

Meta-analysis and Forest plots

Chris Cates 2017

Learning Objectives

1. Understand why we need Meta-analyses
2. Describe the difference between a Systematic Review and a Meta-analysis
3. Interpret the results of a Meta-analysis as shown in a Forest plot
4. Appreciate how to use Relative Risks and Control Group Event Rates to compare risks and benefits of treatment

Clinical Scenario (from last week)

- A pregnant mother comes into A&E with an asthma exacerbation
- There is a debate between the Obstetric and the Respiratory teams
- She is not responding well to oral steroids and nebulised salbutamol
- “Should we add magnesium solution to the nebuliser when delivering nebulised salbutamol?”

A difference of opinion

- The Obstetrician has read a Cochrane review showing how well nebulised magnesium works in acute asthma in pregnancy
- The Respiratory physician is not impressed with the evidence for nebulised magnesium in acute asthma adults

Where to go next?

- The A& E Consultant rings you up
- Could you have a look at the evidence and help formulate a policy for the department?

Assessing the impact of treatment

- Patients
- Intervention
- Comparison
- Outcomes
- Study Design

Defining the Question

- In pregnant mothers with asthma, who have not had a good response to nebulised salbutamol and oral corticosteroids
- Does the addition of magnesium to the nebulised salbutamol
- Compared to continuing nebulised salbutamol
- Have and impact on
 - The risk of Hospitalisation
 - Improvement in Lung Function

Steps in the process

1. Define an answerable question
2. Search for suitable evidence
3. Assess the quality of the evidence
4. Describe the results
5. Interpret the findings
6. Decide if practice needs to be changed

How can Cochrane Reviews help?

- Cochrane Systematic Reviews use transparent processes that are published in advance as protocols
- They aim to **IDENTIFY, ASSESS, SYNTHESIZE and APPLY** the results of Controlled Clinical Trials addressing a defined question

Hospital Librarian finds a Cochrane review on acute asthma in pregnancy

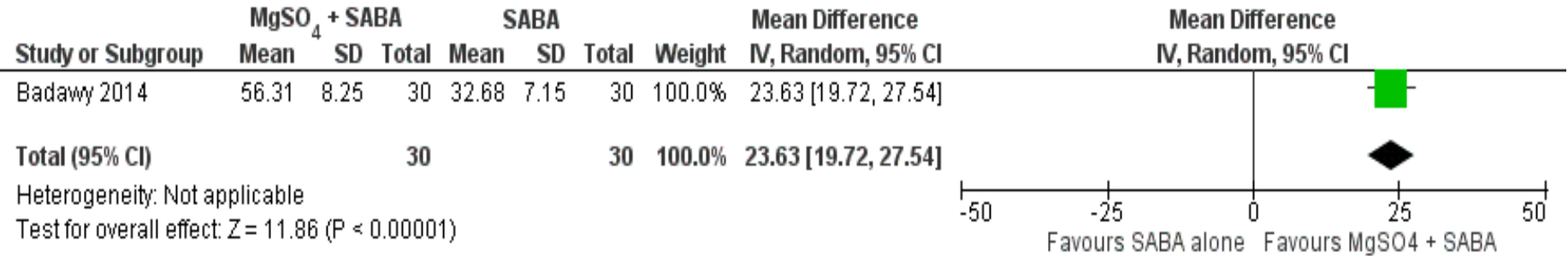
1. You have had a chance to read the Badawy paper on nebulised magnesium in pregnant mothers with acute asthma from this review
2. What were the findings in this trial?

Badawy MSH, Hassanin IMA. The value of magnesium sulfate nebulization in treatment of acute bronchial asthma during pregnancy. Egyptian Journal of Chest Diseases and Tuberculosis 2014;**63**(2):285-89

doi: 10.1016/j.ejcdt.2013.12.011

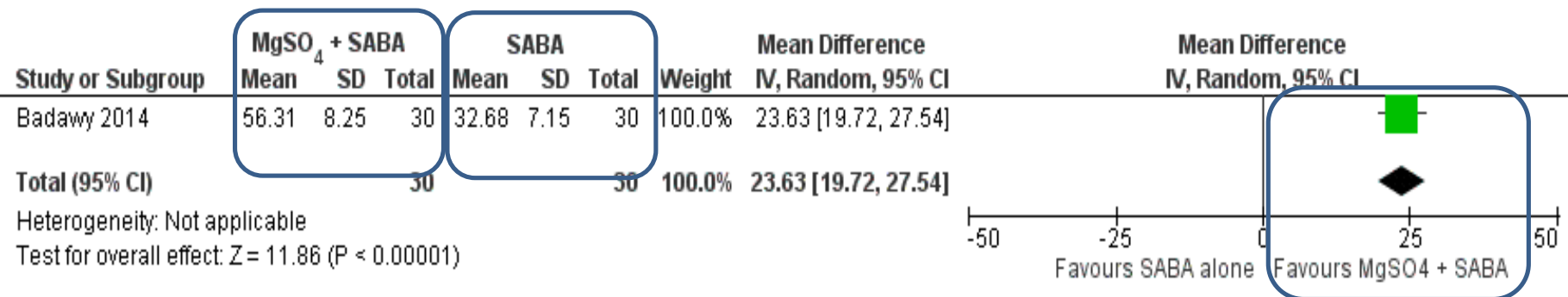
<http://www.sciencedirect.com/science/article/pii/S0422763813003129>

Post Rx % predicted FEV1 in Badawy trial



- What does this Forest plot show?
- How many patients in each group?
- Mean % predicted FEV1 from each group?
- Mean difference in % predicted FEV1?
- Which treatment looks better? How much better?
- How sure are you? (Direction, Size and Uncertainty)

Post Rx % predicted FEV1in Badawy trial



This is a pretty impressive treatment effect

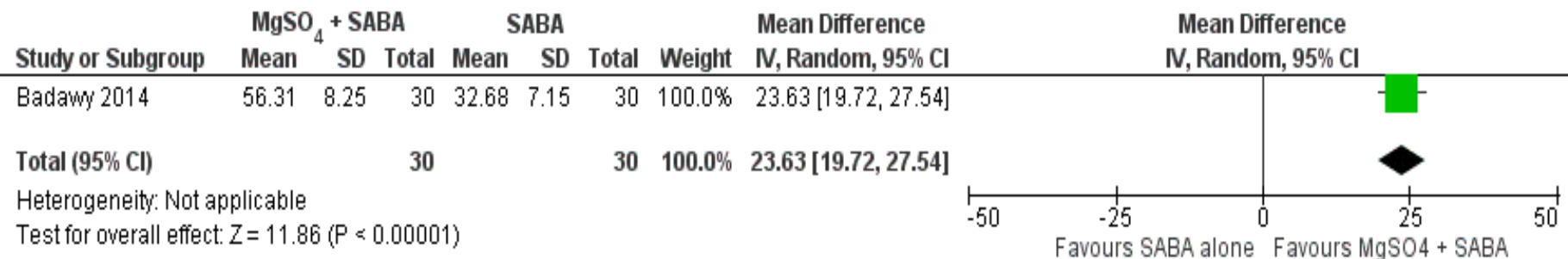
P value and its limitations

- **$P < 0.0001$ means what?**
- **If the null hypothesis is true**
- **Then this result (or one more extreme) can be expected less than once in 10,000 due to the play of chance.**
- **How likely is it that the null is true?**

95% Confidence Interval

- **Is where we are 95% sure that the true population treatment effect lies**
- **This is the “precision” of the estimate of the treatment effect**
- **Narrow confidence intervals give a more precise estimate**

Post Rx % predicted FEV1 in Badawy trial

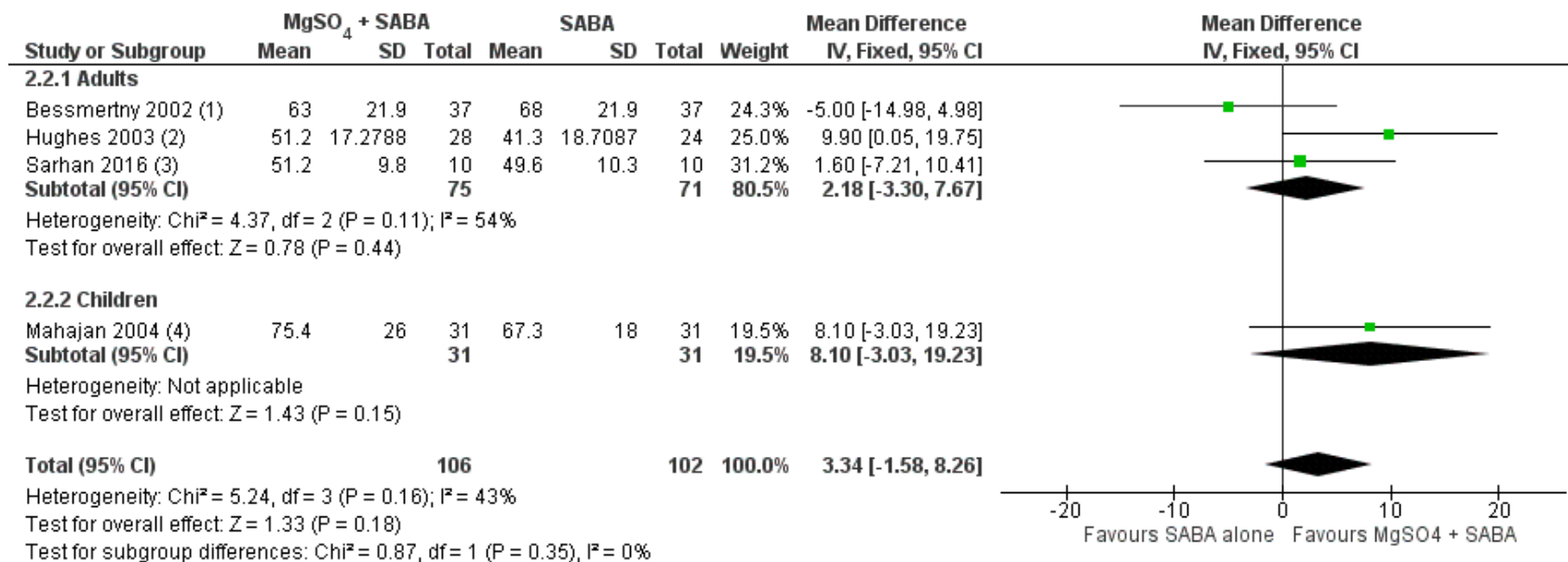


- What does this Forest plot show?
- How many patients in each group?
- Mean % predicted FEV1 from each group?
- Mean difference in % predicted FEV1?
- Which treatment looks better? How much better?
- How sure are you? (Direction, Size and Uncertainty)

What about the other trials?

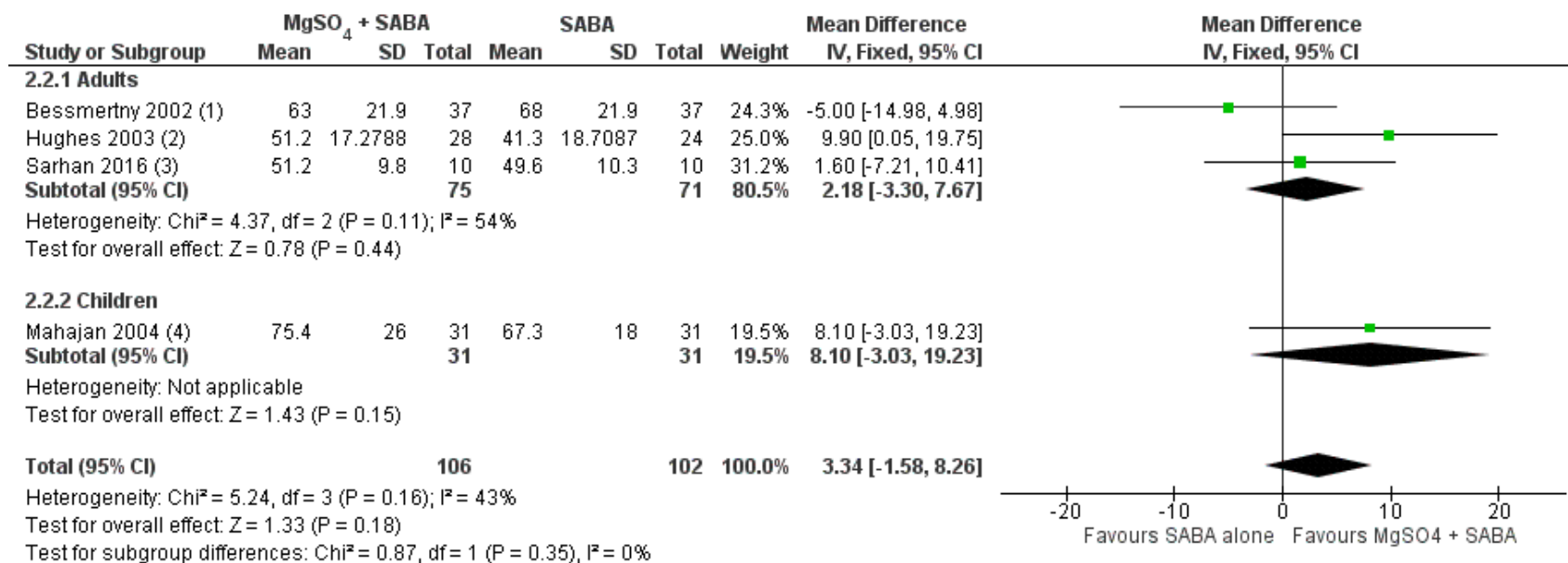
- Don't just rely on the results of a single trial
- How does this trial compare to the other trials?
- Knightly R, Milan SJ, Hughes R, Knopp-Sihota JA, Rowe BH, Normansell R, Powell C. Inhaled magnesium sulfate in the treatment of acute asthma. Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD003898. DOI: [10.1002/14651858.CD003898.pub6](https://doi.org/10.1002/14651858.CD003898.pub6)

Pulmonary function % predicted FEV1



This Forest plot shows a **meta-analysis** of the trials in the Cochrane review reporting change in lung function with nebulised Magnesium Sulphate added to salbutamol

Pulmonary function % predicted FEV1

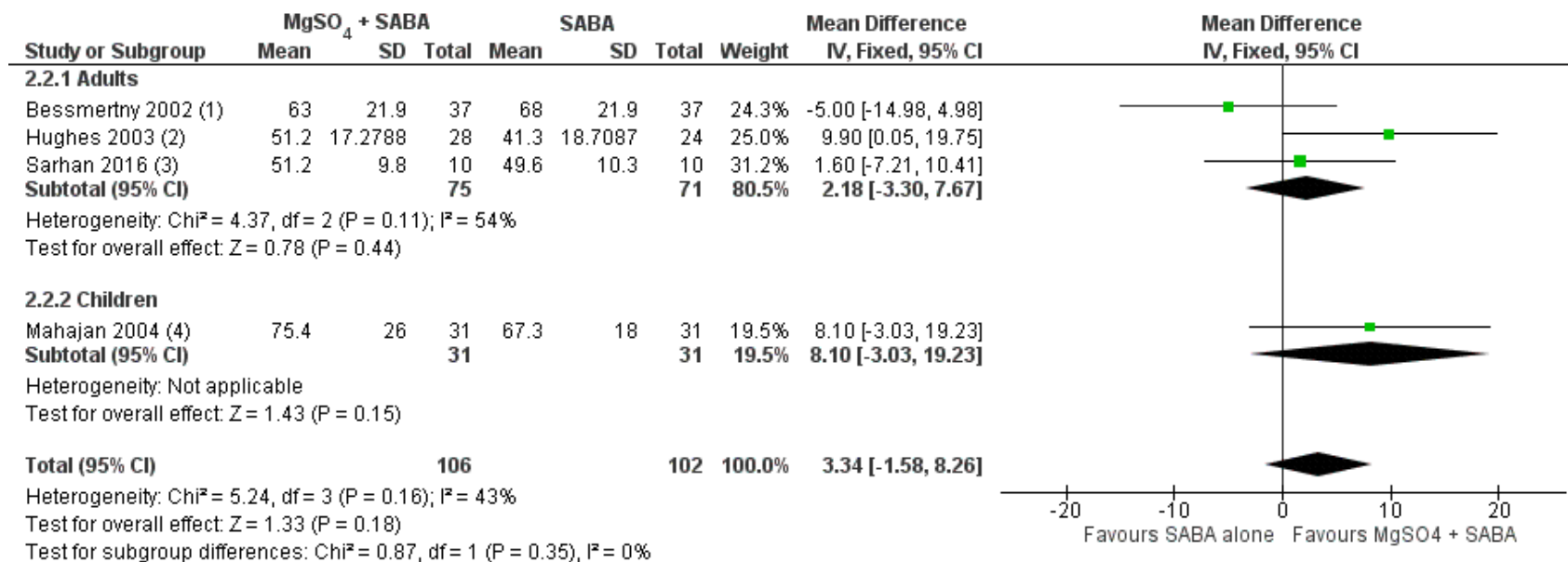


Footnotes

- (1) 65 mins from baseline
- (2) At 90 min from baseline (30 min after the third administration of the study drug)
- (3) Final score (2-3 hours post baseline)
- (4) 20 mins from baseline

A Meta-analysis calculates the **weighted average** and its **95% CI** from the trials (shown as the diamond)

Pulmonary function % predicted FEV1

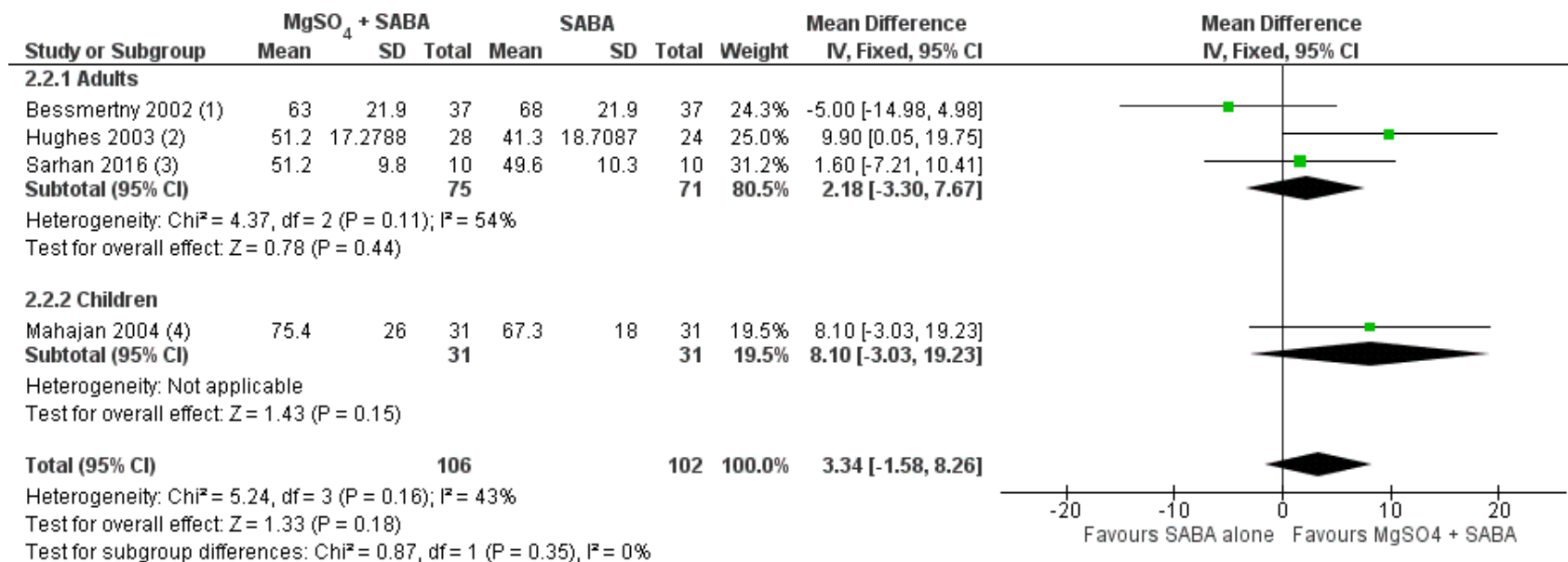


Footnotes

- (1) 65 mins from baseline
- (2) At 90 min from baseline (30 min after the third administration of the study drug)
- (3) Final score (2-3 hours post baseline)
- (4) 20 mins from baseline

- The “weight” of each trial is proportional to its precision.
- Large trials give precise treatment estimates (narrow confidence intervals) and carry more weight

Pulmonary function % predicted FEV1



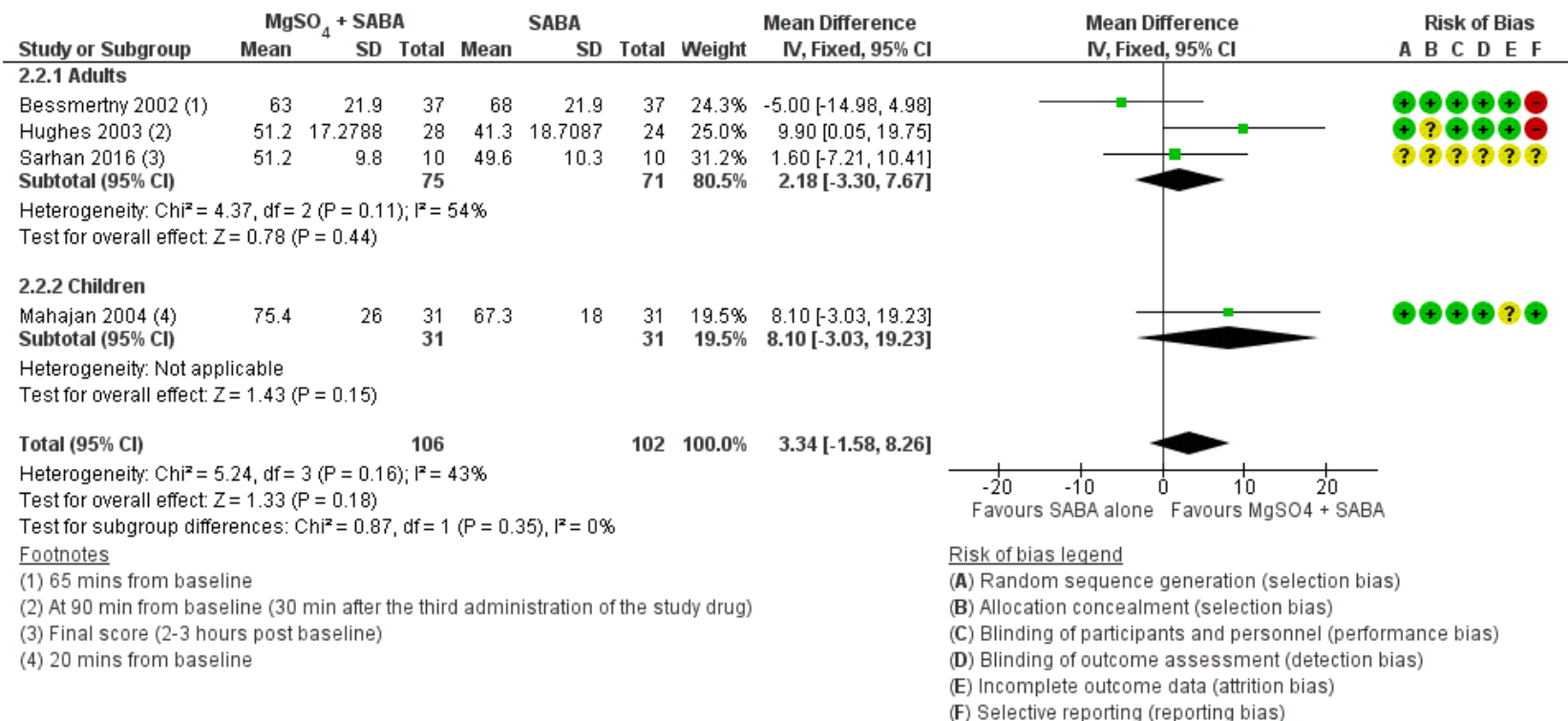
Footnotes

- (1) 65 mins from baseline
- (2) At 90 min from baseline (30 min after the third administration of the study drug)
- (3) Final score (2-3 hours post baseline)
- (4) 20 mins from baseline

Can you describe the average treatment effect from these trials?

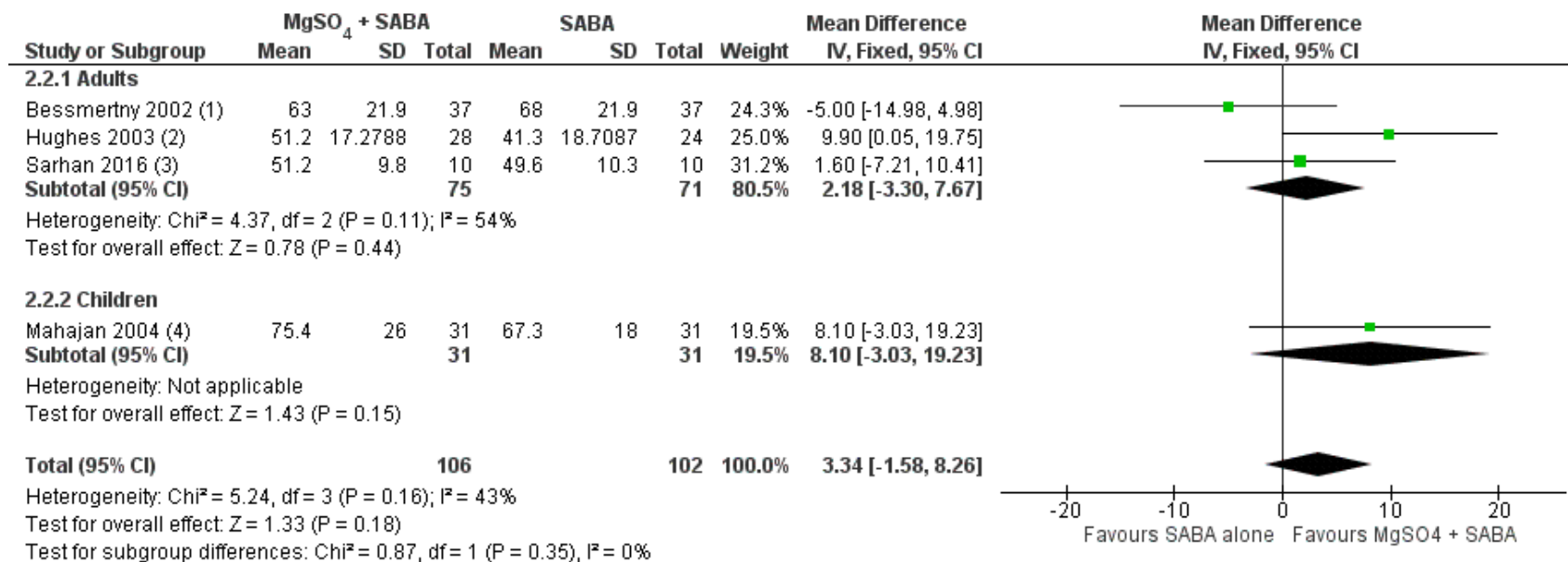
Direction - Size - Uncertainty

Pulmonary function % predicted FEV1



What do the risks of bias in these trials indicate?

Pulmonary function % predicted FEV1

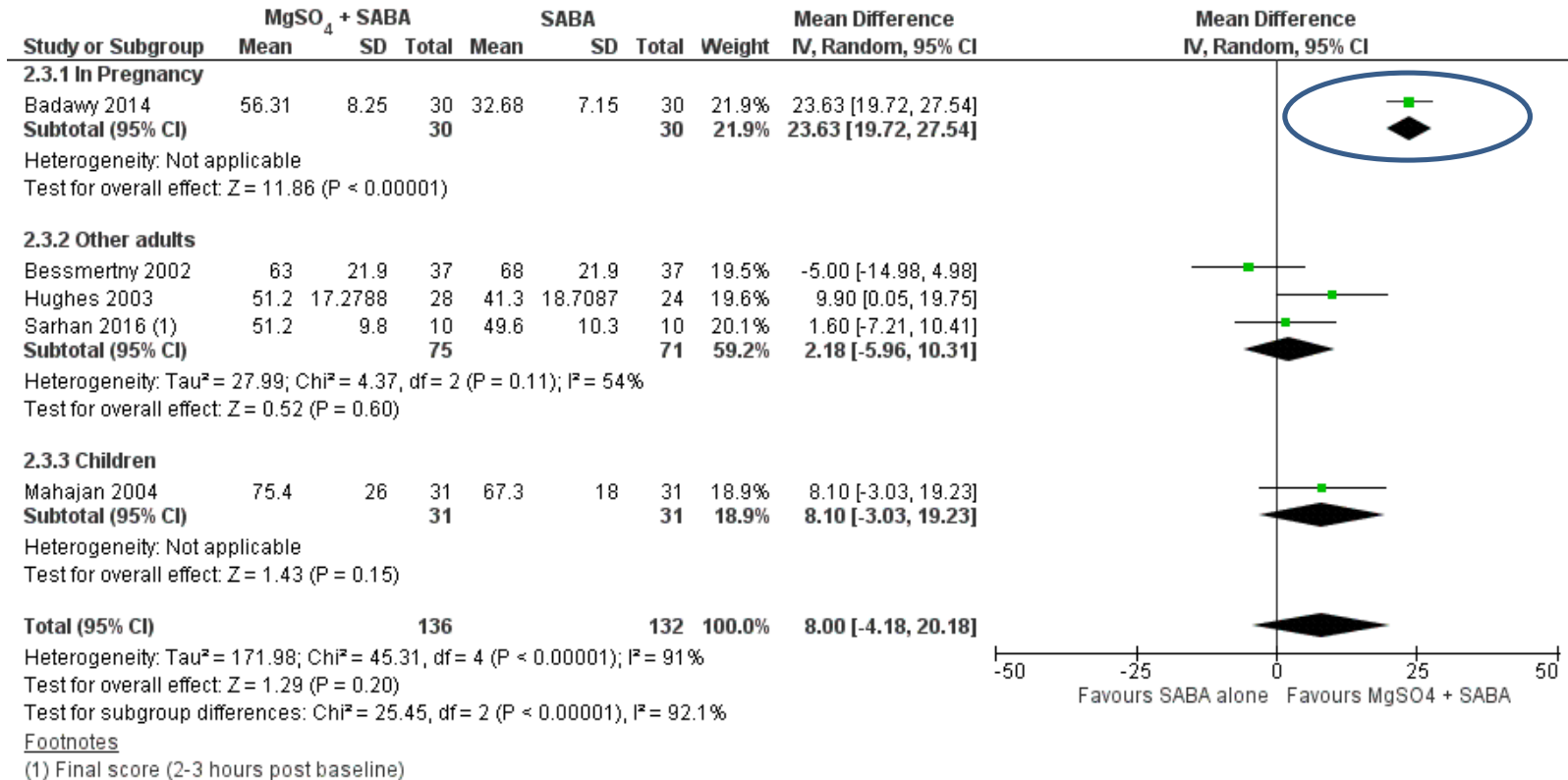


Footnotes

- (1) 65 mins from baseline
- (2) At 90 min from baseline (30 min after the third administration of the study drug)
- (3) Final score (2-3 hours post baseline)
- (4) 20 mins from baseline

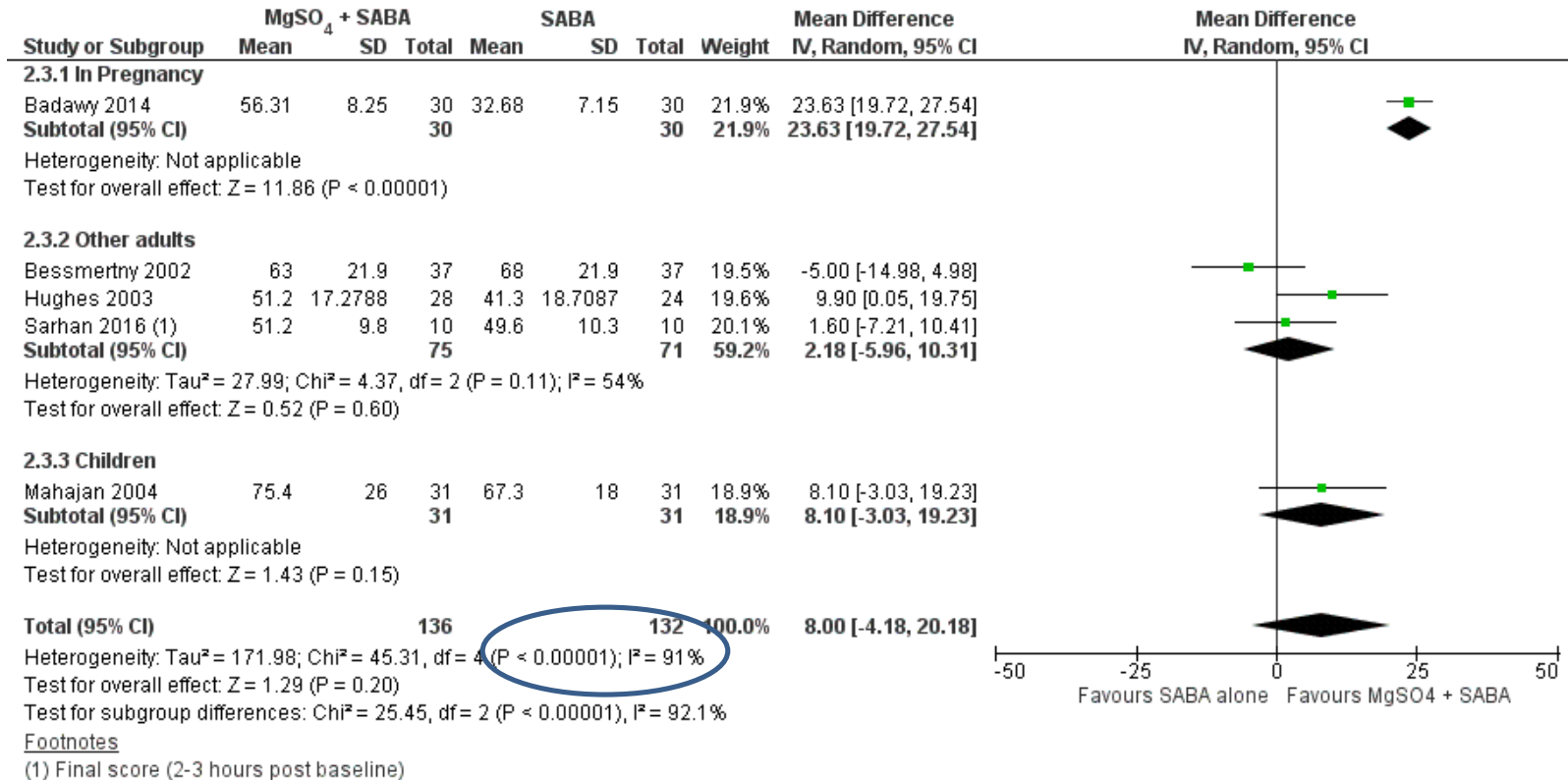
How do these results compare with the Badawy trial?

Badawy results in context of other trials



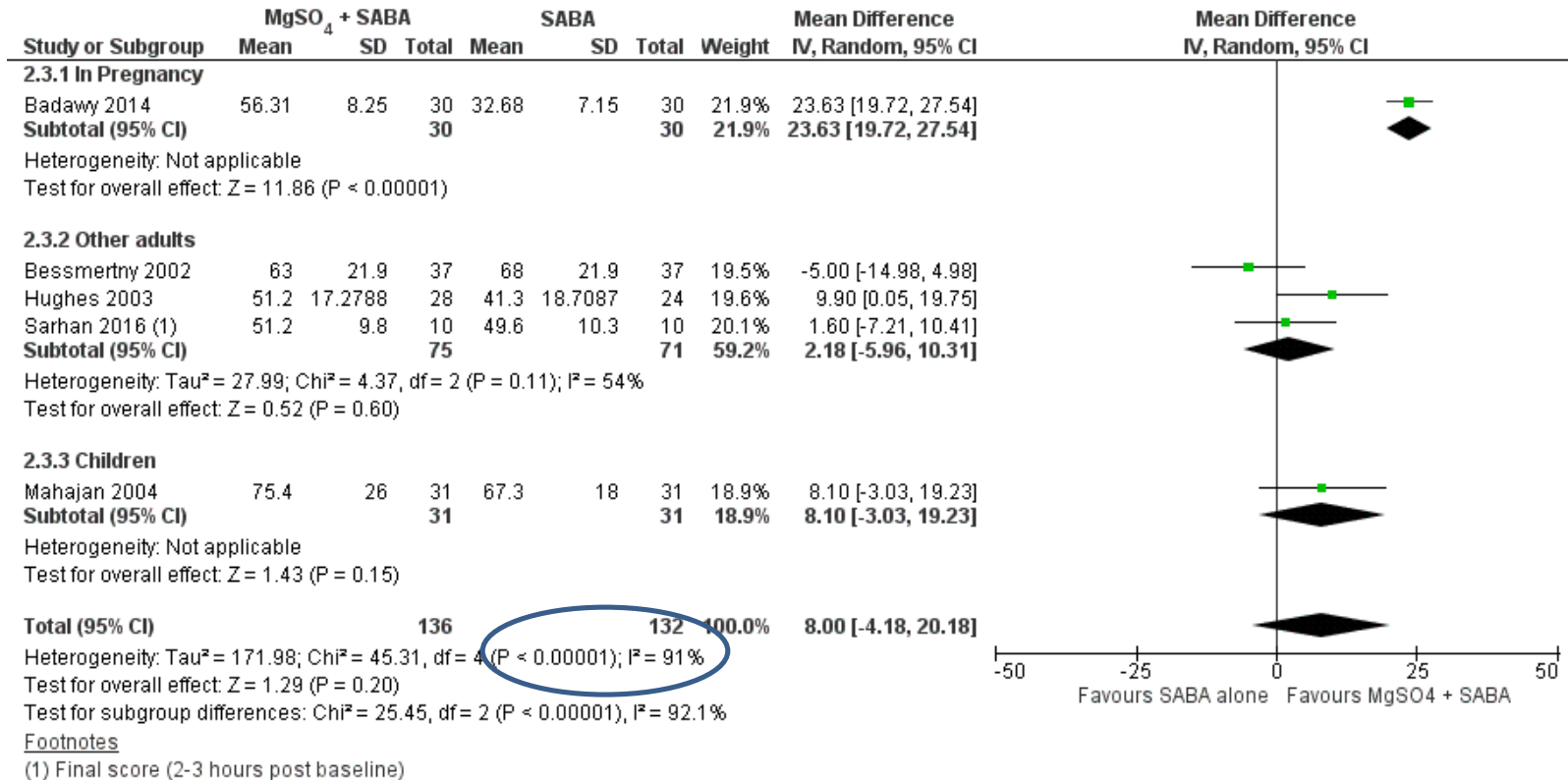
How similar are the results of all these trials?

Badawy results in context of other trials



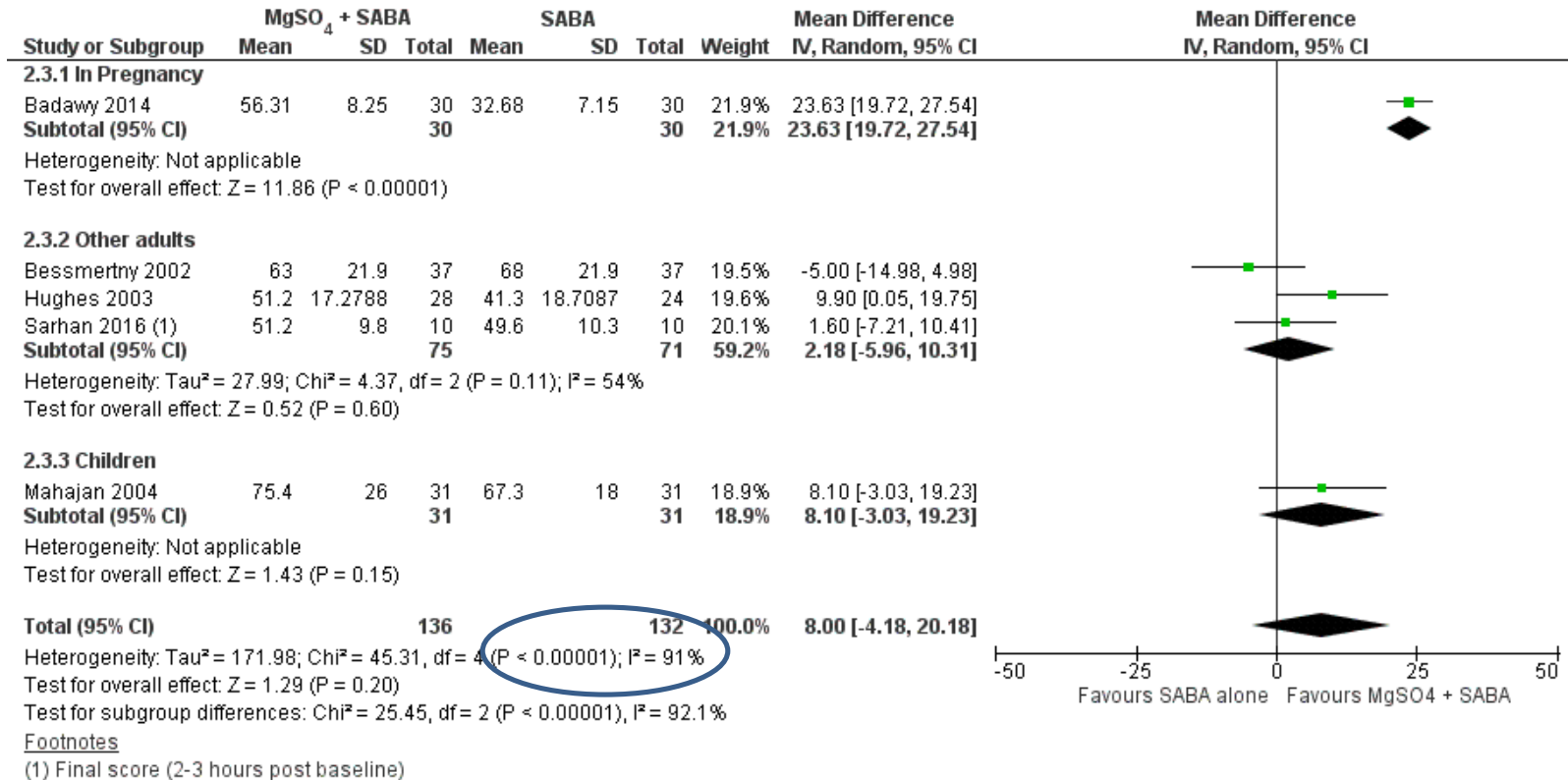
- What is Heterogeneity between trial results?

Badawy results in context of other trials



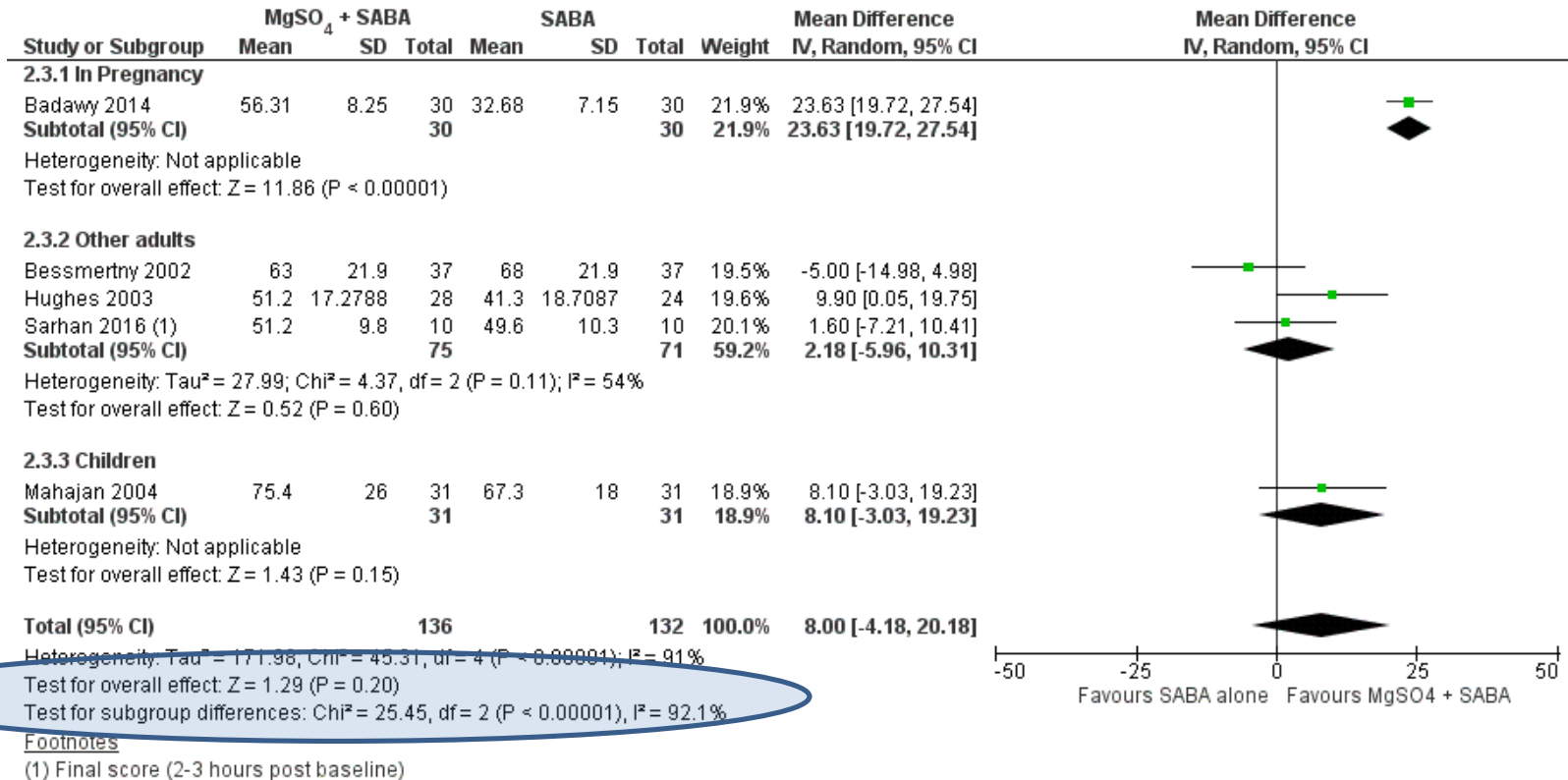
I²=(91%) represents the proportion of the total variability that comes from differences between the trials

Badawy results in context of other trials



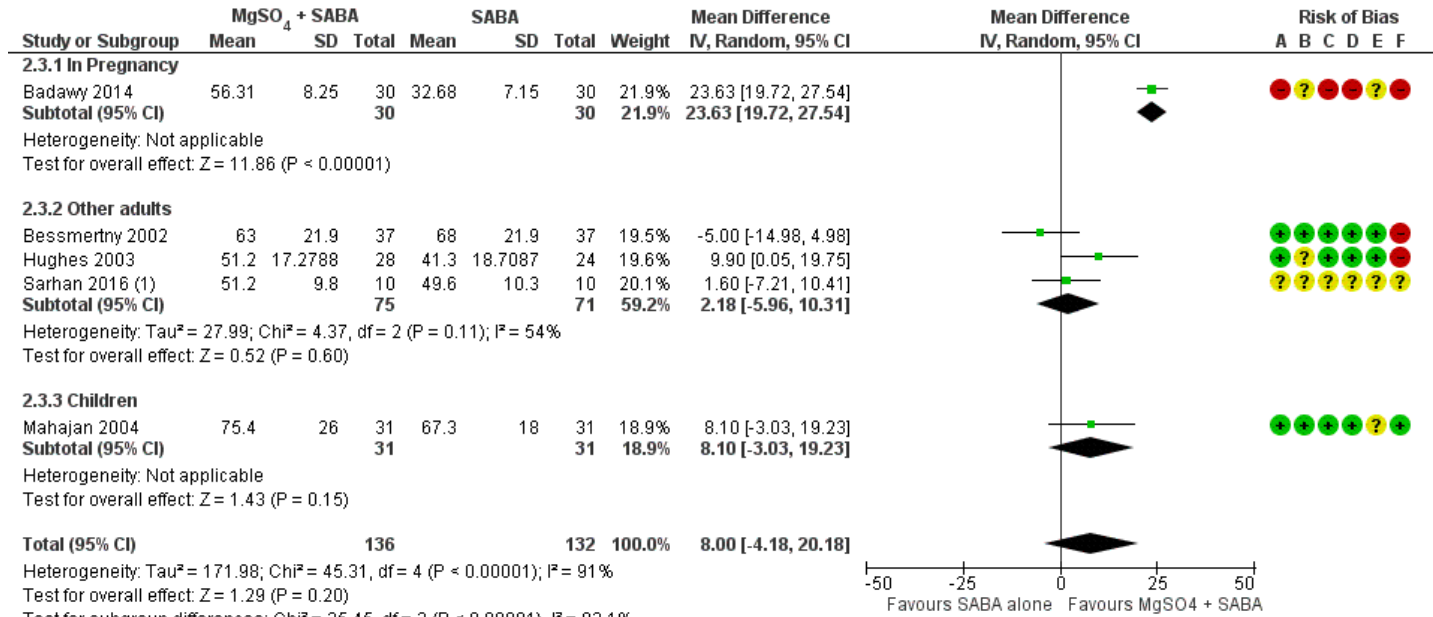
- Should these trial results be combined in a meta-analysis?

Badawy results in context of other trials



- What are possible reasons for the heterogeneity?

Badawy results in context of other trials

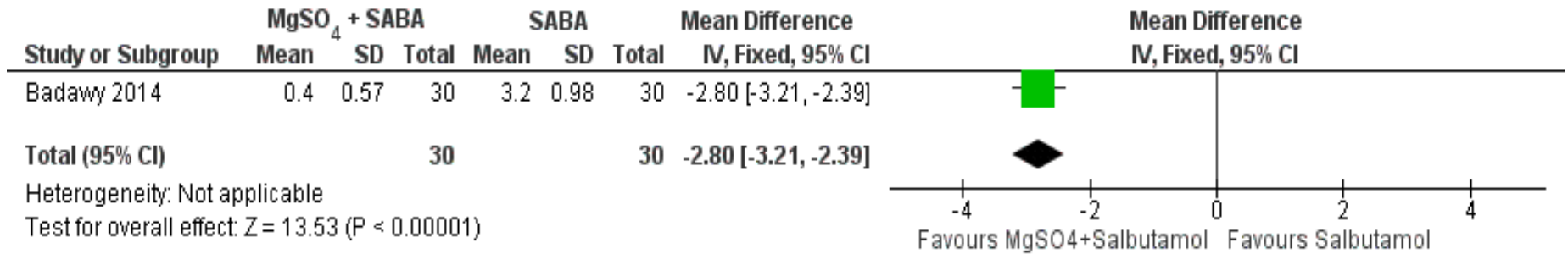


Risk of bias legend
 (A) Random sequence generation (selection bias)
 (B) Allocation concealment (selection bias)
 (C) Blinding of participants and personnel (performance bias)
 (D) Blinding of outcome assessment (detection bias)
 (E) Incomplete outcome data (attrition bias)
 (F) Selective reporting (reporting bias)

- **What are possible reasons for the heterogeneity?**

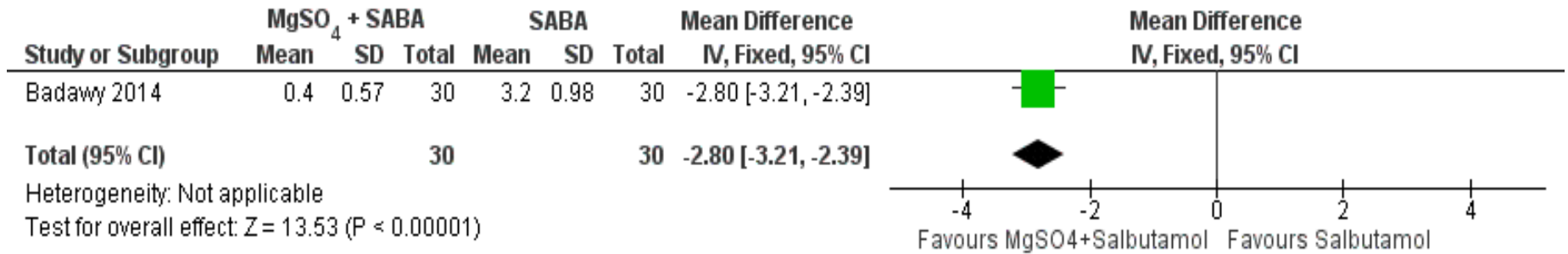
HOSPITAL ADMISSIONS

Rate of asthma hospitalisations until term



Can you describe the difference in admission rates until term in Badawy 2014?
 (Direction - Size - Uncertainty)

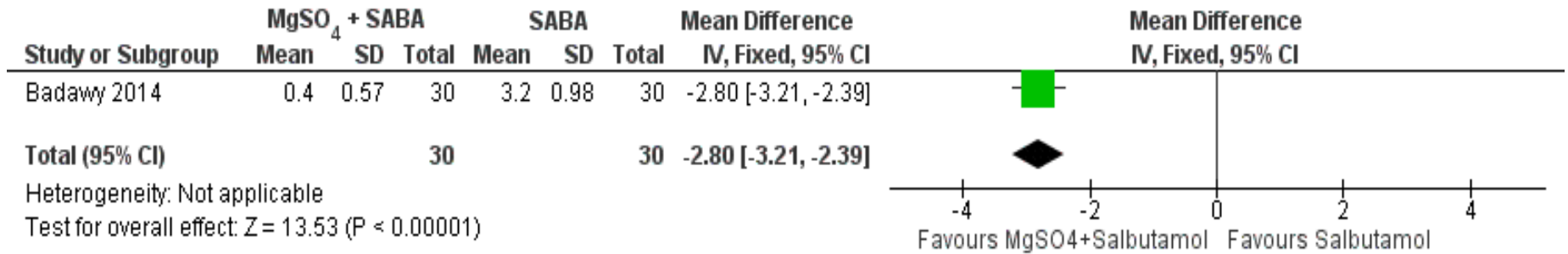
Rate of asthma hospitalisations until term



Can you describe the difference in admission rates until term in Badawy 2014? (Direction - Size - Uncertainty)

What is the ratio of admissions on MgSO₄ compared to SABA alone?

Rate of asthma hospitalisations until term



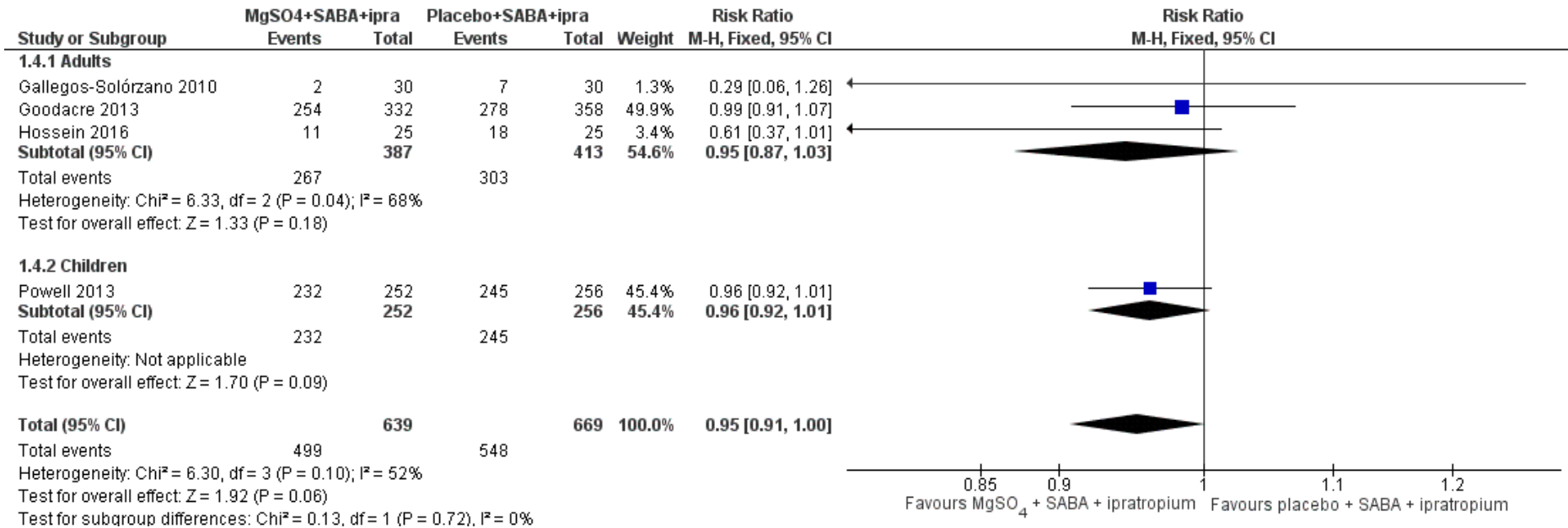
Magnesium = 30*0.4 = 12 admissions

SABA alone = 30*3.2 = 96 admissions

Ratio = 12/96 = 0.125

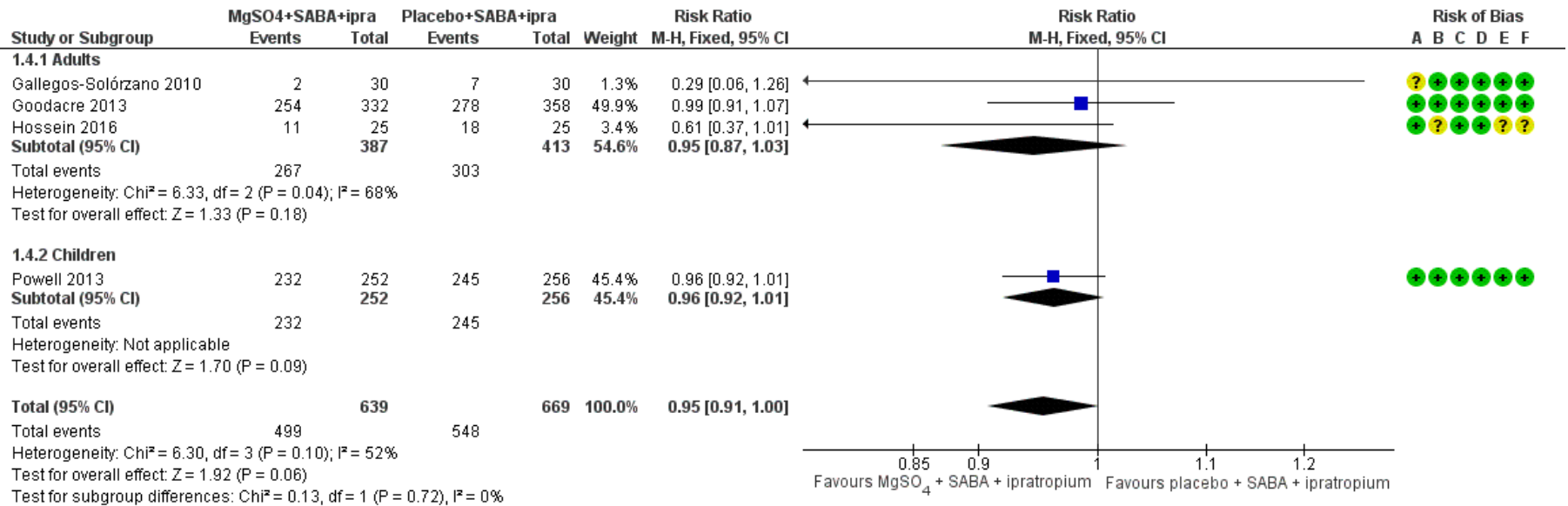
What is the ratio of admissions on MgSO₄ compared to SABA alone?

What about admissions to hospital in the Cochrane Review?



This is a *Meta-analysis of admissions to hospital* for nebulised MgSO₄ in addition to salbutamol and ipratropium
 It has been analysed as a dichotomous outcome using Risk Ratios

What about admissions to hospital in the Cochrane Review?

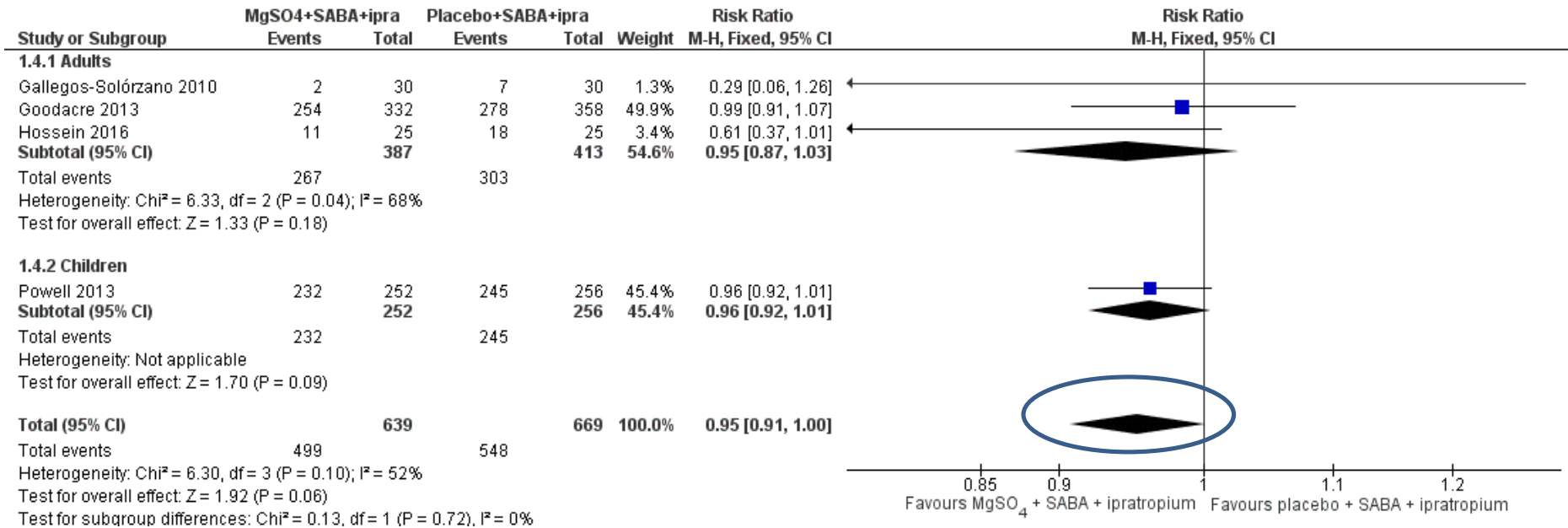


Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

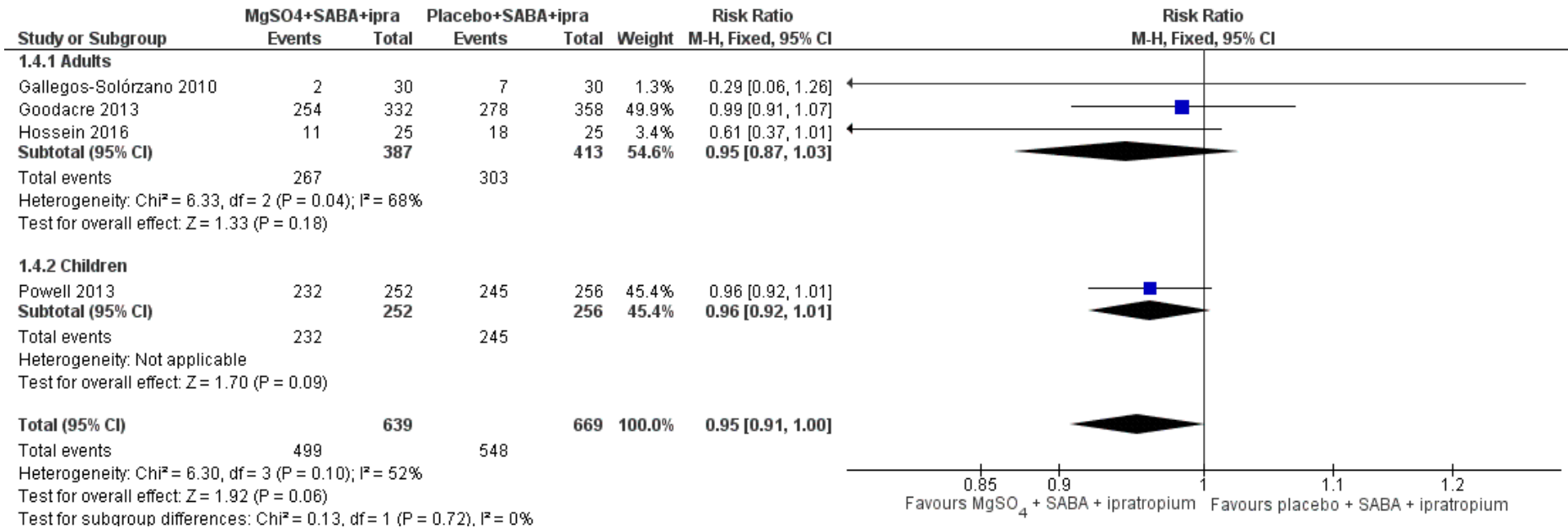
The same meta-analysis showing Risks of Bias. Note that Badawy did not report this outcome so we have no information in pregnancy.

What about admissions to hospital in the Cochrane Review?



How would you explain this effect at the meeting?
(Direction, Size and Uncertainty)

What about admissions to hospital in the Cochrane Review?

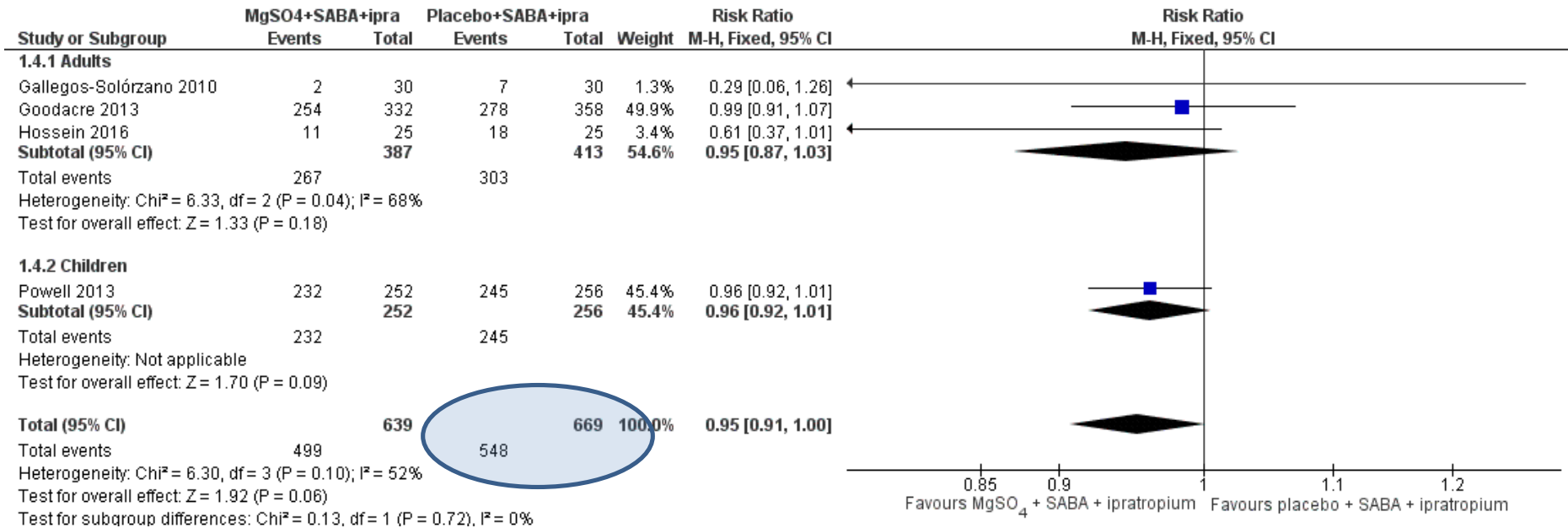


What is the Risk Ratio? 0.95

What is the Relative Risk Reduction on MgSO₄? 100% - 95% = 5%

What is the Absolute Risk Reduction?

What about admissions to hospital in the Cochrane Review?



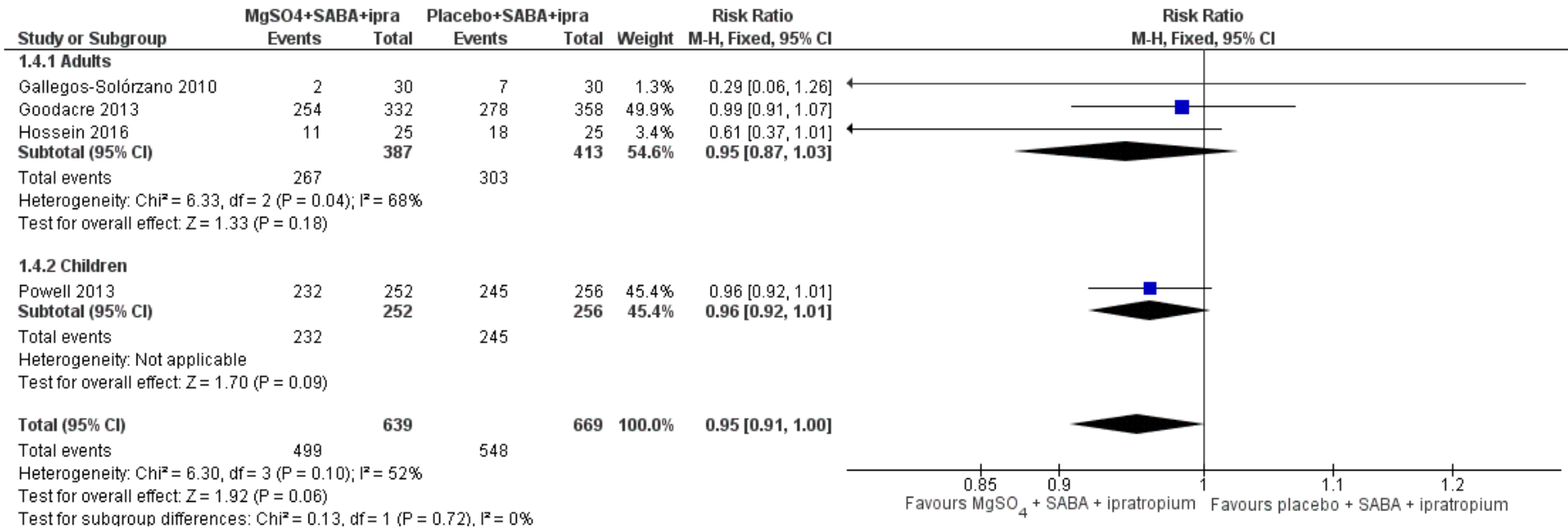
The risk of admission on SABA is 548/669 = 82%

What is the Relative Risk Reduction? 5%

What is the Absolute Risk Reduction?

5% of 82%, which is **4 Percentage Points**

What about admissions to hospital in the Cochrane Review?



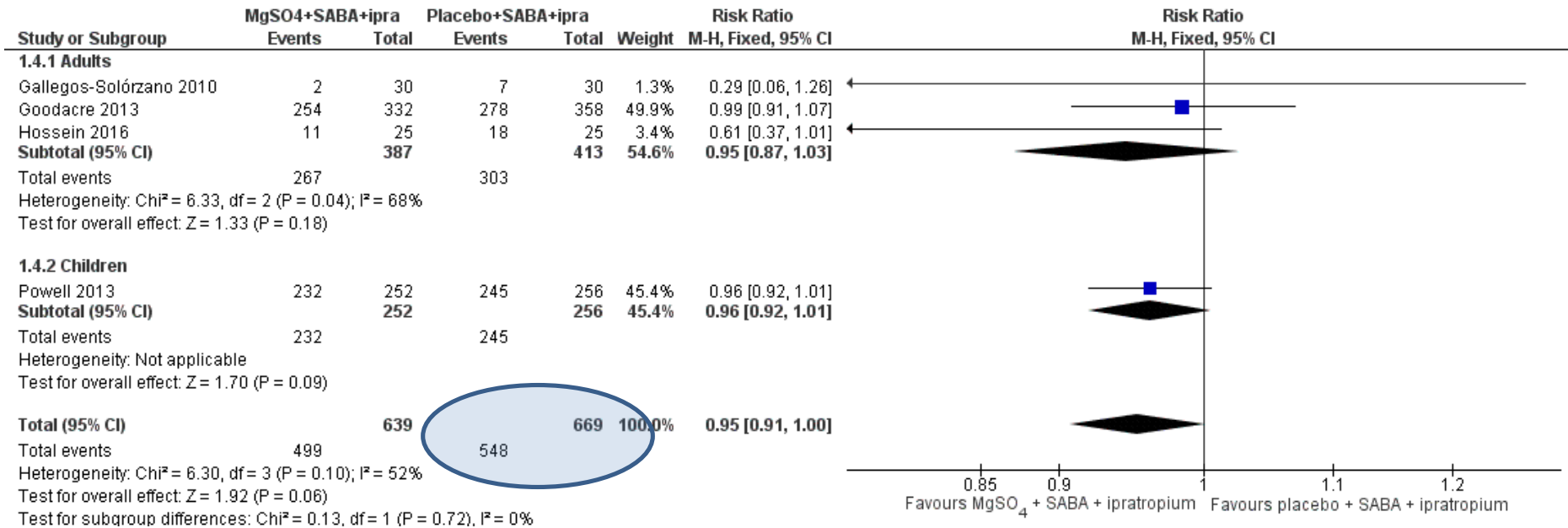
What is the uncertainty?

The Lower 95% CI for the Risk Ratio? 0.91

What is the Relative Risk Reduction on MgSO₄? 100%

- 91% = 9%

What about admissions to hospital in the Cochrane Review?



The risk of admission on SABA is $548/669 = 82\%$

What is the Relative Risk Reduction? 9%

What is the Absolute Risk Reduction?

9% of 82%, which is **7 Percentage Points**

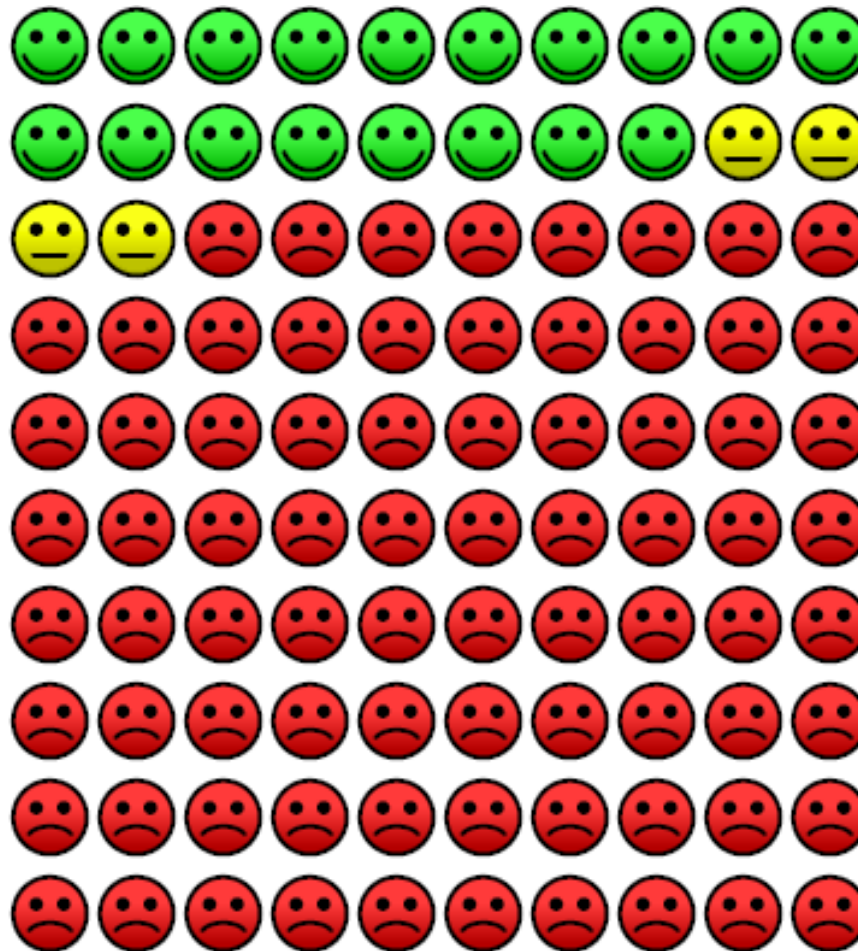
Can we show this as a picture?

- Let's look at a "Cates plot"?



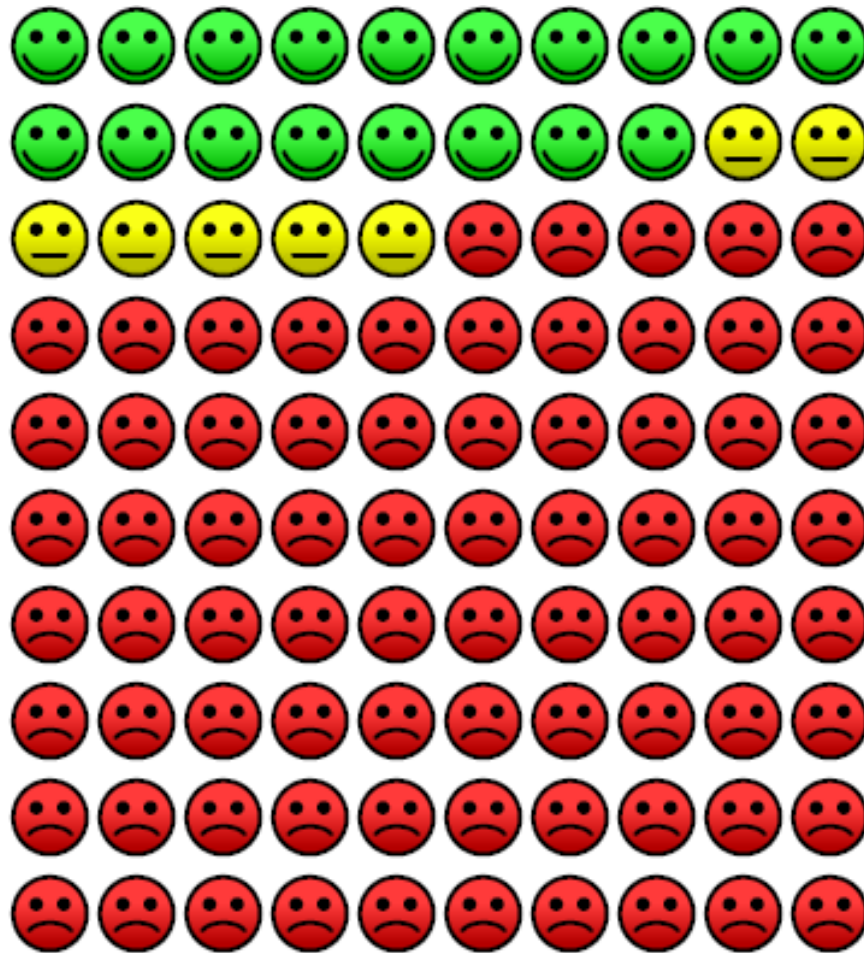
In the control group 82 people out of 100 had participants were admitted, compared to 78 (95% CI 74 to 82) out of 100 for the inhaled magnesium sulphate group.

4 percentage points Absolute Risk Reduction



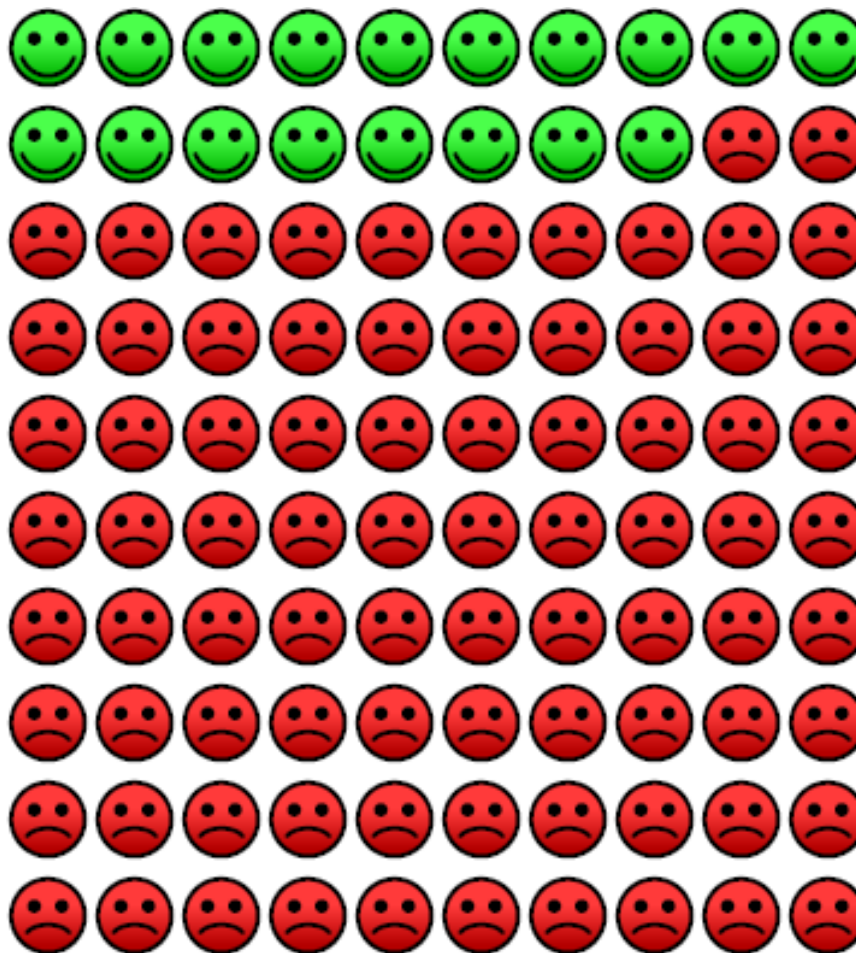
In the control group 82 people out of 100 had participants with one or more hospitalisations, compared to 78 (95% CI 75 to 82) out of 100 for the inhaled magnesium sulphate group.

Lower 95% CI:
9 percentage
points Absolute
Risk Reduction



In the control group 82 people out of 100 had participants were admitted,
compared to 75 out of 100 for the inhaled magnesium sulphate group.

Upper 95% CI:
0 percentage
points Absolute
Risk Reduction



In the control group 82 people out of 100 had participants were admitted,
compared to 82 out of 100 for the inhaled magnesium sulphate group.

Baseline characteristics

Table 1 The socio demographic and pregnancy duration in both groups.

Characteristics	Group (A)		Group (B)	
	No	%	No	%
Age Mean \pm SD	25.93 \pm 4.01		25.66 \pm 3.82	
<i>Education</i>				
Illiterate	5	16.67	4	13.34
Lower than University	21	70	20	66.67
<i>Parity</i>				
Primigravida	8	26.66	10	33
Multigravida	22	73.34	20	67
<i>Duration of pregnancy</i>				
1st trimester	2	6.67	3	10
2nd trimester	19	63.34	18	60
3rd trimester	9	30	9	30

What is missing from this table?

You have seen the evidence! What did you make of the risks of Bias in Badawy?

Risk of bias table 🌟

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk ▼	
Allocation concealment (selection bias)	Unclear risk ▼	
Blinding of participants and personnel (performance bias)	Unclear risk ▼	
Blinding of outcome assessment (detection bias)	Unclear risk ▼	
Incomplete outcome data (attrition bias)	Unclear risk ▼	
Selective reporting (reporting bias)	Unclear risk ▼	

Methods
Participants
Interventions
Outcomes
Notes

You have seen the evidence!
 What did you make of the risks of Bias?

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	
Allocation concealment (selection bias)	Unclear risk	
Blinding of participants and personnel (performance bias)		
Blinding of outcome assessment (detection bias)		
Incomplete outcome data (attrition bias)		
Selective reporting (reporting bias)		

- How would you summarise the evidence you have seen?
- What would your advice be to the A&E consultant?

Take Home messages

1. Don't just rely on the results of a single study
2. Look at the difference between the trials as well as the weighted average!
3. Think about bias as well as the play of chance (as the 95% CI only includes uncertainty around the latter)

There is further reading on my
website

- www.nntonline.net
- Link to the article in Breathe on Understanding Systematic Reviews
- You can have a go at using Visual Rx
- There are short articles on Critical Appraisal
- Short articles on Statistics related to meta-analysis