

# Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial

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## Abstract

**Objectives** To determine if antenatal exposure to betamethasone for the prevention of neonatal respiratory distress syndrome alters psychological functioning and health related quality of life in adulthood.

**Design** Follow-up of the first and largest double blind, placebo controlled, randomised trial of a single course of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome.

**Setting** Tertiary obstetric hospital in Auckland, New Zealand.

**Participants** 192 adult offspring, mean age 31 years, of mothers who took part in a randomised controlled trial of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome (87 exposed to betamethasone and 105 exposed to placebo).

**Interventions** Mothers received two doses of betamethasone or placebo 24 hours apart.

**Main outcome measures** Cognitive functioning assessed with Wechsler abbreviated scale of intelligence; working memory and attention assessed with Benton visual retention test, paced auditory serial addition test, and Brown attention deficit disorder scale; psychiatric morbidity assessed with Beck depression inventory II, state-trait anxiety inventory, and schizotypy traits questionnaire; handedness assessed with Edinburgh handedness inventory; health related quality of life assessed with short form 36 health survey.

**Results** No differences were found between groups exposed to betamethasone and placebo in cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life.

**Conclusions** Prenatal exposure to a single course of betamethasone does not alter cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life in adulthood. Obstetricians should continue to use a single course of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome.

## Introduction

A single course of antenatal glucocorticoids is recommended in the management of preterm labour for the prevention of neonatal respiratory distress syndrome.<sup>1</sup> Although follow-up studies suggest that no adverse effects occur through early childhood after use of antenatal glucocorticoids,<sup>2</sup> information about long term psychological functioning and health in adulthood remains scarce.

Other perinatal exposure to glucocorticoids has been associated with adverse neurodevelopmental outcomes. Non-randomised studies have reported decreased neonatal head circumference and increased risk of hyperactivity in childhood after repeated courses of antenatal glucocorticoids,<sup>3,4</sup> and a randomised trial reported lower IQ scores after postnatal glucocorticoids.<sup>5</sup> However, one small follow-up study of a randomised trial found no difference in cognitive functioning or self report of psychoneuroticism in 81 participants aged 20.<sup>6</sup> Conversely, a non-randomised cohort of 130 children at age 14 suggested better cognitive functioning in those exposed to glucocorticoids.<sup>7</sup>

We followed a cohort of neonatal survivors from the first randomised controlled trial of antenatal glucocorticoids<sup>8</sup> to assess the long term effects on psychological functioning and health related quality of life in adulthood.

## Methods

### Protocol

*Auckland steroid trial*—The Auckland steroid trial and childhood follow-up have been described previously.<sup>2,8</sup> Briefly, between December 1969 and February 1974 all women expected to deliver between 24 and 36 weeks at the National Women's Hospital, Auckland, New Zealand, were eligible for enrolment. Women were randomised to an intramuscular injection of short acting betamethasone phosphate and long acting betamethasone acetate, or an identical looking placebo (trial 1). Treatment was repeated 24 hours later if delivery had not occurred. After the first 717 women had enrolled, the dose of betamethasone was doubled (trial 2). A total of 1142 women were enrolled and delivered 1218 babies. Primary endpoints were neonatal respiratory distress syndrome and perinatal death.

*Follow-up in adulthood*—Between February 2002 and December 2003 attempts were made to trace the surviving "babies," now adults. Those located were invited to enter a follow-up study,<sup>9</sup> and the subgroup of participants who lived in the greater Auckland area were invited to participate in the current study between February 2003 and March 2004. All staff, adult participants, and members of the study team were blinded to treatment group.

### Outcome measures

*Cognitive functioning*—We used the Wechsler abbreviated scale of intelligence to assess cognitive functioning.<sup>10</sup>

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*Working memory and attention*—We used the Benton visual retention test,<sup>11</sup> the paced auditory serial addition test,<sup>12</sup> and the Brown attention deficit disorder scale to assess working memory and attention.<sup>13</sup>

*Psychiatric morbidity*—We used the Beck depression inventory II,<sup>14</sup> the trait portion of the state-trait anxiety inventory,<sup>15</sup> and the schizotypy traits questionnaire to assess psychiatric morbidity.<sup>16</sup>

*Handedness*—We used the Edinburgh handedness inventory to assess handedness.<sup>17</sup>

*Health related quality of life*—We assessed health related quality of life by using the Australasian version of the short form 36 health survey (SF-36), which has been validated in 7862 New Zealanders.<sup>18</sup> Participants were also questioned about visual, hearing, and speech abnormalities.

#### Participant flow and follow-up

Of the 988 neonatal survivors from the Auckland steroid trial, 713 (72%) were successfully traced at 30 years. Of these, 534 completed the follow-up—56% of those presumed to be alive and 80% of those traced and known to be alive.<sup>9</sup> Of these, 280 were eligible for the current study (lived in the greater Auckland area), of whom 192 (69%) participated.

#### Analyses

We analysed data on an intention to treat basis. Primary analyses were unadjusted. Secondary analyses used regression to adjust for confounding by sex, birth weight, gestational age, and socioeconomic status. We explored further confounders by using the change in estimates technique.

#### Results

*Recruitment*—Eighty seven participants exposed to betamethasone and 105 participants exposed to placebo took part (66% *v* 71% of those eligible;  $P=0.36$ ). Mean age at follow-up was 31.2 and 31.1 years respectively.

*Background characteristics*—Those who participated in this study were more likely to have had respiratory distress syndrome but had otherwise similar perinatal characteristics to the entire cohort of non-participants presumed to be alive at age 30. No significant differences in perinatal or adult characteristics existed between the betamethasone and placebo exposed participants who took part.

*Psychological functioning*—No difference existed between groups in measures of cognitive functioning, working memory and attention, depression, anxiety, schizotypy, or handedness (table). Adjustment for previous psychiatric diagnosis did not change the depression, anxiety, or schizotypy results.

*Health related quality of life*—We found no difference between groups in the eight domains of the SF-36 or in the numbers reporting visual or hearing difficulties (table). However, betamethasone exposed participants reported significantly fewer speech difficulties. All participants with speech difficulties reported a mild impairment, in that they were partially understood when speaking to strangers but completely understood when speaking to those who knew them well. Adjustment for sex, birth weight, gestational age, and socioeconomic status did not change the results.

#### Discussion

We studied 192 neonatal survivors at 31 years of age from the first and largest randomised controlled trial of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome. We found that antenatal exposure to betamethasone did not alter cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life at age 31.

The only other report of outcome in adulthood after a randomised controlled trial of antenatal glucocorticoids involved 81 participants at a mean age of 20 and found no differences in cognitive functioning, handedness, or psychopathology.<sup>6</sup> Our study is the first to report health related quality of life into adulthood after exposure to antenatal glucocorticoids.

#### Comparison with other studies

Our findings are consistent with previous childhood follow-up studies from both the Auckland steroid trial and other randomised trials of antenatal glucocorticoids.<sup>2 19</sup> MacArthur et al followed 258 children at age 4 and 250 children at age 6 from the first 318 neonatal survivors of the Auckland steroid trial (trial 1).<sup>2</sup> They reported no overall differences in cognition between the two groups. The authors of the second largest randomised trial of antenatal glucocorticoids followed 339 infants at 36 months of age and also reported no difference in cognitive outcome.<sup>19</sup>

Post hoc calculations indicate that our study had 80% power ( $\alpha=0.05$ ) to detect a difference between treatment groups of 5% for IQ, 7% for Brown attention deficit disorder scale total scores, 3% for state-trait anxiety inventory scores, and 10% for SF-36 mental health scores. Thus clinicians can be confident that the relatively small fetal glucocorticoid exposure resulting from a single course of antenatal betamethasone for the prevention of neonatal respiratory distress syndrome has no clinically detectable effect on cognitive functioning, working memory and attention, or psychiatric morbidity into adulthood. This confidence cannot be extrapolated to larger exposures in the perinatal period, such as repeated courses of antenatal glucocorticoids. Follow-up of 146 school age children from a randomised controlled trial of much larger doses of glucocorticoids for treatment of neonatal chronic lung disease found poorer cognitive functioning in those exposed to glucocorticoids.<sup>5</sup> Long term follow-up of recent randomised controlled trials is essential to clarify the clinical relevance of these effects.

We found that participants exposed to betamethasone reported a lower incidence of speech difficulties than those exposed to placebo. The self reported speech impairment described was clinically mild. MacArthur et al reported no difference between groups in incidence of stammering, stutter, or intelligibility of speech at 4 and 6 years of age.<sup>2</sup> The differences between groups in adulthood must be interpreted with caution in light of the multiple comparisons done in the analysis and hence the possibility of a type I error.

#### Limitations

Only 69% of the eligible cohort of neonatal survivors living in the Auckland region participated in this study.

## Psychological functioning and health related quality of life outcomes in groups exposed to betamethasone and placebo

Outcome	Measurement	Measured outcome		Difference (95% CI)	P value
		Betamethasone (n=87)	Placebo (n=105)		
<b>Cognitive functioning</b>					
Full IQ	Mean (SD)	102.6 (12.5)	103.7 (13.5)	-1.0 (-4.8 to 2.7)	0.58
Verbal IQ	Mean (SD)	97.6 (11.9)	98.3 (12.8)	-0.8 (-4.3 to 2.8)	0.67
Performance IQ	Mean (SD)	107.2 (13.8)	108.3 (14.7)	-1.1 (-5.2 to 3.0)	0.59
<b>Working memory and attention</b>					
Benton: total correct score	Mean (SD)	7.0 (1.7)	7.2 (1.8)	-0.1 (-0.6 to 0.4)	0.59
Benton: total number of errors	Mean (SD)	3.8 (2.6)	3.7 (3.0)	-0.1 (-0.7 to 0.9)	0.89
Paced auditory serial addition test, correct score at:					
2.4 second	Median (IQR)	41 (27-49)	43 (28-49)	-1 (-5 to 3)	0.72
2.0 second	Median (IQR)	37 (27-46)	37 (26-45)	0 (-2 to 5)	0.59
1.6 second	Median (IQR)	29 (22-40)	30 (20-39)	0 (-3 to 4)	0.77
1.2 second	Median (IQR)	24 (14-34)	26 (15-33)	0 (-4 to 2)	0.60
Brown ADD scale: total score	Log mean	25.6	26.9	1 (0.8 to 1.1)*	0.58
Probable ADD (score >39)	No (%)	16 (18)	30 (29)	0.64 (0.38 to 1.1)†	0.10
<b>Psychiatric morbidity</b>					
BDI-II total score	Median (IQR)	5 (2-12)	5 (1-10)	1 (-1 to 2)	0.44
Probable depression (score >13)	No (%)	16 (18)	17 (16)	1.1 (0.61 to 2.1)†	0.69
State-trait anxiety inventory: total	Log mean	34.1	34.5	1 (0.9 to 1.1)*	0.74
Probable anxiety (score >80th centile)	No (%)	17 (20)	27 (26)	0.76 (0.44 to 1.3)†	0.31
Schizotypy traits questionnaire:					
Total	Median (IQR)	11 (6-15)	10 (7-15)	0 (-2 to 2)	0.78
Magical ideation	Median (IQR)	3 (1-4)	3 (1-4)	0 (-1 to 1)	0.93
Unusual perceptual experiences	Median (IQR)	1 (0-3)	2 (0-3)	0 (0 to 0)	0.97
Paranoid ideation and suspiciousness	Median (IQR)	1 (0-3)	1 (0-3)	1 (-1 to 2)	0.70
<b>Handedness</b>					
Laterality quotient	Median (IQR)	90 (71-100)	86 (60-100)	0 (0 to 8)	0.22
<b>Health related quality of life</b>					
SF-36:					
Physical functioning	Mean (SD)	86 (24)	89 (17)	-3 (-9 to 2)	0.27
Role limitation due to physical problems	Mean (SD)	78 (37)	79 (37)	-1 (-12 to 9)	0.82
Bodily pain	Mean (SD)	72 (25)	76 (21)	-4 (-11 to 2)	0.19
General health perception	Mean (SD)	74 (21)	75 (21)	-2 (-7 to 4)	0.61
Vitality	Mean (SD)	59 (19)	62 (19)	-3 (-8 to 2)	0.28
Social functioning	Mean (SD)	79 (25)	83 (23)	-3 (-10 to 3)	0.32
Role limitation due to emotional problems	Mean (SD)	72 (41)	77 (38)	-5 (-16 to 6)	0.37
Mental health	Mean (SD)	72 (18)	75 (17)	-3 (-8 to 2)	0.23
Participants reporting visual difficulty	No (%)	18 (21)	24 (23)	0.91 (0.53 to 1.6)†	0.72
Participants reporting hearing difficulties	No (%)	1 (1.2)	5 (4.8)	0.24 (0.03 to 2.0)†	0.22
Participants reporting speech difficulties	No (%)	1 (1.2)	9 (8.6)	0.13 (0.01 to 1.0)†	0.02

ADD=attention deficit disorder; BDI=Beck depression inventory; SF-36=short form 36 health survey.

\*A difference between log means is a ratio and is non-significant if 95% confidence interval includes 1.

†Relative risk (95% confidence interval).

Although this introduces the potential for selection bias, the likely direction of such bias remains uncertain.<sup>20, 21</sup> However, lack of complete follow-up would bias our results only if the association between exposure to betamethasone and psychological and health related quality of life outcomes differed between those who did and those who did not participate. As the original trial was randomised, we have no reason to think that this might be the case.

Further potential for selection bias is introduced by the geographical restriction of study participants to those living in the Auckland region. However, the only difference in perinatal variables between the participants and the total cohort of neonatal survivors presumed to be alive at age 30 was the higher incidence of neonatal respiratory distress syndrome in participants.

### Implications

Our study only included nine infants born < 30 weeks' gestation. However, the expected neonatal outcome for

these very premature infants today is similar to that of our more mature cohort 30 years ago. Furthermore, most preterm babies are born after 30 weeks' gestation. Further follow-up studies should clarify possible long term effects of exposure to antenatal betamethasone at much earlier gestations than in this study.

### Conclusions

Antenatal exposure to a single course of betamethasone does not alter cognitive functioning, working memory and attention, psychiatric morbidity, handedness, or health related quality of life in adulthood. Obstetricians should continue to use a single course of antenatal glucocorticoids for the prevention of neonatal respiratory distress syndrome.

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### What is already known on this topic

A single course of antenatal glucocorticoids reduces neonatal mortality and morbidity after preterm birth and is widely used for the prevention of neonatal respiratory distress syndrome

No studies have adequately looked at psychological functioning and health related quality of life in adulthood after antenatal exposure to glucocorticoids

### What this study adds

Antenatal exposure to betamethasone did not alter psychological functioning or health related quality of life at 31 years of age

Obstetricians should continue to use a single course of antenatal glucocorticoids for the prevention of neonatal respiratory distress syndrome

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## The holocaust and medicine—a learning moment

A day after holocaust memorial day, I (UW), as an anatomy instructor, was preparing for a first year students' lesson with a colleague. A question arose, and we looked for the answer in the anatomy textbooks that we had at that time. We were surprised to find a copy of *Pernkopf's Atlas*, with its detailed manner and unique style of illustrations. Shocked and trembling, we came across an illustration of a neck dissection of a shaven headed man which, according to the illustrator's signature, had been drawn in 1943.

In 1933 Eduard Pernkopf, head of the anatomy school of Vienna University, began preparing an anatomical atlas. An ardent Nazi, he became dean in 1938 and president of the university in 1943. Among his first actions as dean was to "purify" the medical school of all Jews by expelling a total of 153 of the 197 faculty members. He also arranged for the bodies of nearly 1400 people executed by the Gestapo, most of them for political reasons, to serve as models for his atlas.

Only the day before finding the atlas, we had heard the story behind its creation during a noon conference we hold annually in our faculty, and for us, finding a textbook with such a history, had additional significance. We felt revolted that students had been using this book for so many years without being aware of its history. The fact that these books were discovered in a medical

school in Israel, coincidentally in the same week as we commemorated the holocaust, enhanced those feelings. An inspection revealed further copies on the faculty's library shelves. There was no reference to their background either inside the books or in the library files.

We have decided to share this learning moment. These books, rather than being destroyed, can be used for educating students, faculty, and public. This will also be an appropriate way to commemorate the many victims used in the atlas's production. It would be appropriate to display the books in public, along with an explanation of the horrific background to their creation. We hope that such an exposure will lead to a further search for other sources with similar histories. Our medical students association, in cooperation with the programme for the study of the holocaust and medicine in the faculty, would like to bring this issue to the attention of medical students in Israel and worldwide. The involvement of medical students in such decisions and activities is of great importance. As future doctors or scientists, we should think of ways to learn from the terrible past.

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