Reviewer's report

Title: Effects of Endogenous Sex Hormones on Lung Function and Symptom Control in Adolescents with Asthma

Version: 0 Date: 26 Jan 2018

Reviewer: Anita Kozyrskyj

Reviewer's report:

This is a clearly written manuscript of a rigorously-conducted study of sex differences in asthma severity/control with advancing puberty that addresses a significant gap in the literature. DeBoer et al found lung function in boys to be associated with DHEA levels but with estradiol levels in girls. Lung function tests (spirometry, maximum bronchodilator and methacholine challenge) were conducted by trained personnel; asthma severity and asthma control were assessed according to ATS guidelines and a validated questionnaire, respectively. Both physical and serum biomarkers of adrenarche, thelarche and puberty were evaluated using valid and reliable methods. Univariate comparisons in lung function were performed across puberty stage. Multivariate logistic regression was conducted to derive the most parsimonious model for sex hormones and DHEA in relation to lung function. Results were clearly displayed.

Major comments:

1. Asthma status in children was well characterized but I recommend the addition of the following parameters to Table 1: i) atopic sensitization status and ii) age of asthma diagnosis or years with asthma symptoms. This information would enable the reader to discern whether asthma phenotypes were comparable between boys and girls, namely whether asthma in boys was longstanding and atopic versus the non-atopic asthma of recent onset in girls.

2. Since many readers may not be familiar with the expected changes to DHEA or DHEA-s with adrenarche, I recommend inserting a brief description in the introduction, with a citation by: Mouritsen et al. Longitudinal changes in serum concentrations of adrenal androgen metabolites and their ratios by LC-MS/MS in healthy boys and girls. Clinica Chimica Acta 2015. In general, the paper was lacking a description and citations of expected hormonal changes in adrenarche, thelarche, pubarche and menarche.

3. Potentially, there were 2 confounding factors that were not controlled in study comparisons: i) child overweight and ii) child depression status. Adjusting biomarker models for these factors may not be helpful as they may explain away the association with DHEA or a sex steroid. Hence, I recommend that associations be tested in children
with and without these factors. Since height and weight were measured, minimally I recommend this stratified analysis.

4. Allthough the paper is on sex steroid differences, authors should be prepared to discuss other hormonal changes in puberty such as transient insulin resistance or elevated cortisol, which accompany sex steroid changes. Some of these have been found to be associated with asthma persistence. See Kozyrskyj et al. Am J Resp Crit Care Med 2014;190 and Bahreinian et al. Am J Respir Crit Care Med 2013;187.

Minor comments:

1) Page 4, line 61: Are authors able to comment on the temporality of the discord between peripheral and central changes in girls, namely whether peripheral androgen changes precede the central changes to estradiol and breast development?

2) Page 5, line 5-6: The qualifier "…..of these studies" confuses the purpose of the current study versus that of the studies cited in previous sentences.

3) Methods section: Specify the timing of the blood draw to measure sex hormones in relation to lung function testing since the latter may have influenced the former.

4) Page 8, line 16: It was unclear whether lack of a difference in the covariate distribution in Table 1 was statistically significant. Please add p values to the table.

5) Page 10, line 32: Stating the study N in the first sentence of the Discussion provides context to the discussion of study results that follow.

6) Page 10, line 33: The following sentence was very vague: "In males, lung function was not different and symptom control improved, whereas in females lung function and symptom control were worse."
Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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