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## Antenatal Corticosteroids and Cardio-metabolic Outcomes in Adolescents Born With Very Low Birth Weight

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### Abstract

**Background**—Exposure to antenatal corticosteroids (ANCS) is associated with adverse cardio-metabolic outcomes in animal models; however long-term outcomes in clinical studies are not well characterized. We hypothesized that exposure to ANCS would be associated with markers of increased cardio-metabolic risk in adolescents born with very low birth weight (VLBW).

**Methods**—In an observational cohort of 186 VLBW 14-year-old adolescents we measured resting blood pressure (BP), BP response to cold, ambulatory BP, and anthropometrics; performed dual-energy X-ray absorptiometry; and analyzed blood samples for uric acid, cholesterol, glycated hemoglobin, and high-sensitivity C-reactive protein. Multivariate analyses were used to evaluate associations with ANCS, adjusting for race, sex, and maternal hypertensive pregnancy.

**Results**—There were no ANCS group differences in BP measures or blood biomarkers. Compared to adolescents unexposed to ANCS, those exposed to ANCS were taller [exposed-unexposed mean difference 3.1 cm (95% CI 0.7, 5.5)] and had decreased waist-to-height ratio [exposed-unexposed mean difference  $-0.03$  (95% CI  $-0.058$ ,  $-0.002$ )]. Males exposed to ANCS

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#### Disclosure

The authors have no conflicts of interest to disclose.

had lower total cholesterol [exposed-unexposed mean difference  $-0.54$  mmol/L (95% CI  $-0.83$ ,  $-0.06$ )].

**Conclusion**—Among adolescents born with VLBW, ANCS exposure was not associated with markers of increased cardio-metabolic risk.

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## INTRODUCTION

In the United States (US), treatment with corticosteroids has been recommended since 1994 for pregnant women expected to deliver prior to 34 weeks to reduce mortality and morbidity in the offspring.(1,2) Preclinical studies of antenatal corticosteroid (ANCS) treatment have raised concerns about long-term adverse effects of ANCS on blood pressure (BP) and cardio-metabolic risk in the offspring.(3–6) Clinical studies have not detected associations of ANCS with overt cardio-metabolic disease,(7,8) other than possible alterations in BP, vascular stiffness, and glucose metabolism.(9–11) In the largest follow-up study of patients from a randomized controlled trial of ANCS, the mean gestational age at birth was 34 weeks.(11) Information about ANCS effects at earlier gestational ages is limited to studies with small sample sizes and/or limited racial diversity. Additionally, cohorts with follow-up into adolescence or adulthood were born in the late 1960s to early 1980s.

Currently, almost all very low birth weight (VLBW) infants born in the US are exposed to ANCS, and care has evolved such that fetuses are exposed to ANCS at earlier gestational ages. Contemporary survivors of preterm birth are maturing in the epidemic of obesity, potentially exposing them to a “second hit” that might potentiate putative programming effects of ANCS.(12) Thus, we recruited a racially diverse and contemporary cohort of adolescents born prematurely with VLBW, to study the effects of ANCS exposure on BP and cardio-metabolic risk factors.

## METHODS

### Study design

The study sample was derived from a cohort of consecutive VLBW singleton births at the regional perinatal center in Forsyth County, North Carolina from January 1, 1992 to June 30, 1996 who had no major congenital malformations and returned for evaluation at one year adjusted age. Figure 1 describes the cohort’s participation in the follow-up study. We estimated that a total sample of 158 (79 in each ANCS group) would be needed to provide 90% statistical power to detect a between-group difference in the primary outcome, resting auscultatory systolic BP (SBP), of 4 mmHg ( $\alpha = 0.05$ , two-sided testing). The 4 mmHg difference used for determining sample size is the difference reported by Doyle et al. in a study of VLBW individuals.(9) As ANCS exposure was determined post-enrollment, the study sample exceeded our target due to continuous accrual of participants. This study was approved by the Wake Forest School of Medicine and the Forsyth Medical Center Institutional Review Boards. Informed consent was obtained from parents or legal guardians, and participants gave assent.

Information about the pregnancy including ANCS exposure (betamethasone and/or dexamethasone), maternal hypertension during pregnancy, and type of delivery was obtained

by review of medical records or from research databases. We excluded two participants whose mothers were treated with steroids during pregnancy for other medical conditions.

To estimate gestational age, we used, in order of priority, a first trimester ultrasound, the mother's last menstrual period, or clinical assessment of the neonate. As an index of fetal growth, we used birth weight z-score, calculated using US natality data.(13) Birth weight and postnatal dexamethasone treatment to prevent BPD (defined as use of supplemental oxygen at 36 weeks corrected gestational age) were obtained from review of the participants' medical record. As potential indicators of perinatal social economic status we used mother's marital status (married or non-married) and education status ( < 12 years or > 12 years), and at age 14 years, we used Medicaid health insurance. Participant's race was categorized as black or non-black, based on parent or guardian report at the 14-year visit. Z-scores and percentiles for measurements made at 14 years were derived using Epi Info™ (Centers for Disease Control, Atlanta, Georgia).(14) We categorized BMI > 85<sup>th</sup> percentile as overweight/obese.(15) Pubertal maturation status was assessed in private using self-completed questionnaires based on Tanner staging for pubic hair, breast development in females, and genital development in males.(16) Family history of cardiovascular disease was determined by parent or guardian report of maternal or paternal hypertension, stroke, or heart attack. Current medication use was reported by a parent or guardian and the participants.

Participants were seen for three visits during their 15<sup>th</sup> year of life. The ½ day visits were performed in a General Clinical Research Center. Participants were asked to refrain from caffeine containing beverages for 24 hours prior to the visit. At each visit, BP was measured in the right arm with a mercury sphygmomanometer by nursing staff certified in BP measurement using guidelines established by the National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.(17) Proper cuff size was determined using mid-upper arm circumference. Participants were seated quietly for 5 minutes with the back supported, the forearm at heart level, and feet flat on the floor. The average of three measurements was used to estimate SBP and diastolic BP (DBP). The average of five resting oscillometric BP measurements were recorded using the same procedure with the Dinamap® Pro 100 (Critikon).(18)

The BP response to forehead cold stimulation was performed at the first visit following the procedures of Dysart et al.(19) During the 11th, 13th, and 15th minute of rest, baseline BP measurements were made using the Dinamap® Pro 100 (Critikon). A bag of ice water was placed on the subject's forehead for one minute. At the end of the minute, BP was measured, and the bag was removed. The difference between the peak BP and the average of the three baseline BP measures was calculated.

Ambulatory BP monitoring (AMBP) was utilized in the non-dominant arm after the third visit (Spacelabs 90207, Redmond, WA). Participants were asked to wear the monitor for 24 hours and keep a diary of their activities. The monitors were programmed to inflate every 20 minutes from 7 am to 9 p.m. and every 30 minutes from 9 p.m. to 7 a.m. Studies with at least 70% successful readings and at least one reading every hour were analyzed. The mean of successful daytime and nighttime readings was calculated using self-reported sleep and

awake times, and percentages of nocturnal SBP and DBP decline were determined. BP load was defined as the proportion of measurements above the 95th percentile for age, sex, and height.(20)

In participants willing to undergo venipuncture, a non-fasting sample of blood was obtained at the third visit. Total and HDL cholesterol and uric acid were determined enzymatically and ELISA (ALPCO, Windham, NH) was used to measure high sensitivity C-reactive protein (hs-CRP). Glycated hemoglobin was determined using Roche Tina-quant® assay.

Measurements of height (to the nearest hundredth of a centimeter using a wall-mounted stadiometer) and weight (to the nearest tenth of a kilogram using a digital platform scale) were made at each study visit in triplicate with participants wearing light clothing and no shoes. The averages of each measurement were used for analysis. At the third visit, a nutritionist measured waist circumference (to the nearest tenth of a centimeter with a measuring tape according to procedures of National Health and Nutrition Examination Survey III)(21) and triceps and subscapular skin fold thicknesses (using a Lange skinfold caliper).(22) Fat mass, fat free mass, and bone mineral content were assessed using a Delphi dual-energy X-ray absorptiometer (DXA) (Hologic, Bedford, MA) equipped with pediatric software. Lean body mass was calculated by subtracting bone mineral content from total fat free mass.

### Statistical Analysis

Characteristics were compared using two-sample t and Fisher's Exact tests between ANCS exposed and unexposed study participants and between eligible VLBW patients who were enrolled and not enrolled in the study. Outcome measures that were not approximately normally distributed were transformed prior to analysis using logarithmic or square root transformation as indicated. To adjust for potential confounding and other variables, multiple regression modeling approaches were used, including general linear regression for continuous outcomes and logistic regression for dichotomous outcomes. Outcomes that were measured across multiple participant visits were modeled based on a general linear regression as well, but with a random effect to portray individual differences, and with a first-order autocorrelation structure for the repeated measures within participants across visits. Covariate selection was based on prior reported relationships in the literature, including an ANCS x BMI interaction term, which was included in models for BP measured at rest and in response to cold. The modeling procedures were repeated after stratifying separately by sex and by race. In an effort to differentiate the effect of race and socioeconomic status on ANCS group differences, analyses suggesting ANCS group differences when stratified by race were repeated stratifying by maternal marital status. To allow comparison with results reported by Doyle et al, we estimated the exposed-unexposed mean difference in SBP, adjusting for current weight, among non-black participants.(9) Least squares means between ANCS-exposed and unexposed groups and adjusted odds ratios were used together with their corresponding 95% confidence intervals to evaluate associations with ANCS exposure. P values  $\leq 0.05$  were considered statistically significant. No correction for multiple testing was applied to outcomes, as those selected for analysis

were related and were used to evaluate consistency across findings. All analyses were performed using SAS for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA).

## RESULTS

Compared to those eligible but not included, the 186 participants included in the study had lower gestational age (mean  $\pm$  SD  $27.7 \pm 2.6$  v  $28.3 \pm 2.5$  weeks) and higher birth weight z-score ( $-0.26 \pm 0.81$  versus  $-0.43 \pm 0.81$ ) but were similar in birth weight, race, sex, and mode of delivery (results not shown). Participant characteristics are shown in Table 1.

For the 65 participants for whom complete data on ANCS exposure were available, all were exposed to betamethasone except one who received one dose each of betamethasone and dexamethasone, and one who received only dexamethasone. Of those exposed to multiple courses (two doses of betamethasone separated by one week), five received two courses, and two received three courses. Caesarean delivery and maternal hypertension during pregnancy were more common in those exposed to ANCS. Non-married mothers, mothers with less than or equal to high school education, and mothers of black participants were less likely to be exposed to ANCS (Table 1). Race was related to maternal marital status ( $p < 0.0001$ ) but not maternal education ( $p = 0.21$ ).

At 14 years of age, 186 (94 exposed) participants completed one visit, 179 (92 exposed) completed two visits, and 174 (92 exposed) completed all three study visits. There were no group differences in the BP outcomes as shown in Table 2. Exclusion of participants treated with postnatal dexamethasone to prevent BPD did not alter the results (data not shown). Similarly, exclusion of BP measurements potentially affected by stimulant medications for attention deficit hyperactivity disorder did not affect the results. Although waist-to-height ratio (WHtR) at 14 years was positively correlated with auscultatory and oscillometric SBP ( $r = 0.25$  and  $r = 0.34$ , respectively,  $p < 0.001$ ), we did not detect significant ANCS x BMI interactions. When stratified by sex, ANCS-exposed females had higher resting auscultatory DBP ( $63.2 \pm 0.9$  v  $60.7 \pm 0.9$  mmHg;  $p = 0.072$ ) which was attenuated when adjusted for race, height, and maternal hypertensive pregnancy. When stratified by race, ANCS-exposed non-black participants had higher auscultatory SBP ( $106.0 \pm 1.1$  v  $102.6 \pm 1.4$  mmHg;  $p = 0.063$ ), DBP ( $61.5 \pm 0.9$  v  $58.6 \pm 1.2$  mmHg;  $p = 0.065$ ) and higher peak SBP response to cold stress ( $128.5 \pm 12.6$  v  $123.6 \pm 10.8$  mmHg;  $p = 0.051$ ). The ANCS group differences in non-blacks were attenuated when adjusted for sex, height, and maternal hypertensive pregnancy. However, resting auscultatory SBP was higher in ANCS exposed non-blacks when current BMI replaced height in the model [exposed-unexposed mean difference 3 mmHg (95% CI 0.07, 6.9,  $p = 0.045$ )]. In contrast to results stratified by race, there were no ANCS group differences in BP outcomes when stratified by maternal marital status.

There were also no ANCS group differences in circulating biomarkers (Table 3). However, among males, ANCS exposure was associated with lower total cholesterol [exposed-unexposed mean difference  $-0.54$  mmol/L (95% CI  $-0.83, -0.06$ ),  $p = 0.029$ ] when adjusted for race and hypertensive pregnancy. This relationship was attenuated when adjusted for central adiposity (WHtR) [exposed-unexposed mean difference  $-0.14$  mmol/L (95% CI  $-0.57, 0.28$ ),  $p = 0.52$ ].

Anthropometric measures of the participants at 14 years of age are shown in Table 4. Participants exposed to ANCS were taller, had a lower WHtR and tended to have a lower sum of triceps and subscapular skinfold thicknesses. There were no ANCS group differences in body composition variables obtained by DXA. Three percent of each group were classified as underweight (BMI <5<sup>th</sup> percentile) and about one-third of each group (29% exposed, 37% unexposed;  $p=0.27$ ) were classified as overweight (BMI ≥85<sup>th</sup> percentile). In subgroup analyses, the ANCS group differences in the sum of triceps and subscapular skinfold thicknesses were greater in non-blacks [exposed –unexposed mean difference, –8.7 mm (95% CI –15.2, –2.2),  $p=0.009$ ] than blacks [exposed –unexposed mean difference, 1.3 mm (95% CI –7.4, 10.1),  $p=0.76$ ] adjusted for sex and hypertensive pregnancy, and in males [exposed –unexposed mean difference, –7.5 mm (95% CI –15.1, 0.2),  $p=0.056$ ] compared to females [exposed –unexposed mean difference, –0.9 mm (95% CI –8.2, 6.4),  $p=0.80$ ], adjusted for race and hypertensive pregnancy. In contrast to results stratified by race, there were no ANCS group differences in skin fold thicknesses when stratified by maternal marital status.

## DISCUSSION

In a cohort of adolescents born with VLBW, we found no associations between exposure to ANCS and measures of resting BP, ambulatory BP monitoring (ABPM), or BP response to cold stress, total or HDL cholesterol, HbA<sub>1c</sub>, or uric acid. Exposure to ANCS was associated with increased height and decreased WHtR at 14 years of age. Among males, exposure to ANCS was associated with lower total cholesterol and among non-blacks, ANCS was associated with a lower sum of triceps and subscapular skinfold thickness.

Except for racial diversity, and birth years, our study cohort is similar in birth weight, gestational age, and age at follow-up to that studied by Doyle et al. in which the ANCS group had 4 mmHg higher SBP at age 14 years.(9) In the only other study to describe an association between ANCS and BP during adolescence, SBP was 3–4 mmHg lower among those exposed to ANCS.(7) Like Doyle et al. we found a positive association between SBP and adiposity at age 14 years and when we adjusted for current adiposity (Doyle et al adjusted for current weight z score), we found that among non-blacks, those exposed to ANCS had higher SBP.(9) We also assessed the BP response to cold stress as a potential indicator of future BP and found no ANCS group difference.(23,24)

Kelly et al. reported an association between ANCS and increased vascular stiffness in the aortic arch in young adults, despite there being no difference in peripheral BP.(10) Similarly, we have described physiological (lower heart rate variability) and biochemical [increased ratio of urinary angiotensin II to angiotensin-(1–7)] changes that could predispose ANCS-exposed adolescents to higher BP. (25,26) Given these findings and the knowledge that programmed changes in BP amplify with age, differences in BP may emerge as our cohort ages.(27)

In agreement with Doyle et al., we found that VLBW adolescents exposed to ANCS were taller than their unexposed peers.(9) No studies have described decreased adiposity in those exposed to ANCS. In contrast, Finken et al. described an association of ANCS exposure and



increased abdominal adiposity in young adults who had glucocorticoid receptor gene variant 363S.(28) Likewise, preclinical models suggest ANCS may be associated with increased adiposity.(5) Our finding of decreased WHtR is driven by the increased height in the exposed group; however, there are trends for lower sum of triceps and subscapular skinfold thicknesses in the ANCS-exposed group as well. It is possible that ANCS group differences in height might be attributable to subtle differences in puberty that our self-assessment tool was not sensitive enough to detect; however, other studies have not found ANCS-associated differences in sexual maturity.(7,9) It is also possible that chronic illness might contribute to decreased height, however we have previously reported ANCS was not associated with improved lung function at 14 years in this cohort.(29) Mathai et al. reported increased truncal fat in adults (especially males) who were born preterm to mothers who participated in the Auckland Steroid Trial.(30) Although ANCS-associated effects on anthropometry were not found in follow up of the Auckland Trial,(11) it is possible that exposure to antenatal steroids at an earlier gestational age attenuates this presumed effect of prematurity. Our finding of an ANCS-associated decrease in adiposity in non-blacks might be explained by epigenetic and/or genetic variations in the response to ANCS. We have described racial differences in ANCS-associated changes in heart rate variability, and Myazek et al described racial differences in the programming effects of low birth weight on cardiovascular risk factors at 7–21 years of age.(25,31)

Consistent with prior studies of the relationship between biomarkers of adverse cardiovascular risk and ANCS, we did not detect ANCS group differences in total or HDL cholesterol levels, except among males, in whom ANCS was associated with lower total cholesterol.(8,10,11) We did not find any ANCS-associated differences in hs-CRP or serum uric acid. Others have described ANCS-associated alterations in glucose metabolism, both increased and decreased insulin resistance, and decreased beta cell function.(8,10,11) It is possible that our measure of HbA<sub>1c</sub>, a marker of elevated glucose in the prior three months, might not have been sensitive enough to detect abnormalities in insulin sensitivity.

Our finding that black mothers were less likely to be treated with ANCS has been described by others.(32) Analyses to determine if an indicator of socioeconomic status, maternal marital status, explained the ANCS group differences we describe among non-blacks revealed that race does convey different information than marital status. We acknowledge that race provides information about multiple factors including biological and socioeconomic. Racial differences in socioeconomic status are well described; however, multiple factors such as exposure to adversity over the life course, non-equivalence of socioeconomic indicators across races, racism, and increased exposure to psychological stressors suggest that race influences health outcomes in addition to socioeconomic status. (33)

Our study is limited by its observational design and potential for selection bias; however, randomized trials of ANCS treatment and placebo are no longer ethical. Strengths of our study include multiple measurements of BP using both the auscultatory and oscillometric methods on three different days; measurement of several physiological and molecular markers related to regulation of BP; and the inclusion of a multiracial contemporary cohort.

As exposure to ANCS is increasing and occurring at earlier gestational ages, continued study of the long term effects of ANCS on cardiovascular health is warranted.

## Conclusion

ANCS exposure was not associated with higher BP or adverse cardio-metabolic risk but was associated with increased height and decreased adiposity in 14-year-olds born with VLBW.

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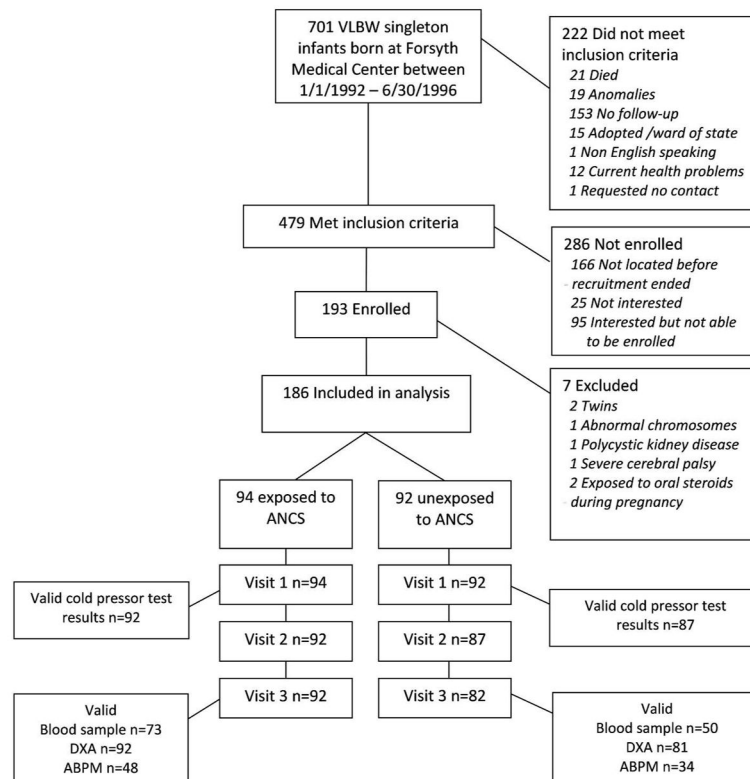
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**Figure 1.**

Eligibility, enrollment, and follow up of the study population.

VLBW- very low birth weight, ANCS- antenatal corticosteroid exposure, DXA- dual-energy X-ray absorptiometry, ABPM-ambulatory blood pressure monitoring

**Table 1**Characteristics of participants [mean  $\pm$  SD or count (%)].

	ANCS+ N=94	ANCS- N=92	<i>P</i> value <sup>a</sup>
<i>Perinatal</i>			
Gestational age, wks	27.7 $\pm$ 2.3	27.7 $\pm$ 2.9	0.93
Birth weight, g	1029 $\pm$ 268	1054 $\pm$ 265	0.52
Birth weight z score	-0.34 $\pm$ 0.74	-0.21 $\pm$ 0.91	0.28
SGA	7 (7)	12 (13)	0.23
Cesarean delivery	55 (59)	39 (42)	0.040
Hypertensive pregnancy	40 (43)	26 (28)	0.047
Male	45 (48)	39 (42)	0.47
Black	27 (29)	51 (55)	0.0003
Dexamethasone for BPD <sup>b</sup>	22 (23)	12 (13)	0.088
BPD	23 (25)	25 (27)	0.73
Maternal education $\geq$ 12 years	43/91(47)	53/78 (68)	0.008
Non-married mother	29 (31)	53 (58)	0.0004
<i>Age 14 years</i>			
Tanner genitalia/breast <sup>4c</sup>	75 (81)	71 (80)	1.0
Tanner pubic hair <sup>4c</sup>	87 (94)	79 (89)	0.30
Family history CV disease	49 (52)	51 (55)	0.66
Medicaid <sup>d</sup>	35 (38)	43 (49)	0.18
Stimulant medication	11 (12)	8 (9)	0.63

<sup>a</sup> *P* value for comparison between ANCS groups based on two-sample t or Fisher's Exact test<sup>b</sup> n=91 ANCS-<sup>c</sup> n=93 ANCS+, n=89 ANCS-<sup>d</sup> n=91 ANCS+, n=88 ANCS-

ANCS-antenatal corticosteroid, SGA-small for gestational age, BPD-bronchopulmonary dysplasia, CV-cardiovascular

**Table 2**

Blood pressure measurements at 14 years of age [mean ± SD or count (%)].

	ANCS+	ANCS-	Unadjusted P value <sup>a</sup>	Adjusted Mean Difference <sup>b</sup> [or Odds Ratio where noted] (95%CI) P value
<i>Resting BP<sup>c</sup></i>	N=94	N=92		
Auscultatory SBP, mmHg	105.5 ± 0.9	104.4 ± 0.9	0.38	0.4 (-2.3, 3.1) p=0.77
Auscultatory DBP, mmHg	61.7 ± 0.7	60.1 ± 0.7	0.13	2.0 (-0.2, 4.2) p=0.080
Oscillometric SBP, mmHg	108.9 ± 0.9	108.4 ± 0.9	0.71	-0.7 (-3.3, 2.0) p=0.62
Oscillometric DBP, mmHg	59.8 ± 0.6	60.1 ± 0.6	0.65	-0.1 (-1.8, 1.6) p=0.90
<i>BP response to cold</i>	N=92	N=87		
SBP delta, mmHg	14.6 ± 9.7	14.2 ± 10.7	0.76	0.2 (-3.0, 3.4) p=0.91
DBP delta, mmHg	6.9 ± 6.7	7.9 ± 7.0	0.31	-0.7 (-2.8, 1.5) p=0.55
<i>Ambulatory BP</i>	N=48	N=34		
24 hour SBP, mmHg	115.7 ± 7.1	114.8 ± 7.1	0.57	0.6 (-2.9, 4.0) p=0.75
24 hour DBP, mmHg	65.8 ± 5.1	64.6 ± 6.2	0.34	2.1 (-0.6, 4.8) p=0.13
SBP load, % <sup>d</sup>	12.3 ± 11.0	11.9 ± 9.7	0.98	0.14 (-0.67, 0.94), <sup>e</sup> p=0.73
DBP load, % <sup>d</sup>	11.3 ± 8.8	9.6 ± 7.7	0.27	0.40 (-0.24, 1.06) <sup>e</sup> p=0.21
Nocturnal SBP dip <10% <sup>f</sup>	22 (54)	15 (50)	0.81	2.1 (0.6, 6.8) <sup>g</sup> p=0.22
Nocturnal DBP dip <10% <sup>f</sup>	7 (17)	2 (7)	0.29	4.0 (0.6, 28.5) <sup>g</sup> p=0.16

<sup>a</sup> P value for comparison between ANCS groups based on two-sample t or Fisher exact test

<sup>b</sup> Exposed – unexposed adjusted for race, hypertensive pregnancy, sex, and height

<sup>c</sup> Mean ± standard error of the mean

<sup>d</sup> Load-proportion of measurements above the 95<sup>th</sup> percentile for age, sex, height; Square root transformed for p value calculation

<sup>e</sup> Exposed – unexposed adjusted for race and hypertensive pregnancy

<sup>f</sup> n=41 ANCS+, n= 30 ANCS-

<sup>g</sup> Odds-ratio- adjusted for race, hypertensive pregnancy, and sex

ANCS-antenatal corticosteroid, BP-blood pressure, SBP-systolic blood pressure, DBP- diastolic blood pressure, delta=BP<sub>peak</sub>-BP<sub>baseline</sub>,

**Table 3**Biomarkers at 14 years of age [mean  $\pm$  SD].

	ANCS+ n=73	ANCS- n=50	Unadjusted p value <sup>a</sup>	Adjusted Mean Difference <sup>b</sup> (95%CI) P value
Hs-CRP, nmol/L	1.42 $\pm$ 3.14	1.32 $\pm$ 1.91	0.85	0.04 (-1.02, 1.10) p=0.94
Uric acid, $\mu$ mol/L	313.5 $\pm$ 76.1	311.7 $\pm$ 73.2	0.90	-19.2 (-43.1, 4.8) p=0.11
Total cholesterol, mmol/L	3.91 $\pm$ 0.79	4.18 $\pm$ 0.92	0.086	-0.29 (-0.62, 0.04) p=0.084
HDL cholesterol, mmol/L	1.22 $\pm$ 0.37	1.29 $\pm$ 0.32	0.26	0.0 (-0.13, 0.13) p=0.98
HbA <sub>1C</sub> , %	5.45 $\pm$ 0.31	5.43 $\pm$ 0.36	0.82	0.04 (-0.08, 0.16) p=0.50

<sup>a</sup>P value for comparison between ANCS groups based on two-sample t test<sup>b</sup>Exposed – unexposed adjusted for race, hypertensive pregnancy, and sexANCS-antenatal corticosteroid, hs-CRP- high sensitivity C- reactive protein, HbA<sub>1C</sub>-glycated hemoglobin

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**Table 4**Anthropometrics at age 14 [mean  $\pm$  SD or count (%)].

	ANCS+ N=94	ANCS- N=92	<i>P</i> value <sup>a</sup>	Adjusted Mean Difference <sup>b,c</sup> [or Odds Ratio where noted] (95% CI) <i>P</i> value N=186
Height, cm	162.8 $\pm$ 8.7	159.7 $\pm$ 9.3	0.018	3.1 (0.7, 5.5) p=0.011
Weight, kg	58.8 $\pm$ 14.8	59.9 $\pm$ 18.3	0.66	-1.2 (-6.2, 3.7) p=0.62
BMI, kg/m <sup>2</sup>	22.1 $\pm$ 5.0	23.3 $\pm$ 6.3	0.14	-1.2 (-3.0, 0.5) p=0.15
BMI 85 <sup>th</sup> percentile	27 (29)	34 (37)	0.27	0.65 (0.34, 1.26) <sup>d</sup> P=0.20
Waist circumference, cm	78.0 $\pm$ 13.3	80.0 $\pm$ 16.7	0.40	-2.9 (-7.6, 1.8) p=0.23
Waist/height ratio	0.478 $\pm$ 0.079	0.500 $\pm$ 0.098	0.106	-0.030 (-0.058, -0.002) p=0.034
Triceps + subscapular skinfold thickness, mm	30.3 $\pm$ 16.7	35.2 $\pm$ 18.5	0.072	-4.8 (-10.1, 0.5) p=0.076
<i>DXA</i>	n=92	n=81		
Lean mass, kg	42.5 $\pm$ 9.8	42.5 $\pm$ 10.3	0.99	-0.1 (-2.8, 2.5) p=0.93
Lean mass index, kg/m <sup>2</sup>	15.9 $\pm$ 2.7	16.5 $\pm$ 2.9	0.18	-0.6 (-1.4, 0.2) p=0.15
Fat mass, kg	15.4 $\pm$ 8.7	17.0 $\pm$ 10.9	0.29	-1.8 (-4.8, 1.2) p=0.23
Fat mass index, kg/m <sup>2</sup>	5.9 $\pm$ 3.3	6.6 $\pm$ 4.1	0.18	-0.8 (-2.0, 0.2) p=0.13

<sup>a</sup>*P* value for comparison between ANCS groups based on two-sample t or Fisher exact test<sup>b</sup>Exposed-unexposed adjusted for race, hypertensive pregnancy, sex<sup>c</sup>General linear model least squares means<sup>d</sup>Odds Ratio- adjusted for race and hypertensive pregnancy

ANCS-antenatal corticosteroid, BMI-body mass index, DXA- dual energy X-ray absorptiometry