

Exercise, physical and brain health in relation to sleep in children with overweight or obesity

Ejercicio, salud física y cerebral
en relación con el sueño en niños
y niñas con sobrepeso u obesidad

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**FACULTAD DE
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Exercise, physical and brain health in relation to
sleep in children with overweight or obesity
*Ejercicio, salud física y cerebral en relación con el
sueño en niños y niñas con sobrepeso u obesidad*

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Que la Tesis Doctoral titulada “Ejercicio, salud física y cerebral en relación con el sueño en niños y niñas con sobrepeso u obesidad” que presenta Dña. Lucía Victoria Torres López al superior juicio del Tribunal que designe la Universidad de Granada, ha sido realizado bajo mi dirección durante los años 2018-2023, siendo expresión de la capacidad técnica e interpretativa de su autora en condiciones tan aventajadas que le hacen merecedora del Título de Doctora, siempre y cuando así lo considere el citado Tribunal.

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En Granada, 13 de enero de 2023



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Somewhere, something incredible
is waiting to be known

En algún lugar, algo increíble está
esperando a ser descubierto

– Carl Sagan

A las **g**randes estrellas que **for**man **pa**rte de mi Universo,
brillan **c**on luz prop**ia**, y ayud**an**
a que mis sueñ**os** sean una realidad.

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List of abbreviations

ADHD	Attention-Deficit Hyperactivity Disorder.
ANCOVA	Analysis Of Covariance.
BMI	Body Mass Index.
BSI	Behavioral Symptoms Index.
CRP	C-Reactive Protein.
DXA	Dual-Energy X-Ray Absorptiometry.
GMV	Gray Matter Volume.
HDL	High Density Lipoprotein.
HOMA	Homeostatic Model Assessment.
IL	Interleukin.
LDL	Low Density Lipoprotein.
MRI	Magnetic Resonance Imaging.
MVPA	Moderate To Vigorous Physical Activity.
OSA	Obstructive Sleep Apnea.
PHV	Peak Height Velocity.
PSQ	Pediatric Sleep Questionnaire.
RCT	Randomized Clinical Trial.
SDB	Sleep-Disordered Breathing.
TNF- α	Tumor Necrosis Factor Alpha.
WASO	Wake After Sleep Onset.
WC	Waist Circumference.

Abstract

Resumen

ABSTRACT

Background: The prevalence of childhood obesity worldwide is currently at extremely high levels and it is known to be linked to a myriad of health-related problems, among them, a poor sleep health or sleep-disordered breathing. It is important to investigate factors that could fight against obesity consequences and physical exercise emerges as a strong candidate.

Objectives and methods: The present International Doctoral Thesis aims to examine the role of sleep-related outcomes in relation to physical and brain health (**section 1**), to study the effects of a physical exercise program on sleep-related outcomes in children with overweight or obesity (**section 2**), and to investigate the impact of fatness and cardiorespiratory fitness on sleep-disordered breathing after 1-year of follow-up in children (**section 3**). Six studies were conducted within the three sections: four cross sectional studies (section 1), one randomized clinical trial (section 2) and one prospective cohort study (section 3).

Main findings: Results from this Doctoral Thesis are described below. Television viewing time, cardiorespiratory fitness, and most adiposity markers were associated with sleep-disordered breathing, being the body mass index and television viewing time the best predictors of sleep-disordered breathing in children with overweight or obesity (**study 1**). Sleep-disordered breathing severity was related to: i) lower school grades (which was driven by inattention/hyperactivity), but not with standardized measurement of academic performance or brain structure (**study 2**), ii) worse behavioral and emotional functioning (i.e., higher external and internal problems and lower adaptability skills) (**study 3**), and iii) higher C-reactive protein levels independently of the adiposity levels, but not to other cardiometabolic or inflammatory risk factors in children with overweight or obesity (**study 4**). This study also suggested that higher levels of cardiorespiratory fitness might attenuate the

adverse effect of sleep-disordered breathing on C-reactive protein. In addition, a 20-week physical exercise program reduced the time awakening after sleep onset in children with overweight or obesity in comparison with control group peers, yet effects were not observed on sleep-disordered breathing (**study 5**). Further, although not statistically significance, all device-assessed sleep outcomes were improved in those days in which the participants attended to the physical exercise session, suggesting acute effects of exercise on sleep-related outcomes. Lastly, severe/morbid obesity, central obesity and low fitness were linked to higher risk of sleep-disordered breathing at baseline in children, but 1-year longitudinal analyses did not show significant associations (**study 6**).

Conclusion: Collectively, the main findings of the present International Doctoral Thesis shed light on the importance of improving sleep-related outcomes in children with overweight or obesity as a strategy to enhance physical and brain health. The use of physical exercise as a tool to improve children's sleep health and sleep-disordered breathing with overweight or obesity is promising and warrants further investigation.

RESUMEN

Contexto: La prevalencia de obesidad infantil en todo el mundo es actualmente muy alta y se sabe que está relacionada con una serie de problemas de salud, entre ellos, patrones de sueño poco saludables o trastornos respiratorios del sueño. Es importante investigar factores que puedan combatir las consecuencias de la obesidad y el ejercicio físico emerge como un firme candidato.

Objetivos y métodos: La presente Tesis Doctoral Internacional tiene como objetivos examinar el papel que juegan las diferentes variables de sueño en relación con la salud física y cerebral (**sección 1**), estudiar los efectos de un programa de ejercicio físico en las variables relacionadas con el sueño en niños y niñas con sobrepeso u obesidad (**sección 2**), e investigar el impacto de la obesidad y la capacidad cardiorrespiratoria en los trastornos respiratorios del sueño después de 1 año en niños y niñas (**sección 3**). Se realizaron seis estudios dentro de las tres secciones: cuatro estudios transversales (sección 1), un ensayo clínico aleatorizado (sección 2) y un estudio prospectivo de cohortes (sección 3).

Resultados principales: Los resultados de esta Tesis Doctoral se describen a continuación. El tiempo viendo la televisión, la capacidad cardiorrespiratoria y la mayoría de los marcadores de adiposidad se asociaron con los trastornos respiratorios del sueño, siendo el índice de masa corporal y el tiempo viendo la televisión los que mejor explican los trastornos respiratorios del sueño en niños y niñas con sobrepeso u obesidad (**estudio 1**). La gravedad de los trastornos respiratorios del sueño se relacionó con: i) peores calificaciones escolares (debido a la falta de atención e hiperactividad), pero no con medidas estandarizadas de rendimiento académico o estructura cerebral (**estudio 2**), ii) peor funcionamiento conductual y emocional (es decir, mayores problemas de externalización e internalización, y menores

habilidades de adaptación) (**estudio 3**), y iii) niveles más altos en sangre de proteína C-reactiva independientemente de los niveles de adiposidad, pero no con otros factores de riesgo cardiometabólico o inflamatorio en niños y niñas con sobrepeso u obesidad (**estudio 4**). Este estudio también sugirió que unos niveles más altos de capacidad cardiorrespiratoria podrían atenuar el efecto adverso de los trastornos respiratorios del sueño sobre la proteína C-reactiva. Además, un programa de ejercicio físico de 20 semanas redujo el tiempo de vigilia tras el inicio del sueño en niños y niñas con sobrepeso u obesidad en comparación con sus compañeros y compañeras del grupo control, aunque no se observaron efectos sobre los trastornos respiratorios del sueño (**estudio 5**). Así mismo, aunque sin significación estadística, todas las variables de sueño evaluadas mediante dispositivos mejoraron en los días en que los participantes asistieron a la sesión de ejercicio físico, lo que sugiere efectos agudos del ejercicio sobre las distintas variables relacionadas con el sueño. Por último, la obesidad severa/mórbida, la obesidad central y la baja forma física se relacionaron con un mayor riesgo de trastornos respiratorios del sueño al inicio del estudio en niños y niñas, pero los análisis longitudinales de 1 año no detectaron asociaciones significativas (**estudio 6**).

Conclusión: En conjunto, los principales hallazgos de la presente Tesis Doctoral Internacional arrojan luz sobre la importancia de mejorar las distintas variables relacionadas con el sueño en los niños y niñas con sobrepeso u obesidad como estrategia para mejorar la salud física y cerebral. El uso del ejercicio físico como herramienta para mejorar la salud del sueño y los trastornos respiratorios del sueño de los niños y niñas con sobrepeso u obesidad es prometedor y merece una mayor investigación.

Key concepts

Sleep: a repetitive, active and reversible brain process of perceptual disconnection characterized by unresponsiveness to environmental stimuli [1,2]. Sleep is considered a construct of physical behavior together with physical activity and sedentary behavior.

SLEEP-RELATED OUTCOMES

Component	Definition	Indicators
Device- Assessed Sleep [3]	In the Thesis, this term refers to the measurement of sleep behaviors using accelerometry device . Accelerometers provide data over the day and night, making the device valuable for estimating sleep by using algorithms [4].	Sleep timing: • Wake time. • Sleep onset time: initiating the sleep period. Sleep duration: • Total time in bed: the time difference between wake and sleep onset times. • Total sleep time: the sum of all minutes classified as sleep within total time in bed. Sleep efficiency: The percentage of time classified as sleep over the total time in bed. The percentage is calculated by dividing <i>total sleep time</i> by <i>total time in bed</i>. Sleep pattern: • Wake after sleep onset (WASO) time: amount of time spent awake after sleep onset and before the final awakening.
Sleep Health [5-7]	A multidimensional pattern of sleep-wake that promotes physical and mental health well-being [5].	Good sleep health characteristics: • Appropriate timing (circadian alignment). • Adequate duration. • High efficiency. • Low variability (regularity).
Objective-Assessed Sleep	In the Thesis, this term refers to the measurement of sleep using polysomnography .	The same device-assessed sleep indicators are included.
Sleep-Disordered Breathing (SDB)	Set of upper airway dysfunctions during sleep, which are characterized by increased breathing effort and/or snoring caused by a narrowing of the pharynx and increased upper airway resistance [8]. One of the most common causes of SDB in childhood is obstructive sleep apnea [6].	Using the SDB scale (ranged 0 to 1) from the reduced version of the Pediatric Sleep Questionnaire [9,10]: • Risk of presence of SDB (scores > 0.33) • SDB severity
Obstructive Sleep Apnea (OSA) [11]	Recurrent episodes of partial or complete collapse of the upper airway during sleep, resulting in reduced (hypopnea) or absent (apnea) airflow lasting for at least 10 seconds).	• The presence of OSA • OSA severity Both are normally calculated by the apnea-hypopnea index (AHI, the number of hypopneas + apneas per hour of sleep)

Brain health: broadly includes biological markers of the brain (e.g., brain structure) and variables related to mental health and academic performance [12].

BRAIN HEALTH

Component	Definition	Indicators
Brain Structure	Comprises white and gray matter, and cerebrospinal fluid. This Thesis is only focused on the gray matter volume .	Gray matter includes the dendrites, cell bodies, and non-myelinated axons. Its function is to contribute to processed the information and the reasoning functioning.
Mental Health In this Thesis represented as behavioral and emotional functioning [13].	Internalizing problems Refers to a group of emotional symptoms characterized primarily by processes within the self, such as depression, anxiety, and depression.	• Depression: feeling of unhappiness, sadness, and stress that may result in an inability to carry out everyday activities or may bring on thoughts of suicide. • Anxiety: the tendency to be nervous, fearful, or worried about real or imagined problems. • Somatization: the tendency to be overly sensitive to and complain about relatively minor physical problems and discomforts.
	Externalizing problems Refers to a group of emotional symptoms characterized primarily by actions in the external world, such as acting out, antisocial behavior and aggression.	• Aggressiveness: the tendency to act in a hostile manner (either physical or verbal) that is threatening to others. • Hyperactivity: the tendency to be overly active, rush through work or activities, and act without thinking. • Behavior problems: the tendency to engage in antisocial and rule-breaking behavior, including destroying property.
	Other problems In this Thesis refers to other problems not examined in the internalizing and externalizing components.	• Attention problems: the tendency to be easily distracted and unable to concentrate more that momentarily. • Atypicality: the tendency to behave in ways that are considered odd or commonly associated with psychosis. • Retreat or withdrawal: the tendency to evade others to avoid social contact.
	Adaptive skills The abilities to adapt to changes in the environment.	• Adaptability: the skill to adapt readily to changes in the environment. • Social skills: the skills necessary for interacting successfully with peers/adults in home, school, and community settings. • Leadership: the skills associated with accomplishing academic, social, or community goals, including the ability to work with others.
Academic Performance	Indicates how they have accomplished in specific goals in education (e.g., language, mathematics, science, etc.)	• School grades. • Standardized test (using the Woodcock-Muñoz test battery)

Physical health: in this Thesis includes cardiometabolic health, inflammation, body composition, and cardiorespiratory fitness.

PHYSICAL HEALTH

Component	Definition	Indicators
Cardiometabolic Health	Factors related to the metabolic and cardiovascular health.	• Lipid biomarkers: high- and low-density lipoprotein cholesterol and triglycerides. • Glycemia biomarkers: insulin and glucose • Systolic and diastolic blood pressure. • Waist circumference.
Inflammation	Inflammatory markers analyzed in plasma.	• Interleukin-6 and interleukin-1β. • Tumor necrosis factor alpha. • C-reactive protein.
Body Composition	The study of the body as a composite of its components: lean and fat mass, and water.	• Body mass index (BMI): calculated as the body weight relative to the height (i.e., kg/m2). There are internationally BMI cut-off points for normal-weight (18.5 – 24.9 kg/m2), overweight (25 – 29.9 kg/m2) and obesity (≥30 kg/m2) [14,15]. The overweight and obesity is defined as abnormal or excessive of body adiposity or weight. • Waist circumference: measurement of central fat. • Fat mass and lean mass index: calculated by dividing the fat mass or lean mass by their squared height (kg/m²).
Cardiorespiratory Fitness [16]	The overall capacity of the cardiovascular and respiratory systems.	In this Thesis the cardiorespiratory fitness, one of the main components of physical fitness, is measured by the 20m shuttle run test (VO _{2max} and laps).

Physical activity: any bodily movement produced by skeletal muscles that results in energy expenditure [17]. The term includes all intensities (e.g., light, moderate, vigorous), types (e.g., walking, running), and domains (e.g., leisure, household) of physical activity.

Physical exercise: a form of physical activity that is planned, structured, repetitive and performed with a purpose [17]. Usually, the major aim of exercise is to improve at least

one component of physical fitness (i.e., cardiorespiratory, muscular and speed-agility) or any health outcome.

Sedentary behavior: any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents, while in a sitting, reclining or lying posture [18]. In this Thesis, the term refers to the time viewing the television and the sedentary time measured with accelerometers.

General introduction

Sleep is increasingly recognized of utmost relevance for health and healthy development [6,19,20]. Sleep health promotes physical and mental well-being [5]. Among the characteristics of good sleep health, the following have been highlighted: an appropriate timing, good quality, adequate duration, high efficiency, and low variability [5-7]. Indeed, a recent review concluded that not having a good sleep is moderately affecting performance and health during childhood [21]. Another important outcome related to sleep health is sleep disorders, which in children include insomnias and sleep-disordered breathing (SDB), among others [22]. Specifically, SDB together with obesity are considered important public health problems in the pediatric population due to the associated consequences of each status [23]. Sleep is not “a waste of time” and requires proper attention for good health [24]. In the present International Doctoral Thesis, the sleep-related outcomes described refers both device-assessed sleep and SDB.

THE IMPORTANCE OF CHILDHOOD SLEEP

Device-assessed sleep

Children's sleep totally differs from adults. One of the clearest differences is the longer sleep time duration [6]. Thus, children aged 6 to 12 years-old must attain 9 to ~12 hours/day on a regular basis [24,25]. The estimated prevalence of 6-to-13 year-old children sleeping less than 9-11 hours/day is 98.1% (measured with accelerometers) and 18.1% (reported in diaries) [26]. Specific attention to sleep development processes is needed in these crucial ages.

Although polysomnography is the gold-standard method for sleep assessment, it has some disadvantages: i) the polysomnography sleep in a laboratory may not represent the real sleep context of the children and the unknown

environment with monitoring equipment makes it difficult for children to achieve a good night's sleep, and ii) is not a feasible method for population-level evaluation. Furthermore, a broadly number of studies in the literature have calculated total sleep time as the difference between self-reported sleep onset and wake times (i.e., subjective measures [21]). This fact could reflect total time in bed instead of total sleep time. Therefore, this previous evidence should be complemented with the use of device-assessed sleep such as accelerometers, which are growing in popularity and are also recognized as a useful assessment for sleep health in free-living conditions. However, accelerometers measure movements/accelerations not whether the brain is actually on a sleep mode or not, which can also lead to certain level of error.

Sleep-disordered breathing

In childhood, one of the most common causes of SDB is the obstructive sleep apnea (OSA). Depending on the measurement method, the estimated prevalence of SDB is raised up to 11% in a general pediatric population [27-29]. OSA symptoms include: i) during the nighttime: snoring, excessive sweating, restless sleep, mouth breathing, labored breathing and witnessed apneas; ii) during the daytime: inattention, behavioral and mood problems, morning headaches, or excessive daytime sleepiness [6].

SLEEP-RELATED OUTCOMES IN CHILDHOOD OBESITY: PHYSICAL AND BRAIN HEALTH

Childhood obesity is one of the major public health issues worldwide due to its epidemic dimensions [30]. Its prevalence has stabilized in most countries, but at very high levels worldwide [30,31], so it seems important to further investigate sleep-related outcomes (i.e., device-assessed sleep and SDB) in children with overweight or obesity and its association with health-related problems.

Device-assessed sleep

A systematic review in children from different countries highlighted the great importance of sleep as a factor related to increased risk of overweight or obesity [32]. In addition to the importance of sleep duration, other sleep health outcomes (as sleep efficiency, waking up after sleep onset and sleep timing) are also relevant in relation to obesity [32]. For instance, adolescents with obesity have shown lower sleep duration and sleep quality compared with normal-weight peers [33]. Although poorer sleep-related outcomes are associated with childhood obesity, there is still a need for studies using reliable and valid tools such as device-assessed sleep to measure sleep health outcomes, especially in children with overweight or obesity. As an example, a previous study from the ActiveBrains project found a link between device-assessed sleep outcomes and brain health (i.e., gray matter volume and academic performance) in children with overweight or obesity [34].

Sleep-disordered breathing

The excess of body weight has been identified as an important risk factor for SDB in childhood. The prevalence of SDB has been

showed to be higher in children with obesity (20.8%) than in children with normal-weight (6.3%) [35], but it could vary depending on the SDB definition, the age of the study sample and obesity level. For instance, in a specific population of children and adolescent with overweight or obesity aged 7-18 years old, the OSA prevalence was 44.6% compared with 9.1% of the normal-weight peers [36]. Moreover, childhood OSA is a risk factor for adverse cardiometabolic health factors such as high systolic blood pressure [37], insulin resistance and systematic inflammation [38]. Furthermore, a current meta-analysis suggests that children with SDB presence are at increased risk of attention-deficit/hyperactive disorder symptoms [39]. The current thesis is focused in children with overweight or obesity, who are more vulnerable to sleep disorders.

EFFECTS OF PHYSICAL EXERCISE PROGRAMS ON SLEEP-RELATED OUTCOMES

Despite the well-known multi-organ beneficial effects of physical exercise [40], the effects on sleep-related outcomes remain rather unknown in pediatric population. In this regard, a meta-analysis in adults demonstrated positive effects of chronic and acute physical exercise on sleep [41]. However, both chronic and acute exercise have small-to-moderate positive effects on objective-assessed sleep (i.e., total sleep time, sleep efficiency or wake after sleep onset among others) [41], nevertheless, heterogeneity among the included studies places the effect of physical exercise on sleep to be still under debate in adulthood. These conclusions and the high prevalence of SDB support the application of physical exercise prescriptions to enhance better sleep quality. Nevertheless, the evidence

on this topic in childhood is scarce and only focused on observational data [42,43]. To the best of our knowledge, the beneficial effect of a physical exercise program on device-assessed sleep has only been investigated in one randomized control trial in children with autism spectrum disorders [44] and in another in adolescents with obesity [33]. The conclusions of both studies were on the same direction, that is, after a 12-week physical exercise program, both children and adolescents improved sleep-related outcomes (i.e., sleep efficiency and total sleep time). The present International Doctoral Thesis tries to shed light on both chronic and acute effects of physical exercise on device-assessed sleep indicators in children with overweight or obesity.

In addition to device-assessed sleep outcomes, this Thesis has also been investigated SDB as a sleep-related outcomes. Meta-analyses examining the effects of physical exercise programs on OSA have been conducted only in adults [45-48]. In children, a single network meta-analysis showed the effectiveness of different types of interventions for OSA [49], but none of the interventions included were based on physical exercise. Apart from meta-analyses, few studies in children with the same characteristics as the population included in this Thesis have been concluded that: i) engaging 40 min/day of aerobic exercise at vigorous intensity during at least 10 weeks could improve SDB severity in 7-11 years-old children with overweight [50], ii) in children with obesity and SDB, a 8 or 16 weeks program of physical exercise (HIIT combined with resistant training) had no effects on SDB severity [51], and iii) after 12-week physical exercise, no significant effect on SDB severity was observed in adolescents with obesity [33]. These findings suggest the need to examine whether physical exercise programs improve SDB in children with overweight or obesity, in order to consider it as a possible future treatment in this pediatric population. It seems that physical exercise programs based on aerobic plus resistance

exercise could be better than aerobic exercise alone in the reduction of SDB severity [52]. The plausible explanation suggesting the observed decrease in OSA severity following physical exercise includes increased strength and fatigue resistance of the upper airway dilators, decreased nasal resistance, and increased respiratory stability through deeper sleep. However, there is still a need to identify accurate mechanisms responsible of the improvements in SDB severity by physical exercise programs.

INTERNATIONAL DOCTORAL THESIS STRUCTURE

This Thesis is mainly focused on SDB severity, yet also including device-assessed sleep outcomes. Three sections are conducted in this Thesis according to the design of the studies included. The **Section 1** responds to those aims associated with cross-sectional studies, addressing the relation of physical and brain health with sleep-related outcomes. The **Section 2** performs a randomized clinical trial (RCT) about the effects of a 20-week exercise program on sleep-related outcomes in children with overweight or obesity. Lastly, the **Section 3** focuses on longitudinal associations of fatness and fitness on SDB after 1-year in children.

SUMMARY OF THE GAPS ADDRESSED IN THIS INTERNATIONAL DOCTORAL THESIS

The main gaps detected in the literature on this topic are addressed by the different six studies of the present International Doctoral Thesis. Furthermore, a summary of these gaps and the contribution of this Thesis to the current knowledge are the following:

- The majority of previous studies have investigated sleep-related outcomes based on subjective measurements of sleep, often with unknown reliability or validity. Therefore, this Doctoral Thesis complements the existing literature with the use of device-assessed sleep such as accelerometers.
- Evidence is lacking regarding the joint role of SDB and obesity on brain health in children. This Thesis identifies not only the associations of SDB severity with an specific brain health indicator such as brain structure but also with academic performance and mental health in the context of childhood obesity, providing meaningful information for public health systems to prevent or attenuate the health-related consequences of obesity.
- There is a lack of well-design RCT investigating the effects of physical exercise interventions on sleep-related outcomes in pediatric population. In this Thesis we shed light on the effects of a 20-week physical exercise program on different device-assessed sleep outcomes and SDB in children with overweight or obesity.

- The longitudinal evidence in pediatric population addressing the association of obesity and fitness with future SDB severity is scarce. Our findings contribute to the previous knowledge by examining the role of total and central fatness and fitness on pediatric SDB after 1-year-follow-up.

Aims

OVERALL AIM

The main aims of this International Doctoral Thesis are: i) to study the role of sleep-related outcomes in relation to physical and brain health; ii) to study the effects of a physical exercise program on sleep in children with overweight or obesity; and iii) to investigate the impact of fatness and fitness on sleep-disordered breathing after 1-year in children. These main aims are addressed in six specific aims corresponding to six studies.

SPECIFIC AIMS

Section 1. Cross-sectional studies: Physical and brain health in relation to sleep-related outcomes in children with overweight or obesity.

- **Specific aim 1:** To examine the associations of sedentary behavior, moderate-to-vigorous physical activity, cardiorespiratory fitness, and body composition parameters with SDB, and to analyze which of these variables is the best predictor of SDB in children with overweight or obesity (**Study 1**).
- **Specific aim 2:** To investigate the associations of SDB severity with academic performance (i.e., standardized tests and school grades) and brain structure (i.e., total brain and gray and white matter volumes and gray matter volume in the hippocampus) in children with overweight or obesity (**Study 2**).
- **Specific aim 3:** To evaluate the associations of SDB and device-assessed sleep (i.e., wake time, sleep onset time, total sleep time, total time in bed and WASO time) with behavioral and emotional functioning (i.e., clinical scale: aggressiveness, hyperactivity, behavior problems, attention problems, atypicality, depression, anxiety, retreat,

and somatization; adaptive scale: adaptability, social skills, and leadership) in children with overweight or obesity (**Study 3**).

- **Specific aim 4:** To explore the association of SDB severity with cardiometabolic and inflammatory markers independently of the adiposity levels; and the role of cardiorespiratory fitness in these associations in children with overweight or obesity (**Study 4**).

Section 2. Randomized clinical trial: Effects of a physical exercise program on sleep-related outcomes in children with overweight or obesity.

- **Specific aim 5:** To investigate the chronic effects of a 20-week physical exercise program on SDB and on device-assessed sleep (i.e., total sleep time, total time in bed, sleep efficiency, and WASO time); and whether attending to a session of the exercise program had effects on device-assessed sleep the subsequent night in children with overweight or obesity (**Study 5**).

Section 3. Prospective cohort study: Association of fatness and fitness on sleep-disordered breathing after 1-year in children.

- **Specific aim 6:** To investigate the cross-sectional differences in SDB between body mass index, waist circumference or cardiorespiratory fitness categories in children at baseline; and whether changes in fatness and fitness are associated with changes in SDB in pediatric population after 1-year follow-up (**Study 6**).

General methods

The present International Doctoral Thesis is mainly performed under the umbrella of the ActiveBrains project including six studies, being the Study 6 also complemented by the GenObEx (Genes, Obesity, and Exercise) project (Study 6). The ActiveBrains project was a randomized clinical trial (Clinical Trial registration no. NCT02295072) which aim was to investigate the effects of a 20-week physical exercise program on brain health indicators in children with overweight or obesity [53,54]. The complete details of the design, characteristics, eligibility criteria and main effects of the exercise program on the brain health have been described elsewhere [53,54]. The GenObEx project was a 1-year follow-up cohort study which primary aimed to examine the impact of obesity (data from the ActiveBrains project) in comparison with normal-weight status, on brain health during childhood. The baseline data collection from the ActiveBrains project were from November 2014 to June 2016; and GenObEx project from May to June 2021 in Granada (Spain). Both projects were approved by the Ethics Committee on Human Research of the University of Granada. The studies are classified in three sections according to their design: cross-sectional (**section 1**), randomized clinical trial (**section 2**) and prospective cohort study (**section 3**). **Table 1** shows a summary of the methods used in each of the studies included in this Thesis.

Table 1. Methodological summary of the six studies included in this Doctoral Thesis

Studies	Project	Design	Participants characteristics	Variables studied (instruments)
Study 1	ActiveBrains	Cross-sectional	109 children (10.04 ± 1.12 years; 45 girls) with overweight or obesity	<u>Predictors:</u> Sedentary behaviors (i.e., television viewing time [YAP questionnaire] and sedentary time [accelerometry]), moderate-to-vigorous physical activity (accelerometry), cardiorespiratory fitness (20mSRT), and body composition parameters (anthropometry and DXA). <u>Outcome:</u> Sleep-disordered breathing (scale of the reduced version of the PSQ [Spanish version]).
Study 2	ActiveBrains	Cross-sectional	109 children (10.04 ± 1.12 years; 45 girls) with overweight or obesity	<u>Predictor:</u> Sleep-disordered breathing severity (scale of the reduced version of the PSQ [Spanish version]). <u>Outcomes:</u> Academic performance (Woodcock-Muñoz standardized test and school grades) and brain structure (MRI).
Study 3	ActiveBrains	Cross-sectional	109 children (10.04 ± 1.12 years; 45 girls) with overweight or obesity	<u>Predictors:</u> Sleep-disordered breathing and its subscales (reduced version of the PSQ [Spanish version]) and device-assessed sleep (accelerometry). <u>Outcome:</u> Behavioral and emotional functioning (BASC-2).
Study 4	ActiveBrains	Cross-sectional	109 children (10.04 ± 1.12 years; 45 girls) with overweight or obesity	<u>Predictor:</u> Sleep-disordered breathing (scale of the reduced version of the PSQ [Spanish version]). <u>Outcomes:</u> Cardiometabolic and inflammatory markers (fasting blood sample). <u>Mediator:</u> cardiorespiratory fitness (20mSRT).
Study 5	ActiveBrains	RCT	99 children (10.1 ± 1.1; 41 girls) with overweight or obesity. Exercise group, n=47; Control group, n=52	<u>Intervention program</u> (Intervention): 20-weeks physical exercise program, 3-5 sessions/week, 90 min/session. Based on high intensity games. <u>Outcomes:</u> sleep-disordered breathing (scale of the reduced version of the PSQ [Spanish version]) and device-assessed sleep (accelerometry).
Study 6	ActiveBrains and GenObEx	Cross-sectional and longitudinal	158 children (10.0 ± 1.2, 67 girls) at baseline. 86 children (11.1 ± 1.2, 39 girls) at 1-year follow-up	<u>Predictors:</u> Body mass index (anthropometry), waist circumference (anthropometry), and cardiorespiratory fitness (20mSRT). <u>Outcome:</u> Sleep-disordered breathing (scale of the reduced version of the PSQ [Spanish version]).

BASC-2= Behavior Assessment System for Children second edition; GenObEx= Genes, Obesity, and Exercise; MRI = magnetic resonance imaging; PSQ = Pediatric Sleep Questionnaire; RCT= randomized clinical trial; SRT = shuttle run test; YAP = Youth Activity Profile

Results and discussion

Section 1	Cross-sectional studies: Physical and brain health in relation to sleep-related outcomes in children with overweight or obesity	Study 1	Associations of sedentary behavior, physical activity, cardiorespiratory fitness and body composition with sleep-disordered breathing in children with overweight or obesity: a cross-sectional study
		Study 2	Does sleep-disordered breathing add to impairments in academic performance and brain structure usually observed in children with overweight or obesity?
		Study 3	Associations of sleep-related outcomes with behavioral and emotional functioning in children with overweight or obesity
		Study 4	Sleep-disordered breathing and cardiometabolic and inflammatory markers in children with overweight or obesity: the role of cardiorespiratory fitness
Section 2	Randomized clinical trial: Effects of a physical exercise program on sleep-related outcomes in children with overweight or obesity	Study 5	Effects of exercise on sleep in children with overweight or obesity: a randomized clinical trial
Section 3.	Prospective cohort study: Association of fatness and fitness with sleep-disordered breathing after 1-year in children	Study 6	Sleep-disordered breathing across levels of total obesity, central obesity and fitness in children: cross-sectional and longitudinal analyses

Study 1

Associations of sedentary behavior, physical activity, cardiorespiratory fitness and body composition with sleep-disordered breathing in children with overweight or obesity: a cross-sectional study

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ABSTRACT

Objective: To examine the associations of sedentary behavior, moderate to vigorous physical activity, cardiorespiratory fitness, and body composition parameters with sleep-disordered breathing (SDB), and to analyze which of these variables is the best predictor of SDB in children with overweight or obesity.

Methods: One-hundred and nine children (10.0 ± 1.1 years old, 45 girls) with overweight ($n = 27$) and obesity ($n = 82$) were included. Television viewing time was self-reported by using the Spanish adaptation of the "Youth Activity Profile" questionnaire. Sedentary time and physical activity were measured with accelerometry. Cardiorespiratory fitness was assessed with the 20-m shuttle-run test and body composition parameters with Dual-energy X-ray absorptiometry. SDB was evaluated by using the Spanish version of the Pediatric Sleep Questionnaire.

Results: Television viewing time was positively associated with SDB ($r = 0.222$, $P = 0.021$). Cardiorespiratory fitness was negatively correlated with SDB ($r = -0.210$, $P = 0.030$). Body composition parameters were positively associated with SDB (all $P < 0.05$), except fat mass index. Stepwise regression analyses showed that body mass index explained the largest proportion of the variance in SDB ($r^2 = 0.063$, $P = 0.01$) and television viewing time was the only one added after body mass index (r^2 change = 0.048 , $P = 0.022$).

Conclusion: This study supports the notion that higher body weight status negatively influences SDB and adds that unhealthy behaviors could contribute to worsen SDB, related to an increased risk of cardiovascular diseases. All the significant association observed in this manuscript were of small magnitude, indicating that other factors in addition to the one hereby studied contribute to explain the variance in SDB.

INTRODUCTION

The International Classification of Sleep Disorders [55] divides sleep-disordered breathing (SDB) into a wide range of breathing abnormalities such as obstructive sleep apnea (OSA), central sleep apnea syndromes, sleep-related hypoventilation and sleep-related hypoxemia disorders [56]. In pediatrics, the term SDB also includes a variety of pathologies ranging from upper airway resistance syndrome and primary snoring to OSA-hypopnea syndrome [57]. SDB is considered a major public health concern due to the high prevalence, closely related to obesity [58]. In childhood, SDB is relatively common, with a prevalence of 12% [59]. More specifically, in a general population of children with 6-8 years, 10% were affected by SDB [60]. Further, the prevalence of OSA is about 1%-6% whilst the prevalence of habitual snoring ranges from 1%-27%, in pediatric [27,28,61,62].

It has been shown that SDB often coexists with some morbidities related to the cardiovascular system (e.g., elevated blood pressure, and pulmonary hypertension) and the central nervous system (e.g., hyperactivity, excessive daytime sleepiness, cognitive deficits/academic problems, and behavioral problems), in childhood [8]. Specifically, current literature in children have shown that SDB was associated with cardiovascular comorbidities and they impacted on sympathetic activity and, left and right, heart function [63]. Furthermore, OSA was related to an increased risk of resistant hypertension [64] and metabolic syndrome [65]. On the other hand, SDB has been associated with multiple comorbidities such as poorer academic performance [66], lower certain aspects of behavioral functioning [67] and decreased parental-reported quality of life [8] at childhood. Therefore, studies examining the relationship between SDB and health outcomes in children are needed.

Nowadays, obesity is one of the main public health-related problems, being considered

one of the main risk factors for developing cardiovascular diseases, insulin resistance, hypertension and some types of cancer [68]. Pediatric obesity is associated with future mortality and morbidity, as well as with greater risk of cardiovascular diseases [69,70]. One study highlighted the importance of treating early overweight or obesity and SDB in children to reduce the risk of future cardiovascular diseases [71]. Further, childhood obesity is another key risk factor for developing SDB, especially in older children and adolescents. In fact, SDB is presented in 26 to 33% of children with obesity [72] showing that the heavier you are, the higher the likelihood to suffer any SDB [29,73-77]. Indeed, the prevalence of OSA, one of the most common causes of SDB in children [61], ranges from 15% to 37% in non-obese children and from 33% to 76% in children with obesity depending on the definition of OSA, the age of the study sample and the degree of obesity [78]. In a specific study of 12-year-old children with overweight or obesity, OSA prevalence was 44.6% [36]. In line with these assumptions, Mathew & Narang concluded that children with overweight or obesity and adolescents could suffer OSA more frequently and may be more severe compared to lean children [79]. However, there is a need to deeply investigate how these factors are associated with SDB in childhood and, further, to study which of them, if any, is the best indicator of SDB to ease its diagnostic.

Sedentary behavior has been linked to SDB [80]. For instance, many sedentary behaviors tend to be associated with an elevated risk of insomnia and sleep disturbance in the existing literature [81]. Indeed, low physical activity levels [48] and exercise capacity [82] have been associated to OSA. Likewise, most of the associated causes and comorbidities of SDB are known to negatively impact cardiorespiratory fitness [83].

Therefore, the aims of the present study were (i) to examine the association of sedentary behavior, moderate to vigorous physical activity (MVPA), cardiorespiratory fitness and body

composition parameters with SDB; and (ii) to analyze which of these variables is the best predictor of SDB in children with overweight or obesity.

METHODS

Study design and participants

The present cross-sectional study is under the framework of the ActiveBrains Project (<http://profith.ugr.es/activebrains>). A detailed description of the study protocol, aims and methods has been published elsewhere [54]. A total of 110 children with overweight or obesity from Granada (south of Spain) were recruited. Recruitment was done at the Unit of Pediatrics of the 'San Cecilio' and 'Virgen de las Nieves' University Hospitals and health care centers of Granada (Spain). Additionally, the head teacher of both private and public schools of Granada were contacted and advertisements in the local media were published [54]. Baseline data collection was performed from November 2014 to February 2016. Of them, one child was excluded for difficulties shown in reading comprehension, and thus, a total 109 children (10.0 ± 1.1 years old, 45 girls) with overweight ($n=27$) and obesity ($n=82$) were included in the analyses.

Parents or legal guardians were informed about the purpose of the study and parental written informed consents for all participants were obtained. This study was conducted according to the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Research (CEIH) of the University of Granada and was registered in ClinicalTrials.gov (identifier: NCT02295072).

Procedures and measurements

Sedentary behavior and physical activity

Television viewing time is known to be the most prevalent and common measure

of leisure time sedentary behavior [84,85]. Television viewing time was self-reported using the Spanish adaptation of the "Youth Activity Profile" questionnaire (YAP-S). The YAP-S was designed to be a self-administered 7-day recall questionnaire suitable for use in children to capture physical activity and sedentary behavior [86]. The YAP questionnaire has been previously calibrated against accelerometer-determined sedentary behavior and physical activity [86] and cross-validated in a different cohorts against accelerometer estimates as well [87,88].

The complete time engaged in sedentary time was objectively measured using wrist-worn accelerometers (ActiGraph GT3X+, Pensacola, FL, USA). Briefly, participants were requested to wear the accelerometers in their non-dominant wrist for the complete 24 hours of the day for 7 consecutive days. Accelerometers were initialized at a sampling frequency of 100 Hz. Then, the raw accelerations were processed in the GGIR package v. 1.5-21 in the R software (<http://cran.r-project.org>). Standard procedures were used to detect and impute non-wear time [89]. Sleep period time was detected using an automatized algorithm guided by reported sleep onset and waking-up times by the participants [90]. Euclidean norm minus one G (ENMO, $1G \sim 9.8 \text{ m/s}^2$) was calculated as (i.e., $-1G$) over 5 second epochs after auto-calibration of the raw acceleration [91,92]. Finally, Hildebrand et al.'s [93] cut points were used to classify ENMO into sedentary time and MVPA. Daily means were used for the analyses (min/day).

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed with the 20-m shuttle-run test as suggested in the ALPHA (Assessing Levels of Physical fitness and Health in Adolescents) health-related fitness test battery for youth [94]. It is known that this fitness test battery is feasible, reliable, valid and related to health in children [95-97]. Briefly, the test consists in running back and forth, between two lines 20m apart,

following an audio signal. Participants finished the test when they did not reach the line in two consecutive trials or stopped due to fatigue. We recorded the last completed lap and then, we translated it into an estimated maximal oxygen consumption measure ($\text{VO}_{2\text{max}}$, ml/kg/min) with the formula described by Léger [98].

Body composition parameters

Weight was assessed with an electronic scale (SECA 861, Hamburg, Germany), while height was measured using a precision stadiometer (SECA 225, Hamburg, Germany) to the nearest 0.1 kg and cm, respectively. Body mass index (BMI) was calculated as weight/height squared (kg/m^2). Children were classified as overweight or obese using the sex- and age-specific international BMI cut offs proposed by the World Obesity Federation [14,15]. Waist circumference (WC) was measured using a homologated flexible steel tape (SECA, Hamburg, Germany). Weight, height and WC were measured twice, and the average was considered for the analyses. Fat mass (kg) and lean mass (kg) were assessed by Dual-energy X-ray absorptiometry (DXA, Discovery densitometer from Hologic), following protocols used in previous studies [99,100]. Participants' fat mass index and lean mass index were calculated by dividing their outcome (i.e., fat mass or lean mass) by their squared height (kg/m^2).

Sleep-disordered breathing

SDB was evaluated with the Spanish version of the Pediatric Sleep Questionnaire (PSQ), which has shown high reliability and internal consistency [9]. This questionnaire was completed by parents, who should rate each item according to their child's usual sleep habits. This questionnaire has been validated for the identification of risk of SDB [55]. A SDB scale was calculated from the 22 items of the questionnaire. The SDB scale consists of 22 closed response question-items of the reduced version of the PSQ, which are divided into three domains as follows [10]:

snoring, sleepiness and behavior. The answer options for each item include "yes", "no", and "I do not know". In the last domain of the questionnaire, the answers were structured in "never", "sometimes", "often" or "almost always". In order to be consistent with these answer options throughout the questionnaire, one of the sections was re-categorized as follows: "never" and "sometimes" answers were categorized as "no", whereas "often" and "almost always" answers were categorized as "yes". The overall scale was calculated as the sum of the affirmative answers divided by 22. Occasional missing answers or responses of "I do not know" were discounted from the denominator when calculating these proportions. Scores > 0.33 were considered suggestive of high risk for a pediatric SDB [10].

Covariates

Age, sex and maternal education level were included as covariates. Maternal education was obtained by a self-reported questionnaire about the maximum education level achieved. Mothers' responses were classified as primary school, secondary school and university degree completed.

Statistical analysis

Descriptive characteristics are presented as means and standard deviations for continuous variables and as frequency and percentages for categorical variables. All variables were checked for normality. Sex differences were examined by t-tests and chi-squared tests for continuous and categorical variables, respectively.

Pearson's bivariate correlations were used to examine the association of sedentary behavior, MVPA, cardiorespiratory fitness and body composition variables with SDB scale. Hierarchical stepwise regressions were used to indicate the main explanatory variables of SDB among sedentary behavior, MVPA, cardiorespiratory fitness and body composition parameters. All the variables (i.e., age, sex, maternal education, television viewing time,

sedentary time, MVPA, cardiorespiratory fitness, BMI, fat mass index, lean mass index and WC) were included together in the regression. We calculated variance inflation factors (VIF) for the models performed and only considered those with $VIF < 10$ to account for the risk of collinearity among explanatory variables.

Additionally, participants were classified into low (≤ 1 hour/day) and high (> 1 hour/day) television viewing groups. Although 2-hour television viewing has been related to negative health consequences [85], we considered that our sample, composed exclusively of children with overweight or obesity, could experience health consequences even with just 1 hour of television viewing per day. Differences between groups were analyzed with a one-way analysis of covariance (ANCOVA) adjusted for age, sex, and maternal education.

All analyses were performed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY). The level of significance was set at $p < 0.05$.

cardiorespiratory fitness and body composition parameters with SDB is presented in **Table 4**. BMI was the predictor which explained the largest proportion of the variance in SDB ($r^2 = 0.063$, $P = 0.011$). Among the rest of predictors, television viewing time was the only one added to this model with a significant contribution (r^2 change = 0.048; $P = 0.022$).

It is important to note that all the significant association observed in this manuscript were of small magnitude, indicating than other factors in addition to the one hereby studied contribute to explain the variance in SDB.

RESULTS

Descriptive characteristics of the participants stratified by sex are presented in **Table 2**. Pearson's bivariate correlation analyses are presented in **Table 3**. In regard to sedentary behaviors, television viewing time was positively associated with SDB ($r=0.222$, $P=0.021$) whilst sedentary time was not ($r=0.129$, $P=0.193$). MVPA was not significantly associated with SDB ($r=0.054$, $P=0.585$). Cardiorespiratory fitness was negatively correlated with SDB ($r=-0.210$, $P=0.030$). Finally, all body composition parameters were positively associated with SDB (r ranging from 0.191 to 0.223, all $P \leq 0.047$), except fat mass index ($r=0.153$, $P=0.114$).

Hierarchical stepwise regression for the association of sedentary behavior, MVPA,

Table 2. Descriptive characteristics of the participants.

	All	Boys	Girls
n (%)	109 (100)	64 (59)	45 (41)
Age (years)	10.0 ± 1.1	10.2 ± 1.1	9.9 ± 1.1
Sedentary behavior			
Television viewing time, n (%) (n=107)			
None	1 (1)	0 (0)	1 (2)
<1h/day	41 (38)	24 (38)	17 (39)
1-2h/day	42 (39)	22 (34)	20 (47)
<2-3h/day	13 (12)	8 (12)	5 (12)
>3h/day	10 (9)	10 (16)	0 (0)
Sedentary time (min/day) (n=103)	520.1 ± 54.7	521.3 ± 52.0	518.4 ± 58.9
Physical activity			
Moderate-to-vigorous physical activity (min/day) (n=103)	51.4 ± 20.1	59.1 ± 21.0	40.2 ± 11.7
Cardiorespiratory fitness			
20m shuttle run test (laps)	16.0 ± 7.7	17.2 ± 8.1	14.4 ± 6.9
20m shuttle run test (VO _{2max} ^a mL/kg/min) ^a	40.7 ± 2.7	40.8 ± 2.7	40.6 ± 2.7
Body composition parameters			
Weight (kg)	56.2 ± 11.2	57.1 ± 11.2	54.9 ± 11.3
Height (cm)	144.2 ± 8.4	145.0 ± 8.0	143.1 ± 9.0
Body mass index (kg/m ²)	26.8 ± 3.6	27.0 ± 3.7	26.6 ± 3.5
Fat mass index (kg/m ²)	11.8 ± 2.9	11.5 ± 2.9	12.1 ± 2.8
Lean mass index (kg/m ²)	14.0 ± 1.4	14.3 ± 1.3	13.5 ± 1.4
Waist circumference (cm)	90.2 ± 9.9	91.3 ± 9.4	88.7 ± 10.5
Sleep-disordered breathing			
SDB scale (0 to 1)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1
Presence of SDB, n (%)	17(16)	10 (16)	7 (16)

Data are presented as mean ± standard deviation or frequency (%). SDB: Sleep-disordered breathing, VO_{2max}^a: maximum oxygen consumption.

^a 20m shuttle run test (VO_{2max}^a) was estimated from the 20-m shuttle run test by the formula described by Léger et al. [98].

Table 3. Pearson's bivariate correlation coefficients of sedentary behavior, physical activity, cardiorespiratory fitness and body composition parameters with sleep-disordered breathing scale.

	SDB scale (0 to 1)	
	r	P
Sedentary behavior		
Television viewing time (h/day)	0.222	0.021
Sedentary time (min/day)	0.129	0.193
Physical activity		
Moderate-to-vigorous physical activity (min/day)	0.054	0.585
Cardiorespiratory fitness (VO_{2max} mL/kg/min) ^a	-0.210	0.030
Body composition parameters		
Body mass index (kg/m ²)	0.209	0.029
Fat mass index (kg/m ²)	0.153	0.114
Lean mass index (kg/m ²)	0.223	0.020
Waist circumference (cm)	0.191	0.047

Statistically significant values (P < 0.05) are shown in bold. SDB: sleep-disordered breathing.

^a Cardiorespiratory fitness (VO_{2max}) was estimated from the 20-m shuttle run test by the formula described by Léger et al. [98].

Table 4. Hierarchical stepwise regression for the association of sedentary behavior, moderate to vigorous physical activity, cardiorespiratory fitness and body composition parameters with sleep-disordered breathing scale (n=102).

	β	P value	Change R ²	R ²
Model 1			0.063	0.063
Body mass index	0.251	0.011		
Model 2			0.048	0.111
Body mass index	0.249	0.010		
Television viewing time	0.220	0.022		

β = standardized coefficients. Variables entered in the stepwise models: age, sex, maternal education, television viewing time, sedentary time, moderate-to-vigorous physical activity, cardiorespiratory fitness, body mass index, fat mass index, lean mass index and waist circumference.

ANCOVA analyses showed that children viewing television for more than 1 hour/day presented higher SDB values than their peers after adjustment for age, sex and maternal education (mean diff = 0.057; P = 0.031; F= 4.779; gl=1) (Figure 1).

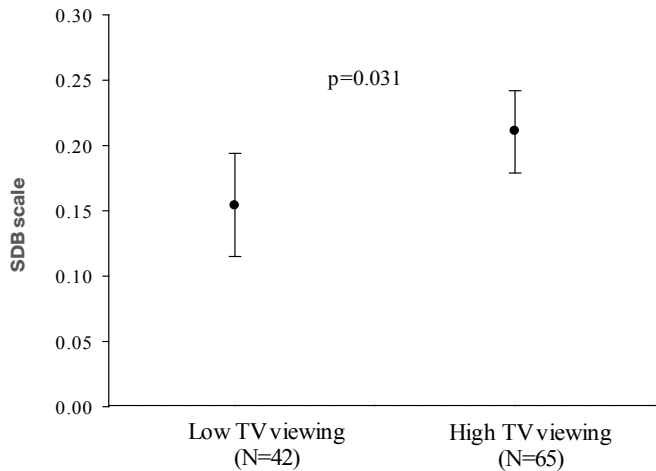


Figure 1. Differences in sleep-disordered breathing scale between low and high television viewing categories. Error bars represent mean and 95% confidence interval. Analyses are adjusted for age, sex and maternal education. Low television viewing: ≤1h/day; High television viewing: >1h/day. TV: television; SDB: sleep-disordered breathing.

DISCUSSION

The main findings of this study were: 1) television viewing time and BMI parameters were positively associated with SDB. Cardiorespiratory fitness was negatively associated with SDB; and 2) among the variables studied, BMI and television viewing time were the best predictors of SDB in children with overweight or obesity, explaining together around 11% of the variance in SDB.

A previous study has shown that sedentary behavior such as television viewing (television mobile screen watching) is strongly related to childhood obesity [101]. Also, it is shown that

higher durations of television viewing and screen time were associated with poorer body composition [102]. Our findings contribute to the existing knowledge by suggesting that those children with overweight or obesity who spend more than 1h viewing television also showed higher SDB values. Likewise, television viewing was a stronger indicator of SDB than objectively assessed sedentary time and MVPA. Paavonen et al. [103] found that television viewing was related to shorter sleep duration, sleeping disorders, and overall sleep disturbances in 5 to 6-year-old normal weight children. Our findings complement these ones by suggesting the same association in older

children, i.e., 8.5-to 12-year-olds. Of note, a cut point of 2 hours of television viewing time is usually considered as being malign for health [85]. However, since our participants were children with overweight or obesity, we assumed that lower doses of television viewing time are especially harmful for this sample, and so, 1 hour of television viewing time was considered to compare subgroups in our study. Concerning sedentary time measured through accelerometers, we did not observe any association with SDB. The lack of capacity to discern between sedentary activities by the accelerometer could partially explain this finding. Similarly, no relationship between MVPA and SDB was found. Although we have not found studies testing the associations between objectively-assessed MVPA and SDB, it seems that 40 minutes per day of vigorous aerobic exercise could improve symptoms of SDB in overweight 7 to 11-year-old children [50].

Cardiorespiratory fitness is an important health marker, not only in adults but also in children and adolescents [16]. In consonance with previous studies [83,104], we found that cardiorespiratory fitness was negatively associated with SDB values. Although this association was weak, our sample size was limited; thus, further studies with larger sample sizes are needed to estimate the real effect size of this association. For instance, Stojek et al. [104] found that higher levels of cardiorespiratory fitness were closely linked to less SDB in inactive children with overweight or obesity aged 7 to 11 years. A possible explanation could be that the high oxygen demanding produced by cardiorespiratory fitness could improve the efficiency of the children's cardiorespiratory system and, therefore, reduce SDB.

Current literature provides evidence that children with overweight or obesity commonly present SDB [29,73-77]. Longitudinal studies showed that overweight or obesity status in adolescents was strongly associated with increased mortality in adulthood due to cardiovascular diseases or other obesity-

related risk factors [105]. One study found that a higher body fat percentage at the age of 6-8 years was associated with a higher risk of having SDB 2 years later [106]. Verhulst et al. [75] found that fat distribution, as represented by WC, waist-to-hip ratio, or fat mass percentage were associated with central sleep apnea but not with OSA in children with overweight or obesity. In concordance with our findings, a questionnaire study in children who were on average 9 years old, observed that WC was correlated with SDB [107]. Additionally, WC was associated with all levels of SDB [29] and an increased amount of visceral fat was associated with serious manifestations of SDB [108] in a population sample of children. Likewise, Bhatia et al. [109] observed that BMI was positively associated with sleep problems (i.e., total arousal index and desaturation index) in children with overweight or obesity. In regard to DXA measures, they found that total body fat mass and trunk fat mass were related to some SDB indicators, but they did not include fat mass index among their measures. Specifically, they concluded that the value of fat mass to study SDB depends in the distribution of the fat over the body, which could explain the lack of association that we found after considering height when calculate fat mass index. In contrast, our results suggested that lean mass index could be a better indicator of SDB than fat mass index. A possible explanation could be that children with more lean mass index have higher obesity levels since they have to carry more fat and also have bigger nocturnal work of breathing and, thus, they develop more lean mass. Furthermore, sarcopenic obesity has been associated with SDB in adults, but not obesity in general. The hypothesis is that an excess of fat is a predictor of SDB only when the lean mass is low [110-112]. However, in children, loss of lean mass is not a common problem, and little has been studied about body composition in relation to SDB. Further studies using gold-standard methods for body composition parameters are

needed to contrast our findings in children with overweight or obesity.

BMI has been very criticized for its lack of ability to distinguish between fat and lean tissues, but also a recent study showed that this index is better in the prediction of mortality than fat mass measured by a gold-standard method [113]. In regard to SDB, we found something similar; BMI was a stronger predictor of SDB than any other body composition outcome measured by a gold-standard (i.e., DXA). Other body composition parameters such as lean mass index or WC were associated with SDB, but they were unable to explain a proportion of variance in SDB more than those already explained by BMI. Andersen et al. found that an increased BMI was associated with increased apnea-hypopnea index and significantly risk of having OSA in children aged 7-18 years with overweight or obesity [36]. These results differ from those provided by Carotenuto et al. [107], who suggested that visceral fat (expressed as WC) was a more reliable measure than total adiposity (expressed as BMI) to predict the risk for developing SDB in children and adolescents with obesity. Differences in study samples (i.e., participants' age) and methodology (i.e., different questionnaires) might be responsible for the differences between these findings and ours. In addition, they only included children with obesity, while we also considered overweight children, which could partially explain the signification of BMI in our sample compared to Carotenuto et al.'s [107] sample. More studies are needed for a better understanding of the relationships between body composition and SDB in children with overweight or obesity.

Among the explanatory variables of SDB included in the present study (i.e., sedentary behavior, moderate to vigorous physical activity, cardiorespiratory fitness and body composition parameters), we found that BMI and television viewing time were the strongest ones, explaining the largest proportion of the variance in SDB. None of the rest of outcomes contributed to the explanation already shown by BMI and television viewing time. Although

more studies are needed to confirm this, these findings suggest that interventions oriented to reduce BMI and television viewing time through the modification of lifestyle habits and practices of physical exercise could be useful for the treatment of SDB in children with overweight or obesity, even if the association is not strong enough.

The high prevalence of obesity and its health-related problems, such as SDB, in the current pediatric population makes crucial the investigation on environmental factors associated with this disorder. Previous research has shown links of sedentary behavior, physical activity and body composition parameters with SDB in pediatric population. Our study complements the current knowledge by: 1) confirming these findings, despite the weak link, and adding more information in the literature due to the lack of knowledge on this topic, and 2) testing which of the factors could be of predominant interest to treat SDB in children with overweight or obesity. However, only an 11% of the variation in SDB was explained by the predictors included. There is an important amount of the variation which is explained by factors not included in our models. Whether this 11% is enough to help in the diagnostic of SDB from early ages is something to be investigated in future research.

Some limitations of the present study need to be acknowledged. Firstly, this is a cross-sectional study; hence, it does not allow us to infer causality for any of the associations studied. Secondly, a gold standard was not used to identify SDB and our data were obtained from parental questionnaires instead of polysomnographic data; therefore, its accuracy in evaluating SDB is limited. Thirdly, the no inclusion of normal weight children cannot allow us the comparison between different weight status populations. Fourthly, our sample size was limited; thus, even more powerful studies with larger sample sizes are needed to confirm or contrast our findings. Caution is advised with the interpretation of these findings regarding younger ages, when

other factors may be major determinants of SDB (e.g., adenotonsillar). Finally, there could be other potential explanatory factors for SDB in addition to those hereby studied that need to be investigated in future studies. The strengths of this study were: 1) the inclusion of objectively measured, sedentary time and physical activity with accelerometry; 2) the inclusion of reliable, valid and related to health field-based fitness tests in children [95-97] and 3) the reliable and valid measures of body composition parameters.

CONCLUSION

Our results suggest that sedentary behavior, cardiorespiratory fitness and body composition parameters were associated with SDB in children with overweight or obesity, being television viewing time and BMI the strongest predictors of SDB. This study supports the notion that higher body weight status negatively influences SDB and adds that unhealthy behaviors such as high television viewing time could independently contribute to worsen SDB. Physical activity interventions focused on reducing sedentary behaviors such as television viewing time and improving both cardiorespiratory fitness and body composition parameters could be a good strategy to treat SDB prevalence in children with overweight or obesity and to reduce cardiovascular diseases risk in adulthood. All the significant association observed in this manuscript were of small magnitude, indicating than other factors in addition to the one hereby studied contribute to explain the variance in SDB. Further randomized controlled trials studies are needed in order to contrast or corroborate our findings.

Study 2

Does sleep-disordered breathing add to impairments in academic performance and brain structure usually observed in children with overweight or obesity?

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ABSTRACT

Background: Approximately 4-11% of children suffer from sleep-disordered breathing (SDB), and children with obesity are at increased risk. Both obesity and SDB have been separately associated with poorer brain health, yet whether SDB severity affects brain health in children with obesity remains unanswered.

Objective: To examine associations of SDB severity with academic performance and brain structure (i.e., total brain and gray and white matter volumes, and gray matter volume in the hippocampus) in children with overweight or obesity.

Methods: One hundred nine children aged 8-12 years with overweight or obesity were included. SDB severity and its subscales (i.e., snoring, daytime sleepiness, and inattention/hyperactivity) were evaluated via the Pediatric Sleep Questionnaire (PSQ), and academic performance was evaluated with

the Woodcock-Muñoz standardized test and school grades. Brain structure was assessed by magnetic resonance imaging.

Results: SDB severity was not associated with academic performance measured by the standardized test (all $|\beta| > 0.160$, $P > 0.076$), yet it was associated with the school grade point average ($\beta = -0.226$, $P = 0.007$) and natural and social science grades ($\beta = -0.269$, $P = 0.024$). Inattention/hyperactivity seemed to drive these associations. No associations were found between SDB severity and the remaining school grades (all $\beta < -0.188$, $P > 0.065$) or brain volumes (all $P > 0.05$).

Conclusion: Our study shows that SDB severity was associated with lower school grades, yet it was not associated with the standardized measurement of academic performance or with brain volumes in children with overweight or obesity. SDB severity may add to academic problems in children beyond the effects contributed by overweight or obesity status alone.

INTRODUCTION

Pediatric obstructive sleep-disordered breathing (SDB) has been recognized as a common health problem [114]. The European Respiratory Society Task Force defined obstructive SDB as a set of respiratory tract dysfunctions during sleep, which are characterized by snoring and/or increased effort to breathe caused by a narrowing of the pharynx and increased airway resistance [8]. SDB affects approximately 4-11% of children, with a range of severities from primary snoring to obstructive sleep apnea (OSA) [27-35]. In a previous study including children 6-15 years of age, those with obesity were at higher risk for SDB (20.8%) than their normal-weight peers (6.3%) [35]. Among children with SDB, obesity has been associated with higher SDB severity [74,115]. These data clearly support the idea that there is an urgent need to address SDB severity in children with overweight or obesity.

A consensus statement by the European Respiratory Society Task Force on the diagnosis and management of SDB in childhood concluded that children with SDB may present an increased prevalence of academic difficulties and cognitive deficits [8]. Relatedly, some previous studies have found that children with SDB might present impaired academic [66,116-118] and neurocognitive [119,120] performance, and that SDB in children as young as 3 years old predicted significantly poorer performance on oral language assessments at 8 years old [121]. However, these findings have been inconsistent [119]. Specifically, research in children and adolescents with overweight or obesity and comorbid SDB has shown lower neurocognitive performance [122,123] and contradictory findings on academic performance [67,124-126]. Thus, children with overweight or obesity may be at increased risk of neurocognitive deficits when they present with SDB symptoms [122,123,127]. However, more research is needed to better understand the associations with academic performance.

Childhood is an important period for the development and maturation of the brain [12,128], and the hippocampus is a key subcortical structure involved in memory consolidation during wakefulness and sleep [129,130]. Among the studies investigating pediatric SDB-brain structure links [131-138], only a few found significant associations in the hippocampus [135,137,139]. Beyond the hippocampus, a recent review concluded that obstructive SDB in children was associated with magnetic resonance imaging (MRI)-assessed brain structure [140]. For example, children with OSA presented smaller regional gray matter volume (GMV) in areas related to cognitive control (i.e., frontal and prefrontal cortices, parietal cortices, temporal lobes, and brainstem) than their peers without any sleep disorder [138]. Conversely, other studies have shown no clear evidence of an association between OSA and brain structure [141,142]. Regarding children with obesity, they have been shown to more prone to suffer from OSA than children with normal weight [143], and they often present impaired regional gray and white matter development [144]. It remains to be elucidated whether SDB increases brain structure impairments in children with overweight or obesity.

Evidence is lacking regarding the joint role of SDB and obesity on academic performance and brain structure in children. Identifying the associations of SDB severity with academic performance and brain structure in the context of childhood obesity could provide meaningful information for public health systems to prevent or attenuate the health-related consequences of obesity with efficient interventions. Therefore, the present study investigated the associations of SDB severity with academic performance using two different measures (i.e., standardized tests and school grades) and with brain structure (i.e., total brain volumes and hippocampal volume as a primary region of interest) in children with overweight or obesity. Identifying these associations might help to provide a

better understanding of the influencing role of SDB on brain health beyond weight status alone.

METHODS

Study design and participants

We used baseline data from ActiveBrains, a randomized controlled trial intended to investigate the effects of an exercise program on the brain and cognition in children with overweight or obesity [53]. Data were collected from November 2014 to February 2016 in a total of 110 overweight/obese children from Granada (Spain). Of them, one child was excluded for being a nonnative Spanish speaker and did not reach the required threshold in Spanish reading comprehension to be properly evaluated. Thus, a total of 109 children (10.04 ± 1.12 years old; 45 girls) were included in this cross-sectional study. Most of the participants were European Caucasian (95%), with only ~5% reported being of other ethnicities. A detailed description of the study protocol, aims and methods has been published elsewhere [54]. All participants met the following inclusion criteria: 1) overweight or obesity, based on the sex- and age-specific international body mass index cutoff points proposed by the World Obesity Federation [14,15]; 2) age between 8 and 12 years old; 3) no physical disabilities or neurological disorders that could affect physical performance; 4) prepubertal status according to the Tanner stages [145]; and 5) for the girls, no menarche.

Legal guardians were informed of the purpose of the study, and written informed consent for all participants was obtained. This study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Research (CEIH) of the University of Granada and registered at ClinicalTrials.gov (identifier: NCT02295072).

Procedures and measurements

Sleep-disordered breathing

The children's legal guardians completed the Spanish version of the Pediatric Sleep Questionnaire (PSQ) to assess SDB, which has shown high reliability and internal consistency [9]. This questionnaire has been validated for the identification of SDB [10,146]. A SDB scale (scores could range from 0 to 1) was calculated from the 22 items of the questionnaire, with higher scores indicating greater severity [146]. The SDB scale consisted of 22 closed response question items as a reduced version of the PSQ, which were divided into the following three subscales [10,146]: snoring (four items), sleepiness (four items) and inattention/hyperactivity (six items). These subscales are valid and reliable for assessing SDB in children [10]. The answer options for each item included "yes", "no", and "I do not know". In the last domain of the questionnaire (inattention/hyperactivity subscale), the answers were structured as "never", "sometimes", "often" or "almost always". To be consistent with these answer options throughout the questionnaire, one of the sections was recategorized as follows: "never" and "sometimes" answers were categorized as "no", whereas "often" and "almost always" answers were categorized as "yes". The overall scale was calculated as the sum of the affirmative answers divided by 22. Occasional missing answers or responses of "I do not know" were discounted from the denominator when calculating these proportions [147]. Scores > 0.33 were considered suggestive of high risk for pediatric SDB [10,146]. A recent meta-analysis indicated that the SDB scale was accurate for detecting OSA in children [148]. The SDB scale score has been validated as a continuous indicator of SDB severity [115].

Academic performance

Academic performance was assessed via the Spanish adaptation of the Woodcock-Johnson III battery (i.e., Woodcock-Muñoz standardized test), which has shown high

reliability and is a well-validated measure of academic performance for individuals aged 5-95 years [149]. For this study, we used the standard battery, which contained three tests of mathematics, three tests of reading, and three tests of written language. The assessment was individually conducted for each child by a trained evaluator in a session lasting 100-120 min. The data registered for each child were individually checked by two trained evaluators. All data were processed using Compuscore and Profile software version 3.1. (Riverside Publishing Company, Itasca, IL, USA) and grouped into components (i.e., total achievement, reading, writing, written expression, mathematics, calculation, and calculation skills). For the current study, a standard T-score based on an average of 100 and a standard deviation of 15 was obtained for the following academic performance indicators: mathematics, reading, writing, and total achievement. Academic performance tests and MRI were conducted within 1 to 3 weeks of each other.

As a second measure of academic performance, official final school grades, closer to the baseline assessment (± 1.5 months), were used for the analyses in 78% of the study sample ($n=85$). Data were not missing at random ($n=24$). The school grades were initially collected in the second wave of participants, so they were missing for the first wave. Since school records were provided in a qualitative manner (i.e., insufficient, sufficient, good, very good, and outstanding) by teachers, we registered the grades based on a scale from 1 to 5. The mean grades in mathematics, Spanish language, English language, and natural and social sciences were recorded. We also determined the individual's grade point average as the mean score across all subjects.

Brain structure

Brain volume was assessed using magnetic resonance imaging (Siemens Magnetom Tim Trio, 3T, Siemens, Erlangen, Germany) equipped with a 32-channel head coil. High-

resolution, T1-weighted images were acquired using a 3D MPRAGE (magnetization-prepared rapid gradient-echo) protocol. Acquisition parameters were as follows: repetition time = 2,300 ms, echo time = 3.1 ms, inversion time = 900 ms, flip angle = 9°, field of view = 256 x 256, acquisition matrix = 320 x 320, 208 slices, and resolution = 0.8 x 0.8 x 0.8 mm. The total acquisition time for the T1 sequence was 7 min and 31 s for each child. Imaging preprocessing included quality control, motion correction, spatial normalization to an MNI (Montreal Neurological Institute) template and spatial smoothing. Detailed information about preprocessing has been described previously [150]. Some missing data were found for brain volumes ($n=9$) and hippocampal GMV ($n=7$). Total brain volume, total white matter volume, total GMV, and total, right and left hippocampal GMV were derived from FreeSurfer software version 5.3.0 (Laboratory for Computational Neuroimaging, Athinoula A. Martinos Center for Biomedical Imaging, Harvard Medical School, Boston MA, USA).

Covariates

Age, sex, maternal and paternal education levels, wave of participation (i.e., ActiveBrains was conducted in three waves for logistic reasons, including seasonality and differences between participants from different waves that may affect the associations), and peak height velocity (PHV) were considered potential confounders. Maternal and paternal maximum education levels were obtained by a self-report questionnaire. The responses of the mothers and fathers were classified as primary school, secondary school, and university degree completed. The wave of participation (1, 2, or 3) was categorized into two dichotomous dummy variables. PHV is an indicator of maturity during childhood and adolescence calculated from standing and seated height using Moore's equations [151].

Statistical analysis

Descriptive characteristics are presented as the means and standard deviations for continuous variables and as frequencies and percentages for categorical variables. Sex differences were examined by t tests and chi-square tests. All variables were checked for normality of distribution using the Kolmogorov-Smirnov test and visual inspection of histograms. After checking for a normal distribution, the SDB scale and subscales were normalized using Blom's formula [152] because the distributions were skewed.

Hierarchical linear regression analyses were performed to examine the associations of SDB severity with academic performance and brain structure indicators (i.e., total GMV and white matter volume, total brain volume, and right and left hippocampal GMV). The stepwise method was used to investigate the influence of potential confounders in the models in step 1 (i.e., age, sex, maternal education level, paternal education level, wave of participation, and PHV). Next, hierarchical regressions were carried out, entering the SDB scale scores as a predictor in step 2 and each academic performance and brain structure variable as outcomes in separate regression analyses after the inclusion of confounders previously defined in step 1. The same procedure was followed to assess the association of each subscale score from the PSQ (i.e., snoring, daytime sleepiness, inattention/hyperactivity) with academic achievement and brain structure.

The Benjamini-Hochberg procedure was applied to account for random effects in multiple comparisons for each dependent domain (i.e., academic performance assessed by standardized test, academic performance assessed by school grades, brain volumes and hippocampal GMV) with $q=0.1$ [153]. All analyses were performed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY). The level of significance was set at $p < 0.05$.

RESULTS

Descriptive characteristics for all participants are presented in **Table 5**. The results were not reported separately by sex since no significant sex interaction was observed in the models (sex was included as a confounder). Hierarchical linear regression analyses for the association of SDB severity with academic performance and brain structure variables are presented in **Table 6**.

Regarding academic performance measured by standardized testing, SDB severity was not significantly associated with mathematics, reading, writing or total academic performance (all $|\beta| > 0.160$, $P \geq 0.076$). Regarding school grades, SDB severity was significantly associated with natural and social sciences grades and grade point average ($\beta=-0.226$, $P=0.024$; $\beta=-0.269$, $P=0.007$, respectively). Nonsignificant associations were found between SDB severity and mathematics, Spanish language and English language (all $\beta < -0.188$, $P > 0.065$), and SDB severity was not associated with any of the brain outcome measures studied (all $P > 0.05$). Sensitivity analyses were performed by adding BMI as a confounder to previous models, and all associations presented in this study remained unchanged.

Additionally, hierarchical linear regression analyses were performed to assess potential associations of SDB subscale scores (snoring, sleepiness and inattention/hyperactivity) with academic performance and brain structure, as shown in **Table 7**. The PSQ inattention/hyperactivity subscale was the only subscale associated with school grades (specifically with mathematics grades, natural and social science grades, and grade point average; all $P < 0.014$). No significant differences were observed in the remaining aspects of academic performance and brain structure variables examined.

Table 5. Descriptive characteristics of the participants.

	All		Boys		Girls		P
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD	
Age (years)	109	10.04 ± 1.12	64	10.16 ± 1.15	45	9.88 ± 1.08	0.197
Weight (kg)	109	56.21 ± 11.23	64	57.11 ± 11.2	45	54.94 ± 11.28	0.323
Height (cm)	109	144.22 ± 8.41	64	144.98 ± 7.97	45	143.13 ± 8.99	0.261
BMI categories^a	109						0.606
Overweight, n (%)		28 (25.7)		16 (25)		12 (26.7)	
Obesity class I, n (%)		47 (43.1)		30 (46.9)		17 (37.8)	
Obesity class II, n (%)		34 (31.2)		18 (28.1)		16 (35.6)	
Sleep-disordered breathing (SDB)							
SDB scale (range: 0 to 1)	109	0.19 ± 0.13	64	0.19 ± 0.13	45	0.18 ± 0.13	0.621
SDB presence, n (%)		17(15.6)		10 (15.6)		7 (15.6)	0.992
Academic performance (Woodcock-Muñoz)^b							
Mathematics	109	102.06 ± 10.91	65	102.66 ± 11.72	44	101.18 ± 9.64	0.490
Reading	109	108.46 ± 12.68	65	108.83 ± 11.02	44	107.91 ± 14.91	0.711
Writing	109	114.1 ± 12.84	65	112.98 ± 12.13	44	115.75 ± 13.8	0.272
Total achievement	109	109.56 ± 11.83	65	109.51 ± 11.07	44	109.64 ± 13.01	0.956
Academic performance (school grades) range: 0 to 5							
Mathematics	85	3.69 ± 1.01	51	3.73 ± 1.01	34	3.63 ± 1.01	0.642
Spanish language	85	3.72 ± 0.97	51	3.61 ± 0.93	34	3.88 ± 1.03	0.211
English language	85	3.65 ± 1.12	51	3.51 ± 1.14	34	3.86 ± 1.08	0.157
Natural and social science	85	3.71 ± 1.02	51	3.64 ± 1.11	34	3.81 ± 0.87	0.424
Grade point average	85	3.77 ± 0.79	51	3.69 ± 0.82	34	3.9 ± 0.73	0.218
Brain volumes (mm³)							
Total gray matter	100	793.48 ± 66.22	60	819.49 ± 56.13	40	754.48 ± 61.36	<0.001
Total white matter	100	406.81 ± 47.97	60	426.88 ± 42.86	40	376.7 ± 38.9	<0.001
Total brain volume	100	1200.29 ± 106.69	60	1246.37 ± 88.88	40	1131.18 ± 93.71	<0.001
Hippocampal GMV							
Right hippocampus	102	3582.42 ± 390.34	60	3675.44 ± 386.45	42	3449.54 ± 360.11	0.004
Left hippocampus	102	3454.5 ± 379.77	60	3522.31 ± 387.57	42	3357.62 ± 350.42	0.030
Total hippocampus	102	7036.92 ± 694.08	60	7197.75 ± 666.26	42	6807.16 ± 675.3	0.005

Data shown are mean ± standard deviation or n, %. Differences between sexes were examined by t-test or chi-square test. Statistically significant values (P < 0.05) are shown in bold. Notes: SD = standard deviation. ^a BMI categories (overweight, obesity class I and obesity class II) were based on the sex-and-age specific international BMI cut-points proposed by the World Obesity Federation. ^bAcademic performance indicators were calculated based on standardized scores centered at 100. Standardized composite scores are presented. BMI= body mass index. SDB = sleep-disordered breathing. GMV= gray matter volume.

Table 6. Hierarchical linear regression for the associations of SDB severity with academic performance, brain volumes and hippocampal gray matter volume variables.

	SDB scale			
	β	R ²	CI	P
Academic performance (Woodcock-Muñoz)				
Mathematics†	0.023	0.228	(-0.150, 0.196)	0.793
Reading‡	-0.030	0.253	(-0.198, 0.139)	0.729
Writing‡	-0.160	0.177	(-0.338, 0.017)	0.076
Total achievement†	-0.058	0.297	(-0.223, 0.107)	0.488
Academic performance (school grades)				
Mathematics‡	-0.176	0.183	(-0.383, 0.026)	0.086
Spanish language‡	-0.188	0.190	(-0.395, 0.012)	0.065
English‡	-0.168	0.149	(-0.379, 0.038)	0.107
Natural and social science†	-0.226	0.250	(-0.427, -0.031)	0.024
Grade point average‡	-0.269	0.238	(-0.470, -0.076)	0.007
Brain volumes				
Total gray matter††	0.058	0.329	(-0.112, 0.225)	0.505
Total white matter‡‡	-0.058	0.450	(-0.212, 0.097)	0.462
Total brain volume†††	0.018	0.373	(-0.145, 0.181)	0.828
Hippocampal GMV				
Right hippocampus†††	-0.090	0.127	(-0.277, 0.098)	0.345
Left hippocampus‡‡‡	0.004	0.046	(-0.191, 0.199)	0.969
Total hippocampus‡‡‡	-0.043	0.079	(-0.235, 0.148)	0.655

The predictor variable was introduced in separate hierarchical regression models. Potential confounders (i.e., age, sex, maternal education level, paternal education level, wave, and peak height velocity) were included into step 1 of the stepwise regression to test their association to the outcomes, so that for each outcome only the relevant confounders were retained in the final models using the method STEPWISE. In step 2, the exposure variable of interest, SDB scale was entered using the method ENTER to force to be in the model. β values are standardized coefficients. Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparisons test (performed for each domain, that is, academic performance assessed by Woodcock-Muñoz battery, academic performance assessed by school grades, brain volumes and hippocampal GMV). †Adjusted by age and maternal education level. ‡Adjusted by maternal education level. ††Adjusted by sex and paternal education level. ‡‡Adjusted by age, sex, paternal education level and peak height velocity. †††Adjusted by sex and peak height velocity. ‡‡‡Adjusted by sex. SDB= sleep-disordered breathing. GMV= gray matter volume.

Table 7. Hierarchical linear regression for the associations of SDB subscales (snoring, sleepiness and inattention/hyperactivity) with academic performance, brain volumes and hippocampal gray matter volume variables.

	Snoring		Daytime sleepiness		Inattention/ Hyperactivity	
	β	P	β	P	β	P
Academic performance (Woodcock-Muñoz)						
Mathematics†	0.060	0.493	-0.086	0.326	0.028	0.747
Reading‡	0.027	0.751	-0.124	0.146	-0.025	0.768
Writing‡	-0.032	0.720	-0.168	0.059	-0.165	0.070
Total achievement†	0.029	0.726	-0.154	0.063	-0.056	0.506
Academic performance (school grades)						
Mathematics‡	0.075	0.461	-0.138	0.181	-0.257	0.014
Spanish language‡	0.015	0.886	-0.094	0.365	-0.182	0.083
English‡	0.036	0.731	-0.105	0.320	-0.145	0.180
Natural and social science†	0.029	0.771	-0.204	0.043	-0.253	0.013
Grade point average‡	-0.004	0.970	-0.141	0.171	-0.297	0.004
Brain volumes						
Total gray matter††	-0.007	0.935	-0.006	0.945	0.132	0.130
Total white matter‡‡	0.035	0.657	-0.087	0.267	0.020	0.800
Total brain volume††	0.026	0.749	-0.046	0.579	0.102	0.225
Hippocampal GMV						
Right hippocampus†††	-0.133	0.164	-0.020	0.833	-0.090	0.349
Left hippocampus‡‡‡	-0.071	0.471	-0.113	0.255	0.026	0.791
Total hippocampus‡‡‡	-0.096	0.320	-0.080	0.415	-0.033	0.735

The predictor variable was introduced in separate hierarchical regression models. Potential confounders (i.e., age, sex, maternal education level, paternal education level, wave, and peak height velocity) were included into step 1 of the stepwise regression to test their association to the outcomes, so that for each outcome only the relevant confounders were retained in the final models using the method STEPWISE. In step 2, the exposure variable of interest (e.g., snoring or sleepiness or inattention/hyperactivity subscale) was entered using the method ENTER to force to be in the model. β values are standardized coefficients. Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparisons test (performed for each domain, that is, academic performance assessed by Woodcock-Muñoz battery, academic performance assessed by school grades, brain volumes and hippocampal GMV). †Adjusted by age and maternal education level. ‡Adjusted by maternal education level. ††Adjusted by sex and paternal education level. ‡‡ Adjusted by age, sex, paternal education level and peak height velocity. †††Adjusted by sex and peak height velocity. ‡‡‡ Adjusted by sex. SDB = sleep-disordered breathing. GMV= gray matter volume.

DISCUSSION

The main findings of this study support the ideas that i) SDB severity was related to lower academic performance at school, particularly with natural and social science grades and grade point average, but not with academic performance measured by a standardized test; ii) inattention/hyperactivity seemed to drive these associations between SDB severity and school grades; and iii) SDB severity was not associated with differences in brain structure in children with overweight or obesity. Therefore, this study adds to the literature by showing that SDB symptoms may worsen academic performance in children beyond the effects of weight status alone.

Our study findings suggest a lower academic performance in children with a high risk of SDB than in their peers with a low risk of SDB. It may be that a single assessment through the administration of a standardized test might not fully capture the performance of children across time in the same manner as school grades do. Other possible factors explaining the differences between the school grade and standardized test outcomes may be the different grading systems between schools or the subjective influence of teachers [154]. To the best of our knowledge, only a few studies have focused on children with overweight or obesity with comorbid SDB and academic performance. Collectively, the conclusions across studies have been inconsistent [67,124-126]. In line with our findings, a previous study showed that academic grades were impaired in children with overweight and SDB compared to children with overweight but without SDB based on reports from parents and children [67]. Beebe et al. [67] found that these associations might be explained by behavioral factors rather than cognitive factors, which may explain why we observed associations with school grades but not with a standardized test. However, other studies measuring other dimensions of school functioning did not observe an impairment in

children with SDB compared to children without SDB [126]. This inconsistency might be primarily explained by the different constructs that were measured, since Biggs et al. [126] focused on school functioning as a measure related to quality of life, yet they did not collect school grades. Moreover, recent studies found that overweight or obesity was inversely associated with school performance in childhood [155,156]. Indeed, both SDB and obesity may adversely influence cognitive functioning [127] and, subsequently, academic performance. Children with overweight or obesity and SDB were at higher risk of neurocognitive deficits than normal-weight children (with and without SDB) [122,123]. As an alternative explanation, they suggested that obesity might worsen neurocognitive performance in children rather than SDB alone, yet they did not include a non-SDB overweight or obesity group. Hence, we added to the literature by showing that SDB symptoms may worsen already-impaired academic achievement in children with overweight or obesity. However, evidence that affirms the association of obesity with academic performance is not strong enough [157], and future research with a healthy-weight control group and proper sample size should further investigate the interactions between obesity and SDB in association with academic performance.

Taken together, our findings and the abovementioned studies suggested that the previously observed association between SDB and school grades in normal-weight children [66,116-118,158,159] is also apparent in children with overweight or obesity. The mechanisms driving the association between SDB and school performance remain unclear [67]. SDB may produce intermittent hypoxia, hypercapnia and reoxygenation, along with changes in cerebral blood flow and sleep fragmentation [160], potentially affecting cognitive functioning. Although variability in cognitive function in children with SDB may be explained by a reduction in cerebral oxygenation [161], the pathophysiology of the

involvement of the central nervous system during OSA is still debated [162]. However, a recent review found that cerebral oxygenation levels were maintained in this population [140] and were not related to cognitive deficits, but they were associated with behavioral problems in children with SDB [163]. This conclusion may explain the association in our study between SDB and school grades, where children's behavior, general functioning and teachers' influence on children's behaviors are relevant. Future studies exploring SDB severity with polysomnography and a proper sample size should corroborate or contrast with our findings.

With regard to brain structure, SDB severity was not related to total brain volume or specifically to hippocampal volume in our sample of children with overweight or obesity. Similarly, a study in 10-year-old children found no significant difference between the OSA and control children in total and regional brain volume and density (i.e., GMV, gray/white matter ratio, total brain volume, and gray/total brain ratio) [141]. Unlike our study, a recent review identified that SDB was associated with changes in the brain using MRI in children with normal weight [140]. Likewise, using polysomnography, recent studies determined that normal-weight children (7-11 y) with OSA had smaller regional GMV [138] and white matter volume [164] than children without OSA. Furthermore, Walter and Horne [139] concluded in a review that previous MRI studies found significant structural changes (i.e., reduced white and gray matter of particular brain areas, including the hippocampus) in children with SDB. Our results may differ from these findings due to the method of measuring SDB (i.e., overnight polysomnography vs. PSQ). It is important to consider that SDB severity in our participants may be mild (i.e., the SDB average score was 0.19 [SD=0.13] on a scale with a range from 0 to 1, with 0.33 indicating higher risk for SDB). Other studies in children with higher SDB severity have found regional gray matter deficits [141]. The lower SDB severity in our

participants could explain the lack of apparent brain volume deficits and the small-sized associations with academic achievement. The lack of significant associations may be due to the low statistical power reached in this analysis. Only 17 participants presented SDB in this study (15.6%). As such, SDB severity might not have been sufficient to affect myelination and neuronal connectivity in our participants [165]. However, it is difficult to compare our findings to other cohorts since no previous study was conducted with children with overweight or obesity. In adults with OSA, lower GMV in the left hippocampus [166] and in the right hippocampus [167,168] has been found, although this association was not observed here in the context of childhood obesity. Differing developmental stages [169] and not using polysomnography in our study may have partly explained the lack of observed associations. Thus, larger studies including both normal-weight children and children with overweight or obesity are needed to confirm these findings.

The high prevalence of pediatric obesity worldwide and its associated health-related problems, such as SDB, provide an impetus for the investigation of brain health factors associated with this disorder. Previous research has shown links between SDB and academic performance and brain structure in the pediatric population. However, information on how SDB severity in children with overweight or obesity is associated with academic performance and brain health is limited. Our study contributes to the current knowledge by suggesting that SDB may worsen academic performance in children with overweight or obesity (who often show impaired performance). We also provided a broader picture of academic performance by including two different assessments: school grades and standardized test results. Although we did not find associations with brain structures, it remains to be elucidated whether these changes in school grades have any clinical significance. Some limitations need to be acknowledged. First, this was a

cross-sectional study; hence, it does not allow for causal inference for any of the observed associations. Second, our data were obtained from a parent-reported questionnaire instead of polysomnographic data (i.e., the gold standard for the detection of SDB and its severity); however, this questionnaire is valid and reliable for the diagnosis of SDB symptoms. Third, including a group of children with normal weight could be informative toward understanding the interaction between obesity and SDB. Unfortunately, we did not collect data in children with normal weight, and we encourage future researchers to gain insight into this interaction by assessing children with varied weight status. Fourth, teachers may have graded the children from different schools differently. Fifth, our sample size and the prevalence of SDB may have limited the statistical power of the analysis. Future research should confirm our findings. Caution is advised with the extrapolation of these findings to younger children or to other determinants of SDB that were not considered in this study (e.g., adenotonsillar disease, ethnicity and levels of deprivation). On the other hand, the strengths of this study include the use of MRI for the quantification of GMV in the hippocampus and total brain volume; the focus on children with overweight or obesity, who are particularly vulnerable to sleep disorders; and a comprehensive academic performance assessment using two different methods, i.e., standardized tests and school grades.

CONCLUSION

Our study contributes to the literature by indicating that SDB severity was related to lower academic performance at school in children with overweight or obesity, which was driven by inattention/hyperactivity. However, we did not observe associations with academic performance measured by a standardized test or brain structure in children with overweight or obesity. Accordingly, our findings suggest that SDB symptoms may adversely affect learning in school in children with overweight or obesity beyond the effects of weight status alone.

Study 3

Associations of sleep-related outcomes with behavioral and emotional functioning in children with overweight or obesity

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ABSTRACT

Objective: To evaluate the associations of parent-reported sleep-disordered breathing (SDB) and device-assessed sleep behaviors with behavioral and emotional functioning in children with overweight or obesity.

Methods: A total of 109 children with overweight or obesity (10.0 ± 1.1 years) were included in this cross-sectional study. We used the Spanish version of the Pediatric Sleep Questionnaire (PSQ) to assess SDB and its subscales (i.e., snoring, daytime sleepiness, and inattention/hyperactivity). Device-assessed sleep behaviors (i.e., wake time, sleep onset time, total time in bed, total sleep time and waking after sleep onset) were estimated with wrist-worn accelerometers. We used the Behavior Assessment System for Children level-2 to assess behavioral and emotional functioning (i.e., clinical scale: aggressiveness, hyperactivity, behavior problems, attention problems, atypicality, depression, anxiety, retreat and somatization; and adaptive scale: adaptability, social skills and leadership).

Results: SDB was positively associated with all clinical scale variables (all $\beta > 0.197$, $P \leq 0.041$), and with lower adaptability and leadership (all $\beta < -0.226$, $P < 0.021$). Specifically, PSQ subscale relating to daytime sleepiness was associated with higher attention problems, depression, anxiety and retreat (all $\beta > 0.196$, $P \leq 0.045$) and lower adaptability ($\beta = -0.246$, $P = 0.011$). The inattention/hyperactivity subscale was significantly associated with the entire clinical and adaptive scales (all $|\beta| > 0.192$, $P \leq 0.046$), except for somatization. The snoring subscale and device-assessed sleep behaviors were not related to any behavioral or emotional functioning variables.

Conclusions: Our study suggests that SDB symptoms, but not device-assessed sleep behaviors, are associated with behavioral and emotional functioning in children with overweight or obesity. Specifically, daytime sleepiness, a potential SDB symptom, was related to higher attention problems, depression, anxiety, retreat, and lower adaptability.

INTRODUCTION

Healthy sleeping is essential for the school-aged children's health, including adequate duration and continuity, consistent sleep onset and wake up timing, and the absence of sleep disorders [5]. However, one-third of the pediatric population experience sleep problems during childhood [170]. Among those problems, obstructive sleep-disordered breathing (SDB) affects 4-11% of children worldwide, with a range of severity from primary snoring to obstructive sleep apnea (OSA) [27]. Pediatric obesity is closely linked to sleep problems [171], and increases the risk of SDB compared with children of normal weight (20.8% vs 6.3%) [35]. Furthermore, children with overweight or obesity often show suboptimal sleeping times, insufficient sleep efficiency, and short sleep duration [32,172-175]. The study of the associations between sleep disorders and behavioral and emotional functioning are particularly relevant in the context of childhood obesity.

A cross-sectional study in children with overweight showed that SDB was related to parent-reported attention problems, anxiety, aggressiveness and depression [67]. Another study found that children and adolescents with comorbid overweight or obesity and SDB had increased risk for externalizing behaviors, such as aggressiveness [126]. Moreover, children and adolescents with SDB are more likely to exhibit signs of attention-deficit/hyperactivity disorder (ADHD), such as hyperactivity and inattention [39].

Device-assessed sleep duration has shown inconsistent associations with behavioral problems in children [176-179]. For example, longer sleep duration was associated with lower risk of internalizing, but not externalizing problems in 8-year-old children [179]. In the present study, we investigated the associations of parent-reported SDB and device-estimated sleep behaviors with behavioral and emotional functioning in children with overweight or obesity.

METHODS

Study design and participants

We used baseline data from the ActiveBrains project, a randomized controlled trial investigating the effects of an exercise program on brain structure and function and cognition in children with overweight or obesity. Data were collected from November 2014 to February 2016 in a total of 110 overweight/obese children from Granada, Spain. One child was excluded for difficulties shown in Spanish reading comprehension; thus, a total of 109 children (mean age, 10.04 ± 1.12 years; 45 girls) were included in this cross-sectional study. A detailed description of the trial protocol, aims, and methods has been published elsewhere [54]. All participants met the following inclusion criteria: (1) overweight or obese, based on the sex- and age-specific international body mass index cutoff points proposed by the World Obesity Federation [14,15]; (2) age 8.0-11.9 years, (3) no physical disabilities or neurologic disorders that affect physical performance, (4) no ADHD, and (5) no menarche at baseline for girls.

Parents/legal guardians of the participants were informed of the purpose of the study, and their written informed consent was obtained. The study was conducted according to the principles outlined in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee on Human Research of the University of Granada, and the study was registered at ClinicalTrials.gov (identifier: NCT02295072).

Procedures and measurements

Sleep-disordered breathing

SDB was evaluated via the Spanish version of the Pediatric Sleep Questionnaire (PSQ), which has shown high reliability and internal consistency [9] as well as validity for identifying SDB [10,146]. This questionnaire was completed by legal guardians, who rated

each item according to their child's usual sleep patterns. The SDB scale (range, 0-1) was used to quantify the SDB diagnosis, with higher scores indicating greater severity. This scale consists of 22 closed-response question items from the reduced version of the PSQ and includes 3 subscales [10,146]: snoring (4 items), sleepiness (4 items), and inattention/hyperactivity (6 items). These subscales have been considered valid and reliable instruments for use in research on SDB in children [180]. The answer options for each item include "yes," "no," and "I don't know." In the last domain of the questionnaire (inattention/hyperactive subscale), the response options are "never," "sometimes," "often," and "almost always." To be consistent with these answer options throughout the questionnaire, one of the sections was recategorized as follows: "never" and "sometimes" answers were categorized as "no," and "often" and "almost always" answers were categorized as "yes." The overall scale was calculated as the sum of the affirmative answers divided by the total number of items (i.e., 22). Occasional missing answers or "I do not know" responses were eliminated from the denominator when calculating the scores. An SDB score >0.33 was considered to indicate high risk for diagnosis of SDB [10,146]. A current meta-analysis indicated that the SDB scale has suitable accuracy in detecting children with OSA with a sensitivity of 0.73 and specificity of 0.59 [148].

Device-assessed sleep behavior

Participants were instructed to wear an accelerometer (GT3X+; ActiGraph) on their nondominant wrist for 7 consecutive days, 24 hours a day, and to record information on sleep onset and wakeup times each day in a sleep diary. The accelerometers were initialized to record accelerations at 100 Hz. Raw accelerations were downloaded in ActiLife version 6.13.3 (ActiGraph) and processed in the R package GGIR version 1.5.12 (<https://www.cran.r-project.org/>) [181]. Detailed information on accelerometer data processing for sleep

analysis can be found elsewhere [182]. Sleep onset and wake times were detected using an algorithm guided by the participants' reported times [90]. First, the algorithm examined potential sleep occurrences throughout the 24 hours. Then the first and last epochs, classified as sleep before and after the reported times, were considered the definitive sleep wake and onset times. An algorithm developed by Sadeh et al. [183] was applied within the total time in bed to classify each minute as "sleep" or "wake" time. Device-assessed sleep behavior included indicators of sleep timing (i.e., wake and sleep onset times), sleep duration (i.e., total time in bed and total sleep time), and sleep pattern (i.e., wake after sleep onset [WASO] time). The total time in bed is the difference between wake and sleep onset times. Total sleep time represents the sum of all minutes classified as sleep within the total time in bed. The total amount of time classified as WASO time each night was also derived.

Behavioral and emotional functioning

The Behavior Assessment System for Children, second edition (BASC-2) was used to assess behavioral and emotional functioning. The assessment was completed by parents to evaluate negative behaviors and positive attributes of children aged 6-12 years [13]. The BASC-2 is divided into 2 scales: the clinical scale (i.e., aggressiveness, hyperactivity, behavior problems, attention problems, atypicality, depression, anxiety, retreat, and somatization) and the adaptive scale (i.e., adaptability, social skills, and leadership). Responses are clustered into 4 global dimensions: external problems, including aggressiveness, hyperactivity, and behavioral problems; internal problems, including anxiety, depression, and somatization; adaptability skills, including adaptability, social skills, and leadership; and a Behavioral Symptoms Index (BSI), including aggressiveness, hyperactivity, attention problems, atypical behaviors, anxiety, and depression. For each indicator, standard t-scores with an average of 50 points and SD of

10 points were used in the analyses. For external and internal problems and BSI, t-scores >70 were considered clinically significant and those of 60-70 were considered at risk. For adaptive skills, t-scores <30 were considered clinically significant and those of 30- 40 were considered at risk [13].

Covariates

Age, sex, parental education level, wave of participation (i.e., ActiveBrains was conducted in 3 waves for logistical reasons), and peak height velocity (PHV) were considered potential confounders. Parental education level was obtained through a self-reported questionnaire. Parents' responses were categorized as none, one, or both had a university level education. The wave of participation (1, 2, or 3) was categorized into 2 dichotomous dummy variables for inclusion in the models. PHV, an indicator of biological maturity during childhood and adolescence, was calculated from anthropometric variables (standing and seated height) and participant age using Moore equations [151].

Statistical analysis

Descriptive characteristics of the study participants are presented as mean and SD for continuous variables and as frequency and percentage for categorical variables. Before analyses, the extreme values (i.e., outliers) were winsorized to limit their influence on the results. In brief, we visually inspected histograms and quantile-quantile plots of the variables included and identified extreme values. Furthermore, all variables were checked for normality. After checking for normal distribution, the SDB scale was normalized using the Blom formula [152] because it showed a skewed distribution. Bivariate Pearson correlation tests were performed as exploratory analyses and to test the correlations between behavioral and emotional functioning variables. Sensitivity analyses were performed using the data before winsorization and normalization, and the findings remained unchanged.

Hierarchical linear regression analyses were performed to examine the associations of sleep-related outcomes (i.e., overall SDB and by subscale, along with device-assessed sleep behaviors) with behavioral and emotional functioning. The stepwise method was used to investigate the influence of potential confounders in the models in step 1 (i.e., age, sex, paternal education level, wave of participation, and PHV). Next, hierarchical regressions were carried out, entering the SDB scale, snoring subscale, daytime sleepiness subscale, inattention-hyperactivity subscale, or each device-assessed sleep behavior variable (i.e., wake time, sleep onset time, total time in bed, total sleep time, and WASO time) separately as a predictor into step 2 and also entering each behavioral and emotional functioning variable as an outcome in separate regression analyses after the inclusion of confounders previously defined in step 1. It should be noted that the PSQ inattention/hyperactivity subscale can overlap BASC-2 hyperactivity and attention problems, and thus SDB could be affected by the strong relationship among these components.

Additionally, the participants were classified into high risk (scores >0.33; score range, 0-1) and low risk (scores < 0.33; score range, 0-1) of SDB diagnosis [10,146]. We used one-way analysis of covariance (ANCOVA) to explore standardized mean differences (SMDs) between the high-risk and low-risk of SDB groups for behavioral and emotional functioning variables, adjusting for the different confounders previously identified as significantly associated with the outcomes in the hierarchical linear regression.

The Benjamini-Hochberg procedure was applied to account for the random effects in multiple comparisons for each independent domain—SDB scale, snoring subscale, sleepiness subscale, inattention/hyperactive subscale, wake time, sleep onset time, total time in bed, total sleep time, and WASO time—with $q = 0.1$ [153]. All analyses were performed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0,

Armonk, NY). The level of significance was set at $P < 0.05$.

RESULTS

Descriptive characteristics for all participants and stratified by sex are presented in **Table 8**. Only 41/105 (39%) participants met the recommendation of sufficient sleep

duration for their age (i.e., 9-11 hours per night). Regarding the external and internal problems, 3/109 (2.8%) and 14/109 (12.8%) participants had clinically important levels, respectively, and 9/109 (8.3%) and 19/109 (17.4%) participants were at risk. Regarding the BSI, 5/109 (4.6%) participants had clinically important levels, and 16/109 (14.7%) were at risk. Regarding adaptative skills, 5/109 (4.6%) participants had clinically important levels and 16/109 (14.7%) were at risk.

Table 8. Descriptive characteristics of the participants.

	All sample		Boys		Girls	
	N	Mean $\pm$ SD	N	Mean $\pm$ SD	N	Mean $\pm$ SD
Age (years)	109	10.04 $\pm$ 1.12	64	10.16 $\pm$ 1.15	45	9.88 $\pm$ 1.08
Weight (kg)	109	56.21 $\pm$ 11.23	64	57.11 $\pm$ 11.2	45	54.94 $\pm$ 11.28
Height (cm)	109	144.22 $\pm$ 8.41	64	144.98 $\pm$ 7.97	45	143.13 $\pm$ 8.99
BMI categories, n (%)						
Overweight		28 (25.7)		16 (25)		12 (26.7)
Obesity type I		47 (43.1)		30 (46.9)		17 (37.8)
Obesity type II		34 (31.2)		18 (28.1)		16 (35.6)
Behavioral and emotional functioning^a						
Clinical scale						
Aggressiveness	109	48.85 $\pm$ 9.86	64	49.53 $\pm$ 10.02	45	47.89 $\pm$ 9.64
Hyperactivity	108	45.67 $\pm$ 8.52	64	45.42 $\pm$ 8.93	44	46.02 $\pm$ 7.97
Behavior problems	109	51.73 $\pm$ 9.05	64	52.2 $\pm$ 9.00	45	51.07 $\pm$ 9.18
Attention problems	109	50.48 $\pm$ 10.31	64	50.05 $\pm$ 9.50	45	51.09 $\pm$ 11.45
Atypicality	109	50.62 $\pm$ 10.74	64	49.19 $\pm$ 10.93	45	52.67 $\pm$ 10.25
Depression	108	54.45 $\pm$ 15.53	64	55.05 $\pm$ 17.20	44	53.64 $\pm$ 12.86
Anxiety	109	53.61 $\pm$ 11.06	64	53.17 $\pm$ 12.18	45	54.24 $\pm$ 9.32
Retreat	108	51.14 $\pm$ 13.21	64	50.78 $\pm$ 14.24	44	51.66 $\pm$ 11.70
Somatization	108	51.81 $\pm$ 14.37	64	48.7 $\pm$ 11.68	44	56.34 $\pm$ 16.69
Adaptative scale						
Adaptability	109	49.56 $\pm$ 10.76	64	48.94 $\pm$ 11.12	45	50.44 $\pm$ 10.30
Social skills	108	51.4 $\pm$ 10.95	64	50.45 $\pm$ 10.67	44	52.77 $\pm$ 11.33
Leadership	109	47.93 $\pm$ 10.53	64	48.03 $\pm$ 9.89	45	47.78 $\pm$ 11.48

	All sample		Boys		Girls	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Global dimensions ^b						
External problems	108	49.04 ± 8.71	64	49.12 ± 9.04	44	48.91 ± 8.31
Internal problems	108	54.42 ± 13.92	64	52.97 ± 13.84	44	56.52 ± 13.92
Adaptability skills	108	49.5 ± 11.18	64	49.02 ± 10.80	44	50.2 ± 11.80
BSI punctuation	108	50.89 ± 11.06	64	50.7 ± 11.66	44	51.16 ± 10.25
Sleep-disordered breathing (range: 0 to 1)						
SDB scale	109	0.19 ± 0.13	64	0.19 ± 0.13	45	0.18 ± 0.13
Snoring subscale	109	0.21 ± 0.30	64	0.19 ± 0.27	45	0.25 ± 0.33
Daytime sleepiness subscale	107	0.17 ± 0.22	64	0.15 ± 0.22	43	0.20 ± 0.22
Inattention/hyperactivity subscale	109	0.13 ± 0.20	64	0.15 ± 0.22	45	0.10 ± 0.17
SDB presence, n (%)	17(16)		10 (16)		7 (16)	
Device-assessed sleep behaviors						
Wake time (hh:mm)	105	8:08 (0:34)	62	8:05 (0:33)	43	8:11 (0:35)
Sleep onset time (hh:mm)	105	23:00 (00:40)	62	23:00 (00:40)	43	23:00 (00:39)
Total time in bed (min/day)	105	529.37 ± 31.76	62	527.52 ± 33.09	43	532.03 ± 29.90
Total sleep time (min/day)	105	460.89 ± 35.84	62	456.51 ± 32.10	43	467.20 ± 40.18
WASO time (min/day)	105	76.58 ± 23.64	62	79.80 ± 20.55	43	71.95 ± 27.07

Notes: SD = standard deviation; BSI = Behavioral symptoms index; SDB: sleep-disordered breathing; WASO= waking after sleep onset.

^a Values based on standard T-scores with an average of 50 and standard deviations of 10 points.

^b External problems include aggressiveness, hyperactivity and behavior problems; internal problems include depression, anxiety and somatization; adaptability skills include adaptability, social skills and leadership; BSI includes aggressiveness, hyperactivity, attention problems, atypicality, depression and anxiety [13].

Hierarchical linear regression analyses for the association of overall SDB scale and the snoring, sleepiness, and inattention/hyperactivity subscales with behavioral and emotional functioning variables are presented in **Table 9**.

Table 10 shows the bivariate correlation between behavioral and emotional functioning variables. Hierarchical linear regression analyses for the association of device-assessed sleep behaviors (i.e., wake time, sleep onset time, total time in bed, total sleep time and WASO time) with behavioral and emotional functioning variables are presented

in **Table 11**. Age, sex, parental education level, wave, and PHV were included as potential confounders hierarchical linear regressions. Anxiety and internal problems were adjusted for age, somatization, for sex, and leadership for parental education level as they were the unique covariates selected in the hierarchical regression (step 1).

SDB and inattention/hyperactivity subscale were associated with all the global dimensions studied (i.e., worse external and internal problems, worse adaptability skills, and worse BSI punctuation; all $\beta > |0.258|$, P 's ≤ 0.007).

Table 9. Hierarchical linear regression for the associations of overall sleep-disordered breathing scale and subscales (snoring, sleepiness and inattention/hyperactivity) with behavioral and emotional functioning variables.

	Overall sleep-disordered breathing scale		Snoring subscale		Daytime sleepiness subscale		Inattention/Hyperactivity subscale	
	β	P	β	P	β	P	β	P
Clinical scale								
Aggressiveness	0.197	0.040	0.109	0.261	0.073	0.453	0.305	0.001
Hyperactivity	0.197	0.041	0.049	0.612	0.115	0.242	0.424	<0.001
Behavior problems	0.231	0.016	0.126	0.193	0.074	0.447	0.345	<0.001
Attention problems	0.422	<0.001	0.204	0.034	0.333	<0.001	0.478	<0.001
Atypicality	0.279	0.003	0.087	0.371	0.172	0.077	0.394	<0.001
Depression	0.336	<0.001	0.116	0.232	0.210	0.030	0.322	0.001
Anxiety†	0.321	<0.001	0.097	0.288	0.206	0.024	0.375	<0.001
Retreat	0.250	0.009	0.179	0.064	0.196	0.045	0.192	0.046
Somatization‡	0.303	0.001	0.113	0.233	0.087	0.364	0.164	0.082
Adaptive scale*								
Adaptability	-0.271	0.004	-0.083	0.392	-0.246	0.011	-0.271	0.004
Social skills	-0.177	0.066	-0.104	0.283	-0.118	0.228	-0.230	0.017
Leadership††	-0.226	0.021	-0.099	0.299	-0.154	0.110	-0.275	0.004
Global dimensions*								
External problems	0.258	0.007	0.129	0.183	0.092	0.347	0.446	<0.001
Internal problems†	0.412	<0.001	0.167	0.078	0.231	0.015	0.335	<0.001
Adaptability skills*	-0.278	0.004	-0.118	0.225	-0.207	0.033	-0.317	0.001
BSI punctuation	0.412	<0.001	0.152	0.117	0.257	0.008	0.524	<0.001

Each association (i.e., pair main exposure-outcome) was introduced in separate hierarchical regression models. Potential confounders (i.e., age, sex, parental education level, wave, and peak height velocity) were included into step 1 of the stepwise regression to test their association to the outcomes, so that for each outcome only the relevant confounders were retained in the final models. In step 2, the exposure variable of interest (e.g., overall SDB scale or snoring or sleepiness or inactive/hyperactivity subscales) was entered using the method ENTER to force to be in the model. β values are standardized coefficients. Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparisons test. †Adjusted by age. ‡Adjusted by sex. ††Adjusted by parental education level. BSI = Behavioral symptoms index; WASO= waking after sleep onset.

* External problems include aggressiveness, hyperactivity and behavior problems; internal problems include depression, anxiety and somatization; adaptability skills include adaptability, social skills and leadership; behavioral symptoms index include aggressiveness, hyperactivity, attention problems, atypicality, depression and anxiety [13]. *Lower values indicate better results (i.e., poorer adaptative skills).

Snoring subscale was not associated with any of the global dimensions (all $\beta < |0.167|$ and P 's ≥ 0.078). Daytime sleepiness subscale was associated with higher internal problems ($\beta = 0.231$, $P = 0.015$) and higher BSI ($\beta = 0.257$, $P = 0.008$), and lower adaptability skills ($\beta = -0.207$, $P = 0.033$). All the associations reported surpassed the correction for multiple comparisons test.

SDB was positively associated with all the variables in the clinical scale (all $\beta > 0.197$, P 's ≤ 0.041). The snoring subscale was significantly associated with higher attention problems ($\beta = 0.204$, $P = 0.037$), yet this association was disregarded by the multiple comparisons' correction test. The daytime sleepiness subscale was associated with higher attention problems, depression, anxiety, and retreat (all $\beta > 0.196$, P 's ≤ 0.045). Inattention/hyperactivity

subscale was positively associated with all the clinical scale variables (all $\beta > 0.192$, P 's ≤ 0.046), except somatization. All the associations reported were corrected for multiple comparisons.

Regarding the adaptive scale, SDB was associated with worse adaptability ($\beta = -0.271$, $P = 0.004$) and leadership ($\beta = -0.226$, $P = 0.021$). The snoring subscale was not associated with any of the adaptive scale variables (all $\beta > -0.104$, P 's ≥ 0.283). Daytime sleepiness subscale was only inversely associated with worse adaptability ($\beta = -0.246$, $P = 0.011$) whereas the inattention/hyperactivity subscale was inversely associated with all the adaptive scale variables (all $\beta < -0.230$, P 's ≤ 0.017). All the associations were corrected for multiple comparisons.

Table 10. Bivariate correlation between behavioral and emotional functioning indicators.

	Aggressiveness	Hyperactivity	Behaviour problems	Attention problems	Atypicality	Depression	Anxiety	Retreat	Somatization	Adaptability	Social skills
Clinical scale											
Aggressiveness	—										
Hyperactivity	0.451**	—									
Behavior problems	0.582**	0.321**	—								
Attention problems	0.306**	0.355**	0.445**	—							
Atypicality	0.196*	0.470**	0.321**	0.423**	—						
Depression	0.532**	0.519**	0.379**	0.451**	0.481**	—					
Anxiety	0.336**	0.350**	0.206*	0.298**	0.323**	0.621**	—				
Retreat	0.276**	0.263**	0.208*	0.328**	0.340**	0.496**	0.494**	—			
Somatization	0.123	0.207*	0.111	0.188	0.375**	0.331**	0.201*	0.260**	—		
Adaptive scale											
Adaptability	-0.391**	-0.273**	-0.320**	-0.451**	-0.296**	-0.428**	-0.386**	-0.473**	-0.172	—	
Social skills	-0.435**	-0.303**	-0.425**	-0.457**	-0.255**	-0.325**	-0.131	-0.404**	-0.005	0.607**	—
Leadership	-0.158	-0.207**	-0.231*	-0.566**	-0.179	-0.310**	-0.253**	-0.331**	-0.045	0.424**	0.630**

*** $P < 0.001$ ** $P < 0.01$ * $P < 0.05$

Table 11. Hierarchical linear regression for the associations of sleep with behavioral and emotional functioning variables.

	Wake time		Sleep onset time		Total time in bed		Total sleep time		WASO time	
	β	P	β	P	β	P	β	P	β	P
Clinical scale										
Aggressiveness	-0.116	0.237	-0.144	0.142	0.046	0.640	0.049	0.620	-0.022	0.827
Hyperactivity	0.094	0.344	0.022	0.823	0.119	0.229	0.048	0.631	-0.018	0.856
Behavior problems	0.002	0.983	0.075	0.447	-0.145	0.140	0.054	0.586	-0.204	0.037
Attention problems	0.186	0.058	0.174	0.075	-0.105	0.288	0.045	0.645	-0.134	0.174
Atypicality	0.181	0.065	0.111	0.259	0.039	0.691	0.033	0.736	-0.056	0.568
Depression	-0.117	0.238	-0.076	0.442	-0.046	0.642	-0.019	0.849	-0.023	0.815
Anxiety†	-0.050	0.588	-0.076	0.411	0.001	0.996	0.108	0.244	-0.140	0.128
Retreat	0.068	0.495	0.155	0.117	-0.154	0.117	-0.018	0.859	-0.163	0.099
Somatization‡	-0.024	0.807	-0.066	0.493	0.017	0.860	0.059	0.543	-0.047	0.632
Adaptive scale										
Adaptability	-0.035	0.727	-0.063	0.521	0.128	0.192	-0.005	0.963	0.185	0.060
Social skills	0.032	0.750	-0.056	0.572	0.193	0.050	0.147	0.136	0.036	0.713
Leadership	0.096	0.332	0.021	0.831	0.193	0.049	0.157	0.110	0.066	0.506
Global dimensions^a										
External problems	-0.008	0.932	-0.020	0.843	0.001	0.989	0.058	0.558	-0.099	0.319
Internal problems†	-0.084	0.383	-0.092	0.338	-0.028	0.776	0.059	0.542	-0.099	0.301
Adaptability skills	0.034	0.734	-0.045	0.648	0.212	0.031	0.119	0.228	0.118	0.232
BSI punctuation‡	0.019	0.844	0.007	0.941	-0.028	0.773	0.028	0.774	-0.079	0.415

Every association (i.e., pair main exposure-outcome) was introduced in separate hierarchical regression models. Potential confounders (i.e., age, sex, parental education level, wave, and peak height velocity) were included into step 1 of the stepwise regression to test their association to the outcomes, so that for each outcome only the relevant confounders were retained in the final models. In step 2, the exposure variable of interest, wake time/sleep onset time/total time in bed/total sleep time/ WASO time was entered using the method ENTER to force to be in the model. β values are standardized coefficients. Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparisons test. †Adjusted by age. ‡Adjusted by sex. BSI = Behavioral symptoms index; WASO= waking after sleep onset. ^a External problems include aggressiveness, hyperactivity and behavior problems; internal problems include depression, anxiety and somatization; adaptability skills include adaptability, social skills and leadership; behavioral symptoms index include aggressiveness, hyperactivity, attention problems, atypicality, depression and anxiety [13].

Figure 2 represents the behavioral and emotional functioning differences (and 95% confidence intervals) between the high-risk (>0.33) vs low-risk (< 0.33) SDB groups. For the global dimensions, the high-risk group had greater external and internal problems, and BSI punctuation (all SMD's> 0.787, P≤ 0.002), and lower adaptability skills (SMD= -1.043, P<0.001) compared with the low-risk group. Children at high risk of SDB had significantly higher aggressiveness, hyperactivity, behavior problems, atypicality, depression, anxiety, retreat, and somatization (all SMD's> 0.489, P≤ 0.046); and lower adaptability, social skills, and leadership (all SMD's≥ -0.810, P≤ 0.002).

For the global dimensions, only the total time in bed was associated with better adaptability skills ($\beta = 0.212, P = 0.031$). However, after applying the multiple comparisons test this association was not significant. Neither of the device-assessed sleep behaviors was associated with the clinical scale variables after controlling for multiple comparisons (all P's ≥ 0.037). Only the total time in bed was associated with better social skills ($\beta = 0.193, P = 0.050$) and leadership ($\beta = 0.193, P = 0.049$), yet these associations did not surpass the multiple comparisons correction. Neither of the remaining device-assessed sleep behaviors variables was associated with the adaptive scale.

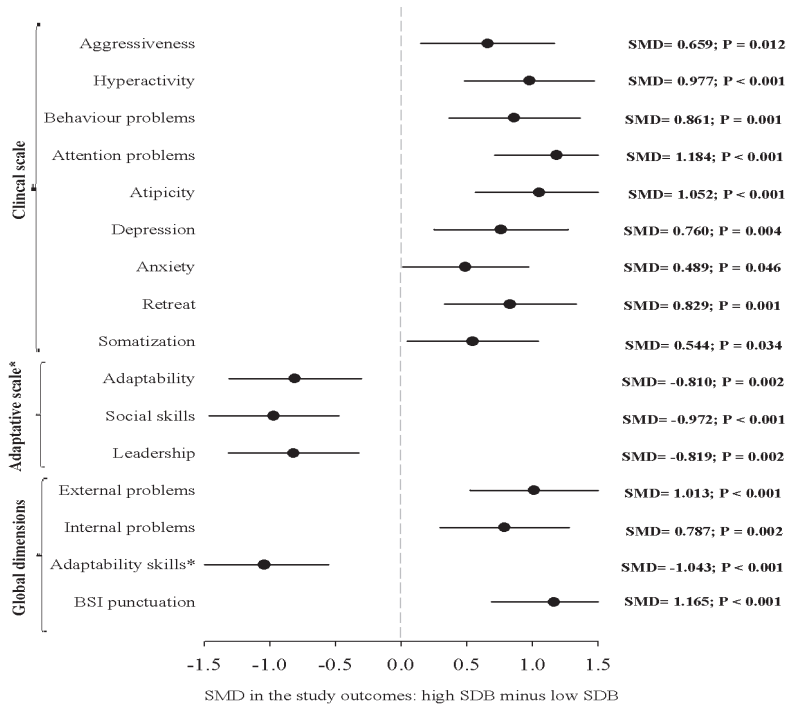


Figure 2. Mean differences between the SDB groups (higher risk of SDB vs lower risk of SDB) on behavioral and emotional functioning outcomes. Dots represent z-score values, and bars represent 95% CIs. Bold type indicates that the specific association surpassed the Benjamini–Hochberg correction for the multiple comparisons test. Scores were adjusted by the different confounders previously found to be significantly associated with the outcomes in hierarchical linear regression. A SDB scale was calculated from the 22 items on the questionnaire. Scores > 0.33 were considered suggestive of high risk for a pediatric SDB [10,146]. SMD=Standardized mean differences. BSI = Behavioral symptoms index. SDB=sleep-disordered breathing. *Lower values indicate better results (i.e., poorer adaptive skills).

DISCUSSION

The main findings of this study support that SDB symptoms are related to worse behavioral and emotional functioning (i.e., higher external and internal problems and lower adaptability skills) in children with overweight or obesity. These associations might be explained in part by the shared symptoms between ADHD and SDB, which may result in overlap between the PSQ and BASC-2 items. Moreover, our findings also support the idea that daytime sleepiness can be related to attention problems, depression, anxiety, retreat, and worse adaptability. We did not observe any associations between device-assessed sleep behaviors and behavioral and emotional functioning.

Our findings are consonant with a previous study in which polysomnography-determined OSA was associated with worse behavioral functioning outcomes (i.e., aggressiveness, hyperactivity, attention problems, anxiety, and depression) but not with social skills, as assessed by the BASC in children with overweight [67]. In contrast, that study did not find any association with atypicality and leadership. Discrepancies between the aforementioned findings in children aged 10-17 years and our findings in children aged 8-12 years could be partially explained by differences in participant age, sample size, and method of measuring OSA (polysomnography vs questionnaire). Using the PSQ, Lande et al showed that higher scores in the SDB scale of the PSQ were significantly associated with worse scores on behavior problems and mood, specifically in externalizing and internalizing behavior and depression, in children with hypertension (~60% with obesity) [184]. A similar association was found in children with obesity, in which those allocated in the OSA group had poorer ratings of parent-reported internalizing and externalizing behaviors, adaptive skills, and overall behavior compared with their peers without OSA [125]. However, our results are not in line with that study's

finding of no significant differences between polysomnography determined OSA and controls in parent-reported internalizing and externalizing problems, adaptive skills, and BSI [125]. The differences between the studies might be explained by the age of the sample (10-18 years), as well as the severity of SDB. Nevertheless, previous studies in normal-weight children are in line with our findings, showing that parent-reported SDB and daytime sleepiness were positively associated with emotional problems [118]. Our findings are supported by Perfect et al, who also observed higher hyperactivity, attention problems, and aggressiveness and lower adaptive skills in children with SDB compared with their peers [185].

Regarding sleep behavior, unlike in our study, a systematic review posited that shorter self-reported sleep duration was consistently associated with adverse mental health outcomes [19]. Despite the limited evidence on device-assessed sleep behavior, several previous studies observed that device-estimated sleep duration was related to behavioral functioning in children [177-179,186]. However, our findings are in agreement with those from Hammam et al supporting that total sleep duration is not a predictor of behavior problems in preschool children [176]. In agreement, Guerlich et al found that longer device-assessed sleep duration was not associated with externalizing problems in 8-year-old children [179]. The variability of the methodological procedures and data processing used in previous studies, as well as characteristics of the study sample, could explain the inconsistencies found. Moreover, even though device-assessed sleep duration might not be related to behavioral and emotional functioning, daytime sleepiness seems to be. A possible explanation for this relationship is that both daytime sleepiness and behavioral and emotional functioning are parents' perceptions, which might be more relevant than the device-assessed sleep duration for characterizing behavioral

and emotional functioning in children with overweight or obesity.

Some limitations of this study must be acknowledged. First, this was a cross-sectional study and thus does not allow for causal inference of any of the studied associations. Second, our data were obtained from parental questionnaires instead of polysomnography, and caution is advised when interpreting these findings regarding younger age when other factors may be major determinants of SDB (eg, adenotonsillar disease). Third, the accelerometer-based estimates of sleep were based on movement patterns, not purely on sleep behavior. Fourth, we did not ask parents to report their child's medical history of sleep symptoms and sleepiness. Interestingly, the SDB scale includes as part of its score items related to attention and hyperactivity because they are known to be strongly related [10]. This might be controversial, given that the behavioral and emotional functioning scale also includes attention problems as an indicator, and, in turn, the SDB could be affected by the strong relationship among these components. For that reason, we further evaluated the SDB by subscales. Therefore, our findings should be considered with caution when the inattention/hyperactivity subscale is included.

The severity of SDB was mild in our participants (only 16% scored >0.33 on the SDB scale), and thus we might have not been able to detect some associations that could be present in more severely affected children. Our exclusion of children with ADHD may explain the mild severity of SDB in our sample. Further studies in children with more severe SDB symptoms (e.g., children with ADHD) are warranted to further explore these associations. Public health implications from this study include the need to support sleep hygiene in children with overweight/obesity.

Study 4

Sleep-disordered breathing and cardiometabolic and inflammatory markers in children with overweight or obesity: the role of cardiorespiratory fitness

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ABSTRACT

Objectives: To investigate the association of sleep-disordered breathing (SDB) severity with cardiometabolic and inflammatory markers independently of the adiposity levels; and to explore the role of cardiorespiratory fitness in these associations in children with overweight or obesity.

Methods: A total of 109 children aged 8-11 years with overweight or obesity were included in this cross-sectional study. SDB was assessed using a scale of the reduce version of the Pediatric Sleep Questionnaire. Cardiometabolic markers included fasting blood lipids biomarkers (i.e., low- and high-density lipoprotein cholesterol, and triglycerides), blood pressure, insulin, glucose, and the homeostatic model assessment index. Inflammatory markers (i.e., interleukin-6, interleukin-1 β , C-reactive protein [CRP], and tumor necrosis factor alpha) were analyzed. Cardiorespiratory fitness was assessed by the 20 m shuttle-run test.

Results: No significant associations were found between SDB severity and most of the cardiometabolic markers after correcting for adiposity and multiple comparisons (all $P_s > 0.05$). SDB severity was positively related to CRP ($\beta = 0.354$, $P = 0.002$), yet not with the remaining inflammatory markers analyzed (all $P_s > 0.05$). The interaction effect of cardiorespiratory fitness presented a positive trend in the association of SDB with CRP ($P = 0.1$). When stratified analyses by cardiorespiratory fitness levels were conducted, a positive relation was found between SDB and CRP in the low cardiorespiratory fitness group ($\beta = 0.465$, $P = 0.014$), but not in the high cardiorespiratory fitness group ($\beta = 0.236$, $P = 0.108$).

Conclusion: SDB severity was positively associated with CRP independently of the adiposity levels, but not with other inflammatory or cardiometabolic risk factors in children with overweight or obesity. Moreover, our results suggest that higher levels of cardiorespiratory fitness may attenuate the adverse effect of SDB severity on systematic inflammation in children with overweight or obesity.

INTRODUCTION

Pediatric sleep-disordered breathing (SDB) is a syndrome characterized by upper airway dysfunction [8]. One of the most common SDB is obstructive sleep apnea (OSA) which is characterized by recurrent episodes of partial or complete closure of the upper airway. The prevalence of OSA, which varies with the severity of the disorder [29], ranges from approximately 1-6% [8,28], worsening to 21-39% in children with obesity [187]. Two landmark studies recognized OSA as a serious clinical diagnosis, and therefore, it is still important to explore the association between OSA and other risk factors in pediatric population [188,189].

There is a body of evidence supporting that pediatric OSA leads to cardiovascular and inflammatory processes similar to those related to cardiovascular disease in adulthood [190]. Moreover, OSA in the context of childhood obesity, may independently affect the cardiometabolic risk factors (i.e., increased dyslipidemia, hypertension and insulin resistance) [191] and increased systematic inflammation [192]. In fact, previous literature in children with overweight or obesity have suggested that OSA severity promotes cardiometabolic impairments [38,193-195], however some inconsistencies have been found regarding inflammatory biomarkers [38,76,196-198]. It seems that both obesity [199,200] and OSA [192] in pediatric population with obesity could share common pathways that lead to inflammation through elevated circulating levels of C-reactive protein (CRP) [201], interleukin-6 (IL-6), and tumor necrosis factor alpha (TNF- α), as well as metabolic abnormalities [76]. Therefore, due to the potential role of total obesity as a contributor in SDB in children with overweight or obesity [147], it appears important to consider adiposity when investigating the associations of cardiometabolic and inflammatory markers, which might provide

further relevant information in this field. Whether the association between SDB severity and cardiometabolic/inflammatory markers may also extend after controlling for adiposity in children with overweight or obesity remains properly unanswered.

Related to SDB and cardiometabolic and inflammatory risk factors, cardiorespiratory fitness is considered a powerful marker of health in youth [202]. Specifically, in this study sample, we previously observed that cardiorespiratory fitness was negatively related to SDB [147]. Likewise, previous literature highlighted the relevant role of cardiorespiratory fitness as a protective factor against cardiometabolic risk [203] and inflammation [204] in children. In fact, cardiorespiratory fitness has been inversely associated with IL-6, TNF- α [205] CRP [206] in prepubertal normal-weight children. These findings have been extrapolated to adolescents with obesity [207] in which the enhance in cardiorespiratory fitness was related to the decrease inflammation. Thus, studies investigating the role of cardiorespiratory fitness on the associations between SDB and cardiometabolic and inflammatory risk markers would provide useful and practical insights.

Therefore, the present study examined i) the association of SDB severity with cardiometabolic and inflammatory markers considering the influence of adiposity, and ii) the role of cardiorespiratory fitness in these associations in children with overweight or obesity. We hypothesized that i) SDB severity will be positively associated with circulating cardiometabolic and inflammatory markers independently of adiposity levels; ii) cardiorespiratory fitness will counteract the negative association of SDB severity on cardiometabolic and inflammatory markers in children with overweight or obesity.

METHODS

Study design and participants

This cross-sectional study used baseline data from the ActiveBrains project, a randomized clinical trial (RCT, Clinical Trial registration n° NCT02295072) which aimed to examine the effect of exercise on brain health outcomes in children with overweight or obesity [53,54]. A detailed description of the study protocol and the effects on the primary outcomes has been published elsewhere [53,54]. A total of 109 pre-pubertal children (8-11 years) with overweight or obesity based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation [14,15], from Granada (Spain), were included. Data were collected from November 2014 to February 2016. The study protocol was approved by the Human Research Ethics Committee of the University of Granada (Reference:848, February 2014), and written informed consent was obtained by legal guardians of all participants.

Procedures and measurements

Sleep-disordered breathing

To assess the SDB, the children's parents filled out the Spanish version of the Pediatric Sleep Questionnaire (PSQ). This questionnaire has shown high internal consistency, reliability [9] and validity for the identification of SDB [10,146]. From the reduced version of the PSQ, a SDB scale (scores ranged 0 to 1) was used, with higher scores indicating greater severity [146]. The SDB scale consists of 22 closed response items, which included three subscales [10,146]: snoring, sleepiness and inattention/hyperactivity. More details on the questionnaire can be found elsewhere [208,209].

Cardiometabolic markers

Blood samples were obtained at the hospital between 8:00-10:30 am after an overnight fasting in all participants. Blood lipids biomarkers included low density lipoprotein

(LDL), high density lipoprotein (HDL) cholesterol, and triglycerides. Systolic and diastolic blood pressure were assessed twice in a sitting position with an automatic sphygmomanometer (Omron M6, Hoofddorp, The Netherlands). The lowest value was considered. Insulin and glucose were obtained from blood samples and the homeostatic model assessment (HOMA) index was calculated as insulin multiplied by glucose and divided by 405. Waist circumference was measured twice using a homologated flexible steel tape (SECA, Hamburg, Germany), and the average was considered.

Lastly, a validated cardiometabolic risk score was obtained based on the most accepted definition of the metabolic syndrome by Alberti et al. [210], yet using European reference values specific for sex and age in youth [211].

Inflammatory markers

Four inflammatory markers analyzed in plasma were included: IL-6, interleukin-1 β (IL-1 β), TNF- α , and CRP. IL-6, IL-1 β , and TNF- α were detected by multiple analyte profiling technology (MILLI-PLEX® MAP Human High Sensitivity T Cell Magnetic Bead Panel, EMD Millipore Corporation, Missouri, USA). CRP was determined by immunoturbidimetry (Alinity c CRP Vario Reagent Kit ref. 07P5620, Abbott, Illinois, USA).

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by the 20 m shuttle-run test, a field-based exercise test used as a powerful marker of cardiovascular health in children and adolescents [212]. This fitness test is valid, reliable, and feasible [95-97]. The last completed lap was recorded in the test, and then, estimated maximal oxygen consumption was calculated ($\text{VO}_{2\text{max}}$, mL/kg/min) [98]. High and low cardiorespiratory fitness was categorized based on sex-specific cut-off points (i.e., 35 and 42 mL/kg/min for girls and boys, respectively) derived from a strong meta-analysis relating cardiorespiratory fitness to cardiovascular disease risk factor for children and adolescents [212].

Covariates

Age, sex, parental education level, the wave of participation, years from peak height velocity (PHV), and fat mass index were considered as potential confounders. Parental education level was obtained by a self-reported questionnaire. Parents' responses were categorized as none, one, or both reached university level education. The wave of participation (i.e., ActiveBrains project was conducted in three waves) was categorized into two dichotomous dummy variables for its inclusion in the models. Years from PHV (an indicator of somatic maturity during childhood) was calculated from seated and standing height as well as the age of the participants using Moore's equations [151]. Fat mass was measured by Dual-energy X-ray absorptiometry (DXA, Discovery densitometer from Hologic). Fat mass index was calculated by dividing fat mass by their squared height (kg/m^2).

Statistical analyses

Data were analyzed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY). The level of significance was set at $P < 0.05$. Descriptive characteristics of the study sample are presented as mean and standard deviations (SD) or percentages and frequencies. All variables were checked for normality using visual check of histograms. After checking for normal distribution, all variables except LDL were normalized using Blom formula [152] due to its skewed distribution.

Hierarchical linear regression analyses were performed to examine the associations of SDB severity with cardiometabolic and inflammatory markers. The stepwise method was used to investigate the influence of potential confounders in the models (i.e., step 1: age, sex, paternal education level, the wave of participation, and PHV). Next, hierarchical regressions were carried out by the following procedure: i) predictors: for model 1 we entered the SDB scale as a predictor into step 2, and for model 2 the SDB scale and fat mass

index were entered as predictors into step 2; and ii) outcomes: each cardiometabolic and inflammatory variable were introduced in separate regression analyses after the inclusion of confounders previously defined in step 1. The Benjamini-Hochberg procedure was applied to account for random effects in multiple comparisons for each dependent domain with $q=0.1$ [153].

Linear regression analysis with interaction effect was used to test the role of cardiorespiratory fitness in the association of SDB severity with cardiometabolic and inflammatory risk markers (i.e., those that were significant in the hierarchical regression analyses). The interaction effect of cardiorespiratory fitness in this association was examined stratifying by high or low levels of cardiorespiratory fitness [212].

RESULTS

Descriptive characteristics of the study participants are presented in **Table 12**. The mean age of the participants was 10 ± 1.1 years and 15.6% of them presented SDB. **Table 13** shows the hierarchical linear regression analyses for the associations of SDB severity with cardiometabolic and inflammatory markers. Regarding to cardiometabolic markers, SDB was associated with HOMA ($\beta = 0.186$ $P=0.041$), before correcting for multiple comparisons. However, after either correcting for multiple comparison or additionally adjusting for adiposity (i.e., fat mass index), the association was not statistically significant ($\beta = 0.140$, $P=0.102$). For inflammatory markers, SDB was positively associated with CRP ($\beta = 0.384$, $P=0.001$), and this association persisted after adjusting for fat mass index ($\beta = 0.354$, $P=0.002$). No significant association was found between SDB with the rest of cardiometabolic and inflammatory indicators examined (all $P_s > 0.05$).

The role of cardiorespiratory fitness in the association of SDB and CRP (i.e., the only biomarker that was significant in the hierarchical regression analyses) is shown in **Figure 3**. This figure presents the β regression coefficients of SDB with CRP according to cardiorespiratory fitness levels. The interaction effect of cardiorespiratory fitness

presented a positive trend in the association of SDB with CRP ($P=0.1$). Stratified analyses by cardiorespiratory levels showed a significant positive association between SDB and CRP in the low cardiorespiratory group ($\beta =0.465$, $P=0.014$), but not in the high cardiorespiratory group ($\beta =0.236$, $P=0.108$).

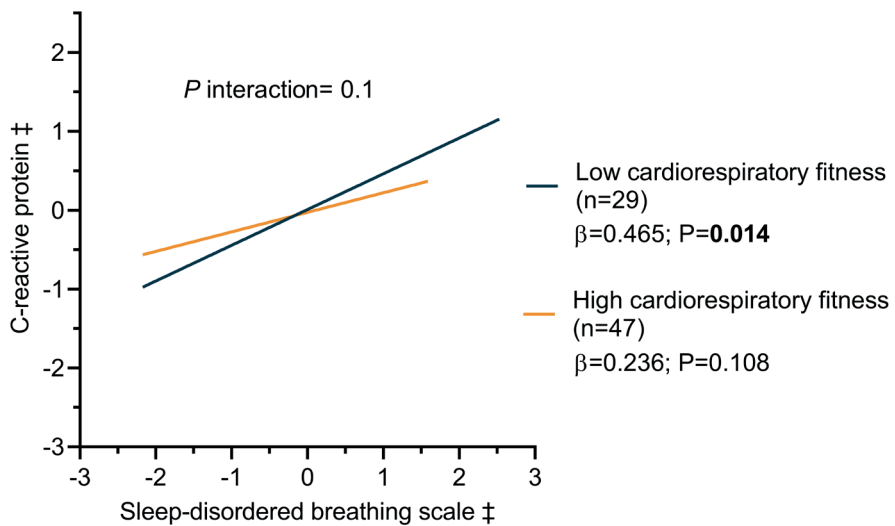


Figure 3. Graphical representation of the regression slopes between sleep-disordered breathing scale and C-reactive protein by levels of cardiorespiratory fitness. High/low cardiorespiratory fitness groups were classified based on the Ruiz et al. [212] cut-off points (i.e., 35 ml/kg/min for girls and 42 ml/kg/min for boys) for cardiorespiratory fitness. Orange color represents the high cardiorespiratory fitness group, while black color refers to those children grouped in the low cardiorespiratory fitness category. The regression model was adjusted for fat mass index. ‡Blom's normalized values were used in the analysis. β = standardized regression coefficient.

Table 12. Descriptive characteristics of the study participants.

	All sample		Boys		Girls	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Age (years)	109	10.04 ± 1.12	64	10.16 ± 1.15	45	9.88 ± 1.08
Weight (kg)	109	56.21 ± 11.23	64	57.11 ± 11.20	45	54.94 ± 11.28
Height (cm)	109	144.22 ± 8.41	64	144.98 ± 7.97	45	143.13 ± 8.99
Fat mass index (kg/m²)	108	11.79 ± 2.92	63	11.53 ± 2.97	45	12.15 ± 2.86
Cardiorespiratory fitness (estimated VO ₂ max)	107	40.71 ± 2.72	63	40.79 ± 2.72	44	40.61 ± 2.73
High cardiorespiratory fitness, n (%)	65 (60.7)		22 (34.9)		43 (97.7)	
Cardiometabolic markers						
LDL (mg/dL)	96	101.02 ± 26.04	60	102.61 ± 23.90	36	98.36 ± 29.43
HDL (mg/dL)	105	50.36 ± 11.76	63	51.71 ± 11.27	42	48.33 ± 12.32
Triglycerides (mg/dL)	105	98.42 ± 56.83	63	88.87 ± 51.36	42	112.74 ± 62.08
Diastolic blood pressure (mmHG)	107	57.60 ± 13.80	63	57.80 ± 15.40	44	57.34 ± 11.31
Systolic blood pressure (mmHG)	107	100.78 ± 13.49	63	100.80 ± 12.42	44	100.75 ± 15.03
Insulin (UI/mL)	100	13.77 ± 10.96	59	11.46 ± 6.30	41	17.08 ± 14.85
Glucose (mg/dL)	106	86.45 ± 6.76	64	87.45 ± 6.32	42	84.93 ± 7.20
HOMA	99	3.00 ± 2.74	59	2.50 ± 1.43	40	3.73 ± 3.86
Cardiometabolic risk score	109	0.00 ± 0.99	64	-0.01 ± 0.98	45	0.02 ± 1.02
Inflammatory markers						
Interleukin-6 (pg/mL)	97	1.82 ± 1.56	58	1.83 ± 1.79	39	1.80 ± 1.15
Interleukin-1β (pg/mL)	101	1.60 ± 0.91	59	1.49 ± 0.87	42	1.74 ± 0.96
Tumor necrosis factor-α (pg/mL)	103	4.07 ± 1.53	60	3.89 ± 1.63	43	4.33 ± 1.37
C-reactive protein (mg/L)	77	3.34 ± 3.47	48	3.58 ± 3.96	29	2.94 ± 2.47
Sleep-disordered breathing						
SDB scale (0 to 1)	109	0.19 ± 0.13	64	0.19 ± 0.13	45	0.18 ± 0.13
SDB presence, n (%)	17(15.6)		10 (15.6)		7 (15.6)	

Notes: SD = standard deviation; SDB= sleep-disordered breathing; SDB = Sleep-disordered breathin; LDL= low density lipoprotein; HDL= high density lipoprotein; HOMA= homeostatic model assessment of insulin resistance. Cardiometabolic risk score was calculated as the re-normalized mean of the z-scores for HDL cholesterol, waist circumference, triglycerides, glucose and the average of systolic and diastolic blood pressure based on European population reference values [211]. High and low cardiorespiratory fitness was categorized based on sex-specific cut-off points (i.e., 35 and 42 ml/kg/min for girls and boys, respectively) [212].

Table 13. Hierarchical linear regression for the associations of sleep-disordered breathing with cardiometabolic and inflammatory markers.

		SDB scale	
	Model	β	P
Cardiometabolic markers			
LDL‡	1	-0.110	0.278
	2	-0.062	0.535
HDL†	1	-0.060	0.548
	2	-0.056	0.578
Triglycerides‡‡	1	-0.035	0.717
	2	-0.059	0.543
Diastolic blood pressure	1	0.162	0.095
	2	0.125	0.189
Systolic blood pressure‡	1	0.029	0.767
	2	-0.009	0.928
Insulin‡	1	0.164	0.069
	2	0.117	0.168
Glucose‡‡	1	0.068	0.477
	2	0.053	0.584
HOMA ‡	1	0.186	0.041
	2	0.140	0.102
Cardiometabolic risk score ‡‡‡	1	0.053	0.577
Inflammatory markers			
Interleukin-6†††	1	0.105	0.297
	2	0.099	0.338
Interleukin-1 β	1	0.015	0.878
	2	0.030	0.771
Tumor necrosis factor- α	1	-0.074	0.460
	2	-0.087	0.392
C-reactive protein	1	0.384	0.001
	2	0.354	0.002

Every association (i.e., pair main exposure-outcome) was introduced in separate hierarchical regression models. Potential confounders (i.e., age, sex, parental education level, wave, and peak height velocity [PHV]). Potential confounders for each model were included into step 1 of the stepwise regression to test their association to the outcomes, so that for each outcome only the relevant confounders were retained in the final models. In step 2, the exposure variable of interest, SDB scale was entered using the method ENTER to force to be in the model 1 and both fat mass index and SDB scale to be in model 2. Blom's normalized values were used in the analysis. β values are standardized coefficients. Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparisons test.

‡Adjusted for PHV †Adjusted by parental education level ‡‡Adjusted by sex †† Adjusted by sex and second wave ‡‡‡ Adjusted by PHV and parental education level ††† Adjusted by third wave.

Cardiometabolic risk score was calculated as the re-normalized mean of the z-scores for HDL cholesterol, waist circumference, triglycerides, glucose and the average of systolic and diastolic blood pressure based on European population reference values [211].

LDL= low density lipoprotein; HDL= high density lipoprotein; HOMA= homeostatic model assessment of insulin resistance; SDB= sleep-disordered breathing.

DISCUSSION

The main findings of this study were the following: i) SDB severity was positively related to CRP, but not with cardiometabolic or other inflammatory risk factors independently of fat mass index and ii) higher levels of cardiorespiratory fitness may attenuate the negative effect of SDB on CRP in children with overweight or obesity. These results contribute to the existing knowledge by investigating the link between SDB and cardiometabolic and inflammatory markers independently of adiposity levels. Furthermore, we shed light on the important role of cardiorespiratory fitness in these associations.

Interestingly, in this study no associations were observed in SDB among all the cardiometabolic risks factors analyzed. These results are consistent with previous evidence in children with obesity which found null significant associations between SDB severity with LDL-cholesterol, HDL-cholesterol, triglycerides, systolic and diastolic blood pressure [194,195], insulin, and HOMA [213]. The evidence in children and adolescents with overweight or obesity has also similar conclusions to ours, finding non-significant relationship between OSA and HOMA after adjusting for adiposity in a younger pediatric sample (i.e., children, 2-12 years-old) [214]. However, in an older subsample of the same study (i.e., adolescents, 12-18 years-old) this association was strongly supported [214]. Even when mild SDB is presented, adolescents could have stronger association with cardiometabolic risk than children [215]. A possible explanation could be that, due to the developmental changes, adolescents may present an etiology similar to adults, having higher risk of SDB in association with excess of body weight [216]. Opposite to our findings, when the authors explored OSA severity in children with overweight or obesity, the results depicted a positive relationship of OSA and glucose, insulin, HOMA [38,195], and two metabolic syndrome scores [194]. Indeed,

it seems that the grade of SDB severity could be related to the significance of the findings, showing thus that the higher the severity, the stronger the association [194]. Therefore, a possible explanation for the lower significant associations observed in our study could be that our participants presented a healthy sleep (i.e., low SDB severity). Differences between studies could be due to the measurement method of the SDB severity (i.e., ActiveBrains: a questionnaire using the SDB scale [range from 0 to 1] vs. Isacco et al. [194]: an objectively overnight sleep monitor). Our measurement method may have limited the sensitivity and accuracy detecting these associations. Future studies in childhood obesity with “poor” sleep health (i.e., higher SDB severity) exploring with polysomnography, and greater sample size should corroborate or contrast our results.

Another important aspect of the present study was the analysis examining the SDB and inflammatory markers. We observed that those children with overweight or obesity that presented higher levels of SDB, showed also greater CRP levels independently of their adiposity. Our results are consistent with previous literature showing a lack of association between SDB severity and circulating levels of pro-inflammatory markers such as IL-6 and TNF- α [76,196,198], but a significant relationship with CRP levels [38,76] in children and adolescents with overweight or obesity. In contrast, others studies in pediatric obesity concluded that was the OSA severity the responsible for the significant increase of IL-6 and TNF- α [38], but it was not predictive of CRP [197]. The non-significance observed for CRP is likely explained by the small sample size ($n=31$) [197], which in turn, could not be able to detect significant associations. Interestingly, we further observed that our findings on CRP were independent of the adiposity levels. This result supports recent evidence in normal-weight children, where elevated CRP levels were positively correlated with OSA severity [217], but without considering the adiposity levels. In contrast, our findings are not in agreement to

those of Canapari et al. [197], who concluded that it was the severity of obesity, and not OSA, the main determinant for inflammation [190]. It could be that both obesity and SDB share similar mechanisms that underlie the inflammation in children with overweight or obesity. A recent systematic review shed light on the possible mechanism underlying the relationship between OSA and inflammation [190]. Indeed, based on the existent evidence coming from circulating cytokines, inflammatory cells, acute-phase reactants, tissue- or organ-specific inflammation, the relationship between inflammatory pathways and OSA is considered complex and likely to be bidirectional [190]. Therefore, it seems plausible that obesity-related inflammation could be a mechanism of OSA in pediatric obesity. Further studies examining different SDB degrees of severity and its association with inflammatory markers are needed in children.

The lack of previous studies examining the role of cardiorespiratory fitness in the association between SDB and CRP (a widely used and an important inflammatory biomarker in epidemiological studies [218,219]) in children with overweight or obesity hampers our ability to compare our results with other studies. Our findings shed light on the role of cardiorespiratory fitness on the relationship between SDB and CRP, highlighting that higher levels of cardiorespiratory fitness could attenuate the negative consequences of SDB on CRP. This finding is in line with the evidence depicting the role of cardiorespiratory fitness as a clinical vital sign [202] and for the reduction of systematic inflammation in children [204].

Some limitations need to be considered. First, the cross-sectional design does not allow the possibility of identify cause-effect for any of the associations. Second, our data was obtained from a parent-reported questionnaire instead of polysomnographic data (i.e., the gold standard for the detection of SDB and its severity); however, this questionnaire is reliable [9] and valid for the identification of SDB [10,146]. Third, the relatively low sample size and

the prevalence of SDB could limited the power of the statistical analyses to detect significant differences. The extrapolation of these findings should be taken with caution in younger children or to other determinants of SDB. On the other hand, the strengths of this study include the focus on children with overweight or obesity, who are particularly vulnerable to sleep disorders and poor cardiometabolic health and inflammation; and the inclusion of a valid, reliable, and related to health-field based fitness test in children [95-97].

CONCLUSION

Our findings contribute to the literature by suggesting that SDB severity is associated with poorer CRP levels in children with overweight or obesity independently of adiposity. Furthermore, our data show that such association was only significant and of medium effects-size in children with low cardiorespiratory fitness, suggesting that higher cardiorespiratory fitness might attenuate the adverse effect of SDB on systematic inflammation in children with overweight or obesity. However, no association was found between SDB severity and the other cardiometabolic and inflammatory markers examined. Our findings suggest that public health policies should promote strategies to improve cardiorespiratory fitness through vigorous physical activity, in order to reduce the negative association found in SDB and inflammation in children with overweight/obesity.

Study 5

Effects of exercise on sleep in children with overweight or obesity: a randomized clinical trial

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ABSTRACT

Objectives: To examine i) the chronic effects of a 20-week physical exercise program on device-assessed sleep and on sleep-disordered breathing (SDB); and ii) whether attending to a session of the exercise program had effects on device-assessed sleep the subsequent night in children with overweight or obesity.

Methods: A total of 99 children with overweight or obesity (n=47 in the exercise group) participated in this secondary analysis of the ActiveBrains randomized clinical trial. The exercise program included a combination of aerobic and resistance exercise training, 3-5 days/week (90 min/session). The control group was asked to maintain usual lifestyle. Sleep outcomes were measured using wrist actigraphy and included: total sleep time, total time in bed, sleep efficiency, and wake after sleep onset (WASO) time. SDB was assessed via the Paediatric Sleep Questionnaire.

Results: The ActiveBrains exercise program had a statistically significant effect on WASO time (-10.8 min/day, -0.5 standard deviations (SD), $P=0.040$). Furthermore, we observed a small non-statistically significant effect on sleep efficiency (+2%, 0.4 SD, $P=0.1$). No other chronic effects were observed on the other sleep outcomes. The nights (at maximum of 4) after attending the ActiveBrains exercise sessions, children showed higher total sleep time (+8 min, $P=0.17$), sleep efficiency (+1%, $P=0.15$), and lower WASO time (-6 min, $P=0.18$) although did not reach statistical significance.

Conclusion: A 20-week physical exercise program reduced WASO time in children with overweight or obesity in comparison with control group peers, yet we did not observe effects on SDB. Future randomized trials that include a clinical sample of children with poor sleep health at baseline are needed to better appreciate the role of exercise in sleep health.

INTRODUCTION

Sleep is essential for children's health and well-being [7]. The current lifestyles (e.g., late-night screen time, energy drinks, and delayed bedtimes) are compromising the sleep habits in children [22]. As a result, the attainment to the sleep recommendations (uninterrupted 9-11 h of sleep/night) is decreasing in children [220]. The estimated prevalence of 6-to-13-year-old children sleeping less than 9-11h/day is 98.1%, as measured with accelerometers, and 18.1% as reported in diaries [26]; and the prevalence of sleep-disordered breathing (SDB) is around 4-11% in children [27]. Shorter sleep duration has been related to worse physical and mental health in children and adolescents [19], and poorer sleep outcomes (i.e., sleep duration and sleep patterns) appear to be associated with childhood obesity [32,173,175]. As an example, we have previously observed a link between device-assessed sleep outcomes [34] and SDB [208] with brain health (i.e., gray matter volume and academic performance) in children with overweight or obesity. Given the well-contrasted multi-organ benefits of physical exercise [40], it is of interest to investigate whether physical exercise improves sleep in children with overweight or obesity.

A large number of studies have supported the positive chronic and acute effects of physical exercise on device-assessed sleep in adults [41]. However, the literature focused on the effects of physical exercise on sleep in the pediatric population is scarce. To date, only one randomized clinical trial (RCT) investigated the effect of exercise intervention on device-assessed sleep in children with autism spectrum disorders [44]. In obesity, the available trials on exercise and sleep are limited to adolescents [33], while the studies in childhood are all observational and focused on lifestyle physical activity and sleep [42,43]. In regards to SDB, few studies showed that engaging in at least 20/40 minutes per day of vigorous aerobic exercise appeared to be

beneficial in palliating symptoms of SDB in children 7 to 11 year-old with overweight, [50] but not in obese children with SDB [51]. There is a need of RCTs on the effects of exercise on sleep in pediatric obesity.

Few studies examined the chronic and acute effects of exercise on sleep outcomes (i.e., sleep time and quality) in adolescents with obesity [33,221]. This information would inform public health recommendations and practice. Therefore, the aims of this study were to examine i) the chronic effects of a 20-week physical exercise program on device-assessed sleep, and on SDB; and ii) whether attending to a session of the exercise program had effects on device-assessed sleep the subsequent night in children with overweight or obesity.

METHODS

Study design and participants

The ActiveBrains project was a RCT (Clinical Trial registration no. NCT02295072) whose primary aim was to investigate the effect of a 20-week exercise program on brain health indicators in children with overweight or obesity [53,54]. This study examined the ActiveBrains RCT effects on sleep (secondary outcomes). Details on the design, eligibility, characteristics, and effects on the primary outcomes can be found elsewhere [53,54]. In brief, 109 children (8-11 years) with overweight or obesity based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation [14,15] took part in this RCT [53,54]. After baseline data collection, participants were randomly allocated to either the wait-list control group (N=52) or exercise program (N=57) using a computer-based simple randomization procedure in a ratio of 1:1 by a person not involved in the assessments. Participants in the wait-list control group continued with their usual routines. **Figure 4** depicts the participants flowchart. Data were collected from November 2014 to June 2016 in

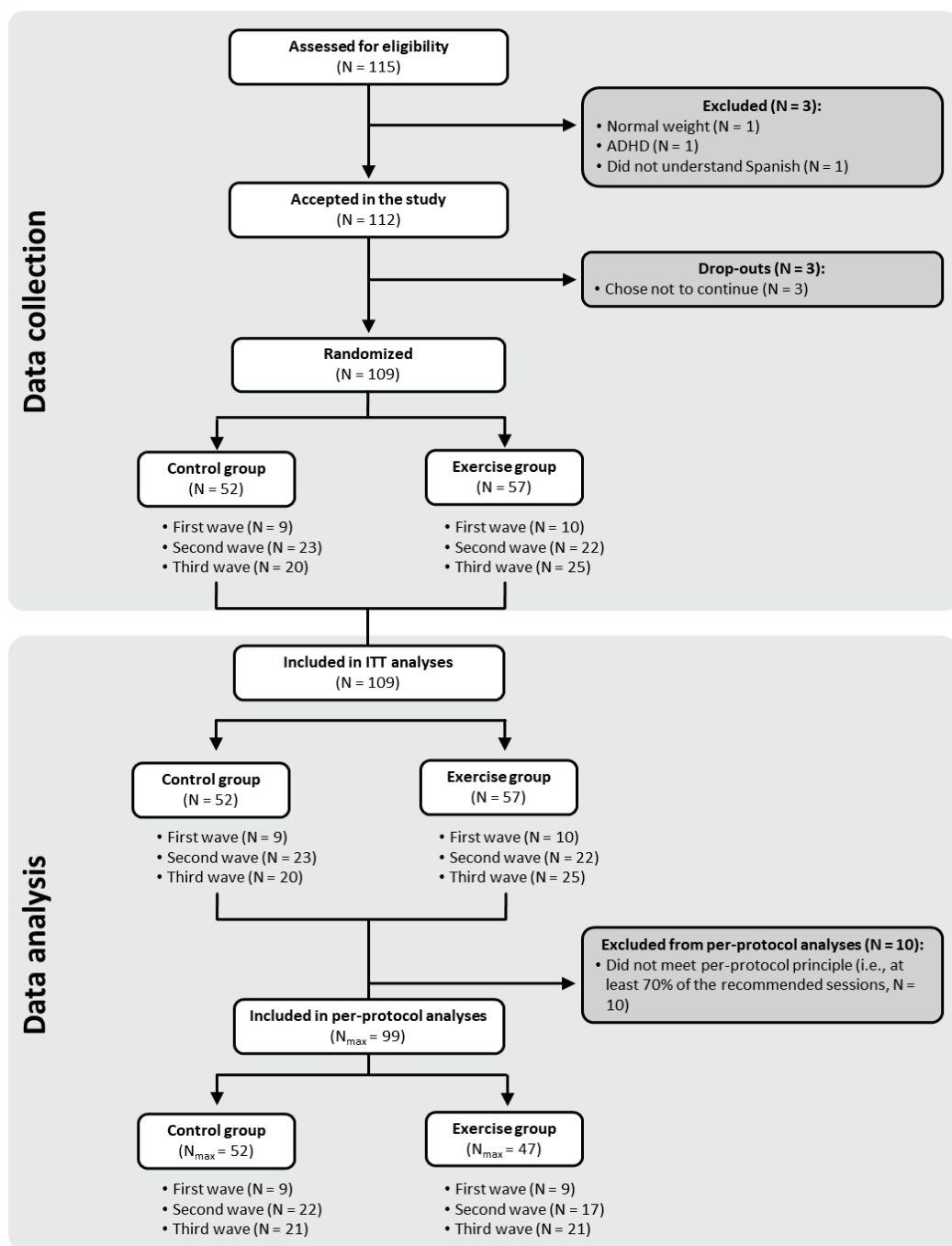


Figure 4. Flowchart of the study participants.

ADHD: Attention-deficit hyperactivity disorder; ITT: Intention-to-treat. For final ITT analyses, those participants that left the study during the physical exercise program or did not complete the post-exercise program assessments were imputed (see Statistical section).

Granada (Spain). The ActiveBrains RCT [53,54] was conducted according to the Declaration of Helsinki and the study protocol was approved by the Ethics Committee on Human Research (CEIH) of the University of Granada. Written informed consent was obtained by the legal guardians or parents of all participants, who were informed of the purpose of the study and provided informed assent. Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed for the reporting of trial results [222].

Physical exercise program

The ActiveBrains physical exercise program had a duration of 20 weeks and was based on the international guidelines on physical activity for children [223]. Participants were recommended to attend a minimum of 3 out of 5 sessions/week. The exercise program was based on aerobic exercise games and resistance exercise using bodyweight, fitballs and/or therabands. Each session lasted 90 min (i.e., 5-min warm-up; 60-min aerobic exercise; 20-min resistance exercise; and 5-min cool-down).

Procedures and measurements

Both control and exercise groups were assessed at baseline and post-intervention. Sleep and physical activity were additionally monitored in the middle of the exercise program (10th week) in both groups. Assessors were not fully blinded to the participant's group allocation due to practical reasons. More information about the measurements can be found elsewhere [53].

Sleep-disordered breathing

The children's legal guardians completed the Spanish version of the Paediatric Sleep Questionnaire (PSQ) to evaluate SDB, which has shown high reliability and internal consistency [9] as well as validity for the identification of SDB [10,146]. The SDB scale (range: 0 to 1) was used to quantify SDB, with higher scores indicating greater breathing severity [146]. This

scale consists of 22 closed response items of the reduced version of the PSQ, which were divided into three subscales: [10,146] snoring, sleepiness and inattention/hyperactivity. Further details on the questionnaire can be found elsewhere [208,209].

Device-assessed sleep

Sleep was monitored with non-dominant wrist-worn accelerometers (ActiGraph GT3X+, Pensacola, FL, USA) for 7 consecutive days (24h/day). Participants reported information on the time they went to bed and woke up every day. Accelerometers were initialized to record accelerations at 100 Hz, and the files were processed in the R package GGIR (v.1.5.12, <https://www.cran.r-project.org/>) [181]. More detailed information on accelerometer data processing for device-assessed sleep outcomes analysis can be found elsewhere [182]. The algorithm developed by Sadeh et al. [183] was applied within the total time in bed frame to classify every minute as "sleep" or "wake" time. Device-assessed sleep outcomes included indicators of sleep timing, sleep duration (i.e., total sleep time and total time in bed), and sleep quality (i.e., sleep efficiency and wake after sleep onset [WASO] time). A valid week was considered if the participant registered at least 4 days (≥ 16 hours/day), including a minimum of 1 weekend day.

Statistical analysis

Descriptive characteristics of the study sample are shown as mean and standard deviations (SD) or percentages and frequencies.

Chronic effect of the physical exercise program on sleep

The chronic effects of the ActiveBrains exercise program on each sleep-related outcome were conducted according to the per-protocol principle (i.e., attending at least 70% of the sessions) using an analysis of covariance (ANCOVA). Per-protocol analyses were the main analyses in this trial to investigate the efficacy rather than effectiveness of our intervention

(i.e., effects of the preconceived intervention). Post-exercise sleep-related outcome values were included as dependent variables, group (i.e., exercise vs. control) as fixed factor, and baseline outcome data as covariates [224]. Raw and standardized (z-scores) estimates are provided, with the post-exercise z-scores calculated relative to the baseline mean and SD as an indicative of the change [53,224]. A difference of 0.2 SDs was considered a small, 0.5 SDs medium, and 0.8 SDs large effect sizes [225]. Differences exceeding 0.2 Cohen's D were interpreted as minimum meaningful effect [226].

Exploratory analyses were conducted following the intention-to-treat-principle, including all the recruited participants, and imputing the missing values using predictive mean matching multiple imputations [227]. We checked that missing data was missing at random prior to performing the multiple imputation.

Acute effect of the physical exercise program on sleep

The acute effects of the ActiveBrains exercise program were investigated over the sleep outcomes from the subsequent nights (at maximum of 4 nights) to the sessions the participants attended versus the sleep outcomes from the nights after the days in which they did not attend to the sessions (at week 10th, in the middle of the intervention). This analysis only included participants allocated to the exercise group. We excluded Fridays, Saturdays and Sundays from the dataset given the expected changes in the sleep patterns during weekends [228]. Linear regression mixed models were used with the attendance indicator (0=non-attendance to exercise program, 1=attendance) as fixed factor, the ID as random factor, and sleep indicators as outcomes. Random and fixed intercepts were defined to investigate the within-group (attendance and non-attendance) and within-participant effect of the exercise session, respectively. Analyses were performed using

the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY) and R v.3.4.1 (<https://cran.r-project.org/>). The level of significance was set at $P < 0.05$.

To better understand the acute effects of the exercise program on sleep, we investigated whether the children compensated the amount of exercise performed in the ActiveBrains session with activities that they usually perform in their daily life. For such purpose, we performed a 1-dimension curve analysis using statistical parametric mapping software (SPM1D; Wellcome Department of Cognitive Neurology, London, UK) to verify whether acceleration values identified a significant physical activity increment in the days attending to the physical exercise sessions compared to the days not attending. From Monday to Thursday, mean acceleration curves were presented from midnight to the following midnight (i.e., 24h curves). T-tests were used to determine significant differences between the curves for attendance and non-attendance exercise group throughout the day.

RESULTS

Descriptive characteristics

A total of 99 children with overweight or obesity ($n=47$ in the exercise group) were included in the per-protocol analysis (90% of the participants initially enrolled); the children who did not adhere to the protocol were not different in baseline characteristics from the included children (**Figure 4**). Descriptive baseline characteristics are shown in **Table 14**.

Chronic effect of the physical exercise program on sleep

The effects of the ActiveBrains physical exercise program on sleep outcomes are presented in **Table 15**. The largest effect of the ActiveBrains physical exercise program was found on WASO time, with an intervention vs.

control difference of -10.79 min/day (95% CI: -21.09 to -0.51; $P=0.040$), showing a difference of medium effect size in the exercise group compared to the control group ($SD=-0.507$ [95% CI: -0.989 to -0.024]). Furthermore, a smaller and non-significant positive effect was observed for sleep efficiency (+2% [95% CI: -0.330 to 3.671]; $SD=0.398$). We found no evidence of exercise effects either on the remaining device-assessed sleep outcomes (i.e., total sleep time, sleep efficiency, and total time in bed) nor on SDB (all $P > 0.05$).

The intention-to-treat analyses showed similar results, yet of smaller magnitude, than per-protocol analyses (Table S1). More participants in the exercise group showed meaningful changes (i.e., reduction of ≥ 0.2 SDs) compared to the control group in WASO time (31% vs. 19%, $P=0.405$) (Figure 5).

Acute effect of the physical exercise program on sleep

The acute effects on device-assessed sleep outcomes of attending ($n=127$) vs. not attending ($n=73$) to the ActiveBrains physical exercise sessions are presented in Figure 6. Attending to the physical exercise sessions resulted in a longer sleeping time by 8 min/day ($P=0.166$), total time in bed by 2 min/day ($P=0.750$) and better sleep efficiency by 1% ($P=0.146$); and a reduced -6 min/day WASO time ($P=0.185$) compared to non-attendance days, although these associations did not reach statistical significance.

The SPM analysis of the 24h activity curve shows how attendance days to exercise intervention significantly increased their activity levels compared with the non-attendance days (Figure 7).

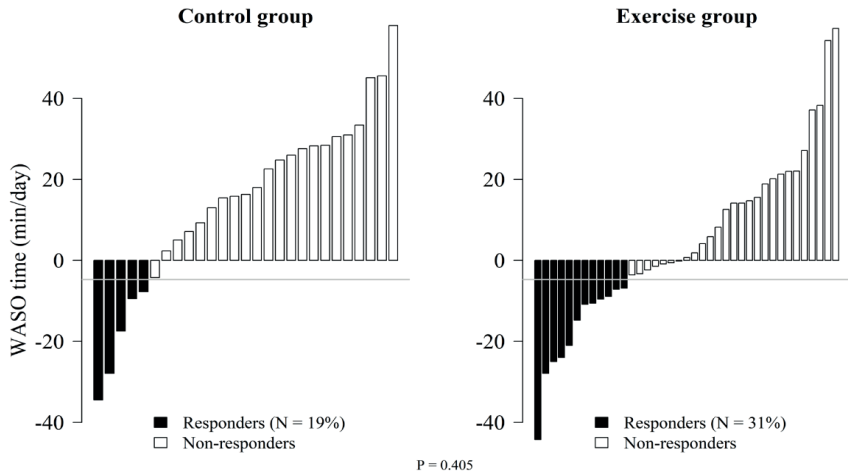


Figure 5. Pre-post change distribution in the outcome significantly affected by the exercise program (i.e., wake after sleep onset time, WASO time). Data analyses were primarily conducted under the per-protocol principle, i.e., attending to 70% of the sessions. Participants were classified as responders when they reduce the WASO time after the intervention (Cohen's $d \geq 0.2$), whilst non-responders were categorized for those participants who did not experience a reduction (Cohen's $d < 0.2$).

Table 14. Descriptive baseline characteristics of the ActiveBrains participants meeting the per-protocol criteria.

	All		Exercise group		Control group	
	N	Mean (SD) or %	N	Mean (SD) or %	N	Mean (SD) or %
Sex						
Girls (n %)	41	41.4	16	34	25	48.1
Boys (n %)	58	58.6	31	66	27	51.9
Age (years)	99	10.1 (1.1)	47	10.0 (1.1)	52	10.1 (1.1)
Weight (kg)	99	56.5 (11.0)	47	57.4 (12.7)	52	55.7 (9.4)
Height (cm)	99	144.6 (8.3)	47	143.9 (8.9)	52	145.2 (7.9)
Parent education level (n%)						
Primary school	65	65.7	33	70.2	32	61.5
Secondary school	16	16.2	6	12.8	10	19.2
University degree	18	18.2	8	17.0	10	19.2
Peak height velocity (years)	99	-2.2 (1.0)	47	-2.4 (0.9)	52	-2.1 (1.1)
Sleep-disordered breathing (SDB)						
SDB scale (0 to 1)	99	0.19 (0.13)	47	0.19 (0.13)	52	0.19 (0.14)
SDB presence (%)		16.2		12.8		19.2
Device-assessed sleep						
Total sleep time (min/day)	97	462.5 (36.0)	47	462 (33.3)	50	463 (38.7)
Total time in bed (min/day)	97	529 (31.0)	47	524.6 (35.1)	50	533.1 (26.4)
Sleep efficiency (%)	97	85 (4.6)	47	85.3 (4.0)	50	84.8 (5.2)
WASO time (min/day)	97	74.9 (22.0)	47	73.9 (19.1)	50	75.8 (24.5)

Data analyses were primarily conducted under the per-protocol principle, i.e., attending to 70% of the sessions or keep the usual lifestyle for exercise and control groups, respectively. SDB was measured using the Spanish version of the Paediatric Sleep Questionnaire. Device-assessed sleep was measured using wrist-worn accelerometer. WASO: wake after sleep onset

Table 15. Per-protocol chronic effects of the ActiveBrains physical exercise program on raw and z-score post-exercise (i.e., z-score of change from baseline) sleep-related outcomes.

		Mean (95% CI)		Difference between groups (exercise <i>minus</i> control)	P
N _{all}	N	Exercise group	Control group		
SDB scale	87	47	40		
Raw score		0.195 (0.165 to 0.225)	0.177 (0.145 to 0.210)	0.017 (-0.027 to 0.062)	0.438
z-score		0.050 (-0.182 to 0.281)	-0.084 (-0.335 to 0.167)	0.134 (-0.208 to 0.476)	
Total sleep time (min/day)	66	39	27		
Raw score		435.231 (422.518 to 447.944)	431.078 (415.799 to 446.357)	4.152 (-15.725 to 24.029)	0.678
z-score		-0.793 (-1.137 to -0.448)	-0.905 (-1.319 to -0.491)	0.113 (-0.426 to 0.651)	
Total time in bed (min/day)	66	39	27		
Raw score		504.153 (491.353 to 516.952)	506.982 (491.594 to 522.370)	-2.829 (-22.860 to 17.202)	0.779
z-score		-0.799 (-1.202 to -0.395)	-0.709 (-1.195 to -0.224)	-0.089 (-0.721 to 0.542)	
Sleep efficiency (%)	66	39	27		
Raw score		84.021 (82.744 to 85.298)	82.351 (80.815 to 83.886)	1.670 (-0.330 to 3.671)	0.100
z-score		-0.338 (-0.642 to -0.033)	-0.736 (-1.102 to -0.370)	0.398 (-0.079 to 0.875)	
WASO time (min/day)	66	39	27		
Raw score		77.798 (71.222 to 84.374)	88.594 (80.689 to 96.499)	-10.796 (-21.085 to -0.508)	0.040
z-score		0.212 (-0.096 to 0.521)	0.719 (0.348 to 1.090)	-0.507 (-0.989 to -0.024)	

z-score values indicate how many standard deviations have the post-exercise program 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-exercise program is 0.50 standard deviations higher than the mean value at baseline, indicating a positive change, with negative values indicating the opposite. All data presented were adjusted for baseline values. SDB = sleep-disordered breathing; WASO = wake after sleep onset; SDB was assessed by the Paediatric Sleep Questionnaire.

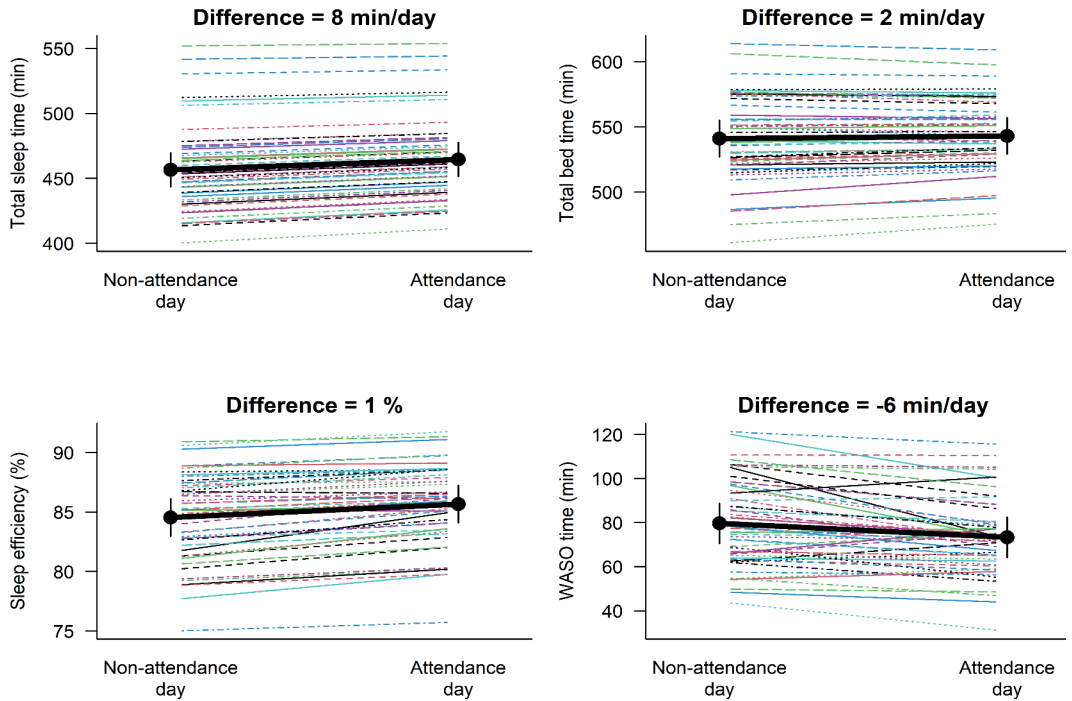


Figure 6. Mean differences for the acute effects four days (excluding Friday, Saturday and Sunday) of the *ActiveBrains* physical exercise program between the attendance days ($n=127$) vs non-attendance days ($n=73$) on device-assessed sleep outcomes. WASO = wake after sleep onset. Differences between attendance days vs non-attendance days were non-significant ($P>0.05$).

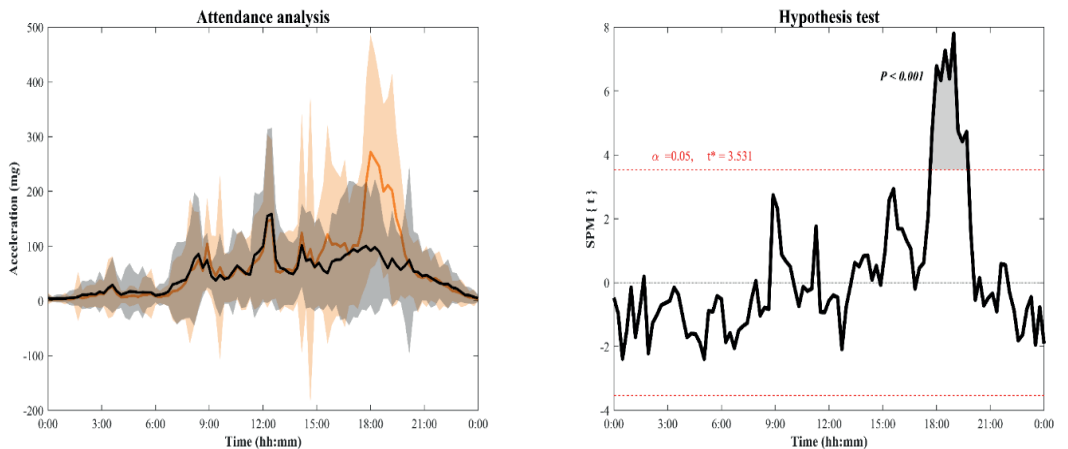


Figure 7. Comparison of means acceleration curves and standard deviation (shaded area) for the attendance (orange line) and non-attendance days (black line) in the exercise group participant during the 10-week of the intervention (excluding Friday, Saturday and Sunday). The hypothesis test shows the threshold ($t^* = 3.531$) at which there are significant physical activity patterns' differences between attendance and non-attendance exercise days. SPM=Statistical parametric mapping.

DISCUSSION

Main findings

The ActiveBrains RCT contributes to the existing literature with the following findings: i) a 20-week physical exercise program reduces the WASO by around 10 min/day and might increase the sleep efficiency by ~2% in children with overweight or obesity; ii) all device-assessed sleep indicators, especially the sleep time and the WASO time, were improved in those days in which the participants attended to the sessions, although did not reach statistical significance and it should be taken with caution.

This is one of the few RCT in the literature examining both chronic and acute effects of a physical exercise program on device-assessed sleep habits in childhood overweight/obesity. This allows to suggest that exercise has chronic and certain acute benefits (yet non-significant) on sleep habits, specifically on WASO (-6-10 minutes per night) and sleep time (+8 minutes per night). On the other hand, we did not observe a statistically significant effect on SDB.

Chronic effect of the physical exercise program on sleep

To date, only one RCT investigated the effect of physical intervention on device-assessed sleep in children, but with autism spectrum disorders [44]. In line with our study, Tse et al. found that a 12-week physical exercise intervention (45 min/session and 2 session/week) had a positive effect on WASO and sleep efficiency [44]. They also found a significant effect on sleep duration measured by non-dominant wrist-worn accelerometry [44]. Moreover, in consonance with our results, but using a questionnaire to measure sleep quality, an RCT in children and adolescents reported that a 12-weeks of both judo or ball games benefited sleep quality (i.e., aspects related to sleep pattern and the frequency with which these may occur) [229]. In adolescents with

obesity, and in contrast with our findings, a 12-week physical exercise intervention (180 min/week) significantly increased sleep efficiency (0.7 SDs) and total sleep time (0.8 SDs) [33]. In our study, the effect of the intervention was significant only on WASO time, yet certain evidence of effects on sleep efficiency was observed. A null effect was observed on sleep duration in contrast with the significant effects observed in both previous studies [33,34]. A possible explanation of these inconsistencies could be: i) this study participants had a healthy sleep at baseline, so there was little room for improvement; ii) children with autism spectrum disorder might have unhealthier sleep habits than children with normal development [230], which could enhance the exercise effects; iii) the age groups (adolescents vs. children), and the methods used to measure sleep (polysomnography vs. accelerometry) [33] could lead to inconsistent findings [231]. Additionally, the type of aerobic exercise (cycling/treadmill/rower vs. running games) or the inclusion or not of resistance exercise might partially explain the differences. A systematic review and meta-analysis in healthy participants concluded that running exercise was related to greater WASO reduction compared to cycling [232] and, therefore, it could be that inflammation and/or muscular damage caused by this type of aerobic exercise (i.e., running) may positively affect WASO time. However, further investigations are required to elucidate the role of inflammation or muscular damage on sleep.

In regard to sleep disorders, the ActiveBrains exercise program did not improve SDB in children with overweight or obesity. Similarly, in a recent study in obese children with SDB, neither 8-weeks nor 16-weeks of exercise (24 min of HIIT plus 20 min of resistance training) influenced the SDB scale or subscales [51]. Consistent with these findings, a previous study in adolescents with obesity observed that apnea-hypopnea index (AHI, measured with polysomnography), an index used to indicate the severity of sleep apnea, was not changed after a 12-week exercise program (180 min/

week) [33]. Likewise, Roche et al. found that a combination of 9-months of aerobic exercise and diet had no effect on OSA measured with polysomnography in adolescents with obesity [233]. However, Davis et al. found that 15 weeks of aerobic exercise (i.e., low-dose exercise of 20 min/day or high-dose of 40 minutes/day) could improve SDB scale, specifically snoring, in 7- to 11-year-old children with overweight [50]. The lack of significant effects in our study might be due to the lower SDB severity in our sample at baseline (score of ~0.19 in a scale range 0 to 1, and 16.2% of our participants presented SDB) compared to in the study by Davis et al. (score of ~0.24, and 25% of participants presented SDB). Further studies in a sample with higher SDB severity at baseline should confirm or contrast our findings. Furthermore, a current meta-analysis highlights the importance of future well-designed RCTs to understand the independent effects of exercise on OSA and sleep health in children and adolescents with obesity [234].

Acute effect of the physical exercise program on sleep

Our results complement the existing literature in normal-weight children [235] by suggesting that acute exercise during the afternoon-evening could improve sleep in children with overweight or obesity. It seems that acute aerobic exercise performed at high-intensity have positive effects on sleep efficiency in children [235]. Our findings are in line with the previous literature, but cannot confirm this acute effect (as it was non-significant) in children with overweight or obesity enrolled in a concurrent aerobic plus strength exercise program. Likewise, in a study in adolescent girls with obesity, the authors showed that acute exercise in the morning has a positive effect on sleep duration and quality measured with accelerometers [221]. Furthermore, it seems that acute exercise performed in the evening does not have an adverse effect on sleep, rather a small positive effect in healthy adults [232]. It could be that

children sleep better due to the exhaustion caused by the exercise, independently of the time of the day when it is performed. However, a previous study showed that exercise was beneficial to improve device-assessed sleep (i.e., decreased WASO time and increased sleep efficiency) only when it was completed 4 hours before bed-time and not 2 hours (i.e., late evening) in healthy young adults [236]. We did not have the opportunity to investigate the timing effect of the exercise on sleep since all participants performed the ActiveBrains exercise sessions at the same time, and we encourage future studies to address that gap in youth. Thus far, the literature in children and youth has examined whether the lifestyle physical activity was associated with sleep the subsequent night's, finding limited evidence to support this relationship [43].

Limitation and strengths

The limitations of this study include: (i) our findings apply to children with overweight or obesity and should not be extrapolated to other populations (e.g., other age groups, normal-weight individuals); (ii) we used questionnaires instead of the gold-standard to measure SDB (polysomnography); (iii) the accelerometer estimates of sleep are based on movement patterns, not purely sleep, yet the accelerometers provide a non-invasive, objective, and valid assessment of sleep in free-living conditions [90,183].

On the other hand, there are some strengths that should be noted. The randomized design, the use of device-assessed sleep behaviour with accelerometers across an entire week, the advance processing on accelerometer raw data, and the focus on children with overweight or obesity, who often show poorer sleep patterns than normal-weight children. The novel analyses of accelerometer-measured physical activity all throughout the day (24 h) to accurately investigate whether changes in overall physical activity levels took place in the attendance days to physical exercise program and at what time of the day.

CONCLUSION

Our findings suggest that exercise can have positive effects on device-assessed sleep habits, particularly chronic effects with certain changes being observed also acutely, by producing ~6-10 minutes lower WASO time per night. No effects were however observed on SDB in children with overweight or obesity. These findings support public health initiatives that promote physical exercise programs in children with overweight or obesity have the potential to improve their sleep quality. Further RCTs, especially in children with sleep difficulties at baseline are needed to better appreciate the role of exercise in sleep health.

Study 6

Sleep-disordered breathing across levels of total obesity, central obesity and fitness in children: cross-sectional and longitudinal analyses

ABSTRACT

Objectives: To examine (i) the cross-sectional differences in sleep-disordered breathing (SDB) between body mass index (BMI), waist circumference (WC) or cardiorespiratory fitness categories in children, and (ii) whether changes in fatness and fitness are associated with changes in SDB in the pediatric population after 1-year follow-up.

Methods: A total of 158 children (aged 8-11 years) from the ActiveBrains and GenObEx projects were included in the cross-sectional analyses. At 1-year follow-up, a total of 86 children (aged 9-12 years) were analyzed. SDB was assessed using the Pediatric Sleep Questionnaire, with the SDB scale of the reduced version. BMI was calculated as weight divided by height squared. Children's BMI was classified into: normal-weight, overweight, obesity type I and obesity type II-III. Children's WC was divided into high and low category. Cardiorespiratory fitness was evaluated by the 20m shuttle-run test, and participants were

classified as fit or unfit based on the total laps achieved.

Results: The prevalence of high risk of SDB in pediatric population was significantly different across BMI, WC or cardiorespiratory fitness categories (Chi squared, all P 's < 0.01). At baseline, higher SDB severity was found in the obesity type II-III compared to the normal-weight category ($P=0.01$), in the high WC compared to the low WC category ($P=0.025$), and in unfit compared to fit group ($P=0.001$). No significant associations were observed in longitudinal analyses ($P > 0.05$).

Conclusions: Severe/morbid obesity, abdominal obesity and poor fitness are all linked to higher risk of SDB in children, suggesting that targeting these modifiable risk factor could improve among other health dimensions, also sleep breathing. However, longitudinal analyses did not show any significant association, which could be due to small variation in the exposures during a relatively short follow-up (1-year).

INTRODUCTION

Sleep-disordered breathing (SDB) and obesity are considered major public health problems in childhood [23]. The estimated prevalence of SDB in the general pediatric population have raised up to 11%, depending on the assessment method [27-29]. Nevertheless, this prevalence has been suggested to be statistically higher in children with obesity than in children with normal-weight [35]. This fact, together with the fact that the prevalence of childhood obesity worldwide has dramatically increased over the last decades [237] and has been stabilized at very high levels [30,31] alert about the risk of more SDB problems in pediatric population.

Previous evidence suggests that obesity might be an important risk factor for childhood SDB prevalence [36,75,78,143,238-243]. However, the extent to which the prevalence of SDB across obesity severity (i.e., severe and morbid obesity) is unknown. In addition, waist circumference (WC, i.e., a measurement of central obesity) was found to be a more reliable indicator than total adiposity (i.e., body mass index [BMI]) in predicting the risk of developing SDB among children and adolescents with obesity [107]. Given that the distribution of body fat could be more relevant than BMI alone in predicting SDB in childhood [28], it is important to investigate the differences in SDB prevalence across different categories of total obesity (i.e., BMI) and central obesity (i.e., WC). Moreover, apart from the well-known benefits of cardiorespiratory fitness on children's health [16], better fitness levels were associated with lower SDB scores among children with overweight or obesity [104,147]. However, the differences in SDB prevalence between fit and unfit (sex- and age-specific categorized) children is unknown.

Further, longitudinal studies in pediatric population focused on the role of obesity predicting the severity of SDB are scarce. For instance, only two studies in children

suggested that higher body adiposity [106] or excessive weight gain [239] seemed to predict the SDB at 2.2-year and 5 years follow-up, respectively. It also appears that childhood central obesity (measured by WC) at baseline predict the persistence of SDB in the transition to adolescence [238,244,245]. In adults, weight change was shown to be a predictor of SDB severity change after 4-5 years follow-up [246,247]. Regarding fitness, it seems that only in the late adolescence, low cardiorespiratory fitness was found to be a risk factor for sleep apnea later in life [248]. These data clearly support the fact that there is a need to longitudinal address the impact of total and central obesity and low fitness in SDB in the pediatric population.

Therefore, the aims of the present study were to examine (i) the cross-sectional differences in SDB between BMI, WC or cardiorespiratory fitness categories in children at baseline, and (ii) whether the change on fitness and fatness are associated with changes in SDB in pediatric population after 1-year follow-up.

METHODS

Study design and participants

The present cross-sectional and longitudinal study included baseline and 1-year follow-up assessment data from the ActiveBrains and GenObEx (Genes, Obesity, and Exercise) projects. The ActiveBrains project was a randomized clinical trial (RCT, Clinical Trial registration no. NCT02295072) whose aim was to investigate the effect of a physical exercise program on brain health in children with overweight or obesity [53,54]. The complete details of the design, characteristics, eligibility criteria and main effects on the brain health outcomes have been described elsewhere [53,54]. The GenObEx project was a 1-year follow-up cohort study which primary aimed to examine the impact of obesity in comparison with normal-weight status, on

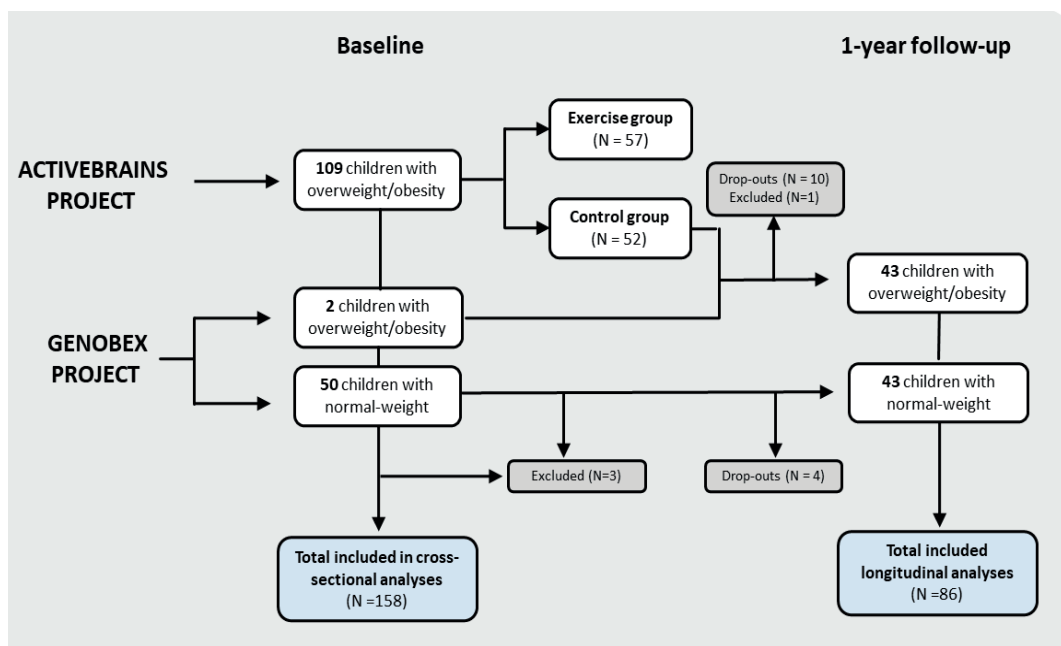


Figure 8. Diagram of the study design and analytical sample

brain health during childhood. For the present study, we included baseline and longitudinal outcome related to SDB, that was assessed in both projects using the same procedure and instrument.

Both ActiveBrains and GenObEx projects followed the same eligibility criteria, except for weigh status. Based on the sex-and-age specific international BMI cut-off points proposed by the World Obesity Federation [14,15], only children (aged 8-11 years) with overweight or obesity or normal-weight took part in ActiveBrains and GenObEx project, respectively. Diagram of the study design and analytical sample can be found in **Figure 8**. At baseline, a total of 109 children with overweight or obesity from the ActiveBrains project were assessed from November 2014 to June 2016. For the GenObEx project, the aim was to recruit only normal-weight children, to be compared with the overweight/obese children from the ActiveBrains project. However, in the eligibility assessments, 2 had overweight and were

allowed to stay in the study, adding a total of 111 participants with overweight or obesity status for cross-sectional analyses. The remaining participants in GenObEx, a total of 50, were normal-weight and were included for cross-sectional analyses. GenObEx evaluations took place from May to June 2021 in Granada (Spain) at baseline. Thus, a final sample of 158 children (111 with overweight or obesity and 47 with normal-weight) were included in the cross-sectional analyses. At 1-year follow-up, only those children from the ActiveBrains project belonging to the control group ($n=52$) and those participants from the GenObEx project were included ($n=50$). A total of 86 children (43 with overweight or obesity and 43 with normal-weight) were longitudinal analyzed. Legal guardians or parents were informed of the purpose of the corresponding study and written informed consent was provided by them. Both projects were approved by the Human Research Ethics Committee of the University of Granada.

Procedures and measurements

Sleep-disordered breathing

SDB was assessed by the Spanish version of the Pediatric Sleep Questionnaire (PSQ), which was filled by children's legal guardians or parents. This questionnaire showed high reliability, internal consistency [9], and validity for presence of SDB [10,146]. To quantify the SDB severity, a SDB scale (ranged from 0 to 1) was used, with higher scores indicating greater severity [146]. This SDB scale is composed of the 22 closed response items that belong to the reduced version of the PSQ [10,146]. The SDB scale scores were validated as a continuous indicator of severity of SDB [115], and scores > 0.33 were considered to be at high risk for SDB [10,146]. More specific details about the SDB scale can be found elsewhere [208,209].

Body composition: total and central obesity

Body weight (kg) was assessed with an electronic scale (SECA 861, Hamburg, Germany). Height (cm) was measured using a stadiometer (SECA 225, Hamburg, Germany). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Children were classified into four categories as followed: normal-weight, overweight, obesity type I and obesity type II-III, according to the sex- and age-specific international BMI cut-offs proposed by the World Obesity Federation (formerly named as International Obesity Task Force) [14,15]. As a measurement of central obesity, WC was also assessed using a flexible tape. Children were divided into high and low WC based on sex-specific cut-off points of Jolliffe and Janssen [249]. All assessments (i.e., weight, height and WC) were performed twice, and the average of the two values was used in the analyses. Further details about body composition measurements can be found elsewhere [53,54].

Cardiorespiratory fitness

Cardiorespiratory fitness was assessed by the 20-m shuttle-run test, a field-based exercise test included in the ALPHA (Assessing

Levels of Physical fitness and Health in Adolescents) battery [94]. This physical fitness test has been shown to be valid, reliable, and feasible in children and adolescents [95-97]. The number of completed laps was recorded in the test for the analyses. Children's cardiorespiratory fitness laps were classified as fit or unfit based on age- and sex-specific cut-off points derived from Tomkinson et al. [250]. More detailed information about the cardiorespiratory fitness test can be found elsewhere [54].

Covariates

Sex, years from peak height velocity (PHV) and parental educational level were considered as potential confounders. Years from PHV was calculated using Moore's equations [151], from seated and standing height, and the age of the children. Parental education level was obtained by a self-reported questionnaire. Parents reported their higher educational level achieved (i.e., none, primary, secondary, and university). Responses were categorized as: none (i.e., neither parent had university education), one (i.e., at least one of the parents had university education), or both (i.e., both parents had university education).

Statistical analyses

Descriptive characteristics of the study participants at baseline and 1-year follow-up are presented as mean $\pm$ standard deviations (SD) or percentages and frequencies. For cross-sectional analyses, differences in SDB scale across different BMIs, WC or cardiorespiratory fitness categories in children at baseline were analyzed by one-way analysis of covariance (ANCOVA), adjusted by sex, PHV and parental education level. Pearson's chi-square test for BMI, WC or cardiorespiratory fitness categories and the dichotomized SDB scale outcome (scores > 0.33) was performed at baseline.

Moreover, for longitudinal analyses, the associations between changes (follow-up *minus* baseline) in total obesity, central obesity and cardiorespiratory fitness and changes

in SDB in children after 1-year follow-up were also studied. Linear regression analyses using changes on fatness and fitness variables as predictors, and SDB changes as an outcome, were performed adjusting for sex, PHV and parental education level (model 1), and for model 1 plus the SDB at baseline (model 2). As supplementary analyses, baseline differences between drop-outs and non-drop-outs were determined by analysis of variance and chi-squared tests for continuous and categorical variables, respectively. As exploratory analyses, ANCOVA were performed to explore the differences in SDB scale across changes in BMI categories in children at follow-up. All statistical analyses were performed using the Statistical Package for Social Science (IBM SPSS Statistics for Windows, version 22.0, Armonk, NY). The level of significance was set at $P < 0.05$ for all the analyses.

RESULTS

Baseline and 1-year follow-up characteristics of the study sample are shown in **Table 16**. All participants allocated in the ActiveBrains intervention group were excluded in follow-up analyses ($n=57$). To explore the differences between those participants that completed the study (i.e., non-drops-outs) and those that did not complete the study (i.e., drop-outs), descriptive characteristics at baseline were showed in **Table S2**.

In regards to cross-sectional analyses, **Figure 9** presents the differences in SDB scale across four categories of BMI (i.e., normal-weight, overweight, obesity type I and obesity type II-III) in children at baseline. Differences in SDB scale across WC categories (i.e., high and low) and cardiorespiratory fitness categories (i.e., fit and unfit) in children at baseline are shown in **Figure 10** and **Figure 11**, respectively. The prevalence of high risk of SDB (scores > 0.33) was significantly different across BMI categories (Chi squared, $P=0.008$),

WC categories (Chi squared, $P=0.003$) and cardiorespiratory fitness categories (Chi squared, $P=0.001$). Moreover, a significant difference in SDB scores was only found between the normal-weight and the obesity type II-III categories ($P=0.01$), with higher SDB severity in the worst fatness category. Higher SDB was also observed in the high WC category compared to the low one ($P=0.025$), and unfit compared to the fit category ($P=0.001$), after adjusting for sex, PHV and parental education level.

Regarding longitudinal analyses, **Table 17** shows the associations between changes in total obesity, central obesity and cardiorespiratory fitness with changes in SDB. No significant relationships were found between changes in fatness and fitness and changes in SDB severity at 1 year follow-up, after adjusting for the different models examined (all $p > 0.05$). Lastly, the exploratory analyses showed that there were no differences in SDB across the different changes in BMI categories at follow-up (**Table S3**).

Table 16. Descriptive characteristics of the participants at baseline and 1-year follow-up.

	Baseline, n=158 (All participants included)	1-year follow-up, n=86 (Intervention group excluded in follow-up analyses*)
	Mean $\pm$ SD or %	Mean $\pm$ SD or %
Age (years)	10.0 $\pm$ 1.2	11.1 $\pm$ 1.2
Weight (kg)	49.0 $\pm$ 14.7	49.0 $\pm$ 16.0
Height (cm)	142.5 $\pm$ 8.9	149.1 $\pm$ 9.3
BMI (kg/m²)	23.8 $\pm$ 5.5	21.7 $\pm$ 5.7
BMI categories, n (%) ^a		
Normal-weight	47 (29.7)	43 (50)
Overweight	29 (18.4)	18 (20.9)
Obesity type I	48 (30.4)	18 (20.9)
Obesity type II-III	34 (21.5)	7 (8.1)
Waist circumference (cm)	80.5 $\pm$ 16.9	76.7 $\pm$ 18.5
Waist circumference categories, n (%) ^b		
Low waist circumference	70 (44.3)	48 (55.8)
High waist circumference	88 (55.7)	38 (44.2)
Cardiorespiratory fitness (laps)	20.7 $\pm$ 11.7	30.8 $\pm$ 15.5
Cardiorespiratory fitness categories, n (%) ^c		
Fit	65 (41.7)	60 (70.6)
Unfit	91 (58.3)	25 (29.4)
Sleep-disordered breathing (SDB)		
SDB scale (range 0 to 1)	0.2 $\pm$ 0.1	0.1 $\pm$ 0.1
High risk SDB presence, n (%)	18 (11.4)	5 (5.8)
Low risk SDB presence, n (%)	140 (88.6)	81 (94.2)

SD = standard deviation; BMI = Body mass index; SDB= sleep-disordered breathing. ^a BMI categories were based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation, formerly International Obesity Task Force [14,15]. ^b High and low waist circumference was categorized based on sex-specific cut-off points of Jolliffe and Janssen [249]. ^c Fit and unfit cardiorespiratory fitness was categorized based on age- and-sex specific cut-off points of Tomkinson et. al [250].

All variables have the sample size shown in the table, except for cardiorespiratory fitness that has 2 missing data at baseline and 1 at follow-up compared with Ns reported in the table.

*Note: Participants allocated in the intervention group were excluded in follow-up analyses (n=57)

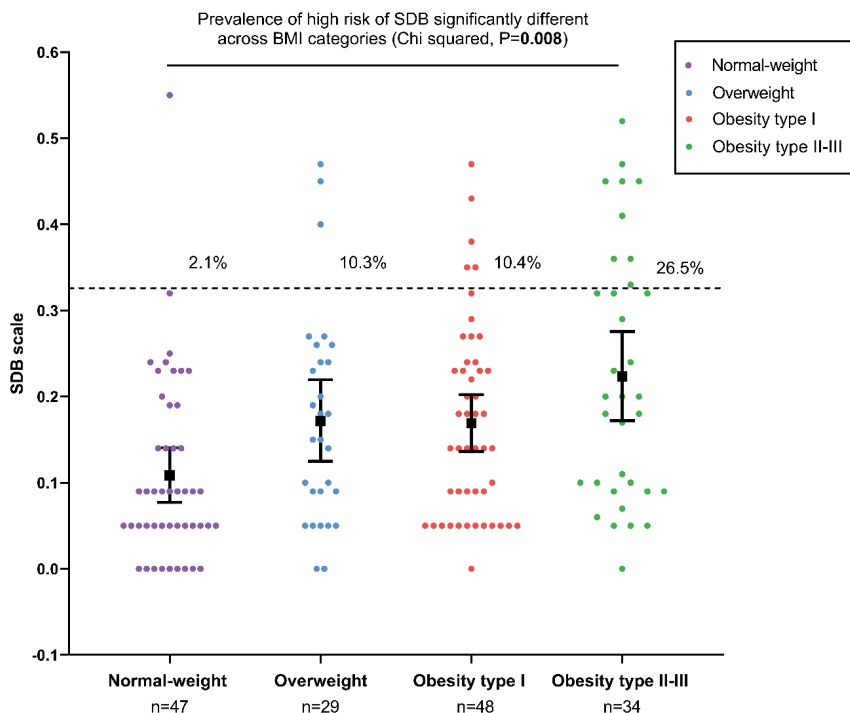


Figure 9. Differences in sleep-disordered breathing (SDB) scale across different categories of body mass index (BMI) at baseline in children. *ANCOVA model adjusted for sex, peak height velocity, and parental education level, showed a significant difference in the mean SDB scores between the normal-weight and the obesity type II-III ($P=0.01$). BMI categories were based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation, formerly named as International Obesity Task Force [14,15]. Means and 95% confidence intervals are represented as the squared dot and error bars. The horizontal dotted line is indicating SDB scores > 0.33 , which are considered suggestive of high risk of diagnosis SDB [10,146]. The percentage of children classified as high risk of SDB presence for each category of body mass index is indicated right above the horizontal dotted line. SDB=sleep-disordered breathing.

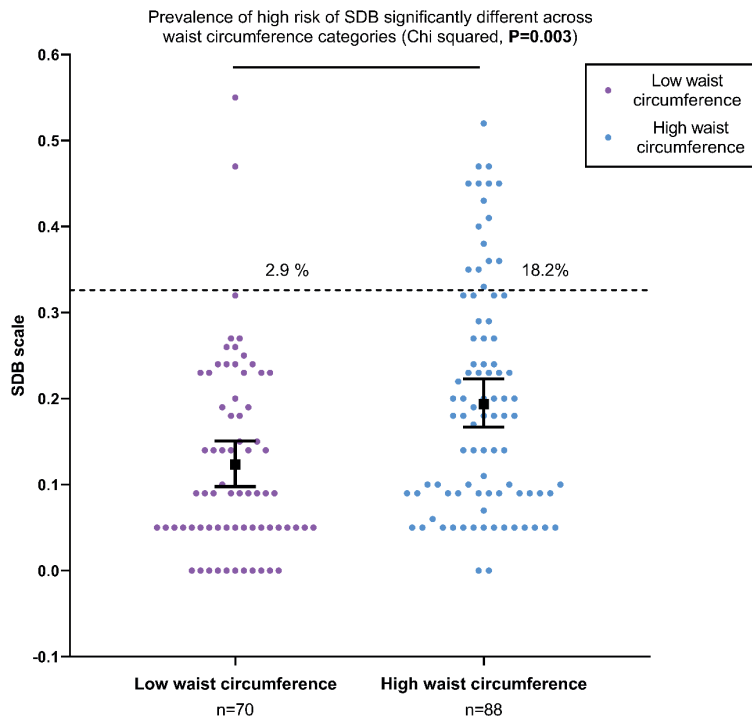


Figure 10. Differences in sleep-disordered breathing (SDB) scale across different waist circumference categories at baseline in children. *ANCOVA model adjusted for sex, peak height velocity, and parental education level, showed a significant difference in the mean SDB scores between the low waist circumference and high waist circumference categories ($P=0.025$). High and low waist circumference was categorized based on sex-specific cut-off points of Jolliffe and Janssen [249]. Means and 95% confidence intervals are represented as the squared dot and error bars. The horizontal dotted line is indicating SDB scores > 0.33 , which are considered suggestive of high risk of diagnosis SDB [10,146]. The percentage of children classified as high risk of SDB presence for each category of waist circumference is indicated right above the horizontal dotted line. SDB=sleep-disordered breathing.

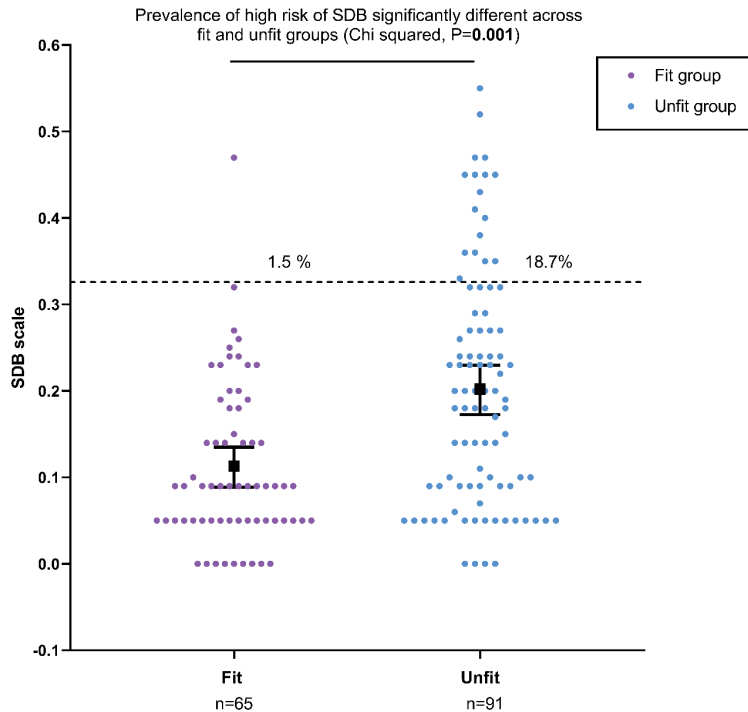


Figure 11. Differences in sleep-disordered breathing (SDB) scale across different cardiorespiratory fitness categories at baseline in children. *ANCOVA model adjusted for sex, peak height velocity, and parental education level, showed a significant difference in the mean SDB scores between fit and unfit categories ($P=0.001$). Fit and unfit cardiorespiratory fitness was categorized based on age- and-sex specific cut-off points of Tomkinson et. al [250]. Means and 95% confidence intervals are represented as the squared dot and error bars. The horizontal dotted line is indicating SDB scores > 0.33 , which are considered suggestive of high risk of diagnosis SDB [10,146]. The percentage of children classified as high risk of SDB presence for each category of cardiorespiratory fitness is indicated right above the horizontal dotted line. SDB=sleep-disordered breathing.

Table 17. Linear regression for associations of changes in total obesity, central obesity and cardiorespiratory fitness with changes in sleep-disordered breathing (SDB) after 1-year follow-up.

		Body mass index changes			Waist circumference changes			Cardiorespiratory fitness changes		
		B (95% CI)	β	P	B (95% CI)	β	P	B (95% CI)	β	P
SDB scale changes	Model 1	0.04 (-0.012 to 0.021)	0.059	0.598	0.001 (-0.004 to 0.007)	0.059	0.597	-0.001 (-0.003 to 0.002)	-0.068	0.541
	Model 2	0.006 (-0.009 to 0.022)	0.084	0.405	0.003 (-0.002 to 0.008)	0.126	0.222	0.000 (0.002 to 0.002)	-0.011	0.915

Changes were calculated by subtracting follow-up minus baseline measurement. Model 1: adjusted by sex, peak height velocity (PHV) and parental education level. Model 2: adjusted by sex, PHV, parental education level and SDB scale at baseline. B= non-standardized coefficients. β = standardized coefficients. CI=Confidence interval

DISCUSSION

The main findings of this study were the following: i) at baseline, we observed that those children with obesity type II-III showed higher SDB severity compared to those children with normal-weight. Likewise, both those children with high WC and those considered unfit showed higher SDB severity compared to low WC and fit children, respectively, and ii) at longitudinal level, no significant association between changes in total obesity, central obesity and fitness and changes in SDB in pediatric population after 1-year follow-up were observed. These results contribute to the existing knowledge by investigating the role of total and central fatness and fitness on pediatric SDB.

Previous literature on the prevalence of pediatric SDB have focused on comparing two combined categories of BMI (e.g., overweight or obesity vs. normal-weight [36,78,143,242], obesity vs. overweight [75]), yet they did not examine how individual total and central obesity categories are related to SDB. Only one study, in agreement with our results found that children with obesity had significantly higher risk of SDB severity (i.e., AHI) than children with normal-weight [243]. However, they also showed a significantly higher SDB severity in children with obesity than in those with overweight [243]. This study further supports the important role of other different levels of total obesity on SDB, showing that those children grouped in the obesity type II-III presented higher SDB severity than those normal weight children. Moreover, it is interesting to highlight the increase on SDB severity as the weight status increase. For instance, although we did not see any significant different between groups, we might highlight that those children with obesity type I presented 16% lower ratio than those peers with obesity type II-III (10.4% vs. 26.5%). It is important to note that this prevalence could depend on the method of measuring SDB (polysomnography vs

questionnaire), the definition of categories of obesity and age of the population. In contrast, other study conducted in children did not find a relationship between obesity and SDB severity [240]. This inconsistency with our results could be explained by i) the wide age range of the participants (aged 3-17 years) in the study of Tamanyan et al. [240], and ii) the fact that they investigated the relation in overall obesity. Given the importance of examining the body fat distribution besides the total obesity in SDB [28], we further investigated how different degrees of central obesity could be related to SDB severity. Our findings are consistent to those observed for total obesity, where those children with high WC presented also higher SDB severity in comparison to those low WC peers. The lack of studies examining the differences across levels of waist circumference on SDB in children hampers to compare our findings with other previous evidence. Lastly, based on the importance on having a good cardiorespiratory fitness level for health in childhood [16,202], we investigated how different levels of cardiorespiratory fitness could be related to SDB severity. Our results depicted that those unfit children presented higher SDB severity than fit children. This is in agreement with previous studies where the authors observed a positive relationship between cardiorespiratory fitness and SDB in children [104,147].

The longitudinal evidence in pediatric population investigating whether changes in obesity predispose to future SDB severity are scarce. In our sample of children, we did not find any significant association in the longitudinal analyses. However, in pediatric longitudinal studies, higher body adiposity [106] or excessive weight gain [239] seemed to predict the development of SDB presence at follow-up (i.e., follow-up period of 2.2 years and 5 years, respectively). Unlike these two studies [106,239], we could not categorize SDB presence at follow-up due to the low sample size in each category. Interestingly, previous studies elucidate that childhood obesity at baseline

predicted in the transition to adolescence the persistence of SDB [238,244]. In regard to central obesity and unlike with our study, Danisi et al. observed that childhood central adiposity (i.e., WC) could predict higher SDB in adolescence (i.e., follow-up) [245]. However, BMI was not a predictor in agreement with our results. Differences could be due to the method of measuring SDB (apnea/hypopnea index using polysomnography vs SDB scale using a questionnaire), as well as wider range age of participants than in our study (i.e., 5–12 years at baseline and 12–23 years at follow-up). Lastly, only in the late adolescence, low cardiorespiratory fitness was found to be a risk factor for sleep apnea later in life [248]. Future studies should be needed to elucidate whether exercise interventions in children could achieve higher cardiorespiratory fitness that would help improve SDB severity in the future. A possible explanation could be that in our study: i) there was not changes in total and central obesity and fitness categories because the follow-up period was relatively small (1 year) and most of children remained in the same group as at baseline; and ii) the total sample size was greatly reduced in longitudinal analyses.

Study limitations should be noted. First, the cross-sectional analyses do not allow to establish causal relationships. Second, obesity was assessed using anthropometry instead of using more accurate methods as Dual energy X-ray absorptiometry. Third, SDB scores were obtained from a parent-reported questionnaire instead of polysomnography. Fourth, approximately 15% of the children from the baseline did not participate in the follow-up, yet no differences in the main outcome (i.e., SDB scale) were observed between dropouts and non-dropouts. At follow-up, relatively low-sample size and low-period of follow-up that could limited the power of the statistical analyses to detect significant differences and could explain the little variability of change in BMI, WC and cardiorespiratory fitness. Although the evaluations of the different projects were conducted in different years,

protocol and instruments of assess used in this study were the same in both projects. On the other hand, strengths of our results include the study of four levels of total obesity. This is a major contribution to the field beyond the investigation of obesity vs. normal-weight categories. Moreover, the use of valid, reliable, and related to health-field based fitness test in children [95–97], and the BMI, WC and fitness categories according to the sex- and age-specific cut-offs points.

CONCLUSION

Our findings suggest that severe/morbid obesity, abdominal obesity and low fitness are linked to higher risk of SDB in children. However, longitudinal analyses did not observe any significant association, which could be due to small variation in the exposures during a relatively short follow-up (1-year). The present study sheds lights on the importance of reducing fatness and promoting fitness through physical exercise, as a strategy to reduce the severity of SDB in childhood. Future randomized controlled trials and longer longitudinal studies that include a sample of children with more severe SDB are needed to contrast or corroborate our results.

SUPPLEMENTARY MATERIAL

Table S1. Intention-to-treat chronic effects of the ActiveBrains physical exercise program on raw and z-score post-exercise (i.e., z-score of change from baseline) sleep-disorders outcomes.

			Mean (95% CI)				
	N _{all}	N	Intervention group	N	Control group	Difference between groups (Intervention minus control)	P
SDB scale							
Raw score	109	57	0.193 (0.167 to 0.220)	52	0.189 (0.162 to 0.217)	0.004 (-0.034 to 0.042)	0.844
z-score			0.045 (-0.158 to 0.247)		0.016 (-0.196 to 0.227)	0.029 (-0.264 to 0.322)	
Total sleep time	109	57		52			
Raw score			437.516 (429.021 to 446.011)		431.294 (422.400 to 440.189)	6.221 (-6.087 to 18.529)	0.319
z-score			-0.665 (-0.906 to -0.424)		-0.841 (-1.094 to -0.589)	0.176 (-0.173 to 0.525)	
Total time in bed	109	57		52			
Raw score			501.652 (491.910 to 511.394)		506.378 (496.176 to 516.580)	-4.726 (-18.874 to 9.422)	0.509
z-score			-0.888 (-1.198 to -0.578)		-0.738 (-1.063 to -0.413)	-0.150 (-0.601 to 0.300)	
Sleep efficiency	109	57		52			
Raw score			83.906 (82.913 to 84.899)		82.843 (81.803 to 83.882)	1.063 (-0.374 to 2.501)	0.145
z-score			-0.167 (-0.375 to 0.040)		-0.390 (-0.607 to -0.172)	0.222 (-0.078 to 0.523)	
WASO time	109	57		52			
Raw score			79.681 (74.502 to 84.860)		84.817 (79.395 to 90.239)	-5.136 (-12.635 to 2.363)	0.177
z-score			0.118 (-0.104 to 0.341)		0.339 (0.106 to 0.572)	-0.221 (-0.543 to 0.102)	

z-score values indicate how many standard deviations have the post-exercise program 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-exercise program is 0.50 standard deviations higher than the mean value at baseline, indicating a positive change, with negative values indicating the opposite. All data presented were adjusted for baseline values. SDB = sleep-disordered breathing; WASO = wake after sleep onset.

Table S2. Descriptive characteristics of the control participants (i.e., excluded the intervention group) that completed the study (i.e., non-drop-outs) and those that did not complete the study (i.e., drop-outs) at baseline

	All (N=101)	Drop-outs (N=14)	Non-drop-outs (N=87)	P
	Mean $\pm$ SD or %	Mean $\pm$ SD or %	Mean $\pm$ SD or %	
Age (years)	10.03 $\pm$ 1.17	10.04 $\pm$ 1.23	10.02 $\pm$ 1.17	0.956
Weight (kg)	44.61 $\pm$ 13.87	50.96 $\pm$ 14.45	43.59 $\pm$ 13.59	0.065
Height (cm)	141.96 $\pm$ 8.91	142.41 $\pm$ 9.05	141.89 $\pm$ 8.94	0.838
BMI (kg/m²)	21.79 $\pm$ 5.26	24.78 $\pm$ 5.36	21.31 $\pm$ 5.12	0.021
BMI categories, n (%) ^a				0.029
Normal-weight	47 (46.5)	4 (28.6)	43 (49.4)	
Overweight	16 (15.8)	2 (14.3)	14 (16.1)	
Obesity type I	26 (25.7)	3 (21.4)	23 (26.4)	
Obesity type II-III	12 (11.9)	5 (35.7)	7 (8.0)	
Waist circumference (cm)	74.73 $\pm$ 16.96	81.95 $\pm$ 17.91	73.57 $\pm$ 16.62	0.086
Waist circumference categories, n (%) ^b				0.023
Low waist circumference	57 (56.4)	4 (28.6)	53 (60.9)	
High waist circumference	44 (43.6)	10 (71.4)	34 (39.1)	
Cardiorespiratory fitness (laps) (N=99)	23.35 $\pm$ 12.53	20.08 $\pm$ 12.54	23.80 $\pm$ 12.54	0.337
Cardiorespiratory fitness categories, n (%) ^c				0.379
Fit	79 (79.8)	5 (41.7)	74 (85.0)	
Unfit	20 (20.2)	7 (58.3)	13 (14.9)	
Sleep-disordered breathing				
SDB scale (range 0 to 1)	0.15 $\pm$ 0.13	0.12 $\pm$ 0.11	0.16 $\pm$ 0.13	0.398
High risk SDB presence, n (%)	11 (10.9)	1 (7.1)	10 (11.5)	0.628
Low risk SDB presence, n (%)	90 (89.1)	13 (92.9)	77 (88.5)	

SD = standard deviation; BMI = Body mass index; SDB= sleep-disordered breathing. ^a BMI categories were based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation, formerly International Obesity Task Force [14,15]. ^b High and low waist circumference was categorized based on sex-specific cut-off points of Jolliffe and Janssen [249]. ^c Fit and unfit cardiorespiratory fitness was categorized based on age- and-sex specific cut-off points of Tomkinson et. al [250]. All variables have the sample size shown in the table, except for cardiorespiratory fitness that has 2 missing data in dropout group compared with Ns reported in the table. Baseline differences between drop-outs and non-drop-outs were determined by one-way analysis of variance (ANOVA) and chi-squared tests for continuous and categorical variables, respectively. Statistically significant values at $P < 0.05$ are shown in bold.

Table S3. Differences in sleep-disordered breathing (SDB) scale across the BMI categories changes at follow-up in children

	Downgraded weight category; N=6 (7%)	Maintained weight category; N=77 (89.5%)	Upgraded weight category; N=3 (3.5%)	Difference between groups	P
Follow-up SDB scale	0.150 (0.048 to 0.251)	0.113 (0.085 to 0.141)	0.243 (0.099 to 0.386)	Upgraded minous downgraded = 0.093	0.299
				Upgraded minous maintained= 0.129	0.083
				Maintained minous downgraded = -0.036	0.494

Adjusted for sex, peak height velocity, and parental education level. BMI categories were based on the sex-and-age specific international body mass index cut-off points proposed by the World Obesity Federation, formerly International Obesity Task Force [14,15].

General discussion

SUMMARY OF THE MAIN FINDINGS

This International Doctoral Thesis has contributed to the existing knowledge with several novel findings in relation to exercise, physical activity, physical health, brain health, and sleep in children with overweight or obesity.

In the **section 1**, our findings complement current evidence, despite the weak link, by confirming the association of television viewing time and body composition indicators (positively) and cardiorespiratory fitness (negatively) with SDB in children with overweight or obesity (**study 1**). Our findings support that BMI and television viewing time are the best predictors of SDB in children with overweight or obesity (around 11% of the variance in SDB), indicating that other factors in addition to the hereby studied contribute to explain the SDB. **Studies 2, 3 and 4** support the idea that SDB severity in children with overweight or obesity is associated with:

- poor academic performance at school, specifically natural and social science grades and grade point average, but not with academic performance assessed by standardized test or brain structure. It seems that inattention/hyperactivity drives these associations between SDB severity and academic performance at school. Thus, this finding shows that SDB severity may worsen school marks in children beyond the effects of weight status alone (**study 2**).
- higher external and internal problems and lower adaptability skills. These relationships might be explained in part by the shared symptom between ADHD and SDB, which may result in overlap between measurement items. Daytime sleepiness can be related to some behavioral and emotional functioning indicators. However, no associations

are observed between device-assessed sleep outcomes and behavioral and emotional functioning(study 3).

- higher CRP independently of the adiposity, but not with cardiometabolic or other inflammatory risk factors. This study points out that higher levels of cardiorespiratory fitness might attenuate the negative effect of SDB severity on CRP (**study 4**).

In **section 2**, the ActiveBrains RCT contributes to the existing literature suggesting that a physical exercise program of 20-week reduces WASO time by around 10 min/day when compared to a control group of children with overweight or obesity. No significant effects are found on the other device-assessed sleep indicators or SDB. Furthermore, although statistical significance is not reached and results should be taken with caution, all device-assessed sleep indicators are enhanced in those days in which the participants attend to the physical exercise session, suggesting therefore acute effects as well as the chronic effects observed (**Study 5**).

At the same time, in the **section 3 (study 6)** findings are based on two different time points levels:

- At baseline levels: those children with obesity type II-III demonstrate higher SDB severity compared to those children with normal-weight. Both those children with high waist circumference and those unfit show higher SDB severity compared with their peers with low waist circumference and fit, respectively.
- At longitudinal level, no significant association of changes in total obesity, central obesity and fitness with changes in SDB in pediatric population after 1-year follow-up is observed.

OVERALL LIMITATIONS AND STRENGTHS

Some **limitations** of the present International Doctoral Thesis need to be acknowledged:

- Five of the studies included in this Thesis have an observational study design, and thus they do not allow for causal inference of any of the associations studied.
- The device-assessed sleep health is based on movement patterns, not purely sleep behavior.
- SDB data were obtained from parental questionnaire instead of the gold standard for detection obstructive sleep apnea prevalence and its severity (polysomnography).
- The relatively low sample size and the mild severity of SDB, may have limited the statistical power of analyses and the detection of some associations that could be present in more severely affected children.
- In the prospective cohort study, the relatively low-sample size (about 15% of the children from baseline did not participate in the follow-up) and low-period of follow-up could limit the power of the statistical analyses to detect significant associations in the longitudinal analyses.

Some **strengths** of the present International Doctoral Thesis need also to be acknowledged:

- The use of an objective, noninvasive and valid measure such as accelerometry to assess sedentary time, moderate to vigorous physical activity and sleep health in free-living conditions.
- The inclusion of a reliable, valid, and related to health field-based fitness test in children.
- Gold-standard measurements were used for the quantification of GMV (MRI),

cardiometabolic and inflammatory risk markers (blood samples) and body composition parameters (DXA).

- The focus on children with overweight or obesity, who have poorer physical and brain health than children with normal-weight, and are particularly vulnerable to sleep-disordered breathing.
- The inclusion of four degrees of overweight or obesity beyond the study of obesity vs. normal-weight categories.
- The fatness and fitness categories according to the sex- and age-specific cut-offs points for children.

FUTURE PERSPECTIVES

- Physical exercise interventions focused on improving modifiable risk factors as sedentary behaviors, cardiorespiratory fitness and most of all body weight status could be a good strategy to improve the SDB severity and its prevalence in childhood.
- Future research, with a normal-weight control group, should further examine the interactions between obesity and SDB severity measured with polysomnography in the association with all brain health dimensions in children.
- Studies in children with higher SDB severity, device-assessed sleep behaviors and proper sample size are warranted to shed light on the relationship with mental health.
- Evidence on the effects of physical exercise programs on sleep in children is still scarce, and further well-designed randomized clinical trials (especially that include children with poor device-assessed sleep health or more severe SDB) are needed to better understand the role of physical exercise on sleep health in this population.

- There is a need for longer and well-powered prospective cohort studies to better understand the role of fitness and fatness in future sleep health and sleep-disordered breathing in the pediatric population.

Conclusions

GENERAL CONCLUSION

The present International Doctoral Thesis sheds light on the importance of improving sleep-related outcomes in children as a strategy to enhance physical and brain health. The use of physical exercise as a tool to improve children's sleep health and sleep-disordered breathing, especially in those with overweight or obesity, is presented.

SPECIFIC CONCLUSIONS

Section 1. Cross-sectional studies: physical and brain health in relation to sleep-related outcomes in children with overweight or obesity.

- **Study 1:** Higher body mass index and unhealthy behaviors such as high television viewing time are linked to worsen SDB in children with overweight or obesity.
- **Study 2:** Driven by children's inattention or hyperactivity, SDB severity is related to lower school grades in children with overweight or obesity, independently of BMI.
- **Study 3:** SDB severity is related to worse behavioral and emotional functioning (i.e., higher external and internal problems and lower adaptability skills) in children with overweight or obesity. Specifically, a potential SDB symptom such as daytime sleepiness can be linked to higher attention problems, anxiety, depression and retreat, and lower adaptability.
- **Study 4:** Independently of children's adiposity levels, SDB severity is linked with higher C-reactive protein levels, but not with other inflammatory or cardiometabolic risk factors. Furthermore, higher cardiorespiratory fitness seems to attenuate the association of SDB on

systematic inflammation in children with overweight or obesity.

Section 2. Randomized clinical trial: Effects of a physical exercise program on sleep-related outcomes in children with overweight or obesity.

- 20-weeks of exercise (aerobic plus resistance) improve quality of sleep in children with overweight or obesity, specifically by lowering the time the children are awake during the night after sleep onset. Although statistical significance is not reached, all device-assessed sleep outcomes are enhanced in those days in which children attended to the physical exercise sessions. However, no effects are found on SDB.

Section 3. Prospective cohort study: Association of fatness and fitness on sleep-disordered breathing after 1-year in children.

- At cross-sectional level, severe/morbid obesity, central obesity and low cardiorespiratory fitness are all related to higher risk of SDB in children. However, longitudinal analyses did not show significant associations of fatness and cardiorespiratory fitness with SDB severity changes in pediatric population, which can be due to small variation in the exposures during 1-year follow-up.

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