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EDITORIAL

Sex, smoking and body mass index: do they aid in uncovering the complex mechanisms behind airway hyperresponsiveness?

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Airway hyperresponsiveness (AHR) is the exaggerated narrowing of the airways in response to physical or chemical stimuli. It is a core characteristic of asthma, but is also present in chronic obstructive pulmonary disease (COPD) patients and the general asymptomatic population. Nowadays, experts agree that AHR has a fixed and a variable component. Generally, the fixed component reflects structural changes of the airways (i.e. airway remodeling) and the variable component reflects airway inflammation [1]. The primary mechanical cause of airway narrowing is contraction of the airway smooth muscle (ASM). The sensitivity of ASM contraction differs between individuals and within the same individual over time. Thus, it is important not to merely focus on differences in ASM contractility, but rather broaden our focus when trying to understand the complexities of AHR by studying various other internal and external factors that contribute to differences in AHR. These internal and external factors can be modifiable: e.g. smoking, body mass index (BMI), and air pollution, or non-modifiable: e.g. sex and age. In the current editorial, we focus on three important risk factors for AHR (i.e. sex, smoking, and BMI), and discuss the existing knowledge on their role in AHR development or severity in relation to understanding the mechanisms underlying AHR.

1. Sex

Many studies have investigated sex-differences in asthma and other respiratory health outcomes. In childhood, asthma is more prevalent in boys whereas it is more common among females in adulthood [2]. Interestingly, this sex-specific shift around puberty is also seen in the non-asthmatic general population [3] and in animal studies [4]. The turning point for this sex-specific shift is puberty, which underlines the role of sex hormones. Indeed, the female sex hormone estrogen is a risk factor for AHR, while protective effects are seen for the male sex hormone testosterone, as it decreases Th2-mediated airway inflammation [2,4]. Estrogen increases goblet cell hyperplasia and the release of IL-13, making females more prone to AHR [5]. Animal studies support this by showing less AHR and airway inflammation in ovariectomized mice and mice deficient in specific estrogen receptors, while lack of testosterone as in castrated male mice increased eosinophil and lymphocyte count and led to airway inflammation [2]. Since sex hormones affect airway inflammation, they likely act on the variable component of AHR. This implies that the effects can be reversible, which is partly reflected by a lower incidence of asthma in post-menopausal women [6]. However, the associations between menopause and AHR have not been studied yet. Another mechanism underlying the sex-specific differences in AHR could be airway physiology, with adult females having lower lung function and narrower airways than males, resulting in increased susceptibility of females to develop AHR [7]. In childhood, lung volumes are not different between boys and girls but boys have lower flow rates than girls indicating narrower airways in boys [8]. A final explanation for the sex-differences in AHR is the different effect of specific environmental factors in males and females. Examples of these are smoking and BMI, with females generally being more susceptible to their effects. Recently, it was shown that prenatal stress also has a sex-differential effect on AHR: female mice subjected to prenatal stress had more severe AHR than males [9]. The high glucocorticoid secretion in mothers as a result of stress may lower the levels of maternal progesterone which can increase the risk of asthma and AHR in female offspring since they have lower levels of progesterone expression in their lungs than males [9,10]. In summary, the association between sex and AHR depends on age, with a higher AHR prevalence in males during childhood and in females during adulthood. Sex-hormones most likely act on the variable component of AHR while differences in airway physiology contribute to the fixed component. Interestingly, airway physiology changes from childhood to adulthood and this indicates that the fixed AHR component might not be entirely stable over a lifetime.

2. Cigarette smoking

A higher number of pack-years and a longer duration of cigarette smoking are both established risk factors for the development of AHR. Smoking contributes to both the variable AHR component, mainly by inducing airway inflammation, and the fixed AHR component, since excessive and prolonged smoking may lead to airway remodeling. Studies have shown higher levels of airway inflammation in smokers compared to non-smokers [11]. Additionally, smoking increases airway vascular permeability and

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causes mucosal edema, which further contribute to AHR [12]. One possible mechanism underlying the association between smoking and the fixed component of AHR might be the increase in ASM responsiveness via increased release and entry of Ca^{2+}. Calcium regulating proteins like CD38 and TRPC3 have increased expression in smokers, adversely affecting the role of Ca^{2+} in ASM function [13]. Studies on both animal and humans have shown that cigarette smoking induces the production of pro-inflammatory cytokines such as IL-1, IL-6, IL-8, and TNF-α alongside a surge in inflammatory cells [14]. Specifically, cigarette smoke has been shown to affect polarization (activation) of M1 macrophages, making these macrophages, which are abundant in small airways, increase the release of IL-23 and IL-1β and promote cellular responses resulting in AHR [15]. Chronic smoking can also increase the excitability of the vagal bronchopulmonary sensory nerves causing severe bronchoconstriction [16]. Secondhand smoking can potentially contribute to AHR. Animal studies show that secondhand smoking from mothers increased airway resistance and activated inflammatory mechanisms in the offspring [17]. Interestingly, quitting smoking leads to a lower AHR severity over time, but it does not entirely normalize AHR in all subjects, indicating that the extensive structural alterations to the airways in some individuals are irreversible [18].

3. Body mass index

Studies have shown that higher BMI is associated with a higher prevalence of AHR, although not all studies agree on this. One postulated mechanical mechanism relating higher BMI to AHR is the accumulation of fat tissue in the thoracic cavity, which is associated with lower lung volumes and with a higher vulnerability to small airway closure, both important risk factors for AHR [19]. In addition, overweight and obesity are associated with higher levels of systemic inflammation, and this might contribute to AHR. However, it is unclear whether obesity causes AHR or whether AHR leads to weight gain due to respiratory symptoms that limit physical activity. Longitudinal studies on adolescents and adults showed that obesity was associated with the development of AHR after 4–6 years [20,21], but a recent study on obese children did not find this higher risk of AHR in adulthood [22]. Studies on weight loss in asthmatics showed that weight-loss is associated with a decrease in AHR [23], which supports the association between higher BMI and AHR. However, research on the effect of weight loss on the severity or prevalence of AHR in the general population is generally lacking. Overall, the evidence suggests that high BMI does not contribute to the fixed component of AHR since no irreversible changes in AHR are observed. In light of this, it is interesting to note that a recent murine study showed that offspring of mothers on a high-fat diet during pregnancy had a higher prevalence of AHR compared to offspring of mothers on a normal fat diet [24]. Whether this higher AHR-prevalence is reversible over time remains to be established.

By reviewing the evidence on three well-established risk factors for AHR (i.e. sex, smoking, and BMI, see Figure 1 for a schematic presentation of the evidence), we found support for the notion that AHR consists of a fixed component,

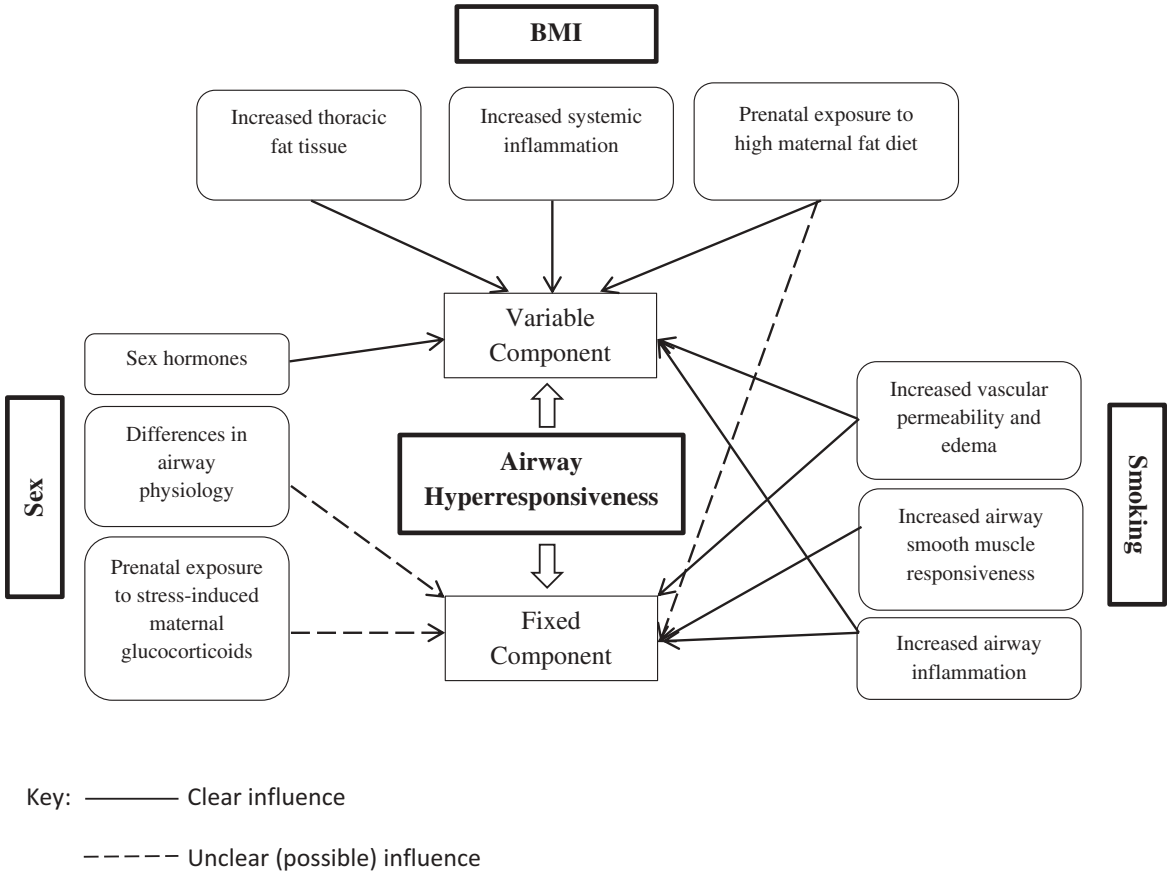

Figure 1. Schematic presentation of the relationship between sex, BMI, smoking and AHR.

reflecting airway remodeling, and a variable component, reflecting airway inflammation. Both sex and smoking exert their effects on AHR via both components whereas BMI mainly targets the variable component of AHR. Interestingly, the sex-specific differences in the fixed component of AHR indicate there might be changes in this fixed component over time. Further research is warranted to determine the exact sex-specific changes over time in lung physiology as this may identify targets for preventing or treating AHR. Both smoking and high BMI are risk factors that can be modified and this editorial indicates that, especially for smoking, it is important to quit as early as possible so that irreversible airway damage will be prevented. Research on these key risk factors for AHR can help in unraveling AHR further, as the current level of evidence is not lucid enough. For example, further research is warranted to pinpoint exact sex-specific changes over time in lung physiology and if this contributes to permanent changes in airway structure. The influence of novel factors such as maternal diet and prenatal exposure to stress and whether these have an enduring effect on lung physiology and AHR, specifically the fixed component, should also be further investigated.

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