

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Review)

Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D



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Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus (Review)
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[Intervention Review]

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

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ABSTRACT

Background

Epidemiological and basic science evidence suggests that magnesium sulphate before birth may be neuroprotective for the fetus.

Objectives

To assess the effects of magnesium sulphate as a neuroprotective agent when given to women considered at risk of preterm birth.

Search strategy

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 August 2008).

Selection criteria

Randomised controlled trials of antenatal magnesium sulphate therapy in women threatening or likely to give birth at less than 37 weeks' gestational age. For one subgroup analysis, studies were broadly categorised by the primary intent of the study into "neuroprotective intent", or "other intent (maternal neuroprotective - pre-eclampsia)", or "other intent (tocolytic)".

Data collection and analysis

At least two authors assessed trial eligibility and quality, and extracted data.

Main results

Five trials (6145 babies) were eligible for this review. Antenatal magnesium sulphate therapy given to women at risk of preterm birth substantially reduced the risk of cerebral palsy in their child (Relative Risk (RR) 0.68; 95% Confidence interval (CI) 0.54 to 0.87; five trials; 6145 infants). There was also a significant reduction in the rate of substantial gross motor dysfunction (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants). No statistically significant effect of antenatal magnesium sulphate therapy was detected on

paediatric mortality (RR 1.04; 95% CI 0.92 to 1.17; five trials; 6145 infants), or on other neurological impairments or disabilities in the first few years of life. Overall there were no significant effects of antenatal magnesium therapy on combined rates of mortality with cerebral palsy, although there were significant reductions for the neuroprotective groups RR 0.85; 95% CI 0.74 to 0.98; four trials; 4446 infants, but not for the other intent subgroups. There were higher rates of minor maternal side effects in the magnesium groups, but no significant effects on major maternal complications.

Authors' conclusions

The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established. The number of women needed to be treated to benefit one baby by avoiding cerebral palsy is 63 (95% confidence interval 43 to 155). Given the beneficial effects of magnesium sulphate on substantial gross motor function in early childhood, outcomes later in childhood should be evaluated to determine the presence or absence of later potentially important neurological effects, particularly on motor or cognitive function.

PLAIN LANGUAGE SUMMARY

Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Magnesium sulphate given to women at risk of preterm birth helps to protect the baby's brain and improve long-term outcomes.

Babies born too early (preterm) have a higher risk of dying in the first weeks of life than babies born at term, and those who survive often have damage in the form of cerebral palsy (a disorder where the ability to move the arms or legs normally is reduced), blindness, deafness or physical disabilities. This can cause huge distress for parents. Magnesium is an important element essential for normal body functions. Magnesium sulphate may help to reduce damage to a preterm baby's brain. However, it has adverse effects in the mother of flushing, sweating, nausea, vomiting, headaches and a rapid heartbeat (palpitations). This review identified five studies involving 6145 infants and shows that magnesium sulphate therapy protects the preterm baby's brain from cerebral palsy.

BACKGROUND

Preterm birth and neurological outcome

Infants born preterm have a higher risk of dying in the first weeks of life. If they survive, they have a greater risk of neurological impairments, such as cerebral palsy, blindness, deafness, or cognitive dysfunction (either developmental delay, or intellectual impairment), and a greater risk of substantial disability as a result of these neurological impairments (Doyle 2001; VICS 1997). Moreover, as the rate of preterm birth is rising, up to 12.8% in the United States in 2006 (Martin 2007), more babies are at risk of death and adverse neurological outcomes. Cerebral palsy and cognitive dysfunction are the most frequent neurological impairments, and any therapy that can reduce their prevalence should have a substantial effect on reducing overall neurological impairments and disabilities in surviving preterm infants.

Cerebral palsy is a term which includes a number of different diseases or conditions that can arise at any time during brain development that involves a disorder of movement or posture, or both, and a disorder of motor function which is permanent but may change over time (Oxford Register 2001; SCPE 2000). The

cerebral palsies remain the most frequent cause of severe motor disability in childhood with a background prevalence of two per thousand live births (Oxford Register 2001; Stanley 1994). The life expectancy shows 92% of affected children surviving to 20 years (Hutton 1994), contributing substantially to the burden of illness into adulthood.

Very preterm birth (less than 34 weeks) and very low birthweight (less than 1500 g) are principal risk factors for cerebral palsy (Drummond 2002; Lorenz 1998; Pharoah 1998; Winter 2002) making up between 17% to 32% of all cases of cerebral palsy. Over 10% of all preterm births are from a multiple pregnancy with higher rates of cerebral palsy than singleton pregnancies. Twins have seven times and triplets 47 times the risk of cerebral palsy compared with singletons (Petterson 1993).

Evidence from population-based registries shows that the prevalence of cerebral palsy in low and very low birthweight infants is rising (Drummond 2002; Hagberg 2001; Oxford Register 2001; Stanley 1992). However, not all population-based registries have reported an increase in cerebral palsy in very low birthweight survivors; some have reported a decrease (Himmelman 2005; Surman 2003). Although suspected from earlier birthweight analyses, Drummond's registry study confirms that the increasing preva-

lence of cerebral palsy is from higher rates in preterm, not term, infants (Drummond 2002). Intraventricular haemorrhage (IVH) is a known risk factor for the later development of cerebral palsy (Kuban 1994) with the risk of IVH and periventricular leucomalacia increasing the earlier the gestational age at birth (Vermeulen 2001).

In order to reduce the impact of cerebral palsy from very preterm birth, efforts must be focused on primary prevention.

A possible role for magnesium

The first report that prenatal magnesium sulphate was associated with a reduction in risk of IVH, from 18.9% to 4.4%, in babies born with a birthweight less than 1500 g was by Kuban and colleagues in 1992 (Kuban 1992). A case-control analysis from the California Cerebral Palsy project investigated whether in utero exposure to magnesium sulphate was associated with a lower prevalence of cerebral palsy in infants born weighing less than 1500 g (Nelson 1995). Cases were children with cerebral palsy who were singletons and whose birthweight had been less than 1500 g. Controls were randomly sampled from live births of less than 1500 g from the same birth populations. Magnesium sulphate given to the mother during labour was associated with a marked reduction in the risk of cerebral palsy (odds ratio 0.14; 95% confidence interval 0.05 to 0.51).

Other observational studies have supported a reduction in cerebral palsy in preterm infants by maternal administration of magnesium sulphate (Hauth 1995; Schendel 1996; Wiswell 1996) and some have found a reduction in the risk of IVH (Finesmith 1997; Perlman 1994; Wiswell 1996) and perinatal mortality (Grether 1998). However, not all observational studies have reported benefit for prenatal magnesium sulphate on the risk of IVH (Canterino 1999; Kimberlin 1998; Paneth 1997; Weintraub 2001), cerebral palsy (Grether 2000; O'Shea 1998; Paneth 1997) or perinatal mortality (Kimberlin 1998). However, observational studies alone cannot be the basis for changing clinical practice.

Animal studies have shown that magnesium can provide a neuroprotective effect (McDonald 1990). It can prevent post hypoxic brain injury by blocking the excess release of glutamate in the calcium channel. Fetal and newborn brains seem to be more susceptible to damage from glutamate release. Consequently, blocking glutamate receptors through agents such as magnesium may reduce the risk of injury in the perinatal period (Espinoza 1991). Magnesium sulphate is widely used in obstetrics as an anticonvulsant for the treatment of eclampsia (Duley 2000; Duley 2003a; Duley 2003b), prevention of eclampsia in women with pre-eclampsia (Duley 2003c; Sibai 2003); it has also been used as a tocolytic, although lacking efficacy for inhibiting preterm labour (Crowther 2002).

Magnesium sulphate, by its peripheral vasodilator effects when infused intravenously, produces flushing, sweating, and a sensation of warmth. Reported maternal side effects, related to dosage

and speed of infusion, include nausea, vomiting, headache, palpitations and, rarely, pulmonary oedema. Administration to levels above the recommended therapeutic range can lead to respiratory depression, respiratory arrest, cardiac arrest and death. For the neonate, hypermagnesaemia can lead to hyporeflexia, poor sucking, and, rarely, respiratory depression needing mechanical ventilation (Levene 1995; Lipsitz 1971).

This review assesses the effectiveness and safety of magnesium sulphate given to women considered to be at risk of preterm birth, as a neuroprotective agent for their babies.

OBJECTIVES

To assess the effectiveness and safety, using the best available evidence, of magnesium sulphate as a neuroprotective agent when given to women considered to be at risk of preterm birth.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised trials with reported data comparing outcomes for women at risk of preterm birth given prenatal magnesium sulphate with outcomes in controls, whether treated or not with placebo. Trials were included if the primary aim of the study was to prevent neurological abnormalities in the unborn baby, or if the primary aim was otherwise but long-term neurological outcomes were reported for the infants. The trials had to use some form of random allocation and report data on one or more of the prestated outcomes. Quasi-randomised trials were excluded.

Types of participants

Women considered to be at risk of preterm birth.

Types of interventions

Magnesium sulphate given to the women at risk of preterm birth, administered intravenously, intramuscularly or orally, compared with either placebo or no placebo. Trials where magnesium sulphate was used with the prime aim of tocolysis (Crowther 2002), prevention and treatment of eclampsia (Duley 2000; Duley 2003a; Duley 2003b), maintenance therapy after preterm labour (Crowther 1998) or as a dietary supplement in pregnancy (Makrides 2001) were not included (unless they reported long-term neurological outcomes in the children), as those trials are covered in separate Cochrane reviews.

Types of outcome measures

We prespecified clinically relevant outcomes after discussion.

Primary outcomes

We chose primary outcomes to be most representative of the clinically important measures of effectiveness and safety, including serious outcomes, for the women and their infants. We recognised that the list of outcomes was extensive and that data for some may not be available but we wanted to encapsulate the types of outcomes that may be of concern to clinicians caring for both the mother and the baby, both now and in the future. In so doing, we also recognised the increased possibility of type I errors because multiple outcomes would be evaluated. Combined outcomes were used for the main analyses, rather than all their components.

For the infants/children

- Fetal, neonatal or later death.
- Neurological impairments (developmental delay or intellectual impairment (developmental quotient or intelligence quotient less than one standard deviation (SD) below the mean), cerebral palsy (abnormality of tone with motor dysfunction), blindness (corrected visual acuity worse than 6/60 in the better eye), or deafness (hearing loss requiring amplification or worse)), or neurological disabilities (abnormal neurological function caused by any of the preceding impairments) at follow up later in childhood. Substantial gross motor dysfunction (defined as motor dysfunction such that the child was not walking at age two years or later, or the inability to grasp and release a small block with both hands).
- Major neurological disability (defined as any of: legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay/intellectual impairment (defined as developmental quotient or intelligence quotient less than two SD below the mean)).
- Paediatric mortality combined with cerebral palsy, substantial gross motor dysfunction, neurological impairment, or major neurological disability (these combined outcomes recognise the competing risks of death or survival with neurological problems).

The major paediatric outcomes were death or neurological (cerebral palsy, impairment or disability), or combinations of death with the neurological outcomes.

For the women

- Serious adverse cardiovascular/respiratory outcome (maternal death, respiratory arrest, cardiac arrest).
- Adverse effects severe enough to stop treatment.

Secondary outcomes

These include other measures of effectiveness, complications, satisfaction with care and health service use.

For the infant

- Any intraventricular haemorrhage (IVH).
- IVH grade 3/4.
- Periventricular leucomalacia.
- Apgar score less than seven at five minutes.
- Need for active resuscitation (assisted ventilation via an endotracheal tube) at birth.
- Neonatal convulsions.
- Neonatal hypotonia.
- Use of respiratory support (mechanical ventilation or continuous positive airways pressure, or both).
- Chronic lung disease (need for continuous, supplemental oxygen at 28 days postnatal age or 36 weeks' post-menstrual age).
- Use of postnatal corticosteroids.

For the child

- Growth assessments at childhood follow up (weight, head circumference, length/height).
- Educational achievements.

For the woman

- Blood pressure changes during infusion.
- Respiratory rate changes during infusion.
- Pulse rate at birth changes during infusion.
- Length of labour.
- Need for augmentation of labour.
- Postpartum haemorrhage.
- Mode of birth.
- Intrapartum fever requiring the use of antibiotics.
- Breastfeeding after hospital discharge.
- Women's satisfaction with the therapy.

Use of health services

- Length of postnatal hospitalisation for the women.
- Admission to intensive care unit for the mother.
- Admission to neonatal intensive care.
- Length of stay in neonatal intensive care unit.
- Length of neonatal hospitalisation.
- Costs of care for mother or baby, or both.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 August 2008).

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. weekly searches of MEDLINE;
3. handsearches of 30 journals and the proceedings of major conferences;
4. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

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 'Specialized Register' section within the editorial information about the [Cochrane Pregnancy and Childbirth Group](#).

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

We did not apply any language restrictions.

Data collection and analysis

At least two review authors evaluated trials under consideration for inclusion without consideration of their results. We also independently assessed the risk of bias in each included trial. We resolved differences of opinion by discussion. There was no blinding of authorship. We processed included trial data as described in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2008](#)). Where one of the authors was a chief investigator in a trial included in the review, at least one other author also extracted data.

Risk of bias assessment

We assessed risk of bias using the dimensions outlined in the Cochrane Handbook for Systematic Reviews of Interventions ([Higgins 2008](#)).

In assessing selection bias, we examined the processes involved in the generation of the random sequence and the method of allocation concealment separately.

We examined performance bias as to whom was blinded in the trials. We sought details of the feasibility and appropriateness of blinding for participant, caregiver, outcome assessment and data analysis.

Analysis

We performed statistical analyses using the Review Manager software ([RevMan 2008](#)) and compared categorical data using relative risks and 95% confidence intervals. We tested for statistical heterogeneity between trials using the I^2 statistic. If substantial heterogeneity was found (I^2 greater than 50%), we used a random-effects model, as well as exploring subgroup analyses. In addition, statistically significant differences between subgroups for primary outcomes were analysed by chi-squared analysis, where possible. We analysed data extracted from the trials on an intention-to-treat basis. Where this was not done in the original report, we performed re-analysis where possible. If missing data were such that it might significantly affect the results, we excluded these data from the analysis. This decision rested with the review authors and was clearly documented. If missing data become available subsequently, they will be included in the analyses.

Sensitivity analyses

A priori it was decided that all eligible trials would be included in the initial analysis and sensitivity analyses carried out to evaluate the effect of trial quality, including aspects of selection, performance and attrition bias. This was done by subgrouping for quality of concealment of treatment allocation and other sensitivity analyses based on the risk of bias assessments as specified above.

Subgroup analyses

We planned subgroup analyses for:

- the major paediatric outcomes of mortality and long-term neurological morbidity according to whether the primary intention of administering magnesium sulphate was for neuroprotection of the fetus, as distinct from other indications such as prevention of eclampsia in women with pre-eclampsia or use for tocolysis.

We also planned subgroup analyses to examine separately the major paediatric outcomes of mortality and long-term neurological morbidity based on;

- the reasons the woman was considered to be at risk of preterm birth, (such as preterm labour, the presence or absence of ruptured membranes at trial entry, pre-eclampsia);
- the number of babies in utero (singleton or multiple);
- the use of prenatal corticosteroids in more than 50% of those at risk;
- the gestational age at which treatment was given;
- the type of magnesium preparation given;
- the dosage of magnesium sulphate given;
- its mode of administration;
- whether repeat treatment was permitted; and
- the time treatment was given prior to expected preterm birth.

We limited primary analysis to the prespecified outcomes and subgroup analyses. In the event of differences in outcomes not prespecified being found, we clearly identified them as such.

RESULTS

Description of studies

See: [Characteristics of included studies](#).

Five trials (6145 babies) qualified for inclusion in this review, one from Australia and New Zealand ([Crowther 2003](#)), two from the US ([Mittendorf 2002](#); [Rouse 2008](#)), one from France ([Marret 2006](#)), and one that was worldwide, but predominantly from developing countries ([Magpie 2006](#)) (see 'Characteristics of included studies' table). The first four trials specifically targeted women who were likely to give birth early and magnesium was being used for neuroprotection, although one study ([Mittendorf 2002](#)) also had a tocolytic arm to the study. The fifth study, the MAGPIE trial ([Magpie 2006](#)) was designed to evaluate whether magnesium prevented eclampsia in women with pre-eclampsia; it included women at all gestational ages. Data from the MAGPIE study relevant to women less than 37 weeks when randomised have been provided by the authors for inclusion in this review.

[Crowther 2003](#) (neuroprotection)

A total of 1062 women with babies less than 30 weeks' gestation and in whom birth was anticipated within 24 hours were enrolled from February 1996 to September 2000 into ACTOMgSO₄ (Australasian Collaborative Trial of Magnesium Sulphate). Women were excluded if birth was imminent (they were in second stage of labour), if they had already received magnesium sulphate during the pregnancy, or if there were contraindications to magnesium sulphate therapy. There were 16 collaborating centres within Australia and New Zealand. Stratification was by centre and multiple pregnancy (three groups - singleton, twin or higher order multiple). Women were randomly allocated to either intravenous magnesium sulphate (n = 535 women, 629 live babies) or an identical volume of saline placebo (n = 527 women, 626 live babies). The magnesium sulphate dose was 4 g over 20 minutes, followed by 1 g/hour for up to 24 hours or until birth, whichever came first. There were no repeat courses of treatment. The primary endpoints of the study were total paediatric mortality up to a corrected age of two years; cerebral palsy at two years' corrected age; and the combined adverse outcome of death or cerebral palsy at two year follow up.

[Magpie 2006](#) (other intent - neuroprotection of the pre-eclamptic mother)

A total of 10,141 women who were either undelivered or within 24 hours of birth with pre-eclampsia and uncertainty about whether to use magnesium sulphate to prevent eclampsia were enrolled

from July 1998 to November 2001 into the Magpie Trial - a randomised controlled trial of either magnesium sulphate or saline placebo. Women were excluded if they had hypersensitivity to magnesium, hepatic coma, or myasthenia gravis. The magnesium sulphate dose was 4 g intravenously over 10 to 15 minutes, followed by either 1 g/hour intravenously for 24 hours, or by 5 g every 4 hours intramuscularly for 24 hours. There were no repeat courses of treatment. The major endpoint of the study was neuroprotection of the mother (avoidance of eclampsia). Secondary endpoints included long-term outcome for the children. Unpublished outcome data were provided from the trial investigators on the 1544 women who were undelivered when treated with magnesium sulphate and who were less than 37 weeks' gestational age at randomisation, as well as for the subgroups less than 34 and less than 30 weeks' gestational age at randomisation, and for the subgroups of singleton pregnancies versus multiple pregnancies. Outcome data for women from the Magpie study were included if the child was selected for follow up and outcomes for the child were known, even if the only outcome available was death.

[Marret 2006](#) (neuroprotection)

A total of 573 women whose birth was planned or expected within 24 hours with singleton, twin or triplet less than 33 weeks' gestation were enrolled at 18 collaborating centres in France into the Premag Trial. Only data from 13 centres (564 women) were included in the final report; two of the 18 centres recruited no women and three centres enrolled fewer than five women and were excluded on the basis of a prespecified criterion for exclusion of centres. Women were not eligible when the fetus had severe malformations, chromosomal abnormalities or growth restriction, and with various maternal complications, such as pre-eclampsia, hypotension, cardiac arrhythmias, electrolyte anomalies, renal insufficiency. Women were randomly allocated to either intravenous magnesium sulphate 4 g or an equal volume of isotonic saline placebo over 30 minutes. There were no repeat courses of treatment. The major endpoint of the study was white matter injury to the infant diagnosed by cranial ultrasound.

[Mittendorf 2002](#) (neuroprotection/other intent: tocolysis)

A total of 149 women in preterm labour 25 to 33 weeks' gestation were enrolled from October 1995 to January 1997 at a single US centre into the MAGNET Trial. Women were excluded if there was non-reassuring fetal assessment, or clinical features of infection or pre-eclampsia, or more than twin pregnancy. Stratification was by race (black versus other), gestational age (25 to 28 weeks and 28 to 33 weeks), and, several months into the trial, plurality (singleton versus twin). There were two treatment strategies dependent upon cervical dilatation at entry: those with active labour and cervical dilatation less than 5 cm were considered candidates for tocolysis with magnesium sulphate (the 'tocolytic' arm); they were randomly allocated to receive magnesium sulphate as a 4 g bolus followed by 2 to 3 g/hour maintenance (n = 46 women, 55 babies), or an alternative tocolytic (non-blinded) (n = 46 women, 51 babies). The remainder (with cervical dilatation greater than

4 cm) were considered for the 'neuroprotective' arm of the study and were randomly allocated to either a 4 g magnesium sulphate bolus (n = 29 women, 30 babies) or saline placebo (n = 28 women, 29 babies). In the 'neuroprotective' arm no further magnesium sulphate treatment occurred. For the purposes of this review, the Mittendorf study was considered as two separate trials.

[Rouse 2008](#) (neuroprotection)

A total of 2241 women were eligible (a singleton or twin pregnancy at least 24 weeks gestation but less than 32 weeks at high risk of spontaneous birth due to ruptured membranes at 22 to 31 weeks gestation, or advanced preterm labour with dilatation 4 to 8 cm and intact membranes; or if an indicated preterm birth was anticipated with 24 hours (e.g. due to fetal growth restriction) but not if birth was anticipated within 2 hours or if cervical dilatation exceeded 8 cm). Women were not eligible if membranes had ruptured prior to 22 weeks; the obstetrician was unwilling to intervene for fetal benefit; or there were major fetal anomalies or demise; presence of hypertension or pre-eclampsia; maternal contraindications to magnesium sulphate; or receipt of intravenous magnesium sulphate within the prior 12 hours.

There were 20 collaborating sites across the United States with recruitment in the BEAM Trial from December 1997 to May 2004.

Stratification was by centre, and, in twin pregnancies, gestational

age below, or at, or above 28 weeks gestation. Women were "randomised in a double-blind fashion" to either intravenous magnesium sulphate (n = 1096 women, 1188 babies) or identical-appearing placebo (n = 1145 women, 1256 babies).

The magnesium sulphate dose was 6 g over 20 to 30 minutes, followed by a maintenance infusion of 2 g/hour. If delivery had not occurred after 12 hours and was no longer considered imminent, the infusion was discontinued and resumed when delivery threatened. If at least 6 hours had transpired, another loading dose was given. Retreatment was withheld if: pre-eclampsia/eclampsia developed; maternal or fetal condition deteriorated so re-treatment would be detrimental; or if the gestational age had reached 34 weeks.

The primary outcome was the composite of 1) stillbirth or infant death by one year of age, or 2) moderate or severe cerebral palsy as assessed at or beyond two years' corrected age.

Risk of bias in included studies

Overall, the methodological quality of the trials was relatively good, with a low risk of bias. However, the quality was better, and the risk of bias lower, in some studies compared with others ([Figure 1](#); [Figure 2](#)).

Figure 1. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

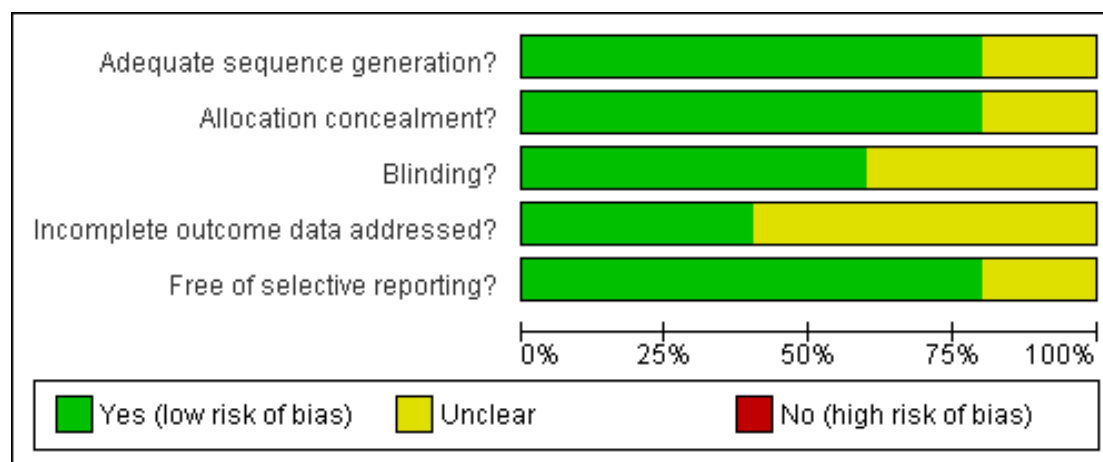


Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of selective reporting?
Crowther 2003	+	+	+	+	+
Magpie 2006	+	+	+	?	+
Marret 2006	+	+	?	?	+
Mittendorf 2002	?	?	?	?	?
Rouse 2008	+	+	+	+	+

Crowther 2003 - This was a blinded trial with randomisation performed centrally by non-clinical staff independent of the chief investigators, with random variation in block sizes of four, six or eight, and separately for singleton, twin, or higher order multiple births. Each study number was placed on a masked treatment pack. Packs were sent to individual hospitals ready for use. No one at individual study sites had access to the treatment code. Outcomes were given for all mothers and fetuses enrolled.

Follow-up component: surviving children were assessed at 24 months of age, corrected for prematurity, by paediatricians and psychologists at individual study sites who were blinded to treatment group allocation. Neurological outcomes included cerebral palsy (criteria included abnormalities of tone and motor dysfunction) and gross motor function assessed by the criteria of **Palisano 1997**. Substantial gross motor dysfunction comprised children who were not walking independently at two years of corrected age. Other outcomes included blindness (bilateral vision worse than 6/60), deafness requiring hearing aids, and developmental delay (defined as an Mental Developmental Index (MDI) on the Bayley Scales of Infant Development less than 85 (less than -1 SD) (**Bayley 1993**)). Major neurological disability was defined as any of moderate or severe cerebral palsy, blindness, deafness or an MDI less than 70. The follow-up rate of survivors at two years was 99% (1047/1061).

Magpie 2006 - This was a blinded trial with randomisation performed centrally, independent of the clinical investigators, with balance for severity of pre-eclampsia, gestational age, undelivered or delivered, anticonvulsants prior to entry, multiple pregnancy, and country. Masked treatment packs were provided to individual hospitals ready for use. No one at individual study sites had access to the treatment code. Outcomes were given for 99.7% of mothers and 98.7% of fetuses enrolled.

Follow-up component: not all surviving children could be followed in this multinational trial for various logistical reasons. In the study overall, approximately 2/3 of surviving children were selected for follow up, and of these children outcomes were determined for 73% (n = 3283), including those who died. Children were assessed by a developmental screening questionnaire at 18 or more months of age, corrected for prematurity where appropriate, and those who failed were invited for a more formal developmental test - usually the Bayley Scales of Infant Development, either the first (**Bayley 1969**) or the second edition (**Bayley 1993**), or alternative tests such as the Griffiths scales. In addition, 20% of screen negative children were also assessed formally. It was intended that children would be at least 18 months old, corrected for prematurity where appropriate, but in some instances children had data only at younger ages. Major neurological disability was defined as any of moderate or severe cerebral palsy, blindness, deafness or a MDI on the Bayley Scales less than 70. Children were not routinely examined by a paediatrician or neurologist for diagnoses such as cerebral palsy. Given the lack of formal assessment of all children it is probable that diagnoses such as developmental delay

(defined as a MDI on the Bayley Scales less than 85 (less than -1 SD)), or cerebral palsy were underestimated. For this review, the Magpie investigators provided data for 1593 infants whose mothers were treated at less than 37 weeks' gestational age out of the total of 3283 children with follow-up data.

Marret 2006 - This was a single-blind trial with randomisation performed centrally, with randomisation numbers generated by computer using variable block size from two to 16 depending on expected recruitment. Randomisation was independent of the clinical investigators, with balance for study centre, multiple pregnancy, and gestational age (less than 27 weeks, 27 to 29 weeks, 30 to 32 weeks). The major endpoint of the study was infant death or white matter injury detected by cranial ultrasound and defined as the presence of periventricular cavitation, intraparenchymal haemorrhage, persisting hyperechogenicity or ventricular dilatation.

Follow-up component: at two years of age. Physicians caring for the children or the study investigators, who were blinded to treatment allocation, obtained data either by clinical examination or telephone with a standardised questionnaire derived from Amiel-Tison's (**Amiel-Tison 2004**) and the Denver Developmental Scale. Motor and cognitive developmental scales were scored, ranging from one (normal) to four (severely impaired). Mild cognitive dysfunction was considered present if the child pointed to an article or an animal without possibility of nomination and/or pointed to the different part of the body and/or tired of quickly and/or had no symbolic games and/or had an uncertain building in and/or use of single words; a moderate cognitive dysfunction was considered if there was no preference for a toy or any activity, if the child only removed, threw out and did not put the cubes or toys in the box, if language was gibberish without identified words, if they were unable to express wish by gesture or attitude; a severe cognitive dysfunction was considered if there was no activity or stereotyped activities, no pointing with finger, no following with eyes and production of stereotyped sounds. The follow-up rate of survivors was 98%.

Mittendorf 2002 - The method of randomisation was not described. The 'tocolytic' arm was unblinded, whereas the 'neuro-protective' arm was blinded. Outcomes were given for all mothers and babies enrolled.

Follow-up component: surviving children were assessed at 4, 8, 12 and 18 months of age, corrected for prematurity, in a special follow-up clinic. Cerebral palsy (criteria not described) was diagnosed or verified at 18 months, by a developmental paediatrician who was blind to treatment allocation. Other long-term outcomes were not described. The follow-up rate of survivors was not described.

Rouse 2008 - This was a blinded trial with group allocation made according to a computer-generated random sequence. The sequence was generated centrally and given to the individual hospital pharmacies. The outcome assessors remained blinded to the treatment allocation (BEAM Study Protocol - unpublished).

Follow-up component: Surviving children were scheduled for fol-

low-up visits at age 6, 12 and 24 months of age corrected for prematurity.

At the one year examination it was considered possible to make a definitive determination that the child did not have cerebral palsy. Infants who had a normal neurological examination and could walk 10 steps independently and had a bilateral pincer grasp, were declared free of cerebral palsy and further assessment (at two years) for cerebral palsy was not made.

Neurological outcomes included cerebral palsy, diagnosed by criteria of delay in gross motor development milestones, abnormalities of muscle tone, motor dysfunction and abnormal reflexes (persistence of primitive or absence of protective reflexes). An annually certified paediatrician or paediatric neurologist made a diagnosis of cerebral palsy if two or more of the following three features were present: a delay of 30% or more in gross motor developmental milestones (e.g., inability to sit without arm support by 9.5 months or walk by 17 months of corrected age) (Capute 1985; Blasco 1994), abnormality in muscle tone (e.g., scissoring), 4+ or absent deep-tendon reflexes, or movement abnormality (e.g., posturing or gait asymmetry); or persistence of primitive reflexes or absence of protective reflexes. The Gross Motor Function Classification Scale (Palisano 1997) was used to assess severity when cerebral palsy was diagnosed. Level one defined mild cerebral palsy, Levels two and three defined moderate, and Levels four and five defined severe. Other outcomes included scores on the Bayley Scales of Infant Development II. The follow-up rate of surviving infants was 95% (2137/2255).

Effects of interventions

This updated review includes the recently published USA study - the BEAM trial (Rouse 2008).

We included five trials with a total of 6145 babies (Crowther 2003; Magpie 2006; Marret 2006; Mittendorf 2002; Rouse 2008). The Mittendorf trial (Mittendorf 2002) has both tocolytic and neuroprotective arms. Results are presented on an 'as randomised' basis, without double counting data.

Infant mortality - fetal, neonatal and later (Graphs 1.1 to 1.3)

Antenatal magnesium sulphate treatment had no overall significant effect on paediatric (fetal, neonatal and later) mortality (relative risk (RR) 1.04; 95% confidence interval (CI) 0.92 to 1.17; five trials; 6145 infants). While Crowther 2003; Magpie 2006; Marret 2006; and Rouse 2008 showed no significant mortality differences between magnesium and no magnesium groups, Mittendorf 2002 showed significantly more deaths in the magnesium group (10/85 versus 1/80). Eight of the 10 deaths in the magnesium group (and no deaths in the no magnesium group) occurred in the 'tocolytic' arms of Mittendorf 2002 compared with two deaths and one death respectively in the 'neuroprotective' arms of the trial.

There were sufficient data to permit subgroup analysis based on the primary intent for giving magnesium sulphate in the study, either specifically for neuroprotection of the infant (the neuroprotective

intent subgroup) or for other intent subgroups of prevention of pre-eclampsia and tocolysis. The RR for the neuroprotective intent subgroup was 0.95; 95% CI 0.80 to 1.12; four trials; 4446 infants; for the other intent subgroup 'prevention of eclampsia' RR 1.11; 95% CI 0.93 to 1.31; one trial; 1593 infants; and the other intent subgroup 'tocolysis' RR 15.79; 95% CI 0.93 to 266.72; one trial; 106 infants. There was moderate heterogeneity overall ($I^2 = 45\%$) between studies, largely due to the different results from the other intent subgroup 'tocolysis', from the tocolytic arm of Mittendorf 2002.

Little difference was seen between the magnesium and no magnesium groups for fetal deaths alone (RR 0.96; 95% CI 0.77 to 1.21; five trials; 6145 infants), in the subgroups by intent, or for deaths of liveborn infants to latest age of follow up (RR 1.06; 95% CI 0.81 to 1.40; five trials; 6145 infants). Most discrepancy between studies was seen for deaths of liveborn infants to latest age of follow up for subgroups by intent (neuroprotective intent subgroup: RR 0.96; 95% CI 0.77 to 1.18; four trials; 4446 infants; and other intent subgroup 'prevention of eclampsia': RR 1.27; 95% CI 0.96 to 1.68; one trial; 1593 infants; and other intent subgroup 'tocolysis': RR 15.79; 95% CI 0.93 to 266.72; one trial 106 infants).

Paediatric neurological outcomes (Graphs 1.4 to 1.10)

Overall antenatal magnesium sulphate treatment significantly reduced the risk for cerebral palsy (overall RR 0.68; 95% CI 0.54 to 0.87; five trials; 6145 infants);

- this remained significant within the neuroprotective intent subgroup (RR 0.71; 95% CI 0.55 to 0.91; four trials; 4446 infants);
- but not for the other intent subgroups;
 - i) pre-eclampsia RR 0.40; 95% CI 0.08 to 2.05; one trial; 1493 infants;
 - ii) tocolysis: RR 0.13 95% CI 0.01 to 2.51; one trial; 106 infants.

There were fewer children with moderate or severe cerebral palsy in the magnesium sulphate treated group compared with placebo (overall RR 0.64; 95% CI 0.44 to 0.92; three trials; 4387 infants). Four trials, Crowther 2003 (neuroprotective intent: 1255 infants), Marret 2006 (neuroprotective intent: 688 infants); Magpie 2006 (other intent: pre-eclampsia 1593 infants) and Rouse 2008 (neuroprotective intent: 2136 infants) reported on a number of other neurological outcomes (four trials; 5980 infants).

Substantial gross motor dysfunction was the only other outcome to show a significant difference between magnesium and placebo overall (RR 0.61; 95% CI 0.44 to 0.85; four trials; 5980 infants) in favour of magnesium, with the result attributable to the trials in the neuroprotective intent group (RR 0.60; 95% CI 0.43 to 0.83; three trials; 4387 children).

Combined results for the other neurological outcomes were:

- any neurological impairment: RR 1.01; 95% CI 0.86 to 1.19; two trials; 2848 infants;

- blindness: RR 0.74; 95% CI 0.17 to 3.30; three trials; 3536 infants;
- deafness: RR 0.79; 95% CI 0.24 to 2.56; three trials; 3536 infants;
- developmental delay or intellectual impairment: RR 0.99; 95% CI 0.91 to 1.09; four trials; 5980 infants;
- major neurological disability: RR 1.07; 95% CI 0.82 to 1.40; two trials; 2848 infants.

Combined paediatric mortality and neurological outcomes (Graphs 1.11 to 1.14)

There was no significant effect of antenatal magnesium sulphate treatment on the combined rate of death or cerebral palsy overall (RR 0.94; 95% CI 0.78 to 1.12; five trials; 6145 infants). However there was a significant reduction for the neuroprotective groups RR 0.85; 95% CI 0.74 to 0.98; four trials; 4446 infants, although not for the other intent subgroups for 'prevention of eclampsia' (RR 1.09; 95% CI 0.92 to 1.29; one trial; 1593 infants, or 'tocolysis' (RR 2.47; 95% CI 0.69 to 8.81; one trial; 106 infants). The level of heterogeneity for the trials overall was $I^2 = 51\%$.

Crowther 2003; Magpie 2006; and Rouse 2008 reported other neurological outcomes. Results for combined death/neurological outcomes are only available from these three trials for a total of 5282 infants.

Neither death nor any neurological impairment (RR 1.00; 95% CI 0.91 to 1.11; two trials; 2848 infants), or death or major neurological disability (RR 1.02; 95% CI 0.90 to 1.15; two trials; 2848 infants) showed statistically significant differences between the magnesium and placebo groups overall. The combined outcome of death or substantial gross motor dysfunction was also not significantly in favour of magnesium overall (RR 0.92; 95% CI 0.75 to 1.12; 4 trials; 5980 infants) overall, but there was substantial heterogeneity in this outcome between the four studies ($I^2 = 65\%$).

Major maternal outcomes (Graphs 1.15 to 1.17)

There were no substantial differences between treatment groups in maternal deaths (RR 1.25; 95% CI 0.51 to 3.07; four trials; 5411 women), cardiac arrest (RR 0.34; 95% CI 0.04 to 3.26; four trials; 5411 women), or respiratory arrest (RR 1.02; 95% CI 0.06 to 16.25; four trials; 5411 women) but few women had these outcomes.

Cessation of maternal therapy (Graph 1.18)

Crowther 2003; Magpie 2006 and Rouse 2008 (three trials; 4847 women) reported on this outcome. Overall, significantly more women in the magnesium group ceased therapy because of side effects (RR 3.26; 95% CI 2.46 to 4.31).

Secondary paediatric outcomes (Graphs 1.19 to 1.26)

The need for ongoing respiratory support was reduced in the magnesium group (borderline statistical significance): RR 0.94; 95% CI 0.89 to 1.00; three trials; 4387 infants.

There were no significant differences seen in any of the other secondary paediatric outcomes in all studies combined:

- intraventricular haemorrhage: RR 0.96; 95% CI 0.86 to 1.08; four trials; 4552 infants;
- intraventricular haemorrhage 3/4: RR 0.83; 95% CI 0.62 to 1.13; two trials; 3699 infants;
- periventricular leucomalacia RR 0.93; 95% CI 0.68 to 1.28; four trials; 4552 infants;
- Apgar score less than seven at five minutes: RR 1.03; 95% CI 0.90 to 1.18; three trials; 4387 infants;
- neonatal convulsions: RR 0.80; 95% CI 0.56 to 1.13; three trials; 4387 infants;
- neonatal hypotonia: RR 1.02; 95% CI 0.77 to 1.36; one trial; 2444 infants;
- chronic lung disease (oxygen at 28 days): RR 1.07; 95% CI 0.94 to 1.22; one trial; 1255 infants;
- chronic lung disease (oxygen at 36 weeks): RR 1.12; 95% CI 0.95 to 1.32; two trials; 1943 infants.

None of the trials reported on need for active resuscitation at birth, how many babies were treated with postnatal steroids, measures of growth such as weight, height or head circumference or educational achievements.

Secondary maternal outcomes (Graphs 1.27 to 1.30)

There was significantly more maternal hypotension (RR 1.51; 95% CI 1.09 to 2.09; two trials; 1626 women) and tachycardia (RR 1.53; 95% CI 1.03 to 2.29; one trial; 1062 women) in the magnesium group than in the placebo group.

No significant differences between magnesium and placebo were seen for:

- maternal respiratory depression: RR 1.31; 95% CI 0.83 to 2.07; two trials; 3303 women;
- postpartum haemorrhage: RR 0.87; 95% CI 0.67 to 1.12; two trials; 1626 women;
- caesarean birth: RR 1.03; 95% CI 0.98 to 1.09; four trials; 5411 women.

Crowther 2003 reported that none of the women in the trial were admitted to the intensive care unit. There were no significant differences in the rates of admission to intensive care for the mother in the Magpie trial (Magpie 2006; RR 0.89; 95% CI 0.54 to 1.47; one trial; 1544 women).

None of the trials reported on length of labour, augmentation of labour, use of intrapartum antibiotics, breastfeeding, or maternal satisfaction.

Consumption of health resources (Graphs 1.31 to 1.32)

No substantial differences were seen between the magnesium and placebo groups for length of mother's hospital stay (mean difference (MD) 0.17 days; 95% CI -0.18 to 0.53; two trials; 2606 women) or infant's primary stay (MD -0.52 days; 95% CI -4.15 to 3.11; two trials; 2828 infants), but there was substantial heterogeneity in the last comparison ($I^2 = 52\%$).

No study reported the number of babies admitted to the neonatal intensive care unit (NICU), duration of any NICU stay or costs of care either for the mother or baby.

Sensitivity Analysis (Graphs 2.1 to 2.7)

Only two studies (Crowther 2003; Rouse 2008) had no major methodological issues of trial quality relating to aspects of selection, performance or attrition bias. Restricting the main paediatric analyses to these two trials at lowest risk of bias, antenatal magnesium sulphate treatment significantly reduced the risk for cerebral palsy (RR 0.68; 95% CI 0.52 to 0.91; two trials; 3699 infants), there was a borderline significant reduction in the combined outcome of death or cerebral palsy (RR 0.86; 95% CI 0.74 to 1.00; two trials; 3699 infants), but there were no statistically significant effects on any other paediatric outcomes.

Subgroup Analysis

Neuroprotective intent only versus other intent (prevention of eclampsia, tocolysis)

This subgroup analysis is discussed in the primary analysis above.

Reasons women considered at risk of preterm birth

Preterm labour

In Crowther 2003, 63% of women in each group were in preterm labour at randomisation and, similarly for Marret 2006 84% in the magnesium group and 88% in the placebo group and for Rouse 2008 11% in the magnesium group and 10% in the placebo group. Results were not reported separately.

Preterm prelabour rupture of the membranes (PPROM) at randomisation

In Crowther 2003, 8% of women in the magnesium group and 10% in the placebo group had PPRM at randomisation, but results were not reported separately. In the study of Marret 2006, 54% of the magnesium group and 47% of the placebo group had PPRM at randomisation but the results were not reported separately for the subgroups. For Rouse 2008, 86% of the magnesium group and 87% of the placebo group had PPRM at randomisation but results were not reported separately.

Pre-eclampsia/eclampsia

In Crowther 2003, 16% of women in the magnesium group and 14% in the placebo group had pre-eclampsia or eclampsia at randomisation but results were not presented separately. Mittendorf 2002; Marret 2006; and Rouse 2008 excluded pre-eclamptic women. In the Magpie trial (Magpie 2006), all women had pre-eclampsia.

Single or multiple pregnancy (Graphs 3.1 to 3.7)

Data were available from Crowther 2003; Magpie 2006; and Rouse 2008 for single and multiple pregnancies separately, with no clear differences seen between any of the primary outcomes, although there was substantial heterogeneity where mortality was considered, either alone or combined with neurological outcomes.

Use of prenatal corticosteroids in more than 50% of those at risk (Graphs 4.1 to 4.7)

Corticosteroids were given to more than 50% of women in the trials of Crowther 2003; Marret 2006; and Rouse 2008 and to the tocolytic arm of the Mittendorf study (Mittendorf 2002), but the results were not reported separately for the subgroups. Analyses confined to these four studies revealed no different conclusions.

Gestational age at randomisation (Graphs 5.01 to 5.07)

Although Mittendorf 2002 reported stratifying by gestational age, their results were not presented by gestational age. In Crowther 2003, all women at entry had fetuses younger than 30 weeks' gestation. In the study of Marret 2006 all fetuses were less than 33 weeks at randomisation. In the Rouse 2008 study all fetuses were less than 32 weeks at randomisation. The Magpie investigators (Magpie 2006) not only provided separate data for all infants less than 37 weeks at randomisation, they also provided separate data for infants less than 34 weeks and less than 30 weeks. There was substantial heterogeneity in most outcomes where mortality was considered, either alone or combined with neurological outcomes. There was a reduction in cerebral palsy for all five studies who recruited women at less than 34 weeks gestation (RR 0.69; 95% CI 0.54 to 0.88; five trials; 5357 infants). No clear differences were seen between treatment groups within the gestational age subgroups for other outcomes.

Type of magnesium preparation given

All four trials used magnesium sulphate.

Dose of magnesium given (Graphs 6.01 to 6.07)

Loading doses were either 4 g or 6 g, while the major protocol difference between studies was in the maintenance dose, ranging from nil (Marret 2006 and Mittendorf 2002 neuroprotective), to 1 g per hour (Crowther 2003 and Magpie 2006), to 2 to 3 g per hour (Mittendorf 2002 2002 tocolytic and Rouse 2008). There was a significant reduction in cerebral palsy in any loading and any maintenance subgroup (RR 0.68; 95% CI 0.51 to 0.91; three trials; 5292 infants), largely due to the results from Rouse 2008. There were no substantial differences between treatment groups within these various dosing regimens for the other outcomes.

Mode of administration of magnesium sulphate

All five trials involved the use of intravenous magnesium, at least for the loading dose. Results for the subgroup of women who received intramuscular magnesium sulphate as maintenance were not reported from the Magpie study (Magpie 2006).

Retreatment with magnesium sulphate permitted (Graphs 7.01 to 7.07)

Retreatment was permitted in the Rouse 2008 trial but not in three trials (Crowther 2003; Magpie 2006 and Marret 2006) or the 'neuroprotective' arm in the Mittendorf 2002 trial. It is unclear whether retreatment was permitted in the 'tocolytic' arm in the Mittendorf 2002 trial. Cerebral palsy showed a significant reduction with magnesium from the one trial in the retreatment

permitted subgroup (RR 0.59; 95% CI 0.40 to 0.85; one trial; 2444 infants).

Time prior to preterm birth magnesium sulphate given

The time prior to expected preterm birth the magnesium sulphate or placebo was stated to be given, varied in the study protocols. For [Crowther 2003](#) and [Marret 2006](#) the trial medication was given to women where birth was planned or expected within 24 hours. This was the same for women with an indicated preterm birth in [Rouse 2008](#) but not for the women at high risk of spontaneous preterm birth. For [Magpie 2006](#) and [Mittendorf 2002](#) there was no specific time prior to anticipated birth treatment was given.

DISCUSSION

In women who are at risk of preterm birth, the available evidence shows that giving antenatal magnesium sulphate therapy substantially improves their unborn baby's chance of survival, free of cerebral palsy. The five included randomised trials with 5645 infants show an absolute risk of 3.7% for babies exposed to antenatal magnesium sulphate therapy and 5.4% for babies unexposed, giving an absolute risk reduction of 1.7% in cerebral palsy. The number of women need to treat to benefit one baby is 63 (95% confidence interval 43 to 155), assuming an event rate of 5% in the no magnesium group.

The body of evidence available is largest where the indication for use of magnesium sulphate was for neuroprotection of the baby. The neuroprotective intent subgroup is the only one showing a statistical benefit overall in the reduction of cerebral palsy.

In keeping with the benefit seen on risk of cerebral palsy there is evidence from three trials now ([Crowther 2003](#); [Magpie 2006](#); [Rouse 2008](#)) of a neuroprotective benefit of antenatal magnesium sulphate therapy on the outcomes of substantial gross motor dysfunction. In the original trials this was a secondary outcome.

Overall, apart from cerebral palsy and substantial gross motor dysfunction there were no significant differences found in the risk of other neurological impairments (developmental delay or intellectual impairment, blindness, deafness) or major neurological disabilities.

There are limitations in this meta-analysis related to long-term neurological outcomes, in part because of methodological limitations of the included studies. Only two studies ([Crowther 2003](#) and [Rouse 2008](#)) were designed to assess long-term effects of magnesium sulphate as the primary outcome. Details of the diagnosis of cerebral palsy were unclear in the study of [Mittendorf 2002](#). In the studies with the outcome of cerebral palsy, children have been assessed early in childhood, usually at two years of age or earlier, when the diagnosis is not always certain ([Stanley 1992](#)). Reassessment of neurological outcomes later in childhood, at least into

school age, in all studies is desirable. Children in the [Crowther 2003](#) study are being reassessed at eight to nine years of age; results should be available in 2009.

The meta-analysis shows no difference in paediatric mortality (fetal and later deaths) between the magnesium or no magnesium treatment groups. This is reassuring given the earlier reported concern about higher paediatric mortality that led to the termination of the Mittendorf study. Substantial heterogeneity between the studies is still evident for deaths of live born infants largely due to the Mittendorf study ([Mittendorf 2002](#)).

Secondary outcomes were not significantly different between treatment groups, but these were not always reported and there were thus less data to examine for effects of magnesium sulphate on these alternative outcomes. As further data become available it is hoped that the effects, if any, of magnesium sulphate therapy on secondary outcomes will become clearer.

The expected higher rate of maternal side effects with magnesium sulphate was observed, but major maternal complications were rare and not significantly different between treatment groups. Different strategies to reduce maternal side effects during administration of magnesium sulphate therapy require evaluation.

Three trials ([Crowther 2003](#); [Magpie 2006](#); [Rouse 2008](#)) reported on need for cessation of maternal therapy. Significantly more women in the magnesium sulphate group had their therapy stopped compared with women in the placebo group (8.0% versus 2.4%, $p < 0.0001$). Further studies are required that assess strategies to reduce maternal side effects during administration of magnesium sulphate therapy.

In the prespecified subgroup analyses:

- when the intent of giving the magnesium sulphate was for neuroprotection, the magnesium group, compared with placebo, showed a significant reduction in the risk of death or cerebral palsy in favour of the magnesium group (RR 0.85; 95% CI 0.74 to 0.98; four trials; 4446 infants) and a significant reduction in substantial gross motor dysfunction (RR 0.60; 95% CI 0.43 to 0.83; three trials; 4387 children).
- for all five studies who recruited women at less than 34 weeks gestation there was a reduction in cerebral palsy (RR 0.69; 95% CI 0.54 to 0.88; five trials; 5357 infants).
- for studies with any loading and any maintenance, there was a significant reduction in cerebral palsy, largely due to the results from [Rouse 2008](#).
- for the one trial where retreatment was permitted [Rouse 2008](#) cerebral palsy showed a significant reduction with magnesium.

The five included trials show diversity in their inclusion and exclusion criteria; reasons women were at risk of preterm birth (preterm labour, preterm prelabour rupture of the membranes, preeclampsia), gestational ages when women were eligible; time of treatment prior to expected preterm birth; and drug treatment protocol (differences in loading dose given whether loading alone, or loading followed by maintenance, whether retreatment was permitted).

Differences in gestational age at birth between the magnesium and no magnesium groups are unlikely to explain the therapeutic benefits of antenatal magnesium sulphate. In the three studies where neuroprotection of the fetus was the primary aim and where data were available, there were negligible differences in mean gestational age at delivery between the magnesium and no magnesium groups (Crowther 2003 mean difference two days; Marret 2006 mean difference zero days; Rouse 2008 mean difference 0.1 weeks). In the neuroprotective arm of the fourth trial (Mittendorf 2002), the proportions delivering <28 weeks' gestational age were 21% (6/28) in the magnesium group and 18% (5/28) in the no magnesium group.

To examine in a more powerful analysis whether antenatal magnesium sulphate treatment is more effective in our prespecified subgroups (of reasons for preterm birth, singleton or multiple pregnancy, gestational age prior to birth treatment given, dosage, maintenance, retreatment) individual patient data meta-analysis may be helpful (Stewart 2002). Support from the individual trialists to contribute their data will need to be gained.

Given the positive findings that antenatal magnesium sulphate reduces the risk of cerebral palsy, further studies are required to clarify how magnesium sulphate works, who should receive magnesium sulphate medication and how best the treatment should be given. Studies comparing the dose, timing of administration and whether maintenance magnesium therapy is required are needed and also whether the magnesium sulphate treatment should be repeated.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence now supports a role for antenatal magnesium sulphate therapy in women at risk of preterm birth as a neuroprotective agent against cerebral palsy for their baby.

Implications for research

Given the beneficial effects of magnesium sulphate reducing the risk of cerebral palsy and on substantial gross motor dysfunction in early childhood, the children in any randomised controlled trial (RCT) should be reassessed later in childhood to determine the presence or absence of other potentially important neurological effects, particularly on motor or cognitive function.

Different strategies to reduce maternal side effects during administration of magnesium sulphate therapy require evaluation.

Studies comparing the dose, timing of administration and whether maintenance magnesium therapy is required are needed and whether the magnesium sulphate treatment should be repeated.

Clarification of who may benefit most may be assisted by individual patient meta-analysis of the data from the available trials.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is 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.

REFERENCES

References to studies included in this review

Crowther 2003 {published and unpublished data}

* Crowther CA, Hiller JE, Doyle LW, Haslam RR for the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMgS)4 Collaborative Group. Effect of magnesium sulfate given for neuroprotection before preterm birth. *JAMA* 2003;**290**(20):2669–76.

Crowther CA, Hiller JE, Doyle LW, Haslam RR for the Australasian Collaborative Trial of Magnesium Sulphate (ACTOMg SO4) Collaborative Group. Effect of magnesium sulfate given for neuropro-

tection before preterm birth: a randomized controlled trial. *JAMA* 2003;**290**(20):2669–76.

Crowther CA, Hiller JE, Doyle LW for the ACTOMgSO4 Collaborators Group. Does prenatal magnesium sulphate reduce the risk of mortality and cerebral palsy in infants born at less than 30 weeks' gestation? - The ACTOMgSO4 trial. Perinatal Society of Australia and New Zealand 7th Annual Congress; 2003 March 9-12; Tasmania, Australia. 2003:A4.

Paradisis M, Evans N, Osborn D, Kluckow M, ACTOMgSO4 Collaborators Group. The effect of antenatal magnesium sulphate on

- early systemic blood flow in very preterm infants. *Pediatric Research* 2004;**55** Suppl:114.
- Smith CA, Crowther CA, Willson K, Hiller JE, Doyle LW. Placental transfer of magnesium sulphate: a randomised placebo controlled trial. Perinatal Society of Australia and New Zealand 7th Annual Congress; 2003 March 9-12; Tasmania, Australia. 2003:P48.
- Magpie 2006 {unpublished data only}**
- Magpie Trial Follow Up Study Collaborative Group. The Magpie Trial: a randomised trial comparing magnesium sulphate with placebo for pre-eclampsia. Outcome for children at 18 months. *BJOG: an international journal of obstetrics and gynaecology* 2007;**114** (3):289-99.
- Marret 2006 {published and unpublished data}**
- Marret S, Marpeau L, Astruc D, Cambonie G, Follet C, Benichou J. Prenatal magnesium sulfate (MgSO₄) and follow up at two years of age in preterm infants: the randomised controlled PREMAG trial. Pediatric Academic Societies Annual Meeting; 2007 May 5-8; Toronto, Canada. 2007.
- Marret S, Marpeau L, Benichou J. Benefit of magnesium sulfate given before very preterm birth to protect infant brain. *Pediatrics* 2008; **121**(1):225-6.
- Marret S, Marpeau L, Follet-Bouhamed C, Cambonie G, Astruc D, Delaporte B, et al. for the PREMAG Group. Effect of magnesium sulphate on mortality and neurologic morbidity of the very=preterm newborn with two-year neurological outcome: results of the prospective PREMAG trial [Effet du sulfate de magnésium sur la mortalité et la morbidité neurologique chez le prématuré de moins de 33 semaines, avec recul à deux ans: résultats de l'essai prospectif multicentrique contre placebo PREMAG]. *Gynécologie Obstétrique & Fertilité* 2008;**36**:278-88.
- * Marret S, Marpeau L, Zupan-Simunek V, Eurin D, Lévêque C, Hellot MF, et al. Magnesium sulfate given before very-preterm birth to protect infant brain: the randomized, controlled PREMAG trial. *BJOG: an international journal of obstetrics and gynaecology* 2007; Vol. 114, issue 3:310-8.
- Marret S, Zupan V, Marpeau L, Adde-Michel C, Benichou J, the Premag Trial Group. Prenatal magnesium sulphate (MgSO₄) and neuroprotection in preterm infants: a randomized controlled trial. Pediatric Academic Societies Annual Meeting; 2005 May 14-17; Washington DC, USA. 2005.
- Mittendorf 2002 {published data only}**
- Mittendorf R, Bentz L, Borg M, Roizen N. Does exposure to antenatal magnesium sulfate prevent cerebral palsy?. *American Journal of Obstetrics and Gynecology* 2000;**182**(1 Pt 2):S20.
- Mittendorf R, Bentz L, Kohn J, Covert R. Use of antenatal magnesium sulfate does not seem to prevent intraventricular hemorrhage. *American Journal of Obstetrics and Gynecology* 2000;**182**(1 Pt 2):S34.
- Mittendorf R, Besinger R, Santillan M, Gianopoulos J. When used in circumstance of preterm labor, is there a paradoxical effect of varying exposures to magnesium sulfate (MgSO₄) on the developing human brain?. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S65.
- Mittendorf R, Covert R, Boman J, Khoshnood B, Lee KS, Siegler M. Is tocolytic magnesium sulphate associated with increased total paediatric mortality?. *Lancet* 1997;**350**(9090):1517-8.
- Mittendorf R, Covert R, Elin R, Pryde P, Khoshnood B, Sun-Lee K. Umbilical cord serum ionized magnesium level and total pediatric mortality. *Obstetrics & Gynecology* 2001;**98**:75-8.
- Mittendorf R, Dambrosia J, Dammann O, Pryde PG, Lee KS, Ben-Ami TE, et al. Association between maternal serum ionized magnesium levels at delivery and neonatal intraventricular hemorrhage. *Journal of Pediatrics* 2002;**140**(5):540-6.
- Mittendorf R, Dambrosia J, Khoshnood B, Lee KS, Pryde P, Yousefzadeh D. Association between magnesium and intraventricular haemorrhage. *American Journal of Obstetrics and Gynecology* 2001; **184**(1):S188.
- Mittendorf R, Dambrosia J, Khoshnood B, Lee K-S, Pryde P, Yousefzadeh D. Magnesium sulfate is no more efficacious than other tocolytic agents. *American Journal of Obstetrics and Gynecology* 2001; **184**(1):S188.
- * Mittendorf R, Dambrosia J, Pryde PG, Lee KS, Gianopoulos JG, Besinger RE, et al. Association between the use of antenatal magnesium sulfate in preterm labor and adverse health outcomes in infants. *American Journal of Obstetrics and Gynecology* 2002;**186**(6):1111-8.
- Mittendorf R, Janeczek S, Macmillan W, Gianopoulos J, Besinger R, Karlman R, et al. Mechanisms of mortality in the magnesium and neurologic endpoints trial (magnet trial): fetal inflammatory response syndrome (firs). *American Journal of Obstetrics and Gynecology* 2001;**185**(6 Suppl):S151.
- Mittendorf R, Kuban K, Pryde PG, Gianopoulos JG, Yousefzadeh D. Antenatal risk factors associated with the development of lenticulostriate vasculopathy (lsv) in neonates. *Journal of Perinatology* 2005; **25**(2):101-7.
- Mittendorf R, Pryde P, Khoshnood B, Lee KS. If tocolytic magnesium sulfate is associated with excess total pediatric mortality, what is its impact?. *Obstetrics & Gynecology* 1998;**92**(2):308-11.
- Mittendorf R, Pryde P, Lee KS, Besinger R, Macmillan W, Karlman R, et al. Umbilical cord serum ionized magnesium levels at delivery are not correlated with neuroprotection in childhood. *American Journal of Obstetrics and Gynecology* 2002;**187**(6 Pt 2):S74.
- Mittendorf R, Pryde P, Lee K-S, Besinger R, MacMillan W, Karlman R, et al. Coagulase negative staphylococci cultured from the placental chorioamnion space at delivery are associated with lower bayley scores. *American Journal of Obstetrics and Gynecology* 2002;**187**(6 Pt 2):S131.
- Santillan M, Besinger RE, Gianopoulos JG, Mittendorf R. An inverse correlation between umbilical cord blood ionized magnesium (IMG) and interleukin-6 (IL-6) levels could not be confirmed in the human. *American Journal of Obstetrics and Gynecology* 2005;**193**(6 Suppl):S183.
- Rouse 2008 {published data only}**
- NICHD. Beneficial effects of antenatal magnesium sulfate. ClinicalTrials.gov (<http://clinicaltrials.gov/>) (accessed 11 January 2007).
- Rouse D. 1: A randomized controlled trial of magnesium sulfate for the prevention of cerebral palsy. *American journal of obstetrics and gynecology* (0002-9378) 2007;**197**(6):S2. [DOI: 10.1016/j.ajog.2007.10.002]
- * Rouse D, Hirtz D, Thom E, Varner M, Alexander J, Spong C, Mercer B, Iams J, Wapner R, Sorokin Y, Harper M, Thorp J, Ramin S, Malone F, Carpenter M, Miodovnik A, Moawad A, O'Sullivan M, Peaceman A, Hankins G, Langer O, Caritis S, Roberts J. Magnesium sulfate for the prevention of cerebral palsy. *New England Journal of Medicine* 2008;**359**:895-905.

Additional references

Amiel-Tison 2004

Amiel-Tison C, Gosselin J, eds. *Démarche clinique en Neurologie du développement*. Paris: Masson, 2004.

Bayley 1969

Bayley N. *Bayley Scales of Infant Development*. San Antonio, TX: The Psychological Corporation, 1969.

Bayley 1993

Bayley N. *Bayley Scales of Infant Development*. Second Edition. San Antonio, TX: The Psychological Corporation, 1993.

Blasco 1994

Blasco PA. Primitive reflexes: their contribution to the early detection of cerebral palsy. *Clinical Pediatrics* 1994;**33**:388–97.

Canterino 1999

Canterino JC, Verma UL, Visintainer PF, Figueroa R, Klein SA, Tejani NA. Maternal magnesium sulfate and the development of neonatal periventricular leukomalacia and intraventricular hemorrhage. *Obstetrics & Gynecology* 1999;**93**:396–402.

Capute 1985

Capute AJ, Shapiro BK. The motor quotient: a method for the early detection of motor delay. *American Journal of Diseases of Children* 1985;**139**:940–2.

Crowther 1998

Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour. *Cochrane Database of Systematic Reviews* 1998, Issue 1. [DOI: 10.1002/14651858.CD000940]

Crowther 2002

Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database of Systematic Reviews* 2002, Issue 4. [DOI: 10.1002/14651858.CD001060]

Doyle 2001

Doyle LW, for the 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.

Drummond 2002

Drummond PM, Colver AF. Analysis by gestational age of cerebral palsy in singleton births in north-east England 1970–94. *Paediatric and Perinatal Epidemiology* 2002;**16**:172–80.

Duley 2000

Duley L, Gulmezoglu AM. Magnesium sulphate versus lytic cocktail for eclampsia. *Cochrane Database of Systematic Reviews* 2000, Issue 3. [DOI: 10.1002/14651858.CD002960]

Duley 2003a

Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD000127]

Duley 2003b

Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD000128]

Duley 2003c

Duley L, Gülmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database of Systematic Reviews* 2003, Issue 2. [DOI: 10.1002/14651858.CD000025]

Espinoza 1991

Espinoza MI, Parer JT. Mechanisms of asphyxial brain damage, and possible pharmacologic interventions, in the fetus. *American Journal of Obstetrics and Gynecology* 1991;**164**(6 Pt 1):1582–9.

Finesmith 1997

Finesmith RB, Roche K, Yellin PB, Walsh KK, Shen C, Zeglis M, et al. Effect of magnesium sulfate on the development of cystic periventricular leukomalacia in preterm infants. *American Journal of Perinatology* 1997;**14**(5):303–7.

Grether 1998

Grether JK, Hoogstrate J, Selvin S, Nelson KB. Magnesium sulfate tocolysis and risk of neonatal death. *American Journal of Obstetrics and Gynecology* 1998;**178**(1 Pt 1):1–6.

Grether 2000

Grether JK, Hoogstrate J, Walsh-Greene E, Nelson KB. Magnesium sulfate for tocolysis and risk of spastic cerebral palsy in premature children born to women without preeclampsia. *American Journal of Obstetrics and Gynecology* 2000;**183**(3):717–25.

Hagberg 2001

Hagberg B, Hagberg G, Beckung E, Uvebrant P. Changing panorama of cerebral palsy in Sweden. VIII. Prevalence and origin in the birth-year period 1991–94. *Acta Paediatrica* 2001;**90**:271–7.

Hauth 1995

Hauth JC, Goldenberg RL, Nelson KG, DuBard MB, Peralta MA, Gaudier FL. Reduction of cerebral palsy with maternal MgSO₄ treatment in newborns weighing 500–1000g [abstract]. *American Journal of Obstetrics and Gynecology* 1995;**172**(1 Pt 2):419.

Higgins 2008

Higgins JPT, Green S, editors. *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.0 [updated February 2008]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Himmelman 2005

Himmelman K, Hagberg G, Beckung E, Hagberg B, Uvebrant P. The changing panorama of cerebral palsy in Sweden. IX. Prevalence and origin in the birth-year period 1995–1998. *Acta Paediatrica* 2005;**94**:287–94.

Hutton 1994

Hutton JL, Cooke T, Pharoah TOD. Life expectancy in children with cerebral palsy. *BMJ* 1994;**309**:431–5.

Kimberlin 1998

Kimberlin DF, Hauth JC, Goldenberg RL, Bottoms SF, Iams JD, Mercer B, et al. The effect of maternal magnesium sulfate treatment on neonatal morbidity in < or = 1000-gram infants. *American Journal of Perinatology* 1998;**15**:635–41.

Kuban 1992

Kuban KCK, Leviton A, Pagano M, Fenton T, Strasfeld R, Wolff M. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. *Journal of Child Neurology* 1992;**7**:70–6.

Kuban 1994

Kuban K, Leviton A, Pagano M, Fenton T, Strasfeld R, Wolff M. Maternal toxemia is associated with reduced incidence of germinal matrix hemorrhage in premature babies. *Journal of Child Neurology* 1992;**7**:70–6.

Levene 1995

Levene M, Blennow M, Whitelaw A, Hanko E, Fellman V, Hartley R. Acute effects of two different doses of magnesium sulphate in infants with birth asphyxia. *Archives of Disease in Childhood. Fetal Neonatal Edition* 1995;**73**:F174–F177.

Lipsitz 1971

Lipsitz P. The clinical and biochemical effects of excess magnesium in the newborn. *Pediatrics* 1971;**47**:501–9.

Lorenz 1998

Lorenz JM, Wooliever DE, Jetton JR, Paneth N. A quantitative review of mortality and developmental disability in extremely premature newborns. *Archives of Pediatrics and Adolescent Medicine* 1998;**152**:425–35.

Makrides 2001

Makrides M, Crowther CA. Magnesium supplementation in pregnancy. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD000937]

Martin 2007

Martin JA, Hamilton BE, Sutton PD, Ventura SJ, Menacker F, Kirmeyer S, et al. Births: final data for 2005. *National Vital Statistics Reports* 2007;**56**(6):1–103.

McDonald 1990

McDonald JW, Silverstein FS, Johnston MV. Magnesium reduces N-methyl-D-aspartate (NMDA)-mediated brain injury in perinatal rats. *Neuroscience Letters* 1990;**109**:234–9.

Nelson 1995

Nelson KB, Grether JK. Can magnesium sulfate reduce the risk of cerebral palsy in very low birthweight infants?. *Pediatrics* 1995;**95**:1–10.

O'Shea 1998

O'Shea TM, Klinepeter KL, Meis PJ, Dillard RG. Intrauterine infection and the risk of cerebral palsy in very low-birthweight infants. *Paediatric and Perinatal Epidemiology* 1998;**12**(1):72–83.

Oxford Register 2001

Oxford Register of Early Childhood Impairments. *National Perinatal Epidemiology Unit 2001 Annual Report*. Oxford: Institute of Health Sciences, 2001.

Palisano 1997

Palisano R, Rosenbaum P, Walter S, Russell D, Wood E, Galuppi B. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Developmental Medicine and Child Neurology* 1997;**39**(4):214–23.

Paneth 1997

Paneth N, Jetton J, Pinto-Martin J, Susser M. Magnesium sulfate in labor and risk of neonatal brain lesions and cerebral palsy in low birth weight infants. The Neonatal Brain Hemorrhage Study Analysis Group. *Pediatrics* 1997;**99**(5):E1.

Perlman 1994

Perlman J, Fernandez C, Gee J, LeVeno K, Risser R. Magnesium sulphate administered to mothers with pregnancy-induced hyperten-

sion is associated with a reduction in periventricular-intraventricular hemorrhage [abstract]. *Pediatric Research* 1994;**37**:231A.

Petterson 1993

Petterson B, Nelson KB, Watson L, Stanley F. Twins, triplets and cerebral palsy in births in Western Australian in the 1980s. *BMJ* 1993;**307**:1239–43.

Pharoah 1998

Pharoah PO, Cooke T, Cooke RW, Rosenbloom L. Epidemiology of cerebral palsy in England and Scotland 1984–1989. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 1998;**79**:F21–F25.

RevMan 2008

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Schendel 1996

Schendel DE, Berg CJ, Yeargin-Allsopp M, Boyle CA, Decoufle P. Prenatal magnesium sulfate exposure and the risk for cerebral palsy or mental retardation among very low-birth-weight children aged 3 to 5 years. *JAMA* 1996;**276**(22):1805–10.

SCPE 2000

Surveillance of Cerebral Palsy in Europe. Surveillance of cerebral palsy in Europe: a collaboration of cerebral palsy surveys and registers. *Developmental Medicine and Child Neurology* 2000;**42**(12):816–24.

Sibai 2003

Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. *Obstetrics & Gynecology* 2003;**102**:181–92.

Stanley 1992

Stanley FJ, Watson L. Trends in perinatal mortality and cerebral palsy in Western Australia, 1967 to 1985. *BMJ* 1992;**304**(6843):1658–63.

Stanley 1994

Stanley FJ. The aetiology of cerebral palsy. *Early Human Development* 1994;**36**:81–8.

Stewart 2002

Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Evaluation and the Health Professions* 2002;**25**(1):76–97.

Surman 2003

Surman G, Newdick H, Johnson A. Cerebral palsy rates among low-birthweight infants fell in the 1990s. *Developmental Medicine and Child Neurology* 2003;**45**:456–62.

Vermeulen 2001

Vermeulen GM, Bruinse HW, de Vries LS. Perinatal risk factors for adverse neurodevelopmental outcome after spontaneous preterm birth. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 2001;**99**:207–12.

VICS 1997

The Victorian Infant Collaborative Study Group. Outcome at 2 years of children 23–27 weeks' gestation born in Victoria in 1991–92. *Journal of Paediatric Child Health* 1997;**33**(2):161–5.

Weintraub 2001

Weintraub Z, Solovechick M, Reichman B, Rotschild A, Waisman D, Davkin O, et al. Effect of maternal tocolysis on the incidence of severe periventricular/intraventricular haemorrhage in very low birthweight

infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2001;**85**:F13–7.

Winter 2002

Winter S, Autry A, Boyle C, Yeargin-Allsop M. Trends in the prevalence of cerebral palsy in a population-based study. *Pediatrics* 2002; **110**:1220–5.

Wiswell 1996

Wiswell TE, Graziani LJ, Caddell JL, Vecchione N, Stanley C, Spitzer AR. Maternally administered magnesium sulphate protects against early brain injury and long-term adverse neurodevelopmental outcomes in preterm infants. A prospective study. *Pediatric Research* 1996;**39**:253A.

References to other published versions of this review

Keirse 1995a

Keirse M. Magnesium sulphate in preterm labour. [revised 07 April 1994]. Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: *The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]*. The Cochrane Collaboration. Issue 2. Oxford: Update Software, 1995.

Keirse 1995b

Keirse M. Magnesium sulphate and betamimetics for tocolysis in preterm labour [revised 07 April 1994]. Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: *The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]*. The Cochrane Collaboration; Issue 2. Oxford: Update Software, 1995.

Keirse 1995c

Keirse M. Magnesium sulphate vs betamimetics for tocolysis in preterm labour. [revised 07 April 1994]. Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: *The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]*. The Cochrane Collaboration; Issue 2. Oxford: Update Software, 1995.

Keirse 1995d

Keirse M. Magnesium sulphate vs ethanol for tocolysis in preterm labour. [revised 07 April 1994]. Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: *The Cochrane Pregnancy and Childbirth Database [database on disk and CDROM]*. The Cochrane Collaboration; Issue 2. Oxford: Update Software, 1995.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Crowther 2003

Methods	Randomised trial.
Participants	1062 women (1255 fetuses) < 30 weeks' gestation likely to deliver within 24 hours. Exclusions: already received magnesium sulphate or magnesium sulphate contraindicated.
Interventions	Active treatment - infusion of 4 g magnesium sulphate over 20 minutes, then 1 g/hour until delivery or for 24 hours, whichever came first. Placebo group - equal volume of 0.9% saline.
Outcomes	Primary outcomes: total paediatric mortality (stillbirths, deaths during the primary hospitalisation and after discharge) up to 2 years of age, cerebral palsy, and combined outcome of death or cerebral palsy. Secondary infant outcomes: major IVH, (grade 3 or 4), cystic periventricular leucomalacia, neurosensory disability (severe - any of severe cerebral palsy (not likely to walk), blindness, or severe developmental delay (MDI < -3 SD); moderate - moderate cerebral palsy (not walking at 2 years, but likely to do so), deafness, moderate developmental delay (MDI -3 SD to < -2 SD); mild - mild cerebral palsy (walking at 2 years) or mild developmental delay (MDI - 2 SD to < -1 SD), substantial gross motor dysfunction (not walking at 2 years of age). Maternal outcomes: adverse cardiovascular and respiratory effects of infusion, postpartum haemorrhage.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central computer-generated randomisation.
Allocation concealment?	Yes	Central telephone randomisation.
Blinding? All outcomes	Yes	Intervention and outcome assessments blinded.
Incomplete outcome data addressed? All outcomes	Yes	Complete follow up for outcomes during primary hospitalisation; 99% of surviving infants traced to 2 years of age.
Free of selective reporting?	Yes	No indication of selective reporting.

Magpie 2006

Methods	Randomised trial.
Participants	1544 women (1593 fetuses) < 37 weeks' gestation with severe pre-eclampsia and randomised prior to delivery. Women were excluded if they had hypersensitivity to magnesium, hepatic coma, or myasthenia gravis. Data provided by the Magpie Investigators for a subset of the women who were < 37 weeks' gestational age and undelivered at the time of randomisation.
Interventions	Active treatment - magnesium sulphate dose 4 g intravenously over 10 to 15 minutes, followed by either 1 g/hour intravenously for 24 hours, or by 5 g every 4 hours intramuscularly for 24 hours.
Outcomes	Primary outcomes: neuroprotection of the mother (avoidance of eclampsia). Secondary endpoints included long-term outcomes for the children.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central computer-generated randomisation.
Allocation concealment?	Yes	Central randomisation.
Blinding? All outcomes	Yes	Intervention and outcome assessments were blinded.
Incomplete outcome data addressed? All outcomes	Unclear	Outcomes were given for 99.7% of mothers and 98.7% of fetuses enrolled. Approximately 2/3 of surviving children were selected for follow up, and of these children outcomes were determined for 73% (n = 3283), including those who died.
Free of selective reporting?	Yes	No indication of selective reporting.

Marret 2006

Methods	Randomised trial.
Participants	564 women (688 fetuses) in labour < 33 weeks' gestation. Exclusion criteria included fetal malformations, growth restriction, or chromosomal anomalies, and various maternal reasons.

Marret 2006 (Continued)

Interventions	4 g magnesium sulphate over 30 minutes (286 women; 354 infants). Placebo (isotonic 0.9% saline) (278 women; 341 infants).	
Outcomes	Primary outcomes: infant death or white matter injury on cranial ultrasound. Secondary outcomes included follow up of children at 2 years of age.	
Notes	Was stopped early due to dwindling recruitment (projected sample size was 1106 new-borns)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central computer-generated randomisation.
Allocation concealment?	Yes	Central randomisation.
Blinding? All outcomes	Unclear	Paediatricians who were blinded to treatment evaluated motor and cognitive functions; however, obstetricians and anaesthetists were not blinded.
Incomplete outcome data addressed? All outcomes	Unclear	573 women were randomised; 564 women with 688 infants were analysed. Of the 616 survivors, 606 infants were followed up (472 by clinical examination and 134 through parent telephone interview); and 10 were lost to follow up.
Free of selective reporting?	Yes	No indication of selective reporting.

Mittendorf 2002

Methods	Randomised trial.
Participants	149 women (165 fetuses) in preterm labour, with or without premature rupture of the membranes. Exclusion criteria: mothers with triplet or higher order gestations.
Interventions	“Tandem” randomisation: 1) eligible for aggressive tocolysis (cervix < = 4 cm dilation), magnesium sulphate tocolysis (n = 46), ‘other’ tocolysis (n = 46); 2) not eligible for tocolysis (cervix > 4 cm dilatation) neuroprotective magnesium sulphate (n = 29), saline control (n = 28).
Outcomes	Fetal and later mortality; CP; Death or CP; IVH.

Mittendorf 2002 (Continued)

Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not described.
Allocation concealment?	Unclear	Method not described.
Blinding? All outcomes	Unclear	Intervention: neuroprotective arm was blinded, but the tocolytic arm was not blinded. Cerebral palsy was assessed by a developmental paediatrician who was blind to the treatment allocation.
Incomplete outcome data addressed? All outcomes	Unclear	Losses to follow up not reported.
Free of selective reporting?	Unclear	Some outcomes not reported in sufficient detail; some possibility of selective reporting.

Rouse 2008

Methods	Randomised trial.
Participants	2241 women (2444 fetuses) at least 24 weeks but less than 32 weeks' gestation, at high risk of spontaneous birth due to ruptured membranes at 22 to 31 weeks' GA, or advanced preterm labor with dilatation 4 to 8 cm and intact membranes; also if an indicated preterm birth was anticipated within 24 hours (e.g. due to fetal growth restriction). Exclusions: not eligible if birth was anticipated within 2 hours or if cervical dilatation exceeded 8 cm. Not eligible if rupture of membranes prior to 22 weeks; obstetrician unwilling to intervene for fetal benefit; major fetal anomalies, or demise; hypertension or pre-eclampsia; maternal contraindications to magnesium sulphate e.g. severe pulmonary disorders; and receipt of intravenous magnesium sulphate within the prior 12 hours.
Interventions	Active treatment - magnesium sulphate dose 6 g intravenously over 20 to 30 minutes, followed by maintenance infusion of 2 g/hour. If delivery had not occurred after 12 hours and was no longer considered imminent the infusion was discontinued and resumed when delivery threatened. If at least 6 hours had transpired another loading dose was given. Re-treatment was withheld if preeclampsia or eclampsia developed, if the maternal or fetal condition had deteriorated such that the delay for re-treatment would be detrimental, or if the gestational age had reached 34 weeks. The placebo group received an 'identical-appearing placebo'.

Rouse 2008 (Continued)

Outcomes	Primary outcomes: the composite of 1) stillbirth or infant death by 1 year of age, or 2 years of age) moderate or severe cerebral palsy as assessed at or beyond 2 years of age (corrected). Secondary outcomes included maternal outcomes and complications, adverse events potentially attributable to the study intervention, neonatal complications, cerebral palsy at 2 years classified as mild, moderate or severe; stillbirth; infant death; and scores on the Bayley Scales of Infant development-II.	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Central computer-generated randomisation.
Allocation concealment?	Yes	Central (pharmacy) randomisation.
Blinding? All outcomes	Yes	Interventions and outcome assessments blinded.
Incomplete outcome data addressed? All outcomes	Yes	The follow-up rate of surviving infants was 95% (2137/2255).
Free of selective reporting?	Yes	No indication of selective reporting.

CP: cerebral palsy
 IVH: intraventricular haemorrhage
 MDI: Mental Developmental Index
 SD: standard deviation
 GA: gestational age

DATA AND ANALYSES

Comparison 1. Magnesium versus no magnesium

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	5	6145	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
1.1 Neuroprotective intent	4	4446	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.12]
1.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.93, 1.31]
1.3 Other intent (tocolytic)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	15.79 [0.93, 266.72]
2 Fetal death	5	6145	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.77, 1.21]
2.1 Neuroprotective intent	4	4446	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.42, 1.46]
2.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.78, 1.27]
2.3 Other intent (tocolytic)	1	106	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3 Livebirth deaths	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 To latest age of follow up - neuroprotective intent	4	4446	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.77, 1.18]
3.2 To latest age of follow up - other intent: maternal neuroprotective (pre-eclampsia)	1	1593	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.96, 1.68]
3.3 To latest age of follow up - other intent: tocolytic	1	106	Risk Ratio (M-H, Random, 95% CI)	15.79 [0.93, 266.72]
3.4 To latest age of follow up - any intent	5	6145	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.81, 1.40]
3.5 During primary hospitalisation - neuroprotective intent	3	4387	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.23]
3.6 During primary hospitalisation - other intent: maternal neuroprotective (pre-eclampsia)	1	1593	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.92, 1.73]
3.7 During primary hospitalisation - any intent	4	5980	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.84, 1.29]
4 Cerebral palsy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 Neuroprotective intent: any CP	4	4446	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.55, 0.91]
4.2 Neuroprotective intent: mild CP	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.52, 1.04]
4.3 Neuroprotective intent: moderate CP	2	1943	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.34, 1.28]
4.4 Neuroprotective intent: moderate/severe CP	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.44, 0.92]

4.5 Neuroprotective intent: severe CP	2	1943	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.37, 1.82]
4.6 Other intent: maternal neuroprotective (pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.08, 2.05]
4.7 Other intent: tocolytic	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.13 [0.01, 2.51]
4.8 Any CP: any intent	5	6145	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.87]
5 Any neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
5.1 Neuroprotective intent	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
5.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.34, 1.74]
6 Substantial gross motor dysfunction	4	5980	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.85]
6.1 Neuroprotective intent	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.43, 0.83]
6.2 Other intent: maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	2.99 [0.12, 73.26]
7 Blindness	3	3536	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.17, 3.30]
7.1 Neuroprotective intent	2	1943	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.14, 6.90]
7.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.05, 5.48]
8 Deafness	3	3536	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.24, 2.56]
8.1 Neuroprotective intent	2	1943	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.05, 4.96]
8.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.06, 15.90]
9 Developmental delay or intellectual impairment	4	5980	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.09]
9.1 Neuroprotective intent	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.09]
9.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.32, 2.01]
10 Major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
10.1 Neuroprotective intent	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.51]
10.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.30, 1.60]
11 Death or cerebral palsy	5	6145	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.12]
11.1 Neuroprotective intent	4	4446	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.74, 0.98]
11.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.92, 1.29]
11.3 Other intent (tocolytic)	1	106	Risk Ratio (M-H, Random, 95% CI)	2.47 [0.69, 8.81]
12 Death or any neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.11]
12.1 Neuroprotective intent	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
12.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.92, 1.28]

13 Death or substantial gross motor dysfunction	4	5980	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.12]
13.1 Neuroprotective intent	3	4387	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 1.00]
13.2 Other intent (maternal neuroprotective - pre-eclampsia)	1	1593	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.94, 1.32]
14 Death or major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
14.1 Neuroprotective intent	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
14.2 Other intent (maternal neuroprotective (pre-eclampsia))	1	1593	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.92, 1.27]
15 Maternal mortality	4	5411	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.51, 3.07]
16 Maternal cardiac arrest	4	5411	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.04, 3.26]
17 Maternal respiratory arrest	4	5411	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.25]
18 Cessation of maternal therapy	3	4847	Risk Ratio (M-H, Fixed, 95% CI)	3.26 [2.46, 4.31]
19 Intraventricular haemorrhage	4	4552	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.08]
20 Intraventricular haemorrhage 3/4	2	3699	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.13]
21 Periventricular leucomalacia	4	4552	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.68, 1.28]
22 Apgar score < 7 at 5 minutes	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.18]
23 Neonatal convulsions	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.56, 1.13]
24 Neonatal hypotonia	1	2444	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.77, 1.36]
25 Ongoing respiratory support	3	4387	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.89, 1.00]
26 Chronic lung disease	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 Oxygen at 28 days	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.94, 1.22]
26.2 Oxygen at 36 weeks	2	1943	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.95, 1.32]
27 Maternal hypotension	2	1626	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.09, 2.09]
28 Maternal tachycardia	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.03, 2.29]
29 Maternal respiratory depression	2	3303	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.83, 2.07]
30 Postpartum haemorrhage	2	1626	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.12]
31 Caesarean birth	4	5411	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
32 Mother admitted to intensive care unit	2	2606	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.54, 1.47]
33 Duration of mother's hospital stay (days)	2	2606	Mean Difference (IV, Fixed, 95% CI)	0.17 [-0.18, 0.53]
34 Duration of primary hospital stay for babies (days)	2	2828	Mean Difference (IV, Random, 95% CI)	-0.52 [-4.15, 3.11]

Comparison 2. Studies with lowest risk of bias only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality	2	3699	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.69, 1.33]
2 Cerebral palsy	2	3699	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.52, 0.91]
3 Neurological impairment	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
4 Major neurological disability	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.51]
5 Death or cerebral palsy	2	3699	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 1.00]

6 Death or neurological impairment	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
7 Death or major neurological disability	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]

Comparison 3. Single or multiple pregnancy subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	3	4984	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.85, 1.26]
1.1 Single	3	4256	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.85, 1.20]
1.2 Multiple	3	728	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.68, 2.18]
2 Cerebral palsy	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.22]
2.1 Single	2	2321	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.57, 1.49]
2.2 Multiple	2	527	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.21, 1.25]
3 Neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]
3.1 Single	2	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.88, 1.28]
3.2 Multiple	2	527	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.61, 1.21]
4 Major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
4.1 Single	2	2321	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.87, 1.59]
4.2 Multiple	2	527	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.44, 1.37]
5 Death or cerebral palsy	2	2848	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.24]
5.1 Single	2	2321	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.82, 1.14]
5.2 Multiple	2	527	Risk Ratio (M-H, Random, 95% CI)	1.14 [0.45, 2.92]
6 Death or neurological impairment	2	2848	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.86, 1.16]
6.1 Single	2	2321	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.90, 1.12]
6.2 Multiple	2	527	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.56, 2.65]
7 Death or major neurological disability	2	2848	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.85, 1.22]
7.1 Single	2	2321	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.89, 1.16]
7.2 Multiple	2	527	Risk Ratio (M-H, Random, 95% CI)	1.20 [0.53, 2.71]

Comparison 4. High antenatal corticosteroids

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	4	4493	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.70, 1.32]
2 Cerebral palsy	4	4493	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.86]
3 Neurological impairment	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
4 Major neurological disability	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.86, 1.51]
5 Death or cerebral palsy	4	4493	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.75, 0.99]

6 Death or neurological impairment	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.07]
7 Death or major neurological disability	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]

Comparison 5. Gestational age subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 < 34 weeks at randomisation	5	5357	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.80, 1.23]
1.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.67, 1.41]
2 Cerebral palsy	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 < 34 weeks at randomisation	5	5357	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.54, 0.88]
2.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.31]
3 Neurological impairment	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 < 34 weeks at randomisation	2	2060	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.86, 1.20]
3.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
4 Major neurological disability	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.1 < 34 weeks at randomisation	2	2060	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.83, 1.43]
4.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.85, 1.48]
5 Death or cerebral palsy	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 < 34 weeks at randomisation	5	5357	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.78, 1.10]
5.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.69, 1.38]
6 Death or neurological impairment	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 < 34 weeks at randomisation	2	2060	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.89, 1.08]
6.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.86, 1.24]
7 Death or major neurological disability	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 < 34 weeks at randomisation	2	2060	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.88, 1.11]
7.2 < 30 weeks at randomisation	2	1537	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.86, 1.24]

Comparison 6. Dose subgroup

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Loading dose 4 g (any or no maintenance)	4	3595	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.18]
1.2 Loading dose 6 g (any or no maintenance)	1	2444	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.87, 1.48]
1.3 No maintenance: any loading dose	2	747	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.35]
1.4 Any maintenance (high or low): any loading dose	3	5292	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.83, 1.24]
1.5 No maintenance: loading dose 4 g	2	747	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.57, 1.35]
1.6 Loading (4 g) and lower-dose maintenance (1 g/hour)	2	2848	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.71, 1.31]
1.7 Loading dose (4 g) and higher-dose maintenance (2-3 g/hour)	1	106	Risk Ratio (M-H, Random, 95% CI)	15.79 [0.93, 266.72]
1.8 Loading dose (6 g) and higher-dose maintenance (2-3 g/hour)	1	2374	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.92, 1.57]
2 Cerebral palsy	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Loading dose 4 g (any or no maintenance)	4	3595	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.10]
2.2 Loading dose 6 g (any or no maintenance)	1	2444	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.85]
2.3 No maintenance: any loading dose	2	747	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.18, 10.70]
2.4 Any maintenance (high or low): any loading dose	3	5292	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.51, 0.91]
2.5 No maintenance: loading dose 4 g	2	747	Risk Ratio (M-H, Random, 95% CI)	1.37 [0.18, 10.70]
2.6 Loading dose (4 g) and lower-dose maintenance (1 g/hour)	2	2848	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.54, 1.23]
2.7 Loading dose (4 g) and higher-dose maintenance (2-3 g/hour)	1	106	Risk Ratio (M-H, Random, 95% CI)	0.13 [0.01, 2.51]
2.8 Loading dose (6 g) and higher-dose maintenance (2-3 g/hour)	1	2444	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.40, 0.85]
3 Neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
3.1 Loading (4 g) and lower-maintenance dose (1 g/hour)	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
4 Major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]

4.1 Loading (4 g) and lower-maintenance dose (1 g/hour)	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
5 Death or cerebral palsy	5	6145	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.12]
5.1 Loading dose (4 g) only	2	747	Risk Ratio (M-H, Random, 95% CI)	1.45 [0.27, 7.72]
5.2 Loading (4 g) and lower-maintenance dose (1 g/hour)	2	2848	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.72, 1.26]
5.3 Loading (4 g) and higher-maintenance dose (2-3 g/hour): tocolytic intent	2	2550	Risk Ratio (M-H, Random, 95% CI)	1.22 [0.49, 3.04]
6 Death or neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.11]
6.1 Loading (4 g) and lower-maintenance dose (1 g/hour)	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.11]
7 Death or major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
7.1 Loading (4 g) and lower-maintenance dose (1 g/hour)	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]

Comparison 7. Retreatment subgroup

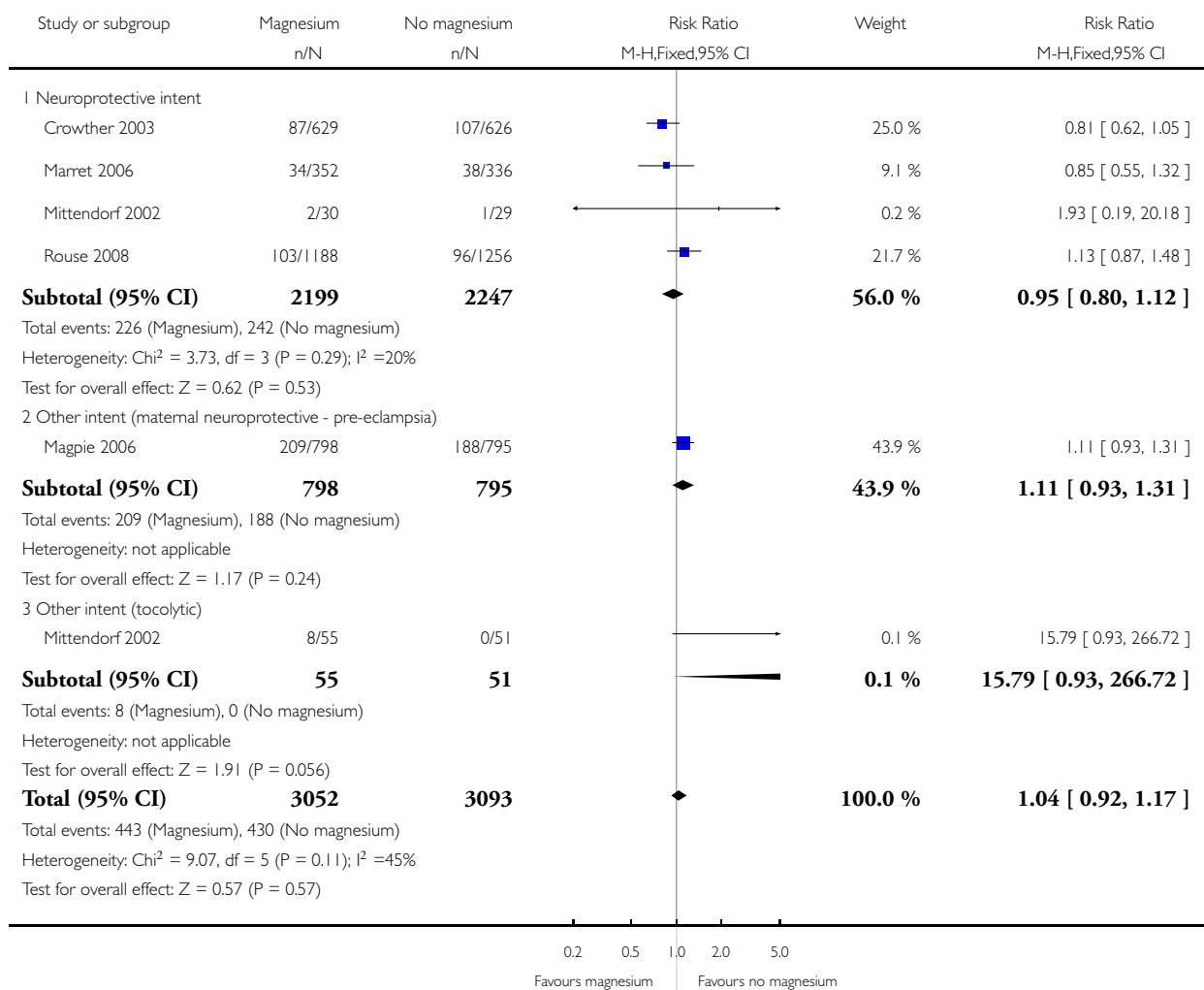
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Paediatric mortality (fetal and later)	5	6145	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.81, 1.27]
1.1 retreatment permitted	1	2444	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.87, 1.48]
1.2 retreatment not permitted	3	3536	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.75, 1.19]
1.3 unclear whether retreatment permitted	1	165	Risk Ratio (M-H, Random, 95% CI)	9.41 [1.23, 71.86]
2 Cerebral palsy	5	6145	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.54, 0.87]
2.1 retreatment permitted	1	2444	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.40, 0.85]
2.2 retreatment not permitted	3	3536	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.55, 1.06]
2.3 unclear whether retreatment permitted	1	165	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.20, 4.53]
3 Neurologic impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
3.1 retreatment not permitted	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.19]
4 Major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
4.1 retreatment not permitted	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.82, 1.40]
5 Death or cerebral palsy	5	6145	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.78, 1.13]
5.1 retreatment permitted	1	2444	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.73, 1.10]
5.2 retreatment not permitted	3	3536	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.74, 1.13]
5.3 unclear whether retreatment permitted	1	165	Risk Ratio (M-H, Random, 95% CI)	3.06 [1.04, 8.99]
6 Death or neurological impairment	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.11]
6.1 retreatment not permitted	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.91, 1.11]
7 Death or major neurological disability	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]
7.1 retreatment not permitted	2	2848	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.90, 1.15]

Analysis 1.1. Comparison 1 Magnesium versus no magnesium, Outcome 1 Paediatric mortality (fetal and later).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

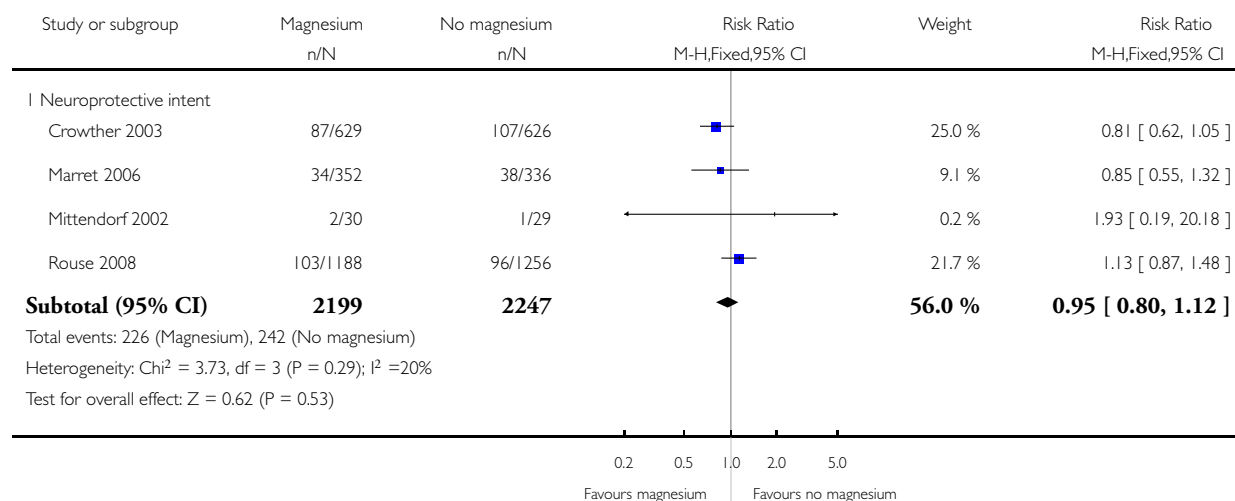
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

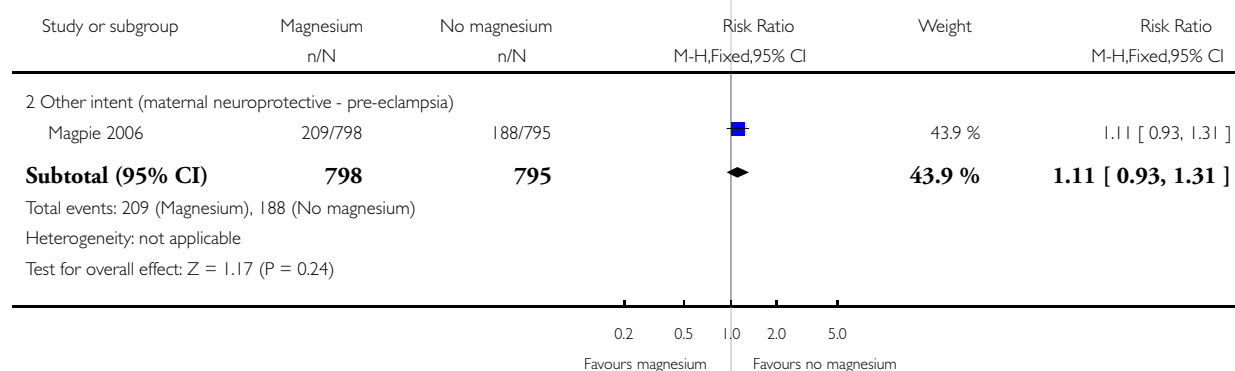
Outcome: I Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

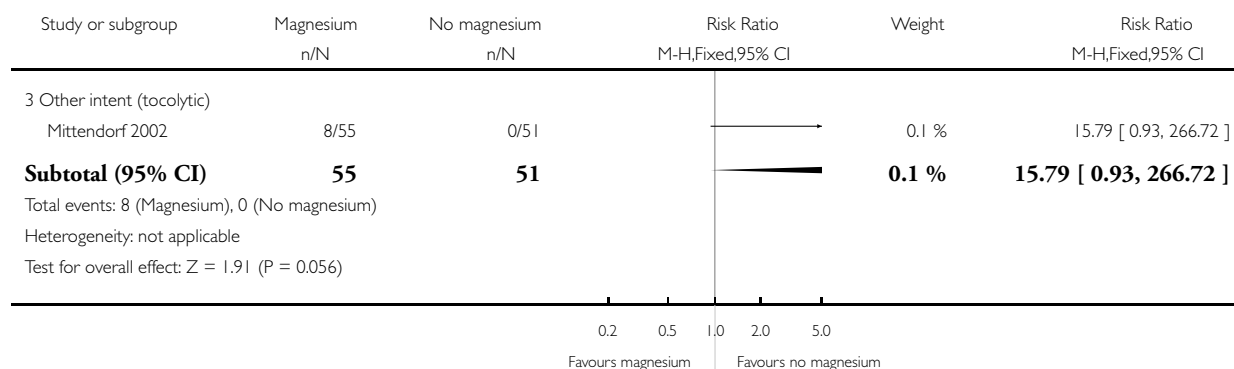
Outcome: I Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 1 Paediatric mortality (fetal and later)

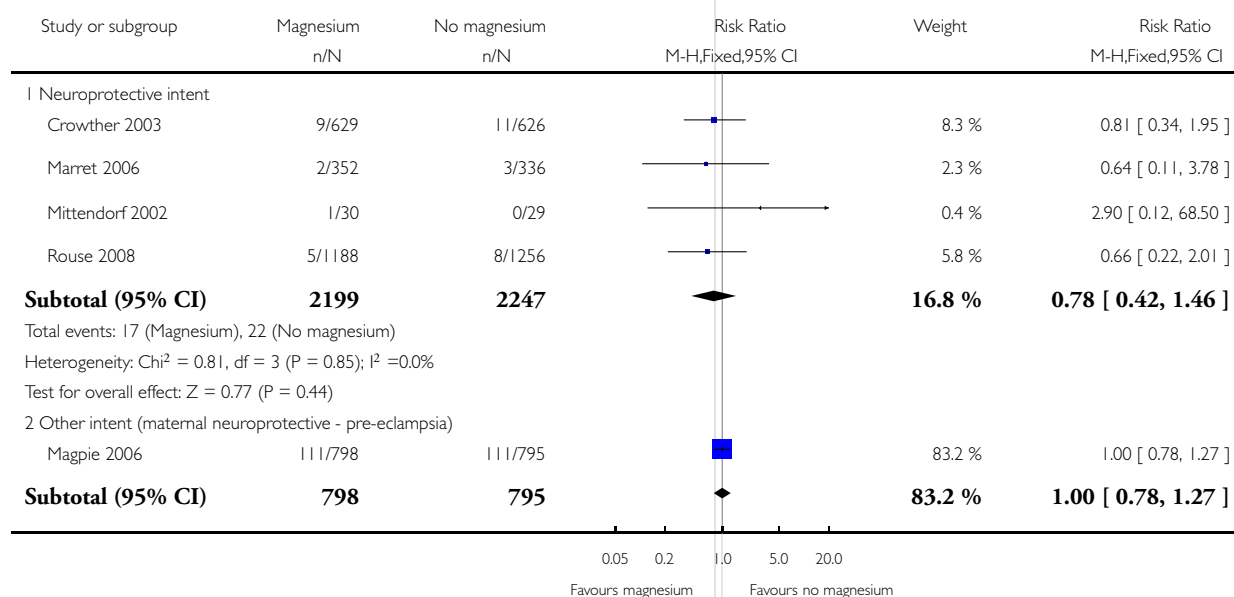


Analysis 1.2. Comparison 1 Magnesium versus no magnesium, Outcome 2 Fetal death.

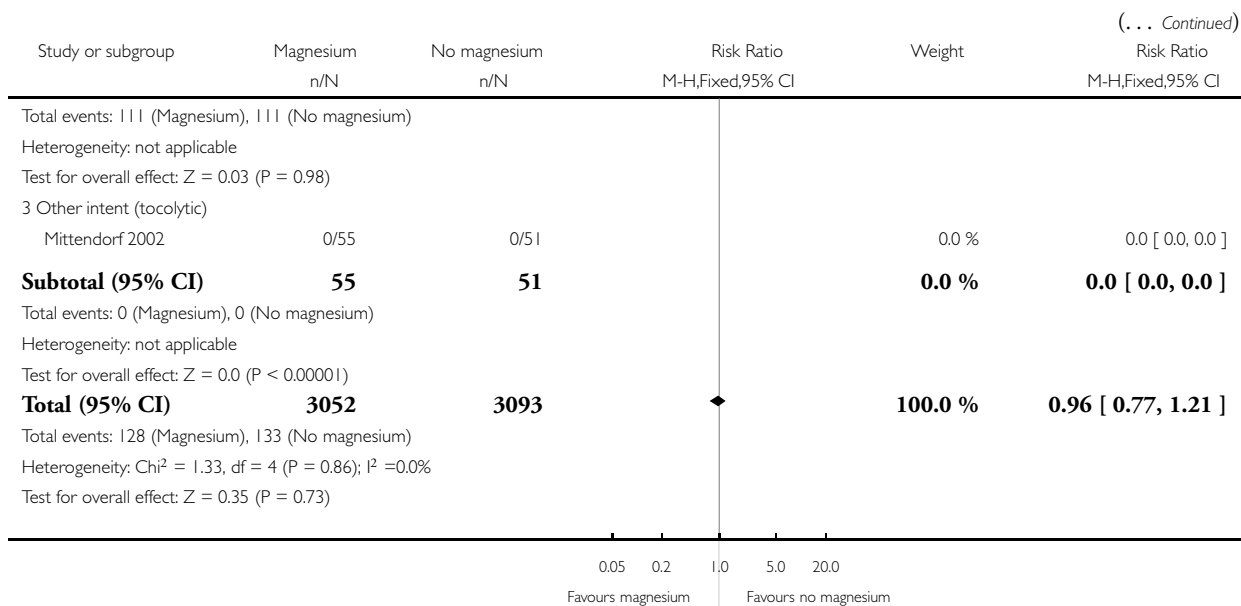
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 2 Fetal death



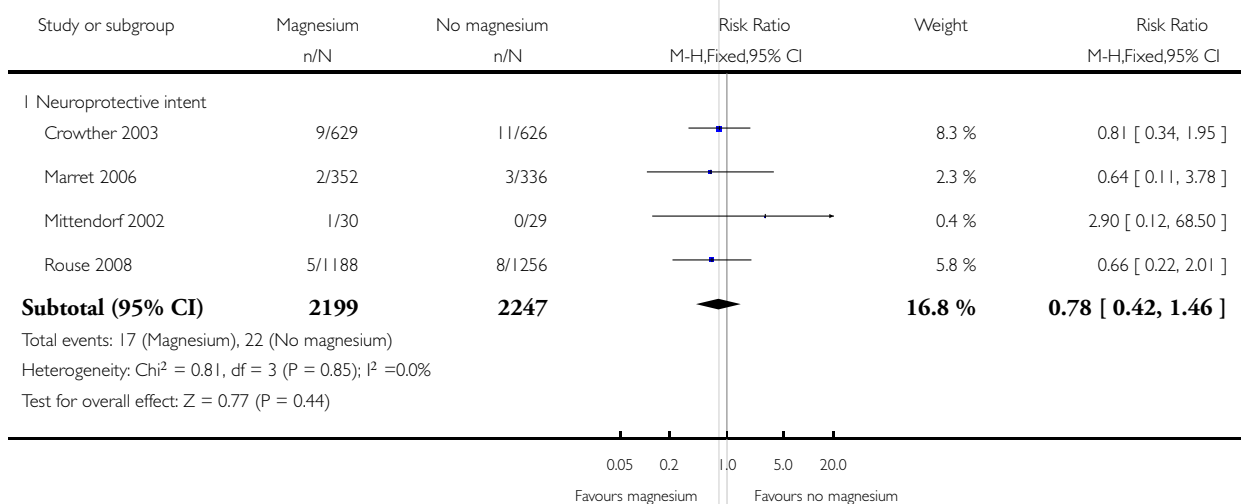
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

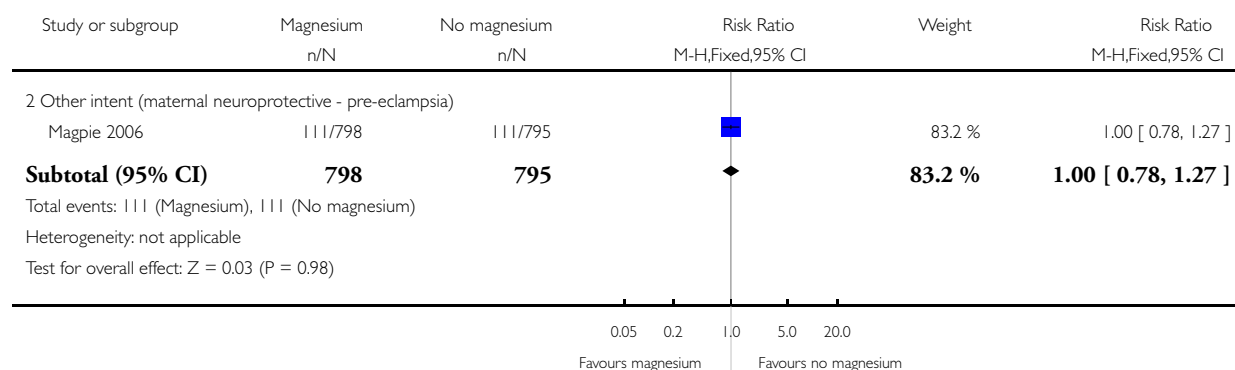
Outcome: 2 Fetal death



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

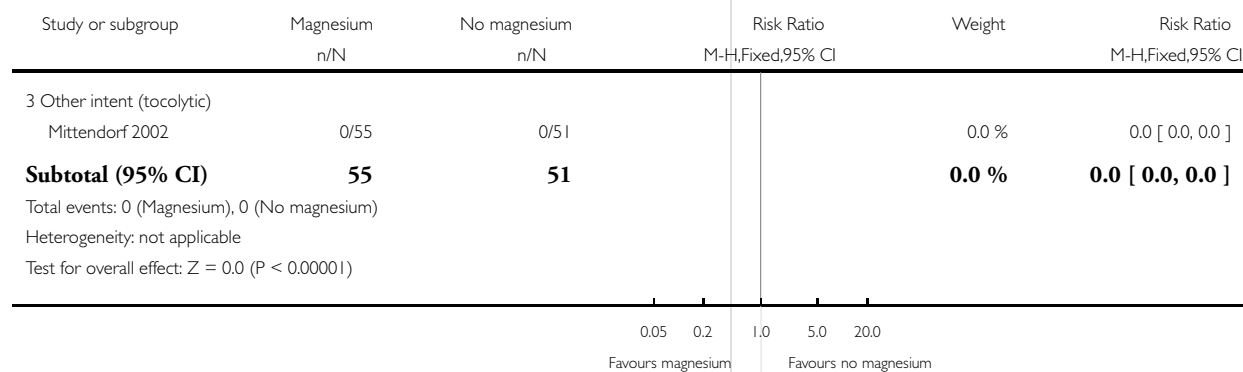
Outcome: 2 Fetal death



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 2 Fetal death

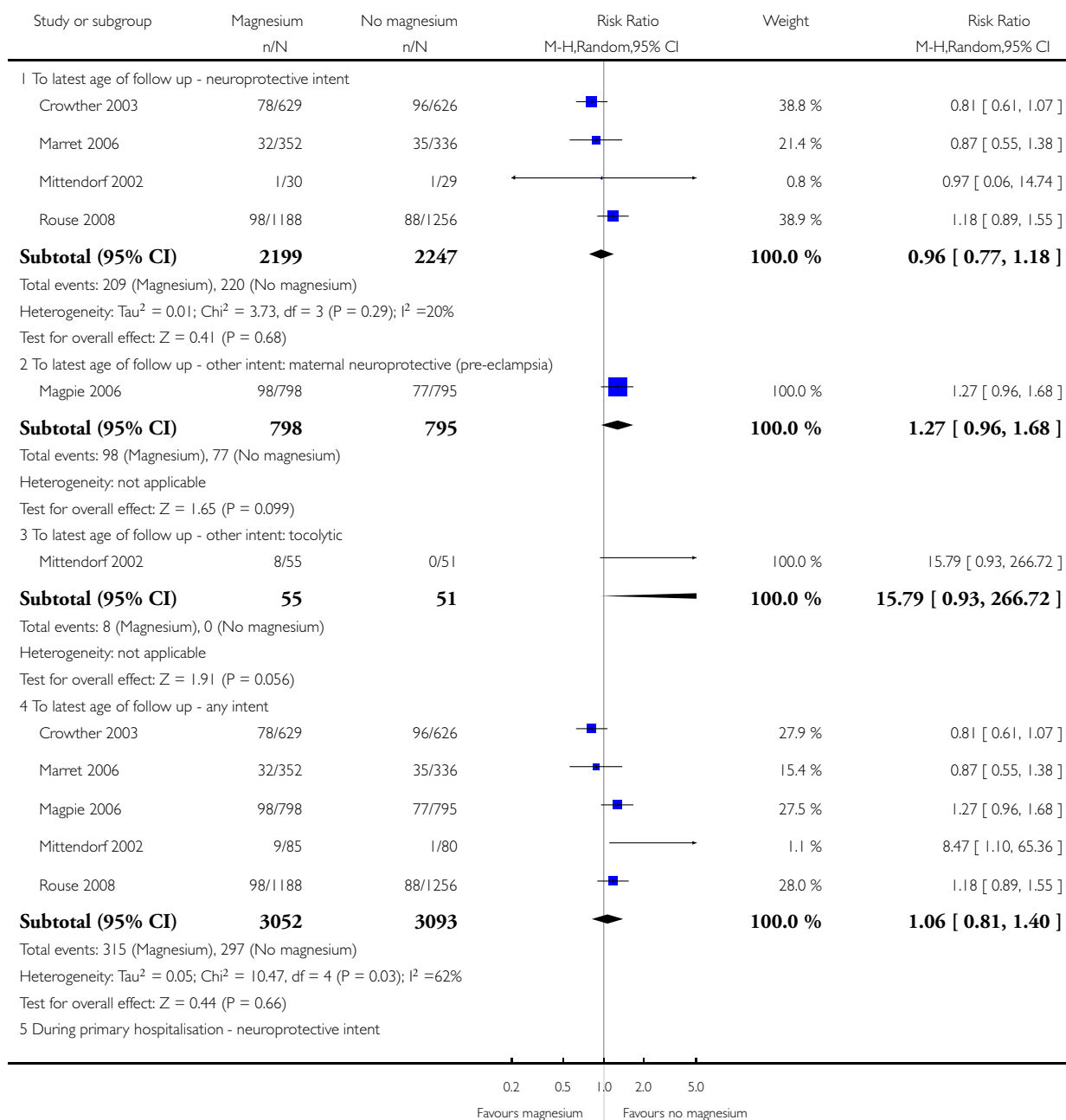


Analysis 1.3. Comparison 1 Magnesium versus no magnesium, Outcome 3 Livebirth deaths.

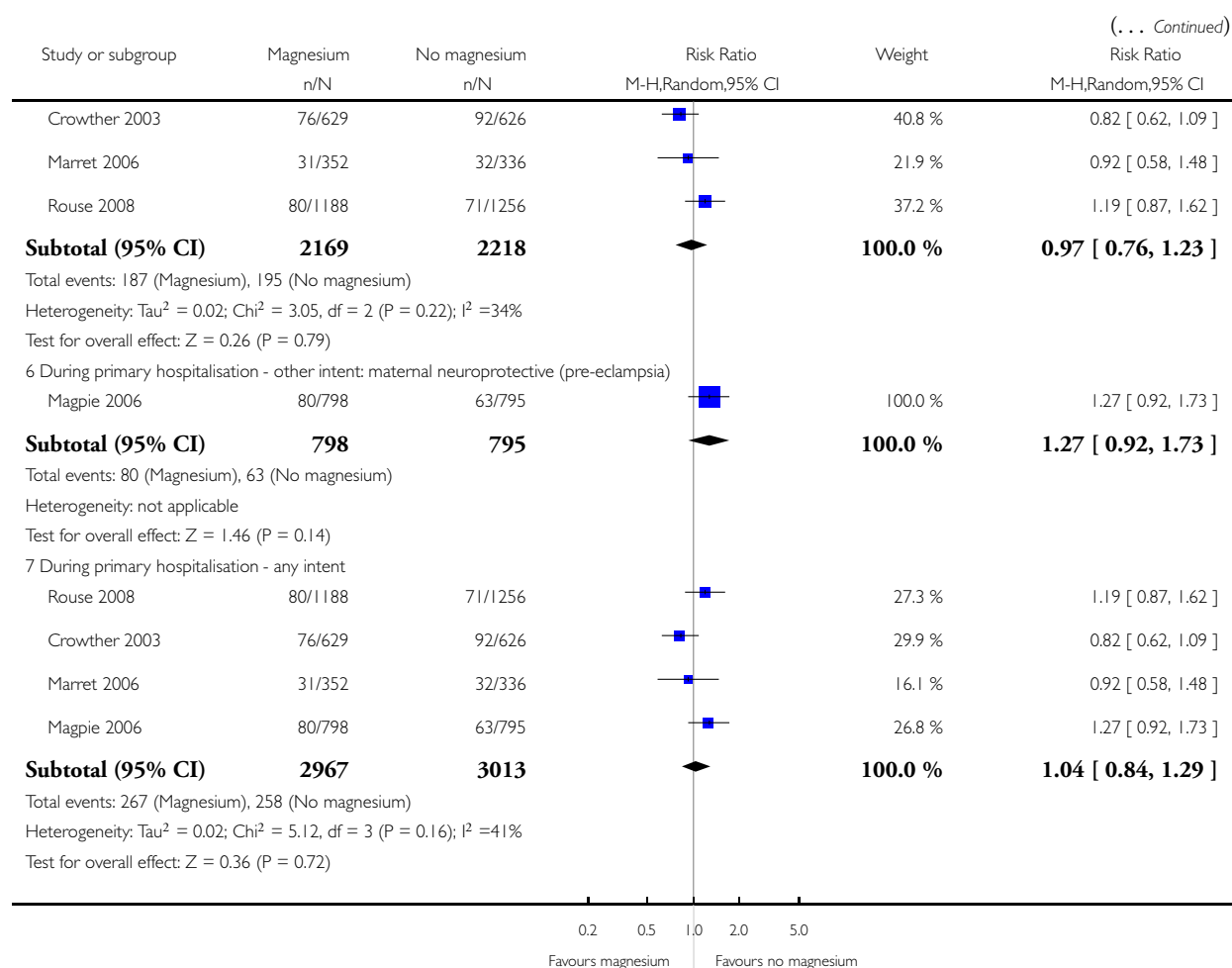
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 3 Livebirth deaths



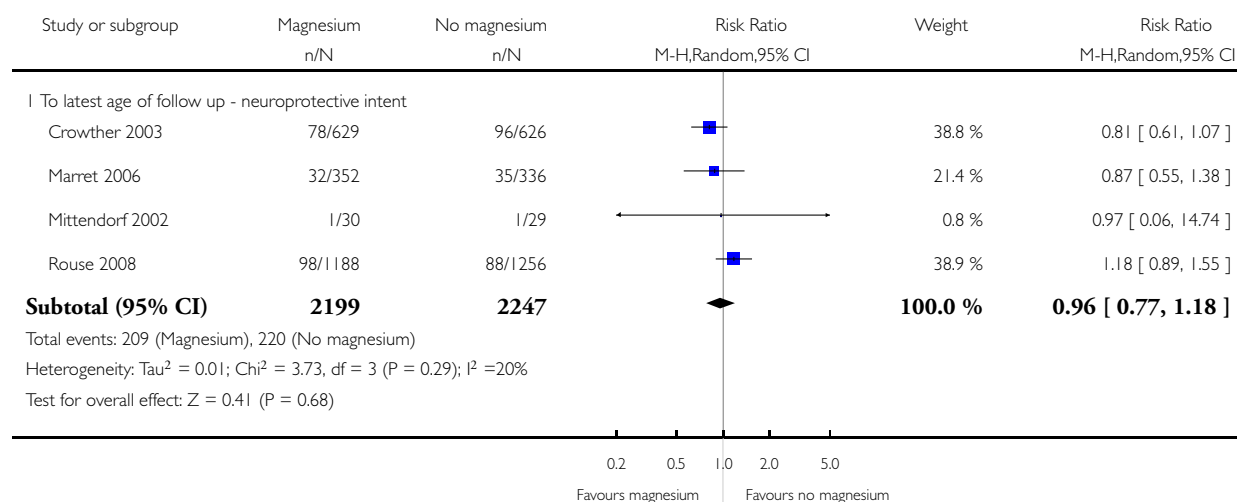
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

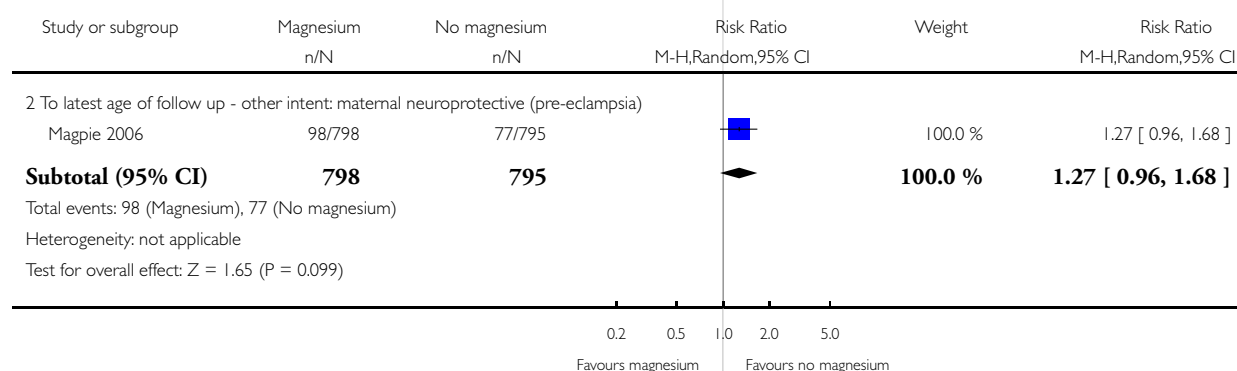
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

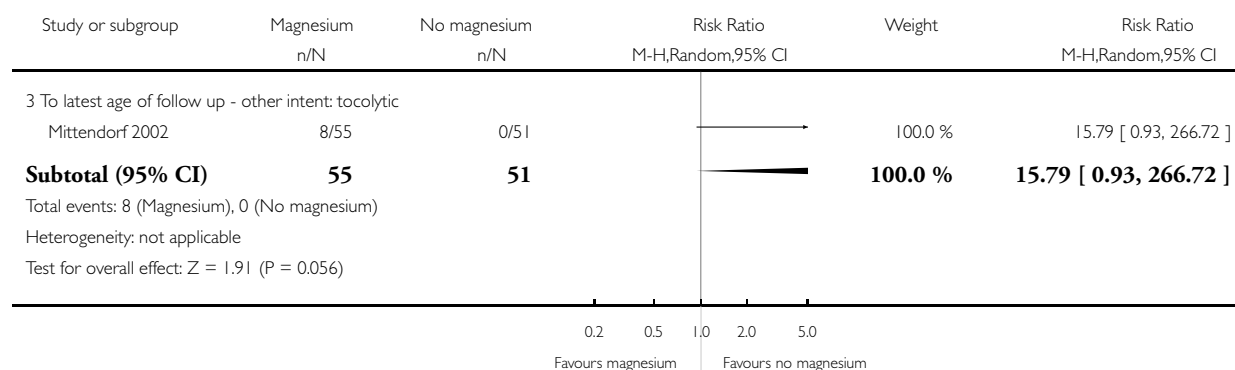
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

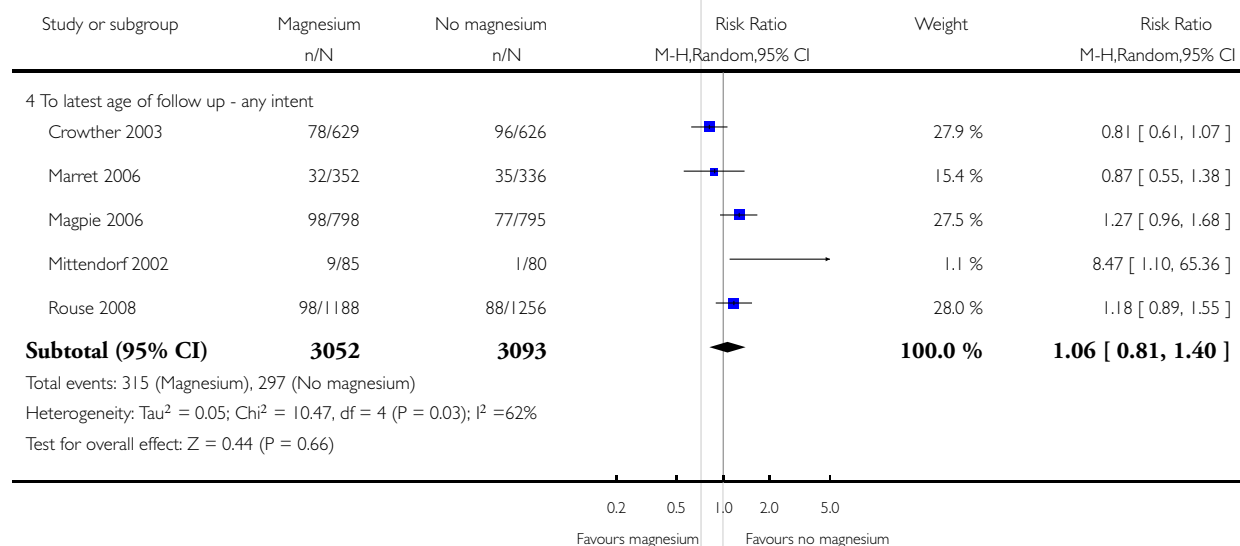
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

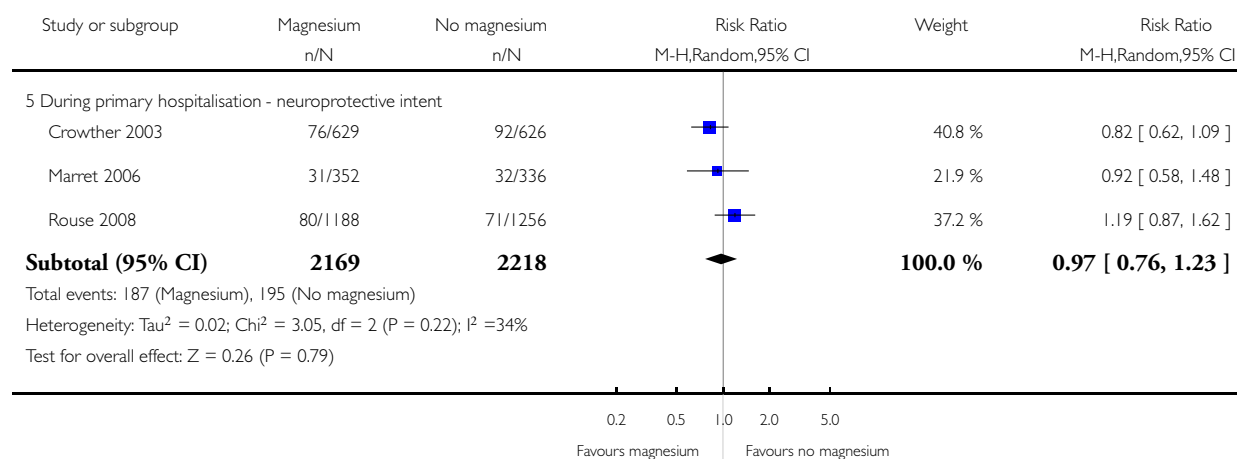
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

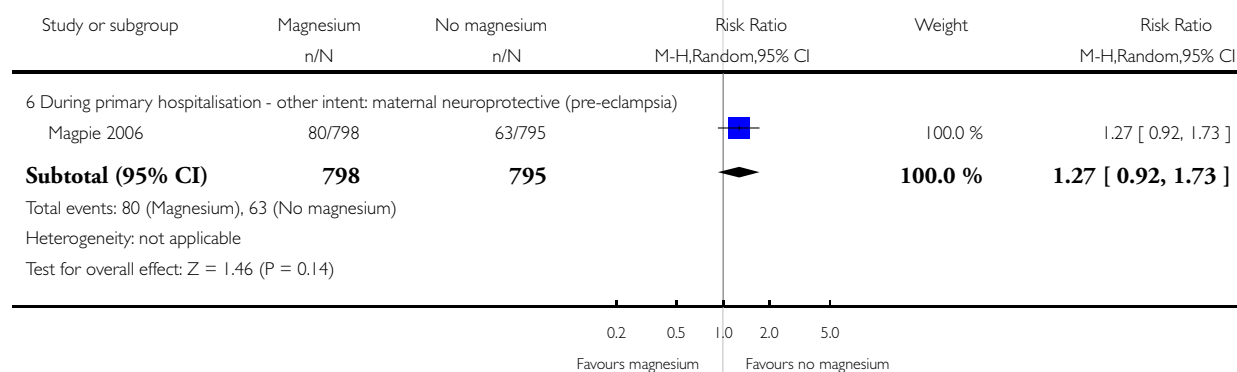
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

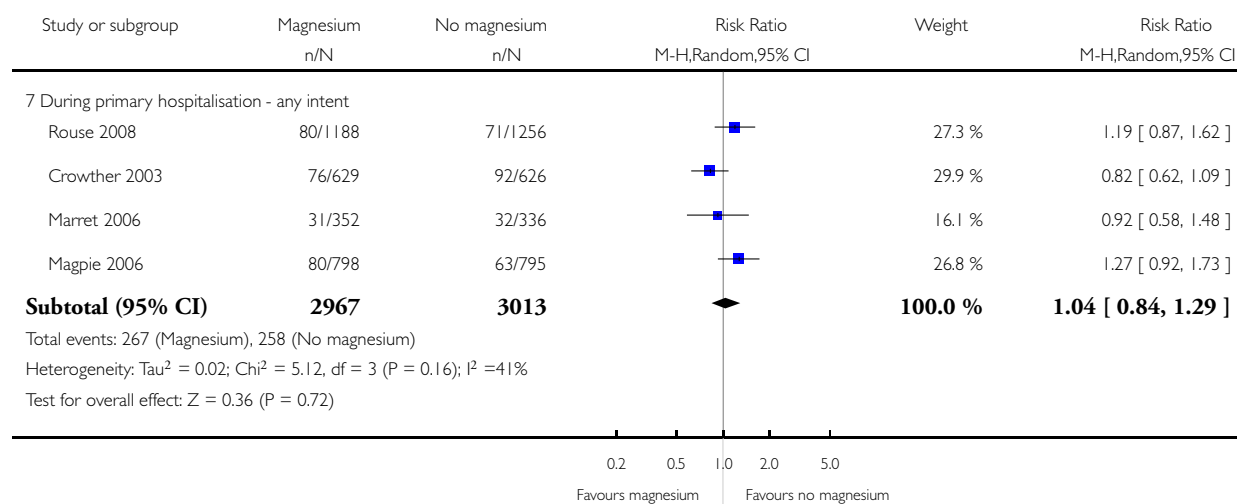
Outcome: 3 Livebirth deaths



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 3 Livebirth deaths

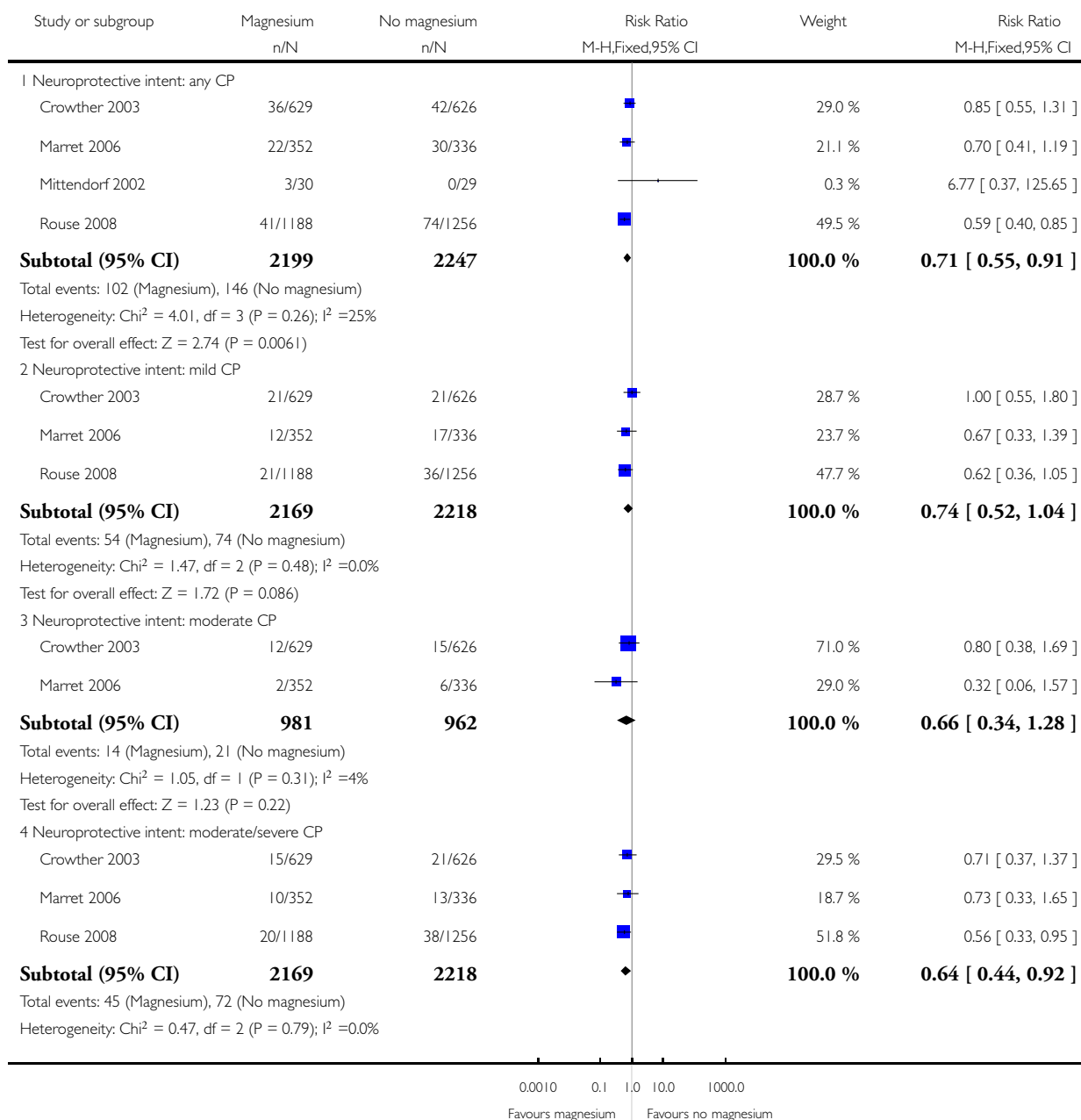


Analysis 1.4. Comparison 1 Magnesium versus no magnesium, Outcome 4 Cerebral palsy.

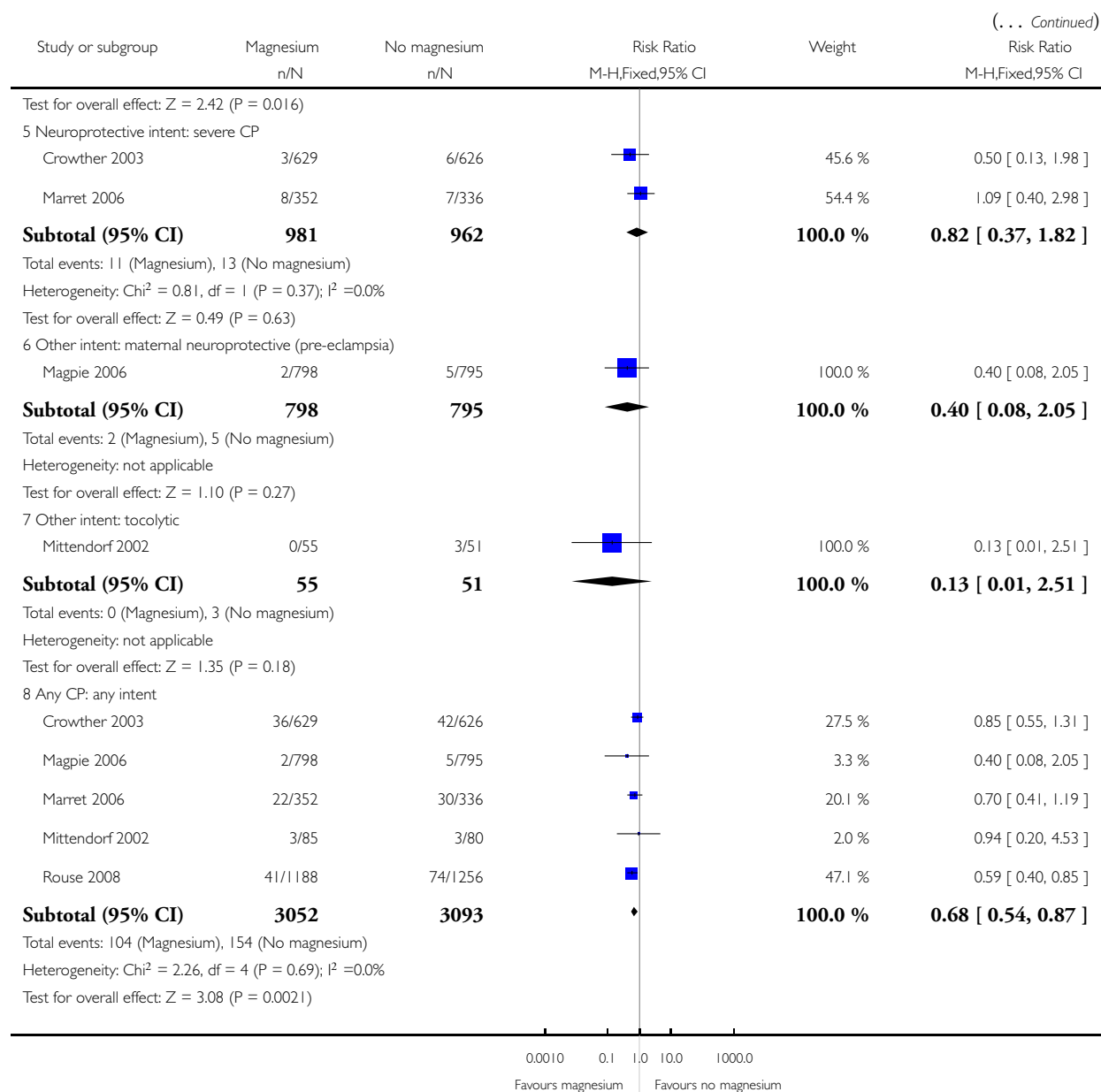
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 4 Cerebral palsy



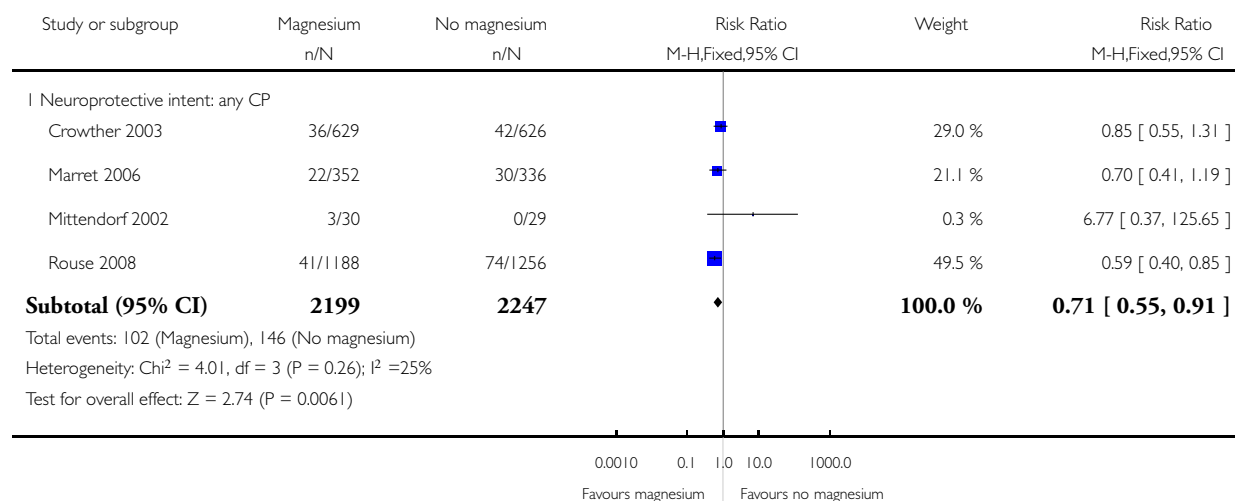
(Continued ...)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

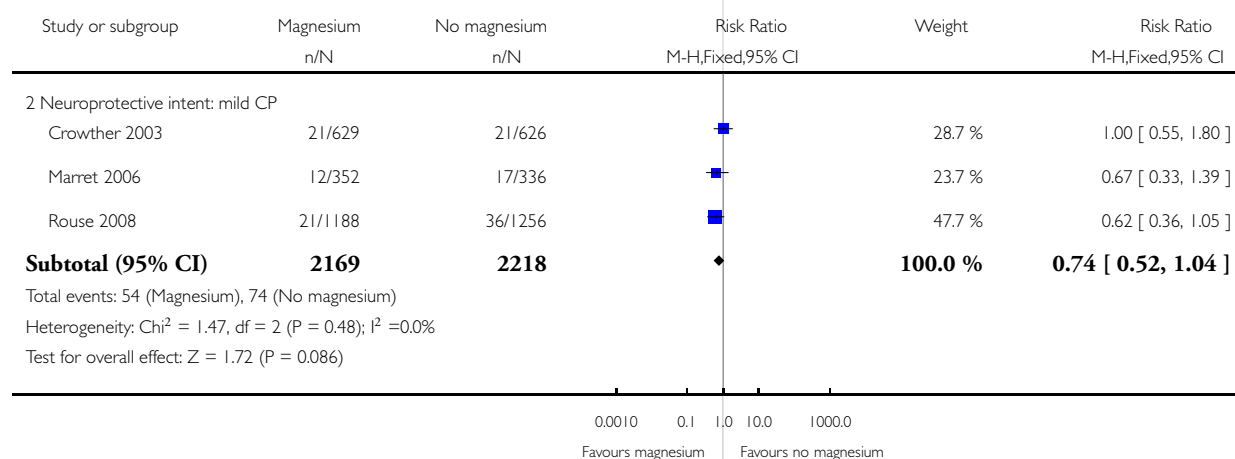
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

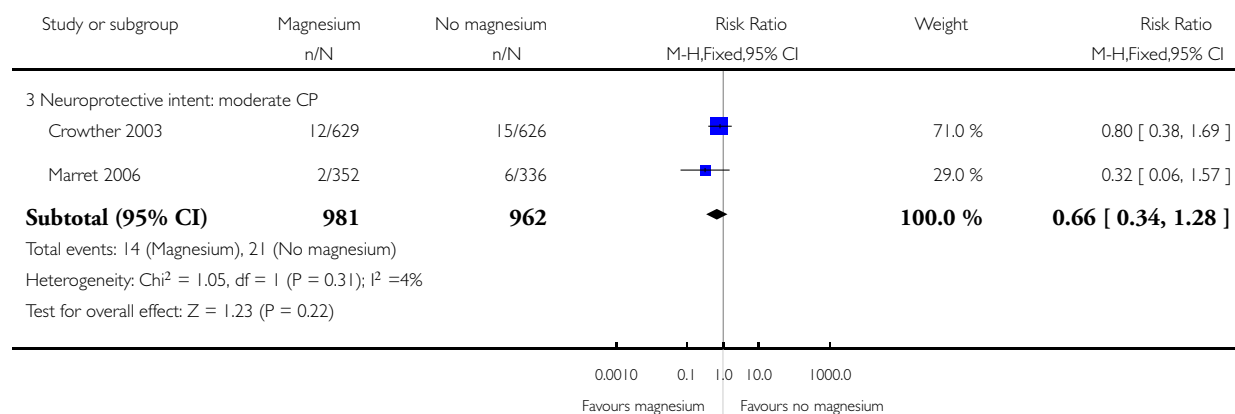
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

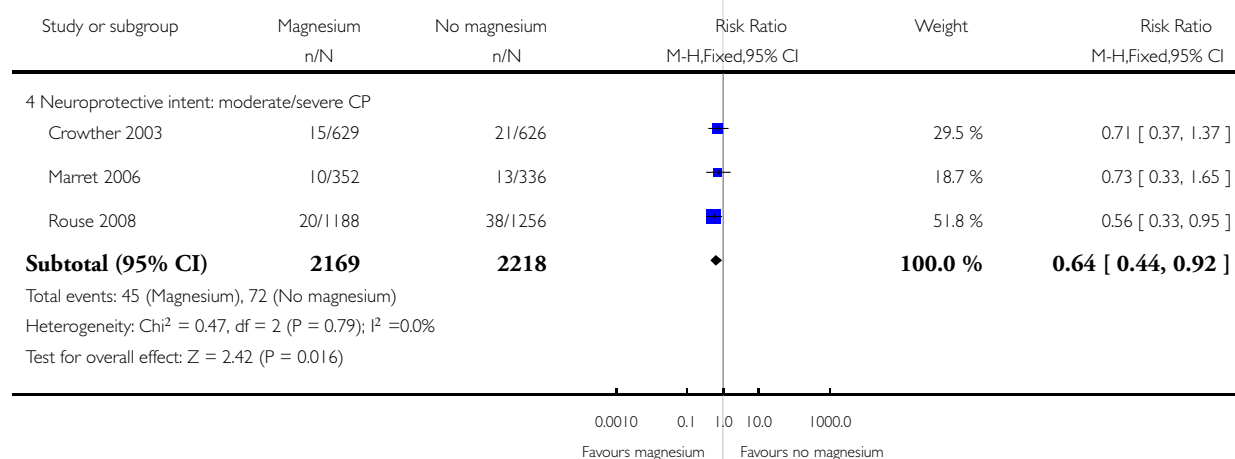
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

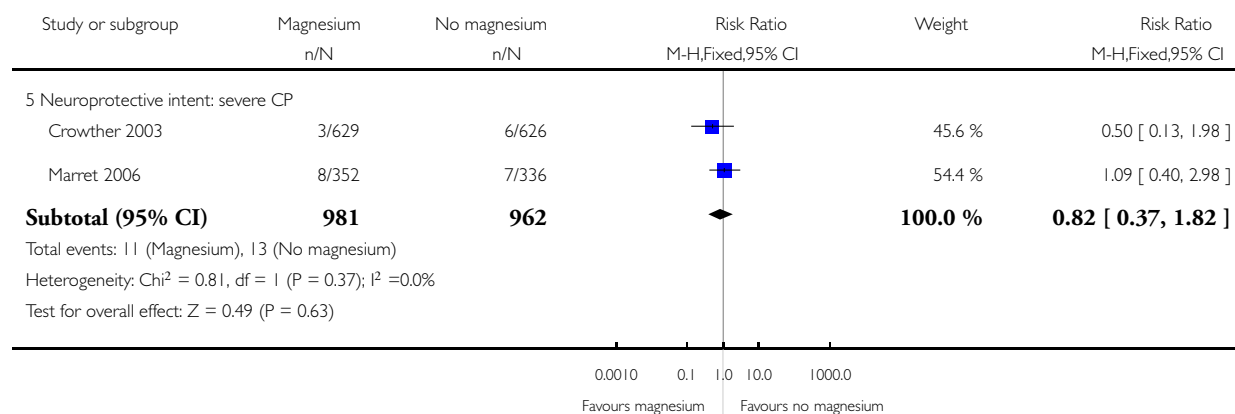
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

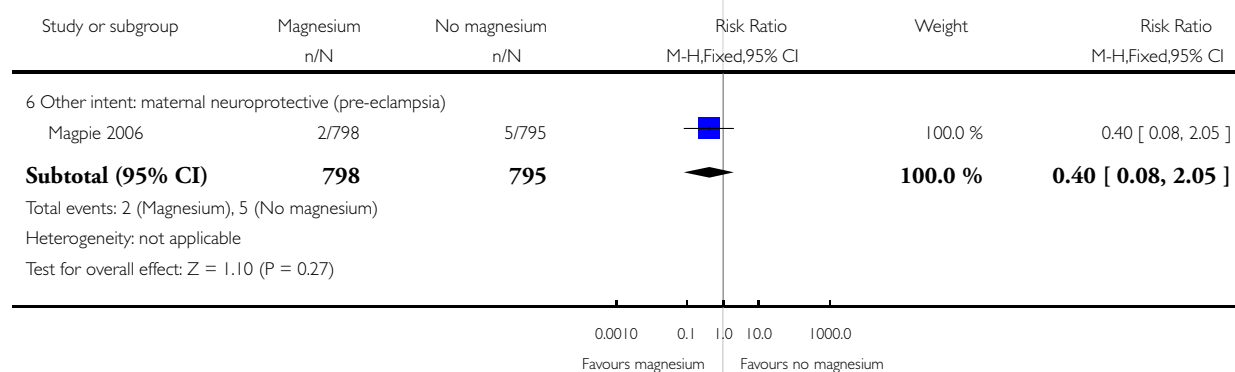
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

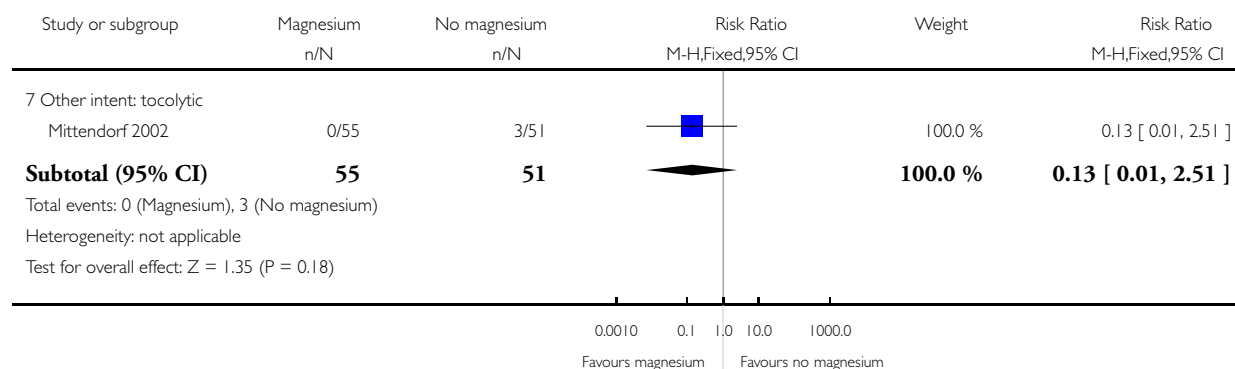
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

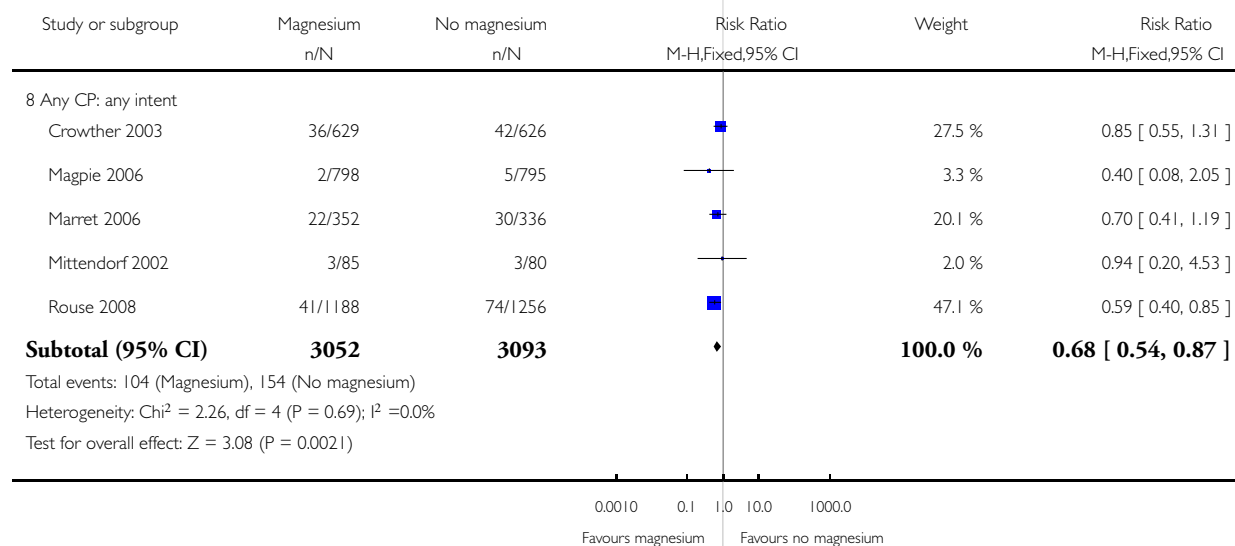
Outcome: 4 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 4 Cerebral palsy

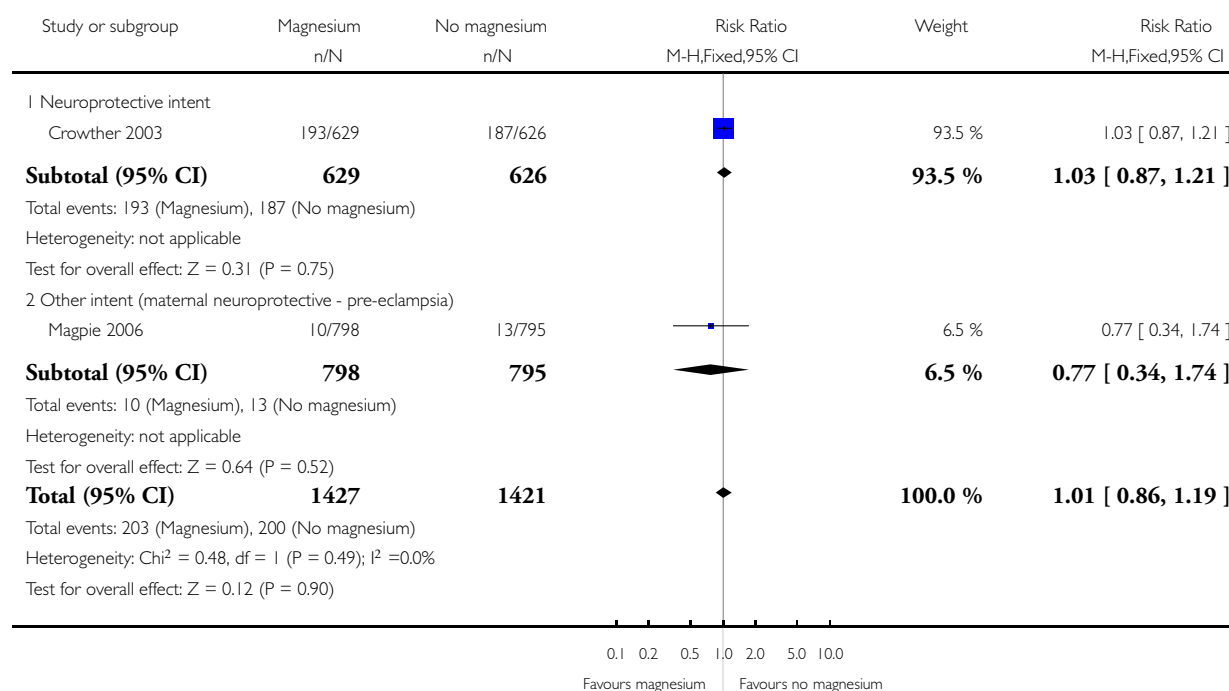


Analysis 1.5. Comparison 1 Magnesium versus no magnesium, Outcome 5 Any neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

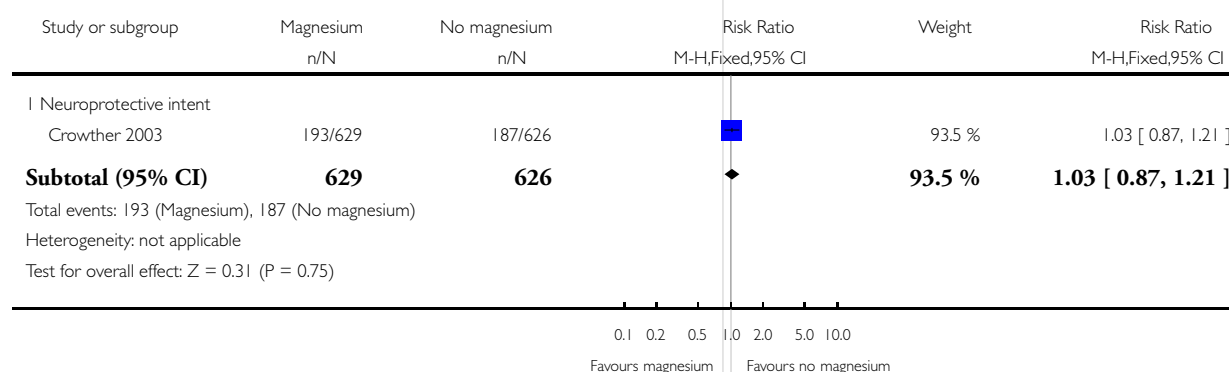
Outcome: 5 Any neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

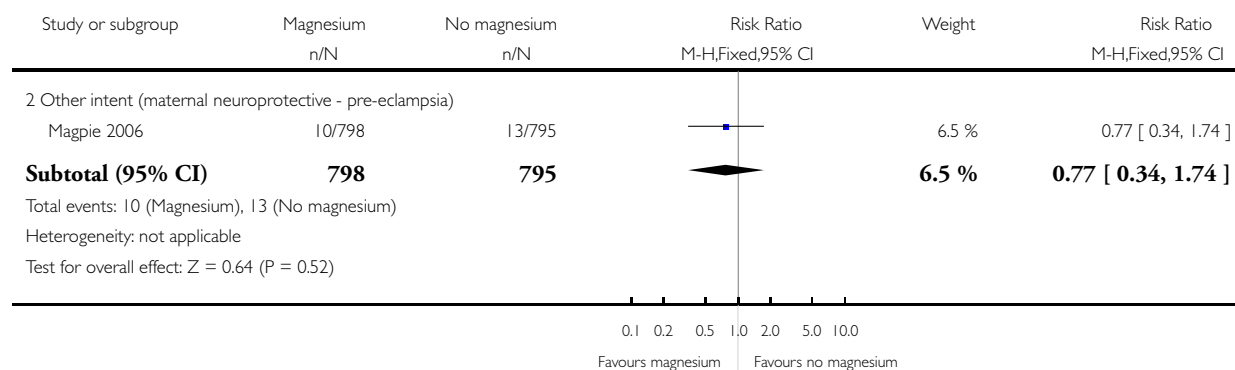
Outcome: 5 Any neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 5 Any neurological impairment

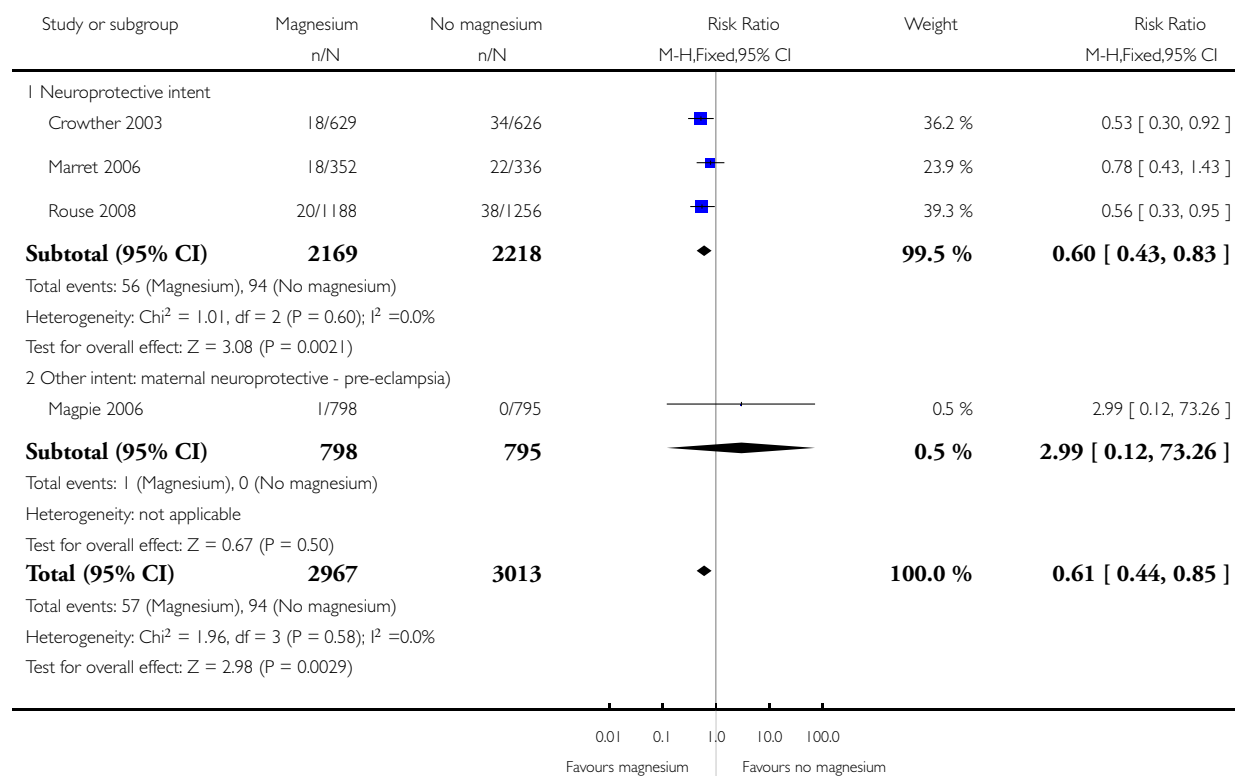


Analysis 1.6. Comparison 1 Magnesium versus no magnesium, Outcome 6 Substantial gross motor dysfunction.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

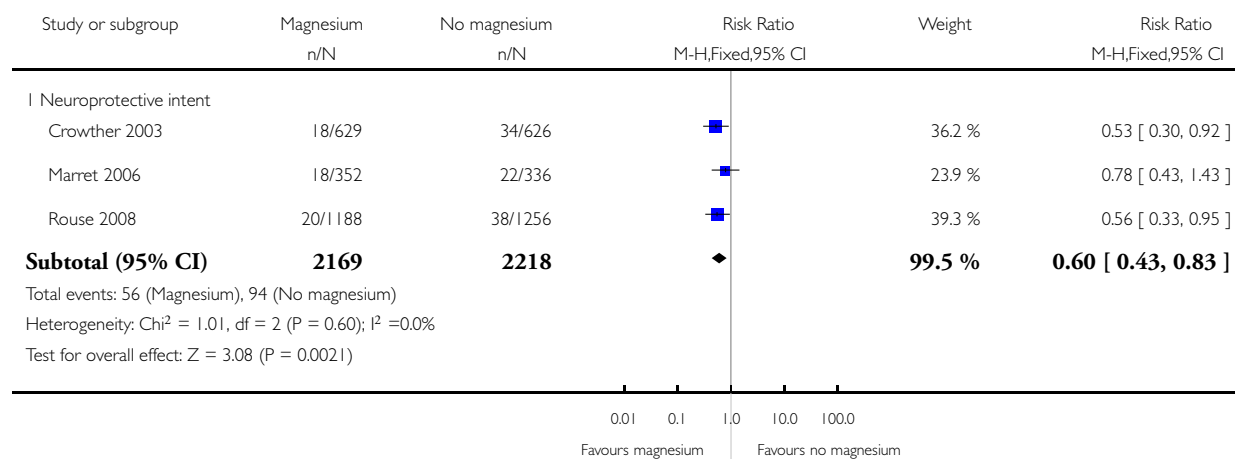
Outcome: 6 Substantial gross motor dysfunction



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

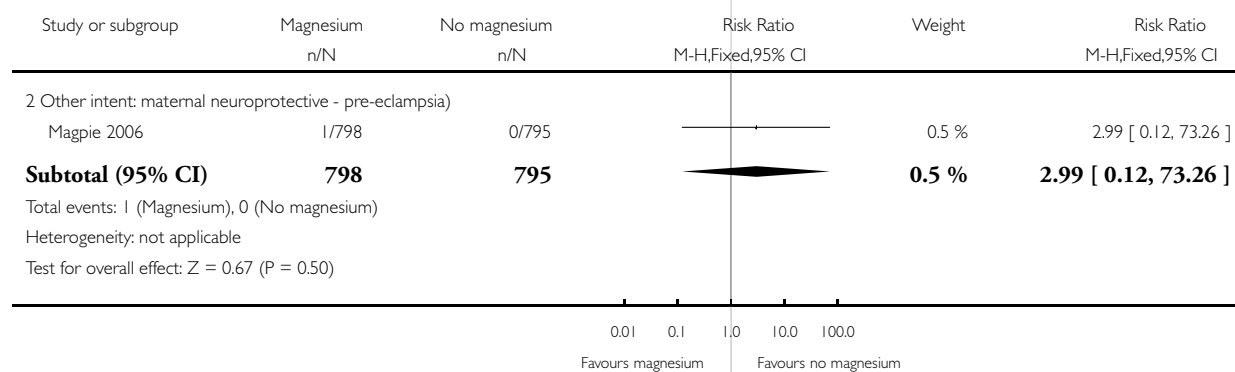
Outcome: 6 Substantial gross motor dysfunction



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 6 Substantial gross motor dysfunction

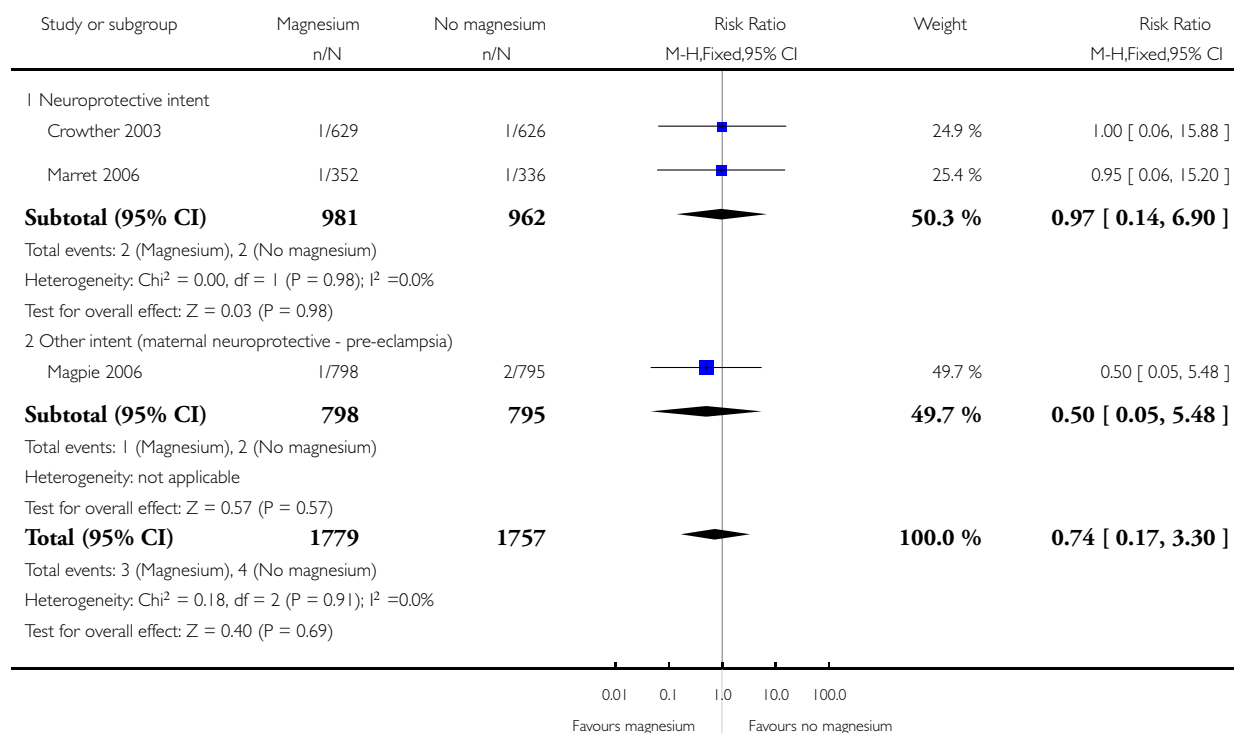


Analysis 1.7. Comparison 1 Magnesium versus no magnesium, Outcome 7 Blindness.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

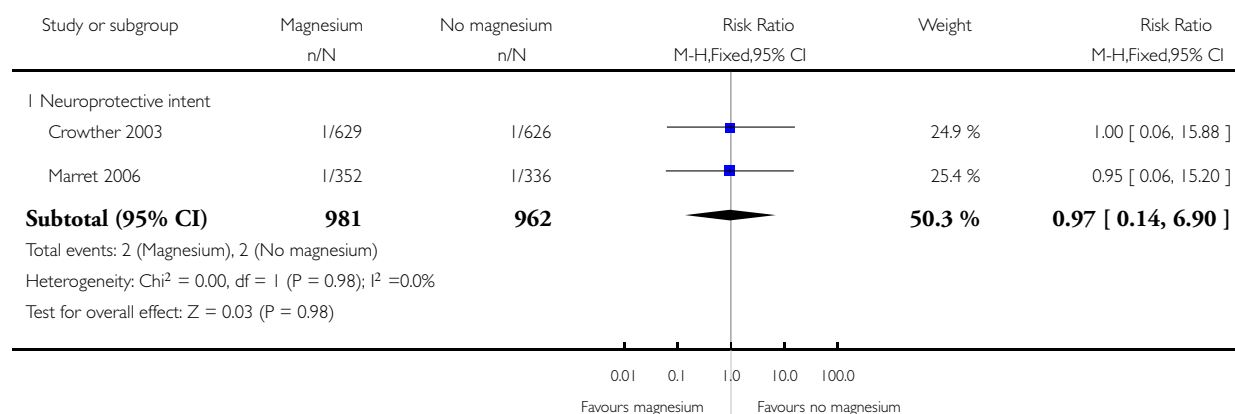
Outcome: 7 Blindness



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

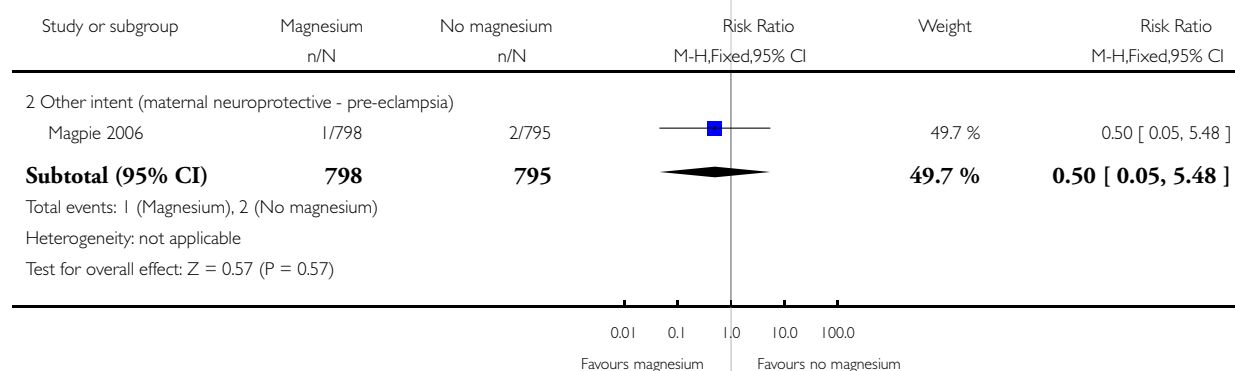
Outcome: 7 Blindness



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 7 Blindness

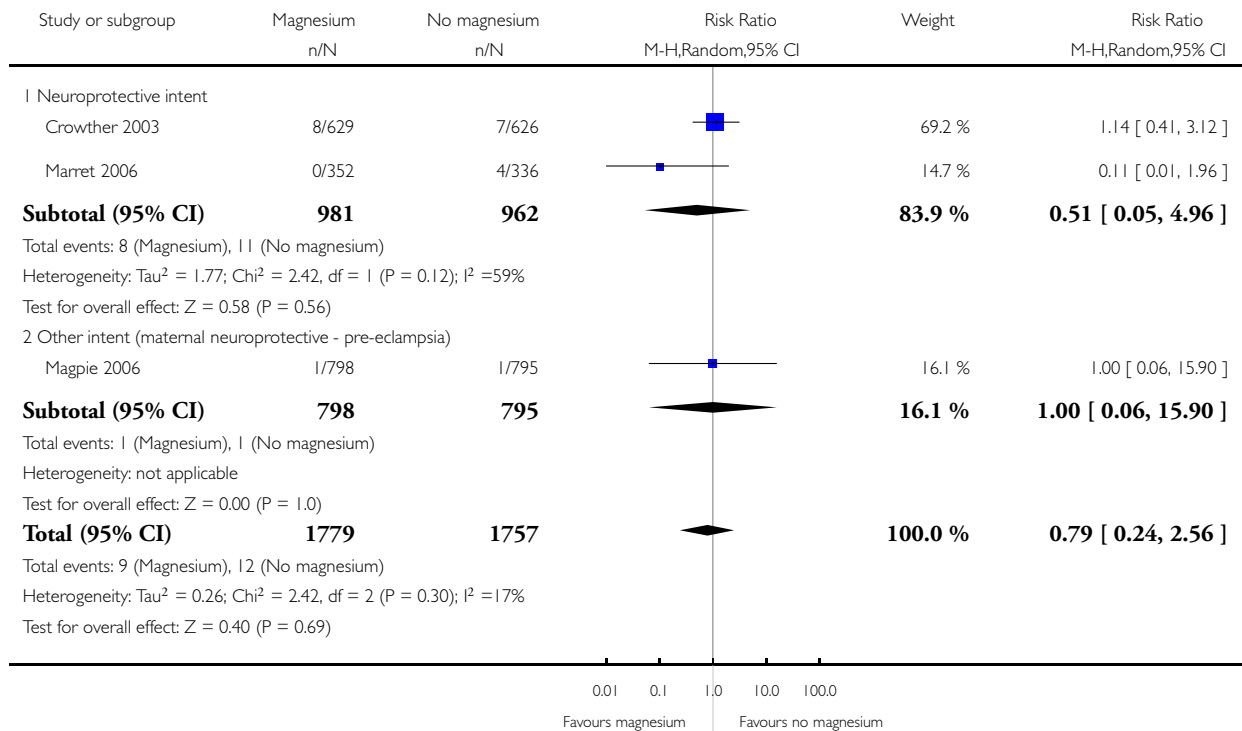


Analysis 1.8. Comparison 1 Magnesium versus no magnesium, Outcome 8 Deafness.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

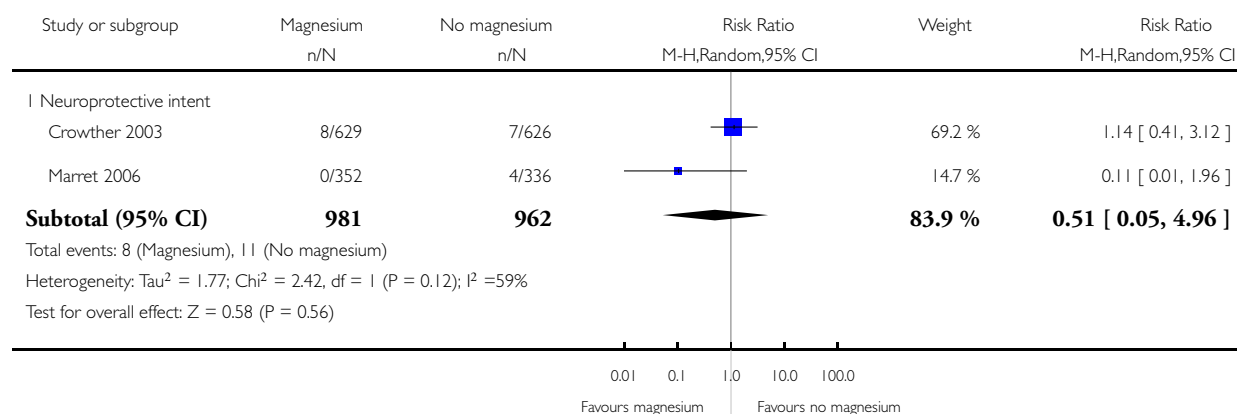
Outcome: 8 Deafness



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

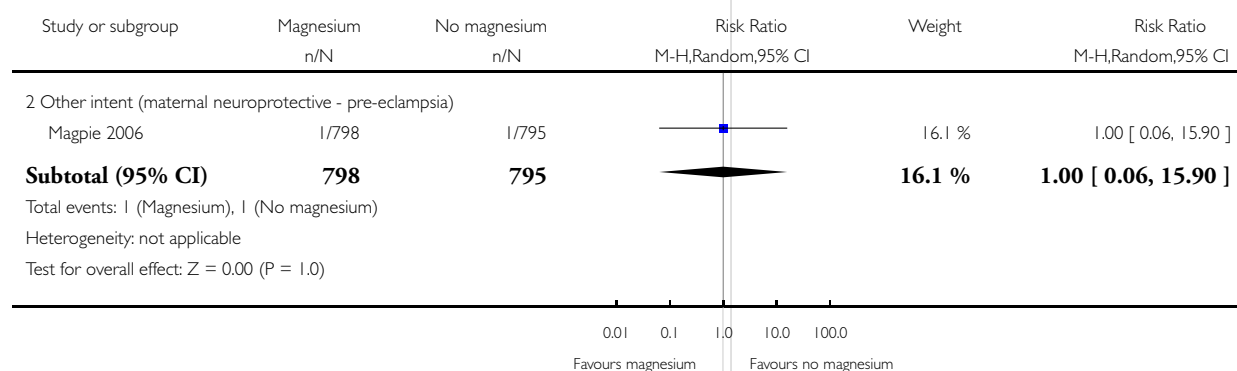
Outcome: 8 Deafness



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 8 Deafness

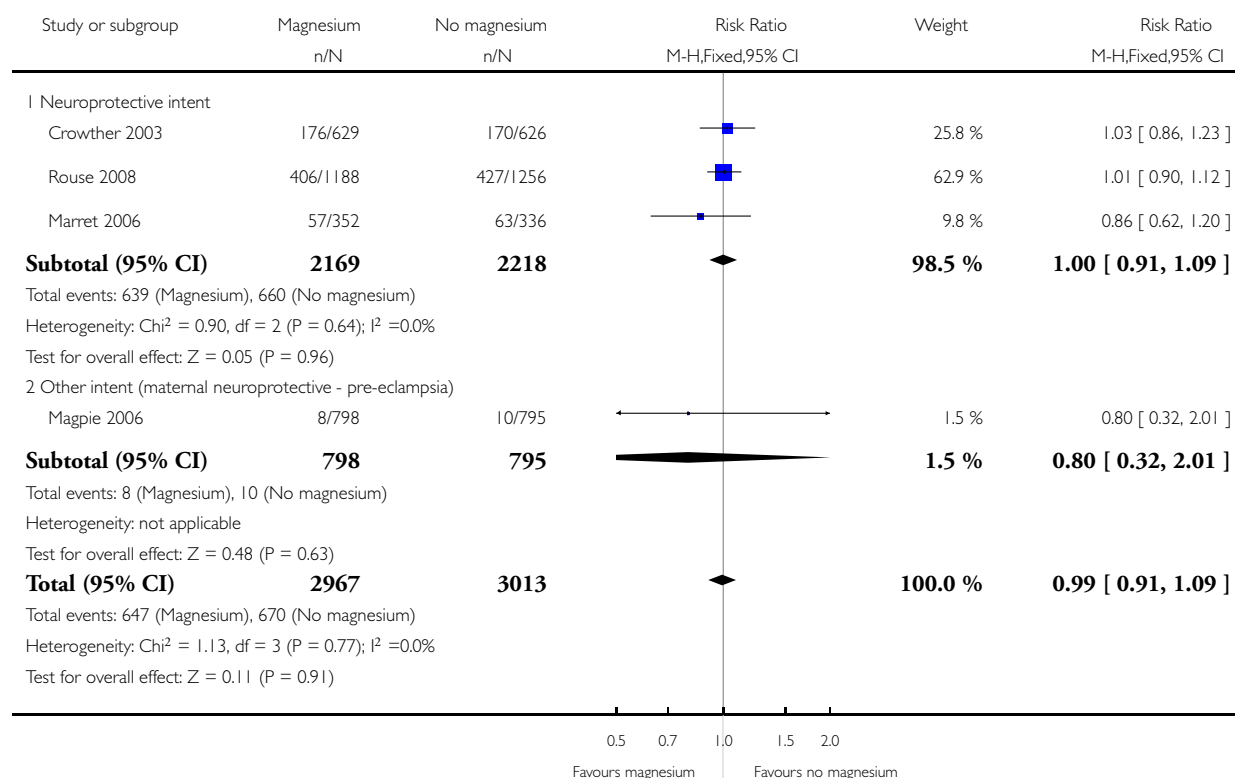


Analysis 1.9. Comparison 1 Magnesium versus no magnesium, Outcome 9 Developmental delay or intellectual impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

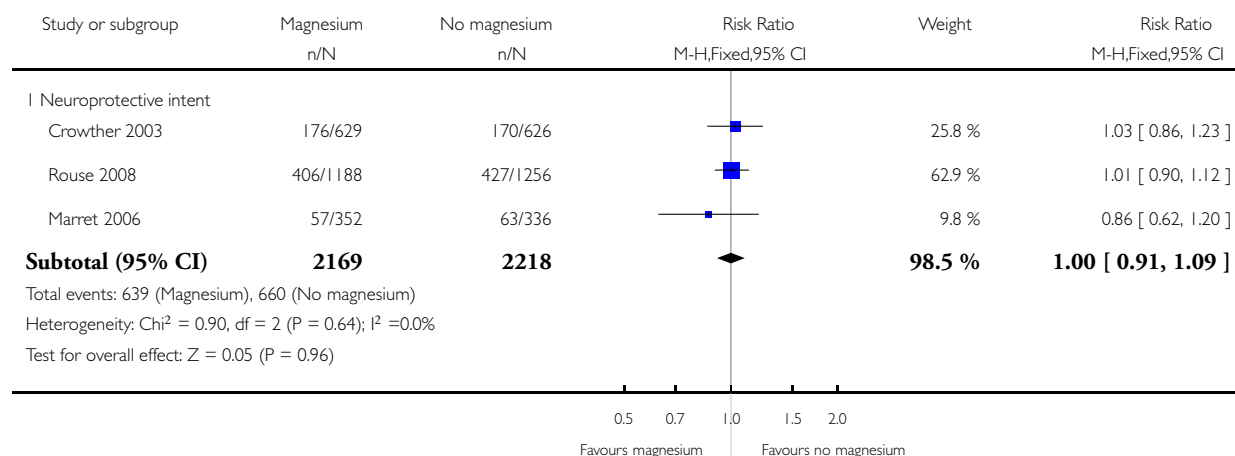
Outcome: 9 Developmental delay or intellectual impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

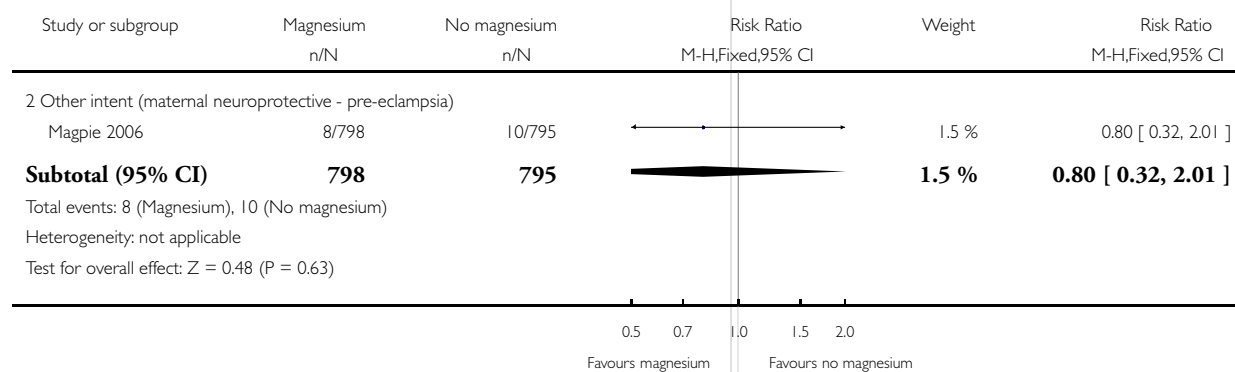
Outcome: 9 Developmental delay or intellectual impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 9 Developmental delay or intellectual impairment

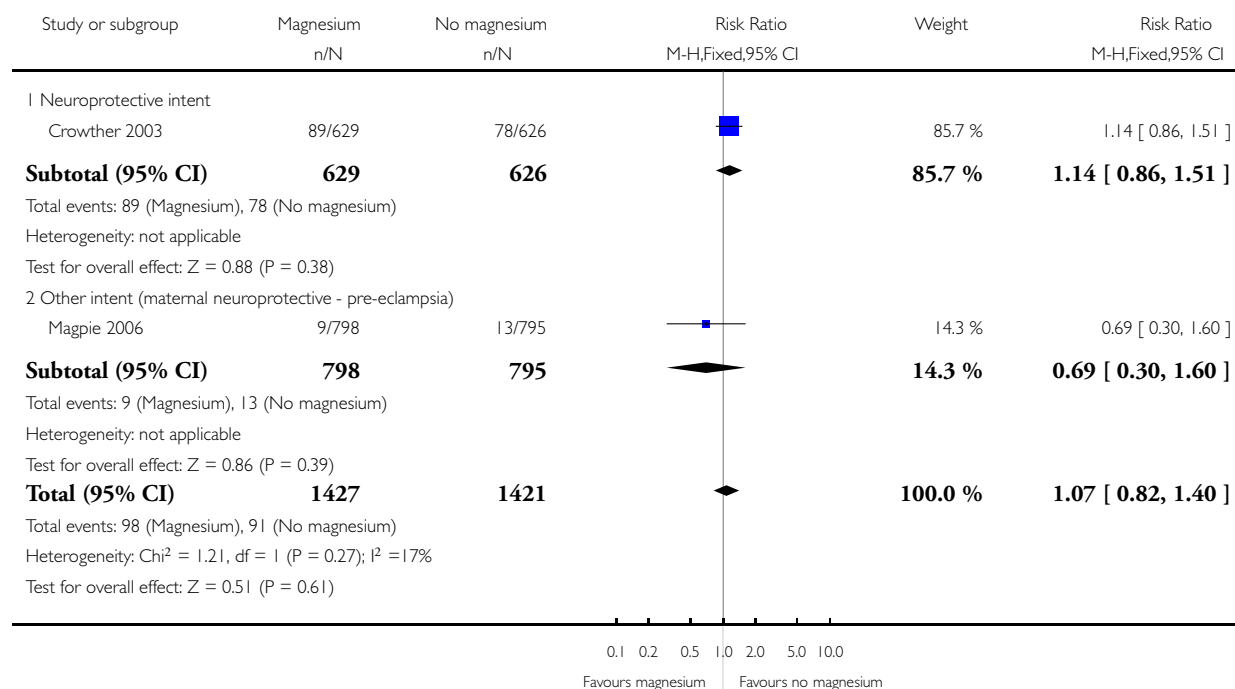


Analysis 1.10. Comparison 1 Magnesium versus no magnesium, Outcome 10 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

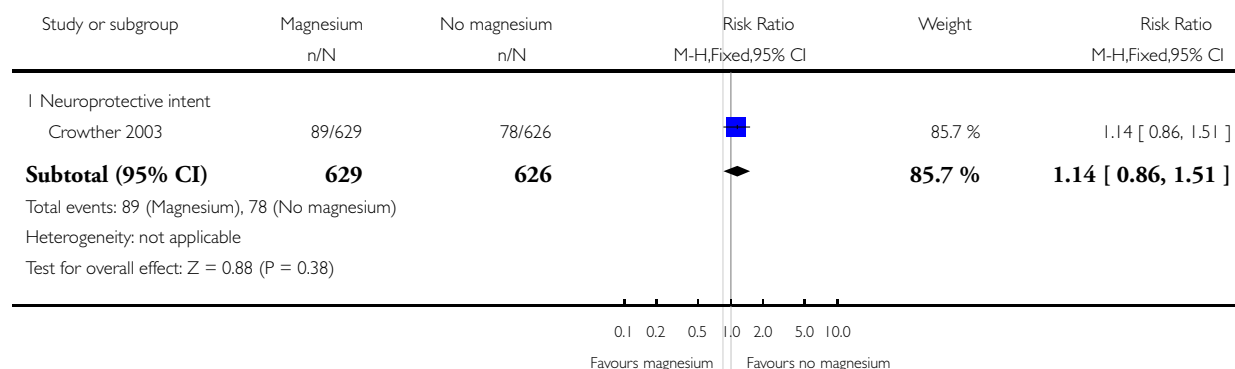
Outcome: 10 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

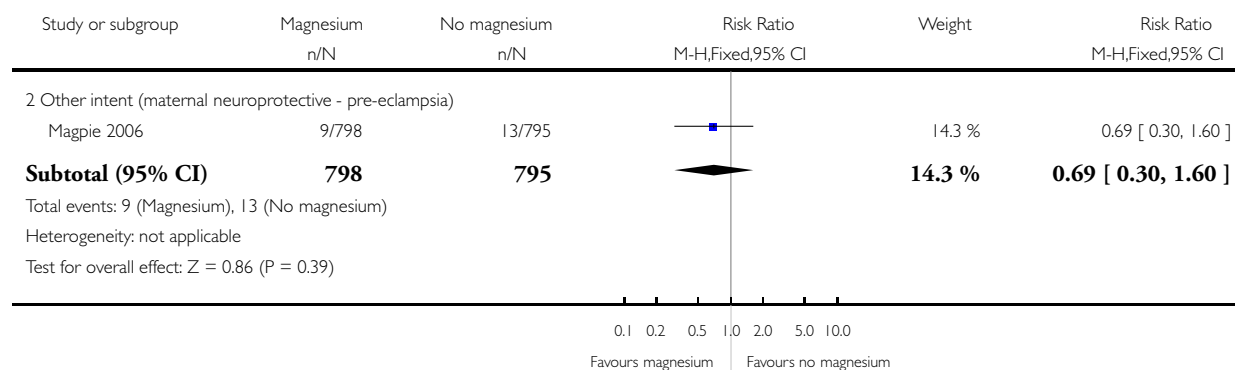
Outcome: 10 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 10 Major neurological disability

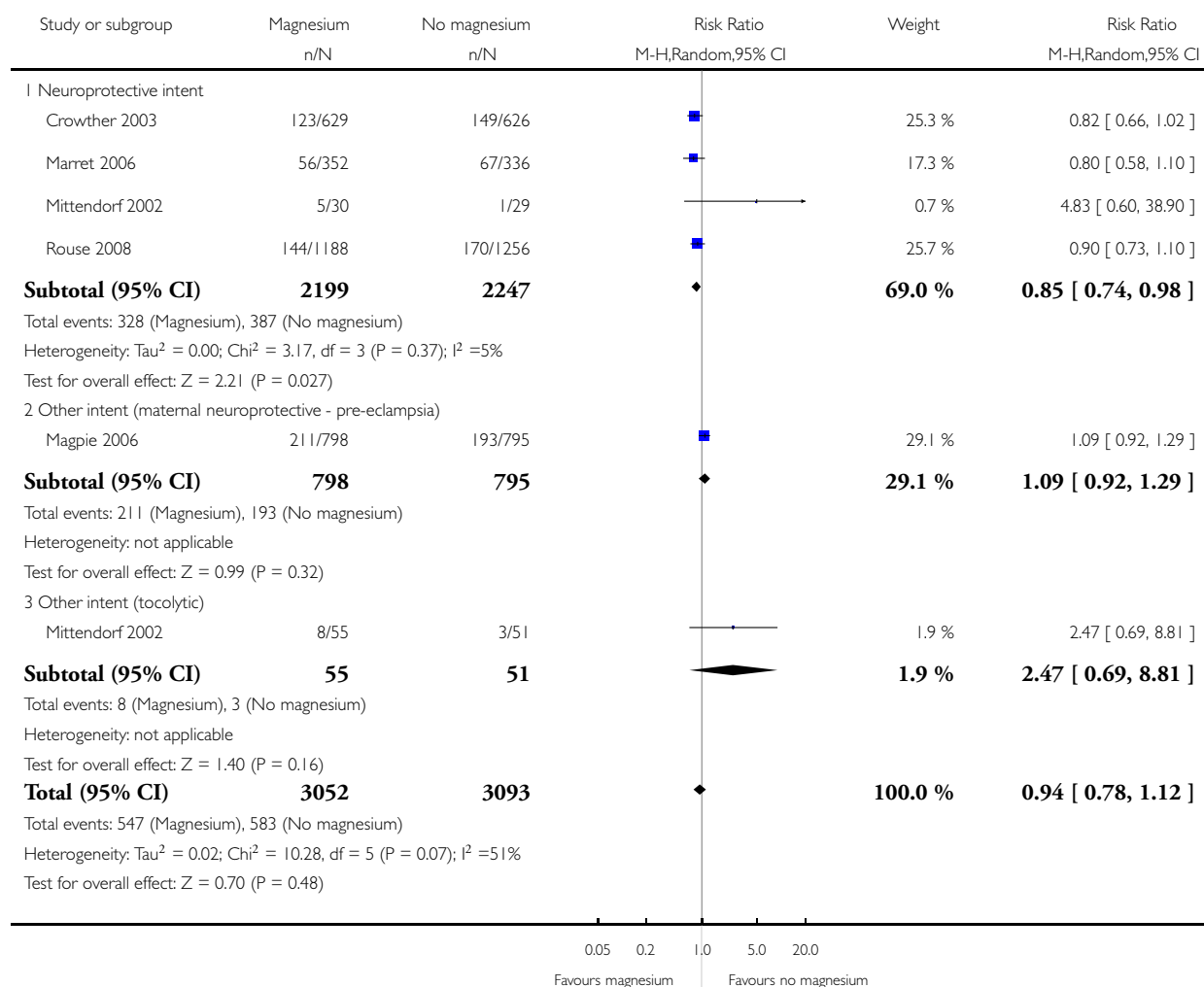


Analysis 1.11. Comparison 1 Magnesium versus no magnesium, Outcome 11 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

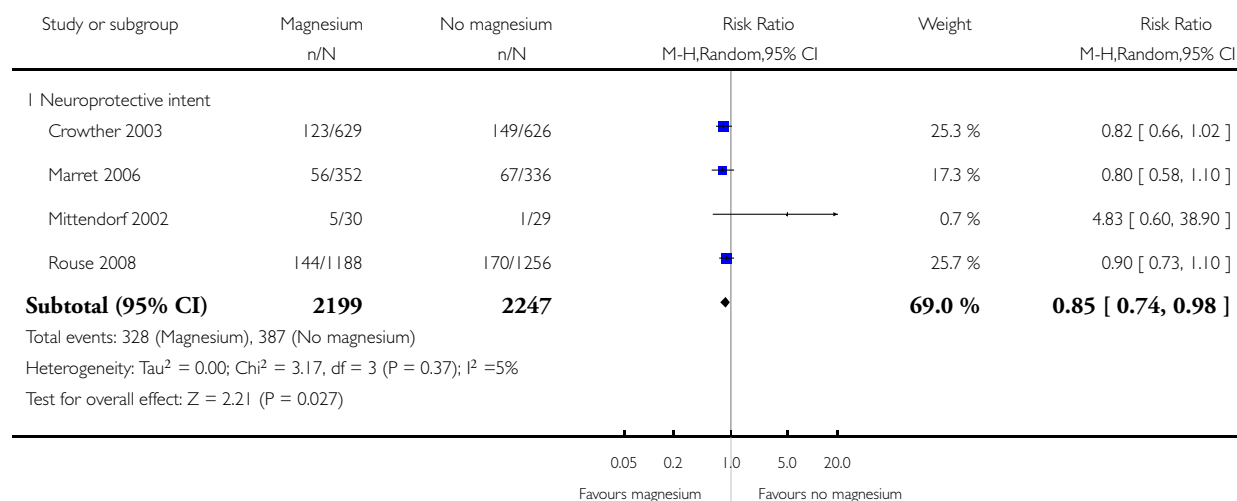
Outcome: 11 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

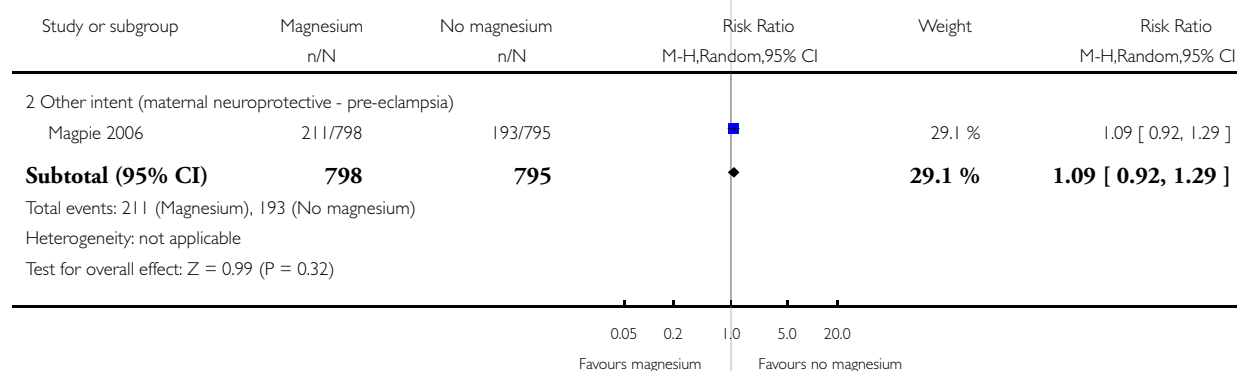
Outcome: II Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

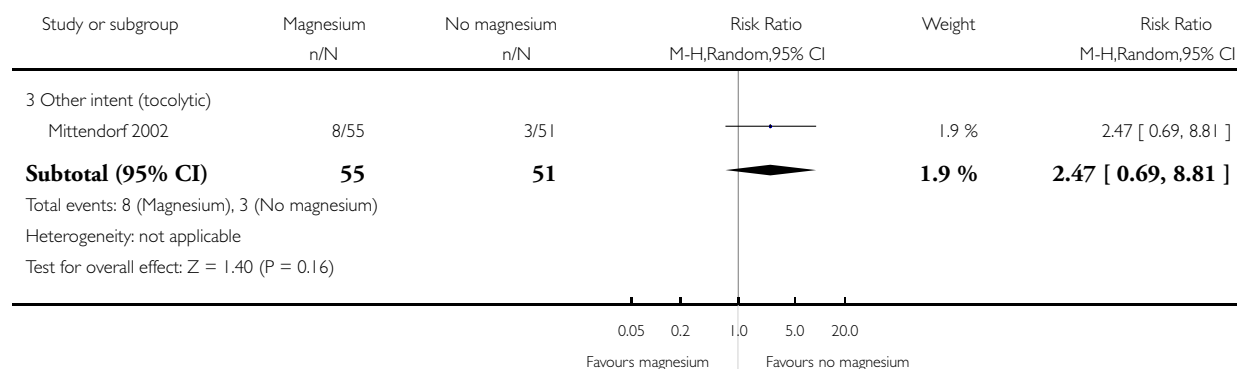
Outcome: II Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 11 Death or cerebral palsy

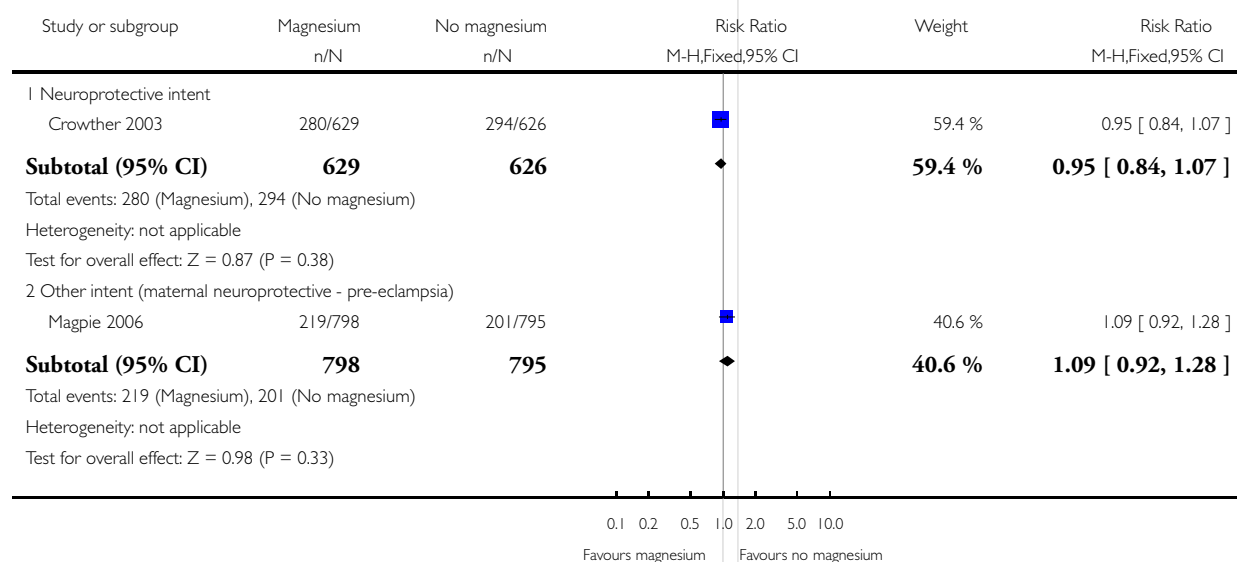


Analysis 1.12. Comparison I Magnesium versus no magnesium, Outcome 12 Death or any neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 12 Death or any neurological impairment



(Continued ...)

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Study or subgroup	Magnesium n/N	No magnesium n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total (95% CI)	1427	1421		100.0 %	1.00 [0.91, 1.11]
Total events: 499 (Magnesium), 495 (No magnesium)					
Heterogeneity: Chi ² = 1.74, df = 1 (P = 0.19); I ² = 42%					
Test for overall effect: Z = 0.07 (P = 0.94)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0
Favours magnesium Favours no magnesium

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 12 Death or any neurological impairment

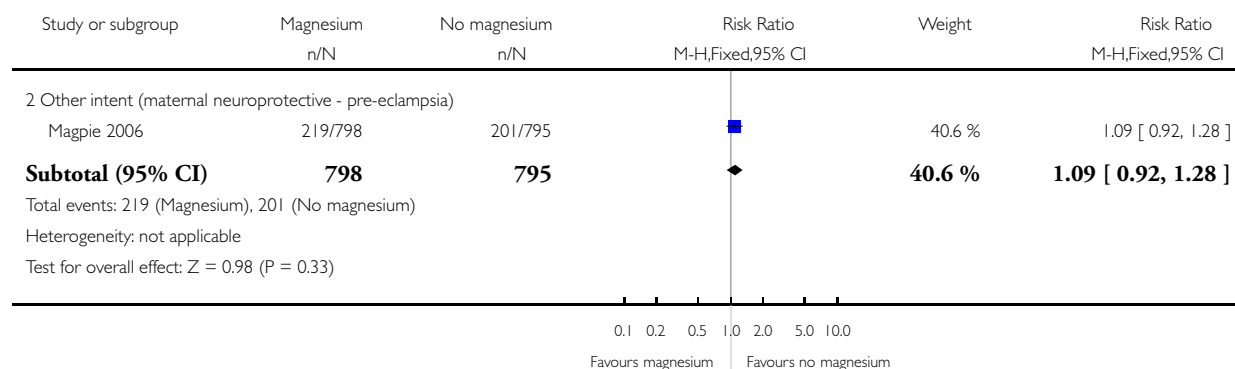
Study or subgroup	Magnesium n/N	No magnesium n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
I Neuroprotective intent					
Crowther 2003	280/629	294/626		59.4 %	0.95 [0.84, 1.07]
Subtotal (95% CI)	629	626		59.4 %	0.95 [0.84, 1.07]
Total events: 280 (Magnesium), 294 (No magnesium)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.87 (P = 0.38)					

0.1 0.2 0.5 1.0 2.0 5.0 10.0
Favours magnesium Favours no magnesium

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 12 Death or any neurological impairment

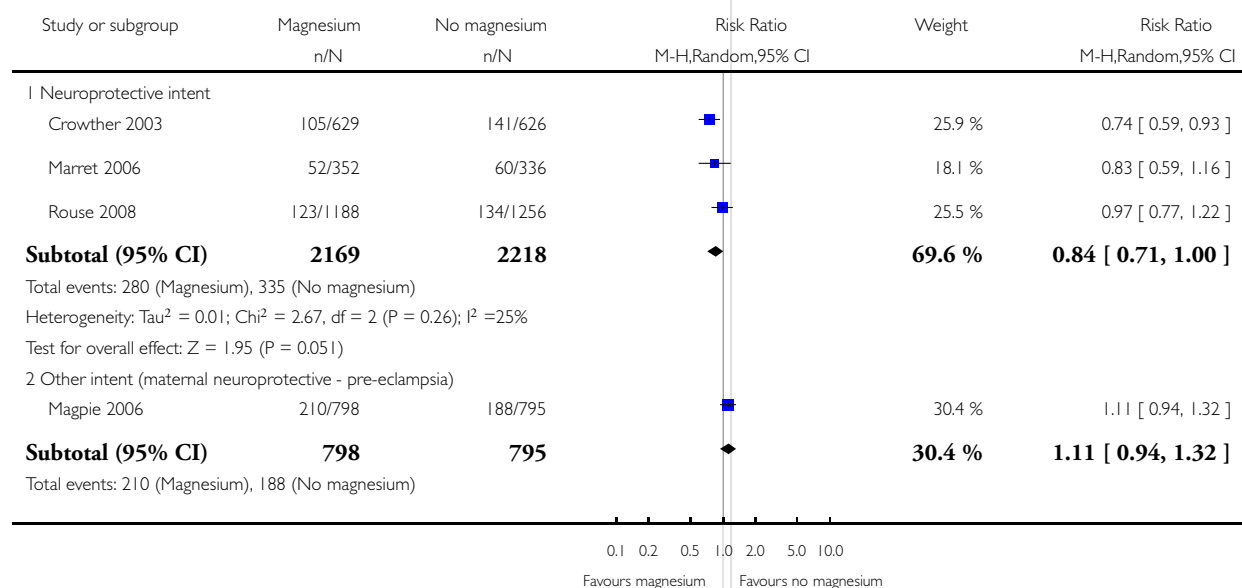


Analysis 1.13. Comparison I Magnesium versus no magnesium, Outcome 13 Death or substantial gross motor dysfunction.

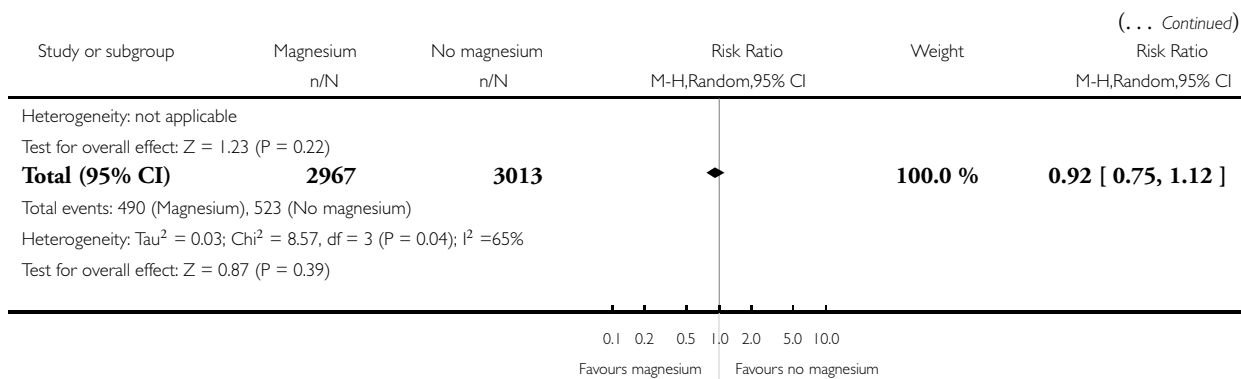
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 13 Death or substantial gross motor dysfunction



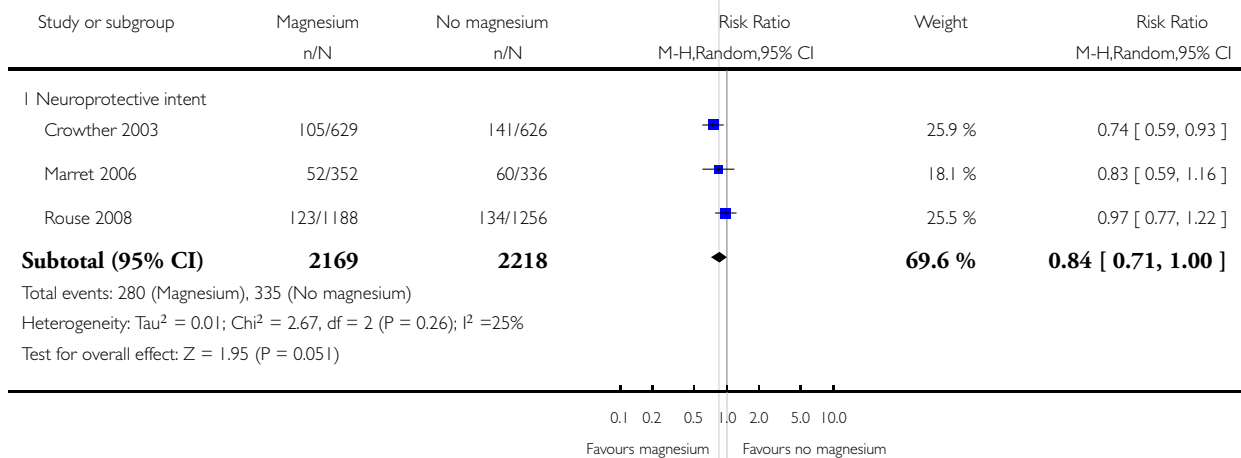
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

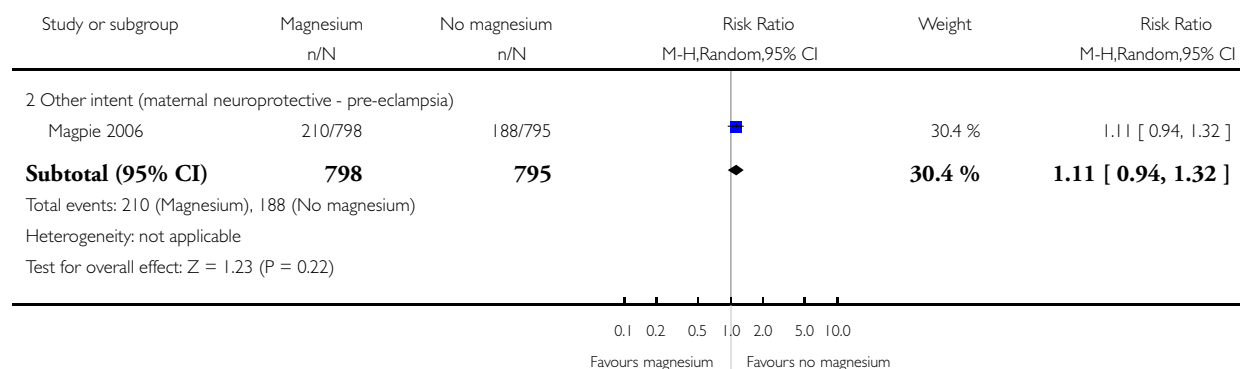
Outcome: 13 Death or substantial gross motor dysfunction



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 13 Death or substantial gross motor dysfunction

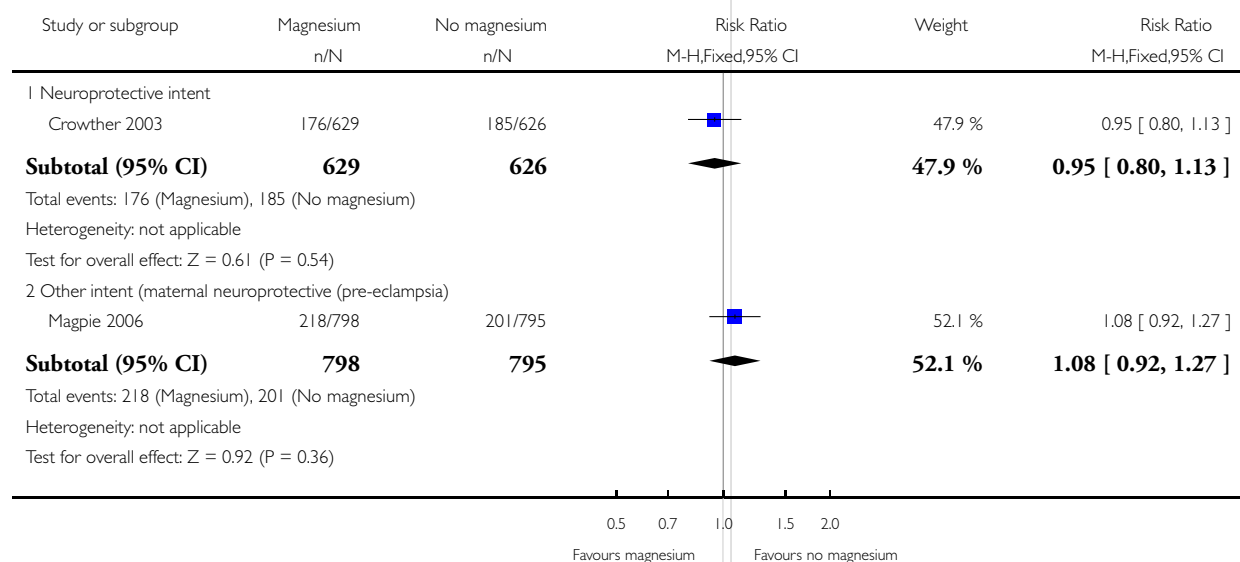


Analysis 1.14. Comparison I Magnesium versus no magnesium, Outcome 14 Death or major neurological disability.

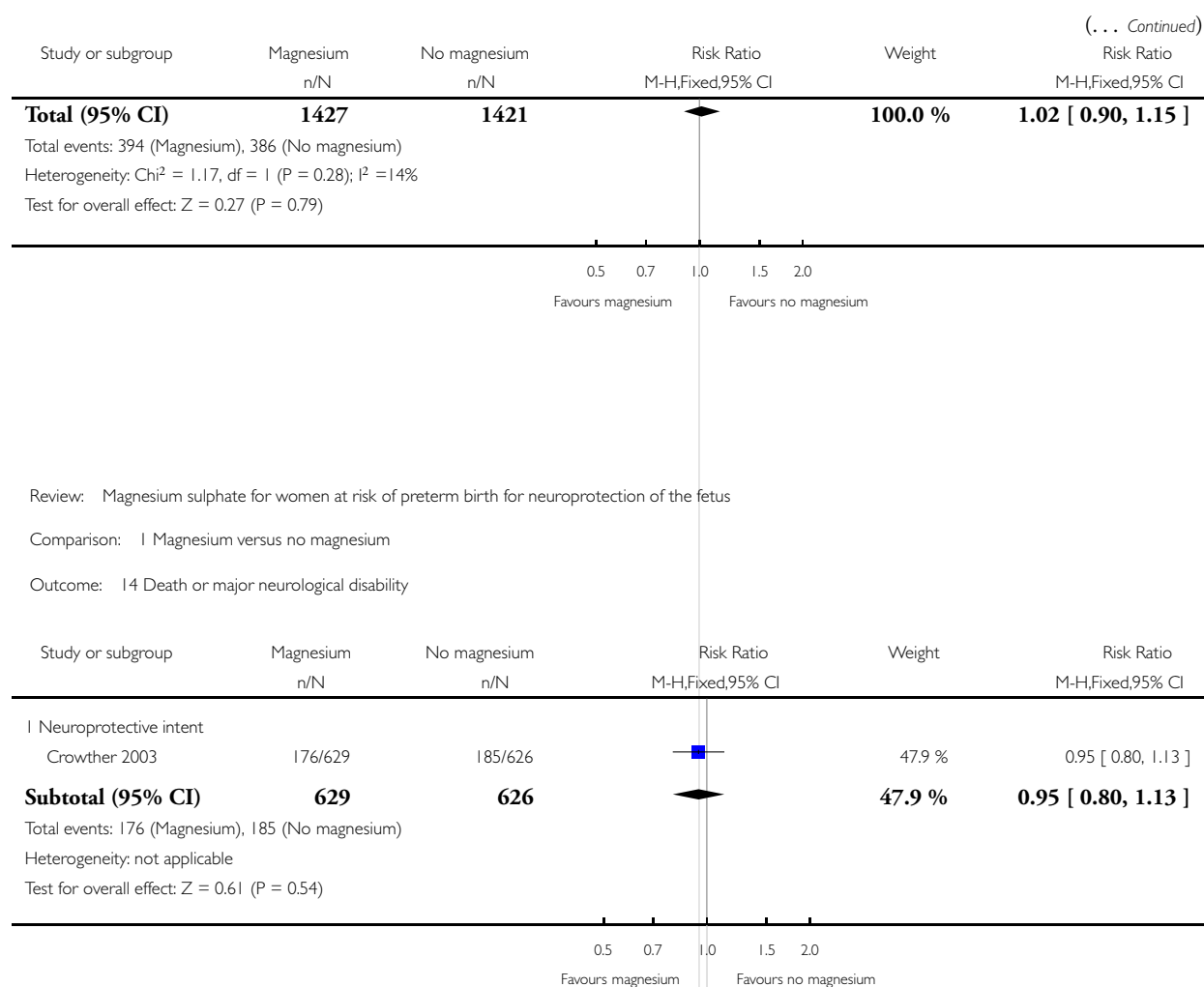
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 14 Death or major neurological disability



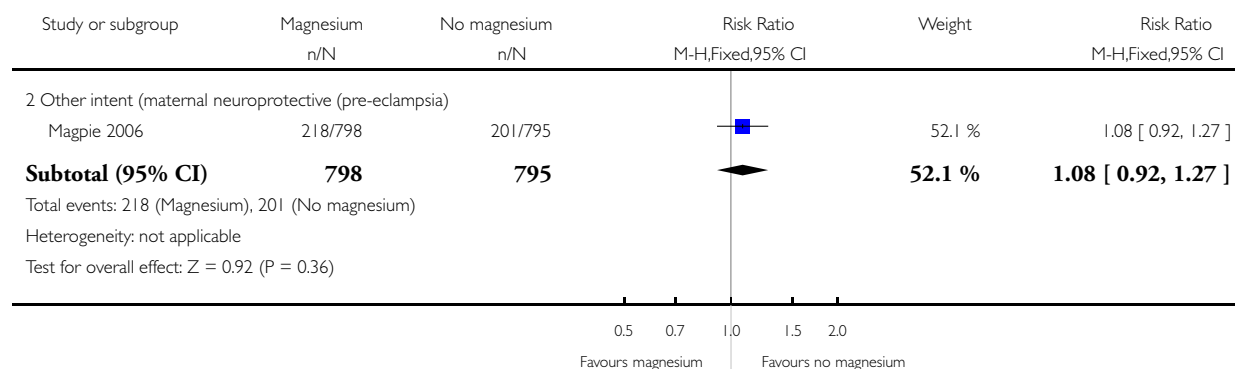
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 14 Death or major neurological disability

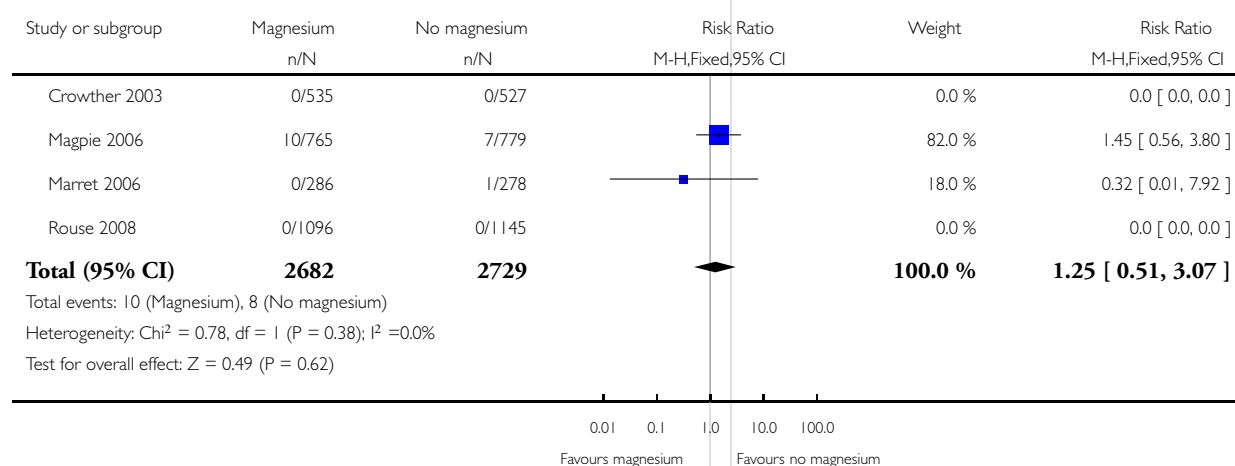


Analysis 1.15. Comparison I Magnesium versus no magnesium, Outcome 15 Maternal mortality.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 15 Maternal mortality

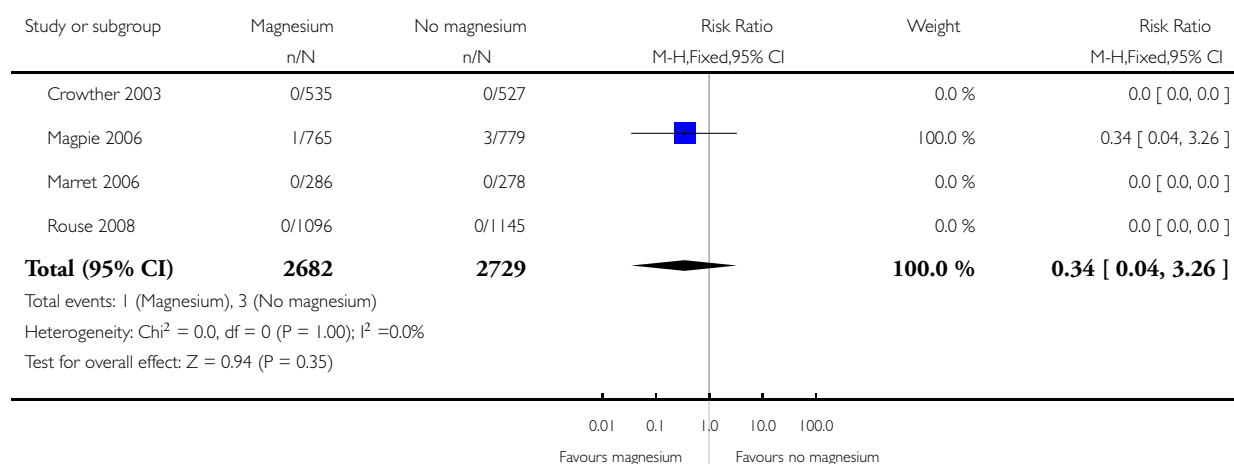


Analysis 1.16. Comparison 1 Magnesium versus no magnesium, Outcome 16 Maternal cardiac arrest.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 16 Maternal cardiac arrest

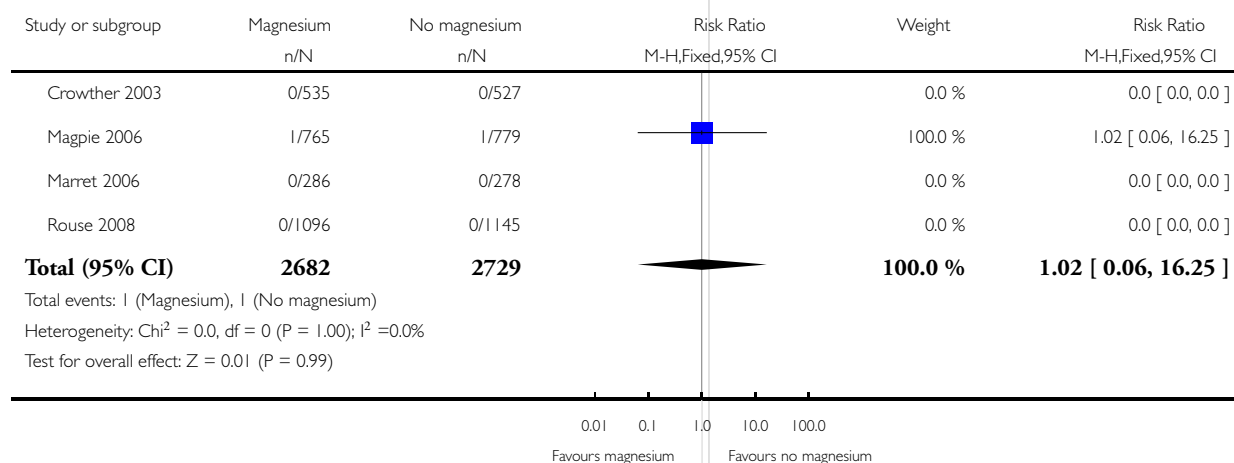


Analysis 1.17. Comparison 1 Magnesium versus no magnesium, Outcome 17 Maternal respiratory arrest.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 17 Maternal respiratory arrest

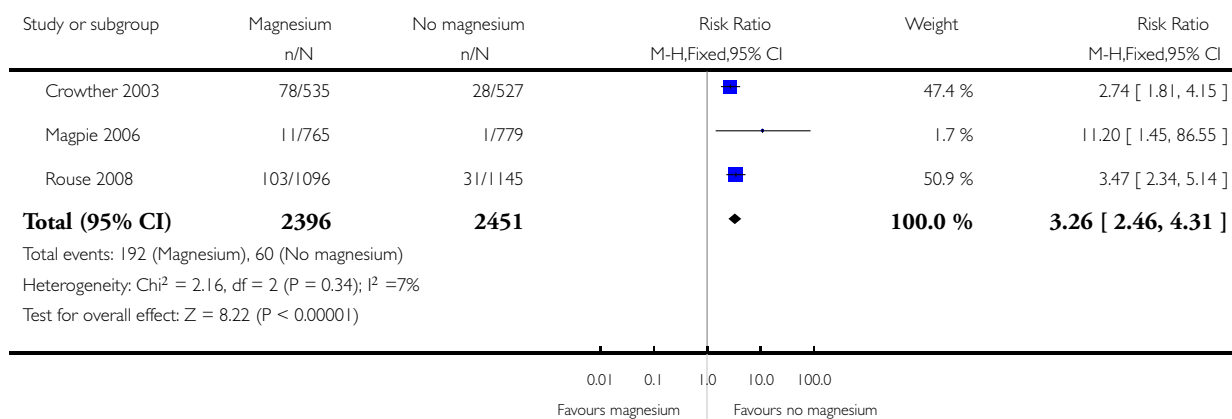


Analysis 1.18. Comparison 1 Magnesium versus no magnesium, Outcome 18 Cessation of maternal therapy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 18 Cessation of maternal therapy

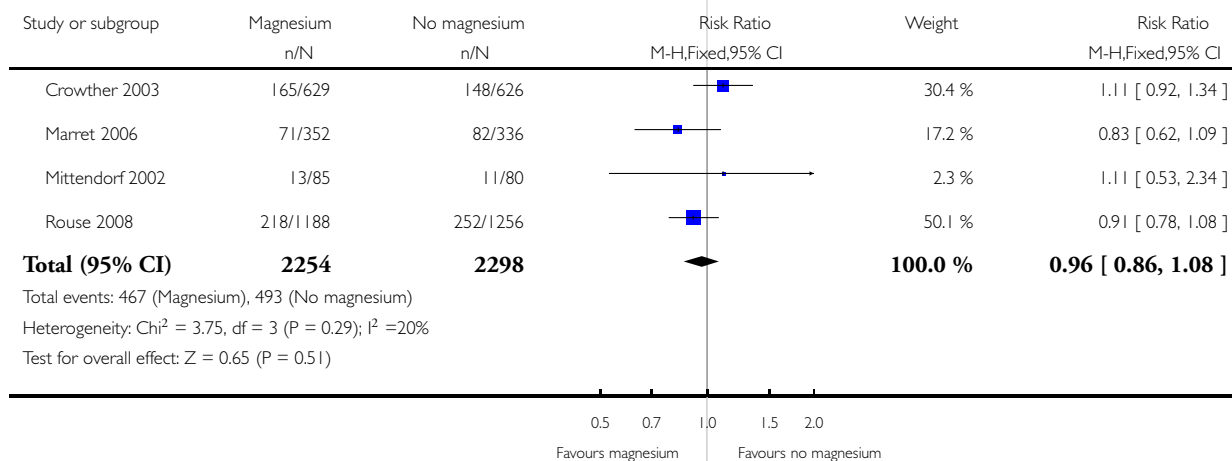


Analysis 1.19. Comparison 1 Magnesium versus no magnesium, Outcome 19 Intraventricular haemorrhage.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 19 Intraventricular haemorrhage

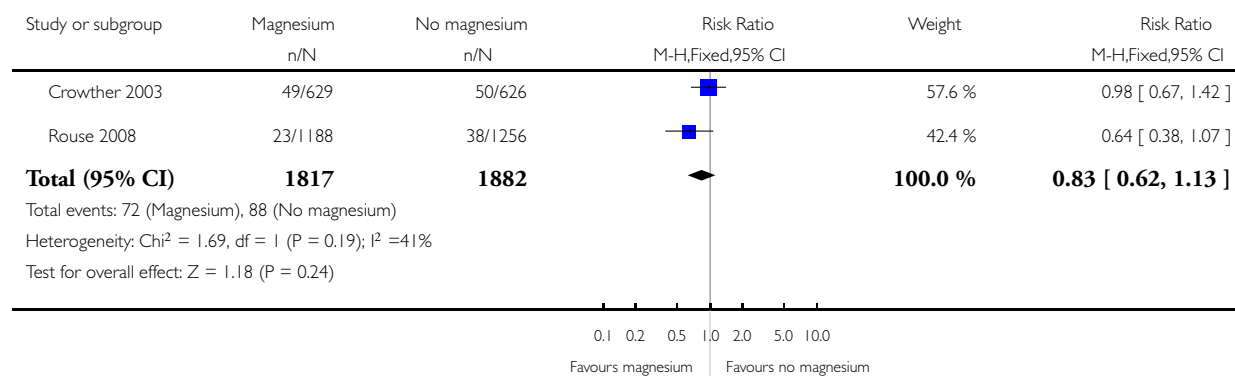


Analysis 1.20. Comparison 1 Magnesium versus no magnesium, Outcome 20 Intraventricular haemorrhage 3/4.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 20 Intraventricular haemorrhage 3/4

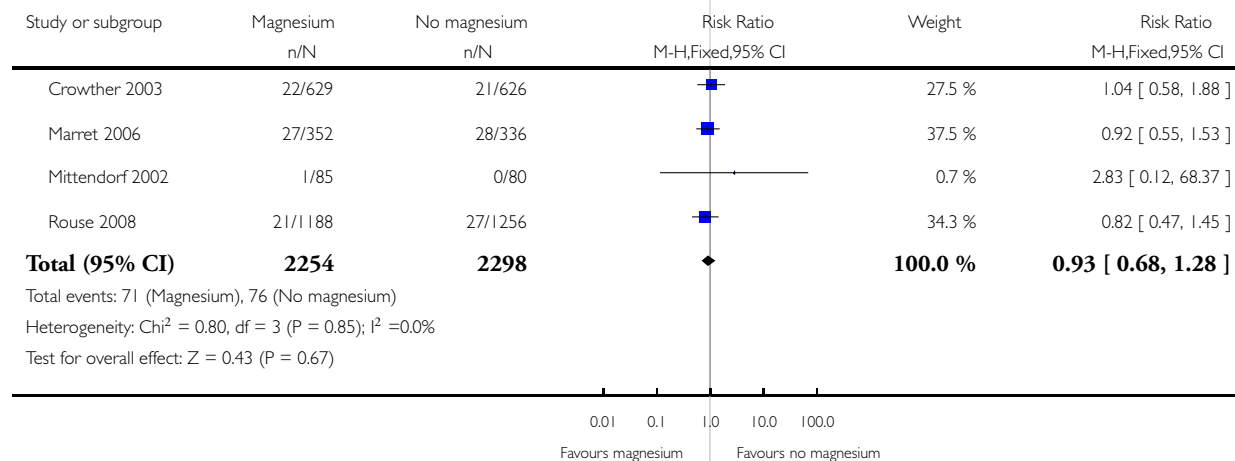


Analysis 1.21. Comparison 1 Magnesium versus no magnesium, Outcome 21 Periventricular leucomalacia.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 21 Periventricular leucomalacia

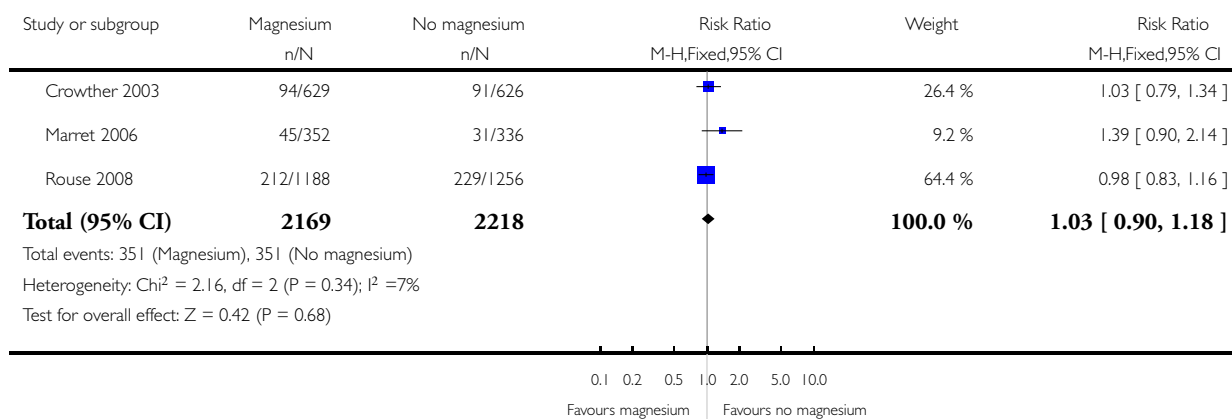


Analysis 1.22. Comparison 1 Magnesium versus no magnesium, Outcome 22 Apgar score < 7 at 5 minutes.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 22 Apgar score < 7 at 5 minutes

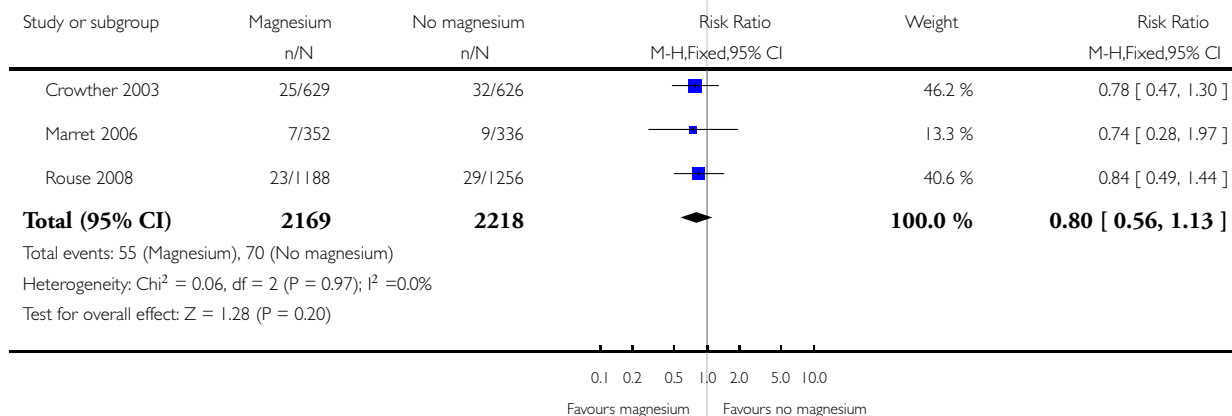


Analysis 1.23. Comparison 1 Magnesium versus no magnesium, Outcome 23 Neonatal convulsions.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 23 Neonatal convulsions

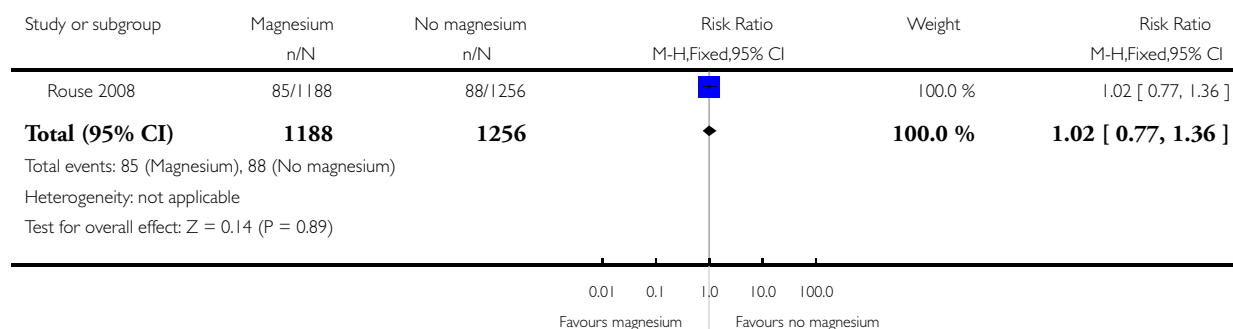


Analysis 1.24. Comparison 1 Magnesium versus no magnesium, Outcome 24 Neonatal hypotonia.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 24 Neonatal hypotonia

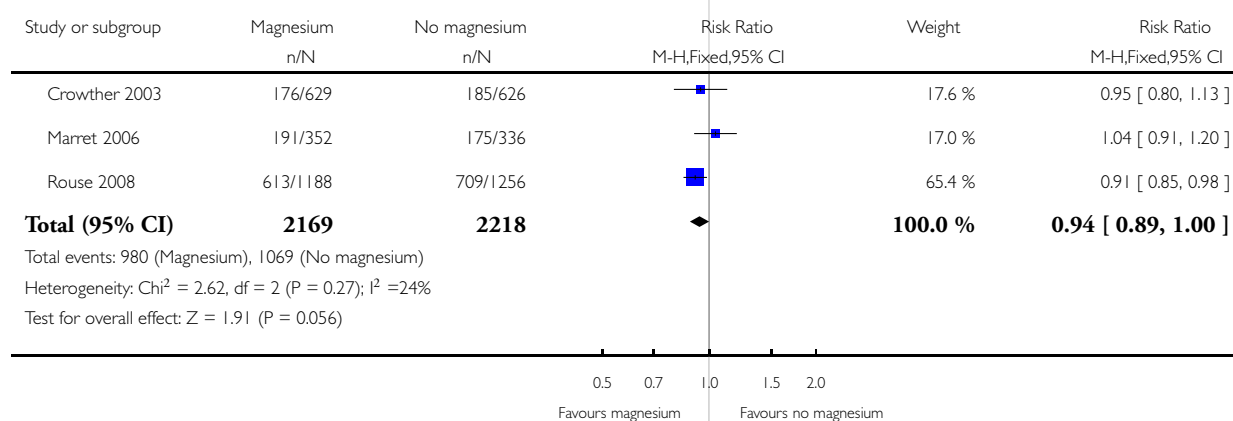


Analysis 1.25. Comparison 1 Magnesium versus no magnesium, Outcome 25 Ongoing respiratory support.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 25 Ongoing respiratory support

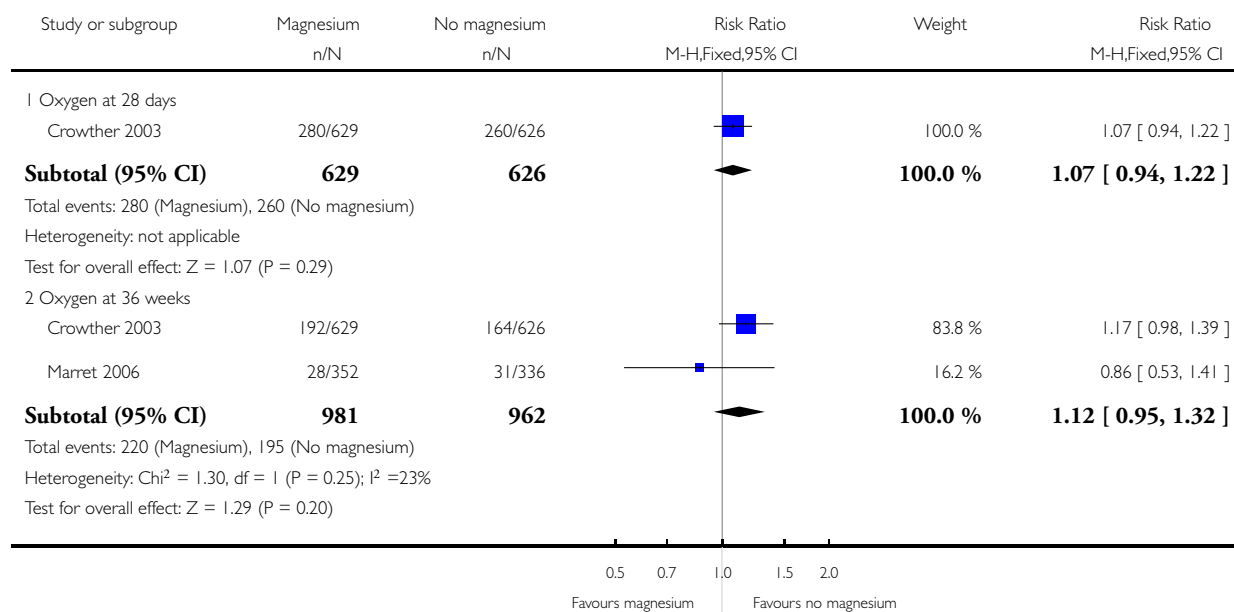


Analysis 1.26. Comparison 1 Magnesium versus no magnesium, Outcome 26 Chronic lung disease.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

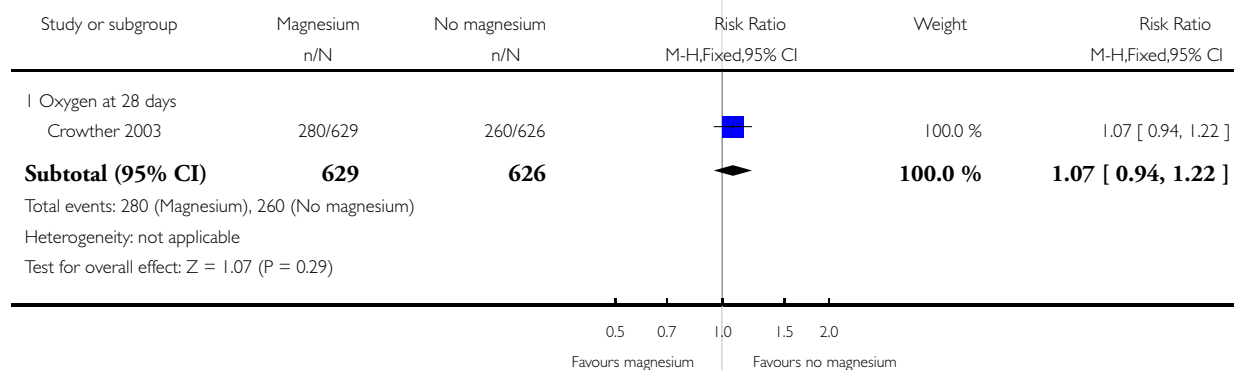
Outcome: 26 Chronic lung disease



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

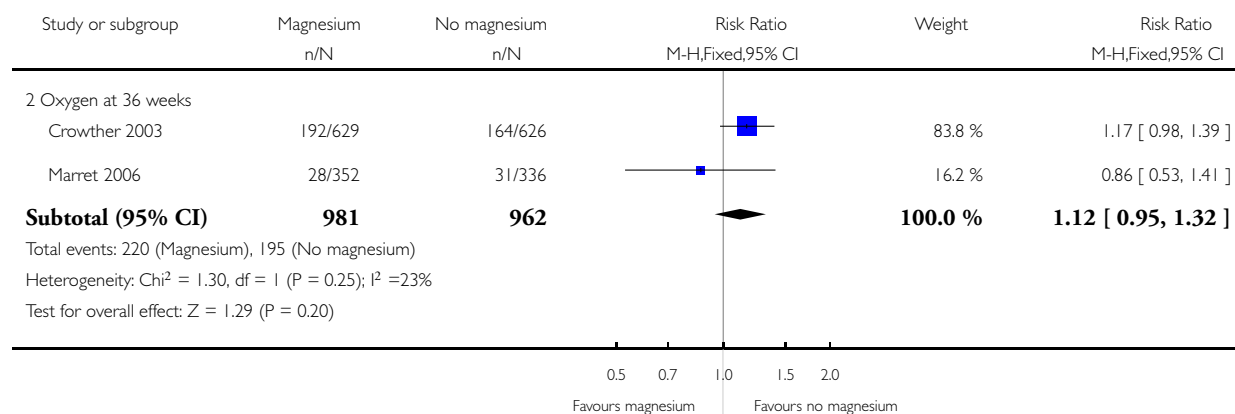
Outcome: 26 Chronic lung disease



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 26 Chronic lung disease

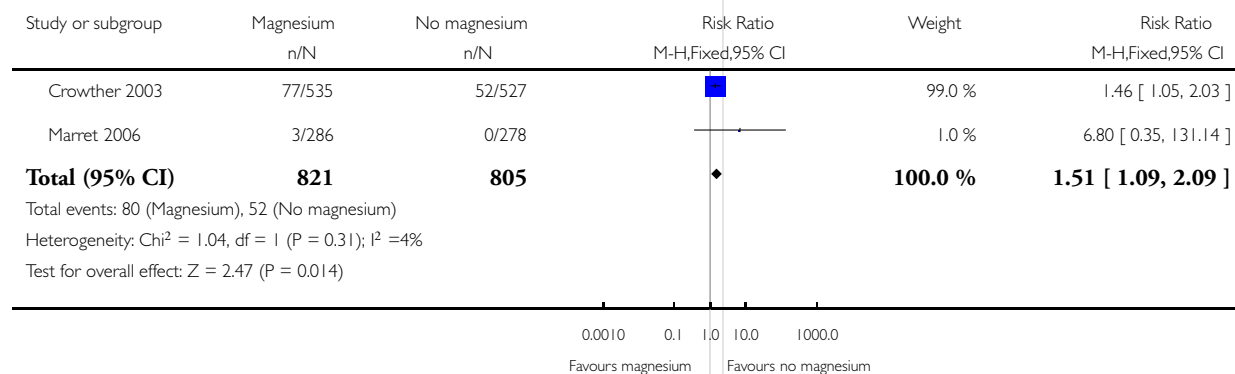


Analysis 1.27. Comparison I Magnesium versus no magnesium, Outcome 27 Maternal hypotension.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: I Magnesium versus no magnesium

Outcome: 27 Maternal hypotension

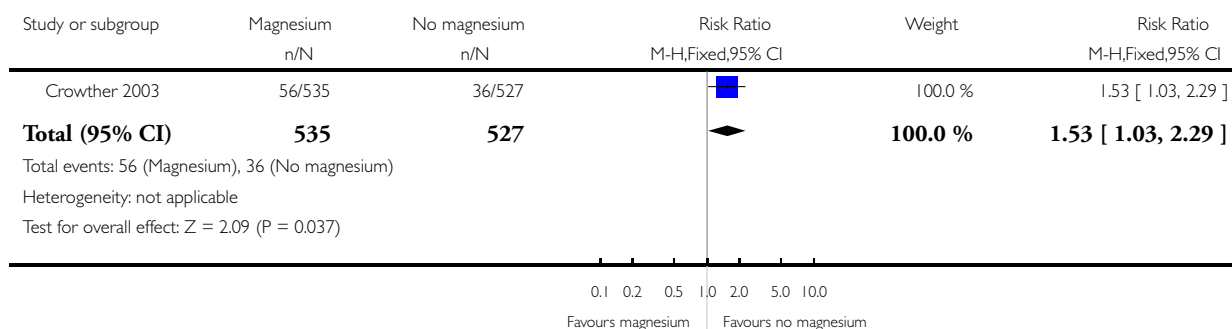


Analysis 1.28. Comparison 1 Magnesium versus no magnesium, Outcome 28 Maternal tachycardia.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 28 Maternal tachycardia

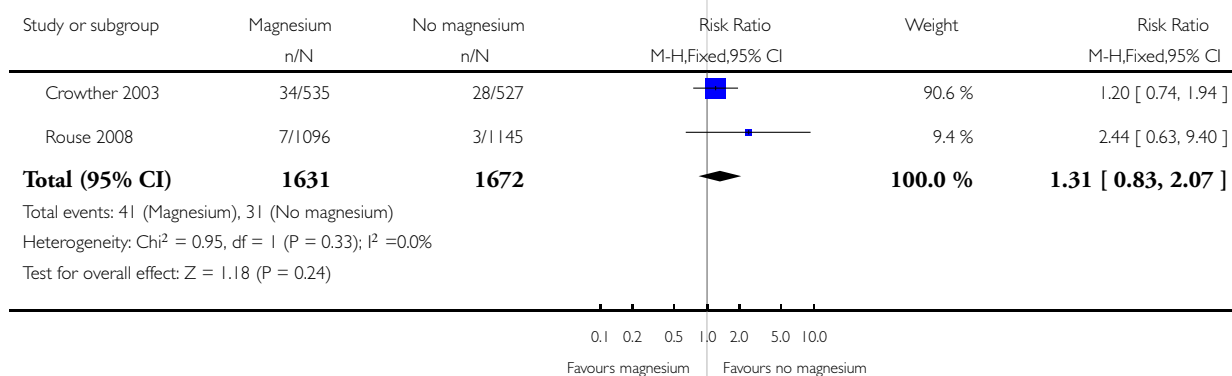


Analysis 1.29. Comparison 1 Magnesium versus no magnesium, Outcome 29 Maternal respiratory depression.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 29 Maternal respiratory depression

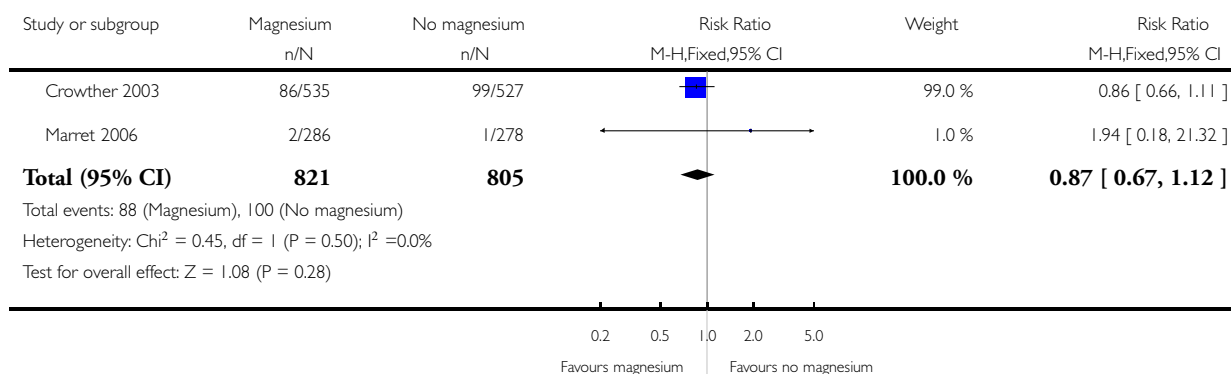


Analysis 1.30. Comparison 1 Magnesium versus no magnesium, Outcome 30 Postpartum haemorrhage.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 30 Postpartum haemorrhage

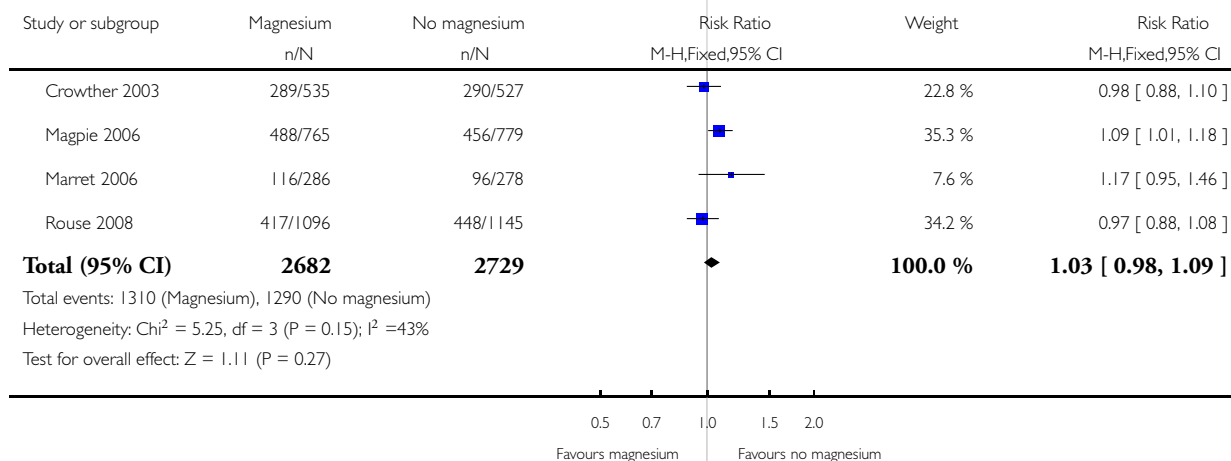


Analysis 1.31. Comparison 1 Magnesium versus no magnesium, Outcome 31 Caesarean birth.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 31 Caesarean birth

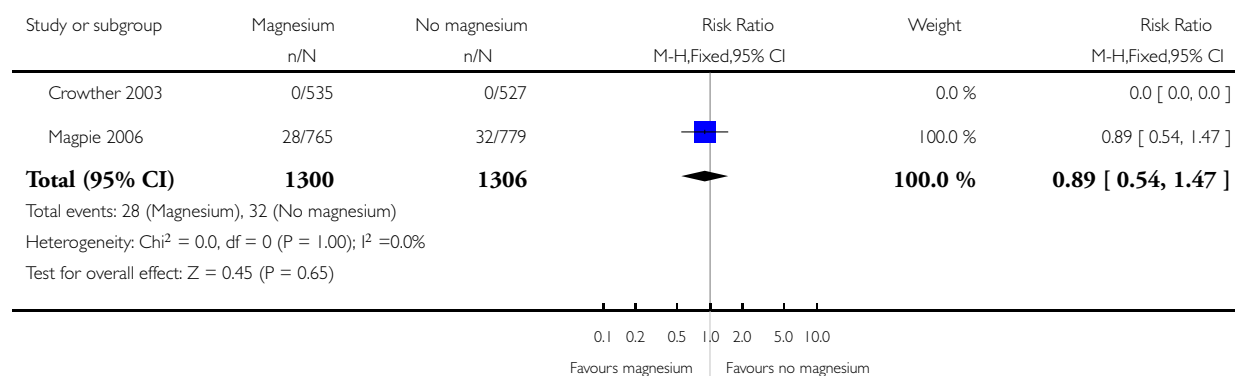


Analysis 1.32. Comparison 1 Magnesium versus no magnesium, Outcome 32 Mother admitted to intensive care unit.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 32 Mother admitted to intensive care unit

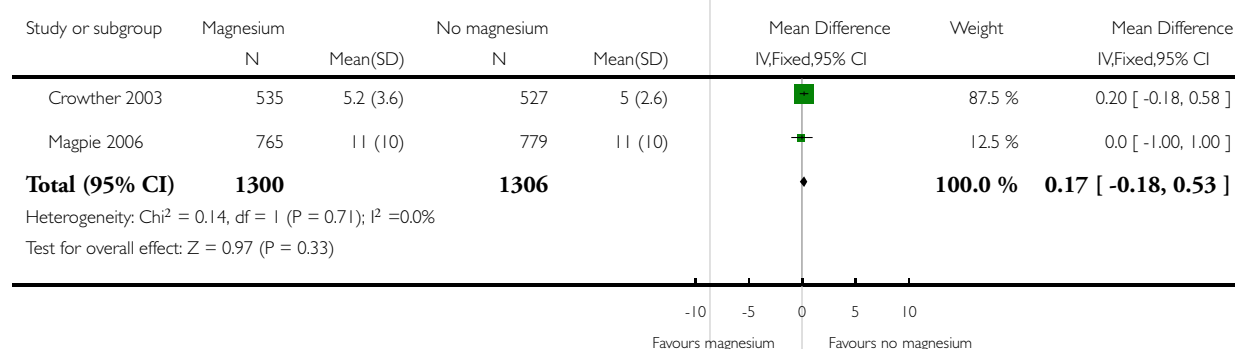


Analysis 1.33. Comparison 1 Magnesium versus no magnesium, Outcome 33 Duration of mother's hospital stay (days).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 33 Duration of mother's hospital stay (days)

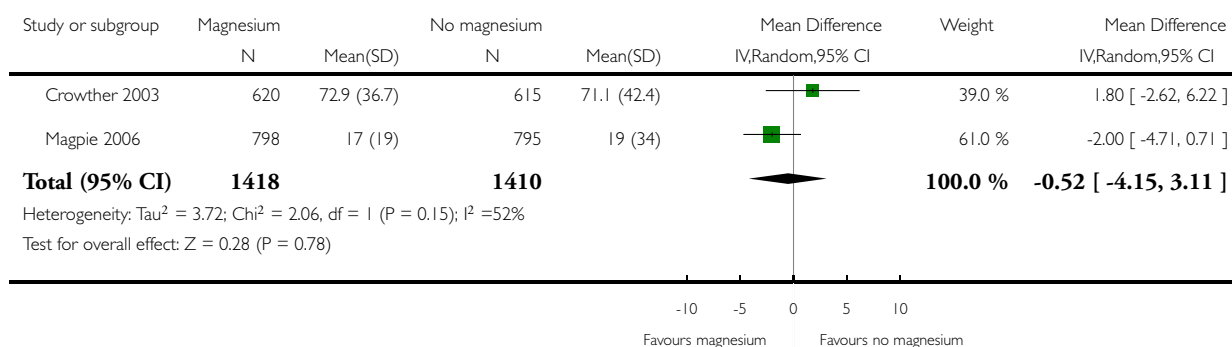


Analysis 1.34. Comparison 1 Magnesium versus no magnesium, Outcome 34 Duration of primary hospital stay for babies (days).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 1 Magnesium versus no magnesium

Outcome: 34 Duration of primary hospital stay for babies (days)

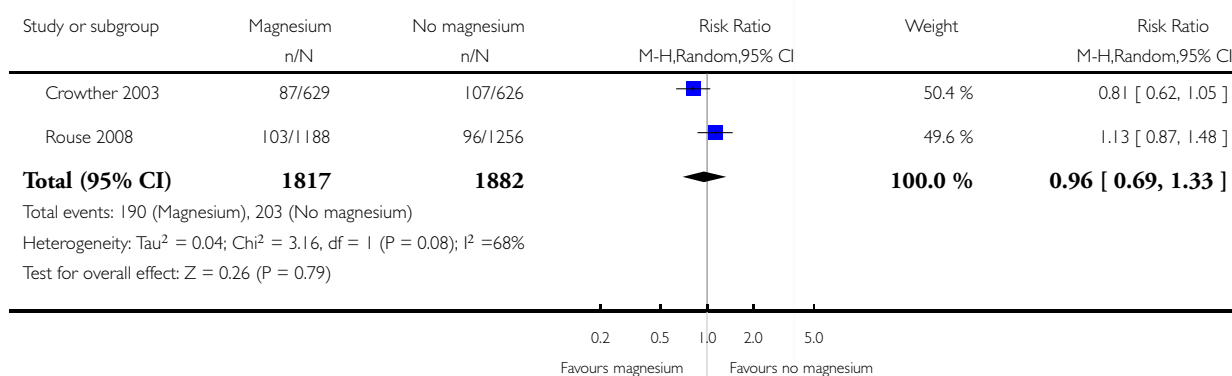


Analysis 2.1. Comparison 2 Studies with lowest risk of bias only, Outcome 1 Paediatric mortality.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 1 Paediatric mortality

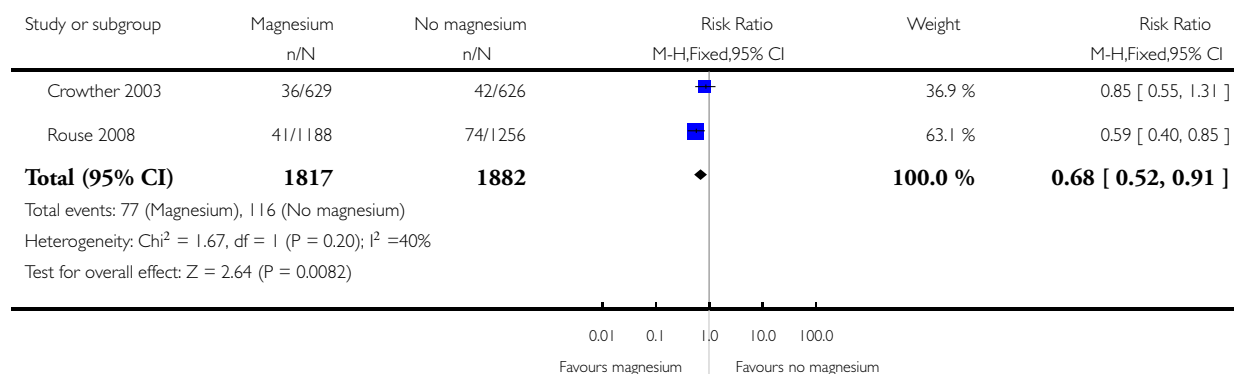


Analysis 2.2. Comparison 2 Studies with lowest risk of bias only, Outcome 2 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 2 Cerebral palsy

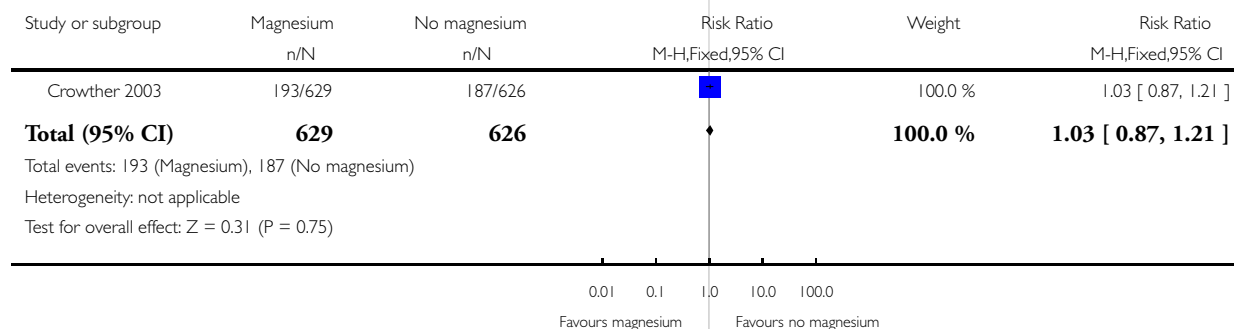


Analysis 2.3. Comparison 2 Studies with lowest risk of bias only, Outcome 3 Neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 3 Neurological impairment

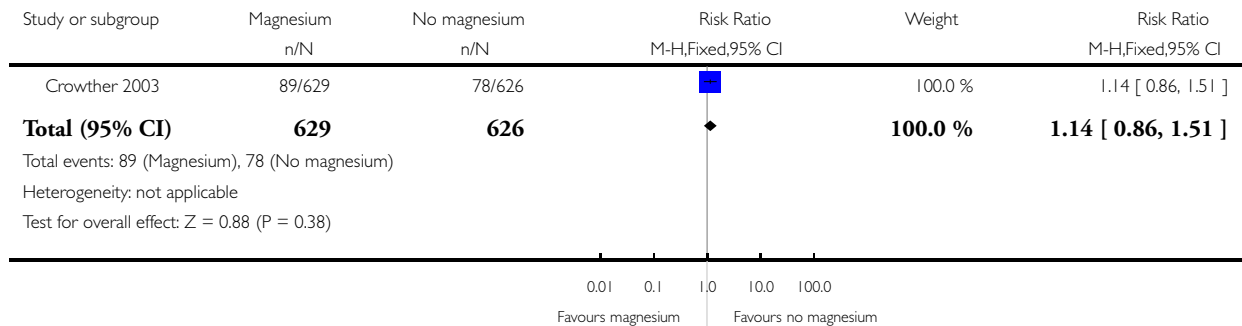


Analysis 2.4. Comparison 2 Studies with lowest risk of bias only, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 4 Major neurological disability

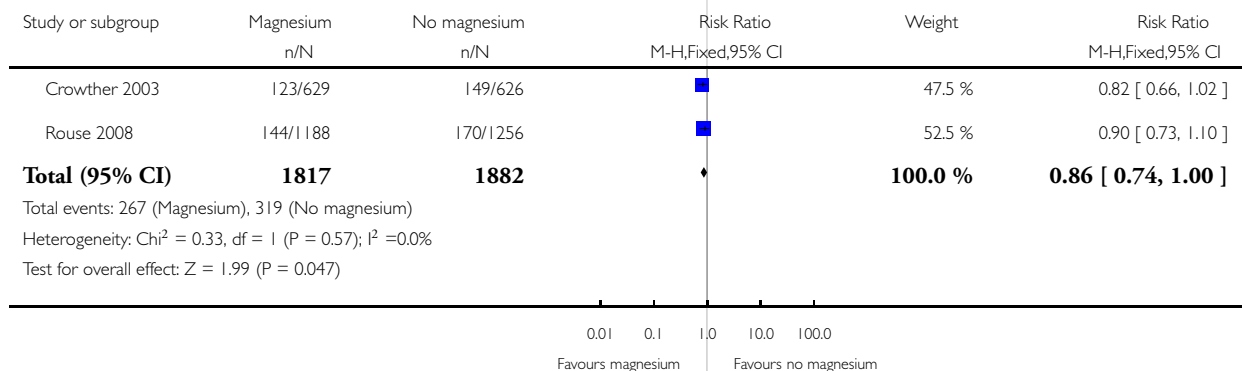


Analysis 2.5. Comparison 2 Studies with lowest risk of bias only, Outcome 5 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 5 Death or cerebral palsy

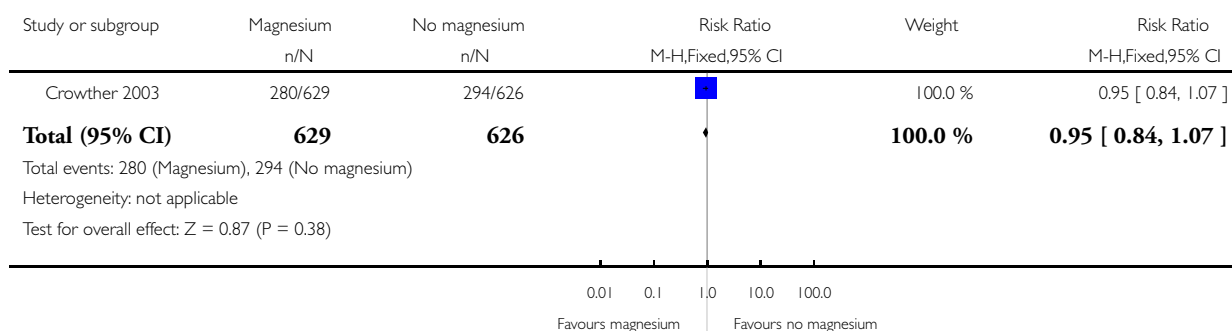


Analysis 2.6. Comparison 2 Studies with lowest risk of bias only, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 6 Death or neurological impairment

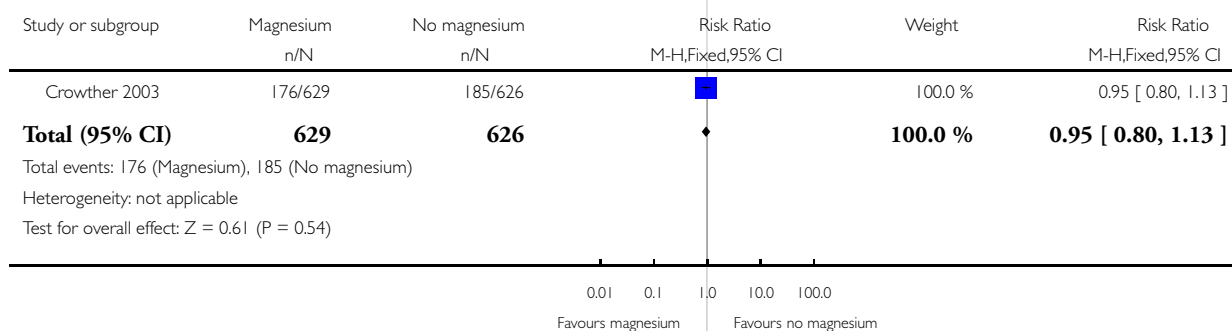


Analysis 2.7. Comparison 2 Studies with lowest risk of bias only, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 2 Studies with lowest risk of bias only

Outcome: 7 Death or major neurological disability

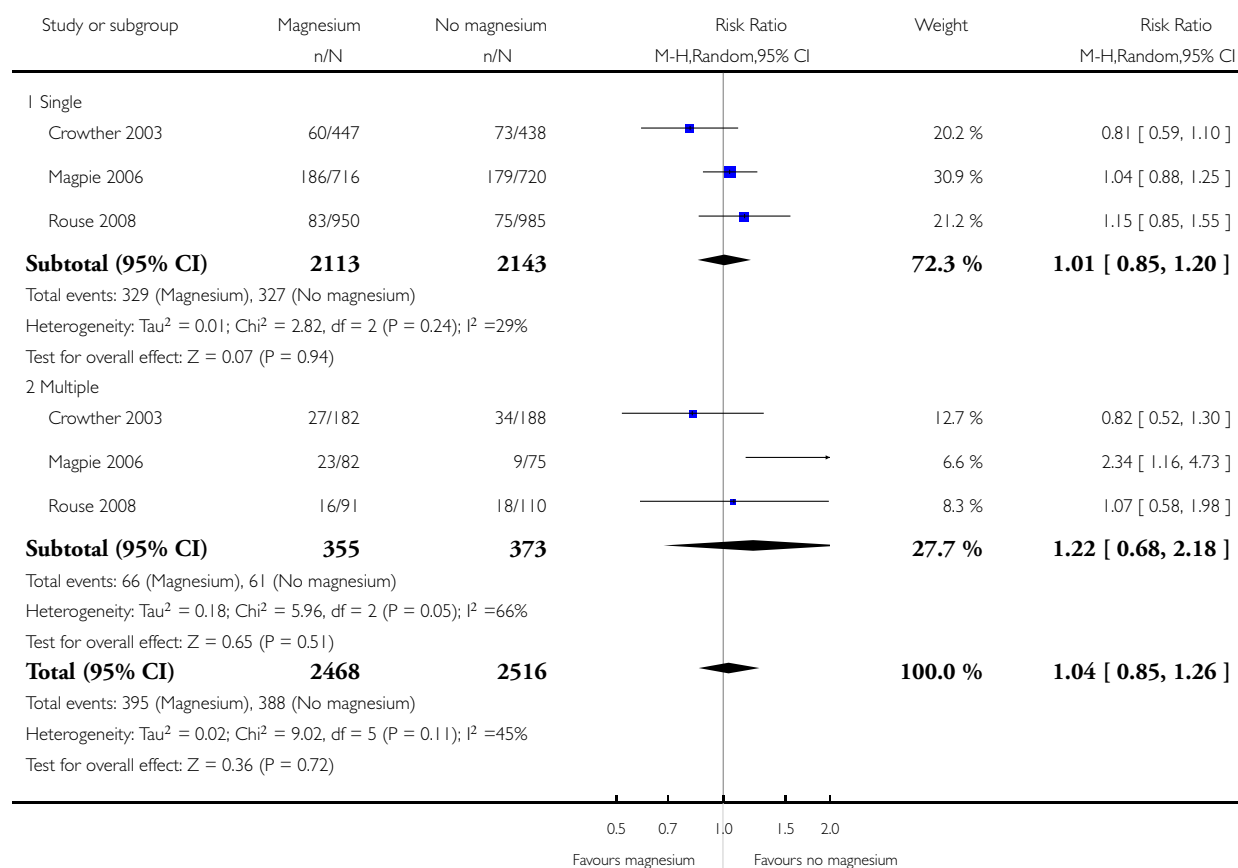


Analysis 3.1. Comparison 3 Single or multiple pregnancy subgroup, Outcome 1 Paediatric mortality (fetal and later).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

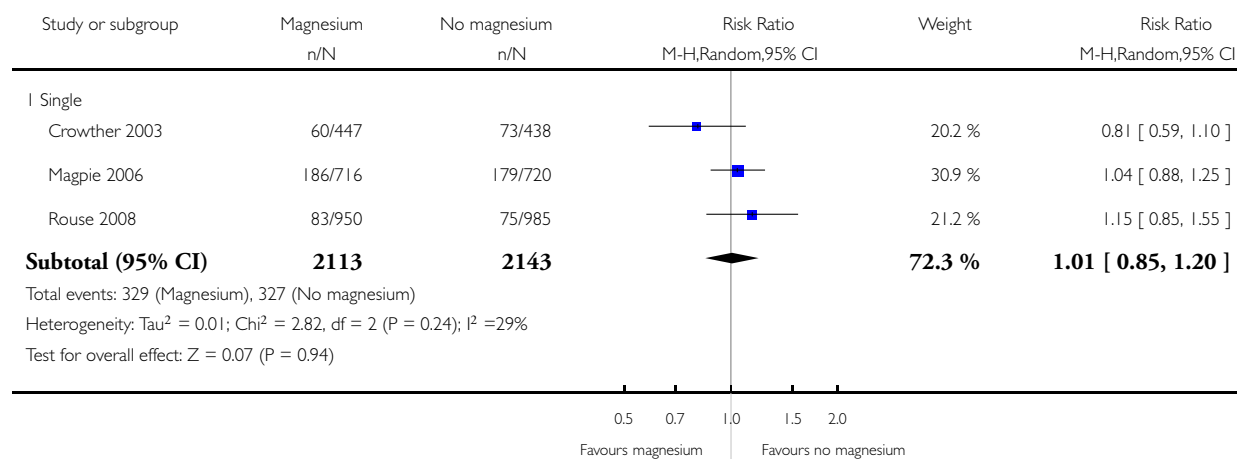
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

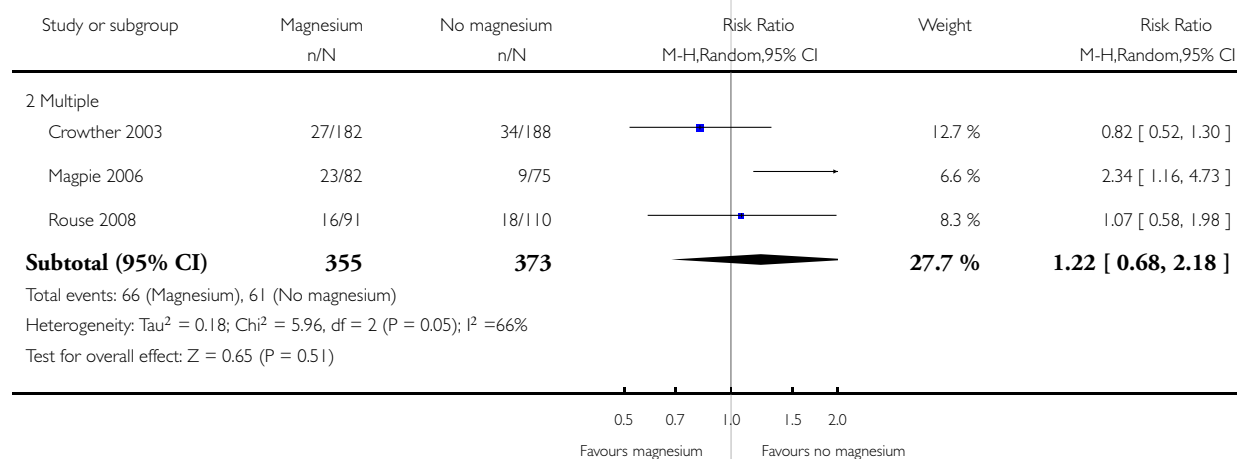
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 1 Paediatric mortality (fetal and later)

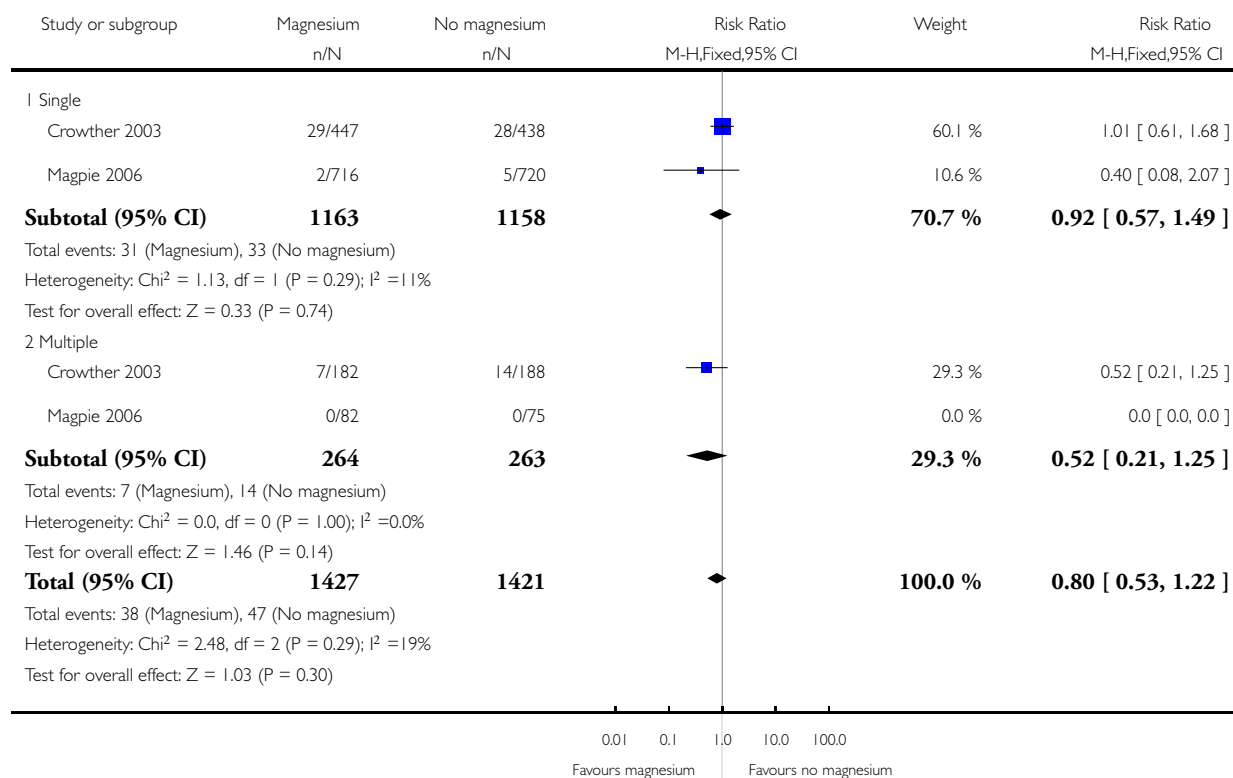


Analysis 3.2. Comparison 3 Single or multiple pregnancy subgroup, Outcome 2 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

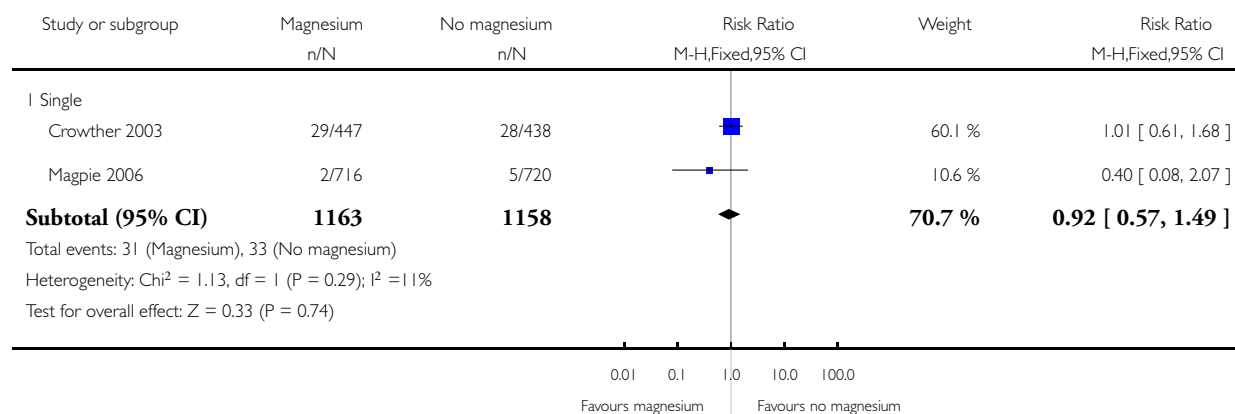
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

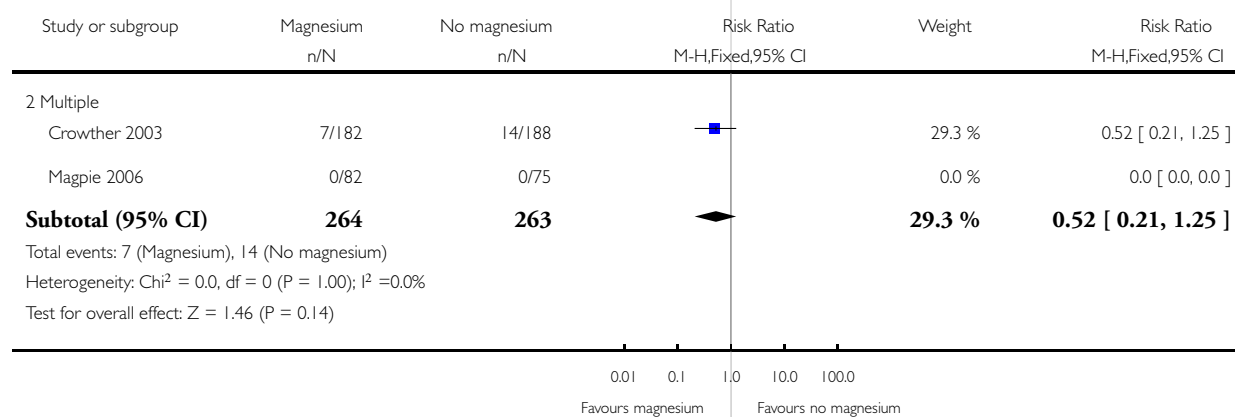
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 2 Cerebral palsy

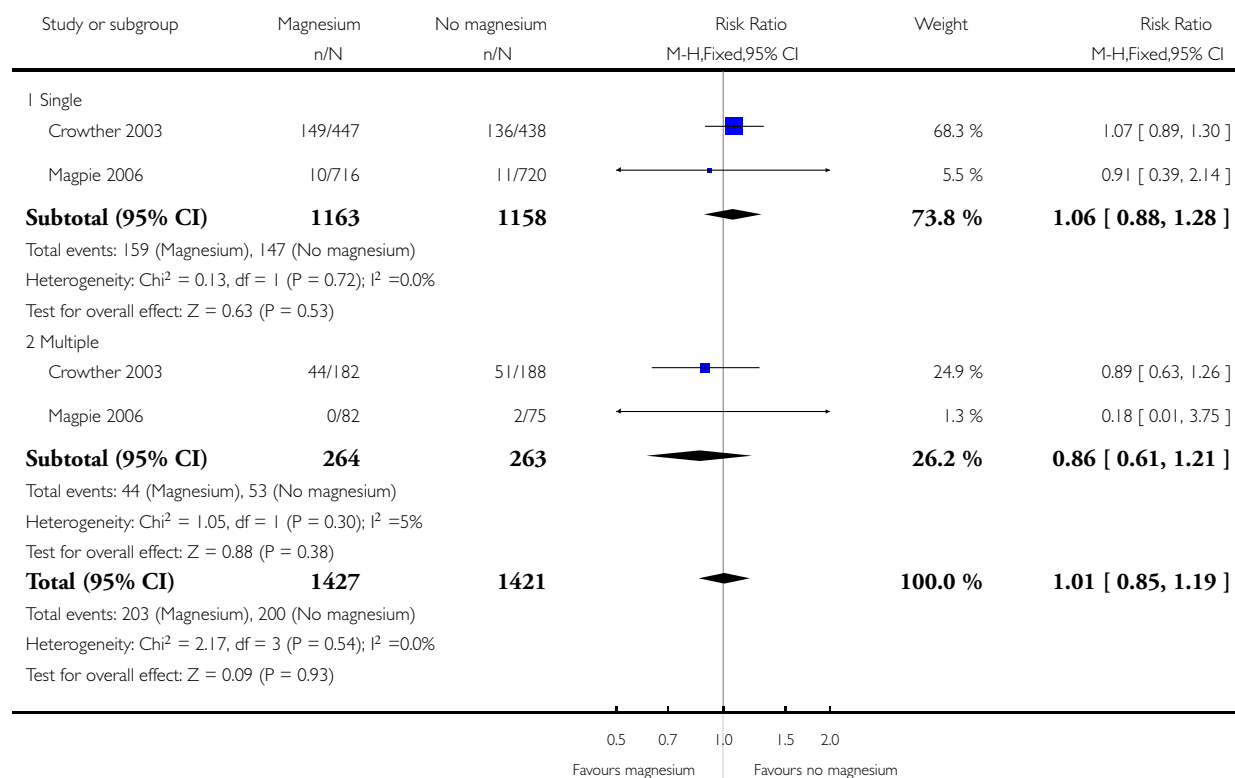


Analysis 3.3. Comparison 3 Single or multiple pregnancy subgroup, Outcome 3 Neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

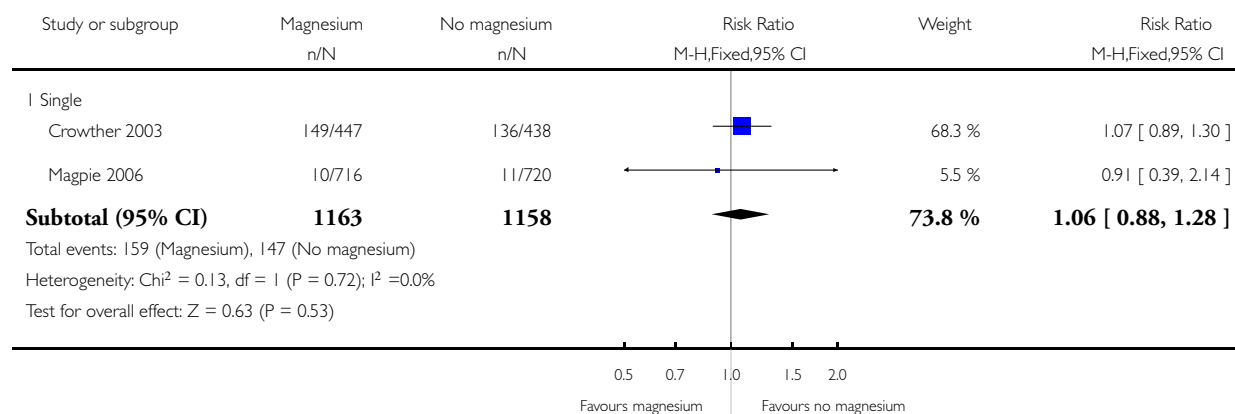
Outcome: 3 Neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

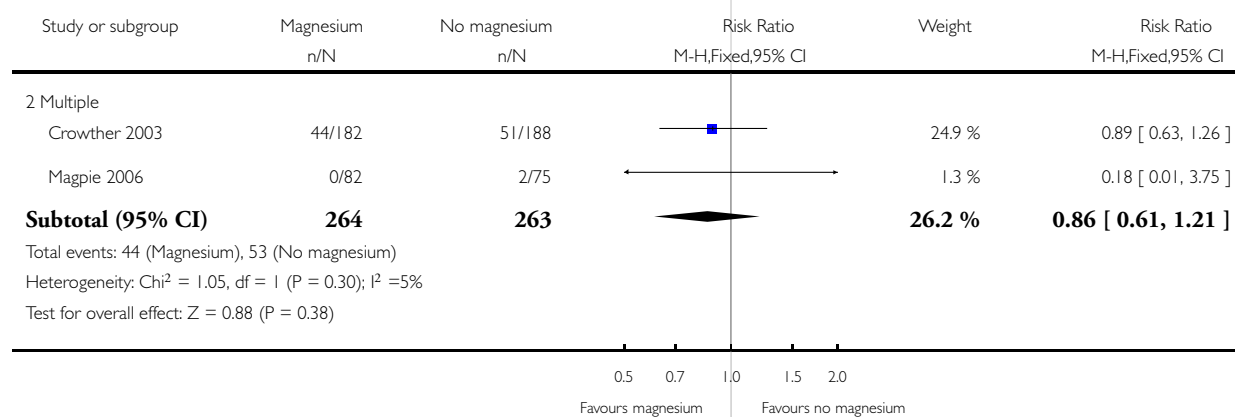
Outcome: 3 Neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 3 Neurological impairment

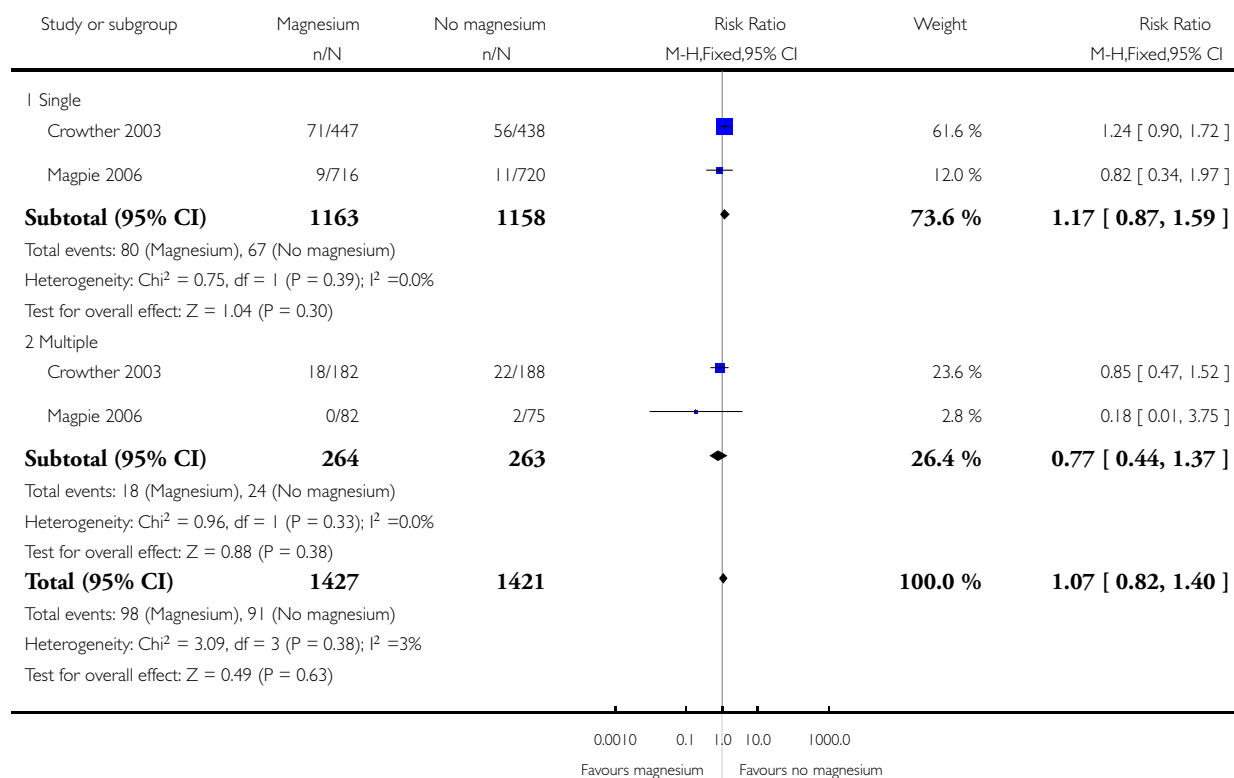


Analysis 3.4. Comparison 3 Single or multiple pregnancy subgroup, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

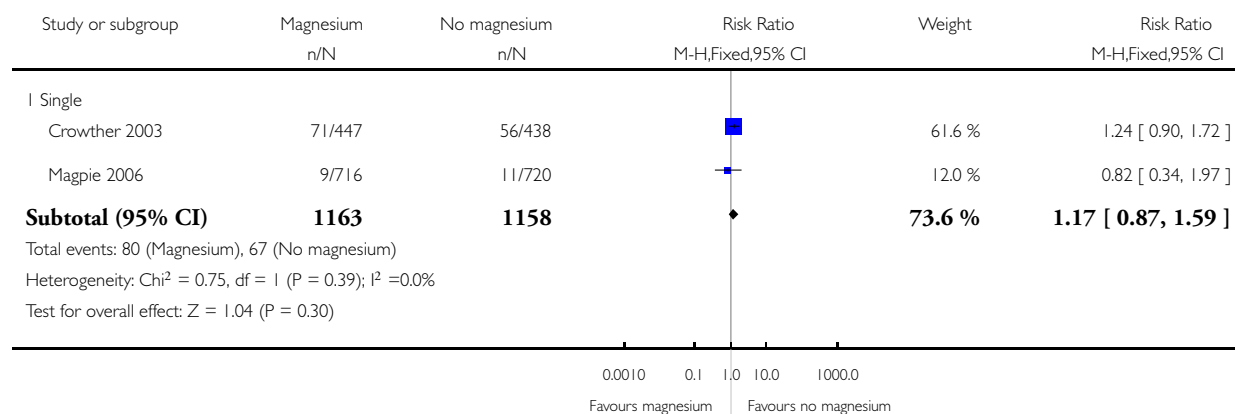
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

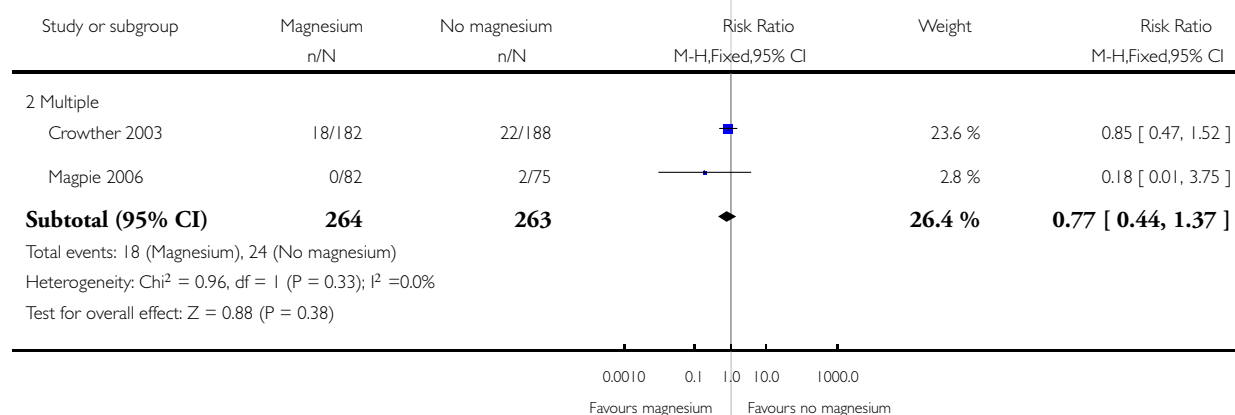
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 4 Major neurological disability

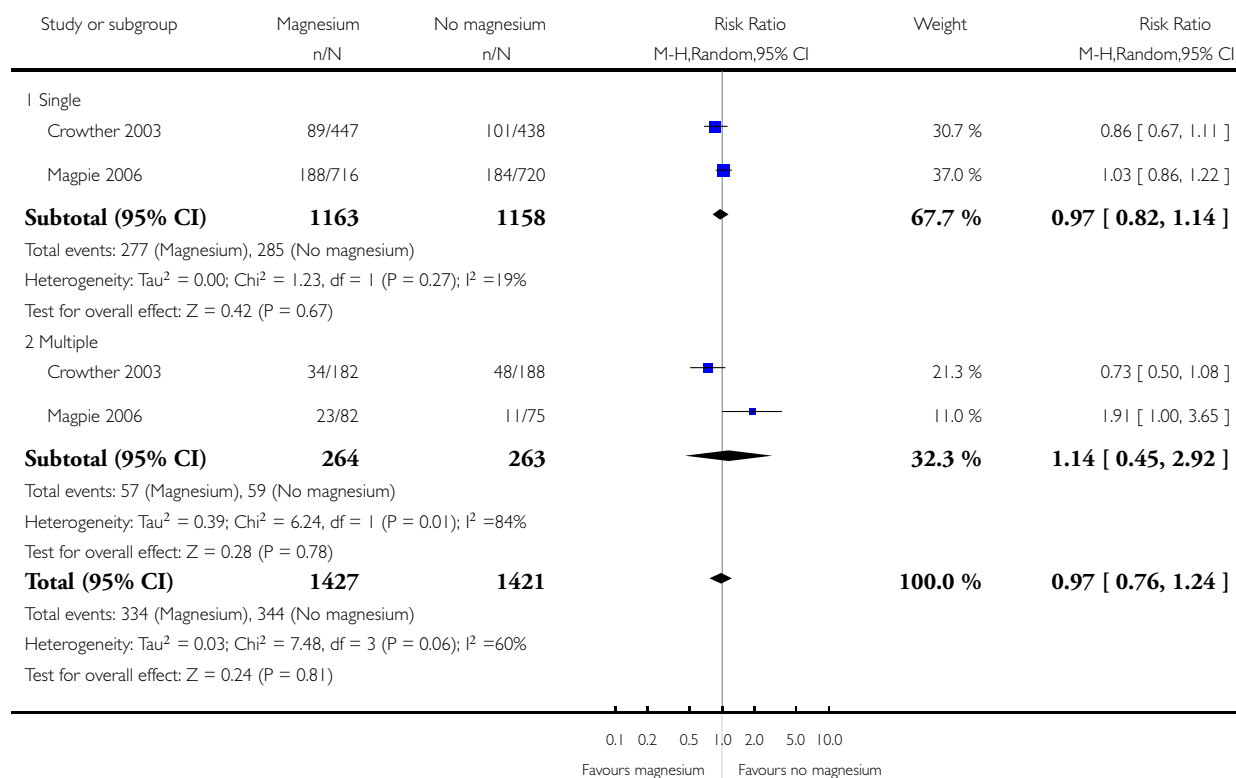


Analysis 3.5. Comparison 3 Single or multiple pregnancy subgroup, Outcome 5 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

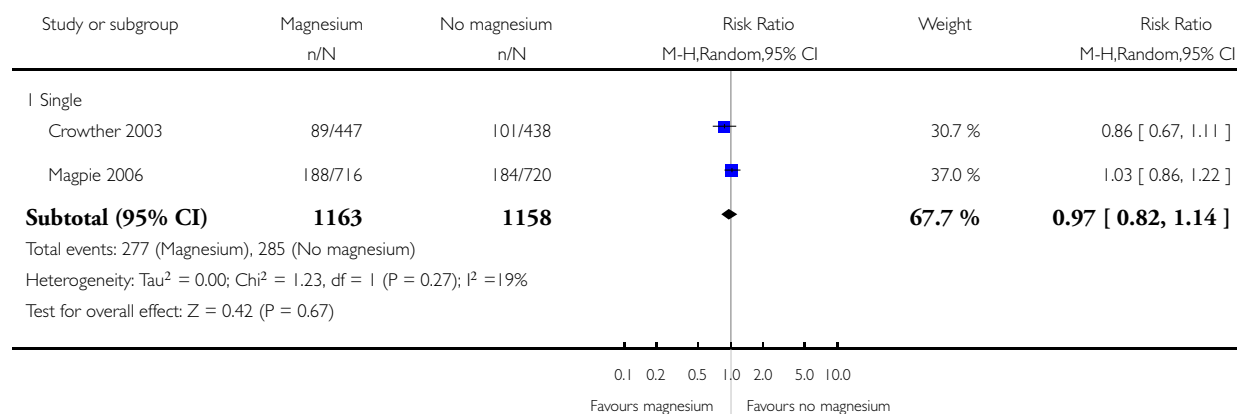
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

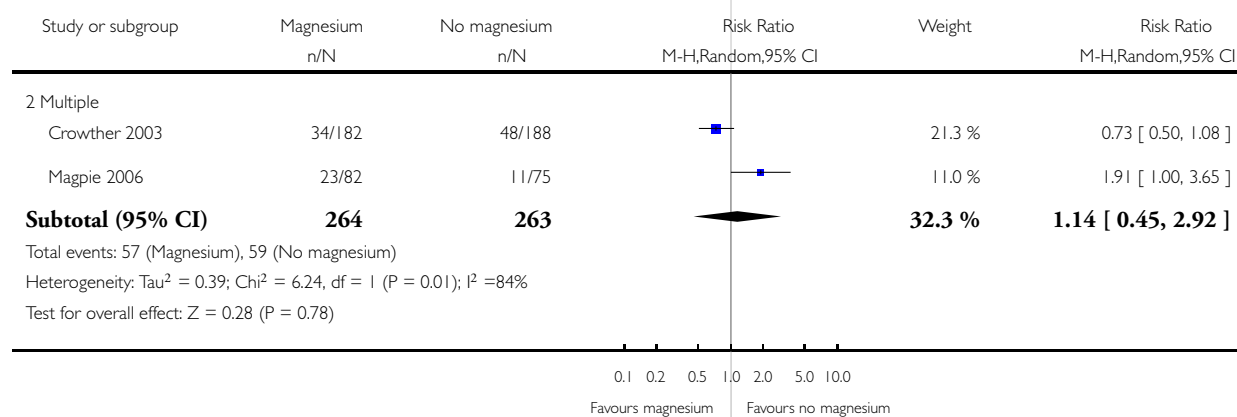
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 5 Death or cerebral palsy

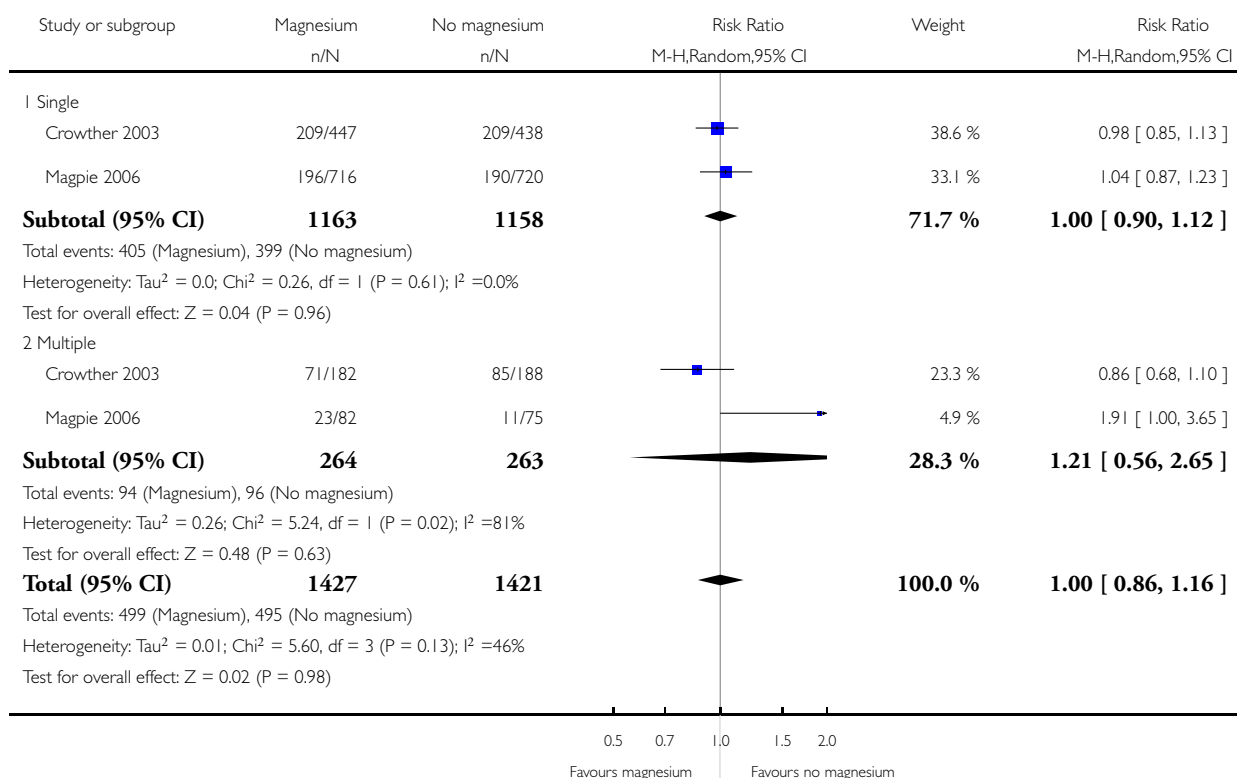


Analysis 3.6. Comparison 3 Single or multiple pregnancy subgroup, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

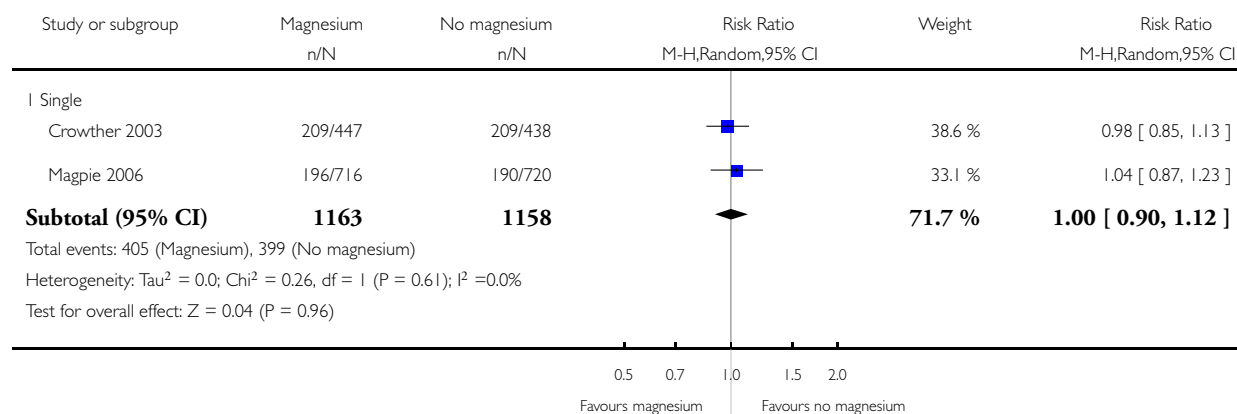
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

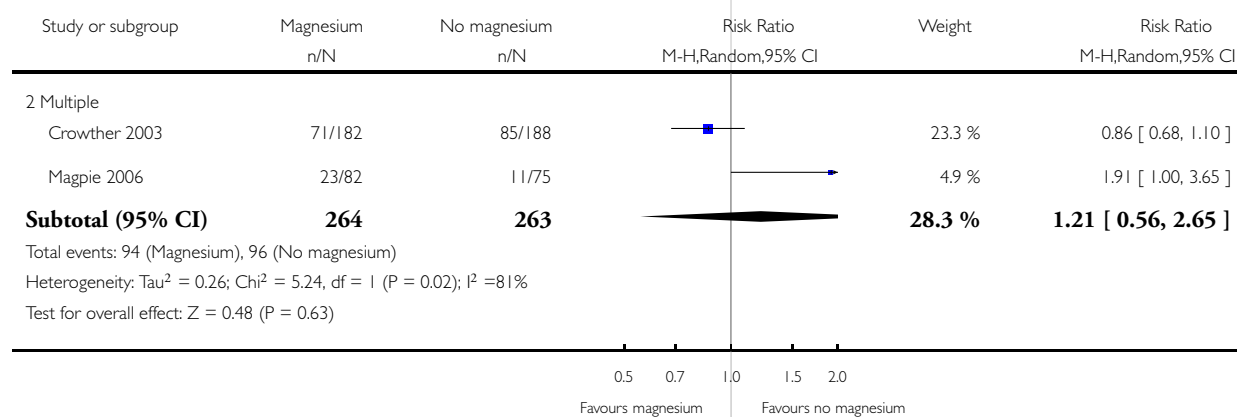
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 6 Death or neurological impairment

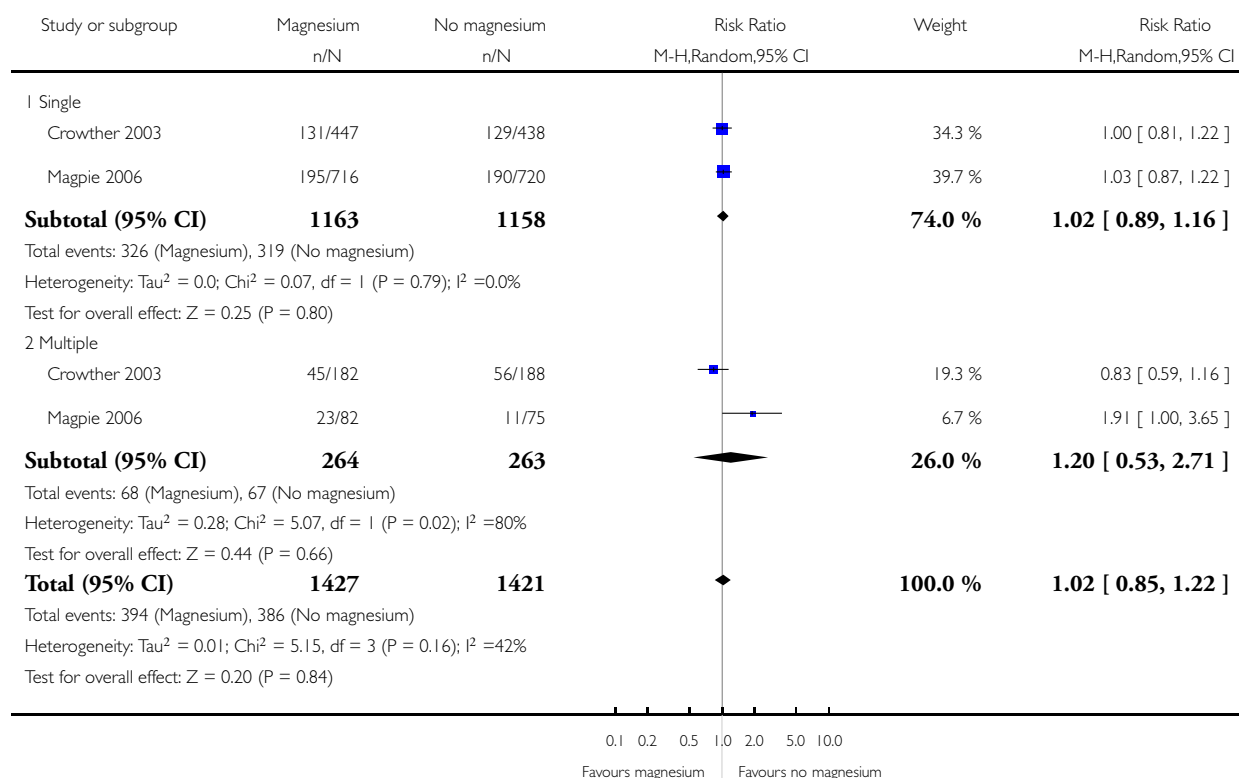


Analysis 3.7. Comparison 3 Single or multiple pregnancy subgroup, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

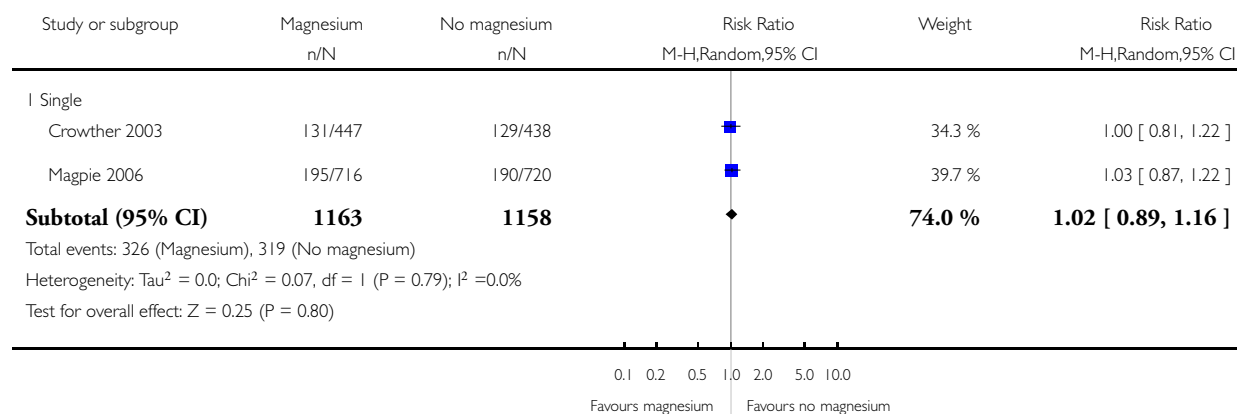
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

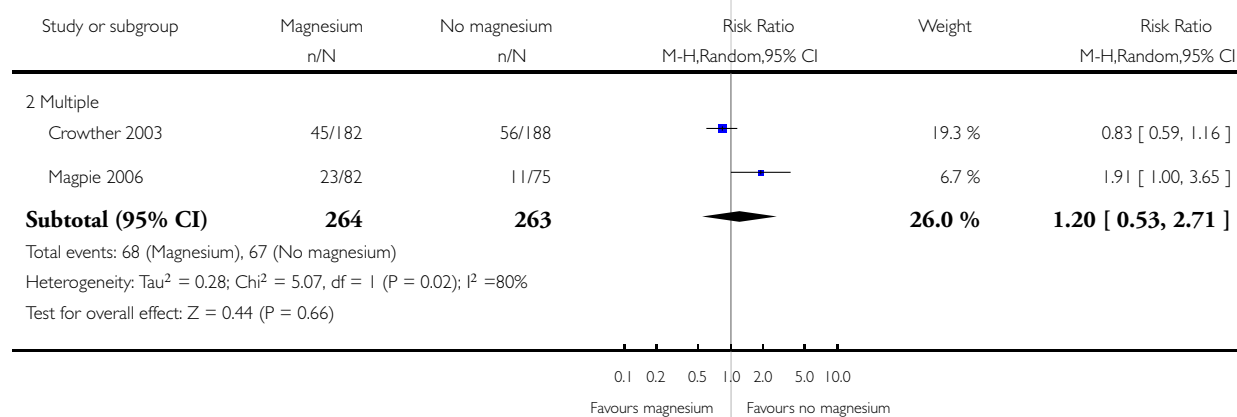
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 3 Single or multiple pregnancy subgroup

Outcome: 7 Death or major neurological disability

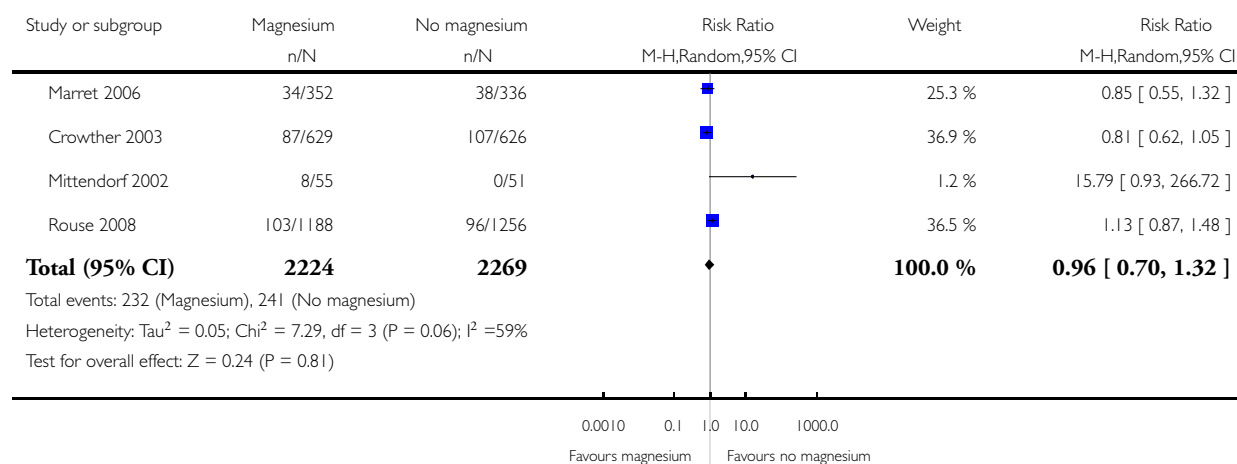


Analysis 4.1. Comparison 4 High antenatal corticosteroids, Outcome 1 Paediatric mortality (fetal and later).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 1 Paediatric mortality (fetal and later)

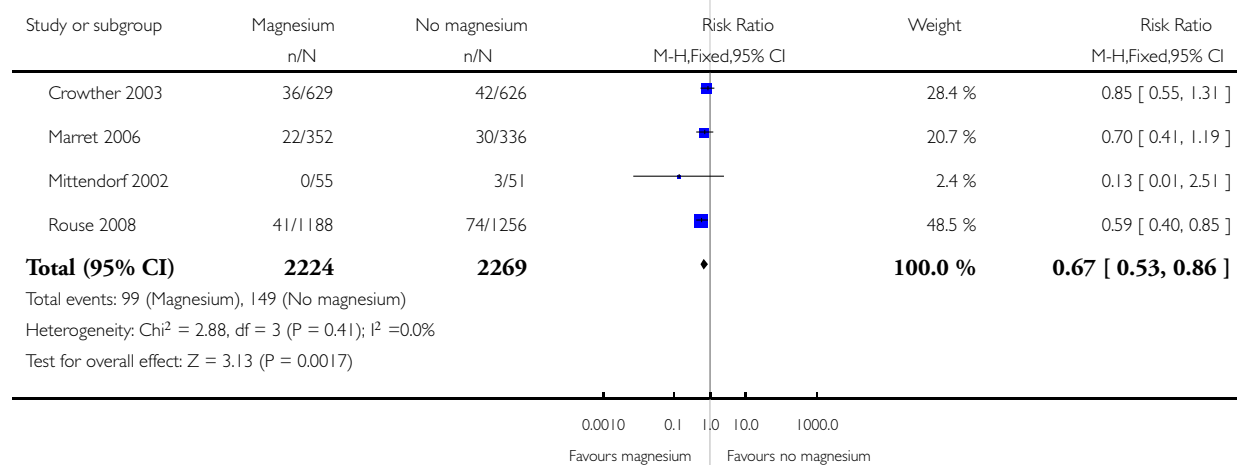


Analysis 4.2. Comparison 4 High antenatal corticosteroids, Outcome 2 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 2 Cerebral palsy

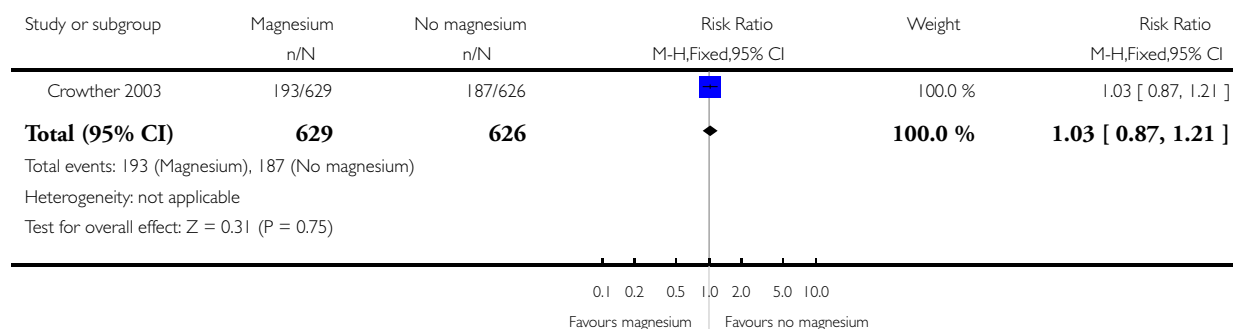


Analysis 4.3. Comparison 4 High antenatal corticosteroids, Outcome 3 Neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 3 Neurological impairment

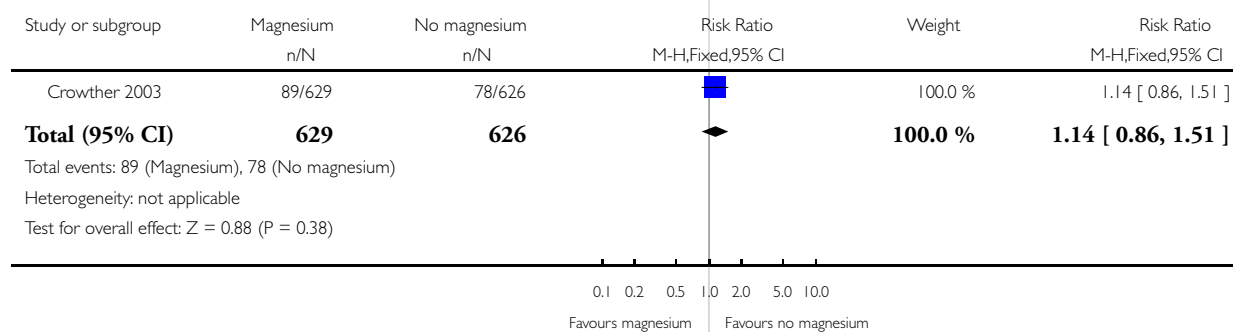


Analysis 4.4. Comparison 4 High antenatal corticosteroids, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 4 Major neurological disability

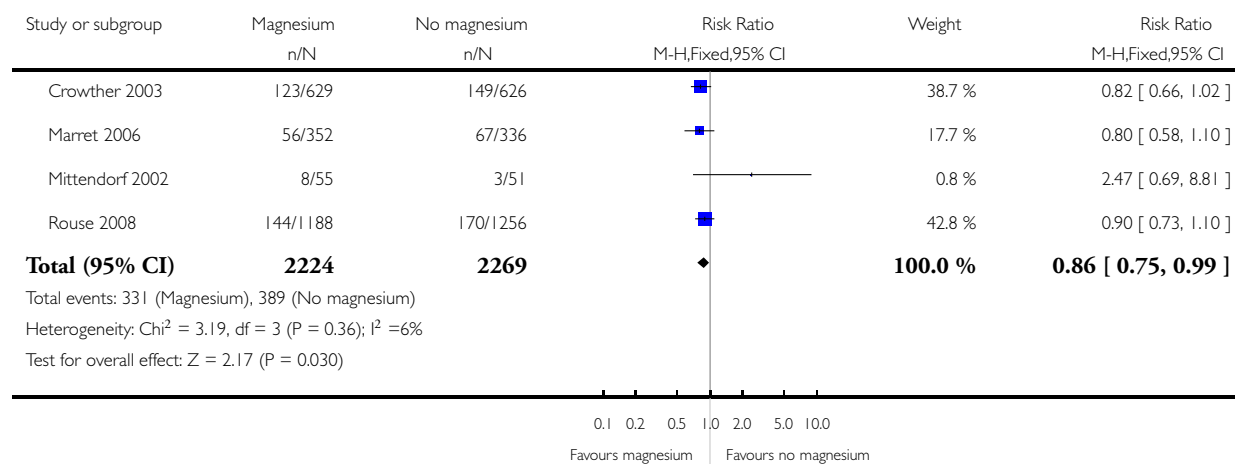


Analysis 4.5. Comparison 4 High antenatal corticosteroids, Outcome 5 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 5 Death or cerebral palsy

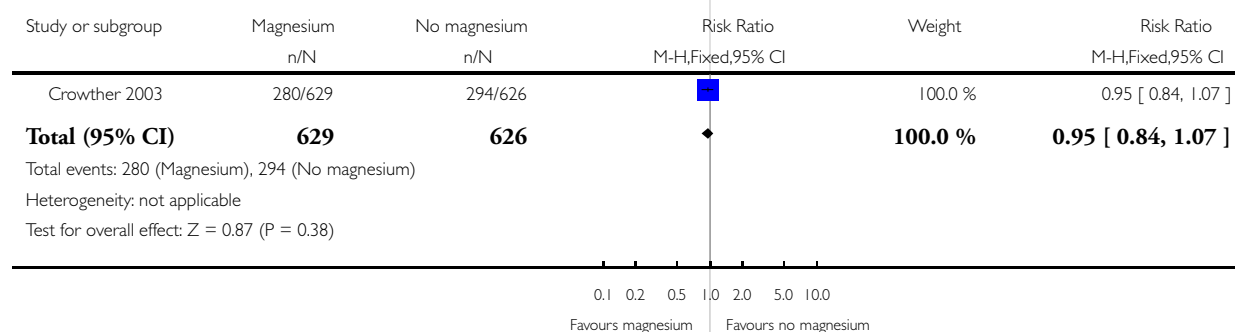


Analysis 4.6. Comparison 4 High antenatal corticosteroids, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 6 Death or neurological impairment

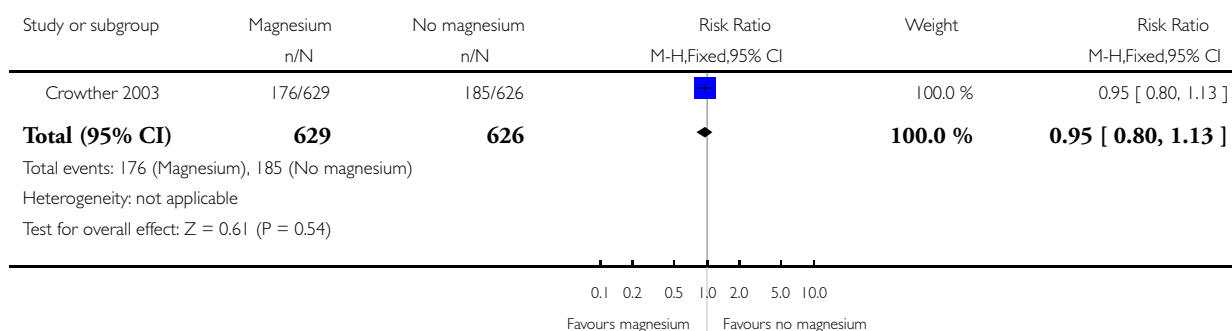


Analysis 4.7. Comparison 4 High antenatal corticosteroids, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 4 High antenatal corticosteroids

Outcome: 7 Death or major neurological disability

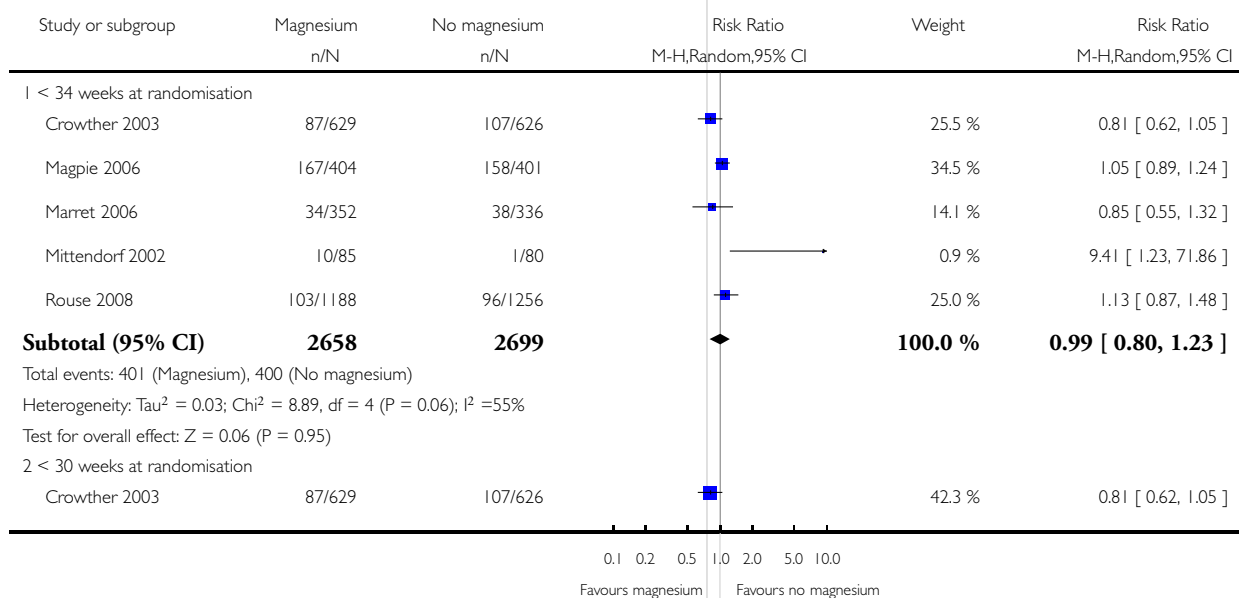


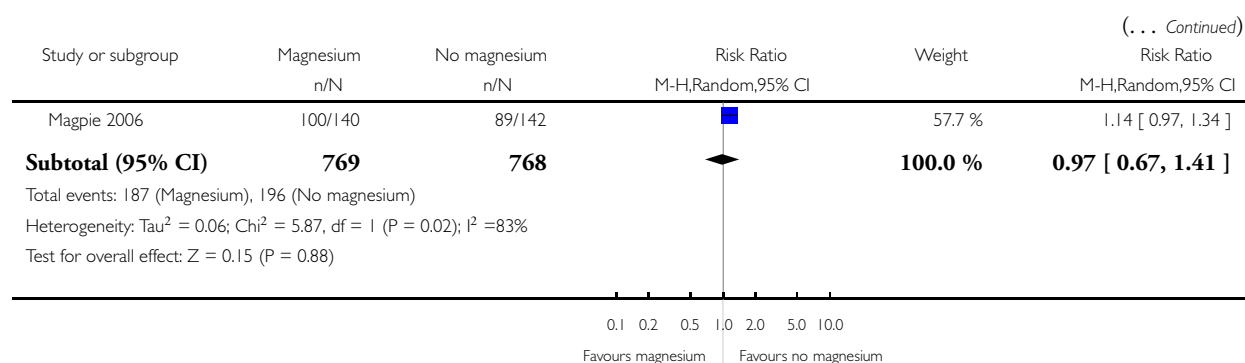
Analysis 5.1. Comparison 5 Gestational age subgroup, Outcome 1 Paediatric mortality (fetal and later).

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 1 Paediatric mortality (fetal and later)

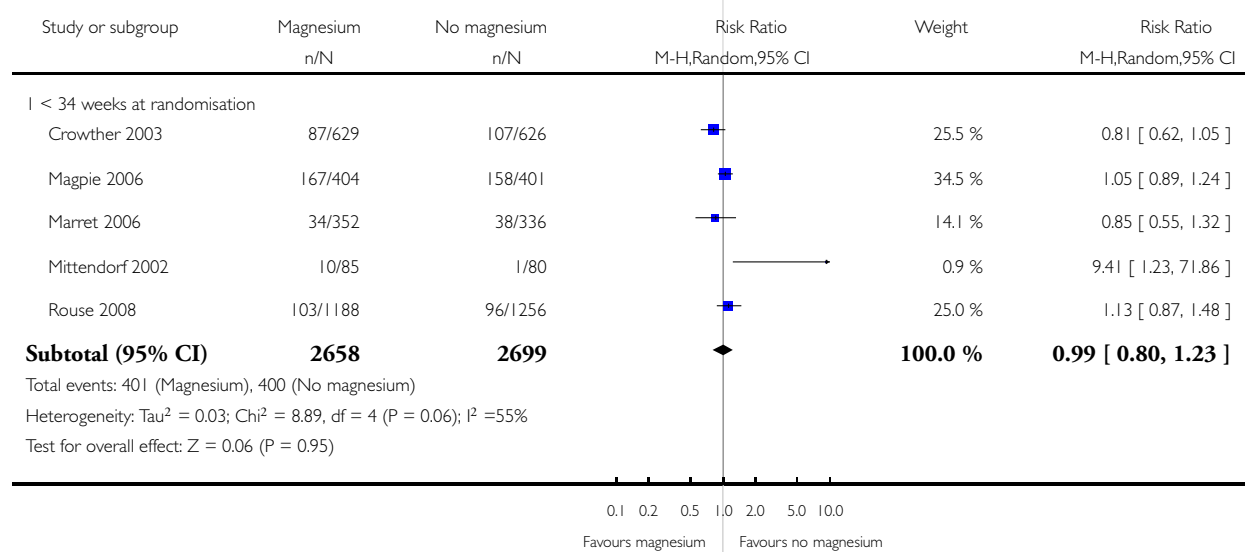




Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

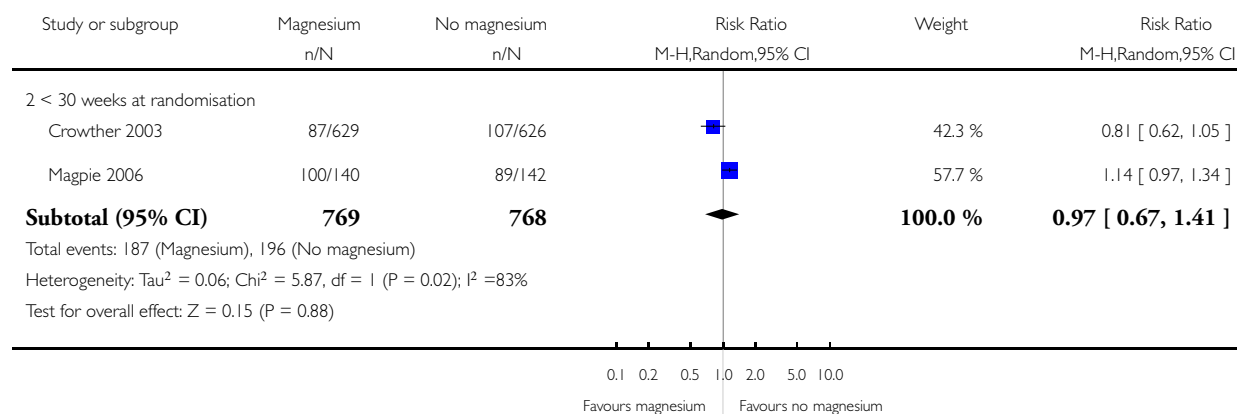
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 1 Paediatric mortality (fetal and later)

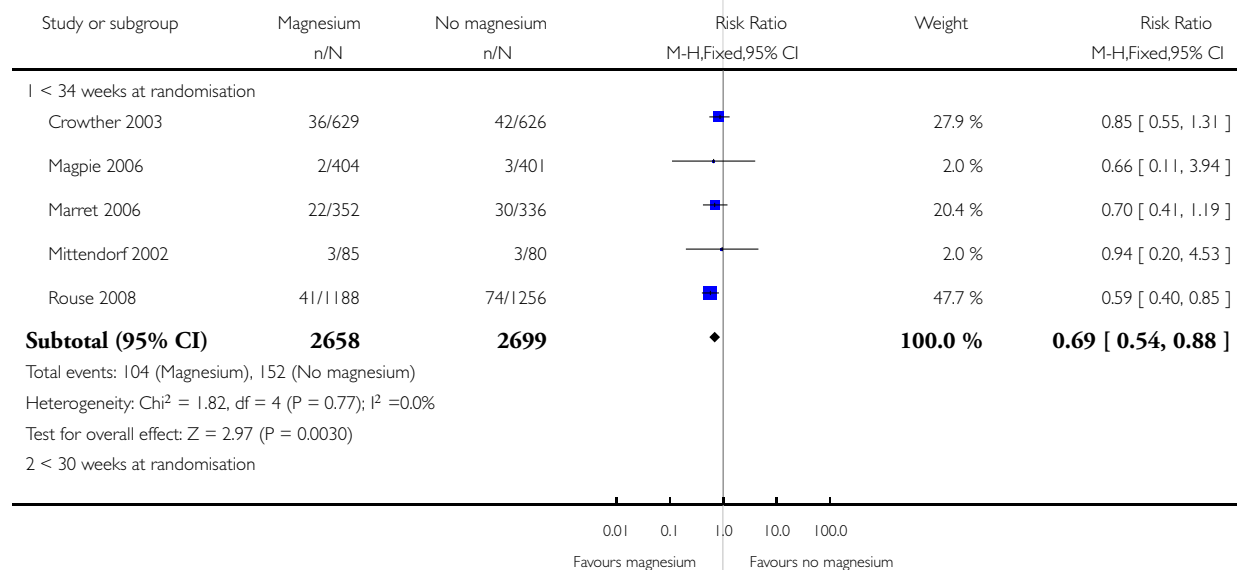


Analysis 5.2. Comparison 5 Gestational age subgroup, Outcome 2 Cerebral palsy.

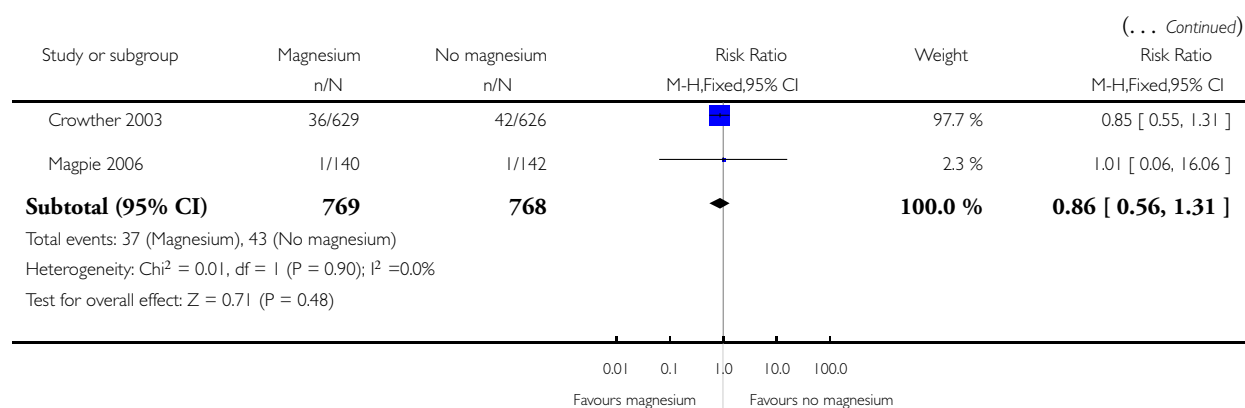
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 2 Cerebral palsy



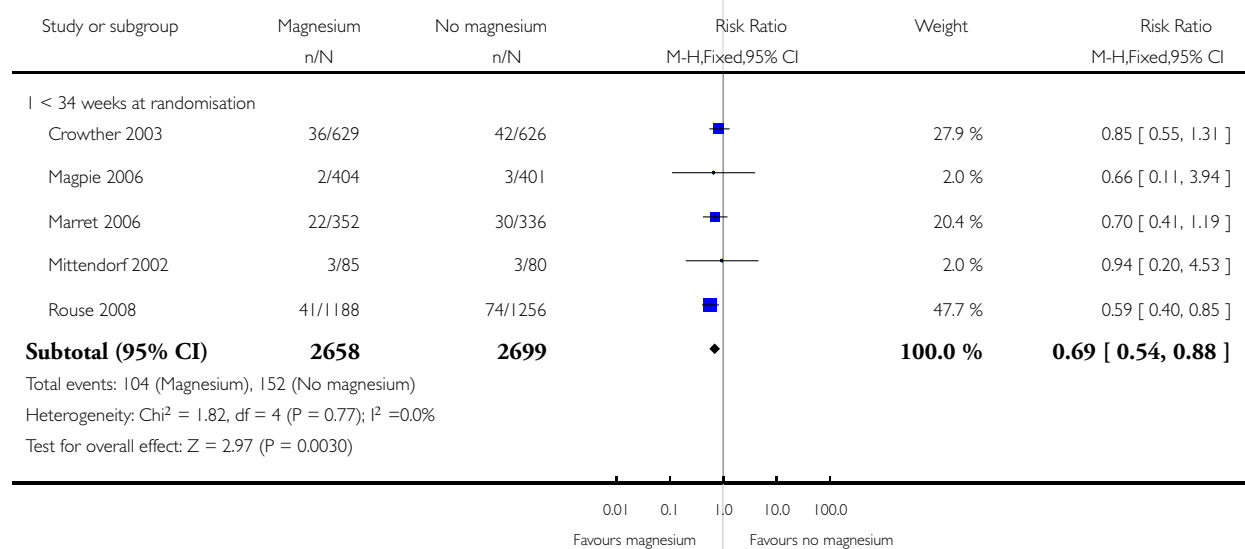
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

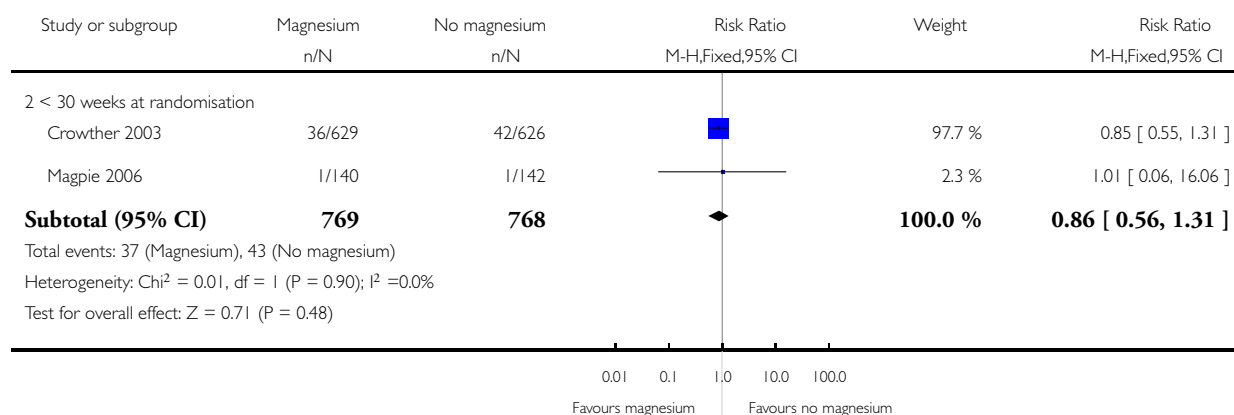
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 2 Cerebral palsy

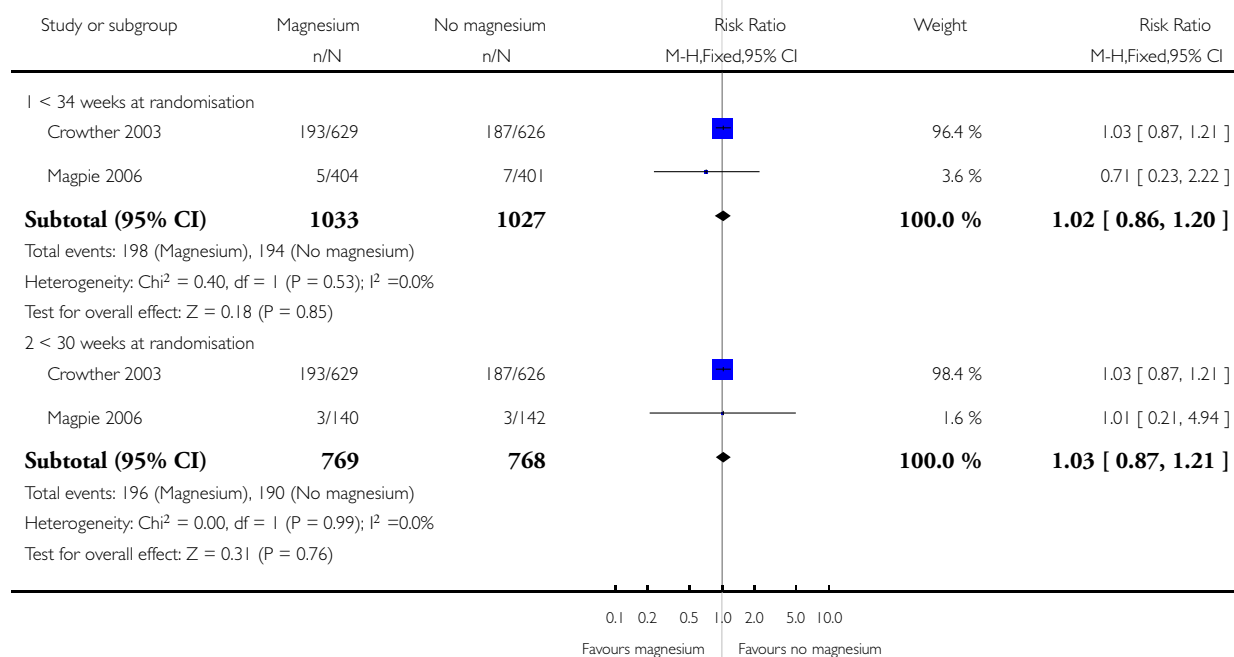


Analysis 5.3. Comparison 5 Gestational age subgroup, Outcome 3 Neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

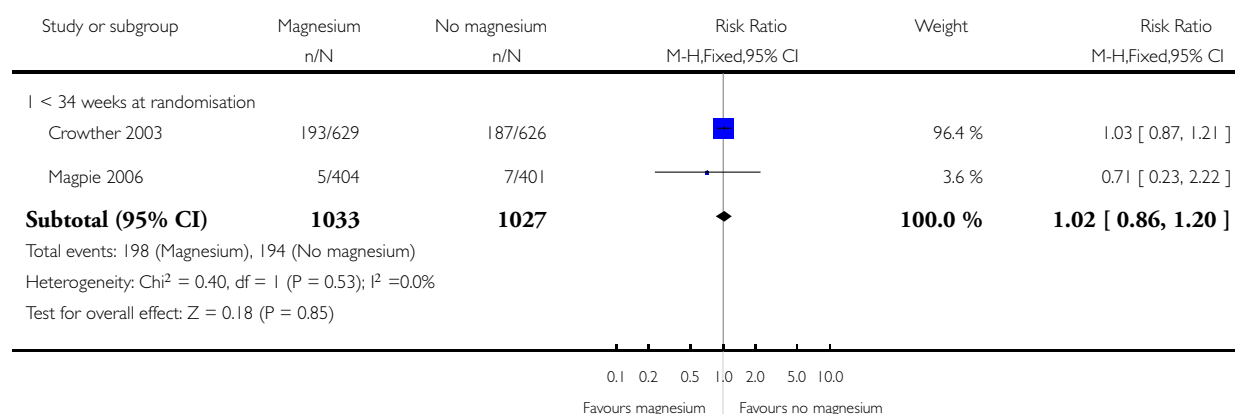
Outcome: 3 Neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

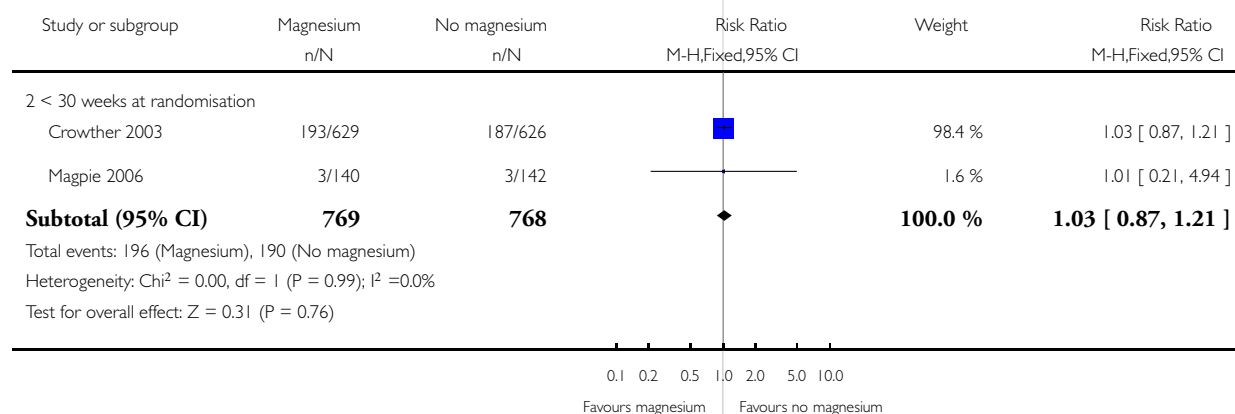
Outcome: 3 Neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 3 Neurological impairment

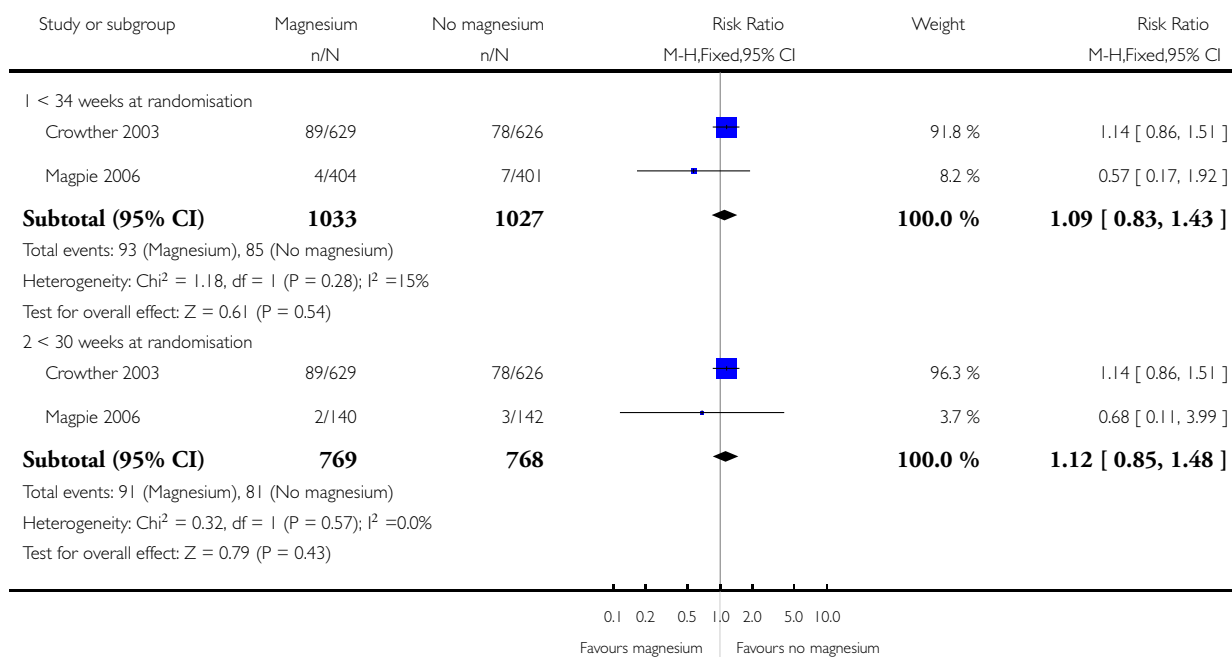


Analysis 5.4. Comparison 5 Gestational age subgroup, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

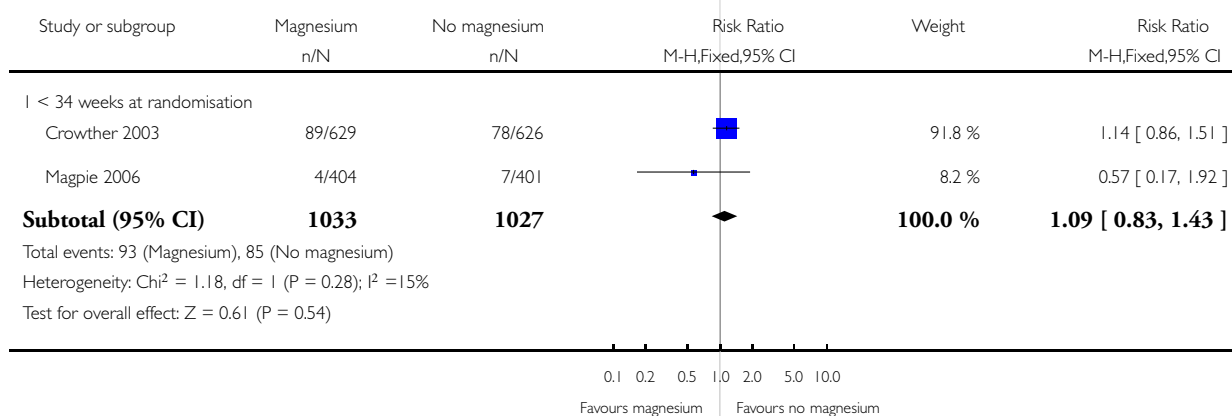
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

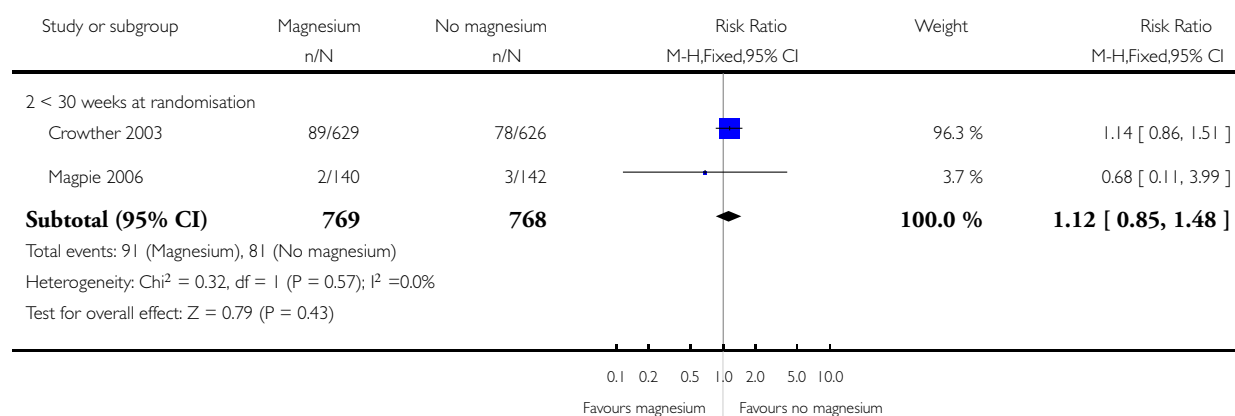
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 4 Major neurological disability

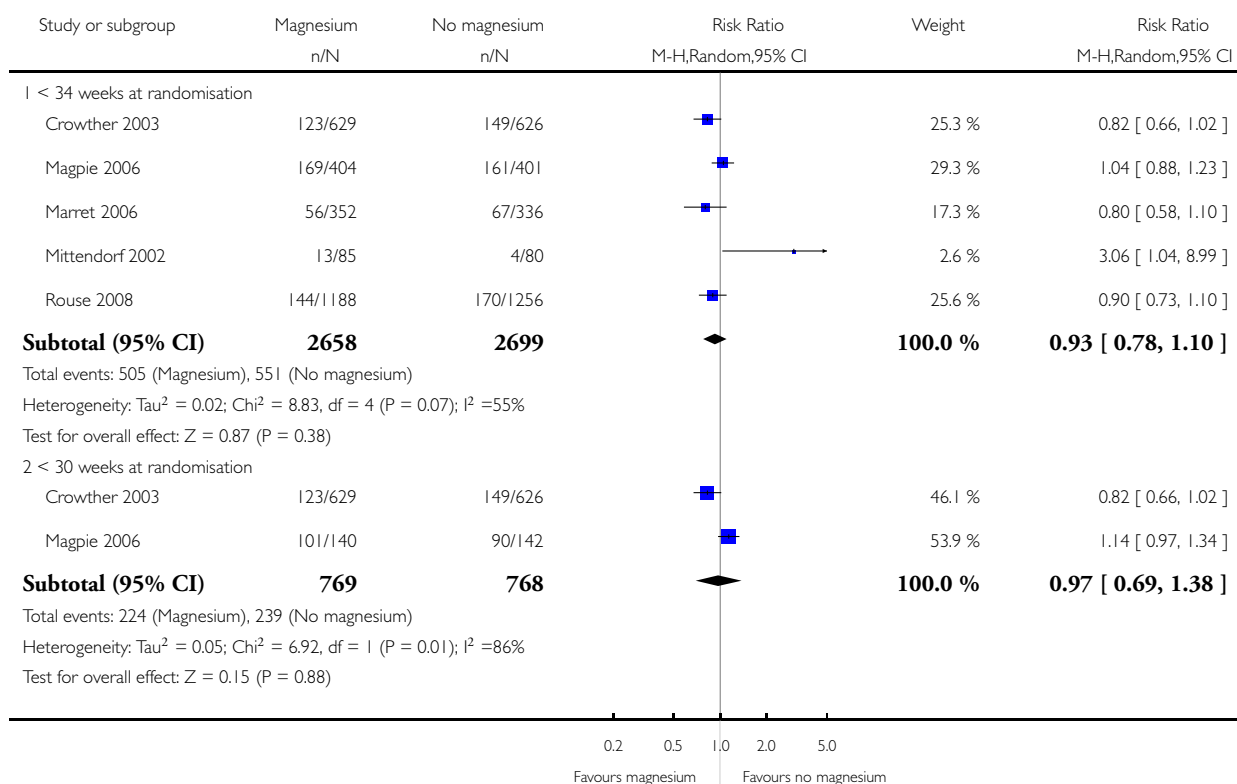


Analysis 5.5. Comparison 5 Gestational age subgroup, Outcome 5 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

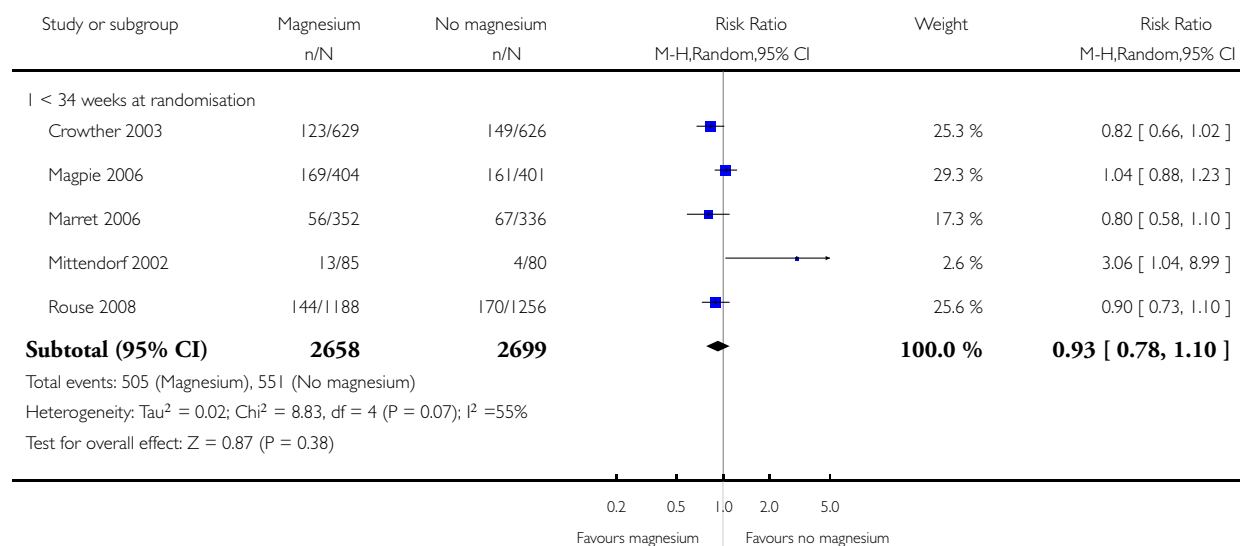
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

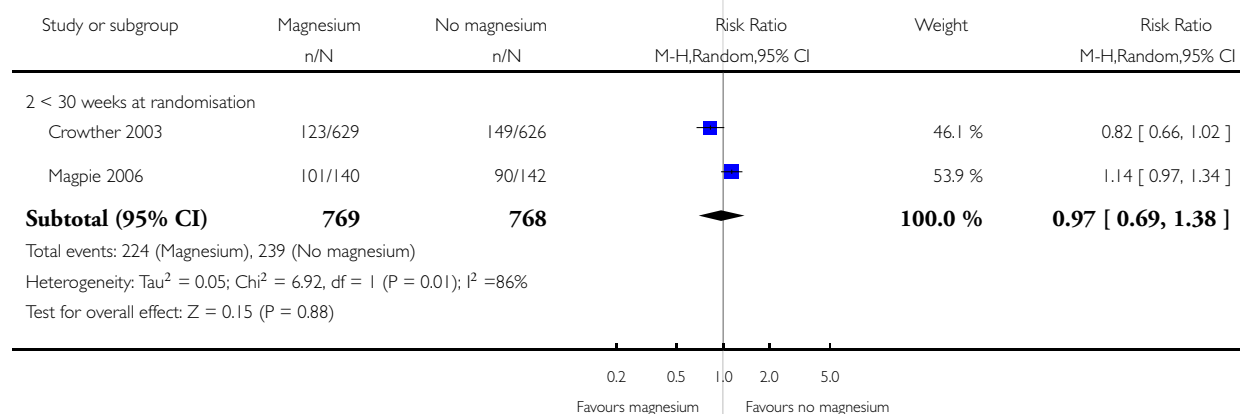
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 5 Death or cerebral palsy

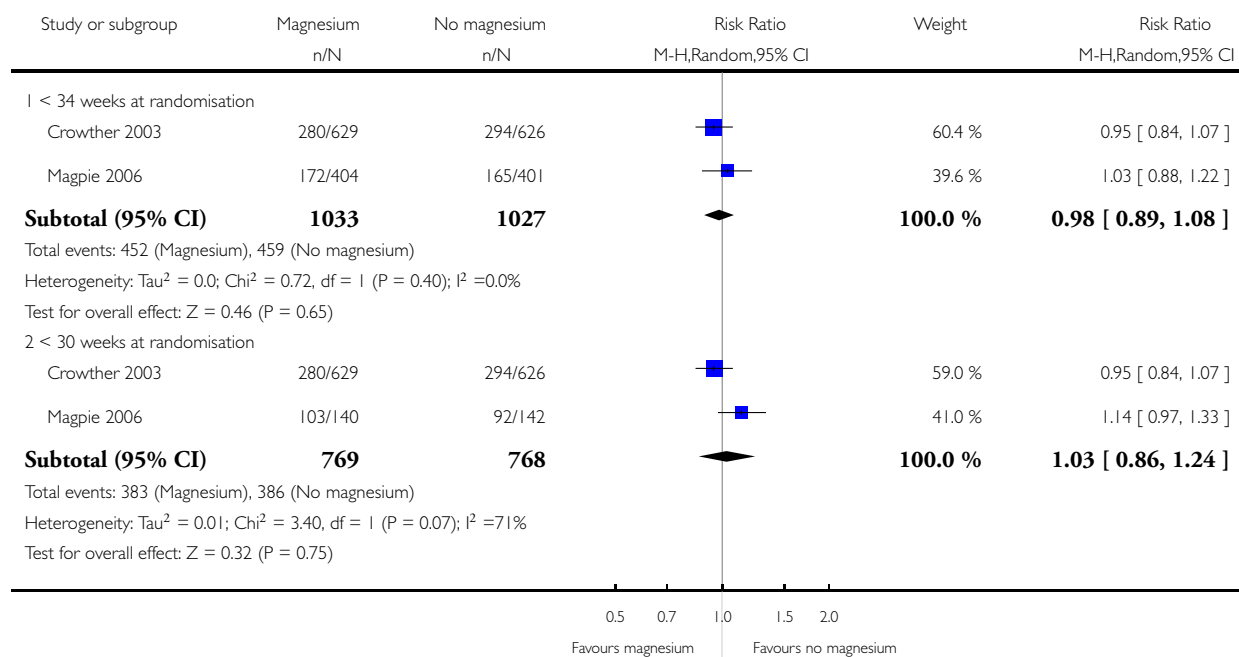


Analysis 5.6. Comparison 5 Gestational age subgroup, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

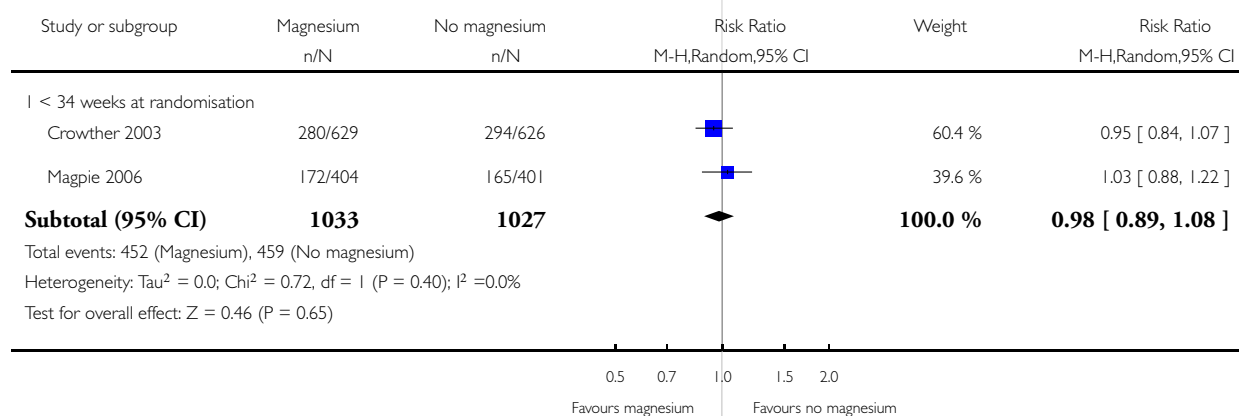
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

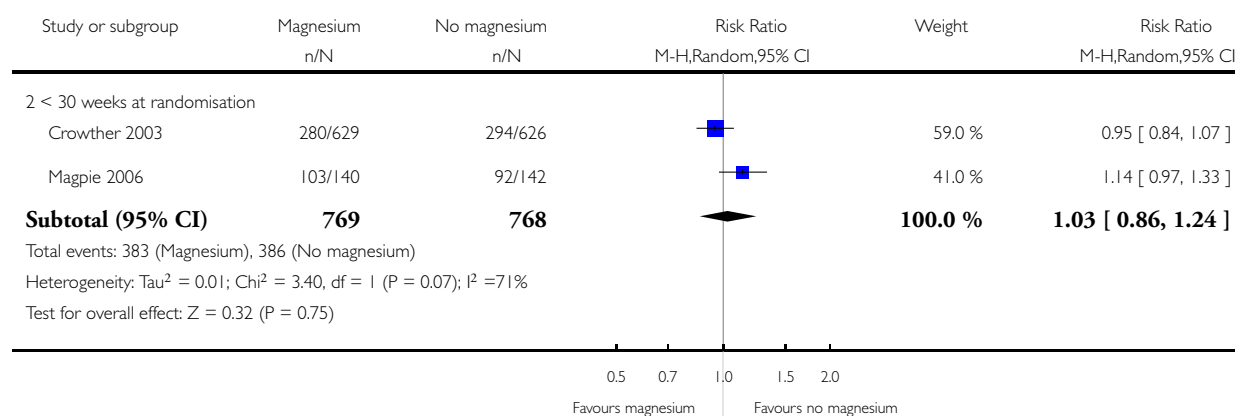
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 6 Death or neurological impairment

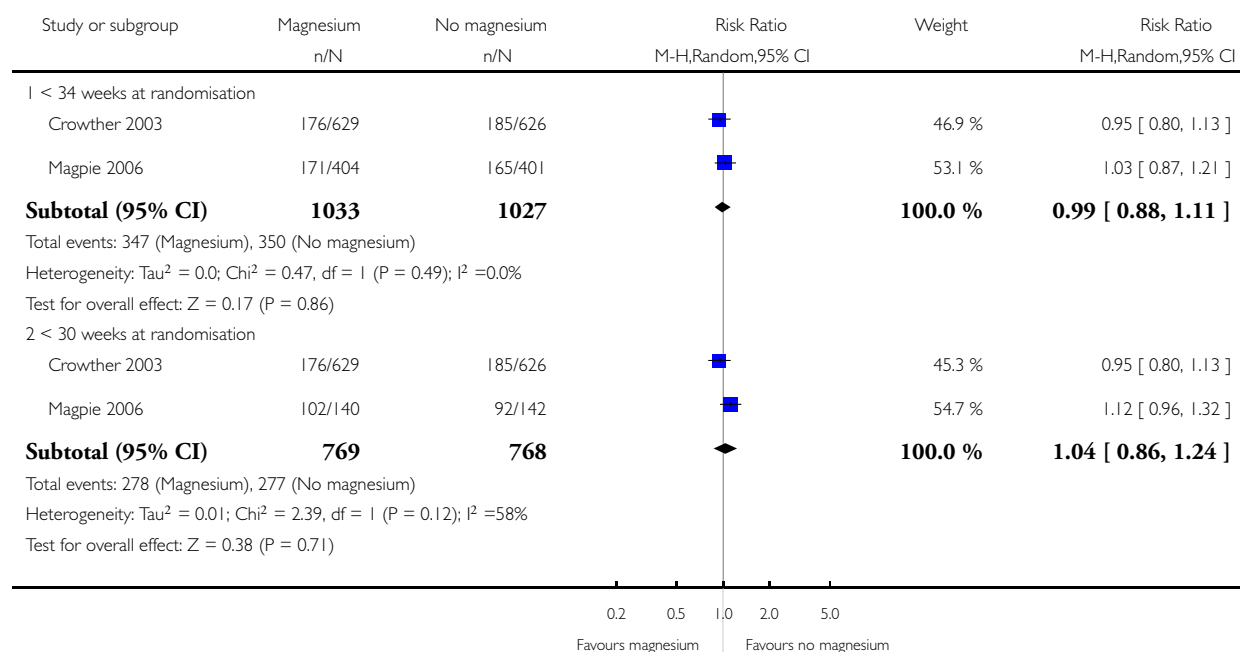


Analysis 5.7. Comparison 5 Gestational age subgroup, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

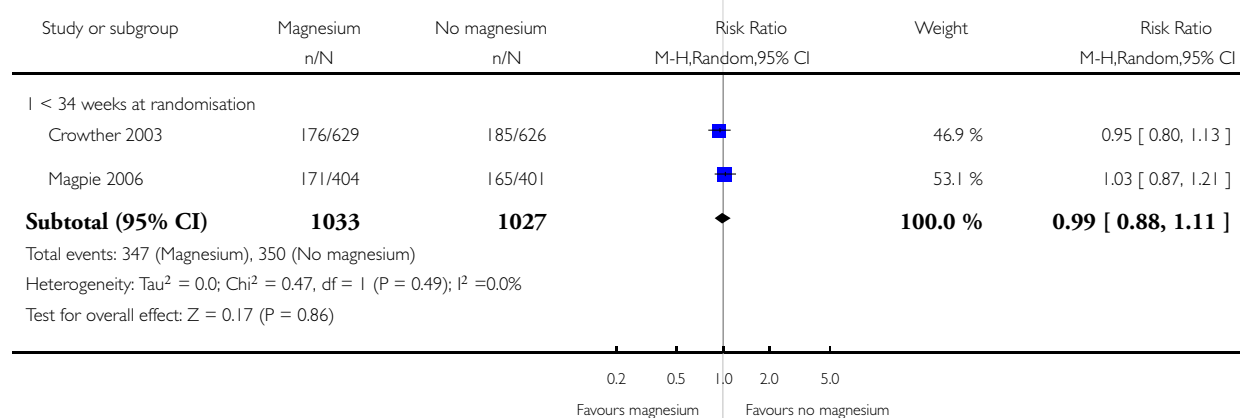
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

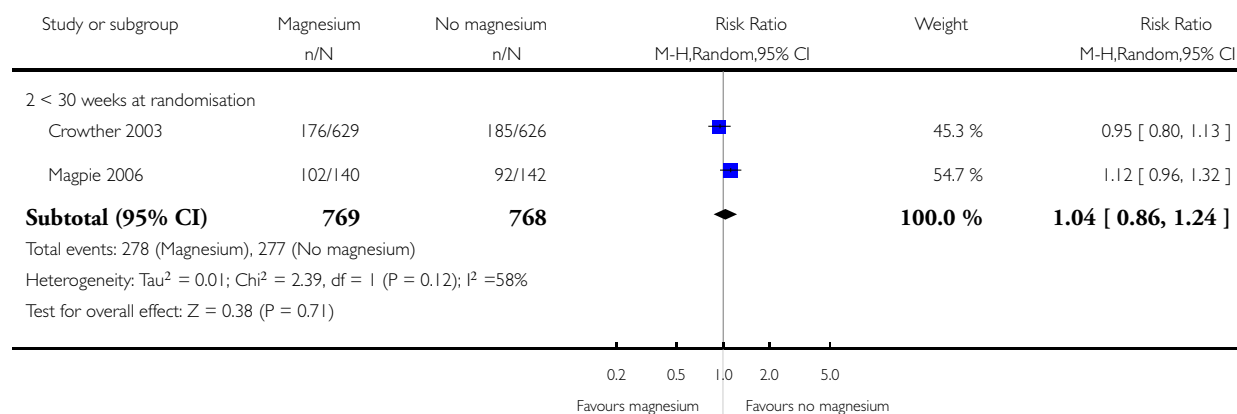
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 5 Gestational age subgroup

Outcome: 7 Death or major neurological disability

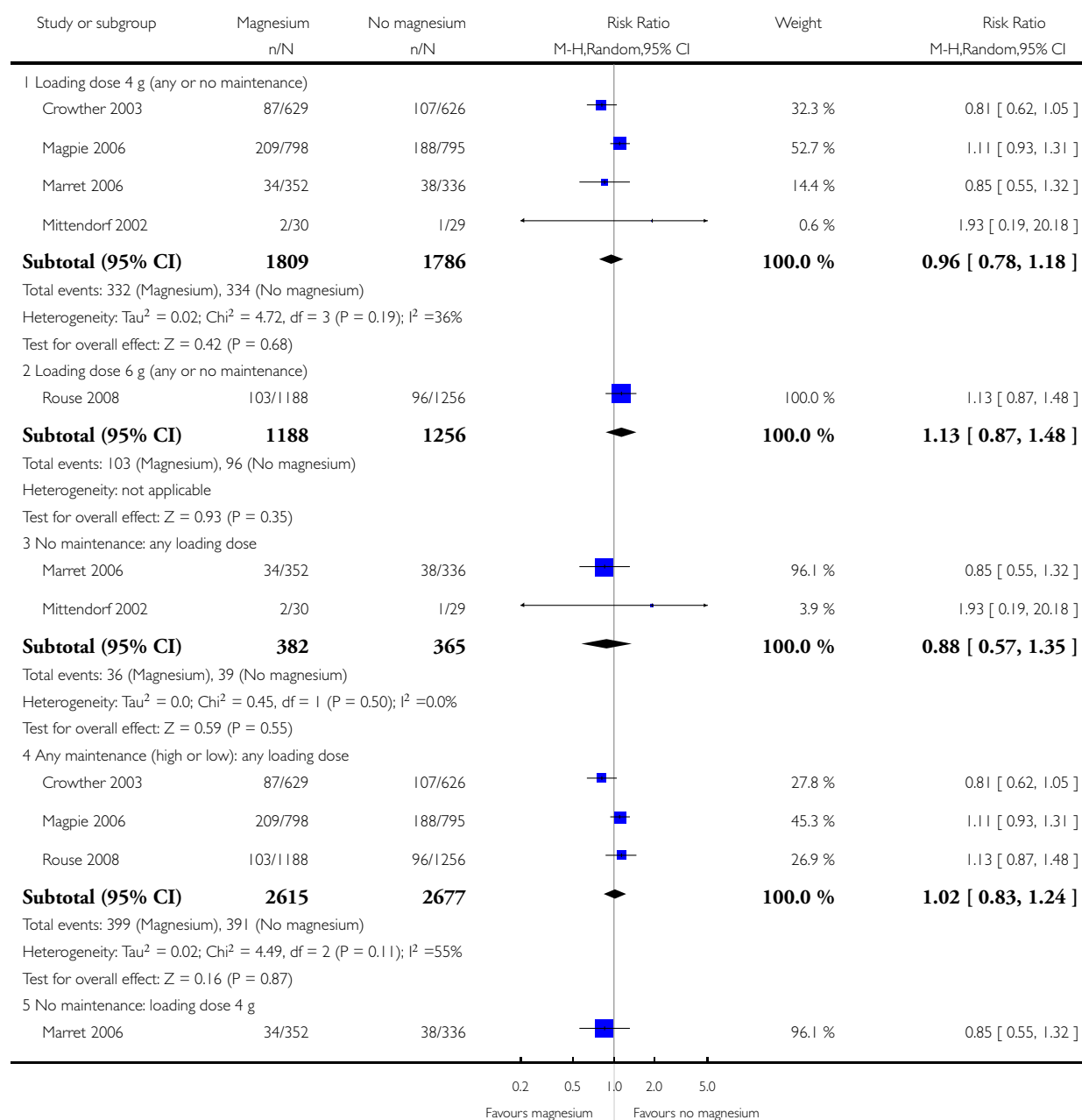


Analysis 6.1. Comparison 6 Dose subgroup, Outcome 1 Paediatric mortality (fetal and later).

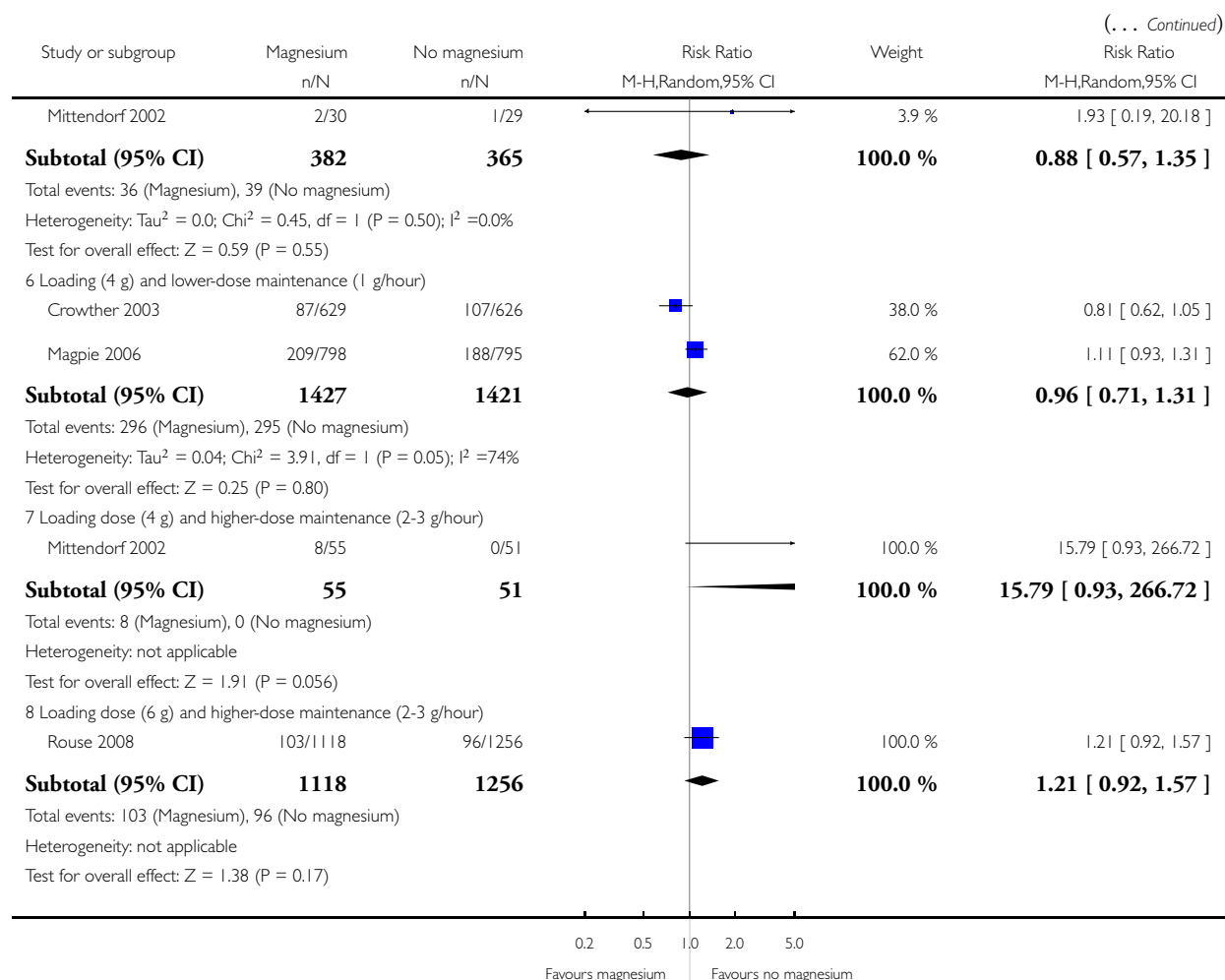
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 1 Paediatric mortality (fetal and later)



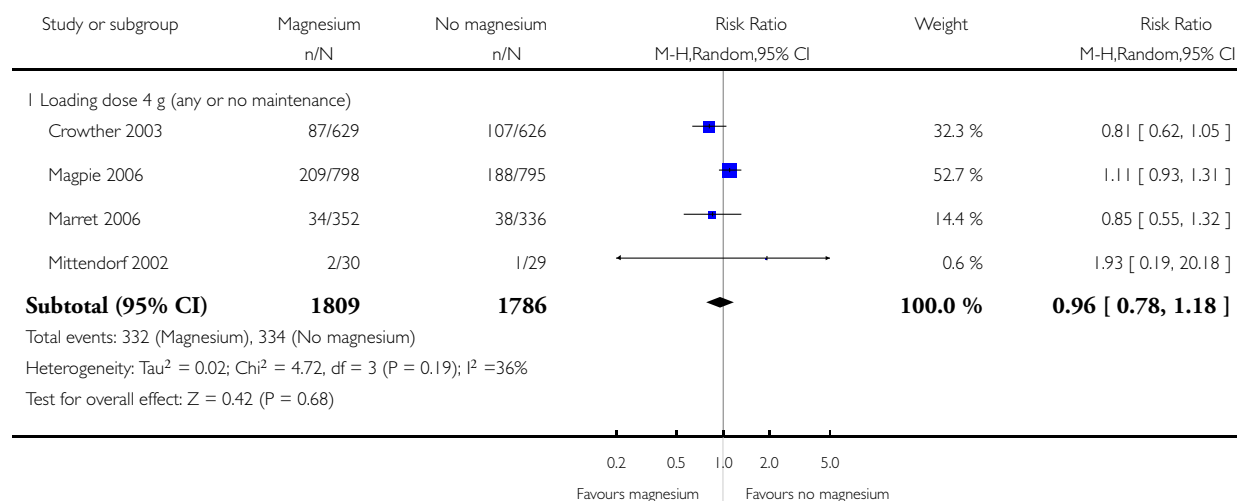
(Continued ...)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

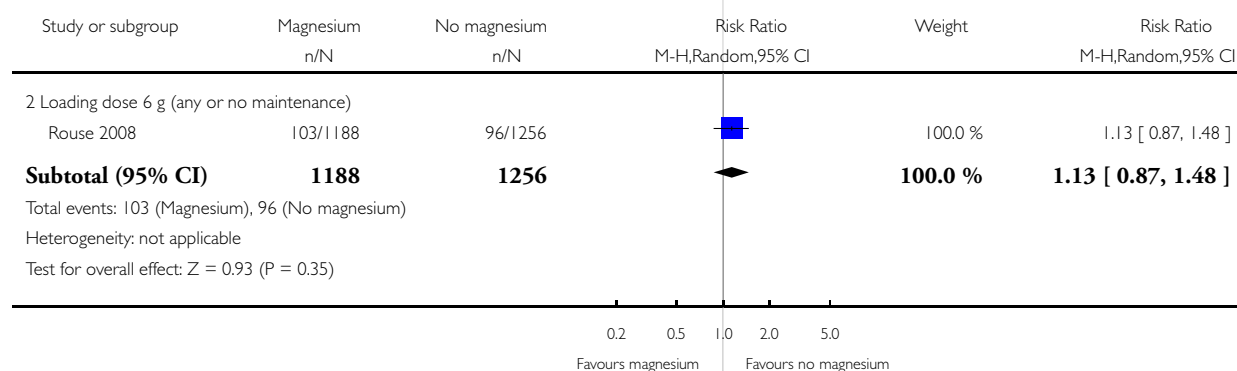
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

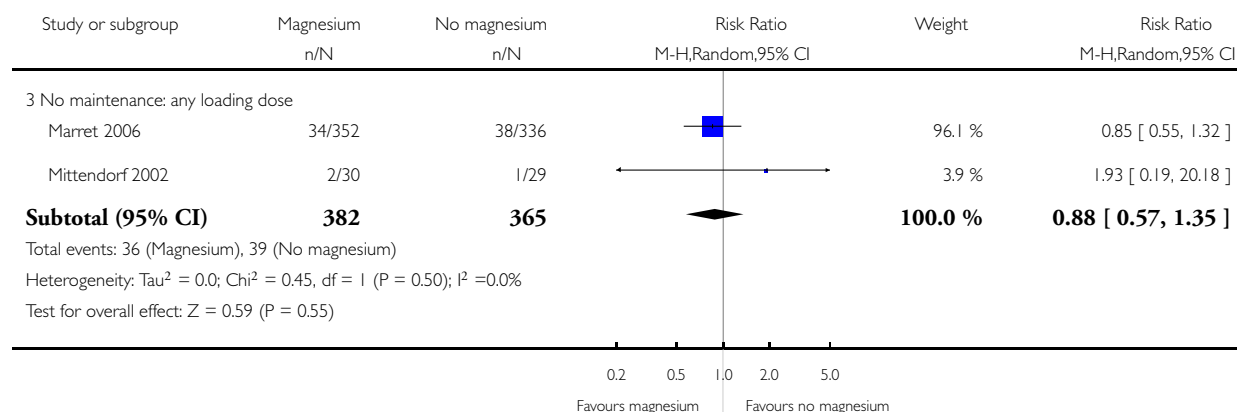
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

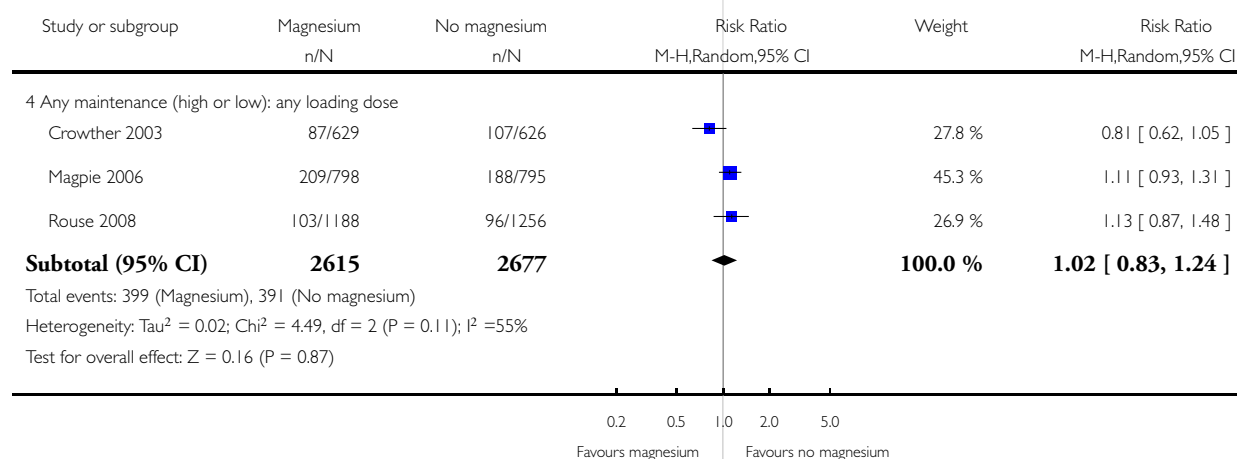
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

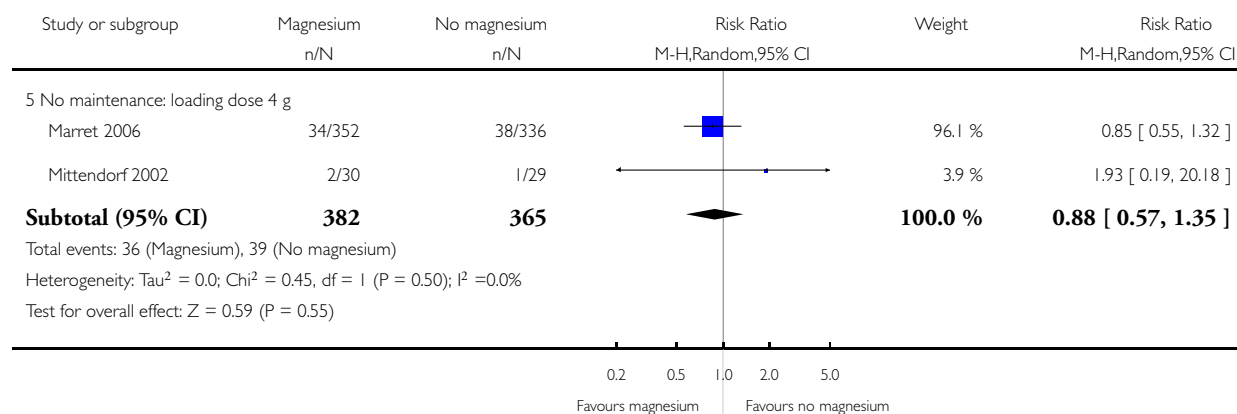
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

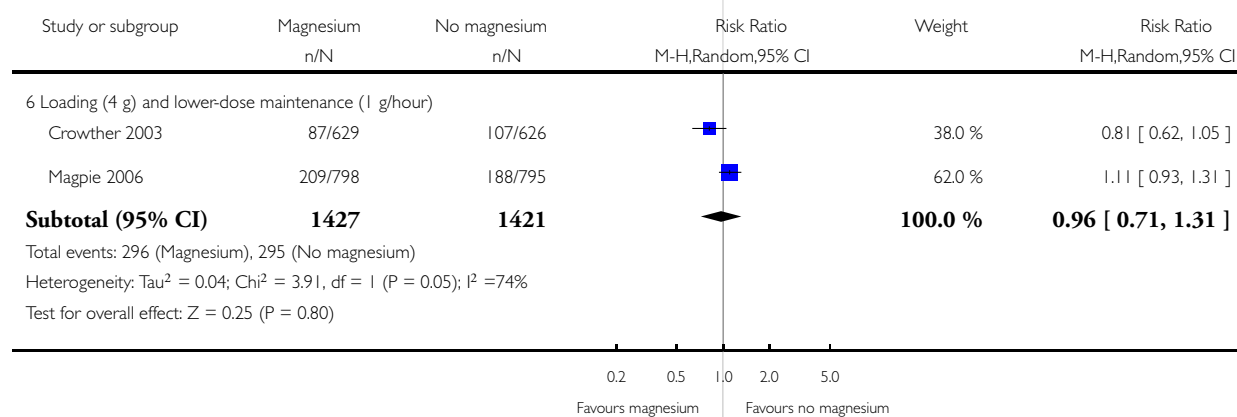
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

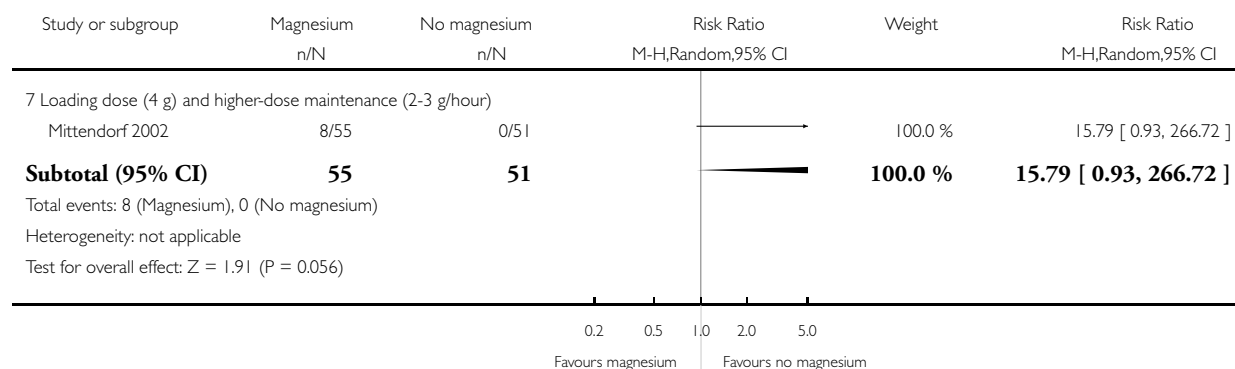
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

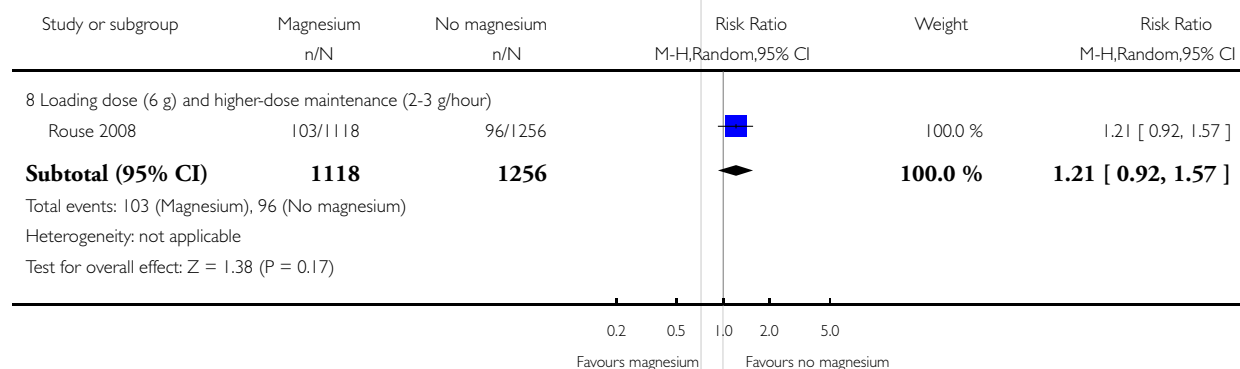
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 1 Paediatric mortality (fetal and later)

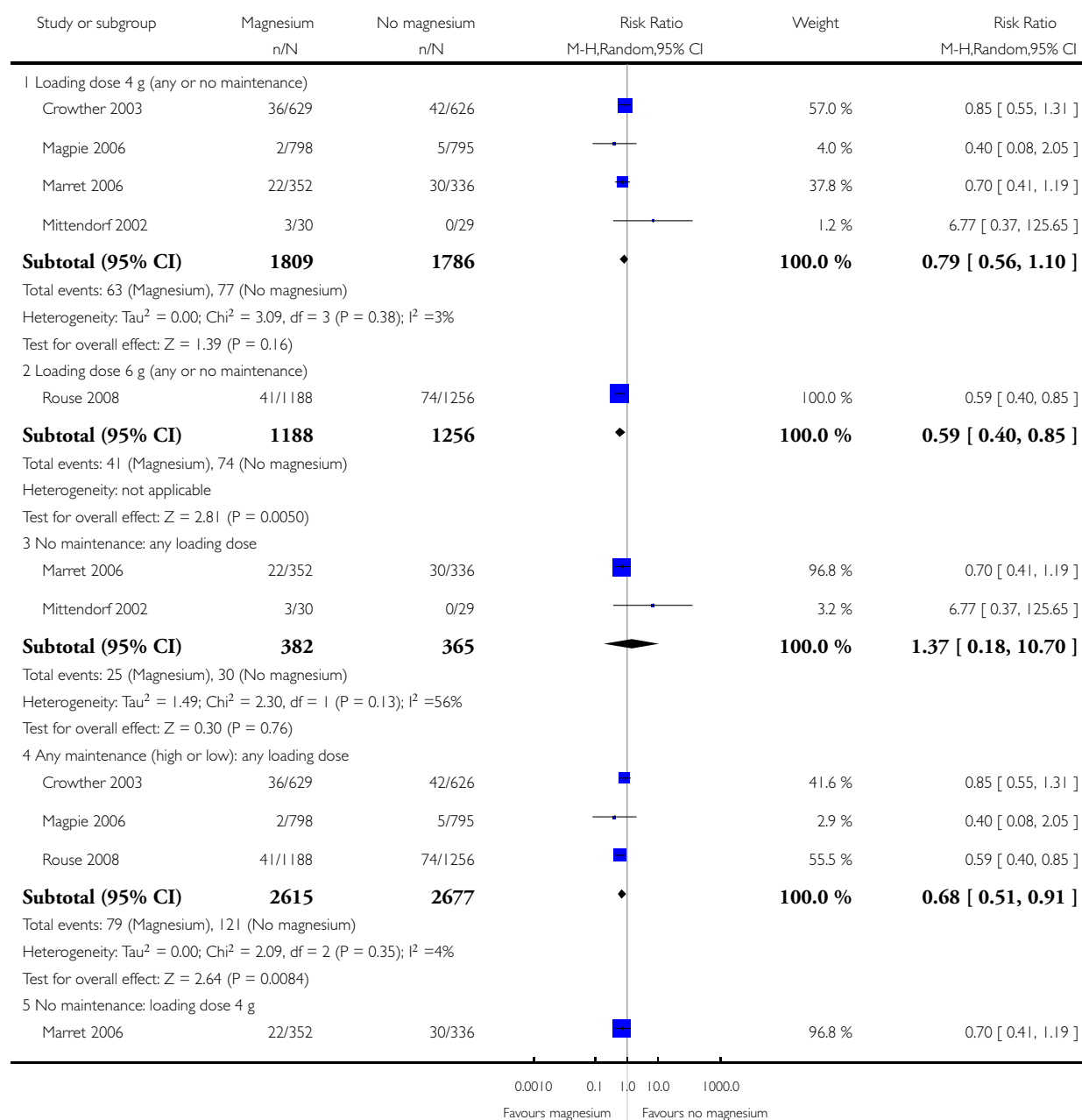


Analysis 6.2. Comparison 6 Dose subgroup, Outcome 2 Cerebral palsy.

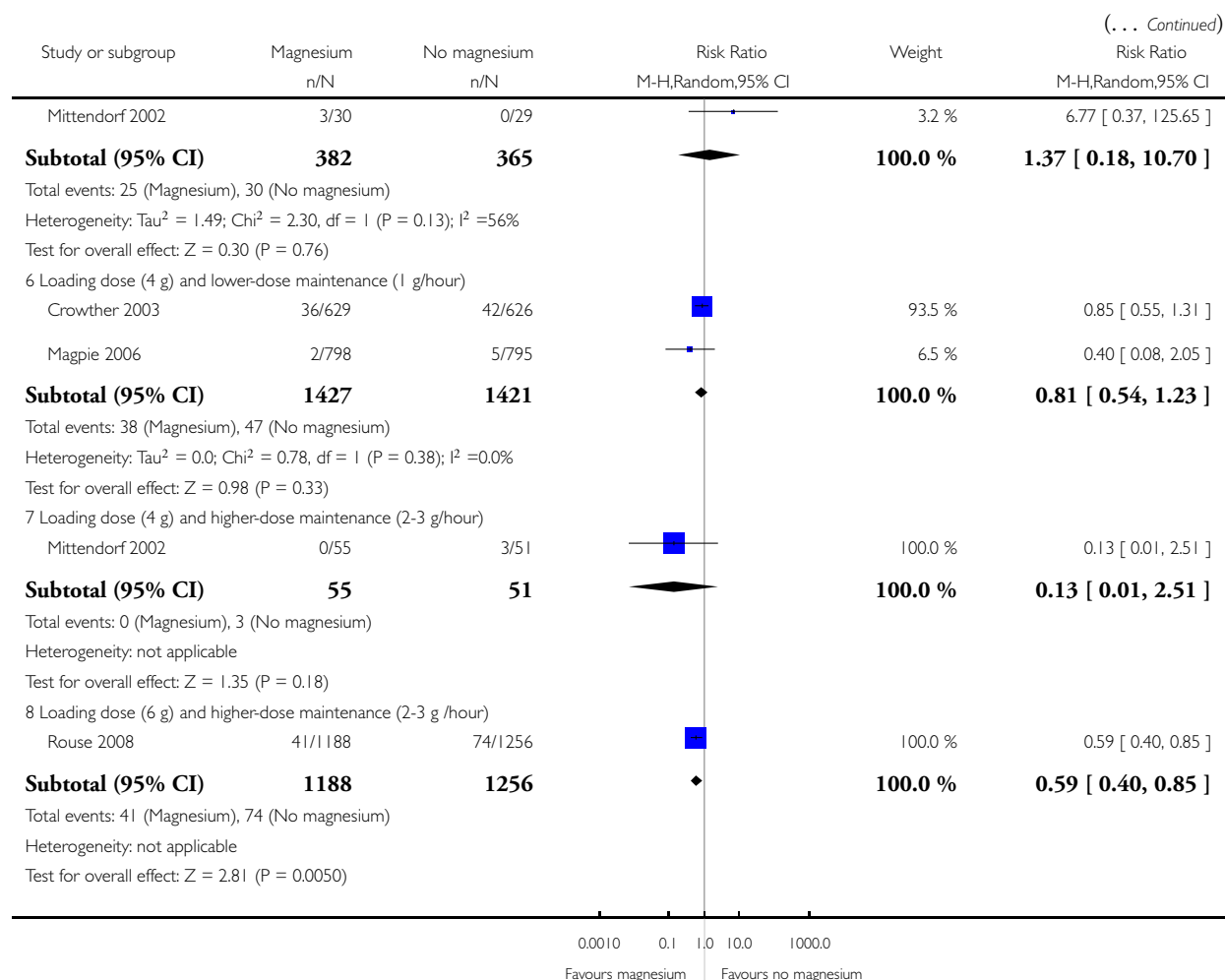
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 2 Cerebral palsy



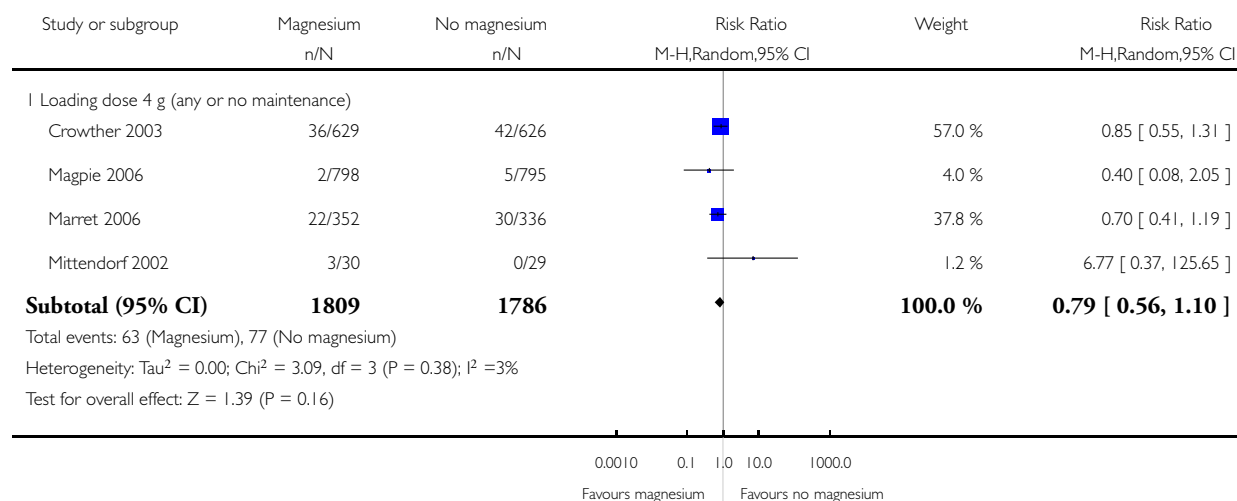
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

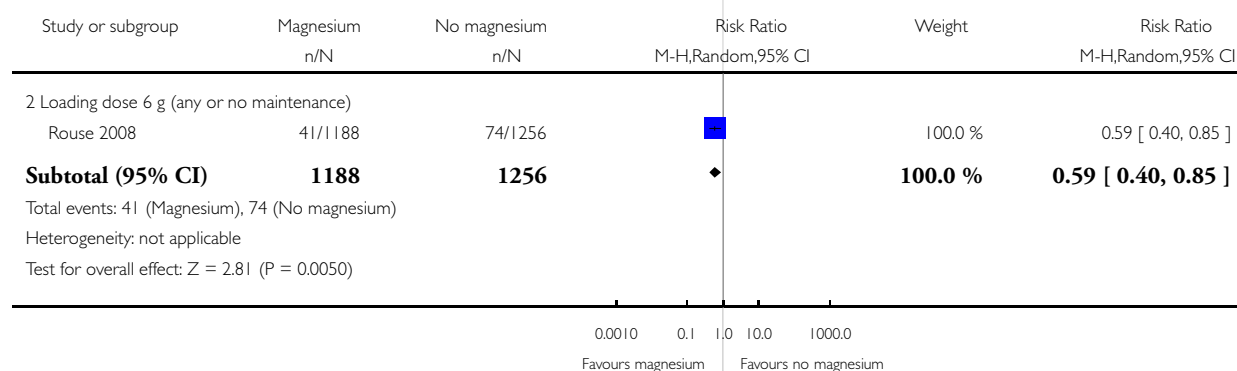
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

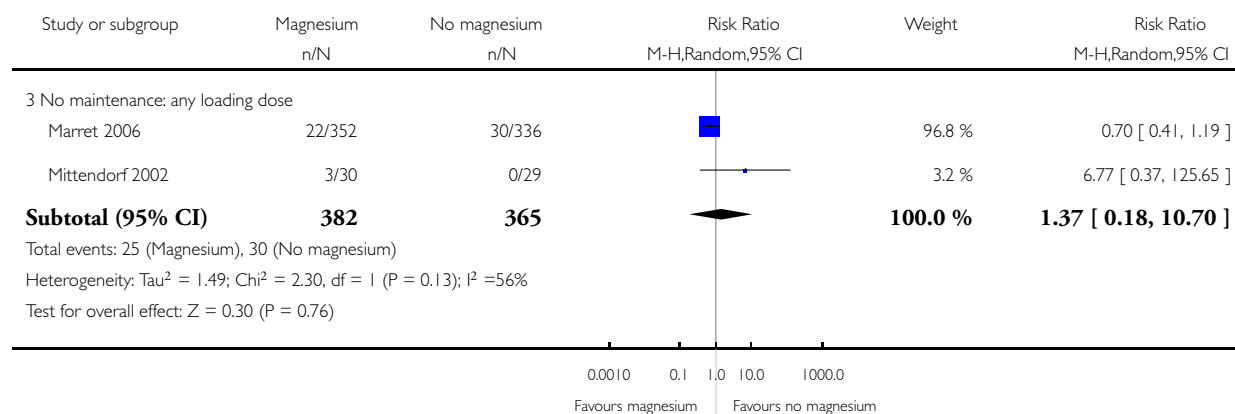
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

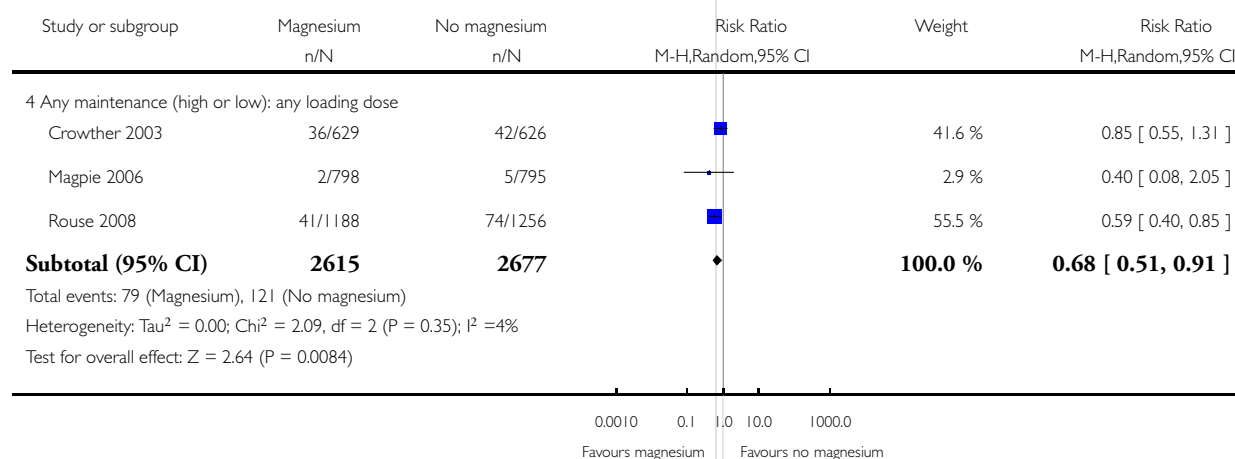
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

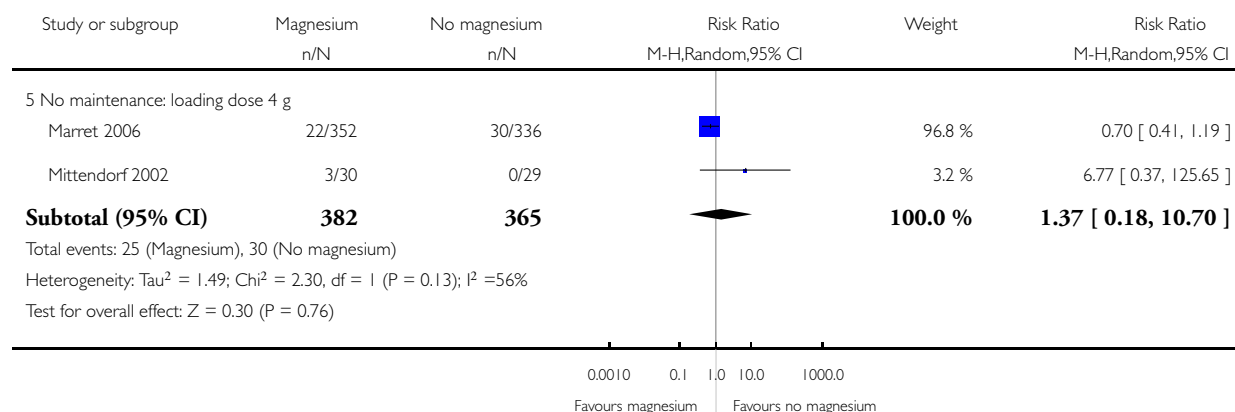
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

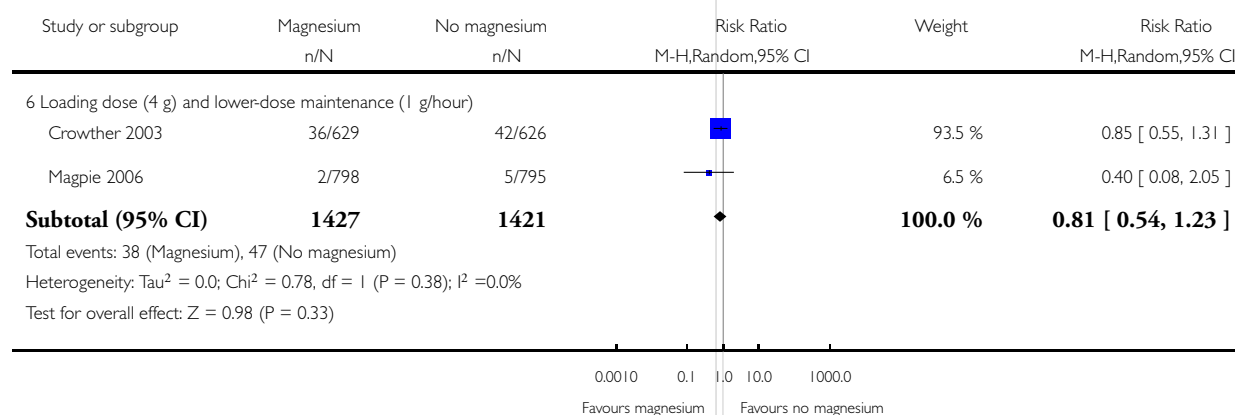
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

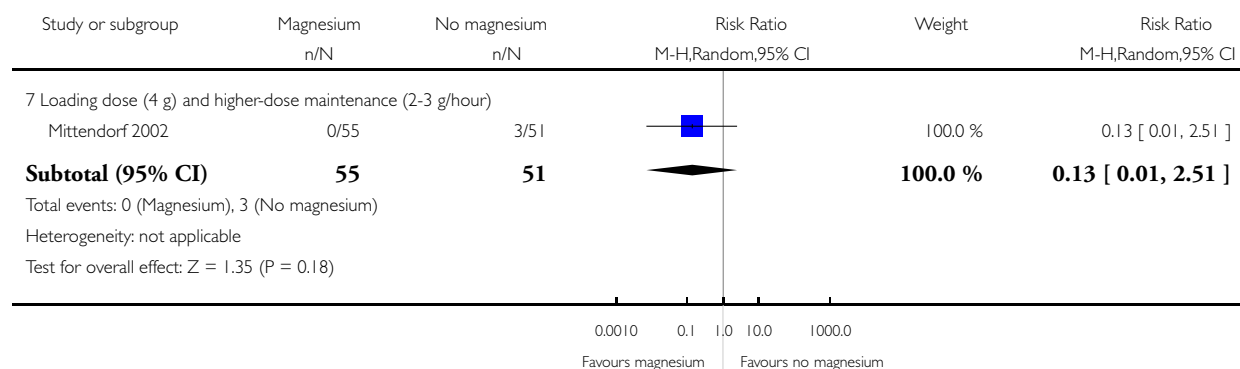
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

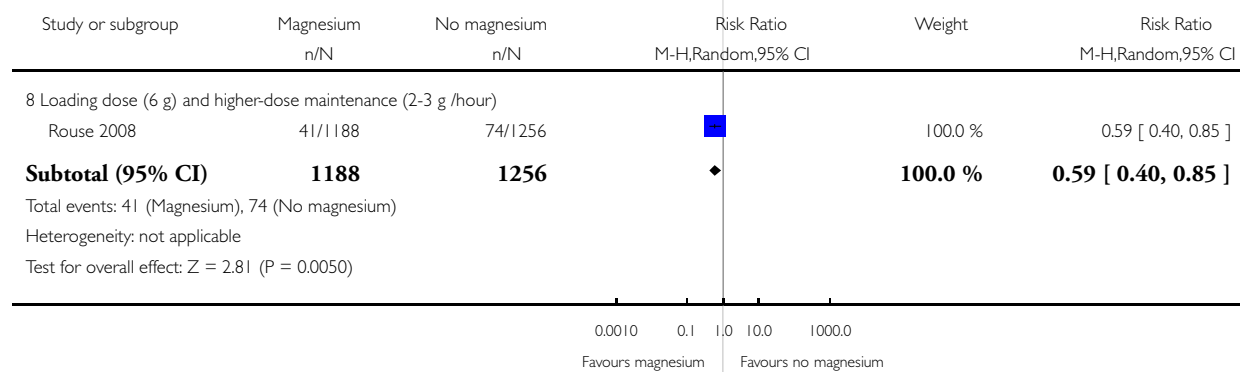
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 2 Cerebral palsy

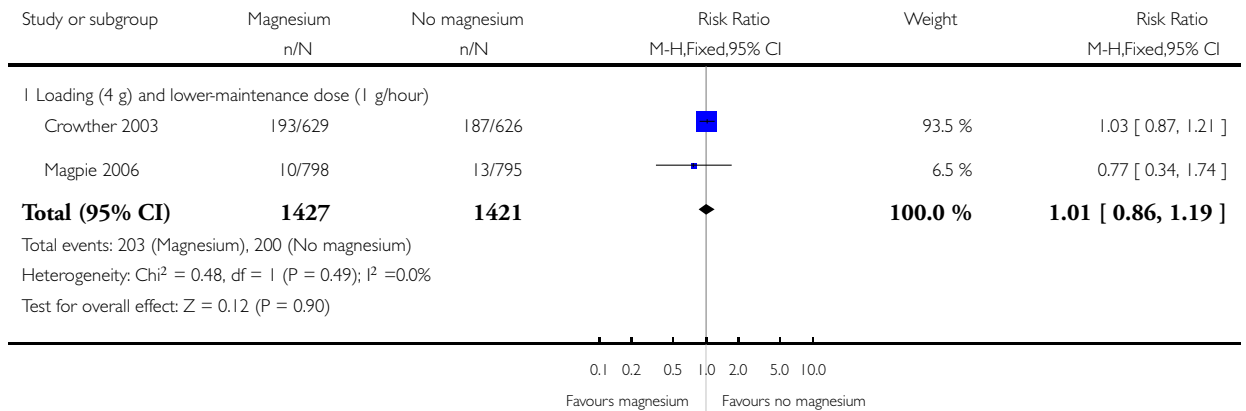


Analysis 6.3. Comparison 6 Dose subgroup, Outcome 3 Neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

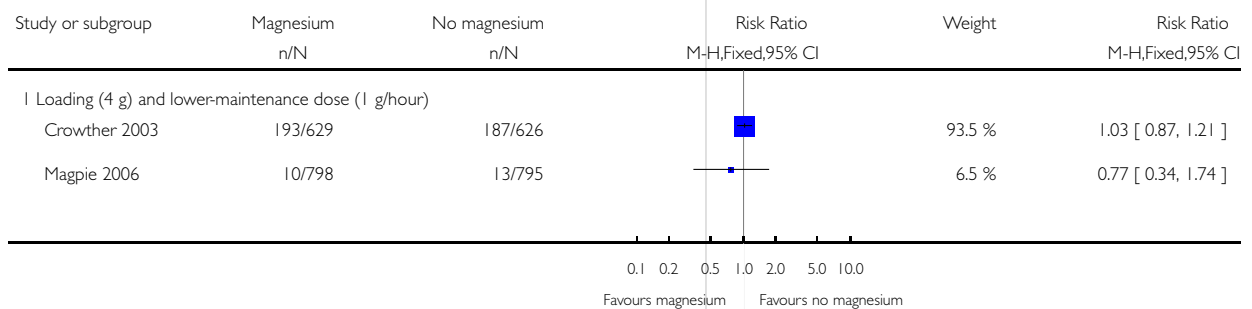
Outcome: 3 Neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 3 Neurological impairment

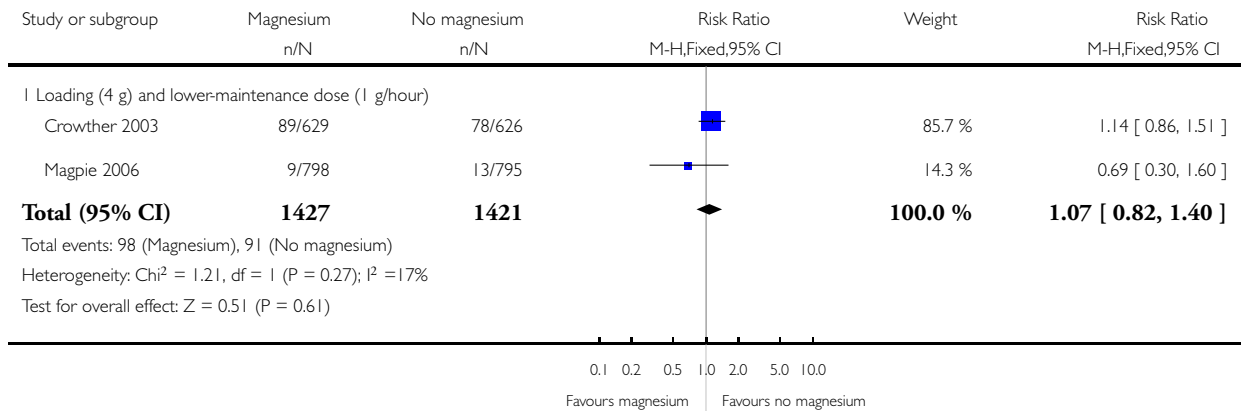


Analysis 6.4. Comparison 6 Dose subgroup, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

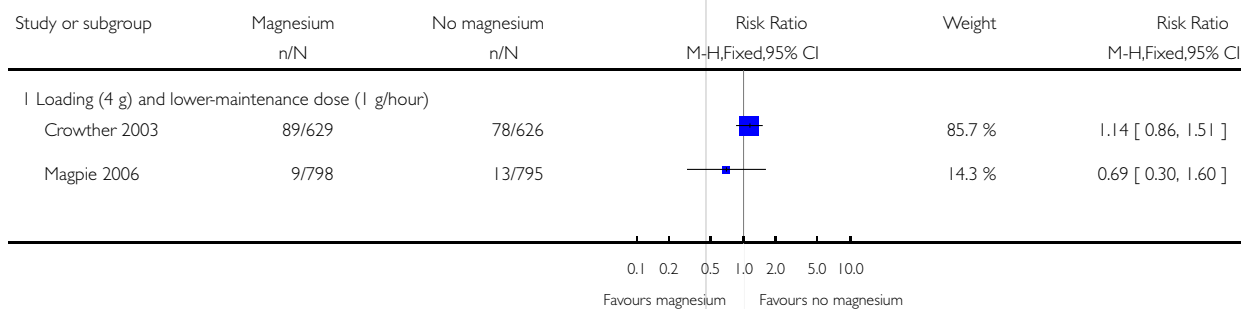
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 4 Major neurological disability

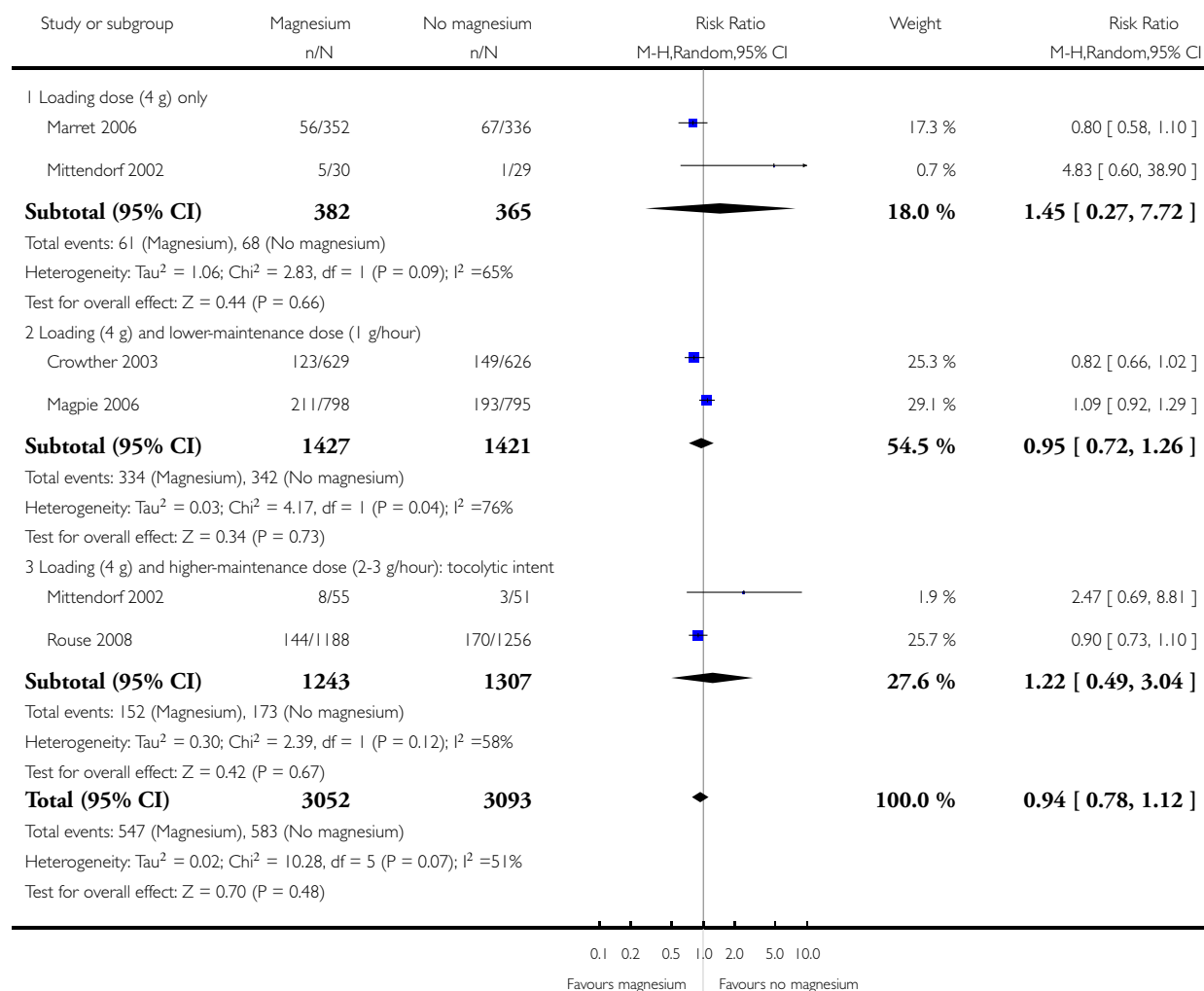


Analysis 6.5. Comparison 6 Dose subgroup, Outcome 5 Death or cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

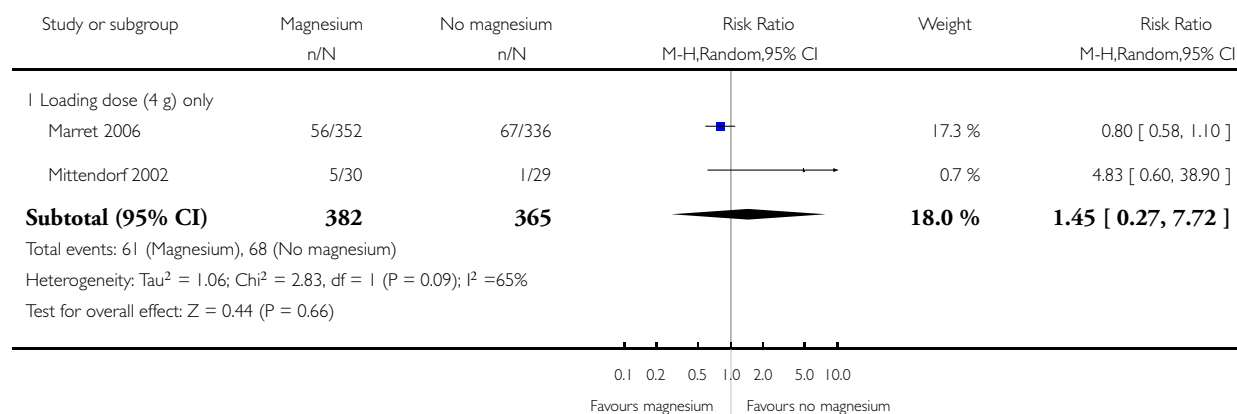
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

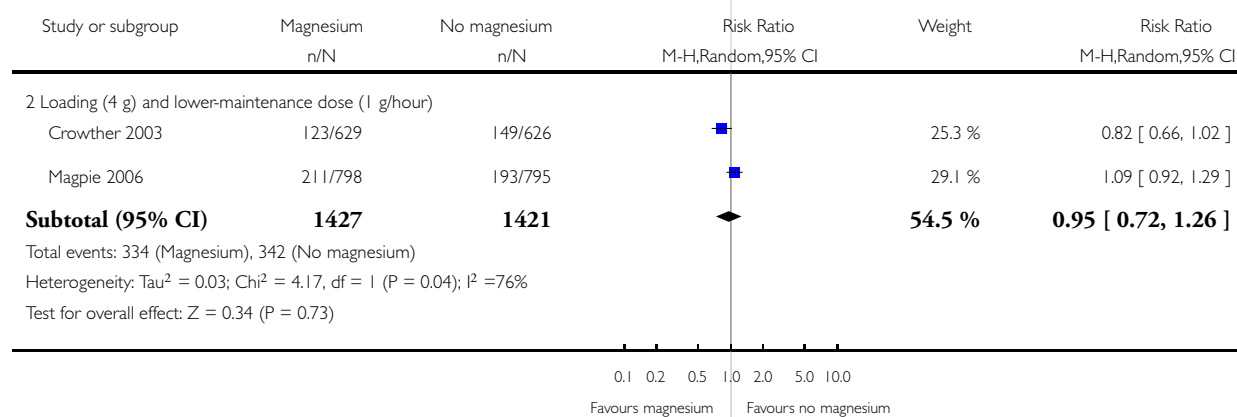
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

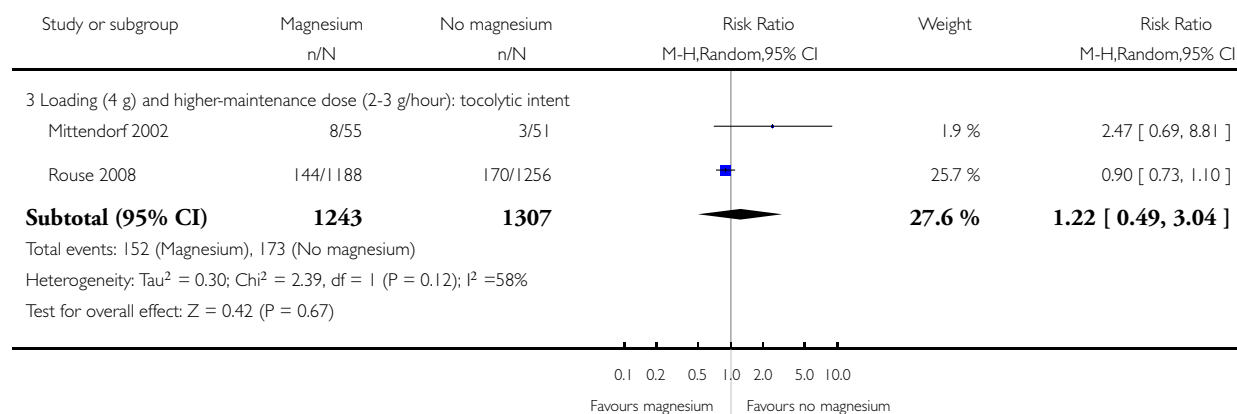
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 5 Death or cerebral palsy

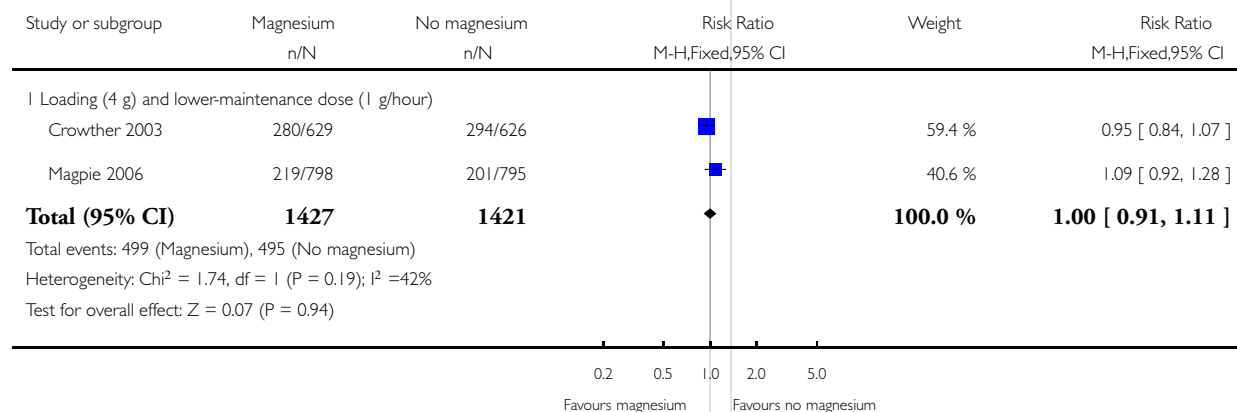


Analysis 6.6. Comparison 6 Dose subgroup, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

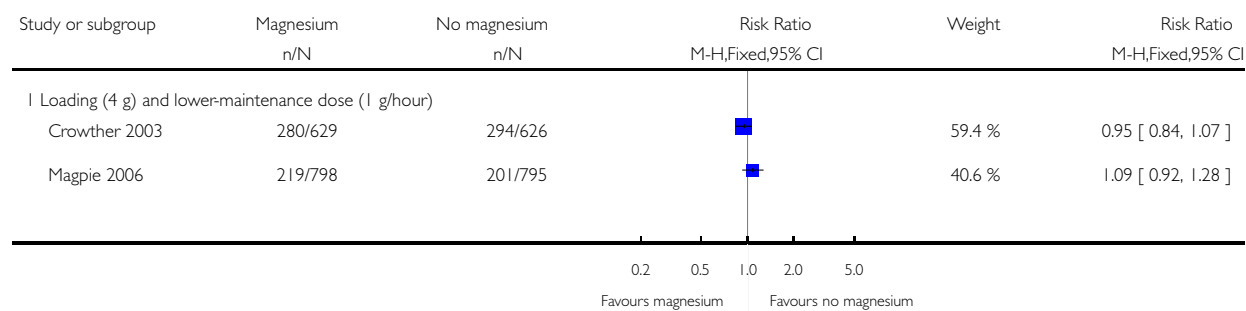
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 6 Death or neurological impairment

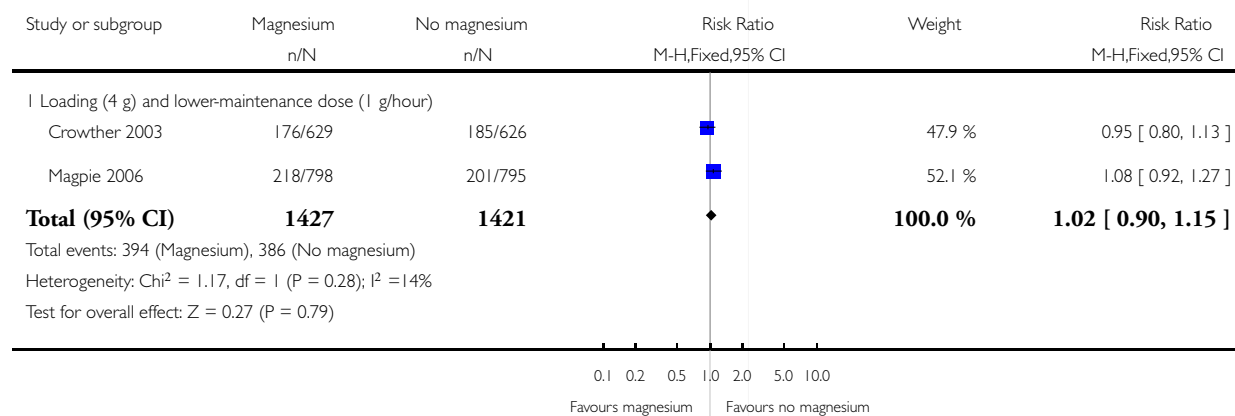


Analysis 6.7. Comparison 6 Dose subgroup, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

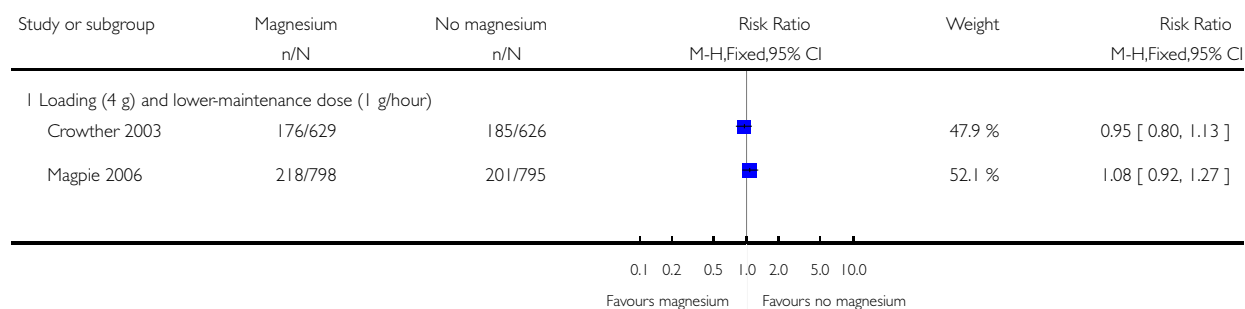
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 6 Dose subgroup

Outcome: 7 Death or major neurological disability

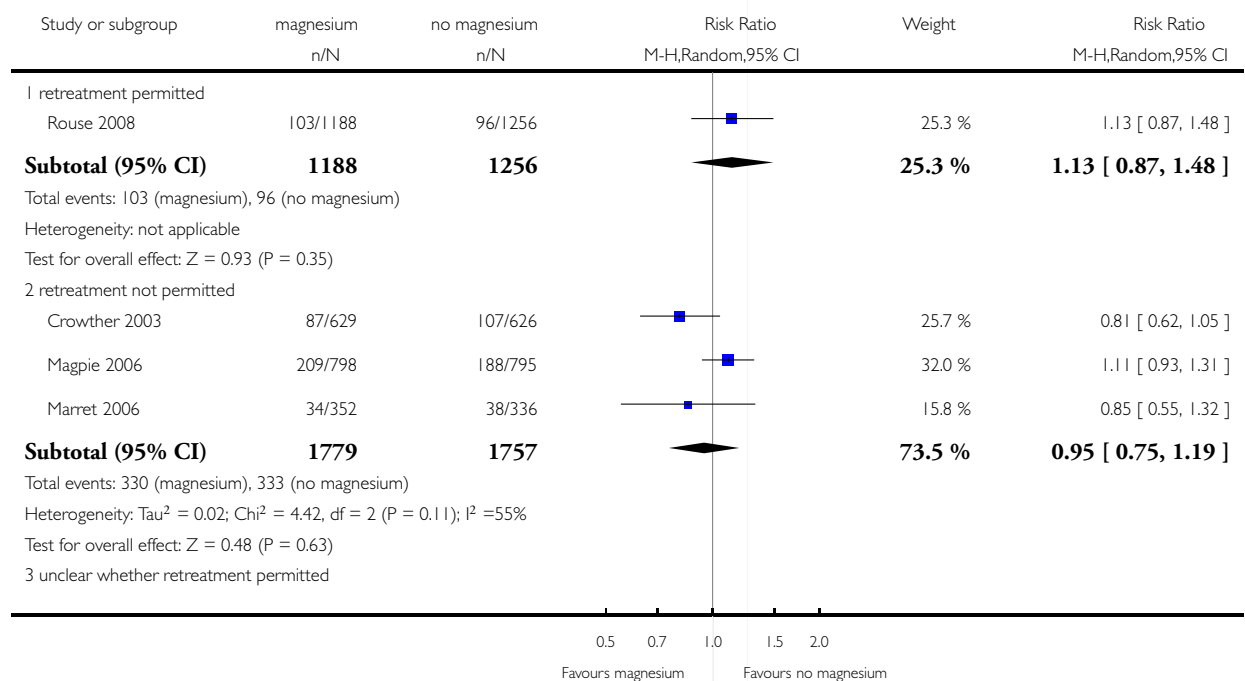


Analysis 7.1. Comparison 7 Retreatment subgroup, Outcome 1 Paediatric mortality (fetal and later).

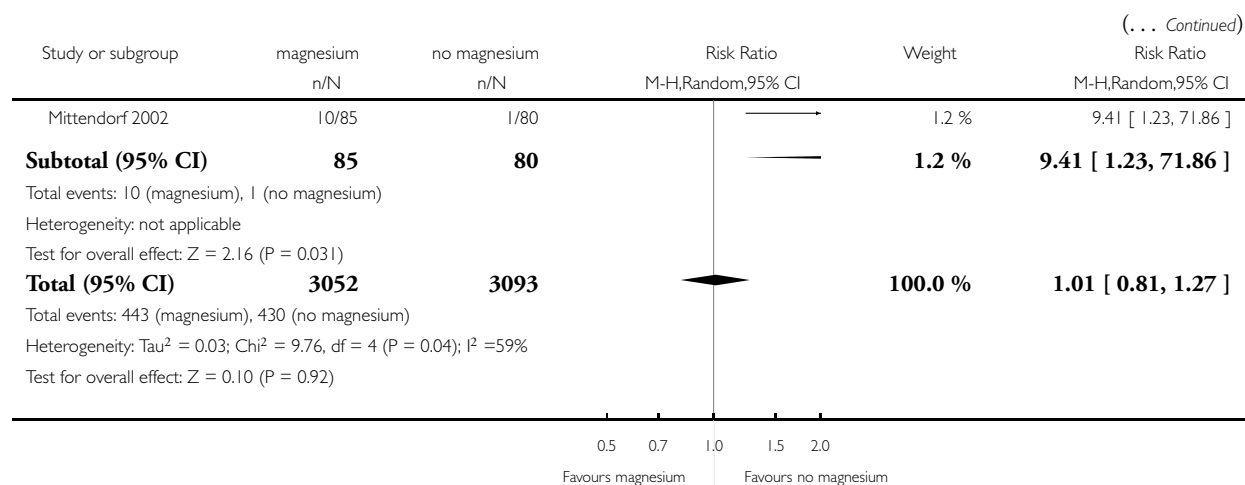
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 1 Paediatric mortality (fetal and later)



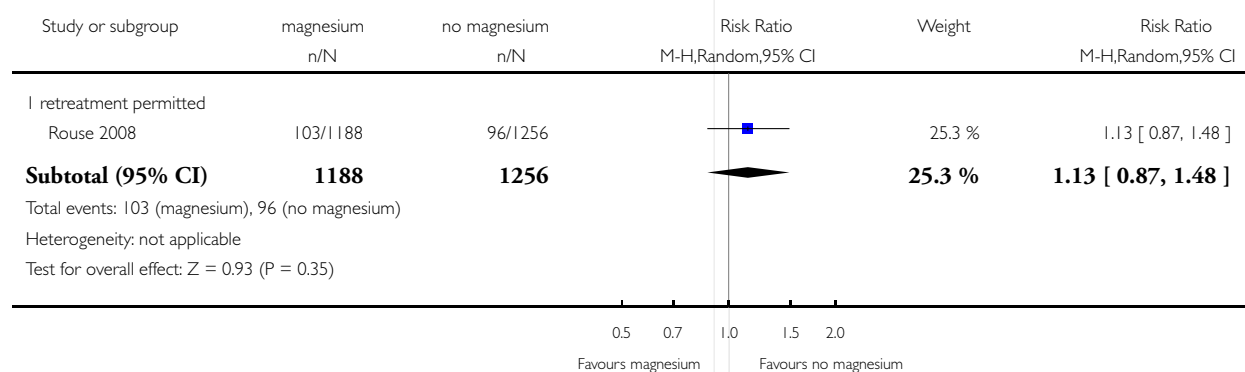
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Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

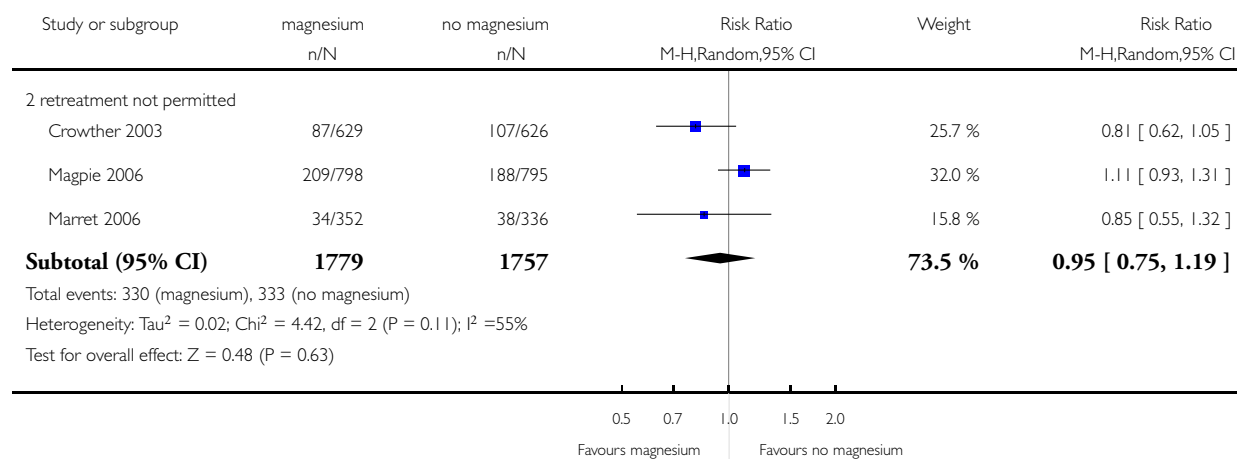
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

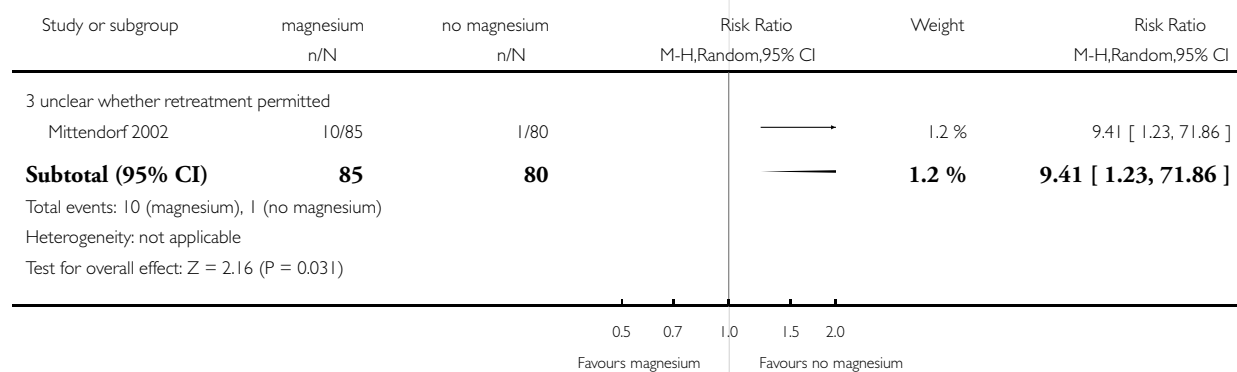
Outcome: 1 Paediatric mortality (fetal and later)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 1 Paediatric mortality (fetal and later)

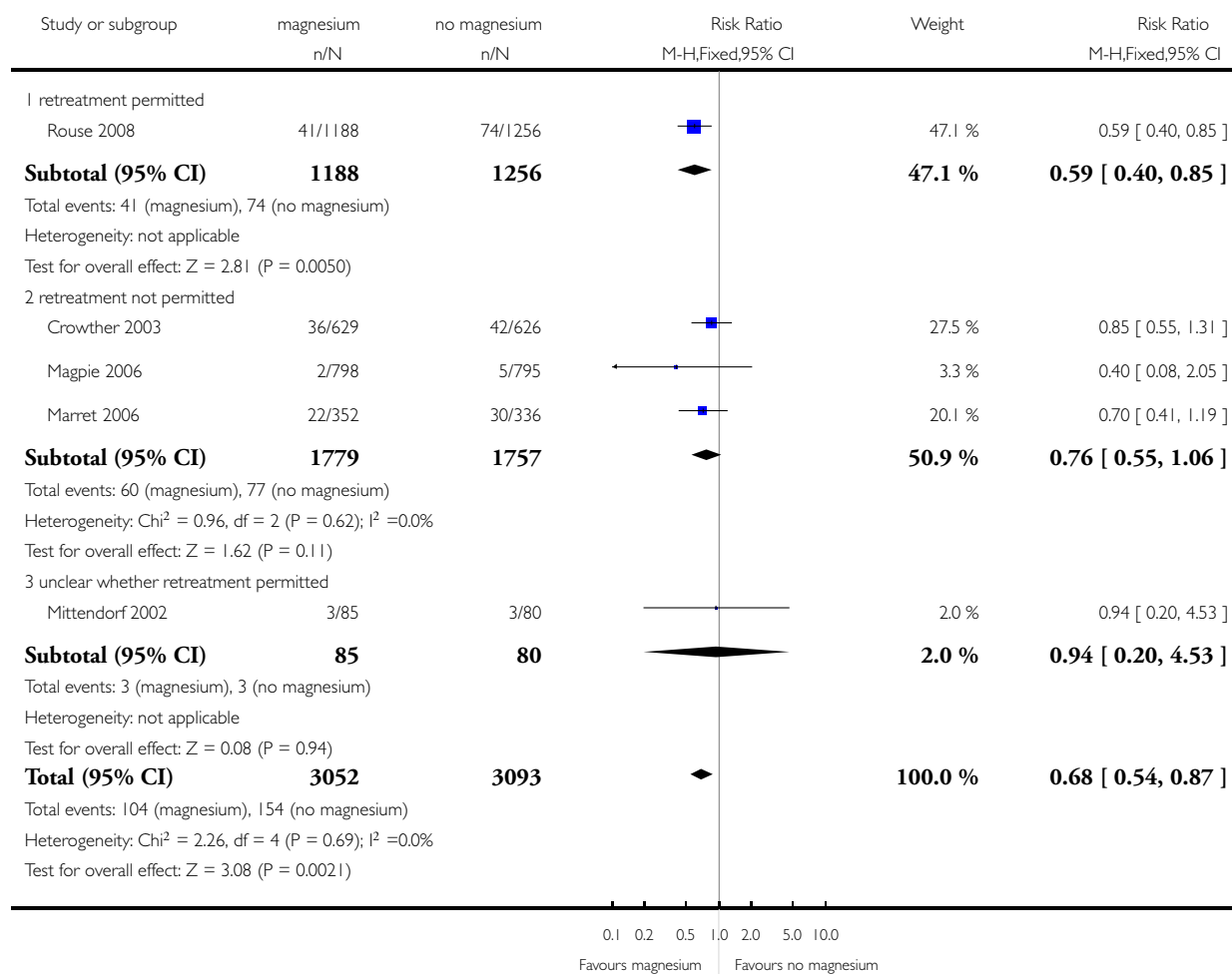


Analysis 7.2. Comparison 7 Retreatment subgroup, Outcome 2 Cerebral palsy.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

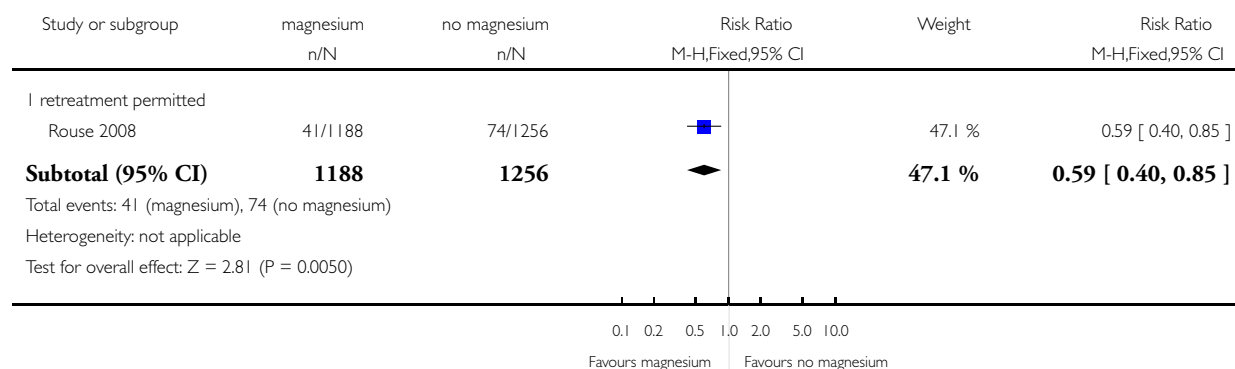
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

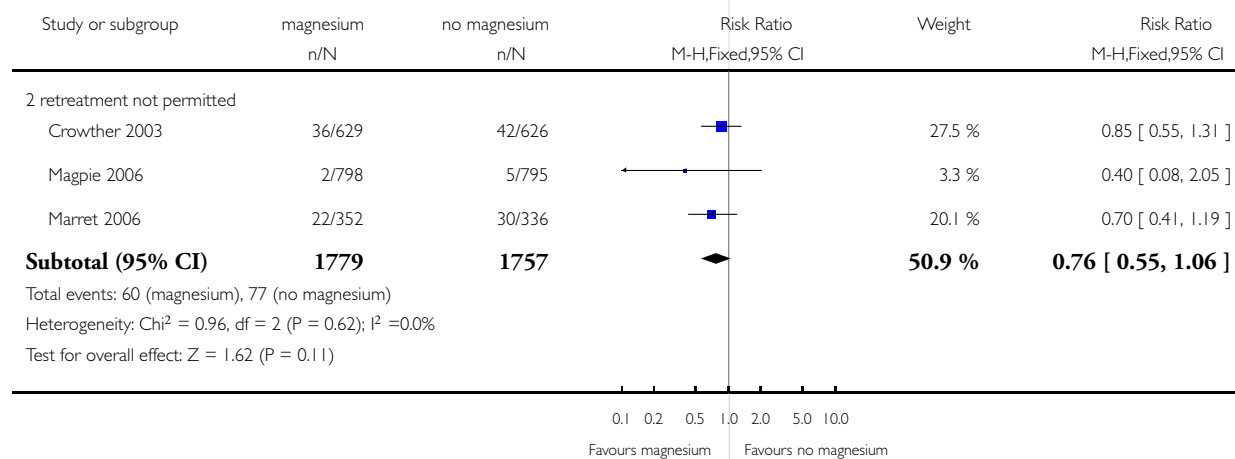
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

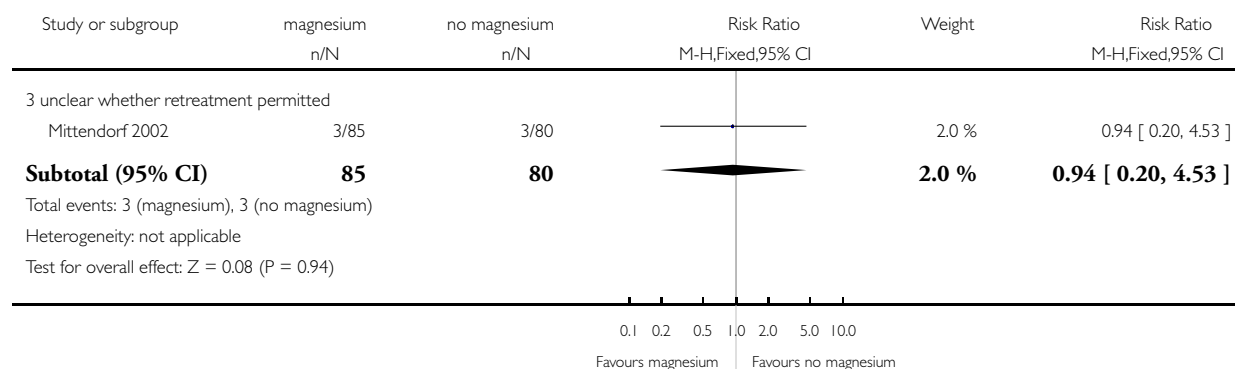
Outcome: 2 Cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 2 Cerebral palsy

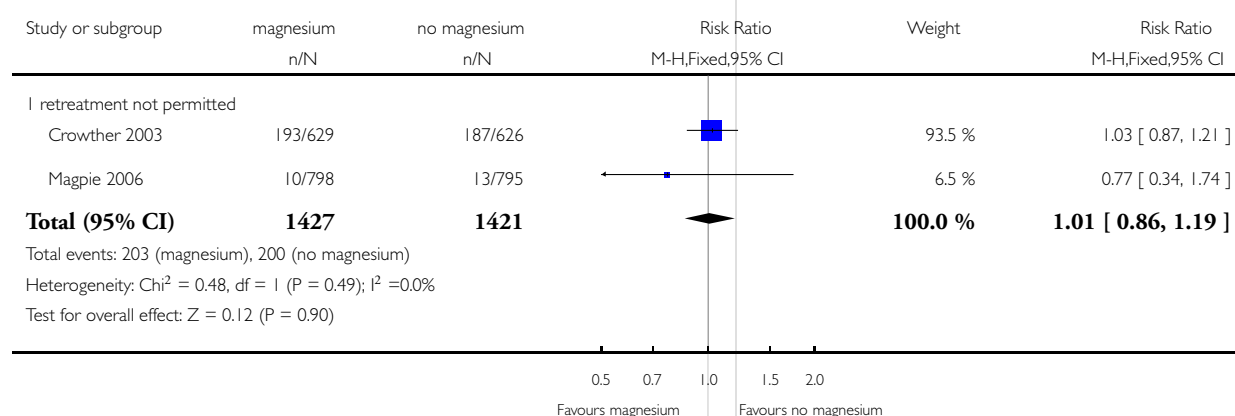


Analysis 7.3. Comparison 7 Retreatment subgroup, Outcome 3 Neurologic impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

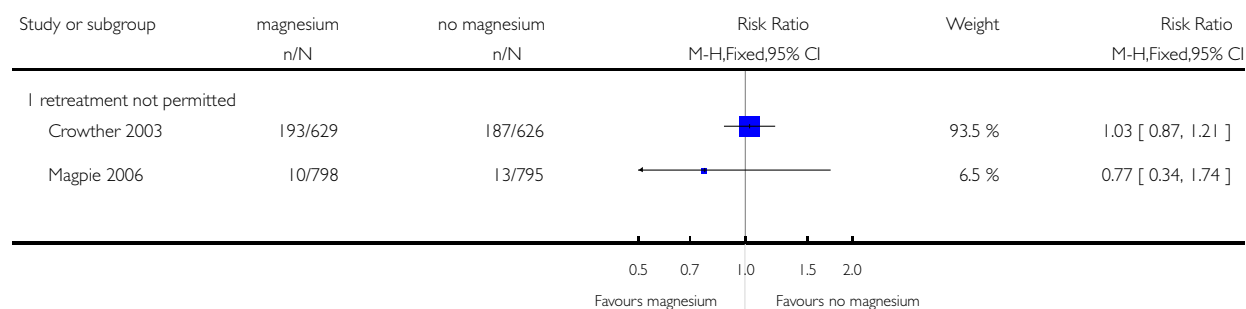
Outcome: 3 Neurologic impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 3 Neurologic impairment

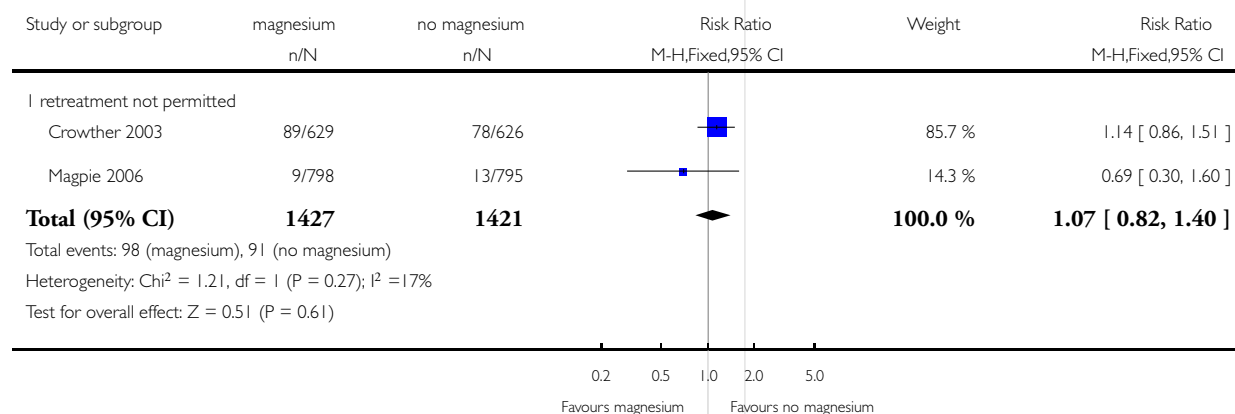


Analysis 7.4. Comparison 7 Retreatment subgroup, Outcome 4 Major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

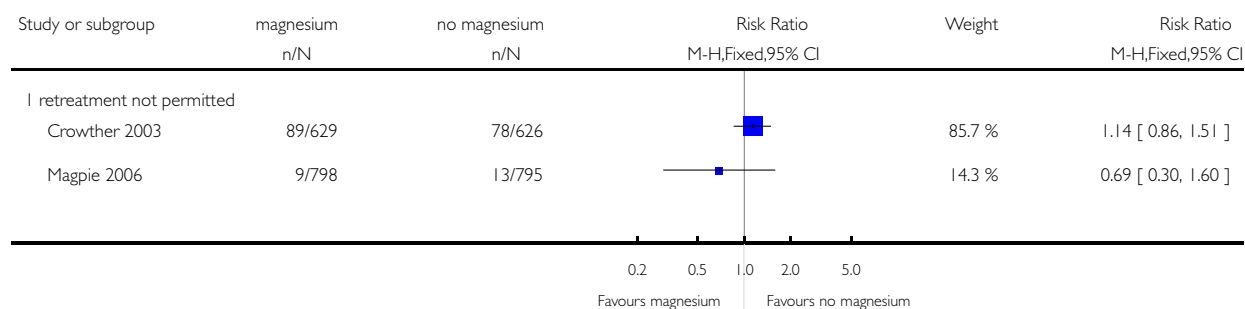
Outcome: 4 Major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 4 Major neurological disability

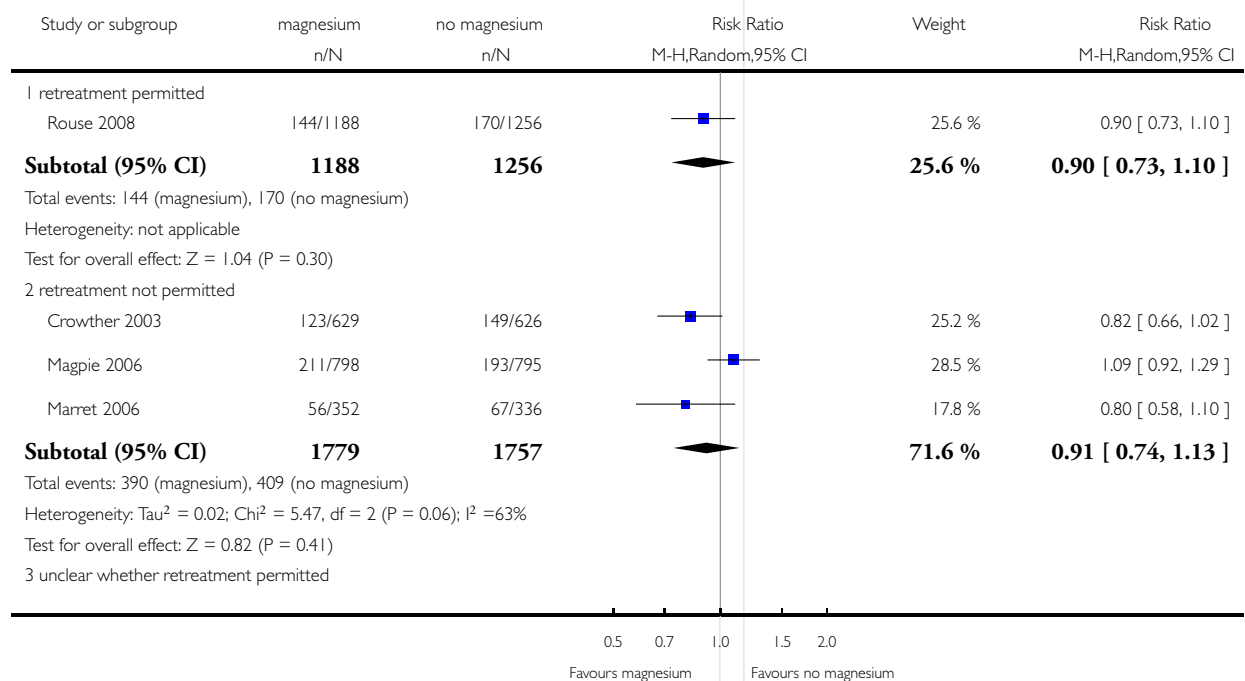


Analysis 7.5. Comparison 7 Retreatment subgroup, Outcome 5 Death or cerebral palsy.

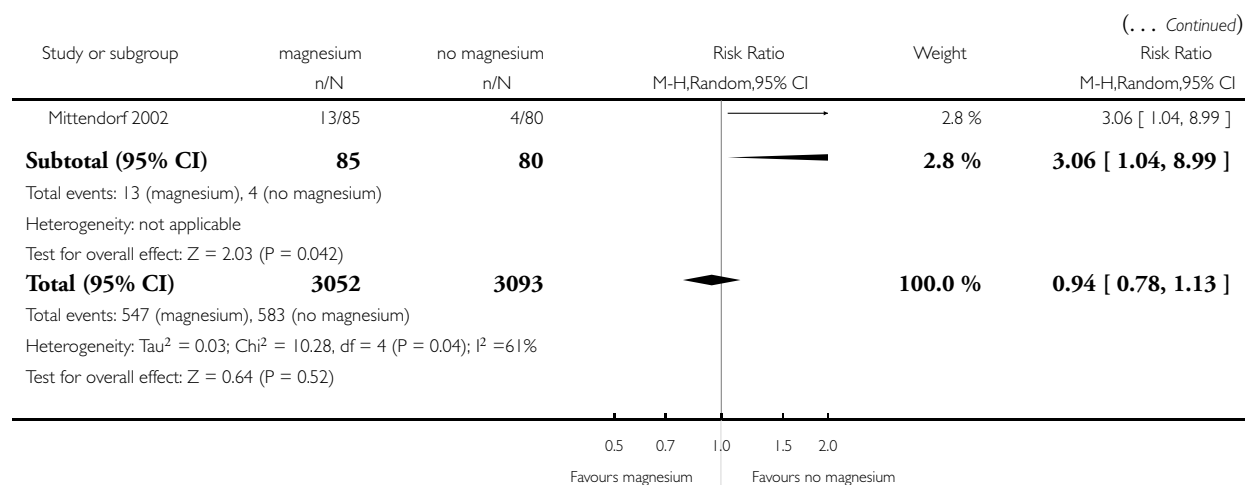
Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 5 Death or cerebral palsy



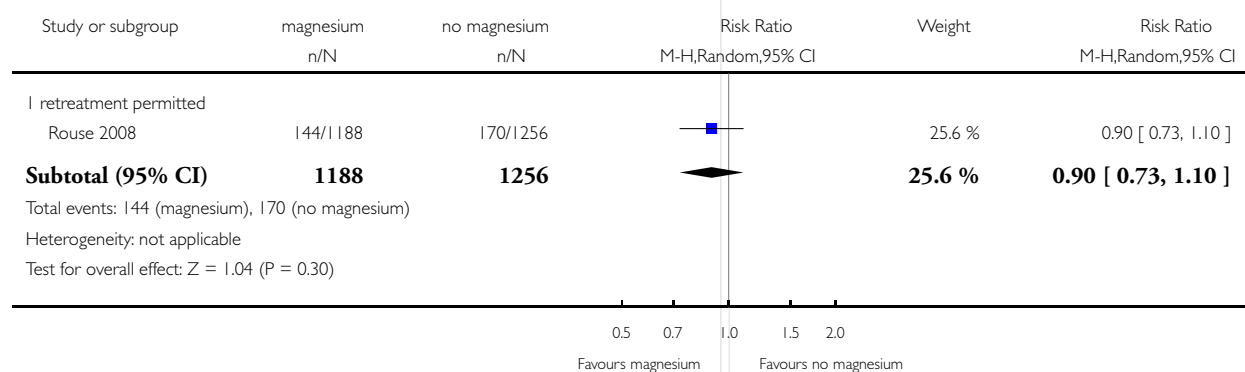
(Continued ...)



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

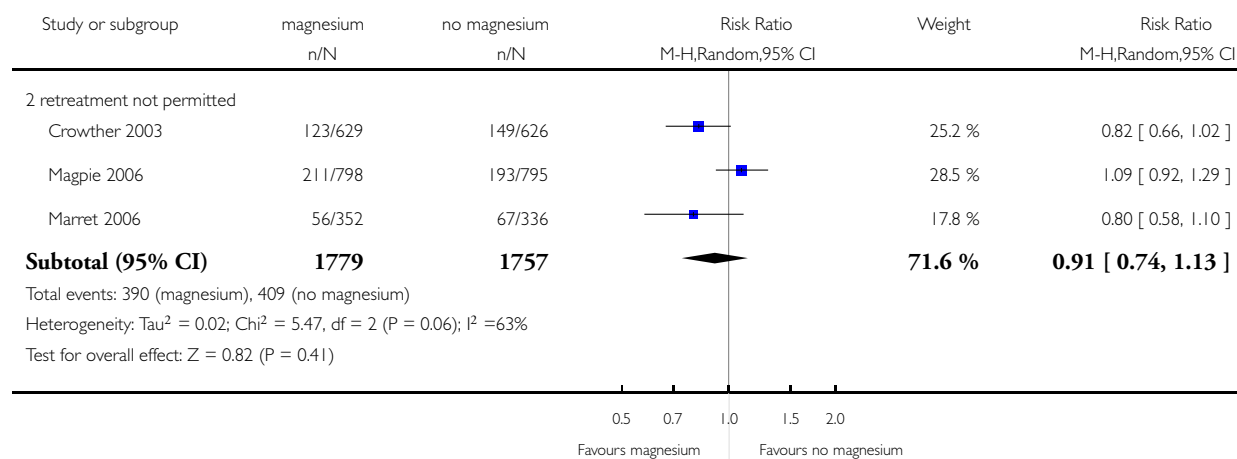
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

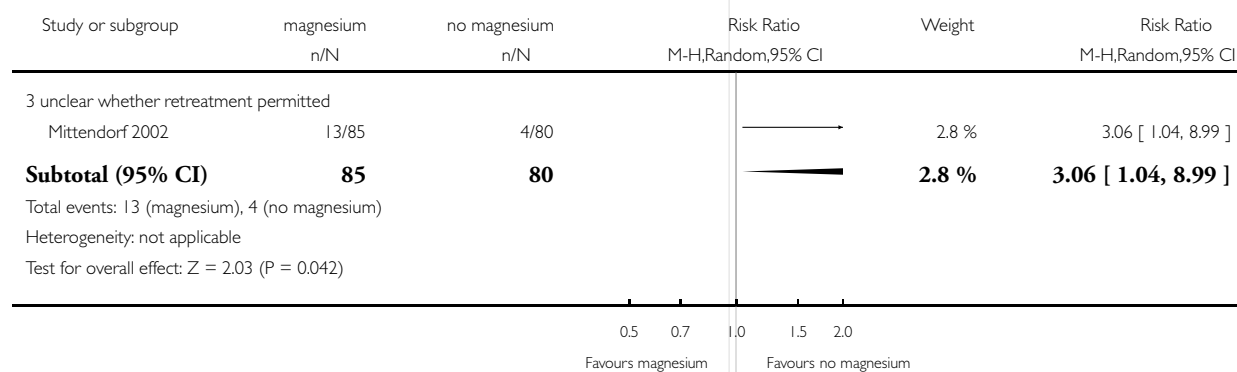
Outcome: 5 Death or cerebral palsy



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 5 Death or cerebral palsy

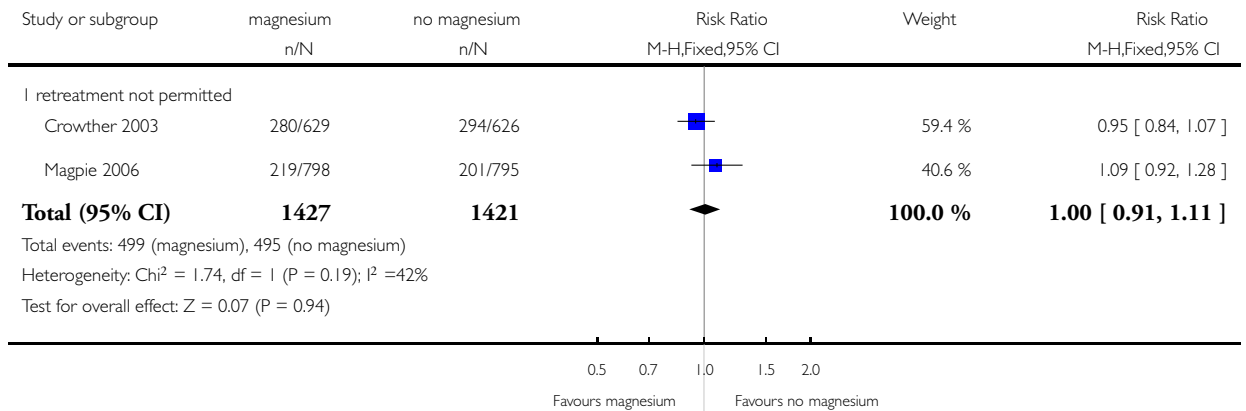


Analysis 7.6. Comparison 7 Retreatment subgroup, Outcome 6 Death or neurological impairment.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

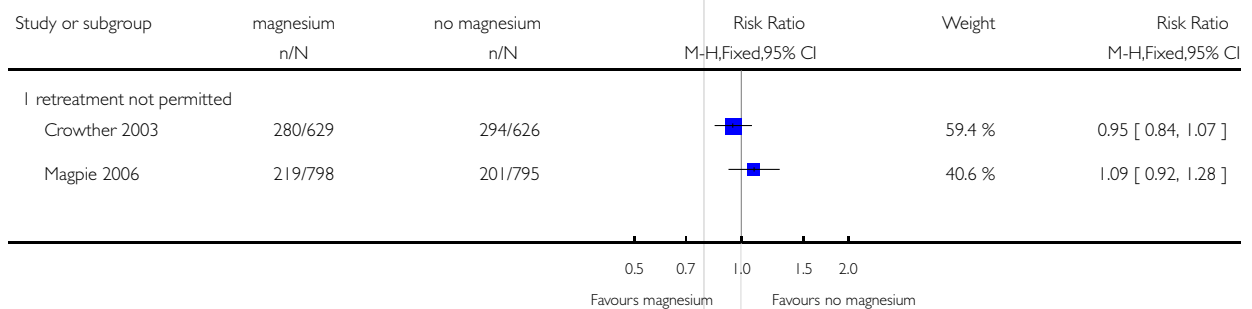
Outcome: 6 Death or neurological impairment



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 6 Death or neurological impairment

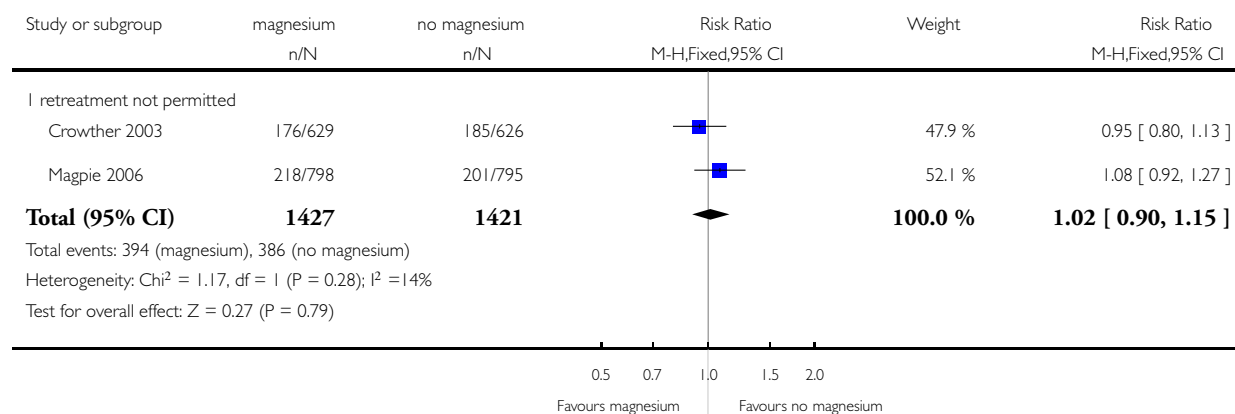


Analysis 7.7. Comparison 7 Retreatment subgroup, Outcome 7 Death or major neurological disability.

Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

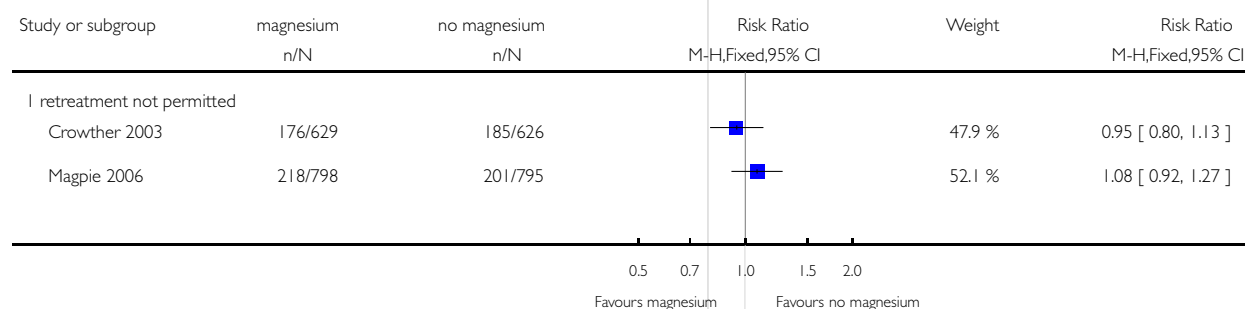
Outcome: 7 Death or major neurological disability



Review: Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus

Comparison: 7 Retreatment subgroup

Outcome: 7 Death or major neurological disability



WHAT'S NEW

Last assessed as up-to-date: 5 November 2008.

16 February 2009	Amended	Error in NNT for cerebral palsy corrected.
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HISTORY

Protocol first published: Issue 1, 2004

Review first published: Issue 3, 2007

6 November 2008	New citation required and conclusions have changed	There is now evidence that magnesium sulphate given to women at risk of preterm birth helps to protect the baby's brain and improve long-term outcomes.
31 August 2008	New search has been performed	Search updated. One new study identified (Rouse 2008) and two additional reports of Marret 2006 added.
24 April 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Lex Doyle and Caroline Crowther wrote the original protocol. Lex Doyle, for the first version of this review, searched the literature, reviewed all possible trials for inclusion, extracted details of the studies' methods and results, entered the data into Review Manager, wrote the initial synthesis of the results, and contributed to all versions of the original review. Caroline Crowther extracted details of the results and contributed to all versions of the original review. Philippa Middleton searched the literature, extracted details of the studies' results, and contributed to all versions of the original review. Stephane Marret searched the literature, extracted details of the studies' results, and contributed to the final version of the original review.

For this update Caroline Crowther and Philippa Middleton searched the literature, extracted details of the study methods and results, entered the data into Review Manager, wrote the initial updated synthesis of results and contributed to all versions of the review. Lex Doyle, Stephane Marret and Dwight Rouse contributed to all versions of this updated review.

DECLARATIONS OF INTEREST

Two review authors (Lex Doyle and Caroline Crowther) are principal investigators in the Australasian Collaborative Trial of Magnesium Sulphate given as a neuroprotective prior to very preterm birth for the prevention of mortality and cerebral palsy in their babies (ACTOMgSO₄ - [Crowther 2003](#)). This trial is funded by the Australian National Health and Medical Research Council. One review author (Stephane Marret) is the principal investigator in the PREMAG study from France ([Marret 2006](#)).

One review author (Dwight Rouse) is protocol chairman of the "BEAM" study that was funded by the United States National Institutes of Health (Eunice Shriver Kennedy National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke) ([Rouse 2008](#)).

The results of these trials were assessed for inclusion and quality using the same criteria as all other potential studies.

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- Department of Obstetrics and Gynaecology, University of Melbourne, Australia.

External sources

- National Health and Medical Research Council, Commonwealth Department of Health and Ageing, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The outcome of intraventricular haemorrhage 3/4 was added at review stage.

In the 2008 update, we have added a subgroup examining the impact of permitting magnesium retreatment.

INDEX TERMS

Medical Subject Headings (MeSH)

Central Nervous System Diseases [*prevention & control]; Cerebral Palsy [mortality; prevention & control]; Fetal Death [*prevention & control]; Infant, Newborn; Infant, Newborn, Diseases [mortality; prevention & control]; Magnesium Sulfate [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; *Premature Birth; Prenatal Care; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy