The puzzle of metabolic effects of obstructive sleep apnoea in children

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In obese children with obstructive sleep apnoea insulin resistance is common while lipids do not show a clear pattern http://ow.ly/XNR9s

In adults, obstructive sleep apnoea (OSA) is often associated with metabolic alterations. Although obesity is a major culprit [1], large epidemiological studies have reported a metabolic risk associated with OSA that is independent of obesity. In particular, meta-analyses have shown that effective treatment of OSA by continuous positive airway pressure (CPAP) improves glycaemic control in both diabetic [2] and nondiabetic patients [3].

Intermittent hypoxia is an important mechanism by which OSA affects metabolism, as supported by experimental observations showing that intermittent hypoxia negatively interferes with both glucose and lipid metabolism [4, 5]. Altered sleep structure, as often found in OSA, may also play an important role. In adult humans, experimental sleep fragmentation [6] and deprivation of slow wave sleep (SWS) [7] decreased insulin sensitivity. In healthy adolescents, two studies found that insulin sensitivity was negatively correlated to stage 1 non-rapid eye movement (non-REM) sleep, and positively to SWS duration [8, 9]. Furthermore, in another population of healthy adolescents, partial sleep deprivation, with preserved SWS and a reduced amount of REM sleep, was followed by an increase in insulin resistance [10]. A correlation between short sleep duration and insulin resistance has also been found with actigraphic studies both in adolescents [11, 12] and in younger children [13].

Paediatric OSA shows major differences compared with the adult disease [14]. First, the number of respiratory events and the degree of nocturnal hypoxaemia are usually lower in children than in adults. Second, sleep duration is physiologically longer in children than in adults and respiratory events, although possibly causing some sleep fragmentation, are associated with a sleep structure that appears to be better preserved than in adults. Third, duration of disease and exposure to additional risk factors for several complications is limited in children, as opposed to the decades of exposure to sleep disordered breathing (SDB) and risk factors typical of adult patients. Therefore, differences between adults and children with OSA could explain a different impact on metabolism. The picture is even more complex if we consider that paediatric disease has two main phenotypes: one typical of lean children with adenotonsillar hypertrophy, which usually occurs at a younger age and has a similar prevalence in both sexes; and one typical of obese children that is more similar to adult OSA and usually appears in adolescence, more often in males [15]. Onset of puberty is an additional factor known to affect metabolism in children, increasing insulin resistance at least in males [16]. The impact of all these variables, and the small sample size of several paediatric studies, probably contribute to the difficulties in clear interpretation of the apparently conflicting data available in the current literature.

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TABLE 1 Summary of studies on glucose and lipid metabolism in paediatric obstructive sleep apnoea (OSA) according to age and body weight

	Insulin resistance/sensitivity		Lipid measurements	
	Worse in OSA	**Not worse in OSA**	**At least one worse in OSA**	**Not worse in OSA**
Early childhood				
Normal body weight		Kaditis *et al.* [19] Stefanini *et al.* [34] Suri *et al.* [35]	Decreased HDL and increased VLDL in OSA [34] Unchanged triglycerides, and increased total cholesterol, HDL and LDL in OSA [35]	Triglycerides, total cholesterol and HDL [19]
Overweight/obese	Caminiti *et al.* [31] Bhushan *et al.* [26]			
Wide range of body weights		Apostolidou *et al.* [36] Kelly *et al.* [37] Koren *et al.* [17]		
Adolescence				
Normal body weight				
Overweight/obese	Kelly *et al.* [37] Hannon *et al.* [28] Watson *et al.* [30] Bhushan *et al.* [27]		Increased triglycerides, and unchanged total cholesterol, HDL and LDL in OSA [20] Increased triglycerides, and unchanged total cholesterol, HDL and LDL in OSA [27]	Triglycerides, total cholesterol, HDL and LDL [28]
Wide range of body weights	Redline *et al.* [29]	DeBoer *et al.* [38] Kelly *et al.* [37]	Unchanged triglycerides, total cholesterol and HDL, and increased LDL in OSA [29]	
Paediatric age (3–18 years)				
Normal body weight			Unchanged triglycerides, total cholesterol and LDL, and decreased HDL in OSA [40]	
Overweight/obese	De La Eva *et al.* [24] Li *et al.* [32]	Canapari *et al.* [20] Flint *et al.* [39]	Increased triglycerides, and unchanged total cholesterol, HDL and LDL in OSA [20] Increased triglycerides, and unchanged total cholesterol and HDL in OSA [39]	
Wide range of body weights	Verhulst *et al.* [25]	Tauman *et al.* [18] Shamsuzzaman *et al.* [21]	Increased triglycerides and total cholesterol, and decreased HDL in OSA [25]	

HDL: high-density lipoprotein cholesterol; VLDL: very low-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol.

The paper by Koren *et al.* [17] in this issue of the *European Respiratory Journal* reports a large amount of metabolic data in over 400 children with SDB aged 5–12 years. The data indicate that both obesity and sleep fragmentation in OSA are significantly associated with altered metabolic variables, including insulin resistance and lipid profile, whereas the frequency of nocturnal respiratory events or severity of nocturnal hypoxaemia exerts a minor effect, if any. The results of this study reinforce the conclusions of studies that demonstrated a prominent role of obesity [17–21] and sleep structure [22, 23] as determinants of alterations in insulin resistance/sensitivity in children with OSA, but are at odds with other studies indicating an independent influence of OSA [24–31].

Important heterogeneity in the design of investigations, and even more heterogeneity in the populations under study, could partly account for the large disagreements in the literature. Even studies with similar populations did not always report similar conclusions, but some trends may be identified (table 1). Most studies including only obese children found a significant effect of OSA on glucose metabolism [24, 26–28, 31–32], in agreement with experimental data showing an adverse interaction of obesity and intermittent hypoxia with metabolism [33]. Studies including only non-obese subjects did not show any significant association [19, 34, 35], but only examined preadolescent subjects. No similar studies are available in adolescents, possibly because of the low

prevalence of OSA in lean adolescents. Studies including both obese and non-obese children with a wide age range do not convey a uniform picture [18, 21, 25, 29, 36–38]. Pubertal state, in addition to age, could exert some influence [37], although a study accounting for the Tanner stage did not support this hypothesis [39].

In addition to data on glucose metabolism, the paper by Koren *et al.* [17] provides a wealth of information on lipids. Table 1 summarises the result of the available studies that reported data on lipid profiles in OSA children. Unfortunately, the picture is far from being clear. Some studies did not find any relationship between OSA and lipids [19, 28], while the results of other studies were discordant about which aspects of lipid metabolism may be affected by OSA, irrespective of age and obesity state of the children [20, 25, 27, 29, 34, 35, 39, 40].

Among the longitudinal studies, which are available only in young children undergoing adenotonsillectomy or followed without interventions, one showed an improvement in glucose and lipid metabolism at least in obese subjects after adenotonsillectomy [41], one observed an improvement in total cholesterol only [42], and one found unchanged glucose or lipid metabolism [43]. The variable degree of resolution of respiratory events during sleep and weight gain commonly occurring in lean children after adenotonsillectomy complicate this approach [14].

The study by Koren *et al.* [17] represents the largest published on metabolic effects of OSA in children, to date, and has to be regarded as one of the most important in this field. The focus on only one age group, *i.e.* young children, is another merit of this paper. To date, altogether the literature seems to suggest that in children age, obesity and, perhaps, pubertal state modulate the relationship between OSA and glucose metabolism, but the real effect of each of these factors needs to be better clarified with large studies that are homogeneous for sample characteristics. OSA severity has mostly been analysed in terms of apnoea–hypopnoea index, and more rarely in terms of nocturnal hypoxaemia, although intermittent hypoxia could be an important mediator of metabolic effects [4, 5]. Besides, the potential importance of the distribution of respiratory disorders in non-REM *versus* REM sleep [44] has not been addressed in children. Finally, the independent role of sleep fragmentation in the context of respiratory events during sleep should be better clarified. As regards lipid metabolism, the picture is poorly defined in both children and adults. However, some factors that could importantly influence serum lipids, like diet or physical activity, have rarely been considered and should be assessed in future studies. In conclusion, studies on the metabolic effects of OSA in children are becoming numerous [14], but the many factors at play mean the puzzle is still far from a definitive solution.

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