

Cardiovascular Risk Factors in Children After Repeat Doses of Antenatal Glucocorticoids: An RCT

Christopher J.D. McKinlay, PhD, FRACP^a, Wayne S. Cutfield, MBChB, FRACP^a, Malcolm R. Battin, MBChB, FRACP^b, Stuart R. Dalziel, PhD, FRACP^c, Caroline A. Crowther, FRANZCOG, MD^{a,d}, Jane E. Harding, DPhil, FRACP^a, on behalf of the ACTORDS Study Group

abstract

BACKGROUND: Treatment of women at risk for preterm birth with repeat doses of glucocorticoids reduces neonatal morbidity but could have adverse long-term effects on cardiometabolic health in offspring. We assessed whether exposure to repeat antenatal betamethasone increased risk factors for later cardiometabolic disease in children whose mothers participated in the Australasian Collaborative Trial of Repeat Doses of Corticosteroids.

METHODS: Women were randomized to betamethasone or placebo treatment, ≥ 7 days after an initial course of glucocorticoids, repeated each week that they remained at risk for preterm birth at < 32 weeks' gestation. In this follow-up study, children were assessed at 6 to 8 years' corrected age for body composition, insulin sensitivity, ambulatory blood pressure, and renal function.

RESULTS: Of 320 eligible childhood survivors, 258 were studied (81%; 123 repeat betamethasone group; 135 placebo [single course] group). Children exposed to repeat antenatal betamethasone and those exposed to placebo had similar total fat mass (geometric mean ratio 0.98, 95% confidence interval [CI] 0.78 to 1.23), minimal model insulin sensitivity (geometric mean ratio 0.89, 95% CI 0.74 to 1.08), 24-hour ambulatory blood pressure (mean difference systolic 0 mm Hg, 95% CI -2 to 2 ; diastolic 0 mm Hg, 95% CI -1 to 1), and estimated glomerular filtration rate (mean difference 1.2 mL/min/1.73m², 95% CI -3.2 to 5.6).

CONCLUSIONS: Exposure to repeat doses of antenatal betamethasone compared with a single course of glucocorticoids does not increase risk factors for cardiometabolic disease at early school age.

^aLiggins Institute, The University of Auckland, Auckland, New Zealand; ^bNewborn Services, National Women's Health, Auckland City Hospital, Auckland, New Zealand; ^cChildren's Emergency Department, Starship Children's Health, Auckland, New Zealand; and ^dAustralian Research Centre for Health of Women and Babies, Discipline of Obstetrics and Gynaecology, The University of Adelaide, Adelaide, Australia

Dr McKinlay conducted the study and collected the data, carried out the initial analyses, and drafted the initial manuscript; Dr Cutfield conceptualized and designed the study, supervised the metabolic assessments, assisted with interpretation of data, and critically reviewed the manuscript; Drs Battin and Crowther conceptualized and designed the study and critically reviewed the manuscript; Dr Dalziel assisted with analyses and critically reviewed the manuscript; Dr Harding conceptualized and designed the study, coordinated and supervised data collection, carried out the initial analyses, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

This trial has been registered at www.isrctn.org (identifier ISRCTN 48656428).

www.pediatrics.org/cgi/doi/10.1542/peds.2014-2408

DOI: 10.1542/peds.2014-2408

Accepted for publication Oct 28, 2014

WHAT'S KNOWN ON THIS SUBJECT:

Administration of repeat doses of antenatal glucocorticoids to women at risk for preterm birth after an initial course reduces neonatal morbidity, without affecting rates of neurologic disability in early childhood. However, data on long-term effects on cardiometabolic health are limited.

WHAT THIS STUDY ADDS: Exposure to repeat doses of antenatal betamethasone did not increase cardiovascular risk factors at early school age. Clinicians wishing to use repeat antenatal glucocorticoids can be reassured that the risk of future cardiometabolic disease from this therapy is low.

Antenatal glucocorticoid therapy is 1 of the few interventions for women at risk for preterm birth that has proven benefit for infants, including reduced neonatal mortality and major morbidity.¹ We have previously shown in the Australasian Collaborative Trial of Repeat Doses of Corticosteroids (ACTORDS) that administration of repeat doses of betamethasone to woman at risk for very preterm birth ≥ 7 days after an initial course of glucocorticoids results in additional neonatal benefit, including reductions in the incidence and severity of neonatal lung disease, clinically significant patent ductus arteriosus, and combined serious infant morbidity.² A systematic review of 10 randomized trials comparing single and repeat courses of antenatal glucocorticoids has supported these findings.³

Despite these benefits, use of repeat doses of glucocorticoids remains controversial, largely because of limited data regarding long-term safety. An important concern is whether fetal exposure to excess glucocorticoids could induce permanent changes in metabolic and cardiovascular function that would predispose to adult diseases such as hypertension, coronary artery disease, stroke, and type 2 diabetes.^{4,5} Although exposure to a single course of antenatal glucocorticoids has not been associated with an increased incidence of these conditions, at least up to early adulthood,^{6,7} several animal studies have demonstrated a dose-dependent effect of antenatal glucocorticoids on physiologic risk factors for disease, such as insulin sensitivity, glucose tolerance, and blood pressure.^{8–10}

Therefore, we tested the hypothesis that exposure to repeat dose(s) of antenatal betamethasone could lead to permanent changes in offspring body composition, insulin and glucose metabolism, ambulatory blood pressure, and renal function

that would increase the risk of later cardiovascular and metabolic disease.

METHODS

We undertook extended follow-up of children whose mothers participated in the ACTORDS placebo-controlled randomized trial of repeat antenatal betamethasone treatment.² Although infants in the original trial had been followed to 2 years' corrected age, we recognized that longer-term follow-up would be important because of concerns about later adverse effects.^{11–14} Therefore, a follow-up study of children at early school age was planned to assess long-term neurologic function, growth, lung function, blood pressure, general intellectual ability, specific cognitive skills, behavior, general health, and health-related quality of life. These results will be reported separately. At the same time, we planned a parallel study, reported here, and which for logistic reasons could be performed only in New Zealand, to investigate the long-term effects of repeat antenatal betamethasone treatment on risk factors for cardiovascular and metabolic disease.

The ACTORDS trial (ISRCTN 48656428) has been reported previously.^{2,11} Briefly, women with single, twin, or triplet pregnancy at < 32 weeks' gestation were eligible if they had received a course of antenatal glucocorticoids ≥ 7 days previously and were judged to have ongoing risk of preterm birth. Women were excluded if they were in the second stage of labor, had chorioamnionitis needing urgent delivery, had mature lung development, or if further glucocorticoid therapy was judged to be essential. A central telephone randomization service was used to assign women to a single intramuscular injection of either Celestone Chronodose, containing 7.8 mg betamethasone sodium phosphate and 6 mg betamethasone

acetate (Schering-Plough, Sydney, Australia) or a saline placebo. The allocated treatment could be repeated each week a woman remained undelivered and was considered by her responsible clinician to be at risk for preterm birth in the next 7 days, up to 32 weeks' gestation. All women, clinicians, and investigators were blinded to treatment allocation. A total of 982 women (1146 fetuses; New Zealand 290 women and 352 fetuses) were enrolled across 23 participating centers in Australia and New Zealand between 1998 and 2004.

Infants exposed to repeat betamethasone compared with placebo had clinically significant reductions in the incidence of respiratory distress syndrome, severe neonatal lung disease, and combined serious neonatal morbidity.² At 2 years' corrected age, the treatment groups did not differ in survival free of major disability, body size, behavioral scores, developmental indices, and the incidence of cerebral palsy, neurosensory disability, or asthma.¹¹

Early School-Age Cardiovascular Risk Factors Study

All children residing in New Zealand who were recruited to the ACTORDS early school-age follow-up study were invited to participate in this parallel study of cardiovascular and metabolic risk factors. Children with severe intellectual disability who could not assent to testing were excluded. Assessments were conducted throughout New Zealand by a single team of investigators who were blinded to treatment allocation. Written informed consent was obtained from caregivers, and assent was sought from the children. Ethical approval was obtained from the New Zealand Multicentre Ethics Committee.

Weight was determined to the nearest 100 g using an electronic scale and height to the nearest 1 mm by fixed wall or spirit level stadiometer. Puberty was defined as Tanner breast stage ≥ 2 in girls or

testicular volume ≥ 4 mL in boys. Body composition was measured by whole-body dual energy x-ray absorptiometry (DXA), with regions of interest, including abdomen (android) and thigh (gynoid), determined using computer generated and manually confirmed default lines on an anterior view planogram. DXA was restricted to 2 main centers (Auckland and Christchurch) so that all measurements could be performed on identical instruments (Lunar Prodigy, GE Healthcare, Madison, WI) using the same pediatric software (Encore, version 8, GE Healthcare).

Insulin sensitivity was calculated with Bergman's minimal model (MinMod version 6.02) using the glucose and insulin values obtained during a 90-minute frequently sampled intravenous glucose test (0.3 g/kg dextrose bolus), modified with insulin (0.015 IU/kg at 20 minutes).¹⁵ Plasma insulin concentrations were measured by using a microparticle enzyme immunoassay on an AxSYM analyzer (Abbott, Abbot Park, IL), and plasma glucose concentrations were measured by using a Roche glucose oxidase colorimetric assay (Indianapolis, IN) on a Hitachi 902 autoanalyzer (Ibaraki, Japan). Fasting glucose and insulin concentrations were determined as the mean of 3 baseline samples over a 20-minute resting phase. Other calculated indices of insulin and glucose metabolism included glucose effectiveness (a minimal model parameter that reflects the ability of glucose to stimulate its own uptake independently of insulin), acute insulin release (first phase insulin secretion calculated as the area under the insulin curve from 0 to 10 minutes), and the glucose disappearance constant (a measure of glucose disposal calculated as the slope of the linear least-square regression line to the logarithm of the glucose curve from 10 to 19 minutes).¹⁶

Ambulatory blood pressure and heart rate were measured over a 24-hour period on the nondominant arm using Spacelabs 90217 monitors (Issaquah, WA; reporting software version 2.0.9). Recordings were obtained every 30 minutes during the daytime and at 30- to 60-minute intervals overnight. Diurnal mean values were determined based on the child's own sleep-wake cycle. In addition, sex- and height-specific z scores were calculated from central European reference data^{17,18} for the fixed-clock intervals of 8:00 to 20:00 and 24:00 to 06:00, using the LMS method.¹⁹ Children with < 7 daytime or < 7 nighttime blood pressure measurements were excluded from analysis.

In children who underwent the intravenous glucose tolerance test, baseline plasma creatinine concentration was measured by using the Roche creatinine plus assay on a Hitachi 902 auto-analyzer. Glomerular filtration rate was estimated after adjustment for height using a prediction equation based on the iohexol plasma disappearance technique.²⁰

Statistical analyses were performed by using SAS JMP (version 8.0.2, SAS Institute, Cary, NC). Outcomes for children whose mothers were randomized to repeat antenatal betamethasone were compared with those whose mothers were randomized to placebo using linear mixed-effects regression, with inclusion of a random effect to account for the nonindependence of children from multiple pregnancy. Treatment effects are reported as the mean difference (MD) for normally distributed data or the ratio of geometric means (RGM) for positively skewed data, both with a 95% confidence interval (CI). If the 95% CI for RGM includes 1, there is no significant difference between groups. Adjustment was made for potential confounders including gestational age at trial entry and ethnicity and antepartum hemorrhage and preterm prelabor rupture of membranes, which

showed imbalance in the original trial cohort.² Body composition data were adjusted for height to account for body size, and comparisons of fat mass were also adjusted for lean mass because this may be a more metabolically relevant measure of adiposity.²¹ We estimated that if 276 children were followed up, the study would have 80% power to detect differences between groups in normally distributed outcomes of 0.34 SDs (2-tailed $\alpha = .05$).

RESULTS

Of the 328 surviving children from the ACTORDS trial presumed to be residing in New Zealand at 6 to 8 years' corrected age, 258 (81% of eligible children) underwent ≥ 1 of the physiologic investigations (Figure 1). Seven children could not be traced, 2 remained overseas during the period of study, 8 were not eligible for study because of severe disability, and 53 declined investigation (32 repeat betamethasone group, 21 placebo group). Children recruited to the Cardiovascular Risk Factors Study were more likely to have had respiratory distress syndrome than those not studied (Table 1). However, there were no significant differences in other neonatal morbidities, demographic, or maternal and obstetric characteristics between children who did or did not participate in the Cardiovascular Risk Factors Study (Table 1).

Of the 258 children in the study, there were no significant differences in baseline demographic, maternal, or obstetric factors between those whose mothers were randomized to repeat doses of antenatal betamethasone or placebo (Table 1). The effect of repeat antenatal betamethasone treatment on primary neonatal respiratory outcomes was similar to that seen in the main trial (Table 1).²

Fat mass did not differ between treatment groups, both for the whole body (RGM 0.96, 95% CI 0.76 to 1.20) and regions of interest (gynoid RGM 0.97, 95% CI 0.81 to 1.17; android RGM 0.94, 95% CI 0.72 to

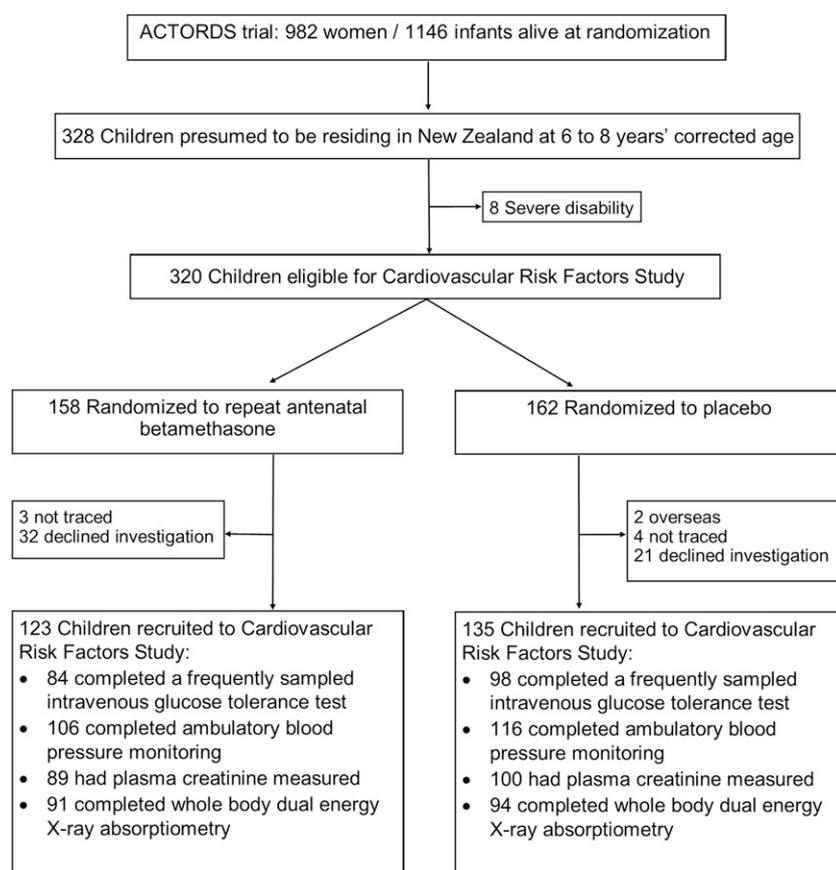


FIGURE 1
Profile of participants in the New Zealand Cardiovascular Risk Factors Study.

1.21). Furthermore, adjustment for height and lean mass did not affect the results (Table 2). Similarly, treatment groups had similar whole body lean mass (RGM 0.97, 95% CI 0.91 to 1.04) and limb lean mass (RGM 0.98, 95% CI 0.91 to 1.07), including when adjusted for height (Table 2).

Insulin sensitivity was similar in both groups (RGM 0.89, 95% CI 0.74 to 1.08), as was glucose effectiveness, acute insulin release, glucose tolerance (glucose disappearance constant), and fasting plasma glucose and insulin concentrations (Table 3). Five children in the repeat betamethasone group (6%) and 8 in the placebo group (8%) had a parent with type 2 diabetes.

Ten children in each group were excluded from the ambulatory blood pressure analysis because of an inadequate number of recordings. Of those who successfully completed the ambulatory

monitoring, the mean number (SD) of recordings was similar in those exposed to repeat antenatal betamethasone and those exposed to placebo: daytime 17.0 (0.6) versus 16.3 (0.6), $P = .41$; nighttime 12.7 (0.3) versus 13.3 (0.3), $P = .16$. Mean blood pressure and heart rate for the 24-hour, daytime and nighttime periods were almost identical in the 2 treatment groups with mean differences of ≤ 1 mm Hg or ≤ 1 beats per minute (Table 4). Diurnal dipping of blood pressure and height-specific diurnal z scores for blood pressure and heart rate were also similar between groups (Table 4). Children exposed to repeat antenatal betamethasone and those exposed to placebo had similar plasma creatinine concentration (MD $-0.6 \mu\text{mol/L}$, 95% CI -2.2 to 1.0) and estimated glomerular filtration rate (MD 1.1

mL/min/1.73 m², 95% CI -3.4 to 5.6) (Table 4).

In sensitivity analysis, exclusion of children with onset of puberty or chronic illness did not alter the results. Similarly, the effect of treatment on insulin sensitivity was not affected by exclusion of children with a parent with type 2 diabetes (RGM 0.89, 95% CI 0.73 to 1.08). Reanalysis of ambulatory blood pressure with inclusion of data from all children did not alter the results (24-hour systolic pressure MD -1 mm Hg, 95% CI -3 to 1; 24-hour diastolic pressure MD 0 mm Hg, 95% CI -1 to 1).

Because of concern about the possibility of dose-dependent effects,^{10,22} in a post hoc analysis, we explored whether the effect of repeat antenatal betamethasone treatment on cardiovascular risk factors was influenced by the number of repeat doses. However, there was no evidence of an interaction between treatment effect and the number of maternal trial treatments (test of interaction: whole body fat mass $P = .64$, insulin sensitivity $P = .80$, 24-hour ambulatory systolic blood pressure $P = .76$, 24-hour ambulatory diastolic blood pressure $P = .83$, estimated glomerular filtration rate $P = .86$).

DISCUSSION

This is the first detailed study in a randomized controlled trial of the longer term effects of repeat antenatal glucocorticoids on risk factors for cardiovascular and metabolic disease. We found no evidence of adverse cardiovascular and metabolic function in children exposed to repeat dose(s) of antenatal betamethasone compared with those exposed to a single course of antenatal glucocorticoids. Specifically, exposure to repeat dose(s) had no effect on fat mass, insulin sensitivity, ambulatory blood pressure, and renal function, as well as several other measures of

TABLE 1 Characteristics of Children, and Their Mothers, in the New Zealand Trial Cohort and CRFS

	New Zealand ACTORDS Trial Cohort		CRFS	
	Participant in CRFS	Nonparticipant in CRFS	Repeat Betamethasone	Placebo
Maternal characteristics at trial entry	<i>n</i> = 215	<i>n</i> = 60	<i>n</i> = 105	<i>n</i> = 110
Randomized to repeat betamethasone	105 (49)	31 (52)		
Maternal age, y	30.6 (5.5)	30.9 (5.8)	30.1 (0.5)	31.0 (0.5)
Parity				
0	80 (37)	18 (30)	45 (43)	35 (32)
1–3	113 (53)	29 (48)	51 (49)	62 (56)
≥4	22 (10)	13 (22)	9 (9)	13 (12)
Multiple pregnancy	44 (20)	13 (22)	19 (18)	25 (23)
Smoking during pregnancy ^a	65 (31)	24 (41)	30 (30)	35 (32)
GA at first glucocorticoids, wk ^b	26.9 (23.8–28.9)	26.7 (23.7–28.6)	26.9 (24.9–28.8)	27.1 (24.7–28.9)
GA at trial entry, wk ^b	28.6 (25.4–30.3)	28.6 (25.1–30.6)	28.6 (26.2–30.4)	28.6 (26.1–30.3)
Main reasons for risk of preterm birth ^c				
Preterm prelabor rupture of membranes	63 (29)	13 (22)	31 (30)	32 (29)
Preterm labor	36 (17)	16 (27)	19 (18)	17 (15)
Severe fetal growth restriction	29 (13)	6 (10)	15 (14)	14 (12)
Preeclampsia or eclampsia	45 (21)	9 (15)	21 (20)	24 (22)
Cervical incompetence	17 (8)	4 (7)	8 (8)	9 (8)
Antepartum hemorrhage	51 (24)	14 (23)	26 (25)	25 (23)
Multiple pregnancy	16 (7)	6 (10)	11 (11)	5 (5)
Other	8 (4)	3 (5)	1 (1)	7 (6)
No. of postrandomization trial treatments				
0	2 (1)	0 (0)	0 (0)	2 (2)
1	103 (48)	27 (45)	48 (46)	55 (50)
2–3	77 (36)	22 (37)	37 (35)	40 (36)
≥4	33 (15)	11 (18)	20 (19)	13 (12)
Infant characteristics at birth	<i>n</i> = 258	<i>n</i> = 70	<i>n</i> = 123	<i>n</i> = 135
Gender, female	114 (44)	36 (51)	56 (46)	58 (43)
Ethnicity ^{c,d}				
Maori	71 (28)	17 (34)	35 (28)	36 (27)
Pacific Peoples	30 (12)	6 (12)	16 (13)	14 (10)
Other non-European	16 (6)	2 (4)	10 (8)	6 (4)
European	141 (55)	25 (50)	62 (50)	79 (55)
Main neonatal outcomes				
Gestational age at birth, wk	31.7 (3.5)	32.5 (3.6)	31.7 (3.5)	31.6 (3.5)
Birth weight, g ^e	1555 (1138–2103)	1694 (1160–2205)	1550 (1114–2100)	1580 (1150–2128)
Birth weight z score	−0.33 (1.10)	−0.54 (1.13)	−0.37 (1.11)	−0.35 (1.08)
Respiratory distress syndrome ^e	109 (42)*	20 (29)	40 (33)**	69 (51)
Severity of lung disease ^f				
Severe	34 (13)	6 (9)	8 (7)**	26 (19)
Moderate	44 (17)	8 (11)	19 (15)	25 (19)
Mild	101 (39)	34 (49)	54 (44)	47 (35)
None	79 (31)	22 (31)	42 (34)	37 (27)
Use of mechanical ventilation	76 (29)	18 (26)	28 (23)*	48 (36)
Use of oxygen therapy	150 (58)	40 (57)	65 (53)	85 (63)
Use of surfactant	70 (27)	14 (20)	25 (20)*	45 (33)
Serious neonatal morbidity ^g	62 (24)	10 (15)	23 (19)*	39 (29)
Characteristics at follow-up				
Age, y	7.2 (1.0)	NA	7.3 (0.9)	7.2 (1.0)
Puberty onset	5 (2)	NA	4 (3)	1 (1)
Chronic medical condition ^h	7 (3)	NA	4 (3)	3 (2)

Data are *n* (%) or mean (SD) unless otherwise noted. CRFS, Cardiovascular Risk Factors Study; GA, gestational age; NA, not available. **P* < .05 or ***P* < .01 for comparison between participants and nonparticipants in the CRFS or between children exposed to repeat betamethasone and placebo.

^a Data are missing for 6 participants and 2 nonparticipants in the CRFS.

^b Median (interquartile range).

^c Not mutually exclusive.

^d Ethnicity prioritized in order of Maori, Pacific Peoples, other non-European, and European.

^e Defined as clinical signs of respiratory distress syndrome and a ground-glass appearance on chest radiograph.

^f Defined as follows: mild, mean airway pressure (MAP) <7 cm or fractional inspired oxygen (FiO₂) <0.4; moderate, MAP 7 to <10 cm H₂O or FiO₂ 0.40 to 0.79; severe, MAP ≥10 cm or FiO₂ ≥0.80.

^g Defined as ≥1 of the following: air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks' postmenstrual age, severe intraventricular hemorrhage (grade 3 or 4), periventricular leukomalacia, proven necrotising enterocolitis, or retinopathy of prematurity.

^h In the repeat betamethasone group, 2 children had celiac disease, 1 had lymphoma, and 1 had received a renal transplant for congenital multicystic disease; in the placebo group, 1 child each had bronchiectasis, cystic fibrosis with diabetes, and steroid-resistant nephrotic syndrome.

TABLE 2 Body Composition of Children Exposed to Repeat Betamethasone or Placebo

	Repeat Betamethasone, <i>n</i> = 103	Placebo, <i>n</i> = 103	Treatment Effect: RGM (95% CI) ^a
Subjects completing testing ^b	91 (88)	94 (91)	
Lean mass, kg			
Whole body	19.3 (16.4–22.2)	19.1 (17.0–22.4)	0.97 (0.91 to 1.04)
Adjusted for height			0.98 (0.95 to 1.00)
Limbs	7.1 (5.8–8.6)	7.3 (5.9–8.9)	0.98 (0.91 to 1.07)
Adjusted for height			0.98 (0.95 to 1.02)
Fat mass, kg			
Whole body	3.7 (2.6–6.3)	3.7 (2.5–6.2)	0.96 (0.76 to 1.20)
Adjusted for height			0.97 (0.82 to 1.15)
Adjusted for lean mass			1.02 (0.86 to 1.21)
Gynoid (thigh)	1.0 (0.7–1.4)	0.9 (0.7–1.4)	0.97 (0.81 to 1.17)
Adjusted for height			0.98 (0.86 to 1.12)
Adjusted for lean mass			1.02 (0.89 to 1.17)
Android (abdominal)	0.2 (0.2–0.4)	0.2 (0.2–0.5)	0.94 (0.72 to 1.21)
Adjusted for height			0.95 (0.77 to 1.17)
Adjusted for lean mass			0.99 (0.81 to 1.23)

Data are *n* (%) or median (interquartile range). RGM, ratio of geometric means.

^a Adjusted for gestational age at trial entry, preterm prelabor rupture of membranes, antepartum hemorrhage, and European ethnicity.

^b Body composition study limited to subjects residing in centers with DXA.

glucose metabolism and body composition. Therefore, it is unlikely that administration of repeat doses of antenatal glucocorticoids for ongoing risk of preterm birth after an initial course, as used in the ACTORDS trial, substantially increases the risk of cardiovascular and metabolic disease in offspring.

An important consideration underpinning this conclusion is the extent to which adult function and disease risk can be predicted from physiologic outcomes in childhood. Longitudinal studies have demonstrated modest tracking of BMI,²³ whole body fat mass,²⁴ blood pressure,²⁵ and glucose homeostasis variables^{26,27} from mid-childhood onward. Furthermore, preclinical

atherosclerosis is strongly associated with higher BMI, cholesterol, and blood pressure in childhood^{28–30}; adults with obesity and cardiovascular disease have been shown to have accelerated gains in weight before 7 years of age^{31,32}; and type 2 diabetes is preceded by substantial reductions in insulin sensitivity over several decades.^{26,33} Similarly, studies in subjects known to be at increased risk of chronic disease, such as those born small for gestational age or preterm, have consistently demonstrated altered physiologic function from childhood to adulthood, including reduced insulin sensitivity,^{34–37} hypercortisolism,³⁸ elevated blood pressure,³⁹ and abdominal adiposity.⁴⁰ Therefore,

if exposure to repeat antenatal glucocorticoids did have a significant long-term effect on metabolic and cardiovascular function, this should be evident by early school age.

We are unlikely to have missed important clinical differences between groups because we used highly accurate and sensitive measures of physiologic function, including Bergman's minimal model, which is recognized as a gold standard measure of whole body insulin sensitivity,⁴¹ and ambulatory blood pressure monitoring, which has superior tracking stability⁴² and is more sensitive for end-organ changes⁴³ than standard clinic blood pressure. Similarly we measured fat and lean

TABLE 3 Indicators of Glucose and Insulin Metabolism of Children Exposed to Repeat Betamethasone or Placebo

	Repeat Betamethasone, <i>n</i> = 123	Placebo, <i>n</i> = 135	Treatment Effect: MD or RGM (95% CI) ^a
Subjects completing testing	84 (68)	98 (73)	
Fasting plasma concentrations ^b			
Glucose, mmol/L	4.7 (0.4)	4.8 (0.4)	−0.1 (−0.2 to 0.0)
Insulin, mIU/L ^c	5.2 (3.6–7.5)	4.8 (3.4–6.3)	1.02 (0.86 to 1.22)
Minimal model ^c			
Insulin sensitivity index, $\times 10^{-4} \text{ min}^{-1} \cdot \text{mIU}^{-1} \cdot \text{L}$	7.8 (4.8–11.9)	9.7 (5.8–13.9)	0.89 (0.74 to 1.08)
Glucose effectiveness, $\times 10^{-2} \text{ min}^{-1}$	2.7 (2.0–3.3)	2.9 (1.9–3.7)	0.93 (0.81 to 1.06)
Acute insulin release, $\text{mIU} \cdot \text{L}^{-1} \cdot \text{min}$	313.8 (187.3–579.9)	268.8 (169.5–485.2)	1.05 (0.84 to 1.31)
Glucose disappearance constant, $\times 10^{-2} \text{ min}^{-1\text{c}}$	2.54 (1.82–3.03)	2.51 (2.00–3.40)	0.92 (0.80 to 1.07)

Data are *n* (%) or mean (SD) unless otherwise noted. MD, mean difference; RGM, ratio of geometric means.

^a Adjusted for gestational age at trial entry, preterm prelabor rupture of membranes, antepartum hemorrhage, and European ethnicity.

^b Average of 3 baseline samples, collected over 20 min.

^c Median (interquartile range) or RGM for treatment effects.

TABLE 4 Ambulatory BP and Renal Function of Children Exposed to Repeat Betamethasone or Placebo

	Repeat Betamethasone, <i>n</i> = 123	Placebo, <i>n</i> = 135	Treatment Effect: MD (95% CI) ^a
Ambulatory monitoring			
Subjects completing testing	106 (86)	116 (86)	
24-h BP, mm Hg			
Systolic	102 (7)	102 (8)	0 (–2 to 2)
Diastolic	62 (5)	62 (5)	0 (–1 to 1)
Daytime BP, mm Hg			
Systolic	107 (7)	108 (9)	–1 (–4 to 1)
Diastolic	67 (5)	68 (6)	–1 (–2 to 1)
Nighttime BP, mm Hg			
Systolic	95 (7)	96 (7)	0 (–2 to 2)
Diastolic	55 (5)	56 (5)	0 (–2 to 1)
BP <i>z</i> score			
Daytime systolic	–0.48 (1.01)	–0.34 (1.25)	–0.16 (–0.48 to 0.16)
Daytime diastolic	–0.70 (0.94)	–0.60 (1.04)	–0.12 (–0.40 to 0.15)
Nighttime systolic	–0.11 (0.93)	–0.09 (1.09)	–0.03 (–0.32 to 0.25)
Nighttime diastolic	0.11 (0.94)	0.16 (0.97)	–0.09 (–0.35 to 0.18)
Percentage diurnal dip in BP			
Systolic	11 (5)	11 (5)	–1 (–2 to 1)
Diastolic	18 (6)	18 (7)	0 (–2 to 2)
Heart rate			
24-h			
Daytime	88 (8)	87 (9)	1 (–1 to 3)
Nighttime	94 (8)	95 (9)	0 (–2 to 2)
Heart rate <i>z</i> score			
Daytime	–0.39 (0.84)	–0.38 (0.95)	–0.01 (–0.26 to 0.24)
Nighttime	0.41 (1.06)	0.25 (1.03)	0.18 (–0.11 to 0.47)
Renal function			
Subjects completing testing	89 (72)	100 (74)	
Plasma creatinine concentration, $\mu\text{mol/L}$	37.2 (4.9)	38.0 (5.3)	–0.6 (–2.2 to 1.0)
Estimated glomerular filtration rate, mL/min/1.73 m ²	106.8 (14.4)	104.9 (14.6)	1.1 (–3.4 to 5.6)

Data are *n* (%) or mean (SD). BP, blood pressure.

^a Adjusted for gestational age at trial entry, preterm prelabor rupture of membranes, antepartum hemorrhage, and European ethnicity.

mass directly, both of which may independently contribute to the risk of metabolic disease.⁴⁴

Moreover, confidence intervals for these outcomes excluded physiologically important effect sizes. For example, elevation of childhood blood pressure by as little as 3 to 5 mm Hg may be associated with an increased risk of high blood pressure in adulthood.^{39,45,46} However, our results excluded differences even as small as these. Similarly, pediatric groups at risk for insulin resistance (*n* = 27 to 50) have consistently shown reductions in minimal model insulin sensitivity of at least 30%,^{34,35,47} and overweight adults were found to have an increase in mid-childhood fat mass of 20% to 30%.³² However, confidence intervals in our study for the ratio of geometric means for insulin

sensitivity and fat mass were narrower than these changes.

Given the limited capacity for experimentation in humans, randomized trials of antenatal glucocorticoid treatment provide a unique opportunity in which to investigate the role of glucocorticoids in disease programming. Small size at birth has been widely associated with an increased risk of cardiovascular and metabolic disease,⁴ and fetal overexposure to glucocorticoids has been proposed as a potential mechanism.⁵ This is supported by the known role of glucocorticoids in the regulation of fetal tissue maturation and growth⁴⁸ and the demonstration in animals that both fetal growth restriction and adult risk factors can be induced by administration of exogenous glucocorticoids^{10,49,50} or by

manipulations that increase placental transfer of maternal glucocorticoids, such as inhibition of placental 11- β -hydroxysteroid dehydrogenase type 2.^{51,52}

In this study, children in the repeat dose group were likely exposed to elevated glucocorticoid concentrations for at least 2 to 3 weeks. The fact that there was no evidence of altered long-term physiologic function between treatment groups suggests that either glucocorticoids have a limited role in the programming of disease in humans or that a very prolonged or different timing of exposure is required. Although our control group was exposed to glucocorticoids before randomization, a single course of antenatal glucocorticoids has not been associated with increased risk of cardiovascular and metabolic disease in clinical trials,^{6,7}

and we found no additional risk with repeat dose(s). Results from observational studies have been conflicting,⁵³⁻⁵⁷ emphasizing the importance of determining long-term outcomes in randomized trials, which have much lower risk of bias. Although there was no difference between treatment groups in size at birth in our study, studies in nonhuman primates have shown that programming effects can occur without effects on fetal growth.^{8,58} It is possible that our results were confounded by the fact that most children were born preterm, which itself may be an important programming stimulus,³⁴ but this does not alter the clinical relevance of our study.

A potential limitation of this study is that it was performed in a subset of the main trial cohort. However, our study population was regionally based, thereby minimizing possible bias due to variation in local practice. Overall, the characteristics of women and infants in the New Zealand arm of the trial were similar to those of the ACTORDS cohort as a whole.² We achieved a high follow-up rate, with 98% of surviving New Zealand children being traced at 6 to 8 years' corrected age. Although only 81% of children participated in the study, given the invasive nature of the tests, the proportion of children completing each investigation was high. Although children in the study had a higher incidence of respiratory distress syndrome than those not studied, exposure to repeat antenatal betamethasone was

similar. The higher incidence of respiratory distress syndrome could be a marker for poorer outcomes, but other important baseline and neonatal prognostic factors were similar between those who were and were not recruited to our study. Therefore, we believe our results are likely to be reflective of both the New Zealand subgroup and the ACTORDS trial study population as a whole.

Although we studied a range of key risk factors for cardiovascular and metabolic disease, data were not collected on several variables, such as blood lipids and diet and activity levels, which may be permanently altered by the changes in the fetal environment.^{59,60} However, given that there was no effect on fat mass or insulin sensitivity in our study, it seems unlikely that any potential effects on lipid concentrations and energy intake and expenditure, if they did exist, would be of any clinical significance.⁶¹

Children in our trial may have had less overall exposure to antenatal glucocorticoids than those in other trials that used higher doses of betamethasone or used it for longer in gestation.^{22,62,63} Thus, some caution is required when applying our results to other treatment regimens. However, a recent report from 1 of these trials that exposure to repeat doses of antenatal glucocorticoids had no effect on blood pressure at 5 years of age is reassuring.⁶⁴

CONCLUSIONS

We have shown that exposure to repeat doses of antenatal betamethasone compared with a single course of antenatal glucocorticoids does not increase physiologic risk factors for cardiovascular and metabolic disease at early school age. Therefore, clinicians who wish to use this treatment to take advantage of the short-term neonatal benefits can be reassured that administration of repeat doses of antenatal glucocorticoids to women at risk for preterm birth are unlikely to increase the risk of future cardiovascular and metabolic disease in offspring.

ACKNOWLEDGMENTS

We thank the women and their children who participated in the ACTORDS trial, Coila Bevan for assistance with tracing and recruitment of New Zealand subjects and with intravenous glucose tolerance testing in twins, and Ann Mansfield from Christchurch Radiology Group for performing DXA scans in children in Canterbury. We are grateful for the support of the ACTORDS Study Group, including the Coordinating Committee (Caroline Crowther, Ross Haslam, Lex Doyle, Peter Anderson, Janet Hiller, Jane Harding, and Jeffrey Robinson); Pat Ashwood, ACTORDS clinical trial coordinator; and Kristyn Willson, trial statistician.

Address correspondence to Jane E. Harding, DPhil, FRACP, Liggins Institute, The University of Auckland, Private Bag 92019, Victoria St West, Auckland 1142, New Zealand. E-mail: j.harding@auckland.ac.nz

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

Copyright © 2015 by the American Academy of Pediatrics

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Supported by grants from the Health Research Council of New Zealand (07/204), National Health and Medical Research Council of Australia (453633), and Auckland Medical Research Foundation, New Zealand (81537). These funding agencies had no role in study design, analysis and interpretation of results, or the decision to publish.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

- Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. *Cochrane Database Syst Rev.* 2006;(3):CD004454. doi:10.1002/14651858.CD004454.pub2
- Crowther CA, Haslam RR, Hiller JE, Doyle LW, Robinson JS; Australasian Collaborative Trial of Repeat Doses of Steroids (ACTORDS) Study Group. Neonatal respiratory distress syndrome after repeat exposure to antenatal corticosteroids: a randomised controlled trial. *Lancet.* 2006;367(9526):1913–1919
- Crowther CA, McKinlay CJD, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database Sys Rev.* 2011;(6):CD003935. doi:10.1002/14651858.CD003935.pub3
- Barker DJP. The developmental origins of well-being. *Philos Trans R Soc Lond B Biol Sci.* 2004;359(1449):1359–1366
- Seckl JR, Holmes MC. Mechanisms of disease: glucocorticoids, their placental metabolism and fetal “programming” of adult pathophysiology. *Nat Clin Pract Endocrinol Metab.* 2007;3(6):479–488
- Dalziel SR, Walker NK, Parag V, et al. Cardiovascular risk factors after antenatal exposure to betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet.* 2005;365(9474):1856–1862
- Dessens AB, Haas HS, Koppe JG. Twenty-year follow-up of antenatal corticosteroid treatment. *Pediatrics.* 2000;105(6):E77
- de Vries A, Holmes MC, Heijnen A, et al. Prenatal dexamethasone exposure induces changes in nonhuman primate offspring cardiometabolic and hypothalamic-pituitary-adrenal axis function. *J Clin Invest.* 2007;117(4):1058–1067
- Nyirenda MJ, Welberg LA, Seckl JR. Programming hyperglycaemia in the rat through prenatal exposure to glucocorticoids-fetal effect or maternal influence? *J Endocrinol.* 2001;170(3):653–660
- Sloboda DM, Moss TJM, Li S, et al. Hepatic glucose regulation and metabolism in adult sheep: effects of prenatal betamethasone. *Am J Physiol Endocrinol Metab.* 2005;289(4):E721–E728
- Crowther CA, Doyle LW, Haslam RR, Hiller JE, Harding JE, Robinson JS; ACTORDS Study Group. Outcomes at 2 years of age after repeat doses of antenatal corticosteroids. *N Engl J Med.* 2007;357(12):1179–1189
- Battin M, Bevan C, Harding J. Growth in the neonatal period after repeat courses of antenatal corticosteroids: data from the ACTORDS randomised trial. *Arch Dis Child Fetal Neonatal Ed.* 2012;97(2):F99–105
- Battin MR, Bevan C, Harding JE. Repeat doses of antenatal steroids and hypothalamic-pituitary-adrenal axis (HPA) function. *Am J Obstet Gynecol.* 2007;197(1):40.e1–6
- Mildenhall L, Battin M, Bevan C, Kuschel C, Harding JE. Repeat prenatal corticosteroid doses do not alter neonatal blood pressure or myocardial thickness: randomized, controlled trial. *Pediatrics.* 2009;123(4). Available at: www.pediatrics.org/cgi/content/full/123/4/e646
- Cutfield WS, Bergman RN, Menon RK, Sperling MA. The modified minimal model: application to measurement of insulin sensitivity in children. *J Clin Endocrinol Metab.* 1990;70(6):1644–1650
- Bergman RN. Lilly Lecture 1989. Toward physiological understanding of glucose tolerance. Minimal-model approach. *Diabetes.* 1989;38(12):1512–1527
- Soergel M, Kirschstein M, Busch C, et al. Oscillometric twenty-four-hour ambulatory blood pressure values in healthy children and adolescents: a multicenter trial including 1141 subjects. *J Pediatr.* 1997;130(2):178–184
- Wühl E, Witte K, Soergel M, Mehls O, Schaefer F; German Working Group on Pediatric Hypertension. Distribution of 24-h ambulatory blood pressure in children: normalized reference values and role of body dimensions. *J Hypertens.* 2002;20(10):1995–2007
- Cole TJ, Green PJ. Smoothing reference centile curves: the LMS method and penalized likelihood. *Stat Med.* 1992;11(10):1305–1319
- Schwartz GJ, Work DF. Measurement and estimation of GFR in children and adolescents. *Clin J Am Soc Nephrol.* 2009;4(11):1832–1843
- Wells JC, Victora CG. Indices of whole-body and central adiposity for evaluating the metabolic load of obesity. *Int J Obes (Lond).* 2005;29(5):483–489
- Wapner RJ, Sorokin Y, Thom EA, et al; National Institute of Child Health and Human Development Maternal Fetal Medicine Course Network. Single versus weekly courses of antenatal corticosteroids: evaluation of safety and efficacy. *Am J Obstet Gynecol.* 2006;195(3):633–642
- Singh AS, Mulder C, Twisk JW, van Mechelen W, Chinapaw MJ. Tracking of childhood overweight into adulthood: a systematic review of the literature. *Obes Rev.* 2008;9(5):474–488
- Goulding A, Taylor RW, Jones IE, Lewis-Barned NJ, Williams SM. Body composition of 4- and 5-year-old New Zealand girls: a DXA study of initial adiposity and subsequent 4-year fat change. *Int J Obes Relat Metab Disord.* 2003;27(3):410–415
- Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. *Circulation.* 2008;117(25):3171–3180
- Nguyen QM, Srinivasan SR, Xu JH, Chen W, Kieleyka L, Berenson GS. Utility of childhood glucose homeostasis variables in predicting adult diabetes and related cardiometabolic risk factors: the Bogalusa Heart Study. *Diabetes Care.* 2010;33(3):670–675
- Thearle MS, Bunt JC, Knowler WC, Krakoff J. Childhood predictors of adult acute insulin response and insulin action. *Diabetes Care.* 2009;32(5):938–943
- Raitakari OT, Juonala M, Kähönen M, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood: the Cardiovascular Risk in Young Finns Study. *JAMA.* 2003;290(17):2277–2283
- Davis PH, Dawson JD, Riley WA, Lauer RM. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through

- middle age: the Muscatine Study. *Circulation*. 2001;104(23):2815–2819
30. Mahoney LT, Burns TL, Stanford W, et al. Coronary risk factors measured in childhood and young adult life are associated with coronary artery calcification in young adults: the Muscatine Study. *J Am Coll Cardiol*. 1996; 27(2):277–284
 31. Barker DJ, Osmond C, Kajantie E, Eriksson JG. Growth and chronic disease: findings in the Helsinki Birth Cohort. *Ann Hum Biol*. 2009;36(5): 445–458
 32. Williams SM, Goulding A. Patterns of growth associated with the timing of adiposity rebound. *Obesity (Silver Spring)*. 2009;17(2):335–341
 33. Martin BC, Warram JH, Krolewski AS, Bergman RN, Soeldner JS, Kahn CR. Role of glucose and insulin resistance in development of type 2 diabetes mellitus: results of a 25-year follow-up study. *Lancet*. 1992;340(8825):925–929
 34. Hofman PL, Regan F, Jackson WE, et al. Premature birth and later insulin resistance. *N Engl J Med*. 2004;351(21): 2179–2186
 35. Hofman PL, Cutfield WS, Robinson EM, et al. Insulin resistance in short children with intrauterine growth retardation. *J Clin Endocrinol Metab*. 1997;82(2): 402–406
 36. Veening MA, Van Weissenbruch MM, Delemarre-Van De Waal HA. Glucose tolerance, insulin sensitivity, and insulin secretion in children born small for gestational age. *J Clin Endocrinol Metab*. 2002;87(10):4657–4661
 37. Norris SA, Osmond C, Gigante D, et al; COHORTS Group. Size at birth, weight gain in infancy and childhood, and adult diabetes risk in five low- or middle-income country birth cohorts. *Diabetes Care*. 2012;35(1):72–79
 38. Jones A, Godfrey KM, Wood P, Osmond C, Goulden P, Phillips DIW. Fetal growth and the adrenocortical response to psychological stress. *J Clin Endocrinol Metab*. 2006;91(5):1868–1871
 39. Bonamy AK, Martin H, Jörneskog G, Norman M. Lower skin capillary density, normal endothelial function and higher blood pressure in children born preterm. *J Intern Med*. 2007;262(6): 635–642
 40. Labayen I, Ruiz JR, Vicente-Rodríguez G, et al; Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) Study Group. Early life programming of abdominal adiposity in adolescents: the HELENA Study. *Diabetes Care*. 2009; 32(11):2120–2122
 41. American Diabetes Association. Consensus Development Conference on Insulin Resistance. 5–6 November, 1997. *Diabetes Care*. 1998;21(2):310–314
 42. Li Z, Snieder H, Harshfield GA, Treiber FA, Wang X. A 15-year longitudinal study on ambulatory blood pressure tracking from childhood to early adulthood. *Hypertens Res*. 2009;32(5):404–410
 43. Sorof JM, Cardwell G, Franco K, Portman RJ. Ambulatory blood pressure and left ventricular mass index in hypertensive children. *Hypertension*. 2002;39(4): 903–908
 44. Dulloo AG, Jacquet J, Solinas G, Montani JP, Schutz Y. Body composition phenotypes in pathways to obesity and the metabolic syndrome. *Int J Obes (Lond)*. 2010;34(Suppl 2):S4–S17
 45. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: the Muscatine Study. *Pediatrics*. 1989; 84(4):633–641
 46. Bayrakci US, Schaefer F, Duzova A, Yigit S, Bakkaloglu A. Abnormal circadian blood pressure regulation in children born preterm. *J Pediatr*. 2007;151(4):399–403
 47. Jefferies CA, Hofman PL, Knoblauch H, Luft FC, Robinson EM, Cutfield WS. Insulin resistance in healthy prepubertal twins. *J Pediatr*. 2004;144(5):608–613
 48. Fowden AL, Li J, Forhead AJ. Glucocorticoids and the preparation for life after birth: are there long-term consequences of the life insurance? *Proc Nutr Soc*. 1998;57(1):113–122
 49. Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CR. Glucocorticoid exposure in utero: new model for adult hypertension. *Lancet*. 1993;341(8841): 339–341
 50. Nyirenda MJ, Lindsay RS, Kenyon CJ, Burchell A, Seckl JR. Glucocorticoid exposure in late gestation permanently programs rat hepatic phosphoenolpyruvate carboxykinase and glucocorticoid receptor expression and causes glucose intolerance in adult offspring. *J Clin Invest*. 1998;101(10): 2174–2181
 51. Lindsay RS, Lindsay RM, Waddell BJ, Seckl JR. Prenatal glucocorticoid exposure leads to offspring hyperglycaemia in the rat: studies with the 11 beta-hydroxysteroid dehydrogenase inhibitor carbenoxolone. *Diabetologia*. 1996;39(11):1299–1305
 52. Lindsay RS, Lindsay RM, Edwards CR, Seckl JR. Inhibition of 11-beta-hydroxysteroid dehydrogenase in pregnant rats and the programming of blood pressure in the offspring. *Hypertension*. 1996;27(6):1200–1204
 53. Norberg H, Stålnacke J, Nordenström A, Norman M. Repeat antenatal steroid exposure and later blood pressure, arterial stiffness, and metabolic profile. *J Pediatr*. 2013;163(3):711–716
 54. Finken MJ, Keijzer-Veen MG, Dekker FW, et al; Dutch POPS-19 Collaborative Study Group. Antenatal glucocorticoid treatment is not associated with long-term metabolic risks in individuals born before 32 weeks of gestation. *Arch Dis Child Fetal Neonatal Ed*. 2008;93(6): F442–F447
 55. de Vries WB, Karemaker R, Mooy NF, et al. Cardiovascular follow-up at school age after perinatal glucocorticoid exposure in prematurely born children: perinatal glucocorticoid therapy and cardiovascular follow-up. *Arch Pediatr Adolesc Med*. 2008;162(8):738–744
 56. Doyle LW, Ford GW, Davis NM, Callanan C. Antenatal corticosteroid therapy and blood pressure at 14 years of age in preterm children. *Clin Sci (Lond)*. 2000; 98(2):137–142
 57. Kelly BA, Lewandowski AJ, Worton SA, et al. Antenatal glucocorticoid exposure and long-term alterations in aortic function and glucose metabolism. *Pediatrics*. 2012;129(5):e1282–e1290
 58. Nyirenda MJ, Carter R, Tang JI, et al. Prenatal programming of metabolic syndrome in the common marmoset is associated with increased expression of 11beta-hydroxysteroid dehydrogenase type 1. *Diabetes*. 2009; 58(12):2873–2879
 59. Langley-Evans SC, Bellinger L, McMullen S. Animal models of programming: early life influences on appetite and feeding behaviour. *Matern Child Nutr*. 2005;1(3): 142–148

60. Boney CM, Verma A, Tucker R, Vohr BR. Metabolic syndrome in childhood: association with birth weight, maternal obesity, and gestational diabetes mellitus. *Pediatrics*. 2005;115(3). Available at: www.pediatrics.org/cgi/content/full/115/3/e290
61. Mericq V, Iñiguez G, Bazaes R, et al. Differences in body composition and energy expenditure in prepubertal children born term or preterm appropriate or small for gestational age. *J Pediatr Endocrinol Metab*. 2009;22(11):1041–1050
62. Murphy KE, Hannah ME, Willan AR, et al; MACS Collaborative Group. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. *Lancet*. 2008;372(9656):2143–2151
63. Guinn DA, Atkinson MW, Sullivan L, et al. Single vs weekly courses of antenatal corticosteroids for women at risk of preterm delivery: A randomized controlled trial. *JAMA*. 2001;286(13):1581–1587
64. Asztalos EV, Murphy KE, Willan AR, et al; MACS-5 Collaborative Group. Multiple courses of antenatal corticosteroids for preterm birth study: outcomes in children at 5 years of age (MACS-5). *JAMA Pediatr*. 2013;167(12):1102–1110

Cardiovascular Risk Factors in Children After Repeat Doses of Antenatal Glucocorticoids: An RCT

Christopher J.D. McKinlay, Wayne S. Cutfield, Malcolm R. Battin, Stuart R. Dalziel, Caroline A. Crowther, Jane E. Harding and on behalf of the ACTORDS Study Group
Pediatrics 2015;135:e405

DOI: 10.1542/peds.2014-2408 originally published online January 19, 2015;

Updated Information & Services	including high resolution figures, can be found at: http://pediatrics.aappublications.org/content/135/2/e405
References	This article cites 60 articles, 17 of which you can access for free at: http://pediatrics.aappublications.org/content/135/2/e405#BIBL
Subspecialty Collections	This article, along with others on similar topics, appears in the following collection(s): Fetus/Newborn Infant http://www.aappublications.org/cgi/collection/fetus:newborn_infant_sub Neonatology http://www.aappublications.org/cgi/collection/neonatology_sub Cardiology http://www.aappublications.org/cgi/collection/cardiology_sub Cardiovascular Disorders http://www.aappublications.org/cgi/collection/cardiovascular_disorders_sub
Permissions & Licensing	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: http://www.aappublications.org/site/misc/Permissions.xhtml
Reprints	Information about ordering reprints can be found online: http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Cardiovascular Risk Factors in Children After Repeat Doses of Antenatal Glucocorticoids: An RCT

Christopher J.D. McKinlay, Wayne S. Cutfield, Malcolm R. Battin, Stuart R. Dalziel, Caroline A. Crowther, Jane E. Harding and on behalf of the ACTORDS Study Group

Pediatrics 2015;135:e405

DOI: 10.1542/peds.2014-2408 originally published online January 19, 2015;

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://pediatrics.aappublications.org/content/135/2/e405>

Pediatrics is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. Pediatrics is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 2015 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 1073-0397.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

