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

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ABSTRACT (238 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 are not well understood.

Methods

We examined sex differences in the prevalence of asthma, allergy, and atopic dermatitis using longitudinal generalized estimating equation models in the $COPSAC_{2000}$ (n=411) and $COPSAC_{2010}$ (n=700) mother-child cohorts followed prospectively from birth. Thereafter, we examined possible mechanisms through airway immune profiles, systemic inflammation markers, functional immune responses, and sex hormone metabolites (androgens, pregnenolones, and progestins).

Results

In both $COPSAC_{2000}$ and $COPSAC_{2010}$, males had a higher prevalence of asthma: odds ratio 1.41 (95% CI, 1.00-1.97) and 1.7 (1.01-2.86), allergic sensitization: 1.69 (1.20-2.39) and 1.58 (0.98-2.55) and experienced more asthma exacerbations: incidence risk ratio 1.79 (1.18-2.27) and 1.92 (1.24-2.97) until age 6 years, which persisted until age 18 in $COPSAC_{2000}$. Furthermore, males had a significantly higher fraction of exhaled nitric oxide, blood eosinophils, specific airway resistance, and increasing bronchial hyperresponsiveness to methacholine. Sex hormone metabolite levels during preschool-age significantly mediated parts of the sex differences in allergic sensitization (proportion mediated: 0.16-0.18) and blood eosinophils (proportion mediated: 0.21-0.25).

Conclusion

Males had a higher prevalence of asthma, allergic sensitization, asthma exacerbations, and were characterized by reduced lung function compared to females through childhood across two mother-child cohorts. This sex difference was mostly driven by a T2-high inflammatory phenotype and partly mediated through differences in levels of sex hormone metabolites in early childhood.