We need a robust evidence base to unravel the relationship between sex hormones and asthma

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There has long been interest in whether sex hormones play a role in the development of asthma and influence its natural history, but much of this evidence base is of poor quality and hence difficult to interpret. This interest stems from clinical experiences, and findings from a substantial body of epidemiological investigations, and a smaller body of mechanistic and experimental studies. These have mainly focused on oestrogen and progesterone in females with inconsistent results. The focus on testosterone in both males and females in the linked study by Han *et al* is therefore welcome but other than these strengths,[1] it suffers from many of the same limitations as much of the previous body of epidemiological work. In this editorial, we seek to contextualise the findings from Han *et al* and offer suggestions on how to strengthen the evidence base for understanding the relationship between sex hormones and asthma.

There is considerable circumstantial evidence implicating sex hormones in asthma. For example, it is widely recognised that asthma is more prevalent in boys in the prepubertal period and that these sex differences reverse after menarche until at least the time of the menopause.[2] These sex differences are also seen in asthma admission patterns.[3] There is in addition evidence that fluctuations in sex hormones associated with menstruation, pregnancy and menopause can influence some women's asthma control.[4] Furthermore, there are a number of reports that exogenous sex hormones in the form of contraceptives and hormone replacement therapy (HRT) can impact on asthma development and outcomes.[5] Thus, for the most part, the focus of investigation has been on female sex hormones, which have potential for both proinflammatory and anti-inflammatory effects.

We recently summarised this evidence base through a systematic review investigating the effects of endogenous and exogenous sex steroid hormones in asthma (and allergy) in females.[6] Of the 57 eligible studies, 51 were observational studies and the remaining six were experimental.[6] We were concerned about the quality of many of these studies. These concerns centred on problems with selection bias, the failure to consider the full range of potential confounders and effect modifiers, selective reporting of outcomes and inadequate sample sizes. More fundamentally, we had reservations about the lack of explicit causal reasoning, inherent limitations in the cross-sectional design used in a number of studies and substandard reporting. That said, the evidence did suggest that early onset of puberty, both early and late onset of menarche, irregular menstruation (indicating anovulatory cycles), onset of menopause and use of HRT may be associated with increased risk of asthma in females.[6] The evidence was less clear in relation to hormonal contraceptives.

In an attempt to strengthen the evidence base, we recently undertook a 17 year cohort study focusing on exogenous sex hormones using a national primary care-based dataset.[7] The first of these analyses has found that use of hormonal contraceptives was associated with reduced risk of new-onset asthma in women of reproductive age. Importantly, longer duration of use was associated with a progressively greater reduction in the risk of developing asthma. Our in progress follow-on work seeks to assess the role of hormonal contraceptives in asthma exacerbations, and the effects of HRT on asthma onset and exacerbations.

The study by Han *et al* represents a step forward in that it focuses on free testosterone in both males and females.[1] This builds on their analysis published earlier this year utilising a subsample of those aged 18–79 years who participated in the US National Health and Nutrition Examination Survey (NHANES),[8] which found that the risk of current asthma was lower in women with higher levels of free testosterone, but not in men.[8] In contrast, oestradiol was not shown to be associated with current asthma in either men or women.[8] The effects of progesterone were not studied.

In their rationale for the current analysis, the authors state that the failure to detect a clear association in their NHANES study between elevated levels of free testosterone in men '*…could be explained by limited statistical power due to relatively small sample size*'. This is somewhat surprising given that the ORs comparing, for example, those with the highest quartile of free testosterone to those with the lowest quartile that is, Q4 versus Q1 was 0.98 (95% CI 0.51 to 1.88) for the model unadjusted for oestradiol and OR=1.18 (95% CI 0.67 to 2.08) in the adjusted analyses. While it is clear from the wide 95% CIs that there is uncertainty around these estimates, the point estimate still reflects the most likely results.

UK Biobank is substantially larger than NHANES, so this addresses their concern about sample size. The present analysis echoed the NHANES findings of the protective effects of higher free testosterone in women for asthma, but also found a protective effect in males: adjusted OR for Q4 versus Q1=0.87 (95% CI 0.82 to 0.91).[1] In the present study, Han *et al* were also able to study other outcomes, which revealed that higher levels of free testosterone were associated with lower risk of current wheeze in both women and men, lower odds of asthma hospitalisation in females and higher FEV1 and FVC in men, but lower FVC in females.[1]

Overall, the current study adds some further evidence that sex hormones may be implicated in the development of lung function and asthma outcomes in both females and males, but the evidence base remains weak. To strengthen an assessment of whether these constitute causal relationships, future studies should unambiguously specify the causal pathway(s) under investigation and express these preferably through directed acyclic graphs (DAGs). Wherever possible, hypotheses should be assessed through a longitudinal study design thereby allowing temporality to be assessed. It is vital that key confounders and effect modifiers are considered and the effects of unmeasured confounders are assessed. Propensity score analysis and use of instrumental variables may also prove helpful. Size matters when considering relatively uncommon outcomes (such as asthma incidence) and

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it is therefore imperative that studies are sufficiently large to allow adequate precision of estimates. Studies should have a statistical analysis plan developed prior to the analysis and this should be published. The use of appropriate reporting guidelines and the deposition of statistical code and, where possible, actual data in a data repository will help aid transparency and reproducibility.

There is a need to now progress to studies that aid causal inference. Taking the above described steps will, we hope, help.

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