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## Antenatal Steroid Exposure and Pulmonary Outcomes in Adolescents Born With Very Low Birth Weight

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### Abstract

**Objective**—To compare asthma history and pulmonary function in adolescents born prematurely with very low birth weight with and without antenatal steroid exposure.

**Study Design**—We studied 188 fourteen-year-olds (94 exposed, 84 male). We used parent report to ascertain asthma and asthma-related symptoms and spirometry to assess pulmonary function. Steroid-exposed and unexposed groups were compared using Mann-Whitney U tests (continuous variables), chi-square analysis (categorical variables), and logistic regression (multivariate analyses).

**Results**—The steroid-exposed group had greater prevalence of larger airway obstruction (35% v. 21%), and steroid-exposed adolescents with birth weights < 1000 grams had 4.5-fold higher odds of larger airway obstruction. Wheezing in the last 12 months was twice as prevalent in steroid-exposed adolescents with birth weights between 1000–1500 g.

**Conclusion**—Antenatal steroid exposure does not provide long-term benefits for pulmonary outcomes in adolescents born prematurely with very low birth weight in the era of surfactant therapy.

### Keywords

Corticosteroids; Prematurity; Lung Function; Asthma

### Introduction

Approximately 1.5% of infants in the US are born each year with very low birth weight (VLBW; < 1500 g).<sup>1</sup> In a recent multi-center study,<sup>2</sup> 44% of VLBW infants had respiratory distress syndrome and 22% developed neonatal chronic lung disease, increasing the risk for asthma and reduced pulmonary function in later years. When preterm delivery is anticipated, treatment of the mother with antenatal corticosteroid therapy (ANCS) is given to promote

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#### CONFLICT OF INTEREST

The authors, Patricia A. Nixon, Lisa K. Washburn, and T. Michael O’Shea, declare no conflicts of interest.

fetal lung maturation.<sup>3</sup> Currently, nearly 80% of VLBW infants are exposed to ANCS,<sup>2</sup> which decreases the risk for respiratory distress syndrome (RDS) and improves neonatal lung function and survival.<sup>4</sup>

Studies examining the long-term effects of ANCS on pulmonary outcomes are limited, and results are conflicting. Four follow-up studies revealed no difference between those exposed and not exposed to ANCS with regard to lung volumes, flow rates and/or lung mechanics, as well as prevalence of asthma and/or wheeze in the past 12 months.<sup>5-9</sup> However, these studies were conducted in the 1970s and 1980s, prior to the availability of exogenous surfactant, a therapy that increased the survival rate for VLBW infants, particularly those born with extremely low gestational age and birth weight.<sup>10,11</sup> Two studies of children in the exogenous surfactant era report lower risk of asthma in those exposed compared to those not exposed to ANCS.<sup>12,13</sup> However, few infants received surfactant (11 and 30%), ANCS exposure varied greatly (24 and 68%), and pulmonary function was not studied. In view of these limitations and the likely differences in neonatal characteristics of samples born before compared to samples born after introduction of surfactant treatment, we evaluated the long-term effects of ANCS on pulmonary outcomes in a cohort of VLBW adolescents born in the surfactant era of whom 66% were treated with surfactant, a level more comparable to current treatment rates in VLBW infants.<sup>2</sup> Our objective was to compare pulmonary function and asthma history and related symptoms between VLBW adolescents exposed to ANCS with those not exposed, with consideration of other factors such as birth weight and obesity which may affect the association between ANCS and these outcomes.

## Methods

### Participants

Participants were 188 fourteen-year-old adolescents recruited from a cohort of 479 survivors born prematurely with VLBW who met the following criteria: 1) birth at Forsyth Medical Center between January 1, 1992 and June 30, 1996; 2) birth weight < 1500 grams; 3) singleton birth; 4) no major congenital anomaly; and 5) follow-up clinical evaluation at one-year adjusted-age. The study was approved by the institutional review boards of Wake Forest University Baptist Medical Center and Forsyth Medical Center. Written informed consent was obtained from a parent or legal guardian, and written assent was obtained from the adolescent.

### Methods

Participants, accompanied by a parent or legal guardian, reported to the Clinical Research Unit at Wake Forest Baptist Medical Center. Height and weight were measured in triplicate, and body mass index (BMI) was calculated (average weight in kilograms divided by average height in meters squared). Age- and gender-specific BMI percentiles and z-values were determined from National Center for Health Statistics 2000 reference data.<sup>14</sup> A BMI percentile  $\geq 85^{\text{th}}$  percentile was considered overweight or obese.

History of asthma and asthma-related symptoms was obtained from parental report using the International Study of Asthma and Allergies in Childhood (ISAAC) Questionnaire.<sup>15</sup> Parents also reported any asthma medications taken by their child in the previous two weeks.

Pulmonary function testing was conducted in accordance with standard guidelines<sup>16</sup> using a Viasys Vmax Encore Metabolic Cart equipped with a heated-wire pneumotachometer and spirometry software. Forced expiratory volumes and flow rates were obtained. Primary variables of interest were forced vital capacity (FVC), forced expiratory volume in 1 second (FEV<sub>1</sub>), and the ratio of FEV<sub>1</sub> to FVC (FEV<sub>1</sub>/FVC). Values were expressed as % of predicted based on reference data specific for gender, race, age, and height, and values below the 5<sup>th</sup> percentile were considered below normal.<sup>17</sup> In order to minimize risk to study participants, they were not told to refrain from taking any of their usual medications.

Airway reactivity was determined in response to progressive maximal exercise and inhaled bronchodilator therapy. Spirometry was repeated five minutes post-exercise and exercise-induced bronchoconstriction was defined as a 15% decrease in FEV<sub>1</sub> from pre-exercise values.<sup>18</sup> Spirometry was also performed 20 minutes following inhalation of two puffs of albuterol, and a 12% increase in FEV<sub>1</sub> from baseline was considered a positive bronchodilator response.<sup>19</sup>

Information about tobacco smoke exposure was also obtained because of its association with asthma risk<sup>20</sup> by asking the participants to complete a form in private regarding whether they smoked or not. Environmental smoke exposure was determined by asking the parents to complete a form indicating if the father or mother currently smoked. Antenatal smoke exposure was assessed by asking if the mother smoked during her pregnancy with the participant.

Neonatal characteristics of the participants were obtained from a research database by research nurses and included: birth weight; gestational age; exposure to ANCS, postnatal dexamethasone, and surfactant; number of days of mechanical ventilation and supplemental oxygen; and diagnosis of bronchopulmonary dysplasia (BPD) based on supplemental oxygen requirement at 36 weeks post-menstrual age.<sup>21</sup>

**Data analysis**—Descriptive statistics were computed, and based on measures of central tendency and dispersion, nonparametric statistical analyses were deemed appropriate. Between-group comparisons (ANCS-exposed v. not exposed) were made using Mann-Whitney U tests for continuous variables and Chi-square analysis for categorical variables. Logistic regression analysis was used to adjust for potential confounders (variables associated with both ANCS and pulmonary outcomes using  $p < 0.2$ ) and also to examine possible mediators and moderators of the association between ANCS and pulmonary outcomes. In view of potential survivor bias associated with ANCS exposure in those with lower birth weight, stratum-specific odds ratios (OR) were computed for birth weight groups (<1000 g v. ≥1000 g).

## Results

As shown in the figure, 193 of 479 eligible VLBW adolescents were enrolled in the study. After enrollment, we found that four participants did not meet eligibility criteria and one was unable to participate due to impaired motor function; consequently, their data were excluded from analysis. Demographic and neonatal characteristics were similar among eligible VLBW survivors who did or did not participate (data not shown) except for gestational age which was lower ( $p = 0.01$ ) in participants [27 (24, 32) v. 28 (24, 33) weeks for median (5<sup>th</sup>, 95<sup>th</sup> percentiles)]. The neonatal characteristics of the remaining 188 participants (94 exposed and 94 not exposed to ANCS) are shown in Table 1. More ANCS-exposed children were Caucasian and exposed postnatally to dexamethasone, but the other neonatal characteristics did not differ between the two groups. Forty-seven percent of the participants (47 ANCS-exposed, 41 unexposed) had extremely low birth weight (ELBW; < 1000 g). In the ANCS-exposed group, 92 of the 94 mothers received betamethasone, one received dexamethasone, and one received both betamethasone and dexamethasone. More detailed information about number of doses and time of dose relative to birth was available on 63 of 94 ANCS-exposed women. The majority of women (62%) received two doses (one full course) and the majority of births (62%) occurred at least 24 hours after initiation of treatment but less than 7 days. No differences in neonatal or current characteristics were found between offspring of ANCS-exposed women with and without detailed data.

Participants' characteristics at the follow-up evaluation are presented for the two groups in Table 2. Median height z-value at 14 years of age was significantly higher in the ANCS-exposed compared to the unexposed group. Weight and BMI z-values did not differ between groups, but 29% of the ANCS-exposed group and 37% of the unexposed group had a BMI >85<sup>th</sup> percentile making them overweight or obese. Only five participants, but nearly half of parents in both groups, reported smoking.

### History of Asthma and Related Symptoms

Parental responses to the ISAAC questionnaire regarding the participant's history of asthma and related symptoms are presented in Table 3. Although history of asthma, wheeze in the last 12 months, and nocturnal cough were reported frequently by both groups, no significant group differences were found. Furthermore, reported use of asthma medications in the past two weeks did not significantly differ between groups (12.8% and 16% for unexposed and ANCS-exposed participants, respectively).

### Pulmonary Function

As shown in the figure, eight children did not perform pulmonary testing and 20 did not give reliable efforts. The pulmonary function test results for the 75 unexposed and 85 ANCS-exposed subjects with acceptable efforts are provided in Table 4. There were no group differences for median values of FVC or FEV<sub>1</sub> (% predicted). Only two participants in each group had FVC values below normal (< 5<sup>th</sup> percentile), whereas 8% of the unexposed and 14% of the ANCS-exposed groups had FEV<sub>1</sub> values < 5<sup>th</sup> percentile. Compared to those unexposed, ANCS-exposed participants had a lower median FEV<sub>1</sub>/FVC, and a greater percentage (35 v. 21%, respectively;  $p=0.06$ ) had FEV<sub>1</sub>/FVC values below normal (< 5<sup>th</sup>

percentile). The below normal FEV<sub>1</sub>/FVC values were accompanied by a positive history of asthma or related symptoms in 81% of unexposed and 83% of exposed participants. It should be noted that of the participants who reported recent use of asthma medications, only two participants reported long-acting bronchodilator use within 12 hours of testing and none reported short-acting bronchodilator use within 4 hours of testing. The test results of one participant (ANCS-exposed) were within normal limits with no evidence of airway obstruction. However, the other participant, (unexposed), despite medication, exhibited both larger and smaller airway obstruction as well as a positive response to bronchodilator therapy given as part of testing. Exclusion of their data from analysis did not alter the results appreciably.

### Airway Reactivity

The prevalence of exercise-induced bronchoconstriction was similar between groups with 9% of unexposed and 6% of ANCS-exposed groups exhibiting 15% decrease in FEV<sub>1</sub> following exercise. A positive response to bronchodilator therapy was observed in 14% of unexposed and 16% of ANCS-exposed groups. Of those with a baseline FEV<sub>1</sub>/FVC value < 5<sup>th</sup> percentile, 37% exhibited 12% improvement.

### Multivariate Analyses

Potential confounding by ANCS group differences in height and race was eliminated by expressing pulmonary function data as % of predicted. Logistic regression analysis revealed that participants exposed to ANCS had increased odds (OR = 2.01, 95% CI: 0.99, 4.09; p=0.05) of having an FEV<sub>1</sub>/FVC < 5<sup>th</sup> percentile compared to those unexposed, and this association persisted when adjusting for postnatal dexamethasone exposure and current BMI z-value (variables correlated with both ANCS and FEV<sub>1</sub>/FVC at p = 0.2). Further analysis, stratified by birth weight (< 1000 grams or ≥ 1000 grams), revealed that ANCS-exposure was associated with below normal FEV<sub>1</sub>/FVC only among those with birth weight < 1000 grams (OR = 4.5; CI: 1.32, 15.36, p=0.02).

ANCS was not associated with history of asthma in the unadjusted analysis as well as analyses that adjusted for group differences in race, postnatal dexamethasone exposure, current height, or birth weight. In contrast to history of asthma, the odds of wheezing in the last 12 months was higher in the ANCS-exposed group (OR=1.90; CI: 0.89, 4.05, p=0.095). This association was accentuated with adjustment for postnatal dexamethasone exposure (adjusted OR = 2.06; CI: 0.96, 4.42, p=0.065). Analysis stratified by birth weight revealed that ANCS was associated with wheeze only in the higher birth weight group (1000–1500 g) (OR= 2.6; CI: 0.98, 6.88, p=.054).

### Discussion

Based on improvements in survival and short-term morbidity, ANCS has become standard practice for preterm labor and conducting a randomized controlled trial of ANCS would be unethical. With nearly 80% of VLBW infants currently exposed,<sup>2</sup> our sample provided us with the unique opportunity to examine the long-term effects of ANCS exposure in a cohort with a 50% exposure rate, primarily due to year of birth relative to the NIH consensus

conference promoting ANCS use.<sup>22</sup> Our results suggest that ANCS exposure is not associated with improved pulmonary outcomes in adolescents born prematurely with VLBW. The lack of long-term benefits of ANCS on pulmonary function has been described previously in persons born prior to the development of exogenous surfactant as a treatment,<sup>5-9</sup> but ours is the first to report no benefit in a cohort born in the era of surfactant therapy. Our finding that ANCS exposure in ELBW adolescents was associated with greater odds of airway obstruction ( $FEV_1/FVC < 5^{\text{th}}$  percentile) was somewhat unexpected, but most likely reflects the positive effects of ANCS on survival in ELBW infants.<sup>10,11</sup>

Although no association between ANCS exposure and history of asthma was evident in our study, we found higher odds of wheeze in the last 12 months in higher birth weight ANCS-exposed adolescents compared to their unexposed peers. Palta et al.<sup>12</sup> likewise reported no association between ANCS-exposure and history of asthma; however, unlike our study, they found lower odds (OR=0.56, 95% CI: 0.29, 1.10) of wheezing in the last 12 months in ANCS-exposed 8 year-old VLBW children. In contrast, Hung et al.<sup>13</sup> reported lower odds (OR=0.38, 95% CI: 0.15, 0.97) of asthma in ANCS-exposed v. unexposed 2-8 year-old VLBW children, but they excluded children who had BPD. The inconsistencies between findings may reflect possible recall error and bias associated with questionnaires, as well as differences in study samples. For example, over 60% of our sample received surfactant therapy compared to only 30% in the study by Palta et al.<sup>12</sup> and 11% in the study by Hung et al.<sup>13</sup> History of asthma was also higher in our study (38%) compared to only 19%<sup>12</sup> and 11%<sup>13</sup> in the two previous studies. Furthermore, our participants were older at follow-up (14 vs. 8 years old) and perhaps the effects of ANCS exposure on pulmonary outcomes change with growth and maturation.

Irrespective of ANCS exposure and its effects, the overall high prevalence of asthma and below normal larger airway function is concerning and may reflect the high rates of overweight and obesity in our sample.<sup>23</sup> The positive bronchodilator response observed in about 1/3 of participants with below normal  $FEV_1/FVC$  suggests that the airway obstruction may be reversed or at least reduced by pharmacotherapy, and lack of a positive response in the laboratory does not preclude the possibility of a clinical response to therapy.<sup>19</sup> It is also possible that a reduced  $FEV_1/FVC$  may reflect abnormal airway development associated with both prenatal and postnatal factors (eg. ANCS, mechanical ventilation, impaired growth).<sup>19</sup>

Animal studies suggest that ANCS promotes fetal lung maturation by inducing septation and thinning of alveolar walls, resulting in larger but fewer alveoli.<sup>24</sup> In humans, alveolarization may be assessed by plethysmography combined with newer technologies such as helium-3 magnetic resonance which suggests that alveolarization continues into childhood and adolescence.<sup>25</sup> Although previous studies revealed no differences in lung volumes, flow rates and/or mechanics,<sup>5-9</sup> these measurements as well as diffusion capacity are more accessible and would have provided insight into the long-term effects of ANCS on other measures of lung function and pulmonary gas exchange.

There are several other limitations with this study. Although we had access to data regarding ANCS exposure for our participants, maternal medical records with information regarding



the amount and frequency of dose, and timing of exposure relative to birth was not available on all of the participants. Neonatal and current characteristics for ANCS-exposed offspring of women with and without detailed exposure information did not differ, and all women were treated by the obstetrical staff at one hospital. Additionally, a greater number of participants in the unexposed group did not do or gave unreliable efforts for pulmonary function testing which may have affected the results and limit representativeness. There are a number of genetic, epigenetic, and environmental factors (e.g. family history of asthma, air pollution, etc.) which may affect pulmonary outcomes and were not assessed or adjusted for in the current study.<sup>20</sup> Finally, due to limited funding and time, we were only able to recruit and evaluate about 40% of the eligible sample. Nonetheless, other than slightly lower gestational age, the neonatal characteristics of those recruited were similar to the overall cohort.

While the benefits of ANCS for improving survival and short-term morbidity in preterm infants are well-documented, there is little evidence of its long-term benefits among adolescent VLBW survivors. The higher odds of wheeze in the last 12 months may simply reflect recall error or bias, but it is possible that the effects of ANCS exposure become more evident with growth and maturation. Others have reported adverse effects of ANCS-exposure on cardiometabolic outcomes in adolescents and young adults,<sup>26–29</sup> thus warranting continued research in VLBW survivors beyond infancy and childhood. Furthermore, the high prevalence of asthma and below normal airway function observed in this cohort indicates the need for closer surveillance and clinical evaluation in this population as they mature.

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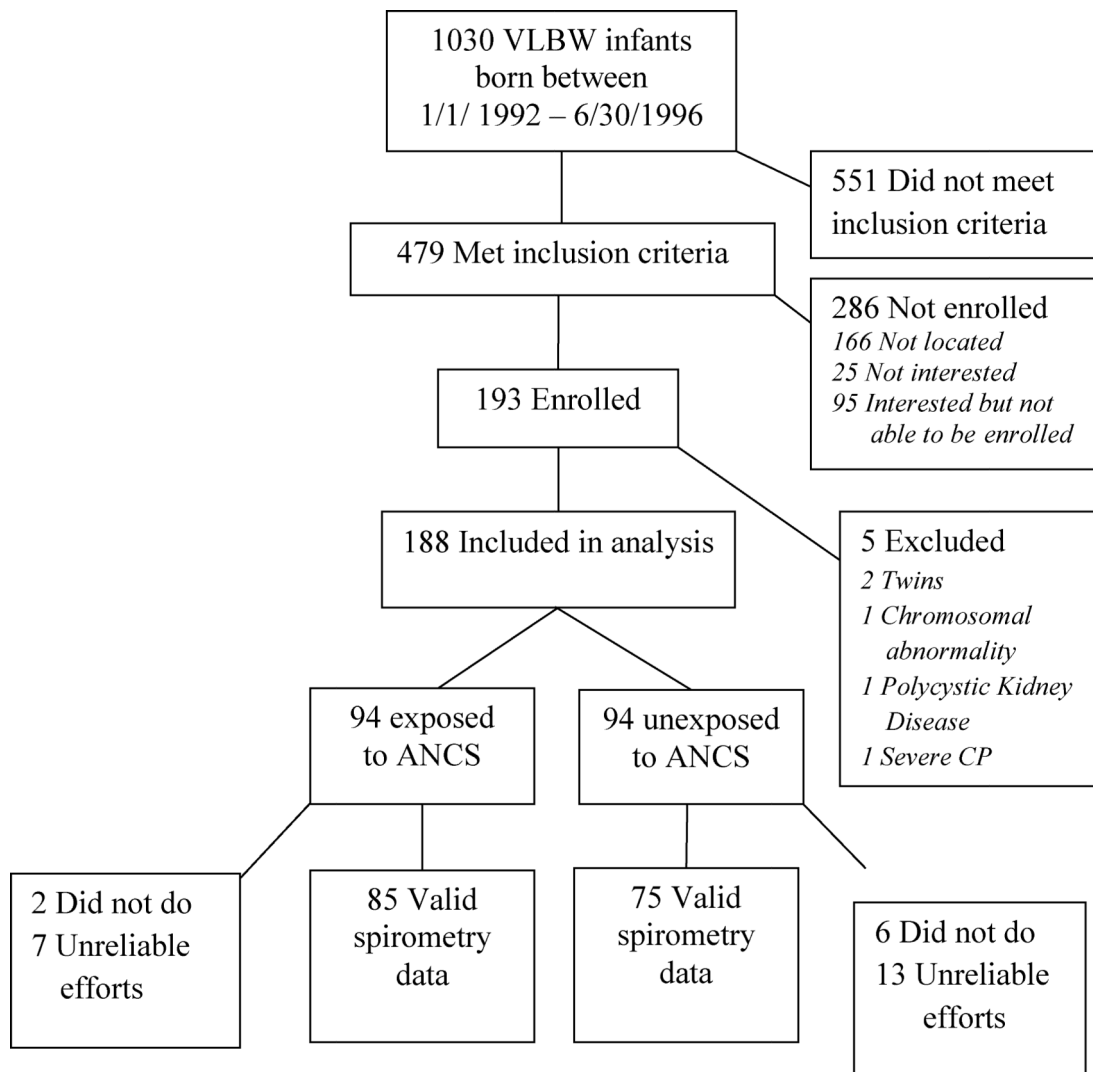
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**Figure 1.**  
Figure Follow-up details of VLBW participants.

**Table 1**

Neonatal characteristics by ANCS exposure expressed as median (5<sup>th</sup>, 95<sup>th</sup> percentile) or n (%).

	Unexposed to ANCS (n = 94)	Exposed to ANCS (n = 94)
Gestational Age, wks	27 (23, 33)	28 (24, 32)
Male Gender, n (%)	39 (42)	45 (48)
Caucasian Race, n (%)	39 (42)	64 (68) <sup>a</sup>
Birth Weight, g	1043 (595, 1461)	1003 (618, 1466)
Birth Weight z-value	-0.164 (-2.013, 1.115)	-0.228 (-1.849, 0.706)
Mechanical ventilation, days	4.0 (0, 60.3)	5.0 (0, 55.3)
Supplemental oxygen, days	25.0 (0, 209.0)	29.0 (0, 191.3)
+ Surfactant Therapy, n (%)	59 (63)	58 (62)
+ Postnatal Dexamethasone Exposure, n (%) <sup>b</sup>	16 (17)	24 (26)
+ BPD diagnosis, n (%)	26 (28)	23 (25)
+ Antenatal smoke exposure, n (%) <sup>c</sup>	17 (20)	11 (12)

<sup>a</sup> p <0.05, ANCS-exposed > unexposed

<sup>b</sup> Postnatal dexamethasone exposure unknown in 2 ANCS-exposed and 1 unexposed

<sup>c</sup> Antenatal smoke exposure unknown in 1 ANCS-exposed and 1 unexposed

**Table 2**

Participants' characteristics at 14 years of age expressed as medians (5<sup>th</sup>, 95<sup>th</sup> percentiles) or n (%).

	Unexposed to ANCS n=94	Exposed to ANCS n=94
Weight Z-value	0.509 (-1.731, 2.302)	0.319 (-1.458, 2.185)
Height Z-value	-0.382 (-2.567, 1.157)	-0.152 <sup>a</sup> (-2.016, 1.337)
BMI Z-value	0.630 (-1.590, 2.398)	0.333 (-1.299, 2.142)
+ Current Smoking Status, n (%)	3 (3)	2 (2)
+ Parental Smoking Status <sup>b</sup> , n (%)	43 (49)	38 (41)

<sup>a</sup> p < 0.05, ANCS-exposed > unexposed

<sup>b</sup> Either parent smoked; unknown in 7 unexposed and 2 ANCS-exposed

**Table 3**Prevalence of asthma and related symptoms as indicated by parental responses to the ISAAC questionnaire.<sup>a</sup>

	Unexposed to ANCS n=94	Exposed to ANCS n=94
Asthma ever <sup>b</sup> , n (%)	33 (36)	39 (42)
Wheeze last 12 mos, n (%)	13 (14)	22 (23)
Wheeze with exercise, n (%)	17 (18)	19 (20)
Sleep disturbed by SOB <sup>c</sup> , n (%)	7 (7)	7 (7)
Nocturnal cough, n (%)	21 (23)	23 (25)

<sup>a</sup> p>0.05 for all between-group comparisons<sup>b</sup> Question not completed by parent of one unexposed participant<sup>c</sup> SOB: shortness of breath

**Table 4**

Forced expiratory volumes and flow rates at 14 years of age. Values are medians (5<sup>th</sup>, 95<sup>th</sup> percentiles).

	Unexposed to ANCS n = 75	Exposed to ANCS n = 85
FVC, % predicted	103 (81, 122)	102 (84, 125)
FEV <sub>1</sub> , % predicted	95 (73, 119)	94 (73, 121)
FEV <sub>1</sub> /FVC, % predicted	96 (78, 107)	94* (77, 104)

\*  
p<0.05, ANCS-exposed < unexposed

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