Antenatal Steroid Exposure, Aerobic Fitness, and Physical Activity in Adolescents Born Preterm with Very Low Birth Weight

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Objective To determine whether antenatal corticosteroid exposure is associated with aerobic fitness or physical activity participation in adolescents born preterm with very low birth weight (VLBW).

Study design Observational cohort study of 14-year-old adolescents (n = 173) born with VLBW between 1992 and 1996 at a regional perinatal center with 91 exposed to antenatal corticosteroids. Aerobic fitness was determined from peak oxygen uptake ($\dot{V}O_2$peak) obtained via maximal exercise testing on a cycle ergometer. Physical activity levels for the past year and past 2 months were estimated from a questionnaire. Between-group comparisons for continuous variables were evaluated using independent *t* tests or Mann–Whitney *U* tests. Generalized linear models were used to compare differences in fitness and physical activity between those exposed to antenatal corticosteroids and not exposed to antenatal corticosteroids, with race and sex in models.

Results Regression analysis revealed an antenatal corticosteroids × sex × race interaction for $\dot{V}O_2$peak ($P \leq .001$). Nonblack male adolescents exposed to antenatal corticosteroids had significantly greater $\dot{V}O_2$peak than nonblack male adolescents not exposed to antenatal corticosteroids expressed relative to body mass (mean difference [95% CI]; 8.5 [2.1-15.0] $mL \cdot kg^{-1} \cdot min^{-1}$) and lean body mass (9.0 [1.1-16.9] $mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$). No antenatal corticosteroid group differences in $\dot{V}O_2$peak were evident in black male adolescents, or black and nonblack female adolescents. Male adolescents exposed to antenatal corticosteroids reported participating in significantly more total physical activity (medians: 14.6 vs 8.5) and vigorous physical activity (3.0 vs 0.95) per week for the past 2 months than male adolescents not exposed to antenatal corticosteroids.

Conclusions Exposure to antenatal corticosteroids was associated with greater physical activity participation and aerobic fitness in adolescents with VLBW, particularly in nonblack male adolescents, which may confer health benefits in this at-risk population. *(J Pediatr 2019;215:98-106)*.

Approximately 1.4% of infants are born in the US with very low birth weight (VLBW; <1500 g), and up to 87% of them are exposed to antenatal corticosteroid therapy to promote fetal lung maturation and survival when preterm delivery appears imminent.[1-3] Although beneficial in the short term, the long-term effects of antenatal corticosteroids on health and functional outcomes are less clear. Some evidence suggests that antenatal corticosteroid exposure is associated with an increased risk for cardiometabolic disease.[4,5] We previously have shown that antenatal corticosteroids are associated with greater prevalence of larger airway obstruction in adolescence, and preclinical studies suggest that antenatal corticosteroids may disrupt normal skeletal and cardiac muscle development.[6-9] These systems play a major role in aerobic fitness and ability to participate in physical activity, which in turn are associated with risk for cardiometabolic disease.[10] Several studies report that persons born preterm and/or with VLBW have lower levels of fitness and physical activity participation.[11-15] With nearly 48 000 infants born each year in the US exposed to antenatal corticosteroids, it is important to determine the long-term effects of antenatal corticosteroid exposure on these functional outcomes.[2]

In this study, we examined aerobic fitness and habitual physical activity in a cohort of 14-year-old individuals born with VLBW, of whom approximately one-half were exposed to antenatal corticosteroids. We hypothesized that aerobic fitness and physical activity levels would be lower in adolescents exposed to antenatal corticosteroids compared with their unexposed peers. Based on our previous work showing sex- and race-specific effects of antenatal corticosteroids,

RER	Respiratory exchange ratio
TOT-hrs	Total hours of physical activity per week
VIG-hrs	Hours spent in vigorous physical activity per week
VLBW	Very low birth weight
$\dot{V}O_2$peak	Peak oxygen uptake

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we examined the interactions of antenatal corticosteroid with sex and race in relation to fitness and physical activity.[16-18]

Methods

The study was approved by the institutional review boards of Wake Forest Baptist and Forsyth Medical Centers (Protocol No. BG05-047). Written informed consent was from a parent/legal guardian, and assent was from the adolescent.

Participants were recruited from a cohort of 479 infants with VLBW born between 1992 and 1996 at a regional perinatal center (Forsyth Medical Center, Winston-Salem, North Carolina) meeting the inclusion criteria of 14 years of age, singleton birth with no major congenital anomaly, clinical evaluation at 1-year adjusted age, and physical ability to undergo testing. Participants were excluded if the mother took oral corticosteroids during pregnancy. The study protocol included 3 study visits.

Aerobic Fitness

Aerobic fitness was assessed at the second study visit and was determined from expired gases collected during progressive exercise testing on a cycle ergometer (Lode Corival cycle ergometer and Carefusion Vmax Encore Metabolic Cart; Medical Graphics, St Paul, Minnesota) following the Godfrey Protocol (work increments of 10, 15, or 20 W each minute based on child's height of <125, 125-150, or >150 cm, respectively).[19] The participant was verbally encouraged to give a maximal effort, defined as peak heart rate >195 bpm, peak respiratory exchange ratio (RER) >1.05, and/or 2 experienced testers agreeing that a maximal effort was given. The test was terminated if significant abnormalities were detected on the electrocardiogram (eg, ventricular arrhythmia) or if systolic blood pressure exceeded 220 mm Hg or diastolic blood pressure exceeded 100 mm Hg. Participants were asked to refrain from eating, drinking caffeinated beverages, or exercising the morning of the study visit. Aerobic fitness was determined from the highest 20-second average of oxygen uptake attained (peak oxygen uptake, or $\dot{V}O_2$peak) and expressed relative to body weight ($mL \cdot kg^{-1} \cdot min^{-1}$), lean body mass ($mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$), and as a percent of predicted age- and sex-specific reference values.[20] Fitness was considered below normal if $\dot{V}O_2$peak was less than 80% of predicted. Lean body mass was determined from a total body scan using dual energy x-ray absorptiometry (Hologic Delphi with pediatric software; Hologic, Marlborough, Massachusetts).

Habitual Physical Activity

Physical activity was assessed using the Kriska Modifiable Activity Questionnaire, for which validity and reliability have been demonstrated in other pediatric populations.[21,22] The Modifiable Activity Questionnaire was administered to the participant by a trained interviewer with a parent present to assist if necessary. The participant was read a list of common leisure activities and asked to indicate those in which he/she had engaged at least 5 times in the past year. The participant also could add leisure activities not included on the list. For indicated activities, the participant was then asked to indicate the specific months in the past year, the average number of times per month or week, and the average number of minutes per session. The total minutes of activity were summed and expressed as the average total hours of physical activity (TOT-hrs) per week for the past year. Activities were assigned estimated metabolic equivalents, and those with an estimated intensity >6 metabolic equivalents were summed and expressed as average hours per week spent in vigorous physical activity (VIG-hrs) for the past year.[23] In view of seasonal variation in physical activity and its potential effect on aerobic fitness, we also calculated average TOT-hrs and VIG-hrs per week for the previous 2 months.[24] We further examined the proportions meeting the national recommendations for physical activity.[25] Physical activity reports were considered unreliable by experienced interviewers when the reporter did not appear to be fully engaged.

Neonatal Characteristics

Neonatal characteristics including birth weight, gestational age, and antenatal corticosteroid exposure (including number of doses and timing relative to birth, when available) were obtained from a research database as well as maternal and participant medical records reviewed by a research nurse. Gestational age was determined in order of availability from either first-trimester ultrasound scan, maternal report of last menstrual period, or clinical assessment of the newborn infant. Chronic lung disease was defined as supplemental oxygen requirement at 36 weeks of postmenstrual age.[26] Birth weight z values were determined from gestational age- and sex-specific reference data,[27] and a z value <-2 SD was considered small for gestational age. Additional information regarding neonatal morbidities were derived from diagnoses recorded by the attending neonatologist at the time when the infant was discharged from neonatal intensive care.

Adolescent Characteristics

Height and weight were measured in light clothing without shoes in triplicate using a wall-mounted stadiometer and digital platform scale, respectively. Body mass index was calculated from the ratio of weight in kg to height in cm^2, and age- and sex-specific percentiles were determined.[28] A body mass index ≥85th percentile was considered overweight or obese. The participant's race was categorized as black or nonblack based on the report by parent/guardian via questionnaire. Puberty stage was self-reported by the participant in private using the Tanner sexual maturation scale, composed of drawings of the 5 progressive stages of secondary sexual characteristics (breast development in females, genital development in males, and pubic hair for both sexes).[29]

Statistical Analyses

Data were analyzed using SPSS, version 25 (IBM Corp, Armonk, New York). Measures of central tendency and dispersion were examined, and transformations were applied to variables with Shapiro–Wilk test of normality results

having a $P < .05$ in attempt to improve distributional characteristics before analyses. Data are presented as means ± SD, median (25th, 75th percentiles), or n (%). Between-group (exposed to antenatal corticosteroids vs not exposed to antenatal corticosteroid) differences were examined using independent samples *t* tests for continuous variables, or Mann–Whitney *U* tests, when transformation (eg, natural log, square root) did not improve a variable's distributional characteristics. Proportional differences in categorical variables were examined via Pearson χ^2 analysis. Generalized linear models were used to compare differences in fitness and physical activity between the group exposed to antenatal corticosteroids and group not exposed to antenatal corticosteroids, and based on our previous work, we decided a priori to include sex, race, and their interaction product terms with antenatal corticosteroids in the model. For interaction terms with $P \leq .10$, stratified regression analyses were run. Logistic regression analysis was used for dichotomous outcome variables. Post hoc pairwise comparisons of estimated marginal means (95% CI) were made with Bonferroni correction.

Results

As shown in **Figure 1** (available at www.jpeds.com), 193 of 479 eligible adolescents with VLBW were enrolled in the study. This sample size met our recruitment goal for the overall study. After enrollment, 6 participants were found to be ineligible, and one was unable to participate because of severe cerebral palsy. After further exclusions for missing data or unreliable reporting of physical activity, the final analysis for participant characteristics and physical activity included 91 adolescents exposed to antenatal corticosteroids (43 male, 64 nonblack) and 82 not exposed to antenatal corticosteroids (33 male, 37 nonblack). Final analysis of aerobic fitness included 85 adolescents exposed to antenatal corticosteroids (40 male, 61 nonblack) and 75 not exposed to antenatal corticosteroids (28 male, 31 nonblack) who gave a maximal effort and had valid exercise test data. Two adolescents (both not exposed to antenatal corticosteroids) were not able to do the exercise test due to neuromotor limitations associated with cerebral palsy. One adolescent (not exposed to antenatal corticosteroids) was unable to perform the test due to cognitive impairment. Three adolescents (2 not exposed to antenatal corticosteroids) had evidence of significant airway obstruction and were not tested. In addition, the exercise test was terminated prematurely in 3 adolescents (all not exposed to antenatal corticosteroids) including 2 who developed ventricular arrhythmia and 1 whose systolic blood pressure exceeded 220 mm Hg.

Participants' characteristics as neonates and adolescents are presented in **Table I**. Additional information regarding prevalence of neonatal morbidities can be found in **Table II** (available at www.jpeds.com). In the group exposed to antenatal corticosteroids, 89 of the 91 mothers received betamethasone, 1 received dexamethasone (black male offspring), and 1 received both betamethasone and dexamethasone (nonblack female offspring). More detailed information about the number of doses and the time of dose relative to birth was available in 60 (26 male, 13 black) of 91 women exposed to antenatal corticosteroids. The majority of women (75%) received 2 doses of betamethasone (1 full course), and the majority of births (62%) occurred at least 24 hours after, but within 7 days, of administration of treatment. No differences in neonatal or current characteristics were found between offspring of mothers treated with antenatal corticosteroids with and without detailed data on exposure. Nonblack participants were more likely to have been exposed to antenatal corticosteroids than black participants. Gestational age, birth weight, and birth weight z values did not differ between the 2 antenatal corticosteroid groups. Only 5 neonates (1 exposed to antenatal corticosteroids) had birth weight z values <2 SD. Twenty-nine adolescents (15 exposed to antenatal corticosteroids) participated postnatally in a randomized controlled trial of dexamethasone to decrease dependency on mechanical ventilation, with 7 exposed to antenatal corticosteroids and 8 not exposed to antenatal corticosteroids receiving dexamethasone. Demographic and neonatal characteristics were similar among eligible survivors with VLBW who did or did not participate (data not shown).

At follow-up, adolescents exposed to antenatal corticosteroids were taller than their unexposed peers. When stratified by sex, height of male adolescents exposed to antenatal corticosteroids was 4.84 cm (mean difference; 95% CI 0.63-9.06; $P = .03$) greater than male adolescents not exposed to antenatal corticosteroids. Female adolescents exposed to antenatal corticosteroids were 1.51 cm taller (95% CI –1.29 to 4.30), but the difference was not statistically significant ($P = .29$). Overweight/obesity was prevalent in 30% or more of both antenatal corticosteroid groups. For pubertal stages, the largest proportion of male adolescents exposed to antenatal corticosteroids reported stage 4 (late pubertal) for both pubic hair (47%) and genital development (57%), whereas the largest proportion of male adolescents not exposed to antenatal corticosteroids reported stage 5 (postpubertal) for both pubic hair (55%) and genital development (46%). In female adolescents, the majority of those exposed to antenatal corticosteroids (60%) and not exposed to antenatal corticosteroids (63%) reported stage 5 for pubic hair. For breast development, 50% of those exposed to antenatal corticosteroids reported stage 4, and an equal percentage of those not exposed to antenatal corticosteroids reported stage 4 (45%) and stage 5 (45%). For neonatal and other adolescent characteristics, stratification by sex did not reveal any significant antenatal corticosteroid group differences.

Aerobic Fitness

Aerobic fitness results for the 85 adolescents exposed to antenatal corticosteroids and 75 not exposed to antenatal corticosteroids who gave a maximal effort and had valid exercise test data are presented in **Table III**. $\dot{V}O_2$peak was

Table I. Participants' characteristics as neonates and at 14 years of age by antenatal corticosteroid exposure

Characteristics	Exposed to antenatal corticosteroids n = 91	Not exposed to antenatal corticosteroids n = 82
Neonatal		
Male, n (%)	43 (47)	33 (40)
Nonblack, n (%)	64 (70)*	37 (45)
Gestational age, wk	28 (26.0, 30.0)	27 (25.8, 30.0)
Birth weight, g	1010 (785, 1250)	1058 (899, 1308)
Birth weight z value	−0.240 (−0.659, 0.266)	−0.026 (−0.722, 0.482)
Birth weight z values <2 SD	1 (1)	4 (5)
Chronic lung disease, n (%)	23 (25)	19 (23)
14 y of age		
Age, y	14.5 (14.3, 14.8)	14.5 (14.3, 14.8)
Weight, kg	55.1 (48.2, 68.4)	56.4 (45.4, 70.4)
Weight z value	0.306 (−0.405, 1.266)	0.540 (−0.788, 1.429)
Lean body mass, kg†	42.5 (36.1, 51.8)	40.6 (36.5, 49.7)
Height, cm	162.8‡ (156.2, 168.7)	158.9 (151.8, 167.0)
Height z value	−0.146§ (−0.845, 1.266)	−0.461 (−1.514, 0.387)
BMI z value	0.268 (−0.635, 1.403)	0.777 (−0.247, 1.569)
BMI ≥85th percentile, n (%)	27 (30)	31 (38)
Puberty stage, n (%)¶		
Breast/genital development		
Stage 1 (prepubertal)	1 (1)	0 (0)
Stage 2 (early pubertal)	0 (0)	1 (1)
Stage 3 (midpubertal)	14 (16)	11 (13)
Stage 4 (late pubertal)	48 (53)	33 (40)
Stage 5 (postpubertal)	27 (30)	37 (45)
Pubic hair		
Stage 1 (prepubertal)	1 (1)	0 (0)
Stage 2 (early pubertal)	0 (0)	0 (0)
Stage 3 (midpubertal)	3 (3)	7 (9)
Stage 4 (late pubertal)	39 (43)	26 (32)
Stage 5 (postpubertal)	47 (52)	49 (60)

BMI, body mass index.
Values are medians (25th, 75th percentiles) or n (%).
*$P < .05$ from χ^2 test.
†n = 85 exposed to antenatal corticosteroids, n = 69 not exposed to antenatal corticosteroids.
‡$P < .05$ from independent *t* tests.
§$P < .05$ from Mann–Whitney *U* tests for variables with non-normal distributions.
¶n = 90, 1 male adolescent not exposed to antenatal corticosteroids refused.

greater in the participants exposed to antenatal corticosteroids compared with those not exposed when expressed relative to body mass as well as lean body mass. When stratified by sex, the significant difference was evident in male adolescents only.

Despite giving maximal efforts, some participants were unable to reach the maximal criterion of RER >1.05. Three (1 not exposed to antenatal corticosteroids) of the 8 participants with cerebral palsy (4 not exposed to antenatal corticosteroids) exhibited a neuromotor limitation, as indicated by difficulty pedaling at greater workloads as well as a peak RER <1.05. In addition, 4 participants (3 not exposed to antenatal corticosteroids) with a history of tracheomalacia had a peak RER ≤1.05 and reported breathing as their reason for stopping. Exclusion of these participants with limitations resulted in slightly greater $\dot{V}O_2$peak for both male adolescents exposed and not exposed to antenatal corticosteroids (mean ± SD: 47.0 ± 8.1 and 41.9 ± 9.5 $mL \cdot kg^{-1} \cdot min$, respectively) and a greater difference between groups. In female adolescents, $\dot{V}O_2$peak increased only in the group exposed to antenatal corticosteroids (to 34.0 ± 6.3 $mL \cdot kg^{-1} \cdot min^{-1}$), but the comparison with female adolescents not exposed to antenatal

Table III. Comparison of aerobic fitness by antenatal corticosteroid exposure for the total group and stratified by sex*

	Total group		Male		Female	
Variables	Exposed (n = 85)	Unexposed (n = 75)	Exposed (n = 40)	Unexposed (n = 28)	Exposed (n = 45)	Unexposed (n = 47)
$\dot{V}O_2$peak, $mL \cdot kg^{-1} \cdot min^{-1}$	39.4 ± 10.1†	35.7 ± 9.4	45.8 ± 9.3†	40.9 ± 9.6	33.6 ± 6.8	32.7 ± 7.9
$\dot{V}O_2$peak, $mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$	51.2 ± 9.2†	47.9 ± 9.4	55.7 ± 9.1†	50.2 ± 8.9	47.2 ± 7.2	46.5 ± 9.5
$\dot{V}O_2$peak, % of predicted	85 ± 19†	78 ± 19	92 ± 19†	82 ± 19	86 ± 17	83 ± 20

*Values presented are unadjusted means ± SD. Between-group (exposed to antenatal corticosteroids vs not exposed to antenatal corticosteroids) comparisons were made using independent *t* tests.
†$P \leq .05$ exposed to antenatal corticosteroids > not exposed to antenatal corticosteroids.

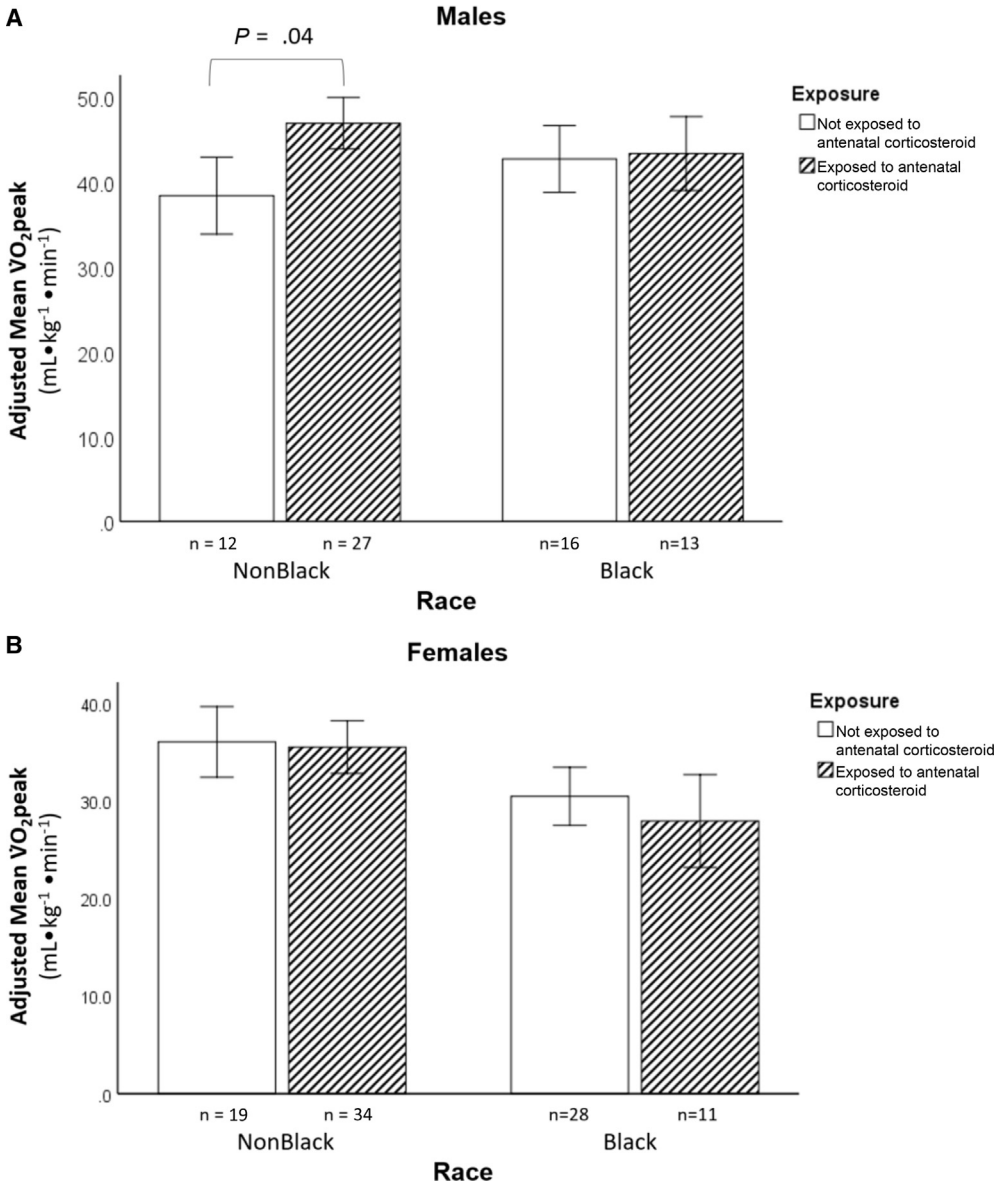

Figure 2. Adjusted Mean $\dot{V}O_2$peak in $mL \cdot kg^{-1} \cdot min^{-1}$ by antenatal corticosteroid exposure, race, and sex. *Bars* represent estimated marginal means and *error bars* represent the 95% CI. Post hoc analysis (with Bonferroni adjustment) indicated that antenatal corticosteroid group differences were significant in **A**, nonblack male but not black male, **B**, nor in black or nonblack female acolescents.

corticosteroids remained nonsignificant. Similar changes were evident in $\dot{V}O_2$peak expressed per $kg_{lean\ body\ mass}$.

Multivariable analysis, with antenatal corticosteroid exposure, sex, race, and interaction terms in the model, revealed a 3-way interaction of antenatal corticosteroids with sex and race for $\dot{V}O_2$peak expressed relative to both body mass ($P = .001$) as well as lean body mass ($P < .001$). Antenatal corticosteroid differences in $\dot{V}O_2$peak were evident in male adolescents and were significant in nonblack but not in black male adolescents (Figure 2, A). The mean adjusted difference in $\dot{V}O_2$peak was 8.5 (95% CI 2.1-15.0) $mL \cdot kg^{-1} \cdot min^{-1}$ with greater values in nonblack male adolescents exposed to antenatal corticosteroids compared with their unexposed nonblack male peers. Similar differences between nonblack male adolescents exposed and not exposed to antenatal corticosteroids were observed in $\dot{V}O_2$peak when expressed relative to lean body mass (adjusted mean difference: 9.0 [95% CI 1.1-16.9] $mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$). No significant antenatal corticosteroid group differences in fitness were observed in female adolescents, irrespective of race (Figure 2, B). The analysis was repeated excluding participants with apparent neuromotor or pulmonary limitations. The nonblack male adolescents exposed to antenatal corticosteroids continued to have greater $\dot{V}O_2$peak than nonblack male adolescents not exposed to antenatal corticosteroids, with the mean adjusted difference in $\dot{V}O_2$peak reduced slightly to 7.7 (95% CI –0.5 to 15.9; $P = .08$) $mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$. Exclusion of the data

Table IV. Comparison of physical activity levels by antenatal corticosteroid exposure and sex*,†

Variables	Total group		Male		Female	
	Exposed (n = 91)	Unexposed (n = 82)	Exposed (n = 43)	Unexposed (n = 33)	Exposed (n = 48)	Unexposed (n = 49)
Physical activity (past year)						
TOT-hrs per wk	9.34 (4.46, 14.87)	8.05 (3.81, 14.64)	12.91 (7.67, 20.95)	9.84 (6.09, 19.05)	5.66 (2.66, 12.08)	6.21 (3.00, 13.69)
VIG-hrs per wk	1.16 (0.05, 4.59)	0.75 (0, 1.99)	4.59‡ (0.99, 8.54)	1.65 (0.13, 6.60)	0.36 (0, 1.72)	0.25 (0, 1.59)
Physical activity (past 2 mo)						
TOT-hrs per wk	8.24 (4.50, 18.23)	7.03 (2.76, 15.48)	14.60§ (6.54, 24.88)	8.5 (3.97, 17.15)	6.36 (2.74, 12.61)	5.47 (1.98, 15.10)
VIG-hrs per wk	0.93§ (0, 3.73)	0.15 (0, 1.96)	3.00§ (0.50, 9.00)	0.95 (0, 4.13)	0 (0, 1.62)	0 (0, 1.00)

*Values are median (25th, 75th percentiles).
†Mann–Whitney *U* tests used to compare rank differences.
‡$P < .10$.
§$P < .05$.

of 15 subjects (7 exposed to antenatal corticosteroids, 8 not exposed to antenatal corticosteroids) who received dexamethasone postnatally (as part of a randomized controlled trial to reduce mechanical ventilator dependence) reduced the mean adjusted difference in $\dot{V}O_2$peak between nonblack male adolescents exposed and not exposed to antenatal corticosteroids as well ($7.2\ mL \cdot kg_{lean\ body\ mass}^{-1} \cdot min^{-1}$) and increased the *P* value to 0.1. No significant antenatal corticosteroid group differences in $\dot{V}O_2$peak were evident for black male adolescents or female adolescents, irrespective of race.

When $\dot{V}O_2$peak was expressed as a percent of age- and sex-specific reference values, 31% of those exposed to antenatal corticosteroids and 48% of those not exposed to antenatal corticosteroids had a $\dot{V}O_2$peak <80% of predicted ($P = .024$). Logistic regression analysis, with antenatal corticosteroid exposure, race, sex, and interaction terms in the model, revealed an interaction between antenatal corticosteroids and race ($P = .10$). Stratification by race further revealed that antenatal corticosteroid differences were significant in nonblack but not black participants. Nonblack participants exposed to antenatal corticosteroids were 2.7 times (aOR; 95% CI 1.04-6.83) more likely to have a $\dot{V}O_2$peak ≥80% of predicted compared with their nonblack unexposed peers.

Physical Activity

Physical activity data are presented in Table IV. Physical activity variables were not normally distributed, and distributions were not improved by various transformations. Consequently, Mann–Whitney *U* tests were used to examine between-group (exposed to antenatal corticosteroids vs not exposed to antenatal corticosteroids) differences for those variables. For males and female adolescents combined, TOT-hrs and VIG-hrs per week for the past year did not differ significantly by antenatal corticosteroid exposure. For the past 2 months, TOT-hrs per week was not different, but VIG-hrs per week was greater in the group exposed to antenatal corticosteroids compared with the group not exposed to antenatal corticosteroids. When stratified by sex, VIG-hrs per week for the past year as well as TOT-hrs and VIG-hrs per week for the past 2 months were significantly greater in the male adolescents exposed to antenatal corticosteroids compared with the male adolescents not exposed to antenatal corticosteroids. No antenatal corticosteroid group differences in physical activity were observed in female adolescents. Exclusion of data of participants who were unable to do the exercise test due to neuromotor or pulmonary limitations increased the TOT-hrs and VIG-hrs for the past year and VIG-hrs for the past 2 months in the male adolescents not exposed to antenatal corticosteroids, but the TOT-hrs and VIG-hrs for the past 2 months remained significantly lower than their male peers exposed to antenatal corticosteroids. In female adolescents, physical activity levels did not change negligibly and no differences by antenatal corticosteroid group remained.

We also examined the proportion of participants meeting the national physical activity recommendations of at least 7 hours per week.[25] For the past year, 59% of adolescents exposed to antenatal corticosteroids and 57% of adolescents not exposed to antenatal corticosteroids reported meeting this recommendation. When stratified by sex, more male (77% of exposed to antenatal corticosteroids and 73% not exposed to antenatal corticosteroids) than female (44% not exposed to antenatal corticosteroids and 47% exposed to antenatal corticosteroids) adolescents met the recommendation, with no antenatal corticosteroid group differences. Similar results were observed for total physical activity in the previous 2 months. The national recommendation also specifies that most of the 60 minutes or more per day should be vigorous physical activity on at least 3 days per week. For the past year, 34% of those exposed to antenatal corticosteroids and 20% of those not exposed to antenatal corticosteroids reported engaging in vigorous physical activity for at least 3 hours per week ($P = .03$). When stratified by sex, a greater proportion of male adolescents exposed to antenatal corticosteroids (57%) met this recommendation compared with those not exposed to antenatal corticosteroids (43%) ($P = .04$). The proportions were slightly different for vigorous physical activity participation in the previous 2 months (54% of those exposed to antenatal corticosteroids and 36% of those not exposed to antenatal corticosteroids). In female adolescents, only 5 exposed

to antenatal corticosteroids (10%) and 4 not exposed to antenatal corticosteroids (8%) met the recommendation for vigorous physical activity for the past year, with slightly greater proportions observed in the previous 2 months (21% and 10% in those exposed to antenatal corticosteroids and those not exposed to antenatal corticosteroids, respectively). Logistic regression analysis, with antenatal corticosteroid exposure, sex, and race in the model, revealed a significant main effect of antenatal corticosteroid exposure on meeting the vigorous physical activity recommendation for the past 2 months. Interactions terms were not significant and were subsequently excluded from the analysis. Adolescents exposed to antenatal corticosteroids were twice as likely to meet the recommendation (aOR 2.14; 95% CI 1.02-4.50; $P = .045$) than their unexposed peers. Notably, 42% of male adolescents not exposed to antenatal corticosteroids compared with 14% of those exposed to antenatal corticosteroids and more than one-half of female adolescents in both groups (52% exposed to antenatal corticosteroids and 53% not exposed to antenatal corticosteroids) reported that they did not participate in any vigorous physical activity in the previous 2 months.

Discussion

The results of our study suggest that antenatal corticosteroid exposure is associated with greater aerobic fitness and physical activity participation in male adolescents born preterm with VLBW, but only among nonblack male adolescents exposed to antenatal corticosteroids. The sex- and race-specific associations are consistent with our previous work showing sex and race differences of antenatal corticosteroid exposure on other outcomes such as heart rate variability, cholesterol levels, and renin–angiotensin system peptide levels.[16-18] The findings, however, are inconsistent with our hypotheses and are somewhat surprising in view of our previous work showing adverse effects of antenatal corticosteroid exposure on pulmonary function in this cohort.[6] Despite a greater prevalence of larger airway obstruction in adolescents exposed to antenatal corticosteroids compared with their unexposed peers (35% vs 21%, respectively),[6] antenatal corticosteroid exposure was not associated with lower aerobic fitness or physical activity participation. Other studies have shown that exercise capacity and physical activity levels are more likely to be associated with impaired pulmonary diffusion, ventilatory inefficiency, and ventilatory flow limitations during exercise rather than resting measures of pulmonary function.[30,31] Future research should examine these parameters and their role in determining aerobic fitness in the population.

Antenatal corticosteroid exposure during critical periods of fetal growth may have affected cardiac development and function. Preclinical studies have shown antenatal corticosteroids promotes myocyte maturation and increases atrial mass, ventricular filling, and aortic flow in piglets born preterm compared with their unexposed littermates.[9] In humans, Kelly et al reported no differences in left ventricular mass or ejection fraction between 16 young adults exposed to antenatal corticosteroids and 16 young adults not exposed to antenatal corticosteroids, but the long-term effects of antenatal corticosteroids on cardiac structure and function, particularly in response to exercise, remain unknown.[4]

In contrast to cardiac muscle development, antenatal corticosteroid exposure has been shown to be detrimental to skeletal muscle growth and development. In animal models, fetal exposure to glucocorticoids has been associated with inhibited myogenesis, reduced myonuclei per myofiber, smaller fiber cross-sectional area and muscle mass, and fewer satellite cells.[7,8] However, in vitro studies suggest that the effects are dependent on the dose and timing of exposure.[32,33] Muscle satellite cells are muscle-specific stem cells that play an important role in fiber plasticity, repair, and regenerative capacity.[34] Aerobic exercise training has been shown to activate satellite cells and promote proliferation and differentiation toward a more oxidative phenotype with greater mitochondrial protein content, oxidative capacity, and capillary density.[35] In our cohort, antenatal corticosteroid exposure was associated with greater participation in vigorous physical activity, particularly in male adolescents, which may have contributed to their greater levels of aerobic fitness. Given the cross-sectional examination of functional parameters, it is also possible that greater fitness may have enabled more participation in vigorous physical activity.

The antenatal corticosteroid group differences in physical activity participation were evident in estimates for the past 2 months but not the past year. Although the past year is more likely to reflect habitual activity levels, it is subject to greater recall error than estimates for the previous 2 months. Estimates for the previous 2 months are more likely to reflect current season-specific physical activity levels and correspond to current aerobic fitness level. The low levels of participation in vigorous physical activity particularly in unexposed male adolescents and both groups of female adolescents are concerning and may contribute to their risk for developing cardiometabolic disease. The large sex differences were not totally unexpected and are consistent with data from the Youth Risk Behavior Survey, which shows that the percentage of male adolescents meeting the national guidelines for vigorous activity is more than double that of female adolescents in North Carolina.[36] The relatively high percentage of adolescents reporting that they met the national recommendation for total physical activity in the previous 2 months was somewhat surprising and may reflect recall error as well as possible inaccuracy associated with self-report measures. Objective assessment with motion sensors would help to reduce these problems and provide a more accurate measurement of short-term physical activity levels.

It is possible that fitness and physical activity in our cohort might be attributed to differences in body size. The male adolescents exposed to antenatal corticosteroids were significantly taller than their unexposed peers, and it may be speculated that the shorter stature of the male adolescents not exposed to antenatal corticosteroids might diminish their ability to compete with their peers in sports and ultimately

lead to less participation in vigorous physical activity and lower aerobic fitness. Furthermore, the groups exposed and not exposed to antenatal corticosteroids had similar lean body mass, and the group differences in fitness persisted when VO_2peak was expressed relative to lean body mass. The differences also are not explained by sexual maturation, as the majority of male adolescents exposed to antenatal corticosteroids reported a lower stage of development (stage 4, late pubertal) than their peers not exposed to antenatal corticosteroids (stage 5, postpubertal).

Finally, antenatal corticosteroid exposure has been associated with reduced risk for cerebral palsy. Although 4 participants in both antenatal corticosteroid groups had a history of cerebral palsy, the group differences persisted when we excluded the data of participants with neuromotor limitations. Antenatal corticosteroid exposure also has been associated with better fine and gross motor control in infants and young children,[37,38] and earlier infant motor development has been associated with greater levels of physical activity, including sports participation at 14 years of age.[39] Consequently, the children exposed to antenatal corticosteroids may have developed better motor proficiency that facilitated motor learning and instilled better self-efficacy or confidence in their ability to engage in physical activity. Future research should examine long-term effects of antenatal corticosteroids on motor proficiency and physical activity self-efficacy and their potential roles as mediators of physical activity participation in this population.

In 2 studies of young adult males with birth weights <10th percentile, aerobic training led to improvements in aerobic fitness, body composition, glucose regulation, and markers of insulin resistance.[40,41] Growing evidence suggests that persons with VLBW have increased risk for developing type 2 diabetes.[42] Consequently, aerobic training may prove beneficial for improving cardiometabolic outcomes and reducing disease risk in the VLBW population.

A limitation is that this study is observational study and not a randomized controlled trial. However, treatment with antenatal corticosteroids for preterm labor is now standard practice, with up to 87% of infants with VLBW currently exposed,[2] and a randomized controlled trial would not be ethical. A major strength is the 50% exposure rate (due to birth years surrounding the 1994 National Institutes of Health Consensus Panel promoting antenatal corticosteroid use) which provided us with a unique opportunity to examine the long-term effects of antenatal corticosteroids exposure. Our cohort is also racially diverse and was born when medical advances such as surfactant were available, making our results more generalizable to current VLBW cohorts. However, given that most of the cohort was exposed to only 1 course of antenatal corticosteroids and birth occurred within 1 week, the results of repeated courses of antenatal corticosteroids and timing relative to birth warrant further examination.

In summary, our study results suggest that antenatal corticosteroid exposure is not detrimental to aerobic fitness and physical activity participation in adolescents with VLBW and may have sex- and race-specific benefits. The low levels of participation in vigorous physical activity, particularly in unexposed male adolescents and both groups of female adolescents, is concerning and may contribute to their risk for developing cardiometabolic disease. Further research is warranted to identify modifiable determinants of physical activity participation, such as motor proficiency and physical activity self-efficacy, which may aid in the development of physical activity interventions. In view of the current antenatal corticosteroid exposure rates and associated risk for cardiometabolic disease, manipulation of physical activity in randomized control trials is needed to determine whether aerobic fitness and habitual activity can be increased and ultimately reduce the risk for developing cardiometabolic disease in the VLBW population. The timing of intervention relative to growth and maturation should be considered and may prove to be critical. ■

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Data Statement

Data sharing statement available at www.jpeds.com.

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Appendix

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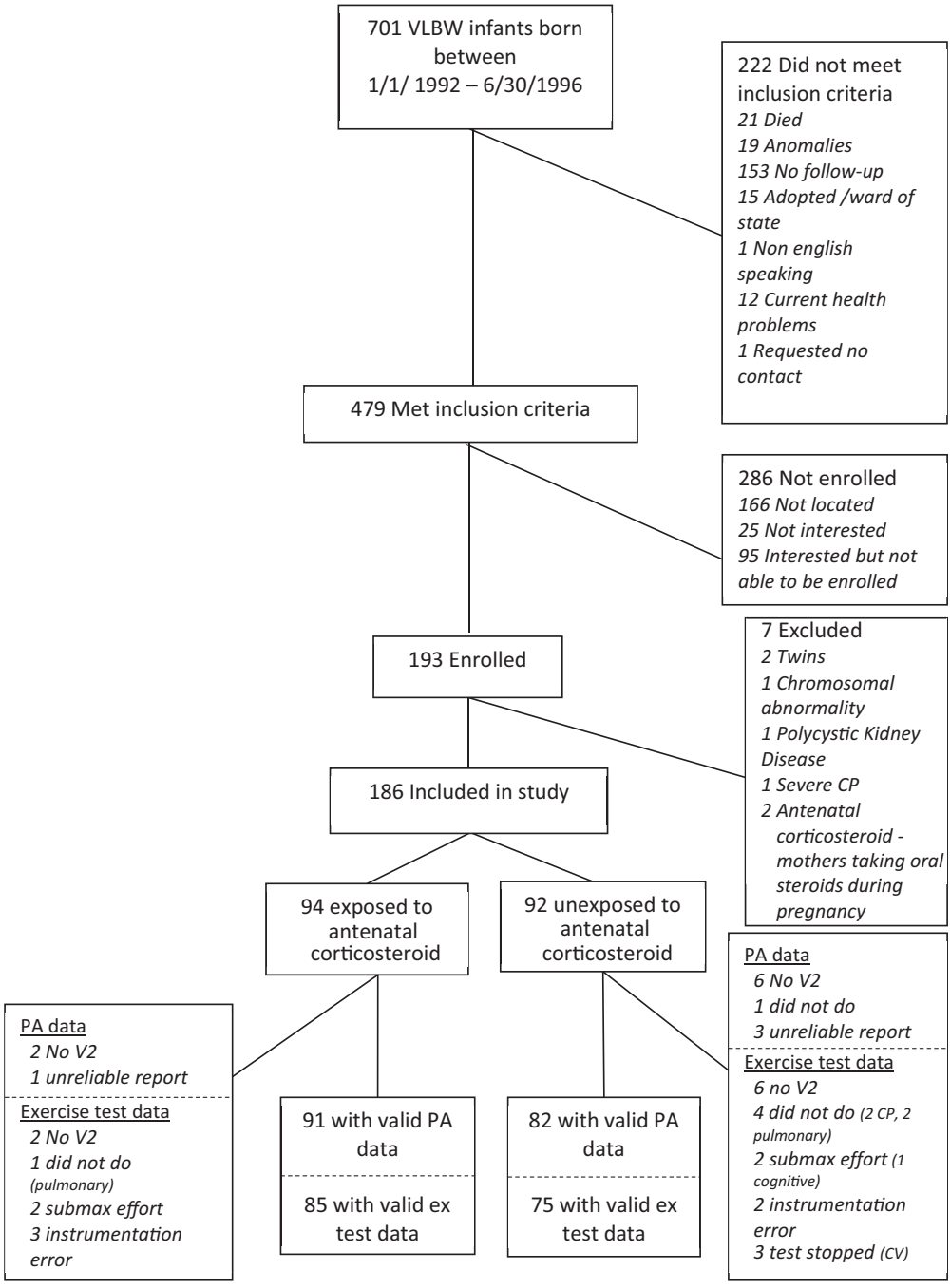

Figure 1. Eligibility, enrollment, exclusions, and inclusion for final analysis at adolescence. *CP*, cerebral palsy; *CV*, cardiovascular; *PA*, physical activity; *V2*, visit 2.

Table II. Prevalence of neonatal morbidities

Morbidities	Exposed to antenatal corticosteroids n = 91	Not exposed to antenatal corticosteroids n = 82
Necrotizing enterocolitis, n (%)	10 (11)	9 (11)
Intraventricular hemorrhage (grade 3 or 4), n (%)	1 (1)	2 (1)
Retinopathy of prematurity (grade 3, 4, 5, or surgery), n (%)	13 (14)	16 (20)
Sepsis, n (%)	1 (1)*	8 (10)
Patent ductus arteriosus		
Treated with Indocin, n (%)	3 (3)	8 (10)
Treated with surgery, n (%)	42 (59)	34 (47)

*$P < .05$ from χ^2 test.