

# Crohn's disease

## Appendix G

*Clinical Guideline <...>*

*Forest plots*

*10 October 2012*

NICE's original guidance on Crohn's disease: management in adults, children and young people was published in October 2012; it was partially updated in May 2016 when a new recommendation on inducing remission was added. It has now undergone a further partial update published in May 2019. The full, current recommendations can be found on the NICE website.

This document preserves evidence for areas of the guideline that have not been updated in 2019. Black shading indicates text from 2012 replaced by the 2019 update.

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# 1 Forest plots

## 1.1 Key

5-aminosalicylates = 5-ASA = 5-asa = ASA

Azathioprine = AZA = aza

Mercaptopurine = MP

Conventional glucocorticosteroid = CGCS

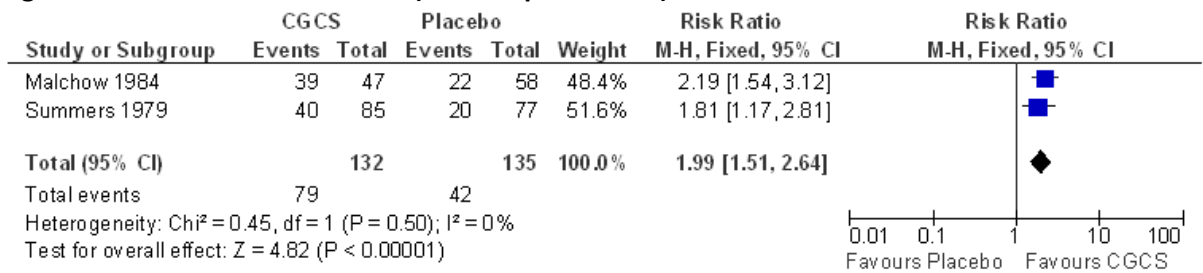
Methotrexate = Mtx

## 1.2 Induction of remission

### 1.2.1 Conventional glucocorticosteroid

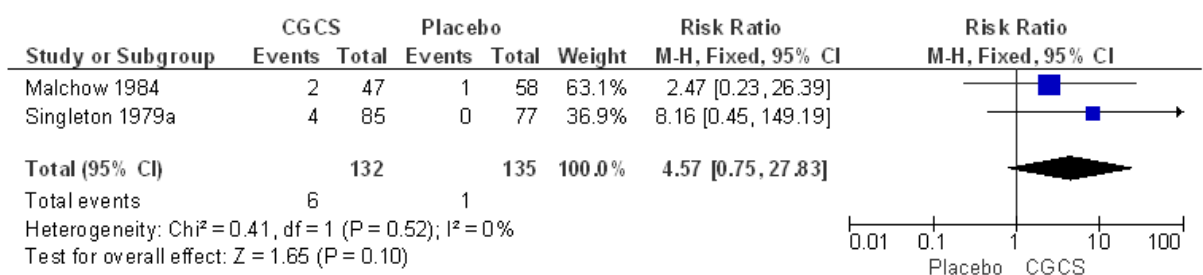
### 1.2.2 Conventional glucocorticosteroid versus placebo

**Figure 1: Induction of remission (follow-up 15 weeks)**



Source: *Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.*

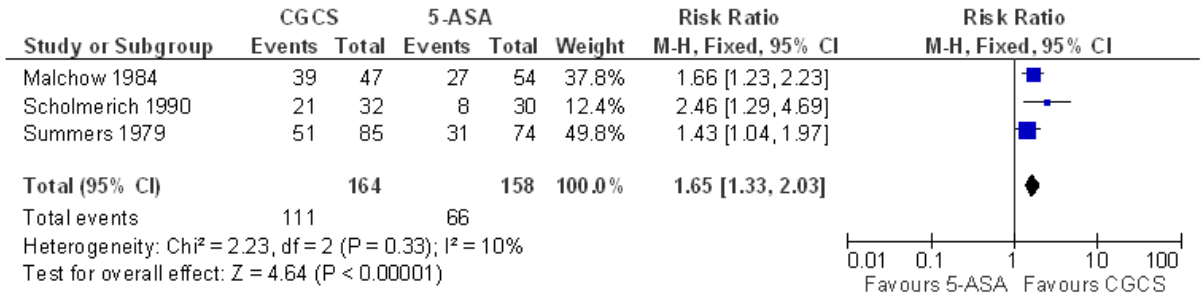
**Figure 2: Withdrawal due to adverse events (follow-up 17-18 weeks)**



Source: *Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010 Copyright Cochrane Collaboration, reproduced with permission.*

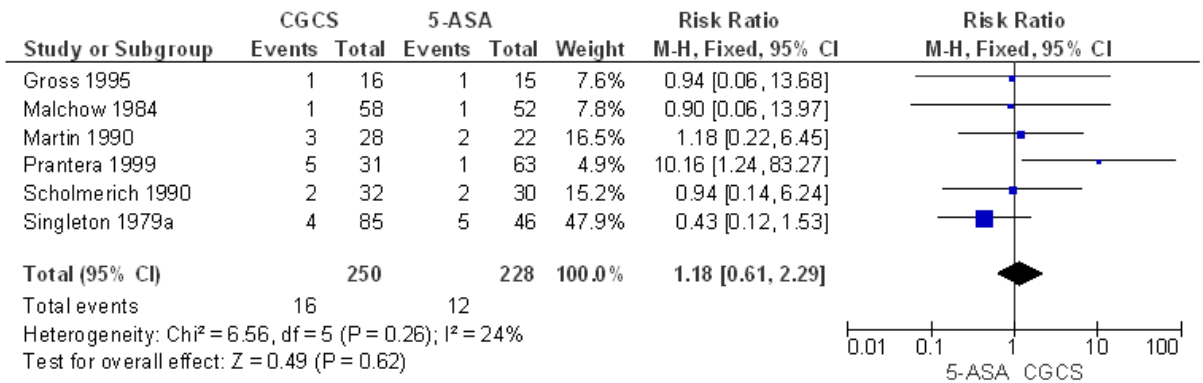
### 1.2.3 Conventional glucocorticosteroid versus 5-aminosalicylate

**Figure 3: Induction of remission (follow-up 15 weeks)**



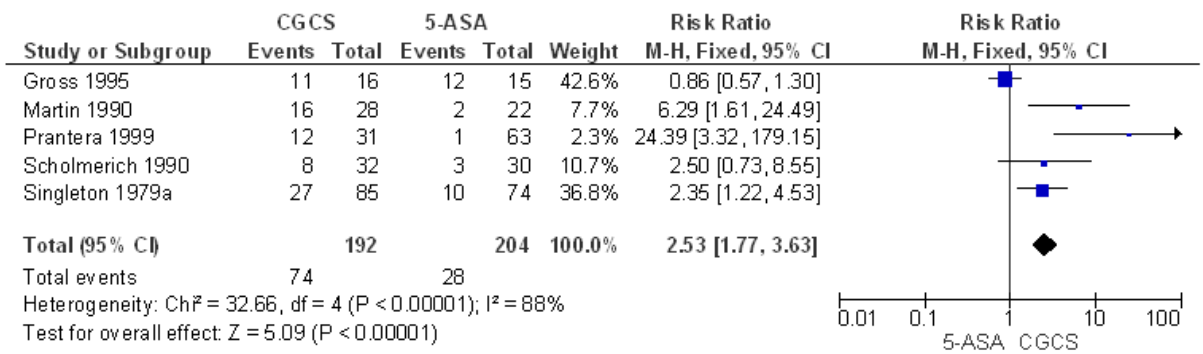
Source: *Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010*  
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**Figure 4: Withdrawal due to adverse events (follow-up 15 weeks)**

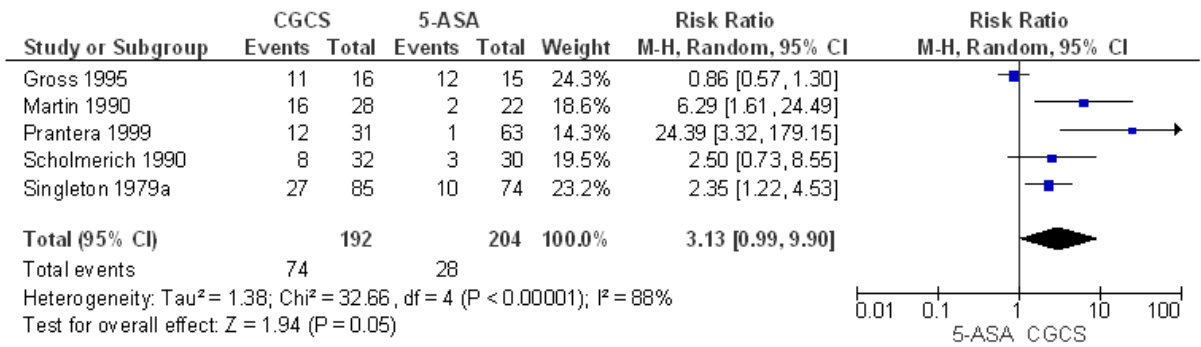


Source: *Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010*  
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**Figure 5: Adverse events – all doses [fixed effects] (follow-up 15 weeks)**



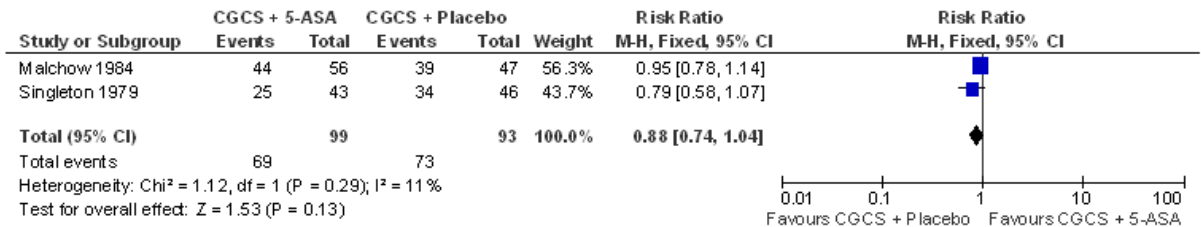
**Figure 6: Adverse events – all doses [random effects] (follow-up 15 weeks)**



Source: Benchimol EI, Seow CH, Steinhart AH, Griffiths AM. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD006792. DOI: 10.1002/14651858.CD006792.pub2. Edited (no change to conclusions), published in Issue 4, 2010  
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### 1.2.4 Conventional glucocorticosteroid plus 5-aminosalicylate (sulfasalazine) versus conventional glucocorticosteroid

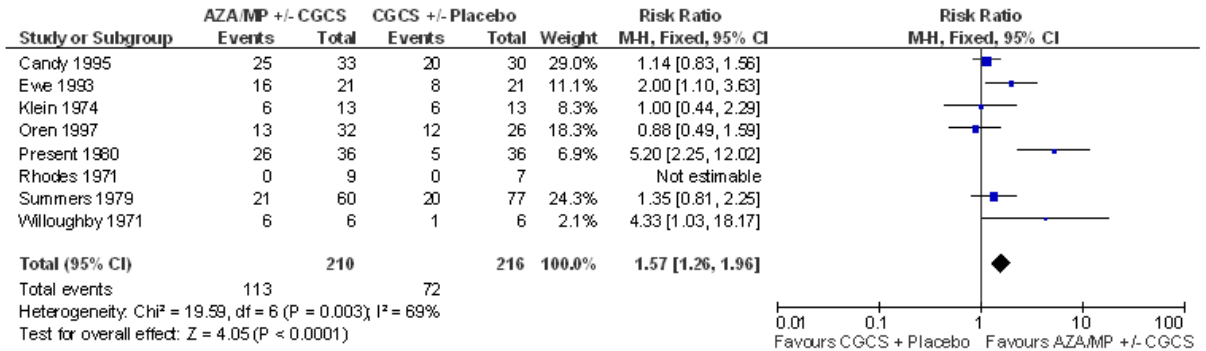
**Figure 7: Conventional glucocorticosteroid plus 5-aminosalicylate (sulfasalazine) versus conventional glucocorticosteroid for induction of remission**



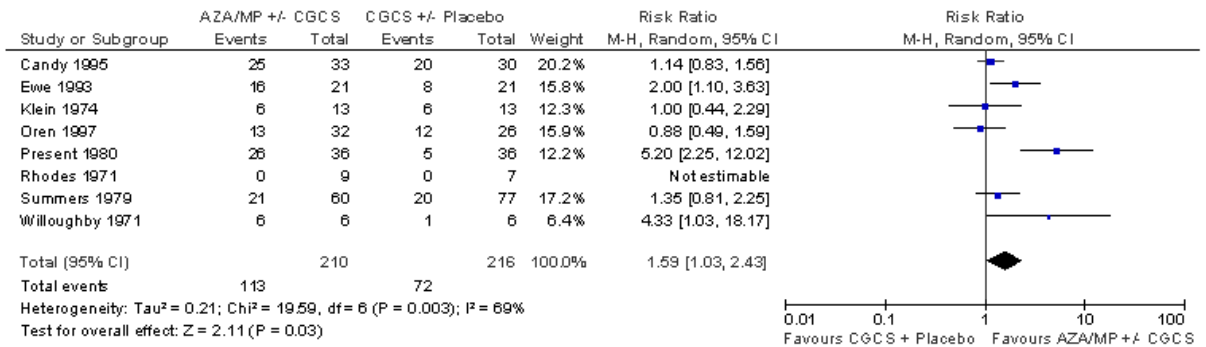


1.2.5 Adjunctive azathioprine versus placebo

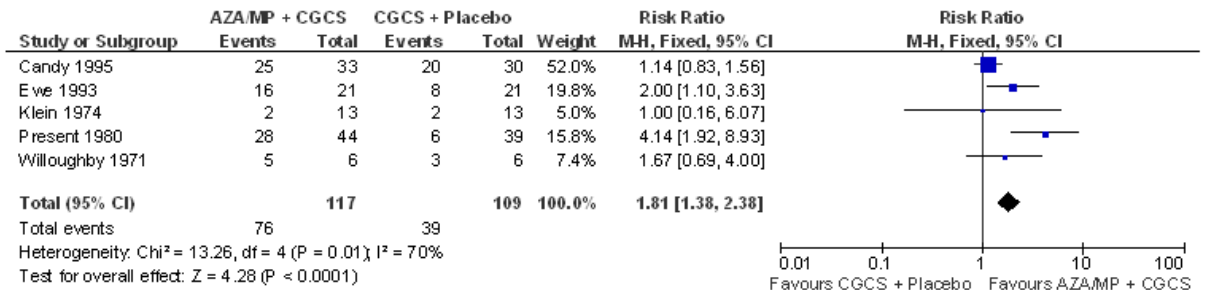
**Figure 8: AZA/MP +/-glucocorticosteroid vs conventional glucocorticosteroid +/- placebo for induction of remission [fixed effect] (follow-up mean 16 weeks)**



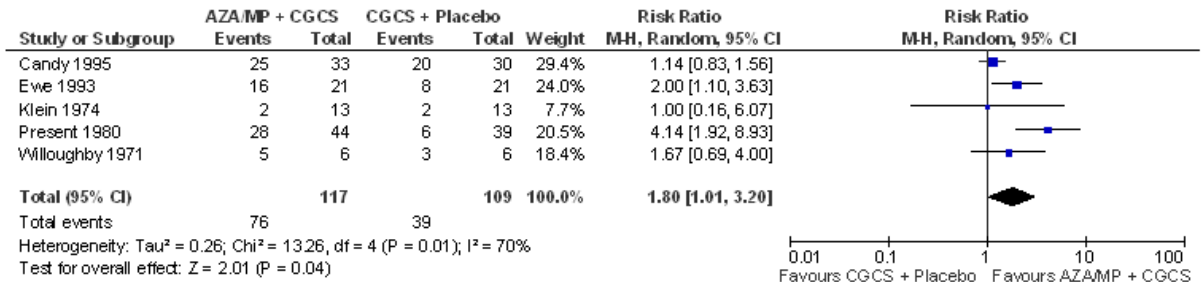
**Figure 9: AZA/MP +/-glucocorticosteroid vs conventional glucocorticosteroid +/- placebo for induction of remission [random effect] (follow-up mean 16 weeks)**



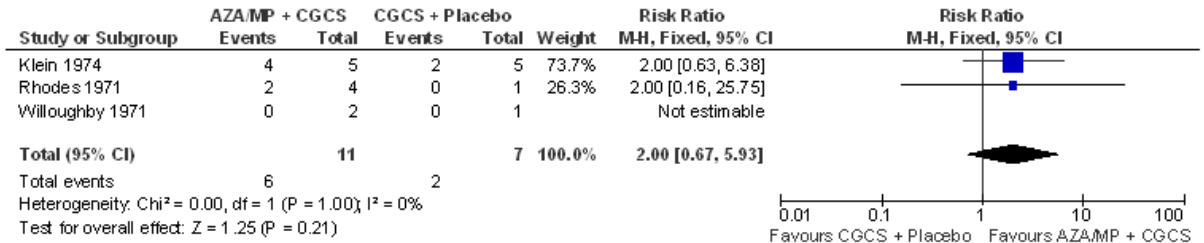
**Figure 10: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for glucocorticosteroid-sparing [fixed effect] (follow-up mean 16 weeks)**



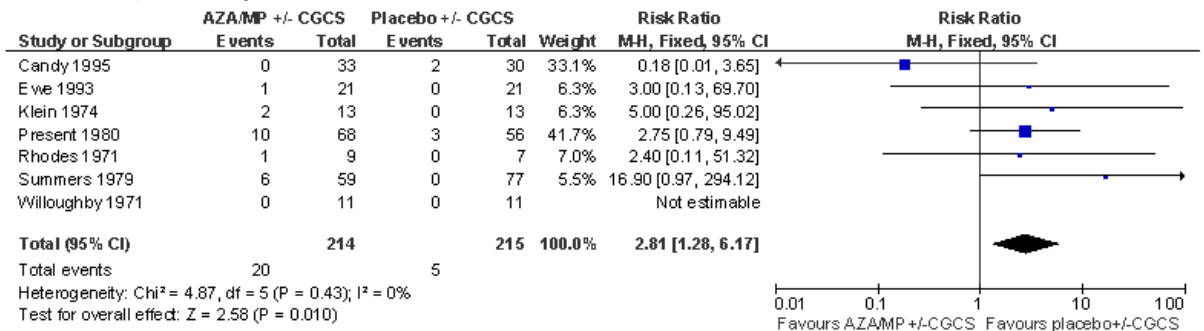
**Figure 11: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for glucocorticosteroid-sparing [random effect] (follow-up mean 16 weeks)**



**Figure 12: AZA/MP + glucocorticosteroid vs. placebo + glucocorticosteroid for fistula healing (follow-up mean 16 weeks)**

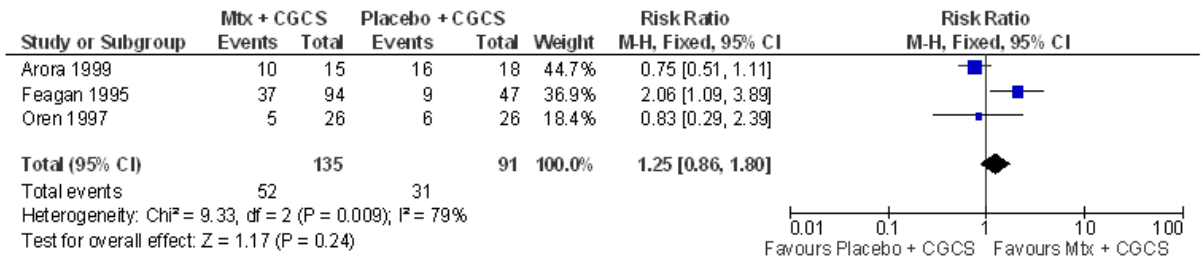


**Figure 13: AZA/MP +/- glucocorticosteroid vs. placebo +/- glucocorticosteroid for adverse events (follow-up mean 16 weeks)**

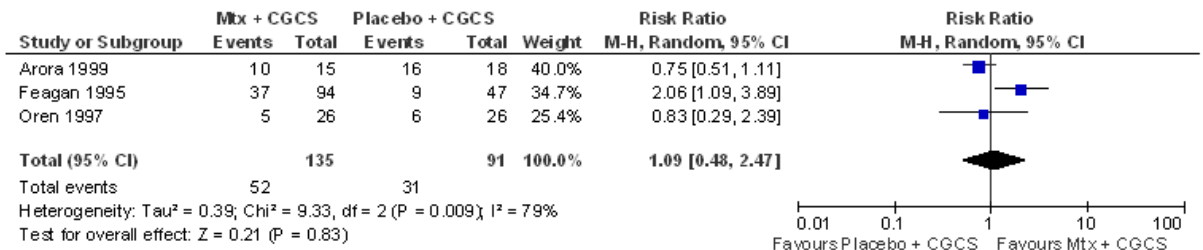


1.2.6 Adjunctive methotrexate versus placebo

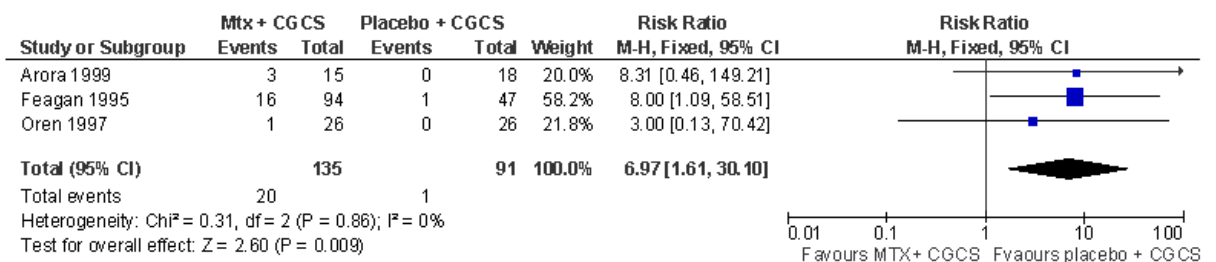
**Figure 14: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for induction of remission [fixed effect] (follow-up 16 weeks)**



**Figure 15: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for induction of remission [random effect] (follow-up 16 weeks)**



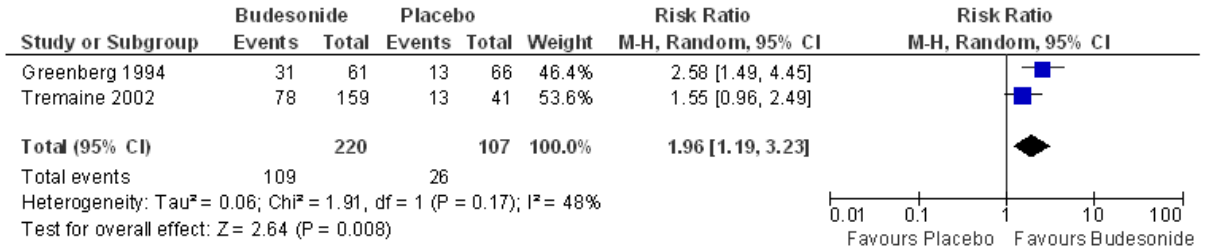
**Figure 16: Methotrexate + glucocorticosteroid vs. placebo + glucocorticosteroid for withdrawal due to adverse events (follow-up 18 months)**



### 1.2.7 Budesonide

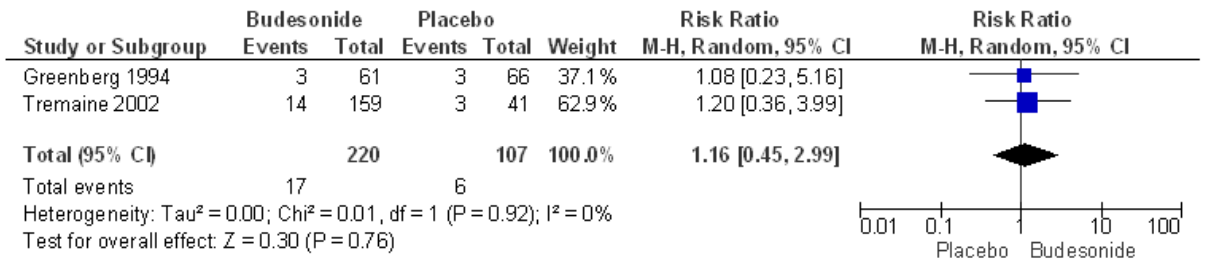
#### 1.2.7.1 Budesonide versus placebo

**Figure 17: Induction of remission (CDAI ≤ 150) (follow-up eight weeks)**



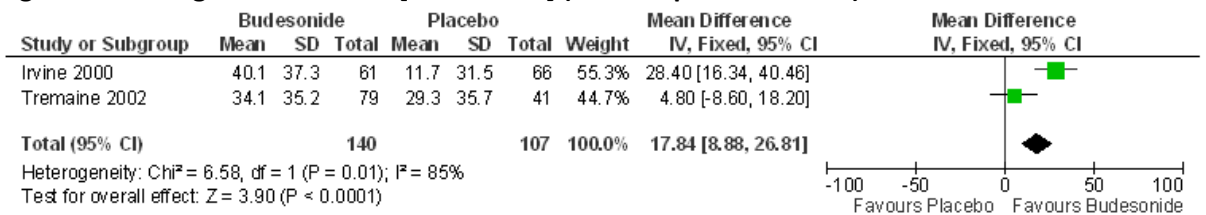
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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**Figure 18: Withdrawal due to adverse events (follow-up 8-10 weeks)**

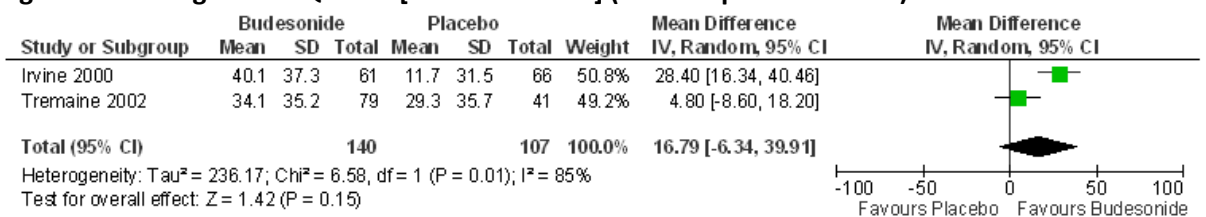


Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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**Figure 19: Change in IBDQ score [fixed effect] (follow-up 8 – 10 weeks)**

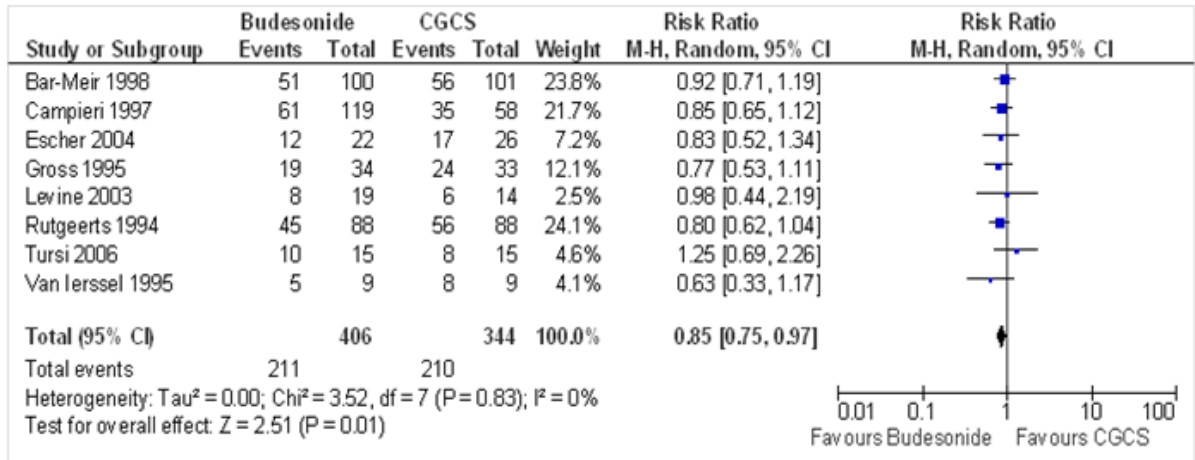


**Figure 20: Change in IBDQ score [random effects] (follow-up 8 – 10 weeks)**



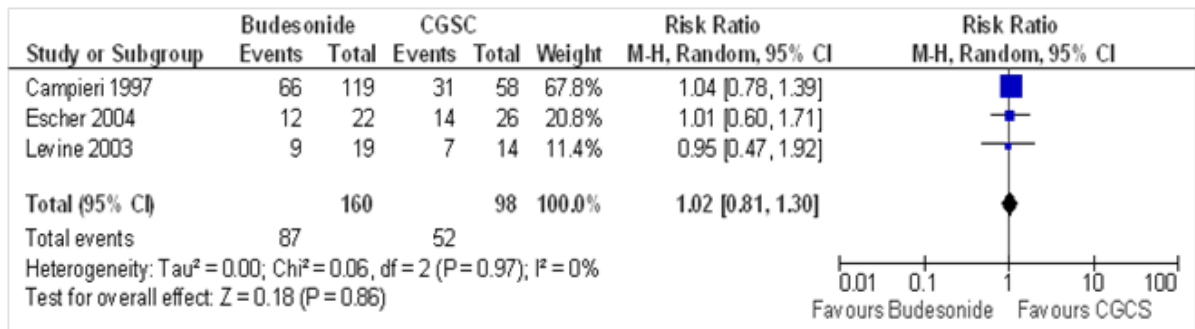
1.2.7.2 Budesonide versus conventional glucocorticosteroid

Figure 21: Induction of remission (follow-up eight weeks)



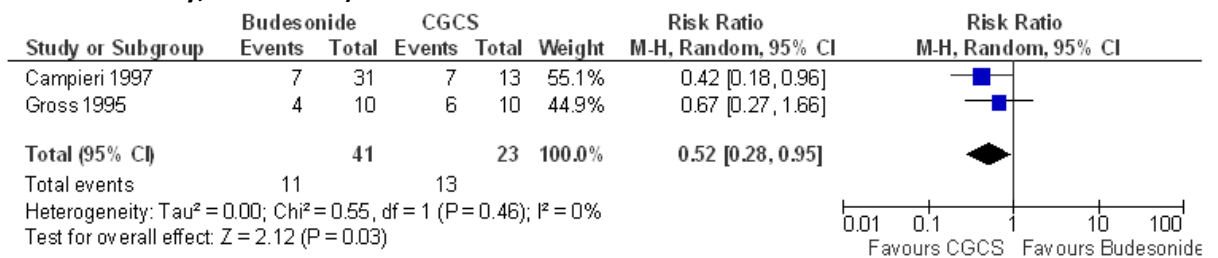
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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Figure 22: Induction of remission (follow-up 12 weeks)



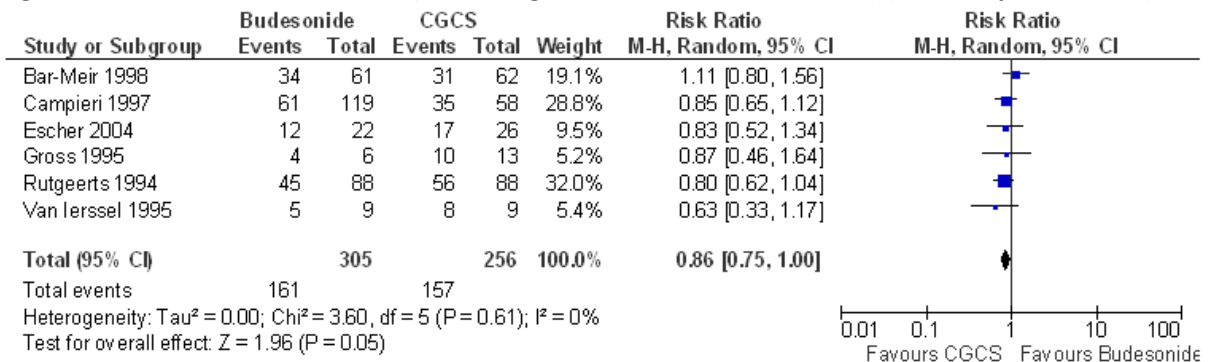
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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Figure 23: Induction of clinical remission at eight weeks (in people with severe disease at trial entry, CDAI ≥ 300)



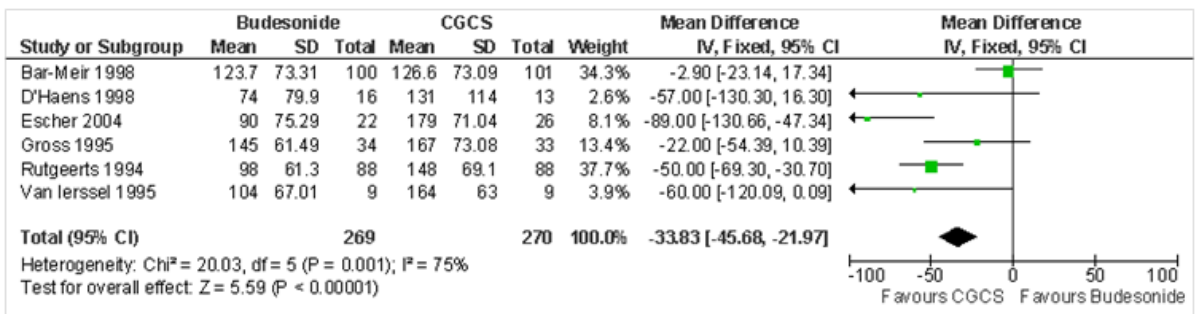
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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**Figure 24: Induction of remission (ileal or right-sided ileocolonic disease)(follow-up not stated)**

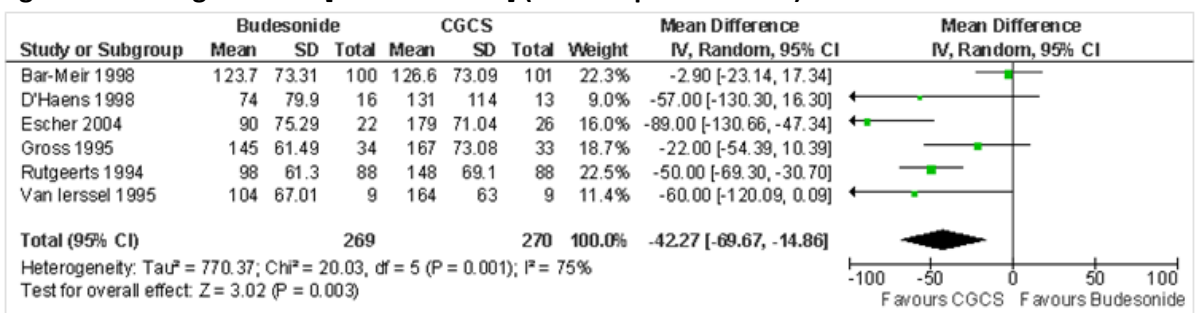


Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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**Figure 25: Change in CDAI [fixed effect] (follow-up 8-12 weeks)**

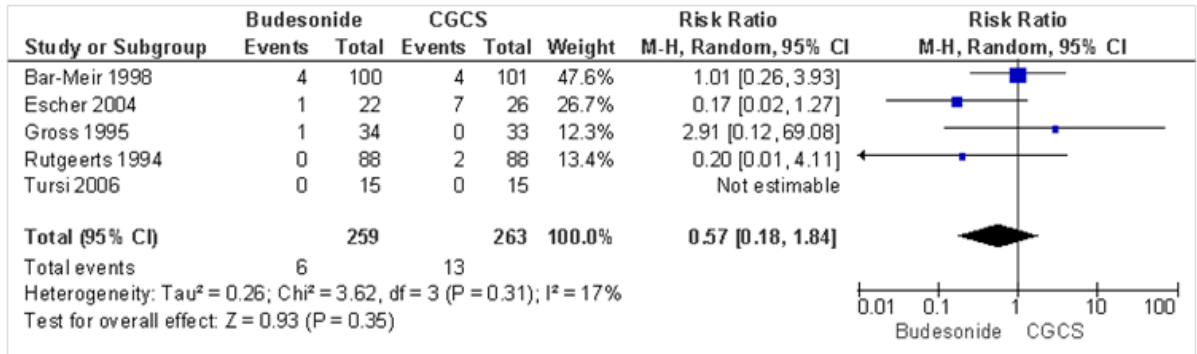


**Figure 26: Change in CDAI [random effect] (follow-up 8-12 weeks)**



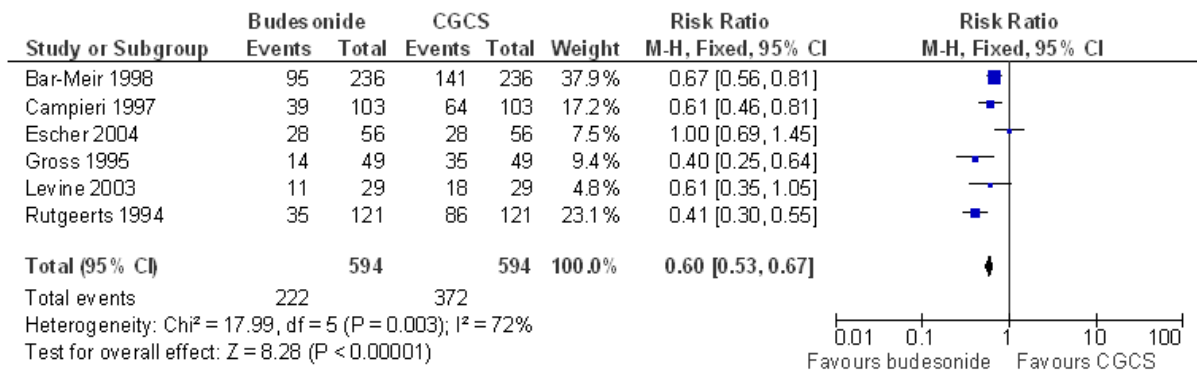
Source: Seow CH, Benchimol EI, Griffiths AM, Otley AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2009  
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**Figure 27: Withdrawal due to adverse events (follow-up 8 – 12 weeks)**



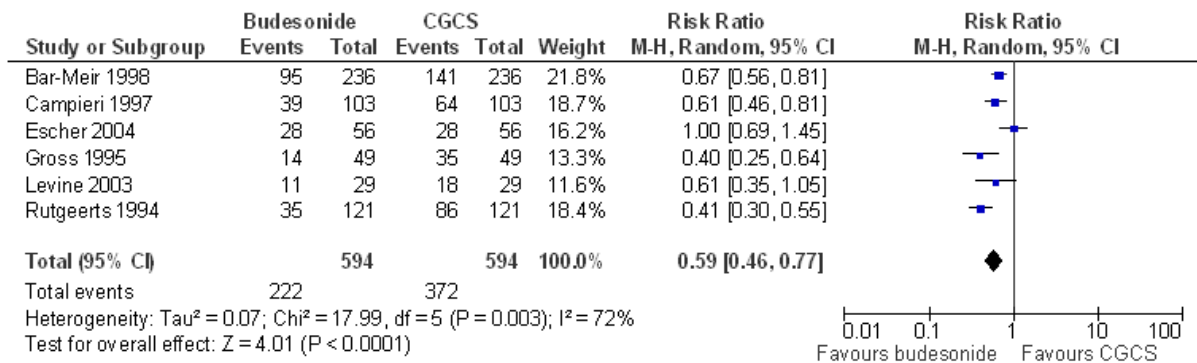
Source: Seow CH, Benchimol EI, Griffiths AM, Otlej AR, Steinhart AH. Budesonide for induction of remission in Crohn's disease. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub3. Edited (no change to conclusions), published in Issue 4, 2010  
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**Figure 28: Glucocorticosteroid-related adverse events [fixed effect] (follow-up 8 – 12 weeks) - adults and children**



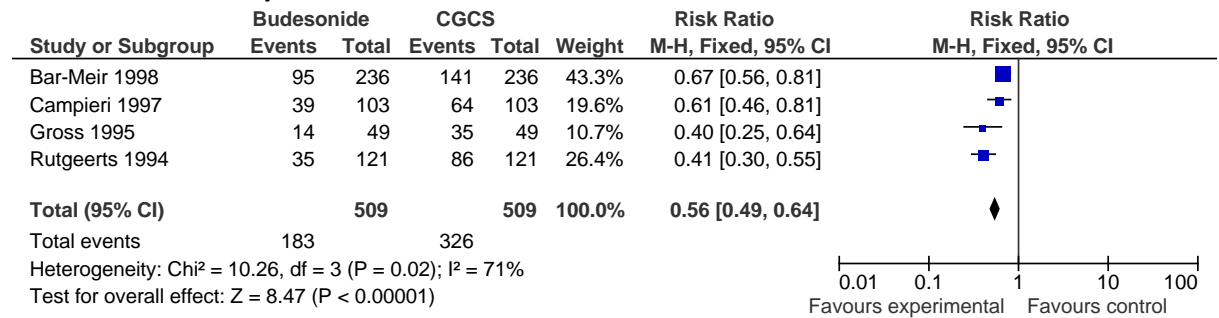
Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis

**Figure 29: Glucocorticosteroid-related adverse events [random effects] (follow-up 8 – 12 weeks) – adults and children**



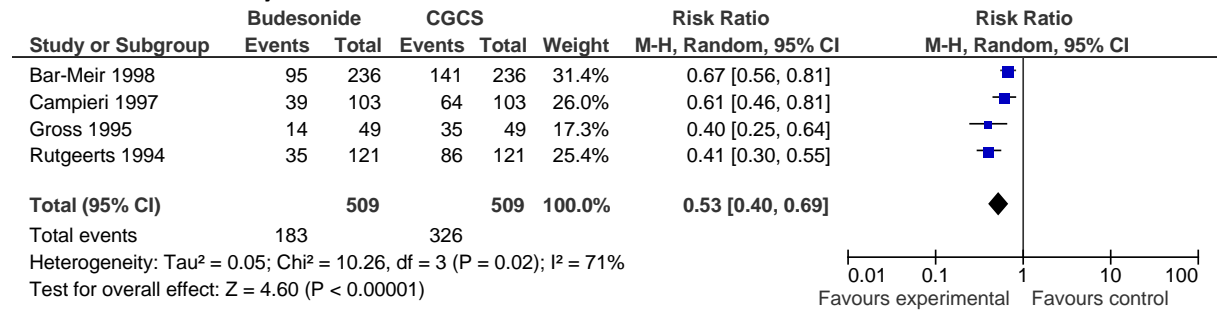
*Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis*

**Figure 30: Glucocorticosteroid-related adverse events [fixed effect] (follow-up 8 – 12 weeks) – adults only**



*Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis*

**Figure 31: Glucocorticosteroid-related adverse events [random effects] (follow-up 8 – 12 weeks) – adults only**



*Glucocorticosteroid-related adverse events including moon face, acne, swollen ankles, easy bruising, hirsutism, buffalo hump, skin striae, nausea, vomiting, heartburn, dyspepsia, abdominal distension, perspiration, flushing, hair loss, dry mouth, leg cramps, tremor, blurred vision, insomnia, headache, fatigue, depression, myalgia and pharyngitis*



1.2.7.3 Budesonide versus 5-aminosalicylates

Figure 32: Budesonide vs. mesalazine - induction of remission [fixed effects] (follow-up eight weeks)

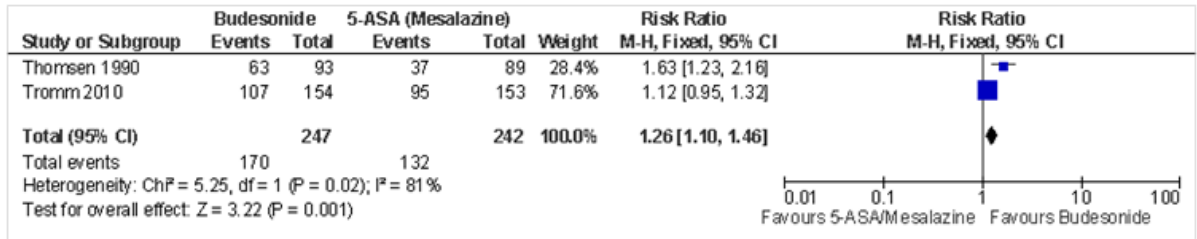


Figure 33: Budesonide vs. mesalazine - induction of remission [random effects] (follow-up eight weeks)

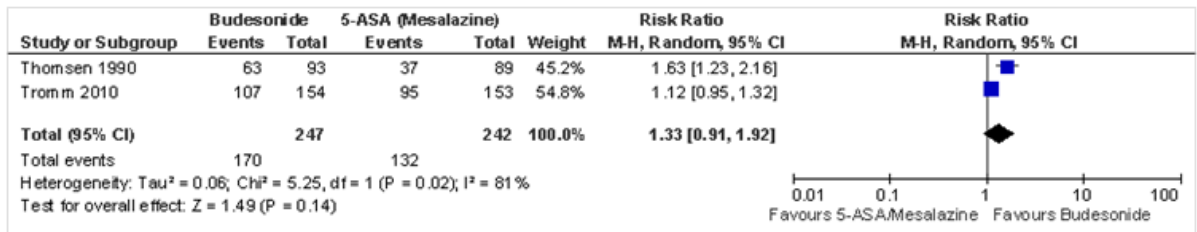
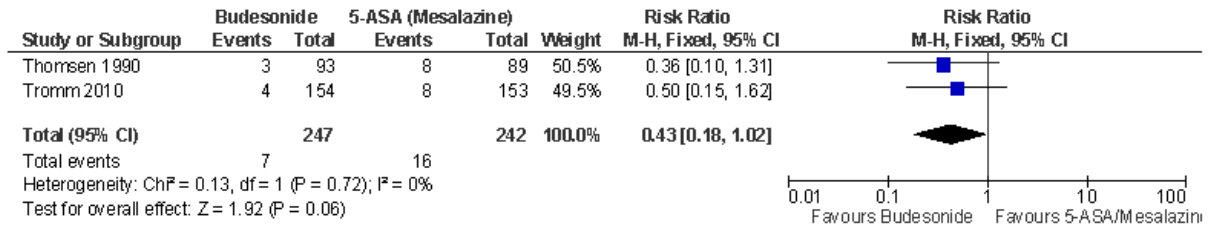


Figure 34: Budesonide vs. mesalazine - withdrawal due to adverse events (follow-up eight weeks)



1.2.7.4 Budesonide in children

Budesonide vs. conventional glucocorticosteroid

Figure 35: Induction of remission in children: eight weeks

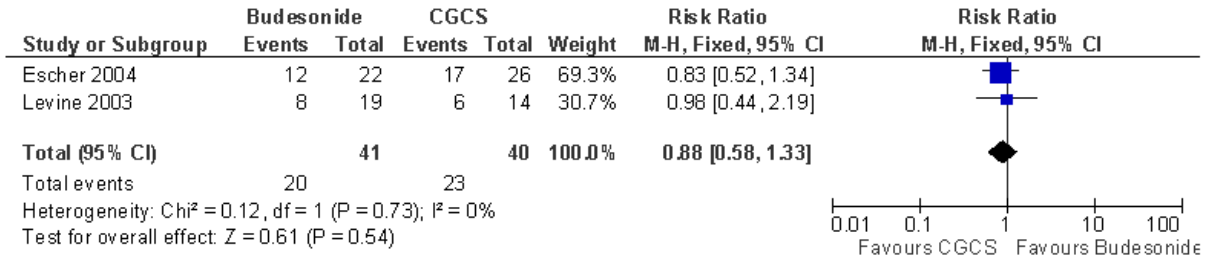


Figure 36: Induction of remission in children: 12 weeks

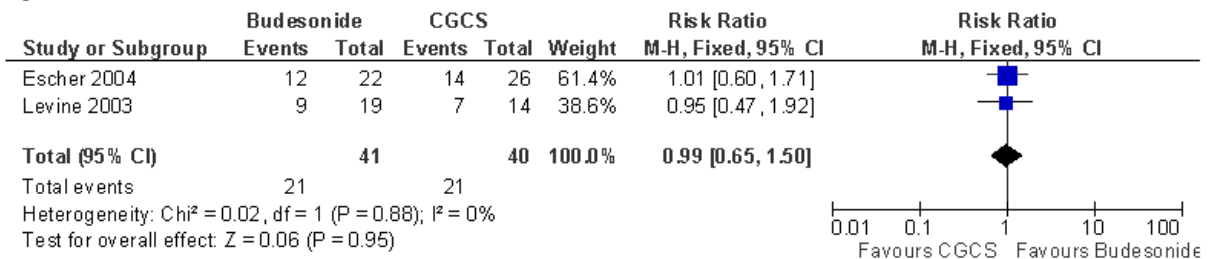
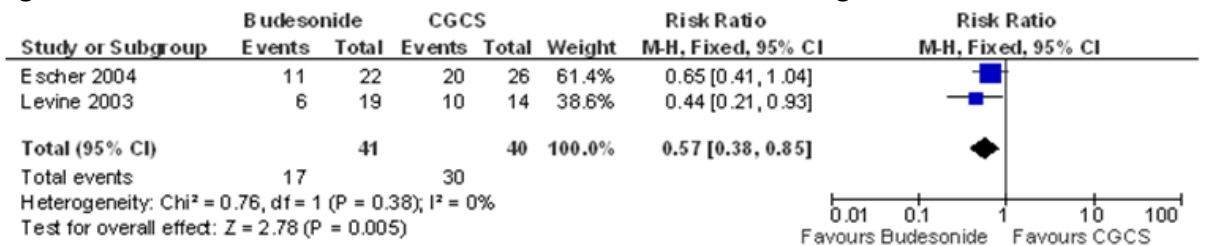


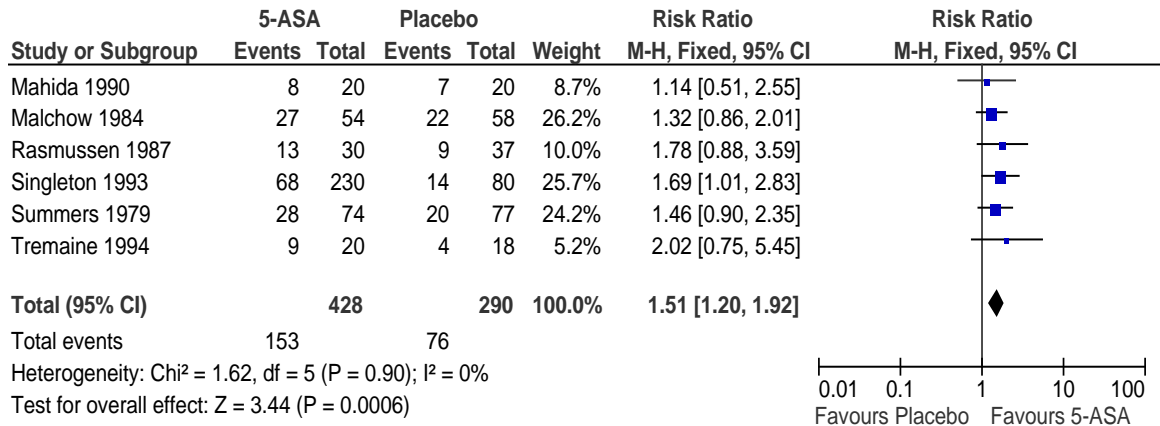
Figure 37: Glucocorticosteroid-related adverse events in children: eight weeks



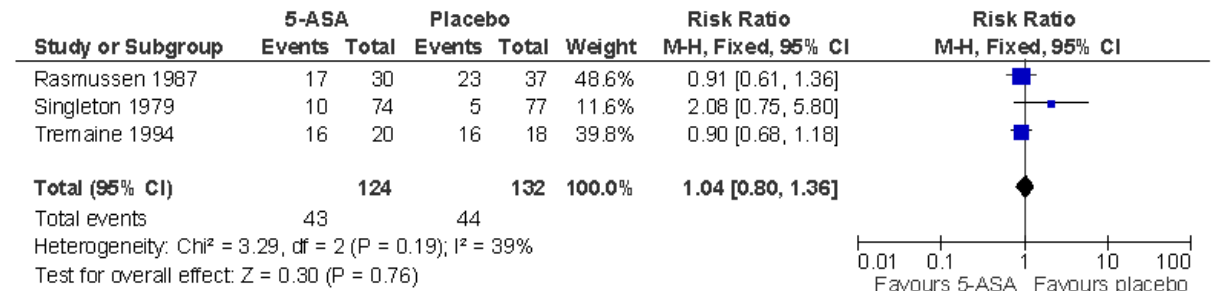
### 1.2.8 5-aminosalicylates

#### 1.2.8.1 5-aminosalicylates versus placebo

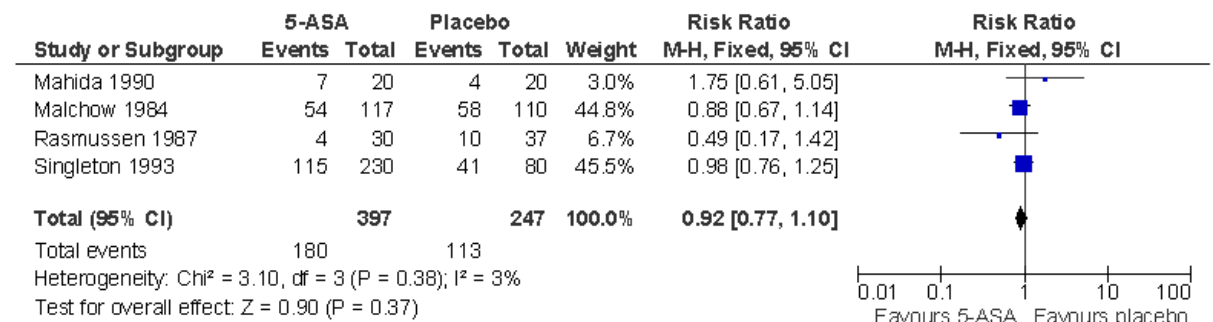
**Figure 38: Induction of remission (follow-up 6-18 weeks)**



**Figure 39: Adverse events (follow-up 16 weeks)**



**Figure 40: Withdrawal for any reason (follow-up 6-18 weeks)**



1.2.8.2 5-aminosalicylates versus azathioprine/mercaptopurine

Figure 41: Induction of remission [fixed effect] (follow-up 16-30 weeks)

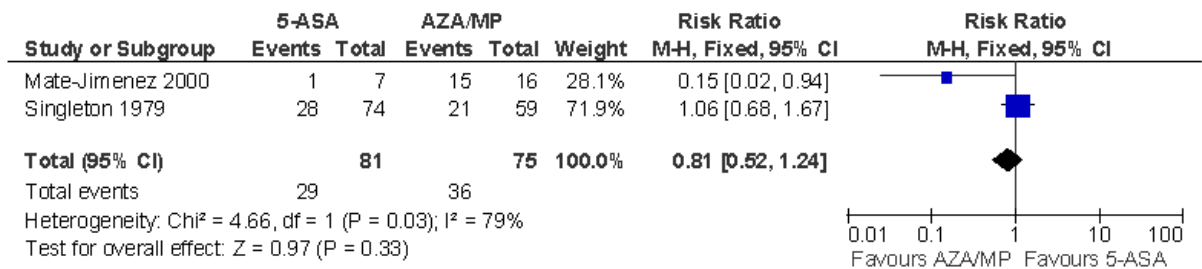
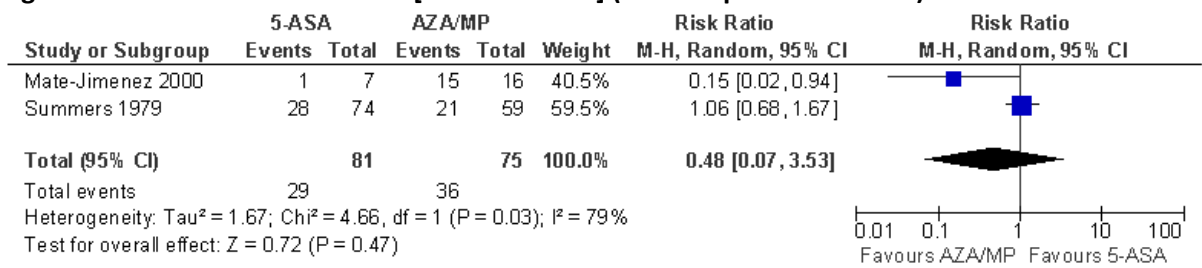


Figure 42: Induction of remission [random effect] (follow-up 16 – 30 weeks)



## 1.2.9 Azathioprine/mercaptopurine

### 1.2.9.1 Azathioprine/mercaptopurine versus methotrexate

Figure 43: Induction of remission (follow-up 24-36 weeks)

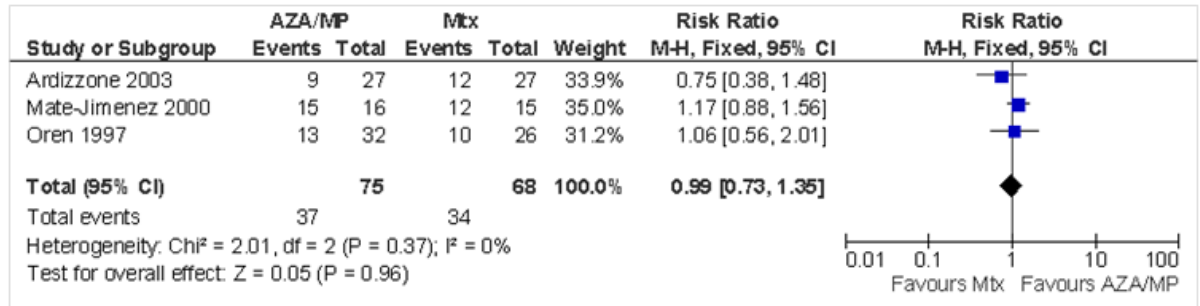
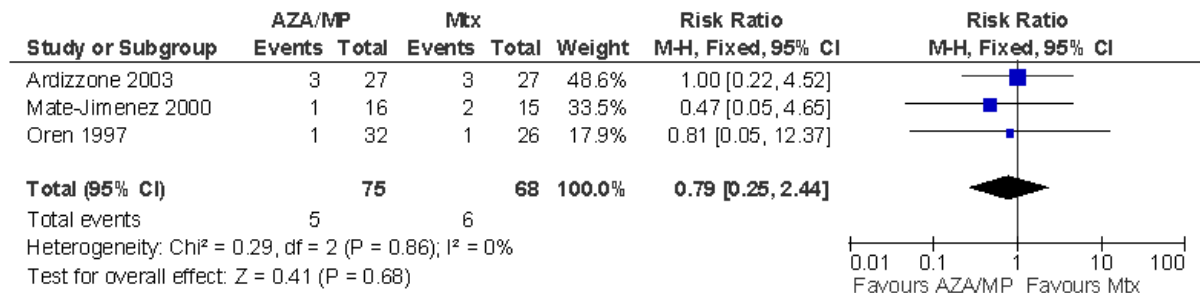


Figure 44: Withdrawal due to adverse events (follow-up 24 – 36 weeks)

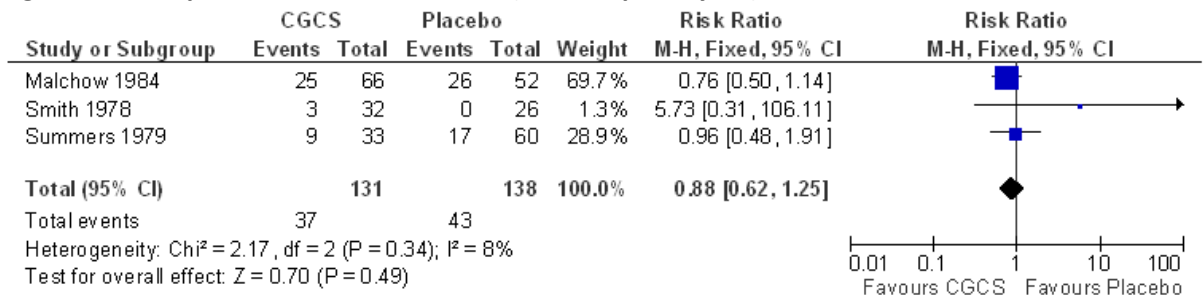


## 1.3 Maintenance

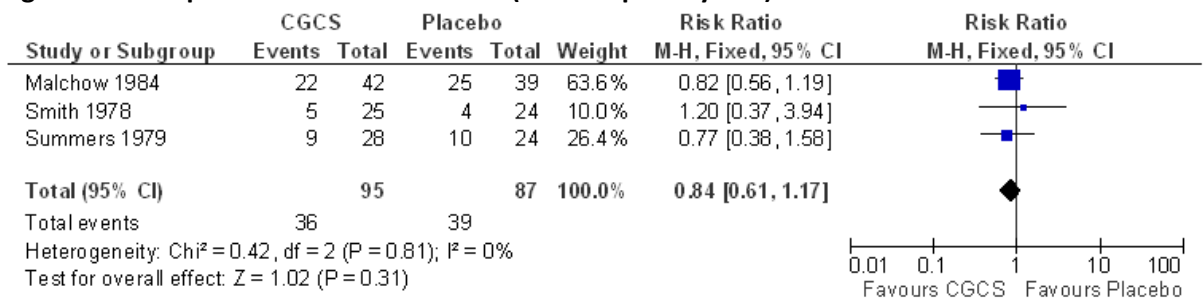
### 1.3.1 Conventional glucocorticosteroid

#### 1.3.1.1 Conventional glucocorticosteroid versus placebo

**Figure 45: Relapse or failure of remission (follow-up one year)**



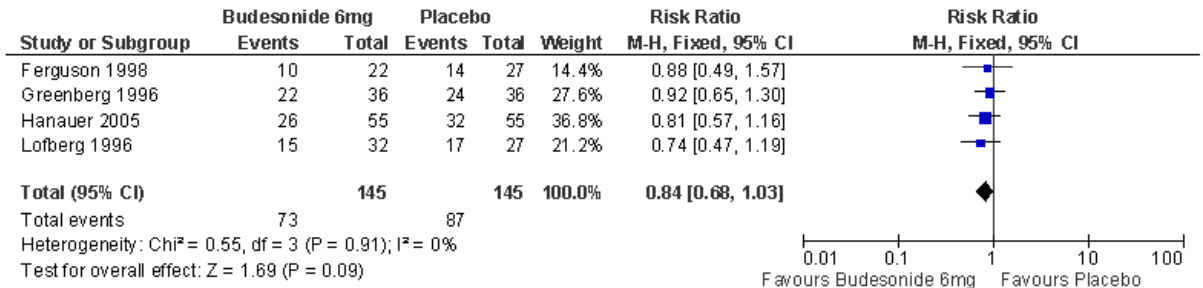
**Figure 46: Relapse or failure of remission (follow-up two years)**



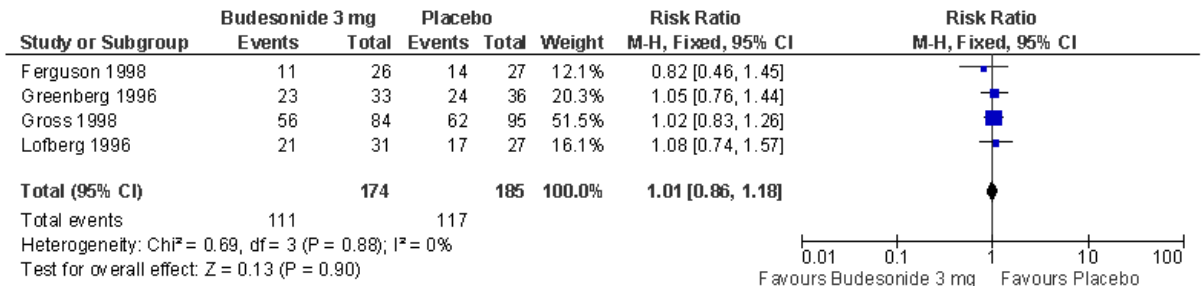
### 1.3.2 Budesonide

#### 1.3.2.1 Budesonide versus placebo

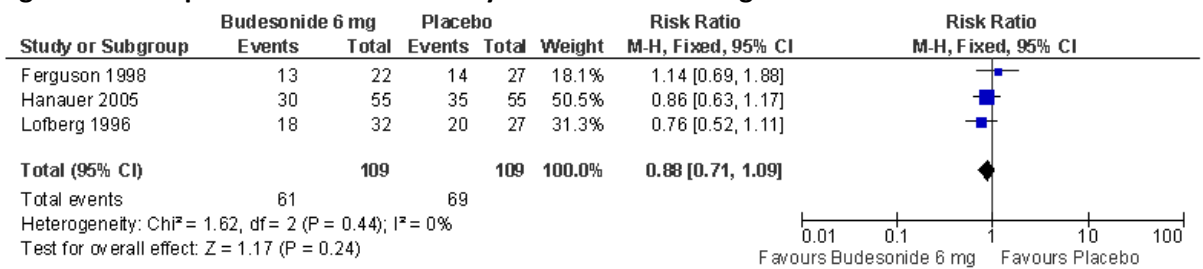
**Figure 47: Relapse at one year [fixed effect]; budesonide 6 mg vs. placebo**



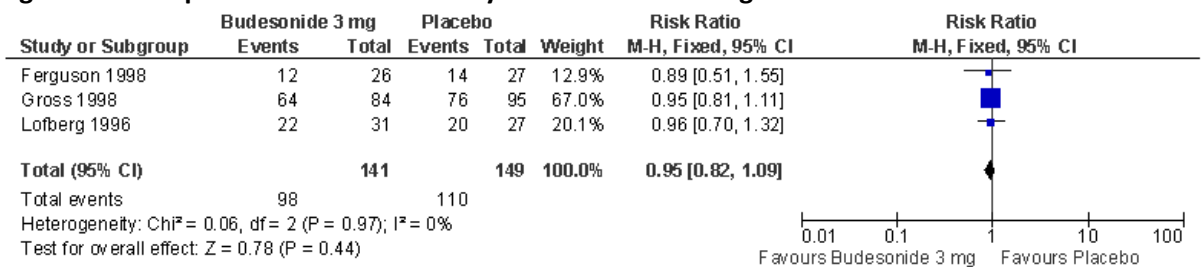
**Figure 48: Relapse at one year budesonide 3 mg vs. placebo**



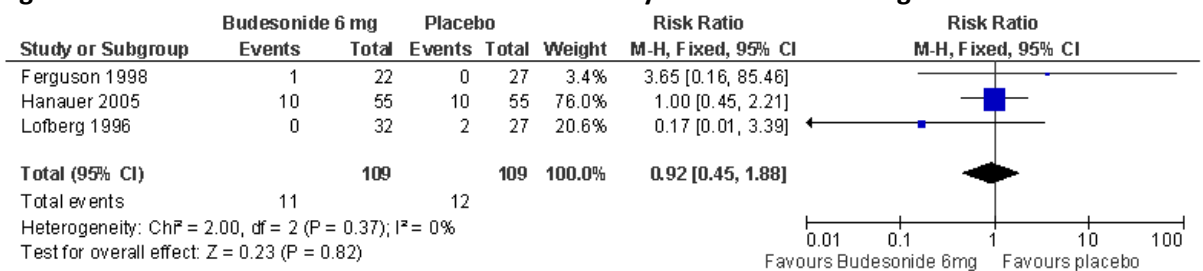
**Figure 49: Relapse + withdrawal at one year budesonide 6 mg**



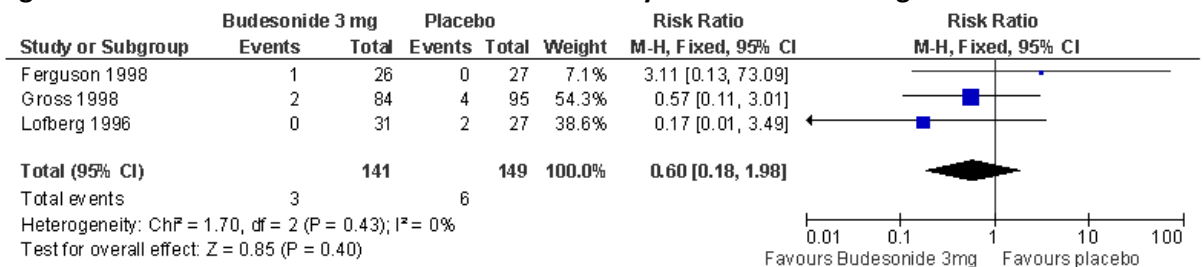
**Figure 50: Relapse + withdrawal at one year budesonide 3 mg**



**Figure 51: Withdrawal due to adverse events at one year budesonide 6 mg**



**Figure 52: Withdrawal due to adverse events at one year budesonide 3 mg**

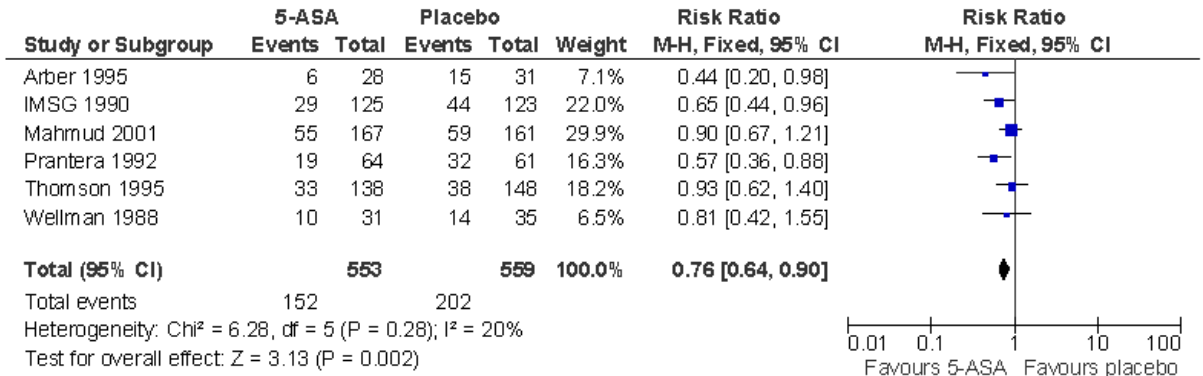




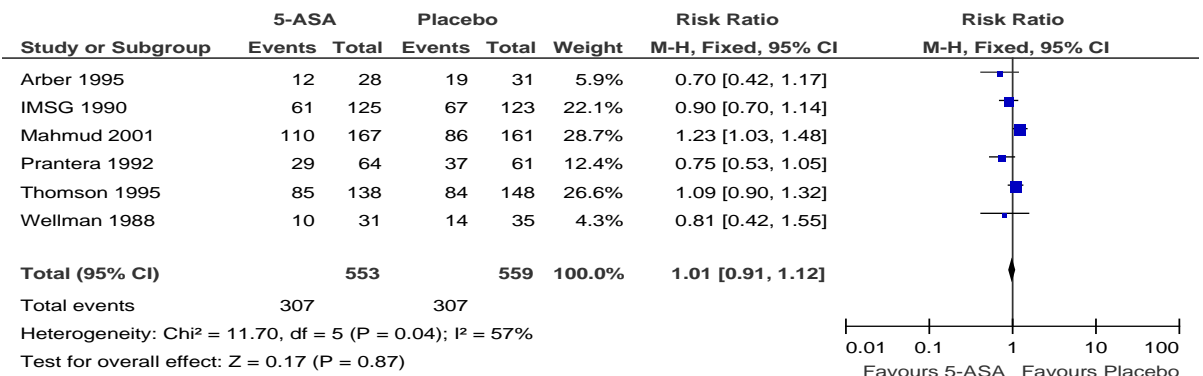
### 1.3.3 5-aminosalicylate maintenance

#### 1.3.3.1 5-aminosalicylate versus placebo

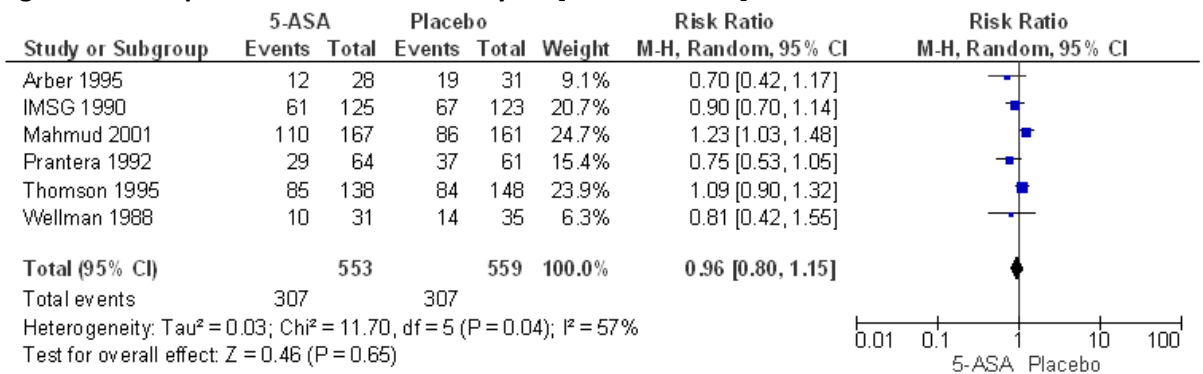
**Figure 53: Relapse at one year [fixed effect]**



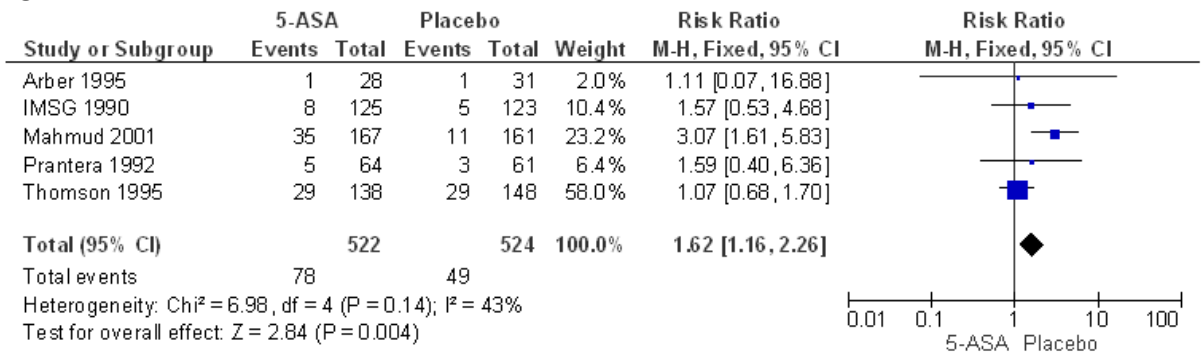
**Figure 54: Relapse + withdrawal at one year [fixed effect]**



**Figure 55: Relapse + withdrawals at one year [random effect]**



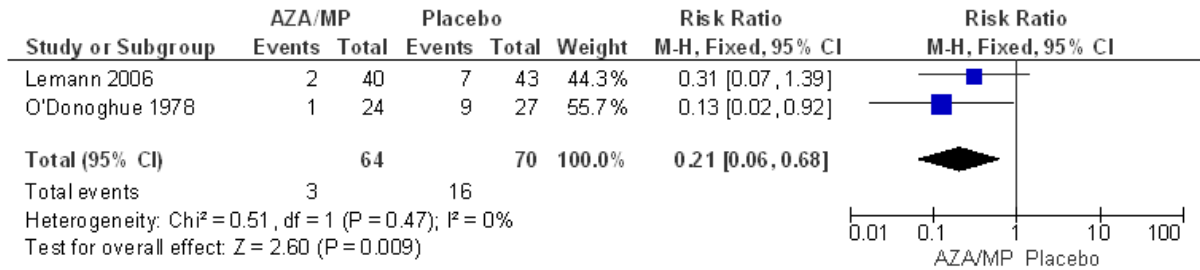
**Figure 56: Withdrawals due to adverse events at 12 months**



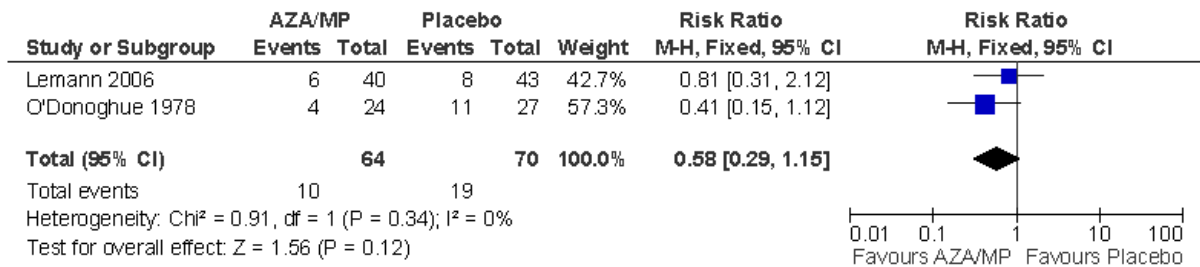
### 1.3.4 Azathioprine/mercaptopurine

#### 1.3.4.1 Azathioprine versus placebo

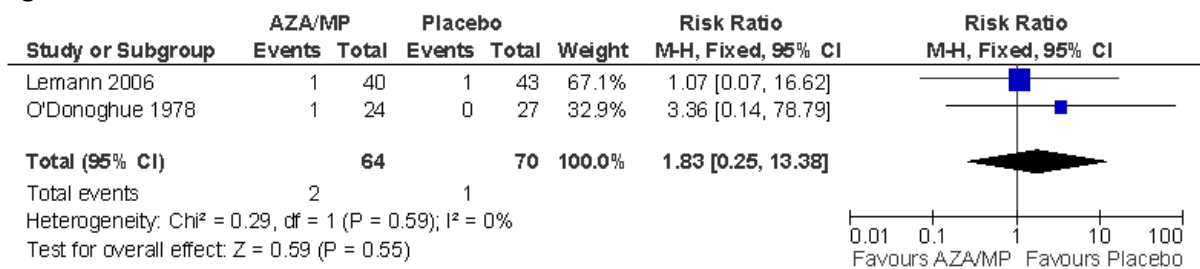
**Figure 57: Relapses at 12 months**



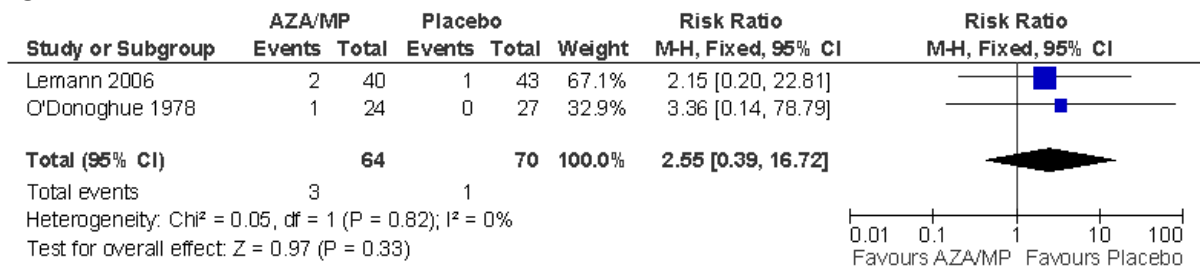
**Figure 58: Relapses + withdrawals at 12 months**



**Figure 59: Withdrawal due to adverse events at 12 months**



**Figure 60: Adverse events at 12 months**



## 1.4 Maintaining remission after surgery

### 1.4.1

#### 1.4.1.1

Please note that evidence on treatments for post-surgical maintenance of remission in Crohn's disease was reviewed in 2019. The updated evidence review and full current recommendations can be found on the NICE website.

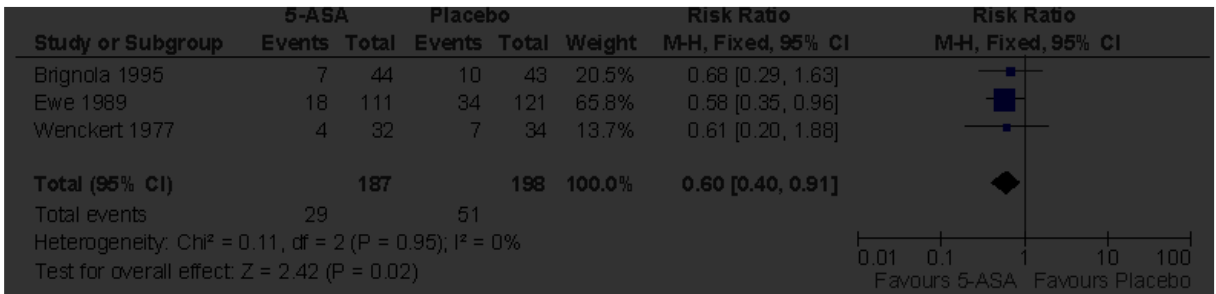


Figure 62: Clinical relapse + all withdrawals at one year

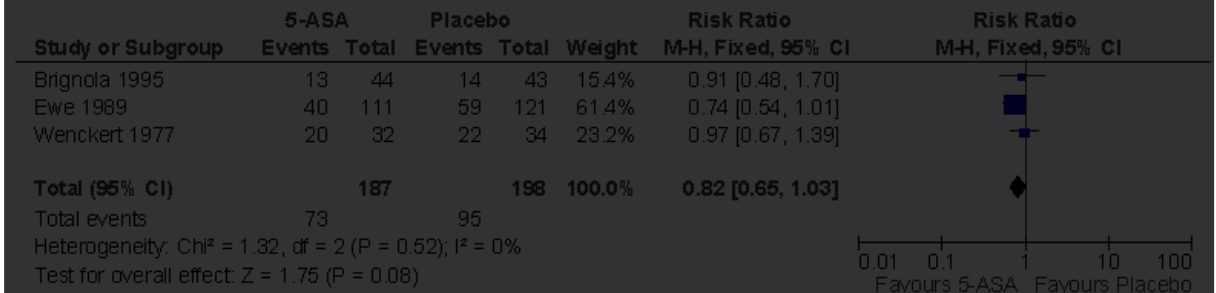
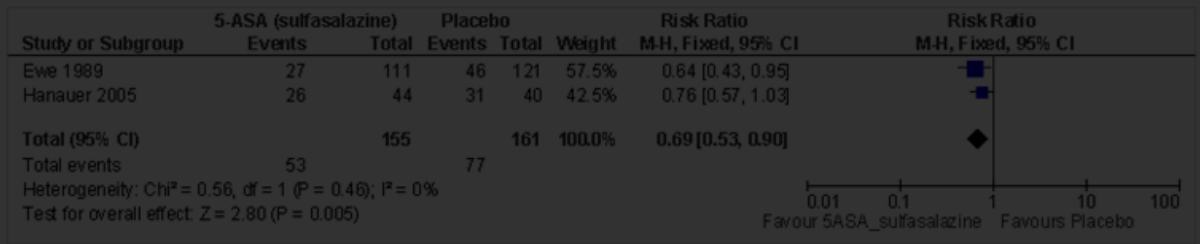


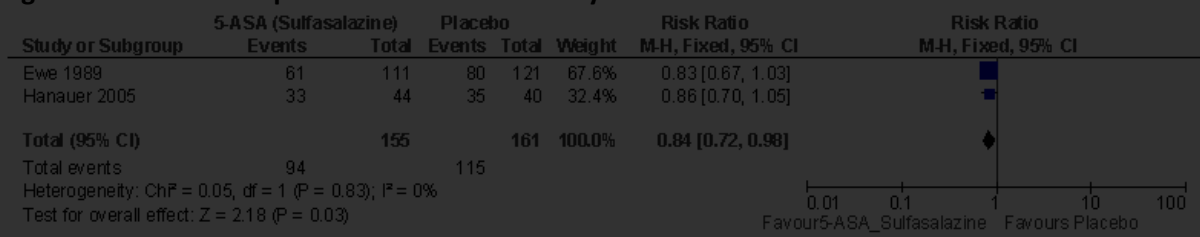
Figure 63: Clinical relapse at 18 months



**Figure 64: Clinical relapse at two years**

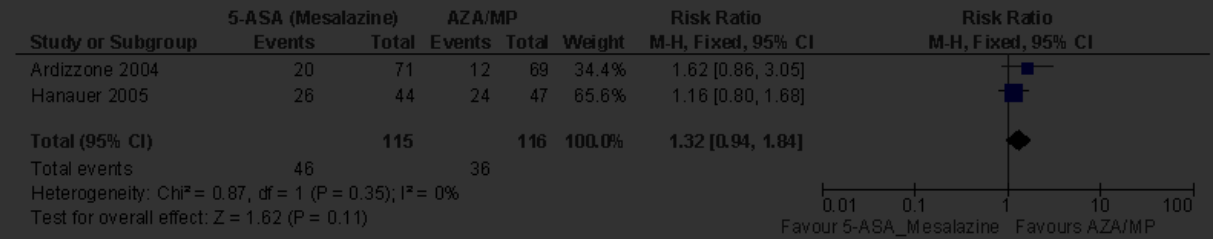


**Figure 65: Clinical relapse + withdrawals at two years**



**1.4.2 5-aminosalicylates versus azathioprine**

**Figure 66: Relapse at 24 months**



**Figure 67: Relapse + withdrawal at 24 months**



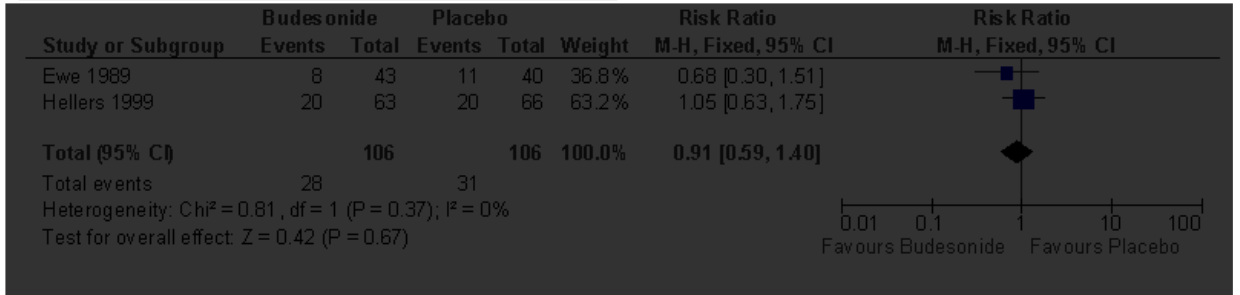
**Figure 68: Withdrawal due to adverse events at 24 months**



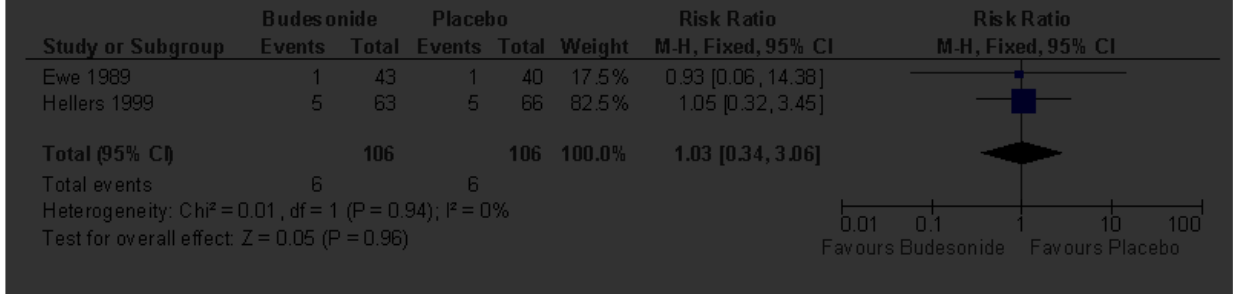
**1.4.3 Budesonide**

**1.4.3.1 Budesonide versus placebo**

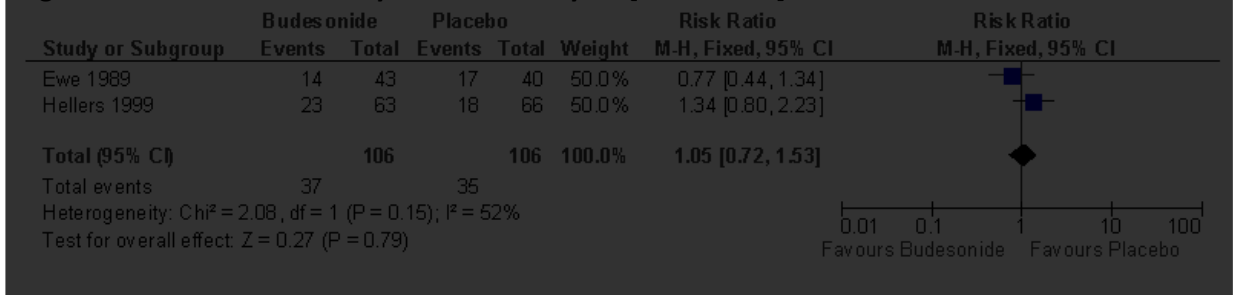
**Figure 69: Recurrence based on CDAl at one year**



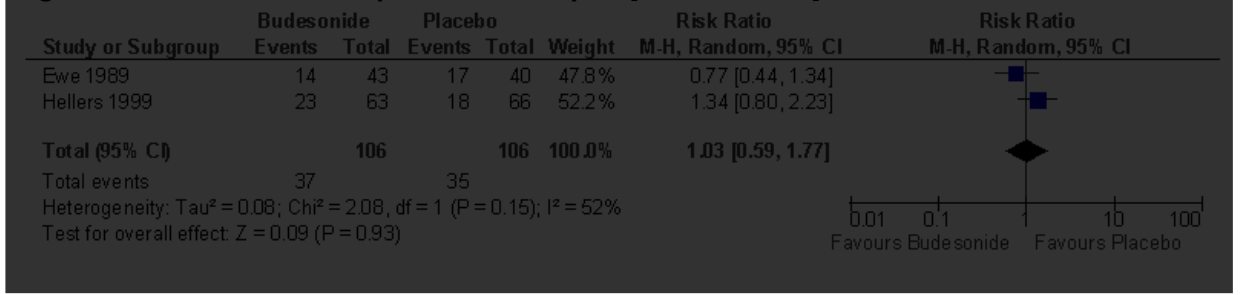
**Figure 70: Withdrawal due to adverse events at one year**



**Figure 71: Withdrawal for any reason at one year [fixed effect]**



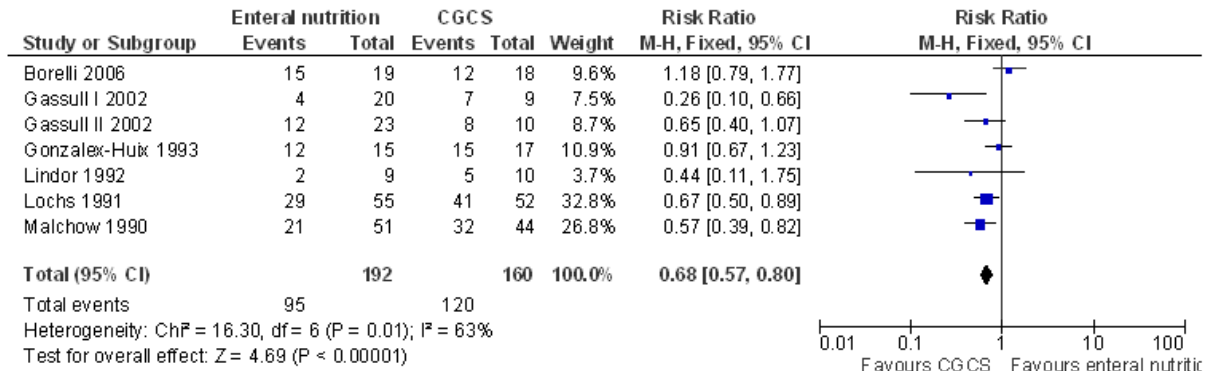
**Figure 72: Withdrawal for any reason at one year [random effect]**



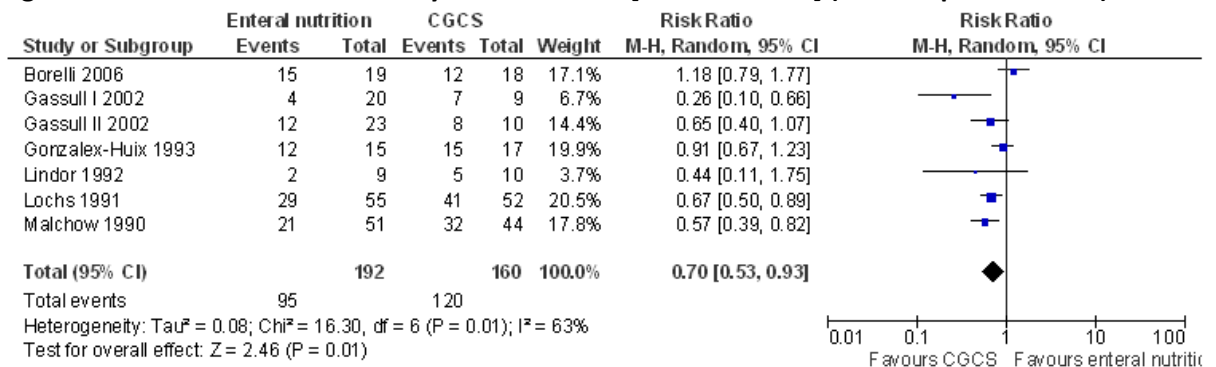
## 1.5 Enteral nutrition - induction of remission

### 1.5.1 Enteral nutrition versus conventional glucocorticosteroid

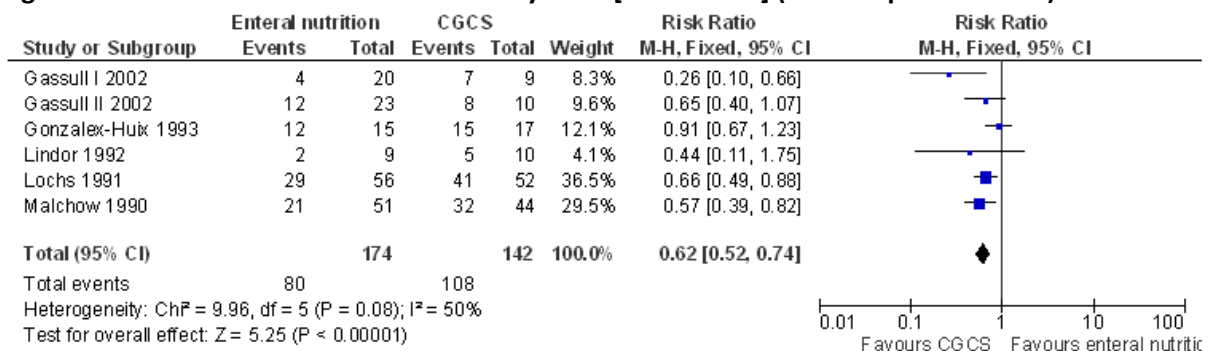
**Figure 73: Induction of remission by CDAI or PCDAI [fixed effect] (follow-up 4-10 weeks)**



**Figure 74: Induction of remission by CDAI or PCDAI [random effect] (follow-up 4-10 weeks)**

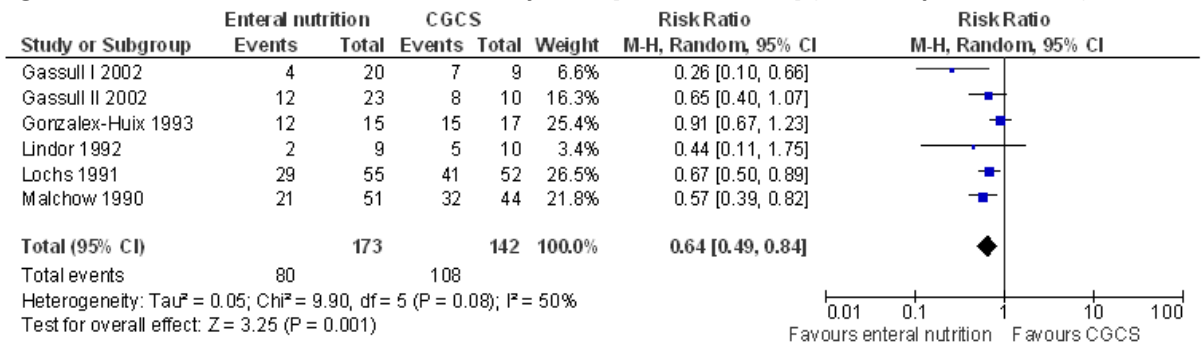


**Figure 75: Induction of remission - adults by CDAI [fixed effect] (follow-up 4-10 weeks)**





**Figure 76: Induction of remission - adults by CDAI [random effect] (follow-up 4-10 weeks)**



## 1.6 Monitoring

### 1.6.1 Monitoring for early relapse

Figure 77: Faecal calprotectin – prediction of relapse

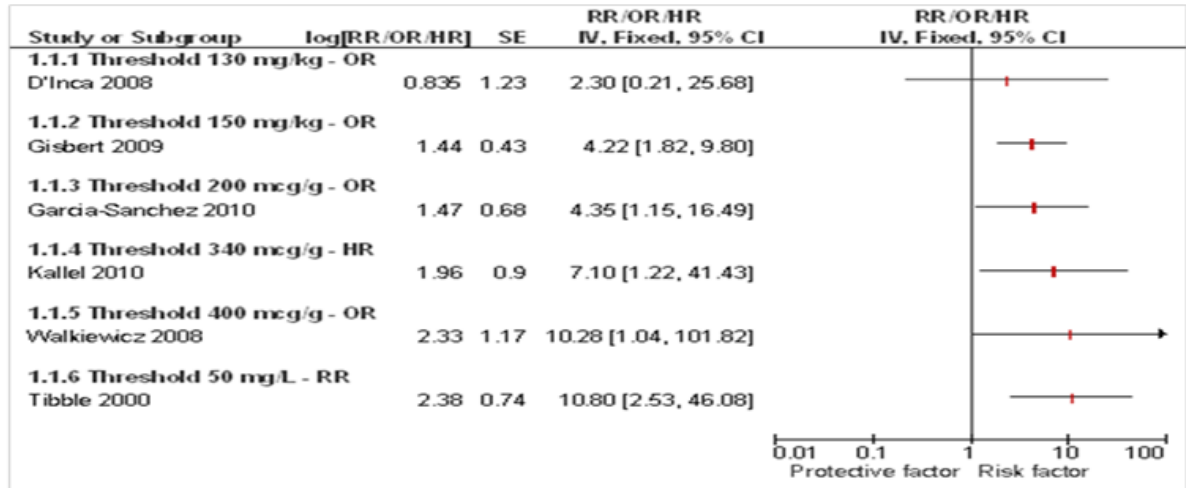


Figure 78: CRP – prediction of relapse

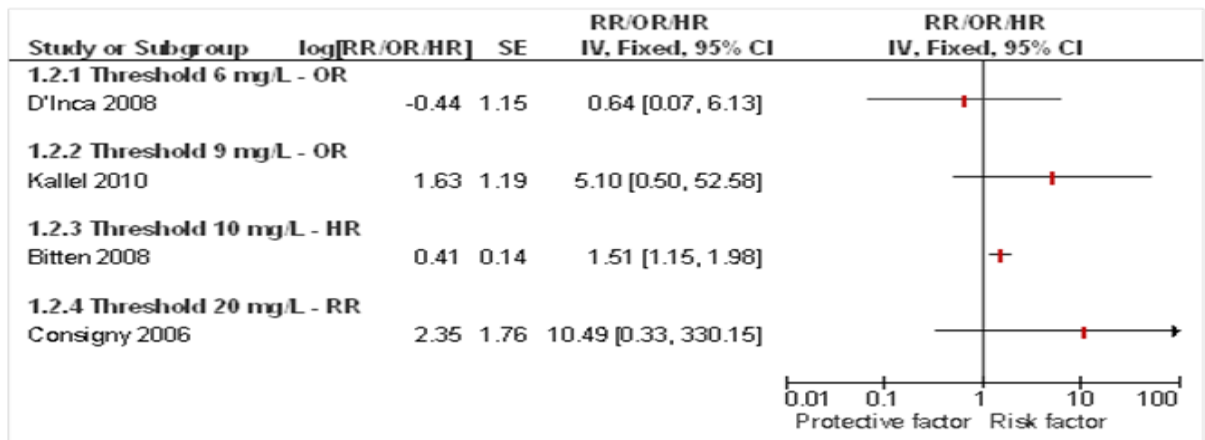


Figure 79: ESR - prediction of relapse

