

EDITORIAL

Clinical & Experimental Allergy

On childhood asthma, obesity and inflammation

This editorial discusses the findings of the paper in this issue by M. B. Bekkers et al. [7], pp. 95–103.

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The prevalence of childhood overweight and obesity has increased during the past decades [1], but the lack of consistency in the classification of overweight and obesity in children makes it difficult to give an overview of the global prevalence in younger age groups. Obesity is defined as abnormal or excessive fat accumulation that may impair health, whereas overweight in children can be defined as having a high body mass index (BMI, kg/m²) [1, 2]. In epidemiological studies, BMI is often used as a marker of both obesity and overweight. Because of the normal changes in weight and height that occur during growth, BMI levels among children must be expressed relative to their age and sex peers, for example using standard deviation scores of BMI for age and sex [2]. Even when this is done, the ability of BMI to identify obese children, i.e. children with excess adiposity, may be uncertain, and the accuracy of BMI as an index of adiposity increases with the level of body fatness [2].

Epidemiological studies have repeatedly shown an association between childhood obesity (often measured as a high BMI) and asthma, but the temporal sequence between these two conditions is not completely understood, especially in young children. Although many of the studies linking obesity to asthma are cross-sectional, several longitudinal studies suggest that obesity precedes asthma in children [3–5]. However, even in longitudinal studies it may not be possible to completely disentangle the influence of current BMI vs.

BMI at earlier ages. This was recently highlighted in a report from the Dutch birth cohort PIAMA, where children with a high BMI at preschool age (1–2 years and 3–5 years, respectively) had an increased risk of asthma symptoms at age 8 years [6]. However, when change in BMI during the first 7 years of life was taken into account, children with high BMI at age 6–7 years had an increased risk regardless of previous BMI, although children with high BMI in preschool age who were of normal weight at age 6–7 years did not have an increased risk [6]. In the present issue of *Clinical & Experimental Allergy*, Bekkers et al. report results on the association between BMI, asthma symptoms and pro-inflammatory proteins among 359 children participating in the same birth cohort [7]. High BMI, measured as standard deviation scores of BMI (BMI SDS) calculated using Dutch reference growth curves, at age 4 years was associated with asthma at the same age, whereas a longitudinal analysis showed no significant association between high BMI at age 4 years and asthma symptoms at age 5–8 years in this population. Thus, these two studies from the PIAMA birth cohort indicate that overweight early in life may not have a lasting effect on childhood asthma symptoms, if the child develops normal weight later on.

In addition, the same Dutch research group has previously shown that the risk of asthma in children at 8 years of age increases if the mother was overweight before pregnancy [8]. This association was, however, restricted to families with at least one parent with allergy, and not seen in families without a genetic predisposition. The latter study supports the hypothesis that fetal programming, epigenetics and shared genetics could be of importance for the obesity–asthma link. Both asthma and obesity are believed to have a strong genetic background, and numerous genetic variants have been associated with each phenotype [9]. Twin studies indicate that shared genetics could be an important common risk factor for the two traits in that some

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10% of the genetic component of obesity is shared with asthma [10]. This shared genetic effect may, however, be restricted to female subjects [11], and little is known if these mechanisms are also important in children. In addition, few convincing examples of genes that affect both asthma and obesity actually exist in the literature [9]. The fact that early overweight does not seem to have a lasting effect on asthma risk among children [6, 7], might argue against epigenetic and shared genetic effects, and rather speak for direct effects of obesity on mechanical function of the lung. In the study by Bekkers et al., the cross-sectional association between BMI SDS and asthma was also found stronger for non-allergic asthma than allergic asthma [7], which could lend support to an unspecific effect on lungs and airways.

Hormonal and pro-inflammatory effects of adipose tissue have also been proposed to explain the observed link between obesity and asthma [5]. Obesity is a pro-inflammatory state with several factors involved. For example, elevated levels of C-reactive proteins have been observed among overweight children [12], whereas raised TNF- α and IL-6 levels have been reported among obese children in some, but not all, studies [13]. In addition, children with asthma may be considered to suffer from chronic, inflammatory stress and cytokines such as IL-6 and TNF- α are also elevated in asthma and affect the endothelial function [5]. Thus, obesity and asthma may share the same inflammatory pathway where TH2 cytokine activation occurs.

In the study by Bekkers et al., the pro-inflammatory proteins hs-CRP, C3 and C4 were measured in serum collected at age 4 years and related to current and subsequent asthma [7]. No clear associations between BMI SDS and the pro-inflammatory proteins were shown. The pro-inflammatory protein C3 was associated with an increased risk of asthma symptoms both cross-sectional and prospectively, but not with BMI SDS. Including the pro-inflammatory proteins in the analyses of BMI SDS and asthma symptoms did not change the observed findings suggesting that the association between overweight and asthma was not explained by these pro-inflammatory proteins in this age group. The

role of other proteins involved in the inflammatory pathways, e.g. IL-6 and TNF- α was not evaluated in this study, and a potential role for these proteins in the asthma–obesity link cannot be ruled out.

Moreover, due to the normal evolution of adipose tissue, adiposity changes during childhood [14]. During the first years of life, adiposity increases rapidly due to the growth in the size of the adipocytes, which then remain stable for several years. During this time, height is still increasing, resulting in the slimming of the child. The onset of the second period of rapid growth in body fat starts around 6 years of age. From this moment both the size and the number of adipocytes increase [14]. Thus, hormonal and pro-inflammatory effects of obesity, hypothesized to be an effect of adipose tissue, might be of less importance in younger children. Therefore, it is plausible that different mechanisms could explain the association between overweight or obesity and asthma at different ages. To gain further insight in the explain that underpin the observed association between overweight or obesity and asthma, causal inference methodology is also an attractive approach. New applications have recently been developed for analysis on several outcomes and joint risk factors such as biomarkers or genetic factors [15].

In summary, the current evidence of an association between overweight or obesity and asthma is rather consistent in the literature, and the study by Bekkers et al. presented in this issue of *Clinical and Experimental Allergy* adds to the support of an association also among young children [7]. The temporal aspect of the asthma–obesity link seems to be rather complex in children and deserves further study. The exact mechanisms behind the observed epidemiological observations are still unknown and the results from Bekkers et al. do not support a major role of common inflammatory mechanisms. Understanding the association between obesity and asthma, and the mechanisms underlying this association will give us the possibility to set strategies for prevention of these two common conditions. Future epidemiological, as well as experimental studies, in this field are clearly needed.

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