

# Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth (Review)

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## A B S T R A C T

### Background

Respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal mortality and disability.

### Objectives

To assess the effects on fetal and neonatal morbidity and mortality, on maternal mortality and morbidity, and on the child in later life of administering corticosteroids to the mother before anticipated preterm birth.

### Search strategy

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 October 2005).

### Selection criteria

Randomised controlled comparisons of antenatal corticosteroid administration (betamethasone, dexamethasone, or hydrocortisone) with placebo or with no treatment given to women with a singleton or multiple pregnancy, expected to deliver preterm as a result of either spontaneous preterm labour, preterm prelabour rupture of the membranes or elective preterm delivery.

### Data collection and analysis

Two review authors assessed trial quality and extracted data independently.

### Main results

Twenty-one studies (3885 women and 4269 infants) are included. Treatment with antenatal corticosteroids does not increase risk to the mother of death, chorioamnionitis or puerperal sepsis. Treatment with antenatal corticosteroids is associated with an overall reduction in neonatal death (relative risk (RR) 0.69, 95% confidence interval (CI) 0.58 to 0.81, 18 studies, 3956 infants), RDS (RR 0.66, 95% CI 0.59 to 0.73, 21 studies, 4038 infants), cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43 to 0.69, 13 studies, 2872 infants), necrotising enterocolitis (RR 0.46, 95% CI 0.29 to 0.74, eight studies, 1675 infants), respiratory support, intensive care admissions (RR 0.80, 95% CI 0.65 to 0.99, two studies, 277 infants) and systemic infections in the first 48 hours of life (RR 0.56, 95% CI 0.38 to 0.85, five studies, 1319 infants). Antenatal corticosteroid use is effective in women with premature rupture of membranes and pregnancy related hypertension syndromes.

### Authors' conclusions

The evidence from this new review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. A single course of antenatal corticosteroids should be considered routine for preterm delivery with few exceptions. Further information is required concerning optimal dose to delivery interval, optimal corticosteroid to use, effects in multiple pregnancies, and to confirm the long-term effects into adulthood.

## PLAIN LANGUAGE SUMMARY

Corticosteroids given to women in early labour help the babies' lungs to mature and so reduce the number of babies who die or suffer breathing problems at birth

Babies born very early are at risk of breathing difficulties (respiratory distress syndrome) and other complications at birth. Some babies have developmental delay and some do not survive the initial complications. In animal studies, corticosteroids are shown to help the lungs to mature and so it was suggested these drugs may help babies in preterm labour too. This review of 21 trials shows that a single course of corticosteroid, given to the mother in preterm labour and before the baby is born, helps to develop the baby's lungs and reduces complications like respiratory distress syndrome. Furthermore, this treatment results in fewer babies dying and fewer common serious neurological and abdominal problems, e.g. cerebroventricular haemorrhage and necrotising enterocolitis, that affect babies born very early. There does not appear to be any negative effects of the corticosteroid on the mother. Long-term outcomes on both baby and mother are also good.

## BACKGROUND

Respiratory distress syndrome (RDS) is a serious complication of preterm birth and the primary cause of early neonatal death and disability. It affects up to one fifth of low birthweight babies (less than 2500 g) and two thirds of extremely low birthweight babies (less than 1500 g).

Respiratory failure in these infants occurs as a result of surfactant deficiency, poor lung anatomical development and immaturity in other organs. Neonatal survival after preterm birth improves with gestation (Doyle 2001a), reflecting improved maturity of organ systems. However, those who survive early neonatal care are at increased risk of long-term neurological disability (Doyle 2001b).

### History

While researching the effects of the steroid dexamethasone on premature parturition in fetal sheep in 1969, Liggins found that there was some inflation of the lungs of lambs born at gestations at which the lungs would be expected to be airless (Liggins 1969). He theorised, from these observations, that dexamethasone might have accelerated the appearance of pulmonary surfactant. The hypothesis is that corticosteroids act to trigger the synthesis of ribonucleic acid that codes for particular proteins involved in the biosynthesis of phospholipids or in the breakdown of glycogen. Subsequent work has suggested that, in animal models, corticosteroids mature a number of organ systems (Padbury 1996; Vyas 1997). Liggins and Howie performed the first randomised controlled trial in humans of betamethasone for the prevention of RDS in 1972 (Liggins 1972b).

### Fetal lung development

Some understanding of fetal lung development may be useful in understanding why RDS occurs and why corticosteroids work. Fetal lung development can be divided into five stages: embryonic, pseudoglandular, canalicular, terminal sac and alveolar. The lung first appears as an outgrowth of the primitive foregut at 22 to 26 days after conception. By 34 days, the outgrowth has divided into left and right sides and further to form the major units of the lung.

Mature lungs contain more than 40 different cell types derived from this early tissue. From 8 to 16 weeks' gestation, the major bronchial airways and associated respiratory units of the lung are progressively formed. At this time the lung blood vessels also begin to grow in parallel. From 17 to 25 weeks' gestation, the airways grow, widen and lengthen (canalisation). Terminal bronchioles with enlargements that subsequently give rise to terminal sacs (the primitive alveoli) are formed. These are the functional units of the lung (respiratory lobules). It is at this stage that the increasing proximity of blood capillaries begins the air-blood interface, required for effective air exchange. This can only take place at the terminal bronchioles. At the end of the canalicular stage, type I and II pneumocytes can be seen in the alveoli. From 28 to 35 weeks' gestation, the alveoli can be counted and with increasing age they become more mature. Lung volume increases four-fold between 29 weeks and term. Alveolar number shows a curvilinear increase with age but a linear relationship with bodyweight. At birth there are an average of 150 million alveoli (half the expected adult number). The alveoli produce surfactant. The alveolar stage continues for one to two years after birth. In the preterm infant, low alveolar numbers probably contribute to respiratory dysfunction.

The fetal lung also matures biochemically with increasing gestation. Lamellar bodies, which store surfactant, appear at 22 to 24 weeks. Surfactant is a complex mixture of lipids and apoproteins, the main constituents of which are dipalmitoylphosphatidyl choline, phosphatidylglycerol and apoproteins A, B, C and D. Surfactant is needed to maintain stability when breathing out, to prevent collapse of the alveoli. Premature infants have a qualitative and quantitative deficiency of surfactant, which predisposes to RDS. At the low lung volume associated with expiration, surface tension becomes very high, leading to atelectasis with subsequent intrapulmonary shunting, ventilation perfusion inequalities and ultimately respiratory failure. Capillary leakage allows inhibitors from plasma to reach alveoli and inactivate any surfactant that may be present. Hypoxia, acidosis and hypothermia (common problems in the very preterm infant) can reduce surfactant synthesis

required to replenish surfactant lost from the system. The pulmonary antioxidant system develops in parallel to the surfactant system and deficiency in this also puts the preterm infant at risk of chronic lung disease.

### **Effects of antenatal corticosteroids for preterm birth**

Several clinical trials have been performed on the effects of corticosteroids before preterm birth since the original Liggins study. The first structured review on corticosteroids in preterm birth was published in 1990 (Crowley 1990). This review showed that corticosteroids given prior to preterm birth (as a result of either preterm labour or elective preterm delivery) are effective in preventing respiratory distress syndrome and neonatal mortality. Corticosteroid treatment was also associated with a significant reduction in the risk of intraventricular haemorrhage. Corticosteroids appear to exert major vasoconstrictive effects on fetal cerebral blood flow, protecting the fetus against intraventricular haemorrhage at rest and when challenged by conditions causing vasodilatation such as hypercapnia (Schwab 2000). Crowley found no effect on necrotising enterocolitis or chronic lung disease from antenatal corticosteroid administration. The influence of the results of the original trial and Crowley's review was the subject of a Wellcome Witness Seminar (Wellcome 2005) held in 2004.

Corticosteroids have become the mainstay of prophylactic treatment in preterm birth, as a result of these findings and subsequent work. However, there have remained a number of outstanding issues regarding the use of antenatal corticosteroids. The original trial by Liggins suggested an increased rate of stillbirth in women with hypertension syndromes (Liggins 1976). There is concern about using corticosteroids in women with premature rupture of membranes due to the possible increased risk of neonatal and maternal infection (Imseis 1996; NIH 1994). The efficacy of this treatment in multiple births has only been addressed retrospectively (Turrentine 1996). From the time of the original Liggins paper, debate has continued around whether the treatment is effective at lower gestations and at differing treatment-to-delivery intervals. These issues will be addressed in this review in subgroup analyses. The effectiveness and safety of repeat doses of corticosteroids for women who remain undelivered, but at increased risk of preterm birth after an initial course of treatment, is addressed in a separate review (Crowther 2000).

Recent epidemiological evidence and animal work strongly suggests that there may be adverse long-term consequences of antenatal exposure to corticosteroids (Seckl 2000). Exposure to excess corticosteroids before birth is hypothesised to be a key mechanism underlying the fetal origins of adult disease hypothesis (Barker 1998; Benediktsson 1993). This hypothesis postulates a link between impaired fetal growth and cardiovascular disease and type 2 diabetes in later life and their risk factors of impaired glucose tolerance, dyslipidaemia, and hypertension (Barker 1998). A large body of animal experimental work has documented impaired glucose tolerance and increased blood pressure in adult animals after

antenatal exposure to corticosteroids (Clark 1998; Dodic 1999; Edwards 2001). Thus this review will consider blood pressure, glucose intolerance, dyslipidaemia, and hypothalamo-pituitary-adrenal axis function in childhood and adulthood.

Experimental animal studies have shown decreased brain growth in preterm and term infants exposed to single courses of corticosteroid (Huang 1999; Jobe 1998). This review will therefore also address long-term neurodevelopment and other childhood and adult outcomes after antenatal corticosteroid exposure.

### **The reasons for an updated review**

There is need for an updated systematic review of the effects of prophylactic corticosteroids for preterm birth, as a result of current interest and due to further published trials. We also have the ability to re-analyse the Auckland Steroid Study by intention to treat. This study contributes a third of the participants to the review so this is an important development for the review. Because of this, the time since the last version of the review (Crowley 1996), new Cochrane guidelines for inclusion and exclusion of studies and the need for the review to be standardised with the repeat courses review (Crowther 2000), it seemed preferable to start with a new protocol to set out the rationale and the proposed methods. This update has been developed following this new protocol.

## **OBJECTIVES**

To assess the effects on fetal and neonatal morbidity and mortality, on maternal mortality and morbidity, and on the child in later life of administering corticosteroids to the mother prior to anticipated preterm birth. The review addresses whether corticosteroids are more effective than placebo or 'no corticosteroids' in reducing the risk of respiratory distress syndrome, neonatal death, intraventricular haemorrhage, necrotising enterocolitis, chronic lung disease in survivors of neonatal intensive care, the use of surfactant in the newborn, the cost of neonatal care, and the duration of neonatal hospital care. The review will also address the effect of corticosteroids on the risk of stillbirth, fetal or neonatal infection, maternal infection, and long-term abnormality in survivors during childhood and adulthood.

## **CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW**

### **Types of studies**

All randomised controlled comparisons of antenatal corticosteroid administration (betamethasone, dexamethasone, or hydrocortisone) with placebo, or with no treatment, given to women prior to anticipated preterm delivery (elective, or following spontaneous labour), regardless of other co-morbidity, were considered for inclusion in this review. Quasi-randomised trials (e.g. allocation by

date of birth or record number) were excluded. Trials where the method of randomisation was not specified in detail were included in the expectation that their inclusion in this review will encourage the authors to make available further information on the method of randomisation. Trials where non-randomised cohorts were amalgamated with randomised subjects were excluded if the results of the randomised subjects could not be separated out. Trials which tested the effect of corticosteroids along with other co-interventions were also excluded. Trials in which placebo was not used in the control group were included as were trials in which post-randomisation exclusions occurred. Published, unpublished and ongoing randomised trials with reported data were included.

### **Types of participants**

Women, with a singleton or multiple pregnancy, expected to deliver preterm as a result of either spontaneous preterm labour, preterm prelabour rupture of the membranes or elective preterm delivery.

### **Types of intervention**

A corticosteroid capable of crossing the placenta (betamethasone, dexamethasone, hydrocortisone) compared with placebo or with no treatment. Data from trials involving the use of methyl-prednisolone (Block 1977; Schmidt 1984) were discarded, as this corticosteroid has not been shown to induce maturation in animal models and is known to have altered placental transfer (Block 1977). Predefined subgroups were planned to separately examine primary outcomes in women and infants depending on the specific drug used.

### **Types of outcome measures**

Primary outcomes chosen were those which were thought to be the most clinically valuable in assessing effectiveness and safety of the treatment for the woman and her offspring. Secondary outcomes included possible complications and other measures of effectiveness.

Groups in which the outcomes were considered:

- women/mother;
- fetus/neonate;
- child;
- child as adult;
- health services.

### **Primary outcomes**

For the woman:

- death;
- chorioamnionitis (however defined by authors);
- puerperal sepsis (however defined by authors).

For the fetus/neonate:

- death (fetal/neonatal);
- respiratory distress syndrome (RDS);
- moderate/severe RDS;
- chronic lung disease (need for continuous supplemental oxygen at 28 days postnatal age or 36 weeks' postmenstrual age, whichever was later);
- cerebroventricular haemorrhage (diagnosed by ultrasound, diagnosed by autopsy);
- severe cerebroventricular haemorrhage;
- mean birthweight.

For the child:

- death;
- neurodevelopmental disability at follow up (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or development delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviation below population mean)).

For the child as adult:

- death;
- neurodevelopmental disability at follow up (blindness, deafness, moderate/severe cerebral palsy (however defined by authors), or development delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than -2 standard deviation below population mean)).

### **Secondary outcomes**

For the woman:

- fever after trial entry requiring the use of antibiotics;
- intrapartum fever requiring the use of antibiotics;
- postnatal fever;
- admission to intensive care unit;
- side-effects of therapy;
- glucose intolerance (however defined by authors);
- hypertension (however defined by authors).

For the fetus/neonate:

- Apgar score less than seven at five minutes;
- interval between trial entry and birth;
- mean length at birth;
- mean head circumference at birth;
- mean skin fold thickness at birth;

- small-for-gestational age (however defined by authors);
- mean placental weight;
- neonatal blood pressure;
- admission to neonatal intensive care;
- need for inotropic support;
- mean duration of inotropic support (days);
- need for mechanical ventilation/continuous positive airways pressure;
- mean duration of mechanical ventilation/continuous positive airways pressure (days);
- air leak syndrome;
- duration of oxygen supplementation (days);
- surfactant use;
- systemic infection in first 48 hours of life;
- proven infection while in the neonatal intensive care unit;
- necrotising enterocolitis;
- hypothalamo-pituitary-adrenal (HPA) axis function (however defined by authors).

For the child:

- mean weight;
- mean head circumference;
- mean length;
- mean skin fold thickness;
- abnormal lung function (however defined by authors);
- mean blood pressure;
- glucose intolerance (however defined by authors);
- HPA axis function (however defined by authors);
- dyslipidaemia (however defined by authors);
- visual impairment (however defined by authors);
- hearing impairment (however defined by authors);
- developmental delay (defined as developmental quotient less than -2 standard deviation below population mean);
- intellectual impairment (defined as intelligence quotient less than -2 standard deviation below population mean);
- cerebral palsy (however defined by authors);
- behavioural/learning difficulties (however defined by authors).

For the child as adult:

- mean weight;
- mean head circumference;
- mean length;
- mean skin fold thickness;
- abnormal lung function (however defined by authors);
- mean blood pressure;
- glucose intolerance (however defined by authors);
- HPA axis function (however defined by authors);
- dyslipidaemia (however defined by authors);
- mean age at puberty;
- bone density (however defined by authors);
- educational achievement (completion of high school, or however defined by authors);
- visual impairment (however defined by authors);
- hearing impairment (however defined by authors);
- intellectual impairment (defined as intelligence quotient less than -2 standard deviation below population mean).

For health services:

- mean length of antenatal hospitalisation for women (days);
- mean length of postnatal hospitalisation for women (days);
- mean length of neonatal hospitalisation (days);
- cost of maternal care (in 10s of 1000s of \$);
- cost of neonatal care (in 10s of 1000s of \$).

Although all outcomes were sought from included trials, only trials with relevant data appear in the analysis tables. Outcomes were included in the analysis if reasonable measures were taken to minimise observer bias and data were available for analysis according to original allocation.

### *Subgroup analysis*

The following subgroups were analysed:

- singleton versus multiple pregnancy;
- gestational age at delivery (< 28 weeks, < 30 weeks, < 32 weeks, < 34 weeks, < 36 weeks, at least 34 weeks, at least 36 weeks);
- entry to delivery interval (< 24 hours, < 48 hours, one to seven days, > seven days);
- prelabour rupture of membranes (at trial entry, > 24 hours before delivery, > 48 hours before delivery);
- pregnancy induced hypertension syndromes;

- type of glucocorticoid (betamethasone, dexamethasone, hydrocortisone).

As the case-fatality rate for respiratory distress syndrome has reduced with advanced neonatal care, we postulated that the effect of corticosteroids may not be apparent in later trials; hence trials were analysed separately by the main decade of recruitment (if this was not stated in trial manuscripts it was estimated using the date of first publication).

There is potential for bias introduced by differential neonatal mortality rates on ascertainment of intraventricular haemorrhage by autopsy versus ascertainment by ultrasound. We therefore analysed these two groups separately. Subgroup analysis was performed for primary outcomes.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Pregnancy and Childbirth Group methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register (30 October 2005).

The Cochrane Pregnancy and Childbirth Group's trials register is maintained by the Trials Search Co-ordinator and contains trials identified from:

- (1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
- (2) monthly searches of MEDLINE;
- (3) handsearches of 30 journals and the proceedings of major conferences;
- (4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

We did not apply any language restrictions.

## METHODS OF THE REVIEW

Two review authors assessed the trials for eligibility and methodological quality without consideration of the results. Reasons for excluding any trial are detailed in the 'Characteristics

of excluded studies' table. Trials were not assessed blind, as we knew the author's name, institution and the source of publication. We resolved any disagreement until we reached consensus. Two review authors extracted the data, checked them for discrepancies and processed them as described in Higgins 2005a. We contacted authors of each included trial for further information, if we thought this to be necessary.

For each included trial, we assessed allocation concealment using the criteria described in Section six of the Cochrane Reviewers' Handbook (Higgins 2005b): adequate (A), unclear (B), inadequate (C), not used (D). We did not use studies rated D. We collected information about blinding, and the extent to which all randomised women and their babies were accounted for. Completeness of follow up was assessed as follows: less than 5% participants excluded (A), 5% to 9.9% participants excluded (B), 10% to 19.9% excluded (C), 20% or more excluded (D), unclear (E). We excluded studies rated D. We analysed outcomes on an intention-to-treat basis. For this update, previously included studies were scrutinized again and two review authors extracted the data. We resolved discrepancies by discussion. We performed statistical analysis using the Review Manager software (RevMan 2000). In the original review, a weighted estimate of the typical treatment effect across studies was performed using the 'Peto method' (i.e. 'the typical odds ratio': the odds of an unfavourable outcome among treatment-allocated participants to the corresponding odds among controls). For this update, we have calculated relative risks and 95% confidence intervals for dichotomous data. Although odds ratios have been commonly used in meta-analysis, there is potential for them to be interpreted incorrectly and current advice is that relative risks should be used wherever possible (Higgins 2005a).

We limited primary analysis to prespecified outcomes. We performed subgroup analysis for the prespecified groups. We did not undertake any data-driven post hoc analyses. However, as the review progressed, it became apparent that gestational age at entry may be a useful category in which to study the primary outcomes. Post hoc subgroup analysis was performed for gestational at entry to trial (less than 26 weeks, between 26 and 29 + 6 weeks, between 30 and 32 + 6 weeks, between 33 and 34 + 6 weeks, between 35 and 36 + 6 weeks, greater than 36 weeks).

We also found that some trials included in this review had a protocol of weekly repeat doses of corticosteroid if the mother remained undelivered. None of the trials that allowed weekly repeat doses reported outcomes separately for those exposed to repeat doses. We performed a post hoc analysis for primary outcomes of trials where a single course was used versus those where weekly repeat doses were allowed in the protocol, to determine if the inclusion of such trials biased our results. Single versus multiple doses of corticosteroids is the subject of another review (Crowther 2000). The analysis in this update will differ from that of the single versus multiple doses review, as the latter review includes

only those studies where the women were randomised to either single or multiple doses.

We calculated heterogeneity between trial results using an  $I^2$  test. In multiple pregnancies, the number of babies was used as the denominator for fetal and neonatal outcomes.

## DESCRIPTION OF STUDIES

Twenty-one studies met our inclusion criteria, with data available for 3885 women and 4269 infants (*see* 'Characteristics of included studies' table). Six new studies have been included since the previous review involving 802 women and 819 infants (Amorim 1999; Dexiprom 1999; Fekih 2002; Lewis 1996; Nelson 1985; Qublan 2001).

Six of the included studies used dexamethasone as the corticosteroid in the treatment arm (1391 women and 1514 infants), while 14 studies used betamethasone (2476 women and 2737 infants) and one study did not specify the corticosteroid used (Cararach 1991; 18 women and infants).

The included studies were conducted over a wide range of gestational ages, including those of extreme prematurity; obstetric indications for recruitment were premature rupture of membranes, spontaneous preterm labour and planned preterm delivery.

The included studies came from a range of healthcare systems and treatment eras. Ten of the studies were conducted in the USA, with two studies conducted in Finland and one study from each of the following countries; Brazil, Spain, South Africa, Canada, Tunisia, UK, New Zealand, Jordan, and The Netherlands. Six of the included studies completed recruitment mainly in the 1970s (1753 women and 1994 infants), six of the included studies completed recruitment mainly in the 1980s (1100 women and 1173 infants), and nine of the included studies completed recruitment mainly in the 1990s (1032 women and 1102 infants).

## METHODOLOGICAL QUALITY

The methods of randomisation used in the included studies are summarised in the 'Characteristics of included studies' table. Eight studies used computer-generated or random number-generated randomisation sequences with either coded drug boxes/vials or sealed envelopes used in order to conceal the randomisation sequence or study treatment. These studies were coded A for allocation concealment. Twelve studies either did not state the method of randomisation, or it was unclear, or the method of allocation concealment was not stated, or unclear, and no further information was available from the authors. These studies were coded B for allocation concealment. In the remaining study (Collaborative 1984), a major potential for bias was introduced by attaching a sealed envelope containing the trial allocation to the coded drug

boxes supplied to the study centres. This was to be opened "only in an emergency". There was no information available in the study manuscripts or from the authors as to how many times this envelope was opened. Thus this study was given C, inadequate, for allocation concealment. Performance bias is unlikely to have occurred in the studies included in this review but if it did it was most likely to have occurred in those where allocation concealment was inadequate.

Thirteen of the included studies were placebo controlled (3255 women and 3626 infants), with the majority of these studies using normal saline, or the vehicle of the corticosteroid preparation, as the placebo. The remainder of the included studies used expectant management in the control arm.

Eight of the included studies allowed weekly repeat courses of study medication in their study protocols (821 women and 848 infants). These studies were included in the review. As stated above, separate analysis of primary outcomes for those studies allowing a single course of study medication and those studies allowing weekly repeat courses of study medication was conducted post hoc.

In only six studies was evidence available to suggest that sample-size calculations had been performed prospectively (Amorim 1999; Collaborative 1981; Dexiprom 1999; Kari 1994; Silver 1996; Tausch 1979). Intention-to-treat analysis was possible from study data in only nine of the studies included in the review (Cararach 1991; Doran 1980; Gamsu 1989; Kari 1994; Liggins 1972b; Nelson 1985; Parsons 1988; Qublan 2001; Teramo 1980). However, in the remaining studies losses to follow up were generally small and less than 5%. There is no evidence to suggest that these exclusions occurred preferentially in one arm or the other of the studies. The four studies (Collaborative 1981; Kari 1994; Liggins 1972b; Schutte 1980) that reported long-term follow up after the neonatal period had their follow-up data included regardless of the follow-up rate unless there was evidence of bias in follow-up rates between the treatment and control groups; this was not found to be the case.

Three studies that were included in the previous review have been excluded from this update. Two (Papageorgiou 1979; Schmidt 1984) were excluded because of greater than 20% postrandomisation exclusions. The third (Morales 1986) was excluded as it was quasi-randomised.

## RESULTS

Twenty-one studies involving 3885 women and 4269 infants were included.

### 1. Antenatal corticosteroids versus placebo or no treatment (all included studies)

#### *Primary outcomes*

Data were not available for all primary outcomes from all included studies.

#### *For the mother*

No statistically significant differences were seen for maternal death (relative risk (RR) 0.98, 95% confidence interval (CI) 0.06 to 15.50, three studies, 365 women), chorioamnionitis (RR 0.91, 95% CI 0.70 to 1.18, 12 studies, 2485 women) or puerperal sepsis (RR 1.35, 95% CI 0.93 to 1.95, eight studies, 1003 women).

#### *For the fetus or neonate*

Treatment with antenatal corticosteroids was associated with an overall reduction in combined fetal and neonatal death (RR 0.77, 95% CI 0.67 to 0.89, 13 studies, 3627 infants). This reduction is mainly due to a reduction in neonatal death (RR 0.69, 95% CI 0.58 to 0.81, 18 studies, 3956 infants), rather than fetal death (RR 0.98, 95% CI 0.73 to 1.30, 13 studies, 3627 infants). Treatment with antenatal corticosteroids was also associated with an overall reduction in respiratory distress syndrome (RDS) (RR 0.66, 95% CI 0.59 to 0.73, 21 studies, 4038 infants), moderate to severe RDS (RR 0.55, 95% CI 0.43 to 0.71, six studies, 1686 infants), cerebroventricular haemorrhage (RR 0.54, 95% CI 0.43 to 0.69, 13 studies, 2872 infants) and severe cerebroventricular haemorrhage (RR 0.28, 95% CI 0.16 to 0.50, five studies, 572 infants). The reduction in intraventricular haemorrhage was seen both in cases diagnosed at autopsy (RR 0.48, 95% CI 0.29 to 0.79, five studies, 1846 infants) and by ultrasound (RR 0.58, 95% CI 0.44 to 0.77, seven studies, 889 infants). No statistically significant differences between those exposed to antenatal corticosteroids and controls were seen for chronic lung disease (RR 0.86, 95% CI 0.61 to 1.22, six studies, 818 infants) or birthweight (fixed weighted mean difference (FWMD) -17.48 grams, 95% CI -62.08 to 27.13 grams, 11 studies, 3586 infants).

#### *For the child*

No statistically significant differences were seen for death in childhood (RR 0.68, 95% CI 0.36 to 1.27, four studies, 1010 children) or neurodevelopmental delay (RR 0.64, 95% CI 0.14 to 2.98, one study, 82 children).

#### *For the child as adult*

No statistically significant difference was seen for death into adulthood (RR 1.00, 95% CI 0.56 to 1.81, one study, 988 adults). No data were available for neurodevelopmental delay in adulthood.

#### **Secondary outcomes**

Data were available for several of the secondary outcomes that relate to the mother, fetus or neonate, child, adult and health services.

#### *For the mother*

One study (Amorim 1999) reported that women in the corticosteroid arm were more likely to have glucose intolerance than in the control arm (RR 2.71, 95% CI 1.14 to 6.46, one study, 123 women). This study used a treatment regimen that included weekly repeat doses of corticosteroids if the infant remained un-

delivered. No statistically significant differences between those treated with antenatal corticosteroids and controls were seen for fever after trial entry requiring the use of antibiotics (RR 1.11, 95% CI 0.74 to 1.67, four studies, 481 women), intrapartum fever requiring the use of antibiotics (RR 0.60, 95% CI 0.15 to 2.49, two studies, 319 women), postnatal fever (RR 0.92, 95% CI 0.64 to 1.33, five studies, 1323 women), admission to adult intensive care unit (RR 0.74, 95% CI 0.26 to 2.05, two studies, 319 women), hypertension (RR 1.00, 95% CI 0.36 to 2.76, one study, 220 women) or reported side-effects of treatment (no events reported in 101 women).

#### *For the fetus or neonate*

Treatment with antenatal corticosteroids was associated with a reduction in the incidence of necrotising enterocolitis (RR 0.46, 95% CI 0.29 to 0.74, eight studies, 1675 infants). Treatment with antenatal corticosteroids was also associated with fewer infants having systemic infection in the first 48 hours after birth (RR 0.56, 95% CI 0.38 to 0.85, five studies, 1319 infants) and a trend towards fewer infants having proven infection while in the neonatal intensive care unit (NICU) (RR 0.83, 95% CI 0.66 to 1.03, 11 studies, 2607 infants). Furthermore, treatment with antenatal corticosteroids was associated with less need for neonatal respiratory support; with a reduction in the need for mechanical ventilation/continuous positive airways pressure (CPAP) (RR 0.69, 95% CI 0.53 to 0.90, four studies, 569 infants), less time requiring mechanical ventilation/CPAP (FWMD -3.47 days, 95% CI -5.08 to -1.86 days, two studies, 198 infants) less time requiring oxygen supplementation (FWMD -2.86 days, 95% CI -5.51 to -0.21 days, one study, 73 infants) and a trend towards a reduction in the need for surfactant (RR 0.72, 95% CI 0.51 to 1.03, three studies, 456 infants). No statistically significant differences between those exposed to antenatal corticosteroids and controls were seen for air leak syndrome (RR 0.69, 95% CI 0.19 to 2.47, one study, 138 infants), Apgar scores less than seven at five minutes (RR 0.85, 95% CI 0.70 to 1.03, six studies, 1712 infants), interval between trial entry and delivery (FWMD 0.23 days, 95% CI -1.86 to 2.32 days, three studies, 1513 infants), incidence of small-for-gestational age infants (RR 0.96, 95% CI 0.63 to 1.44, three studies, 378 infants) or hypothalamo-pituitary-adrenal (HPA) axis function (cortisol FWMD 3.94, 95% CI -3.12 to 11.00 days, one study, 27 infants). Overall, treatment with antenatal corticosteroids was associated with fewer infants being admitted into a NICU (RR 0.80, 95% CI 0.65 to 0.99, two studies, 277 infants).

#### *For the child*

Treatment with corticosteroids was associated with less developmental delay in childhood (RR 0.49, 95% CI 0.24 to 1.00, two studies, 518 children, age at follow up three years in one study and unknown in one study) and a trend towards fewer children having cerebral palsy (RR 0.60, 95% CI 0.34 to 1.03, five studies, 904 children, age at follow up two to six years in four studies, and unknown in one study). No statistically significant differences between those exposed to antenatal corticosteroids and

controls were seen for childhood weight (FWMD 0.30 kg, 95% CI -0.39 to 1.00 kg, two studies, 333 children), height (FWMD 1.02 cm, 95% CI -0.26 to 2.29 cm, two studies, 334 children), head circumference (FWMD 0.27 cm, 95% CI -0.08 to 0.63 cm, two studies, 328 children), lung function (vital capacity FWMD -1.68 % predicted, 95% CI -5.12 to 1.75 % predicted, two studies, 150 children), systolic blood pressure (FWMD -1.60 mmHg, 95% CI -4.06 to 0.86 mmHg, one study, 223 children), visual impairment (RR 0.55, 95% CI 0.24 to 1.23, two studies, 166 children), hearing impairment (RR 0.64, 95% CI 0.04 to 9.87, two studies, 166 children), behavioural/learning difficulties (RR 0.86, 95% CI 0.35 to 2.09, one study, 90 children) or intellectual impairment (RR 0.86, 95% CI 0.44 to 1.69, three studies, 778 children).

#### *For the child as adult*

One study (Liggins 1972b) showed increased insulin release 30 minutes following a fasting 75 g oral glucose tolerance test (FWMD 0.16 log insulin units, 95% CI 0.04 to 0.28 log insulin units, one study, 412 adults) in 30 year olds who had been exposed to antenatal corticosteroid. However, the study reported no difference between those exposed to antenatal corticosteroids and controls in the prevalence of diabetes. No statistically significant differences between those exposed to antenatal corticosteroids and controls were seen for weight (FWMD 0.80 kg, 95% CI -2.02 to 3.62 kg, two studies, 538 adults), height (FWMD 0.91 cm, 95% CI -0.28 to 2.10 cm, two studies, 537 adults), head circumference (FWMD 0.03 cm, 95% CI -0.33 to 0.38 cm, two studies, 537 adults), skinfold thickness (triceps FWMD -0.02 log units, 95% CI -0.11 to 0.07 log units, one study, 456 adults), systolic blood pressure (FWMD -0.87 mmHg, 95% CI -2.81 to 1.07 mmHg, two studies, 545 adults), HPA axis function (Cortisol FWMD 0.06 log units, 95% CI -0.02 to 0.14 log units, one study, 444 adults), cholesterol (FWMD -0.11 mmol/L, 95% CI -0.28 to 0.06 mmol/L, one study, 445 adults), age at puberty (FWMD for females 0 years, 95% CI -0.94 to 0.94 years, one study, 38 adults), educational attainment (RR 0.94, 95% CI 0.80 to 1.10, one study, 534 adults), visual impairment (RR 0.91, 95% CI 0.53 to 1.55, one study, 192 adults), hearing impairment (RR 0.24, 95% CI 0.03 to 2.03, one study, 192 adults) or intellectual impairment (RR 0.24, 95% CI 0.01 to 4.95, two studies, 273 adults).

#### *For the health services*

No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for length of antenatal hospitalisation for women (FWMD 0.50 days, 95% CI -1.40 to 2.40 days, one study, 218 women), postnatal hospitalisation for women (FWMD 0.00 days, 95% CI -1.72 to 1.72 days, one study, 218 women) or neonatal hospitalisation for infants (FWMD 0.78 days, 95% CI -2.43 to 3.99 days, three studies, 321 infants).

## **2. Subgroup analysis**

### ***Antenatal corticosteroids versus placebo or no treatment (by single or multiple pregnancy)***

Data were available for several of the primary outcomes that relate to the mother and fetus or neonate for pregnancies complicated by multiple birth. However most of these were from just two studies (Collaborative 1981; Liggins 1972b). No statistically significant differences between groups treated with antenatal corticosteroids (in women with multiple pregnancies) and controls were seen for chorioamnionitis (RR 0.48, 95% CI 0.04 to 4.49, one study, 74 women), fetal death (RR 0.53, 95% CI 0.20 to 1.40, two studies, 252 infants), neonatal death (RR 0.79, 95% CI 0.39 to 1.61, two studies, 236 infants), RDS (RR 0.85, 95% CI 0.60 to 1.20, four studies, 320 infants), cerebroventricular haemorrhage (RR 0.39, 95% CI 0.07 to 2.06, one study, 137 infants) or birthweight (FWMD 82.36 grams, 95% CI -146.23 to 310.95 grams, one study, 150 infants), although the RRs were similar to those in the overall analysis, though small numbers meant the confidence intervals were wide and crossed one.

### ***Antenatal corticosteroids versus placebo or no treatment (by gestational age at delivery)***

Data were available by gestational age at delivery for several of the primary outcomes that relate to the mother and fetus or neonate. Combined fetal and neonatal death was significantly reduced in corticosteroid treated infants born before 32 weeks (RR 0.71, 95% CI 0.57 to 0.88, three studies, 453 infants), before 34 weeks (RR 0.73, 95% CI 0.58 to 0.91, one study, 598 infants) and before 36 weeks (RR 0.75, 95% CI 0.61 to 0.94, two studies, 969 infants), but not in those born before 28 weeks (RR 0.81, 95% CI 0.65 to 1.01, two studies, 129 infants), before 30 weeks (RR 0.86, 95% CI 0.70 to 1.05, one study, 201 infants) and at a gestation of at least 34 weeks (RR 1.13, 95% CI 0.66 to 1.96, one study, 770 infants). In infants born at a gestation of at least 36 weeks, there was a non-significant trend towards an increase in combined fetal and neonatal death (RR 3.25, 95% CI 0.99 to 10.66, two studies, 498 infants). Neonatal death was significantly reduced in corticosteroid treated infants born before 32 weeks (RR 0.59, 95% CI 0.43 to 0.80, three studies, 378 infants), before 34 weeks (RR 0.69, 95% CI 0.52 to 0.92, two studies, 715 infants) and before 36 weeks (RR 0.68, 95% CI 0.50 to 0.92, two studies, 869 infants), but not in those born before 28 weeks (RR 0.79, 95% CI 0.56 to 1.12, two studies, 89 infants), before 30 weeks (RR 0.82, 95% CI 0.60 to 1.11, one study, 150 infants), at a gestation of at least 34 weeks (RR 1.58, 95% CI 0.71 to 3.50, two studies, 808 infants), and at a gestation of at least 36 weeks (RR 2.62, 95% CI 0.77 to 8.96, three studies, 514 infants).

RDS was significantly reduced in corticosteroid treated infants born before 30 weeks (RR 0.67, 95% CI 0.52 to 0.87, four studies, 218 infants), before 32 weeks (RR 0.56, 95% CI 0.45 to 0.71, six studies, 583 infants), before 34 weeks (RR 0.58, 95% CI 0.47 to 0.72, five studies, 1177 infants) and before 36 weeks (RR 0.54, 95% CI 0.41 to 0.72, three studies, 922 infants), but not in those born before 28 weeks (RR 0.79, 95% CI 0.53 to 1.18, four studies, 102 infants), at a gestation of at least 34 weeks (RR 0.66, 95% CI 0.38 to 1.16, five studies, 1261 infants) and at a gestation of

at least 36 weeks (RR 0.30, 95% CI 0.03 to 2.67, five studies, 557 infants). Cerebroventricular haemorrhage was significantly reduced in corticosteroid treated infants born before 28 weeks (RR 0.34, 95% CI 0.14 to 0.86, one study, 62 infants), before 32 weeks (RR 0.52, 95% CI 0.28 to 0.99, one study, 277 infants) and before 34 weeks (RR 0.53, 95% CI 0.29 to 0.95, one study, 515 infants), but not in those born before 30 weeks (RR 0.56, 95% CI 0.29 to 1.10, one study, 150 infants), before 36 weeks (RR 0.56, 95% CI 0.31 to 1.02, one study, 102 infants), at a gestation of at least 34 weeks (RR 1.13, 95% CI 0.07 to 17.92, one study, 746 infants) and at a gestation of at least 36 weeks (no events reported in 459 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for fetal deaths, birthweight or chorioamnionitis in the different subgroups of gestational age at delivery examined.

#### ***Antenatal corticosteroids versus placebo or no treatment (by entry to delivery interval)***

Data were available by entry to delivery interval for several of the primary outcomes that relate to the mother and fetus/neonate. Combined fetal and neonatal death was significantly reduced in corticosteroid treated infants born before 24 hours (RR 0.60, 95% CI 0.39 to 0.94, three studies, 293 infants) and before 48 hours after the first dose (RR 0.59, 95% CI 0.41 to 0.86, one study, 373 infants), but not those born between one and seven days (RR 0.81, 95% CI 0.60 to 1.09, three studies, 606 infants) and after seven days after the first dose (RR 1.42, 95% CI 0.91 to 2.23, three studies, 598 infants). Neonatal death was significantly reduced in corticosteroid treated infants born before 24 hours (RR 0.53, 95% CI 0.29 to 0.96, four studies, 295 infants) and before 48 hours after the first dose (RR 0.49, 95% CI 0.30 to 0.81, one study, 339 infants), but not those born between one and seven days (RR 0.74, 95% CI 0.51 to 1.07, three studies, 563 infants) and after seven days after the first dose (RR 1.45, 95% CI 0.75 to 2.80, three studies, 561 infants). RDS was significantly reduced in corticosteroid-treated infants born before 48 hours (RR 0.63, 95% CI 0.43 to 0.93, three studies, 374 infants) and between one and seven days after the first dose (RR 0.46, 95% CI 0.35 to 0.60, nine studies, 1110 infants), but not those born before 24 hours (RR 0.87, 95% CI 0.66 to 1.15, nine studies, 517 infants) and after seven days after the first dose (RR 0.82, 95% CI 0.53 to 1.28, eight studies, 988 infants). Cerebroventricular haemorrhage was significantly reduced in corticosteroid treated infants born before 48 hours after the first dose (RR 0.26, 95% CI 0.09 to 0.75, one study, 339 infants), but those born not before 24 hours (RR 0.54, 95% CI 0.21 to 1.36, three studies, 264 infants), between one and seven days (RR 0.51, 95% CI 0.23 to 1.13, one study, 482 infants) and after seven days after the first dose (RR 2.01, 95% CI 0.37 to 10.86, one study, 453 infants). Birthweight was significantly reduced in infants born between one and seven days (FWMD -105.92 grams, 95% CI -212.52 to 0.68 grams, one study, 520 infants) and more than seven days after the first dose (FWMD -147.01 grams, 95% CI -291.97 to -2.05 grams, one

study, 485 infants), but not those born before 24 hours (FWMD 46.52 grams, 95% CI -94.26 to 187.29 grams, two studies, 242 infants) and before 48 hours after the first dose (FWMD -5.90 grams, 95% CI -131.95 to 120.15 grams, one study, 373 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for fetal deaths or chorioamnionitis in the different subgroups of entry to delivery interval examined.

#### ***Antenatal corticosteroids versus placebo or no treatment (by presence or absence of ruptured membranes)***

Data were available by status of ruptured membranes for several of the primary and secondary outcomes that relate to the mother and fetus or neonate. No statistically significant differences were seen for maternal death, chorioamnionitis or puerperal sepsis in mothers with rupture of membranes present at the time of first dose or with rupture of membranes for greater than 24 hours. Combined fetal and neonatal death was significantly reduced in corticosteroid treated infants born following rupture of membranes present at time of first dose (RR 0.62, 95% CI 0.46 to 0.82, four studies, 733 infants), but not following rupture of membranes for greater than 24 (RR 0.77, 95% CI 0.51 to 1.17, two studies, 508 infants) and greater than 48 hours (RR 0.93, 95% CI 0.57 to 1.51, one study, 255 infants). No statistically significant differences between groups exposed to antenatal corticosteroids and controls were seen for fetal deaths following rupture of membranes at first dose (RR 0.86, 95% CI 0.46 to 1.61, five studies, 790 infants), for greater than 24 (RR 1.23, 95% CI 0.62 to 2.44, two studies, 508 infants) or greater than 48 hours (RR 1.10, 95% CI 0.52 to 2.32, one study, 255 infants). The reduction in combined fetal and neonatal death is due to a reduction in neonatal death in corticosteroid-treated infants born following rupture of membranes present at time of first dose (RR 0.58, 95% CI 0.43 to 0.80, seven studies, 984 infants). RDS was significantly reduced in corticosteroid treated infants born following rupture of membranes present at first dose (RR 0.67, 95% CI 0.55 to 0.82, 11 studies, 1089 infants) and for greater than 24 hours (RR 0.68, 95% CI 0.51 to 0.90, six studies, 626 infants), but not following rupture of membranes for greater than 48 hours (RR 0.71, 95% CI 0.36 to 1.41, two studies, 247 infants). Cerebroventricular haemorrhage was significantly reduced in corticosteroid treated infants born following rupture of membranes present at time of first dose (RR 0.47, 95% CI 0.28 to 0.79, five studies, 895 infants), but not following rupture of membranes for greater than 24 (RR 0.55, 95% CI 0.16 to 1.84, two studies, 477 infants) and greater than 48 hours (RR 0.87, 95% CI 0.18 to 4.22, one study, 230 infants). Birthweight was significantly reduced in corticosteroid treated infants born following rupture of membranes for greater than 24 (FWMD -196.46 grams, 95% CI -335.19 to -57.73 grams, 1 study, 349 infants) and for greater than 48 hours (FWMD -201.79 grams, 95% CI -363.30 to -40.28 grams, one study, 255 infants), but not following prolonged rupture of membranes present at the time of the first dose (FWMD -42.68 grams, 95% CI -108.91 to 23.55

grams, five studies, 835 infants).

No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for postnatal fever (RR 1.00, 95% CI 0.36 to 2.75, one study, 204 women) or fever after trial entry requiring the use of antibiotics (RR 0.25, 95% CI 0.03 to 2.06, one study, 44 women) in women with prolonged rupture of membranes at first dose. Infants whose mothers were treated with corticosteroids following rupture of membranes present at the time of the first dose had significantly reduced chronic lung disease (RR 0.50, 95% CI 0.33 to 0.76, one study, 165 infants), necrotising enterocolitis (RR 0.39, 95% CI 0.18 to 0.86, four studies, 583 infants) and duration of mechanical ventilation or CPAP (FWMD -3.50 days, 95% CI -5.12 to -1.88 grams, one study, 165 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for neonatal infection (RR 1.26, 95% CI 0.86 to 1.85, seven studies, 796 infants), systemic infection in the first 48 hours of life (RR 0.96, 95% CI 0.44 to 2.12, two studies, 249 infants) or need for mechanical ventilation or CPAP (RR 0.90, 95% CI 0.47 to 1.73, one study, 206 infants) in infants following prolonged rupture of membranes at first dose.

#### ***Antenatal corticosteroids versus placebo or no treatment (by the presence or absence of hypertension syndromes in pregnancy)***

Data were available by presence or absence of hypertension syndromes in pregnancy for several of the primary outcomes that relate to the mother and fetus/neonate. Infants born to pregnancies complicated by hypertension syndromes treated with corticosteroids had significantly reduced risk of neonatal death (RR 0.50, 95% CI 0.29 to 0.87, two studies, 278 infants), RDS (RR 0.50, 95% CI 0.35 to 0.72, five studies, 382 infants) and cerebroventricular haemorrhage (RR 0.38, 95% CI 0.17 to 0.87, two studies, 278 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for combined fetal and neonatal death (RR 0.83, 95% CI 0.57 to 1.20, two studies, 313 infants), fetal death (RR 1.73, 95% CI 0.91 to 3.28, three studies, 331 infants), birthweight (FWMD -131.72 grams, 95% CI -319.68 to 56.24 grams, one study, 95 infants), chorioamnionitis (RR 2.36, 95% CI 0.36 to 15.73, two studies, 311 women) or puerperal sepsis (RR 0.68, 95% CI 0.30 to 1.52, one study, 218 women) in pregnancies complicated by hypertension syndromes.

#### ***Antenatal corticosteroids versus placebo or no treatment (by type of corticosteroid)***

Data were available by type of corticosteroid used for several of the primary outcomes that relate to the mother and fetus or neonate. Both dexamethasone and betamethasone significantly reduced combined fetal and neonatal death, neonatal death, RDS and cerebroventricular haemorrhage. Betamethasone treatment (RR 0.56, 95% CI 0.48 to 0.65, 14 studies, 2563 infants) resulted in a greater reduction in RDS than dexamethasone treatment (RR 0.80, 95% CI 0.68 to 0.93, six studies, 1457 infants). No statistically sig-

nificant differences between groups treated with antenatal corticosteroids and controls in fetal death, birthweight or chorioamnionitis were seen in subgroups treated with dexamethasone or betamethasone separately. However, dexamethasone significantly increased the incidence of puerperal sepsis (RR 1.74, 95% CI 1.04 to 2.89, four studies, 536 women) while betamethasone did not (RR 1.00, 95% CI 0.58 to 1.72, four studies, 467 women).

#### ***Antenatal corticosteroids versus placebo or no treatment (by decade of recruitment to study)***

Data were available by decade of recruitment for several of the primary outcomes that relate to the mother and fetus or neonate. RDS (1970s RR 0.55, 95% CI 0.43 to 0.70, six studies, 1847 infants; 1980s RR 0.71, 95% CI 0.58 to 0.87, six studies, 1127 infants; 1990s RR 0.69, 95% CI 0.59 to 0.81, nine studies, 1064 infants) and cerebroventricular haemorrhage (1970s RR 0.50, 95% CI 0.29 to 0.85, four studies, 1646 infants; 1980s RR 0.61, 95% CI 0.39 to 0.94, two studies, 238 infants; 1990s RR 0.53, 95% CI 0.38 to 0.74, seven studies, 988 infants) were significantly reduced in infants treated with corticosteroids in all three decades of recruitment. Combined fetal and neonatal death, and neonatal death alone (1970s RR 0.73, 95% CI 0.56 to 0.93, six studies, 1876 infants; 1980s RR 0.98, 95% CI 0.69 to 1.40, five studies, 1056 infants; 1990s RR 0.50, 95% CI 0.38 to 0.66, seven studies, 1024 infants), were significantly reduced in infants treated with corticosteroids in the 1970s and 1990s, but not the 1980s. No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for fetal death, birthweight, puerperal sepsis or chorioamnionitis for any of the individual decades of recruitment subgroups.

### **3. Post hoc analysis**

#### ***Antenatal corticosteroids versus placebo or no treatment (by gestational age at entry to trial)***

Data were available by gestational age at entry for several of the primary outcomes that relate to the mother and fetus or neonate. Chorioamnionitis was significantly reduced in corticosteroid-treated women entering a trial from 30 to 32 + 6 weeks (RR 0.19, 95% CI 0.04 to 0.86, one study, 194 women), but not from less than 26 weeks (RR 2.18, 95% CI 0.62 to 7.69, one study, 46 women), 26 to 29 + 6 weeks (RR 1.06, 95% CI 0.55 to 2.06, one study, 242 women), 33 to 34 + 6 weeks (RR 0.47, 95% CI 0.12 to 1.80, one study, 333 women), 35 to 36 + 6 weeks (RR 0.18, 95% CI 0.01 to 3.36, one study, 181 women) and greater than 36 weeks (no events in 40 women). Neonatal death was significantly reduced in corticosteroid treated infants entering a trial from 26 to 29 + 6 weeks (RR 0.67, 95% CI 0.45 to 0.99, one study, 227 infants), but not from less than 26 weeks (RR 1.87, 95% CI 0.61 to 5.72, one study, 27 infants), 30 to 32 + 6 weeks (RR 0.51, 95% CI 0.23 to 1.11, one study, 195 infants), 33 to 34 + 6 weeks (RR 1.11, 95% CI 0.49 to 2.48, one study, 339 infants), 35 to 36 + 6 weeks (RR 0.62, 95% CI 0.06 to 6.76, one study, 191 infants) and greater than 36 weeks (RR 9.21, 95% CI 0.51 to 167.82, one study, 42 infants). RDS was significantly reduced

in corticosteroid-treated infants entering a trial from 26 to 29 + 6 weeks (RR 0.49, 95% CI 0.34 to 0.72, two studies, 242 infants), 30 to 32 + 6 weeks (RR 0.56, 95% CI 0.36 to 0.87, two studies, 361 infants) and 33 to 34 + 6 weeks (RR 0.53, 95% CI 0.31 to 0.91, two studies, 434 infants), but not from less than 26 weeks (RR 2.86, 95% CI 0.37 to 21.87, one study, 24 infants), 35 to 36 + 6 weeks (RR 0.61, 95% CI 0.11 to 3.26, one study, 189 infants) and less than 36 weeks. Cerebroventricular haemorrhage was significantly reduced in corticosteroid-treated infants entering a trial from 26 to 29 + 6 weeks (RR 0.45, 95% CI 0.21 to 0.95, one study, 227 infants), but not from less than 26 weeks (RR 1.20, 95% CI 0.24 to 6.06, one study, 27 infants), 30 to 32 + 6 weeks (RR 0.23, 95% CI 0.03 to 2.00, one study, 295 infants), 33 to 34 + 6 weeks (RR 1.11, 95% CI 0.23 to 5.40, one study, 339 infants), 35 to 36 + 6 weeks (no events in 191 infants) and greater than 36 weeks (no events in 42 infants). Birthweight was significantly decreased in infants entering a trial from 30 to 32 + 6 weeks (FWMD -190.64 grams, 95% CI -359.98 to -21.30 grams, one study, 319 infants), but not from less than 26 weeks (FWMD 63.14 grams, 95% CI -607.37 to 733.65 grams, one study, 49 infants), 26 to 29 + 6 weeks (FWMD 26.41 grams, 95% CI -215.55 to 268.37 grams, one study, 261 infants), 33 to 34 + 6 weeks (FWMD -38.72 grams, 95% CI -172.29 to 94.85 grams, one study, 353 infants), 35 to 36 + 6 weeks (FWMD -13.57 grams, 95% CI -175.45 to 148.31 grams, one study, 194 infants) and greater than 36 weeks (FWMD 73.89 grams, 95% CI -270.89 to 418.67 grams, one study, 42 infants). No statistically significant differences between groups treated with antenatal corticosteroids and controls were seen for combined fetal and neonatal deaths or fetal deaths alone in the different subgroups of gestational age at trial entry examined.

***Antenatal corticosteroids versus placebo or no treatment (by presence or absence in protocol of weekly repeat doses of corticosteroid)***

Data were available by the presence or absence in the protocol of weekly repeat doses of corticosteroid if the mother remained undelivered for several of the primary outcomes that relate to the mother and fetus/neonate. There was no difference in effect of corticosteroid treatment on chorioamnionitis, puerperal sepsis, combined fetal and neonatal death, fetal death, neonatal death, RDS or cerebroventricular haemorrhage between studies which used a single course of antenatal corticosteroid and studies that allowed weekly repeats if the women remained undelivered.

## DISCUSSION

The results of the 21 studies included in this updated review categorically support the conclusion of the previous review (Crowley 1996), that treatment with antenatal corticosteroids reduces neonatal death, respiratory distress syndrome (RDS), and cerebroventricular haemorrhage in preterm infants. Furthermore,

treatment with antenatal corticosteroids is not associated with changes in the rates of maternal death, maternal infection, fetal death, neonatal chronic lung disease or birthweight. Treatment with antenatal corticosteroids is also associated with a reduction in the incidence of neonatal necrotising enterocolitis and systemic infections in the first 48 hours of life, as well as a reduction in the need for respiratory support or neonatal intensive care unit admission. However, one trial (Amorim 1999) recruiting women with severe preeclampsia, using a protocol that included repeat weekly courses of antenatal betamethasone if the women remained undelivered, suggested that the treated women were at increased risk of gestational diabetes. The women in this trial had a fasting glucose tolerance test more than 72 hours after the initiation of the study treatment if they were undelivered; 123 (56%) women under went the glucose tolerance test. It may not be appropriate to generalise this to women without pre-eclampsia. It is also difficult to determine whether the fact that the protocol in this study used weekly repeat courses of antenatal corticosteroids was of relevance to the outcome.

Concern has been expressed as to whether antenatal corticosteroids are beneficial in the current era of advanced neonatal practice, on the basis that previous conclusions concerning their benefits were based mainly on data from the 1970s. This update shows that combined fetal and neonatal death, neonatal death, RDS and cerebroventricular haemorrhage are all significantly reduced in the subgroup of trials conducted in the 1990s. These trials contributed 26% of the overall data to the review. This supports the continued use of antenatal corticosteroids.

The gestational age range at which antenatal corticosteroids provide benefit has been subject to debate, with some reviews suggesting no benefit at less than 28 weeks (Crowley 1996). Previously the effect of antenatal corticosteroids has been examined by subgroups based on gestational age at delivery. This review shows that antenatal corticosteroids reduce the incidence of cerebroventricular haemorrhage even in those infants born before 28 weeks. However, this review also examined outcomes by subgroups based on the clinically more relevant measure; gestational age at first dose of treatment (gestational age at trial entry). RDS is reduced when corticosteroids are first given at 26 to 29.9 weeks, 30 to 32.9 weeks and 33 to 34.9 weeks. Furthermore, both cerebroventricular haemorrhage and neonatal death are reduced at 26 to 29.9 weeks. No difference is shown for primary outcomes at gestational ages of less than 26 weeks. While eight trials included in this review recruited pregnancies from less than 26 weeks' gestation, and a further three did not specify the lower gestational age for entry, only one trial (n = 49 infants) contributed data to this review at this extreme gestation.

Antenatal corticosteroid use reduces neonatal death even when infants are born less than 24 hours after the first dose has been given. Reduction in RDS is seen in infants born up to seven days after the first dose. This review has not shown any benefit in pri-

mary outcomes for infants delivered greater than seven days after treatment with antenatal corticosteroids. In fact, birthweight is reduced in this subgroup. This lack of benefit is not a new finding, and in the past has led to the practice of repeating courses of antenatal corticosteroid weekly if women remained undelivered. Eight of the included studies in this review used treatment protocols that included repeated weekly courses. These studies were included in the review as they examined corticosteroid treatment versus no corticosteroid treatment, but they were analysed separately, post hoc, as a sensitivity analysis to determine if they biased the overall results. This does not appear to be the case. However, it would be misleading to draw conclusions from this subgroup analysis concerning the risks or benefits of repeat courses of antenatal corticosteroids. Information concerning the number of repeat courses used in individual studies was not provided and there may have been few repeat courses. It would be meaningful to perform an individual patient data analysis to look at the relationship between the interval from first dose to delivery and outcome, and how this was influenced by factors such as whether corticosteroids were given and how many doses each individual got. The effect of repeated courses of antenatal corticosteroids is the subject of a separate review (Crowther 2000), which suggests that although repeated courses reduce the severity of neonatal lung disease, there are insufficient data to exclude other beneficial or harmful effects to the mother or infant. The recommendation of those authors is to await the outcome of trials looking at the long-term effects of repeated courses of antenatal corticosteroids.

This review should dispel concerns about the use of antenatal corticosteroids in the subgroup of women with hypertension syndromes. In such women antenatal corticosteroids reduce the risk of neonatal death, RDS and cerebroventricular haemorrhage in their offspring. In the previous review, fetal death was increased amongst offspring of such women treated with antenatal corticosteroids. However, since this review, an additional study has contributed data (Amorim 1999). Furthermore, in this new review, individual participant data were available for the one study that had contributed to the previous result (Liggins 1972b). This study had never been completely analysed in full or by intention to treat. As it is responsible for approximately 30% of all women and infants randomised to corticosteroids, its inclusion in this new manner increases the validity of the review's conclusions. This new analysis of the Liggins study resulted in further cases of fetal death being assigned to women with hypertension syndromes in the control arm of the study.

In this new review, antenatal corticosteroids are shown to be beneficial in the subgroup of infants whose mothers have premature rupture of membranes. Neonatal death, RDS, cerebroventricular haemorrhage, necrotising enterocolitis and duration of neonatal respiratory support are all significantly reduced by corticosteroid treatment in this subgroup without an increase in either maternal or neonatal infection. Birthweight was not significantly altered by corticosteroid treatment in the five studies (Dexiprom 1999; Lewis

1996; Liggins 1972b; Nelson 1985; Morales 1989) that reported this outcome in the subgroup of women with premature rupture of membranes at time of the first glucocorticoid dose. However, in one study (Liggins 1972b) birthweight was reduced in those neonates exposed to corticosteroids who experienced rupture of membranes for greater than 24 or greater than 48 hours. The clinical significance of this finding remains unclear and it may reflect a type one error.

Currently, there is not enough evidence to support the use of antenatal corticosteroids in multiple pregnancies. Although data for most primary outcomes were available from the two largest studies (Collaborative 1981; Liggins 1972b) the numbers of multiple pregnancies included in this review remained small ( $n = 252$  infants). A further 10 studies (Dexiprom 1999; Doran 1980; Fekih 2002; Gamsu 1989; Garite 1992; Kari 1994; Schutte 1980; Silver 1996; Taeusch 1979; Teramo 1980) included in this review had recruited an additional 252 infants from multiple pregnancies. Analysis of these data may help clarify the risks and benefits of corticosteroids in multiple pregnancies without the need for further trials.

No randomised studies have directly compared the two common types of corticosteroid used in clinical practice, betamethasone and dexamethasone. Although this review suggests that betamethasone treatment causes a larger reduction in RDS than dexamethasone, the reasons for this may be a different background prevalence of RDS in the different study populations examined and not due to greater efficacy of the betamethasone. A large non-randomised retrospective study has suggested that infants exposed to antenatal betamethasone have less neonatal cystic periventricular leukomalacia (which is strongly associated with later cerebral palsy) than infants exposed to antenatal dexamethasone (Baud 1999). However there is no evidence from this review of a difference in incidence of later cerebral palsy in infants exposed to either antenatal betamethasone or dexamethasone. Further research is required to determine the optimal dose and drug for use in this situation.

We have included the results of the subgroup analyses in this update because we recognise that clinicians will want to see this information for its practical implications and also because it has been the subject of much conjecture following the first review. Caution, must however, be expressed in the interpretation of the subgroup analyses conducted in this review. There is the possibility of a type one error due to the number of analyses conducted. Furthermore, the subgroups of gestational age at delivery, length of premature rupture of membranes and entry to delivery interval, involve post-randomisation variables. Conducting subgroup analysis based on post-randomisation variables is liable to considerable bias as the variable on which the subgroup is based may be affected by the intervention that occurs at randomisation. The clinician should therefore not draw too many conclusions from the results of the subgroup analyses.

This updated review has included the results of four long-term, follow-up studies into childhood (Collaborative 1981; Kari 1994; Liggins 1972b; Schutte 1980) and two into adulthood (Liggins 1972b; Schutte 1980). Results suggest that antenatal corticosteroids result in less neurodevelopmental delay and possibly less cerebral palsy in childhood. This probably reflects the lower neurological and respiratory morbidity experienced by corticosteroid treated infants in the neonatal period. Concern regarding long-term neurological function has largely come from animal studies showing decreased brain growth after antenatal corticosteroid exposure (Huang 1999; Jobe 1998). However, follow up of two studies (Liggins 1972b; Schutte 1980), which only used a single course of antenatal corticosteroids, into adulthood, has failed to demonstrate any psychological differences between those exposed to antenatal corticosteroids and those exposed to placebo.

Exposure to excess corticosteroids before birth is hypothesised to be a key mechanism underlying the fetal origins of adult disease hypothesis (Barker 1998; Benediktsson 1993). Increased insulin release has been found 30 minutes following a 75 g oral glucose tolerance test in one follow-up study conducted at age 30 (Liggins 1972b). However, the same study found no difference in blood pressure, fasting lipids, body size, hypothalamo-pituitary-adrenal axis function or the prevalence of diabetes or cardiovascular disease. Thus, while the finding of increased insulin resistance in adulthood provides support to excess corticosteroids as a mechanism underlying the fetal origins of adult disease hypothesis, it should not be seen as a reason to withhold antenatal corticosteroids given the large and clinically substantial benefits seen in the neonatal period.

## AUTHORS' CONCLUSIONS

### Implications for practice

The evidence from this new review supports the continued use of a single course of antenatal corticosteroids to accelerate fetal lung maturation in women at risk of preterm birth. Treatment with antenatal corticosteroids reduces the risk of neonatal death, respiratory distress syndrome, cerebroventricular haemorrhage, necrotising enterocolitis, infectious morbidity, need for respiratory support and neonatal intensive care unit admission. There is evidence to suggest benefit across a wide range of gestational ages from 26 to 34 + 6 weeks and in the current era of neonatal practice. Furthermore, there is evidence to suggest benefit in the subgroups of women with premature rupture of membranes and those with hypertension syndromes. A single course of antenatal corticosteroids should be considered routine for preterm delivery.

### Implications for research

There is no need for further trials of a single course of antenatal corticosteroids versus placebo in singleton pregnancies. Data are sparse regarding risks and benefits of antenatal corticosteroids

in multiple pregnancies. However, authors of previous studies are encouraged to provide further information as the use of antenatal corticosteroids in such pregnancies may be able to be answered without the need for further randomised controlled trials. Follow-up studies in adulthood should be undertaken to confirm the long-term effects of this treatment. Future studies are needed to determine the optimal dose and drug for this purpose, and to determine the risks and benefits of repeat courses of corticosteroids.

## FEEDBACK

### Nachum, September 2002

#### Summary

Are there enough data to indicate the efficacy of antenatal steroids in twins?

(Summary of comment received from Zohar Nachum, September 2002.)

#### Author's reply

Only two small trials report outcome following a multiple pregnancy. Therefore there is currently not enough evidence to support the use of corticosteroids in multiple pregnancy. Nevertheless, in view of the strength of the overall evidence, it would seem sensible to offer a single course of steroids to women with a multiple pregnancy at risk of preterm birth.

(Summary of response from Devender Roberts and Stuart Dalziel, May 2006.)

#### Contributors

Zohar Nachum

### Preston, August 2002

#### Summary

It is unclear whether quasi-randomised trials should be included. The abstract states they are included, types of studies says they are excluded, and a quasi-randomised study has been included (Morales 1986).

Also some data appear to be missing from the meta-analysis. Silver 1995 does not contribute any information to the outcome neonatal death, yet the data are reported in the abstract you reference (7/54 deaths on dexamethasone, 8/42 deaths on placebo).

(Summary of comments received from Carol Preston, August 2002.)

#### Author's reply

The protocol for the updated review excluded quasi-randomised studies, and Morales 1986 has therefore been excluded. The data for neonatal deaths in Silver 1995 are now included in the meta-analysis.

(Summary of response from Devender Roberts and Stuart Dalziel, May 2006.)

Contributors

Carol Preston

### **Liabsuetrakul, September 2003**

Summary

The results, and reviewer's conclusions, are that administering corticosteroids (24 mg betamethasone, or 24 mg dexamethasone) to women who are expected to give birth at 28-34 weeks' gestation reduces neonatal morbidity and mortality. However, there is no clarification of how this should be prescribed. Standard regimens are for 48 hours treatment, using either 12 mg betamethasone IM every 24 hours, or 6 mg dexamethasone IM every 12 hours. But data in this review show the maximum benefit for corticosteroids is after 24 hours of treatment.

I have some questions about how to maximise the benefit in clinical practice.

- 1) For a woman in preterm labor who is being given tocolytic treatment to facilitate steroid administration, how long should tocolytics be continued, 24 hours or 48 hours?
- 2) Would the benefit of steroids be the same for a modified regimen over 24 hours, for example 8 mg dexamethasone IM every 8 hours for 3 doses, or 12 mg dexamethasone IM every 12 hours? Will this affect adrenal suppression and fetal growth like repeated doses?
- 3) Do we need a review comparing the benefits and adverse events between different regimens of prophylactic corticosteroids?

(Summary of comments from Tippawan Liabsuetrakul, September 2003.)

Author's reply

These questions have all been addressed by sub-group analyses in the updated review.

(Summary of response from Devender Roberts and Stuart Dalziel, May 2006.)

Contributors

Tippawan Liabsuetrakul

### **Selinger, December 2005**

Summary

Why do the corticosteroids need to be administered by intramuscular injection? Is there any evidence that this is preferable to oral administration?

(Summary of comment from Mark Selinger, December 2005.)

Author's reply

Presumably the original sheep studies were done with parenteral steroids, so perhaps the initial extrapolation to humans was intramuscular use. We are not aware of evidence about the effects of oral administration.

(Summary of response from Devender Roberts and Stuart Dalziel, May 2006.)

Contributors

Mark Selinger

### **Hutchon, May 2006**

Summary

There have been two recent reports<sup>(1,2)</sup> of 30-year follow-up of people recruited whilst in utero to Liggins 1972a. Both used intention-to-treat analysis, as does this review. One of these reports (1) stated "that there were similar numbers of neonatal survivors with much the same perinatal morbidity in both treatment and control groups". Clearly this means that Liggins 1972a showed no overall benefit in terms of survival or morbidity, which to me seem the most important end points.

Liggins 1972a forms a major part of this Cochrane review, yet the data from the follow-up reports differ from those in the review. This new evidence therefore raises questions about the validity of the Cochrane meta-analysis. There are also discrepancies between this version of the review, and its earlier published versions, for some of the other trials. The version published in *Effective care in Pregnancy and Childbirth* (3) contained 12 trials reporting the effect of corticosteroids on early neonatal death (0-7 days). Some of these 12 are in the analysis presented here of corticosteroids versus placebo for the outcome neonatal death (0-28 days). However, for Liggins 1972a, Block 1977, Gamsu 1989, and Morales 1989 the data remain unchanged between the two reviews. Does this mean there were no deaths from 8-28 days? We now know this is not true for Liggins 1972a. There is also something peculiar about the randomisation in Schmidt 1984. Between appearing in *Effective Care in Pregnancy and Childbirth* and inclusion in the Cochrane review 15 women were added to this study, all in the treatment group and with no change in the number of deaths.

I understand an update of the review is in preparation. However, since the early nineties it would have been considered unethical to carry out a randomised trial of steroids versus placebo and so I do not expect any new trials to have become available since the last Cochrane review in 2002.

(Summary of feedback from David Hutchon, May 2006.)

References

1. Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A et al. Cardiovascular risk factors after exposure to antenatal betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005;365:1856-62.

2. Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in a randomised controlled trial. *BMJ* 2005;331:665-8.

3. Table 45.12 In: Chalmers I, Enkin M, Keirse MJNC, eds. *Effective care in pregnancy and childbirth*. Oxford: Oxford University Press, 1989:754.

#### Author's reply

Since *Effective Care in Pregnancy and Childbirth* appeared, nine randomised controlled trials of antenatal corticosteroids have been published. These trials are now included in the updated Cochrane review. This updated review shows the contribution of each study to the outcome measures, and describes the methodological quality of each included trial.

For Liggins 1972a, the previous Cochrane review (Crowley 1996) included data that were published at that time. Hence, data for perinatal death (stillbirth or death in the first week of life) were included. However, the updated Cochrane review includes an intention-to-treat analysis of the original data from Liggins 1972a. These data were not available for the previous review (Crowley 1996). This updated review therefore now includes data for neonatal death (death in the first 28 days of life) in Liggins 1972a.

Data reported for Schmidt 1984 included a third arm of women and infants who had been excluded from randomisation. This study is now excluded from the review.

(Summary of response from Devender Roberts and Stuart Dalziel, May 2006.)

#### Contributors

David Hutchon

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## POTENTIAL CONFLICT OF INTEREST

None known.

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As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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## REFERENCES

### References to studies included in this review

#### Amorim 1999 *{published and unpublished data}*

Amorim MM, Santos LC, Faundes A. Corticosteroid therapy for prevention of respiratory distress syndrome in severe preeclampsia. *American Journal of Obstetrics and Gynecology* 1999;**180**(5):1283–8.

#### Block 1977 *{published data only}*

Block MF, Kling OR, Crosby WM. Antenatal glucocorticoid therapy for the prevention of respiratory distress syndrome in the premature infant. *Obstetrics & Gynecology* 1977;**50**:186–90.

#### Cararach 1991 *{published data only}*

Botet F, Cararach V, Sentis J. Premature rupture of membranes in early pregnancy. Neonatal prognosis. *Journal of Perinatal Medicine* 1994;**22**:45–52.

Cararach V, Botet F, Sentis J, Carmona F. A multicenter, prospective randomized study in premature rupture of membranes (PROM). Maternal and perinatal complications. Proceedings of the 13th World Congress of Gynaecology and Obstetrics (FIGO); 1991; Singapore. 1991:267.

\* Cararach V, Sentis J, Botet F, De Los Rios L. A multicenter, prospective randomized study in premature rupture of membranes (PROM). Respiratory and infectious complications in the newborn. Proceedings of the 12th European Congress of Perinatal Medicine; 1990; Lyon, France. 1990:216.

#### Carlan 1991 *{published data only}*

Carlan SJ, Parsons M, O'Brien WF, Krammer J. Pharmacologic pulmonary maturation in preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1991;**164**:371.

#### Collaborative 1981 *{published data only}*

Bauer CR, Morrison JC, Poole WK, Korones SB, Boehm JJ, Rigatto H, et al. A decreased incidence of necrotizing enterocolitis after prenatal glucocorticoid therapy. *Pediatrics* 1984;**73**:682–8.

Burkett G, Bauer CR, Morrison JC, Curet LB. Effect of prenatal dexamethasone administration on the prevention of respiratory distress syndrome in twin pregnancies. *Journal of Perinatology* 1986;**6**:304–8.

Collaborative Group on Antenatal Steroid Therapy. Amniotic fluid phospholipids after maternal administration of dexamethasone. *American Journal of Obstetrics and Gynecology* 1983;**145**:484–90.

Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration in the infant: long term follow-up. *Journal of Pediatrics* 1984;**105**:259–67.

\* Collaborative Group on Antenatal Steroid Therapy. Effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1981;**141**:276–87.

Curet LB, Rao AV RD, Zachman RD, Morrison J, Burkett G, Poole K, et al. Maternal smoking and respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1983;**147**:446–50.

Haning RV, Curet LB, Poole K, Boehnlein LM, Kuzma DL, Meier SM. Effects of fetal sex and dexamethasone on preterm maternal

serum concentrations of human chorionic gonadotropin, progesterone, estrone, estradiol, and estriol. *American Journal of Obstetrics and Gynecology* 1989;**161**:1549–53.

Wiebicke W, Poynter A, Chernick V. Normal lung growth following antenatal dexamethasone treatment for respiratory distress syndrome. *Pediatric Pulmonology* 1988;**5**:27–30.

Zachman RD. The NIH multicenter study and miscellaneous clinical trials of antenatal corticosteroid administration. In: Farrell PM editor(s). *Lung development: biological and clinical perspectives*. Vol. II, London & New York: Academic Press, 1982:275–96.

Zachman RD, Bauer CR, Boehm J, Korones SB, Rigatto H, Rao AV. Effect of antenatal dexamethasone on neonatal leukocyte count. *Journal of Perinatology* 1988;**8**:111–3.

#### Dexiprom 1999 *{published and unpublished data}*

Pattinson RC. A meta-analysis of the use of corticosteroids in pregnancies complicated by preterm premature rupture of membranes. *South African Medical Journal* 1999;**89**(8):870–3.

Pattinson RC, Funk M, Makin JD, Ficki H. The effect of dexamethasone on the immune system of women with preterm premature rupture of membranes: a randomised controlled trial. 15th Conference on Priorities in Perinatal Care in Southern Africa; 1996 March 5-8; Goudini Spa, South Africa. 1996.

\* Pattinson RC, Makin JD, Funk M, Delpont SD, Macdonald AP, Norman K. The use of dexamethasone in women with preterm premature rupture of membranes: a multicentre double blind, placebo controlled randomised trial. *South African Medical Journal* 1999;**89**(8):865–70.

Pattinson RC, Makin JD, Funk M, Delpont SD, Macdonald AP, Norman K, et al. The use of dexamethasone in women with preterm premature rupture of membranes: a multicentre placebo controlled randomised controlled trial. 16th Conference on Priorities in Perinatal Care; 1997; South Africa. 1997:32–4.

#### Doran 1980 *{published data only}*

Doran TA, Swyer P, MacMurray B, Mahon W, Enhorning G, Bernstein A, et al. Results of a double blind controlled study on the use of betamethasone in the prevention of respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1980;**136**:313–20.

#### Fekih 2002 *{published data only}*

Fekih M, Chaieb A, Sboui H, Denguezli W, Hidar S, Khairi H. Value of prenatal corticotherapy in the prevention of hyaline membrane disease in premature infants. Randomized prospective study [Apport de la corticothérapie antenatale dans la prévention de la maladie des membranes hyalines chez le premature. Etude prospective randomisée]. *Tunisie Medicale* 2002;**80**(5):260–5.

#### Gamsu 1989 *{published data only}*

Donnai P. UK multicentre trial of betamethasone for the prevention of respiratory distress syndrome. Proceedings of the 6th European Congress of Perinatal Medicine; 1989; Vienna, Austria. 1978:81.

\* Gamsu HR, Mullinger BM, Donnai P, Dash CH. Antenatal administration of betamethasone to prevent respiratory distress syndrome

- in preterm infants: report of a UK multicentre trial. *British Journal of Obstetrics and Gynaecology* 1989;**96**:401–10.
- Garite 1992** *{published data only}*  
 Garite TJ, Rumney PJ, Briggs GG. A randomized, placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24–28 weeks gestation. *Surgery, Gynecology and Obstetrics* 1993;**176**:37.
- \* Garite TJ, Rumney PJ, Briggs GG, Harding JA, Nageotte MP, Towers CV, et al. A randomized placebo-controlled trial of betamethasone for the prevention of respiratory distress syndrome at 24–28 weeks gestation. *American Journal of Obstetrics and Gynecology* 1992;**166**:646–51.
- Kari 1994** *{published data only}*  
 Eronen M, Kari A, Pesonen E, Hallman M. The effect of antenatal dexamethasone administration on the fetal and neonatal ductus arteriosus: a randomised double-blind study. *American Journal of Diseases of Children* 1993;**147**:187–92.
- Kari MA, Akino T, Hallman M. Prenatal dexamethasone (DEX) treatment before preterm delivery and rescue therapy of exogenous surfactant- surfactant components and surface activity in airway specimens (AS). Proceedings of the 14th European Congress of Perinatal Medicine; 1994; Helsinki, Finland. 1994:486.
- \* Kari MA, Hallman M, Eronen M, Teramo K, Virtanen M, Koivisto M, et al. Prenatal dexamethasone treatment in conjunction with rescue therapy of human surfactant: a randomised placebo-controlled multicenter study. *Pediatrics* 1994;**93**:730–6.
- Salokorpi T, Sajaniemi N, Hallback H, Kari A, Rita H, von Wendt L. Randomized study of the effect of antenatal dexamethasone on growth and development of premature children at the corrected age of 2 years. *Acta Paediatrica* 1997;**86**:294–8.
- Lewis 1996** *{published data only}*  
 Lewis D, Brody K, Edwards M, Brouillette RM, Burlison S, London SN. Preterm premature ruptured membranes: a randomized trial of steroids after treatment with antibiotics. *Obstetrics & Gynecology* 1996;**88**(5):801–5.
- Liggins 1972a** *{published and unpublished data}*  
 Dalziel SR, Liang A, Parag V, Rodgers A, Harding JE. Blood pressure at 6 years of age after prenatal exposure to betamethasone: follow-up results of a randomized, controlled trial. *Pediatrics* 2004;**114**:e373–e377.
- Dalziel SR, Lim VK, Lambert A, McCarthy D, Parag V, Rodgers A, et al. Antenatal exposure to betamethasone: psychological functioning and health related quality of life 31 years after inclusion in randomised controlled trial. *BMJ* 2005;**331**:665–8.
- Dalziel SR, Parag V, Harding JE. Blood pressure at 6 years of age following exposure to antenatal bethamethasone. 7th Annual Congress of the Perinatal Society of Australia and New Zealand; 2003 March 9–12; Tasmania, Australia. 2003:P13.
- Dalziel SR, Walker NK, Parag V, Mantell C, Rea HH, Rodgers A, et al. Cardiovascular risk factors after exposure to antenatal betamethasone: 30-year follow-up of a randomised controlled trial. *Lancet* 2005;**365**:1856–62.
- Harding JE, Pang J, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes?. *American Journal of Obstetrics and Gynecology* 2001;**184**:131–9.
- Howie RN. Pharmacological acceleration of lung maturation. In: VilleeCA, VilleeDB, ZuckermanJ editor(s). *Respiratory distress syndrome*. London & New York: Academic Press, 1986:385–96.
- Howie RN, Liggins GC. Clinical trial of antepartum betamethasone therapy for prevention of respiratory distress in pre-term infants. In: AndersonABM, BeardRW, BrudenellJM, DunnPM editor(s). *Pre-term labour*. London: RCOG, 1977:281–9.
- Howie RN, Liggins GC. Prevention of respiratory distress syndrome in premature infants by antepartum glucocorticoid treatment. In: VilleeCA, VilleeDB, ZuckermanJ editor(s). *Respiratory distress syndrome*. London & New York: Academic Press, 1973:369–80.
- Howie RN, Liggins GC. The New Zealand study of antepartum glucocorticoid treatment. In: FarrellPM editor(s). *Lung development: biological and clinical perspectives, II*. Academic Press: London & New York, 1982:255–65.
- Liggins GC. Prenatal glucocorticoid treatment: prevention of respiratory distress syndrome. Lung maturation and the prevention of hyaline membrane disease, report of 70th Ross Conference on Paediatric Research. Ross Labs, 1976:97–103.
- Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;**50**:515–25.
- Liggins GC, Howie RN. Prevention of respiratory distress syndrome by antepartum corticosteroid therapy. Proceedings of Sir Joseph Barcroft Centenary Symposium, Fetal and Neonatal Physiology. Cambridge University Press, 1973:613–7.
- Liggins GC, Howie RN. Prevention of respiratory distress syndrome by maternal steroid therapy. In: GluckL editor(s). *Modern perinatal medicine*. Chicago: Yearbook Publishers, 1974:415–24.
- MacArthur B, Howie RN, DeZoete A, Elkins J. Cognitive and psychosocial development of 4-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* 1981;**68**:638–43.
- MacArthur B, Howie RN, DeZoete A, Elkins J. School progress and cognitive development of 6-year-old children whose mothers were treated antenatally with betamethasone. *Pediatrics* 1982;**70**:99–105.
- MacArthur B, Howie RN, DeZoete A, Elkins J, Liang AYL. Long term follow up of children exposed to betamethasone in utero. In: TejaniN editor(s). *Obstetrical events and developmental sequelae*. CRC Press, 1989:81–9.
- Morales 1989** *{published data only}*  
 Morales WJ, Angel JL, O'Brien WF, Knuppel RA. Use of ampicillin and corticosteroids in premature rupture of membranes: a randomized study. *Obstetrics & Gynecology* 1989;**73**:721–6.
- Nelson 1985** *{published data only}*  
 Nelson LH, Meis PJ, Hatjis CG, Ernest JM, Dillard R, Schey HM. Premature rupture of membranes: a prospective randomized evaluation of steroids, latent phase and expectant management. *Obstetrics & Gynecology* 1985;**66**:55–8.

**Parsons 1988** {published data only}

Parsons MT, Sobel D, Cummiskey K, Constantine L, Roitman J. Steroid, antibiotic and tocolytic vs no steroid, antibiotic and tocolytic management in patients with preterm PROM at 25-32 weeks. Proceedings of the 8th Annual Meeting of the Society of Perinatal Obstetricians; 1988; Las Vegas, Nevada. 1988:44.

Sobel D, Parsons M, Roitman J, McAlpine L, Cumminsky K. Antenatal antibiotics in PROM prevents congenital bacterial infection. *Pediatric Research* 1988;**23**:476A.

**Qublan 2001** {published data only}

Qublan H, Malkawi H, Hiasat M, Hindawi IM, Al-Taani MI, Abu-Khait SA, et al. The effect of antenatal corticosteroid therapy on pregnancies complicated by premature rupture of membranes. *Clinical & Experimental Obstetrics & Gynecology* 2001;**28**(3):183-6.

**Schutte 1980** {published data only}

Dessens AB, Haas HS, Koppe JG. Twenty year follow up of antenatal corticosteroid treatment. *Pediatrics* 2000;**105**(6):1325.

Dessens AB, Smolders-de Haas H, Koppe JG. Twenty year follow up in antenatally corticosteroid-treated subjects. *Prenatal and Neonatal Medicine* 1998;**3** Suppl 1:32.

Schmand B, Neuvel J, Smolder-de Haas H, Hoeks J, Treffers PE, Koppe JG. Psychological development of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome. *Pediatrics* 1990;**86**:58-64.

Schutte MF, Koppe JG, Treffers PE, Breur W. The influence of 'treatment' in premature delivery on incidence of RDS. Proceedings of the 6th European Congress of Perinatal Medicine; 1978 August 29-September 1; Vienna, Austria. 1978.

\* Schutte MF, Treffers PE, Koppe JG, Breur W. The influence of betamethasone and orciprenaline on the incidence of respiratory distress syndrome in the newborn after preterm labour. *British Journal of Obstetrics and Gynaecology* 1980;**87**:127-31.

Schutte MF, Treffers PE, Koppe JG, Breur W, Filedt Kok JC. The clinical use of corticosteroids for the acceleration of fetal lung maturity [Klinische toepassing van corticosteroiden ter bevordering van de foetale long-rijpheid]. *Nederlands Tijdschrift voor Geneeskunde* 1979;**123**:420-7.

Smolders-de Haas H, Neuvel J, Schmand B, Treffers PE, Koppe JG, Hoeks J. Physical development and medical history of children who were treated antenatally with corticosteroids to prevent respiratory distress syndrome: a 10- to 12- year follow up. *Pediatrics* 1990;**86**(1):65-70.

**Silver 1996** {published data only}

Silver RK, Vyskocil CR, Solomon SL, Farrell EE, MacGregor SN, Neerhof MG. Randomized trial of antenatal dexamethasone in surfactant-treated infants delivered prior to 30 weeks of gestation. *American Journal of Obstetrics and Gynecology* 1995;**172**:254.

\* Silver RK, Vyskocil CR, Solomon SL, Ragin A, Neerhof MG, Farrell EE. Randomized trial of antenatal dexamethasone in surfactant-treated infants delivered prior to 30 weeks of gestation. *Obstetrics & Gynecology* 1996;**87**:683-91.

**Tausch 1979** {published data only}

Tausch HW Jr, Frigoletto F, Kitzmiller J, Avery ME, Hehre A, Fromm B, et al. Risk of respiratory distress syndrome after prenatal dexamethasone treatment. *Pediatrics* 1979;**63**:64-72.

**Teramo 1980** {published data only}

Teramo K, Hallman M, Raivio KO. Maternal glucocorticoid in unplanned premature labor. *Pediatric Research* 1980;**14**:326-9.

## References to studies excluded from this review

**Abuhamad 1999**

Abuhamad A, Green G, Heyl P, de Veciana M. The combined use of corticosteroids and thyrotropin releasing hormone in pregnancies with preterm rupture of membranes: a randomised double blind controlled trial. *American Journal of Obstetrics and Gynecology* 1999;**180** (1 Pt 2):S96.

**Butterfill 1979**

Butterfill AM, Harvey DR. Follow-up study of babies exposed to betamethasone before birth. *Archives of Disease in Childhood* 1979;**54**:725.

**Dola 1997**

Dola C, Nageotte M, Rumney P, Towers C, Asrat T, Freeman R, et al. The effect of antenatal treatment with betamethasone and thyrotropin releasing hormone in patients with preterm premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1997;**176**(1 Pt 2):S49.

**Egerman 1998**

Egerman RS, Mercer B, Doss JL, Sibai BM. A randomized controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *Acta Obstetrica et Gynecologica Scandinavica* 1998;**178**(1 Pt 2):S19.

\* Egerman RS, Mercer BM, Doss JL, Sibai BM. A randomized, controlled trial of oral and intramuscular dexamethasone in the prevention of neonatal respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1998;**179**(5):1120-3.

Egerman RS, Pierce WF 4th, Andersen RN, Umstot ES, Carr TL, Sibai BM. A comparison of the bioavailability of oral and intramuscular dexamethasone in women in late pregnancy. *Obstetrics & Gynecology* 1997;**89**(2):276-80.

Egerman RS, Walker RA, Doss JL, Mercer B, Sibai BM, Andersen RN. A comparison between oral and intramuscular dexamethasone in suppressing unconjugated estriol levels during the third trimester. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 2):S182.

Egerman RS, Walker RA, Mercer BM, Doss JL, Sibai BM, Andersen RA. Comparison between oral and intramuscular dexamethasone in suppressing unconjugated estriol levels during the third trimester. *American Journal of Obstetrics and Gynecology* 1998;**179**(5):1234-6.

**Garite 1981**

Garite TJ, Freeman RK, Linzey EM, Braly PS, Dorchester WL. Prospective randomized study of corticosteroids in the management of premature rupture of the membranes and the premature gestation. *American Journal of Obstetrics and Gynecology* 1981;**141**:508-15.

**Halac 1990**

Halac E, Halac J, Begue EF, Casanas JM, Idiveri DR, Petit JF, et al. Prenatal and postnatal corticosteroid therapy to prevent neonatal

- necrotizing enterocolitis: a controlled trial. *Journal of Pediatrics* 1990; **117**:132–8.
- Iams 1985**  
Iams JD, Talbert ML, Barrows H, Sachs L. Management of preterm prematurely ruptured membranes: a prospective randomized comparison of observation vs use of steroids and timed delivery. *American Journal of Obstetrics and Gynecology* 1985; **151**:32–8.
- Kuhn 1982**  
Kuhn RJP, Speirs AL, Pepperell RJ, Eggers TR, Doyle LW, Hutchinson A. Betamethasone, albuterol and threatened premature delivery. *Obstetrics & Gynecology* 1982; **60**:403–8.
- Magee 1997**  
Magee LA, Dawes GS, Moulden M, Redman CW. A randomised controlled comparison of betamethasone with dexamethasone: effects on the antenatal fetal heart rate. *British Journal of Obstetrics and Gynaecology* 1997; **104**(11):1233–8.
- Minoui 1996**  
Minoui S, Ville Y, Senat M, Multon O, Fernandez H, Frydman R. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labour: a randomized study. *British Journal of Obstetrics and Gynaecology* 1998; **105**:749–55.  
  
Minoui S, Ville Y, Senat MV, Multon O, Fernandez H, Frydman R. Effect of dexamethasone and betamethasone on fetal heart rate variability in preterm labor a randomized study. *Prenatal and Neonatal Medicine* 1996; **1 Suppl 1**:156.
- Morales 1986**  
Morales WJ, Diebel D, Lazar AJ, Zadrozny D. The effect of antenatal dexamethasone administration on the prevention of respiratory distress syndrome in preterm gestations with premature rupture of membranes. *American Journal of Obstetrics and Gynecology* 1986; **154**:591–5.
- Morrison 1978**  
Morrison JC, Schneider JM, Whybrew WD, Bucovaz ET. Effect of corticosteroids and fetomaternal disorders on the L:S ratio. *Surgery, Gynecology and Obstetrics* 1981; **153**:464.  
  
Morrison JC, Whybrew WD, Bucovaz ET, Scheiner JM. Injection of corticosteroids into mother to prevent neonatal respiratory distress syndrome. *American Journal of Obstetrics and Gynecology* 1978; **131**:358–66.
- Mulder 1997**  
Mulder EJ, Derks JB, Visser GH. Antenatal corticosteroid therapy and fetal behaviour: a randomised evaluation of betamethasone and dexamethasone. *British Journal of Obstetrics and Gynaecology* 1997; **104**(11):1239–47.
- Papageorgiou 1979**  
Papageorgiou AN, Desgranges MF, Masson M, Colle E, Shatz R, Gelfand MM. The antenatal use of betamethasone in the prevention of respiratory distress syndrome: a controlled blind study. *Pediatrics* 1979; **63**:73–9.
- Rotmensch 1999**  
Rotmensch S, Liberati M, Vishne T, Celentano C, Ben-Rafael Z, Bellati U. The effects of betamethasone versus dexamethasone on computer-analysed fetal heart rate characteristics: a prospective randomized trial. *American Journal of Obstetrics and Gynecology* 1998; **178**(1 Pt 2):S185.  
  
Rotmensch S, Liberati M, Vishne TH, Celentano C, Ben-Rafael Z, Bellati U. The effect of betamethasone and dexamethasone on the fetal heart rate patterns and biophysical activities. A prospective randomized trial. *Acta Obstetrica et Gynecologica Scandinavica* 1999; **78**(6):493–500.
- Schmidt 1984**  
Schmidt PL, Sims ME, Strassner HT, Paul RH, Mueller E, McCart D. Effect of antepartum glucocorticoid administration upon neonatal respiratory distress syndrome and perinatal infection. *American Journal of Obstetrics and Gynecology* 1984; **148**:178–86.
- Simpson 1985**  
Simpson G, Harbert G. Use of beta-methasone in management of preterm gestation with premature rupture of membranes. *Obstetrics & Gynecology* 1985; **66**:168–75.
- Whitt 1976**  
Whitt GG, Buster JE, Killam AP, Scragg WH. A comparison of two glucocorticoid regimens for acceleration of fetal lung maturation in premature labor. *American Journal of Obstetrics and Gynecology* 1976; **124**:479–82.

## References to studies awaiting assessment

- Goodner 1979**  
Goodner DM. Antenatal steroids in the treatment of respiratory distress syndrome. 9th World Congress of Gynecology and Obstetrics; 1979 October 26-31; Tokyo, Japan. 1979:362.
- Grgic 2003**  
Grgic G, Fatusic Z, Bogdanovic G. Stimulation of fetal lung maturation with dexamethasone in unexpected premature labor. *Medicinski Arhiv* 2003; **57**(5-6):291–4.

## Additional references

- Barker 1998**  
Barker DJP. *Mothers, babies and health in later life*. 2nd Edition. London: Churchill Livingstone, 1998.
- Baud 1999**  
Baud O, Foix-L'Helias L, Kaminski M, Audibert F, Jarreau PH, Papiernik E, et al. Antenatal glucocorticoid treatment and cystic periventricular leukomalacia in very premature infants. *New England Journal of Medicine* 1999; **341**:1190–6.
- Benediktsson 1993**  
Benediktsson R, Lindsay RS, Noble J, Seckl JR, Edwards CR. Glucocorticoid exposure in utero: new model for adult hypertension. *Lancet* 1993; **341**(8841):339–41.
- Clark 1998**  
Clark PM. Programming of the hypothalamo-pituitary-adrenal axis and the fetal origins of adult disease hypothesis. *European Journal of Pediatrics* 1998; **157**(1 Suppl):S7–S10.
- Collaborative 1984**  
Collaborative Group on Antenatal Steroid Therapy. Effects of antenatal dexamethasone administration in the infant: long-term follow-up. *Journal of Pediatrics* 1984; **104**:259–67.
- Crowley 1990**  
Crowley P, Chalmers I, Keirse MJNC. The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. *British Journal of Obstetrics and Gynaecology* 1990; **97**:11–25.

**Crowther 2000**

Crowther CA, Harding J. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease. In: *Cochrane Database of Systematic Reviews*, 2, 2000.

**Dodic 1999**

Dodic M, Wintour EM, Whitworth JA, Coghlan JP. Effect of steroid hormones on blood pressure. *Clinical & Experimental Pharmacology & Physiology* 1999;**26**(7):550–2.

**Doyle 2001a**

Doyle LW. Victorian Infant Collaborative Study Group. Outcome at 5 years of age of children 23 to 27 weeks' gestation: refining the prognosis. *Pediatrics* 2001;**108**(1):134–41.

**Doyle 2001b**

Doyle LW, Casalaz D. Victorian Infant Collaborative Study Group. Outcome at 14 years of extremely low birthweight infants: a regional study. *Archives of Diseases in Childhood: Fetal and Neonatal Edition* 2001;**85**(3):F159–F164.

**Edwards 2001**

Edwards LJ, Coulter CL, Symonds ME, McMillen IC. Prenatal undernutrition, glucocorticoids and the programming of adult hypertension. *Clinical & Experimental Pharmacology & Physiology* 2001;**28**(11):938–41.

**Higgins 2005a**

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* 4.2.5 [updated May 2005]. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.

**Higgins 2005b**

Higgins JPT, Green S, editors. *Cochrane Reviewers' Handbook* 4.2.5 [updated May 2005]; Section 6. In: The Cochrane Library, Issue 3, 2005. Chichester, UK: John Wiley & Sons, Ltd.

**Huang 1999**

Huang WL, Beazley LD, Quinlivan JA, Evans SF, Nenham JB, Dunlop SA. Effect of corticosteroids on brain growth in fetal sheep. *Obstetrics & Gynecology* 1999;**94**(2):213–8.

**Imseis 1996**

Imseis HM, Iams JD. Glucocorticoid use in patients with preterm premature rupture of fetal membranes. *Seminars in Perinatology* 1996;**20**(5):439–50.

**Jobe 1998**

Jobe AH, Wada N, Berry LM, Ikegami M, Ervin MG. Single and repetitive maternal glucocorticoid exposures reduce fetal growth in sheep. *American Journal of Obstetrics and Gynecology* 1998;**178**(5):880–5.

**Liggins 1969**

Liggins GC. Premature delivery of foetal lambs infused with corticosteroids. *Journal of Endocrinology* 1969;**45**:515–23.

**Liggins 1972b**

Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of the respiratory distress syndrome in premature infants. *Pediatrics* 1972;**50**(4):515–25.

**Liggins 1976**

Liggins GC. Prenatal glucocorticoid treatment: prevention of respiratory distress syndrome. Lung maturation and the prevention of hyaline membrane disease, Report of the Seventieth Ross Conference on Pediatric Research, Columbus, Ohio. 1976:97–103.

**NIH 1994**

National Institutes of Health (NIH) Consensus Development Conference Statement. Effect of corticosteroids for fetal maturation on perinatal outcomes. *American Journal of Obstetrics and Gynecology* 1994;**173**:246–52.

**Padbury 1996**

Padbury JF, Ervin MG, Polk DH. Extrapulmonary effects of antenatally administered steroids. *Journal of Pediatrics* 1996;**128**(2):167–72.

**RevMan 2000**

The Cochrane Collaboration. Review Manager (RevMan). 4.1 for Windows. Oxford, England: The Cochrane Collaboration, 2000.

**Schwab 2000**

Schwab M, Roedel M, Akhtar Anwar M, Muler T, Schubert H, Buchwalder LF, et al. Effects of betamethasone administration to the fetal sheep in late gestation on fetal cerebral blood flow. *Journal of Physiology* 2000;**528**(3):619–32.

**Seckl 2000**

Seckl JR, Cleasby M, Nyirenda MJ. Glucocorticoids, 11beta-hydroxysteroid dehydrogenase, and fetal programming. *Kidney International* 2000;**57**(4):1412–7.

**Turrentine 1996**

Turrentine MA, Wilson PD, Wilkins IA. A retrospective analysis of the effect of antenatal steroid on the incidence of respiratory distress syndrome in preterm twin pregnancies. *American Journal of Perinatology* 1996;**13**(6):351–4.

**Vyas 1997**

Vyas J, Kotecha S. Effects of antenatal and postnatal corticosteroids on the preterm lung. *Archives of Disease in Childhood: Fetal and Neonatal Edition* 1997;**77**(2):F147–F150.

**Wellcome 2005**

Reynolds LA, Tansey EM. Prenatal corticosteroids for reducing morbidity and mortality after preterm birth. The transcript of a Witness Seminar. London: The Wellcome Trust Centre for History of Medicine at UCL, 2005; Vol. 25.

**References to other published versions of this review****Crowley 1996**

Crowley P. Prophylactic corticosteroids for preterm birth. In: *Cochrane Database of Systematic Reviews*, 1, 1996.

\* Indicates the major publication for the study

## TABLES

### Characteristics of included studies

Study	<b>Amorim 1999</b>
Methods	Type of study: randomised controlled trial. Method of treatment allocation: computer-generated randomisation sequence with randomisation code kept by the chief pharmacist. The pharmacy provided coded drug boxes. Stratification: none stated. Placebo: yes, same volume of similar appearing vehicle. Sample size calculation: yes. Intention-to-treat analyses: no. Losses to follow up: yes, 2 (1%) women in the placebo group dropped out after randomisation. Funding: Instituto Materno-Infantil de Pernambuco, Brazil.
Participants	Location: Instituto Materno-Infantil de Pernambuco, Recife, state of Pernambuco, Brazil. Timeframe: April 1997 to June 1998. Eligibility criteria: women with severe pre-eclampsia, singleton pregnancy with a live fetus and gestational age between 26 and 34 weeks. Likely minimal interval of 24 hours between drug administration and delivery. Lung immaturity was confirmed by the foam test in fetuses of 30 to 34 weeks. Gestational age range: 26 to 34 weeks. Exclusion criteria: indication for immediate delivery, diabetes, PROM, maternal disease, congenital malformations, perinatal haemolytic disease, Group B streptococcal infection. Total recruited: 220 women and infants. 110 women and infants in each arm.
Interventions	12 mg betamethasone IM, repeated after 24 hours and weekly thereafter if delivery had not occurred. Control group received identical placebo. Delivery was at 34 weeks or in the presence of maternal or fetal compromise in both groups.
Outcomes	Maternal outcomes (death, chorioamnionitis, puerperal sepsis, fever after trial entry requiring antibiotics, intrapartum fever requiring antibiotics, postnatal fever, admission to ICU, glucose intolerance, hypertension), fetal/neonatal outcomes (fetal death, neonatal death, RDS, chronic lung disease, IVH, birthweight, Apgar score < 7, interval between trial entry and delivery, small-for-gestational age, admission to NICU, need for mechanical ventilation/CPAP, duration of oxygen supplementation, surfactant use, systemic infection in the first 48 hours of life, proven infection while in the NICU, necrotising enterocolitis), childhood outcomes (death, developmental delay, cerebral palsy) and health service outcomes reported (length of antenatal hospitalisation for women, length of postnatal hospitalisation for women, length of neonatal hospitalisation).
Notes	Further information obtained from the authors, including substantial unpublished data.
Allocation concealment	A – Adequate

Study	<b>Block 1977</b>
Methods	Type of study: randomised controlled trial. Method of treatment allocation: computer-generated randomisation sequence. Coded drug boxes were provided. Stratification: none stated. Placebo: yes, normal saline. Sample size calculation: no. Intention-to-treat analyses: no. Losses to follow up: yes, 14 (10%) women delivered elsewhere and were lost to follow up. 6 (4%) women were excluded from analyses as they failed to complete the protocol.

### Characteristics of included studies (Continued)

	Funding: Schering Corporation, Kenilworth, New Jersey, USA; and The Upjohn Company, Kalamazoo, Michigan, USA.
Participants	Location: Department of Gynecology and Obstetrics at the University of Oklahoma College of Medicine, Oklahoma City, Oklahoma, USA. Timeframe: not stated in manuscript, the study is coded as 1970s for the review. Eligibility criteria: women with preterm labour and PROM. Gestational age range: not stated. Exclusion criteria: not stated. Total recruited: the number randomised to each group is not stated. Data are available on 114 infants; 60 infants in the treatment arm and 54 infants in the control arm.
Interventions	12 mg betamethasone IM repeated after 24 hours if delivery had not occurred. Control group received 1 ml normal saline IM repeated after 24 hours if delivery had not occurred. If there was evidence of progressive cervical dilatation an alcohol infusion was given in order to attempt to delay delivery for at least 48 hours. In women with PROM delivery was induced if serial white blood cell counts or temperatures became elevated regardless of time elapsed since drug administration.
Outcomes	Fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, need for mechanical ventilation/CPAP).
Notes	This study included a third arm (125 mg methylprednisolone IM repeated after 24 hours if delivery had not occurred). The data for the review reports the betamethasone and control arms only. Overall data were available for 150 living infants, of whom 128 were preterm. Further information was requested from the authors but there was no reply.
Allocation concealment	A – Adequate

#### Study

#### Cararach 1991

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Stratification: none stated. Placebo: no. Sample size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: no. Funding: FIS; Perinatal Section of SEGO.
Participants	Location: Hospital Clinic, University of Barcelona, Spain. Timeframe: 1987 to 1990. Eligibility criteria: women with PROM. Gestational age range: 28 to 30 weeks. Exclusion criteria: none stated. Total recruited: 18 women and infants; 12 women and infants in the treatment arm and 6 women and infants in the control arm.
Interventions	Type and dose of corticosteroid used in the treatment group is not stated. Control group received expectant management.
Outcomes	Fetal/neonatal outcome reported (RDS).
Notes	Study only available as an abstract. Further information was requested from the authors but there was no reply.
Allocation concealment	B – Unclear

#### Study

#### Carlan 1991

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Stratification: none stated. Placebo: no.
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## Characteristics of included studies (Continued)

	Sample size calculation: no. Intention-to-treat analyses: no. Losses to follow up: yes, 2 (8%) infants with documented pulmonary maturity and 5 (17%) women with subsequent sealed membranes were not analysed. Funding: not stated.
Participants	Location: University of South Florida Medical School, Tampa, Florida, USA. Timeframe: not stated in manuscript, the study is coded as 1990s for the review. Eligibility criteria: women with PROM. Gestational age range: 24 to 34 weeks. Exclusion criteria: not stated. Total recruited: the number randomised to each group is not stated. Data are available on 24 women and infants; 13 women and infants in the treatment arm and 11 women and infants in the control arm.
Interventions	12 mg betamethasone IM repeated after 24 hours and weekly thereafter until delivery or 34 weeks. Control group received expectant management.
Outcomes	Maternal outcome (chorioamnionitis), fetal/neonatal outcomes (RDS, birthweight, days of mechanical ventilation/CPAP) and health service outcomes reported (days in NICU, neonatal days in hospital, neonatal hospital cost). However due to lack of SD data only chorioamnionitis and RDS data were included in the review.
Notes	This study included a third arm (12 mg betamethasone IM 24 hourly for 2 doses and 400 mcg methylprednisolone IV 8 hourly for 6 doses repeated weekly until delivery or 34 weeks. The data for the review reports the betamethasone and control arms only. Further information was requested from the authors but there was no reply.
Allocation concealment	B – Unclear

## Study

### Collaborative 1981

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Coded drug boxes with sequentially numbered vials containing study drug were used. Sealed envelope containing the identity of the contents of was attached to each vial “to be opened in emergency only in case of an emergency”. The manuscripts do not state how often these were opened. Stratification: yes, within each hospital. Placebo: yes, identical appearing. Sample size calculation: yes. Intention-to-treat analyses: no. Losses to follow up: yes, 2 (0%) infants in the control arm were lost to RDS follow up as neonates and 240 (37%) children were lost to follow up at age 3 (124 in the treatment arm and 116 in the control arm). Funding: National Institutes of Health, USA.
Participants	Location: 5 university hospitals in the USA. Timeframe: March 1977 to March 1980. Eligibility criteria: women at high risk of preterm delivery. L/S ratio < 2.0 in cases of uncertain gestation, hyperthyroidism, hypertension, placental insufficiency, drug addiction, methadone use or gestational age > 34 weeks. Gestational age range: 26 to 37 weeks. Exclusion criteria: > 5 cm of cervical dilatation, anticipated delivery < 24 hours or > 7 days, intrauterine infection, previous glucocorticoid treatment, history of peptic ulcer disease, active tuberculosis, viral keratitis, severe fetal Rh sensitisation, infant unlikely to be available for follow up. Total recruited: 696 women and 757 infants; 349 women and 378 infants in the treatment arm and 347 women and 379 infants in the control arm.
Interventions	4 doses of 5 mg dexamethasone phosphate IM 12 hours apart. Control group received placebo.

## Characteristics of included studies (Continued)

Outcomes	Maternal outcomes (postnatal fever), fetal/neonatal outcomes (fetal death, neonatal death, RDS, birthweight, interval between trial entry and delivery, systemic infection in the first 48 hours of life, proven infection while in the NICU, necrotising enterocolitis), childhood outcomes (death, lung function, developmental delay, intellectual impairment, cerebral palsy) and health service outcomes were reported (length of neonatal hospitalisation).
Notes	Further information was requested from the authors but there was no reply.
Allocation concealment	C – Inadequate

### Study **Dexiprom 1999**

Methods	Type of study: randomised controlled trial. Method of treatment allocation: computer-generated randomisation. Sequentially numbered envelopes were used. Stratification: yes, by hospital. Placebo: yes, normal saline. Sample size calculation: yes. Intention-to-treat analyses: no. Losses to follow up: yes, 7 (3%) women and infants were excluded from analysis (3 women did not have PROM, 2 women were < 26 weeks at randomisation, 1 woman received off protocol corticosteroid, a neonatal bed was not available in 1 case). Funding: Medical Research Council, South Africa; Donmed Pharmaceuticals, South Africa.
Participants	Location: 6 hospitals in South Africa. Timeframe: not stated in the manuscripts, the study is coded as 1990s for the review. Eligibility criteria: women with PROM between 28 to 34 weeks or with an estimated fetal weights of 1000 g to 2000 g if the gestational age was unknown. Gestational age range: 28 to 34 weeks. Exclusion criteria: cervical dilatation > 4 cm, evidence of infection, evidence of antepartum haemorrhage, < 19 years old. Total recruited: 204 women and 208 infants; 102 women and 105 infants in the treatment arm and 102 women and 103 infants in the control arm.
Interventions	2 doses of 12 mg dexamethasone IM 24 hours apart. Control group received placebo. All women also received ampicillin, metronidazole and hexaprenaline if contractions present in < 24 hours.
Outcomes	Maternal outcomes (maternal death, chorioamnionitis, puerperal sepsis, postnatal fever), fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, IVH, birthweight, need for mechanical ventilation/CPAP, systemic infection in the first 48 hours of life, necrotising enterocolitis).
Notes	Authors supplied additional data.
Allocation concealment	A – Adequate

### Study **Doran 1980**

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Coded drug boxes were provided. Randomisation code was kept on file at the Pharmacy Department of Toronto General Hospital. Stratification: yes, by gestational age into two subgroups; 24 to 32 weeks and 33 to 34 weeks. Placebo: yes, vehicle of steroid preparation consisting of 0.2 mg benzalkonium chloride and 0.1 mg disodium edentate per millilitre. Sample size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: no. Funding: The Hospital for Sick Children Foundation, Canada; Schering Corporation, Canada; Ontario Ministry of Health Provincial Research Grant PR 279, Canada.
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## Characteristics of included studies (Continued)

Participants	Location: 6 teaching hospitals in Toronto, Canada. Timeframe: January 1975 to June 1978. Eligibility criteria: women with PROM, spontaneous preterm labour or planned elective preterm delivery. Gestational age range: 24 and 34 weeks. Exclusion criteria: women with pre-eclampsia or in whom steroids were contraindicated on medical grounds. Total recruited: 137 women and 144 infants; 75 women and 81 infants in the treatment arm and 62 women and 63 infants in the control arm.
Interventions	4 doses of 3 mg betamethasone acetate and 3 mg betamethasone sodium phosphate IM 12 hours apart. Control group received 4 doses of identical placebo.
Outcomes	Fetal/neonatal outcomes were reported (fetal death, neonatal death, RDS, IVH, birthweight, days of mechanical ventilation).
Notes	
Allocation concealment	B – Unclear

### Study **Fekih 2002**

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Stratification: none stated. Placebo: no. Sample size calculation: no. Intention-to-treat analyses: no. Losses to follow up: yes, number of post-randomisation exclusions not stated. Funding: not stated.
Participants	Location: CHU Farhat Hached, Sousse, Tunisia. Timeframe: January 1998 to June 1999. Eligibility criteria: women in preterm labour. Gestational age range: 26 to 34 weeks. Exclusion criteria: gestational diabetes, > 4 cm cervical dilatation, fetal abnormalities, contraindication to corticosteroids, delivery elsewhere or after 34 weeks (postrandomisation exclusions). Total recruited: 118 women and 131 infants; 59 women and 63 infants in the treatment arm and 59 women and 68 infants in the control arm.
Interventions	2 doses of 12 mg betamethasone IM 24 hours apart. Control group received expectant management.
Outcomes	Maternal outcomes (chorioamnionitis, postnatal fever) and fetal/neonatal outcomes reported (neonatal death, RDS, IVH).
Notes	Article in French, abstract in English. Article translated by review authors. Further information was requested from the authors but there was no reply.
Allocation concealment	B – Unclear

### Study **Gamsu 1989**

Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Stratification: yes, by hospital. Placebo: yes, vehicle of betamethasone preparation. Sample size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: no. Funding: Glaxo Group Research Ltd, Greenford, Middlesex, UK.
Participants	Location: 11 hospitals in the UK. Timeframe: mid 1975 to February 1978. Eligibility criteria: women with spontaneous or planned preterm delivery.

### Characteristics of included studies (Continued)

	<p>Gestational age range: &lt; 34 weeks. Exclusion criteria: contraindication to corticosteroids, contraindications to postponing delivery, diabetes, suspected intrauterine infection. Total recruited: 251 women and 268 infants; 126 women and 131 infants in the treatment arm and 125 women and 137 infants in the control arm.</p>
Interventions	<p>6 doses of 4 mg betamethasone phosphate IM 8 hours apart. Control group received 6 doses of placebo. All women with spontaneous labour received IV salbutamol.</p>
Outcomes	<p>Fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, IVH, birthweight, systemic infection in the first 48 hours of life).</p>
Notes	
Allocation concealment	<p>B – Unclear</p>

<b>Study</b>	<b>Garite 1992</b>
Methods	<p>Type of study: randomised controlled trial. Method of treatment allocation: random-number table generated randomisation sequence by pharmacy. The pharmacy provided consecutive sealed envelopes. Stratification: none stated. Placebo: yes, normal saline. Sample size calculation: no. Intention-to-treat analyses: no. Losses to follow up: yes, 5 (7%) women delivered elsewhere and were lost to follow up (4 in treatment arm and 1 in control arm). Funding: Long Beach Memorial Foundation, USA.</p>
Participants	<p>Location: Long Beach Memorial Women's Hospital, California, USA. Timeframe: December 1984 to May 1990. Eligibility criteria: women likely to deliver between 24 hours and 7 days with spontaneous preterm labour or planned preterm delivery. Gestational age range: 24 to 27 + 6 weeks. Exclusion criteria: PROM, clinical or laboratory evidence of infection, contraindication to or previously given corticosteroids, diabetes. Total recruited: 76 women and 82 infants; 37 women and 40 infants in the treatment arm and 39 women and 42 infants in the control arm.</p>
Interventions	<p>2 doses of 6 mg betamethasone acetate and 6 mg betamethasone phosphate IM 24 hours apart, repeated weekly if still &lt; 28 weeks and thought likely to deliver within the next week. Control group received 2 doses of placebo. Women undelivered after 28 weeks and 1 week post their last dose of study medication were allowed glucocorticoids at the discretion of their physicians.</p>
Outcomes	<p>Maternal outcomes (chorioamnionitis, puerperal sepsis), fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, chronic lung disease, IVH, birthweight, Apgar &lt; 7, need for mechanical ventilation/CPAP, duration of mechanical ventilation/CPAP, proven neonatal infection while in NICU).</p>
Notes	<p>It is not stated how many women received corticosteroids off protocol.</p>
Allocation concealment	<p>A – Adequate</p>

<b>Study</b>	<b>Kari 1994</b>
Methods	<p>Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Stratification: yes, according to gestational age (24 to 27.9 weeks and 28 to 31.9 weeks) at each hospital. Placebo: yes, normal saline. Sample size calculation: yes. Intention-to-treat analyses: yes.</p>

## Characteristics of included studies (Continued)

	<p>Losses to follow up: yes, 10 (11%) children in the follow up study at age 2 (2 in the treatment arm and 8 in the control arm).</p> <p>Funding: Foundation for Pediatric Research, Finland; Orange County Infant Care Specialists, Finland; The Orion Corporation Research Foundation, Finland; Instrumentarium Corporation Research Foundation, Finland; Arvo and Lea Ylppo Foundation, Finland; Rinnekoti Foundation, Finland; and Organon Company, Oss, The Netherlands.</p>
Participants	<p>Location: 5 hospitals in Finland.</p> <p>Timeframe: April 1989 to October 1991.</p> <p>Eligibility criteria: women with preterm labour or threatened preterm delivery due to pre-eclampsia.</p> <p>Gestational age range: 24 to 31.9 weeks.</p> <p>Exclusion criteria: rupture of membranes, chorioamnionitis, congenital abnormalities, proven lung maturity, insulin treated diabetes, previously treated with corticosteroids.</p> <p>Total recruited: 157 women and 189 infants; 77 women and 95 infants in the treatment arm and 80 women and 95 infants in the control arm.</p>
Interventions	<p>4 doses of 6 mg dexamethasone sodium phosphate IM 12 hours apart.</p> <p>Control group received 4 doses of placebo. Rescue treatment with exogenous human surfactant was given to infants born 24 to 33 weeks, who at 2 to 24 hours of age required mechanical ventilation with &gt; 40% oxygen for RDS.</p>
Outcomes	<p>Maternal outcome (chorioamnionitis), fetal/neonatal outcomes (fetal death, neonatal death, RDS, chronic lung disease, IVH, birthweight, surfactant use, necrotising enterocolitis, small-for-gestational age) and childhood outcomes reported (death, neurodevelopmental delay).</p>
Notes	<p>Efficacy analysis restricted to 91 infants in treatment arm and 88 infants in control arm. 3 infants excluded for protocol violations (1 mother with twins in placebo arm was given corticosteroid, 1 infant in the treatment arm developed RDS but was not given surfactant as it was not available) and 6 infants were excluded because of congenital malformations (2 treatment, 4 placebo).</p>
Allocation concealment	B – Unclear

## Study

### Lewis 1996

Methods	<p>Type of study: randomised controlled trial.</p> <p>Method of treatment allocation: random-number table generated randomisation sequence by clinical research nurse uninvolved in clinical care. Sequentially number sealed opaque envelopes used. Stratification: none stated.</p> <p>Placebo: no.</p> <p>Sample size calculation: no.</p> <p>Intention-to-treat analyses: no.</p> <p>Losses to follow up: yes, 2 (2%) women left hospital after randomisation and were lost to follow up (one women in each arm).</p> <p>Funding: not stated.</p>
Participants	<p>Location: Louisiana State University Medical Center, Shreveport, Louisiana, USA.</p> <p>Timeframe: not stated in manuscript, the study is coded as 1990s for the review.</p> <p>Eligibility criteria: women with singleton pregnancies with PROM. Women were randomised 12 to 24 hours after receiving IV ampicillin-sulbactam.</p> <p>Gestational age range: 24 to 34 weeks.</p> <p>Exclusion criteria: evidence of infection, vaginal examination, cerclage, allergic to penicillin, contraindication to expectant management, lung maturity confirmed by L/S ratio if 32 weeks or more.</p> <p>Total recruited: 79 women and infants; 39 women and infants in the treatment arm and 40 women and infants in the control arm.</p>
Interventions	<p>12 mg IM betamethasone repeated at 24 hours and weekly if the women had not delivered.</p> <p>Control group received expectant management.</p>

## Characteristics of included studies (Continued)

Outcomes Maternal outcomes (chorioamnionitis, puerperal sepsis), fetal/neonatal outcomes (neonatal death, RDS, IVH, birthweight, Apgar < 7, interval between trial entry and delivery, admission to NICU, surfactant use, proven neonatal infection while in NICU, necrotising enterocolitis) and health service outcome reported (length of neonatal hospitalisation).

### Notes

Allocation concealment A – Adequate

## Study **Liggins 1972a**

Methods Type of study: randomised controlled trial. Method of treatment allocation: random-number table generated randomisation sequence by chief pharmacist. Pharmacy provided coded drug ampoules containing treatment or placebo. Stratification: no. Placebo: yes, of identical appearance. Sample-size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: yes, 54 (18%) children in the follow-up study at ages 4 to 6 (31 in the treatment arm and 23 in the control arm) and 412 (44%) adults in the follow up study at age 30 (219 in the treatment arm and 193 in the control arm). Funding: Health Research Council of New Zealand, Auckland, New Zealand; Auckland Medical Research Foundation, Auckland, New Zealand; and New Zealand Lottery Grants Board, Wellington, New Zealand.

Participants Location: National Women's Hospital, Auckland, New Zealand. Timeframe: December 1969 and February 1974. Eligibility criteria: women with threatened or planned preterm delivery. Gestational age range: 24 to 36 weeks. Exclusion criteria: imminent delivery, contraindication to corticosteroids. Total recruited: 1142 women and 1218 infants; 560 women and 601 infants in the treatment arm and 582 women and 617 infants in the control arm.

Interventions 2 doses of 6 mg betamethasone phosphate and 6 mg betamethasone acetate IM 24 hours apart. After the first 717 women had enrolled the treatment intervention was doubled to 2 doses of 12 mg betamethasone phosphate and 12 mg betamethasone acetate IM 24 hours apart. Control group received 6 mg cortisone acetate, which has 1/70th of the corticosteroid potency of the betamethasone.

Outcomes Maternal outcome (chorioamnionitis), fetal/neonatal outcomes (fetal death, neonatal death, RDS, cerebroventricular haemorrhage, mean birthweight, Apgar score < 7, mean interval between trial entry and delivery, proven infection while in NICU), childhood outcomes (death, mean weight, mean height, mean head circumference, mean lung function, mean blood pressure, intellectual impairment, cerebral palsy) and adulthood outcomes were reported (death, mean weight, mean height, mean head circumference, mean skin-fold thickness, mean blood pressure, glucose impairment, HPA axis function, mean cholesterol, educational achievement, visual impairment, hearing impairment, intellectual impairment).

Notes Review includes new intention-to-treat analysis of the complete study and additional data due to the authors providing individual participant study records.

Allocation concealment A – Adequate

## Study **Morales 1989**

Methods Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Sealed envelopes were used. Stratification: none stated. Placebo: no. Sample size calculation: no. Intention-to-treat analyses: no. Losses to follow up: no. Funding: not stated.

Participants Location: 3 hospitals in Florida, USA. Timeframe: January 1986 to March 1988. Eligibility criteria: women with singleton pregnancies with PROM.

## Characteristics of included studies (Continued)

	<p>Gestational age range: 26 and 34 weeks.</p> <p>Exclusion criteria: PROM &lt; 12 hours before onset of labour, uterine tenderness, foul smelling lochia, fetal tachycardia, allergy to penicillin, congenital abnormalities, L/S ratio 2 or more, unable to obtain an L/S ratio, Dubowitz assigned gestational age different from obstetric assessment by 3 weeks (postrandomisation exclusion).</p> <p>Total recruited: 165 women and infants; 87 women and infants in the treatment arm and 78 women and infants in the control arm.</p>
Interventions	Four treatment arms. Group 1, expectant management. Group 2, expectant management plus 2 doses of 12 mg betamethasone IM 24 hours apart, repeated weekly if the women remained undelivered. Group 3, expectant management plus 2 g ampicillin IV every 6 hours until cervical cultures were negative. Group 4, combination of group 2 and 3 management. Groups 2 and 4 were combined in the treatment arm for the review and groups 1 and 3 were combined in the control arm for the review.
Outcomes	Maternal outcome (chorioamnionitis), fetal/neonatal outcomes reported (neonatal death, RDS, chronic lung disease, IVH, birthweight, proven neonatal infection while in NICU, necrotising enterocolitis, duration of mechanical ventilation/CPAP).
Notes	Further information requested from authors but there was no reply. No information was available on post-randomisation exclusions.
Allocation concealment	B – Unclear

### Study

#### Nelson 1985

Methods	<p>Type of study: randomised controlled trial.</p> <p>Method of treatment allocation: random-number table generated randomisation sequence with consecutive sealed envelopes used. Stratification: none stated.</p> <p>Placebo: no.</p> <p>Sample size calculation: no.</p> <p>Intention-to-treat analyses: yes.</p> <p>Losses to follow up: no.</p> <p>Funding: not stated.</p>
Participants	<p>Location: Wake Forest University Medical Center, North Carolina, USA.</p> <p>Timeframe: not stated in manuscript, the study is coded as 1980s for the review.</p> <p>Eligibility criteria: women with PROM.</p> <p>Gestational age range: 28 and 34 weeks.</p> <p>Exclusion criteria: fetal distress, active labour, cervical dilatation &gt; 3 cm, sensitivity to tocolytics, PROM &gt; 24 hours, existing infection.</p> <p>Total recruited: 44 women and infants; 22 women and infants in each arm.</p>
Interventions	Three treatment arms. Group 1, 2 doses of 6 mg or 12 mg betamethasone IM 12 hours apart, delivery 24 to 48 hours after PROM and after 24 hours of corticosteroid therapy. Group 2, delivery 24 to 48 hours after PROM. Group 3, expectant management. Group 3 was not included in the review.
Outcomes	Fetal/neonatal outcomes (neonatal death, RDS, proven neonatal infection while in NICU) and health service outcome reported (length of neonatal hospitalisation).
Notes	Authors provided further information.
Allocation concealment	A – Adequate

### Study

#### Parsons 1988

Methods	<p>Type of study: randomised controlled trial.</p> <p>Method of treatment allocation: method of randomisation not stated. Stratification: none stated.</p> <p>Placebo: no.</p> <p>Sample size calculation: no.</p> <p>Intention-to-treat analyses: yes.</p>
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## Characteristics of included studies (Continued)

	Losses to follow up: no. Funding: not stated.
Participants	Location: University of Illinois, Chicago, USA. Timeframe: not stated in manuscript, the study is coded as 1980s for the review. Eligibility criteria: women with PROM and < 4 cm of cervical dilatation. Gestational age range: 25 to 32 weeks. Exclusion criteria: infection, fetal distress, fetal anomalies, contraindication to tocolysis. Total recruited: 45 women and infants; 23 women and infants in the treatment arm and 22 women and infants in the control arm.
Interventions	2 doses of 12 mg betamethasone IM 12 hours apart repeated weekly until 32 weeks. Control group received expectant management.
Outcomes	Fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, systemic infection in the first 48 hours of life, proven neonatal infection while in NICU).
Notes	
Allocation concealment	B – Unclear

Study	Qublan 2001
Methods	Type of study: randomised controlled trial. Method of treatment allocation: random-number table generated randomisation sequence. Allocation concealment unclear. Stratification: none stated. Placebo: no. Sample size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: no. Funding: not stated.
Participants	Location: 2 military hospitals in Jordan. Timeframe: January 1997 to February 1999. Eligibility criteria: women with singleton pregnancies and PROM. Gestational age range: 27 to 34 weeks. Exclusion criteria: lethal congenital anomaly, fetal death, infection, expected delivery within 12 hours. Total recruited: 137 women and infants; 72 women and infants in the treatment arm and 67 women and infants in the control arm.
Interventions	4 doses of 6 mg dexamethasone IM 12 hours apart, repeated if women had not delivered after 1 week. Control group received expectant management.
Outcomes	Maternal outcomes (chorioamnionitis, puerperal sepsis), fetal/neonatal outcomes (fetal death, neonatal death, RDS, IVH, proven neonatal infection while in NICU, necrotising enterocolitis, Apgar < 7) and health service outcome reported (length of neonatal hospitalisation).
Notes	Authors contacted for further information but no reply. Discrepancy in number of infants with necrotising enterocolitis in manuscript.
Allocation concealment	B – Unclear

Study	Schutte 1980
Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Coded drug ampoules were provided. Randomisation code was only known to pharmacist. Stratification: none stated. Placebo: yes, normal saline. Sample size calculation: no. Intention-to-treat analyses: no.

## Characteristics of included studies (Continued)

	<p>Losses to follow up: yes, 12 (12%) children in the follow-up study at ages 10 to 12 (4 in the treatment arm and 8 in the control arm) and 21 (21%) adults in the follow-up study at age 20 (10 in the treatment arm and 11 in the control arm).</p> <p>Funding: Dutch Foundation for Research on Prevention (Praeventiefonds Project 28-1145), The Netherlands.</p>
Participants	<p>Location: Department of Obstetrics and Gynaecology and Department of Neonatology, Wilhelmina Gasthuis, University of Amsterdam, Amsterdam, The Netherlands.</p> <p>Timeframe: April 1974 to April 1977.</p> <p>Eligibility criteria: women with preterm labour in whom it was possible to delay delivery by at least 12 hours. Gestational age range: 26 to 32 weeks. Exclusion criteria: no contraindications to the use of corticosteroids or ociprenaline (insulin-treated diabetes, hyperthyroidism, infection, severe hypertension, cardiac disease, marked fetal growth retardation or fetal distress).</p> <p>Total recruited: 101 women and 123 infants; 50 women and 65 infants in the treatment arm and 51 women and 58 infants in the control arm.</p>
Interventions	<p>8 mg betamethasone phosphate and 6 mg betamethasone acetate IM repeated after 24 hours. Control group received an identical placebo. All women received ociprenaline infusion and bed-rest until 32 weeks.</p>
Outcomes	<p>Maternal outcomes (death, chorioamnionitis, puerperal sepsis, fever after trial entry requiring antibiotics, intrapartum fever requiring antibiotics, postnatal fever, admission to ICU, side-effects of therapy), fetal/neonatal outcomes (fetal death, neonatal death, RDS, IVH, birthweight, Apgar score &lt; 7), childhood outcomes (weight, height, head circumference, lung function, visual impairment, hearing impairment, intellectual impairment, cerebral palsy, behavioural/learning difficulties) and adulthood outcomes were reported (weight, height, head circumference, blood pressure, intellectual impairment, age at puberty).</p>
Notes	<p>Initial study report included a third arm of women and infants who had been excluded from randomisation, these women and infants are not included in the review.</p>
Allocation concealment	B – Unclear
<b>Study</b>	<b>Silver 1996</b>
Methods	<p>Type of study: randomised controlled trial.</p> <p>Method of treatment allocation: computer-generated randomisation sequence used. Pharmacy provided identical syringes labelled with the woman's study number. Stratification: none stated.</p> <p>Placebo: yes, normal saline.</p> <p>Sample size calculation: yes.</p> <p>Intention-to-treat analyses: no.</p> <p>Losses to follow up: 124 women initially recruited, of whom 49 (40%) remained undelivered after 29 weeks and were not included in the review.</p> <p>Funding: not stated.</p>
Participants	<p>Location: Northwestern University Medical School, Chicago, Illinois, USA.</p> <p>Timeframe: April 1990 to June 1994.</p> <p>Eligibility criteria: women at risk of delivery between 24 to 29 weeks.</p> <p>Gestational age range: 24 to 29 weeks.</p> <p>Exclusion criteria: infection, maternal or fetal indications for urgent delivery.</p> <p>Total recruited: 75 women and 96 infants; 39 women and 54 infants in the treatment arm and 36 women and 42 infants in the control arm.</p>
Interventions	<p>4 doses of 5 mg dexamethasone IM 12 hours apart, repeated weekly if the women remained undelivered. Control group received placebo. All infants born &lt; 30 weeks received prophylactic surfactant at birth.</p>
Outcomes	<p>Maternal outcomes (chorioamnionitis, puerperal sepsis) and fetal/neonatal outcomes reported (neonatal death, RDS, chronic lung disease, IVH, small-for-gestational age, birthweight, necrotising enterocolitis).</p>
Notes	<p>Those women undelivered after 29 weeks were eligible for corticosteroid outside the study protocol. These women and their infants are not included in the review as it was not possible to separate out control women who subsequently received corticosteroids.</p>

## Characteristics of included studies (Continued)

Allocation concealment A – Adequate

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<b>Study</b>	<b>Tausch 1979</b>
Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Coded drug boxes used. Stratification: yes, by gestational age at entry. Placebo: yes, normal saline. Sample size calculation: yes. Intention-to-treat analyses: no. Losses to follow up: yes, data not available for maternal outcomes on 4 women (2 in each treatment arm). Funding: not stated.
Participants	Location: 2 hospitals in Boston, USA. Timeframe: January 1975 to March 1977. Eligibility criteria: women with preterm labour, PROM or with cervical dilatation < 5 cm at 33 weeks or less and women with an L/S ratio < 2 if > 33 weeks or who had a previous infant with RDS. Gestational age range: not stated. Exclusion criteria: indication for immediate delivery, obstetrician objection, preeclampsia, previously received corticosteroids. Total recruited: 122 women and 127 infants; 39 women and 54 infants in the treatment arm and 36 women and 42 infants in the control arm.
Interventions	6 doses of 4 mg dexamethasone phosphate IM 8 hours apart. Control group received placebo.
Outcomes	Maternal outcomes (puerperal sepsis, fever after trial entry requiring antibiotics) and fetal/neonatal outcomes reported (fetal death, neonatal death, RDS, chronic lung disease, IVH, proven neonatal infection while in NICU).
Notes	Authors contacted for further information but there was no reply.
Allocation concealment	B – Unclear

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<b>Study</b>	<b>Teramo 1980</b>
Methods	Type of study: randomised controlled trial. Method of treatment allocation: method of randomisation not stated. Coded drug boxes used. Stratification: none stated. Placebo: yes, normal saline. Sample size calculation: no. Intention-to-treat analyses: yes. Losses to follow up: no. Funding: not stated.
Participants	Location: University of Helsinki, Finland. Timeframe: not stated in manuscript, the study is coded as 1980s for the review. Eligibility criteria: women with preterm labour and cervical dilatation < 4 cm without progression of labour upon initial observation of up to 12 hours. Gestational age range: 28 to 35 weeks. Exclusion criteria: pre-eclampsia, diabetes. Total recruited: 74 women and 80 infants; 36 women and 38 infants in the treatment arm and 38 women and 42 infants in the control arm.
Interventions	2 doses of 12 mg betamethasone IM 24 hours apart. Control group received placebo.
Outcomes	Fetal/neonatal outcomes reported (RDS, HPA axis function).
Notes	

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Allocation concealment B – Unclear

CPAP: continuous positive airways pressure

HPA: hypothalamic-pituitary-adrenal

ICU: intensive care unit

IM: intramuscular

IV: intravenous

NICU: neonatal intensive care unit

PROM: premature rupture of membranes

RDS: respiratory distress syndrome

Rh: Rhesus

SD: standard deviation

## Characteristics of excluded studies

Study	Reason for exclusion
Abuhamad 1999	This abstract compares TRH + betamethasone with betamethasone + placebo.
Butterfill 1979	Randomised participants are combined with a non-randomised cohort and cannot be analysed separately.
Dola 1997	This abstract compares TRH + betamethasone with betamethasone + placebo.
Egerman 1998	This trial compares oral versus IM dexamethasone in the prevention of RDS. It does not meet our entry criteria for inclusion of studies for the review.
Garite 1981	This trial compares a policy of corticosteroid therapy followed by elective delivery with a policy of withholding corticosteroids and awaiting delivery so the independent effect of the two co-interventions cannot be evaluated separately.
Halac 1990	Not a randomised trial. Women were allocated to placebo if they were expected to deliver within 24 hours and to betamethasone if labour was not expected within 24 hours.
Iams 1985	Corticosteroid therapy (hydrocortisone) and co-intervention of elective delivery was compared to expectant management in PROM. The independent effect of the two co-interventions cannot be evaluated separately.
Kuhn 1982	Randomised participants are combined with a non-randomised cohort and cannot be analysed separately.
Magee 1997	This study compares the effects of betamethasone vs dexamethasone on antenatal fetal heart rate.
Minoui 1996	This study compares the effects of betamethasone vs dexamethasone on antenatal fetal heart rate.
Morales 1986	Quasi-randomised using medical record number.
Morrison 1978	This study was included in original review. It is excluded from this update because of > 20% postrandomisation exclusions and the fact that it was possibly quasi-randomised.
Mulder 1997	This study compares the effects of betamethasone vs dexamethasone on antenatal fetal heart rate.
Papageorgiou 1979	This study was included in original review. It is excluded from this update because of > 20% post-randomisation exclusions. Of 146 babies included in the study, the paper only reports outcomes for 61.
Rotmensch 1999	This study compares the effects of betamethasone vs dexamethasone on antenatal fetal heart rate.
Schmidt 1984	This study was included in original review. It is excluded from this update because of > 20% postrandomisation exclusions. The paper only reports results from 92 of 144 randomised mothers and 97 of 149 randomised babies.
Simpson 1985	Quasi-randomised study. Randomised participants are combined with a non-randomised cohort and cannot be analysed separately.
Whitt 1976	This trial compares IM betamethasone with IV cortisol. It does not meet our entry criteria for inclusion of studies for the review.

IM: intramuscular

IV: intravenous

PROM: premature rupture of membranes

RDS: respiratory distress syndrome

TRH: thyrotropin-releasing hormone

## Characteristics of excluded studies (Continued)

vs: versus

### ANALYSES

#### Comparison 01. Corticosteroids versus placebo or no treatment

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death			Relative Risk (Fixed) 95% CI	Subtotals only
02 Chorioamnionitis			Relative Risk (Fixed) 95% CI	Subtotals only
03 Puerperal sepsis			Relative Risk (Fixed) 95% CI	Subtotals only
04 Fetal and neonatal deaths			Relative Risk (Fixed) 95% CI	Subtotals only
05 Fetal deaths			Relative Risk (Fixed) 95% CI	Subtotals only
06 Neonatal deaths			Relative Risk (Fixed) 95% CI	Subtotals only
07 Respiratory distress syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
08 Moderate/severe respiratory distress syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
09 Chronic lung disease			Relative Risk (Fixed) 95% CI	Subtotals only
10 Cerebroventricular haemorrhage			Relative Risk (Fixed) 95% CI	Subtotals only
11 Mean birthweight (grams)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
12 Death in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
13 Neurodevelopmental delay in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
14 Death into adulthood			Relative Risk (Fixed) 95% CI	Subtotals only
15 Fever in women after trial entry requiring the use of antibiotics			Relative Risk (Fixed) 95% CI	Subtotals only
16 Intrapartum fever in woman requiring the use of antibiotics			Relative Risk (Fixed) 95% CI	Subtotals only
17 Postnatal fever in woman			Relative Risk (Fixed) 95% CI	Subtotals only
18 Admission into adult intensive care unit			Relative Risk (Fixed) 95% CI	Subtotals only
19 Side-effects of therapy in women			Relative Risk (Fixed) 95% CI	Subtotals only
20 Glucose intolerance			Relative Risk (Fixed) 95% CI	Subtotals only
21 Hypertension			Relative Risk (Fixed) 95% CI	Subtotals only
22 Apgar < 7 at 5 minutes			Relative Risk (Fixed) 95% CI	Subtotals only
23 Mean interval between trial entry and birth (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
24 Small-for-gestational age			Relative Risk (Fixed) 95% CI	Subtotals only
25 Admission to neonatal intensive care unit			Relative Risk (Fixed) 95% CI	Subtotals only
26 Need for mechanical ventilation/CPAP			Relative Risk (Fixed) 95% CI	Subtotals only
27 Mean duration of mechanical ventilation/CPAP (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
28 Air leak syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
29 Mean duration of oxygen supplementation (days)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
30 Surfactant use			Relative Risk (Fixed) 95% CI	Subtotals only
31 Systemic infection in the first 48 hours of life			Relative Risk (Fixed) 95% CI	Subtotals only

32	Proven infection while in the neonatal intensive care unit			Relative Risk (Fixed) 95% CI	Subtotals only
33	Necrotising enterocolitis			Relative Risk (Fixed) 95% CI	Subtotals only
34	Mean infant HPA axis function (cortisol)	3	27	Weighted Mean Difference (Fixed) 95% CI	3.94 [-3.12, 11.00]
35	Mean childhood weight (kg)	3	333	Weighted Mean Difference (Fixed) 95% CI	0.30 [-0.39, 1.00]
36	Mean childhood head circumference (cm)	3	328	Weighted Mean Difference (Fixed) 95% CI	0.27 [-0.08, 0.63]
37	Mean childhood height (cm)	3	334	Weighted Mean Difference (Fixed) 95% CI	1.02 [-0.26, 2.29]
38	Mean childhood VC (% predicted)	3	150	Weighted Mean Difference (Fixed) 95% CI	-1.68 [-5.12, 1.75]
39	Mean childhood FEV1 (% predicted)	2	75	Weighted Mean Difference (Fixed) 95% CI	-4.73 [-10.13, 0.67]
40	Mean childhood FEV1/VC	3	150	Weighted Mean Difference (Fixed) 95% CI	-1.06 [-3.23, 1.11]
41	Mean childhood systolic blood pressure (mmHg)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
42	Visual impairment in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
43	Hearing impairment in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
44	Developmental delay in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
45	Intellectual impairment in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
46	Cerebral palsy in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
47	Behavioural/learning difficulties in childhood			Relative Risk (Fixed) 95% CI	Subtotals only
48	Mean adult weight (kg)	3	538	Weighted Mean Difference (Fixed) 95% CI	0.80 [-2.02, 3.62]
49	Mean adult head circumference (cm)	3	537	Weighted Mean Difference (Fixed) 95% CI	0.03 [-0.33, 0.38]
50	Mean adult height (cm)	4	537	Weighted Mean Difference (Fixed) 95% CI	0.91 [-0.28, 2.10]
51	Mean adult skinfold thickness (log values)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
52	Mean adult systolic blood pressure (mmHg)	3	545	Weighted Mean Difference (Fixed) 95% CI	-0.87 [-2.81, 1.07]
53	Mean adult glucose (mmol/L)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
54	Mean adult insulin (log values)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
55	Mean adult HPA axis function (mean log fasting cortisol)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
56	Mean cholesterol in adulthood (mmol/L)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
57	Mean age at puberty (years)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
58	Educational achievement by adulthood (university or polytechnic education)			Relative Risk (Fixed) 95% CI	Subtotals only
59	Visual impairment in adulthood			Relative Risk (Fixed) 95% CI	Subtotals only
60	Hearing impairment in adulthood			Relative Risk (Fixed) 95% CI	Subtotals only
61	Intellectual impairment in adulthood			Relative Risk (Fixed) 95% CI	Subtotals only

62 Mean length of antenatal hospitalisation (days)	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
63 Mean length of postnatal hospitalisation (days)	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
64 Mean length of neonatal hospitalisation (days)	Weighted Mean Difference (Fixed) 95% CI	Subtotals only

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## COVER SHEET

<b>Title</b>	Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth
<b>Authors</b>	Roberts D, Dalziel S
<b>Contribution of author(s)</b>	P Crowley prepared the first version of the Cochrane review in 1996. S Dalziel and D Roberts revised the protocol for the 2005 update. Both review authors identified included and excluded studies, extracted the data and wrote the discussion. S Dalziel entered the data and reanalysed data from the New Zealand Trial using intention to treat. D Roberts entered the tables and contacted authors for additional data.
<b>Issue protocol first published</b>	2003/4
<b>Review first published</b>	2006/3
<b>Date of most recent amendment</b>	24 May 2006
<b>Date of most recent SUBSTANTIVE amendment</b>	15 May 2006
<b>What's New</b>	<p>October 2005</p> <p>The review has been substantially updated due to new Cochrane guidelines for inclusion and exclusion of studies and the need for the review to be standardised with the repeat courses of prenatal corticosteroids review. Six new trials have been included (Amorim 1999; Dexiprom 1999; Fekih 2002; Lewis 1996; Nelson 1985; Qublan 2001). Three studies that were included in the previous review have been excluded. The results are now presented as relative risks. Results from recent follow-up studies have been included. Individual participant data were available from the Liggins and Howie study and these were analysed completely by intention-to-treat analysis for the first time. These data contribute nearly a third of the data to the review. This represents an important development. The review also provides new information on corticosteroid use in the presence of rupture of membranes, hypertension syndromes, in multiple pregnancies and according to gestational age at first corticosteroid dose.</p>
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	30 October 2005
<b>Date authors' conclusions section amended</b>	Information not supplied by author
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**DOI** 10.1002/14651858.CD004454.pub2  
**Cochrane Library number** CD004454  
**Editorial group** Cochrane Pregnancy and Childbirth Group  
**Editorial group code** HM-PREG

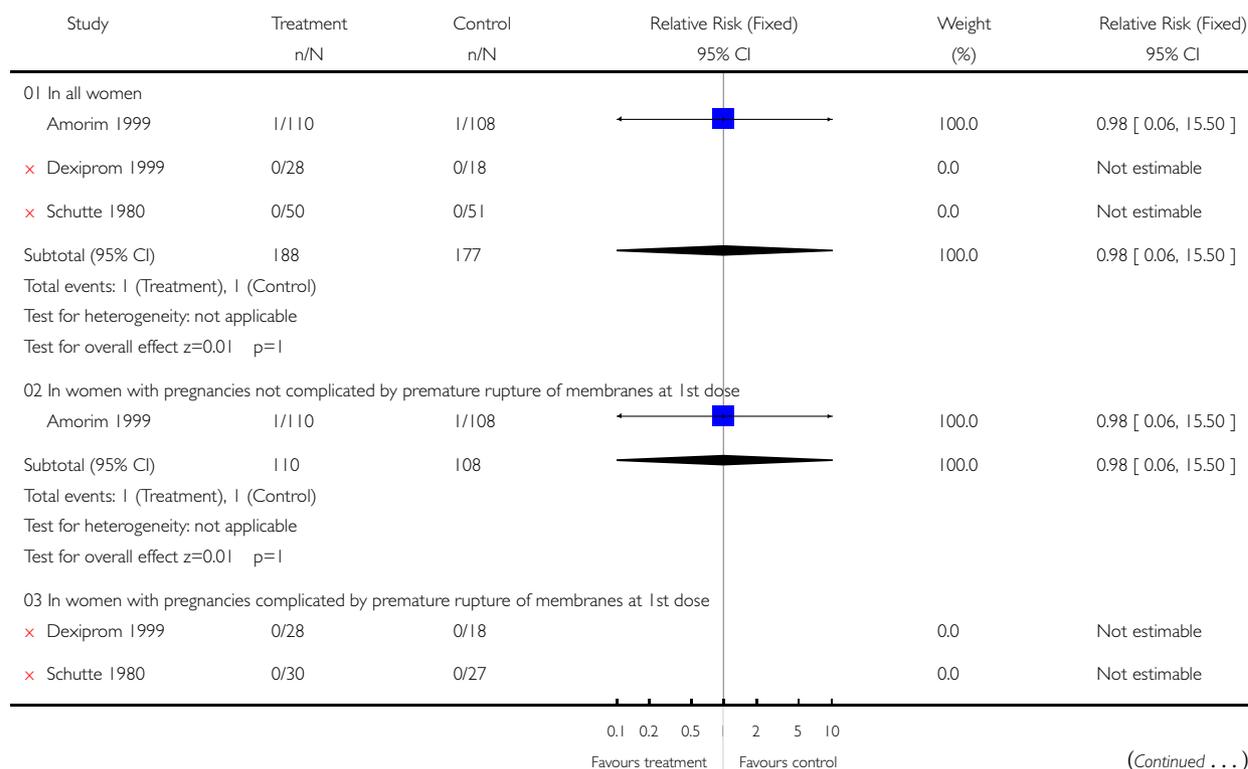
## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 01 Maternal death

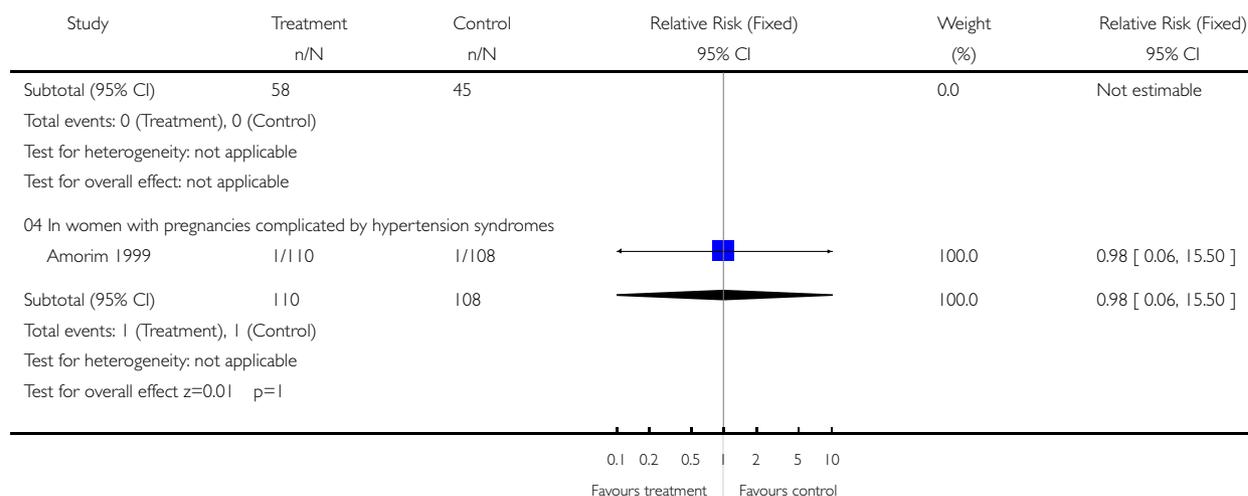
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 01 Maternal death



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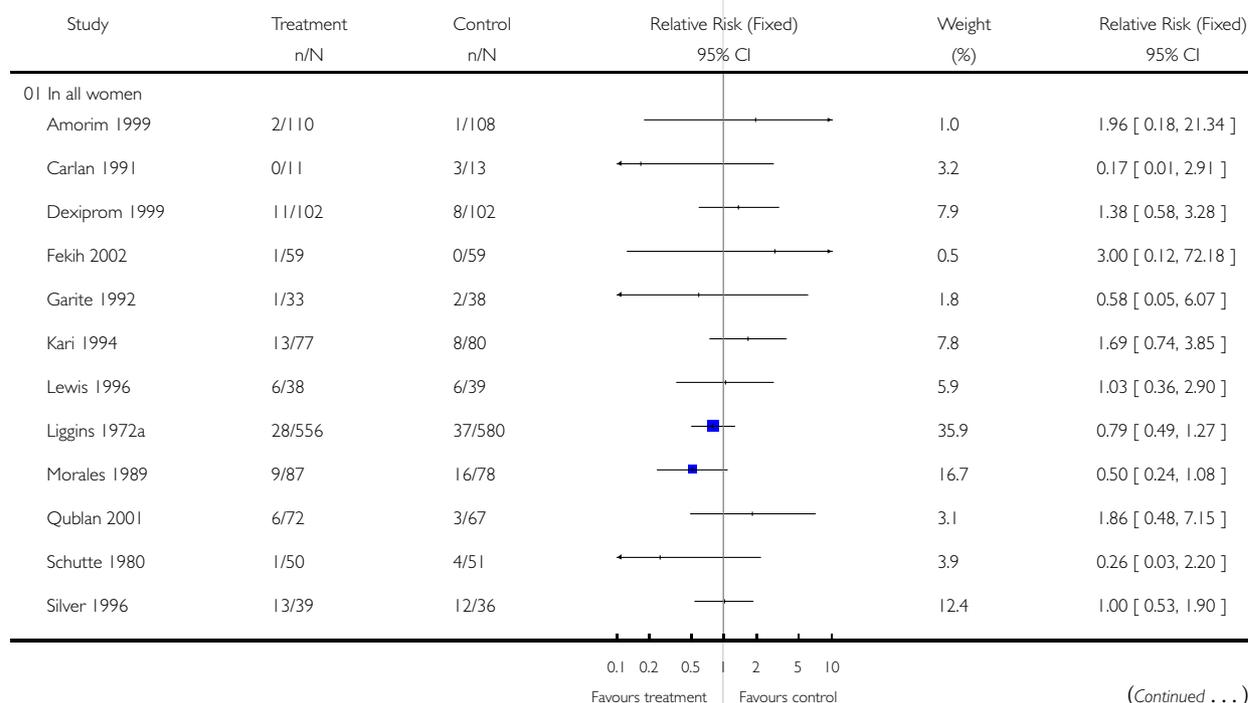


### Analysis 01.02. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 02 Chorioamnionitis

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

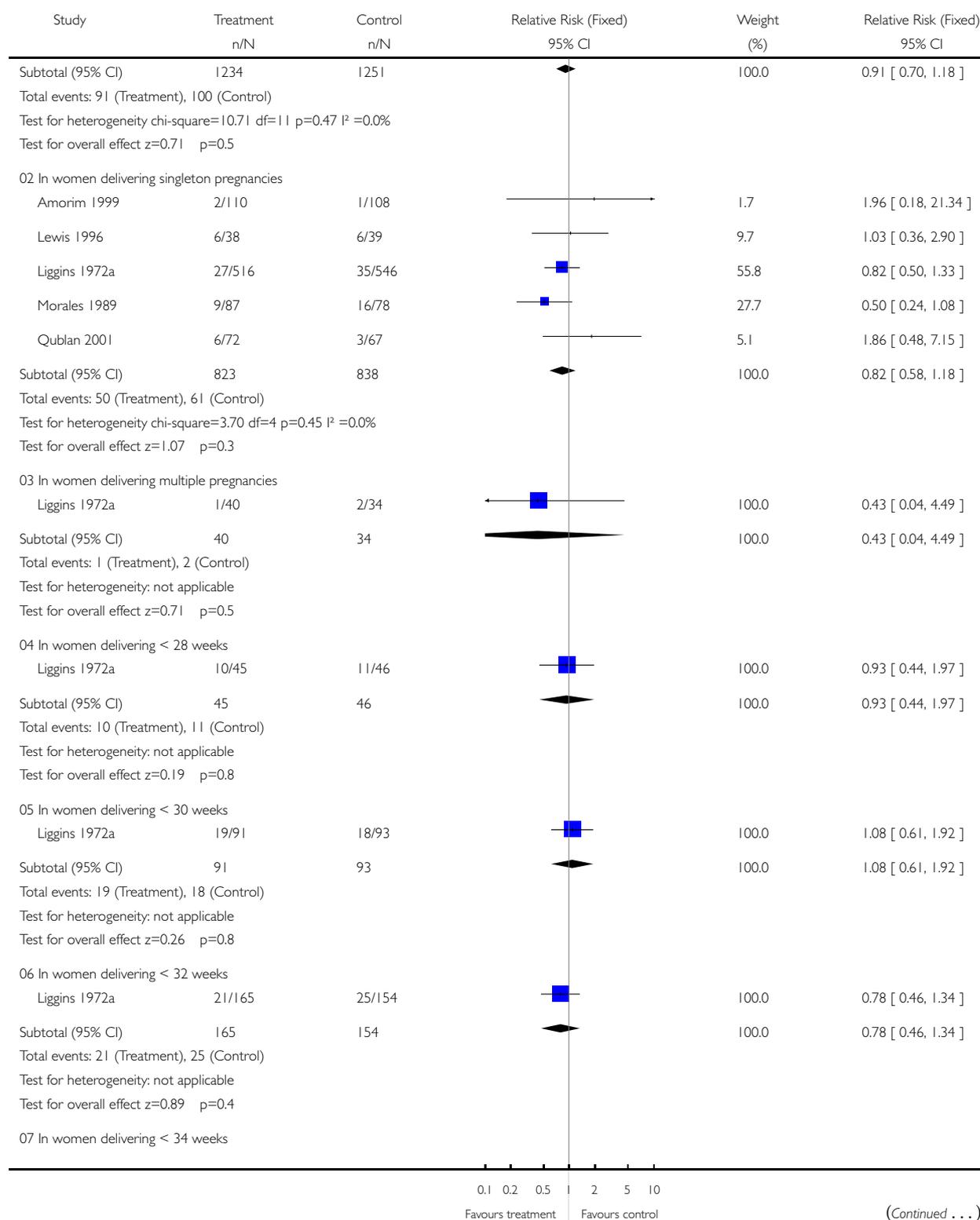
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 02 Chorioamnionitis



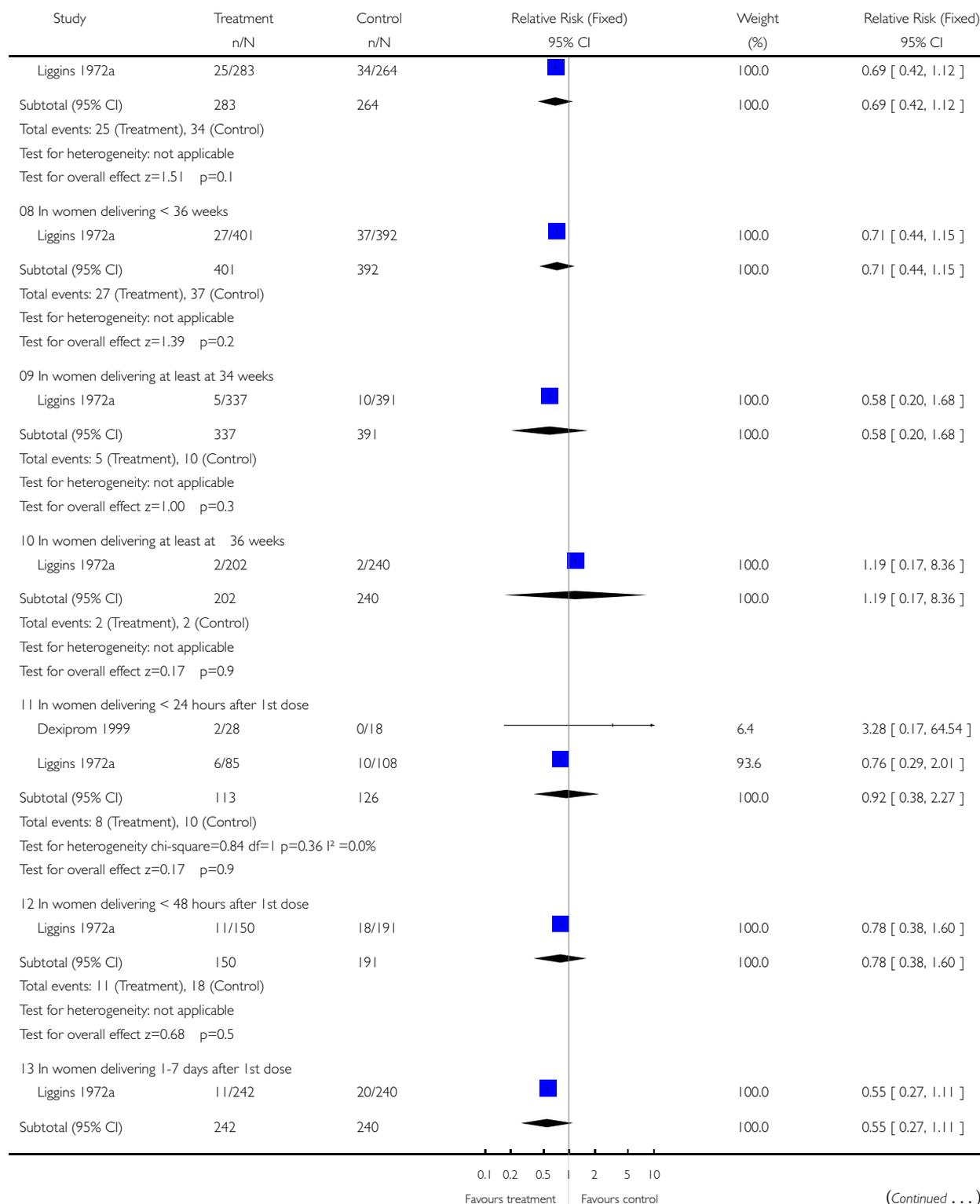
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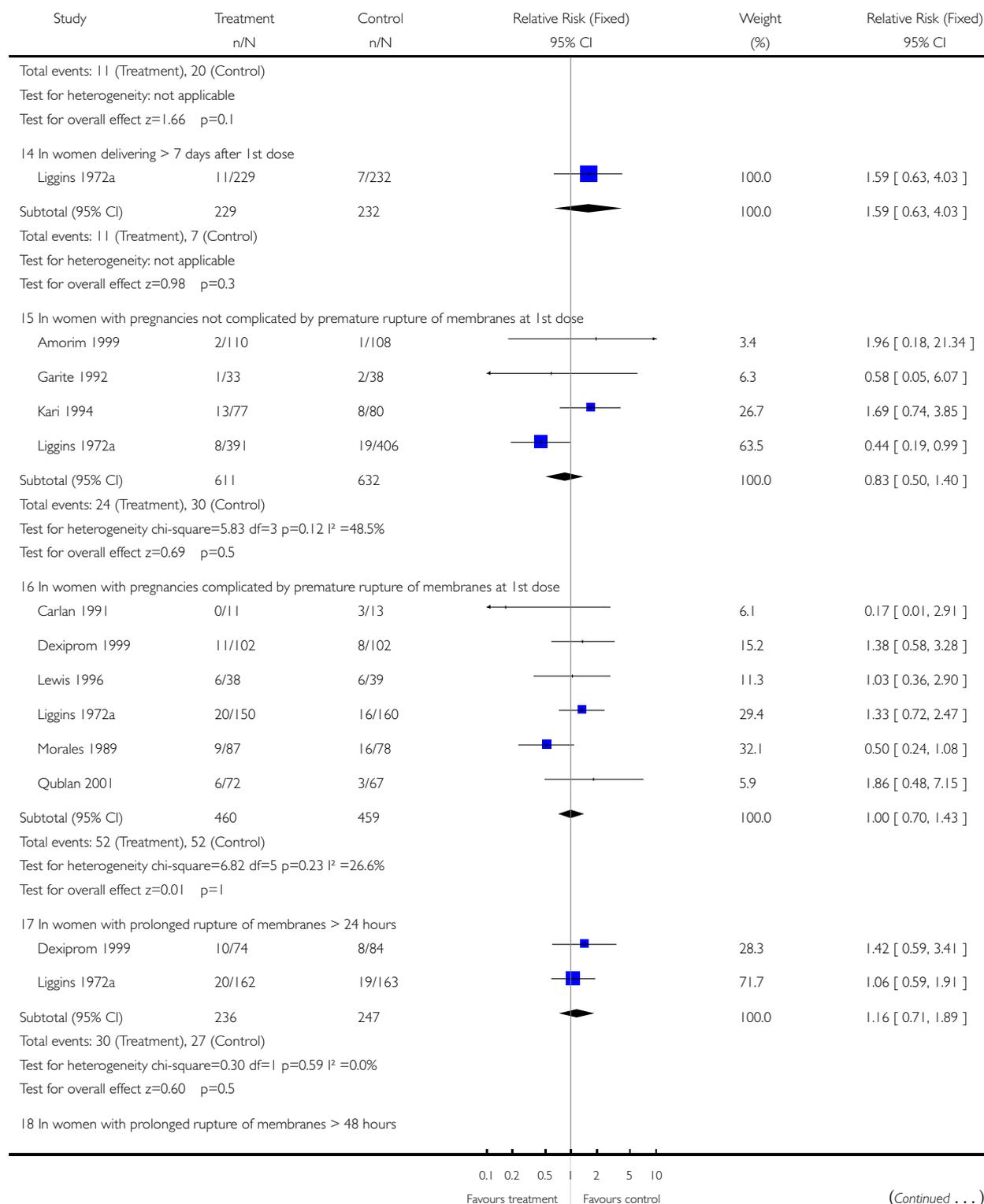
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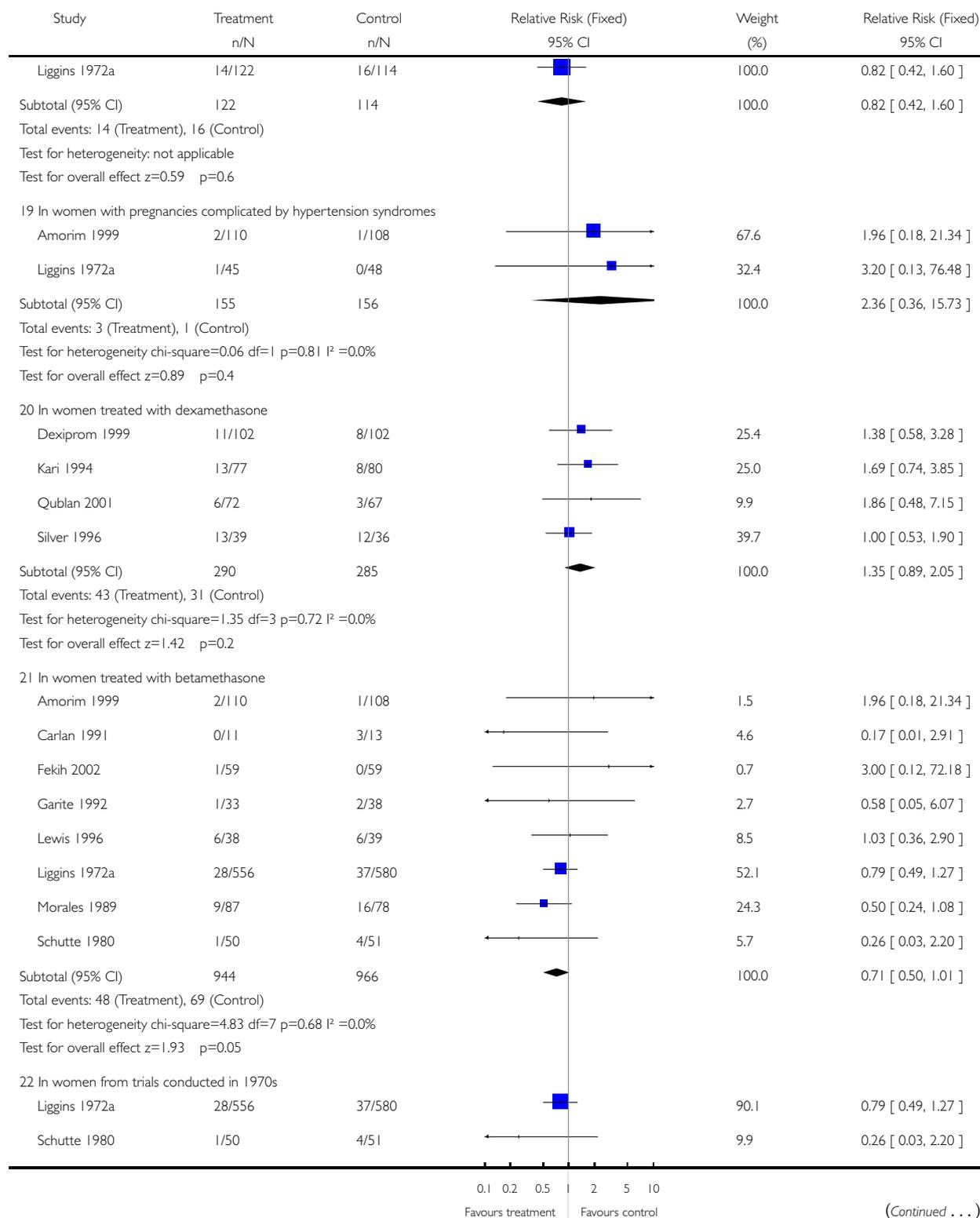
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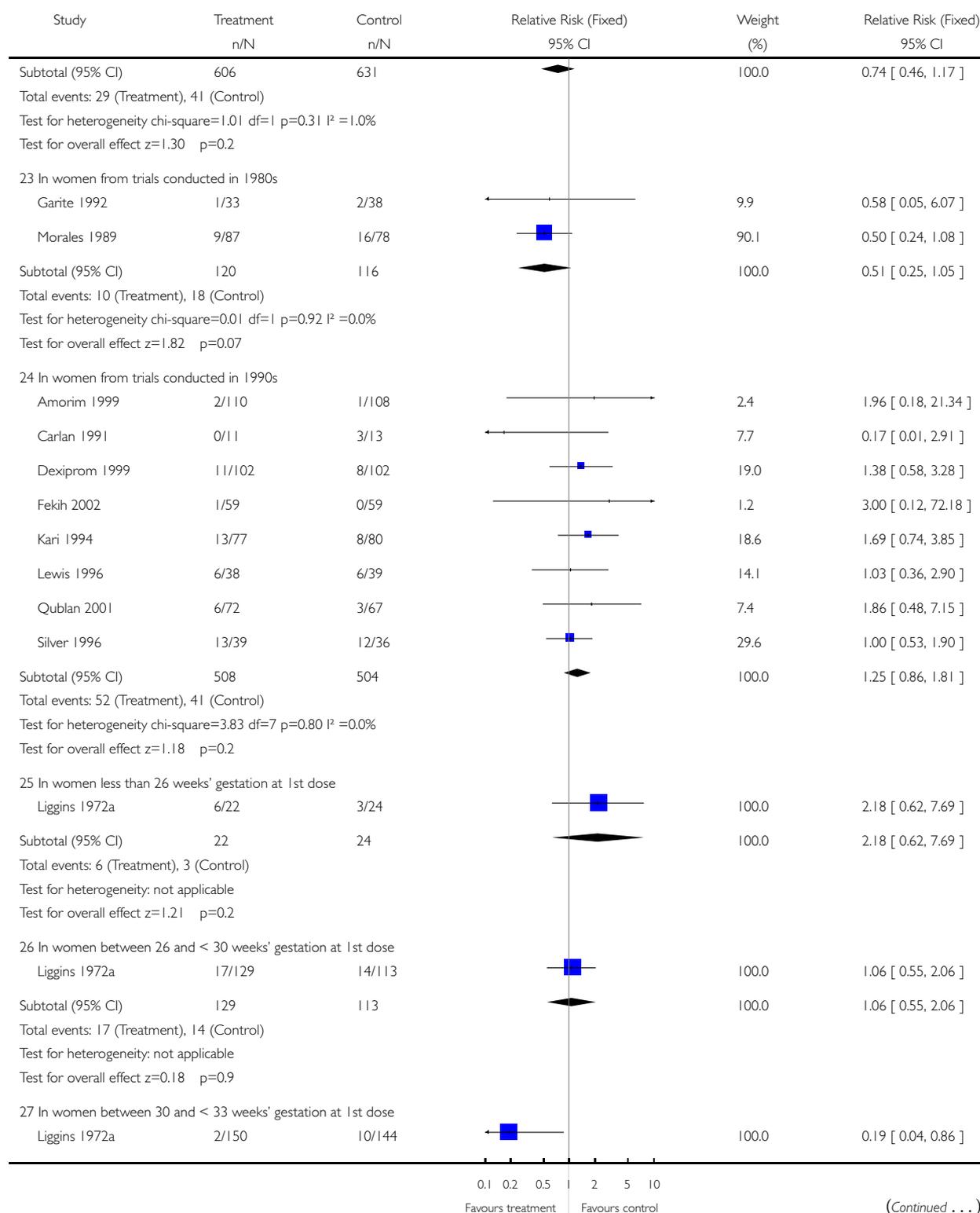
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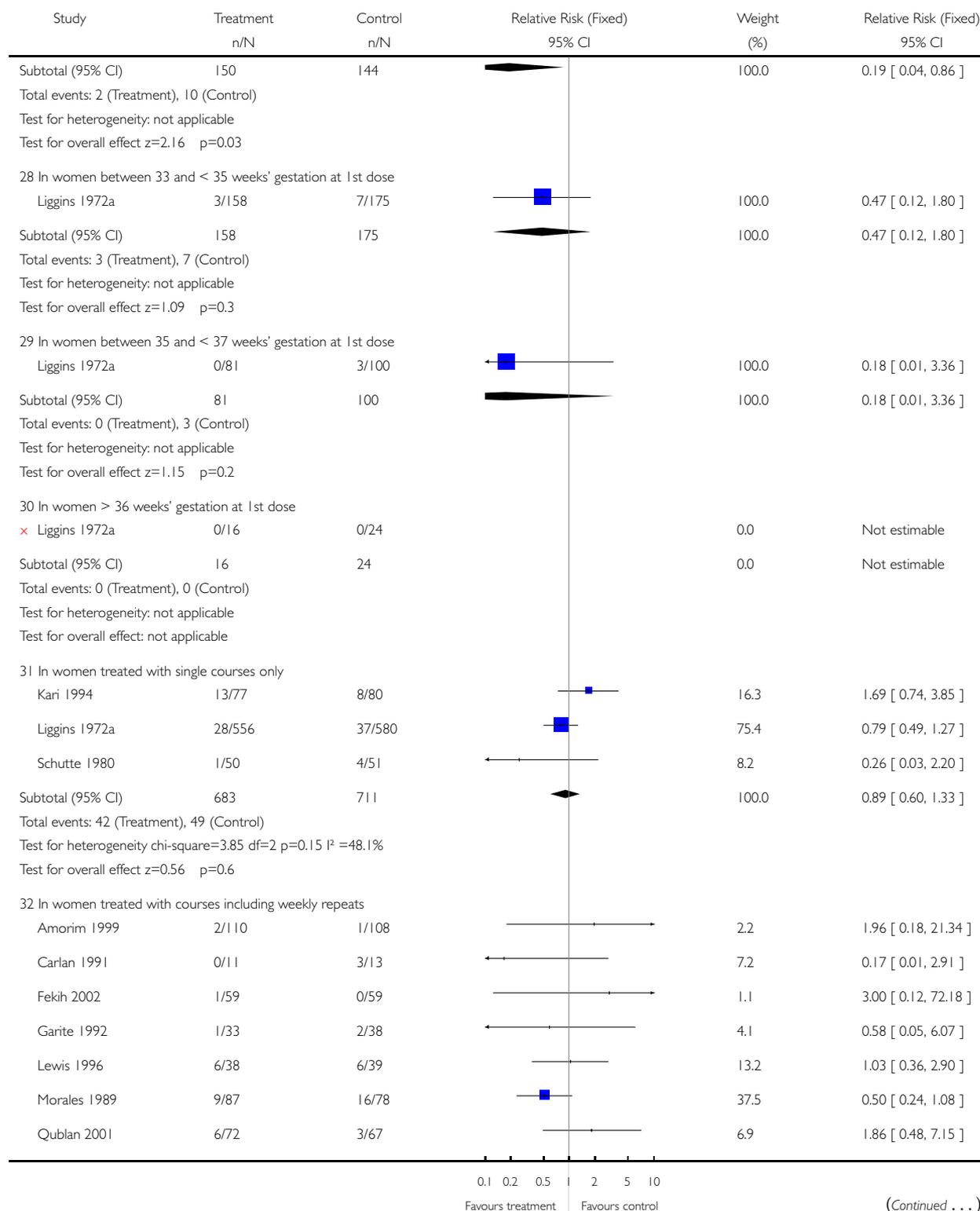
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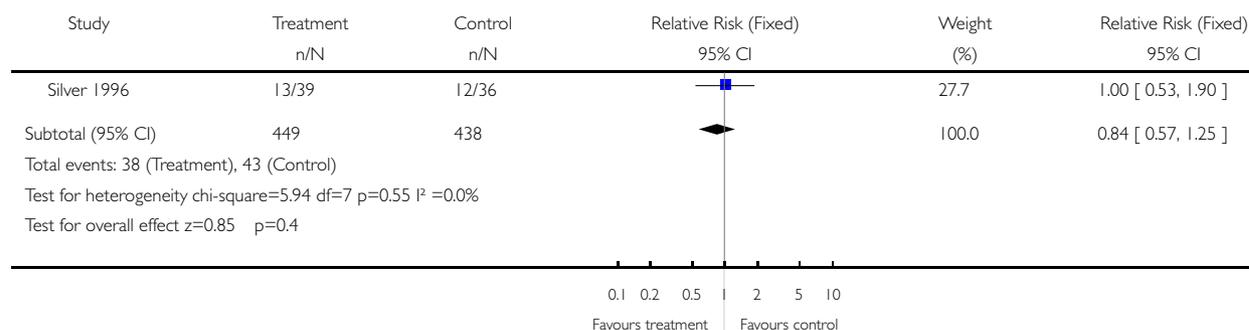
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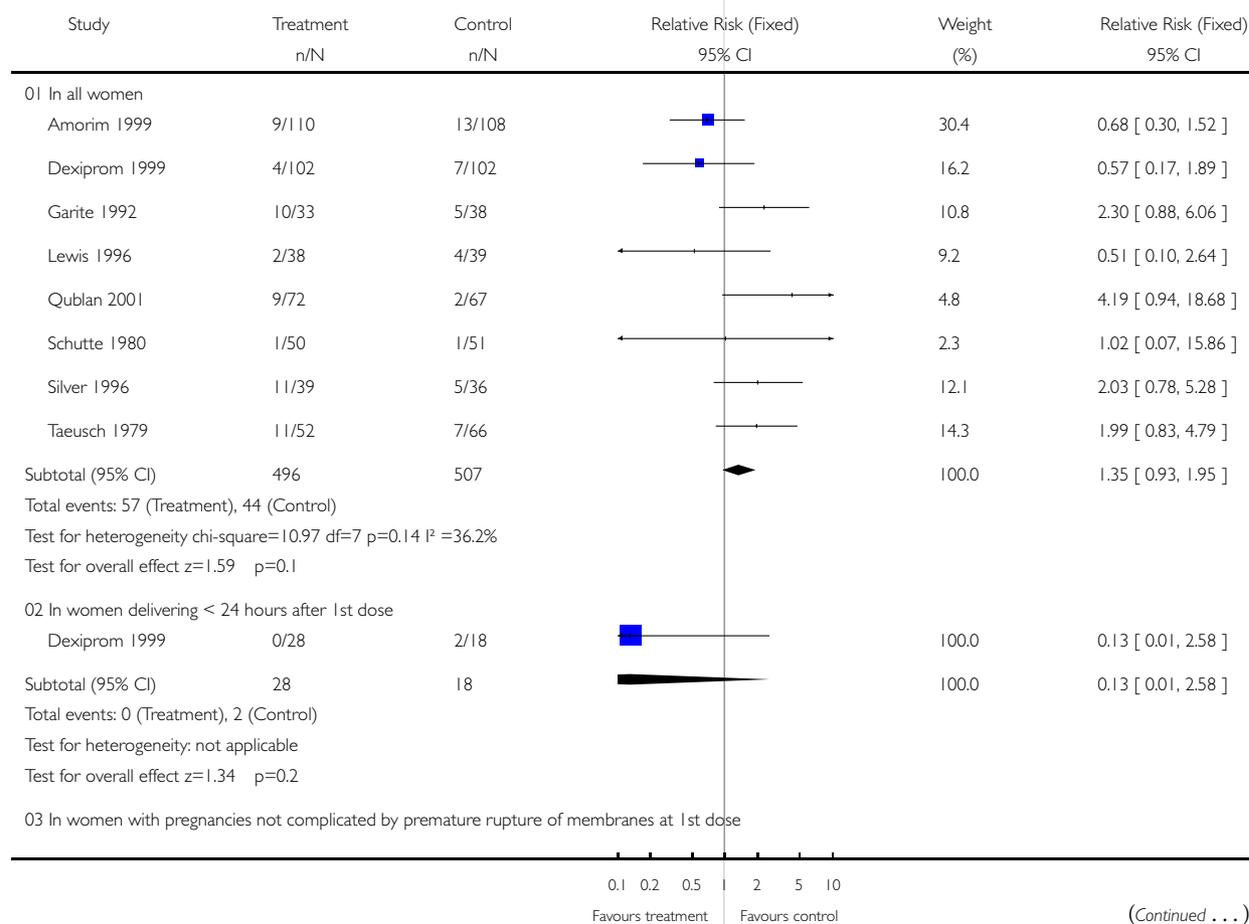


### Analysis 01.03. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 03 Puerperal sepsis

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

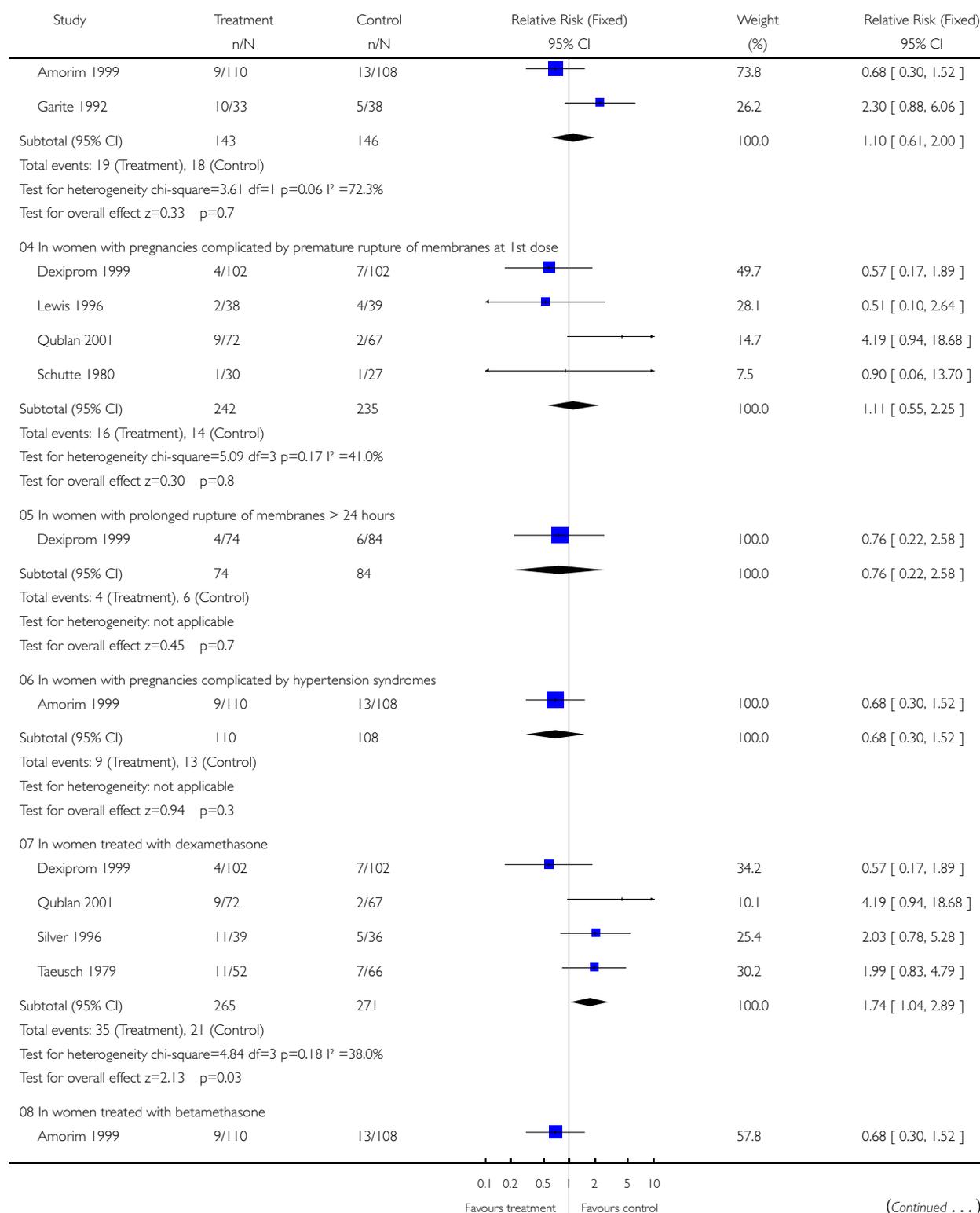
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 03 Puerperal sepsis



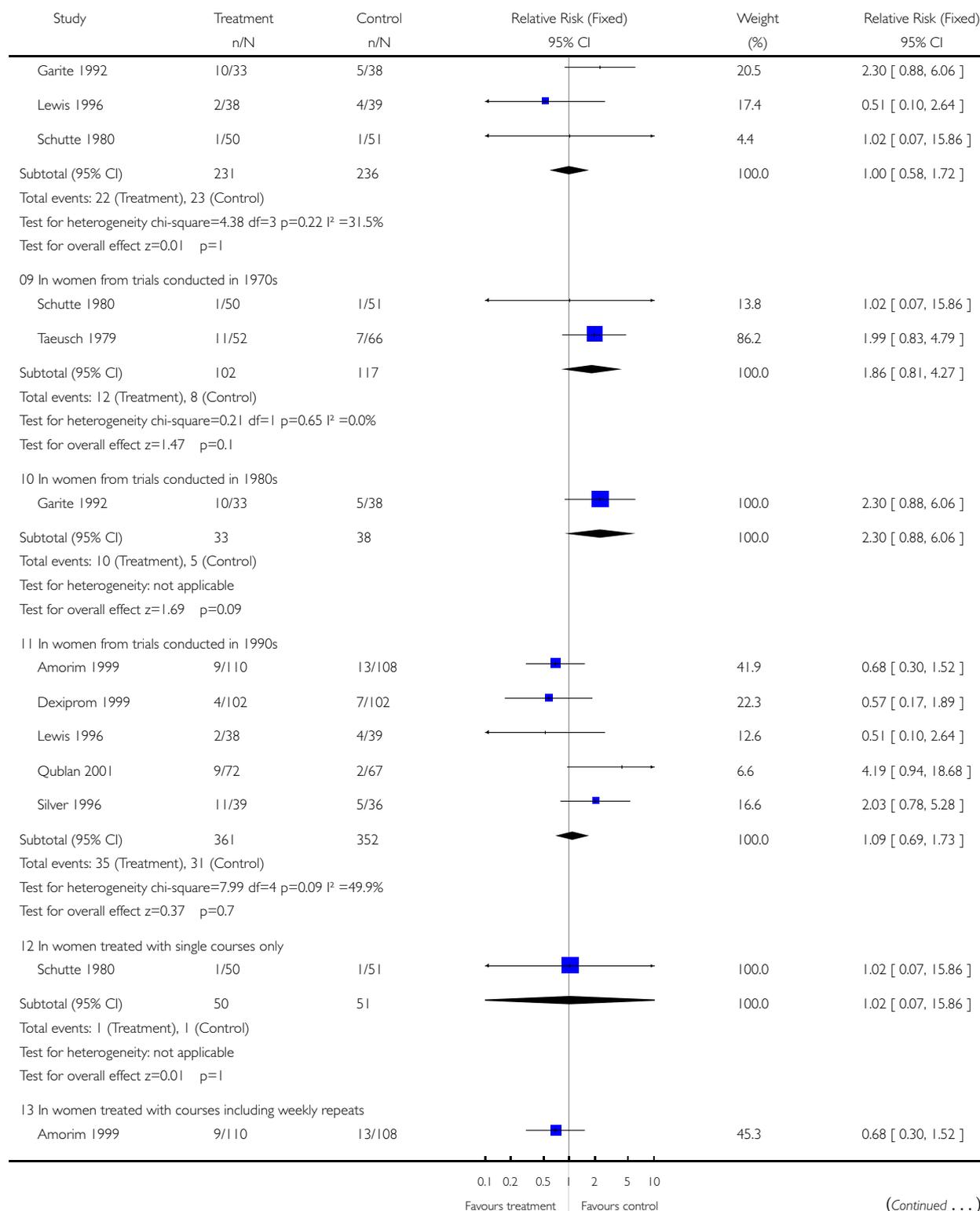
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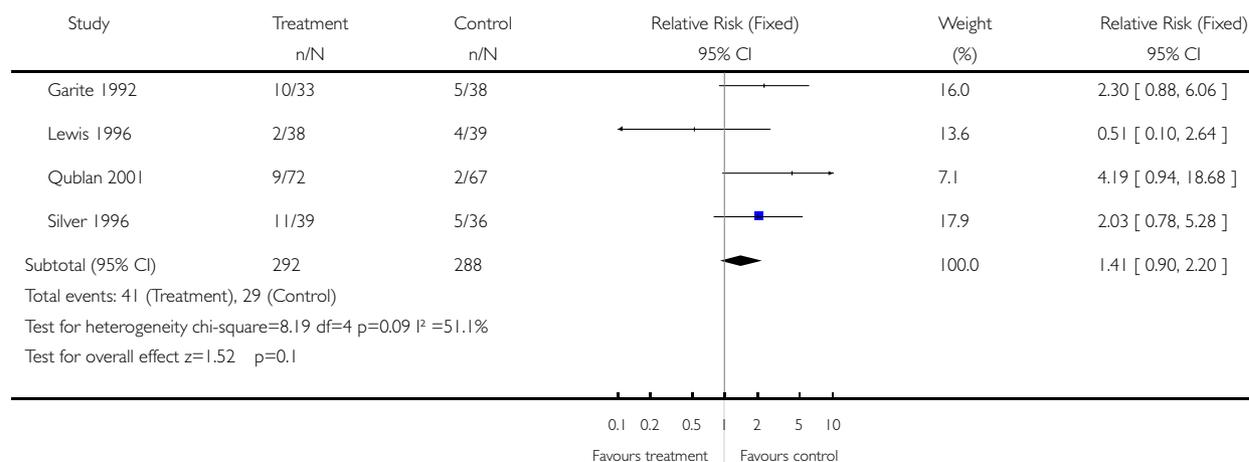
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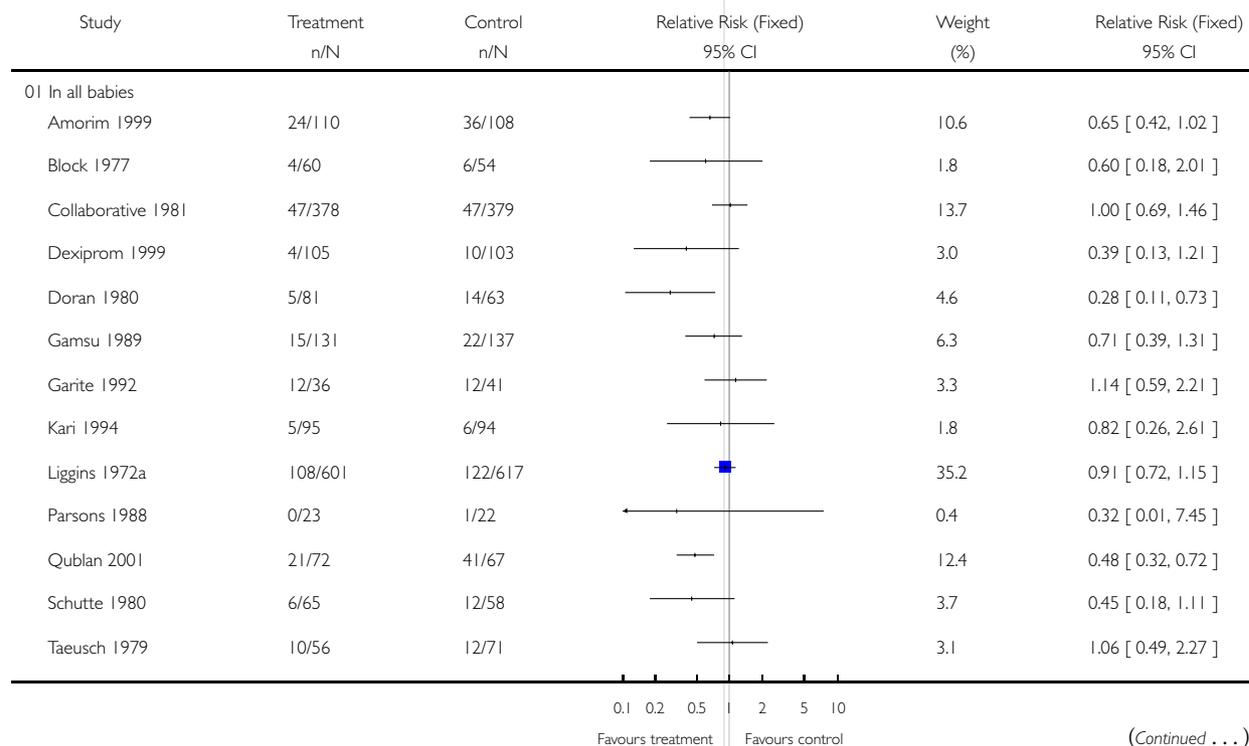


### Analysis 01.04. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 04 Fetal and neonatal deaths

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

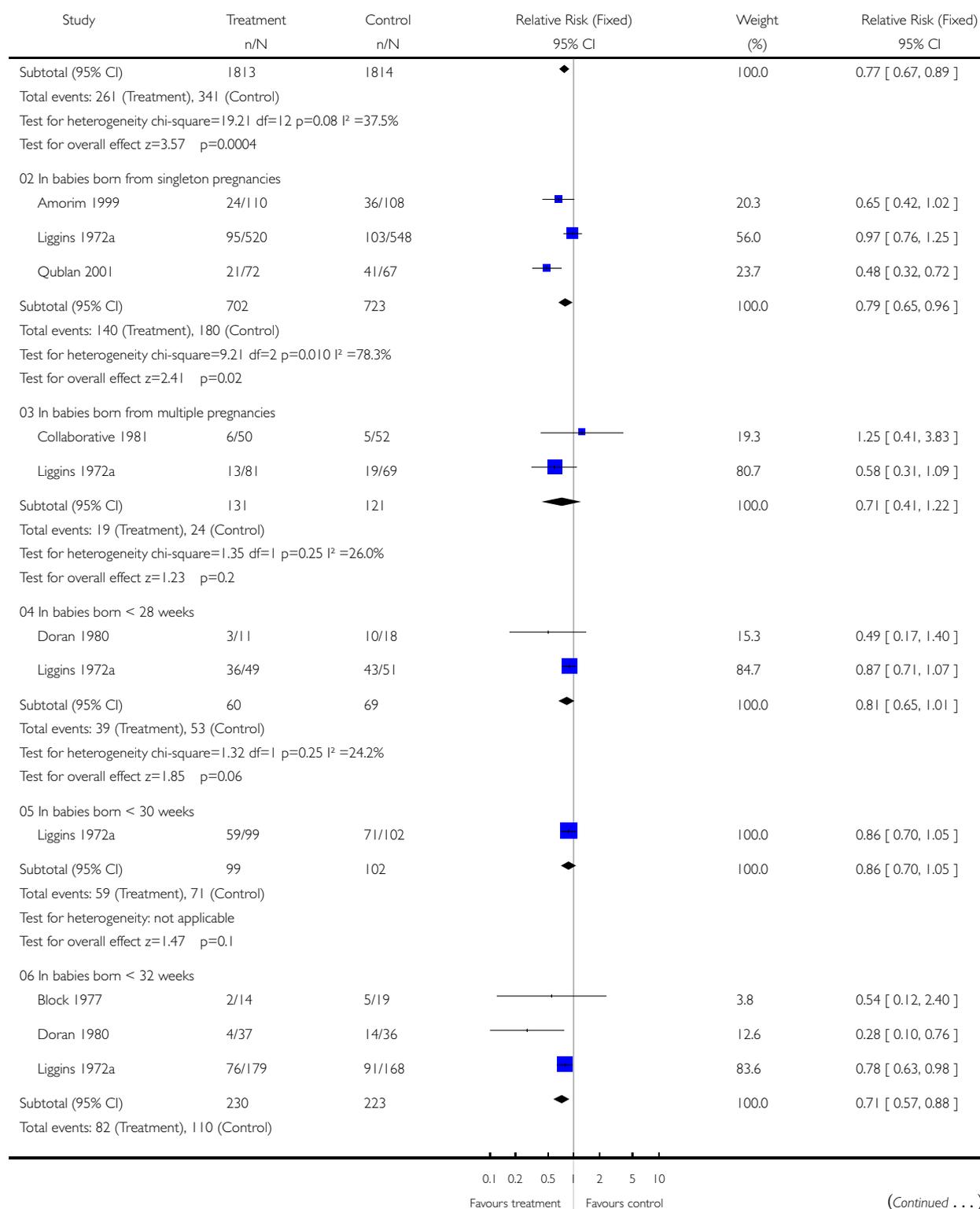
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 04 Fetal and neonatal deaths

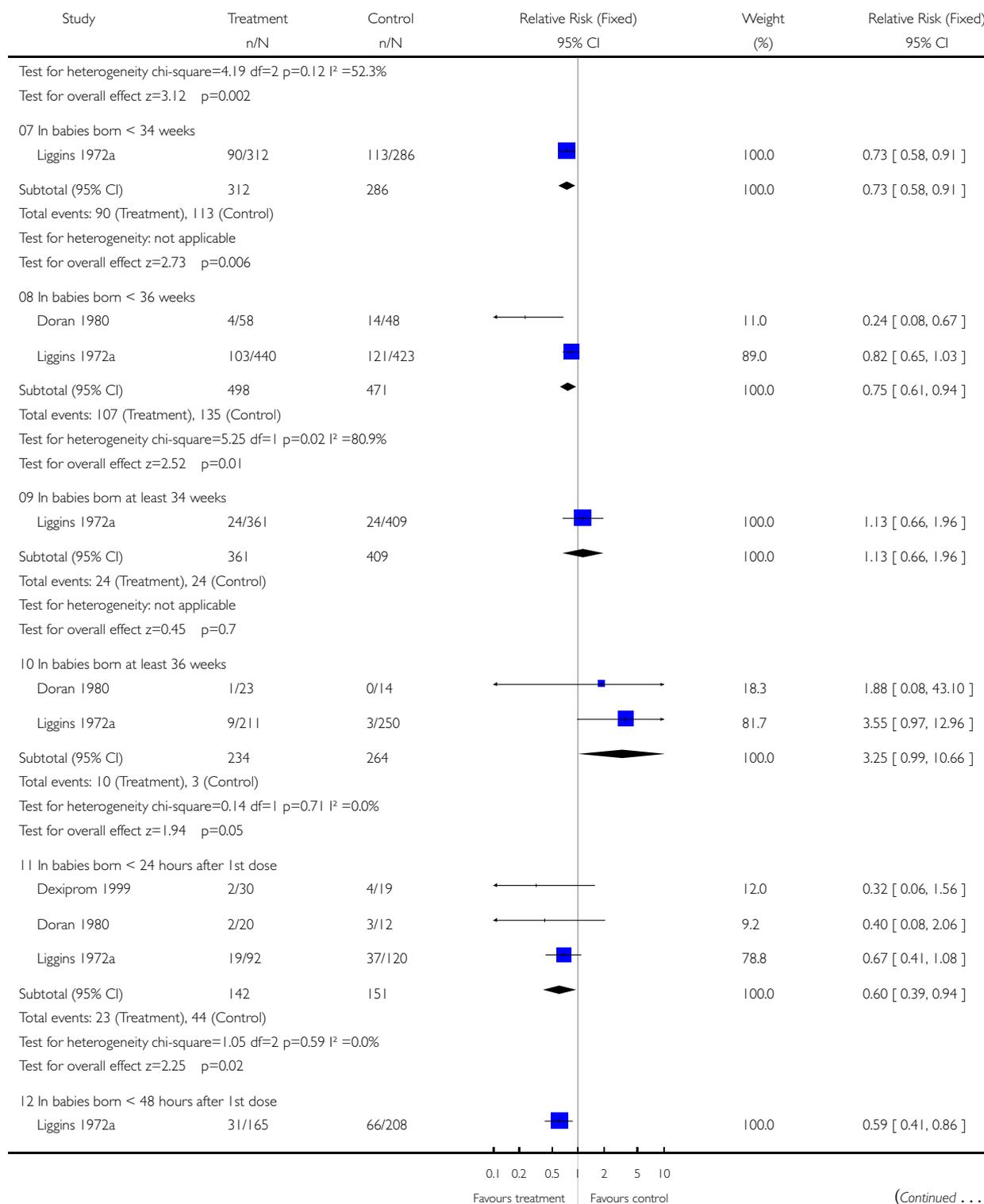


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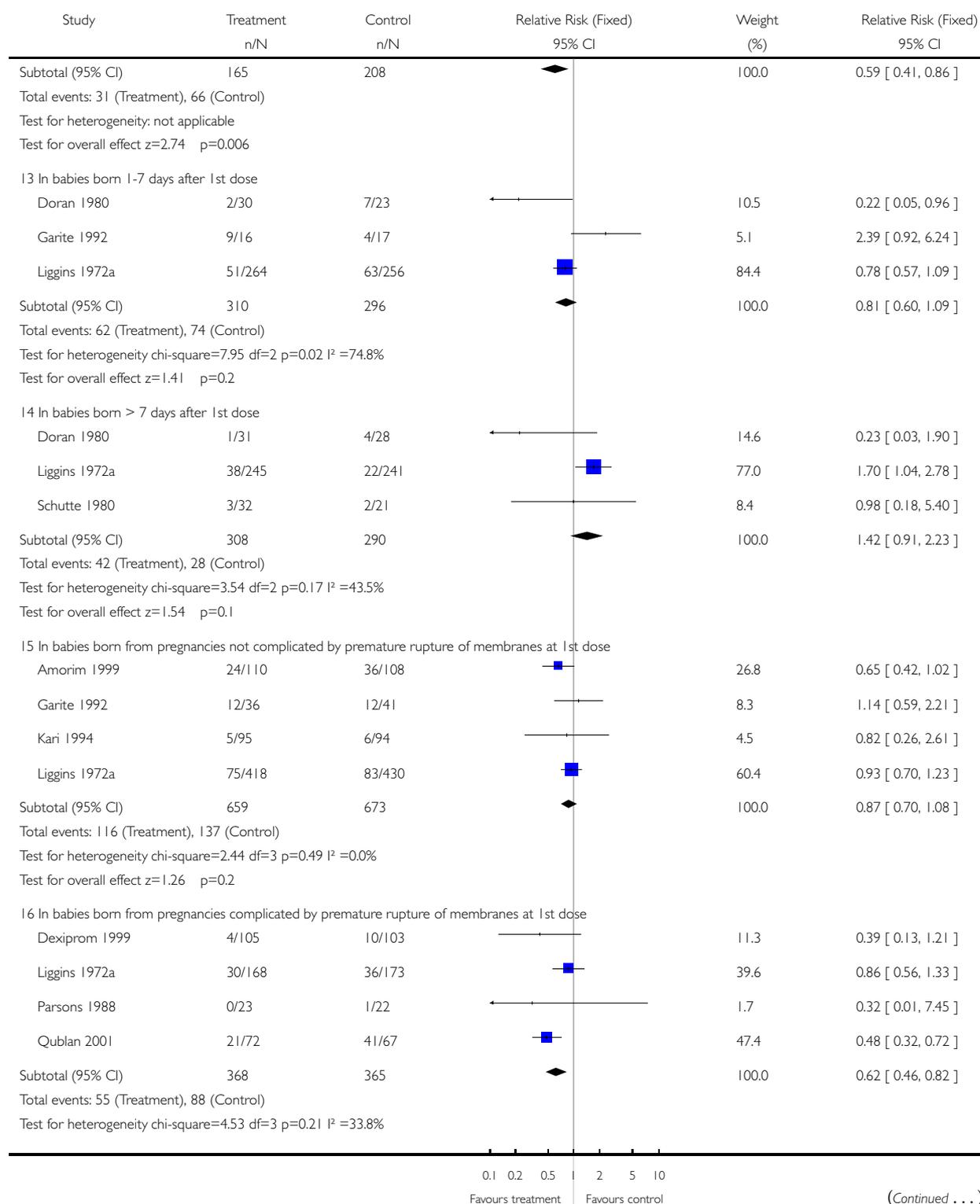


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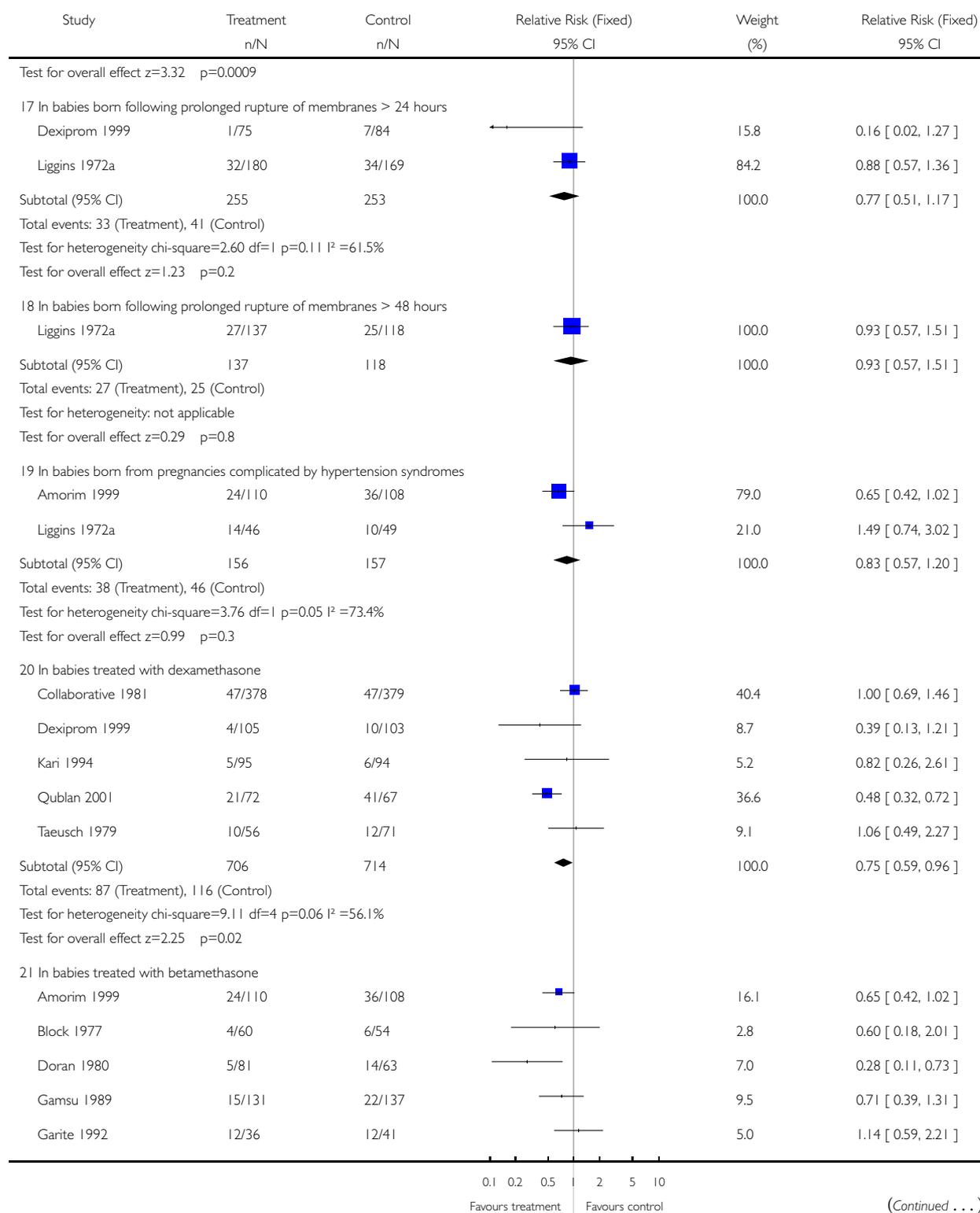
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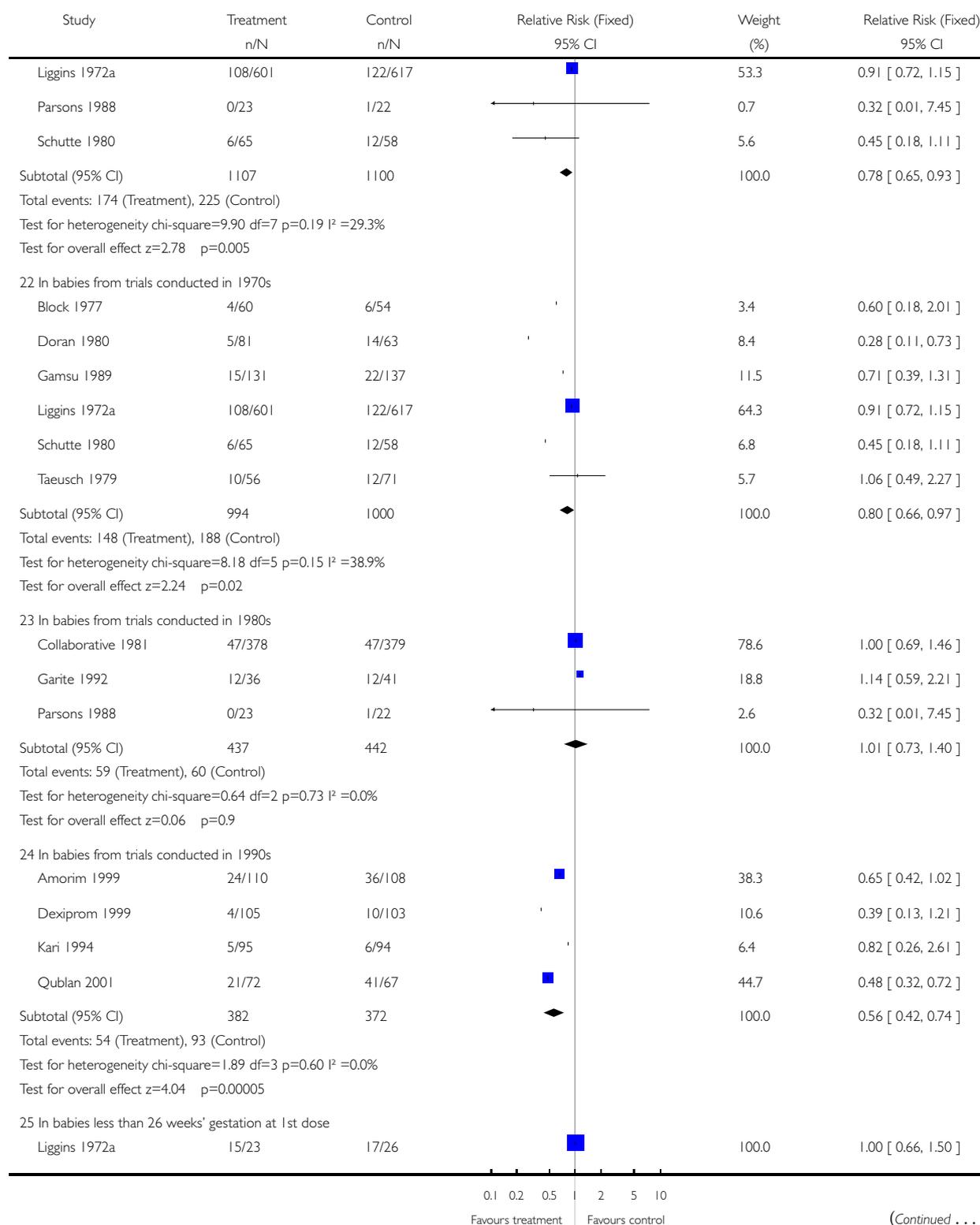
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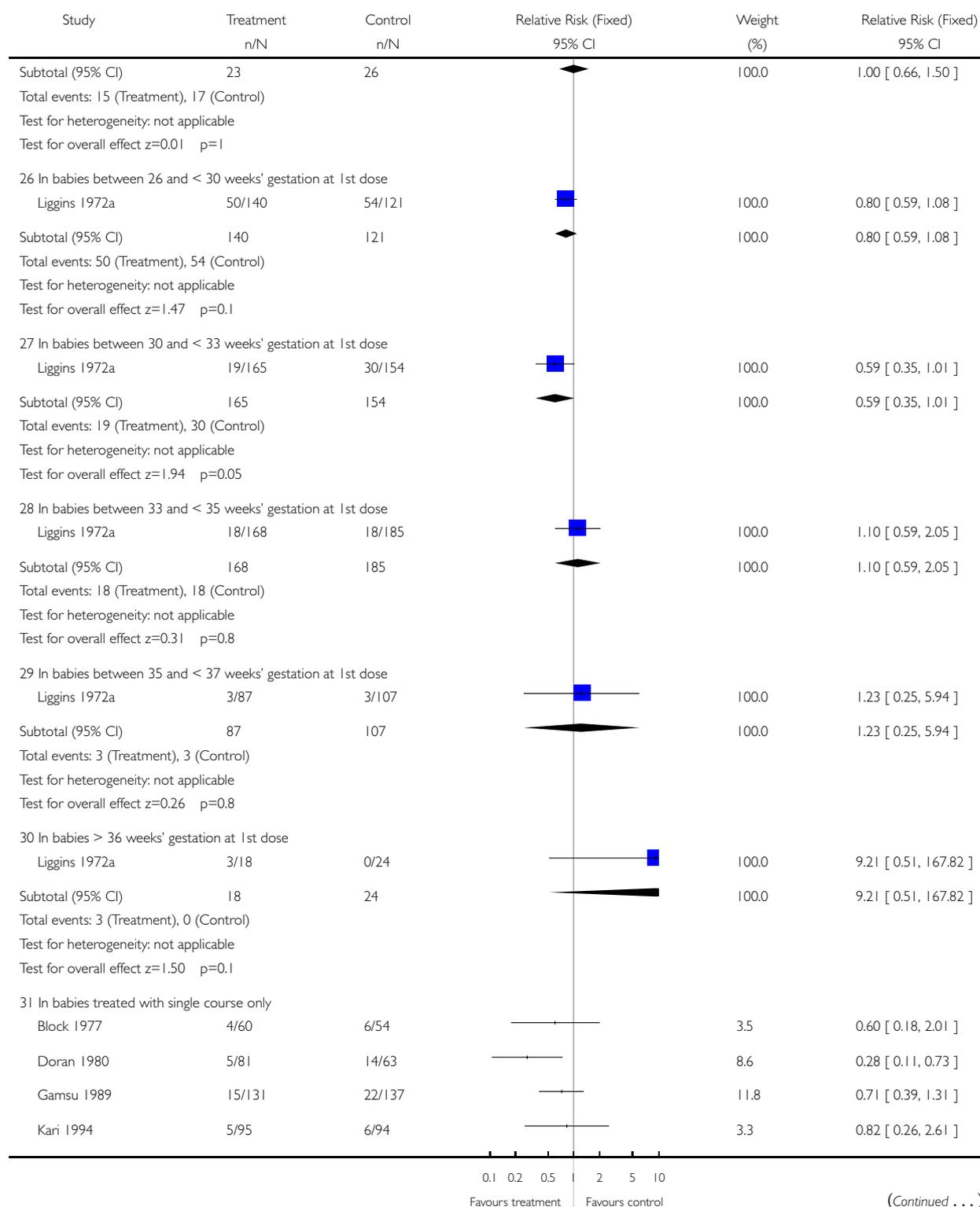
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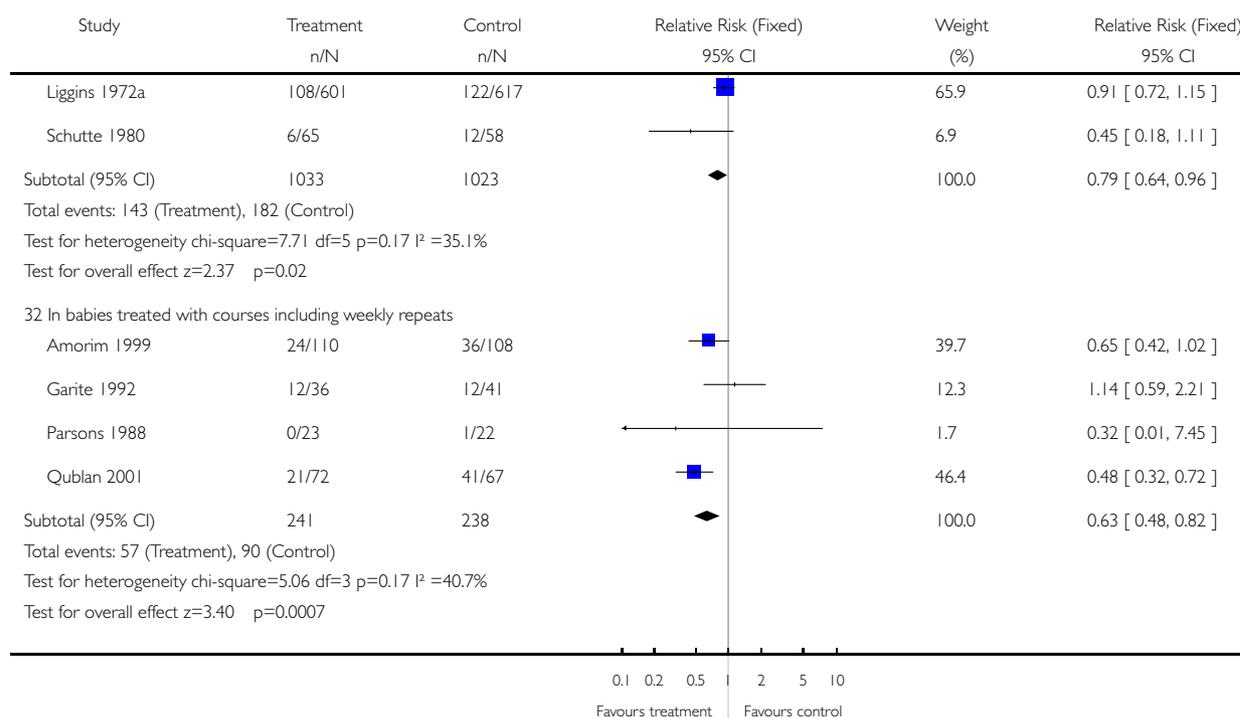
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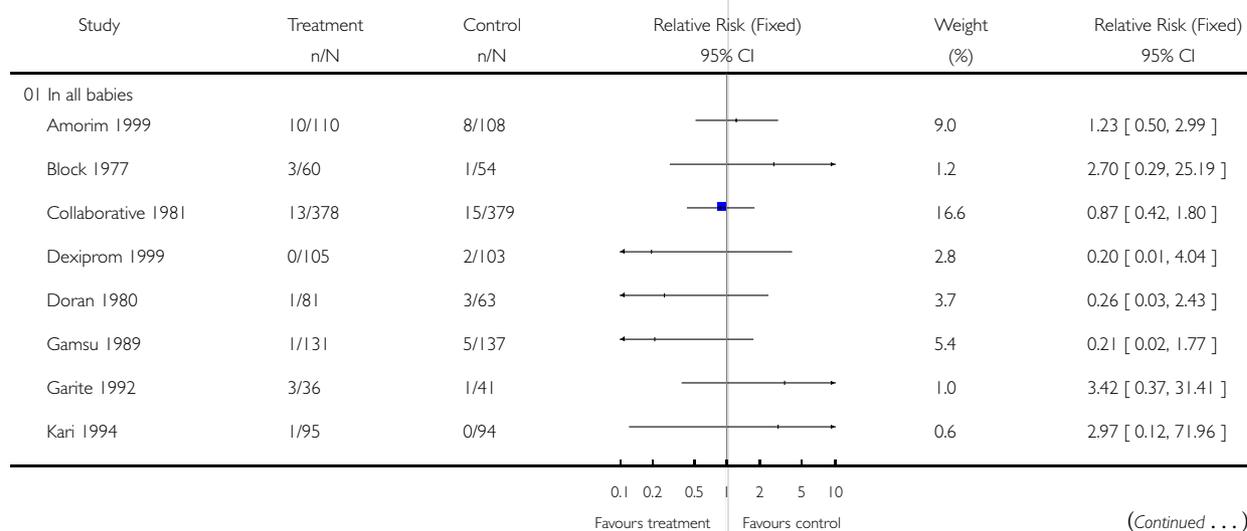


### Analysis 01.05. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 05 Fetal deaths

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

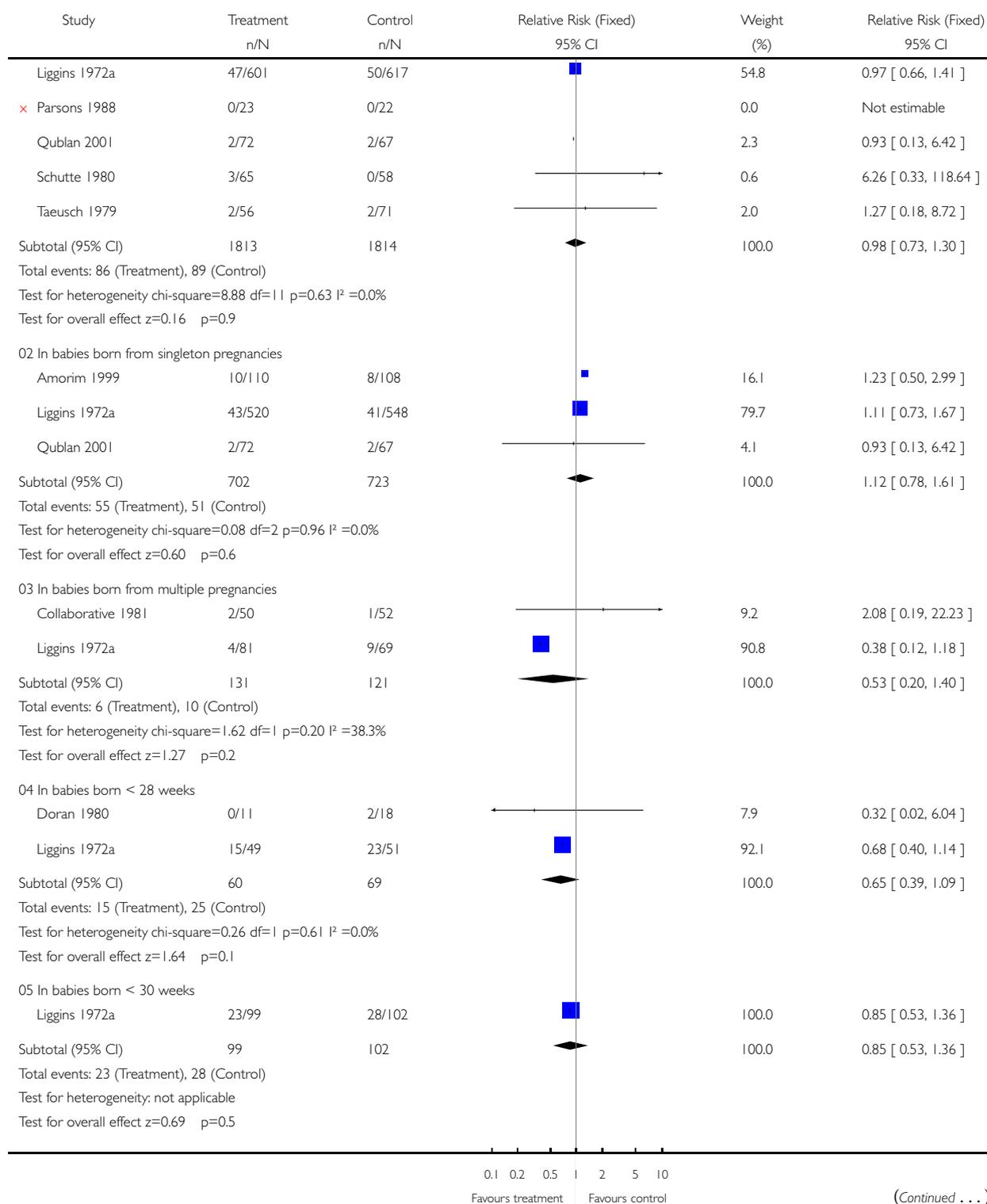
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 05 Fetal deaths



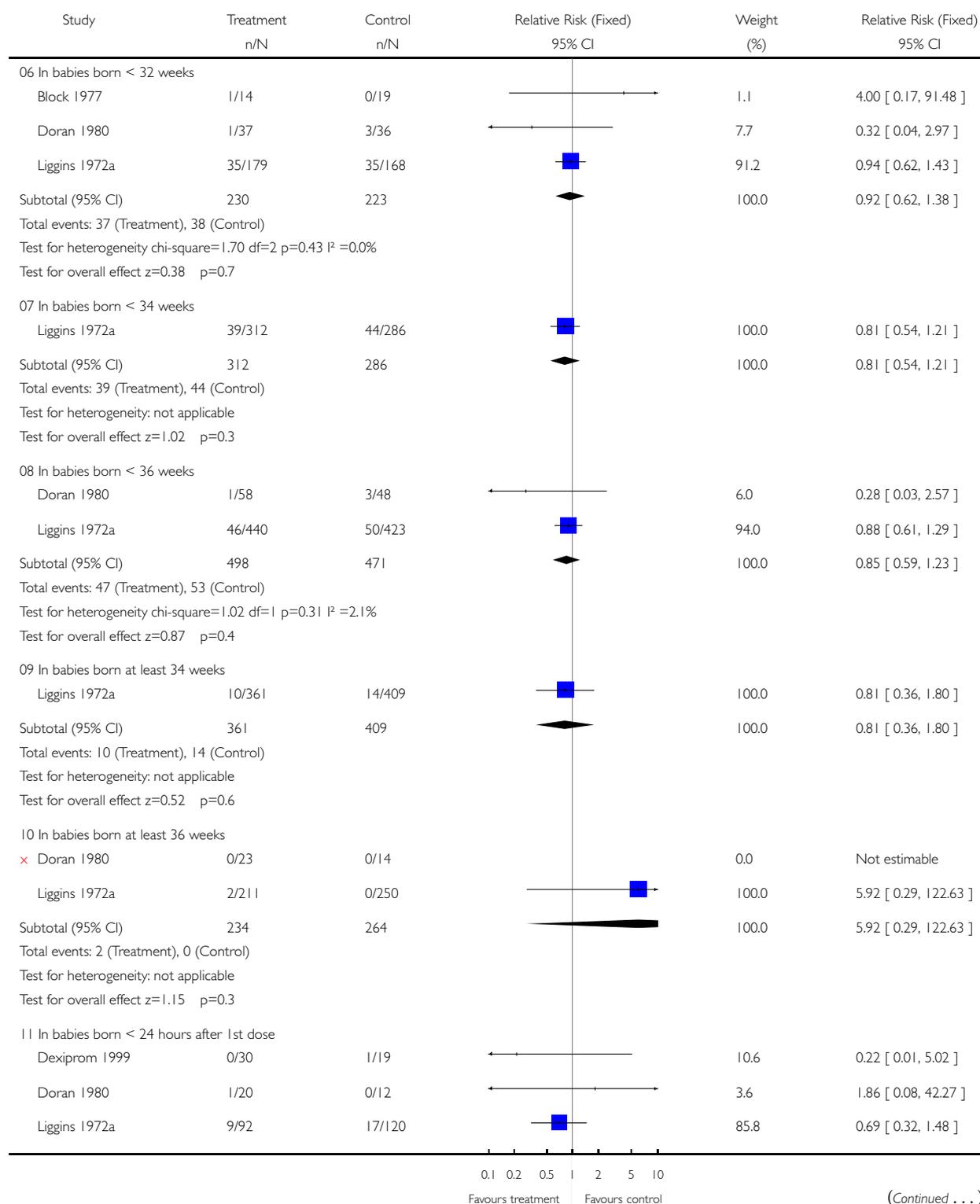
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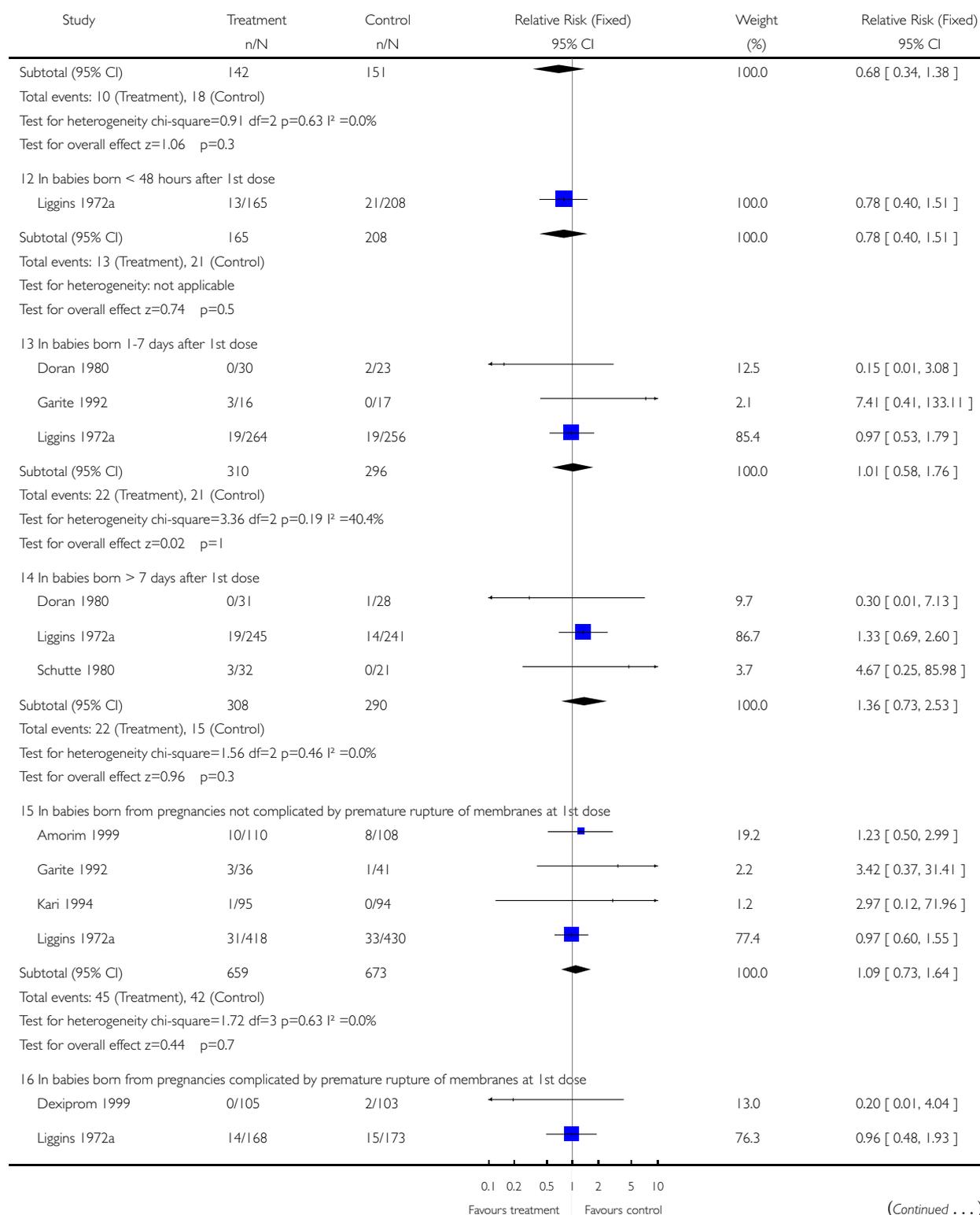
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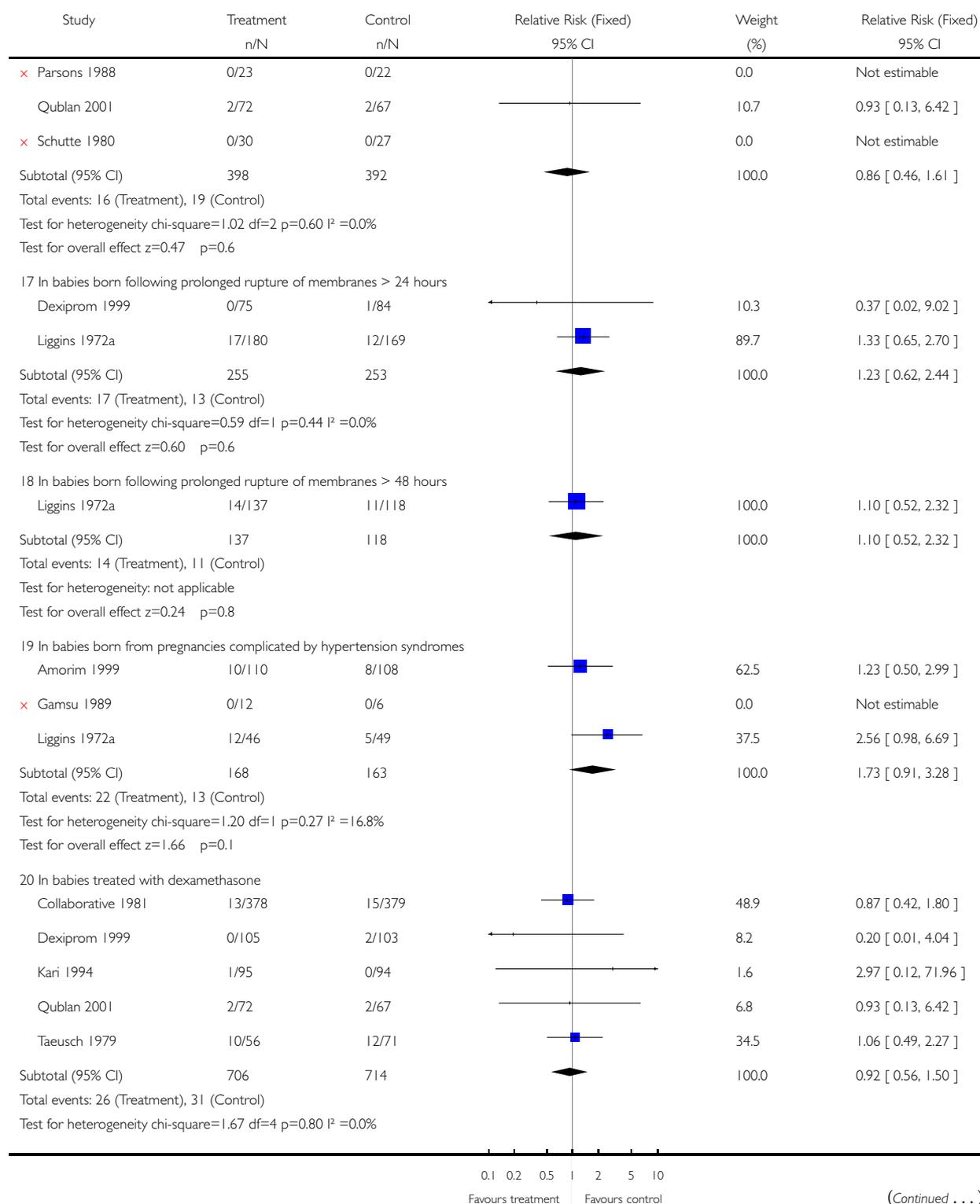
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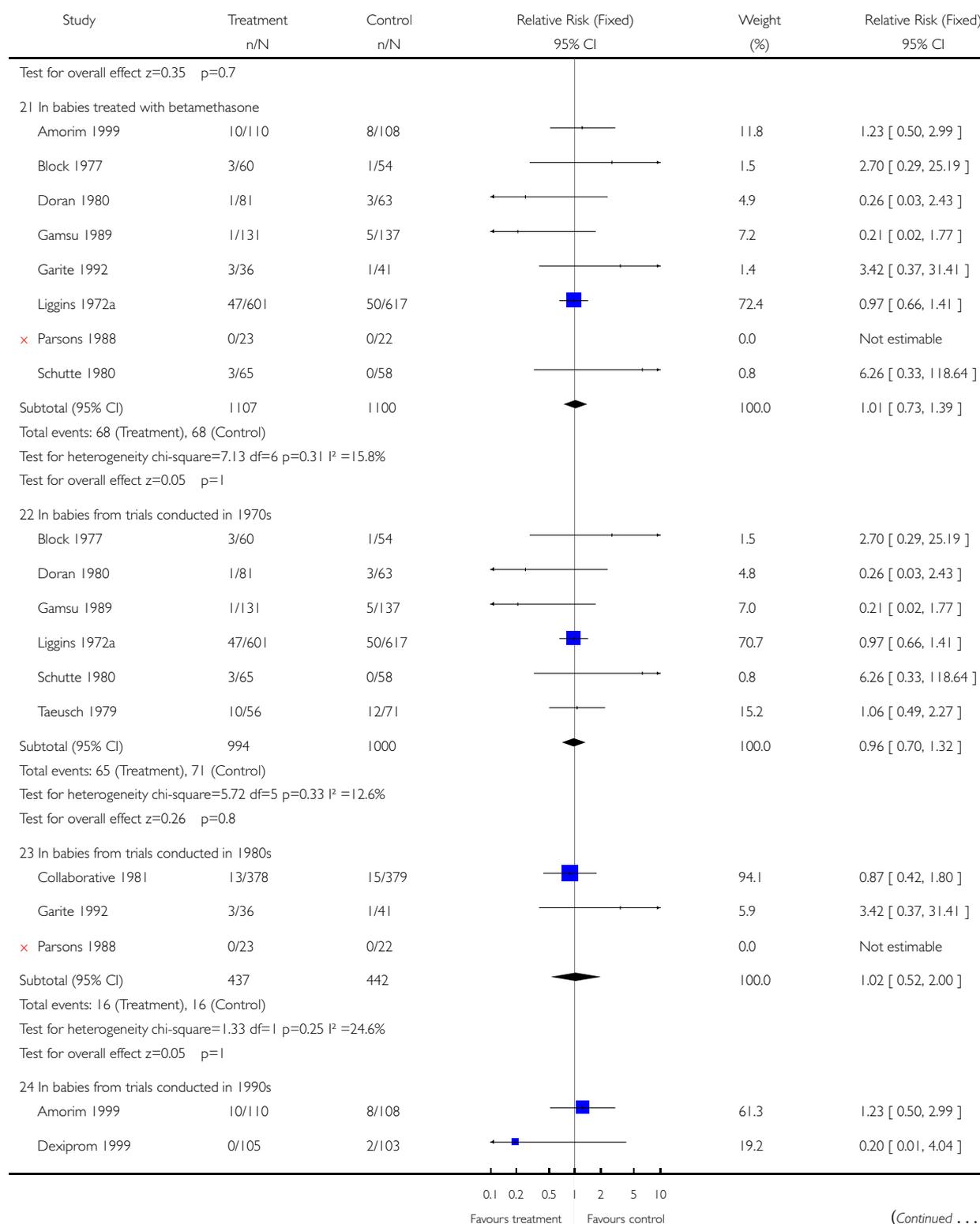
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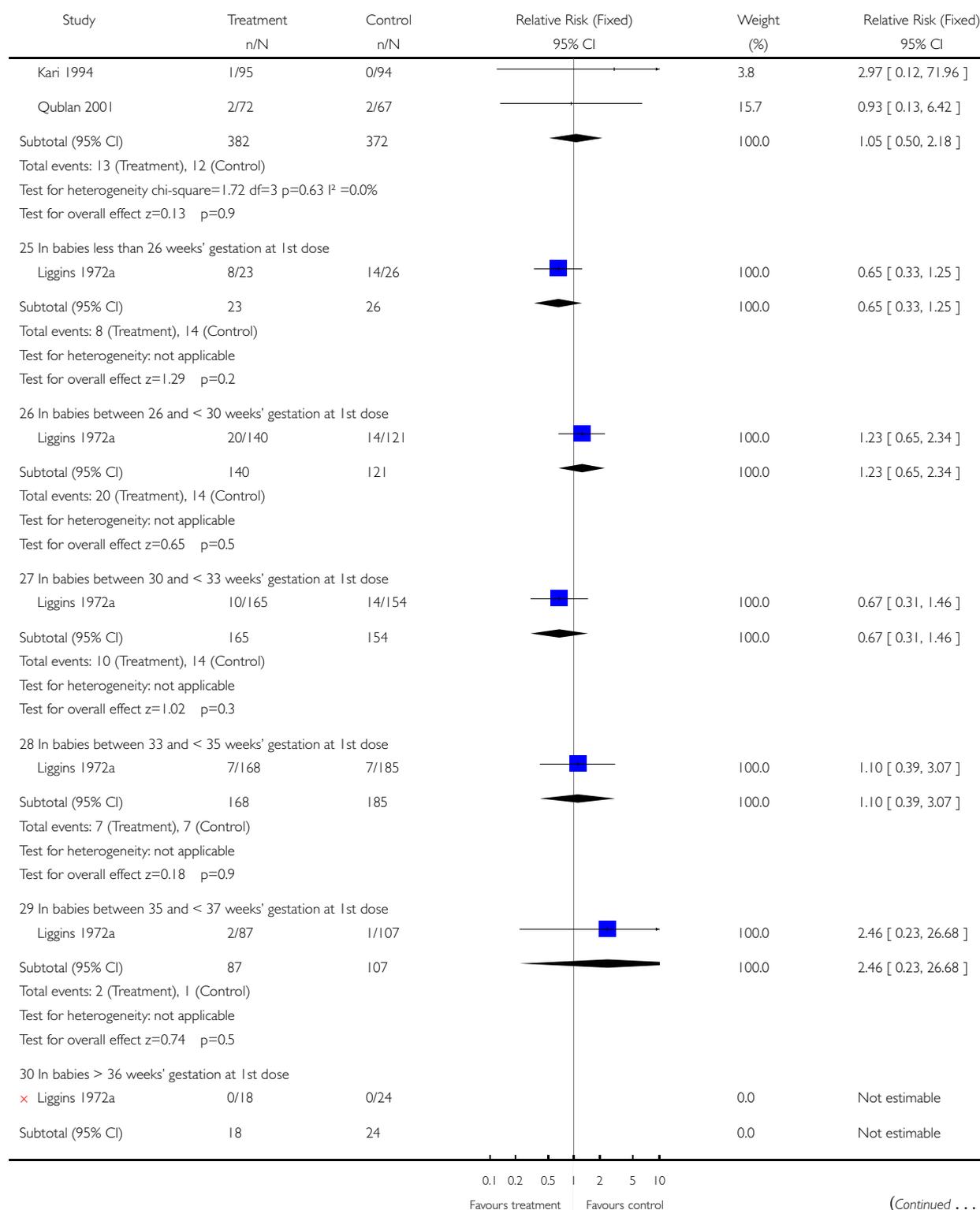
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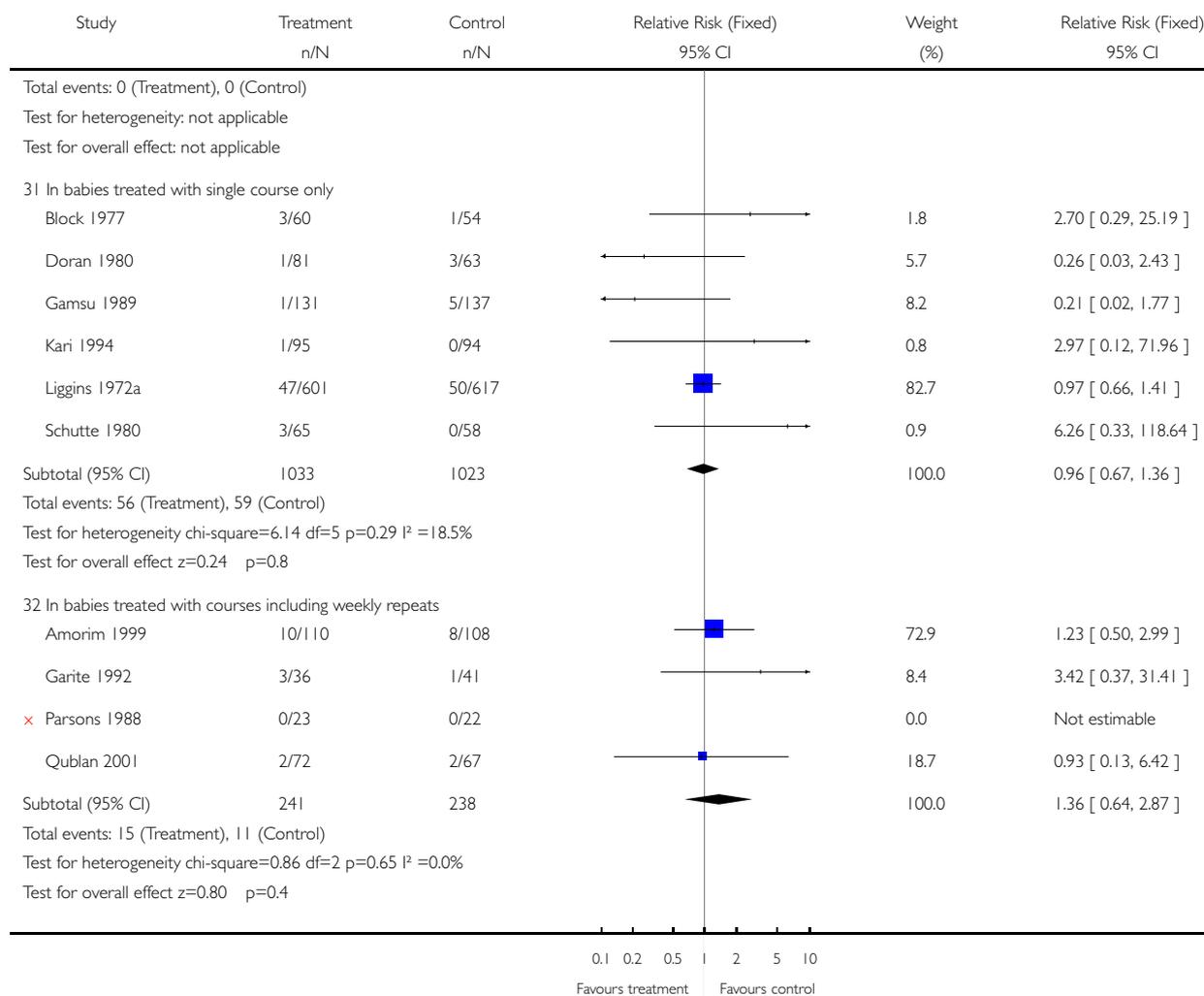
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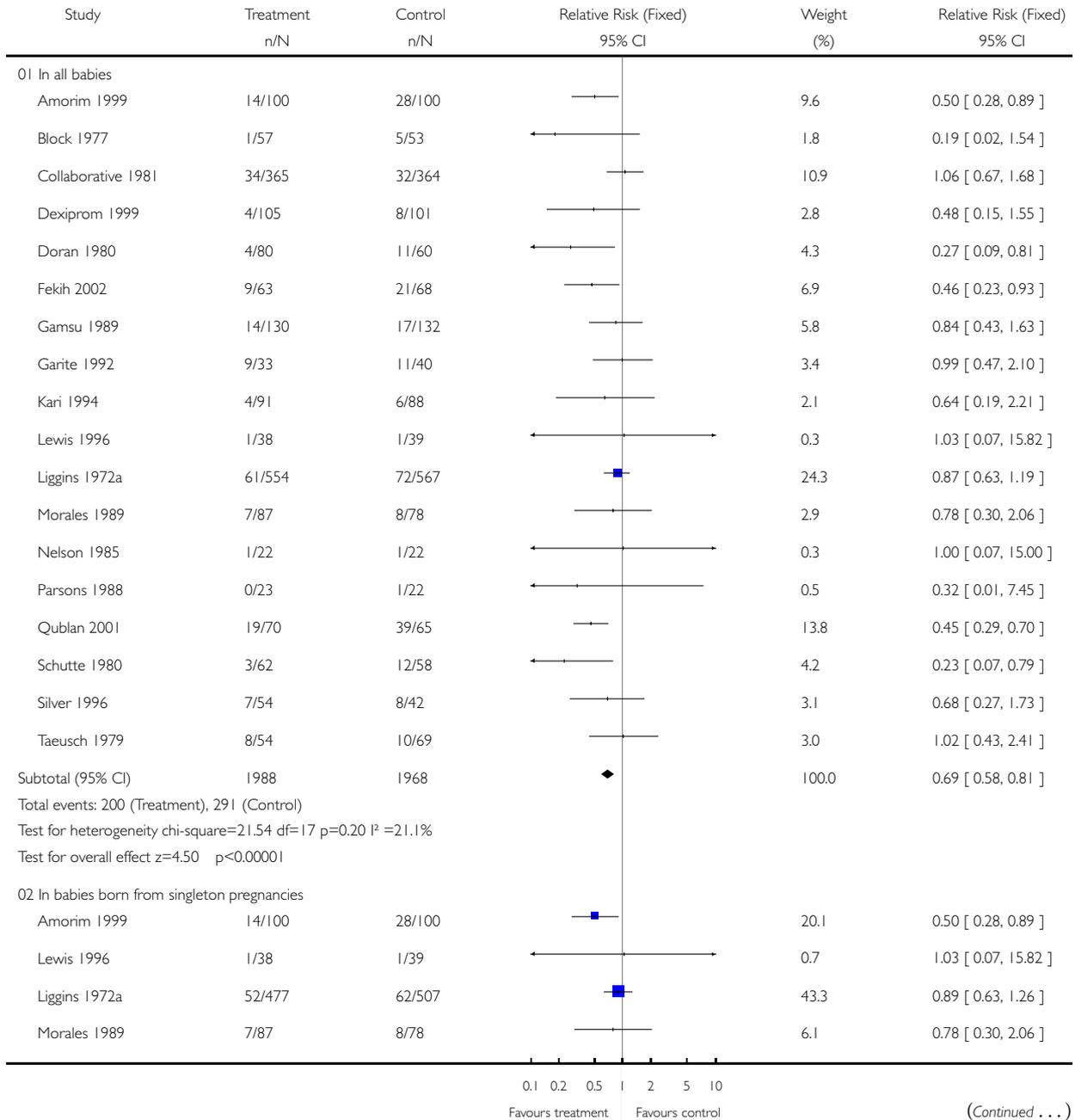


### Analysis 01.06. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 06 Neonatal deaths

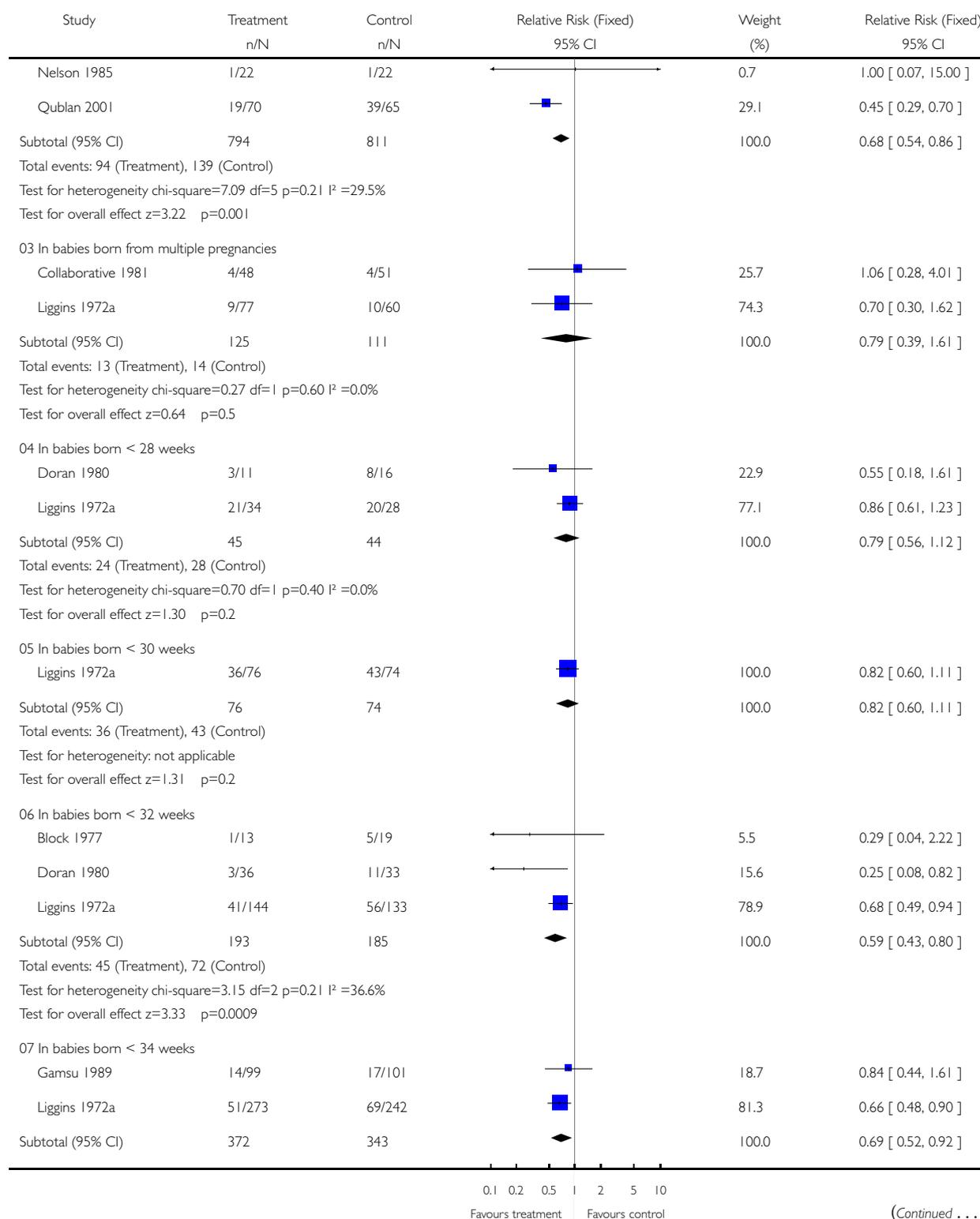
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 06 Neonatal deaths

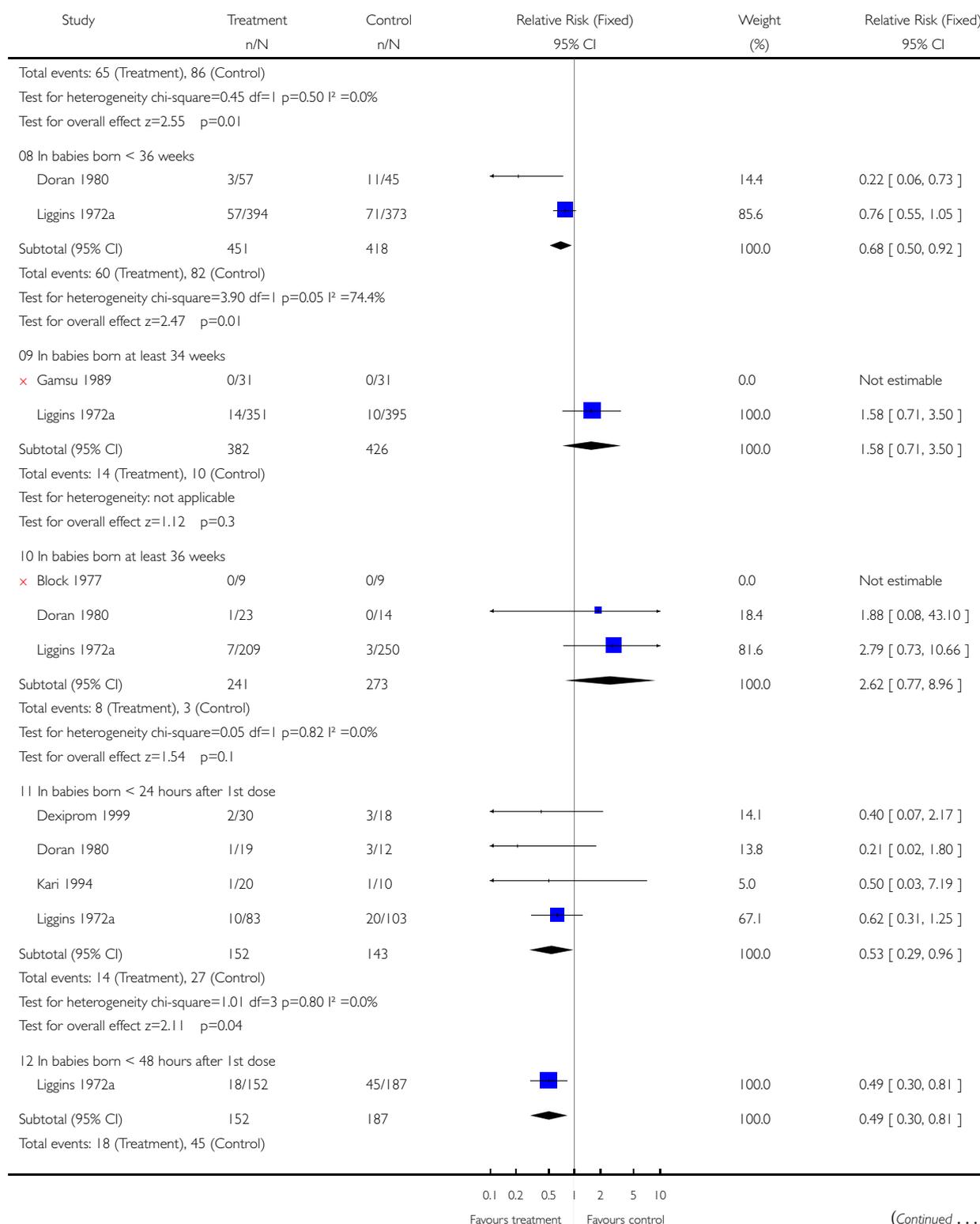


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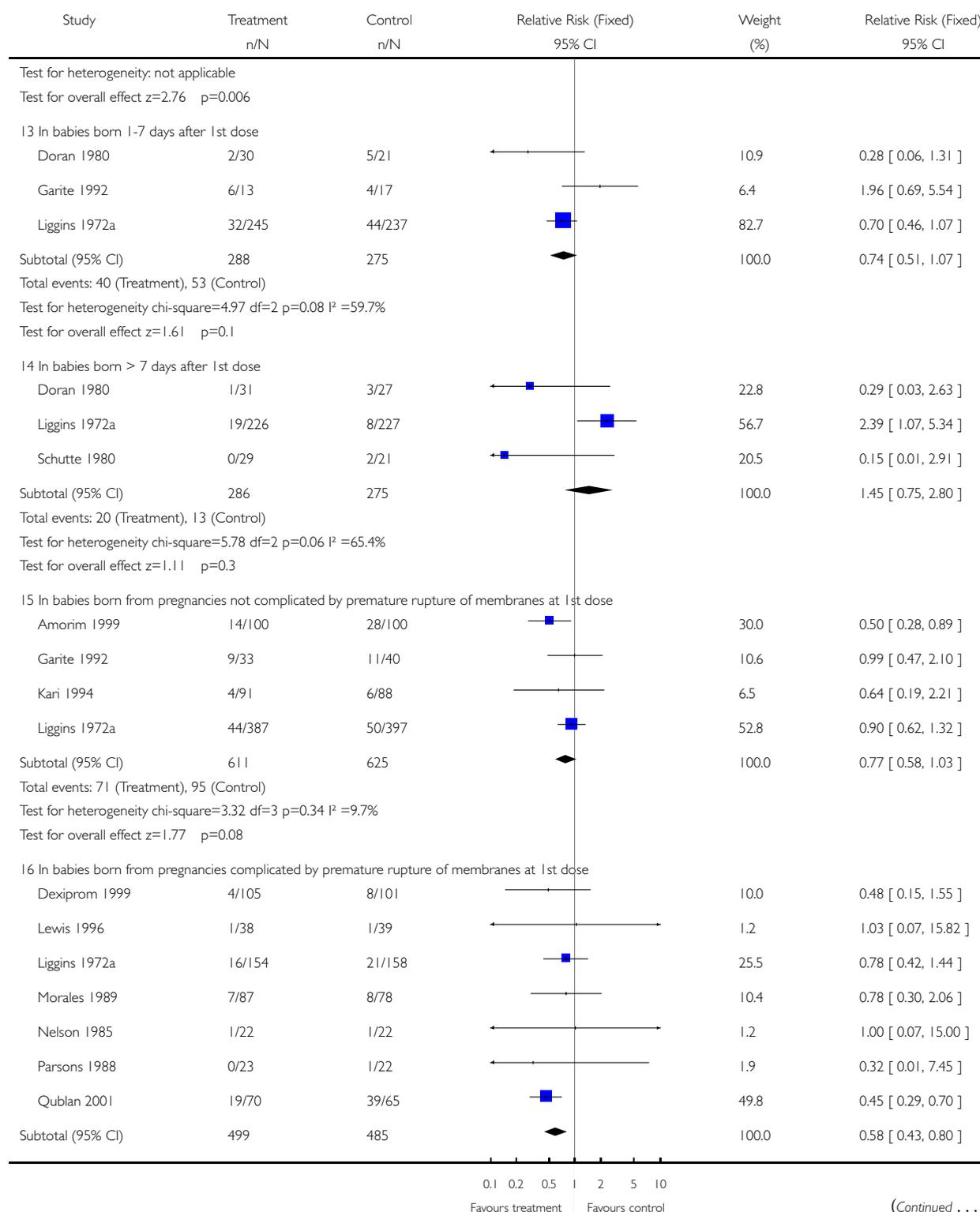
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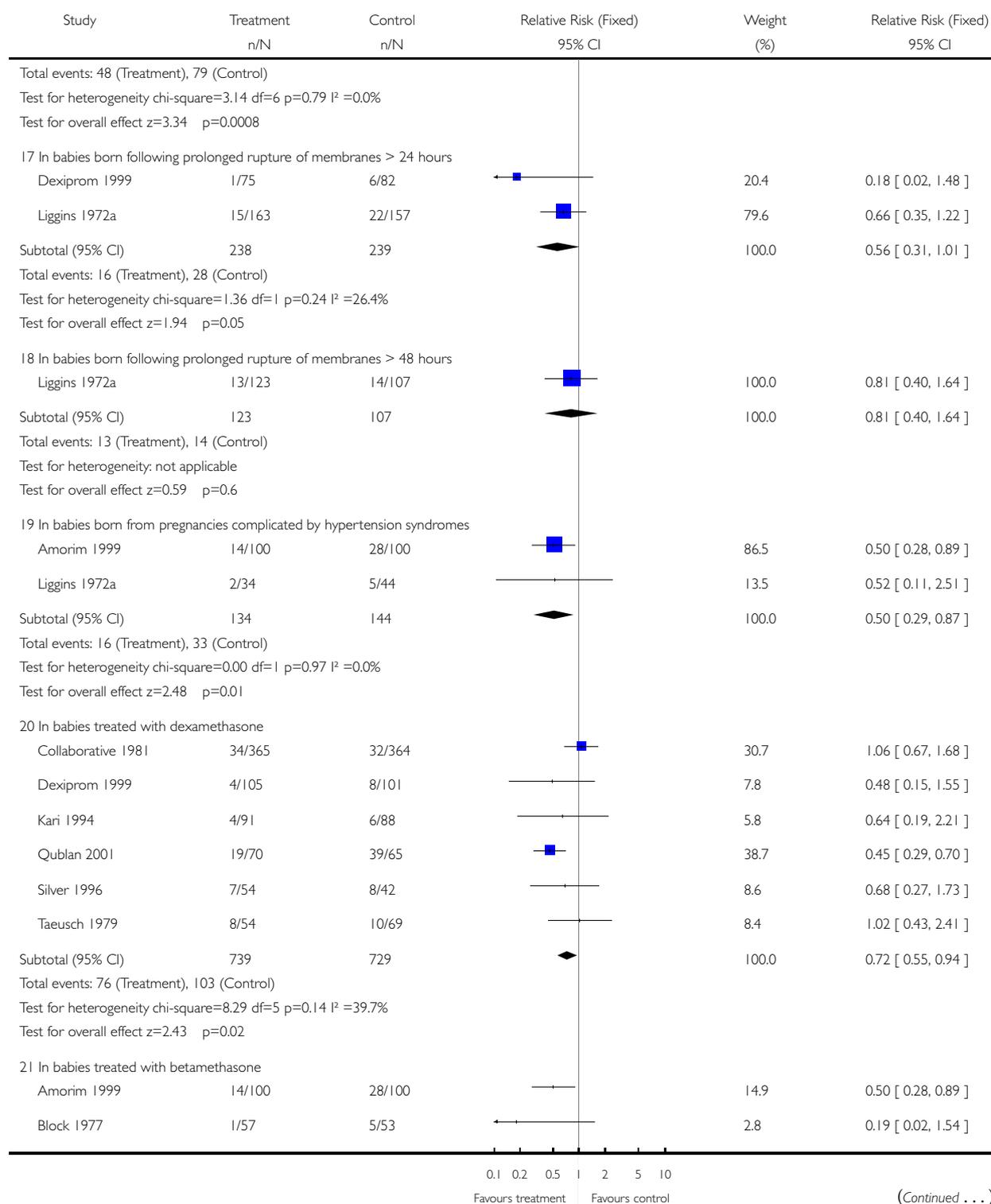
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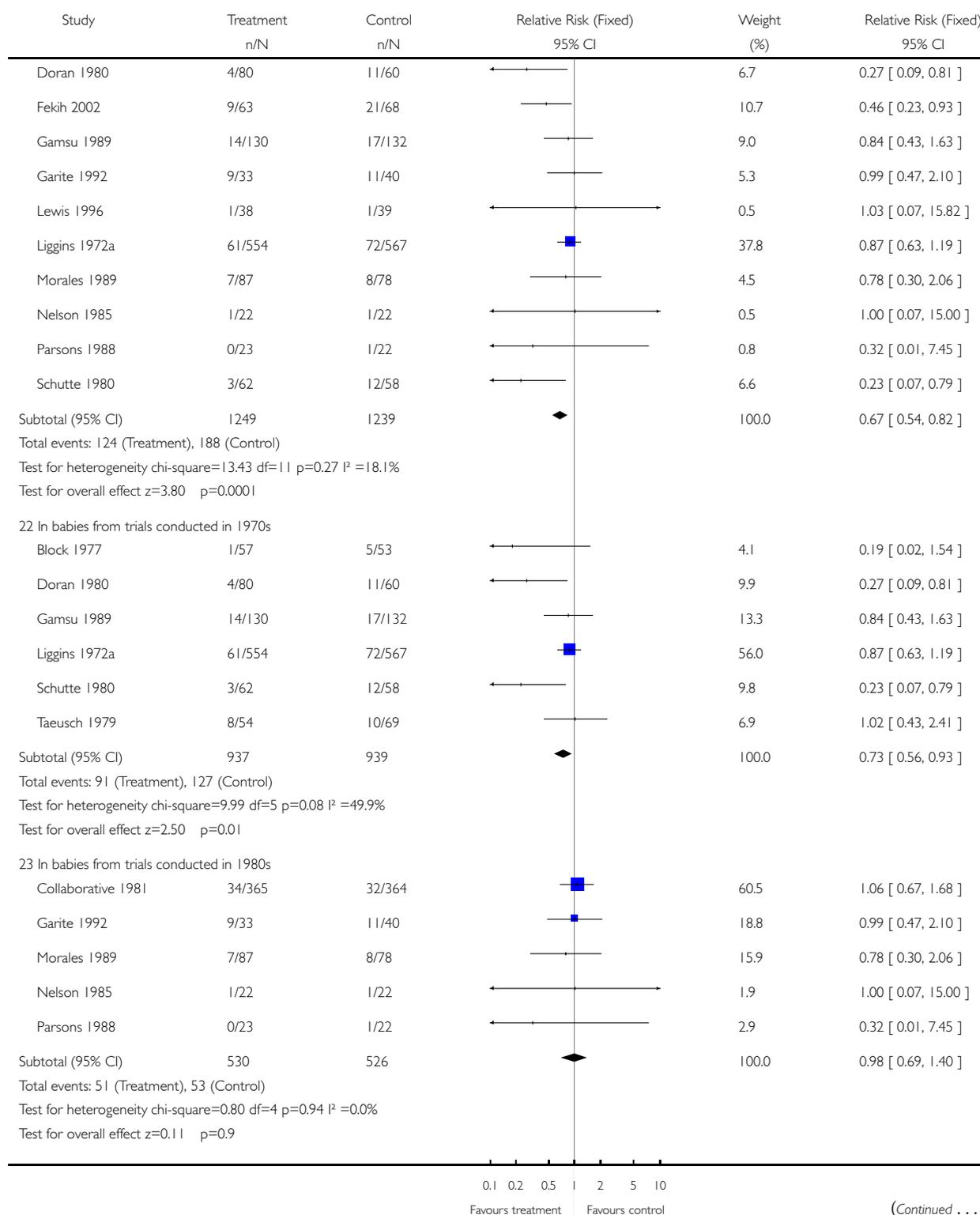
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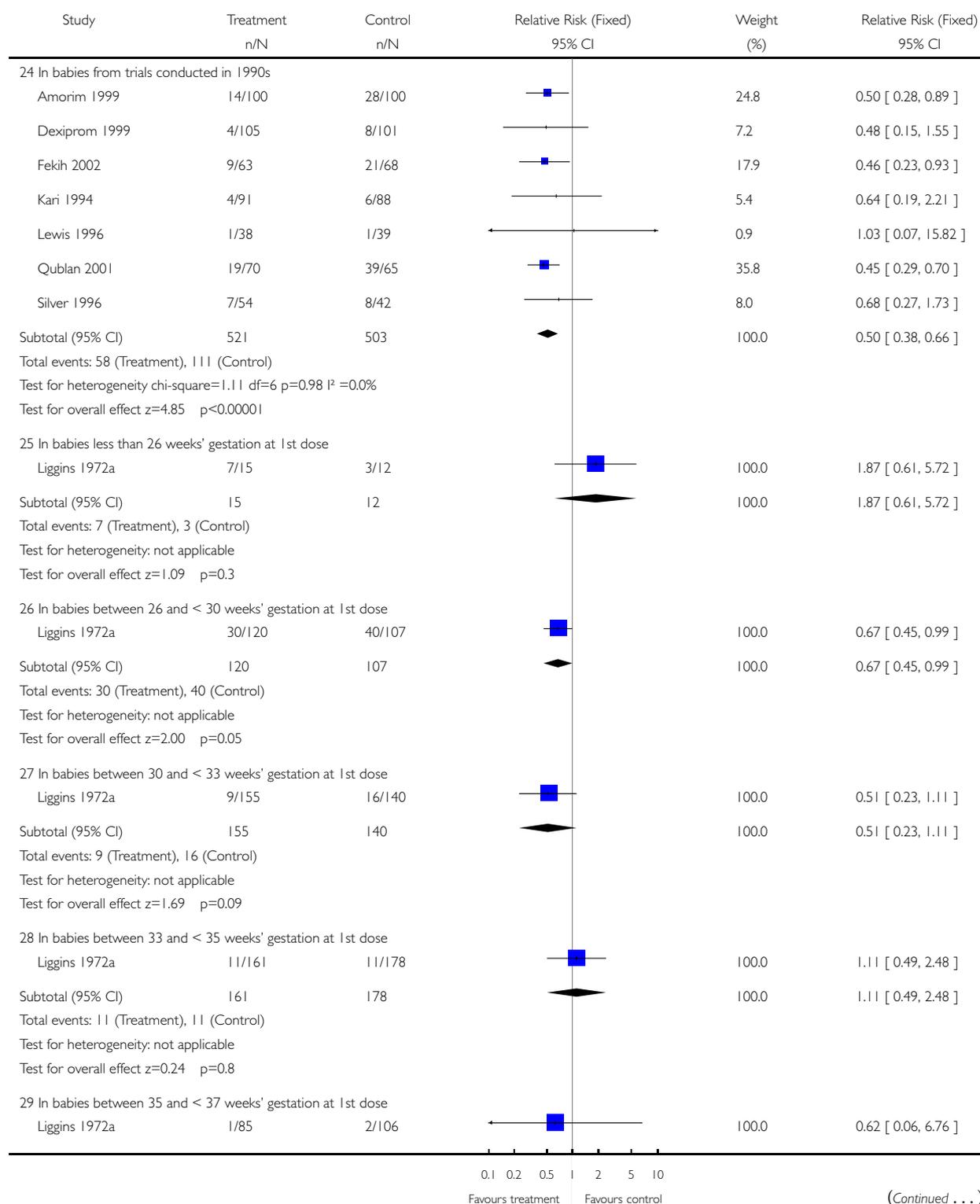
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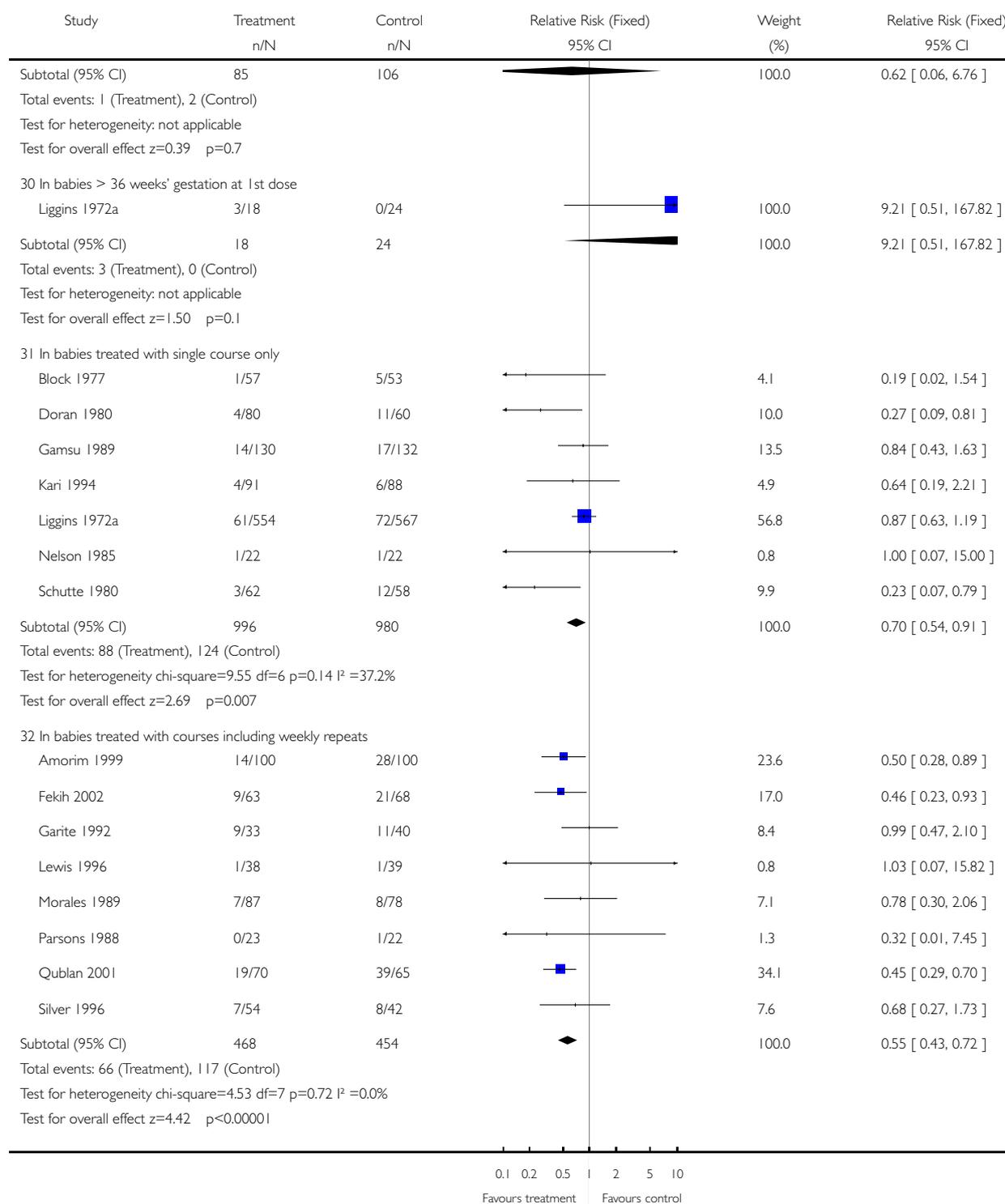
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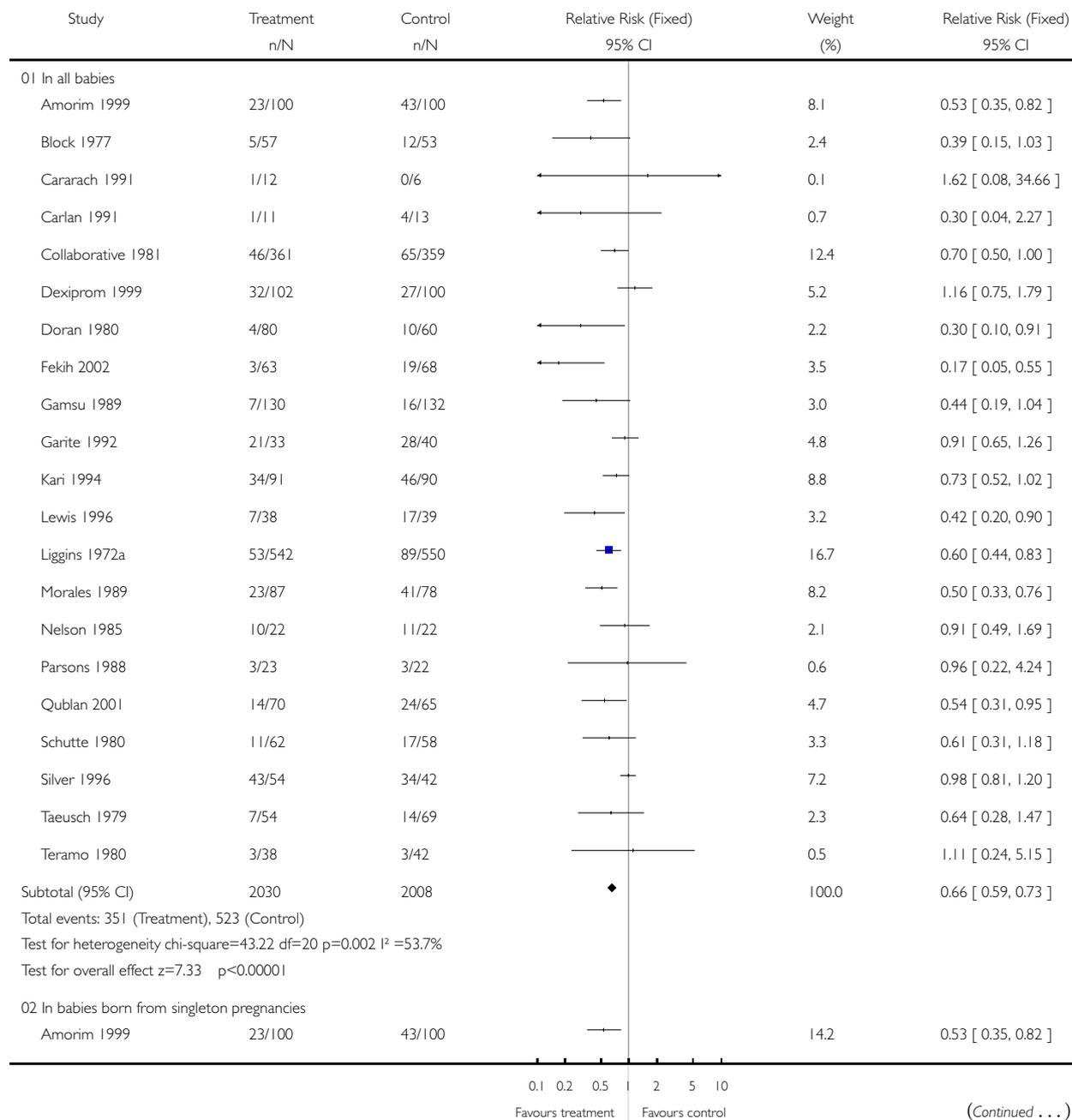


### Analysis 01.07. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 07 Respiratory distress syndrome

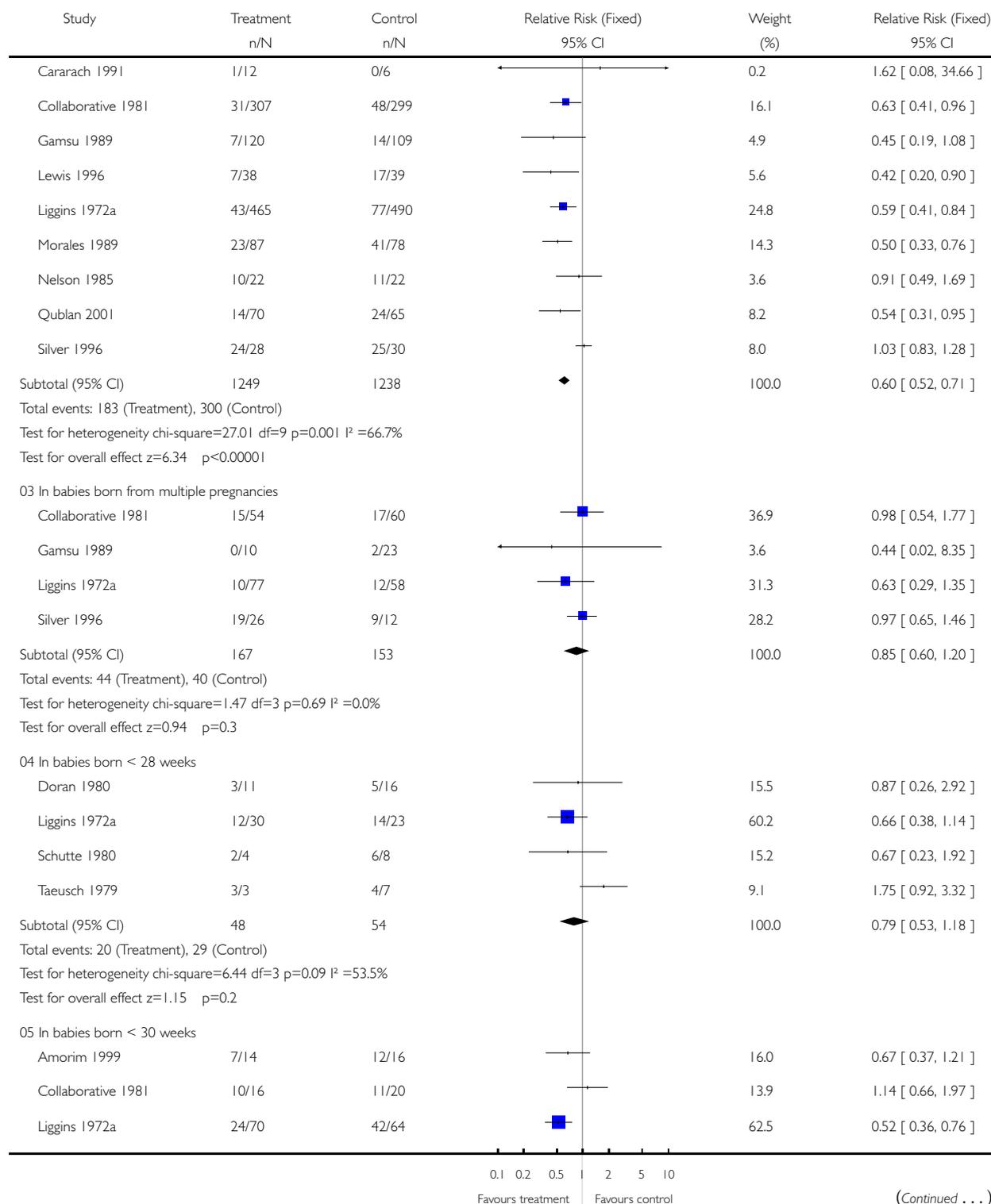
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 07 Respiratory distress syndrome

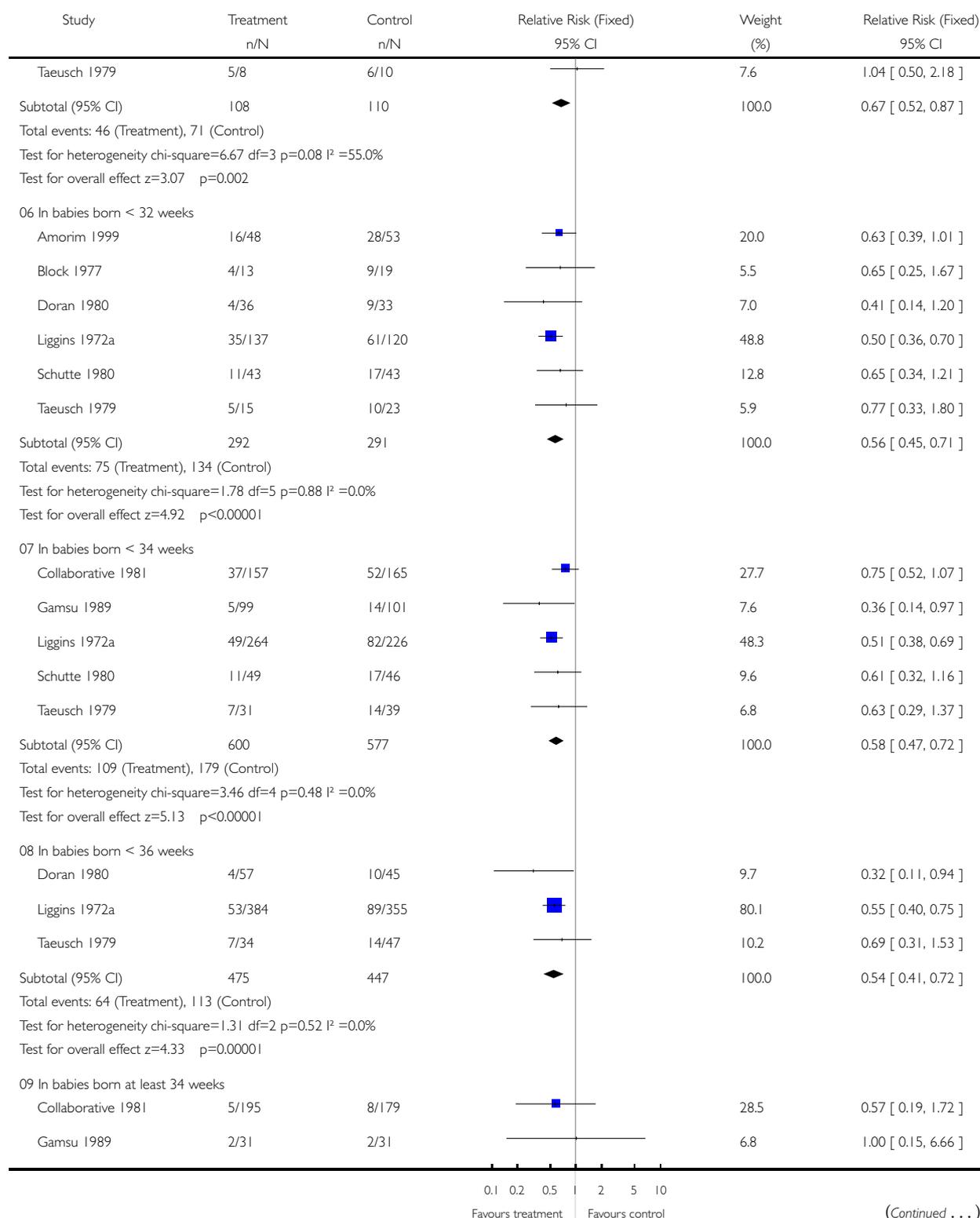


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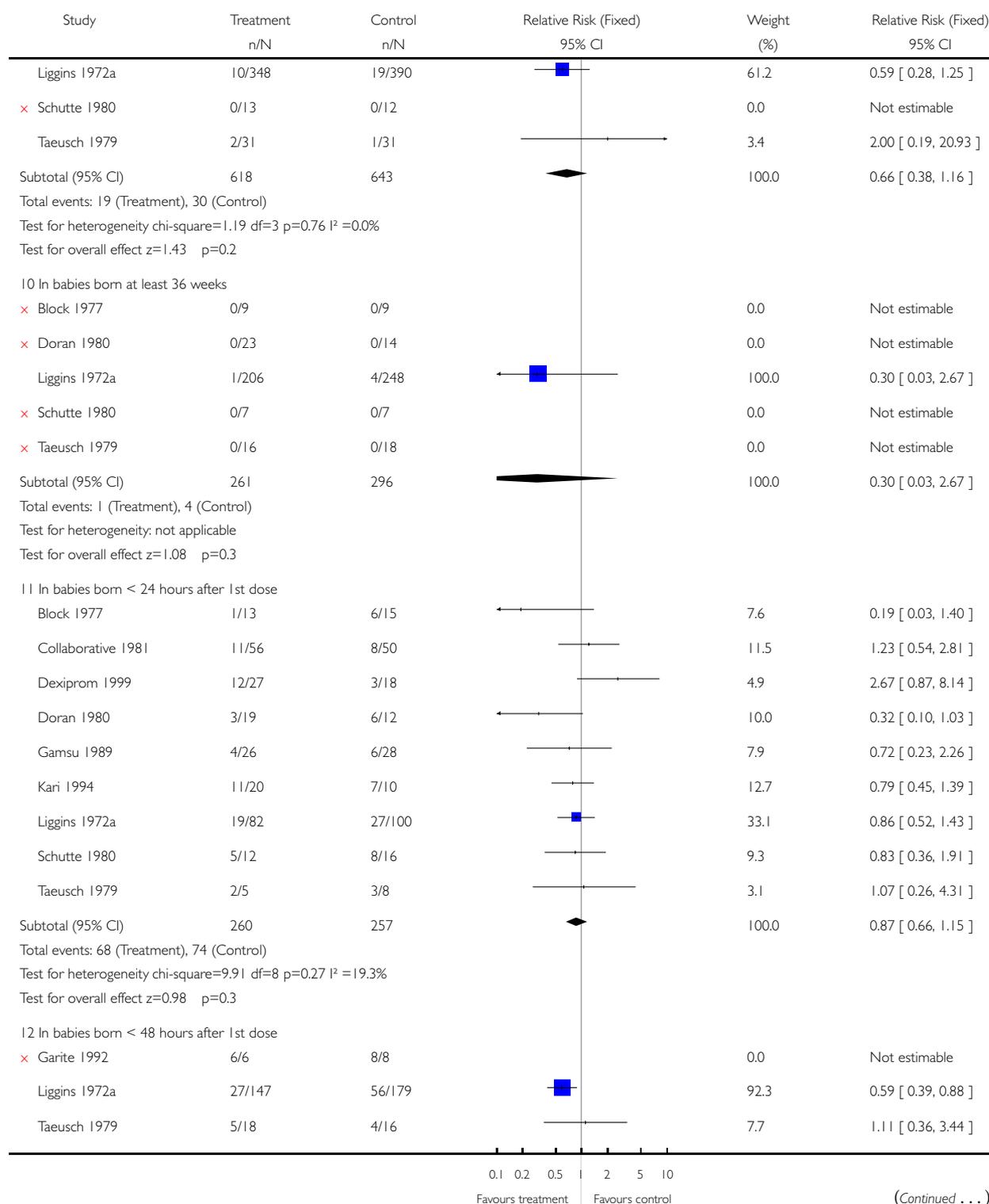
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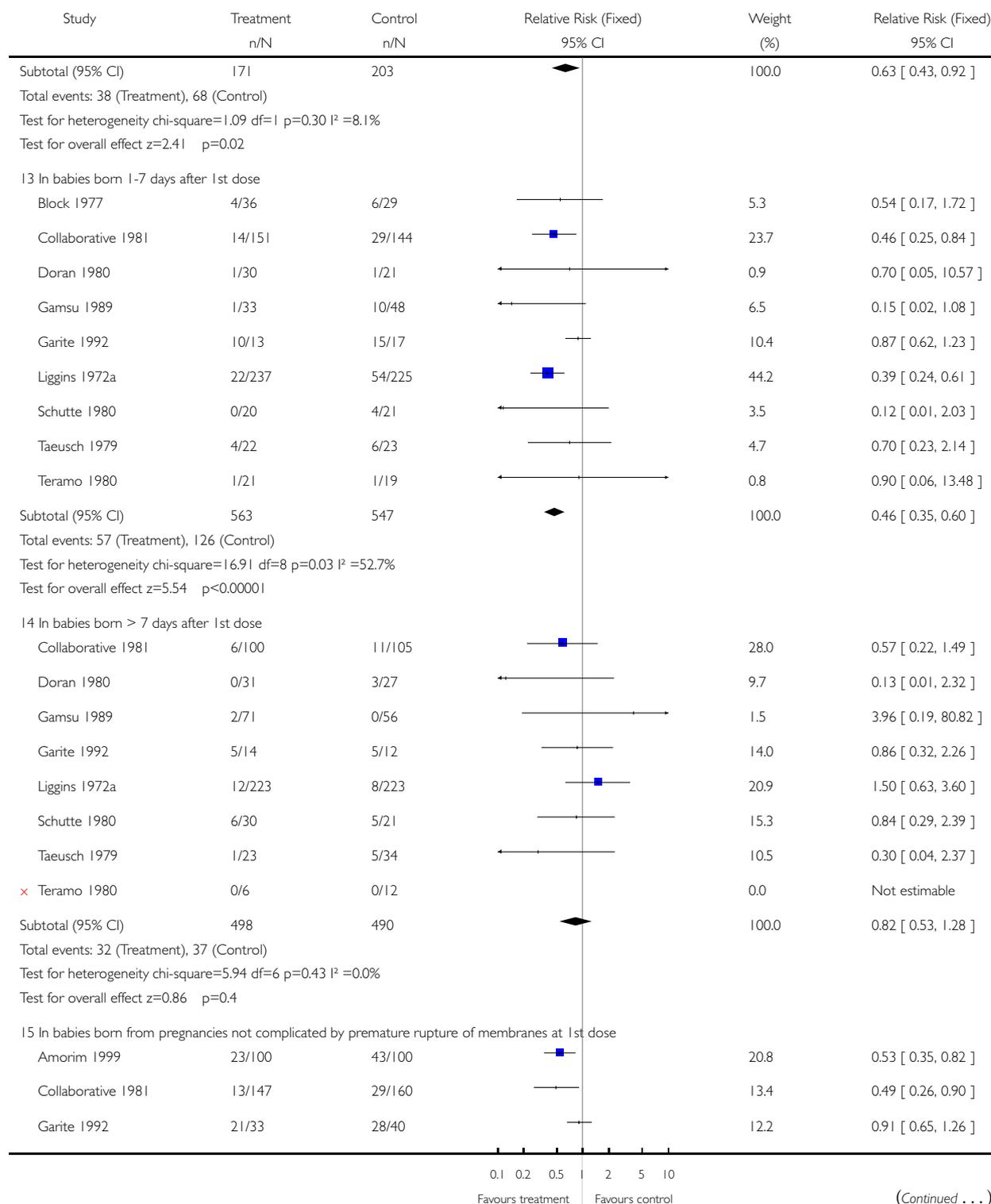
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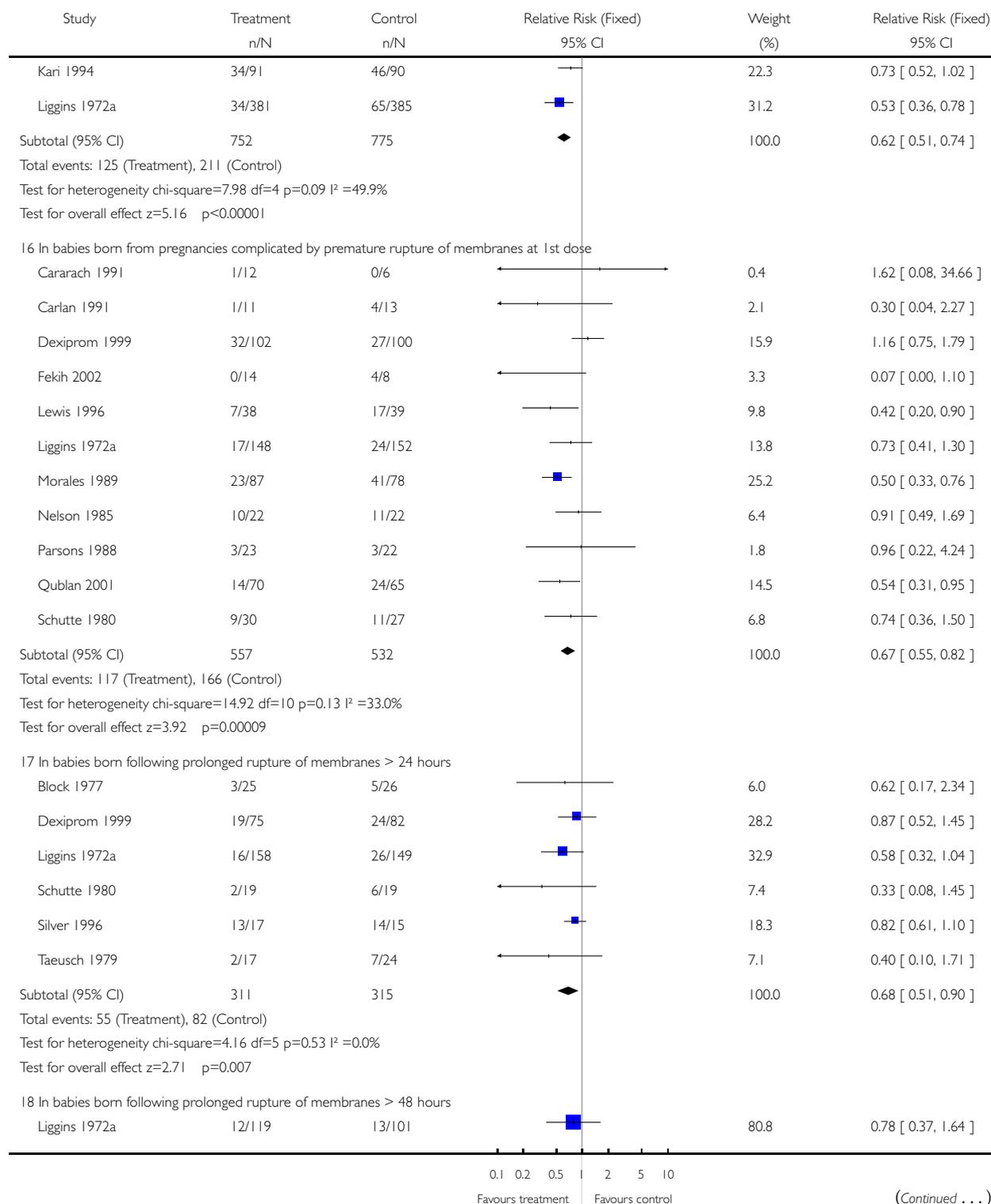
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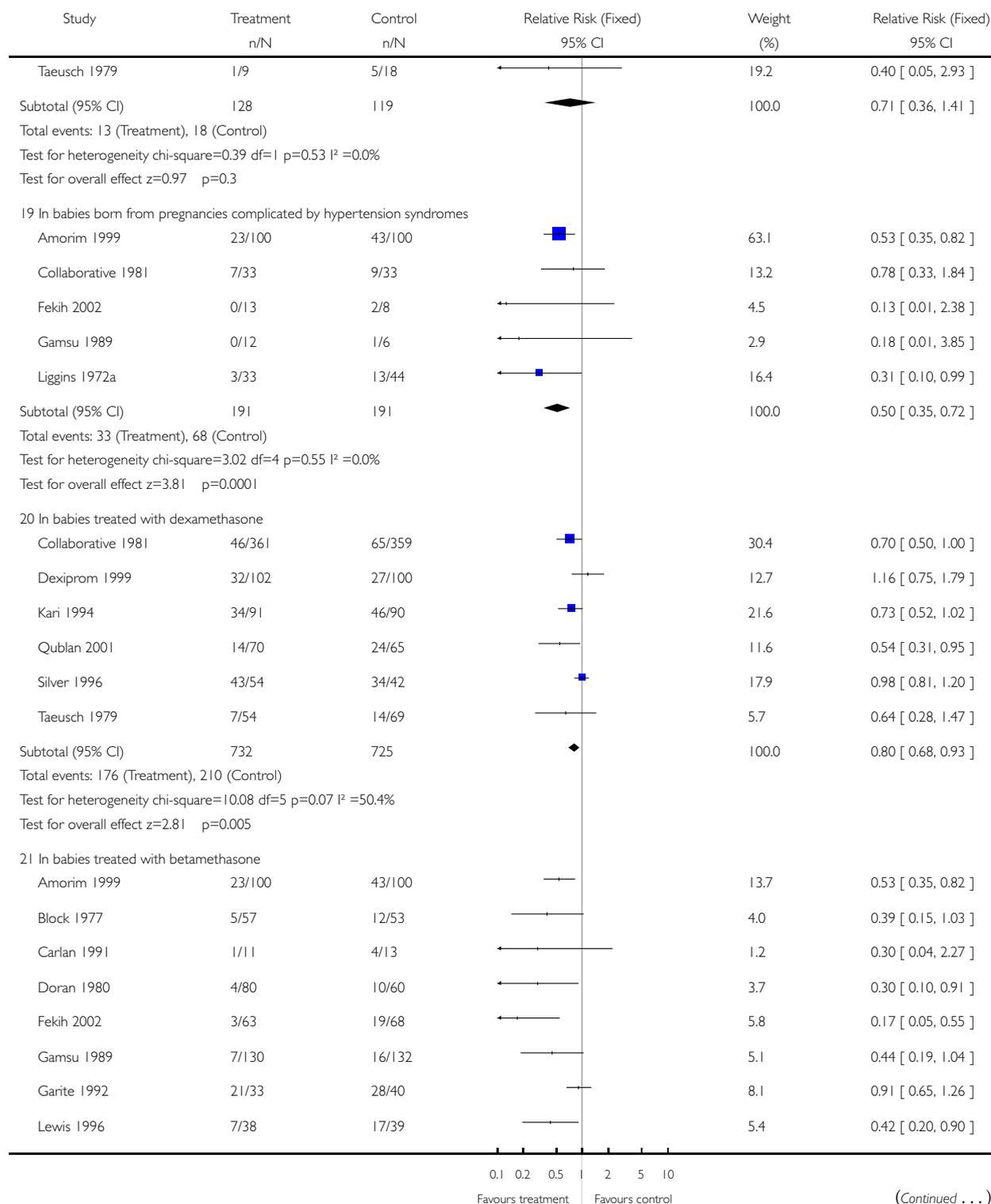
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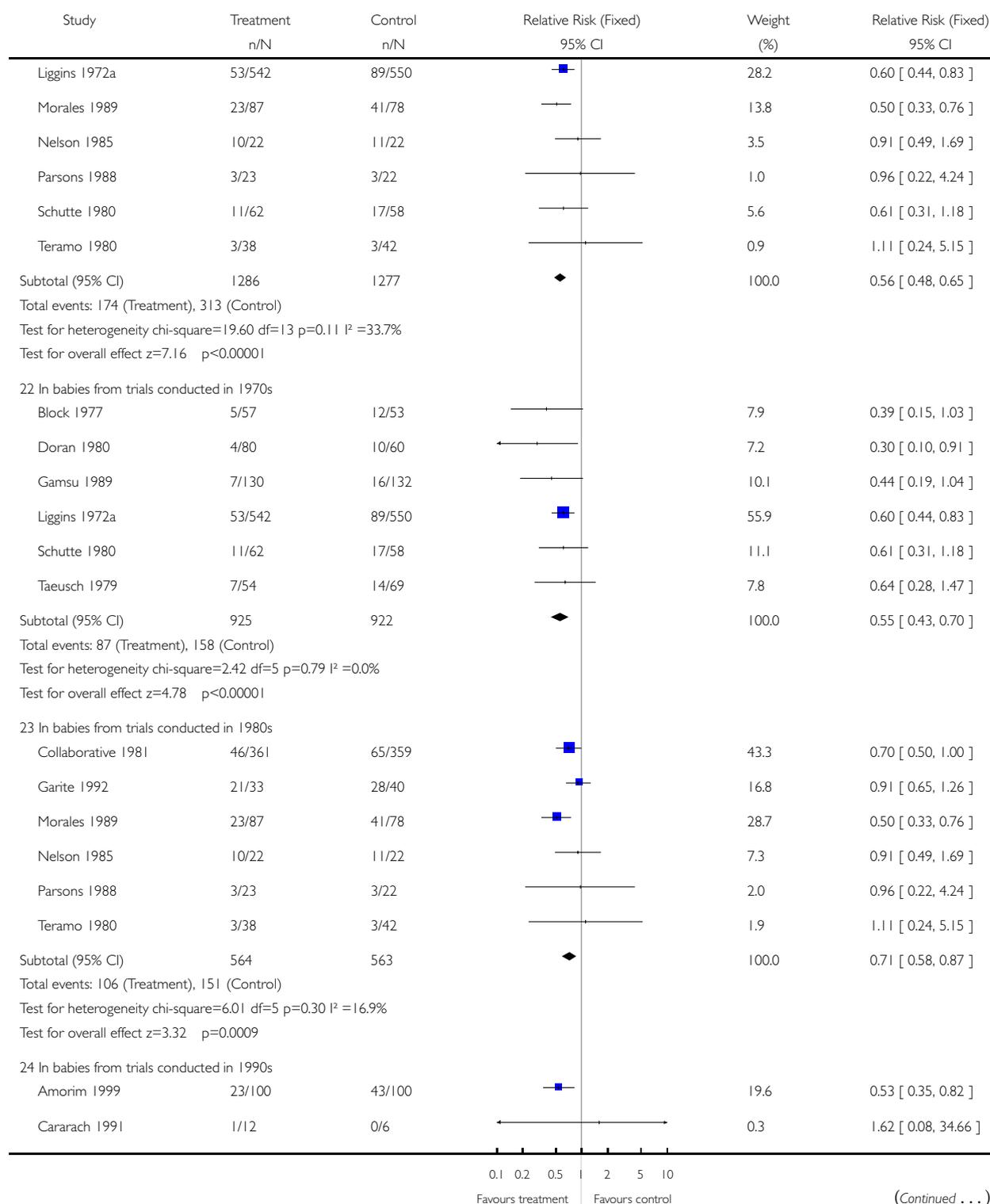
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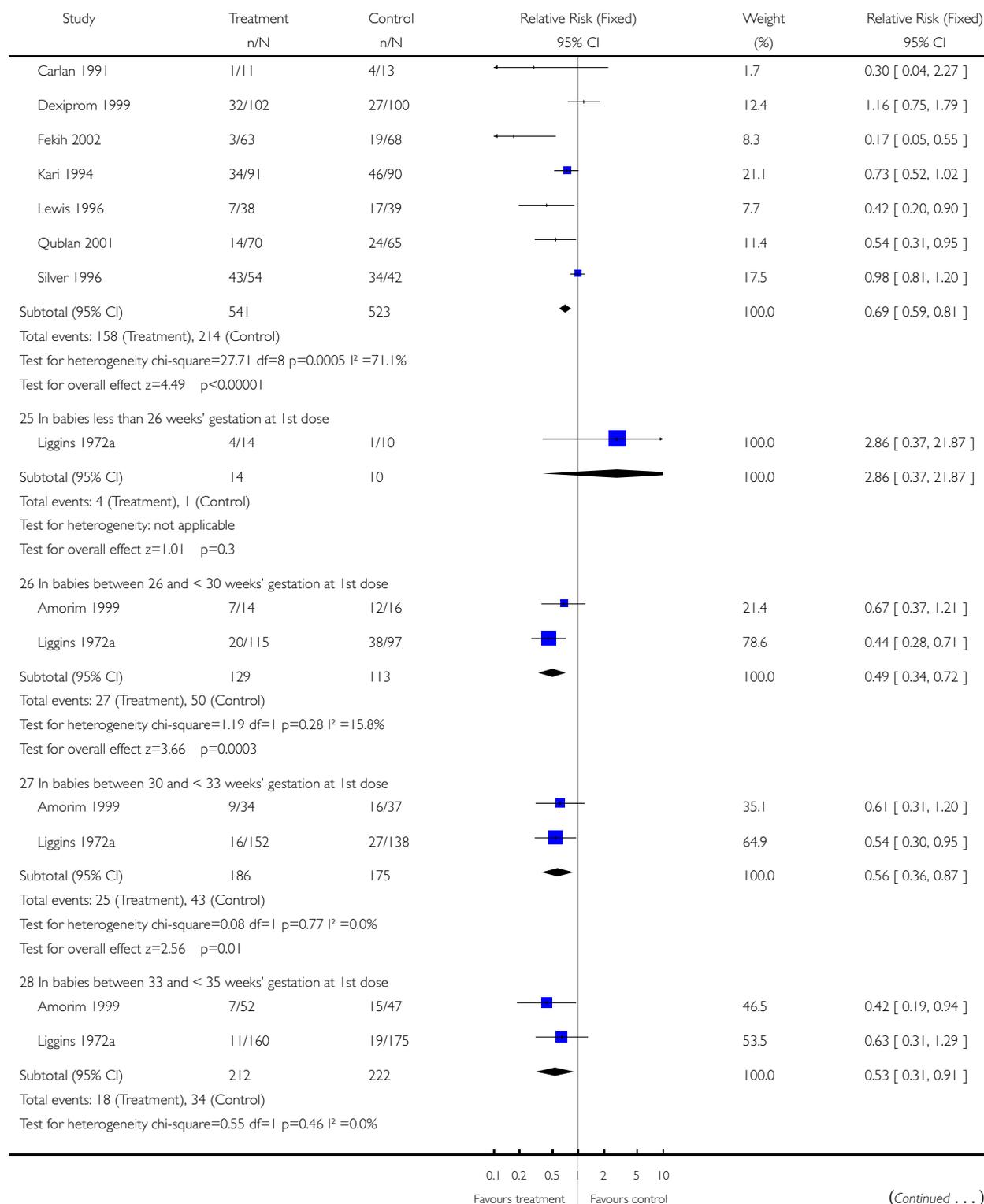
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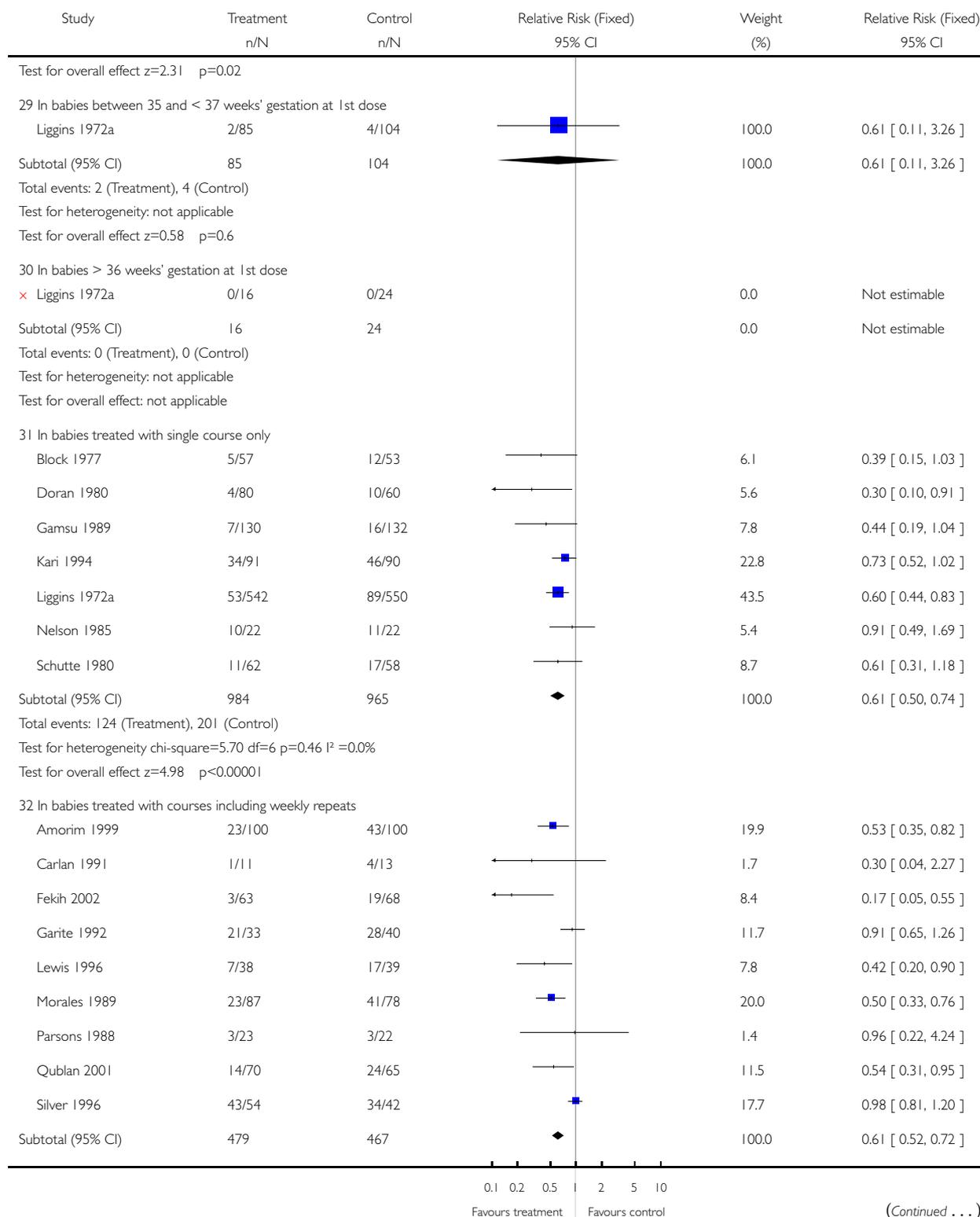
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Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
-------	------------------	----------------	---------------------------------	---------------	---------------------------------

Total events: 138 (Treatment), 213 (Control)  
 Test for heterogeneity chi-square=34.76 df=8 p<<0.0001 I<sup>2</sup> =77.0%  
 Test for overall effect z=5.93 p<0.00001

0.1 0.2 0.5 2 5 10  
 Favours treatment Favours control

**Analysis 01.08. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 08 Moderate/severe respiratory distress syndrome**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

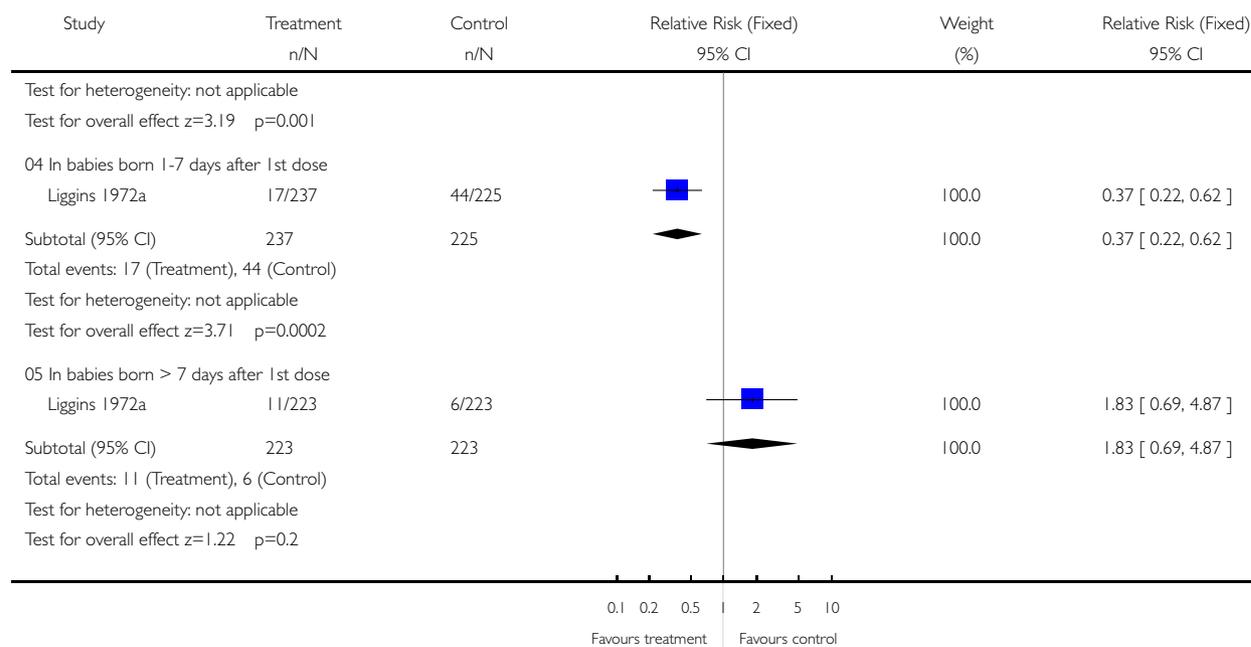
Outcome: 08 Moderate/severe respiratory distress syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Amorim 1999	9/100	23/100		16.0	0.39 [ 0.19, 0.80 ]
Fekih 2002	1/63	15/68		10.0	0.07 [ 0.01, 0.53 ]
Liggins 1972a	41/542	73/550		50.3	0.57 [ 0.40, 0.82 ]
Nelson 1985	6/22	6/22		4.2	1.00 [ 0.38, 2.62 ]
Silver 1996	18/54	14/42		10.9	1.00 [ 0.57, 1.77 ]
Taesch 1979	6/54	14/69		8.5	0.55 [ 0.23, 1.33 ]
Subtotal (95% CI)	835	851		100.0	0.55 [ 0.43, 0.71 ]
Total events: 81 (Treatment), 145 (Control) Test for heterogeneity chi-square=10.49 df=5 p=0.06 I <sup>2</sup> =52.3% Test for overall effect z=4.55 p<0.00001					
02 In babies born < 24 hours after 1st dose					
Liggins 1972a	13/82	23/100		100.0	0.69 [ 0.37, 1.27 ]
Subtotal (95% CI)	82	100		100.0	0.69 [ 0.37, 1.27 ]
Total events: 13 (Treatment), 23 (Control) Test for heterogeneity: not applicable Test for overall effect z=1.19 p=0.2					
03 In babies born < 48 hours after 1st dose					
Liggins 1972a	18/147	49/179		100.0	0.45 [ 0.27, 0.73 ]
Subtotal (95% CI)	147	179		100.0	0.45 [ 0.27, 0.73 ]
Total events: 18 (Treatment), 49 (Control)					

0.1 0.2 0.5 2 5 10  
 Favours treatment Favours control

(Continued ...)

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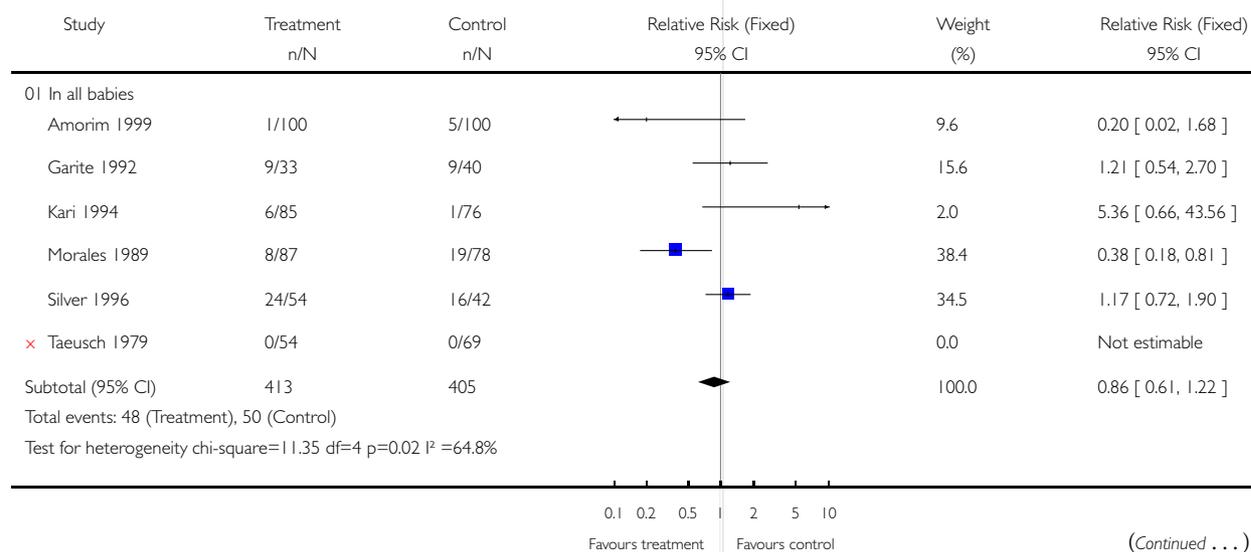


### Analysis 01.09. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 09 Chronic lung disease

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

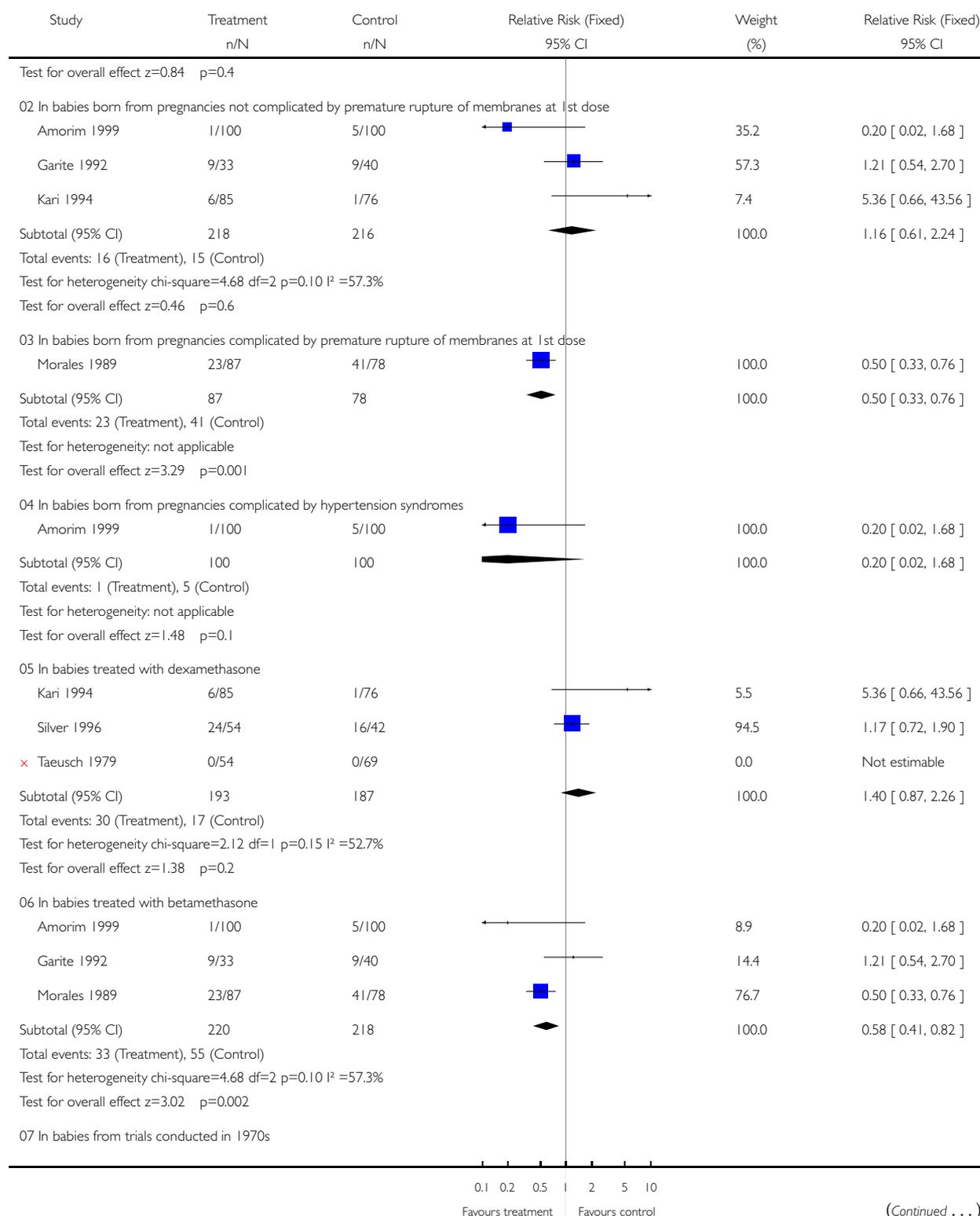
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 09 Chronic lung disease



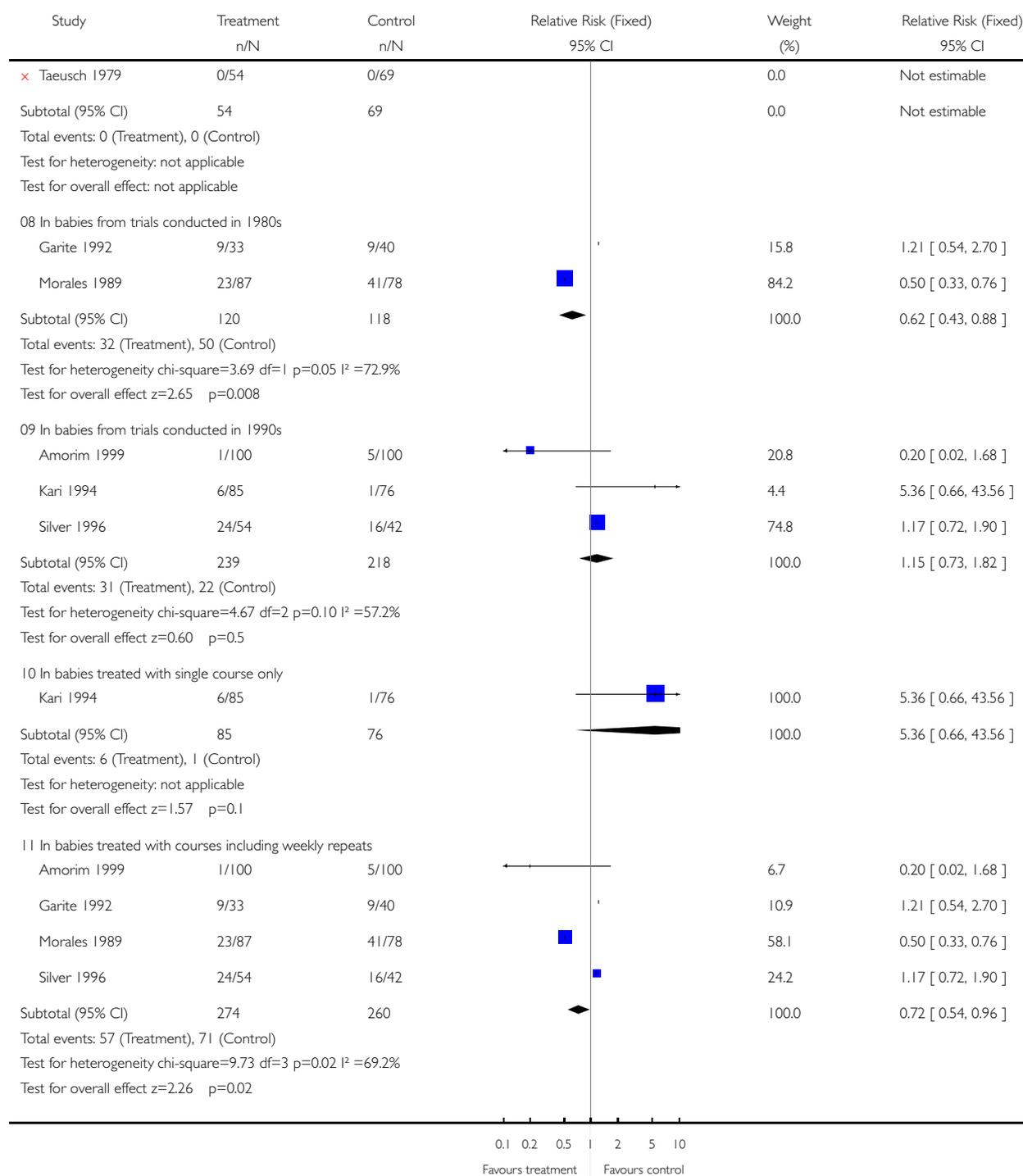
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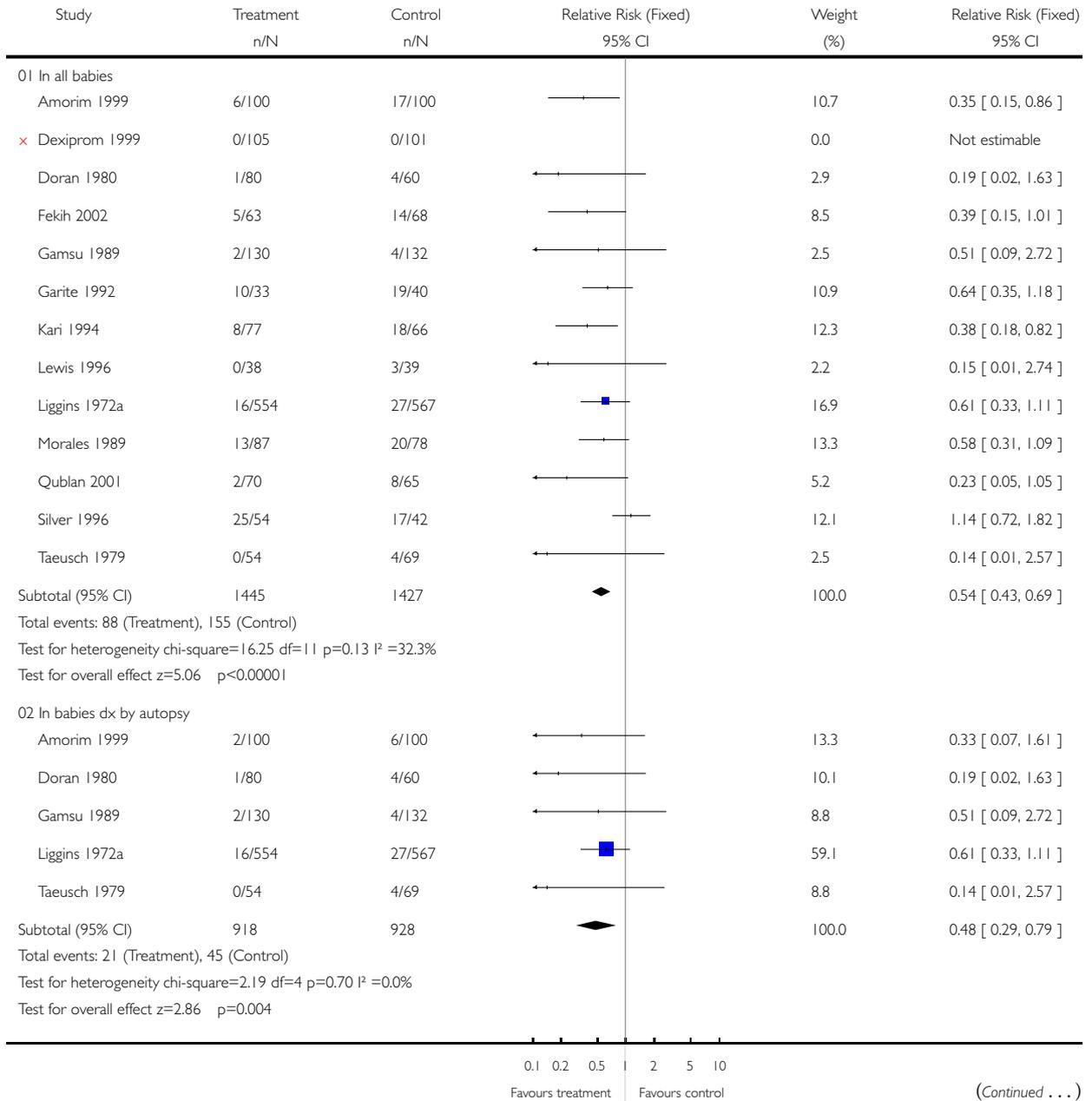


### Analysis 01.10. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 10 Cerebroventricular haemorrhage

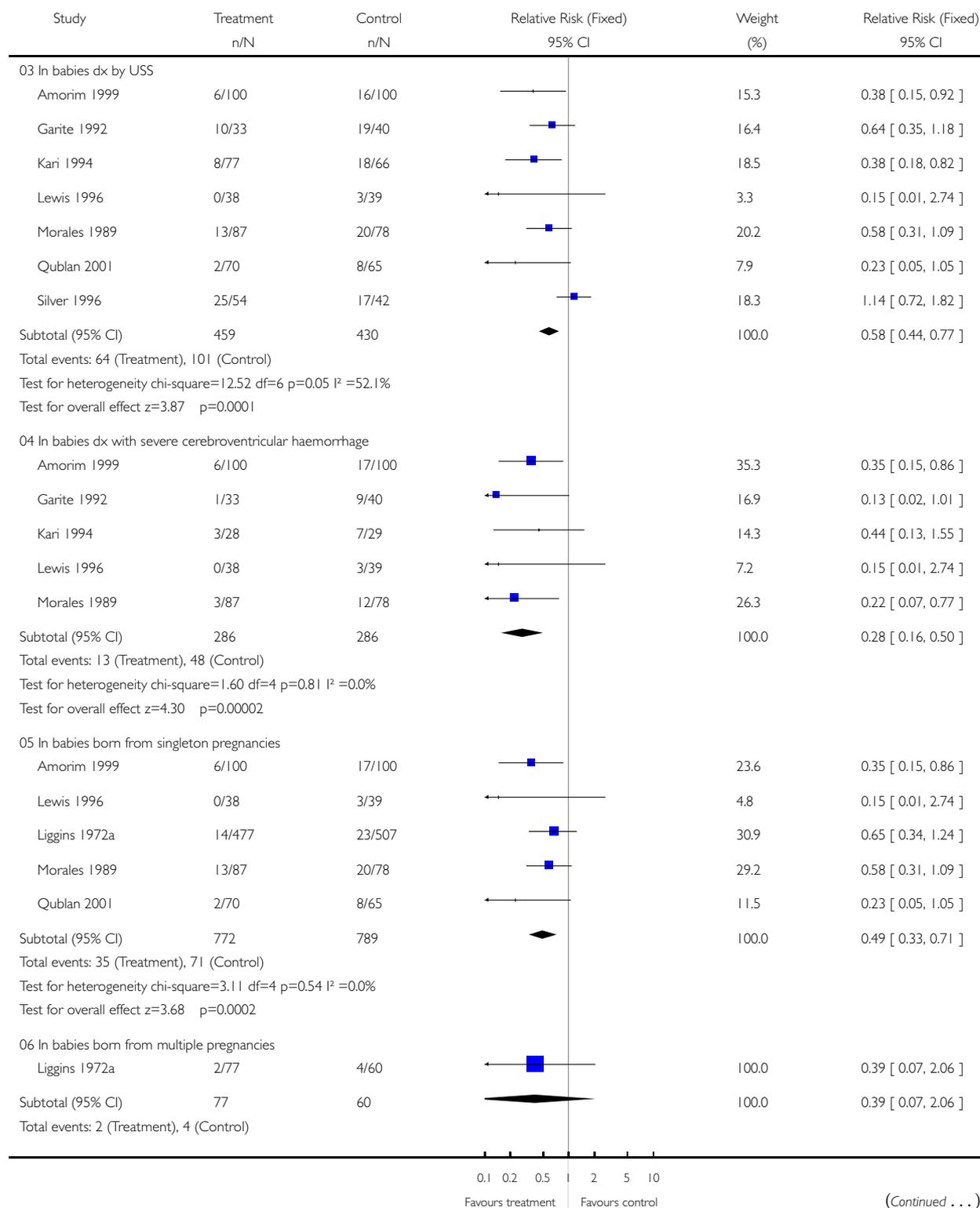
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 10 Cerebroventricular haemorrhage

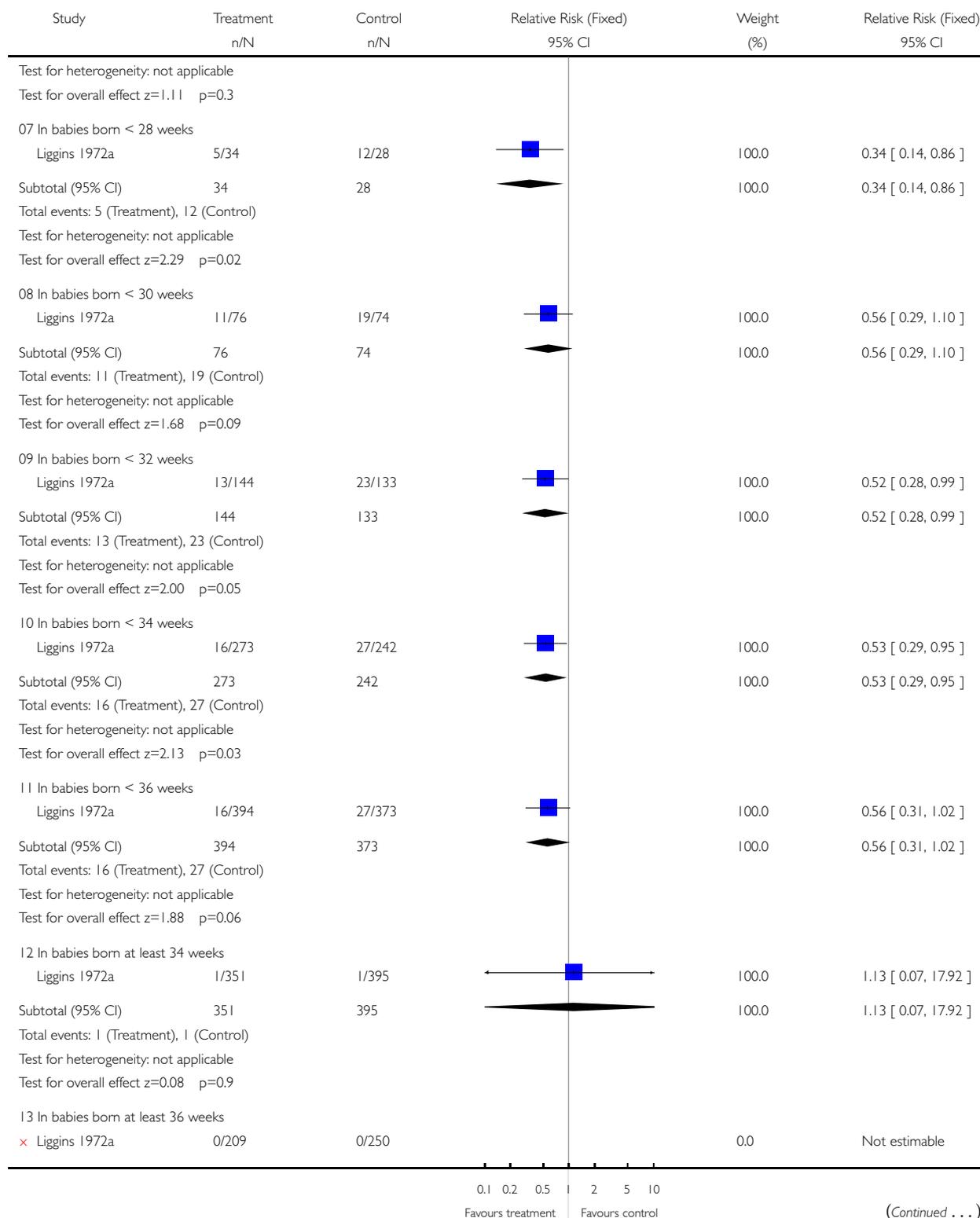


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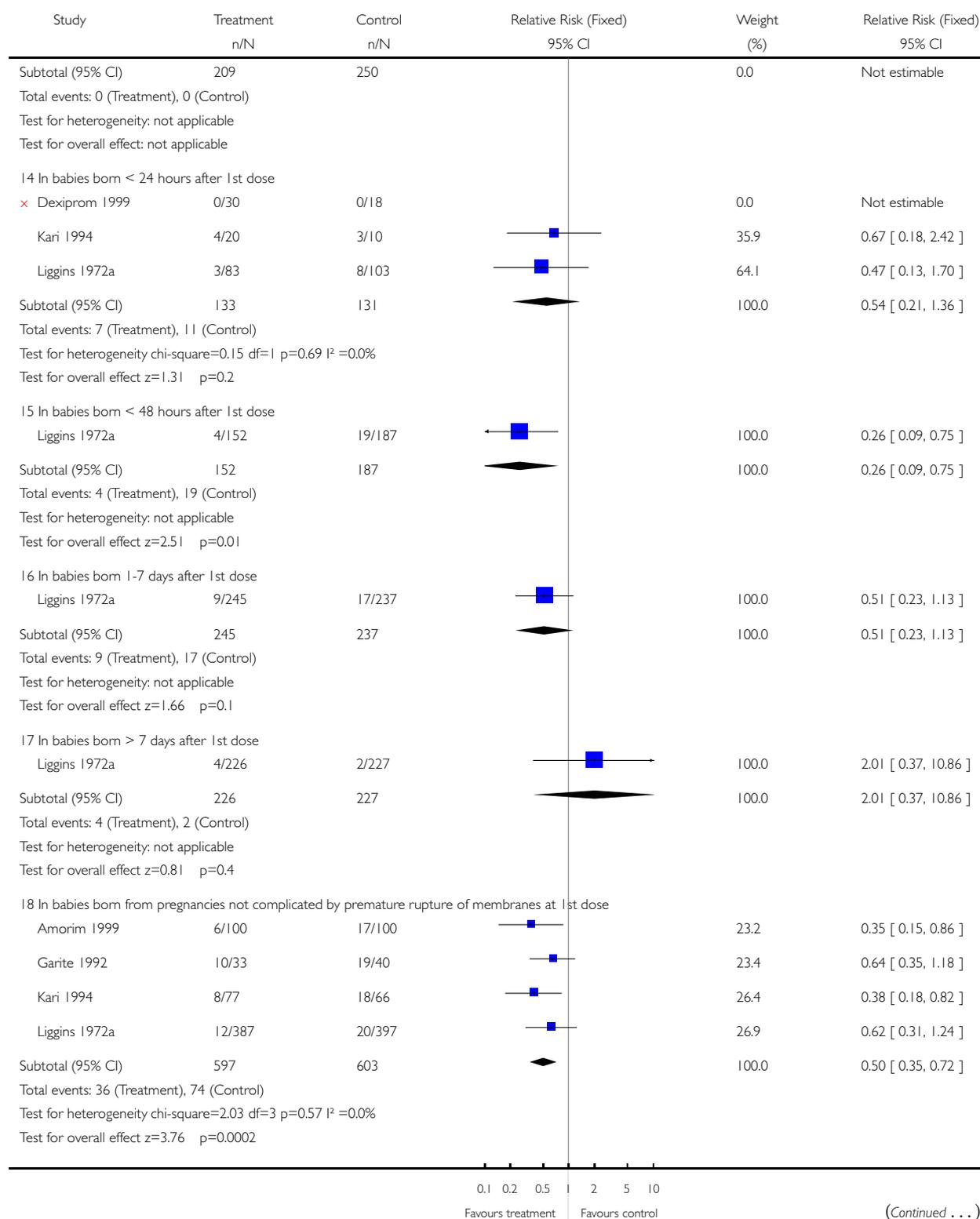
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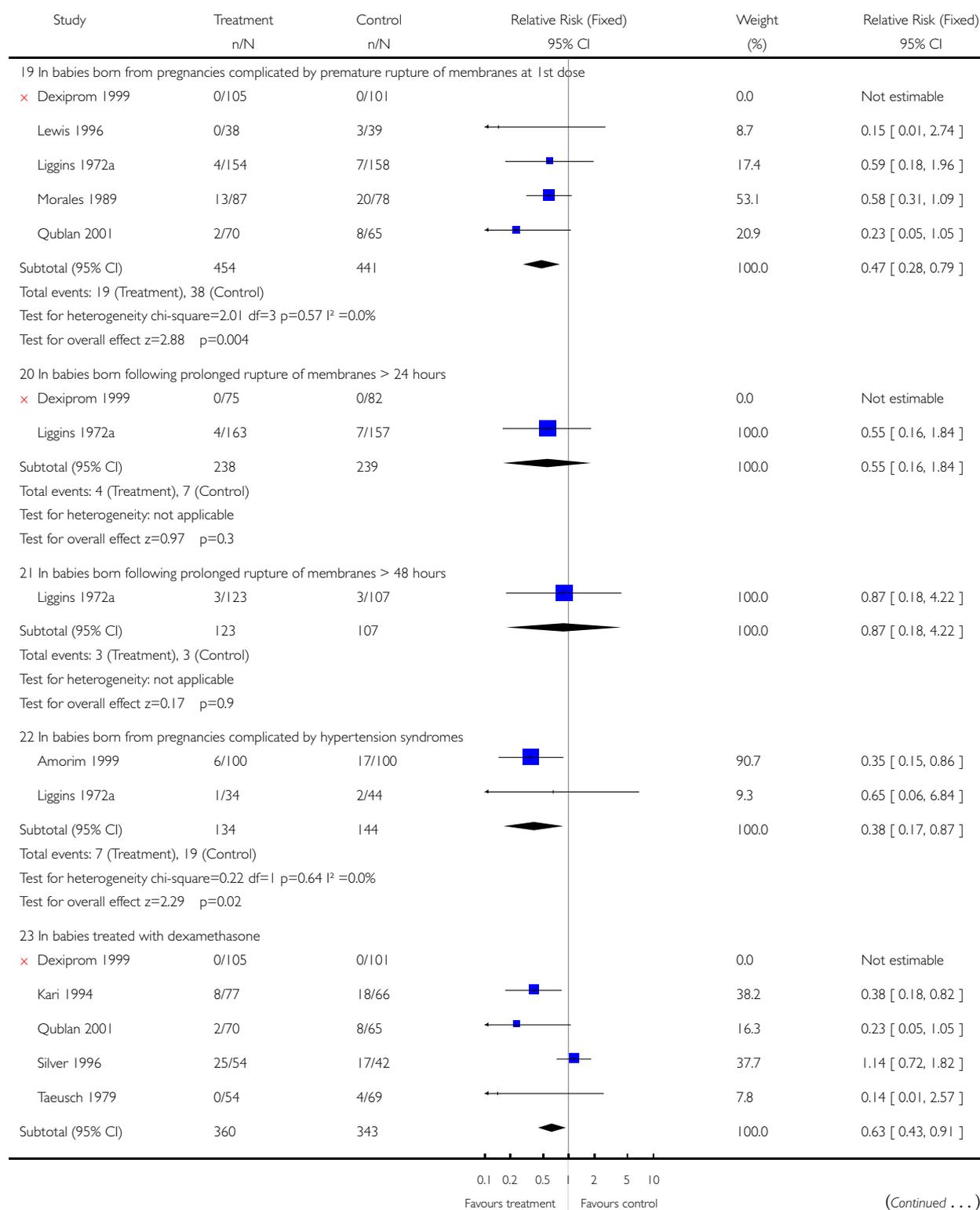
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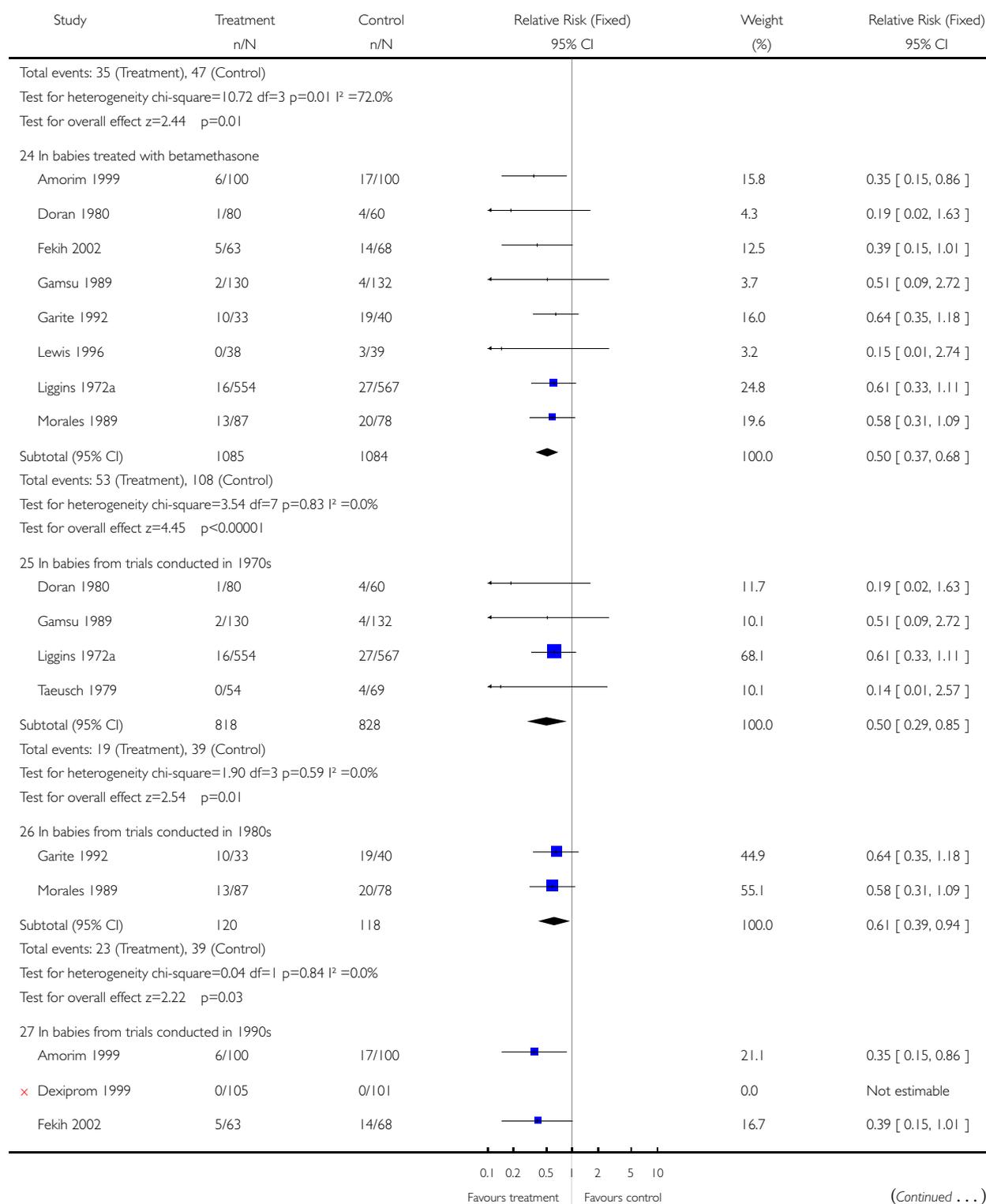
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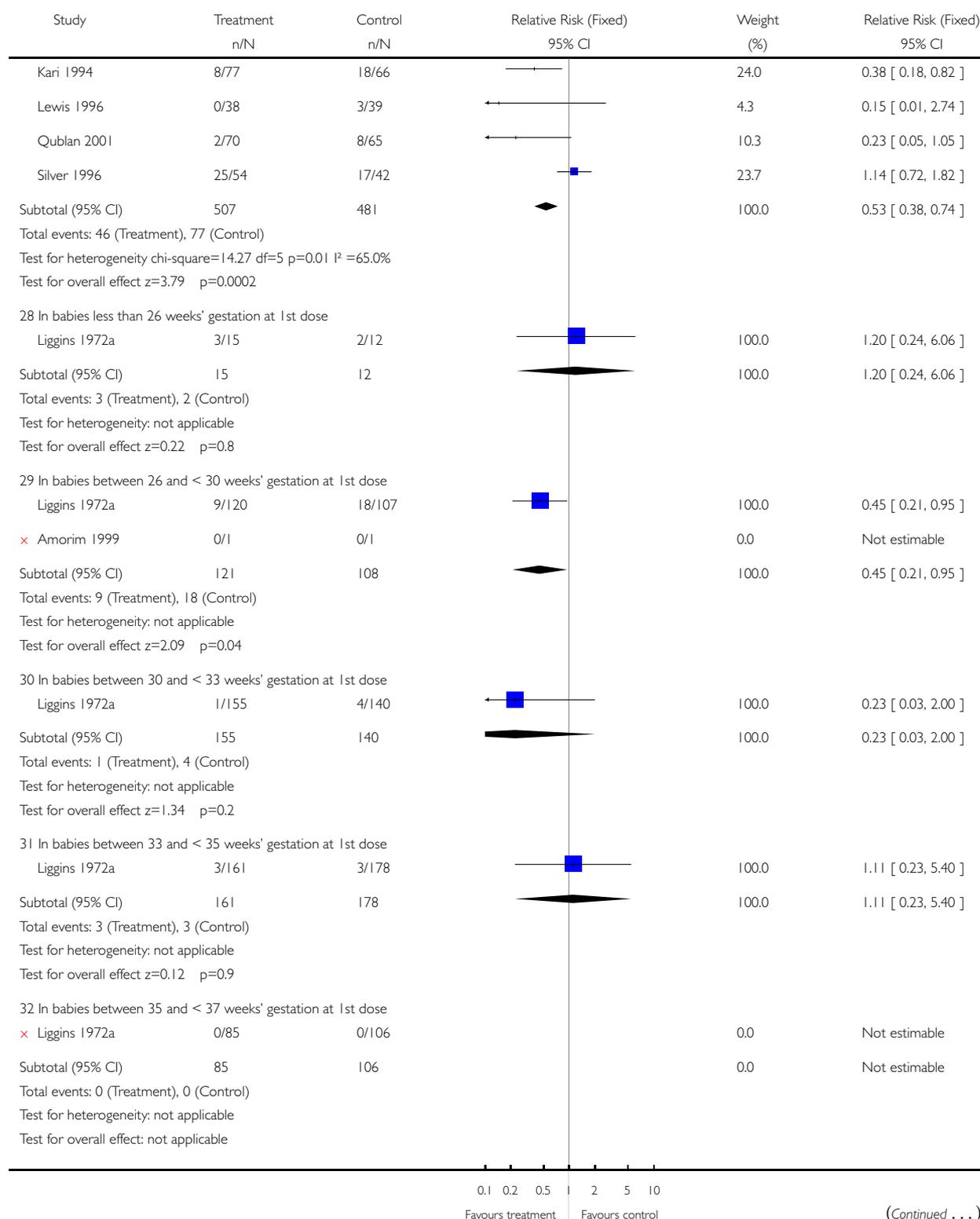
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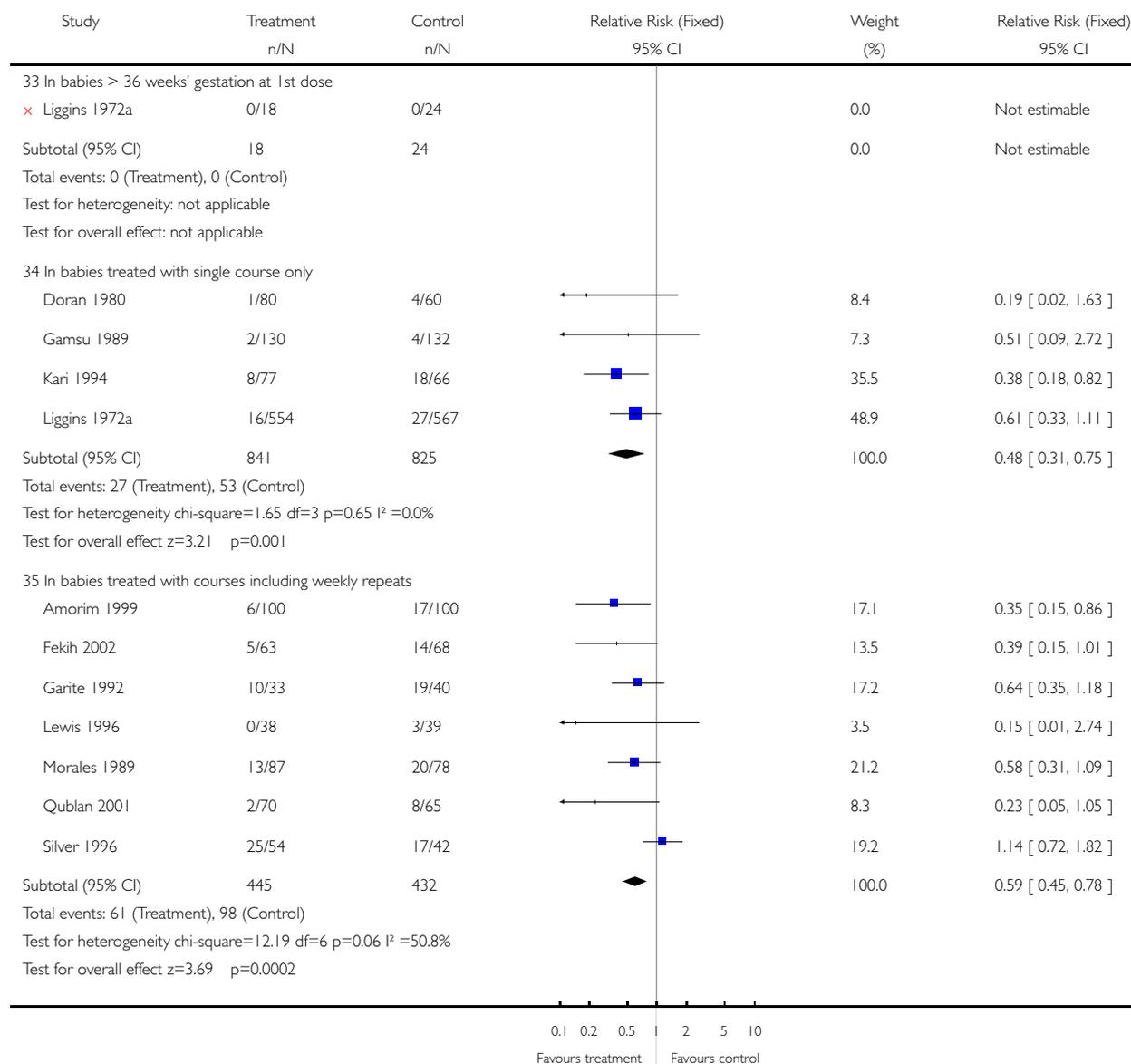
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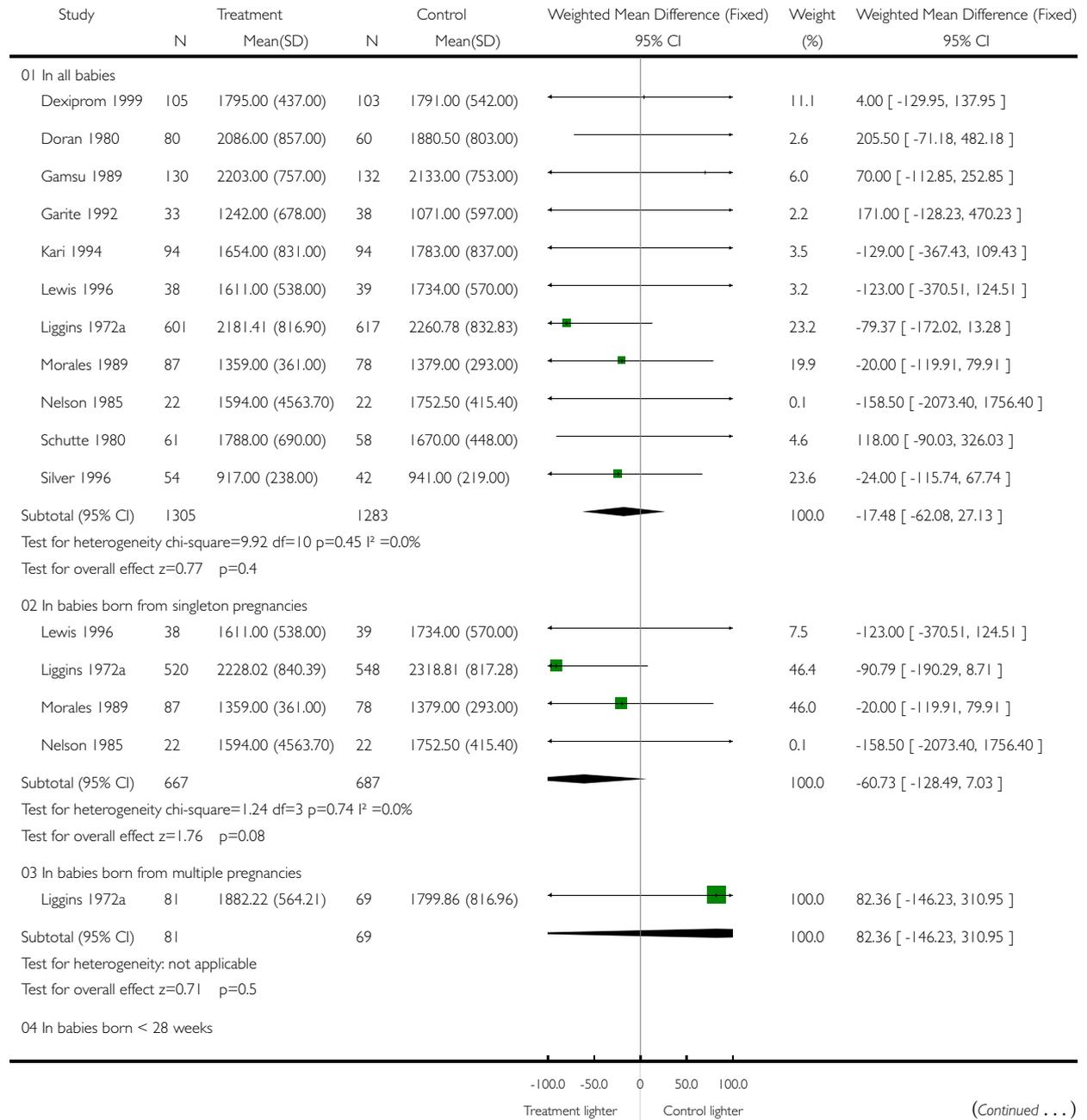


### Analysis 01.11. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 11 Mean birthweight (grams)

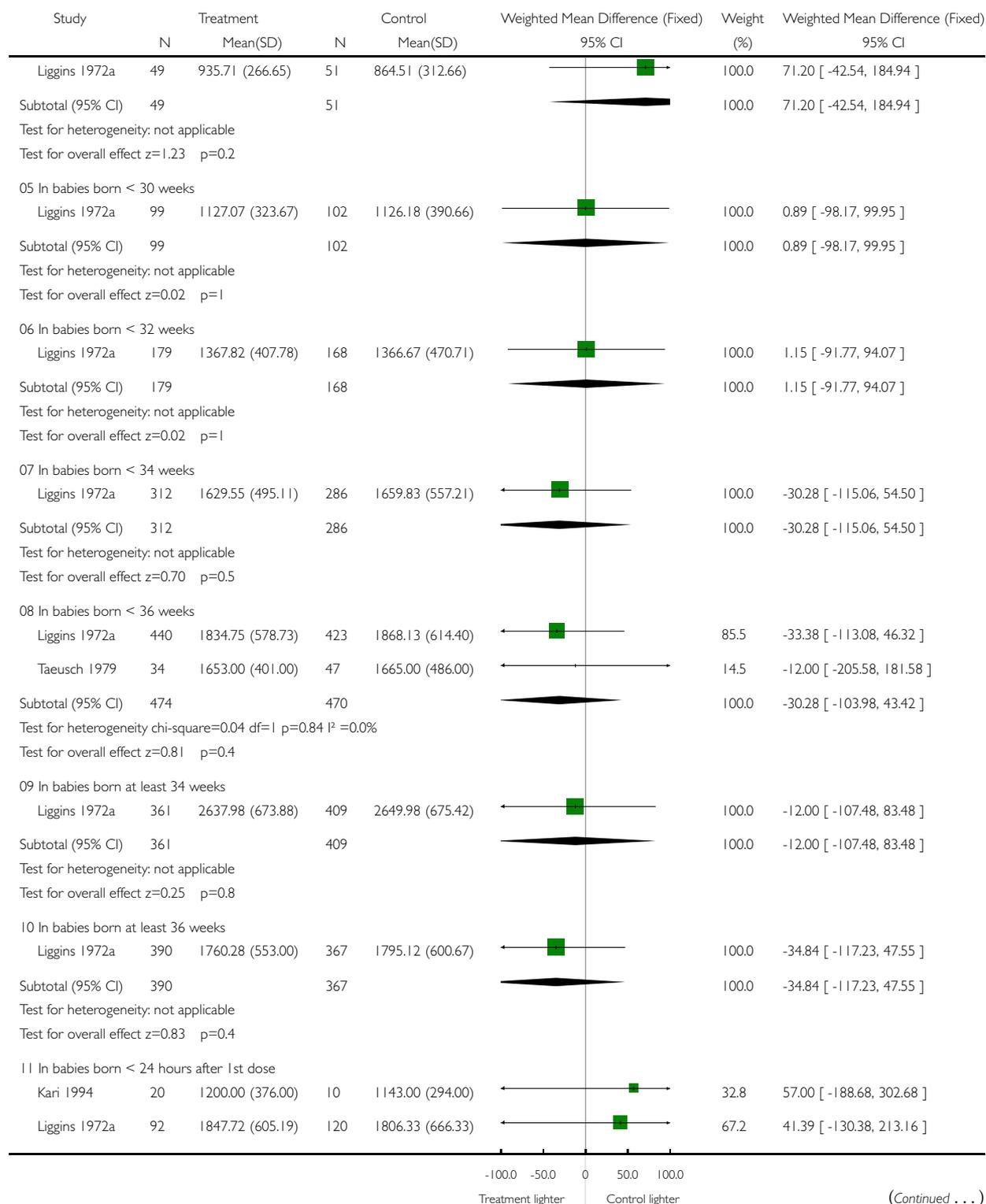
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 11 Mean birthweight (grams)

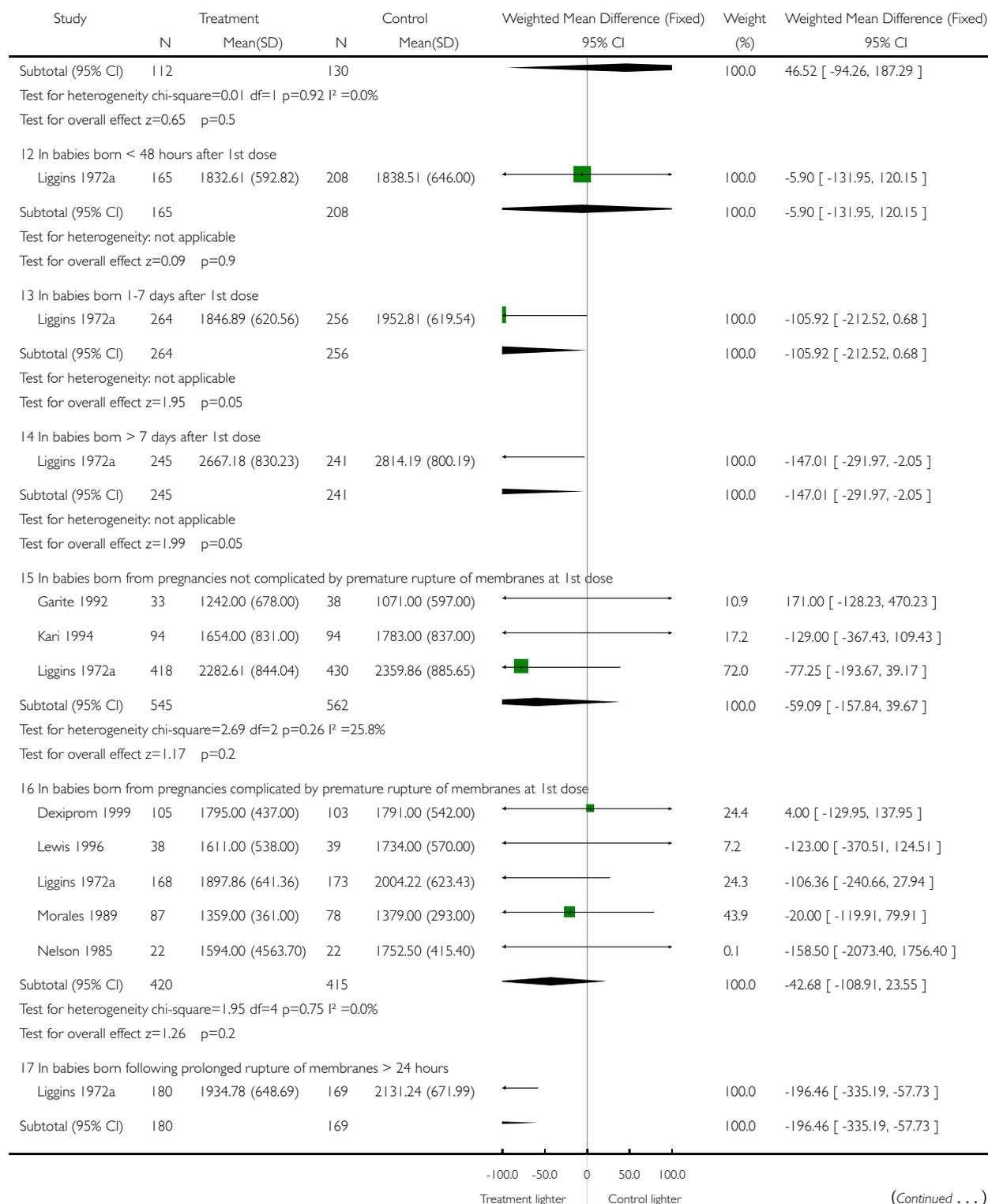


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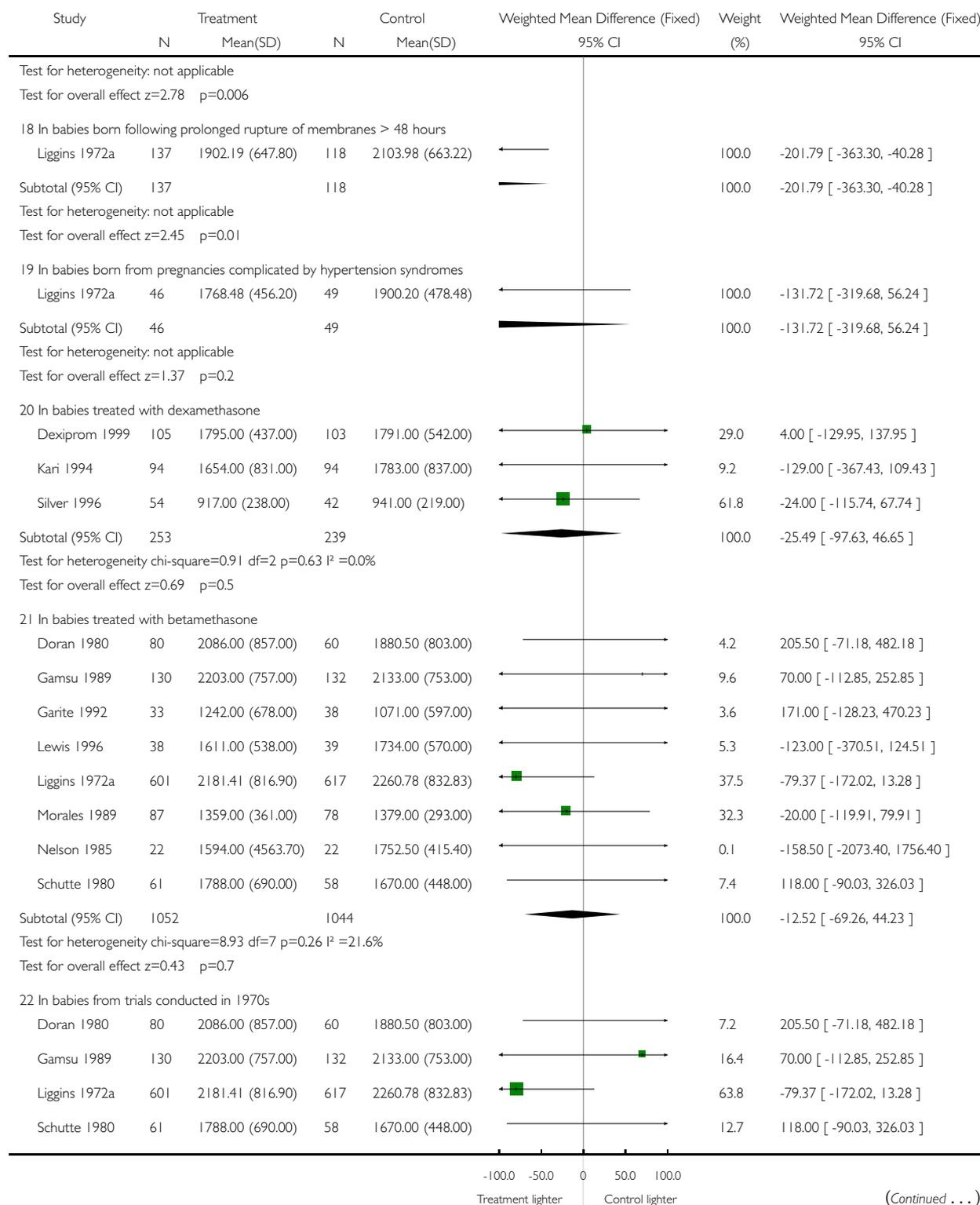
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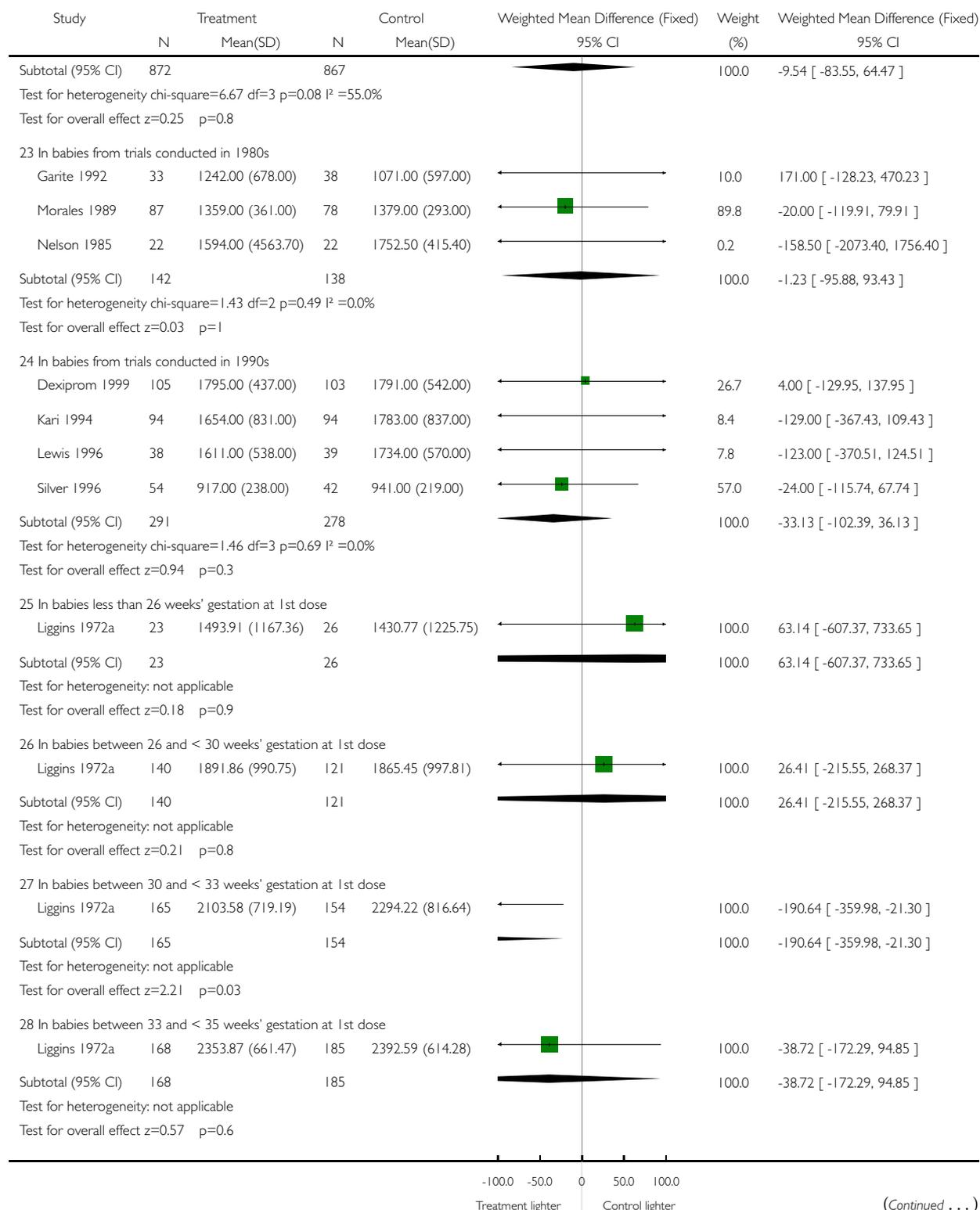
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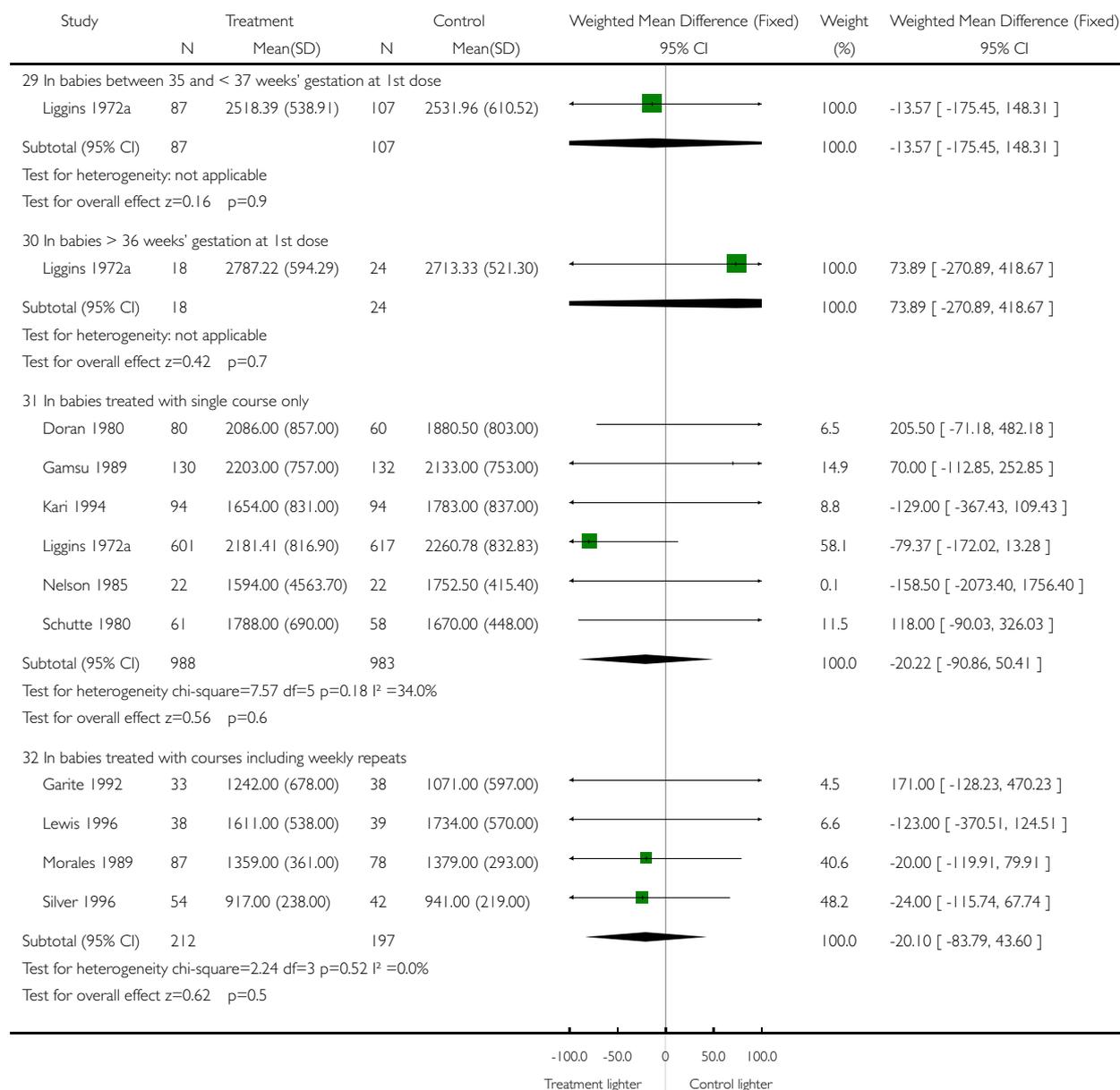
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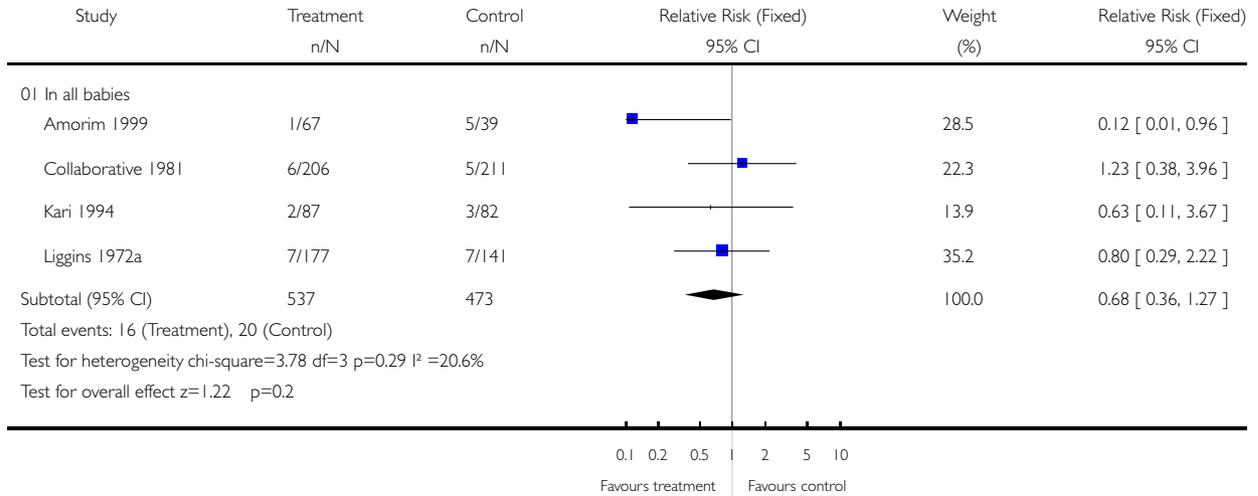


### Analysis 01.12. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 12 Death in childhood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 12 Death in childhood

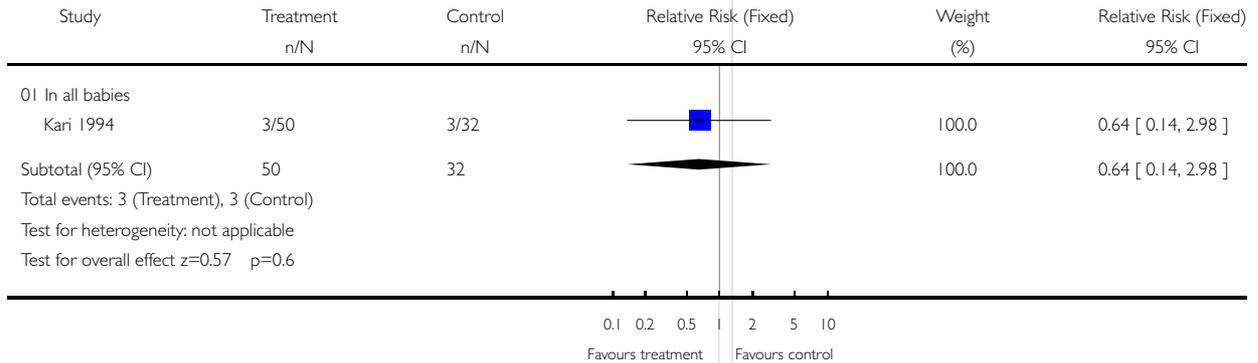


### Analysis 01.13. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 13 Neurodevelopmental delay in childhood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 13 Neurodevelopmental delay in childhood

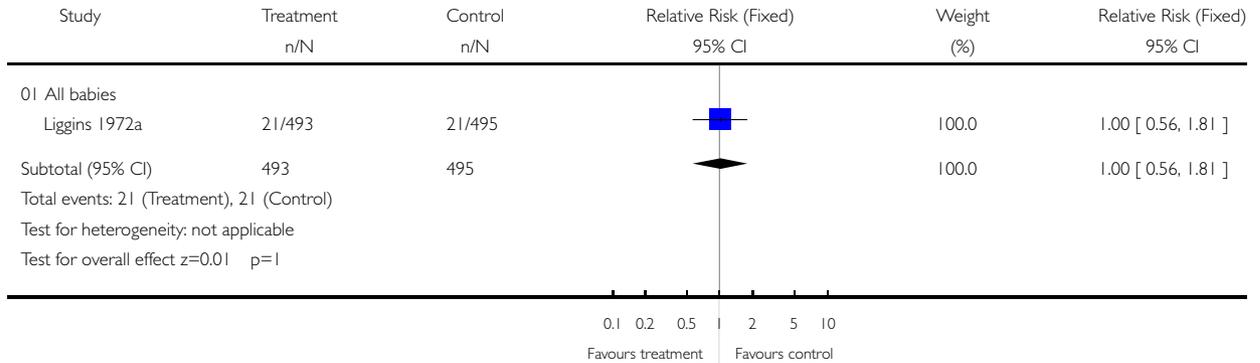


### Analysis 01.14. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 14 Death into adulthood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 14 Death into adulthood

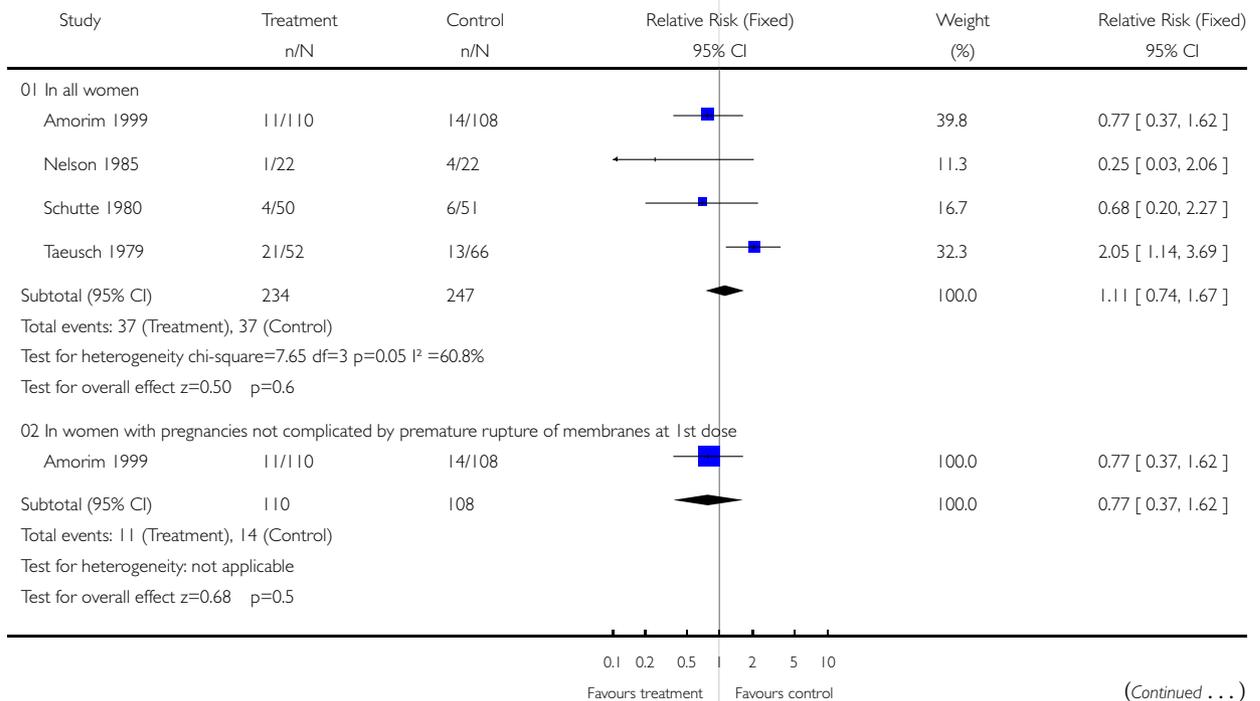


### Analysis 01.15. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 15 Fever in women after trial entry requiring the use of antibiotics

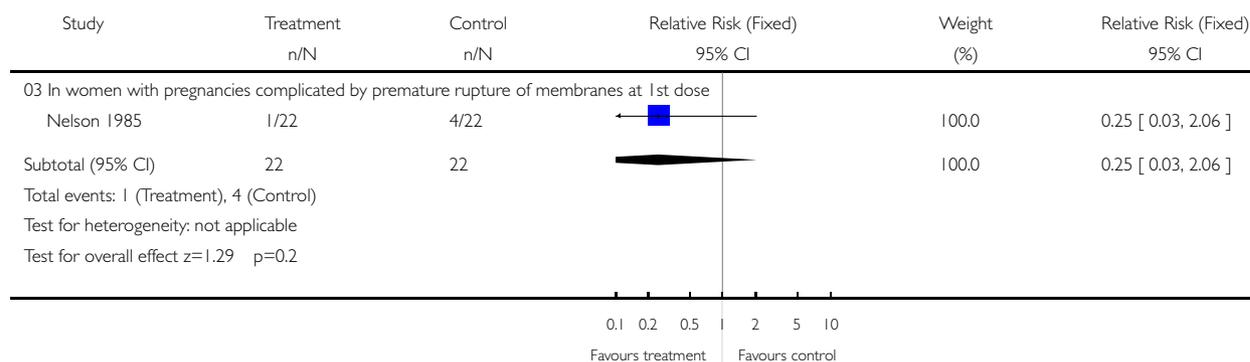
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 15 Fever in women after trial entry requiring the use of antibiotics



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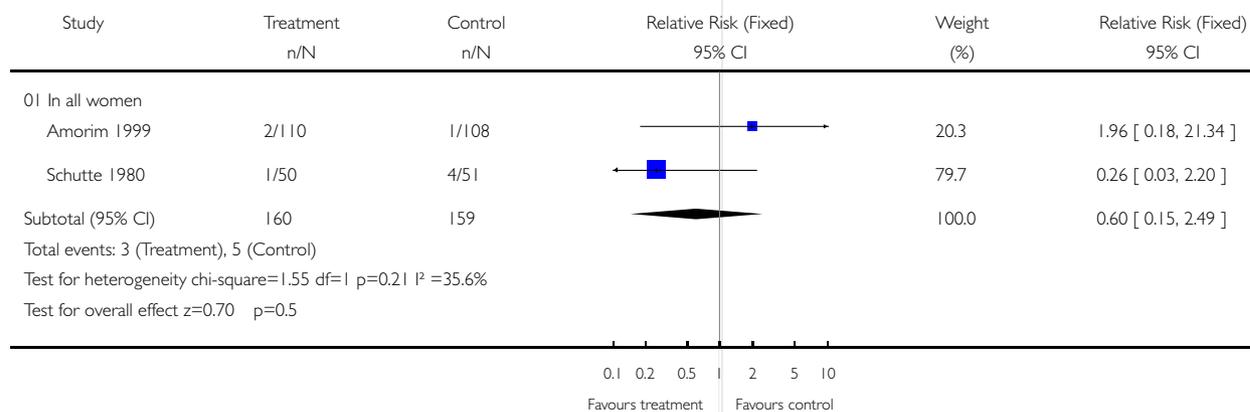


### Analysis 01.16. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 16 Intrapartum fever in woman requiring the use of antibiotics

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 16 Intrapartum fever in woman requiring the use of antibiotics

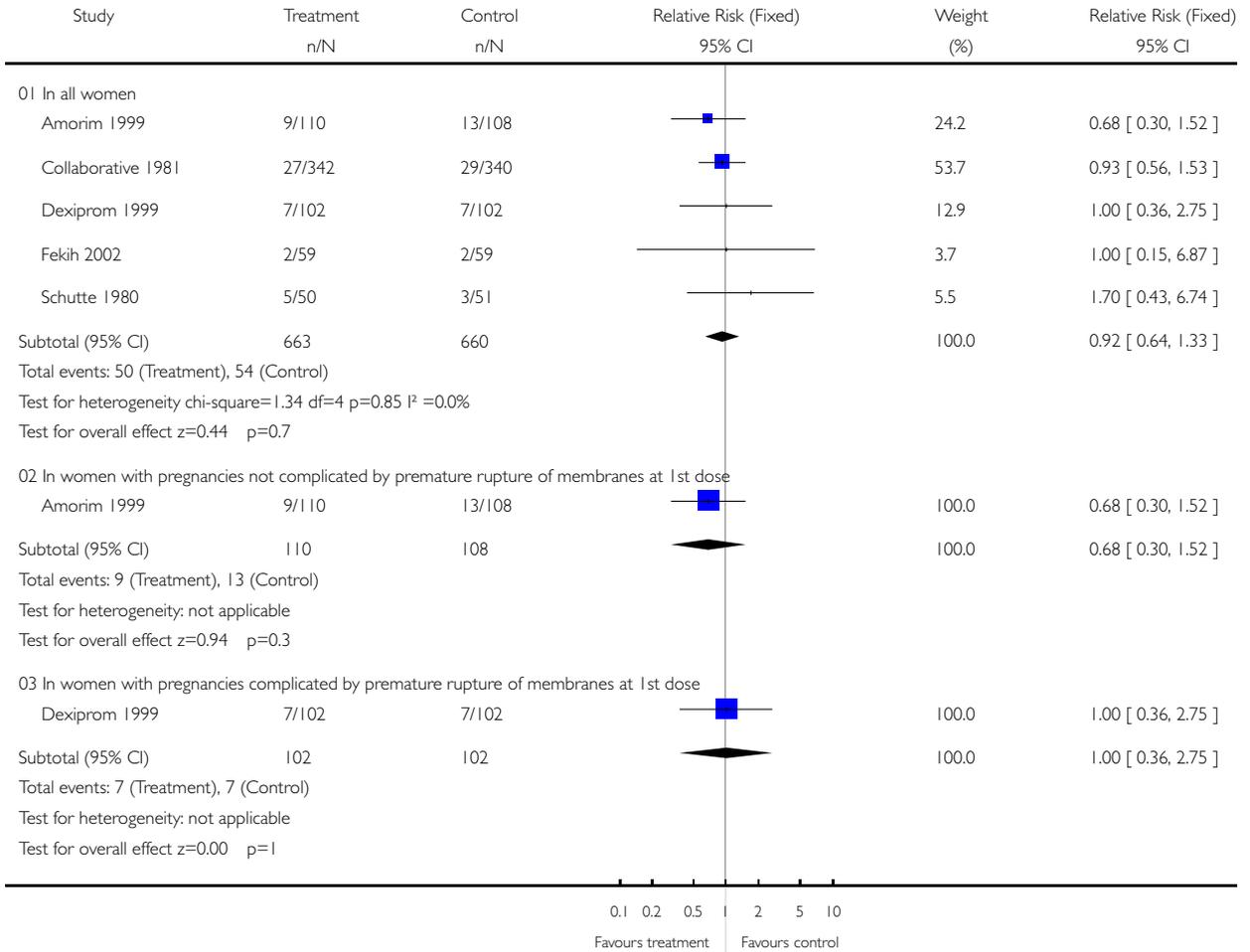


**Analysis 01.17. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 17 Postnatal fever in woman**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

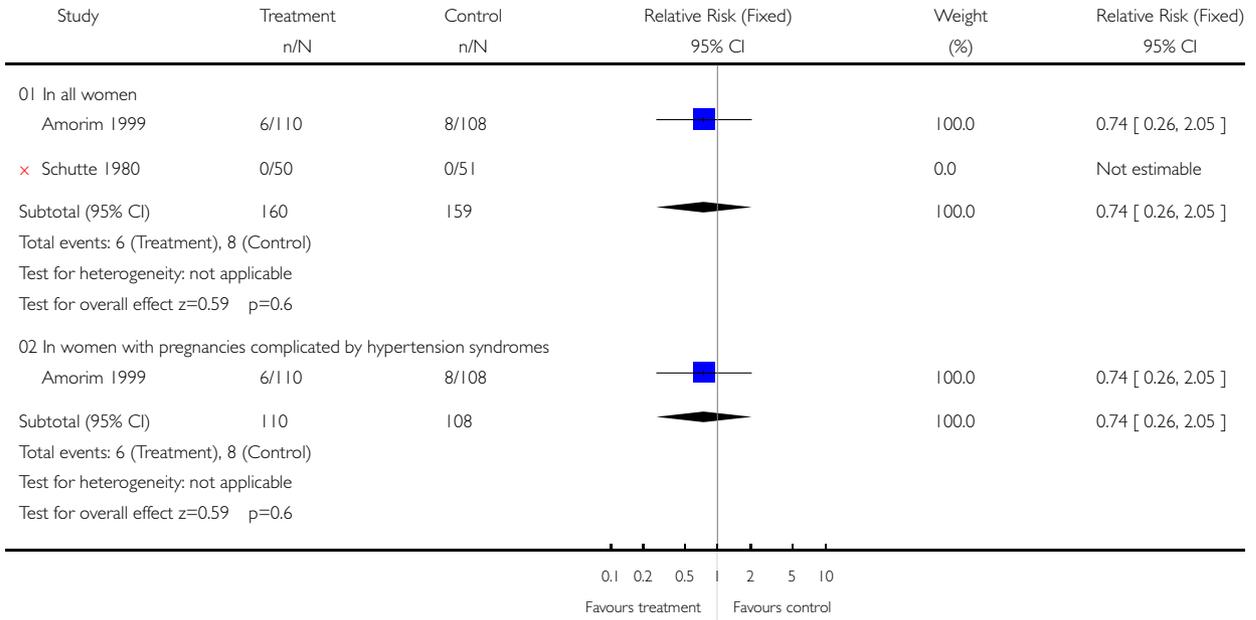
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 17 Postnatal fever in woman



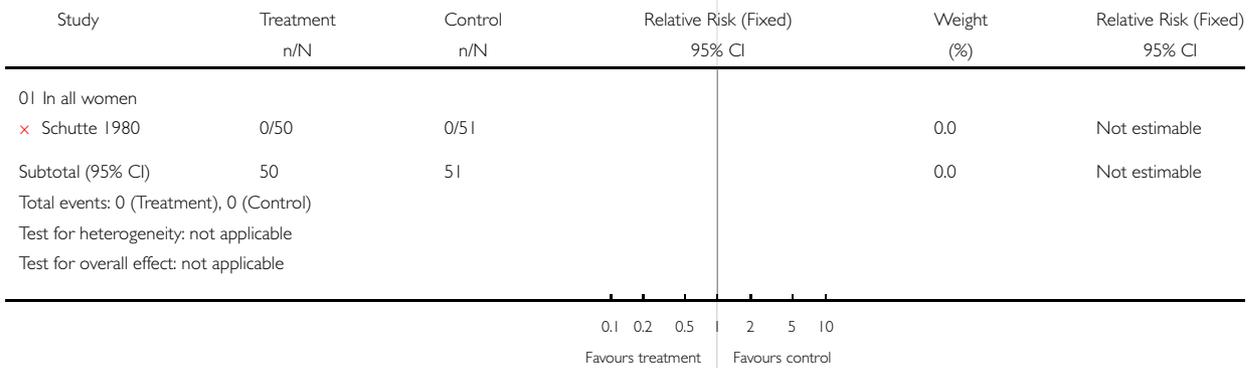
**Analysis 01.18. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 18 Admission into adult intensive care unit**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 18 Admission into adult intensive care unit



**Analysis 01.19. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 19 Side-effects of therapy in women**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 19 Side-effects of therapy in women

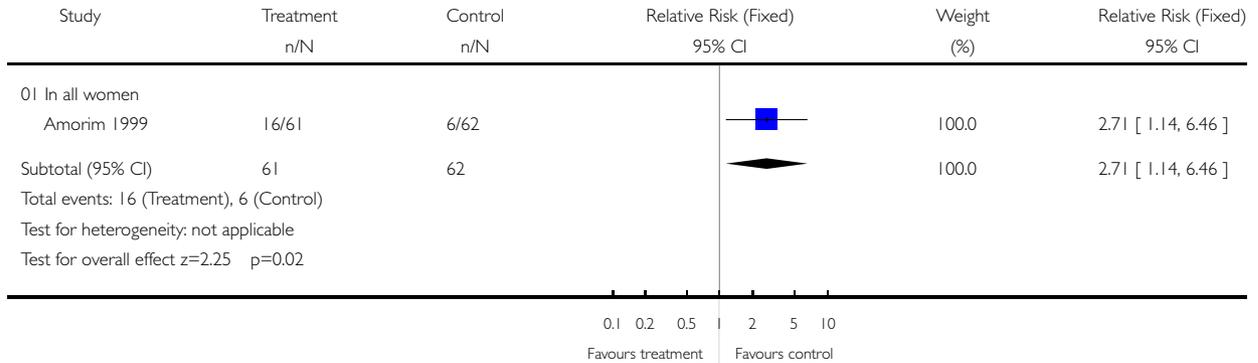


### Analysis 01.20. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 20 Glucose intolerance

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 20 Glucose intolerance

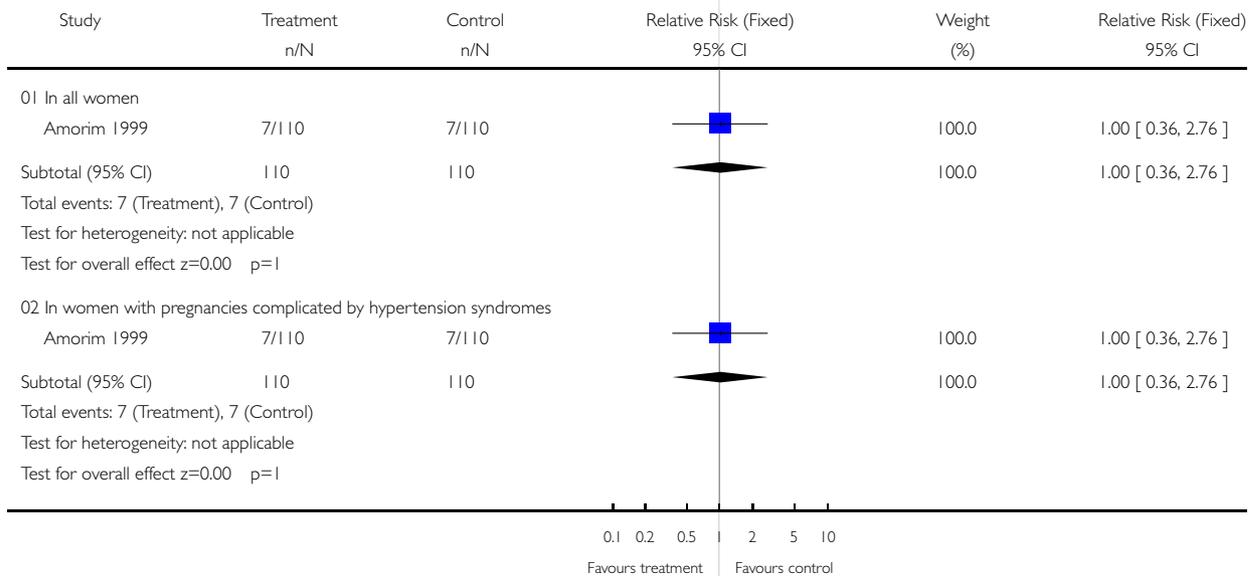


### Analysis 01.21. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 21 Hypertension

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 21 Hypertension

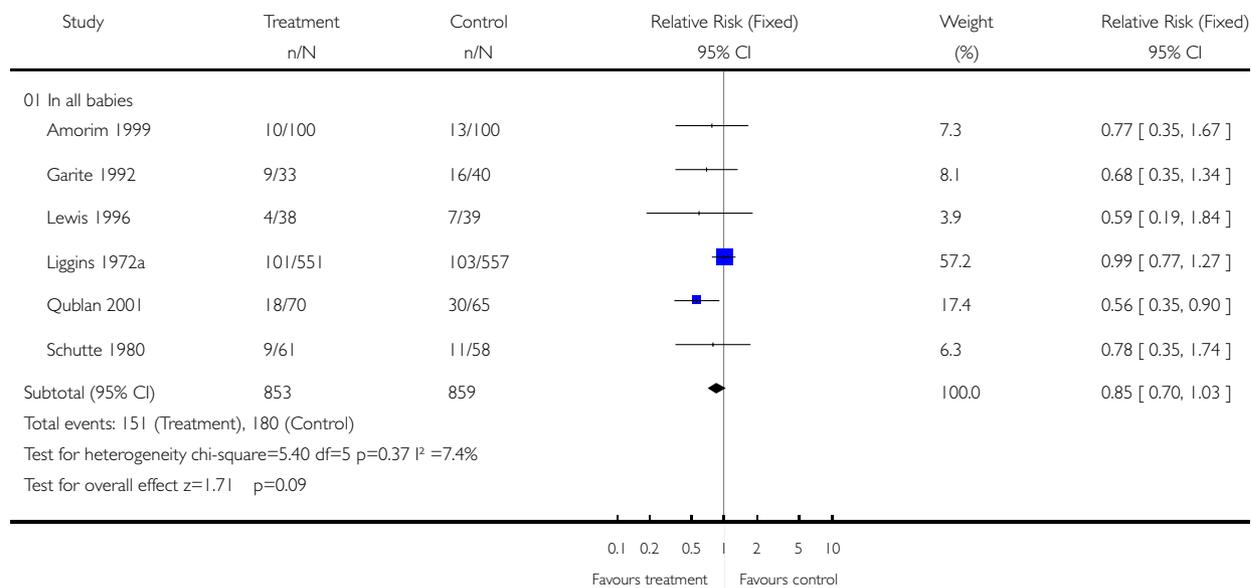


### Analysis 01.22. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 22 Apgar < 7 at 5 minutes

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 22 Apgar < 7 at 5 minutes

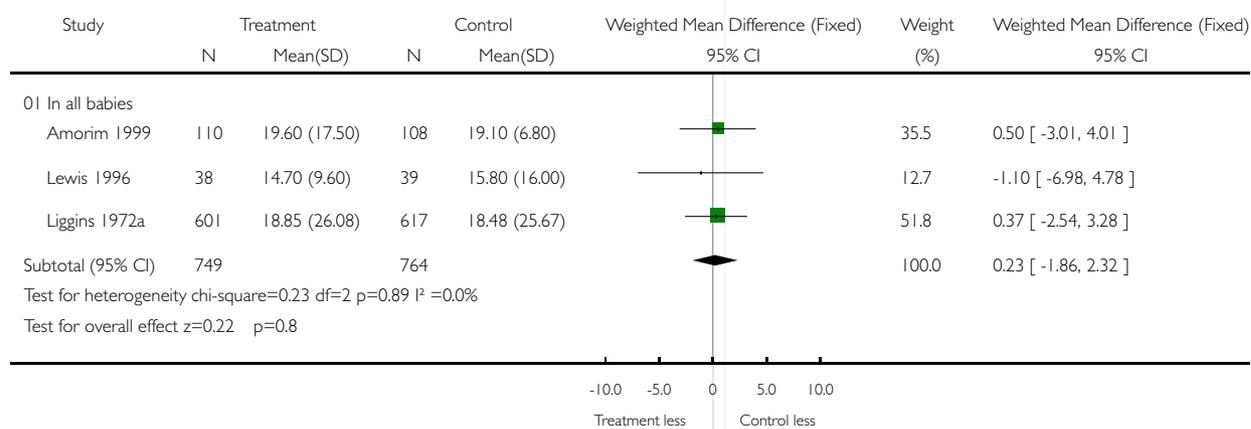


### Analysis 01.23. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 23 Mean interval between trial entry and birth (days)

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

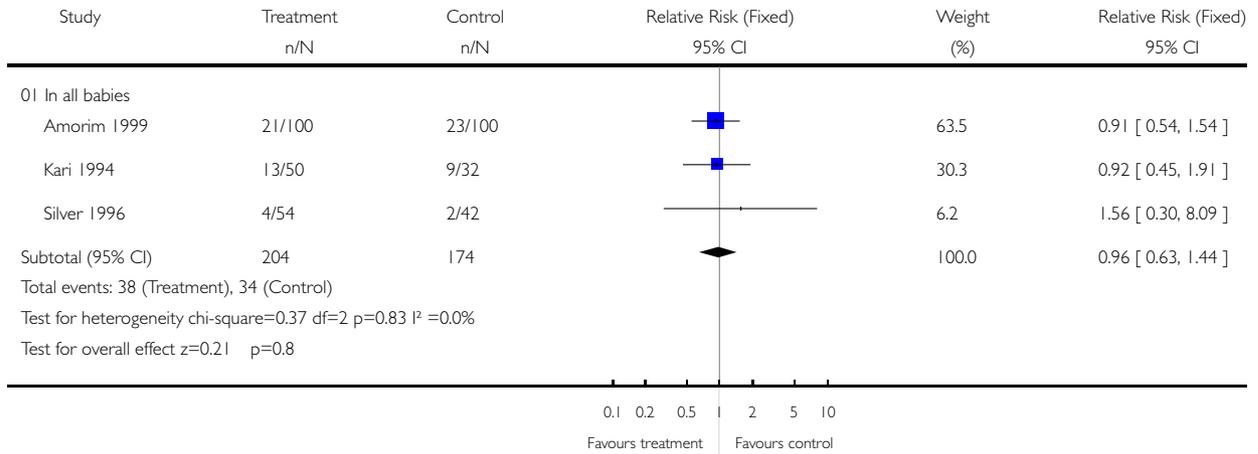
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 23 Mean interval between trial entry and birth (days)



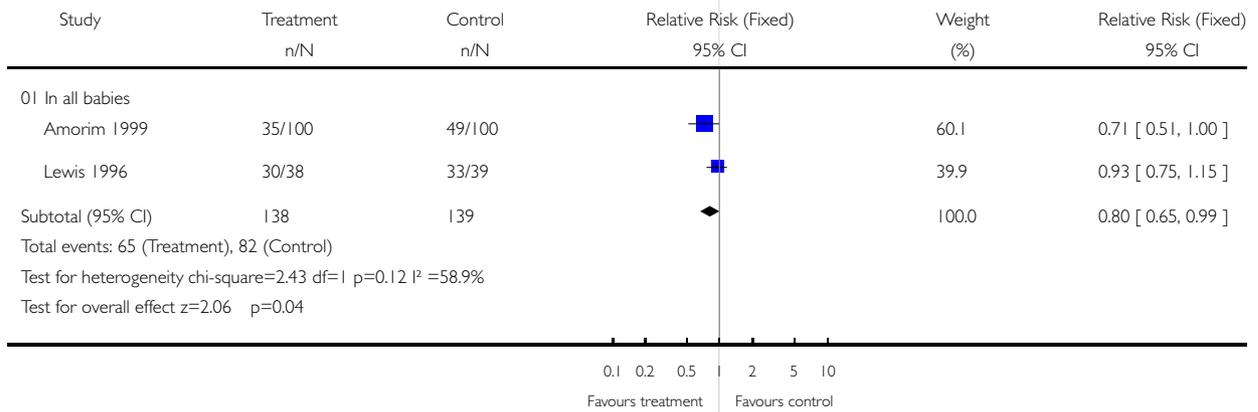
**Analysis 01.24. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 24 Small-for-gestational age**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 24 Small-for-gestational age



**Analysis 01.25. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 25 Admission to neonatal intensive care unit**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 25 Admission to neonatal intensive care unit

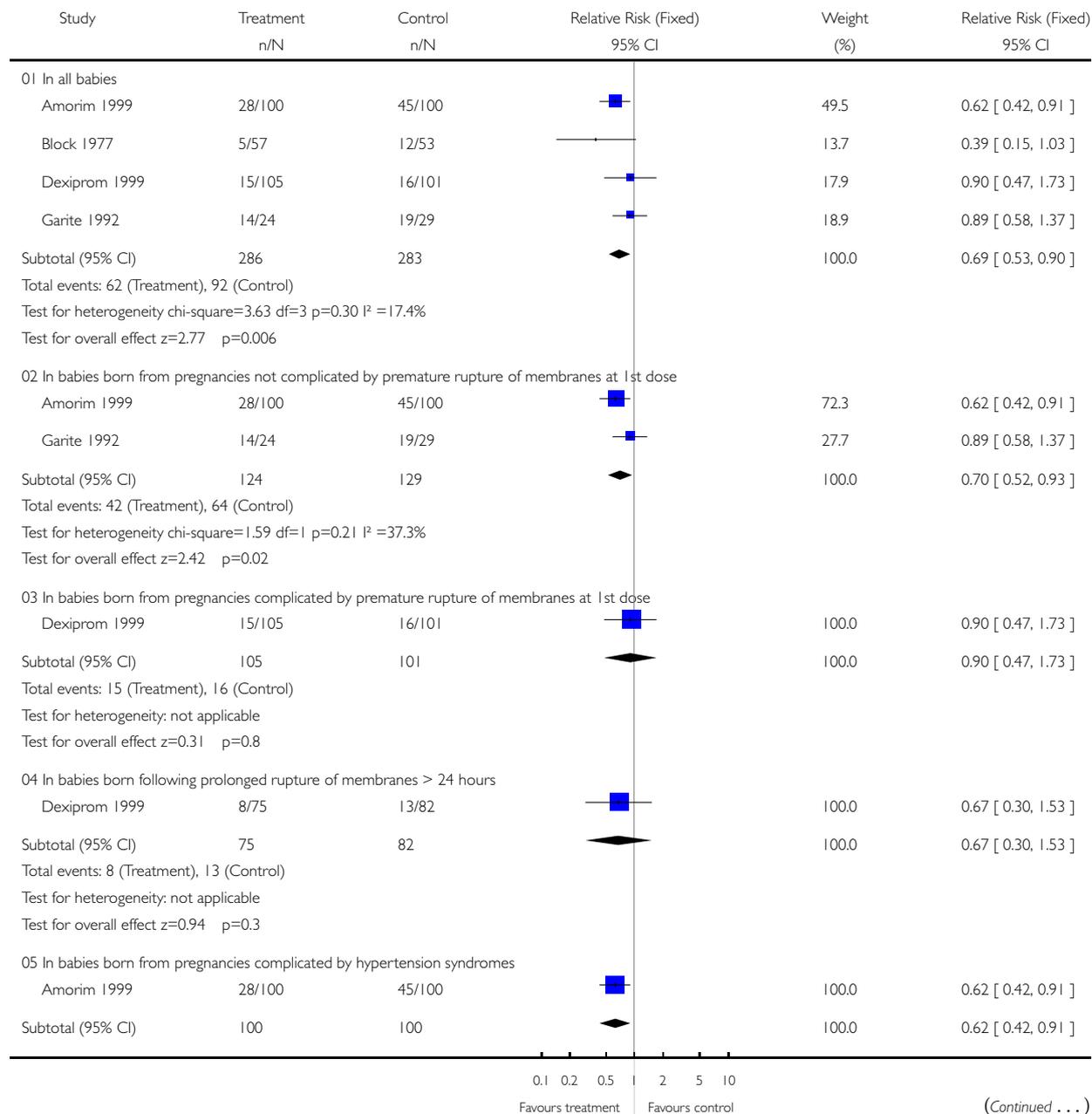


## Analysis 01.26. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 26 Need for mechanical ventilation/CPAP

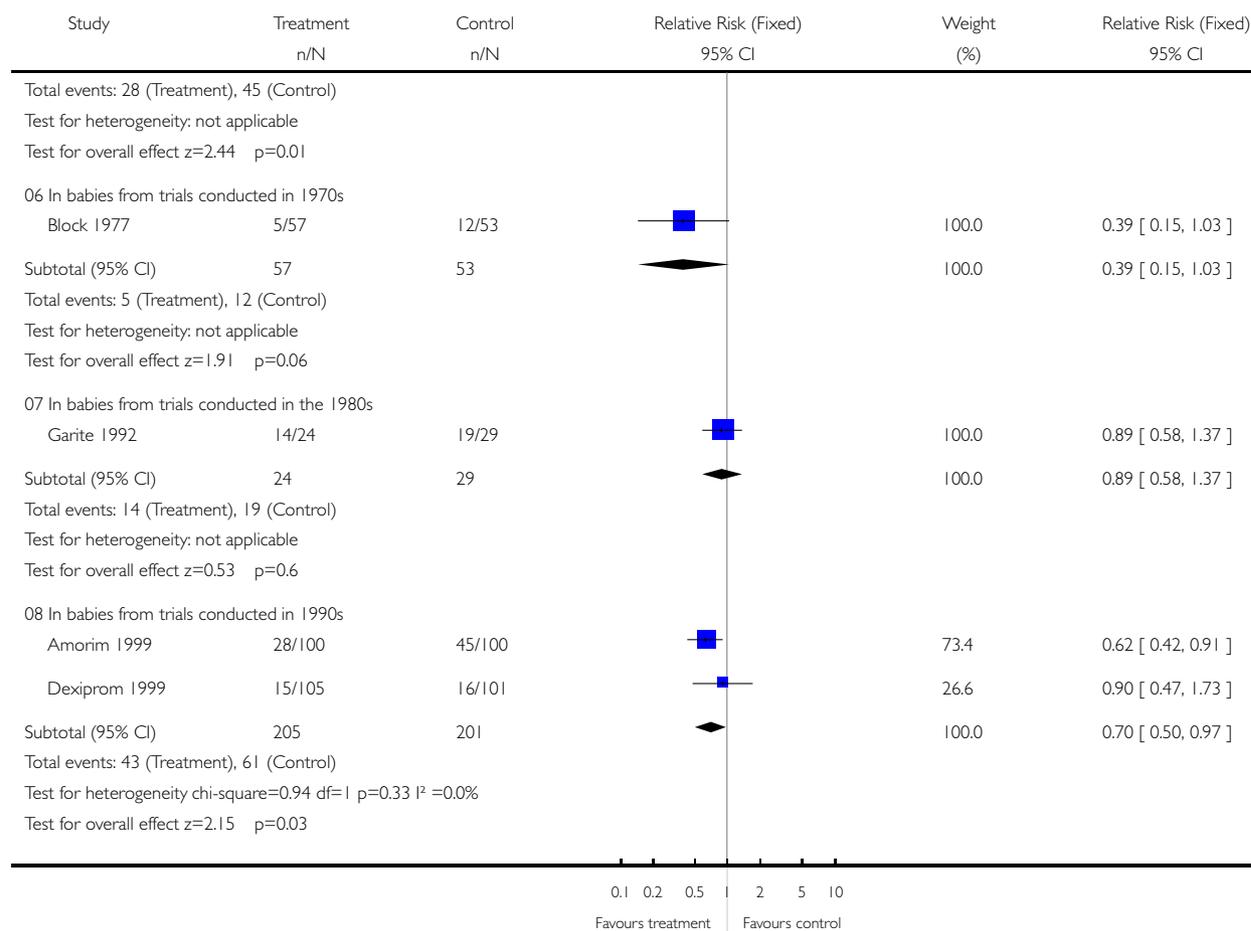
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 26 Need for mechanical ventilation/CPAP



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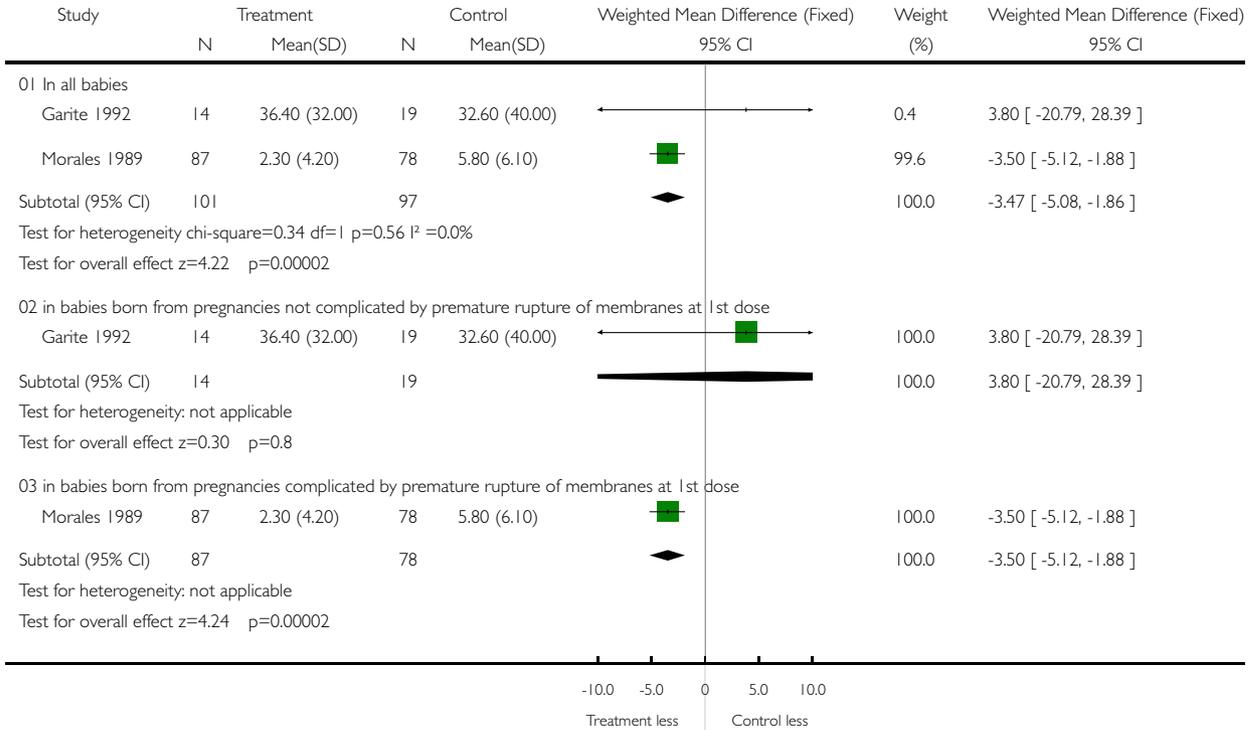


**Analysis 01.27. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 27 Mean duration of mechanical ventilation/CPAP (days)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 27 Mean duration of mechanical ventilation/CPAP (days)

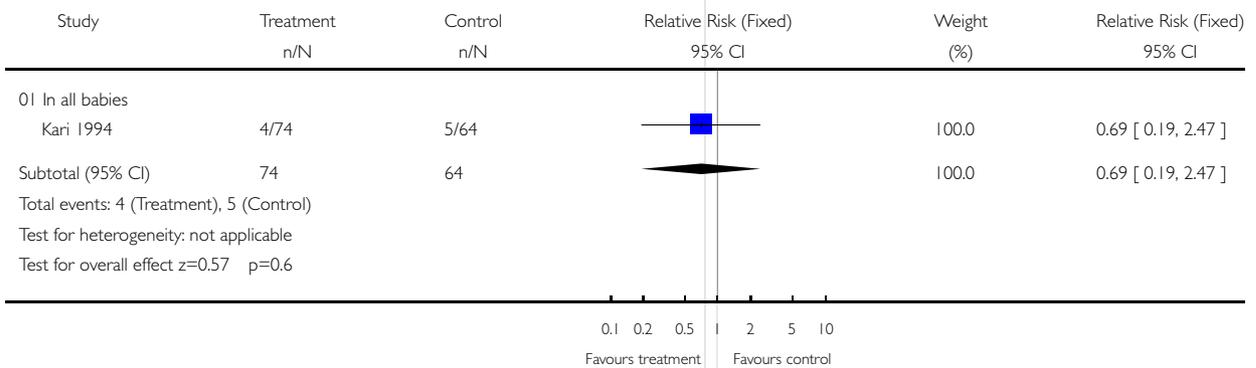


**Analysis 01.28. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 28 Air leak syndrome**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 28 Air leak syndrome

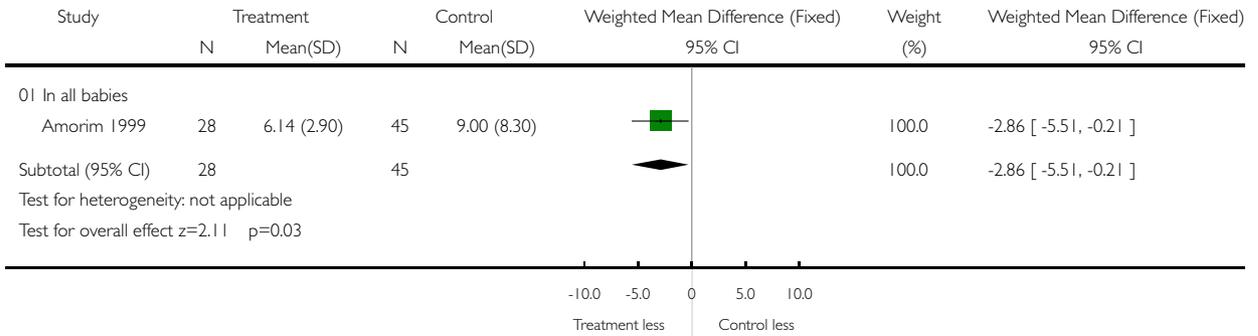


**Analysis 01.29. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 29 Mean duration of oxygen supplementation (days)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 29 Mean duration of oxygen supplementation (days)

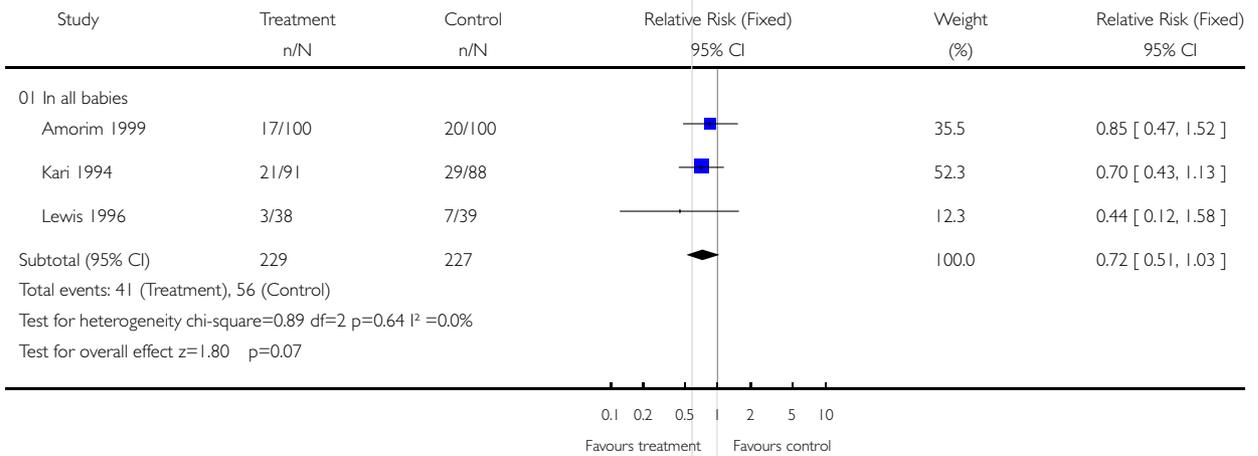


**Analysis 01.30. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 30 Surfactant use**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 30 Surfactant use

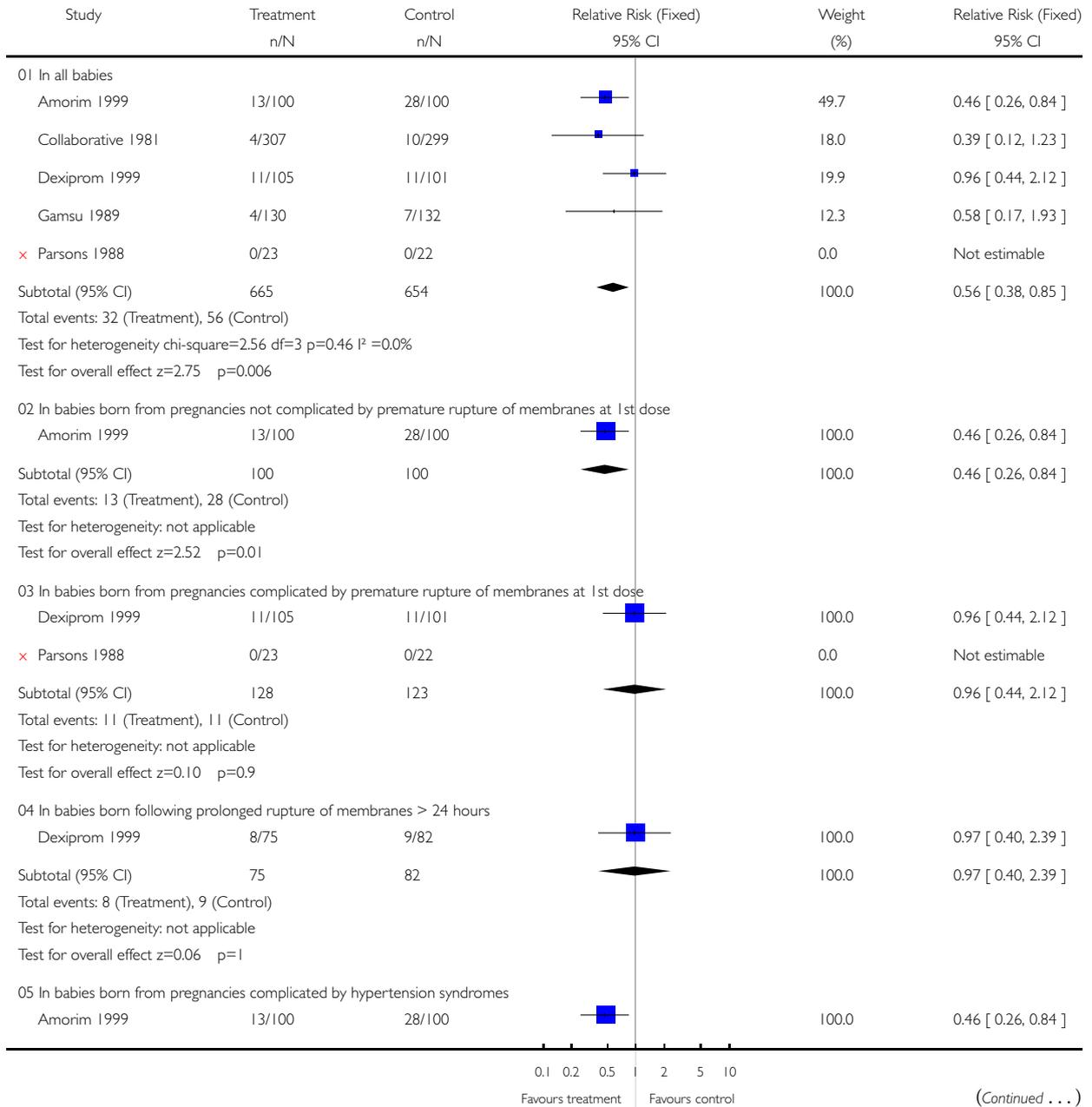


### Analysis 01.31. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 31 Systemic infection in the first 48 hours of life

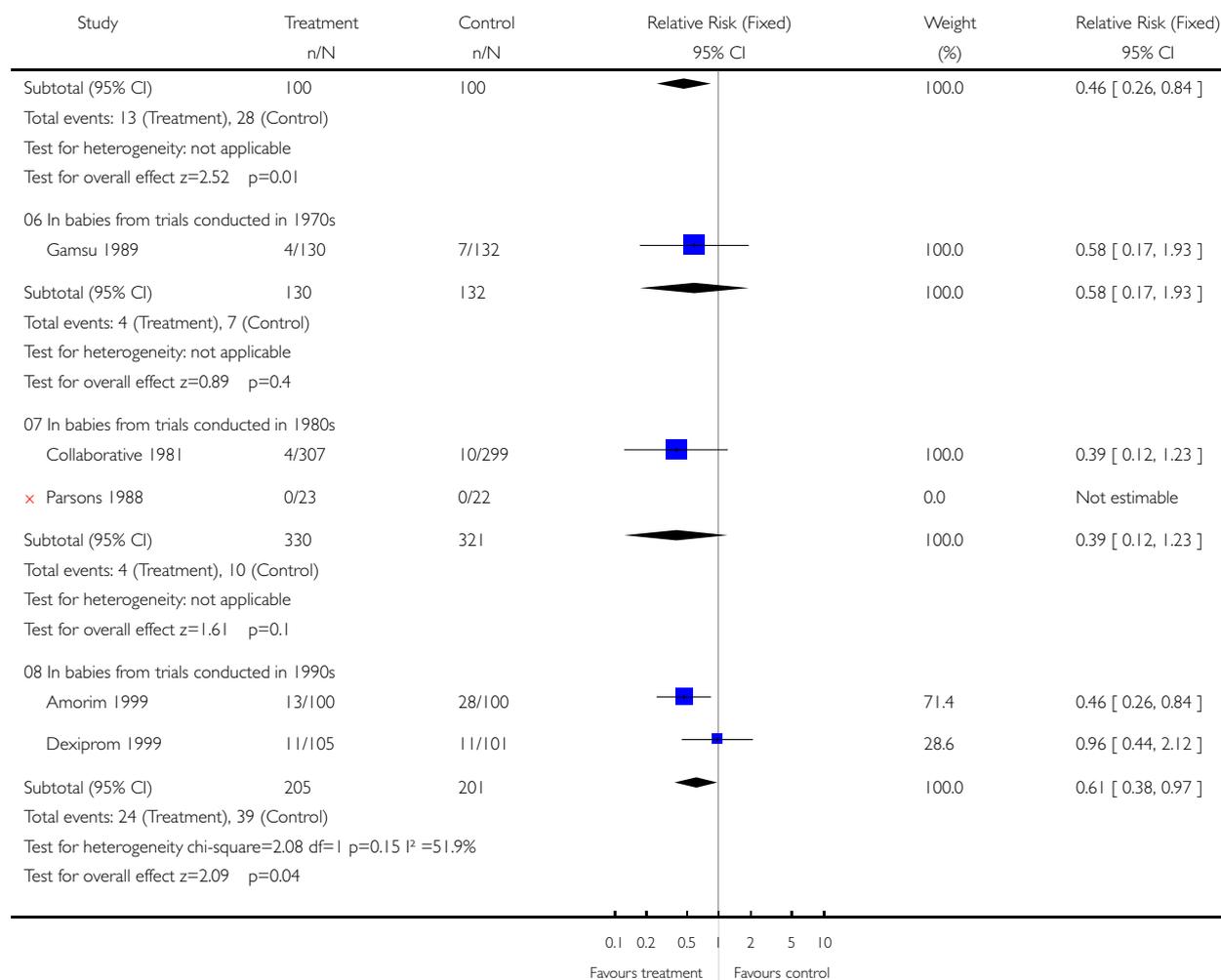
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 31 Systemic infection in the first 48 hours of life



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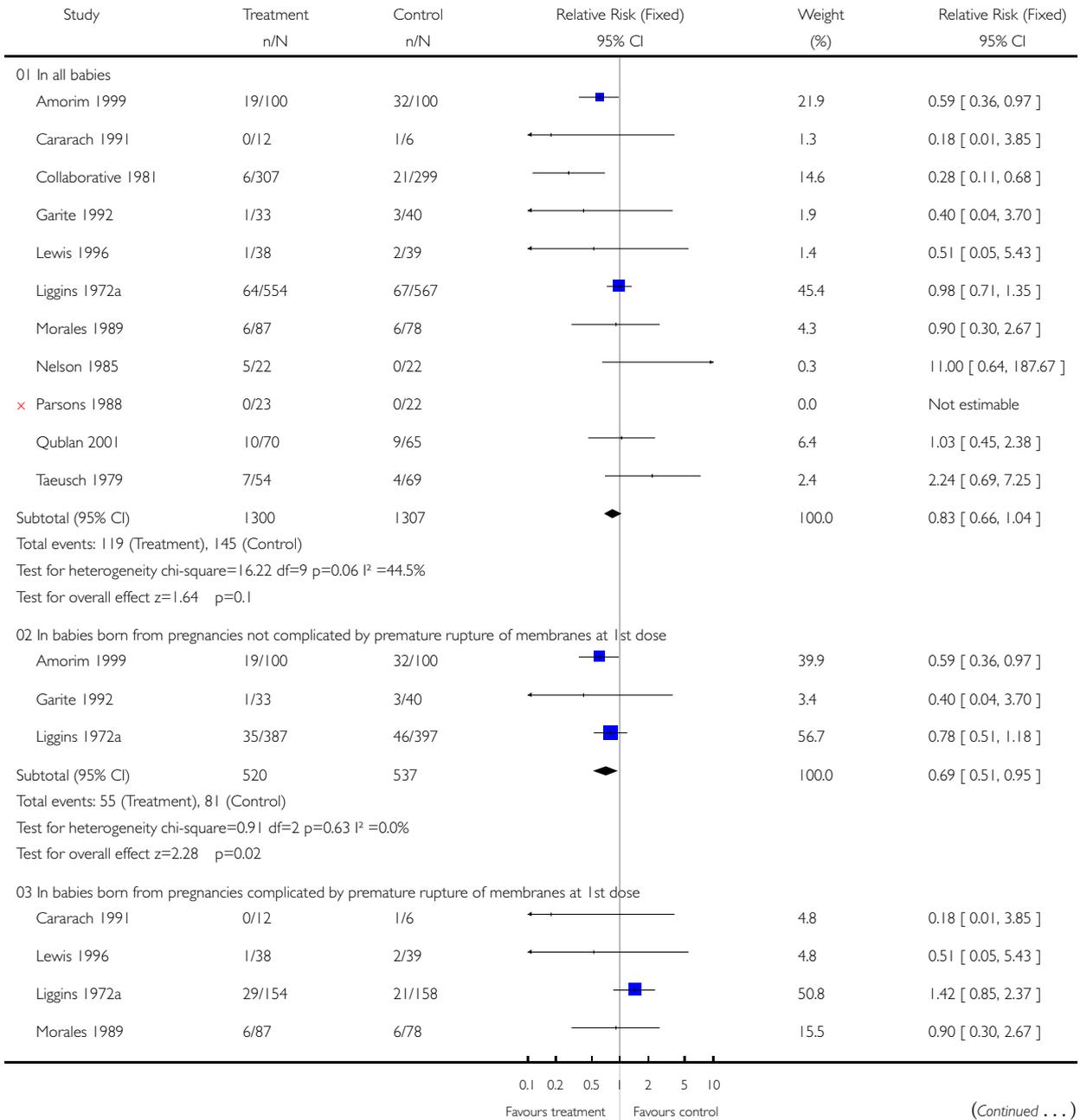


### Analysis 01.32. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 32 Proven infection while in the neonatal intensive care unit

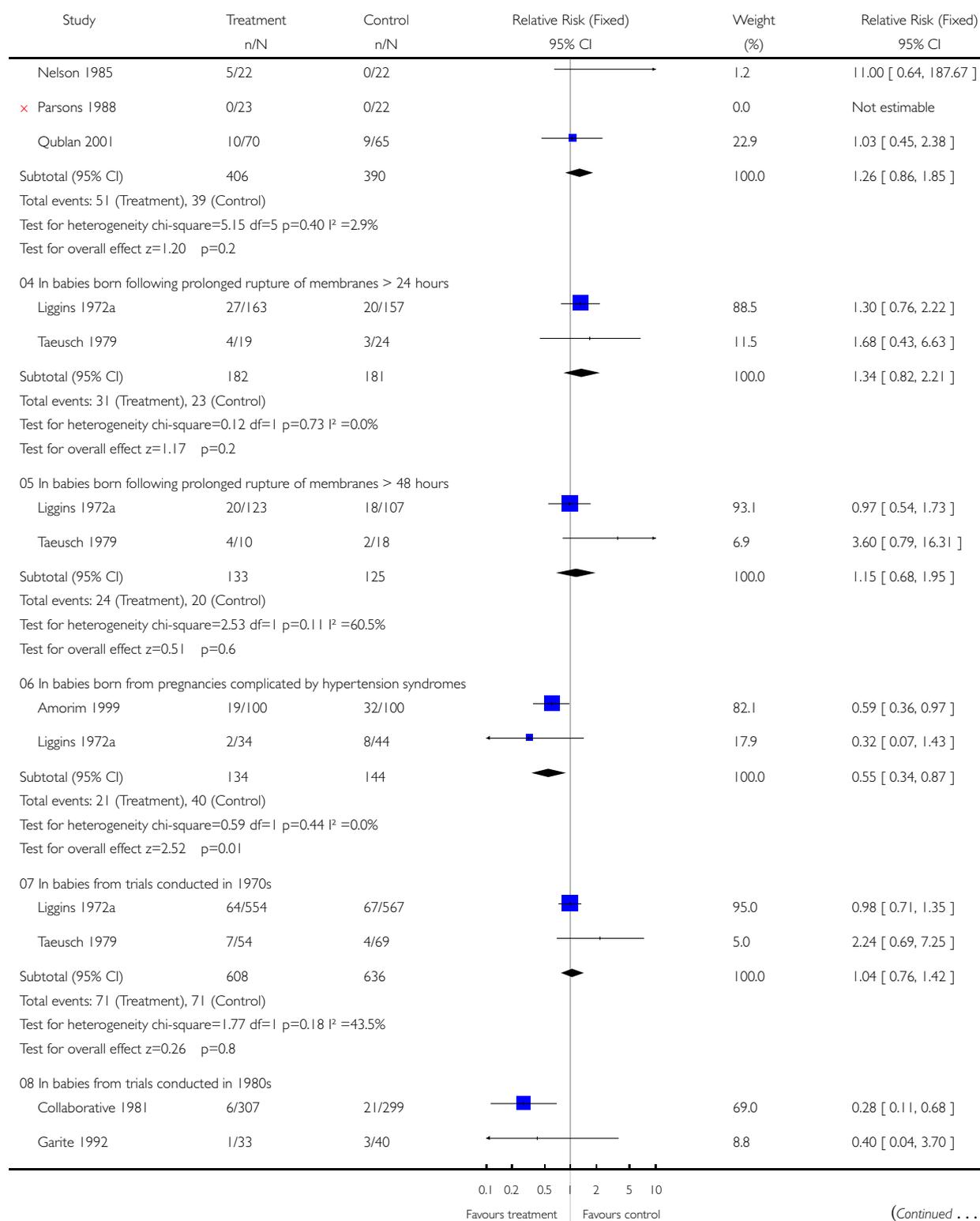
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 32 Proven infection while in the neonatal intensive care unit

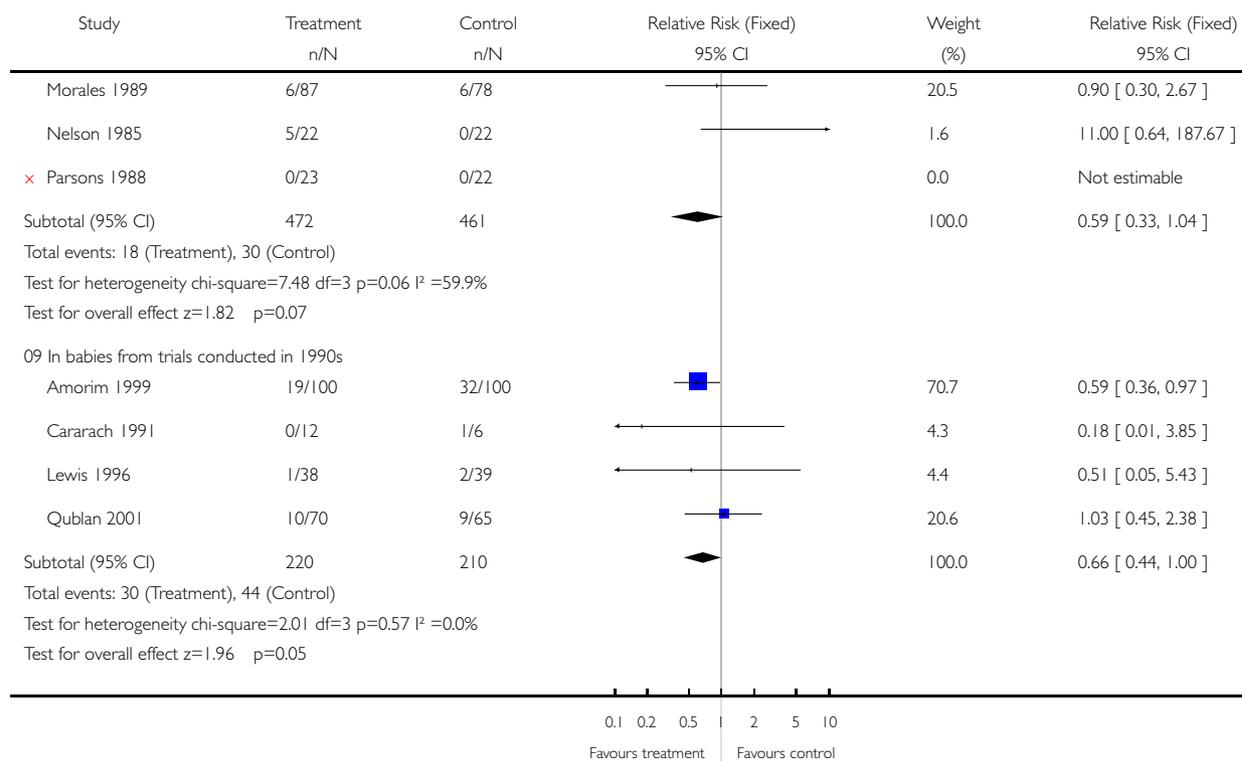


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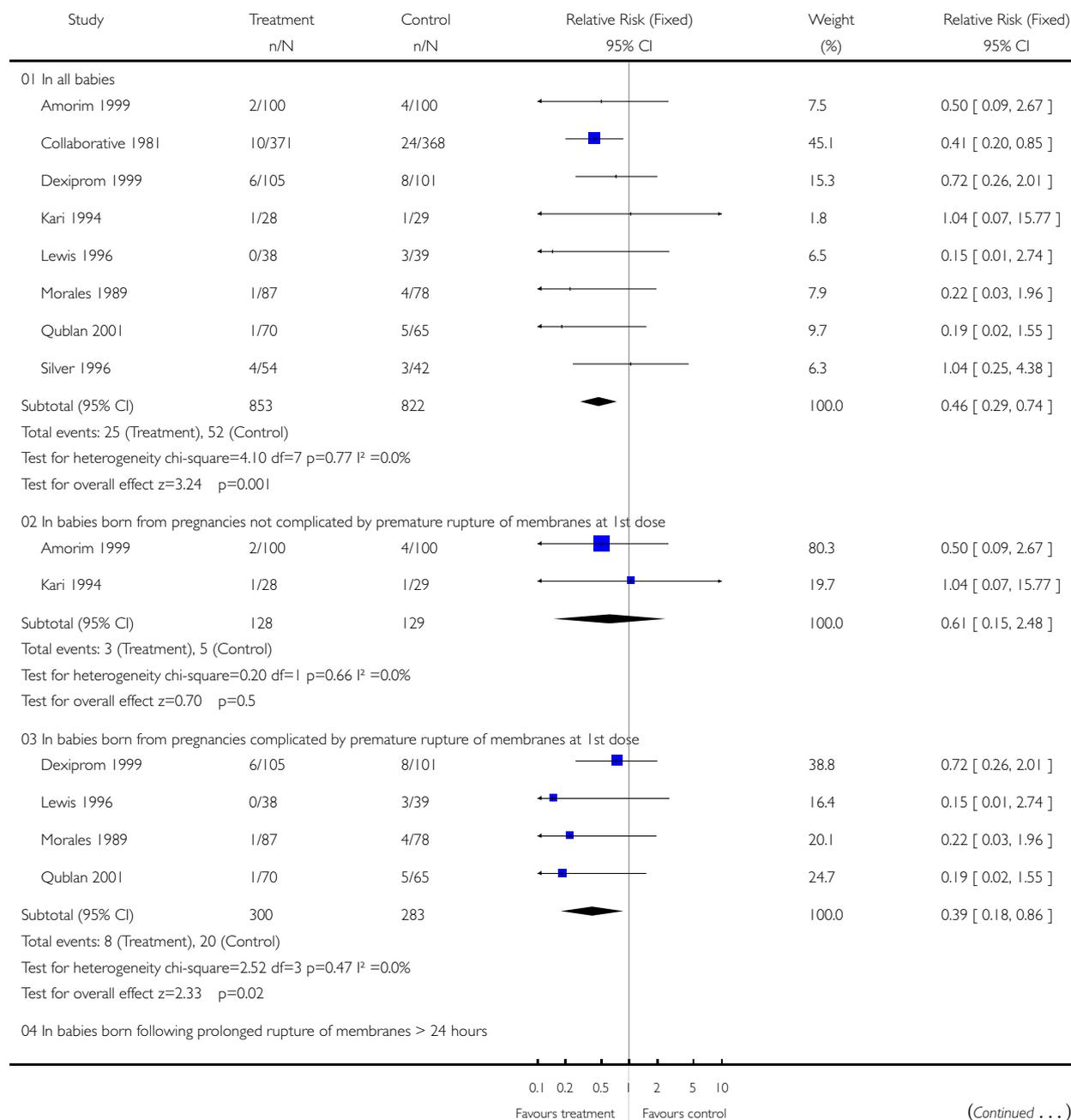


### Analysis 01.33. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 33 Necrotising enterocolitis

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

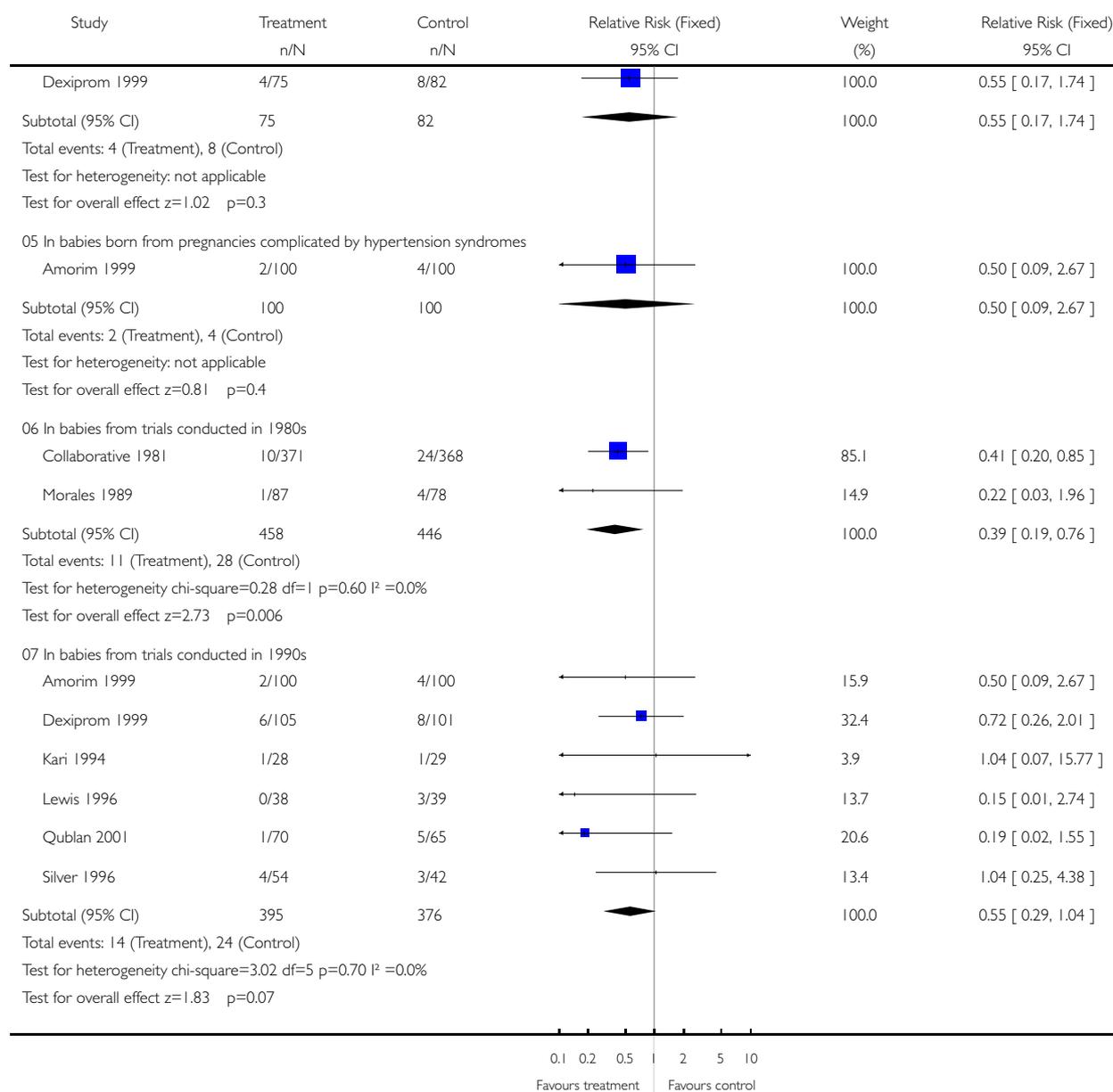
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 33 Necrotising enterocolitis



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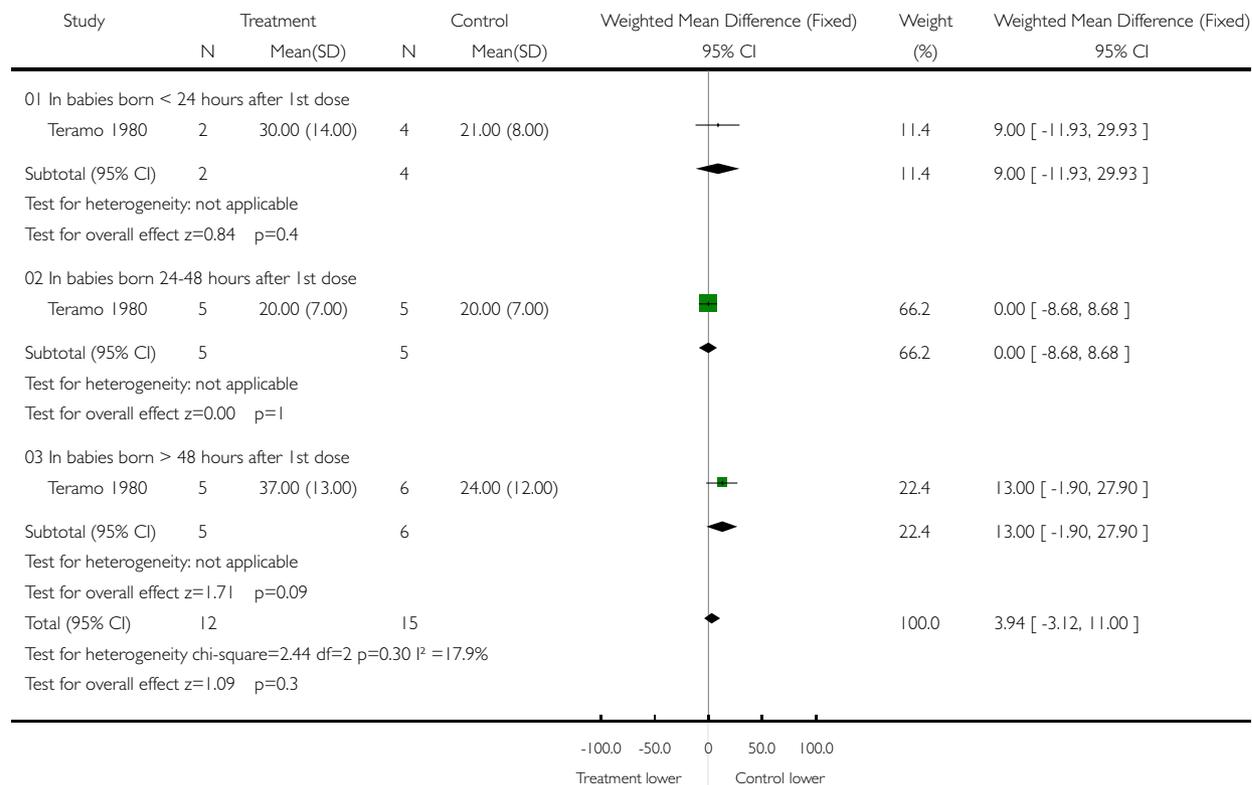


**Analysis 01.34. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 34 Mean infant HPA axis function (cortisol)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 34 Mean infant HPA axis function (cortisol)

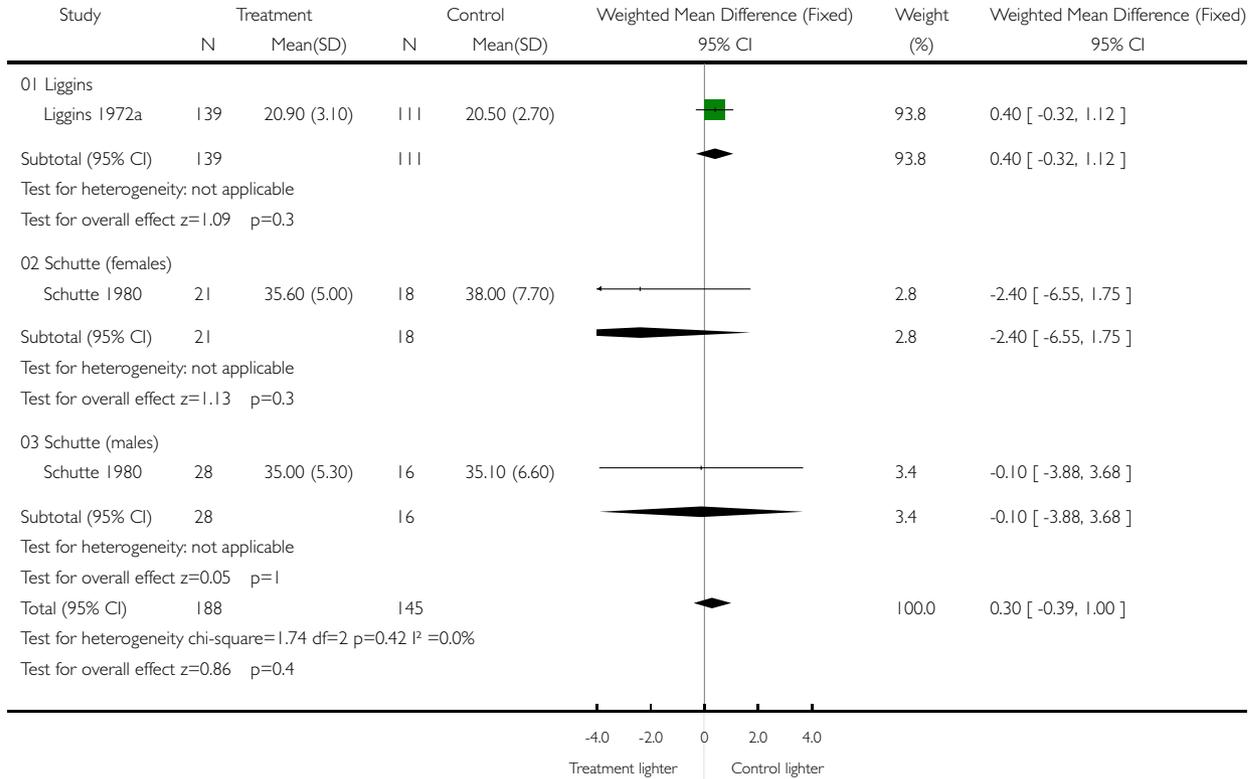


### Analysis 01.35. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 35 Mean childhood weight (kg)

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 35 Mean childhood weight (kg)

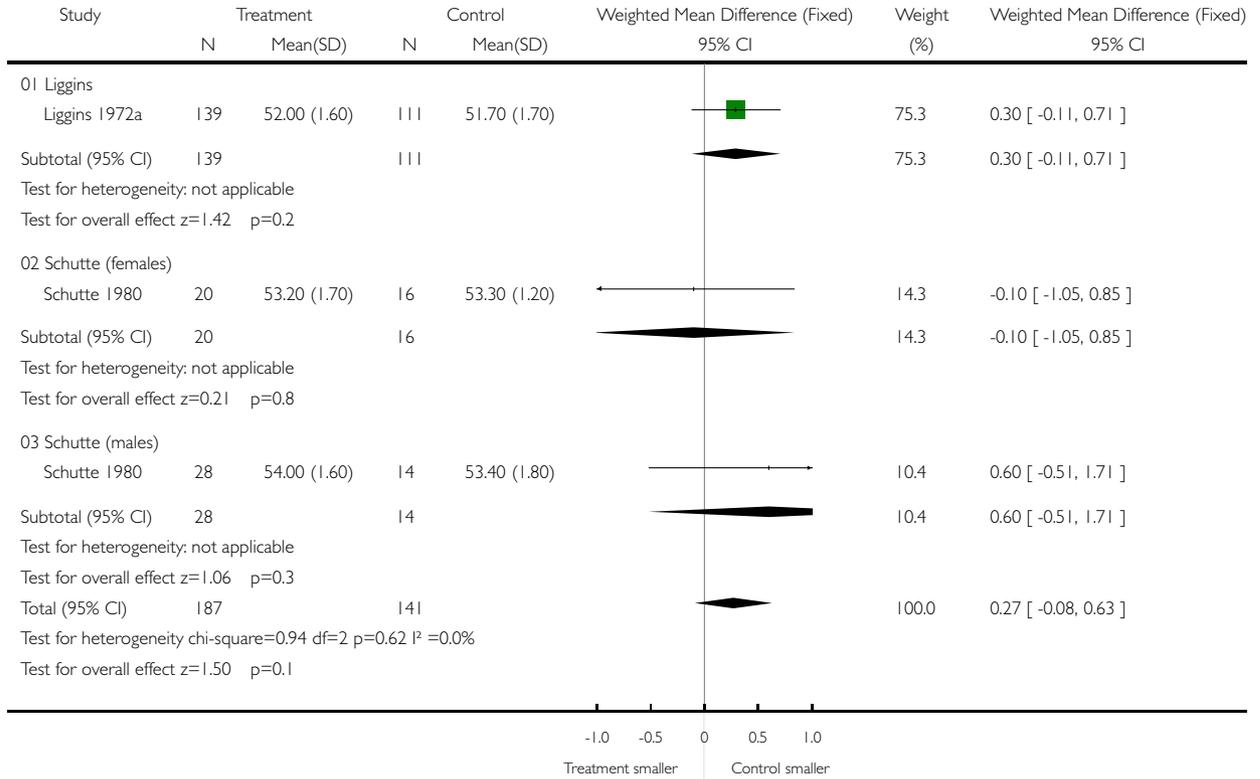


**Analysis 01.36. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 36 Mean childhood head circumference (cm)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 36 Mean childhood head circumference (cm)

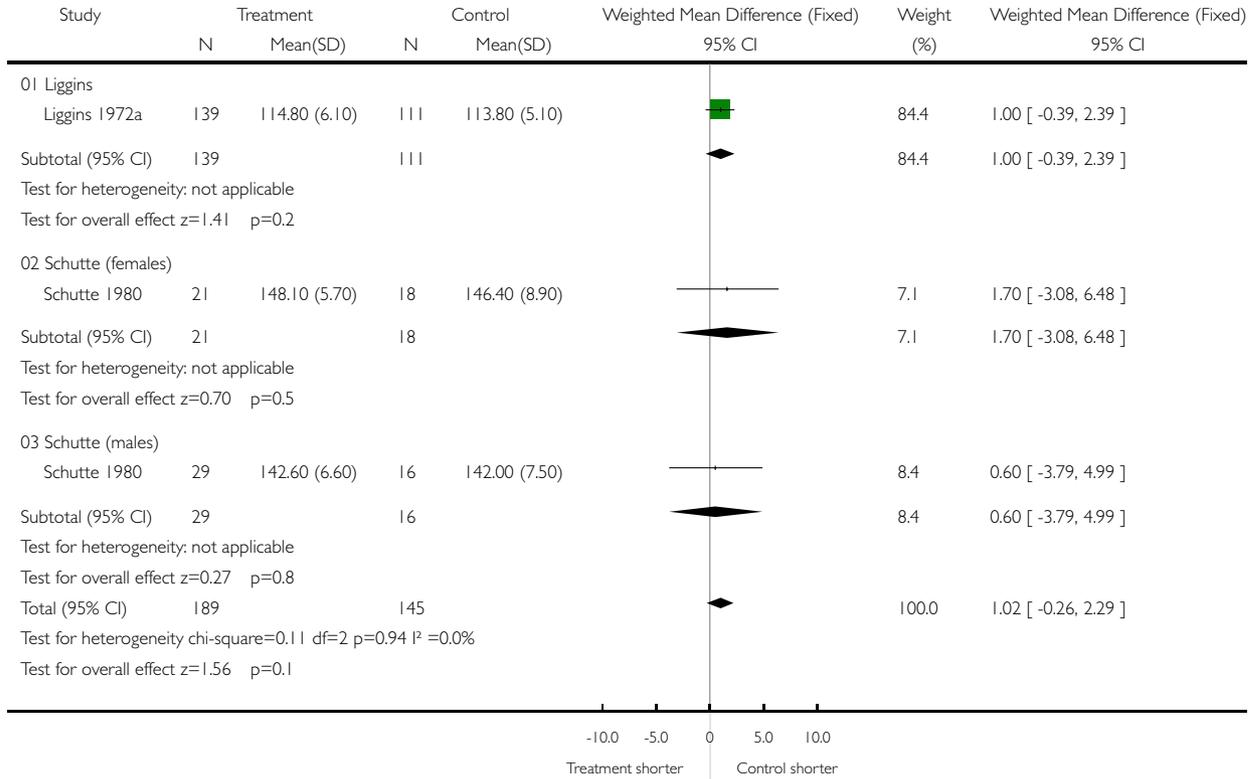


**Analysis 01.37. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 37 Mean childhood height (cm)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 37 Mean childhood height (cm)

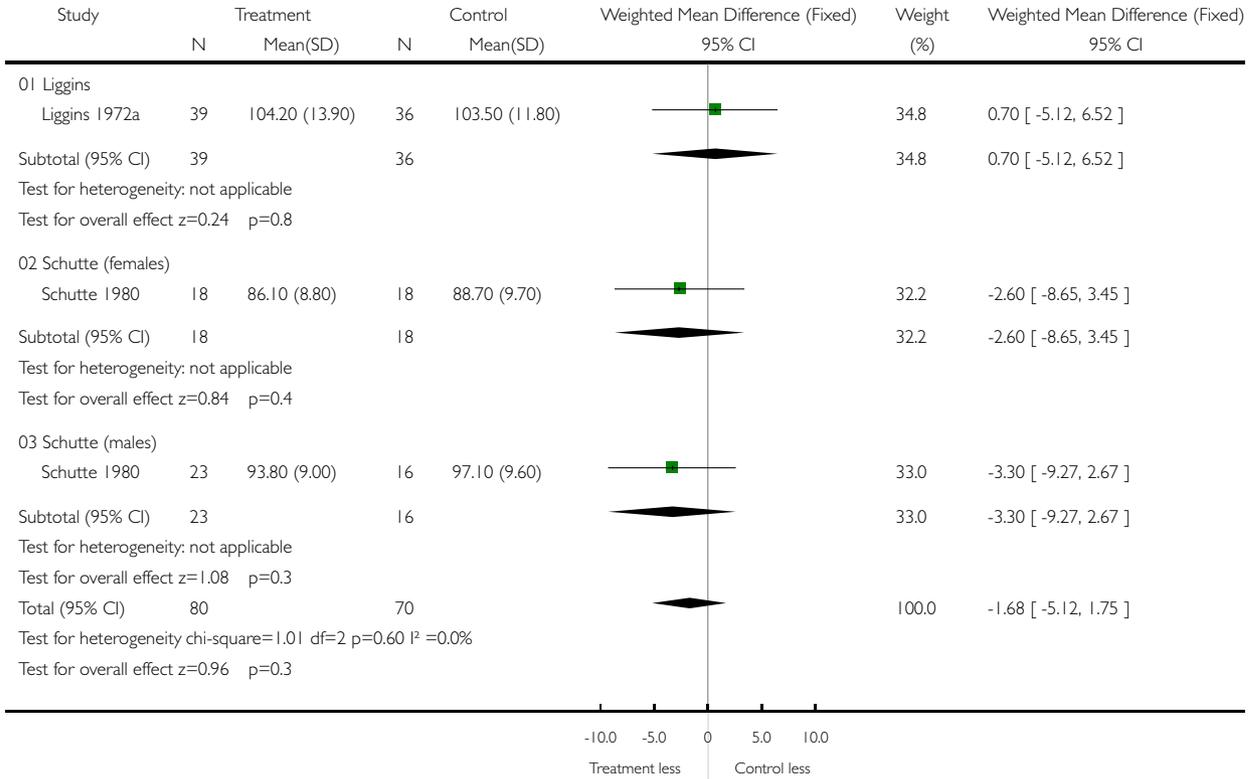


**Analysis 01.38. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 38 Mean childhood VC (% predicted)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 38 Mean childhood VC (% predicted)

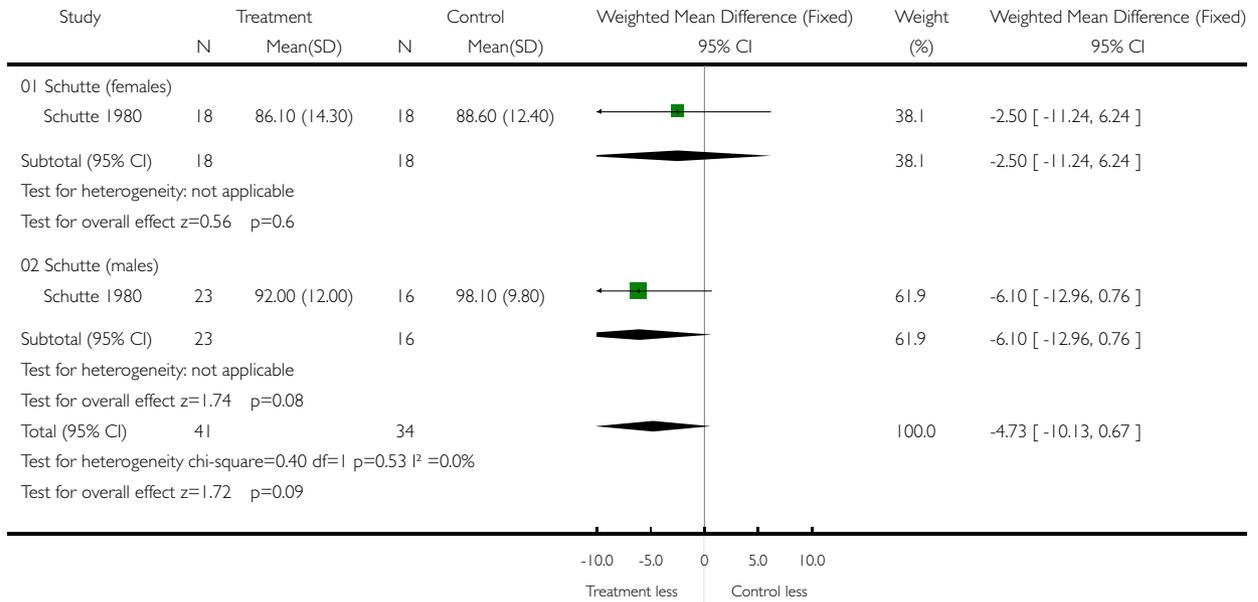


**Analysis 01.39. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 39 Mean childhood FEV1 (% predicted)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 39 Mean childhood FEV1 (% predicted)

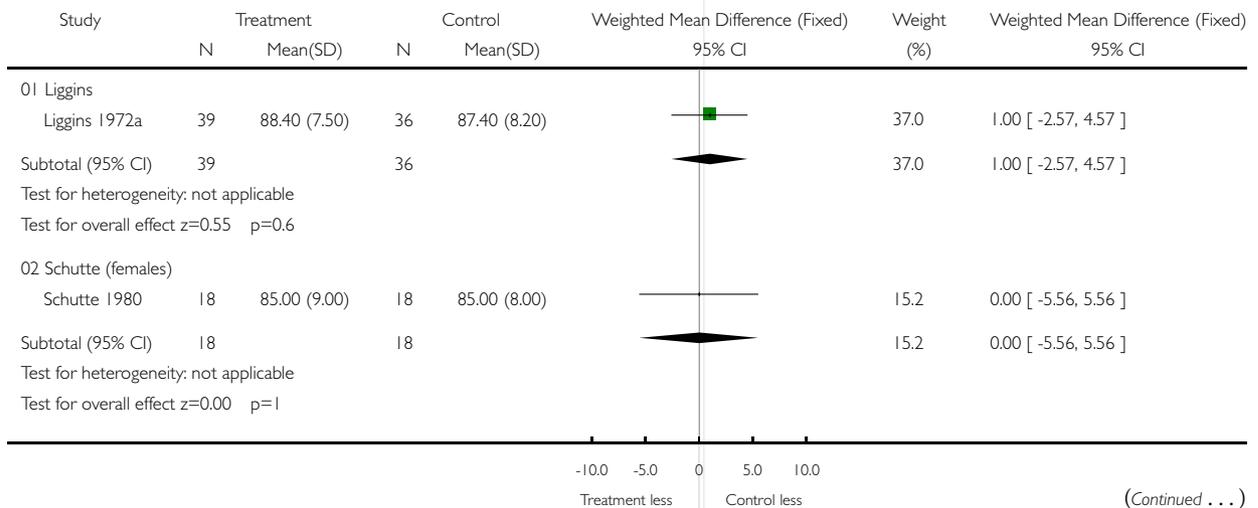


**Analysis 01.40. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 40 Mean childhood FEV1/VC**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

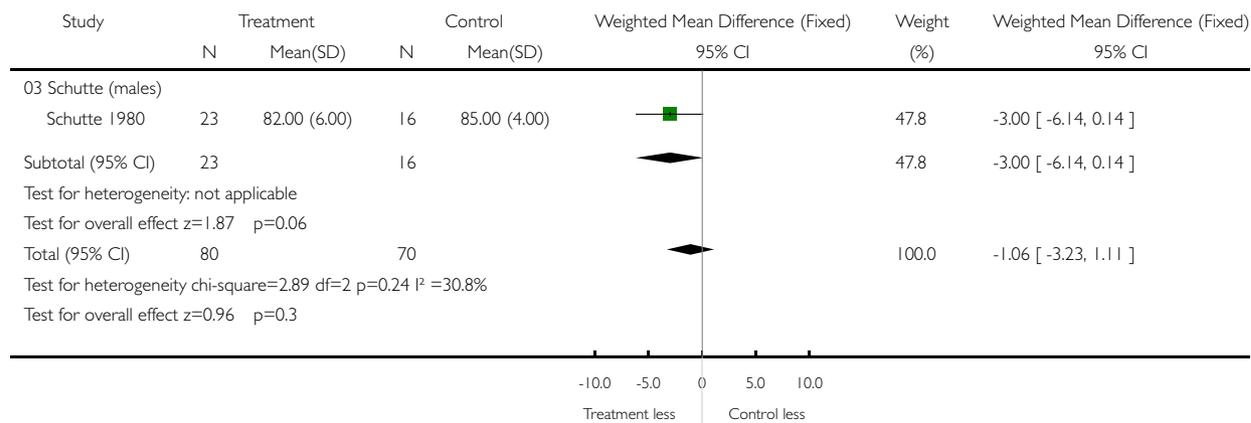
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 40 Mean childhood FEV1/VC



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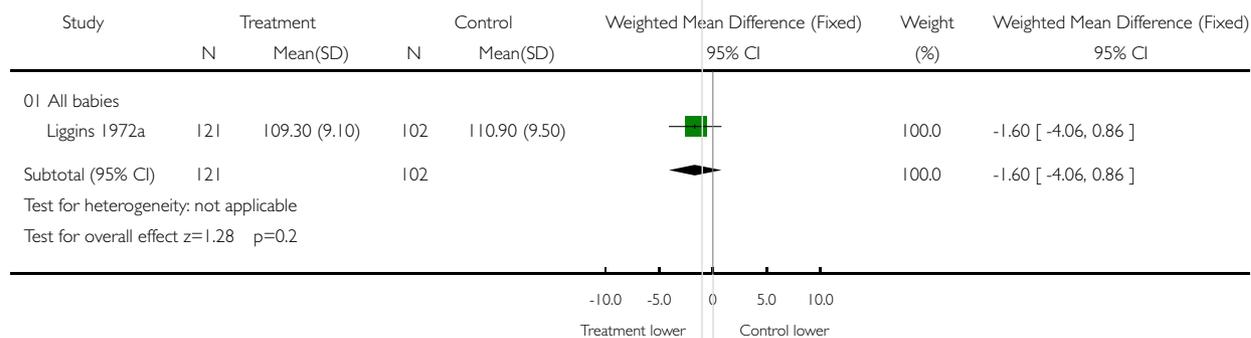


**Analysis 01.41. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 41 Mean childhood systolic blood pressure (mmHg)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

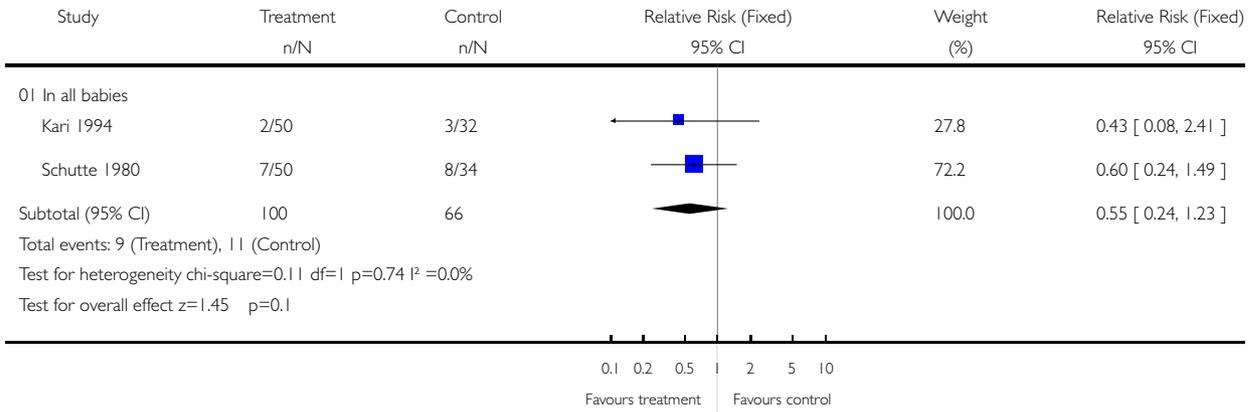
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 41 Mean childhood systolic blood pressure (mmHg)



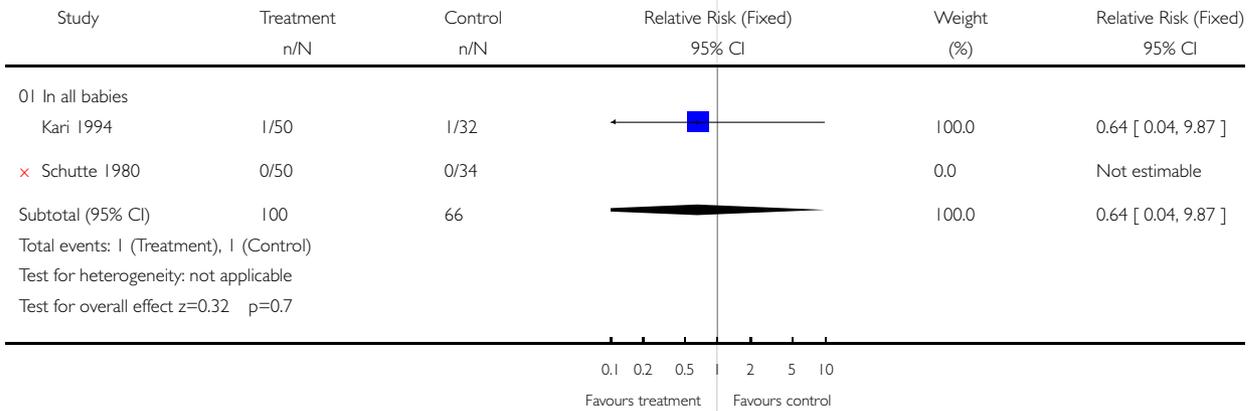
**Analysis 01.42. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 42 Visual impairment in childhood**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 42 Visual impairment in childhood



**Analysis 01.43. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 43 Hearing impairment in childhood**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 43 Hearing impairment in childhood

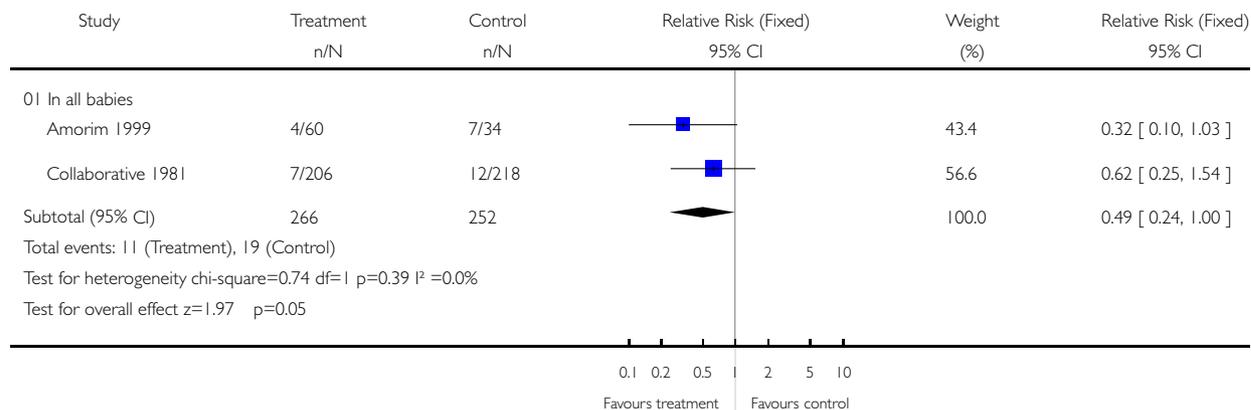


### Analysis 01.44. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 44 Developmental delay in childhood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 44 Developmental delay in childhood

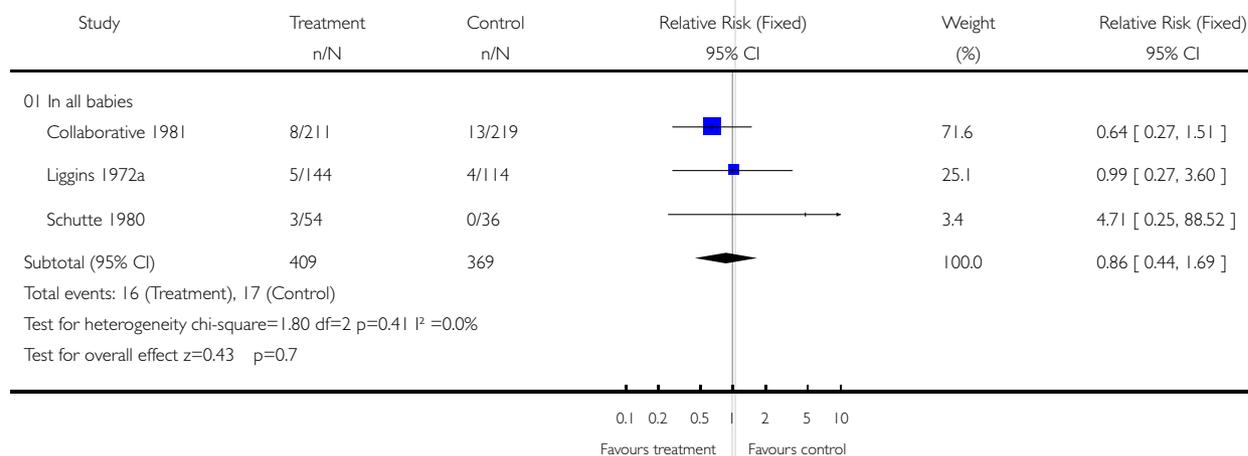


### Analysis 01.45. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 45 Intellectual impairment in childhood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 45 Intellectual impairment in childhood

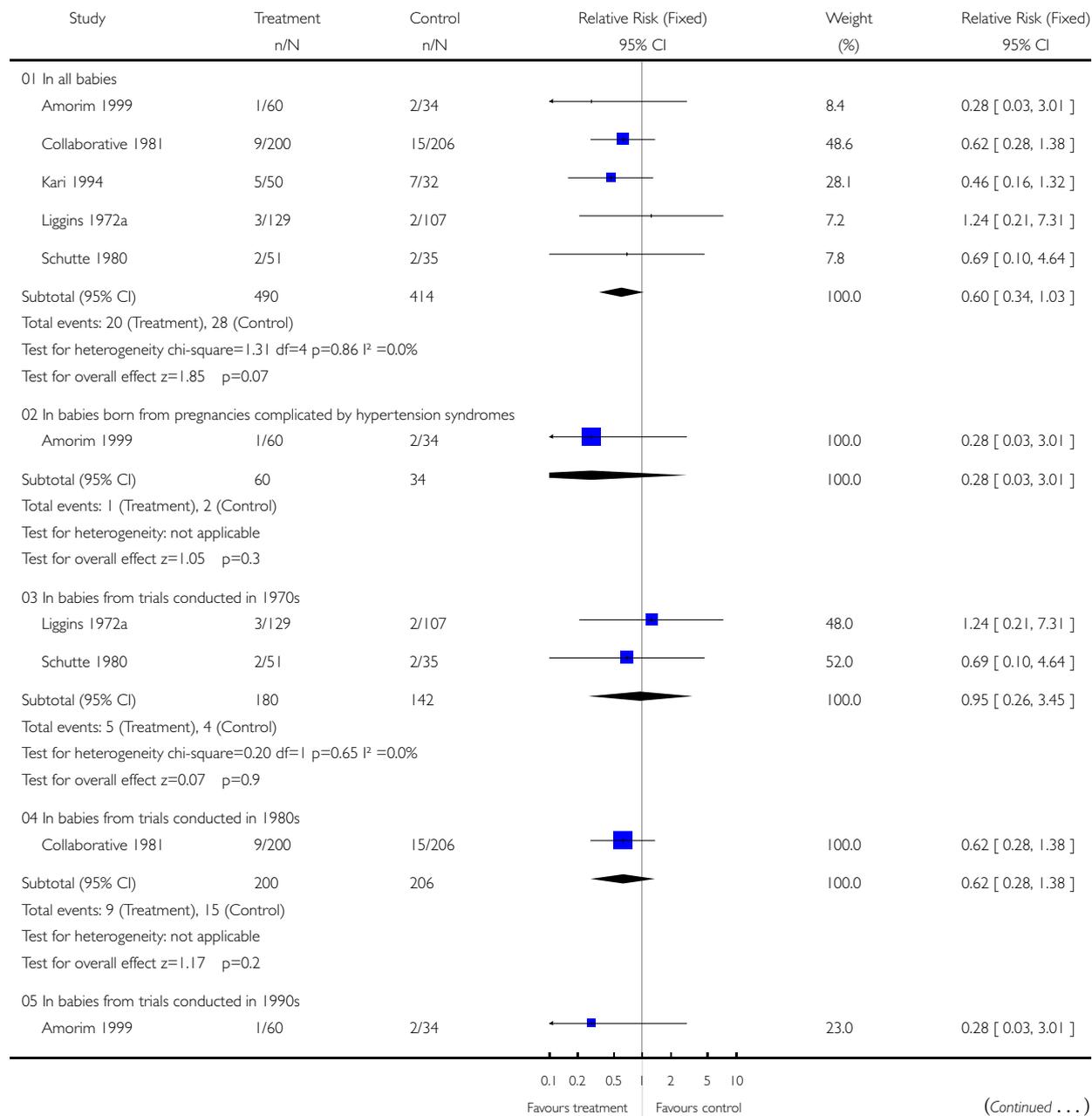


### Analysis 01.46. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 46 Cerebral palsy in childhood

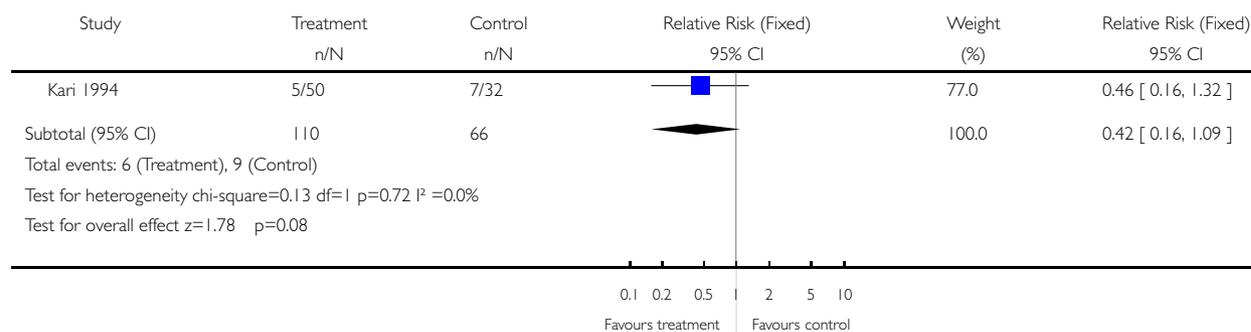
Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 46 Cerebral palsy in childhood



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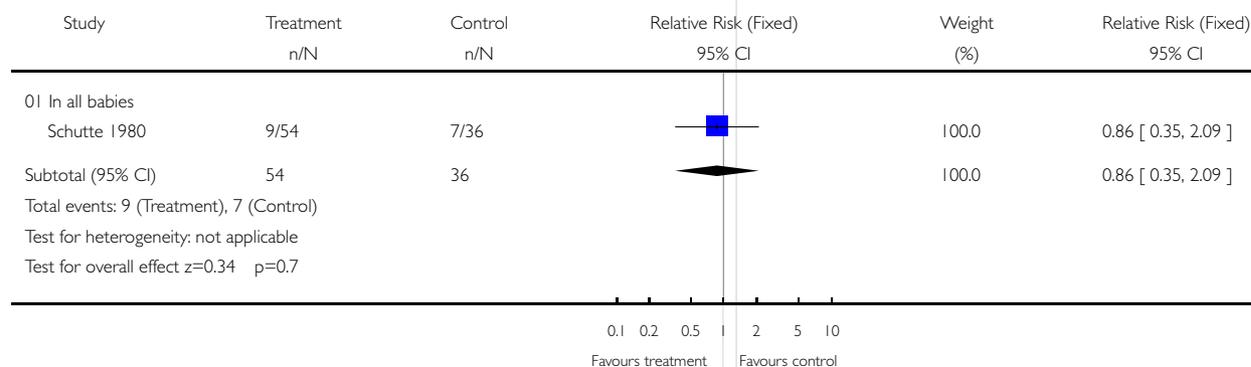


### Analysis 01.47. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 47 Behavioural/learning difficulties in childhood

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 47 Behavioural/learning difficulties in childhood

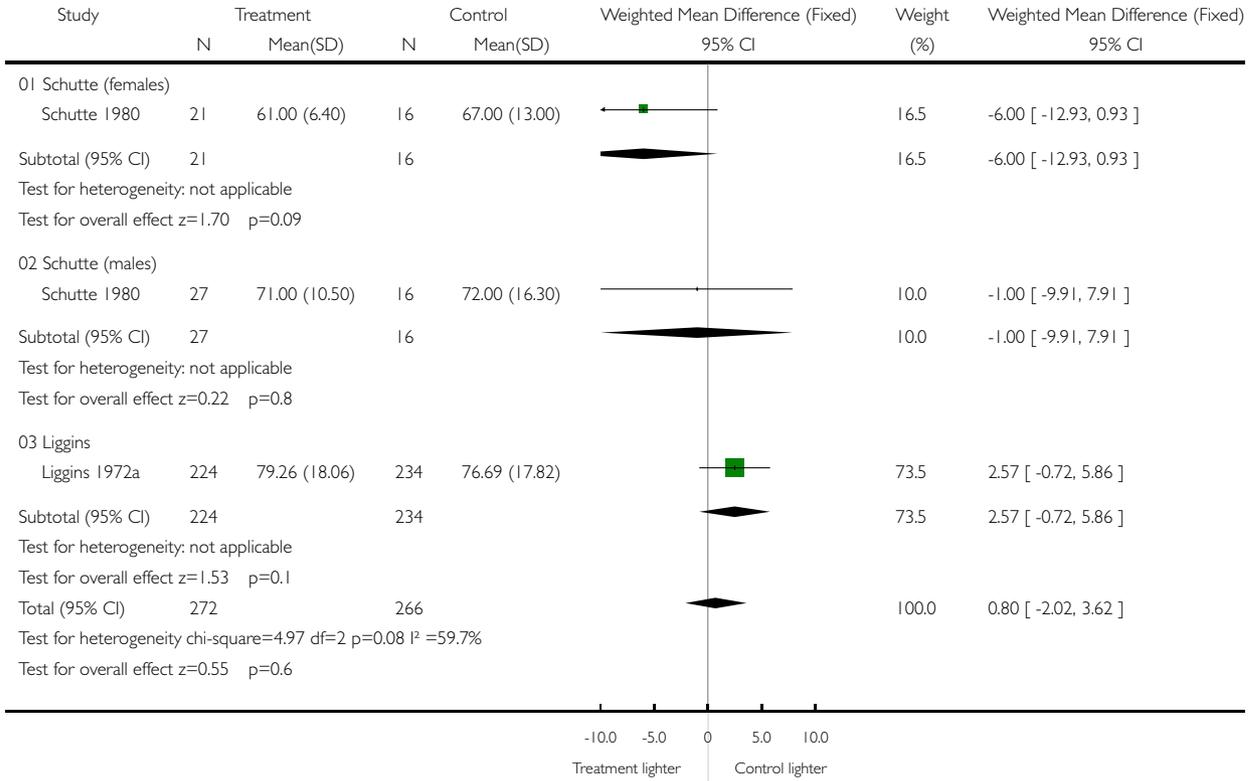


**Analysis 01.48. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 48 Mean adult weight (kg)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 48 Mean adult weight (kg)

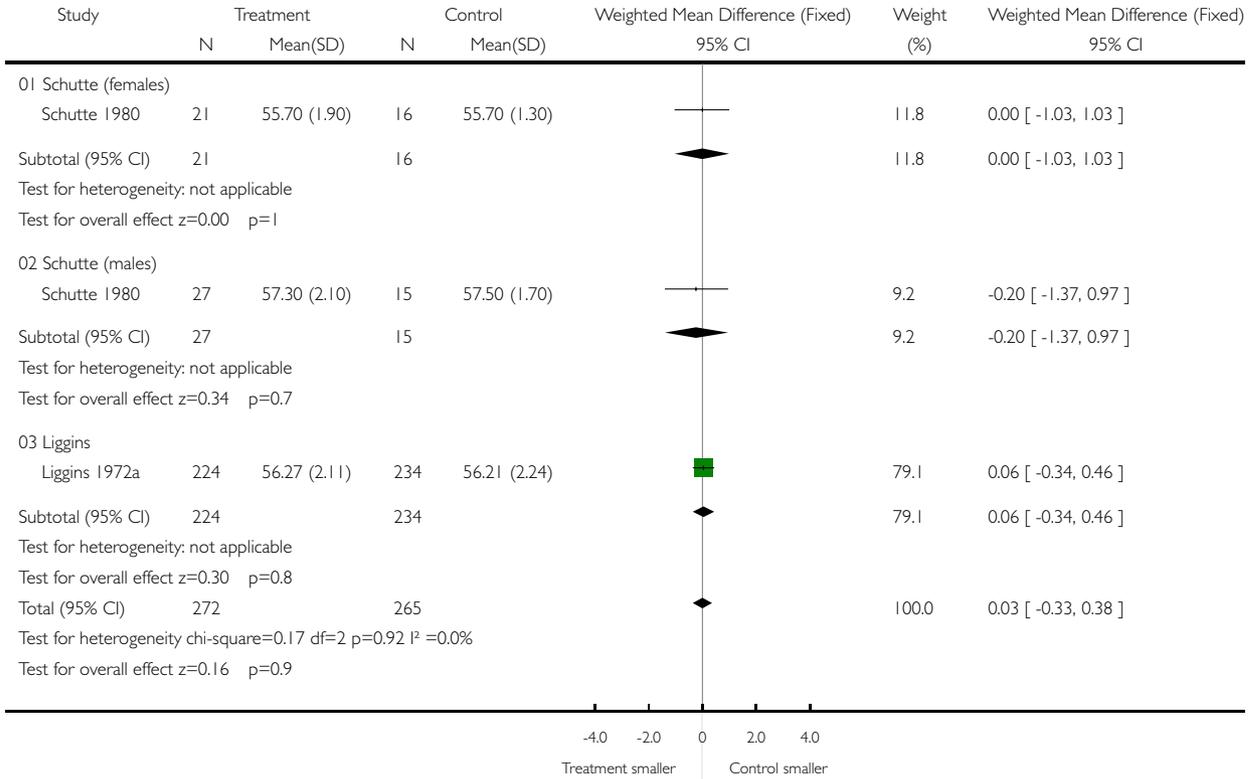


**Analysis 01.49. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 49 Mean adult head circumference (cm)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 49 Mean adult head circumference (cm)

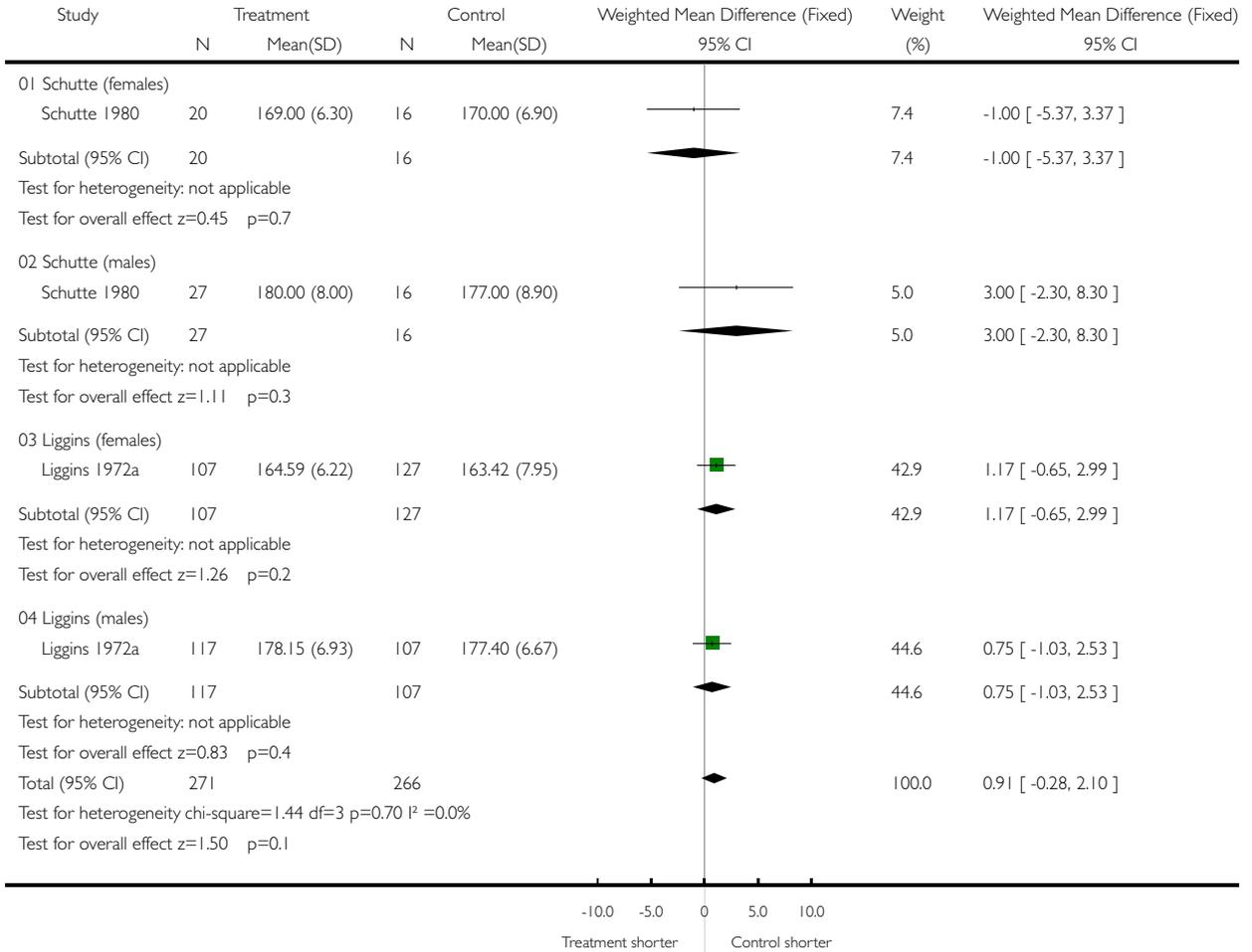


**Analysis 01.50. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 50 Mean adult height (cm)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 50 Mean adult height (cm)

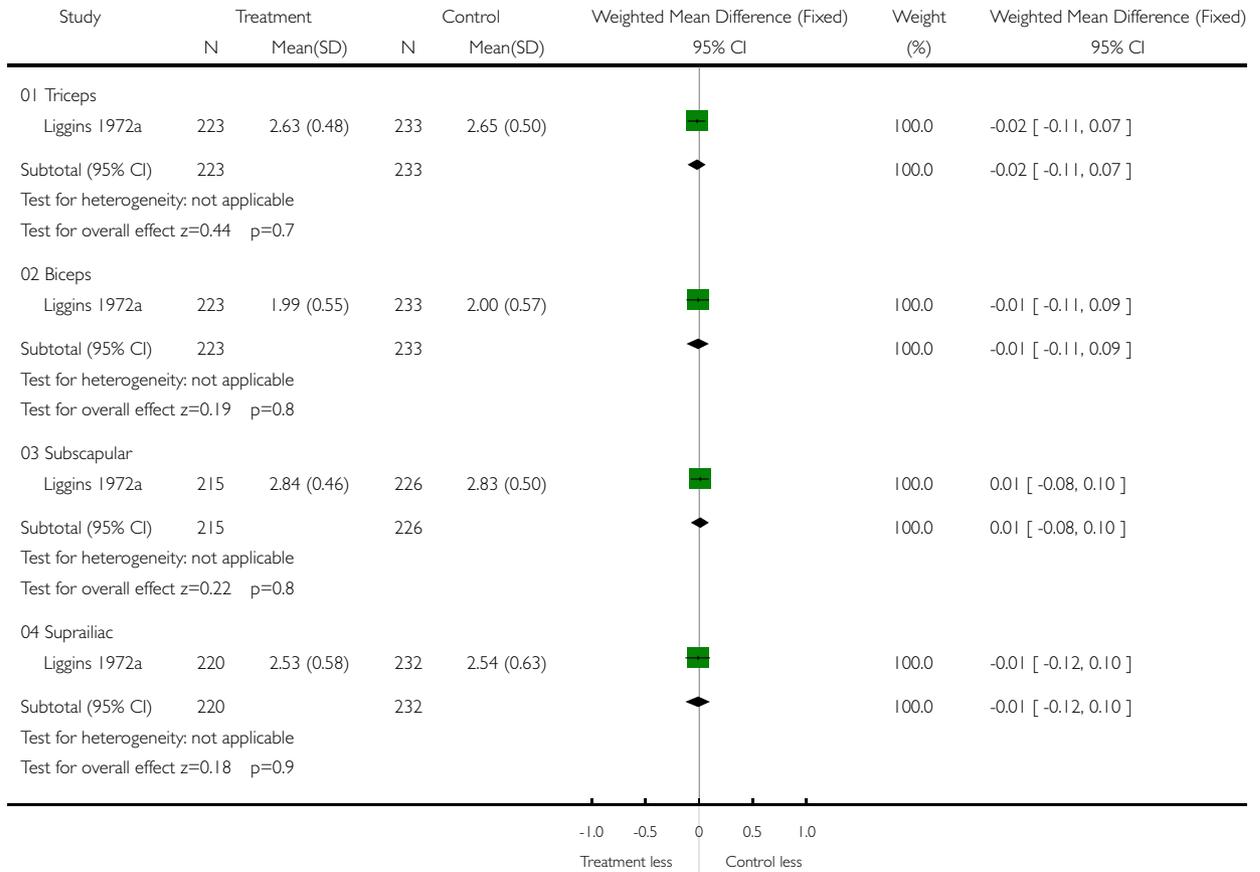


**Analysis 01.51. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 51 Mean adult skinfold thickness (log values)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 51 Mean adult skinfold thickness (log values)

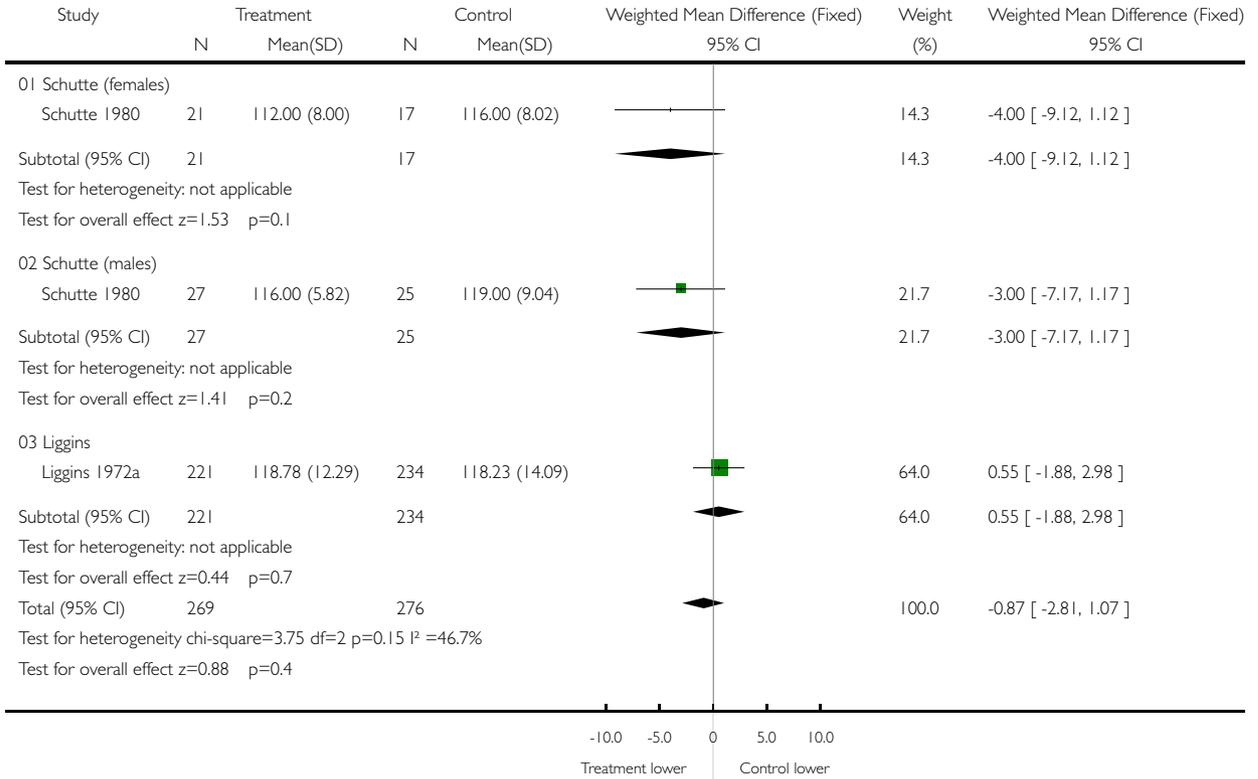


**Analysis 01.52. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 52 Mean adult systolic blood pressure (mmHg)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 52 Mean adult systolic blood pressure (mmHg)

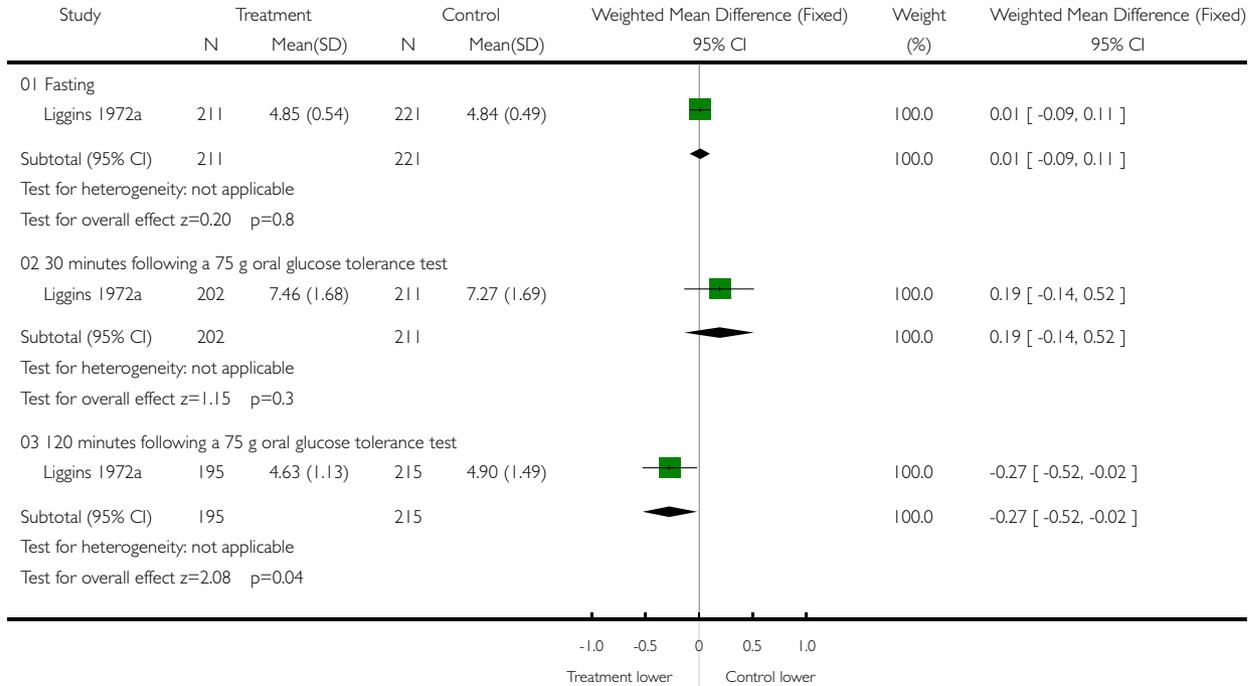


**Analysis 01.53. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 53 Mean adult glucose (mmol/L)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 53 Mean adult glucose (mmol/L)

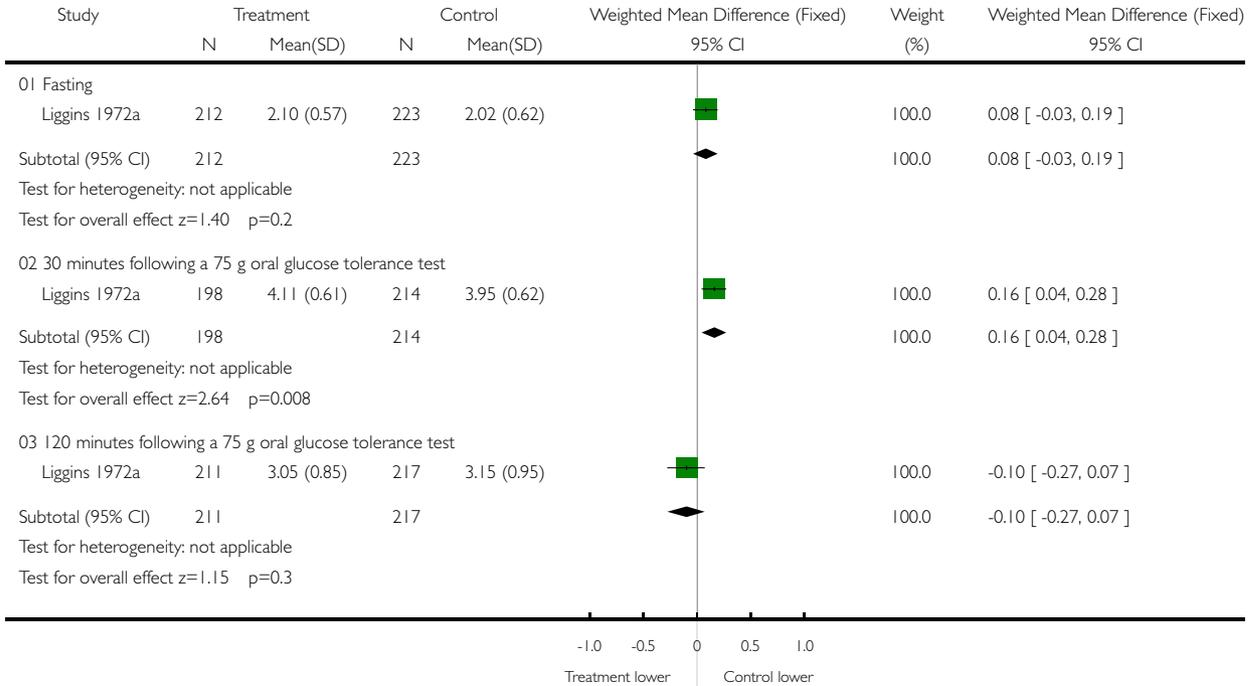


**Analysis 01.54. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 54 Mean adult insulin (log values)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 54 Mean adult insulin (log values)

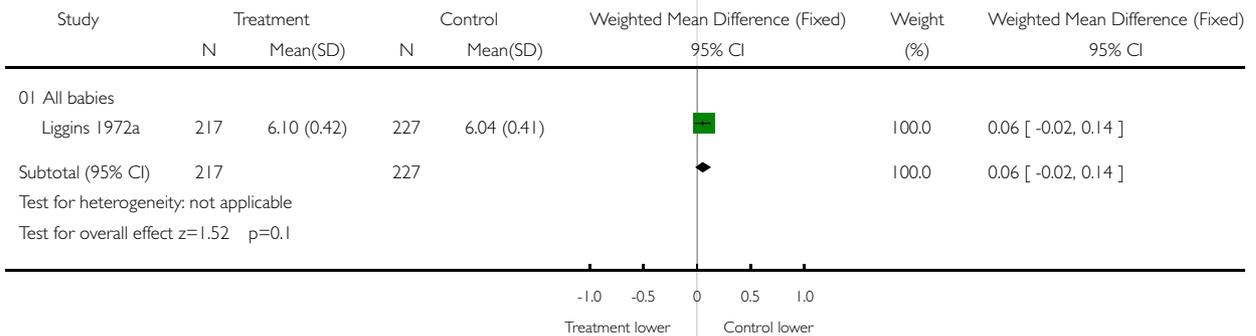


**Analysis 01.55. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 55 Mean adult HPA axis function (mean log fasting cortisol)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 55 Mean adult HPA axis function (mean log fasting cortisol)

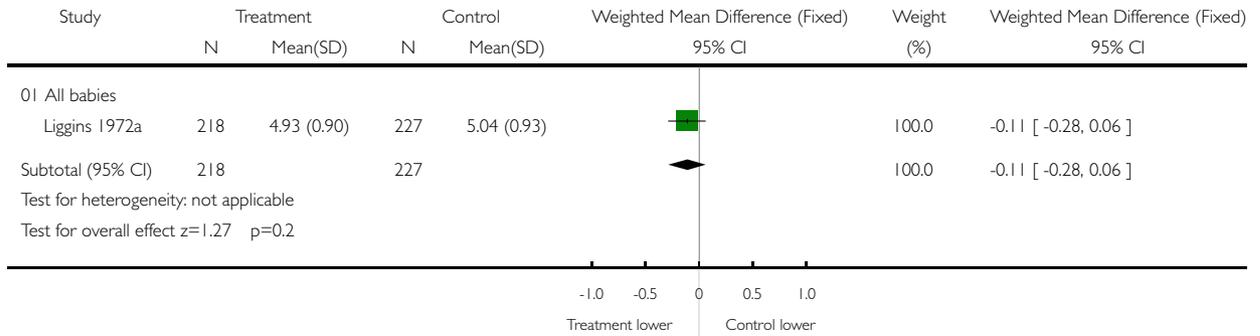


**Analysis 01.56. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 56 Mean cholesterol in adulthood (mmol/L)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 56 Mean cholesterol in adulthood (mmol/L)

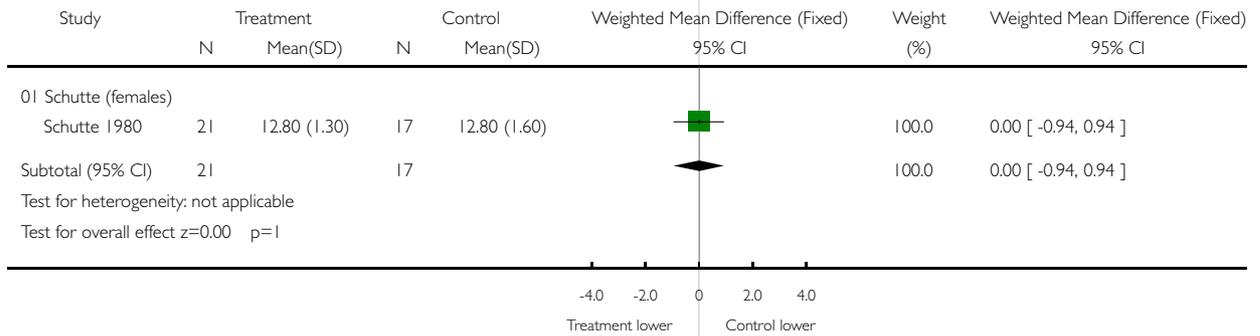


**Analysis 01.57. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 57 Mean age at puberty (years)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 57 Mean age at puberty (years)

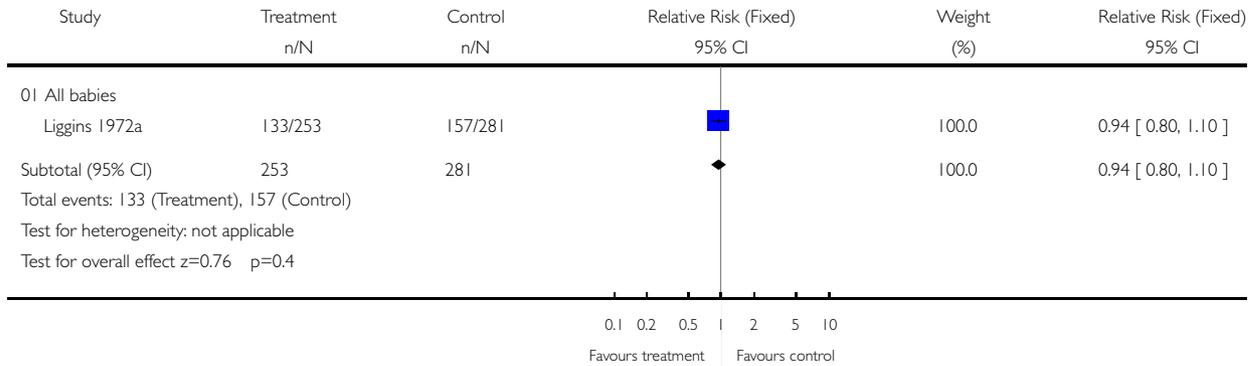


**Analysis 01.58. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 58 Educational achievement by adulthood (university or polytechnic education)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 58 Educational achievement by adulthood (university or polytechnic education)

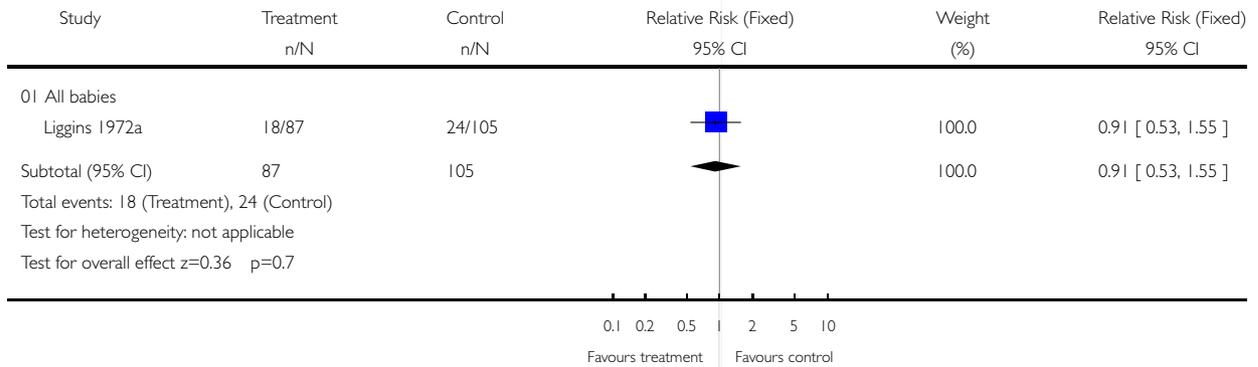


**Analysis 01.59. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 59 Visual impairment in adulthood**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

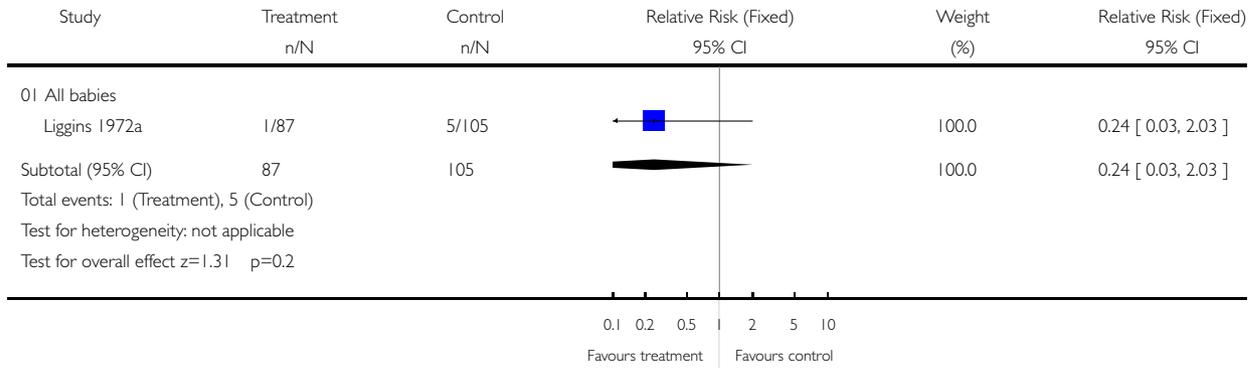
Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 59 Visual impairment in adulthood



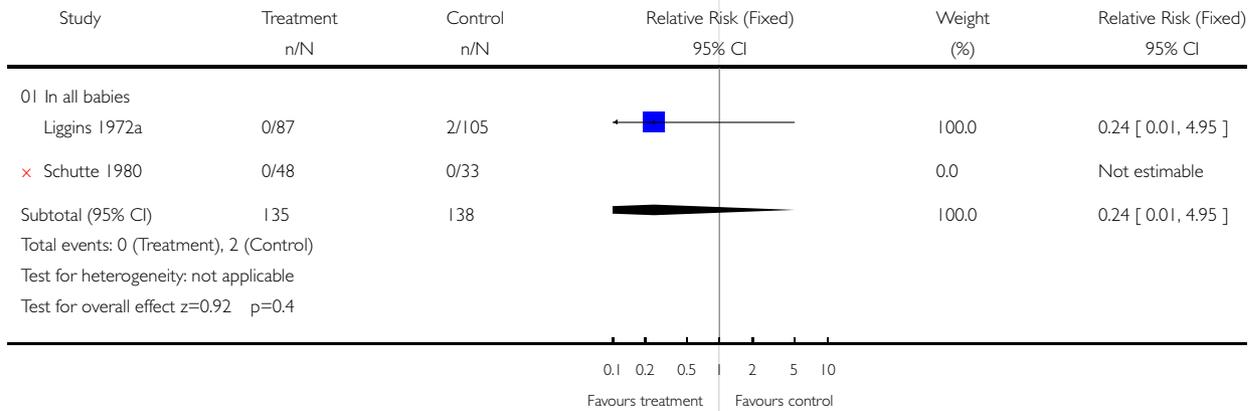
**Analysis 01.60. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 60 Hearing impairment in adulthood**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 60 Hearing impairment in adulthood



**Analysis 01.61. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 61 Intellectual impairment in adulthood**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth  
 Comparison: 01 Corticosteroids versus placebo or no treatment  
 Outcome: 61 Intellectual impairment in adulthood

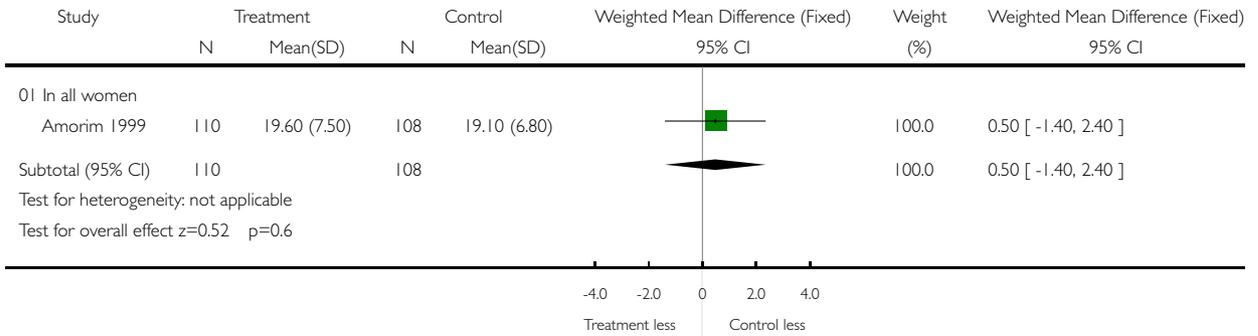


**Analysis 01.62. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 62 Mean length of antenatal hospitalisation (days)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 62 Mean length of antenatal hospitalisation (days)

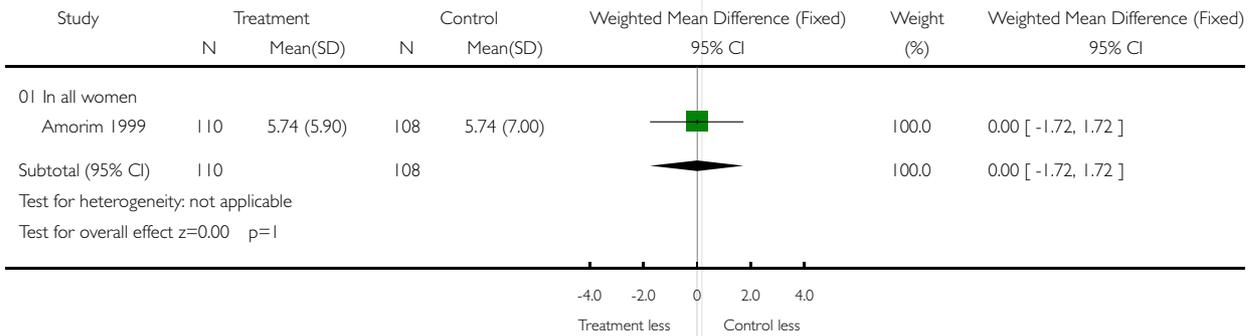


**Analysis 01.63. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 63 Mean length of postnatal hospitalisation (days)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 63 Mean length of postnatal hospitalisation (days)



**Analysis 01.64. Comparison 01 Corticosteroids versus placebo or no treatment, Outcome 64 Mean length of neonatal hospitalisation (days)**

Review: Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth

Comparison: 01 Corticosteroids versus placebo or no treatment

Outcome: 64 Mean length of neonatal hospitalisation (days)

