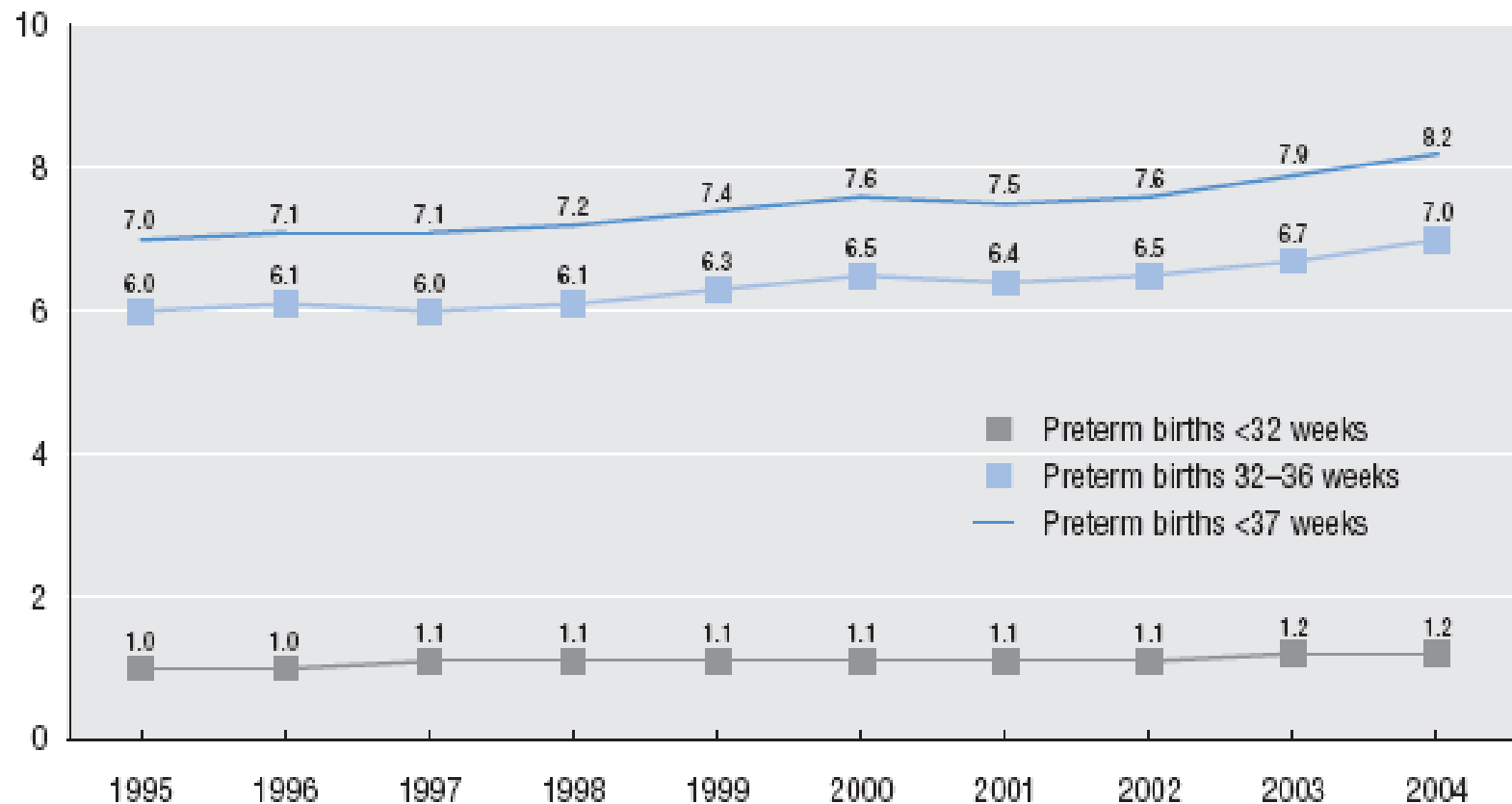


**Antenatal magnesium sulfate in women
in preterm labour to prevent cerebral
palsy in the fetus**



Preterm birth rate in Canada (excludes Ontario), 1995-2004*

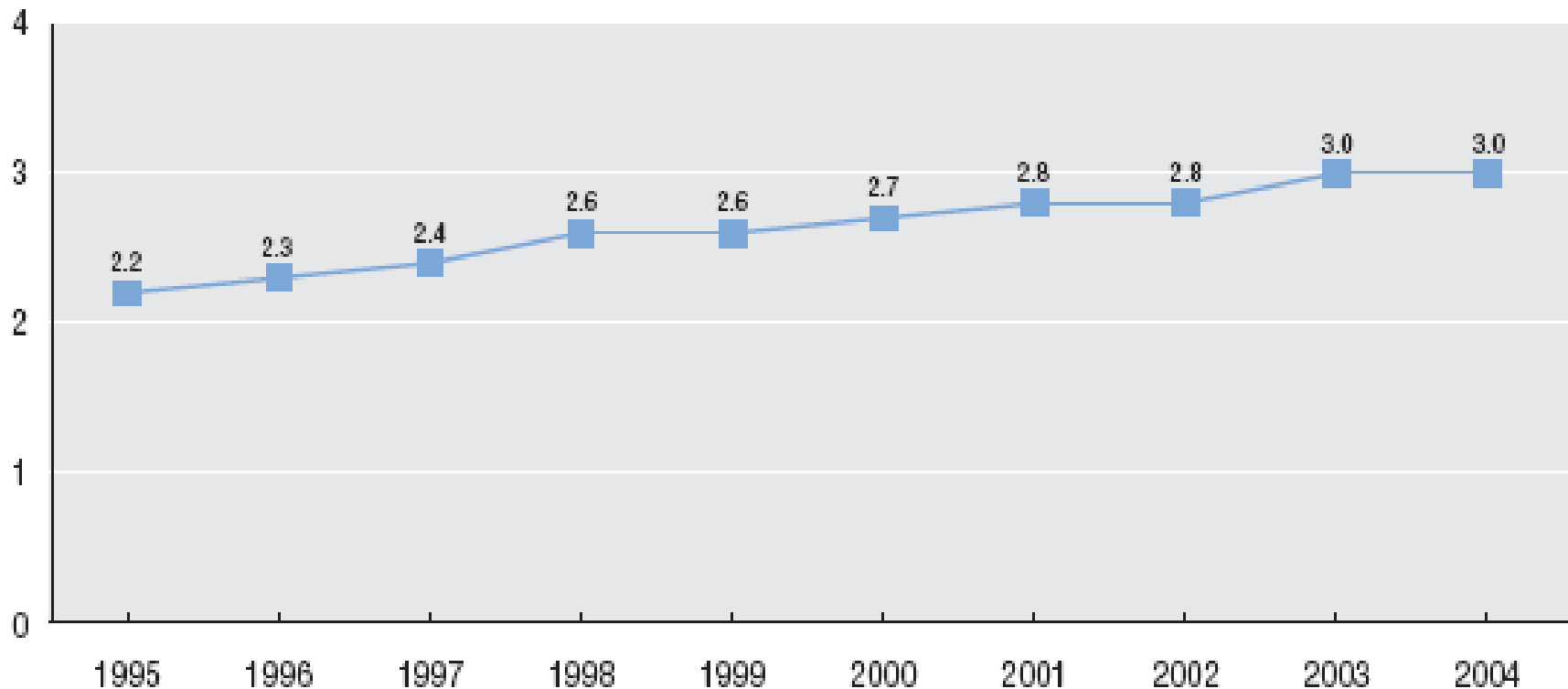
Preterm births per 100 live births**



* Public Health Agency of Canada. (2008). *Canadian perinatal health report* (No. HP10-12/2008E). Ottawa, ON: Minister of Health.

Rate of multiple birth in Canada (excludes Ontario) 1995-2004

Multiple births per 100 total births



* Public Health Agency of Canada. (2008). *Canadian perinatal health report* (No. HP10-12/2008E). Ottawa, ON: Minister of Health.

PEDIATRICS®

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Increasing Prevalence of Cerebral Palsy Among Very Preterm Infants: A Population-Based Study

by

Michael J. Vincer, Alexander C. Allen, K. S. Joseph,
Dora A. Stinson, Heather Scott and Ellen Wood

Pediatrics 2006;118;e1621-1626

Cerebral palsy



- A group of disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occurred in the developing fetal or infant brain. The motor disorders of cerebral palsy are often accompanied by disturbances of sensation, cognition, communication, perception, and/or behavior, and/or by a seizure disorder (Bax M et al. Dev Med Child Neurol 2005;47:571-576)
- Birth prevalence of cerebral palsy is approximately 2 per 1,000 live births (for the entire birth cohort)
- Recognized more commonly in preterm births with as many as 10-20% of infants < 31 weeks

Characteristics of magnesium

- 4th most abundant cation in the human body (2nd most common intracellular cation)
- Extracellular Mg accounts for only 1% of the body's Mg
 - Serum a poor measure of body Mg (monocyte Mg is better)
- $\frac{1}{3}$ of skeletal Mg is exchangeable

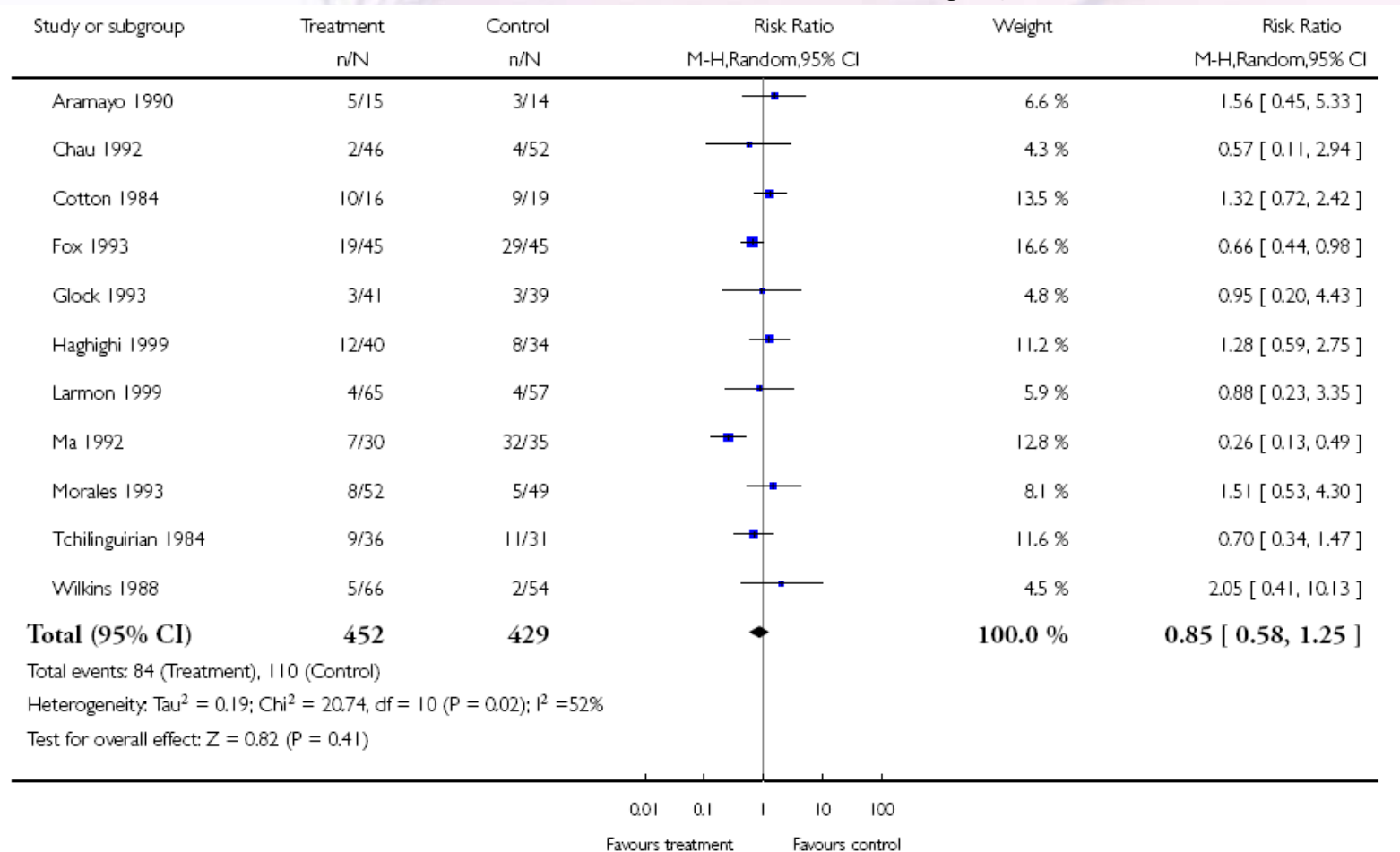
Physiologic role of magnesium

- Mg^{++} catalyzes > 325 enzymes
- Activates PO_4 groups & reactions involving ATP
- Regulates DNA synthesis
- Regulates cell membrane permeability
- Pivotal role in:
 - Neuronal activity
 - Neuromuscular transmission
 - Muscle contraction & vasomotor tone
 - BP regulation
 - Peripheral blood flow

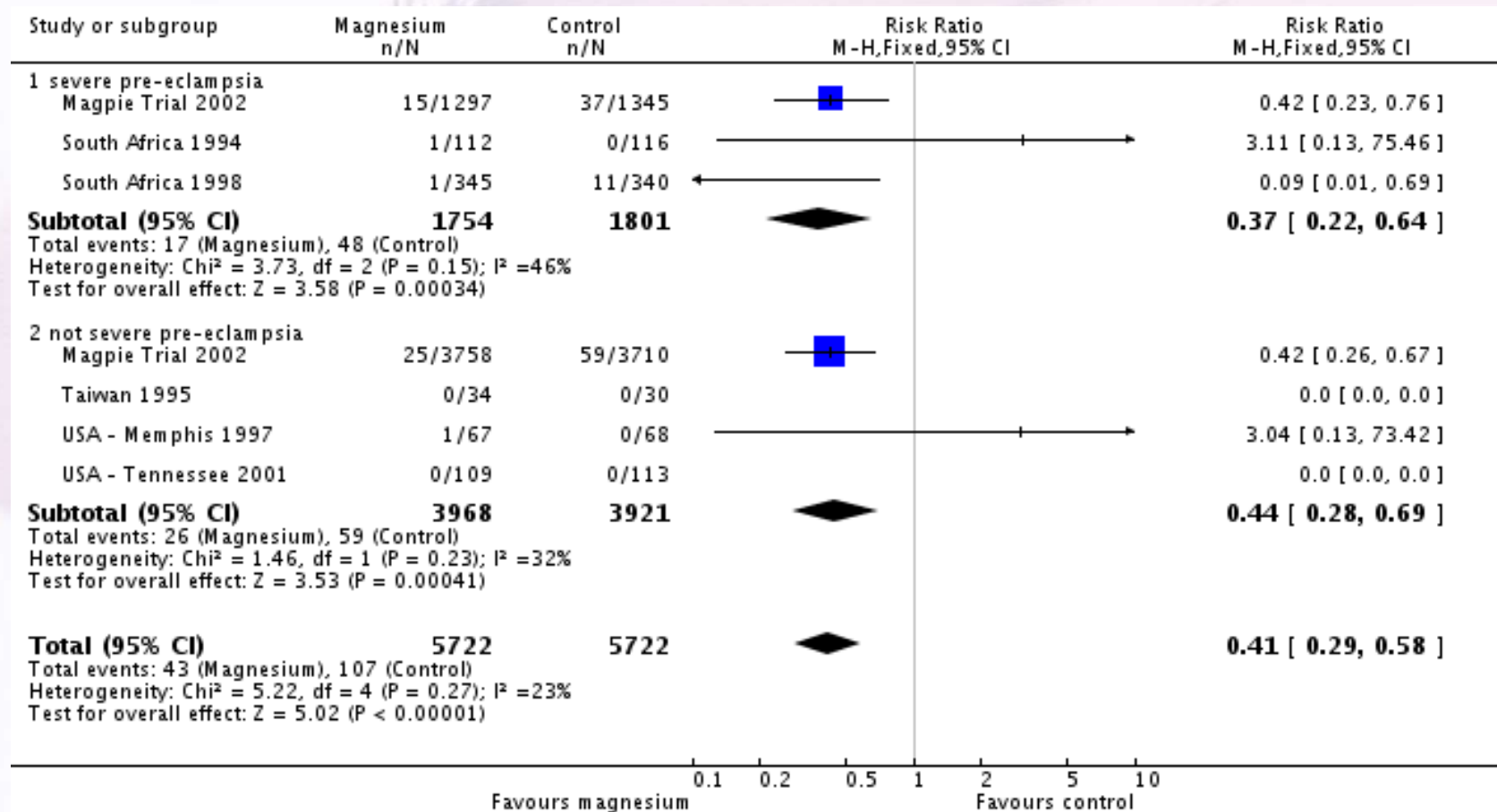


Uses of MgSO_4 in obstetrics

MgSO₄ to prevent preterm birth (outcome: delivery \leq 48 hours from trial entry)



MgSO₄ for the prevention of eclampsia



Historical background to the hypothesis that MgSO_4 may result in a lower prevalence of CP

- IVH in babies of women with PET was at a lower prevalence
 - van de Bor (1987)
 - Leviton (1988)
- IVH was felt to be due to MgSO_4 exposure in women with PET
 - Kuban (1992)
- Case control trial noted that VLBW infants with CP had a lower exposure to MgSO_4 than those without CP
 - Nelson (1995)

MgSO₄ use for the prevention of cerebral palsy

- In 1996, when this talk was first delivered there were no RCT's
 - “MgSO₄ should be studied in mothers in preterm labour to determine whether or not we can prevent or ameliorate CP”
- Since then, MgSO₄ has been the subject of six RCT's describing long-term outcome in infants and has been summarized in a Cochrane review (Doyle, L. W. et al, 2009)

Authors' conclusions

“The neuroprotective role for antenatal magnesium sulphate therapy given to women at risk of preterm birth for the preterm fetus is now established.”‡

‡ Doyle, L. W., Crowther, C. A., Middleton, P., Marret, S., & Rouse, D. (2009). Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database of Systematic Reviews (Online)*, (1)(1), CD004661.

Cochrane systematic review by primary intention

1. Fetal neuroprotection

- Crowther 2003
- Marret 2006
- Mittendorf 2002 (n=59 vs placebo) – Arm 2
- Rouse 2008

2. Maternal pre-eclampsia

- Magpie 2006

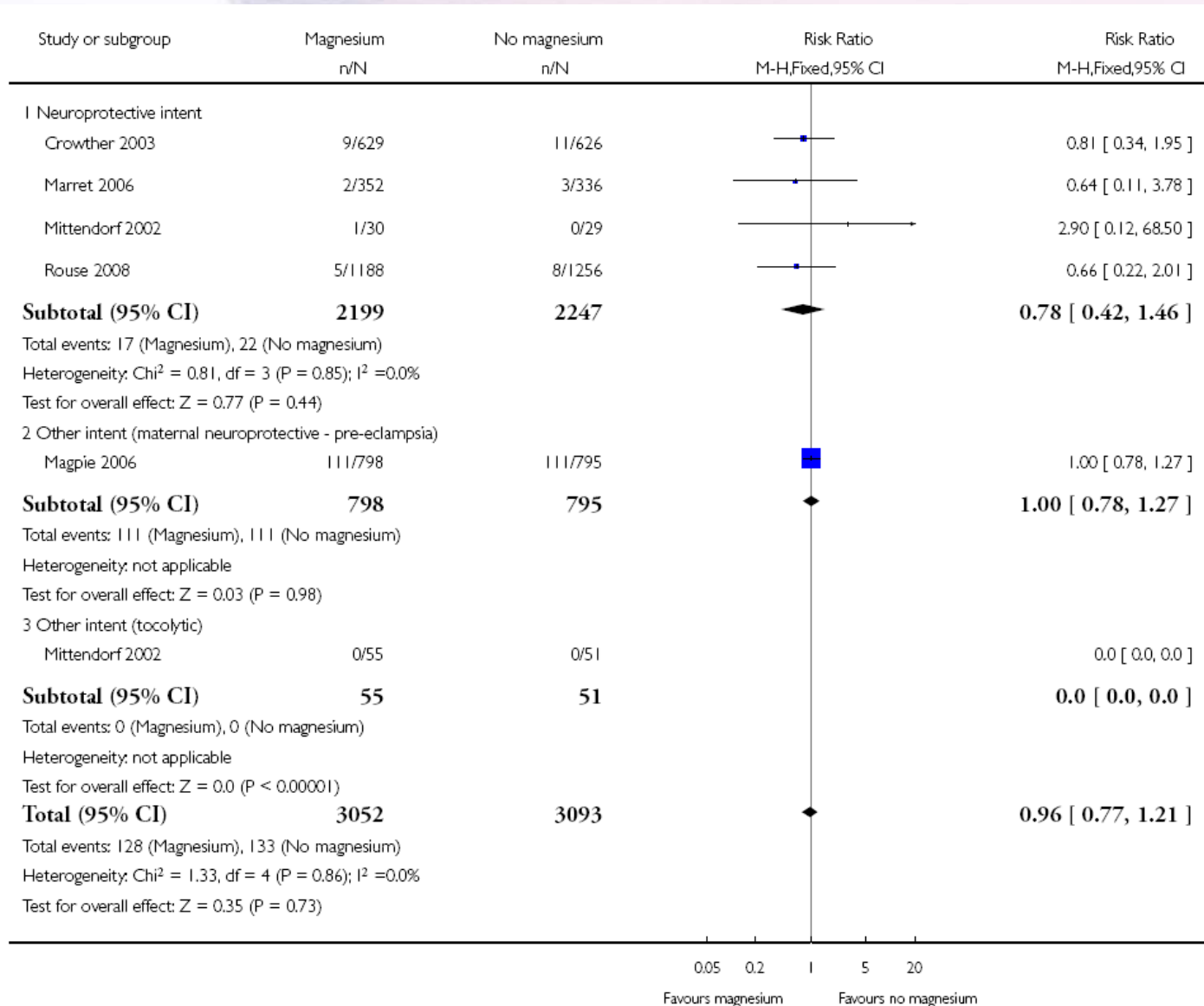
3. Tocolytic

- Mittendorf 2002 (n=106 vs “other” tocolytic) – Arm 1

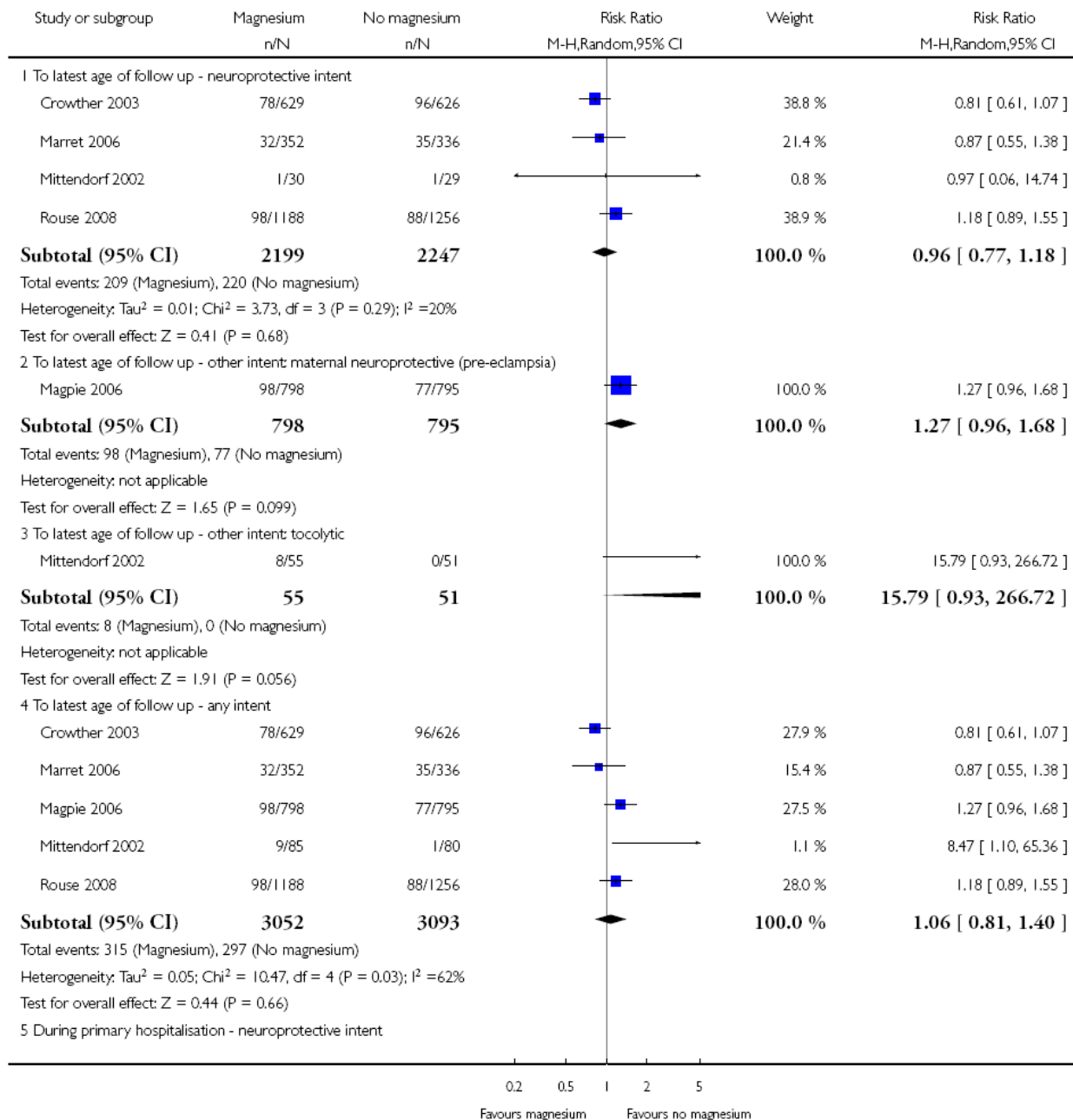
The PICO(T) question

In women with threatened preterm labour, does the use of MgSO_4 (for any indication in the mother) compared to placebo (or “other tocolytic”) result in a lower prevalence of cerebral palsy in the baby. The time interval for follow-up should be at least 18 months.

Fetal deaths only

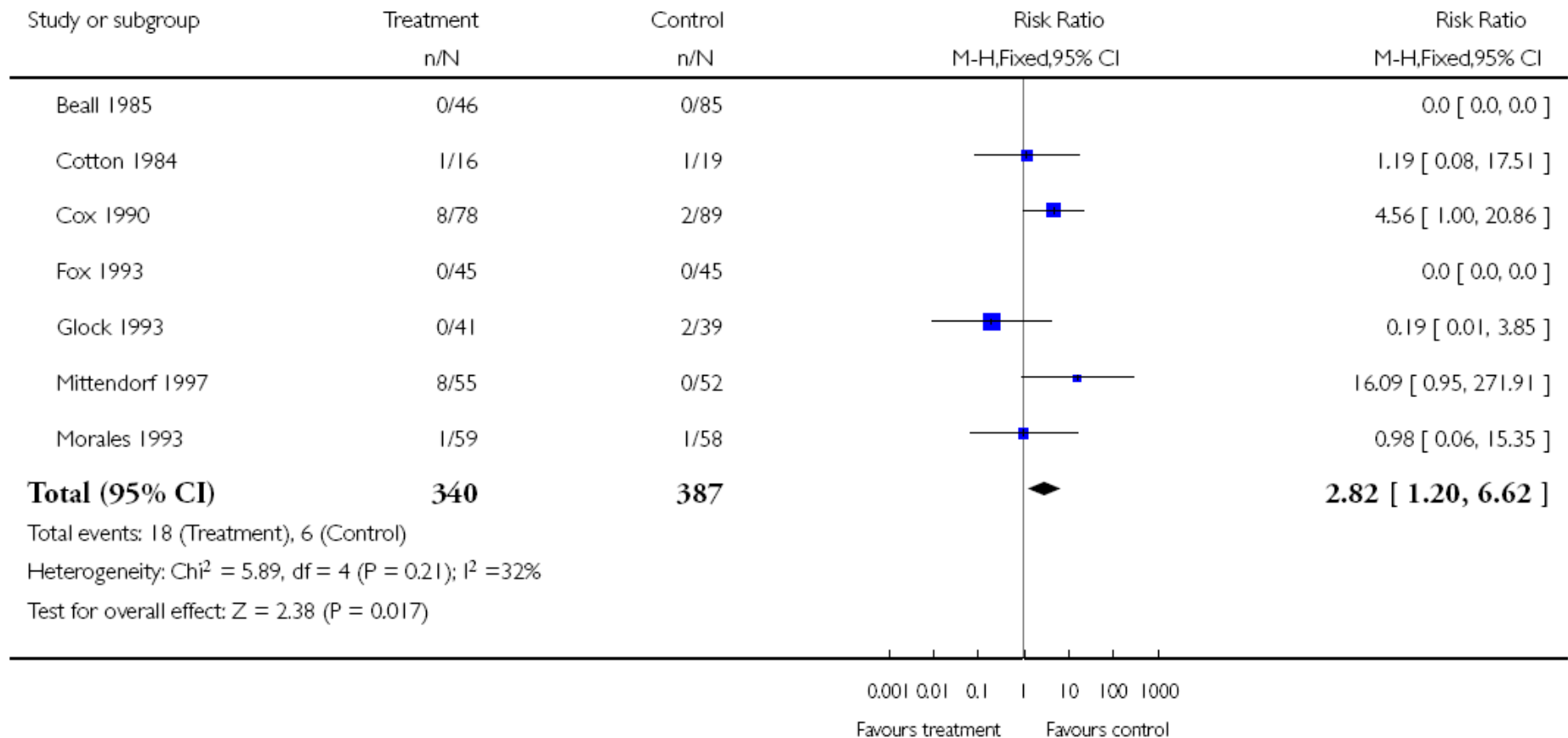


Paediatric deaths only

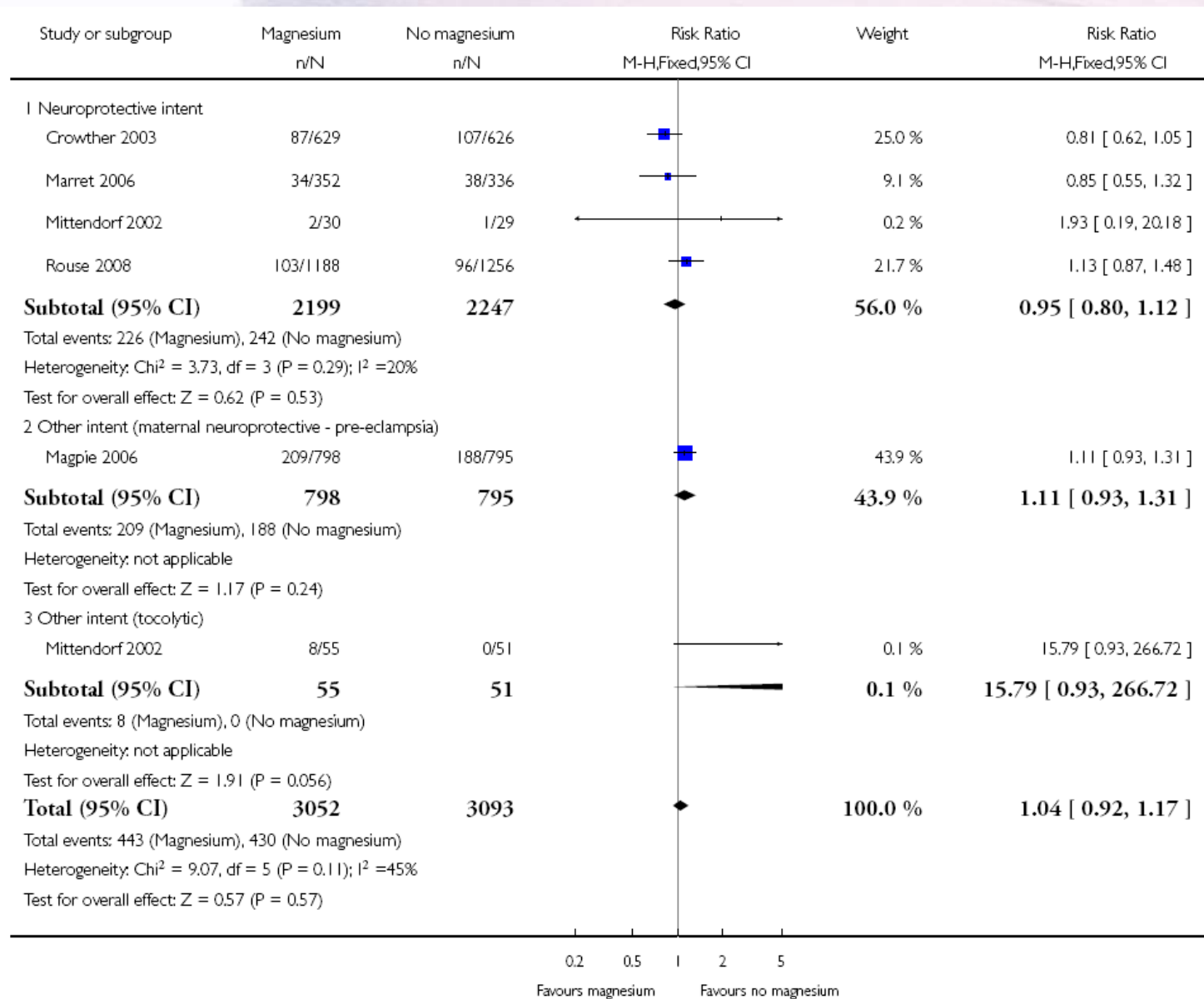


Total deaths when magnesium sulfate used as a tocolytic

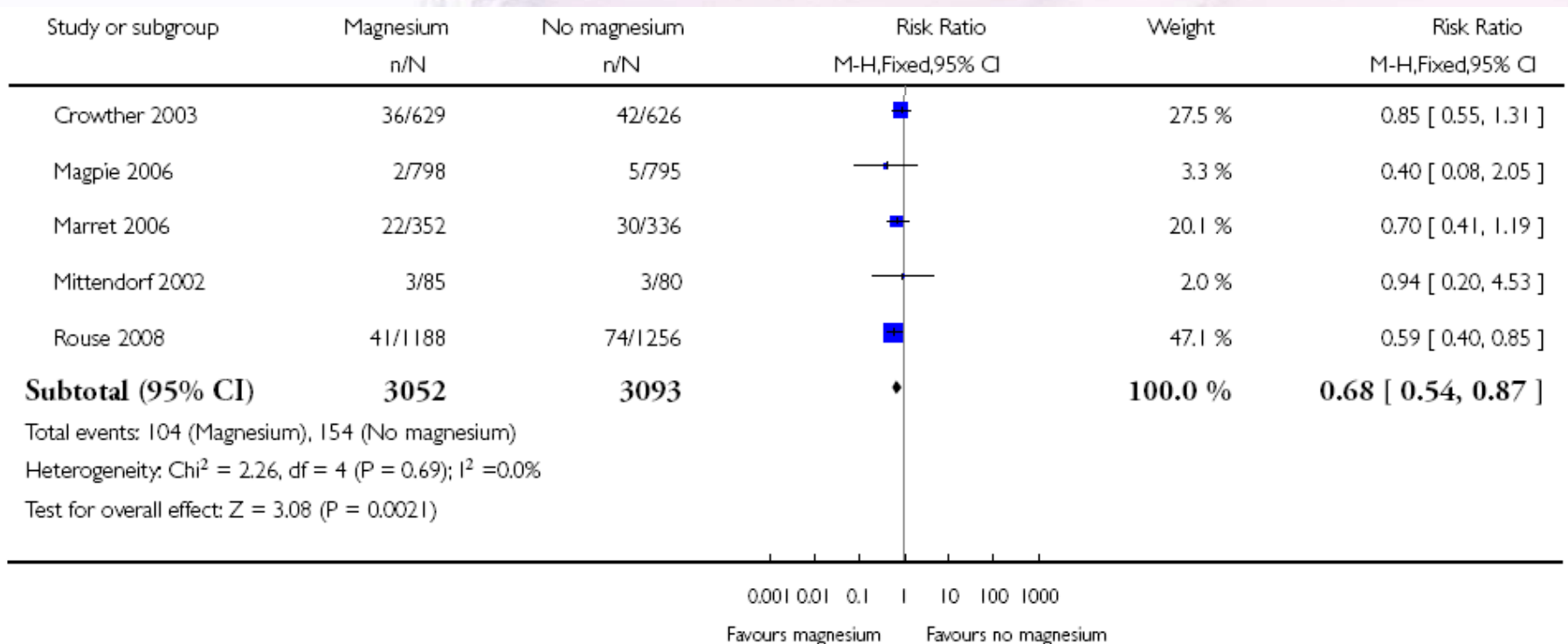
(fetal, neonatal and infant)



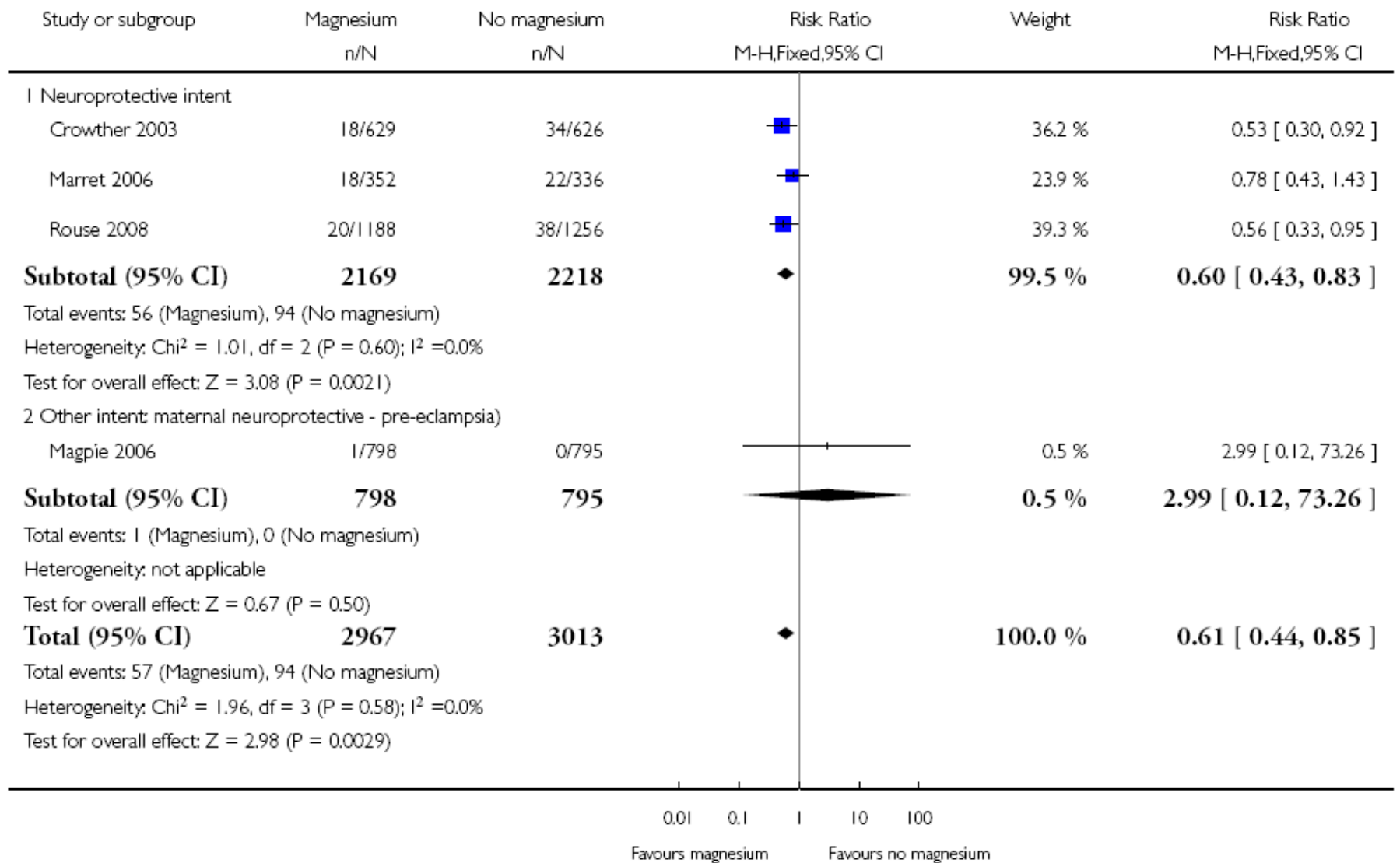
Fetal or paediatric deaths



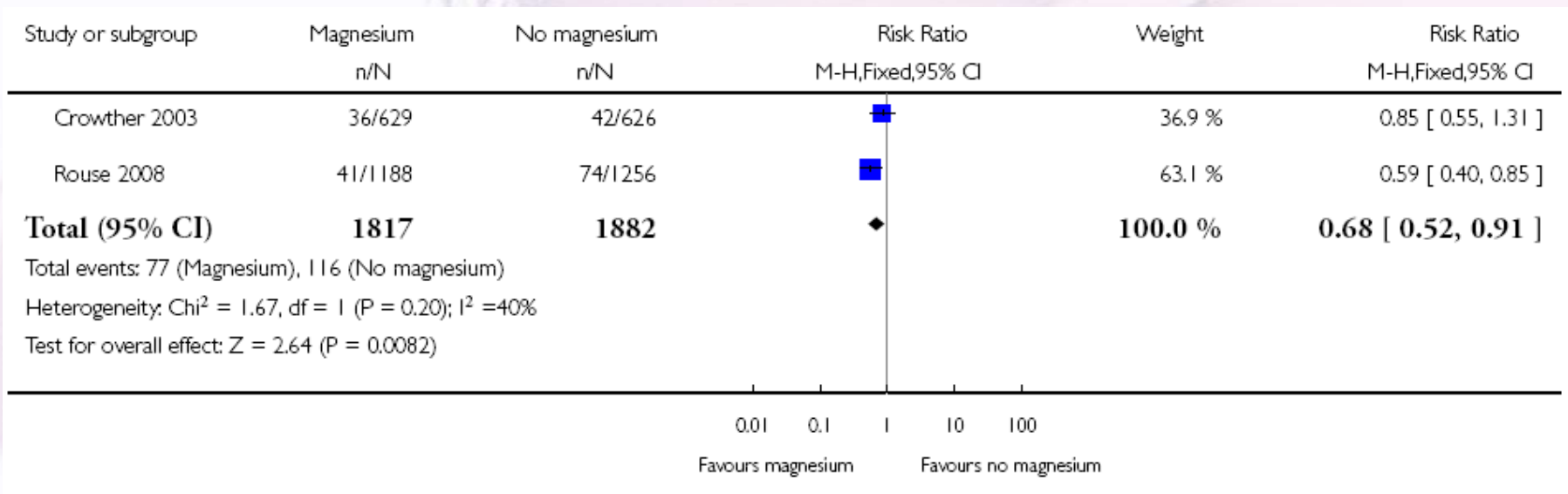
Cerebral Palsy by any intent of MgSO₄



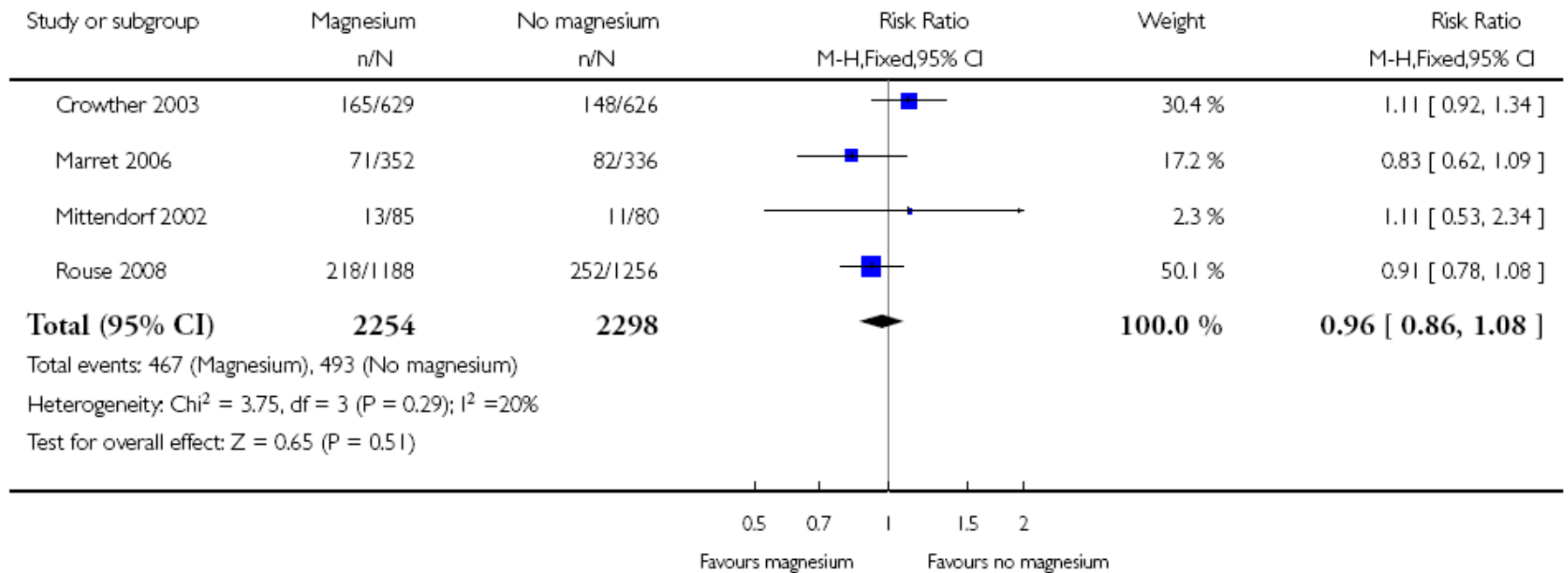
Substantial gross motor dysfunction



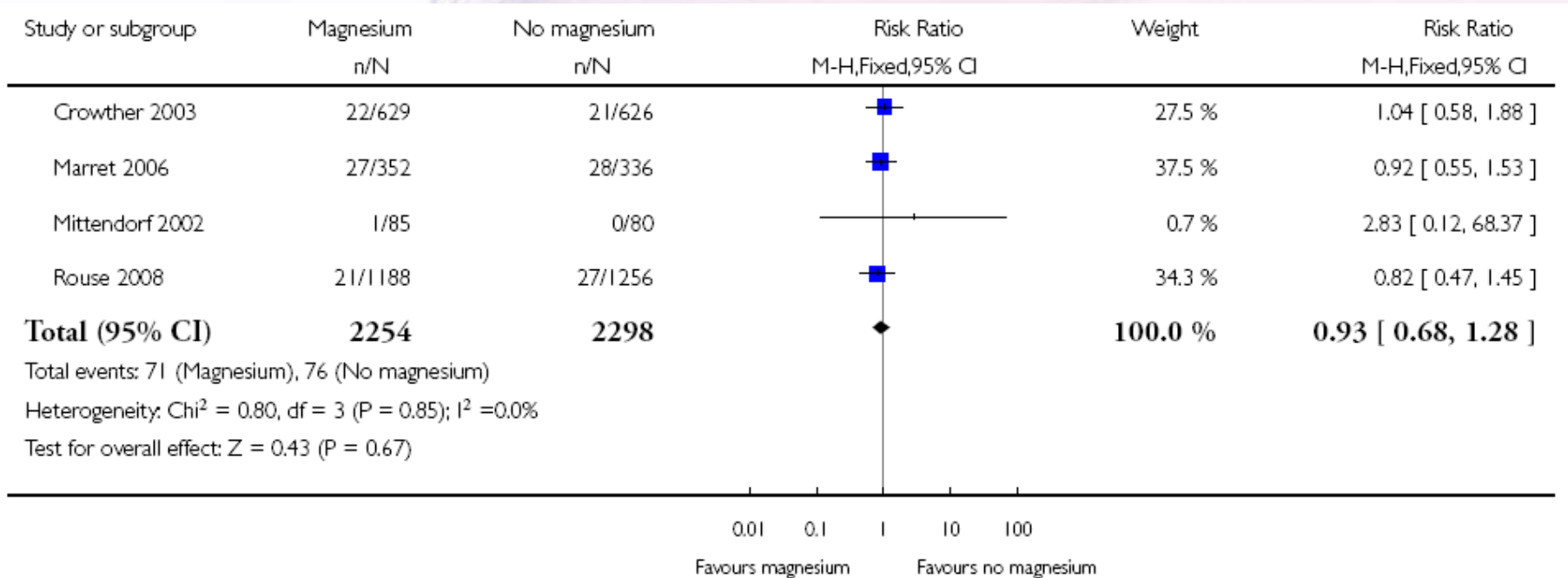
Cerebral palsy in studies with the lowest bias



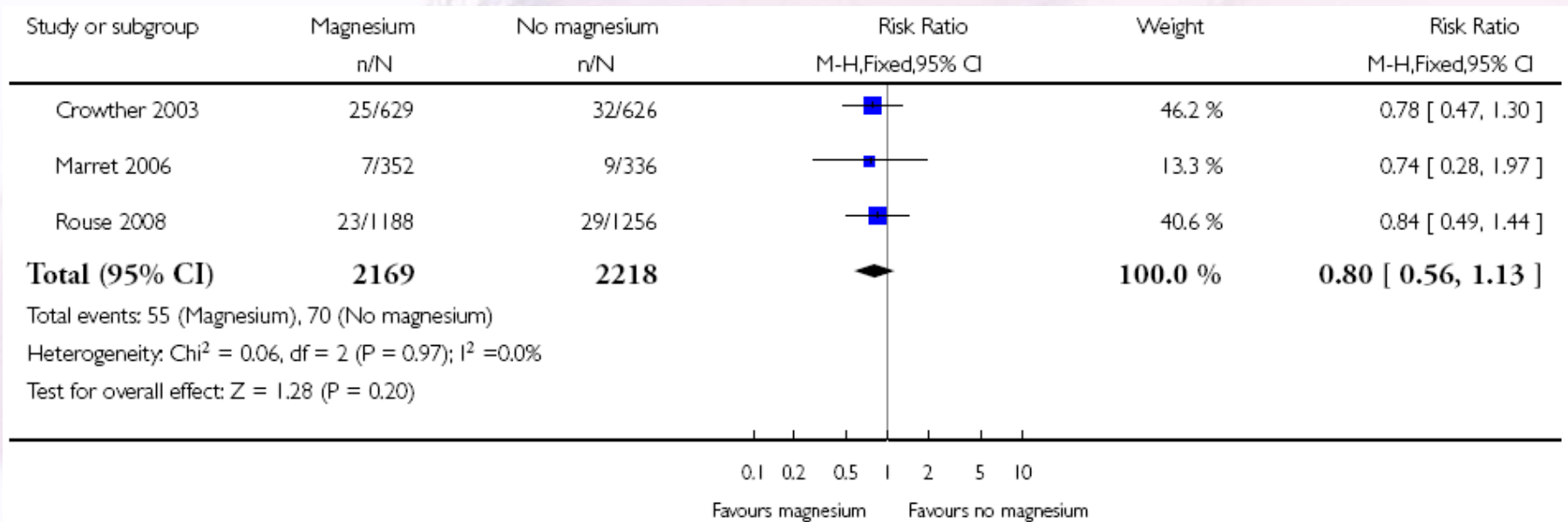
Intraventricular haemorrhage



Periventricular leukomalacia



Neonatal seizures

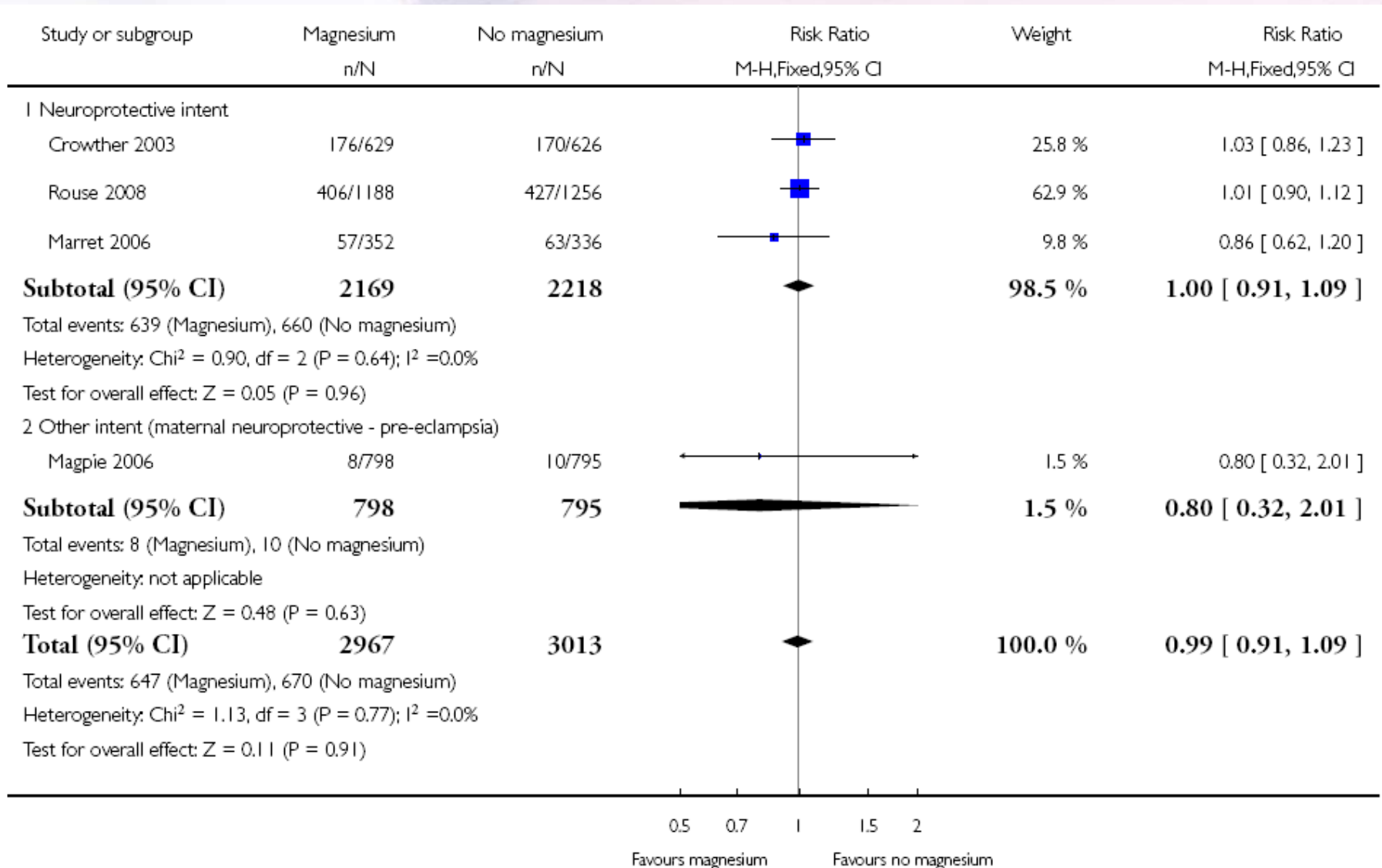


Other neurodevelopmental impairment

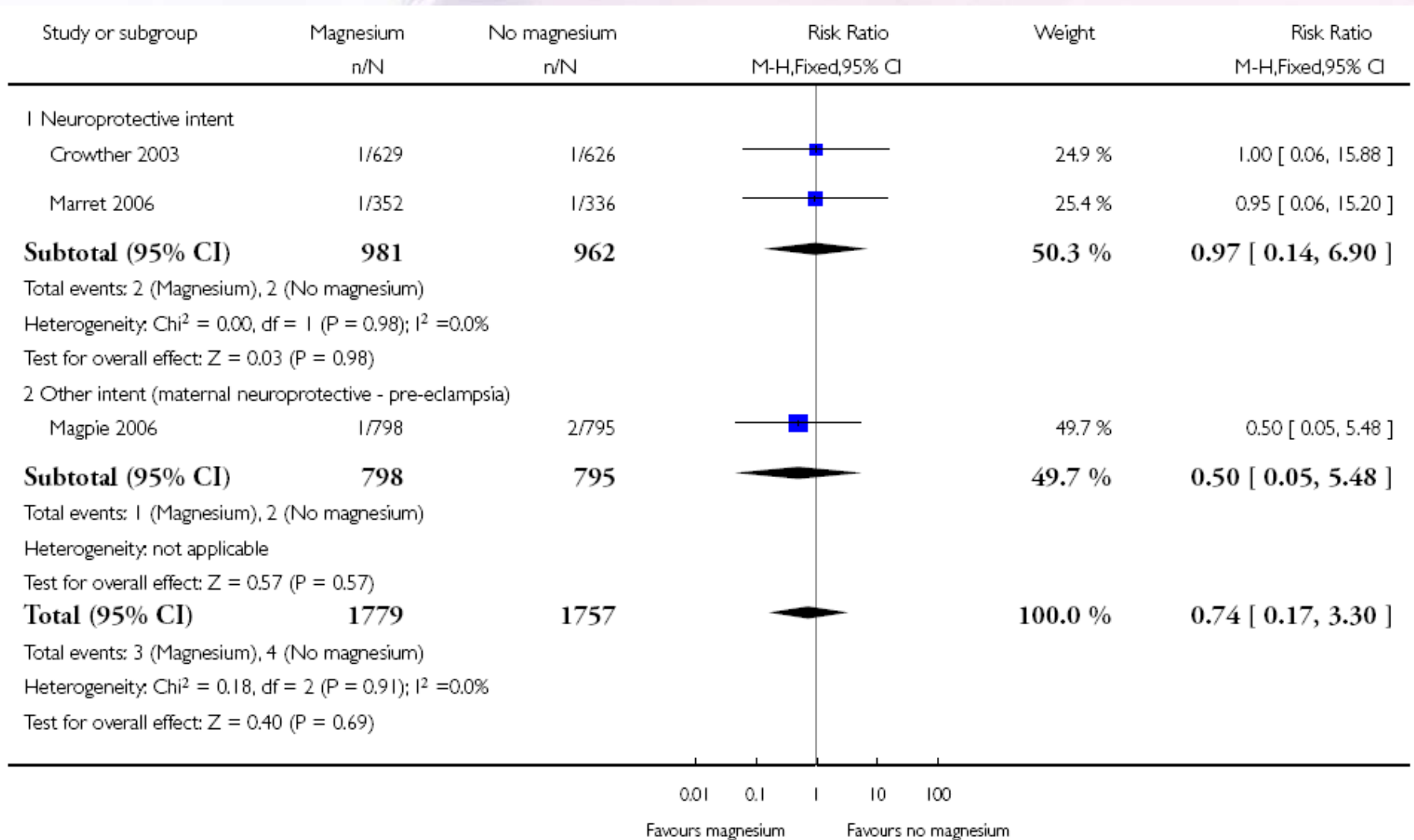


- Cognitive (& language) delay
- Blind
- Deaf

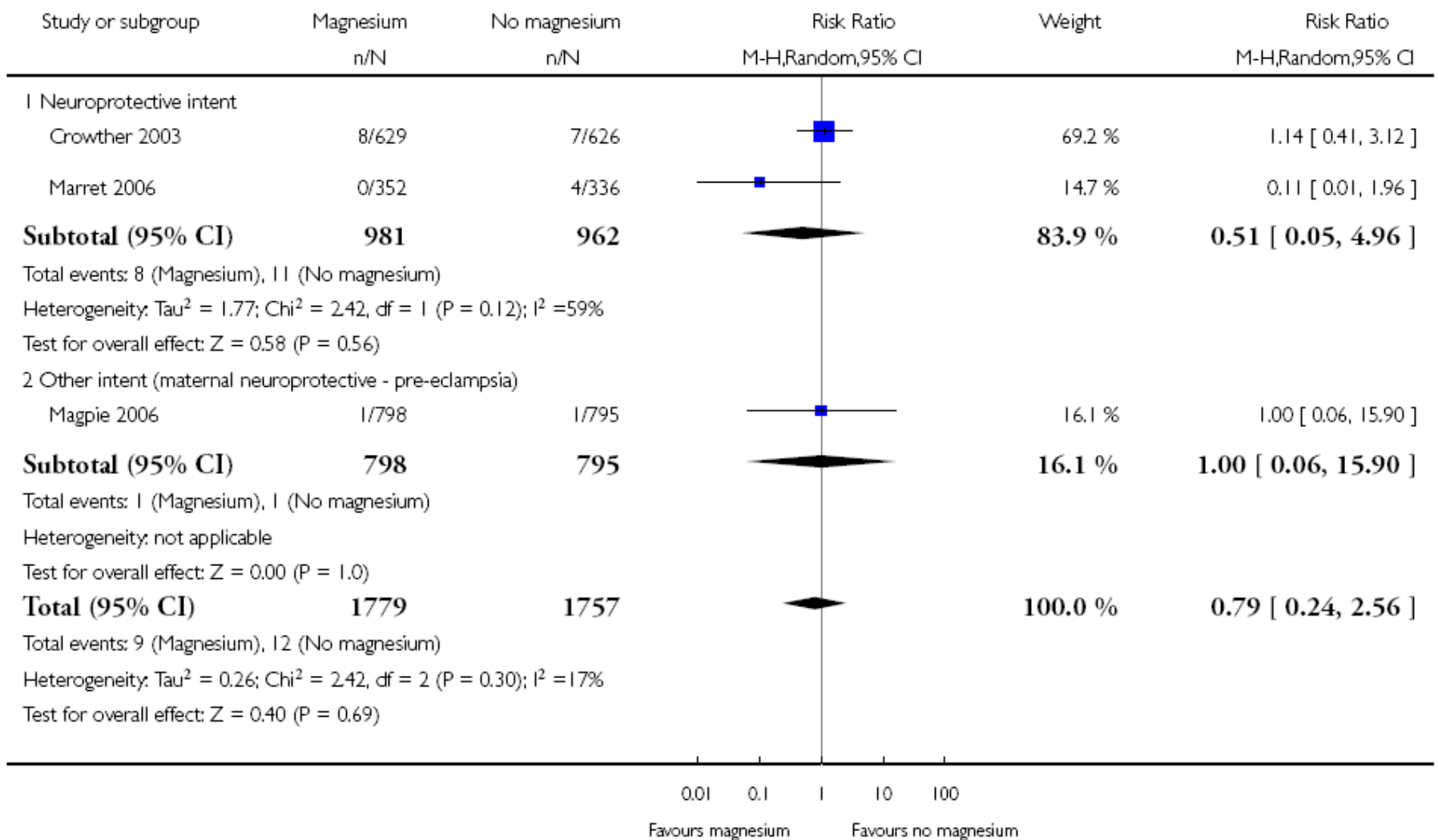
Cognitive impairment



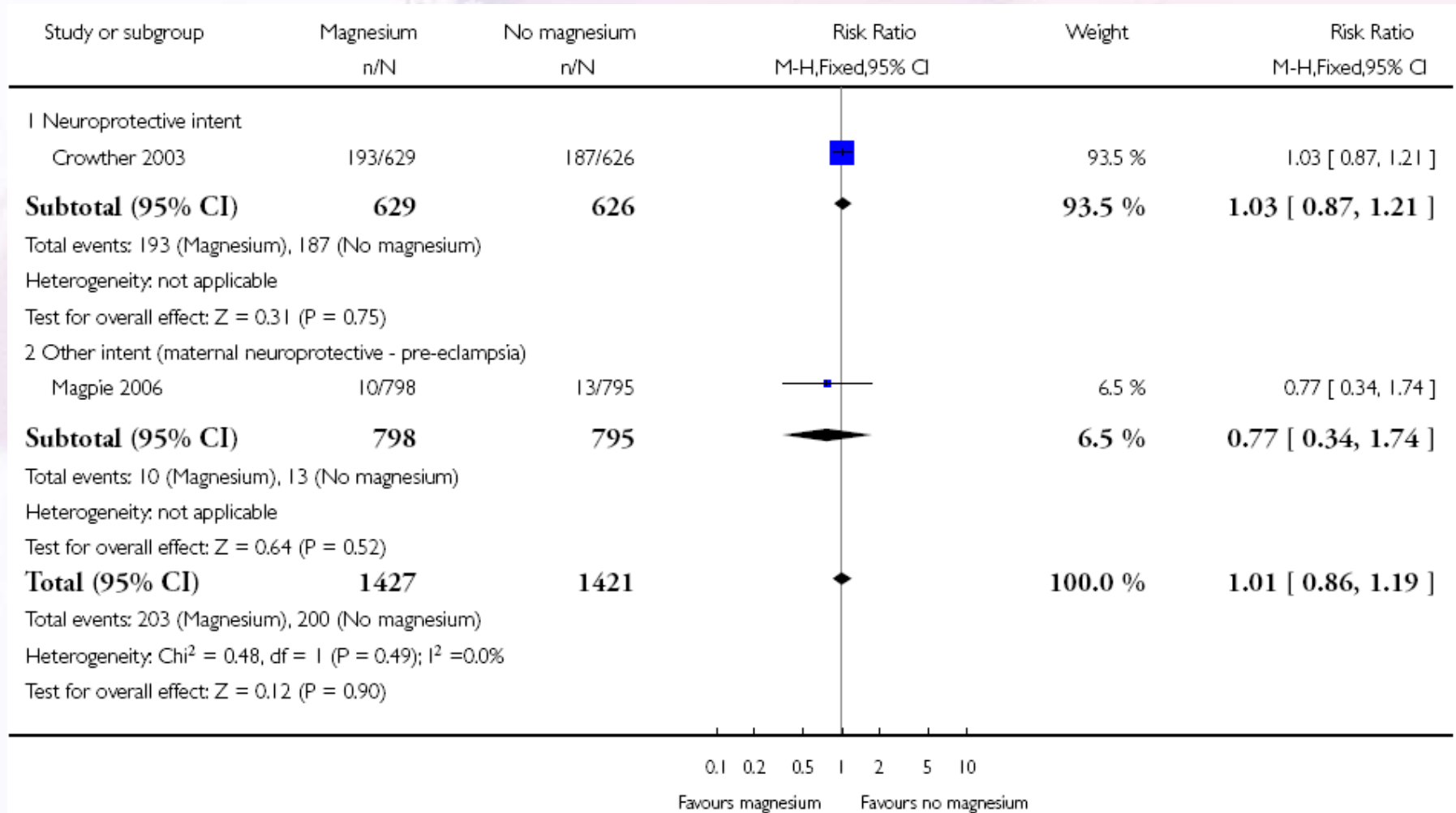
Blindness



Deafness

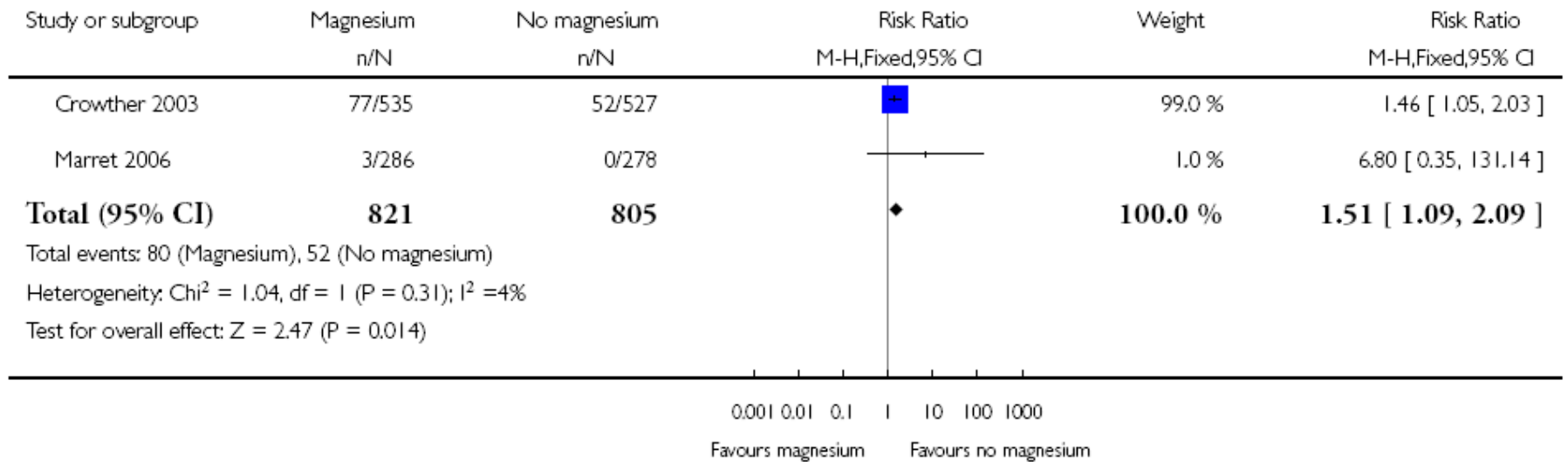


Any neurodevelopmental impairment

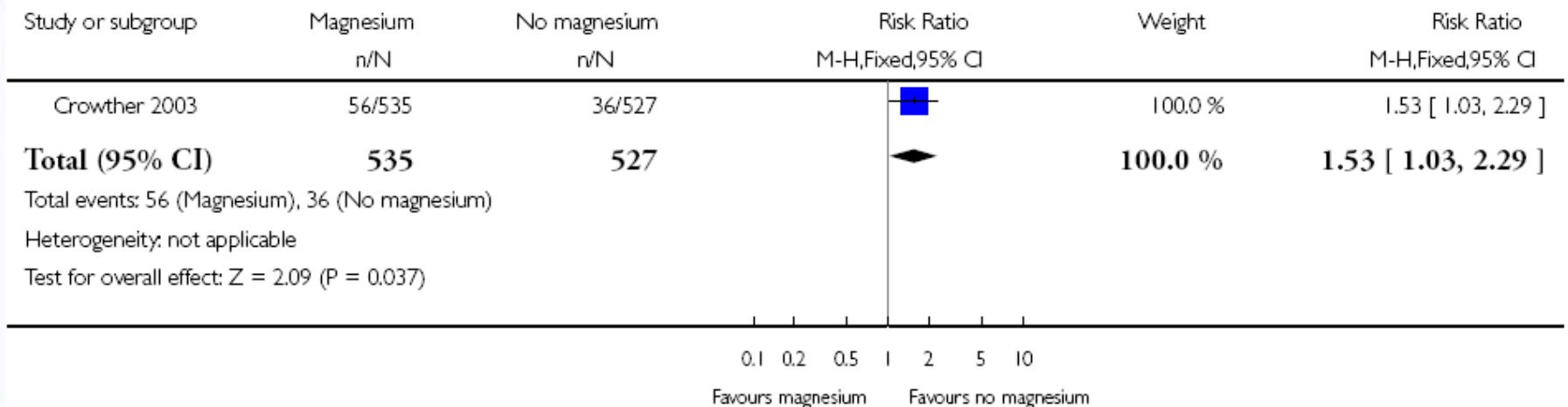


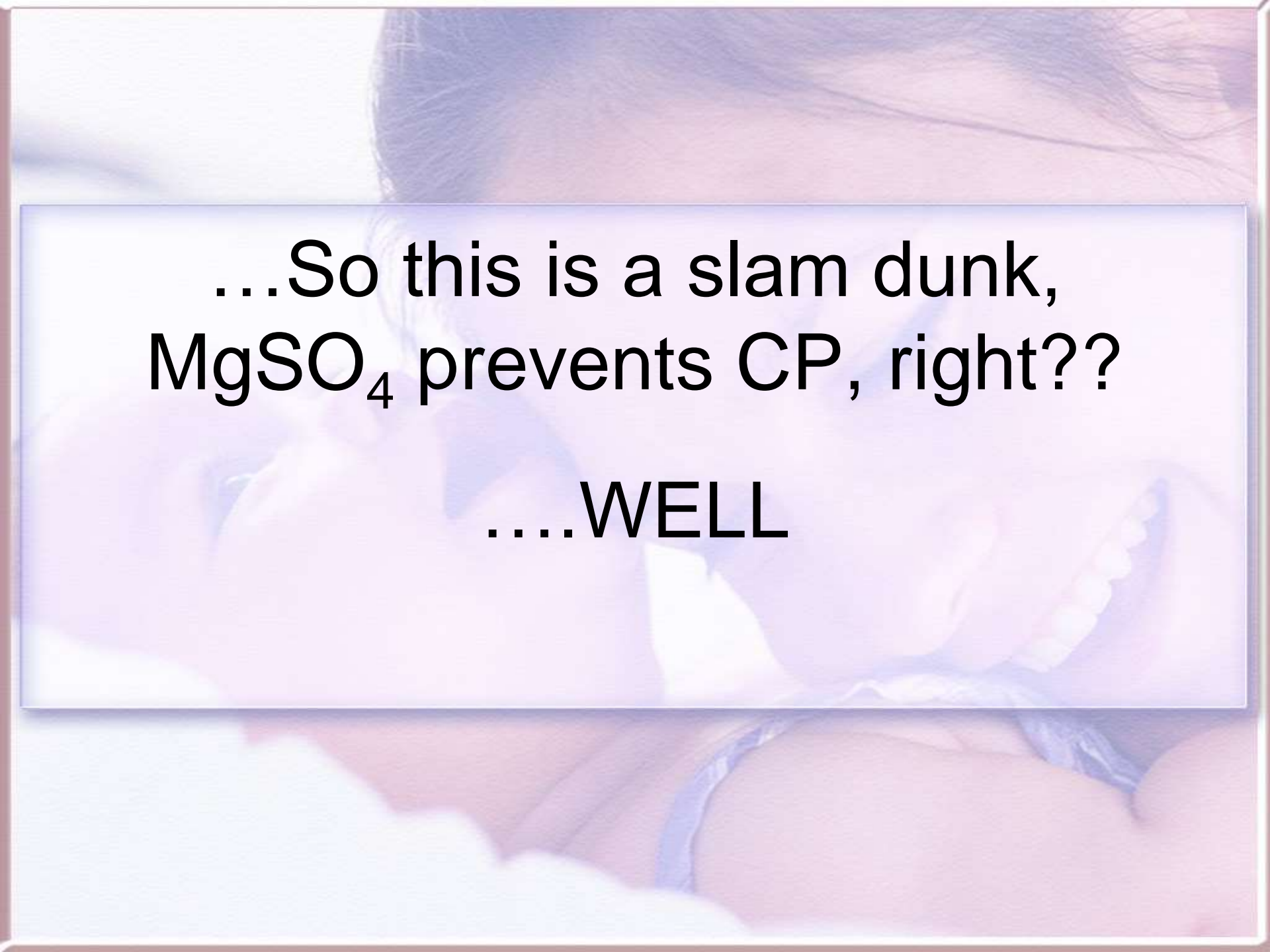
Maternal complications

hypotension



tachycardia





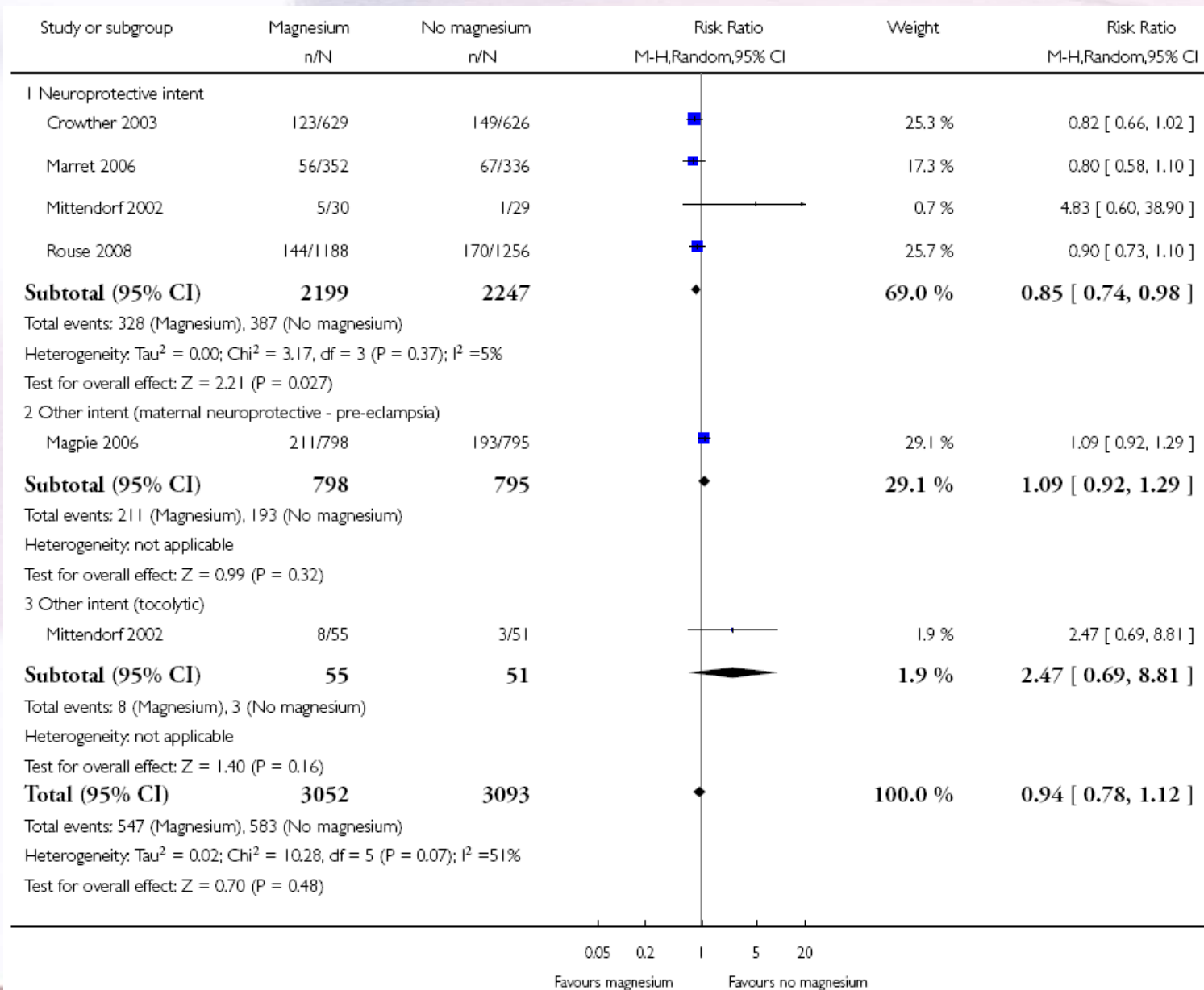
...So this is a slam dunk,
MgSO₄ prevents CP, right??

....WELL



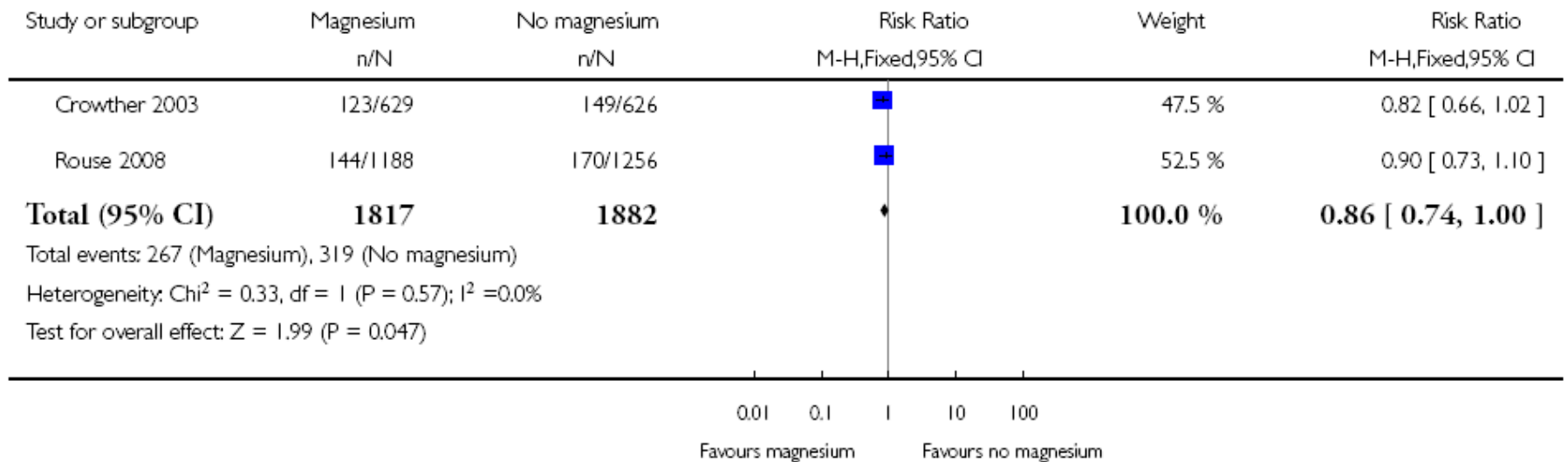
Composite outcomes

Death or cerebral palsy



Death or cerebral palsy in studies with the lowest bias

Outcome: 5 Death or cerebral palsy



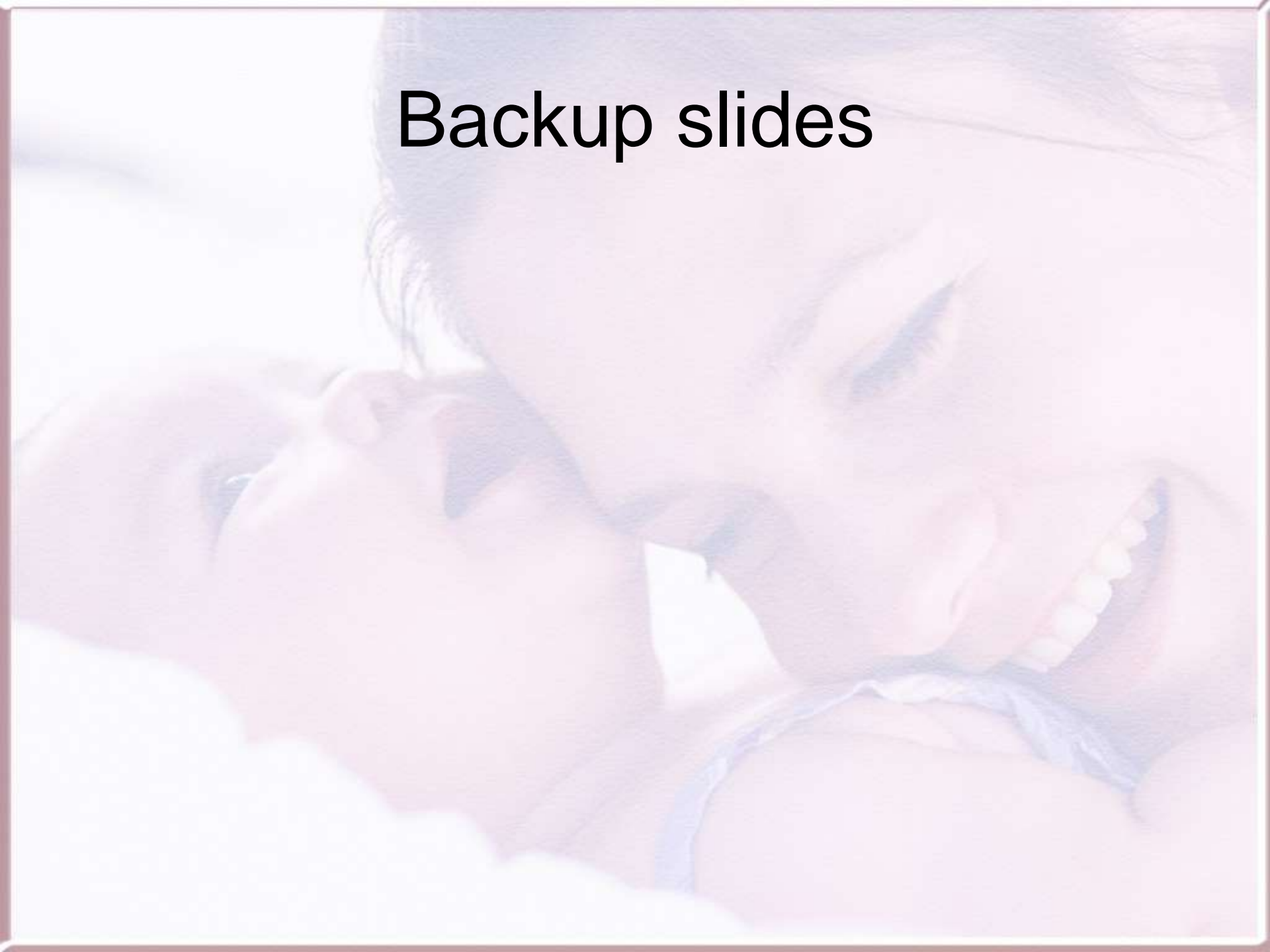
Conclusions

- MgSO_4 may prevent cerebral palsy or death especially when used as a fetal neuroprotector
- Some concern must be expressed about the possibility of increased mortality when magnesium sulfate is used as a tocolytic
- While MgSO_4 prevents of eclamptic convulsions in mothers with PET, it may be accompanied by an increase in paediatric mortality in the baby
- For the most part, maternal side effects are controllable

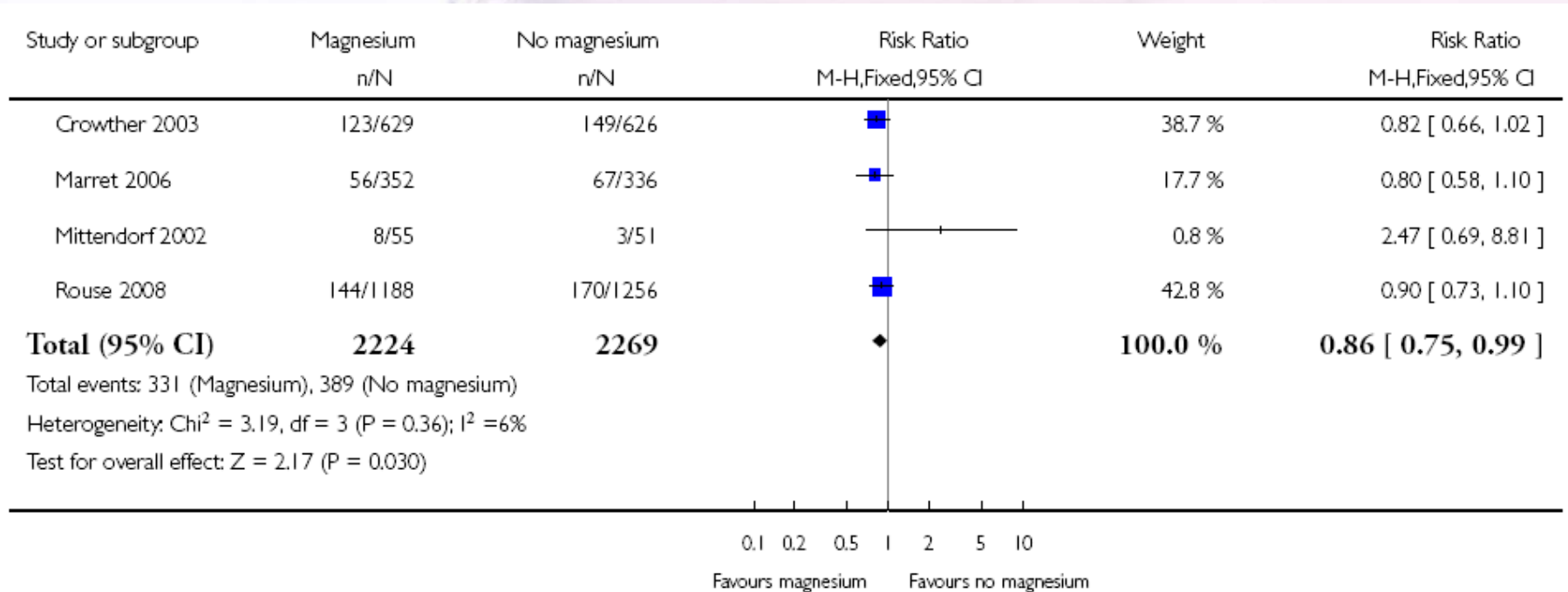


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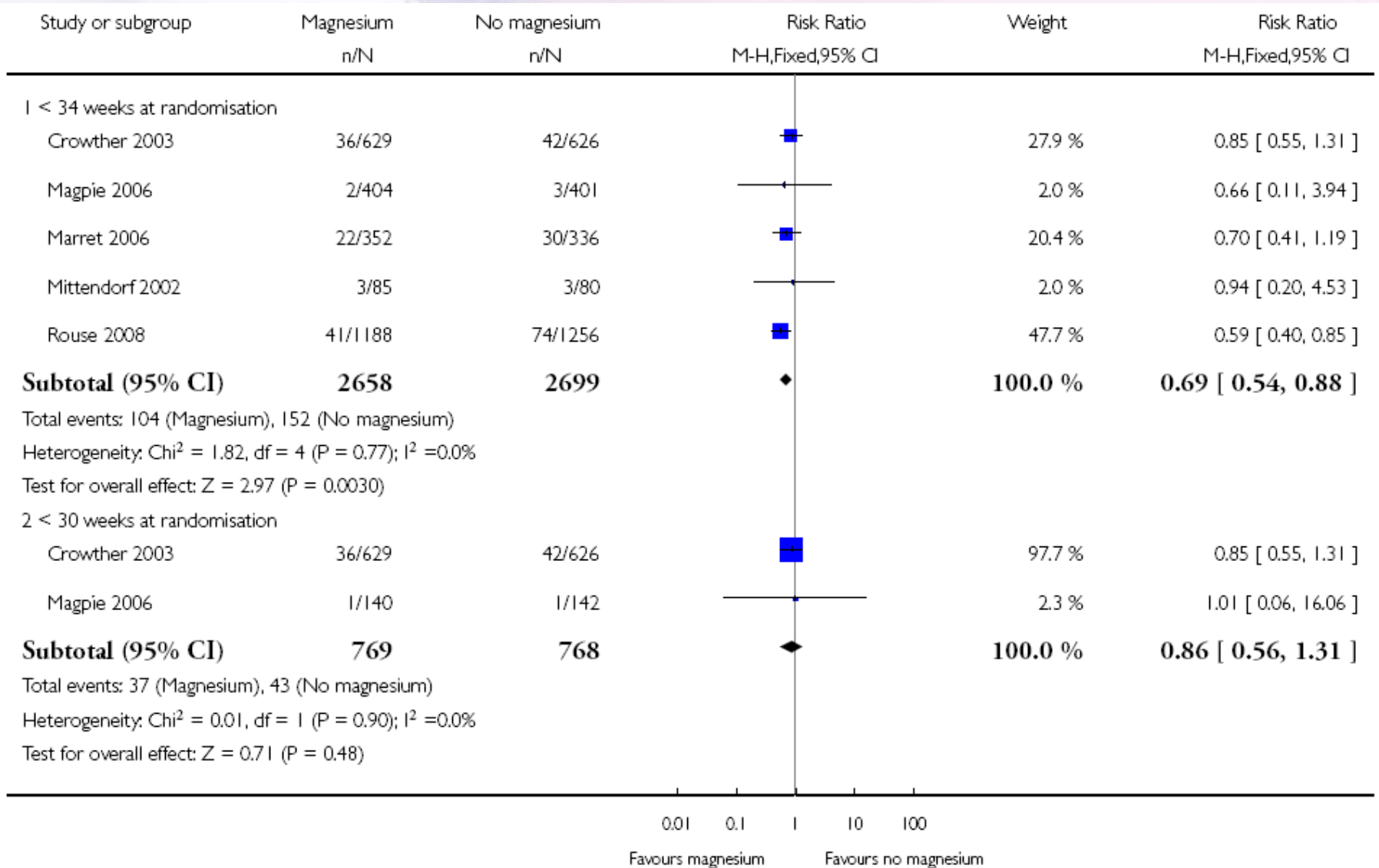
Backup slides



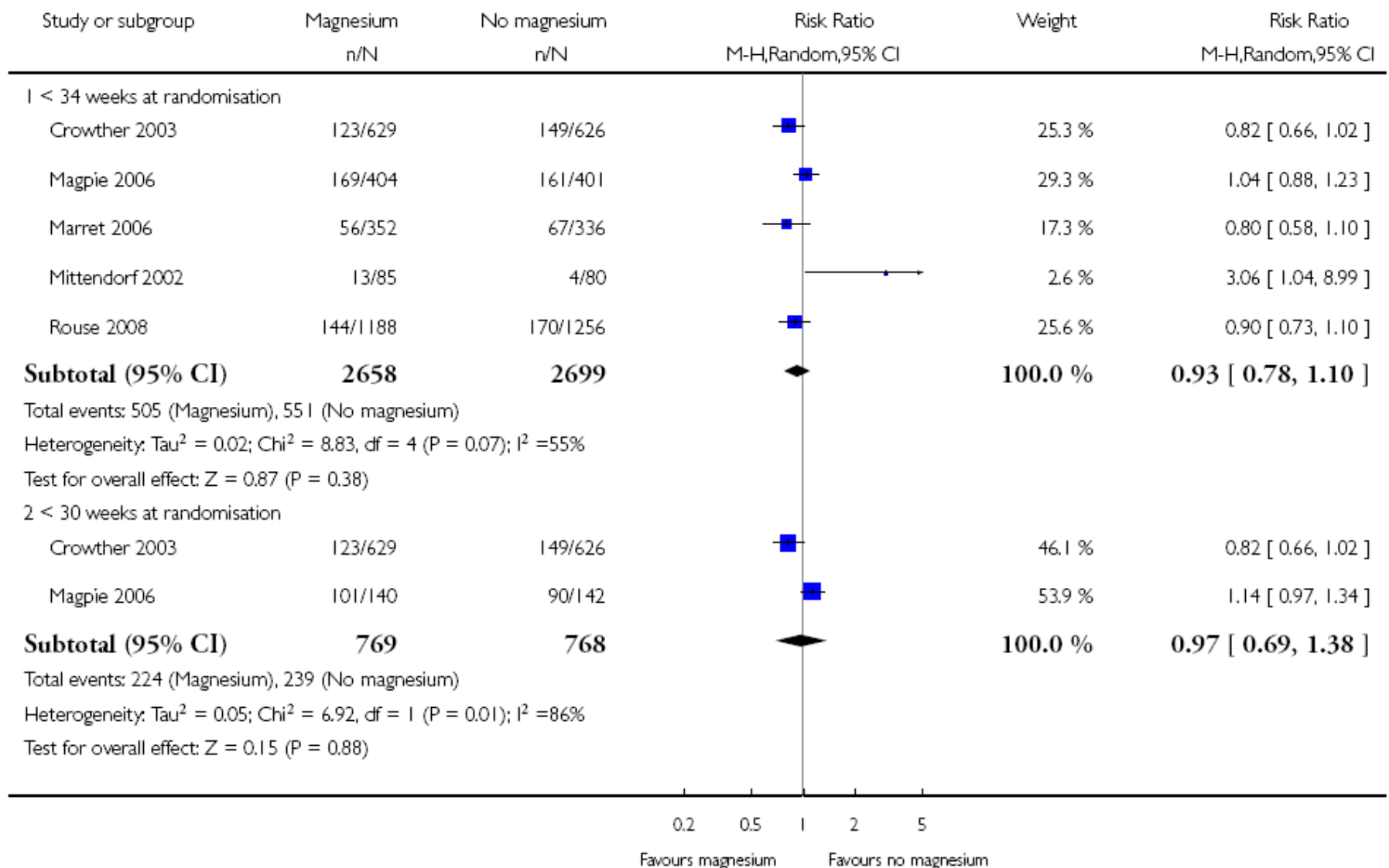
Death or CP when antenatal steroids are used



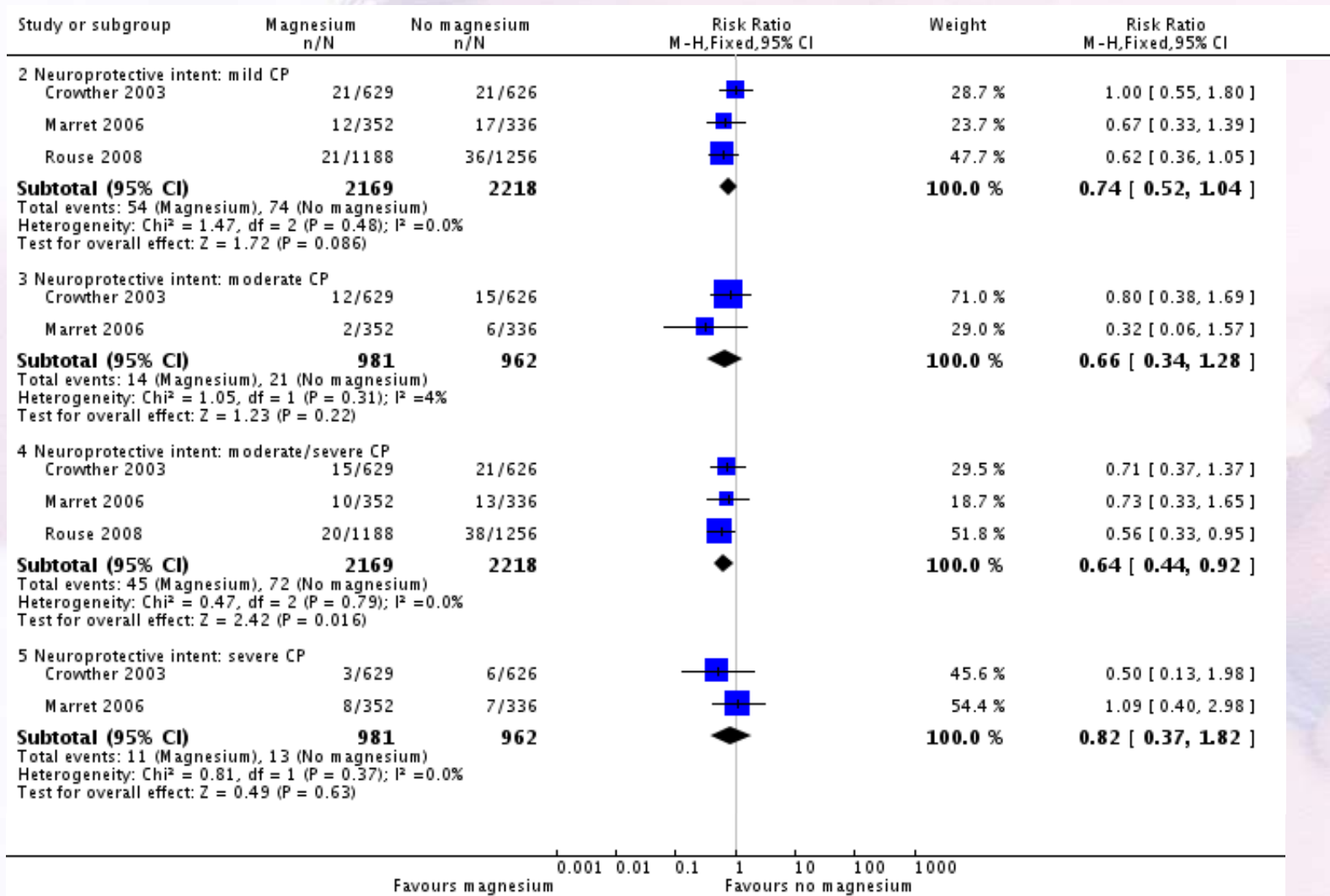
CP by gestational age



Death or CP by gestational age



Degree of CP vs MgSO₄



Hypotheses generated about how MgSO_4 reduces brain injury resulting in CP

- MgSO_4 inhibits Ca influx to cells by blocking N-methyl-D-aspartic acid
- MgSO_4 causes vasodilation with improved cerebral blood flow
- MgSO_4 reduces oxygen free radicals
- MgSO_4 reduces inflammatory cytokines