airways. Although it was beyond the scope of our study to investigate
the etiology of reduced TAC, our data suggest that the same
remodeling process that occurs in the TBs may extend to the larger
airways and be measured by MDCT.

We acknowledge that this was a retrospective study, and
therefore it was not possible to access preoperative MDCT images to
compare the relationship with TAC using clinical and explant CT
images. The lung specimens have no chest wall and MDCT images
were acquired at a fixed lung volume, without any motion artifacts,
and therefore an increased number of airways may be quantified in
specimen MDCT. MDCT LA950 measurements may also be
overestimated in lung specimens due to a lack of blood
flow/volume. However, our primary objective was to investigate the
association between TAC and TBs, which are not impacted by the
lack of blood flow/volume. We also note that although we used
random sampling to obtain cores for micro-CT analysis from donor
lungs, we used selective sampling to avoid regions of severe
emphysema in the COPD lungs, as such regions have been reported
to lack TBs (1, 2). This may have resulted in biased estimates of the
number of TBs in the COPD lungs and may partially explain the
lack of correlation between TBs and TAC in COPD.

In conclusion, this study shows that TAC is associated with both
the number of TBs and the distortion/remodeling that occurs in the
TBs that remain in COPD lungs. Thus, TAC may be used as an
imaging biomarker (9) to estimate the number and distortion of small
airways and may provide a valuable outcome measure for clinical trials
of new therapies aimed at the prevention and treatment of small
airways disease.
afterload, a comprehensive evaluation of RV–PA coupling is central in the characterization of cardiopulmonary function (1). Recent work from our group demonstrated that prematurity leads to RV dysfunction and early evidence of PVD in young adulthood, but little is known regarding the long-term impact on RV–PA coupling (2). This coupling interaction was not available to report in our original study or a previously reported abstract (2, 3). We hypothesize that young adults born preterm have subclinical RV dysfunction with impaired RV–PA coupling.

We analyzed prospectively acquired data from our original study (2), obtained from adults who were born premature (n = 10, five male; current age 26.9 ± 0.3 yr; gestational age 28.6 ± 0.9 wk) and were recruited from the Newborn Lung Project, which includes a cohort of infants who were born in Wisconsin and Iowa between 1988 and 1991 and were longitudinally followed. Control subjects were born at term (n = 9, seven male; current age 25.8 ± 0.3 yr; gestational age 40.2 ± 0.2 wk) and recruited from the general population. The Institutional Review Board of the University of Wisconsin–Madison School of Medicine and Public Health approved all procedures. Informed consent was obtained from all subjects.

RV–PA coupling can be calculated as the ratio of end-systolic elastance (Ees, a measure of contractility) to effective arterial elastance (Ea, a measure of RV afterload). In this study, RV and PA elastance (Ees, a measure of contractility) to effective arterial load, a comprehensive evaluation of RV function

<table>
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<th>Table 1. Baseline Characteristics</th>
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<tr>
<td>Anthropometric data</td>
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<td>Gestational age, wk</td>
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<td>Current age, yr</td>
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<td>BSA, m²</td>
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<td>Sex, male, n (%)</td>
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<td>Structure and function</td>
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<td>HR, bpm</td>
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<tr>
<td>MPA max area, cm²/m²</td>
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<td>MPA RAC</td>
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<td>Ao max area, cm²/m²</td>
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<td>Ao RAC</td>
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<tr>
<td>(MPA/Ao)/BSA, m⁻²</td>
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<td>RV EDVi, ml/m²</td>
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<td>RV ESVi, ml/m²</td>
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<td>RV SVi, ml/m²</td>
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<td>RV EF</td>
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<td>LV EDVi, ml/m²</td>
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<td>LV ESVi, ml/m²</td>
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<td>LV SV/ESVi</td>
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<td>Cardiopulmonary hemodynamics</td>
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<td>mPAP, mm Hg</td>
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<td>Piso, mm Hg</td>
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<td>Pes, mm Hg</td>
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<td>Ea, mm Hg/ml</td>
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<td>Ees, mm Hg/ml</td>
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<td>Zc, mm Hg · s/ml</td>
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<td>Zm, mm Hg · s/ml</td>
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<td>τweiss, ms</td>
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Definition of abbreviations: Ao = aorta; BSA = body surface area; Ea = effective arterial elastance; EDVi = end-diastolic volume index (EDV/BSA); Ees = end-systolic elastance; EF = ejection fraction (SV/EDV); ESVi = end-systolic volume index (ESV/BSA); HR = heart rate; LV = left ventricle; MPA = main pulmonary artery; mPAP = mean pulmonary artery pressure; Pes = end-systolic pressure; Piso = isovolumetric pressure obtained from the single-beat method; RAC = relative area change; RV = right ventricle; SV = stroke volume index (SV/BSA); τweiss = time constant of ventilator relaxation; Zc = characteristic impedance; Zm = zero Hz impedance.

Data are shown as mean ± SE. Bold indicates P < 0.05.

in the body surface area indexed chamber volumes (end-diastolic volume index and ESV index) between the preterm and term-born subjects.

Pressure waveform analysis revealed that preterm subjects had increased total pulmonary vascular resistance (Zm) that contributed to increased RV afterload (0.11 ± 0.02 vs. 0.20 ± 0.02 mm Hg/ml; P = 0.035). This contributed to increased Pes (11.2 ± 1.6 vs. 17.9 ± 1.9 mm Hg; P = 0.030) and reduced RV ejection fraction (0.62 ± 0.01 vs. 0.59 ± 0.01; P = 0.041) and RV stroke volume index (52.99 ± 2.20 vs. 47.58 ± 1.36 ml/m²; P = 0.056), which could indicate the beginning stages of RV systolic dysfunction.
Analysis of the CMR phase-contrast images revealed increased PA dilation in preterm subjects, whereas the Ao area was comparable between the preterm and term-born subjects. However, no difference in the stiffness of the PA was measured between the preterm and term-born subjects, as estimated noninvasively via the relative area change and invasively by the characteristic impedance, \( Z_c \).

Preterm subjects had an increased RV relaxation time constant, \( \tau_{\text{relax}} \) (27.46 \( \pm \) 2.76 vs. 42.25 \( \pm \) 6.05 ms; \( P = 0.085 \)), suggesting reduced RV diastolic function. Lastly, no compensatory changes in RV contractility were observed in preterm subjects. Maintained contractility with increased RV afterload led to reduced RV–PA coupling. Several preterm subjects also presented with PA pressures consistent with pulmonary hypertension (2). This study was not designed to address the causation or mechanistic progression of reduced RV–PA coupling; however, we previously demonstrated mitochondrial DNA damage and dysregulated biogenesis in a rat model of prematurity-related lung disease (8). These animals also developed RV–PA uncoupling in a setting of modest pulmonary hypertension, which we proposed represents an intrinsic RV insult of prematurity. Future studies are needed to test these mechanisms.

The results of this study should be interpreted within the framework of its inherent limitations, primarily the small sample size and the asynchronous acquisition of RV pressures and volumes. The single-beat method was not validated against the gold-standard, multibeat method with a preload reduction in subjects with PVD; however, the benefits associated with the single-beat method as a measure of RV–PA coupling have been well described (4).

In summary, otherwise healthy, young adults who were born preterm were found to have high-resistance/low-compliance pulmonary vascular beds with attenuated RV adaptation in the face of increased vascular load. This resulted in impaired RV–PA coupling, as demonstrated by two different methods. These findings add to the growing evidence that preterm birth has profound lifelong consequences that warrant further study.

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**CORRESPONDENCE**

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

Ashley Mulchrone, Ph.D.
University of Wisconsin–Madison
Madison, Wisconsin

Alessandro Bellofiore, Ph.D.
San José State University
San José, California

Johannes M. Douwes, M.D., Ph.D.
University Medical Center Groningen
Groningen, the Netherlands

Neal Duong
Arij G. Beshish, M.B. B.Ch., Ph.D.
Gregory P. Barton, Ph.D.
Christopher J. Francois, M.D.
Marlowe W. Eldridge, M.D.
Kara N. Goss, M.D.
Naomi C. Chesler, Ph.D.*
University of Wisconsin–Madison
Madison, Wisconsin

ORCID ID: 0000-0002-7612-5796 (N.C.C.).

*Corresponding author (e-mail: naomi.chesler@wisc.edu).

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**References**


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**Correspondence**

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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 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://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/FASTQX_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/FASTQX_H.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://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/DEMO_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/DEMO_H.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://wwwn.cdc.gov/Nchs/Nhanes/2013-2014/RHQ_H.htm and Cycle 2015-2016: https://wwwn.cdc.gov/Nchs/Nhanes/2015-2016/RHQ_L.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.atjournal.org.

Yuewei Liu, M.D., Ph.D.*
Sun Yat-sen University
Guangzhou, China

Yun Zhou, Ph.D.
Guangzhou Medical University
Guangzhou, China

ORCID IDs: 0000-0001-5970-4262 (Y.L.); 0000-0002-1758-7499 (Y.Z.).

*Corresponding author (e-mail: liuyuewei@mail.sysu.edu.cn).

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