

EDITORIAL

Clinical & Experimental Allergy

Sex, asthma and obesity: an intimate relationship?

This editorial discusses the findings of the papers in this issue by C. Murray et al. [3] pp. 78–85 and T.-N. Wang et al. [4] pp. 72–77.

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The evidence for an association between obesity and asthma is increasingly compelling. Consistent evidence from numerous cross-sectional studies supports the view that obesity is associated with an increased risk of asthma. Furthermore, evidence from meta-analyses of cohort studies in adults [1] and children [2], showing that obesity precedes the development of asthma, suggests that the association may be causal. Nevertheless, the mechanisms underlying the obesity–asthma association remain a mystery.

Excess fat has profound effects on the body. It changes the mechanical properties of the breathing apparatus, by limiting downward movement of diaphragm and stiffening the respiratory system and by taking up space in the pleural cavity. However, fat is not just inert space filler. Adipose tissue, consisting of fat cells and infiltrating macrophages, is metabolically active, producing hormones and adipokines that affect immune function and result in a low-grade systemic inflammation that is a consistent feature of obesity. The question is how can these effects of obesity change airway function to induce the clinical manifestations that we recognize as asthma?

Two studies reported in this issue of *Clinical & Experimental Allergy* have addressed this question [3, 4]. Both have confirmed the association between excessive body weight and asthma or wheeze and, as in many previous studies, both have found that the association is stronger in females than males. If sex is an important factor in the obesity–asthma association, then this may provide some clues about the underlying mechanism. Although many papers report differences in the association according to sex, the findings are mixed and depend to some extent on the outcome variable being measured. In adults, most papers report a significant association between high body

mass index (BMI) and asthma in women, but some fail to find a significant association in men. This difference could just reflect differences between women and men in the prevalence of either obesity or asthma, so that the power of some studies to detect the association in men may be limited. A recent meta-analysis of cohort studies, involving some 13 000 subjects, showed that both overweight and obesity were significant risks for the subsequent development of asthma, but found no differences in odds ratios between men and women [1]. In one of the few studies to show an effect of obesity on airway hyperresponsiveness (AHR), Chinn et al. [5] found a significant association in men, but not women. In children, meta-analysis has shown that both high birth weight and high weight in middle childhood are risks for the later development of asthma, but the analysis was unable to determine whether the risks were different between girls and boys [2]. In the paper by Murray et al. [3] in this issue of *Clinical & Experimental Allergy*, data from a birth cohort of 731 children followed until age 8 years showed that high BMI increased the risk of current wheeze at ages 3, 5 and 8 years, but at age 8 the risk was significantly greater in girls than boys. At ages 3 and 5 years, the risk of high BMI for current wheeze or for subsequent development of wheeze did not differ between girls and boys. Thus, it seems that sex-related differences in the association between asthma and obesity depend on age and on whether we are looking at risks for current or future development of asthma.

Both the inflammatory and mechanical effects of obesity, which potentially contribute to the development of asthma, could be influenced by sex. Systemic inflammation in the obese is characterized by high circulating levels of a variety of inflammatory molecules such as TNF- α , IL-6, plasminogen activator inhibitor-1 and macrophage chemotactic protein-1. Increased levels of C-reactive protein (CRP) have been associated with both obesity and asthma, and the paper by Wang et al. [4] in this issue of *Clinical & Experimental Allergy* considers whether the obesity–asthma association can be explained by CRP

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Cite this as: C. M. Salome and G. B. Marks, *Clinical & Experimental Allergy*, 2011 (41) 6–8.

levels in either men or women. Their findings indicate that high BMI is associated with asthma, that the strength of the association is greater in women than men, but that the difference in strength between the sexes cannot be explained by circulating high sensitivity CRP levels. Adipocytes also produce a number of hormones, including leptin and adiponectin, which have been associated with asthma. The strength of these associations is typically modest, but, importantly, they appear to be sex and age dependent. Increased leptin levels are associated with asthma in pre-pubertal boys [6] and pre-menopausal women [7]. However, adjusting for leptin levels does not alter the strength of the relationship between BMI and asthma, suggesting that the obesity asthma association is not explained by differences in leptin [7]. Fat tissue is also a source of oestrogen [8] but the role of oestrogen as a promoter or preventer of asthma remains poorly understood, since studies of asthma related to the menstrual cycle and to the use of oestrogen-only hormone replacement therapy have produced contradictory results. Obesity is associated with earlier sexual maturation in girls, but with later maturation in boys [9]. Girls who reach menarche before the age of 11 years are at increased risk of developing asthma symptoms if they are obese in childhood [10], and are likely to have more severe asthma symptoms if they become obese as adults [11]. Taken together these studies provide tantalizing suggestions of a role for fat-derived hormones in the obesity–asthma association, particularly in women, but as yet there is no definitive mechanism.

The mechanical effects of obesity on lung function depends on the regional distribution of fat, and since this differs in men and women, may have different effects on lung function in men and women [12]. Central obesity has a greater effect on lung function than BMI and is a more significant risk factor for asthma than BMI, even in women [13]. However, central obesity is less common in women than men, and seems unlikely to explain a stronger obesity–asthma association in women.

The papers by Murray et al. and Wang et al. also highlight sex differences in the prevalence of asthma. These sex differences change with age. It is well established that the prevalence of wheeze, asthma and AHR is higher in pre-pubertal boys than girls [14]. The most plausible explanation for this is that boys have larger lungs than girls in relation to stature and airway size [15] with consequently greater specific airway resistance at any given lung volume [16]. This would be expected to make boys more susceptible to wheezing illness. The prevalence of allergic sensitisation is higher in boys than girls [17] and this may be an additional explanation for the sex difference in asthma prevalence.

In adolescence and early adult life, there is a change in the sex distribution of asthma. Females are more likely than males to first manifest AHR after age 8–12 [18] and wheeze after age 10 [14]. This results in a higher prevalence of asthma and AHR in adult women compared with men [19]. There are also profound sex-specific changes in hospitalisation rates for asthma during adolescence [20]. This change in the sex pattern of incidence of asthma may be related to changes in the pattern of growth in lung function. In contrast to the findings in young children, longitudinal studies in adolescents reveal that growth of airways relative to lung volumes occurs more rapidly in males than females at this age [21]. Furthermore, dysanapsis, that is disproportionate growth of airways and lung size, appears to be more common in females at this age [21]. In a general population cohort examined at two yearly intervals from childhood to adult life, there are substantial sex differences in the relation between growth in height and growth in lung function during adolescence [22]. Among girls, the peak rate of growth in spirometric lung volumes coincided with the peak rate of growth in stature (around age 11–13). In contrast, among boys this peak occurred 2 years after the peak rate of growth in stature and growth in lung volume continued through to age 18–20 years. However, among adults the mean FEV₁/FVC ratio, a volume-adjusted index of airway calibre, is slightly higher in women compared with men [23]. Hence the higher prevalence of asthma in women is unlikely to be explained by dysanapsis alone.

This age-related change in the sex pattern of incidence of asthma does not appear to be related to changes in the pattern of atopy. In the cohort described above, the incidence of first onset of atopy remained higher in males than females after age 8–12 years [18]. In a large multinational study conducted in young adults, the prevalence of sensitization to house dust mite and to grass pollen was higher in men than women [24].

'Hormonal' effects on the airways are frequently cited as the basis for sex differences in the pattern of asthma. The existence of cyclical variations in airway function, pre-menstrual aggravation of asthma and changes in asthma control during pregnancy have been well recognized for many years. However, the nature of the relation between pubertal changes during adolescence and changes in airway function remain unclear.

While the papers by Wang et al. [4] and Murray et al. [3] add to the growing evidence of an association between obesity and asthma, and the likelihood that this association may be dependent in part on sex, the mechanism of the association among sex, obesity and asthma remains a mystery. The epidemic of obesity in western societies means that this is clearly an important priority for further research.

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