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Association of Sex Steroid Hormones with Adult Asthma in the United States, 2013–2016

To the Editor:

We read with great interest the article by Han and colleagues on the association between sex steroid hormones and asthma in U.S. adults (1). The sex disparity in asthma prevalence is well established, and compelling evidence links it to sex hormones (2). Using National Health and Nutrition Examination Survey (NHANES) data from 2013–2014 and 2015–2016, the authors found that elevated serum-free testosterone was significantly associated with lower odds of current asthma in women only. Analyses stratified by obesity showed a similar association only in obese women and nonobese men. Here, we raise some methodological considerations.

First, the statistical power is considered low (especially for men) because of the small number of subjects with current asthma (239 men and 450 women), as the authors indicated, but it could benefit from excluding fewer NHANES participants. In this study, 728 (6.0%) adults ≥ 80 years of age were excluded for no specific reason. In addition, 1,623 (17.6%) adults were further excluded owing to missing data on annual household income ($n = 516$), body mass index ($n = 84$), smoking status ($n = 4$), second-hand smoke exposure ($n = 4$), pack-years ($n = 138$), family history of asthma ($n = 182$), or ever use of birth control pills or any form of female hormones ($n = 695$). However, the authors could have included the adults with missing data on certain covariates in the analyses by using several analytic strategies, including assigning an “unknown” category for missing values in a given covariate, and dealing with the missing data using multiple imputation (3). It would be of great interest to determine whether the results would vary if the sample size were increased by $>20\%$. Also note that the information on ever use of female hormones was available only for females ≥ 20 years of age. In this study, excluding women without this information actually restricted the analyses to women ≥ 20 years of age.

Second, the session time of venipuncture and the season when the examination was performed were not considered in this study. Diurnal variations in serum testosterone levels (i.e., peaking in the morning and decreasing afterward) have been well documented in both men and women, although the amplitude of variation declines with age (4, 5). Despite these inconsistencies, the evidence suggested a significant seasonal variation in serum testosterone (6). Association studies on testosterone and health outcomes are expected to

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take these two covariates into account to minimize possible misclassifications. In NHANES, the time of venipuncture was classified as a morning, afternoon, or evening session and can be found in the Fasting Questionnaire file (Cycle 2013–2014: https://www.cdc.gov/Nchs/Nhanes/2013-2014/FASTQX_H.htm and Cycle 2015–2016: https://www.cdc.gov/Nchs/Nhanes/2015-2016/FASTQX_I.htm) (variable PHDSESN). The season when the examination was performed can be obtained from the Demographic Variables and Sample Weights file (Cycle 2013–2014: https://www.cdc.gov/Nchs/Nhanes/2013-2014/DEMO_H.htm and Cycle 2015–2016: https://www.cdc.gov/Nchs/Nhanes/2015-2016/DEMO_I.htm) (variable RIDEXMON) pertaining to a 6-month time period, either November 1 through April 30 or May 1 through October 31.

Third, the interaction between menopausal status and sex hormones on current asthma in women may not have been adequately investigated. The authors tried to explore this interaction using age with a cutoff of 51 years and serum estradiol in women, as they stated that there were no data on menopausal status in NHANES. However, menopausal information can be obtained in the Reproductive Health file (Cycle 2013–2014: https://www.cdc.gov/Nchs/Nhanes/2013-2014/RHQ_H.htm and Cycle 2015–2016: https://www.cdc.gov/Nchs/Nhanes/2015-2016/RHQ_I.htm) based on several questions, including “Have you had at least one menstrual period in the past 12 months?”, “What is the reason that you have not had a period in the past 12 months?”, and “How old were you when you had your last menstrual period?” Information on hysterectomy and bilateral oophorectomy were also available to help identify the subjects’ menopausal status. Analyses stratified by menopausal status may help us better understand the association between sex hormones and current asthma in women. ■

Author disclosures are available with the text of this letter at www.atsjournals.org.

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Reply to Liu and Zhou

From the Authors:

We thank Dr. Liu and Dr. Zhou for their interest and thoughtful comments about our cross-sectional study of sex steroid hormones and asthma among adult participants in the National Health and Nutrition Examination Survey (NHANES) (1). We reported that elevated serum levels of free testosterone were associated with lower odds of current asthma in women. After stratification by obesity, we found that elevated serum levels of both free testosterone and

estradiol were associated with lower odds of current asthma in obese women and that an elevated serum estradiol level was associated with lower odds of current asthma in nonobese men (1).

Dr. Liu and Dr. Zhou questioned why we excluded participants ≥ 80 years of age from the analysis. This decision was made because we lacked the exact ages of those subjects (e.g., data from a 91-yr-old participant was clustered in the same category as those from an 80-yr-old participant) and because of high potential for comorbidities that could be misclassified as asthma in elderly subjects (e.g., heart failure).

We acknowledged having lower statistical power to detect an association between sex hormones and asthma in men than in women. Dr. Liu and Dr. Zhou suggested an analysis including subjects with missing data for covariates and accounting for the time of the day (morning, afternoon, or evening) and the season (November–April or May–October) of collection of blood samples, as testosterone level may vary according to these variables. According to NHANES analytical guidelines (2), mobile examination center operations avoid certain geographic areas during the winter. Thus, the statistical

Table 1. Multivariable Analysis of Sex Hormone Levels and Current Asthma by Sex ($n = 9,238$)

Serum Sex Hormone Quartile	Odds Ratio (95% Confidence Interval)		
	Model 1	Model 2	Model 3*
Men ($n = 4,502$)			
Free testosterone (pmol/L)			
Q1 (<137.8)	1.0 (reference)	—	1.0 (reference)
Q2 (137.8–197.1)	0.96 (0.61–1.52)	—	1.04 (0.67–1.60)
Q3 (197.1–263.7)	0.65 (0.40–1.07)	—	0.72 (0.46–1.12)
Q4 (≥ 263.7)	0.97 (0.47–1.94)	—	1.11 (0.60–2.06)
Estradiol (pmol/L)			
Q1 (<68.3)	—	1.0 (reference)	1.0 (reference)
Q2 (68.3–87.2)	—	0.68 (0.38–1.21)	0.68 (0.39–1.17)
Q3 (87.2–108.6)	—	0.71 (0.42–1.21)	0.71 (0.45–1.12)
Q4 (≥ 108.6)	—	0.74 (0.44–1.26)	0.73 (0.48–1.13)
Women ($n = 4,736$)			
Free testosterone (pmol/L)			
Q1 (<3.2)	1.0 (reference)	—	1.0 (reference)
Q2 (3.2–5.6)	0.71 (0.52–0.95) [†]	—	0.71 (0.53–0.96) [†]
Q3 (5.6–9.3)	0.85 (0.64–1.12)	—	0.85 (0.63–1.15)
Q4 (≥ 9.3)	0.55 (0.39–0.78) ^{‡§}	—	0.57 (0.40–0.80) [‡]
Estradiol (pmol/L)			
Q1 (<22.8)	—	1.0	1.0
Q2 (22.8–87.7)	—	0.86 (0.55–1.34)	0.94 (0.59–1.49)
Q3 (87.7–307.5)	—	0.67 (0.48–0.94) [†]	0.75 (0.54–1.05)
Q4 (≥ 307.5)	—	0.86 (0.54–1.35)	0.97 (0.60–1.57)

Definition of abbreviation: Q = quartile.

All models adjusted for age, race/ethnicity, annual household income, body mass index, family history of asthma, secondhand smoke, smoking status, pack-years of smoking, ever use of birth control pills or any sex hormones (in women), the 6-month period of the examination, and the time of day when the examination was performed.

*Model 1 assessed free testosterone without adjusting for estradiol, model 2 assessed estradiol without adjusting for free testosterone, and model 3 adjusted for a given other sex hormone.

[†] $P < 0.05$.

[‡] $P < 0.01$.

[§] P for trend < 0.05 .

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efficiency of the sample is diminished for any variable that may be related to seasonal variation and differs by region of the country (2). In an effort to address the concerns outlined here, we repeated the analysis after assigning an “unknown” category for missing data on categorical covariates (e.g., ever use of sex hormones in women) and a median value for missing data on continuous covariates.