Sex differences in childhood asthma is driven by a T2-high phenotype and mediated through sex hormone metabolites

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ABSTRACT (257 words)

Introduction

Sex differences in childhood asthma, allergy and atopic dermatitis have previously been described, but the development, clinical phenotype and nature of these sex differences is not well understood. Therefore, we investigated sex differences in these diseases throughout childhood and explored possible underlying mechanisms.

Methods

This study was conducted in the $COPSAC_{2000}$ (n=411) and $COPSAC_{2010}$ (n=700) mother-child cohorts, which were followed prospectively from birth until age 18 and 10 years, respectively. We examined sex differences in the prevalence of asthma, allergy, and atopic dermatitis outcomes using longitudinal generalized estimating equation models. Thereafter, we examined if the airway immune profile, systemic inflammation, functional stimulated immune responses or sex hormone metabolites (androgens, pregnenolones and progestins) mediated the observed sex differences.

Results

In both cohorts ($COPSAC_{2000}$ and $COPSAC_{2010}$), boys had a higher prevalence of asthma: OR=1.41 (95% CI, 1.00-1.97 and 1.7 (1.01-2.86), especially T2-high asthma, higher prevalence of allergic sensitisation: 1.69 (1.20-2.39) and 1.58 (0.98-2.55), and more exacerbations: IRR=1.79 (1.18-2.27) and 1.92 (1.24-2.97) until age 6 years, which persisted till age 18 in $COPSAC_{2000}$. Furthermore, boys had higher FeNO, blood eosinophil count, sRaw and increasing bronchial hyperresponsiveness to methacholine. Sex hormone metabolite levels in blood significantly mediated parts of the sex differences in allergic sensitisation and blood eosinophils.

Conclusion

Boys had higher prevalence of asthma and allergy outcomes, more asthma exacerbations and poorer lung function compared to girls through childhood across two birth cohort. This sex divergence was mostly driven by a T2 inflammatory phenotype and was partly mediated through differences in levels of sex hormone metabolites in early childhood.