Review

Exploring the Complex Interplay of Obesity, Allergic Diseases, and Sleep-Disordered Breathing In Children

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Exploring the Complex Interplay of Obesity, Allergic Diseases, and Sleep-Disordered Breathing in children

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Abstract: This study explores the link between obesity, allergies, and sleep-disordered breathing in children. Sleep-disordered breathing causes repeated upper airway obstructions, leading to apneas and restless sleep. Childhood obesity, which affects around 20% of children, is often associated with sleep-disordered breathing and allergies such as asthma and allergic rhinitis. It distinguishes between diet-induced obesity (due to diet and physical activity) and genetic obesity (such as Down syndrome and Prader-Willi syndrome). In children with diet-induced obesity, chronic inflammation linked to weight can worsen allergies and increase the risk and severity of asthma and rhinitis. Furthermore, the nasal congestion typical of rhinitis can contribute to upper airway obstruction and sleep-disordered breathing. A vicious circle is created between asthma and sleep-disordered breathing: uncontrolled asthma and sleep-disordered breathing can worsen each other. In children with genetic obesity, despite alterations in the immune system, fewer allergies are found compared to the general population. The causes of this reduced allergenicity are unclear but probably involve genetic, immunological, and environmental factors. Further studies are needed to understand the mechanisms. The study emphasizes the importance of jointly evaluating and managing allergies, obesity, and sleep-disordered breathing in children, considering their close interconnection.

Keywords: allergy; children; Down syndrome; inflammation; obesity; obstructive sleep apnoea; Prader-Willi syndrome; sleep-disordered breathing

1. Introduction

1.1. Definition of OSA

Obstructive sleep apnoea (OSA), the most common form of sleep-disordered breathing (SDB), involves repeated obstructions of the upper airways, causing brief periods of apnoea and sleep disruptions. SDB in children, including snoring and OSA itself, can significantly affect sleep, daytime behaviour, cognitive performance, physical development [1–3], and cardiovascular risk [4]. Paediatric OSA can be classified into three phenotypes, with obesity being a significant risk factor such as obesity. Children with obesity are more likely to develop OSA compared to children of normal weight [5,6].

The prevalence of OSA varies globally, affecting between 1.2% and 5.7% of children [1]. Male children are more commonly affected, and conditions like obesity can increase the likelihood of developing OSA [7,8]. A study found that the prevalence of OSA was 38.7% in children with BMI z-scores less than 2, compared to 60% in children with BMI z-scores 2 or higher [9]. Polysomnography is the gold standard for diagnosing SDB [1,10].

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2. Diet-Induced Obesity

Commonly affecting around 19.7% of children and adolescents, obesity is characterized by excess weight without further syndromic features [11]. Children affected by obesity exhibit a greater prevalence of OSA, with about 36% affected and 60% with the syndrome [12]. Excess fatty tissue can lead to serious health issues such as diabetes and cardiovascular complications. Regular check-ups are crucial for overweight and obese children [13,14].

Paediatric obesity is a significant risk factor for OSA, mainly due to anatomical and inflammatory reasons. Fat deposition in these areas can increase airway resistance and impair respiratory dynamics [15,16]. Obese children also exhibit anomalies during sleep, such as positive pharyngeal pressure and less pharyngeal dilatory activity [17]. Adenotonsillar hypertrophy is a significant risk factor for OSA in obese children, but surgical removal of tonsils may only have a partial effect on improving the condition [18]. Some studies report a significant reduction in lung function in obese children. Obesity also increases the risk of developing obesity hypoventilation syndrome (OHS), a condition recently identified in children as well [19].

3. Obesity in Genetic Conditions

Prader-Willi syndrome (PWS) and Down syndrome (DS) are both genetic conditions but exhibit significant differences. PWS and DS are two distinct genetic disorders characterized by some common clinical features, such as obesity, muscle hypotonia, ligament laxity, and intellectual disability [20]. However, PWS is characterized by obesity due to hyperphagia and genetic abnormalities on chromosome 15, occurring in 1:10,000–1:30,000 live births [21]. Studies show that youth with DS experience a higher prevalence of overweight and obesity compared to their peers in the general population. Estimates suggest that 49% to 80% of young individuals with DS are overweight or obese, with this number rising to 90% by adulthood [22]. The aetiology of obesity in youth with DS is multifactorial [22].

3.1. Obesity in Down Syndrome

DS is associated with a heightened risk of obesity. Several physiological processes can contribute to this increased risk. An underactive thyroid gland (hypothyroidism) and a naturally slower metabolism can both reduce the body's ability to burn calories. Additionally, consuming more calories than what's expended through physical activity creates a calorie surplus that can lead to weight gain [23]. Consequently, the prevalence of OSA in children with DS is significantly higher than in the general population [24]. A meta-analysis reports that the prevalence of OSA in children with DS is 69%-76% [25]. Children with DS are at increased risk of SDB due to features commonly associated with the syndrome, such as a small oropharynx, midface hypoplasia, narrow nasopharynx, and macroglossia. Additionally, factors such as obesity, hypothyroidism, and other medical comorbidities are also known to contribute to the severity of SDB [26,27].

3.2. Obesity in Prader-Willi Syndrome

PWS is a rare but significant genetic condition resulting from an anomaly on chromosome 15. It initially presents with neonatal hypotonia, feeding challenges, and diminished appetite, followed by a later phase of weight gain, insatiable hunger, and uncontrollable eating tendencies, typically emerging between the ages of 2 and 3 [28]. It is considered the most common genetic cause of obesity [21], manifesting in approximately 1 in 10,000 to 1 in 30,000 live births. Patients with PWS have a particular tendency to gain weight and may develop serious health problems related to obesity, such as hypertension and sleep apnea [29–31].

4. Purpose of the Narrative Review

Obesity and allergies are prevalent among individuals with SDB [32]. Obesity and SDB often coexist, with inflammation associated with obesity potentially influencing asthma control and the bidirectional relationship between sleep apnea and asthma or allergic rhinitis (AR) [33]. Utilizing

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recent research, this investigation aims to refine current understanding of how allergies and SDB interact in children, specifically comparing those with diet-induced obesity to those with genetic obesity.

5. Diet-Induced Obesity and Allergic Disease

5.1. Obesity and Inflammation

Chronic inflammation is closely associated with allergies. In fact, it can be a key driver in the development of allergic diseases and their ongoing management. Childhood obesity is increasingly being recognized as a condition with potential immediate health consequences, including the development of chronic low-grade inflammation [34].

Adipose tissue releases various compounds that influence immune function. These include cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukins (IL-1, IL-6), and chemokines like monocyte chemoattractant protein-1 (MCP-1) and eotaxin, which specifically attract monocytes and eosinophils, respectively [35]. Moreover, obesity correlates with elevated levels of circulating acute-phase reactants, such as C-reactive protein (CRP), providing additional evidence of systemic inflammation [36].

Adipokines, a group of cytokines synthesized by fatty tissue, are essential for modulating metabolism and immune system functions. Among them, leptin and adiponectin exhibit contrasting functions [37]. Leptin levels increase with fat mass and may contribute to a pro-inflammatory state by promoting the Th1 immune response. In contrast, adiponectin has anti-inflammatory properties, inhibiting the NFκB signalling pathway and protecting against insulin resistance and atherosclerosis [36,38]. However, its levels decrease in obese individuals, contributing to the pro-inflammatory state. Many cytokines and adiponectin are essential in creating chronic low-grade inflammation, increasing susceptibility to OSA and atopic diseases like asthma and AR [39].

5.2. Obesity and Allergy

Childhood obesity is associated with various immediate and long-term health implications, including an increased susceptibility to allergies [39]. A 2021 study found that being obese (OR 1.71; 95% CI: 1.08-2.71, p=0.021) or overweight (OR 1.62; 95% CI: 1.06-2.50, p=0.026) was linked to a higher likelihood of allergic disease in prepubertal children compared to those with a normal weight [40].

5.3. Obesity, Allergic Rhinitis, and OSAS

Over time, there has been a rise in the prevalence of AR. Certain studies suggest that the medically diagnosed ARstood at 10.5%, whereas the overall prevalence of self-reported current AR (within the past 12 months) was 18.1% [41].

A direct correlation between obese girls and AR (OR 1.48; $p < 0.05$) has previously been reported [42]. Another study found that obese children aged 6-7 years had higher sensitization (measured by SPT > 6 mm) (OR=1.84; P=0.017) [43]. Research revealed a direct link between elevated body mass index (BMI) and AR, particularly among young adult females and children [35]. Obesity is recognized as a factor that can worsen AR symptoms, and it is associated with elevated levels of IL-1β and leptin simultaneously [44]. Obesity negatively influences the severity of AR when children with AR experience higher CO and ambient PM^{10} [45].

The link between obesity and AR, however, is not straightforward. Some studies suggest that obesity may be linked to a lower risk of AR, regardless of gender [35]. The relationship between obesity and AR in children is complex, with conflicting findings. A nationwide study in the United States found that central obesity in children was associated with reduced odds of AR, regardless of gender [33]. Additionally, a study in Korea found that obesity in children with AR was associated with increased vulnerability to air pollution, leading to exacerbated AR symptoms [45]. The precise mechanisms linking obesity to worsened allergies and AR symptoms remain unclear. However, some studies suggest that obesity-induced increases in leptin levels may contribute to heightened inflammation and more severe symptoms through its interaction with interleukin-1 β (IL-1β) [44].

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AR is strongly correlated with OSA development for several reasons. Firstly, nasal congestion reduces airflow through the upper airways [46], causing fatigue, snoring, and poor sleep quality. Secondly, nasal congestion can lead to mouth breathing, which causes the tongue and jaw to shift downwards. This results in a reduced pharyngeal diameter and altered position of the upper airway dilator muscles, further reducing airflow [47]. This increased nasal resistance forces individuals to switch from nasal to mouth breathing, potentially contributing to upper airway collapse and apnoea generation. Studies have shown that nasal obstruction, whether due to anatomical issues or chronic allergies, can destabilize the upper airways and worsen sleep apnoea by disrupting normal breathing patterns [48,49]. Lofaso et al. demonstrated that persistent vasomotor and non-vasomotor rhinitis are risk factors for SDB and OSA [50]. Recent studies have highlighted that the Th17/Treg ratio in peripheral blood is higher in children with OSA and AR than children without AR, suggesting that AR may play a central role in promoting OSA [51].

5.4. Obesity, Asthma, and OSAS

The association between obesity and asthma in children is well-established, with numerous epidemiological studies demonstrating a link between the two conditions [52,53]. Children who are consistently overweight have shown a prolonged impact on the development of asthma (relative risk 2.47, 95% CI 1.18–5.12) and rhinitis (relative risk 1.44, 95% CI 1.12–1.84) that can persist into adolescence and early adulthood [54]. Obesity might play a role in asthma development by fostering a chronic low-grade inflammatory state, releasing pro-inflammatory cytokines and adipokines from adipose tissue [52]. Specifically, research suggests a significant involvement of leptin in the pathophysiology of asthma in obese individuals [55]. Additionally, obesity is characterized by various alterations in both innate and adaptive immunity, with a shift from a Th2 to a Th1 response [56].

OSA is the most common form of SDB in children, particularly those with severe asthma. There is a well-established association between childhood asthma and OSA [57]. Several studies have highlighted a bidirectional relationship between the two conditions. A problematic link exists between asthma and SDB in children. Uncontrolled asthma predisposes children to OSA, which can then exacerbate asthma control and increase the likelihood of asthma attacks [58]. This bidirectional relationship is further supported by the significant overlap in symptoms and underlying mechanisms (pathophysiology) between the two conditions. For instance, children with severe asthma have been found to have a higher risk of apneas and hypopneas compared to those without asthma [58].

6. Obesity in Down Syndrome and Allergic Diseases

6.1. Down Syndrome and Immunity

Patients with DS show impairments in their immune system [59,60]. A reduced thymus size in DS patients contributes to lymphopenia and leukopenia. Individuals with DS show a notable decreasein T lymphocyte count, affecting both CD4+ and CD8+ cells [61,62].

Regarding innate immunity, children with DS have a decrease in CD16+CD56+ natural killer (NK) cells, while the number of CD16- CD57+ cells increases in both children and adults [59]. Individuals with DS also exhibit excessive expression of the SOD1 and ITGB2 genes, which are essential for neutrophil function. Nutritional deficiencies and accelerated ageing are potential causes of secondary immunodeficiency in DS [61].

The rate of telomere loss in patients with DS is reported to be higher than in the general population. Immunogenetic abnormalities might contribute to this phenomenon by potentially promoting increased cell division [63].

Additionally, an increase in CD11c+Tbet+CD21low B cells has been observed. These cells may be involved in the production of auto-reactive antibodies. Specifically, CD11c+ B cells could contribute to autoimmunity in DS [64].

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6.2. Down Syndrome and Inflammation

Some studies suggest that trisomy 21 is characterized by an upregulation of the inflammatory response [65]. This is evidenced by elevated levels of both pro-inflammatory and anti-inflammatory cytokines, including IL-2, IL-6, IL-10, and IL-1ra, in individuals with DS [66].

6.3. Down Syndrome, Allergic Sensitization, and Atopic Eczema

Allergic sensitization, defined as developing specific IgE antibodies to allergens in the blood (serum) following exposure, is estimated to affect 27-40% of children in Western countries [67]. Multiple factors, including genetics, environmental triggers, and the body's immune response, work together in a complex way to influence a person's risk of developing allergies and becoming sensitized to allergens [68,69]. However, patients with DS appear to have a lower prevalence of allergic sensitization [70,71].

This lower allergic sensitization in DS is generally reflected by low levels of total IgE and fewer positive skin prick tests [70]. While parents of children with DS may report food allergies more frequently, confirmation by a doctor is less common [72]. Furthermore, the limited research on the incidence of allergic diseases in these children suggests they may be less susceptible to such conditions.

Supporting this notion, recent studies have found a prevalence of atopic eczema (a type of eczema) of up to 5% in patients with DS, which is similar to the general population [73].

6.4. Down Syndrome and Wheezing

Children with DS have been found to have a higher frequency of persistent wheezing and symptoms of chronic rhinitis compared to their siblings without DS or the general population [74]. Recurrent wheezing is common in children with DS, and it is likely due to specific factors associated with DS, but it may not be directly associated with asthma [71,74]. In summary, although wheezing and other respiratory symptoms are common in children with DS, the diagnosis of asthma in these children is less frequent and may not always be confirmed [74,75]. Likely, the anatomical and physiological alterations found in the respiratory tract of DS contribute to the development of respiratory symptoms such as wheezing and coughing [72].

6.5. Down Syndrome, Allergy, Asthma, and OSAS

The specific relationship between allergies and OSA in children with DS has been less directly investigated. Existing literature suggests that the immune system in individuals with DS may function differently, potentially affecting the prevalence and severity of allergies [67,76]. However, given the established correlation between allergies and OSA in the general population and the high prevalence of OSA in children with DS, we can hypothesize that allergies may further complicate the presentation and management of OSA in this population [77]. Early screening for sleep apnoea in children with DS is crucial due to the high prevalence and the fact that the presence of comorbidities, including allergies, does not necessarily predict the severity of OSA [78].

7. Obesity in Prader-Willi Syndrome and Allergic Diseases

7.1. Prader-Willi Syndrome and Immunity

Research suggests that individuals with PWS may have an altered immune profile. A study published in the Orphanet Journal of Rare Diseases found that individuals with PWS had elevated levels of matrix metalloproteinase (MMP-9) and myeloperoxidase (MPO), along with decreased levels of macrophage inhibitory factor (MIF) [79].

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7.2. Prader-Willi Syndrome and Inflammation

Four chemokines (MCP1, MDC, Eotaxin, RANTES) were significantly higher in children with PWS than controls. These chemokines are known to be pro-inflammatory. Interestingly, chemokine levels were not correlated with total body fat percentage [80]. Elevated levels of interleukin (IL)-1β and IL-13 in patients with PWS are associated with various psychopathological symptoms. Additionally, most serum inflammatory cytokines, including IL-1β, IL-2R, IL-12p70, and TNF-α, are increased in PWS. Notably, there is a significant elevation in CD16+ monocytes, a type of immune cell, among individuals diagnosed with PWS [81]. These findings suggest that activation of the innate immune system, the body's first line of defence, maybe a specific feature of PWS and occur independently of factors like central obesity and insulin resistance [79,82].

7.3. Prader-Willi Syndrome and Allergic Diseases

Individuals with PWS may have a lower prevalence of allergies and rhinitis compared to the general population. It is even though patients with PWS have altered ventilatory control and many other factors that predispose them to SDB. While obesity is common in PWS, the link between obesity and pulmonary function in children is complex [83].

8. Conclusions

The study highlights several key points regarding the interconnection between obesity, allergic diseases, and SDB. Diet-induced obesity is associated with the onset of persistent low-grade inflammation and a higher prevalence and severity of allergies like asthma and AR.

Various inflammatory pathways and adipokines mediate this relationship. Additionally, the severity of AR is correlated with diet-induced obesity, and nasal congestion in AR may contribute to upper airway obstruction and the development of SDB. In diet-induced obesity, there is a bidirectional relationship between asthma and SDB, with uncontrolled asthma increasing the risk of SDB and vice versa.

In cases of genetic obesity such as DS and PWS, despite alterations in the immune system, allergies are less prevalent compared to the general population. While the precise causes behind this phenomenon in PWS and DS remain unclear, a combination of genetic, immunological, and environmental factors likely plays a role. Further research is needed to understand the underlying mechanisms fully.

These conclusions underscore the importance of a holistic approach to assessing and managing allergic diseases and SDB in patients with either diet-induced or genetic obesity, considering the complex interconnections between them.

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