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Mr. Pickwick and his child went on a field trip and returned almost empty handed.....What we do not know and imperatively need to learn about obesity and breathing during sleep in children!

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The emergence of a global epidemic centered around obesity, i.e., "globesity", has forced us to ruminate on our own lifestyle: What and when we eat, whether we are physically fit, on how we sleep and on how we feel. Indeed, the rather astounding number of obesity-related publications scattered across a wide variety of medical and non-medical journals merely symbolizes the range of viewpoints and concerns associated with the excess of weight. Metaphorically spoken, these divergent opinions merely echo some of the possible field trips by Mr. Pickwick in his quest to find out the facts about his children. Obesity and sleep seem to both share and not share a large array of risk factors, consequences, and potentially even pathogeneses. The two papers included in this issue of the Journal deal with the obesity epidemic from a pediatric sleep medicine point of view [1,2]. Kohler and van den Heuvel question the validity of a 'straightforward' association between overweight-obesity and increased prevalence of sleep disordered breathing [1]. In contrast, Verhulst and colleagues provide their unwavering belief that such association between obesity indeed occurs, and relates to all types of sleep disordered breathing [2].

In this context, how does Mr. Pickwick explain his child's difficult breathing during sleep? In other words, what are the anatomical correlates of adiposity and upper airway function during sleep? The potential mass effect by adipose tissue on the upper airway, while well-recognized, has engendered a great deal of differing view points. On the one hand, the three-dimensional disposition of adipose tissue maydirectly contribute to narrowing of the upper airway. On the other hand, the interaction of fat tissues with a developing upper airway system maybe the culprit. And yet on another hand, fat itself whether within the upper airway or even in remote sites may provide a biological substrate for upper airway dysfunction, through inflammation and/or changes in respiratory control. Several problems arise however, primarily with the intertwined levels of defining and assessment of how much fat does Mr Pickwick have.

Excess bodily fat, or obesity, has been commonly expressed as a ratio of weight relative to height (weight/height^2, kg/m^2) or Body Mass Index (BMI), which actually is a proxy measure of adiposity, and in adults correlates with more direct measures of adiposity. The variability in the distribution of fat appears to be better dealt with via the BMI as compared for example with skinfold thickness, i.e. another proxy measure of adiposity. While these 2 measures are clearly more convenient than most direct measures of adiposity, they may not provide adequate

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correlates on the biological importance of fat location. Conversely, the pattern of fat and lean tissue relationships throughout growth and development exhibits critical periods as well as cyclicity [3], and therefore an important issue to remember with the use of BMI is that it remains a proxy measure because an increase in mass stands for increase in the form of fat, lean tissue, or bone. In any case, standardized percentiles curves of the BMI for white children and adolescents were first developed in 1971 to 1974 (First National Health and Nutrition Examination Study).

Subsequent sets of normative data have incorporated age, gender, and some ethnicity considerations, but do not include body habitus. The later reference standards remain very useful clinically, and consequently are commonly applied, particularly when defining cut-off points. For example, among Caucasian, overweight and obesity are a BMI score above the 85th percentile and above 95th percentile, respectively. Finally, the socio-developmental pattern of BMI is acknowledged, but its pitfalls are widely ignored. Indeed, BMI derivates such as percentage, z-scores or centiles are widespread [4], with the BMI z-score seemingly the most useful for research purposes, and yet perhaps not as useful for capturing adiposity changes elicited by treatment (because the variability of z-scores is smaller at the extreme ends of the distribution of z-score) or when assessing adipose tissue disposition throughout development. Thus, we should always remember that BMI does not reflect body habitus or measures adiposity directly, and therefore, international anthropometric reference curves are needed, particularly for more accurate risk assessment. Such limitations become all the more relevant to Mr. Pickwick because at any level of BMI, you can sleep and breathe poorly or not.

Development of the upper airway system affects its structure and its function, is also related to lung volumes, and is potentially affected by overall body composition. Such confluence of various determinants of upper airway growth and function take on increased importance during sleep. In recent years, a widespread quest for the turning point between normal and abnormal respiratory indices during sleep has yielded more questions than answers. What to measure and how to measure is continuously being debated in the literature and the partial degree of consensus is periodically challenged. Cut-offs for the diagnosis of sleep disordered breathing have been suggested and readily applied in research and clinical activities, and yet their validity and reliability remain to be demonstrated. Indeed, the published literature mirrors the diversity of interpretations and applications of sleep disordered breathing cut-offs within pediatric sleep medicine. Age, gender and ethnicity considerations of course will always emerge, and are rarely addressed properly because of the lack of extensive normative data in children. So, Mr. Pickwick can not receive the proper answer to his question of what is normal and what is disease. Of course, things become even more confusing when Mr. Pickwick wishes to know how the age-gender-ethnicity triad interacts with adiposity and upper airway during sleep. Both papers by Kohler et al [1] and Verhulst et al [2] provide some anchor points, such as the differences in these interactions among children older or younger than 8 years of age, the discrepancies in risk among males and among African American, and the persistent role of the enlargement of adenoids and/or tonsils even when the elusive BMI exceeds the “desirable” value. So, the conciliatory summary from these 2 papers, is that obesity may play a role in sleep disordered breathing in children, but that their exact role(s) remains to be defined, and may be more prominent in older children, or among specific ethnic groups.

So, let’s have a closer look at Mr. Pickwick, and check out his metabolic function. Common in sleep disordered breathing and/or in obesity are metabolic aberrations that form the umbrella condition known as syndrome X, syndrome Z, or the metabolic syndrome. Indeed altered sympathetic nervous system activation is suggested in both sleep disordered breathing and obesity, with inflammation [5], hypertension, cardiovascular disease [6] being now relatively well documented. Furthermore, altered fat and carbohydrate metabolism along with their key role players, namely insulin, leptin, and ghrelin have been linked to drive to eat [7] and poor sleep.

Thus, we seem willing to accept the concept that both the underlying adiposity and the presence of poor sleep quality will further promote the constellation of behaviors that will ultimately exacerbate obesity, and make sleep matters worse. Unequivocal denominators in this complex set of interactions are genetics, especially 'susceptibility genes' whereby the presence of a genotype with increased risks of disease in a particular environment will further promote the links between obesity and sleep. We also need to take into account the family and school settings, namely the obesogenic environment that may promote food intake quantity and quality, and the level of physical activity, particularly in the realm of short- versus long-term goals for public health, prevention, and treatment, since obesity is assumed to be a highly relapsing condition. In addition, the reciprocal role of eating as an improper coping strategy or reaction to stress, be it of metabolic or environmental origin, has great societal interest and signifies that the duration of sleep disordered breathing and/or obesity status might very likely be an imperative determinant. Consequently, age, gender, ethnicity, genetic, environmental, and psychological predisposition might form key factors and fundamental areas requiring quantification, especially if we wish to understand the phenotypic implications for the obese child with sleep disordered breathing. However, all studies published thus far have failed to include all of these factors, and as noted by both authors the number of factors included highly fluctuates among studies.

Therefore Mr Pickwick, while we can not provide you with definitive answers, the little that we have learned thus far implies that sleep-adiposity are related, affect each other in many metabolic ways, and that these interactions may last for a lifetime [8]. The impact of these rather "guessed" interactions only emphasizes the vital importance of clear answers to fight the '21st century epidemic' of the ever increasing "bulge" among our children.

How can we help Mr. Pickwick's child to grow old happily and healthy ever after? or let's look at his treatment options. For the weight issues, modifying lifestyle is not easy. Weight gain prevention as well as weight loss treatment studies have been outlined by the authors, and have yielded mixed results [9]. Conversely, none of the treatment studies has thus far incorporated sleep, with for example, attempting weight loss and sleep gain. Hitherto, obesity treatments range from one on one to community interventions. For the breathing disturbances during sleep component, treatments have centralized around adenotonsillectomy, with ready made assumptions that such approach is generally sufficient. Much better work needs to be done to determine the role, efficacy, and adequacy of each intervention among children. Additional challenges include the duality of short-term and long-term treatment outcomes, especially because lifestyle and overall quality of life are at stake in the context our modern obesogenic society. Thus, the majority of future studies should incorporate much lengthier follow-up durations, include nutritional education within the family or the school environments, and promote self-motivated or behavior modification based weight control and exercise programs. The NIH Obesity Task force[10] has highlighted the importance of lifestyle modifications, pharmacological, medical, and surgical approaches, and underlined the links with associated conditions such as type 2 diabetes, cardiovascular disease, and others. However, the current treatment approaches to sleep disordered breathing and obesity among children is disastrously lagging behind, and the impact of such treatment on adult well being is unavailable.

In conclusion, geographical, ethnic, socio-economic and nutritional considerations are imperative in designing the sampling frame of our pediatric studies on adiposity and sleep, as they determine their internal and external validity. This becomes very clear not only in the 2 papers included in this issue, but also in the many papers reviewed by these authors. Both commonalities and gaps are revealed in these 2 reviews with regard to the conclusions drawn on both obesity and breathing during sleep: for example, the hidden cohort effects as dictated by the ethnic context; the obesogenic lifestyle transformation of third generation youngsters when compared to their ancestors; the impact of breastfeeding on adenoid/tonsil hypertrophy

and risk for sleep disordered breathing; the bibliometric sampling style and method from within the bulk of the available papers.

Anyhow, anno 2008, Mr. Pickwick[11] came to visit us quite worried about his child. He then returned home even more worried, and yet was unclear what he should specifically fear, and what he should and could do about it. Trying to help Mr. Pickwick with these 2 papers will not give him a straightforward answer, but illuminates a serious pediatric health condition on the possible interaction of two known high risk diseases. We therefore share the worry that even in the absence of clear-cut definitive scientific evidence on the reciprocal causal relationships between pediatric sleep disordered breathing and obesity, the mere possibility of such interactions warrants a concerted effort to alleviate Mr. Pickwick's anxiety and fear, and make sure that the future of his child is healthier than his own.

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