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

Shepherd ES, Goldsmith S, Doyle LW, Middleton P, Marret S, Rouse DJ, Pryde P, Wolf HT, Crowther CA

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TABLE OF CONTENTS

ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
SUMMARY OF FINDINGS 4
BACKGROUND 8
OBJECTIVES 8
METHODS 8
Figure 1. 11
RESULTS 14
Figure 2. 15
Figure 3. 18
Figure 4. 19
DISCUSSION 26
AUTHORS' CONCLUSIONS 28
ACKNOWLEDGEMENTS 29
REFERENCES 30
CHARACTERISTICS OF STUDIES 38
DATA AND ANALYSES 62
Analysis 1.1. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 63
Analysis 1.2. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 64
Analysis 1.3. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 64
Analysis 1.4. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 4: Major neurodevelopmental disability (up to 2 years' corrected age) 65
Analysis 1.5. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 5: Death or major neurodevelopmental disability (up to 2 years' corrected age) 65
Analysis 1.6. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 6: Death (fetal, neonatal, or later (up to school age)) 65
Analysis 1.7. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 7: Cerebral palsy (school age) 66
Analysis 1.8. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 8: Death or cerebral palsy (up to school age) 66
Analysis 1.9. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 9: Major neurodevelopmental disability (school age) 66
Analysis 1.10. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 10: Death or major neurodevelopmental disability (up to school age) 67
Analysis 1.11. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 11: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest) 67
Analysis 1.12. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 12: Adverse effects severe enough to stop treatment 68
Analysis 2.1. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 1: Fetal death 70
Analysis 2.2. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 2: Neonatal death 71
Analysis 2.3. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 3: Birthweight 72
Analysis 2.4. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 4: Length at birth 72
Analysis 2.5. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 5: Head circumference at birth 73
Analysis 2.6. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 6: Gestational age at birth (weeks) 73
Analysis 2.7. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 7: Apgar score less than 7 at 5 minutes 74

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Analysis 2.8. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 8: Use of active resuscitation at birth 75
Analysis 2.9. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 9: Intraventricular haemorrhage 76
Analysis 2.10. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 10: Severe intraventricular haemorrhage (grade 3 or 4) 76
Analysis 2.11. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 11: Cystic periventricular leukomalacia 77
Analysis 2.12. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 12: Ventriculomegaly 77
Analysis 2.13. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 13: Neonatal encephalopathy 78
Analysis 2.14. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 14: Neonatal convulsions 78
Analysis 2.15. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 15: Neonatal hypotonia 79
Analysis 2.16. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 16: Necrotising enterocolitis 79
Analysis 2.17. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 17: Retinopathy of prematurity 80
Analysis 2.18. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 18: Patent ductus arteriosus 80
Analysis 2.19. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 19: Respiratory distress syndrome 81
Analysis 2.20. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 20: Chronic lung disease/bronchopulmonary dysplasia 81
Analysis 2.21. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 21: Use of respiratory support (endotracheal intubation) 82
Analysis 2.22. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 22: Use of respiratory support (mechanical ventilation or continuous positive airway pressure) 82
Analysis 2.23. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 23: Use of inotropic support 83
Analysis 2.24. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 24: Air leak syndrome 83
Analysis 2.25. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 25: Early- or late-onset sepsis 84
Analysis 2.26. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 26: Severe adverse neonatal outcome composite 85
Analysis 3.1. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 1: Later death (up to 2 years' corrected age) 88
Analysis 3.2. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 2: Cerebral palsy severity (up to 2 years' corrected age) 89
Analysis 3.3. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 3: Any neurodevelopmental disability (up to 2 years' corrected age) 90
Analysis 3.4. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 4: Death or any neurodevelopmental disability (up to 2 years' corrected age) 90
Analysis 3.5. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 5: Blindness (up to 2 years' corrected age) 91
Analysis 3.6. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 6: Deafness (up to 2 years' corrected age) 91
Analysis 3.7. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 7: Developmental delay/intellectual impairment (up to 2 years' corrected age) 92
Analysis 3.8. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 8: Gross motor dysfunction (up to 2 years' corrected age) 93
Analysis 3.9. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 9: Psychomotor dysfunction (up to 2 years' corrected age) 93

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Analysis 3.10. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 10: Death or substantial gross motor dysfunction (up to 2 years' corrected age) 94
Analysis 3.11. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 11: Growth (up to 2 years' corrected age) 95
Analysis 3.12. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 12: Respiratory function (up to 2 years' corrected age) 96
Analysis 3.13. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 13: Blood pressure (up to 2 years' corrected age) 96
Analysis 3.14. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 14: Blood pressure (up to 2 years' corrected age) 97
Analysis 3.15. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 15: Behaviour (up to 2 years' corrected age) 98
Analysis 4.1. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 1: Later death (school age) 103
Analysis 4.2. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 2: Cerebral palsy severity (school age) 103
Analysis 4.3. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 3: Any neurodevelopmental disability (school age) 104
Analysis 4.4. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 4: Death or any neurodevelopmental disability (school age) 105
Analysis 4.5. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 5: Blindness (school age) 105
Analysis 4.6. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 6: Deafness (school age) 105
Analysis 4.7. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 7: Developmental delay/intellectual impairment (school age) 106
Analysis 4.8. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 8: Gross motor dysfunction (school age) 107
Analysis 4.9. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 9: Death or substantial gross motor dysfunction (school age) 108
Analysis 4.10. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 10: Growth (school age) 108
Analysis 4.11. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 11: Respiratory function (school age) 109
Analysis 4.12. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 12: Behaviour (school age) 110
Analysis 4.13. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 13: Behaviour (school age) 112
Analysis 4.14. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 14: Educational achievement (school age) 114
Analysis 4.15. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 15: Educational achievement (school age) 115
Analysis 5.1. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 1: Death 117
Analysis 5.2. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 2: Cardiac arrest . 117
Analysis 5.3. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 3: Respiratory arrest 118
Analysis 5.4. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 4: Side effects of treatment 118
Analysis 5.5. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 5: Side effect: respiratory depression 119
Analysis 5.6. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 6: Side effect: hypotension 119
Analysis 5.7. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 7: Side effect: tachycardia 120
Analysis 5.8. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 8: Side effect: warmth over body/flushing 120

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Analysis 5.9. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 9: Side effect: arm discomfort with infusion 121
Analysis 5.10. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 10: Side effect: mouth dryness 121
Analysis 5.11. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 11: Side effect: nausea or vomiting 122
Analysis 5.12. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 12: Side effect: sleepiness 122
Analysis 5.13. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 13: Side effect: sweating 122
Analysis 5.14. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 14: Side effect: dizziness 123
Analysis 5.15. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 15: Side effect: blurred vision 123
Analysis 5.16. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 16: Side effect: tendon reflex abolition 123
Analysis 5.17. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 17: Side effect: "curarisation" 124
Analysis 5.18. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 18: Side effect: headache 124
Analysis 5.19. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 19: Mode of birth: caesarean birth 124
Analysis 5.20. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 20: Chorioamnionitis 125
Analysis 5.21. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 21: Postpartum haemorrhage 125
Analysis 6.1. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 1: Maternal admission to the intensive care unit 126
Analysis 6.2. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 2: Length of postnatal hospitalisation for women (days) 126
Analysis 6.3. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 3: Length of neonatal/infant hospitalisation (days) 127
Analysis 6.4. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 4: Hospital admissions (up to 2 years' corrected age) 127
Analysis 6.5. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 5: Postdischarge service (up to 2 years' corrected age) 127
Analysis 6.6. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 6: Hospital admissions (school age) 128
Analysis 7.1. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 130
Analysis 7.2. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 131
Analysis 7.3. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 132
Analysis 7.4. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age) 133
Analysis 7.5. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 5: Death (fetal, neonatal, or later (up to school age)) 134
Analysis 7.6. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 6: Cerebral palsy (school age) 135
Analysis 7.7. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 7: Major neurodevelopmental disability (school age) 135
Analysis 7.8. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 8: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest) 136
Analysis 7.9. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 9: Adverse effects severe enough to stop treatment 137

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Analysis 8.1. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 139
Analysis 8.2. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 140
Analysis 8.3. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 141
Analysis 8.4. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age) 142
Analysis 8.5. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 5: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest) 143
Analysis 8.6. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 6: Adverse effects severe enough to stop treatment 144
Analysis 9.1. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 146
Analysis 9.2. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 147
Analysis 9.3. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 148
Analysis 9.4. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age) 149
Analysis 9.5. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 5: Death (fetal, neonatal, or later (up to school age)) 150
Analysis 9.6. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 6: Cerebral palsy (school age) 150
Analysis 9.7. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 7: Major neurodevelopmental disability (school age) 151
Analysis 9.8. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 8: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest) 152
Analysis 9.9. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 9: Adverse effects severe enough to stop treatment 153
Analysis 10.1. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 155
Analysis 10.2. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 156
Analysis 10.3. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 157
Analysis 10.4. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age) 158
Analysis 10.5. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 5: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest) 159
Analysis 10.6. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 6: Adverse effects severe enough to stop treatment 160
Analysis 11.1. Comparison 11: Sensitivity analysis, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age)) 161
Analysis 11.2. Comparison 11: Sensitivity analysis, Outcome 2: Cerebral palsy (up to 2 years' corrected age) 161
Analysis 11.3. Comparison 11: Sensitivity analysis, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age) 162
Analysis 11.4. Comparison 11: Sensitivity analysis, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age) 162
Analysis 11.5. Comparison 11: Sensitivity analysis, Outcome 5: Cerebral palsy (school age) 163
ADDITIONAL TABLES 163
APPENDICES 167
WHAT'S NEW 171
HISTORY 172
CONTRIBUTIONS OF AUTHORS 172
DECLARATIONS OF INTEREST 172
SOURCES OF SUPPORT 173
DIFFERENCES BETWEEN PROTOCOL AND REVIEW 173

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INDEX TERMS 174

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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

Magnesium sulphate is a common therapy in perinatal care. Its benefits when given to women at risk of preterm birth for fetal neuroprotection (prevention of cerebral palsy for children) were shown in a 2009 Cochrane review. Internationally, use of magnesium sulphate for preterm cerebral palsy prevention is now recommended practice. As new randomised controlled trials (RCTs) and longer-term follow-up of prior RCTs have since been conducted, this review updates the previously published version.

Objectives

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

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) on 17 March 2023, as well as reference lists of retrieved studies.

Selection criteria

We included RCTs and cluster-RCTs of women at risk of preterm birth that assessed prenatal magnesium sulphate for fetal neuroprotection compared with placebo or no treatment. All methods of administration (intravenous, intramuscular, and oral) were eligible. We did not include studies where magnesium sulphate was used with the primary aim of preterm labour tocolysis, or the prevention and/or treatment of eclampsia.

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Data collection and analysis

Two review authors independently assessed RCTs for inclusion, extracted data, and assessed risk of bias and trustworthiness. Dichotomous data were presented as summary risk ratios (RR) with 95% confidence intervals (CI), and continuous data were presented as mean differences with 95% CI. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included six RCTs (5917 women and their 6759 fetuses alive at randomisation). All RCTs were conducted in high-income countries. The RCTs compared magnesium sulphate with placebo in women at risk of preterm birth at less than 34 weeks' gestation; however, treatment regimens and inclusion/exclusion criteria varied. Though the RCTs were at an overall low risk of bias, the certainty of evidence ranged from high to very low, due to concerns regarding study limitations, imprecision, and inconsistency.

Primary outcomes for infants/children: *Up to two years' corrected age*, magnesium sulphate compared with placebo reduced cerebral palsy (RR 0.71, 95% CI 0.57 to 0.89; 6 RCTs, 6107 children; number needed to treat for additional beneficial outcome (NNTB) 60, 95% CI 41 to 158) and death or cerebral palsy (RR 0.87, 95% CI 0.77 to 0.98; 6 RCTs, 6481 children; NNTB 56, 95% CI 32 to 363) (both high-certainty evidence). Magnesium sulphate probably resulted in little to no difference in death (fetal, neonatal, or later) (RR 0.96, 95% CI 0.82 to 1.13; 6 RCTs, 6759 children); major neurodevelopmental disability (RR 1.09, 95% CI 0.83 to 1.44; 1 RCT, 987 children); or death or major neurodevelopmental disability (RR 0.95, 95% CI 0.85 to 1.07; 3 RCTs, 4279 children) (all moderate-certainty evidence). *At early school age*, magnesium sulphate may have resulted in little to no difference in death (fetal, neonatal, or later) (RR 0.82, 95% CI 0.66 to 1.02; 2 RCTs, 1758 children); cerebral palsy (RR 0.99, 95% CI 0.69 to 1.41; 2 RCTs, 1038 children); death or cerebral palsy (RR 0.90, 95% CI 0.67 to 1.20; 1 RCT, 503 children); and death or major neurodevelopmental disability (RR 0.81, 95% CI 0.59 to 1.12; 1 RCT, 503 children) (all low-certainty evidence). Magnesium sulphate may also have resulted in little to no difference in major neurodevelopmental disability, but the evidence is very uncertain (average RR 0.92, 95% CI 0.53 to 1.62; 2 RCTs, 940 children; very low-certainty evidence).

Secondary outcomes for infants/children: Magnesium sulphate probably reduced severe intraventricular haemorrhage (grade 3 or 4) (RR 0.76, 95% CI 0.60 to 0.98; 5 RCTs, 5885 infants; NNTB 92, 95% CI 55 to 1102; moderate-certainty evidence) and may have resulted in little to no difference in chronic lung disease/bronchopulmonary dysplasia (average RR 0.92, 95% CI 0.77 to 1.10; 5 RCTs, 6689 infants; low-certainty evidence).

Primary outcomes for women: Magnesium sulphate may have resulted in little or no difference in severe maternal outcomes potentially related to treatment (death, cardiac arrest, respiratory arrest) (RR 0.32, 95% CI 0.01 to 7.92; 4 RCTs, 5300 women; low-certainty evidence). However, magnesium sulphate probably increased maternal adverse effects severe enough to stop treatment (average RR 3.21, 95% CI 1.88 to 5.48; 3 RCTs, 4736 women; moderate-certainty evidence).

Secondary outcomes for women: Magnesium sulphate probably resulted in little to no difference in caesarean section (RR 0.96, 95% CI 0.91 to 1.02; 5 RCTs, 5861 women) and postpartum haemorrhage (RR 0.94, 95% CI 0.80 to 1.09; 2 RCTs, 2495 women) (both moderate-certainty evidence). Breastfeeding at hospital discharge and women's views of treatment were not reported.

Authors' conclusions

The currently available evidence indicates that magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus, compared with placebo, reduces cerebral palsy, and death or cerebral palsy, in children up to two years' corrected age, and probably reduces severe intraventricular haemorrhage for infants. Magnesium sulphate may result in little to no difference in outcomes in children at school age.

While magnesium sulphate may result in little to no difference in severe maternal outcomes (death, cardiac arrest, respiratory arrest), it probably increases maternal adverse effects severe enough to stop treatment.

Further research is needed on the longer-term benefits and harms for children, into adolescence and adulthood. Additional studies to determine variation in effects by characteristics of women treated and magnesium sulphate regimens used, along with the generalisability of findings to low- and middle-income countries, should be considered.

PLAIN LANGUAGE SUMMARY

Is magnesium sulphate for women at risk of preterm birth better than placebo for protecting their babies' brains?

Key messages

Magnesium sulphate given to women at risk of preterm birth for protecting their babies' brains reduces cerebral palsy, and the combined outcome of death or cerebral palsy, in their children up to two years of age, when compared with placebo.

Future research in this area should focus on the effects of treatment:

• on children when they are adolescents and adults; and

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• for different groups of women at risk of preterm birth, and with different ways of giving magnesium sulphate.

What is magnesium sulphate?

Magnesium sulphate is a common medicine used across the world for different complications in pregnancy.

Why is this important for women at risk of preterm birth and their babies?

Babies born early (preterm, before 37 weeks of pregnancy) have a higher risk of complications including death and disabilities, such as cerebral palsy. In recent years, magnesium sulphate has been given to women who are likely to have their babies preterm (because of spontaneous preterm labour, or a medical indication to plan an induction of labour or caesarean birth early) to help protect their babies' brains and prevent these complications.

What did we want to find out?

We wanted to find out if magnesium sulphate is better than placebo (a 'dummy' treatment that does not contain any medicine but appears identical to the medicine being tested) at protecting the brains of babies likely to be born preterm.

We were interested in the effect of magnesium sulphate on important outcomes, including: death (of the babies, or later as children), cerebral palsy, and major 'neurodevelopmental disability' (which might include serious outcomes like cerebral palsy, blindness, deafness, or global cognitive or intellectual impairment). We were also interested in the effect on important outcomes for women, including serious complications of magnesium sulphate (death, respiratory or cardiac arrest), and stopping treatment because of side effects.

What did we do?

We searched for studies that looked at whether magnesium sulphate caused benefits or harms for women and their preterm babies when compared to placebo or no treatment. We compared and summarised results and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found six studies involving 5917 women at less than 34 weeks of pregnancy and their 6759 babies. The studies were all conducted in high-income countries. The included studies compared magnesium sulphate with placebo.

Main results

Compared with placebo, magnesium sulphate in women at risk of having their babies preterm:

• reduces cerebral palsy (evidence from 6 studies with 6107 children) and the combined outcome of death or cerebral palsy (6 studies, 6481 children) for children up to two years of age;

• probably makes little to no difference in death (6 studies, 6759 children), major neurodevelopmental disability (1 study, 987 children), or the combined outcome of death or major neurodevelopmental disability (3 studies, 4279 children), for children up to two years of age;

• may make little to no difference in the above-mentioned outcomes for children at early school age;

• may make little to no difference in serious complications of treatment for women (4 studies, 5300 women), but probably increases women stopping treatment because of side effects (3 studies, 4736 women).

What are the limitations of the evidence?

We are confident in our finding that magnesium sulphate reduces cerebral palsy, and the combined outcome of death or cerebral palsy, in children up to two years of age.

We have little confidence in the evidence for outcomes of children at school age, as studies could not provide data for all children, and there are not yet enough studies/data to be certain about the results.

We have little confidence in our finding that magnesium sulphate makes little to no difference in serious complications of treatment for women, as there was only one complication reported in one study. We have moderate confidence in our findings that magnesium sulphate probably increases women stopping treatment because of side effects, as the findings differed across studies, probably because of different decision-making processes for stopping treatment.

The results of further research for the outcomes in which we have limited confidence could differ from the results of this review.

How up-to-date is this evidence?

The evidence is current to 17 March 2023.

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SUMMARY OF FINDINGS

Summary of findings 1. Magnesium sulphate versus placebo (outcomes for infants/children, up to 2 years' corrected age)

Magnesium sulphate versus placebo (outcomes for infants/children, up to 2 years' corrected age)

Patient or population: women at risk of preterm birth (< 34 weeks' gestation)
Setting: hospitals in high-income countries
Intervention: magnesium sulphate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with magnesium sulphate			
Death (fetal, neonatal, or later (up to 2 years' corrected age))**	81 per 1000	78 per 1000 (66 to 92)	**RR 0.96** (0.82 to 1.13)	6759 (6 RCTs)	⊕⊕⊕⊖ Moderate[a]
Cerebral palsy (up to 2 years' corrected age)**	58 per 1000	41 per 1000 (33 to 52)	**RR 0.71** (0.57 to 0.89)	6107 (6 RCTs)	⊕⊕⊕⊕ High
Death or cerebral palsy (up to 2 years' corrected age)**	138 per 1000	120 per 1000 (106 to 135)	**RR 0.87** (0.77 to 0.98)	6481 (6 RCTs)	⊕⊕⊕⊕ High
Major neurodevelopmental disability (up to 2 years' corrected age)**	162 per 1000	177 per 1000 (135 to 233)	**RR 1.09** (0.83 to 1.44)	987 (1 RCT)	⊕⊕⊕⊖ Moderate[a]
Death or major neurodevelopmental disability (up to 2 years' corrected age)**	223 per 1000	212 per 1000 (190 to 239)	**RR 0.95** (0.85 to 1.07)	4279 (3 RCTs)	⊕⊕⊕⊖ Moderate[a,b]
Severe intraventricular haemorrhage (grade 3 or 4) (newborn/infant)**	45 per 1000	34 per 1000 (27 to 44)	**RR 0.76** (0.60 to 0.98)	5885 (5 RCTs)	⊕⊕⊕⊖ Moderate[c]
Chronic lung disease/bronchopulmonary dysplasia (newborn/infant)**	183 per 1000	168 per 1000 (141 to 201)	**RR 0.92** (0.77 to 1.10)	6689 (5 RCTs)	⊕⊕⊖⊖ Low[a,d]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Outcomes as defined by RCT authors.
CI: confidence interval; **RCT:** randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

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Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to imprecision, as the 95% CI includes both benefit and harm.
[b]Not downgraded for risk of bias; however, data from 1 RCT from secondary analysis (result remained similar when this RCT was excluded from meta-analysis).
[c]Downgraded 1 level due to risk of bias, as when data from 1 RCT with potential methodological concerns were excluded from the meta-analysis the 95% CI includes the null value.
[d]Downgraded 1 level due to inconsistency as evidenced by statistical heterogeneity that could be due to variations in outcome definitions.

Summary of findings 2. Magnesium sulphate versus placebo (outcomes for infants/children, up to school age)

Magnesium sulphate versus placebo (outcomes for infants/children, up to school age)

Patient or population: women at risk of preterm birth (< 34 weeks' gestation)
Setting: hospitals in high-income countries
Intervention: magnesium sulphate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with placebo	Risk with magnesium sulphate			
Death (fetal, neonatal, or later (up to school age))**	169 per 1000	139 per 1000 (112 to 172)	**RR 0.82** (0.66 to 1.02)	1758 (2 RCTs)	⊕⊕⊖⊖ Low[a,b]
Cerebral palsy (school age)**	103 per 1000	102 per 1000 (71 to 145)	**RR 0.99** (0.69 to 1.41)	1038 (2 RCTs)	⊕⊕⊖⊖ Low[a,b]
Death or cerebral palsy (up to school age)**	283 per 1000	255 per 1000 (190 to 340)	**RR 0.90** (0.67 to 1.20)	503 (1 RCT)	⊕⊕⊖⊖ Low[a,b]
Major neurodevelopmental disability (school age)**	116 per 1000	107 per 1000 (62 to 188)	**RR 0.92** (0.53 to 1.62)	940 (2 RCTs)	⊕⊖⊖⊖ Very low[a,b,c]
Death or major neurodevelopmental disability (up to school age)**	259 per 1000	210 per 1000 (153 to 290)	**RR 0.81** (0.59 to 1.12)	503 (1 RCT)	⊕⊕⊖⊖ Low[a,b]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**Outcomes as defined by RCT authors.

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CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 1 level due to risk of bias, as the included RCTs were judged to have some limitations due to missing outcome data at school age follow-up.
[b]Downgraded 1 level due to imprecision, as the 95% CI includes both benefit and harm.
[c]Downgraded 1 level due to inconsistency as evidenced by statistical heterogeneity that could be due to variations in outcome definitions.

Summary of findings 3. Magnesium sulphate versus placebo (outcomes for women)

Magnesium sulphate versus placebo (outcomes for women)

Patient or population: women at risk of preterm birth (< 34 weeks' gestation)
Setting: hospitals in high-income countries
Intervention: magnesium sulphate
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with magnesium sulphate				
Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)**	1 per 1000	1 per 1000 (0 to 8)	**RR 0.32** (0.01 to 7.92)	5300 (4 RCTs)	⊕⊕⊖⊖ Low[a]	
Adverse effects severe enough to stop treatment**	19 per 1000	61 per 1000 (36 to 104)	**RR 3.21** (1.88 to 5.48)	4736 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	
Mode of birth (caesarean section)**	476 per 1000	457 per 1000 (433 to 486)	**RR 0.96** (0.91 to 1.02)	5861 (5 RCTs)	⊕⊕⊕⊖ Moderate[c]	
Postpartum haemorrhage**	216 per 1000	203 per 1000 (173 to 235)	**RR 0.94** (0.80 to 1.09)	2495 (2 RCTs)	⊕⊕⊕⊖ Moderate[d]	

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Breastfeeding at hospital discharge**	-	-	-	-	-	No RCTs reported data for this outcome.
Women's views of treatment**	-	-	-	-	-	No RCTs reported data for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).
**Outcomes as defined by RCT authors.
CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded 2 levels due to imprecision, as there was only 1 event and a wide 95% CI includes both benefit and harm.
[b]Downgraded 1 level due to inconsistency as evidenced by statistical heterogeneity that could be due to differences in protocols for stopping treatment.
[c]Downgraded 1 level due to inconsistency as evidenced by statistical heterogeneity that could be due to differences in birth intervention practices.
[d]Downgraded 1 level due to imprecision, as the 95% CI includes both benefit and harm.

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BACKGROUND

Description of the condition

Cerebral palsy is a heterogeneous group of disorders of movement and posture, causing activity limitation, attributed to a non-progressive maldevelopment or insult to the developing brain. It is commonly accompanied by disorders of sensation, perception, cognition, communication, and behaviour (Bekteshi 2023; Rosenbaum 2007). Despite variation in definitions and classifications of cerebral palsy, there is wide agreement that it is the most prevalent physical disability in childhood. Though recent evidence suggests that the birth prevalence of cerebral palsy in high-income countries is declining, it continues to affect approximately one in 600 babies (1.6 per 1000 live births; 95% confidence interval (CI) 1.5 to 1.7). While limited, available cerebral palsy data from low- and middle-income countries suggest a markedly higher birth prevalence (up to 3.4 per 1000; 95% CI 3.0 to 3.9 live births) (McIntyre 2022).

For approximately 94% of individuals with cerebral palsy, their maldevelopment or brain insult is believed to have occurred in utero or the neonatal period (ACPR 2023). The causal pathways to cerebral palsy are complex, resulting from multiple interacting pre-, peri-, and/or postnatal environmental factors, and influenced by genetic background (summarised in Shepherd 2017; Shepherd 2018). For many individuals, the exact cause(s) remains unknown (Korzeniewski 2018). Despite there being many risk factors for cerebral palsy (e.g. preterm birth, at less than 37 weeks' gestation, with over 40% of individuals with cerebral palsy born preterm versus ~8% to 9% of the general population (ACPR 2023)), there is no cure. Prevention remains crucial.

Description of the intervention

Magnesium sulphate is a common therapy in perinatal care, with longstanding use globally for preventing and treating eclampsia and pre-eclampsia (Duley 2010; Fishel 2022), preterm labour tocolysis (though controversial) (Elliott 2016), and, in the last decade, for preterm fetal neuroprotection, or cerebral palsy prevention (Doyle 2009).

Two landmark observational studies in the 1990s first reported reduced risks of perinatal brain injury and cerebral palsy among infants who were exposed to magnesium sulphate in utero, when given to their mothers for pre-eclampsia treatment (Kuban 1992; Nelson 1995). Subsequent to these, and further observational studies (Wolf 2012), five randomised controlled trials (RCTs) (conducted from 1995 to 2004) assessed prenatal magnesium sulphate and outcomes associated with preterm fetal neuroprotection, including cerebral palsy (Crowther 2003; Magpie 2006; Marret 2006; Mittendorf 2002; Rouse 2008). These RCTs were included in the previous version of this Cochrane review, published in 2009, which confirmed a neuroprotective role for magnesium sulphate. That review reported that 63 babies (95% CI 44 to 155) need to be exposed to prenatal magnesium sulphate to prevent one case of cerebral palsy (risk ratio 0.68, 95% CI 0.54 to 0.87; 5 RCTs, 6145 infants) (Doyle 2009).

Subsequent systematic reviews and meta-analyses reached similar conclusions (Conde-Agudelo 2009; Costantine 2009; Crowther 2017; Zeng 2016). A systematic review of economic studies supported health gains and cost savings with this treatment (Shih 2018). Further, Cochrane overviews of systematic reviews demonstrated it to be one of only two interventions for cerebral palsy prevention supported by high-certainty evidence (Shepherd 2017; Shepherd 2018).

How the intervention might work

While the exact mechanism(s) by which magnesium sulphate confers preterm fetal neuroprotection remains unclear, recent advances from pre-clinical and clinical studies suggest that it may be important in modulating brain excitotoxic cell death and inflammatory pathways (Chollat 2019; Galinsky 2020), both of which are implicated in the pathophysiology of perinatal brain injury and cerebral palsy.

Why it is important to do this review

In response to the compelling Cochrane review findings (Doyle 2009), professional bodies in many high-income countries began recommending prenatal magnesium sulphate for preterm fetal neuroprotection in clinical practice guidelines (Jayaram 2019). In its 2015 guidelines on interventions to improve preterm birth outcomes, the World Health Organization provided a strong recommendation supporting the use of magnesium sulphate (WHO 2015). Over the last decade, international adoption of prenatal magnesium sulphate for preterm cerebral palsy prevention has ensued.

In recent years, further RCTs and longer-term follow-up from the RCTs included in the Doyle 2009 Cochrane review have been published, which may be eligible for inclusion in this review update.

Over a decade into the knowledge translation on prenatal magnesium sulphate for neuroprotection, this update will support future clinical practice guideline review and revision and/or the continued implementation of this evidence-based practice.

OBJECTIVES

To assess the effectiveness and safety of magnesium sulphate as a fetal 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

Randomised controlled trials (RCTs) and cluster-RCTs were eligible. Both RCTs published in full-text and those in abstract form only were eligible. Quasi-RCTs (with a quasi-random method of allocation, such as alternation) and cross-over trials were not eligible.

Types of participants

RCTs of women at risk of preterm birth (at less than 37 weeks' gestation) were eligible, irrespective of the reason(s) women were considered at risk of preterm birth (and how risk of preterm birth was determined), the number of babies in utero, gestational age, socio-demographic factors, setting and location.

We included RCTs with some 'eligible' and some 'ineligible' participants only if data from the 'eligible' participants could be retrieved.

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Types of interventions

RCTs assessing magnesium sulphate given for fetal neuroprotection compared with placebo or no treatment were eligible, irrespective of treatment regimen used, considering mode of administration (intravenous, intramuscular, oral), dose (loading and/or maintenance used), and timing of treatment prior to anticipated preterm birth.

RCTs where magnesium sulphate was used with the primary aim of tocolysis (Crowther 2014) (including maintenance therapy after preterm labour (Han 2013)), prevention and treatment of eclampsia and pre-eclampsia (Duley 2010; Duley 2010a; Duley 2010b; Duley 2010c), or as a dietary supplement in pregnancy were not eligible (Makrides 2014). These RCTs are covered in separate Cochrane reviews.

Types of outcome measures

Reporting the outcome measures listed below was not an eligibility criterion.

Considering time points, where relevant, we planned to synthesise outcomes from infancy/childhood/adulthood.

We did not restrict outcomes according to measurement methods or tools used, and planned wherever possible to synthesise different measures of the same outcome (or outcome domain).

Primary outcomes

For infants/children/adults

- Death (fetal, neonatal, or later)
- Cerebral palsy
- Death or cerebral palsy
- Major neurodevelopmental disability (defined as any of: moderate to severe cerebral palsy (Gross Motor Function Classification System (GMFCS) levels II to V, or as defined by trialists), legal blindness, sensorineural deafness requiring amplification or worse, or developmental delay/intellectual impairment (standardised score more than 2 standard deviations (SD) below the mean))
- Death or major neurodevelopmental disability

For women

- Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)
- Adverse effects severe enough to stop treatment

Secondary outcomes

For infants

- Fetal death
- Neonatal death
- Body size at birth (weight, length, head circumference z-scores)
- Gestational age at birth
- Apgar score less than seven at five minutes
- Use of active resuscitation at birth
- Intraventricular haemorrhage
- Severe intraventricular haemorrhage (grade 3 or 4)
- Cystic periventricular leukomalacia
- Post-haemorrhagic hydrocephalus or ventriculomegaly
- Neonatal encephalopathy
- Neonatal convulsions
- Neonatal hypoglycaemia
- Neonatal hypotonia
- Necrotising enterocolitis
- Intestinal perforation
- Retinopathy of prematurity
- Patent ductus arteriosus
- Respiratory distress syndrome
- Chronic lung disease/bronchopulmonary dysplasia
- Use of respiratory support (mechanical ventilation or continuous positive airway pressure)
- Use of postnatal corticosteroids to prevent or treat chronic lung disease/bronchopulmonary dysplasia
- Use of inotropic support
- Air leak syndrome
- Early- and late-onset sepsis
- Severe adverse neonatal outcome composite (e.g. death, severe intraventricular haemorrhage, neonatal encephalopathy, necrotising enterocolitis, stage 3 or worse retinopathy of prematurity, patent ductus arteriosus requiring treatment, chronic lung disease/bronchopulmonary dysplasia; or as defined by trialists)

For infants/children/adults

- Later death
- Cerebral palsy severity
- Any neurodevelopmental disability (defined as any of: cerebral palsy (GMFCS level I to V, or as defined by trialists), blindness (corrected visual acuity worse than 6/60 in the better eye), deafness (hearing loss requiring amplification or worse), or developmental delay/intellectual impairment (standardised score more than 1 SD below the mean))
- Death or any neurodevelopmental disability
- Blindness
- Deafness
- Developmental delay/intellectual impairment
- Gross motor dysfunction
- Psychomotor dysfunction
- Death or substantial gross motor dysfunction
- Growth (weight, head circumference, length/height)
- Respiratory function
- Blood pressure
- Behaviour
- Educational achievement

For women

- Individual components of severe maternal outcome potentially related to treatment
- Maternal side effects of treatment (including nausea, vomiting, flushing, infusion arm discomfort, mouth dryness, sweating, dizziness, blurred vision, changes in blood pressure, respiratory rate, or pulse)
- Time between randomisation and birth

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- Mode of birth (caesarean section)
- Chorioamnionitis
- Postpartum haemorrhage
- Breastfeeding at hospital discharge
- Women's views of treatment

Use of health services

- Maternal admission to the intensive care unit
- Length of postnatal hospitalisation for women
- Admission to the neonatal intensive care unit
- Length of stay in neonatal intensive care unit
- Length of neonatal/infant hospitalisation
- Costs of maternal care
- Costs of neonatal care
- Use and costs of care for infant/child/adult (e.g. related to neurodevelopmental disability)

Search methods for identification of studies

The following methods section is based on a standard template used by Cochrane Pregnancy and Childbirth.

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (17 March 2023).

The Register was a database containing over 34,000 reports of controlled trials in the field of pregnancy and childbirth. It represented over 30 years of searching, including handsearched journals and conference proceedings, and journals reviewed via a current awareness service. For the detailed search strategies used to populate Cochrane Pregnancy and Childbirth's Trials Register for the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and CINAHL (Cumulative Index to Nursing and Allied Health Literature), see Appendix 1; Appendix 2; Appendix 3; Appendix 4.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register was maintained by their Information Specialist and contains trials identified from:

- monthly searches of CENTRAL;
- weekly searches of MEDLINE (Ovid);
- weekly searches of Embase (Ovid);
- monthly searches of CINAHL (EBSCO);
- handsearches of 30 journals and the proceedings of major conferences;
- weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

All search results were screened by two people, and the full texts of all relevant RCT reports were reviewed. Based on the intervention described, each trial report was assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and was then added to the Register. The Information Specialist searched the Register for each review using this topic number rather than keywords. This resulted in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

We also searched ClinicalTrials.gov (clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (trialsearch.who.int) on 17 March 2023 for unpublished, planned, and ongoing trial reports using the search methods detailed in Appendix 5.

Searching other resources

We searched the reference lists of included studies, and Google Scholar (scholar.google.com).

We did not apply any language or date restrictions. We also revisited all records identified through searching from the previously published version of this review.

Data collection and analysis

For the methods used in the previous version of this review, see Doyle 2009.

For this update, we used the following methods to assess the reports that were identified as a result of the updated search.

Selection of studies

Two review authors (ES and one of HW, PP, PM, CC, or LD) independently assessed all studies identified as a result of the search strategy for inclusion in the review. We resolved any disagreements through discussion.

Screening eligible studies for scientific integrity/trustworthiness

Two review authors (ES and SG) evaluated all studies meeting our inclusion criteria against predefined criteria to select studies that, based on the available information, were deemed to be sufficiently trustworthy to be included in the analysis. The criteria were as follows.

Research governance

- Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this RCT?
- Was the RCT prospectively registered (for those studies published after 2010)? If not, was there a plausible reason?
- If requested, did the RCT authors provide/share the protocol or ethics approval letter (or both)?
- Did the RCT authors engage in communication with the Cochrane review authors within the agreed timelines?
- Did the RCT authors provide individual participant data if requested? If not, was there a plausible reason?

Baseline characteristics

- Is the RCT free from characteristics of the study participants that appear too similar (e.g. distribution of the mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017)?

Feasibility

- Is the RCT free from characteristics that could be implausible (e.g. large numbers of women with a rare condition (such as severe cholestasis in pregnancy) recruited within 12 months)?

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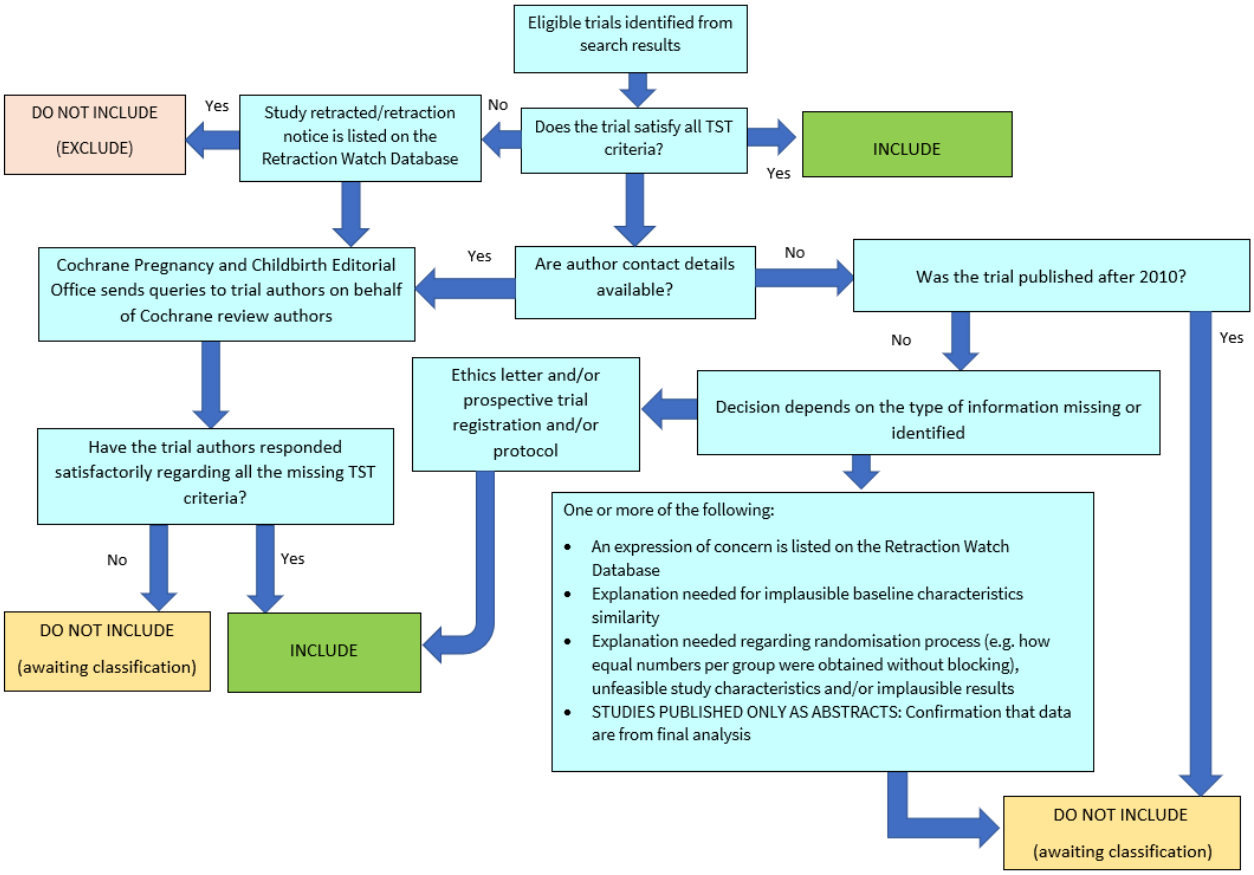
- In cases with (close to) zero losses to follow-up, is there a plausible explanation?

Results

- Is the RCT free from results that could be implausible (e.g. massive risk reduction for main outcomes with small sample size)?
- Do the numbers randomised to each group suggest that adequate randomisation methods were used (e.g. is the RCT free from issues such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods, if the authors say 'no blocking was used' but still end up with equal numbers, or if the authors say they used 'blocks of 4' but the final numbers differ by six)?

Where a study was classified as potentially 'high risk' based on the above criteria, it was added to Studies awaiting classification, and the reasons and communications with the author(s) (or lack thereof) were described in detail. The process is described in Figure 1.

Figure 1. Process for screening eligible studies for scientific integrity/trustworthiness. Figure produced with permission from Cochrane Pregnancy and Childbirth.



Abstracts

We planned to include data from abstracts only if, in addition to the trustworthiness assessment, the RCT authors confirmed in writing that the data to be included in the review had come from the final analysis and would not change. If such information was not available/provided, we added the study to Studies awaiting classification (as above).

Data extraction and management

We designed a data extraction form. Two review authors (ES and SG) independently extracted data from the included studies using the agreed-upon form. We resolved any discrepancies through discussion. We entered data into RevMan software (RevMan 2024), which we checked for accuracy.

Assessment of risk of bias in included studies

Two review authors (ES and SG) independently assessed the risk of bias for each RCT using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved any disagreements by discussion.

(1) Random sequence generation (checking for possible selection bias)

We described for each included RCT the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We have assessed the method as:

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- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included RCT the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We have assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered, sealed, opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included RCT the methods used, if any, to blind participants and personnel from knowledge of which intervention a participant received. We considered RCTs to be at low risk of bias if they were blinded, or if we judged that the lack of blinding was unlikely to have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high, or unclear risk of bias for participants;
- low, high, or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included RCT the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high, or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature, and handling of incomplete outcome data)

We described for each included RCT the completeness of data, including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the study authors, we planned to re-include missing data in the analyses we undertook.

We assessed the methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included RCT how we investigated the possibility of selective outcome reporting bias and what we found.

We have assessed the methods as:

- low risk of bias (where it was clear that all of the RCT's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all of the RCT's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest were reported incompletely and so could not be used; the RCT failed to include results of a key outcome that would be expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included RCT any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether RCTs were at high risk of bias, according to the criteria given in the *Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias, and whether we considered it likely to impact on the findings. We explored the impact of the level of bias through sensitivity analyses (see Sensitivity analysis).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RR) with 95% confidence intervals (CI).

Continuous data

For continuous data measured on the same scale, we used the mean difference (MD) with 95% CIs. For studies that measured the same outcome on different scales, we planned to report the standardised mean difference (SMD) with 95% CIs.

Unit of analysis issues

Cluster-RCTs

Had we found cluster-RCTs, we would have included them in the analyses along with individual RCTs. We planned to adjust the sample sizes of cluster-RCTs using the methods described in the *Cochrane Handbook* (Higgins 2022), employing an estimate of the intracluster correlation coefficient (ICC) derived from the RCT (if possible), from a similar RCT, or from a study of a similar population.

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Had we used ICCs from other sources, we would have reported this and conducted sensitivity analyses to investigate the effect of variation in the ICC. In future updates, if we identify both cluster-RCTs and individually randomised RCTs, we will synthesise the relevant information. We will consider it reasonable to combine the results from both types of studies if there is little heterogeneity between study designs, and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Multiple pregnancy

There may be unit of analysis issues that arise when women randomised have a multiple pregnancy. We have presented maternal data as per woman randomised, and fetal/neonatal/infant/child data as per fetus/neonate/infant/child.

Multiple-arm RCTs

In future updates of this review, if an RCT has multiple intervention arms, we will avoid 'double-counting' of participants by combining groups to create a single pairwise comparison if possible. Where this is not possible, we will split the 'shared' group into two or more groups with smaller sample size and include two or more (reasonably independent) comparisons.

Dealing with missing data

We noted levels of attrition in the included studies. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis.

For all outcomes, we carried out analyses, to the greatest degree possible, on an intention-to-treat (ITT) basis, that is we attempted to include all participants randomised to each group in the analyses, and all participants were analysed in the group to which they were allocated, regardless of whether they received the allocated intervention. The denominator for each outcome in each study was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2, and Chi^2 statistics. We regarded heterogeneity as substantial if I^2 was greater than 30%, and either Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

In future updates of this review, if 10 or more RCTs are included in a given meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using RevMan software (RevMan 2024). We used fixed-effect meta-analyses for combining data where it was reasonable to assume that RCTs were estimating the same underlying treatment effect (i.e. where RCTs were examining the same intervention, and the RCTs' populations and methods were judged to be sufficiently similar). Where we detected substantial statistical heterogeneity, we used random-effects meta-analysis to produce an overall summary, as we considered an average treatment effect across RCTs to be clinically meaningful. We treated the random-effects summary as the average of the range of possible treatment effects, and we have discussed the clinical implications of treatment effects differing between RCTs.

Where we used random-effects analyses, we have presented the results as the average treatment effect with 95% CIs, and the estimates of Tau^2 and I^2.

Subgroup analysis and investigation of heterogeneity

For this update, where data were available, we performed the following subgroup analyses for our primary outcomes:

- gestational age at randomisation (we prespecified the following groups: < 26; 26 to < 28; 28 to < 30; 30 to < 32; 32 to < 34 completed weeks at randomisation; however, groups were combined, as RCTs did not present stratified results);
- loading-dose regimen (4 g; > 4 g);
- maintenance dose regimen (no; 1 g/hour; > 1 g/hour);
- repeat treatment permitted (yes; no).

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2024).

We also planned to conduct the following subgroup analyses for our primary outcomes:

- primary reason the woman was considered at high risk of preterm birth (e.g. preterm labour; prelabour rupture of membranes; chorioamnionitis; pre-eclampsia; antepartum haemorrhage; fetal distress; intrauterine growth restriction; other);
- number of babies in utero (singleton; multiple)
- mode of administration (intravenous; intramuscular);
- time treatment was intended to be started prior to preterm birth (0 to < 4 hours; 4 to < 8 hours; 8 to < 12 hours; 12 to < 24 hours; we planned to combine groups if data were insufficient).

However, we were unable to undertake meaningful subgroup analyses for these characteristics, as for most RCTs their inclusion/exclusion criteria did not enable allocation to one or the other subgroup, or the results were not presented stratified by the relevant characteristic, or both; or all included RCTs were eligible for the same subgroup.

Sensitivity analysis

We carried out sensitivity analyses to explore the impact of risk of bias on our primary outcomes. Specifically, we explored the impact restricting the primary outcome analyses to those RCTs judged to be at low risk of selection bias.

During data collection and analysis, it appeared that most RCTs reported adjusted effect size(s) (RRs or odds ratios (ORs) with 95% CIs) for at least one of the primary outcomes for the infants/children (death (fetal, neonatal, later), cerebral palsy, death or cerebral palsy, major neurodevelopmental disability, or death or major neurodevelopmental disability), including to account for clustering

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due to multiple births. We therefore decided to perform post hoc sensitivity analyses for our primary outcomes for the infant/child/adult (where at least one RCT reported an adjusted effect size for that outcome), using the generic inverse variance method to pool results.

Summary of findings and assessment of the certainty of the evidence

Two review authors (ES and SG) assessed the certainty of the evidence using the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013), for the outcomes for our main comparison ('magnesium sulphate versus placebo'), as described below.

For infants/children

- Death (fetal, neonatal, or later)
- Cerebral palsy
- Death or cerebral palsy
- Major neurodevelopmental disability
- Death or major neurodevelopmental disability
- Severe intraventricular haemorrhage (grade 3 or 4)*
- Chronic lung disease/bronchopulmonary dysplasia*

*These outcomes are not relevant to children up to school age and so were not included in Summary of findings 2.

For women

- Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)
- Adverse effects severe enough to stop treatment
- Mode of birth (caesarean section)
- Postpartum haemorrhage
- Breastfeeding at hospital discharge
- Women's views of treatment

We created summary of findings tables in RevMan (RevMan 2024). The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each outcome. The evidence can be downgraded from high certainty by one level for serious (or two levels for very serious) limitations, depending on the assessment of these factors.

RESULTS

Description of studies

See Characteristics of included studies.

Results of the search

See Figure 2.

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Figure 2. Study flow diagram.

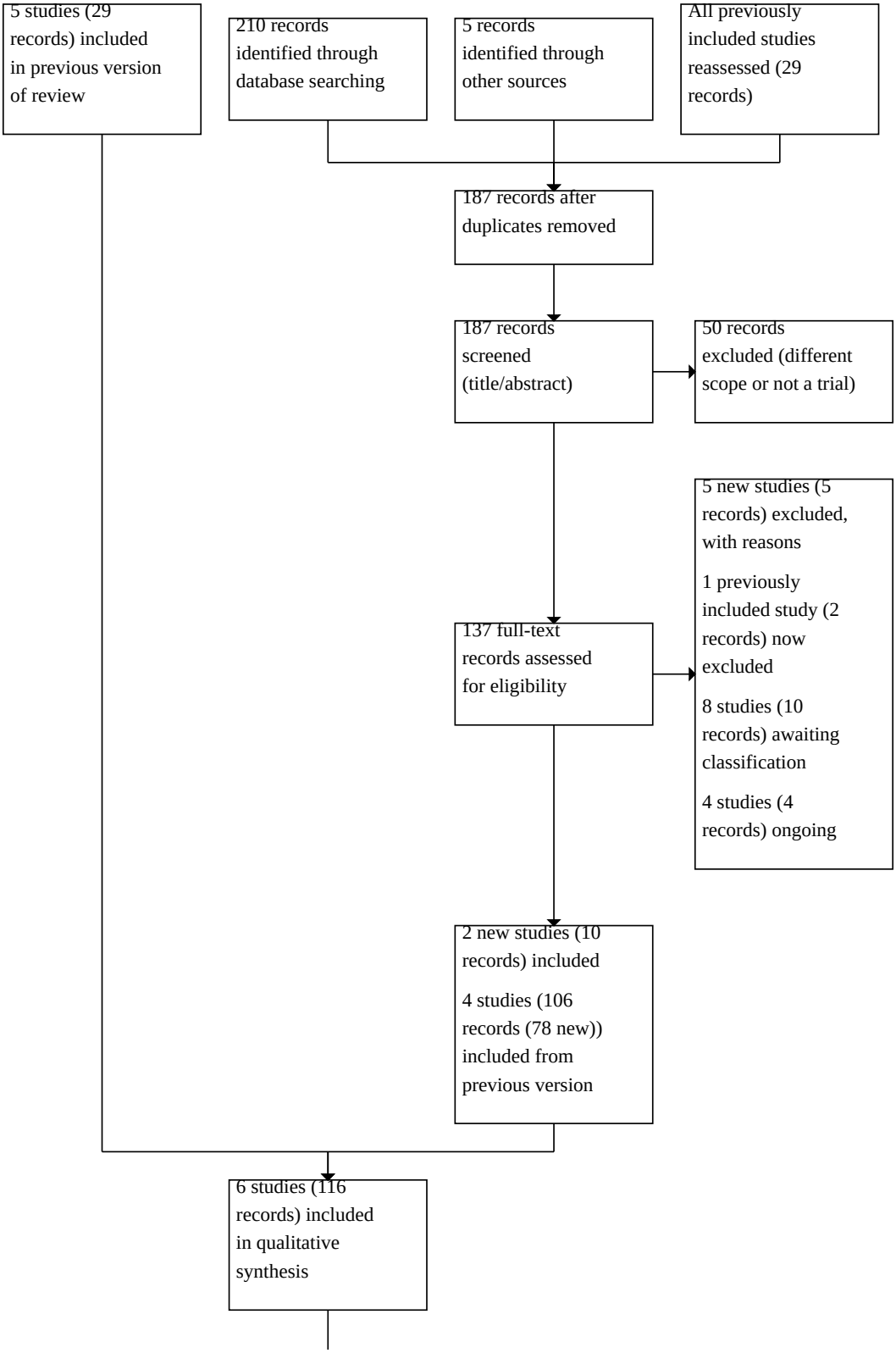

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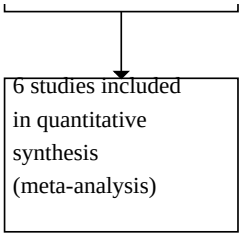
Figure 2. (Continued)



The previous version of this review included five RCTs (29 records). We reassessed these records, along with 215 new records identified through database searching and other sources. Following removal of duplicate and irrelevant records, we assessed 137 records in full. We included two new RCTs (10 records), and excluded five new studies (five records). Eight studies (10 records) are awaiting classification, and four studies (four records) are ongoing. The remaining 78 records were additional records for four previously included RCTs.

Following prespecified revision to the Criteria for considering studies for this review for this update, we also excluded one previously included RCT (two records). We included a total of six RCTs (116 records).

Screening eligible studies for trustworthiness

We categorised eight studies as awaiting classification as they did not fulfil our trustworthiness criteria (see Characteristics of studies awaiting classification). At the time of publication, the study authors had not responded to our various queries/concerns (Bachnas 2014; Gupta 2021; Manoj 2017; Muhammed 2019; Parashi 2017; Petrov 2013; Sharma 2021; Sheeba 2022).

Included studies

Six RCTs met our eligibility and trustworthiness criteria (Crowther 2003; Crowther 2023; Marret 2006; Mittendorf 2002; Rouse 2008; Wolf 2020). For further details, see Characteristics of included studies.

Study design

The included RCTs were all individually randomised (Crowther 2003; Crowther 2023; Marret 2006; Mittendorf 2002; Rouse 2008; Wolf 2020).

Setting

All RCTs were conducted in high-income countries: two in the USA (Mittendorf 2002; Rouse 2008), two across Australian and New Zealand (Crowther 2003; Crowther 2023), and one each in Denmark (Wolf 2020) and France (Marret 2006).

Study dates

The included RCTs commenced between 1995 (Mittendorf 2002) and 2018 (Wolf 2020).

Sample sizes

The total number of women randomised ranged from 57 (Mittendorf 2002) to 2241 (Rouse 2008), with a total of 5917 women and their 6759 fetuses alive at randomisation (Crowther 2003; Crowther 2023; Marret 2006; Mittendorf 2002; Rouse 2008; Wolf 2020).

Participants

All RCTs included pregnant women in preterm labour or with expected or planned preterm birth. The lower limit of gestational age was 24 weeks' gestation (Mittendorf 2002; Rouse 2008; Wolf 2020) or above (30 weeks' gestation in Crowther 2023), but no lower limit was set for two studies (Crowther 2003; Marret 2006). The upper limit of gestational age ranged from less than 30 to 34 weeks' gestation (less than 30 weeks' (Crowther 2003), less than 32 weeks' (Rouse 2008; Wolf 2020), less than 33 weeks' (Marret 2006), and less than 34 weeks' gestation (Crowther 2023; Mittendorf 2002)).

Four RCTs included singletons and twins (Crowther 2023; Mittendorf 2002; Rouse 2008; Wolf 2020), while two studies also included higher-order multiple gestations (Crowther 2003; Marret 2006).

Additional inclusion and exclusion criteria varied (see Characteristics of included studies and Table 1).

Interventions and comparisons

Intervention

A single loading dose of magnesium sulphate was reported in three RCTs:

- 4 g intravenous (IV) over 30 minutes (Crowther 2023; Marret 2006);
- 4 g IV bolus (Mittendorf 2002).

A magnesium sulphate maintenance dose followed the loading dose in three RCTs:

- 4 g IV loading dose over 20 minutes, followed by 1 g/hour IV until birth (if within 24 hours) or up to 24 hours (Crowther 2003);
- 5 g IV loading dose over 20 to 30 minutes, followed by 1 g/hour IV maintenance dose until birth or for 24 hours if birth had not occurred. If at least six hours had passed since discontinuation of treatment, and birth had not occurred, the loading dose was repeated if birth was again imminent at less than 32 weeks' gestation (Wolf 2020);
- 6 g IV loading dose over 20 to 30 minutes, followed by 2 g/hour IV maintenance dose. If birth had not occurred after 12 hours and was no longer considered imminent, the treatment was discontinued and resumed when birth was deemed imminent

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again; if at least six hours had passed since discontinuation, another loading dose was given (Rouse 2008).

Comparison

All six RCTs used a saline placebo.

A single dose/infusion was reported in three RCTs:

- IV saline infusion over 30 minutes (Crowther 2023; Marret 2006);
- bolus saline solution (Mittendorf 2002).

A loading and maintenance dose/infusion was reported in the other three RCTs, with regimens matching those used in the magnesium sulphate treatment group (Crowther 2003; Rouse 2008; Wolf 2020).

For further details on the intervention/comparison regimens, see Table 2.

Outcomes

Primary outcomes

The RCTs' primary outcomes focused on death and cerebral palsy. One RCT reported on neonatal mortality before hospital discharge (Marret 2006), while two RCTs reported total paediatric mortality including fetal/stillbirths, neonatal and post-neonatal mortality (Crowther 2003; Mittendorf 2002).

Three RCTs reported on cerebral palsy as a primary outcome at age 18 months (Mittendorf 2002) or two years' corrected age (Crowther 2003), while one RCT reported on moderate to severe cerebral palsy (GMFCS level II-V) at a minimum of 18 months' corrected age (Wolf 2020).

Three RCTs reported a composite outcome of death or cerebral palsy (Crowther 2003; Crowther 2023; Rouse 2008).

Finally, one RCT reported a primary outcome of neonatal cranial ultrasound abnormalities (severe white matter injury) and a combination of severe white matter injury and/or neonatal mortality (Marret 2006).

The RCTs reported on various secondary outcomes, many of which were relevant to this review. See Characteristics of included studies, where the review outcomes reported by each RCT are summarised.

Sources of funding

All RCTs reported funding sources. Crowther 2003 reported funding from the National Health and Medical Research Council Australia (NHMRC) (main and school age follow-up), the Channel 7 Research Foundation Australia, the Queen Victoria Hospital Research Foundation Australia, and support from the Department of Obstetrics and Gynaecology at the University of Adelaide, Australia, and the Victorian Government, Australia (school age follow-up). Crowther 2023 reported funding from the NHMRC and the Cerebral Palsy Alliance Research Foundation Australia. Marret 2006 reported funding from the French Department of Health, Rouen University Hospital, and school age follow-up funding from the European Regional Development Fund and the Upper-Normandy region. Mittendorf 2002 reported funding from the United Cerebral Palsy Research and Education Foundation USA, and Rouse 2008 reported funding from the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke USA. Wolf 2020 reported funding from the Elsass Foundation, the Hospital Institutional Board at Hvidovre Hospital, the Department of Obstetrics and Gynaecology at Hvidovre Hospital, the Research Foundation at Hvidovre Hospital, Dagmar Marchall's Foundation, Inge and Per Refshall's Research Grant, NFOG Fund, Aase and Ejnar Danielsen's Foundation, and Reprounion.

Authors' declarations of interest

Crowther 2023, Rouse 2008, and Wolf 2020 reported no conflict of interests. Crowther 2003 and Marret 2006 did not include a declaration of interest in the main RCT paper, but their school age follow-up reported no conflicts of interest. Mittendorf 2002 did not report whether they had any conflicting interests.

Ongoing studies

We identified four ongoing studies (CTRI/2018/06/014386; IRCT20120826010664N5; NCT02506894; NCT05674565). For further details, see Characteristics of ongoing studies.

Excluded studies

We excluded six studies (see Characteristics of excluded studies).

One study was not randomised (Gulczynska 2006). In four studies, the indication for magnesium sulphate treatment was not fetal neuroprotection (CTRI/2010/091/000578; Dasgupta 2012; Magpie 2006; Sayin 2010). Further, in one of the studies, the comparator was not placebo or no treatment (it was ritodrine) (Sayin 2010). In one study, although magnesium sulphate was assessed for fetal neuroprotection, the comparator was not placebo or no treatment (it was nifedipine) (NCT02591004).

Risk of bias in included studies

We judged the overall risk of bias for most domains across RCTs to be low. See Figure 3; Figure 4.

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Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

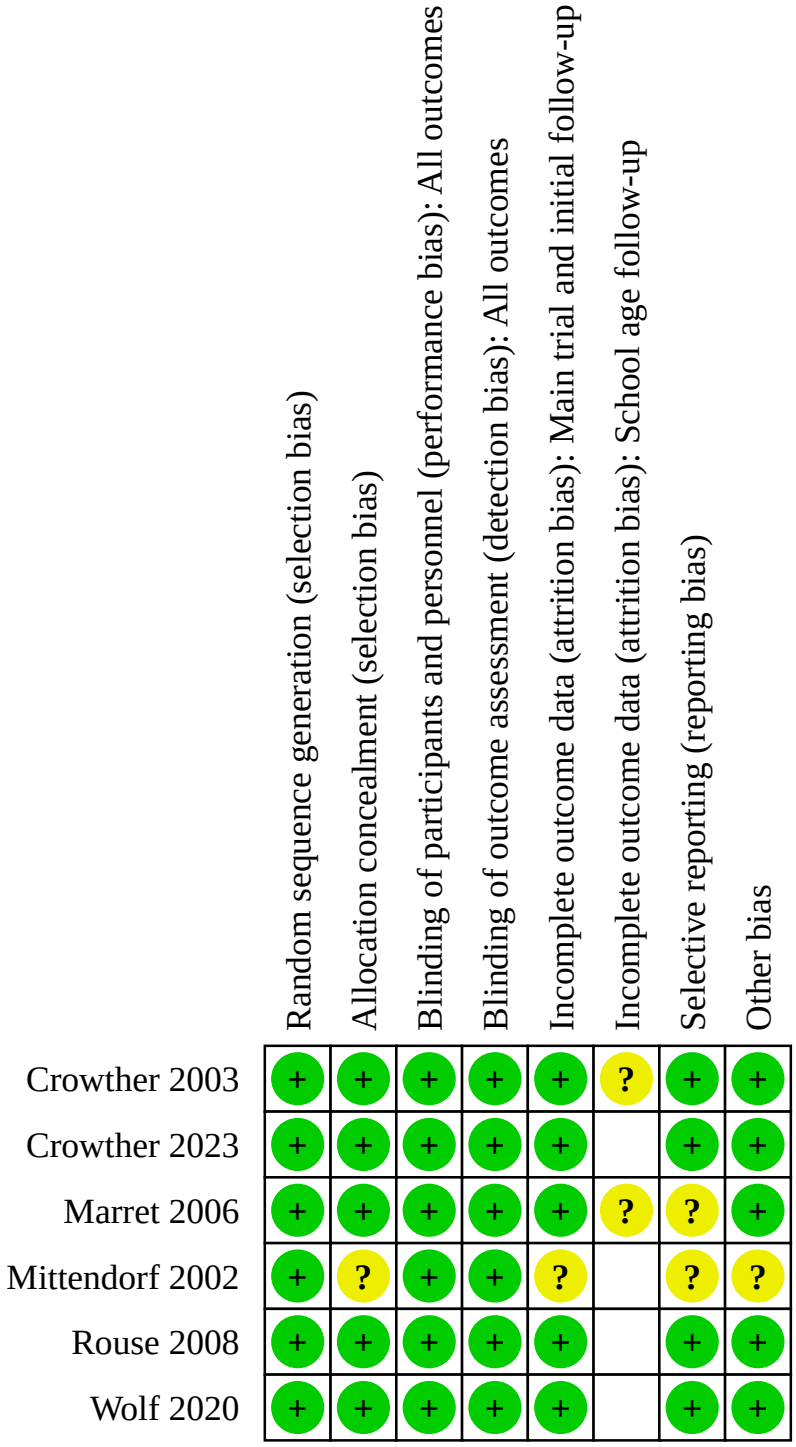

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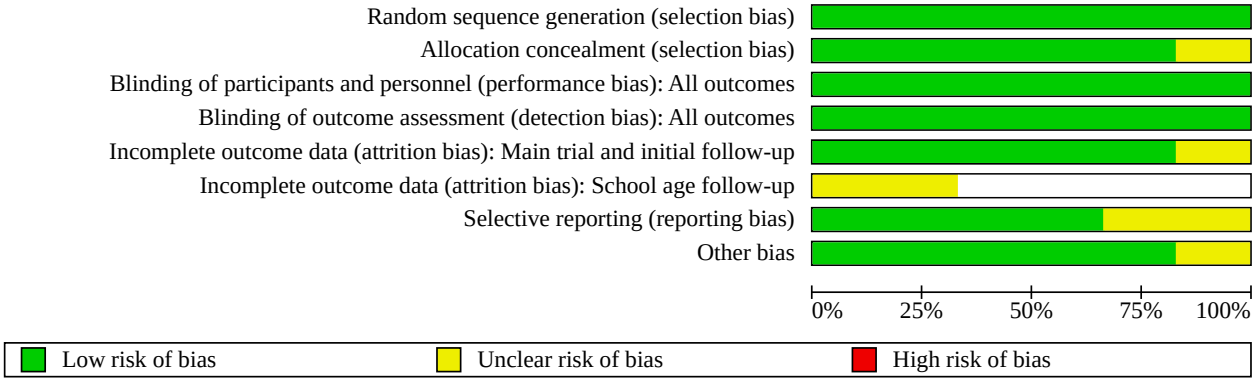
Figure 4. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Allocation

We judged all RCTs as at low risk of selection bias for random sequence generation, as all used a computer-generated random sequence.

We judged five RCTs as at low risk of selection bias for allocation concealment: in two studies, randomisation was conducted centrally (Crowther 2023; Rouse 2008), and in three studies treatment packs were prepared by central/independent staff (Crowther 2003; Marret 2006; Wolf 2020). We assessed one RCT as at unclear risk of bias as the method of allocation concealment was not stated (Mittendorf 2002).

Blinding

We judged all RCTs as at low risk of performance bias due to blinding of participants and personnel. Treatment packs looked identical, ensuring blinding of participants, and clinicians were reported to be blinded to treatment group allocation (Crowther 2003; Crowther 2023; Wolf 2020). While Wolf 2020 reported unblinding of two women due to serious side effects, we judged that this was unlikely to introduce significant risk of bias. Mittendorf 2002 and Rouse 2008 were reported to be double-blind, with Rouse 2008 specifying use of an identical-appearing placebo. One RCT described incomplete blinding, as there was no attempt to blind anaesthetists/obstetricians to enable immediate treatment of side effects if necessary, and given characteristic maternal flushing from magnesium sulphate (Marret 2006). We considered that the review outcomes were not likely to be influenced by this lack of blinding.

We judged all RCTs to be at low risk of detection bias due to blinding of outcome assessment. Outcome assessors/investigators were reported to be blinded to treatment group allocation (Crowther 2003; Crowther 2023; Marret 2006; Mittendorf 2002; Rouse 2008; Wolf 2020). Mittendorf 2002 specified blinding of technicians and researchers processing biologic specimens, and the developmentalist; while they did not specify blinding of paediatric radiologists conducting cranial ultrasounds, we deemed that blinding was likely. The school age follow-up of Marret 2006 did not specify blinding of outcome assessors; however, we judged the risk of bias to be low.

Incomplete outcome data

We judged four RCTs as at low risk of attrition bias as there was minimal loss to follow-up in the main RCT and initial follow-up (and/or the loss to follow-up was considered unlikely to impact the findings) (Crowther 2003; Crowther 2023; Marret 2006; Rouse 2008; Wolf 2020). However, we judged the risk of bias to be unclear in the associated school age follow-up of two of these RCTs (Crowther 2003; Marret 2006). In the school age follow-up of Crowther 2003, two of the original sites did not participate, leaving 867 of 1060 known survivors available, of which school age outcomes were determined for 669 (77%). Marret 2006 reported that 185 children (27%) of the original 688 randomised were lost to school age follow-up (72 children were known to have died before two years).

We judged one RCT to be at unclear risk of attrition bias (Mittendorf 2002), as there was insufficient reporting of attrition/exclusions to permit a judgement.

Selective reporting

We judged four RCTs as at low risk of reporting bias as there was no clear indication of selective reporting (Crowther 2003; Crowther 2023; Rouse 2008; Wolf 2020). Detailed study protocols/registrations were not available for two RCTs (Marret 2006; Mittendorf 2002), preventing a judgement of risk of bias due to selective reporting.

Other potential sources of bias

There was no indication of other sources of bias in five RCTs (Crowther 2003; Crowther 2023; Marret 2006; Rouse 2008; Wolf 2020). We judged Mittendorf 2002 to be at unclear risk of bias due to insufficient methodological detail to permit an assessment.

Effects of interventions

See: **Summary of findings 1** Magnesium sulphate versus placebo (outcomes for infants/children, up to 2 years' corrected age); **Summary of findings 2** Magnesium sulphate versus placebo (outcomes for infants/children, up to school age); **Summary of findings 3** Magnesium sulphate versus placebo (outcomes for women)

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See Summary of findings 1; Summary of findings 2; Summary of findings 3.

Magnesium sulphate versus placebo

Primary outcomes

For infants/children

Death (fetal, neonatal, or later (up to two years' corrected age))

Magnesium sulphate compared with placebo probably resulted in little to no difference in death (fetal, neonatal, or later (up to two years' corrected age)) (risk ratio (RR) 0.96, 95% confidence interval (CI) 0.82 to 1.13; 6 RCTs, 6759 children; moderate-certainty evidence; Analysis 1.1).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.1; loading-dose regimen: Analysis 8.1; maintenance dose regimen: Analysis 9.1; repeat treatment permitted: Analysis 10.1). In a sensitivity analysis based on RCT quality, we removed one RCT due to unclear risk of selection bias (Mittendorf 2002), and the result remained similar to the overall analysis (RR 0.96, 95% CI 0.82 to 1.12; 5 RCTs, 6700 children). In a post hoc sensitivity analysis pooling adjusted effects sizes, where reported, the result also remained similar to the overall analysis (RR 0.96, 95% CI 0.81 to 1.13; 6 RCTs, 6759 children; Analysis 11.1).

Cerebral palsy (up to two years' corrected age)

Magnesium sulphate compared with placebo reduced the risk of cerebral palsy up to two years' corrected age (RR 0.71, 95% CI 0.57 to 0.89; 6 RCTs, 6107 children; number needed to treat for additional beneficial outcome (NNTB) 60, 95% CI 41 to 158; high-certainty evidence; Analysis 1.2).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.2; loading-dose regimen: Analysis 8.2; maintenance dose regimen: Analysis 9.2; repeat treatment permitted: Analysis 10.2). In a sensitivity analysis on RCT quality, we removed one RCT due to unclear risk of selection bias (Mittendorf 2002), and the result remained similar to the overall analysis (RR 0.69, 95% CI 0.55 to 0.86; 5 RCTs, 6051 children). In a post hoc sensitivity analysis pooling adjusted effect sizes, where reported, the result also remained similar to the overall analysis (RR 0.70, 95% CI 0.55 to 0.88; 6 RCTs, 6107 children; Analysis 11.2).

Death or cerebral palsy (up to two years' corrected age)

Magnesium sulphate compared with placebo reduced the risk of death or cerebral palsy up to two years' corrected age (RR 0.87, 95% CI 0.77 to 0.98; 6 RCTs, 6481 children; NNTB 56, 95% CI 32 to 363; high-certainty evidence; Analysis 1.3).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.3; loading-dose regimen: Analysis 8.3; maintenance dose regimen: Analysis 9.3; repeat treatment permitted: Analysis 10.3). In a sensitivity analysis on RCT quality, we removed one RCT due to unclear risk of selection bias (Mittendorf 2002), and the result remained similar to the overall analysis (RR 0.86, 95% CI 0.76 to 0.97; 5 RCTs, 6422 children). In a post hoc sensitivity analysis pooling adjusted effects sizes, where reported, the result also remained similar to the overall analysis (RR 0.85, 95% CI 0.74 to 0.97; 6 RCTs, 6481 children; Analysis 11.3).

Major neurodevelopmental disability (up to two years' corrected age)

Magnesium sulphate compared with placebo probably resulted in little to no difference in major neurodevelopmental disability up to two years' corrected age (RR 1.09, 95% CI 0.83 to 1.44; 1 RCT, 987 children; moderate-certainty evidence; Analysis 1.4). Subgroup and sensitivity analyses were not applicable (no adjusted effect; single RCT).

Death or major neurodevelopmental disability (up to two years' corrected age)

Magnesium sulphate compared with placebo probably resulted in little to no difference in death or major neurodevelopmental disability up to two years' corrected age (RR 0.95, 95% CI 0.85 to 1.07; 3 RCTs, 4279 children; moderate-certainty evidence; Analysis 1.5).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.4; loading-dose regimen: Analysis 8.4 maintenance dose regimen: Analysis 9.4; repeat treatment permitted: Analysis 10.4). In a post hoc sensitivity analysis pooling adjusted effects sizes, where reported, the result remained similar to the overall analysis (RR 0.94, 95% CI 0.84 to 1.05; 3 RCTs, 4279 children; Analysis 11.4).

Death (fetal, neonatal, or later (up to school age))

Magnesium sulphate compared with placebo may have resulted in little to no difference in death (fetal, neonatal, or later (up to school age)) (RR 0.82, 95% CI 0.66 to 1.02; 2 RCTs, 1758 children; low-certainty evidence; Analysis 1.6).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.5; maintenance dose regimen: Analysis 9.5). Sensitivity analyses were not applicable (no adjusted effects reported).

Cerebral palsy (school age)

Magnesium sulphate compared with placebo may have resulted in little to no difference in cerebral palsy at school age (RR 0.99, 95% CI 0.69 to 1.41; 2 RCTs, 1038 children; low-certainty evidence; Analysis 1.7).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.6; maintenance dose regimen: Analysis 9.6). In a post hoc sensitivity analysis pooling adjusted effects sizes, where reported, the result remained similar to the overall analysis (RR 1.09, 95% CI 0.79 to 1.52; 2 RCTs, 1038 children; Analysis 11.5).

Death or cerebral palsy (up to school age)

Magnesium sulphate compared with placebo may have resulted in little to no difference in death or cerebral palsy at school age (RR 0.90, 95% CI 0.67 to 1.20; 1 RCT, 503 children; low-certainty evidence; Analysis 1.8). Subgroup and sensitivity analyses were not applicable (no adjusted effect; single RCT).

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Major neurodevelopmental disability (school age)

Magnesium sulphate compared with placebo may have resulted in little or no effect on major neurodevelopmental disability at school age, but the evidence is very uncertain (average RR 0.92, 95% CI 0.53 to 1.62; $Tau^2 = 0.09$; $I^2 = 57\%$; 2 RCTs, 940 children; very low-certainty evidence; Analysis 1.9).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.7; maintenance dose regimen: Analysis 9.7). Sensitivity analyses were not applicable (no adjusted effects reported).

Death or major neurodevelopmental disability (school age)

Magnesium sulphate compared with placebo may have resulted in little to no difference in death or major neurodevelopmental disability at school age (RR 0.81, 95% CI 0.59 to 1.12; 1 RCT, 503 children; low-certainty evidence; Analysis 1.10). Subgroup and sensitivity analyses were not applicable (no adjusted effect; single RCT).

For women

Severe maternal outcome potentially related to treatment

Magnesium sulphate compared with placebo may have resulted in little to no difference in severe maternal outcomes (death, cardiac arrest, respiratory arrest) potentially related to treatment, in part because there was only one such adverse event (maternal death) overall (RR 0.32, 95% CI 0.01 to 7.92; 4 RCTs, 5300 women; low-certainty evidence; Analysis 1.11).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.8; loading-dose regimen: Analysis 8.5; maintenance dose regimen: Analysis 9.8; repeat treatment permitted: Analysis 10.5). Sensitivity analysis based on RCT quality was not applicable (Mittendorf 2002 did not report this outcome).

Adverse effects severe enough to stop treatment

Magnesium sulphate compared with placebo probably increased adverse effects severe enough to stop treatment (average RR 3.21, 95% CI 1.88 to 5.48; $Tau^2 = 0.10$; $I^2 = 46\%$; 3 RCTs, 4736 women; moderate-certainty evidence; Analysis 1.12).

Interaction tests demonstrated no evidence of a difference between subgroups with the available data (gestational age at randomisation: Analysis 7.9; loading-dose regimen: Analysis 8.6; maintenance dose regimen: Analysis 9.9; repeat treatment permitted: Analysis 10.6).

Secondary outcomes

For fetuses/neonates/infants

Fetal death

There was no evidence of a difference in fetal death between the magnesium sulphate and placebo groups (RR 0.83, 95% CI 0.46 to 1.52; 6 RCTs, 6805 fetuses; Analysis 2.1).

Neonatal death

There may be little to no difference in neonatal death between the magnesium sulphate and placebo groups (variously defined: RR 0.97, 95% CI 0.80 to 1.17; 6 RCTs, 6751 infants; defined, where possible, as up to hospital discharge: RR 0.96, 95% C 0.80 to 1.15; 6 RCTs, 6751 infants; Analysis 2.2).

Body size at birth (weight, length, head circumference z-scores)

There were no evidence of a difference in birthweight, length, and head circumference at birth between the magnesium sulphate and placebo groups. Birthweight: mean difference (MD) 5.6 g, 95% CI −18.8 to 30.1; 4 RCTs, 6009 infants; z-score, MD 0.03, 95% CI −0.08 to 0.14; 1 RCT, 1679 infants (Analysis 2.3); length at birth: MD 0.30 cm, 95% CI −0.04 to 0.64; z-score MD 0.06, 95% CI −0.05 to 0.17; both 1 RCT, 1559 infants (Analysis 2.4); head circumference at birth: MD 0.10, 95% CI −0.10 to 0.30; z-score MD −0.01, 95% CI −0.12 to 0.10; both 1 RCT, 1642 infants (Analysis 2.5).

One RCT reported no evidence of a difference in median (interquartile range (IQR)) birthweight (magnesium sulphate group: 1350 g (1080 to 1670 g) (N = 352); placebo group: 1415 g (1120 to 1680 g) (N = 336)); length at birth (both groups, 40 cm (38 to 42 cm) (N = 352 and N = 336)); and head circumference at birth (both groups 28 cm (26 to 29 cm) (N = 352 and N = 336)) (Marret 2006).

Gestational age at birth

There was no evidence of a difference in gestational age at birth between the magnesium sulphate and placebo groups (MD 0.10 weeks, 95% CI −0.02 to 0.22; 2 RCTs, 4123 infants; Analysis 2.6).

Two RCTs reported no evidence of a difference in median (IQR) gestational age at birth (Crowther 2003: magnesium sulphate group: 27 weeks, 5 days (26 to 29 weeks) (N = 629); placebo group: 27 weeks, 3 days (25 weeks, 6 days to 29 weeks) (N = 626); Marret 2006: magnesium sulphate group: 30 weeks, 1 day (24 weeks, 1 day to 32 weeks, 6 days (N = 352); placebo group: 30 weeks, 1 day (23 weeks, 4 days to 32 weeks, 6 days) (N = 336)). One RCT reported that gestational age was "similar in the two groups" (mean 30 weeks; SD 4 days) (N = 343 and N = 337) (Wolf 2020).

Apgar score less than seven at five minutes

There may be little to no difference in Apgar score less than seven at five minutes between the magnesium sulphate and placebo groups (RR 1.02, 95% CI 0.89 to 1.16; 4 RCTs, 5006 infants; Analysis 2.7).

Use of active resuscitation at birth

Regarding resuscitation at birth, there may be little to no differences between the magnesium sulphate and placebo groups in: any resuscitation (RR 0.99, 95% CI 0.96 to 1.03; 3 RCTs, 3776 infants); use of supplementary oxygen (RR 1.03, 95% CI 0.96 to 1.10; 2 RCTs, 3093 infants); and use of chest compressions (RR 1.17, 95% CI 0.78 to 1.75; 2 RCTs, 3093 infants). Fewer infants required intubation for resuscitation in the magnesium sulphate group compared with the placebo group (RR 0.88, 95% CI 0.80 to 0.98; 2 RCTs, 3093 infants) (all Analysis 2.8).

Intraventricular haemorrhage

There was no evidence of a difference in intraventricular haemorrhage between the magnesium sulphate and placebo groups (RR 0.94, 95% CI 0.85 to 1.04; 6 RCTs, 6550 infants; Analysis 2.9).

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Severe intraventricular haemorrhage (grade 3 or 4)

Magnesium sulphate compared with placebo probably reduced severe intraventricular haemorrhage (grade 3 or 4) (RR 0.76, 95% CI 0.60 to 0.98; 5 RCTs, 5885 infants; NNTB 92, 95% CI 55 to 1102; moderate-certainty evidence; Analysis 2.10).

Cystic periventricular leukomalacia

There was no evidence of a difference in cystic periventricular leukomalacia between the magnesium sulphate and placebo groups (RR 0.88, 95% CI 0.65 to 1.17; 6 RCTs, 6550 infants; Analysis 2.11).

Post-haemorrhagic hydrocephalus or ventriculomegaly

There was no evidence of a difference in ventriculomegaly between the magnesium sulphate and placebo groups (RR 0.88, 95% CI 0.53 to 1.46; 1 RCT, 1776 infants; Analysis 2.12).

Neonatal encephalopathy

There was evidence of a difference in neonatal encephalopathy between the magnesium sulphate and placebo groups (RR 0.96, 95% CI 0.06 to 15.27; 1 RCT, 1679 infants; Analysis 2.13).

Neonatal convulsions

There was no evidence of a difference in neonatal convulsions between the magnesium sulphate and placebo groups (RR 0.87, 95% CI 0.63 to 1.20; 5 RCTs, 6689 infants; Analysis 2.14).

Neonatal hypoglycaemia

Not reported.

Neonatal hypotonia

There was no evidence of a difference in neonatal hypotonia between the magnesium sulphate and placebo groups (RR 1.03, 95% CI 0.77 to 1.37; 1 RCT, 2415 infants; Analysis 2.15).

Necrotising enterocolitis

There was no evidence of a difference in necrotising enterocolitis between the magnesium sulphate and placebo groups (RR 1.22, 95% CI 0.98 to 1.50; 5 RCTs, 6689 infants; Analysis 2.16).

Intestinal perforation

Not reported.

Retinopathy of prematurity

There was no evidence of a difference in retinopathy of prematurity between the magnesium sulphate and placebo groups (RR 0.99, 95% CI 0.86 to 1.13; 3 RCTs, 3639 infants; Analysis 2.17).

Patent ductus arteriosus

There was no evidence of a difference in patent ductus arteriosus between the magnesium sulphate and placebo groups (RR 0.88, 95% CI 0.73 to 1.06; 3 RCTs, 4771 infants; Analysis 2.18).

Respiratory distress syndrome

There was no evidence of a difference in respiratory distress syndrome between the magnesium sulphate and placebo groups (average RR 0.95, 95% CI 0.83 to 1.08; $Tau^2 = 0.01$; $I^2 = 69\%$; 3 RCTs, 4777 infants; Analysis 2.19).

Chronic lung disease/bronchopulmonary dysplasia

Magnesium sulphate compared with placebo may have resulted in little to no difference in chronic lung disease/bronchopulmonary dysplasia (average RR 0.92, 95% CI 0.77 to 1.10; $Tau^2 = 0.02$; $I^2 = 55\%$; 5 RCTs, 6689 infants; low-certainty evidence; Analysis 2.20).

Use of respiratory support

There was no evidence of a difference in endotracheal intubation (average RR 0.86, 95% CI 0.58 to 1.28; $Tau^2 = 0.07$; $I^2 = 89\%$; 2 RCTs, 1360 infants; Analysis 2.21) or in mechanical ventilation or continuous positive airway pressure (average RR 0.98, 95% CI 0.91 to 1.05; $Tau^2 = 0.00$; $I^2 = 77\%$; 4 RCTs, 6012 infants; Analysis 2.22) between the magnesium sulphate and placebo groups.

Use of postnatal corticosteroids to prevent or treat chronic lung disease/bronchopulmonary dysplasia

Not reported.

Use of inotropic support

There was no evidence of a difference in use of inotropic support between the magnesium sulphate and placebo groups (average RR 0.81, 95% CI 0.50 to 1.29; $Tau^2 = 0.10$; $I^2 = 82\%$; 2 RCTs, 3092 infants; Analysis 2.23).

Air leak syndrome

There was no evidence of a difference in air leak syndrome between the magnesium sulphate and placebo groups (RR 0.55, 95% CI 0.23 to 1.30; 1 RCT, 1679 infants; Analysis 2.24).

Early- and late-onset sepsis

There was no evidence of a difference between the magnesium sulphate and placebo groups in culture-proven sepsis (RR 0.97, 95% CI 0.81 to 1.15; 1 RCT, 2415 infants); early-onset sepsis (RR 1.28, 95% CI 0.29 to 5.68; 1 RCT, 1679 infants); or late-onset sepsis (RR 1.03, 95% CI 0.49 to 2.18; 1 RCT, 1679 infants); however, there were more neonates with reported maternal-fetal infection in the magnesium sulphate versus placebo group (RR 1.53, 95% CI 1.09 to 2.14; 1 RCT, 683 infants) (all Analysis 2.25).

Severe adverse neonatal outcome composite

There was no evidence of a difference in severe adverse neonatal outcome composite between the magnesium sulphate and placebo groups (RR 0.93, 95% CI 0.72 to 1.19; 2 RCTs, 863 infants; Analysis 2.26).

For infants/children/adults

Later death

There was no evidence of a difference in later death (up to two years' corrected age) between the magnesium sulphate and placebo groups (RR 1.09, 95% CI 0.66 to 1.78; 5 RCTs, 6646 children; Analysis 3.1).

There was no evidence of a difference in later death (school age) between the magnesium sulphate and placebo groups (RR 0.50, 95% CI 0.12 to 1.97; 2 RCTs, 1738 children; Analysis 4.1).

Cerebral palsy severity

There were fewer children with mild cerebral palsy (up to two years' corrected age) (RR 0.73, 95% CI 0.53 to 1.00; 6 RCTs, 6108 children)

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and moderate or severe cerebral palsy (up to two years' corrected age) in the magnesium sulphate group compared with the placebo group (RR 0.69, 95% CI 0.50 to 0.95; 6 RCTs, 6108 children; Analysis 3.2).

There was no evidence of a difference in mild to moderate cerebral palsy (school age) (RR 1.07, 95% CI 0.72 to 1.60; 2 RCTs, 1065 children) or severe cerebral palsy (school age) (RR 0.81, 95% CI 0.34 to 1.92; 2 RCTs, 1038 children) between the magnesium sulphate and placebo groups (Analysis 4.2).

Any neurodevelopmental disability

There was no evidence of a difference in any neurodevelopmental disability (up to two years' corrected age) between the magnesium sulphate and placebo groups (RR 0.99, 95% CI 0.84 to 1.16; 1 RCT, 987 children; Analysis 3.3).

There were no evidence of a difference in any (RR 0.95, 95% CI 0.85 to 1.05; 2 RCTs, 940 children), mild (RR 0.88, 95% CI 0.63 to 1.24; 1 RCT, 511 children), moderate (RR 1.00, 95% CI 0.87 to 1.14; 2 RCTs, 940 children), or severe (RR 0.80, 95% CI 0.50 to 1.29; 2 RCTs, 940 children) neurodevelopmental disability (all at school age) between the magnesium sulphate and placebo groups (Analysis 4.3).

Death or any neurodevelopmental disability

Fewer children died or had any neurodevelopmental disability (up to two years' corrected age) in the magnesium sulphate compared with the placebo group (RR 0.91, 95% CI 0.83 to 1.00; 3 RCTs, 3194 children; Analysis 3.4).

There was no evidence of a difference in death or any neurodevelopmental disability (at school age) between the magnesium sulphate and placebo groups (RR 0.94, 95% CI 0.86 to 1.02; 1 RCT, 501 children; Analysis 4.4).

Blindness

There was no evidence of a difference in blindness between the magnesium sulphate and placebo groups (up to two years' corrected age: RR 1.61, 95% CI 0.39 to 6.69; 4 RCTs, 3633 children; Analysis 3.5; at school age: RR 1.05, 95% CI 0.86 to 1.28; 2 RCTs, 983 children; Analysis 4.5).

Deafness

There was no evidence of a difference in deafness between the magnesium sulphate and placebo groups (up to two years' corrected age: RR 0.67, 95% CI 0.32 to 1.42; 4 RCTs, 3633 children; Analysis 3.6; at school age: RR 0.72, 95% CI 0.38 to 1.38; 2 RCTs, 1013 children; Analysis 4.6).

Developmental delay/intellectual impairment

There was no evidence of a difference in developmental delay/intellectual impairment (up to two years' corrected age) between the magnesium sulphate and placebo groups: any (RR 0.98, 95% CI 0.90 to 1.06; 4 RCTs, 5245 children); mild (RR 0.94, 95% CI 0.84 to 1.06; 3 RCTs, 4639 children); moderate or severe (RR 1.06, 95% CI 0.91 to 1.24; 3 RCTs, 4639 children) (all Analysis 3.7).

There was no evidence of a difference in developmental delay/intellectual impairment (school age) between the magnesium sulphate and placebo groups: moderate (RR 1.04, 95% CI 0.88 to 1.24; 1 RCT, 429 children); severe (RR 0.66, 95% CI 0.35 to 1.24; 1 RCT, 429 children) (both Analysis 4.7).

Gross motor dysfunction

There was no evidence of a difference in any gross motor dysfunction (up to two years' corrected age) between the magnesium sulphate and placebo groups (RR 0.88, 95% CI 0.72 to 1.07; 2 RCTs, 1648 children). There were fewer children with substantial gross motor dysfunction (up to two years' corrected age) in the magnesium sulphate group compared with the placebo group (RR 0.61, 95% CI 0.41 to 0.92; 2 RCTs, 1648 children) (both Analysis 3.8).

There were no evidence of a difference in various measures of gross motor dysfunction (at school age) between the magnesium sulphate and placebo groups: motor dysfunction/deficits (RR 0.96, 95% CI 0.82 to 1.12; 2 RCTs, 1026 children); no cerebral palsy, other motor disorder (RR 0.94, 95% CI 0.73 to 1.22; 1 RCT, 429 children); GMFCS levels I-V (RR 1.12, 95% CI 0.73 to 1.70; 1 RCT, 618 children); Movement Assessment Battery for Children (MABC) suspect/abnormal (RR 1.01, 95% CI 0.82 to 1.25; 1 RCT, 598 children) (all Analysis 4.8).

Psychomotor dysfunction

There was no evidence of a difference in any psychomotor dysfunction (up to two years' corrected age) (average RR 0.92, 95% CI 0.72 to 1.18; $Tau^2 = 0.02$; $I^2 = 52\%$; 2 RCTs, 3696 children) or moderate or severe psychomotor dysfunction (up to two years' corrected age) (RR 1.02, 95% CI 0.82 to 1.25; 2 RCTs, 3696 children) between the magnesium sulphate and placebo groups (both Analysis 3.9).

Death or substantial gross motor dysfunction

Fewer children died or had substantial gross motor dysfunction (up to two years' corrected age) in the magnesium sulphate group compared with the placebo group (RR 0.86, 95% CI 0.74 to 0.98; 6 RCTs, 5097 children; Analysis 3.10).

There was no evidence of a difference in death or substantial gross motor dysfunction (at school age) between the magnesium sulphate and placebo groups (RR 0.93, 95% CI 0.80 to 1.08; 1 RCT, 501 children; Analysis 4.9).

Growth

There was no evidence of a difference in weight, height, and head circumference (all up to two years' corrected age) between the magnesium sulphate and placebo groups: weight (MD 0.00 kg, 95% CI −0.22 to 0.22; z-score MD 0.03, 95% CI −0.09 to 0.15; both 1 RCT, 1330 children); height (MD −0.20 cm, 95% CI −0.75 to 0.35; z-score MD 0.05, 95% CI −0.08 to 0.18; both 1 RCT, 1305 children); head circumference (MD 0.00 cm, 95% CI −0.21 to 0.21; z-score MD 0.01, 95% CI −0.13 to 0.15; both 1 RCT, 1265 children) (all Analysis 3.11).

There was no evidence of a difference in weight, head circumference, height, and body mass index (BMI) (all SD scores) (at school age) between the magnesium sulphate and placebo groups: weight (MD −0.23, 95% CI −0.45 to −0.01;* 1 RCT, 614 children); head circumference (MD −0.21, 95% CI −0.40 to −0.02;* 1 RCT, 609 children); height (MD −0.16, 95% CI −0.35 to 0.03; 1 RCT, 618 children); and BMI (MD −0.19, 95% CI −0.41 to 0.03; 1 RCT, 612 children) (all in Analysis 4.10).

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**Effect size reported by RCT (adjusting for clustering within mother and study centre, and using multiple imputation to handle missing data) indicated no difference for these outcomes.*

Respiratory function

There was no evidence of a difference in childhood respiratory morbidity (up to two years' corrected age) (RR 0.93, 95% CI 0.80 to 1.08; 1 RCT, 1365 children) or asthma or wheezing (up to two years' corrected age) (RR 0.95, 95% CI 0.78 to 1.15; 1 RCT, 1365 children) between the magnesium sulphate and placebo groups (both Analysis 3.12).

There was no evidence of a difference in asthma (at school age) between the magnesium sulphate and placebo groups (RR 0.72, 95% CI 0.51 to 1.03; 1 RCT, 424 children; Analysis 4.11).

Blood pressure

There was no evidence of differences in systolic or diastolic blood pressure or hypertension (all up to two years' corrected age) between the magnesium sulphate and placebo groups (systolic hypertension: RR 1.01, 95% CI 0.76 to 1.34; systolic blood pressure: MD 0.06 mmHg, 95% CI −1.52 to 1.64; z-score MD 0.00, 95% CI −0.15 to 0.15; all 1 RCT, 679 children) (diastolic hypertension: RR 0.99, 95% CI 0.81 to 1.20; diastolic blood pressure: MD −0.93 mmHg, 95% CI −2.46 to 0.60; MD −0.08, 95% CI −0.22 to 0.06; all 1 RCT, 674 children) (Analysis 3.13; Analysis 3.14).

Behaviour

There were more children (up to two years' corrected age) with behavioural scores (assessed by the Child Behaviour Checklist) within the clinical problem range overall (RR 1.62, 95% CI 1.00 to 2.64; 1 RCT, 768 children) and for the following scales: anxiety (RR 2.14, 95% CI 1.18 to 3.88; 1 RCT, 793 children); withdrawal (RR 1.47, 95% CI 1.06 to 2.04; 1 RCT, 791 children); sleeping problems (RR 2.54, 95% CI 1.14 to 5.67; 1 RCT, 795 children); and other (RR 7.92, 95% CI 1.00 to 63.00; 1 RCT, 774 children) in the magnesium sulphate group compared with the placebo group. There was no evidence of a difference between magnesium sulphate and placebo groups for the scales: somatic problem (RR 1.01, 95% CI 0.59 to 1.74; 1 RCT, 785 children); aggressive behaviour (RR 4.34, 95% CI 0.94 to 19.97; 1 RCT, 786 children); and destructive behaviour (RR 0.96, 95% CI 0.06 to 15.30; 1 RCT, 796 children) (all Analysis 3.15).

There was no evidence of a difference (at school age) between the magnesium sulphate and placebo groups for behavioural and psychiatric disorder (moderate) (RR 0.87, 95% CI 0.67 to 1.12) or borderline and abnormal scores for: Strengths and Difficulties Questionnaire (SDQ) total difficulties score (RR 0.74, 95% CI 0.55 to 1.00); emotional symptom scale (RR 0.95, 95% CI 0.76 to 1.20); conduct problem scale (RR 1.05, 95% CI 0.76 to 1.46); hyperactivity scale (RR 0.85, 95% CI 0.61 to 1.19); peer problem scale (RR 0.91, 95% CI 0.67 to 1.24); or prosocial scale (RR 1.06, 95% CI 0.49 to 2.27) (all in 1 RCT, 431 children Analysis 4.12). In Crowther 2003, there was no evidence of a difference (at school age) between the magnesium sulphate and placebo groups for SDQ total difficulties scores (median, range): parent scores: magnesium sulphate group: 11 (6 to 17) (N = 304) versus placebo group: 10 (6 to 15) (N = 318); teacher scores: magnesium sulphate group: 8 (4 to 14) (N = 269) versus placebo group: 8 (4 to 13) (N = 279).

There was no evidence of a difference (at school age) for Conners ADHS/DSM-IV Scales (CADS) parent T scores (all in 1 RCT, 623 children): ADHD index (MD 1.00, 95% CI −0.75 to 2.75); DSM-IV inattentive (MD 0.70, 95% CI −1.05 to 2.45); DSM-IV hyperactive-impulsive (MD 0.20, 95% CI −1.71 to 2.11); DSM-IV (MD 0.60, 95% CI −1.20 to 2.40); or CADS teacher T scores (all in 1 RCT, 552 children): ADHD index (MD 0.50, 95% CI −1.32 to 2.32); DSM-IV inattentive (MD 0.60, 95% CI −0.82 to 2.02); DSM-IV hyperactive-impulsive (MD 0.70, 95% CI −0.96 to 2.36); DSM-IV (MD 0.80, 95% CI −0.81 to 2.41); Behavior Rating Inventory of Executive Function (BRIEF) teacher T scores: global executive composite (MD 0.90, 95% CI −1.14 to 2.94; 1 RCT, 507 children); metacognition index (MD 0.50, 95% CI −1.59 to 2.59; 1 RCT, 495 children); or Behavioral Regulation Index (MD 0.50, 95% CI −1.42 to 2.42; 1 RCT, 537 children) (all in Analysis 4.13).

Educational achievement

There was no evidence of a difference in measures of educational achievement (at school age) between the magnesium sulphate and placebo groups: specialised classroom (RR 0.87, 95% CI 0.32 to 2.35); specialised institution (RR 0.99, 95% CI 0.25 to 3.91); repeated grades (RR 0.52, 95% CI 0.24 to 1.15); specific education assistance (RR 0.75, 95% CI 0.40 to 1.39); home education services (RR 0.39, 95% CI 0.17 to 0.91*); and language disorder (RR 0.90, 95% CI 0.53 to 1.52) (all in 1 RCT, 422 children; Analysis 4.14).

**Effect size reported by RCT (gestational age, singleton/multiple pregnancy, socioeconomic variables, sex, and birthweight) indicated no difference for this outcome.*

There was no evidence of a difference in other measures of educational achievement (at school age) between the magnesium sulphate and placebo groups: Wide Range Achievement Test (WRAT3) academic skills scales for: reading (MD 0.50, 95% CI −2.24 to 3.24; 1 RCT, 588 children); spelling (MD 1.20, 95% CI −1.31 to 3.71; 1 RCT, 584 children); and arithmetic (MD 0.30, 95% CI −2.35 to 2.95; 1 RCT, 587 children) (all Analysis 4.15).

Regarding general cognitive function/intelligence quotient (IQ), there was no evidence of a difference in full scale IQ (Wechsler Intelligence Scale for Children - Fourth Edition: WISC-IV) (MD −1.10, 95% CI −3.60 to 1.40; 1 RCT, 583 children); or for the WISC-IV: verbal comprehension index (MD −0.70, 95% CI −3.00 to 1.60; 1 RCT, 601 children); perceptual reasoning index (MD −1.50, 95% CI −3.95 to 0.95; 1 RCT, 601 children); working memory index (MD −1.30, 95% CI −3.68 to 1.08; 1 RCT, 592 children); or processing speed index (MD 0.40, 95% CI −1.97 to 2.77; 1 RCT, 585 children) (all Analysis 4.15).

For women

Individual components of severe maternal outcome potentially related to treatment

There was no evidence of a difference in maternal death between the magnesium sulphate and placebo groups (only one event in placebo group) (RR 0.32, 95% CI 0.01 to 7.92; 4 RCTs, 5300 women; Analysis 5.1). There were no maternal cardiac arrests (4 RCTs, 5300 women; Analysis 5.2) or respiratory arrests in the RCTs included in the meta-analyses (4 RCTs, 5300 women; Analysis 5.3). One RCT described "For two women, unblinding was performed due to serious side effects (respiratory arrest and hypotension)"; however, as reporting was unclear (group/s not reported), these data were not incorporated in the meta-analysis (Wolf 2020).

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Maternal side effects of treatment

More women experienced any side effects of treatment in the magnesium sulphate group compared with the placebo group (average RR 4.49, 95% CI 2.53 to 7.97; $Tau^2 = 0.29$; $I^2 = 97\%$; 4 RCTs, 5300 women; Analysis 5.4), along with the following side effects: hypotension (RR 1.70, 95% CI 1.29 to 2.25; 3 RCTs, 3059 women; Analysis 5.6); tachycardia (RR 1.53, 95% CI 1.03 to 2.29; 1 RCT, 1062 women; Analysis 5.7); warmth over body/flushing (average RR 7.13, 95% CI 4.28 to 11.86; $Tau^2 = 0.19$; $I^2 = 91\%$; 4 RCTs, 5300 women; Analysis 5.8); arm discomfort with infusion (RR 9.64, 95% CI 7.85 to 11.83; 3 RCTs, 4736 women; Analysis 5.9); mouth dryness (average RR 3.26, 95% CI 1.31 to 8.15; $Tau^2 = 0.41$; $I^2 = 93\%$; 2 RCTs, 2495 women; Analysis 5.10); nausea or vomiting (average RR 3.99, 95% CI 2.05 to 7.74; $Tau^2 = 0.35$; $I^2 = 88\%$; 4 RCTs, 5300 women; Analysis 5.11); sleepiness (RR 2.49, 95% CI 1.82 to 3.42; 1 RCT, 1062 women; Analysis 5.12); sweating (average RR 6.12, 95% CI 2.86 to 13.10; $Tau^2 = 0.40$; $I^2 = 89\%$; 3 RCTs, 4736 women; Analysis 5.13); dizziness (average RR 3.16, 95% CI 1.50 to 6.68; $Tau^2 = 0.24$; $I^2 = 82\%$; 2 RCTs, 2495 women; Analysis 5.14); blurred vision (average RR 4.33, 95% CI 1.05 to 17.88; $Tau^2 = 0.84$; $I^2 = 79\%$; 2 RCTs, 2495 women; Analysis 5.15).

There was no evidence of a difference between the magnesium sulphate and placebo groups in the following side effects: respiratory depression (variously defined) (RR 1.14, 95% CI 0.82 to 1.61; 3 RCTs, 4736 women; RR 1.31, 95% CI 0.83 to 2.07; 2 RCTs, 3303 women; Analysis 5.5); tendon reflex abolition (RR 1.94, 95% CI 0.18 to 21.32; 1 RCT, 564 women; Analysis 5.16); "curarisation" (RR 2.92, 95% CI 0.12 to 71.29; 1 RCT, 564 women; Analysis 5.17); and headache (RR 3.89, 95% CI 0.44 to 34.57; 1 RCT, 564 women; Analysis 5.18).

Time between randomisation and birth

Two RCTs reported no evidence of a difference in time between randomisation and birth (Crowther 2003 (median, IQR): magnesium sulphate group: 3.7 hours (1.4 to 13.8 hours) (N = 535); placebo group: 3.1 hours (1.3 to 12.9 hours) (N = 527); Marret 2006 (median, range - from infusion to birth): magnesium sulphate group: 1 hour, 38 minutes (5 minutes to 25 hours, 5 minutes) (N = 286); placebo group: 1 hour, 30 minutes (8 minutes to 61 hours, 30 minutes) (N = 278)). In one RCT, the time between randomisation and birth was longer in the magnesium sulphate group compared with the placebo group (Wolf 2020: (median, IQR): magnesium sulphate group: 24 hours (3 to 195 hours) (N = 283); placebo group: 7 hours (2 to 81 hours) (N = 277)).

Mode of birth (caesarean section)

There was probably little to no difference in caesarean section between the magnesium sulphate and placebo groups (RR 0.96, 95% CI 0.91 to 1.02; 5 RCTs, 5861 women; moderate-certainty evidence; Analysis 5.19).

Chorioamnionitis

There was no evidence of a difference in chorioamnionitis between the magnesium sulphate and placebo groups (RR 1.01, 95% CI 0.81 to 1.27; 1 RCT, 2241 women; Analysis 5.20).

Postpartum haemorrhage

There was probably little to no difference in postpartum haemorrhage between the magnesium sulphate and placebo groups (RR 0.94, 95% CI 0.80 to 1.09; 2 RCTs, 2495 women; moderate-certainty evidence). There was no evidence of a difference in severe postpartum haemorrhage between the magnesium sulphate and placebo groups (RR 1.36, 95% CI 0.90 to 2.05; 3 RCTs, 3059 women) (both Analysis 5.21).

Breastfeeding at hospital discharge

Not reported.

Women's views of treatment

Not reported.

Use of health services

Maternal admission to the intensive care unit

There were no maternal admissions to the intensive care unit (1 RCT, 1062 women; Analysis 6.1).

Length of postnatal hospitalisation for women

There was no evidence of a difference in length of maternal hospitalisation for women between groups (MD 0.20 days, 95% CI −0.18 to 0.58; 1 RCT, 1062 women; Analysis 6.2).

Admission to the neonatal intensive care unit

Not reported.

Length of stay in neonatal intensive care unit

Not reported.

Length of neonatal/infant hospitalisation

There was no evidence of a difference in length of neonatal/infant hospitalisation between groups (MD 1.80 days, 95% CI −2.62 to 6.22; 1 RCT, 1235 infants; Analysis 6.3).

Two RCTs also reported no evidence of a difference in length of neonatal/infant hospitalisation between groups (Crowther 2003 (median, IQR): magnesium sulphate group: 76 days (61 to 94 days) (N = 620); placebo group: 74 days (59 to 95 days) (N = 615); Wolf 2020 (median, range): magnesium sulphate group: 45 days (26 to 67 days) (N = 343); placebo group: 47 days (29 to 70 days) (N = 337)).

Costs of maternal care

Not reported.

Costs of neonatal care

Not reported.

Use of care for infant/child/adult

There may be little to no differences between the magnesium sulphate and placebo groups in hospital admissions (up to two years' corrected age) (RR 0.91, 95% CI 0.79 to 1.03; 1 RCT, 1365 children; Analysis 6.4); postdischarge service (up to two years' corrected age) (RR 0.95, 95% CI 0.83 to 1.10; 1 RCT, 1352 children; Analysis 6.5); and hospital admissions (school age) (RR 0.83, 95% CI 0.69 to 1.00; 1 RCT, 420 children; Analysis 6.6).

Costs of care for infant/child/adult

Not reported.

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DISCUSSION

Summary of main results

We included six RCTs (enrolling 5917 women at less than 34 weeks' gestation and their 6759 fetuses alive at randomisation) that compared magnesium sulphate with placebo for women at risk of preterm birth for neuroprotection of the fetus in this review.

Regarding our **primary outcomes** *for infants/children*, up to two years' corrected age, magnesium sulphate compared with placebo reduced cerebral palsy (6 RCTs, 6107 children) and reduced death or cerebral palsy (6 RCTs, 6481 children) (both high-certainty evidence). At up to two years' corrected age, magnesium sulphate probably resulted in little to no difference in death (fetal, neonatal, or later) (6 RCTs, 6759 children), major neurodevelopmental disability (1 RCT, 987 children), and death or major neurodevelopmental disability (3 RCTs, 4279 children) (all moderate-certainty evidence). At early school age, magnesium sulphate may have resulted in little to no difference in death (fetal, neonatal, or later) (2 RCTs, 1758 children), cerebral palsy (2 RCTs, 1038 children), death or cerebral palsy (1 RCT, 503 children) and death or major neurodevelopmental disability (1 RCT, 503 children) (all low-certainty evidence). Magnesium sulphate may have resulted in little to no effect on major neurodevelopmental disability, but the evidence was very uncertain (2 RCTs, 940 children; very low-certainty evidence).

For women, magnesium sulphate may have resulted in little to no difference in severe maternal outcomes potentially related to treatment (death, cardiac arrest, respiratory arrest) (4 RCTs, 5300 women; low-certainty evidence). However, magnesium sulphate probably increased adverse effects severe enough to stop treatment (3 RCTs, 4736 women; moderate-certainty evidence).

Subgroup analyses for our primary outcomes (based on gestational age at randomisation, loading-dose regimen, maintenance dose regimen, and whether repeat treatment was permitted) revealed no clear differential treatment effects according to the characteristics assessed. Insufficient information precluded an assessment of the impact of the primary reason women were considered at high risk of preterm birth, number of babies in utero, mode of magnesium sulphate administration, and time treatment was intended to be started prior to preterm birth. Sensitivity analyses (restricting to the RCTs at low risk of selection bias, and including adjusted effect sizes where reported) supported the findings observed in the main analyses.

Considering **secondary outcomes assessed using GRADE** *for infants/children*, magnesium sulphate probably reduced severe intraventricular haemorrhage (grade 3 or 4) (5 RCTs, 5885 infants; moderate-certainty evidence) and may have resulted in little to no difference in chronic lung disease/bronchopulmonary dysplasia (5 RCTs, 6689 infants) (low-certainty evidence). *For women*, magnesium sulphate probably resulted in little or no difference in caesarean section (5 RCTs, 5861 women) and postpartum haemorrhage (2 RCTs, 2495 women) (both moderate-certainty evidence). No data were reported for breastfeeding at discharge and women's views of treatment.

For the majority of other **secondary outcomes not assessed using GRADE** *for infants/children*, no evidence of differences was observed. However, we did observe a number of possible benefits in the magnesium sulphate versus placebo group: fewer infants required intubation for resuscitation (2 RCTs, 3093 infants); and up to two years' corrected age, fewer children had moderate or severe cerebral palsy (6 RCTs, 6108 children); died or had any neurodevelopmental disability (3 RCTs, 3194 children); had substantial gross motor dysfunction (2 RCTs, 1648 children); and died or had substantial gross motor dysfunction (6 RCTs, 5097 children). No harms for infants/children were observed with magnesium sulphate versus placebo, except for possibly more children up to two years' corrected age with behavioural scores (assessed by the Child Behaviour Checklist) within the clinical problem range overall, and on the following scales: anxiety, withdrawal, sleeping problems, other (all in 1 RCT, up to 795 children). *For women*, in large part, no evidence of differences in outcomes, including no benefits, was observed. However, we did observe some possible harms in the magnesium sulphate versus placebo group: more women experienced any side effects of treatment (4 RCTs, 5300 women) and the following side effects: hypotension (3 RCTs, 3059 women), tachycardia (1 RCT, 1062 women), warmth over body/flushing (4 RCTs, 5300 women), arm discomfort with infusion (3 RCTs, 4736 women), mouth dryness (2 RCTs, 2495 women), nausea or vomiting (4 RCTs, 5300 women), sleepiness (RCT, 1062 women), sweating (3 RCTs, 4736 women), dizziness (2 RCTs, 2495 women), and blurred vision (2 RCTs, 2495 women).

Overall completeness and applicability of evidence

The evidence assessing the effects of magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus is incomplete.

While for our primary outcomes of death, cerebral palsy, and death or cerebral palsy up to two years' corrected age, we were able to include data from all six RCTs, for many outcomes, only one to five RCTs contributed data. Only two of the six RCTs reported data up to early school age, and none reported on follow-up beyond this into adolescence or adulthood.

For a variety of prespecified review outcomes (neonatal hypoglycaemia, intestinal perforation, use of postnatal corticosteroids to prevent or treat chronic lung disease/bronchopulmonary dysplasia, breastfeeding at hospital discharge, women's views of treatment, maternal admission to the intensive care unit, length of postnatal hospitalisation for women, admission to the neonatal intensive care unit, length of stay in neonatal intensive care unit, costs of maternal care, costs of neonatal care, costs of care for infant/child/adult), no data were reported by the included RCTs. This review thus presents an incomplete picture of the benefits and harms of magnesium sulphate for women and their infants/children.

The review's findings are limited by notable variations in the characteristics of the enrolled women, and the magnesium sulphate regimens used in the included RCTs (as summarised in Table 1 and Table 2). While we chose to combine RCTs in one comparison, and attempted to explore variation through subgroup analyses, this was limited by the difficulty in meaningfully grouping RCTs according to important characteristics (as the inclusion criteria did not enable allocation to one or the other subgroup, or stratified results were not presented, or both).

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All included RCTs were conducted in high-income countries (Australia, Denmark, France, New Zealand, the USA). The studies commenced the enrolment/randomisation of women between 1995 and 2018. Thus, although there are nearly 6000 women and their children in the included RCTs, it is important to consider the potential limitations of the review's findings in terms of applicability (to low- and middle-income countries) and generalisability (to present-day clinical context/practice).

For example, the RCTs used specific and varied approaches to childhood follow-up, including different definitions/diagnostic criteria for important outcomes, including cerebral palsy. Today, a cerebral palsy diagnosis (including the interim use of a 'high risk of cerebral palsy' diagnosis) may be made according to 2017 international clinical practice guideline recommendations (Novak 2017). These guidelines suggest that to make the most accurate, earliest (possible under the age of six months) diagnosis, a combination of clinical history, neuroimaging, standardised neurological assessments, and standardised motor assessments are used (Novak 2017). Within the RCTs included in this review, the diagnosis of cerebral palsy was commonly made following a clinical (e.g. paediatric) examination, and/or parent interview/questionnaire at up to two years' corrected age. While a clinical examination at up to two years' corrected age was previously regarded as the most accurate available approach, it has recognised limitations. The diagnosis of cerebral palsy continues to present challenges. Indeed, despite early diagnosis being highlighted as important - particularly to facilitate early intervention (Spittle 2018) - the value of time, including to rule out other diagnoses, is still recognised. For example, certain national cerebral palsy registries do not consider a child's record as 'complete' until it is 'confirmed' at five years of age, recognising the potential for new information to potentially change a previous diagnosis of cerebral palsy (ACPR 2023).

Following screening of potentially eligible studies for trustworthiness, a total of eight studies were classified as Studies awaiting classification. These studies were conducted in various low- or middle-income countries (Moldova, India, Indonesia, Iran, and Iraq; see Characteristics of studies awaiting classification). Their future potential inclusion (along with potential inclusion of Ongoing studies) may extend the applicability and generalisability of the review's findings. We await further information from the study authors. Direct evidence from such settings would be beneficial, given the inherent advantages of magnesium sulphate treatment, which are particularly relevant to low- and middle-income countries, such as its relative low cost, widespread availability (Lingam 2018), favourable safety profile (Bain 2013; Shepherd 2019), and long history of use in perinatal care globally, particularly for preventing and treating eclampsia and treating pre-eclampsia (Duley 2010; Fishel 2022).

Quality of the evidence

We judged the overall risk of bias of the six RCTs to be low. Sensitivity analyses restricted to the five RCTs at low risk of selection bias supported the findings from the main analyses (Crowther 2003; Crowther 2023; Marret 2006; Rouse 2008; Wolf 2020). To date, only two RCTs have reported on school age follow-up (Crowther 2003; Marret 2006); the risk of attrition bias due to the proportion of participants lost was judged to be unclear for relevant outcomes.

For the outcomes assessed using GRADE, we judged the evidence to be of high certainty (cerebral palsy (up to two years' corrected age); death or cerebral palsy (up to two years' corrected age)); moderate certainty (maternal adverse effects severe enough to stop treatment; mode of birth (caesarean section); postpartum haemorrhage; death (fetal, neonatal, or later (up to two years' corrected age)); major neurodevelopmental disability (up to two years' corrected age); death or major neurodevelopmental disability (up to two years' corrected age); any severe intraventricular haemorrhage (grade 3 or 4)); low certainty (severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest); chronic lung disease/bronchopulmonary dysplasia; death (fetal, neonatal, or later (up to school age)); cerebral palsy (school age); death or cerebral palsy (school age); death or major neurodevelopmental disability (school age)); or very low certainty (major neurodevelopmental disability (school age)). We downgraded the certainty of the evidence predominantly due to imprecision (uncertain effect estimates, with 95% CIs including both benefit and harm), design limitations (risk of bias, considering attrition for school age outcomes), and/or inconsistency (statistical heterogeneity). We did not downgrade outcomes for indirectness; however, we have noted potential concerns regarding our review's findings concerning applicability/generalisability above. See Summary of findings 1; Summary of findings 2; Summary of findings 3.

We recognise that with our many review outcomes, there is a risk of statistical type 1 error (a 'false-positive' result). Results where there are very few RCTs included, or with moderate or substantial heterogeneity, and/or 'borderline statistical significance', should be interpreted with caution.

Potential biases in the review process

We took steps to minimise bias throughout the review process. The Cochrane Pregnancy and Childbirth Information Specialist conducted a detailed and systematic search, without language, date, or publication status restrictions. It is possible that additional RCTs assessing magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus have been published but not identified, and that further RCTs have been conducted but are not yet published, or both. Should we identify such RCTs in the future, we will assess them for inclusion in an update to this review. As there were a maximum of six RCTs included in our meta-analyses, we were not able to formally investigate reporting biases (such as publication bias) using funnel plots.

At least two review authors independently assessed RCTs for inclusion (including trustworthiness assessment), performed data extraction including risk of bias assessment, and assessed the certainty of the evidence (using GRADE), with any disagreements discussed until consensus was reached. Despite independent assessments, these processes, particularly assessing risk of bias and the certainty of the evidence, are inherently subjective and require a degree of interpretation. In all cases, we sought to be consistent and transparent, documenting our decisions and rationale.

Seven of the nine review authors are also trialists/authors for one or more of the included RCTs (Crowther 2003: Caroline A Crowther, Lex W Doyle; Crowther 2023: Caroline A Crowther, Philippa Middleton; Marret 2006: Stéphane Marret; Mittendorf 2002: Peter Pryde; Rouse 2008: Dwight J Rouse; Wolf 2020: Hanne Trap Wolf). For these RCTs,

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Emily Shepherd and a second review author not involved in the RCT assessed it for eligibility. Emily Shepherd and Shona Goldsmith conducted data extraction including risk of bias assessment for all RCTs.

Agreements and disagreements with other studies or reviews

Our review provides the most up-to-date and comprehensive assessment of trustworthy evidence.

The results and conclusions of our review are broadly consistent with those of prior systematic reviews (Conde-Agudelo 2009; Costantine 2009; Wolf 2020; Zeng 2016). These reviews have previously confirmed the neuroprotective role of magnesium sulphate in women at risk of preterm birth, demonstrating reductions in outcomes for children up to two years' corrected age, including cerebral palsy, moderate or severe cerebral palsy, substantial gross motor dysfunction, and death or cerebral palsy, without an increase in death. Our review is also broadly consistent with previous comprehensive reviews of adverse maternal and neonatal outcomes associated with magnesium sulphate (when used for the prevention or treatment of eclampsia, for preventing preterm labour and birth (tocolysis), and fetal neuroprotection) (Bain 2013; Shepherd 2019). Magnesium sulphate has not been shown to increase serious maternal adverse effects (death, cardiac arrest, respiratory arrest), though an increase in comparatively 'minor' adverse effects and treatment cessation has been shown (Bain 2013). Magnesium sulphate has also not been shown to increase neonatal adverse outcomes, including death (Shepherd 2019).

The most recent systematic review on this topic (Wolf 2020) was the first to include data from the Wolf 2020 RCT. While it also included the Magpie 2006 RCT (now excluded from this review; see Differences between protocol and review), its overall findings/conclusions are consistent with ours. Our review is the first to include data from the Crowther 2023 RCT. This RCT was designed to assess the effect of magnesium sulphate at 30 to 34 weeks' gestation (beyond the gestational age currently recommended in some countries based on the previous version of this review (Doyle 2009)) (Jayaram 2019). While a reduction in the RCT's composite primary outcome (death or cerebral palsy for children at two years' corrected age; or the separate components) was not shown, the authors recognised the limited power to detect small between-group differences due to the lower event rates for death and cerebral palsy than predicted and the RCT's sample size (Crowther 2023). Despite the absence of benefit observed in Crowther 2023, the addition of its data to our review's meta-analysis did not negate the overall neuroprotective benefits observed with this treatment.

To date, only one other systematic review has reported on school age outcomes of antenatal magnesium sulphate for fetal neuroprotection (Kobayashi 2023). Its findings supported ours, that is an absence of clear benefits or harms, and the need for additional follow-up data to determine effects with greater certainty.

The findings of our review's limited subgroup analyses are consistent with those from a previous individual participant data meta-analysis (Crowther 2017), which similarly demonstrated reductions for children up to two years' corrected age in cerebral palsy, and death or cerebral palsy, with benefit not clearly affected by characteristics including preterm gestational age, and treatment regimen. With the availability of individual participant data, the meta-analyses were able to assess the impacts of characteristics (such as the reason women were at risk of preterm birth; and total dose received by women) that we were not able to explore in our review, due to limitations of the aggregate data available from the included RCTs. There is now an important opportunity and need to extend/update the previous individual participant data meta-analysis to include the more recent RCTs (Crowther 2023; Wolf 2020), and longer-term (school age) follow-up data (from Crowther 2003; Marret 2006).

The current international guideline from the World Health Organization on interventions to improve preterm birth outcomes used the previous version of this Cochrane review, Doyle 2009, on which to base their recommendation (WHO 2015). Similarly, the clinical practice guideline recommendations provided by professional bodies in many high-income countries (summarised in the systematic review Jayaram 2019) are based on the previous version of this review (Doyle 2009). While available guidelines all support the use of this treatment for preterm cerebral palsy prevention, as systematic reviews and meta-analysis have not supported a particular upper gestational age or dosing regimen, recommendations vary (e.g. recommending use in women at less than 30 weeks' gestation, or up to 34 weeks' gestation) (Jayaram 2019). As noted above, the opportunity to further investigate which women to treat (i.e. considering the primary reason women are at risk of preterm birth, the number of babies in utero, and gestational age); when to treat (i.e. considering how long prior to anticipated or planned preterm birth); and how to treat (i.e. considering both loading-dose and maintenance dose regimens) through an updated individual participant data meta-analysis should be explored.

AUTHORS' CONCLUSIONS

Implications for practice

There is high-certainty evidence that magnesium sulphate given to women at risk of preterm birth for neuroprotection of the fetus reduces cerebral palsy, and death or cerebral palsy, for children up to two years' corrected age when compared to placebo. There is moderate-certainty evidence that magnesium sulphate probably reduces severe intraventricular haemorrhage for neonates. There is low- to very low-certainty evidence that magnesium sulphate may result in little to no difference in outcomes at school age.

While there is low-certainty evidence that magnesium sulphate may result in little to no difference in severe maternal outcomes (death, cardiac arrest, respiratory arrest), there is moderate-certainty evidence that magnesium sulphate probably increases adverse effects severe enough to stop treatment.

The available data are from six randomised controlled trials that randomised women at less than 34 weeks' gestation and were conducted in high-income countries.

Implications for research

Further research is needed on the longer-term benefits and harms of magnesium sulphate when given to women at risk of preterm birth for neuroprotection of the fetus, including follow-up of children into adolescence and adulthood. Any future studies should use robust methodology, and aim for consistency in

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outcome measurement and reporting (using standardised, ideally contemporary assessment methods), to facilitate pooling of data.

As the available evidence does not support clear variation in treatment effects according to characteristics of women treated and treatment regimens used, further studies addressing persisting uncertainties regarding which women to treat, when, and how, should be prioritised. This will help to ensure that women whose children are likely to benefit from exposure are not denied treatment; and that women whose children will likely not benefit from treatment are not exposed unnecessarily. Research to address the generalisability of review findings to low- and middle-income countries should also be considered.

The Studies awaiting classification and Ongoing studies may contribute to addressing some of these gaps.

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2023 update

Editorial and peer-reviewer contributions

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The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Zarko Alfirevic, University of Liverpool, Department of Women's and Children's Health, United Kingdom;
- Managing Editor (selected peer reviewers, provided editorial guidance to authors, edited the article): Leanne Jones, Cochrane Central Editorial Service;
- Editorial Assistant (conducted editorial policy checks, collated peer-reviewer comments, and supported the editorial team): Jacob Hester, Cochrane Central Editorial Service;
- Copy Editor (copy editing and production): Lisa Winer, Cochrane Central Production Service;
- Peer reviewers (provided comments and recommended an editorial decision): Khalid N Haque, University of Child Health Sciences, Pakistan (clinical/content review), César Hernán Meller, MD, MSc, Obstetrics Department, Hospital Italiano de Buenos Aires & Universidad Hospital Italiano de Buenos Aires (clinical/content review), M Dulce Estêvão School of Health – University of Algarve, Faro, Portugal (consumer review), Nuala Livingstone, Cochrane Evidence Production and Methods Directorate (methods review), Jo Platt, Central Editorial Information Specialist (search review).

Other

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Crowther 2003

Study characteristics	
Methods	**Study design:** RCT (multicentre). **Study setting:** Australia and New Zealand: 16 tertiary hospitals with a NICU (13 Australia; 3 New Zealand). School age follow-up: 14 of the 16 original sites. **Study period/dates:** 1996 to 2000 (women recruited). 2005 to 2011 (school age follow-up). **Registration number:** ACTRN12606000252516 (registered after main RCT, prior to school age follow-up).
Participants	**Total randomised:** 1062 women, 1262 infants (1255 alive at randomisation). **Inclusion criteria:** women pregnant with single, twin, triplet, or quadruplet fetuses < 30 weeks' gestation, if birth was planned or expected within 24 h (no lower gestational age limit). **Exclusion criteria:** women in the second stage of labour, who had received magnesium sulphate in this pregnancy, with contraindications to magnesium sulphate (respiratory rate < 16/min, absent patellar reflexes, urine output < 100 mL in previous 4 h, renal failure, hypocalcaemia).
Interventions	**Intervention:** magnesium sulphate: 4 g (16 mmol) IV loading dose (8 mL) over 20 min; followed by maintenance of 1 g/h (2 mL) IV until birth (if within 24 h) or up to 24 h. Infusion bag of 60 mL with 0.5 g/mL solution of magnesium sulphate. N = 535 women, 633 infants (629 alive at randomisation).

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Crowther 2003 *(Continued)*

Comparison: placebo: 8 mL loading dose of saline over 20 min; followed by maintenance of 2 mL/h IV until birth (if within 24 h) or up to 24 h. Infusion bag of 60 mL with isotonic sodium chloride solution (0.9%).

N = 527 women, 629 infants (626 alive at randomisation).

Outcomes

Outcomes reported that are considered for this review:

Primary outcomes (infants/children): death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age); major neurodevelopmental disability (up to 2 years' corrected age); death or major neurodevelopmental disability (up to 2 years' corrected age); death (fetal, neonatal, or later (up to school age)); cerebral palsy (school age); major neurodevelopmental disability (school age).

Primary outcomes (women): severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest); adverse effects severe enough to stop treatment.

Secondary outcomes (infants/children): fetal death; neonatal death; birthweight; Apgar score < 7 at 5 min; intraventricular haemorrhage; any severe intraventricular haemorrhage (grade 3 or 4); cystic periventricular leukomalacia; neonatal convulsions*; necrotising enterocolitis; chronic lung disease/bronchopulmonary dysplasia; use of respiratory support (mechanical ventilation or continuous positive airway pressure); later death (up to 2 years' corrected age); cerebral palsy severity (up to 2 years' corrected age); any neurodevelopmental disability (up to 2 years' corrected age); death or any neurodevelopmental disability (up to 2 years' corrected age); blindness (up to 2 years' corrected age); deafness (up to 2 years' corrected age); developmental delay/intellectual impairment (up to 2 years' corrected age); gross motor dysfunction (up to 2 years' corrected age); psychomotor dysfunction (up to 2 years' corrected age); death or substantial gross motor dysfunction (up to 2 years' corrected age); later death (school age); cerebral palsy severity (school age); any neurodevelopmental disability (school age); blindness (school age); deafness (school age); gross motor dysfunction (school age); growth (school age); behaviour (school age); educational achievement (school age).

Secondary outcomes (women): death; cardiac arrest; respiratory arrest; side effects of treatment; respiratory depression; hypotension; tachycardia; warmth over body/flushing; arm discomfort with infusion; mouth dryness; nausea or vomiting; sleepiness; sweating; dizziness; blurred vision; mode of birth: caesarean birth; postpartum haemorrhage.

Secondary outcomes (use of health services): maternal admission to the intensive care unit*; length of postnatal hospitalisation for women*; length of neonatal/infant hospitalisation*.

Follow-up method/s for outcome assessment:

2 years' corrected age: children assessed by developmental paediatricians and psychologists. Cerebral palsy criteria: "abnormalities of tone and loss of motor function" (apart from being provided criteria, assessors were not trained in diagnosis; judgement relied on individual developmental paediatricians). Gross motor function assessed by criteria derived from Palisano and colleagues (walking normally; walking with minimal limitation; not walking independently: substantial gross motor dysfunction). Vision assessed (blindness: vision in both eyes worse than 6/60). Hearing assessed (deafness: requiring hearing aids). Psychological assessment included BSID PDI and MDI. Severe neurosensory disability comprised any of: severe cerebral palsy (permanently non-ambulant), severe developmental delay (MDI < 3 SDs) or blindness; moderate disability comprised any of: moderate cerebral palsy (non-ambulant at 2 years but likely to walk), moderate developmental delay (MDI −3 SDs to < −2 SDs), or deafness; mild disability: mild cerebral palsy (walking at 2 years), or mild developmental delay (MDI −2 SDs to < −1 SD).

School age (6 to 11 years): motor outcomes: developmental paediatrician assessed children for cerebral palsy (diagnosis: non-progressive loss of motor function with disordered tone or tendon reflexes); severity of gross motor function classified by GMFCS (severe: level IV or V; moderate: level II or III; mild: level I); some children without cerebral palsy had gross motor dysfunction assigned according to GMFCS. Motor function assessed by MABC first edition (< 15th centile: borderline motor function; < 5th centile: definite motor problem). Psychological outcomes: general cognitive ability assessed with WISC-IV (general intellectual ability: full-scale IQ; index sores (verbal comprehension, perceptual reasoning, working memory, processing speed): specific elements of cognitive functioning); scores age-

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Crowther 2003 *(Continued)*

standardised (mean (SD): 100 (15); scores < 85: intellectual impairment; < 70: moderate intellectual impairment). Academic skills assessed with WRAT3 (reading, spelling, arithmetic scales; age-standardised, mean (SD): 100 (15)). Behaviour assessed with BRIEF questionnaire (parent and teacher versions). Behaviour and attention-deficit/hyperactivity disorder (ADHD) symptoms assessed with CADS (Psychological Corporation) (parent and teacher versions) (age/sex T scores, mean (SD): 50 (10), with higher scores indicating more problems). General behaviour problems assessed with SDQ (parent and teacher reports) (scores from 0 to 40: normal: 0 to 13; borderline: 14 to 16; abnormal: > 17). Weight and height values for SD scores computed from British Growth Reference data. Visual acuity assessed with standard eye chart (blindness: both eyes worse than 20/200). Hearing assessed (deafness: required hearing aids or worse). Neurosensory disability classified as: severe: any of severe cerebral palsy, IQ < 55, or blindness; moderate disability: any of moderate cerebral palsy, deafness, or IQ 55 to 69; mild disability: any of mild cerebral palsy, or IQ from 70 to 85.

*Additional data from trialists (2009 version), not in trial reports.

Notes

Funding source:

Main RCT: Funded by a 5-year epidemiological project grant from the National Health and Medical Research Council Australia, the Channel 7 Research Foundation of South Australia Inc, and the Queen Victoria Hospital Research Foundation, Adelaide, South Australia, and supported by the Department of Obstetrics and Gynaecology at the University of Adelaide, Adelaide, Australia.

School age follow-up: Funded by a project grant from the National Health and Medical Research Council Australia and the Victorian Government's Operational Infrastructure Support Program.

Declarations of interest:

Main RCT: not reported.

School age follow-up: "All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported."

Analyses:

Main RCT: an adjusted analysis performed for mortality based on baseline variables with imbalance (race, hospital, public patient status, antepartum haemorrhage or PPROM as reason for preterm birth); where appropriate, analyses adjusted for clustering within mother – adjusted RRs reported.

School age follow-up: where appropriate, analyses adjusted for study centre and for clustering within mother – adjusted ORs or adjusted MDs reported; where appropriate, analyses also carried out using multiple imputation to handle missing data (N = 867).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The study randomization numbers were generated by computer."
Allocation concealment (selection bias)	Low risk	Quote: "The study randomization… managed by nonclinical staff at the University of Adelaide's Maternal Perinatal Clinical Trials Unit. Each study number was placed on a masked treatment pack. Packs were sent to participants centers ready to use."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Each treatment pack looked identical… Clinicians were asked not to measure magnesium levels to maintain blinding… All perinatal staff were blinded to treatment group allocation."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All pediatric deaths were reviewed by an independent committee, blinded to therapy… Surviving children were assessed at a corrected age of 2

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Crowther 2003 *(Continued)*

		years by developmental pediatricians and psychologists blinded to treatment group allocation." School follow-up, quote: "Children were assessed without reference to any previous results by members of the study team who were blinded to treatment group allocation."
Incomplete outcome data (attrition bias) Main trial and initial follow-up	Low risk	Quote: "Outcome data were obtained, up to the time of hospital discharge, on all 1062 women and their 1255 infants alive at the time of randomization, and 2-year corrected age outcomes were available for 1047 children (99% of 2-year survivors). Fourteen children (9 in the magnesium sulfate group and 5 in the placebo group without 2-year corrected age cerebral palsy assessments were treated as missing data and excluded from the cerebral palsy analysis".
Incomplete outcome data (attrition bias) School age follow-up	Unclear risk	School age follow-up, quote: "Of the 1060 known survivors at the 2-year follow-up, 3 children died before the school-age follow-up and 190 were from centers that did not participate in the school-age follow-up protocol, leaving 867 children (443 magnesium sulfate and 424 placebo) available for follow-up at school age (Figure). Of these 867 children, outcomes at school age were determined for 669 (77%), with the outcome data available for between 552 (64%) for the teacher-reported questionnaires and 649 (75%) for the psychological tests (Figure)"; and "Multiple imputation was carried out to impute the missing outcomes in the sites participating in the follow-up (including all 867 participants eligible for follow-up)." Children assessed at school age versus children not assessed were born at a lower gestational age, with a lower birthweight, were more likely to be from a multiple pregnancy, had more exposure to postnatal corticosteroids, and had a higher MDI score at 2 years.
Selective reporting (reporting bias)	Low risk	The RCT protocol is available (via the school follow-up paper) and the RCT's prespecified primary and secondary outcomes are reported in the pre-specified way.
Other bias	Low risk	No indication of other sources of bias.

Crowther 2023

Study characteristics	
Methods	**Study design:** RCT (multicentre). **Study setting:** Australia and New Zealand: 24 sites. **Study period/dates:** 2012 to 2018 (inclusion period). **Registration number:** ACTRN12611000491965.
Participants	**Total randomised:** 1433 women (1679 children). **Inclusion criteria:** women at risk of preterm birth between 30 and 34 weeks' gestation, with singleton or twin pregnancies, who gave written consent, where birth was planned or definitely expected within 24 h, and there were no contraindications to the use of magnesium sulphate (e.g. respiratory depression, hypotension, absent patellar reflexes, renal failure, myasthenia gravis). **Exclusion criteria:** women for whom magnesium sulphate therapy was considered essential for treating pre-eclampsia.
Interventions	**Intervention:** magnesium sulphate: 4 g IV over 30 min.

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Crowther 2023 *(Continued)*

N = 729 women, 858 fetuses alive at randomisation.

Comparison: placebo: IV placebo over 30 min.

N = 704 women, 821 fetuses alive at randomisation.

Outcomes

Outcomes reported that are considered for this review:

Primary outcomes (infants/children): death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age); death or major neurodevelopmental disability (up to 2 years' corrected age).

Primary outcomes (women): severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest); adverse effects severe enough to stop treatment.

Secondary outcomes (infants/children): fetal death; neonatal death; birthweight; length at birth; head circumference at birth; gestational age at birth (weeks); intraventricular haemorrhage; any severe intraventricular haemorrhage (grade 3 or 4); cystic periventricular leukomalacia; neonatal encephalopathy; neonatal convulsions; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus; respiratory distress syndrome; chronic lung disease/bronchopulmonary dysplasia; use of respiratory support (mechanical ventilation or continuous positive airway pressure); air leak syndrome; early- or late-onset sepsis; severe adverse neonatal outcome composite; later death (up to 2 years' corrected age); cerebral palsy severity (up to 2 years' corrected age); death or any neurodevelopmental disability (up to 2 years' corrected age); blindness (up to 2 years' corrected age); deafness (up to 2 years' corrected age); developmental delay/intellectual impairment (up to 2 years' corrected age); growth (up to 2 years' corrected age); respiratory function (up to 2 years' corrected age); blood pressure (up to 2 years' corrected age); behaviour (up to 2 years' corrected age); hospital admissions (up to 2 years' corrected age); postdischarge service (up to 2 years' corrected age).

Secondary outcomes (women): death; cardiac arrest; respiratory arrest; side effects of treatment; respiratory depression; hypotension; warmth over body/flushing; arm discomfort with infusion; mouth dryness; nausea or vomiting; sweating; dizziness; blurred vision; mode of birth: caesarean birth; postpartum haemorrhage.

Follow-up method/s for outcome assessment:

2 years' corrected age: children assessed by paediatrician and assessor trained to administer BSID-III (cognitive, motor and language scales, standardised mean (SD): 100 (15)). Assessment included neurological examination to diagnose cerebral palsy (loss of motor function and abnormalities of muscle tone and power, with gross motor dysfunction classified using the GMFCS), other disability outcomes, assessment of vision (blindness: visual acuity in both eyes worse than 6/60), hearing (deafness: hearing loss sufficient to require hearing aids or cochlear implant), and measurement of height, weight, head circumference (including z-scores for age, height and sex, using UK-WHO growth reference) and blood pressure (including systolic or diastolic blood pressure > 95th percentile using nomograms). Caregivers completed questionnaires about child's health (including respiratory morbidity), use of health services since birth, and behaviour (CBC, higher score indicating more problems). If caregivers were unable to attend assessments/complete questionnaires, they provided information to meet minimum data requirement (cerebral palsy diagnosed: caregiver reported, or unable to walk or sit without assistance, or control head without support). Definitions: any neurosensory disability: any cerebral palsy, blindness, deafness, or cognitive or language score on BSID-III > 1 SD below mean; major neurosensory disability: legal blindness, deafness, moderate or severe cerebral palsy (GMFCS levels II-V), or cognitive or language score > 2 SD below mean; motor delay: BSID-III motor score > 1 SD below the mean; moderate or severe, > 2 SD below mean.

Notes

Funding source: funded by grants from the National Health and Medical Research Council in Australia and the Cerebral Palsy Alliance Research Foundation Australia.

Declarations of interest: none reported.

Analyses: where appropriate, analyses were adjusted for hospital site, gestational age at entry, number of fetuses (and 2-year outcomes, for sex of child, socioeconomic status, and language spoken at

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Crowther 2023 *(Continued)*

home); generalised estimating equations were used (for infant/childhood outcomes) with exchangeable correlations to count for clustering due to twins – adjusted RRs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “The randomization schedule used balanced, variable block sizes and was performed by an investigator not involved in clinical care. There was stratification by hospital site, gestational age (30-31 weeks’ gestation and 32-33 weeks’ gestation), and the number of fetuses (1 or 2).”
Allocation concealment (selection bias)	Low risk	Quote: "using a central telephone randomization service."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “A study number was allocated at randomization that corresponded to a treatment pack containing either magnesium sulfate or placebo (an isotonic sodium chloride solution). Participants, staff, investigators, and assessors of the children were blinded to the treatment allocation.”
Blinding of outcome assessment (detection bias) All outcomes	Low risk	As per blinding of participants and personnel.
Incomplete outcome data (attrition bias) Main trial and initial follow-up	Low risk	Of 1679 fetuses randomised, there were 19 deaths before 2 years. Of 1660 children eligible for 2 year follow-up, 825/846 (98%) in magnesium sulphate group and 789/814 (97%) in placebo group provided follow-up data; 679/846 (80%) and 667/814 (82%) received 2 year paediatric evaluations. Quotes: “Of the infants alive at trial entry, 691 of 858 (80.5%) in the magnesium group and 674 of 821 (82.1%) in the placebo group were included for the primary outcome of death or cerebral palsy (determined by pediatric assessment) at 2 years. The sensitivity analysis, which incorporated data from all sources (pediatrician, psychometrist, caregiver questionnaires, and caregiver), included 823 children (95.9%) in the magnesium group and 785 children (95.6%) in the placebo group” and “the findings were unchanged when inclusion of additional information from parents allowed analysis for 1608 of the 1679 infants (96%) randomized.”
Selective reporting (reporting bias)	Low risk	RCT registration and published protocol available. No indication of selective reporting.
Other bias	Low risk	No indication of other sources of bias.

Marret 2006

Study characteristics

Methods	**Study design:** RCT (multicentre). **Study setting:** France: 18 tertiary hospitals with a NICU. **Study period/dates:** 1997 to 2003 (women enrolled). 2009 to 2012 (school age follow-up). **Registration number:** NCT00120588 (retrospective registration).

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Marret 2006 *(Continued)*

Participants	**Total randomised:** 564 women (9 excluded from 573 randomised at 3 centres including < 5 women), 695 fetuses (688 alive at randomisation). **Inclusion criteria:** women pregnant with singleton, twin, or triplet fetuses < 33 weeks' gestation (no lower limit for gestational age), if birth was expected or planned within 24 h; the women could not have had received betamimetics, aminoglycosides, or steroids for ≥ 1 h. **Exclusion criteria:** fetal severe malformations or chromosomal abnormalities; women with any of: hypotension, cardiac rhythm abnormalities, hydroelectrolyte abnormalities, renal insufficiency, ingestion during the last 24 h of calcium channel blockers, digitalins or indomethacin, persistent signs of cardiovascular toxicity or tachycardia > 1 h after cessation of tocolytic intake, myasthenia, indication for emergency caesarean section, pregnancy-associated vascular disease (e.g. pre-eclampsia, growth restriction, HELLP syndrome; retroplacental haematoma).
Interventions	**Intervention:** magnesium sulphate: 4 g (16 mmol) IV in a single 40 mL infusion (0.1 g/mL) over 30 min. N = 286 women, 354 fetuses (352 alive at randomisation). **Comparison:** placebo: IV single infusion of 40 mL isotonic 0.9% saline infusion over 30 min. N = 278 women, 341 fetuses (336 alive at randomisation).
Outcomes	**Outcomes reported that are considered for this review:** **Primary outcomes (infants/children):** death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age); death (fetal, neonatal, or later (up to school age)); cerebral palsy (school age); death or cerebral palsy (up to school age); major neurodevelopmental disability (school age); death or major neurodevelopmental disability (up to school age). **Primary outcomes (women):** severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest). **Secondary outcomes (infants/children):** fetal death; neonatal death; Apgar score < 7 at 5 min; use of active resuscitation at birth; intraventricular haemorrhage; cystic periventricular leukomalacia; neonatal convulsions; necrotising enterocolitis; respiratory distress syndrome; chronic lung disease/bronchopulmonary dysplasia; use of respiratory support (endotracheal intubation); use of respiratory support (mechanical ventilation or continuous positive airway pressure); early- or late-onset sepsis; later death (up to 2 years' corrected age); cerebral palsy severity (up to 2 years' corrected age)*; death or any neurodevelopmental disability (up to 2 years' corrected age); blindness (up to 2 years' corrected age)*; deafness (up to 2 years' corrected age)*; developmental delay/intellectual impairment (up to 2 years' corrected age); gross motor dysfunction (up to 2 years' corrected age) [substantial*]; death or substantial gross motor dysfunction (up to 2 years' corrected age); later death (school age); cerebral palsy severity (school age); any neurodevelopmental disability (school age); death or any neurodevelopmental disability (school age); blindness (school age); deafness (school age); developmental delay/intellectual impairment (school age); gross motor dysfunction (school age); death or substantial gross motor dysfunction (school age); respiratory function (school age); behaviour (school age); educational achievement (school age); hospital admissions (school age). **Secondary outcomes (women):** death; cardiac arrest; respiratory arrest; side effects of treatment; hypotension; warmth over body/flushing; nausea or vomiting; tendon reflex abolition; "curarisation"; headache; mode of birth: caesarean birth; postpartum haemorrhage. **Follow-up method/s for outcome assessment:** *2 years of age:* paediatricians evaluated motor and cognitive functions using a questionnaire with developmental items extracted from Amiel-Tison and Denver scales, and the European Cerebral Palsy Network definition. If direct examination was not possible, assessment was performed through parent interview. *School age (7 to 14 years):* parents completed a 48-item questionnaire of neuropsychomotor development items, including: "the long-term follow-up etude epidemiologique sur les petits ages gestation-

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Marret 2006 *(Continued)*

	nels questionnaire" and the SDQ. Outcome indicators developed from questionnaires to assess *neuromotor deficits* (severe cerebral palsy (unable to walk, or walking only with aid, or treated with botulinum toxin infusion or tenotomy); mild to moderate cerebral palsy (walks without aid); no cerebral palsy but other motor disorder (co-ordination disorders, difficulties in cycling, drawing, cutting with scissors, playing with construction toys or puzzles, washing him/herself, dressing or tying shoes, receiving psychomotor or ergotherapy sessions); none); *cognitive deficits/learning disabilities* (severe (special school/class); moderate (has repeated a grade and/or receives/needs special support at school, has schooling difficulties, language disorder – treatment by a speech-language pathologist at the time the questionnaire was received); none identified (mainstream class appropriate for age without any special support)); *psychiatric disorders* (severe (autism, pervasive development disorders, treated with risperidone); moderate (hyperactivity or attention deficit disorder or methylphenidate medication or overall SDQ > 17 or SDQ hyperactivity subscale > 7 or conduct disorder as reason for a visit to a psychiatrist or a psychologist at 11 years); none); and *overall deficiencies* (severe (≥ 1 of severe cerebral palsy, other motor disorder, moderate cognitive deficit or moderate psychiatric disorder); moderate (≥ 1 or moderate cerebral palsy, other motor disorder, moderate cognitive deficit or moderate psychiatric disorder); none). *Additional data from trialists (2009 version), not in trial reports.
Notes	**Funding source:** funded by a 3-year grant, "Programme Hospitalier de Recherche Clinique", from the French Department of Health, and a grant from Rouen University Hospital. School age follow-up: funded by the European Regional Development Fund and the Upper-Normandy region. **Declarations of interest:** Main RCT: not reported. School age follow-up: “The authors declare no conflicts of interest.” **Analyses:** Main RCT: where appropriate, analyses were adjusted for clustering within mother, gestational age (< 27, 27 to 29, 29 to 32 weeks), singleton/multiple pregnancy, and birthweight (using residuals of the linear regression of birthweight on gestational age) factors – adjusted ORs reported. School age follow-up: where appropriate, analyses accounted for twins or triplets, and adjusted for stratification variables, gestational age, singleton/multiple pregnancy, socioeconomic variables, sex, and birthweight (using the residual of the linear regression of birthweight on gestational age) – adjusted ORs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: “Randomisation numbers were generated by computer using variable block size from 2 to 16 depending on expected recruitment.”
Allocation concealment (selection bias)	Low risk	Quote: “Central telephone randomisation…Treatment packs were prepared by the coordinating centre’s pharmacy.”
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote (participants): “The two solutions looked identical so that the women were unaware of whether they received a MgSO4 or placebo solution.” Quote (anaesthetists/obstetricians): “Treatment assignment was single blind” to enable immediate treatment of side effects if necessary, and due to characteristic flushes. Judgement: Incomplete blinding; overall, outcomes considered not likely to be influenced by lack of blinding.

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Marret 2006 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main RCT and 2 year follow-up, quotes: "CUS was conducted by a senior neonatologist or radiologist… in a blind manner relative to treatment allocation" and "Pediatricians, who were blinded to treatment, evaluated motor and cognitive functions." School age follow-up: blinding of outcome assessors was not described.
Incomplete outcome data (attrition bias) Main trial and initial follow-up	Low risk	Main RCT and 2 year follow-up, quotes: "Outcome data were obtained until hospital discharge for all 564 women and 688 infants;" and "Of the 616 survivors, 472 (76.6%) were assessed at 2 years through clinical examination, 134 (21.7%) were assessed through parent telephone interview, and 10 (1.6%) were lost to follow-up." CUS not available for 3.3% of infants (deaths); similar number across intervention and control groups.
Incomplete outcome data (attrition bias) School age follow-up	Unclear risk	School age follow-up, quotes: "At school-age, 185 children were lost to follow-up (26.9%);" and "The main characteristics of participants and families lost to follow-up, except for prenatal corticosteroid exposure, were also similar in the two groups". Of 688 infants originally randomised, there were 72 known deaths before 2 years, and 185 lost/declined school age follow-up: data available for 431 children.
Selective reporting (reporting bias)	Unclear risk	Detailed study protocol is not available; insufficient reporting to permit a judgement.
Other bias	Low risk	No indication of other sources of bias; however, authors note some baseline differences, as below: Main RCT, quote: "The only notable difference between the two groups was a slightly higher proportion of women with PPROM in the MgSO4 group (53.9 versus 46.6%)." School age follow-up, quote: "Overall characteristics of children and mothers were broadly similar in the 2 groups; however, the MgSO4 group included more boys and had a lower mean birth weight."

Mittendorf 2002

Study characteristics	
Methods	**Study design:** RCT. **Study setting:** USA (details not provided). **Study period/dates:** 1995 to 1997 (women screened). **Registration number:** not reported.
Participants	**Total randomised:** 57 women, 59 fetuses. **Inclusion criteria:** women in preterm labour at > 24 and < 34 weeks' gestation (with or without PROM), reassuring fetal assessment, and absence of clinical features suggestive of infection or pre-eclampsia. Subgroup included in this review: for cerebral injury 'preventive' treatment group, women deemed 'poor candidates' for tocolysis, due to active labour with cervical dilatation > 4 cm. **Exclusion criteria:** women with triplet or higher-order gestations.

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Mittendorf 2002 *(Continued)*

Interventions	**Intervention:** magnesium sulphate: 4 g IV bolus only, with no further infusion. N = 29 women, 30 infants. **Comparison:** placebo: bolus saline solution. N = 28 women, 29 infants.
Outcomes	**Outcomes reported that are considered for this review:** **Primary outcomes (infants/children):** death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age). **Secondary outcomes (infants/children):** fetal death; neonatal death; intraventricular haemorrhage; any severe intraventricular haemorrhage (grade 3 or 4); cystic periventricular leukomalacia; severe adverse neonatal outcome composite; cerebral palsy severity (up to 2 years' corrected age); death or substantial gross motor dysfunction (up to 2 years' corrected age). **Follow-up method/s for outcome assessment:** *18 months' corrected age:* neurodevelopmental examinations were conducted in specialised clinic visits at 4, 8, 12, and 18 months' corrected age to diagnose cerebral palsy (diagnosis made or verified by developmental paediatrician after last assessment).
Notes	**Funding source:** funding was provided by the United Cerebral Palsy Research and Education Foundation, Washington, DC. **Declarations of interest:** not reported. **Analyses:** no adjusted analyses reported. **Comment(s):** MagNET included 'tandem' RCTs: tocolytic and preventive. Preventive (neuroprotective) arm only included in this review, for which very little information is provided.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "To ensure balance in the randomization process, a computerized program… was used".
Allocation concealment (selection bias)	Unclear risk	Method of allocation concealment was not stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In the doubly masked "preventive" arms…"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The technicians and researchers who processed all biologic specimens were masked to previous and subsequent health outcomes" and "The developmentalist was masked to the antenatal exposure variables." Judgement: Blinding of paediatric radiologists conducting cranial ultrasound was not stated, but likely given that other outcome assessment was blinded.
Incomplete outcome data (attrition bias) Main trial and initial follow-up	Unclear risk	Insufficient reporting of attrition/exclusions to permit a judgement.

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Mittendorf 2002 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Study protocol not available; insufficient reporting to permit a judgement.
Other bias	Unclear risk	Insufficient methodological detail to assess possible other sources of bias.

Rouse 2008

Study characteristics	
Methods	**Study design:** RCT (multicentre). **Study setting:** USA (20 participating Eunice Kennedy Shriver National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network sites). **Study period/dates:** 1997 to 2004 (women enrolled). **Registration number:** NCT00014989 (retrospective registration).
Participants	**Total randomised:** 2241 women, 2444 fetuses. **Inclusion criteria:** women with singletons or twins at 24 to 31.9 weeks' gestation, at high risk for spontaneous birth because of ROM (at 22 to 31 weeks' gestation), or because of advanced preterm labour with dilatation of 4 to 8 cm and intact membranes, or because an indicated preterm birth was anticipated within 2 to 24 h (e.g. because of fetal growth restriction). **Exclusion criteria:** women with birth anticipated within < 2 h, or if cervical dilatation exceeded 8 cm; women with ROM before 22 weeks' gestation; unwillingness of the obstetrician to intervene for fetal benefit; major fetal anomalies or death; maternal hypertension or pre-eclampsia; maternal contraindications to magnesium sulphate (e.g. severe pulmonary disorders); receipt of IV magnesium sulphate within previous 12 h.
Interventions	**Intervention:** magnesium sulphate: 6 g IV loading dose over 20 to 30 min; followed by 2 g/h IV maintenance infusion; if birth had not occurred after 12 h and was no longer considered imminent, the treatment was discontinued and resumed when birth was deemed imminent again; if ≥ 6 h had passed since discontinuation, another loading dose was given. N = 1096 women, 1188 fetuses. **Comparison:** placebo: identical-appearing placebo. N = 1145 women, 1256 fetuses.
Outcomes	**Primary outcomes (infants/children):** death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age); death or major neurodevelopmental disability (up to 2 years' corrected age).* **Primary outcomes (women):** severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest); adverse effects severe enough to stop treatment. **Secondary outcomes (infants/children):** fetal death; neonatal death; birthweight; gestational age at birth (weeks); Apgar score > 7 at 5 min; use of active resuscitation at birth; intraventricular haemorrhage; any severe intraventricular haemorrhage (grade 3 or 4); cystic periventricular leukomalacia; ventriculomegaly**; neonatal convulsions; neonatal hypotonia; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus; respiratory distress syndrome; chronic lung disease/bronchopulmonary dysplasia; use of respiratory support (mechanical ventilation or continuous positive airway pressure); early- or late-onset sepsis; use of inotropic support; later death (up to 2 years' corrected age); cerebral palsy severity (up to 2 years' corrected age); developmental delay/intellectual impairment (up to 2 years' corrected age); psychomotor dysfunction (up to 2 years' corrected age); death or substantial gross motor dysfunction (up to 2 years' corrected age).

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Rouse 2008 *(Continued)*

Secondary outcomes (women): death; cardiac arrest; respiratory arrest; side effects of treatment; respiratory depression; warmth over body/flushing; arm discomfort with infusion; nausea or vomiting; sweating; mode of birth: caesarean birth; chorioamnionitis.

Follow-up method/s for outcome assessment:

2 years' corrected age: certified research nurses scheduled follow-up visits at 6 months', 1 and 2 years' corrected age. Annually certified paediatrician or paediatric neurologist made cerebral palsy diagnosis (2 or more of the 3 features present: 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' corrected age); 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). GMFCS assessed severity (mild: level I; moderate: level II or III; severe: level IV or V). Goal was to make diagnosis on basis of 2-year examination; however, infants with normal examinations at 1 year, who could walk 10 steps independently and had bilateral pincer grasp, were declared free of cerebral palsy, and no further examinations were conducted. For infants not declared free of cerebral palsy at 1 year, and not evaluated at 2 years, the 1-year examination was reviewed by 2 paediatric neurologists to determine diagnosis. The BSID-II was also administered at 2-year examination by a trained psychologist or psychometrist.

*Data taken from secondary analysis (Manuck 2014), which included singleton and twin infants delivered < 34 weeks' gestation alive at initial hospital discharge, with 2-year outcome data (excluding infants with chromosomal abnormalities or major congenital malformation).

**Data taken from secondary analysis (Hirtz 2015), which included infants discharged alive with a term CUS (conducted at 35 weeks' gestation or later) and 2-year cerebral palsy outcome data.

Notes

Funding source: supported by grants from the NICHD and the National Institute of Neurological Disorders and Stroke.

Declarations of interest: "No potential conflict of interest relevant to this article was reported."

Analyses: where appropriate, analyses were adjusted for clustering of neonates within pregnancies – adjusted RRs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Group assignment was made according to a computer-generated random sequence."
Allocation concealment (selection bias)	Low risk	Central (pharmacy) randomisation (confirmed by trialists).
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "In a double-blind fashion" and "identical-appearing placebo".
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessments blinded (confirmed by trialists); quotes: "Double-blind" and "For 28 children who were not evaluated at 2 years' of age but were not declared free of cerebral palsy at the age of 1 year, two pediatric neurologists who were unaware of the treatment"; and "cranial ultrasound examinations were performed on all neonates and were read centrally by three independent pediatric radiologists", and "a single geneticist (without knowledge of study-group assignment) classified anomalies".
Incomplete outcome data (attrition bias)	Low risk	Quote: "The primary outcome was assessed for 95.6% of fetuses. Ninety-five percent of examinations for cerebral palsy were completed by 32 months of corrected age… The baseline characteristics of the women whose fetus-

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Rouse 2008 *(Continued)*

Main trial and initial follow-up		es were lost to follow-up did not differ significantly between the two study groups." Data extracted from secondary analyses (for death or major neurodevelopmental disability (1771/2444, 72%); and ventriculomegaly (1776/2444, 73%)) at unclear risk of attrition bias.
Selective reporting (reporting bias)	Low risk	No clear indication of selective reporting, however RCT registration notes some outcomes not reported in main paper (e.g., days in neonatal intensive care unit and placental abruption). Some non-prespecified analyses conducted but clearly described as such.
Other bias	Low risk	No indication of other sources of bias.

Wolf 2020

Study characteristics	
Methods	**Study design:** RCT (multicentre). **Study setting:** Denmark: 14 sites. **Study period/dates:** 2011 to 2018 (inclusion period). **Registration number:** NCT01492608.
Participants	**Total randomised:** 560 women (680 children). **Inclusion criteria:** women aged 18 years or older, pregnant with singleton or twin pregnancies, at gestational age of 24 + 0 to 31 + 6 weeks, expected to give birth within 2 to 24 h. **Exclusion criteria:** known major fetal anomalies potentially leading to neurological disabilities, maternal contraindications to magnesium sulphate, magnesium sulphate administered for other reasons, inability to read Danish.
Interventions	**Intervention:** magnesium sulphate: 5 g loading dose IV over 20 to 30 min, followed by 1 g/h IV maintenance dose until birth or for 24 h if birth had not occurred. If ≥ 6 hours had passed since discontinuation of treatment, and birth had not occurred, the loading dose was repeated if birth was again imminent < 32 weeks. N = 283 women, 343 infants (2 stillbirths after randomisation). **Comparison:** placebo: an isotonic sodium chloride solution (0.9%) in identical volumes. N = 277 women, 337 infants (1 stillbirth after randomisation).
Outcomes	**Outcomes reported that are considered for this review:** **Primary outcomes (infants/children):** death (fetal, neonatal, or later (up to 2 years' corrected age)); cerebral palsy (up to 2 years' corrected age); death or cerebral palsy (up to 2 years' corrected age). **Secondary outcomes (infants/children):** fetal death; neonatal death; birthweight; Apgar score < 7 at 5 min; use of active resuscitation at birth; intraventricular haemorrhage; any severe intraventricular haemorrhage (grade 3 or 4); cystic periventricular leukomalacia; neonatal convulsions; necrotising enterocolitis; retinopathy of prematurity; patent ductus arteriosus; chronic lung disease/bronchopulmonary dysplasia; use of respiratory support (endotracheal intubation); use of inotropic support; later death (up to 2 years' corrected age); cerebral palsy severity (up to 2 years' corrected age); blindness (up to 2 years' corrected age); deafness (up to 2 years' corrected age); death or substantial gross motor dysfunction (up to 2 years' corrected age).

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Wolf 2020 *(Continued)*

Secondary outcomes (women): mode of birth: caesarean birth.

Follow-up method/s for outcome assessment:

18 months' corrected age minimum: medical records "scrutinised" for diagnosis of cerebral palsy and GMFCS level (moderate to severe cerebral palsy: GMFCS level II-V), and deaths. In Denmark, children born < 32 weeks' gestation offered routine clinical follow-up free of charge by paediatrician (neonatologist experienced in preterm infant follow-up, or paediatric neurologist); children born > 32 weeks' gestation offered routine clinical follow-up free of charge by general practitioners (refer children with suspected neurological disabilities to paediatric department). As "corroboration" for information obtained from medical records, parents asked to complete ASQ (standardised, age-specific, validated) at minimum of 18 months' corrected age (parents who did not reply were sent reminder; if parents still did not reply, information obtained by telephone interview). ASQ was completed first; if suggestive of cerebral palsy, but medical records revealed no cerebral palsy, telephone interview with parents conducted to confirm no cerebral palsy (gross motor skills age-appropriate and child not being seen by physiotherapists or doctors), or explore cerebral palsy diagnosis (child examined by independent neuro-paediatrician for a possible diagnosis).

Notes

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Declarations of interest: "None to declare".

Analyses: where appropriate, analyses were adjusted for plurality and gestational age (< 28 weeks versus ≥ 28 weeks) at randomisation – adjusted ORs reported.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation was performed by a computer-generated random allocation sequence".
Allocation concealment (selection bias)	Low risk	Quote: "The randomisation process was carried out by a third party (DEFACTUM, Central Region Denmark… a web-based programme (Trialpartner) with a centre-specific log-on procedure. A trial number with a corresponding prepacked set of infusion bags produced by the Pharmacy of the Capital Region (Copenhagen, Denmark) was abstracted."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quotes: "The infusion bags containing MgSO4 and placebo were identical in appearance. The participants, caregivers and study coordinators at all sites, as well as the investigators, were blinded to treatment assignment…"; and "For two women, unblinding was performed due to serious side effects (respiratory arrest and hypotension)." Judgement: Unblinding of 2 women unlikely to introduce significant risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "The infusion bags containing MgSO4 and placebo were identical in appearance. The participants, caregivers and study coordinators at all sites, as well as the investigators, were blinded to treatment assignment…"
Incomplete outcome data (attrition bias) Main trial and initial follow-up	Low risk	There were no eligible children excluded from primary or secondary outcomes analysis, but a very small proportion (1.6%) of comparison group had data from medical records only (missing ASQ outcome data).
Selective reporting (reporting bias)	Low risk	Outcomes reported as per pre-specification in protocol and registration. Further secondary outcomes were added quote: "after initiation of the trial, but

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Wolf 2020 *(Continued)*

		prior to unblinding… to be comparable to the outcomes of previous randomised controlled trials".
Other bias	Low risk	No indication of other sources of bias.

Abbreviations: ASQ: Ages and Stages Questionnaire; BRIEF: Behavior Rating Inventory of Executive Function; BSID: Bayley Scales of Infant Development; CADS: Conners ADHD/DSM-IV Scales; CBC: Child Behavior Checklist; CHQ: Child Health Questionnaire; CUS: cranial ultrasound; GMFCS: Gross Motor Function Classification System; HELLP: haemolysis, elevated liver enzymes, low platelet count; IQ: intelligence quotient; IV: intravenous; MABC: Movement Assessment Battery for Children; MD: mean difference; MDI: Mental Developmental Index; NICHD: National Institute of Child Health and Human Development; NICU: neonatal intensive care unit; OR: odds ratio; PDI: Psychomotor Developmental Index; PPROM: preterm prelabour rupture of membranes; PROM: prelabour rupture of membranes; RCT: randomised controlled trial; ROM: rupture of membranes; RR: risk ratio; SD: standard deviation; SDQ: Strengths and Difficulties Questionnaire; TEACh: Test of Everyday Attention for Children; UK-WHO: United Kingdom-World Health Organization; WISC-IV: Wechsler Intelligence Scale for Children - Fourth Edition; WRAT3: Wide Range Achievement Test.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
CTRI/2010/091/000578	Wrong indication: magnesium sulphate prior to birth for women with intrauterine fetal death and prior caesarean section (to determine effects on mode of birth)
Dasgupta 2012	Wrong indication: magnesium sulphate for mild pre-eclampsia or gestational hypertension
Gulczynska 2006	Wrong study design: not an RCT
Magpie 2006	Wrong indication: magnesium sulphate for pre-eclampsia
NCT02591004	Wrong comparator: nifedipine
Sayin 2010	Wrong intervention: magnesium sulphate for tocolysis in preterm labour. Wrong comparator: ritodrine

RCT: randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

Bachnas 2014

Methods	**Study design:** RCT. **Study setting:** Indonesia. **Study period/dates:** 2012 to 2013 (women recruited). **Registration number:** not reported.
Participants	**Total randomised:** 72 women, number of infants not reported. **Inclusion criteria:** Groups I and II (preterm pregnancy): women pregnant ≤ 34 weeks' gestation, in the active phase of labour or planning to have immediate termination of pregnancy for medical reasons; all had received corticosteroids for lung maturation. Group III (control): women pregnant at 37 to 42 weeks' gestation, inactive phase of labour or having a termination of pregnancy for medical reasons. **Exclusion criteria:** Group I and II (preterm pregnancy): unwilling to participate, previous complications using magnesium sulphate, and previous use of magnesium sulphate.

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Bachnas 2014 *(Continued)*

	Note: there was also Group III (control): full-term pregnancy.
Interventions	**Intervention:** Group 1 (preterm pregnancy with magnesium sulphate): IV magnesium sulphate; initial dose 4 g, maintained at 1 g/h up to maximum of 24 h. N = 24 women. **Comparison:** Group 2 (preterm pregnancy without magnesium sulphate): "not given any special treatment." N = 24 women.
Outcomes	**Outcomes reported that are relevant to this review:** birthweight. Other: cord blood BDNF levels (blood samples of newborns taken from umbilical cord (± 5 mL) shortly after birth).
Notes	**Funding source:** not reported. **Declarations of interest:** "The authors stated that there are no conflicts of interest regarding the publication of this article". **Comment(s):** we emailed the authors in April 2023 to request information regarding protocol, trial registration, ethical approval, the randomisation process, and the outcome data reported. Awaiting reply. **Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Gupta 2021

Methods	**Study design:** RCT. **Study setting:** India. **Study period/dates:** 2018 to 2020. **Registration number:** not reported.
Participants	**Total randomised:** 100 women, 100 infants. **Inclusion criteria:** women pregnant with single or multiple pregnancy, < 37 weeks' (28 to 36 weeks 6 days) gestational age, in labour, with the birth planned or expected within 24 h. **Exclusion criteria:** women in second stage of labour or when delivery was imminent (within 2 h); women who received magnesium sulphate therapy in pregnancy for other reasons; if there was a contraindication to magnesium sulphate (respiratory rate < 100 mL during the previous 4 h, any sign of renal failure or hypocalcaemia, absent patellar reflex); women with ≥ 1 of hypotension, cardiac rhythm abnormalities, electrolyte abnormalities, ingestion of calcium channel blockers, indomethacin or digitalis in the last 24 h, myasthenia gravis, or indication for emergency caesarean section; women with growth restriction, HELLP syndrome, and retroplacental haematoma; severe fetal malformation or chromosomal abnormalities; intrauterine fetal demise.
Interventions	**Intervention:** magnesium sulphate: 4 g bolus dose of magnesium sulphate over 20 to 30 min followed by 1 g/h (discontinued if not delivered by 12 h). N = 50 women. **Comparison:** no magnesium sulphate; no details provided.

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Gupta 2021 *(Continued)*

	N = 50 women.
Outcomes	**Outcomes reported that are relevant to this review:** primary and secondary outcomes were not clearly specified. However, the study described: gestational age, maternal side effects (flushing, nausea, sweating, hypotension, tachycardia, postpartum haemorrhage), birthweight, Apgar score at 1 and 5 min, neonatal seizures, respiratory distress, mechanical ventilation, neonatal enterocolitis, intensive resuscitation, intrauterine growth restriction, neonatal mortality, NICU admission, intraventricular haemorrhage, periventricular leukomalacia, mild, moderate, or severe cerebral palsy, and mode of delivery (caesarean or vaginal).
Notes	**Funding source:** nil. **Declarations of interest:** "Conflict of interest: None". **Comment(s):** we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the randomisation process, baseline characteristics, and the outcome data reported. Awaiting reply. **Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Manoj 2017

Methods	**Study design:** RCT. **Study setting:** India. **Study period/dates:** 2014 to 2015. **Registration number:** not reported.
Participants	**Total randomised:** 126 women (134 neonates; however, only 118 included). **Inclusion criteria:** women pregnant with singleton, twin, or triplet fetuses, between 24 and 34 weeks' gestation, if birth was expected or planned within 24 h. **Exclusion criteria:** fetuses with severe malformations or chromosomal abnormalities, maternal hypotension, cardiac rhythm or electrolyte abnormalities, renal or hepatic insufficiency, maternal contraindications to magnesium sulphate, unwillingness of the obstetrician to intervene for fetal benefit, and receipt of magnesium sulphate within the previous 12 h.
Interventions	**Intervention:** magnesium sulphate: IV magnesium sulphate (a 4 g bolus followed by a constant infusion of 1 g/h for 24 h or until birth, whichever came first). N = women (not reported); N = 58 neonates. **Comparison:** matching placebo (normal saline). N = women (not reported); N = 60 neonates.
Outcomes	**Outcomes reported that are relevant to this review:** primary outcome: composite of death and intraventricular haemorrhage by CUS in surviving preterm infants. Secondary outcomes: resuscitation at birth, respiratory distress syndrome, surfactant administration, type and duration of ventilator support, hypoxic ischaemic encephalopathy, apnoea of prematurity, sepsis, anaemia requiring transfusion, necrotising enterocolitis, and patent ductus arteriosus. Maternal adverse effects also reported.
Notes	**Funding source:** none.

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Manoj 2017 *(Continued)*

	Declarations of interest: "Conflict of interest: None stated".
	Comment(s): we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the randomisation process, baseline characteristics, and outcome data. Awaiting reply.
	Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).

Muhammed 2019

Methods	**Study design:** RCT.
	Study setting: Iraq.
	Study period/dates: 2018 to 2019 (women recruited).
	Registration number: not reported.
Participants	**Total randomised:** 60 women.
	Inclusion criteria: pregnant women, 28 to 34 weeks gestation.
	Exclusion criteria: not reported.
Interventions	**Intervention:** magnesium sulphate: 4 g in 200 cm^3 normal saline over 20 min as a bolus dose, then 1 g/h as a maintenance dose (max 12 g).
	N = 28 women (N for neonates not reported).
	Comparison: "normal saline".
	N = 32 women (N for neonates not reported).
Outcomes	**Outcomes reported that are relevant to this review:** primary and secondary outcomes not specified.
	Outcomes described in methods: Apgar score at 1 and 5 min; NICU admission and length of admission; CUS at 1 week of age; neurological assessment at 28 days (including abnormal signs like hypotonia, abnormal tone, abnormal reflexes and state of consciousness). Mortality described.
Notes	**Funding source:** not reported.
	Declarations of interest: not reported.
	Comment(s): we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the randomisation process, baseline characteristics, and outcome data. Awaiting reply.
	Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).

Parashi 2017

Methods	**Study design:** RCT/clinical trial
	Study setting: Iran.

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Parashi 2017 *(Continued)*

	Study period/dates: not reported in paper; registration states date of first enrolment 2015-06-01. **Registration number:** IRCT2016080729223N1 (not prospectively registered).
Participants	**Total randomised:** 120 women; 120 neonates. **Inclusion criteria:** pregnant women with PROM “at 34 weeks gestation” (unclear whether women were less than or greater than). **Exclusion criteria:** lack of hypertension, pre-eclampsia, trauma, gestational or aggravated diabetes, any type of metabolic disease affecting the pregnancy outcome, long-term drug use, and gestational histories affecting the pregnancy outcomes.
Interventions	**Intervention:** magnesium sulphate: 6 g IV magnesium sulphate over 20 to 30 min, followed by 2 g/h during 12 h before labour. N = 60 women (60 neonates). **Comparison:** conventional treatment with normal saline infusion. N = 60 women (60 neonates).
Outcomes	**Outcomes reported that are relevant to this review:** primary (main) outcome: intraventricular haemorrhage (grade I-IV) (CUS day 3 or day 7, and MRI in "suspected cases"). Also reported various laboratory results.
Notes	**Funding source:** not reported. **Declarations of interest:** not reported. **Comment(s):** we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the randomisation process, inclusion criteria, and baseline characteristics. Awaiting reply. **Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Petrov 2013

Methods	**Study design:** unclear if RCT ("divided into 2 groups"). **Study setting:** unclear (assumed to be Moldova based on author affiliation). **Study period/dates:** not reported. **Registration number:** not reported.
Participants	**Total randomised:** 140 women. **Inclusion criteria:** pregnant women with "monofetal pregnancy" from 26 to 33 + 6 weeks' gestation, who delivered until "term of 34 weeks of gestation". **Exclusion criteria:** not reported.
Interventions	**Intervention:** magnesium sulphate: "neuroprotective theraphy with MgSO4(sol. MgSO4 25% - 20.0ml + sol. NaCl 0.9% -20.0 ml in bolus time of 15 min (slowly, i/v), with continuing perfusion sol. MgSO4 25% - 20.0ml + sol. NaCl 0.9% -200.0 ml (1g/h)." N = 80 women. **Comparison:** "the same scheme we perfused NaCl as placebo."

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Petrov 2013 *(Continued)*

	N = 60 women.
Outcomes	**Outcomes reported that are relevant to this review:** maternal and newborn complications (hypotensive effects – blood pressure and pulse; postpartum haemorrhage); early central nervous system complications (intraventricular haemorrhage, seizures); neurological complications after 1-year follow-up.
Notes	**Funding source:** not reported. **Declarations of interest:** not reported. **Comment(s):** information extraction from 2 published conference abstracts only. We emailed the authors in April 2023 to request information regarding methodology to confirm eligibility. Awaiting reply. **Not included in 2023 update because of lack of response from authors to determine eligibility, and regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Sharma 2021

Methods	**Study design:** RCT. **Study setting:** India. **Study period/dates:** 2019 to 2020 (women recruited). **Registration number:** not reported.
Participants	**Total randomised:** 600 women. **Inclusion criteria:** women pregnant with single or twin fetuses < 32 weeks' gestational age in preterm labour; consented to participate. **Exclusion criteria:** gestational age > 32 weeks; second stage of labour; history of receiving magnesium sulphate in this pregnancy; contraindications to magnesium sulphate (respiratory rate < 16/min; absent patellar reflex; urine output < 100 mL in previous 4 h; renal failure; hypocalcaemia).
Interventions	**Intervention:** magnesium sulphate: loading infusion of 8 mL (4 g) [16 mmol] for 20 min followed by a maintenance infusion of 2 mL/h until birth (if occurred within 24 h) or up to 24 h. N = 300 women allocated; 294 received treatment (N for neonates unclear). **Comparison:** infusion of 8 mL of sodium chloride solution for 20 min followed by maintenance infusion of 2 mL/h until birth (if occurred within 24 h) or up to 24 h. N = 300 women allocated; 292 received treatment (N for neonates unclear).
Outcomes	**Outcomes reported that are relevant to this review:** birth characteristics and neonatal morbidities described: gestational age, birthweight, head circumference, NICU admission, neurological disabilities, Apgar at 5 min < 7, intubation, external cardiac massage, epinephrine, mortality, necrotising enterocolitis, intraventricular haemorrhage, fetal infection. Maternal complications due to intervention: headache, hypotension, nausea and vomiting, flushing and sweating, respiratory depression, hyporeflexia, palpitation, postpartum haemorrhage.
Notes	**Funding source:** not reported. **Declarations of interest:** not reported.

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Sharma 2021 *(Continued)*

	Comment(s): we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the recruitment and randomisation process, and outcome data reported. Awaiting reply. **Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Sheeba 2022

Methods	**Study design:** RCT. **Study setting:** India. **Study period/dates:** 2015 to 2016. **Registration number:** not reported.
Participants	**Total randomised:** 83 women (somewhat unclear). **Inclusion criteria:** expectant mothers, gestational ages 24 to 34 weeks, if birth was expected within 24 h. **Exclusion criteria:** fetuses with severe malformations such as neural tube defects, and chromosomal abnormalities like trisomies; cases of maternal hypotension, renal insufficiency, hepatic insufficiency, and cardiac rhythm or electrolyte abnormalities.
Interventions	**Intervention:** magnesium sulphate: 4 g IV bolus initially, then infusion of 1 g/h for 24 h or until birth, whichever came first. N = 45 neonates; 43 analysed. **Comparison:** placebo infusion of normal saline. N = 45 women; 40 analysed.
Outcomes	**Outcomes reported that are relevant to this review:** birthweight; gestational age; neonatal sepsis; neonatal deaths; Amiel-Tison angles; Trivandrum Development Screening Chart.
Notes	**Funding source:** not reported. **Declarations of interest:** "Financial or other competing interests: None". **Comment(s):** we emailed the authors in April 2023 to request information regarding protocol, registration, ethical approval, the randomisation process, baseline characteristics, and outcome data reported. Awaiting reply. **Not included in 2023 update because of lack of response from authors regarding our trustworthiness criteria (published since 2010 without prospective registration).**

Abbreviations: BDNF: brain-derived neurotrophic factor; CUS: cranial ultrasound; HELLP: haemolysis, elevated liver enzymes, low platelet count; IV(i/v): intravenous; MgSO4: magnesium sulphate; MRI: magnetic resonance imaging; NaCl: sodium chloride; NICU: neonatal intensive care unit; PROM: prelabour rupture of membranes; RCT: randomised controlled trial; sol: solution.

Characteristics of ongoing studies *[ordered by study ID]*

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CTRI/2018/06/014386

Study name	Antenatal magnesium sulphate for neuroprotection in preterm infants: An open label randomized control trial
Methods	**Study design:** RCT. **Study setting:** India. **Registration number:** CTRI/2018/06/014386.
Participants	**Total to be randomised:** 30 women. **Inclusion criteria:** women aged 19 to 35 years, pregnant with singleton or multiple pregnancy at ≤ 32 weeks' gestation, at risk of delivery within next 24 h; active preterm labour with cervix 4 to 8 cm dilated, or PPROM, or indicated preterm birth within next 24 h. **Exclusion criteria:** maternal contraindications to receiving magnesium sulphate including renal failure, cardiac arrythmia, myasthenia gravis, hypersensitive to drug, heart block, diabetic coma, electrolyte disorder; pre-eclampsia or eclampsia; fetal distress, abruptio placenta, severe antepartum haemorrhage where urgent delivery is indicated; precipitate labour; chorioamnionitis; major fetal abnormalities; intrauterine fetal death.
Interventions	**Intervention:** magnesium sulphate: bolus of 4 g (8 mL) (50% w/v) in 12 mL normal saline IV over 20 min followed by 1 g/h until birth or up to 12 h, whichever is earlier, plus standard care as per antenatal and neonatal protocol of the unit. **Comparison:** standard care currently as per protocol of the unit.
Outcomes	**Outcomes prespecified that are relevant to this review:** primary outcome: mortality or abnormal neurodevelopmental outcome at 6 months' corrected age as determined by DASII. Secondary outcomes: neurodevelopmental outcome as determined by DASII (6 months); maternal adverse events following magnesium sulphate infusion (until maternal discharge); neonatal mortality (after birth).
Starting date	Planned date of first enrolment 04/06/2018 (however recruitment status: "not yet recruiting").
Contact information	Geeta Gathwala, Senior Professor and Head Department of Pediatrics, PGIMS, Rohtak 124001 Panipat, Haryana India 9896489650 geetagathwala@gmail.com
Notes	

IRCT20120826010664N5

Study name	Evaluation of neuroprotective effects of magnesium sulfate on preterm infants with a gestational age of 32-36 weeks
Methods	**Study design:** RCT. **Study setting:** Iran.

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IRCT20120826010664N5 *(Continued)*

	Registration number: IRCT20120826010664N5.
Participants	**Total to be randomised:** 246 women. **Inclusion criteria:** women aged 15 to 45 years pregnant with single fetus, 32 to 36 weeks' gestation, spontaneous labour. **Exclusion criteria:** maternal underlying diseases; fetal abnormalities; intrauterine growth retardation; contraindications for use of magnesium sulphate; iatrogenic preterm birth.
Interventions	**Intervention:** magnesium sulphate: IV infusion 50% diluted in Ringer's lactate serum, 2 g/h for 12 h. **Comparison:** no intervention (routine care including fetal heart rate monitoring and control of labour progress).
Outcomes	**Outcomes prespecified that are relevant to this review:** primary outcomes: neurodevelopmental status of infants (including Apgar score, arterial blood pH after birth, and neurodevelopment status after the age of 4 months) (0, 4, 6, 8, 10, and 12 months after birth) (ASQ). Secondary outcomes: not reported.
Starting date	Expected: 22 December 2019.
Contact information	A/Prof Reihaneh Pirjani Tehran University of Medical Sciences Eastern 162th St, Baghdarnia st, Resalat Highway, Tehranpars Tehran Iran +98 21 7788 3288 pirjani@razi.tums.ac.ir
Notes	

NCT02506894

Study name	Fetal middle cerebral artery doppler in preterm births receiving magnesium sulfate for neuroprotection
Methods	**Study design:** RCT. **Study setting:** Egypt. **Registration number:** NCT02506894.
Participants	**Total to be randomised:** 60 women. **Inclusion criteria:** women pregnant with a single fetus < 32 weeks' gestation. **Exclusion criteria:** contraindication or hypersensitivity to magnesium, pre-eclampsia, multiple pregnancy, prior intake of magnesium sulphate in this pregnancy.
Interventions	**Intervention:** magnesium sulphate: 6 g in 500 cm^3 of Ringer's solution over 20 min, then maintenance dose of 1 g/h for 24 h.

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NCT02506894 *(Continued)*	
	Comparison: placebo: IV sodium chloride 0.9% solution over 24 h.
Outcomes	**Outcomes prespecified that are relevant to this review:** primary outcome: changes in fetal middle cerebral artery doppler indices (time frame: 3 months). Secondary outcome: maternal adverse effects of magnesium sulphate (time frame: 3 months).
Starting date	July 2015.
Contact information	A/Prof Ghada Abdel Fattah Abdel Moety Cairo University, Egypt Contact details not provided.
Notes	Recruitment status: completed.

NCT05674565	
Study name	The neuroprotective impact of magnesium sulphate therapy for preterm deliveries. Loading dose alone strategy versus loading plus maintenance dose strategy
Methods	**Study design:** RCT. **Study setting:** Egypt. **Registration number:** NCT05674565.
Participants	**Total to be randomised:** 336 women. **Inclusion criteria:** women at 24 + 0 to 33 + 6 weeks of gestation, at risk of preterm birth (planned or expected within 24 h), regardless of plurality or parity, reason for the risks of preterm birth, anticipated mode of birth, or whether antenatal corticosteroids have been given or not. **Exclusion criteria:** women with known hypersensitivity to magnesium, caution regarding dosage for patients with renal impairment, preterm delivery after 34 weeks.
Interventions	**Intervention:** magnesium sulphate loading dose only: 4 g infusion over 20 min within 1 h of delivery. Magnesium sulphate loading with maintenance dose: 4 g infusion over 20 min followed by 1 g/h maintenance until delivery. **Comparison:** control (no magnesium sulphate).
Outcomes	**Outcomes prespecified that are relevant to this review:** primary outcomes: neonatal neurological insult (at 18 months) including cerebral palsy, brain leukomalacia, intraventricular haemorrhage, and neonatal seizures. Maternal magnesium sulphate toxicity (until 12 h after end of therapy) (affected reflexes, respiratory and cardiac, postpartum haemorrhage). Primary postpartum haemorrhage (first 24 h after delivery). Secondary outcomes: late-appearing neurologic insults (at 24 months): gross motor delay, epilepsy, impaired fine motor skills, sensorineural (hearing and vision) impairment, *possibly 2 years of age developmental quotient;* neonatal death.
Starting date	20 January 2023.
Contact information	Study Chair: Hytham Atia MD

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NCT05674565 *(Continued)*	Faculty of Medicine, Zagazig University Zagazig, Sharkia, Egypt 44519 +9660538308500 hythamatia@gmail.com Principal Investigator: Amro Alnemr MD +201224581528 amrabmohsen@yahoo.com
Notes	

Abbreviations: ASQ: Ages & Stages Questionnaires; DASII: Developmental Assessment Scale for Indian Infants; RCT: randomised controlled trial; IV: intravenous; pH: potential of hydrogen; PPROM: preterm prelabour rupture of membranes; w/v: weight/volume.

DATA AND ANALYSES

Comparison 1. Magnesium sulphate versus placebo: primary outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6	6759	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
1.2 Cerebral palsy (up to 2 years' corrected age)	6	6107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.57, 0.89]
1.3 Death or cerebral palsy (up to 2 years' corrected age)	6	6481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
1.4 Major neurodevelopmental disability (up to 2 years' corrected age)	1	987	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.83, 1.44]
1.5 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3	4279	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
1.6 Death (fetal, neonatal, or later (up to school age))	2	1758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
1.7 Cerebral palsy (school age)	2	1038	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.41]
1.8 Death or cerebral palsy (up to school age)	1	503	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.67, 1.20]
1.9 Major neurodevelopmental disability (school age)	2	940	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.62]
1.10 Death or major neurodevelopmental disability (up to school age)	1	503	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.59, 1.12]

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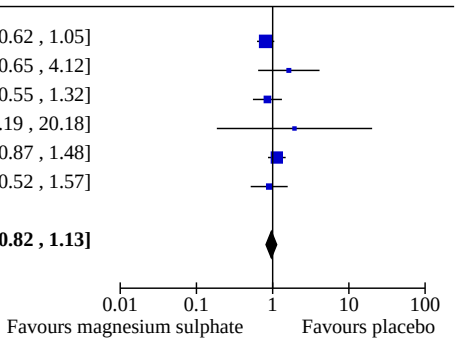
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
1.12 Adverse effects severe enough to stop treatment	3	4736	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.88, 5.48]

Analysis 1.1. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	87	629	107	626	39.5%	0.81 [0.62 , 1.05]
Crowther 2023 (2)	12	837	7	796	2.6%	1.63 [0.65 , 4.12]
Marret 2006 (3)	34	352	38	336	14.3%	0.85 [0.55 , 1.32]
Mittendorf 2002 (4)	2	30	1	29	0.4%	1.93 [0.19 , 20.18]
Rouse 2008 (5)	103	1188	96	1256	34.3%	1.13 [0.87 , 1.48]
Wolf 2020 (4)	22	343	24	337	8.9%	0.90 [0.52 , 1.57]
Total (95% CI)		**3379**		**3380**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	260		273			

Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are total randomised; 2 years' corrected age
(2) Denominators are total randomised, minus children unable to contact/lost; 2 years' corrected age
(3) Denominators are total randomised; 2 years
(4) Denominators are total randomised; 18 months' corrected age
(5) Denominators are total randomised; 1 year corrected age

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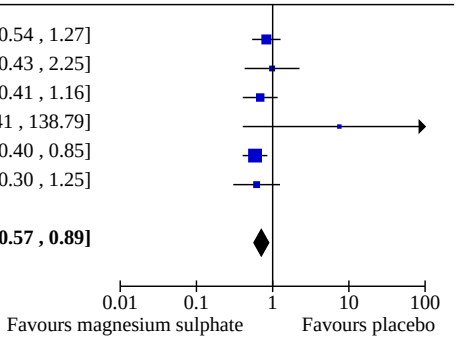
Analysis 1.2. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	36	533	42	514	24.2%	0.83 [0.54 , 1.27]
Crowther 2023 (2)	11	679	11	667	6.3%	0.98 [0.43 , 2.25]
Marret 2006 (3)	22	313	30	293	17.6%	0.69 [0.41 , 1.16]
Mittendorf 2002 (4)	3	27	0	29	0.3%	7.50 [0.41 , 138.79]
Rouse 2008 (5)	41	1174	74	1244	40.7%	0.59 [0.40 , 0.85]
Wolf 2020 (6)	12	321	19	313	10.9%	0.62 [0.30 , 1.25]
Total (95% CI)		**3047**		**3060**	**100.0%**	**0.71 [0.57 , 0.89]**
Total events:	125		176			



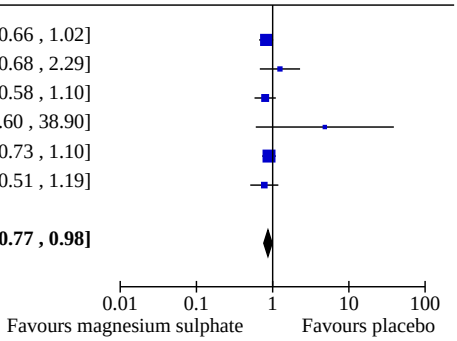
Heterogeneity: Chi² = 4.75, df = 5 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.02 (P = 0.003)
Test for subgroup differences: Not applicable

Footnotes

(1) Denominators are surviving children with data; 2 years' corrected age; criteria included abnormalities of tone and loss of motor function
(2) Denominators are surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnormalities of
(3) Denominators are livebirths with data; 2 years
(4) Denominators are livebirths; 18 months' corrected age
(5) Denominators are livebirths; 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) delay of 30% or more in gross motor develo
(6) Denominators are surviving children at 18 months' corrected age or older

Analysis 1.3. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	123	629	149	626	33.5%	0.82 [0.66 , 1.02]
Crowther 2023 (2)	23	691	18	674	4.1%	1.25 [0.68 , 2.29]
Marret 2006 (3)	56	347	67	331	15.4%	0.80 [0.58 , 1.10]
Mittendorf 2002 (4)	5	30	1	29	0.2%	4.83 [0.60 , 38.90]
Rouse 2008 (5)	144	1188	170	1256	37.1%	0.90 [0.73 , 1.10]
Wolf 2020 (6)	34	343	43	337	9.7%	0.78 [0.51 , 1.19]
Total (95% CI)		**3228**		**3253**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	385		448			



Heterogeneity: Chi² = 4.84, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)
Test for subgroup differences: Not applicable

Footnotes

(1) Denominators are total randomised; 2 years' corrected age; cerebral palsy: criteria included abnormalities of tone and loss of motor function
(2) Denominators are deaths and surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnor
(3) Denominators are deaths and livebirths with data; 2 years
(4) Denominators are total randomised; 18 months' corrected age
(5) Denominators are total randomised; death by 1 year, cerebral palsy at 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) de
(6) Denominators are total randomised; 18 months' corrected age (death) or later (cerebral palsy)

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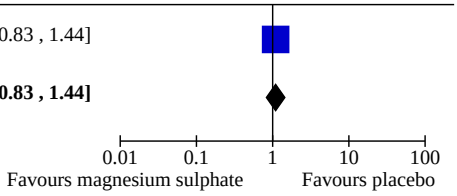
Analysis 1.4. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 4: Major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	89	504	78	483	100.0%	1.09 [0.83 , 1.44]
Total (95% CI)		**504**		**483**	**100.0%**	**1.09 [0.83 , 1.44]**
Total events:	89		78			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.63 (P = 0.53)
Test for subgroup differences: Not applicable



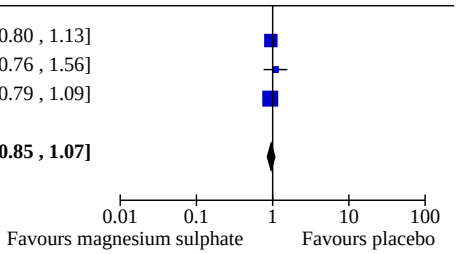
Footnotes

(1) Denominators are children with 2 year assessments; severe neurosensory disability: severe cerebral palsy (permanently non-ambulant), severe developm

Analysis 1.5. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 5: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	176	629	185	626	39.0%	0.95 [0.80 , 1.13]
Crowther 2023 (2)	57	629	52	624	11.0%	1.09 [0.76 , 1.56]
Rouse 2008 (3)	213	854	246	917	50.0%	0.93 [0.79 , 1.09]
Total (95% CI)		**2112**		**2167**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	446		483			

Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)
Test for subgroup differences: Not applicable



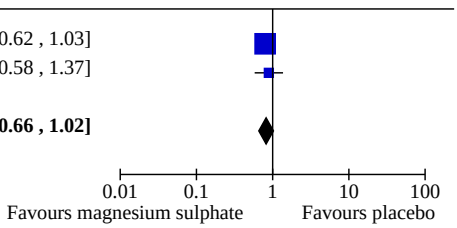
Footnotes

(1) Denominators are total randomised; severe neurosensory disability: severe cerebral palsy (permanently non-ambulant), severe developmental delay (ME
(2) Denominators are deaths and livebirths with paediatric assessments; major neurosensory disability: any of: blindness (corrected visual acuity worse than
(3) *From secondary analysis; denominators are infants born < 34 weeks' gestation, alive at initial hospital discharge, with 2 year outcome data; defined as

Analysis 1.6. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 6: Death (fetal, neonatal, or later (up to school age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	88	629	110	626	74.3%	0.80 [0.62 , 1.03]
Marret 2006 (2)	34	252	38	251	25.7%	0.89 [0.58 , 1.37]
Total (95% CI)		**881**		**877**	**100.0%**	**0.82 [0.66 , 1.02]**
Total events:	122		148			

Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.76 (P = 0.08)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are total randomised
(2) Denominators are those with 7-14 year outcomes, including deaths

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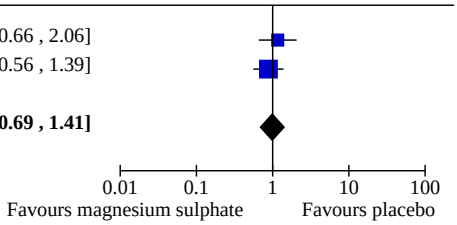
Analysis 1.7. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 7: Cerebral palsy (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	23	295	21	314	37.8%	1.17 [0.66 , 2.06]
Marret 2006 (2)	30	218	33	211	62.2%	0.88 [0.56 , 1.39]
Total (95% CI)		**513**		**525**	**100.0%**	**0.99 [0.69 , 1.41]**
Total events:	53		54			

Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)
Test for subgroup differences: Not applicable



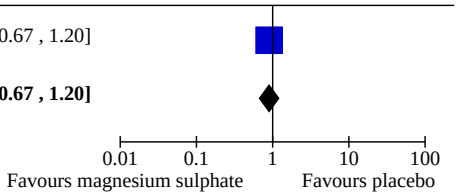
Footnotes

(1) Denominators are children with 6-11 year follow up data; cerebral palsy: nonprogressive loss of motor function with disordered tone or tendon reflexes
(2) Denominators are children with 7-14 year follow up data

Analysis 1.8. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 8: Death or cerebral palsy (up to school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	64	252	71	251	100.0%	0.90 [0.67 , 1.20]
Total (95% CI)		**252**		**251**	**100.0%**	**0.90 [0.67 , 1.20]**
Total events:	64		71			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.73 (P = 0.46)
Test for subgroup differences: Not applicable



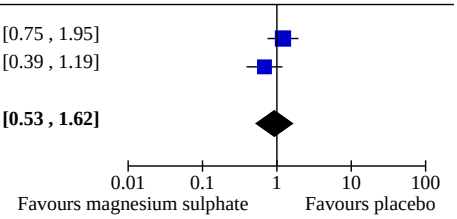
Footnotes

(1) Denominators are deaths and children with 7-14 year follow up data

Analysis 1.9. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 9: Major neurodevelopmental disability (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	33	257	27	254	53.2%	1.21 [0.75 , 1.95]
Marret 2006 (2)	19	218	27	211	46.8%	0.68 [0.39 , 1.19]
Total (95% CI)		**475**		**465**	**100.0%**	**0.92 [0.53 , 1.62]**
Total events:	52		54			

Heterogeneity: Tau² = 0.09; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are children with 6-11 year follow up data; severe disability comprised any of severe cerebral palsy, an IQ less than 55, or blindness and mode
(2) Denominators are children with 7-14 year follow up data; severe overall deficits at school age: at least 1 of severe cerebral palsy, severe cognitive deficit/lea

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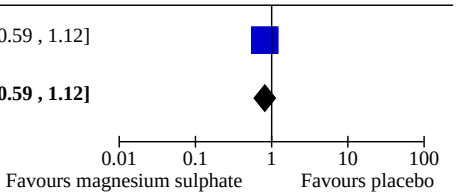
Analysis 1.10. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 10: Death or major neurodevelopmental disability (up to school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	53	252	65	251	100.0%	0.81 [0.59 , 1.12]
Total (95% CI)		**252**		**251**	**100.0%**	**0.81 [0.59 , 1.12]**
Total events:	53		65			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.28 (P = 0.20)
Test for subgroup differences: Not applicable



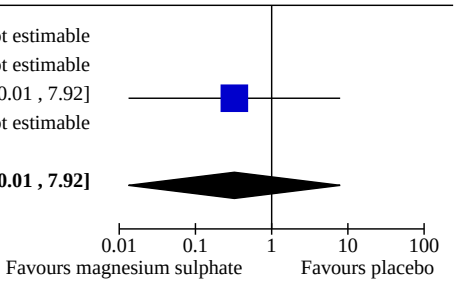
Footnotes

(1) Denominators are deaths and children with 7-14 year follow up data; severe overeall deficits: at least 1 of severe cerebral palsy, severe cognitive deficit/l

Analysis 1.11. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 11: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (2)	0	729	0	704		Not estimable
Marret 2006 (3)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Rouse 2008 (4)	0	1096	0	1145		Not estimable
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, respiratory arrest)
(2) Denominators are total randomised; serious adverse outcomes (maternal death, cardiac or respiratory arrest)
(3) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, prolonged mechanical ventilation)
(4) Denominators are total randomised; death or "lifethreatening events"

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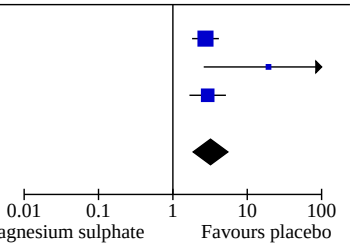
Analysis 1.12. Comparison 1: Magnesium sulphate versus placebo: primary outcomes, Outcome 12: Adverse effects severe enough to stop treatment

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	78	535	28	527	52.2%	2.74 [1.81 , 4.15]
Crowther 2023 (2)	20	729	1	704	6.5%	19.31 [2.60 , 143.53]
Rouse 2008 (3)	45	1096	16	1145	41.2%	2.94 [1.67 , 5.17]
Total (95% CI)		**2360**		**2376**	**100.0%**	**3.21 [1.88 , 5.48]**
Total events:	143		45			

Heterogeneity: Tau² = 0.10; Chi² = 3.68, df = 2 (P = 0.16); I² = 46%
Test for overall effect: Z = 4.26 (P < 0.0001)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are total randomised; infusion stopped due to adverse effects
(2) Denominators are total randomised; infusion discontinued for side effects
(3) Denominators are total randomised; infusion stopped because of adverse event

Comparison 2. Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Fetal death	6	6805	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.46, 1.52]
2.2 Neonatal death	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.2.1 Variously defined	6	6751	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.17]
2.2.2 Defined, where possible, as up to hospital discharge	6	6751	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.80, 1.15]
2.3 Birthweight	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.3.1 Birthweight (grams)	4	6009	Mean Difference (IV, Fixed, 95% CI)	5.63 [-18.85, 30.12]
2.3.2 Birthweight (z-scores)	1	1679	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.08, 0.14]
2.4 Length at birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.4.1 Length (cm)	1	1559	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.04, 0.64]
2.4.2 Length (z-scores)	1	1559	Mean Difference (IV, Fixed, 95% CI)	0.06 [-0.05, 0.17]
2.5 Head circumference at birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5.1 Head circumference (cm)	1	1642	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.10, 0.30]
2.5.2 Head circumference (z-scores)	1	1642	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.12, 0.10]
2.6 Gestational age at birth (weeks)	2	4123	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.02, 0.22]
2.7 Apgar score less than 7 at 5 minutes	4	5006	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.89, 1.16]
2.8 Use of active resuscitation at birth	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.8.1 Any	3	3776	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.96, 1.03]
2.8.2 Supplementary oxygen	2	3093	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.96, 1.10]
2.8.3 Intubation	2	3093	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.98]
2.8.4 Chest compressions	2	3093	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.78, 1.75]
2.9 Intraventricular haemorrhage	6	6550	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.85, 1.04]
2.10 Severe intraventricular haemorrhage (grade 3 or 4)	5	5885	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.98]
2.11 Cystic periventricular leukomalacia	6	6550	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.17]
2.12 Ventriculomegaly	1	1776	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.53, 1.46]
2.13 Neonatal encephalopathy	1	1679	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.06, 15.27]
2.14 Neonatal convulsions	5	6689	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.20]
2.15 Neonatal hypotonia	1	2415	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.77, 1.37]
2.16 Necrotising enterocolitis	5	6689	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.98, 1.50]
2.17 Retinopathy of prematurity	3	3639	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.13]
2.18 Patent ductus arteriosus	3	4771	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.73, 1.06]
2.19 Respiratory distress syndrome	3	4777	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.83, 1.08]
2.20 Chronic lung disease/bronchopulmonary dysplasia	5	6689	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.10]
2.21 Use of respiratory support (endotracheal intubation)	2	1360	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.58, 1.28]

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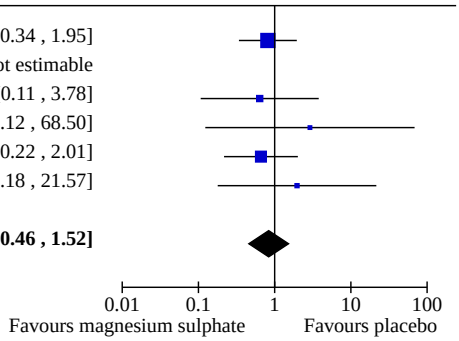
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.22 Use of respiratory support (mechanical ventilation or continuous positive airway pressure)	4	6012	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.91, 1.05]
2.23 Use of inotropic support	2	3092	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.50, 1.29]
2.24 Air leak syndrome	1	1679	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.23, 1.30]
2.25 Early- or late-onset sepsis	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.25.1 Maternal-fetal infection	1	683	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.09, 2.14]
2.25.2 Sepsis	1	2415	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.15]
2.25.3 Early onset sepsis	1	1679	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.29, 5.68]
2.25.4 Late onset sepsis	1	1679	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.18]
2.26 Severe adverse neonatal outcome composite	2	863	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.72, 1.19]

Analysis 2.1. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 1: Fetal death

Study or Subgroup	Magnesium sulphate Events	Magnesium sulphate Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	9	629	11	626	47.1%	0.81 [0.34 , 1.95]
Crowther 2023 (1)	0	858	0	821		Not estimable
Marret 2006 (1)	2	352	3	336	13.1%	0.64 [0.11 , 3.78]
Mittendorf 2002 (1)	1	30	0	29	2.2%	2.90 [0.12 , 68.50]
Rouse 2008 (1)	5	1188	8	1256	33.3%	0.66 [0.22 , 2.01]
Wolf 2020 (1)	2	343	1	337	4.3%	1.97 [0.18 , 21.57]
Total (95% CI)		**3400**		**3405**	**100.0%**	**0.83 [0.46 , 1.52]**
Total events:	19		23			

Heterogeneity: Chi² = 1.35, df = 4 (P = 0.85); I² = 0%
Test for overall effect: Z = 0.59 (P = 0.55)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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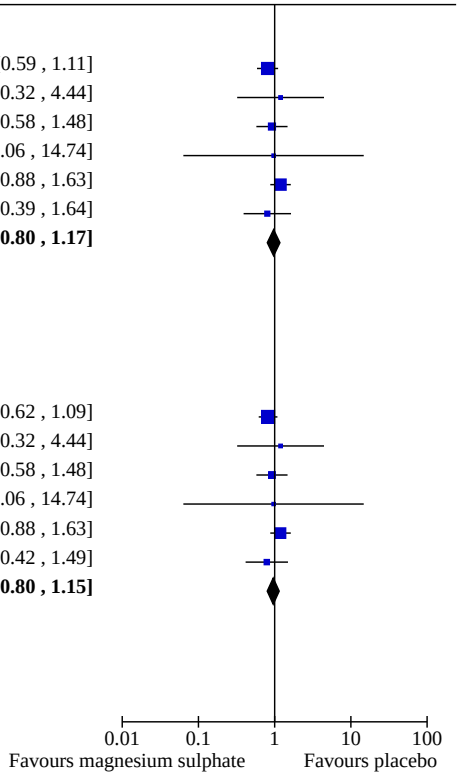
Analysis 2.2. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 2: Neonatal death

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 Variously defined						
Crowther 2003 (1)	61	620	75	615	38.0%	0.81 [0.59 , 1.11]
Crowther 2023 (2)	5	858	4	821	2.1%	1.20 [0.32 , 4.44]
Marret 2006 (3)	31	350	32	333	16.5%	0.92 [0.58 , 1.48]
Mittendorf 2002 (4)	1	30	1	29	0.5%	0.97 [0.06 , 14.74]
Rouse 2008 (5)	80	1174	71	1244	34.8%	1.19 [0.88 , 1.63]
Wolf 2020 (6)	13	341	16	336	8.1%	0.80 [0.39 , 1.64]
Subtotal (95% CI)		**3373**		**3378**	**100.0%**	**0.97 [0.80 , 1.17]**
Total events:	191		199			
Heterogeneity: Chi² = 3.43, df = 5 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.33 (P = 0.74)						
2.2.2 Defined, where possible, as up to hospital discharge						
Crowther 2003 (7)	76	620	92	615	42.1%	0.82 [0.62 , 1.09]
Crowther 2023 (2)	5	858	4	821	1.9%	1.20 [0.32 , 4.44]
Marret 2006 (3)	31	350	32	333	15.0%	0.92 [0.58 , 1.48]
Mittendorf 2002 (4)	1	30	1	29	0.5%	0.97 [0.06 , 14.74]
Rouse 2008 (5)	80	1174	71	1244	31.4%	1.19 [0.88 , 1.63]
Wolf 2020 (8)	16	341	20	336	9.2%	0.79 [0.42 , 1.49]
Subtotal (95% CI)		**3373**		**3378**	**100.0%**	**0.96 [0.80 , 1.15]**
Total events:	209		220			
Heterogeneity: Chi² = 3.61, df = 5 (P = 0.61); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						



Footnotes

(1) Denominators are livebirths; liveborn deaths prior to discharge, ≤ 28 days
(2) Denominators are livebirths; death of liveborn infant before hospital discharge
(3) Denominators are livebirths; neonatal mortality before discharge
(4) Denominators are livebirths; unclear timing of deaths
(5) Denominators are livebirths; deaths before initial discharge home
(6) Denominators are livebirths; death < 28 days
(7) Denominators are livebirths; liveborn deaths prior to discharge
(8) Denominators are livebirths; death prior to initial discharge

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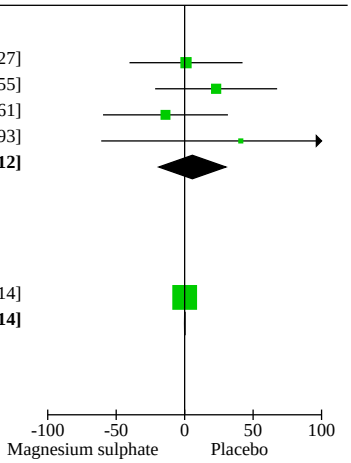
Analysis 2.3. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 3: Birthweight

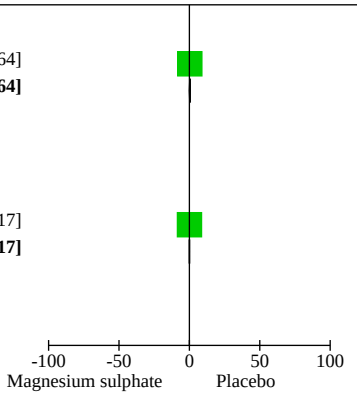
Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.3.1 Birthweight (grams)								
Crowther 2003 (1)	1027	370	620	1026	370	615	35.2%	1.00 [-40.27 , 42.27]
Crowther 2023 (1)	1797	464	858	1774	467	821	30.2%	23.00 [-21.55 , 67.55]
Rouse 2008 (1)	1410	567	1174	1424	577	1244	28.8%	-14.00 [-59.61 , 31.61]
Wolf 2020 (1)	1498	691	341	1457	662	336	5.8%	41.00 [-60.93 , 142.93]
Subtotal (95% CI)			**2993**			**3016**	**100.0%**	**5.63 [-18.85 , 30.12]**
Heterogeneity: Chi² = 1.81, df = 3 (P = 0.61); I² = 0%								
Test for overall effect: Z = 0.45 (P = 0.65)								
2.3.2 Birthweight (z-scores)								
Crowther 2023 (2)	0.1	1.11	858	0.07	1.14	821	100.0%	0.03 [-0.08 , 0.14]
Subtotal (95% CI)			**858**			**821**	**100.0%**	**0.03 [-0.08 , 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.55 (P = 0.59)								



Footnotes
(1) Denominators are livebirths
(2) Denominators are livebirths; UK-WHO growth reference

Analysis 2.4. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 4: Length at birth

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.4.1 Length (cm)								
Crowther 2023 (1)	42.4	3.4	791	42.1	3.4	768	100.0%	0.30 [-0.04 , 0.64]
Subtotal (95% CI)			**791**			**768**	**100.0%**	**0.30 [-0.04 , 0.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.74 (P = 0.08)								
2.4.2 Length (z-scores)								
Crowther 2023 (2)	-0.07	1.15	791	-0.13	1.13	768	100.0%	0.06 [-0.05 , 0.17]
Subtotal (95% CI)			**791**			**768**	**100.0%**	**0.06 [-0.05 , 0.17]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.04 (P = 0.30)								



Footnotes
(1) Denominators are livebirths with data
(2) Denominators are livebirths with data; UK-WHO growth reference

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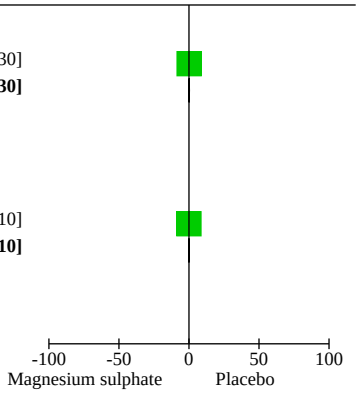
Analysis 2.5. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 5: Head circumference at birth

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
2.5.1 Head circumference (cm)								
Crowther 2023 (1)	29.7	2.1	837	29.6	2	805	100.0%	0.10 [-0.10 , 0.30]
Subtotal (95% CI)			**837**			**805**	**100.0%**	**0.10 [-0.10 , 0.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.99 (P = 0.32)								
2.5.2 Head circumference (z-scores)								
Crowther 2023 (2)	-0.11	1.13	837	-0.1	1.09	805	100.0%	-0.01 [-0.12 , 0.10]
Subtotal (95% CI)			**837**			**805**	**100.0%**	**-0.01 [-0.12 , 0.10]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								



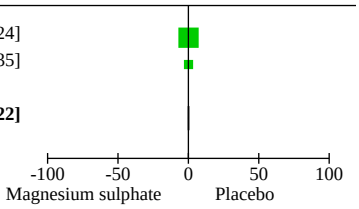
Footnotes

(1) Denominators are livebirths with data

(2) Denominators are livebirths with data; UK-WHO growth reference

Analysis 2.6. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 6: Gestational age at birth (weeks)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Crowther 2023 (1)	32.4	1.5	858	32.3	1.4	821	75.9%	0.10 [-0.04 , 0.24]
Rouse 2008 (2)	29.8	3.1	1188	29.7	3.1	1256	24.1%	0.10 [-0.15 , 0.35]
Total (95% CI)			**2046**			**2077**	**100.0%**	**0.10 [-0.02 , 0.22]**
Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0\%$								
Test for overall effect: Z = 1.62 (P = 0.10)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Denominators are total randomised/livebirths

(2) Denominators are total randomised

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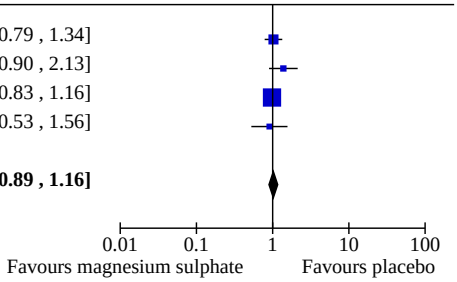
Analysis 2.7. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 7: Apgar score less than 7 at 5 minutes

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	94	620	91	615	24.6%	1.02 [0.79 , 1.34]
Marret 2006 (1)	45	350	31	333	8.6%	1.38 [0.90 , 2.13]
Rouse 2008 (2)	212	1171	229	1240	60.0%	0.98 [0.83 , 1.16]
Wolf 2020 (1)	23	341	25	336	6.8%	0.91 [0.53 , 1.56]
Total (95% CI)		**2482**		**2524**	**100.0%**	**1.02 [0.89 , 1.16]**
Total events:	374		376			

Heterogeneity: Chi² = 2.28, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.30 (P = 0.76)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are livebirths
(2) Denominators are livebirths with data

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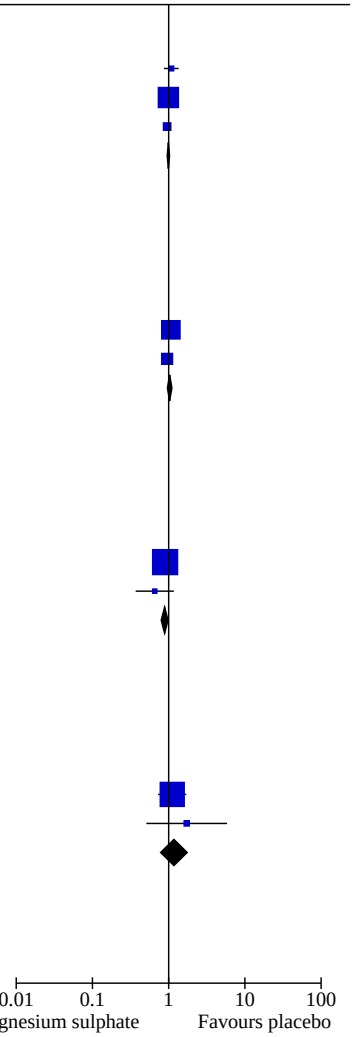
Analysis 2.8. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 8: Use of active resuscitation at birth

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 Any						
Marret 2006 (1)	115	350	101	333	7.5%	1.08 [0.87 , 1.35]
Rouse 2008 (2)	978	1172	1047	1244	73.6%	0.99 [0.96 , 1.03]
Wolf 2020 (3)	251	341	259	336	18.9%	0.95 [0.88 , 1.04]
Subtotal (95% CI)		**1863**		**1913**	**100.0%**	**0.99 [0.96 , 1.03]**
Total events:	1344		1407			
Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						
2.8.2 Supplementary oxygen						
Rouse 2008 (4)	524	1172	520	1244	65.9%	1.07 [0.98 , 1.17]
Wolf 2020 (5)	251	341	259	336	34.1%	0.95 [0.88 , 1.04]
Subtotal (95% CI)		**1513**		**1580**	**100.0%**	**1.03 [0.96 , 1.10]**
Total events:	775		779			
Heterogeneity: Chi² = 3.64, df = 1 (P = 0.06); I² = 72%						
Test for overall effect: Z = 0.87 (P = 0.38)						
2.8.3 Intubation						
Rouse 2008 (6)	412	1172	487	1244	94.6%	0.90 [0.81 , 1.00]
Wolf 2020 (5)	18	341	27	336	5.4%	0.66 [0.37 , 1.17]
Subtotal (95% CI)		**1513**		**1580**	**100.0%**	**0.88 [0.80 , 0.98]**
Total events:	430		514			
Heterogeneity: Chi² = 1.10, df = 1 (P = 0.29); I² = 9%						
Test for overall effect: Z = 2.33 (P = 0.02)						
2.8.4 Chest compressions						
Rouse 2008 (6)	42	1172	40	1244	90.6%	1.11 [0.73 , 1.71]
Wolf 2020 (5)	7	341	4	336	9.4%	1.72 [0.51 , 5.84]
Subtotal (95% CI)		**1513**		**1580**	**100.0%**	**1.17 [0.78 , 1.75]**
Total events:	49		44			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.44)						



Footnotes

(1) Denominators are livebirths; tracheal intubation and/or epinephrine
(2) Denominators are livebirths with data; resuscitation in the delivery room: oxygen bag, mask, or both; intubation; chest compressions
(3) Denominators are livebirths; resuscitation in delivery: any of: supplementary oxygen; endotracheal intubation; chest compressions
(4) Denominators are livebirths with data; oxygen bag, mask or both
(5) Denominators are livebirths
(6) Denominators are livebirths with data

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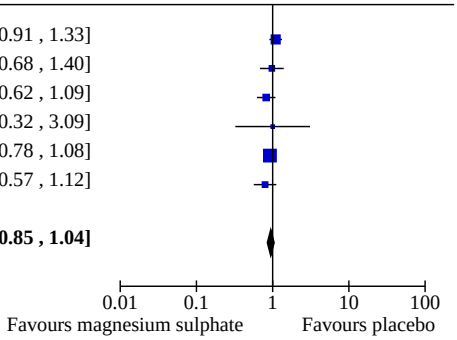
Analysis 2.9. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 9: Intraventricular haemorrhage

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	165	596	148	586	24.8%	1.10 [0.91 , 1.33]
Crowther 2023 (2)	56	854	55	818	9.3%	0.98 [0.68 , 1.40]
Marret 2006 (3)	71	341	82	324	14.0%	0.82 [0.62 , 1.09]
Mittendorf 2002 (4)	5	29	5	29	0.8%	1.00 [0.32 , 3.09]
Rouse 2008 (1)	218	1112	252	1184	40.6%	0.92 [0.78 , 1.08]
Wolf 2020 (4)	50	341	62	336	10.4%	0.79 [0.57 , 1.12]
Total (95% CI)		**3273**		**3277**	**100.0%**	**0.94 [0.85 , 1.04]**
Total events:	565		604			

Heterogeneity: Chi² = 4.41, df = 5 (P = 0.49); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



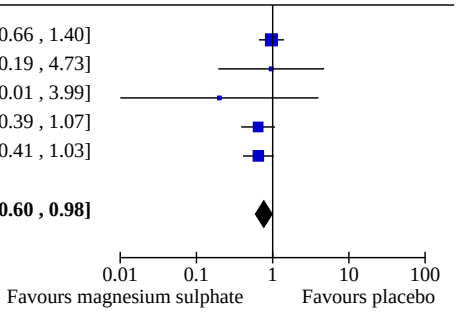
Footnotes

(1) Denominators are livebirths with cranial ultrasound data
(2) Denominators are livebirths with data; defined as IVH identified from cranial ultrasound within the first 7 days. No ultrasound scan assumed to be equal
(3) Denominators are livebirths with cranial ultrasound data; sum of intraparenchymal and nonparenchymal haemorrhage
(4) Denominators are livebirths

Analysis 2.10. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 10: Severe intraventricular haemorrhage (grade 3 or 4)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	49	596	50	586	37.6%	0.96 [0.66 , 1.40]
Crowther 2023 (1)	3	854	3	818	2.3%	0.96 [0.19 , 4.73]
Mittendorf 2002 (2)	0	29	2	29	1.9%	0.20 [0.01 , 3.99]
Rouse 2008 (1)	23	1112	38	1184	27.4%	0.64 [0.39 , 1.07]
Wolf 2020 (3)	27	341	41	336	30.8%	0.65 [0.41 , 1.03]
Total (95% CI)		**2932**		**2953**	**100.0%**	**0.76 [0.60 , 0.98]**
Total events:	102		134			

Heterogeneity: Chi² = 3.21, df = 4 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.12 (P = 0.03)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are livebirths with data
(2) Denominators are livebirths
(3) Denominators are livebirths; grade II-IV

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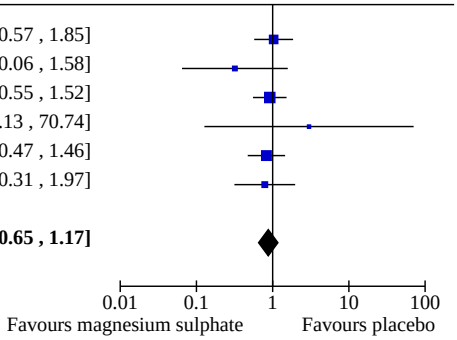
Analysis 2.11. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 11: Cystic periventricular leukomalacia

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	22	596	21	586	22.8%	1.03 [0.57 , 1.85]
Crowther 2023 (1)	2	854	6	818	6.6%	0.32 [0.06 , 1.58]
Marret 2006 (2)	27	341	28	324	31.0%	0.92 [0.55 , 1.52]
Mittendorf 2002 (3)	1	29	0	29	0.5%	3.00 [0.13 , 70.74]
Rouse 2008 (1)	21	1112	27	1184	28.2%	0.83 [0.47 , 1.46]
Wolf 2020 (3)	8	341	10	336	10.9%	0.79 [0.31 , 1.97]
Total (95% CI)		**3273**		**3277**	**100.0%**	**0.88 [0.65 , 1.17]**
Total events:	81		92			

Heterogeneity: Chi² = 2.53, df = 5 (P = 0.77); I² = 0%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable



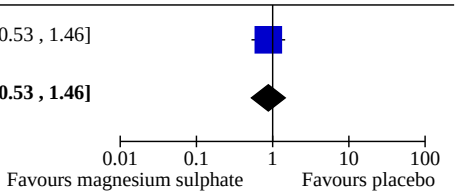
Footnotes

(1) Denominators are livebirths with cranial ultrasound data
(2) Denominators are livebirths with cranial ultrasound data; cysts reported
(3) Denominators are livebirths

Analysis 2.12. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 12: Ventriculomegaly

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rouse 2008 (1)	26	854	32	922	100.0%	0.88 [0.53 , 1.46]
Total (95% CI)		**854**		**922**	**100.0%**	**0.88 [0.53 , 1.46]**
Total events:	26		32			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.50 (P = 0.61)
Test for subgroup differences: Not applicable



Footnotes

(1) *From secondary analysis; denominators are infants discharged alive with a term ultrasound (conducted at 35 weeks' gestation or later) and 2 year cereb

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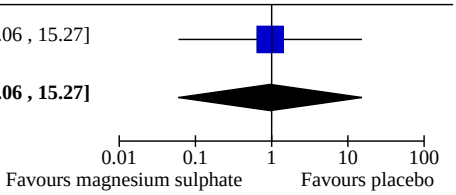
Analysis 2.13. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 13: Neonatal encephalopathy

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	1	858	1	821	100.0%	0.96 [0.06 , 15.27]
Total (95% CI)		**858**		**821**	**100.0%**	**0.96 [0.06 , 15.27]**
Total events:	1		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.03 (P = 0.98)
Test for subgroup differences: Not applicable

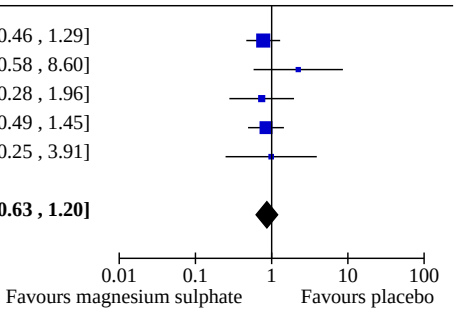


Footnotes
(1) Denominators are livebirths

Analysis 2.14. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 14: Neonatal convulsions

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	25	620	32	615	42.0%	0.77 [0.46 , 1.29]
Crowther 2023 (2)	7	858	3	821	4.0%	2.23 [0.58 , 8.60]
Marret 2006 (3)	7	350	9	333	12.0%	0.74 [0.28 , 1.96]
Rouse 2008 (4)	23	1171	29	1244	36.7%	0.84 [0.49 , 1.45]
Wolf 2020 (2)	4	341	4	336	5.3%	0.99 [0.25 , 3.91]
Total (95% CI)		**3340**		**3349**	**100.0%**	**0.87 [0.63 , 1.20]**
Total events:	66		77			

Heterogeneity: $Chi^2 = 2.22$, df = 4 (P = 0.70); $I^2 = 0\%$
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are livebirths; additional data from trialists (2009 version)
(2) Denominators are livebirths
(3) Denominators are livebirths; seizures
(4) Denominators are livebirths with data; seizures

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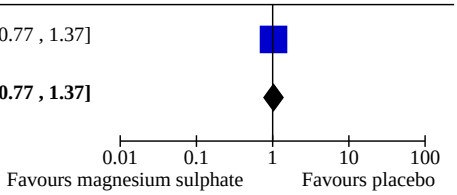
Analysis 2.15. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 15: Neonatal hypotonia

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rouse 2008 (1)	85	1171	88	1244	100.0%	1.03 [0.77 , 1.37]
Total (95% CI)		**1171**		**1244**	**100.0%**	**1.03 [0.77 , 1.37]**
Total events:	85		88			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)
Test for subgroup differences: Not applicable



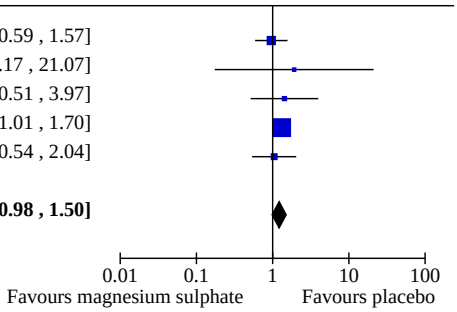
Footnotes

(1) Denominators are livebirths with data; generalised hypotonicity

Analysis 2.16. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 16: Necrotising enterocolitis

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	30	620	31	615	21.4%	0.96 [0.59 , 1.57]
Crowther 2023 (2)	2	858	1	821	0.7%	1.91 [0.17 , 21.07]
Marret 2006 (1)	9	350	6	333	4.2%	1.43 [0.51 , 3.97]
Rouse 2008 (3)	116	1171	94	1244	62.6%	1.31 [1.01 , 1.70]
Wolf 2020 (1)	17	341	16	336	11.1%	1.05 [0.54 , 2.04]
Total (95% CI)		**3340**		**3349**	**100.0%**	**1.22 [0.98 , 1.50]**
Total events:	174		148			

Heterogeneity: $Chi^2 = 1.64$, df = 4 (P = 0.80); $I^2 = 0\%$
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are livebirths
(2) Denominators are livebirths; at least 1 of: diagnosis at surgery or postmortem; radiological diagnosis with a clinical history plus pneumatosis intestinalis
(3) Denominators are livebirths with data

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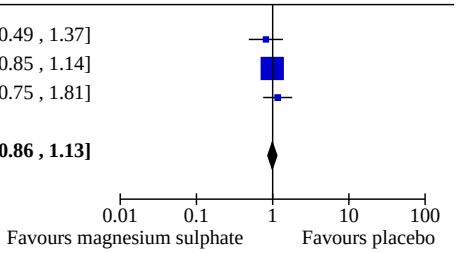
Analysis 2.17. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 17: Retinopathy of prematurity

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	23	265	30	282	8.6%	0.82 [0.49 , 1.37]
Rouse 2008 (2)	263	1171	283	1244	81.5%	0.99 [0.85 , 1.14]
Wolf 2020 (3)	39	341	33	336	9.9%	1.16 [0.75 , 1.81]
Total (95% CI)		**1777**		**1862**	**100.0%**	**0.99 [0.86 , 1.13]**
Total events:	325		346			

Heterogeneity: Chi² = 1.07, df = 2 (P = 0.59); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)
Test for subgroup differences: Not applicable

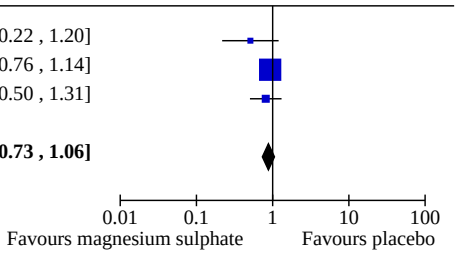


Footnotes
(1) Denominators are livebirths with data; retinopathy of prematurity needing treatment
(2) Denominators are livebirths with data
(3) Denominators are livebirths

Analysis 2.18. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 18: Patent ductus arteriosus

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	8	858	15	821	7.1%	0.51 [0.22 , 1.20]
Rouse 2008 (2)	151	1171	173	1244	77.2%	0.93 [0.76 , 1.14]
Wolf 2020 (3)	28	341	34	336	15.8%	0.81 [0.50 , 1.31]
Total (95% CI)		**2370**		**2401**	**100.0%**	**0.88 [0.73 , 1.06]**
Total events:	187		222			

Heterogeneity: Chi² = 1.93, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.38 (P = 0.17)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are livebirths; patent ductus arteriosus requiring treatment
(2) Denominators are livebirths with data
(3) Denominators are livebirths; patent ductus arteriosus requring treatment

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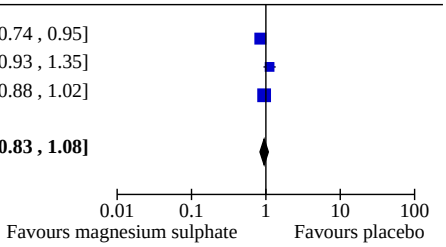
Analysis 2.19. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 19: Respiratory distress syndrome

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2023 (1)	294	858	334	821	33.9%	0.84 [0.74 , 0.95]
Marret 2006 (2)	145	350	123	333	24.1%	1.12 [0.93 , 1.35]
Rouse 2008 (3)	585	1171	656	1244	42.0%	0.95 [0.88 , 1.02]
Total (95% CI)		**2379**		**2398**	**100.0%**	**0.95 [0.83 , 1.08]**
Total events:	1024		1113			

Heterogeneity: Tau² = 0.01; Chi² = 6.44, df = 2 (P = 0.04); I² = 69%
Test for overall effect: Z = 0.81 (P = 0.42)
Test for subgroup differences: Not applicable



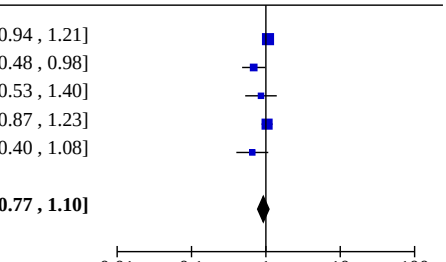
Footnotes

(1) Denominators are livebirths; defined as increasing respiratory distress or oxygen requirements, or need for ventilatory support from the first 6 hours of life v
(2) Denominators are livebirths
(3) Denominators are livebirths with data

Analysis 2.20. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 20: Chronic lung disease/bronchopulmonary dysplasia

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	280	620	260	615	34.8%	1.07 [0.94 , 1.21]
Crowther 2023 (2)	48	858	67	821	15.3%	0.69 [0.48 , 0.98]
Marret 2006 (3)	28	350	31	333	9.9%	0.86 [0.53 , 1.40]
Rouse 2008 (4)	213	1171	218	1244	30.3%	1.04 [0.87 , 1.23]
Wolf 2020 (5)	24	341	36	336	9.7%	0.66 [0.40 , 1.08]
Total (95% CI)		**3340**		**3349**	**100.0%**	**0.92 [0.77 , 1.10]**
Total events:	593		612			

Heterogeneity: Tau² = 0.02; Chi² = 8.85, df = 4 (P = 0.07); I² = 55%
Test for overall effect: Z = 0.89 (P = 0.37)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are livebirths; chronic lung disease: defined as receiving oxygen at 28 days
(2) Denominators are livebirths; chronic lung disease defined as oxygen dependent at 36 weeks gestation or 28 days of life if born after 32 weeks gestation
(3) Denominators are livebirths; oxygen dependency at 36 weeks
(4) Denominators are livebirths with data; bronchopulmonary dysplasia
(5) Denominators are livebirths; need for continuous supplemental oxygen at 36 weeks of postmenstrual age

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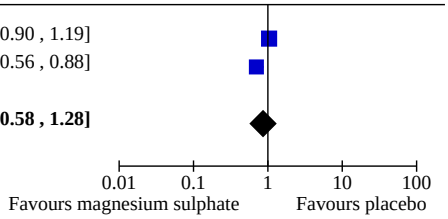
Analysis 2.21. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 21: Use of respiratory support (endotracheal intubation)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Marret 2006 (1)	191	350	175	333	52.4%	1.04 [0.90 , 1.19]
Wolf 2020 (2)	91	341	128	336	47.6%	0.70 [0.56 , 0.88]
Total (95% CI)		**691**		**669**	**100.0%**	**0.86 [0.58 , 1.28]**
Total events:	282		303			

Heterogeneity: Tau² = 0.07; Chi² = 8.95, df = 1 (P = 0.003); I² = 89%
Test for overall effect: Z = 0.75 (P = 0.46)
Test for subgroup differences: Not applicable

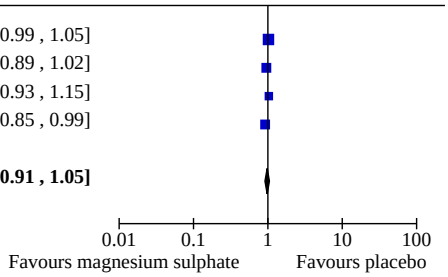


Footnotes
(1) Denominators are livebirths; endotracheal ventilation
(2) Denominators are livebirths; endotracheal intubation for administration of surfactant and respiration support

Analysis 2.22. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 22: Use of respiratory support (mechanical ventilation or continuous positive airway pressure)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	577	620	562	615	31.9%	1.02 [0.99 , 1.05]
Crowther 2023 (2)	533	858	535	821	24.8%	0.95 [0.89 , 1.02]
Marret 2006 (3)	235	350	217	333	18.6%	1.03 [0.93 , 1.15]
Rouse 2008 (4)	613	1171	709	1244	24.7%	0.92 [0.85 , 0.99]
Total (95% CI)		**2999**		**3013**	**100.0%**	**0.98 [0.91 , 1.05]**
Total events:	1958		2023			

Heterogeneity: Tau² = 0.00; Chi² = 12.84, df = 3 (P = 0.005); I² = 77%
Test for overall effect: Z = 0.62 (P = 0.54)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are livebirths; 'mechanical ventilation' reported
(2) Denominators are livebirths; 'use of respiratory support'
(3) Denominators are livebirths; 'non-invasive ventilation' reported
(4) Denominators are livebirths with data; 'mechanical ventilation' reported

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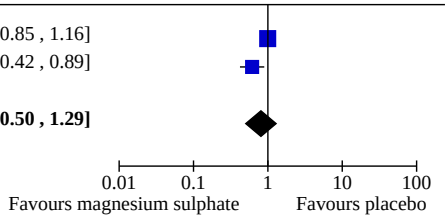
Analysis 2.23. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 23: Use of inotropic support

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Rouse 2008 (1)	248	1171	265	1244	56.6%	0.99 [0.85 , 1.16]
Wolf 2020 (2)	38	341	61	336	43.4%	0.61 [0.42 , 0.89]
Total (95% CI)		**1512**		**1580**	**100.0%**	**0.81 [0.50 , 1.29]**
Total events:	286		326			

Heterogeneity: Tau² = 0.10; Chi² = 5.43, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

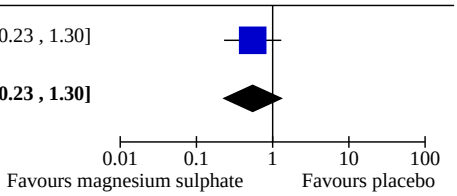


Footnotes
(1) Denominators are livebirths with data; hypotension treated with vasopressors
(2) Denominators are livebirths; hypotension treated with inotropes

Analysis 2.24. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 24: Air leak syndrome

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	8	858	14	821	100.0%	0.55 [0.23 , 1.30]
Total (95% CI)		**858**		**821**	**100.0%**	**0.55 [0.23 , 1.30]**
Total events:	8		14			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.37 (P = 0.17)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are livebirths

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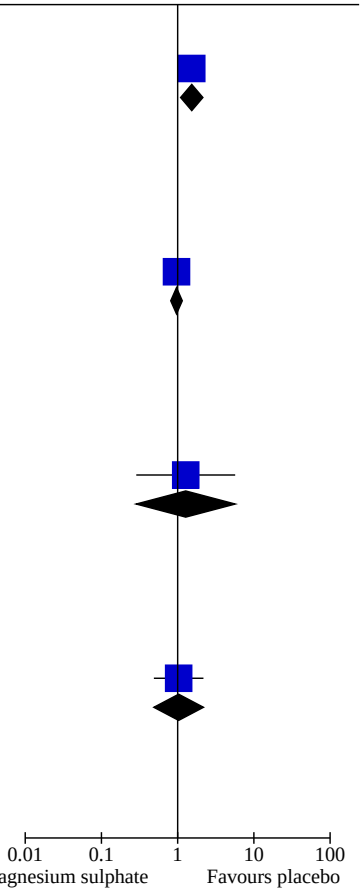
Analysis 2.25. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 25: Early- or late-onset sepsis

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.25.1 Maternal-fetal infection						
Marret 2006 (1)	74	350	46	333	100.0%	1.53 [1.09 , 2.14]
Subtotal (95% CI)		**350**		**333**	**100.0%**	**1.53 [1.09 , 2.14]**
Total events:	74		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.48 (P = 0.01)						
2.25.2 Sepsis						
Rouse 2008 (2)	200	1171	220	1244	100.0%	0.97 [0.81 , 1.15]
Subtotal (95% CI)		**1171**		**1244**	**100.0%**	**0.97 [0.81 , 1.15]**
Total events:	200		220			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
2.25.3 Early onset sepsis						
Crowther 2023 (3)	4	858	3	821	100.0%	1.28 [0.29 , 5.68]
Subtotal (95% CI)		**858**		**821**	**100.0%**	**1.28 [0.29 , 5.68]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.32 (P = 0.75)						
2.25.4 Late onset sepsis						
Crowther 2023 (4)	14	858	13	821	100.0%	1.03 [0.49 , 2.18]
Subtotal (95% CI)		**858**		**821**	**100.0%**	**1.03 [0.49 , 2.18]**
Total events:	14		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						



Footnotes

(1) Denominators are livebirths; maternal-fetal infection: defined as the presence of at least 2 criteria among clinical signs of infection, leucocyte count > 30

(2) Denominators are livebirths with data; "Culture-proven sepsis"

(3) Denominators are livebirths; proven infection in first 48 hours (confirmed by culture)

(4) Denominators are livebirths; proven infection after first 48 hours (confirmed by culture)

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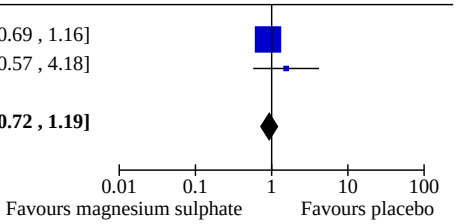
Analysis 2.26. Comparison 2: Magnesium sulphate versus placebo: secondary outcomes for fetuses/neonates/infants, Outcome 26: Severe adverse neonatal outcome composite

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	81	384	99	420	94.9%	0.89 [0.69 , 1.16]
Mittendorf 2002 (2)	8	30	5	29	5.1%	1.55 [0.57 , 4.18]
Total (95% CI)		**414**		**449**	**100.0%**	**0.93 [0.72 , 1.19]**
Total events:	89		104			

Heterogeneity: Chi² = 1.09, df = 1 (P = 0.30); I² = 8%
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators include deaths and livebirths with data; defined as stillbirth, death of liveborn infant before hospital discharge, severe respiratory disease,
(2) Denominators are total randomised; "composite adverse outcomes variable" (IVH, PVL, pediatric death); cerebral palsy data not included

Comparison 3. Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Later death (up to 2 years' corrected age)	5	6646	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.66, 1.78]
3.2 Cerebral palsy severity (up to 2 years' corrected age)	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.2.1 Mild	6	6108	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.53, 1.00]
3.2.2 Moderate to severe	6	6108	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.50, 0.95]
3.3 Any neurodevelopmental disability (up to 2 years' corrected age)	1	987	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.84, 1.16]
3.4 Death or any neurodevelopmental disability (up to 2 years' corrected age)	3	3194	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.83, 1.00]
3.5 Blindness (up to 2 years' corrected age)	4	3633	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.39, 6.69]
3.6 Deafness (up to 2 years' corrected age)	4	3633	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.32, 1.42]
3.7 Developmental delay/intellectual impairment (up to 2 years' corrected age)	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.7.1 Any	4	5245	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.90, 1.06]
3.7.2 Mild	3	4639	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.84, 1.06]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.7.3 Moderate to severe	3	4639	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.91, 1.24]
3.8 Gross motor dysfunction (up to 2 years' corrected age)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.8.1 Any	2	1648	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.72, 1.07]
3.8.2 Substantial	2	1648	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.41, 0.92]
3.9 Psychomotor dysfunction (up to 2 years' corrected age)	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.9.1 Any	2	3696	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.18]
3.9.2 Moderate to severe	2	3696	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.25]
3.10 Death or substantial gross motor dysfunction (up to 2 years' corrected age)	5	5097	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.74, 0.98]
3.11 Growth (up to 2 years' corrected age)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.11.1 Weight (kg)	1	1330	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.22, 0.22]
3.11.2 Height (cm)	1	1305	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.75, 0.35]
3.11.3 Head circumference (cm)	1	1265	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.21, 0.21]
3.11.4 Weight (z-score)	1	1330	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.09, 0.15]
3.11.5 Height (z-score)	1	1305	Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.08, 0.18]
3.11.6 Head circumference (z-score)	1	1265	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.13, 0.15]
3.12 Respiratory function (up to 2 years' corrected age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.12.1 Childhood respiratory morbidity	1	1365	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.08]
3.12.2 Asthma or wheezing	1	1365	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.78, 1.15]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.13 Blood pressure (up to 2 years' corrected age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.13.1 Systolic hypertension	1	679	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.76, 1.34]
3.13.2 Diastolic hypertension	1	674	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.81, 1.20]
3.13.3 Hypertension (any)	1	674	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
3.14 Blood pressure (up to 2 years' corrected age)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.14.1 Systolic blood pressure (mmHg)	1	679	Mean Difference (IV, Fixed, 95% CI)	0.06 [-1.52, 1.64]
3.14.2 Diastolic blood pressure (mmHg)	1	674	Mean Difference (IV, Fixed, 95% CI)	-0.93 [-2.46, 0.60]
3.14.3 Systolic blood pressure (z-score)	1	679	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.15, 0.15]
3.14.4 Diastolic blood pressure (z-score)	1	674	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.22, 0.06]
3.15 Behaviour (up to 2 years' corrected age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.15.1 Child Behavior Checklist, total (scores in clinical range (> 97.5th percentile))	1	768	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [1.00, 2.64]
3.15.2 Child Behavior Checklist, anxiety (scores in clinical range (> 97.5th percentile))	1	793	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [1.18, 3.88]
3.15.3 Child Behavior Checklist, withdrawal (scores in clinical range (> 97.5th percentile))	1	791	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [1.06, 2.04]
3.15.4 Child Behavior Checklist, sleeping problem (scores in clinical range (> 97.5th percentile))	1	795	Risk Ratio (M-H, Fixed, 95% CI)	2.54 [1.14, 5.67]
3.15.5 Child Behavior Checklist, somatic problem (scores in clinical range (> 97.5th percentile))	1	785	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.59, 1.74]
3.15.6 Child Behavior Checklist, aggressive behaviour (scores in clinical range (> 97.5th percentile))	1	786	Risk Ratio (M-H, Fixed, 95% CI)	4.34 [0.94, 19.97]

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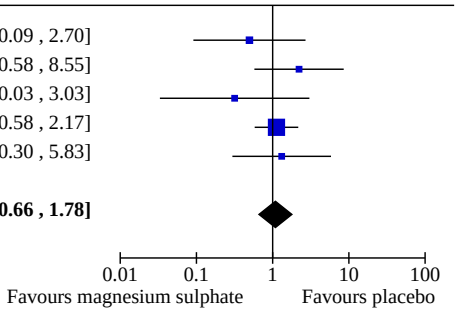
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.15.7 Child Behavior Checklist, destructive behaviour (scores in clinical range (> 97.5th percentile))	1	796	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.06, 15.30]
3.15.8 Child Behavior Checklist, other (scores in clinical range (> 97.5th percentile))	1	774	Risk Ratio (M-H, Fixed, 95% CI)	7.92 [1.00, 63.00]

Analysis 3.1. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 1: Later death (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	2	620	4	615	13.5%	0.50 [0.09 , 2.70]
Crowther 2023 (2)	7	837	3	796	10.4%	2.22 [0.58 , 8.55]
Marret 2006 (3)	1	350	3	333	10.4%	0.32 [0.03 , 3.03]
Rouse 2008 (4)	18	1174	17	1244	55.6%	1.12 [0.58 , 2.17]
Wolf 2020 (5)	4	341	3	336	10.2%	1.31 [0.30 , 5.83]
Total (95% CI)		**3322**		**3324**	**100.0%**	**1.09 [0.66 , 1.78]**
Total events:	32		30			

Heterogeneity: Chi² = 3.11, df = 4 (P = 0.54); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are livebirths; post discharge deaths up to 2 years' corrected age
(2) Denominators are livebirths minus children unable to contact or lost; death after discharge up to 2 years' corrected age
(3) Denominators are livebirths; post discharge deaths up to 2 years
(4) Denominators are livebirths; infant deaths between discharge and 1 year examination
(5) Denominators are livebirths; post discharge deaths up to 18 months' corrected age

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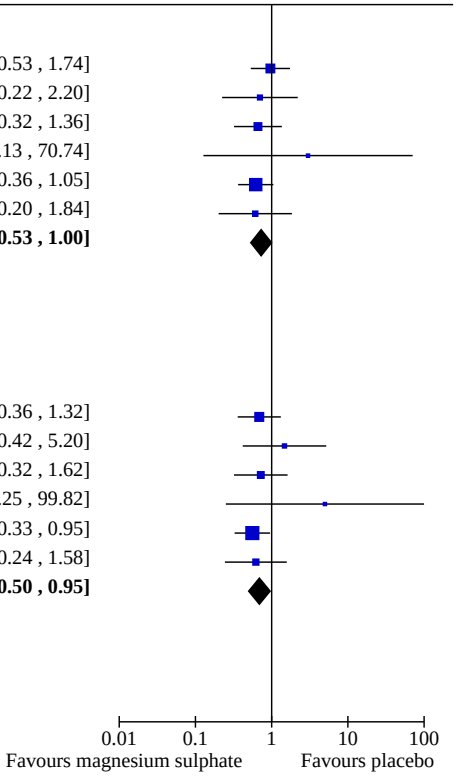
Analysis 3.2. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 2: Cerebral palsy severity (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Mild						
Crowther 2003 (1)	21	533	21	513	23.9%	0.96 [0.53 , 1.74]
Crowther 2023 (2)	5	679	7	667	7.9%	0.70 [0.22 , 2.20]
Marret 2006 (3)	12	313	17	293	19.6%	0.66 [0.32 , 1.36]
Mittendorf 2002 (4)	1	29	0	29	0.6%	3.00 [0.13 , 70.74]
Rouse 2008 (5)	21	1174	36	1244	39.0%	0.62 [0.36 , 1.05]
Wolf 2020 (6)	5	321	8	313	9.0%	0.61 [0.20 , 1.84]
Subtotal (95% CI)		**3049**		**3059**	**100.0%**	**0.73 [0.53 , 1.00]**
Total events:	65		89			
Heterogeneity: Chi² = 2.16, df = 5 (P = 0.83); I² = 0%						
Test for overall effect: Z = 1.98 (P = 0.05)						
3.2.2 Moderate to severe						
Crowther 2003 (7)	15	533	21	513	24.5%	0.69 [0.36 , 1.32]
Crowther 2023 (8)	6	679	4	667	4.6%	1.47 [0.42 , 5.20]
Marret 2006 (3)	10	313	13	293	15.4%	0.72 [0.32 , 1.62]
Mittendorf 2002 (9)	2	29	0	29	0.6%	5.00 [0.25 , 99.82]
Rouse 2008 (10)	20	1174	38	1244	42.2%	0.56 [0.33 , 0.95]
Wolf 2020 (11)	7	321	11	313	12.7%	0.62 [0.24 , 1.58]
Subtotal (95% CI)		**3049**		**3059**	**100.0%**	**0.69 [0.50 , 0.95]**
Total events:	60		87			
Heterogeneity: Chi² = 3.74, df = 5 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.24 (P = 0.02)						



Footnotes

(1) Denominators are children with 2 year assessments; mild: walking at 2 years; 2 years' corrected age
(2) Denominators are children with 2 year corrected age paediatric assessments; GMFCS level 1
(3) Denominators are livebirths with data; 2 years; additional data from trialists (2009 review)
(4) Denominators are livebirths; 1 child with 'mild hemiplegia'; 18 months' corrected age
(5) Denominators are livebirths; GMFCS level I; 2 years' corrected age
(6) Denominators are surviving children at 18 months' corrected age or older; GMFCS level I
(7) Denominators are children with 2 year assessments; severe: permanently nonambulant, or moderate: nonambulant at 2 years but likely to walk; 2 years c
(8) Denominators are children with 2 year corrected age paediatric assessments; sum of GMFCS levels 2-3 (moderate) and 4-5 (severe)
(9) Denominators are livebirths; 1 child with 'moderate hemiplegia', 1 child with 'spastic quadriplegia'; 18 months corrected age
(10) Denominators are livebirths; GMFCS level II-V; 2 years corrected age
(11) Denominators are surviving children at 18 months corrected age or older; GMFCS level II-V

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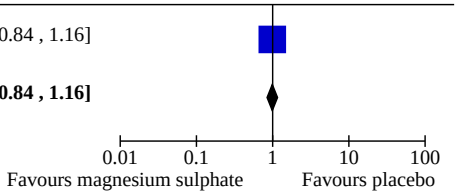
Analysis 3.3. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 3: Any neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	193	504	187	483	100.0%	0.99 [0.84 , 1.16]
Total (95% CI)		**504**		**483**	**100.0%**	**0.99 [0.84 , 1.16]**
Total events:	193		187			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
Test for subgroup differences: Not applicable						

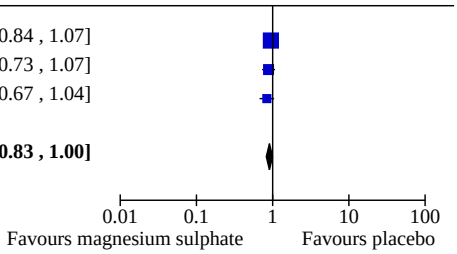


Footnotes

(1) Denominators are children with 2 year assessments; any neurosensory disability (sum of mild, moderate, severe): at least mild cerebral palsy (walking at

Analysis 3.4. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 4: Death or any neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	280	629	294	626	50.9%	0.95 [0.84 , 1.07]
Crowther 2023 (2)	146	631	165	630	28.5%	0.88 [0.73 , 1.07]
Marret 2006 (3)	102	347	116	331	20.5%	0.84 [0.67 , 1.04]
Total (95% CI)		**1607**		**1587**	**100.0%**	**0.91 [0.83 , 1.00]**
Total events:	528		575			
Heterogeneity: $Chi^2 = 1.07$, df = 2 (P = 0.59); $I^2 = 0\%$						
Test for overall effect: Z = 2.04 (P = 0.04)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; any neurosensory disability (sum of mild, moderate, severe): at least mild cerebral palsy (walking at 2 years), or mil
(2) Denominators are children with data at 2 years' corrected age; any neurosensory disabilities: cerebral palsy (GMFCS level 1-5), blindness (corrected visı
(3) Denominators are deaths and livebirths with data; combined death and cerebral palsy or cognitive dysfunction at 2 years

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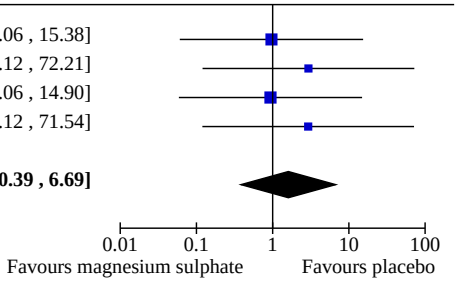
Analysis 3.5. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 5: Blindness (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	1	533	1	514	33.3%	0.96 [0.06 , 15.38]
Crowther 2023 (2)	1	679	0	667	16.5%	2.95 [0.12 , 72.21]
Marret 2006 (3)	1	313	1	293	33.7%	0.94 [0.06 , 14.90]
Wolf 2020 (4)	1	321	0	313	16.5%	2.93 [0.12 , 71.54]
Total (95% CI)		**1846**		**1787**	**100.0%**	**1.61 [0.39 , 6.69]**
Total events:	4		2			

Heterogeneity: Chi² = 0.55, df = 3 (P = 0.91); I² = 0%
Test for overall effect: Z = 0.65 (P = 0.52)
Test for subgroup differences: Not applicable



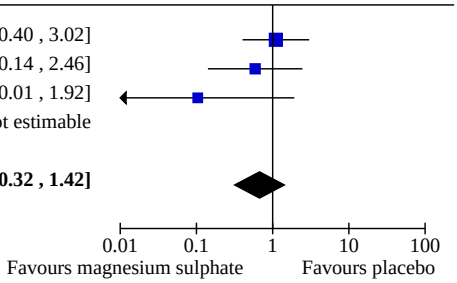
Footnotes

(1) Denominators are children included in secondary outcome analyses at 2 years' corrected age; blindness: vision in both eyes worse than 6/60
(2) Denominators are children with 2 year corrected age paediatric assessments; blindiness: visual acuity in both eyes worse than 6/60
(3) Denominators are livebirths with data; 2 years; additional data from trialists (2009 review)
(4) Denominators are surviving children at 18 months' corrected age or older

Analysis 3.6. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 6: Deafness (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	8	533	7	514	42.4%	1.10 [0.40 , 3.02]
Crowther 2023 (2)	3	679	5	667	30.0%	0.59 [0.14 , 2.46]
Marret 2006 (3)	0	313	4	293	27.6%	0.10 [0.01 , 1.92]
Wolf 2020 (4)	0	321	0	313		Not estimable
Total (95% CI)		**1846**		**1787**	**100.0%**	**0.67 [0.32 , 1.42]**
Total events:	11		16			

Heterogeneity: Chi² = 2.53, df = 2 (P = 0.28); I² = 21%
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are children included in secondary outcome analyses at 2 years' corrected age; deaf: required hearing aids
(2) Denominators are children with 2 year corrected age paediatric assessments; deafness: requring hearing aid(s) or worse
(3) Denominators are livebirths with data; 2 years; additional data from trialists (2009 review)
(4) Denominators are surviving children at 18 months' corrected age or older

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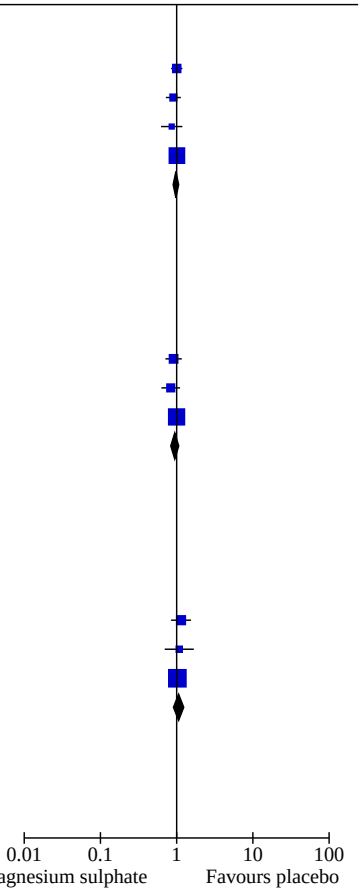
Analysis 3.7. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 7: Developmental delay/intellectual impairment (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.7.1 Any						
Crowther 2003 (1)	176	494	170	478	22.2%	1.00 [0.85 , 1.19]
Crowther 2023 (2)	116	625	128	624	16.4%	0.90 [0.72 , 1.13]
Marret 2006 (3)	57	313	62	293	8.2%	0.86 [0.62 , 1.19]
Rouse 2008 (4)	406	1174	427	1244	53.2%	1.01 [0.90 , 1.12]
Subtotal (95% CI)		**2606**		**2639**	**100.0%**	**0.98 [0.90 , 1.06]**
Total events:	755		787			
Heterogeneity: Chi² = 1.42, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
3.7.2 Mild						
Crowther 2003 (5)	97	494	103	478	23.5%	0.91 [0.71 , 1.17]
Crowther 2023 (6)	77	625	92	624	20.7%	0.84 [0.63 , 1.11]
Rouse 2008 (7)	241	1174	256	1244	55.8%	1.00 [0.85 , 1.17]
Subtotal (95% CI)		**2293**		**2346**	**100.0%**	**0.94 [0.84 , 1.06]**
Total events:	415		451			
Heterogeneity: Chi² = 1.27, df = 2 (P = 0.53); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
3.7.3 Moderate to severe						
Crowther 2003 (8)	79	494	67	478	25.2%	1.14 [0.85 , 1.54]
Crowther 2023 (9)	39	625	36	624	13.3%	1.08 [0.70 , 1.68]
Rouse 2008 (10)	165	1174	171	1244	61.5%	1.02 [0.84 , 1.25]
Subtotal (95% CI)		**2293**		**2346**	**100.0%**	**1.06 [0.91 , 1.24]**
Total events:	283		274			
Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.74 (P = 0.46)						



Footnotes

(1) Denominators are children included in secondary outcome analyses at 2 years' corrected age; 'delayed development' (any)
(2) Denominators are children with data at 2 years' corrected age; cognitive/language delay (BSID-III cognitive or language score < -1 SD)
(3) Denominators are children with data at 2 years; cognitive dysfunction (questionnaire with developmental items extracted from the Amiel-Tison and Den
(4) Denominators are livebirths; BSID-II MDI < 85; 2 years' corrected age
(5) Denominators are children included in secondary outcome analyses at 2 years' corrected age; 'delayed development' (mild)
(6) Denominators are children with data at 2 years' corrected age; cognitive/language delay (BSID-III cognitive or language score < -1 SD, but not < -2 SD)
(7) Denominators are livebirths; BSID-II MDI < 85, but not < 70; 2 years' corrected age
(8) Denominators are children included in secondary outcome analyses at 2 years' corrected age; 'delayed development' (moderate or severe)
(9) Denominators are children with data at 2 years' corrected age; cognitive/language delay (BSID-III cognitive or language score < -2 SD)
(10) Denominators are livebirths; BSID-II MDI < 70; 2 years' corrected age

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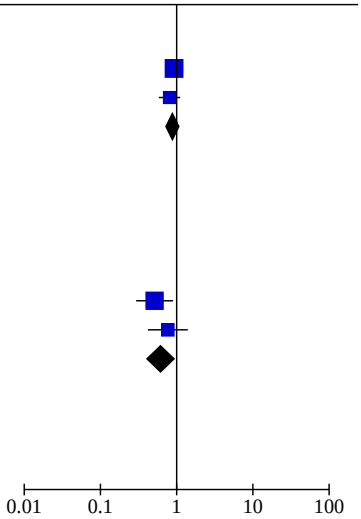
Analysis 3.8. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 8: Gross motor dysfunction (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.8.1 Any						
Crowther 2003 (1)	102	529	107	513	62.2%	0.92 [0.73 , 1.18]
Marret 2006 (2)	55	313	64	293	37.8%	0.80 [0.58 , 1.11]
Subtotal (95% CI)		**842**		**806**	**100.0%**	**0.88 [0.72 , 1.07]**
Total events:	157		171			
Heterogeneity: Chi² = 0.45, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
3.8.2 Substantial						
Crowther 2003 (3)	18	529	34	513	60.3%	0.51 [0.29 , 0.90]
Marret 2006 (4)	18	313	22	293	39.7%	0.77 [0.42 , 1.40]
Subtotal (95% CI)		**842**		**806**	**100.0%**	**0.61 [0.41 , 0.92]**
Total events:	36		56			
Heterogeneity: Chi² = 0.91, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						

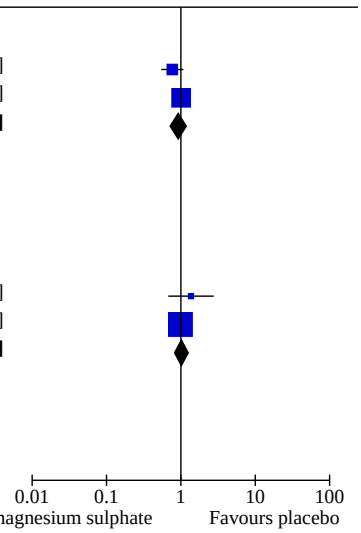


Footnotes

(1) Denominators are children included in secondary outcome analyses at 2 years' corrected age; gross motor dysfunction (minimal and substantial)
(2) Denominators are children with data at 2 years; gross motor dysfunction (questionnaire with developmental items extracted from the Amiel-Tison and D
(3) Denominators are children included in secondary outcome analyses at 2 years' corrected age; gross motor dysfunction (substantial)
(4) Denominators are livebirths with data; 2 years; additional data from trialists (2009 review)

Analysis 3.9. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 9: Psychomotor dysfunction (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.9.1 Any						
Crowther 2003 (1)	52	643	67	635	32.4%	0.77 [0.54 , 1.08]
Rouse 2008 (2)	299	1174	315	1244	67.6%	1.01 [0.88 , 1.15]
Subtotal (95% CI)		**1817**		**1879**	**100.0%**	**0.92 [0.72 , 1.18]**
Total events:	351		382			
Heterogeneity: Tau² = 0.02; Chi² = 2.07, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.64 (P = 0.52)						
3.9.2 Moderate to severe						
Crowther 2003 (3)	18	643	13	635	9.0%	1.37 [0.68 , 2.77]
Rouse 2008 (4)	134	1174	144	1244	91.0%	0.99 [0.79 , 1.23]
Subtotal (95% CI)		**1817**		**1879**	**100.0%**	**1.02 [0.82 , 1.25]**
Total events:	152		157			
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.14 (P = 0.89)						



Footnotes

(1) Denominators are children with data at 2 years' corrected age; motor delay (BSID-III motor score < -1 SD)
(2) Denominators are livebirths; BSID-II PDI < 85; 2 years' corrected age
(3) Denominators are children with data at 2 years' corrected age; motor delay (BSID-III motor score < -2 SD)
(4) Denominators are livebirths; BSID-II PDI < 70; 2 years' corrected age

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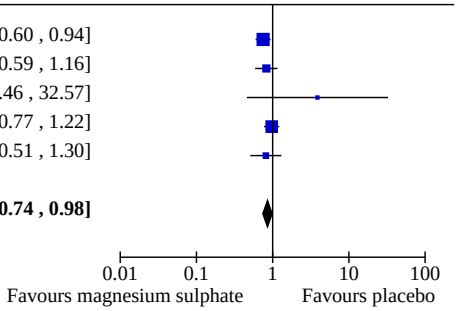
Analysis 3.10. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 10: Death or substantial gross motor dysfunction (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	105	616	141	620	38.1%	0.75 [0.60 , 0.94]
Marret 2006 (2)	52	347	60	331	16.7%	0.83 [0.59 , 1.16]
Mittendorf 2002 (3)	4	30	1	29	0.3%	3.87 [0.46 , 32.57]
Rouse 2008 (4)	123	1188	134	1256	35.3%	0.97 [0.77 , 1.22]
Wolf 2020 (5)	29	343	35	337	9.6%	0.81 [0.51 , 1.30]
Total (95% CI)		**2524**		**2573**	**100.0%**	**0.86 [0.74 , 0.98]**
Total events:	313		371			

Heterogeneity: Chi² = 4.45, df = 4 (P = 0.35); I² = 10%
Test for overall effect: Z = 2.20 (P = 0.03)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are deaths and children included in secondary outcome analyses at 2 years' corrected age; death or substantial gross motor dysfunction (cr
(2) Denominators are deaths and children with data at 2 years; additional data from trialists (2009 review)
(3) Denominators are total randomised; death or moderate/severe cerebral palsy at 18 months' corrected age
(4) Denominators are total randomised; death or moderate/severe cerebral palsy (GMFCS level II-V); 2 years' corrected age
(5) Denominators are total randomised; death (18 months' corrected age) or moderate/severe cerebral palsy (or later)

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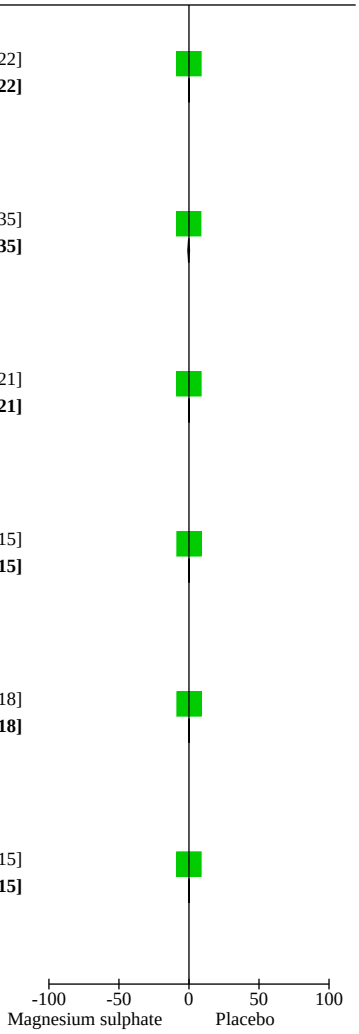
Analysis 3.11. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 11: Growth (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.11.1 Weight (kg)								
Crowther 2023 (1)	12.9	2.1	668	12.9	2	662	100.0%	0.00 [-0.22 , 0.22]
Subtotal (95% CI)			**668**			**662**	**100.0%**	**0.00 [-0.22 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.11.2 Height (cm)								
Crowther 2023 (1)	88.2	5.1	658	88.4	5.1	647	100.0%	-0.20 [-0.75 , 0.35]
Subtotal (95% CI)			**658**			**647**	**100.0%**	**-0.20 [-0.75 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.71 (P = 0.48)								
3.11.3 Head circumference (cm)								
Crowther 2023 (1)	49	1.9	636	49	1.9	629	100.0%	0.00 [-0.21 , 0.21]
Subtotal (95% CI)			**636**			**629**	**100.0%**	**0.00 [-0.21 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.11.4 Weight (z-score)								
Crowther 2023 (2)	0.31	1.17	668	0.28	1.14	662	100.0%	0.03 [-0.09 , 0.15]
Subtotal (95% CI)			**668**			**662**	**100.0%**	**0.03 [-0.09 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
3.11.5 Height (z-score)								
Crowther 2023 (2)	-0.08	1.27	658	-0.13	1.17	647	100.0%	0.05 [-0.08 , 0.18]
Subtotal (95% CI)			**658**			**647**	**100.0%**	**0.05 [-0.08 , 0.18]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.74 (P = 0.46)								
3.11.6 Head circumference (z-score)								
Crowther 2023 (2)	0.68	1.25	636	0.67	1.28	629	100.0%	0.01 [-0.13 , 0.15]
Subtotal (95% CI)			**636**			**629**	**100.0%**	**0.01 [-0.13 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								

Test for subgroup differences: $Chi^2 = 0.91$, df = 5 (P = 0.97), $I^2 = 0\%$



Footnotes

(1) Denominators are children with 2 year corrected age follow up data

(2) Denominators are children with 2 year corrected age follow up data; UK-WHO growth reference

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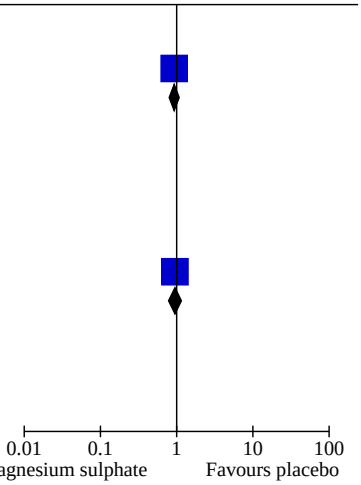
Analysis 3.12. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 12: Respiratory function (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.12.1 Childhood respiratory morbidity						
Crowther 2023 (1)	226	702	230	663	100.0%	0.93 [0.80 , 1.08]
Subtotal (95% CI)		**702**		**663**	**100.0%**	**0.93 [0.80 , 1.08]**
Total events:	226		230			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.98 (P = 0.33)						
3.12.2 Asthma or wheezing						
Crowther 2023 (2)	159	702	158	663	100.0%	0.95 [0.78 , 1.15]
Subtotal (95% CI)		**702**		**663**	**100.0%**	**0.95 [0.78 , 1.15]**
Total events:	159		158			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						



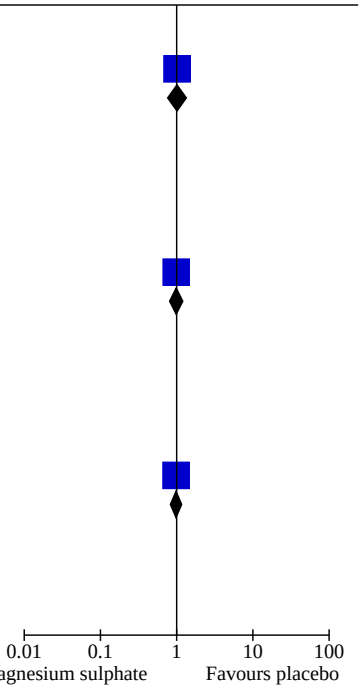
Footnotes

(1) Denominators are children with 2 year corrected age follow up data; defined as asthma, wheezing or respiratory tract infection by parental report

(2) Denominators are children with 2 year corrected age follow up data

Analysis 3.13. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 13: Blood pressure (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.13.1 Systolic hypertension						
Crowther 2023 (1)	76	340	75	339	100.0%	1.01 [0.76 , 1.34]
Subtotal (95% CI)		**340**		**339**	**100.0%**	**1.01 [0.76 , 1.34]**
Total events:	76		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.94)						
3.13.2 Diastolic hypertension						
Crowther 2023 (2)	123	338	124	336	100.0%	0.99 [0.81 , 1.20]
Subtotal (95% CI)		**338**		**336**	**100.0%**	**0.99 [0.81 , 1.20]**
Total events:	123		124			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
3.13.3 Hypertension (any)						
Crowther 2023 (3)	148	338	150	336	100.0%	0.98 [0.83 , 1.16]
Subtotal (95% CI)		**338**		**336**	**100.0%**	**0.98 [0.83 , 1.16]**
Total events:	148		150			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
Test for subgroup differences: Chi² = 0.03, df = 2 (P = 0.98), I² = 0%						



Footnotes

(1) Denominators are children with 2 year corrected age follow up data; defined as z-score systolic blood pressure > 95th percentile using nomograms

(2) Denominators are children with 2 year corrected age follow up data; defined as z-score diastolic blood pressure > 95th percentile using nomograms

(3) Denominators are children with 2 year corrected age follow up data; defined as z-score systolic/diastolic blood pressure > 95th percentile using nomogra

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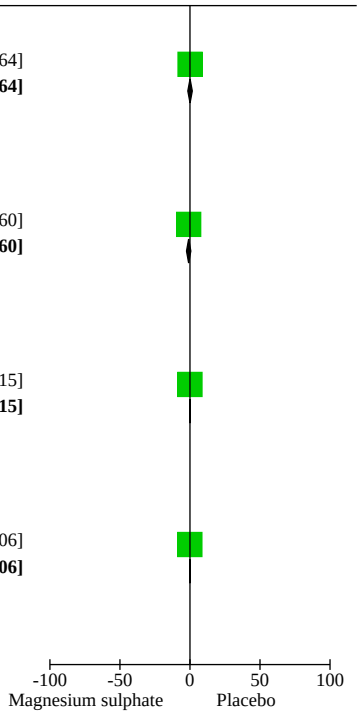
Analysis 3.14. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 14: Blood pressure (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.14.1 Systolic blood pressure (mmHg)								
Crowther 2023 (1)	97.46	11.07	340	97.4	9.96	339	100.0%	0.06 [-1.52 , 1.64]
Subtotal (95% CI)			**340**			**339**	**100.0%**	**0.06 [-1.52 , 1.64]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.07 (P = 0.94)								
3.14.2 Diastolic blood pressure (mmHg)								
Crowther 2023 (1)	57.92	10.19	338	58.85	10.02	336	100.0%	-0.93 [-2.46 , 0.60]
Subtotal (95% CI)			**338**			**336**	**100.0%**	**-0.93 [-2.46 , 0.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.23)								
3.14.3 Systolic blood pressure (z-score)								
Crowther 2023 (1)	0.81	1.06	340	0.81	0.96	339	100.0%	0.00 [-0.15 , 0.15]
Subtotal (95% CI)			**340**			**339**	**100.0%**	**0.00 [-0.15 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
3.14.4 Diastolic blood pressure (z-score)								
Crowther 2023 (1)	1.22	0.95	338	1.3	0.89	336	100.0%	-0.08 [-0.22 , 0.06]
Subtotal (95% CI)			**338**			**336**	**100.0%**	**-0.08 [-0.22 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								

Test for subgroup differences: $Chi^2 = 1.89$, df = 3 (P = 0.60), $I^2 = 0\%$



Footnotes

(1) Denominators are children with 2 year corrected age follow up data

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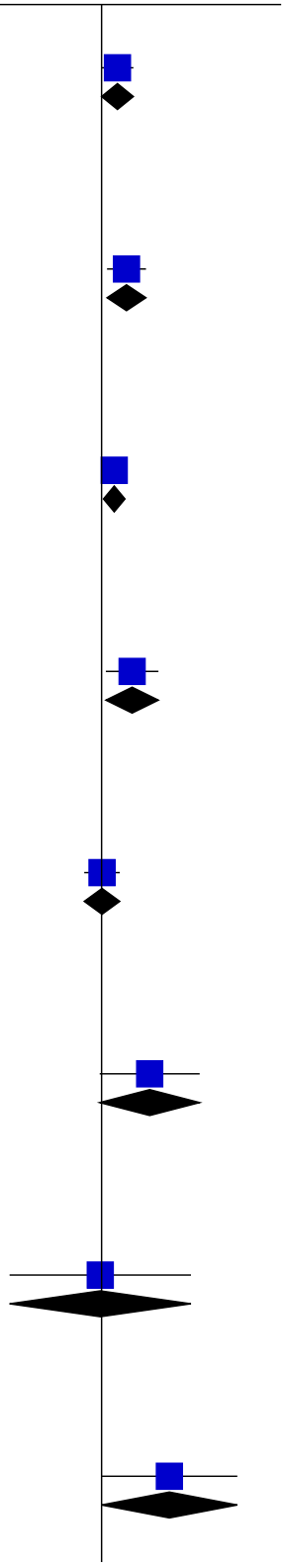
Analysis 3.15. Comparison 3: Magnesium sulphate versus placebo: secondary outcomes for children (up to 2 years' corrected age), Outcome 15: Behaviour (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.15.1 Child Behavior Checklist, total (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	40	389	24	379	100.0%	1.62 [1.00 , 2.64]
Subtotal (95% CI)		**389**		**379**	**100.0%**	**1.62 [1.00 , 2.64]**
Total events:	40		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.96 (P = 0.05)						
3.15.2 Child Behavior Checklist, anxiety (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	33	402	15	391	100.0%	2.14 [1.18 , 3.88]
Subtotal (95% CI)		**402**		**391**	**100.0%**	**2.14 [1.18 , 3.88]**
Total events:	33		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.51 (P = 0.01)						
3.15.3 Child Behavior Checklist, withdrawal (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	76	402	50	389	100.0%	1.47 [1.06 , 2.04]
Subtotal (95% CI)		**402**		**389**	**100.0%**	**1.47 [1.06 , 2.04]**
Total events:	76		50			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.30 (P = 0.02)						
3.15.4 Child Behavior Checklist, sleeping problem (scores in clinical range (> 97.5th percentile))						
Crowther 2023	21	404	8	391	100.0%	2.54 [1.14 , 5.67]
Subtotal (95% CI)		**404**		**391**	**100.0%**	**2.54 [1.14 , 5.67]**
Total events:	21		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.28 (P = 0.02)						
3.15.5 Child Behavior Checklist, somatic problem (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	25	398	24	387	100.0%	1.01 [0.59 , 1.74]
Subtotal (95% CI)		**398**		**387**	**100.0%**	**1.01 [0.59 , 1.74]**
Total events:	25		24			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
3.15.6 Child Behavior Checklist, aggressive behaviour (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	9	400	2	386	100.0%	4.34 [0.94 , 19.97]
Subtotal (95% CI)		**400**		**386**	**100.0%**	**4.34 [0.94 , 19.97]**
Total events:	9		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
3.15.7 Child Behavior Checklist, destructive behaviour (scores in clinical range (> 97.5th percentile))						
Crowther 2023	1	406	1	390	100.0%	0.96 [0.06 , 15.30]
Subtotal (95% CI)		**406**		**390**	**100.0%**	**0.96 [0.06 , 15.30]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.03 (P = 0.98)						
3.15.8 Child Behavior Checklist, other (scores in clinical range (> 97.5th percentile))						
Crowther 2023 (1)	8	389	1	385	100.0%	7.92 [1.00 , 63.00]
Subtotal (95% CI)		**389**		**385**	**100.0%**	**7.92 [1.00 , 63.00]**
Total events:	8		1			
Heterogeneity: Not applicable						



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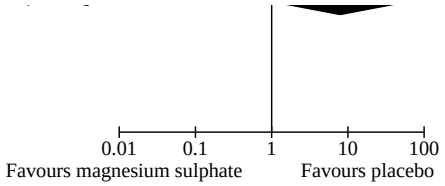
Analysis 3.15. (Continued)

Total events: 8 1

Heterogeneity: Not applicable

Test for overall effect: Z = 1.96 (P = 0.05)

Test for subgroup differences: Chi² = 9.24, df = 7 (P = 0.24), I² = 24.2%



Footnotes

(1) Denominators are children with 2 year corrected age follow up data

Comparison 4. Magnesium sulphate versus placebo: secondary outcomes for children (school age)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Later death (school age)	2	1738	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.12, 1.97]
4.2 Cerebral palsy severity (school age)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.2.1 Mild to moderate	2	1065	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.60]
4.2.2 Severe	2	1038	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.34, 1.92]
4.3 Any neurodevelopmental disability (school age)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.3.1 Mild	1	511	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.63, 1.24]
4.3.2 Moderate	2	940	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.87, 1.14]
4.3.3 Severe	2	940	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.50, 1.29]
4.3.4 Any	2	940	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.05]
4.4 Death or any neurodevelopmental disability (school age)	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.86, 1.02]
4.5 Blindness (school age)	2	983	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.86, 1.28]
4.6 Deafness (school age)	2	1013	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.38, 1.38]
4.7 Developmental delay/intellectual impairment (school age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.7.1 Moderate	1	429	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.24]
4.7.2 Severe	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.35, 1.24]
4.8 Gross motor dysfunction (school age)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.8.1 Motor dysfunction/deficits	2	1026	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.12]
4.8.2 Motor deficits: no cerebral palsy, other motor disorder	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.73, 1.22]
4.8.3 Gross Motor Function Classification System (GMFCS): levels I-V	1	618	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.70]
4.8.4 Movement Assessment Battery for Children (MABC): suspect/abnormal	1	598	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.82, 1.25]
4.9 Death or substantial gross motor dysfunction (school age)	1	501	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.80, 1.08]
4.10 Growth (school age)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.10.1 Weight (SD scores)	1	614	Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.45, -0.01]
4.10.2 Head circumference (SD scores)	1	609	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.40, -0.02]
4.10.3 Height (SD scores)	1	618	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.35, 0.03]
4.10.4 BMI (SD scores)	1	612	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.41, 0.03]
4.11 Respiratory function (school age)	1	424	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.51, 1.03]
4.12 Behaviour (school age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.12.1 'Behavioral and psychiatric disorder' (moderate)	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.67, 1.12]
4.12.2 Borderline and abnormal Total Difficulties Score	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
4.12.3 Borderline and abnormal Emotional Symptoms Scale	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.76, 1.20]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.12.4 Borderline and abnormal Conduct Problem Scale	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.76, 1.46]
4.12.5 Borderline and abnormal Hyperactivity Scale	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.61, 1.19]
4.12.6 Borderline and abnormal Peer Problems Scale	1	431	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.67, 1.24]
4.12.7 Borderline and abnormal Prosocial Scale	1	431	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.49, 2.27]
4.13 Behaviour (school age)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.13.1 CADS parent T scores: ADHD index	1	623	Mean Difference (IV, Fixed, 95% CI)	1.00 [-0.75, 2.75]
4.13.2 CADS parent T scores: DSM-IV inattentive	1	623	Mean Difference (IV, Fixed, 95% CI)	0.70 [-1.05, 2.45]
4.13.3 CADS parent T scores: DSM-IV hyperactive-impulsive	1	623	Mean Difference (IV, Fixed, 95% CI)	0.20 [-1.71, 2.11]
4.13.4 CADS parent T scores: DSM-IV	1	623	Mean Difference (IV, Fixed, 95% CI)	0.60 [-1.20, 2.40]
4.13.5 CADS teacher T scores: ADHD index	1	552	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.32, 2.32]
4.13.6 CADS teacher T scores: DSM-IV inattentive	1	552	Mean Difference (IV, Fixed, 95% CI)	0.60 [-0.82, 2.02]
4.13.7 CADS teacher T scores: DSM-IV hyperactive-impulsive	1	552	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.96, 2.36]
4.13.8 CADS teacher T scores: DSM-IV	1	552	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.81, 2.41]
4.13.9 BRIEF teacher T scores: global executive composite	1	507	Mean Difference (IV, Fixed, 95% CI)	0.90 [-1.14, 2.94]
4.13.10 BRIEF teacher T scores: metacognition index	1	495	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.59, 2.59]
4.13.11 BRIEF teacher T scores: behavioral regulation index	1	537	Mean Difference (IV, Fixed, 95% CI)	0.50 [-1.42, 2.42]
4.14 Educational achievement (school age)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.14.1 Schooling: specialised class room	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.32, 2.35]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.14.2 Schooling: specialised institution	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.25, 3.91]
4.14.3 Schooling: repeated grades	1	422	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.24, 1.15]
4.14.4 Schooling: specific education assistance	1	418	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.40, 1.39]
4.14.5 Schooling: home education services	1	414	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.17, 0.91]
4.14.6 Language disorder	1	127	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.53, 1.52]
4.15 Educational achievement (school age)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.15.1 Academic skills: reading	1	588	Mean Difference (IV, Fixed, 95% CI)	0.50 [-2.24, 3.24]
4.15.2 Academic skills: spelling	1	584	Mean Difference (IV, Fixed, 95% CI)	1.20 [-1.31, 3.71]
4.15.3 Academic skills: arithmetic	1	587	Mean Difference (IV, Fixed, 95% CI)	0.30 [-2.35, 2.95]
4.15.4 General cognitive function: full scale IQ	1	583	Mean Difference (IV, Fixed, 95% CI)	-1.10 [-3.60, 1.40]
4.15.5 General cognitive function: verbal comprehension index	1	601	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-3.00, 1.60]
4.15.6 General cognitive function: perceptual reasoning index	1	601	Mean Difference (IV, Fixed, 95% CI)	-1.50 [-3.95, 0.95]
4.15.7 General cognitive function: working memory index	1	592	Mean Difference (IV, Fixed, 95% CI)	-1.30 [-3.68, 1.08]
4.15.8 General cognitive function: processing speed index	1	585	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.97, 2.77]

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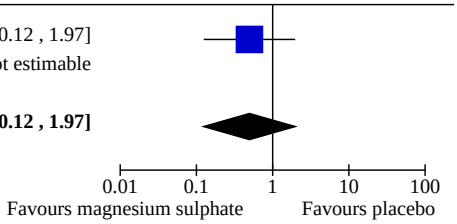
Analysis 4.1. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 1: Later death (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	3	620	6	615	100.0%	0.50 [0.12 , 1.97]
Marret 2006 (2)	0	252	0	251		Not estimable
Total (95% CI)		**872**		**866**	**100.0%**	**0.50 [0.12 , 1.97]**
Total events:	3		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Not applicable						



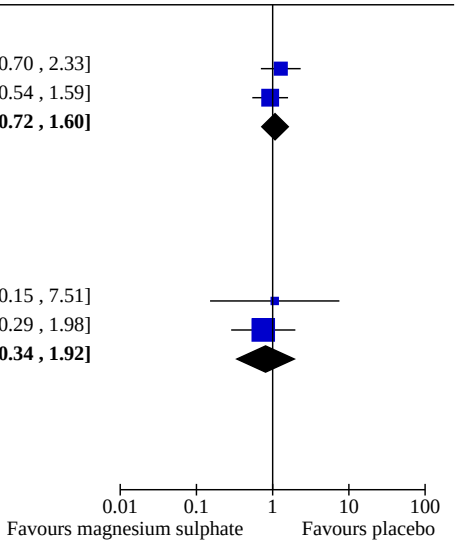
Footnotes

(1) Denominators are livebirths; post-discharge deaths to 6-11 year follow up

(2) Denominators are deaths (between 2 years and school age) and children with 7-14 year follow up data

Analysis 4.2. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 2: Cerebral palsy severity (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Mild to moderate						
Crowther 2003 (1)	21	295	19	341	41.9%	1.28 [0.70 , 2.33]
Marret 2006 (2)	23	218	24	211	58.1%	0.93 [0.54 , 1.59]
Subtotal (95% CI)		**513**		**552**	**100.0%**	**1.07 [0.72 , 1.60]**
Total events:	44		43			
Heterogeneity: Chi² = 0.60, df = 1 (P = 0.44); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
4.2.2 Severe						
Crowther 2003 (3)	2	295	2	314	17.5%	1.06 [0.15 , 7.51]
Marret 2006 (4)	7	218	9	211	82.5%	0.75 [0.29 , 1.98]
Subtotal (95% CI)		**513**		**525**	**100.0%**	**0.81 [0.34 , 1.92]**
Total events:	9		11			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.48 (P = 0.63)						



Footnotes

(1) Denominators are children with 6-11 year follow up data; sum of mild (GMFCS level I) and moderate (GMFCS level II-III)

(2) Denominators are children with 7-14 year follow up data; cerebral palsy, but walks without aid

(3) Denominators are children with 6-11 year follow up data; severe (GMFCS level IV-V)

(4) Denominators are children with 7-14 year follow up data; cerebral palsy, unable to walk, or walking only with aid, or treated with botulinum toxin infusi

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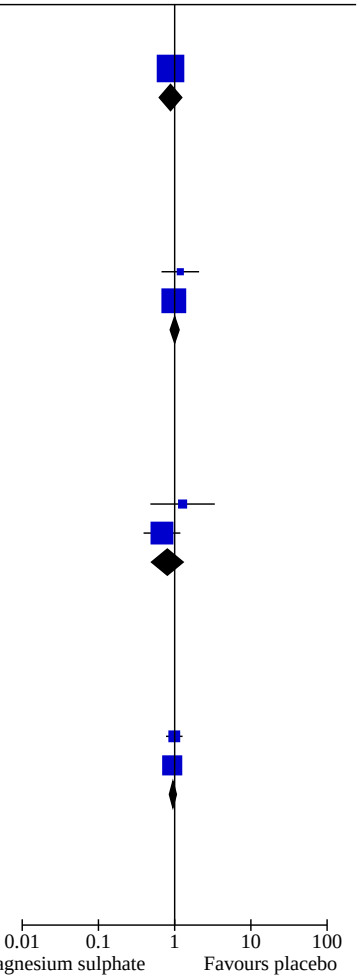
Analysis 4.3. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 3: Any neurodevelopmental disability (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Mild						
Crowther 2003 (1)	50	257	56	254	100.0%	0.88 [0.63 , 1.24]
Subtotal (95% CI)		**257**		**254**	**100.0%**	**0.88 [0.63 , 1.24]**
Total events:	50		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.72 (P = 0.47)						
4.3.2 Moderate						
Crowther 2003 (2)	24	257	20	254	11.9%	1.19 [0.67 , 2.09]
Marret 2006 (3)	147	218	146	211	88.1%	0.97 [0.86 , 1.11]
Subtotal (95% CI)		**475**		**465**	**100.0%**	**1.00 [0.87 , 1.14]**
Total events:	171		166			
Heterogeneity: Chi² = 0.50, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
4.3.3 Severe						
Crowther 2003 (4)	9	257	7	254	20.4%	1.27 [0.48 , 3.36]
Marret 2006 (5)	19	218	27	211	79.6%	0.68 [0.39 , 1.19]
Subtotal (95% CI)		**475**		**465**	**100.0%**	**0.80 [0.50 , 1.29]**
Total events:	28		34			
Heterogeneity: Chi² = 1.19, df = 1 (P = 0.27); I² = 16%						
Test for overall effect: Z = 0.91 (P = 0.36)						
4.3.4 Any						
Crowther 2003 (6)	83	257	83	254	32.2%	0.99 [0.77 , 1.27]
Marret 2006 (7)	166	218	173	211	67.8%	0.93 [0.84 , 1.02]
Subtotal (95% CI)		**475**		**465**	**100.0%**	**0.95 [0.85 , 1.05]**
Total events:	249		256			
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						



Footnotes

(1) Denominators are children with 6-11 year follow up data; mild disability: any of mild cerebral palsy or an IQ from 70-85 (WISC-IV)
(2) Denominators are children with 6-11 year follow up data; moderate disability: any of moderate cerebral palsy, deafness or an IQ of 55-69 (WISC-IV)
(3) Denominators are children with 7-14 year follow up data; overall deficits, moderate: at least 1 of moderate cerebral palsy, other motor disorder, moderat
(4) Denominators are children with 6-11 year follow up data; severe disability: any of severe cerebral palsy, an IQ < 55 (WISC-IV), or blindness
(5) Denominators are children with 7-14 year follow up data; overall deficits, severe: at least 1 of severe cerebral palsy, severe cognitive deficit/learning dis
(6) Denominators are children with 6-11 year follow up data; mild disability: any of mild cerebral palsy or an IQ from 70-85 (WISC-IV); moderate disabilit
(7) Denominators are children with 7-14 year follow up data; overall deficits, moderate: at least 1 of moderate cerebral palsy, other motor disorder, moderat

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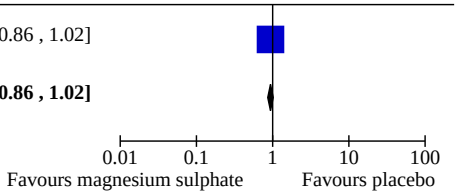
Analysis 4.4. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 4: Death or any neurodevelopmental disability (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	200	252	211	249	100.0%	0.94 [0.86 , 1.02]
Total (95% CI)		**252**		**249**	**100.0%**	**0.94 [0.86 , 1.02]**
Total events:	200		211			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.56 (P = 0.12)
Test for subgroup differences: Not applicable



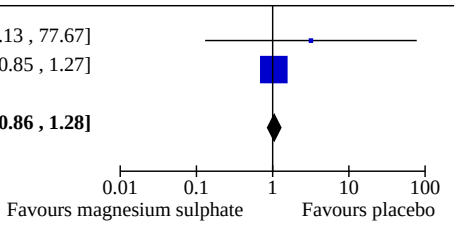
Footnotes

(1) Denominators are deaths and children with 7-14 year follow up data; death and/or motor and/or cognitive deficits and/or psychiatric disorder

Analysis 4.5. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 5: Blindness (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	1	269	0	285	0.5%	3.18 [0.13 , 77.67]
Marret 2006 (2)	105	218	98	211	99.5%	1.04 [0.85 , 1.27]
Total (95% CI)		**487**		**496**	**100.0%**	**1.05 [0.86 , 1.28]**
Total events:	106		98			

Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.45 (P = 0.65)
Test for subgroup differences: Not applicable



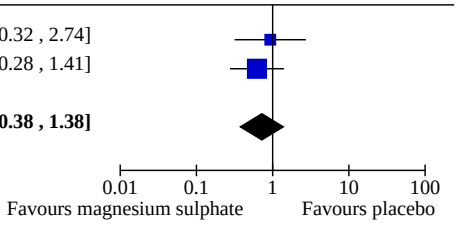
Footnotes

(1) Denominators are children with 6-11 year follow up data; vision in both eyes worse than 20/20
(2) Denominators are children with 7-14 year follow up data; visual deficiency was defined by poor vision (as assessed by parents) and wearing glasses

Analysis 4.6. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 6: Deafness (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	6	280	7	304	32.1%	0.93 [0.32 , 2.74]
Marret 2006 (2)	9	218	14	211	67.9%	0.62 [0.28 , 1.41]
Total (95% CI)		**498**		**515**	**100.0%**	**0.72 [0.38 , 1.38]**
Total events:	15		21			

Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 0.99 (P = 0.32)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are children with 6-11 year follow up data; deafness: requiring hearing aids or worse
(2) Denominators are children with 7-14 year follow up data; hearing deficiency was defined as poor hearing (as assessed by parents) or wearing a hearing a

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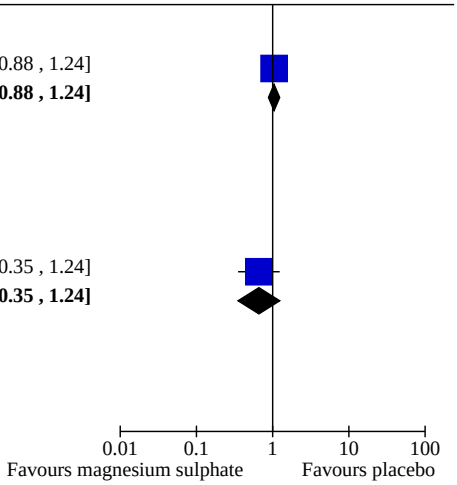
Analysis 4.7. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 7: Developmental delay/intellectual impairment (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 Moderate						
Marret 2006 (1)	124	218	115	211	100.0%	1.04 [0.88 , 1.24]
Subtotal (95% CI)		**218**		**211**	**100.0%**	**1.04 [0.88 , 1.24]**
Total events:	124		115			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.50 (P = 0.62)						
4.7.2 Severe						
Marret 2006 (2)	15	218	22	211	100.0%	0.66 [0.35 , 1.24]
Subtotal (95% CI)		**218**		**211**	**100.0%**	**0.66 [0.35 , 1.24]**
Total events:	15		22			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: Chi² = 1.91, df = 1 (P = 0.17), I² = 47.5%						



Footnotes

(1) Denominators are children with 7-14 year follow up data; cognitive deficits/learning disabilities: moderate (has repeated a grade and/or receives/needs s

(2) Denominators children with 7-14 year follow up data; cognitive deficits/learning disabilities: severe (special school/class)

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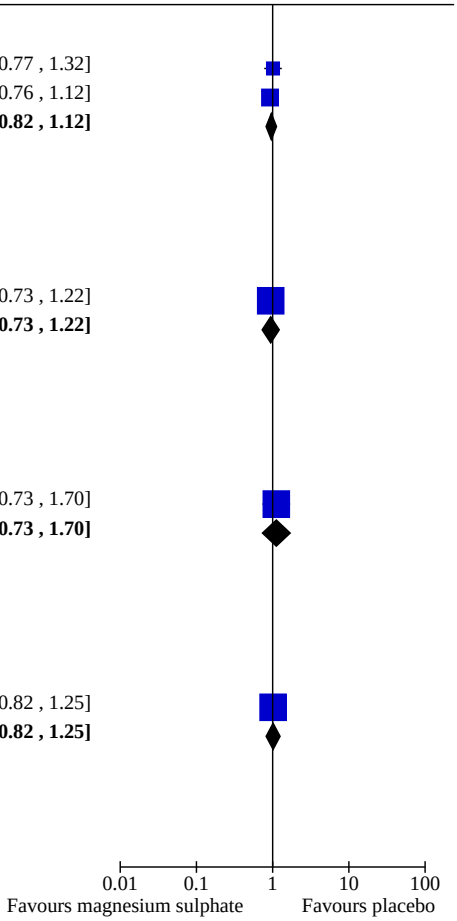
Analysis 4.8. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 8: Gross motor dysfunction (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 Motor dysfunction/deficits						
Crowther 2003 (1)	80	297	80	300	41.8%	1.01 [0.77 , 1.32]
Marret 2006 (2)	104	218	109	211	58.2%	0.92 [0.76 , 1.12]
Subtotal (95% CI)		**515**		**511**	**100.0%**	**0.96 [0.82 , 1.12]**
Total events:	184		189			
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
4.8.2 Motor deficits: no cerebral palsy, other motor disorder						
Marret 2006 (3)	74	218	76	211	100.0%	0.94 [0.73 , 1.22]
Subtotal (95% CI)		**218**		**211**	**100.0%**	**0.94 [0.73 , 1.22]**
Total events:	74		76			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
4.8.3 Gross Motor Function Classification System (GMFCS): levels I-V						
Crowther 2003 (4)	40	304	37	314	100.0%	1.12 [0.73 , 1.70]
Subtotal (95% CI)		**304**		**314**	**100.0%**	**1.12 [0.73 , 1.70]**
Total events:	40		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.52 (P = 0.61)						
4.8.4 Movement Assessment Battery for Children (MABC): suspect/abnormal						
Crowther 2003 (5)	110	297	110	301	100.0%	1.01 [0.82 , 1.25]
Subtotal (95% CI)		**297**		**301**	**100.0%**	**1.01 [0.82 , 1.25]**
Total events:	110		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.12 (P = 0.90)						
Test for subgroup differences: Chi² = 0.63, df = 3 (P = 0.89), I² = 0%						



Footnotes

(1) Denominators are children with 6-11 year follow up data; definite motor dysfunction (< 5th centile with MABC, or cerebral palsy)

(2) Denominators are children with 7-14 year follow up data; motor deficits (any): cerebral palsy, or no cerebral palsy but dyspraxia or motor coordination d

(3) Denominators are children with 7-14 year follow up data; no cerebral palsy but dyspraxia or motor coordination disorder (defined as coordination disord

(4) Denominators are children with 6-11 year follow up data; sum of GMFCS levels I-V (includes some children without cerebral palsy)

(5) Denominators are children with 6-11 year follow up data; sum of suspect (< 15th centile) and abnormal (< 5th centile)

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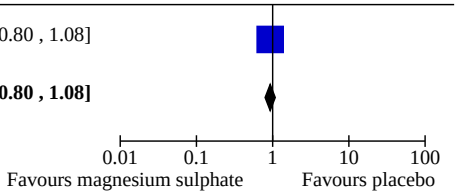
Analysis 4.9. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 9: Death or substantial gross motor dysfunction (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	138	252	147	249	100.0%	0.93 [0.80 , 1.08]
Total (95% CI)		**252**		**249**	**100.0%**	**0.93 [0.80 , 1.08]**
Total events:	138		147			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.97 (P = 0.33)						
Test for subgroup differences: Not applicable						

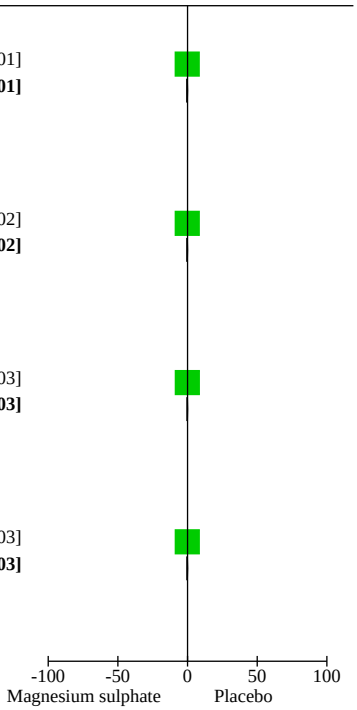


Footnotes

(1) Denominators are deaths or children with 7-14 year follow up data; death and/or motor deficit

Analysis 4.10. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 10: Growth (school age)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.10.1 Weight (SD scores)								
Crowther 2003 (1)	-0.18	1.43	298	0.05	1.33	316	100.0%	-0.23 [-0.45 , -0.01]
Subtotal (95% CI)			**298**			**316**	**100.0%**	**-0.23 [-0.45 , -0.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.06 (P = 0.04)								
4.10.2 Head circumference (SD scores)								
Crowther 2003 (1)	-1.07	1.13	298	-0.86	1.26	311	100.0%	-0.21 [-0.40 , -0.02]
Subtotal (95% CI)			**298**			**311**	**100.0%**	**-0.21 [-0.40 , -0.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.17 (P = 0.03)								
4.10.3 Height (SD scores)								
Crowther 2003 (1)	-0.25	1.24	302	-0.09	1.2	316	100.0%	-0.16 [-0.35 , 0.03]
Subtotal (95% CI)			**302**			**316**	**100.0%**	**-0.16 [-0.35 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.63 (P = 0.10)								
4.10.4 BMI (SD scores)								
Crowther 2003 (1)	-0.04	1.43	297	0.15	1.37	315	100.0%	-0.19 [-0.41 , 0.03]
Subtotal (95% CI)			**297**			**315**	**100.0%**	**-0.19 [-0.41 , 0.03]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.68 (P = 0.09)								
Test for subgroup differences: Chi^2 = 0.25, df = 3 (P = 0.97), I^2 = 0%								



Footnotes

(1) Denominators are children with 6-11 year follow up data; SD scores computed from British Growth Reference data

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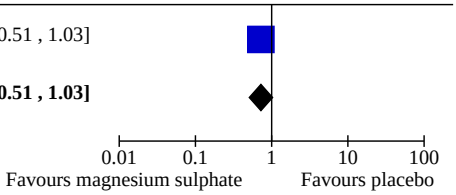
Analysis 4.11. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 11: Respiratory function (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	42	214	57	210	100.0%	0.72 [0.51 , 1.03]
Total (95% CI)		**214**		**210**	**100.0%**	**0.72 [0.51 , 1.03]**
Total events:	42		57			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.81 (P = 0.07)
Test for subgroup differences: Not applicable



Footnotes

(1) Denominators are children with 7-14 year follow up data; asthma

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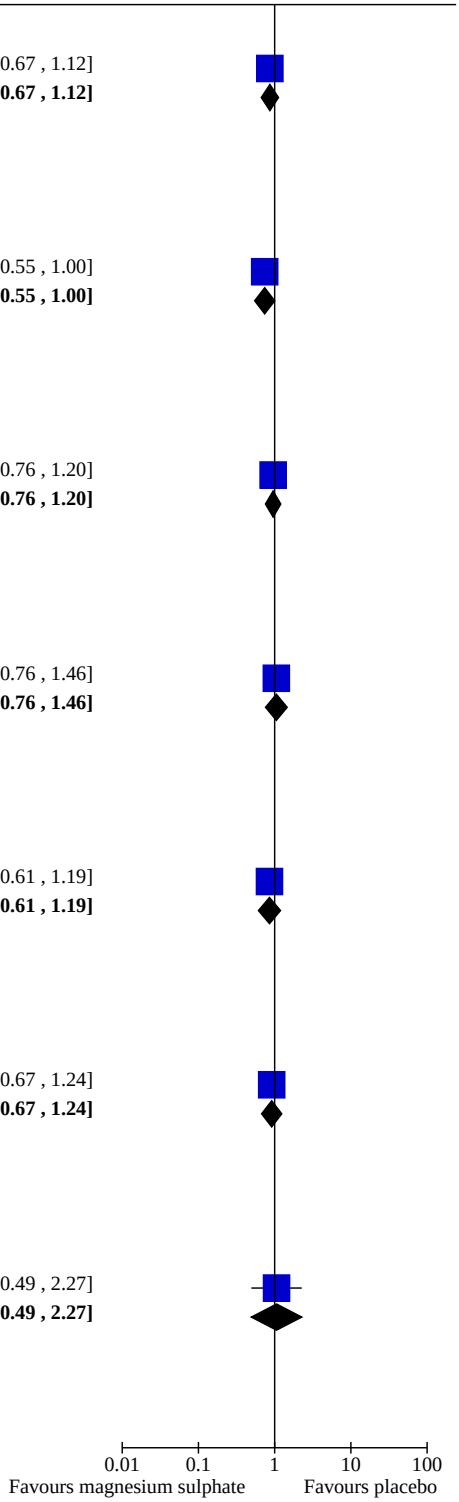
Analysis 4.12. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 12: Behaviour (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.12.1 'Behavioral and psychiatric disorder' (moderate)						
Marret 2006 (1)	70	218	79	213	100.0%	0.87 [0.67 , 1.12]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**0.87 [0.67 , 1.12]**
Total events:	70		79			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.08 (P = 0.28)						
4.12.2 Borderline and abnormal Total Difficulties Score						
Marret 2006 (2)	53	218	70	213	100.0%	0.74 [0.55 , 1.00]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**0.74 [0.55 , 1.00]**
Total events:	53		70			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.95 (P = 0.05)						
4.12.3 Borderline and abnormal Emotional Symptoms Scale						
Marret 2006 (2)	85	218	87	213	100.0%	0.95 [0.76 , 1.20]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**0.95 [0.76 , 1.20]**
Total events:	85		87			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.39 (P = 0.69)						
4.12.4 Borderline and abnormal Conduct Problem Scale						
Marret 2006 (2)	56	218	52	213	100.0%	1.05 [0.76 , 1.46]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**1.05 [0.76 , 1.46]**
Total events:	56		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.31 (P = 0.76)						
4.12.5 Borderline and abnormal Hyperactivity Scale						
Marret 2006 (2)	49	218	56	213	100.0%	0.85 [0.61 , 1.19]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**0.85 [0.61 , 1.19]**
Total events:	49		56			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
4.12.6 Borderline and abnormal Peer Problems Scale						
Marret 2006 (2)	58	218	62	213	100.0%	0.91 [0.67 , 1.24]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**0.91 [0.67 , 1.24]**
Total events:	58		62			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
4.12.7 Borderline and abnormal Prosocial Scale						
Marret 2006 (2)	13	218	12	213	100.0%	1.06 [0.49 , 2.27]
Subtotal (95% CI)		**218**		**213**	**100.0%**	**1.06 [0.49 , 2.27]**
Total events:	13		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
Test for subgroup differences: Chi² = 3.10, df = 6 (P = 0.80), I² = 0%						



Footnotes

(1) Denominators are children with 7-14 year follow up data; "Hyperactivity or attention deficit disorder or methylphenidate medication or overall SDQ >17

(2) Denominators are children with 7-14 year follow up data; assessed with SDQ

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Analysis 4.12. (Continued)

(1) Denominators are children with 7-14 year follow up data; "Hyperactivity or attention deficit disorder or methylphenidate medication or overall SDQ >17
(2) Denominators are children with 7-14 year follow up data; assessed with SDQ

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Analysis 4.13. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 13: Behaviour (school age)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.13.1 CADS parent T scores: ADHD index								
Crowther 2003 (1)	57.3	11.5	305	56.3	10.7	318	100.0%	1.00 [-0.75 , 2.75]
Subtotal (95% CI)			**305**			**318**	**100.0%**	**1.00 [-0.75 , 2.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
4.13.2 CADS parent T scores: DSM-IV inattentive								
Crowther 2003 (1)	56.1	11.6	305	55.4	10.7	318	100.0%	0.70 [-1.05 , 2.45]
Subtotal (95% CI)			**305**			**318**	**100.0%**	**0.70 [-1.05 , 2.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.43)								
4.13.3 CADS parent T scores: DSM-IV hyperactive-impulsive								
Crowther 2003 (1)	56.1	12.3	305	55.9	12	318	100.0%	0.20 [-1.71 , 2.11]
Subtotal (95% CI)			**305**			**318**	**100.0%**	**0.20 [-1.71 , 2.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.21 (P = 0.84)								
4.13.4 CADS parent T scores: DSM-IV								
Crowther 2003 (1)	56.6	11.7	305	56	11.2	318	100.0%	0.60 [-1.20 , 2.40]
Subtotal (95% CI)			**305**			**318**	**100.0%**	**0.60 [-1.20 , 2.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.51)								
4.13.5 CADS teacher T scores: ADHD index								
Crowther 2003 (1)	54.3	11.3	271	53.8	10.5	281	100.0%	0.50 [-1.32 , 2.32]
Subtotal (95% CI)			**271**			**281**	**100.0%**	**0.50 [-1.32 , 2.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.54 (P = 0.59)								
4.13.6 CADS teacher T scores: DSM-IV inattentive								
Crowther 2003 (1)	50	8.6	271	49.4	8.4	281	100.0%	0.60 [-0.82 , 2.02]
Subtotal (95% CI)			**271**			**281**	**100.0%**	**0.60 [-0.82 , 2.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
4.13.7 CADS teacher T scores: DSM-IV hyperactive-impulsive								
Crowther 2003 (1)	51.9	10.4	271	51.2	9.4	281	100.0%	0.70 [-0.96 , 2.36]
Subtotal (95% CI)			**271**			**281**	**100.0%**	**0.70 [-0.96 , 2.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
4.13.8 CADS teacher T scores: DSM-IV								
Crowther 2003 (1)	52.8	10.2	271	52	9.1	281	100.0%	0.80 [-0.81 , 2.41]
Subtotal (95% CI)			**271**			**281**	**100.0%**	**0.80 [-0.81 , 2.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.97 (P = 0.33)								
4.13.9 BRIEF teacher T scores: global executive composite								
Crowther 2003 (1)	54	12.4	246	53.1	10.9	261	100.0%	0.90 [-1.14 , 2.94]
Subtotal (95% CI)			**246**			**261**	**100.0%**	**0.90 [-1.14 , 2.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.87 (P = 0.39)								
4.13.10 BRIEF teacher T scores: metacognition index								
Crowther 2003 (1)	54.5	12.6	243	54	11.1	252	100.0%	0.50 [-1.59 , 2.59]
Subtotal (95% CI)			**243**			**252**	**100.0%**	**0.50 [-1.59 , 2.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								

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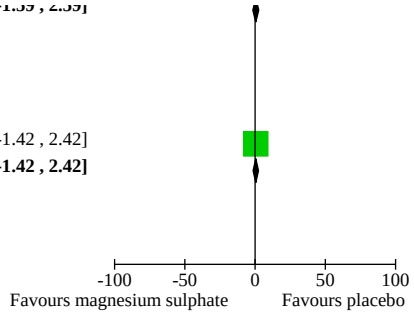
Analysis 4.13. (Continued)

Subtotal (95 % CI)			**243**			**252**	**100.0 %**	**0.50 [-1.39 , 2.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								
4.13.11 BRIEF teacher T scores: behavioral regulation index								
Crowther 2003 (1)	52	11.9	265	51.5	10.7	272	100.0%	0.50 [-1.42 , 2.42]
Subtotal (95% CI)			**265**			**272**	**100.0%**	**0.50 [-1.42 , 2.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.51 (P = 0.61)								
Test for subgroup differences: Chi² = 0.54, df = 10 (P = 1.00), I² = 0%								



Footnotes

(1) Denominators are children with 6-11 year follow up data

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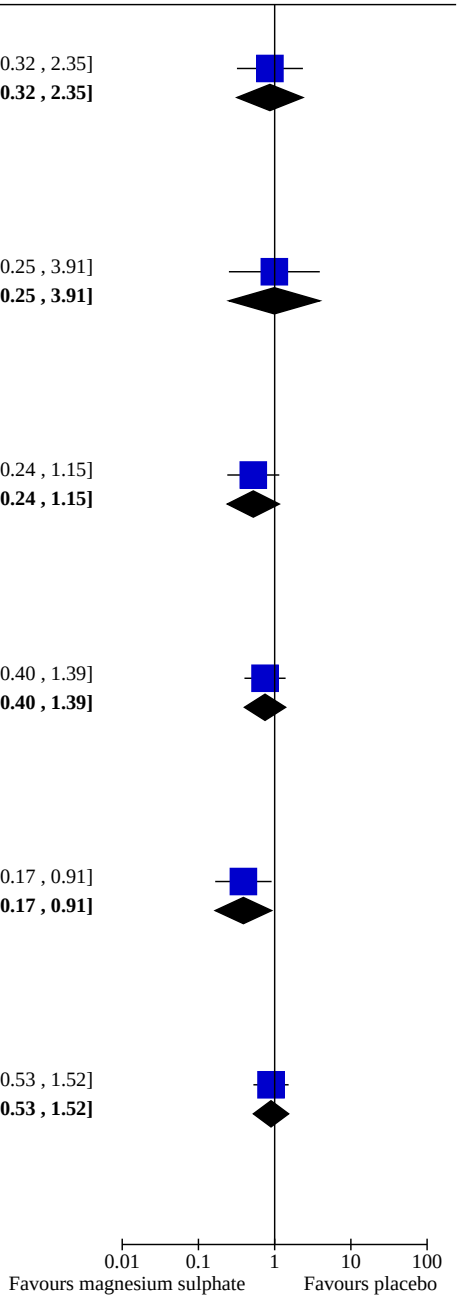
Analysis 4.14. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 14: Educational achievement (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.14.1 Schooling: specialised class room						
Marret 2006 (1)	7	212	8	210	100.0%	0.87 [0.32 , 2.35]
Subtotal (95% CI)		**212**		**210**	**100.0%**	**0.87 [0.32 , 2.35]**
Total events:	7		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
4.14.2 Schooling: specialised institution						
Marret 2006 (1)	4	212	4	210	100.0%	0.99 [0.25 , 3.91]
Subtotal (95% CI)		**212**		**210**	**100.0%**	**0.99 [0.25 , 3.91]**
Total events:	4		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
4.14.3 Schooling: repeated grades						
Marret 2006 (2)	9	212	17	210	100.0%	0.52 [0.24 , 1.15]
Subtotal (95% CI)		**212**		**210**	**100.0%**	**0.52 [0.24 , 1.15]**
Total events:	9		17			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
4.14.4 Schooling: specific education assistance						
Marret 2006 (3)	16	211	21	207	100.0%	0.75 [0.40 , 1.39]
Subtotal (95% CI)		**211**		**207**	**100.0%**	**0.75 [0.40 , 1.39]**
Total events:	16		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.92 (P = 0.36)						
4.14.5 Schooling: home education services						
Marret 2006 (1)	7	207	18	207	100.0%	0.39 [0.17 , 0.91]
Subtotal (95% CI)		**207**		**207**	**100.0%**	**0.39 [0.17 , 0.91]**
Total events:	7		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						
4.14.6 Language disorder						
Marret 2006 (4)	19	67	19	60	100.0%	0.90 [0.53 , 1.52]
Subtotal (95% CI)		**67**		**60**	**100.0%**	**0.90 [0.53 , 1.52]**
Total events:	19		19			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.41 (P = 0.68)						
Test for subgroup differences: Chi² = 3.63, df = 5 (P = 0.60), I² = 0%						



Footnotes

(1) Denominators are children with 7-14 year follow up data

(2) Denominators are children with 7-14 year follow up data; defined as a 2 year delay compared with a normal age for a given grade

(3) Denominators are children with 7-14 year follow up data; defined as use of special education services and home care

(4) Denominators are children with 7-14 year follow up data; defined as treatment by a speech-language pathologist

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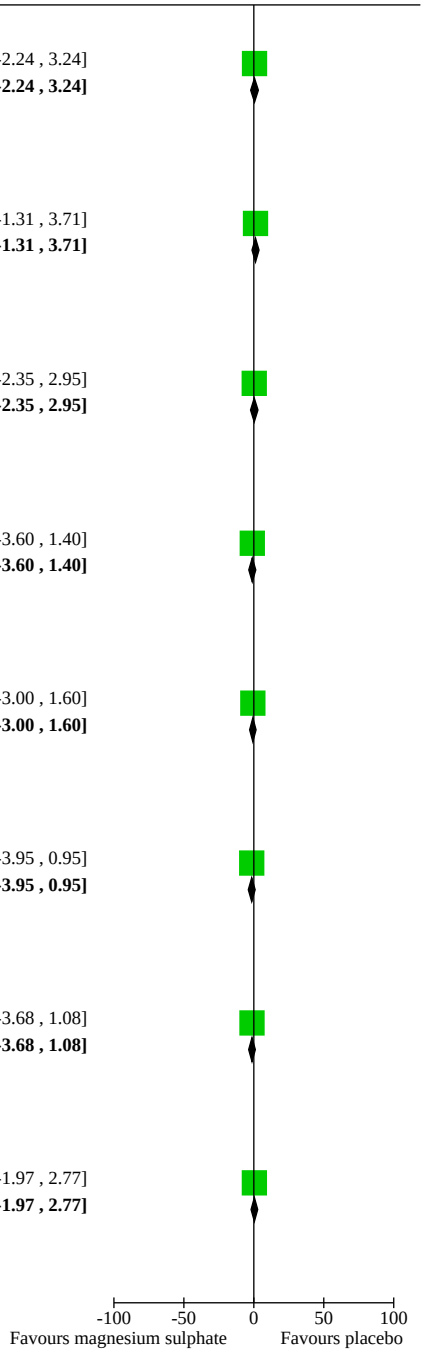
Analysis 4.15. Comparison 4: Magnesium sulphate versus placebo: secondary outcomes for children (school age), Outcome 15: Educational achievement (school age)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.15.1 Academic skills: reading								
Crowther 2003 (1)	99.4	17	287	98.9	16.9	301	100.0%	0.50 [-2.24 , 3.24]
Subtotal (95% CI)			**287**			**301**	**100.0%**	**0.50 [-2.24 , 3.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								
4.15.2 Academic skills: spelling								
Crowther 2003 (1)	98.3	15.7	285	97.1	15.2	299	100.0%	1.20 [-1.31 , 3.71]
Subtotal (95% CI)			**285**			**299**	**100.0%**	**1.20 [-1.31 , 3.71]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.94 (P = 0.35)								
4.15.3 Academic skills: arithmetic								
Crowther 2003 (1)	89.8	16.6	288	89.5	16.1	299	100.0%	0.30 [-2.35 , 2.95]
Subtotal (95% CI)			**288**			**299**	**100.0%**	**0.30 [-2.35 , 2.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.22 (P = 0.82)								
4.15.4 General cognitive function: full scale IQ								
Crowther 2003 (2)	93.8	15.8	290	94.9	15	293	100.0%	-1.10 [-3.60 , 1.40]
Subtotal (95% CI)			**290**			**293**	**100.0%**	**-1.10 [-3.60 , 1.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.86 (P = 0.39)								
4.15.5 General cognitive function: verbal comprehension index								
Crowther 2003 (2)	94.2	15.1	298	94.9	13.6	303	100.0%	-0.70 [-3.00 , 1.60]
Subtotal (95% CI)			**298**			**303**	**100.0%**	**-0.70 [-3.00 , 1.60]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
4.15.6 General cognitive function: perceptual reasoning index								
Crowther 2003 (2)	96.1	15.4	298	97.6	15.2	303	100.0%	-1.50 [-3.95 , 0.95]
Subtotal (95% CI)			**298**			**303**	**100.0%**	**-1.50 [-3.95 , 0.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.20 (P = 0.23)								
4.15.7 General cognitive function: working memory index								
Crowther 2003 (2)	95.1	14.9	294	96.4	14.7	298	100.0%	-1.30 [-3.68 , 1.08]
Subtotal (95% CI)			**294**			**298**	**100.0%**	**-1.30 [-3.68 , 1.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.07 (P = 0.29)								
4.15.8 General cognitive function: processing speed index								
Crowther 2003 (2)	94.9	15.1	291	94.5	14.1	294	100.0%	0.40 [-1.97 , 2.77]
Subtotal (95% CI)			**291**			**294**	**100.0%**	**0.40 [-1.97 , 2.77]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Test for subgroup differences: Chi² = 4.34, df = 7 (P = 0.74), I² = 0%								



Footnotes

(1) Denominators are children with 6-11 year follow up data; assessed with WRAT3

(2) Denominators are children with 6-11 year follow up data; assessed with WISC-IV

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Comparison 5. Magnesium sulphate versus placebo: secondary outcomes for women

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Death	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
5.2 Cardiac arrest	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.3 Respiratory arrest	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
5.4 Side effects of treatment	4	5300	Risk Ratio (M-H, Random, 95% CI)	4.49 [2.53, 7.97]
5.5 Side effect: respiratory depression	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.5.1 As defined	3	4736	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.82, 1.61]
5.5.2 As defined	2	3303	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.83, 2.07]
5.6 Side effect: hypotension	3	3059	Risk Ratio (M-H, Fixed, 95% CI)	1.70 [1.29, 2.25]
5.7 Side effect: tachycardia	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [1.03, 2.29]
5.8 Side effect: warmth over body/flushing	4	5300	Risk Ratio (M-H, Random, 95% CI)	7.13 [4.28, 11.86]
5.9 Side effect: arm discomfort with infusion	3	4736	Risk Ratio (M-H, Fixed, 95% CI)	9.64 [7.85, 11.83]
5.10 Side effect: mouth dryness	2	2495	Risk Ratio (M-H, Random, 95% CI)	3.26 [1.31, 8.15]
5.11 Side effect: nausea or vomiting	4	5300	Risk Ratio (M-H, Random, 95% CI)	3.99 [2.05, 7.74]
5.12 Side effect: sleepiness	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [1.82, 3.42]
5.13 Side effect: sweating	3	4736	Risk Ratio (M-H, Random, 95% CI)	6.12 [2.86, 13.10]
5.14 Side effect: dizziness	2	2495	Risk Ratio (M-H, Random, 95% CI)	3.16 [1.50, 6.68]
5.15 Side effect: blurred vision	2	2495	Risk Ratio (M-H, Random, 95% CI)	4.33 [1.05, 17.88]
5.16 Side effect: tendon reflex abolition	1	564	Risk Ratio (M-H, Fixed, 95% CI)	1.94 [0.18, 21.32]
5.17 Side effect: "curarisation"	1	564	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 71.29]
5.18 Side effect: headache	1	564	Risk Ratio (M-H, Fixed, 95% CI)	3.89 [0.44, 34.57]
5.19 Mode of birth: caesarean birth	5	5861	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.91, 1.02]
5.20 Chorioamnionitis	1	2241	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.27]
5.21 Postpartum haemorrhage	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

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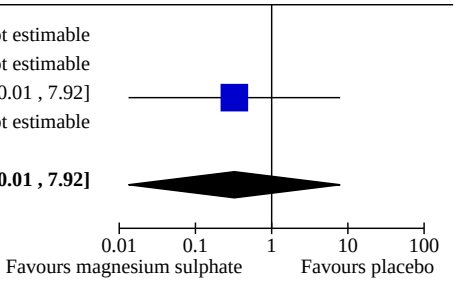
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.21.1 Postpartum haemorrhage	2	2495	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.09]
5.21.2 Severe postpartum haemorrhage	3	3059	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.90, 2.05]

Analysis 5.1. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 1: Death

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (1)	0	729	0	704		Not estimable
Marret 2006 (1)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Rouse 2008 (1)	0	1096	0	1145		Not estimable
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.69 (P = 0.49)
Test for subgroup differences: Not applicable

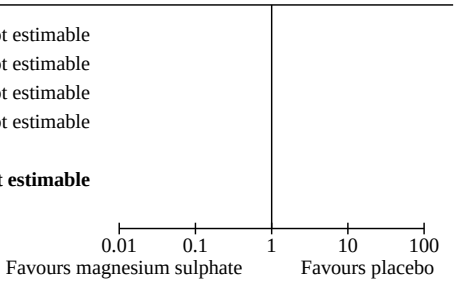


Footnotes
(1) Denominators are total randomised

Analysis 5.2. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 2: Cardiac arrest

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (1)	0	729	0	704		Not estimable
Marret 2006 (1)	0	286	0	278		Not estimable
Rouse 2008 (1)	0	1096	0	1145		Not estimable
Total (95% CI)		**2646**		**2654**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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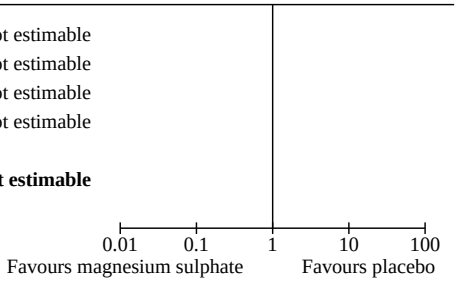
Analysis 5.3. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 3: Respiratory arrest

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (1)	0	729	0	704		Not estimable
Marret 2006 (2)	0	286	0	278		Not estimable
Rouse 2008 (1)	0	1096	0	1145		Not estimable
Total (95% CI)		**2646**		**2654**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

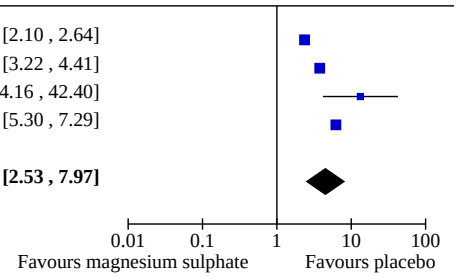


Footnotes
(1) Denominators are total randomised
(2) Denominators are total randomised; prolonged mechanical ventilation

Analysis 5.4. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 4: Side effects of treatment

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	476	535	199	527	29.1%	2.36 [2.10 , 2.64]
Crowther 2023 (2)	531	729	136	704	28.8%	3.77 [3.22 , 4.41]
Marret 2006 (3)	41	286	3	278	13.3%	13.28 [4.16 , 42.40]
Rouse 2008 (4)	833	1096	140	1145	28.8%	6.22 [5.30 , 7.29]
Total (95% CI)		**2646**		**2654**	**100.0%**	**4.49 [2.53 , 7.97]**
Total events:	1881		478			

Heterogeneity: Tau² = 0.29; Chi² = 114.82, df = 3 (P < 0.00001); I² = 97%
Test for overall effect: Z = 5.14 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised; any adverse effects (clinical and self-assessed maternal adverse effects of the infusion)
(2) Denominators are total randomised; participant side effects of the infusion
(3) Denominators are total randomised; mild adverse effects
(4) Denominators are total randomised; any adverse event

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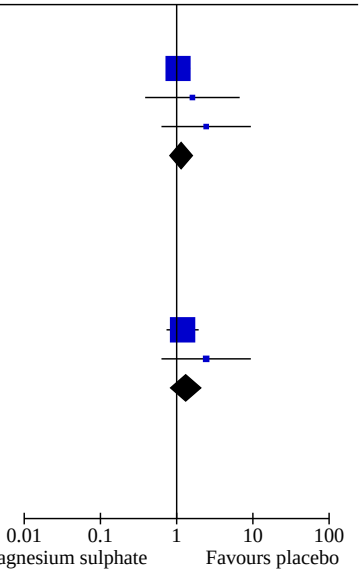
Analysis 5.5. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 5: Side effect: respiratory depression

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.5.1 As defined						
Crowther 2003 (1)	54	535	51	527	89.6%	1.04 [0.73 , 1.50]
Crowther 2023 (2)	5	729	3	704	5.3%	1.61 [0.39 , 6.71]
Rouse 2008 (3)	7	1096	3	1145	5.1%	2.44 [0.63 , 9.40]
Subtotal (95% CI)		**2360**		**2376**	**100.0%**	**1.14 [0.82 , 1.61]**
Total events:	66		57			
Heterogeneity: Chi² = 1.68, df = 2 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.78 (P = 0.43)						
5.5.2 As defined						
Crowther 2003 (4)	34	535	28	527	90.6%	1.20 [0.74 , 1.94]
Rouse 2008 (3)	7	1096	3	1145	9.4%	2.44 [0.63 , 9.40]
Subtotal (95% CI)		**1631**		**1672**	**100.0%**	**1.31 [0.83 , 2.07]**
Total events:	41		31			
Heterogeneity: Chi² = 0.95, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						



Footnotes

(1) Denominators are total randomised; decrease > 4/minute from baseline

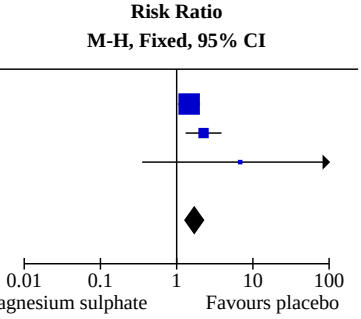
(2) Denominators are total randomised; respiratory rate decrease > 4/minute from baseline or breaths < 12/minute

(3) Denominators are total randomised; "All cases either were self-limited or responded to diuresis and supplemental oxygen"

(4) Denominators are total randomised; respiratory rate < 16/minute

Analysis 5.6. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 6: Side effect: hypotension

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	77	535	52	527	73.6%	1.46 [1.05 , 2.03]
Crowther 2023 (2)	42	729	18	704	25.7%	2.25 [1.31 , 3.88]
Marret 2006 (3)	3	286	0	278	0.7%	6.80 [0.35 , 131.14]
Total (95% CI)		**1550**		**1509**	**100.0%**	**1.70 [1.29 , 2.25]**
Total events:	122		70			
Heterogeneity: Chi² = 2.71, df = 2 (P = 0.26); I² = 26%						
Test for overall effect: Z = 3.72 (P = 0.0002)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; diastolic blood pressure decrease > 15 mmHg

(2) Denominators are total randomised; decrease > 15 mmHg below baseline

(3) Denominators are total randomised

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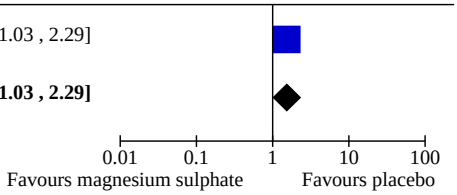
Analysis 5.7. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 7: Side effect: tachycardia

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	56	535	36	527	100.0%	1.53 [1.03 , 2.29]
Total (95% CI)		**535**		**527**	**100.0%**	**1.53 [1.03 , 2.29]**
Total events:	56		36			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.09 (P = 0.04)
Test for subgroup differences: Not applicable

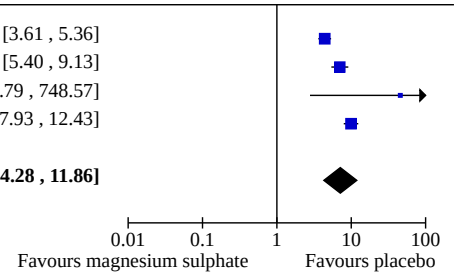


Footnotes
(1) Denominators are total randomised; pulse rate > 160/minute or > 20/minute from baseline

Analysis 5.8. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 8: Side effect: warmth over body/flushing

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	393	535	88	527	32.9%	4.40 [3.61 , 5.36]
Crowther 2023 (2)	400	729	55	704	31.7%	7.02 [5.40 , 9.13]
Marret 2006 (2)	23	286	0	278	3.0%	45.69 [2.79 , 748.57]
Rouse 2008 (2)	703	1096	74	1145	32.4%	9.92 [7.93 , 12.43]
Total (95% CI)		**2646**		**2654**	**100.0%**	**7.13 [4.28 , 11.86]**
Total events:	1519		217			

Heterogeneity: Tau² = 0.19; Chi² = 32.32, df = 3 (P < 0.00001); I² = 91%
Test for overall effect: Z = 7.56 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised; warmth over body
(2) Denominators are total randomised; flushing

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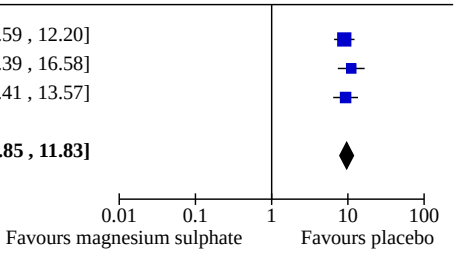
Analysis 5.9. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 9: Side effect: arm discomfort with infusion

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	355	535	39	527	42.7%	8.97 [6.59 , 12.20]
Crowther 2023 (2)	275	729	24	704	26.5%	11.07 [7.39 , 16.58]
Rouse 2008 (3)	259	1096	29	1145	30.8%	9.33 [6.41 , 13.57]
Total (95% CI)		**2360**		**2376**	**100.0%**	**9.64 [7.85 , 11.83]**
Total events:	889		92			

Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 21.62 (P < 0.00001)
Test for subgroup differences: Not applicable

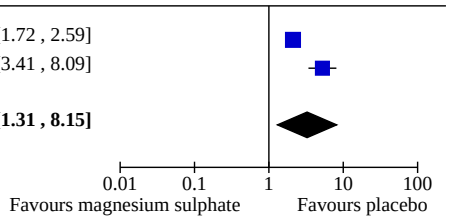


Footnotes
(1) Denominators are total randomised; arm discomfort with infusion
(2) Denominators are total randomised; 'discomfort arm'
(3) Denominators are total randomised; pain/burning at IV site

Analysis 5.10. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 10: Side effect: mouth dryness

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	212	535	99	527	52.2%	2.11 [1.72 , 2.59]
Crowther 2023 (1)	125	729	23	704	47.8%	5.25 [3.41 , 8.09]
Total (95% CI)		**1264**		**1231**	**100.0%**	**3.26 [1.31 , 8.15]**
Total events:	337		122			

Heterogeneity: Tau² = 0.41; Chi² = 14.63, df = 1 (P = 0.0001); I² = 93%
Test for overall effect: Z = 2.53 (P = 0.01)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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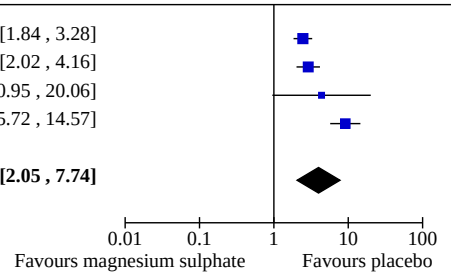
Analysis 5.11. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 11: Side effect: nausea or vomiting

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	137	535	55	527	30.5%	2.45 [1.84 , 3.28]
Crowther 2023 (2)	108	729	36	704	29.6%	2.90 [2.02 , 4.16]
Marret 2006 (3)	9	286	2	278	12.0%	4.37 [0.95 , 20.06]
Rouse 2008 (3)	166	1096	19	1145	27.9%	9.13 [5.72 , 14.57]
Total (95% CI)		**2646**		**2654**	**100.0%**	**3.99 [2.05 , 7.74]**
Total events:	420		112			

Heterogeneity: Tau² = 0.35; Chi² = 24.09, df = 3 (P < 0.0001); I² = 88%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable

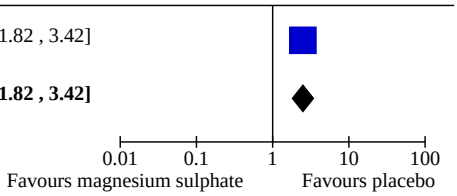


Footnotes
(1) Denominators are total randomised; nausea only
(2) Denominators are total randomised; nausea only; trial also reports vomiting separately
(3) Denominators are total randomised

Analysis 5.12. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 12: Side effect: sleepiness

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	119	535	47	527	100.0%	2.49 [1.82 , 3.42]
Total (95% CI)		**535**		**527**	**100.0%**	**2.49 [1.82 , 3.42]**
Total events:	119		47			

Heterogeneity: Not applicable
Test for overall effect: Z = 5.68 (P < 0.00001)
Test for subgroup differences: Not applicable

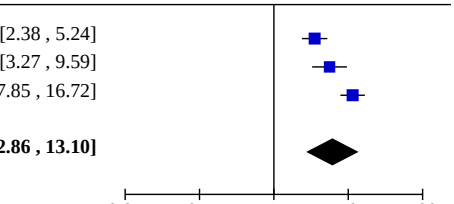


Footnotes
(1) Denominators are total randomised

Analysis 5.13. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 13: Side effect: sweating

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	104	535	29	527	34.1%	3.53 [2.38 , 5.24]
Crowther 2023 (1)	87	729	15	704	31.6%	5.60 [3.27 , 9.59]
Rouse 2008 (1)	307	1096	28	1145	34.3%	11.45 [7.85 , 16.72]
Total (95% CI)		**2360**		**2376**	**100.0%**	**6.12 [2.86 , 13.10]**
Total events:	498		72			

Heterogeneity: Tau² = 0.40; Chi² = 18.76, df = 2 (P < 0.0001); I² = 89%
Test for overall effect: Z = 4.66 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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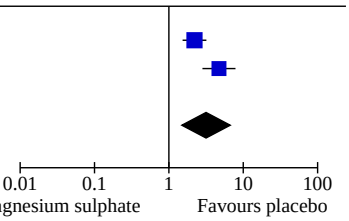
Analysis 5.14. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 14: Side effect: dizziness

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	83	535	37	527	52.8%	2.21 [1.53 , 3.19]
Crowther 2023 (1)	83	729	17	704	47.2%	4.71 [2.83 , 7.86]
Total (95% CI)		**1264**		**1231**	**100.0%**	**3.16 [1.50 , 6.68]**
Total events:	166		54			

Heterogeneity: Tau² = 0.24; Chi² = 5.66, df = 1 (P = 0.02); I² = 82%
Test for overall effect: Z = 3.01 (P = 0.003)
Test for subgroup differences: Not applicable

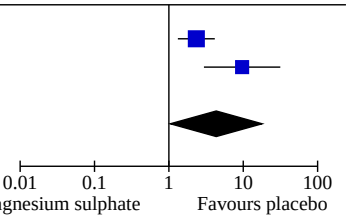


Footnotes
(1) Denominators are total randomised

Analysis 5.15. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 15: Side effect: blurred vision

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Crowther 2003 (1)	38	535	16	527	56.5%	2.34 [1.32 , 4.14]
Crowther 2023 (2)	30	729	3	704	43.5%	9.66 [2.96 , 31.50]
Total (95% CI)		**1264**		**1231**	**100.0%**	**4.33 [1.05 , 17.88]**
Total events:	68		19			

Heterogeneity: Tau² = 0.84; Chi² = 4.74, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 2.03 (P = 0.04)
Test for subgroup differences: Not applicable

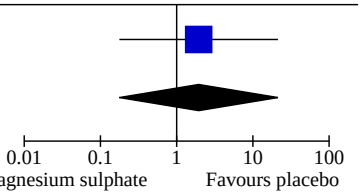


Footnotes
(1) Denominators are total randomised
(2) Denominators are total randomised; blurred sight

Analysis 5.16. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 16: Side effect: tendon reflex abolition

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	2	286	1	278	100.0%	1.94 [0.18 , 21.32]
Total (95% CI)		**286**		**278**	**100.0%**	**1.94 [0.18 , 21.32]**
Total events:	2		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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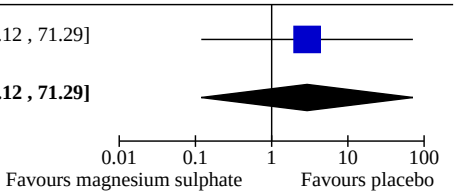
Analysis 5.17. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 17: Side effect: "curarisation"

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	1	286	0	278	100.0%	2.92 [0.12 , 71.29]
Total (95% CI)		**286**		**278**	**100.0%**	**2.92 [0.12 , 71.29]**
Total events:	1		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.66 (P = 0.51)
Test for subgroup differences: Not applicable

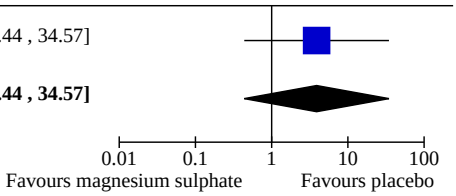


Footnotes
(1) Denominators are total randomised

Analysis 5.18. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 18: Side effect: headache

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	4	286	1	278	100.0%	3.89 [0.44 , 34.57]
Total (95% CI)		**286**		**278**	**100.0%**	**3.89 [0.44 , 34.57]**
Total events:	4		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.22 (P = 0.22)
Test for subgroup differences: Not applicable

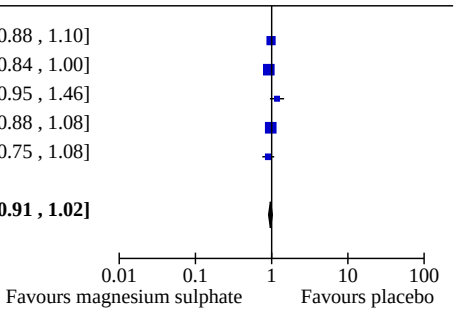


Footnotes
(1) Denominators are total randomised

Analysis 5.19. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 19: Mode of birth: caesarean birth

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2003 (1)	289	535	290	527	20.9%	0.98 [0.88 , 1.10]
Crowther 2023 (1)	406	729	427	704	31.1%	0.92 [0.84 , 1.00]
Marret 2006 (1)	116	286	96	278	7.0%	1.17 [0.95 , 1.46]
Rouse 2008 (1)	417	1096	448	1145	31.3%	0.97 [0.88 , 1.08]
Wolf 2020 (1)	124	283	135	278	9.7%	0.90 [0.75 , 1.08]
Total (95% CI)		**2929**		**2932**	**100.0%**	**0.96 [0.91 , 1.02]**
Total events:	1352		1396			

Heterogeneity: $Chi^2 = 5.11$, df = 4 (P = 0.28); $I^2 = 22\%$
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

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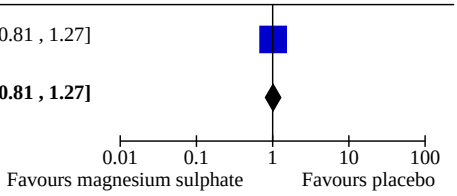
Analysis 5.20. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 20: Chorioamnionitis

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Rouse 2008 (1)	127	1096	131	1145	100.0%	1.01 [0.81 , 1.27]
Total (95% CI)		**1096**		**1145**	**100.0%**	**1.01 [0.81 , 1.27]**
Total events:	127		131			

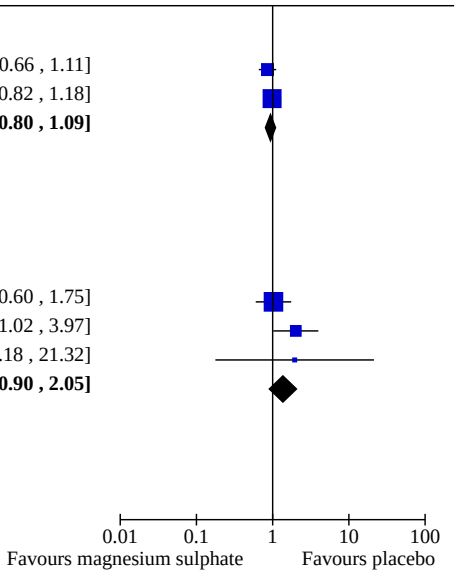
Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.91)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are total randomised

Analysis 5.21. Comparison 5: Magnesium sulphate versus placebo: secondary outcomes for women, Outcome 21: Postpartum haemorrhage

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
5.21.1 Postpartum haemorrhage						
Crowther 2003 (1)	86	535	99	527	37.0%	0.86 [0.66 , 1.11]
Crowther 2023 (2)	170	729	167	704	63.0%	0.98 [0.82 , 1.18]
Subtotal (95% CI)		**1264**		**1231**	**100.0%**	**0.94 [0.80 , 1.09]**
Total events:	256		266			
Heterogeneity: Chi² = 0.71, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.39)						
5.21.2 Severe postpartum haemorrhage						
Crowther 2003 (3)	26	535	25	527	65.6%	1.02 [0.60 , 1.75]
Crowther 2023 (4)	25	729	12	704	31.8%	2.01 [1.02 , 3.97]
Marret 2006 (5)	2	286	1	278	2.6%	1.94 [0.18 , 21.32]
Subtotal (95% CI)		**1550**		**1509**	**100.0%**	**1.36 [0.90 , 2.05]**
Total events:	53		38			
Heterogeneity: Chi² = 2.43, df = 2 (P = 0.30); I² = 18%						
Test for overall effect: Z = 1.48 (P = 0.14)						



Footnotes
(1) Denominators are total randomised; primary postpartum haemorrhage (blood loss > 600 mL)
(2) Denominators are total randomised; postpartum haemorrhage (blood loss ≥ 500 mL)
(3) Denominators are total randomised; major postpartum haemorrhage (blood loss > 1000 mL)
(4) Denominators are total randomised; major postpartum haemorrhage (blood loss ≥ 1000 mL)
(5) Denominators are total randomised; major/severe postpartum haemorrhage

Comparison 6. Magnesium sulphate versus placebo: secondary outcomes for health services

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Maternal admission to the intensive care unit	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

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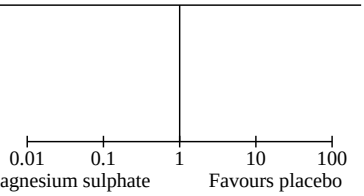
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Length of postnatal hospitalisation for women (days)	1	1062	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.18, 0.58]
6.3 Length of neonatal/infant hospitalisation (days)	1	1235	Mean Difference (IV, Fixed, 95% CI)	1.80 [-2.62, 6.22]
6.4 Hospital admissions (up to 2 years' corrected age)	1	1365	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.79, 1.03]
6.5 Postdischarge service (up to 2 years' corrected age)	1	1352	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.83, 1.10]
6.6 Hospital admissions (school age)	1	420	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 1.00]

Analysis 6.1. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 1: Maternal admission to the intensive care unit

	Magnesium sulphate		Placebo			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
Crowther 2003 (1)	0	535	0	527		Not estimable	
Total (95% CI)		**535**		**527**		**Not estimable**	
Total events:	0		0				

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

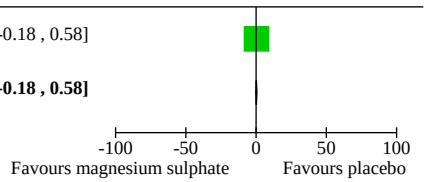


Footnotes
(1) Additional data from trialists (2009 review)

Analysis 6.2. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 2: Length of postnatal hospitalisation for women (days)

	Magnesium sulphate			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Crowther 2003 (1)	5.2	3.6	535	5	2.6	527	100.0%	0.20 [-0.18 , 0.58]	
Total (95% CI)			**535**			**527**	**100.0%**	**0.20 [-0.18 , 0.58]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.04 (P = 0.30)
Test for subgroup differences: Not applicable



Footnotes
(1) Additional data from trialists (2009 review) - reported as duration of mother's hospital stay

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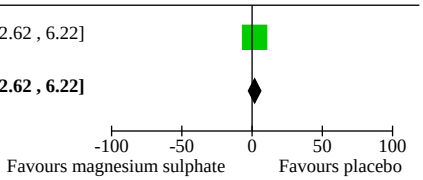
Analysis 6.3. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 3: Length of neonatal/infant hospitalisation (days)

Study or Subgroup	Magnesium sulphate Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Crowther 2003 (1)	72.9	36.7	620	71.1	42.4	615	100.0%	1.80 [-2.62 , 6.22]
Total (95% CI)			**620**			**615**	**100.0%**	**1.80 [-2.62 , 6.22]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.80 (P = 0.43)
Test for subgroup differences: Not applicable

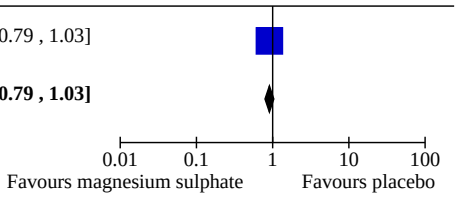


Footnotes
(1) Denominators are livebirths; additional data from trialists (2009 review)

Analysis 6.4. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 4: Hospital admissions (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	261	702	272	663	100.0%	0.91 [0.79 , 1.03]
Total (95% CI)		**702**		**663**	**100.0%**	**0.91 [0.79 , 1.03]**
Total events:	261		272			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.46 (P = 0.15)
Test for subgroup differences: Not applicable

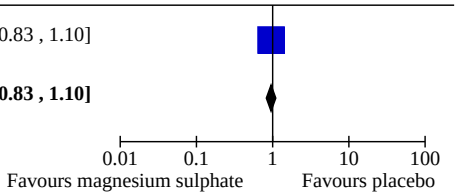


Footnotes
(1) Denominators are children with 2 year corrected age follow up data

Analysis 6.5. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 5: Postdischarge service (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Crowther 2023 (1)	241	691	242	661	100.0%	0.95 [0.83 , 1.10]
Total (95% CI)		**691**		**661**	**100.0%**	**0.95 [0.83 , 1.10]**
Total events:	241		242			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.51)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are children with 2 year corrected age follow up data

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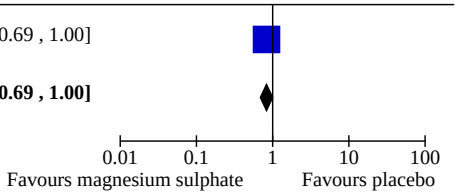
Analysis 6.6. Comparison 6: Magnesium sulphate versus placebo: secondary outcomes for health services, Outcome 6: Hospital admissions (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Marret 2006 (1)	102	216	116	204	100.0%	0.83 [0.69 , 1.00]
Total (95% CI)		**216**		**204**	**100.0%**	**0.83 [0.69 , 1.00]**
Total events:	102		116			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.97 (P = 0.05)
Test for subgroup differences: Not applicable



Footnotes
(1) Denominators are children with 7-14 year follow up data

Comparison 7. Subgroup analysis: gestational age at randomisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6	6759	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
7.1.1 < 30 weeks' gestation	2	1466	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.09]
7.1.2 < 32 weeks' gestation	2	2913	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.83, 1.39]
7.1.3 < 34 weeks' gestation	3	2380	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.47]
7.2 Cerebral palsy (up to 2 years' corrected age)	6	6107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.57, 0.89]
7.2.1 < 30 weeks' gestation	2	1223	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.53, 1.19]
7.2.2 < 32 weeks' gestation	2	2876	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.42, 0.84]
7.2.3 < 34 weeks' gestation	3	2008	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.29]
7.3 Death or cerebral palsy (up to 2 years' corrected age)	6	6481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
7.3.1 < 30 weeks' gestation	2	1466	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.70, 1.03]
7.3.2 < 32 weeks' gestation	2	2913	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.70, 1.04]
7.3.3 < 34 weeks' gestation	3	2102	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.24]
7.4 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3	4279	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
7.4.1 < 30 weeks' gestation	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
7.4.2 < 32 weeks' gestation	1	1771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.4.3 < 34 weeks' gestation	1	1253	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.56]
7.5 Death (fetal, neonatal, or later (up to school age))	2	1758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
7.5.1 < 30 weeks' gestation	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.62, 1.03]
7.5.2 < 34 weeks' gestation	1	503	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.37]
7.6 Cerebral palsy (school age)	2	1038	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.41]
7.6.1 < 30 weeks' gestation	1	609	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.66, 2.06]
7.6.2 < 34 weeks' gestation	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.39]
7.7 Major neurodevelopmental disability (school age)	2	940	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.62]
7.7.1 < 30 weeks' gestation	1	511	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.75, 1.95]
7.7.2 < 34 weeks' gestation	1	429	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.19]
7.8 Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
7.8.1 < 30 weeks' gestation	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.8.2 < 32 weeks' gestation	1	2241	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
7.8.3 < 34 weeks' gestation	2	1997	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
7.9 Adverse effects severe enough to stop treatment	3	4736	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.88, 5.48]
7.9.1 < 30 weeks' gestation	1	1062	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.81, 4.15]
7.9.2 < 32 weeks' gestation	1	2241	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.67, 5.17]
7.9.3 < 34 weeks' gestation	1	1433	Risk Ratio (M-H, Random, 95% CI)	19.31 [2.60, 143.53]

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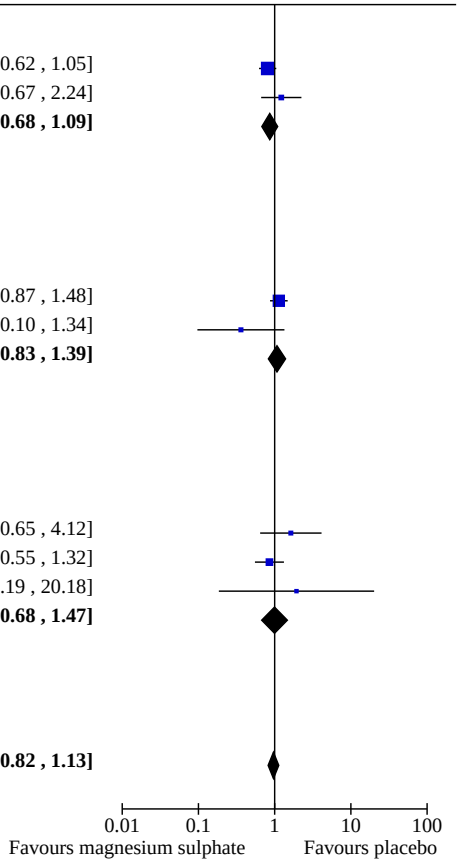
Analysis 7.1. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 < 30 weeks' gestation						
Crowther 2003 (1)	87	629	107	626	39.5%	0.81 [0.62 , 1.05]
Wolf 2020 (2)	19	104	16	107	5.8%	1.22 [0.67 , 2.24]
Subtotal (95% CI)		**733**		**733**	**45.3%**	**0.86 [0.68 , 1.09]**
Total events:	106		123			
Heterogeneity: Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 1.22 (P = 0.22)						
7.1.2 < 32 weeks' gestation						
Rouse 2008 (3)	103	1188	96	1256	34.4%	1.13 [0.87 , 1.48]
Wolf 2020 (4)	3	239	8	230	3.0%	0.36 [0.10 , 1.34]
Subtotal (95% CI)		**1427**		**1486**	**37.4%**	**1.07 [0.83 , 1.39]**
Total events:	106		104			
Heterogeneity: Chi² = 2.81, df = 1 (P = 0.09); I² = 64%						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.1.3 < 34 weeks' gestation						
Crowther 2023 (5)	12	837	7	796	2.6%	1.63 [0.65 , 4.12]
Marret 2006 (6)	34	352	38	336	14.3%	0.85 [0.55 , 1.32]
Mittendorf 2002 (7)	2	30	1	29	0.4%	1.93 [0.19 , 20.18]
Subtotal (95% CI)		**1219**		**1161**	**17.3%**	**1.00 [0.68 , 1.47]**
Total events:	48		46			
Heterogeneity: Chi² = 1.87, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
Total (95% CI)		**3379**		**3380**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	260		273			
Heterogeneity: Chi² = 7.76, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 0.45 (P = 0.65)						
Test for subgroup differences: Chi² = 1.51, df = 2 (P = 0.47), I² = 0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age; < 30 weeks' gestation
(2) Denominators are total randomised; 18 months' corrected age; < 28 weeks' gestation
(3) Denominators are total randomised; 1 year corrected age; 24 to < 32 weeks' gestation
(4) Denominators are total randomised; 18 months' corrected age; ≥ 28 and < 32 weeks' gestation
(5) Denominators are total randomised, minus children unable to contact/lost; 2 years' corrected age; 30-34 weeks' gestation
(6) Denominators are total randomised; 2 years; < 33 weeks' gestation
(7) Denominators are total randomised; 18 months' corrected age; > 24 and < 34 weeks' gestation

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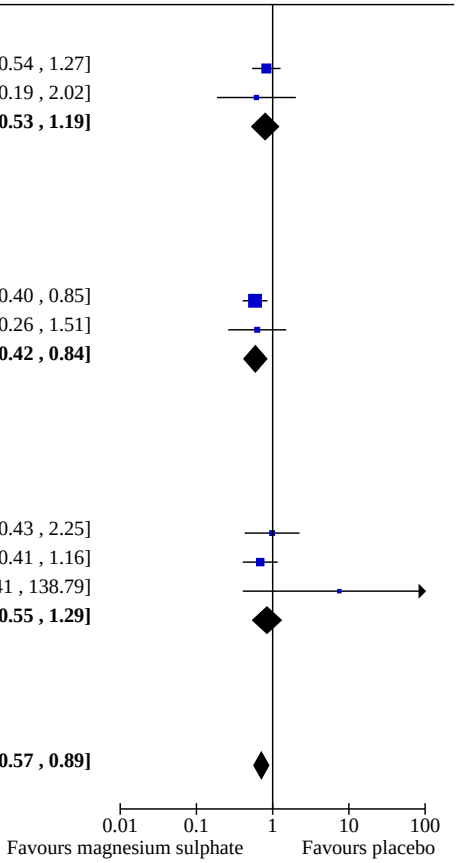
Analysis 7.2. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 < 30 weeks' gestation						
Crowther 2003 (1)	36	533	42	514	24.3%	0.83 [0.54 , 1.27]
Wolf 2020 (2)	4	85	7	91	3.8%	0.61 [0.19 , 2.02]
Subtotal (95% CI)		**618**		**605**	**28.1%**	**0.80 [0.53 , 1.19]**
Total events:	40		49			
Heterogeneity: Chi² = 0.22, df = 1 (P = 0.64); I² = 0%						
Test for overall effect: Z = 1.10 (P = 0.27)						
7.2.2 < 32 weeks' gestation						
Rouse 2008 (3)	41	1174	74	1244	40.8%	0.59 [0.40 , 0.85]
Wolf 2020 (4)	8	236	12	222	7.0%	0.63 [0.26 , 1.51]
Subtotal (95% CI)		**1410**		**1466**	**47.8%**	**0.59 [0.42 , 0.84]**
Total events:	49		86			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%						
Test for overall effect: Z = 2.98 (P = 0.003)						
7.2.3 < 34 weeks' gestation						
Crowther 2023 (5)	11	679	11	667	6.3%	0.98 [0.43 , 2.25]
Marret 2006 (6)	22	313	30	293	17.6%	0.69 [0.41 , 1.16]
Mittendorf 2002 (7)	3	27	0	29	0.3%	7.50 [0.41 , 138.79]
Subtotal (95% CI)		**1019**		**989**	**24.1%**	**0.84 [0.55 , 1.29]**
Total events:	36		41			
Heterogeneity: Chi² = 2.87, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**3047**		**3060**	**100.0%**	**0.71 [0.57 , 0.89]**
Total events:	125		176			
Heterogeneity: Chi² = 4.73, df = 6 (P = 0.58); I² = 0%						
Test for overall effect: Z = 3.01 (P = 0.003)						
Test for subgroup differences: Chi² = 1.97, df = 2 (P = 0.37), I² = 0%						



Footnotes

(1) Denominators are surviving children with data; 2 years' corrected age; criteria included abnormalities of tone and loss of motor function; < 30 weeks' ge
(2) Denominators are surviving children at 18 months' corrected age or older; < 28 weeks' gestation
(3) Denominators are livebirths; 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) delay of 30% or more in gross motor develo
(4) Denominators are surviving children at 18 months' corrected age or older; ≥ 28 and < 32 weeks' gestation
(5) Denominators are surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnormalities of
(6) Denominators are livebirths with data; 2 years; < 33 weeks' gestation
(7) Denominators are livebirths; 18 months' corrected age; > 24 and < 34 weeks' gestation

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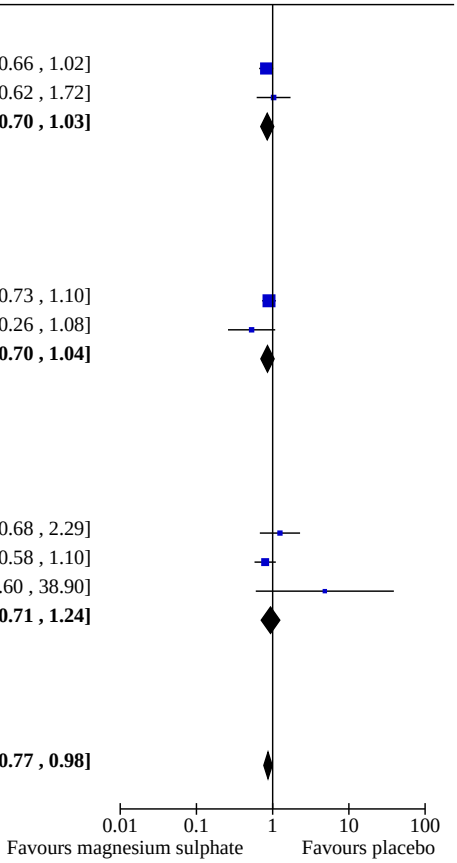
Analysis 7.3. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.3.1 < 30 weeks' gestation						
Crowther 2003 (1)	123	629	149	626	33.5%	0.82 [0.66 , 1.02]
Wolf 2020 (2)	23	104	23	107	5.1%	1.03 [0.62 , 1.72]
Subtotal (95% CI)		**733**		**733**	**38.6%**	**0.85 [0.70 , 1.03]**
Total events:	146		172			
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.43); I² = 0%						
Test for overall effect: Z = 1.64 (P = 0.10)						
7.3.2 < 32 weeks' gestation						
Rouse 2008 (3)	144	1188	170	1256	37.1%	0.90 [0.73 , 1.10]
Wolf 2020 (4)	11	239	20	230	4.6%	0.53 [0.26 , 1.08]
Subtotal (95% CI)		**1427**		**1486**	**41.7%**	**0.86 [0.70 , 1.04]**
Total events:	155		190			
Heterogeneity: Chi² = 1.93, df = 1 (P = 0.16); I² = 48%						
Test for overall effect: Z = 1.54 (P = 0.12)						
7.3.3 < 34 weeks' gestation						
Crowther 2023 (5)	23	691	18	674	4.1%	1.25 [0.68 , 2.29]
Marret 2006 (6)	56	347	67	331	15.4%	0.80 [0.58 , 1.10]
Mittendorf 2002 (7)	5	30	1	29	0.2%	4.83 [0.60 , 38.90]
Subtotal (95% CI)		**1068**		**1034**	**19.7%**	**0.94 [0.71 , 1.24]**
Total events:	84		86			
Heterogeneity: Chi² = 4.19, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**3228**		**3253**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	385		448			
Heterogeneity: Chi² = 6.86, df = 6 (P = 0.33); I² = 13%						
Test for overall effect: Z = 2.21 (P = 0.03)						
Test for subgroup differences: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age; cerebral palsy: criteria included abnormalities of tone and loss of motor function; < 30 weeks
(2) Denominators are total randomised; 18 months' corrected age (death) or later (cerebral palsy); < 28 weeks' gestation
(3) Denominators are total randomised; death by 1 year, cerebral palsy at 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) de
(4) Denominators are total randomised; 18 months' corrected age (death) or later (cerebral palsy); ≥ 28 and < 32 weeks' gestation
(5) Denominators are deaths and surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnor
(6) Denominators are deaths and livebirths with data; 2 years; < 33 weeks' gestation
(7) Denominators are total randomised; 18 months' corrected age; > 24 and < 34 weeks' gestation

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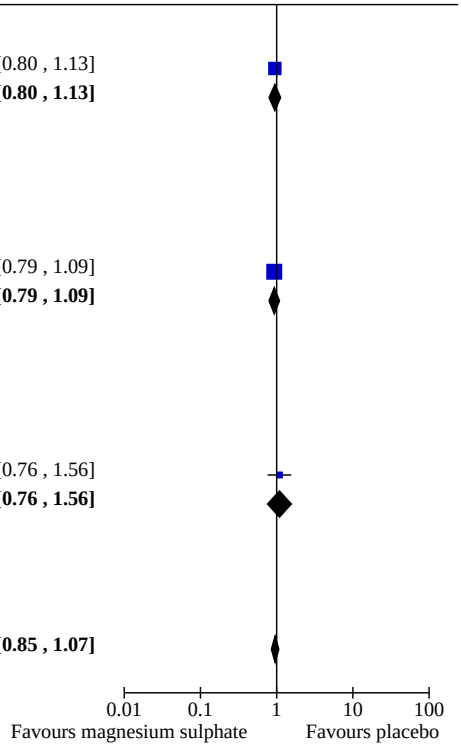
Analysis 7.4. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.4.1 < 30 weeks' gestation						
Crowther 2003 (1)	176	629	185	626	39.0%	0.95 [0.80 , 1.13]
Subtotal (95% CI)		**629**		**626**	**39.0%**	**0.95 [0.80 , 1.13]**
Total events:	176		185			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
7.4.2 < 32 weeks' gestation						
Rouse 2008 (2)	213	854	246	917	50.0%	0.93 [0.79 , 1.09]
Subtotal (95% CI)		**854**		**917**	**50.0%**	**0.93 [0.79 , 1.09]**
Total events:	213		246			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
7.4.3 < 34 weeks' gestation						
Crowther 2023 (3)	57	629	52	624	11.0%	1.09 [0.76 , 1.56]
Subtotal (95% CI)		**629**		**624**	**11.0%**	**1.09 [0.76 , 1.56]**
Total events:	57		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
Total (95% CI)		**2112**		**2167**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	446		483			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² = 0%						



Footnotes

(1) Denominators are total randomised; severe neurosensory disability: severe cerebral palsy (permanently nonambulant), severe developmental delay (MDI

(2) *From secondary analysis; denominators are infants born < 34 weeks' gestation, alive at initial hospital discharge, with 2 year outcome data; defined as c

(3) Denominators are deaths and livebirths with paediatric assessments; major neurosensory disability: any of: blindness (corrected visual acuity worse than

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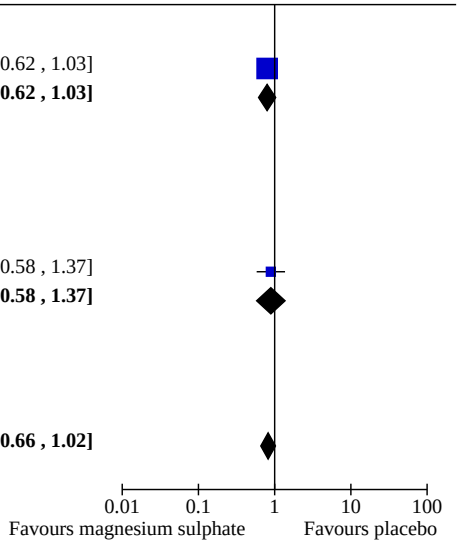
Analysis 7.5. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 5: Death (fetal, neonatal, or later (up to school age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.5.1 < 30 weeks' gestation						
Crowther 2003 (1)	88	629	110	626	74.3%	0.80 [0.62 , 1.03]
Subtotal (95% CI)		**629**		**626**	**74.3%**	**0.80 [0.62 , 1.03]**
Total events:	88		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
7.5.2 < 34 weeks' gestation						
Marret 2006 (2)	34	252	38	251	25.7%	0.89 [0.58 , 1.37]
Subtotal (95% CI)		**252**		**251**	**25.7%**	**0.89 [0.58 , 1.37]**
Total events:	34		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**881**		**877**	**100.0%**	**0.82 [0.66 , 1.02]**
Total events:	122		148			
Heterogeneity: Chi^2 = 0.20, df = 1 (P = 0.66); I^2 = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi^2 = 0.20, df = 1 (P = 0.66), I^2 = 0%						



Footnotes

(1) Denominators are total randomised; < 30 weeks' gestation

(2) Denominators are those with 7-14 year outcomes, including deaths; < 33 weeks' gestation

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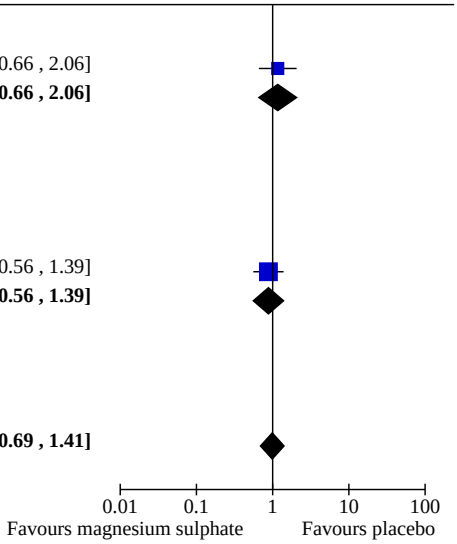
Analysis 7.6. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 6: Cerebral palsy (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.6.1 < 30 weeks' gestation						
Crowther 2003 (1)	23	295	21	314	37.8%	1.17 [0.66 , 2.06]
Subtotal (95% CI)		**295**		**314**	**37.8%**	**1.17 [0.66 , 2.06]**
Total events:	23		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
7.6.2 < 34 weeks' gestation						
Marret 2006 (2)	30	218	33	211	62.2%	0.88 [0.56 , 1.39]
Subtotal (95% CI)		**218**		**211**	**62.2%**	**0.88 [0.56 , 1.39]**
Total events:	30		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
Total (95% CI)		**513**		**525**	**100.0%**	**0.99 [0.69 , 1.41]**
Total events:	53		54			
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						

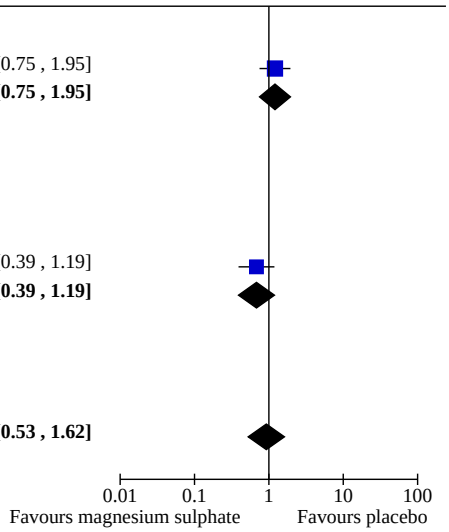


Footnotes

(1) Denominators are children with 6-11 year follow up data; cerebral palsy: nonprogressive loss of motor function with disordered tone or tendon reflexes;
(2) Denominators are children with 7-14 year follow up data; < 33 weeks' gestation

Analysis 7.7. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 7: Major neurodevelopmental disability (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
7.7.1 < 30 weeks' gestation						
Crowther 2003 (1)	33	257	27	254	53.2%	1.21 [0.75 , 1.95]
Subtotal (95% CI)		**257**		**254**	**53.2%**	**1.21 [0.75 , 1.95]**
Total events:	33		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
7.7.2 < 34 weeks' gestation						
Marret 2006 (2)	19	218	27	211	46.8%	0.68 [0.39 , 1.19]
Subtotal (95% CI)		**218**		**211**	**46.8%**	**0.68 [0.39 , 1.19]**
Total events:	19		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
Total (95% CI)		**475**		**465**	**100.0%**	**0.92 [0.53 , 1.62]**
Total events:	52		54			
Heterogeneity: Tau² = 0.09; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%						



Footnotes

(1) Denominators are children with 6-11 year follow up data; severe disability comprised any of severe cerebral palsy, an IQ less than 55, or blindness and mod
(2) Denominators are children with 7-14 year follow up data; severe overall deficits at school age: at least 1 of severe cerebral palsy, severe cognitive deficit/lea

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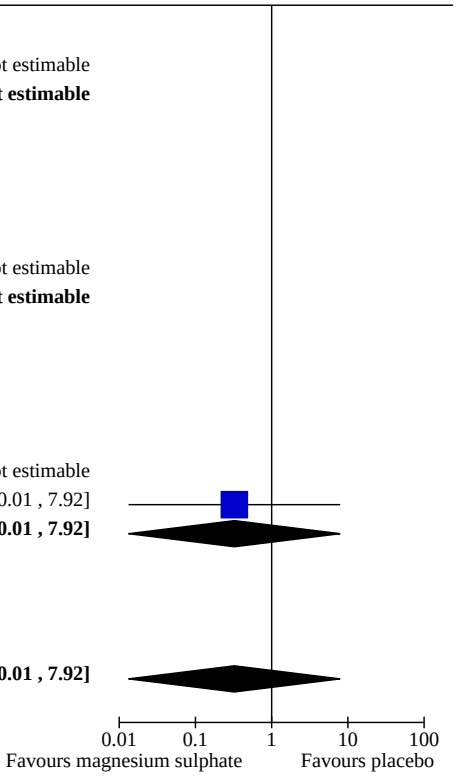
Analysis 7.8. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 8: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.8.1 < 30 weeks' gestation						
Crowther 2003 (1)	0	535	0	527		Not estimable
Subtotal (95% CI)		**535**		**527**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.8.2 < 32 weeks' gestation						
Rouse 2008 (2)	0	1096	0	1145		Not estimable
Subtotal (95% CI)		**1096**		**1145**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
7.8.3 < 34 weeks' gestation						
Crowther 2023 (3)	0	729	0	704		Not estimable
Marret 2006 (4)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Subtotal (95% CI)		**1015**		**982**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, respiratory arrest); < 30 weeks' gestation

(2) Denominators are total randomised; death or "lifethreatening events"; 24 to < 32 weeks' gestation

(3) Denominators are total randomised; serious adverse outcomes (maternal death, cardiac or respiratory arrest); 30-34 weeks' gestation

(4) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, prolonged mechanical ventilation); < 33 weeks' gestation

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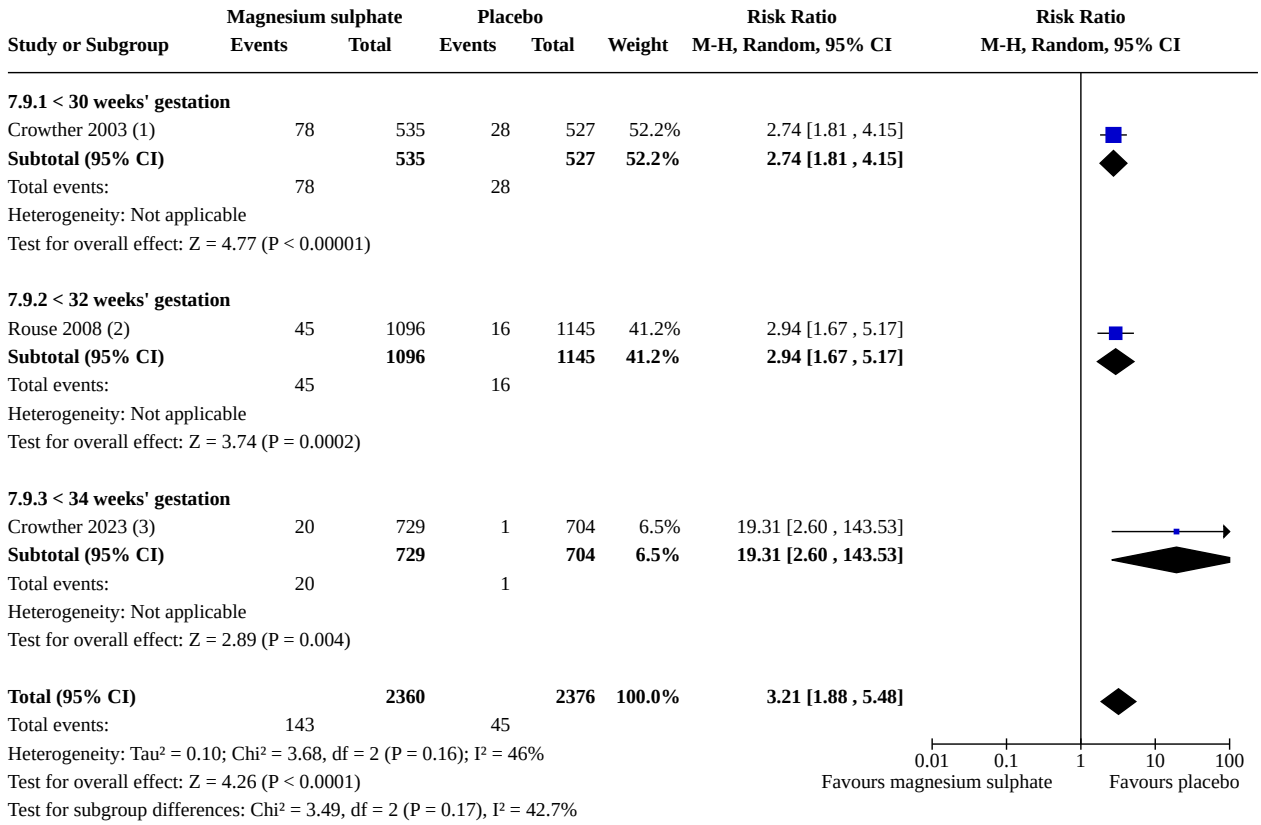
Analysis 7.9. Comparison 7: Subgroup analysis: gestational age at randomisation, Outcome 9: Adverse effects severe enough to stop treatment



Footnotes

(1) Denominators are total randomised; infusion stopped due to adverse effects; < 30 weeks' gestation

(2) Denominators are total randomised; infusion stopped because of adverse event; 24 to < 32 weeks' gestation

(3) Denominators are total randomised; infusion discontinued for side effects; 30-34 weeks' gestation

Comparison 8. Subgroup analysis: loading-dose regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6	6759	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
8.1.1 4 g	4	3635	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.07]
8.1.2 > 4 g	2	3124	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.38]
8.2 Cerebral palsy (up to 2 years' corrected age)	6	6107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.57, 0.89]
8.2.1 4 g	4	3055	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.13]
8.2.2 > 4 g	2	3052	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.82]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 Death or cerebral palsy (up to 2 years' corrected age)	6	6481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
8.3.1 4 g	4	3357	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.02]
8.3.2 > 4 g	2	3124	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.05]
8.4 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3	4279	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
8.4.1 4 g	2	2508	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]
8.4.2 > 4 g	1	1771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
8.5 Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
8.5.1 4 g	3	3059	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
8.5.2 > 4 g	1	2241	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
8.6 Adverse effects severe enough to stop treatment	3	4736	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.88, 5.48]
8.6.1 4 g	2	2495	Risk Ratio (M-H, Random, 95% CI)	5.74 [0.83, 39.53]
8.6.2 > 4 g	1	2241	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.67, 5.17]

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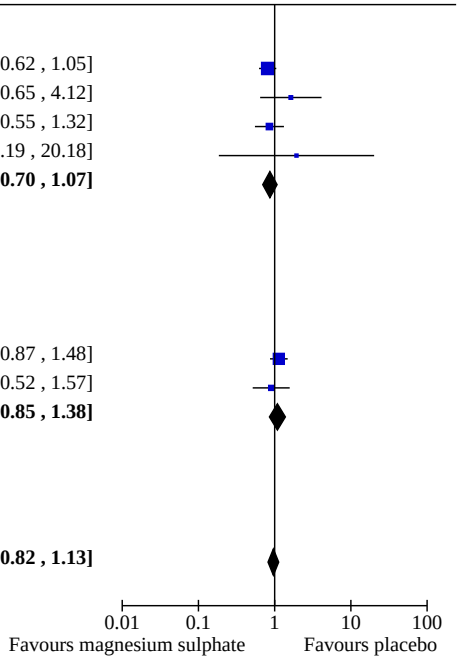
Analysis 8.1. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 4 g						
Crowther 2003 (1)	87	629	107	626	39.5%	0.81 [0.62 , 1.05]
Crowther 2023 (2)	12	837	7	796	2.6%	1.63 [0.65 , 4.12]
Marret 2006 (3)	34	352	38	336	14.3%	0.85 [0.55 , 1.32]
Mittendorf 2002 (4)	2	30	1	29	0.4%	1.93 [0.19 , 20.18]
Subtotal (95% CI)		**1848**		**1787**	**56.8%**	**0.87 [0.70 , 1.07]**
Total events:	135		153			
Heterogeneity: Chi² = 2.50, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
8.1.2 > 4 g						
Rouse 2008 (5)	103	1188	96	1256	34.3%	1.13 [0.87 , 1.48]
Wolf 2020 (6)	22	343	24	337	8.9%	0.90 [0.52 , 1.57]
Subtotal (95% CI)		**1531**		**1593**	**43.2%**	**1.09 [0.85 , 1.38]**
Total events:	125		120			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**3379**		**3380**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	260		273			
Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 1.89, df = 1 (P = 0.17), I² = 47.0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age
(2) Denominators are total randomised, minus children unable to contact/lost; 2 years' corrected age
(3) Denominators are total randomised; 2 years
(4) Denominators are total randomised; 18 months' corrected age
(5) Denominators are total randomised; 1 year corrected age; 6 g
(6) Denominators are total randomised; 18 months' corrected age; 5 g

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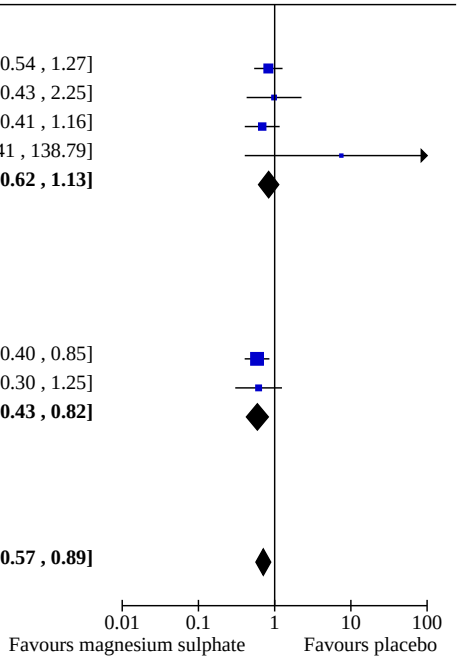
Analysis 8.2. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.2.1 4 g						
Crowther 2003 (1)	36	533	42	514	24.2%	0.83 [0.54 , 1.27]
Crowther 2023 (2)	11	679	11	667	6.3%	0.98 [0.43 , 2.25]
Marret 2006 (3)	22	313	30	293	17.6%	0.69 [0.41 , 1.16]
Mittendorf 2002 (4)	3	27	0	29	0.3%	7.50 [0.41 , 138.79]
Subtotal (95% CI)		**1552**		**1503**	**48.4%**	**0.83 [0.62 , 1.13]**
Total events:	72		83			
Heterogeneity: Chi² = 2.85, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
8.2.2 > 4 g						
Rouse 2008 (5)	41	1174	74	1244	40.7%	0.59 [0.40 , 0.85]
Wolf 2020 (6)	12	321	19	313	10.9%	0.62 [0.30 , 1.25]
Subtotal (95% CI)		**1495**		**1557**	**51.6%**	**0.59 [0.43 , 0.82]**
Total events:	53		93			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**3047**		**3060**	**100.0%**	**0.71 [0.57 , 0.89]**
Total events:	125		176			
Heterogeneity: Chi² = 4.75, df = 5 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: Chi² = 2.22, df = 1 (P = 0.14), I² = 54.9%						



Footnotes

(1) Denominators are surviving children with data; 2 years' corrected age; criteria included abnormalities of tone and loss of motor function

(2) Denominators are surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnormalities of

(3) Denominators are livebirths with data; 2 years

(4) Denominators are livebirths; 18 months' corrected age

(5) Denominators are livebirths; 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) delay of 30% or more in gross motor develo

(6) Denominators are surviving children at 18 months' corrected age or older; 5 g

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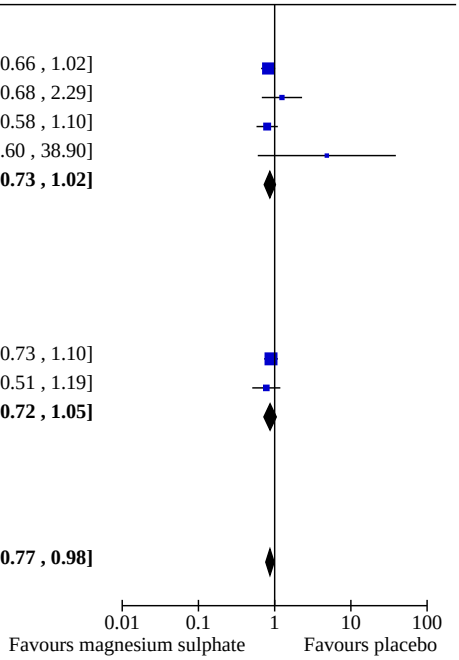
Analysis 8.3. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 4 g						
Crowther 2003 (1)	123	629	149	626	33.5%	0.82 [0.66 , 1.02]
Crowther 2023 (2)	23	691	18	674	4.1%	1.25 [0.68 , 2.29]
Marret 2006 (3)	56	347	67	331	15.4%	0.80 [0.58 , 1.10]
Mittendorf 2002 (4)	5	30	1	29	0.2%	4.83 [0.60 , 38.90]
Subtotal (95% CI)		**1697**		**1660**	**53.2%**	**0.86 [0.73 , 1.02]**
Total events:	207		235			
Heterogeneity: Chi² = 4.47, df = 3 (P = 0.21); I² = 33%						
Test for overall effect: Z = 1.69 (P = 0.09)						
8.3.2 > 4 g						
Rouse 2008 (5)	144	1188	170	1256	37.1%	0.90 [0.73 , 1.10]
Wolf 2020 (6)	34	343	43	337	9.7%	0.78 [0.51 , 1.19]
Subtotal (95% CI)		**1531**		**1593**	**46.8%**	**0.87 [0.72 , 1.05]**
Total events:	178		213			
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.15)						
Total (95% CI)		**3228**		**3253**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	385		448			
Heterogeneity: Chi² = 4.84, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age; cerebral palsy: criteria included abnormalities of tone and loss of motor function

(2) Denominators are deaths and surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnor

(3) Denominators are deaths and livebirths with data; 2 years

(4) Denominators are total randomised; 18 months' corrected age

(5) Denominators are total randomised; death by 1 year, cerebral palsy at 2 years corrected age or older; diagnosis made if 2 or more features present: 1) del

(6) Denominators are total randomised; 18 months corrected age (death) or later (cerebral palsy); 5 g

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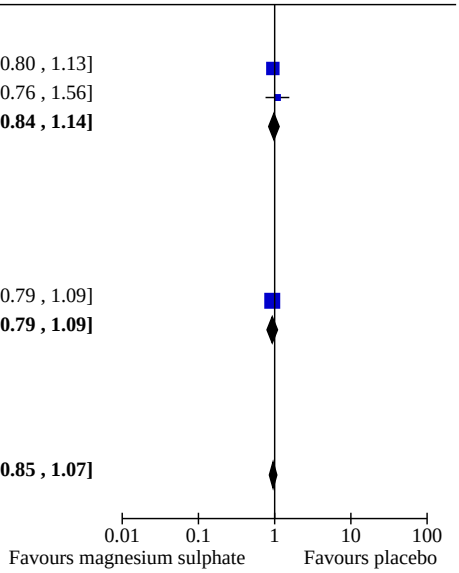
Analysis 8.4. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.4.1 4 g						
Crowther 2003 (1)	176	629	185	626	39.0%	0.95 [0.80 , 1.13]
Crowther 2023 (2)	57	629	52	624	11.0%	1.09 [0.76 , 1.56]
Subtotal (95% CI)		**1258**		**1250**	**50.0%**	**0.98 [0.84 , 1.14]**
Total events:	233		237			
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
8.4.2 > 4 g						
Rouse 2008 (3)	213	854	246	917	50.0%	0.93 [0.79 , 1.09]
Subtotal (95% CI)		**854**		**917**	**50.0%**	**0.93 [0.79 , 1.09]**
Total events:	213		246			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**2112**		**2167**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	446		483			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						



Footnotes

(1) Denominators are total randomised; severe neurosensory disability: severe cerebral palsy (permanently nonambulant), severe developmental delay (MDI

(2) Denominators are deaths and livebirths with paediatric assessments; major neurosensory disability: any of: blindness (corrected visual acuity worse than

(3) *From secondary analysis; denominators are infants born < 34 weeks' gestation, alive at initial hospital discharge, with 2 year outcome data; defined as d

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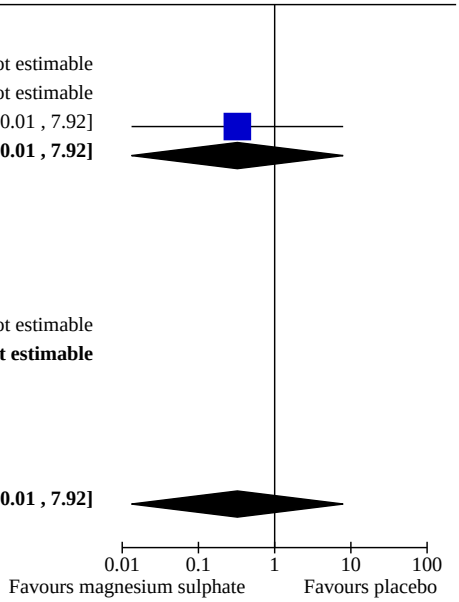
Analysis 8.5. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 5: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.5.1 4 g						
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (2)	0	729	0	704		Not estimable
Marret 2006 (3)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Subtotal (95% CI)		**1550**		**1509**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
8.5.2 > 4 g						
Rouse 2008 (4)	0	1096	0	1145		Not estimable
Subtotal (95% CI)		**1096**		**1145**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, respiratory arrest)
(2) Denominators are total randomised; serious adverse outcomes (maternal death, cardiac or respiratory arrest)
(3) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, prolonged mechanical ventilation)
(4) Denominators are total randomised; death or "lifethreatening events"; 6 g

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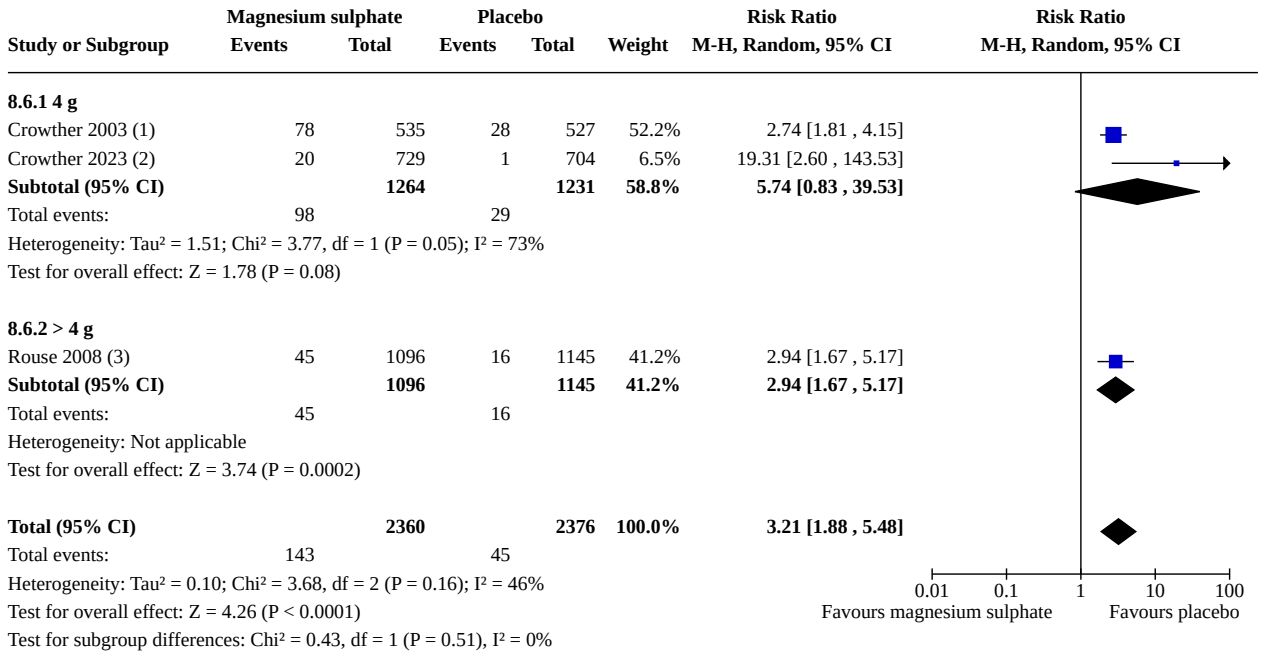
Analysis 8.6. Comparison 8: Subgroup analysis: loading-dose regimen, Outcome 6: Adverse effects severe enough to stop treatment



Footnotes

(1) Denominators are total randomised; infusion stopped due to adverse effects

(2) Denominators are total randomised; infusion discontinued for side effects

(3) Denominators are total randomised; infusion stopped because of adverse event; 6 g

Comparison 9. Subgroup analysis: maintenance dose regimen

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6	6759	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
9.1.1 No	3	2380	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.47]
9.1.2 1 g/hour	2	1935	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.65, 1.05]
9.1.3 2 g/hour	1	2444	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.87, 1.48]
9.2 Cerebral palsy (up to 2 years' corrected age)	6	6107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.57, 0.89]
9.2.1 No	3	2008	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.29]
9.2.2 1 g/hour	2	1681	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.53, 1.10]
9.2.3 2 g/hour	1	2418	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.40, 0.85]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.3 Death or cerebral palsy (up to 2 years' corrected age)	6	6481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
9.3.1 No	3	2102	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.24]
9.3.2 1 g/hour	2	1935	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.67, 0.98]
9.3.3 2 g/hour	1	2444	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.73, 1.10]
9.4 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3	4279	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
9.4.1 No	1	1253	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.76, 1.56]
9.4.2 1 g/hour	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
9.4.3 2 g/hour	1	1771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
9.5 Death (fetal, neonatal, or later (up to school age))	2	1758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
9.5.1 No	1	503	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.58, 1.37]
9.5.2 1 g/hour	1	1255	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.62, 1.03]
9.6 Cerebral palsy (school age)	2	1038	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.41]
9.6.1 No	1	429	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.56, 1.39]
9.6.2 1 g/hour	1	609	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.66, 2.06]
9.7 Major neurodevelopmental disability (school age)	2	940	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.53, 1.62]
9.7.1 No	1	429	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.39, 1.19]
9.7.2 1 g/hour	1	511	Risk Ratio (M-H, Random, 95% CI)	1.21 [0.75, 1.95]
9.8 Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
9.8.1 No	2	1997	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
9.8.2 1 g/hour	1	1062	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.8.3 2 g/hour	1	2241	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.9 Adverse effects severe enough to stop treatment	3	4736	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.88, 5.48]

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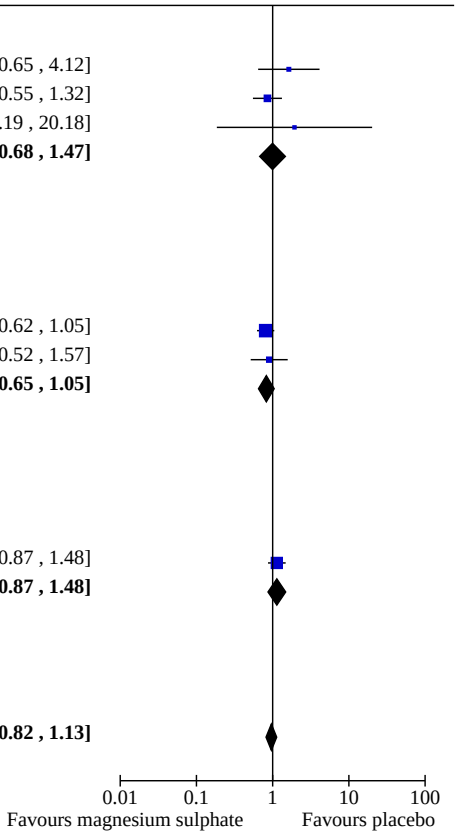
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.9.1 No	1	1433	Risk Ratio (M-H, Random, 95% CI)	19.31 [2.60, 143.53]
9.9.2 1 g/hour	1	1062	Risk Ratio (M-H, Random, 95% CI)	2.74 [1.81, 4.15]
9.9.3 2 g/hour	1	2241	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.67, 5.17]

Analysis 9.1. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 No						
Crowther 2023 (1)	12	837	7	796	2.6%	1.63 [0.65 , 4.12]
Marret 2006 (2)	34	352	38	336	14.3%	0.85 [0.55 , 1.32]
Mittendorf 2002 (3)	2	30	1	29	0.4%	1.93 [0.19 , 20.18]
Subtotal (95% CI)		**1219**		**1161**	**17.3%**	**1.00 [0.68 , 1.47]**
Total events:	48		46			
Heterogeneity: Chi² = 1.87, df = 2 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.02 (P = 0.98)						
9.1.2 1 g/hour						
Crowther 2003 (4)	87	629	107	626	39.5%	0.81 [0.62 , 1.05]
Wolf 2020 (3)	22	343	24	337	8.9%	0.90 [0.52 , 1.57]
Subtotal (95% CI)		**972**		**963**	**48.4%**	**0.83 [0.65 , 1.05]**
Total events:	109		131			
Heterogeneity: Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.59 (P = 0.11)						
9.1.3 2 g/hour						
Rouse 2008 (5)	103	1188	96	1256	34.3%	1.13 [0.87 , 1.48]
Subtotal (95% CI)		**1188**		**1256**	**34.3%**	**1.13 [0.87 , 1.48]**
Total events:	103		96			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.93 (P = 0.35)						
Total (95% CI)		**3379**		**3380**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	260		273			
Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 3.10, df = 2 (P = 0.21), I² = 35.4%						



Footnotes

(1) Denominators are total randomised, minus children unable to contact/lost; 2 years' corrected age
(2) Denominators are total randomised; 2 years
(3) Denominators are total randomised; 18 months' corrected age
(4) Denominators are total randomised; 2 years' corrected age
(5) Denominators are total randomised; 1 year corrected age

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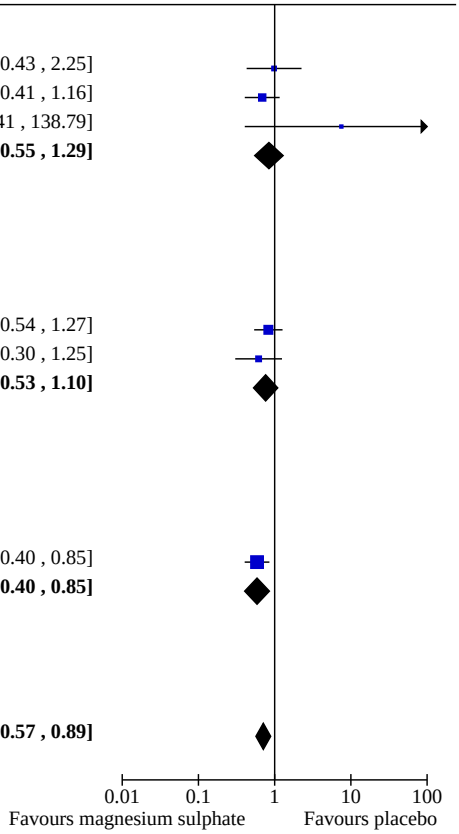
Analysis 9.2. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 No						
Crowther 2023 (1)	11	679	11	667	6.3%	0.98 [0.43 , 2.25]
Marret 2006 (2)	22	313	30	293	17.6%	0.69 [0.41 , 1.16]
Mittendorf 2002 (3)	3	27	0	29	0.3%	7.50 [0.41 , 138.79]
Subtotal (95% CI)		**1019**		**989**	**24.1%**	**0.84 [0.55 , 1.29]**
Total events:	36		41			
Heterogeneity: Chi² = 2.87, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 0.79 (P = 0.43)						
9.2.2 1 g/hour						
Crowther 2003 (4)	36	533	42	514	24.2%	0.83 [0.54 , 1.27]
Wolf 2020 (5)	12	321	19	313	10.9%	0.62 [0.30 , 1.25]
Subtotal (95% CI)		**854**		**827**	**35.1%**	**0.76 [0.53 , 1.10]**
Total events:	48		61			
Heterogeneity: Chi² = 0.49, df = 1 (P = 0.48); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.14)						
9.2.3 2 g/hour						
Rouse 2008 (6)	41	1174	74	1244	40.7%	0.59 [0.40 , 0.85]
Subtotal (95% CI)		**1174**		**1244**	**40.7%**	**0.59 [0.40 , 0.85]**
Total events:	41		74			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.80 (P = 0.005)						
Total (95% CI)		**3047**		**3060**	**100.0%**	**0.71 [0.57 , 0.89]**
Total events:	125		176			
Heterogeneity: Chi² = 4.75, df = 5 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: Chi² = 1.73, df = 2 (P = 0.42), I² = 0%						



Footnotes

(1) Denominators are surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnormalities of
(2) Denominators are livebirths with data; 2 years
(3) Denominators are livebirths; 18 months' corrected age
(4) Denominators are surviving children with data; 2 years' corrected age; criteria included abnormalities of tone and loss of motor function
(5) Denominators are surviving children at 18 months' corrected age or older
(6) Denominators are livebirths; 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) delay of 30% or more in gross motor develo

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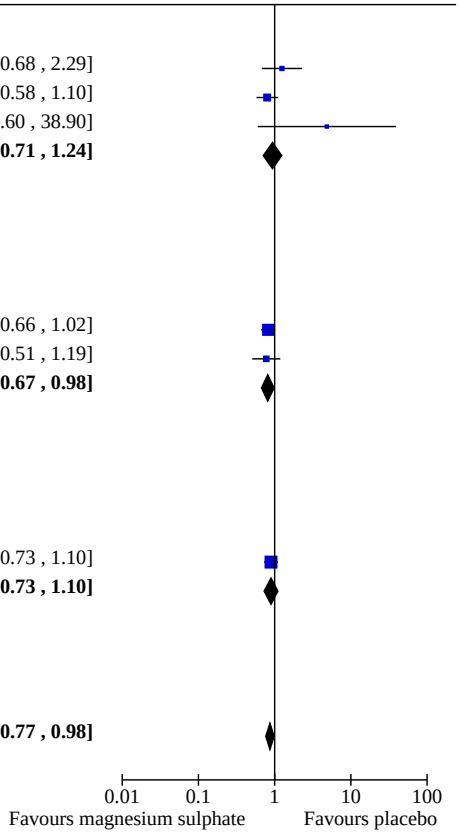
Analysis 9.3. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 No						
Crowther 2023 (1)	23	691	18	674	4.1%	1.25 [0.68 , 2.29]
Marret 2006 (2)	56	347	67	331	15.4%	0.80 [0.58 , 1.10]
Mittendorf 2002 (3)	5	30	1	29	0.2%	4.83 [0.60 , 38.90]
Subtotal (95% CI)		**1068**		**1034**	**19.7%**	**0.94 [0.71 , 1.24]**
Total events:	84		86			
Heterogeneity: Chi² = 4.19, df = 2 (P = 0.12); I² = 52%						
Test for overall effect: Z = 0.46 (P = 0.65)						
9.3.2 1 g/hour						
Crowther 2003 (4)	123	629	149	626	33.5%	0.82 [0.66 , 1.02]
Wolf 2020 (5)	34	343	43	337	9.7%	0.78 [0.51 , 1.19]
Subtotal (95% CI)		**972**		**963**	**43.2%**	**0.81 [0.67 , 0.98]**
Total events:	157		192			
Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%						
Test for overall effect: Z = 2.16 (P = 0.03)						
9.3.3 2 g/hour						
Rouse 2008 (6)	144	1188	170	1256	37.1%	0.90 [0.73 , 1.10]
Subtotal (95% CI)		**1188**		**1256**	**37.1%**	**0.90 [0.73 , 1.10]**
Total events:	144		170			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Total (95% CI)		**3228**		**3253**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	385		448			
Heterogeneity: Chi² = 4.84, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 0.86, df = 2 (P = 0.65), I² = 0%						



Footnotes

(1) Denominators are deaths and surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnor
(2) Denominators are deaths and livebirths with data; 2 years
(3) Denominators are total randomised; 18 months' corrected age
(4) Denominators are total randomised; 2 years' corrected age; cerebral palsy: criteria included abnormalities of tone and loss of motor function
(5) Denominators are total randomised; 18 months' corrected age (death) or later (cerebral palsy)
(6) Denominators are total randomised; death by 1 year, cerebral palsy at 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) de

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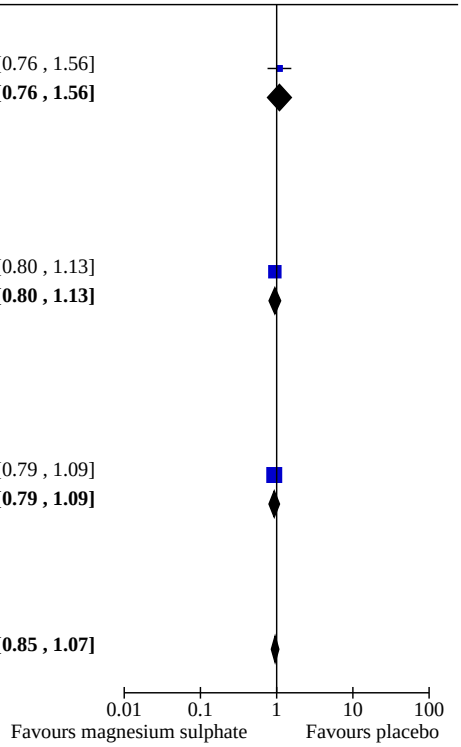
Analysis 9.4. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.4.1 No						
Crowther 2023 (1)	57	629	52	624	11.0%	1.09 [0.76 , 1.56]
Subtotal (95% CI)		**629**		**624**	**11.0%**	**1.09 [0.76 , 1.56]**
Total events:	57		52			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.65)						
9.4.2 1 g/hour						
Crowther 2003 (2)	176	629	185	626	39.0%	0.95 [0.80 , 1.13]
Subtotal (95% CI)		**629**		**626**	**39.0%**	**0.95 [0.80 , 1.13]**
Total events:	176		185			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.61 (P = 0.54)						
9.4.3 2 g/hour						
Rouse 2008 (3)	213	854	246	917	50.0%	0.93 [0.79 , 1.09]
Subtotal (95% CI)		**854**		**917**	**50.0%**	**0.93 [0.79 , 1.09]**
Total events:	213		246			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**2112**		**2167**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	446		483			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 0.62, df = 2 (P = 0.73), I² = 0%						



Footnotes

(1) Denominators are deaths and livebirths with paediatric assessments; major neurosensory disability: any of: blindness (corrected visual acuity worse than
(2) Denominators are total randomised; severe neurosensory disability: severe cerebral palsy (permanently nonambulant), severe developmental delay (MDI
(3) *From secondary analysis; denominators are infants born < 34 weeks' gestation, alive at initial hospital discharge, with 2 year outcome data; defined as c

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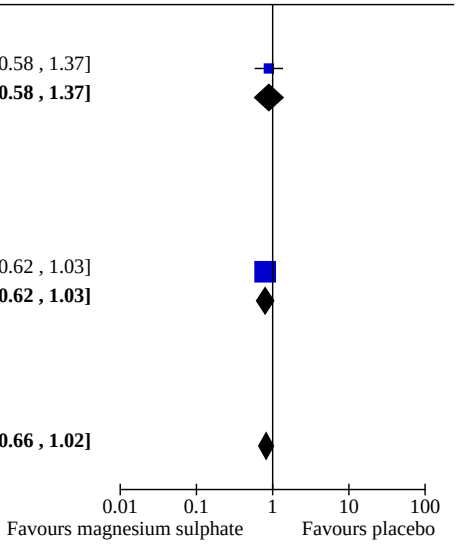
Analysis 9.5. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 5: Death (fetal, neonatal, or later (up to school age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.5.1 No						
Marret 2006 (1)	34	252	38	251	25.7%	0.89 [0.58 , 1.37]
Subtotal (95% CI)		**252**		**251**	**25.7%**	**0.89 [0.58 , 1.37]**
Total events:	34		38			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
9.5.2 1 g/hour						
Crowther 2003 (2)	88	629	110	626	74.3%	0.80 [0.62 , 1.03]
Subtotal (95% CI)		**629**		**626**	**74.3%**	**0.80 [0.62 , 1.03]**
Total events:	88		110			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.73 (P = 0.08)						
Total (95% CI)		**881**		**877**	**100.0%**	**0.82 [0.66 , 1.02]**
Total events:	122		148			
Heterogeneity: Chi² = 0.20, df = 1 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.76 (P = 0.08)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						



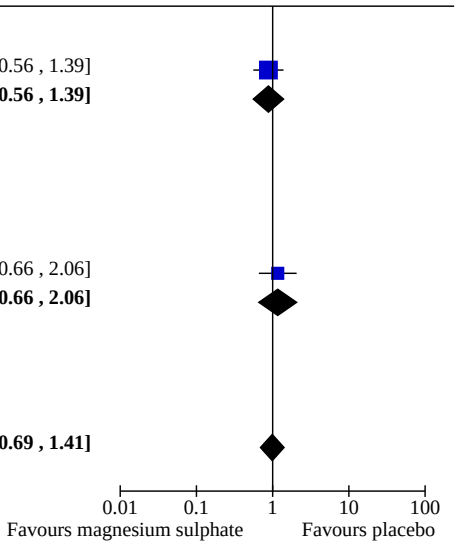
Footnotes

(1) Denominators are those with 7-14 year outcomes, including deaths

(2) Denominators are total randomised

Analysis 9.6. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 6: Cerebral palsy (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.6.1 No						
Marret 2006 (1)	30	218	33	211	62.2%	0.88 [0.56 , 1.39]
Subtotal (95% CI)		**218**		**211**	**62.2%**	**0.88 [0.56 , 1.39]**
Total events:	30		33			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.55 (P = 0.58)						
9.6.2 1 g/hour						
Crowther 2003 (2)	23	295	21	314	37.8%	1.17 [0.66 , 2.06]
Subtotal (95% CI)		**295**		**314**	**37.8%**	**1.17 [0.66 , 2.06]**
Total events:	23		21			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.53 (P = 0.60)						
Total (95% CI)		**513**		**525**	**100.0%**	**0.99 [0.69 , 1.41]**
Total events:	53		54			
Heterogeneity: Chi² = 0.57, df = 1 (P = 0.45); I² = 0%						
Test for overall effect: Z = 0.07 (P = 0.95)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						



Footnotes

(1) Denominators are children with 7-14 year follow up data

(2) Denominators are children with 6-11 year follow up data; cerebral palsy: nonprogressive loss of motor function with disordered tone or tendon reflexes

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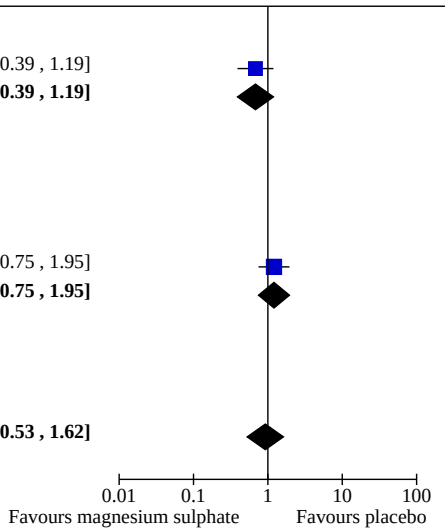
Analysis 9.7. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 7: Major neurodevelopmental disability (school age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
9.7.1 No						
Marret 2006 (1)	19	218	27	211	46.8%	0.68 [0.39 , 1.19]
Subtotal (95% CI)		**218**		**211**	**46.8%**	**0.68 [0.39 , 1.19]**
Total events:	19		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.35 (P = 0.18)						
9.7.2 1 g/hour						
Crowther 2003 (2)	33	257	27	254	53.2%	1.21 [0.75 , 1.95]
Subtotal (95% CI)		**257**		**254**	**53.2%**	**1.21 [0.75 , 1.95]**
Total events:	33		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.77 (P = 0.44)						
Total (95% CI)		**475**		**465**	**100.0%**	**0.92 [0.53 , 1.62]**
Total events:	52		54			
Heterogeneity: Tau² = 0.09; Chi² = 2.35, df = 1 (P = 0.13); I² = 57%						
Test for overall effect: Z = 0.28 (P = 0.78)						
Test for subgroup differences: Chi² = 2.35, df = 1 (P = 0.13), I² = 57.4%						



Footnotes

(1) Denominators are children with 7-14 year follow up data; severe overall deficits at school age: at least 1 of severe cerebral palsy, severe cognitive deficit/lea

(2) Denominators are children with 6-11 year follow up data; severe disability comprised any of severe cerebral palsy, an IQ less than 55, or blindness and mode

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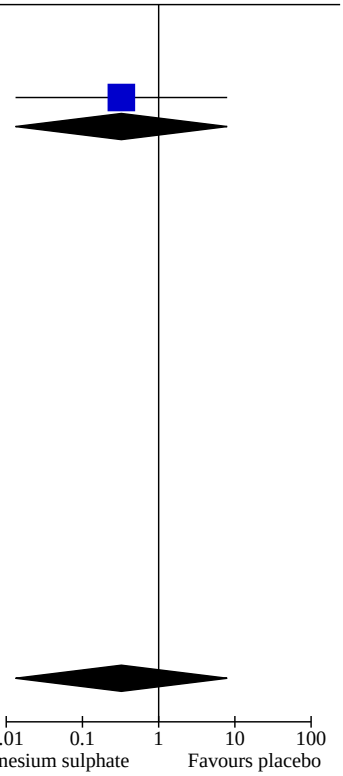
Analysis 9.8. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 8: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.8.1 No						
Crowther 2023 (1)	0	729	0	704		Not estimable
Marret 2006 (2)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Subtotal (95% CI)		**1015**		**982**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
9.8.2 1 g/hour						
Crowther 2003 (3)	0	535	0	527		Not estimable
Subtotal (95% CI)		**535**		**527**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.8.3 2 g/hour						
Rouse 2008 (4)	0	1096	0	1145		Not estimable
Subtotal (95% CI)		**1096**		**1145**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; serious adverse outcomes (maternal death, cardiac or respiratory arrest)
(2) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, prolonged mechanical ventilation)
(3) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, respiratory arrest)
(4) Denominators are total randomised; death or "lifethreatening events"

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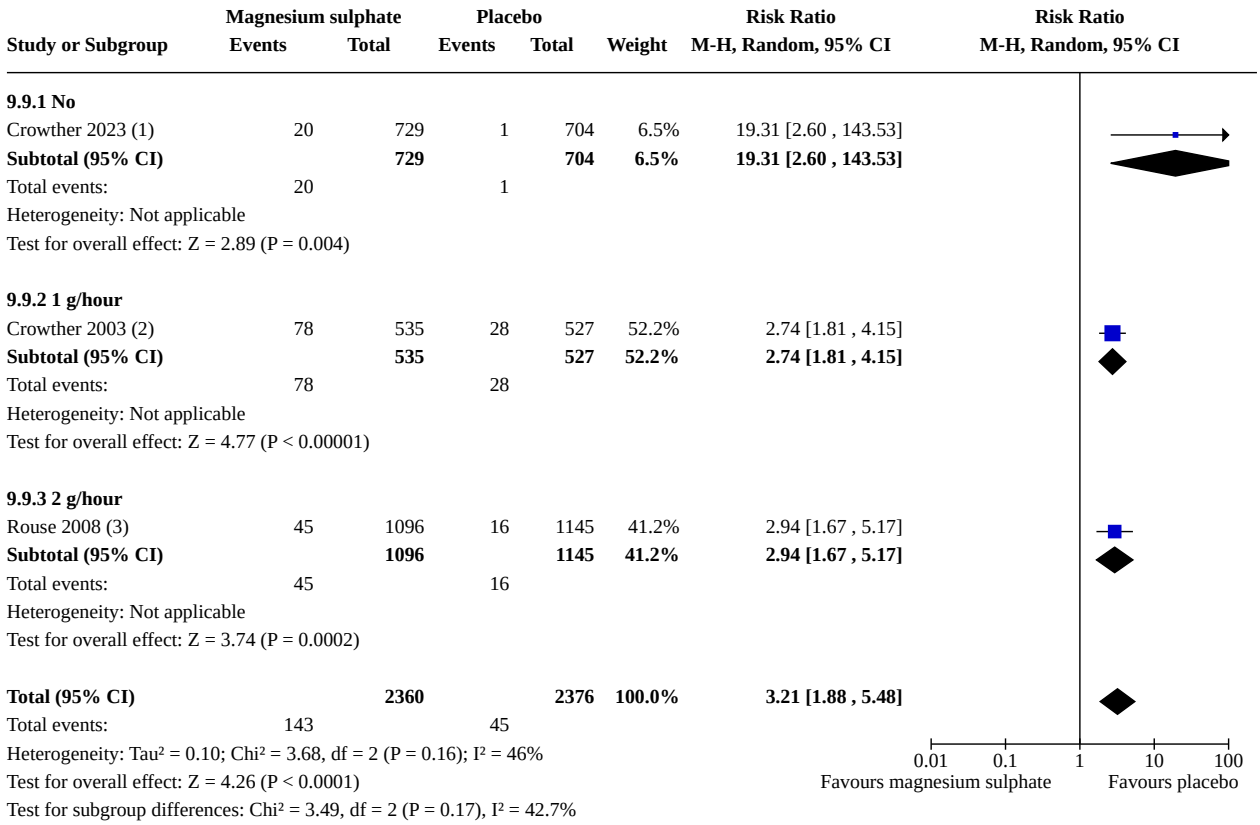
Analysis 9.9. Comparison 9: Subgroup analysis: maintenance dose regimen, Outcome 9: Adverse effects severe enough to stop treatment



Footnotes

(1) Denominators are total randomised; infusion discontinued for side effects
(2) Denominators are total randomised; infusion stopped due to adverse effects
(3) Denominators are total randomised; infusion stopped because of adverse event

Comparison 10. Subgroup analysis: repeat treatment permitted

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6	6759	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]
10.1.1 No	4	3635	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.07]
10.1.2 Yes	2	3124	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.38]
10.2 Cerebral palsy (up to 2 years' corrected age)	6	6107	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.57, 0.89]
10.2.1 No	4	3055	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.62, 1.13]
10.2.2 Yes	2	3052	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.43, 0.82]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.3 Death or cerebral palsy (up to 2 years' corrected age)	6	6481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.77, 0.98]
10.3.1 No	4	3357	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.73, 1.02]
10.3.2 Yes	2	3124	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.72, 1.05]
10.4 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3	4279	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.85, 1.07]
10.4.1 No	2	2508	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.14]
10.4.2 Yes	1	1771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.09]
10.5 Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)	4	5300	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
10.5.1 No	3	3059	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.92]
10.5.2 Yes	1	2241	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.6 Adverse effects severe enough to stop treatment	3	4736	Risk Ratio (M-H, Random, 95% CI)	3.21 [1.88, 5.48]
10.6.1 No	2	2495	Risk Ratio (M-H, Random, 95% CI)	5.74 [0.83, 39.53]
10.6.2 Yes	1	2241	Risk Ratio (M-H, Random, 95% CI)	2.94 [1.67, 5.17]

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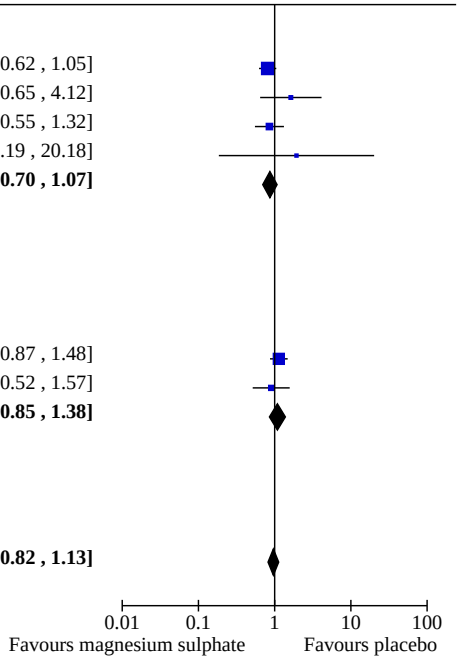
Analysis 10.1. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 No						
Crowther 2003 (1)	87	629	107	626	39.5%	0.81 [0.62 , 1.05]
Crowther 2023 (2)	12	837	7	796	2.6%	1.63 [0.65 , 4.12]
Marret 2006 (3)	34	352	38	336	14.3%	0.85 [0.55 , 1.32]
Mittendorf 2002 (4)	2	30	1	29	0.4%	1.93 [0.19 , 20.18]
Subtotal (95% CI)		**1848**		**1787**	**56.8%**	**0.87 [0.70 , 1.07]**
Total events:	135		153			
Heterogeneity: Chi² = 2.50, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 1.30 (P = 0.19)						
10.1.2 Yes						
Rouse 2008 (5)	103	1188	96	1256	34.3%	1.13 [0.87 , 1.48]
Wolf 2020 (4)	22	343	24	337	8.9%	0.90 [0.52 , 1.57]
Subtotal (95% CI)		**1531**		**1593**	**43.2%**	**1.09 [0.85 , 1.38]**
Total events:	125		120			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Total (95% CI)		**3379**		**3380**	**100.0%**	**0.96 [0.82 , 1.13]**
Total events:	260		273			
Heterogeneity: Chi² = 5.08, df = 5 (P = 0.41); I² = 2%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 1.89, df = 1 (P = 0.17), I² = 47.0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age
(2) Denominators are total randomised, minus children unable to contact/lost; 2 years' corrected age
(3) Denominators are total randomised; 2 years
(4) Denominators are total randomised; 18 months' corrected age
(5) Denominators are total randomised; 1 year corrected age

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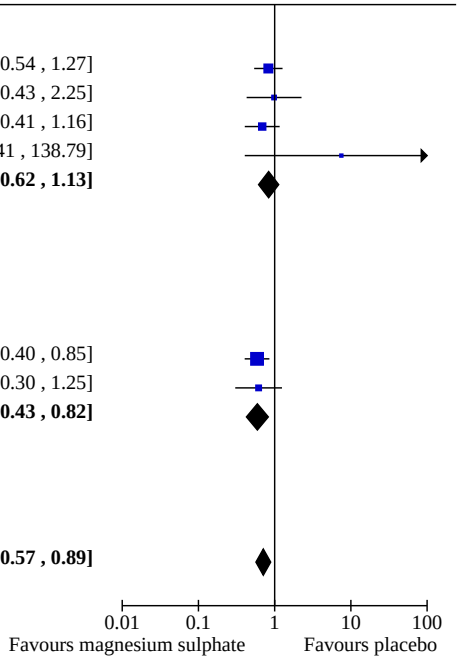
Analysis 10.2. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.2.1 No						
Crowther 2003 (1)	36	533	42	514	24.2%	0.83 [0.54 , 1.27]
Crowther 2023 (2)	11	679	11	667	6.3%	0.98 [0.43 , 2.25]
Marret 2006 (3)	22	313	30	293	17.6%	0.69 [0.41 , 1.16]
Mittendorf 2002 (4)	3	27	0	29	0.3%	7.50 [0.41 , 138.79]
Subtotal (95% CI)		**1552**		**1503**	**48.4%**	**0.83 [0.62 , 1.13]**
Total events:	72		83			
Heterogeneity: Chi² = 2.85, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.18 (P = 0.24)						
10.2.2 Yes						
Rouse 2008 (5)	41	1174	74	1244	40.7%	0.59 [0.40 , 0.85]
Wolf 2020 (6)	12	321	19	313	10.9%	0.62 [0.30 , 1.25]
Subtotal (95% CI)		**1495**		**1557**	**51.6%**	**0.59 [0.43 , 0.82]**
Total events:	53		93			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**3047**		**3060**	**100.0%**	**0.71 [0.57 , 0.89]**
Total events:	125		176			
Heterogeneity: Chi² = 4.75, df = 5 (P = 0.45); I² = 0%						
Test for overall effect: Z = 3.02 (P = 0.003)						
Test for subgroup differences: Chi² = 2.22, df = 1 (P = 0.14), I² = 54.9%						



Footnotes

(1) Denominators are surviving children with data; 2 years' corrected age; criteria included abnormalities of tone and loss of motor function

(2) Denominators are surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnormalities of

(3) Denominators are livebirths with data; 2 years

(4) Denominators are livebirths; 18 months' corrected age

(5) Denominators are livebirths; 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) delay of 30% or more in gross motor develo

(6) Denominators are surviving children at 18 months' corrected age or older

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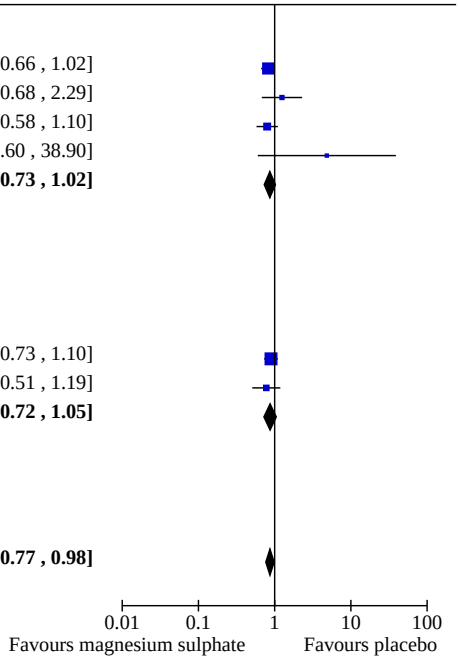
Analysis 10.3. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 No						
Crowther 2003 (1)	123	629	149	626	33.5%	0.82 [0.66 , 1.02]
Crowther 2023 (2)	23	691	18	674	4.1%	1.25 [0.68 , 2.29]
Marret 2006 (3)	56	347	67	331	15.4%	0.80 [0.58 , 1.10]
Mittendorf 2002 (4)	5	30	1	29	0.2%	4.83 [0.60 , 38.90]
Subtotal (95% CI)		**1697**		**1660**	**53.2%**	**0.86 [0.73 , 1.02]**
Total events:	207		235			
Heterogeneity: Chi² = 4.47, df = 3 (P = 0.21); I² = 33%						
Test for overall effect: Z = 1.69 (P = 0.09)						
10.3.2 Yes						
Rouse 2008 (5)	144	1188	170	1256	37.1%	0.90 [0.73 , 1.10]
Wolf 2020 (6)	34	343	43	337	9.7%	0.78 [0.51 , 1.19]
Subtotal (95% CI)		**1531**		**1593**	**46.8%**	**0.87 [0.72 , 1.05]**
Total events:	178		213			
Heterogeneity: Chi² = 0.35, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 1.46 (P = 0.15)						
Total (95% CI)		**3228**		**3253**	**100.0%**	**0.87 [0.77 , 0.98]**
Total events:	385		448			
Heterogeneity: Chi² = 4.84, df = 5 (P = 0.44); I² = 0%						
Test for overall effect: Z = 2.23 (P = 0.03)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



Footnotes

(1) Denominators are total randomised; 2 years' corrected age; cerebral palsy: criteria included abnormalities of tone and loss of motor function

(2) Denominators are deaths and surviving children with paediatric assessments; 2 years' corrected age; diagnosis required loss of motor function and abnor

(3) Denominators are deaths and livebirths with data; 2 years

(4) Denominators are total randomised; 18 months' corrected age

(5) Denominators are total randomised; death by 1 year, cerebral palsy at 2 years' corrected age or older; diagnosis made if 2 or more features present: 1) de

(6) Denominators are total randomised; 18 months' corrected age (death) or later (cerebral palsy)

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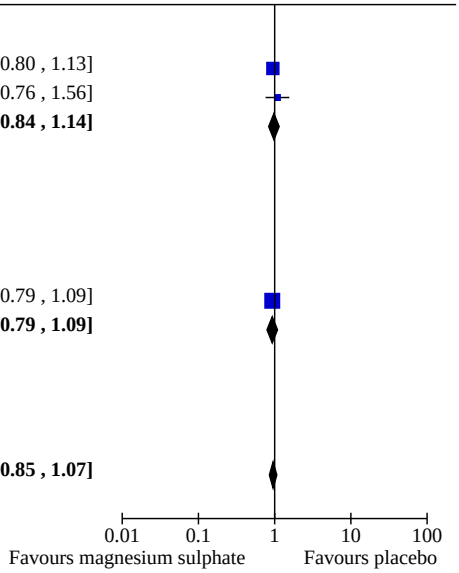
Analysis 10.4. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.4.1 No						
Crowther 2003 (1)	176	629	185	626	39.0%	0.95 [0.80 , 1.13]
Crowther 2023 (2)	57	629	52	624	11.0%	1.09 [0.76 , 1.56]
Subtotal (95% CI)		**1258**		**1250**	**50.0%**	**0.98 [0.84 , 1.14]**
Total events:	233		237			
Heterogeneity: Chi² = 0.47, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.28 (P = 0.78)						
10.4.2 Yes						
Rouse 2008 (3)	213	854	246	917	50.0%	0.93 [0.79 , 1.09]
Subtotal (95% CI)		**854**		**917**	**50.0%**	**0.93 [0.79 , 1.09]**
Total events:	213		246			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**2112**		**2167**	**100.0%**	**0.95 [0.85 , 1.07]**
Total events:	446		483			
Heterogeneity: Chi² = 0.62, df = 2 (P = 0.73); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						



Footnotes

(1) Denominators are total randomised; severe neurosensory disability: severe cerebral palsy (permanently nonambulant), severe developmental delay (MDI

(2) Denominators are deaths and livebirths with paediatric assessments; major neurosensory disability: any of: blindness (corrected visual acuity worse than

(3) *From secondary analysis; denominators are infants born < 34 weeks' gestation, alive at initial hospital discharge, with 2 year outcome data; defined as c

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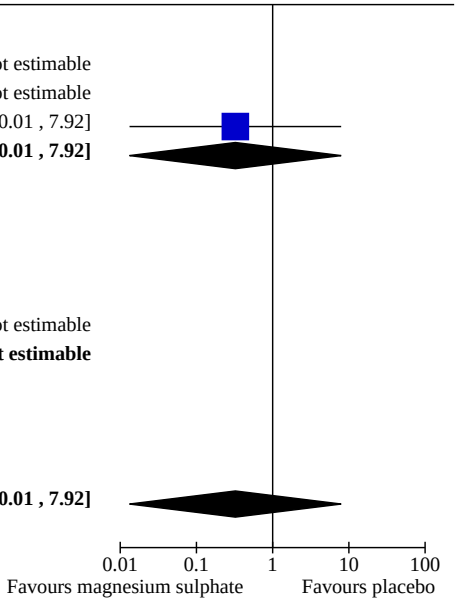
Analysis 10.5. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 5: Severe maternal outcome potentially related to treatment (death, respiratory arrest, or cardiac arrest)

Study or Subgroup	Magnesium sulphate Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.5.1 No						
Crowther 2003 (1)	0	535	0	527		Not estimable
Crowther 2023 (2)	0	729	0	704		Not estimable
Marret 2006 (3)	0	286	1	278	100.0%	0.32 [0.01 , 7.92]
Subtotal (95% CI)		**1550**		**1509**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
10.5.2 Yes						
Rouse 2008 (4)	0	1096	0	1145		Not estimable
Subtotal (95% CI)		**1096**		**1145**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2646**		**2654**	**100.0%**	**0.32 [0.01 , 7.92]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.69 (P = 0.49)						
Test for subgroup differences: Not applicable						



Footnotes

(1) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, respiratory arrest)
(2) Denominators are total randomised; serious adverse outcomes (maternal death, cardiac or respiratory arrest)
(3) Denominators are total randomised; major maternal adverse effects (death, cardiac arrest, prolonged mechanical ventilation)
(4) Denominators are total randomised; death or "lifethreatening events"

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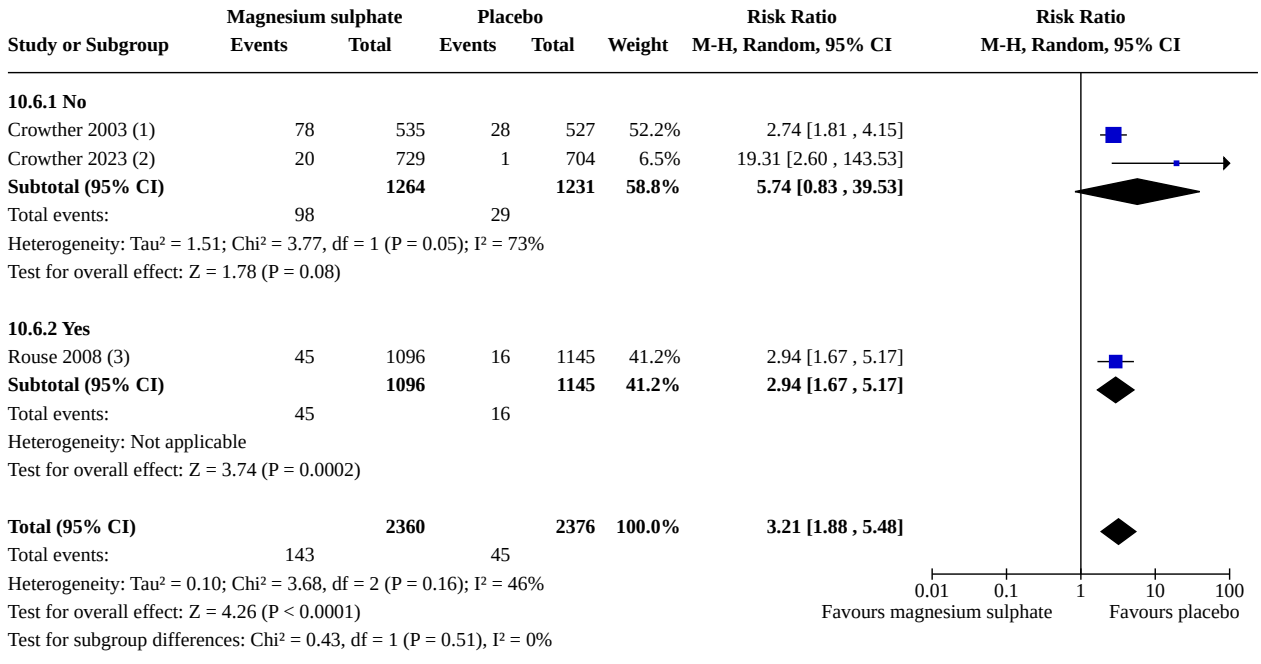
Analysis 10.6. Comparison 10: Subgroup analysis: repeat treatment permitted, Outcome 6: Adverse effects severe enough to stop treatment



Footnotes

(1) Denominators are total randomised; infusion stopped due to adverse effects

(2) Denominators are total randomised; infusion discontinued for side effects

(3) Denominators are total randomised; infusion stopped because of adverse event

Comparison 11. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Death (fetal, neonatal, or later (up to 2 years' corrected age))	6		Risk Ratio (IV, Fixed, 95% CI)	0.96 [0.81, 1.13]
11.2 Cerebral palsy (up to 2 years' corrected age)	6		Risk Ratio (IV, Fixed, 95% CI)	0.70 [0.55, 0.88]
11.3 Death or cerebral palsy (up to 2 years' corrected age)	6		Risk Ratio (IV, Fixed, 95% CI)	0.85 [0.74, 0.97]
11.4 Death or major neurodevelopmental disability (up to 2 years' corrected age)	3		Risk Ratio (IV, Fixed, 95% CI)	0.94 [0.84, 1.05]
11.5 Cerebral palsy (school age)	2		Risk Ratio (IV, Fixed, 95% CI)	1.09 [0.79, 1.52]

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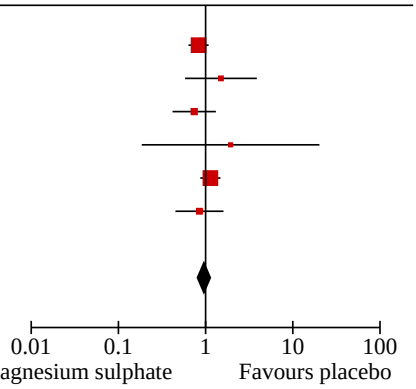
Analysis 11.1. Comparison 11: Sensitivity analysis, Outcome 1: Death (fetal, neonatal, or later (up to 2 years' corrected age))

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Crowther 2003 (1)	-0.18633	0.135835	40.3%	0.83 [0.64 , 1.08]
Crowther 2023 (2)	0.405465	0.483528	3.2%	1.50 [0.58 , 3.87]
Marret 2006 (3)	-0.301105	0.292131	8.7%	0.74 [0.42 , 1.31]
Mittendorf 2002 (4)	0.659246	1.196739	0.5%	1.93 [0.19 , 20.18]
Rouse 2008 (4)	0.126042	0.135969	40.2%	1.13 [0.87 , 1.48]
Wolf 2020 (5)	-0.162519	0.323606	7.1%	0.85 [0.45 , 1.60]
Total (95% CI)			**100.0%**	**0.96 [0.81 , 1.13]**

Heterogeneity: Chi² = 4.78, df = 5 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.59)
Test for subgroup differences: Not applicable



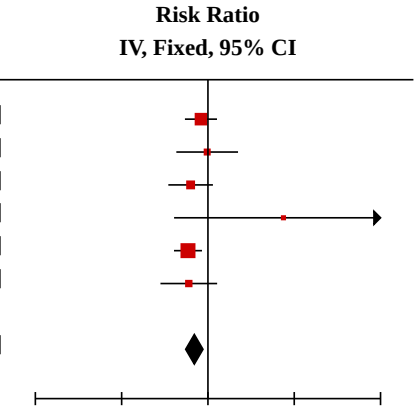
Footnotes

(1) Adjusted for clustering within mother
(2) Adjusted for hospital site, gestational age at entry, plurality, and sex of the infant; and accounted for a within-participant clustering el
(3) Adjusted OR; adjusted for clustering within mother, gestational age, singleton/multiple pregnancy, and birth weight factors
(4) Adjusted effect size not available
(5) Adjusted OR; adjusted for plurality and gestational age at randomisation; the correlation between twins was accounted for

Analysis 11.2. Comparison 11: Sensitivity analysis, Outcome 2: Cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Crowther 2003 (1)	-0.18633	0.218168	29.1%	0.83 [0.54 , 1.27]
Crowther 2023 (2)	-0.020203	0.419898	7.8%	0.98 [0.43 , 2.23]
Marret 2006 (3)	-0.462035	0.303471	15.0%	0.63 [0.35 , 1.14]
Mittendorf 2002 (4)	2.014903	1.488847	0.6%	7.50 [0.41 , 138.79]
Rouse 2008 (4)	-0.532578	0.190389	38.2%	0.59 [0.40 , 0.85]
Wolf 2020 (5)	-0.510826	0.385717	9.3%	0.60 [0.28 , 1.28]
Total (95% CI)			**100.0%**	**0.70 [0.55 , 0.88]**

Heterogeneity: Chi² = 4.92, df = 5 (P = 0.43); I² = 0%
Test for overall effect: Z = 3.09 (P = 0.002)
Test for subgroup differences: Not applicable



Footnotes

(1) Adjusted for clustering within mother
(2) Adjusted for hospital site, gestational age at entry, and plurality; and accounted for a within-participant clustering effect
(3) Adjusted OR; adjusted for clustering within mother, gestational age, singleton/multiple pregnancy, and birth weight factors
(4) Adjusted effect size not available
(5) Adjusted OR; adjusted for plurality and gestational age at randomisation; the correlation between twins was accounted for

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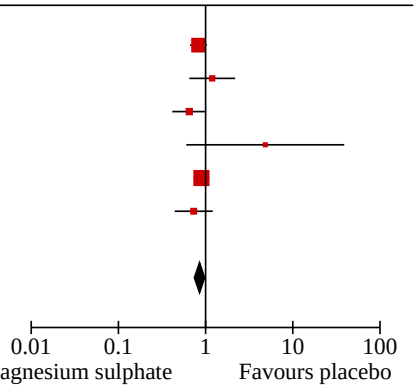
Analysis 11.3. Comparison 11: Sensitivity analysis, Outcome 3: Death or cerebral palsy (up to 2 years' corrected age)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Crowther 2003 (1)	-0.18633	0.113541	36.5%	0.83 [0.66 , 1.04]
Crowther 2023 (2)	0.173953	0.308707	4.9%	1.19 [0.65 , 2.18]
Marret 2006 (3)	-0.430783	0.228846	9.0%	0.65 [0.42 , 1.02]
Mittendorf 2002 (4)	1.575536	1.064041	0.4%	4.83 [0.60 , 38.90]
Rouse 2008 (4)	-0.110324	0.105777	42.0%	0.90 [0.73 , 1.10]
Wolf 2020 (5)	-0.314711	0.255949	7.2%	0.73 [0.44 , 1.21]
Total (95% CI)			**100.0%**	**0.85 [0.74 , 0.97]**

Heterogeneity: Chi² = 5.87, df = 5 (P = 0.32); I² = 15%
Test for overall effect: Z = 2.34 (P = 0.02)
Test for subgroup differences: Not applicable



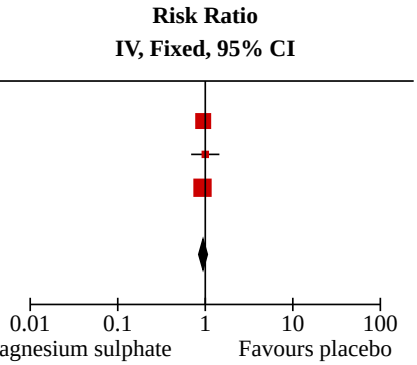
Footnotes

(1) Adjusted for clustering within mother
(2) Adjusted for hospital site, gestational age at entry, plurality, sex of the infant, and language spoken at home; and accounted for a wit
(3) Adjusted OR; adjusted for clustering within mother, gestational age, singleton/multiple pregnancy, and birth weight factors
(4) Adjusted effect size not available
(5) Adjusted OR; adjusted for plurality and gestational age at randomisation; the correlation between twins was accounted for

Analysis 11.4. Comparison 11: Sensitivity analysis, Outcome 4: Death or major neurodevelopmental disability (up to 2 years' corrected age)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Crowther 2003 (1)	-0.054653	0.088882	41.1%	0.95 [0.80 , 1.13]
Crowther 2023 (2)	0	0.189449	9.0%	1.00 [0.69 , 1.45]
Rouse 2008 (1)	-0.072863	0.080613	49.9%	0.93 [0.79 , 1.09]
Total (95% CI)			**100.0%**	**0.94 [0.84 , 1.05]**

Heterogeneity: Chi² = 0.13, df = 2 (P = 0.94); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable



Footnotes

(1) Adjusted effect size not available
(2) Adjusted for hospital site, gestational age at entry, plurality, sex of the infant, and language spoken at home; and accounted for a wit

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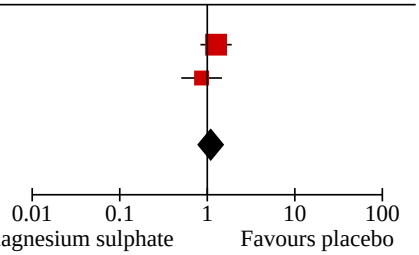
Analysis 11.5. Comparison 11: Sensitivity analysis, Outcome 5: Cerebral palsy (school age)

Study or Subgroup	log[Risk Ratio]	SE	Weight	Risk Ratio IV, Fixed, 95% CI
Crowther 2003 (1)	0.231112	0.209559	62.9%	1.26 [0.84 , 1.90]
Marret 2006 (2)	-0.149969	0.273081	37.1%	0.86 [0.50 , 1.47]
Total (95% CI)			**100.0%**	**1.09 [0.79 , 1.52]**

Heterogeneity: Chi² = 1.23, df = 1 (P = 0.27); I² = 18%
Test for overall effect: Z = 0.54 (P = 0.59)
Test for subgroup differences: Not applicable



Footnotes

(1) Adjusted OR; adjusted for study center and for clustering within mother; analysis carried out using multiple imputation to handle mi
(2) Adjusted effect size not available

ADDITIONAL TABLES

Table 1. Participant characteristics related to planned subgroup analyses

RCT	Primary reason women were at high risk of preterm birth	Number of babies in utero	Gestational age at entry/randomisation
Crowther 2003	**Inclusion criteria**		
	Women if birth was planned or expected within 24 h; excluded women in the second stage of labour	Singleton, twin, triplet, or quadruplet pregnancies	< 30 weeks' gestation (no lower gestational age limit)
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		
	Reason for preterm birth Preterm labour: 335 (62.6) vs 330 (62.6) Pre-eclampsia/eclampsia: 86 (16.1) vs 75 (14.2) Chorioamnionitis: 73 (13.6) vs 72 (13.7) Antepartum haemorrhage: 70 (13.1) vs 81 (15.4) Severe IUGR: 50 (9.3) vs 42 (8.2) PROM: 43 (8.0) vs 54 (10.2) Fetal distress: 20 (3.7) vs 13 (2.5) Other: 29 (5.4) vs 30 (5.7)	Multiples: 88 (16.4) vs 89 (16.9)	Median (IQR) gestational age at entry: 27 weeks 3 days (25 weeks 5 days to 28 weeks 5 days) vs 27 weeks 2 days (25 weeks 5 days to 28 weeks 5 days)
Crowther 2023	**Inclusion criteria**		
	Women if birth was planned or definitely expected within 24 h	Singleton or twin pregnancies	30 to < 34 weeks' gestation
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		

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Table 1. Participant characteristics related to planned subgroup analyses *(Continued)*

	Reason at risk for preterm birth Preterm labour: 207 (28.4) vs 182 (25.9) PPROM: 206 (28.3) vs 183 (26.0) Fetal compromise: 129 (17.7) vs 129 (18.3) Pre-eclampsia: 65 (8.9) vs 81 (11.5) Antepartum haemorrhage: 72 (9.9) vs 67 (9.5) Unspecified: 50 (6.9) vs 62 (8.8)	Twin pregnancy: 130 (17.8) vs 120 (17.0)	Mean (SD) gestational age at entry: 32.1 (1.1) vs 32.1 (1.1) 30 to < 32 weeks: 323 (44.3) vs 308 (43.8) 32 to < 34 weeks: 406 (55.7) vs 396 (56.3)
Marret 2006	**Inclusion criteria**		
	Women if birth was expected or planned within 24 h	Singleton, twin, or triplet pregnancies	< 33 weeks' gestational age (no lower limit, except those established at individual participating centres concerning viability)
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		
	Reasons for preterm birth Preterm labour: 236 (84.0) vs 242 (88.3) PPROM: 187 (53.9) vs 156 (46.6) Chorioamnionitis: 27 (9.5) vs 34 (12.6) Antepartum haemorrhage: 54 (19.0) vs 54 (20.0) Other: 33 (9.8) vs 43 (13.3)	Singleton pregnancy: 222 (77.6) vs 220 (79.1)	Median (range) gestational age at entry: 30 weeks (24 weeks to 32 weeks 6 days) vs 30 weeks (23 weeks 4 days to 32 weeks 6 days)
Mittendorf 2002	**Inclusion criteria**		
	Women in preterm labour (subgroup of women in active labour with cervical dilatation > 4 cm)	Triplet and higher-order gestations were excluded.	> 24 and < 34 completed weeks' gestation
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		
	Not reported	Twin pregnancy: 1 (3.4) vs 1 (3.6)	< 28 weeks' gestation: 6 (20.7) vs 5 (17.9)
Rouse 2008	**Inclusion criteria**		
	Women at high risk of spontaneous birth because of ROM, or advanced preterm labour with cervical dilatation of 4 to 8 cm and intact membranes, or an indicated preterm birth anticipated within 2 to 24 h; birth < 2 h or cervical dilatation > 8 cm, and ROM < 22 weeks' gestation excluded	Singleton or twin pregnancies	24 to 31 completed weeks' gestation (< 32 weeks' gestation)
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		
	Qualifying eligibility criterion PROM: 947 (86.4) vs 995 (86.9)	Twin pregnancy: 92 (8.4) vs 111 (9.7)	Mean (SD) gestational age at randomisation: 28.3 (2.5) vs 28.2 (2.4)

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Table 1. Participant characteristics related to planned subgroup analyses *(Continued)*

	Advanced preterm labour: 116 (10.6) vs 114 (10.0) Indicated preterm delivery: 33 (3.0) vs 36 (3.1)		
Wolf 2020	**Inclusion criteria**		
	Women expected to give birth preterm within 2 to 24 h	Singleton or twin pregnancies	24 + 0 to 31 + 6 weeks' gestation
	Population characteristics, magnesium sulphate vs placebo, N (%) unless stated		
	Primary reason for preterm birth Advanced preterm labour: 183 (64.7) vs 174 (62.8) Antepartum haemorrhage: 19 (6.7) vs 22 (7.9) Chorioamnionitis: 11 (3.9) vs 7 (2.5) Fetal distress: 5 (1.8) vs 4 (1.4) Pre-eclampsia, eclampsia, HELLP: 3 (1.1) vs 4 (1.4) PPROM: 42 (14.8) vs 37 (13.4) Severe IUGR: 20 (7.1) vs 29 (10.5)	Twin pregnancy: 60 (21.2) vs 60 (21.7)	Mean (SD) gestational age at randomisation: 28.6 (2.3) vs 28.7 (2.2)

Abbreviations: HELLP: haemolysis, elevated liver enzymes, low platelet count; IQR: interquartile range; IUGR: intrauterine growth restriction; PPROM: preterm prelabour rupture of membranes; PROM: prelabour rupture of membranes; RCT: randomised controlled trial; ROM: rupture of membranes; SD: standard deviation

Table 2. Treatment characteristics related to planned subgroup analyses

RCT	Mode of administration	Loading-dose regimen	Maintenance dose regimen	Repeat treatment permitted	Time of starting treatment prior to birth
Crowther 2003	**Treatment intended**				
	IV	4 g over 20 min	1 g/h until birth (if within 24 h) or up to 24 h	No	Women eligible if birth was planned or expected within 24 h
	Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
	-	Started: 522 (97.5) vs 509 (96.6) Completed: 484 (90.5) vs 495 (93.9)	Started: 451 (84.2) vs 459 (87.1) Completed: 70 (13.1) vs 77 (14.6)	N/A	Not reported
Crowther 2023	**Treatment intended**				
	IV	4 g over 30 min	None	No	Women eligible if birth was planned or definitely expected within 24 h

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Table 2. Treatment characteristics related to planned subgroup analyses *(Continued)*

	Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
	-	Received: 690 (94.7) vs 667 (94.7)	N/A	N/A	Not reported
Marret 2006	**Treatment intended**				
	IV	4 g over 30 min	None	No	Women eligible if birth was expected or planned within 24 h
	Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
	-	Started: 266 (93.0) vs 257 (92.4) Completed: 259 (90.6) vs 249 (89.6)	N/A	N/A	Interval from infusion to delivery, median (range): 1 h 38 min (5 min to 25 h 5 min) vs 1 h 30 min (8 min to 61 h 30 min)
Mittendorf 2002	**Treatment intended**				
	IV	4 g bolus	None	No	Not reported
	Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
	-	Not reported	N/A	N/A	Not reported
Rouse 2008	**Treatment intended**				
	IV	6 g over 20 to 30 min	2 g/h until birth or for up to 12 h (resumed if < 6 h had passed and birth again appeared imminent)	If ≥ 6 h had passed since discontinuation, another loading dose was given.	Not clear, although women were not eligible if delivery was anticipated within less than 2 h; women with indicated preterm deliveries were eligible if birth was anticipated within 24 h
	Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
	-	Did not receive treatment: 18 (1.6) vs 20 (1.7)	Received treatment for < 3 h: 996 (90.9) vs 1024 (89.4) Received treatment for ≥ 3 h: 82 (7.5) vs 101 (8.8) Median (IQR) total dose: 31.5 g (29.0 to 44.6)	Eligible for retreatment (total population): 1602 (71.5) Of eligible for retreatment, receiving drug at delivery (total population): 947 (59.1)	Not reported
Wolf 2020	**Treatment intended**				
	IV	5 g over 10 to 30 min	1 g/h until birth, or for 24 h if birth had not occurred	Loading dose repeated if ≥ 6 h had passed since discontinuation of treatment and birth was	Women eligible if expected to give birth within 2 to 24 h

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Table 2. Treatment characteristics related to planned subgroup analyses *(Continued)*

			again imminent < 32 weeks' gestation.	
Treatment as received, magnesium sulphate vs placebo, N (%) unless stated				
-	Started: 273 (96.5) vs 268 (96.7) Completed: 268 (94.7) vs 266 (96.0)	Started: 235 (83.0) vs 230 (83.0) Completed: 116 (41.0) vs 95 (34.3)	Eligible for repeat loading dose (total population): 147 (26.3) Of those eligible for repeat loading dose, received it (total population): 78 (53.1)	Not reported

Abbreviations: IQR: interquartile range; IV: intravenous; N/A: not applicable; RCT: randomised controlled trial

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Pregnancy] explode all trees

#2 MeSH descriptor: [Pregnancy Complications] explode all trees

#3 MeSH descriptor: [Infant, Newborn] explode all trees

#4 MeSH descriptor: [Fetus] explode all trees

#5 MeSH descriptor: [Fetal Development] explode all trees

#6 MeSH descriptor: [Prenatal Diagnosis] explode all trees

#7 MeSH descriptor: [Fetal Monitoring] explode all trees

#8 MeSH descriptor: [Fetal Therapies] explode all trees

#9 MeSH descriptor: [Heart Rate, Fetal] explode all trees

#10 MeSH descriptor: [Extraembryonic Membranes] explode all trees

#11 MeSH descriptor: [Placenta] explode all trees

#12 MeSH descriptor: [Placental Function Tests] explode all trees

#13 MeSH descriptor: [Uterine Monitoring] explode all trees

#14 MeSH descriptor: [Pelvimetry] explode all trees

#15 MeSH descriptor: [Oxytocics] explode all trees

#16 MeSH descriptor: [Tocolytic Agents] explode all trees

#17 MeSH descriptor: [Tocolysis] explode all trees

#18 MeSH descriptor: [Maternal Health Services] explode all trees

#19 MeSH descriptor: [Peripartum Period] explode all trees

#20 MeSH descriptor: [Parity] explode all trees

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#21 MeSH descriptor: [Perinatal Care] explode all trees

#22 MeSH descriptor: [Postpartum Period] explode all trees

#23 MeSH descriptor: [Labor Pain] explode all trees

#24 MeSH descriptor: [Anesthesia, Obstetrical] explode all trees

#25 MeSH descriptor: [Obstetric Surgical Procedures] explode all trees

#26 MeSH descriptor: [Analgesia, Obstetrical] explode all trees

#27 MeSH descriptor: [Obstetric Nursing] explode all trees

#28 MeSH descriptor: [Maternal-Child Nursing] explode all trees

#29 MeSH descriptor: [Midwifery] explode all trees

#30 MeSH descriptor: [Apgar Score] explode all trees

#31 MeSH descriptor: [Breast Feeding] explode all trees

#32 MeSH descriptor: [Bottle Feeding] explode all trees

#33 MeSH descriptor: [Milk, Human] explode all trees

#34 {OR #1-#33}

#35 pregnan*

#36 fetus

#37 foetus

#38 fetal

#39 foetal

#40 newborn

#41 "new born"

#42 birth

#43 childbirth

#44 laboring

#45 labour*

#46 antepart*

#47 prenatal*

#48 antenatal*

#49 perinatal*

#50 postnatal*

#51 postpart*

#52 caesar*

#53 cesar*

#54 obstetric*

#55 tocoly*

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#56 oxytoci*

#57 placent*

#58 parturi*

#59 preeclamp*

#60 eclamp*

#61 intrapart*

#62 puerper*

#63 episiotom*

#64 amnio*

#65 matern*

#66 gestation*

#67 lactati*

#68 breastfe*

#69 breast NEXT fe*

#70 preconcept*

#71 periconcept*

#72 interconcept*

#73 {OR #35-#72}

#74 #34 OR #73

Appendix 2. MEDLINE search strategy

1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. drug therapy.fs.
6. randomly.ab.
7. trial.ab.
8. groups.ab.
9. or/1-8
10. exp Pregnancy/
11. exp Pregnancy Complications/
12. exp Maternal Health Services/
13. exp Fetus/
14. exp Fetal Therapies/
15. exp Fetal Monitoring/
16. exp Prenatal Diagnosis/
17. Perinatal Care/
18. Labor pain/
19. Analgesia, Obstetric/
20. exp Obstetric Surgical Procedures/
21. Infant, Newborn/
22. exp Postpartum Period/
23. Breastfeeding/
24. or/10-23
25. 9 and 24
26. exp animals/ not humans.sh.

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27. 25 not 26

Appendix 3. Embase search strategy

1. CROSSOVER PROCEDURE/
2. DOUBLE BLIND PROCEDURE/
3. SINGLE BLIND PROCEDURE/
4. RANDOMIZED CONTROLLED TRIAL/
5. crossover$.ti,ab
6. (cross ADJ over$).ti,ab
7. placebo$.ti,ab
8. (doubl$ ADJ blind$).ti,ab
9. allocat$.ti,ab
10. random$.ti,ab
11. trial$.ti
12. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11
13. exp PREGNANCY/
14. exp PREGNANCY DISORDER/
15. exp OBSTETRIC PROCEDURE/
16. exp BREAST FEEDING/ OR exp BREAST FEEDING EDUCATION/
17. exp CHILDBIRTH/ OR exp CHILDBIRTH EDUCATION/
18. exp LABOR PAIN/
19. (antenatal* OR prenatal* OR puerper* OR postnatal* OR post-natal* OR post ADJ natal* OR postpartum OR post-partum OR post ADJ partum).ti,ab
20. (prepregnancy OR pre-pregnancy OR pre ADJ pregnancy OR preconcept* OR pre-concept* OR pre ADJ concept* OR periconcept* OR peri-concept* OR peri ADJ concept*).ti,ab
21. ((preterm OR premature) AND (labour OR labor)).ti,ab
22. (eclamp* OR preeclamp* OR pre ADJ eclamp*).ti,ab
23. amniocentes*.ti,ab
24. (chorion* ADJ vill*).ti,ab
25. (breastfe* OR breast-fe* OR breast ADJ fe* OR lactation).ti,ab
26. (caesarean OR cesarean OR caesarian OR cesarian OR cesarien OR caesarien).ti,ab
27. (newborn OR new ADJ born).ti,ab
28. (pregnancy OR pregnant OR pregnancies).ti
29. episiotom*.ti,ab
30. 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29
31. 12 AND 30

Appendix 4. CINAHL search strategy

1. exp CLINICAL TRIALS/
2. (clinic* ADJ trial*).ti,ab
3. (trebl* ADJ mask*).ti,ab
4. (tripl* ADJ blind*).ti,ab
5. (tripl* ADJ mask*).ti,ab
6. (doubl* ADJ blind*).ti,ab
7. (doubl* ADJ mask*).ti,ab
8. (singl* ADJ blind*).ti,ab
9. (singl* ADJ mask*).ti,ab
10. (randomi* ADJ control* ADJ trial*).ti,ab
11. RANDOM ASSIGNMENT/
12. (random* ADJ allocat*).ti,ab
13. placebo*.ti,ab
14. PLACEBOS/
15. QUANTITATIVE STUDIES/

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16.(allocat* ADJ random*).ti,ab
17.breastfeeding.ti,ab
18.breastfed.ti,ab
19.exp BREAST FEEDING/
20.breast-fe*.ti,ab
21.exp PREGNANCY/
22.exp PREGNANCY COMPLICATIONS/
23.(prenatal OR antenatal OR antepartum OR postpartum OR postnatal).ti,ab
24.(pregnant OR pregnancy).ti
25.((preterm OR premature) AND (labor OR labour)).ti,ab
26.(midwife OR midwifery).ti,ab
27.CHILDBIRTH EDUCATION/
28.exp PREGNANCY, MULTIPLE/ OR exp PREGNANCY TRIMESTERS/
29.exp MATERNAL-CHILD CARE/
30.(prenatal* OR pre-natal* OR perinatal* OR peripartum OR antenatal* OR postnatal* OR post-natal* OR postpart* OR post-part* OR puerper* OR prepregnancy OR pre-pregnancy OR preconcept* OR pre-concept* OR periconcept* OR peri-concept*).ti,ab
31.OBSTETRIC EMERGENCIES/
32.OBSTETRIC NURSING/
33.exp SURGERY, OBSTETRICAL/
34.exp DIAGNOSIS, OBSTETRIC/
35.1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16
36.17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34

Appendix 5. Search methods for ClinicalTrials.gov and ICTRP

We searched each line separately and manually removed duplicates

ClinicalTrials.gov

Advanced search

Interventional Studies | Preterm Labor | Magnesium sulfate (this also searched premature and MgSO4)

neuroprotection | Interventional Studies | Magnesium sulfate

Interventional Studies | Intraventricular Hemorrhage | Magnesium sulfate

ICTRP (searched to include all synonyms)

preterm AND magnesium

premature AND magnesium

neuroprotection AND magnesium

WHAT'S NEW

Date	Event	Description
10 May 2024	New search has been performed	We reassessed 29 records identified in the previous version of the review, along with 215 new records. We included six RCTs (116 records), four of which were included in the previous version of the review (Crowther 2003; Marret 2006; Mittendorf 2002; Rouse 2008) and two new RCTs (Crowther 2023; Wolf 2020).
10 May 2024	New citation required but conclusions have not changed	No changes to conclusions of review

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HISTORY

Protocol first published: Issue 1, 2004
Review first published: Issue 3, 2007

Date	Event	Description
22 September 2009	Amended	Corrected error in figures reported in the first paragraph of the Discussion.
16 February 2009	Amended	Error in NNT for cerebral palsy corrected.
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

2023 update

For this update, all authors (Emily Shepherd, Shona Goldsmith, Hanne Wolf, Peter Pryde, Dwight Rouse, Stephane Marret, Philippa Middleton, Caroline Crowther, and Lex Doyle) contributed to updating the protocol. Emily Shepherd, Hanne Wolf, Peter Pryde, Philippa Middleton, Caroline Crowther, and Lex Doyle assessed identified studies for eligibility. Emily Shepherd and Shona Goldsmith performed data extraction, trustworthiness assessments, and risk of bias assessment for each randomised controlled trial. Emily Shepherd entered the data into RevMan software, wrote the initial synthesis of results, and prepared the first full draft, with assistance from Shona Goldsmith. All authors commented on subsequent drafts and approved the final version.

Previous versions

Lex Doyle and Caroline Crowther wrote the original protocol (2004). Lex Doyle, for the first version of this review (2007), searched the literature, reviewed all identified studies for eligibility, extracted details of the studies' methods and results, entered data into RevMan software, 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 (2007). Philippa Middleton searched the literature, extracted details of the studies' results, and contributed to all versions of the original review (2007). Stephane Marret searched the literature, extracted details of the studies' results, and contributed to the final version of the original review (2007).

For the previous update of this review (2009), Caroline Crowther and Philippa Middleton searched the literature, extracted details of the study methods and results, entered data into RevMan software, wrote the initial updated synthesis of results, and contributed to all versions of the updated review (2009). Lex Doyle, Stephane Marret, and Dwight Rouse contributed to all versions of the updated review (2009).

DECLARATIONS OF INTEREST

Emily Shepherd: former Editor for Cochrane Pregnancy and Childbirth and current Sign-off Editor for Cochrane Central Editorial Service, but had no involvement in the editorial processing of this review.

Shona Goldsmith: senior research fellow with Cerebral Palsy Alliance, The University of Sydney.

Lex Doyle: investigator for an included randomised controlled trial (RCT) (Crowther 2003), and published opinions in medical journals relating to magnesium sulphate use in neuroprotection.

Philippa Middleton: investigator for an included RCT (Crowther 2023); former Editor for Cochrane Pregnancy and Childbirth and current Sign-off Editor for Cochrane Central Editorial Service, but had no involvement in the editorial processing of this review; and Independent Contractor for National Health and Medical Research Council Stillbirth Centre for Research Excellence.

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Stephane Marret: investigator for included RCT (Marret 2006), and works as a health professional in neonatology and neuropaediatrics, Rouen University Hospital, Rouen, France.

Dwight Rouse: investigator for an included RCT (Rouse 2008).

Peter Pryde: investigator for an included RCT (Mittendorf 2002); published opinions in medical journals relating to magnesium sulphate to reduce cerebral palsy; is a retired clinician; and maintains an adjunct faculty position at the University of Wisconsin School of Medicine and Public Health strictly for academic purposes.

Hanne Wolf: investigator for an included RCT (Wolf 2020), and works as a Gynaecologist and Obstetrician, University Hospital, Denmark.

Caroline Crowther: investigator for included RCTs (Crowther 2003; Crowther 2023).

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Internal sources

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  Support for Emily Shepherd's salary
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- Cerebral Palsy Alliance, Australia

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

2023 update

We made the following changes for the 2023 update.

New authors

Emily Shepherd, Shona Goldsmith, Hanne Wolf, and Peter Pryde are new authors on this update.

Revised criteria for considering studies for this review

We clarified that cluster-randomised controlled trials (RCTs) and RCTs published in abstract form only were eligible.

We restricted inclusion to RCTs assessing magnesium sulphate given for fetal neuroprotection (RCTs assessing magnesium sulphate for another indication, such as pre-eclampsia/eclampsia, reporting on long-term neurological outcomes, were no longer eligible).

We reworded the primary outcomes for infants/children/adults as follows.

- Death (fetal, neonatal, or later)
- Cerebral palsy
- Death or cerebral palsy
- Major neurodevelopmental disability
- Death or major neurodevelopmental disability

We added the following secondary outcomes (not prespecified in the previous version) for **infants**: fetal death, neonatal death, body size at birth, gestational age at birth, post-haemorrhagic hydrocephalus or ventriculomegaly, neonatal encephalopathy, neonatal hypoglycaemia, necrotising enterocolitis, intestinal perforation, retinopathy of prematurity, patent ductus arteriosus, respiratory distress syndrome, use of inotropic support, air leak syndrome, early- and late-onset sepsis, severe adverse neonatal outcome composite; for **infants/children/adults**: later death, cerebral palsy severity, any neurodevelopmental disability, death or any neurodevelopmental disability, blindness, deafness, developmental delay/intellectual impairment, gross motor dysfunction, psychomotor dysfunction, death or substantial gross

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motor dysfunction, respiratory function, blood pressure, behaviour; for **women**: individual components of severe maternal outcome potentially related to treatment, maternal side effects of treatment (including nausea, vomiting, flushing, infusion arm discomfort, mouth dryness, sweating, dizziness, blurred vision), time between randomisation and birth [we removed length of labour, need for augmentation of labour], chorioamnionitis [we removed intrapartum fever requiring the use of antibiotics]; for **use of health services**: use and costs of care for infant/child/adult.

Search methods for identification of studies

We updated as per standard Cochrane Pregnancy and Childbirth methods.

Selection of studies

We updated as per standard Cochrane Pregnancy and Childbirth methods, with incorporation of an assessment of scientific integrity (trustworthiness) using a tool developed by Cochrane Pregnancy and Childbirth.

Data extraction and management

We updated as per standard Cochrane Pregnancy and Childbirth methods.

Assessment of risk of bias in included studies

We updated as per standard Cochrane Pregnancy and Childbirth methods.

Unit of analysis issues

We updated as per standard Cochrane Pregnancy and Childbirth methods to clarify handling of cluster-RCTs, multiple pregnancy, and multiple-arm RCTs.

Assessment of reporting biases

We updated as per standard Cochrane Pregnancy and Childbirth methods.

Subgroup analysis and investigation of heterogeneity

We updated as per standard Cochrane Pregnancy and Childbirth methods. We removed subgroup analyses based on: the use of prenatal corticosteroids in more than 50% of those at risk; and the type of magnesium preparation given. We clarified that subgroup analyses would be conducted separately based on loading-dose regimen and maintenance dose regimen.

Sensitivity analysis

We post hoc included sensitivity analyses for primary outcomes for the infant/child/adult, using the generic inverse variance method to pool, where possible, adjusted effect sizes.

Summary of findings and assessment of the certainty of the evidence

We updated as per standard Cochrane Pregnancy and Childbirth methods, with the inclusion of GRADE summary of findings tables to present the certainty of the evidence for key prespecified outcomes.

Previous version

We added the outcome of intraventricular haemorrhage 3/4 at the review stage.

We 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]; Magnesium Sulfate [*therapeutic use]; Neuroprotective Agents [*therapeutic use]; *Premature Birth; Prenatal Care; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy

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