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Sex-related Differences in Pulmonary Physiologic Outcome Measures in a High Risk Birth Cohort

Amy O. Thomas, MD¹, Daniel J. Jackson, MD¹, Michael D. Evans, MS³, Victoria Rajamanickam, MS³, Ronald E. Gangnon, PhD³, Sean B. Fain, PhD^{5,6}, Ronald L. Sorkness, PhD^{1,2,4}, Adesua Y. Okupa, MD¹, Alex Thomas, MD¹, James E. Gern, MD^{1,2}, and Robert F. Lemanske Jr., MD^{1,2}

¹ Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI

² Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

³ Department of Biostatistics and Medical Informatics, University of Wisconsin School of Medicine and Public Health, Madison, WI

⁴ Department of Pharmacy, University of Wisconsin School of Medicine and Public Health, Madison, WI

⁵ Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI

⁶ Department of Medical Physics. University of Wisconsin School of Medicine and Public Health, Madison, WI

Abstract

BACKGROUND—Sex influences the risk of wheezing illnesses and the prevalence of asthma throughout childhood.

OBJECTIVE—To better understand mechanisms of these effects, we analyzed longitudinal relationships between sex, lung physiology and asthma in the Childhood Origins of ASThma (COAST) birth cohort study.

METHODS—COAST children were followed prospectively from birth and assessed annually. Results of spirometry, fractional exhaled nitric oxide (FeNO), mannitol provocation testing (MPT), and ³He gas MRI were assessed by sex using multivariate models including age, asthma diagnosis, and wheezing histories.

Corresponding Author: Daniel J. Jackson, MD Assistant Professor Department of Pediatrics Section of Allergy, Immunology and Rheumatology University of Wisconsin School of Medicine and Public Health K4/936 Clinical Sciences Center 600 Highland Avenue Madison, WI 53792-9988 djj@medicine.wisc.edu 608-263-7686.

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RESULTS—Girls had higher pre-bronchodilator FEV_{0.5}/FVC values than boys (mean difference 0.017, 95% CI 0.000-0.034; p=0.05) of equivalent age. Post-bronchodilator findings were more pronounced, with boys demonstrating reduced FEV_{0.5}/FVC values compared to girls of equivalent age (mean difference 0.032, 95% CI 0.014-0.049; p=0.0005). Conversely, girls were noted to have higher ventilation defects on ³He MRI than boys (p=0.01). No differences were noted in the rate of positive responses to mannitol provocation or FeNO measurements.

CONCLUSIONS—Lower airflow values are present by spirometry for prepubertal males when compared to age matched females; however, greater ³He ventilation defects were noted in girls. This could represent a greater degree of subclinical air trapping in prepubertal girls, as residual volumes are not detected on standard spirometric readings. No differences were noted between the two sexes with airway hyper-responsiveness (MPT) or inflammation (FeNO). Prospective peripubertal follow up will determine if these differences persist or change with the de novo expression and remission of asthma based on sex and age.

Keywords

sex; gender; asthma; pulmonary physiology; spirometry; helium MRI; ventilation defects; mannitol; airway hyperreactivity; fractional exhaled nitric oxide

Introduction

Previous studies have demonstrated sex differences in asthma over time, with males exhibiting a higher prevalence early in life.¹ This finding reverses sometime during the time of puberty, and then females develop higher incidence and prevalence rates that persist into the adult years. Mechanisms responsible for these findings remain elusive, but could be related to changes in lung physiology related to sex and age.

Childhood Origins of ASThma (COAST) is a prospective high-risk birth cohort study designed to evaluate the interactions amongst age, patterns of immune dysfunction, and viral infections with respect to the subsequent development of asthma and allergic diseases.² Previously, we identified sex differences in patterns of immune development (as measured by cytokine responses of peripheral blood mononuclear cells) that were associated with wheezing illnesses. In children with recurrent wheezing during the first three years of life, boys were found to have increased levels of IFN- γ , IL-5 and IL-13 responses at age 3 compared to age matched females³. Boys also had increased rates of allergic sensitization, total IgE levels, and peripheral eosinophil counts at age 3.³ Genotyping of the IFN- γ single nucleotide polymorphisms (SNPs) by Loisel et al identified an interaction by sex in which male heterozygotes for specific SNPs (rs2069727 and rs2430561) had the highest risk for asthma development, with heterozygote girls conversely showing the lowest risk. These findings suggest specific genotype-by-sex effects on asthma risk that are associated with distinct cytokine response profiles.⁴

Other research groups have further evaluated pre-pubertal physiologic sex differences in pulmonary function,⁵ fractional exhaled nitric oxide (FeNO),⁶ and methacholine airway responsiveness.⁷ These findings indicate that sex affects several aspects of lung physiology. To prospectively identify relationships among sex, lung physiology and asthma, we

longitudinally evaluated spirometry and FeNO within the COAST study, and in addition, conducted cross sectional analysis of mannitol airway responsiveness and structure function relationships using hyperpolarized ^3He gas magnetic resonance imaging (MRI).

Methods

After obtaining informed consent, 289 participants were enrolled at birth in the COAST study beginning in November 1998 and ending in May 2000. At least one parent was required to have respiratory allergies and/or physician diagnosed asthma. 285 participants remained enrolled at 1 year, with 259 enrolled at year 6 and 217 enrolled at year 11 (Table 1). Details of the study design have been described previously.² The University of Wisconsin Human Subjects Committee approved the study.

Children were diagnosed with asthma if they fulfilled at least one of the following criteria⁸: (1) physician-diagnosed asthma; (2) frequent albuterol use for coughing or wheezing episodes as prescribed by a physician; (3) use of a prescribed daily controller medication; (4) an implemented step-up plan, including use of albuterol or inhaled corticosteroids during illness as prescribed by a physician; (5) use of prednisone for an asthma exacerbation.

Spirometry Testing Procedures

Spirometry was performed using the Jaeger Masterscope System on study participants aged 4-11 years (n=240). Reproducibility and acceptability standards developed by ATS and modified through the CARE Network were followed.^{10, 11}

Fractional Exhaled Nitric Oxide

FeNO testing was performed on study participants aged 5-11 years (n=226). Measurements (in parts per billion) were performed via the online NIOX system according to ATS standards adapted for children.¹² The expiratory flow rate was 0.05 L/s, with exhalation times of at least 6 seconds. Acceptability was defined as 3 measurements within 10% or 2 measurements within 5%. Measurements were taken before the performance of spirometry.

Mannitol Bronchoprovocation

Mannitol bronchoprovocation was performed at age 11 (171 participants attempted, 144 completed). Dry powder mannitol (AridolTM) was administered in cumulative doses (0, 5, 10, 20, 40, 80, 160, 160mg). A positive challenge was defined as the dose causing a 15% fall in FEV₁.¹³

Magnetic Resonance Imaging

Pulmonary MRI with inhaled ^3He gas was performed on children aged 9 to 10 years (n=44) as previously described.¹⁴ Briefly, 19 female and 25 male participants were recruited from the highest and lowest quartiles of FEV₁ measured at age 8 (FEV₁ ≥ 109.9% of predicted value or FEV₁ ≤ 91.4% of predicted value), and from those with or without a moderate-to-severe rhinovirus illness prior to age one year, in approximately equal numbers. Quartile cutoffs were selected to increase chances of observing differences in imaging amongst the mild asthma phenotypes of the cohort. ^3He was polarized using spin-exchange optical

pumping in a commercial polarizer (HeliSpin; GE Healthcare, Durham, NC). The polarized ^3He gas (~30% polarization) was diluted with nitrogen to produce a volume adjusted for each subject (14% of the subjects total lung capacity (TLC)). Imaging studies were performed on a 1.5 T clinical magnetic resonance scanner (SignaHDx; GE Healthcare, Waukesha, WI) with broadband imaging capability. Fast MRI acquisitions were used to limit breath-hold time to 15 seconds or less. The anoxic dose of ^3He and N_2 did not cause any adverse effects. A ventilation defect was assigned a score based on extent of lobar involvement (1 less than 25%; 2, 26-50%; 3, 51-75%; 4, at least 76% of a lobe). The total ventilation defect score used for analysis was the summation of the scores across the whole lung.

Statistical Analysis

Spirometry measurements were compared by sex using longitudinal mixed effect models with fixed effects for year, sex, 'asthma ever' (ages 6, 8 or 11 years) diagnosis, and their interactions, and a random effect for participant to account for repeated measures over the years. Fractional exhaled nitric oxide measurements were compared by sex using a longitudinal mixed effect model with fixed effects for sex, year, asthma ever, and their interactions, and a random effect for participant. Mannitol bronchoprovocation data were compared by sex and current asthma using logistic regression. Ventilation defect scores were square-root transformed for analysis and compared by sex using linear models with sex, current asthma, and total lung capacity as covariates. In the absence of significant sex-by-asthma and sex-by-year interactions, the p-value for the main effect for sex is reported. A two-sided p-value less than 0.05 was regarded as statistically significant.

Results

Spirometry

For spirometric values obtained between ages 5-11 years, girls had higher pre-bronchodilator $\text{FEV}_{0.5}/\text{FVC}$ values than boys (mean difference 0.017, 95% CI 0.000-0.034; $p=0.05$). Post-bronchodilator findings were more pronounced, with boys demonstrating reduced $\text{FEV}_{0.5}/\text{FVC}$ values compared to girls of equivalent age (mean difference 0.032, 95% CI 0.014-0.049; $p=0.0005$). Similar sex findings were noted for FEV_1/FVC (post-bronchodilator mean difference 0.015, 95% CI 0.002- 0.028; $p=0.02$). There was no evidence that the sex difference varied over time (sex-by-year interaction p -values > 0.2). There was no evidence that the effect of asthma differed between girls and boys (asthma-by-sex interaction p -values > 0.2) (Figure 1).

Fractional Exhaled Nitric Oxide

FeNO measurements increased significantly from ages 6-11 years for both sexes ($p<0.0001$); however, there were no significant differences noted between boys and girls ($p=0.49$) (Figure 2). The effect of asthma on FeNO did not differ significantly between boys and girls (sex-by-asthma interaction $p=0.12$) and there was no evidence of a sex-by-year interaction ($p=0.68$). Prior to puberty, FeNO measurements were higher in both sexes for children with asthma who also had concurrent allergic sensitization ($p = 0.0009$)

Mannitol Bronchoprovocation

Of 171 children who attempted the mannitol challenge, 144 children completed the procedure, resulting in a procedure completion success rate of 84%. Out of all participants with asthma ($n=57$), 23 had a positive mannitol challenge, corresponding to a sensitivity of 40%. Out of all subjects without asthma ($n=87$), 69 had a negative challenge, corresponding to a specificity of 79%. In terms of airway hyperresponsiveness, there were no sex differences observed in positive mannitol responses performed at age 11 ($p=0.75$) (sex-by-asthma interaction $p=0.97$) (Figure 3).

³He MRI and Ventilation Defect Scores

Participants diagnosed with asthma had a higher ventilation defect score ($p = 0.03$) compared with non-asthmatic participants. Girls were noted to have a higher ventilation defect scores than boys ($p=0.01$) regardless of asthma diagnosis status (sex-by-asthma interaction $p=0.68$) (Figure 4).

Discussion

Sex strongly influences the risk of wheezing illnesses and the incidence and prevalence of asthma throughout childhood. While some of these effects can be attributed to sex related effects on immune development,³ the goal of the current study was to define longitudinal associations between sex and pulmonary physiologic outcome measures. It has been previously established that during fetal development, females demonstrate earlier lung development and maturation, with surfactant production and mature lung phospholipid profiles occurring ahead of their male counterparts.¹ Additionally, compared to boys, large airway growth in girls outpaces surrounding parenchymal development.¹ The end result is that young males have narrower airways than females shortly after birth. The impact of these early life airway alterations has not clearly been linked to phenotypic manifestations (such as asthma) in the developing child and adolescent, though they have spurred ongoing interest in determining their influence on disease outcomes.

Our data showing higher post-bronchodilation $FEV_{0.5}/FVC$ and FEV_1/FVC in girls compared with boys are consistent with the notion that boys may have narrower airways relative to lung volume, and are consistent with studies from multiple cohorts reporting higher FEV_1/FVC in girls.¹⁵ Our data also show that a diagnosis of asthma at any age is associated with an additional reduction in post-bronchodilation $FEV_{0.5}/FVC$ and FEV_1/FVC that is similar in boys and girls. Rasmussen reported reduced post-bronchodilation FEV_1/FVC ratios in 18 and 26 year-olds with a history of asthma in a cohort that had been followed since age 9.¹⁶ The lowest ratios were associated with male sex, airway hyperresponsiveness, and lower pre-bronchodilation FEV_1/FVC at younger ages. Belgrave reported similar patterns of higher specific airway resistance in males and in children with a diagnosis of asthma, however did not report findings of post-bronchodilator assessment.¹⁷ In a 4-6 year follow-up of asthmatic children in the Childhood Asthma Management Program, deterioration of post-bronchodilation FEV_1/FVC was greatest in those children with the greatest airflow limitation at the time of enrollment, and in those with eosinophilic inflammation.¹⁸ Thus, our data show that this indicator of progressive

airflow limitation is already present at age 5. Continued monitoring of the COAST cohort through adolescence will provide a more complete picture of how the asthmatic airways evolve from childhood to adulthood.

FeNO has been used as a surrogate marker to assess airway inflammation in asthma.¹⁹ Buchvald and collaborators looked to establish normative values for FeNO through a multicenter study measuring FeNO in 405 healthy subjects (191 male, 214 female) between the ages of 4 to 17 years.⁶ While they found that FeNO increased significantly with age for both sexes, they found no difference in measured FeNO between sexes. These data were echoed in our high-risk cohort; FeNO values increased with age but did not vary by sex.

Airway hyperresponsiveness can be evaluated using a number of different bronchoprovocation agents and increased responsiveness is a characteristic physiologic feature of asthma. Using methacholine as the challenging agent, Tantisira and colleagues in the Childhood Asthma Management Program (CAMP) reported similar results for methacholine PC₂₀ values in boys and girls prior to puberty, but a significant divergence in reactivity (boys became less reactive) post puberty.⁷ In contrast to methacholine that acts directly on bronchial smooth muscle, mannitol is an indirect challenge agent that appears to affect airway diameter through the creation of a hyperosmolar environment,²⁰ and was chosen for use in COAST due to the thought that it is a more specific test of airway responsiveness than methacholine. In COAST, mannitol had low sensitivity (40%) and modest specificity (79%) for asthma diagnosis. Similar to results reported with methacholine, we found no sex differences in mannitol airway responsiveness prior to puberty. It will be of interest to determine if sex differences also emerge post puberty using indirect airway challenge in the COAST cohort.

³He MRI of ventilation is a useful tool for viewing subclinical degrees of airway narrowing and gas trapping without the need for exposure to harmful radiation. The size and extent of local ventilation defects, defined as lung regions with limited or no hyperpolarized gas signal intensity, has been shown to correlate with asthma severity and decreased lung function.²¹ Previously within the COAST population, Cadman et al used both gas spin density and diffusion weighted helium MRI techniques to show that children with a history of asthma had lower mean gas diffusion lengths (a measure proportional to acinar size), and increased ventilation defect scores (VDS) than those without asthma. These associations were also true for children with early life wheezing due to rhinovirus infections.¹⁴ In the current study we extended these findings and demonstrated the presence of distinct sex differences, noting that girls demonstrated higher ventilation defect scores than boys (p=0.01) regardless of asthma diagnosis status (Figure 4). These findings suggest a greater degree of subclinical airway narrowing and air trapping in prepubertal girls than that found in age-matched boys. The higher defect scores in girls may foreshadow more pronounced decreases in lung function and worsening asthma severity in girls compared to boys post-adolescence. Thus, this innovative imaging modality may offer early detection of regional airway narrowing that cannot be detected by standard spirometry. Prospective follow up extending through puberty is needed to determine if these differences persist or change based on sex and age.

In conclusion, the findings of our study confirm previous work in healthy and asthmatic populations noting pre-pubertal sex differences in selected pulmonary physiologic outcome measures. In addition, our findings expand on these observations by using different methods of bronchoprovocation (i.e., mannitol) and novel imaging techniques (e.g., ventilation defect assessment). As the children participating in this study enter adolescence, pre- and post-pubertal airway physiologic evaluations will provide additional insights as to how the sex-specific changes in lung physiology identified in this study track with the expression, remission, and progression of asthma.

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Abbreviations

ATS	American Thoracic Society
CAMP	Childhood Asthma Management Program
CARE	Childhood Asthma Research and Education
COAST	Childhood Origins of Asthma
FeNO	fractional exhaled nitric oxide
FEV_{0.5}	forced expiratory volume in 0.5 seconds
FEV_{1.0}	forced expiratory volume in 1 second
FVC	forced vital capacity
IFN	interferon
MPT	mannitol provocation test
MRI	magnetic resonance imaging
SNP	single nucleotide polymorphism
TLC	total lung capacity

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Summary

Sex and age can influence immunologic responses in early life. The findings reported herein identify sex-related effects on pulmonary physiologic outcome measures, including ventilation defects assessed using a novel imaging modality.

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Clinical Implications

The sex of an individual influences the inception, remission, and severity of asthma throughout life. The results of this study provide insight into sex-related physiologic differences that accompany the clinical developmental expression of asthma during childhood and adolescence.

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Figure 1. A-D Spirometry

Effects of sex and asthma diagnosis on pre- and post-bronchodilation $FEV_{0.5}/FVC$ and FEV_1/FVC in children age 5-11 years.

Figure 2. Fractional Exhaled Nitric Oxide

No significant differences in FeNO were noted between sexes for ages 6-11 years.

Figure 3. Mannitol Challenge

No significant differences were noted between sexes for positive mannitol challenges regardless of asthma status.

Figure 4. ^3He MRI Ventilation Defect Scores

Girls had higher ventilation defect scores than boys, regardless of asthma diagnosis.

Table 1

Demographics of COAST subjects

	Girls		Boys	
Asthma Ever (6, 8, or 11 years)	No	Yes	No	Yes
N	74	38	84	63
Maternal age at birth (years)	31.7 ± 5.3	31.5 ± 5.2	31.5 ± 4.4	30.7 ± 5.3
Caucasian	89%	74%	88%	90%
African American	4%	18%	4%	8%
Hispanic or Latino	3%	8%	2%	2%
Other	4%	0%	6%	0%
Breastfed at birth	91%	82%	92%	95%
Breastfed at age 3 months	73%	63%	75%	76%
Passive smoke exposure year 1	24%	39%	20%	22%
Positive mannitol challenge year 11 *	22%	38%	20%	35%
Ventilation defect score year 9/10 **	11.5 ± 8.6	17.7 ± 10.3	6.4 ± 6.5	10.8 ± 6.8
FeNO year 6	9.2 ± 8.8	12.7 ± 9.7	10.9 ± 8.5	10.4 ± 7.9
FeNO year 11	14.1 ± 8.9	25.6 ± 24.5	16.9 ± 15.0	21.4 ± 23.9
FEV1/FVC pre-BD year 5	0.90 ± 0.06	0.90 ± 0.07	0.92 ± 0.04	0.89 ± 0.07
FEV1/FVC pre-BD year 11	0.83 ± 0.07	0.81 ± 0.08	0.82 ± 0.06	0.79 ± 0.06
FEV0.5/FVC pre-BD year 5	0.70 ± 0.08	0.69 ± 0.06	0.70 ± 0.07	0.67 ± 0.07
FEV0.5/FVC pre-BD year 11	0.64 ± 0.08	0.62 ± 0.08	0.62 ± 0.06	0.58 ± 0.08
FEV1/FVC post-BD year 5	0.90 ± 0.06	0.94 ± 0.04	0.93 ± 0.05	0.97 ± 0.01
FEV1/FVC post-BD year 11	0.86 ± 0.06	0.87 ± 0.04	0.85 ± 0.04	0.81 ± 0.07
FEV0.5/FVC post-BD year 5	0.73 ± 0.11	0.73 ± 0.06	0.72 ± 0.09	0.75 ± 0.05
FEV0.5/FVC post-BD year 11	0.66 ± 0.06	0.68 ± 0.05	0.64 ± 0.05	0.61 ± 0.10

* grouped by asthma diagnosis at time of mannitol challenge visit

** grouped by asthma diagnosis at time of imaging visit