International Doctoral Thesis / Tesis Doctoral Internacional

Role of physical activity, sedentary behavior and physical fitness in mental health and white matter in children and adolescents

El papel de la actividad física, el sedentarismo y la condición física en la salud mental y la sustancia blanca en niños y adolescentes

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María Rodríguez García

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Autor: María Rodríguez García
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ABSTRACT/RESUMEN

ABSTRACT

Childhood and adolescence are periods of dynamic behavioral, cognitive and emotional development that can increase vulnerability to mental disorders. Obesity and related issues represent important public health concerns in terms of prevalence, incidence and economic burden. In addition, nearly 75% of young people have insufficient levels of physical activity in developed countries. In tandem with this fact, most of the young people are "digital natives", which means that they have grown up surrounded by digital information and entertainment on screens. All these facts together prove that a major change in the lifestyle of young people is taking place in the last decades, which in turn might have an effect on their mental and brain health. In this context, white matter, which is important for efficient transmission of information between brain areas, has been considered one of the brain features susceptible of being modified by physical activity and other related factors (i.e., sedentary behavior and physical fitness) in young people, yet the body of evidence is still in its infancy, and further studies are needed to shed light on the many questions that remain unanswered. Therefore, the overall aim of the present International Doctoral Thesis is to study the role of physical activity, sedentary behavior and physical fitness in the mental health (part I), and white matter (part II) in young people.

The general results of this Doctoral Thesis show that physical activity had a small but positive effect on mental health in young people. In terms of white matter, we did not find any significant effect on white matter microstructure after a 20-week physical exercise intervention in children with overweight or obesity, although cross-sectional studies of this Doctoral Thesis indicated a positive relationship between physical activity and white matter. Sedentary behavior seems to be negatively associated with mental health. However, the relationship with white matter microstructure is not clear yet. For instance, while we found that watching TV was negatively associated with white matter microstructure in children with overweight or obesity, no association was found in a bigger cohort of children. Future work should continue to explore longitudinal data in order to more concretely decipher the temporality of these associations. Regarding to physical fitness, muscular fitness was the most promising physical fitness component in relation to mental health, and white matter in children with overweight or obesity. Specifically, we encourage researchers to study the potential role of muscular fitness in the white matter of young people as well as the mechanisms that might be explaining this relationship.

Collectively, the results of the present International Doctoral Thesis enhance our understanding about the implications that health-related behaviors and factors such as physical activity, sedentary behavior and physical fitness may have for mental and brain health in young people.

RESUMEN

Durante la niñez y la adolescencia, se experimentan grandes cambios a nivel comportamental, emocional y cognitivo que podrían derivar en una mayor vulnerabilidad en cuanto al desarrollo de trastornos mentales. Los efectos del sobrepeso y la obesidad en la salud de los jóvenes representan hoy en día un problema de salud pública. Además, alrededor del 75% de los jóvenes no cumplen con las recomendaciones de actividad física. Unido a estos altos niveles de inactividad física, nos enfrentamos a una sociedad cada vez más sedentaria donde los jóvenes son considerados "nativos digitales", es decir, son jóvenes que han crecido rodeados de información digital. Todos ello, demuestra que en las últimas décadas, se están produciendo grandes cambios en el estilo de vida de los jóvenes, los cuales podrían repercutir no solo en su salud física sino también en su salud mental y cerebral. En este contexto, la sustancia blanca, cuya función principal es garantizar una buena transmisión de la información en el sistema nervioso, parece susceptible de ser modificada por los cambios en los niveles de actividad física así como en otros predictores como el comportamiento sedentario o la condición física. Por lo tanto, el objetivo de esta Tesis Doctoral Internacional es estudiar el papel de la actividad física, el sedentarismo y la condición física en la salud mental (Parte I) y la sustancia blanca (Parte II) en jóvenes.

Los resultados de la presente Tesis Doctoral muestran que la actividad física tuvo un efecto positivo, pero pequeño, en la salud mental de los jóvenes. En cuanto a la sustancia blanca, destacar que no encontramos cambios significativos tras un programa de ejercicio físico de 20 semanas de duración en niños con sobrepeso u obesidad. Sin embargo, en estudios de diseño trasversal, pudimos comprobar que existe una relación positiva entre los niveles de actividad física y la microestructura de sustancia blanca de los niños. El comportamiento sedentario, refiriéndonos específicamente al tiempo que los niños dedican al uso de la pantalla de forma recreativa, parece relacionarse negativamente con la salud mental de los jóvenes. Sin embargo, su relación con la microestructura de sustancia blanca no está clara. Por ejemplo, mientras que una mayor cantidad de tiempo viendo la televisión se asoció negativamente con la microestructura de sustancia blanca en niños con sobrepeso u obesidad, no se encontró ninguna asociación en una mayor cohorte de niños. Futuros estudios deberán explorar la relación longitudinal entre el comportamiento sedentario y la sustancia blanca en jóvenes, con el objetivo de determinar la relación temporal entre ambas variables. En relación a la condición física, destacar que la fuerza muscular fue el componente de la condición física que se asociación de forma más consistente con la salud mental y la sustancia blanca en niños. Por lo tanto, con los hallazgos de esta Tesis Doctoral queremos alentar a la comunidad científica a examinar el papel de la fuerza muscular en la salud mental y cerebral de los jóvenes así como los mecanismos que podrían estar explicando esta relación.

En resumen, los resultados de esta Tesis Doctoral avanzan en el conocimiento sobre las implicaciones que ejercen factores relacionados con la salud, tales como la actividad física, el comportamiento sedentario o la condición física sobre la salud mental y cerebral de los jóvenes.

ABBREVIATIONS

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ACSM: American college of sport medicine

AD: Axial diffusivity

ADHD: Attention deficit hyperactivity disorder

ALPHA: Assessing levels of physical fitness and health in adolescents

AMSTAR: A measurement tool to assess systematic reviews

ANCOVA: Analysis of co-variance

BDNF: Brain-derived neurotrophic factor

BEDPOSTx: Bayesian estimation of diffusion parameters obtained using sampling techniques

BMI: Body mass index

CBCL: Child behavior checklist school-age version

CDI: Children´s depression inventory

CDSI: Children's daily stress inventory

DARTEL: Diffeomorphic anatomical registration through exponentiated lie

DTI: Diffusion tensor imaging

DVD: Digital video disc

ENMO: Euclidean norm minus one

FA: Fractional anisotropy

FDR: False discovery rate

FITKids2: Enhancing children's cognitive and brain health through physical activity training

FSL: Functional MRI of the brain software library

GLM: General linear model

IQ: Intelligence quotient

K-BIT: Kaufman brief intelligence test

KIDMED: Mediterranean diet quality index for children and teenagers

KTEA2: Kaufman test of educational abilities

LOT-R: Life orientation test-revised

MD: Mean diffusivity

MET: Metabolic equivalent

MRI: Magnetic resonance imaging

PANAS-C: Positive and negative affect schedule for children

PGC1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha

PHV: Peak height velocity

PRISMA: Preferred reporting items for systematic review and meta-analysis

RCT: Randomized controlled trials

RD: Radial diffusivity

RSE: The Rosenberg self-esteem scale

SAAFE: the supportive, active, autonomous, fair, enjoyable

SD: Standard deviation

SHS: Subjective happiness scale

SPSS: Statistical package for the social sciences

SPM: Statistical parametric mapping

STAIC-T: The state-trait anxiety inventory for children

SSE: Sum-of-squares error

SWB: Subjective well-being

TBSS: Tract-based spatial statistics

TBV: Total brain volume

TV: Television

USA: United States of America

WHO: World health organization

YAP-S: Youth activity profile-Spain

DEFINITIONS OF THE MAIN TERMS USED IN THIS DOCTORAL THESIS

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Physical activity, sedentary behavior, and physical fitness definitions

Aerobic physical activity: Activity in which the body's large muscles move in a rhythmic manner for a sustained period of time. Aerobic activity, also called endurance or cardio activity, improves **cardiorespiratory or aerobic fitness**. Examples include brisk walking, running, swimming, and bicycling. Aerobic physical activity has three components: intensity, duration and frequency [1].

Cardiorespiratory fitness (also known as aerobic fitness): The overall capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged strenuous exercise [2].

Motor fitness (includes speed-agility): A combination of speed, agility and coordination [2]. Speed is the ability to move the body (or some parts of the body) as fast as possible [2]. Agility is the ability to move quickly and change direction while maintaining control and balance [2].

Muscle-strengthening activity (also known as resistance training): Physical activity, including exercise that increases skeletal muscle strength, power, endurance, and mass. Muscle-strengthening activity includes strength training, resistance training, or muscular strength and endurance exercises. Muscle-strengthening activity has four components: intensity, frequency, sets and repetitions [1] .

Muscular fitness (also known as muscular strength) The capacity to carry out work against a resistance [2].

Physical activity: Any bodily movement produced by skeletal muscles that result in energy expenditure [3]. **Leisure-time physical activity** is the subdomain of physical activity when practiced during leisure-time.

Physical exercise: A form of physical activity that is planned, structured, repetitive, and performed with the goal of improving health or fitness. All exercise is physical activity, but not all physical activity is exercise [1].

Physical fitness: Capacity to perform physical activity, and makes reference to a full range of physiological and psychological qualities [2]. Physical fitness is composed of several components, such as cardiorespiratory fitness, muscular fitness and motor fitness.

Physical inactivity: An insufficient physical activity level to meet present physical activity recommendations [4].

Screen time: Time spent on screen-based behaviors [5]. These behaviors can be performed while being sedentary or physically active.

- **Recreational screen time:** Time spent in screen behaviors that are not related to school or work [6].
- **Stationary screen time:** Time spent using a screen-based device (e.g., smartphone, tablet, computer, TV) while being stationary (either sitting, reclining, or standing) in any context (e.g., school, work, recreational).
- **Sedentary screen time:** Time spent using a screen-based device (e.g., smartphone, tablet, computer, TV) while being sedentary in any context (e.g., school, work, recreational).

- **Active screen time:** Time spent using a screen-based device (e.g., smartphone, tablet, computer, TV) while being active in any context (e.g., school, work, recreational).

Non-screen-based sedentary time: Time spent in sedentary behaviors that do not involve the use of screens.

- **Recreational non-screen sedentary time:** Time spent in non-screen based sedentary behaviors that are not related to school or work.

Sedentary behavior: Any waking behavior characterized by an energy expenditure ≤1.5 METs, while in a sitting, reclining or lying posture [7] (see Figure 5, Study I).

Sport participation: Sport is one type of leisure time **physical activity**. It is a human activity of achieving a result requiring physical exertion and/or physical skill which, by its nature and organization, is competitive. Sport was sometimes defined as including both **team** and **individual** sports or encompassing different categorical groups for both team and individual sports participants, whilst others categorized groups as **structured versus unstructured** activities. In addition, some studies distinguished between participation in **school sport** and **club sport.**

Mental health definitions

Anxiety: It is a feeling of worry, nervousness, or unease about something with an uncertain outcome. Anxiety is characterized by excessive and persistent (yet often unrealistic) worry which can inhibit one's ability to carry out activities of daily living [8]

Depression: The generic word 'depression' implies a lowering – here, a lowering of mood. Depressive diagnostic constructs include lowered mood, decreased self-esteem and increased self-criticism; guilt about acts of commission and omission; and feelings of hopelessness and helplessness [9]. As an extension, Beck's negative 'cognitive triad' emphasizes a negative view of the self (i.e. deficient, inadequate and unworthy), the world and of the future [10].

Global self-concept: It is used to describe an individual's awareness of their qualities and limitations. Self-concept is a person's perceptions of himself or herself, namely, what a person thinks about himself [11]. **Perceived appearance** (sometimes referred to as perceived physical attractiveness), perceived fitness (typically aerobic and muscular fitness) and perceived competence (sport and movement skill competence) are sub-domains of physical self-concept [12], which in turn generalises to global self-concept.

Global self-esteem: It is the evaluative and affective dimension of self-concept [13], and is considered equivalent to self-regard, self-estimation and self-worth [14]. In other words, self-esteem is the degree to which an individual values himself or herself.

Happiness: It is a loose term with many meanings and so is often avoided in the scientific literature [15]. Happiness has been broadly used to describe positive subjective experiences. The two most accepted definitions come from Diener [16] and Seligman [17]. Diener's model is comprised of three components including the cognitive appraisal of one’s life (i.e., satisfaction with life) as well as positive and negative affect (i.e., emotions), which are viewed as two separate dimensions. The combination of these three components creates a holistic view of the overall perception of happiness [18]. On the other hand, Seligman [17] proposed another conceptualization of happiness which includes three components: experiencing positive emotion (the pleasant life), being engaged in life activities (the engaged life), and finding a sense of purpose or meaning (the meaningful life). However, unlike Diener, Seligman has not addressed the role of negative affect in this model.

Stress: It is a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being [19].

Subjective well-being: It is defined as people´s overall evaluations of their live and their emotional experience. SWB thus includes broad appraisals, such as satisfaction with life and health satisfaction judgments, and specific feelings that reflect how people are reacting to the events and circumstances in their lives [20]. SWB is commonly conceptualized as having two primary components- affective (**positive affect** and **negative affect**) and cognitive (**satisfaction with life**) [15].

- **Positive affect:** It is a dimension reflecting one´s levels of pleasurable engagement with the environment. High positive affect is composed of terms reflecting one´s enthusiasm, energy levels mental alertness, interest, joy, and determination, whereas low positive affect is best defined by descriptors reflecting lethargy and fatigue [21]**.**
- **Negative affect:** It is a general factor of subjective distress, and subsumes a broad range of negative mood sates, including fear, anxiety, hostility, scorn, and

disgust. Mood state related to depression such as sadness and loneliness also have substantial loadings on this factor [21].

- **Satisfaction with life:** Life satisfaction refers to a judgmental process, in which individuals assess the quality of their lives on the basis of their own unique set of criteria [18].

White matter definitions

Diffusion tensor imaging: DTI is a MRI technique that provides high-resolution *in vivo* measurements of the coherence and direction of neuronal fiber tracts [22]. DTI is based on the self-diffusion properties of water [23]. The property of water molecules diffusing freely, equally in all planes, is known as **isotropic diffusion**. However, in tissue (i.e., cell membranes) when boundaries exist, the orientation of the diffusion is often differentially restricted and is termed **anisotropic diffusion** [24] **(see Figure 1)**. The 2 most common quantitative scalar measures used in DTI are FA and MD [25]. In addition, there are other scalar measures used such as AD or RD.

- **Eigen Value (λ):** the value of the displacement/diffusion for each specific vector or length of the axis in the tensor.
- **Axial diffusivity (λ1):** AD tends to be variable in white matter changes and pathology. In axonal injury AD decreases. The ADs of white matter tracts have been reported to increase with brain maturation.
- **Fractional anisotropy:** FA is a measure of the degree to which water diffuses preferentially along one axis. This scalar measure ranges from 0 which means no preferred direction (i.e., isotropic diffusion) to 1 which means unidirectional movement (i.e., anisotropic diffusion). Higher FA values are thought to reflect a higher degree of neuronal organization.
- **Mean diffusivity (λ1+λ2+λ3)/3:** MD provides a measure of the mean molecular diffusion. This value provides a measure of barriers to free diffusion in the volume, but it does not provide information about the direction of movement. Higher MD indicate relatively unimpeded diffusion (i.e., it is negatively correlated with FA).

- **Radial diffusivity (λ2+λ3)/2:** RD increases in white matter with de- or dys-myelination. Changes in the axonal diameters or density may also influence RD.

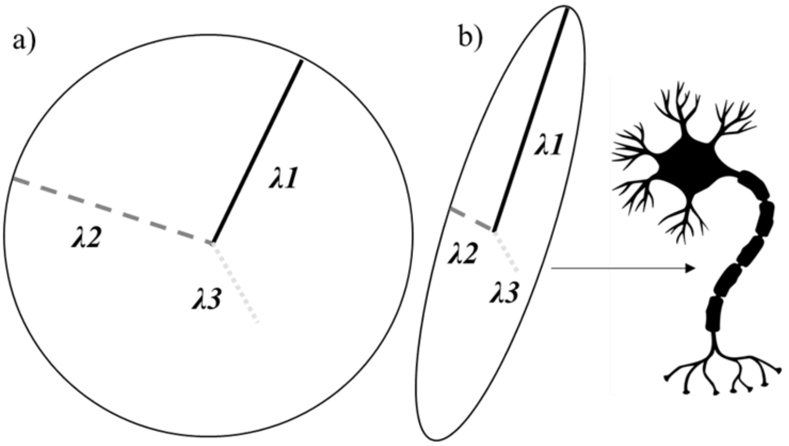

Figure 1. Isotropic diffusion (a) which is equal in all orientations and anisotropic diffusion (b) which is orientation-specific. λ1= Axial diffusivity, (λ2+λ3)/2= Radial diffusivity, (λ1+λ2+λ3)/3= Mean diffusivity.

White matter: Neural tissue of the brain and spinal cord which mainly consists of myelinated nerve fibers bundled into **tracts**. Then, white matter is composed of millions of bundles of nerve fibers (**axons)** that connect neurons in different brain regions into functional circuits. Many of these nerve fibers are surrounded by a type of sheath called **myelin**. Myelin gives the white matter its color and protects the nerve fibers from injury. Also, it improves the speed and transmission of electrical nerve signals along extensions of the nerve cells called axons.

White matter microstructure: The microstructure of white matter consists of millions of individual neurons wrapped within a compact, multi-layered lipid and protein sheath (i.e., myelin). It is the combination of the lipid membrane of the neurons and the myelin sheath that restricts **water diffusion** [26].

REFERENCES

1. Physical Activity Guidelines for Americans. 2nd edition. 2018;Washington, DC: US Department of Health and Human Services. https://healt h.gov/pagui delin es/secon d-editi on/pdf/Physical_Activity_Guide lines 2nd_editi on.pdf. Accessed 15 Nov 2018.

2. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes. 2008;32:1–11.

3. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100:126–31.

4. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act. 2017;14:75.

5. Stamatakis E, Hamer M, Dunstan DW. Screen-Based Entertainment Time, All-Cause Mortality, and Cardiovascular Events. J Am Coll Cardiol. 2011;57:292–9.

6. Tremblay MS, Carson V, Chaput J-P, Connor Gorber S, Dinh T, Duggan M, et al. Canadian 24-Hour Movement Guidelines for Children and Youth: An Integration of Physical Activity, Sedentary Behaviour, and Sleep. Appl Physiol Nutr Metab. 2016;41:S311–27.

7. Sedentary Behaviour Research Networ. Letter to the Editor: Standardized use of the terms “sedentary” and “sedentary behaviours.” Appl Physiol Nutr Metab. 2012;37:540–2.

8. Gale C, Oakley-Browne M. Anxiety disorder. BMJ. 2000;321:1204–7.

9. Engel GL. The need for a new medical model: a challenge for biomedicine. Science.

1977;196:129–36.

10. Parker G, Paterson A. Differentiating ‘clinical’ and ‘non-clinical’ depression. Acta Psychiatr Scand. 2015;131:401–7.

11. Simons J, Capio CM, Adriaenssens P, Delbroek H, Vandenbussche I. Self-concept and physical self-concept in psychiatric children and adolescents. Res Dev Disabil. 2012;33:874–81.

12. Marsh HW, Shavelson R. Self-Concept: Its Multifaceted, Hierarchical Structure. Educ Psychol. 1985;20:107–23.

13. Sonstroem RJ, Morgan WP. Exercise and self-esteem: rationale and model. Med Sci Sports Exerc. 1989;21:329–37.

14. Mann M, H Hosman CM, Schaalma HP, de Vries NK. Self-esteem in a broad-spectrum approach for mental health promotion. 2004; 19:357-372

15. Diener E, Heintzelman SJ, Kushlev K, Tay L, Wirtz D, Lutes LD, et al. Findings all psychologists should know from the new science on subjective well-being. Can Psychol Can. 2017;58:87–104.

16. Diener E. Subjective well-being. The science of happiness and a proposal for a national index. Am Psychol. 2000;55:34–43.

17. Seligman MEP. Authentic happiness: Using the new positive psychology to realize your potential for lasting fulfillment. New York, NY, US: Free Press; 2002.

18. Pavot W, Diener E. Review of the Satisfaction With Life Scale. Psychol Assess. 1993;5:164–72.

19. Butler G. Definitions of stress. Occas Pap R Coll Gen Pract. Royal College of

General Practitioners; 1993;1–5.

20. Diener E, Suh EM, Lucas RE, Smith HL. Subjective well-being: Three decades of progress. Psychol Bull. 1999;125:276–302.

21. Watson D, Clark LA, Carey G. Positive and Negative Affectivity and Their Relation to Anxiety and Depressive Disorders. J. Abnorm. Psychol. 1988.

22. Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J. 1994;66:259–67.

23. Basser PJ, Mattiello J, Lebihan D. Estimation of the Effective Self-Diffusion Tensor from the NMR Spin Echo. J Magn Reson Ser B. Academic Press; 1994;103:247–54.

24. Pajevic S, Pierpaoli C. Color schemes to represent the orientation of anisotropic tissues from diffusion tensor data: application to white matter fiber tract mapping in the human brain. Magn Reson Med. 1999;42:526–40.

25. Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, et al. A review of diffusion tensor imaging studies in schizophrenia. J. Psychiatr. Res. 2007. 41: 15–30.

26. Brady ST, Witt AS, Kirkpatrick LL, de Waegh SM, Readhead C, Tu PH, et al. Formation of compact myelin is required for maturation of the axonal cytoskeleton. J Neurosci. 1999;19:7278–88.

GENERAL INTRODUCTION

GENERAL INTRODUCTION

Traditionally, childhood and adolescence has been considered the healthiest periods of life [1]. Nonetheless, childhood and adolescence are also periods of dynamic behavioral, cognitive and emotional development that can increase vulnerability to mental disorders. Among young people, mental health problems are a growing public health concern, affecting between 10% and 20% of children and adolescents worldwide [2]. It is known that young people who experience mental health problems are at an increased risk for continued psychopathology later in life [3]. Therefore, characterization of any associated neurodevelopmental features at these ages is crucial. On the other hand, genetic factors interact with environmental factors to modify the risk of mental health problems. The risk factors for mental health problems are well established [4]. For instance, it is know that poverty and social disadvantage are strongly associated with mental disorders [4]. Yet, identifying protective factors that might contribute to preserve mental health at these ages is a challenge of the scientific community.

Obesity and related issues represent important public health concerns in terms of prevalence, incidence and economic burden. According to the World Obesity Federation (https://www.worldobesity.org/), approximately 20% of school age-children in Europe have overweight or obesity. This figure is considerably higher in Spain, where 33% of young people have excess of body weight. At the same time, the rates of physical activity are decreasing drastically [5]. Near 75% of children have insufficient levels of physical activity in developed countries. In tandem with this fact, most of the young people are “digital natives”, which means that they have grown up surrounded by digital information and entertainment on screens. All these facts together prove that several changes are occurring in the lifestyle of young people, which in turn might have an effect on their general health. For instance, previous studies have shown that increased levels of physical activity and decreased levels of sedentary behavior improve physical fitness [6,7], build strong bones [8,9], control weight [7,10] and reduce the risk of cardiovascular risk factors [11] in young people. However, the benefits of increased physical activity and reduced sedentary behavior for mental and brain health outcomes, at those ages, has received less attention in comparison to the physical health benefits.

Physical activity, sedentary behavior, physical fitness and mental health

Despite the vast amount of systematic reviews and meta-analyses investigating the role of physical activity and sedentary behavior in the mental health of young people [12–22], robust conclusions have not been established so far. For instance, previous systematic reviews and meta-analyses have focused on specific physical activity practices [23,24] , a narrow age ranges [25,26] or specific mental health outcomes [27–32]. In addition, most of those reviews have considered physical activity [27,30,31] and sedentary behavior [15,18] as independent behaviors in relation to mental health. Physical activity and sedentary behavior are two independent but related behaviors. For instance, a person/one may engage in one hour of physical activity per day but, at the same time, watching TV or playing on the computer for more than four hours per day [33]. Therefore, more research is needed to understand the complete picture of the relationship between physical activity, sedentary behavior and overall mental health in children and adolescents (**Study I**, **Study II**).

Physical fitness is an integrated measure of most the body functions involved in the performance of daily physical activity. Physical fitness is in part genetically determined, but it can also be greatly influenced by environmental factors such as physical activity. Therefore, physical activity and physical fitness are considered two different but related concepts. Over the past years, researchers have shown an increased interest in studying how physical fitness is related to mental health in young people. It is already known that different components of physical fitness (i.e., cardiorespiratory, muscular and motor fitness) have a positive effect on mental health in children and adolescents, both at these ages [34,35] and later in life [36,37]. However, less is known about the relationship between physical fitness and mental health in children with overweight or obesity. Overweight/obesity is bidirectionally associated with a higher risk of depression [38]. Additionally, it is known that children with overweight or obesity have worse self-esteem and physical appearance, as well as higher levels of depression and mood disorders than normal-weight children [39]. Thus, examining the association of protective risk factors, such as physical fitness, with mental health is particularly important in children with overweight/obesity [40] (**Study III**).

Physical activity, sedentary behavior, physical fitness and white matter

Significant progress has been made in understanding how physical activity protects the brain. In animal models, many studies have demonstrated that physical activity targets many aspects of brain structure and function [41–46]. For example, a growing number of studies have indicated that regular physical activity leads to an increase in BDNF in the central nervous system, which in turn promotes improvement in cognition and mental health [42–44]. In line with the animal studies, the rapid advances in neuroimaging techniques have opened the possibility to address new questions about the potential role of physical activity and other related factors (i.e., sedentary behavior and physical fitness) in the human brain.

White matter is considered one of the brain features that susceptible of being modified by physical activity both in adults [47,48] and children [49–51], yet the body of evidence, especially in children, is still in its infancy, and further studies are needed to shed light on many questions that remain unanswered. First, the relationship of daily physical activity and white matter in the absence of a structured intervention has not been previously tested in children. In this context, observational studies complement experimental studies and can help identify characteristics of children's daily physical activity (e.g., spontaneous and intermittent) that may benefit white matter microstructure (**Study IV**, **Study V**). Second, previous studies addressing the relationship between physical fitness and white matter only focused on cardiorespiratory fitness [49,52] and muscular fitness or motor fitness should also be studied as more novel health-related physical fitness components (**Study VI**, **Study VII**). Third, despite a few studies tested the effect of physical activity on white matter microstructure in children [50,51,53], number of gaps in the knowledge were identified. For instance, it is unknown if the effect of physical activity on white matter microstructure is global or restricted to a particular set of white matter bundles. In addition, the effect of physical activity on white matter has been tested only on some tracts (i.e., the corpus callosum, corona radiata, superior longitudinal fasciculus, posterior thalamic radiation, and uncinate fasciculus), remaining underexplored the pattern of white matter in the whole brain (**Study VIII**).

Lastly, excess body mass has been linked to poorer structural connectivity [54] and white matter development [55] in children. Taking into account the previously observed negative influence of childhood obesity on brain health and the lack of studies in children with overweight or obesity, there is a clear need for studies that examine the role of physical activity, sedentary behavior and physical fitness in white matter, particularly in children with overweight or obesity (**Studies V, VI, VII, VIII**).

Background summary

To sum up, this Doctoral Thesis arrives timely, as nowadays children are becoming increasingly unfit and sedentary, and educators reduce or eliminate opportunities for physical activity during school time. In tandem with this fact, more and more young people are affected by mental health problems which lead to other comorbidities, lower quality of life and increased health care costs. Moreover, in the context of typical brain development, several recent studies have investigated the consequences of environmental experience on white matter macrostructure and microstructure [34–36], yet little work has explored to what extent physical activity, sedentary behaviors, and physical fitness are associated or have an effect on white matter in young people. Therefore, the present Doctoral Thesis is structured in two parts based on the main outcome studied. In **Part I (Studies I, II, III)**, the Thesis provides evidence concerning the role of physical activity, sedentary behavior and physical fitness in mental health. In **Part II (Studies IV, V, VI, VII, VIII,** the present Doctoral Thesis provides novel findings about the role of these behaviors/factors in white matter in children.

REFERENCES

1. Engelman M, Seplaki CL, Varadhan R. A Quiescent Phase in Human Mortality? Exploring the Ages of Least Vulnerability. Demography. Springer New York LLC; 2017;54:1097–118.

2. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime Prevalence and Age-of-Onset Distributions of DSM-IV Disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry. 2005;62:593.

3. Pine DS, Cohen E, Cohen P, Brook J. Adolescent depressive symptoms as predictors of adult depression: Moodiness or mood disorder? Am J Psychiatry. American Psychiatric Association; 1999;156:133–5.

4. Patel V, Flisher AJ, Hetrick S, McGorry P. Mental health of young people: a global public-health challenge. Lancet. 2007. 369: 1302-1313.

5. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012; 380:247–57.

6. Pozuelo-Carrascosa DP, García-Hermoso A, Álvarez-Bueno C, Sánchez-López M, Martinez-Vizcaino V. Effectiveness of school-based physical activity programmes on cardiorespiratory fitness in children: a meta-analysis of randomised controlled trials. Br J Sports Med. 2018;52:1234–40.

7. Rezende LFM de, Rodrigues Lopes M, Rey-López JP, Matsudo VKR, Luiz O do C. Sedentary Behavior and Health Outcomes: An Overview of Systematic Reviews. PLoS One. 2014;9:e105620.

8. Bielemann RM, Martinez-Mesa J, Gigante DP. Physical activity during life course and bone mass: A systematic review of methods and findings from cohort studies with young adults. BMC Musculoskelet. Disord. 2013; 14: 77

9. Sioen I, Michels N, Polfliet C, De Smet S, D'Haese S, Roggen I, et al. The influence of dairy consumption, sedentary behaviour and physical activity on bone mass in Flemish children: a cross-sectional study. BMC Public Health. 2015;15:717.

10. Hills AP, Andersen LB, Byrne NM. Physical activity and obesity in children. Br. J. Sports Med. 2011. 45: 866-870.

11. Ekelund U. Moderate to Vigorous Physical Activity and Sedentary Time and Cardiometabolic Risk Factors in Children and Adolescents. JAMA. 2012;307:704.

12. Carson V, Hunter S, Kuzik N, Gray CE, Poitras VJ, Chaput J-P, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth: an update. Appl Physiol Nutr Metab. 2016;41:240–65.

13. Costigan SA, Barnett L, Plotnikoff RC, Lubans DR. The health indicators associated with screen-based sedentary behavior among adolescent girls: A systematic review. J Adolesc Heal; 2013;52:382–92.

14. Biddle SJH, Ciaccioni S, Thomas G, Vergeer I. Physical activity and mental health in children and adolescents: An updated review of reviews and an analysis of causality. Psychol Sport Exerc; 2018;1–10.

15. Hoare E, Milton K, Foster C, Allender S. The associations between sedentary behaviour and mental health among adolescents: a systematic review. Int J Behav Nutr Phys Act. 2016;13:108.

16. Liu M, Wu L, Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: A meta-analysis of observational studies. Br J Sports Med. 2015;1–8.

17. Suchert V, Hanewinkel R, Isensee B. Sedentary behavior and indicators of mental health in school-aged children and adolescents: A systematic review. Prev Med. 2015;76:48–57.

18. Teychenne M, Costigan SA, Parker K. The association between sedentary behaviour and risk of anxiety: a systematic review. BMC Public Health. 2015;15:513.

19. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act. 2011;8:98.

20. Cairns KE, Yap MBH, Pilkington PD, Jorm AF. Risk and protective factors for depression that adolescents can modify: A systematic review and meta-analysis of longitudinal studies. J Affect Disord; 2014;169:61–75.

21. Hoare E, Skouteris H, Fuller-Tyszkiewicz M, Millar L, Allender S. Associations between obesogenic risk factors and depression among adolescents: A systematic review. Obes Rev. 2014;15:40–51.

22. Biddle SJH, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. Br J Sports Med. 2011;45:886–95.

23. Ferreira-Vorkapic C, Feitoza JM, Marchioro M, Simões J, Kozasa E, Telles S. Are There Benefits from Teaching Yoga at Schools?A Systematic Review of Randomized Control Trials of Yoga-Based Interventions. Evidence-Based Complement Altern Med. 2015;2015:1–17.

24. Eime RM, Young JA, Harvey JT, Charity MJ, Payne WR. A systematic review of the psychological and social benefits of participation in sport for children and adolescents: informing development of a conceptual model of health through sport. Int J Behav Nutr Phys Act. 2013;10:98.

25. Spruit A, Assink M, van Vugt E, van der Put C, Stams GJ. The effects of physical activity interventions on psychosocial outcomes in adolescents: A meta-analytic review. Clin Psychol Rev; 2016;45:56–71.

26. Ruotsalainen H, Kyngäs H, Tammelin T, Kääriäinen M. Systematic review of physical activity and exercise interventions on body mass indices, subsequent physical activity and psychological symptoms in overweight and obese adolescents. J Adv Nurs. 2015;71:2461–77.

27. Babic MJ, Morgan PJ, Plotnikoff RC, Lonsdale C, White RL, Lubans DR. Physical Activity and Physical Self-Concept in Youth: Systematic Review and Meta-Analysis. Sport Med. 2014;44:1589–601.

28. Liu M, Wu L, Ming Q. How does physical activity intervention improve self-esteem and self-concept in children and adolescents? Evidence from a meta-analysis. PLoS

One. 2015;10:1–17.

29. Korczak DJ, Madigan S, Colasanto M. Children's Physical Activity and Depression: A Meta-analysis. Pediatrics. 2017;139:e20162266.

30. Carter T, Morres ID, Meade O, Callaghan P. The Effect of Exercise on Depressive Symptoms in Adolescents: A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry. 2016; 55: 580-590

31. Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJH. Physical Activity Interventions and Depression in Children and Adolescents. Sport Med. 2013;43:195–206.

32. Bursnall P. The Relationship Between Physical Activity and Depressive Symptoms in Adolescents: A Systematic Review. Worldviews Evidence-Based Nurs. 2014;11:376–82.

33. Biddle SJ, Gorely T, Marshall SJ, Murdey I, Cameron N. Physical activity and sedentary behaviours in youth: issues and controversies. J R Soc Promot Health. 2004;124:29–33.

34. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes. 2008;32:1–11.

35. Smith JJ, Eather N, Morgan PJ, Lubans DR. The Health Benefits of Muscular Fitness for Children and Adolescents : A Systematic Review and Meta-Analysis. 2014;1209–23.

36. Henriksson P, Leppänen MH, Henriksson H, Delisle Nyström C, Cadenas-Sanchez C, Ek A, et al. Physical fitness in relation to later body composition in pre-school children. J Sci Med Sport. 2019;22:574–9.

37. Henriksson H, Henriksson P, Tynelius P, Ortega FB. Muscular weakness in adolescence is associated with disability 30 years later: a population-based cohort study of 1.2 million men. Br J Sports Med. 2018; 53: 1221-1230.

38. Luppino FS, de Wit LM, Bouvy PF, Stijnen T, Cuijpers P, Penninx BWJH, et al. Overweight, Obesity, and Depression. Arch Gen Psychiatry. 2010;67:220.

39. Sanders RH, Han A, Baker JS, Cobley S. Childhood obesity and its physical and psychological co-morbidities: a systematic review of Australian children and adolescents. Eur J Pediatr. 2015;174:715–46.

40. Rankin J, Matthews L, Cobley S, Han A, Sanders R, Wiltshire HD, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolesc Health Med Ther. Dove Press; 2016;7:125–46.

41. Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. Trends Cogn. Sci. 2013. 17: 525–44.

42. Marais L, Stein DJ, Daniels WMU. Exercise increases BDNF levels in the striatum and decreases depressive-like behavior in chronically stressed rats. Metab Brain Dis. 2009;24:587–97.

43. Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Physical activity and antidepressant treatment potentiate the expression of specific brain-derived neurotrophic

factor transcripts in the rat hippocampus. Neuroscience. 2000;101:305–12.

44. Cotman CW, Berchtold NC, Christie LA. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007; 30: 464–72.

45. Pedersen BK. Physical activity and muscle–brain crosstalk. Nat Rev Endocrinol. Nature Publishing Group; 2019;15:383.

46. Xiao Q, Wang F, Luo Y, Chen L, Chao F, Tan C, et al. Exercise protects myelinated fibers of white matter in a rat model of depression. J Comp Neurol. 2018;526:537–49.

47. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. Neuroimage. 2016;131:81–90.

48. Wassenaar TM, Yaffe K, van der Werf YD, Sexton CE. Associations between modifiable risk factors and white matter of the aging brain: insights from diffusion tensor imaging studies. Neurobiol Aging. 2019;80:56–70.

49. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014;8:584.

50. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette E, Raine L, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci; 2018;12:950.

51. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51:728–33.

52. Herting MM, Colby JB, Sowell ER, Nagel BJ. White matter connectivity and aerobic fitness in male adolescents. Dev Cogn Neurosci. 2014;7:65–75.

53. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved frontoparietal white matter integrity in overweight children is associated with attendance at an after-school exercise program. Dev Neurosci. 2014;36:1–9.

54. Augustijn MJCM, Di Biase MA, Zalesky A, Van Acker L, De Guchtenaere A, D’Hondt E, et al. Structural connectivity and weight loss in children with obesity: a study of the “connectobese.” Int J Obes. Nature Publishing Group; 2019;1–13.

55. Ou X, Andres A, Pivik RT, Cleves MA, Badger TM. Brain gray and white matter differences in healthy normal weight and obese children. J Magn Reson Imaging. 2015;42:1205–13.

AIMS

AIMS

Overall aim

The overall aim of the present International Doctoral Thesis is to study the role of physical activity, sedentary behavior and fitness in mental health and white matter in children and adolescents. This overall aim is addressed in eight specific aims which correspond to eight different studies.

Specific aims

Part I: Physical activity, sedentary behavior, fitness and mental health

- **Specific aim I:** To provide an updated synthesis of the evidence on the effects and associations of physical activity and sedentary behavior with mental health in young people by conducting a review of reviews (**Study I**).
- **Specific aim II:** (i) To determine the overall effect of physical activity on mental health in preschoolers, children and adolescents by conducting a meta-analysis of available intervention studies, and (ii) to systematically synthesize recent observational evidence (both longitudinal and cross-sectional) on the association between physical activity and sedentary behavior with mental health in various pediatric age groups (**Study II**).
- **Specific aim III:** To examine the associations of physical fitness components (i.e. cardiorespiratory fitness, muscular strength, and speed/agility) with psychological distress indicators (i.e. stress, anxiety, depression, and negative affect) and psychological well-being indicators (i.e. positive affect, happiness, optimism, and self-esteem) in children with overweight or obesity from the ActiveBrains project (**Study III**).

Part II: Physical activity, sedentary behavior, fitness and white matter

- **Specific aim IV:** To examine the associations of physical activity and screen time with white matter microstructure in a population-based sample of 10-year old children from the Generation R project (**Study IV**).
- **Specific aim V:** (i) To identify any associations of physical activity and sedentary behavior with global white matter microstructure in children with overweight or obesity from the ActiveBrains project, and (ii) to determine whether the association with white matter microstructure was global, or rather, restricted to a particular set of white matter bundles. As such, associations with FA and MD within individual tracts were also tested when exposures showed an association with global DTI metrics (**Study V**).
- **Specific aim VI:** (i) To examine the association between cardiorespiratory fitness and white matter volume in two projects with similar age participants (i.e., the ActiveBrains project and the FITKids2), (ii) to examine whether the abovementioned associations differ between normal-weight and children with overweight or obesity using data from the FITKids2 project, and (iii) to analyse the association between other physical fitness components (i.e., motor and muscular) and white matter volume using data from the ActiveBrains project (**Study VI**).
- **Specific aim VII:** To examine the associations of components of physical fitness (i.e., cardiorespiratory, muscular, and motor fitness) with white matter microstructure in children with overweight or obesity from the ActiveBrains project (**Study VII**)
- **Specific aim VIII: (**i) To investigate the effects of a 20-week randomized controlled physical activity trial on global white matter microstructure in

children with overweight or obesity from the ActiveBrains project, and (ii) in order to determine whether the effect of physical activity on white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, the effect of the exercise intervention on FA and MD within individual tracts was also tested **(Study VIII).**

METHODOLOGICAL OVERVIEW OF THE STUDIES INCLUDED

METHODOLOGICAL OVERVIEW OF THE STUDIES INCLUDED

The present International Doctoral Thesis is composed of a total of 8 studies. They are classified in two different parts based on the main outcome of the study, i.e., **Part I** is focused on mental health outcomes, while **Parte II** is focused on white matter. The methodological overview has been explained according to this criterion. Then, **Table 1** shows the methodological overview of studies included into the **Part I** (i.e., **Studies I**, **II**, **III**) while **Table 2** shows the methodological overview of studies included into the **Part II** (**Studies IV**, **V**, **VI**, **VII**, **VIII**).

Table 1. Methodological overview of studies included in the **Part I** of this Doctoral Thesis.

Study	Design	Search Strategy	Inclusion criteria (both Study I and Study II)	Independent variables (both Study I and Study II)	Dependent variables (both Study I and Study II)
Study I	Review of reviews	The search was conducted on PubMed and WOS from Jan 1st 2011 to July 31th 2018	(1) Design criterion: Study I included systematic review and meta-analyse while Study II included individual intervention studies (RCT, non-RCTs), prospective longitudinal studies and cross-sectional studies; (2) language criterion: articles only published in English or Spanish; (3) age criterion: preschoolers (2–5 years of age), children (6–11 years of age) and/or adolescents (12–18 years of age)	Physical activity: physical activity practises contain elements of sports or exercise, implemented in different settings) Sedentary behavior: recreational screen time (i.e., viewing TV, using computer game, playing videogames, using mobile phone, using internet), non-recreational screen time (i.e., homework using a screen) and non-screen time (i.e., music, passive transport, homework, reading, creative hobbies, talking)	At least one psychological well-being outcome (i.e., perceived appearance, self-concept, self-esteem, positive affect, happiness and life satisfaction) and/or psychological distress outcome (i.e., depression, anxiety, stress or negative affect)
Study II	Systematic review and meta-analysis	The search was conducted in the PubMed and WOS from Jan 1st 2013 to April 9th 2018			
Study	Design; target population	Project	Participants	Independent variables (instruments)	Dependent variables (instruments)
Study III	Cross-sectional study; children with overweight or obesity	ActiveBrains	110 children with overweight or obesity (10.0 ± 1.1 years old; 65% boys) from Granada (southern Spain)	CRF (20mSRT and maximal incremental treadmill), muscular strength (handgrip and SLJ) and speed-agility (4x10m)	Stress (CDSI), Anxiety (STAIC-R), Depression (CDI), Positive and Negative affect (PANAS-C), Happiness (SHS), Optimism (LOT-R), Self-Esteem (RSE)

CDSI= the Children's Daily Stress Inventory. CDI= the Children Depression Inventory. CRF = Cardiorespiratory fitness. LOT-R=the Life Orientation Test. PANAS-C=the Positive and Negative Affect Scale for Children. RSE= the Rosenberg self-esteem questionnaire. RCT = Randomized controlled trial. STAIC-R= the State-Trait Anxiety Inventory. SHS= the Subjective Happiness Scale. SLJ = Standing long jump test. SRT = Shuttle run test. WOS= Web of Science.

Table 2. Methodological overview of studies included in the **Part II** of this Doctoral Thesis.

Study	Design; target population	Project	Participants	Independent variables (instruments)	Dependent variables (instruments)
Study IV	Cross-sectional study; Children from a population-based study	Generation R	2532 children (mean age 10.12 ± 0.58 years; 50.04% boys) from Rotterdam, the Netherlands	Physical activity and screen time (Parent-reported questionnaire)	White matter microstructure (MRI, DTI using tractography)
Study V	Cross-sectional study; children with overweight or obesity	ActiveBrains	103 children with overweight or obesity (10.02±1.15 years old; 42 girls) from Granada, Spain	Physical activity and sedentary behavior (ACC and YAP-S)	White matter microstructure (MRI, DTI using tractography)
Study VI	Cross-sectional study; children	ActiveBrains & FITKids2	242 children of which 100 children with overweight or obesity belong to the ActiveBrains project (10.0±1.1 years; 40girls) and 142 children belong to the FITKids2 project (8.6±0.5 years; 109 girls)	CRF (20mSRT in the ActiveBrains project and maximal incremental treadmill in the FITKids2 project), muscular strength (handgrip and SLJ) and speed-agility (4x10m)	White matter volume (MRI, T1-weighted images acquired with a 3.0 T S Magnetom Tim Trio system)
Study VII	Cross-sectional study; children with overweight or obesity	ActiveBrains	104 children (10.04±1.15 years old; 43 girls) with overweight or obesity from Granada, Spain	CRF (20mSRT), muscular strength (handgrip and SLJ) and speed-agility (4x10m)	White matter microstructure (MRI, DTI, using tractography and TBSS)
Study VIII	RCT; children with overweight or obesity	ActiveBrains	83 children with overweight or obesity (10.06±1.11 years old; 39 girls) from Granada, Spain	Intervention program: 4.5-month of the exercise program. 3-5 sessions/week, 90 min/session.	White matter microstructure (MRI, DTI, using tractography)

ACC = Accelerometry. CRF = Cardiorespiratory fitness. MRI = Magnetic resonance imagining. DTI=Diffusion tensor imaging. SLJ = Standing long jump test. SRT = Shuttle run test. TBSS= tract-based spatial statistics. RCT = Randomized controlled trial.

RESULTS AND DISCUSSION

Part I. Physical activity, sedentary behavior, physical fitness and mental health

STUDY I

Physical activity, sedentary behavior and mental health in young people: A review of reviews.

María Rodriguez-Ayllon, Fernando Estévez-López, Cristina Cadenas-Sánchez, Luis Gracia-Marco, David R. Lubans, Francisco B. Ortega, Irene Esteban-Cornejo.

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INTRODUCTION

According to the WHO, mental health is crucial to the overall well-being of individuals and societies. In many cultures, unfortunately, mental health and mental disorders are often overlooked or, at least, neglected in comparison to physical health. However, mental disorders are one of the main causes of disability in developed countries [1]. The prevention of mental health disorders not only depends on the absence of psychological ill-being but also on the presence of psychological well-being [2]. In this chapter, the term psychological ill-being will be used to represent either preclinical psychological states (e.g., high levels of negative affect and stress) or clinically diagnosed mental health disorders such as depression and anxiety. Psychological well-being is the combination of positive affective states and functioning with optimal effectiveness in personal and social life [2]. There is overlap among common indicators of psychological well-being. Thus, the umbrella term of ‘psychological well-being’ will be used to describe positive indicators of mental health such as self-esteem, self-concept, perceived appearance, and the affective and cognitive dimensions of SWB (i.e., positive affect and life satisfaction).

Both childhood and adolescence are stages of the human lifespan characterized by brain plasticity [3, 4], identity development [5] and the establishment of behavioral patterns, which might affect mental health [6]. In addition, in this period, young people experience increased autonomy for making decisions that may influence their mental health status, which highlights the importance of prevention during this period of life. Public health institutions in the area of mental health have focused on encouraging early help seeking, rather than equipping young people with the skills to preserve their mental health. Indeed, there is a need for literature identifying what actions youths can undertake in their daily lives in order to lower their risk of mental health disorders.

Despite compelling evidence suggesting physical activity plays an important role in health [7], a substantial proportion of young people do not meet the recommended levels of physical activity [8, 9]. Specifically, physical activity has been routinely linked to a variety of mental health benefits. For instance, a 2011 review of reviews showed the potential and beneficial effect of physical activity on mental health in children and adolescents [10]. In the last few years, several systematic reviews and meta-analyses have been published [11]. However, these have been focused on a particular mental health [12–17], on specific physical activity or exercise practices [18, 19], on specific age ranges [20, 21], on mechanisms (i.e., neurobiological, psychosocial and behavioral mechanisms) [22] explaining the relationship between physical activity and mental health or context (e.g., leisure-time physical activity, school sport) [23], making it difficult to obtain the overall picture.

Furthermore, youths are now remarkably exposed to screens, achieving exposure times never seen before [24]. The *American Psychological Association* [25] and the *American Pediatric Society* [26] recommend that parents and caregivers limit on the time and the type of media use. In addition, they suggest caregivers make sure media does not take the place of adequate sleep, physical activity and other behaviors essential to health. However, more evidence is needed to support these recommendations in young people [27]. In this context, a vast of separate systematic reviews and meta-analyses have investigated the role of sedentary behavior, especially recreational screen time (e.g., watching TV, computer/internet use, and video gaming) in the mental health of young people [28–36]. However, robust conclusions have not been established so far due to inconsistencies in the literature.

The aims of this chapter, therefore, are (i) to provide an updated synthesis of findings on the effects and associations of physical activity and sedentary behavior with mental health in young people, (ii) to identify gaps in knowledge and (iii) to suggest directions for future research. For these purposes, we performed a comprehensive and methodological review of systematic reviews and meta-analyses focused on the role of physical activity and/or sedentary behavior on psychological ill-being (i.e., depression, anxiety, stress or negative affect) and/or psychological well-being (i.e., perceived appearance, self-concept, self-esteem, positive affect, happiness and life satisfaction) in young people. A detailed description of the main methods and results used to retrieve the available information on this topic is available in the **Supplemental Material.** Specifically, a detailed description of the search strategy, a summary of systematic reviews and/or meta-analyses investigating the relationship between physical activity and/or sedentary behavior and mental health outcomes, and the results of the risk of bias assessment can be found in **Table S1**, **Table S2**, and **Table S3**, respectively. Moreover, a flow chart illustrating the results of the selection process is shown in **Fig. 1**.

Physical activity and psychological ill-being in young people

Summary

Researchers have been primarily interested in identifying modifiable factors (e.g., physical activity) associated with psychological ill-being symptoms in youths, with the focus on depression. Existing evidence suggests that higher levels of physical activity are related to lower depression, with a small to moderate significant mean effect size in youths (see **Sect. 2.1**). Although previous literature have shown that higher levels of physical activity are related to lower levels of anxiety, stress and negative affect, we found minimal evidence in our review (see **Sect. 2.2**). A summary of the associations between physical activity and psychological ill-being outcomes is shown in **Fig. 2**.

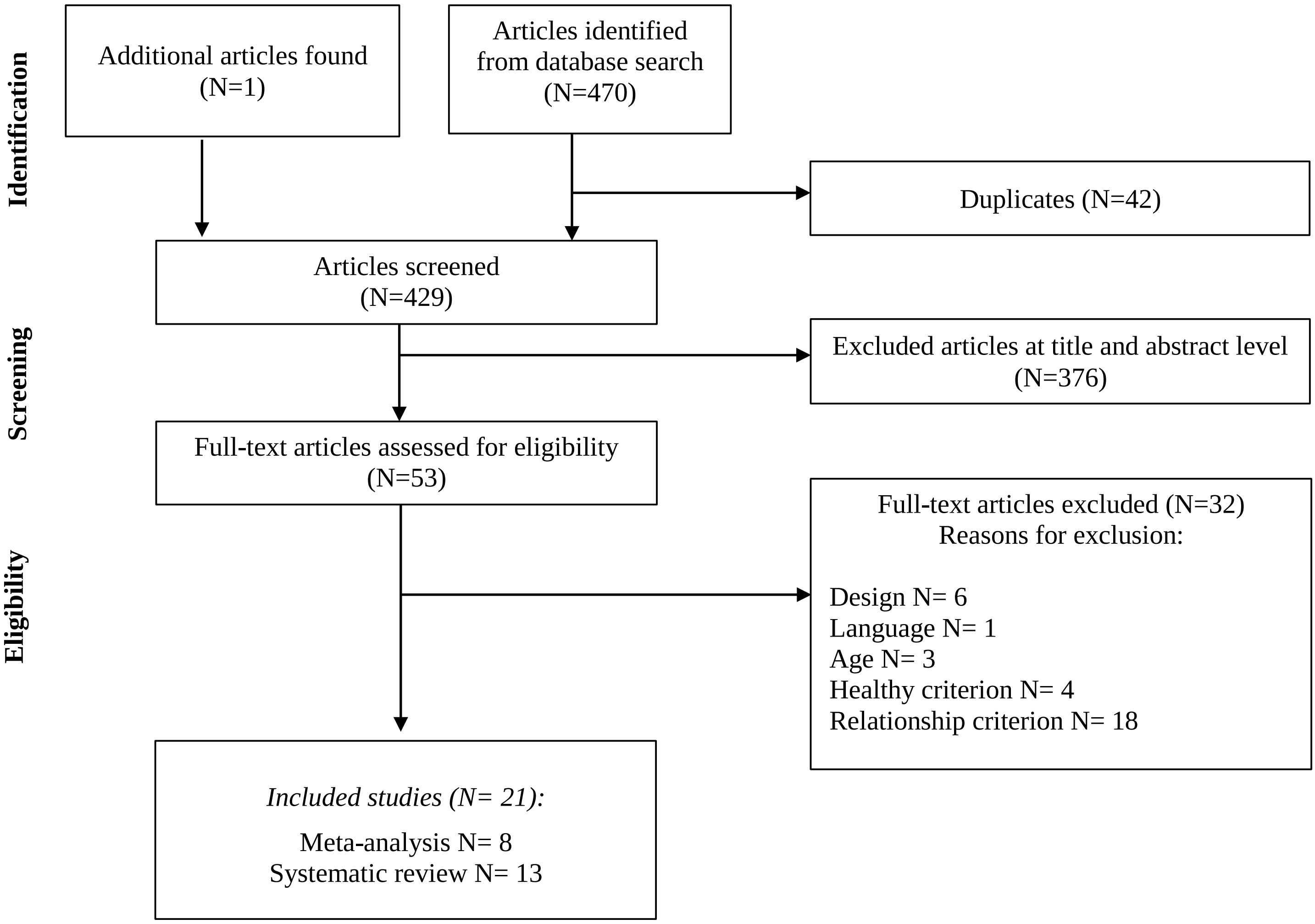

Figure 1. Flow chart showing the results of the selection process.

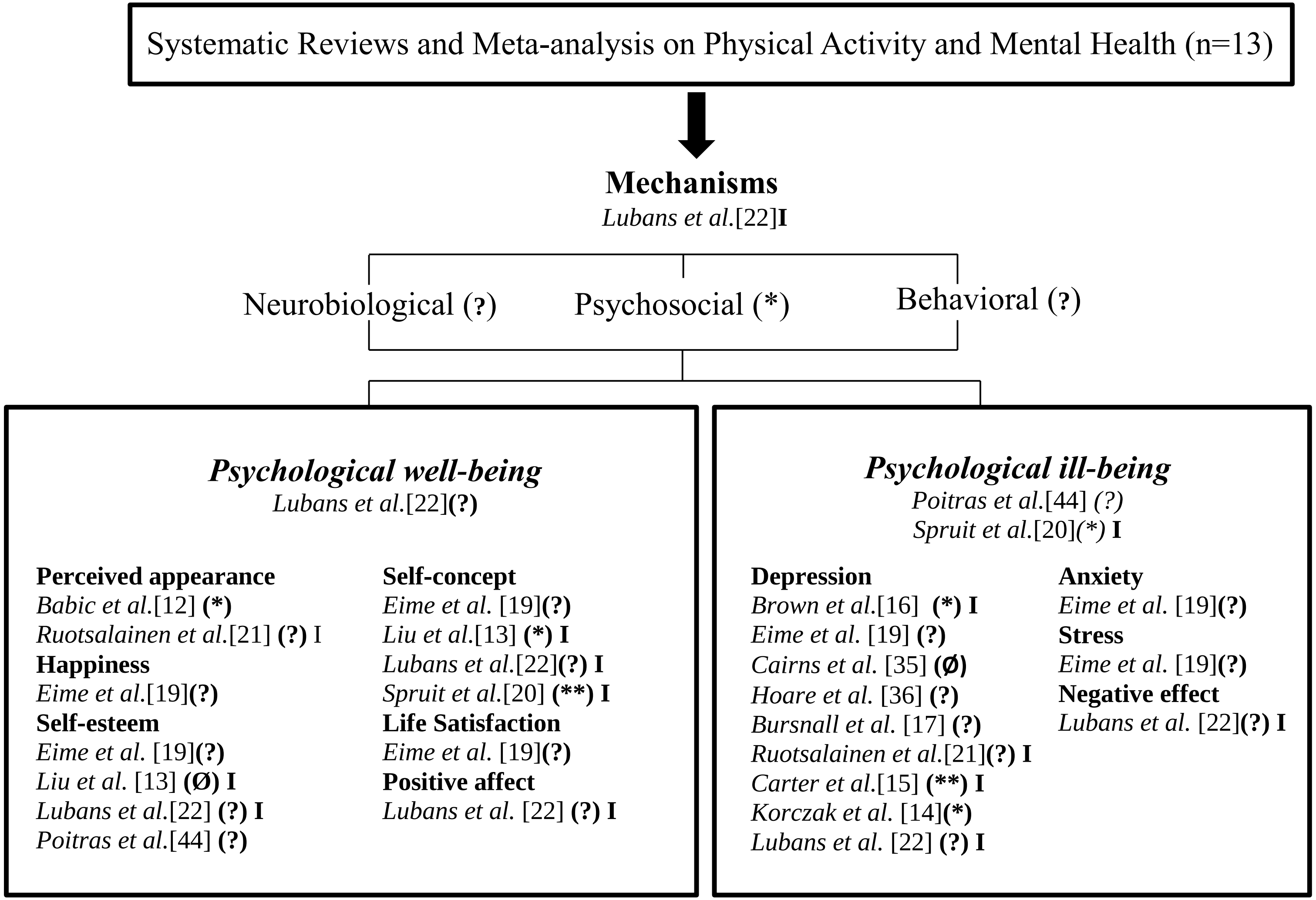

Figure 2. Relationships summary between physical activity and mental health outcomes. **(*)** = low evidence, **(**)** = moderate evidence, **(***)** = strong evidence, **(?)**=unclear evidence, **(Ø)** = no significant association/effect. **I**= reviews included only intervention studies.

Physical activity and depression

Depression is a major human health concern. Globally, it is responsible for more ‘years lost’ to disability than any other condition [37]. Consequently, most of the studies on physical activity and mental health have focused exclusively on reducing and preventing depressive symptoms.

Korczak et al. [14] synthesized observational, mostly cross-sectional, studies concluding that physical activity and depression were negatively associated in young people. The association was moderated by study design (stronger associations in cross-sectional versus longitudinal designs), type depression measure (stronger associations for self-reported versus interviewed depression), and type of measure of physical activity (stronger associations emerged with more informative measures including, for instance, frequency and intensity versus only one of this characteristics). In 2011, Biddle et al. [10] underlined that evidence base was limited, suggesting that experimental designs of high quality were required. In their recent update [11], they found a small improvement in trial quality.

Experimental evidence suggests that exercise interventions are effective for reducing depression, yet the effect size fluctuates across reviews. In 2006, Larun et al. [38] summarised findings provided by intervention studies suggesting that the effect of exercise on depression was moderate. In a similar review published in 2013, Brown et al. [16] concluded that the effect of exercise on reducing depression was small. Most recently, Carter et al. [15] concluded that the effect size of exercise for reducing depressive symptoms was moderate. Interestingly, the latter review pointed out that the effectiveness of exercise on depression was not significant in high quality studies. This finding was also reported by Ferguson et al. [27] who suggested that studies in which researchers used unstandardized outcome measures and poor quality methods produced higher, potentially inflated effect sizes.

Overall, physical activity has a small-moderate significant effect on depression in young people. However, it is important to take into account important moderators such as age, sex, social risk factors and level of depression at baseline. For instance, it seems that physical activity has a stronger positive effect on children with unknown social risk factors compared with those with social risks (e.g. low income). A possible explanation for this might be that children from low socioeconomic environments might be exposed to many more risk factors for depression (e.g., poorer nutrition and other lifestyle behaviors). Similarly, in trials with exclusively clinical samples, exercise showed a larger beneficial effect on depression in comparison to those from the general population. These findings are not surprising and highlight the importance of conducting and reporting moderation analyses to determine the effect of health promotion interventions in both general young population and those at risk of poor mental health.

Finally, those interventions focused exclusively on reducing depression (with no additional outcomes) were more effective than those including secondary outcomes [16]. Therefore, it seems plausible that specific interventions, rather than generic "one-size-fits-all" approaches, are needed in order to reduce depression among children and adolescents. Until robust evidence from well-designed RCTs is available, educational and health institutions may collectively consider these findings when designing physical activity interventions for decreasing depressive symptoms in youths.

Psychological ill-being outcomes with minimal evidence in relation physical activity: anxiety, stress, and negative affect

In comparison to depression, less attention has been paid to anxiety, stress and negative affect. However, these negative indicators might also have a serious impact on young people's health. For instance, anxiety has been shown to be linked to other serious diseases such as increased risk of cardiovascular disease and cancer [39].

Biddle et al. [11] concluded that literature on physical activity and anxiety in young people remains small and fragmented. They suggested that there is a relationship between physical activity and anxiety, although further work is required. For instance, the scarce evidence already available in the literature suggests that participation in team sports has a positive effect on anxiety in young people [40]. In regard to stress, a longitudinal study found that involvement in school sport during adolescence was a significant predictor of lower stress in young adulthood [41]. In addition, Martikainen et al. [42] found that objectively measured physical activity was associated with diurnal hypothalamic-pituitary-adrenocortical axis activity, which in turn was related to lower psychosocial stress in children. Lastly, a RCT conducted in obese and morbidly obese adolescents showed that physical activity therapy did not reduce negative affect after 8 weeks, 14 weeks and 28 weeks [43].

In summary, more research is required to determine the link between physical activity, anxiety, stress and negative affect in young people. Given the current state-of-the-art, even observational studies may be worthy to suggest whether physical activity is associated with anxiety, stress, and negative affect. Experimental studies testing the effectiveness of exercise interventions for reducing these psychological ill-being outcomes in young people are needed.

Physical activity and psychological well-being in young people

Summary

The relationship between physical activity and psychological well-being outcomes (i.e., perceived appearance, self-concept, self-esteem, positive affect, life satisfaction and happiness) has been investigated in seven reviews [12, 13, 19–22, 44]. Evidence suggests that higher levels of physical activity are related to better global self-concept and perceived appearance, with a small-to-moderate significant mean effect size (see **Sect. 3.1**, **Sect. 3.2**). The association of physical activity with self-esteem is unclear due to the inconsistencies in the findings of different studies [19, 22, 44] (see **Sect. 3.3**). Lastly, only a few studies have shown that higher levels of physical activity are related to higher levels of happiness, life satisfaction and positive affect (see **Sect. 3.4**). Relationships summary between physical activity and psychological well-being outcomes is shown in **Fig. 2**.

Physical activity and global self-concept

Global self-concept is the term used to describe an individual’s awareness of their qualities and limitations. In other words, global self-concept is a person’s perceptions of himself or herself, namely, what a person thinks about himself or herself [45]. Perceived appearance (sometimes referred to as perceived physical attractiveness), perceived fitness (typically aerobic and muscular fitness) and perceived competence (sport and movement skill competence) are sub-domains of physical self-concept [46], which in turn generalise to global self-concept. Thus, in this chapter, findings related to global-self-concept are shown in this section and findings related to perceived appearance are shown in **Sect. 3.2**.

A small-to-moderate effect of physical activity on global self-concept has been consistently demonstrated in two meta-analyses [13, 20]. First, Liu et al. [13] showed a small but significant positive effect of physical activity interventions on global self-concept. Then, Spruit et al. [20] showed that there was a significant small-to-moderate effect of physical activity interventions on global self-concept, which has been corroborated in diverse studies, regardless of the participants' characteristics (i.e., proportion of males, and proportion of youth from ethnic minority groups). However, the study settings [13] and the type of physical activity programs (sport vs. exercise) [20] might moderate the effect of physical activity on self-concept in youths.

For instance, Liu et al. [13] revealed stronger effects in studies which involved school- and gymnasium-based interventions, compared with family-, clinic-, and detention facility-based interventions [13]. Thus, in order to promote global self-concept through physical activity engagement, interventions in youth daily life settings may be encouraged. In settings such as schools, youths potentially experience a higher level of autonomy compared with clinic-based settings, which in turn, may increase enjoyment and, therefore, enhance global self-concept levels. Thus, although there is emerging evidence on the association between physical activity and self-concept [13], high quality school-based physical activity interventions are warranted [47].

On the other hand, Spruit et al. [20] showed that none of the sample characteristics (i.e., sample type, proportion of males, and proportion of youth from ethnic minority groups) moderated the effect of physical activity interventions on global self-concept [20]. In addition, no moderating effects were found for the type of intervention, the duration and frequency of the intervention, whether the intervention consisted of team or individual physical activities, and whether or not the instructor/therapist had any pedagogical background. However, they found a significant moderating effect of the type of physical activity (sports vs. exercise) implemented in the intervention. Specifically, larger effects on global self-concept were found when the intervention consisted of exercise (typically aerobic). One possible explanation is that participation in aerobic-based activity is important for maintaining a healthy body weight, which might enhance global self-concept via the mechanism of improved physical appearance. Alternatively, exercise interventions often focus on generating a minimum level of physical exertion, which may release endogenous opioids and interact with other neurotransmitters [22]. Thus, exercise may be more strongly related to the sense of “feeling well about your-self” than sports activities, which are also focused on the social environment and the competitive element. They proposed that the sports element of winning a game can lead to increased self-concept, whereas losing the game may have adverse effects on global self-concept. In line with these findings, Lubans et al. [22] explained that competitive sport environments can be intimidating for young people with low levels of movement skill competency.

To sum up, in order to promote global self-concept through physical activity engagement, interventions in youth daily life settings may be recommended. In addition, it is important to take into account that exercise interventions might be more effective than sport-based interventions, particularly in populations with low levels of physical self-concept (i.e., perceived competence, perceived fitness and perceived appearance). However, youths who feel good about themselves and their abilities, being resilient when they lose the game, might also experience benefits on global self-concept from participating in sport programs. Therefore, well-designed school-based physical activity interventions, attending to the individual physical self-concept (i.e., perceived competence, perceived fitness and perceived appearance) of youths, are needed to improve global self-concept at these ages.

Physical activity and perceived appearance

Perceived appearance is defined as subjective perceptions and attitudes that people have about their own physical body attributes (e.g., body shape). Poor body image is an important concern for youth. Of note, approximately one-third of adolescent boys and two-thirds of girls are dissatisfied with their appearance [48], which consequently may have a negative impact on their overall mental health [49].

Babic et al. [12] conducted a systematic review studying the link between physical activity and physical appearance in young people. They found a significant, yet weak association between physical activity and perceived appearance ($r = 0.12$, $p<0.001$). Interestingly, age was found to significantly moderate this association, with the strongest associations found in young adolescents. Sex and study designs were not significant moderators.

Adolescents with overweight or obesity reported lower levels of perceived appearance compared to their normal-weight counterparts[50]. Thus, prevention and treatment efforts are particularly needed for this at-risk population. In this context, Ruotsalainen et al. [21] performed a systematic review focused on children with overweight or obesity to synthesise the effects of physical activity interventions on perceived appearance. While the review suggested that physical activity interventions can improve perceived appearance in overweight/obese adolescents, only two studies were identified. In this line, Daley et al. [43] found a positive effect of physical activity on self-perception in obese and morbidly obese adolescents at the 14-week and 28-week follow-up, but not immediately after the intervention. In a multicomponent intervention conducted in adolescent females (behavioral change and education), DeBar et al. [51] showed that those in the intervention group reported greater body satisfaction post-treatment compared with the control group.

Therefore, more studies both in boys and girls are needed to corroborate the early evidence suggesting that physical activity might have a positive effect on perceived appearance in young people. Special attention is required in the adolescence period and also in special populations, such as overweight and obese individuals.

Physical activity and self-esteem

Self-esteem is the evaluative and affective dimension of self-concept [52], and is considered equivalent to self-regard, self-estimation and self-worth [53]. In other words, self-esteem is the degree to which an individual values himself or herself. Although it is widely believed that physical activity is associated with the development of self-esteem in young people, the findings are inconsistent [11].

Of note, Eime et al. [19] highlighted that, in addition to physical activity, sport participation may positively affect self-esteem [19]. In a longitudinal study with a sample of 500 adolescents, team sport achievements in early adolescence were found to be positively associated with self-esteem three years later in middle adolescence [54]. On the other hand, many studies have observed an unclear association [44], or effect [13], of physical activity on self-esteem. For instance, Liu et al. [13] performed a meta-analysis and concluded that exercise did not improve self-esteem in young people. The same finding emerged when only objective measurements of physical activity were considered in observational studies [44]. This inconsistency might be explained in part by the definitional and conceptual ambiguity found between studies [11].Therefore, future studies should defined consistently self-esteem term in order to establish robust conclusions. We suggest the aforementioned definition to refer to self-esteem.

It is noteworthy that, even when significant associations were found, the effect of this association differs according to youths' characteristics. For instance, the positive influence that participating in sport club activities had on the development of self-esteem may differ by sex and age [55]. Furthermore, consistent with the *Exercise and Self-esteem Model* proposed by Sonstroem et al. [52], Lubans et al. [22] improvements in self-esteem should be expected in the presence of positive changes in self-perceptions or global self-concept. It is important to note, that changes in physical self-perceptions will need to be relatively large to promote improvements in global self-esteem.

To conclude, it seems that there is an unclear relationship between physical activity and global self-esteem in youths [13, 19, 22, 44]. A potential reason behind this finding is a paucity of high quality studies and the conceptual ambiguity, among other reasons. Furthermore, the expectation of obtaining significant and positive effects of physical activity or sport participation on self-esteem seems to be unrealistic, at least, as far as improvements on physical self-concept are not reached (see **Sect. 6**).

Psychological well-being outcomes with minimal evidence in relation physical activity: happiness, positive affect, and life satisfaction.

In addition to the above discussed indicators, the literature has focused less on other important psychological well-being indicators: happiness, positive affect, and life satisfaction. SWB, refers to perceptions on whether one’s own life is good, meaningful, and worthwhile [56]. Although sometimes used interchangeably with happiness, SWB includes evaluations that are both affective (i.e., positive affect) and cognitive (i.e., life satisfaction) in nature [57].

Previous research has shown that increasing physical activity is associated with higher levels of happiness [58]. Increasing the volume of physical activity was strongly associated with higher levels happiness, while increasing the intensity had a small effect [58]. Identifying mechanisms through which physical activity promotes happiness are of interest (see **Sect. 6**). As suggested by Lubans et al. [22] a potential path is via changes in one or more brain monoamines (i.e., dopamine, adrenaline, and serotonin), which requires corroboration in studies involving young people [59].

Moreover, higher levels of extracurricular sport participation were related to higher life satisfaction among adolescents [60]. Similarly, playing team sports has been associated with greater life satisfaction among high school adolescents [61]. Lastly, only one RCT has tested the effects of physical activity on positive affect in obese adolescents and no association was found [43].

Overall, few studies have examined the associations between physical activity and happiness, positive affect, and life satisfaction. Future studies are needed to address this gap of knowledge.

Yoga and mental health in young people

According to the *ACSM's top 10 Worldwide Fitness Trends for 2018*, Yoga was ranked number 7, which first appeared in the top 10 in this survey in 2008 [62]. Yoga is a holistic system of multiple mind-body practices that include physical postures and exercises, breathing techniques, deep relaxation practices, cultivation of awareness/mindfulness, and meditation [18]. In addition, yoga is a very different form of exercise since it requires lower energy expenditure and higher emphasis on breath regulation, mindfulness during practice, and maintenance of postures. Thus, in this chapter, findings related to yoga and mental health are shown in an independent section.

The positive effect of yoga on mental health in adult populations is well established [63, 64]. However, less is known about its effectiveness in youths. Ferreira-Vorkapic et al. [18] conducted a systematic review on benefits from teaching yoga at schools. They found nine intervention studies focused on the effect of yoga on the mental health of youths. Results showed no significant changes between groups in self-reported positive affect, global self-worth or internalizing problems. However, they found that negative affect increased for those children participating in yoga when compared to a regular physical education program. They suggested several possible explanations for these results [18]. First, the practice of yoga requires effort and discipline. Therefore, the child’s first contact with yoga is often demanding and the child may experience higher levels of stress over the short term. Second, the “dose” and type of yoga may not have been appealing to the participants. Third, one of the outcomes of yoga practice may be greater self-awareness and mindfulness and these variables were not assessed in the included studies in that review. Lastly, the sample size of included studies was small.

In conclusion, future yoga programs in young people should address the adaptation process, the attentional control and the adequacy of yoga practice for young people. These findings must be interpreted with caution because of the reduced number of RCTs in school settings and the conflicting findings.

Possible negative effects of physical activity interventions on young people’s mental health.

In general, physical activity might have beneficial effects on the mental health of young people. However, physical activity can also have negative effects on the mental health of young people in certain contexts and circumstances. For instance, poorly designed physical education lessons may thwart student´s needs satisfaction and lead to decreases in perceived competence and global self-esteem [65]. Moreover, some studies have suggested that physical activity interventions can have a negative effect on social inclusion [66, 67],since social inequalities between players can actually be emphasized through the competitive component of sports [68].

It is important highlight that when young people do not experience increased physical competence or perceived appearance (e.g., by not gaining strength, not experiencing weight loss, or losing games all the time), physical activity may actually have a negative influence on global self-concept [22]. This may be due to the fact that individuals may have unrealistic expectations regarding the effects of exercise training on body shape, which may lead to reduced physical self-concept.

Possible mechanisms for the effect of physical activity on mental health in young people

Clarifying how and under which conditions mental health changes occur might facilitate the successful development of physical interventions [22]. In this context, Lubans et al. [22] proposed a conceptual model to explain the effect of physical activity on young people's mental health (see **Fig. 3**). They suggested three groups of potential mechanisms (neurobiological, psychosocial, and behavioral).

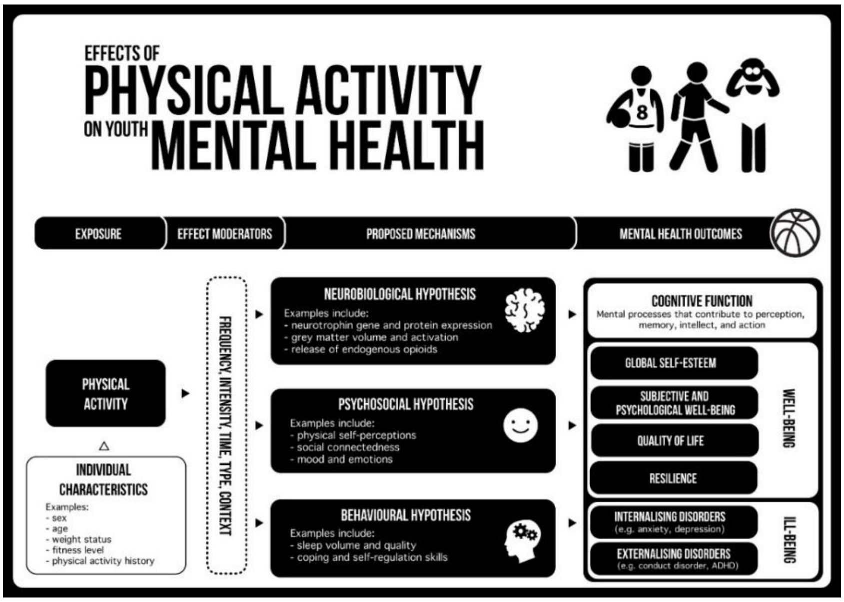

Figure 3. Conceptual model for the effects of physical activity on mental health outcomes in children and adolescents. ADHD, attention-deficit/hyperactivity disorder. Lubans et al. [22].

Firstly, the neurobiological mechanism posits that physical activity may have a positive effect on the structure and function of the brain. For instance, previous studies have used neuroimaging techniques to identify structural and functional mechanisms that may explain the relationship between physical activity and mental health in young people [69]. It is important to note that these neuroimaging techniques do not provide a direct measure of mechanism change; instead, they represent the outcome of some other mechanistic changes in the brain. In this regard, it is well known that decreased levels of BDNF, a 14-kDa neurotrophin involved in the growth and healthy maintenance of neurons, is associated with increased levels anxiety and depression [70, 71]. Exercise is known to increase BDNF levels in the central nervous system, and consequently, may improve anxiety and depressive symptoms [72]. Another possible explanation is that exercise stimulates the growth of new capillaries, which are critical for the transport of nutrients to neurons [73], which may influence mental health. Lastly, the release of endogenous opioids and their interactions with other neurotransmitter systems might also provide a possible neurobiological explanation for the effects of physical activity on mental health [74]. For instance, non-pharmacological methods for raising brain dopamine, noradrenaline, and serotonin, such as exercise, may prevent the onset of mental disorders [75, 76]. However, more studies are needed to test if the short-term pleasure that individuals experience during physical activity can enhance mental health in young people over time.

Secondly, as noted by Lubans et al. [22], the most commonly evaluated psychosocial mechanisms are physical self-concept subdomains. They suggested that there is emerging evidence for a causal link between physical self-perceptions, improved by physical activity interventions, and indicators of psychological well-being (e.g., global self-concept, self-esteem). Social support and autonomy are other plausible psychosocial mechanisms that may mediate the effect of physical activity on mental health in young people. For instance, Lubans et al. [77] found that autonomy mediated the effect of the physical activity on psychological well-being in adolescent boys. However, more studies are needed to corroborate these findings.

Finally, behavioral mechanisms may also explain the effect of physical activity on mental health outcomes. Of note, participation in physical activity may improve sleep duration, sleep efficiency, sleep onset latency, and reduce sleepiness [22]. Lubans et al. [22] did not identify relevant studies investigating behavioral mechanism variables in their systematic review, highlighting a clear gap in the literature. However, they suggested that additional behaviors, such as drug taking (e.g., smoking and alcohol), diet, and recreational screen-time may also mediate the effect of physical activity interventions on mental health outcomes in youths.

Collectively, neurobiological, psychosocial, and behavioral mechanisms might be responsible for the effects of physical activity on mental health in young people. However, there are not enough studies to draw firm conclusions about any of these potential mechanisms. Indeed, only physical self-perceptions have been tested as a potential psychosocial mechanism of the effect of physical activity in self-esteem. Thereby, future mediation models of the relationship of physical activity with mental health are warranted.

Sedentary behavior and psychological ill-being in young people

Summary

Evidence in regard to the sedentary behavior and psychological ill-being outcomes (i.e., non-specific psychological ill-being, depression, anxiety, stress, and negative affect) is shown in **Fig. 4**.

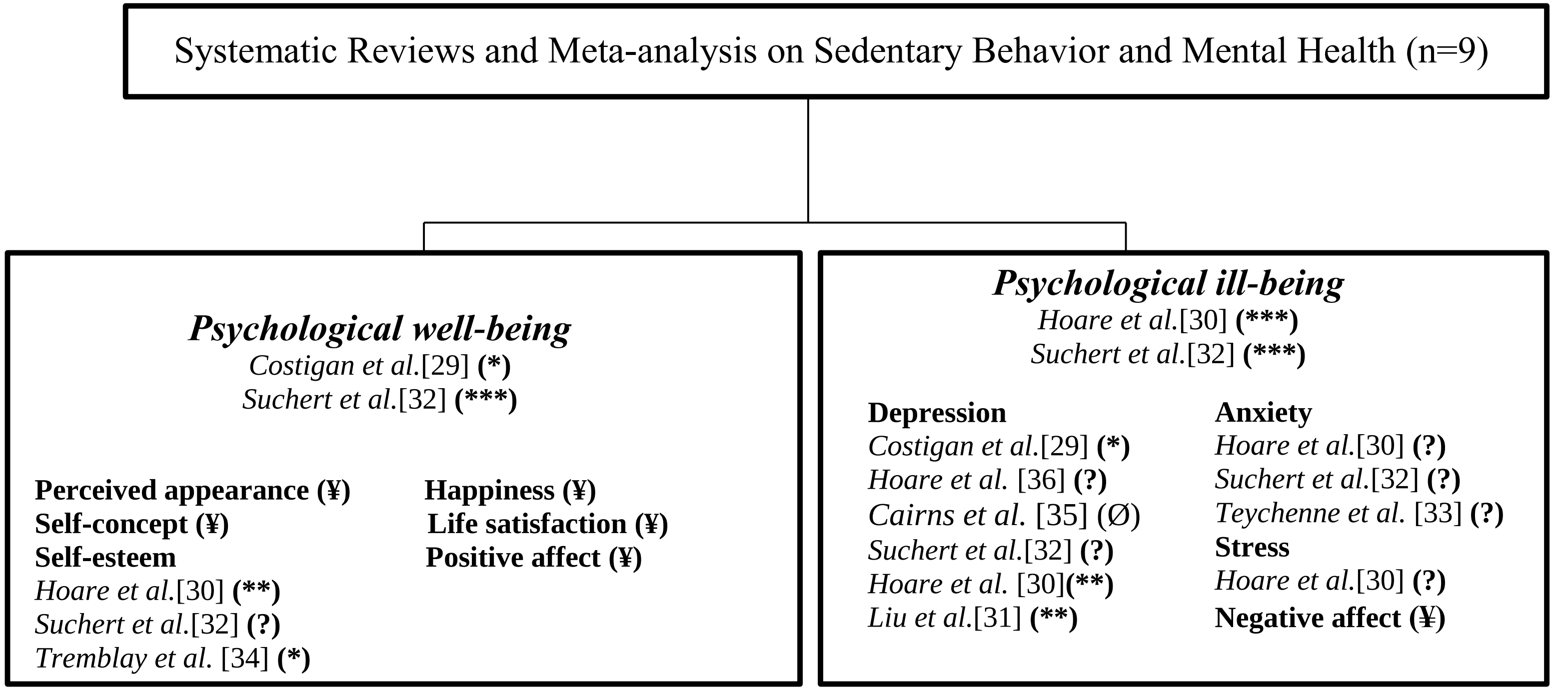

Figure 4. Relationships summary between sedentary behaviour and mental health outcome. **(*)** = low evidence, **(**)** = moderate evidence, **(***)** = strong evidence, **(?)**=unclear evidence, **(Ø)** = no significant association/effect, **(¥) =** reviews did not included this outcome into the search terms.

Emerging evidence suggests that higher levels of sedentary behavior are related to higher levels of psychological ill-being in children and adolescents (see **Sect. 7.1** and **Sect. 7.2**). To date, the majority of studies have focused on associations between sedentary behavior and depression (see **Sect. 7.2**). Less is known regarding associations between sedentary behavior and anxiety, stress and negative affect (See **Sect. 7.3**).

Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤1.5 METs, while in a sitting, reclining or lying posture (See **Fig. 5**). Sedentary behavior includes screen-based sedentary behavior (i.e., recreational screen time or non-recreational screen time) and non-screen-based sedentary behavior. For the purpose of this chapter, types of sedentary behaviors examined were mainly watching TV, computer/internet use, and video gaming, and is henceforth referred to as 'sedentary behaviors'. Studies that examined diagnosed sedentary behavior disorders (e.g., internet or gaming addiction) to the point that they disregard other life responsibilities, were not explored, due to the focus of this chapter on habitual sedentary behaviors in young people and, the involvement of these conditions in the mental health outcomes.

Sedentary behavior and non-specific psychological ill-being

The term psychological ill-being includes both internalising (e.g., depression, anxiety, negative affect) and externalising disorders (e.g., aggression and ADHD). The Child Behavior Checklist and the Strengths and Difficulties Questionnaire are two of the most commonly used measures of internalising problems. Findings of this chapter indicated strong evidence for a positive relationship between sedentary behavior and non-specific psychological ill-being in young people [30, 32].

Two studies demonstrated that exceeding two hour per day average screen time was significantly associated with higher odds of psychological ill-being compared to two hours or less [78, 79]. Of note, one of these studies [78] found this relationship to be independent of physical activity levels and stronger in boys. Among Australian adolescents, after adjusting for sex, age, socio-economic status and BMI, those who reported a high level of video game use were more likely to report high/very high levels of psychological ill-being compared to those who did not play games [80]. Suchert et al. [32] found seven studies examining the association between sedentary behavior and overall psychological ill-being in children and adolescents. One study employed a longitudinal design showing that screen time predicted emotional problems two years later [81]. While one cross-sectional study found no relationship between the time children spent watching TV and internalizing problems [82], the other five cross-sectional studies revealed a positive association.

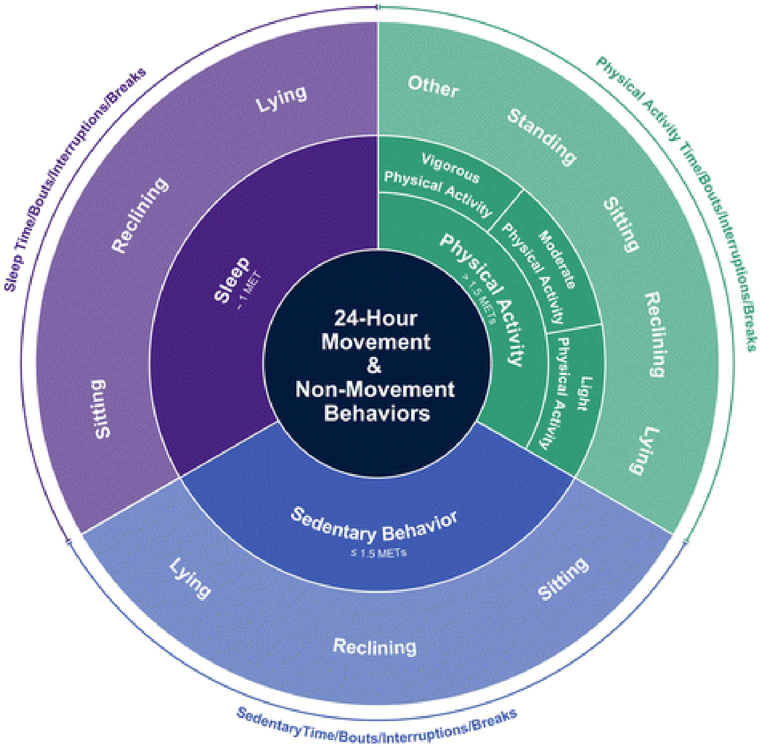

Figure 5. Illustration of the final conceptual model of movement-based terminology arranged around a 24-h period. The figure organizes the movements that take place throughout the day into two components: The inner ring represents the main behavior categories using energy expenditure. The outer ring provides general categories using posture. The proportion of space occupied by each behavior in this figure is not prescriptive of the time that should be spent in these behaviors each day. Tremblay [119].

In summary, there is strong evidence for a positive association between sedentary behavior and psychological ill-being in young people when psychological ill-being is assessed as a unique dimension which include multiple aspects of ill-being (e.g., depression, anxiety, stress, negative affect). However, researchers are encouraged to use standardized, well-validated psychological ill-being measures to confirm these findings. Lastly, evidence is based on observational studies, and mainly on cross-sectional studies. Therefore, RCTs are required to corroborate these findings.

Sedentary behavior and depression

A large number of studies have examined the relationship between sedentary behavior and depression in young people. For instance, Costigan et al. [29] found a positive association between sedentary behavior and depressive symptoms among adolescent girls in their systematic review of the literature. However, as these studies employed observational designs, causation cannot be established. On the other hand, Suchert et al. [32] found that the relationship between using internet or playing video games, and depressive symptoms followed a curvilinear U-shaped trend (i.e. students reporting a moderate amount of time engaging in these sedentary activities reported the lowest scores of depressive symptoms) [83–85]. Moreover, Hoare et al. [30] concluded that there was evidence to suggest that lower levels of screen time for leisure were associated with lower levels of depressed mood, with adverse findings only appearing at more than two to three hours per day of average of screen time.

In line with these findings, Liu et al.[31] conducted a meta-analysis of observational studies to pool the risk of depression with sedentary time in children and adolescents, and quantified a dose–response relationship. Overall, higher levels of sedentary behavior in children and adolescents were significantly associated with a higher risk of depression. Screen type, age, and population acted as significant moderators. In addition, they found that only computer use was related to depression risk. Potentially, this effect could be due to the relative openness of the computer content, especially the internet, compared to TV and video games, if youth are being exposed more readily to negative information on their computers than they would otherwise encounter. Moreover, they observed a significant association between sedentary time and depression risk in teenagers <14 years, but not in those over 14 years. Compared with the reference group, teenagers <14 years with more sedentary time per day had a 25% increased risk of depression.

The result is consistent with a previous research [86] which found a significant interaction effect of age group on the association between sedentary time and depression, suggesting that higher sedentary time was associated with higher depression risk, especially for younger children. A possible explanation for this might be that younger children are typically more active. Therefore, replacing time spent participating in physical activity with sedentary pursuits may affect younger children more substantially. Besides, younger children have greater vulnerability to negative information from screen use, which also reduces their opportunities for self-development and interpersonal communication [86, 87] and thus may be more susceptible to depression.

Liu et al. [31] also found that compared with the reference group who had no sedentary behavior, there was a non-linear dose–response association of screen time-based sedentary behavior (i.e., watching TV, computer/internet use, and video gaming) with a decreasing risk of depression at sedentary time <2 hour/day, with the lowest risk being observed for 1 hour/day (see **Fig. 6**). This finding is supported by the *Digital Goldilocks Hypothesis* which suggested that screen time at moderate levels is not harmful and may be advantageous in a connected world, whereas “overuse” may displace alternate activities, for example, interfering with school or with extracurricular or other social activities[88]. Of note, Przyibylsk et al.[88] found that the relationships between screen time and mental health were non-linear and that moderate engagement in screen time was not harmful. Such relation depended, in part, on whether the activities occurred on weekdays or weekends. They suggested that young people could engage in digital activities between 22 min and 2 hour 13 min longer on weekend days than on weekdays before they found evidence of negative effects. This findings were replicated by Ferguson et al. [89] who additionally suggested that depression were highly elevated among youth who consumed over six hours of media a day.

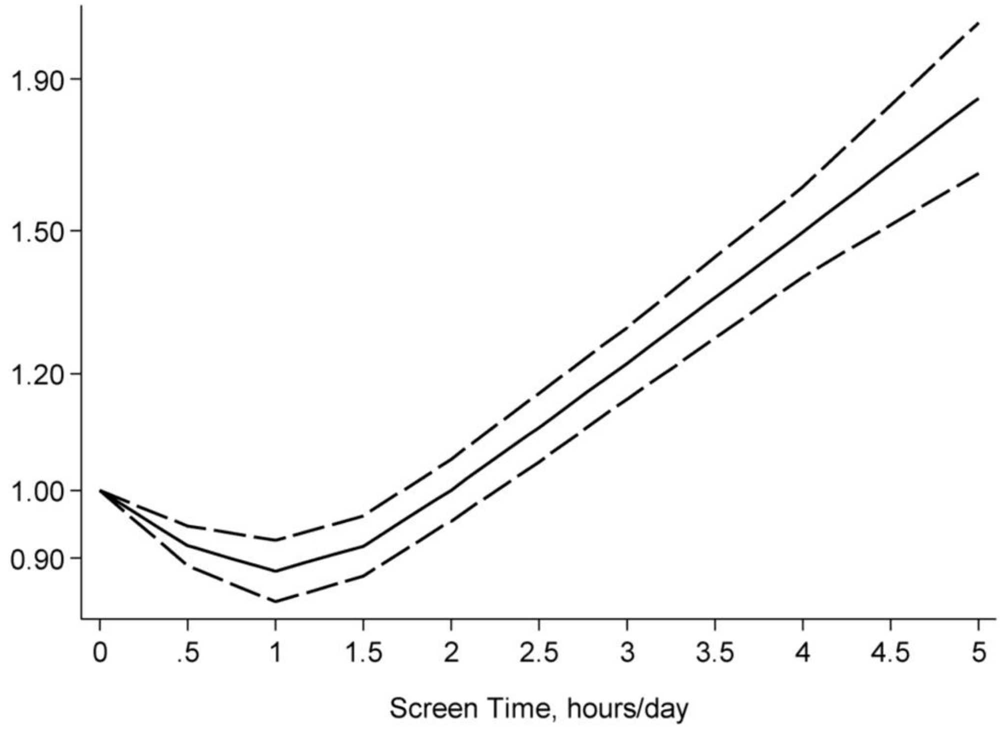

Figure 6. The dose–response relationship for the association between screen time in children and adolescents and risk of depression (solid line) as estimated by a generalised least squares trend estimation. Screen time was modelled with a restricted cubic spline in a two-stage random-effects dose–response model. The ORs are plotted on the log scale. Dashed lines represent the 95% confidence intervals for the spline model. Zero hours/day of screen time served as the referent category. Liu et al. [31]

A key aspect that was not addressed in this meta-analysis was whether the content of the screen activity, for example watching violence on screen-time (e.g., violence vs. non-violence), may be related to depressive symptoms in young people. This issue continues to be hotly contested in the scientific community. Ferguson et al. [27] found in their meta-analysis that playing violent video games was associated with increased aggression, decreased prosocial behavior, and reduced academic performance but not with depression. However, they suggested that research field may improve in theoretical and empirical rigor. Therefore, future studies might consider the content of screen time to provide more information in this regard.

To sum up, limiting sedentary time to 2 hour/day s associated with a lower risk of depression, and the lowest risk is detected at sedentary time of 1 hour/day. Therefore, guidelines should recommend not to exceed screen time in more than 2 hours per day for mental health benefits as well. It is important to consider that young people could engage in screen time longer on weekend days than on weekdays. In addition, how adolescents watch, what they watch, and with whom may have important implications [90].

Psychological ill-being outcomes with minimal evidence in relation sedentary behavior: anxiety, stress, and negative affect

Evidence demonstrates that sedentary behavior is inversely associated with symptoms of depression and non-specific psychological ill-being. There is, however, much less evidence for the association of sedentary behavior with anxiety, stress and negative affect. For instance, Griffiths et al. [91] found that sedentary behavior was inversely associated with the risk of anxiety in girls (i.e. those who spent less than 2 hours in screen-based entertainment were more likely to suffer symptoms related to anxiety). Similarly, another study involving Chinese adolescents found that sedentary time was a risk factor for anxiety [92]. However, three systematic reviews have investigated the associations between sedentary behavior and anxiety in youth and all of them suggested that limited evidence is available to draw conclusions [30, 32, 33]. Likewise, a recent review concluded that there was not enough evidence to determine the strength of association between sedentary behavior and stress in young people [30]. However, Fang et al. [93] found that total amount of time spent using screen time per day was positively associated with perceived stress among young people. Lastly, no systematic review or original research were found on the association between sedentary behavior and negative affect in youth.

Therefore, original research, cross-sectional, longitudinal and experimental studies, are needed to test the association between sedentary behavior, anxiety, stress and negative affect in young people.

Sedentary behavior and psychological well-being in young peole

Summary

The relation between sedentary behavior and psychological well-being outcomes (i.e., perceived appearance, self-concept, self-esteem, positive affect, life satisfaction and happiness) has been widely investigated, although usually much less than the relationship with physical activity and well-being. Emerging evidence was found on sedentary behavior and overall psychological well-being [29, 32] and self-esteem [30, 32, 34] (see **Sect. 8.1** and **Sect. 8.2**, respectively). Regarding to self-perception, self-concept, happiness, life satisfaction and positive affect outcomes, the evidence is unclear since no previous reviews included these outcomes in the search terms (see **Sect .8.3**). Evidence in regard to the sedentary behavior and psychological well-being outcomes is shown in **Fig. 4**.

Sedentary behavior and non-specific psychological well-being

For this brief section of the chapter, we review systematic reviews addressing links between sedentary behavior and non-specific psychological well-being in young people. For the purpose of this chapter, we will use the non-specific psychological well-being term to refer to an overall/combined measurement of psychological well-being outcomes (e.g., global self-esteem or optimism).

In their systematic review of the literature, Costigan and colleagues. [29] found an inverse association between sedentary behavior and psychological well-being among adolescents [94]. In addition, Suchert et al. [32] conducted a systematic review on the association between sedentary behavior and indicators of mental health in school-aged children and adolescents. They conceptualized psychological well-being and quality of life within the same construct and combined findings of both into one common outcome. They concluded that there is strong evidence suggesting higher levels of screen time are associated with poor psychological well-being and perceived quality of life. However, due to the inconsistency of definitions used, more studies focused on psychological well-being are needed to confirm these findings. In addition, it is recommended that researchers use standardized, well-validated psychological well-being measures in future studies.

Sedentary behavior and self-esteem

Self-esteem was the most studied psychological well-being outcome. First, Tremblay et al. [34] conducted a systematic review of sedentary behaviors and health indicators in school-aged youth. They suggested decreased levels of sedentary behavior (combined with physical activity) lead to improved self-esteem [95–97]. However it is not possible to establish a direct causal-effect between sedentary behavior and self-esteem because the majority of studies were cross-sectional. Of note, Tremblay et al. [34] combined self-esteem, self-worth and self-concept into one common outcome called self-esteem. Therefore, a standardised definition of the self-esteem term is needed to confirm these findings. In addition, Russ et al. [98] found that each additional hour of screen time increases the risk of poor self-esteem. In accordance with the previous studies, Hoare et al. [30] concluded that there is a moderate evidence for relationship negative association between sedentary behavior and self-esteem. In contrast to these findings, Suchert et al. [99], concluded that the association between sedentary behaviors and self-esteem was indeterminate. However, they identified two studies indicating an inverted U-shaped association, i.e. children and adolescents reporting a moderate use of video games or TV showed the highest score of self-esteem [84, 100]. This is in line with the meta-analysis performed by Liu et al. [31] focused on the dose–response association of screen time and depression in youths.

Collectively, although self-esteem was widely studied, more high quality studies on the effects of sedentary behaviors on self-esteem are needed to make strong conclusions. In addition, there is a need to define consistently self-esteem in order to establish robust conclusions. We suggest the aforementioned definition to refer to self-esteem (see **Sect. 3.3**).

Psychological well-being outcomes with minimal evidence in relation sedentary behavior: self-concept, perceived appearance, happiness, life satisfaction, and positive affect

No previous reviews have examined the associations between sedentary behavior and self-concept, perceived appearance, happiness, life satisfaction and positive affect outcomes in young people. Therefore, future literature might aim to synthesise findings of existing cross-sectional, longitudinal and experimental studies. However, some evidence regarding to these outcomes has been found in a small number of original studies. For instance, Schneider et al. [101] found that the amount of time spent watching TV correlated with higher body dissatisfaction in female adolescents. Babic et al. [90] found that changes in total recreational screen-time and tablet/mobile phone use were negatively associated with physical self-concept in adolescents over a six-month study period. These relationships may partly be explained by the emerging influence of social media technology commonly used by young people on tablets/mobile phone (e.g., Facebook, Instagram and Snapchat) which may encourage adolescents to compare themselves with their peers [90], and consequently increase their body dissatisfaction when discrepancies are found between perceived and ideal body shape.

Booker et al. [102] found that young people with heavy screen-based media use were less happy than moderate users and more likely to have socioemotional difficulties. Interestingly, Padilla-Moledo et al. [103] found that watching TV for more than two hours was correlated with lower life satisfaction in children but not in adolescents. Of note, we did not find any study testing the association of sedentary behavior with positive affect in youth. Evidence suggested that positive affect is the hallmark of well-being and may also be the cause of many of the desirable characteristics, resources, and successes correlated with happiness [104]. Therefore, more studies on sedentary behavior and positive affect are needed.

Possible positive effects of sedentary behavior on mental health in young people

Time spent engaged in sedentary behaviors may have some benefits for young people’s mental health. First, socially interactive screen-based recreation (e.g., multiplayer electronic games or social networking games) may produce social health gains for adolescents [105]. Second, engaging in small amounts of screen time (1 h/day) is unlikely to have any negative effects [31], but may be potentially beneficial for the primary prevention of depression (see **Fig. 6**). These potential benefits could be related to screen behaviors enhancing children's ability to read and visualise images and, consequently, improving academic performance. In addition, youth may psychologically benefit from processing humorous content in TV, the internet and video games [106].

Possible mechanisms for the effect of sedentary behavior on mental health in young people

While the evidence examining physical activity and mental health mechanisms is emerging [22], there is an important gap regarding the underlying mechanisms responsible for the possible effects of sedentary behavior on mental health in young people.

In regards to a potential psychosocial mechanism, more time spent watching TV or using the internet may lead to social withdrawal, social isolation, and hence to psychological ill-being problems and less psychological well-being [107]. For instance, Hoare et al. proposed that sedentary behavior may elicit feelings of loneliness, given they often take place alone, and this solitude diminish mental health [36].

Alternatively, the behavioral mechanism hypothesis proposes that changes in mental health outcomes resulting from sedentary behavior are mediated by changes in relevant and associated behaviors. Evidence indicates that specific sedentary activities, such as TV and video viewing, are associated with poor dietary behaviors (e.g., unhealthy snacking/overconsumption of food and high-energy drinks). Moreover, Primack et al. [108] suggested that excessive media exposure often occurs at night and can displace sleep, which is valuable for normal cognitive and emotional development. In addition, they proposed that cultural messages transmitted through media may affect other behaviors related to mental health such as eating disorders and aggressive behavior [108]. Lastly, the displacement hypothesis suggests that time spent on screen-based activities may replace time participating in more productive and/or active activities, especially activities involving physical activity [109] and interpersonal communication [107], and thus may affect the mental health of young people.

Therefore, more studies focused on mechanism explaining the relationship between sedentary behavior and mental health are needed to confirm these hypotheses. Specially, studies may be focused on neurobiological mechanism since they are completely unknown.

Recommendations to improve mental health in young people.

Overall, we recommend the use of evidence based-physical activity strategies to maximise the positive effect of physical activity on mental health outcomes. In order to guide the planning of organized physical activity sessions in school, and after-school programs, we specifically advise the use of *the SAAFE principles and practical strategies* designed by Lubans et al. [110] (see **Fig. 7**). The SAAFE principles are based on the self-determination theory [111, 112], achievement goal theory [113], competence motivation theory [114], and Epstein's TARGET framework [Task (design of activities), Authority (distribution of decision-making and student autonomy), Recognition (use of incentives, rewards and feedback), Grouping (formation of students into groups), Evaluation (methods used to assess performance) and Time (appropriateness of workload and lesson pace)] [115]. In addition, given the current state-of-the-art, educational and health institutions may consider the general physical activity guidelines for children and adolescents when designing physical activity interventions for preserve mental health in young people (e.g., *The 2008 Physical Activity Guidelines for Americans* [116]). In this context, it is highly advisable the use of the recently published *2018 Physical Activity Guidelines Advisory Committee Scientific Report* [117], which include an special section for the effects of physical activity on brain health. Although the later guidelines are inspiring, they are not focused in young people in this specific section. Thus, further research is warranted in order to provide robust evidence for physical activity recommendations specifically designed for promoting mental health in young people.

Figure 7. Overview of *SAAFE* teaching principles and strategies for physical activity programs intending to improve mental health in children and adolescents. Lubans et al.[110]

In regard to sedentary behavior, we support the use of the *American Psychological Association* [25] and the *American Pediatric Society* [26] recommendations. Of note, both instructions advice the establishment of consistent limits on the time spent using media and the types of media but they did not specify how much time of screens is recommended to preserve mental health. We suggest not to exceed screen time in more than 2 hours per day (see **Fig. 6**). In addition, it is important to consider that young people could engage in screen time longer on weekend days than on weekdays. However, further research is needed to support these recommendations.

Literature gaps and future research

The output of this chapter provides evidence to reconsider some important concerns in the physical activity, sedentary behavior and mental health field. In this section, we offer to researchers in this field some practical suggestions for improving in theoretical and empirical rigor.

General concerns/gaps.

- *The "hypodermic needle" theory proposed by Ferguson et al*. [27]. Researchers sometimes believe that physical activity or sedentary behavior is "injected" into passive individuals who automatically experience an effect on mental health. However, more effort is required to understand this relationship from other perspectives. For instance, understanding *when* young people practise physical activity or play videogames (e.g. weekdays vs. weekends), *where* (e.g., at school vs. out of school), *what* they do (e.g., moderate-to-vigorous physical activity vs. light physical activity) or watch (e.g., violence vs. non-violence), *how much* (e.g., more than 2 hours vs. less than 2 hours of screen time or at least 60 minutes vs. less than 60 minutes of moderate-to-vigorous physical activity every day) and *with whom (e.g., team sports vs. individual sports or gaming alone vs. gaming with friends)*, might be useful to better understand the effect of physical activity or sedentary behavior on the mental health of young people.
- *Selective reporting bias and interpretation.* Researchers sometimes only cite and report other studies that support their personal hypotheses, and consequently a selective interpretation is performed. We encourage researchers to publish null results and to consider all available literature in contrast or in line to their current findings.

- *Standardized measures and rigorous methods.* Future studies in this field might provide well-validated and standardized measures of physical activity, sedentary behavior and mental health to avoid inconsistent findings between studies.
- *Standardized mental health terminology.* We found that several inconsistencies between studies are due to a problem with the terminology used. Throughout this chapter we have proposed how to define and to understand these terms. However, a consensus of experts in this field is needed to provide a standardized mental health terminology.

Directions for future research on physical activity and mental health in young people.

- Moderators such as age, sex, social risk factors and mental health at baseline should be considered for researchers testing the effect of physical activity on mental health in young people.
- Specific physical activity interventions focus on improving mental health outcomes, rather than generic "one-size-fits-all" approaches, are needed. In addition, interventions might attend to young people's physical self-concept (i.e., perceived competence, perceived fitness and perceived appearance). The *SAAFE principles and practical strategies* might be useful for this purpose.
- More studies on physical activity, psychological ill-being (anxiety, stress, negative affect) and psychological well-being outcomes (happiness, life satisfaction and positive affect) based on minimal or unclear (i.e., self-esteem) evidence are needed. Even observational studies may be worthy due to the lack of research.
- Frequency, duration, intensity, type of physical activity practise, and setting (e.g., at school or out-of-school) should be considered.

- Mediation models are needed to identify the mechanisms (i.e., neurobiological, psychological and behavioral) responsible for any changes in mental health resulting from participation in physical activity.

Future directions on sedentary behavior and mental health in young people.

- Answering the questions how young people watch, what they watch, and with whom is needed to understand the relationship between sedentary behavior and mental health in young people.
- There is limited evidence to conclude whether, or to what degree, associations between sedentary behavior and mental health are explained by the content (e.g., violence, no violence) or the type (e.g., watching TV, computer/internet use, and video gaming) of sedentary behavior versus sedentariness itself.
- More studies focused on the relationship between sedentary behavior, psychological ill-being (anxiety, stress, negative affect) and psychological well-being outcomes (self-concept, perceived appearance, happiness, life satisfaction and positive affect) based on minimal evidence are needed. Even observational studies may be worthy due to the lack of research.
- Experimental studies on sedentary behavior and mental health are required to draw conclusions in regard to cause and effect.
- Mechanism explaining the relationship between sedentary behavior and mental health are needed. Specially, studies may be focused on neurobiological mechanism since they are completely unknown.

REFERENCES

1. Murray CJL, Lopez AD, Organization WH, Bank W, Health HS of P (1996) The Global burden of disease : a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020 / edited by Christopher J. L. Murray, Alan D. Lopez.

2. Seligman ME, Csikszentmihalyi M (2000) Positive psychology. An introduction. Am Psychol 55:5–14

3. Schmithorst VJ, Yuan W (2010) White matter development during adolescence as shown by diffusion MRI. Brain Cogn 72:16–25

4. Lenroot RK, Giedd JN (2006) Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev 30:718–729

5. Nelson SC, Kling J, Wängqvist M, Frisén A, Syed M (2018) Identity and the body: Trajectories of body esteem from adolescence to emerging adulthood. Dev Psychol 54:1159–1171

6. Beauchamp MR, Puterman E, Lubans DR (2018) Physical Inactivity and Mental Health in Late Adolescence. JAMA Psychiatry 75:543

7. Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, Lancet Physical Activity Series Working Group (2012) Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet 380:219–229

8. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, Lancet Physical Activity Series Working Group (2012) Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet 380:247–257

9. (2014) World Health Organisation. Global Strategy on Diet, Physical Activty and Health. In Physical Activity and Young People.

10. Biddle SJH, Asare M (2011) Physical activity and mental health in children and adolescents: a review of reviews. Br J Sports Med 45:886–895

11. Biddle SJH, Ciaccioni S, Thomas G, Vergeer I (2018) Physical activity and mental health in children and adolescents: An updated review of reviews and an analysis of causality. Psychol Sport Exerc 1–10

12. Babic MJ, Morgan PJ, Plotnikoff RC, Lonsdale C, White RL, Lubans DR (2014) Physical Activity and Physical Self-Concept in Youth: Systematic Review and Meta-Analysis. Sport Med 44:1589–1601

13. Liu M, Wu L, Ming Q (2015) How does physical activity intervention improve self-esteem and self-concept in children and adolescents? Evidence from a meta-analysis. PLoS One 10:1–17

14. Korczak DJ, Madigan S, Colasanto M (2017) Children's Physical Activity and Depression: A Meta-analysis. Pediatrics 139:e20162266

15. Carter T, Morres ID, Meade O, Callaghan P (2016) The Effect of Exercise on Depressive Symptoms in Adolescents: A Systematic Review and Meta-Analysis. J Am Acad Child Adolesc Psychiatry. doi: 10.1016/j.jaac.2016.04.016

16. Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJH (2013) Physical Activity Interventions and Depression in Children and Adolescents. Sport Med 43:195–206

17. Bursnall P (2014) The Relationship Between Physical Activity and Depressive Symptoms in Adolescents: A Systematic Review. Worldviews Evidence-Based Nurs 11:376–382

18. Ferreira-Vorkapic C, Feitoza JM, Marchioro M, Simões J, Kozasa E, Telles S (2015) Are There Benefits from Teaching Yoga at Schools?A Systematic Review of Randomized Control Trials of Yoga-Based Interventions. Evidence-Based Complement Altern Med 2015:1–17

19. Eime RM, Young JA, Harvey JT, Charity MJ, Payne WR (2013) A systematic review of the psychological and social benefits of participation in sport for children and adolescents: informing development of a conceptual model of health through sport. Int J Behav Nutr Phys Act 10:98

20. Spruit A, Assink M, van Vugt E, van der Put C, Stams GJ (2016) The effects of physical activity interventions on psychosocial outcomes in adolescents: A meta-analytic review. Clin Psychol Rev 45:56–71

21. Ruotsalainen H, Kyngäs H, Tammelin T, Kääriäinen M (2015) Systematic review of physical activity and exercise interventions on body mass indices, subsequent physical activity and psychological symptoms in overweight and obese adolescents. J Adv Nurs 71:2461–2477

22. Lubans D, Richards J, Hillman C, Faulkner G, Beauchamp M, Nilsson M, Kelly P, Smith J, Raine L, Biddle S (2016) Physical Activity for Cognitive and Mental Health in Youth: A Systematic Review of Mechanisms. Pediatrics 138:e20161642–e20161642

23. White RL, Babic MJ, Parker PD, Lubans DR, Astell-Burt T, Lonsdale C (2017) Domain-Specific Physical Activity and Mental Health: A Meta-analysis. Am J Prev Med 52:653–666

24. Wang H, Hu R, Zhong J, Du H, Fiona B, Wang M, Yu M (2018) Prevalence of high screen time and associated factors among students: a cross-sectional study in Zhejiang, China. BMJ Open 8:e021077

25. Digital Guidelines: Promoting Healthy Technology Use for Children. https://www.apa.org/helpcenter/digital-guidelines.aspx. Accessed 26 Oct 2018

26. American Academy of Pediatrics Announces New Recommendations for Children’s Media Use. https://www.aap.org/en-us/about-the-aap/aap-press-room/Pages/American-Academy-of-Pediatrics-Announces-New-Recommendations-for-Childrens-Media-Use.aspx. Accessed 26 Oct 2018

27. Ferguson CJ (2015) Do Angry Birds Make for Angry Children? A Meta-Analysis of Video Game Influences on Children’s and Adolescents’ Aggression, Mental Health,

Prosocial Behavior, and Academic Performance. Perspect Psychol Sci 10:646–666

28. Carson V, Hunter S, Kuzik N, et al (2016) Systematic review of sedentary behaviour and health indicators in school-aged children and youth: an update. Appl Physiol Nutr Metab 41:240–265

29. Costigan SA, Barnett L, Plotnikoff RC, Lubans DR (2013) The health indicators associated with screen-based sedentary behavior among adolescent girls: A systematic review. J Adolesc Heal 52:382–392

30. Hoare E, Milton K, Foster C, Allender S (2016) The associations between sedentary behaviour and mental health among adolescents: a systematic review. Int J Behav Nutr Phys Act 13:108

31. Liu M, Wu L, Yao S (2015) Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: A meta-analysis of observational studies. Br J Sports Med 1–8

32. Suchert V, Hanewinkel R, Isensee B (2015) Sedentary behavior and indicators of mental health in school-aged children and adolescents: A systematic review. Prev Med (Baltim) 76:48–57

33. Teychenne M, Costigan SA, Parker K (2015) The association between sedentary behaviour and risk of anxiety: a systematic review. BMC Public Health 15:513

34. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, Goldfield G, Gorber S (2011) Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act 8:98

35. Cairns KE, Yap MBH, Pilkington PD, Jorm AF (2014) Risk and protective factors for depression that adolescents can modify: A systematic review and meta-analysis of longitudinal studies. J Affect Disord 169:61–75

36. Hoare E, Skouteris H, Fuller-Tyszkiewicz M, Millar L, Allender S (2014) Associations between obesogenic risk factors and depression among adolescents: A systematic review. Obes Rev 15:40–51

37. Smith K (2014) Mental health: A world of depression. Nature 515:180–181

38. Larun L, Nordheim L V., Ekeland E, Hagen KB, Heian F (2006) Exercise in prevention and treatment of anxiety and depression among children and young people. Cochrane Database Syst Rev CD004691

39. Roy-Byrne PP, Davidson KW, Kessler RC, et al (2008) Anxiety disorders and comorbid medical illness. Gen Hosp Psychiatry 30:208–225

40. Schumacher Dimech A, Seiler R (2011) Extra-curricular sport participation: A potential buffer against social anxiety symptoms in primary school children. Psychol Sport Exerc 12:347–354

41. Jewett R, Sabiston CM, Brunet J, O’Loughlin EK, Scarapicchia T, O’Loughlin J (2014) School sport participation during adolescence and mental health in early adulthood. J Adolesc Heal 55:640–644

42. Martikainen S, Pesonen A-K, Lahti J, et al (2013) Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. J Clin Endocrinol Metab 98:E619-27

43. Daley AJ, Copeland RJ, Wright NP, Roalfe A, Wales JKH (2006) Exercise Therapy as a Treatment for Psychopathologic Conditions in Obese and Morbidly Obese Adolescents: A Randomized, Controlled Trial. Pediatrics 118:2126–2134

44. Joan Poitras V, Ellen Gray C, Borghese MM, et al (2016) Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth 1. Public Heal Agency Canada Appl Physiol Nutr Metab 41:197–239

45. Simons J, Capio CM, Adriaenssens P, Delbroek H, Vandenbussche I (2012) Self-concept and physical self-concept in psychiatric children and adolescents. Res Dev Disabil 33:874–881

46. Marsh HW, Shavelson R (1985) Self-Concept: Its Multifaceted, Hierarchical Structure. Educ Psychol 20:107–123

47. Hills AP, Dengel DR, Lubans DR (2015) Supporting Public Health Priorities: Recommendations for Physical Education and Physical Activity Promotion in Schools. Prog Cardiovasc Dis 57:368–374

48. Mäkinen M, Puukko-Viertomies L-R, Lindberg N, Siimes MA, Aalberg V (2012) Body dissatisfaction and body mass in girls and boys transitioning from early to mid-adolescence: additional role of self-esteem and eating habits. BMC Psychiatry 12:35

49. Blashill AJ, Wilhelm S (2014) Body Image Distortions, Weight, and Depression in Adolescent Boys: Longitudinal Trajectories into Adulthood. Psychol Men Masc 15:445–451

50. Chung RJ, Sherman L, Goodman E, Bickham DS, Rich M (2013) Exploring the Perspectives of Obese Adolescent Girls. Qual Health Res 23:1369–1376

51. DeBar LL, Stevens VJ, Perrin N, Wu P, Pearson J, Yarborough BJ, Dickerson J, Lynch F (2012) A Primary Care-Based, Multicomponent Lifestyle Intervention for Overweight Adolescent Females. Pediatrics 129:e611–e620

52. Sonstroem RJ, Morgan WP (1989) Exercise and self-esteem: rationale and model. Med Sci Sports Exerc 21:329–37

53. Mann M, H Hosman CM, Schaalma HP, de Vries NK Self-esteem in a broad-spectrum approach for mental health promotion. doi: 10.1093/her/cyg041

54. Pedersen S, Seidman E (2004) Team Sports Achievement and Self-Esteem Development Among Urban Adolescent Girls. Psychol Women Q 28:412–422

55. Brettschneider W (2001) Effects of sport club activities on adolescent development in Germany. Eur J Sport Sci 1:1–11

56. Lyubomirsky S (2008) The how of happiness: A scientific approach to getting the life you want.

57. Diener E (2000) Subjective well-being. The science of happiness and a proposal for a national index. Am Psychol 55:34–43

58. Richards J, Jiang X, Kelly P, Chau J, Bauman A, Ding D (2015) Don’t worry, be happy: cross-sectional associations between physical activity and happiness in 15 European countries. BMC Public Health 15:53

59. Raichlen DA, Foster AD, Seillier A, Giuffrida A, Gerdeman GL (2013) Exercise-induced endocannabinoid signaling is modulated by intensity. Eur J Appl Physiol 113:869–875

60. Michaud P-A, Jeannin A, Suris J-C (2006) Correlates of extracurricular sport participation among Swiss adolescents. Eur J Pediatr 165:546–555

61. Valois RF, Zullig KJ, Huebner ES, Drane JW (2004) Physical activity behaviors and perceived life satisfaction among public high school adolescents. J Sch Health 74:59–65

62. Thompson WR (2017) Wordwide survery of fitness trends for 2018: The CREP edition. ACSMs Health Fit J 21:10–19

63. Taspinar B, Aslan UB, Agbuga B, Taspinar F (2014) A comparison of the effects of hatha yoga and resistance exercise on mental health and well-being in sedentary adults: A pilot study. Complement Ther Med 22:433–440

64. Bonura KB, Tenenbaum G (2014) Effects of Yoga on Psychological Health in Older Adults. J Phys Act Heal 11:1334–1341

65. Kipp LE, Weiss MR (2013) Physical activity and self-perceptions among children and adolescents. 187–199

66. Haudenhuyse RP, Theeboom M, Skille EA (2014) Towards understanding the potential of sports-based practices for socially vulnerable youth. Sport Soc 17:139–156

67. Spaaij R, Farquharson K, Marjoribanks T (2015) Sport and Social Inequalities. Sociol Compass 9:400–411

68. Richards J, Foster C (2013) Sport-for-Development Interventions: Whom Do They Reach and What Is Their Potential for Impact on Physical and Mental Health in Low-Income Countries? Setting and Local Context. J Phys Act Heal 10:929–931

69. Hillman CH, Pontifex MB, Castelli DM, Khan NA, Raine LB, Scudder MR, Drollette ES, Moore RD, Wu C-T, Kamijo K (2014) Effects of the FITKids Randomized Controlled Trial on Executive Control and Brain Function. Pediatrics 134:e1063–e1071

70. Leibrock J, Lottspeich F, Hohn A, Hofer M, Hengerer B, Masiakowski P, Thoenen H, Barde Y-A (1989) Molecular cloning and expression of brain-derived neurotrophic factor. Nature 341:149–152

71. Martinowich K, Manji H, Lu B (2007) New insights into BDNF function in depression and anxiety. Nat Neurosci 10:1089–1093

72. Cotman CW, Berchtold NC, Christie L-A (2007) Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci 30:464–472

73. Kleim JA, Cooper NR, VandenBerg PM (2002) Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. Brain Res 934:1–6

74. Dishman RK, O’Connor PJ (2009) Lessons in exercise neurobiology: The case of endorphins. Ment Health Phys Act 2:4–9

75. Young SN, Leyton M (2002) The role of serotonin in human mood and social interaction. Insight from altered tryptophan levels. Pharmacol Biochem Behav 71:857–65

76. Young SN (2007) How to increase serotonin in the human brain without drugs. J Psychiatry Neurosci 32:394–9

77. Lubans DR, Smith JJ, Morgan PJ, Beauchamp MR, Miller A, Lonsdale C, Parker P, Dally K (2016) Mediators of Psychological Well-being in Adolescent Boys. J Adolesc Heal 58:230–236

78. Trinh L, Wong B, Faulkner GE (2015) The independent and interactive associations of screen time and physical activity on mental health, school connectedness and academic achievement among a population-based sample of youth. J Can Acad Child Adolesc Psychiatry 24:17–24

79. Arbour-Nicitopoulos KP, Faulkner GE, Irving HM (2012) Multiple health-risk behaviour and psychological distress in adolescence. J Can Acad Child Adolesc Psychiatry 21:171–8

80. Mathers M, Canterford L, Olds T, Hesketh K, Ridley K, Wake M (2009) Electronic Media Use and Adolescent Health and Well-Being: Cross-Sectional Community Study. Acad Pediatr 9:307–314

81. Parkes A, Sweeting H, Wight D, Henderson M (2013) Do television and electronic games predict children’s psychosocial adjustment? Longitudinal research using the UK Millennium Cohort Study. Arch Dis Child 98:341–8

82. Ozmert E, Toyran M, Yurdakök K (2002) Behavioral correlates of television viewing in primary school children evaluated by the child behavior checklist. Arch Pediatr Adolesc Med 156:910–4

83. Do YK, Shin E, Bautista MA, Foo K (2013) The associations between self-reported sleep duration and adolescent health outcomes: What is the role of time spent on Internet use? Sleep Med 14:195–200

84. Durkin K, Barber B (2002) Not so doomed: computer game play and positive adolescent development. J Appl Dev Psychol 23:373–392

85. Kim JY (2012) The nonlinear association between Internet using time for non-educational purposes and adolescent health. J Prev Med Public Health 45:37–46

86. Kremer P, Elshaug C, Leslie E, Toumbourou JW, Patton GC, Williams J (2014) Physical activity, leisure-time screen use and depression among children and young adolescents. J Sci Med Sport 17:183–187

87. Marshall SJ, Biddle SJH, Gorely T, Cameron N, Murdey I (2004) Relationships between media use, body fatness and physical activity in children and youth: a meta-

analysis. Int J Obes 28:1238–1246

88. Przybylski AK, Weinstein N (2017) A Large-Scale Test of the Goldilocks Hypothesis: Quantifying the Relations Between Digital-Screen Use and the Mental Well-Being of Adolescents. Psychol Sci 28:204–215

89. Ferguson CJ (2017) Everything in Moderation: Moderate Use of Screens Unassociated with Child Behavior Problems. Psychiatr Q 88:797–805

90. Babic MJ, Smith JJ, Morgan PJ, Eather N, Plotnikoff RC, Lubans DR (2017) Longitudinal associations between changes in screen-time and mental health outcomes in adolescents. Ment Health Phys Act 12:124–131

91. Griffiths LJ, Dowda M, Dezateux C, Pate R (2010) Associations between sport and screen-entertainment with mental health problems in 5-year-old children. Int J Behav Nutr Phys Act 7:30

92. Cao H, Qian Q, Weng T, Yuan C, Sun Y, Wang H, Tao F (2011) Screen time, physical activity and mental health among urban adolescents in China. Prev Med (Baltim) 53:316–320

93. Fang L, Zhang VF, Poon HLM, Fung WLA, Katakia D (2014) Lifestyle Practices, Psychological Well-Being, and Substance Use among Chinese-Canadian Youth. J Ethn Cult Divers Soc Work 23:207–222

94. Ussher MH, Owen CG, Cook DG, Whincup PH (2007) The relationship between physical activity, sedentary behaviour and psychological wellbeing among adolescents. Soc Psychiatry Psychiatr Epidemiol 42:851–856

95. Robinson TN, Killen JD, Kraemer HC, et al (2003) Dance and reducing television viewing to prevent weight gain in African-American girls: the Stanford GEMS pilot study. Ethn Dis 13:S65-77

96. Goldfield GS, Mallory R, Parker T, Cunningham T, Legg C, Lumb A, Parker K, Prud’homme D, Adamo KB (2007) Effects of Modifying Physical Activity and Sedentary Behavior on Psychosocial Adjustment in Overweight/Obese Children. J Pediatr Psychol 32:783–793

97. Simon C, Wagner A, DiVita C, Rauscher E, Klein-Platat C, Arveiler D, Schweitzer B, Triby E (2004) Intervention centred on adolescents’ physical activity and sedentary behaviour (ICAPS): concept and 6-month results. Int J Obes 28:S96–S103

98. Russ SA, Larson K, Franke TM, Halfon N (2009) Associations Between Media Use and Health in US Children. Acad Pediatr 9:300–306

99. Suchert V, Hanewinkel R, Isensee B, Hansen J, Johannsen M, Krieger C, M??ller K, Sauer I, Weisser B (2015) Sedentary behavior, depressed affect, and indicators of mental well-being in adolescence: Does the screen only matter for girls? J Adolesc 42:50–58

100. Tin SPP, Ho DSY, Mak KH, Wan KL, Lam TH (2012) Association Between Television Viewing and Self-Esteem in Children. J Dev Behav Pediatr 33:479–485

101. Schneider S, Weiß M, Thiel A, Werner A, Mayer J, Hoffmann H, Diehl K (2013)

Body dissatisfaction in female adolescents: Extent and correlates. Eur J Pediatr 172:373–384

102. Booker CL, Skew AJ, Kelly YJ, Sacker A (2015) Media use, sports participation, and well-being in adolescence: Cross-sectional findings from the UK Household Longitudinal Study. Am J Public Health 105:173–179

103. Padilla-Moledo C, Castro-Piñero J, Ortega FB, Pulido-Martos M, Sjöström M, Ruiz JR (2015) Television viewing, psychological positive health, health complaints and health risk behaviors in Spanish children and adolescents. J Sports Med Phys Fitness 55:675–83

104. Lyubomirsky S, King L, Diener E (2005) The Benefits of Frequent Positive Affect: Does Happiness Lead to Success? Psychol Bull 131:803–855

105. Brox E, Fernandez-Luque L, Tøllefsen T (2011) Healthy Gaming – Video Game Design to promote Health. Appl Clin Inform 02:128–142

106. American Academy of Pediatrics. Committee on Public Education (2001) American Academy of Pediatrics: Children, adolescents, and television. Pediatrics 107:423–6

107. Kraut R, Patterson M, Lundmark V, Kiesler S, Mukopadhyay T, Scherlis W (1998) Internet paradox. A social technology that reduces social involvement and psychological well-being? Am Psychol 53:1017–31

108. Primack BA, Swanier B, Georgiopoulos AM, Land SR, Fine MJ (2009) Association Between Media Use in Adolescence and Depression in Young Adulthood. Arch Gen Psychiatry 66:181

109. Ohannessian CM (2009) Media Use and Adolescent Psychological Adjustment: An Examination of Gender Differences. J Child Fam Stud 18:582–593

110. Lubans DR, Lonsdale C, Cohen K, Eather N, Beauchamp MR, Morgan PJ, Sylvester BD, Smith JJ (2017) Framework for the design and delivery of organized physical activity sessions for children and adolescents: Rationale and description of the "SAAFE" teaching principles. Int J Behav Nutr Phys Act. doi: 10.1186/s12966-017-0479-x

111. Deci E, Ryan R (1985) Intrinsic motivation and self-determination in human behavior.

112. Deci EL, Ryan RM (2009) The " What " and " Why " of Goal Pursuits : Human Needs and the Self- Determination of Behavior. Psychol Inq 11:227–268

113. Nicholls JG (1984) Achievement motivation: Conceptions of ability, subjective experience, task choice, and performance. Psychol Rev 91:328–346

114. Weiss MR (2000) Motivating kids in physical activity.

115. Cecchini JA, Fernandez-Rio J, Mendez-Gimenez A (2014) Effects of Epstein's TARGET on adolescents' intentions to be physically active and leisure-time physical activity. Health Educ Res 29:485–490

116. Odphp 2008 Physical Activity Guidelines for Americans.

117. HHS (2018) 2018 Physical Activity Guidelines Advisory Committee Scientific Report.

118. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary behavior research network (SBRN)—terminology consensus project process and outcome. Int J Behav Nutr Phys Act. 2017;14:75.

Supplemental Material

Study I

STUDY II

Role of physical activity and sedentary behavior in the mental health of preschoolers, children and adolescents: A systematic review and meta-analysis.

María Rodriguez-Ayllon, Cristina Cadenas-Sánchez, Fernando Estévez-López, Nicolas Ernesto Muñoz, Jose Mora-Gonzalez, Jairo H. Migueles, Pablo Molina-García, Hanna Henriksson, Alejandra Mena-Molina, Vicente Martínez-Vizcaíno, Andrés Catena, Marie Löf, Kirk I. Erickson, David Lubans, Francisco B. Ortega, Irene Esteban-Cornejo.

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INTRODUCTION

Mental disorders are expected to be one of the main causes of disability in developed countries by 2020 [1]. Prevention of mental disorders not only depends on the absence of psychological ill-being, but also on the presence of psychological well-being. For the purpose of this review, the term psychological ill-being will be used to represent unpleasant feelings or emotions that impact the level of functioning, as well as pre-clinical and clinically diagnosed psychological disorders (e.g., depression and anxiety) [2,3]. Conversely, psychological well-being is the combination of positive affective states and functioning with optimal effectiveness in personal and social life [2,3]. Childhood and adolescence represent periods of rapid growth and development characterized by neuronal plasticity [4,5], development of identity [6], and the establishment of behavioral patterns that may enhance or diminish mental health [7]. Thus, it is of interest to identify environmental exposures during these ages that may decrease the development of mental health disorders later in life [8].

Physical activity and sedentary behavior are two independent but related lifestyle behaviors that occupy all waking hours of a day. Physical activity is defined as any bodily movement that increases energy expenditure above resting energy expenditure [9]. Exercise is a subset of physical activity that is planned, structured, repetitive and purposeful which might have a different effect on mental health depending on the constituent elements (e.g., competitive vs. non-competitive) [10]. Sedentary behavior is defined as any waking behavior characterized by an energy expenditure ≤ 1.5 METs, while in a sitting, reclining or lying posture [11].

The underlying mechanisms responsible for the effects of physical activity and sedentary behavior on mental health are unclear. However, several hypotheses have been proposed. For instance, it seems that participation in physical activity might enhance mental health via the release of endorphins [12], increases in BDNF [13] and growth of new capillaries [14], which in turn might enhance the structural and functional composition of the brain. Other theoretical frameworks propose that increased levels of physical activity and reduced sedentary behavior might help to satisfy basic psychological needs (e.g., social connectedness, self-acceptance, and purpose in life), and consequently improve overall mental health in young people [15].

The recently published second edition of the Physical Activity Guidelines for Americans highlights that moving more and sitting less have enormous benefits for everyone [16]. However, the benefits of physical activity for mental health has received less attention in comparison to the physical health benefits. A previous review of reviews, published in 2011, showed that physical activity has beneficial effects on mental health in children and adolescents [17]. Nevertheless, the majority of included reviews were considered to be of low quality [17]. From 2010 to 2017, several systematic reviews and meta-analyses of this topic were published [18]. Most of the studies concluded there was a small significant overall association between physical activity and indicators of mental health [10,19–24]. However, these systematic reviews and meta-analyses were focused on: specific mental health outcomes (e.g., depression) [19–21,24,25], specific activities [26], mechanisms (i.e., neurobiological, psychosocial, and behavioral) [15] or specific age ranges (e.g., adolescents) [10]. Therefore, it is important to examine the overall effect of physical activity on mental health of young people in order to guide health policies for this population.

Sedentary time has become a central component of our daily lives [27]. A review of review demonstrated that screen time was negatively associated with young people’s mental health in cross-sectional studies [17]. A recent systematic review in adolescents showed that leisure screen-based sedentary behaviors were related to higher psychological distress and lower self-esteem [28]. However, time spent in leisure screen-based activities is only a small part of the total sedentary time, and each sedentary activity may have a different effect on mental health [29]. For example, playing an instrument or reading a book may positively influence mental health, while excessive watching TV may diminish mental health. A previous systematic review concluded that, due to the low quality of the research done, the relationship between sedentary behavior and indicators of mental health in school-aged children and adolescents was indeterminate [30].

In summary, systematic reviews and meta-analyses have focused on specific lifestyle behaviors, mental health outcomes or a narrow age range, which dramatically limits their conclusions. Therefore, it is imperative to extend and update all relevant literature, mapping the links between physical activity, sedentary behavior and mental health in preschoolers, children and adolescents. Although intervention studies can provide evidence for cause and effect, observational longitudinal studies provide complementary information, particularly about the longer-term effects of physical activity and sedentary behavior. Therefore, an integrated review of both intervention and observational studies is needed.

The aims of this review were (i) to determine the overall effect of physical activity on mental health in preschoolers, children and adolescents by conducting a systematic review and meta-analysis of available intervention studies; and (ii) to systematically synthesize recent observational evidence (both longitudinal and cross-sectional) on the association between physical activity and sedentary behavior with mental health in various pediatric age groups.

METHODS

This study follows the PRISMA [32]. Inclusion and exclusion criteria as well as analytical methods were specified in advance and registered in the PROSPERO (http://www.crd.york.ac.uk/PROSPERO) database, an international database of systematic reviews (PROSPERO reference number, CRD42017060373).

Search strategy and inclusion criteria

The search was conducted in two databases (PubMed and Web of Science). Dates of published articles included in the search were from January 1st 2013 to April 9rd 2018. Search terms were selected based on the eligibility criteria and outcomes of interest described in the following paragraph (see Supplementary Material **Table S1**). Two researchers (MRA and NMM) independently identified relevant articles by screening the titles and reviewing abstracts. Full-text articles deemed eligible for review were examined to determine final eligibility; this process was conducted by the same two individuals (MRA and NMM).

Inclusion criteria were: (i) design: intervention studies (RCT, non-RCT), prospective longitudinal and cross-sectional studies focused on physical activity, sedentary behavior and mental health; (ii) language criterion: only articles in English or Spanish; (iii) age criterion: preschoolers (2–5 years), children (6–11 years) and adolescents (12–18 years); (iv) topic criterion: articles examining the association between physical activity and/or sedentary behavior and at least one psychological ill-being (i.e., depression, anxiety, stress or negative affect) and/or psychological well-being (i.e., self-esteem, self-concept, self-efficacy, self-image, positive affect, optimism, happiness and satisfaction with life) outcome. With regard to exclusion criteria, we did not include conference proceedings and other types of grey literature because of feasibility and limitations in the quality of reporting in conference abstracts [33]. Studies including individuals with physical or psychological disorders diagnosed by medical records, elite athletes and animals were also excluded. Lastly, multiple health behavior intervention studies were excluded (e.g., co-interventions such as a dietary program combined with physical activity) because they preclude drawing conclusions on the isolated effect of physical activity or sedentary behavior on mental health outcomes.

Data extraction

One author (MRA) extracted the following information from each eligible study: study background (name of the first author, year, and study location), sample characteristics (number of participants, age of participants and number of girls and boys), design (intervention –RCT and non-RCT- or observational -cross-sectional or longitudinal-), and instruments used to assess physical activity and/or sedentary behavior and mental health outcomes. For intervention studies (RCTs and non-RCTs), we also extracted: weeks of intervention, description of the program, intensity, duration and frequency. For longitudinal studies, we also extracted years of follow-up.

To reduce heterogeneity, sedentary behavior data were combined into three groups: recreational screen time (i.e., watching TV, using computer game, playing videogames, using mobile phone, using internet), non-recreational screen time (i.e., homework using a screen) and non-screen time (i.e., music, passive transport, homework, reading, creative hobbies, talking). In regards to physical activity, data from general physical activity, outdoor play and sport participation were combined.

Meta-analysis of intervention studies

All statistical analyses were performed using the Comprehensive Meta-Analysis software (version 3, Englewood, NJ:Biostat, USA). P values <0.05 were accepted to indicate statistical significance. The meta-analysis of the intervention studies (RCT and non-RCT) was performed comparing intervention vs. control group. Mean difference (post-test minus baseline values) and standardized mean difference were calculated for each group.

We also calculated the effect size using Cohen's d and 95% confidence interval for standardized mean difference (post minus pre) on overall mental health (i.e., psychological ill-being and psychological well-being outcomes). For overall analyses, we reversed the ES obtained in studies focused on psychological ill-being in order to present results in the same direction (the higher the effect size, the better the effect, as occurs with psychological well-being outcomes). Pooled effect size of the effect of physical activity on psychological ill-being and well-being was obtained using random-effects models. Heterogeneity was measured using the I^2 statistic (total variability attributed to between-study heterogeneity, i.e., $I^2 < 25\%$, 50% and 75% was considered as low, moderate and high heterogeneity, respectively) [34]. In addition, we examined how the duration of the physical activity interventions (grouped as follows: <60min or ≥60 min) could influence mental health. Funnel plots were calculated and the Egger's test was conducted to assess risk of publication bias. The trim and fill procedure was also performed to adjust for the suspected publication bias where the pooled effect size was recalculated to incorporate hypothetical missing studies if necessary.

Subgroup analyses were performed comparing the RCT and non-RCT studies. Also, we performed a sensitivity analysis excluding those studies categorized as high risk of bias. As secondary analysis, we performed one meta-analysis of only those studies that measured psychological ill-being outcomes and another meta-analysis of only those studies that measured psychological well-being outcomes. Lastly, we performed a sub-group analysis examining preschoolers, children and adolescents, separately.

Data synthesis of observational studies

Findings from observational studies were rated using the method first employed by Sallis et al. [35], and more recently used by Lubans et al. [36] and Smith et al. [37]. If 0–33 % of studies reported a statistically significant association for the outcome of interest, the result was classified as no association (Ø). If 34–59 % of studies reported a significant association or if fewer than four studies reported on the outcome, the result was classified as being inconsistent/uncertain (?). If ≥60 % of studies found a statistically significant association, the result was classified as positive (+) or negative (−), depending on the direction of the association. When the association was examined only in girls or boys, we specified it as "♀" or "♂", respectively. If the association between independent and dependent variables was tested or significant only in one sex (girls or boys), we quantified it with a 0.5 score instead of 1.

Criteria for risk of bias assessment

Risk of bias was individually assessed for each eligible study by two researchers (MRA and FEL) and disagreements were solved in a consensus meeting. Inter-rater agreement for the risk of bias assessment was determined by the percentage agreement between evaluators (MRA and FEL). Furthermore, an intraclass correlation coefficient analysis was conducted using SPSS software, version 21.0 (SPSS Inc, Chicago, IL, USA).

Different checklists depending on the study design were used to assess the risk of bias. First, the Cochrane Collaboration´s tool was used for assessing risk of bias in RCTs. The scores for each criterion were summed to provide a total score out of 7 with the following categories: 1-2 'low risk', 3-4 'medium risk' and 5-7 'high risk' [38]. The criteria for assessing risk of bias in non-RCTs, prospective longitudinal studies and cross-sectional studies were created based on the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) [39] and Effective Public Health Practice Project (EPHPP) [40]. A risk of bias score was calculated based on the following five criteria, first employed by Smith et al. [41]: (a) adequate description of the study sample (i.e., number of participants, mean age and sex); (b) adequate assessment/ reporting of physical activity (i.e., validity/reliability of physical activity measurement reported and/or detailed description of the testing protocol); (c) adequate assessment of the mental health outcomes (i.e., validity/reliability of outcome measure reported and/or measurement procedure adequately described); (d) adequate adjustment of confounders (i.e., age and sex); and (e) description of both the numbers and reasons for withdrawals and drop-outs. Based on previous methodology, the scores were summed to provide a total score out of 5 with the following categories: 0–2 'low risk', 3 'medium risk', and 4–5 'high risk'.

RESULTS

Selection process

The search yielded 4624 original articles from which 282 were screened in full text (see **Figure 1** for full search details). Finally, a total of 114 original articles were included in the systematic review: 4 RCTs, 14 non-RCTs, 28 prospective longitudinal studies and 68 cross-sectional studies. Of the 18 intervention studies, 12 (3 RCTs [42–44] and 9 non-RCTs [45–53]) were included in the meta-analysis and five were excluded (three did not report the effect size data needed [54–56], two included an active control group performing other types of physical activity [57,58] (i.e., yoga vs. combined exercise [57] and Tai-Chi vs. gymnastics [58]) and one did not include a control group [59]). The list of excluded articles categorized based on the exclusion criteria can be seen in Supplementary Material **Table S2**.

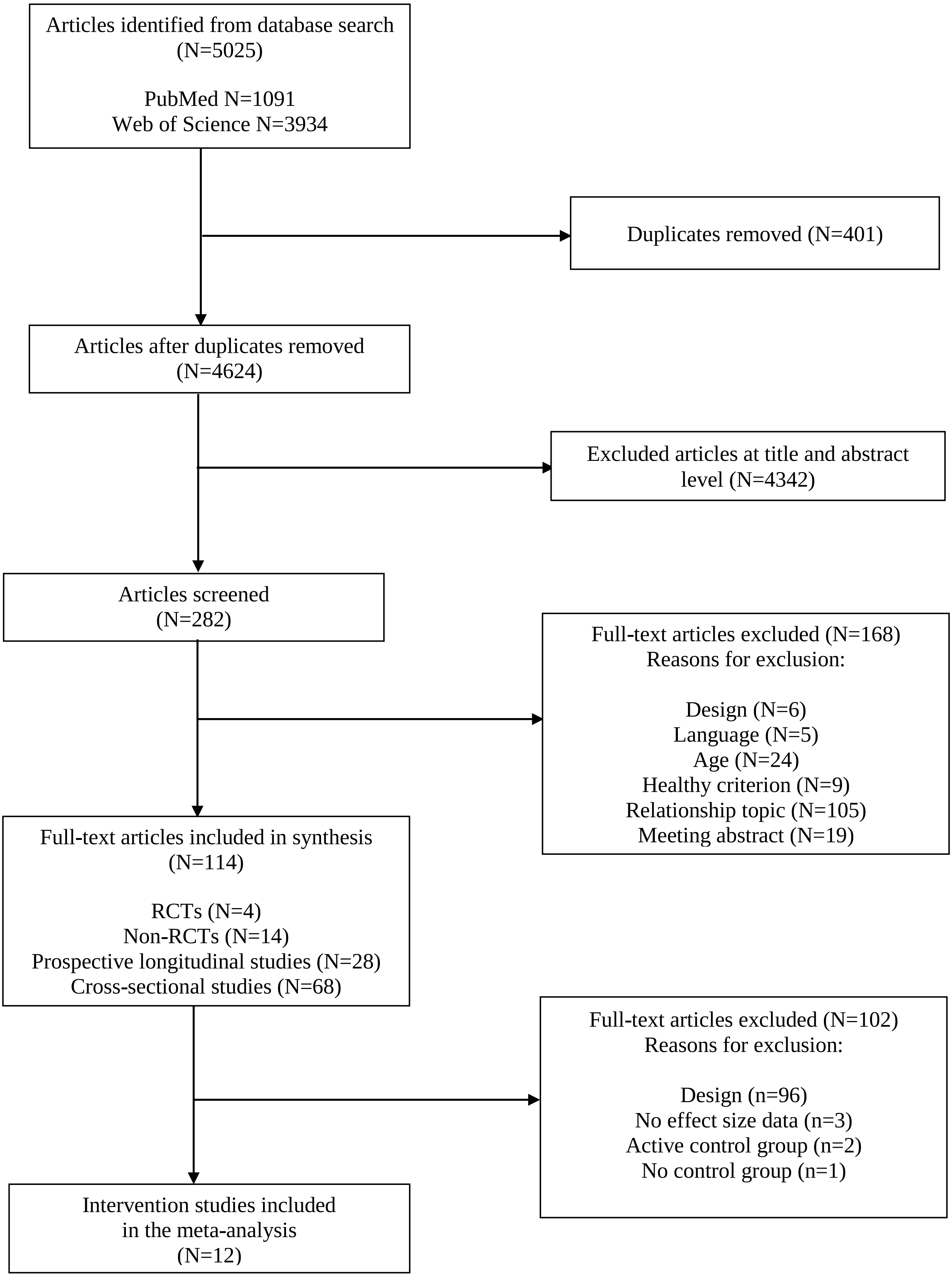


Figure 1. Flow chart showing the results of the selection process. RCT=Randomized controlled trial

Summary of included studies

A detailed description of the intervention studies (RCTs and non-RCTs) is provided in **Table 1.** We conducted a meta-analysis of the RCT and non-RCT studies (see **Figure 2**) to determine the overall effect of physical activity on mental health in different pediatric age groups. A summary of the associations of different types of physical activities (i.e., physical activity, sport participation and outdoor play) and different types of sedentary behaviors (i.e., recreational screen time, non-recreational screen time and non-screen time) with psychological ill-being and psychological well-being in the different pediatric age groups is reported in **Table 2** and **Table 3**, respectively. Further details on study characteristics of prospective longitudinal studies and cross-sectional studies are presented in Supplementary Material **Table S3** and Supplementary Material **Table S4**, respectively. Moreover, the results of the risk of bias assessment can be found in Supplementary Material **Table S5- S8**.

Characteristics of intervention studies (RCTs and non-RCTs)

Sample characteristics

Sample sizes of intervention studies (n=18) ranged from 20 [48] to 420 [50]. One study did not have a control group [59] while two studies included an active control group performing other types of physical activity [57,58] (i.e., yoga vs. combined exercise [57] and Tai-Chi vs. gymnastics [58]). Lastly, 10 studies included adolescents [42–46,49–52,58] while 8 included children [47,48,53–57,59] of whom four were focused on overweight/obese adolescents [43,46] or children [48,55]. We did not find any studies focused on preschoolers (2 to 5 years).

Outcome characteristics

Of the 18 studies included in the systematic review, eight studies provided data on psychological ill-being [44,45,47,49,51,54,55,58]. Specifically, five studies provided data on generic psychological ill-being [44,47,49,51,54], two on depression [49,55], three on anxiety [49,55,58] and one on stress [45]. On the other hand, 13 studies provided data on psychological well-being [42–44,46,48,50–53,56–59]. Specifically, one study focused on a total score of psychological well-being [44], seven on self-esteem [42,43,46,48,51,53,57], six on self-image [43,44,48,52,58,59], one on self-concept [56], one on self-efficacy [50,56], two on happiness [53,58] and two on positive emotions [43,44].

Exposures and comparison conditions

Most of the study interventions ranged from eight to 28 weeks [42–46,48,49,51–57,59]. However, two studies lasted for more than 28 weeks [47,58] and one study for less than eight weeks [50]. Of note, our search also included physical activity and sedentary behavior interventions yet only exercise and sport interventions were available: mind-body exercise programs [45,50,52,53,57,58], aerobic exercise programs [43,44,55], resistance exercise programs [43], combined exercise programs (aerobic + resistance) [42–44,47,49,56], football [48,59], exergames [46,54] and CrossFit [51]. The majority of the studies (80%) implemented exercise sessions for 60 minutes [42,46,48,51,52,55,58], 2-3 times per week (80%) [42–44,46–49,51–53,56,59]. Finally, only five studies reported the intensity during the program (50%-80% maximum heart rate) [42,44,48,49,51]. However, none of them controlled individual intensity, for instance by heart rate monitors, to estimate the time spent in 50–80% of their maximum heart rates.

Table 1. Summary of randomized controlled trial and non-randomized controlled trial research investigating the effect of exercise on mental health (n=18).

Risk of bias	Study, country	Cases/n (age range;%girls) Design; target population	Weeks of intervention; description; intensity; duration; frequency	Mental health indicators Instruments	Main findings
Medium	Telles et al., 2013 [57], India	49/98 (8-13y; 30.8 % girls) RCT; children	12 weeks; yoga vs physical exercise; data not shown; 45 min; 5 d/w.	Self-esteem Battle's Self-Esteem Inventory	There was only one significant difference between the groups in social self-esteem which was higher in the exercise group and all other differences were not significant.
High	Hasanpour et al., 2014 [42][a], Iran	33/66 (13-19y; 100% girls) RCT; adolescents living with no natural family	8 weeks; vs control; 60% to 80% max heart rate; 60 min; 3 d/w.	Self-esteem Coopersmith Self-Esteem Inventory	A significant difference between groups was obtained in post self-esteem scores (p = 0.001). One month after intervention, results showed that despite the amount of time elapsed, the effects of aerobic exercise still persisted (p =0.002).
Medium	Goldfield et al., 2015 [43][a], Canada	Aerobic 75/304, resistance 78/304, combined 75/304, control 76/304 (14-18y; 70% girls) RCT; obese adolescents	22 weeks; aerobic exercise vs control, resistance exercise vs control, combined exercise vs control; data not shown; 45 min; 3 d/w.	Mood; body image; global self-esteem Brunel Mood Scale; Multiple Body Self-Relations Questionnaire; Physical Self-Perceptions Questionnaire	All groups (included the control group) improved on body image. Only the resistance group showed a significant reduction in depressive symptoms (p=0.02). The resistance group showed greater increases than controls on global self-esteem but all group (excluded control group) improved on vigor and global self-esteem.
Medium	Costigan et al., 2016 [44][a], Australia	Aerobic 21/65, combined 22/65,control 22/65 (14–16y; 13% girls) RCT; adolescents	8 weeks; high-intensity interval training with aerobic vs control and combined vs control); >85% max heart rate; 8-10 min; 3 d/w	Psychological well-being; psychological distress; physical self-concept; feelings state Flourishing; Kessler Psychological Distress; Physical Self-Description; one-item Feelings State	Results were not significant, but a small improvement in psychological well-being was observed in the aerobic exercise group (mean change (95% CI) 2.81 (-2.06, 7.68), d = 0.34). Small improvements in psychological well-being (mean change (95% CI) 2.96 (-1.82, 7.75), d = 0.36) and perceived appearance (mean change (95% CI) 0.32 (-0.25, 0.86), d = 0.35), were observed in the combined group. Feelings improved in both groups but it was significant only in the aerobic group (p= 0.001).

Table 1. Continues...

Low	Lee et al., 2013 [45][a], China	32/69 (11-16y; 27.5% girls) Non-RCT; adolescents	10 weeks; Chen-style Tai Chi vs control; data not shown; 80 min; 1 d/w.	Stress Perceived Stress Scale	No significant difference was noted in changes in stress levels before and after the intervention between the two groups.
Low	Staiano et al., 2013[46][a], USA	19/54 competitive, 19/54 cooperative, 16/54 control (15-19y; 55.6% girls) Non-RCT; overweight/obese adolescents	20 weeks; active video game program (competitive vs control and cooperative vs control); data not shown; 30-60 min; 3 d/w.	Self-esteem Rosenberg Self-Esteem Scale	The growth curve analysis of self-esteem change yielded no condition effects. There were no significant changes in self-esteem in any group.
High	Tubić & Đorđić, 2013[47][a], Serbia	17/167 (5-7y, data not shown) Non-RCT; preschoolers/children	72 weeks; exercise vs control; data not shown; 60 min; 3 d/w.	Internalizing problems The Aberrant Behavior Questionnaire	The intervention program had significant but weak effect on indicators of internalizing problems.
Low	Seabra et al., 2014[48][a], USA	12/20 (8–12y; 0% girls) Non-RCT; overweight children	20 weeks; football vs control; >80% max heart rate; 60-90 min; 2 d/w.	Body image; self-esteem Collins' Child Figure Drawings Scale; Rosenberg Self-Esteem Scale	Intervention group participants improved their body image (lower values represent better body image) (F = 6.79, p = 0.021, Cohen's d =−1.44) and self-esteem (F (1, 18) = 4.96, p = 0.046, Cohen's d =−1.27).
Low	Bao & Jin et al., 2015[58], China	80/160 (13-16y; 53.2% girls) Non-RCT; adolescents	48 weeks; Tai Chi vs gymnastic; data not shown; 60 min; 5 d/w.	Physical appearance; anxiety; happiness I am good looking; I cry easily; I am a happy person	Significant reduction of anxiety in the experimental group compared with the control group was observed. No significant differences, in relation to physical appearance and happiness between the Tai Chi and control groups were found.
Low	Bunketorp Kall et al., 2015[54], Sweden	182/349 (10-12y; 47% girls) Non-RCT; children	24 weeks; non-competitive games vs control; data not shown; 30-45 min; 4 d/w.	Internalizing problems The Strengths and Difficulties Questionnaire	There were no significant differences between the intervention and control groups in internalizing problems (all p >0.05)

Table 1. Continues…

Low	Peng et al., 2015[49][a], China	62/121 (14-19y; 50% girls) Non-RCT; adolescents	12 weeks; exercise vs control; 50%-80% max heart rate; 80 min; 2 d/w.	Depression; anxiety stress; emotional problems; psychological distress Mental Health Scale by Wang	The intervention group was superior to the control group in terms anxiety, depression, emotional imbalance, psychological imbalance and the difference was statistically significant (p < 0.05).
Medium	Romero-Pérez et al., 2015[55], México	59/119, (8-11y, 60% girls) Non-RCT; obese children	20 weeks; aerobic exercise vs control; 60%-80% max heart rate; 60 min; 2 d/w.	Anxiety; depression Spence Children's Anxiety Scale; Children Depression Scale	The intervention program had significant but weak effect on total depressive symptoms (p<0.05). There were no significant differences between the intervention and control groups in anxiety levels (all p >0.05).
High	Kyle et al., 2016[56], Spain	31/63 (10-12y; 52% girls) Non-RCT; children	28 weeks; exercise vs control; data not shown; data not shown; 2/4 d/w.	Self-concept; self-efficacy The Self-Concept Form 5; the Self-Efficacy Scale for Children	The results indicated a significant effect on physical self-concept and academic self-concept. Also, a significant effect was observed in academic self-efficacy and social self-efficacy.
High	Rinaldo et al., 2016[59], Italy	60 (9-10y; 0% girls) Pre- and post-intervention; children	12 weeks; football without control group; data not shown; 120 min; 2 d/w.	Body image dissatisfaction Discrepancy between the self-perceived figure and the ideal figure	No difference was found in the nine-year-old group. In the 10-year-old group, the feel–ideal difference index significantly decreased. The mean index values showed underestimations in both age groups, represented as negative values, but especially in the 10-year-old boys.
Medium	Das et al., 2016[50][a], India	210/420; (11-16y; 33.3 % girls) Non- RCT; adolescents	2 weeks; yoga vs control; data not shown; 60-120 min; every weekday.	Self-efficacy (social, academic and emotional self-efficacy) Self-Efficacy Scale for Children	Yoga group showed a significant increase in academic self-efficacy (p < 0.001), social self-efficacy (p < 0.001), and emotional self-efficacy (p < 0.001), whereas there were no significant changes in the scores of the control group.
Low	Eather et al., 2016[51][a], Australia	51/96 (15.4y; 51.5% f girls) Non-RCT; adolescents	8 weeks; CrossFit vs control; high intensity; 60 min; 2 d/w.	Internalizing problems; self-esteem Strength and Difficulties Questionnaire; Physical Self-Description Questionnaire	There were no significant intervention effects on mental health or potential mediators in the full study sample. Intervention participants categorized as 'at risk' of internalizing problems demonstrated improvements in self-esteem, perceived body fat, perceived appearance, physical self-concept, and total difficulties score. A medium-large positive effect on perceived body fat was also observed in boys.

Table 1. Continues…

Low	Cox et al., 2017 [52][a], USA	20/43, (13-17y, 72% girls) Non-RCT; adolescents	12 weeks; yoga vs control; data not shown; 60 min; 2 d/w.	Body surveillance; Physical self-worth; body appreciation Objectified Body Consciousness Scale; Physical Self-Description Questionnaire; The Body Appreciation Scale	Results showed significant (p = 0.004), moderate decreases in trait body surveillance and minimal no significant (p = 0.110) increases in physical self-worth. Change in trait body surveillance was inversely related to change in physical self-worth and body appreciation in yoga participants.
Medium	Yook et al., 2017 [53][a], Korea	23/46 (9-11y; 46% girls) Non-RCT; children	8 weeks; Kinball and yoga vs control; data not shown; 40 min; 2 d/w.	Self-esteem; happiness Rosenberg Self-Esteem Scale; Korean version of the Psychological Well-Being Scale	Participants in the experimental group increased self-esteem (F= 3.47, p= 0.049) and happiness (F= 31.61, p= 0.001).

RCT and Non-RCT=randomized controlled trial and non-randomized. Y=year. d/w=days per week. CI= confidence interval. Max= maximum. USA= the United States of America. RCTs risk of bias was assessed by The Cochrane Collaboration´s tool. The scores for each criterion were summed to provide a total score out of 7. For rating the overall risk of bias of the RCTs studies, the following categories were used: 0=no risk, 1-2 =low risk, 3-4=medium risk and 5-7=high risk. Non-RCTs risk of bias was assessed by the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) and a quality assessment tool for quantitative studies from the Effective Public Health Practice Project. The scores for each criterion were summed to provide a total score out of 5. Studies that scored 0–2 =low risk, 3 =medium risk, and 4–5 high risk. For the risk of bias for each item specifically, see Supplementary Material **Tables S3** and **S4.** [a]= It means that the article was included in the meta-analysis.

Synthesis of findings

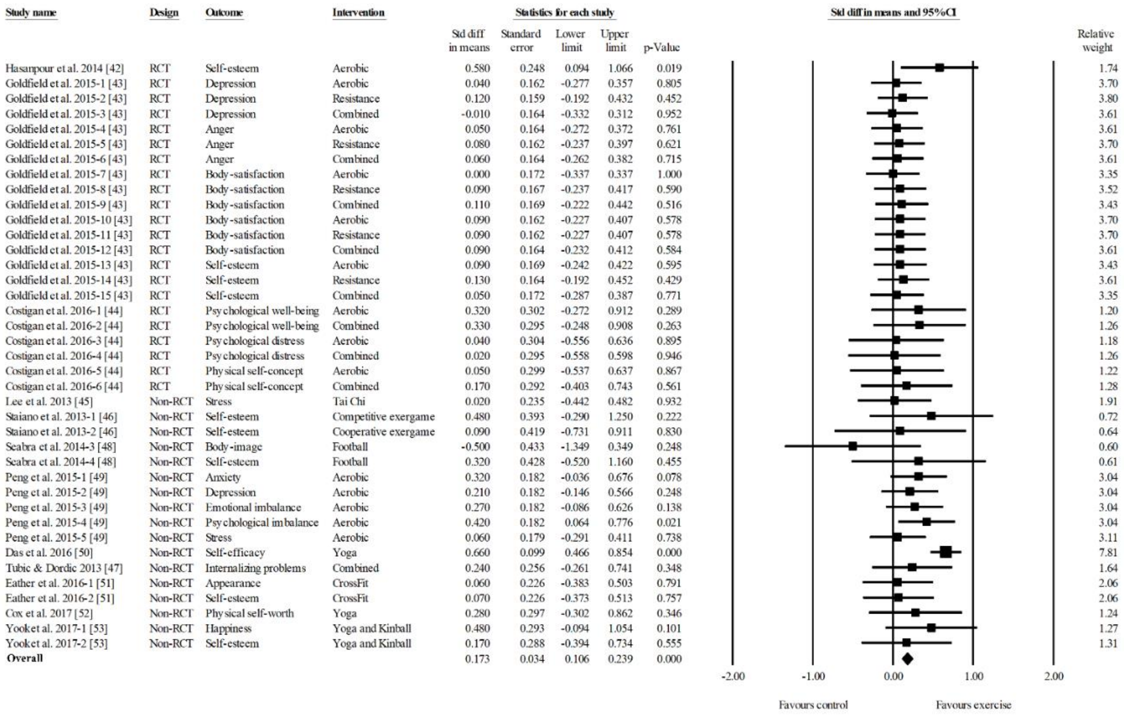
Meta-analysis of intervention studies

Figure 2 presents the meta-analysis of the exercise vs. control effects showing a small significant pooled effect size for the efficacy of the exercise on overall mental health (effect size=0.173, 95% confidence interval = 0.106 to 0.239; $P<0.001$, $I^2=11.3\%$). No significant publication bias was detected based on Egger's test ($P=0.139$) and visual inspection of the funnel plot (**Figure 3**). Moreover, the trim and fill procedure showed that the ES estimate was not changed and thus, no correction for potential publication bias was needed. The analysis conducted by meeting the physical activity recommendations during the exercise program (<60 min or ≥60 min) showed that those programs with ≥60 min of exercise activities significantly improved the overall mental health compared to those peers who engaged in an exercise program of less than 60 min (effect size=0.277, 95% confidence interval: 0.138 to 0.415; $P<0.001$, $I^2=37.22\%$) (**Figure 4**).

When the analyses were performed separately for RCTs and non-RCTs, the results were effect size=0.094, 95% confidence interval: 0.017 to 0.172; $P=0.017$, $I^2=0\%$ for RCTs, and effect size= 0.269, 95% confidence interval: 0.137 to 0.400; $P<0.001$, $I^2=31.8\%$ for non-RCTs. Further, after removing the studies with a high risk of bias, the result was similar (effect size= 0.165, 95% confidence interval: 0.098 to 0.232; $P<0.001$, $I^2=10.3\%$) (data not shown).

Secondary analyses showed that exercise improved psychological ill-being (effect size= 0.130, 95% confidence interval: 0.036 to 0.224; $P=0.007$, $I^2=0\%$) and psychological well-being (effect size= 0.189, 95% confidence interval: 0.084 to 0.294; $P<0.001$, $I^2=32.3\%$) when they were considered as two independent constructs (Supplementary Material **Figure S1a** and **S1b**, respectively). No significant publication bias was observed for either psychological ill-being or well-being (Egger's test, P=0.906 and 0.138, respectively). Funnel plots are shown in Supplementary Material **Figure S2a** and **S2b**. Therefore, trim and fill procedure showed no correction for potential publication bias for psychological ill-being and well-being respectively.

Lastly, when the analyses were performed separately for children and adolescents (no studies were found in preschoolers), the results were similar for adolescents (effect size= 0.181, P≤0.001; I^2=15.7%) and children (effect size= 0.209, P=0.141; I^2=0%). However, the summary effect for children was not statistically significant.



Study name	Design	Outcome	Intervention	Std diff in means	Standard error	Lower limit	Upper limit	p-Value	Relative weight
Hasanpour et al. 2014 [42]	RCT	Self-esteem	Aerobic	0.580	0.248	0.094	1.066	0.019	1.74
Goldfield et al. 2015-1 [43]	RCT	Depression	Aerobic	0.040	0.162	-0.277	0.357	0.805	3.70
Goldfield et al. 2015-2 [43]	RCT	Depression	Resistance	0.120	0.159	-0.192	0.432	0.452	3.80
Goldfield et al. 2015-3 [43]	RCT	Depression	Combined	-0.010	0.164	-0.332	0.312	0.952	3.61
Goldfield et al. 2015-4 [43]	RCT	Anger	Aerobic	0.050	0.164	-0.272	0.372	0.761	3.61
Goldfield et al. 2015-5 [43]	RCT	Anger	Resistance	0.080	0.162	-0.237	0.397	0.621	3.70
Goldfield et al. 2015-6 [43]	RCT	Anger	Combined	0.060	0.164	-0.262	0.382	0.715	3.61
Goldfield et al. 2015-7 [43]	RCT	Body-satisfaction	Aerobic	0.000	0.172	-0.337	0.337	1.000	3.35
Goldfield et al. 2015-8 [43]	RCT	Body-satisfaction	Resistance	0.090	0.167	-0.237	0.417	0.590	3.52
Goldfield et al. 2015-9 [43]	RCT	Body-satisfaction	Combined	0.110	0.169	-0.222	0.442	0.516	3.43
Goldfield et al. 2015-10 [43]	RCT	Body-satisfaction	Aerobic	0.090	0.162	-0.227	0.407	0.578	3.70
Goldfield et al. 2015-11 [43]	RCT	Body-satisfaction	Resistance	0.090	0.162	-0.227	0.407	0.578	3.70
Goldfield et al. 2015-12 [43]	RCT	Body-satisfaction	Combined	0.090	0.164	-0.232	0.412	0.584	3.61
Goldfield et al. 2015-13 [43]	RCT	Self-esteem	Aerobic	0.090	0.169	-0.242	0.422	0.595	3.43
Goldfield et al. 2015-14 [43]	RCT	Self-esteem	Resistance	0.130	0.164	-0.192	0.452	0.429	3.61
Goldfield et al. 2015-15 [43]	RCT	Self-esteem	Combined	0.050	0.172	-0.287	0.387	0.771	3.35
Costigan et al. 2016-1 [44]	RCT	Psychological well-being	Aerobic	0.320	0.302	-0.272	0.912	0.289	1.20
Costigan et al. 2016-2 [44]	RCT	Psychological well-being	Combined	0.330	0.295	-0.248	0.908	0.263	1.26
Costigan et al. 2016-3 [44]	RCT	Psychological distress	Aerobic	0.040	0.304	-0.556	0.636	0.895	1.18
Costigan et al. 2016-4 [44]	RCT	Psychological distress	Combined	0.020	0.295	-0.558	0.598	0.946	1.26
Costigan et al. 2016-5 [44]	RCT	Physical self-concept	Aerobic	0.050	0.299	-0.537	0.637	0.867	1.22
Costigan et al. 2016-6 [44]	RCT	Physical self-concept	Combined	0.170	0.292	-0.403	0.743	0.561	1.28
Lee et al. 2013 [45]	Non-RCT	Stress	Tai Chi	0.020	0.235	-0.442	0.482	0.932	1.91
Staiano et al. 2013-1 [46]	Non-RCT	Self-esteem	Competitive exergame	0.480	0.393	-0.290	1.250	0.222	0.72
Staiano et al. 2013-2 [46]	Non-RCT	Self-esteem	Cooperative exergame	0.090	0.419	-0.731	0.911	0.830	0.64
Seabra et al. 2014-3 [48]	Non-RCT	Body-image	Football	-0.500	0.433	-1.349	0.349	0.248	0.60
Seabra et al. 2014-4 [48]	Non-RCT	Self-esteem	Football	0.320	0.428	-0.520	1.160	0.455	0.61
Peng et al. 2015-1 [49]	Non-RCT	Anxiety	Aerobic	0.320	0.182	-0.036	0.676	0.078	3.04
Peng et al. 2015-2 [49]	Non-RCT	Depression	Aerobic	0.210	0.182	-0.146	0.566	0.248	3.04
Peng et al. 2015-3 [49]	Non-RCT	Emotional imbalance	Aerobic	0.270	0.182	-0.086	0.626	0.138	3.04
Peng et al. 2015-4 [49]	Non-RCT	Psychological imbalance	Aerobic	0.420	0.182	0.064	0.776	0.021	3.04
Peng et al. 2015-5 [49]	Non-RCT	Stress	Aerobic	0.060	0.179	-0.291	0.411	0.738	3.11
Das et al. 2016 [50]	Non-RCT	Self-efficacy	Yoga	0.660	0.099	0.466	0.854	0.000	7.81
Tubic & Dordic 2013 [47]	Non-RCT	Internalizing problems	Combined	0.240	0.256	-0.261	0.741	0.348	1.64
Eather et al. 2016-1 [51]	Non-RCT	Appearance	CrossFit	0.060	0.226	-0.383	0.503	0.791	2.06
Eather et al. 2016-2 [51]	Non-RCT	Self-esteem	CrossFit	0.070	0.226	-0.373	0.513	0.757	2.06
Cox et al. 2017 [52]	Non-RCT	Physical self-worth	Yoga	0.280	0.297	-0.302	0.862	0.346	1.24
Yooket al. 2017-1 [53]	Non-RCT	Happiness	Yoga and Kinball	0.480	0.293	-0.094	1.054	0.101	1.27
Yooket al. 2017-2 [53]	Non-RCT	Self-esteem	Yoga and Kinball	0.170	0.288	-0.394	0.734	0.555	1.31
Overall				0.173	0.034	0.106	0.239	0.000	

Figure 2. Forest plot of pooled effect size and confidence intervals of exercise on overall mental health. RCT=Randomized Controlled Trial. Diff= difference. CI= Confidence Interval.

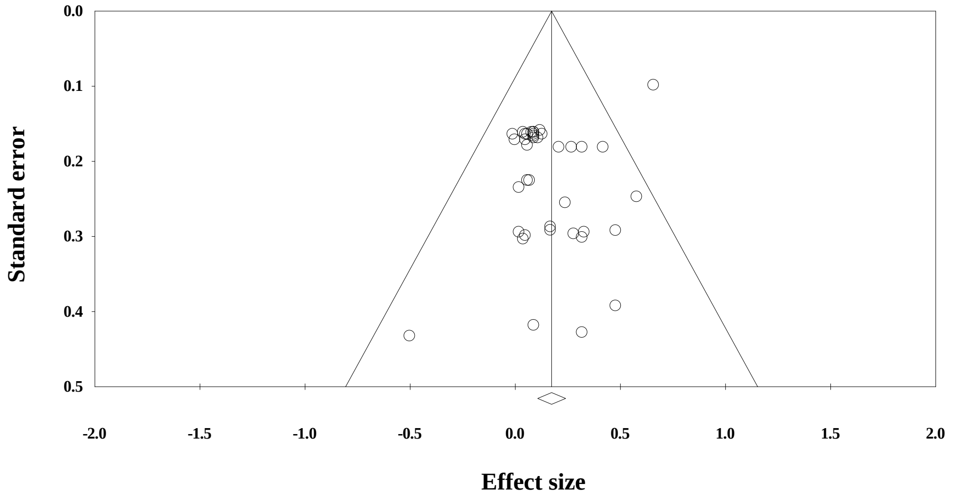
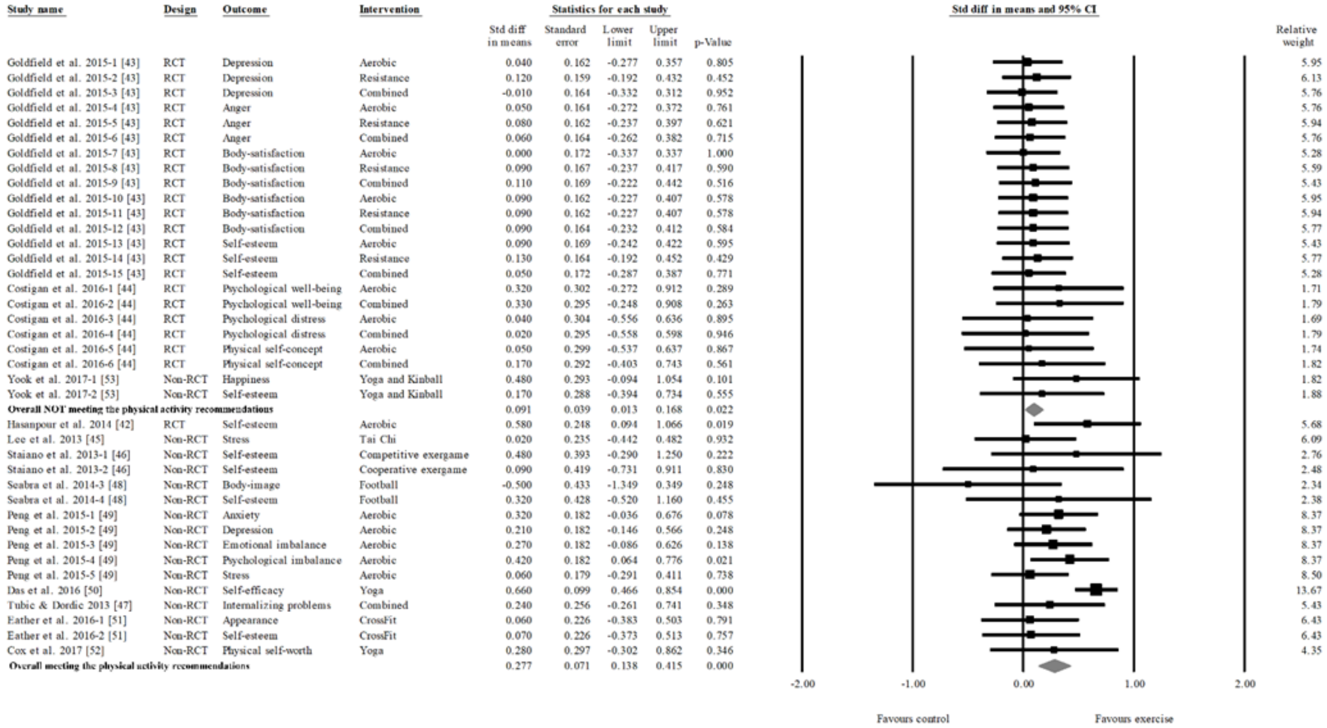


Figure 3. Funnel plot to assess publication bias in effects of exercise on overall mental health. Diagonal lines represent pseudo-95% confidence intervals. The Y axis represents the standard error (weight in the pooled analysis). The X axis shows the effect size; thus, the vertical line represents the calculated estimated effect of overall mental health.



Study name	Design	Outcome	Intervention	Statistics for each study					Relative weight
				Std diff in means	Standard error	Lower limit	Upper limit	p-Value	
Goldfield et al. 2015-1 [43]	RCT	Depression	Aerobic	0.040	0.162	-0.277	0.357	0.805	5.95
Goldfield et al. 2015-2 [43]	RCT	Depression	Resistance	0.120	0.159	-0.192	0.432	0.452	6.13
Goldfield et al. 2015-3 [43]	RCT	Depression	Combined	-0.010	0.164	-0.332	0.312	0.952	5.76
Goldfield et al. 2015-4 [43]	RCT	Anger	Aerobic	0.050	0.164	-0.272	0.372	0.761	5.76
Goldfield et al. 2015-5 [43]	RCT	Anger	Resistance	0.080	0.162	-0.237	0.397	0.621	5.94
Goldfield et al. 2015-6 [43]	RCT	Anger	Combined	0.060	0.164	-0.262	0.382	0.715	5.76
Goldfield et al. 2015-7 [43]	RCT	Body-satisfaction	Aerobic	0.000	0.172	-0.337	0.337	1.000	5.28
Goldfield et al. 2015-8 [43]	RCT	Body-satisfaction	Resistance	0.090	0.167	-0.237	0.417	0.590	5.59
Goldfield et al. 2015-9 [43]	RCT	Body-satisfaction	Combined	0.110	0.169	-0.222	0.442	0.516	5.43
Goldfield et al. 2015-10 [43]	RCT	Body-satisfaction	Aerobic	0.090	0.162	-0.227	0.407	0.578	5.95
Goldfield et al. 2015-11 [43]	RCT	Body-satisfaction	Resistance	0.090	0.162	-0.227	0.407	0.578	5.94
Goldfield et al. 2015-12 [43]	RCT	Body-satisfaction	Combined	0.090	0.164	-0.232	0.412	0.584	5.77
Goldfield et al. 2015-13 [43]	RCT	Self-esteem	Aerobic	0.090	0.169	-0.242	0.422	0.595	5.43
Goldfield et al. 2015-14 [43]	RCT	Self-esteem	Resistance	0.130	0.164	-0.192	0.452	0.429	5.77
Goldfield et al. 2015-15 [43]	RCT	Self-esteem	Combined	0.050	0.172	-0.287	0.387	0.771	5.28
Costigan et al. 2016-1 [44]	RCT	Psychological well-being	Aerobic	0.320	0.302	-0.272	0.912	0.289	1.71
Costigan et al. 2016-2 [44]	RCT	Psychological well-being	Combined	0.330	0.295	-0.248	0.908	0.263	1.79
Costigan et al. 2016-3 [44]	RCT	Psychological distress	Aerobic	0.040	0.304	-0.556	0.636	0.895	1.69
Costigan et al. 2016-4 [44]	RCT	Psychological distress	Combined	0.020	0.295	-0.558	0.598	0.946	1.79
Costigan et al. 2016-5 [44]	RCT	Physical self-concept	Aerobic	0.050	0.299	-0.537	0.637	0.867	1.74
Costigan et al. 2016-6 [44]	RCT	Physical self-concept	Combined	0.170	0.292	-0.403	0.743	0.561	1.82
Yook et al. 2017-1 [53]	Non-RCT	Happiness	Yoga and Kinball	0.480	0.293	-0.094	1.054	0.101	1.82
Yook et al. 2017-2 [53]	Non-RCT	Self-esteem	Yoga and Kinball	0.170	0.288	-0.394	0.734	0.555	1.88
Overall NOT meeting the physical activity recommendations				0.091	0.039	0.013	0.168	0.022	
Hasanpour et al. 2014 [42]	RCT	Self-esteem	Aerobic	0.580	0.248	0.094	1.066	0.019	5.68
Lee et al. 2013 [45]	Non-RCT	Stress	Tai Chi	0.020	0.235	-0.442	0.482	0.932	6.09
Staiano et al. 2013-1 [46]	Non-RCT	Self-esteem	Competitive exergame	0.480	0.393	-0.290	1.250	0.222	2.76
Staiano et al. 2013-2 [46]	Non-RCT	Self-esteem	Cooperative exergame	0.090	0.419	-0.731	0.911	0.830	2.48
Seabra et al. 2014-3 [48]	Non-RCT	Body-image	Football	-0.500	0.433	-1.349	0.349	0.248	2.34
Seabra et al. 2014-4 [48]	Non-RCT	Self-esteem	Football	0.320	0.428	-0.520	1.160	0.455	2.38
Peng et al. 2015-1 [49]	Non-RCT	Anxiety	Aerobic	0.320	0.182	-0.036	0.676	0.078	8.37
Peng et al. 2015-2 [49]	Non-RCT	Depression	Aerobic	0.210	0.182	-0.146	0.566	0.248	8.37
Peng et al. 2015-3 [49]	Non-RCT	Emotional imbalance	Aerobic	0.270	0.182	-0.086	0.626	0.138	8.37
Peng et al. 2015-4 [49]	Non-RCT	Psychological imbalance	Aerobic	0.420	0.182	0.064	0.776	0.021	8.37
Peng et al. 2015-5 [49]	Non-RCT	Stress	Aerobic	0.060	0.179	-0.291	0.411	0.738	8.50
Das et al. 2016 [50]	Non-RCT	Self-efficacy	Yoga	0.660	0.099	0.466	0.854	0.000	13.67
Tubic & Dordic 2013 [47]	Non-RCT	Internalizing problems	Combined	0.240	0.256	-0.261	0.741	0.348	5.43
Eather et al. 2016-1 [51]	Non-RCT	Appearance	CrossFit	0.060	0.226	-0.383	0.503	0.791	6.43
Eather et al. 2016-2 [51]	Non-RCT	Self-esteem	CrossFit	0.070	0.226	-0.373	0.513	0.757	6.43
Cox et al. 2017 [52]	Non-RCT	Physical self-worth	Yoga	0.280	0.297	-0.302	0.862	0.346	4.35
Overall meeting the physical activity recommendations				0.277	0.071	0.138	0.415	0.000	

Figure 4. Grouping analysis of not meeting the physical activity recommendations (<60 min) and meeting physical activity recommendations (≥ 60 minutes) against the effect size on overall mental health. The more positive the effect size, the better are the changes in overall mental health. Overall effect size for each group (meet or not meet recommendations) is colored in grey. RCT=Randomized Controlled Trial. Diff= difference. CI= Confidence Interval.

Summary of findings from observational studies: prospective longitudinal and cross-sectional studies

Association between physical activity and mental health

The association between physical activity and psychological ill-being components (i.e., depression, anxiety, stress, negative affect, total psychological distress) was investigated in 52 studies, of which 13 studies were longitudinal, 35 were cross-sectional, and four studies reported both longitudinal and cross-sectional data. Furthermore, the association between physical activity and psychological well-being components (i.e., self-esteem, self-concept, self-efficacy, self-image, positive affect, satisfaction with life and optimism) was investigated in 39 studies of which eight were longitudinal, and 31 were cross-sectional.

No studies were conducted on preschoolers, while 11 studies were conducted on children, 63 studies were conducted on adolescents, and three studies were conducted on children and adolescents together. Only five studies evaluated objectively measured physical activity by accelerometry [60–63]. Depression was the most studied psychological ill-being outcome (80%). In addition, self-esteem, self-image and satisfaction with life were the most studied psychological well-being outcomes (28%, 23%, and 30%, respectively).

There was evidence for a statistically significant association between physical activity and depression (27.5 of 42 studies, 65.4%), stress (6 of 6 studies, 100%), negative affect (3 of 4 studies, 75%) and a total psychological distress (5 of 8, 62.5%). There was an unclear association between physical activity and anxiety (7 of 12 studies, 58.3%) in children and adolescents. Regarding psychological well-being outcomes, there was evidence for a statistically significant association between physical activity and self-image (6.5 of 9 studies, 72.2%), satisfaction with life (10 of 12, 83.3%) and total psychological well-being (7 of 7, 100%). There was an unclear association between physical activity and self-esteem (5 of 11.5, 43.5%). Lastly, there were insufficient studies (<4 studies) to determine the association between physical activity and self-concept, self-efficacy, positive affect and optimism in children and adolescents.

Association between sedentary behavior and mental health

The association between sedentary behavior and psychological ill-being outcomes (i.e., depression, anxiety, stress, negative affect) was investigated in 32 studies of which eight were longitudinal, 19 were cross-sectional, and five reported both longitudinal and cross-sectional data. The association between sedentary behavior and psychological well-being outcomes (i.e., self-esteem, self-concept, self-efficacy, self-image, positive affect, satisfaction with life and optimism) was investigated in 16 studies of which three were longitudinal, and 13 were cross-sectional.

Only three studies were conducted on preschoolers, eight studies were conducted on children, 28 studies were conducted on adolescents, and three studies were conducted on children and adolescents. Only three studies evaluated objectively sedentary behavior by accelerometry [64–66]. Depression was the most studied psychological ill-being outcome examined (65%) while self-esteem and self-image were the most studied psychological well-being outcomes (35% and 32%, respectively).

There was only evidence for a statistically significant positive association between sedentary behavior and depression (35 of 21.5 studies, 61.4%). However, the associations between sedentary behavior and anxiety (4.5 of 10 studies, 45%) and total psychological distress (7 of 17 studies, 41.1%) were considered to be unclear. Insufficient studies were found testing the association between sedentary behavior and stress [67] and negative affect [68] in children and adolescents. Regarding psychological well-being, there was evidence for a statistically significant inverse association between sedentary behavior and satisfaction with life (4 of 5 studies, 80%). There was an unclear association between sedentary behavior and self-esteem (7 of 14.5 studies, 48%), self-image (5 of 13.5 studies, 37%) and total psychological well-being score (4 of 9 studies, 44.4%). There were insufficient studies (<4 studies) testing the association between sedentary behavior and self-concept, self-efficacy, and positive affect, and optimism in children and adolescents.

Risk of bias assessment

There was a strong agreement among researchers in the risk of bias assessment (intraclass correlation coefficient =0.80). Overall, three RCTs showed medium risk of bias [43,44,57], while only one showed a high risk of bias [42]. Furthermore, eight non-RCTs showed low risk of bias [45,46,48,49,51,52,54,58], three medium risk of bias [50,53,55] and three high risk of bias [47,56,59]. Most studies included an adequate description of the study sample (95%), as well as an adequate assessment of outcome measures (93%).

In addition, 20 prospective longitudinal studies showed a low risk of bias (71.4%), and eight studies showed a medium risk of bias (28.6%). Additionally, 33 cross-sectional studies showed a low risk of bias (48.5%), 19 cross-sectional studies showed a medium risk of bias (28%) and 16 cross-sectional studies showed a high risk of bias (23.5%). Only 46.5% of longitudinal cohort studies used a validated and/or reliable tool to evaluate physical activity or sedentary behavior while 44% of cross-sectional studies used a validated and/or reliable tool to evaluate physical activity or sedentary behavior.

Table 2. Relationships summary between physical activity and mental health outcomes.

				Psychological ill-being					Psychological well-being							
Longitudinal	Study	N	Population	Depression	Anxiety	Stress	Negative Affect	Distress	Self-esteem	Self-concept	Self-efficacy	Self-image	Positive affect	SWL	Optimism	WB
Physical activity	Brunet et al.[78]	1,293	Adol	Ø												
	Raudsepp el al.[109]	272	Adol									+♀				
	Stavrakakis et al.[110]	1,396	Adol	Ø												
	Toseeb et al.[60][a]	736	Adol	Ø												
	Carter et al. [76]	6,504	Adol	-												
	McPhie et al.[75]	3,676	Adol	-												
	Van Dijk et al.[61][a]	158	Adol	Ø					Ø							
	Hoare et al. [111]	634	Adol	- ♂ Ø♀												
	Ishii et al.[112]	292	Child		Ø		Ø				+♀-♂					
	Reddon et al.[113]	2,278	Child						+							
	Ahn et al. [64]	6,153	Child					-								
Sports	Brunet et al.[78]	1,293	Adol													
	Conn et al.[114]	134	Adol	-												
	Adachi & Willoughby[81]	1,492	Child						Ø							
	Wagnsson et al.[82]	1,358	Adol						+							
	Jewett et al.[115]	853	Adol	-		-										+
	Vella et al.[116]	4,042	Child					-								
	Sabiston et al.[77]	860	Adol	-												
	Vella et al.[80]	4023	Adol					-								
Outdoor play	Shin & You [117]	3,188	Adol			-								+		
	Poulsen & Biering [118]	1,589	Adol	Ø♂-♀												
	Gunnell et al.[93]	236	Adol	Ø	Ø											
Cross-sectional																
Physical activity	Brunet et al.[78]	1,293	Adol	-												
	Stavrakakis et al.[110]	1,396	Adol	-												
	Bilinski et al.[62]	269	Child											+		
	Bilinski et al.[62][a]	269	Child											Ø		
	Bulhões et al.[119]	1,988	Adol	Ø												
	Shriver et al.[120]	214	Child						Ø							
	Fararouei et al.[121]	8,159	Adol											+		
	Martikainen et al.[63][a]	252	Child			-										
	Haugen et al.[122]	1,207	Adol									+				
	Skrove et al.[123]	7,639	Adol	Ø	Ø											
	Altintas et al.[124]	1,012	Adol		+♂ Ø ♀				+♂ Ø ♀			+♂ Ø ♀				
	Marques et al.[125]	1,082	Adol									-♀				
	Gomes et al.[126]	192	Adol		-							+				
	Kovacs et al.[127]	881	Adol	Ø										Ø	Ø	
	Wang et al.[128]	3,096	Adol	-	-											
	Park [129]	73,238	Adol			-										
	Kremer et al.[99]	8,256	Adol	-												
	Moljord et al.[130]	11,005	Adol	Ø♂-♀												
	Reigal et al.[83]	2,079	Adol								+			+		
	Zach & Netz [131]	48	Adol		Ø											
	Sun et al.[132]	30,399	Adol	-												
	Hoare et al.[133]	800	Adol	Ø												
	Carter et al.[76]	6,504	Adol	-												
	Trinh et al.[134]	2,660	Adol	Ø				Ø	Ø							
	Ho et al.[84]	775	Adol								Ø					+

Table 2. Continues…

				Psychological ill-being					Psychological well-being							
	Study	N	Population	Depression	Anxiety	Stress	Negative Affect	Distress	Self-esteem	Self-concept	Self-efficacy	Self-image	Positive affect	SWL	Optimism	WB
Physical activity	Esmaeilzadeh [135]	456	Child	-♂												
	Reid et al.[136]	20,000	Child/Adol				-						+			
	Asare et al.[137]	296	Adol	-								+				
	Hyakutake et al.[138]	409	Adol	-												
	Alghadir et al.[139]	150	Child/Adol	-												
	Wu et al.[96]	5,200	Child					Ø	+							
	Mak et al.[140]	905	Adol						+♂-♀							
	Mouissi et al.[141]	256	Adol													+
	Hayward et al.[142]	3,295	Adol	-♂ Ø♀												
	Baldursdottir et al.[143]	32,860	Adol	-												
	Szamreta et al.[144]	120	Child									+ ♀				
	Chae et al.[145]	848	Adol	-												
	McDowell et al. [146]	481	Adol	-	-											
	Khan et al. [147]	898	Adol	-												
	Martin et al.[148]	13,486	Adol											+		
	Min et al.[149]	370,568	Adol			-								+		
	Taik et al.[150]	1,747	Adol	Ø	-	-										
	McMahon et al.[151]	11,110	Adol	-	-											+
	Brunet et al.[78]	1,293	Adol	-												
Sports	Noack et al.[152]	595	Adol						Ø			Ø				
	Karr et al.[153]	627	Adol									+♀				
	Gigisladottir et al.[154]	10,987	Adol									+				+
	Booker et al.[155]	4,899	Adol				-							+		
	Fatiregun & Kumapayi[156]	1,713	Adol	-												
	Dalton et al.[157]	639	Adol					-								
	Booker et al.[158]	4,899	Adol											+		
	Sipos et al.[159]	1,091	Adol						+							
	Asfou et al.[160]	575	Adol					Ø								
	Baldursdottir et al.[143]	32,860	Adol	-												
	Sabiston et al.[77]	860	Adol	-												
	McMahon et al.[151]	11,110	Adol	-	-											+
	Reverdito et al.[161]	821	Adol								+					
	Schneider et al.[74]	451	Adol									+♀				
AC	Sun et al.[162]	21,596	Child/Adol	-												
Dance	Monteiro et al. [163]	283	Adol						Ø♀			-♀				
Outdoor play	Herman et al.[164]	7,725	Adol													+
	Badura et al.[165]	10,503	Adol											+		
	Gunnell et al.[93]	236	Adol	Ø	-											
	Janssen et al. [68]	20,122	Adol				-							+		
	Asfour et al.[160]	575	Adol					-								
+				0	0.5	0	0	0	5	0	2.5	6.5	1	10	0	7
-				27.5	7	6	3	5	0.5	0	0.5	1	0	0	0	0
Ø				14.5	4.5	0	1	3	6	0	1	1.5	0	2	1	0
Total score				-	?	-	-	-	?	?	?	+	?	+	?	+

SWI= Satisfaction with life and happiness. WB= Well- being. (*) = Physical activity evaluated by an objectively measure. AC = Active commuting. Child=children. Adol= adolescents. (+) = positive association (all sample). (-) = negative association (all sample). (Ø) = no association (all sample). Ø♂= no association (100% boys). Ø♀= no association (100% girls). +/-♂=positive/negative association (100% boys). +/- ♀=positive/negative association (100% girls). +/-♂ Ø♀= positive/negative association boys and no association for girls (all sample). Ø♂+/-♀ = no association for boys and positive/negative association girls (all sample). If 0–33 % of studies reported a significant association, the result was classified as no association (Ø). If 34–59 % of studies reported a significant association or if fewer than four studies reported on the outcome, the result was classified as being inconsistent/uncertain (?). If ≥60 % of studies found a significant association, the result was classified as positive (+) or negative (-), depending on the direction of the association.^{a}= objectively measured physical activity.

Table 3. Relationships summary between sedentary behavior and psychological health outcomes.

					Psychological ill-being					Psychological well-being				
Longitudinal	Behavior	Study	N	Population	Depression	Anxiety	Stress	Negative affect	Global distress	Self-esteem	Self-efficacy	Self-image	SWL	WB
Recreational ST	TV	Hinkley et al.[90]	3,604	Preschoolers					Ø	Ø				Ø
	C	Hinkley et al.[90]	3,604	Preschoolers					Ø♂ +♀	Ø				Ø
	TV & C	Allen &Vella[91]	3,956	Preschoolers					+					
	TV & C	Allen &Vella[91]	3,956	Child					Ø					
	TV	Bickham et al.[101]	126	Adol	+									
	C	Bickham et al.[101]	126	Adol	Ø									
	M	Bickham et al.[101]	126	Adol	+									
	TV & C	Carter et al.[76]	6,504	Adol	Ø									
	TV	Grøntved et al.[102]	435	Child	+									
	C	Grøntved et al.[102]	435	Child	Ø									
	TV & C	Hamer et al.[166]	2,038	Adol					Ø					-
	TV	McVeigh et al.[75]	2,411	Preschoolers	Ø	Ø	Ø							
	TV & C	Hoare et al.[111]	634	Adol	+ ♂ Ø♀									
	TV & C	Gunnell et al.[93]	236	Adol	Ø	Ø								
Non ST	Music	Bickham et al.[101]	126	Adol	Ø									
	Homework	Hamer et al.[166]	2,038	Adol					Ø					Ø
Total SB		Raudsepp[167]	253	Adol	+									
		Ahn et al.[64][a]	6,153	Child					Ø					
		Ishii et al.[112]	292	Child		Ø			Ø		Ø			
Cross-sectional														
Recreational ST	TV & C	Nihill et al.[65]	357	Adol						-				
	TV	Nihill et al.[65]	357	Adol						-				
	C	Nihill et al.[65]	357	Adol						-				
	TV	Schneider et al.[74]	451	Adol								-♀		
	I	Schneider et al.[74]	451	Adol								Ø♀		
	TV & C	Benson et al.[98]	117	Child/Adol	+									
	TV & C	Kremer et al.[99]	8,256	Adol	+									
	TV & C	Wang et al.[128]	3,096	Adol	+	+								
	TV & C	Hoare et al.[133]	800	Adol	+									
	TV & C	Allen &Vella[91]	3,800	Preschoolers					Ø					
	TV & C	Allen &Vella[91]	3,800	Child					+					
	TV	Bickham et al.[101]	126	Adol	Ø									
	C	Bickham et al.[101]	126	Adol	Ø									
	M	Bickham et al.[101]	126	Adol	+									
	TV & C	Carter et al.[76]	6,504	Adol	+									
	TV, C, M	Babic et al.[104]	322	Adol								-		-
	TV	Babic et al.[104]	322	Adol								Ø		Ø
	C	Babic et al.[104]	322	Adol								Ø		-
	M	Babic et al.[104]	322	Adol								-		Ø
	TV, C, M	Trinh et al.[134]	2,660	Adol	+				+	-				
	TV	Booker et al.[158]	4,899	Adol									Ø	
	C	Booker et al.[158]	4,899	Adol									-	
	I	Booker et al.[158]	4,899	Adol									-	
	TV & C	Herman et al.[164]	7,725	Adol										-

Table 3. Continues…

					Psychological ill-being					Psychological well-being				
	Behavior	Study	N	Population	Depression	Anxiety	Stress	Negative affect	Global distress	Self-esteem	Self-efficacy	Self-image	SWL	WB
Recreational ST	TV	Maras et al. [95]	2,482	Adol	-	-								
	C	Maras et al. [95]	2,482	Adol	+	+								
	TV & C	Maras et al. [95]	2,482	Adol	+	+								
	TV, C, M	Suchert et al.[168]	1,296	Adol	Ø♂ +♀					+♂ -♀	-	Ø♂ -♀		
	TV	Padilla-Moledo et al.[169]	680	Child/Adol									-	
	TV, C, M	Asfour[160]	575	Adol					Ø					
	TV & C	Wu et al.[96]	5,200	Child					+	-				
	TV	Wu et al.[96]	5,200	Child					+	-				
	C	Wu et al.[96]	5,200	Child					Ø	Ø				
	TV	Goldfield et al.[103]	358	Adol	-									
	C	Goldfield et al.[103]	358	Adol	+									
	TV & C	Goldfield et al.[103]	358	Adol	+									
	TV & C	Suchert et al.[170]	1,228	Adol								-		
	TV & C	Gunnell et al.[93]	236	Adol	+	+								
	TV & C	Hayward et al.[142]	3,295	Adol	Ø♂ +♀									
	C	Janssen et al.[68]	20,122	Adol				+						
	I	Hoare et al.[97]	5,500	Child/Adol	Ø♂ +♀				+					
	TV & C	Khan et al.[147]	898	Adol	+									
	TV & C	Martin et al. [148]	13,486	Child/Adol									-	
	C	Mundy et al.[171]	876	Child					+ ♂ Ø♀					
	C	Ohannessian et al[172]	411	Adol		-♂+♀								
	TV & C	Szamreta et al. [144]	120	Child								Ø♀		
Non-recreational ST	Homework	Babic et al.[104]	322	Adol								Ø		
Non ST	Magazines	Schneider et al.[74]	451	Adol								Ø♀		
	Music	Bickham et al.[101]	126	Adol	Ø									
	¥	Suchert et al.[168]	1,296	Adol	+					Ø	Ø	Ø		
Total SB		Webb et al.[173]	238	Adol						Ø♀		-♀		
		Nihill et al.[65][a]	357	Adol						Ø				
		Suchert et al.[168]	1,296	Adol	Ø♂ +♀					Ø♂ -♀	-	Ø♂ -♀		
		Asare et al.[137]	296	Adol	+					Ø		Ø		
		Ishii et al. [66][a]	967	Child		Ø								
		Raudsepp[167]	253	Adol	+									
+					21.5	4.5	0	1	7	0.5	0	0	0	0
-					2	1.5	0	0	0	7	2	5	4	4
Ø					11.5	4	1	0	10	7	2	8.5	1	5
Total score					+	?	?	?	?	?	?	?	-	?

No studies were found with self-concept and positive affect outcomes. SWI= Satisfaction with life and happiness. WB= Well- being. ST= Screen time. Child=children. Adol= adolescents. (+) = positive association (all sample). (-) = negative association (all sample). (Ø) = no association (all sample). Ø♂= no association (100% boys). Ø♀= no association (100% girls). +/-♂=positive/negative association (100% boys). +/- ♀=positive/negative association (100% girls). +/-♂ Ø♀= positive/negative association boys and no association for girls (all sample). Ø♂+/-♀ = no association for boys and positive/negative association girls (all sample). C=computer. TV=television. M=mobile. I=internet. ¥=Music, transport, homework, reading, creative hobbies, talking. If 0–33 % of studies reported a significant association, the result was classified as no association (Ø). If 34–59 % of studies reported a significant association or if fewer than four studies reported on the outcome, the result was classified as being inconsistent/uncertain (?). If ≥60 % of studies found a significant association, the result was classified as positive (+) or negative (-), depending on the direction of the association. [a]= objectively measured sedentary time.

DISCUSSION

The aims of this review were to: (i) determine the overall effect of physical activity on mental health in preschoolers, children and adolescents; and (ii) synthesize recent observational evidence (both longitudinal and cross-sectional studies) examining the association between physical activity, sedentary behavior and mental health in these pediatric age groups. The main findings of this review are as follows: (i) there was a small positive effect of exercise interventions on mental health outcomes (i.e., psychological ill-being and psychological well-being) in adolescents; (ii) physical activity was inversely associated with psychological ill-being (i.e., depression, stress, negative affect, total physiological distress) and positively associated with psychological well-being (i.e., self-image, satisfaction with life and happiness and psychological well-being); and (iii) there was an inverse association between sedentary behavior and depression and a positive association between sedentary behavior and satisfaction with life and happiness in children and adolescents. Therefore, findings from the present research suggest that, increased physical activity and decreased sedentary behavior, may enhance mental health in children and adolescents.

Effects of intervention studies on mental health

Our meta-analytical approach allowed us to determine the overall effect of exercise interventions on mental health in children and adolescents. The results suggest that there are small significant effects of exercise on reducing psychological ill-being and improving psychological well-being, as separate effects. Larger effects may not be expected due to the good levels of mental health experienced by the majority of young people. Future interventions are warranted to determine if physical activity effects are consistent in youth with poor mental health. It is important to note that not all young people will experience increased physical competence or improved perceived appearance after completing a physical activity regimen (e.g., by not gaining strength, not experiencing weight loss, or losing games all the time). Indeed, poorly designed physical activity interventions may thwart the satisfaction of young people´s needs and lead to decreases in perceived competence and global self-esteem [71]. Therefore, future intervention studies might consider the use of evidence-based physical activity strategies to maximize the positive effect of physical activity on mental health outcomes; e.g., the SAAFE principles and practical strategies designed by Lubans et al. [72].

Of note, when the analyses were performed separately for children and adolescents (no studies were found in preschoolers), the results were similar. However, the summary effect was not statistically significant for children. This finding is likely due to the small number of studies including children (3 unique studies). As such, more studies are needed in preschoolers (2-5 years old) and children (6-11 years old) to test the effect of physical activity on mental health.

The relationship between interventions and overall mental health (i.e., both psychological ill-being and psychological well-being) has not been previously studied using meta-analyses. As such, this work complements previous meta-analyses and reviews focused on specific mental health components. For instance, our findings are consistent with the meta-analysis published by Brown and colleagues [19] who found a small positive effect of exercise on depression. Similarly, our findings are in accord with the review conducted by Larun and colleagues [69], who found a significant moderate effect of exercise on depressive symptoms. The larger effect sizes observed in Larun and colleagues´ review [69] may be explained by their inclusion of children and adolescents with major depression symptoms, who were not included in this review.

This hypothesis is consistent with the findings of Carter and colleagues [70], who found that exercise appears to improve depressive symptoms in adolescents, especially in clinical samples diagnosed with major psychological disorders.

In the present review, we found that, compared to those peers who engaged in exercise activities less than 60 min/day, participants who met the physical activity recommendations significantly improved their overall mental health. In the context of the literature, this review expands upon the compelling evidence of general cardio-metabolic health benefits of physical activity recommendations by providing further evidence for the mental health benefits for children and adolescents [73]. However, it is important to note that most of the intervention studies were non-RCTs (nine of 13 studies, 70%) and none had a low risk of bias. Moreover, most of the intervention studies included adolescents (11 of 13 studies, 85%). Therefore, well-designed intervention studies are needed to confirm our findings, especially in preschoolers and children.

Observational studies on the association between physical activity and mental health

Physical activity was inversely associated with psychological ill-being (i.e., depression, stress, negative affect, overall physiological distress) and positively associated with psychological well-being (i.e., self-image, satisfaction with life and happiness and overall psychological well-being) in children and adolescents. Therefore, findings from the present systematic review suggest that increased levels of physical activity may have a positive effect on mental health in children and adolescents.

Each type of physical activity (e.g., sports participation, outdoor play or active commuting) may contribute in distinct ways to mental health in children and adolescents. For instance, Schneider and colleagues [74] found that adolescents who participated in non- aesthetic sports (e.g., swimming, horseback, judo or hockey) were satisfied with their physical appearance, while participation in aesthetic activities such as ballet and rhythmic gymnastics was significantly correlated with body dissatisfaction [74]. This is perhaps not surprising considering the strong focus on physical appearance inherent in aesthetic activities. In addition, it seems that adolescents who continue to participate in team sports during high school report lower levels of depression in early adulthood [75,76]. In contrast, number of years participating in individual sports was not significantly associated with depressive symptoms in early adulthood [76,77]. Moreover, Brunet and colleagues [78] found that sport participation during adolescence, but not overall physical activity, was associated with decreased levels of depression in adulthood. Therefore, it seems that sport participation, especially team sports without any aesthetic implication, is the type of physical activity most strongly associated with mental health in young people. This result may be explained by the fact that team sports provide important peer support during childhood and adolescence, which might help to buffer the effects of stressful life events that occur during adolescence [79]. Of note, the relationship between sport and mental health might be potentially bidirectional [80]. Specifically, it seems that young people who experience greater levels of psychological ill-being have lower subsequent levels of sport participation [80]. Therefore, experimental studies on sport participation and mental health are required to draw conclusions about the causality of our findings.

Interestingly, the relation between physical activity and mental health may be influenced by several potential moderators and mediators. For instance, Adachi and colleagues [81] suggested that enjoyment of physical activity positively influences self-esteem. Wagnsson and colleagues [82] demonstrated that perceived sport competence plays an important mediating role in the relationship between sport participation and self-esteem. In addition, Reigal and colleagues revealed that the association between physical activity and satisfaction with life may be influenced by the social context [83]. Moreover, Ho and colleagues [84] found that resilience was a significant mediator of the association between physical activity and psychological well-being in young people.

In the present review, we observed a paucity of studies analyzing the relationship between physical activity and anxiety, self-esteem, self-concept, self-efficacy, positive affect, and optimism. Although experimental studies are considered to provide the highest level of evidence, observational studies may be useful for determining the relationship between physical activity and less studied mental health outcomes. Of note, type of physical activity (e.g., sports participation, outdoor play or active commuting) might be considered when studying the relationship between physical activity and mental health in young people. Lastly, further studies might consider the interrelationship between other environmental factors such as enjoyment or perceived sport competence that could differently influence the mental health of children and adolescents.

Possible mechanisms for the role of physical activity in mental health.

While the evidence examining the relationship between physical activity and mental health is growing, the underlying plausible mechanisms of this association cannot be elucidated in our review. In this context, a range of neurobiological, psychosocial and behavioral mechanisms have been proposed previously by Lubans and colleagues [15].

Firstly, physical activity may have a positive effect on the structure and function of the brain, which is now quantifiable as a result of technological advancement (e.g., MRI). Using this technology, for instance, a recent RCT in children showed that a 9-month physical activity intervention improved the structure and function of brain networks related to cognitive function [85]. Therefore, it is possible that physical activity changes brain structure and function, which in turn has a positive effect on mental health. Regarding the cellular and molecular bases of mental health, it is well known that decreased levels of BDNF, which plays a crucial role in the growth and healthy maintenance of neurons [86], is associated with increased levels of anxiety and depression [87]. Exercise is known to increase BDNF levels in the central nervous system, which may improve anxiety and depressive symptoms [13]. Another explanation might be that exercise –by increasing brain dopamine, serotonin, and noradrenaline concentrations– might not only improve mood but also protect against the onset of mental disorders [88]. More research is needed to understand the neurobiological mechanisms that elicit the positive effects of physical activity on mental health in young people.

Secondly, evidence suggests a causal link between physical self-concept (i.e., perceived appearance, perceived fitness and perceived competence) and mental health (e.g., global self-concept, self-esteem) [15]. Social support and autonomy are also plausible psychosocial contributors to mental health in young people [89]. Therefore, the effects of physical activity on mental health in young people might be mediated by several psychosocial paths.

Finally, a range of potential behavioral mechanisms might explain the effect of physical activity on mental health outcomes, including sleep duration, sleep efficiency, sleep onset latency, and reduced sleepiness [15]. However, there are insufficient studies to draw firm conclusions about any of these behavioral mechanisms.

Observational studies on the association between sedentary behavior and mental health

Significant associations were found between higher time spent in sedentary behaviors and higher depression, lower satisfaction with life and lower happiness in children and adolescents, while other psychological ill-being and psychological well-being outcomes (i.e., stress, anxiety, negative affect, self-esteem, self-concept, self-efficacy, positive affect and optimism) have not been studied. Therefore, the present research suggests that decreasing sedentary behavior may have a positive effect on depression, satisfaction with life and happiness in children and adolescents [67,90,91]. There is a lack of data for preschoolers (2-5 years). Given that there are a variety of developmental changes happening in the brain during the early stages of human life [5], more studies involving preschoolers are warranted.

The findings of this systematic review are consistent with those from Hoare and colleagues [28], who provided strong evidence for the positive relationship between sedentary behavior and depressive symptoms among adolescents [28]. These findings were also reported by Liu and colleagues [92] in a meta-analysis of observational studies in children and adolescents. However, these investigators found that compared with the reference group who had no sedentary behavior, there was a non-linear dose–response association of screen time-based sedentary behavior (i.e., watching TV, computer/internet use, and video gaming) with a decreasing risk of depression at sedentary time <2 hour/day, with the lowest risk being observed for 1 hour/day. These findings suggest that recreational screen time in moderation is not harmful. On the other hand, a number of longitudinal studies suggested that lower levels of sedentary behavior were weakly or not associated with lower levels of anxiety [67,93], stress [67] and total psychological distress [94]. A stronger association between sedentary behavior and anxiety [93,95] and total psychological distress [96,97] was found in cross-sectional studies. Moreover, as discussed for physical activity, the association between sedentary behavior and psychological distress may be bidirectional. Therefore, experimental studies on sedentary behavior and mental health are required to elucidate the causality of these associations.

While the eligibility criteria allowed for a broad range of sedentary behaviors, the most frequently examined behavior in children and adolescents was a measure of total recreational screen time (i.e., recreational use of computer and watching TV) [76,91,97–99]. It is widely known that prolonged watching TV is the most prevalent and pervasive sedentary behavior in developed countries and has been associated with morbidity and mortality [100]. This finding is consistent with that of Bickham and colleagues [101] who found that watching TV, and not recreational use of computers during adolescence, was associated with depressive symptoms over time. In addition, similar findings were reported by Grøntved and colleagues [102] for children. However, this finding is contrary to other studies which have suggested that recreational use of computers was more strongly associated with poorer mental health than watching TV in children and adolescents [95,103]. In addition, social media technology commonly used by young people on tablets/mobile phone (e.g., Facebook, Instagram and Snapchat) may encourage adolescents to compare themselves with their peers [104], and consequently increase their body dissatisfaction when discrepancies are found between perceived and ideal body shape. Therefore, research is required to examine if the type (e.g., watching TV, using computer/internet, or playing videogames) of sedentary behavior versus sedentariness itself explains the association between sedentary behavior and mental health in young people.

Due to the lack of research, it was not possible to determine the strength of association between sedentary behavior and stress, anxiety, negative affect, self-esteem, self-concept, self-efficacy, positive affect and optimism, more research (including observational studies). As such, experimental research is needed to elucidate the effect of reducing sedentary behavior on young people's mental health. Future studies are encouraged to explore the following: (i) how much screen-time is acceptable for young people (e.g., more than 2 hours vs. less than 2 hours), (ii) to what extent does screen-time content influence young people's mental health (e.g., violence vs. non-violence), and (iii) are the effects of screen time consistent if young people are watching or playing with others (e.g., gaming alone vs. gaming with friends).

Possible mechanisms for the role of sedentary behavior in mental health.

Although the underlying mechanisms responsible for the effects of sedentary behavior on mental health in children and adolescents are still unclear, several hypotheses have been proposed. Firstly, given that it often takes place alone, sedentary behavior may elicit feelings of loneliness and, consequently, negatively impacts on mental health [105]. Thus, it seems that higher levels of screen time (e.g., time spent watching TV and using the internet) may lead to social isolation, and hence to mental health problems [107]. Secondly, cultural messages transmitted through media may affect other behaviors related to the mental health (e.g., eating disorders and aggressive behavior) [106]. Thirdly, excessive media exposure often occurs at day or night. During the day, time spent on screen-based activities may replace time participating in more productive and/or active activities, especially activities involving physical activity [107] and interpersonal communication [108]. At night, screen-based activities can displace sleep, which is crucial for normal cognitive and emotional development [106]. In both scenarios, the replacement of healthy by unhealthy behaviors may have negative consequences on mental health of young people. Given the limited evidence, more studies focused on potential mechanisms explaining the relationship between sedentary behavior and mental health are needed to confirm these hypotheses. Since nothing is known about them, studies focusing on neurobiological mechanisms are of particular interest.

Literature gaps and future research

- Most of the studies included in this review were focused on adolescents. Therefore, future research is required especially in preschoolers and children.
- Well-designed physical activity interventions are needed to confirm our findings. In addition, experimental studies on sedentary behavior and mental health are required to draw conclusions in regard to cause and effect.
- Mediation models are needed to identify the mechanisms (i.e., neurobiological, psychological and behavioral) responsible for any changes in mental health resulting from physical activity and sedentary behavior.
- Type of physical activity (e.g., sports participation, outdoor play or active commuting) and type of sedentary behavior (e.g., watching TV, playing videogames, social media technology) might be considered when the relationship between physical activity, sedentary behavior and mental health is studied in young people.
- More studies focused on the relationship between physical activity and mental health (i.e., anxiety, self-esteem, self-concept, self-efficacy, positive affect and optimism), for which we currently have minimal or unclear evidence are required. Likewise, research focused on the relationship between sedentary behavior and mental health (i.e., stress, anxiety, negative affect, self-esteem, self-concept, self-efficacy, positive affect and optimism) for which there is also

minimal evidence, are also needed. Even observational studies may be worthwhile, given the lack of research to date.

Limitations and strengths

Our review has several limitations. Firstly, the so-called grey literature (i.e. System for Information on Grey Literature in Europe (SIGLE) database, dissertations, conference proceedings, and trial registries) was not included in the review. Secondly, the search was conducted in only two databases (PubMed and Web of Science), although this is consistent with the AMSTAR critical appraisal tool for systematic reviews; i.e., at least two electronic sources should be searched to perform a comprehensive literature search. However, we could have missed eligible studies from other databases. Thirdly, studies written in languages other than English and Spanish were excluded from our review. In addition, because of the heterogeneity of the outcome measures, it was not possible to conduct a meta-analysis of the prospective longitudinal studies. Lastly, because most of the intervention studies were focused on adolescents (12 in adolescents vs. 3 in children) and no studies were found in preschoolers, we cannot rule out a cause and effect relationship between physical activity and mental health in preschoolers and children.

The present review also has several strengths. Firstly, this review employed stringent systematic review methodology as per with the PRISMA guidelines to ensure relevant literature was identified and evaluated with the greatest possible scientific rigor. Secondly, this review provided an *a priori* design registered in the Prospero database. Therefore, research questions and inclusion criteria were established before conducting this review. Thirdly, two electronic sources were searched and the search strategies are reported in this article. Moreover, we provided a list of the studies included and excluded (together with the specific reason for exclusion per study) in Supplementary Material **Table S2**. In addition, the quality of included studies was examined, and hence, conclusions drawn by this review are strengthened by the use of the quality assessment tool. Finally, a meta-analysis was performed including intervention studies (RCTs and non-RCTs) making it possible to map the link between exercise and global mental health across childhood and adolescence for the first time.

CONCLUSION

Findings from the present research suggest that physical activity has a small but significant positive effect on adolescents' mental health. Due to the small number of studies, it was not possible to determine the effect of physical activity on preschoolers' and children's mental health. In addition, physical activity (i.e., active commuting, outdoor play or sport participation) may influence mental health in children and adolescents. In regards to type of physical activity, participation in team sports was found to be a consistent positive correlate of mental health in children and adolescents. Conversely, sedentary behavior was negatively associated with mental health in children and adolescents. In particular, higher levels of recreational screen time (i.e., beyond 2 h/day of recreational screen time) were associated with poorer mental health outcomes in children and adolescents. In summary, there is sufficient evidence to conclude that interventions targeting increases in physical activity and decreases in sedentary behavior are justified and will support the current and future mental health of children and adolescents.

REFERENCES

1. Murray CJL, Lopez AD, World Health Organization, World Bank, Harvard School of Public Health. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020: summary. Murray CJL, Lopez AD (eds). 1996; Geneva: World Health Organization. http://www.who.int/iris/handle/10665/41864

2. Antaramian SP, Huebner ES, Hills KJ, Valois RF. A dual-factor model of mental health: Toward a more comprehensive understanding of youth functioning. Am J Orthopsychiatry. 2010;80:462–72.

3. Seligman MEP, Csikszentmihalyi M. Positive psychology: an introduction. Am Psychol. 2000; 55: 5–14.

4. Schmithorst VJ, Yuan W. White matter development during adolescence as shown by diffusion MRI. Brain Cogn. 2010; 72:16-25.

5. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006;30:718–29.

6. Nelson SC, Kling J, Wängqvist M, Frisén A, Syed M. Identity and the body: trajectories of body esteem from adolescence to emerging adulthood. Dev Psychol. 2018;54:1159–71.

7. Beauchamp MR, Puterman E, Lubans DR. Physical inactivity and mental health in late adolescence. JAMA Psychiatry. 2018;75:543.

8. Hofstra MB, van der Ende J, Verhulst FC. Child and adolescent problems predict DSM-IV disorders in adulthood: A 14-year follow-up of a dutch epidemiological sample. J Am Acad Child Adolesc Psychiatry. 2002;41:182–9.

9. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100:126–31.

10. Spruit A, Assink M, van Vugt E, van der Put C, Stams GJ. The effects of physical activity interventions on psychosocial outcomes in adolescents: a meta-analytic review. Clin Psychol Rev. 2016;45:56–71.

11. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary behavior research network (SBRN) – terminology consensus project process and outcome. Int J Behav Nutr Phys Act. 2017;14:75.

12. Dishman RK, O'Connor PJ. Lessons in exercise neurobiology: the case of endorphins. Ment Health Phys Act. 2009;2:4–9.

13. Cotman CW, Berchtold NC, Christie L-A. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007;30:464–72.

14. Kleim JA, Cooper NR, VandenBerg PM. Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. Brain Res. 2002;934:1–6.

15. Lubans D, Richards J, Hillman C, Faulkner G, Beauchamp M, Nilsson M, et al. Physical activity for cognitive and mental health in youth: a systematic review of mechanisms. Pediatrics. 2016; 14:114.

16. Physical Activity Guidelines for Americans 2nd edition. 2018; Washington, DC: US: Department of Health and Human Services. https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf.

17. Biddle SJH, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. Br J Sports Med. 2011;45:886–95.

18. Biddle SJH, Ciaccioni S, Thomas G, Vergeer I. Physical activity and mental health in children and adolescents: an updated review of reviews and an analysis of causality. Psychol Sport Exerc. 2018;1–10.

19. Brown HE, Pearson N, Braithwaite RE, Brown WJ, Biddle SJH. Physical activity interventions and depression in children and adolescents. Sports Med. 2013;43:195–206.

20. Babic MJ, Morgan PJ, Plotnikoff RC, Lonsdale C, White RL, Lubans DR. Physical activity and physical self-concept in youth: systematic review and meta-analysis. Sports Med. 2014;44:1589–601.

21. Liu M, Wu L, Ming Q. How does physical activity intervention improve self-esteem and self-concept in children and adolescents? evidence from a meta-analysis. PLoS One. 2015;10:1–17.

22. Ruotsalainen H, Kyngäs H, Tammelin T, Kääriäinen M. Systematic review of physical activity and exercise interventions on body mass indices, subsequent physical activity and psychological symptoms in overweight and obese adolescents. J Adv Nurs. 2015;71:2461–77.

23. Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput J-P, Janssen I, et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. Appl Physiol Nutr Metab. 2016;41:197–239.

24. Cairns KE, Yap MBH, Pilkington PD, Jorm AF. Risk and protective factors for depression that adolescents can modify: A systematic review and meta-analysis of longitudinal studies. J Affect Disord. 2014;169:61–75.

25. Bursnall P. The relationship between physical activity and depressive symptoms in adolescents: a systematic review. Worldviews Evid Based Nurs. 2014;11:376–82.

26. Ferreira-Vorkapic C, Feitoza JM, Marchioro M, Simões J, Kozasa E, Telles S. Are there benefits from teaching yoga at schools? a systematic review of randomized control trials of yoga-based interventions. Evid Based Complement Alternat Med. 2015;2015:1–17.

27. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act. 2011;8:98.

28. Hoare E, Milton K, Foster C, Allender S. The associations between sedentary

behaviour and mental health among adolescents: a systematic review. Int J Behav Nutr Phys Act. 2016;13:108.

29. Cliff DP, Hesketh KD, Vella SA, Hinkley T, Tsiros MD, Ridgers ND, et al. Objectively measured sedentary behaviour and health and development in children and adolescents: systematic review and meta-analysis. Obes Rev. 2016;17:330–44.

30. Suchert V, Hanewinkel R, Isensee B. Sedentary behavior and indicators of mental health in school-aged children and adolescents: a systematic review. Prev Med. 2015;76:48–57.

31. von Klitzing K, Döhnert M, Kroll M, Grube M. Mental disorders in early childhood. Dtsch Arztebl Int. 2015;112:375–86.

32. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-analyses: The PRISMA Statement. PLoS Med. 2009;6:e1000097.

33. Kho ME, Eva KW, Cook DJ, Brouwers MC. The Completeness of Reporting (CORE) index identifies important deficiencies in observational study conference abstracts. J Clin Epidemiol. 2008;61:1241–1249.

34. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.

35. Sallis JF, Prochaska JJ, Taylor WC. A review of correlates of physical activity of children and adolescents. Med Sci Sports Exerc. 2000;32:963–75.

36. Lubans DR, Morgan PJ, Cliff DP, Barnett LM, Okely AD. Fundamental movement skills in children and adolescents. Sports Med. 2010;40:1019–35.

37. Smith JJ, Eather N, Morgan PJ, Lubans DR. The health benefits of muscular fitness for children and adolescents : A systematic review and meta-analysis. Sports Med. 2014;1209–23.

38. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials. BMJ. 2011;1–9.

39. Elm E Von, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement : guidelines for reporting observational studies. PLoS Med. 2008;61:344–9.

40. Armijo-Olivo S, Stiles CR, Hagen, NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract. 2012; 18(1): 12-8.

41. Smith S, Madden AM. Body composition and functional assessment of nutritional status in adults: a narrative review of imaging, impedance, strength and functional techniques. J Hum Nutr Diet. 2016;1–19.

42. Hasanpour M, Tabatabaei M, Alavi M, Zolaktaf V. Effect of aerobics exercise on self-esteem in Iranian female adolescents covered by welfare organization. Sci World J.

2014;2014: Article ID 456483.

43. Goldfield GS, Alberga AS, Hadjiyannakis S, Phillips P, Malcolm J, Wells GA, et al. Effects of aerobic training, resistance training, or both on psychological health in adolescents with obesity: The HEARTY Randomized Controlled Trial. J Consult Clin Psychol. 2015;83:1123–35.

44. Costigan SA, Eather N, Plotnikoff RC, Hillman CH, Lubans DR. High-intensity interval training for cognitive and mental health in adolescents. Med Sci Sports Exerc. 2016;48:1985–93.

45. Lee LYK, Chong YL, Li NY, Li MC, Lin LN, Wong LY, et al. Feasibility and effectiveness of a chen-style Tai Chi programme for stress reduction in junior secondary school students. Stress Health. 2013;29:117–24.

46. Staiano AE, Abraham AA, Calvert SL. Adolescent exergame play for weight loss and psychosocial improvement: a controlled physical activity intervention. Obesity. 2013;21:598–601.

47. Tubić T, Đorđić V. Exercise effects on mental health of preschool children. An Psicol. 2013;29:249–56.

48. Seabra AC, Seabra AF, Brito J, Krustrup P, Hansen PR, Mota J, et al. Effects of a 5-month football program on perceived psychological status and body composition of overweight boys. Scand J Med Sci Sport. 2014;24:10–6.

49. Peng S, Qi A, Yuan F. Experimental study on the effects of exercise prescription on the mental health of left-behind school children in rural areas. Rev Argent Clin Psic. 2015; 24 (3): 267-76.

50. Das M, Deepeshwar S, Subramanya P, Manjunath NK. Influence of Yoga-based personality development program on psychomotor performance and self-efficacy in school children. Front Pediatr. 2016;4:62.

51. Eather N, Morgan PJ, Lubans DR. Effects of exercise on mental health outcomes in adolescents: Findings from the CrossFit^{TM} teens randomized controlled trial. Psychol Sport Exerc. 2016;26:14–23.

52. Cox AE, Ullrich-French S, Howe HS, Cole AN. A pilot yoga physical education curriculum to promote positive body image. Body Image. 2017;23:1–8.

53. Yook YS, Kang SJ, Park IK. Effects of physical activity intervention combining a new sport and mindfulness yoga on psychological characteristics in adolescents. Int J Sport Exerc Psychol. 2017;15:109–17.

54. Bunketorp Käll L, Malmgren H, Olsson E, Lindén T, Nilsson M. Effects of a curricular physical activity intervention on children’s school performance, wellness, and brain development. J Sch Health. 2015;85 (10):704-13.

55. Romero-Perez M, De Paz-Fernandez A, Camberos-Castaneda A, Tanori-Tapia M, Bernal-Reyes F, Marquez-Rosa S. Assessment of depression and anxiety states of obese children after participating in an exercise program. Biotecnia. 2015;17:11–5.

56. Kyle TL, Mendo AH, Reigal Garrido RE, Sánchez VM. Effects of physical activity

on self-concept and self-efficacy in preadolescents. RETOS. Nuevas Tendencias en Educacion Fisica Deporte y Recreacion. 2016;2041:61–5.

57. Telles S, Singh N, Bhardwaj A, Kumar A, Balkrishna A. Effect of yoga or physical exercise on physical, cognitive and emotional measures in children: a randomized controlled trial. Child Adolesc Psychiatry Ment Health. 2013;7:37.

58. Bao X, Jin K. The beneficial effect of Tai Chi on self-concept in adolescents. Int J Psychol. 2015;50:101–5.

59. Rinaldo N, Zaccagni L, Gualdi-Russo E. Soccer training programme improved the body composition of pre-adolescent boys and increased their satisfaction with their body image. Acta Paediatr. 2016;105:492–5.

60. Toseeb U, Brage S, Corder K, Dunn VJ, Jones PB, Owens M, et al. Exercise and depressive symptoms in adolescents. JAMA Pediatr. 2014;168:1093.

61. Van Dijk ML, Savelberg HHCM, Verboon P, Kirschner PA, De Groot RHM. Decline in physical activity during adolescence is not associated with changes in mental health. BMC Public Health; 2016;16:300.

62. Bilinski H, Henry C, Humbert L, Spriggs P. The connection between psychosocial health, health behaviors and the environment in rural children. Child Indic Res. 2013;6:659–72.

63. Martikainen S, Pesonen A-K, Lahti J, Heinonen K, Feldt K, Pyhälä R, et al. Higher levels of physical activity are associated with lower hypothalamic-pituitary-adrenocortical axis reactivity to psychosocial stress in children. J Clin Endocrinol Metab. 2013;98:E619-27.

64. Ahn JV, Sera F, Cummins S, Flouri E. Associations between objectively measured physical activity and later mental health outcomes in children: findings from the UK Millennium Cohort Study. J Epidemiol Community Health. 2018;72:94–100.

65. Nihill GFJ, Lubans DR, Plotnikoff RC. Associations between sedentary behavior and self-esteem in adolescent girls from schools in low-income communities. Ment Health Phys Act. 2013;6:30–5.

66. Ishii K, Shibata A, Adachi M, Mano Y, Oka K. Objectively measured sedentary behavior, obesity, and psychological well-being: a cross-sectional study of Japanese schoolchildren. J Phys Act Health. 2017;14:270–4.

67. McVeigh J, Smith A, Howie E, Straker L. Trajectories of television watching from childhood to early adulthood and their association with body composition and mental health outcomes in young adults. PLoS One. 2016;11:1–12.

68. Janssen I. Estimating whether replacing time in active outdoor play and sedentary video games with active video games influences youth’s mental health. J Adolesc Health. 2016;59:517–22.

69. Larun L, Nordheim LV, Ekeland E, Hagen KB, Heian F. Exercise in prevention and treatment of anxiety and depression among children and young people. Cochrane Database Syst Rev. 2006; 3.

70. Carter T, Morres ID, Meade O, Callaghan P. The effect of exercise on depressive symptoms in adolescents: a systematic review and meta-Analysis. J Am Acad Child Adolesc Psychiatry. 2016; 55(7), 580-590.

71. Kipp LE, Weiss MR. Physical activity and self-perceptions among children and adolescents. Routledge Handbook of Physical Activity and Mental Health; 2013; 1: 187–99. Routledge, New York.

72. Lubans DR, Lonsdale C, Cohen K, Eather N, Beauchamp MR, Morgan PJ, et al. Framework for the design and delivery of organized physical activity sessions for children and adolescents: Rationale and description of the “SAAFE” teaching principles. Int J Behav Nutr Phys Act. 2017; 14: 24.

73. Eisenmann JC. Physical activity and cardiovascular disease risk factors in children and adolescents: an overview. Can J Cardiol. 2004;20:295–301.

74. Schneider S, Weiß M, Thiel A, Werner A, Mayer J, Hoffmann H, et al. Body dissatisfaction in female adolescents: Extent and correlates. Eur J Pediatr. 2013;172:373–84.

75. McPhie ML, Rawana JS. The effect of physical activity on depression in adolescence and emerging adulthood: A growth-curve analysis. J Adolesc. 2015;40:83–92.

76. Carter JS, Dellucci T, Turek C, Mir S. Predicting depressive symptoms and weight from adolescence to adulthood: stressors and the role of protective factors. J Youth Adolesc. 2015;44:2122–40.

77. Sabiston CM, Jewett R, Ashdown-Franks G, Belanger M, Brunet J, O´Loughlin E, et al. Number of years of team and individual sport participation during adolescence and depressive symptoms in early adulthood. J Sport Exerc Psychol. 2016;38:105–10.

78. Brunet J, Sabiston CM, Chaiton M, Barnett TA, O’Loughlin E, Low NCP, et al. The association between past and current physical activity and depressive symptoms in young adults: a 10-year prospective study. Ann Epidemiol. 2013;23:25–30.

79. Patrick Auerbach R, Bigda-Peyton JS, Eberhart NK, Webb CA, Ringo Ho M-H. Conceptualizing the prospective relationship between social support, stress, and depressive symptoms among adolescents. J Abnorm Child Psychol. 2010; 39: 475-487.

80. Vella SA, Swann C, Allen MS, Schweickle MJ, Magee CA. Bidirectional associations between sport involvement and mental health in adolescence. Med Sci Sport Exerc. 2017;49:687–94.

81. Adachi PJC, Willoughby T. It’s not how much you play, but how much you enjoy the game: the longitudinal associations between adolescents’ self-esteem and the frequency versus enjoyment of involvement in sports. J Youth Adolesc. 2014;43:137–45.

82. Wagnsson S, Lindwall M, Gustafsson H. Participation in organized sport and self-esteem across adolescence: the mediating role of perceived sport competence. J Sport Exerc Psychol. 2014;36:584–94.

83. Reigal R, Videra A, Gil J. Physical exercise, general self-efficacy and life

satisfaction in adolescence. Rev Int Med Cienc Ac. 2014;14:561–76.

84. Ho FKW, Louie LHT, Chow CB, Wong WHS, Ip P. Physical activity improves mental health through resilience in Hong Kong Chinese adolescents. BMC Pediatr. 2015;15:48.

85. Hillman CH, Pontifex MB, Castelli DM, Khan NA, Raine LB, Scudder MR, et al. Effects of the FITKids randomized controlled trial on executive control and brain function. Pediatrics. 2014;134:e1063–71.

86. Leibrock J, Lottspeich F, Hohn A, Hofer M, Hengerer B, Masiakowski P, et al. Molecular cloning and expression of brain-derived neurotrophic factor. Nature. 1989;341:149–52.

87. Martinowich K, Manji H, Lu B. New insights into BDNF function in depression and anxiety. Nat Neurosci. 2007;10:1089–93.

88. Young SN. How to increase serotonin in the human brain without drugs. J Psychiatry Neurosci. 2007;32:394–9.

89. Lubans DR, Smith JJ, Morgan PJ, Beauchamp MR, Miller A, Lonsdale C, et al. Mediators of psychological well-being in adolescent boys. J Adolesc Health. 2016;58:230–6.

90. Hinkley T, Verbestel V, Ahrens W, Lissner L, Molnár D, Moreno LA, et al. Early childhood electronic media use as a predictor of poorer well-being. JAMA Pediatr. 2014;168:485.

91. Allen MS, Vella SA. Screen-based sedentary behaviour and psychosocial well-being in childhood: Cross-sectional and longitudinal associations. Ment Health Phys Act. 2015;9:41–7.

92. Liu M, Wu L, Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: A meta-analysis of observational studies. Br J Sports Med. 2015; 50:1252-1258

93. Gunnell KE, Flament MF, Buchholz A, Henderson KA, Obeid N, Schubert N, et al. Examining the bidirectional relationship between physical activity, screen time, and symptoms of anxiety and depression over time during adolescence. Prev Med. 2016;88:147–52.

94. Hamer M, Coombs N, Stamatakis E. Associations between objectively assessed and self-reported sedentary time with mental health in adults: an analysis of data from the Health Survey for England. BMJ Open. 2014;4:e004580

95. Maras D, Flament MF, Murray M, Buchholz A, Henderson KA, Obeid N, et al. Screen time is associated with depression and anxiety in Canadian youth. Prev Med. 2015;73:133–8.

96. Wu X, Kirk SFL, Ohinmaa A, Veugelers P. Health behaviours, body weight and self-esteem among grade five students in Canada. Springerplus. 2016;5:1099.

97. Hoare E, Milton K, Foster C, Allender S. Depression, psychological distress and Internet use among community-based Australian adolescents: a cross-sectional study.

BMC Public Health. 2017;17:365.

98. Benson LP, Williams RJ, Novick MB. Pediatric obesity and depression: a cross-sectional analysis of absolute BMI as it relates to children's depression index scores in obese 7- to 17-year-old children. Clin Pediatr (Phila). 2013;52:24–9.

99. Kremer P, Elshaug C, Leslie E, Toumbourou JW, Patton GC, Williams J. Physical activity, leisure-time screen use and depression among children and young adolescents. J Sci Med Sport. 2014;17:183–7.

100. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality. JAMA. 2011; 305: 2448-2455.

101. Bickham DS, Hswen Y, Rich M. Media use and depression: exposure, household rules, and symptoms among young adolescents in the USA. Int J Public Health. 2015;60:147–55.

102. Grøntved A, Singhammer J, Froberg K, Møller NC, Pan A, Pfeiffer KA, et al. A prospective study of screen time in adolescence and depression symptoms in young adulthood. Prev Med. 2015;81:108–13.

103. Goldfield GS, Murray M, Maras D, Wilson AL, Phillips P, Kenny GP, et al. Screen time is associated with depressive symptomatology among obese adolescents: a HEARTY study. Eur J Pediatr. 2016;175:909–19.

104. Babic MJ, Smith JJ, Morgan PJ, Eather N, Plotnikoff RC, Lubans DR. Longitudinal associations between changes in screen-time and mental health outcomes in adolescents. Ment Health Phys Act. 2017;12:124–31.

105. Hoare E, Skouteris H, Fuller-Tyszkiewicz M, Millar L, Allender S. Associations between obesogenic risk factors and depression among adolescents: a systematic review. Obes Rev. 2014;15:40–51.

106. Primack BA, Swanier B, Georgiopoulos AM, Land SR, Fine MJ. Association between media use in adolescence and depression in young adulthood. Arch Gen Psychiatry. 2009;66:181.

107. Ohannessian CM. Media Use and adolescent psychological adjustment: an examination of gender differences. J Child Fam Stud. 2009;18:582–93.

108. Kraut R, Patterson M, Lundmark V, Kiesler S, Mukopadhyay T, Scherlis W. Internet paradox. A social technology that reduces social involvement and psychological well-being? Am Psychol. 1998;53:1017–31.

109. Raudsepp L, Neissaar I, Kull M. A longitudinal assessment of the links between physical activity and physical self-worth in adolescent females. Eur J Sport Sci. 2013;13:716–22.

110. Stavrakakis N, Oldehinkel AJ, Nederhof E, Oude Voshaar RC, Verhulst FC, Ormel J, et al. Plasticity genes do not modify associations between physical activity and depressive symptoms. Health Psychol. 2013;32:785–92.

111. Hoare E, Millar L, Fuller-Tyszkiewicz M, Skouteris H, Nichols M, Malakellis M, et al. Depressive symptomatology, weight status and obesogenic risk among Australian

adolescents: a prospective cohort study. BMJ Open. 2016;6:e010072.

112. Ishii K, Shibata A, Adachi M, Oka K. Association of physical activity and sedentary behavior with psychological well-being among Japanese children. Percept Mot Skills. 2016;123:445–59.

113. Reddon H, Meyre D, Cairney J. Physical activity and global self-worth in a longitudinal study of children. Med Sci Sports Exerc. 2017;49:1606–13.

114. Conn AM, Calais C, Szilagyi M, Baldwin C, Jee SH. Youth in out-of-home care: Relation of engagement in structured group activities with social and mental health measures. Child Youth Serv Rev. 2014;36:201–5.

115. Jewett R, Sabiston CM, Brunet J, O’Loughlin EK, Scarapicchia T, O’Loughlin J. School sport participation during adolescence and mental health in early adulthood. J Adolesc Health. 2014;55:640–4.

116. Vella SA, Cliff DP, Magee CA, Okely AD. Associations between sports participation and psychological difficulties during childhood: A two-year follow up. J Sci Med Sport. 2015;18:304–9.

117. Shin K, You S. Leisure type, leisure satisfaction and adolescents’ psychological wellbeing. J Pacific Rim Psychol. 2013;7:53–62.

118. Hoegh Poulsen P, Biering K, Andersen JH. The association between leisure time physical activity in adolescence and poor mental health in early adulthood: a prospective cohort study. BMC Public Health; 2015;16:3.

119. Bulhões C, Ramos E, Lindert J, Dias S, Barros H. Depressive symptoms and its associated factors in 13-year-old urban adolescents. Int J Environ Res Public Health. 2013;10:5026–38.

120. Shriver LH, Harrist AW, Page M, Hubbs-Tait L, Moulton M, Topham G. Differences in body esteem by weight status, gender, and physical activity among young elementary school-aged children. Body Image. 2013;10:78–84.

121. Fararouei M, Brown IJ, Akbartabar Toori M, Estakhrian Haghighi R, Jafari J. Happiness and health behaviour in Iranian adolescent girls. J Adolesc. 2013;36:1187–92.

122. Haugen T, Ommundsen Y, Seiler S. The relationship between physical activity and physical self-esteem in adolescents: the role of physical fitness indices. Pediatr Exerc Sci. 2013;25:138–53.

123. Skrove M, Romundstad P, Indredavik MS. Resilience, lifestyle and symptoms of anxiety and depression in adolescence: The Young-HUNT study. Soc Psychiatry Psychiatr Epidemiol. 2013;48:407–16.

124. Altıntaş A, Aşçı FH, Kin-İşler A, Güven-Karahan B, Kelecek S, Özkan A, et al. The role of physical activity, body mass index and maturity status in body-related perceptions and self-esteem of adolescents. Ann Hum Biol. 2014;41:395–402.

125. Marques R, Assis M, Maranhao Neto GA, Resende F, Palma A. Body image dissatisfaction among 14-15 year old females in Rio de Janeiro, Brazil. Int J Sport

Psychol. 2014;45:39–56.

126. Gomes R, Gonçalves S, Costa J. Exercise, eating disordered behaviors and psychological well-being: a study with Portuguese adolescents. Rev Latinoam Psicol. 2015;47:66–74.

127. Kovacs E, Piko BF, Keresztes N. The interacting role of physical activity and diet control in Hungarian adolescents' substance use and psychological health. Subst Use Misuse. 2014;49:1278–86.

128. Wang H. Fu J, Lu Q, Tao F, Hao J. Physical activity, body mass index and mental health in Chinese adolescents: a population based study. J Phys Fit Sports Med. 2014;54: 518-525.

129. Park S. Associations of physical activity with sleep satisfaction, perceived stress, and problematic internet use in Korean adolescents. BMC Public Health. 2014;14:1143.

130. Moljord IEO, Moksnes UK, Espnes GA, Hjemdal O, Eriksen L. Physical activity, resilience, and depressive symptoms in adolescence. Ment Health Phys Act. 2014;7:79–85.

131. Zach S, Netz Y. Self-presentation concerns and physical activity in three-generation families. Soc Behav Personal. 2014;42:259–67.

132. Sun Y, An J, Wang X, Zu P, Tao F-B. Gender- and puberty-dependent association between physical activity and depressive symptoms: national survey among Chinese adolescents. J Phys Act Health. 2014;11:1430–7.

133. Hoare E, Millar L, Fuller-Tyszkiewicz M, Skouteris H, Nichols M, Jacka F, et al. Associations between obesogenic risk and depressive symptomatology in Australian adolescents: a cross-sectional study. J Epidemiol Community Health. 2014;68:767–72.

134. Trinh L, Wong B, Faulkner GE. The independent and interactive associations of screen time and physical activity on mental health, school connectedness and academic achievement among a population-based sample of youth. J Can Acad Child Adolesc Psychiatry. 2015;24:17–24.

135. Esmaeilzadeh S. The association between depressive symptoms and physical status including physical activity, aerobic and muscular fitness tests in children. Environ Health Prev Med. 2015;20:434–40.

136. Reid M-A, MacCormack J, Cousins S, Freeman JG. Physical Activity, school climate, and the emotional health of adolescents: findings from 2010 Canadian Health Behaviour in School-Aged Children (HBSC) Study. School Ment Health. 2015;7:224–34.

137. Asare M, Danquah SA. The relationship between physical activity, sedentary behaviour and mental health in Ghanaian adolescents. Child Adolesc Psychiatry Ment Health. 2015;9:11.

138. Hyakutake A, Kamijo T, Misawa Y, Washizuka S, Inaba Y, Tsukahara T, et al. Cross-sectional observation of the relationship of depressive symptoms with lifestyles and parents' status among Japanese junior high school students. Environ Health Prev Med. 2016;21:265–73.

139. Alghadir AH, Gabr SA, Al-Eisa E. Effects of physical activity on trace elements and depression related biomarkers in children and adolescents. Biol Trace Elem Res. 2016;172:299–306.

140. Mak K-K, Cerin E, McManus AM, Lai C-M, Day JR, Ho S-Y. Mediating effects of body composition between physical activity and body esteem in Hong Kong adolescents: a structural equation modeling approach. Eur J Pediatr. 2016;175:31–7.

141. Mouissi F. Physical activity and sport and their impact on mental health of Algerian adolescents. J Phys Educ Sport Health Recr. 2015;4:1807–13.

142. Hayward J, Jacka FN, Skouteris H, Millar L, Strugnell C, Swinburn BA, et al. Lifestyle factors and adolescent depressive symptomatology: Associations and effect sizes of diet, physical activity and sedentary behaviour. Aust N Z J Psychiatry. 2016;50:1064–73.

143. Baldursdottir B, Valdimarsdottir HB, Krettek A, Gylfason HF, Sigfusdottir ID. Age-related differences in physical activity and depressive symptoms among 10−19-year-old adolescents: A population based study. Psychol Sport Exerc. 2017;28:91–9.

144. Szamreta EA, Qin B, Ohman-Strickland PA, Devine KA, Stapleton JL, Ferrante JM, et al. Associations of anthropometric, behavioral, and social factors on level of body esteem in peripubertal girls. J Dev Behav Pediatr. 2017;38:58–64.

145. Chae SM, Kang HS, Ra JS. Body esteem is a mediator of the association between physical activity and depression in Korean adolescents. Appl Nurs Res. 2017;33:42–8.

146. McDowell CP, MacDonncha C, Herring MP. Brief report: associations of physical activity with anxiety and depression symptoms and status among adolescents. J Adolesc. 2017;55:1–4.

147. Khan A, Burton NW. Is physical inactivity associated with depressive symptoms among adolescents with high screen time? Evidence from a developing country. Ment Health Phys Act. 2017;12:94–9.

148. Matin N, Kelishadi R, Heshmat R, Motamed-Gorji N, Djalalinia S, Motlagh ME, et al. Joint association of screen time and physical activity on self-rated health and life satisfaction in children and adolescents: The CASPIAN-IV study. Int Health. 2017;9:58–68.

149. Min JH, Lee E-Y, Spence JC, Jeon JY. Physical activity, weight status and psychological well-being among a large national sample of South Korean adolescents. Ment Health Phys Act. 2017;12:44–9.

150. Tajik E, Abd Latiff L, Adznam SN, Awang H, Yit Siew C, Abu Bakar AS. A study on level of physical activity, depression, anxiety and stress symptoms among adolescents. J Sports Med Phys Fitness. 2017;57:1382–7.

151. McMahon EM, Corcoran P, O’Regan G, Keeley H, Cannon M, Carli V, et al. Physical activity in European adolescents and associations with anxiety, depression and well-being. Eur Child Adolesc Psychiatry. 2017;26:111–22.

152. Noack P, Kauper T, Benbow AEF, Eckstein K. Physical self-perceptions and self-esteem in adolescents participating in organized sports and religious groups. Eur J Dev

Psychol. 2013; 10 (6): 663–75.

153. Karr TM, Davidson D, Bryant FB, Balague G, Bohnert AM. Sport type and interpersonal and intrapersonal predictors of body dissatisfaction in high school female sport participants. Body Image. 2013;10:210–9.

154. Gísladóttir TL, Matthíasdóttir Á, Kristjánsdóttir H. The effect of adolescents' sports clubs participation on self-reported mental and physical conditions and future expectations. J Sports Sci. 2013;31:1139–45.

155. Booker CL, Skew AJ, Sacker A, Kelly YJ. Well-Being in adolescence—An association with health-related behaviors. J Early Adolesc. 2014;34:518–38.

156. Fatiregun AA, Kumapayi TE. Prevalence and correlates of depressive symptoms among in-school adolescents in a rural district in southwest Nigeria. J Adolesc. 2014;37:197–203.

157. Dalton B, Wilson R, Evans JR, Cochrane S. Australian indigenous youth's participation in sport and associated health outcomes: Empirical analysis and implications. Sport Manag Rev. 2015;18:57–68.

158. Booker CL, Skew AJ, Kelly YJ, Sacker A. Media use, sports participation, and well-being in adolescence: Cross-sectional findings from the UK Household Longitudinal Study. Am J Public Health. 2015;105:173–9.

159. Sipos E, Jeges S, Tóth Á. Sport, sense of coherence, and self-esteem among 16 and 17-year-olds. Eur J Ment Health. 2015;10:62–78.

160. Asfour L, Koussa M, Perrino T, Stoutenberg M, Prado G. The association of organized and unorganized physical activity and sedentary behavior with internalizing and externalizing symptoms in Hispanic adolescents. Child Adolesc Ment Health. 2016;21:109–14.

161. Reverdito RS, Carvalho HM, Galatti LR, Scaglia AJ, Gonçalves CE, Paes RR. Effects of youth participation in extra-curricular sport programs on perceived self-efficacy: a multilevel analysis. Percept Mot Skills. 2017;124:569–83.

162. Sun Y, Liu Y, Tao F. Associations between active commuting to school, body fat, and mental well-being : population-based, cross-sectional study in China. J Adolesc Health. 2015;57:679–85.

163. Monteiro LA, Novaes JS, Santos ML, Fernandes HM. Body dissatisfaction and self-esteem in female students aged 9-15: the effects of age, family income, body mass index levels and dance practice. J Hum Kinet. 2014;43:25–32.

164. Herman KM, Hopman WM, Sabiston CM. Physical activity, screen time and self-rated health and mental health in Canadian adolescents. Prev Med. 2015;73:112–6.

165. Badura P, Geckova AM, Sigmundova D, van Dijk JP, Reijneveld SA. When children play, they feel better: organized activity participation and health in adolescents. BMC Public Health. 2015;15:1090.

166. Hamer M, Yates T, Sherar LB, Clemes SA, Shankar A. Association of after school sedentary behaviour in adolescence with mental wellbeing in adulthood. Prev Med.

2016;87:6–10.

167. Raudsepp L. Bidirectional association between sedentary behaviour and depressive symptoms in adolescent girls. Eur J Sport Sci. 2016;16:1153–8.

168. Suchert V, Hanewinkel R, Isensee B, Hansen J, Johannsen M, Krieger C, et al. Sedentary behavior, depressed affect, and indicators of mental well-being in adolescence: Does the screen only matter for girls? J Adolesc. 2015;42:50–8.

169. Padilla-Moledo C, Castro-Piñero J, Ortega FB, Pulido-Martos M, Sjöström M, Ruiz JR. Television viewing, psychological positive health, health complaints and health risk behaviors in Spanish children and adolescents. J Sports Med Phys Fitness. 2015;55:675–83.

170. Suchert V, Hanewinkel R, Isensee B. Screen time, weight status and the self-concept of physical attractiveness in adolescents. J Adolesc. 2016;48:11–7.

171. Mundy LK, Canterford L, Olds T, Allen NB, Patton GC. The association between electronic media and emotional and behavioral problems in late childhood. Acad Pediatr. 2017;17:620–4.

172. Ohannessian CMC. Video game play and anxiety during late adolescence: The moderating effects of gender and social context. J Affect Disord. 2018;226:216–9.

173. Webb OJ, Benjamin CC, Gammon C, McKee HC, Biddle SJH. Physical activity, sedentary behaviour and physical self-perceptions in adolescent girls: A mediation analysis. Ment Health Phys Act. 2013;6:24–9.

Supplemental Material

Study II

STUDY III

Physical fitness and psychological health in overweight/obese children: A cross-sectional study from the ActiveBrains project.

María Rodriguez-Ayllon, Cristina Cadenas-Sánchez, Irene Esteban-Cornejo, Jairo H. Migueles, Jose Mora-González, Pontus Henriksson, Miguel Martín-Matillas, Alejandra Mena-Molina, Pablo Molina-García, Fernando Estévez-López, Jonatan R. Ruiz, Andrés Catena, F. B. Ortega.

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INTRODUCTION

Mental disorders are expected to be the most pervasive type of all-cause disorders in developed countries in 2020 [1]. In fact, mental disorders are estimated to affect around 35% of children in Europe. Bearing in mind that childhood is a crucial period of life when many physiological and psychological changes occur, psychological health at this age may be determinant for later periods of life [2]. Psychological health is understood as the absence of psychological distress with the presence of psychological well-being. Specifically, psychological distress is understood as unpleasant feelings or emotions that impact the level of functioning (e.g. anxiety, depression, stress, mood disorders). However, psychological well-being is defined as some combination of positive affective states and functioning with optimal effectiveness in individual and social life (e.g. happiness, self-esteem, optimism) [3]. Previous studies have suggested that better psychological well-being is expected to increase qualities and source of resilience, prevent pathologies, and emotional disorders [4]. Hence, strategies to increase psychological well-being and decrease psychological distress in children are needed.

Another common worldwide health issue is the high rate of overweight/obesity; according to the World Obesity Federation, around 30% of children are overweight or obese. Importantly, overweight/obesity status is associated with poorer physical and mental health [5]. For instance, overweight/obesity is bidirectionally associated with a higher risk of depression [6]. Additionally, it is known that children with overweight or obesity have worse self-esteem and physical appearance, as well as higher levels of depression and mood disorders than normal-weight children [5]. Thus, examining the association of protective risk factors, such as physical fitness, with psychological health is particularly important in children with overweight or obesity [7].

Physical fitness has been shown to be a powerful marker of health in early years and later in life [8]. Physical fitness is defined as the capacity to perform physical activity and is composed of a set of physical components such as cardiorespiratory fitness (i.e. the capacity of the cardiovascular and respiratory systems and the ability to carry out prolonged strenuous exercise), muscular strength (i.e. the capacity to exert work against a resistance), and speed/agility (i.e. the ability to move the body as fast as possible)[9]. Numerous benefits of physical fitness for physical and cognitive health are well known in children and adolescents [9,10]. Likewise, being physically fit might be associated with different psychological health indicators [2,11]. Importantly, recent studies showed that improvements in physical fitness, especially cardiorespiratory fitness, were associated with reductions in levels of depression and anxiety in adolescents [12,13]. Similarly, muscular strength was related to better self-esteem and self-perception [11], as well as a reduced risk of any future psychiatric diagnosis and suicide mortality [2]. However, to the best of our knowledge, there are no studies examining the influence of speed/agility on psychological health. It is relevant to differentiate which components of physical fitness may be more strongly associated with different aspects of psychological health in children with overweight or obesity since no previous studies examined this association in that target population.

Therefore, the aim of the present study was to examine the associations of physical fitness components (i.e. cardiorespiratory fitness, muscular strength, and speed/agility) with psychological distress indicators (i.e. stress, anxiety, depression, and negative affect) and psychological well-being indicators (i.e. positive affect, happiness, optimism, and self-esteem) in children with overweight or obesity.

METHODS

The present cross-sectional study was developed within the ActiveBrains project framework (http://profith.ugr.es/activebrains?lang=en). A detailed description of the study design and methods has been published elsewhere [14]. A total of 110 children with overweight or obesity (10.0 ± 1.1 years old; 65% boys) from Granada (southern Spain) were recruited and evaluated from November 2014 to February 2016. The study protocol was approved by the Review Committee for Research Involving Human Subjects at the University of Granada and was registered in ClinicalTrials.gov (Identifier: NCT02295072).

Body weight (kg) was measured with an electronic scale (SECA 861, Hamburg, Germany), while *height (cm)* was assessed using a precision stadiometer (SECA 225, Hamburg, Germany). We calculated *BMI* by dividing the weight (kg) and height (m^2). The participants were classified into BMI categories (i.e. overweight, obesity type I, and obesity type II), according to Cole et al. (2012) cut-offs. *PHV* is the most commonly used indicator of maturity in studies of children and adolescents [15]. PHV was calculated from the Mirwald et al. (2002) equations for boys and girls.

The different components of *physical fitness* (i.e. cardiorespiratory fitness, muscular strength and speed/agility) were assessed following the ALPHA health-related fitness test battery for youth [16], which is valid, reliable, feasible, and safe for the assessment of health-related physical fitness in children [16]. Additionally, cardiorespiratory fitness was evaluated by a laboratory fitness test [17]. *Cardiorespiratory fitness* from the ALPHA battery was assessed by the 20m shuttle run test [16]. The two metrics used from the 20m shuttle run test were: the last completed stage recorded and translated into an estimated maximal oxygen consumption measure (VO_2max, ml/kg/min) using the Léger equation [18], and the last completed lap. We evaluated *cardiorespiratory fitness* from laboratory conditions using a gas analyzer (General Electric Corporation) while performing a maximal incremental treadmill (hp-cosmos ergometer) test modified for unfit children. Maximal oxygen consumption (VO_2max, ml/kg/min) was then obtained [16].

Upper and *lower-body muscular strength* were evaluated by the handgrip strength test (kg) and the standing broad jump test (cm), respectively [16]. The handgrip test evaluates absolute upper-body muscular strength. Additionally, relative upper-body muscular strength was expressed per kg of body weight. The standing broad jump test evaluates relative lower-body muscular strength; the distance in cm was multiplied by the weight in order to obtain absolute lower-body muscular strength [16]. Lastly, *speed/agility* was assessed by the 4x10m shuttle run test [16]. The fastest time was recorded in seconds.

Stress was evaluated by The CDSI. The CDSI evaluates the daily impact of relatively minor stressful events in four areas: health, school, peers, and family. The final version includes 30 dichotomous items. Possible answers were yes/no and the answers were summed (The score ranges from 0 to 30). The higher scores in the CDSI indicate the higher stress levels. The inventory was reliable and validated in primary school students from Spain [19].

Childhood *trait anxiety* was evaluated by the STAIC-T. The STAI is among the most widely used measures of general anxiety. The STAI evaluates worry, tension, apprehension, and nervousness, although it is used as a global anxiety measure [20]. It is a 20 trichotomous item self-administered instrument categorized from 1 (almost never) to 3 (often). The score ranges from 20 to 60. The higher scores show the higher trait anxiety levels. It is widely used, reliable (Cronbach alpha= 0.94), and extensively validated [19].

Depression was evaluated by the CDI, which assesses rates of symptoms related to depression or dysthymic disorder in children. The 27 items of the CDI are grouped into five factor areas: Negative mood, interpersonal problems, ineffectiveness, anhedonia, and negative self-esteem, although a global score was used for analysis in that study. Response options range from 0 to 2. The final score was obtained from the sum of the 27 items, with values ranging from 0 (lowest depression level) to 54 (highest depression level). The Cronbach alpha was 0.84 for males and 0.87 for females [21].

The PANAS-C was used to evaluate *negative and positive affect* [22]. Negative and positive affect have been shown to be interrelated but separable properties of mood state. PANAS-C includes 20 items with answers ranging from 1 to 3. *Negative affect* was calculated from the sum of 10 items. The final score ranges from 10 to 30. The higher scores show the higher negative affect. The PANAS-C has shown a Cronbach alpha from 0.87 to 0.94 for the negative affect subscale [22]. *Positive affect* was also evaluated using 10 items from the PANAS-C [22]. The final score ranges from 10 (the lowest positive affect) to 30 (the highest positive affect). The PANAS-C has shown a Cronbach alpha from 0.87 to 0.90 for the positive affect subscale [22].

Happiness was measured by the SHS a 4-item scale designed to measure subjective happiness [23]. It includes 4 questions with answers ranging from 1 to 7. The final score was obtained from the sum of the 3 first items with values ranging from 3 (the lowest happiness) to 21 (the highest happiness). The Spanish version of SHS showed an adequate internal consistency, appropriate test-retest reliability and convergent validity [24].

Dispositional optimism was evaluated with the LOT-R, a 10-item measure of optimism versus pessimism [25]; answers range from 1 (totally disagree) to 5 (totally agree). The final score was calculated by summing the 6 items that evaluated optimism (range score from 6 to 30). The higher score indicates the higher optimism. LOT-R is a useful, valid, and reliable self-report measure to properly assess optimism in children [26].

Self-esteem was assessed by the RSE, a 10-item scale that measures global self-worth by measuring both positive and negative feelings [27]. Response options range from 1 (strongly disagree) to 4 (strongly agree). The final score ranges are from 10 to 40. The higher scores indicate the higher self-esteem. The RSE scale is a valid and reliable self-report to assess self-esteem in children [27].

Data were shown as means ± standard deviation or percentages. Interactions between sex and physical fitness variables in relation to psychological health indicators were tested, and overall, the analyses were performed with boys and girls together. In those cases in which sex-interactions were found, additional analyses were performed separately by sex and the results were similar (data not shown). Firstly, we explored the association of the potential confounders with the psychological health indicators. Maternal education and socioeconomic status were tested, but they were not significantly related to the psychological health indicators (all p-values >0.102). Hence, they were excluded from the subsequent analyses. PHV was more strongly correlated to psychological health indicators than chronological age (years); therefore, we included PHV as a confounder.

Separate linear regressions adjusted for sex and PHV were used to examine the association between physical fitness components (i.e. cardiorespiratory fitness, muscular strength, and speed-agility) and psychological health indicators in children with overweight or obesity. Each set separately examined the relationships between one physical fitness component and one psychological health indicator.

The main significant associations found were also presented separately by sex and weight status (overweight, obesity type 1, and obesity type 2) in order to test the consistency of these findings and discard the possible interaction between variables. Finally, we additionally examined how the psychological health indicators correlated to each other using partial correlation adjusted for sex and PHV. All analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 20.0, Armonk, NY) and the level of significance was set at $p<0.05$.

RESULTS

Descriptive characteristics are presented in **Table 1**. Girls showed a higher PHV than boys ($p<0.001$). Overall, boys and girls did not significantly differ in BMI (27.0 vs. 26.6 kg/m^2; $P >0.05$). 24% of the participants were overweight and 76% were obese (44% obesity type I, 32% obesity type II). 67% of children belonged to a low to medium socioeconomic level. Additionally, we found a fairly wide variation in physical fitness compared to specific international normative values in normal-weight children [28]. For instance, cardiorespiratory fitness ranged from 1st to 60th percentile compared to specific international normative values in normal-weight children.

Associations of physical fitness components with psychological distress (stress, anxiety, depression, and negative affect) and psychological well-being (positive affect, happiness, optimism, and self-esteem) adjusted for sex and PHV are showed in **Table 2**. Absolute upper-body muscular strength was negatively associated with stress and negative affect (Standardized β, hereinafter just $\beta=-0.246$, $p=0.047$; $\beta=-0.329$, $p=0.010$, respectively). Absolute lower-body muscular strength was negatively associated with negative affect ($\beta=-0.301$, $p=0.029$).

Table 1. Descriptive characteristics of the study sample.

	N	Total sample		N	Boys		N	Girls		P_{sex}
Age (years)	110	10.0	(1.1)	65	10.1	(1.1)	45	9.9	(1.1)	0.218
Weight (kg)	110	56.3	(11.2)	65	57.3	(11.2)	45	54.9	(11.2)	0.291
Height (cm)	110	144.3	(8.4)	65	145.0	(7.9)	45	143.2	(9.0)	0.258
Body mass index (kg/m^2)	110	26.8	(3.6)	65	27.0	(3.7)	45	26.6	(3.4)	0.956
Overweight (%)	27	24.5		16	24.6		11	24.4		
Obesity type I (%)	48	43.6		29	44.6		19	42.2		
Obesity type II (%)	35	31.8		20	30.8		15	33.3		
Peak height velocity (years)	108	-1.9	(1.0)	65	-2.5	(0.8)	43	-1.1	(0.8)	**<0.001**
Mother education (%)										0.115
Non-university	79	72.5		50	78.1		29	64.4		
Socioeconomic level (%)										0.194
Low-medium	73	67		46	71.9		27	60.0		
Cardiorespiratory fitness										
VO_2max (Maximal incremental treadmill)	107	36.8	(5.0)	63	37.2	(5.1)	44	36.3	(4.9)	0.360
VO_2max (20 m shuttle run) †	108	40.7	(2.7)	64	40.8	(2.7)	44	40.6	(2.7)	0.741
Last completed lap (20 m shuttle run)	108	16.0	(7.7)	64	17.1	(8.1)	44	14.4	(6.9)	0.080
Muscular strength ¥										
Absolute upper-body muscular strength (kg)	109	16.9	(4.2)	65	17.5	(4.5)	44	16.0	(3.4)	0.055
Relative upper-body muscular strength (kg/kg)	109	0.3	(0.1)	65	0.3	(0.1)	44	0.3	(0.1)	0.283
Absolute lower-body muscular strength (cm x kg)	108	5860.0	1444.0	64	6003.1	(1437. 4)	44	5652.0	(1445.3)	0.216
Relative lower-body muscular strength (cm)	108	104.8	(18.3)	64	105.7	(17.4)	44	103.6	(19.8)	0.555
Speed/agility (sec)‡	108	15.1	(1.6)	64	15.0	(1.6)	44	15.4	(1.5)	0.181
Psychological distress										
Stress (CDSI)	107	5.7	(3.2)	63	4.9	(2.9)	44	6.7	(3.3)	**0.004**
Anxiety (STAIC-R)	105	33.6	(7.3)	63	32.2	(7.4)	42	35.8	(6.7)	**0.015**
Depression (CDI)	107	25.3	(2.5)	64	25.4	(2.6)	43	25.0	(2.4)	0.344
Negative affect (PANAS-C)	106	16.0	(3.4)	64	15.6	(3.4)	42	16.5	(3.2)	0.180
Psychological well-being										
Positive affect (PANAS-C)	106	24.4	(3.4)	64	24.0	(3.6)	42	25.0	(2.9)	0.141
Happiness (SHS)	110	17.7	(3.1)	65	17.5	(3.5)	45	17.9	(2.4)	0.577
Optimism (LOT-R)	108	19.0	(4.0)	65	19.4	(3.6)	43	18.4	(4.5)	0.216
Self-Esteem (RSE)	108	33.1	(4.7)	65	34.0	(4.7)	43	31.9	(4.5)	**0.027**

Values are mean (standard deviation) or percentages. VO_2max: maximum oxygen consumption, CDSI: Children's Daily Stress Inventory, STAIC-R: State-Trait Anxiety Inventory for Children, CDI: Children Depression Inventory, PANAS-C: Positive and Negative Affect Scale for Children, SHS: Subjective Happiness Scale, LOT-R: Life Orientation Test-Revised. RSE: The Rosenberg Self-Esteem Scale. Statistically significant values are shown in bold. †20 m shuttle run (VO_2max) was estimated from the 20-meter shuttle run test by the formula described by Leger et al. (1988) (18). ¥ Upper and lower-body muscular strength were evaluated by the handgrip strength test and the standing broad jump test, respectively ‡The lower the score in the 4x10m shuttle run test (i.e. less seconds to cover a fixed distance) the higher the performance (i.e. the faster and more agile the child

Cardiorespiratory fitness, expressed by the last completed lap, and relative upper-body muscular strength were positively associated with optimism (β=0.220, p=0.042; β=0.240, p=0.017, respectively). Absolute upper-body muscular strength and absolute lower-body muscular strength were positively associated with self-esteem (β=0.362, p=0.003; β=0.352, p=0.008, respectively). Results were virtually the same when including sex and/or chronological age in the model. **Figure 1** shows that the association between absolute upper-body muscular strength and self-esteem was consistent in boys, girls, and children with different weight status (p for interactions >0.3). **Table S1** shows partial correlation between the different psychological health indicators for a better interpretation of our main findings. Overall, self-esteem and negative affect, our most consistent associations found, were correlated with almost all psychological health indicators (p<0.05).

Table 2. Associations between physical fitness components and psychological health in children with overweight or obesity.

	Psychological distress				Psychological well-being			
	Stress (CDSI)	Anxiety (STAIC-R)	Depression (CDI)	Negative Affect (PANAS-C)	Positive Affect (PANAS-C)	Happiness (SHS)	Optimism (LOT-R)	Self-Esteem (RSE)
Cardiorespiratory fitness								
VO2max (Maximal incremental treadmill)	0.028	0.098	-0.077	-0.054	-0.016	-0.055	0.137	-0.067
VO2max (20 m shuttle run)[†]	-0.010	0.019	0.068	-0.006	0.100	-0.079	0.114	0.088
Last completed lap (20 m shuttle run)	0.042	0.059	-0.037	0.082	0.116	-0.061	**0.220***	0.061
Muscular strength[¥]								
Absolute upper-body muscular strength (kg)	**-0.246***	-0.188	0.193	**-0.329****	0.150	0.127	0.171	**0.362****
Relative upper-body muscular strength (kg/kg)	-0.107	-0.040	0.045	-0.076	0.070	-0.010	**0.240***	0.134
Absolute lower-body muscular strength (cm*kg)	-0.081	-0.228	0.122	**-0.301***	0.237	-0.049	0.036	**0.352****
Relative lower-body muscular strength (cm)	0.062	-0.042	-0.027	-0.089	0.205	-0.144	0.146	0.133
Speed/agility (sec)[‡]	-0.168	-0.083	-0.044	0.062	0.087	0.156	-0.152	-0.032

Analyses were adjusted by sex and peak height velocity (years). CDSI: Children's Daily Stress Inventory, STAIC-R: State-Trait Anxiety Inventory for Children, CDI: Children Depression Inventory, PANAS-C: Positive and Negative Affect Scale for Children, SHS: Subjective Happiness Scale, LOT-R: Life Orientation Test-Revised. RSE: The Rosenberg Self-Esteem Scale. * P<0.05, ** P< 0.01 denotes statistical significant. Values are standardized regression coefficients.

† 20 m shuttle run (VO2max) was estimated from the 20-meter shuttle run test by the formula described by Leger et al. (1988) (18).

¥Upper and lower-body muscular strength were evaluated by the handgrip strength test and the standing broad jump test, respectively.

‡ The lower the score in the 4x10m shuttle run test (i.e. less seconds to cover a fixed distance) the higher the performance (i.e. the faster and more agile the child is)

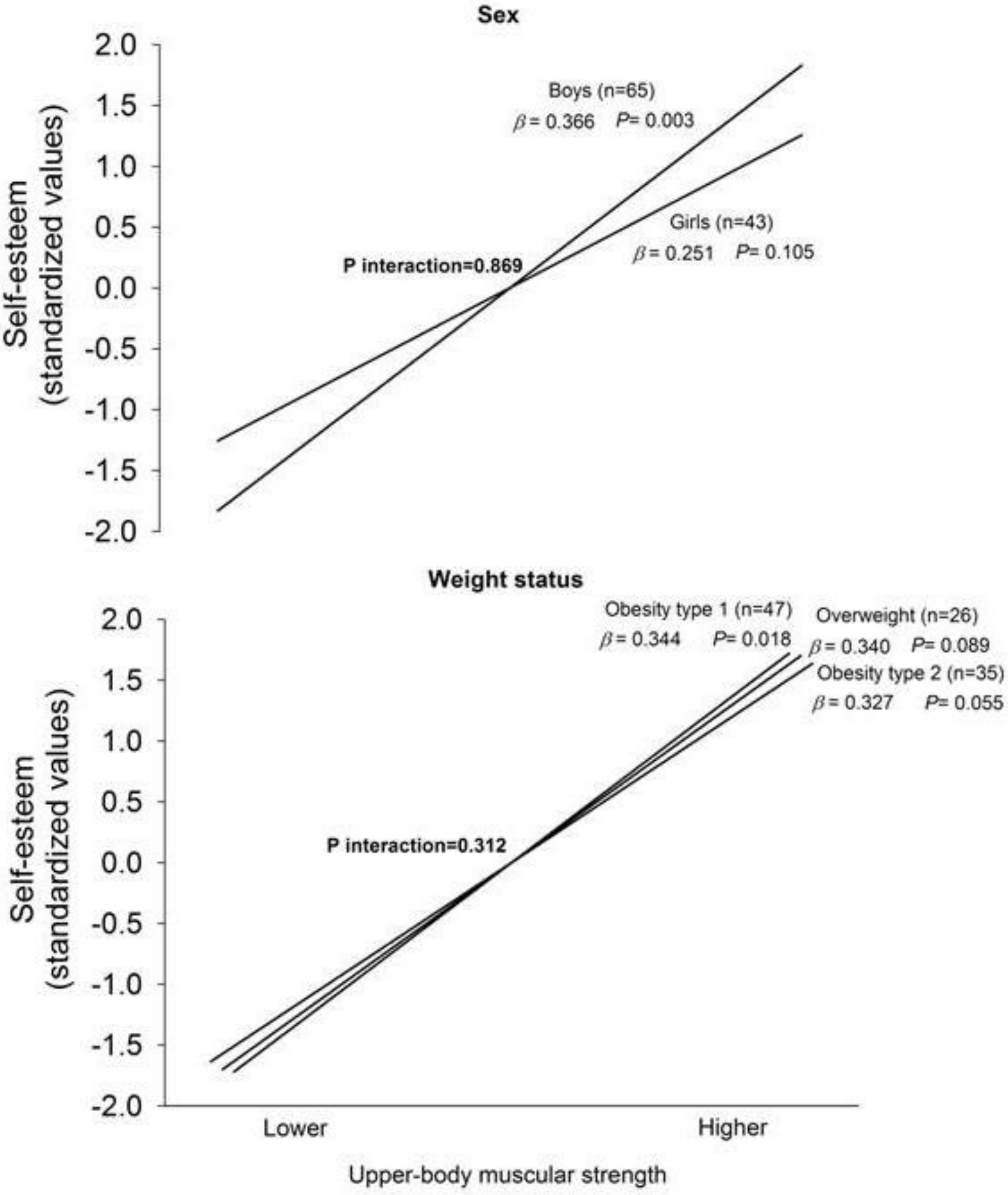

Figure 1. Association between upper-body muscular strength and self-esteem by sex and weight status.

DISCUSSION

The aim of the present study was to examine the association of physical fitness components with psychological distress and psychological well-being in children with overweight or obesity. Regarding psychological distress indicators, children with higher muscular strength showed lower levels of stress and of negative affect. Regarding psychological well-being indicators, higher muscular strength was associated with higher levels of optimism and self-esteem. Moreover, a positive association between cardiorespiratory fitness and optimism was observed, yet it was not consistent across the different measures of cardiorespiratory fitness used in this study (i.e. laboratory vs. field-based tests). Therefore, this study mainly highlights the potential benefits of muscular strength on psychological distress (i.e. stress and negative affect) and psychological well-being (i.e. optimism and self-esteem) in children with overweight or obesity.

Muscular strength was associated with psychological distress (stress and negative affect). Specifically, absolute upper-body muscular strength was negatively associated with stress. Previous studies have identified that lower levels of stress are associated with cardiovascular disease reduction, higher resilience, and capacity to solve problems in adolescents [29]. Moreover, higher levels of stress are associated with higher risk of cardiovascular disease through its influence on the hypothalamic pituitary adrenal axis and the sympathetic nervous system, which might alter metabolic and cardiac autonomic control as well as resulting in inflammation [29]. Therefore, increasing muscular strength might decrease levels of stress and in turn have a positive influence over physical and psychological health.

Absolute upper-body and lower-body muscular strength were inversely associated with negative affect. Present results are in line with previous research that supported the hypothesis that higher levels of muscular strength were associated with less risk of having any diagnosis of psychosis and mood disorder in young people [2]. The same study reported that a combination of decrement of negative affect and an improvement of cardiorespiratory fitness had 63% less risk of premature death. Although there are no studies examining the influence of muscular strength on negative affect, it is important to highlight that improvement of muscular strength might decrease levels of negative affect in children with overweight or obesity, which in turn, could have important benefits of health and longevity.

Another interesting finding was that absolute upper and lower-body muscular strength were positively associated with self-esteem. Our results were in accordance with a previous meta-analysis about muscular strength in relation to self-esteem and self-perception in children [11]. Besides, we also found that the role of sex and weight status did not modify the influence of absolute upper-body muscular strength on self-esteem in children with overweight or obesity. Importantly, psychological health indicators are highly interrelated. Therefore, an improvement or decrement in one aspect could suppose changes in other psychological health indicators. For instance, we observed that self-esteem was positively correlated to happiness and optimism, as well as, negatively correlated with stress, depression, and negative affect. Thus, increased levels of self-esteem could also improve other psychological health indicators. Nevertheless, more studies are needed to examine the possible mechanism of this association.

Cardiorespiratory fitness and muscular strength were associated with psychological well-being (optimism and self-esteem). Particularly, cardiorespiratory fitness may positively influence optimism, which plays an important role in self-regulation and adaptive behavior in children and adolescents [30]. In line with our results, Galper et al. (2006) found that a high level of cardiorespiratory fitness was associated with better psychological well-being in adults. However, to the best of our knowledge, there are no studies examining the association between physical fitness and psychological well-being indicators in children with overweight or obesity. Although the mechanisms behind this association are unclear, possible strategies promoting cardiorespiratory fitness improvement could aid the increase not only of optimism, but also other psychological health indicators in children with overweight or obesity. For instance, additional correlation analyses between psychological health indicators (**Table S1**) showed that optimism was not only strongly correlated with self-esteem and happiness but it was also negatively correlated to stress and negative affect. Considering that self-esteem may be a key factor for psychological health, at least in children with overweight or obesity, increased self-esteem could be determinant for an optimum state of psychological health. Interestingly, the strongest and most consistent association found in this study was between muscular strength and self-esteem, pointing to muscular strength as a candidate for exercise interventions aiming to improve psychological health in children.

Concerning depression and anxiety, no relationship between physical fitness components and these indicators was found. Our results were not in line with previous literature which affirmed that physical fitness improvement, specifically cardiorespiratory fitness, was associated with lower levels of depression in overweight/obese adolescents [30]. However, the population in that study consisted of overweight/obese adolescents, whereas the present study included children with overweight or obesity. This could perhaps be the reason behind such discrepancies.

Cardiorespiratory fitness could be a protective factor of depression symptoms for overweight/obese population during adolescence but not during childhood.

Finally, speed/agility was the only physical fitness component not associated with any psychological distress and/or psychological well-being indicator. Additionally, to the best of our knowledge, this is the first study which analyzes the association between speed/agility and psychological health in children with overweight or obesity; as such, it is difficult to compare present results with previous studies.

Our study has several limitations. Firstly, this is a cross-sectional study; hence, it does not allow inferences about causality to any of the associated factors. Secondly, the similar characteristics of the study sample (i.e. all participants were overweight or obese) and the sample size could explain the few associations found in the analyses. The study has several strengths, including the standardization, accuracy and objective physical fitness measurements (including a lab measure of VO_2max), a broad set of psychological health indicators, and the focus on children with overweight or obesity.

CONCLUSION

Our results suggest that higher levels of muscular strength may have a positive influence on psychological distress (i.e. negative affect and stress) and psychological well-being indicators (i.e. self-esteem and optimism), as well as higher levels of cardiorespiratory fitness on optimism, in children with overweight or obesity, yet this results need to be confirmed in RCTs.

REFERENCES

1. Biddle, S. J, Mutrie, N. Psychology of physical activity: Determinants, well-being and interventions. Routledge, 2007.

2. Ortega FB, Silventoinen K, Tynelius P et al. Muscular strength in male adolescents and premature death : cohort study of one million participants. Br Med J 2012; 345:1–12.

3. Antaramian SP, Huebner ES, Hills, KJ et al. A dual-factor model of mental health: Toward a more comprehensive understanding of youth functioning. Am J Orthopsychiat 2010; 80: 462-472.

4. Seligman, ME, Csikszentmihalyi M. Positive psychology: An introduction. Am Psychol 2000; 55 (1): 5–14.

5. Sanders RH, Han A, Baker JS et al. Childhood obesity and its physical and psychological co-morbidities: a systematic review of Australian children and adolescents. Eur J Pediatr 2015; 174: 715-746.

6. Luppino FS, de Wit LM, Bouvy PF et al. Overweight, obesity, and depression: a systematic review and meta-analysis of longitudinal studies. Arch Gen Psychiatry 2010; 67: 220-229.

7. Rankin J, Matthews L, Cobley S et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolesc Health Med Ther. 2016; 7: 125-146.

8. Ruiz JR, Castro-Piñero J, Artero EG et al. Predictive validity of health-related fitness in youth: a systematic review. Br J Sports Med 2009; 43: 909–923.

9. Ortega FB, Ruiz JR, Castillo MJ et al. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obesity 2008; 32: 1–11.

10. Voss MW, Chaddock L, Kim JS et al. Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. Neuroscience 2012; 199: 166–176.

11. Smith JJ, Eather N, Morgan PJ et al. The Health Benefits of Muscular Fitness for Children and Adolescents : A Systematic Review and Meta-Analysis. Sports Med 2014; 44(9): 1209–1223.

12. Shomaker LB, Tanofsky-kraff M, Zocca JM et al. Depressive Symptoms and Cardiorespiratory Fitness in Obese Adolescents. J Adolescent Health 2012; 50: 87–92.

13. Williams, SE, Carroll D, Veldhuijzen JJ et al. Anxiety symptom interpretation : A potential mechanism explaining the cardiorespiratory fitness – anxiety relationship. J Affective Disorders 2016; 193: 151–156.

14. Cadenas-Sánchez C, Mora-González J, Migueles et al. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): Rationale, design and methods. Contemp Clin Trials 2016; 47: 315-324.

15. Malina RM, Rogol AD, Cumming SP et al. Biological maturation of youth athletes: assessment and implications. Br J Sports Med 2015; 49: 852 859.

16. Ruiz JR, Castro-Pinero J, Espana-Romero V et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. Br J Sports Med 2010; 45: 518–524.

17. Davis CL, Pollock NK, Waller JL et al. Exercise Dose and Diabetes Risk in Overweight and Obese Children: a randomized controlled trial. Jama 2012; 308: 1103–1112.

18. Léger LA, Mercier D, Gadoury C et al. The multistage 20 metre shuttle run test for aerobic fitness. J Sports Sci 1988; 6: 93–101.

19. Trianes Torres MV, Blanca Mena MJ, Fernández Baena FJ et al. Assessment of stress in childhood: Children’s Daily Stress Inventory (Inventario Infantil de Estresores Cotidiano, IIEC). Psicothema 2009; 21: 598–603.

20. Rodrigo G, Lusiardo M. Spanish version of the Revised Children’s Manifest Anxiety Scale in Uruguay: reliability and concurrent validity. Psychol Rep 1989; 65: 94-94.

21. Knight D, Hensley VR, Waters B Validation of the Children's Depression Scale and the Children's Depression Inventory in a prepubertal sample. J Child Psychol Psychiatry1988; 29: 853-863.

22. Laurent J, Catanzaro SJ, Joiner TEJ et al. A measure of Positive and Negative Affect for Children: Scale Development and Preliminary Validation. Psychol Assess 1999; 11: 326–338.

23. Lyubomirsky S, Lepper H. A measure of subjective happiness: Preliminary reliability and construct validation. Soc Indic Res 1999; 46: 137–155.

24. Extremera N, Fernández-Berrocal P. The Subjective Happiness Scale: Translation and Preliminary Psychometric Evaluation of a Spanish Version. Soc Indic Res 2014; 119: 473-481.

25. Scheier ME, Charles S, Bridges MW. Distinguishing Optimism From Neuroticism and Trait Anxiety , Self-Mastery , and Self-Esteem: a reevaluation of the Life Orientation Test. J Pers Soc Psychol 1994; 67: 1063–1078.

26. Ey S, Hadley W, Allen DN et al. A new measure of children’s optimism and pessimism: The youth life orientation test. J Child Psychol Psyc 2005; 46: 548–558.

27. Gómez-Lugo M, Espada JP, Morales A et al. Adaptation, Validation, Reliability and Factorial Equivalence of the Rosenberg Self-Esteem Scale in Colombian and Spanish Population. Span J Psychol 2016; 19: 1-12.

28. Tomkinson GR, Lang JJ, Tremblay MS et al. International normative 20 m shuttle run values from 1 142 026 children and youth representing 50 countries. Br J Sports Med 2016;0:1-14.

29. Bergh C, Udumyan R, Fall K et al. Stress resilience and physical fitness in adolescence and risk of coronary heart disease in middle age. Heart 2015; 101: 623–629.

30. Lai JCL. Dispositional optimism buffers the impact of daily hassles on mental health in Chinese adolescents. Pers Indiv Differ 2009; 47: 247–249.

Supplemental Material

Study III

Part II. Physical activity, sedentary behavior, physical fitness and white matter

STUDY IV

Associations of physical activity and screen time with white matter microstructure in children from the general population.

María Rodriguez-Ayllon, Ivonne P.M. Derks, Michiel van den Dries, Irene Esteban-Cornejo, Jeremy A. Labrecque, Junwen Yang-Huang, Hein Raat, MD, Meike W. Vernooij, Tonya White, Francisco B. Ortega, Henning Tiemeier, Ryan L. Muetzel.

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INTRODUCTION

Despite compelling evidence suggesting physical activity plays an important role in general health [1], a substantial proportion of youth do not meet the recommended levels of physical activity [2]. During childhood and adolescence, the brain undergoes a variety of developmental changes in white and gray matter structure [3,4], which also coincide with changes in behavior and cognition. During this sensitive period of maturation, a number of environmental factors have been shown to be related to the brain's white matter macrostructure and microstructure [5–7], yet little work has explored to what extent physical activity and sedentary behaviors, associate with white matter in children.

Physical activity and sedentary behavior are the two independent behaviors that occupy all waking hours of a day. Physical activity, defined as any body movement that increases energy expenditure (e.g. active commuting, outdoor play, or sport participation) [8], has been consistently linked to mental health benefits across a person's lifespan [9,10]. On the other hand, sedentary behavior, defined as any waking behavior characterized by an energy expenditure ≤1.5 METs, while in a sitting, reclining or lying posture [11], has become a central component of the daily lives of children. Therefore, the debate about whether sedentary behavior, specifically recreational screen time, negatively impacts children mental health is becoming increasingly important. Recent work has suggested that while negative associations are observed between screen time (i.e., technology use and playing videogames) and mental health and cognition in young people, they are likely too small in magnitude to warrant policy change [12,13]. Though previous work has studied the association of these two behaviors with indicators of mental health in childhood, little work has examined any neural correlates.

MRI offers an *in vivo* view into the developing brain. White matter neuronal tissue consists of axons wrapped in the lipid-rich myelin sheath and is responsible for providing fast and efficient connections throughout cortex and subcortex. DTI is able to sample features of the microstructural architecture of white matter. FA and MD are two commonly derived scalar metrics from DTI. FA represents the degree to which water diffuses preferentially along one axis (i.e., the diffusion is hindered by structures such as myelin and tightly packed axons), and has shown to increase with age during child and adolescent brain development [3,14,15] and in many cases to be lower in the context of various neurological and psychiatric diseases [16–18]. MD is the simple average diffusion, with higher levels indicating relatively unimpeded diffusion (i.e., it is negatively correlated with FA). Numerous studies have demonstrated that developmental changes in white matter microstructure occur throughout childhood [3,19], and the technique has been shown to be sensitive to subtle features of psychopathology [20]. However, little work has explored whether physical activity or screen time are associated with white matter microstructure.

In one RCT of overweight 8–11 year-old children, the effect of an 8-month exercise intervention on white matter microstructure was examined [21,22]. This study showed that FA increased in the uncinate and superior longitudinal fasciculus in the intervention group. Similarly, another RCT examined the effects of an after-school exercise program on the microstructure of white matter tracts in 7- to 9-year-old children. This study found that children who participated in the exercise program showed increased white matter microstructure in the genu of the corpus callosum [23].

In addition, a cross-sectional study demonstrated that, in 9-to-10 year-old children, higher levels of cardiorespiratory fitness were associated with greater FA in sections of the corpus callosum, corona radiata, and superior longitudinal fasciculus [24]. However, greater cardiorespiratory fitness was also related to lower FA in the corticospinal tract [25]. Collectively, it is difficult to draw conclusions from this limited literature, which largely focuses on the relation between cardiorespiratory fitness, exercise and white matter microstructure, omitting the constructs of physical activity (e.g., outdoor play, active commuting, and sport participation). Further, to our knowledge, no other studies have examined whether screen time is associated with white matter microstructure in children.

The present study examined the associations of physical activity and screen time with white matter microstructure in 10-year old children from the general population. Based on previous literature, we hypothesized higher levels of physical activity would be related to higher FA and lower MD. We hypothesized increased screen time would be related to lower FA and higher MD, however, in line with previous literature [12,13,26], we expect these relationships to be relatively small.

METHODS

Study design and participants

The study was part of the Generation R Study, a prenatal population-based cohort. A detailed description of the study design and methods has been published elsewhere [27]. In total, 3992 children visited our study-dedicated imaging facility for an MRI scan at the mean age of 10 [28]. Of the 3992 children, a total of 942 were excluded due to missing a complete DTI scan (n=285), image artifacts (n=37), poor image quality (n=406), an incidental finding (n=13) or their data were collected using different parameters on the MRI system (n=201), leaving 3050 participants for analysis. After excluding children with missing information on physical activity (n=518), the study sample included 2532 children (mean age 10.12 ± 0.58 years; 50.04% boys). Supplemental **Table S1** shows the sample characteristics of children included in analyses of screen time (N=2346), which is highly similar to those included in analyses of physical activity. A flow chart illustrating the exclusion of data is depicted in **Figure 1**. The Medical Ethics Committee of the Erasmus Medical Center approved the study procedures and participants provided written informed consent.

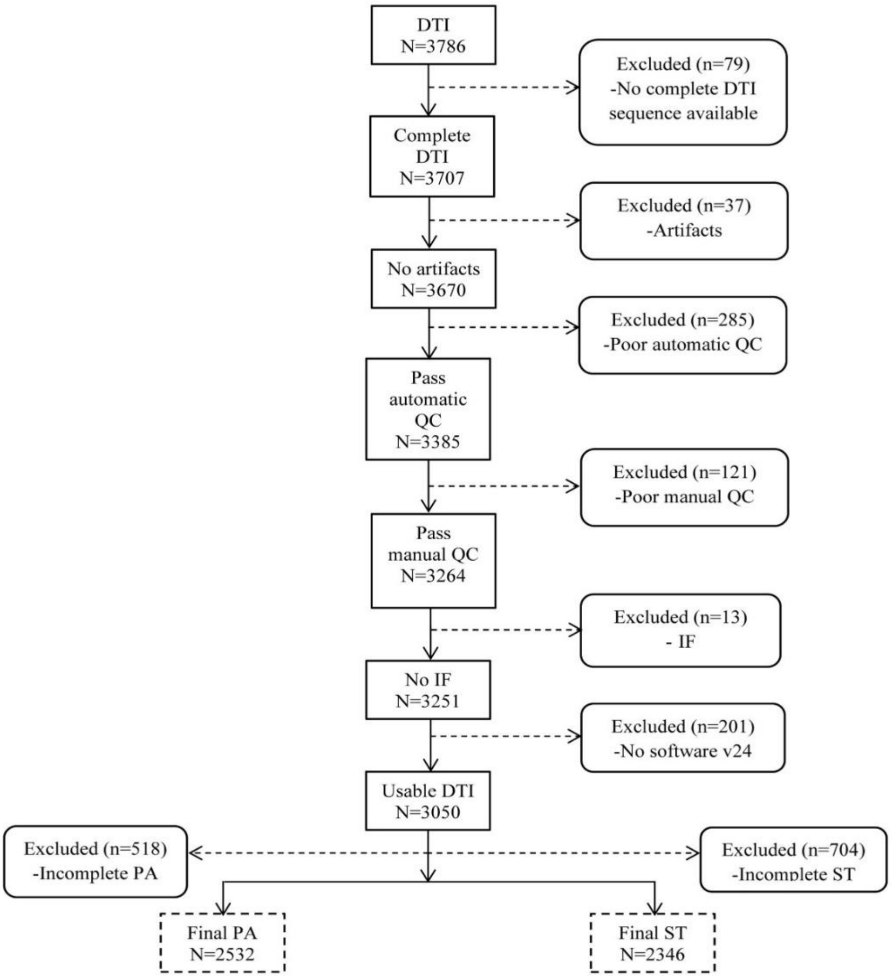

Figure 1. Flow chart indicating data exclusion. Note: Box with dotted lines indicate the sample used in the current study. QC = quality control, IF= incidental of finding, PA = physical activity, ST = screen time, MRI= magnetic resonance imaging, DTI=diffusion tensor imaging.

Physical activity and screen time assessments

Information on the level of physical activity and screen time were obtained through a parent-reported questionnaire administered when children were 10 years old. The questionnaires were intended for the primary caregiver who was most often the mother (97%). To assess the level of physical activity, respondents indicated both the number of days per week and duration per day their child engages in: (i) walking or cycling to/from school, (ii) outdoor play, and (iii) sports. Time per week spent on each activity was calculated by using the following formula: weekly time spent on the activity = (days per week) * (hours per day). A total physical activity score was calculated by adding the hours of active commuting, outdoor play, and sport participation per week.

Respondents were also asked to indicate the number of days and hours per day their child: (i) watches TV (including videos/DVDs) and (ii) uses a computer or similar device (including video games). Screen times were assessed separately for weekdays and weekend days but were combined to estimate the total hours per week spent in each activity. A total weekly screen time score was calculated by adding the hours of playing video games and watching TV.

MRI

Image acquisition

MRI data were acquired with a 3Tesla GE MR-750W system (General Electric, Milwaukee, WI). The DTI sequence consisted of a 35 direction echo planar imaging (EPI) sequence using the following sequence parameters: TR = 12,500 ms, TE = 72 ms, flip angle = 90, matrix=120 x 120, FOV= 240 mm x 240 mm, slice thickness= 2 mm, number of slices = 65 and voxel resolution= 2 x 2 x 2 mm^3 [20].

Image preprocessing

Image preprocessing was conducted using the Functional MRI of the Brain´s Software Library [29] and the CAMINO toolkit [30] through python interfaces (https://fsl.fmrib.ox.ac.uk) [31]. Images were first adjusted for minor head motion and eddy-current induced artifacts [32,33]. In order to account for rotations applied to the image data [34,35], the resulting transformation matrices were used to rotate the diffusion gradient direction table. Non-brain was removed using the FSL Brain Extraction Tool [36]. The diffusion tensor was fit using the RESTORE method [30,37], and common scalar maps (i.e., FA, MD, AD, RD) were subsequently computed. Fully automated probabilistic tractography was run using a predefined series of seed- and target- masks from the FSL AutoPtx plugin [20,38]. Briefly, following a nonlinear registration of the FA map to standard space (FMRIB58 1mm), a predefined library of seed, target, and exclusion masks were warped to each individual's native space FA map. FSL's BEDPOSTx and Probtrackx were used to conduct probabilistic fiber tractography, accounting for two fiber orientations [39]. Resulting connectivity distributions were normalized based on the total number of successful seed-to-target attempts, and were thresholded based on established values to remove voxels with a low probability [20]. Average DTI scalar metrics were extracted for each tract (see **Supplemental Material**), with each voxel being weighted by the normalized connectivity value from probabilistic tractography. Global, whole brain estimates of DTI metrics (i.e., FA, MD, RD, AD) were calculated using a confirmatory factor analysis across multiple tracts described in detail elsewhere [20].

Image quality assurance

Raw image quality was assessed with both an automated software and with a visual inspection [20]. Briefly, slice-wise variations in signal intensity were examined using the DTIprep package (https://www.nitrc.org/projects/dtiprep). The SSE maps from the tensor estimation were also calculated and visually inspected for structured noise.

Lastly, nonlinear registration to standard space was inspected for accuracy to ensure seed and target masks were properly aligned to native space. Datasets determined to be of insufficient quality for statistical analyses were excluded (n=285 from automated quality control of slice-wise variation in signal and n=121 from an additional visual inspection of SSE maps and registration quality). Example images of FA maps from children representative of the sample are presented in the Supplementary Material (see **Figure S1**).

Covariates

Age at MRI scanning and sex were included as covariates. Further, maternal education level and ethnicity were assessed by questionnaires. Ethnicity was based on the country of birth of the mother and mother's parents. Maternal education level was defined by the highest completed education and divided into three categories ranging from low (from no education to primary school), middle (high school or vocational training) to high education level (from higher vocational education to university). Height and weight were measured at the age of 10 years at the research center and BMI was calculated using standardized scores according to the Dutch reference growth curves (https://growthanalyser.org) [40]. A non-verbal IQ was assessed at approximately 6 years of age using the Snijders-Oomen Niet-verbale intelligentie Test- Revisie (SON-R 2.5-7) [41]. Emotional and behavioral problems were assessed at age of 10 years by parent-report using the validated Child Behavior Checklist school-age version (CBCL/6-18) (Achenbach and Rescorla, 2003). Apart from non-verbal IQ (12%), the percentage of missing values did not exceed 10%.

Statistical analysis

All analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, p set at < 0.05). Multiple imputation was used to impute missing data of covariates. In total, 10 imputed datasets were created and pooled results are presented. Multiple linear regression analyses were performed with physical activity or screen time measures as independent variables (predictors) and DTI scalar metrics (i.e., FA, and MD) as dependent variables (outcomes). Independently, as they provide added information in the interpretation of the underlying white matter microstructure, we also tested the association of physical activity and screen time variables with global RD and global AD. Linear regression analyses were hierarchically adjusted for covariates by creating two models. Model 1 included age at the time of scanning, sex, ethnicity, maternal education, and BMI. Model 2 was additionally adjusted for behavior problems and non-verbal IQ. In order to determine whether the association with white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, associations with FA and MD within individual tracts were also tested if exposures showed an association with global DTI metrics. For tract-specific analyses, FDR correction was applied to account for the number of tests performed.

Additionally, a number of sensitivity analyses were run. First, total physical activity and total screen time were entered into the model simultaneously to adjust estimates for one another. Second, we divided the total sample in four subgroups of participants according to their physical activity and screen time levels to compare global FA and MD amongst the groups. Physical activity and screen time groups were defined according to the sample median (high/low physical activity/screen time). Third, different interaction terms were tested to ascertain whether associations were different across sub-groups of subjects (i.e., sex, parental educational level, ancestral background). Lastly, we tested quadratic and cubic age terms, as well as an age-by-sex interaction term (using a quadratic age term). We also tested quadratic screen time and physical activity term, as well as the interactions between quadratic total physical activity variable and quadratic total screen time variable in association with white matter microstructure.

RESULTS

Table 1 presents participant demographic characteristics. Differences between physical activity and screen time levels between boys and girls are shown in **Table S2**. Characteristics of included and excluded participants are shown in **Table S3**.

Association of physical activity and screen time with global white matter microstructure

Total physical activity was positively associated with global FA (β=0.051, 95% CI= (0.010, 0.092), p=0.016) when the model was adjusted for sociodemographic factors. Further, the positive association between physical and global FA remained after additional adjustment for behavior problems and non-verbal IQ (β=0.057, 95% CI= (0.016, 0.098), p=0.007). Results from analyses of global FA and MD are presented in **Table 2**, and follow-up analyses with global RD and AD to better describe the diffusion profile are presented in **Table S4**. To determine whether a particular type of physical activity (i.e. active commuting, outdoor play and sport participation) was responsible for the total physical activity association with global FA, each type of physical activity was examined separately. In the fully adjusted model (model 2), positive associations between outdoor play and global FA (β=0.041, 95% CI= (0.000, 0.083), p=0.047) and between sport participation and global FA were observed (β=0.053, 95% CI= (0.010, 0.096), p=0.015).

Table 1. Sample characteristics

	N	Mean/%	SD
Sex			
Boys,%	1267	50.04	
Age at MRI assessment ,years	2532	10.12	0.58
Age at CBCL assessment, years	2495	9.71	0.28
Ethnicity, %			
Dutch	1671	66.63	
Other western	213	8.49	
Non-western	624	24.88	
Body mass index, kg/m^2	2526	17.36	2.50
Behavior problems, sum score (CBCL)	2475	16.76	14.63
Non-verbal IQ	2218	104.32	14.59
Maternal education,%			
Low	187	8.06	
Medium	618	26.65	
High	1514	65.29	
Exposures characteristics			
Total physical activity, h/w	2532	9.06	5.10
Total screen time, h/w	2346	17.10	11.63

*Note: 86 participants had no data on physical activity but they were included in analyses of screen time. MRI=magnetic resonance imaging, CBCL= Child Behavior Checklist school-age, IQ= intelligence quotient. h/w= hours per week. Total physical activity= hours of active commuting, outdoor play, and sport participation per week. Total screen time= hours of computer time, playing video games, and watching TV. Maternal education level was defined by the highest completed education and divided into three categories ranging from low (from no education to primary school), middle (high school or vocational training) to high education level (from higher vocational education to university).

Table 2. Association between physical activity and screen time with global fractional anisotropy and mean diffusivity.

Fractional anisotropy

	Model 1			Model 2		
	β	95% CI	p	β	CI	p
Physical activity (n=2532)						
Total physical activity, h/w	0.051	(0.010, 0.092)	0.016	0.057	(0.016, 0.098)	0.007
Active commuting, h/w	0.021	(-0.020, 0.062)	0.325	0.023	(-0.018, 0.064)	0.272
Outdoor play, h/w	0.035	(-0.006, 0.076)	0.093	0.041	(0.000, 0.083)	0.047
Sport participation, h/w	0.052	(0.009, 0.094)	0.017	0.053	(0.010, 0.096)	0.015
Screen time (n=2346)						
Total screen time, h/w	-0.021	(-0.065, 0.023)	0.347	-0.010	(-0.054, 0.035)	0.668
Playing computer games, h/w	-0.003	(-0.045, 0.039)	0.880	0.000	(-0.041, 0.042)	0.985
Watching television ,h/w	-0.028	(-0.073, 0.017)	0.219	-0.014	(-0.060, 0.031)	0.532

Mean diffusivity

	Model 1			Model 2		
	β	95% CI	p	β	CI	p
Physical activity (n=2532)						
Total physical activity, h/w	-0.079	(-0.119, -0.038)	<0.001	-0.079	(-0.120, -0.038)	<0.001
Active commuting, h/w	-0.005	(-0.045, 0.036)	0.821	-0.005	(-0.046, 0.036)	0.812
Outdoor play, h/w	-0.073	(-0.114, -0.032)	<0.001	-0.074	(-0.114, -0.033)	<0.001
Sport participation ,h/w	-0.043	(-0.086, -0.001)	0.045	-0.043	(-0.086, 0.000)	0.049
Screen time (n=2346)						
Total screen time, h/w	-0.028	(-0.072, 0.015)	0.203	-0.031	(-0.075, 0.013)	0.170
Playing computer games, h/w	-0.024	(-0.066, 0.017)	0.250	-0.026	(-0.067, 0.016)	0.230
Watching television , h/w	-0.022	(-0.067, 0.022)	0.325	-0.025	(-0.070, 0.020)	0.280

*Note: Model 1 was adjusted for sex, age at the time of scanning, ancestral background, body mass index and maternal education. Model 2 was additionally adjusted for emotional and behavior problems and non-verbal intelligence quotient. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction), MD= mean diffusivity (high MD corresponds to relatively unimpeded water diffusion), h/w= hours per week.

Total physical activity was inversely associated with global MD (β=-0.079, 95% CI= (-0.119, -0.038), p<0.001) when the model was adjusted for sociodemographic covariates (model 1). After, additional adjustment for behavioral problems and non-verbal IQ the association remained similar (model 2) (β=-0.079, 95% CI= (-0.120, -0.038), p<0.001). Each type of physical activity was examined separately to determine whether all or a subset of activities were responsible for the associations with total physical activity. In the fully adjusted model (model 2), outdoor play and sport participation were inversely associated with MD (β=-0.074, 95% CI= (-0.114, -0.033), p<0.001; β=-0.043, 95% CI= (-0.086, 0.000), p=0.049 respectively). In order to better describe these associations with FA and MD, further analyses explored which underlying diffusivity metrics (i.e., RD and/or AD) were associated with physical activity. Both RD and AD were significantly associated with total physical activity (β=-0.079, 95% CI= (-0.120, -0.039), p<0.001; β=-0.054, 95% CI= (-0.094, 0.014), p=0.008, respectively).

No association was found between individual or aggregate screen time variables and global DTI metrics (all p>0.05) **(Table 2).**

Association between physical activity, screen time and tract-specific FA and MD.

Associations between total physical activity and tract- specific FA and MD are shown in **Table S5**. Briefly, no association was found between total physical activity and FA within individual tracts when significance levels were adjusted for multiple testing. However, total physical activity was associated with MD in nearly all tracts when adjusted for multiple comparisons. **Figure 2** graphically represents the significant negative associations between total physical activity and MD across individual tracts.

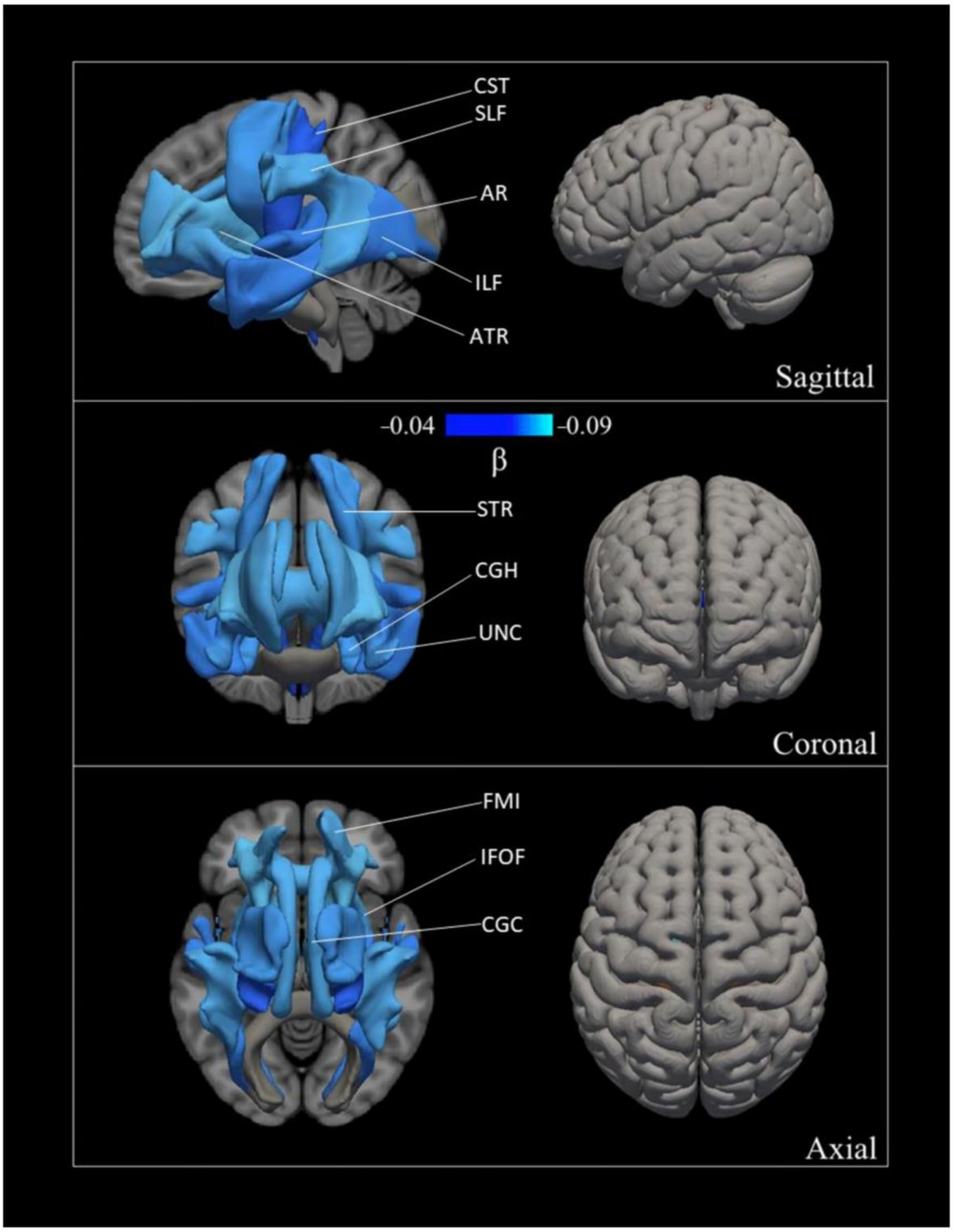

Figure 2. Association between total physical activity and tract- specific MD. Colour bar represents standardized beta coefficients with lighter blue referring to negative association. Lighter blue referring to stronger association between total physical activity and MD. Corticospinal tract (CST), acoustic radiation (AR), anterior thalamic radiation (ATR), superior longitudinal fasciculus (SLF), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), uncinate fasciculus (UNC), cingulate gyrus part of cingulum (CGC), hippocampal part of the cingulum (CGH), forceps minor (FMI), and superior thalamic radiations (STR).

Lastly, exploratory analyses testing the association between total screen time and tract-specific FA and MD are shown in **Table S6.**

Sensitivity Analyses

Results remained similar when models for physical activity and global white matter microstructure were additionally adjusted for total screen time, suggesting that physical activity is positively associated with white matter microstructure, independent of total screen time (**Table S7**). Screen time was still unrelated to global DTI metrics after additional adjustment for total physical activity (**Table S7**).

Next, when categorically subdividing the sample based on physical activity and screen time levels (e.g., high screen time, low physical activity), the subgroup with high physical activity (>8.4 hours/week) and high screen time (> 14.8 hours/week seem) showed lower MD compared to the rest of subgroups **(Figure S2 and Figure S3, respectively)**.

Then, different interaction terms were tested to ascertain whether associations were different across sub-groups of subjects. The association between physical activity and white matter microstructure was consistent across parents' education categories. Similarly, no interaction between sex or ethnicity and physical activity was observed.

Lastly, we have included into the model nonlinear age terms, specifically a quadratic age term (**Table S8**) and also included a cubic age term and results remain highly similar (**Table S9**). We also tested age-by-sex interaction effects with these variables (i.e., age^2 and age^3) and the interaction term was not significant (all P>0.470). Importantly, the model estimates for the association with physical activity and screen time also remained highly similar. Finally, nonlinear screen time and physical activity terms were not associated with FA or MD (See **Supplemental Material**).

DISCUSSION

Using neuroimaging data from over 2,500 children, we found that physical activity is associated with white matter microstructure, specifically outdoor play and sport participation time. On the other hand, no association was observed between screen time and white matter microstructure. In the context of the literature, this study expands upon the compelling evidence of general health benefits of physical activity by demonstrating a new association with white matter microstructure in children.

Previous work on typical brain development has shown a positive association between FA and age, as well as a negative association with MD [3,14,15,43–46]. Further, a similar pattern of association has been shown with cognitive function, where white matter microstructure is associated with better neuropsychological performance [47]. Within this context, the positive link between physical activity and white matter microstructure shown in the present study could explain the improvements observed in cognition [48,49]. Importantly, specific aspects of physical activity, namely outdoor play and sport participation, were associated with white matter microstructure. The relationship between physical activity and white matter microstructure has not been studied previously, which hampers further comparisons with similar studies. Nonetheless, this work compliments previous studies focused on the relation between cardiorespiratory fitness and exercise with white matter microstructure. For instance, previous studies demonstrated that, in 9-to-10 year-old children, higher levels of cardiorespiratory fitness were associated with higher FA in sections of the corpus callosum, corona radiata, and superior longitudinal fasciculus [24]. In contrast, adolescents with better cardiorespiratory fitness showed greater number of streamlines, especially in the corticospinal tract and forceps minor [25], but also lower FA in the corticospinal tract [25]. Additionally, an 8-month exercise intervention showed increased FA in sections of the uncinate fasciculus and superior longitudinal fasciculus in overweight children in the exercise group when compared to controls [21,22]. Moreover, an 9-month exercise intervention showed increased white matter microstructure in the genu of the corpus callosum in 7- to 9-year-old children in the exercise group when compared to controls [23] .

In the present study, no association was found between active commuting and white matter microstructure. Previous work has also shown that active commuting was not associated with cognitive performance in children [50]. Thus, results are in line with an increasing literature suggesting that increases in cognitive functioning in childhood due to physical activity are most clearly observed in tasks that involve executive functioning (e.g., sport participation) [51].

Previous work has demonstrated that increased levels of physical activity might improve cerebral blood flow [48], and DTI has proven to be sensitive to white matter microstructural changes that may result from cardio- and neuro-vascular risk factors [52,53]. A possible physiological mechanism could be the positive influence physical activity has on cardio-metabolic risk factors, such as insulin resistance, blood lipids, blood pressure and inflammatory proteins [54]. Moreover, previous literature showed higher levels physical activity are associated with better mental health in children [9,55]. As childhood is a period where many physiological and psychological changes occur, public health advocation for novel approaches to increasing physical activity in children could be useful for improved (neuro) physiological and psychological health.

In this line, a recent large study of physical activity and cognition showed higher levels of physical activity were associated with better global cognition [56]. Our results suggest that these improvements in cognition could be facilitated by better underlying white matter microstructure.

Another important finding was that screen time was not associated with white matter microstructure. To the best of our knowledge, this is the first study to examine the association between screen time and white matter microstructure in children. These results further support the work from Ferguson et al. and Orben et al. [12,13] who showed that the relationship between screen time and different mental health outcomes (e.g., externalizing problems, internalizing problems and academic performance) was null or very small. Overall, the relationship between screen time and mental health are likely nonlinear, and moderate engagement in certain screen time activities may not lead to behavioral or emotional problems [12]. For instance, previous research found that meeting the 2 hours or less recreational screen time per day recommendations was associated with superior global cognition [56]. In contrast, frequent weekly use of video games was associated with conduct problems, as well as, increased levels of watching TV were negatively associated with neurocognitive development of children [57]. In addition to these discrepancies in the literature, advances in technology (e.g., availability of hand-held media devices, and social media) compared to the construct of purely passive watching TV, further underscore the importance of maintaining well-characterized measures of screen time, as differing amounts/types of screen time could influence the brain differently. Interestingly, associations between physical activity and white matter remained after adjusting for levels of screen time. Thus, though purely speculative, the benefits of physical activity may not be negatively influenced by playing computer games and watching TV moderately, which has been reported previously for other general cardiometabolic outcomes [58].

Key strengths of the current study are the large sample size, and incorporation of population-based neuroimaging. The nature and size of the cohort allocates us with the data and power to adjust for multiple confounding factors. Further, the population-based sampling offers increased generalizability of the findings compared to previous studies. However, several limitations require discussion. First, this is a cross-sectional study, limiting inferences about causality and directionality to any of the associated factors. Further, though residual confounding remains a possibility, effect estimates were not substantially changed after adjusting for a number of potential confounding factors. Future work should consider other environmental confounders including well-characterized measures of socioeconomic status. Second, physical activity and screen time levels were assessed by parental-reported questionnaires, lending to the possibility of under- or overestimations of the behaviors. Therefore, objective measures such as accelerometry and experience sampling should be utilized in future studies. Lastly, the effect sizes for the association between physical activity and white matter microstructure are relatively small. However, similar effect sizes are observed in structure-function associations with cognition and white matter microstructure [47], and the clinical relevance of such effect sizes in the context of DTI has yet to be formally evaluated.

CONCLUSION

This study demonstrates that higher levels of physical activity are associated with greater white matter microstructure in children ages 9-to-10 years old from the general population. No association was observed between screen time and white matter microstructure. Future work should continue to explore longitudinal data in order to more concretely decipher the temporality of the associations, so that educational and health institutions can consider whether to promote physical activity during childhood as a potential (modifiable) protective factor in the context of brain health.

REFERENCES

1. Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012

2. Hallal PC, Andersen LB, Bull FC, Guthold R, Haskell W, Ekelund U, et al. Global physical activity levels: surveillance progress, pitfalls, and prospects. Lancet. 2012 ;380:247–57.

3. Schmithorst VJ, Yuan W. White matter development during adolescence as shown by diffusion MRI. Brain Cogn. 2010; 72: 16–25.

4. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006;30:718–29.

5. Frodl T, Carballedo A, Fagan AJ, Lisiecka D, Ferguson Y, Meaney JF. Effects of early-life adversity on white matter diffusivity changes in patients at risk for major depression. J Psychiatry Neurosci. Canadian Medical Association; 2012;37:37–45.

6. Hanson JL, Adluru N, Chung MK, Alexander AL, Davidson RJ, Pollak SD. Early neglect is associated with alterations in white matter integrity and cognitive functioning. Child Dev. NIH Public Access; 2013;84:1566–78.

7. Bick J, Nelson CA. Early Adverse Experiences and the Developing Brain. Neuropsychopharmacology. Nature Publishing Group; 2016;41:177–96.

8. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100:126–31.

9. Biddle SJH, Ciaccioni S, Thomas G, Vergeer I. Physical activity and mental health in children and adolescents: An updated review of reviews and an analysis of causality. Psychol Sport Exerc. Elsevier; 2018;1–10.

10. Chekroud SR, Gueorguieva R, Zheutlin AB, Paulus M, Krumholz HM, Krystal JH, et al. Association between physical exercise and mental health in 1·2 million individuals in the USA between 2011 and 2015: a cross-sectional study. The Lancet Psychiatry. 2018;5:739–46.

11. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Network (SBRN) – Terminology Consensus Project process and outcome. Int J Behav Nutr Phys Act. 2017;14:75.

12. Ferguson CJ. Everything in Moderation: Moderate Use of Screens Unassociated with Child Behavior Problems. Psychiatr Q. 2017;88:797–805.

13. Orben A, Przybylski AK. The association between adolescent well-being and digital technology use. Nat Hum Behav. Nature Publishing Group; 2019;3:173–82.

14. Giorgio A, Watkins KE, Chadwick M, James S, Winmill L, Douaud G, et al. Longitudinal changes in grey and white matter during adolescence. Neuroimage. 2010;49:94–103.

15. Tamnes CK, Roalf DR, Goddings A-L, Lebel C. Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. Dev Cogn Neurosci. 2018;33:161–75.

16. Hulvershorn LA, Cullen K, Anand A. Toward dysfunctional connectivity: a review of neuroimaging findings in pediatric major depressive disorder. Brain Imaging Behav. 2011;5:307–28.

17. Aoki Y, Cortese S, Castellanos FX. Research Review: Diffusion tensor imaging studies of attention-deficit/hyperactivity disorder: meta-analyses and reflections on head motion. J Child Psychol Psychiatry. 2018;59:193–202.

18. Ayling E, Aghajani M, Fouche JP, Van Der Wee N. Diffusion tensor imaging in anxiety disorders. Curr. Psychiatry Rep. 2012; 14: 197–202.

19. Stiles J, Jernigan TL. The Basics of Brain Development. 2010;327–48.

20. Muetzel RL, Blanken LME, van der Ende J, El Marroun H, Shaw P, Sudre G, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. Am J Psychiatry. 2017;175:54-62.

21. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51:728–33.

22. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved frontoparietal white matter integrity in overweight children is associated with attendance at an after-school exercise program. Dev Neurosci. 2014;36:1–9.

23. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette E, Raine L, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci. Frontiers; 2018;12:950.

24. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014;8:584.

25. Herting MM, Colby JB, Sowell ER, Nagel BJ. White matter connectivity and aerobic fitness in male adolescents. Dev Cogn Neurosci. 2014;7:65–75.

26. Ferguson CJ. Do Angry Birds Make for Angry Children? A Meta-Analysis of Video Game Influences on Children's and Adolescents' Aggression, Mental Health, Prosocial Behavior, and Academic Performance. Perspect Psychol Sci. 2015;10:646–66.

27. Kooijman MN, Kruithof CJ, van Duijn CM, Duijts L, Franco OH, van IJzendoorn MH, et al. The Generation R Study: design and cohort update 2017. Eur J Epidemiol. Springer; 2016;31:1243–64.

28. White T, Muetzel RL, El Marroun H, Blanken LME, Jansen P, Bolhuis K, et al. Paediatric population neuroimaging and the Generation R Study: the second wave. Eur J Epidemiol. 2018;33:99–125.

29. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012; 62: 782–90.

30. Cook P a, Bai Y, Seunarine KK, Hall MG, Parker GJ, Alexander DC. Camino: Open-Source Diffusion-MRI Reconstruction and Processing. 14th Sci Meet Int Soc Magn Reson Med. 2006;14:2759.

31. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, et al. Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python. Front Neuroinform. 2011;5:13.

32. Haselgrove JC, Moore JR. Correction for distortion of echo-planar images used to calculate the apparent diffusion coefficient. Magn Reson Med. 1996;36:960–4.

33. Jenkinson M, Smith S. A global optimisation method for robust affine registration of brain images. Med Image Anal. 2001;5:143–56.

34. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed. 2010; 23: 803–20.

35. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med. 2009;61:1336–49.

36. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002;17:143–55.

37. Chang LC, Jones DK, Pierpaoli C. RESTORE: Robust estimation of tensors by outlier rejection. Magn Reson Med. 2005;53:1088–95.

38. De Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, Van Der Lugt A, et al. Tract-specific white matter degeneration in aging: The Rotterdam Study. Alzheimer's Dement. 2015;11:321–30.

39. Behrens TEJ, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. Magn Reson Med. 2003;50:1077–88.

40. Fredriks AM, van Buuren S, Burgmeijer RJ, Meulmeester JF, Beuker RJ, Brugman E, et al. Continuing positive secular growth change in The Netherlands 1955-1997. Pediatr Res. 2000;47:316–23.

41. Tellegen, Winkel, Wijnberg-Williams, Laros. Snijders-Oomen Niet-Verbale Intelligentietest: SON-R 2-1/2 -to-7. Boom Testu. Ansterdam; 2005.

42. Achenback TM, Rescorla L a. Reliability, Internal Consistency, Cross-Informant Agreement, and Stability. Man. ASEBA Sch. -Age Forms Profiles. 2003; 99–107.

43. Eluvathingal TJ, Hasan KM, Kramer L, Fletcher JM, Ewing-Cobbs L. Quantitative diffusion tensor tractography of association and projection fibers in normally developing children and adolescents. Cereb Cortex. 2007;17:2760–8.

44. Barnea-Goraly N, Menon V, Eckert M, Tamm L, Bammer R, Karchemskiy A, et al. White matter development during childhood and adolescence: A cross-sectional diffusion tensor imaging study. Cereb Cortex. 2005;15:1848–54.

45. Brouwer RM, Mandl RCW, Schnack HG, Soelen ILC va., Baal GC van, Peper JS, et al. White matter development in early puberty: A longitudinal volumetric and diffusion

tensor imaging twin study. He Y, editor. PLoS One. 2012;7:e32316.

46. Asato MR, Terwilliger R, Woo J, Luna B. White matter development in adolescence: A DTI study. Cereb Cortex. Oxford University Press; 2010;20:2122–31.

47. Muetzel RL, Mous SE, van der Ende J, Blanken LME, van der Lugt A, Jaddoe VWV, et al. White matter integrity and cognitive performance in school-age children: A population-based neuroimaging study. Neuroimage. 2015;119:119–28.

48. Hillman CH, Erickson KI, Kramer AF. Be smart, exercise your heart: exercise effects on brain and cognition. Nat Rev Neurosci. 2008;9:58–65.

49. Hillman CH, Khan NA, Kao S-C. The Relationship of Health Behaviors to Childhood Cognition and Brain Health. Ann Nutr Metab. 2015;66 Suppl 3:1–4.

50. Van Dijk ML, De Groot RH, Van Acker F, Savelberg HH, Kirschner PA. Active commuting to school, cognitive performance, and academic achievement: an observational study in Dutch adolescents using accelerometers. BMC Public Health. 2014;14:799.

51. Tomporowski PD, Davis CL, Miller PH, Naglieri JA. Exercise and Children’s Intelligence, Cognition, and Academic Achievement. Educ Psychol Rev. NIH Public Access; 2008;20:111–31.

52. Shefer G, Marcus Y, Stern N. Is obesity a brain disease?Neurosci. Biobehav. Rev. 2013. 37: 2489–503.

53. Lee DY, Fletcher E, Martinez O, Ortega M, Zozulya N, Kim J, et al. Regional pattern of white matter microstructural changes in normal aging, MCI, and AD. Neurology. American Academy of Neurology; 2009;73:1722–8.

54. Eisenmann JC. Physical activity and cardiovascular disease risk factors in children and adolescents: an overview. Can J Cardiol. 2004;20:295–301.

55. Biddle SJH, Asare M. Physical activity and mental health in children and adolescents: a review of reviews. Br J Sports Med. 2011;45:886–95.

56. Walsh JJ, Barnes JD, Cameron JD, Goldfield GS, Chaput J-P, Gunnell KE, et al. Associations between 24 hour movement behaviours and global cognition in US children: a cross-sectional observational study. Lancet Child Adolesc Heal. 2018;2:783–91.

57. Takeuchi H, Taki Y, Hashizume H, Asano K, Asano M, Sassa Y, et al. The impact of television viewing on brain structures: Cross-sectional and longitudinal analyses. Cereb Cortex. 2015;25:1188–97.

58. Rezende LFM de, Rodrigues Lopes M, Rey-López JP, Matsudo VKR, Luiz O do C. Sedentary Behavior and Health Outcomes: An Overview of Systematic Reviews. Lucia A, editor. PLoS One. 2014;9:e105620.

Supplemental Material

Study IV

STUDY V

Physical activity, sedentary behavior and white matter microstructure in children with overweight or obesity

M. Rodriguez-Ayllon, I. Esteban Cornejo, J. Verdejo-Román, RL Muetzel, J. H. Migueles, J. Mora-Gonzalez, P. Solis-Urra, K.I. Erickson, C.H. Hillman, A. Catena, H. Tiemeier, F. B. Ortega.

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In press

INTRODUCTION

The structure of white matter is responsible for providing fast and efficient connectivity throughout cortical and subcortical regions, as well as for integrating brain areas into structural networks which support cognition [1]. In children and adolescents, the brain undergoes a variety of developmental changes in white matter structure [1,2]. Further, a number of environmental factors such as early-life adversity (e.g., stress exposure) are related to white matter microstructure during childhood and adolescence [3,4]. However, although there is emerging evidence in adult populations [5], only a few studies have explored the extent to which other modifiable lifestyle factors, namely physical activity and sedentary behavior, are associated with white matter microstructure in children. In fact, excess body mass has been linked to poorer structural connectivity [6] and white matter development [7] in children. For instance, childhood obesity is associated with differences in white matter organization [7], mainly in frontal and temporal brain regions. These associations, together with the fact that physical activity may protect against the development of obesity, suggest that optimal levels of physical activity and sedentary behavior may attenuate the adverse influence of obesity on white matter microstructure; however, this hypothesis needs to be investigated.

Neuroimaging offers an *in vivo* view into the developing brain. Specifically, DTI affords the ability to sample features of the microstructural architecture of white matter [1]. In addition, previous research has demonstrated that this technique is sensitive to features of psychopathology in children [8]. FA and MD are the two most commonly-used scalar metrics derived from DTI, which are related to microstructural white matter architecture. FA represents the degree to which water molecules diffuse preferentially along one axis and tends to increase with white matter maturation during development

[1,9,10]. It is typically lower in the context of various neurological and psychiatric diseases. MD is the simple average diffusion, with higher levels indicating relatively unimpeded diffusion in any direction. Biologically, higher FA and lower MD tend to reflect more strongly myelinated tracts, with a higher axonal conduction speed [11].

Physical activity and sedentary behavior are two independent lifestyle behaviors which play an important role as markers and determinants of general health [12]. In this context, the recently published second edition of the Physical Activity Guidelines for Americans [13] includes a section on the relationship between physical activity, sedentary behavior and brain health. Although these guidelines are inspiring, only a few previous studies examined the role of physical exercise (i.e., planned, structured, systematic and purposeful physical activity [14]) and physical fitness (i.e., the capacity to perform physical activity [15]) in white matter microstructure during childhood [16–20]. These studies contribute to the understanding of how increased levels of structured physical activity or physical fitness are related to white matter in children. However, it is also important to understand the relationship of daily physical activity and sedentary behavior and white matter in the absence of a structured intervention due to the low levels of moderate-to-vigorous physical activity typically observed in children with overweight/obesity.

Collectively, observational studies complement experimental studies and can help identify characteristics of children's daily physical activity (e.g., spontaneous and intermittent) that may benefit white matter microstructure. To our knowledge, no prior research has examined whether sedentary behavior is associated with white matter microstructure in children with overweight or obesity. Accordingly, the aim of the present study was twofold. The primary aim was to identify any associations of physical activity and sedentary behavior with global white matter microstructure in children with overweight or obesity. For this purpose, we used both objective and self-reported measures of physical activity and sedentary behavior. The secondary aim was to determine whether the association with white matter microstructure was global, or rather, restricted to a particular set of white matter bundles. As such, associations of physical activity and sedentary behavior with FA and MD within individual tracts were also tested when exposures showed an association with global DTI metrics. Based on previous literature, we hypothesized that higher levels of physical activity would relate to higher FA and lower MD. We further hypothesized that greater sedentary behavior, specifically recreational screen time, would relate to lower FA and higher MD; however, based on previous literature [21,22], we expected the magnitude of these relationships to be relatively small.

METHODS

Participants

This study used data from the ActiveBrains project (http://profith.ugr.es/activebrains), a RCT designed to examine the effects of an exercise intervention on brain, cognition and academic performance, as well as on selected physical and mental health outcomes in children with overweight or obesity. The complete methodology for this project has been described elsewhere [23]. In total, 110 children with overweight or obesity, aged 8-11 years were recruited from Granada, Spain. Briefly, a total of 7 participants were excluded (n=2 did not complete the DTI sequence, n = 2 presented poor quality control, and n=3 had incomplete self-reported physical activity and sedentary behavior data). A final sample of 103 children with overweight or obesity (10.02±1.15 years old; 42 girls) were included in this study (see **Figure S1**). Of these, only 99 participants presented valid data for the objectively measured physical activity and time in sedentary behavior and were therefore included in the analyses for these variables. Baseline data were collected from November 2014 to February 2016. Parents or legal guardians were informed of the purpose of the study and written informed parental consent was obtained. The ActiveBrains project was approved by the Human Research Ethics Committee of the University of Granada and was registered in ClinicalTrials.gov (identifier: NCT02295072).

Procedure

After being contacted, participants were invited to participate in the study at the Sport and Health Research Centre, University of Granada, Spain. Data on the age, weight, height, BMI, and PHV of participants were collected mostly during their first visit to the Research center. Self-report physical activity was always collected when participants brought back accelerometers. However, we had not MRI into consideration for scheduling physical activity data collections, although there was a maximum of 31 days between the MRI scan and the physical activity data collection. Lastly, IQ was always assessed at the same day of the MRI scan.

Objectively measured physical activity and time in sedentary behaviors

Objectively measured physical activity and time in sedentary behaviors were assessed with accelerometers (GT3X+, ActiGraph, Pensacola, FL, USA). Children simultaneously wore two accelerometers located on the right hip and non-dominant wrist during 7 consecutive days (24h/day), and they were instructed to remove them only for water-based activities (i.e., bathing or swimming). In brief, total minutes per day of total physical activity (including light physical activity, moderate-to-vigorous physical activity), light physical activity, moderate-to-vigorous physical activity and time in sedentary behaviors were calculated using the GGIR package in R (v. 1.5-18, https://cran.r-project.org/web/packages/GGIR/). physical activity and sedentary behavior were classified into different intensities following Hildebrand et al.'s hip- and wrist-based cut-off points for the ENMO metric [24,25], Chandler et al.'s wrist-based cut-off points for counts metric[26], and Romanzini et al. and Evenson et al.'s hip-based cut-off points for counts metric[27,28]. Further information about accelerometer data processing has been previously published[29].

Self-reported physical activity and sedentary behavior

Information on self-reported physical activity and sedentary behavior were obtained through the YAP-S questionnaire, a cross-translated and adapted version of the original YAP. The original YAP was developed by the Physical Activity and Health Promotion lab at Iowa State University (www.physicalactivitylab.org) and calibrated through a series of studies by Saint Maurice et al.[30–32]. The YAP questionnaire was translated into Spanish and back-translated in collaboration with the original authors of the YAP (available at: http://profith.ugr.es/yap?lang=en). The YAP-S was designed to be a self-administered 7-day recall questionnaire suitable for use in children.

Items of physical activity in the school setting included participation in physical activity during 5 specific periods of the day (i.e., transportation to school, activity during physical education, recess, lunch, and transportation from school). Items of physical activity out of the school setting included activity before school (6am-9am), activity immediately after school (2pm – 6pm), activity during the evening (6pm – 10pm) and activity during each weekend day (Saturday and Sunday). Composite z-scores for physical activity at school and out of school were computed by averaging the z-scores for their individual components. Then, a total physical activity z-score was calculated by adding the time of physical activity in the school and out of the school setting per week. In addition, participants were asked “how much time”, on average, they spent in four sedentary activities per day during the last week (i.e., watching TV, playing videogames, using the computer and using a cell phone). Each question was scored using a Likert scale that ranged from 1 to 5: (i) 0 min, (ii) less than 1 hour, (iii) between 1 and 2 hours, (iv) between 2 and 3 hours and (v) more than 3 hours. We excluded the items regarding computer and cell phone usage because 91% and 86% of sample, respectively, were categorized as 0 min or less than 1 hour usage. Lastly, children were asked about “how much time in a normal week”, they spent in total in sedentary behaviors. The participants rated their responses using a 5-point Likert type scale, from 1=“almost none of free time sitting” to 5=“almost all free time sitting”.

MRI procedure

Image acquisition

MRI data were acquired with a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). DTI data were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR = 3,300 ms, TE = 90 ms, flip angle = 90, matrix=128 x 128, FOV= 230 mm x 230 mm, slice thickness= 4 mm, number of slices = 25 and voxel resolution= 1.8 x 1.8 x 4 mm^3. One volume without diffusion weighting ($b=0s/mm^2$) and 30 volumes with diffusion weighting ($b=1000s/mm^2$) were collected.

Image preprocessing

Image preprocessing was conducted using the FSL [33]. Images were first adjusted for minor head motion using eddy, a new tool to correct for eddy current-induced distortions and participants´ movements. Outlier detection was also performed to identify slices where the signal was lost as a consequence of subject movement during the diffusion encoding. Next, a Gaussian process was used for outlier replacement (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/eddy). In order to account for rotations applied to the image data, the resulting transformation matrices were used to rotate the diffusion gradient direction table. Non-brain tissue was removed using the FSL Brain Extraction Tool. Then, the diffusion tensor was fit, and common scalar maps (i.e., FA, MD, AD, RD) were subsequently computed.

Probabilistic fiber tractography

Diffusion data were firstly processed using the BEDPOSTx, accounting for two fiber orientations at each voxel [34,35]. Next, for each participant, the FA map was aligned to the FMRIB-58 FA template image with the FSL nonlinear registration tool (FNIRT). The inverse of this nonlinear warp field was computed, and applied to a series of predefined seed, target, exclusion, and termination masks provided by the AutoPtx plugin [36].

Probabilistic fiber tracking was then performed with the FSL Probtrackx module using these supplied tract-specific masks (i.e., seed, target, etc.) that were warped to the native diffusion image space of each subject [34]. The resulting path distributions were normalized to a scale from 0 to 1 using the total number of successful seed-to-target attempts and were subsequently thresholded to remove low-probability voxels likely related to noise.

White matter tract segmentation was performed by thresholding the normalized tract density images based on previously established values (cingulate gyrus part of cingulum: 0.01, corticospinal tract: 0.005, forceps major: 0.005, forceps minor: 0.01, inferior longitudinal fasciculus: 0.005, superior longitudinal fasciculus: 0.001, uncinate fasciculus: 0.01; de Groot et al. (2015) [36]. Then, average FA and MD values were computed for each tract. Connectivity distributions were estimated for 7 large fiber bundles (i.e., cingulate gyrus part of cingulum, corticospinal tract, forceps minor, forceps major, inferior longitudinal fasciculus, superior longitudinal fasciculus, and uncinate fasciculus) selected based on previous reports [8,37]. Average of FA and MD in the left and right hemisphere was calculated in those tracts present in both hemispheres (i.e., corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and cingulate gyrus part of cingulum). To assess whether exposures were related to global measures of white matter integrity (i.e., global FA, MD, RD, AD), selected tracts [8] were combined into a single factor ("global factor"). The global factor was computed by averaging all tracts and weighting this average by the size (volume) of the tracts (to ensure small regions do not contribute equally as larger regions, which is common practice in the neuroimaging literature, in particular cortical morphology studies). This method was based on previous work [38–40].

Image quality assurance

Raw image quality was assessed via visual inspection [8]. The SSE maps from the tensor estimation were calculated and visually inspected for structured noise. Image quality was rated using a 4-point scale, with 1= "excellent", 2= "minor", 3= "moderate", and 4= "severe". Datasets determined to be of insufficient quality (i.e., moderate and severe) for statistical analyses were excluded (see **Figure S1**). Lastly, probabilistic tractography data were visually inspected. First, the native space FA map registration was inspected to ensure images were all properly aligned to the template (masks were properly mapped to native space). Second, all tracts were visualized to ensure accurate path reconstruction.

Covariates

Body weight and height were obtained with participants barefoot and wearing only underclothes. Weight (kg) was measured with an electronic scale (SECA 861, Hamburg, Germany), and height (cm) with a stadiometer (SECA 225, Hamburg, Germany). Both measurements were performed twice, and averages were used. BMI was expressed as kg/m^2. PHV is a common indicator of maturity in children and adolescents [41]. PHV was obtained from anthropometric variables (weight, height and/or seated height) using Moore's equations [42]. The total composite IQ was assessed by the Spanish version of the K-BIT [43], a reliable and valid measure of IQ. The KIDMED questionnaire was used to evaluate the adherence to the Mediterranean Diet [44]. Socioeconomic status was assessed by the educational level of mother and father reported (i.e., no elementary school, elementary school, middle school, high school and university completed). Parent answers were combined into a trichotomous variable (i.e., none of the parents had a university degree, one of the parents had a university degree and both parents had a university degree) [45].

Statistical analysis

The characteristics of the study sample are presented as means and standard deviations (SD). Of these, only sex was presented as percentage. To examine the associations of self-reported and objectively measured physical activity and sedentary behavior with DTI global scalar metrics, linear regression models adjusted for sex, PHV, BMI and IQ were performed. Objectively measured physical activity was additionally adjusted for daytime. Each regression model separately examined the relationships of one physical activity or sedentary behavior component with one DTI scalar metric.

Additionally, in order to determine whether the relationship with white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, associations with FA and MD within individual tracts were also tested if exposures showed an association with global DTI metrics. FDR (Benjamini-Hochberg method) was used to adjust for multiple comparisons [46]. Correction for multiple comparisons was based on 7 tracts, 2 DTI metrics and 6 physical activities and time in sedentary behavior domains for a total of 84 tests.

Additionally, a number of sensitivity analyses were run. First, in order to better describe the diffusion profile we tested the association of physical activity and sedentary behavior variables with global RD and global AD. Second, we divided the total sample in four subgroups according to their watching TV levels (i.e., not watching TV, less than 1 hour, between 2-3 hours and more than three hours) to compare global FA amongst the groups. Third, we additionally included into the models the adherence to the Mediterranean diet and the socioeconomic status as possible confounders in the relationship between physical activity, sedentary behavior and white matter microstructure.

Lastly, partial correlations adjusted for sex, PHV, BMI, and IQ between self-reported and objectively measured total physical activity and time in sedentary behavior variables in children with overweight or obesity were performed. All statistical analyses were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, p set at < 0.05).

RESULTS

Table 1 presents participant characteristics**.** The associations of self-reported physical activity and sedentary behavior variables with global FA and global MD metric are shown in **Table 2.** Self-reported total physical activity was positively associated with global FA (β=0.236, P=0.038). Watching TV (β=-0.270, P= 0.014), but not playing videogames (P=0.146), was inversely associated with global FA. Lastly, no association was found between self-reported sedentary behavior and physical activity variables and global MD metric (all P>0.071) (**Table 2**).

Table 1. Participants' characteristics (n=103).

	Mean or %	SD or nr.
Sex (%, nr.)		
Boys	59.2	61
Girls	40.8	42
Age (years)	10.02	1.15
Peak height velocity (years)	-1.92	1.03
Weight (kg)	56.04	11.30
Height (cm)	144.21	8.58
Body mass index (kg/m^2)	26.72	3.62
Intelligence (Test-KBIT)	48.00	25.07

Values are expressed as means± standard deviations, unless otherwise indicated. Test-KBIT= The Kaufman Brief Intelligence Test.

Table 2. Association of self-reported physical activity and sedentary behavior with global FA and MD (n=89)

	Global FA		Global MD	
	β	*P*	β	*P*
Total PA	**0.236**	**0.038**	-0.144	0.190
PA at school	0.179	0.109	***-0.192***	***0.071***
PA outside of school	0.183	0.103	-0.042	0.695
Time in sedentary behaviors	0.087	0.425	-0.148	0.154
Watching television	**-0.270**	**0.014**	0.134	0.210
Videogames	-0.179	0.146	-0.070	0.552

Single linear regression models were adjusted for sex, peak height velocity (PHV), body mass index (BMI) (kg/m^2), and intelligence quotient (IQ). P values were set at <0.05. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction and indicates a high level of tissue organization), MD= mean diffusivity (high MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). β values show standardized regression coefficients. Statistically significant values are shown in bold (P<0.05), and borderline significant values are shown in italics and bold (P<0.1). PA= Physical activity.

The association of objectively measured physical activity and time in sedentary behaviors using different cut-points, accelerometer locations and metrics (i.e., Hildebrand-ENMO wrist, Hildebrand-ENMO hip, Chandler-Counts wrist, Romanzini-Counts hip and Evenson-Counts hip) with global FA and global MD metric is shown in **Table S1**. Using single regression models, only when Hildebrand-ENMO hip cut -points were used for analyses, light physical activity (β=0.273, P=0.016), moderate-to-vigorous physical activity (β=0.257, P=0.035), and total physical activity (β=0.294, P=0.013) were positively associated with global FA (see **Figure 1**).

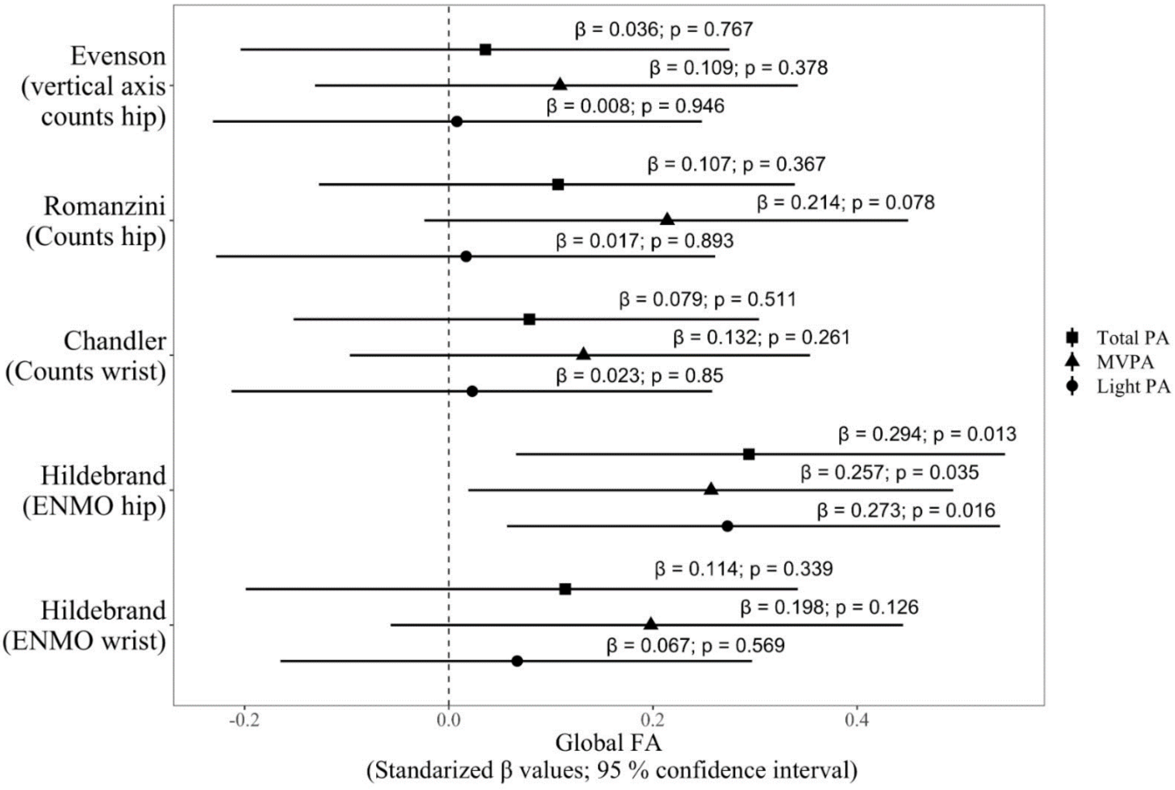

Figure 1. Association of objectively measured total physical activity, light physical activity, and moderate-to-vigorous physical activity with global FA using different cut of points, accelerometer location and metrics (n=85). PA= Physical activity. MVPA= Moderate-to-vigorous PA. Total PA= light PA+MVPA.

The association of self-reported and objectively measured physical activity and sedentary behavior with tract-specific FA and MD is shown in **Table 3**. Overall, no associations were found between self-reported and objectively measured physical activity and sedentary behavior variables and tract- specific FA and MD (all P>0.05).

The association of self-reported and objectively measured physical activity and sedentary behavior with global RD and global AD is shown in **Table S2**. Overall, objectively measured total physical activity was negatively associated with global RD (β=-0.236, P=0.044) and playing videogames was negatively associated with global AD (β=-0.254, P=0.028). In addition, when categorically subdividing the sample based on watching TV levels (i.e., not watching TV, less than 1 hour, between 2-3 hours and more than three hours), the subgroup watching TV more than 3 hours showed lower global FA compared to those who did not watch TV (mean difference=1.026, P=0.049) or watched TV less than 1 hour (mean difference=1.091, P=0.034) (**Figure S2**). Lastly, when we included the adherence to the Mediterranean diet and SES into the model, all results were virtually the same (data not shown).

Partial correlations adjusted for sex, PHV, BMI, and IQ between self-reported and objectively measured total physical activity and time in sedentary behavior variables in children with overweight or obesity are shown in **Table S3**. Briefly, the correlation between self-reported total physical activity and objectively measured total physical activity is lower but remains significant (all P<0.023). However, self-reported time in sedentary behavior and objectively measured time in sedentary behavior are not correlated to each other (all P>0.991).

Table 3. Self-reported physical activity and sedentary behavior with tract-specific FA and MD.

	Self-reported PA and sedentary behavior (n=103)				Objectively measured PA and time in sedentary behaviors (Hildebrand, ENMO hip, n=99)							
	Total PA		Watching television		Total PA		Light PA		Moderate-to-vigorous PA		Time in sedentary behaviors	
	FA	MD	FA	MD	FA	MD	FA	MD	FA	MD	FA	MD
Cingulate gyrus part of cingulum [a]	-0.069	-0.078	-0.029	0.044	0.149	-0.202	0.132	-0.183	0.133	-0.178	0.073	0.081
Corticospinal tract	0.031	-0.093	-0.153	0.103	-0.056	-0.007	-0.105	-0.003	0.018	-0.011	0.071	-0.003
Inferior longitudinal fasciculus	0.072	-0.086	-0.132	0.074	0.071	-0.118	0.035	-0.096	0.099	-0.118	0.113	-0.001
Superior longitudinal fasciculus	0.180	-0.046	-0.140	0.011	0.140	-0.018	0.075	0.046	0.189	-0.094	-0.015	0.037
Uncinate fasciculus	-0.130	-0.039	-0.001	0.115	0.042	-0.082	0.095	-0.080	-0.035	-0.065	0.014	-0.022
Forceps major	0.028	-0.039	-0.086	0.137	-0.017	0.017	-0.027	0.008	0.000	0.024	0.003	0.114
Forceps minor	0.050	-0.121	0.069	-0.018	-0.016	0.123	0.058	0.150	-0.105	0.062	-0.070	-0.164

Linear regression model was adjusted for sex, peak height velocity, body mass index (kg/m^2) and intelligence quotient. Objectively measured PA was additionally adjusted for daytime. β = standardized regression coefficients.Values are standardized regression coefficients (β). FA= fractional anisotropy, MD= mean diffusivity, PA= physical activity. Total PA= light PA+ Moderate-to-vigorous PA. [a]= in the cingulate gyrus part of cingulum n=89 (self-reported PA and watching television) and n=85 (objectively measured PA and time in sedentary behaviors). False discovery rate (FDR. Benjamini-Hochberg method) was used to adjust for multiple comparisons. Correction for multiple comparisons was based on 7 tracts, 2 DTI metrics and 6 physical activity and time in sedentary behavior domains for a total of 84 tests. * $P < 0.05$; ** $P > 0.01$.

DISCUSSION

The aim of the present study was to examine the associations of objectively measured and self-reported physical activity and sedentary behavior with white matter microstructure in children with overweight or obesity. Overall, self-reported total physical activity was positively associated with global FA. This association was confirmed by the objective measures of physical activity but only when Hildebrand-ENMO hip cut -point was used for analyses. Therefore, more studies are needed to corroborate these findings due to the controversy about the optimal and appropriate cut-points used to test the association of objectively measured physical activity and time in sedentary behaviors with white matter microstructure [24–28]. Additionally, watching TV was negatively associated with global FA. Lastly, no associations were found between self-reported and objectively measured physical activity and sedentary behavior variables and tract- specific FA and MD.

Total self-reported physical activity was associated with global FA but not with tract-specific FA. Therefore, it seems that the association between physical activity and FA might be more global than focal to specific tracts. Previous literature investigated the effect of structured physical activity and tract specific FA in children and adolescents, but the relationship with global FA remains less explored. For instance, an 8-month exercise intervention showed that, compared to controls, overweight children in the exercise group increased FA in sections of the uncinate fasciculus[16] and superior longitudinal fasciculus[17]. Moreover, another 9-month exercise intervention showed that, compared to controls, those children who participated in the exercise program showed increased FA in the genu of the corpus callosum[18]. These intervention studies contribute to the understanding of how increased levels of structured physical activity relate to white matter development in children. However, it is also important to understand the relationship between daily physical activity and white matter in the absence of an intervention. For instance, in adult populations, previous literature found that light physical activity was positively associated with FA in the temporal lobe [47]. In addition, Strömmer and colleagues [48] found that higher levels of unstructured physical activity were associated with FA in anterior white matter tracts, namely the genu of the corpus callosum, uncinate fasciculus, anterior limb of the internal capsule, and external capsule [48]. Collectively, it is difficult to draw conclusions from this limited literature, which largely focused on the effect of structured physical activity in white matter microstructure during childhood, omitting unstructured physical activity (e.g., outdoor play, active commuting, and sport participation) in children, which is the concept investigated in this study. In addition, future studies should examine whether physical activity (i.e., structured and unstructured physical activity) is associated with global DTI metrics.

To the best of our knowledge, this is the first study to investigate the relationship between physical activity and white matter microstructure using both self-reported and objective measurements of physical activity. Inconsistent associations were found between objectively measured physical activity variables (i.e., total physical activity, light physical activity, moderate-to-vigorous physical activity) and white matter microstructure in children with overweight or obesity. Therefore, although our findings suggest that self-reported physical activity is associated with white matter microstructure in children with overweight or obesity, these results should be cautiously interpreted, since these associations are limited by the measurement tools (i.e., self-reports vs. accelerometry), and the cut-points used (i.e., Hildebrand et al.'s hip- and wrist-based cut-off points for the ENMO metric [24,25], Chandler et al.'s wrist-based cut-off points for counts metric [26], and Romanzini et al. and Evenson et al.'s hip-based cut-off points for counts metric [27,28]). Similar discrepancies with respect to objectively measured and self-reported physical activity have been found with academic achievement variables in young people. For instance, Marques and colleagues [49] found inconsistencies in their systematic review between physical activity and academic achievement; particularly when physical activity was measured by accelerometry. There are numerous possibilities for this inconsistency. For instance, the lack of consensus among researchers with regard to the body attachment site (i.e., hip or wrist in the majority of studies) or acceleration metrics used [50]. In addition, it could be argued that accelerometers located in the wrist are more sensitive to activities which require movements in the upper-limbs while accelerometers located on the hip to activities which require a movement of the centre of mass, but there is not conclusive information published in this regard. Furthermore, the choice of cut-points to categorize sedentary behavior and physical activity intensity result in dramatic differences on physical activity quantification as has been tested with this sample elsewhere [29]. The different patterns of sedentary behavior and physical activity identified from hip and wrist and from the different cut-points could be related differently to white matter microstructure. Unfortunately, since we do not have a criterion measure, we cannot know which of these measures of physical activity is more accurate. In this context, our report of physical activity and time in sedentary behavior using different approaches for processing accelerometry data might provide more comprehensive conclusions and the possibility of enhancing the comparability of our results with potential future studies.

It was found that watching TV, but not self-reported and objectively measured total time in sedentary behaviors (any waking behavior characterized by an energy expenditure ≤1.5 METs, while sitting, reclining or lying) was negatively associated with global FA in children with overweight or obesity. Interestingly, there is limited evidence to conclude whether associations between sedentary behavior and brain outcomes are explained by the specific type of sedentary behavior (e.g., watching TV, playing videogames) versus time in sedentary behaviors. However, there are previous studies on this topic focusing on academic achievement and cognition. For instance, Esteban-Cornejo and colleagues [51] found that time spent in screen-based activities, but not objectively measured time in sedentary behaviors, may impair academic performance in youth. Furthermore, they found time spent in doing homework/study without computer and reading for fun were positively associated with academic achievement while low studying-high TV/video patterns were negatively associated with academic achievement. Therefore, it seems reasonable to speculate that non-screen-based sedentary behavior (i.e., reading a book, painting, studying) and recreational screen time (i.e., watching TV and playing videogame) might be differentially related to white matter microstructure in children with overweight or obesity. Future studies should examine the associations between different sedentary behaviors (e.g., reading a book vs. watching TV), and white matter microstructure in children and confirm or contrast our findings.

Although we found that physical activity and watching TV were associated with global FA, we did not observe associations with MD in children with overweight or obesity. Thus, other tissue differences may explain these associations. For instance, decreased levels of BDNF, a 14-kDa neurotrophin involved in the growth and healthy maintenance of neurons [52] might influence white matter microstructure. Physical activity is known to increase BDNF levels in the central nervous system [53], and consequently, may improve white matter microstructure. Another possible explanation is that exercise stimulates the growth of new capillaries, which are critical for the transport of nutrients to neurons [54]. On the other hand, mental health might be another potential psychosocial mechanism through which physical activity might be related to white matter microstructure in children. In this context, a recent study found that higher ratings for externalizing and internalizing symptoms predicted smaller increases in global FA over time [8]. A recent review of reviews showed that physical activity has a positive effect on mental health in children and adolescents [55], which, consequently, might improve white matter microstructure at these ages. Alternatively, the behavioral mechanism hypothesis proposes that changes in white matter resulting from physical activity and sedentary behavior are mediated by changes in relevant and associated behaviors. For instance, evidence indicates that specific sedentary activities, such as TV, are associated with poor dietary behaviors (e.g., unhealthy snacking/overconsumption of food and high-energy drinks), which might have a negative impact on white matter microstructure development during childhood[56]. Therefore, although the association between physical activity and sedentary behavior with white matter microstructure should be confirmed in future research, based on previous evidence from children and animal models, the positive associations between physical activity, sedentary behavior and white matter microstructure in children with overweight or obesity appear to be neurologically and biologically plausible.

Key strengths of the current study are the inclusion of neuroimaging data, and both objective (using different cut- points, accelerometer locations and metrics), and self-reported measurements to assess physical activity and sedentary behavior. Despite the named limitations, we consider the measurement of physical activity and sedentary behavior using accelerometers to be a strength of the present study. However, since we do not have a criterion measure, we cannot know which of these measures of physical activity is more accurate. In addition, self-reported measures remain a valuable tool for understanding how different types of sedentary behavior and physical activity settings are related to health outcomes such as white matter microstructure. In addition, several limitations require discussion. First, its cross-sectional design does not allow us to draw temporal associations. Second, we focused only on overweight and obese children, which limits the generalizability of our findings to the entire range of the BMI distribution. Third, voxel size was a 4-mm-section nonisotropic voxel (1.8 x 1.8 x 4 mm^3). Therefore, FA could be underestimated in regions containing crossing fibers (i.e., superior longitudinal fasciculus). On the other hand, the FA measured in regions without crossing fibers (i.e., corticospinal tract) is not prone to underestimation [57]. Four, previous studies have found that physical exercise has a positive effect on white matter microstructure in crucial (e.g., motor) circuits in children [18]. However, our tract-specific approach did not have tract-specific masks for all brain regions. For instance, we did not encompass the corpus callosum outsize of the forceps major and forceps minor fiber bundles. Then, future works using different approaches are needed to explore whether unstructured physical activity is also related to greater white matter microstructure in other brain regions [18]. Lastly, our study relied on watching TV and playing videogames as indicators of screen time. However, advances in technology (e.g., availability of hand-held media devices, and social media) compared to the construct of purely passive watching TV, further underscores the importance of maintaining well-characterized measures of screen time, as differing amounts/types or content of screen time could influence the brain differently.

CONCLUSION

Total physical activity was positively associated with global FA in children with overweight or obesity; however more studies are needed to corroborate these findings due to the controversy about the optimal and appropriate cut-points used to test the association of objectively measured physical activity and time in sedentary behaviors with white matter microstructure. Among the sedentary behaviors assessed, watching TV was negatively associated with global FA. Although longitudinal data are necessary to more concretely decipher the temporality of these associations, we suggest that physical activity and watching TV might be related to white matter microstructure in children with overweight or obesity. Lastly, mediation models are needed to identify the mechanisms (i.e. neurobiological, psychological and behavioral) responsible for any changes in white matter microstructure resulting from physical activity and sedentary behavior.

REFERENCES

1. Schmithorst VJ, Yuan W. White matter development during adolescence as shown by diffusion MRI. Brain and Cognition. 2010; 72: 16–25.

2. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006; 30:718–29.

3. Tanti A, Kim JJ, Wakid M, Davoli M-A, Turecki G, Mechawar N. Child abuse associates with an imbalance of oligodendrocyte-lineage cells in ventromedial prefrontal white matter. Mol Psychiatry. 2018;23:2018–28.

4. Jensen SKG, Pangelinan M, Björnholm L, Klasnja A, Leemans A, Drakesmith M, et al. Associations between prenatal, childhood, and adolescent stress and variations in white-matter properties in young men. Neuroimage. 2018;182:389–97.

5. Wassenaar TM, Yaffe K, van der Werf YD, Sexton CE. Associations between modifiable risk factors and white matter of the aging brain: insights from diffusion tensor imaging studies. Neurobiol Aging. 2019;80:56–70.

6. Augustijn MJCM, Di Biase MA, Zalesky A, Van Acker L, De Guchtenaere A, D'Hondt E, et al. Structural connectivity and weight loss in children with obesity: a study of the "connectobese." Int J Obes. 2019;1–13.

7. Ou X, Andres A, Pivik RT, Cleves MA, Badger TM. Brain gray and white matter differences in healthy normal weight and obese children. J Magn Reson Imaging. 2015;42:1205–13.

8. Muetzel RL, Blanken LME, van der Ende J, El Marroun H, Shaw P, Sudre G, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. Am J Psychiatry. 2017; 175: 54-62.

9. Giorgio A, Watkins KE, Chadwick M, James S, Winmill L, Douaud G, et al. Longitudinal changes in grey and white matter during adolescence. Neuroimage. 2010;49:94–103.

10. Tamnes CK, Roalf DR, Goddings A-L, Lebel C. Diffusion MRI of white matter microstructure development in childhood and adolescence: Methods, challenges and progress. Dev Cogn Neurosci. 2018;33:161–75.

11. Dennis EL, Thompson PM. Typical and atypical brain development: A review of neuroimaging studies. Dialogues Clin Neurosci. 2013 Sep;15:359–84.

12. Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380:219–29.

13. Physical Activity Guidelines for Americans. 2nd edition. 2018;Washington, DC: US Department of Health and Human Services. https://healt h.gov/pagui delin es/secon d-editi on/pdf/Physical_Activity_Guide lines 2nd_editi on.pdf. Accessed 15 Nov 2018.

14. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical

fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100:126–31.

15. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes. 2008;32:1–11.

16. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51:728–33.

17. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved Frontoparietal White Matter Integrity in Overweight Children Is Associated with Attendance at an After-School Exercise Program. Dev Neurosci. 2014;36:1–9.

18. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette E, Raine L, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci. 2018;12:950.

19. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014;8:584.

20. Herting MM, Colby JB, Sowell ER, Nagel BJ. White matter connectivity and aerobic fitness in male adolescents. Dev Cogn Neurosci. 2014;7:65–75.

21. Ferguson CJ. Do Angry Birds Make for Angry Children? A Meta-Analysis of Video Game Influences on Children’s and Adolescents’ Aggression, Mental Health, Prosocial Behavior, and Academic Performance. Perspect Psychol Sci. 2015;10:646–66.

22. Orben A, Przybylski AK. The association between adolescent well-being and digital technology use. Nat Hum Behav. 2019;3:173–82.

23. Cadenas-Sánchez C, Mora-González J, Migueles JH, Martín-Matillas M, Gómez-Vida J, Escolano-Margarit MV, et al. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): Rationale, design and methods. Contemp Clin Trials. 2016 Mar;47:315–24.

24. Hildebrand M, VAN Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc. 2014;46:1816–24.

25. Hildebrand M, Hansen BH, van Hees VT, Ekelund U. Evaluation of raw acceleration sedentary thresholds in children and adults. Scand J Med Sci Sports. 2017;27:1814–23.

26. Chandler JL, Brazendale K, Beets MW, Mealing BA. Classification of physical activity intensities using a wrist-worn accelerometer in 8-12-year-old children. Pediatr Obes. 2016;11:120–7.

27. Romanzini M, Petroski EL, Ohara D, Dourado AC, Reichert FF. Calibration of ActiGraph GT3X, Actical and RT3 accelerometers in adolescents. Eur J Sport Sci. 2014;14:91–9.

28. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci. 2008;26:1557–65.

29. Migueles JH, Cadenas-Sanchez C, Tudor-Locke C, Löf M, Esteban-Cornejo I, Molina-Garcia P, et al. Comparability of published cut-points for the assessment of physical activity: Implications for data harmonization. Scand J Med Sci Sport. 2019;29:566–74.

30. Saint-Maurice PF, Welk GJ, Beyler NK, Bartee RT, Heelan KA. Calibration of self-report tools for physical activity research: the Physical Activity Questionnaire (PAQ). BMC Public Health. 2014;14:461.

31. Saint-Maurice PF, Welk GJ. Validity and Calibration of the Youth Activity Profile. Watz H, editor. PLoS One. 2015;10:e0143949.

32. Saint-Maurice PF, Kim Y, Hibbing P, Oh AY, Perna FM, Welk GJ. Calibration and Validation of the Youth Activity Profile: The FLASHE Study. Am J Prev Med. 2017;52:880–7.

33. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. NeuroImage. 2012; 62: 782–90.

34. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage. 2007;34:144–55.

35. Behrens TEJ, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. Magn Reson Med. 2003;50:1077–88.

36. De Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, Van Der Lugt A, et al. Tract-specific white matter degeneration in aging: The Rotterdam Study. Alzheimer's Dement. 2015;11:321–30.

37. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp. 2005;26:139–47.

38. Rodriguez-Ayllon M, Derks IPM, van den Dries MA, Esteban-Cornejo I, Labrecque JA, Yang-Huang J, et al. Associations of physical activity and screen time with white matter microstructure in children from the general population. Neuroimage. 2019;205:116258.

39. Mulder TA, Kocevska D, Muetzel RL, Koopman-Verhoeff ME, Hillegers MH, White T, et al. Childhood sleep disturbances and white matter microstructure in preadolescence. J Child Psychol Psychiatry. 2019;60:1242–50.

40. Bolhuis K, Tiemeier H, Jansen PR, Muetzel RL, Neumann A, Hillegers MHJ, et al. Interaction of schizophrenia polygenic risk and cortisol level on pre-adolescent brain structure. Psychoneuroendocrinology. 2019;101:295–303.

41. Malina RM, Rogol AD, Cumming SP, Coelho E Silva MJ, Figueiredo AJ. Biological maturation of youth athletes: assessment and implications. Br J Sports Med.

2015;49:852–9.

42. Moore SA, McKay HA, Macdonald H, Nettlefold L, Baxter-Jones ADG, Cameron N, et al. Enhancing a somatic maturity prediction model. Med Sci Sports Exerc. 2015;47:1755–64.

43. Kaufman A, Kaufman N. Kaufman Brief Intelligence Test. Madrid: Tea; 2000.

44. Serra-Majem L, Ribas L, Ngo J, Ortega RM, García A, Pérez-Rodrigo C, et al. Food, youth and the Mediterranean diet in Spain. Development of KIDMED, Mediterranean Diet Quality Index in children and adolescents. Public Health Nutr. 2004 Oct;7:931–5.

45. Huppertz C, Bartels M, de Geus EJC, van Beijsterveldt CEM, Rose RJ, Kaprio J, et al. The effects of parental education on exercise behavior in childhood and youth: a study in Dutch and Finnish twins. Scand J Med Sci Sports. 2017;27:1143–56.

46. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. 1995; 57: 289-300.

47. Burzynska AZ, Chaddock-Heyman L, Voss MW, Wong CN, Gothe NP, Olson EA, et al. Physical Activity and Cardiorespiratory Fitness Are Beneficial for White Matter in Low-Fit Older Adults. Margulies D, editor. PLoS One. 2014;9:e107413.

48. Strömmer JM, Davis SW, Henson RN, et al. Physical Activity Predicts Population-Level Age-Related Differences in Frontal White Matter. bioRxiv, 2018; 311050.

49. Marques A, Santos DA, Hillman CH, Sardinha LB. How does academic achievement relate to cardiorespiratory fitness, self-reported physical activity and objectively reported physical activity: a systematic review in children and adolescents aged 6–18 years. Br J Sports Med. 2018;52:1039–1039.

50. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nyström C, Mora-Gonzalez J, Löf M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sport Med. 2017;47:1821–45.

51. Esteban-Cornejo I, Martinez-Gomez D, Sallis JF, Cabanas-Sánchez V, Fernández-Santos J, Castro-Piñero J, et al. Objectively measured and self-reported leisure-time sedentary behavior and academic performance in youth: The UP&DOWN Study. Prev Med (Baltim). 2015;77:106–11.

52. Leibrock J, Lottspeich F, Hohn A, Hofer M, Hengerer B, Masiakowski P, et al. Molecular cloning and expression of brain-derived neurotrophic factor. Nature. 1989; 341:149–52.

53. Cotman CW, Berchtold NC, Christie L-A. Exercise builds brain health: key roles of growth factor cascades and inflammation. Trends Neurosci. 2007; 30:464–72.

54. Kleim JA, Cooper NR, VandenBerg PM. Exercise induces angiogenesis but does not alter movement representations within rat motor cortex. Brain Res. 2002;934:1–6.

55. Biddle SJH, Ciaccioni S, Thomas G, Vergeer I. Physical activity and mental health in children and adolescents: An updated review of reviews and an analysis of causality.

Psychol Sport Exerc. 2018;1:1–10.

56. Keunen K, van Elburg RM, van Bel F, Benders MJNL. Impact of nutrition on brain development and its neuroprotective implications following preterm birth. Pediatr Res. 2015;77:148–55.

57. Oouchi H, Yamada K, Sakai K, Kizu O, Kubota T, Ito H, et al. Diffusion Anisotropy Measurement of Brain White Matter Is Affected by Voxel Size: Underestimation Occurs in Areas with Crossing Fibers. Am J Neuroradiol. 2007;28:1102–6.

Supplemental Material

Study V

STUDY VI

Physical fitness, white matter volume and academic performance in children: findings from the ActiveBrains and FITKids2 projects

Irene Esteban-Cornejo, Maria Rodriguez-Ayllon, Juan Verdejo-Roman, Cristina Cadenas-Sanchez, Jose Mora-Gonzalez, Laura Chaddock-Heyman, Lauren B. Raine, Chelsea M. Stillman, Arthur F. Kramer, Kirk I. Erickson, Andrés Catena, Francisco B Ortega, Charles H. Hillman.

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INTRODUCTION

The brain undergoes significant changes during childhood [1]. Further, aspects of cognition, including academic performance, continue to develop throughout the school-aged years. This period of neurodevelopment may be particularly sensitive to health-related factors that influence brain and behavior [2,3]. In particular, physical fitness is a powerful marker of health that has been associated with brain structure and function, as well as cognition in children [2,4–6]. The three main components of physical fitness are cardiorespiratory, motor and muscular fitness, each of them may have different influences on the brain. Cardiorespiratory fitness is the capacity to carry out prolonged strenuous exercise; motor fitness is a combination of speed, agility and coordination, and muscular fitness is the capacity to carry out work against a resistance [4]. Specifically, we have previously shown that cardiorespiratory fitness is associated with greater gray matter volume of the hippocampus and the basal ganglia in both normal–weight and children with overweight or obesity [7–9]. Additionally, cardiorespiratory fitness and motor fitness, but not muscular fitness, were associated with greater gray matter volume in distinct cortical regions (i.e., frontal, temporal and calcarine cortices) in children with overweight or obesity [9]. In turn, these brain-related associations were coupled with better executive function and academic performance [7–9]. However, less is known about how the different components of physical fitness (i.e., cardiorespiratory, motor and muscular) may influence white matter tissue, and in turn, academic performance during childhood.

White matter is primarily comprised of glial cells and myelinated neurons. White matter growth is the main source of increased brain volume during child development and continues well into the second decade of life for some brain regions. While cortical gray matter seems to develop in a nonlinear trend, with a preadolescent increase followed by a postadolescent decrease, white matter follows a linear trend and continues to mature during childhood and adolescence, increasing its volume and becoming more myelinated [1,10]. Damage to white matter yields slower processing speed [11], which may impair academic performance [12]. To date, only two previous studies in youth have examined the association between cardiorespiratory fitness and structure of white matter [13,14]. Specifically, cardiorespiratory fitness was positively related to the microstructure of white matter fiber tracts (i.e., corpus callosum, corona radiata and longitudinal fasciculus) in children [13]; whereas among adolescents, cardiorespiratory fitness was negatively related to white matter microstructure in the corticospinal tract [14]. As such, it is difficult to draw a conclusion from those studies due to their contradictory findings. In addition, other dimensions of fitness (i.e., muscular and motor fitness) may have differential effects on white matter, and in turn, academic performance, similar to previous reports in relation to gray matter [9]. Lastly, those studies were mainly focused on normal-weight populations; however, obesity has also been associated with alterations in white matter volume and integrity as compared to normal-weight individuals [15,16]. Indeed, the brain's volumetric structure of individuals with overweight and obesity is 10 years older compared to that of their lean peers, pointing to accelerated aging of white matter structure in overweight/obese [17]. For example, obese children have shown white matter reduction in the cerebellar peduncles and lower academic performance than their normal-weight peers [18,19]. Therefore, there is a clear need for studies that examine the different components of fitness and their associations with white matter volume in both normal-weight and overweight/obese populations, as well as their coupled influence on academic performance to better determine the relation of health factors on brain structure and cognition during child development.

We have a unique opportunity to test these hypotheses using baseline data from two independently, relatively large, trials conducted on children in Spain and the United States: the ActiveBrains project (Spain) which includes children with overweight or obesity and the FITKids2 project (United States) which includes both normal-weight and children with overweight or obesity. As such, our main aim was to examine the association between cardiorespiratory fitness and white matter volume in these two similarly designed, yet independent, studies to better determine the consistency of the relationship between this aspect of fitness and white matter. In addition, we examined whether the abovementioned associations differ between normal-weight and children with overweight or obesity using data from the FITKids2 project and we analyzed the association between other physical fitness components (i.e., motor and muscular) and white matter volume using data from the ActiveBrains project. To achieve these aims, we performed whole-brain exploratory analyses because, to date, there is no a substantial body of evidence on the associations between physical fitness components and white matter in children. Lastly, we examined whether the fitness-related associations in white matter volume were related to academic performance across these two independent studies.

METHODS

Participants

The ActiveBrains and FTIKids2 projects are RCTs designed to examine the effects of an exercise program on brain, cognition and academic performance in children aged 7-11 years. For the ActiveBrains project (http://profith.ugr.es/activebrains), a total of 110 children with overweight or obesity aged 8-11 years were recruited from schools in Granada, Spain [20]. Eligible children were required to: 1) be overweight or obese based on World Obesity Federation cut-off points 2) be 8 to 11 years-old, 3) not have any physical disabilities or neurological disorder that affects their physical performance, and 4) in the case of girls, not to have started the menstruation at the moment of the assessments. Baseline data were collected from November 2014 to February 2016. Parents or legal guardians were informed of the purpose of the study and written informed parental and child consents were obtained. The ActiveBrains project was approved by the Human Research Ethics Committee of the University of Granada, and was registered in ClinicalTrials.gov (identifier: NCT02295072).

For the FITKids2 project, a total of 252 children aged 7-9 years were recruited from schools in East-Central Illinois, USA. Eligible children were required to 1) report an absence of school related learning disabilities (i.e., individual education plan related learning), adverse health conditions, physical incapacities, or neurological disorders, 2) qualify as prepubescent (Tanner pubertal timing score ≤ 2), 3) report no use of medications that influence central nervous system function, and 4) demonstrate right handedness as measured by the Edinburgh Handedness Questionnaire. Data were collected from June 2010 to October 2017. Children signed an informed assent and parents or legal guardians provided written informed consent in accordance with the Institutional Review Board of the University of Illinois at Urbana-Champaign, and was registered in ClinicalTrials.gov (identifier: NCT01619826).

For the present study, we selected children from the ActiveBrains and FITKids2 projects with complete baseline data on physical fitness, academic performance and brain outcomes (i.e., white matter volume). A total of 100 children with overweight or obesity from the ActiveBrains project (10.0±1.1 years; 40% girls) met all the criteria. A total of 142 children from the FITKids2 project (8.6±0.5 years; 54% girls; 36% overweight/obese) met all the criteria; FITKids2 children included in the present study did not differ from those not included across measures of height, weight, PHV, BMI, parental education, cardiorespiratory fitness, total white matter and academic performance data (all p>0.05). The present study includes a total of 242 children.

Physical fitness

In the ActiveBrains project, physical fitness was assessed following the ALPHA health-related fitness test battery for youth, a feasible, reliable and valid battery for this age group [21–23]. All tests were performed in a single session. The three main physical fitness components were assessed: cardiorespiratory, motor and muscular fitness.

Cardiorespiratory fitness was assessed by the 20-m shuttle-run test. The test was performed once and always at the end of the fitness testing session. Participants were required to run between two lines 20-m apart, while keeping pace with a pre-recorded audio CD. The initial speed was 8.5 km/h, which was increased by 0.5 km/h each minute (1 min = 1 stage). Participants were instructed to run in a straight line, to pivot on completing a shuttle (20-m), and to pace themselves in accordance with the audio signals. The test was finished when the participant failed to reach the end lines concurrently with the audio signals on two consecutive occasions. The last stage completed was recorded and transformed to maximal oxygen consumption (VO_2max, mL/kg/min) using the Léger equation [24].

Motor fitness was assessed with the 4 × 10-m shuttle-run test of speed-of-movement, agility and coordination. The test was performed twice and the fastest time was recorded in seconds [25]. Participants were required to run back and forth twice between two lines 10-m apart. Children were instructed to run as fast as possible and every time they crossed any of the lines, they were instructed to pick up (the first time) or exchange (second and third time) a sponge that had earlier been placed behind the lines. Since a longer time indicates poorer performance (i.e., the person is slower and less agile and coordinated), the variable expressed in seconds was inverted by multiplying by −1, so that a higher score indicates better performance.

Muscular fitness was assessed using maximum handgrip strength and the standing long jump tests [26]. A hand dynamometer with an adjustable grip was used (TKK 5101 Grip D, Takey, Tokyo Japan) for the handgrip strength test. The participant squeezed the dynamometer continuously for at least 2-s, alternatively with right and left hand, with the elbow in full extension [27]. The test was performed twice and the maximum score for each hand was recorded in kilograms (kg). The average score of the left and right hands was calculated in kg as an absolute measurement of upper body muscular fitness [27,28]. Standing long jump test was performed from a starting position behind a line, standing with feet approximately shoulder width apart [29]. Children jumped as far forward as possible, landing with feet together. The test was performed three times. The longest distance was recorded in centimeters, and subsequently multiplied by body weight in order to obtain an absolute measurement of lower body muscular fitness. A single muscular fitness score was computed from the two muscular tests. The individual score of each test was standardized as follows: Z-standardized value = (value – the sample mean)/ SD. The muscular fitness score was calculated as the mean of the two standardized scores.

In the FITKids2 project, only cardiorespiratory fitness was assessed. It was determined by measuring VO_{2max} using a computerized indirect calorimetry system (Parvo Medics True Max 2400, Sandy, UT) during a modified Balke Protocol. Children walked and/or ran on a treadmill at a constant speed with increasing grade increments of 2.5% every 2 min until volitional exhaustion occurred [30]. Average for oxygen consumption and respiratory exchange ratio assessed every 20 s. A polar heart rate monitor (Polar WearLink+ 31; Polar Electro, Finland) was used to measure heart rate throughout the test, and ratings of perceived exertion were assessed every 2 min using the children's OMNI [31]. VO_{2max} was expressed in mL/kg/min and based upon maximal effort as evidenced by (i) a plateau in oxygen consumption corresponding to an increase of less than 2 mL/kg/min despite an increase in workload; (ii) a peak heart rate ≥ 185 beats per minute [30] and heart rate plateau [32]; (iii) RER ≥ 1.0 [33]; and/or (iv) a score on the children's OMNI ratings of perceived exertion scale ≥ 8 [31].

MRI procedure

Data acquisition

Data were collected using a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil in the ActiveBrains project and a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 12-channel head coil in the FITKids2 project. Three-dimensional, high-resolution, T1-weighted images were acquired using a magnetization-prepared rapid gradient-echo sequence. In the ActiveBrains project, the parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.1 ms, inversion time (TI) = 900 ms, flip angle = 9º, Field of view (FOV) = 256 x 256, acquisition matrix = 320 x 320, 208 slices, resolution = 0.8 x 0.8 x 0.8 mm, and scan duration of 6 min and 34 s. In the FITKids2 project, the parameters were as follows: TR = 1900 ms, TE = 2.32 ms, TI = 900 ms, flip angle = 9º, FOV= 230 x 230 acquisition matrix= 256 x 256, 192 slices, resolution = 0.9 x 0.9 x 0.9 mm, and scan duration of 4 min and 26 s.

Structural image processing

Structural imaging data were pre-processed using SPM software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (The MathWorks, Inc, Natick, MA). Before tissue classification we checked each individual image for acquisition artifacts and alignment along the horizontal anterior commissure and posterior commissure plane.

Detailed information about the pre-processing steps is available elsewhere and is outlined briefly in this section [9]. First, T1-weighted structural images of each participant were segmented into gray matter tissue, white matter tissue, and cerebrospinal fluid using the segmentation algorithm implemented in SPM12 [34]. Second, we used segmented gray matter/white matter tissues for all participants to create a customized template using DARTEL algebra [35]. DARTEL estimates a best set of smooth deformations from every participant’s tissue to their common average and reiterates the process until convergence. The resultant images were spatially normalized to Montreal Neurological Institute space with affine transformation to create the DARTEL template. We create a DARTEL template for the ActiveBrains project and a DARTEL template for the FITKids2 project. Subsequently, we normalized each participant’s segmented images in each study to each specific DARTEL template via nonlinear transformation. To perform a volume change correction, the normalized images were modulated with Jacobian determinants derived from the spatial normalization [36]. Finally, the volumetric images were smoothed by convolving them with an isotropic Gaussian kernel of 8 mm full-width at half-maximum.

Academic performance

In the ActiveBrains project, academic performance was assessed via the Spanish version of the Woodcock-Johnson III (i.e., Bateria III Woodcock-Muñoz, pruebas de aprovechamiento). This battery is a well validated measure of academic performance from individuals aged 5 to 95 years [37]. We applied 12 tests: 11 from the standard battery (i.e. 3 tests of reading, 3 tests of mathematics, 2 tests of oral language and 3 tests of written language) and one from the extended battery (i.e. a test based on science, social science and humanities). All the tests were individually administered by a trained evaluator in one session of 100-120 min. The data collected for each participant was independently checked by two trained evaluators. In the FITKids2 project, participants completed the KTEA2 to assess academic performance. Subtests of the KTEA2 were administered to assess their achievements in the content areas of mathematics, reading, and writing. The KTEA2 was individually administrated by a trained evaluator in one session of 60-80 minutes. The main dependent measures in both projects were the standard scores of 6 academic indicators: mathematics, mathematics calculation skills, reading, writing, written expression and total achievement. Science was also included as an additional academic indicator in the ActiveBrians project.

Covariates

TBV

TBV was calculated by adding the volumes of gray and white matters derived from non-normalized segmented images.

BMI

Body weight and height were performed with participants having bare feet and wearing underclothes; weight was measured with an electronic scale (ActiveBrains: SECA 861, Hamburg, Germany; FITKids2: Tanita WB-300 Plus digital scale,Tokyo, Japan) and height (cm) with a stadiometer (ActiveBrains: SECA 225, Hamburg, Germany; FITKids2: SECA 240, Hamburg, Germany). Both measurements were performed twice in the ActiveBrains project and three times in the FITIKids2 project in the same session, and averages were used. BMI was expressed as kg/m^2 and children were categorized as normal-weight, overweight and obesity according to Cole et al [38].

Biological maturation

PHV is a common indicator of maturity in children and adolescents and it used as a maturational landmark due to its relevance in previous studies [39]. In both projects, PHV was obtained from anthropometric variables (weight, height and/or seated height) using Moore's equations through validated sex-specific algorithms for children [40]. Years from PHV were calculated by subtracting the age of PHV from the chronological age. The difference in years was defined as a value of maturity offset.

Parental education level

In both projects, socioeconomic status was assessed by the educational level of the mother and father reported as none, elementary school, middle school, high school and university completed. Parent responses were combined as: none of the parents with university studies, one of them had university studies and both had university studies [41].

Statistical analysis

All the analyses were performed separately for the ActiveBrains project and the FITKids2 project. In the ActiveBrains project, the analyses were performed for the whole overweight/obese sample together; in the FITKids2 project, the analyses were performed separately for normal-weight and children with overweight or obesity. Descriptive statistics are presented as means (SD) or percentages using IBM SPSS Statistics (version 18.0 for Windows; P set at < 0.05).

Statistical analyses of imaging data were performed using the GLM approach implemented in SPM12. The individual association between each component of physical fitness (i.e., cardiorespiratory, motor and muscular in the ActiveBrains project and cardiorespiratory in the FITKids2 project) and white matter volume was analyzed using whole-brain voxel-wise multiple regression models, adjusted for sex, PHV offset, parent education, BMI and TBV. Additionally, we extracted the eigenvalues from the peak coordinates of each significant cluster. The associations of the extracted mean white matter volumes as predictor variables and academic performance indicators as outcomes, adjusted for sex, PHV offset, parental education and BMI were examined by linear regressions in SPSS. We corrected for assessing multiple white matter-academic performance regressions by defining statistical significance as a Benjamini-Hochberg False Discovery Rate q less than 0.05 [42].

The statistical threshold in the imaging analyses was calculated with AlphaSim, as implemented in Resting-State fMRI Data Analysis Toolkit toolbox (RESTplus) [43]. Parameters were defined as follows: cluster connection radius (rmm) = 5 mm and the actual smoothness of the data after model estimation, incorporating a white mask volume of 302567 voxels. The voxel-level alpha significance (threshold, $p<0.001$ uncorrected) along with the appropriate cluster size for controlling for multiple comparisons in each analysis were indicated in the results. The resulting cluster extents were further adjusted to account for the non-isotropic smoothness of structural images, in accordance with Hayasaka et al. [44].

RESULTS

Background characteristics

Table 1 shows the characteristics of the study sample from the ActiveBrains and the FITKids2 projects. The percentage of both parents having completed university studies was 16% in the ActiveBrains Project, 34% in overweight/obese FITKids2 children, and 48% in normal-weight FITKids2 children. In the ActiveBrains project, all participants were overweight/obese (26% overweight children from the total overweight/obese sample). In the FITKids2 project, 64% were normal-weight, 17% were overweight and 19% were obese. BMI was higher in overweigh/obese children from the ActiveBrains project (26.7±3.7 kg/m^2) relative to their overweight/obese peers from the FITKids2 project (22.5±3.4 kg/m^2). Cardiorespiratory fitness levels were higher for the normal-weight FITKids2 children (45.4 ±6.7 mL/kg/min) than for the overweight/obese FITKids2 children (37.7 ±5.6 mL/kg/min) and the ActiveBrains children (40.8 ±2.8 mL/kg/min).

Table 1. Characteristics of samples from the ActiveBrains and FITKids2 projects.

	ActiveBrains (n=100)	*FITKids2 (n=142)*	
	Overweight/obese	*Normal-weight*	*Overweight/obese*
n	100	91	51
Physical characteristics			
Girls (%)	40	54	55
Age (years)	10.0±1.1	8.6±0.6	8.7±0.5
Peak height velocity offset (years)	-2.3±1.0	-3.3±0.6	-3.0±0.7
Weight (kg)	55.8±11.0	28.7±4.0	43.8±8.8
Height (cm)	143.9±8.3	133.0±5.8	139.0±7.1
Body mass index (kg/m^2)	26.7±3.7	16.2±1.4	22.5±3.4
Overweight (%)	26	-	47
Parental education university level (%)			
Neither parent	66	26	33
One parent	18	26	33
Both parents	16	48	34
Physical fitness components			
Cardiorespiratory fitness (mL/kg/min)[*]	40.8 ±2.8	45.4 ±6.7	37.7 ±5.6
Motor fitness (s) [†]	15.1 ±1.6	-	-
Muscular fitness (z-score) [‡]	0.0 ±0.9	-	-
Total brain volume (cm^3)	1200.3±106.7	1199.3 ±107.4	1217.9 ±105.5
Academic performance[**]			
Mathematics	101.7 ±10.6	109.8 ±16.5	105.3 ±13.6
Math calculation skills	103.4 ±12.0	107.4 ±16.1	102.6 ±13.2
Reading	108.2 ±13.0	112.8 ±14.6	107.6 ±15.3
Writing	113.6 ±12.7	105.6 ±15.5	105.0 ±15.6
Written expression	103.4 ±8.7	102.2 ±17.6	102.3 ±17.5
Science	96.6 ±11.5	-	-
Total achievement	109.1 ±11.8	110.4 ±14.7	106.4 ±14.9

Values are mean ±SD or percentages. [*]Measured by the 20-m shuttle run test in the ActiveBrains project and by the treadmill test in the FITKids2 project. [†] Measured by the 4x10-m shuttle run test; values were multiplied by -1 before analyses so that higher values indicate better performance. [‡]z-score computed from handgrip strength (kg) and standing long jump (cm*kg) tests. [**] Assessed by the Spanish version of the Woodcock-Johnson III in the ActiveBrains project and by the Kaufman Test of Educational Abilities in the FITKids2 project.

White matter correlates of individual physical fitness components

Table 2 and **Figure 1** present the brain regions showing positive associations between each of the components of physical fitness and white matter volume in children, after adjustment for potential confounders.

In the ActiveBrains project, cardiorespiratory fitness (**figure A.1**) was associated with greater white matter volume (P< 0.001, *k*=177) in two regions, inferior fronto-opercular gyrus and inferior temporal gyrus; motor fitness (**figure B**) was related to greater white matter volume (P< 0.001, *k*=173) in six regions, specifically, insular cortex, caudate, bilateral superior temporal gyrus and bilateral supramarginal gyrus; muscular fitness (**figure C**) was associated with greater white matter volumes (P< 0.001, *k*=191) in two regions, particularly, the bilateral caudate and bilateral cerebellum IX. In the FITKids2 project, among children with overweight or obesity, cardiorespiratory fitness (**figure A.2**) was associated with greater white matter volumes (P< 0.001, *k*=117) in four regions, namely inferior temporal gyrus, cingulate gyrus, middle occipital gyrus and fusiform gyrus; whereas, no brain regions showed a statistically significant positive association between cardiorespiratory fitness and white matter volume among normal-weight children from the FITKids2 project. In both projects, no brain regions showed a statistically significant negative association between any physical fitness component and white matter volume.

Table 2. Brain regions showing separate positive associations of the components of physical fitness with white matter volume in children from the ActiveBrains and FITKids2 projects

	ActiveBrains (n=100)					FITKids2 (n=142)				
Brain Regions (mm^3)	X	Y	Z	Peak t	Cluster size	X	Y	Z	Peak t	Cluster size
Normal-weight (n=91)	n=0					n=91				
	No available data					Non-significant regions				
Overweight/obese(n=151)	n=100					n=51				
Cardiorespiratory fitness (mL/kg/min)[*]										
Inferior temporal gyrus	-53	-12	-33	4.1	312	-53	-6	-32	4.6	357
Inferior fronto-opercular gyrus	-44	17	23	4.2	552	-	-	-	-	-
Cingulate gyrus	-	-	-	-	-	12	9	44	4	138
Middle Occipital Gyrus	-	-	-	-	-	39	-66	2	4.4	342
Fusiform Gyrus	-	-	-	-	-	-26	-92	-9	4.5	951
Motor fitness (s^{-1})[†]										
Insular cortex	-30.0	32.0	8.0	3.7	1459	No available motor fitness data				
Caudate	33.0	30.0	12.0	3.9	1327					
Superior temporal gyrus	39.0	-32.0	5.0	3.9	1407					
Superior temporal gyrus	-56.0	-21.0	3.0	4.1	510					
Supramarginal gyrus	47.0	-38.0	29.0	5	768					
Supramarginal gyrus	-50.0	-41.0	26.0	3.6	216					
Muscular fitness (z-score)[‡]										
Caudate	24	26	11	4.4	13261	No available muscular fitness data				
Caudate	-12	11	-15	4.7	17512					
Cerebellum IX	14	-50	-42	3.9	755					
Cerebellum IX	-11	-51	-42	4.2	486					

Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/ both), body mass index (kg/m^2) and total brain volume (cm^3). Each physical fitness component was introduced in separate models. All contrasts were thresholded using AlphaSim at $P < 0.001$with k=177 voxels for cardiorespiratory fitness in the ActiveBrains project and k=117 voxels in the FITKids2 project, k=173 for speed-agility and k= 191 for muscular fitness, and surpassed Hayasaka correction. Anatomical coordinates (X,Y,Z) are given in Montreal Neurological Institute (MNI) Atlas space. [*]Estimated by the Leger equation in the ActiveBrains project and directly measured by the treadmill test in the FITKids2 study. [†]The original score of the motor fitness test expressed in seconds was multiplied by -1 to invert the variable, so that a higher score indicate higher fitness performance. [‡] z-score computed from handgrip strength and standing long jump tests.

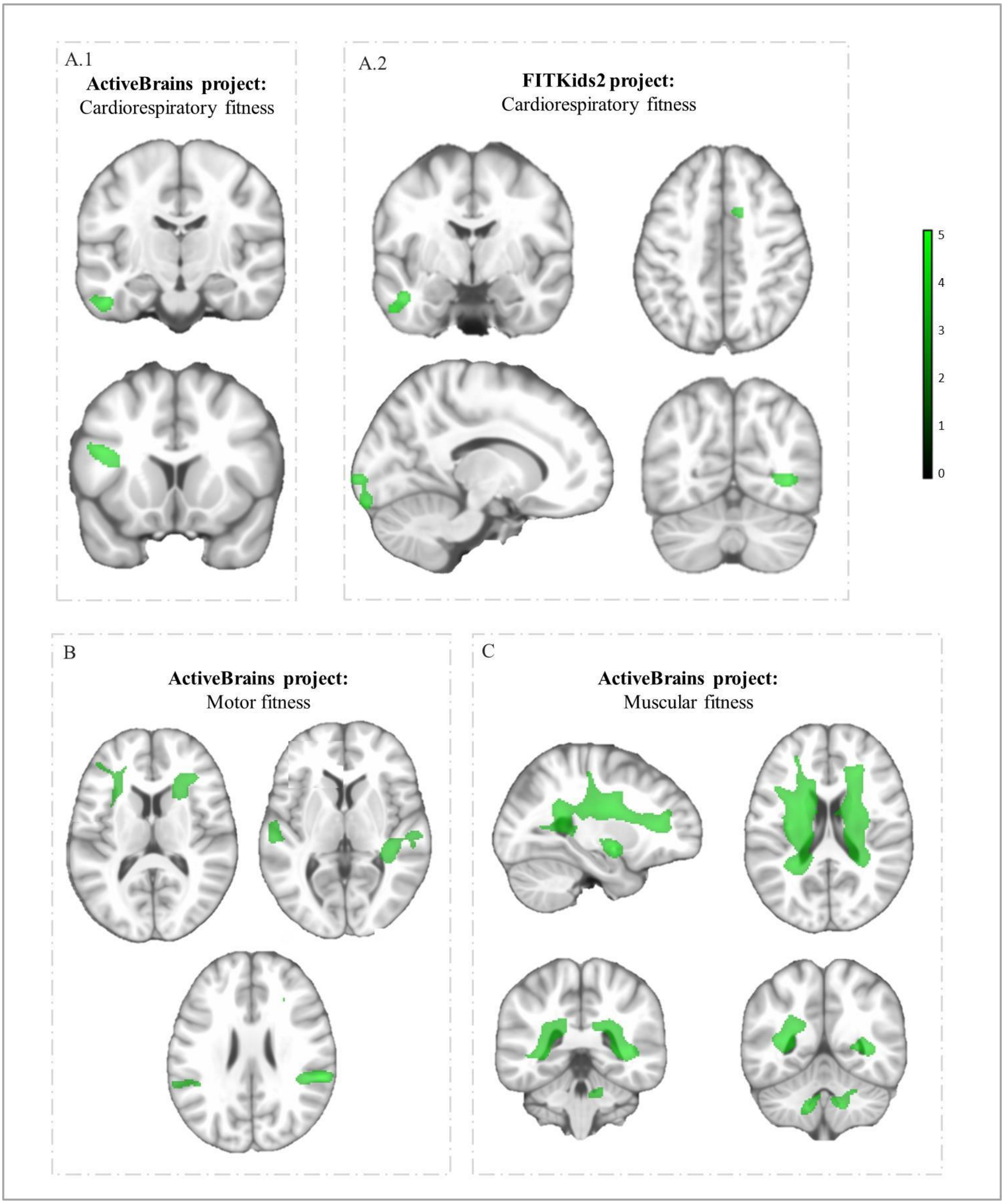

Figure 1. Brain regions showing positive separate associations of (A) cardiorespiratory fitness, (B) motor fitness and (C) muscular fitness with white matter volume in children from the ActiveBrains (A.1, B,C) and FITKids2 (A.2) projects. Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/ both), body mass index (kg/m^2) and total brain volume (cm^3). Each physical fitness component was introduced in separate models. Maps were thresholded using AlphaSim at $P < 0.001$ with k=177 voxels for cardiorespiratory fitness in the ActiveBrains project and k=117 voxels in the FITKids2 project, k=173 for motor fitness, and k= 191 for muscular fitness, and surpassed Hayasaka correction (see table 2). The color bar represents T-values, with lighter green color indicating higher significant association. Images are displayed in neurological convention, whereby the right hemisphere corresponds to the right side in coronal displays. Sagittal planes show the left hemisphere.

Association between white matter and academic performance.

Table 3 displays the associations between fitness-related associations in white matter volume and academic performance, after controlling for potential confounders.

In the ActiveBrains project, among the brain regions previously associated with cardiorespiratory fitness, both regions were related or demonstrated a trend with an academic indicator; inferior temporal gyrus was related to written expression (β=0.210; P=0.030) and inferior fronto-opercular gyrus was marginally related to math calculation skills (β=0.163; P=0.079). Regarding the brain regions previously associated with motor fitness, insular cortex was related to mathematics and math calculations skills (β=0.199 and β=0.258, respectively; both P<0.05); superior temporal gyrus and supramarginal gyrus were related to science (β=0.194 and β=0.208, respectively; both P<0.05), and supramarginal gyrus was also marginally related to mathematics, math calculation skills, reading and total achievement (β ranging from 0.154 to 0.174; all P<0.1). Regarding the brain regions previously associated with muscular fitness, caudate was related to math calculation skills and science (β=0.189 and β=0.228, respectively; both P<0.05), and marginally related to writing and total achievement (β=0.164 and β=0.151, respectively; both P≤0.01); cerebellum IX was related to science (β=0.199; P=0.040). However, after correcting for multiple comparisons, only the insular cortex remained significantly related to math calculations skills (β=0.258; P<0.005). In the FITKids2 project, none of the brain regions previously associated with cardiorespiratory fitness were related to academic performance.

Table 3. Fitness-related associations in white matter volume and academic performance† in children with overweight or obesity from the ActiveBrains and FITKids2 projects.

Fitness-related component	***Brain Regions (mm^3)***	Mathematics		Math calculation skills		Reading		Writing		Written expression		Science		Total achievement	
		β	P	β	P	β	P	β	P	β	P	β	P	β	P
ActiveBrains															
Cardiorespiratory fitness (mL/kg/min)															
	Inferior temporal gyrus	0.034	0.718	-0.006	0.950	-0.095	0.320	0.071	0.465	**0.207**	**0.030**	0.144	0.140	-0.010	0.913
	Inferior fronto-opercular gyrus	0.114	0.217	*0.163*	*0.079*	-0.014	0.886	0.030	0.756	0.036	0.710	0.091	0.350	0.035	0.705
Motor fitness (s^{-1})															
	Insular cortex	**0.199**	**0.031**	**0.258**	**0.005***[*]	0.063	0.511	0.116	0.233	0.057	0.553	0.150	0.122	0.132	0.155
	Caudate	0.054	0.561	0.093	0.317	0.034	0.720	0.030	0.755	0.100	0.917	0.108	0.264	0.041	0.657
	Superior temporal gyrus	0.132	0.155	0.156	0.093	0.113	0.237	0.080	0.412	0.035	0.719	**0.194**	**0.044**	0.139	0.133
	Supramarginal gyrus	*0.155*	*0.094*	*0.154*	*0.098*	*0.174*	*0.065*	0.083	0.393	0.074	0.443	**0.208**	**0.031**	*0.166*	*0.071*
Muscular fitness (z-score)															
	Caudate	0.134	0.147	**0.189**	**0.040**	0.107	0.260	*0.164*	*0.087*	0.090	0.346	**0.228**	**0.017**	*0.151*	*0.100*
	Cerebellum IX	0.112	0.230	0.118	0.208	0.142	0.136	0.020	0.838	0.117	0.225	**0.199**	**0.040**	0.115	0.215
FITKids2															
Cardiorespiratory fitness (mL/kg/min)															
	Inferior temporal gyrus	0.114	0.485	-0.041	0.802	0.092	0.556	-0.043	0.780	-0.016	0.916	-	-	0.117	0.455
	Cingulate gyrus	-0.025	0.889	-0.113	0.521	0.003	0.986	-0.056	0.741	-0.069	0.677	-	-	0.031	0.857
	Middle Occipital Gyrus	0.153	0.365	0.061	0.715	0.070	0.664	0.041	0.799	0.016	0.919	-	-	0.112	0.490
	Fusiform Gyrus	0.192	0.237	0.136	0.398	0.094	0.545	-0.132	0.392	-0.142	0.348	-	-	0.086	0.585

Values are standardized regression coefficients (β).Analyses were adjusted by sex, peak height velocity offset (years), parent education university level (neither/one/ both) and body mass index (kg/m^2). †Academic performance was assessed by the Spanish version of the Woodcock-Johnson III in the ActiveBrains project and by the Kaufman Test of Educational Abilities in the FITKids2 project. Statistically significant values are shown in bold ($P<0.05$), and borderline significant values are shown in italics ($P<0.1$); [*]This was the only association that remained significant when P values were adjusted for multiple comparisons using the Benjamini and Hochberg method to control for the false discovery rate

DISCUSSION

The main finding of the present study is that cardiorespiratory fitness was positively related to white matter volume in children with overweight or obesity across two independent studies. In addition, other physical fitness components (i.e., motor and muscular) were also associated with white matter volume. Specifically, cardiorespiratory and motor fitness were related to white matter volume located in association fiber tracts, and muscular fitness was related to white matter regions located in thalamic radiations and projection fiber tracts. Moreover, some of these fitness-related associations in white matter volume were coupled with better academic performance. These results suggest that physical fitness might have the potential to enhance brain development and academic performance during childhood.

There are several possible explanations for the present findings. First, given that physical fitness has been previously related to gray matter in cortical and subcortical regions in children [7–9], it is reasonable that white matter structure connecting gray matter areas might also benefit from physical fitness. Indeed, white matter might be a neural mechanism via which physical fitness enhances integration of regions into networks and facilitates efficient transmission of information to support executive function and academic performance [45]. Second, mouse models show that exercise, a major determinant of physical fitness, increases the number of oligodentrocytes, which are the cells responsible for myelinating axons in white matter tissue [46]. Lastly, other biological mechanisms triggered by exercise, such as increased neurotrophic factors and vascularization, have been shown to influence white matter in rodents [47]. Therefore, based on previous evidence from children and animal models, the positive associations between physical fitness and white matter found in children with overweight or obesity are neurologically and biologically plausible.

The major finding of the present report suggests that cardiorespiratory fitness may influence white matter volume in children with overweight or obesity across two independent, relatively large studies conducted in Spain and the United States. To note, although we focused on white matter volume, we superimposed the findings in a white matter tracts atlas for easier comparing and discussing present study with previous studies. Specifically, white matter brain regions that overlap between the ActiveBrains and FITKids project were located in the superior longitudinal fasciculus. Indeed, in the ActiveBrains project, all the white matter brain regions influenced by cardiorespiratory fitness were only located in the superior longitudinal fasciculus, whereas the white matter regions found in the FITKids2 project were located in the superior longitudinal fasciculus and the inferior longitudinal fasciculus. Both superior and inferior longitudinal fasciculi are long association fiber tracts that connect more distant cortical areas within the same cerebral hemisphere, converging in the parietal lobe, and may be involved in common pathways [48]. The superior longitudinal fasciculus links the frontal and parietal lobes, and may be engaged in attention, inhibition and articulatory aspects of language [48,49]. The inferior longitudinal fasciculus links the parieto-occipital and temporal lobes, and has been shown to be engaged in object recognition, discrimination and memory [48]. Therefore, although only one brain region located in the superior longitudinal fasciculus overlapped between the ActiveBrains and FITKids2 projects, possibly due to methodological differences between studies (e.g., measurement of cardiorespiratory fitness, differences among the MRI scanners or the MRI sequence acquisition parameters, participant demographics, etc.), the fact that this finding was observed across the two different studies conducted on children strengthens conclusions regarding the specificity of the relations between cardiorespiratory fitness and white matter.

The analysis of the different components of physical fitness, assessed in the ActiveBrains project, allows us to further speculate on the relevance of each fitness component for white matter structure. Our data suggest that not only cardiorespiratory fitness, but also other components, such as motor and muscular fitness, were related to white matter volume among children with overweight or obesity. This effect in children supports and extends the associations between cardiorespiratory fitness and white matter in the older adults [50]. Among youth, there are only two studies examining the association between cardiorespiratory fitness and white matter structure in normal-weight youth and these studies exhibited contradictory findings [13,14]. Herting et al., revealed that cardiorespiratory fitness was negatively related to white matter microstructure in the corticospinal tract in male adolescents aged 15 to 18 years [14]. In contrast, Chaddock et al. found that cardiorespiratory fitness was positively related to the microstructure of white matter fiber tracts (i.e., body of the corpus callosum, superior corona radiata and superior longitudinal fasciculus) in 9-10 year old children [13]. The present findings comparing data from the ActiveBrains and FITKids2 project partially concur with the previous report from Chaddock et al., since we found that the white matter brain regions predicted by cardiorespiratory fitness were mainly located in the superior longitudinal fasciculus and the inferior longitudinal fasciculus in children with overweight or obesity of the same approximate ages. However differences in white matter assessment (i.e., white matter volume vs. white matter microstructure) and in cardiorespiratory fitness levels (i.e., lower fit children vs. higher and lower fit children) among the present and the previous study should be acknowledged. Therefore, our findings shed light on the implications of cardiorespiratory fitness for brain health during childhood.

Specifically, the abovementioned cardiorespiratory fitness-white matter associations were only found in children with overweight or obesity, but not in their normal-weight peers. The reasons explaining why cardiorespiratory fitness might improve white matter volume only in children with overweight or obesity cannot be elucidated from the current datasets; yet two mechanisms might be speculated upon. First, moving an excessive amount of body mass is related to various musculoskeletal complaints associated with movement restrictions and motor difficulties during childhood [51], which may have harmful implications for the musculoskeletal system, affecting skeletal neuromuscular function and the brain [15]. For example, obese children have shown lower motor competence and white matter reduction in the cerebellar peduncles than their normal-weight peers [18]. Experimental studies using mice exposed to prolonged movement restrictions has also shown negative effects on neurogenesis and the role of trophic determinants (i.e., nerve growth factor mRNA and BDNF) involved in this phenomenon [52,53]. Consequently, children with overweight or obesity may benefit more from increased cardiorespiratory fitness. Second, in children with overweight or obesity, not only is there an excess of body mass, but there is also an excess in a particular type of mass (i.e., fat mass vs. lean mass) which may have implications for maturation. That is, children with overweight or obesity demonstrate higher levels of fat mass than their normal-weight counterparts [54], which may confer additional white matter reductions [15]. For example, when comparing correlations between total white matter volume and fat mass among normal-weight and children with overweight or obesity from the FITKids2 project, we found that fat mass was not associated with white matter in normal-weight children, but it was negatively associated with white matter in children with overweight or obesity. Therefore, the positive contributions of cardiorespiratory fitness to white matter might be more apparent in individuals with white matter reductions, such as children with overweight or obesity.

There is no previous evidence linking the other two physical fitness components, motor and muscular fitness, with white matter structure in youth, which hampers comparisons to other studies. The novel findings observed herein indicated that motor fitness was related to greater white matter volume in brain regions located in association fiber tracts (i.e., inferior fronto-occipital fasciculus and superior longitudinal fasciculus), and specifically, with larger white matter regions in the inferior fronto-occipital fasciculus. The inferior fronto-occipital fasciculus is the major white matter tract linking the ventrolateral and medial orbitofrontal cortices to the posterior parietal and occipital cortices. As such, greater white matter volume in brain regions located in this fasciculus could contribute to better prefrontal functioning, and in turn academic performance [55]. Additionally, we found that muscular fitness was associated with greater white matter volume in brain regions mainly located in thalamic radiations (i.e., anterior thalamic radiation) and projection fiber tracts (i.e., middle cerebellar peduncle) in children with overweight or obesity. The anterior thalamic radiation is involved in reciprocal communication of limbic regions with prefrontal and anterior cingulate cortex, and the peduncle connects the cerebellum and other parts of the brain [56]. Whereas these two tracts have been previously shown to be involved in higher-order motor tasks and influence cognitive inhibition [49,57], we provide new support that muscular training aimed at improving upper- and lower-body muscular strength may influence white matter regions located in those motor tracts, and ultimately, academic performance during childhood. However, more research is warranted to understand how different components of physical fitness may effect white matter structures in both normal-weight and children with overweight or obesity.

Another interesting finding from the present study revealed that the white matter volume of regions related to fitness may influence academic performance. White matter helps enhance efficiency of neural transmission throughout the brain, and is thought to contribute to enhanced processing speed and executive function resulting in improvements of academic performance [45]. In particular, a previous study in children aged 7 to 9 years suggested that microstructure in left white matter tracts (i.e., superior corona radiata and inferior longitudinal fasciculus) were related to better mathematical skills [12]. In addition, Li et al. showed that the inferior fronto-occipital fasciculus was related to better arithmetic scores [57]. Consonant with those findings, we found that after correcting for multiple comparisons, motor fitness-related changes in white matter volume located in the left inferior fronto-occipital fasciculus was the only region related to better academic performance (i.e., math calculation skills) among children with overweight or obesity. As such, this finding must be interpreted with caution. Taken together, these findings raise the possibility that a reduction of physical activity opportunities across the school day might confer white matter reduction coupled with academic failure in children.

Some limitations need to be considered. First, the cross-sectional design does not allow us to draw causal inferences, therefore these findings should be taken with caution; it is also possible that children with higher academic performance, had greater white matter volume and then performed better on physical fitness tests. Moving forward, it is important to replicate these preliminary findings using randomized controlled intervention studies. Second, since we approached the study with voxel-based morphometry, future studies should employ DTI to examine white matter microstructure using a whole brain approach. Third, while both studies used a 3.0 Tesla Siemens Magnetom Tim Trio system, the head coils differed between studies, with a

32-channel head coil in the ActiveBrains study and a 12-channel head coil in the FITKids2 project. Previous studies have indeed shown signal-to-noise ratio improvements in the cortex for 32-channel head coils compared to 12-channel coils; these differences across coils are reversed for subcortical regions [58]. However, the fact that we observed a similar pattern of results across studies with different scan parameters could be seen as a strength as it speaks to the robustness of the observed effects. Because these and other methodological differences between the ActiveBrains and FITKids2 studies exist (e.g., assessment of cardiorespiratory fitness, the MRI sequence acquisition parameters, participant demographics, etc.), data from both projects were analyzed separately instead of pooling the datasets. While this approach limits the power of our findings, it offers replication across and the opportunity to qualitatively compare across studies. Lastly, some confounding variables that may influence the findings (e.g., diet, sleep, or self-discipline) were not available in both projects. Strengths of the present report include the use of data from two independent relatively large studies which speaks to the robustness of the observed findings, the complete and standardized assessment of the three physical fitness components, the whole-brain analysis, and the entire range of the BMI distribution among participants.

CONCLUSION

In conclusion, our findings across two independent studies suggest that cardiorespiratory fitness may positively relate to white matter volume in children with overweight or obesity, and in turn, academic performance. In addition, other physical fitness components (i.e., motor and muscular) may also influence white matter volume coupled with better academic performance. Specifically, cardiorespiratory and motor fitness were related to white matter volume in brain regions located in association fiber tracts and muscular fitness was related to white matter regions located in thalamic radiations and projection fiber tracts. From a public health perspective, implementing exercise interventions that combine aerobic, motor and muscular training to enhance physical fitness may benefit brain development and academic success.

REFERENCES

1. Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, et al. Brain development during childhood and adolescence: a longitudinal MRI study. Nature neuroscience. 1999; Oct;2:861-3.

2. Donnelly JE, Hillman CH, Castelli D, Etnier JL, Lee S, Tomporowski P, et al. Physical Activity, Fitness, Cognitive Function, and Academic Achievement in Children: A Systematic Review. Medicine and science in sports and exercise. 2016; Jun;48:1197-222.

3. Andersen SL. Trajectories of brain development: point of vulnerability or window of opportunity? Neuroscience and biobehavioral reviews. 2003 Jan-Mar;27:3-18.

4. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. International journal of obesity. 2008 ;32:1-11.

5. Esteban-Cornejo I, Tejero-Gonzalez CM, Martinez-Gomez D, del-Campo J, Gonzalez-Galo A, Padilla-Moledo C, et al. Independent and combined influence of the components of physical fitness on academic performance in youth. The Journal of pediatrics. 2014; 165:306-12 e2.

6. Voss MW, Chaddock L, Kim JS, Vanpatter M, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater efficiency of the network underlying cognitive control in preadolescent children. Neuroscience. 2011;199:166-76.

7. Chaddock L, Erickson KI, Prakash RS, Kim JS, Voss MW, Vanpatter M, et al. A neuroimaging investigation of the association between aerobic fitness, hippocampal volume, and memory performance in preadolescent children. Brain research. 2010;1358:172-83.

8. Chaddock L, Erickson KI, Prakash RS, VanPatter M, Voss MW, Pontifex MB, et al. Basal ganglia volume is associated with aerobic fitness in preadolescent children. Developmental neuroscience. 2010;32:249-56.

9. Esteban-Cornejo I, Cadenas-Sanchez C, Contreras-Rodriguez O, Verdejo-Roman J, Mora-Gonzalez J, Migueles JH, et al. A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. NeuroImage. 2017;159:346-54.

10. Paus T, Collins DL, Evans AC, Leonard G, Pike B, Zijdenbos A. Maturation of white matter in the human brain: a review of magnetic resonance studies. Brain research bulletin. 2001;54:255-66.

11. Kail R. Speed of information processing in patients with multiple sclerosis. Journal of clinical and experimental neuropsychology. 1998;20:98-106.

12. van Eimeren L, Niogi SN, McCandliss BD, Holloway ID, Ansari D. White matter microstructures underlying mathematical abilities in children. Neuroreport. 2008;19:1117-21.

13. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Frontiers in human neuroscience. 2014;8:584.

14. Herting MM, Colby JB, Sowell ER, Nagel BJ. White matter connectivity and aerobic fitness in male adolescents. Dev Cogn Neurosci. 2014;7:65-75.

15. Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. Obesity reviews : an official journal of the International Association for the Study of Obesity. 2015;16:273-81.

16. van Bloemendaal L, Ijzerman RG, Ten Kulve JS, Barkhof F, Diamant M, Veltman DJ, et al. Alterations in white matter volume and integrity in obesity and type 2 diabetes. Metabolic brain disease. 2016;31:621-9.

17. Ronan L, Alexander-Bloch AF, Wagstyl K, Farooqi S, Brayne C, Tyler LK, et al. Obesity associated with increased brain age from midlife. Neurobiology of aging. 2016;47:63-70.

18. Augustijn M, Deconinck FJA, D'Hondt E, Van Acker L, De Guchtenaere A, Lenoir M, et al. Reduced motor competence in children with obesity is associated with structural differences in the cerebellar peduncles. Brain Imaging Behav. 2017; 12: 1000-1010

19. Raine L, Drollette E, Kao SC, Westfall D, Chaddock-Heyman L, Kramer AF, et al. The Associations between Adiposity, Cognitive Function, and Achievement in Children. Medicine and science in sports and exercise. 2018;50:1868-74.

20. Cadenas-Sanchez C, Mora-Gonzalez J, Migueles JH, Martin-Matillas M, Gomez-Vida J, Escolano-Margarit MV, et al. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): Rationale, design and methods. Contemporary clinical trials. 2016; 47:315-24.

21. Ruiz JR, Castro-Pinero J, Espana-Romero V, Artero EG, Ortega FB, Cuenca MM, et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. British journal of sports medicine. 2011;45:518-24.

22. Castro-Pinero J, Artero EG, Espana-Romero V, Ortega FB, Sjostrom M, Suni J, et al. Criterion-related validity of field-based fitness tests in youth: a systematic review. British journal of sports medicine. 2010;44:934-43.

23. Ortega FB, Artero EG, Ruiz JR, Vicente-Rodriguez G, Bergman P, Hagstromer M, et al. Reliability of health-related physical fitness tests in European adolescents. The HELENA Study. International journal of obesity. 2008;32:S49-57.

24. Leger LA, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. Journal of sports sciences. 1988;6:93-101.

25. Vicente-Rodriguez G, Rey-Lopez JP, Ruiz JR, Jimenez-Pavon D, Bergman P, Ciarapica D, et al. Interrater reliability and time measurement validity of speed-agility field tests in

adolescents. Journal of strength and conditioning research / National Strength & Conditioning Association. 2011;25:2059-63.

26. Artero EG, Espana-Romero V, Castro-Pinero J, Ruiz J, Jimenez-Pavon D, Aparicio V, et al. Criterion-related validity of field-based muscular fitness tests in youth. The Journal of sports medicine and physical fitness. 2012;52:263-72.

27. Espana-Romero V, Ortega FB, Vicente-Rodriguez G, Artero EG, Rey JP, Ruiz JR. Elbow position affects handgrip strength in adolescents: validity and reliability of Jamar, DynEx, and TKK dynamometers. Journal of strength and conditioning research / National Strength & Conditioning Association. 2010;24:272-7.

28. Espana-Romero V, Artero EG, Santaliestra-Pasias AM, Gutierrez A, Castillo MJ, Ruiz JR. Hand span influences optimal grip span in boys and girls aged 6 to 12 years. The Journal of hand surgery. 2008;33:378-84.

29. Castro-Pinero J, Ortega FB, Artero EG, Girela-Rejon MJ, Mora J, Sjostrom M, et al. Assessing muscular strength in youth: usefulness of standing long jump as a general index of muscular fitness. Journal of strength and conditioning research / National Strength & Conditioning Association. 2010;24:1810-7.

30. Medicine ACoS. ACSM’s Guidelines for Exercise Testingand Prescription. 9th ed Wolters Kluwer/Lippincott Williams & Wilkins,Philadelphia, PA. 2014.

31. Utter AC, Robertson RJ, Nieman DC, Kang J. Children's OMNI Scale of Perceived Exertion: walking/running evaluation. Medicine and science in sports and exercise. 2002;34:139-44.

32. Freedson PS, Goodman, T.L.,. Measurement of oxygen consumption. Measurement of oxygen consumption In: Rowland TW, editor Pediatric Laboratory Exercise Testing: Clinical Guidelines Champaign (IL): Human Kinetics. 1993:91-113.

33. O B-O. Pediatric Sports Medicine for the Practitioner: From Physiologic Principles to Clinical Applications. Katz M,Stiehm ER, editors New York: Springer-Verlag. 1983.

34. Ashburner J, Friston KJ. Unified segmentation. NeuroImage. 2005;26:839-51.

35. Ashburner J. A fast diffeomorphic image registration algorithm. NeuroImage. 2007;38:95-113.

36. Ashburner J, Friston KJ. Voxel-based morphometry--the methods. NeuroImage. 2000;11:805-21.

37. McGrew K, Woodcock R. Woodcock-Johnson III: Technical Manual. Itasca, IL: Riverside Publishing Company; 2001.

38. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatric obesity. 2012;7:284-94.

39. Malina RM, Rogol AD, Cumming SP, Coelho e Silva MJ, Figueiredo AJ. Biological maturation of youth athletes: assessment and implications. British journal of sports medicine. 2015;49:852-9.

40. Moore SA, McKay HA, Macdonald H, Nettlefold L, Baxter-Jones AD, Cameron N, et al. Enhancing a Somatic Maturity Prediction Model. Medicine and science in sports and exercise. 2015;47:1755-64.

41. Huppertz C, Bartels M, de Geus EJ, van Beijsterveldt CE, Rose RJ, Kaprio J, et al. The effects of parental education on exercise behavior in childhood and youth: a study in Dutch and Finnish twins. Scandinavian journal of medicine & science in sports. 2017; 27, 1143-1156

42. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. Journal of the Royal Statistical Society Series B (Methodological). 1995;57:289-300.

43. Song XW, Dong ZY, Long XY, Li SF, Zuo XN, Zhu CZ, et al. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PloS one. 2011;6:e25031.

44. Hayasaka S, Phan KL, Liberzon I, Worsley KJ, Nichols TE. Nonstationary cluster-size inference with random field and permutation methods. NeuroImage. 2004;22:676-87.

45. Mabbott DJ, Noseworthy M, Bouffet E, Laughlin S, Rockel C. White matter growth as a mechanism of cognitive development in children. NeuroImage. 2006;33:936-46.

46. Krityakiarana W, Espinosa-Jeffrey A, Ghiani CA, Zhao PM, Topaldjikian N, Gomez-Pinilla F, et al. Voluntary exercise increases oligodendrogenesis in spinal cord. The International journal of neuroscience. 2010;120:280-90.

47. Ding YH, Li J, Zhou Y, Rafols JA, Clark JC, Ding Y. Cerebral angiogenesis and expression of angiogenic factors in aging rats after exercise. Current neurovascular research. 2006;3:15-23.

48. Schmahmann JD, Smith EE, Eichler FS, Filley CM. Cerebral white matter: neuroanatomy, clinical neurology, and neurobehavioral correlates. Annals of the New York Academy of Sciences. 2008;1142:266-309.

49. Chaddock-Heyman L, Erickson KI, Voss MW, Powers JP, Knecht AM, Pontifex MB, et al. White matter microstructure is associated with cognitive control in children. Biological psychology. 2013;94:109-15.

50. Sexton CE, Betts JF, Demnitz N, Dawes H, Ebmeier KP, Johansen-Berg H. A systematic review of MRI studies examining the relationship between physical fitness and activity and the white matter of the ageing brain. NeuroImage. 2016; 1;131:81-90.

51. Paulis WD, Silva S, Koes BW, Van Middelkoop M. Overweight and obesity are associated with musculoskeletal complaints as early as childhood: A systematic review. Obesity Reviews. 2014; 15, 52-67

52. Desaphy JF, Pierno S, Liantonio A, De Luca A, Didonna MP, Frigeri A, et al. Recovery of the soleus muscle after short- and long-term disuse induced by hindlimb unloading: effects on the electrical properties and myosin heavy chain profile. Neurobiology of disease. 2005;18:356-65.

53. Adami R, Pagano J, Colombo M, Platonova N, Recchia D, Chiaramonte R, et al. Reduction of Movement in Neurological Diseases: Effects on Neural Stem Cells Characteristics. Frontiers in neuroscience. 2018;12:336.

54. Herda TJ, Ryan ED, Kohlmeier M, Trevino MA, Gerstner GR, Roelofs EJ. Examination of muscle morphology and neuromuscular function in normal weight and overfat children aged 7 to 10 years. Scandinavian journal of medicine & science in sports. 2018; 28: 2310-2321.

55. Wu Y, Sun D, Wang Y, Wang Y. Subcomponents and Connectivity of the Inferior Fronto-Occipital Fasciculus Revealed by Diffusion Spectrum Imaging Fiber Tracking. Frontiers in neuroanatomy. 2016;10:88.

56. Mori S WS, Nagae-Poetscher LM, van Zijl PCM MRI Atlas of human white matter. Amsterdam: Elsevier BV. 2005.

57. Glickstein M, Doron K. Cerebellum: connections and functions. Cerebellum. 2008;7:589-94.

58. Li Y, Hu Y, Wang Y, Weng J, Chen F. Individual structural differences in left inferior parietal area are associated with schoolchildrens' arithmetic scores. Frontiers in human neuroscience. 2013;7:844.

59. Kaza E, Klose U, Lotze M. Comparison of a 32-channel with a 12-channel head coil: are there relevant improvements for functional imaging? Journal of magnetic resonance imaging : JMRI. 2011;34:173-83.

Study VII

Physical fitness and white matter microstructure in children with overweight or obesity: The ActiveBrains project.

M. Rodriguez-Ayllon, I. Esteban-Cornejo, J. Verdejo-Román, RL Muetzel, J. Mora-Gonzalez, C. Cadenas-Sanchez, A. Plaza-Florido, P. Molina-García, A. F. Kramer, A. Catena, F. B. Ortega

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INTRODUCTION

Physical fitness is a powerful marker of health in children and adolescents [1]. Previous evidence suggests that different components of physical fitness (i.e., cardiorespiratory, muscular and motor fitness) have a positive effect on physical and mental health in children and adolescents, both immediately [1,2] and later in life [3,4]. However, recent research have also shed light on the positive role of physical fitness on brain structure and function [5]. For instance, a recent ACSM Position Stands[5] based on physical fitness and brain suggested that physical fitness may have a positive influence on brain structure and function during childhood. However, few studies have explored the extent to which physical fitness is associated with brain structure, including white matter microstructure in children.

Childhood is a critical period for neurodevelopment [6]. Particularly, the neurobiological mechanisms associated with white matter development in childhood and adolescence include further axon myelination via thickening of the myelin sheaths, axonal growth, and increasing calibre of fibre tracts [7]. DTI is able to sample features of the microstructural architecture of white matter. FA and MD are two commonly derived scalar metrics from DTI. FA expresses the degree to which water diffuses preferentially along one axis, and has shown to increase with age [8] during development and to be lower in the context of various neurological and psychiatric diseases [9]. MD is a scalar describing the average diffusion in all directions, with higher levels indicating relatively unimpeded diffusion (i.e., negatively correlated with FA). Of note, although previous literature suggests that obesity is associated with alterations in white matter microstructure [10–12], studies have primarily focused on normal-weight populations.

To date, only two studies focused on the relationship between cardiorespiratory fitness and white matter microstructure in young people [13,14]. Chaddock et al. [14] found that higher levels of cardiorespiratory fitness were associated with greater FA in sections of the corpus callosum, corona radiata, and superior longitudinal fasciculus in children. On the other hand, Herting et al. [13] found that greater cardiorespiratory fitness was related to lower FA in the corticospinal tract in adolescents. Apart from cardiorespiratory fitness (i.e., the capacity to carry out prolonged strenuous exercise), there are two other physical fitness components (i.e., muscular fitness, motor fitness) that have been proven to differentially influence physical and brain health [1,15]. However, previous studies addressing the relationship between physical fitness and white matter microstructure only focused on cardiorespiratory fitness and did not examine muscular fitness (i.e., the capacity to carry out work against a resistance) or motor fitness (i.e., a combination of speed, agility and coordination). Furthermore, taking into account the previously observed negative influence of childhood obesity on brain health and the lack of studies in children with overweight or obesity, there is a clear need for studies that examine the different components of physical fitness and their associations with white matter microstructure, particularly in younger populations.

Therefore, the aim of the present study was to examine the associations of components of physical fitness (i.e., cardiorespiratory, muscular, and motor fitness) with white matter microstructure in children with overweight or obesity. We hypothesized that greater physical fitness would relate to higher FA and lower MD. However, on the basis of the previous literature [13,14], it was uncertain as to the potential strength or anatomical location of these relationships.

METHODS

Study design and participants

This cross-sectional study is part of the ActiveBrains project (http://profith.ugr.es/activebrains), a RCT, with the primary aim of examining the effects of exercise on brain, cognition and academic performance in children with overweight or obesity according to sex and age specific World Obesity Federation cut-off points [16,17]. The complete methodology of the project has been described elsewhere [18]. In total, 110 children with overweight or obesity, ages 8-to-11 years were recruited from Granada (southern Spain). Of these, 104 (10.04±1.15 years old; 43 girls) were included in the present analyses. Data were collected from November 2014 to February 2016. Parents or legal guardians were informed of the goal of the study and written informed parental consents were obtained. This study was conducted according to the Declaration of Helsinki, approved by the Human Research Ethics Committee of the University of Granada, and registered in ClinicalTrials.gov (identifier: NCT02295072).

Physical fitness components and MRI procedure

Physical fitness components

Physical fitness components (i.e., cardiorespiratory fitness, muscular fitness, and motor fitness) were assessed using the ALPHA health-related physical fitness test battery [19]. This battery has been shown to be valid, reliable, feasible, and safe for the assessment of the physical fitness components in children and adolescents [19].

Cardiorespiratory fitness was estimated by the 20-meter shuttle-run test [20]. This test was always performed at the end of the fitness battery testing session. The total number of completed laps were registered. Upper- and lower-body muscular fitness were assessed using the handgrip strength test and the standing long jump test, respectively. A digital hand dynamometer with an adjustable grip (TKK 5101 Grip D, Takei, Tokyo, Japan) was used to assess upper-body muscular fitness. Each child performed the test twice, and the maximum scores of left and right hands were averaged and used as a measurement of absolute upper-body muscular fitness in kilograms (kg). Relative upper-body muscular fitness was expressed per kg of body weight. The standing long jump test was performed three times and the longest jump was recorded in centimeters (cm) as a measurement of relative lower-body muscular fitness. The distance in cm was multiplied by the weight in order to obtain an absolute measurement of lower-body muscular fitness. Motor fitness was assessed using the 4×10-meter shuttle-run test. Participants were required to run back and forth twice between two lines 10-m apart. Children were instructed to run as fast as possible and every time they crossed any of the lines, they were instructed to pick up (the first time) or exchange (second and third time) a sponge that had earlier been placed behind the lines. The test was performed twice and the fastest time was recorded in seconds. Since a longer completion time indicates a lower fitness level, for analysis purposes we inverted this variable by multiplying test completion time (sec) by −1. Thus, higher scores indicated higher motor fitness levels.

Image acquisition

MRI data were collected with a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). DTI data were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR = 3,300 ms, TE = 90 ms, flip angle = 90, matrix=128 x 128, FOV= 230 mm x 230 mm, slice thickness= 4 mm, number of slices = 25 and voxel resolution= 1.8 x 1.8 x 4 mm^3. One volume without diffusion weighting (b=0s/mm^2) and 30 volumes with diffusion weighting (b=1000s/mm^2) were collected.

Image preprocessing

FSL (https://fsl.fmrib.ox.ac.uk) was used to processed MRI data [21,22]. First, images were adjusted for minor head motion [23], which included a Gaussian process for outlier replacement [24]. Then, the resulting transformation matrices were used to rotate the diffusion gradient direction table [25,26]. Non-brain tissue was removed using the FSL Brain Extraction Tool [27]. Lastly, the diffusion tensor was fit, and common scalar maps were subsequently computed.

Probabilistic fiber tractography

Fully automated probabilistic fiber tractography was performed using the FSL plugin, “AutoPtx”. Diffusion data were processed using the BEDPOSTx, accounting for two fiber orientations at each voxel [28,29]. Then, for each subject, the FA map was aligned to the FMRIB-58 FA template image with the FSL nonlinear registration tool (FNIRT). Next, the inverse of this nonlinear warp field was computed, and applied to a series of predefined seed, target, exclusion, and termination masks provided by the AutoPtx plugin [30]. Probabilistic fiber tracking was then execute with the FSL Probtrackx module using these supplied tract-specific masks (i.e., seed, target, etc.) that were warped to the native diffusion image space of each subject [28]. Lastly, the resulting path distributions were normalized to a scale from 0 to 1 using the total number of successful seed-to-target attempts and were subsequently thresholded to remove low-probability voxels likely related to noise.

Once the tracts were thresholded [30], average FA and MD values were then computed for each fiber bundle. Connectivity distributions were estimated for 7 large fiber bundles (i.e., corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, cingulate gyrus part of cingulum, forceps minor and forceps major) selected based on previous reports [31–33]. Average of FA and MD in the left and right hemisphere was calculated in those tracts present in both hemispheres (i.e., corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and cingulate gyrus part of cingulum).

To assess whether physical fitness components (i.e., cardiorespiratory fitness, muscular fitness, and motor fitness) were related to global measures of white matter integrity (i.e., global FA, MD), selected tracts were combined into a single factor (“global factor”). The global factor was computed by averaging all tracts and weighting this average by the size (volume) of the tracts.

TBSS

TBSS was used to perform voxel-wise statistical analyses of the DTI data [34]. A mean FA image was calculated and thinned to create a mean FA skeleton, which represents the center of white matter tracts. A threshold of FA > 0.2 was selected to exclude voxels not belonging to white matter. FA maps of each participant were then projected onto the skeleton. The same procedure was applied to the MD maps.

Image quality assurance

Raw image quality was assessed via visual inspection. In addition, the SSE maps from the tensor estimation were calculated and visually inspected for structured noise [32]. Image quality was rated using a 4-point scale, with 1= “excellent”, 2= “minor”, 3= “moderate”, and 4= “severe”. Datasets determined to be of insufficient quality (i.e., moderate and severe) for statistical analyses were excluded (n=2). Lastly, probabilistic tractography data were inspected visually. First, the native space FA map registration was inspected to ensure images were all properly aligned to the template (masks were properly mapped to native space). Second, all tracts were visualized to ensure accurate path reconstruction.

Covariates

Sex, BMI, PHV and IQ were included as covariates in the analyses. Body weight and height were performed with participants having bare feet and wearing underclothes; weight was measured with an electronic scale (SECA 861, Hamburg, Germany) and height (cm) with a stadiometer (SECA 225, Hamburg, Germany). Both measurements were performed twice, and averages were used. BMI was expressed in kg/m^2. PHV is a common indicator of maturity in children and adolescents [35]. PHV was obtained from anthropometric variables (weight, height and/or seated height) using Moore's equations [36]. The total composite IQ was assessed by the Spanish version of the K-BIT, a validated and reliable instrument [37].

Statistical analysis

All analyses, with the exception of TBSS analyses, were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, p set at < 0.05). The characteristics of the study sample are presented as means and standard deviations (SD) or percentages. Interaction analyses of sex with physical fitness variables were performed. No significant interactions with sex were found ($P \geq 0.10$) and therefore analyses are presented for the whole sample. In addition, we explored the association of several confounders (i.e., sex, PHV, BMI, IQ, parental education, socioeconomic status, and emotional and behavioral problems) with tractography-derived white matter variables using a Pearson's bivariate correlation analysis. Among all of the potential confounders, parental education, socioeconomic status, and emotional and behavioral problems were not significantly related to white matter microstructure (all P-values >0.1) and were therefore excluded from the subsequent analyses.

Separate linear regression analyses adjusted for sex, PHV, BMI and IQ were performed to examine the association between physical fitness components and tracts-extracted DTI scalar metrics (i.e. FA, MD). Each regression model examined separately the relationships between a single physical fitness component and a single DTI scalar metric. Physical fitness variables were first associated with global DTI metrics (i.e., global FA, MD).

Then, in order to determine whether the association of physical fitness with white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, and to facilitate comparison with future studies, we applied two commonly used methodologies: (1) probabilistic tractography of large, commonly studied white matter tracts and (2) TBSS, which is a voxel-based approach. For probabilistic tractography analyses, false discovery rate (FDR. Benjamini-Hochberg method) was used to adjust for multiple comparisons [38]. Correction for multiple comparisons was based on 7 tracts, 2 DTI metrics and 6 physical fitness components for a total of 84 tests. For TBSS analyses, the association between physical fitness components and DTI scalar metrics were tested voxel-wise using general linear models, including sex, PHV, BMI and IQ as covariates. A permutation-based statistical approach (5000 permutations) within FSL's Randomise [34] was performed including the threshold-free cluster enhancement (TFCE) multiple comparison correction method. Significance was set at $P < 0.05$, corrected for family-wise error.

RESULTS

Table 1 presents demographic participant characteristics. The association between physical fitness components (i.e., cardiorespiratory fitness, muscular fitness, and motor fitness) and global FA and global MD is shown in **Table 2**. Briefly, no associations were found between physical fitness components and any of the global white matter metrics (i.e., FA, and MD) (all P-values >0.05).

Table 1. Descriptive sample characteristics.

	Mean/%	SD
Sex		
Girls,%	41.35	
Age (years)	10.04	1.15
Peak Height Velocity (years)	-1.90	1.04
Body Mass Index	26.68	3.63
Parental education university level (%)		
Neither parent	63.46	
One parent	19.23	
Both parents	17.31	
Intelligence (Test-KBIT)	48.10	24.97
Physical fitness components		
Cardiorespiratory fitness		
Last completed lap (20 m shuttle run)	16.14	7.88
Muscular fitness		
Relative upper-body muscular fitness (kg/kg)	0.30	0.06
Relative lower-body muscular fitness (cm)	104.95	18.64
Absolute upper-body muscular fitness (kg)	16.77	4.22
Absolute lower-body muscular fitness (cm×kg)	5825.13	1450.83
Motor fitness (s)	15.12	1.60

Values are expressed as means± standard deviations, unless otherwise indicated. Test-KBIT= The Kaufman Brief Intelligence Test.

Table 2. Association of physical fitness components with global FA, and global MD in children with overweight/obesity (n=89).

	Global FA		Global MD	
	β	*P*	β	*P*
Cardiorespiratory fitness (laps)	0.104	0.473	-0.026	0.851
Relative upper-body muscular fitness (kg/kg)	0.131	0.328	-0.155	0.225
Relative lower-body muscular fitness (cm)	-0.173	0.178	0.209	0.085
Absolute upper-body muscular fitness (kg)	0.114	0.452	-0.221	0.127
Absolute lower-body muscular fitness (cm×kg)	-0.279	0.099	0.278	0.082
Motor fitness (s^{-1})	-0.089	0.547	0.022	0.876

Lineal regression model was adjusted for sex, peak height velocity, body mass index (kg/m^2) and intelligence quotient. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction an indication a high level of tissue organization), MD= mean diffusivity (high MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). Values are standardized regression coefficients (β).

Association between physical fitness components and tract-specific FA and MD is shown in **Table 3**. Cardiorespiratory fitness was positively associated with FA in the inferior longitudinal fasciculus (β=0.273, P=0.039). In addition, relative upper-body muscular fitness was negatively associated with MD in the inferior longitudinal fasciculus (β=-0.237, P=0.035). All these associations became non-significant when analyses were adjusted for multiple comparisons (all P-values >0.05). No association was found between motor fitness and tract-specific FA and MD (all P-values >0.05).

Figure 1 presents the results of the voxel-wise DTI parameter analyses (i.e. TBSS). A statistically significant positive association between absolute upper-body muscular fitness and FA in the left lateral frontal lobe (X_{MNI}=-25, Y=30, Z=34, cluster size=13, $P_{FWE\text{-}corrected}$ =0.042) was found between physical fitness components and voxel-wise DTI parameters (i.e., FA and MD) after correction for multiple comparisons.

Table 3. Association of physical fitness components and tract-specific FA and MD in children with overweight or obesity.

	Cardiorespiratory fitness		*Relative upper-body MF*		*Relative lower-body MF*		*Absolute upper-body MF*		*Absolute lower-body MF*		*Motor fitness*	
	FA	MD	FA	MD	FA	MD	FA	MD	FA	MD	FA	MD
CGC[b]	-0.126	-0.107	-0.010	-0.155	-0.116	0.070	-0.064	-0.154	-0.159	0.181	-0.234	0.003
CST	0.100	-0.089	-0.011	-0.106	-0.098	0.047	-0.003	-0.108	-0.106	0.084	0.032	-0.072
ILF	**0.273***	-0.103	***0.212***	**-0.237***	0.024	0.084	0.159	***-0.214***	-0.075	0.205	0.151	-0.040
SLF	0.119	0.006	0.152	-0.138	-0.048	0.111	0.197	***-0.236***	-0.056	0.080	0.056	-0.026
UNC	-0.010	-0.060	0.006	-0.081	0.050	0.029	-0.052	-0.089	0.050	0.062	-0.021	-0.016
FMA	0.182	-0.023	0.106	0.062	-0.122	0.183	0.057	0.032	***-0.270***	***0.272***	0.090	0.004
FMI	0.129	-0.151	-0.120	0.114	-0.075	0.100	-0.152	0.069	-0.164	0.086	-0.079	-0.070

Lineal regression model was adjusted for sex, peak height velocity, body mass index (kg/m^2) and intelligence quotient. FA= Fractional anisotropy (high FA corresponds to preferential diffusion along one direction an indication a high level of tissue organization), MD= mean diffusivity (high MD corresponds to relatively unimpeded water diffusion and indicates regions of low tissue organization). MF=Muscular fitness. Cingulate gyrus part of cingulum (CGC), corticospinal tract (CST), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), uncinate fasciculus (UNC), forceps major (FMA), and forceps minor (FMI). Values are standardized regression coefficients (β). Statistically significant values are shown in bold ($P<0.05$), and borderline significant values are shown in italics and bold ($P<0.1$).* $P < 0.05$; ** $P > 0.01$. All the associations showed in the table disappeared when analyses were adjusted for multiple comparisons. [b]= in the cingulate gyrus part of cingulum n=89.

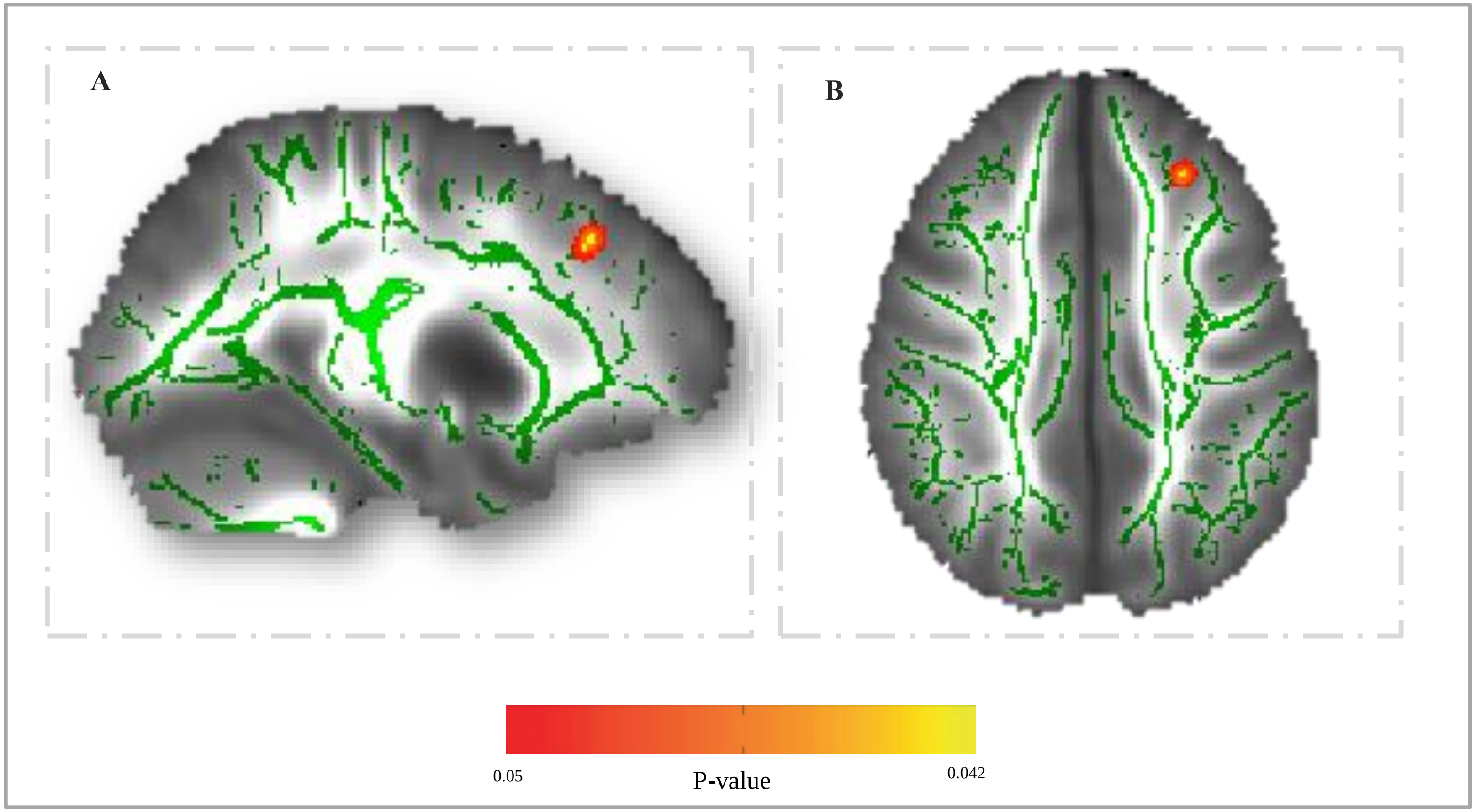

Figure 1. Positive association between absolute upper-body muscular fitness and FA in the left lateral frontal lobe (Montreal Neurological Institute –MNI- coordinates x= -25, y= 30, z=34; cluster size=13; corrected-p=0.042). A=sagittal view and B=axial view. The colour bar represents P-values, with yellow colour indicating higher significant association. The left hemisphere corresponds to the right side of the axial view.

DISCUSION

The aim of the present study was to examine the associations of physical fitness components (i.e., cardiorespiratory fitness, muscular fitness, and motor fitness) with white matter microstructure in children with overweight or obesity. No significant association was found between physical fitness components and global DTI scalar metrics (i.e., global FA, and global MD). Within individual tracts, all associations became non-significant when analyses were adjusted for multiple comparisons. However, results of the voxel-wise DTI parameter analyses showed that absolute upper-body muscular fitness was positively associated with FA in the left lateral frontal lobe after adjusting for multiple comparisons.

Cardiorespiratory fitness was not related to global metrics of DTI (i.e., global FA, and global MD) in children with overweight or obesity. The current study found that cardiorespiratory fitness was positively associated with FA in the inferior longitudinal fasciculus, although this association became non-significant when analyses were adjusted for multiple comparisons. These findings were consistent with the TBBS analyses showing no association with cardiorespiratory fitness. Chaddock-Heyman et al. [14], using data from the FITKids project, found that higher levels of cardiorespiratory fitness were associated with greater FA in sections of the corpus callosum, corona radiata and superior longitudinal fasciculus in children. These associated tracts differ from our results and may be partially explained by the different analysis approach used (i.e., Chaddock et al. used region-of-interest analyses vs. our study that used data-driven analysis adjusted for multiple comparison). In addition, measurement differences differ between the studies (e.g., different methodology of cardiorespiratory fitness assessment, differences among the MRI scanners or the MRI sequence acquisition parameters, participant demographics, participants BMI, etc.). Of note, our group, using data from the ActiveBrains and FITKids project, recently published that the white matter brain regions volumes associated with cardiorespiratory fitness were mainly located in the superior longitudinal fasciculus and the inferior longitudinal fasciculus in children with overweight or obesity of the same approximate ages [39]. Consequently, although our results cannot conclude that cardiorespiratory fitness is related to white matter microstructure in children with overweight or obesity, these results, in line with previous literature [14], seem to indicate that the association between cardiorespiratory fitness and white matter microstructure in children with overweight or obesity might be more focal than global white matter, and related to long association fiber tracts.

Regarding the other two physical fitness components, both muscular and motor fitness were not related to global metrics of DTI (i.e., global FA, and global MD) in children with overweight or obesity. In addition, while motor fitness was not associated with tract-specific white matter microstructure, relative upper-body muscular fitness was negatively associated with MD in the inferior longitudinal fasciculus. Of note, this association became non-significant when analyses were adjusted for multiple comparisons. However, when using the TBSS approach, we identified a small cluster in the left lateral frontal lobe where children with greater absolute upper-body muscular fitness showed higher FA, after adjusting for multiple comparison. Previous literature regarding both muscular and motor fitness in relation to white matter microstructure is not available, which hampers direct comparisons with other studies. Nonetheless, in line with our results, previous studies found that adolescents with higher muscular fitness, specifically upper-body muscular fitness, had a 20-30% lower risk of death from suicide and were 15-65% less likely to have any psychiatric diagnosis such as schizophrenia and mood disorders [40]. In addition, it was found that higher muscular fitness during adolescence predicts lower risk of obtaining disability pension due to all causes [4]. Of note, our group recently published that higher upper-body muscular fitness was negatively associated with stress and negative affect, and positively associated with self-esteem in children with overweight or obesity [41]. Therefore, we speculate that muscular fitness plays an undefined role in white matter microstructure which in turn could mediate or moderate mental health. Future work with a larger sample should confirm or contrast this hypothesis.

The underlying plausible mechanisms of the role of muscular fitness on white matter in children with overweight or obesity cannot be elucidated in our study. However, previous literature suggested that muscle contraction induced peripheral factors (e.g., irisin, and cathepsin B) which passes through the blood-brain barrier to enhance BDNF and hence neurogenesis, memory and learning[42]. However, it is unknown whether this myokine is a determining factor in muscle-induced enhanced white matter microstructure in children. It has been also suggested that exercised skeletal muscle leads to upregulation of PGC1α in mouse model and human skeletal muscle cells [43]. Likewise, endurance exercise training can lead to activation of the PGC1α, which stimulates the expression of kynurenine aminotransferase within skeletal muscle [43]. Moreover, higher expression of kynurenine aminotransferase can lead to increased conversion of neurotoxic kynurenine into neuroprotective kynurenic acid. The fact that kynurenic acid is not able to cross the blood-brain barrier protects the brain from stress-induced kynurenine accumulation, neuroinflammation and changes in synaptic plasticity. Therefore, although much still needs to be explored about the mechanisms that explain a relationship between muscular fitness and white matter microstructure in children, based on previous evidence in animal models, the positive associations between upper-body muscular fitness and greater FA in the frontal lobe is neurologically and biologically plausible.

The limitations of this study include (i) its cross-sectional design, which does not allow us to draw causal associations; (ii) our focus on children with overweight or obesity, which limits the generalizability of our findings to the entire range of the BMI distribution; (iii) the relatively small sample size, which could explain the few associations found in the analyses, although the sample size is respectable for neuroimaging studies in children; (iv) and the voxel size which was a 4-mm-section nonisotropic voxel (1.8 x 1.8 x 4 mm3). Therefore, FA could be underestimated in regions containing crossing fibers (i.e., superior longitudinal fasciculus). On the other hand, the FA measured in regions without crossing fibers (i.e., corticospinal tract) is not prone to underestimation (54). Lastly, the effect sizes for the association between physical fitness components and white matter microstructure were statistically non-significant or relatively small. Larger effects may not be expected due to the preservation of white matter microstructural development in the majority of young people, which probably has not yet achieved the maturational peak in most of the tracts [8]. Key strengths of the current study are the inclusion of neuroimaging data, and the combination of probabilistic fiber tractography and voxel-wise analyses of white matter tracts.

CONCLUSION

We found that physical fitness components are not associated with global DTI metrics (i.e., global FA, and global MD). Within individual tracts, all associations became non-significant when analyses were adjusted for multiple comparisons. However, using the TBSS approach, we identified a small cluster in the left lateral frontal lobe where children with greater absolute upper-body muscular fitness showed higher FA, after adjusting for multiple comparison. Our results cannot conclude that physical fitness components are related to white matter microstructure; however, the results seem to indicate that the association between physical fitness components (i.e., specifically muscular fitness) and white matter microstructure is more focal on specific tracts, as opposed to global differences. Future longitudinal and randomized control trials should explore the role of different physical fitness components on white matter microstructure.

REFERENCES

1. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes (Lond). 2008;32:1–11.

2. Smith JJ, Eather N, Morgan PJ, Lubans DR. The Health Benefits of Muscular Fitness for Children and Adolescents : A Systematic Review and Meta-Analysis. 2014;1209–23.

3. Henriksson P, Leppänen MH, Henriksson H, Delisle Nyström C, Cadenas-Sanchez C, Ek A, et al. Physical fitness in relation to later body composition in pre-school children. J Sci Med Sport. 2019;22:574–9.

4. Henriksson H, Henriksson P, Tynelius P, Ortega FB. Muscular weakness in adolescence is associated with disability 30 years later: a population-based cohort study of 1.2 million men. Br J Sports Med. 2018;bjsports-2017-098723.

5. Donnelly JE, Hillman CH, Castelli D, Etnier JL, Lee S, Tomporowski P, et al. Physical Activity, Fitness, Cognitive Function, and Academic Achievement in Children. Med Sci Sport Exerc. 2016;48:1197–222.

6. Lenroot RK, Giedd JN. Brain development in children and adolescents: Insights from anatomical magnetic resonance imaging. Neurosci Biobehav Rev. 2006;30:718–29.

7. Paus T. Growth of white matter in the adolescent brain: Myelin or axon? Brain Cogn. 2010;72:26–35.

8. Slater DA, Melie-Garcia L, Preisig M, Kherif F, Lutti A, Draganski B. Evolution of white matter tract microstructure across the life span. Hum Brain Mapp. 2019; 40: 2252-2268

9. White T, Magnotta VA, Bockholt HJ, Williams S, Wallace S, Ehrlich S, et al. Global white matter abnormalities in schizophrenia: a multisite diffusion tensor imaging study. Schizophr Bull. Oxford University Press; 2011; 37:222–32.

10. Kullmann S, Schweizer F, Veit R, Fritsche A, Preissl H. Compromised white matter integrity in obesity. Obes Rev. 2015;16:273–81.

11. van Bloemendaal L, Ijzerman RG, ten Kulve JS, Barkhof F, Diamant M, Veltman DJ, et al. Alterations in white matter volume and integrity in obesity and type 2 diabetes. Metab Brain Dis. 2016;31:621–9.

12. Ronan L, Alexander-Bloch AF, Wagstyl K, Farooqi S, Brayne C, Tyler LK, et al. Obesity associated with increased brain age from midlife. Neurobiol Aging. 2016;47:63–70.

13. Herting MM, Colby JB, Sowell ER, Nagel BJ. White matter connectivity and aerobic fitness in male adolescents. Dev Cogn Neurosci. 2014;7:65–75.

14. Chaddock-Heyman L, Erickson KI, Holtrop JL, Voss MW, Pontifex MB, Raine LB, et al. Aerobic fitness is associated with greater white matter integrity in children. Front Hum Neurosci. 2014;8:584.

15. Esteban-Cornejo I, Cadenas-Sanchez C, Contreras-Rodriguez O, Verdejo-Roman J, Mora-Gonzalez J, Migueles JH, et al. A whole brain volumetric approach in

overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. Neuroimage. 2017;159:346–54.

16. Bervoets L, Massa G. Defining morbid obesity in children based on BMI 40 at age 18 using the extended international (IOTF) cut-offs. Pediatr Obes. 2014 [cited 2019 Jun 21];9:e94–8.

17. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7:284–94.

18. Cadenas-Sánchez C, Mora-González J, Migueles JH, Martín-Matillas M, Gómez-Vida J, Escolano-Margarit MV, et al. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): Rationale, design and methods. Contemp Clin Trials. 2016;47:315–24.

19. Ruiz JR, Castro-Piñero J, España-Romero V, Artero EG, Ortega FB, Cuenca MM, et al. Field-based fitness assessment in young people: the ALPHA health-related fitness test battery for children and adolescents. Br J Sports Med. 2011;45:518–24.

20. Léger L a, Mercier D, Gadoury C, Lambert J. The multistage 20 metre shuttle run test for aerobic fitness. J Sports Sci. 1988;6:93–101.

21. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012; 62: 782–90.

22. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, et al. Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python. Front Neuroinform. 2011;5:13.

23. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016;125:1063–78.

24. Andersson JLR, Graham MS, Zsoldos E, Sotiropoulos SN. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage. 2016;141:556–72.

25. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed. 2010; 23: 803–20.

26. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med. 2009;61:1336–49.

27. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002;17:143–55.

28. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage. 2007;34:144–55.

29. Behrens TEJ, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. Magn Reson Med. 2003;50:1077–88.

30. De Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, Van Der Lugt A, et al. Tract-specific white matter degeneration in aging: The Rotterdam Study. Alzheimer's Dement. 2015;11:321–30.

31. Navas-Sánchez FJ, Alemán-Gómez Y, Sánchez-Gonzalez J, Guzmán-De-Villoria JA, Franco C, Robles O, et al. White matter microstructure correlates of mathematical giftedness and intelligence quotient. Hum Brain Mapp. 2014;35:2619–31.

32. Muetzel RL, Blanken LME, van der Ende J, El Marroun H, Shaw P, Sudre G, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. Am J Psychiatry. 2017; 175: 54–62.

33. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp. 2005;26:139–47.

34. Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, et al. Tract-based spatial statistics: Voxelwise analysis of multi-subject diffusion data. Neuroimage. 2006;31:1487–505.

35. Malina RM, Rogol AD, Cumming SP, Coelho E Silva MJ, Figueiredo AJ. Biological maturation of youth athletes: assessment and implications. Br J Sports Med. 2015;49:852–9.

36. Moore SA, McKay HA, Macdonald H, Nettlefold L, Baxter-Jones ADG, Cameron N, et al. Enhancing a somatic maturity prediction model. Med Sci Sports Exerc. 2015;47:1755–64.

37. Kaufman A, Kaufman N. Kaufman Brief Intelligence Test. Madrid: Tea; 2000.

38. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. 1995.

39. Esteban-Cornejo I, Rodriguez-Ayllon M, Verdejo-Roman J, Cadenas-Sanchez C, Mora-Gonzalez J, Chaddock-Heyman L, et al. Physical Fitness, White Matter Volume and Academic Performance in Children: Findings From the ActiveBrains and FITKids2 Projects. Front Psychol. Frontiers; 2019;10:208.

40. Ortega FB, Silventoinen K, Tynelius P, Rasmussen F. Muscular strength in male adolescents and premature death : cohort study of one million participants. 2012;7279:1–12.

41. Rodriguez-Ayllon M, Cadenas-Sanchez C, Esteban-Cornejo I, Migueles JH, Mora-Gonzalez J, Henriksson P, et al. Physical fitness and psychological health in overweight/obese children: A cross-sectional study from the ActiveBrains project. J Sci Med Sport. 2017.

42. Pedersen BK. Physical activity and muscle–brain crosstalk. Nat Rev Endocrinol. Nature Publishing Group; 2019;1.

43. Agudelo LZ, Femenía T, Orhan F, Porsmyr-Palmertz M, Goiny M, Martinez-Redondo V, et al. Skeletal Muscle PGC-1α1 Modulates Kynurenine Metabolism and Mediates Resilience to Stress-Induced Depression. Cell. 2014;159:33–45.

STUDY VIII

Effect of an exercise-based randomized controlled trial on white matter microstructure in children with overweight or obesity: The ActiveBrains project.

M. Rodriguez-Ayllon, I. Esteban-Cornejo, F. B. Ortega et al.

In preparation.

INTRODUCTION

Childhood physical inactivity is a worldwide pandemic [1]. Literature has suggested that an inactive lifestyle not only increases the risk of becoming overweight or obese, but also contributes to a worst physical and mental health [2,3]. In this context and with the rapid advances in brain imaging technologies, new studies have emerged to evaluate the impact of physical activity on brain health. For instance, the 2018 physical activity Guidelines for Americans have discussed for the first time the effect of physical activity on brain [4]. Specifically, it seems that there is a moderate grade of evidence to suggest that both acute and chronic moderate- to vigorous-intensity physical activity interventions improve brain structure and function in children aged 6-13 [5]; however, only few studies have explored the extent to which physical exercise has an effect on white matter microstructure during childhood [6–8].

DTI is a MRI technique that measures the diffusion of water molecules in tissue [9]. FA and MD are the two most common quantitative scalar measures used in DTI studies. FA is a measure of the degree to which water diffuses preferentially along one direction. MD provides a measure of the mean molecular diffusion. This value provides a measure of barriers to free diffusion in the volume, but it does not provide information about the direction of movement. Higher FA values are thought to reflect a higher degree of neuronal organization while higher MD indicate relatively unimpeded diffusion (i.e., it is negatively correlated with FA). Of note, excess body mass has been linked to poorer white matter development in children and adolescents [10,11]. These associations, together with the fact that physical activity may protect against the development of obesity, suggest that optimal levels of physical activity might have a positive impact on white matter microstructure; however, this hypothesis need to be further investigated.

In a previous study with over 2,500 children from the Generation R Study, we found that total self-reported physical activity was positively associated with global FA and negatively associated with global MD [12]. In addition, we confirmed in our sample of children with overweight or obesity from the ActiveBrains project that self-reported total physical activity was positively associated with global FA [13]. This association was supported for objective measures of physical activity but only when the Hildebrand-ENMO hip cut -points were used for analyses. Although the effect sizes for these associations were, in both studies, relatively small, we concluded that the association between unstructured physical activity and white matter microstructure seems more global than focal on specific tracts. In addition to those cross-sectional studies, only two previous intervention studies have focused on the effect of structured physical activity on white matter microstructure. First, an 8-month physical exercise intervention showed that, compared to controls, overweight children, in the exercise group increased FA in sections of the uncinate fasciculus [7] and superior longitudinal fasciculus [8]. Moreover, another 9-month physical exercise intervention showed that, compared to controls, those children who participated in the physical exercise program showed increased FA in the genu of the corpus callosum [6].

Collectively, these intervention studies contribute to the understanding of how increased levels of structured physical activity improves white matter development in children, yet the body of evidence is still in its infancy, and further well-designed RCTs are needed to confirm or contrast previous findings. In this context, many questions remain unanswered. For instance, are 20 weeks (half of the duration of previous studies) of combined muscular and aerobic exercise enough to induce changes in white matter microstructure? If any, is it global or restricted to a particular set of white matter bundles?

Therefore, the aim of this study was to investigate the effects of a 20-week randomized controlled physical exercise trial, based on a combination of aerobic and muscular exercise, on global white matter microstructure in children with overweight or obesity (primary aim). Second, in order to determine whether the effect of physical exercise on white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, analyses on individual tracts were run as well (secondary aim). We further hypothesized that exercise increase FA and decrease MD; however, based on previous literature [6–8], due to the shorter duration of the physical exercise program, the magnitude of these relationships are expected to be smaller.

METHODS

Trial Design and Participants

This study used data from the ActiveBrains project (http://profith.ugr.es/activebrains, web available in Spanish and English), a RCT designed to examine the effects of a 20-week physical exercise program on brain, and cognitive and academic performance, as well as on selected physical and mental health outcomes in children with overweight/obesity. The ActiveBrains project was approved by the Human Research Ethics Committee of the University of Granada, and it was registered in ClinicalTrials.gov (identifier: NCT02295072).

Details of the ActiveBrains project methodology have been described elsewhere.[14] Briefly, inclusion/exclusion criteria were: i) to be 8 to 11.9 years-old; ii) to be classified as overweight or obese based on sex and age specific World Obesity Federation cut-off points [15,16]; iii) to not suffer from physical disabilities or neurological disorders that impeded them to exercise; iv) in the case of girls, not to have started the menstruation at the moment of baseline assessments; v) to report no use of medications that influenced central nervous system function; vi) to be right-handed (i.e., measured by the Edinburgh inventory) [17] since right-handed individuals substantially differ in brain hemisphere structure (i.e., dominant and non-dominant hemisphere) from left-handed ones; and vii) to not report an ADHD over the 85th percentile measured by the ADHD rating scale [18].

All data were collected at baseline and post-intervention from November 2014 through June 2016, and the study was conducted in three waves temporarily differentiated due to practical reasons.

Randomization

The participants were randomly allocated to an intervention group, which participated in the physical exercise program, or to a wait-list control group. The wait-list control group strategy has been previously used by other similar studies [19,20], and implied that the individuals belonging to this group also received the exercise program after all the assessments of the project had been completed. Randomization of the participants into exercise or control group was done using a computer random number generator in SPSS software for Windows (version 20.0; Armonk, NY, USA).

With the aim of reducing the risk of bias, several protocols were followed. First, the computer random generation was conducted by a person who was not involved in the outcome evaluations. Second, randomization was done immediately after the baseline evaluation. Lastly, the physical exercise instructors who carried out the exercise program were not involved in the outcome evaluations. In addition, the staff involved in the post-exercise MRI evaluations were fully blinded to the participants´ group allocation.

Per-protocol

Protocol criteria were to attend to at least a 70% of the recommended 3 sessions/week (i.e., exercise group). In total, 83 children with overweight or obesity who completed the pre-test and post-test DTI assessment, with a good quality of DTI data, met the per-protocol criteria (see **Figure 1**).

Intention-to-treat

In total, 112 children with overweight/obesity meeting the inclusion/exclusion criteria participated in this study. Of them, 109 were randomly allocated to an exercise group, which participated in the exercise program, or to a wait-list control group. Four children were excluded from analysis due to visible motion on the reconstructed DTI data. Then, intention-to-treat analyses were performed for all children who completed the pre-test and post-test DTI assessment, with a good quality of DTI data (N =89) (see Figure 1).

Multiple imputation on MRI data was not performed due to it is extremely complex and is not common in this field.

Physical exercise intervention program

The physical exercise program was designed according to the international physical activity guidelines for children (http://www.health.gov/paguidelines/). Briefly, the program had a duration of 20-week. Participants had the possibility to attend to the program daily from Monday to Friday (i.e., 5 sessions/week), and the attendance criterion was set as a minimum of 3 times/week, yet we advised the families that "the more, the better" up to the 5 sessions/week.

The duration of the session was 90 min/session. Each session was structured in three parts. First, a 5-10 min warm-up consisting of 1-2 physical games of 5 min each. Second, a 60-min aerobic part consisting of around four to five physical multi-games demanding moderate-to-vigorous intensities, with special emphasis on high intensity activities (i.e., above 80% of maximal heart rate). Of note, we emphasized on the playful component of the games in order to increase the adherence to the program. Third, a 20-min strength training consisting of muscle- and bone-strengthening game-based activities. The strength part included around 6-7 global muscle strength exercises in sets of 10-12 repetitions using therabands, fitballs and/or own bodyweight. Lastly, a 5-10 min cool-down part consisting of stretching and relaxation exercises.

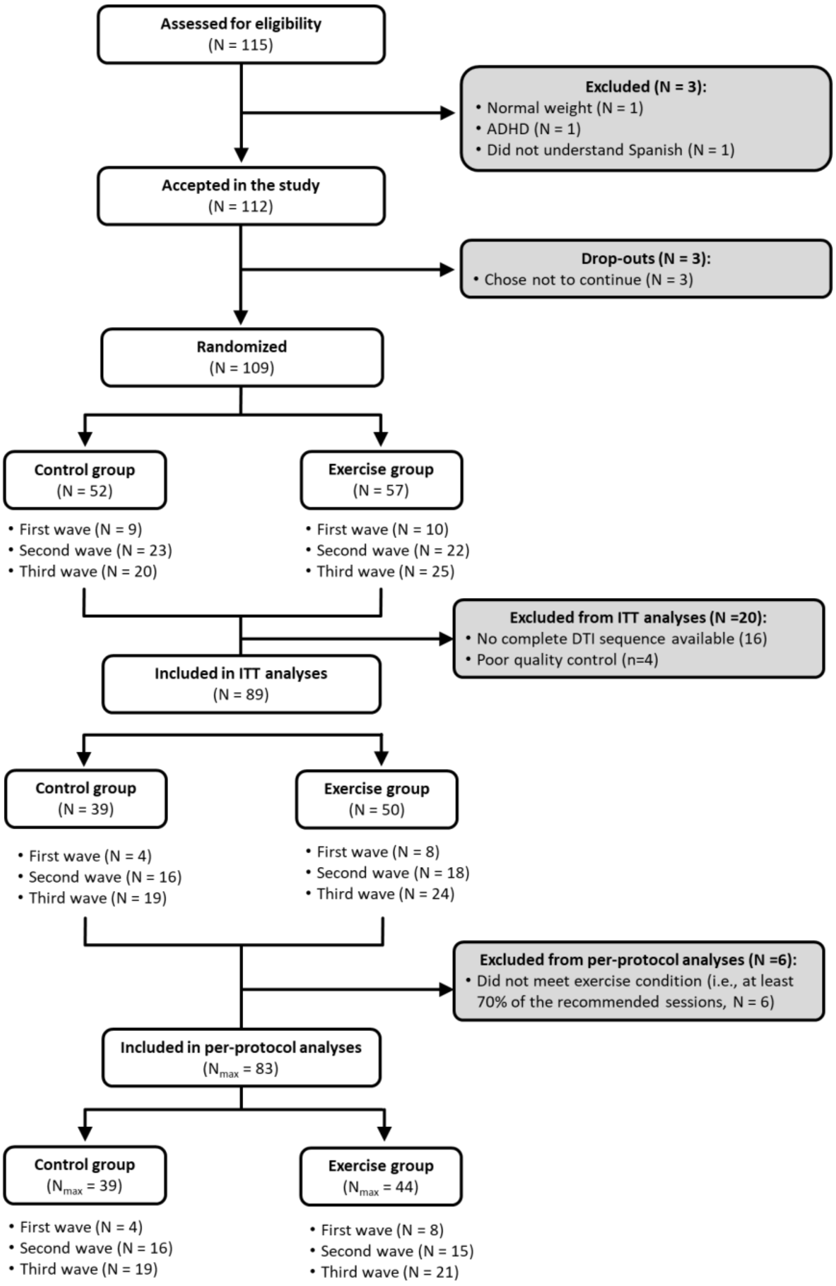

Figure 1. Flow chart.

TO SPECIFY AS FOOTNOTE

ITT = Intention-to-treat

N_{max} = Maximum N for analyses, it changes depending on the variable, see tables X for specific sample sizes per variable.

Control group condition

Children allocated into the control group were advised to continue with their usual life. However, we provided them a pamphlet which included some nutrition and physical activity recommendations. For ethical reasons, all the children in the control group received the exercise intervention after the trial was completed.

MRI procedure

Image acquisition

MRI data were acquired with a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany). DTI data were acquired using an echo planar imaging (EPI) sequence with the following parameters: TR = 3,300 ms, TE = 90 ms, flip angle = 90, matrix=128 x 128, FOV= 230 mm x 230 mm, slice thickness= 4 mm, number of slices = 25 and voxel resolution= 1.8 x 1.8 x 4 mm^3. One volume without diffusion weighting ($b=0s/mm^2$) and 30 volumes with diffusion weighting ($b=1000s/mm^2$) were collected.

Image preprocessing

Image preprocessing was conducted using the FSL (https://fsl.fmrib.ox.ac.uk) [21,22]. Images were first adjusted for minor head motion [23] using eddy, a new tool to correct for eddy current-induced distortions and participants movements. Then, a Gaussian process for outlier replacement [24] was used. In order to account for rotations applied to the image data [25,26], the resulting transformation matrices were used to rotate the diffusion gradient direction table. Non-brain tissue was removed using the FSL Brain Extraction Tool [27]. Then, the diffusion tensor was fit, and common scalar maps (e.g., FA, MD) were subsequently computed.

Probabilistic fiber tractography

Diffusion data were first processed using the BEDPOSTx, accounting for two fiber orientations at each voxel [28,29]. Next, for each participant, the FA map was aligned to the FMRIB-58 FA template image with the FSL nonlinear registration tool (FNIRT). The inverse of this nonlinear warp field was computed, and applied to a series of predefined seed, target, exclusion, and termination masks provided by the AutoPtx plugin [30].

Probabilistic fiber tracking was then performed with the FSL Probtrackx module using these supplied tract-specific masks (i.e., seed, target, etc.) that were warped to the native diffusion image space of each subject[28]. The resulting path distributions were normalized to a scale from 0 to 1 using the total number of successful seed-to-target attempts, and were subsequently thresholded to remove low-probability voxels likely related to noise.

After the tracts were thresholded [30], average FA, and MD values were then computed for each fiber bundle. Connectivity distributions were estimated for 7 large fiber bundles (i.e., corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, cingulate gyrus part of cingulum, forceps minor and forceps major) selected based on previous reports [31–33]. Average of FA and MD in the left and right hemisphere was calculated in those tracts present in both hemispheres (i.e., corticospinal tract, superior longitudinal fasciculus, inferior longitudinal fasciculus, uncinate fasciculus, and cingulate gyrus part of cingulum).

Lastly, to assess whether exposures were related to global measures of white matter integrity (i.e., global FA, MD), selected tracts [32] were combined into a single factor (“global factor”). The global factor was computed by averaging all tracts and weighting this average by the size (volume) of the tracts (to ensure small regions do not contribute equally as larger regions, which is common practice in the neuroimaging literature, in particular cortical morphology studies). This method was based on previous work [12,34,35].

Image quality assurance

Raw image quality was assessed via visual inspection [32]. The SSE maps from the tensor estimation were calculated and visually inspected for structured noise. Image quality was rated using a 4-point scale, with 1= "excellent", 2= "minor", 3= "moderate", and 4= "severe". Datasets determined to be of insufficient quality (i.e., moderate and severe) for statistical analyses were excluded (n=4). Lastly, probabilistic tractography data were visually inspected. First, the native space FA map registration was inspected, to ensure images were all properly aligned to the template (masks were properly mapped to native space). Second, all tracts were visualized to ensure accurate path reconstruction.

Statistical analysis

All the statistical procedures were performed using the Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY, p set at < 0.05). For the main analysis, the effects on the outcomes for each dimension were tested according to the per-protocol principle with ANCOVA using post-intervention data as dependent variables, group (i.e., intervention vs. control) as fixed factor, and baseline data as covariates. Raw scores from each outcome were first winsorized to limit the influence of extreme values; this method allows replacing extreme high/low values for the closest (highest/lowest) valid value [36].

According to previous RCTs [36], the z-scores for each outcome at post-exercise program were calculated by dividing the difference of the raw score of each participant from the baseline mean by the baseline standard deviation (i.e., (post-exercise individual value – baseline mean) / baseline standard deviation). This variable means how many standard deviations the outcome has changed from baseline. Therefore, we interpreted it as an effect size indicator. A value around 0.2 was considered a small effect size, 0.5 was considered a medium effect size and 0.8 was considered a large effect size [37].

First, we examined the effect of our physical exercise trial on DTI global scalar metrics. Then, in order to determine whether the relationship with white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, associations with FA and MD within individual tracts were also tested. False discovery rate (FDR. Benjamini-Hochberg method) was used to adjust for multiple comparisons [38]. Correction for multiple comparisons was based on 7 tracts and 2 DTI metrics for a total of 14 tests.

Lastly, supplementary analyses were conducted using the intention-to-treat principle (N=89).

RESULTS

All the baseline characteristics of the study sample are presented in **Table 1**. The study sample had an average age of 10.06 years (SD = 1.11), a biological maturation age of 2.27 years (SD = 0.95) before the age at which the maximum PHV occurs, and an average BMI of 26.44 kg/m^2 (SD = 3.62) at baseline. Between all the characteristic tested, the intervention group had significantly higher BMI (p=0.038) than the control group. No more differences were found between the intervention and the control group (all p>0.05).

Table 1. Descriptive baseline characteristics of the *ActiveBrains* participants meeting per-protocol criteria (n=83).

	All		Intervention group		Control group		
	N	Values	N	Values	N	Values	*P*
Sex	83		44		39		
Girls (n %)	32	39	14	32	18	46	0.180
Boys (n %)	51	61	30	68	21	54	
Age (years)	83	10.06±1.11	44	10.00±1.13	39	10.14±1.10	0.548
Weight (kg)	83	55.63±11.21	44	56.86±12.70	39	54.24±9.23	0.290
Height (cm)	83	144.46±8.40	44	143.74±9.08	39	145.26±7.57	0.413
Body mass index (kg/m^2)	83	26.44±3.62	44	27.21±4.07	39	25.56±2.84	**0.038**
Peak height velocity offset (years)	83	-2.27±0.95	44	-2.42±0.93	39	-2.11±0.96	0.137
Wave of participation. (%)	83		44		39		
First (n %)	12	15	8	18	4	10	
Second (n %)	31	37	15	34	16	41	0.557
Third (n %)	40	48	21	48	19	49	

Values are expressed as means ± standard deviations (SD), unless otherwise indicated.

The effect of the exercise program on global FA and global MD after adjustment for baseline values of the study outcomes according to the per-protocol analyses is shown in **Table 2**. No effect was found in terms of global DTI metrics (all p>0.813). The effect of the exercise program on tract-specific FA and MD is shown in **Table 3**. Briefly, a negative effect (of the whole exercise intervention was observed on FA in the forceps minor (p=0.020). However, this association disappeared when analyses were adjusted for multiple comparisons (p_{fdr}= 0.212). In addition, a positive small effect was observed in MD, particularly in the corticospinal tract (p=0.030), but again this effect disappeared when analyses were adjusted for multiple comparisons (p_{fdr}= 0.212).

To sum up, no effect of the exercise program on both global and tract-specific FA and MD was found in children with overweight or obesity.

Intention-to-treat analyses

All main analyses (i.e., **Table 2** and **Table 3**) were replicated following the intention-to-treat principle (i.e., including participants not meeting the requirement of a minimum 70% attendance to the exercise program). These analyses has been shown in **Table S1** and **Table S2**. Overall, the effects shown in the intention-to-treat analyses were similar compared to the per-protocol effects. Then, no effect of physical exercise was found on global DTI metrics (see **Table S1**). In addition, no effect of physical exercise on tract-specific FA and MD was found after adjustments for multiple comparisons (all $p_{fdr} > 0.191$) in children with overweight or obesity (see **Table S2**).

Table 2. Per-protocol effects of the ActiveBrains intervention on raw and Z-Score post-intervention white matter microstructure (n=83).

	Mean (95% CI)			
	Intervention group*	Control group*	Difference between groups	*P*
Global FA				
Raw score	0.458 (0.455 to 0.461)	0.458 (0.455 to 0.461)	0.000 (-0.004 to 0.004)	0.931
z Score	0.112 (-0.058 to 0.282)	0.101 (-0.080 to 0.282)	0.011 (-0.238 to 0.259)	
Global MD				
Raw score	82.548 (82.269 to 82.828)	82.499 (82.201 to 82.798)	0.049 (-0.363 to 0.461)	0.813
z Score	-0.072 (-0.205 to 0.061)	-0.096 (-0.238 to 0.046)	0.023 (-0.173 to 0.220)	

Z-score values indicate how many standard deviations have the post-intervention values changed with respect to the baseline mean and standard deviation. E.g., a 0.50 z-score means that the mean value at post-intervention is 0.50 standard deviations higher than the mean value at baseline, indicating a positive change, with negative values indicating the opposite. MD values were multiplied by 100000 due to MD values were very small making difficult the values interpretations.

*Adjusted for baseline values.

Table 3. Per-protocol effects of the ActiveBrains intervention on raw and Z-score post-intervention white matter microstructure.

	Mean (95% CI)							
	Fractional anisotropy				*Mean diffusivity*			
	Intervention group*	Control group*	Difference between groups	p p_{FDR}	Intervention group*	Control group*	Difference between groups	p p_{FDR}
Cingulate gyrus part of cingulum								
Raw score	0.416 (0.406 to 0.425)	0.417 (0.407 to 0.427)	-0.001 (-0.015 to 0.013)	0.883	80.754 (80.141 to 81.366)	80.941 (80.287 to 81.594)	-0.187 (-1.088 to 0.714)	0.680
z Score	0.083 (-0.197 to 0.362)	0.113 (-0.186 to 0.411)	-0.030 (-0.439 to 0.379)	0.942	-0.020 (-0.286 to 0.246)	0.061 (-0.223 to 0.345)	-0.081 (-0.473 to 0.311)	0.942
Corticospinal tract								
Raw score	0.537 (0.534 to 0.540)	0.535 (0.532 to 0.538)	0.002 (-0.002 to 0.006)	0.411	77.691 (77.378 to 78.005)	77.184 (76.851 to 77.517)	0.507 (0.049 to 0.965)	**0.030**
z Score	0.118 (-0.011 to 0.248)	0.040 (-0.098 to 0.177)	0.079 (-0.111 to 0.268)	0.942	0.051 (-0.124 to 0.225)	-0.231 (-0.416 to -0.046)	0.282 (0.027 to 0.536)	0.212
Inferior longitudinal fasciculus								
Raw score	0.483 (0.479 to 0.486)	0.481 (0.478 to 0.485)	0.001 (-0.004 to 0.006)	0.649	85.727 (85.401 to 86.054)	85.690 (85.342 to 86.037)	0.038 (-0.439 to 0.515)	0.875
z Score	0.123 (-0.031 to 0.277)	0.071 (-0.092 to 0.234)	0.052 (-0.174 to 0.278)	0.942	-0.133 (-0.250 to -0.016)	-0.147 (-0.271 to -0.023)	0.014 (-0.157 to 0.184)	0.942
Superior longitudinal fasciculus								
Raw score	0.390 (0.387 to 0.393)	0.388 (0.385 to 0.392)	0.002 (-0.003 to 0.007)	0.453	80.996 (80.646 to 81.347)	80.950 (80.578 to 81.323)	0.046 (-0.465 to 0.558)	0.858
z Score	0.131 (-0.068 to 0.331)	0.021 (-0.190 to 0.233)	0.110 (-0.181 to 0.401)	0.942	-0.089 (-0.241 to 0.064)	-0.109 (-0.270 to 0.053)	0.020 (-0.202 to 0.242)	0.942
Uncinate fasciculus								
Raw score	0.408 (0.402 to 0.413)	0.408 (0.402 to 0.414)	0.000 (-0.009 to 0.008)	0.942	84.014 (83.559 to 84.470)	83.936 (83.452 to 84.420)	0.078 (-0.587 to 0.743)	0.816
z Score	-0.099 (-0.311 to 0.114)	-0.087 (-0.313 to 0.139)	-0.011 (-0.323 to 0.300)	0.942	-0.084 (-0.291 to 0.123)	-0.120 (-0.340 to 0.100)	0.036 (-0.267 to 0.338)	0.942
Forceps major								
Raw score	0.561 (0.556 to 0.565)	0.562 (0.557 to 0.567)	-0.001 (-0.008 to 0.006)	0.749	91.207 (90.077 to 92.337)	90.341 (89.140 to 91.542)	0.866 (-0.790 to 2.521)	0.301
z Score	0.124 (-0.046 to 0.294)	0.164 (-0.017 to 0.345)	-0.040 (-0.288 to 0.208)	0.942	-0.061 (-0.238 to 0.115)	-0.197 (-0.384 to -0.009)	0.135 (-0.123 to 0.394)	0.942
Forceps minor								
Raw score	0.627 (0.616 to 0.638)	0.647 (0.635 to 0.659)	-0.020 (-0.036 to -0.003)	**0.020**	82.404 (81.314 to 83.494)	82.708 (81.550 to 83.866)	-0.304 (-1.894 to 1.286)	0.704
z Score	-0.182 (-0.479 to 0.115)	0.338 (0.022 to 0.654)	-0.520 (-0.956 to -0.054)	0.212	-0.074 (-0.346 to 0.199)	0.002 (-0.287 to 0.291)	-0.076 (-0.474 to 0.321)	0.942

Z-score values indicate how many standard deviations have the post-intervention values changed with respect to the baseline mean and standard deviation. E.g., a 0.50 Z-score means that the mean value at post-intervention is 0.50 standard deviations higher than the mean value at baseline, indicating a positive change, with negative values indicating the opposite. MD values were multiplied by 100000 due to MD values were very small making difficult the values interpretations.

*Adjusted for baseline values.

DISCUSSION

The aim of this study was to investigate the effects of a 20-week randomized controlled physical exercise trial on global white matter microstructure in children with overweight or obesity. In addition, in order to determine whether the effect of physical exercise on white matter microstructure was indeed only global or restricted to a particular set of white matter bundles, the effect of physical exercise on FA and MD within individual tracts was also tested. In short, we found that a 20-week physical exercise intervention had no effect on white matter microstructure in children with overweight or obesity.

A possible explanation could be that 20-week physical exercise intervention might be not enough to induce changes in the white matter during childhood. In line with this hypothesis, a previous 8-month physical exercise intervention showed that, compared to controls, overweight children in the exercise group, increased FA in sections of the uncinate fasciculus and superior longitudinal fasciculus [7,39]. In addition, another 9-month physical exercise intervention showed that, compared to controls, those children who participated in the exercise program showed increased FA in the genu of the corpus callosum [6]. Therefore, it could be possible that at least 8 months of physical exercise might be needed to induce changes in white matter microstructure during childhood.

Of note, not only duration of the program (i.e., 4.5 months vs. more than 8 months) might be important to induce changes in the white matter during childhood, but also the type of intervention (e.g., aerobic training vs. muscular training). In our sample of children with overweight or obesity from the ActiveBrains project, we found that those children with higher muscular fitness showed greater white matter in terms of volume [40] and microstructure (see **Study VII**). While cardiorespiratory fitness and motor fitness were also related to white matter volume, those associations were weaker.

In addition, no association was found between cardiorespiratory fitness, motor fitness and white matter microstructure in those children. In line with those findings, a network meta-analysis found that high-intensity and frequent resistance exercises may be the most effective for global cognition in adults with mild cognitive impairment, followed by exergames, aerobic exercises, and mind–body exercises [41]. Specifically in terms of white matter, a previous intervention study found that a 4-week muscular training intervention significantly decreased MD in the left corticospinal tract in adults [42]. Therefore, muscular training interventions with the aim of improving muscular fitness are needed to test its influence on white matter in young people.

In contrast with our experimental findings, our observational evidence suggests that there is a positive relationship between physical activity and white matter microstructure in children [12,13]. For instance, in over 2,500 children from the Generation R Study, we found that total self-reported physical activity was positively associated with global FA and negatively associated with global MD [12]. We confirmed in our sample of children with overweight/obese from the ActiveBrains Study that self-reported total physical activity was positively associated with global FA [13]. This association was supported for objective measures of physical activity but only when Hildebrand-ENMO hip cut -points were used for analyses. There are several possible explanations for these discrepancies. First, it is unclear whether the reverse relationship (i.e., those children with greater white matter microstructure practice more physical activity over time) could explain the positive association found between physical activity and white matter microstructure in our previous cross-sectional studies. In adult populations, a few studies found that greater brain volume predicts better adherence to a physical activity intervention. For instance, Best et al. [43] found that a higher grey matter volume in the lateral prefrontal cortex predicts a better adherence to a physical activity intervention among older women. Moreover, Gujral et al. [44] found that higher grey matter volume in prefrontal, motor, somatosensory, temporal and parietal regions predicts greater adherence to a physical activity intervention among older people. Hence, to test if greater white matter microstructure predicts higher levels of physical activity over time in young people is needed. Second, physical activity may reflect stable behavioural patterns of people. However, our physical exercise intervention lasted 4.5 months. Thus, our findings might suggest that to change lifestyle could provide benefits on white matter that are not observable in brief exercise-based interventions, although longitudinal cohort studies are needed to confirm or contrast this hypothesis.

Lastly, most previous evidence has shown that the brain of older adults tends to be less plastic than that of younger individuals [45]. However, Yotsumoto et al. [46] indicated that significant changes in FA in the white matter only occurred with older individuals after a visual perceptual training for 3 daily sessions [46]. They concluded that mechanisms for visual perceptual learning were different between the younger and older people. For instance, while young people might experiment the improvement in the strengthening of synaptic efficacies [47] in terms of activity/activation, in older adults changes might reflect the degrees of FA values, in terms of axonal transmission related to myelination, axon caliber or crossing fibers in white matter. In this line, a few studies found evidence that physical activity may influence brain networks and task-evoked activation patterns in children [19,48–50]. However, those studies showed inconsistent activation patterns and had small sample sizes, which precludes the ability to make definitive conclusions. Future studies with larger sample sizes and defined activation patterns combining fMRI and DTI data might provide valuable information about the potential mechanisms across physical activity might improve white matter in different age populations (e.g., strengthening of synaptic efficacies in terms of activity/activation vs. axonal transmission related to myelination).

Some limitations needs to be considered. First, effects observed is limited to a sample of children with overweight/obesity. Second, the sample size of this study might seem relatively small (n=83), however it is the second largest trial (after the FITitKid2 trial with n=143 [6]) examining effects of exercise on white matter microstructure. Third, it is unknown whether the effects observed would have been larger if the intervention would have lasted longer. Fourth, voxel size was a 4-mm-section nonisotropic voxel (1.8 x 1.8 x 4 mm^3). Therefore, FA could be underestimated in regions containing crossing fibers (i.e., superior longitudinal fasciculus). On the other hand, the FA measured in regions without crossing fibers (i.e., corticospinal tract) is not prone to underestimation [51]. Lastly, previous studies have found that physical exercise has a positive effect on white matter microstructure in crucial (e.g., motor) circuits in children [6]. However, our tract-specific approach did not have tract-specific masks for all brain regions. For instance, we did not encompass the corpus callosum outsize of the forceps major and forceps minor fiber bundles. Then, future works using different approaches are needed to explore whether structured physical activity is also related to greater white matter microstructure in other brain regions [6].

Strengths of the present RCT were to be one of the few studying examining the chronic effects of exercise, specifically the combined effect of muscular and aerobic exercise, on brain outcomes in children, the intention-to-treat exploratory analyses, and the design, which allows causal inferences (i.e. it is the strongest empirical evidence of a treatment's efficacy). Lastly, the physical exercise instructors who carried out the exercise program were not involved in the outcome evaluations. In addition, the staff involved in the post-exercise MRI evaluations were fully blinded to the participants´ group allocation.

CONCLUSIONS

We found that a 20-week physical exercise intervention had no effect on white matter microstructure in children with overweight or obesity. Therefore, a 20-week physical exercise intervention, based on a combination of aerobic and muscular exercise, might be not enough to induce changes in the white matter during childhood. Further larger RCTs should examine the effect of longer exercise intervention combining both aerobic and muscular training on the white matter microstructure in children.

REFERENCES

1. Kohl HW, Craig CL, Lambert EV, Inoue S, Alkandari JR, Leetongin G, et al. The pandemic of physical inactivity: global action for public health. Lancet. 2012;380:294–305.

2. Lee I-M, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT, et al. Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. Lancet. 2012;380:219–29. 6

3. Rodriguez-Ayllon M, Cadenas-Sánchez C, Estévez-López F, Muñoz NE, Mora-Gonzalez J, Migueles JH, et al. Role of Physical Activity and Sedentary Behavior in the Mental Health of Preschoolers, Children and Adolescents: A Systematic Review and Meta-Analysis. Sport Med. 2019; 49:1383-1410

4. Physical Activity Guidelines for Americans 2nd edition. 2018; Washington, DC: US: Department of Health and Human Services. https://health.gov/paguidelines/second-edition/pdf/Physical_Activity_Guidelines_2nd_edition.pdf.

5. Erickson KI, Hillman C, Stillman CM, Ballard RM, Bloodgood B, Conroy DE, et al. Physical Activity, Cognition, and Brain Outcomes: A Review of the 2018 Physical Activity Guidelines. Med Sci Sports Exerc. 2019;51:1242–51.

6. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette E, Raine L, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci. Frontiers; 2018;12:950.

7. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51:728–33.

8. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved Frontoparietal White Matter Integrity in Overweight Children Is Associated with Attendance at an After-School Exercise Program. Dev Neurosci. 2014;36:1–9.

9. Le Bihan D. Molecular diffusion, tissue microdynamics and microstructure. NMR Biomed. 1995;8:375–86.

10. Ou X, Andres A, Pivik RT, Cleves MA, Badger TM. Brain gray and white matter differences in healthy normal weight and obese children. J Magn Reson Imaging. 2015;42:1205–13.

11. Yau PL, Kim M, Tirsi A, Convit A. Retinal Vessel Alterations and Cerebral White Matter Microstructural Damage in Obese Adolescents With Metabolic Syndrome. JAMA Pediatr. 2014;168:e142815.

12. Rodriguez-Ayllon M, Derks IPM, van den Dries MA, Esteban-Cornejo I, Labrecque JA, Yang-Huang J, et al. Associations of physical activity and screen time with white matter microstructure in children from the general population. Neuroimage [Internet]. 2019;205:116258.

13. M. Rodriguez-Ayllon, I. Esteban Cornejo, J. Verdejo-Román, RL Muetzel, J. H. Migueles, J. Mora-Gonzalez, P. Solis-Urra, K.I. Erickson, C.H. Hillman, A. Catena, H. Tiemeier FBO. Physical activity, sedentary behavior and white matter microstructure in children with overweight or obesity. Med Sci Sport Exerc. In press.

14. Cadenas-Sánchez C, Mora-González J, Migueles JH, Martín-Matillas M, Gómez-Vida J, Escolano-Margarit MV, et al. An exercise-based randomized controlled trial on brain, cognition, physical health and mental health in overweight/obese children (ActiveBrains project): Rationale, design and methods. Contemp Clin Trials; 2016;47:315–24.

15. Cole TJ, Lobstein T. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr Obes. 2012;7:284–94.

16. Bervoets L, Massa G. Defining morbid obesity in children based on BMI 40 at age 18 using the extended international (IOTF) cut-offs. Pediatr Obes. 2014;9:e94–8.

17. Oldfield RC. The assessment and analysis of handedness: The Edinburgh inventory. Neuropsychologia. Pergamon; 1971;9:97–113.

18. DuPaul GJ, Power TJ, Anastopoulos AD, Reid R. ADHD rating scale IV: Checklists, norms, and clinical interpretation. New York: Guilford Press; 1998.

19. Chaddock-Heyman L, Erickson KI, Voss MW, Knecht AM, Pontifex MB, Castelli DM, et al. The effects of physical activity on functional MRI activation associated with cognitive control in children: a randomized controlled intervention. Front Hum Neurosci. 2013;7:72.

20. Drollette ES, Pontifex MB, Raine LB, Scudder MR, Moore RD, Kao S-C, et al. Effects of the FITKids physical activity randomized controlled trial on conflict monitoring in youth. Psychophysiology. 2018;55:e13017.

21. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM. FSL. Neuroimage. 2012. 1: 782–90.

22. Gorgolewski K, Burns CD, Madison C, Clark D, Halchenko YO, Waskom ML, et al. Nipype: A Flexible, Lightweight and Extensible Neuroimaging Data Processing Framework in Python. Front Neuroinform. 2011;5:13.

23. Andersson JLR, Sotiropoulos SN. An integrated approach to correction for off-resonance effects and subject movement in diffusion MR imaging. Neuroimage. 2016;125:1063–78.

24. Andersson JLR, Graham MS, Zsoldos E, Sotiropoulos SN. Incorporating outlier detection and replacement into a non-parametric framework for movement and distortion correction of diffusion MR images. Neuroimage. 2016;141:556–72.

25. Jones DK, Cercignani M. Twenty-five pitfalls in the analysis of diffusion MRI data. NMR Biomed. 2010; 23: 803–20.

26. Leemans A, Jones DK. The B-matrix must be rotated when correcting for subject motion in DTI data. Magn Reson Med. 2009;61:1336–49.

27. Smith SM. Fast robust automated brain extraction. Hum Brain Mapp. 2002;17:143–55.

28. Behrens TEJ, Berg HJ, Jbabdi S, Rushworth MFS, Woolrich MW. Probabilistic diffusion tractography with multiple fibre orientations: What can we gain? Neuroimage. 2007;34:144–55.

29. Behrens TEJ, Woolrich MW, Jenkinson M, Johansen-Berg H, Nunes RG, Clare S, et al. Characterization and Propagation of Uncertainty in Diffusion-Weighted MR Imaging. Magn Reson Med. 2003;50:1077–88.

30. De Groot M, Ikram MA, Akoudad S, Krestin GP, Hofman A, Van Der Lugt A, et al. Tract-specific white matter degeneration in aging: The Rotterdam Study. Alzheimer's Dement. 2015;11:321–30.

31. Navas-Sánchez FJ, Alemán-Gómez Y, Sánchez-Gonzalez J, Guzmán-De-Villoria JA, Franco C, Robles O, et al. White matter microstructure correlates of mathematical giftedness and intelligence quotient. Hum Brain Mapp. 2014;35:2619–31.

32. Muetzel RL, Blanken LME, van der Ende J, El Marroun H, Shaw P, Sudre G, et al. Tracking Brain Development and Dimensional Psychiatric Symptoms in Children: A Longitudinal Population-Based Neuroimaging Study. Am J Psychiatry. 2017; 175: 54-62

33. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Cognitive functions correlate with white matter architecture in a normal pediatric population: a diffusion tensor MRI study. Hum Brain Mapp. NIH Public Access; 2005;26:139–47.

34. Mulder TA, Kocevska D, Muetzel RL, Koopman-Verhoeff ME, Hillegers MH, White T, et al. Childhood sleep disturbances and white matter microstructure in preadolescence. J Child Psychol Psychiatry. 2019;60:1242–50.

35. Bolhuis K, Tiemeier H, Jansen PR, Muetzel RL, Neumann A, Hillegers MHJ, et al. Interaction of schizophrenia polygenic risk and cortisol level on pre-adolescent brain structure. Psychoneuroendocrinology. 2019;101:295–303.

36. Sink KM, Espeland MA, Castro CM, Church T, Cohen R, Dodson JA, et al. Effect of a 24-month physical activity intervention vs health education on cognitive outcomes in sedentary older adults. JAMA. 2015;314:781.

37. Nakagawa S, Cuthill IC. Effect size, confidence interval and statistical significance: A practical guide for biologists. Biol. Rev. 2007; 82: 591–605.

38. Benjamini Y, Hochberg Y. Controlling the False Discovery Rate: A Practical and Powerful Approach to Multiple Testing. 1995; 57: 289-300.

39. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al.

Improved frontoparietal white matter integrity in overweight children is associated with attendance at an after-school exercise program. Dev Neurosci. 2014;36:1–9.

40. Esteban-Cornejo I, Rodriguez-Ayllon M, Verdejo-Roman J, Cadenas-Sanchez C, Mora-Gonzalez J, Chaddock-Heyman L, et al. Physical Fitness, White Matter Volume and Academic Performance in Children: Findings From the ActiveBrains and FITKids2 Projects. Front Psychol.Frontiers; 2019;10:208.

41. Wang S, Yin H, Wang X, Jia Y, Wang C, Wang L, et al. Efficacy of different types of exercises on global cognition in adults with mild cognitive impairment: a network meta-analysis. Aging Clin. Exp. Res. Springer International Publishing; 2019; 1: 1391–400.

42. Palmer HS, Håberg AK, Fimland MS, Solstad GM, Iversen VM, Hoff J, et al. Structural brain changes after 4 wk of unilateral strength training of the lower limb. 2013;167–75.

43. Best JR, Chiu BK, Hall PA, Liu-Ambrose T. Larger Lateral Prefrontal Cortex Volume Predicts Better Exercise Adherence Among Older Women: Evidence From Two Exercise Training Studies. J Gerontol A Biol Sci Med Sci. 2017;72:804–10.

44. Gujral S, McAuley E, Oberlin LE, Kramer AF, Erickson KI. Role of Brain Structure in Predicting Adherence to a Physical Activity Regimen. Psychosom Med. 2018;80:69–77.

45. Bloss EB, Janssen WG, Ohm DT, Yuk FJ, Wadsworth S, Saardi KM, et al. Evidence for reduced experience-dependent dendritic spine plasticity in the aging prefrontal cortex. J Neurosci. 2011;31:7831–9.

46. Yotsumoto Y, Chang LH, Ni R, Pierce R, Andersen GJ, Watanabe T, et al. White matter in the older brain is more plastic than in the younger brain. Nat Commun. Nature Publishing Group; 2014;5: 5504.

47. Schwartz S, Maquet P, Frith C. Neural correlates of perceptual learning: A functional MRI study of visual texture discrimination. Proc Natl Acad Sci U S A. 2002;99:17137–42.

48. Davis CL, Tomporowski PD, Mcdowell JE, Austin BP, Miller PH, Allison JD. Exercises improves executive function and achievement and alters brain activation in overweight children A randomized controlled trial. Nih. 2011;30:91–8.

49. Naidoo A, Naidoo K, Yende-zuma N, Gengiah TN. An 8-Month Randomized Controlled Exercise Trial Alters Brain Activation During Cognitive Tasks in Overweight Children. Obesity (Silver Spring). 2014;22:232–42.

50. Krafft CE, Pierce JE, Schwarz NF, Chi L, Weinberger AL, Schaeffer DJ, et al. An eight month randomized controlled exercise intervention alters resting state synchrony in overweight children. Neuroscience. 2014;256:445–55.

51. Oouchi H, Yamada K, Sakai K, Kizu O, Kubota T, Ito H, et al. Diffusion

Anisotropy Measurement of Brain White Matter Is Affected by Voxel Size: Underestimation Occurs in Areas with Crossing Fibers. Am J Neuroradiol. 2007;28:1102–6.

Supplemental Material
Study VIII

GENERAL DISCUSSION

GENERAL DISCUSSION

The general aim of the present International Doctoral Thesis was to study the role of physical activity, sedentary behavior and physical fitness in mental health and white matter in children and adolescents. This section offers a general discussion of the main results presented across the studies of this Doctoral Thesis, insights into relevant methodological considerations, and proposes future directions for the field.

Main findings of the present Doctoral Thesis

Overall, we found that physical activity has a small positive effect on mental health in young people**.** In terms of white matter, we did not find any significant effect, although cross-sectional studies of the present Doctoral Thesis seems to indicate there is a positive relationship. Sedentary behavior seems to be negatively associated with mental health. However, the relationship with white matter microstructure is not clear yet. For instance, while we found that watching TV was negatively associated with white matter microstructure in children with overweight or obesity from Spain, no association was found in a bigger cohort of children from a population-based study in the Netherlands. In addition, future work should continue to explore longitudinal data in order to more concretely decipher the temporality of these associations. Regarding to physical fitness components, muscular fitness was the most promising physical fitness component in relation to mental health, and white matter in young people. Due to most of the literature has been focused on studying the benefits of cardiorespiratory fitness in mental health and white matter microstructure, we encourage researchers to study the potential role of muscular fitness in mental and brain health in young people as well as the mechanisms that might explain this relationship.

Part I. Physical activity, sedentary behavior, physical fitness and mental health

Physical activity and mental health

Findings from the present Doctoral Thesis suggest that physical activity has a small but significant positive effect on young people´s mental health (**Study I**, **Study II**). Historically, researchers have focused on studying how higher levels of physical activity improve mental health in terms of duration, frequency or intensity. In this line, there has been a tendency to think that physical activity or sedentary behavior are "injected" into passive individuals who automatically experience an effect on mental health. This "theory" could be useful to improve some parameters of physical health (e.g., reduce total adiposity, the risk of cardiovascular diseases or type II diabetes) in term of dose-response [1]. However, when studying the relationship between physical activity and mental health, other important factors should be also considered.

As an example, the type of physical activity program (i.e., aerobic exercise program vs. sport-based program) might moderate the effect of physical activity on self-concept in youths. Interestingly, self-concept is considered an important pathway across physical activity may improve other mental health outcomes such as depression in young people [2]. Specifically, larger effects on self-concept were found in intervention focused on exercise (typically aerobic) instead of sport-based. One possible explanation is that participation in aerobic-based activities are important for maintaining a healthy body weight, which might enhance physical self-concept via the mechanism of improved physical appearance. Another neurobiological mechanisms could be that aerobic exercise –by increasing brain dopamine, serotonin or noradrenaline concentrations- might create a sense of "feeling well about your-self". On the other hand, intervention based on sports interact also with other factors such as the social environment and the competitive elements [2]. The sports element of winning a game can lead to increased self-concept, whereas losing the game may have adverse effects on self-concept and in turn on other mental health outcomes. Therefore, future intervention with the aim of improve mental health across physical activity might consider not only "classical" characteristics of the intervention such as weeks of intervention, frequency or intensity but also other characteristics such as enjoyment, perceived competence or young people's motivation to maximise the positive effect of physical activity on mental health in youths [3].

Sedentary behavior and mental health

Sedentary behaviour of young people is nowadays a big worry for parents, caregivers or public health institutions. Systematic reviews and meta-analyses have shown that sedentary behavior, especially recreational screen time, is negatively associated with mental health in young people (**Study I**, **Study II**). However, most of the studies had a cross-sectional design. Therefore, experimental studies on sedentary behavior and mental health are required to draw conclusions in regard to cause and effect.

Literature on the field of sedentary behavior and mental health in young people has been focused on answering "how much time of recreational screen time based on sedentary behavior is harmful for the mental health of young people". In this regard, research suggests a limit of two hours per day (**Study I**, **Study II**); however those recommended levels need more scientific support. For instance, some researchers suggest no more than two hours of watching TV [4] while other researchers recommend no more than two hours of any type [5]. In addition, advances in technology (e.g., availability of hand-held media devices, and social media) compared to the construct of purely passive watching TV, further underscore the importance of maintaining well-characterized measures of screen time, as differing amounts/types of screen time could differently influence the mental health.

Another source of uncertainty is the trend of the relationship between sedentary behavior and mental health (e.g., linear vs. curvilinear). In this line, Liu et al. [5] found that compared with the reference group who had not sedentary behavior, there was a non-linear dose-response association of screen time-based sedentary behavior with a decreasing risk of depression at sedentary time < 2 hour/day, with the lowest risk being observed for 1 hour/day. Przyibylsky et al. [6] found that the relationship between screen time and mental health was non-linear and that moderate engagement in screen time was not harmful. In addition, Ferguson et al. [7] suggested that depressive symptoms were highly elevated among youth who consumed over six hours of media a day. To sum up, screen time at moderate levels could not be harmful and may be advantageous in a "connected technological world", whereas "overuse" may displace alternate activities, for example, interfering with school or with extracurricular or other social activities.

In addition to the number of hours, other questions should be addressed. First, the issue of whether violent or nonviolent recreational screen time "harm" children and adolescents continues to be hotly contested in the scientific community. In this line, Ferguson [8] in his meta-analyses *"Do Angry Birds Make for Angry Children?"* indicate that video games, whether violent or nonviolent, have minimal deleterious influence on children's well-being. Second, the role of social context (e.g., alone vs. in company) in the relationship between sedentary behavior and mental health will require more research. Given that it often takes place alone, sedentary behavior could elicit feelings of loneliness and, consequently, negatively impact on mental health. In contrast, moderate use of recreational screen time to connect with other people could have a positive effect on the mental health of young people (e.g., video games chats or social media use) [9,10]. Third, there is limited evidence to conclude whether associations between sedentary behavior and mental health are explained by the specific type of sedentary behavior (e.g., watching TV, playing videogames) versus time in sedentary behaviors itself. Addressing above-mentioned research questions could guide researchers in the design of future interventions with the aim of decreasing the negative consequences of sedentary behavior in the mental health of young people.

Physical fitness and mental health

Previous literature found that higher levels of physical fitness are related to a better mental health in young people [11,12]. In line with previous findings, we found that that higher levels of muscular fitness were negatively associated with psychological distress (i.e., negative affect and stress) and positively associated with psychological well-being (i.e., self-esteem and optimism) in children with overweight or obesity (**Study III**). Moreover, a positive association between cardiorespiratory fitness and optimism was observed. Lastly, motor fitness was not associated with any mental health outcome assessed in our study. Therefore, this study mainly highlights the potential benefits of muscular fitness on mental health in children with overweight or obesity.

Physical self-concept (e.g. sport competence, physical appearance or physical strength) seems to be an important pathway across physical activity improves mental health in young people (**Study I**, **Study II**). The extent to which physical self-concept sub-domains might impact on overall young people physical self-concept, and in turn on other mental health outcomes, depends on the value placed on each sub-domain [13]. For instance, among girls, perceived body attractiveness appears to be the physical self-concept sub-domain most predictive. In contrast, perceptions of muscular strength have been shown to relate more strongly to physical self-concept among boys [13]. Children with overweight or obesity have shown a worst physical self-concept in some specific domains such as physical appearance or sport competence compared with their normal weight peer [14,15]. Therefore, muscular strength could play an important role, specifically in children with overweight/obesity, in the preservation of overall physical self-concept. Future research is needed to test whether muscular strength could mediate the relationship between physical activity and mental health across an improvement in physical self-concept in children with overweight or obesity.

Part II. Physical activity, sedentary behavior, physical fitness and white matter

Physical activity and white matter

There is considerable support in the extant literature for the psychosocial pathways across physical activity might have a positive effect on mental health in young people (e.g., physical self-concept) (**Study I**, **Study II**). However, there is a paucity of research investigating the neurobiological mechanisms which may serve to mediate this relationship. This hypothesis, which remains to be corroborated, suggests that physical activity might enhance mental health via the release of endorphins, increases in brain-derived neurotropic factor and growth of new capillaries, which in turn might have a positive effect on the structure and function of the brain.

Structural connectivity is one of the brain features that seems to be susceptible of being modified by physical activity; however more research is need to corroborate this hypothesis. In this context, we found that self-reported physical activity was associated with white matter microstructure in children (**Study IV, Study V**). Those results were similar in two different samples (i.e., ActiveBrains and Generation R) from different countries (i.e., Spain and the Netherlands). Of note, inconsistent associations were found between objectively measured physical activity variables (i.e., total physical activity, light physical activity, moderate-to-vigorous physical activity) and white matter microstructure in children with overweight or obesity from the ActiveBrains project (**Study V**). Therefore, although our findings suggest that self-reported physical activity is associated with white matter microstructure in children, these results should be cautiously interpreted, since these associations are limited by the measurement tools (i.e., self-reports vs. accelerometry), and the cut-points used. In addition, we investigated the effects of a 20-week randomized controlled physical activity intervention on white matter microstructure in children with overweight or obesity (**Study VIII**). Briefly, we found that a 20-week physical activity intervention had no effect on white matter microstructure in children with overweight or obesity. Those findings open new questions and future directions on the physical activity and brain health field in young people. First, the majority of studies has assumed that higher levels of physical activity predict greater white matter and has investigated the association in this direction. However, it is unclear whether the reverse relationship also holds (i.e., those children with greater white matter microstructure practice more physical activity over time). Hence, testing if greater white matter microstructure predicts higher levels of physical activity over time might contribute to identify a possible neurobiological pathway across some social or cognitive factors might increase physical activity levels over time. Second, 20-week physical activity intervention could be not enough to induce changes in the white matter during childhood. In this line, an 8-month exercise intervention showed that, compared to controls, children with overweight, in the exercise group increased FA in sections of the uncinate fasciculus and superior longitudinal fasciculus [16,17]. Moreover, another 9-month exercise intervention showed that, compared to controls, those children who participated in the exercise program showed increased FA in the genu of the corpus callosum [18]. In contrast, our tract-specific approach did not have tract-specific masks for all brain regions. For instance, we did not encompass the corpus callosum outsize of the forceps major and forceps minor fiber bundles. Then, future works using different approaches are needed to explore whether physical activity has definitively an effect on white matter microstructure during childhood. In addition, future studies should test if white matter microstructure is a neurobiological pathway across physical activity may improve mental health in young people.

Sedentary behavior and white matter

Recreational screen based sedentary behavior (i.e., watching TV and playing computer game) was not associated with white matter microstructure in children from the Netherlands (**Study IV**). However, higher levels of watching TV were negatively associated with white matter microstructure in children with overweight or obesity from Spain (**Study V**). To the best of our knowledge, in addition to our studies (**Study IV** and **Study V**) only Hutton JS et al. [19] tested the relationship between screen time and white matter microstructure in a sample of young people, specifically in preschoolers. This study found an association between increased screen-based media use and lower microstructural integrity of brain white matter tracts supporting language and emergent literacy skills in preescholers living in a household of native English speakers from United States [19]. Differences in white matter assessment (e.g., voxel resolution= 2 x 2 x 2 mm^3 in the Generation R and Hutton JS et al. [19] study vs. voxel resolution= 1.8 x 1.8 x 4 mm^3 in the ActiveBrains project) and in sample characteristics (e.g., preescholers, children with overweight or obesity or children from a population-based study) among the studies should be acknowledged. In addition, other possible characteristics of watching TV such as TV content might be considered. For instance, TV programs are not dubbed into their own languages in the Netherlands. Whereas, in Spain and United States, they translate the TV into the country language. Interestingly, purely passive watching TV but in a different language could attenuate the negative consequences of watching TV on white matter during childhood (**Study IV**) [20,21]. In this context, more research is needed to test if TV content could moderate the relationship between watching TV and white matter microstructure in young people.

Physical fitness and white matter

We previously shown that cardiorespiratory fitness and motor fitness, but not muscular fitness were associated with greater gray matter volume in children with overweight or obesity [22]. However, **Study VI** of this Doctoral Thesis, found that not only cardiorespiratory and motor fitness, but also muscular fitness, was related to white matter volume among children with overweight or obesity. On the other hand, **Study VII** found that physical fitness components were not associated with global DTI metrics. Within individual tracts, all associations became non-significant when analyses were adjusted for multiple comparisons. Using the TBSS approach, we identified a small cluster in the left lateral frontal lobe where children with greater muscular fitness showed higher FA. Combining results from **Study VI** and **Study VII**, we provide new support that muscular training aimed at improving muscular fitness could influence white matter in young people.

Of note, most of the associations between physical fitness components and white matter were found in white matter volume (**Study VI**) instead of the white matter microstructure (i.e., only a small cluster in the left lateral frontal lobe where children with greater muscular fitness showed higher FA) (**Study VII**). There are several possible explanations for this result. First, white matter plasticity is determine by several white matter features such as new myelin formation, changes in myelin thickness, internode length modulation or axon diameter. Interestingly, most of the contrast in T1-weighted images is provided by myelin and iron concentration [23]. Therefore, other parameters such axon diameter, internode length or ion channel density, which could contribute to white matter plasticity, are not reflected in the white matter volume. In contrast, diffusion imaging provides other white matter features such as axon diameter and density, fiber organization, myelin content, glial cells, and the condition or permeability of the membrane [24]. It is possible that physical fitness might affect just a few characteristics of white matter plasticity such as myelin formation or thickness during child development, making difficult to see any change in white matter measures such as FA or MD, which are capturing the sum of all changes in white matter microstructure (e.g., axon diameter and density or fiber organization). In this line, future studies using both T1-weighted images and DTI in a bigger cohort of children are needed to corroborate our hypothesis.

REFERENCES

1. Physical Activity Guidelines for Americans. 2nd edition. 2018;Washington, DC: US Department of Health and Human Services. https://healt h.gov/pagui delin es/secon d-editi on/pdf/Physical_Activity_Guide lines 2nd_editi on.pdf. Accessed 15 Nov 2018.

2. Spruit A, Assink M, van Vugt E, van der Put C, Stams GJ. The effects of physical activity interventions on psychosocial outcomes in adolescents: A meta-analytic review. Clin Psychol Rev. 2016;45:56–71.

3. Lubans DR, Lonsdale C, Cohen K, Eather N, Beauchamp MR, Morgan PJ, et al. Framework for the design and delivery of organized physical activity sessions for children and adolescents: Rationale and description of the "SAAFE" teaching principles. Int. J. Behav. Nutr. Phys. 2017.14:24

4. Padilla-Moledo C, Castro-Piñero J, Ortega FB, Pulido-Martos M, Sjöström M, Ruiz JR. Television viewing, psychological positive health, health complaints and health risk behaviors in Spanish children and adolescents. J Sports Med Phys Fitness. 2015;55:675–83.

5. Liu M, Wu L, Yao S. Dose-response association of screen time-based sedentary behaviour in children and adolescents and depression: A meta-analysis of observational studies. Br J Sports Med. 2015;1–8.

6. Przybylski AK, Weinstein N. A Large-Scale Test of the Goldilocks Hypothesis: Quantifying the Relations Between Digital-Screen Use and the Mental Well-Being of Adolescents. Psychol Sci. 2017;28:204–15.

7. Ferguson CJ. Everything in Moderation: Moderate Use of Screens Unassociated with Child Behavior Problems. Psychiatr Q. 2017;88:797–805.

8. Ferguson CJ. Do Angry Birds Make for Angry Children? A Meta-Analysis of Video Game Influences on Children's and Adolescents' Aggression, Mental Health, Prosocial Behavior, and Academic Performance. Perspect Psychol Sci. 2015;10:646–66.

9. Jones CM, Scholes L, Johnson D, Katsikitis M, Carras MC. Gaming well: Links between videogames and flourishing mental health. Front Psychol. Frontiers Media SA; 2014;5.

10. Ferguson CJ. Should we panic about teens' social media use? HoustonChronicle.com. 2017.

11. Smith JJ, Eather N, Morgan PJ, Lubans DR. The Health Benefits of Muscular Fitness for Children and Adolescents : A Systematic Review and Meta-Analysis. 2014;1209–23.

12. Ortega FB, Ruiz JR, Castillo MJ, Sjöström M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes. 2008;32:1–11.

13. Lubans DR, Cliff DP. Muscular fitness, body composition and physical self-perception in adolescents. J Sci Med Sport. 2011;14:216–21.

14. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. Eur Neuropsychopharmacol. Elsevier B.V.; 2011;21:718–79.

15. Bang KS, Chae SM, Hyun MS, Nam HK, Kim JS, Park KH. The mediating effects of perceived parental teasing on relations of body mass index to depression and self-perception of physical appearance and global self-worth in children. J Adv Nurs. 2012;68:2646–53.

16. Schaeffer DJ, Krafft CE, Schwarz NF, Chi L, Rodrigue AL, Pierce JE, et al. An 8-month exercise intervention alters frontotemporal white matter integrity in overweight children. Psychophysiology. 2014;51:728–33.

17. Krafft CE, Schaeffer DJ, Schwarz NF, Chi L, Weinberger AL, Pierce JE, et al. Improved frontoparietal white matter integrity in overweight children is associated with attendance at an after-school exercise program. Dev Neurosci. 2014;36:1–9.

18. Chaddock-Heyman L, Erickson KI, Kienzler C, Drollette E, Raine L, Kao S-C, et al. Physical Activity Increases White Matter Microstructure in Children. Front Neurosci. Frontiers; 2018;12:950.

19. Hutton JS, Dudley J, Horowitz-Kraus T, Dewitt T, Holland SK. Associations between Screen-Based Media Use and Brain White Matter Integrity in Preschool-Aged Children. JAMA Pediatr. American Medical Association; 2019;

20. Perani D, Abutalebi J. Bilingualism, dementia, cognitive and neural reserve. Curr. Opin. Neurol. Lippincott Williams and Wilkins; 2015. p. 618–25.

21. Moreno S, Lee Y, Janus M, Bialystok E. Short-Term Second Language and Music Training Induces Lasting Functional Brain Changes in Early Childhood. Child Dev. Blackwell Publishing Inc.; 2015;86:394–406.

22. Esteban-Cornejo I, Cadenas-Sanchez C, Contreras-Rodriguez O, Verdejo-Roman J, Mora-Gonzalez J, Migueles JH, et al. A whole brain volumetric approach in overweight/obese children: Examining the association with different physical fitness components and academic performance. The ActiveBrains project. Neuroimage. 2017;159:346–54.

23. Stüber C, Morawski M, Schäfer A, Labadie C, Wähnert M, Leuze C, et al. Myelin and iron concentration in the human brain: A quantitative study of MRI contrast. Neuroimage. Academic Press Inc.; 2014;93:95–106.

24. Sampaio-Baptista C, Johansen-Berg H. White Matter Plasticity in the Adult Brain. Neuron. Cell Press; 2017. 96: 1239-1251.

FUTURE PERSPECTIVES

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- Most of the studies focused on physical activity, sedentary behavior and mental health, included in **Study I** and **Study II,** were focused on adolescents. Therefore, future research is required especially in preschoolers and children.
- We found that physical activity had a small positive effect on mental health in young people. However, future intervention with the aim of improve mental health across physical activity might consider not only “classical” characteristics such as weeks of intervention, frequency or intensity but also other characteristics such as enjoyment, perceived competence or young people’s motivation to maximise the positive effect of physical activity on mental health in youths [2].
- Experimental studies on sedentary behavior and mental health are required to draw conclusions in regard to cause and effect.

- Findings from this Doctoral Thesis suggests that white matter microstructure is one of the brain features susceptible of being modified by physical activity, sedentary behavior and physical fitness. On the other hand, other studies found that white matter microstructure was related to the experience of psychiatric symptoms in young people [22–24]. However, it is unknown if white matter microstructure is a neurobiological pathway across those behavior/factors may reduce psychiatric symptoms in young people. Therefore, mediation models are needed to identify the mechanisms (i.e., neurobiological, psychological and behavioral) responsible for any changes in mental health resulting from participation in physical activity or sedentary behavior activities.

- Cross-sectional and experimental studies of this Doctoral Thesis (**Study IV**, **V**, **VI**, **VII, VIII)** testing the role of physical activity, sedentary behavior and fitness in white matter were focused on children, being most of them specifically focused on children with overweight or obesity. Therefore, those findings need to be corroborate in preescholers and adolescents as well as in young people with the entire range of the BMI distribution.

- Further longitudinal studies could elucidate the temporal relationship between physical activity, sedentary behavior, physical fitness and white matter in young people.
- Muscular training interventions with the aim of improving muscular fitness are needed to test if muscular fitness influence white matter in young people.
- Longer interventions are needed to contrast or confirm the combined effect of muscular and aerobic exercise on white matter microstructure in children.

OVERALL LIMITATIONS AND STRENGTHS OF THIS THESIS

OVERALL LIMITATIONS AND STRENGTHS OF THIS THESIS

An integrative view of the general limitations and strengths of the present International Doctoral Thesis can be found in **Table 1**. Studies´ limitations and strengths has been classified in two different parts depending on the main outcome of the study, i.e., **Part I** is focused on mental health outcomes, while **Parte II** is focused on white matter.

Table 1. Limitations and Strengths of the present Doctoral Thesis

Study	Limitations	Strengths
Part I		
I II	- Grey literature was not included. - The search was conducted in only two databases (PubMed and Web of Science). - Studies written in languages other than English and Spanish were excluded. - Because of the heterogeneity of the outcome measures, it was not possible to conduct a meta-analysis of the prospective longitudinal studies (Study II). - Because most of the intervention studies were focused on adolescents and no studies were found in preschoolers, we cannot rule out a cause and effect relationship between physical activity and mental health in preschoolers (Study II).	- Both reviews employed stringent systematic review methodology as per with the PRISMA guidelines. - The search strategies has been reported. - Quality of included studies was examined. - Priori design registered in the Prospero database (Study II). - We provided a list of the studies included and excluded (Study II). - We performed a meta-analysis, including intervention studies, which made possible to map the link between exercise and mental health across young people (Study II).
III	-This study applied a cross-sectional design, and therefore, drawing causal associations is not possible. - Although we explored the role of potential confounders in the analyses of this study, it is not possible to guarantee that other confounders not measured in the present study could explain the observed associations. -We focused on children with overweight or obesity, which limits the generalizability of our findings to the entire range of the BMI distribution.	- The complete and standardized assessment of the three physical fitness components. - The inclusion of a broad set of mental health indicators.
Part II		
IV V VI VII VIII	- Those studies applied a cross-sectional design. Then, drawing causal associations is not possible (not applicable for Study VIII) - Although we explored the role of potential confounders, it is not possible to guarantee that other confounders not measured in the present Thesis could explain the observed associations. - We focused on children with overweight or obesity, which limits the generalizability of our findings to the entire range of the BMI distribution (Studies V, VII, VIII). - Voxel size was a 4-mm-section nonisotropic voxel (1.8 x 1.8 x 4 mm^3). Therefore, FA could be underestimated in regions containing crossing fibers (Studies V, VII, VIII). - It is unknown whether the effects observed would have been larger if the intervention would have lasted longer (Study VIII)	- The inclusion of neuroimaging data. - The complete and standardized assessment of the three physical fitness components (Studies VI, VII). - The large sample size, and the population-based sampling offers increased generalizability of the findings compared to previous studies (Study IV). - The inclusion of both objective (using different cut- points, accelerometer locations and metrics), and self-reported measurements to assess physical activity and sedentary behavior (Study V). - The use of data from independent relatively large studies which speaks to the robustness of the observed findings (Study IV, V, VI). - Exploratory analyses using the intention-to-treat and the design, which allows causal inferences (Study VIII) - The physical exercise instructors who carried out the exercise program were not involved in the outcome evaluations. In addition, the staff involved in the post-exercise MRI evaluations were fully blinded to the participants´ group allocation (Study VIII)

OVERALL CONCLUSION

OVERALL CONCLUSION

Higher levels of physical activity and physical fitness and lower levels of sedentary behavior are associated with a better mental health in young people. In this line, experimental studies suggest that there is a small positive effect of physical activity on mental health; however no interventions on sedentary behavior were found. In term of white matter, higher levels of physical activity seem to be associated with greater white matter microstructure in children. However those findings have been not confirm in our RCT. Therefore, we cannot establish cause-effect between physical activity and white matter. Findings regarding to sedentary behavior are inconsistent between different studies of this Doctoral Thesis, which used different cohorts of children from Spain and the Netherlands. Lastly, not only cardiorespiratory and motor fitness, but also muscular fitness, seems to be related to white matter volume among children with overweight or obesity from the ActiveBrains project. In contrast, muscular fitness seems to be the only physical fitness component positively associated with white matter microstructure in children with overweight or obesity from the ActiveBrains project. Accordingly, muscular training interventions with the aim of improving muscular fitness are needed to test if muscular fitness influence white matter in young people. All those findings together suggest that physical activity, sedentary behavior and physical fitness might influence mental health in young people. However, the role of those behavior/factors in the white matter of young people requires more research. Lastly, further research is needed to test if white matter is a neurobiological pathway across those behaviors/factors that improve mental health in young people.

SPECIFIC CONCLUSIONS

PART I. Physical activity, sedentary behavior, physical fitness and mental health

- **Study I:** From our review of reviews, a small but significant positive effect of physical activity on mental health among youths emerges. Furthermore, increased levels of sedentary behavior, particularly excessive recreational screen time seems to be related to a poorer mental health among young people. In this context, answering the questions how young people watch, what they watch, and with whom might be important to understand the relationship between sedentary behavior and mental health in young people. Lastly, more studies are needed to better understand the specific mechanisms responsible for the effect of physical activity and sedentary behavior on mental health in young people.
- **Study II:** Findings from the present systematic review and meta-analyses suggest that physical activity has a small but significant positive effect on adolescents' mental health. Due to the small number of studies, it is not possible to determine the effect of physical activity on preschoolers' and children's mental health. Conversely, time spent in sedentary behavior seems to be negatively associated with mental health in children and adolescents; although more research regarding to its context, content or type is needed.
- **Study III:** Higher levels of muscular strength may have a positive influence on psychological distress (i.e. negative affect and stress) and psychological well-being indicators (i.e. self-esteem and optimism), as well as higher levels of cardiorespiratory fitness on optimism, in children with overweight or obesity, yet this results need to be confirmed in RCTs.

Part II. Physical activity, sedentary behavior, physical fitness and white matter

- **Study IV:** Higher levels of physical activity are associated with greater white matter microstructure in children ages 9-to-10 years old from a population-based study. No association is observed between screen time and white matter microstructure. Future work should continue to explore longitudinal data in order to more concretely decipher the temporality of the associations.
- **Study V:** Total physical activity is positively associated with white matter microstructure in children with overweight or obesity; however, more studies are needed to corroborate these findings, due to the controversy about the optimal and appropriate cut-points used to test the association of objectively measured physical activity and sedentary behavior with white matter microstructure. Among the sedentary behaviors assessed, watching TV seems to be negatively associated with white matter microstructure.
- **Study VI:** Our findings across two independent studies suggest that cardiorespiratory fitness may positively relate to white matter volume in children with overweight or obesity, and in turn, academic performance but not in normal-weight children. In addition, other physical fitness components (i.e., motor and muscular) may also influence white matter volume coupled with better academic performance.
- **Study VII:** Physical fitness components are not associated with global DTI metrics (i.e., global FA, and global MD). Within individual tracts, all associations became non-significant when analyses are adjusted for multiple comparisons. However, using the TBSS approach, we identify a small cluster in the left lateral frontal lobe where children with greater absolute upper-body muscular fitness show higher FA, after adjusting for multiple comparisons.

- **Study VIII:** A 20-week physical exercise intervention has no effect on white matter microstructure in children with overweight or obesity. Therefore, a 20-week physical exercise intervention, based on a combination of aerobic and muscular exercise, might be not enough to induce changes in the white matter during childhood. Further larger RCTs should examine the effect of longer exercise intervention combining both aerobic and muscular training on the white matter microstructure in children.

APPENDICES

PAPERS DERIVED FROM THE THESIS

1. M. Rodriguez-Ayllon, I. Esteban-Cornejo, F. Estevez-Lopez, C. Cadenas-Sanchez, L. Gracia-Marco, D. Lubans, F.B. Ortega. Physical activity, sedentary behaviour and mental health in young people. Adolescent health and wellbeing: Current Strategies and Future Trends. **Springer.** 2019; 1: 35-73. https://doi.org/10.1007/978-3-030-25816-07

2. M. Rodriguez-Ayllon, C. Cadenas-Sánchez, F. Estévez-López, N. Ernesto Muñoz, J. Mora-González, J. H. Migueles, P. Molina-García, H. Henriksson, A. Mena-Molina, V. Martínez-Vizcaíno, A. Catena, M. Löf, K. I. Erickson, D.R. Lubans, F. B. Ortega, I. Esteban-Cornejo. Role of physical activity and sedentary behaviour in the mental health of children and adolescents: A systematic review and meta-analysis. **Sports Medicine**. 2019; 49:1383-1410

3. M. Rodriguez-Ayllon, C. Cadenas-Sánchez, I. Esteban-Cornejo, J. H. Migueles, J. Mora-González, P. Henriksson, M. Martín-Matilla, A. Mena-Molina, P. Molina-García, F. Estévez-López, J. C. Perales, J. R. Ruiz, A. Catena, F. B. Ortega. Physical fitness and psychological health in overweight/obese children. A cross-sectional study from the ActiveBrains project. **Journal of Sciences & Medicine in Sport**. 2018; 21: 179-184.

4. M. Rodriguez-Ayllon, I. P. M. Derks, M. A van den Dries, I. Esteban-Cornejo, J. A. Labrecque, J. Yang-Huang, H. Raat, M. W. Vernooij, T. White, F.B. Ortega, H. Tiemeier, R.L. Muetzel. Associations of physical activity and screen time with white matter microstructure in healthy children. **NeuroImage.** 2019; 205: 116258.

5. M. Rodriguez-Ayllon, I. Esteban Cornejo, J. Verdejo-Román, R. L. Muetzel, J. H. Migueles, J. Mora-Gonzalez, P. Solis-Urra, K.I. Erickson, C.H. Hillman, A. Catena, H. Tiemeier, F. B. Ortega. Associations of physical activity and sedentary behaviour with white matter microstructure in children with overweight/obesity: the ActiveBrains project. Submitted in **Medicine & Science in Sport and Exercise.** 2019; In press.

6. I. Esteban-Cornejo, M. Rodriguez-Ayllon, J. Verdejo-Roman, C. Cadenas-Sanchez, J. Mora-Gonzalez, L. Chaddock-Heyman, L. B. Raine, C. M. Stillman, A. F. Kramer, K. I. Erickson, A. Catena, F. B Ortega, Charles H. Hillman. Physical fitness, white matter volume and academic performance in children: findings from the ActiveBrains and FITKids2 studies. **Frontiers in Psychology**. 2019; 10:208.

7. M. Rodriguez-Ayllon, I. Esteban-Cornejo, J. Verdejo-Román, R. L. Muetzel, J. Mora-Gonzalez, C. Cadenas-Sanchez, A. Plaza-Florido, P. Molina-García, A. F. Kramer, A. Catena, F. B. Ortega. Physical fitness and white matter microstructure in children with overweight or obesity: The ActiveBrains project. *Submitted in Scientific Reports.*

8. M. Rodriguez-Ayllon, I. Esteban-Cornejo, F. B. Ortega et al. Effect of an exercise-based randomized controlled trial on white matter microstructure in children with overweight or obesity: The ActiveBrains project. *In Preparation.*

CURRICULUM VITAE

María Rodriguez-Aylion

E-mail: rodriguezm@ugr.es

Birthday date: 14/ August /1992.

Position: Predoctoral research fellow.

Affiliation: Department of Physical Education and Sport, University of Granada, Granada, Spain.

ACADEMIC BACKGROUND

- 2016 / 2020— International PhD in **Biomedicine**, University of Granada, Granada, Spain. Supervisors: **Francisco B. Ortega Porcel** and **Irene Esteban Cornejo.**
- 2015 / 2016— Master´s degree in **Physical Activity and sport Research**, Physical activity and health specialization, University of Granada, Granada, Spain.
- 2012 / 2015— Bachelor´s degree in **Physical Activity Sciences and Sport,** University of Granada, Granada, Spain.

PREVIOUS FUNDING (fellowships, travel grants, awards)

- 2019—Grant of the attendance to national of international congress 2019. University of Granada.
- 2019/2020—Predoctoral Fellowship for research (Ref: 5337). Research project: Peripheral mechanisms inducing neurogenesis, hippocampal function and mental health in children: The role of exercise. Main researcher: Francisco B. Ortega Porcel.
- 2019— **Erasmus Internship Program,** Erasmus University Medical Centre Rotterdam (The Netherlands). Department of Child and Adolescent Psychiatry. Advisors: **Ryan L. Muetzel**.
- 2018/2019—Annual award, in collective category to the research group **PROFITH**. El Ilustre Colegio Oficial de Licenciados en Educación Física y en Ciencias de la Actividad Física y el Deporte de Asturias (**COLEF**). Spain.
- 2018/2019— Research award “Dr. Fernando González Foretic”. Second position for the work presented in the III International Symposium Exercise and Physical Activity Science. Santiago, Chile. April. **M. Rodriguez Ayllon** was a coautor in this work.
- 2018/2019— **Predoctoral Fellowship for research**, the National Operational Programme for the implementation of the **Youth Employment**, University of Granada, Spain.
- 2017— **Mobility and International Exchange** Fellowship for Predoctoral research, Department of child and adolescents psychiatry, Erasmus University Medical Centre in Rotterdam, The Netherlands.

- 2016/2017— **Research Initiation Fellowship,** Department of physiology, University of Granada, Spain.
- 2016/2017— **Contract research project,** University of Granada (Ref: DEP201347540-R).
- 2015/2016— **Distinguished Master's Thesis Award** in the Master´s degree in **Physical Activity and sport Research**, Physical activity and health specialization, University of Granada, Spain.
- 2015— **Erasmus Internship Program,** Faculty of Clinical and Health Psychology (Faculty Social and Behavioral Science), University of Utrecht, the Netherlands.
- 2014/2015— **ERASMUS+ programme,** Faculty of Physical Culture**,** Univerzita Palackého v Olomouci, Czech Republic.

VISITING RESEARCHER

- 2019 August-October— Erasmus University Medical Centre Rotterdam (The Netherlands). Department of Child and Adolescent Psychiatry. Advisor: Ryan Muetzel, PhD.

- 2019 July— University of Pittsburgh (Pensilvania). Department of Psychology. Advisor: Kirk Erickson.

- 2018 October/December — University of Ulster (Northern Ireland). Institute of Nursing and Health Research. Advisor: Ciara Hughes, PhD.

- 2017 July/September— Erasmus University Medical Centre Rotterdam (The Netherlands). Department of Child and Adolescent Psychiatry. Advisors: **Henning Tiemeier**, PhD and **Tonya White**, PhD.

- 2015 July/September— **University of Utrecht** (The Netherlands). Faculty of social and Behavioural Sciences. Advisor: **Rinie Geenen**, PhD.

RESEARCH PROJECTS PARTICIPATION

- Peripheral mechanisms inducing neurogenesis, hippocampal function and mental health in children: The role of exercise (REF: DEP2017-91544-EXP; ALICIAK-2018). Main researcher: **Francisco B. Ortega Porcel**

- The **ActiveBrains** project— Effects of an exercise-based randomized controlled trial on cognitive performance, brain structure and brain function in overweight children (REF: DEP2013-47540-R; RYC-2011-09011). Main researcher: **Francisco B. Ortega Porcel.**

- The **Gestafit** project— Effects of supervised aerobic and strength training in overweight and grade I obese pregnant women on maternal and foetal health markers (REF: COFUND–Grant Agreement n°291780; PI-0395-2016) Main researcher: **Virginia Aparicio García-Molina.**

- The **al-Ándalus** project— Physical activity in women with fibromyalgia: effects on pain, health and quality of life (REF: DEP2010-15639; DEP2013-40908-R). Main researcher: **Manuel Delgado Fernández.**

- Hot water balneotherapy effect and hot water physical exercise on acute body temperature and pain in fibromyalgia women. Main researcher: **Víctor Segura Jiménez.**

ARTICLES IN JCR JOURNALS

1. **M. Rodriguez-Ayllon**, C. Cadenas-Sánchez, I. Esteban-Cornejo, J. H. Migueles, J. Mora-González, P. Henriksson, M. Martín-Matilla, A. Mena-Molina, P. Molina-García, F. Estévez-López, J. C. Perales, J. R. Ruiz, A. Catena, F. B. Ortega. Physical fitness and psychological health in overweight/obese children. A cross-sectional study from the ActiveBrains project. **Journal of Sciences & Medicine in Sport.** 2018; 21: 179-184.
2. F. Estévez-López, **M. Rodriguez-Ayllon**, A. Soriano-Maldonado, I. C. Álvarez-Gallardo, V. Segura-Jiménez, M. Herrador-Colmenero, M. Pulido-Martos, R. Geenen, A. Carbonell-Baeza, M. Delgado-Fernández. Independent and combined associations of overall physical fitness and subjective well-being components with fatigue in fibromyalgia: the al-Ándalus project. **Pain Medicine**. 2019; 20:2506-2515.
3. **M. Rodriguez-Ayllon**, C. Cadenas-Sánchez, F. Estévez-López, N. Ernesto Muñoz, J. Mora-González, J. H. Migueles, P. Molina-García, H. Henriksson, A. Mena-Molina, V. Martínez-Vizcaíno, A. Catena, M. Löf, K. I. Erickson, D. R. Lubans, F. B. Ortega, I. Esteban-Cornejo. Role of physical activity and sedentary behaviour in the mental health of children and adolescents: A systematic review and meta-analysis. **Sports Medicine.** 2019; 49:1383-1410.
4. **M. Rodriguez-Ayllon**, P. Acosta-Manzano, I. Coll-Risco, L. Romero-Gallardo, M. Borges-Cosic, F. Estévez-López, A. A. Virginia. Association of physical activity, sedentary time, and physical fitness with psychological health during early pregnancy: The Gestafit project. **Journal of Sport and Health Science.** 2019; In press.
5. I. Esteban-Cornejo, **M. Rodriguez-Ayllon**, J. Verdejo-Roman, C. Cadenas-Sanchez, J. Mora-Gonzalez, L. Chaddock-Heyman, L. B. Raine, C. M. Stillman, A. F. Kramer, K. I. Erickson, A. Catena, F. B Ortega, Charles H. Hillman. Physical fitness, white matter volume and academic performance in children: findings from the ActiveBrains and FITKids2 studies. **Frontiers in Psychology.** 2019; 10:208.
6. P. Molina-Garcia, J. H Migueles, C. Cadenas-Sanchez, I. Esteban-Cornejo, J. Mora-Gonzalez, **M. Rodriguez-Ayllon**, A. Plaza-Florido, A. Molina-Molina, G. Garcia-Delgado, E. D'Hondt, J. Vanrenterghem, F. B Ortega. Fatness and fitness in relation to functional movement quality in overweight and obese children. **Journal of Sports Science.** 2019; 37:878-885.
7. I. Esteban-Cornejo, J. Mora-Gonzalez, C. Cadenas-Sanchez, O. Contreras-Rodriguez, J. Verdejo-Roman, P. Henriksson, J. H. Migueles, **M. Rodriguez-Ayllon**, P. Molina-García, C. Suo, C. H. Hillman, A. F. Kramer, K. I.Erickson, A. Catena, A. Verdejo-García, F.B Ortega. Fitness, cortical thickness and surface

area in overweight/obese children: the mediating role of body composition and relationship with intelligence. **NeuroImage.** 2019; 86:771-781.

8. J. H Migueles, C. Cadenas-Sanchez, C. Tudor-Locke, M. Löf, I. Esteban-Cornejo, P. Molina-Garcia, J. Mora-Gonzalez, **M. Rodriguez-Ayllon**, E. Garcia-Marmol, U. Ekelund, F.B. Ortega. Comparability of published cut-points for the assessment of physical activity: Implications for data harmonization. **Scandinavian Journal of Medicine and Science in Sports.** 2019; 29:566-574.
9. J. Mora-Gonzalez, I. Esteban-Cornejo, C. Cadenas-Sanchez, J. H Migueles, P. Henriksson, **M. Rodriguez-Ayllon**, P. Molina-Garcia, M. Pontifex, A. Catena, F.B. Ortega. Physical fitness, physical activity, and the executive function in overweight and obese children: a cross-sectional study from The ActiveBrains project. **The Journal of Pediatrics.** 2019; 208:50-5.
10. P. Molina-Garcia, J. H Migueles, C. Cadenas-Sanchez, I. Esteban-Cornejo, J. Mora-Gonzalez, **M. Rodriguez-Ayllon**, A. Plaza-Florido, A. Molina-Molina, G. Garcia-Delgado, E. D’Hondt, J. Vanrenterghem & F. B Ortega. A systematic review on biomechanical characteristics of walking in children and adolescents with overweight/obesity: possible implications for the development of musculoskeletal disorders. **Obesity Review.** 2019; 20:1033-1044.
11. A. Plaza-Florido, J. H. Migueles, J. Mora-Gonzalez, P. Molina-Garcia, **M. Rodriguez-Ayllon**, C. Cadenas-Sanchez, I. Esteban-Cornejo, P. Solis-Urra, C. De Teresa, Á. Gutiérrez, N. Michels, J. Sacha, F. B. Ortega. Heart rate is a better predictor of cardiorespiratory fitness than heart rate variability in overweight/obese children: The ActiveBrains project. **Frontiers in Physiology, section Exercise Physiology.** 2019; 10:510.
12. J. Mora-Gonzalez, I. Esteban-Cornejo, C. Cadenas-Sanchez, J. H. Migueles, **M. Rodriguez-Ayllon**, P. Molina-Garcia, C.H. Hillman, A. Catena, M. B Pontifex, F. B Ortega. Fitness, physical activity, working memory and neuroelectric activity in children with overweight/obesity. **Scandinavian Journal of Medicine and Science in Sports.** 2019; 29:1352-1363.
13. J. Mora-Gonzalez, J. H. Migueles, I. Esteban-Cornejo, C. Cadenas-Sanchez, B. Pastor-Villaescusas, P. Molina-García, **M. Rodriguez-Ayllon**, M. C. Risco, A. Gil, C.M. Aguilera, M. V. Escolano-Margarit, A. Kaer Gejl, L.B. Andersen, A. Catena, F.B. Ortega. Sedentarism, physical activity, steps, and neurotrophic factors in obese children. **Medicine & Science in Sports & Exercise.** 2019; 51:2325-2333.
14. A. Plaza-Florido, J. H. Migueles, J. Mora-Gonzalez, P. Molina-Garcia, **M. Rodriguez-Ayllon**, C. Cadenas-Sanchez, I. Esteban-Cornejo, S. Navarrete, R. Maria-Lozano, N. Michels, Jerzy Sacha, F. B. Ortega. The role of heart rate on the associations between body composition and heart rate variability in children with overweight/obesity: The ActiveBrains project. **Frontiers in Physiology, section Exercise Physiology.** 2019; 10:895.
15. M. Adelantado-Renau, I. Esteban-Cornejo, **M. Rodriguez-Ayllon**, C. Cadenas-Sánchez, J. Juan Gil Cosano, J. Mora-Gonzalez, P. Solis-Urra, J. Verdejo-Román, M. Aguilera Concepción, M. Victoria Escolano-Margarit, A. Verdejo-Garcia, A. Catena, D. Moliner-Urdiales, F. B Ortega. Inflammatory biomarkers and brain health indicators in children with overweight and obesity: The

ActiveBrains project. Submitted in **Brain Behavior and Immunity.** 2019; 81:588-597.

16. A. Plaza-Florido, J.H. Migueles, A. Piepoli, P. Molina-García, **M. Rodriguez-Ayllon**, C. Cadenas-Sanchez, I. Esteban-Cornejo, J. Mora-Gonzalez, F.B. Ortega. Blood flow restricted training in older adults: A narrative review. **Journal of Science in Sport and Exercise.** 2019; In press.
17. C. Cadenas-Sanchez, J. H. Migueles, I. Esteban-Cornejo, J. Mora-Gonzalez, P. Henriksson, **M. Rodriguez-Ayllon**, P. Molina-García, M. Löf, I. Labayen, C. H. Hillman, A. Catena, F. B. Ortega. Fitness, physical activity, and academic achievement in overweight/obese children. **Journal of Sports Sciences.** 2019; In press.
18. P. Molina-Garcia, D. Miranda-Aparicio, A. Molina-Molina, A. Plaza-Florido, J. H. Migueles, J. Mora-Gonzalez, C. Cadenas-Sanchez, I. Esteban-Cornejo, **M. Rodriguez-Ayllon**, P. Solis-Urra, J. Vanrenterghem, F.B. Ortega. Effects of Exercise on Plantar Pressure during Walking in Children with Overweight/Obesity. **Medicine & Science in Sports & Exercise.** 2019; In press.
19. D. Munguia-Izquierdo, M. Pulido-Martos, F.M. Acosta, P. Acosta-Manzano, B. Gavilán-Carrera**, M. Rodriguez-Ayllon**, R. Geenen, M. Delgado-Fernández, I. C. Álvarez-Gallardo, V. Segura-Jiménez, B. Walitt, F. Estévez-López. Objective and subjective measures of physical functioning in women with fibromyalgia: what type of measure is associated most clearly with subjective well-being? **Disability and Rehabilitation.** 2019; 1: 1-8.
20. P. Solis-Urra, I. Esteban-Cornejo, C. Cadenas-Sanchez, **M. Rodriguez-Ayllon**, J. Mora-Gonzalez, J. H. Migueles, I. Labayen, J. Verdejo-Román, Arthur F. Kramer, K.I. Erickson, C. H. Hillman, A. Catena, F. B. Ortega. Early life factors, gray matter brain volume and academic performance in overweight/obese children: The ActiveBrains project. **NeuroImage**. 2019; 202:116130.
21. **M. Rodriguez-Ayllon**, I. P. M. Derks, M. A van den Dries, I. Esteban-Cornejo, J. A. Labrecque, J. Yang-Huang, H. Raat, M. W. Vernooij, T. White, F.B. Ortega, H. Tiemeier, R.L. Muetzel. Associations of physical activity and screen time with white matter microstructure in healthy children. Submitted in **NeuroImage**. 2019; 205:116258.
22. **M. Rodriguez-Ayllon**, I. Esteban Cornejo, J. Verdejo-Román, RL Muetzel, J. H. Migueles, J. Mora-Gonzalez, P. Solis-Urra, K.I. Erickson, C.H. Hillman, H. Tiemeier, F. B. Ortega. Associations of physical activity and sedentary behaviour with white matter microstructure in children with overweight/obesity: the ActiveBrains project. Submitted in **Medicine & Science in Sport and Exercise**. 2019; In press.
23. J. H. Migueles, C. Cadenas-Sanchez, A. V. Rowlands, P. Henriksson, E. J. Shiroma, F. M. Acosta, **M. Rodriguez-Ayllon**, I. Esteban-Cornejo, A. Plaza-Florido, J. J. Gil-Cosano, U. Ekelund, V. T. van Hees, F. B. Ortega. Comparability of accelerometer signal aggregation metrics across placements and dominant wrist cut points for the assessment of physical activity in adults. **Scientific Reports.** 2019; 9:18235
24. L. Gracia-Marco, I. Esteban-Cornejo, E. Ubago-Guisado, **M. Rodriguez-Ayllon**, J. Mora-Gonzalez, P. Solis-Urra, C. CadenasSanchez, J. Verdejo-Roman, A. Catena, K. I Erickson, F. B Ortega. Lean mass index is positively associated with

white matter volumes in several brain regions in children with overweight/obesity. **Pediatric Obesity.** 2019; In press.

BOOK CHAPTERS

1. **M. Rodriguez-Ayllon**, I. Esteban-Cornejo, F. Estevez-Lopez, C. Cadenas-Sanchez, L. Gracia-Marco, D. Lubans, F.B. Ortega. Physical activity, sedentary behaviour and mental health in young people. Adolescent health and wellbeing: Current Strategies and Future Trends. **Springer.** https://doi.org/10.1007/978-3-030-25816-07

CONFERENCE PRESENTATIONS

- **32nd ECNP Congress of Applied and Translational Neuroscience. Copenhagen, Denmark. September 7-10/2019.**
    - **M. Rodriguez-Ayllon,** I. Esteban Cornejo, J. Verdejo-Román, J. Mora-Gonzalez, C. Cadenas-Sanchez, P. Solis-Urra, P. Molina-García, J. H. Migueles, A. Plaza-Florido, L. Torres-Lopez, F.B. Ortega. Physical fitness and tract-specific white matter microstructure in children with overweight or obesity: The ActiveBrains project.
- **I Congress of researcher in the PTS. Granada, Spain. February 13-15/2019.**
    - **M. Rodriguez-Ayllon**, I. Esteban-Cornejo, J. Mora-Gonzalez, J. Verdejo-Roman, C. Cadenas-Sanchez, P. Solis-Urra, A. Catena, F.B. Ortega. Actividad física y comportamiento sedentario medidos objetiva y subjetivamente e integridad de la sustancia blanca del cerebro en niños con sobrepeso/obesidad: Resultados preliminares del proyecto ActiveBrains.
- **ECSS Congress. Prague, Czech Republic. July 03/06/2019.**
    - P. Acosta-Manzano, F. M. Acosta, **M. Rodriguez-Ayllon**. Resistance training as potential therapeutic intervention in type 2 diabetes mellitus: a meta-analysis of randomized control trials.
- **VI Symposium Exernet: Research in exercise, health and well-being: "Exercise is Medicine". Pamplona, Spain. October/19-20/2018.**
    - **M. Rodriguez-Ayllon**, I. Esteban-Cornejo, J. Mora-González, Juan Verdejo-Roman, C. Cadenas-Sánchez, P. Solis-Urra, A. Catena, F. B. Ortega. Tiempo viendo la televisión e integridad de la sustancia blanca del cerebro en niños con sobrepeso/obesidad: Resultados preliminares del proyecto ActiveBrains.
- **The Cognitive Neuroscience Society (CNS) 2018 Annual Meeting. Boston, MA. March/24-27/2018.**
    - I. Esteban-Cornejo, J. Mora-González, C. Cadenas-Sánchez, O. Contreras-Rodriguez, J. Verdejo-Roman, P. Henriksson, J. H. Migueles, **M. Rodriguez-Ayllon**, P. Molina-García, C. Suo, C. H. Hillman, A. Catena, A. Verdejo-García, F. B Ortega. The role of physical fitness components on overall and regional cortical thickness in overweight/obese children: preliminary results from the ActiveBrains Project.
- **I International Conference on Health Science: An update of the current knowledge.** Granada, Spain. January/20/2017.

  - **M. Rodriguez-Ayllon**, C. Cadenas-Sánchez, I. Esteban-Cornejo, J. H. Migueles, J. Mora-González, P. Henriksson, M. Martín-Matillas, A. Mena-Molina, P. Molina García, F. Estévez-López, G. M. Enriquez, J. C. Perales, J. R. Ruiz, A. Catena, F. B. Ortega. Physical fitness and psychological distress in overweight/obese children. A cross-sectional study from the ActiveBrains Project.
- **International Meeting of Research in Physical Activity and Health. Cuenca, Spain. December/13-14/2017.**
  - **M. Rodriguez-Ayllon,** I. Esteban-Cornejo, P. Molina-García, A. A. Plaza Florido, P. Solis-Urra, F. B. Ortega. Fatness and fitness in relation to internalizing and externalizing problems in overweigh/obese children: The ActiveBrains project.
- **II Conference Researchers in Training - Promoting Interdisciplinary Research (JIFFI). Granada, Spain. May/17-19/2017.**
  - **M. Rodriguez-Ayllon**, I. Esteban-Cornejo, C. Cadenas-Sánchez, P. Henriksson, A. Catena, F. B. Ortega. Capacidad cardiorrespiratoria y salud psicosocial en niños con sobrepeso/obesidad: Resultados preliminares del proyecto ActiveBrains.
- **I International CIMCYC Workshop on Brain and Cognition. Granada, Spain. April/19-20/2017.**
  - **M. Rodriguez-Ayllon**, C. Cadenas-Sanchez, I. Esteban-Cornejo, J. Mora-González, J. H. Migueles, P. Molina-García, A. Catena, F. B. Ortega. Asociación de la fuerza de prensión manual y el rendimiento académico medido y percibido en niños con sobrepeso/obesidad: Resultados preliminares del proyecto ActiveBrains.
- **I International Symposium Active Brains for all: Brain, Cognition and Mental health. Granada, Spain. June/12/2017.**
  - **M. Rodriguez-Ayllon**, C. Cadenas-Sanchez, I. Esteban-Cornejo, J. Mora-González, J. H. Migueles, P. Molina-García, A. Catena, F. B. Ortega. Association of muscular strength with measured and perceived academic achievement in overweight/obese children: Preliminary results from the ActiveBrains project.
- **V Symposium Exernet: Research in exercise, health and well-being: "Exercise is Medicine**". Cádiz, Spain. October/14-15/2016.
  - **M. Rodriguez-Ayllon**, C. Cadenas-Sánchez, I. Esteban-Cornejo, J. H. Migueles, J. Mora-González, P. Henriksson, M. Martín-Matillas, A. Mena-Molina, P. Molina-García, F. Estévez-López, G. M. Enriquez, J. C. Perales, J. R. Ruiz, A. Catena, F. B. Ortega. Fuerza muscular y salud psicológica positiva en niños con sobrepeso/obesidad: Resultados preliminares del proyecto ActiveBrains.

INVITED LECTURES

- **The ActiveBrains-SmarterMove International Seminar: Exercise, Cognition and Brain in Childhood and Older Age. Granada, Spain. March/08/2018.** Physical activity and white matter integrity in Children.

ORGANISATION OF SCIENTIFIC MEETINGS

- 2018 March— Secretary. The ActiveBrains-SmarterMove International Seminar: Exercise, Cognition and Brain in Childhood and Older Age. Granada, Spain. March/08/2018.
- 2017 January— Member of the Organizing Committees. I International Conference on Health Science: An update of the current knowledge. Granada, Spain. January/20/2017.
- 2017 June— Member of the Organizing Committees. I International Symposium Active Brains for all: Brain, Cognition and Mental health. Granada, Spain. June/12/2017.

ADDITIONAL TRAINING

- 2019 May—“Multivariate pattern analysis (MVPA)” by the University of Granada.
- 2017 October — “XII Scientific Conference Alicia Koplowitz foundation”. Development and mental health during childhood. Prevention and early attention in childhood psychiatry by the Health Professions Continuous Formation Commission of the Community of Madrid.
- 2017 November —“Missing Data. Multiple Imputation and analysis” by the University of Granada.
- 2017 February —“Mobile apps in the research field and I+D research projects” by the University of Granada.
- 2016 November — “Research, innovation, Intellectual property and knowledge transfer” by Jose Antonio Morales Molina, School of Health Sciences, doctoral programs.
- 2015 October — “Mindfulness and meditation” by the University of Granada.
- 2013 September —“Education for the equality between men and women” by the Department of Equal Opportunities.
- 2013 June — English Certificate. Level B1 by the University of Cambridge ESOL.
- 2013 June —“Sports Technician in Rhythmic Gymnastics, level II” by the Andalusian Federation of Gymnastic.
- 2013 June —“Sports Technician in cycling, level I” by the Andalusian Federation of cycling.
- 2011 June —“Sports Technician in Rhythmic Gymnastics, level I” by the Andalusian Federation of Gymnastic.
- 2010 November— “Promotion of Ethical Attitudes through Physical Activity and Sport” by the University of Granada.
- 2008 June —“Management and Promotion of Children's and Youth Camps” by the Youth Andalusian Institute.

VOLUNTEER ACTIVITIES

- May 2015— Invited lecture in a high school “the different professional careers of the undergraduate degree Sports Science” La Presentación, Granada, Spain.
- June 2018— Invited lecture in a jail “global recommendations on physical activity for health” Penitentiary of Albolote, Granada, Spain.

REVIEWER IN JCR JOURNALS

- BMC Public Health.
- Childhood obesity.
- Vascular Health and Risk Management.
- European Child & Adolescent Psychiatry.
- Environmental Research and Public Health.
- Medicine & Science in Sport & Exercise.

MEMBERSHIPS OF SCIENTIFIC SOCIETIES

- Memberships of EXERNET "Exercise is Medicine". Spanish exercise science organization (http://www.spanishexernet.com/)
- Memberships of the ACSM (https://afly.co/b1d2).
- Memberships of the EVBRES – COST Action CA17117. Working group Evidence-Based Research (EBR) methods (https://www.cost.eu/actions/CA17117/).
- Member of the ALBA Network (http://www.alba.network/). The ALBA Network aims to promote equality and diversity in the brain sciences.

DISSEMINATION EXPERIENCE

- **ActiveBrains Project:** https://bit.ly/35tDNBw **(See min 11) and** https://afly.co/b1g2

- **Article** "Role of physical activity and sedentary behaviour in the mental health of children and adolescents: A systematic review and meta-analysis. Published in **Sports Medicine":** UGR Divulga, Granada es Noticia, IDEAL, la Vanguardia, 20 minutos, Onda 0 Radio (03-10-2019 at 13:00), Radio Televisión Española en el espacio Neurociencia InquietaMENTE, Calidad en Vida-programa de radio de salud y culturas (radio program from the Universidad Nacional de Mar del Plata en Argentina). Links:https://bit.ly/2oKX4NX;https://bit.ly/2pA3tM5;https://bit.ly/2oNOHRu;https://bit.ly/2nh4bxe;https://bit.ly/2naF66T;https://bit.ly/2nN941g;https://bit.ly/32zNRXO.

ACKNOWLEDGEMENTS/AGRADECIMIENTOS

Cuando comencé a pensar sobre los agradecimientos de esta tesis doctoral y sobre las personas y acontecimientos que han hecho que hoy esté aquí, pensé en un hilo de acontecimientos que han tenido un efecto unos sobre otros y que juntos han hecho que escriba esta tesis doctoral. Todo se podría explicar a través del *Efecto Mariposa*, que por cierto también es el título de una película que me enseño un gran amigo. El *Efecto Mariposa* plantea que, "dadas las condiciones iniciales de un sistema dinámico caótico, una pequeña alteración imperceptible puede arrojar consecuencias enormes en el sistema completo, distinguiéndolo por completo de otro totalmente idéntico en el que dicha perturbación no se haya producido".

Bloque de acontecimientos I: Gimnasia

En la *Fuente Santa* conocí a mi mejor amiga **Marina**. Sus padres, **Masmen** y **Kike**, decidieron apuntar a **Marina** a Gimnasia Rítmica y como éramos tan inseparables **mis padres** decidieron que sería buena idea que fuésemos juntas. Entre todas las personas que conocí gracias a este deporte, me gustaría destacar a mi conjunto **Marina, Lara, Xio y Viki**, a mis entrenadora **Patri** y **Ro** y al club **Medina Lauxa**. También me gustaría dar las gracias a **Sandra Morón** por ayudarme e impulsarme a disfrutar de ser entrenadora. Haciendo gimnasia aprendí la importancia del compañerismo, disciplina, perseverancia, a tener metas y objetivos a corto y largo plazo y a no rendirme, herramientas imprescindibles proporcionadas por el **deporte** y de gran utilidad para desarrollar una **tesis doctoral**. Me gustaría agradecer especialmente a **Patri** y **Ro, Ro y Patri** por educarnos, por aguantarnos en la adolescencia, por llevarnos a viajes que estaban fuera de su horario laboral, por los buenos consejos y por ser mis referentes y uno de los motivos que me impulsaron a estudiar Ciencias del Deporte en la Universidad de Granada.

Bloque de acontecimientos II: La facultad de Ciencias del Deporte

2.1 Los primeros años

Cuando pienso en mis primeros años de carrera y en la gente que conocí, me vienen a la cabeza acontecimientos que han sumado y otros que han restado “en el buen sentido” para que hoy tenga una tesis doctoral. En primero de carrera entre muchísimos compañeros conocí a **Alba, Fran, Carlangas, Nacho y Pablo de Orbe, Loli, Álvaro, Inma, Luci** (bueno a este personaje ya lo conocía antes)**, Carlos, Alberto, Edu, Calde y muchos más.** Ellos han sido responsables entre otras cosas de que mi cara apareciera en los servilleteros de la facultad, de mi labio partido en Tavira, de las noches de fiesta y de los bocadillos del Parra, entre otros. Me gustaría deciros que no lo cambio por nada del mundo ya que fueron unos de los años más felices de mi vida en los que cada día lloraba de la risa gracias a vosotros.

2.2 Proyecto al-Ándalus

A parte de lo bien que me lo pasaba en la facultad, no sabía muy bien por qué había estudiado esta carrera, me gustaba el deporte sí, pero a qué me quería dedicar. En tercero de carrera, una mujer con fibromialgia vino a clase de salud para hablar del **proyecto Al-Ándalus** y de lo que había significado para ella. Fue la primera vez que fui consciente de que la práctica de actividad física podría mejorar la vida de las personas. En cuarto de carrera, **Manuel Delgado** me acepto para hacer mi TFG y las prácticas en su grupo de investigación. Este fue mi primer contacto con la investigación por lo que aprovecho para agradecérselo de corazón. Allí tuve la oportunidad de trabajar con parte del **equipo Al-Ándalus,** un grupo de personas muy motivadas con las que hice más trabajo de campo que con mi propio grupo de investigación en años posteriores. Ellos me enseñaron y me dieron cierta responsabilidad en mis primeros pasos en investigación por lo que también me gustaría agradecérselo profundamente.

2.3 Utrecht

Mi interés por viajar y conocer otros lugares me llevó a decidir hacer una estancia de investigación en mi último año de carrera en la Universidad de Utrecht. Aquí me gustaría agradecer a **Rinie y Fer** que me acogieran y que permitieran que tres personajes que forman el **Equipo Bigotudo** disfrutaran de su primera estancia de investigación. **Fer** muchas gracias por despertarme ese interés por la salud mental y por explicarme con una pizarra haciendo dibujitos, como a ti te gusta, la diferencia entre afecto positivo, afecto negativo y satisfacción con la vida. Muchas gracias también por las actividades que nos mandaste y nunca revisaste.

Rinie, *I would like to thank you for giving me the opportunity of doing my first stay abroad. This stay was very important for me and for my scientific career because I learned how to write a scientific article and even more important I enjoyed a lot doing that. Thanks a lot for the friendly dinners at your place (Thanks also to* ***Meike****).* ***Michelle*** *and* ***Vera,*** *thanks for giving me a second opportunity of being my friends. I remember when I met you for the first time in Triunfo, I couldn´t say any word in English. Thanks for all the nice moments in the Netherlands with good and bad weather.*

2.4 Equipo bigotudo

En primero de carrera conocí a un chico en la clase de voleibol que viendo lo malísima que era jugando, decidió mandarme un mensaje de ánimo por *Tuenti* diciendo que no me preocupará que seguro que mejoraría (eso nunca ocurrió). **Fran**, muchas gracias por tu apoyo incondicional todos estos años, no tengo palabras para agradecértelo. Muchas gracias por contagiarme tu ilusión por viajar, por ser tan buena influencia, por confiar en mí y por haber crecido junto a mí no solo profesionalmente sino también personalmente. Lo que nunca te agradeceré es que tuvieras un hermano como **Pedro**. Pedro, cuando no estas cerca te echo de menos y cuando llevamos juntos un minuto ya tengo ganas de perderte de vista (es broma, pero siempre me gusta picarte). Quiero que sepas que te tengo un cariño infinito. Juntos formamos el ***Equipo Bigotudo*** y eso nunca cambiará, os quiero mucho chicos. Esta tesis doctoral es un logro común más para el **Equipo Bigotudo**.

2.5 **Mis directores/*Mentors***

Pedro, el más adelantado del **Equipo Bigotudo**, defendió su TFM el primero de los tres, y en equipo fuimos a animarlo. Fue allí donde vi por primera a **Fran Ortega** y a **Jonatan Ruiz** en acción. Pronto supimos que queríamos formar parte de su equipo y comenzamos a investigarlos, nunca mejor dicho. Especialmente el proyecto **ActiveBrain**s me encantó y decidí ponerme en contacto con **Fran** para pedir una Beca de Colaboración que nunca conseguí pero que me sirvió de excusa para acercarme a él y finalmente poder hacer mi TFM en el proyecto ActiveBrains. **Fran** muchas gracias por acogerme sin ni siquiera conocerme, por confiar en mí, por valorarme y por darme independencia y apoyo al mismo tiempo. Una vez en el proyecto ActiveBrains conocí a mi directora **Irene**, como a ella le gusta que la llame. Ire es una de mis mejores amigas y un apoyo incondicional. Muchas gracias por todo, no tengo palabras para agradecértelo. Esta tesis no hubiese sido posible sin tu constante apoyo tanto profesionalmente como emocionalmente día tras día. En general, me siento muy orgullosa de decir que siento una profunda admiración por mis dos directores. Mis directores son dos personas luchadoras y trabajadoras que no se rinden, que aman su trabajo pero al mismo tiempo son capaces de disfrutar de la vida y de la cerveza. He aprendido muchísimo de vosotros y espero poder seguir haciéndolo. Me siento muy afortunada de haberos tenido como directores, ¡Sois geniales!

*My third mentor **Ryan**. I have to say that officially I have two mentors but extra-officially I have three. **Ryan**, thanks a lot for all the support that you have provided me all these years. I feel that I´m very lucky because I have had the opportunity of learning from you. This thesis wouldn´t be possible without you. I have no words to acknowledge you everything.*

2.6 Amigos y compañeros de investigación

En la primera reunión en la sala de becarios (becarios con y sin beca) de la facultad conocí a **Pepe**, **Cristina y Jairo** representantes del equipo ActiveBrains en aquellos entonces. **Pepe** (el Dios de la base de datos) muchas gracias por todo lo que me has enseñado en investigación y fuera de ella, siento que me llevo un gran amigo de esta experiencia y eso me hace feliz. **Cristina** muchas gracias por el gran apoyo en mis inicios, fue muy importante para mí y decisivo para que esté hoy aquí. **Jairo**, un chico aparentemente callado pero que cuando coge las confianzas, le encanta hacer bromas, eres muy crack.

Más tarde, en la primera reunión en **IMUDS** conocí al que sería mi pareja de investigación **Pablo**. **Pablo** hemos crecido juntos y para nosotros, al igual que para otros muchos investigadores/as, los comienzos no fueron fáciles, hemos tenido incluso que aprender de volcanes, pero aquí estamos. No me hubiese imaginado un mejor compañero y amigo de investigación. **Pato**, llegaste más tarde pero con fuerza. Tenemos mucha suerte de tenerte en el equipo y no solo como investigador, que eso es indiscutible, sino también como persona. Gracias por enseñarme tantas palabras chulas (i.e., parlante, botar, pieza, etc.) y por todas las risas que nos hemos pegado juntos.

Lucía, Jose Juan, Juan Pablo, Alejandra, Esther, Luis y las nutris (i.e., Victoria, Eli y Daniela) todos ellos/as han sumado al buen ambiente y a los buenos momentos dentro del equipo ActiveBrains. Muchas gracias a todos. **Miguelón** nos conocimos en las primeras evaluaciones de ActiveBrains y te llamé Manuel muchísimas veces, pero ya no se me olvida tu nombre, te has convertido en un buen amigo.

Además de los investigadores **ActiveBrainers**, también he tenido la suerte de conocer y contar con otros muy buenos investigadores y aún más importante, buenas personas. **Jonatan** me costó tener confianza contigo y a ti te costó aprenderte mi nombre. Pero al final hemos conseguido conocernos. Gracias por transmitirme esa buena energía y confianza. Gracias también por esos debates no solo de investigación sino también de la vida. Eres una gran persona. **Borja** eres un gran amigo, muchas gracias por el apoyo, por los buenos consejos, por los buenos momentos en Granada y Holanda, por las risas y por enseñarme tu corazón tantas veces. **Guille, Juanma, Hui, Lourdes, Manu, Fran Amaro, Ana Yara, Lucas nutri, Lucas entrenador, Cristina, Irene Coll, Lidia, Alex, Hanna, Pontus, Mireia** sois o habéis sido unos compañeros geniales de cubículos, gracias por los buenos momentos y por hacerme sentir como en casa en mi trabajo, sois geniales. **Palma** gracias por esa energía que trasmites. Algo que se me ha quedado grabado, fue cuando un día nos estabas contando tu experiencia en uno de tus viajes, y alguien te preguntó: ¿No te dio miedo? Y tú respondiste, lo que me da miedo es que todos los días sean iguales. Para mi eres un referente no solo a nivel profesional sino también de vida. **Virginia**, gracias por acogerme en **Gestafit,** disfrute mucho participando en alguna evaluación y trabajando con vosotros. Me alegra conocer a personas como tú con las que se puede tener conversaciones interesantes no solo en el trabajo sino también de cervezas. **Juan** eres mi salvador de la neuroimagen pero también un buen amigo. Muchas gracias por la paciencia y por todo el tiempo que has dedicado a enseñarme. Muchas gracias además, por hacerlo divertido, por dejarme invadir tu despacho y por hacerme sentir integrada los días de trabajo en el CIMCYC.

Kirk, *thank you very much for the opportunity you give me of visiting your lab. I learnt a lot but also I enjoy so much. You have really nice people in your lab.* ***Alina*** *thanks a lot for your time, for your help with the DTI analyses, for your patience with me and for make me feel at the same time comfortable working with you. Espero verte pronto y poder enseñarte español, aunque sabes más de lo que tú crees. Gracias a los dos de corazón.*

Lastly, I would like to say thanks to all the people that I met in the ***Erasmus MC****. Thanks all of you for the nice lunch, coffee time, beers and support. I hope to see you guys soon!*

Bloque de acontecimientos III: Amigas antes y después de la aventura de la tesis

Aunque me siento súper agradecida de todos los amigos que he hecho gracias a la investigación. Agradezco muchísimo tener unas amigas maravillosas, las cuales hacen que me olvide de lo que es la investigación. **Ana,** gracias por quererme aunque mi presentación en el autobús del Medina Lauxa no fue la mejor. Gracias por ser una súper compañera de instituto, por las risas, por las fiestas en tu piso de abajo y por ser como tú eres, no cambies nunca. **Lara**, no olvidaré nunca tus ahogaillas dobles en el Frontil, la trenza que le hice a esa niña de Sabinillas, la hamburguesa de esa mujer del Puerto, las risas perrunas, y todas las experiencias que hemos vivido juntas. Te quiero mucho perruna mía. **Luzma** gracias por los bailes de Zumba, por las risas, por esa confianza que transmites y por estar siempre ahí pase lo que pase. **Marina**, me faltan palabras para agradecer que nuestros abuelos decidieran de forma aleatoria irse a vivir juntos en la nada. No todo el mundo tiene la suerte de poder contar con una hermana como tú.

Gracias por aceptarme como soy, por escuchar mis penas y alegrías, por hacer que mi vida sea más fácil, por enseñarme tanto y simplemente por estar ahí siempre. Te quiero mucho hermana. **Mary,** gracias por ser una gran compañera de instituto, por compartir mi primera experiencia en Granada con todas las consecuencias que tuvo, por esos cafelillos y tapillas de charlas, eres unas pedazo de mujer, más fuerte y luchadora de lo que tú te puedes imaginar. **Nata,** gracias por todas las experiencias que hemos compartido en nuestros diferentes pisos, por tus consejos de moda cuando más bloqueada estaba y por ser una grandísima amiga, gracias por estar siempre. Especialmente me gustaría darte las gracias por el apoyo emocional durante los últimos días de escritura de esta tesis doctoral. **Xio,** no olvidaré nunca esa patada en la barriga de presentación. Desde entonces decidimos no separarnos desde el colegio hasta hoy. Gracias por estar siempre ahí, por compartir conmigo esa pasión por la gimnasia y por ser un ejemplo de lucha, trabajo y perseverancia. Chicas siento mucho todo el tiempo que no he pasado con vosotras por el trabajo o por estar siempre fuera. Os quiero mucho. Muchas gracias por todo lo que me aportáis, sois todas y cada una de vosotras únicas y maravillosas.

Bloque de acontecimientos IV: Auto-agradecimiento

Es indiscutible que el desarrollo de esta tesis doctoral ha sido solo posible gracias a todas las personas que de una forma u otra han contribuido a que hoy esté aquí. Muchas gracias a todos de corazón. Pero también es importante reconocer que al final somos nosotros los que luchamos y no nos rendimos cuando las cosas no salen a la primera (análisis que no salen, una revisión sistemática que nunca acaba o una beca que tarda en llegar). Somos nosotros, los que rechazamos planes que nos apetecían por completar algún trabajo o llegar a algún deadline (a veces por falta de organización). Somos nosotros los que a veces nos sentimos frustrados por no conseguir alguna meta u objetivo difícil o casi imposible de conseguir. Por lo tanto, me gustaría darme las gracias a mi misma. Gracias **María**, por ser resiliente, luchadora, perseverante y por confiar en ti.

Bloque de acontecimientos V: La Fuente Santa

La **Fuente Santa**, es una fuente que se encuentra a tan solo unos metros de he crecido y vivido toda mi infancia. Cerca de esta fuente, se encuentran las casas donde mis abuelos y los abuelos de Marina, por casualidad (o eso creo) decidieron formar sus familias. Además, mis titos Florencio y Fefi, años más tarde, también decidieron unir una casa más. En este maravilloso lugar, se ha formado una familia enorme de la que me siento muy orgullosa y agradecida de formar parte. **Titos Kini y Elo, Gema, Paula, Kinillo, Masmen, Kike, Celia, Marina, María la Vecina y Nono, Abuela y Abuelo, Mamá, Papá, Lidia, Manolo, Fer, Titos Florencio y Fefi, Esther y Jorge, Guillermo y Sofía, Javi y Ana, Laura y Javier**. Todos ellos forman parte de la Fuente Santa y de esa maravillosa familia que se ha formado de sangre y no de sangre. Todos y cada uno de vosotros sois únicos. Muchas gracias por todo lo que cada uno me habéis aportado, que es muchísimo. Muchas gracias también por quererme, respetarme, por hacerme sentir especial y arropada por todos vosotros. Os quiero y os valoro mucho a todos.

Me gustaría hacer especial mención a mi pilar fundamental, **mis padres**. Ellos son dos personas trabajadoras al máximo, que nunca se rinden, humildes, con un corazón enorme y que siempre me han enseñado la importancia de esforzarse al máximo en el trabajo respetando siempre a los demás. **Mamá** muchas gracias por quererme, por cuidarme, por apoyar y respetar mis decisiones siempre, por dejarme libertad para cometer mis errores, por confiar en mí, por escucharme, por todo el cariño y apoyo incondicional, te quiero muchísimo, eres una persona maravillosa. **Papá** muchas gracias por todo lo que me has enseñado. Gracias por todo el cariño, por apoyarme, por sentirte orgulloso de mí y respetar mis decisiones. Gracias por enseñarme que aunque las cosas a veces no salen como uno espera, hay que seguir luchando y no pararse nunca, te quiero mucho. **Lidia,** muchas gracias por quererme tal y como soy, por respetarme, por estar siempre ahí, por cuidarme y por valorarme. Te quiero mucho hermana, tengo mucha suerte de poder tenerte siempre mi lado, yo también lo estaré siempre. **Abuela**, para mi eres una segunda madre. Gracias por obligarme a comer fruta, por llevarme al autobús, por cuidarme y por quererme tanto. Quizás no entiendas nada, pero lo que ves aquí escrito es un resumen de lo que siempre he hecho, pegar saltos, y ver si las personas que pegan más saltos y no paran quietos están más sanos.

Por último, me gustaría dar la gracias a mi persona favorita, la cual conocí gracias la investigación. **Fer**, muchas gracias por hacerme tan feliz, por quererme y mimarme tanto. No podría haberme imaginado un mejor compañero de vida. Gracias por todo tu apoyo en tantos aspectos de mi vida, por confiar en mí y por hacerme sentir tan especial y feliz a tu lado. Te adoro mucho.