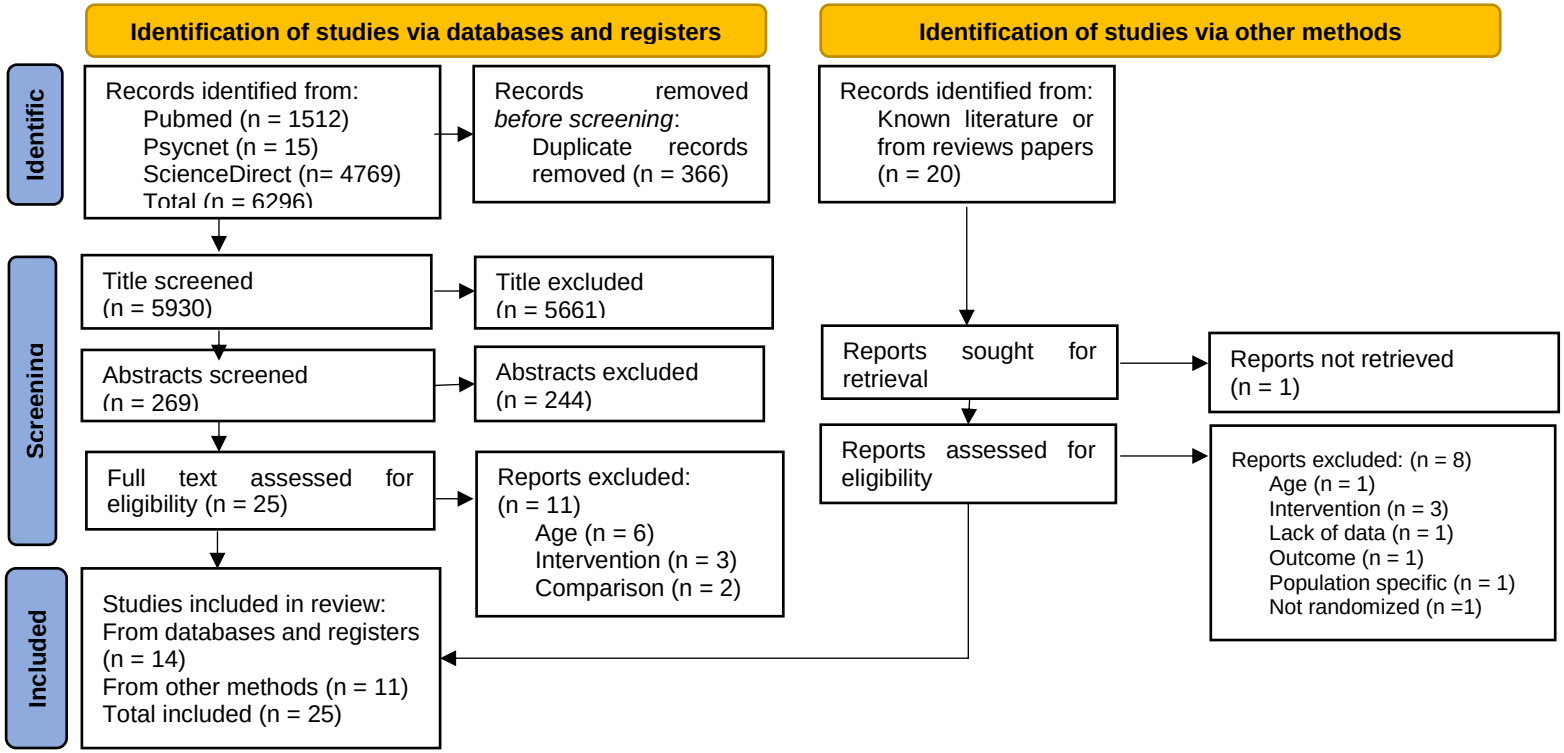

Table 1: Pedro scale evaluation for 25 included studies

Articles	Critères											
	1	2	3	4	5	6	7	8	9	10	11	Total
Alsaraireh 2017	-	+	-	+	-	-	-	+	-	+	+	5
Bonhauser 2005	+	+	-	+	-	-	-	+	+	+	+	6
Carter 2015	+	+	+	+	-	-	-	-	+	+	+	6
Dabidy Roshan 2011	-	+	-	+	-	-	-	-	-	+	+	4
Daley 2006	+	+	+	+	-	-	-	+	+	+	+	7
Fidelix 2019	+	+	-	+	+	-	-	-	+	+	+	6
Gallego 2015	+	+	?	+	-	-	-	-	-	+	+	4
Hemat Far 2010	+	+	-	+	-	-	-	-	-	+	+	4
Herbert 2020	+	+	+	+	-	-	-	-	-	+	+	5
Hugues 2013	+	+	-	+	-	-	+	+	-	+	+	6
Lucibello 2020	+	+	-	+	-	-	-	-	-	+	+	4
Mohammadi 2011	-	+	-	+	-	-	-	-	-	+	+	3
Nabkasorn 2006	+	+	-	-	-	-	-	-	-	+	+	3
Nasstasia 2019	+	+	+	+	-	-	+	-	+	+	+	7
Olson 2017	+	+	-	+	-	-	-	-	-	+	+	4
Paolucci 2017	?	+	?	?	-	-	-	+	+	+	+	5
Philippot 2019	+	+	-	+	-	-	-	+	-	+	+	5
Rethorst 2010	+	+	+	+	-	-	-	-	-	+	+	4
Sadeghi 2016	+	+	-	+	-	-	-	-	-	+	+	4
Sadeghi 2017	+	+	-	+	-	-	-	-	-	+	+	4
Saltan 2020	+	+	+	+	-	-	+	+	-	+	+	7
Wipfli 2009	+	+	-	+	-	-	-	+	-	+	+	5
Wunram 2017	+	-	-	+	-	-	-	-	-	+	+	3
Yavari 2008	-	+	-	+	-	-	-	-	-	+	+	4
Yu 2020	-	+	-	+	-	-	-	-	-	+	+	4

Participants

Descriptive data concerning demographic characteristics of the study participants are reported in Table 2. The total sample included in this systematic review represented 2180 individuals, of whom 1324 took part in an experimental intervention, while the remaining 856 were in a control group. 15 studies were conducted in a university student population, three in a high school student population, two in primary school students, four among outpatients and one in inpatients at a psychiatric clinic. The studies could also be grouped by age: two studies focused on pre-teens (10-12 years), eight on teenagers (13-17 years) and fifteen on young adults (18-25 years). Three studies did not specify the average age of participants, but did report their current education level. Girls represented 61.7% of the total sample, neglecting the two studies that did not specify the gender (191, 192). The instruments used to assess severity of depression were mainly auto-questionnaires. Only two studies entailed evaluation in the form of an interview: HAM-D (193) and SKID-1 (170). The majority of studies (n=18) used a population with clinical symptoms, in which the depressive symptoms were rated as severe in six studies, moderate in six studies, mild in five, and clinically at risk in one study. Seven studies included participants with no clinical symptoms of depression. The main part of studies included populations not under treatment for depression at baseline (n= 20). However, in five of the included studies, participants were undergoing treatments, which included psychotherapy, antidepressant medications, and (in one trial) a multidisciplinary inpatient treatment. One study did not provide any

indication of medical treatment or psychotherapy, although their sample included individuals rated as having severe depression (194).

Table 2- Characteristics of the studies

Author	**Design**	**Country**	**Sample :** Origin; n total participants; Mean age (±standard deviation); Range (in years); Proportion of girls	**Severity of depression**	**Under treatment? If so, which one?**	**Depression measurement**	**Comorbidity? If so, which one?**
Alsaraireh et al. 2017 (195)	RT	Jordan	University; 200; 22 (± 2.1);18 to 31; 62%	Clinical	No	CESD-R	No
Bonhauser et al. 2005 (196)	RCT	Chile	Secondary; 198; 15.54 (±0.89) ; 7 to 18; 51.5%	Non-clinical	No	HADS	No
Carter et al. 2015 (169)	RCT	England	Outpatient care; 87; 15.4 (±1);14 to 17 ; 78.16%	Severe	Mental health service (90% psychotherapy; 8% under medication).	CDI-2	Minor musculoskeletal disorders
Dabidy Roshan et al. 2011 (193)	RCT	Iran	Secondary; 24; 16.83 (±0.82); 15 to 18 ; 100%	Severe (diagnostic)	No	HAM-D	No
Daley et al. 2006 (197)	RCT	England	Outpatient care; 81; 13.1 (± NR); 11 to 16; 55.6%	Non-clinical	No	CDI	77.7% obese
Fidelix et al. 2019 (187)	RT	Brazil	Obese adolescents; 62; 14.64 (±1.18) ; 13 to 18; 54.84%	Moderate	No	BDI	Obese
Gallego et al. 2015 (198)	RCT	Spain	University; 125; 20.07 (±3.68); 18 to 43; 57.6%	Non-clinical	No	DASS-21	No

Hemat Far et al. 2010 (199)	RCT	Iran	University; 20; ? (±NR); 18 to 25; 100%	Moderate (diagnostic)	No	BDI	No
Herbert et al. 2020 (200)	Double RCT	Germany	University; 123; 22.54 (±2.93); 24 to 33; 84.86%	Non-clinical	No	BDI-II	70% anxiety
Hughes et al. 2013 (188)	RCT	United States	Outpatient care; 30; 17 (±0.9); 12 to 18; 33%	Severe (diagnostic)	31% under medication for related disorders.	CDRS-R	-33% Attention deficit disorder -Anxiety
Lucibello et al. 2020 (201)	RCT	Canada	University; 60; 19.8 (±2.2); 18 to 30; 63%	Light	No	BDI-II	Anxiety
Mohammadi et al. 2011 (192)	RCT	Iran	Secondary education; 100; NR; NR	Moderate	No	BDI	?
Nabkasorn et al. 2006 (183)	RCT (cross over)	Thailand	University; 59; 18.8 (±0.7); 18 to 20; 100%	Light	No	CES-D	No
Nasstasia et al. 2019 (189)	RCT (cross over)	Australia	Universities and youth welfare services; 68; 20.75 (±2.56); 15 to 25; 77.9%	Severe (diagnostic)	67% under medication (for at least 15 months)	BDI	Overweight and tobacco
Olson et al. 2017 (202)	RCT	United States	Universities and surrounding care communities; 50; 21.1 (±2); 18 to 30 ; 80%	Severe (diagnostic)	Only stable treatments for at least 6 weeks (medicinal and psychological)	BDI-II	18% anxiety
Paolucci et al. 2018 (194)	RCT	Canada	Academics; 61; 21 (±2); 18 to 30; 72%	Light	NR	BDI-II	No
Philippot et al. 2019 (203)	RT	Belgium	Primary education; 27; 10.6 (±0.7); 9 to 12 ; 47.8%	Non-clinical	No	CDI.BDI.HADS.SDS	No

Rethorst et al. 2010 (191)	RCT	United States	University; 171; NR; 18 to 23; NR	Non-clinical	No	BDI	No
Sadeghi et al. 2016 (204)	RCT	Iran	University; 46; 20.93 (± 1.06); NR; 21.27%	Moderate	No	BDI-II	No
Sadeghi et al. 2017 (205)	RCT	Iran	University; 85; 21.81 (± 3.25); NR; 43.52%	Moderate	No	BDI-II	No
Saltan et al. 2020 (190)	RCT	Turkey	University; 105; 18.82 (±1.07); NR; 81.52%	Light	No	BDI-II	No
Wipfli et al. 2009 (206)	RCT	United States	University; 72; 20.66 (±2.1); NR; 76.9%	Non-clinical	No	BDI	25% overweight
Wunram et al. 2017 (170)	Partial TCR	Germany	Inpatient care; 64 (of which 41 randomized); 15.9 (±1.15); 12 to 18; 71.9%	Severe (diagnostic)	Psychiatric hospital	DIKJ	-21.9% anxiety -12.5% Somatic disorders -Overweight
Yavari et al. 2008 (207)	RCT	Iran	University; 74; NR ; 19 to 22; 0%	Moderate	No	BDI	No
Yu et al. 2020 (208)	RCT	China	Primary education; 188; 9.8 (±0.7); NR; 20.5%	Clinical	No	SASC	Obese

Legend, RT= randomized trial; RCT= randomized controlled trial; clinical= above the pathological threshold following the depression used test; non-clinical= below the pathological threshold following the depression used test; CESD-R= The Center for Epidemiologic Studies Depression Scale; HADS= Hospital Anxiety and Depression Scale; CDI-2= Children's Depression Inventory; BDI= Beck Depression Inderx; DASS-21= The Depression, Anxiety and Stress Scale - 21 Items; CDRS-R= Children's Depression Rating Scale; CES-D= Center for Epidemiologic Studies- Depression: SDS= Zung Self-Rating Depression Scale; DIKJ= Depressionsinventar für Kinder und Jugendliche

Exercise interventions characteristics

Table 3 depicts the characteristics of the interventions. Among all the studies (n=25), 35 exercise interventions were reported. The different interventions could be categorized into: aerobic standard fitness interventions (n=22), aerobic interventions involving games or sports (n=7), four of which were included in one study (192) and two in another (185) sessions with coordination exercises (181), and anaerobic training, in the form of Pilates and "whole-body vibration training" (n=2). Seven interventions were mixed, including anaerobic and aerobic parts. There were 15 passive and five active control groups. Two interventions implemented a non-strenuous placebo exercise as control (197, 201) and three others included stretching (188, 202, 206). Other designs compared exsercise interventions with cognitive behavioural therapy (204), meditation programmes (195), meditation and mindfulness (198), and emotive writing programmes (200).

Only 19 physical exercise among 14 studies reported effort in terms of heart frequency, energy expendure, and psychosocial scale analysis. 15 other exercise programs did not include analysis of their intensity, including five programs in which intensity was reported by the authors without reference to a scale, and ten programs for which we we assessed intensity according to the compendium of physical activities (179). Of the 35 exercise programs, we assigned intensity levels as low (n=2); low-to-moderate (n=2); moderate (n=16); moderate-to-vigorous (n=5); vigorous (n=9); and preferred intensity (n=1).

In terms of programme duration, three studies, which included three interventions, lasted less than six weeks (181, 191, 203). 19 studies, including 29 programs, lasted between six and twelve weeks, and only three programs were longer than twelve weeks (187, 196, 208). Regarding the frequency of interventions per week, 20 studies proposed an intervention three or more times per week. Four studies, had an intervention offered less than three times a week, and one did not report the frequency (204).

Supervision, group-based, attendance and drop out rate

Few studies specified properly if the interventions were carried out individually, or involved group activities . 15 of the 25 studies described 20 physical exercise interventions that were group-based and five reported on individual face-to-face sessions. There were ten studies not reporting clearly if the interventions were individual or group-based. In general, the interventions delivered in group or face-to-face settings lacked information on the quality of interactions between subjects, peers, and supervisors (see Table 3).

Nine trials did not offer a fully elaborated description on the programs' supervision, and five did not present any information in this regard. Amonf the furnished description, the sessions were managed by fitness experts, researchers, physiotherapists, and physical education teachers.

The participation rates were not provided in many studies. Thirteen studies reported a participation rate for at least one of the groups, which represented a total of 24 interventions in which participation rate was indicated. Two interventions had a 100% participation rate, five had a rate between 90 and

100%, eight had a rate between 80 and 90%, six had a rate between 70 and 80%, and one study (182) had only 50% participation for its intervention group.

Among 35 interventions involving exercise, the drop-out rate of participants was furnished for 22 cases included in 15 studies. Here, 15 interventions had drop-out rates between 0-15%, four between 15-30%, one between 30-45% and only two more than 45% (187). Among 25 control groups, the drop-out rate was reported for 14 cases. Here, eight groups had drop-out between 0-15%, two between 15-30%, two between 30-45%, and none less than 45%.

Antidepressant effect of exercise

In order to analyse whether the effects of an intervention, we considered cases involving analysis of the interaction by independent statistical tests (see table 3). Of the twenty-five studies analysed, two did not calculate the interaction (195, 199). As Herbert et al. (200) included a double RCT, this added an additional analysis. Thus, a total of 24 designs were included in the analysis of the effects of interventions on depression. Of these 24designs, three were RTs comparing different exercise intensities, and will thus be included only in the intensity analysis. The vast majority of studies were limited to assessing depression scores at baseline (before the intervention) and time 1 (after the intervention). However, ten studies assessed the evolution of symptoms over a follow-up period as long as 52 weeks. However, only three studies reported a statistical analysis of interactions at their follow-up.

Of the RCTs including clinical samples, 11 out of 14 showed a significant improvement in depression scores in the exercise group compared to the

control group after intervention. One of the three studies with initially negative results demonstrated a positive finding at six months of follow-up (169). The two others studies revealing no significant effects of the intervention included samples pre-adolescents (10) and university students (201) with only mild symptoms of depression. In contrast, three studies exhibited significant improvements in young adults with mild symptoms (10, 190, 194). All studies that included samples with initially moderate to severe clinical symptoms indicated significant improvement over time for exercise therapy in adolescents (169, 188, 192, 193) and young adults (189, 202, 204, 205, 207).

Of the RCTs that enrolled non-clinical samples (below the pathological threshold in used depression test), four of seven studies found a significant result in favour of the exercise group compared to the control group after intervention. These four studies only included university students. The non-significant RCTs comprised two samples of adolescents (196, 197) and one university sample (181).

Characteristics of the antidepressant effects of exercise

To analyze the relationship between reduction of depression and intensity or effortfulness of the intervention, we were obliged to compile studies with moderate and vigorous intensities. Several interventions contained moderate and high intensity parts in their programs, making it impossible to distinguish their intensity. Only five of the twenty-five interventions failed to show significant improvements in depression scores for moderate to vigorous intensity (10, 196, 198, 201, 207). The particular case of High Intensity

Interval Training (HIIT) showed mixed results, with one study showing significant reduction in depression scores after sessions with 80% of maximal heart rate (HR) for 20 minutes in each session (194) and another without significant effects despite sessions with 90-95% of maximal HR lasting 25-30 minutes (201). For low intensity interventions, there were few studies with comparison to a control group, with only three showing mixed results (181, 190, 197). The single intervention that was conducted with preferred intensity revealed positive results only after the follow-up of six months (209). The three RTs did not demonstrate significant differences in the effects of interventions of different intensities. Two of the RTs studies compared high versus low intensity and one compared two vigorous interventions, i.e. aerobic versus an anaerobic "whole body vibration training" program.

Among the 22 RCTs, with interventions lasting less than six weeks, only one study showed a significant result (191), while the another was without significant result (181). For the 17 studies with interventions lasting between six and twelve weeks, fourteen yielded a significant result, and three were non-significant (197, 201, 209), including studies with a non-clinical sample (49), mild depressive symptoms (48), and significant reduction only after six months of follow-up (59). Finally, none of the three studies (187, 196, 208) lasting more than twelve weeks showed a significant result.

We were unable to compare the efficacies of individual versus group-based exercise due to the lack of information in the exercise protocols. There was scant documentation of the quality of interactions between subjects, peers, and supervisors.

Amongs 22 RCTs, fourteen of the twenty aerobic fitness programs gave significantly better improvement in depression scores compared to their control group, with one showing improvement only after six months. Among the five aerobic game/sport interventions, all indicated a better improvement than in the control group. On the four programs combining games and aerobic fitness, only one indicated an improvement in depression symptoms compared to the control group (188).

Table 3 - Characteristics of interventions

Author	Interventions content (n per group)	Intensity	Duration (weeks); n Sessions/week; Session duration (minutes)	Group; Supervised; Provider; Attendance; Drop-out	Main results on depressive symptoms (p-value interaction)
Alsaraireh 2017	Physical exercise lesson (n=100) : 20' stretching, 20' aerobics training, 20' muscular strengthening	Moderate to vigorous [a]	10 ; 3 ; 60	Group ; NR ; NR ; NR ; 10% ; NR	NR
	Mindfulness meditation lesson (n=100) : 20' breathing, 20' body scanning, 20' walking	Nul		Group; Yes; Mindfulness Meditation Expert; NR	
Bonhauser 2005	Physical exercise (n=98) : -Activity without weight transfer (stretching and light body movements) -Weight transfer activities (fast walking, running, jumping) -Sports (girls: dance, aerobics exercise and volleyball; boys: football, basketball, volleyball and aerobic exercise)	Moderate to vigorous [a]	40 ; 3 ; 90	Group; Yes; School teachers; 87%; 8.16	Exercise = control (p=0.44)
	Control (n=100) : regular school exercises (running, jumping, games and sports)	Nul	40 ; 1 ; 90	Group; Yes; School teachers; NR	
Carter 2015	Circuit training (n=44) : Eight aerobic and anaerobic (strengthening) exercises; stretching	Preferred intensity	6 ; 2 ; 60	Group; Yes; Qualified therapist and staff member; 70%; 25%.	Exercise = Control (p-v=0.23) AI; Exercise > TH at 24 weeks
	Control (n=43): TH: Psychological / pharmacological therapy, no exercise	Nul	6 ; / ; /	/ ; / ; / ; / ; 32,56%	
Dabidy Roshan 2011	Water walking (n=12) : Walking in water, of increasing distance, according to sub-groups defined by the level of VO2 max	Moderate [b]	2 ; 2 ; NR 4 ; 3 ; NR	Group ; yes ; NR ; NR ; NR	Water walking > Control (p≤0.001)
	Control (n=12) : /	Nul	6 ; / ; /	/ ; / ; / ; / ; NR	

Daley 2006	Exercise therapy (n=28) : Aerobic exercise (walking, cycling, dancing, etc); mini-games; cognitive behavioural intervention; home exercise programme for 6 weeks after the intervention		Moderate [b]	8 ; 3 ; 30	Individual; Yes; Physical therapist; 89%; 14.28%	Exercise = Placebo Exercise = Control (p=0.28)
	Control (n=30) : Placebo exercises: gentle body movements, stretching, conditioning and advice		Low [b]		Individual; Yes ; Physical therapist; 83%; 4.34%.	
	Control (n=23) : /		Nul	8 ; / ; /	/ ; / ; / ; / : 16,6%	
Fidelix 2019	High intensity (n=31) : Aerobic programme on treadmill with medical, nutritional and psychological follow-up		Vigorous [b]	24 ; 3 ; Time required to expend 350Kcal	NR ; NR ; NR ; NR ; 54,8%	High intensity = Low intensity (p-v=0.4)
	Low intensity (n=31) : Aerobic programme on treadmill with medical, nutritional and psychological follow-up		Low [b]			
Gallego 2015	Cognitive therapy (n=41) : Mindfulness: yoga, breathing, meditation, body exploration, etc. (Possibility to continue at home via MP3)		Nul [a]	8 ; 1 ; 60	Group; Yes; Mindfulness therapist; >80%; NR	Cognitive therapy > Control (p<0.05) Physical exercise = control Physical exercise = cognitive therapy
	Physical exercise (n=42) : 15' stretching and breathing exercises, 30' adapted sports games with emphasis on breathing and posture, 15' stretching in pairs		Moderate [a]		Group; Yes; Experienced exercise specialist; >80%; NR	
	Control (n=42) : /		Nul	8 ; / ; /	/ ; / ; / ; / ; NR	
Hemat Far 2010	Exercises (n=10) : Aerobic exercises: 10' warm-up (jogging, stretching and mobility), running 3 x 6' (1' more per session)		Moderate [b]	8 ; 3 ; 40 à 60	NR; Yes, Researcher ; NR; NR	NR
	Control (n=10) : No physical exercise during the procedure		Nul	8 ; / ; /	/ ; / ; / ; NR ; NR	
Herbert 2020	Online study	Exercise (n=30) : Warm-ups; aerobics (cardiovascular and muscular endurance, including legs and arms, related to physical health); stretching	Moderate [c] , *increasing every 2 weeks*	2 ; 2 ; 8 Then 2 ; 2 ; 12 Then 2 ; 2 ; 16	Individual, Yes; University students, via a video to be sent online; 92.08%; 3.33%.	Exercise > Writing and waiting list? (p<0,005)
		Cognitive/control (n=30) : Writing exercise on the most stressful part of their week	Nul	6 ; 2 ; 15	Individual ; NR ; NR ; 94.08% ; 20% ; NR	
		Control: Waiting list (n=31): /	Nul	6 ; / ; /	/ ; / ; / ; / ; 0%	

	Laboratory study	Exercise (n=11) : Warm-ups; aerobics (cardiovascular and muscular endurance, including legs and arms, related to physical health); stretching	Moderate[c] , *increasing every 2 weeks*	1; 3; (1x8) and (2x12) Then 1 ; 2 ; 16	Individual; Partly; Trainer; NR	Not significant
		Motor coordination (n=11) : Warm up; balance and motor coordination exercises; cool down	Low [a]		Individual ; Yes ; In the laboratory ; ?	
		Control: Waiting list (n=10): /	Nul	2 ; / ; /	/ ; / ; / ; / ; 10%	
Hughes 2013	Exercise (n=16) : At the institute, treadmill or bicycle; at home, Wii Sport, jazzercise, jogging, strength training, at the participant's preference		Vigorous [b]	12; 3; 30 to 40' (depending on energy expenditure)	NR; Yes; Trainer; 77%; 12.5%.	Exercise > Control in S6 (p-v<0.016) and S9 (p-v<0.001). S12 (p=0.07), and no statistics for S26 and S52)
	Control (n=14) : 5' to 10' Stretching of the main muscles as a warm-up and 10' to 15' short stretching exercises		Low [a]	12 ; 3 ; 30	NR; Yes; Trainer; 81%; 14,28%.	
Lucibello 2020	HIIT (n=28) : 20' Interval training on cycloergometer; alternated with 1' sprint at 90%-95% HR max and 1' active rest (cycloergometer 30% of maximum power)		Vigorous [b]	9 ; 3 ; 25 à 30	Group; NR ; NR ; 99.7% ; 10.71%.	HIIT = Placebo exercise (p=0.3)
	Placebo control exercise (n=32) : Completely inactive, but they are told that they are in an intensive exercise group because they have participated in the 2 VO2max tests		Nul	9 ; / ; /	/ ; / ; / ; / ; 34,37%	
Mohammadi 2011	Football (n=20) : Team sport		Moderate or Vigorous [a]	8 ; 3 ; 75	Group ; NR ; NR ; NR ; NR	All sports (IE) > Control (p-v≤0.00) And Collective > Individual (p-v≤0.00)
	Volleyball (n=20) : Team sport		Moderate to vigorous [a]			
	Table tennis (n=20) : Individual" sport		Moderate [a]			
	Badminton (n=20) : Individual" sport		Moderate [a]			
	Control (n=20) : /		Nul	8 ; / ; /	/ ; / ; / ; NR ; NR	

Nabkasorn 2006	Exercises (n=28) : 5' Warm up, 30' group jog, 5-10' cool down	Intervention and crossover controls at mid-study (after 8 weeks)	Moderate [c]	8 ; 5 ; 50	Group; Yes; Fitness instructor ; Group 1: 78.25%; 25%. Group2: 73.75%; 9%. (Cross-over)	Phase 1: Exercises > Control (P=0.003) Phase 2: Exercises > Control (P=0,008)
	Control (n=31) : Maintain your usual daily activity level		Nul	8 ; / ; /		
Nasstasia 2019	Exercises (n=34) : Motivational interviewing (1 session); Progressive intensity strength training (50% 1RM to 70% 1RM, 12-15 reps, 2-3 sets) and encouragement to do 30min of physical activity between sessions	Intervention and cross-over controls at mid-study (after 12 weeks)	Vigorous [b]	12 ; 3 ; 60	Group; Yes; Personal trainer ; Group 1: 49.7%; 20.1 Group 2: 50.5%; 20.1 (Cross-over)	Exercise > Control (p<0.001)
	Control (n=34) : No change of activities while waiting for the intervention		Nul			
Olson 2017	Aerobic exercises (n=25) : Cycloergometer; Treadmill		Moderate [b]	8 ; 3 ; 45	NR; Yes; Researchers; 75%; 40%.	Aerobic Exercise > Control F(1,28)=4.54, p=0.04, n2p = 0.14
	Control (n=25) : Placebo stretchings		Low [a]			
Paolucci 2017	HIIT (n=20) : High-intensity split training on a cycloergometer: 10 sets of 1' at 80% of maximum power, alternated with 1' of active rest at 30% of maximum power		Vigorous [b]	6 ; 3 ; 20	NR; Yes; Researchers; 100%; 10%.	Continuous > Control (p=0.005) HIIT > Control (p=0.012) Continuous = HIIT (p=0.77)
	Continuous training (n=19) : Cycloergometer at 40% of maximum power for 27.5', with warm-up and cool-down		Moderate [b]	6 ; 3 ; 27,5	NR; Yes; Researchers; 100%; 0%.	
	Control (n=22) : Remain sedentary for the duration of the study		None	6 ; / ; /	/ ; / ; / ; / ; 18,18%	
Philippot 2019	High intensity programme (n=14) : Jogging, interactive games, strengthening, warming up and stretching		Vigorous [b]	5 ; 4 ; 50	Group; Yes; Physiotherapist and physical educator; 93,11%; 14,28%.	High Intensity = Low to moderate intensity (p=0.25)
	Low to moderate intensity programme (n=13) : Sitting games, postural control, gentle movements, proprioception, warm-up		Low to moderate [b]		Group; Yes; Physiotherapist and	

				physical educator; 96.65%; 15.38%.	
Rethorst 2010	Exercises (n=70) : Cycloergometer	Moderate [b]	5 ; 3 ; 30	NR ; NR ; NR ; 79% ; 7,2%	Exercise > Control (p<0.01)
	Control (n=101) : /	None	5 ; / ; /	/ ; / ; / ; / ; 36,7%	
Sadeghi 2016	Cognitive therapy (n=16): Cognitive-behavioural therapy according to the Michel Frey model	None	8; 1 to 2; 45 to 60	NR ; Yes ; NR ; NR ; NR	Cognitive therapy = Aerobic exercise (p=0.75) Cognitive therapy > Control (p=0.008) Exercises > Control (p=0.049)
	Exercises (n=16) : 10' Warm-up; 30-35' full-body aerobic exercise and stationary run; 10'-15' cool-down	Moderate [b]	8 ; NR ; 45 à 60	NR ; Yes ; Sports expert ; NR ; NR	
	Control (n=14) : Meeting in class or in the lecture theatre to discuss their problems and try to find solutions on their own.	Nul	8 ; ? ; 45 à 60	Group ; NR ; NR ; NR ; NR	
Sadeghi 2017	Exercise (n=37) : 10' Warm-up; 30'-35' body aerobics without materials and full body; 10' cool-down	Moderate [b]	8 ; 3 ; 45 à 60	NR ; yes ; Physical education teacher ; NR ; NR	Exercise > Control (p=0,001)
	Control (n=48) : /	Nul			
Saltan 2020	Pilates (n=35) : Breathing, cognitive focus, relaxation, spinal lengthening and posture, abdominal muscle control and spinal mobility, and full body mat strength.	Moderate [a]	12 ; 3 ; 40 à 60	NR; Yes; Researcher; NR; 17.14	Pilates and Therapeutic Exercise > Control (p<0.00)
	Therapeutic exercises (n=35) : 10' warm-up, 3x 6' to 14' running (gradually increasing from week to week), 3' cool-down	Low to moderate [c]		NR; Yes; Researcher; NR; 20%.	
	Control (35) : /	Nul	12 ; / ; /	/ ; / ; / ; / ; 0%	
Wipfli 2009	Exercises (n=35) : Cycloergometer	Moderate [b]	7 ; 3 ; 30	Group; Yes; Researcher; NR	Exercise > Control (p<0.05)
	Control (n=37) : Stretching	Light [a]		Group; Yes; Researcher; NR	
Wunram 2017	Vibration (n=21) : six strengthening exercises and vibrating plate and whole body	Vigorous [b]	6 ; ≈3 ; 12 à 18	Group; Yes; Researchers; 81%; 14.25%.	Vibration = Exercise (p>0.05)

	Exercises (n=20) : 30' Cycloergometer in interval	Vigorous [b]	6 ; ≈3 ; 30	Group; Yes; Researchers; 84%; 15%.	
	Control (n=23) : Not analysed due to absence of randomisation	Nul	6 ; / ; /	/	
Yavari 2008	Swimming (n=37)	Vigorous [a]	10 to 12; 1 to 2; ?	NR ; NR ; NR ; NR ; NR	Swimming > Control (p<0.001)
	Control (n=37) : Usual activities	Nul	10 à 12 ; / ; /		
Yu 2020	Exercises (n=106) : 20' Jogging, 40' badminton, relay race (200m), rope jumping; lifestyle modification (advice to children and parents, setting nutritional and physical activity targets)	Moderate to vigorous [a]	34; 2 x 5; 20' then 40'.	Group; Yes; Sports teacher; NR; 6.6%.	Exercises = Control (p=0.452)
	Control (n=82) : Regular school activities	Nul	34 ; / ; /	/ ; / ; / ; NR; 12,2%	

Legend: NR= no reported; [a] Intensity based on METs, according to the updated version of the compendium (179) ; [b] Intensity calculated by objective measures such as heart rate, energy expenditure, or others; [c] Intensity described by the author, without objective measurement

Discussion

In this systematic review, we sought to identify the efficacy of exercise programs compared to randomized active or passive interventions as a control or experimental arm as interventions against clinical and non-clinical depression in youth. We also attempted to determine the optimal physical exercise characteristics and the antidepressant effects as a function of intensity-dosage. Our systematic review and qualitative synthesis assembled 25 randomised studies (22 RCTs and the RTs) in individuals aged 10-24 years. In accord with our hypothesis, physical exercise appeared to reduce symptoms in young people with moderate to severe depression as compared to active or passive control treatments. In the few studies in groups with non-clinical symptoms, i.e., below the pathological threshold, the beneficial effects were less pronounced. Moderate to vigorous intensity exercise with three sessions per week and lasting 6 to 12 weeks, seemed effective in relieving depression scores in young people.

The RCTs collected revealed clearly decreasing clinical symptoms of depression in youth, as also reported in previous meta-analyses (87, 89, 126, 130, 167). The present systematic review indicates a robust effect of exercise programs in alleviating moderate to severe depression in a young population. These results are very encouraging in light of the demand for effective complementary (non-medical) treatments for young people, who are experiencing a high incidence of depression (77, 85). Indeed, in the clinical management of youth with MDD, clinical guidelines only recommend psychotherapy (especially cognitive-behavioural therapy or interpersonal

therapy) as the main intervention (37, 85, 86). Pharmacotherapy has provided limited impact in this population (80, 84), unlike the general consensus in adults (76). For the present, exercise is not specified in clinical guidelines for depression care for youth, even though its use is recommended in adults with depression (77). Our youth results are consistent with adult findings (115), and support the proposition that exercise might serve as an complementary anti-depressant therapy for moderate to severe depression in young people. In addition, we collected four reports with exercise as add-on interventions to usual care, of which four were conducted with outpatients (169, 188, 189, 202) and one in inpatients (170). All these complementary exercise therapies impart additional benefits to patients already receiving antidepressant treatment and/or psychotherapy. However, we were obliged to omit the study of Wunram et al. (170) in our analysis of antidepressant effect of exercise due to the lack of a randomized control group. Nonetheless, we note that, compared to control treatment, complementary physical exercise program offered an improved reduction in depression scores in a psychiatric setting offering multi-disciplinary care (170). Our own recent trial was also conducted in a psychiatric hospital for adolescent inpatients who were receiving antidepressant, psychological and supportive therapies (210). This RCT demonstrated that an add-on exercise therapy involving games/sports more effectively reduced depressive symptoms compared to control treatment with an active and social program (210). Recent efforts aim to integrate exercise into care guidelines for youth with depressive disorders, also with application in psychiatric mental health services, which calls for investigation of the combined effect or interaction of exercise with usual care. However, further RCTs should be conducted to consolidate these findings in outpatients and inpatients. In addition, the psychosocial, neurobiological and behavioral

effects of exercise should be studied in youth with depression. The antidepressant mechanisms is not completely understood, especially in young people (112, 133-135). Recent research in depressed hospitalized adolescents suggests that aerobic exercise promotes the sustained formation of neutrophic factors, which may promote synaptic plasticity (211). That finding may lead to a more physiological understanding of the maxim *mens sana in corpore sano*.

In our systematic review, exercise demonstrated a limited effect in reducing depression in non-clinical samples, i.e., participants who obtained a score below the pathological threshold defining clinical depression. Among the seven RCTs emerging from our review, five were performed in young adults. Four RCTs indicated a positive impact of exercise on depressive symptoms, whereas one did not yield a significant effect. However, the two included trials in adolescents did not exhibit a comparable reduction in depression. We do not have sufficient data to account for the differing results in young adults and adolescents. The resolution of these mixed results calls for further studies across different age groups. We note that the potential of exercise for reducing depression in nonclinical individuals may be masked by the inherently lower changes in depression scores, which is a matter of inadequate statistical power. In addition, a decrease in depression score may not be a valued factor in considering the impact of exercise on prevention of more serious depression, which may often be preceded by mild, subclinical symptoms or others mental troubles as stress and anxiety. Indeed, this interpretation resonates with a meta-analytic finding that school-based exercise interventions did not reduce depressive symptoms in non-clinical children and adolescents, but nonetheless did have beneficial effects on resilience,

positive mental health, well-being, and anxiety (212). Exercise may protect the brain from stress-induced changes, conducting depression (142). In addition, lower social acceptance, body satisfaction, and self-perception may each predict the emergence of depressive symptoms (157), and these factors may be improved by physical activities (158).

Thus, while exercise appears to have a lesser effect on non-clinical symptoms than on clinical symptoms, physical activity may nevertheless have a protective effect against increased symptoms of depression, as it has demonstrated in adults (213). Through the effects of physical activity, it may be possible to mitigate risk factors for the incidence of depression, such as stress (214), poor executive function (150), low social support, poor body image and poor self-perception (158). For instance, a longitudinal study spanning several years showed that participation in physical activity impeded the development of depressive symptoms (165) and MDD in youth (21, 121). Hence, future studies of RCT design could investigate exercise interventions as a prophylaxis against the onset of depressive symptoms. But, such studies must be conducted over a long term and in consideration of other psychosocial aspects that could be risk factors of depression.

Moderate to vigorous intensity appeared to be effective in reducing depressive symptoms, primarily in the depressed youth samples that matches with other systematic review (127). This intensity may be effective, but we cannot state that it may be more efficient than others. In addition, a systematic review collecting four meta-analyses for a total of 23 studies in the age range 5-20 years also yielded no consensus among the authors on the best dose-response relationship in terms of intensity, duration, and frequency (168). Finally, in depressed adolescents, a meta-analysis depicted a lesser effect of

low intensity exercise, with the caveat that interventions of moderate to vigorous intensity greatly outnumbered the few interventions of low intensity (127). In our study, we only reported two RTs comparing the efficacy of high versus low intensity and they did not indicate a clear difference in response. Low intensity exercise has not been frequently used, thus precluding a contrast of dose-response with more intense regimens. Altogether, on the basis of this SR results, we cannot demonstrate the superiority of an intensity over others.

We emphasize that the measurement of effort expended during physical exercise lacks sufficient precision. Some studies have reported their protocol of exercise without providing any specific measures of intensities such as a psychosocial scale, heart rate or caloric consumption. We were obliged to interpolate or estimate intensity from the physical activity compendium with MET measurements. Regarding duration and frequency, the main significant benefits were observed from three to four exercise sessions per week lasting from six to twelve weeks. That result is in agreement with previous systematic reviews reporting the first benefits at from seven (126) or eight weeks (89). The available data do not support drawing strong conclusions about the precise relationship between dose/intensity, type of exercise, and benefits.

Similarly, we were uncertain whether game-based exercise or standard physical exercise would differentially affect depressive symptoms in youth. When including only depressed adolescents, an earlier meta-analysis found statistically similar benefits for both interventions (167). However, there is a greater body of knowledge concerning effects of on aerobic base measured on a treadmill or cycle ergometer. In healthy subjects, team sport-

interventions in young people have proven good efficiency in improving executive functions, in particular working memory working and executive functions (154) and in social components (134). Observed deficits in social support and neuropsychological functions may determine the efficacy of treatments for depression (56, 159, 177). Further research could be undertaken on the anti-depressant effect of physical activity to establish if type of intervention modulates the neurobiological and psycho-social mechanisms underlying treatment response.

Appropriate supervision is essential to ensure safe, attractive, and adapted exercise programs for young people (215) with mental illnesses, including depression (134). However, nine of the 25 included studies did not comprehensively inform about the manner of supervision of the sessions. This deficiency in the literature points to another way to improve the quality of evidence-based research into the antidepressant benefits of exercise. Another issue arising is that some authors neglected to specify whether participants experienced group or individual sessions, and did not describe the nature of interactions between peers and providers. A poor social environment has been frequently observed in youth depression (11) and its continuance may moderate the effectiveness of long-term treatment (159). Hence, future studies should address how the group aspect of physical exercise may contribute to the well-being of participants.

Our systematic review indicates incomplete documentation of program attendance and drop-out rates. However, among the available description, we note furthermore that there was a generally low reported drop-out rate and good attendance to program. This may itself reflect that exercise programs could motivate the young with depression. We note the necessity to identify

intervention designs that promote participation and adherence. Certainly, poor adherence to a program could be a significant barrier to the successful application of exercise therapy (216). Furthermore, the dropout rate indicates the potential for bias, in that those completing the programs may be those most inclined to benefit from the intervention.

Given these issues, we see a need for future systematic research aiming to define better the specific impact of exercise on depressive symptoms in youth, with more rigorous standards regarding the reporting to variables in the intervention protocol such as heart rate/energy expenditure during exercise, management of effort, type of exercise, total session duration, and time allocation for each component of the session, duration of the program, group or individual activities, and type of peer-provider interaction. There should be information on quality of supervision, adherence, and dropout rate, along with documentation of reasons for leaving the study. In addition, studies need further description regarding participants' profiles with respect to general health, habitual physical activity participation, physical activity history, present fitness condition, gender, severity of depression, mental and physical comorbidities, medication history, and family mental health history. This additional information could minimize heterogeneity and disparate outcomes between trials.

Strength and limitations

This systematic review shows compelling evidence that exercise therapy can be an effective antidepressant treatment for youth with moderate to severe depression symptoms. Our sample includes 22 RCTs and 3RT comprising

together a sample of 2180 participants. The seeming add-on effect of exercise with other therapies such as antidepressant medication and psychotherapy indicate a potential for positive interactions between antidepressant treatments. Our study also documents the requirements for improved standards of future research into the efficacy of exercise therapy within an overall strategy for alleviating depressive disorders in youth, and preventing progression to chronic and more severe states. We have emphasized the strengths and weaknesses of the available studies highlighting areas for improvement for future exercise interventions.

Our systematic review is not a meta-analysis, due to the incomplete and heterogeneous reporting of endpoints. Furthermore, we did not investigate the effect size of our collected data, limiting our discussion to a qualitative analysis, with emphasis on the statistically significant findings across studies. The present analysis of exercise characteristics was conducted on mixed groups of clinical and nonclinical youth with depression, with age extending from 10 to 24 years. While this provides an overview of the current state of knowledge in youth, the resultant heterogeneity calls for some caution in generalizing our results. The widespread lack of information on exercise intensity, group versus individual supervision, adherence, and dropout rate necessarily weakened the strength of our findings. A psychiatric diagnosis based on structured interview is the gold standard for measuring the severity of depression, but only two of the 25 trials conducted a semi-interview of depression. Finally, according to the PEDRO scale, the quality of trials were mainly medium, with three trials considered weak, 15 as medium, and only seven as good. However, by including only randomized studies with baseline comparability, we assured a minimal standard for design quality and

comparability between studies. We see a need for better assessment of reporting bias and more quantitative exercise parameters and outcome measures.

CHAPTER II: Exercise at school to prevent depression and anxiety

Study 2 : Impact of physical exercise on symptoms of depression and anxiety in pre-adolescents: a pilot randomized trial

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As this study is already published, responses to the jury members were added to the text as footnotes.

Abstract

Aim: The intensity of the most appropriate exercise to use in depressed youth is unclear due to differences in methodology and the lack of evidence documenting the effect of physical activity in children. Therefore, the authors of this study attempted to document the effectiveness of different training intensities to reduce symptoms of depression and anxiety in pre-teens. **Method:** The study included twenty-seven, randomly selected pre-adolescents (aged between 9-11 years of age) all of whom had Primary education. The participants were enrolled and, over a five-week period, were subject to either intensive or low-to-moderate exercise programmes four times a week. Psychological self-reports, as well as physical examinations, were conducted before and after such programmes in blinded assessments. Psychological effects were considered the primary outcome, whilst physical condition was secondary. **Results:** Four subjects were lost and twenty-three were analyzed. General linear model with 2 criteria revealed significant changes ($p=0.05$) in trait anxiety symptoms over time in the low-to-moderate intensity group (LMIG). Within group changes followed a significant decrease in levels of anxiety (38.82 ± 2.20 to 33.36 ± 2.83 $p=0.004$) and depression (10.36 ± 2.83 to 6.73 ± 1.88 $p=0.006$) related symptoms amongst those in the LMIG. **Interpretation:** This study indicated that depression and anxiety symptoms were reduced amongst a non-clinical sample of Primary educated pre-adolescents when they were subject to a low-to-moderate exercise programme. The programme focused on associating movement with pleasure, encouraged positive and non-competitive interactions between participants.

Introduction

Although often clinically undiagnosed, symptoms of depression and anxiety can be seen in pre-adolescent children aged 9 to 12. These signs often go unrecognized, despite their prevalence: 8-9% of children and adolescents show depressive symptoms (217) and levels of anxiety disorders range from 2.5-30% due to the heterogeneity of diagnostic methods (30). Detecting these symptoms at an early stage is important in the treatment of present and future mental-health issues; children and pre-adolescents with early signs of depression are more likely to have a severe depression later in life (21). Nonetheless, the optimal treatment for those symptoms in this age bracket should focus on non-pharmaceutical options, as anti-depressant medication is shown to increase the risk of suicidal thoughts amongst children (82).

There are many cohort studies or Randomized Controlled Trials (RCT) indicating that physical activity (PA) or adapted physical exercise programs are associated with decreased depressive symptoms in adulthood. There is also evidence that indicates that physical exercise reduces levels of depression in adolescents and pre-adolescents. However, additional studies with higher methodological quality are needed to corroborate these findings (126, 130, 218)

An important question is “what is the most appropriate exercise intensity in children and adolescents?”. The few studies in this issue have yielded contradictory results. The first study showed no therapeutic difference as per the intensity of the exercise for children and young people up to the age of 20 (124). A program of varying intensity, based on individual preferences, reduced symptoms of depression in a sample of 87 adolescents(209).

According to a meta-analysis, a low or moderate intensity exercise program (three times a week for 6 to 12 weeks) is most effective in reducing depression scores in this age group (126). Another systematic review found that more frequent and intense sessions were associated with fewer depressive symptoms (218). The limited amount of meta-analyses available incurs a high level of inter-study heterogeneity, in terms of intervention methods and outcome measures. This is especially apparent in children and adolescents in non-clinical settings (124, 126). To date, there is no evidence that indicates physical activity or adapted exercise programs that have a negative effect on psychological status.

Researchers attempted to evaluate the link between fit physical condition and depression. A meta-analysis clearly indicates that there is a negative correlation between fit behavior in young people and depressive behavior (218). In addition, a RCT with a high methodological quality (confirmed 6/10 score according to the Physiotherapist Evidence Database (PEDro scale)) showed that adolescents meeting the DSM-IV MDD criteria reduced their score of depression from 6 weeks of intervention (3 sessions per week) with a vigorous intensity (>12 Kilocalories/Kilogram/Week (KKW)) compared to the low intensity (<4KKW) exercise (219). Another point of view is that these behaviors seemed to be closely linked with the cognitive functions. At present, they found some evidence that hippocampal volume could be bigger in higher-fit compared to lower-fit pre-adolescents. A bigger hippocampal volume would be related to better memory tasks (220). Then cognitive function scored lower in children and adolescents with depressive disorder (221). The cingulate cortex and prefrontal areas seem to exhibit altered functioning in depressive patients and this appeared to explain the poor performance in cognitive processes (222). Eventually, considering that a

better cardiovasuclar fitness may enable improving the cognitive function and seems to protect from depressive symptoms and we provide a short time period of intervention (5 weeks), we could support the notion that a high-intensity program may be effective in reducing depressive symptoms in children. In matter of fact, the purpose of this intensity would be to improve the participants 'physical condition by giving a protect effect on the mental health compared to a lower intensity that could change the physical condition to a lesser extent in a 5 weeks duration of experiment.

The main objective of this study was to investigate the impact of structured physical activity on the prevention of depressive and anxiety symptoms in a non-clinical sample of schoolchildren. A low-to-moderate intensity physical activity was compared to a high intensity physical activity. We also sought to evaluate whether such physical activities, implemented in the form of games, could affect the above-mentioned symptoms. We hypothesized that high intensity physical activity would lead to greater psychological improvement than low-to-moderate intensity, assuming that physical condition was closely linked to individual psychology.

Anxiety and depressive symptoms have common risk factors, indicating that a similar prevention for both disorders may be useful in many cases. Therefore, we studied the common effect of physical activity on these symptoms (27).

Methods

Participants

Participants were recruited from a primary school on a voluntary basis and the study was presented in classrooms. The inclusion criteria were as follows: 1. Be involved in an official education program; 2. Aged between 9 and 12 years; 3. Acceptance of the randomization principle; 4. Absence of neurological or psychiatric history; 5. Absence of uncorrected sensory disorder preventing the understanding of instructions; 6. Absence of conduct disorders. The exclusion criteria were as follows: 1. Refusal to participate; 2. Body Mass Index above P95; 3. Unstable diabetes; 4. Coagulation disorders (apart from specific exceptions and medical authorization); 5. Severe and unstable asthma; 6. History of heart malformation or cardiovascular disease; 7. Medical conditions prohibiting sport or physical activity. All parents completed a medical questionnaire before starting the research[1] [2] (223). Accordingly, only the children who met the inclusion and exclusion criteria were included. The others (who were treated by medications or therapy) were kindly excluded.

The study was undertaken at the "elementary school Parmentier - Jean XXIII" in Brussels and its facilities (a classroom, gymnasium and park). Participants

[1] The medical questionnaire used is reported in the Appendix 2.

[2] The ACSM created the Physical Activity Readiness Questionnaire (PAR-Q) to assess the potential risk to practice physical activity. This questionnaire has recently been adapted in PAR-Q+. Based on participants responses, the questionnaire informs whether a discussion with the referring physician and/or an expert exercise therapist about physical activity is required before starting an exercise program. For future research, it would be relevant to use this instrument (223).

were informed that they would not be allowed to choose the group to which they would be assigned and could leave the study at any time if they wished. Their parents provided their written informed consent before the start of the experiment. The ethical Committee of the School of Medicine of the Université Catholique de Louvain approved the study.

Design

We conducted a low-to-moderate intensity intervention and a high intensity intervention in parallel, focusing on pleasure, interaction and non-competition. Each intervention took place for 5 weeks at a rate of 4 sessions per week (Monday, Tuesday, Thursday and Friday) during the lunch hour. Thus, the study followed children from two groups for a total of 20 sessions that lasted 50 minutes. There was an assessment period in the week before and the week after the program, where tests of the participants were gathered. Quantifiers for the randomization included individual scores for the CDI, BMI, duration of the Léger shuttle test, age, sex and school year. Thereafter, the principal investigator assorted the participants into two equivalent groups. Randomization at the group level was done by an external blind researcher who provided the intervention allowance by e-mail. Eventually the participants who met the inclusion criteria were assigned randomly to either the HIG (n=14) or the LMIG (n=13) based on the pre-evaluation. During the intervention sessions, therapists and participants were not aware of individual scores used for randomization. The two pairs of therapists (two physical educators and two physiotherapists) managed the same number of sessions in

each group alternately. The principal investigator provided medical security, as well as the components of each program.

The Metabolic Equivalent of Task (MET) was used to define the intensity of interventions (91). World Health Organization (WHO) saw that an activity included between 1.6 and 3 MET was a low intensity, 3 and 6 MET was a moderate intensity and more than 6 MET was a high intensity.

An HIG intervention session combined jogging and interactive games (Children Games (5 MET), teach physical education (6.5 MET), run at 5 to 7 miles per hour (mph) (8 at 11.5 MET)), which included muscle building (6 MET). Each session began with a warm-up and ended with a muscle stretching. This program aimed to improve Leger's VO2max score, muscle building, and overall physical fitness. For instance, sessions included a treasure hunt across a large perimeter jog/walk combination (6 – 6.5 MET), wheelbarrow racing, spider walking and reinforcement exercises through gym weights. For each participant, 75% to 80% of the theoretical maximum heart rate for their age was recommended with verification of their heart rate during the sessions.

Each LMIG intervention combined games that highlighted the sensation of (gentle and slow) movements (proprioception) with seated play (sitting with children plays (2.8 MET)), postural control (stretching, yoga (2.5 MET)) and interactive games (walking children’s games (MET 5), walk/run –playing

with children, with moderate period (MET 4)). Each session started with a warm-up and aimed not to focus on performance and not exertion to the point of breathlessness. The sessions included, for example, a slow relay race with variations of movement, interactive games in teams (walking or running slowly whilst perpetuating equilibration), a treasure hunt in a small area, mime games, riddles and optical illusions.

In both interventions, the experimenters recorded the duration of all exercises and the participants' feelings and heart rates. Positive remarks were regularly written in an individual file to motivate each participant. The exercises were explained, customized and set up by the therapists. Every effort has been made to create a non-competitive atmosphere (mockery was forbidden). At the end of each session, a similar gift was provided to each participant (juice and a pack of candies or gums). At the end of each week, an extra gift was given (a small toy, a game, stickers, etc.) to reward efforts and increase motivation.

Primary outcomes

The Child Depression Inventory (CDI) is a 27-item self-report instrument (224) that provides a score based on the child's statement describing how she or he felt during the two previous weeks. The average score in the general population is 9 points (224), and a score of 19 or more is considered pathological (225). The CDI showed good internal reliability (Cronbach'alpha = 0.86), sensitivity, specificity and a low level of bias (226). The pooled estimate for internal reliability is considered as high. This scale is mainly used in research to assess mood and depression (ICD-10-CM F32.9) in a longitudinal follow-up.

The State-Trait Anxiety inventory (STAI) (227) consists of two subscales with twenty items, the STAI, form Y-A, which assesses the recent state (i.e. what the participants felt during the week of testing), and the STAI, form Y-B, which assesses the long-term anxiety trait (i.e., what the participants felt during the past year). Each part (A or B) of the STAI provides a state score or an anxiety trait score ranging from 20 to 80. The pathological threshold is 39-40 (228). This test has a high degree of reliability (Cronbach'alpha = 0.86) and validity. This is widely used to detect anxiety (ICD-10-CM F41.9).

In this study, the abbreviated BDI-13 (229), The Hospital Anxiety & Depression Scale (HADS) (230), the Zung Self-Rating Depression Scale (SDS) (231), the Self Perception profile for Children (232) were also used to determine their relevance and reliability in testing pre-adolescents.

The Beck Depression Inventory (BDI) (229) consists in 13 questions with multiple-choice answers evaluating depression severity. A Likert scale from 0 to 3 is assigned for each answer and the item scores are summed to give a total score ranging from 0 to 39. The higher is the score, the higher is the severity of depression. The BDI has a high internal consistency (alpha coefficients = 0.86 for non-clinical population).

The Hospital Anxiety & Depression Scale (HADS) is a reliable questionnaire (230) that allows detecting anxiety and depressive disorders. It has 14 items rated from 0 to 3. There are 7 questions related to anxiety (subscale A) and 7 others to the depressive dimension (subscale D) providing 2 scores. Maximal scores for anxiety and for depression range from 0 to 21. A score of 0 to 7 for either subscale indicates an absence of symptoms while a score of 11 or more

is probably pathological. The internal reliability is correct (alpha Cronbach = 0.79 to 0.86).

The Zung Self-Rating Depression Scale questionnaire (231) is used to assess depression severity. There are 20 items in the scale. Each question is scored on a Likert scale ranging from 1 (rarely) to 4 (nearly always). The sum of item scores is multiplied by 1.25 and divided by 100 to provide the depression score in percentage. Most people with depression have a score between 0,50 and 0,69 while a score of 0,70 and above indicates a severe depression. The SDS score may give an indicative range for the severity of depression but is not sufficient to confirm the pathology (WHO, 2017). The internal consistency is correct (Cronbach's alpha = 0.79).

To assess self-esteem, the Self Perception profile for Children (233) has been used in its French version, the "Questionnaire de perception de soi pour jeunes, QPSJ". There are 6 categories including 6 questions, for a total of 36 questions. Each category refers to a competence (social, athletic, scholastic, physical, behavioral and global self-worth). The internal consistency is acceptable to good (Cronbach alpha's of the 6 categories are ranged 0.71 to 0.86).

Secondary outcomes

A body composition mass monitor (OMRON BF 511®), used in humans aged 6 to 80 years, was used to measure body mass, body fat, muscle percentage and skeletal muscle percentage. A medical device was also used to measure height.

The *Leger shuttle test* is a 20-meter multi-steps shuttle run test, providing an extrapolated assessment of maximal oxygen uptake (VO2max) (234). A meta-analysis showed that *"the 20m shuttle test seems to be a useful alternative to estimate cardiorespiratory fitness"* and this test has a high validity in young people (235). We used POLAR FT2® heart-rate monitors with a transmitter belt at the sternum level to record maximum heart rate, average heart rate and session time.

Pre-assessment and post-assessment tests took place respectively the week before and the week after the intervention.

Statistical analysis

A sample size was defined from a previous study, whereby CDI II was used to measure variance in depression among adolescents receiving physical exercise as treatment (10). Accordingly, with a detected change of -9, a detected change in SD of 10.2, a desired power of 0.8 and a $p = 0.05$, 12 children per group were needed to obtain significant results.

Since some measures were based on Likert scores, a graphical tool (quantile-quantile plot) and a Kolmogorov Smirnov test were used to assess the distribution of normality. If the data were not normal, a logarithmic transformation was performed to obtain normal data (if it were possible). General Linear Model (GLM), with two criteria, or the Mann-Whitney test was performed to determine the difference between the two groups and two tests sessions. Due to a prior assumption of greater changes in depression / anxiety scores for HIG, two dependent tests (t-test or Wilcoxon test) were used to determine the change in a variable (STAI, CDI, etc.) over time in each

experimental group (HIG or LMIG). The effect size based on the partial eta squared (η^2) was performed to calculate the number of participants required for future research. A Pearson correlation test was used to evaluate the potential correlation between the variables in the two groups. All statistical procedures were performed using the SPSS software. The data were anonymized for the statistical analysis so that the two groups could not be identified.

Results

Participation analysis

Among the recruited 27 pre-adolescents in pre-test, four participants, two in each group, were lost during the experimentation. The statistical analysis of pre- and post-test measures was restricted to the remaining 23 participants who were involved in the whole study (see Figure 1 for details). The mean age at assessment was 10.7 ± 0.7 with 6 girls and 6 boys in HIG and 10.6 ± 0.7 with 5 girls and 6 boys in LMIG (p=0.690, Student t test).

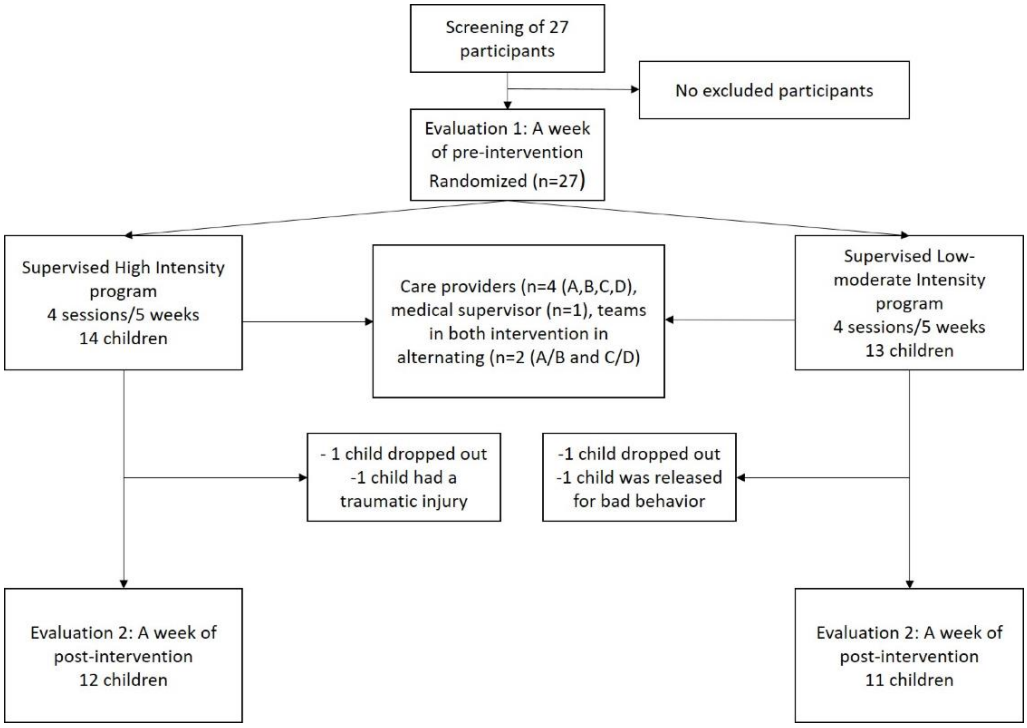

Figure 1 : Flow chart of study design

Among the 27 pre-adolescents who were recruited and randomized (quantifiers: CDI, BMI, Léger shuttle test, age, sex and school year), four participants were lost during the experimentation. The statistical analysis of T1 and T2 measures was restricted to the 23 participants involved in the whole study.

The mean attendance rate was 93.11 % in HIG and 96.65 % in LMIG (p=0.290, Mann-Whitney test). The mean individual "tiredness score" (0-3, 0 = not tired at all; 1 = a little bit tired; 2 = moderately tired; 3 = exhaustively tired), averaged for all sessions, was slightly higher in HIG than LMIG (0.64 versus 0.43) without significant difference between groups (p=0.600, Mann-

Whitney test). The participants enjoyed the interventions, as reported in a mean "fun index" (0-3, 0 = very fun; 1 = quite fun; 2 = moderately boring; 3 = very boring), averaged for all sessions, which revealed no difference between groups (0.45 in HIG and 0.52 in LMIG, p=0.710, Mann-Whitney test).

A HIG intervention session lasted an average of 43 minutes, combining 15 minutes of jogging and interactive games, 15 minutes of muscle building and 8 minutes of warm-up and stretching. Each LMIG intervention lasted also an average of 43 minutes, combining 16 minutes of seated play, postural control and very gentle movements, 23 minutes of games exerting the sensation of movement (proprioception), with gentle and slow movements, and a warm-up (2 minutes).

Primary outcome

Self-reported data from primary questionnaires are summarized in Table 1. The Likert score variables, with a non-normal distribution, were the CDI and the BDI-13. However, a transformation was made on the CDI and BDI scores with this formula "Ln(variable)" to obtain a normal distribution. Only CDI score variables became normal after this procedure.

It should be noted that, although participants were randomly assigned, STAI-B scores at baseline (T1) were slightly higher in LMIG than in HIG. However, the group difference was not significant (p=0.52, unpaired t-test). A GLM performed on the STAI-B scores revealed a significant group x time interaction (p=0.050) and a time effect (p=0.030). With respect to the LMIG, we found that this program induced lower anxiety symptoms over time with

a significant and reproducible effect in small samples (F (1.21) = 4.17, p = 0.050, η^2 =0.17). The eta-squared (η^2) measure from independent t-test ranges between 0 and 1. Following the Cohen guidelines (236) for the eta-squared (small effect =0.01, moderate effect = 0.06, large effect= 0.14), the outcome of η^2 =0.17 showed a large effect size.

It was only in the LMIG that the STAI B scores, on average, decreased from 38.82 (SEM (Standard Error of Mean) 2.20) at T1 to 33.36 (SEM 2.83) at T2 (p=0.004, Student paired t-test, see Table 1 and Figure 2). On average, the scores remained stable in HIG, evolving from 36.58 (SEM 2.75) to 36.33 (SEM 2.30).

Moreover, analysis of data from the children with "pathological" scores (39 and higher), with a GLM performed on their STAI-B scores, revealed no group x time interaction effect (p=0.270). Among children with "pathological" scores, only those who attended LMIG sessions improved their STAI-B scores at post-test (36.17 ± (SEM 1.65) relative to the pretest (44.00 ± (SEM 2.89) (p=0.019, Student paired t-test).

The analysis of STAI-A scores did not reveal any group difference nor time-dependent changes (all p values >0.05, see Table 1).

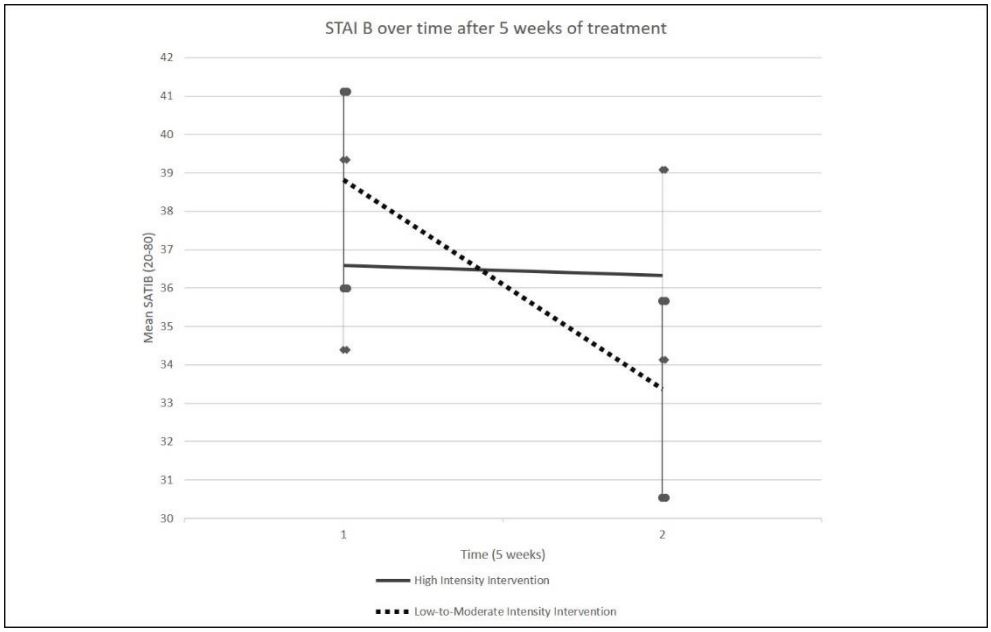

Figure 1 : Evolution of STAI-B score

The STAI-B scores, on average, decreased between T1 and T2 in LMIG (p=0.004) whereas these scores remained on average stable in HIG. The cut-off considered for pathological score was 39-40.

A GLM performed on the CDI scores did not reveal a group x time interaction (p-value=0.25) but a time effect (p-value=0.007). Concerning the LMIG, we observed that this program induced a moderate size effect, resulting from the eta squared, to lower depressive symptoms although the results did not reach the level of significance (F (1.21) = 1.60, p=0.25, η^2=0.071). It was only in the LMIG that a significant improvement in CDI scores was observed; the CDI scores decreased, on average, from 10.36 (SEM 2.83) at T1 to 6.73 (SEM

1.88) at T2 (p=0.006, Student paired t-test, see Table 1 and Figure 3). The average scores remained stable in HIG, evolving from 11.00 (SEM 2.75) to 10.08 (SEM 2.98) (p>0.05, Student test).

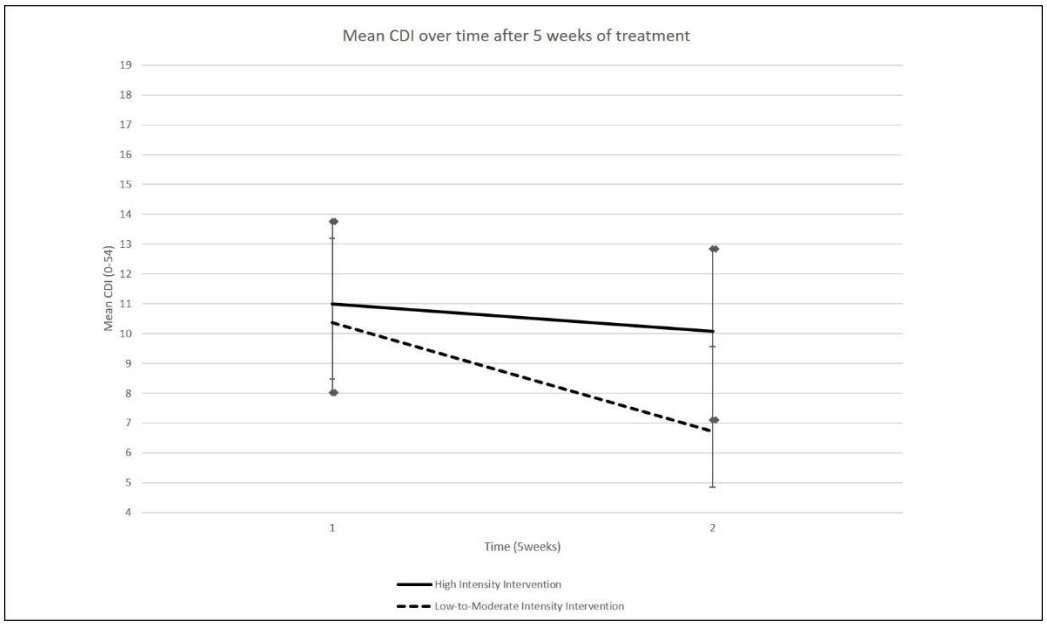

Figure 2 : Evolution of CDI score

The CDI scores, on average, decreased between T1 and T2 in LMIG (p=0.006) whereas these scores remained on average stable in HIG. The cut-off considered for pathological score was 19.

The GLM analysis of pathological CDI scores (19 and higher) was not considered since only four patients (2 in each group) had pathological scores.

The STAI A, the abbreviated BDI-13, the HADS, the SDS and the Self Perception profile for Children did not reveal any group difference for depression nor for anxiety (all p-value >0.05).

Table 1: Mean scores in psychological l tests for both groups over time.

		High intensity group		**Low-to-moderate intensity group**				
Self-reports	Time	Mean (SEM)	p-value °	Mean (SEM)	p-value °	Group x time effect*	Group effect*	Time effect*
STAI A	T1	29.25 (2.47)	0.856	30.55 (2.60)	0.628	0.690	0.868	0.912
	T2	29.83 (2.78)		29.36 (2.04)				
STAI B	T1	36.58 (2.75)	0.911	38.82 (2.20)	**0.004**	**0.050**	0.912	**0.030**
	T2	36.33 (2.30)		33.36 (2.83)				
CDI	T1	11.00 (2.75)	0.447	10.36 (2.83)	**0.006**	0.250	0.480	**0.007**
	T2	10.08 (2.98)		6.73 (1.88)				
SDS	T1	0.49 (0.03)	0.342	0.48 (0.04)	0.518	0.79	0.83	0.25
	T2	0.47 (0.03)		0.46 (0.03)				
BDI-13	T1	2.42 (1.12)	0.953	4.00 (1.24)	0.719	0.71	/	/
	T2	2.58 (1.08)		3.64 (1.68)				
HADS A	T1	6.75 (1.18)	0.749	6.27 (1.24)	0.939	0.785	0.854	0.876
	T2	6.42 (1.17)		6.36 (0.91)				
HADS D	T1	3.58 (0.86)	0. 874	4.36 (0.45)	0.242	0.360	0.733	0.273
	T2	3.50 (1.026)		4.45 (0.73)				
QPSJ A	T1	2.98 (0.17)	0.633	2.92 (0.18)	0.858	0.617	0.645	0.726
	T2	3.07 (0.20)		2.90 (0.19)				

QPSJ B	T1	2.75 (0.17)	0.805	2.98 (0.18)	0.518	0.967	0.419	0.676
	T2	2.80 (0.28)		3.03 (0.20)				
QPSJ C	T1	2.86 (0.11)	0.810	2.60 (0.20)	0.740	0.711	0.386	0.970
	T2	2.80 (0.24)		2.65 (0.13)				
QPSJ D	T1	3.02 (0.25)	0.722	2.92 (0.16)	0.918	0.781	0.798	0.925
	T2	2.99 (0.27)		2.93 (0.18)				
QPSJ E	T1	2.87 (0.13)	0.655	2.96 (0.16)	0.715	0.578	0.887	0.870
	T2	2.95 (0.19)		2.92 (0.18)				
QPSJ F	T1	2.95 (0.18)	0.719	2.96 (0.18)	0.161	0.522	0.779	0.273
	T2	3.00 (0.22)		3.13 (0.19)				

*Legend for table 1**: P-value < 0.05 is considered significant;** SEM: standard error of the mean; °p-value from dependent test; *p-value from independent t-test; Details of the denomination of self-reports in the manuscript*

Secondary outcome

These data are summarized in Table 2. The Likert score variables, with a non-normal distribution, were the BMI and the body fat. A transformation was made on these two variables scores with this formula "Ln(variable)" to obtain a normal distribution. However, the two variables scores remained non-normal after the procedure.

When a GLM and was used to analyze physical measures, it did not reveal a group x time interaction ($p>0.05$). The children's weight and size increased similarly in each group at the end of the five-week program. There was no

difference between groups regarding weight, height, body mass index, muscle or body fat percentages, nor at T1, nor at T2 (all p-values >0.05).

A GLM performed on the VO2max estimations, as evaluated using the Léger shuttle test, did not reveal any group x time interaction (p=0.174). Although there was a trend for improvement in both groups (time effect: p=0.060), it was only in HIG that a significant improvement of VO2max estimation was observed at T2 (44.88 (SEM 1.46) ml/min/kg) relative to T1 (42.21 (SEM 1.53) ml/min/kg) (p=0.014, paired t-test, see Figure 4). The scores remained generally stable in LMIG, evolving from 42.45 (SEM 1.34) ml/min/kg at T1 to 42.89 ± (SEM 1.77) ml/min/kg at T2.

Additional Pearson correlation analyses were performed to test the relationship between the changes in CDI/STAI-B/Léger shuttle test over time (T2-T1). Only the variables that showed a significant time-related change in paired t-tests were analyzed according to the Pearson correlation. The pre-test scores were, first, subtracted from the post-test scores for each variable (CDI, STAI-B, VO2max) and the obtained index of time-related change was further correlated with each other. This analysis did not reveal any correlation between variables.

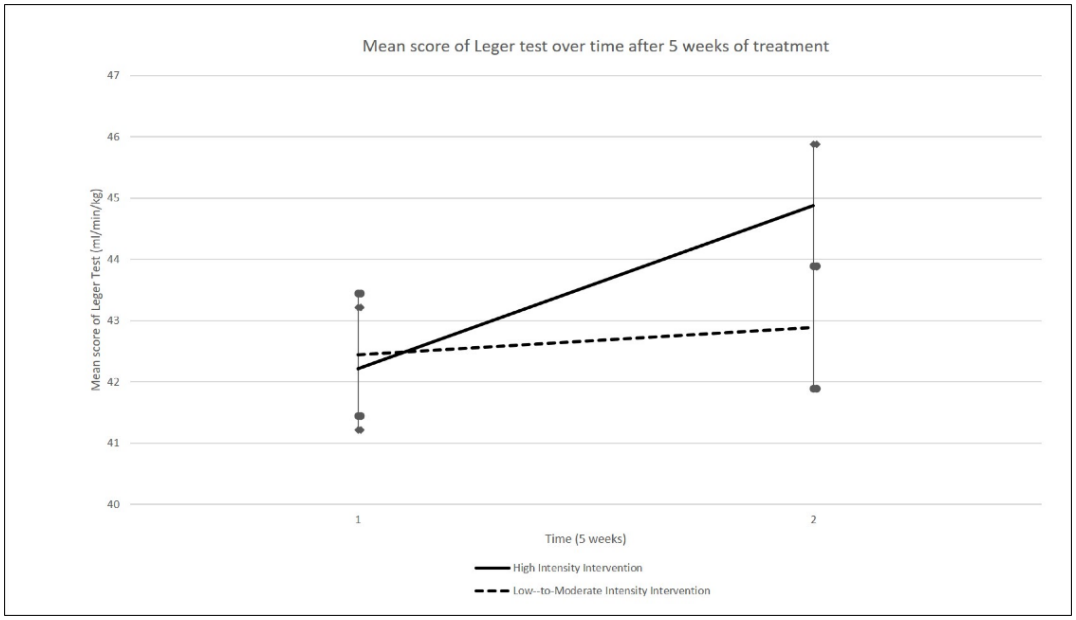

Figure 3 : Evolution of VO2Max indices.

The VO2max indices as evaluated using the Léger shuttle test, on average, evolved better between T1 and T2 in HIG compared to LMIG. Although there was a trend for improvement of these indices in both groups, a significant improvement of VO2max indices (p=0.014) was only observed in HIG group. The errors bars represent Standard Error of the Mean (SEM).

Table 2: Mean scores in physical tests for both groups over time.

		High intensity group		**Low-to-moderate intensity group**				
Physical measures	Time	Mean (SEM)	p-value (T2-T1)°	Mean (SEM)	p-value (T2-T1)°	Group x time effect*	Group effect*	Time effect*
Size (cm)	T1	143.88 (2.63)	**0.010**	139.72 (3.05)	**0.001**	0.36	0.30	**0.00**
	T2	144.71 (2.68)		140.27 (3.12)				
Body Mass (kg)	T1	37.19 (3.26)	**0.003**	34.28 (1.74)	**0.004**	0.54	0.43	**0.00**
	T2	38.1 (3.21)		35.00 (1.74)				
Body Mass Index (Kg/m²)	T1	17.68 (0.95)	**0.040**	17.49 (0.54)	0.075	0.97	/	/
	T2	17.88 (0.91)		17.97 (0.54)				
Body Fat (% of Body Mass)	T1	17.69 (2.11)	**0.003**	19.1 (1.74)	**0.033**	0.47	/	/
	T2	19.52 (2.02)		21.17 (1.76)				
Muscular mass (% of Body Mass)	T1	33.5 (0.79)	0.464	33.43 (1.13)	**0.033**	0.25	0.75	**0.03**
	T2	33.19 (0.66)		32.44 (1.15)				
Resting Metabolic rate (cal)	T1	1238 (46.15)	0.069	1213.45 (32.22)	0.387	0.44	0.63	**0.05**
	T2	1247.25 (44.90)		1217.63 (30.84)				
VO2peak (ml/min/kg)	T1	42.21 (1.53)	**0.014**	42.45 (1.77)	0.740	0.174	0.60	0.06
	T2	44.88 (1.46)		42.89 (1.34)				

Discussion

This study sought to compare high intensity and low-to-moderate intensity physical exercise programs, as per their impact on self-reported depression and/or anxiety scores among a non-clinical sample of 5th-6th grade pupils. The results of the participants from both groups were examined separately, and we found that CDI (self-report scale for depression) and STAI-B (self-report scale for trait anxiety) scores significantly improved, over time, in the low-to-moderate intensity group (LMIG). The high intensity group (HIG) did not show this improvement, but there was an upward trend in improving the VO2max indices compared to the LMIG group.

Main results

Trials investigating the influence of PA on anxiety/depression symptoms in children and adolescents are few. They have yielded different results in terms of duration and intensity despite usually indicating that PA should have a beneficial effect on depressive symptoms (218). For instance, a study involving 43 adolescents with depression, where the intervention was a six weeks circuit-training made of 12 separate sessions done twice weekly at preferred intensity (209), saw significant beneficial effects on CDI 2 version scores. However, these improvements were only statistically significant at a six-month follow up post the intervention, and were not apparent immediately after its duration. When the sample size was measured from this previous study alongside the significant follow-up results, 12 children could be said to have markedly reduced levels of depressive symptoms because of the exercise

therapy. The follow-up results were used to obtain the necessary sample size for our post-intervention because our program contained more sessions (20 sessions). Without lost participants, we would have been able to perform a significant change. Eventually, we performed a 5-week program, which is a short time period in comparison with another randomized clinical trial (219). An intervention of six to twelve weeks was used and effective in alleviating depression in adolescents aged 12 to 18. Although we intended to do 50 minutes sessions, the average duration was 43 minutes approximately in each group. However, this duration was sufficient in demonstrating effective change, and average attendance was very good (92.21%) in both groups. A precise monitoring of the interventions, with continuous supervision on site, ensured that participants correctly performed the requested exercises with little deviation.

Thus, twenty sessions in five weeks seems adapted to decrease depression symptoms at post-intervention. According to a systematic review based on a meta-analysis mixing children and adolescents (123), PA could have a significant but small effect in the prevention and treatment of depression. A recent study in a large community-based sample of participants, indicated that physical activity, objectively measured as moderate to vigorous, at six and eight years of age lowered the average level of depressive symptoms two years later (121). Our observations indicate that a high intensity exercise intervention would not be the optimum to improve anxiety and depression symptoms in pre-adolescents, despite a better increase of physical condition. Even with positive coaching, high intensity training can be restricting for some participants who feel unable to achieve their goals due to poor physical

condition caused by a lack of prior exercise[3]. In independent t-test in STAI-B, the eta squared value (η^2=0.17) demonstrated a large effect size and can thus suggest that the children in our study benefited from the low-to-moderate program to reduce their anxiety symptoms compared to the high intensity program. Accordingly, combining low-to-moderate intensity exercise with interaction and play should better reduce the anxiety/depression symptoms. Additional studies are clearly needed to test this hypothesis in adolescents with a medical diagnosis of depression and/or anxiety.

Limitations

A first limitation concerns our population who was highly heterogeneous with regards to depression/anxiety symptoms; it was not a clinical population, which also explains why some variables did not have a normal distribution. The self-rated questionnaires used in this study are regarded as highly valid and reliable (226), although CDI and STAI cannot be considered substitutes for a medical diagnosis made by a psychiatrist (237). Thus, the results may not be inferred to patients since participants, even those who had scores above the cut-offs at pre-test, were not submitted to a neuropsychiatric interview. Secondly, with a small sample size (23 participants in the both groups), caution must be applied, as the findings for a reduction of anxiety in LMIG might not be for the reduction of anxiety score. Furthermore, the small sample size might be a contributing factor to the non-significance group x time effect in independent t-test for depression symptoms. It is therefore

[3] The term "exercise" is specific and the term "physical activity", being broader, is more appropriate here.

likely that more participants should be included in studies to evaluate the efficiency of the low-to-moderate intensity among pre-adolescents to reduce the psychological symptoms. Another potential problem is that we cannot exclude the possibility that participants of each group knew what their peers in the other group were doing. We attempted every effort to avoid mutual influence; the different questionnaires were used in random order to minimize outside influence. Then the inferred results were obtained from tests performed twice, once before and once after the five-week period. This gives us a limited scope of data and knowledge, especially concerning any long-term effects of the intervention; a six-month follow up examination would be required to rectify this problem, but could not be achieved due to practicalities. In addition, when we tried to correlate changes in physical condition with changes in depression/anxiety scores there was no significant correlation, although poor physical condition may promote increased scores of depression due to the prevention effect of physical activity (PA) described in the literature (218, 219). It should be noted, however, that any correlation should not allow disentangling between the two hypotheses in terms of cause and effect (lack of PA favoring depression, depression favoring lack of PA).

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Ethical approval.

The ethical Committee of the School of Medicine of the Université catholique de Louvain approved the study. N°: CEHF-FORM-003/REV005 –B40320

Study 3: Effect of physical exercise training on bullying and depression in a classroom: a case report

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As this study is already published, responses to the jury members were added to the text as footnotes.

Abstract

In a previous study conducted to assess the impact of physical exercise on the symptoms of depression and anxiety in preadolescents in the school environment, which included a subgroup of participants comprising eleven randomly selected teens (aged 9–11) and all enrolled in primary education, it was immediately observed that one participant referred to as Andy was being bullied and teased, and the teachers were completely unaware of this scenario. All the participants of the study were volunteers, and five were subjected to low-to-moderate intensity exercise four times a week for five weeks. Psychological self-assessments and physical examinations were performed before and after the program as a part of a blind assessment. In the intervention sessions, the therapists and participants remained unaware of the individual scores. The sessions included the games that highlighted the feeling of movement, postural control, and slow relay races with balancing, in combination with other cooperative, interactive games focused on fun and social contact rather than focusing on the performance. It was reiterated to the participants that mockery was completely prohibited during the program. After the intervention, a significant decrease was observed in the anxiety levels and depression scores of the participants. The most significant change was observed in the participant who was a victim of bullying during the initial exercise sessions. No changes were observed in the general atmosphere of the classroom. Bullying is quite common (>10%) and is most often completely overlooked. The present study demonstrated a decrease in the symptoms of depression and anxiety in a non-clinical sample of pre-teens attending elementary school when they completed a low-to-moderate exercise program that combined movement and pleasure and encouraged positive and non-

competitive interactions among the participants. The program proved to be particularly beneficial for a bullied individual.

Introduction

Bullying is a phenomenon that most students are exposed to during their school years. A meta-analysis estimated a mean prevalence of 35% for traditional bullying (including both victims and bullies) and 15% for cyberbullying among adolescents (238). These children could be witnesses, victims, or the perpetrators of bullying. There is evidence that bullying critically affects the mental health development in the young student population. Bullies and the victims of bullying are at the risk of short-term and long-term negative impacts, such as depression, anxiety, low self-esteem, and delinquency (239-241). It is noteworthy that young people already suffering from depressive symptoms might be more vulnerable to bullying because of the differences and the difficulties they experience in emotional regulation and coping (242). Depression causes the affected child to be vulnerable and different from the peer group, thereby increasing their risk of being bullied. The condition of such children becomes worse as bullying by their peers adds to their discomfort. The symptoms of depression may worsen to a further severe level, leading to an increased risk of suicide. It is reported that bullying victimization may be a significant risk factor for adolescent suicide attempts worldwide (241), while depression may strongly influence this relationship between bullying and the risk of suicide (243). The high prevalence of bullying and depressive symptoms among children and

adolescents renders it imperative to manage this public health problem (238, 243). Furthermore, this situation is often associated with reduced physical activity leading to a severe sedentary lifestyle (218, 244) with worse long-term consequences developing in adulthood (21).

The phenomenon of bullying is quite common in the dynamics among peers within a classroom. In this context, group physical activity could serve as a support to children, assisting them to interact and learn new skills together, and improve their social skills and their ability to control their emotions. To date, few studies have examined the role of exercise interventions in reducing bullying incidences in school, with not a single study investigating depressive symptoms in addition to bullying. The limited number of studies available in the literature indicate that physical activity may mitigate the effects of bullying (245) and reduce depression (218). In the underprivileged neighborhood of Santiago (Chile), a reduction in the level of bullying victimization was reported after participation in an 8-week-long physical activity[4] intervention, compared to the control group. As stated in that report, the objective of the physical activity[4] program was not limited to improving rules, conflict resolution, positive interaction, and skill learning, all of which could explain, at least in part, the observed effect on bullying (246). It is also reported that a reliable environment is essential to properly involve children and adolescents in physical activities (247). These findings indicate that an efficient physical activity[4] program in schools could prevent or reduce bullying within the classrooms, provided that the program is well-structured, task-oriented, safe, and non-competitive.

[4] The term “physical activity” is too broad and the term “exercise” is more appropriate.

Chapter II: Exercise at school to prevent depression and anxiety
Study 3

We previously conducted a study to document the effectiveness of different training[4] intensities in reducing the symptoms of depression and anxiety in pre-teens within school settings (248) and observed that low-to-moderate intensity physical exercise implemented in the form of games could reduce the scores for anxiety and depression in a non-clinical sample. The training[5] program combined movement with pleasure and encouraged positive and non-competitive interactions among the participants. It was hypothesized that such a structured group physical activity program could influence the mood of the participants and alter the peer dynamics, and was, therefore, beneficial for all the participants, particularly the ones who are inhibited, insecure, and physically weak or non-athletic. One participant was bullied during the initial training[5] sessions, which was inconsistent with the focus of the program to include movement and fun in a positive and non-competitive atmosphere. We, therefore, describe the case of this child, a boy (referred to as Andy) who became the victim of bullying, and his evolution through the course of this intervention. The objective of the present case report is to highlight the impact of this exercise program, over time, on Andy's well-being and fitness in parallel with the evolution of his peer group.

[5] The term "training" is specific to physical fitness improvement. Here, the term "exercise" is more appropriate.

Methods

General Design

The details of the general design are available in a previous report (248). Briefly, in a prospective and randomized pilot trial with two arms, two subgroups of participants, the randomly selected pre-teens (aged 9–11) attending school, thirteen in each group, were compared. The main objective of the trial was to study the effects of structured physical activity on the prevention or treatment of anxiety and depressive symptoms in a non-clinical sample of school children. Low-to-moderate-intensity physical activity[6] was compared with high-intensity physical activity[6], to determine the most appropriate exercise intensity for application in depressed youth. In addition, the trial assessed whether such physical activities, implemented in the form of games, could affect peer dynamics and encourage the physically-weak children to participate in sport. There was no control group.

The low-to-moderate intensity intervention and the high-intensity intervention, both focused on pleasure, interaction, and non-competition, were conducted in parallel for five weeks at a rate of 4 sessions per week (Monday, Tuesday, Thursday, and Friday) during the lunch hour. Therefore, the study followed the two groups of children for 20 sessions that lasted for a total of 50 min. There was an assessment period in the week before and after the program, in which test results of the participants were collected. The quantifiers for randomization included individual scores for the Child

[6] The term "physical activity" is too broad and the term "exercise" is more appropriate.

Depression Inventory (CDI), Body Mass Index (BMI), duration of the Léger shuttle test, age, sex, and school year. Thereafter, the principal investigator assorted the participants into two equivalent groups. Randomization at the group level was performed by an external blinded researcher, who provided the intervention allowance through e-mail. In the intervention sessions, the therapists and participants remained unaware of the individual scores used for randomization. The two pairs of therapists (two physical educators and two physiotherapists) managed an equal number of sessions in each group alternately.

The study was conducted at the "elementary school Parmentier–Jean XXIII" in Brussels and its facilities (a classroom and a gymnasium within the school premises, and a park surrounding the school). The project was conducted, including recruitments, evaluations, and experimental intervention periods, from November 2016 to December 2016, and was preceded by information sessions and a cooling-off period the month before. The study was approved by the Ethical Committee of the School of Medicine of the Université Catholique de Louvain. The ethical committee of the School of Medicine of the Université catholique de Louvain approved this study (N°. CEHF-FORM-003/REV005-B403201627586), april 2016, revised and updated May, 20, 2020. The study is considered as a part of the clinical trial "Move and feel good" registred as NCT02970825, ClinicalTrials.gov, Autumn 2016 (https://clinicaltrials.gov/ct2/show/NCT02970825).

Selection Process

Participants were recruited from the primary school on a voluntary basis. The study was conducted inside classrooms, in the presence of teachers, and was

presented to the parents in a separate session conducted at the school. The inclusion criteria for participation were as follows: (1) enrolled in an official education program; (2) aged between 9 and 12 years; (3) acceptance of the randomization principle; (4) absence of neurological or psychiatric history; (5) absence of uncorrected sensory disorder that could prevent the understanding of instructions; and (6) absence of conduct disorders. The exclusion criteria for the study were: (1) refusal to participate; (2) Body Mass Index above P95; (3) unstable diabetes; (4) coagulation disorders (besides specific exceptions and medical authorization); (5) severe and unstable asthma; (6) history of heart malformation or cardiovascular disease; and (7) medical conditions prohibiting sport or physical activity. No particular fitness level was a prerequisite for participation, and the teachers did not train the participants before or during the project. The parents of participants completed a medical questionnaire prior to the commencement of the research and also provided written informed consent for participation. Only the children who fulfilled the inclusion were allowed participation. All the participants were informed that they would not be allowed to select the group to which they would be assigned and that they could leave the study at any time if they wished.

Intervention

One of the two interventions was a low-to-moderate intensity physical exercise program. A greater reduction in the anxiety and depression scores was observed in this group compared to the other one, in which the participants followed high-intensity physical exercise (248).

The low-to-moderate intensity intervention focused on pleasure, positive interaction among the peers, and promotion of a general atmosphere that encouraged movement. A task-oriented climate with a learning component was promoted as it is reported to be associated with adaptive behaviors, healthy habits, and autonomous motivation to practice activities (249). The intervention combined games that highlighted the feeling of movement, postural control, awareness of body, and slow relay races with balancing, mime games, and walk/run plays while perpetuating equilibration, and the other cooperative, interactive games focused on fun and social contact without a focus on performance. Each session began with a warm-up and ended with muscle stretching along with information and details regarding muscles. It was insisted repeatedly that mockery was completely prohibited during the program. The intervention was adapted to each participant to find an equivalent place for all the students. Positive remarks were regularly written in an individual's file to motivate each participant to attend all sessions (20 sessions in total). The principal investigator provided medical security and discussed the daily components of the program with the therapists, who were trained in physical education and physiotherapy from the Université Catholique de Louvain, Belgium.

Andy's Case (*)

(*) This is a fictitious first name for use in the present report to maintain the anonymity of the student. It was observed during the initial training[7] sessions that one participant was being bullied and teased, which the teachers were

[7] The term "training" is specific to physical fitness improvement. Here, the term "exercise" is more appropriate.

completely unaware of. This scenario was not known before the study commenced. In the initial sessions, it was observed that Andy had an inhibited behavior and stopped participating when the other participants referred to him as “Andy, handicap”. When this was discussed with him separately, he informed that he encountered verbal mockeries in the classroom every day and that he felt excluded from everyone in the class. As a tall and thin figure, although not muscular, he was quite happy with his appearance. He disliked having trouble in making friends and did not seem to know why he failed in such attempts, except the guess that he was new to this school. He recognized that he was not sure of himself and his intelligence despite his good academic results. He was eleven years old, had no learning troubles, and his medical history was uneventful. He did not wish to inform his parents regarding his experience and was convinced that his teachers would do nothing to help him in this regard. We promised him that he would not have to experience bullying at least during the sessions, and “a bad atmosphere would imply the end of the intervention”. We proposed referring to him as Drew (abbreviation for Andrew) during the sessions and everyone in the sessions followed. As the content of the intervention was adapted according to each child, it was also adapted to include Andy better without changing the principle of the physical exercise program. Each attempt to tease someone in the group was followed by a “You laugh, you need to relax” break (relaxation implied expulsion from the current play and one-minute individual neck massages by one of the physiotherapists). It was observed that during the subsequent sessions, Andy no longer had complaints and appeared happy to learn the new movements. The evolution of the mean scores obtained in the psychological and physical tests was analyzed for the group as well as individually for Andy. The aim

was to determine the potential effect of such a program on bullying by analyzing the evolution of Andy's scores after five weeks of intervention.

2.5 Primary Outcomes

Pre-assessments and post-assessments were conducted the week before and the week after the intervention, respectively, as a part of a blind assessment.

The Child Depression Inventory (CDI) is a 27-item self-reporting tool (224) with scores based on the child's statement describing how she or he felt during the two previous weeks. The average score in the general population is 9 points (224), and a score of 19 or above is considered pathological (225). The CDI has good internal reliability (Cronbach's alpha = 0.86), sensitivity, specificity, and a low level of bias (226).

The State-Trait Anxiety Inventory (STAI) (227) consists of two subscales, each with twenty items: the STAI form Y-A that assesses the participants' recent state (i.e., what the participants felt during the week of testing), and the STAI form Y-B that assesses the long–term anxiety trait (i.e., what the participants felt during the past year). Each part (A or B) of the STAI generates a state score or an anxiety trait score in the range of 20–80 and the pathological threshold is 39–40 (228). STAI has a high degree of reliability (Cronbach's alpha = 0.86) and validity.

Secondary Outcomes

A medical device and a scale were used to measure the height and weight, respectively, of the participants. The *Leger shuttle test*, a 20-meter multi-steps shuttle run test, was conducted to provide an extrapolated assessment of the maximal oxygen uptake (VO_2 max) (234). A meta-analysis has reported that

"the 20 m shuttle test seems to be a useful alternative to estimate cardio-respiratory fitness" and that the test has high validity in young people (235).

Harassment assessment was not conducted as the study was not formulated for that initially. However, a self-perception profile for children (233) was used in its French version to document the way each child assessed his skills (social, athletic, school, physical, behavioral, and self-esteem) before and after the intervention. After each session, the participants documented a quality assessment according to the two dimensions of well-being in an individual file: a "tiredness score" (0–3, 0: not tired; 1: a little tired; 2: moderately tired; 3: exhausted) and a "pleasure index" (0–3, 0: very fun; 1: quite fun; 2: moderately boring; 3: very boring). This file was referred to when adapting the subsequent physical exercise sessions according to each participant.

Statistical Analysis

As certain measures were based on Likert scores, a graphical tool (quantile-quantile plot) and a Kolmogorov Smirnov test were employed to assess the distribution of normality. If the data were not normal, a logarithmic transformation was performed to obtain the normalized data (if that was possible). As it was assumed that there would be changes in the depression/anxiety scores after the intervention, the dependent tests (Student's paired t-test or Wilcoxon's test) were performed to determine the change in a variable (STAI, CDI, etc.) over time. All the statistical procedures were performed using the SPSS software.

Results

Group Evolution

Among the 13 preadolescents recruited in the study, two were excluded during the experiment; one withdrew voluntarily and the other was excluded on account of bad behavior (opposition to the exercise instructions). The statistical analysis of the pre-test and post-test measures was performed for the remaining 11 participants. There were five girls and six boys, and the mean age at assessment was 10.6 ±0.7 years. The mean attendance rate was 96.65%. The mean individual "tiredness score" was low (0.43). The participants enjoyed the intervention, as evidenced by the mean “fun index” value of 0.52 (very fun to quite fun).

The self-reported data from the primary questionnaires are summarized in *Table 1*. The Likert score variable that demonstrated a non-normal distribution was the CDI. However, the CDI scores were transformed using the formula “Ln(variable)” to obtain a normal distribution.

The STAI B scores, on an average, decreased from 38.82 [SEM (Standard Error of Mean) 2.20] at T1 to 33.36 (SEM 2.83) at T2 ($p = 0.004$, Student’s paired t-test) [refer to *Table 1*].

The analysis of the STAI-A scores did not reveal any time-dependent change (p-value > 0.05).

The CDI scores decreased, on average, from 10.36 (SEM 2.83) at T1 to 6.73 (SEM 1.88) at T2 ($p = 0.006$, Student’s paired t-test, *refer to Table 1 and Figure 1*).

A Student's paired t-test was performed on the VO2 max estimations that were evaluated using the Léger shuttle test, and no significant changes were revealed. The scores remained stable in general, evolving from 42.45 (SEM 1.34) mL/min/kg at T1 to 42.89 (SEM 1.77) mL/min/kg at T2. The weight and height measures demonstrated significant changes, while the BMI score remained stable (refer to *Table 1*).

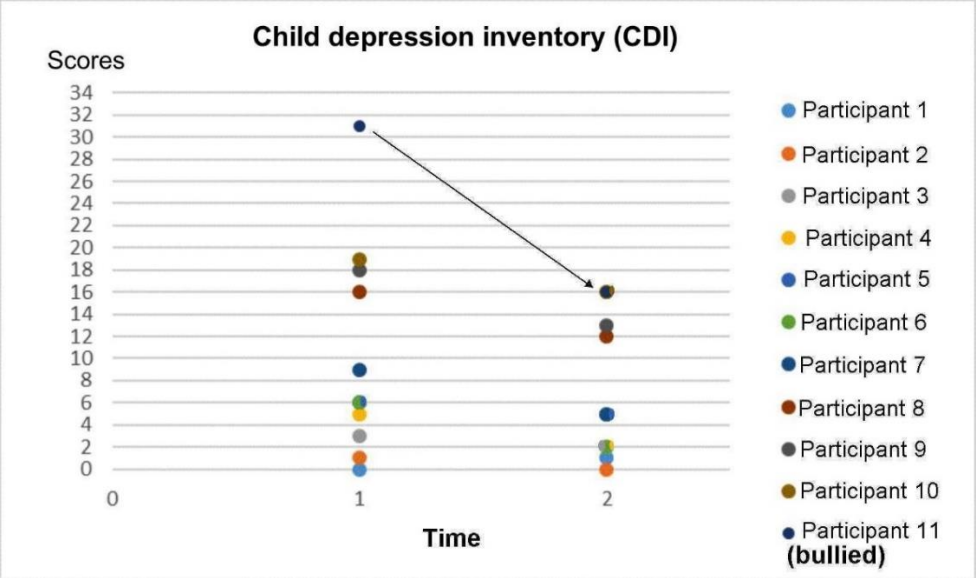

Figure 1 Individual scores in the Child Depression Inventory (CDI).

Table 1 Mean scores obtained in psychological self-assessments and physical tests.

Variables	Time	N	Mean	SEM	p-value°
STAI A	T1	11	30.55	2.60	.628
	T2	11	29.36	2.04	
STAI B	T1	11	38.82	2.20	**.004**
	T2	11	33.36	2.83	
CDI	T1	11	10.36	2.83	**.006**
	T2	11	6.73	1.88	
Height (cm)	T1	11	139.72	3.05	**.001**
	T2	11	140.27	3.12	
Weight (kg)	T1	11	34.28	1,74	**.004**
	T2	11	35.00	1.74	
BMI (kg/m2)	T1	11	17.49	0.54	.149
	T2	11	17.97	0.54	
VO2Max (mL/min/kg)	T1	11	42.45	1.34	.738
	T2	11	42.89	1.77	
Age		11	10.6	0.70	

Legend for Table 1. P-value < 0.05 is considered significant; SEM: standard error of the mean; °p-value in dependent test. Modified from ([12] doi: 10.3389/fpsyg.2019.01820. The cited original work is licensed under the Creative Commons Attribution 4.0 International License.

Andy's Evolution

The statistical analysis was conducted anonymously at the group level. A posteriori, it was observed that Andy had the most severe scores in the group for the symptoms of depression, as assessed by the CDI test, with a pathological score of 31 before the intervention, which was way higher than the cut-off score of 19 set for the test. Andy also appeared to be suffering from a low level of anxiety, with scores of 38 and 43 for anxiety in state and trait, respectively. Prior to the intervention, Andy obtained the lowest result in the physical test, with an estimate of the VO2Max of 30.35 mL/min/kg. According to the international standards of the 20 m shuttle test (250), Andy was in the lowest 5 percentiles as per the international norms for boys. *Table 2* lists all the scores of Andy.

After the intervention, Andy's depressive symptoms fell below the pathological threshold, with a lower score of 16, which was closer to that of the other children in the group (*Figure 1*). Andy then remained relatively stable in terms of the evolution of anxiety symptoms.

Andy had benefited from the program on a physical basis as well, as evidenced by his improved cardio-respiratory score. His estimated VO2Max was improved by 1.47 mL/min/kg, and he was no longer the weakest member of the group.

The changes in Andy's responses in the self-perception profile for children indicated improved self-esteem in the athletic and behavioral dimensions.

At the group level, a significant ($p = 0.006$) reduction in the CDI scores was observed after five weeks of intervention. The individual score for Andy, the child who was bullied in the beginning, fell below the set threshold and was closer to the scores for other children after the intervention. The pathological threshold was set at 19.

Table 2 Andy's scores in psychological self-assessments and physical tests.

Variables	Time	Mean
STAI A	T1	38
	T2	35
STAI B	T1	43
	T2	43
CDI	T1	31
	T2	16
Height (cm)	T1	127
	T2	127
Weight (kg)	T1	25.7
	T2	27.0
BMI (kg/m2)	T1	15.9
	T2	16.7
VO2Max (mL/min/kg)	T1	30.35
	T2	31.82
Age		11

Discussion

The present study aimed to introduce an original intervention for physical exercise in schools and assess the potential effects of this intervention on the symptoms of depression and anxiety in the participating children, including the child who was bullied. It was observed that physical exercise at low-to-moderate intensity implemented in the form of games could reduce the anxiety and depression scores in this non-clinical sample and exerted a beneficial impact over time on the mental and physical health of the bullied participant in parallel with the evolution of the group.

Group Evolution

The present study demonstrated that a five-week-long program of physical exercise at a low-to-moderate intensity could reduce the symptoms of depression and anxiety in a non-clinical sample of pre-teens attending elementary primary school. In addition to the beneficial effects on the whole group, the intervention appeared to be particularly beneficial for a bullied individual. There are several potential explanations for this observation of improved mood in the peer group as a whole. First, the program provided a positive experience of movement and peer interaction with the inclusion of all children. The intervention included physical activities without a sense of competition and not requiring a demonstration of performance. The sessions were conducted in a group, allowing the children to collaborate and form teams with the common goal of executing the suggested movements

accurately. Second, the program, conducted within the school premises, was appreciated as recreational and full of fun. A high rate of participation (96.65%) despite the voluntary nature of participation highlighted the importance of engaging children. It is reported that children, mostly girls, increased their level of participation in physical activities when a motivational and task-oriented climate was established (160). In our study also, we promoted a task-oriented climate with a learning component as such an environment is reported to be more associated with adaptive behaviors, healthy habits, and autonomous motivation to practice sports outside of school (160). The interventions based on light-to-moderate physical activity, body awareness, and yoga practice may have synergizing benefits, reducing the negative effects of chronic stress (251). On the contrary, physical exercise programs conducted in an ego-oriented climate could lead to an extrinsic motivation, which is associated with further abandonment of physical activity (160). Third, physical activity might be effective in decreasing bullying tendencies in children. In a cohort study with 1,248 high-school students, a trend was observed that the teenagers who regularly engaged in physical activity could alter their levels of aggressivity more than those with sedentary behavior. This led the authors to suggest the promotion of healthy (non-competitive) sport to prevent violence among children (252). Another hypothesis could be that physical exercise reduces depressive symptoms and improves mental well-being among children through its beneficial effects on brain functions. Previous authors have demonstrated that in the general young population, physical exercise improves the performance of executive functions and modifies the activation pattern of the brain areas underlying these functions (220, 253). Cognitive and executive functions are often impaired in depressed young people (55, 222). To date, there are no published

studies on the impact of exercise on the brain in the children and adolescents with depressive symptoms. A few systematic reviews and meta-analyses have evidenced that exercise interventions reduce the symptoms of depression in children and adolescents, with a greater impact on the clinical symptoms (126, 130). Nonetheless, additional studies with better methodological quality are required to corroborate and confirm these results, particularly in school settings.

Andy's Evolution

Prior to the intervention, Andy obtained a considerably high score on the depression scoring scale (CDI). This observation was consistent with the findings of a recent study on the association between bullying and depressive symptoms conducted with 4,829 adolescents (245). Although Andy did not express morbid ideas, it has been long known that bullies, victims, and bully-victims are at risk of suffering from depressive symptoms that can even lead to suicide in certain cases (245). In the early sessions, the bullying was clearly influenced by both his inhibited individual behavior and the dynamics of an already-formed group in which he was new and poorly accepted because of these personal characteristics. The intervention was adapted to include him better and foster a non-competitive and benevolent climate where he could participate at the same level as the other children of the group and acquire new skills with pleasure without focusing on his performance. After the intervention, it was observed that Andy was the one to make the most of this kind of physical exercise program. As evidenced by his individual score, Andy felt much better after the intervention, obtaining a score under the

pathological threshold score. The intervention appeared to have exerted a beneficial impact on his mood. It is reported that participation in sports may be an effective way to reduce the impact of bullying on the risk of developing depression (245). A previous study demonstrated that physical activity[8] at moderate-to-vigorous intensity for eight weeks resulted in reduced physical and verbal victimization among school children (aged 8–10 years) (246). Furthermore, a cohort study with a sample of 29,207 adolescents from private and public high schools demonstrated that exercise reduced sadness and suicidal ideation in adolescents who were bullied at school (254, 255). Our findings are consistent with these previously reported observations, although it must be noted that we report no objective measure that could indicate that Andy was no longer bullied in school after the program. We had access to the reduction in his depressive symptoms only until immediately after the intervention. Further studies based in school settings are clearly required to elucidate the extent to which such a program could result in the prevention or treatment of bullying.

Physical Activity: A Tool for use within a Reliable Environment

It is noteworthy that physical activity may provide opportunities for bullying to occur. In turn, bullying may cause reduced participation in physical activity (256). If students develop a negative feeling regarding sports activity, they would have a negative experience and would ultimately reject the desire and motivation to participate in any physical activity. Therefore, it is advised to maintain a motivational atmosphere that is adapted according to the child to

[8] The term "physical activity" is too broad and the term "exercise" is more appropriate.

prevent intimidation behaviors and support positive interaction (160). On similar lines, a critical qualitative study conducted with a sample of 15 boys explored the social-behavior mechanisms that motivate or dissuade participation in physical activities at the dawn of adolescence (257). Studies have identified different mediation mechanisms to promote participation in physical activity, such as emotions, the pleasure of moving, and the feeling of connection to the activity [9] (258-260). While negative self-perceptions, unsatisfaction with own body, repeated negative experiences, and bullying are reported to lead to apathy and attrition from physical exercise (257), a safe atmosphere provided by the monitors, an atmosphere of motivation oriented toward the task (160), and sessions focused on enjoyment motivate the children and even those with a potential reluctance to participate (257). The most appropriate intensity and frequency of exercise for reducing depressive symptoms are not yet clearly defined (124), although there is good evidence demonstrating that moderate-intensity exercise reduces depression (126, 130, 261). A mild-to-moderate or moderate level of intensity may be required when the objectives of the intervention are to promote positive interaction, collaboration among the participants, and improvement in their physical

[9] Based on self-determination theory, a systematic review revealed that the development of autonomous self-regulation (internalized extrinsic regulations and intrinsic regulation) supported physical activity participation (258). On the one hand, internalized extrinsic regulations (i.e., identified and integrated motivation) may predict better short-term physical activity adoption. Identified and integrated forms of behavioral regulation are defined as those in which an individual's actions are self-approved because they are personally valued. In the other hand, intrinsic motivation is particularly important for long-term physical activity participation. An intrinsically motivated individual experiences feelings of pleasure, skill exercise, self-actualization, and excitement (258). Future research needs to investigate exercise interventions that are aimed at promoting feelings of self-determination and their effects on the long-term physical activity participation in individuals in mental illnesses (259-260)

condition. Young people who are depressed might experience more difficulty in performing the usual tasks. Therefore, high-intensity tasks may appear like a huge burden and effort to them, lowering their available capacities to collaborate in the program and interact with the other participants. In overly competitive sports clubs, this might encourage intimidation from assertive participants toward their vulnerable peers. On the contrary, low-to-moderate intensity would be a convenient way to gain the experience of success, encouraging adherence to the exercise regimen. In our opinion, such a program would increase the likelihood of young people adhering to exercise for a longer period of time, thereby facilitating the prevention of all kinds of physical and mental illnesses. Nonetheless, additional studies with good methodological quality are necessary to corroborate and confirm these results, particularly in school settings. A few systematic reviews and meta-analyses have already evidenced that physical exercise interventions reduced the depressive symptoms in children and adolescents compared to control groups, with a higher impact on clinical symptoms (126, 130). The limited number of meta-analyses available in the literature present a high level of inter-study heterogeneity in terms of the intervention methods and the measurement of results, particularly apparent in adolescents (124, 126). The present study observed that if children, including the victims of bullying, followed an adapted physical exercise program, they could achieve a positive development in their well-being. We observed a reduction in the depression scores of children after five weeks of low-to-moderate intensity physical exercise program conducted in a non-competitive learning-climate that favored peer interaction. The current public fitness rooms are generally not adapted to realize this goal. Further studies in school settings are clearly

required to elucidate the extent to which such a program could assist in the prevention or treatment of bullying.

COVID-19 Context of School Closures

The COVID-19 pandemic crisis has significantly affected numerous students worldwide. The lockdown restrictions force the students to undertake their school programs online and also limit their social life. Students often experience fears and uncertainties with the ongoing physical and social isolation, which puts them at potential risk of cyberbullying. Children and adolescents react differently as they are at different stages of development, although higher rates of depression, anxiety, and post-traumatic symptoms are being reported across all age groups (262, 263). In regard to the preventive measures required to be adopted concerning the mental health of students, a rapid systematic review demonstrated the protective effect of a routine of physical activity during the COVID-19 period. Maintaining physical fitness has also been demonstrated to reduce the risk of developing symptoms of depression by 12%–32% and the risk of experiencing anxiety by 15%–34% in the general population (264). Therefore, during forced isolation, such as the one during the pandemic crisis, certain authors have suggested studying the role of online exercise programs, such as the #StayHomeStayFit project by the University of Milan (265), in promoting fitness and preventing mental health disorders (264).

A few countries have decided to keep the schools open. In keeping with health precautions, it would be desirable to evaluate the maintenance of physical education classes through inexpensive, feasible, and effective programs.

Racket sports, climbing, fitness, and aerobic games can be conducted in a ventilated room or outdoors with distance adjusted according to the intensity of the exercise and while wearing a mask. However, to date, it has proved difficult, in practice, to estimate the distance necessary to avoid the transmission of infection during a rigorous sport.

Limitations

As with all research, the present study also has certain limitations, particularly in the interpretation of results. First, we did not expect that a child would be bullied during this experiment. The bullying event was revealed during the initial sessions when Andy, after being teased and bullied, informed us regarding his situation. We present him in this study as a special case as the results obtained related to his evolution were encouraging and could assist in the investigation of the impact of a physical activity[10] intervention on the well-being of a bullied child. However, these results should be interpreted with caution. No harassment assessment (266, 267) was performed in this trial as the trial was initially not designed to collect the measures regarding bullying of participants. Only the data collected from the primary study has been discussed (248). The long-term effects of the treatment could be determined by analyzing the psychological scores and the class atmosphere after the intervention, although this was not realized as there was no follow-up and we had only one window of five weeks. The study included only 11 participants who completed the whole study and this small sample was not sufficient to explore whether the course was different depending on the social

[10] The term "physical activity" is too broad and the term "exercise" is more appropriate.

characteristics of the participants. Moreover, we did not include a control group without intervention. Further experimental interventions involving physical exercise should be conducted to address the issue of bullying and assess mental health in children, including tests that would describe the bullying/aggressor position for each child. The general atmosphere in the classroom and the family environment (239) should also be considered while measuring the potential impact of physical exercise in different situations.

Conclusion

The present study indicated that the symptoms of depression were reduced in a non-clinical sample of 11 school children, including the case of a victim of bullying, when the children were on a low-to-moderate intensity exercise program that combined movement and pleasure in a task-oriented and non-competitive climate. Further comparative and randomized studies are necessary to document the reduction in depression in the context of bullying after conducting an intervention involving physical activities adapted according to school to promote physical exercise as care.

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CHAPTER III: Exercise in a psychiatric hospital

Study 4: Impact of physical exercise on depression and anxiety in adolescent inpatients: a randomized controlled trial

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As this study is already published, responses to the jury members were added to the text as footnotes.

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.

Key-words: physical exercise, depression, anxiety, adolescents, psychiatry

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Study 4

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 (268), 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 (268, 269). Furthermore, there is evidence for a causal association whereby anxiety precedes depression (36), such that many young people with depressive symptoms suffer from 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 (270), and calls for attention to the risk of suicidality in adolescents treated with antidepressant medications (271).

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 (272) or adolescents (89, 124, 126, 130, 166, 273). Previous studies with a RCT design have shown the positive effects of exercise on depression in adolescent outpatients (209, 219), some of which have been conducted in adolescents with severe depression (193). 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 (126, 130, 273). 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.

Methods

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*.

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This trial was registred as follows : Move and Feel Good, NCT02970825, https://clinicaltrials.gov/ct2/show/NCT02970825.

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.

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.

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).

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.

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).

Physical Exercise intervention

The physical exercise intervention was conducted with moderate physical intensity and supervised by exercise specialists (274). The target heart rate during exercise was 40 to 59% of Heart Rate Reserve (HRR), which is an indicator of moderate intensity exercise (275). 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.

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.

Outcome measures

Details on outcome measures (description, reliability, severity thresholds) are provided in Data in brief (276).

Primary outcome

The Hospital Anxiety & Depression Scale (HADS) is a reliable and valid questionnaire (230) 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 (277) 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)* (225), *Beck's abbreviated Depression Inventory (BDI-13)* (229) and the *Zung Self-Assessment Depression Scale (SDS)* (231). 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 (228).

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* (278) 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.

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 (279). 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.

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.

Results

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 *Figure 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*.

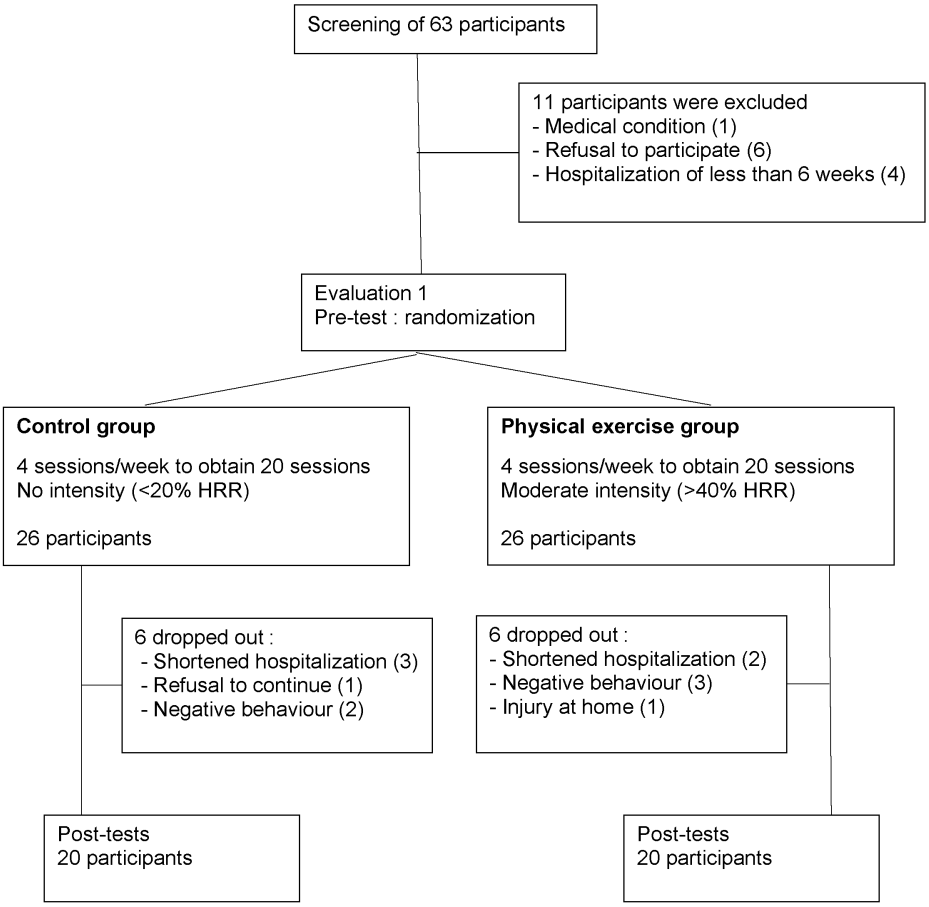

Figure 1 : Flow chart of study design:

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.

Table 1: Characteristics of the participants.

	Control (n=20)	Physical exercise (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		
(1) Cannabis	6 30%	5 25%
(2) 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%

Legend : 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 (77).

(***) 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.

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).

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

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-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 between groups (*Table 3).*

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 (278), corresponded to the 5th percentile based on normative values from 1,142,026 children and adolescents worldwide (250). The linear mixed model with F-test performed on these VO_2max 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_2max 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_2max 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 Figure 2.*

Table 2: Psychological and physical assessements

	Baseline		Post-test	
	Control	Physical exercise	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 (²7)	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 (³ 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 (³ 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 (³ 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 (³ 0.70)	13	12	10	8

Table 2 (continued): Psychological and physical assessements

	Baseline		Post-test	
	Control	Physical exercise	Control	Physical exercise
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 (² 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 (² 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)

Legend: 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_2max	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.

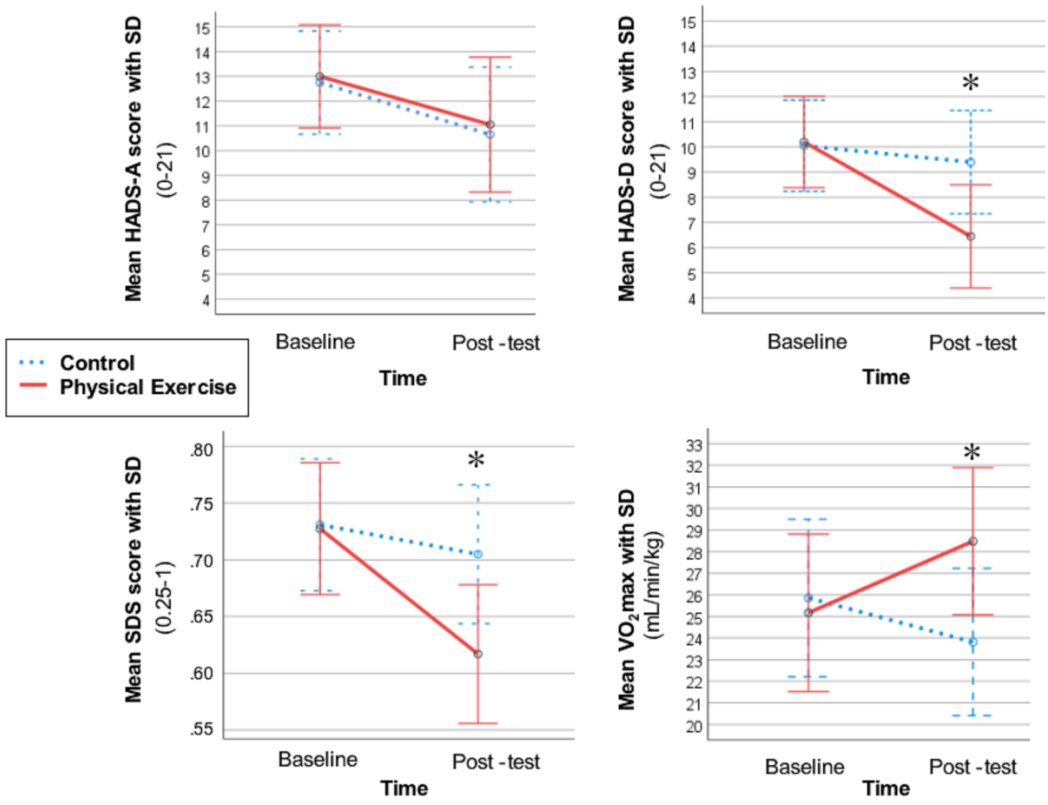

Figure 2 : ***Changes from baseline in main outcomes.***

*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.*

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.

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.

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 (209, 249), 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 (280), as has also been reported in adults (281). 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 (253, 282). Furthermore, hippocampal volume and memory performance are better in athletic participants compared to age-matched but sedentary participants (220). Since major depressive disorder in adolescents is associated with impaired executive function and mental ruminations (54, 55, 222), 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 (124, 125, 283), in contrast to observations made in adults (284, 285). 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 (248). Additional research should explore if tailored interventions can benefit outpatients and inpatients with clinical symptoms of anxiety.

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 used HAM-D scale for clinical research in adults includes somatic symptoms of depression as well as some symptoms of anxiety (286) 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_2max indices, although still low after treatment, increased significantly in the exercise group, thus attaining the 10th percentile for girls (60% of the sample) (250). At baseline, the mean VO_2max 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 (287)[11](288). Since depressive symptoms *per se* in otherwise healthy adolescents may influence later risk of cardiovascular disease (289), 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 (219) and 70% for 6 weeks (209)).

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

[11] Caution is warranted for our cardiorespiratory data. Some VO2Max measurements are closed to the independent living level, 17.7 ml/kg per min for men and 15.4 ml/kg per min for women (288), meaning that they would have the cardiorespiratory condition of elderly people. This indicates that their level is certainly underestimated. Possible explanations for these low results are: 1) the formula of the modified Astrand Rhyming score (used here) was defined based on an adult sample, the correction factors are thus not adapted for age here 2) in this modified version, age is adjusted according to the maximum heart rate subtracted from the age of the participant, whereas the original test uses a specific correction factor for adolescents compared with adults 3) finally, the original Astrand Rhyming test varies these results by gender unlike the modified Astrand Rhyming test.

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 (193, 209, 219). 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 (89, 126, 130). Although noticeably smaller effect sizes were found in studies that used non-physical activity as control treatments compared to studies without control group (166), 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 (290). 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.

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 (291). We did not have information on prior physical activity from a physical activity questionnaire such as the SIMPAQ that is validated in adolescents (292). Furthermore, we note that physical activity [12] 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.

[12] The term of "Physical activity" includes sport, fitness and psychomotor sessions. So, psychomotor sessions were included in the described mean rate of 1.2 session per week for the control group and 1.3 session per week for the exercise group.

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[13] history, comorbidity, cognitive and social functioning on exercise programs in youth with mood disorders are urgently required.

Acknowledgments

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Funding

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[13] The term "exercise" is specific and the term "physical activity", being broader, is more appropriate here.

Study 5: Data on the impact of physical exercise treatment on depression and anxiety in a psychiatric hospital for adolescents

Published as :

Philippot, A., Dubois, V., Lambrechts, K., Grogna, D., Robert, A., Jonckheer, U., Chakib, W., Beine, A., Bleyenheuft, Y., De Volder, A. G (2022). Data on the impact of physical exercise treatment on depression and anxiety in a psychiatric hospital for adolescents. Data in Brief, 108165.

As this study is already published, responses to the jury members were added to the text as footnotes.

Abstract

The present data article provides a dataset of psychological scores, additional description of used measures, and descriptive data of participants related to the research article entitled “Impact of physical exercise on depression and anxiety in adolescent inpatients: a randomized controlled trial” (210). This randomized controlled trial aimed at assessing the effect of add-on treatment with structured physical exercise compared to social relaxation activities in a clinical population of adolescents hospitalized for depression and anxiety in a psychiatric hospital. A group of 40 adolescents was randomly assigned to either a physical exercise or a control program three to four times per week over six weeks. The primary outcome was the Hospital Anxiety Depression Scale (HADS) for evaluation of depression and anxiety symptoms. Secondary outcomes were psychological self-assessments (The Zung Self-Assessment Depression Scale (SDS), Beck’s abbreviated Depression Inventory (BDI-13), The Child Depression Inventory (CDI), The State-Trait Anxiety Inventory (STAI)), diagnostic interview (Hamilton Depression Rating Scale), and physical examinations (an adapted version of the Astrand-Rhyming Sub-Maximal Effort Test and BMI measures). These questionnaires and tests were filled at baseline and after intervention.

Keywords

Exercise ; Depression ; Anxiety ; Psychiatry ; Adolescence ; Adolescent Medicine

Specifications Table

Subject	Health and Medical Sciences
Specific subject area	Exercise treatment for clinical depression and anxiety in a psychiatric hospital for adolescents
Type of data	Table Dataset
How data were acquired	**Dataset :** Data were collected by self-reports completed by the participants, by semi-structured interviews with a psychiatrist, and by physical tests on a cycloergometer with anthropometric measurments. **Table:** Characteristics were acquired directly from servers with electronic medical records
Data format	Raw Analyzed
Description of data collection	*Self-reported questionnaires (HADS, SDS, BDI, CDI, STAI) were* completed by the participant in a quiet room in presence of the experimenter who gave instructions to ensure that conditions were the same for all participants. *HAM-D questionnaires were* completed by a psychiatrist during a semi-structured interview with the participant in a quiet room. *For physical condition assessment,* VO2Max was evaluated by cycle ergometer with an adapted version of the Astrand-Rhyming Sub-Maximal Effort Test, BMI was calculated as weight in kilograms divided by the square of height in meters. Characteristics of participants are providing additional information on origins, education, and family status.
Data source location	Institution: AREA+, Epsylon ASBL City/Town/Region: Brussels Country: Belgium

	Latitude and longitude (and GPS coordinates, if possible) for collected samples/data: Q8VW+39 Uccle
Data accessibility	Data are provided with the present article. Supplement information supporting the data is available from the corresponding author upon reasonable request.
Related research article	Arnaud Philippot, Vincent Dubois, Kate Lambrechts, Denis Grogna, Annie Robert, Ugo Jonckheer, Wagdan Chakib, Alexandre Beine, Yannick Bleyenheuft, Anne G De Volder, Impact of physical exercise on depression and anxiety in adolescent inpatients: a randomized controlled trial. *In review in Journal of Affective Disorder.*

Value of the Data

The database describes the effect of exercise add-on treatment on clinical symptoms of depression, anxiety, and physical condition in inpatients in a psychiatric hospital for adolescents, using a randomized controlled trial (RCT) design that is the best procedure for inference.

The data can provide better knowledge for researchers on the efficiency of exercise treatment or to observe the efficiency of hospitalization for depression and anxiety in adolescents or more globally gather information about the severity of symptoms in inpatients in a psychiatric setting.

The data can provide reference on the impact of exercise treatment on psychological symptoms and cardiovascular conditions to develop future research study design in the field of exercise in mental health.

All psychological data could be compared with physical data that correspond to the cardio-vascular condition.

Data Description

From an RCT evaluating a physical exercise intervention compared to a control group, this Data in Brief provides psychological and physical scores at baseline and after intervention for inpatients in AREA+, a psychiatric hospital for adolescents (Dataset 1). Participants completed self-reports for depression (HADS D, CDI, BDI, SDS) and anxiety symptoms (HADS A and STAI). A semi-structured interview was conducted by a psychiatrist to provide a diagnosis of depression (HAM-D). Physical condition was assessed using BMI and VO2max estimated from an adapted version of the Astrand-Rhyming Sub-Maximal Effort Test. In each group, two participants did not perform the test for estimating the VO2Max because of technical problems or a malaise on the day of physical testing.

Additional descriptive characteristics of participants are provided on age, gender, origin, education, and family history (*Table 1*).

Table 1: Additional characteristics of participants modified from Philippot et al.	**Total n=40**	**Control n=20**	**Physical exercise n=20**
Age	15.4 ±1.6 (SD)	15.2 ± 1.5 (SD)	15.5 ± 1.8 (SD)
Gender			
Male	15 38%	7 35%	8 40%
Female	25 63%	13 65%	12 60%
Origin			
European	27 68%	11 55%	16 80%
European/Middle-Eastern	7 18%	4 20%	3 15%
European/African/South American	6 15%	5 25%	1 5%
Education			
School-level			
≤ 1st cycle	15 38%	8 40%	7 35%
≥ 2nd cycle	23 58%	11 55%	12 60%
unknown	2 5%	1 5%	1 5%
School Attendance			
Regular	8 20%	4 20%	4 20%
Altered	8 20%	3 15%	5 25%
Drop out>3 months	11 28%	7 35%	4 20%
Drop out>6 months	13 33%	6 30%	7 35%
≥ 1 failed year	26 65%	14 70%	12 60%
Experience of bullying	22 55%	11 55%	11 55%

Family						
Status						
Parents living together	11	28%	5	25%	6	30%
Custody by 50% Father /50% Mother	3	8%	2	10%	1	5%
Custody by mainly/only one parent	23	58%	11	55%	12	60%
Other*	3	8%	1	5%	2	10%
History						
Mental health issues**	19	48%	10	50%	9	45%
Alcohol/Substance abuse	10	25%	4	20%	6	30%
Disabled physical disease***	8	20%	4	20%	4	20%
Parent Death****	14	35%	7	35%	7	35%
Youth service support	22	55%	11	55%	11	55%
Preferential tariff or precariousness	13	33%	5	25%	8	40%

* Living in youth center (legal decision)

** Depression/schizophrenia/bipolar trouble in family

*** Cancer, stroke, neurological disease in family

**** Death by accident, severe disease or suicide, concerning closed family

Modified from the co-submission paper : A. Philippot, V. Dubois, K. Lambrechts, D. Grogna, A. Robert, U. Jonckheer, W. Chakib, A. Beine, Y. Bleyenheuft, A.G. De Volder, Impact of physical exercise on depression and anxiety in adolescent inpatients: A randomized controlled trial, Journal of affective disorders (2022).

Experimental Design, Materials and Methods

Design

The design used in the dataset was a randomized controlled trial aimed at evaluating the add-on effect of structured and supervised physical exercise compared to a social relaxation activity in a psychiatric hospital for adolescents for the treatment of clinical depression and anxiety. The participants completed the psychological and physical tests at the baseline three days before the beginning of the programs. We used a fixed randomization procedure. A sequential list of 40 numbers was set up and sealed before beginning the trial, using random permuted blocks of size 2 or 4 at random. Pair or odd numbers in the list corresponded to each of the two treatment arms. Each time an adolescent was recruited, the principal investigator was contacted by email with an entry badge number, blind to identity as well as to data of participant, and he responded by email either pair or odd, according to his list. The two interventions entailed four sessions of 1 hour per week during five to six weeks to reach a total of twenty hours of activity per program. Participants completed on average 18.2 (SD 2.2) sessions in the control group and 18.4 (SD 2.1) sessions in the exercise group. The mean attendance rate was 76% for the exercise group and 79% for the control group. Adolescents completed the same psychological and physical measures to evaluate their evolution three days after interventions.

Chapter III: Exercise in a psychiatric hospital
Study 5

Setting

Data were collected in AREA+, Epsylon ASBL, a psychiatric hospital offering care for adolescents.

The siteweb is : https://www.epsylon.be/index.php/hospitalisations/area

Primary outcomes

The Hospital Anxiety & Depression Scale (HADS) is a reliable and valid questionnaire (230) for hospitalized populations, consisting of seven items (rated 0, 1, 2 and 3) related to anxiety (subscale A) and seven others to depression (subscale D), thus providing two scores. The internal reliability of HADS was good (Cronbach's alpha = 0.79 to 0.86). In each subscale, the score ranges between 0 and 21, with a diagnostic interpretation as no symptoms (0-7), probably pathological (8-10), considered clinical (11-21). From 57 studies including 10 664 participants and 1048 with major depression, a recent systematic review demonstrated a sensitivity (0.74, 95% Confiance Interval (CI) : 0.68 to 0.79) and specificity (0.84, 95% CI : 0.81 to 0.87) for a cut-off value of eight or higher (293). Results from the French version of HADS showed good consistency and good psychometric properties in Western cultures (294) and in the primary care population in Quebec (295), according to other studies in different countries (294) (295).

Secondary outcomes

The Hamilton Depression Rating Scale (HAM-D) is a semi-structured diagnostic interview evaluating depression (277) using the criteria of the diagnostics and statistics manual (DSM), that was administered by psychiatrists who were blind to the therapy group in this study. The HAM-D is still considered as a gold standard for this purpose because it is multidimensional, easy to use by psychiatrists, and has adequate internal and inter-rater reliability (296). The score ranges from 0 to a maximum of 52, and the interpretation is: no depression (0-7), mild depression (8-16), moderate depression (17-23) or severe depression (24-52) (297).

The Child Depression Inventory (CDI) is a 27-item self-assessment tool used in longitudinal follow-up at school that provides a score based on the participant's statements over the preceding two weeks (225). From 54 studies (66 data points, 34,542 participants), the CDI shows good reliability (0.89, CI: 0.86-0.92), sensitivity (0.80, 95% CI: 0.76-0.84), specificity (0.78, 95% CI: 0.74-0.83), and it has a low level of bias (226). The score ranges from 0 to a maximum of 54, and its interpretation is: normal, i.e. mean score in the general population (0-9), moderate (10-18), or pathological (19-54).

Beck's abbreviated Depression Inventory (BDI-13) (229) includes 13 multiple-choice questions. The BDI-13 has a high internal consistency (0.86 for a non-clinical population) and demonstrates good internal reliability (0.89, 95% CI: 0.86-0.92), sensitivity (0.80, 95% CI: 0.76-0.84), and specificity (0.78, 95% CI: 0.74-0.83) (226). The score ranges from 0 to a maximum of

39, with an interpretation of non clinical score if below cut-off (< 8) or pathological score if above cut-off (≥ 8).

The Zung Self-Assessment Depression Scale (SDS) (231) allows to assess the severity of depression according to 20 items. The internal consistency is adequate (Cronbach's alpha = 0.79). A meta-analysis demonstrated that the symptom-specific depressive factors in SDS seem to be relatively robust and well established (298).The score ranges from 0.25 to a maximum of 1, and its interpretation is: no depression (0.25-0.49), mild depression (0.50-0.59), moderate depression (0.60-0.69), severe depression (0.70-1).

The State-Trait Anxiety Inventory (STAI) (299) consists of two subscales with twenty items each, consisting of the STAI, form Y-A, which assesses the recent state (i.e. how participants felt during the test week) and the STAI, form Y-B, which assesses the long-term trait anxiety (i.e., how participants felt in the past year). This test has a high reliability (Cronbach's alpha = 0.86). The internal consistency and test-retest reliability (two weeks) were good among a western Spanish sample in a non-clinical and clinical sample (300). The score ranges from 20 to a maximum of 80, and its clinical interpretation of anxiety is very low (20-35), low (36-45), average (46-55), high (56-65), or very high (65-80) (228).

A medical height gauge and a mechanical doctor's scale were used to measure height and weight for calculating the Body Mass Index (BMI) before and after the intervention.

An adapted version of the Astrand-Rhyming Sub-Maximal Effort Test (301) (278) was used to estimate the maximal oxygen consumption (VO2 max)

using a bicycle ergometer. This method is based on the relationship between heart rate recovery (HRR) and oxygen consumption reserve. In our study, we measured heart rate with a POLAR FT2® heart-rate monitor every minute (starting at rest). The work intensity began at 15 watts with 60 rotations per minute (RPM) and increased by 15 watts every minute to reach a target of 55% of the theoretical maximum heart rate for the age (220 bpm less age in years). When the adolescent reached this target, he/she continued to cycle for an additional five minutes. We averaged the heart rate from the two last minutes of the test.

Correlation between attendance rate and reduction of depression in exercise group

We looked at the correlation between the attendance rate and the difference in the reduction of depression in the exercise group. There was no correlation (for HADS D, r= -0.09, p-value= 0.71, and for SDS, r = 0.33, p-value = 0.15; r stands for Pearson cross-product correlation coefficient).

Sample size

As reported in the co-submission study (210) , to measure variance in depression scores in HADS, the required sample size should be at least 18 participants per group in order to detect a difference of 2.4 at the 0.05 significance level with a power of 82%, and assuming an effect size of 1.0. In our data after interventions, the observed difference was 3.1 between the two

groups of 20 participants; the size of our study has a power of 87% to detect such a treatment effect.

Ethics Statement

Ethics authorization was received from the Ethics Committee of the Faculty of Medicine of the Université catholique de Louvain, and from the local Ethics Committee of Epsylon ASBL (N°. CEHF-2016/17FEV/060-B403201627586). Written informed consent according to the Declaration of Helsinki and 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.

Acknowledgments

We thank the staff of the AREA+ psychiatric hospital for their invaluable professional quality and dedication, including Mrs. S. Pedulla, C. Wilmart and Dr. A. Mairy. We thank R. Araneda, D. Ebner and G. Saussez and the MSL-In team for support and advice.

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CHAPTER IV: Exercise among students in lockdown

Study 6 : feasibility of online High-Intensity Interval Training (HIIIT) [14] on psychological symptoms in students in lockdown during the covid-19 pandemic: a randomized controlled trial.

Published as:

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As this study is already published, responses to the jury members were added to the text as footnotes.

[14] High-Intensity Functionnal Training (HIFT) is more appropriate. For explanations, see footnotes 16.

Abstract:

Objective: We aimed to evaluate the feasibility of an online High-Intensity Interval Training (HIIT) program on clinical psychological symptoms in higher education students in the context of the COVID-19 pandemic lockdown. **Materials and methods**: During the lockdown, 30 students aged 18-25 years, who had been screened previously with a cut-off score ≥ 5 in the Generalized Anxiety Disorder-7 (GAD-7) questionnaire, were randomly assigned to either the four-week HIIT program with three sessions per week conducted through online videos, or a no-intervention control group. The primary outcome was the feasibility assessment. The secondary outcome was a psychological self-report with the 21-items Depression, Anxiety, and Stress Scale (DASS-21). Assessment and intervention were performed in compliance with social distancing rules. **Results:** Two participants in the HIIT were lost to follow-up, leaving 13 participants versus 15 in the control group. We observed high adherence (87%) and complete safety for mental and physical status with the HIIT intervention delivered by online videos. The Mann-Whitney test demonstrated a significant (group x time, p-value=0.046) reduction of clinical stress symptoms and a trend (group x time, p-value = 0.08) towards reduction of clinical depression symptoms, both favoring the HIIT group. No significant (group x time, p-value=0.118) interaction was found for anxiety symptoms. **Conclusion:** The online HIIT program was found to be feasible and safe in a clinical sample of young adults, who were experiencing social and physical restrictions due to COVID-19. HIIT reduced stress and depressive symptoms and thus these preliminary results show promise for broader application among higher education students during the present lockdown necessitated by the global COVID-19 health crisis.

Chapter IV: Exercise among students in lockdown
Study 6

Introduction

The incidences of depression and anxiety symptoms doubled to 21% between 2018 and 2021 in the Belgian adult population, according to data collected during the lockdown necessitated by the COVID-19 pandemic(5). A recent meta-analysis and meta-regression including 226,638 individuals in 60 studies similarly showed a 24.0% global prevalence of depression and 21.3% for anxiety across the world during the COVID-19 pandemic (302); clinically significant symptoms were noted in association with risk factors such as female gender and youth (1, 2). Indeed, during the second lockdown in Belgium (March 2021), 38% of young people (18-29 years) suffered from depression, as evaluated by a Patient Health Questionnaire, and 34% suffered from anxiety, as evaluated by Generalized Anxiety Disorder-7 (GAD-7) (5), in accordance with surveys during COVID-19 waves in Western countries (303-305) (306). Another recent meta-analysis for students in higher education in China (12 studies) and other countries (8 studies) revealed approximate doubling of the prevalences of depression (54%) or anxiety (37%) relative to corresponding results in surveys conducted prior to March, 2020 (2). Generally speaking, young people are apt to experience fears and uncertainties arising from their continued physical and social isolation during pursuit of a degree course. There is evidence for a causal association whereby anxiety precedes depression, such that many young people with depressive symptoms suffer from comorbid anxiety (36). The reduction of physical activity and sports due to constraints from the COVID-19 pandemic contributes to the stress experienced by students in higher education (307). Formerly active individuals who had been obliged to reduce their physical

activity showed more symptoms of depression and loneliness, increased stress, and diminished ratings of positive mental health (308). On the other hand, individuals in the general population who managed to maintain their physical fitness in the face of the pandemic showed a 12–32% lower risk of experiencing anxiety and a 15–34% lower incidence of depression during the COVID-19 pandemic (264).

A recent meta-analysis compiling nine randomized control trials (RCTs), performed before the COVID-19 pandemic, showed a moderate improvement in state anxiety upon engaging in structured physical activity[15], as compared to no intervention or a minimal intervention control condition in groups of children and young people aged up to 25 years (125). However, there is a need for caution in interpretating such results, particularly with respect to establishing the dose-response relationship of different levels of intensity of exercise on anxiety symptoms in young people (125). Indeed, there is currently no consensus on the optimal frequency, intensity, type and duration of exercise to treat anxiety symptoms (125, 309). Moreover, High-Intensity Interval Training (HIIT) has gained increasing interest in recent years and has been ranked among the top fitness trends by the Association College of Sport Medicine (2022). In the adult population, HIIT has been shown to significantly improve cardiorespiratory fitness, cardiovascular function, anthropometric variables, exercise capacity, muscle structure and function (310). In addition, this type of training has been shown to reduce symptoms of anxiety and depression in non-clinical individuals (310) and depressed

[15] The term "physical activity" is too broad and the term "exercise" is more appropriate.

moods in people with severe mental illness (310) with better enhancements than moderate continuous fitness session (310).

In contrast, in young people, HIIT yielded mixed results in depression (194, 201, 311), anxiety and stress decreasing (194, 311-313). Despite the particular context of COVID-19, after restrictions in China, an encouraging RCT demonstrated depression reduction by running training supervised in person in a clinical sample in middle school (314). Concerning stress and anxiety, HIIT has raised questions about its impact on generating or reducing mechanisms (315). However, whereas the COVID-19 pandemic was a trigger for stress and anxiety in youth, home-based HIIT demonstrated a positive effect on symptoms of stress, anxiety in young people (312) and depression in adults (316), as well as showing a strong beneficial effect on moderate to severe anxiety symptoms pre-existing the pandemic (317). The inconsistency in results could be explained by the fact that the impact of HIIT has been overlooked on anxiety and stress disorders, as reported in a recent meta-analysis (318).

Therefore, given the deterioration of physical and psychological status observed in young people following the onset of the COVID-19 crisis, we sought to investigate the feasibility of an online HIIT intervention in a Belgian tertiary education student sample (aged 18-25 years) screened for clinical symptoms of anxiety during the lockdown arising from the COVID-19 pandemic. In addition, we also aimed to analyse preliminary findings on depression, anxiety, and stress symptoms after online HIIT. We hypothesized that the participants in the online HIIT would show better improvement in psychological symptoms compared to a passive control group.

Methods

Trial design

We conducted a RCT to evaluate the feasibility of online HIIT intervention on psychological symptoms compared to a passive control group in tertiary education. The HIIT intervention entailed three sessions of ten minutes per week and lasted for four weeks. Baseline and post psychological testings were carried out the week before and after the 4-weeks follow-up. For the complete Consolidated Standards of Reporting Trials (CONSORT) checklist, please see Supporting Appendix S1.

Participants

Participants were recruited in a physical therapy higher education setting (Haute Ecole Bruxelles-Brabant (HE2B), Brussels, Belgium). We offered them to participate in the study by contacting them through an email sent to all students in the month prior to the start of the study. We recorded descriptive characteristics and medication status of participants. Screening of general anxiety of participants was assessed with the GAD-7 (319). Written informed consent according to the Declaration of Helsinki and medical history was obtained from each participant. The study was approved by the Bio-Ethical Committee for Research and Higher Education, Brussels (N° B200-2020-088).

COVID-19 lockdown conditions

Sciensano, the Belgian research centre and national public health institute in charge of the pandemic statistics, reported that 21% of intensive care beds were occupied by COVID-19 patients in March 2021. The transmission rate was 1.02, and 288 of 100,000 Belgian citizens were infected on average per day in March 2021 (5). In response to the burgeoning caseload, Belgian government had decided to order closed the majority of non-essential shops, as well as sports clubs. The restrictive measures lasted between October 26, 2020 and June 9, 2021. A curfew was introduced from 10 pm to 6 am in Brussels, the capital city.

Eligibility criteria

The inclusion criteria for participants were being a student in higher education, age between 18 and 25 years, having a score ≥ 5 in GAD-7, and accepting the principle of randomization in the trial. The exclusion criteria were refusal to participate, neurological history such as illness or head trauma, present severe and unstable respiratory disease, history of heart defect or cardiovascular disease or any other medical conditions prohibiting high-intensity sport or physical activity, substance abuse, i.e., alcohol or drugs, and being a high-level athlete. A comprehensive self-questionnaire was provided to students to collect all medical conditions to inform potential exclusion criteria and ensure safe participation.

Randomization and blinding

The week before and after the intervention, the students completed the DASS-21 questionnaire. Participants were anonymously assigned sequentially to one of two groups (HIIT and control group) using permuted block

randomization with secret assignation. During the intervention sessions, therapists and participants were unaware of the individual scores used for randomization. The analysis was carried out in unlabelled group datasets.

High-Intensity Interval Training group[16](320-322)

The HIIT intervention was conducted with session videos produced by a physical therapist (PM), which were available on an online platform for the participants. Table 1 displays two variants of sessions based on the main variables that can be manipulated to prescribe a HIIT session (323). Participants were free to decide when they wanted to perform their sessions during the week. We recommended having a rest day between sessions due to the high-intensity effort produced. The intervention consisted of 12 structured sessions of bodyweight intermittent aerobic and muscular strengthening exercises, designed to remedy a decline of aerobic fitness in lockdown (324). A block of three sessions to complete was sent to participants each week for four weeks, to a total of 12 sessions. Each session entailed alternating of High-Intensity Intervals (HIT) and active recovery intervals, each lasting 30 seconds to reach ten minutes. It was depicted by the Table S1 in the supplementary information. The HIT comprised, for instance, jump squats, burpees, mountain climbers, jump forward lunge, jumping jack

[16] The term "HIIT" is used for aerobic programs, performed for instance on treadmill or cycloergometer. HIIT exercise is characterized by relatively short bursts of repeated vigorous activity interspersed with periods of rest or low-intensity exercise for recovery. In our study, we provided varied exercise based on body weight movements with high intensity. Therefore, another term might have been more appropriate, namely High-Intensity Functional Training (HIFT) (320-321). HIFT uses varied and consistent functional exercise and varying durations of activity with or without rest (321), corresponding to our protocol. Interestingly, in healthy individuals, a meta-analysis from 3 studies, found no difference in VO2Max levels after chronic program between HIFT and HIIT (322).

with a Rate of Perceived Exertion (RPE) of 6 or greater (1-10)[17] (312, 325, 326), following the modified Borg Analog Scale, which corresponded to a HRmax at least 80% (327). The active recovery intervals included plank, lateral plank, push-up, squat at a requested RPE of 4 or less. We encouraged to maintain the required intensity during each interval of the sessions. To promote motivation, each session was videotaped in different outdoor and indoor locations. All exercises employed own body weight for resistance, without use of special equipment. The HIIT sessions were carried out at the participants' home, thus in compliance with social contact regulations.

[17] Borg's Perceived Exertion Index (PEI) is a widely used psychophysical tool to assess subjective perception of exertion (ACSM). The PEI was used primarily for aerobic exercise according to the "Guidelines for Monitoring Aerobic Exercise Intensity," published by the ACSM, in Appendix 1. One of the program based on functional strengthening is not aerobic. Therefore, caution is warranted on the interpretation of the results.

Table 1: Two variants of HIIT sessions

Bodyweight HIIT circuit, variant 1		
Bear Back and forth squat jump Plank Ice skater Squat pulse Burpees Squat hold Back and forth lunge (left side) Superman breaststroke Back and forth lunge (right side)	30 s per exercice interval	Alternating between High intensity exercices (30s) ≥ 6 RPE and active recovery exercices (30s) < 4 RPE
Repeated twice		

The 10-minutes session consisted circuit of 10 exercises (30 seconds each), repeated twice.

Bodyweight HIIT circuit, variant 2		
Lateral lunge Run on the spot Back lunges Jumping jack Spider plank Diagonal knee kick, right hand/ankle touch Squat Diagonal knee kick, left hand/ankle touch Squat hold Floor touch jump squat	30 s per exercice interval	Alternating between High intensity exercices (30s) ≥ 6 RPE and active recovery exercices (30s) ≤ 4 RPE
Repeated twice		

The 10-minutes session consisted circuit of 10 exercises (30 seconds each), repeated twice.

Participants recorded their participation in the sessions in weekly reports sent to the trainer, who regularly guaranteed the monitoring for safe participation. These reports included attendance at the three sessions per week, their rate of perceived exertion, and possible questions about recovery, movement execution, and other issues addressed. The global RPE was assessed by the modified Borg Analog Scale (0-10) at the end of each session, as is standard in clinical studies (328). Participants were given a descriptive document indicating the corresponding intensity for each level between 1 and 10 (329),

assuring validity and good reliability (327). Participants were physical therapy students and underwent fitness training during their course of study, ensuring proper execution of movements and knowledge on HIIT principles before starting the study.

Control group

Participants were requested to continue their usual activities without particular modification.

Feasibility primary outcome

We evaluated the feasibility of the online HIIT intervention compared to a passive control group in the specific context of closure and distance measures imposed by the COVID-19 spread. We analysed several outcomes: mean program adherence, individuals completed their sessions in a document sent each week to the supervisor; dropout rate per intervention; protocol monitoring with the collection of the mean RPE per session for each participant with the modified Borg scale (328); and safety concerning participants mental and physical progress with the psychological outcome and participant feedback.

Psychological secondary outcome

The Depression, Anxiety, and Stress scales - 21 Items (DASS-21) (330) is a set of three self-reports. For each scale, there are seven questions (rated 0, 1,

2, and 3) related to depression, anxiety, and stress, thus providing three scores, each ranging from 0 to 21. The depression scale assesses dysphoria, hopelessness, devaluation of one's life, self-deprecation, lack of interest/involvement, anhedonia, and inertia. The anxiety scale assesses autonomic arousal, skeletal muscle tension, situational anxiety, and the subjective experience of anxious affect. The stress scale is sensitive to levels of chronic non-specific arousal, assessing difficulty in relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive, and impatient. Scores for the three dimensions were calculated by summation, and the final severity score was obtained by multiplying by two. The DASS-21 has shown excellent internal consistency and temporal stability in large clinical samples (331).

Sample size

The sample size was calculated from a previous RCT, wherein we had evaluated Beck anxiety inventory scores after two weeks of physical exercise in tertiary education students suffering from clinical anxiety symptoms (332). To detect a decline in -8 points out of the maximum of 42 in the DASS-21 at the 5% significance level with a power of 85%, and assuming a standard deviation of seven points, we calculated a sample size of at least 15 participants per group.

Statistical analysis

The Mann–Whitney test was performed to determine the difference between the two groups over time regarding the outcomes for psychological scores. All statistical procedures were performed using the SPSS software (IBM SPSS Statistics 27.0). The group identity of the data was anonymized for the statistical analysis. Results were reported along with their 95% confidence intervals (95%CI). A p-value <0.05 was considered significant. The Empirical Rule Effect Size (ERES), defined at one half SD from the baseline score, was used to define clinically significant effect sizes of the treatment (333). A Pearson correlation analysis was performed on psychological symptoms between the baseline and difference scores (T1-T2) in the HIIT group to observe whether the level of symptom severity could be related to change over time.

Results

Study sample

The experimental period ran from March 5, 2021 to April 2, 2021. Among the 30 students recruited at the baseline, two members of the HIIT were lost to follow-up (see Flow-chart, Figure 1 for details). The statistical analysis of pre-and post-test measures was thus restricted to the remaining 28 participants. The control group consisted of 14 women and 1 man of mean age 20.93 years (SD 1.94), whereas the final HIIT groups contained 11 women and 2 men of mean age 20.69 years (SD 1.44). For details of the study

population, see Table 2. We calculated The Metabolic Equivalent of Task (MET) per hour to measure their physical activities following the updated compendium (179) and classified them per week following the recommendations from WHO (2021).

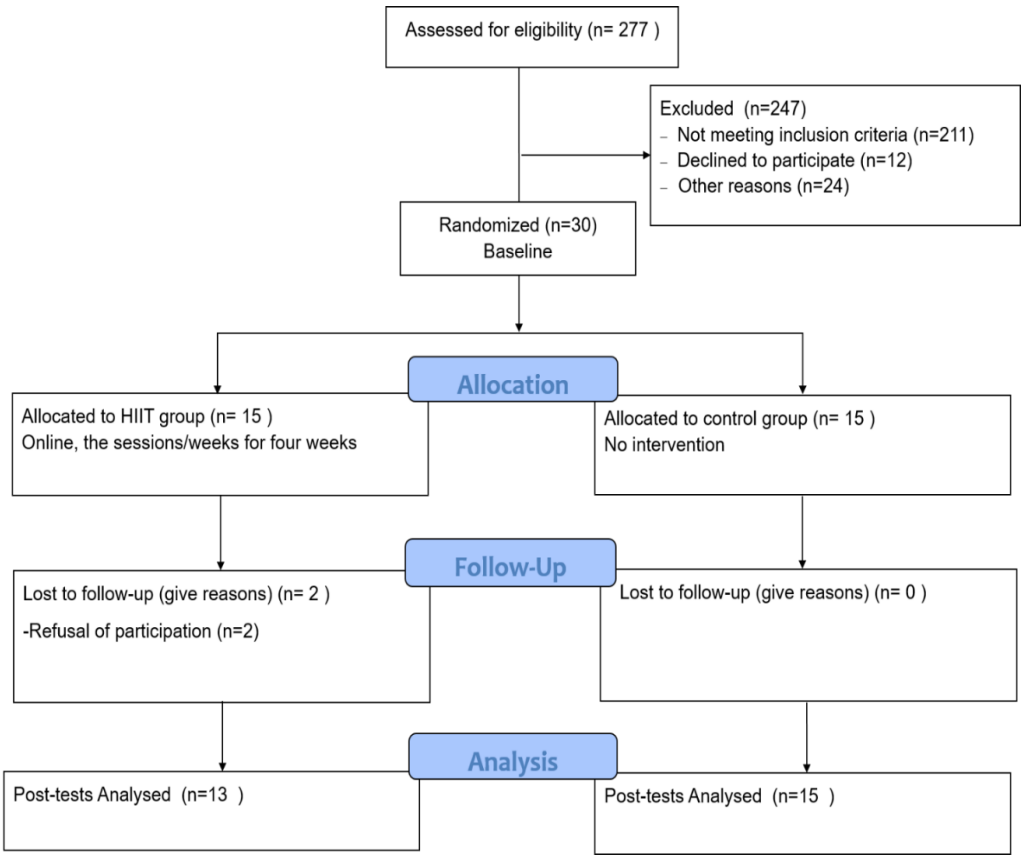

Figure 1: Consort Flow-Chart

Table 2: Demographic characteristics of participants

	HIIT (n=13)	Control (n=15)
Mean Age (SD*)	20.69 (1.44)	20.93 (1.94)
Gender		
Female	11	14
Male	2	1
Others	0	0
Mean BMI (SD*)	22.67 (4.21)	21.35 (3.01)
Living environment (Family, cohabitating, alone)		
Alone	2	1
Cohabitating	6	7
Family	5	7
Daily physical activities (MET.hour per week) (†)		
(<7.5 MET)	6	8
(7.5 – 15 MET)	5	4
(>15 MET)	2	3
GAD severity		
GAD 5-10 (mild)	5	7
GAD 11-15 (moderate)	5	5
GAD 16-21 (severe)	3	3
SARS-2 infection (‡)	3	3
Co-morbidities		
ADHD	1	3
Eating behavior problems	1	0
Tobacco dependence	1	5
Physical disease	1	2
Antidepressant or anxiolytic medication	1	0
Family history of mental illness (1st and 2nd degree relatives)	6	4

Legend for table 2 : SD=Standard deviation; (†) 7.5-15 Metabolic Equivalent of Task (MET) is recommended by the World Health Organization 2021; (‡) SARS-2 infection diagnosed before the study

Feasibility primary outcome

In the HIIT group, the mean participation rate was 87%, and the dropout rate was assessed at 13.33%, with two participants lost because they refused to continue. The overall intensity set per session for each participant by the modified Borg scale (1-10) demonstrated a mean of 5.77 (SD 1.29), which is considered "hard" and a good execution of the intense effort provided by the participants. Regarding the safety assessment, the HIIT intervention did not reveal any increase in psychological levels, with the exception of one participant with a higher anxiety score of 2, increasing from 2 to 4 on 42-point scale anxiety of DASS-21. The control group yielded higher scores for 7 participants, including 5 for anxiety, 6 for stress, and 3 for depression scales in the DASS-21. The students reported no adverse physical events, except for stiffness due to the heavy exertion.

Psychological secondary outcome

Scores and the level of severity according to the pathological thresholds at baseline and after intervention are presented in Table 3. In the stress scale of DASS-21, the Mann-Whitney test revealed a significant (group x change from baseline) interaction ($p = 0.046$) in favor of the HIIT group (Table 4 and Figure 2). After the intervention, students in the HIIT group had a mean decline (T1-T2) of 7.5 points on the 42-point scale [95% Confidence Interval (CI), 5.3 to 9.8] in their stress symptoms, progressing from a mean score indicating moderate stress symptoms, to a mean mild score. Students in the control group had a mean decline (T1-T2) of 2.5 points [95% (CI), -1.9 to 6.9] in their stress symptoms, this remaining on average at a moderate stress score. In the depression scale of DASS-21, Mann-Whitney test revealed a

trend interaction (p = 0.080) in favor of the HIIT group (Table 4 and Figure 2). After the intervention, students in the HIIT group had a mean decline of 9.5 points [95% (CI), 5.4 to 13.7] in their DASS depression symptoms, thus progressing from a mean score of moderate depression to a mean normal score. Students in the control group had a mean decline (T1-T2) of 3.7 [95%(CI), -1 to 8.4] in their depressive symptoms, thus progressing on average from a score of moderate depression to one indicating mild depression. In contrast, the Mann-Whitney test showed no significant interaction (p=0.118) in T1-T2 anxiety score changes between groups (Table 4 and Figure 2).

A correlation analysis was performed to determine if a connection existed between the severity at the baseline and the reduction over time in psychological scores in the HIIT group. A significant and negative result was found for depression (p-value =0.004, r=-0.734, Pearson correlation), meaning that higher depression scores at baseline have a high potential to decrease. No significant result was shown for stress and anxiety (all p-values > 0.05, Pearson correlation).

In the HIIT group, the mean score of improvement in symptoms of stress (7.5) exceeded the ERES score (4.4) and as did likewise the mean improvements in depression (9.5) compared to its corresponding ERES (4.8), demonstrating a clinically significant effect size of HIIT treatment. In the HIIT group, all 13 participants experienced a reduction in their stress scores, while only 8 of 15 (53%) of control participants experienced a reduction, versus 6 of 15 (40%) who experienced a worsening, and one of 15 (7%) with unchanged stress.

Figure 2: Graphs of depression, anxiety, and stress scales from DASS-21

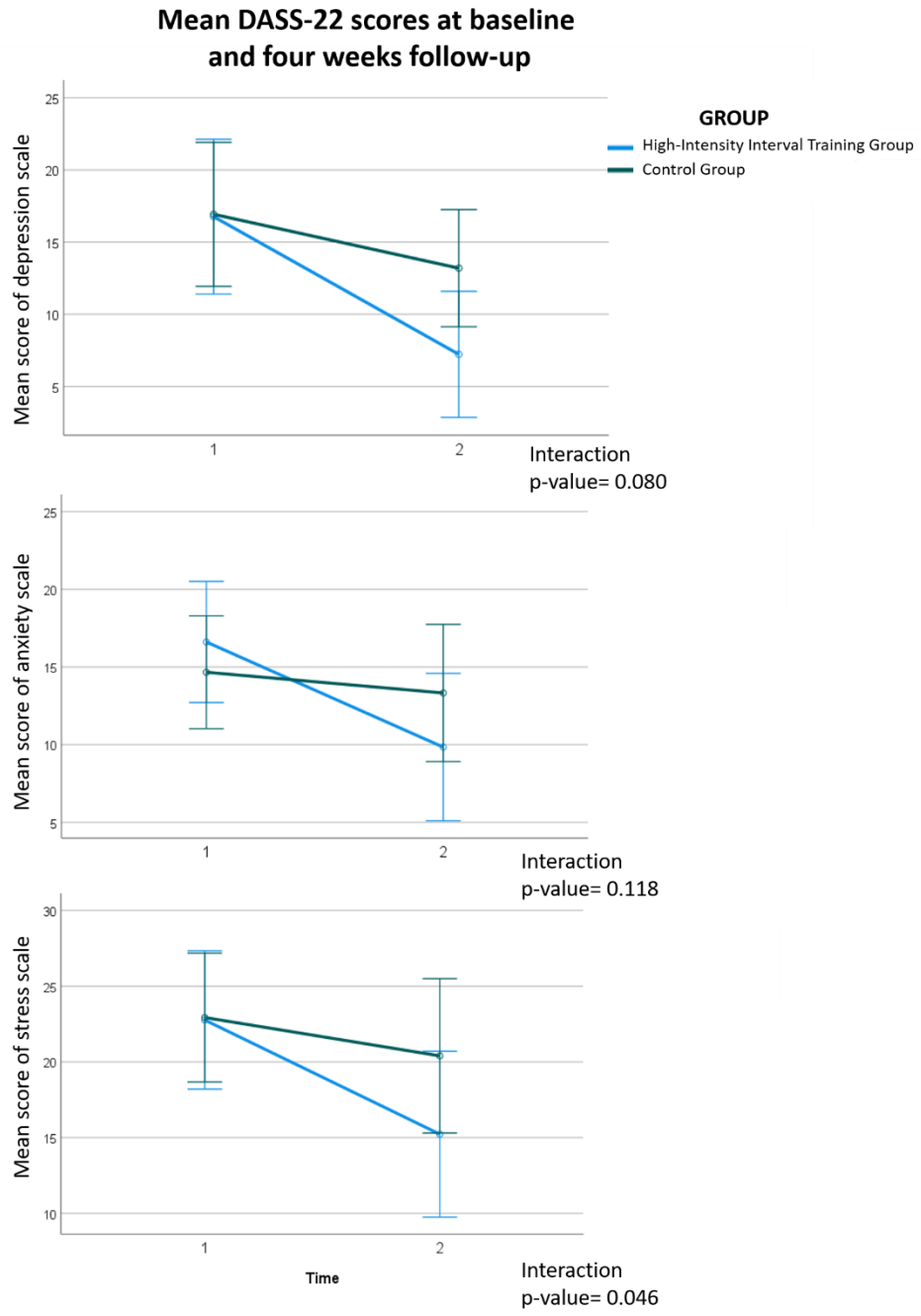

Table 3: DASS-21 Assessment

DASS-21	**Baseline**			**Post-intervention**		
Symptoms	Depression	Anxiety	Stress	Depression	Anxiety	Stress
HIIT group (n=13)						
mean (SD)	16.8 (9.6)	16.6 (7.2)	22.8 (8.7)	7.2 (6.6)	9.8 (7.5)	15.2 (8.3)
median (Min-Max)	16 (4-32)	18 (4-26)	22 (12-38)	4 (0-22)	8 (2-26)	14 (2-32)
Severity						
Normal	4	2	3	9	6	8
Mild	2	0	3	2	1	2
Moderate	1	3	1	1	3	1
Severe	6	8	6	1	3	2
Control group (n=15)						
mean (SD)	16.9 (9.2)	14.7 (6.5)	22.9 (7.3)	13.2 (8.5)	13.3 (8.9)	20.4 (10.6)
median (min-max)	16 (4-32)	14 (6-26)	22 (10-34)	12 (0-26)	14 (0-34)	22 (6-42)
Severity						
Normal	4	1	3	5	4	5
Mild	1	3	2	3	0	1
Moderate	5	5	3	4	4	4
Severe	7	6	7	3	7	5

Table 4: Results from the Mann–Whitney test on the difference (T1-T2) in intervention and control groups

	HIIT group				**Control group**				Interaction
	n	Mean	(SEM)	[95%CI, Lower to Upper]	n	Mean	(SEM)	[95%CI, Lower to Upper]	p-value*
DASS-21									
Depression									
Symptoms	13	9.5	(2.1)	5.4 13.7	15	3.7	(2.4)	-1 8.4	0.80
Anxiety symptoms	13	6.8	(1.7)	3.5 10.0	15	1.3	(2.7)	-3.9 6.6	0.118
Stress symptoms	13	7.5	(1.1)	5.3 9.8	15	2.5	(2.2)	-1.9 6.9	0.046

*Legend : *Evaluated by Mann-Whitney test*

Discussion

We undertook a RCT to test the feasibility of participating in a brief, online HIIT program that could decrease scores of clinical anxiety, stress, and depressive symptoms compared to a passive control group from sample of students undertaking higher education, while screening with the GAD-7 for symptoms of anxiety, during a government mandated lockdown context during the COVID-19 pandemic. The HIIT intervention was considered feasible with high adherence (87%), acceptable dropout rate (13%), and safe intervention for physical and mental health. As predicted, HIIT group enjoyed a significant decrease in stress symptoms and a trend for reduction of depressive symptoms as compared to the control group. Contrary to expectations, we did not find that the intervention reduced the extent of anxiety experienced by the participants.

The HIIT intervention exhibited high participation, limited participant dropout rates, and good tracking of the intensity of effort produced during the sessions. Online training with short 10-minute sessions, freedom to decide when to practise, and weekly supervision appeared to work well. Previous studies with an online exercise intervention in youth have also demonstrated good adherence and a correct dropout rate in adults with HIIT during confinement imposed by COVID-19 with 77.78% and 22% (316) and a moderate aerobic program in college students with 92.08% and 3.33% (200). Another online HIIT during the COVID-19 pandemic in youth revealed no dropouts but did not inform adherence (312). In contrast, a face-to-face HIIT

session with university students resulted in lower average participation of 66.7%, likely due partly to the chosen schedule (8:15 am) (334). The online mode with the freedom to decide when you want to train, as we performed, could be interesting to continue to be explored. HIIT did not produce any adverse effects for physical and mental health safety in the present study. Only one participant slightly increased his anxiety score, but it could be negligible due to his weak score under the cut-off. Moreover, the difference is striking when compared to the control group, where seven participants observed a deterioration in one or several psychological symptoms. Being a student during the COVID-19 pandemic, accentuated by a state of confinement, may expose these youth to more negative emotions (1, 2). As previously suggested, exercise[18] may have a protective effect on mental health (133, 216). Our HIIT intervention may have revealed this protective effect during a major social crisis compared to the control group. Finally, our results are consistent with those of the face-to-face HIIT intervention, with average adherence rates greater than 80% and no acute injuries throughout the population, according to a meta-analysis of 33 systematic reviews(310). Attendance is crucial to achieving effective exercise treatment in mental health (133, 216). Our online HIIT might be a feasible intervention strategy for the prevention and treatment in mental health. Despite this promising result, our sample size is small, and further work is needed to establish the viability of online HIIT in a clinical sample of youth.

The robust reduction of depressive symptoms in the HIIT intervention group was in line with a previous systematic review and meta-analysis (89), and also

[18] The term "exercise" is specific and the term "physical activity", being broader, is more appropriate here.

in accordance with our recent RCT on the effect of physical activity[19] in young people (aged 12-25 years) experiencing a present diagnosis or threshold symptoms of depression (210). Following the high and negative correlation (r=-0.734) between the severity of depression and its reduction in the HIIT group, this intervention may be considered as an efficient antidepressant for clinical symptoms. The antidepressant effect of HIIT in this present study could be explained by biological and psycho-social mechanisms (133). In the brief course of our four week program, we suppose that clinical improvement might reflect neuroplasticity pathways involving such factors as improved brain-wide vasculature function, a well as neuronal effects mediated by neurotrophin release. Downstream effects on neuroendocrine response, neuroinflammation, and oxidative stress may also contribute to the improved depression scores in the HIIT group (335, 336). Regarding psycho-social mechanisms, exercising participants might experience improved physical and body image self-perceptions. While brief in duration, completing our HIIT program is a difficult task calling for a considerable expenditure of effort. Thus, it may suffice to improve participants' skill mastery and lower their barriers against self-efficacy. HIIT may also simultaneously enhance the quality of sleep and depression and thus could be a good complement to current therapeutic modalities (337). The reductions in depression and perceived stress favoring the present HIIT group also seem in accord with two systematic reviews concluding that initial first positive effects of HIIT on mental health are mediated by acute improvements in cardiorespiratory fitness. However, those studies were conducted in older subject groups with history of psychiatric illness (310, 338). Previous tests of

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an HIIT program in younger subjects did not indicate significant changes in depression symptoms (201). This difference might reflect differences in participant samples or HIIT design or their context preceding the onset of the COVID-19 pandemic and associated restrictive social measures.

Unexpectedly, we did not find any effect of the HIIT on the extent of anxiety experienced by our participants. Present results are thus at odds with a recent meta-analysis showing that physical activity[20] could help to alleviate anxiety symptoms in young people (125). However, that study did not address the clinically relevant anxiety considered in our study, nor did it consider specific effects of the pandemic on anxiety. Furthermore, the changes in anxiety in the present study, although not significant, showed a moderate effect size (Cohen's d = 0.8). Hence, the p-value (p=0.118) for the interaction does not exclude the possibility that a larger sample might have yielded significant results; given the variances in anxiety scores, we can estimate that a population size of 20 per group might suffice to detect effects of the intervention. An additional consideration is that our participants had at recruitment elevated scores of trait anxiety on the GAD-7 score, such that their specific anxious symptoms might have been more resistant to the intervention. Given the mixed results for RCTs against anxiety (194, 201, 316, 317, 334) we see a need for further investigation of the impact of HIIT on anxiety symptoms. A clinical sample screened for anxiety may show better improvements (312, 317). It seems that severity of anxiety, current fitness, exercise[21] history, and exercise volume may be moderating factors for

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[21] The term "exercise" is specific and the term "physical activity", being broader, is more appropriate here.

changes in cardiovascular and mental health after HIIT. Still, the mechanisms explaining their interactions are not clearly elucidated (201, 309).

The social isolation exacerbated by lockdown during the COVID-19 pandemic has detrimental psychological effects resembling those seen previously in diverse contexts such as space travel, polar or submarine expeditions, prison detention, certain military situations, or for patients in intensive care units (339). Therefore, we see prospects for a general utility of HIIT interventions in circumstances enforcing social isolation. The high adherence (87%) observed in our online HIIT intervention group indicates good tolerance, and may reflect its positive effects on wellbeing, notably with respect to reduction of depressive symptoms.

Strengths and limitations

We demonstrated a feasible trial with high adherence (87%) with the HIIT intervention delivered by online videos. Safety was assured for participants mental and physical health who practised HIIT, with even a potential protective effect in mental health during the current social crisis. This is the first RCT demonstrating a positive impact of HIIT on psychological[22] symptoms in a clinical sample of adult students in higher education. Furthermore, we tested the effect of the intervention in the context of

[22] The use of "a positive impact of HIIT on psychological symptoms" is not correct due to the broad meaning of the word "psychological". Therefore, it is more appropriate to report "…a significant impact of our physical exercise on stress and a tendency to be significant on depressive symptoms …".

lockdown during the COVID-19 crisis, which is a distinct stressor and risk factor for this population.

However, we must exercise caution in the interpretation of the preliminary results in our feasibility trial, given the small sample (n=28), which may have been insufficient to detect effects on anxiety scores. We see scope for testing dose-effects of the intervention, as well as the long-term effects of the intervention on psychological scores. Due to circumstances of the COVID-19 pandemic, the HIIT providers were not present face-to-face during the sessions, which might have reduced the quality of follow-up, although we did supervise participation online. The participants were physiotherapy students, which could contribute to their strong adherence to the program. The HIIT group received more attention than the passive control group, which may be involved to some extent in the improvement in psychological symptoms. For generalization of present results, we need to investigate a broader group of participants from the general population.

Conclusions

Our study could be considered feasible and safe. The preliminary observations supported our hypothesis that the HIIT intervention could reduce stress and with a tendency depression symptoms in a clinical sample of adult students engaged in tertiary higher education during a challenging lockdown period of the COVID-19 pandemic. The analysis was unable to demonstrate a significant impact on anxiety. Further studies are recommended to confirm and extend these positive effects of the HIIT program on the mental health of young people, notably in a broader

population and with consideration of possible dose-effects of a longer HIIT program. In addition, the neurobiological, psycho-social, and behavioural mechanisms induced by HIIT need to be explored to understand better its effect on mental health in a clinical sample of youth.

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DISCUSSION

Discussion

The present dissertation aimed to investigate the anti-depressant and anxiolytic effects of structured physical exercise on youth mental health.

Chapter I explored exercise programs that reduce clinical and non-clinical depression in youth (10-24 years) with a systematic review (Study 1). Of the 25 included trials (22 RCTs and 3 RTs), this systematic review reported that the physical exercise program appears to be an antidepressant intervention in youth. It highlighted that exercise was particularly efficient in the decline of moderate to severe depression. The addition of exercise therapy to usual mental health care also demonstrated a reduction in further depression. This strongly suggests that exercise therapy should be considered to alleviate distress in youth. However, the lack of information regarding exercise protocols, the amount of peer social interaction induced, program adherence, and dropout rates implied a cautious attitude in interpreting the results. In particular, it was difficult to define the optimal dosage because of the lack of specific descriptions in the included articles. We suggested using more valid instruments to quantify intensity, such as a cardiovascular monitor.

Chapter II investigated the efficiency of two exercise programs regarding two different intensities, high intensity and low to moderate intensity, in decreasing symptoms of depression and anxiety in preadolescents (9-12 years old) at school (Study 2) (185). The results of the two groups were examined separately and we found that CDI (depression self-report scale) and STAI-B (anxiety self-report scale) scores decreased significantly over time in the low-to-moderate intensity group (LMIG). Significant group x time effect was found for anxiety in favor of LMIG but not for depression symptoms. Finally, the case of a young student, Andy, who was bullied, was reported to illustrate

the potential effect of exercise on school well-being (Study 3) (340). It was noticed that exercise, at low-to-moderate intensity, implemented in the form of games, exerted a beneficial impact over time on the bullied participant's mental and physical health.

Chapter III presented the first randomized controlled trial comparing the effect of an add-on exercise program to a control social relaxation program in a psychiatric hospital for adolescents (Study 4) (210). Compared with social relaxation, the exercise intervention resulted in a better significant reduction in depressive symptoms after 6 weeks. Contrary to our initial expectations, both interventions exhibited similar benefits in reducing anxiety. Both groups had poor cardiovascular fitness at baseline, which improved significantly in the exercise group only. Exercise appeared to be an effective adjunct antidepressant intervention integrated with substantial, multidisciplinary care. These findings are critical for adolescents with depression, to the benefits to their physical and mental health.
The dataset, participant characteristics, and tools were reported in a supplemental article (Study 5) (276). These data allowed researchers to (1) gain insight into the effectiveness of exercise treatment (2) observe the effectiveness of hospitalization for depression and anxiety in adolescents (3) gather more global information on symptom severity in psychiatric inpatients. In addition, these data also reported the impact of exercise treatment on psychological symptoms and cardiovascular conditions to develop future research study designs in the area of exercise in mental health care.

The chapter IV described the results of a randomised controlled trial comparing online high-intensity interval training to a passive control group

to reduce the psychological symptoms in higher students during the lockdown induced by the COVID-19 health crisis (study 6) (214). As predicted, the HIFT group demonstrated a significant decrease in stress symptoms and a trend for reduction of depressive symptoms as compared to the control group. Clinically significant effect sizes of the treatment were obtained for stress and for depressive reductions by exercise. A correlation also revealed that higher depressive symptoms were better relieved by the HIFT intervention, suggesting its value in clinical depression. Contrary to expectations, we did not find significant interactions after intervention for anxiety experienced by the participants. We should mention that in Chapter IV we used the term HIIT for the training program but HIFT is more appropriate for the functional exercises used in the experimental program.

The anti-depressant effect of exercise

Exercise: a protective effect against depression?

The exercise interventions in the non-clinical sample appeared to display a discrete antidepressant effect in this dissertation. No difference was found between low- to moderate-intensity and high-intensity exercise programs on independent analysis, except for a time effect for depression reduction (203). However, we calculated that a larger sample might highlight significant interaction results for low-to-moderate intervention. Comparison to others studies is difficult due to few available data in this age range. Our trial, described in Chapter II, was the only one including a non-clinical pre-adolescents as shown in our systematic review in chapter I. Our systematic review was thus unable to reveal a real impact of depression reduction score

in non-clinical sample in pre-adolescents but also in adolescents, mainly due to the lack of studies. In addition, the sensitivity of tests, such as CDI, BDI and SDS may be insufficient to capture the impact of exercise interventions in a nonclinical sample. However, in young adults, several RCTs have been published demonstrating depression symptoms decline, calling for further studies in younger age.

Cohort studies have shown that participation in daily physical activities could prevent the development of MDD over time (21, 121). Physical activity seems efficient as a protective intervention to the development of subclinical symptoms in young people. Furthermore, none of the studies incorporated in this manuscript, including in the systematic review, highlighted a worsening of depressive symptoms after exercise programs. This is in afreement with recent systematic reviews in the field (168). Subthreshold depression in young people may be underestimated and could be less detected. Depressed mood and sadness are not always at the forefront of depressive symptoms in this age category. The specific expression of depression in children and adolescents may convey irritability, behavioural troubles (hetero-aggressivity, running away, delinquency, bullying) and dropout at school (11, 20). These attitudes could lead to distress going unnoticed. However, untreated psychological suffering may lead to the development of psychiatric disorders in the future (34, 35). Bullying at school, for example, as reported in Chapter II with Andy (340), should never be overlooked because it could be a sign of psychological distress (241). The young people with uneasiness are frequently victims or persecutors (239). Chapter III, half of our recruited adolescents experienced a history of bullying. Therefore, early and careful identification by supervisors and, in addition, bullying prevention in school

and higher education should be implemented. In this perspective, regular physical activities could be encouraged to favour positive mental health development and prevent these types of behaviours.

Further research should then be conducted with a broader mental health assessment to better capture the different psychosocial components that express in depression in adolescence to explore the potential protective effects of exercise as a preventive strategy for depression in association, for example, with self-esteem, self-efficacy, body satisfaction and social support.

Exercise treatment

Antidepressant effects of exercise programs are observed in our depressed samples studied from the psychiatric hospital (210), in higher students who had scores above the cut-off (chapter IV) and in our systematic review with 12 RCTs among a total of 14 reporting in young people (10-24 years) with clinical symptoms. This is congruent with previous systematic reviews showing reduction in depression after exercise interventions above the cut-off in adolescents (126, 127) and young adults (89). Furthermore, we revealed a specific effect on decreasing of moderate to severe depression in adolescents and young adults (chapter I).

In addition, our chapter I also highlights that it is a promising add-on approach in young people. Exercise combined with in- or out-patient care seems to alleviate depressive symptoms: with psychotherapies (187) (169), with drugs treatment (169, 188, 189) and among youth with major depression treated in multi-disciplinary care (170). The effect is also supported by our study described in chapter III (210). Our RCT is the first that have been carried out

in a psychiatric hospital for adolescents with substantial cares and exercise demonstrated good results on depression and participation rate (210). Then, these encouraging first results need to be confirmed to support implementation of exercise in mental health hospitals for young individuals. High-quality RCTs would be required to examine whether individual factors (e.g., diagnosis, medications, age at onset, length of hospitalization, and treatment history) affect the extent to which exercise reduces depression.

A potential factor that may explain the antidepressant effect of exercise is the regulation of BDNF. In a meta-analysis, in young adults, an increase in BDNF was correlated with the execution of a single moderate to vigorous aerobic session (341). The involvement of neurotrophic factors in neural plasticity and regulation of neural function could be involved in the improvement of executive functions (48). We suggested that a similar phenomenon might be observed in our study after the sessions performed by the hospitalized adolescents in Chapter III. Indeed, these young people improved their cardiorespiratory level after 6 weeks after an average of 18 sessions, suggesting induced neurotrophic factors, potentially related to the reduction in depression observed. An interesting trial in psychiatrically hospitalized adolescents with MDD revealed that two different exercise therapies, aerobic and strengthening programs, induced higher BDNF levels compared to usual treatment (211).

Another potential explanation for depression reduction by exercise is the positive effect on executive functions. Indeed, poorer functions have been found in depressed teenagers (54, 55) whereas better scores tend to predict greater evolution in mental health (56, 155). In adolescents with clinical depression, there are few data but the preliminary results are encouraging. In

inpatients teenagers, a first feasibility trial yielded an improved inhibitory control after a single fitness session (12-min of circuit training consisting of 4 full body exercises) (155).

Changes in neurotrophic factors and executive functions, both potentially related (107), might also be driven not only by the exercise per se in depression, but also by the characteristics of interventions and the context in which it is performed. We hypothesize that our programs conducted as games stimulating neuropsychological and affective responses might contribute to a potential better improvement of executive functions. On one hand, combining physical and cognitive activities seems to have a larger impact on executive functions in adults with depression symptoms than with aerobics standard program (342). On the other hand, complex and varied movements, requiring adaptation to a dynamic environment encouraging social and emotional development could be a better way to improve neuropsychological tests than standard treadmill and cycle ergometer aerobic exercise (151, 154). In summary, the production of neurotrophic factors and the subsequent improved executive functions may predict larger improvements in the treatment of adolescents with mental illnesses (56, 155). This should be specifically studied in future protocols through the measure of neurobiological changes in the running of different exercise programs in depressive young people (45).

Our RCT exploring the impact of HIFT in Chapter IV, without peer interaction, online and with limited supervisor contact, demonstrated reduction on stress and depressive symptoms, highlighting potential neurophysiological effects of exercise. Nonetheless, a poorer social

environment was frequently observed in youth depression and may moderate the long-term effectiveness of the treatment (159). The inclusion of peer interactions such as in team sports may potentiate the reduction of the symptoms of depression and anxiety with an impact on social isolation, social relationship, and social anxiety (134).

In this dissertation, Chapters II and III studied physical and control programs with social interaction between peers and providers. However, we did not explore the impact of our different interventions on potential changes in social support or the possible psychosocial effect of exercise. Social support through exercise could be prominent in improvement and might vary by type of activity. In Chapter I, we showed that exercise is primarily offered in standard group and individual fitness programs with the goal of reducing depression. But few studies have considered the potential group effect, and only a handful of authors have adequately described the type of peer interactions. Future research should be more comprehensive regarding social interactions during exercise and investigate the social impact of exercise.

Supervision is essential to ensure a safe atmosphere and to foster a good motivational climate and appropriate peer interactions (160). In our 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 behaviours, healthy habits, and autonomous motivation to practice group activities. Task oriented-climate, with its dimensions of cooperative learning, effort/improvement and an important role is associated with a better academic performance and lower levels of life stress. This is in contrast to the ego climate with its respective dimensions of punishment of

mistakes, unequal recognition and rivalry between group members (215). People with a poorer social support may require additional attention from mental health workers in order to promote better physical exercise climate to increase peer support as ways of buffering of future psychiatric disorders.

However, these concepts are primarily investigated in the young general population at school and university. Yet, a substantial gap exists in this topic, and future research should confirm the results in depressed young people.

The anxiolytic effect of exercise

The anxiolytic effects of exercise in this dissertation yielded mixed results. Elementary school students aged 9 to 11 years reduced their non-clinical symptoms with low to moderate intensity exercise programs compared to high intensity exercise programs. Adolescents aged 12 to 19 years from a psychiatric hospital declined their high clinical scores without revealing differences between the both group; moderate intensity exercise and control social relaxation interventions. Finally, higher education students reduced their severe stress scores, but we were unable to observe a decrease in anxiety compared to control.

The comparison between our studies should be considered with caution as there are differences in age, symptom severity, lifestyle and intervention. Indeed, the first two studies conducted a group-supervised and game-based program. The last one was an online HIFT without peer interaction, based on a fitness program and monitored by a remote supervisor. In addition, this one was carried out in the exceptional context of COVID-19 confinement. In our

experimental study in a psychiatric environment, the absence of difference between the exercise and the active control group of social relaxation in the global reduction of the anxious symptoms could be explained by a medical follow-up and a multidisciplinary management inducing benefits which are overlapping with the potential anxiolytic effect of the exercise. Moreover, the active control intervention, by its psychosocial aspects, could produce better results than a passive control situation. A meta-analysis, comprising nine studies of young people, showed a moderate effect on anxiety but could not exhibit the potential impact of exercise on high levels of anxiety (125). Low-to-moderate intensity interventions seemed to show good results in anxiety reduction, as highlighted in elementary school in our study and supported by a recent systematic review in children (212).

However, supervised and structured exercise programs did not systematically reduce anxiety in young people, while a reduction in depression was more frequently observed. This corroborates with three recent studies showing no changes in anxiety after HIIT intervention in university students (194, 334) (201) while depression was diminished (194, 311).

In psychiatric disorders, as depression and anxiety (39, 69), higher ratios of pro-inflammatory/anti-inflammatory cytokines are also observed in blood (TNF-α/IL10, TNF-α/IL4, IFN-γ/IL10, and IFN-γ/IL4) (69). Physical activity may interact with the HPA system by attenuating the glucocorticoid response to stressful stimuli, thereby reducing anxiety symptoms after moderate intensity physical activity (112).

However, recent results are mixed, especially at high intensities. A RCT tested two physical exercise, one with Moderate Continuous Training (MCT)

relieving psychological distress and in reducing pro-inflammatory cytokines, and another with HIIT providing adverse action in increasing stress symptoms and the pro-inflammatory cytokines as TNF-α and IL-6 (194). In additional trials, HIIT did not alter the level of IL-6 in the resting state (343) and nor decrease the anti-inflammatory action of IL10 (344). These findings do not support our chapter IV demonstrating that high intensity could reduce stress. Thus, caution is warranted since the role of exercise, mostly at high intensity is still unclear.

To explain these mixed results, we hypothesized that High Intensity Training (HIT) effect may be different following the individuals characteristics. Anxiety symptom severity may moderate changes in cardiovascular condition during training. High anxiety level demonstrated a non-responder phenotype in improvement of cardiovascular condition after HIIT compared to the placebo exercise and a mild level of anxiety (201). HIT may be too intense to be tolerated for an individual and may even exacerbate feelings of anxiety, especially in individuals unaccustomed to vigorous physical activity or with sedentary lifestyle (201). Following our sample size analysis, a bigger sample in chapter IV might induce a significant p-value. This result could be related to the specific profile of our participants. They were all physiotherapists students, more likely to alleviate anxiety symptoms with exercise due to their regular physical activity practice and supposed good physical condition, compared to physical inactive participants in other study with symptoms reduction (201). One key to understand the various response to HIT in anxiety levels might thus be the participant profile.

Additionally, in our trial with HIFT, more flexibility on the engagement on their intensity with functional training could also explain better results.

Intensity might also be more modulated in our study than in previous studies using a stationary cycle training at 80% (194) or 90-95% of HRmax (201). The response to HIT may vary following the type of exercise and participant effort management.

The volume session could be another factor that might account for the inconsistent results observed in high-intensity programs. In our sample of pre-adolescents at school, a session of 50 minutes of high intensity did not show a reduction in anxiety symptoms. A positive evolution was also not observed in previous HIIT programs of 20 minutes (194, 201). Finally, in chapter IV, we achieved short sessions of 10 minutes with a positive evolution.

In summary, it seems that comprehensive protocols are essential for studying the effects of exercise on anxiety symptoms and more studies are necessary to test the relation to clinical symptoms in young people (125). In addition, the mechanisms of physical activity are not perfectly understood and require further attention (110, 112, 309).

Physical health in mental illness

A low cardio-respiratory fitness in our hospitalized adolescents was assessed by the modified Astrand-Rhyming submaximal test (278). We need to point out that this level is probably underestimated because of the lack of adaptation to sex and age. The use of the original Astrand Rhyming (301) should have allowed to benefit from the age and gender adjustments. In chapter I, we observed a value below the 50th percentile in our elementary school preadolescents sample assessed by the 20-m shuttle test (234). Significant

negative correlations were found between estimated cardiovascular outcomes and depressive symptoms at baseline. Our results are consistent with a systematic review and meta-analysis showing that higher cardio-respiratory fitness is inversely associated with depressive symptoms in children and adolescents (345). In our sample from chapter 3, their VO2Max indices were below the threshold expected to prevent the risk of cardiovascular disease later in life (287). Indeed, people with mental illnesses have an earlier onset of multimorbidity than the general population (346, 347). The American Heart Association has emphasized that MDD and bipolar disorder in youth should be considered conditions at moderate risk for early CVD (Cardio-Vascular Disease). Early acceleration of atherosclerosis, increased obesity, dyslipidemia, and insulin resistance are major concerns in adolescents with MDD (348). This burden that begins in young people with MDD, along with anxiety, is likely to continue into adulthood. In a large-scale meta-analysis of 3,211,768 patients and 113,383,368 controls, patients with MDD had a 53% higher risk of developing Cardio-Vascular Risk (CVR), a 78% higher risk of developing CVD, and an 85% higher risk of death from CVD (349). According to the American Heart Association, metabolic syndrome, also called insulin resistance syndrome, is diagnosed with three or more of the following conditions: high blood pressure, large waist circumference, high blood glucose, low HDL cholesterol and high triglycerides level. Compared to general population, individuals with severe mental illnesses could develop metabolic syndrome with a raised prevalence of 33% (95% CI: 30.8%-34.4%; N studies = 198; n = 52,678) (350) and of 40% for cardiac diseases, hypertension, stroke, diabetes, or obesity (347).

The link between depression and CVD might actually be multidirectionnal. A variety of behavioural and psychosocial factors may contribute to the increased association between CVD and psychiatric disorders across lifespan through the pathophysiological mechanisms (eg, inflammation, oxidative stress, autonomic dysfunction) and cardiovascular risk factors (eg, increased blood pressure, overweight and obesity, atherosclerosis, …). Common behavioral and environmental risks factors for excessive and premature CVD in adolescents with depression symptoms such as childhood maltreatment, adverse experiences, sleep disturbance, sedentary lifestyle and physical inactivity, unbalanced nutrition, excessive alcohol consumption, smoking and abuse substance may also concur to the comorbidity (348, 351). Finally treatment related to depression may also have an impact on CVD as illustred in Figure 1.

In addition, general practitioners may be generally less comfortable with psychiatric patients. As a result, patients may be less willing or have fewer opportunities to communicate their physical health problems to their physicians and less adherence to treatment medications (statins, angiotensins, antihypertensives) (348, 352). Antidepressants (including SSRIs) can cause weight gain and affect other metabolic parameters (348). The potentially shared neurobiological pathways between multiple lifestyle factors and mental health require further research (351, 353), especially in anxiety disorders (354).

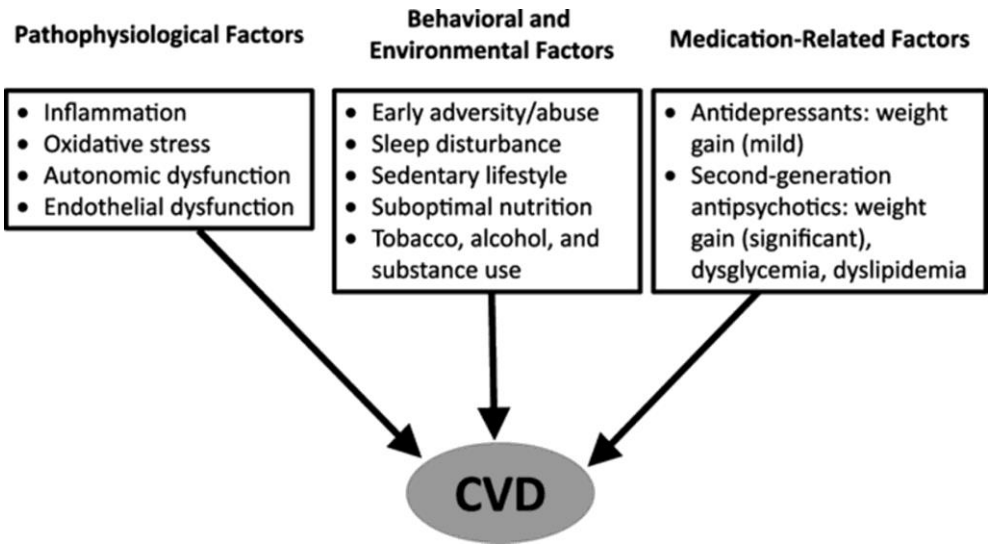

Figure 1: *Putative reasons for excessive and premature cardiovascular disease (CVD) among youth with major depressive disorder and bipolar disorder (348).*

Prevention is the key to limiting the development of CVD risks. National health strategies must urgently address the significant damage to physical health caused by mental illnesses (347). Consistent with the existing literature, we suggest increasing physical activity levels not only to improve mental health, but also to enhance the physical health of people with mental disorders (213, 347). We thought it was essential to act by intervening early with young people suffering from psychological distress in outpatient and inpatient services. In our study in a psychiatric hospital, aerobic programs of 6 weeks with 3 sessions per week, including strengthening exercise, is already efficient to enhance their cardio-vascular level. Long-term interventions should be undertaken to observe if CV risks are attenuated in young people

with MDD and GAD. If such interventions are successfull, it would be another argument to introduce exercise into clinical mental health recommendations.

Which programs?

The WHO guidelines on physical activity and sedentary behaviour recommended that children and adolescents participate in 60 minutes per day of moderate to vigourous intensity, mostly aerobic, physical programs, incorporating at least three sessions of vigorous physical activies and muscular strengthening 3 days a week, as illustred in figure 2. In general population of adults, including youth between 18 to 25 years, 150 to 300 minutes of moderate physical activities or 75 to 150 minutes of vigorous physical with muscle-strengthening activities are recommended (355).

Figure 2 : *WHO guidelines on physical activity in children and adolescents (aged 5-17 years) (355).*

Discussion

In youth with depression and anxiety, negative self-perception, dissatisfaction with one's own body, repeated negative experiences, and bullying could lead to apathy and withdrawal from physical activity (257). A depressed mood, lack of motivation and loss of vital energy are others barriers to participating in physical activities. However, it seems that exercise programs could be appreciated anyway (210, 356) (357) and induce a good adherence without difference in dropout rate compared to active or passive control groups (89, 167, 210). The WHO recommends starting with small amounts of physical activity and gradually increasing the frequency, intensity and duration over time (355).

Supervision

Chapter I noted that the description of supervision of physical sessions was often incomplete, yet supervision seems essential. It ensures safe, engaging and appropriate programs for both youth and adults with mental illnesses, including depression and anxiety. In particular, trained and specialized trainers are needed to tailor sessions to adolescents with their specific symptoms. In addition, exercise therapists in the mental health field should be instructed in psychological models to develop motivation in youth to engage in regular, long-term physical activity. The transtheoretical model of change assumes that health behavior change involves going through six stages of change: precontemplation, contemplation, preparation, action, maintenance and relapse (358). These principles could be integrated into physical exercise in mental health. For another example, the decisional

balance could be used to support regular physical activity (359) in mental health.

Content of sessions

Aerobic programs showed moderate to large effects for clinical symptoms of depression (89, 167, 168), may produce a neutrophic effect (137, 360) and play a role as a potential regulator in inflammation rate (97, 344). Less evidence was found on the effect of anaerobic programs in depression and anxiety reduction (125, 167) but it seems coherent to introduce this component in mixed program to prevent CVR and CVD (348). Physical exercise with cognitive ability could also be suggested to potentiate brain plasticity (151, 154). Chapter I reported that few studies examined game-based exercise programs (k=7) versus traditional fitness programs (k=22). A meta-analysis revealed no significant difference in psychological symptoms between traditional fitness programs (cycloergometer, treadmill) and game-based exercise (167). However, these studies did not associate potential changes in the antidepressant effect with the impact on executive function and social support, two factors supporting the alleviation of long-term depression (155, 159). Team sport interventions carried out good results in executive functions and social skills in healthy subjects (134, 151, 154), suggesting they might be a useful combination in exercise therapy in mental health allowing for a better depression reduction in long term.

In addition, how to develop adherence seems essential to follow physical activity recommendations (174). Affective response to exercise is the subjective experience of positive and/or negative feelings in response to

exercise, as well as satisfaction of psychological needs (perceived competence, relatedness, and autonomy) to exercise. It may contribute to autonomous self-regulation (361) and consequently could predict better long-term participation in physical activities (259, 362). Therefore, there is a need to design exercise programs for patients with psychiatric disorders that are adapted and as enjoyable and pleasant as possible (363, 364).

Intensity

In the studies included in Chapter I, as well as in a recent review for anxiety (125), a lack of description of intensity has been observed. However, it seems that **moderate and high levels of intensity** could demonstrate good results for the prevention and treatment of **depression**. Regarding **anxiety, moderate intensity** is suggested, due to the promising results of moderate intensity interventions compared to the lack of evidence for high and very high intensity. When the co-morbidities of depression and anxiety are observed, we suggest using moderate intensity, supervised by cardio-vascular measures and with the possibility for participants to regulate their intensity during the session.

Frequency and duration

Being close to WHO recommendation for weekly physical activities is an ultimate goal, but patients cannot always reach these recommendations. Following chapter 1 and the literature, 3 to 4 sessions during a minimum of 6 weeks could be efficient to reduce psychological symptoms. Maintaining more extended participation may continue to decrease the severity or could provide a protective effect for higher-level development of distress.

Finally, as described in the chapter IV, future studies could then better investigate the specific impact of exercise if future trials more rigorously reported different exogenous variables in the intervention protocol such as: heart rate/energy expenditure during exercise, management of the effort, type of exercise, volume session, duration of each component of session, duration of the program, group or individual activities, type of peer-provider interaction, quality of supervision, adherence, and dropout rate with its reasons for leaving the study. In addition, further description is also needed regarding participants profiles such as: general health, actual physical activity participation, physical activity history, actual fitness condition, gender, severity of depression, mental and physical comorbidities, medication prescription and mental health family history. In both adults and young people, the exploration of different exercise protocols, well-informed, is necessary to control these different variables and to prevent heterogeneity and disparate outcomes.

CONCLUSION

Conclusion

Physical exercise has gained a lot of interest in various neurological, metabolic and cardio-vascular diseases in medicine over the past few decades, both for prevention and treatment. In individuals suffering from mental illnesses, it is essential to consider a comprehensive approach for managing physical and psychological health, which are closely linked. In this dissertation, we provided strong evidence that exercise is a promising approach in the overall strategy to reduce depression in young people, both in educational and hospital settings. Furthermore, we have demonstrated that exercise therapy appears to be most efficient in reducing depressive symptoms when youth suffer from moderate to severe levels of depression. These findings are critical because of the lack of robust and effective treatment in this population. Furthermore, the early onset of cardiovascular risks in young people suffering from mental illnesses is also a major concern which reinforce the key role of exercise in mental health treatment. Our results support that exercise deserves to be investigated as a therapy to be integrated into the comprehensive care of mental health disorders. The evidence of anxiolytic effects of exercise is less straight-forward. In addition, the implementation of exercise therapy in mental health care guidelines still requires the confirmation of our results in larger multidisciplinary settings, especially in a multi-centric perspective, ensuring the transferability of the concepts from one clinical setting to another. In this context, the effects of physical activity could be studied with a holistic assessment allowing to appreciate the effects of physical activity on mental health, neurobiological (neuroplasticity, inflammation levels), psychosocial (interpersonal and intrapersonal relationships) and behavioral (sleep, emotion regulation, eating habits) mechanisms in outpatient and hospitalized youth with clinical symptoms.

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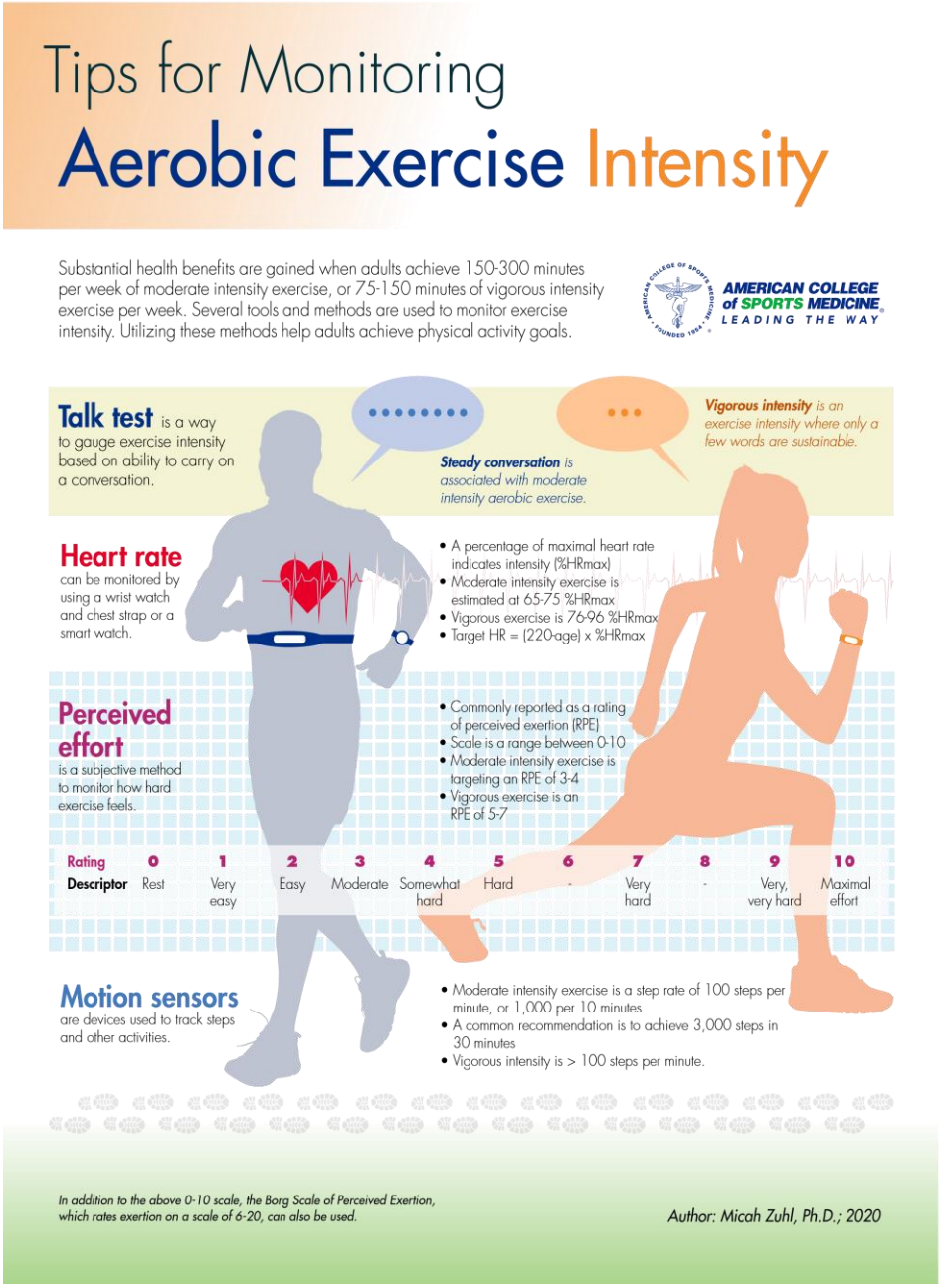
APPENDIX

Appendix 1: Tips for monitoring aerobic exercise intensity from ACSM



Appendix 2. Used medical questionnaire

Pour connaître votre enfant et voir s'il peut participer

Programme

Effets de l'entraînement physique sur le bien être psychologique.

(Responsable porte-parole : Prof. A. De Volder, médecin neuropédiatre)

Si vous êtes intéressés, votre enfant va participer à une étude effectuée à l'école Parmentier concernant l'effet d'un programme de remise en forme. Pour cela nous vous demandons de bien vouloir indiquer des informations importantes pour le médecin responsable de l'étude. Ces informations seront gardées confidentielles.

Nom et Prénom de l'enfant :

Son âge est compris entre 9 et 12 ans :(merci d'indiquer sa date de naissance : .....)

-Il ne présente aucune des contre-indications suivantes (sauf avis favorable du médecin traitant à joindre en annexe) à la pratique sportive (entourez s'il vous plaît)

diabète insulino dépendant instable : oui - non

troubles de la coagulation (hémophilie etc.) : oui - non

asthme sévère non contrôlé : oui - non

malformation cardiaque : oui - non

maladie cardio-vasculaire : oui - non

traumatisme crânien : oui - non

-Il a suivi le cours de gymnastique à l'école : oui / non (si non, merci d'indiquer ci-dessous pourquoi) : ……

-Il ne présente aucun problème médical / il présente un problème médical : (entourez s'il vous plaît)

asthme contrôlé par puff (à avoir avec soi durant les séances) : oui - non

épilepsie contrôlée par médicaments : oui - non (si oui, merci d'indiquer lesquels *)

dépression traitée par (précisez les médications * s'il vous plaît) : oui - non

anxiété traitée par (précisez les médications * s'il vous plaît) : oui - non

trouble déficitaire de l'attention traité / non traité : oui - non (si traité merci de préciser le traitement)

Rilatine / Concerta / Logopédie / Revalidation neuropsychologique / Autre :

trouble d'apprentissage : dyslexie / dysorthographie / Dyscalculie / Aucun (si traité merci de préciser) :

Logopédie / Revalidation neuropsychologique / Autre :

autre problème médical (précisez s'il vous plaît) :

* Mon enfant prend les médicaments suivants :

En cas de fièvre dans les 24 h précédent une séance, l'intervenant dira à votre enfant qu'il ne peut pas participer à cette séance-là (le programme pourra ensuite être poursuivi).

J'ai rempli ce questionnaire en date du Signature
ou paraphe s'il vous plaît