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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 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.

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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This multivariable analysis, which included all 9,238 eligible participants, yielded very similar results to those reported in our recent article (Table 1).

Finally, we appreciate Dr. Liu and Dr. Zhou's comment on our definition of menopause. We used the mean age at menopause in U.S. women (51 yr) to define menopause. Indeed, average estradiol levels dropped markedly after age 50 years among women included in our analysis. In a secondary analysis, we did not find a significant interaction between menopause (as defined here) and serum estradiol on asthma in participating women. Given the comments by Dr. Liu and Dr. Zhou, we repeated the secondary analysis redefining menopause as not having had a menstrual period for at least a year ([age when interviewed/examined] – [self-reported age at the last menstrual period] $\geqslant$1 yr) or self-report of having had a hysterectomy in which both ovaries were removed. Using this alternative definition, we also found no significant interaction between menopause and serum estradiol on current asthma.

Large longitudinal studies with precise information on menopausal status should help better understand the relation between sex hormones and current asthma in adults. ■

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Early Disruption of VEGF Receptor Signaling and the Risk for Adult Emphysema

To the Editor:

We read with interest two recent letters to the editor that describe the remarkable effects of the combination of SU5416, an inhibitor of VEGFR2 signaling, with chronic hypoxia on pulmonary circulation in adult rats (1, 2). Over time, this exposure causes marked elevations of pulmonary artery pressure, with right ventricular hypertrophy, striking hypertensive remodeling of the pulmonary arteries, and, most interestingly, obstructive intimal lesions that resemble the extreme histopathology of severe human pulmonary artery hypertension (PAH). These findings are consistent with the original description of this rodent PAH model (3), which greatly stimulated the field because of the presence of the unique feature of obliterative vascular disease, which is generally missing from other animal models of PAH.

Interestingly, one of the letters convincingly noted the additional finding of enlarged distal airspaces in this model, which supports the concept that the combination of SU5416 with chronic hypoxia causes histologic features of emphysema in addition to PAH (1, 3). This striking association of impaired vascular structure and function with the development of emphysema supports the unique opportunities of using this model to investigate fundamental mechanisms through which paracrine vascular signals modulate airspace structure and that disruption of "angiocrine signals" could contribute to the pathobiology of emphysema. Thus, the presence of emphysema-like changes may provide unique opportunities to use the SU-hypoxia model to further understand the pathogenesis and treatment of chronic lung diseases in adults, such as emphysema and chronic obstructive pulmonary disease, as well as severe PAH.

As suggested in the letter from Bogaard and colleagues (1), however, findings of airspace enlargement may not be consistently observed between the different reports involving the SU-hypoxia model to study PAH in adult rats. The authors question the degree of changes in lung airspace size and that such an effect may be milder than reported by Kojonazarov and colleagues (2).

How to best reconcile these differences is uncertain; however, one clear message from published data emerges regarding the important role of the developmental timing of disrupted VEGF signaling (4–6). Intrauterine treatment of fetal sheep with a VEGF-specific aptamer not only causes striking pulmonary hypertension (PH) and vascular remodeling but further reduces vascular and airspace growth and causes severe neonatal PH at birth (4). Similarly, hemodynamic pulmonary vascular stress *in utero* causes sustained PH but also inhibits angiogenesis and decreases distal airspace growth before birth (4). Perinatal disruption of VEGF signaling also has long-lasting implications regarding the risk for emphysema in adult life. Importantly, SU5416 injection on the first day of life is sufficient to cause PH and alveolar simplification in 3-week-old rats and also leads to sustained abnormalities of lung alveolar structure that persist into adulthood (3–4 mo of age) with reduced pulmonary vascular density and increased right ventricular hypertrophy (6) (Figure 1). These changes are linked to the critical role of developmental timing of lung vascular injury on early (infant) and late (adult) lung structure, which are independent of hypoxia.

Thus, despite controversies on the impact of SU5416 with or without chronic hypoxia in the adult lung, strong data remain that support the concept of developmental origins of lung disease, in which early disruption of angiogenesis (by early disruption of VEGF receptor signaling or other critical pathways) not only impairs alveolar growth throughout infancy but also can extend into adult life, which likely increases

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