Does the combination of obesity and obstructive sleep apnea place children at greater risk of executive function impairment?

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Abstract

Paediatric obstructive sleep apnoea (OSA) affects 1.2% to 5.7% of children. It is characterised by upper airway collapse during sleep, resulting in oxygen desaturation, and sleep fragmentation leading to cognitive impairment. There is evidence in the literature to suggest that OSA in children can lead to a deficit in executive function (EF), and recent evidence suggests this effect might be intensified in children who are also overweight. Obesity is considered to be an independent risk factor for OSA in children, and preceding evidence suggests that obesity itself is an independent contributor to cognitive impairment. However, the moderating influences of body mass index (BMI) on EF has not yet been fully elucidated in children with OSA. Given the increasing prevalence of obesity in children, an objective understanding of the impact of body mass on EF in children with OSA is necessary. This was a retrospective case study involving 176 children (7 to 9 years of age) who were evaluated for OSA using polysomnography between January 2008 and September 2011. Participants were stratified into four groups: treated/normal-weight (n = 27, BMI < 85th percentile), treated/overweight (n = 58, BMI > = 85th percentile), untreated/normal-weight (n = 36, BMI < 85th percentile) and untreated/overweight (n = 55, BMI > = 85th percentile). The children also underwent neurocognitive assessment (BRIEF & NEPSY) which was administered at baseline and re-administered after 7 months, and after treatment by adenotonsillectomy in the treatment groups. Scores for measures of EF were compared across groups to determine the relative contribution of body mass to executive function in children with OSA. Results revealed that BMI was a predictor of EF outcome in the BRIEF subtest Organisation of Materials only. Furthermore, no association was found between Organisation of Materials and OSA severity of OAHI, AI, ODI and minimum oxygen saturation.

Keywords: obstructive sleep apnea, obesity, executive function, BMI

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

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Contribution Statement

In writing this thesis, my supervisor and I collaborated to get an understanding of the CHAT data set, and workout the study design and analyses. I conducted the literature review, and thesis write-up.

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Introduction

1.1. Paediatric obstructive sleep apnoea (OSA)

Obstructive sleep apnoea syndrome (OSAS) was first described as a clinical entity in children in 1976 (Guilleminault et al; 1976). It has since been identified as a common and highly prevalent disorder in children with potentially serious clinical consequences, and has unfolded as a major public health issue (Tauman and Gozal, 2011). If left untreated, obstructive sleep apnoea (OSA) can result in serious morbid consequences that affect neurocognitive and behavioural outcomes (Beebe and Gozal, 2002). The prototypical syndrome of OSA in children differs from that which is seen in adults, particularly relating to clinical symptoms, diagnostic criteria, polysomnographic findings, and treatment approaches (Dayat et al; 2007). However, increases in body mass index (BMI) and in the prevalence of obesity in children has resulted in the development of a phenotypic alternative of OSA in children that bears a resemblance to that of adults with OSA (Dayyat et al; 2007).

OSA is characterised by intermittent upper airway (UA) obstruction during sleep, resulting in recurrent partial (hypopnea) or complete (apnea) reductions in airflow (Guilleminault et al; 1976; Marcus et al; 2012, Olaithe et al; 2017). The main consequence of these recurrent apneas and hypopneas is intermittent blood gas abnormalities (hypoxemia and hypercapnia), and sleep fragmentation (Beebe and Gozal, 2002; Olaithe et al; 2017; Sforza and Roche 2016). Intermittent blood gas abnormalities have a detrimental effect on the characteristics of sleep architecture which results in less restorative sleep. For example, in OSA, sleep architecture is constantly disrupted by recurring transient awakenings or microarousals which modifies sleep depth and quality. This triggers a range of cellular and biochemical damage, leading to oxidative stress and inflammation which affects the integrity of neuronal and glial cells within specific brain regions (Martin et al; 1997; Smurra et al; 2001; Beebe and Gozal, 2002; Lavie, 2003).

Depending on the developmental stages of children there are various nocturnal and daytime symptoms linked with OSA. Table 1 gives a comprehensive list of symptoms and signs of paediatric OSA by age (Guilleminault et al; 2005; Chang and Chae, 2010). Additionally, some studies have identified neuropsychological consequences, including diminished memory and concentration, learning problems and poor decision making (Kaemingk et al; 2003; Kennedy et al; 2004; Beebe, 2006; Mulvaney et al; 2006).

Table 1

Common symptoms and signs of childhood OSA by age

Infants 3-12 months	Toddlers, 1-3 years	Preschool-aged children	School-aged children
Interrupted nocturnal sleep/repetitive crying	Noisy breathing or snoring	Regular heavy snoring	Restless sleep
Noisy breathing	Nocturnal sweating	Sleep walking	Sleep talking
Poor suck	Mouth breathing	Night terrors	Morning headache
Failure to thrive	Night terrors	Enuresis	Difficulty to wake-
Delayed development	Poor eating	Hyperactivity	Emotional Instability
	Poor growth	Growth problems	Learning difficulties
		Poor eating	Excessive daytime sleepiness
			Aggressiveness
			Obesity

1.1.1. Diagnosis of OSA

A diagnosis of OSA in children may be suspected based on parental reports about their children's sleep, clinical questionnaires, physical examination findings (including tonsil and adenoid size), and risk factors. However, these factors are not sufficient to precisely discriminate between habitual snoring and OSA, or predict its severity (Carroll et al; 1995; Nolan et al; 2011; Mitchell et al; 2015). Further diagnostic testing such as audio-visual taping, overnight pulse oximetry, or nocturnal, laboratory-based polysomnography (PSG) is recommended by the American Academy of Paediatrics (AAP). PSG is considered to be the

only gold standard diagnostic test for OSA in children (AAP, 2002; Marcus et al; 2002 & 2012; Guilleminault, 2005).

1.1.2. Epidemiology of OSA

The prevalence of OSA in children has two distinct phases. The first phase occurs in children between two and eight years of age, coinciding with the peak age of adenotonsillar hypertrophy (AH), and the second phase occurs during adolescence in association with weight gain (Arens et al; 2001; Jung et al; 2010). Depending on the population studied, techniques used to measure breathing during sleep, and the diagnostic criteria used, the prevalence rates of OSA in children varies. For example, ten studies between 2001 and 2010 found a prevalence rate of OSA in the general paediatric population of 0% to 5.7% (Marcus et al; 2012). However, only three of those studies had large sample sizes where they reported a prevalence of OSA between 1.2% and 5.7% (O'Brien et al; 2003; Bixler et al; 2009; Li et al; 2010).

Several studies indicate higher rates of OSA amongst certain subgroups, such as African American children and children from lower socio-economic backgrounds (Lumeng and Chervin, 2008; Redline et al; 2011; Marcus et al; 2012). While some studies have demonstrated an equal prevalence of OSA in children between boys and girls (Redline et al; 1999; Sogut et al; 2005; Vitelli et al; 2014; Wing et al; 2003), a literature review by Lumeng and Chervin (2008) concluded that the prevalence of OSA does differ by sex, with boys being burdened at rates that are 50 to 100% higher than those for girls. Other studies demonstrated that adolescent boys are more affected by OSA than girls (Goodwin et al; 2003; Li et al; 2010), implying that gender effects may be attributed to sex hormones. Interestingly, the production of testosterone in adolescent boys has been shown to intensify upper-airway (UA) collapsibility and respiratory disturbance index (Cistulli et al; 1994; Carden & Malhotra,

2003). Contrastingly, the production of oestrogen and progesterone in girls are thought to be protective against UA collapse (Wilhoit & Suratt, 1987; Cistulli et al; 1994).

1.1.3. Pathophysiology of childhood OSA

Children with OSA tend to have a narrow upper airway (UA) caused by both anatomic and physiologic factors (Bodenner et al; 2014). Adenotonsillar hypertrophy is a major contributor to UA narrowing in children, and is deemed to be the main risk factor for OSA in pre-pubertal children (Arens et al; 2004). Narrowing of the UA and its potential subsequent collapsibility causes a decrease in respiratory control and weakens the muscles supporting the UA (Pierce et al; 2007). Diverse techniques such as cephalometrics, lateral neck radiographs and magnetic resonance imaging (MRI) have demonstrated that the UA of children with OSA is narrower on average than that of a child without OSA (Kulnis et al; 2000; Arens et al; 2001; Gozal et al; 2004). Obesity also contributes to UA narrowing, and is considered an independent risk factor for OSA in children (Kohler et al; 2008; Kang et al; 2012).

Evidence also suggests that viral respiratory infections during early life, may activate an immunomodulatory reaction within the UA of lymphoid tissue of children with OSA (Goldbart et al; 2007). Furthermore, laboratory studies have shown substantial increases in inflammatory cell proliferation and production of pro-inflammatory cytokines and inflammatory mediators, such as tumour necrosis factor alpha (TNFα), interleukin-6 and interleukin-1 alpha (IL-6, IL-1α) in adenotonsillar tissue taken from children with OSA, in comparison to adenotonsillar tissue taken from children who had been treated for recurring tonsillitis (Serpero et al; 2009; Dayyat et al; 2009; Kim et al; 2009). Moreover, treatment studies have shown anti-inflammatory agents to be effective in treating OSA under these conditions (Brouillette et al; 2001; Kheirandish et al; 2006). In obese children, adipokines

such as TNFα, IL-6 and leptin are also substantially elevated, and their somnogenic activity can lead to a reduction in central nervous system (CNS) activity and UA neuromuscular control. Consequently, this may increase the severity of OSA and subsequently trigger further pro-inflammatory cytokines, generating an endless loop (Churchill et al; 2008).

1.2. Obesity as a risk factor for OSA

A literature review by Tauman and Gozal, 2006 established that childhood obesity is clearly correlated with increased risk for development of OSA, and suggested that the large difference in the prevalence rates amongst different studies is due to such factors as, ethnicity and different diagnostic criteria for OSA and obesity. Up until recent years, the prevailing viewpoint was that anatomic as opposed to metabolic factors were central in the development of OSA in children. However, with the increasing prevalence of obesity in childhood (in girls from 0.7% in 1975 to 5.6% in 2016, and 0.9% to 7.8% in boys), the incidence of OSA in children is significantly increased (Anderson et al; 2016; Di Cesare et al; 2019). For example, the prevalence of OSA in the general paediatric population is estimated to be 1-6% (Marcus et al; 2012), whereas in children and adolescents who are overweight/obese, OSA is reported to occur in 19-61% (Verhulst et al; 2007). Consequently, the archetypal presentation of children with OSA having adenotonsillar hypertrophy and being underweight, is being overshadowed by an increasing percentage of children with OSA who are overweight or obese (Gozal et al; 2006).

Redline et al; 1999 demonstrated that the risk of OSA was increased four to five-fold in obese children. Indeed, for every increase in body mass index (BMI) above the mean in children, the risk of OSA was increased by 12%. Kohler et al; 2009 showed that for each standard-deviation increase in BMI z-score, the risk of OSA in adolescents (>12 years) was amplified 3.5-fold. Additionally, obesity combined with adenotonsillar hypertrophy places

children at even greater risk of OSA (Silvestri et al; 1993; Xu et al; 2008). This phenotypic alternative of OSA in children is very similar to what we see in adults with OSA (Dayyat et al; 2007). In fact, the proportion of obese children who have remaining OSA post-adenotonsillectomy is substantially greater than in non-obese children (Bhattacharjee et al; 2010).

1.2.1. Prevalence and association of obesity with OSA

There is sufficient evidence to indicate that OSA associated with obesity is highly prevalent in children and adolescents (Narang and Mathew, 2012). Verhulst et al. (2007) established that the prevalence of OSA by polysomnography in obese children and adolescents can be as high as 59%. Other studies have also demonstrated a high prevalence of OSA amongst obese children and adolescents, as well as a higher percentage of OSA in children who are obese (Silvestri et al; 1993; Marcus et al; 1996; Verhulst et al; 2008). This suggests that the association between obesity and OSA is reciprocal, with obesity influencing OSA and the consequences of OSA subscribing to obesity. Interestingly, data from The Tucson Children's Assessment of Sleep Apnoea Study (TuCASA) revealed that children with sustained OSA after five years are at an increased risk of becoming obese (Goodwin et al; 2010). Further, it has been demonstrated that the severity of OSA is proportionate to the level of obesity (Mallory et al; 1989; Redline et al; 1999; Sogut et al; 2005). It has also been proposed that children who have better quality sleep have lower BMIs and lower rates of obesity five years later (Snell et al; 2007).

1.2.2. Mechanisms for increased risk of OSA in obese children

Several factors combine to increase the risk of OSA amongst obese children, and these may act synergistically. Comparable to non-obese children, airway obstruction due to adenotonsillar hypertrophy is a frequent cause of OSA in obese children. In fact, 45% of

obese children have airway obstruction due to adenotonsillar hypertrophy (Narang and Mathew, 2012). However, following adenotonsillectomy, OSA is sustained in up to around 50% of obese children contrasting with 10-20% in non-obese children (Mitchell and Kelly, 2004; Tan et al; 2013; Slaats et al; 2015). This suggests that adenotonsillar hypertrophy is not necessarily as influential in the development of OSA in obese children (Shine et al; 2005; Verhulst et al; 2008; Dayyat et al; 2009).

Obese children tend to have surplus build-up of adipose tissue around the pharynx and neck (Schwab et al; 2003; Schwartz et al; 2010; Tan et al; 2017). This obesity linked change results in alterations to neuromuscular tone leading to increased UA collapsibility during sleep (Schwab et al; 2003; Schwartz et al; 2010). In fact, evidence shows that obese children, even with mild negative inspiratory pressure have a positive critical closing pressure (Pcrit) of the pharynx, predisposing the airway to collapse during sleep (Marcus et al; 1994; Marcus et al; 2006). Additionally, there is also evidence to indicate that central obesity in particular may have adverse effects on neuromuscular activity in the upper airway (Schwartz et al; 2008). Adipose build-up around the thorax and abdomen regions places excess mechanical load on the chest wall and reduces the functional residual capacity (FRC) of the lungs and tidal volumes. Subsequently, pharyngeal collapsibility may be further aggravated by this reduction in functional residual capacity with subsequent decrease in caudal traction on UA structures, further increasing the risk of pharyngeal collapse during sleep.

1.3 Neurocognitive consequences of OSA

Neurocognitive impairments, behavioural and academic problems are among the most common morbidities associated with OSA in children (Chervin et al; 2003; Gottlieb et al; 2003). The renowned paper by Gozal in 1998 was the first to emphasise the possible causal associations between OSA and its adverse consequences on academic performance. His study

involved 297 first-grade children whose school performance was in the lowest 10th percentile of their class, and demonstrated a noticeable increase in the frequency of OSA. Moreover, following subsequent treatment for OSA, the children showed substantial improvements in their school grades, whereas the grades for the untreated children failed to improve. Since then, there have been several studies looking at the association between OSA and neurocognitive performance (Friedman et al; 2003; Kaemingk et al; 2003; Chevrin et al; 2006; Gozal & Kheirandish-Gozal, 2007; Kohler et al; 2009; Owens, 2009). Interestingly, not all of these studies have shown a direct correlation between OSA severity and cognitive impairments (Owens, 2009; Gozal and Kheirandish-Gozal, 2007), or improvement in neurocognitive performance post treatment (Kohler et al; 2009). Furthermore, it has become clear that not all children with OSA demonstrate cognitive impairments. This suggests that individual genetic susceptibility and environmental (e.g. obesity) factors may play a part in making some children more vulnerable to the neurocognitive consequences of OSA (Gozal et al; 2007; Kheirandish-Gozal and Gozal, 2013).

1.3.1. OSA and its impact on Executive Function

Executive function (EF) is a broad term that refers to a set of top-down mental processes required in managing emotion, behaviour, problem solving, and planning future goals and outcomes (Bickel et al; 2012). There are numerous brain regions involved in EF, such as the dorsolateral Prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), and the medial prefrontal cortex (MPFC), and each of these regions have considerable functional connections with sub-cortical regions and the brainstem (Miller et al; 2015). EF skills are essential for success in many areas of life, and a healthy EF system is vital in order for children to realise their full cognitive potential. Core EF skills include working memory, problem solving, shifting, inhibitory control, cognitive flexibility,

and planning (Miller et al; 2014). These processes are highly interconnected, and the successful application of EF skills requires them to act in unison (Diamond, 2013).

In children, EF skills develop during critical periods correlating with neuronal myelination and maturation of the prefrontal cortex (Welch et al; 1991). It has been suggested that executive domains have different developmental trajectories during childhood (Anderson, 2002). They initially develop during the formative years, and continue developing through adolescence and young adulthood (Best et al; 2009; Reinert et al; 2013). As mentioned earlier, OSA can cause structural neuron damage and dysfunction in the central nervous system (Beebe et al; 2002), this can disrupt brain architecture and impair the development of EF. For example, Halbower et al. (2006) demonstrated that children (6-16 years) with severe OSA had impairments in EF, and likely associated neuronal injury in the hippocampus and frontal cortex. An impaired EF system hinders the capacity to integrate all aspects of cognition to the full potential. As such, if OSA is not treated and causes executive impairment in developing children, and if these skills are indelibly damaged before maturation of the PFC, it could adversely hinder their cognitive potential, eventually affecting both their health and how they interact in society (Halbower et al; 2006).

1.3.2. OSA and prefrontal cortex dysfunction

Because frontal lobes have abundant connections to other cortical areas, frontal impairment will increasingly affect other brain regions, generating further cognitive impairment (Beebe and Gozal, 2002). Electrophysiological and blood flow techniques have demonstrated that the PFC is critical for integrative behaviour (Knight et al; 1999), and it has been suggested that the PFC sub-serves EF by modulating activity in posterior cortical and subcortical brain structures that are biologically susceptible to sleep loss and sleep fragmentation (Thomas et al; 2000; Aron, 2008).

The prevailing viewpoint asserts that neurocognitive deficits seen in OSA are due to the deleterious effects of sleep fragmentation and/or intermittent hypoxia and hypercapnia, causing malfunction in neural networks, particularly in the frontal lobes (Beebe and Gozal, 2002). Consistent with this view, a meta-analysis by Beebe et al; 2003 reported that extensive hypoxia in the brain may impact several cognitive functions with potentially considerable deterioration in EF. A theoretical model by Beebe and Gozal, 2002 was presented to explain impairments on EF as observed in OSA. They proposed the prefrontal cortex (PFC) as a connection between sleep disturbances experienced in OSA and cognitive dysfunction. Particularly, they postulated that hypoxemia and continuous awakening can interfere with the restorative processes in the PFC, leading to a disruption of cellular or chemical homeostasis. Consequently, this can lead to impairment of the cognitive executive system, resulting in maladaptive daytime behaviours (Beebe and Gozal, 2002).

1.4. Obesity and its impact on Executive Function

Obesity tends to emerge during early childhood when there is rapid neural development (Miller et al; 2015). Consequently, children are vulnerable to the repercussions of obesity-related biology during developmentally critical or sensitive periods when their capacity for behavioural self-regulation and corresponding neural circuitry are maturing and beginning to form long term cognitive outcomes (Reinart et al; 2013). Although the precise rationale for the relationship between obesity and EF in children has not yet been fully elucidated, there is sufficient evidence to indicate obesity is linked with deficiencies in EF and related cognitive skills in children and adolescents (Smith et al; 2011; Reinert et al; 2013; Liang et al; 2014; Yang et al; 2017). According to Holcke et al. (2008), children who are obese have a twofold increase in executive impairment compared to the normal population. Neuroimaging studies indicate that the PFC and its integration with EF may be the last region

of the brain to mature (Casey et al., 2000; Best et al; 2009). As such, EF is particularly susceptible to a stressor such as obesity during childhood.

The directionality of the relationship between EF deficits and obesity is equivocal. It is possible that impairments on EF happen prior to obesity, or conversely, it might be that obesity develops prior to EF impairment (Miller et al; 2014). Deficits in EF might make children and adolescents more susceptible to obesity. For instance, without the necessary inhibitory processes to assist in decision-making, children and adolescents are especially vulnerable to making poor health behaviour choices (Somerville et al., 2010). A review by Reinart et al. (2013) showed that impaired EF is correlated with obesity-related behaviours, such as increased food consumption, uncurbed eating, and reduced physical activity. In contrast to normal weight children, obese children demonstrate increased difficulty with delay of gratification and inhibition for food incentives (Bonato and Boland 1983).

1.4.1. Possible mechanisms linking obesity to EF

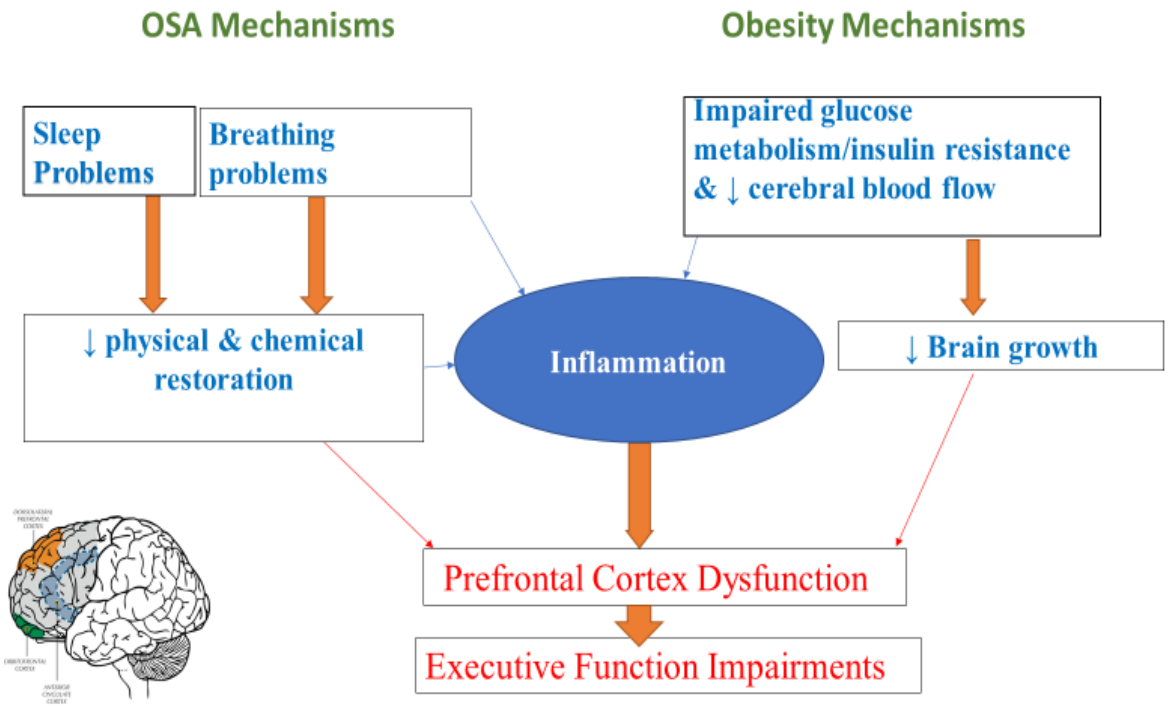
Obesity is linked to several pathophysiological changes which are capable of having a detrimental effect on EF in children, including inflammation, which may be a cause and a consequence of obesity (Miller & Spencer, 2014). As mentioned previously, adipokines such as TNFα, IL-6 and leptin are chronically activated with obesity, as well as decreasing the production of adiponectin, which has an entirely anti-inflammatory function (Ong et al; 2012; Mohammed et al; 2017). Obesity activated inflammation can directly hinder synaptic transmission in the hippocampus (Erion et al; 2014). This can damage hippocampus delayed memory (Harrison et al; 2014), which is key for recalling personal goals and action plans that are essential for self-regulation. Consequently, inflammation is potentially acting on the developing brain, promoting alterations which have the potential to adversely influence EF skills (Shields et al; 2017).

1.5. An interaction between OSA and Obesity on EF

Altogether, the findings described above highlight the fact that OSA, obesity and EF outcomes are all interdependent (Figure 1). It is possible that OSA may affect obesity and cause damage in EF, while obesity may affect OSA and cause comparable EF damage, or EF impairment may exacerbate obesity and consequently promote OSA (Spruyt and Gozal, 2012). The biological effects of obesity and sleep disturbances associated with OSA can potentially impact EF separately in children with either obesity or OSA (Miller et al; 2015). However, it is likely that the combination of obesity and OSA will exacerbate this impairment in EF (Watach et al; 2019). For instance, obesity is a considerable risk factor in the pathogenesis of OSA, however, OSA in itself feeds back into an intricate system that induces either the development or augmentation of obesity (Ong et al; 2013). Furthermore, research has shown higher levels of oxidative stress and inflammation in obese children with OSA (Tauman et al; 2007; Verhulst et al; 2007).

Figure 1

Combination of obesity and OSA leading to EF impairment adapted from Watach et al. (2019)



Despite awareness of these two conditions (obesity and OSA) separately impairing EF, little is known about their combined effects. Inflammatory cascades appear to be a common pathway linking both OSA and obesity with impaired EF. Because children's brains undergo rapid development during the early years and continue to develop throughout adolescence and young adulthood (Reinert et al; 2013), it is crucial to evaluate the impact of obesity on EF in children with OSA during this critical period of development, especially during the development of EF. Moreover, the increasing prevalence of obesity in children further substantiates this need. The main aim of the current study was to gain an objective understanding of the impact of obesity on EF in children with OSA. We compared EF performance of both overweight and normal weight children pre adenotonsillectomy at

baseline with follow-up performance post adenotonsillectomy after 7 months. Additionally, we looked at EF performance of both overweight and normal weight children in a non-treatment group. We hypothesised that: (1) Overweight/obesity in children with OSA would have a negative influence on EF, and (2) Treated groups would show improved EF scores post-treatment.

Methods

2.1 Participants

This was a retrospective study with data obtained from The Childhood Adenotonsillectomy Trial (CHAT). Details of the CHAT study design have previously been presented (Marcus et al; 2013; Redline et al; 2011). CHAT was a randomised controlled trial designed to evaluate neuropsychological and health outcomes in children with OSA who were assigned to either early adenotonsillectomy or a strategy of watchful waiting with supportive care. Between January 2008 and September 2011, children with symptoms of OSA were recruited from sleep programmes, otolaryngology, and sleep clinics, at six academic sleep centres in the USA. 1,447 children were screened for OSA using overnight, laboratory-based polysomnography (PSG). Ultimately there were 464 children included in the study. Physiological measures of sleep, cognitive testing and other clinical laboratory assessments were taken at baseline and re-administered after seven months (post adenotonsillectomy). Eligible children were five to nine years of age, had OSA without prolonged desaturation, defined as an AHI between 2-30 per hour of sleep, or an OAI between 1-20 per hour of sleep, and time with arterial oxygen saturation (SpO2) < 90% that was < 2% of total sleep time, and were deemed suitable for adenotonsillectomy. BMI z score was calculated in kilograms per square metre and then converted to a sex and age specific BMI percentile value as per the Centre of Disease Control (Marcus et al; 1992). Exclusion criteria included children with very severe PSG findings (AHI score > 30 events per hour of sleep, OAI score >20 events per hour of sleep), recurring tonsillitis, a BMI z score $\geqslant$ 3 (i.e. extreme obesity), craniofacial anomalies, including cleft lip and palate, intellectual disability as defined by the Differential Ability Scales (DAS) score < 55 at baseline assessment (Elliott, 1990), or if the child was taking psychotropic medication. The AHI and OAI thresholds were

established based on published normative paediatric data (Marcus et al; 1992). Categorising of ethnicity was obtained by parent/caregiver report, using the NIH categorisation method (Redline et al; 2011).

Approval for the study was obtained from the review board at each participating centre, and it was supported by a Data Coordination Centre (University of Pennsylvania, Philadelphia, PA), and the CHAT Data and Safety Monitoring Board (DSMB). Parents or guardians gave written consent, and approval was obtained from children who were ⩾ 7 years old. The current study involved 176 children, aged 7 to 9 years (M = 7.85 ± 0.8). Females = 105 (59.7%), Males = 71 (40.3%). Approval for data use was obtained from the National Sleep Research Resource (NSRR), and subsequent approval by the research team was obtained from the University of South Australia Human Research Ethics Committee.

As per the CHAT study, all participants had mild to moderate OSA (Apnea Hypopnea Index ⩾ 2 per hour, or an Obstructive Apnea Index (OAI) ⩾ 1 per hour, as confirmed by nocturnal, laboratory-based PSG). We excluded any children who were underweight (weight < 5th percentile), and narrowed the age range between 7 to 9 years. Our rationale for narrowing the age range was based on the fact that the frontal lobe in children undergoes a second growth spurt between the age of 7 and 9 years (Anderson, 2002), with the first growth spurt occurring from birth to 5 years of age. Additionally, children's ability to cope with multi-dimensional switching tasks substantially improves between 7 and 9 years of age, and their planning and organisational skills evolve quickly between the ages of 7 and 10 years of age (Anderson, 2002). EEG data also indicates that information processing, cognitive flexibility, and goal setting undergo a critical period of development between 7 and 9 years of age, in line with the second growth spurt in the frontal lobe (Hudspeth and Pribram, 1990).

2.2 Materials

Neuropsychological assessment utilised in the current study was the Developmental Neuropsychological Assessment (NEPSY 1 & 2) (Korkman et al; 1998; 2007). The NEPSY assessment is grounded in developmental and neuropsychological theory and practice, and has well-established psychometric properties (Korkman et al; 1998). It looks at assessment of neuropsychological development in toddlers through early adolescence, and assesses the development of neuropsychological functions in five functional domains: Attention/Executive Functions, language, Sensorimotor Functions, Visuospatial Processing, and Memory and Learning. These domains are comprised of 32 subtests and four delayed tasks (Korkman et al; 1998). The general assessment takes 45 minutes to administer to pre-school-age, and one hour for school-age, while the full assessment takes 90 minutes for pre-school age, and 2.5 – 3.5 hours for school-age (Miller, 2013). The standard scores are generated ranging from 50 to 150, with 100 representing the population mean and higher scores indicating better functioning (Korkman et al; 1998). The NEPSY 2 does not use standard scores, but instead utilises scaled scores. They are often combined to form standard scores, and the average range for a scaled score is between 8 and 10. Around 50% of children will fall within this range (Miller, 2013). Subtest scores are used to determine strengths and weaknesses of specific cognitive abilities. In this study we evaluated the sub-components of Attention/Executive Functions, including: Tower Test, Inhibition–Inhibition, Inhibition Naming, and Inhibition Switching, and Auditory Attention and Response Set. These sub-components assessed planning, monitoring, self-regulation, and problem solving, the speed, fluency, and efficiency of processing facilitators/inhibitors: performance fluency and accuracy, cognitive flexibility (set-shifting): verbal and visual set-shifting, selective/focused attention, and sustained attention. All of the subtests have good to excellent reliability (r =

0.77 to 0.91) (Ahmad et al; 2001). Moreover, it is strongly correlated with measures of IQ such as the Differential Ability Scales (DAS) (Ahmad et al; 2001).

Neurobehavioural assessments included parent/caregiver and teacher ratings of executive functioning on the Behaviour Rating Inventory Executive Function (BRIEF) (Gioia et al; 2000). The BRIEF is an 86-item questionnaire which assesses EF and behaviour on the basis of children's performance in activities of daily living, with separate forms for parents/caregivers and teachers. For our study we only looked at the parent/caregiver ratings. It takes 10 to 15 minutes to administer and 15 to 20 minutes to score. Parent/caregiver-rated scores range from 28 to 101, and teacher-rated scores range from 37 to 131, with higher scores indicating worse functioning (Gioia et al; 2000). T-scores are used to interpret the child's level of executive functioning as reported by parents and/or teachers on the BRIEF rating forms. It consists of three summary measures: The Behavioural Regulation Index (BRI), Metacognition Index (MI) and Global Executive Composite (GEC) scales (Gioia et al; 2000). The BRI assesses emotional control, shifting (being able to move freely from one activity/situation to another; to alternate attention; to endure change), and inhibition (ability to control impulses and to cease engaging in a particular behaviour). MI demonstrates the child's capacity to initiate activities and generate ideas, as well as monitor their work and assess their performance, with the capacity to keep track of performance. It also assesses working memory (ability to hold information when performing a task or generating goals), and organisation of materials (orderliness of work, play, and storage spaces). Jointly, they produce the GEC index, which is a summary score of the child's overall performance. The mean GEC score is 50, with scores $\geqslant$ 60 considered clinically significant (Gioia et al; 2015). The BRIEF has demonstrated good reliability, with high test-retest reliability (r = .88 for teachers, .82 for parents/caregivers) internal consistency (Cronbach's alphas = .80 to .98), and moderate correlations between parent and teacher ratings (r = .32 to .34) (Gioia et al; 2000).

The Differential Ability Scales (DAS) is a battery of cognitive tests designed to evaluate reasoning and conceptual ability, and general cognitive ability (GCA) in children aged 2 to 17 years (Elliott, 1990). In this study we utilised the DAS GCA core subtest T-scores as a measure to control for the influence of general cognitive ability. The T-score average = 50, with 40 to 60 usually considered the average range (Elliott, 2007). The DAS GCA has excellent reliability, with an average internal consistency reliability coefficient of .95 for school-age level (Elliott, 1990).

2.3 Polysomnography

All the PSG equipment was CHAT certified and central scoring for PSG was done at the Brigham and Women's Sleep Reading Centre to ensure consistency. Available laboratory apparatus was used and boosted by interface to a Nonin model 3012 or other comparable on-board oximeter, and a Novametrix Capnogard model 1265 ETCO2 Monitor. A capnograph by other manufacturers (i.e. BCI) was allowed for the initial eligibility PSG. All technicians who performed PSGs were trained and certified on the CHAT montage in accordance with a standardised protocol, using comparable sensors, and following American Academy of Sleep Medicine (AASM). Additionally, the technicians were blinded to all other study data, and calculated the scores in compliance with the AASM paediatric criteria. The PSG range used to assess OSA severity were the AHI and oxygen desaturation index (the number of times per hour of sleep that the blood oxygen level drops by 3% or more from baseline). The AHI depicts both sleep fragmentation and hypoxemia, while the ODI evaluates intermittent hypoxemia. The AHI was specified as the total amount of obstructive and mixed apneas, plus hypopneas linked with a 50% decrease in airflow, and a $\geqslant$ 3% desaturation or electroencephalographic arousal, divided by the total sleep hours. The obstructive apnea index (OAI) was specified as all obstructive apneas per hours of sleep, and the oxygen desaturation index (ODI) specified as the amount of oxyhemoglobin desaturations $\geqslant$ 3% per

hour of sleep. In the CHAT study, the inter-scorer reliability, as determined by the intra-class correlation coefficient was 0.98 for the AHI, and for other PSG variables it varied between 0.75 to 0.99 (Marcus et al; 2013). The specific aspects of sleep assessed in our study were: obstructive apnea hypopnea index (OAHI) (including all desaturations), all arousal index (AI), ODI > 3%, and minimum oxygen saturation for total sleep time. Our rationale for using these particular measures of sleep was due to the prevailing viewpoint which suggests that detrimental effects of sleep fragmentation and/or intermittent hypoxia and hypercapnia, cause dysfunction in neural networks, particularly in the frontal lobes, potentially leading to EF impairment (Beebe and Gozal, 2002; Smurra et al; 2001; Sforza and Roche, 2016).

2.4 Procedures

Demographics included in the current study were age, gender, race, BMI, waist-hip ratio, mother's and father's education, with scoring from 1 to 8 (1 being 8th grade or less and 8 being a professional degree). BMI z-scores were calculated in accordance with standardised formulas established by the Centres for Disease Control and Prevention (Marcus et al; 2013). Overweight was defined as BMI $\geqslant$ 85th percentile for a child's age and gender. Participants were stratified into four groups: treated/normal-weight (males = 10, females = 17, BMI < 85th percentile), treated/overweight (males = 19, females = 39, BMI $\geqslant$ 85th percentile), untreated/normal-weight (males = 17, females = 19, BMI < 85th percentile), and untreated/overweight (males = 25, females = 30, BMI $\geqslant$ 85th percentile). As per the CHAT study, participants were assessed in a repeated measures design at baseline and 7 months later, and after treatment by adenotonsillectomy in the treated groups. They underwent both overnight recording of sleep using PSG, and daytime neurocognitive and neurobehavioural assessment (NEPSY and BRIEF). Scores for measures of Inhibition, Planning, Organisation, Set-shifting and Attention, Behavioural Regulation, Metacognition, Working Memory, and Organisation of Materials were compared across groups and time points to determine the

relative contribution of BMI to EF within participants. The DAS general cognitive ability (GCA) composite score was used as a measure to control for the influence of general cognitive ability.

2.5 Statistical analysis

All data analyses were performed using SPSS version 27 (SPSS, Inc; Chicago IL). P-values reported were two tailed, with statistical significance determined at $\alpha = 0.05$. Based on an estimate from one previous study (Kohler et al; 2018), we calculated (using G * Power 3.1.92) that with a minimum sample size of 48 children, stratified into four groups, the study would have 80% power to detect a medium effect size of $f = .29$ or more, with an alpha of .05 (Cohen, 1988), in the primary outcome of change in EF scores between baseline and the 7-month follow-up assessment of EF. Our sample size was 176, so it was well above the sample size of 48. The assumption of normality was evaluated using histograms and quantile-quantile plots; normality was found tenable for all variables. To assess group differences (between and within) in descriptive and EF performance at baseline, a One-Way Welch ANOVA was conducted.

To determine the effects of EF performance as a function of treatment and BMI, a linear mixed model (LMM) analysis was used. In order to run the LMM in SPSS, it was necessary to convert the data from regular format into "long format" using data restructure. In this conversion, the repeated observation becomes a separate case with a measurement point added in. The key advantage to using a LMM approach as opposed to a mixed ANOVA is that it allows for the control of variance at an individual level rather than just at the group level only (Baayen, Davidson & Bates, 2008). Additionally, LMM does not require data averaging and has the leverage of dealing with multiple sources of variation by incorporating both random and fixed effects. Fixed effects included in our analysis were BMI group,

treatment group, and time (baseline and 7-month follow-up), along with the interactions of treatment group * BMI group, treatment group * time, BMI group * time, and treatment group * BMI group * time. The random effect included was participant ID. Time was also added as a repeated effect to determine the outcome of changes in variables from baseline to follow-up. To control for the influence of general cognitive ability on the outcomes for effects of EF, the DAS GCA T-score was added as a covariate.

Where there were significant effects and interactions in the LMM, follow-up post hoc t-tests were carried out to determine which groups specifically had significant differences in the mean scores between baseline and follow-up. Both independent and paired samples t-tests were conducted. Independent samples t-tests were conducted to compare baseline scores between the treated groups and the non-treated groups, and to compare follow-up scores between the treated groups and the non-treated groups. Paired samples t-tests were conducted to compare baseline scores in the treated groups with follow-up scores in the treated groups, and to compare baseline scores in the non-treated groups with follow-up scores in the non-treated groups.

A linear step-wise regression analysis was performed to assess the variability of EF accounted for by OAHI, AI, ODI, and minimum oxygen saturation (across total sleep time). This allowed us to estimate how much EF scores changed in relation to changes with the various sleep indices. With each regression, the DAS GCA T-score was added at the first step as a control for cognitive ability. The dependent variable was entered as a change in score from baseline to follow-up. Likewise, the independent variables (OAHI, AI, ODI and minimum oxygen saturation for total sleep time) were also entered as a change in score, and were added to each model separately. In order to assess the proportion of variance contributed by each independent variable, $R2$ change was requested in SPSS.

Results

3.1 Sample

This study involved 176 children, aged 7 to 9 years (M = 7.85 ± 0.8). Females = 105 (59.7%), Males = 71 (40.3%). All participants had mild to moderate OSA (AHI range = 2-30) without prolonged oxygen desaturation, and a mean age of 7.85 ± 0.8 years. The BMI z-score for age overall had a mean value of 1.27 ± 1.15. Ethnicities in the sample included: African American n = 105 (59.7%), Caucasian n = 59 (33.5%) and Other (majority being Hispanic) n = 12 (6.8%). The participants were predominantly overweight/obese n = 113 (64.2%), with n = 63 (35.8%) being normal weight. Furthermore, a cross tabulation showed that 62.83% of the overweight participants were African American. At baseline, children who were overweight were more likely to have lower scores on the NEPSY Attention and EF domain, and higher scores on sub-tests of the BRIEF (indicating reduced executive function) than normal weight children. An observation of the descriptive data at baseline when stratified into the 4 groups (untreated/normal weight, treated/normal weight, untreated/overweight, treated/overweight), showed this to be true in the majority of cases, albeit the difference was very minimal (Table 2). Additionally, the baseline NEPSY and BRIEF scores were close to the population mean in all groups. The average range for a scaled score on the NEPSY is between 8 and 10 (Korkman et al; 1998), while the average range for a T-score on the BRIEF is between 40 and 60 (Gioia et al; 2000).

Table 2

Baseline group comparisons of DAS scores, EF performance measures, and descriptives Mean (SD)

Variable	UNW	TNW	UOW	TOW	*F*-value
DAS-Sum of Core Subtest T-Scores GCA	295.81 (31.32)	298.28 (35.68)	276.5 (31.20)	279.88 (34.37)	3.24*
NEPSY-Tower Attention/EF Scaled-score	11.28 (2.26)	10.59 (2.75)	10.33 (2.85)	10.35 (2.87)	1.25
NEPSY-Inhib/Inhibition Combined Scaled Score	8.53 (3.51)	8.96 (3.60)	7.67 (3.50)	7.96 (2.82)	.993
NEPSY-Inhib/Switching Combined Scaled-score	8.33 (3.29)	8.93 (3.72)	7.94 (2.30)	7.85 (3.34)	.635
NEPSY-Auditory Attention and Response Set	10.72 (2.42)	9.96 (1.79)	9.56 (2.43)	10.39 (1.90)	2.09
NEPSY-Inhibition/Naming Combined Scaled-Score	9.25 (3.55)	10.52 (3.33)	8.80 (3.51)	9.29 (3.57)	1.54
BRIEF-Monitor T-Score	45.75 (11.51)	43.33 (8.36)	50.98 (11.40)	51.10 (12.92)	2.71
BRIEF-GEC T-Score	48.61 (12.35)	45.52 (10.30)	52.84 (11.99)	52.09 (11.92)	3.36*
BRIEF-Metacognition T-Score	50.96 (11.79)	54.75 (10.98)	59.31 (12.34)	59.11 (12.57)	4.72*
BRIEF T-Score	52.15 (10.01)	48.81 (6.48)	55.36 (13.53)	56.62 (17.34)	3.02*
BRIEF-Shift T-Score	52.42 (9.10)	50.69 (8.66)	54.17 (12.31)	55.22 (14.20)	.866

BRIEF-Working Memory T-Score	50.54 (12.56	55.19 (11.82)	59.11 (12.70)	57.93 (13.60)	2.60
BRIEF-Inhibit T-Score	50.81 (11.64)	49.19 6.41)	54.50 (12.89)	56.58 (17.84)	2.50
BRIEF-Organisation of Materials T-Score	50.88 (11.64)	50.63 (7.73)	58.44 (14.20)	57.58 (12.91	3.24*
Mother's Education	2.83 (1.25)	2.85 (1.23)	2.65 (.985)	2.64 (1.17	.349
Father's Education	2.49 (1.38)	2.69 (1.51)	2.47 (1.10)	2.35 (1.12)	.376
BMI z-score For age	-.05 (.683)	-.06 (.776)	2.00 (.449)	2.01 (.678)	17.51 ***
Age	7.64 (.833)	7.63 (.742)	7.93 (.790)	8.03 (.837)	2.63
Waist Hip Ratio	.84 (.052)	.87 (.093)	.91 (.070)	.91 (.066)	13.12 ***

Table *p<.05, **p<.01, ***p<.001
UNW = Untreated normal weight, TNW = Treated normal weight, UOW = Untreated overweight, TOW = Treated overweight

3.2 One-way Welch ANOVA

Baseline group comparisons of descriptive and EF performance were evaluated using a One-way Welch ANOVA. Analyses revealed statistically significant differences between groups on BMI z score for age $F(3,172) = 137.51$, $p < .001$, $\eta^2 = .75$, waist/hip ratio $F(3,171) = 13.12$, $p < .001$, $\eta^2 = .14$, and age $F(3,172) = 2.636$, $p = .055$, $\eta^2 = .044$. No group differences emerged for the mother and father's educational scores. $F(3,170) = .349$, $p = .765$, $\eta^2 = .007$, and $F(3,158) = .376$, $p = .717$, $\eta^2 = .008$, respectively. The BRIEF Global Executive Composite (GEC) scores differed significantly across groups $F(3, 172) = 3.362$, p

= .023, η^2 = .049, along with three of the subtest scores: Metacognition (MI) F(3, 172) = 4.723, *p* = .004, η^2 =.064, Behavioural Rating Index (BRI) *F*(3, 61) = 3.020, p = .036, η^2 = .037, and Organisation of Materials *F*(3, 172) = 3.241, *p* = .026, η^2 = .047. No significant group differences were found with the remaining four BRIEF subtest scores or the Attention/EF NEPSY domain scores. The effect sizes of the group differences in the EF measures were small to medium.

3.3 Linear Mixed Model

To further assess the BRIEF variables that were statistically significant at baseline (Metacognition, Behavioural Rating Index, GEC, and Organisation of Materials), a LMM analysis was conducted to determine the changes between groups over time. The results showed no effects or interactions of "Fixed Effects" in EF for Metacognition, Behavioural Rating Index, and GEC (Table 3). However, results did demonstrate main effects of BMI (*p* = .001) and time (*p* < .001) in Organisation of Materials. Additionally, there was a significant interaction between treatment group and time (Table 3) (*F*(1, 151) = 4.867, *p* = 0.29. This indicated that ratings on this function were greater (i.e. greater impairment) for overweight/obese children, and that overall the ratings for this function improved (i.e. reduced scores) at follow-up compared to baseline. Furthermore, it showed that there was a change in one treatment group from baseline to follow-up, which was larger than the change across time in the other treatment group.

Table 3

Linear mixed model outcomes for effects of EF performance as a function of treatment and body mass

		Baseline		**Follow-up**		***F* -value**						
		Treated	Non-treated	Treated	Non-treated	Treatment Arm	BMI	Time	Treatment * BMI	Treatment * Time	BMI * Time	Treatment * BMI * Time
BRIEF-Metacognition M1 T-Score	Normal Weight	51.44 (12.09)	52.43 (9.87)	55.89 (14.28)	53.14 (11.13)	.477	2.06	.081	3.43	.259	2.065	.154
	Overweight	57.88 (13.33)	58.58 (12.71)	54.71 (13.86)	59.62 (16.60)							
BRIEF-GEC T-Score	Normal Weight	44.94 (7.13)	49.38 (12.41)	55.19 (11.58)	54.29 (10.49)	.458	3.31	14.74	.004	.272	1.136	.362
	Overweight	51.63 (12.40)	53.89 (13.02)	55.51 (14.19)	58.32 (13.81)							
BRI T-Score	Normal Weight	48.22 (6.0)	53.21 (9.72)	51.78 (10.34)	56.50 (14.67)	.001	.675	1.52	.095	.001	2.685	.070
	Overweight	56.15 (18.68)	54.77 (13.90)	54.91 (17.93)	55.35 (15.21)							
BRIEF Organisation of materials T-Score	Normal Weight	45.60 (9.36)	48.33 (11.32)	43.32 (7.77)	49.58 (12.02)	3.23	11.11	24.95	.127	4.87	.776	.77
	Overweight	50.41 (11.32)	53.77 (10.17)	47.69 (10.83)	52.46 (10.35)							

3.4 Post-hoc t-tests

Independent Samples t-tests in the BRIEF Organisation of Materials T-scores determined that there was no statistically significant difference in the mean scores between treated and non-treated groups at baseline (treated M = 49.11 ± 1.88; non-treated M =51.21 ± 10.94), t (174) = -1.278, p = .203. However, there was a statistically significant difference in the mean scores between treated and non-treated groups at follow-up (treated M = 46.37 ± 10.16; non-treated M = 51.28 ± 11.09), t (169) = -3.013, p = .003. This is indicative of the treated group improving more than the non-treated group over time.

Paired Samples *t*-tests compared baseline scores in the BRIEF Organisation of Materials in the treated groups with follow-up scores in the treated groups. Results showed statistically significant differences between the scores of the treated groups at baseline (M = 55.72 ± 12.21) and the treated groups at follow-up (M = 46.60 ± 10.00), t (59) = 4.832, p < .001 (Figure 2).

Paired Samples *t*-test also compared baseline scores in the non-treated groups with follow-up scores in the non-treated groups. Results showed statistically significant differences between the scores of the non-treated groups at baseline (M = 55.27 ± 13.61), and the non-treated groups at follow-up (M = 50.95 ± 10.43), t(61) = 2.392, p = .020 (Figure 1).

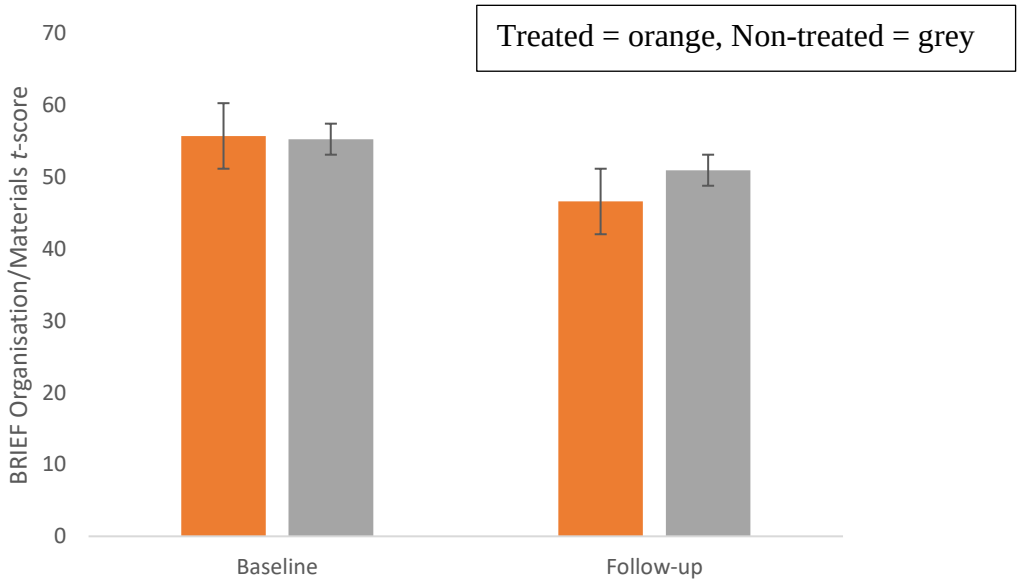
3.5 Linear Regression Analysis

To evaluate the potential relationship between the BRIEF Organisation of Materials and the PSG indices of OSA severity (OAHI, AI, ODI, and minimum oxygen saturation) a linear step-wise regression analysis was conducted. With each regression, the DAS GCA T-score was added at the first step as a control for cognitive ability. Results showed that the association of the DAS GCA T-score between the BRIEF Organisation of Materials scores was not statistically significant, R (165) = .006, p = .329. Likewise, the association between

OAHI, AI, ODI, and minimum oxygen saturation (total sleep time) between the scores were not statistically significant.

Figure 2

Changes in EF score on BRIEF Organisation of Materials as a function of treatment and time



Respectively the results were as follows: R (164) = .008, p = .513 (R^2 change = .002), R (164) = .014, p = .307 (R^2 change = .008), R (164) = .006, p = .604 (R^2 change = .001), R (164) = .006, p = .606 (R^2 change = .001). This indicates that the proportion of variance contributed by each of these sleep variables to the BRIEF Organisation of Materials score was very minimal. The addition of each of these variables to the models did not improve the predictability of the models, and showed that there was no association between the BRIEF Organisation of Materials and sleep indices of OSA severity (OAHI, AI, ODI, and minimum oxygen saturation).

3.6 Summary

In summary, the results indicated very little change in EF performance between baseline and the 7-month follow-up. The Organisation of Materials was the only subtest on

the BRIEF which showed significant differences in mean scores between baseline and follow-up, or demonstrated any interaction between time and other factors such as BMI or treatment. Furthermore, there were no significant differences in mean scores between baseline and follow-up with the Attention/EF NEPSY domain scores. Analyses revealed that BMI was a predictor of EF outcome in the Organisation of Materials, and both treatment and time modified the outcome. No relationship was found between Organisation of Materials and OSA severity of OAHI, AI, ODI and minimum oxygen saturation.

Discussion

4.1 Overview of Findings

Notwithstanding the fact that recent evidence suggests that a deficit in EF might be intensified by the combination of OSA and obesity (Watach et al; 2019), the effect of BMI on EF in children with OSA is not clear-cut. The principal aim of this study was to evaluate the impact of BMI on EF in children with mild to moderate OSA. Overall the results indicated very little change in EF performance between baseline and the 7-month follow-up. Although there were no effects of BMI, treatment or time in the Attention/EF domain of the NEPSY, or in the majority of sub-tests from the BRIEF, subtle differences were observed in the mean scores at baseline (Table 2). The baseline NEPSY and BRIEF scores were close to the population mean in all groups, suggesting that EF of participants in the current study was not impaired to a large extent at baseline. Interestingly, the BRIEF Metacognition, Working Memory, Behavioural Regulation, Shifting, Inhibition, and Organisation of Materials scores in the overweight groups at baseline were on the higher end of the average scale (indicating reduced EF) compared to normal weight groups (Table 2). This suggests that the overweight participants had somewhat lower EF skills in each of these areas. However, the results of the current study did not reveal any effects of BMI, treatment or time in the BRIEF subtests Metacognition, Behavioural Regulation, Shifting, and Inhibition. Conversely, there were effects of BMI and treatment across time in Organisation of Materials.

4.2 Predicted significant findings

Greater body mass overall was predictive of impaired EF in relation to the BRIEF Organisation of Materials only. Additionally, treatment across time modified the outcome of the scores on this subtest, with the treated groups showing greater improvement than the non-treated groups at the 7 month follow-up. As evident from the mean scores at baseline, the

overweight participants had higher scores on the BRIEF subtest Organisation of Materials (indicating reduced EF) compared to the normal weight participants. As such, both of our hypotheses: (1) Overweight/obesity in children with OSA would have a negative influence on EF and (2) Treated groups would show improved EF scores post-treatment were supported within the context of EF in Organisation of Materials. However, the hypotheses were not supported in relation to the other remaining neuropsychological or neurobehavioural tests of EF.

Nevertheless, when you consider that the development of children's organisational skills is at a critical juncture in this age group (Anderson, 1996; Krikorian and Bartok, 1998), it is a significant outcome. Organisational skills are paramount for children and they become increasingly important as they move through different levels of school. It is important that children have the ability to integrate their EF skills to meet increased academic demands (Brocki and Bohlin, 2004). If their organisational skills are inadequate they will struggle to manage information effectively and logically, and will quite often have difficulty setting priorities, making plans, sticking to a task and getting things done (Anderson, 1998). Consequently, impairment of EF skills in this area could have detrimental effects on the child's academic progress and lifelong achievements. As such, it is extremely important to ensure children have good EF skills in this area.

4.3 Non-significant findings

Planning skills also develop rapidly in this age group (Anderson, 2002). However, the current study failed to reveal any effects of BMI, treatment or time in the NEPSY Tower of London test (planning ability task). Additionally, there was a similar lack of findings established for the other Attention/EF domains. This may reflect the notion that children might function better on tasks administered in a well-structured and quiet setting with

minimal distractions (Sbordone, 2000), which are not necessarily characteristic of home, classroom or social environments. However, even though the BRIEF is an assessment based on real world interactions (Gioia et al; 2000), there was only one subtest (Organisation of Materials) in the current study where body mass was predictive of impaired EF.

Although the CHAT study did not evaluate the impact of BMI on EF specifically, it is interesting to note that similar to this current study, they found no significant difference between groups in the change from baseline to follow-up in the Attention/EF domain scores of the NEPSY (Marcus et al; 2013). They also reported that relative improvements with early adenotonsillectomy were significantly smaller among African American (AA) children than among other races on the BRIEF (Marcus et al; 2013). Considering that the majority of participants in the current study were AA (59.7%), and 67% were overweight (51 in the treatment group and 64 in the non-treatment group), it is likely that this may have had some bearing on the outcome at follow-up. Despite the fact that adenotonsillectomy is reported to improve AHI and oxygenation nadir substantially in obese/overweight children with OSA, residual OSA persists in around 50% of obese children (Costa, 2009;). Furthermore, AA children are more likely to have residual OSA post adenotonsillectomy than children from other ethnic backgrounds (Bhattacharjee et al; 2010; Dudley and Patel, 2016). Therefore, this may have influenced the outcome of this study.

4.4 Practical and theoretical implications

To our knowledge, there are only a few studies which have looked at the combined effects of obesity and OSA on EF in children. While Vitelli et al; (2014) reported that obese children with OSA are associated with greater cognitive impairment, it should be noted that their study evaluated IQ which is not EF specifically. They administered the Wechsler Intelligence Scale for children – Third Edition which generates a Full-Scale IQ that

represents a child's general intellectual ability (Vitelli et al; 2014). Likewise, Spruyt et al; (2012) reported that BMI elevated the risk of sleep disordered breathing and cognitive impairment by around 0.39 to 0.40-fold respectively. Once again, the instrument which they utilised (Differential Ability Scales), does not assess EF specifically, but rather reasoning and conceptual ability, or general cognitive ability (Elliott, 1990).

There are also a few studies that have looked at the risk of EF impairment in adolescents with both obesity and OSA. However, the findings of these studies are conflicting, with two of them (Hannon et al; 2012; Tan et al; 2014), finding no differences in EF scores between adolescents with both obesity and OSA and adolescents with obesity and without OSA. In two other studies, there were significant differences in EF impairment between the two groups (McNally et al; 2012; Xanthopoulos, 2015). The potential difference in findings between studies may be related to the type of EF assessments and the different OSA and BMI criteria. For instance, McNally et al; (2012) utilised the Iowa Gambling Task (IGT) which has been shown to assess more multi-trait tasks involving novel problem-solving and attentional domains as opposed to EF (Gansler et al; 2011). Both Tan et al; (2014) and Xanthopoulos (2014) used the BRIEF, and Hannon et al; (2012) used the Wechsler Abbreviated Scale of Intelligence.

A more recent pilot study by Watach et al; (2019) looked at EF impairment in obese adolescents with OSA. To assess EF, they used BRIEF-2 (Gioia et al; 2015) which contains both parent and self-report forms. It is important to note however that the sample size was small (n = 20) and the BMI was $\geqslant$ 95th percentile for all participants. Contrastingly, this current study had a large sample size and participants were a mix of normal weight (BMI < 85th percentile) and obese/overweight (BMI $\geqslant$ 85th percentile). Research has demonstrated that OSA severity is proportional to the degree of obesity, such that for every increase in BMI of 1 kg/m^2 beyond the mean BMI for age and gender, the risk of OSA will increase by 12%

(Redline et al; 1999). Considering this and the fact that obesity is a known risk factor for reduced neurocognitive performance (Bauer et al; 2015), it is unsurprising that the results revealed significantly worse EF in in their study sample compared to the normative sample.

4.5 Strengths of study

This study has a number of notable strengths, including its large varied sample recruited from several paediatric sleep centres, randomised design, standardisation of the NEPSY and BRIEF measurements, and high follow-up rates. cognitive assessments were administered by psychometrists blinded to group allocation and standardisation of polysomnography ensured consistency of participant selection and quantification of sleep parameters. Finally, the DAS GCA score was used as a control for the influence of general cognitive ability of the participants in this study.

4.6 Limitations of study

Due to ethical concerns, the children in the current study had mild OSA (median AHI 4.7/h TST) with no significant oxygen desaturations, preventing a full assessment of the extent to which pronounced hypoxemia or sleep disruption may contribute to EF impairment. More severe OSA cases might alter the outcome and exhibit greater EF impairment (Halbower et al; 2006). It may also explain the lack of association between Organisation of Materials and the sleep indices of OSA severity (OAHI, AI, ODI, and minimum oxygen saturation). Therefore, the results of this study cannot be generalised to children with pronounced hypoxemia. However, it is important to note that there is substantial phenotypic variation where some children with severe OSA do not demonstrate neurocognitive impairment, while some children with relatively mild OSA do (Kheirandish-Gozal and Gozal, 2013). It is possible that this can be partly explained by individual protective mechanisms and individual variability in neuroplasticity which are modified by genetic and

environmental factors (Kheirandish-Gozal and Gozal, 2013). Additionally, children with intellectual disabilities and those with mental or medical problems were excluded, such that generalisation of our findings are restricted to otherwise normally developing children.

Although the BRIEF assessment was a useful supplement to the NEPSY, it should be noted that the measures of the BRIEF are intrinsically subjective. Furthermore, parents in the treatment arm of CHAT were not blinded (Marcus et al; 2013), so it is possible that the knowledge of the adenotonsillectomy may have affected their ratings of improved outcome in Organisation of Materials. However, considering the rest of the BRIEF subtest measures did not indicate improved outcome at follow-up, it is likely that the result is reliable. Finally, the follow-up period of seven months was relatively short, and this study did not include a control group. Despite these limitations, results did reveal that obesity in children combined with OSA has a negative influence on EF relating to Organisation of Materials. Nevertheless, this result should be considered within the context that there was no control group, or a group of obese participants without OSA to allow analysis of obesity alone and how it might independently impair EF. Perhaps a further study could extend on this one by including a control group and having an additional follow-up two years after the 7-month follow-up. Alternatively, future research could avail of a longitudinal study design which includes a control group of obese/overweight children without OSA. This would allow follow-up of participants in real time and establish the real sequence of events, allowing insight into cause-and-effect relationships. Furthermore, longitudinal designs are considered more valid and reliable for assessing developmental changes such as EF (Anderson, 2002).

4.7 Conclusion

In conclusion, we found that BMI was a significant predictor of EF in the context of Organisation of Materials. This is indicative that the combination of both obesity and OSA

heightens the risk of impaired EF beyond the risk of either condition alone. In view of the increasing prevalence of overweight and obesity in childhood (WHO, 2020), the high prevalence of OSA amongst obese children (Verhulst et al; 2008), and the importance of good executive functioning, this association is of concern. Future longitudinal studies will be required to verify our understanding of the additive effect of obesity and its synergistic action with that exerted by OSA on EF impairment, especially during critical periods of EF development. Furthermore, additional research is needed to investigate the impact of more severe oxygen desaturation on EF impairment in children with OSA, along with respiratory and blood gas exchange abnormalities.

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