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# **Impact of corticosteroids exposure for preterm labor in neonates eventually born at term**

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Running title: Antenatal corticotherapy consequences in term born neonates

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## **ABSTRACT**

**Objective:** To evaluate the impact of antenatal corticosteroid therapy (ACS) on birth parameters of full-term newborns exposed during pregnancy for prematurity threat.

**Study Design:** Exposed newborns were randomly compared to non-exposed controls in a 1-to-2 design. Data were retrospectively collected in infants' files. Multivariate analysis assessed the impact of ACS on neonatal outcome.

**Result:** 408 term born neonates were included, 136 exposed to ACS compared to 272 non-exposed controls. Mean $\pm$ SD Head Circumference (HC) was 33.7 $\pm$ 1.4 vs 34.3 $\pm$ 1.6 cm,  $p=0.001$  in exposed vs controls; birth weight (BW) 3.1 $\pm$ 0.4 vs 3.3 $\pm$ 0.4 Kg;  $p = 0.0001$ ; Birth Height (BH) 47.9 $\pm$ 2.1 vs. 49.1 $\pm$ 2.0 cm;  $p<0.0001$ . Hypocalcemia (4.4 vs 0.7%  $p=0.019$ ) and eating difficulties (5.1 vs 1.5%  $p=0.047$ ) were significantly higher in exposed newborns. Multivariate analysis for HC showed a significant independent association with ACS ( $\beta=-0.5$ ,  $p=0.009$ ).

**Conclusion:** Term neonates exposed to ACS have a smaller HC at birth and a higher risk of neonatal complications.

## **ABBREVIATIONS**

ACS: Antenatal Corticosteroid therapy

BH: Birth height

BW: Birth weight

C- Section: Caesarian section

CNS: Central Nervous System

GA: Gestational Age

HC: Head Circumference

IQR: Inter-Quartile Range

IRDS: Infantile respiratory distress syndrome

WA: Weeks of Amenorrhea

## 1. INTRODUCTION

Antenatal corticosteroid therapy (ACS) described by Liggins fifty years ago(1)and generalized since the 2000s has greatly improved the prognosis of premature newborns(2). Nowadays, the global survival is over 85%(3).

ACS allows a significant decrease in the incidence of hyaline membrane disease (or Infantile respiratory distress syndrome (IRDS)), neonatal cerebral intraventricular hemorrhage and necrotizing enterocolitis when it is administered between 25 and 33 weeks GA, in a context of premature delivery threat(4,5).

Premature delivery threat is defined as an association of cervical changes and uterine regular and painful contractions occurring between 22- and 36-weeks GA, which may evolve spontaneously towards premature delivery. Consequently, the latest French National Council of Gynecology and Obstetrics recommendations is to administer one course of intramuscular betamethasone with two doses of 12mg 24 hours apart, in case of premature delivery threat before 34 weeks GA(6). Of note, the period of optimal effectiveness of this treatment is identified as extending from 24 hours after administration to the following 7 days (7,8).

However, the tools for the diagnosis of preterm delivery available to gynecologists (vaginal touch, intravaginal ultrasounds, and fibronectin) do not allow a formal reliable identification of this pathology. Many false positives are notified (9). Only one third of pregnant women hospitalized for a risk of preterm delivery will deliver before 37 weeks GA and only 10% of them within the 7 days period (French Health Authority 2010). So, many newborns will be unnecessarily exposed to ACS with unknown short- or long-term consequences.

In animal studies, maternal betamethasone exposure has been associated with fetal growth retardation(10) and reduce brain cell proliferation (11). In human studies, impact of antenatal glucocorticoid exposure on fetal growth have been described in studies mainly focused on premature newborns. Thus, reduced birth weight, reduced birth length and reduce head circumference have been previously reported in those infants(12),(13). Other studies highlighted an impact on neurodevelopment with a higher risk of neurocognitive disorders in exposed children(14–16).

Based on these elements, further studies are necessary to assess the impact of ACS on fetal growth and adrenal function in full-term newborns.

The main objective of this study was to evaluate the impact of ACS on fetal growth (birth head circumference (HC), length and weight) of infants born at term and exposed to one or more courses of ACS. A secondary objective was to evaluate the impact of ACS on exposed newborns at birth by evaluating the incidence of neonatal pathologies such as hypoglycemia, hypocalcemia, or jaundice, that could be possible indirect signs of adrenal insufficiency post exposure to corticosteroids.

## **2. METHODS**

### **2.1. Study description**

The study, conducted at the Regional Maternity Hospital of Nancy, was a retrospective observational study, with an exposed-not exposed design (1 to 2 design).

Full-term newborns (>36 weeks GA) born between January 1<sup>st</sup>, 2017 and December 31<sup>th</sup>, 2020, at the Regional Maternity Hospital of Nancy who received at least one course of ACS (betamethasone) before 34 weeks GA for preterm delivery threat were included and defined as exposed patients. Exposure to an ACS therapy was defined as the administration of at least

one course of intramuscular betamethasone (i.e. two doses of 12 mg, 24 hours apart), before 34 WA, for a threat of premature delivery. Newborns who received a fetal maturation for another reason, or patients born before 36GA were excluded.

Full-term newborns (>36 weeks GA) born during the study period at the Regional Maternity Hospital of Nancy who had not been exposed to ACS therapy were defined as the non-exposed group. Two non-exposed neonates were selected for one case, paired on the year of birth, and on the sex of each case patient.

## 2.2. Data sources

Data were extracted retrospectively from the maternal and pediatric medical files.

The families of the involved patients were informed by letter of their eligibility. An objection form was attached to the letter. Data could be collected in the absence of objection form received by the investigators one month after sending the letter of information.

This study was reviewed and approved by the Ethical Committee of the University Hospital of Nancy and was registered in Clinical Trial under the identification number NCT05640596.

## 2.3. Collected variables

The following data were collected: social and demographic characteristics (sex, month and year of birth of neonates), pregnancy data (single or multiple pregnancy, parity, associated complications such as gestational diabetes or preeclampsia), maternal exposures during pregnancy (smoking, alcohol consumption, toxics or drugs exposure), data concerning delivery and extrauterine adaptation of newborns (instrumental or non-instrumental vaginal delivery or caesarean section (C- section), APGAR score), birth parameters of neonates (weight, length and HC), incidence of postnatal pathologies (jaundice requiring phototherapy, hypoglycemia, hypocalcemia, eating disorders, early onset sepsis (EOS)) and the duration of



neonatal hospitalization. We considered that neonates presented eating disorders if there was a necessity to add nasogastric tube to feed them or if the duration of hospitalization was prolonged due to difficulties of sucking.

For the “exposed” group, the number of courses of corticosteroid therapy and the GA of administration were also recorded.

Children’s birth parameters were integrated and interpreted according to the AUDIPOG reference curves (curves’-best suited to our population (17), presented in Supplementary Information). Therefore, we were able to formulate data in exact centiles and organize them according to the following subgroups:  $\leq 1^{\text{st}}$  centile,  $< 10^{\text{th}}$  centile,  $[10^{\text{th}} - 25^{\text{th}}$  centile],  $[25^{\text{th}} - 50^{\text{th}}$  centile],  $[50^{\text{th}} - 75^{\text{th}}$  centile],  $[75^{\text{th}} - 90^{\text{th}}$  centile],  $>90^{\text{th}}$  centile. Results were expressed in centiles values to neutralize the effect of GA at birth.

Confounding factors (known to have a direct impact on fetal growth such as maternal diabetes, toxic exposure or preeclampsia) were identified to adjust and to conduct multivariate analyses.

#### 2.4. Statistical analyses

##### Number of required subjects

The number of required subjects was calculated to obtain a statistical power of 80% to evidence a difference of at least 0.5 cm on head circumference of newborns with an alpha risk of 0.05.

Consequently, 136 exposed subjects and 272 non-exposed patients were needed and randomized over the 2017-2020 period.

### Descriptive and comparative analyses

Characteristics of sample were described in the exposed and unexposed groups to ACS by percentage for categorical variables and mean, standard deviation, median, quartiles and min/max values for continuous variables. Comparisons were performed between exposed and non-exposed groups to ACS with Chi-2 or Fisher's exact Test for categorical variables and Student or Wilcoxon Test for continuous variables when appropriate

A matching on sex and year of birth of newborns was performed.

### Primary analysis

The characteristics of the patients associated with smallHC were identified with a bivariate linear regression model. Variables with a p-value <0.2 in the bivariable model were eligible for the multivariable model. A stepwise selection procedure was applied to retain significant independent factors.

### Secondary analyses

The characteristics of the patients associated with small length and low BW were identified with a bivariate linear regression model. Variables with a p-value<0.2 in the bivariable model were eligible for the multivariable model. A stepwise selection procedure was applied to retain significant independent factors.

The same model was used to identify the characteristics of the patients associated with neonatal adaptation (APGAR' score).

Frequencies of early neonatal complications were compared between exposed and non-exposed patients to ACS with Chi-2 or Fisher's exact Test for categorical variables and Student or Wilcoxon Test for continuous variables

The significance threshold was set at 5%

These statistical analyses were performed using SAS version 9.4 software (SAS Institute).

### 3. RESULTS

#### 3.1. Patient characteristics

One hundred and thirty-six patients were randomly selected over the 321 eligible patients in the exposed arm. They were associated with 272 controls selected among non -exposed neonates.

Demographic, medical and obstetric characteristics of the two groups are shown in Table 1.

Median GA at birth between exposed and non-exposed groups were respectively 38 weeks of amenorrhea (WA) + 2 days (IQR: 37 WA + 5 days – 39 WA + 3 days) versus 39 WA + 3 days (IQR 38 WA + 4 days – 40 WA + 3 days) ( $p < 0.0001$ ).

Concerning ACS, median exposition for the first course was at 31 weeks GA + 2 days (IQR 29 WA + 3 days – 32 WA + 6 days,). Only 10 patients (7.5%) were exposed to a second course of ACS. The median GA for this second exposition was 32 WA (IQR 30 WA + 3 day – 32 WA + 2).

#### 3.2. Birth Head Circumference

Mean HC (cm $\pm$ SD) were 33.7 $\pm$ 1.4 cm in exposed group versus and 34.3 $\pm$ 1.6 cm in the non-exposed group ( $p= 0.0001$ ), and median HC expressed in centiles was 34.3 (IQR 17.6– 57.9) in exposed group versus 45.6 (IQR 18.8 – 68.8) in non-exposed group ( $p=0.0605$ )(Table 2). Distribution between both groups is represented in Figure 2a.

In multivariate regression, antenatal corticosteroid therapy was significantly associated with lower HC expressed in cm ( $p=0.0009$ ) or in centiles ( $p=0.0299$ ) (Table 3).

Smoking exposure was also significantly associated with lower HC expressed in centiles ( $p=0.0065$ ) (Table 3).

### 3.3. Birth weight

Mean BW  $\pm$  SD were respectively  $3.1 \pm 0.4$ kg and  $3.3 \pm 0.4$  kg in the exposed and non-exposed group ( $p < 0.0001$ ) (Table 2). The median value for BW expressed in centiles in the exposed group was 37.7 (IQR 18.3 – 63.3) versus 46.1 (IQR 20.8 – 71.2) in the non-exposed group ( $p = 0.0385$ ) (Table 2). The distribution between both groups is represented in Figure 1b.

In multivariate regression, antenatal corticosteroid therapy was not significantly associated with lower birth weight in centiles (Table 3).

Antenatal smoking exposure was associated with lower BW expressed in centiles in multivariate regression ( $p = 0.0012$ ).

### 3.4. Birth height

Mean BH  $\pm$  SD were respectively  $47.9 \pm 2.1$ cm and  $49.1 \pm 2.0$  cm in the exposed and non-exposed group ( $p < 0.0001$ ) (Table 2). The median value for BH centile in the exposed group was 27.7 (IQR 12.4 – 42.6) versus 33.5 (IQR 15.0 – 63.0) in the non-exposed group ( $p = 0.0059$ ) (Table 2). The distribution between both groups is represented in Figure 1c.

In multivariate regression, ACS was significantly associated with lower BH expressed in centiles ( $p=0.0125$ ) (Table 3).

Gestational diabetes was significantly associated with a higher BH expressed in centiles ( $p=0.0221$ ).

### 3.5. Neonatal adaptation

Neonatal adaptation was assessed by checking the APGAR' score of all neonates at 1 and 5 minutes after birth. There was no significant difference between the 2 groups regarding corticosteroid exposure ( $p = 0.7177$  at 1 minute,  $p = 0.4483$  at 5 minutes).

### 3.6. Neonatal pathologies

Hypocalcemia (4.4% in the exposed group versus 0.7% in the non-exposed group,  $p = 0.0187$ ), and eating disorders (5.1% in the exposed group versus 1.5% in the non-exposed group,  $p = 0,0474$ ) were significantly more frequent in case of ACS exposure (Table 6). There is no significant difference between frequencies of hypoglycemia, neonatal jaundice or EOS.

## 4. DISCUSSION

This retrospective study highlights some consequences of ACS exposure on fetal growth and on metabolic functions in term born neonates. ACS exposure in these neonates is significantly associated with a smaller HC at birth, and a smaller BH, even after adjustment for confounding factors. Moreover, neonatal complications such as hypocalcemia and eating disorders are significantly more frequent in ACS exposed newborn.

The impact of ACS exposure on cerebral growth has been previously described and our results are consistent with previous studies. Many of them, particularly in the population of preterm neonates, showed reduced HC at birth, more important in case of multiple courses of ACS (18–21). Although many studies concluded on a significant difference in HC after ACS exposure, a recent historical French cohort study moderates these results (22). Despite an important population, no difference on the rate of very small head circumference (i.e. HC < 5<sup>th</sup> percentile) was demonstrated between ACS exposed and non-exposed newborns. It can be

suggested that, even if there is a restriction of HC growth secondary to ACS, the restriction of head growth stays moderate and does not lead to microcephaly.

In addition to the association of ACS exposure with a restriction of brain growth, studies showed an impact of ACS on neurodevelopment such as learning disabilities (23), mental and behavioral disorders in exposed children (14). In 2007, a study warned about a possible higher rate of cerebral palsy among exposed children and asks for further studies (24). A recent meta-analysis highlighted a significant reduction in the risk of neurodevelopmental impairment for extremely preterm neonates but suggested a higher risk for neurocognitive disorders for late-preterm births and a higher risk of mental or behavioral disorders for full term newborns exposed to ACS (25). Regarding Intelligence Quotient (IQ), a reduction of IQ in ACS exposed children have been described in comparison with non-exposed controls (26). The mechanisms leading to these neurological impairments are not well identified, but some assumptions are made: betamethasone could impact blood – brain barrier permeability (11), the concentration (27) or the localization of certain proteins (28) such as glucocorticoid receptors.

Regarding birth height, our results suggest an impact of ACS on fetal growth. This impact on fetal length have been reported in others studies (10-25). Diguisto at al., demonstrated a higher frequency of exposed newborn with a birth length under the 5e percentile (22).

Regarding birth weight, the impact of ACS exposure is still uncertain, with a few studies conducted in term neonates (29,30). Previous studies evidenced growth restriction on preterm neonates exposed to ACS, especially if there is more than one course of corticosteroids (19,31,32). Assessing the precise role of ACS exposure on fetal growth is difficult because of numerous confusion factors. Many risk factors of intra-uterine growth restriction have already been identified. First, sociodemographic factors which can be changeable or not (mother's age, mother's intrauterine growth, toxics or alcohol exposure, mother's nutritional

status BMI < 18 kg/m<sup>2</sup>) (33–37). Then, on the obstetrical level, multiple pregnancies or closed pregnancies are well known risk factors. In this study, we did not collect sociodemographic data apart alcohol, smoking and toxics exposure so adjustment on confounding factors is imperfect. In this study, maternal smoking exposure represents the main confusion factor, with a smoking exposure twice more frequent in the exposed group. There is an easy explanation for this difference as smoking exposure was recently identified as a risk factor for preterm delivery (38). Nevertheless, there is still a significant association between ACS exposure with HC and BH in multivariate regression analysis.

- On a metabolic point of view, we chose to evaluate neonatal complications, which could be secondary to adrenal insufficiency. Neonatal hypocalcemia and eating disorders are more frequent in exposed term neonates compared to non-exposed controls. We did not evidence significant difference on hypoglycemia at birth but this risk had already been notified in various studies but for preterm birth (39–41). The higher frequencies of these neonatal complications raised the question of the consequence of ACS exposure on hypothalamic-pituitary-adrenal axis function as suggested by previous studies(42,43).

All the above-mentioned neonatal metabolic complications are influenced by weight birth, even eating disorders. Intrauterine Growth Restriction (IUGR) could be a confounding factor but there was no significant difference of newborn with growth restriction in the 2 groups of this study.

The strengths of the study are the focus on term newborn exposed to ACS, the number of patients included, calculated a priori to obtain a statistical power of 80% to evidence a difference of 0,5 cm on head circumference of newborns. For birth parameters we chose to use the AUDIPOG curves, most appropriate to our population, with an expression in centiles in order to neutralize the effect of GA at birth. The AUDIPOG curves are adapted to evaluate

birth parameters for a French group of patients and with frequent use for scientific studies (<https://www.audipog.net>). Nevertheless, our study presents some limitations. The most important one is the retrospective design of the study. However, because of the recognized beneficial effects of corticosteroids for premature neonates, it would be unethical to perform a randomized controlled trial. It would be interesting to lead a retrospective analysis but with a prospective recruitment, on a predefined period, including mothers and newborns at discharge. It could help to reduce missing data or misinformation and may allow an exhaustive recruitment of exposed patients. A second limitation is that the group sizes were too small to perform subgroup analysis (number of ACS courses, gestational age of ACS for example). In our study, due to the small number of second course (N =10, 7.4%), subgroups analyses to study the impact of multiple courses of ACS exposure on growth parameters could not be performed. It would have been interesting to study if neonates exposed earlier in pregnancy to corticosteroids would have been more or less impacted.

This study is in line with the current trend to reduce ACS to the minimum effective dose, to prevent neonatal and post-partum complications. However, the French multicenter BETADOSE study evaluating 3244 women was not able to show a non-inferiority of a half-dose of betamethasone compared to a full dose (44). Numerous studies discuss the possibility of decreasing the empiric doses of betamethasone, but no one supports a practice change towards antenatal betamethasone dose reduction. A possible solution, to limit the prescription of ACS could be the identification of new markers improving the reliability of the risk of premature delivery, in case of premature labor.



## **5. CONCLUSION**

Under the conditions of the study, ACS exposure was associated with a smaller head circumference and a smaller height at birth. The neonates also presented a higher risk of hypocalcemia and neonatal eating disorders in full term exposed newborn.

These results do not question the indication of ACS in case of a risk of preterm delivery but raise caution on excessive ACS prescription in low-risk pregnancies. Further studies should be designed to explore new markers or to actualize scores to identified better situations at risk for preterm delivery to reduce the number of newborns unnecessarily exposed to ACS.

Long term follow-up of ACS exposed term born neonates are necessary to evaluate potential consequences of this exposure.

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## 6. Tables

**Table 1:** Demographic, medical and obstetric characteristics of the patients included in the study in exposed and non-exposed group.

	ACS exposed group N = 136 (33.3%)				Non-exposed group N = 272 (66.7%)				P**
	N	%			N	%			
<b>Growth restriction Under 10th percentile</b>	19	14			32	11.8			0.5254
<b>Parity - primiparous</b>	69	50.7			104	38.2			<b>0.0160</b>
<b>Maternal smoking</b>	23	16.9			24	8.8			<b>0.0159</b>
<b>Alcohol consumption</b>	0	0.0			1	0.4			1.0000
<b>Toxics exposure</b>	2	1.5			8	2.9			0.5068
<b>Pre-eclampsia</b>	1	0.7			2	0.7			1.0000
<b>Gestational diabetes</b>	14	10.3			36	13.2			0.3931
	N	med†	Q1†	Q3†	N	med†	Q1†	Q3†	
<b>Gestational age at birth</b>	136	38.2	37.5	39.3	272	39.3	38.4	40.3	<b>&lt; 0.0001</b>

†MED: median

\*\* Chi- 2 test or exact Fisher's test for categorical variables, Wilcoxon test for quantitative variables.

**Table 2:** Birth parameters (head circumference, birth height and birth weight) in the two groups of newborns exposed and non-exposed to antenatal corticosteroid therapy.

	ACS exposed group N = 136 (33.3%)				Non-exposed group N = 272 (66.7%)				p**
	N	med†	Q1†	Q3†	N	med†	Q1†	Q3†	
<b>Head</b>									
<b>Circumference (cm)</b>	136	34.0	33.0	35.0	272	34.5	33.0	35.0	<b>0.0001</b>
<b>HC Centiles</b>	136	34.3	17.6	57.9	272	45.6	18.8	68.8	0.0605
<b>Birth Height (cm)</b>	135	48.0	47.0	49.0	271	49.0	48.0	50.5	<b>&lt;0.0001</b>
<b>BH Centiles</b>	135	27.7	12.4	42.6	271	33.5	15.0	63.0	<b>0.0059</b>
<b>Birth Weight (kg)</b>	136	3.1	2.7	3.3	272	3.3	3.0	3.6	<b>&lt;0.0001</b>
<b>BW Centiles</b>	136	37.7	18.3	63.3	272	46.1	20.8	71.2	<b>0.0385</b>
<b>APGAR 1 mn</b>	135	9.0	8.0	9.0	270	9.0	8.0	9.0	0.7177
<b>APGAR 5 mn</b>	135	10.0	9.0	10.0	270	10.0	9.0	10.0	0.4483

†MED: median, Q1: 1<sup>st</sup> quartile, Q3 3<sup>rd</sup> quartile

\*\* Chi- 2 test or exact Fisher's test for categorical variables, Wilcoxon test for quantitative variables.

Table3: Associated factors with birth parameters in univariate and bivariate regression

	<i>Head circumference (in centiles)</i>				<i>Birth weight (in centiles)</i>				<i>Birth height (in centiles)</i>			
	Bivariate regression		Multivariate regression		Bivariate regression		Multivariate regression		Bivariate regression		Multivariate regression	
	Moy/r*	P**	Beta	P	Moy/r*	P**	Beta	P	Moy/r*	P**	Beta	P
			69	<0.0001			15	0.0222			60	<0.0001
<b><i>Antenatal corticosteroid therapy</i></b>		<b>0.0598</b>		<b>0.0299</b>		<b>0.0379</b>				<b>0.0057</b>		<b>0.0125</b>
Exposed	39.3		-6.5		40.8				31.3		-6.9	
non exposed	45.4		0		47.2				39.7		0	
<b><i>Maternal smoking</i></b>		<b>0.0273</b>		<b>0.0065</b>		<b>0.0003</b>		<b>0.0012</b>		<b>0.0311</b>		
Non exposed	44.5		12		46.8		14		37.9			
Exposed	34.7		0		31.4		0		29.1			
<b><i>Alcohol consumption</i></b>		0.4862				<b>0.2013</b>				<b>0.1399</b>		
Non exposed	43.3				45.1				37			
Exposed	57.9				11				4			
<b><i>Pre-eclampsia</i></b>		0.5443				<b>0.627</b>				<b>0.3198</b>		
Non exposed	43.3				45				36.8			
Exposed	53.4				52.8				52			
<b><i>Gestational diabetes</i></b>		0.148				<b>0.0829</b>				<b>0.0442</b>		<b>0.0221</b>
Non exposed	42.6				44.1				35.9		-9.1	
Exposed	48.9				51.4				44		0	

\* Mean value for categorical variables, simple linear regression coefficient for quantitative variables

Exposed group N = 136, unexposed group N = 272

**Table 4:** Comparison of incidences of neonatal pathologies between exposed and non-exposed groups

	ACS exposed group N = 136 (33.3%)		Non-exposed group N = 272 (66.7%)		p
	N	%	N	%	
<b>Eating disorders</b>	<b>7</b>	<b>5.1</b>	<b>4</b>	<b>1.5</b>	<b>0.0474</b>
<b>Hypoglycemia</b>	11	8.1	10	3.7	0.0573
<b>Hypocalcemia</b>	<b>6</b>	<b>4.4</b>	<b>2</b>	<b>0.7</b>	<b>0.0187</b>
<b>Phototherapy</b>	15	11.0	18	6.6	0.1234
<b>Early Onset Sepsis</b>	0	0.0	5	1.8	0.1743



## **7. Figure legends :**

Figure 1a: Distribution of head circumference (cm) and centiles of HC in the ACS exposed and non-exposed group

Figure 1b: Distribution of birth weight (kg) and centiles of birth weight in the ACS exposed and non-exposed group

Figure 1c: Distribution of birth height (cm) and centiles of birth height in the ACS exposed and non-exposed group

Figure 1a

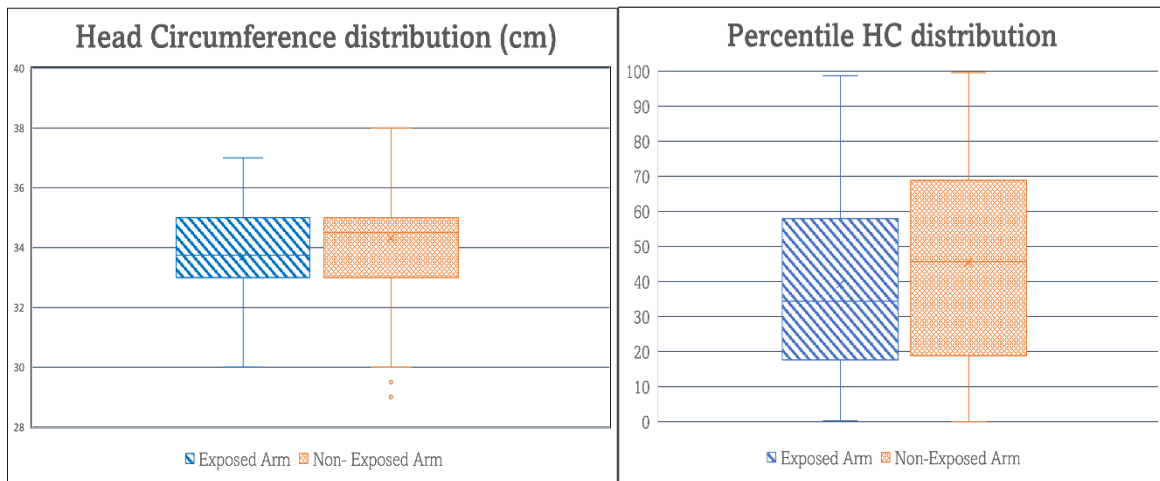


Figure 1b

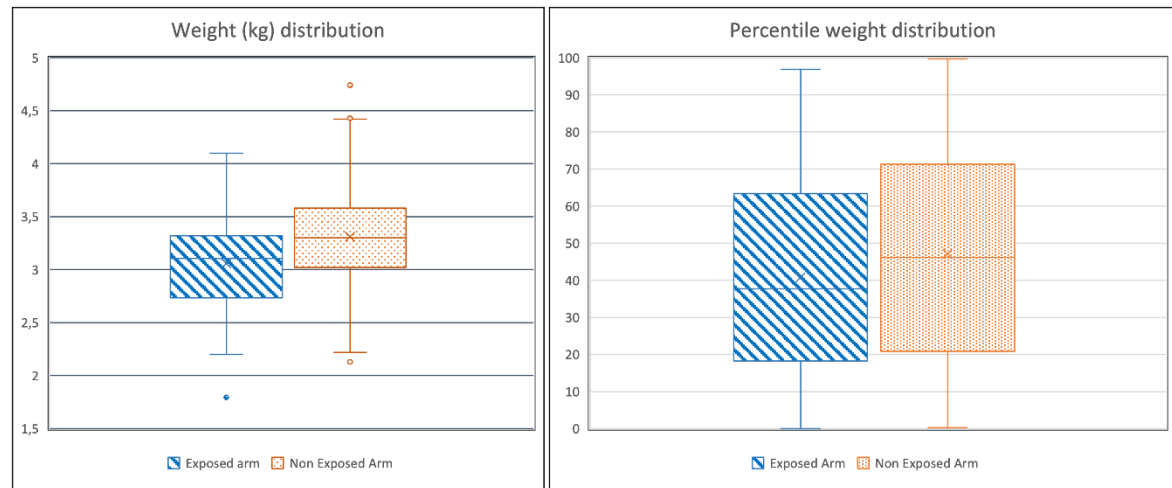


Figure 1c

