

## APPENDIX 21: INTERVENTIONS FOR LONG-TERM MANAGEMENT – FOREST PLOTS

1.1	Lithium .....	3
1.1.1	Outcomes for low dose of lithium compared with standard dose .....	3
1.1.2	Outcomes for lithium every other day compared with lithium daily.....	4
1.1.3	Number of participants who relapsed (mania) .....	4
1.1.4	Number of participants who relapsed (depression) .....	4
1.1.5	Number of participants discontinuing (for any reason) .....	4
1.2	Outcomes for lithium compared with placebo .....	5
1.2.1	Number of participants who relapsed (any type).....	5
1.2.2	Outcomes for lithium compared with carbamazepine.....	10
1.2.3	Outcomes for lithium compared with lamotrigine.....	12
1.2.4	Outcomes for lithium compared with valproate.....	13
1.2.5	Outcomes for olanzapine compared with lithium.....	15
1.2.6	Outcomes for valproate compared with lithium and valproate combination.....	17
1.2.7	Outcomes for lithium compared with lithium and valproate combination.....	18
1.3	Antipsychotics .....	20
1.3.1	Outcomes for aripiprazole compared with placebo (all participants taking lamotrigine).....	20
1.3.2	Outcomes for aripiprazole compared with placebo (all participants taking lithium or valproate) .....	21
1.3.3	Outcomes for olanzapine compared with placebo (all participants taking lithium or valproate) .....	23
1.3.4	Outcomes for olanzapine compared with placebo .....	24
1.3.5	Outcomes for paliperidone compared with placebo .....	25
1.3.6	Outcomes for quetiapine compared with placebo .....	26
1.3.7	Outcomes for quetiapine compared with placebo (all participants were taking lithium or valproate).....	27
1.3.8	Outcomes for quetiapine compared with valproate.....	29
1.3.9	Outcomes for risperidone long-acting injectable compared with placebo injection.....	29
1.3.10	Outcomes for risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual).....	31
1.3.11	Outcomes for risperidone long-acting injectable and treatment as usual compared with treatment as usual alone .....	32
1.4	Anticonvulsants.....	32
1.4.1	Outcomes for oxcarbazepine compared with placebo (all participants were taking lithium) .....	32

1.4.2	Outcomes for gabapentin compared with placebo (all participants were taking lithium, valproate, carbamazepine or combination).....	34
1.4.3	Outcomes for lamotrigine compared with placebo .....	34
1.4.4	Outcomes for valproate compared with placebo .....	35
1.5	Antidepressants.....	37
1.5.1	Outcomes for imipramine compared with placebo .....	37
1.5.2	Outcomes for imipramine compared with placebo (all participants were taking lithium) .....	38
1.5.3	Outcomes for imipramine and lithium combination compared with lithium.....	39
1.6	Definitions of relapse in studies of long-term management.....	41

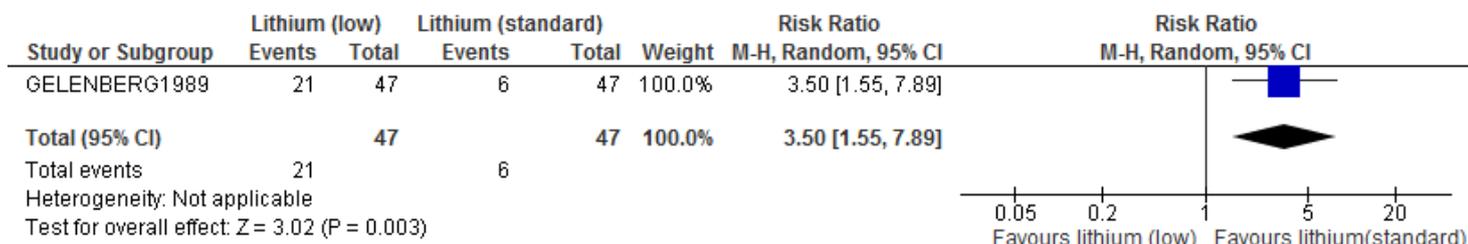
**Abbreviations**

BRMaS	Bech-Rafaelsen Mania Scale
BRMeS	Bech-Rafaelsen Melancholia Scale
CGI(-BP, -C, -S)	Clinical Global Impressions (-Bipolar, -Children, -Severity)
CI	confidence interval
DSM(-III, -IV, -TR)	<i>Diagnostic and Statistical Manual of Mental Disorders</i> (3rd edition, 4th edition, Text Revision)
ECT	electroconvulsive therapy
GAF	Global Assessment of Functioning scale
GAS	Global Assessment Scale
IV	intravariance
K	number of studies
MADRS	Montgomery Åsberg Depression Rating Scale
M-H	Mantel-Haenszel
MRS	Mania Rating Scale
NR	not reported
RR	risk ratio
SD	standard deviation
TAU	treatment as usual
YMRS	Young Mania Rating Scale

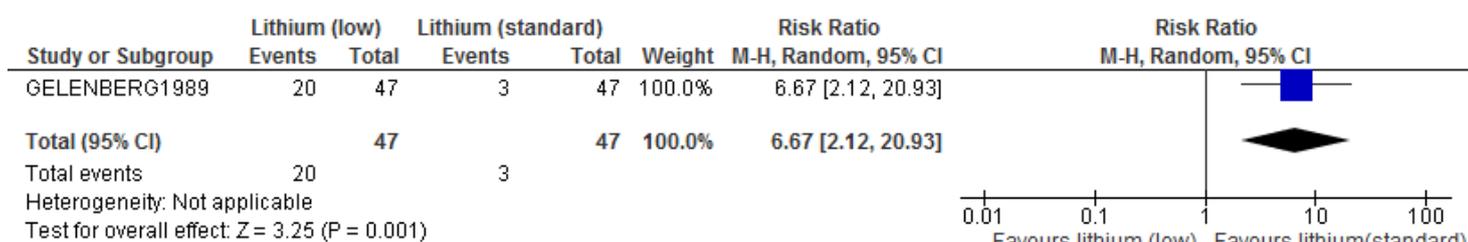
## 1.1 LITHIUM

### 1.1.1 Outcomes for low dose of lithium compared with standard dose

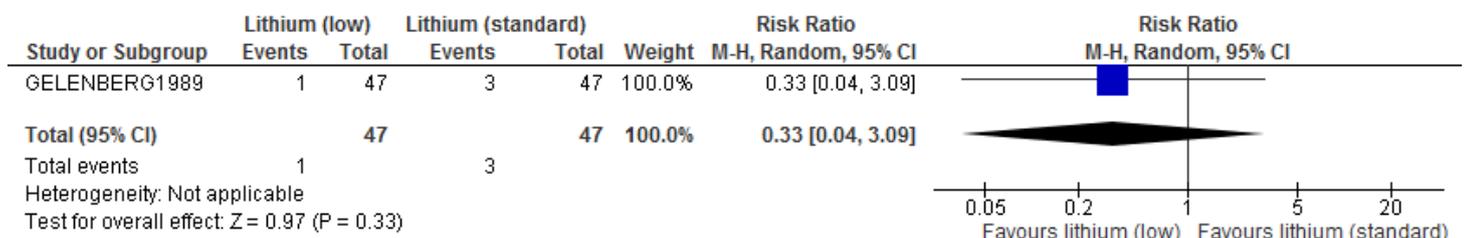
#### Number of participants who relapsed<sup>1</sup> (any type)



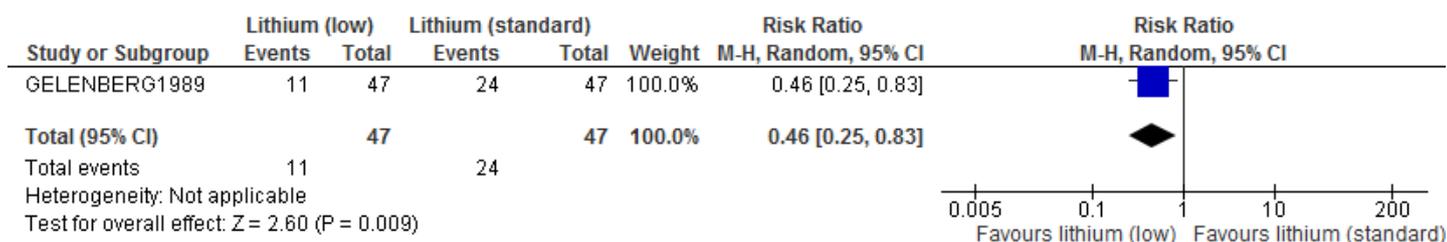
#### Number of participants who relapsed (mania)



#### Number of participants who relapsed (depression)



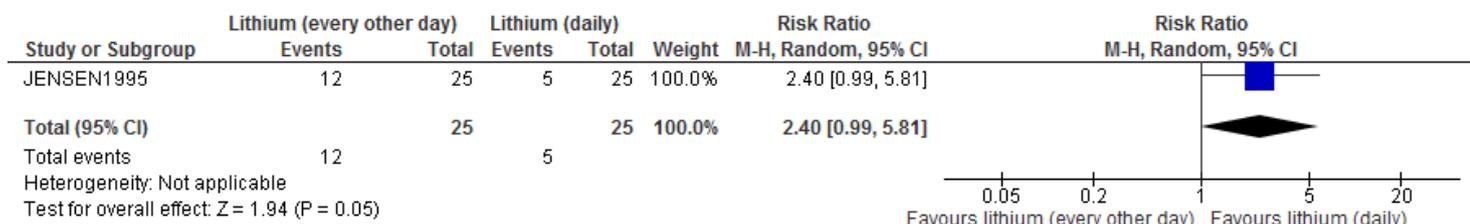
#### Number of participants discontinuing (for any reason)



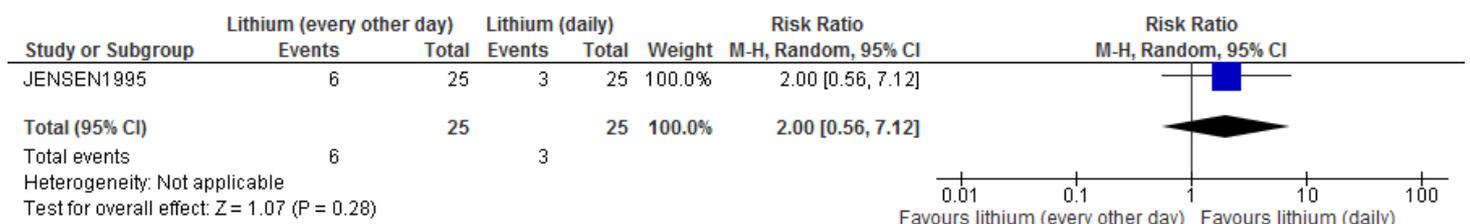
<sup>1</sup> The definition of relapse differs between studies. Please refer to Table 1.6 below for a full definition.

### 1.1.2 Outcomes for lithium every other day compared with lithium daily

#### Number of participants who relapsed (any type)



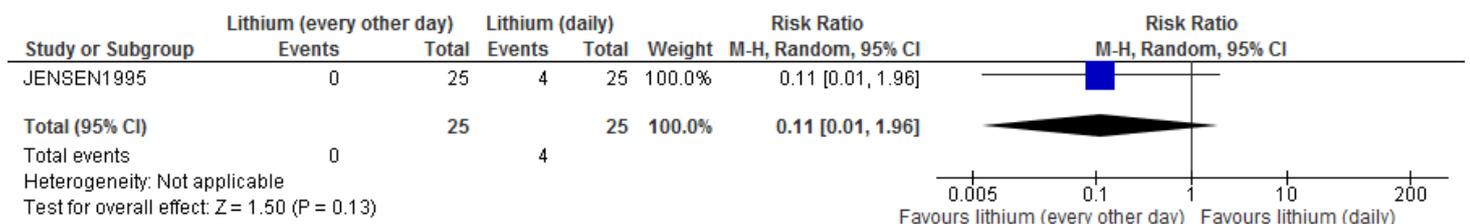
### 1.1.3 Number of participants who relapsed (mania)



### 1.1.4 Number of participants who relapsed (depression)

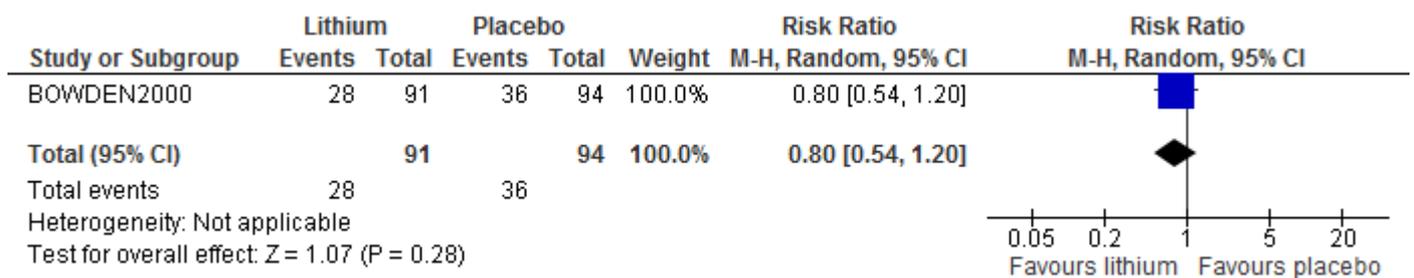
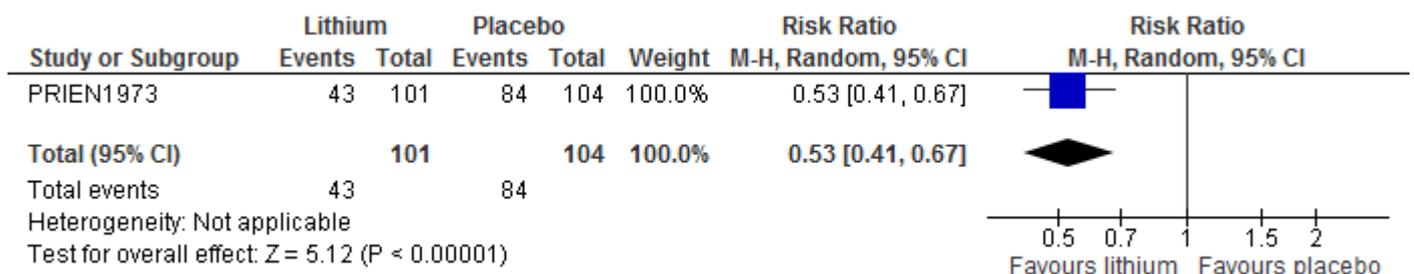
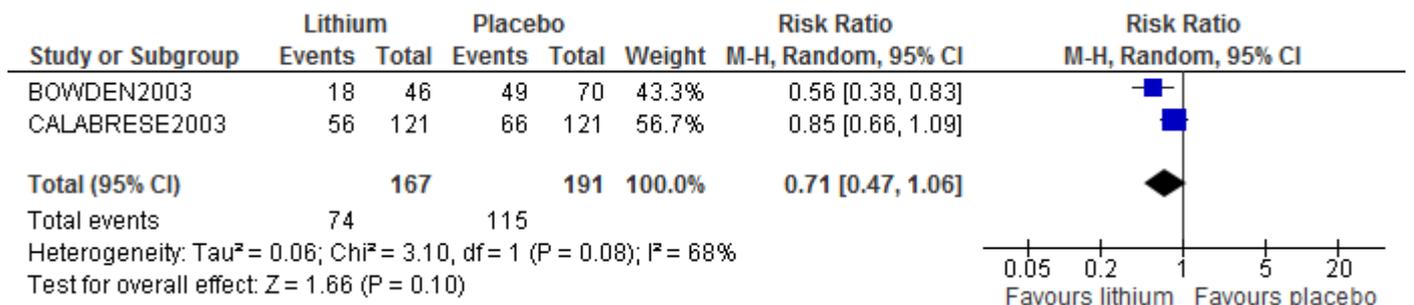
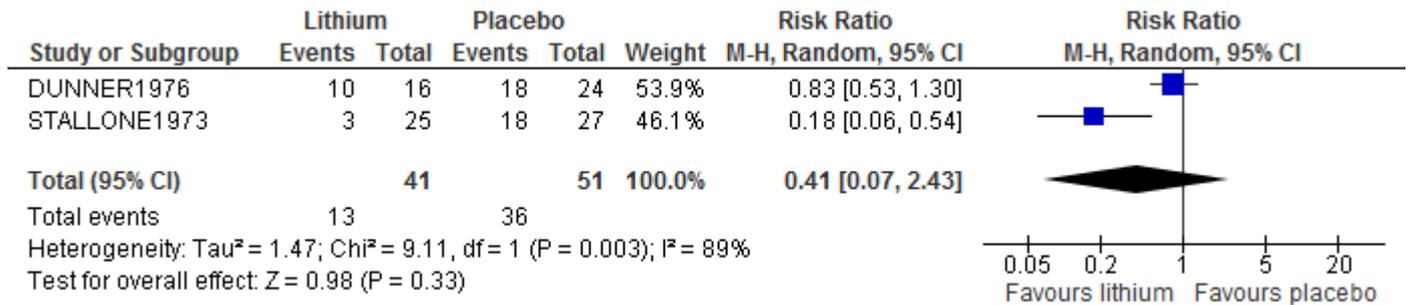


### 1.1.5 Number of participants discontinuing (for any reason)

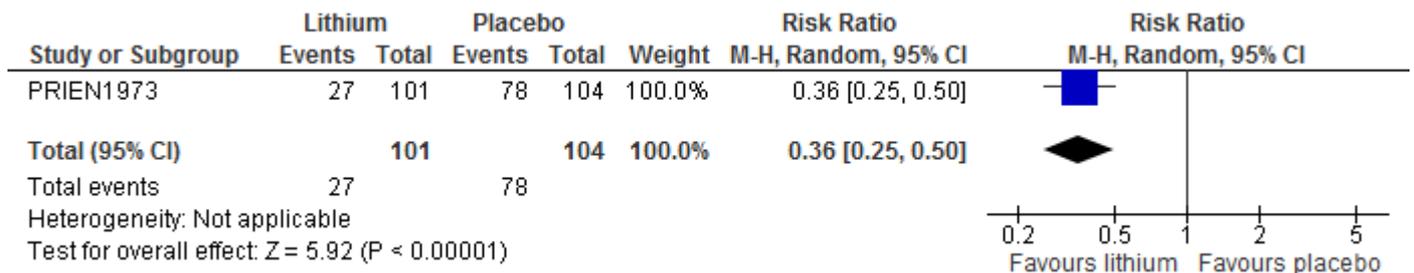
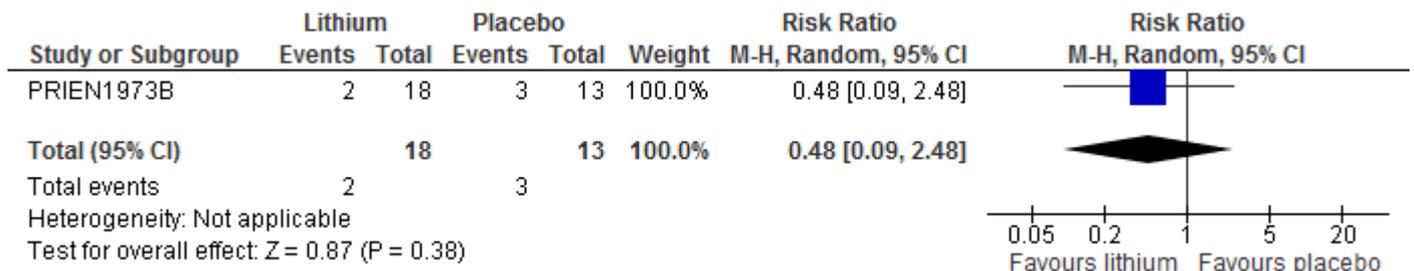
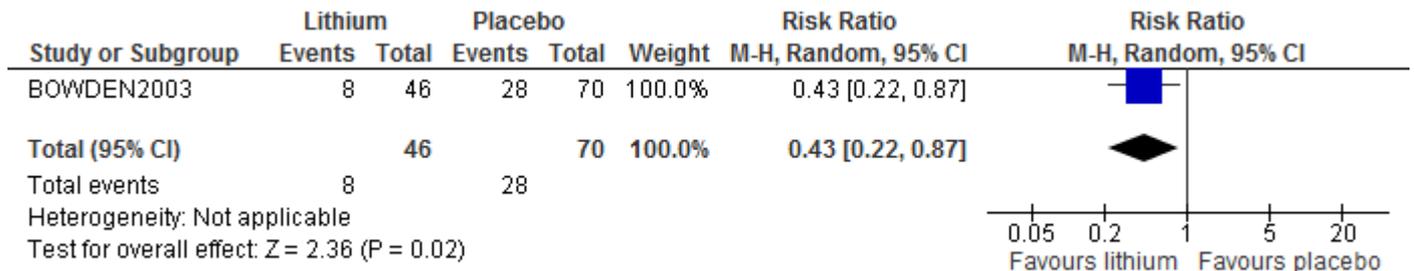
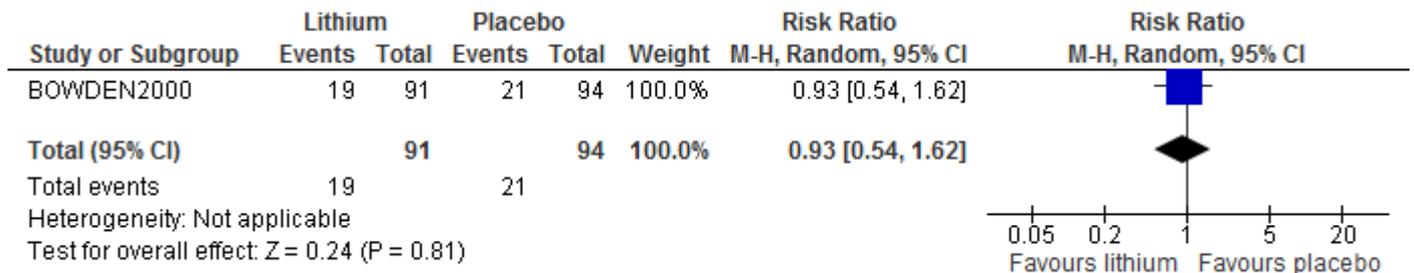


## 1.2 OUTCOMES FOR LITHIUM COMPARED WITH PLACEBO

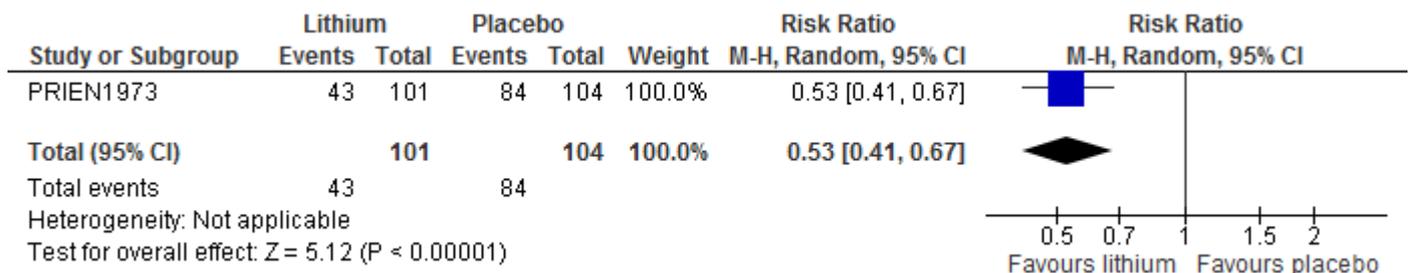
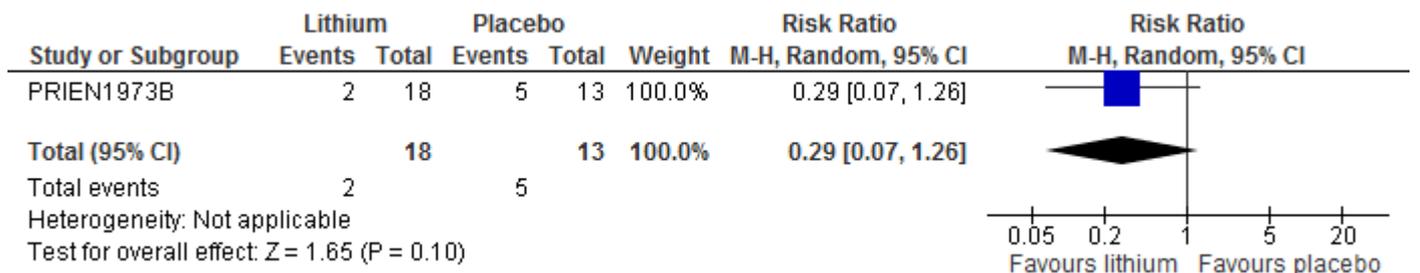
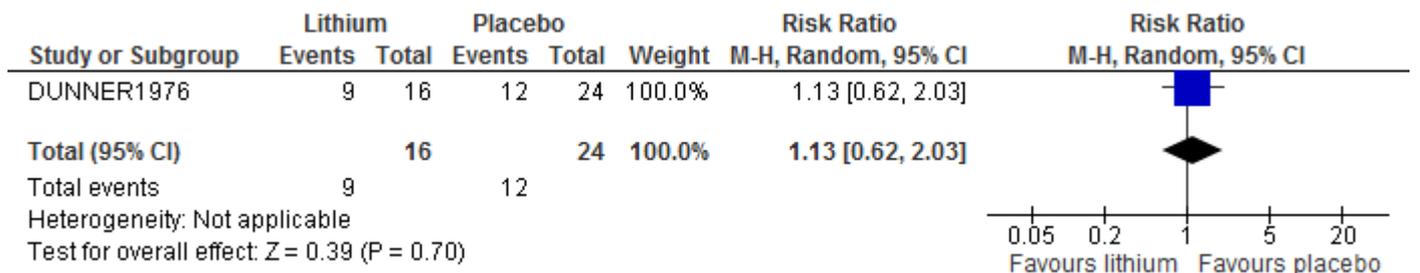
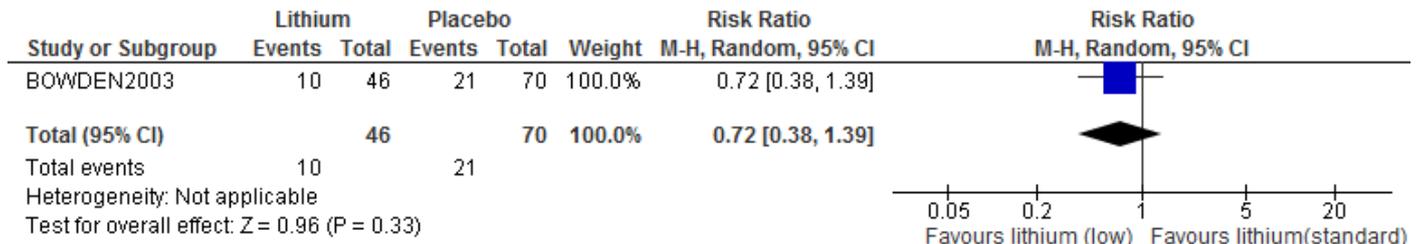
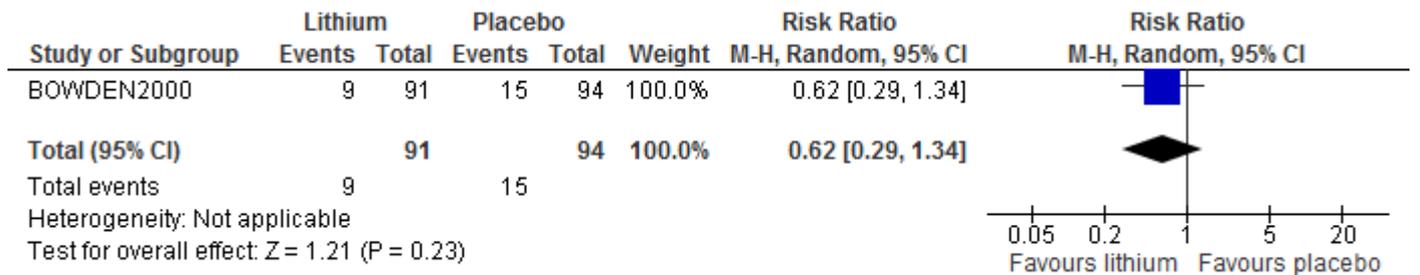
### 1.2.1 Number of participants who relapsed (any type)



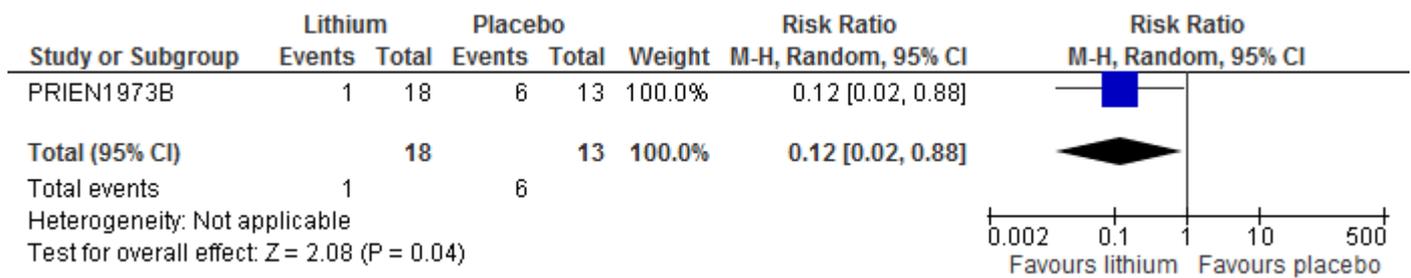
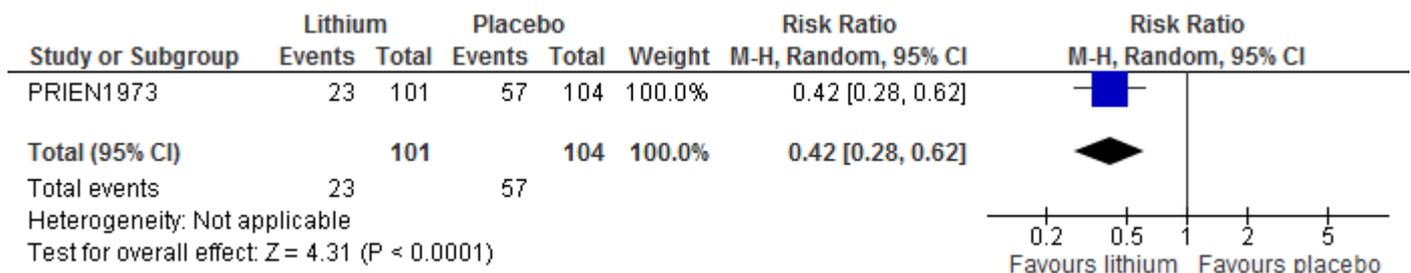
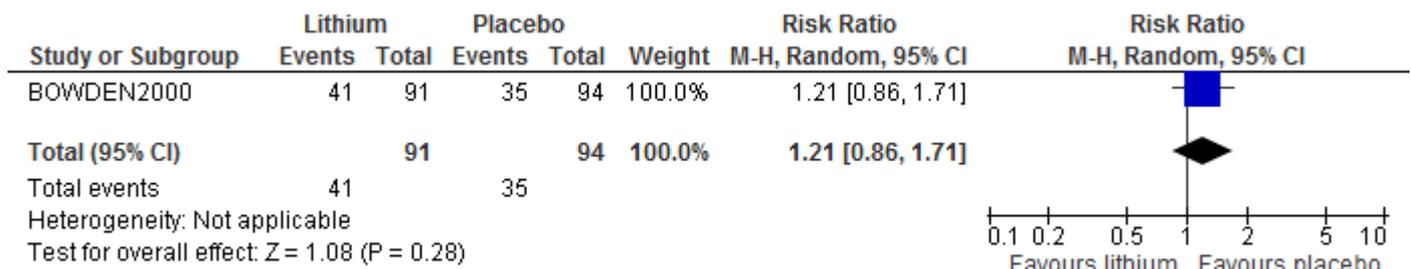
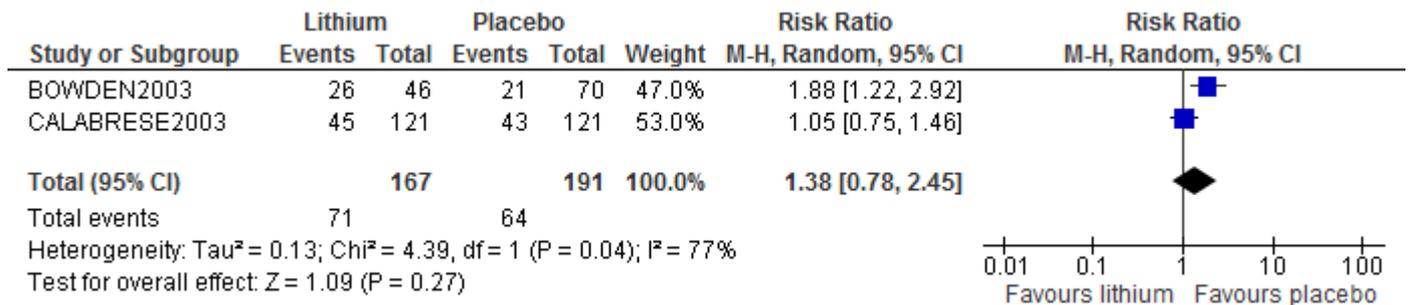
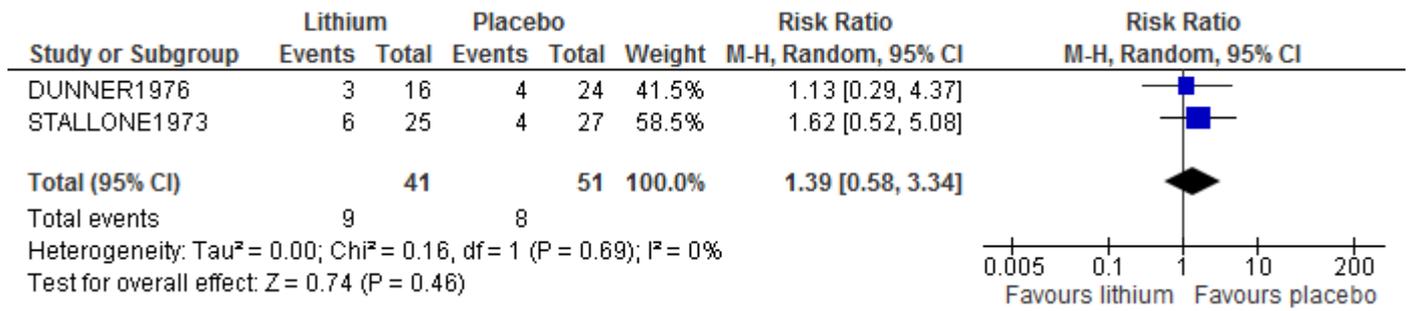
**Number of participants who relapsed (mania)**



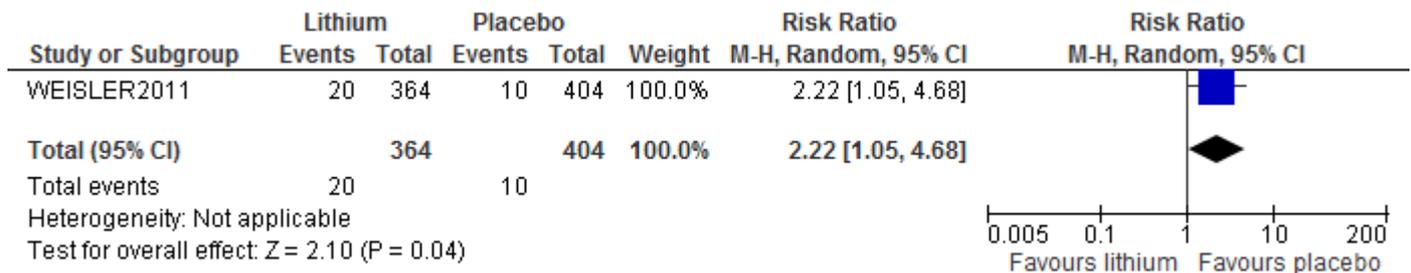
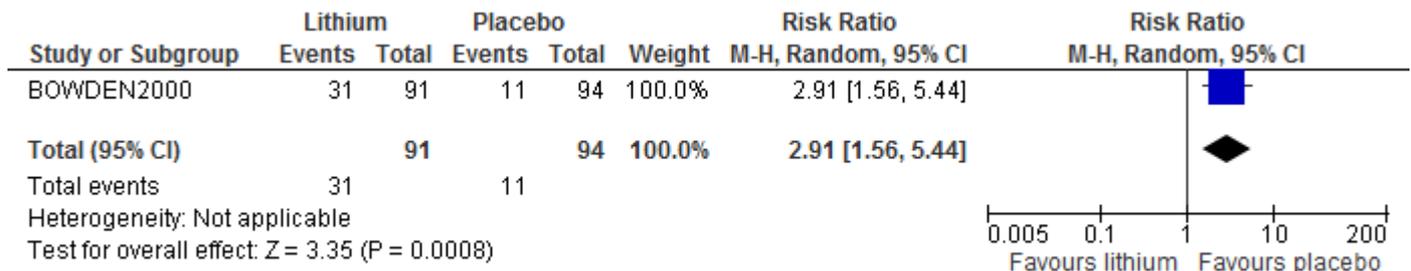
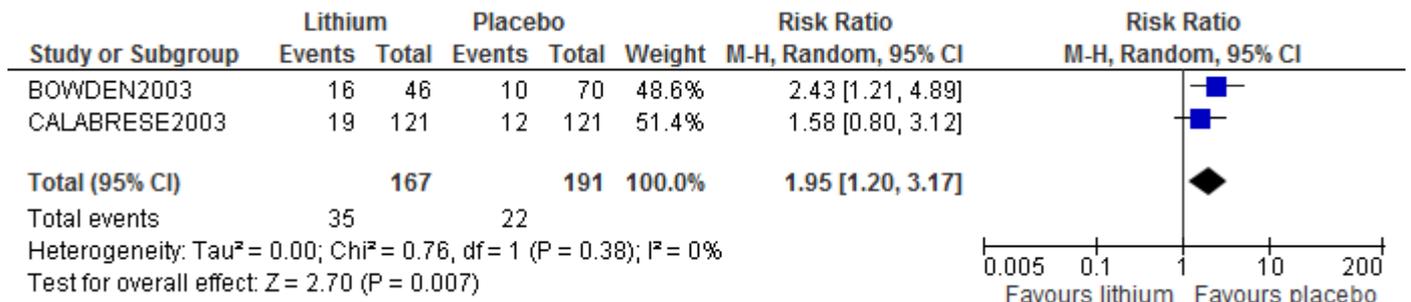
**Number of participants who relapsed (depression)**



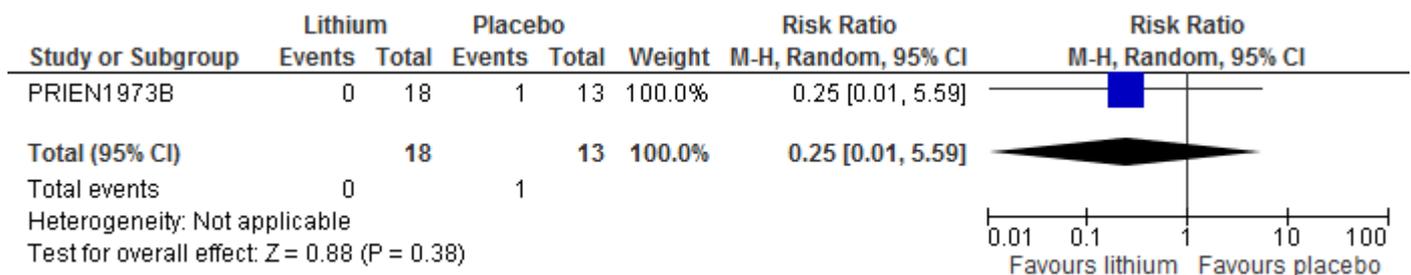
Number of participants discontinuing (for any reason)



### Number of participants discontinuing due to side effects



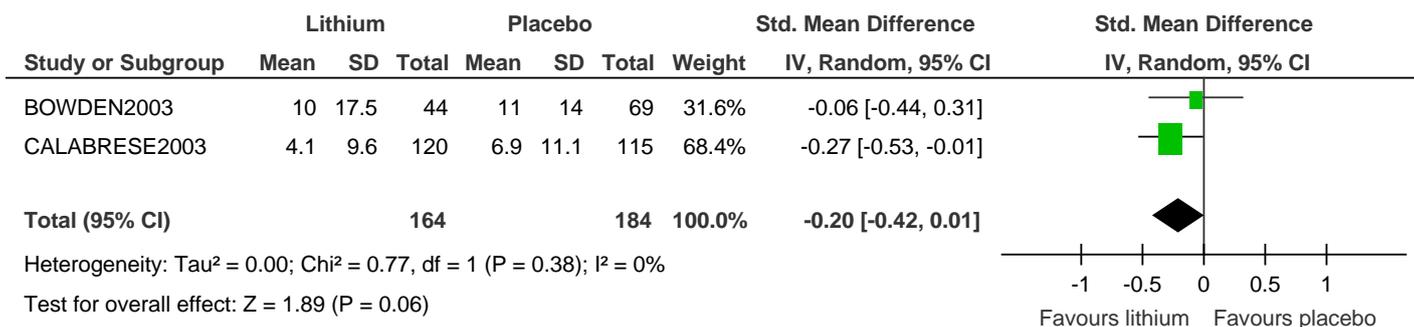
### Number of suicides



### Number of deaths

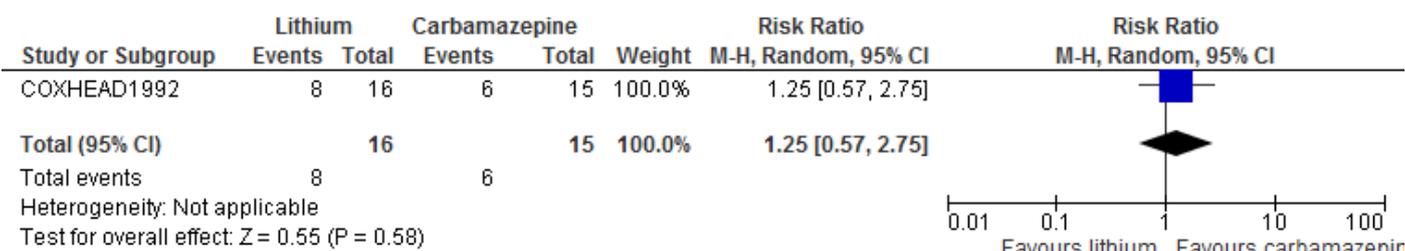
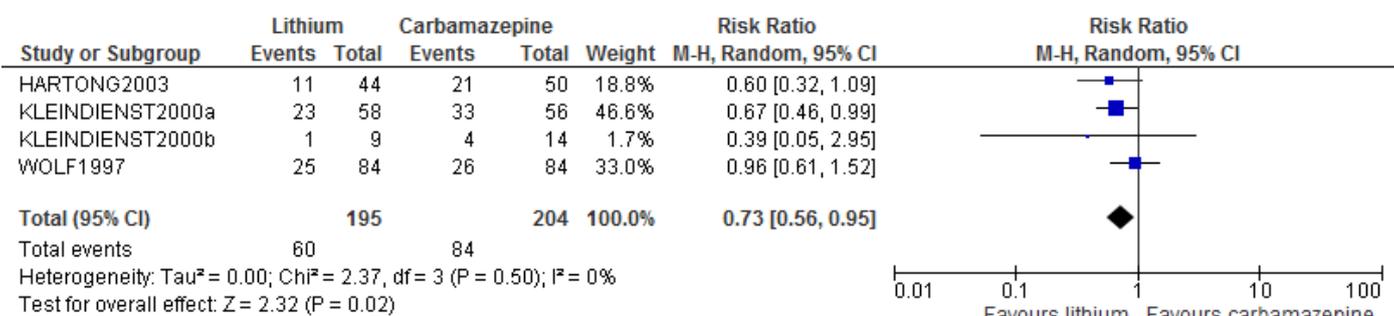


## Psychosocial functioning (Global Assessment Scale)<sup>2</sup>

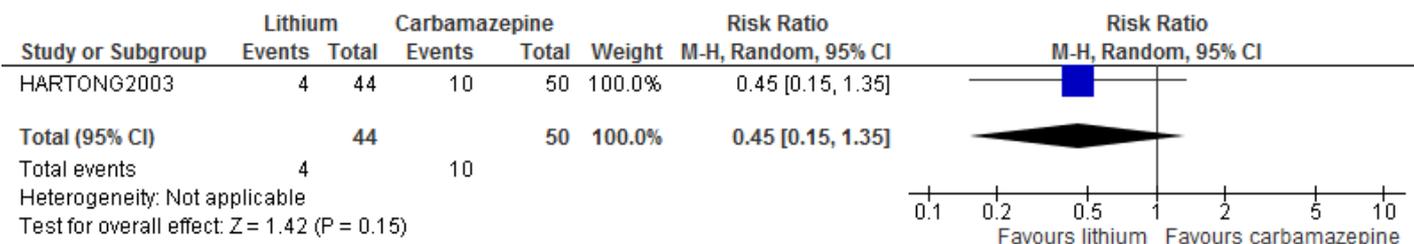


## 1.2.2 Outcomes for lithium compared with carbamazepine

### Number of participants who relapsed (any type)



### Number of participants who relapsed (mania)



<sup>2</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

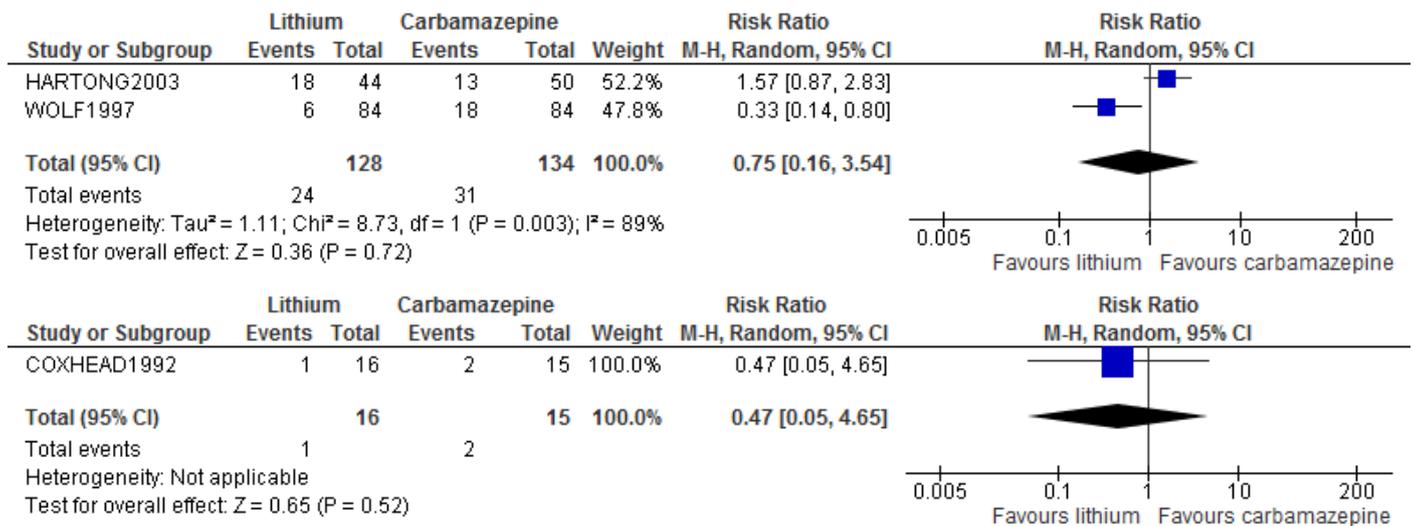
**Number of participants who relapsed (depression)**



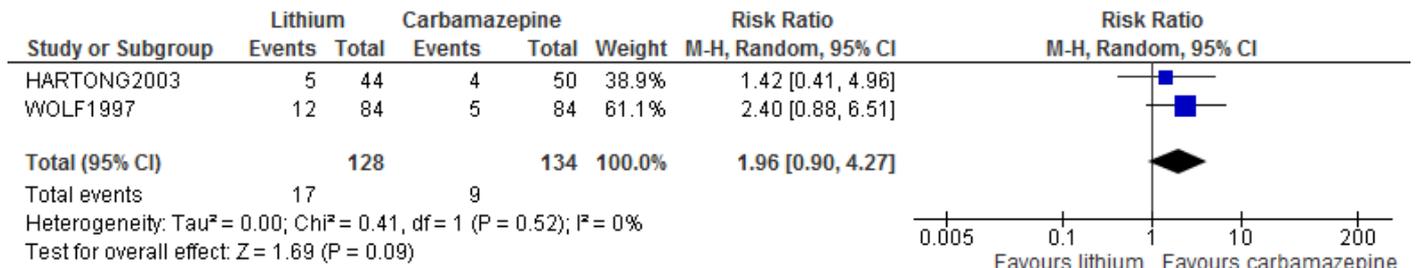
**Number of participants who were hospitalised**



**Number of participants discontinuing (for any reason)**



### Number of participants discontinuing due to side effects

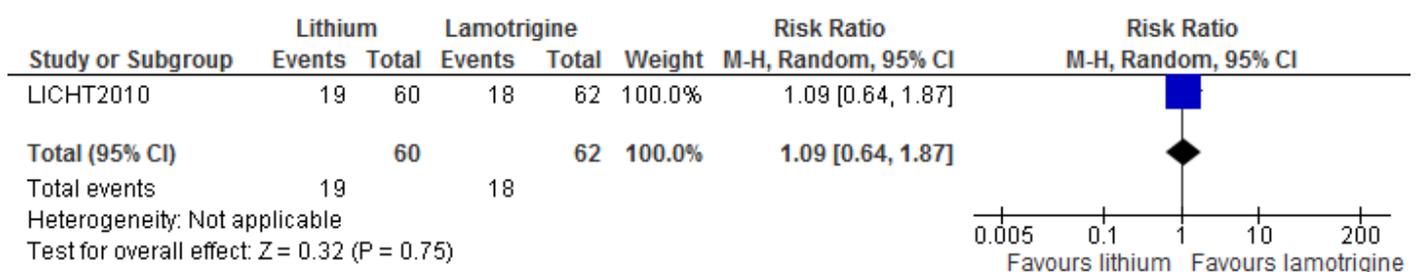


### 1.2.3 Outcomes for lithium compared with lamotrigine

#### Number of participants who relapsed (any type)

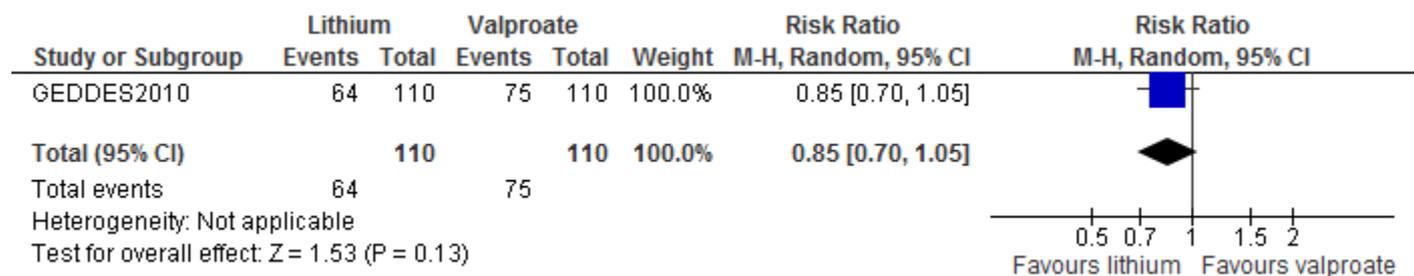


#### Number of participants discontinuing (for any reason)

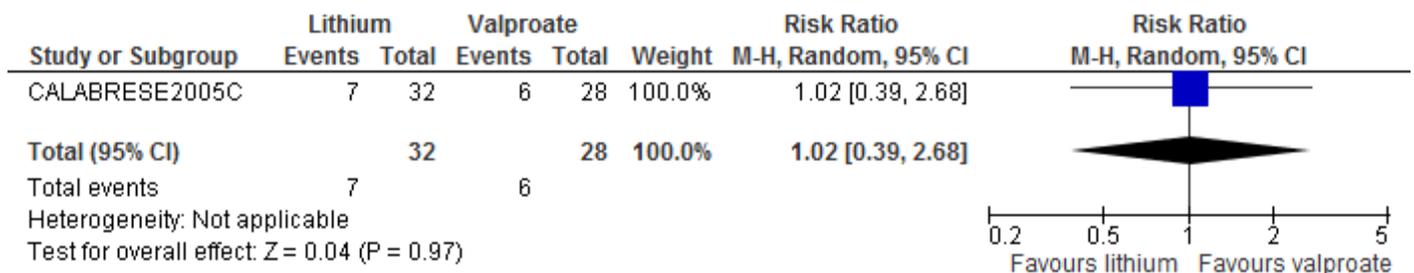
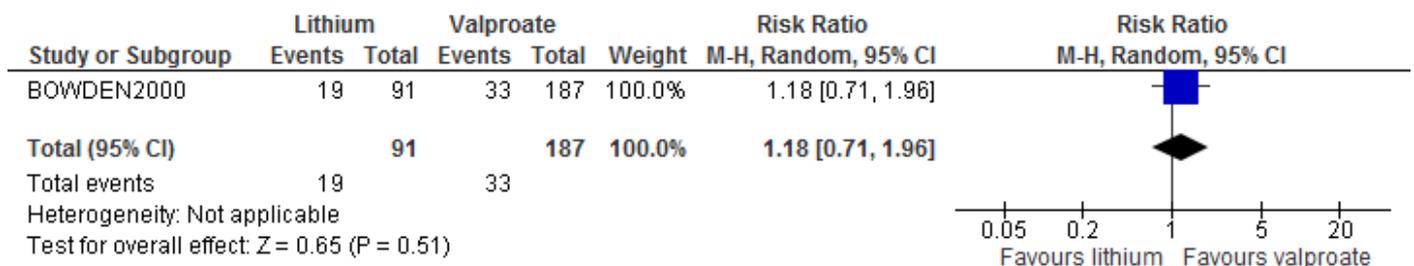


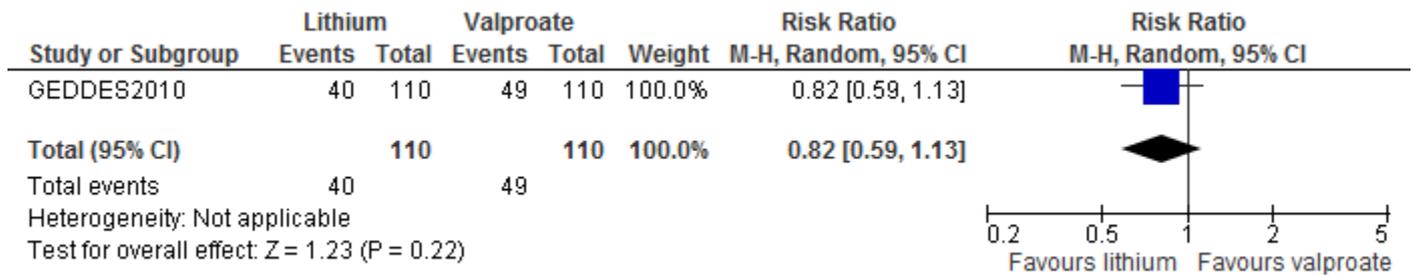
## 1.2.4 Outcomes for lithium compared with valproate

### Number of participants who relapsed (any type)

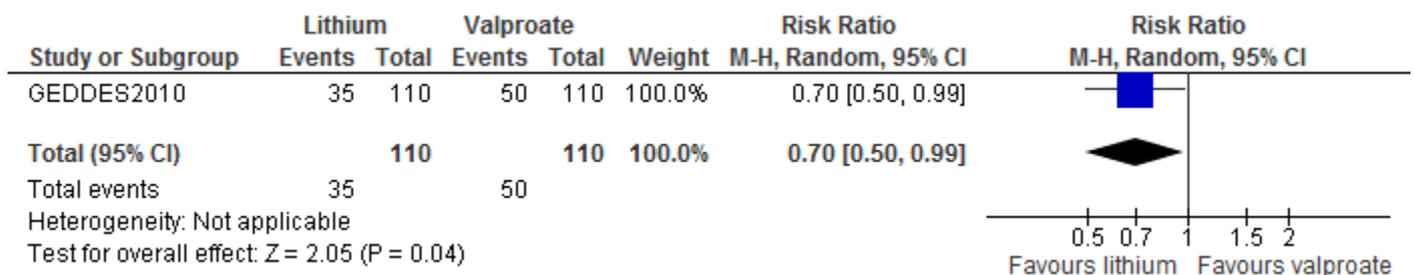
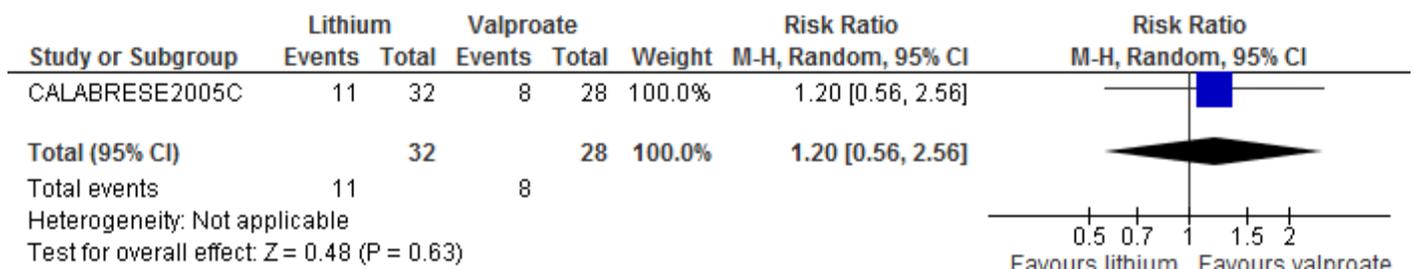
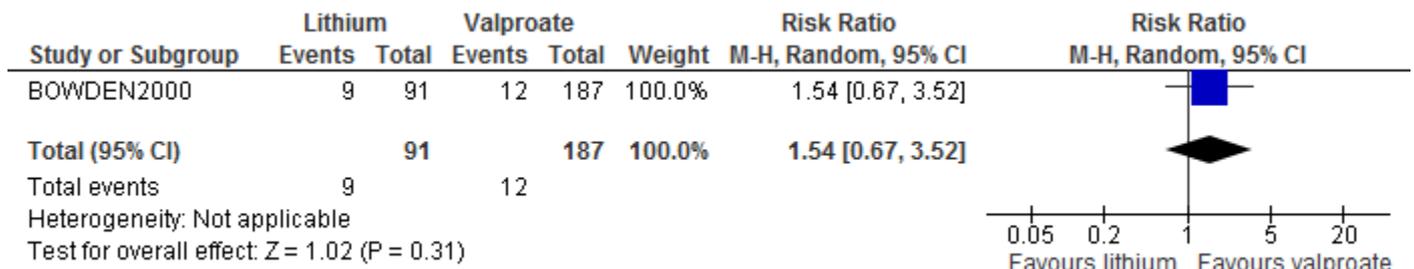


### Number of participants who relapsed (mania)

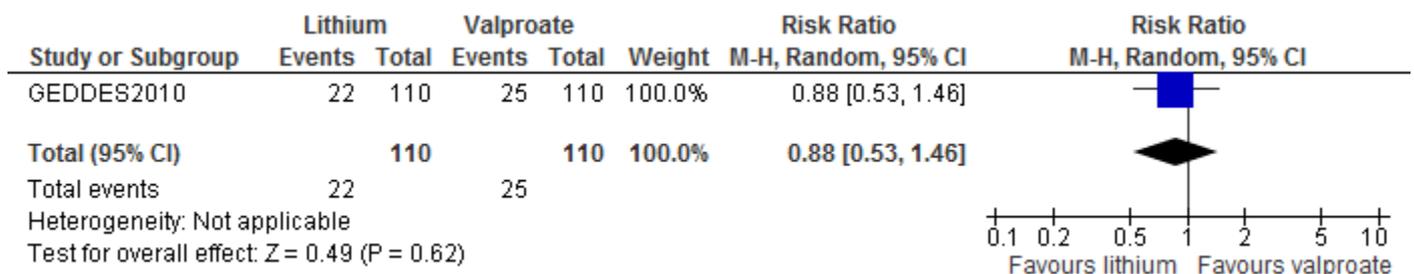




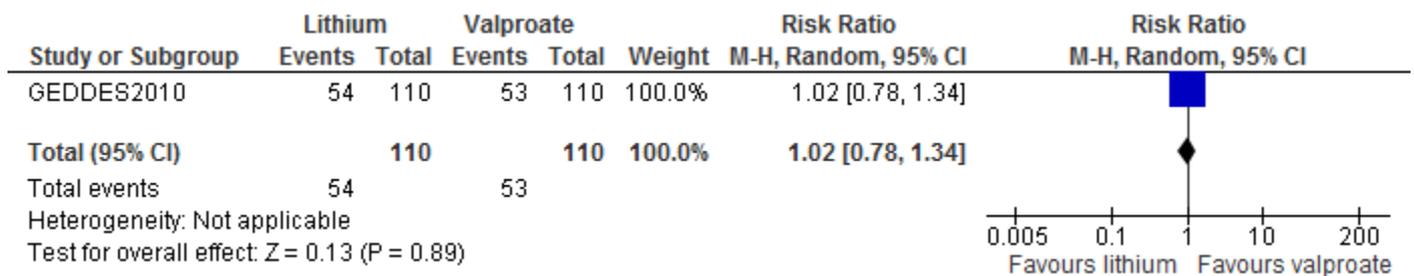
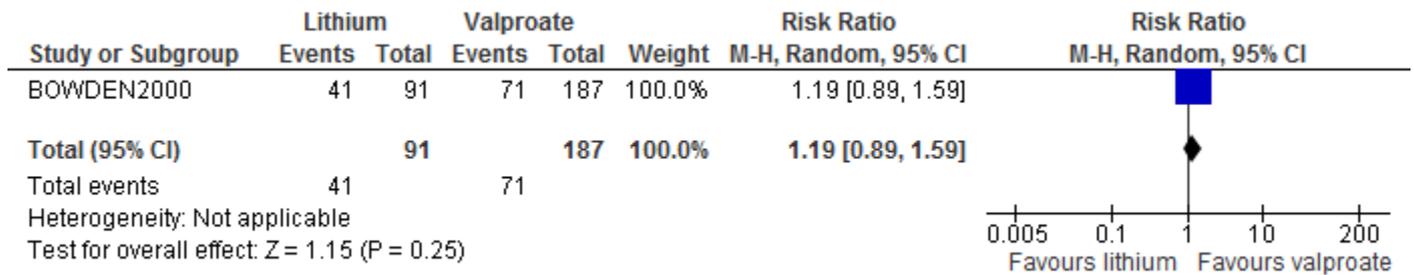
*Number of participants who relapsed (depression)*



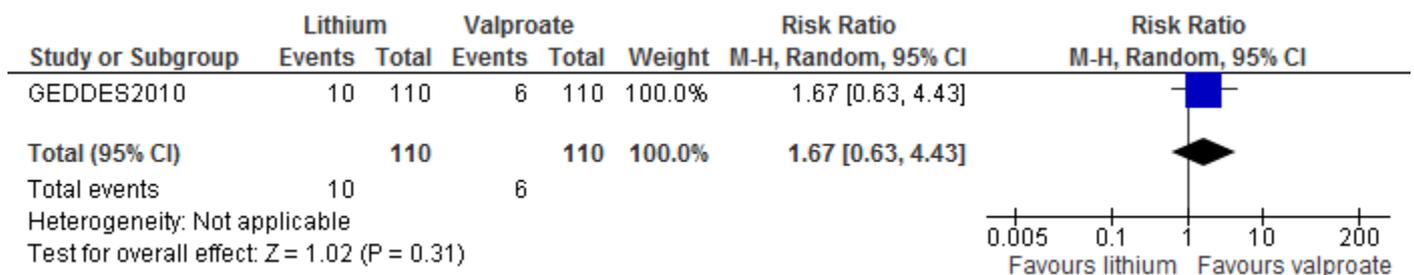
*Number of participants who were hospitalised*



**Number of participants discontinuing (for any reason)**

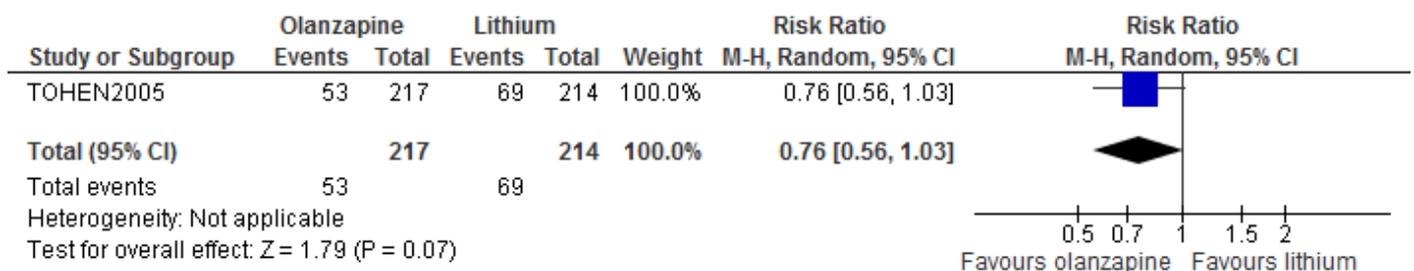


**Number of participants discontinuing due to side effects**

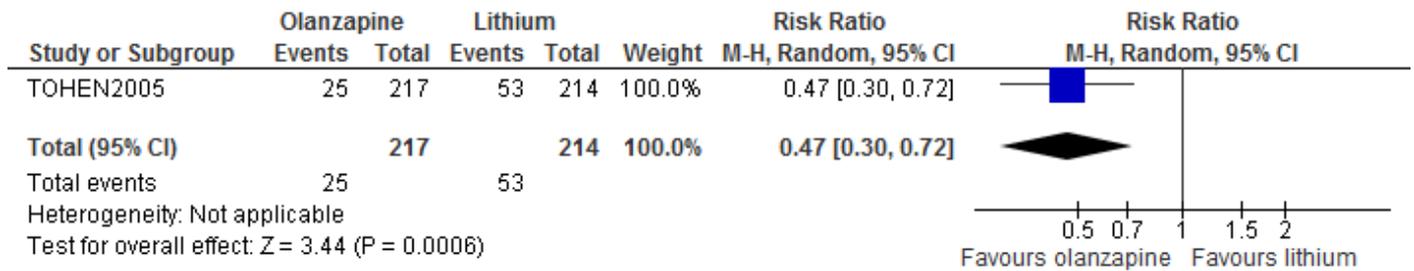


**1.2.5 Outcomes for olanzapine compared with lithium**

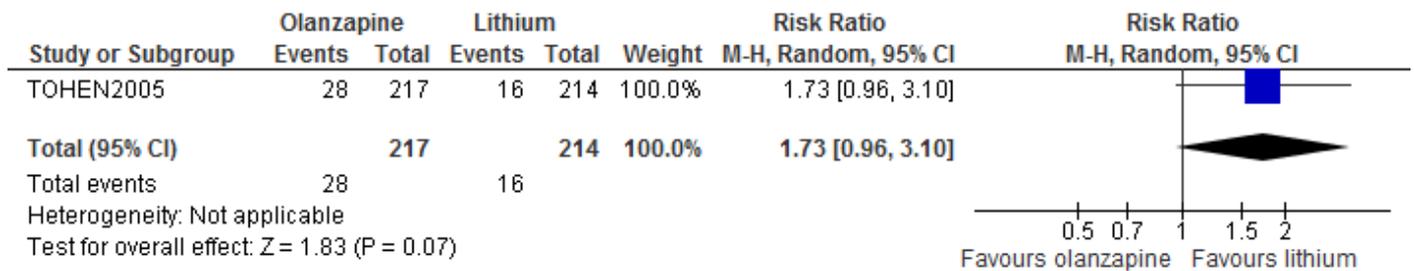
**Number of participants who relapsed (any type)**



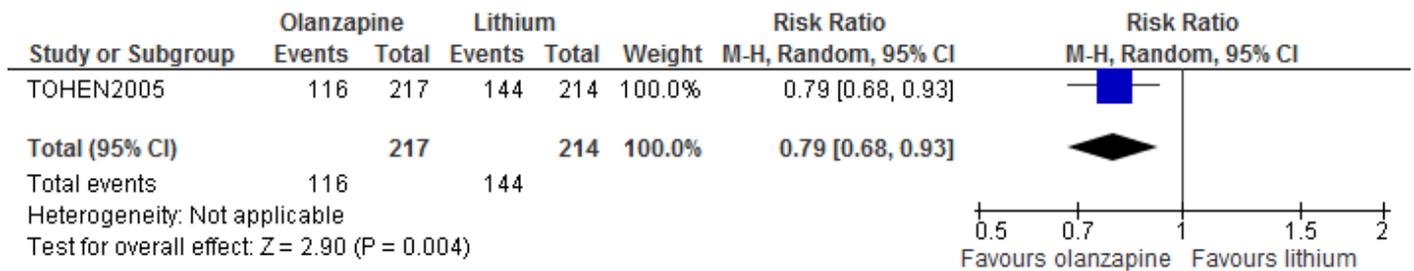
**Number of participants who relapsed (mania)**



**Number of participants who relapsed (depression)**



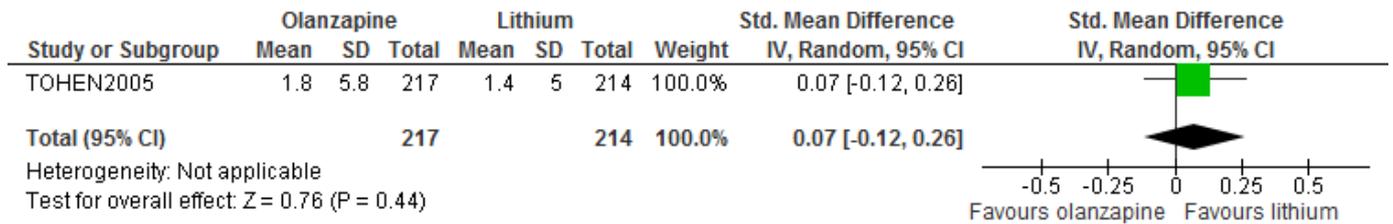
**Number of participants discontinuing (for any reason)**



**Number of participants discontinuing due to side effects**



**Change in weight (kg)**



**1.2.6 Outcomes for valproate compared with lithium and valproate combination**

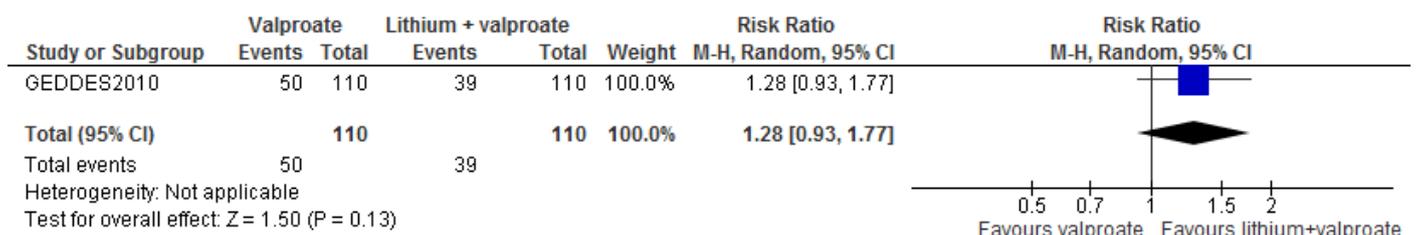
*Number of participants who relapsed (any type)*



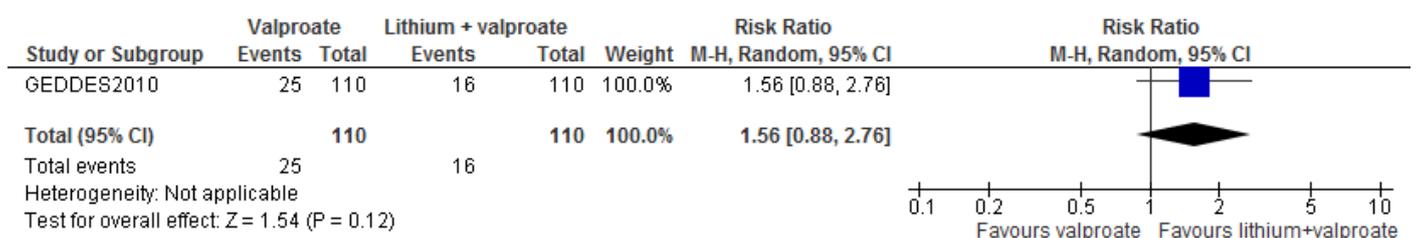
*Number of participants who relapsed (mania)*



*Number of participants who relapsed (depression)*



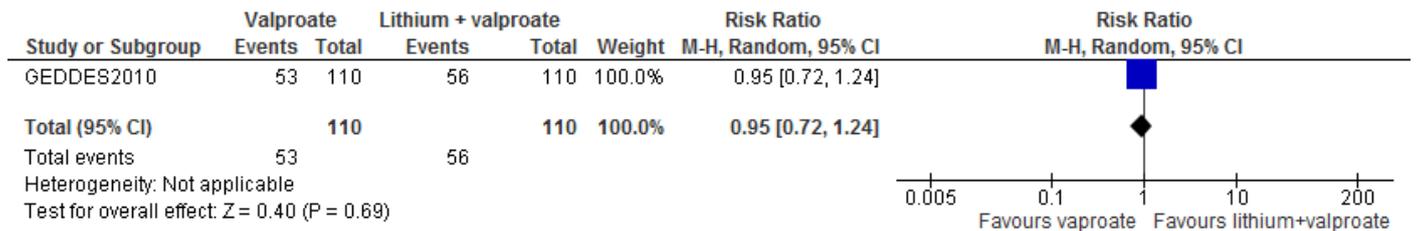
*Number of participants who were hospitalised*



**Number of participants discontinuing (for any reason)**

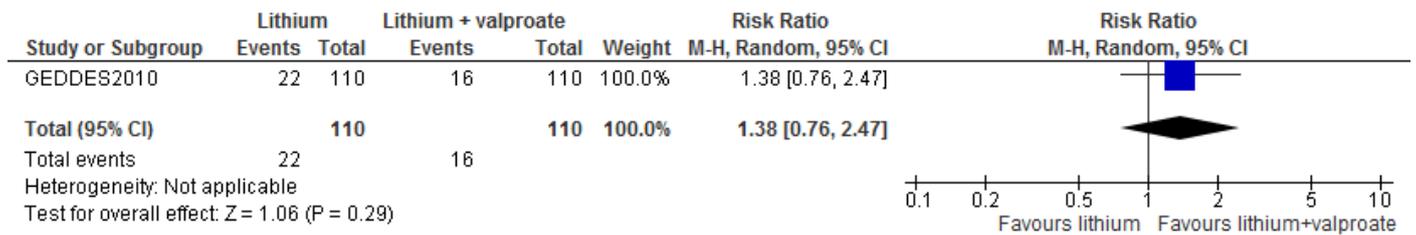


**Number of participants discontinuing due to side effects**

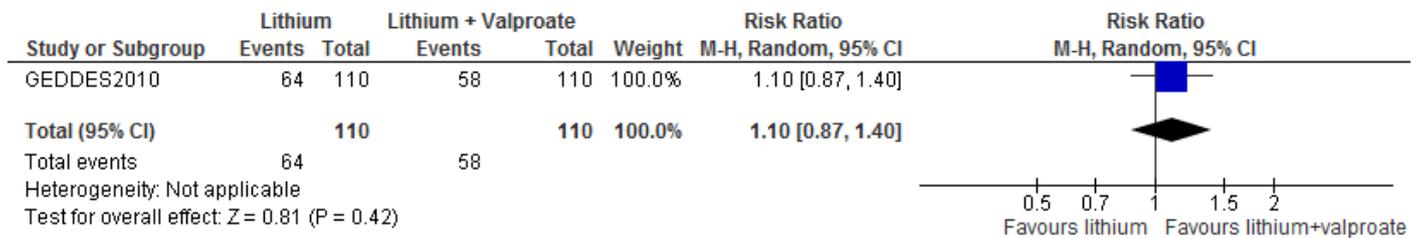


**1.2.7 Outcomes for lithium compared with lithium and valproate combination**

**Number of participants who were hospitalised**



**Number of participants who relapsed (any type)**



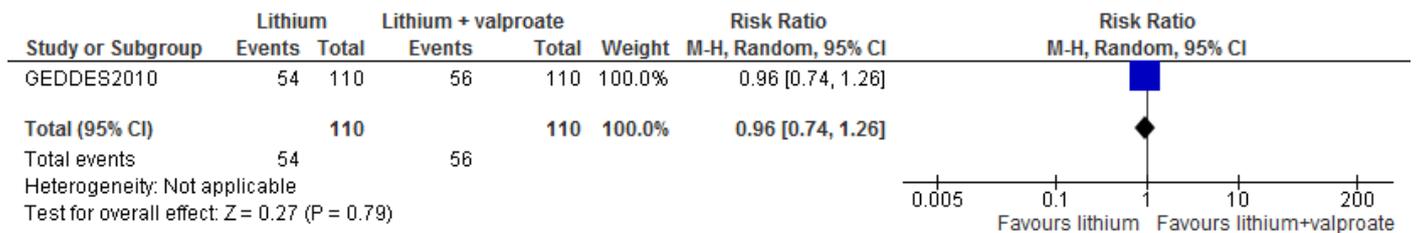
**Number of participants who relapsed (mania)**



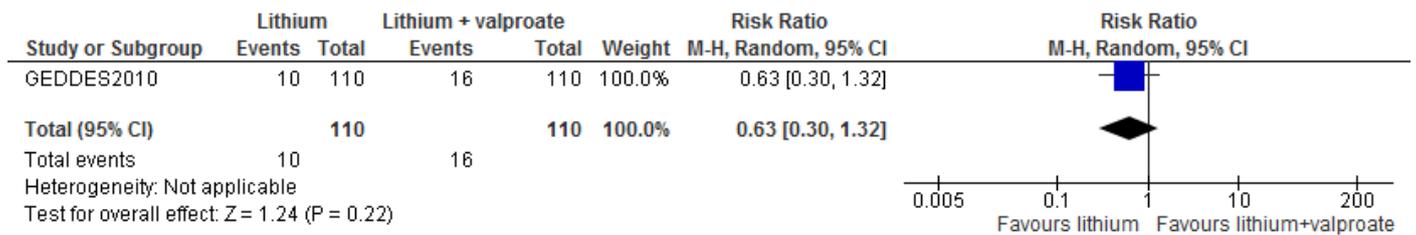
**Number of participants who relapsed (depression)**



**Number of participants discontinuing (for any reason)**



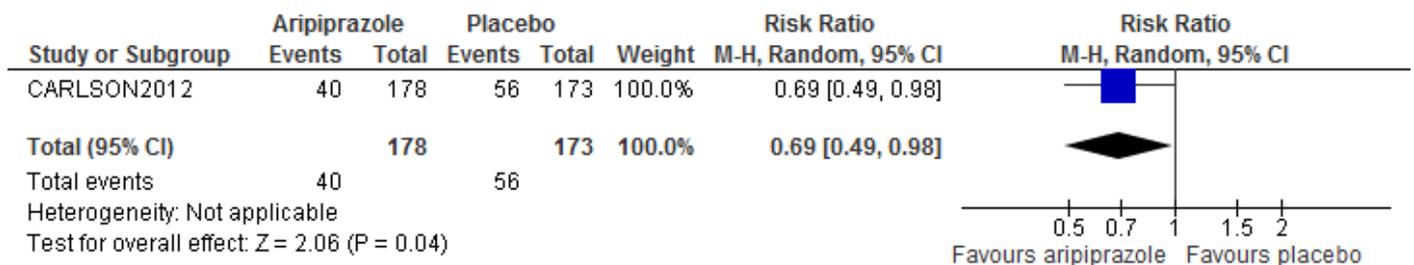
**Number of participants discontinuing due to side effects**



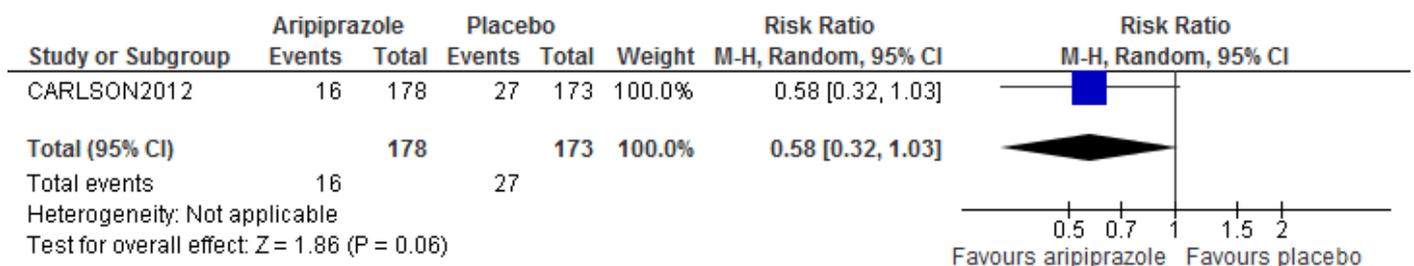
### 1.3 ANTIPSYCHOTICS

#### 1.3.1 Outcomes for aripiprazole compared with placebo (all participants taking lamotrigine)

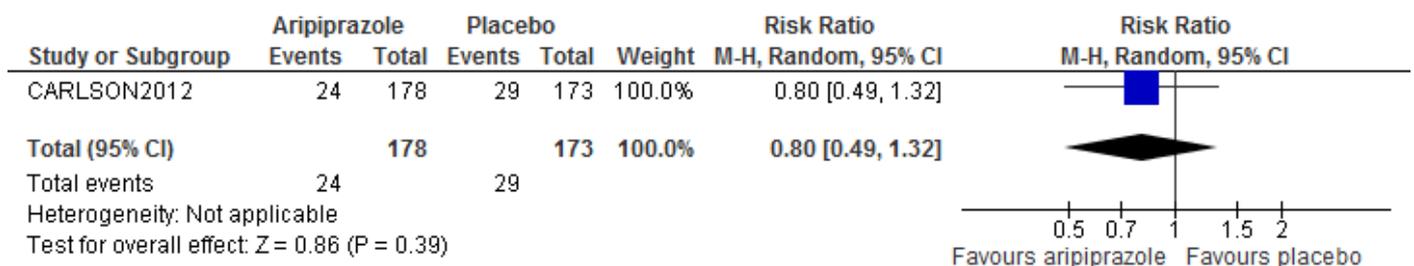
##### Number of participants who relapsed (any type)



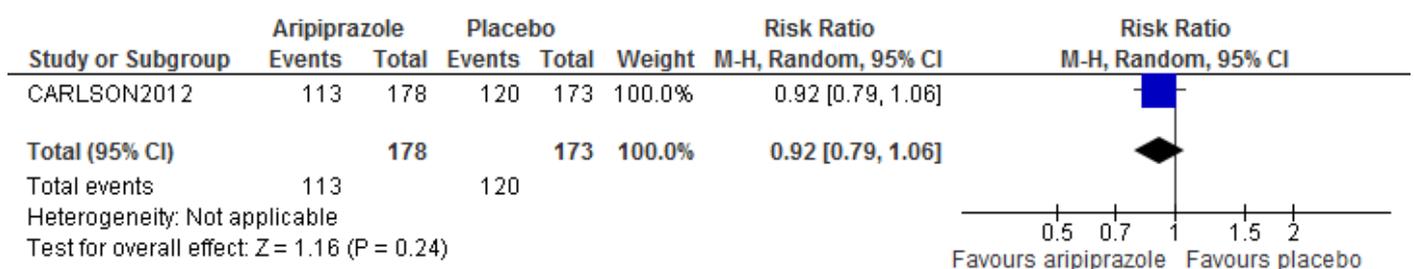
##### Number of participants who relapsed (mania)



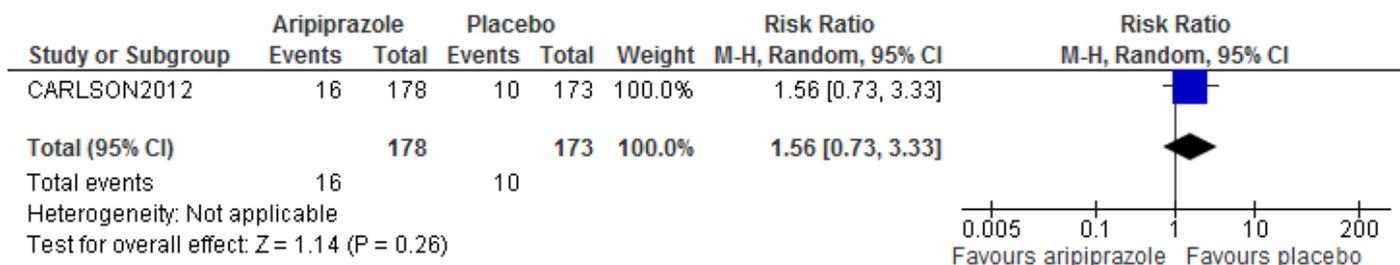
##### Number of participants who relapsed (depression)



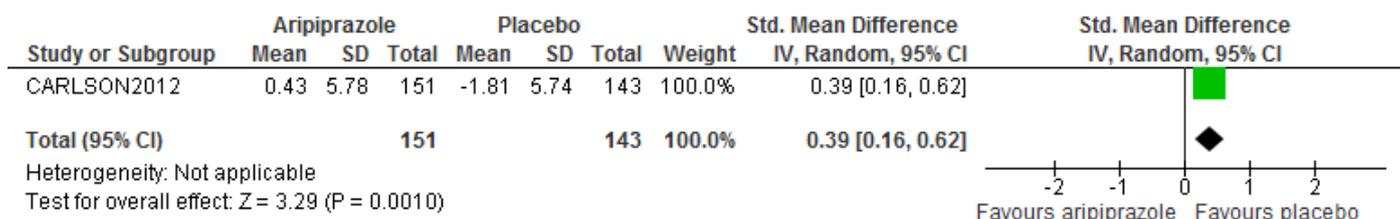
##### Number of participants discontinuing (for any reason)



**Number of participants discontinuing due to side effects**



**Change in weight (kg)**

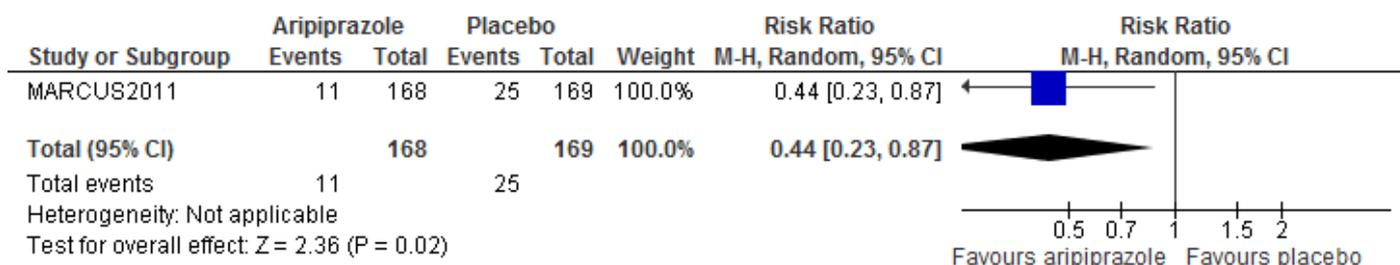


**1.3.2 Outcomes for aripiprazole compared with placebo (all participants taking lithium or valproate)**

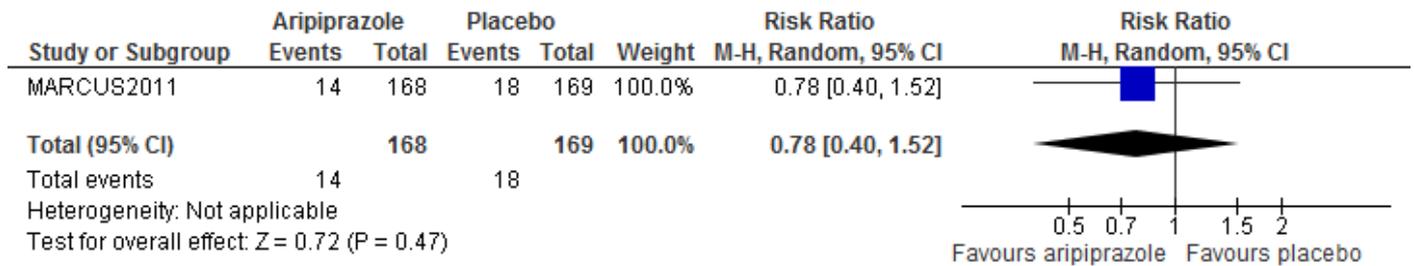
**Number of participants who relapsed (any type)**



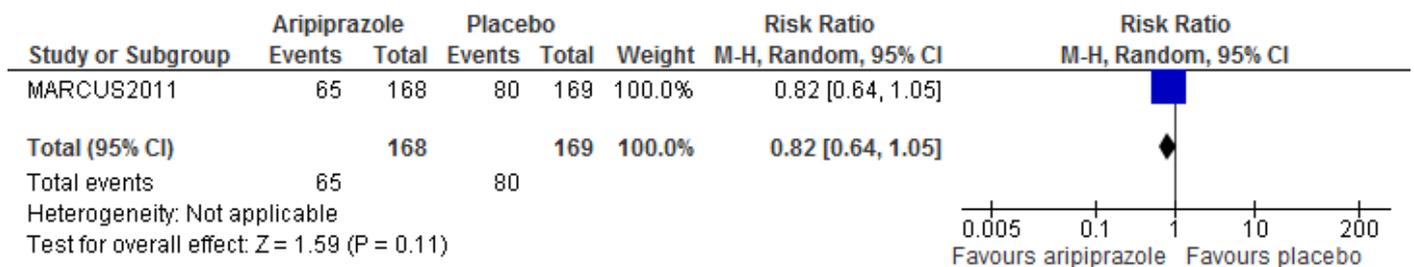
**Number of participants who relapsed (mania/mixed)**



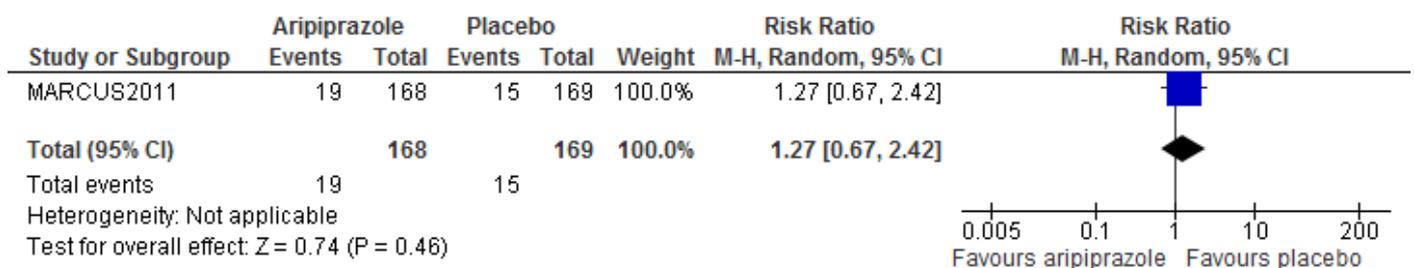
**Number of participants who relapsed (depression)**



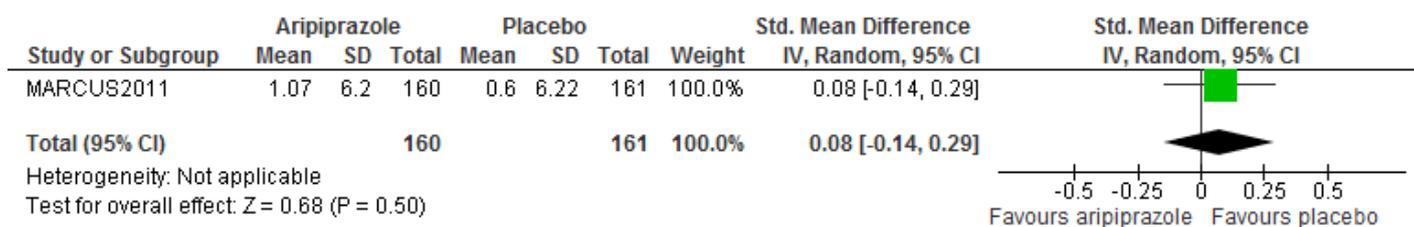
**Number of participants discontinuing (for any reason)**



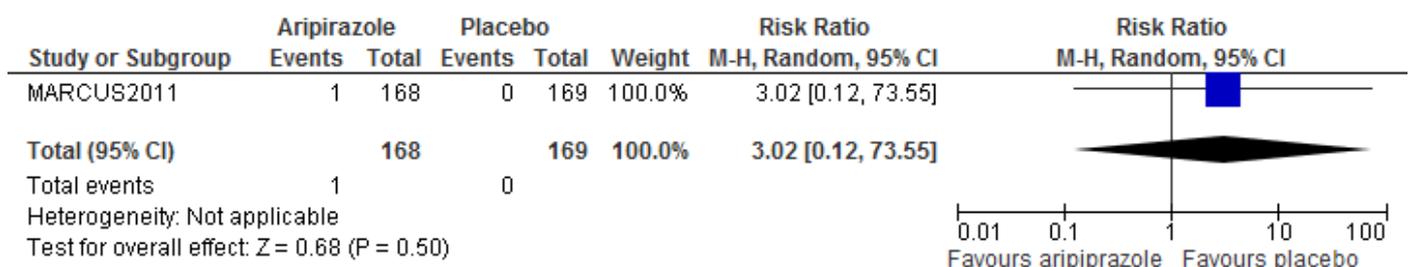
**Number of participants discontinuing due to side effects**



**Change in weight (kg)**

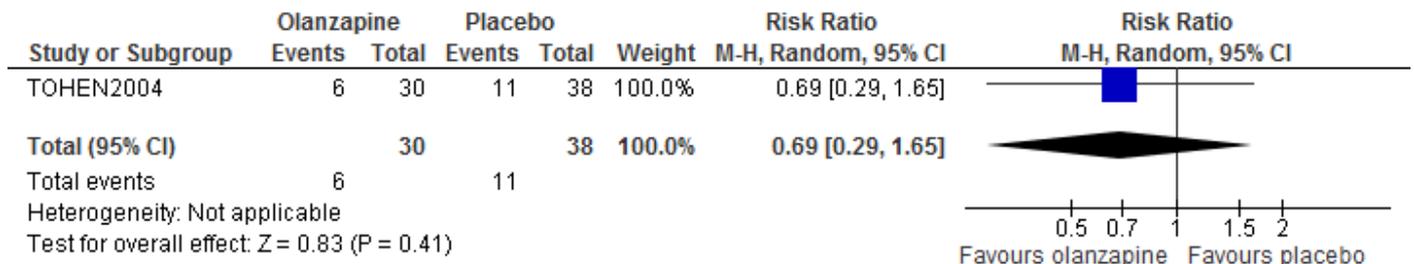


**Number of suicides**

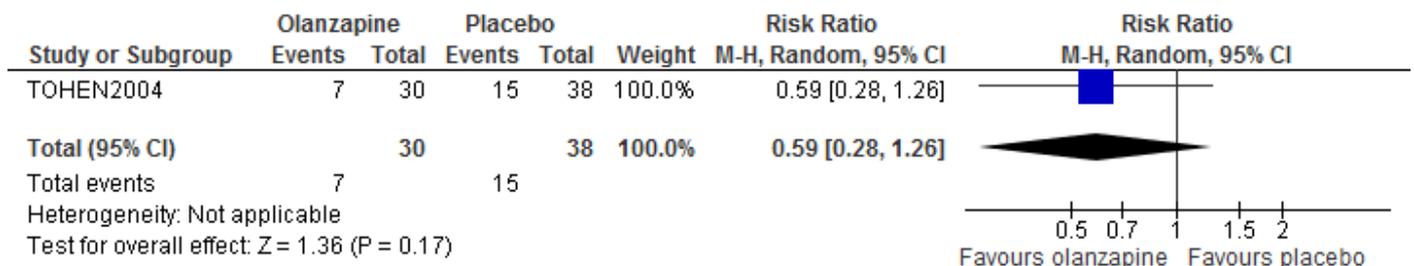


### 1.3.3 Outcomes for olanzapine compared with placebo (all participants taking lithium or valproate)

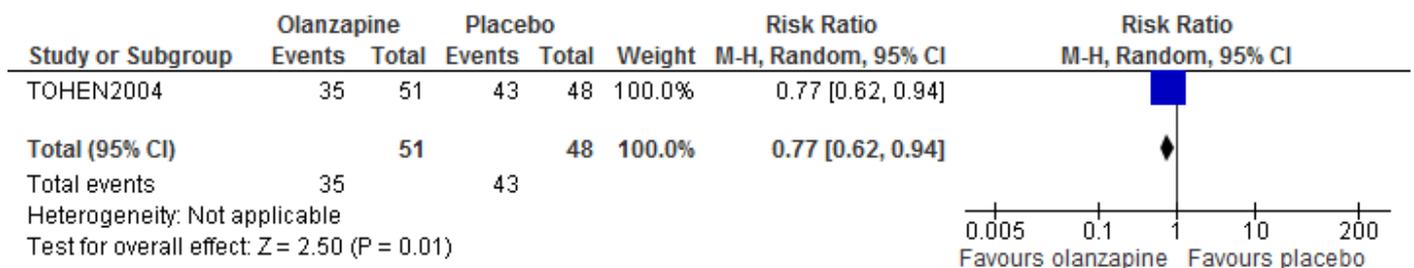
#### Number of participants who relapsed (mania)



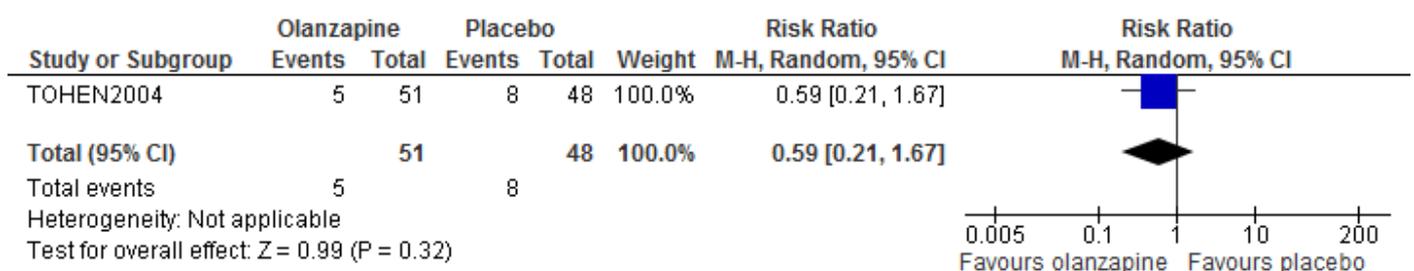
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)

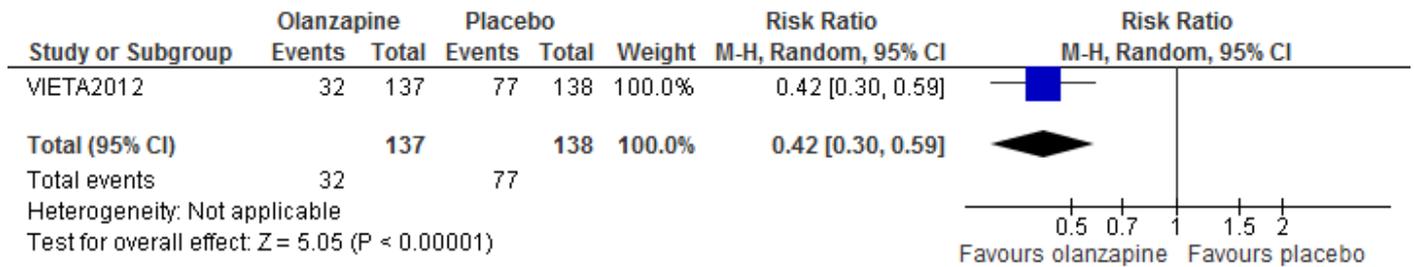


#### Number of participants discontinuing due to side effects

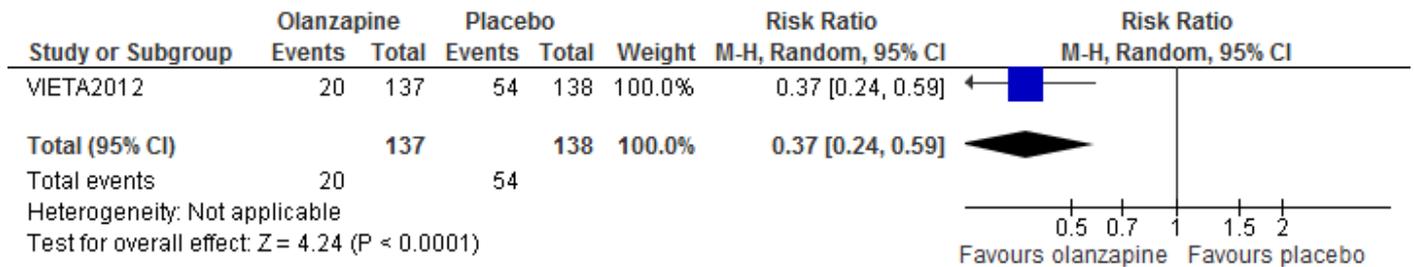


### 1.3.4 Outcomes for olanzapine compared with placebo

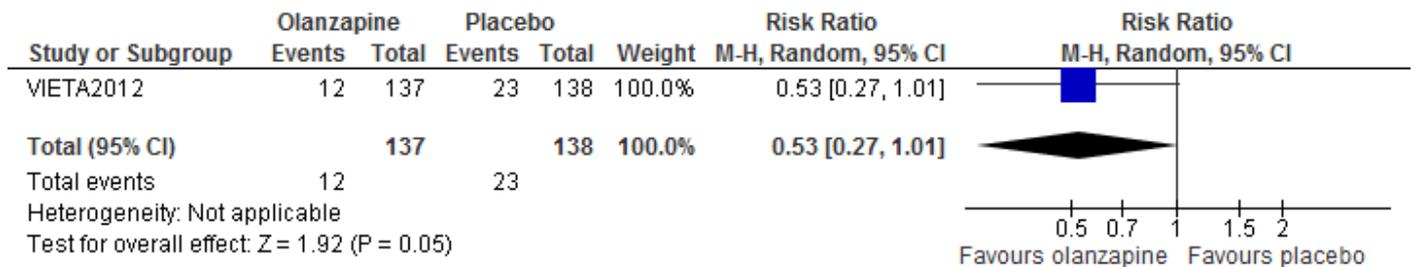
#### Number of participants who relapsed (any type)



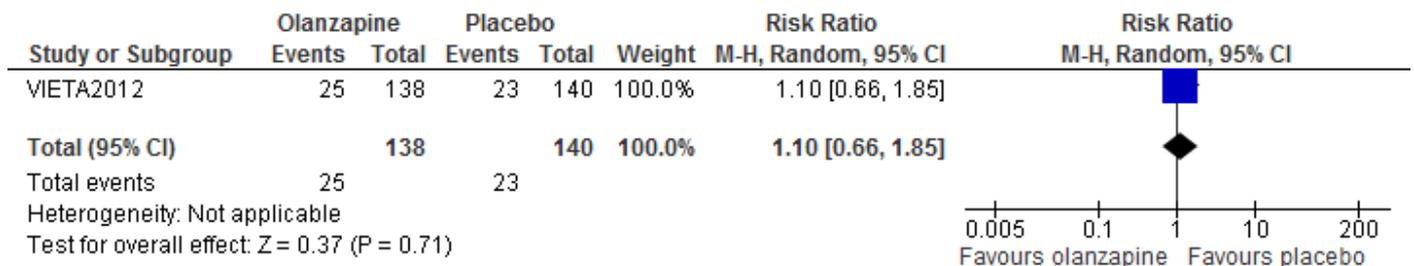
#### Number of participants who relapsed (mania)



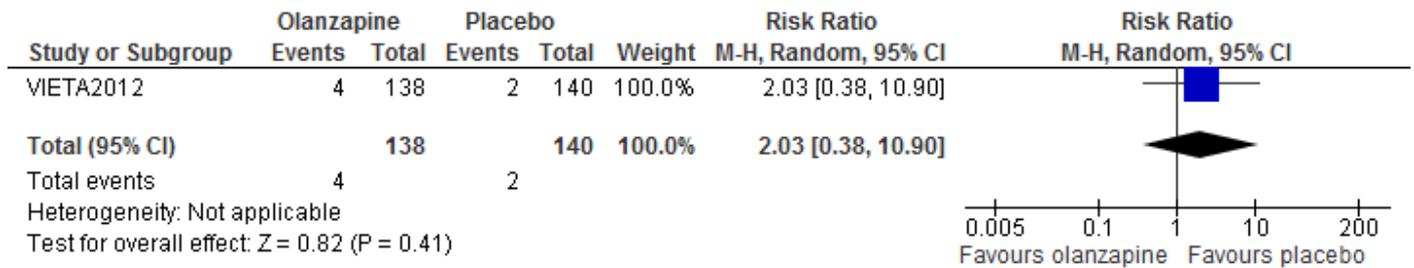
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)



**Number of participants discontinuing due to side effects**

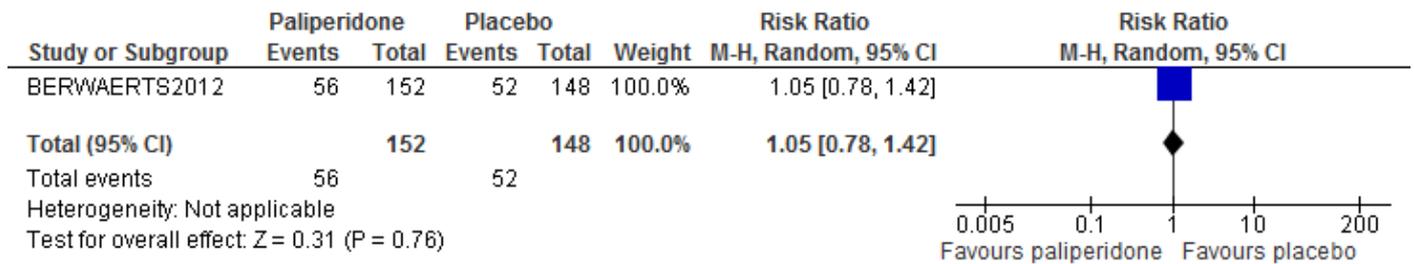


**1.3.5 Outcomes for paliperidone compared with placebo**

**Number of participants who relapsed (any type)**



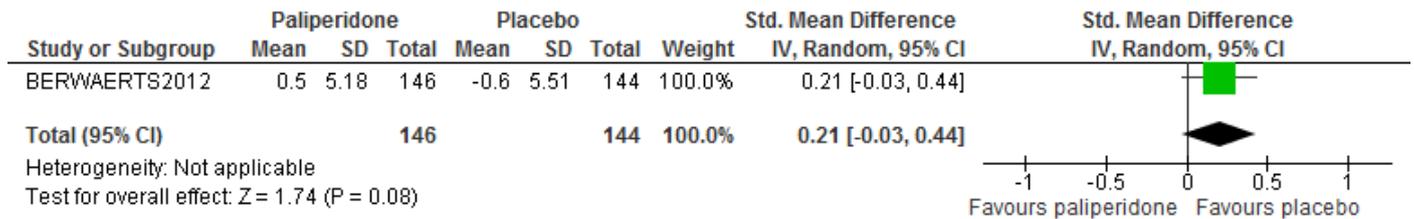
**Number of participants discontinuing (for any reason)**



**Number of participants discontinuing due to side effects**



### Change in weight (kg)

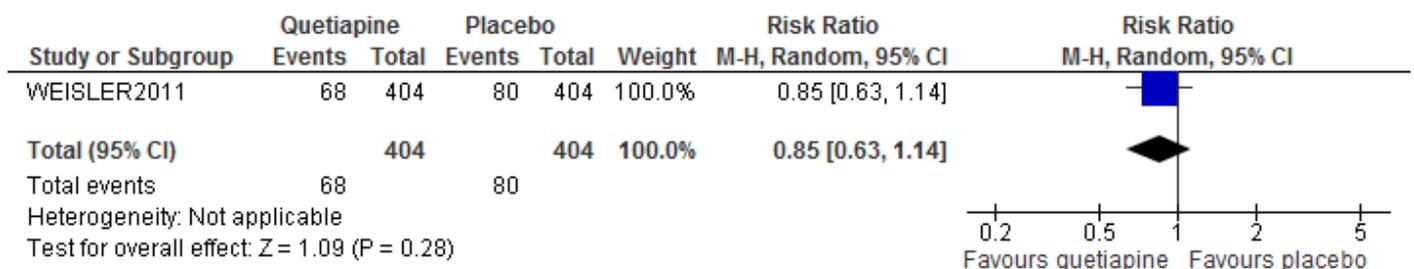


### 1.3.6 Outcomes for quetiapine compared with placebo

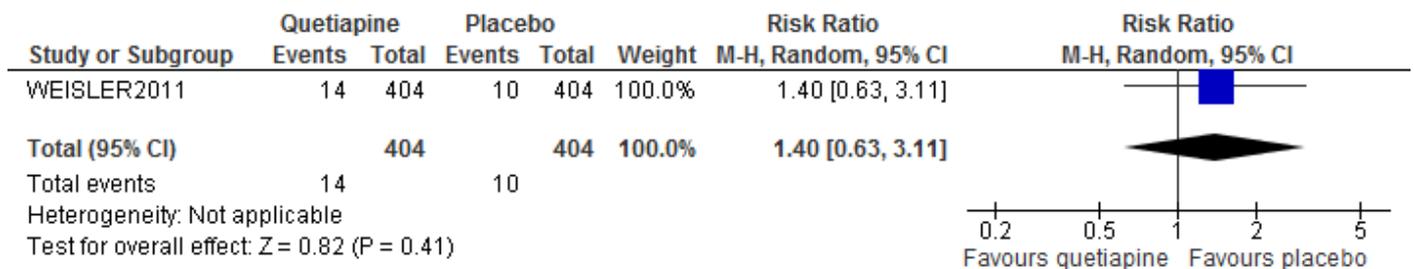
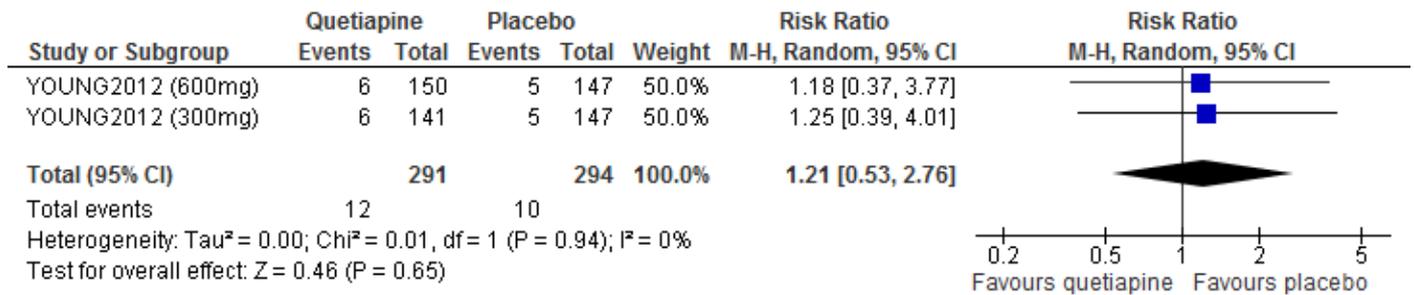
#### Number of participants who relapsed (any type)



#### Number of participants discontinuing (for any reason)

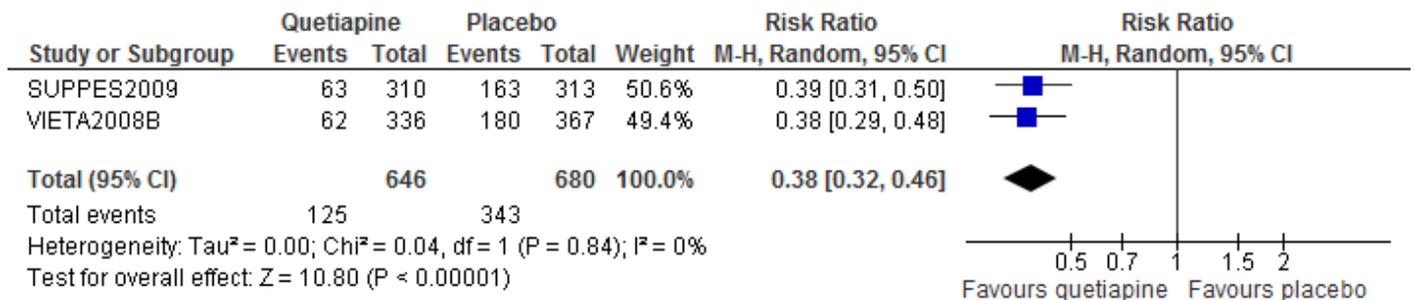


**Number of participants discontinuing due to side effects**

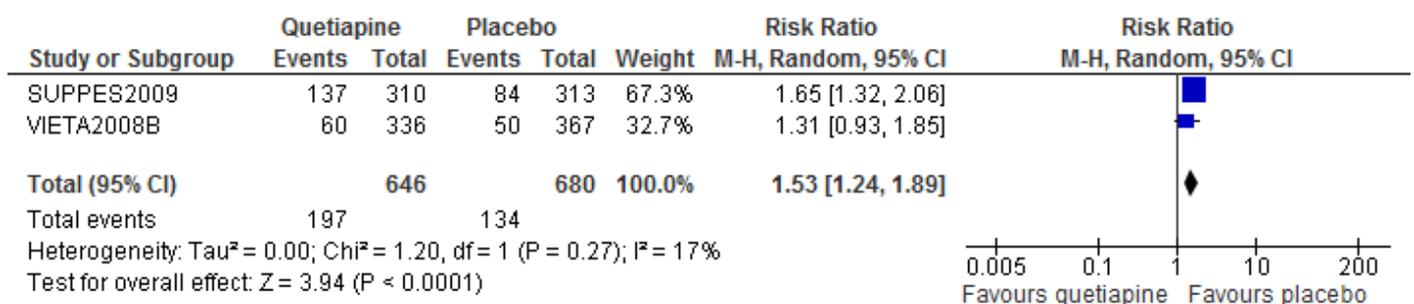


**1.3.7 Outcomes for quetiapine compared with placebo (all participants were taking lithium or valproate)**

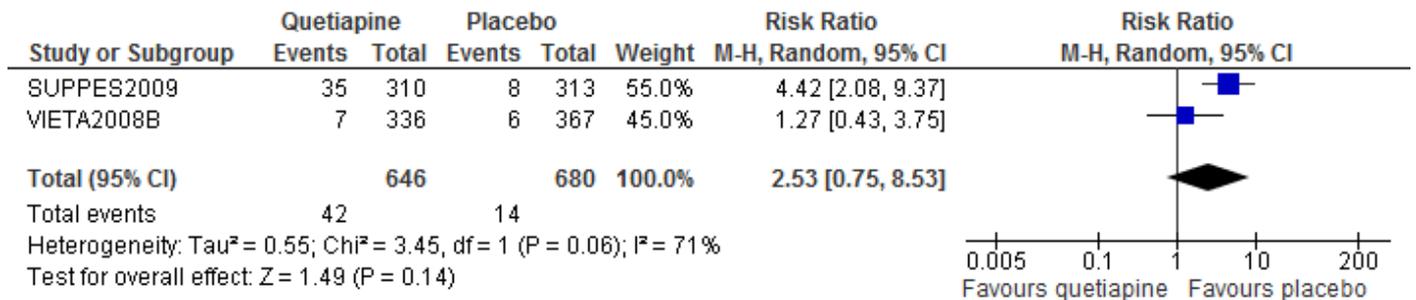
**Number of participants who relapsed (any type)**



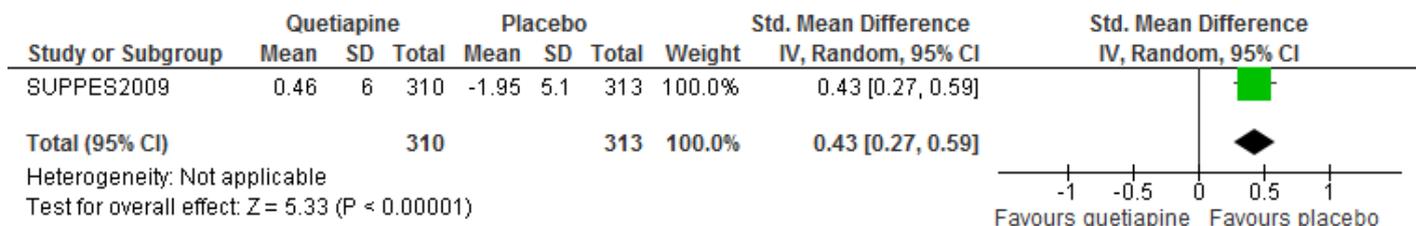
**Number of participants discontinuing (for any reason)**



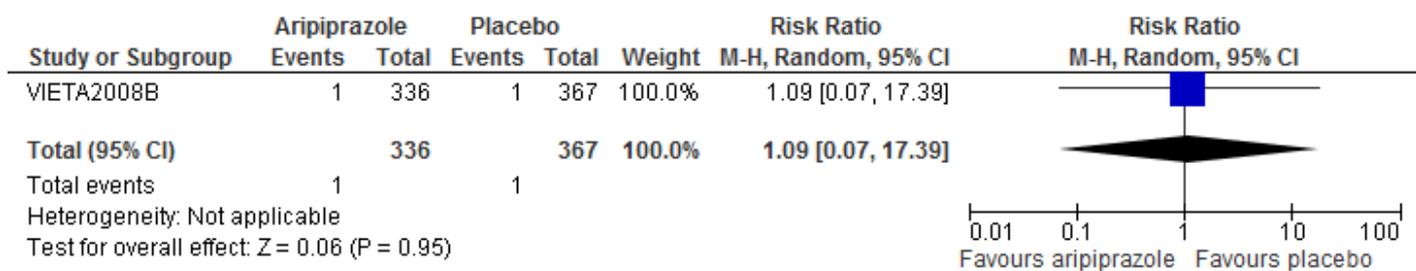
**Number of participants discontinuing due to side effects**



**Change in weight (kg)**



**Number of suicides**



**Number of deaths**



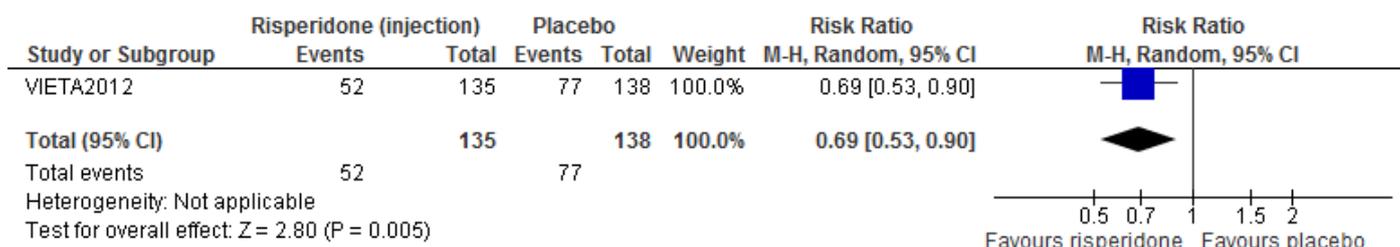
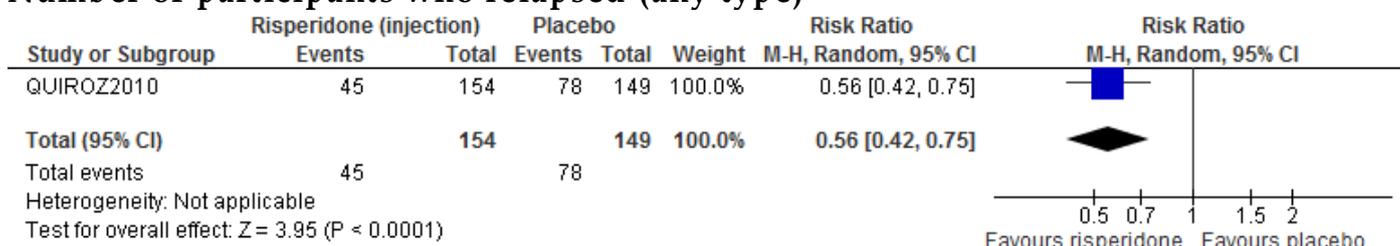
### 1.3.8 Outcomes for quetiapine compared with valproate

#### Number of participants discontinuing (for any reason)

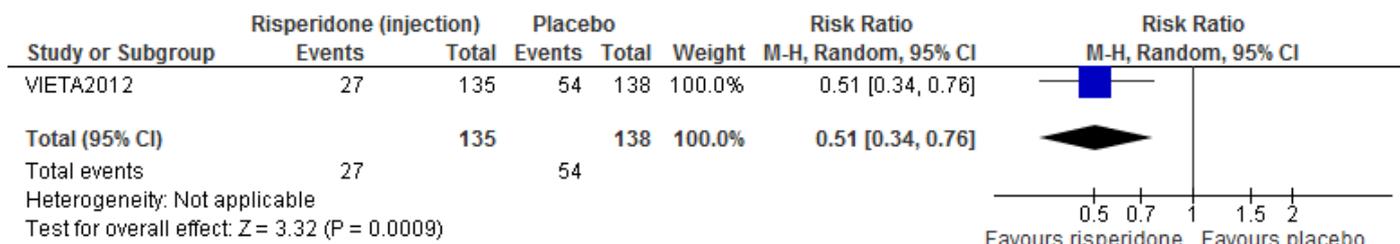
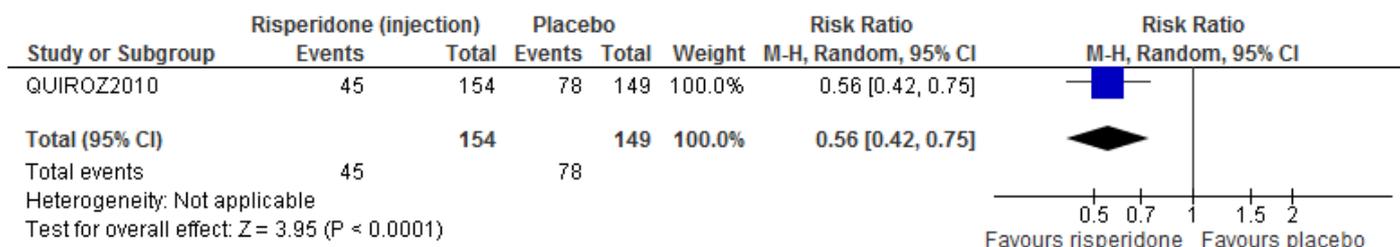


### 1.3.9 Outcomes for risperidone long-acting injectable compared with placebo injection

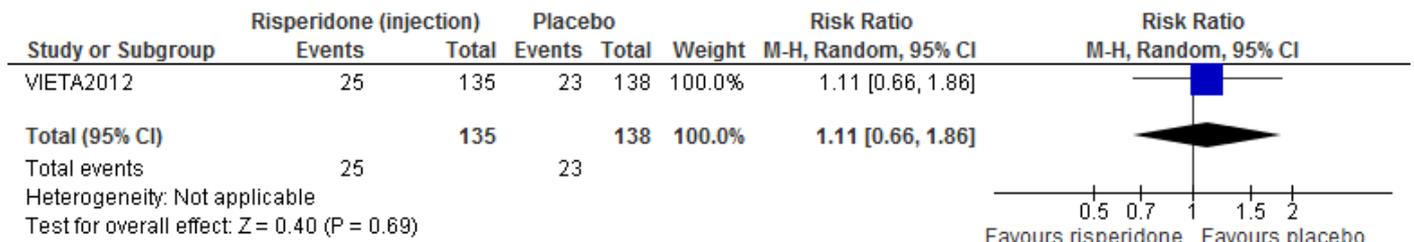
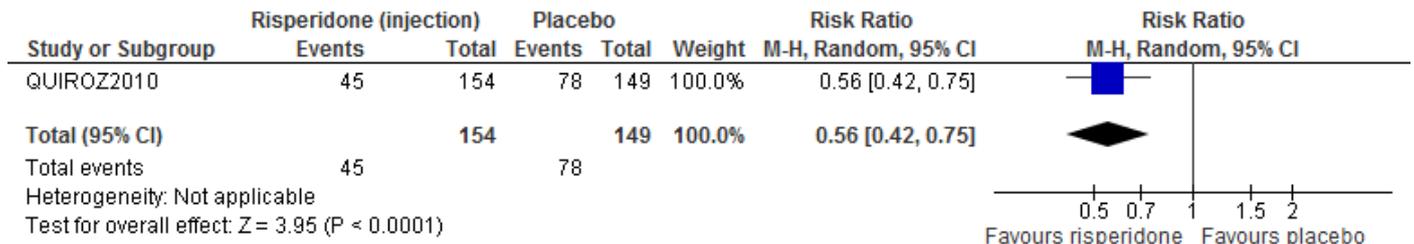
#### Number of participants who relapsed (any type)



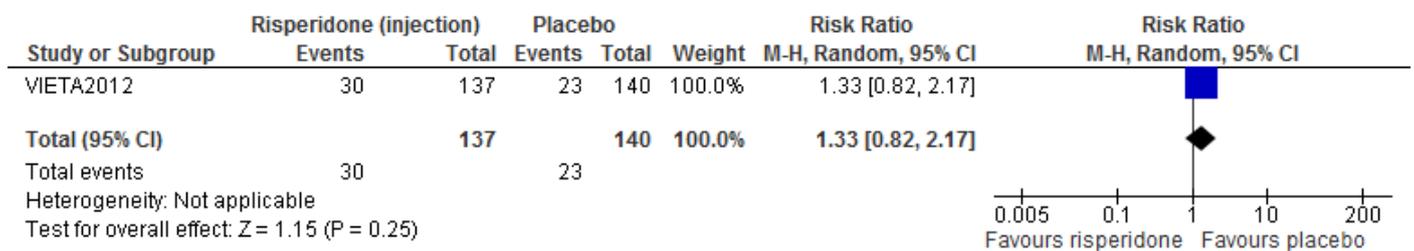
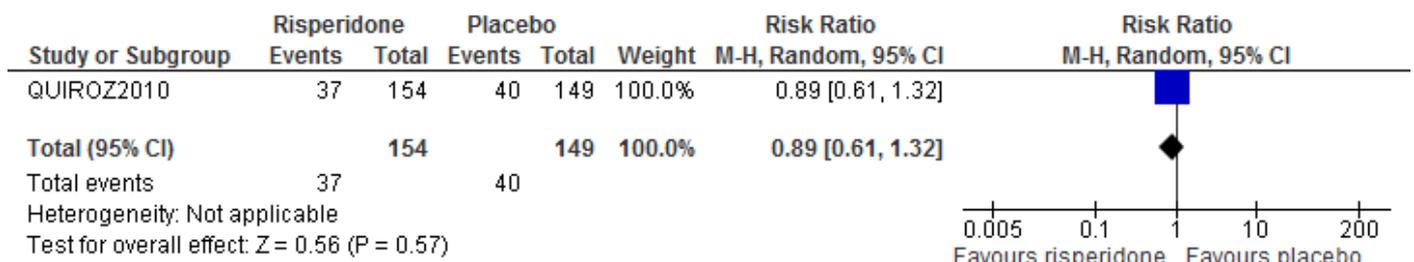
#### Number of participants who relapsed (mania)



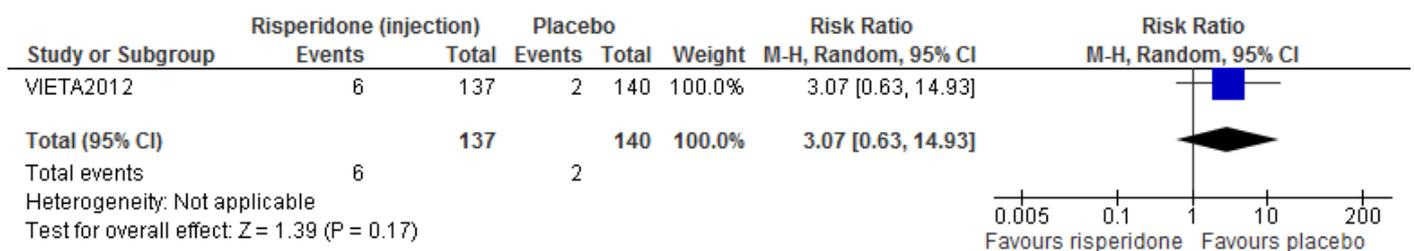
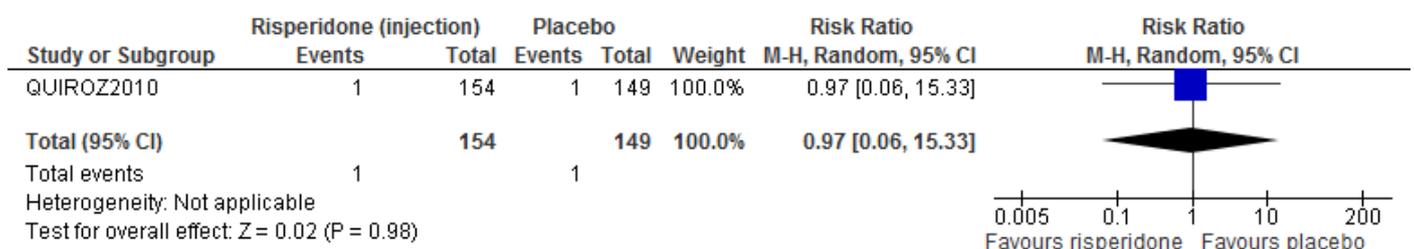
**Number of participants who relapsed (depression)**



**Number of participants discontinuing (for any reason)**

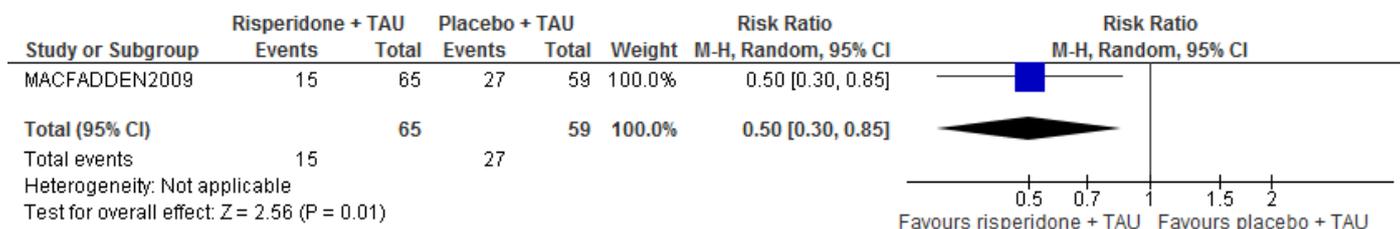


**Number of participants discontinuing due to side effects**

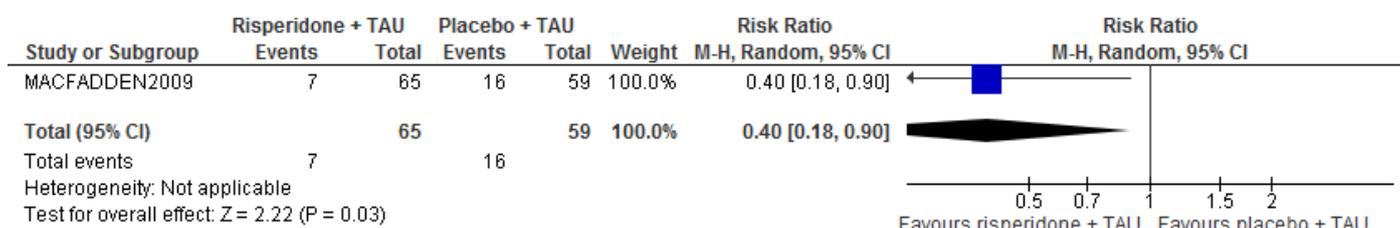


### 1.3.10 Outcomes for risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual)

#### Number of participants who relapsed (any type)



#### Number of participants who relapsed (mania)



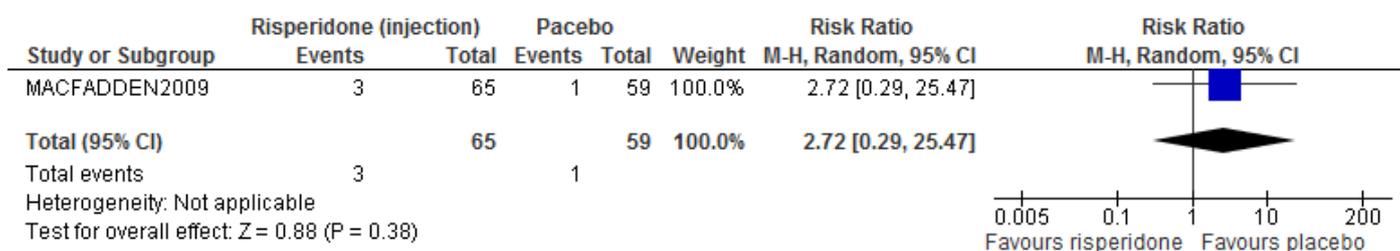
#### Number of participants who relapsed (depression)



#### Number of participants discontinuing (for any reason)



#### Number of participants discontinuing due to side effects

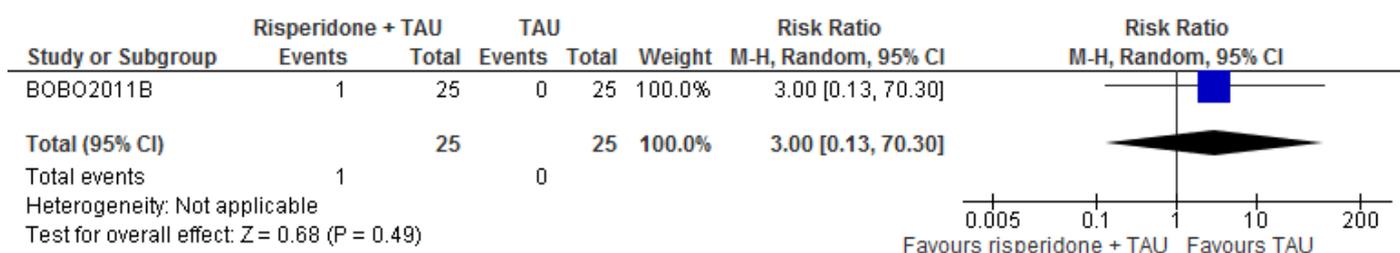


### 1.3.11 Outcomes for risperidone long-acting injectable and treatment as usual compared with treatment as usual alone

#### Number of participants discontinuing (for any reason)



#### Number of participants discontinuing due to side effects



## 1.4 ANTICONVULSANTS

### 1.4.1 Outcomes for oxcarbazepine compared with placebo (all participants were taking lithium)

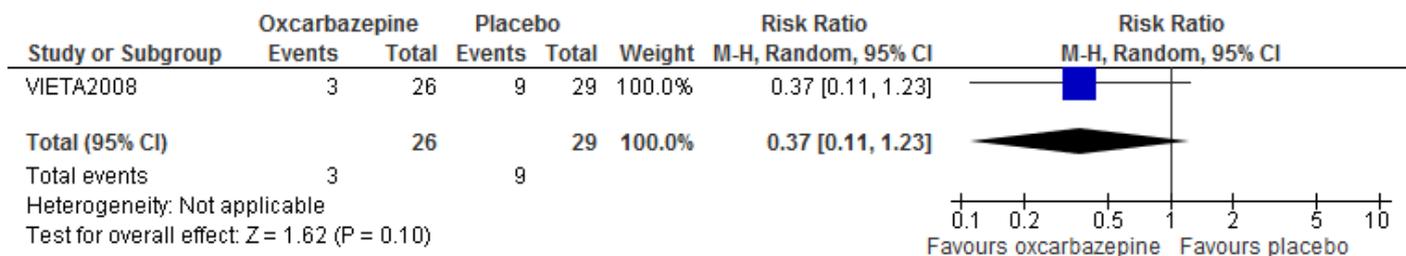
#### Number of participants who relapsed (any type)



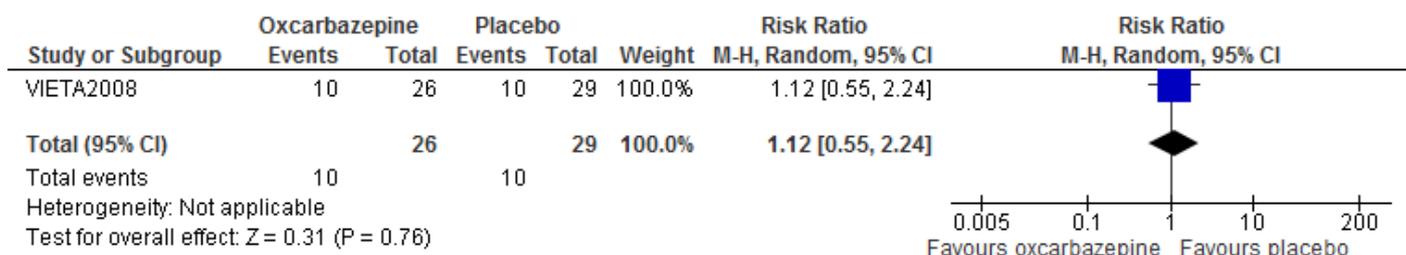
#### Number of participants who relapsed (mania)



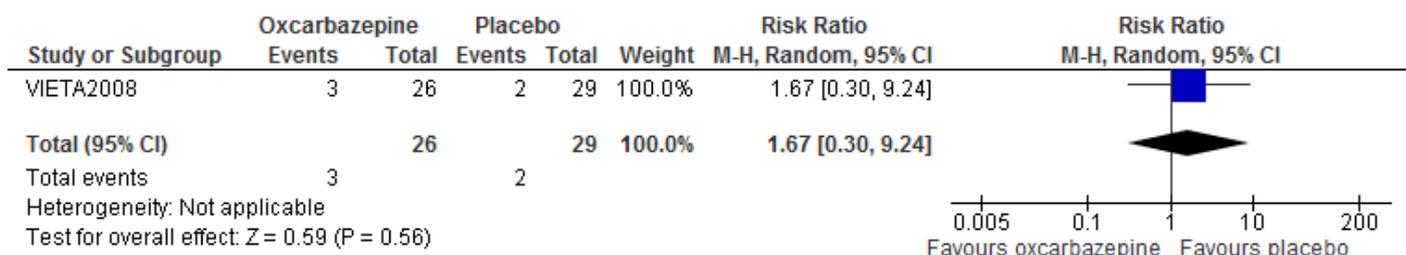
**Number of participants who relapsed (depression)**



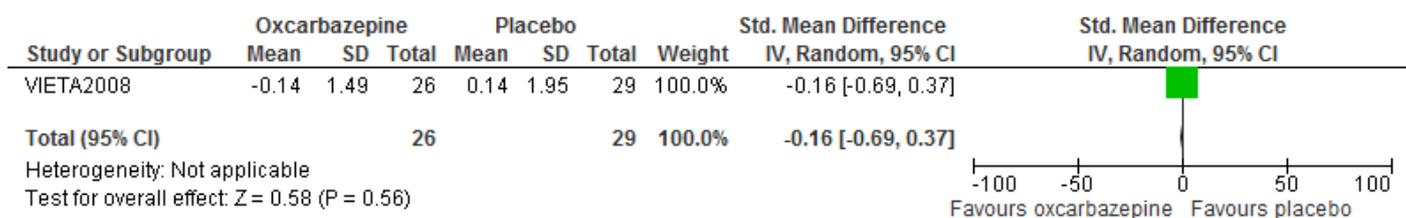
**Number of participants discontinuing (for any reason)**



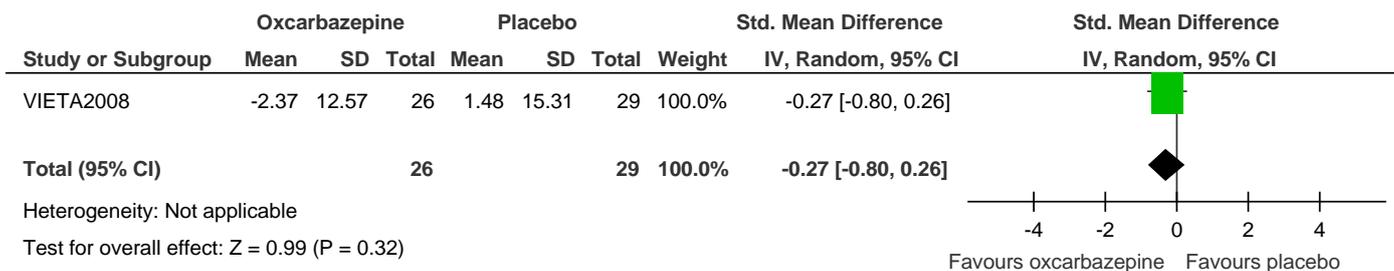
**Number of participants discontinuing due to side effects**



**Change in weight (kg)**

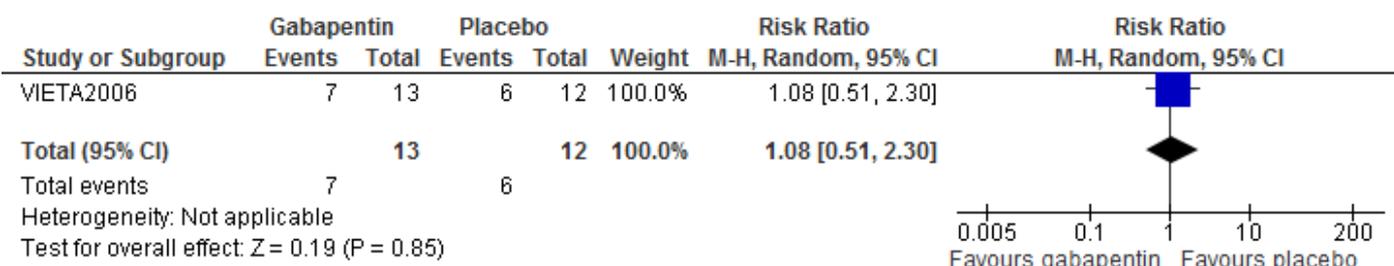


### Psychosocial functioning (Global Assessment of Functioning)<sup>3</sup>

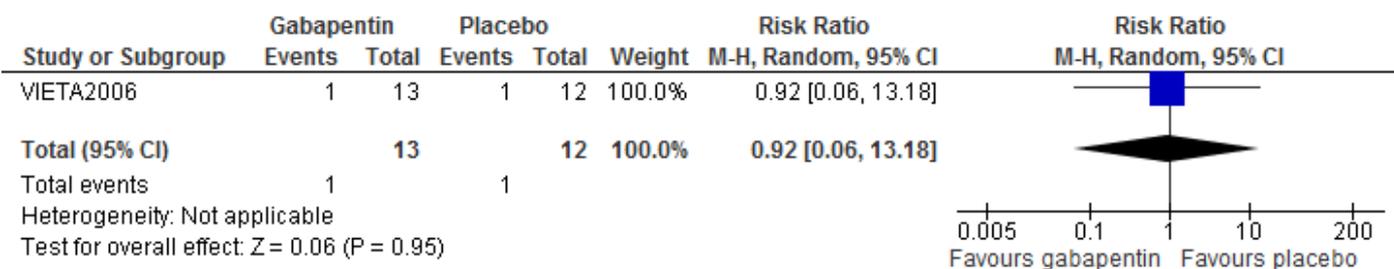


### 1.4.2 Outcomes for gabapentin compared with placebo (all participants were taking lithium, valproate, carbamazepine or combination)

#### Number of participants discontinuing (for any reason)

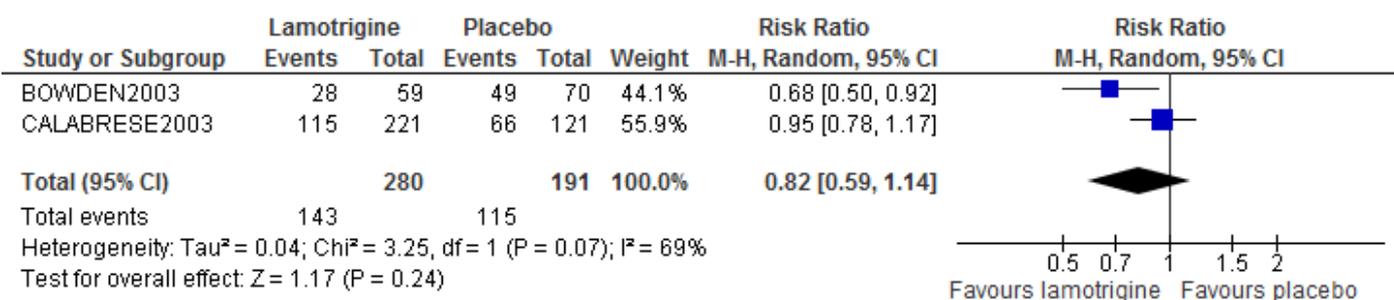


#### Number of participants discontinuing due to side effects



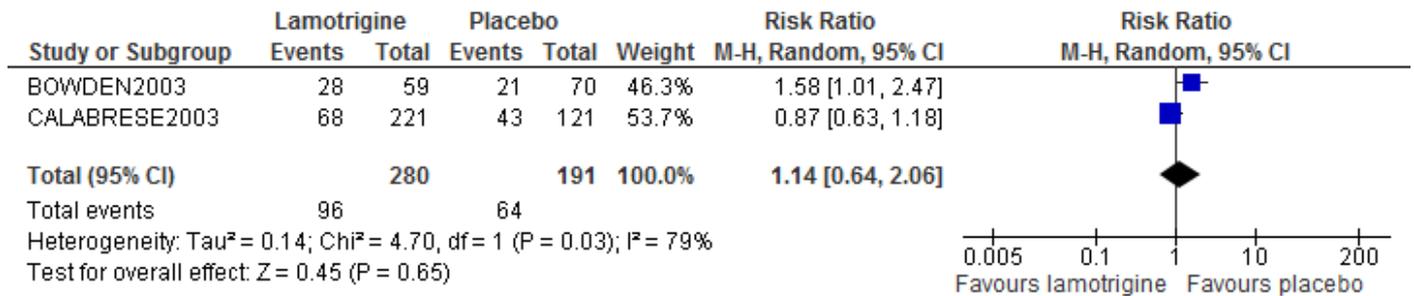
### 1.4.3 Outcomes for lamotrigine compared with placebo

#### Number of participants who relapsed (any type)



<sup>3</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

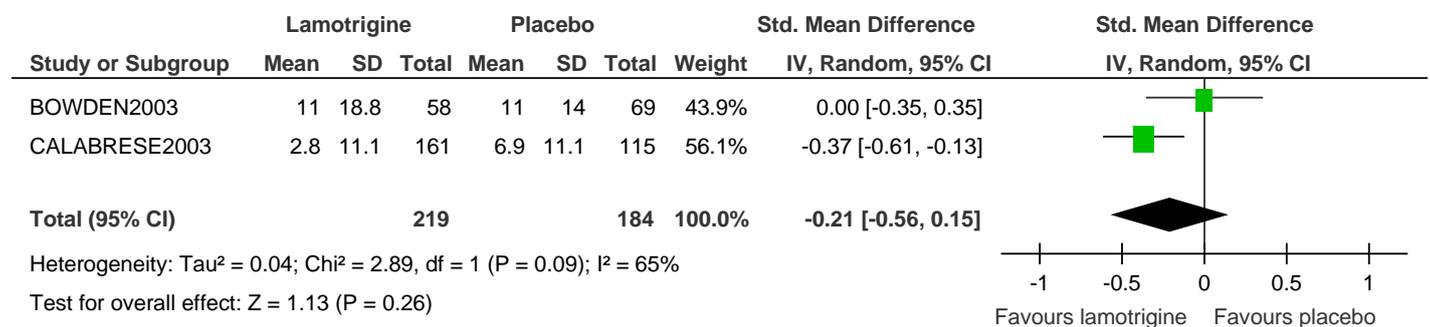
**Number of participants discontinuing (for any reason)**



**Number of participants discontinuing due to side effects**



**Psychosocial functioning (Global Assessment Scale)<sup>4</sup>**



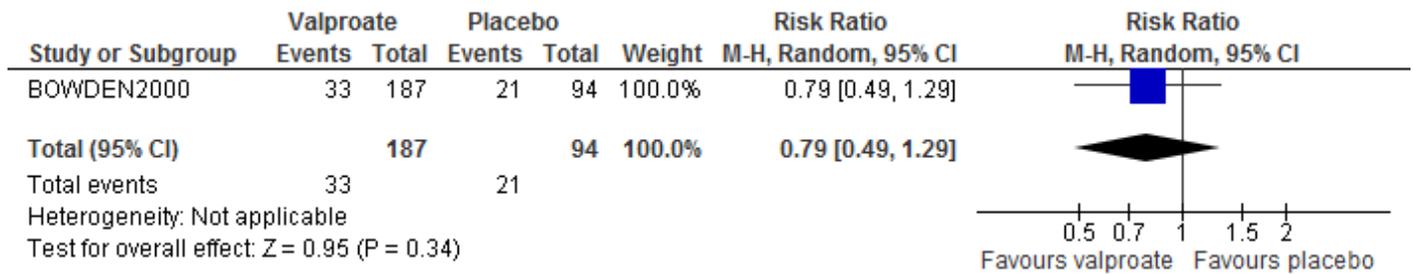
**1.4.4 Outcomes for valproate compared with placebo**

**Number of participants who relapsed (any type)**

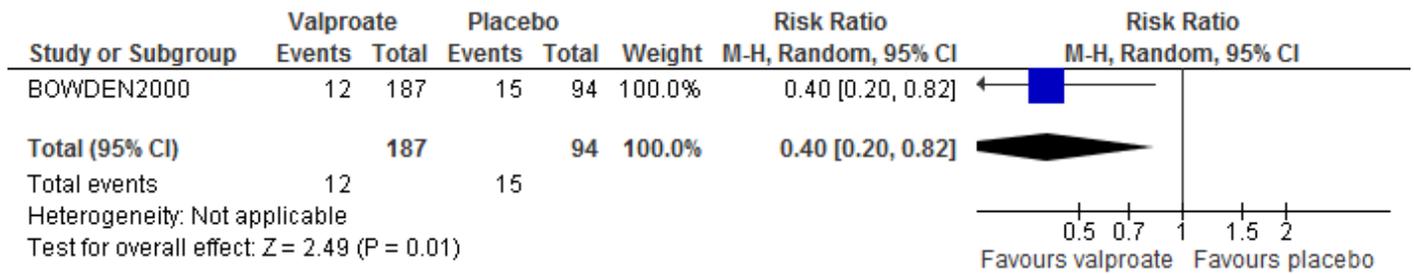


<sup>4</sup> Scores have been reversed so that higher change scores indicate a worsening of functioning.

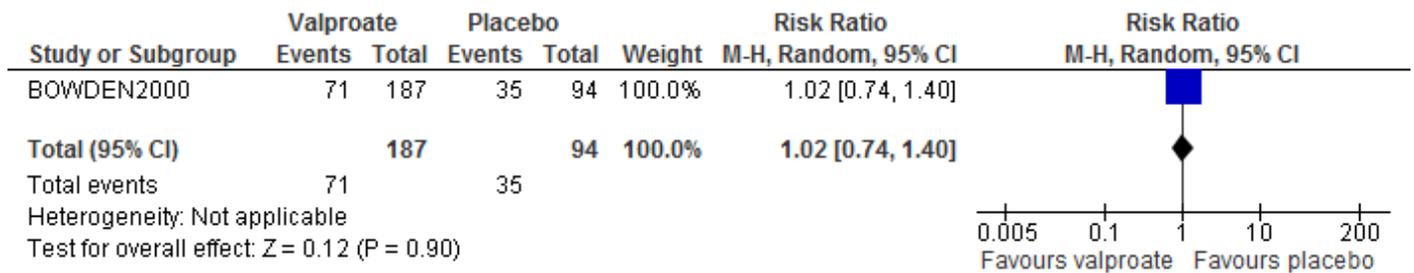
**Number of participants who relapsed (mania)**



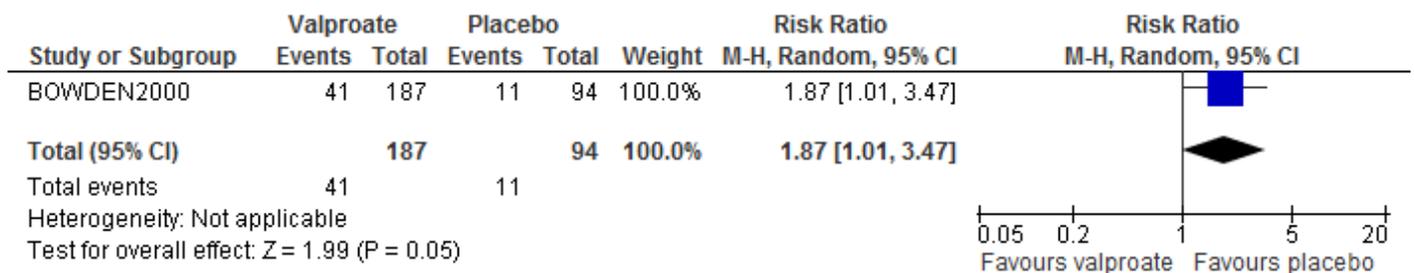
**Number of participants who relapsed (depression)**



**Number of participants discontinuing (for any reason)**



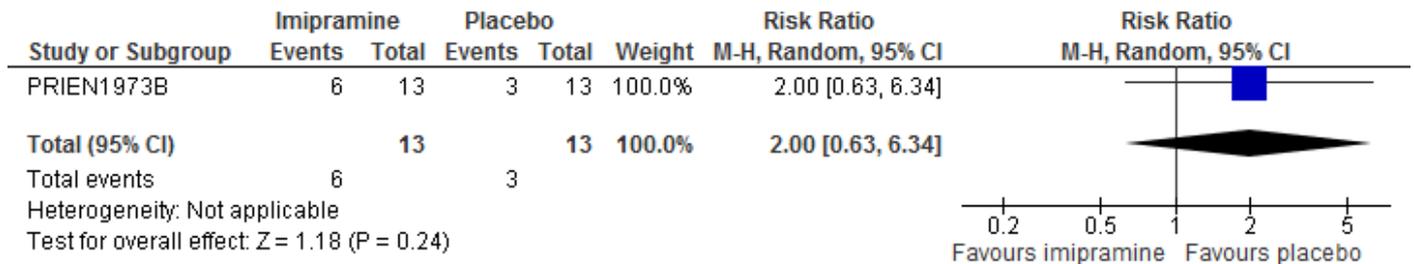
**Number of participants discontinuing due to side effects**



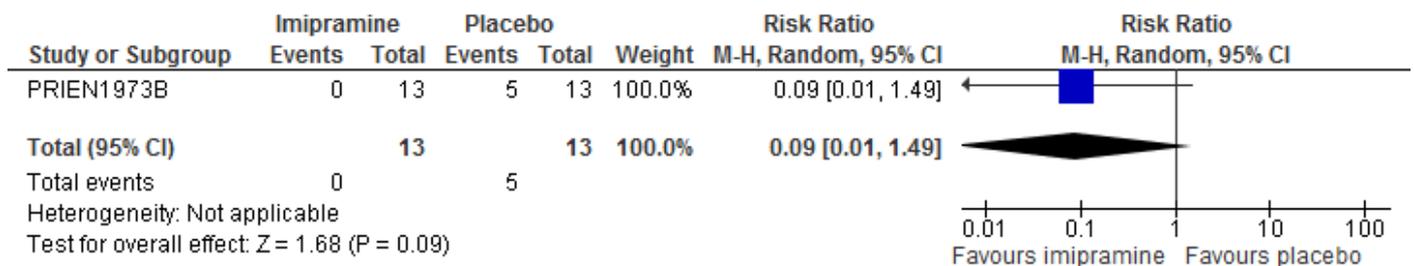
## 1.5 ANTIDEPRESSANTS

### 1.5.1 Outcomes for imipramine compared with placebo

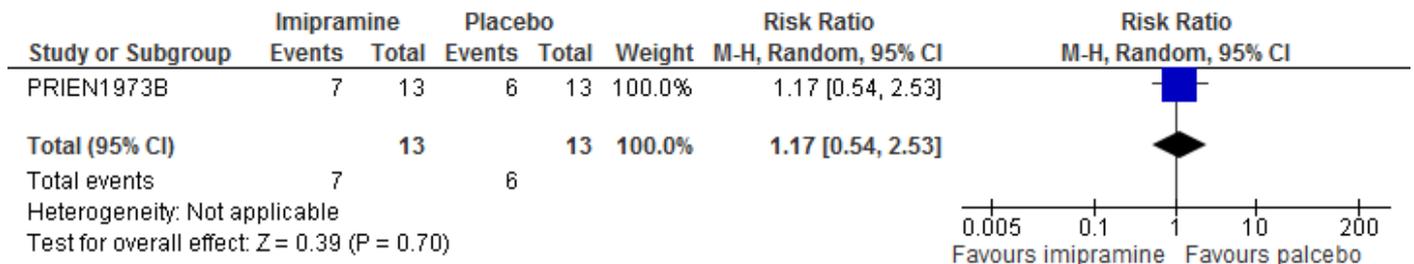
#### Number of participants who relapsed (mania)



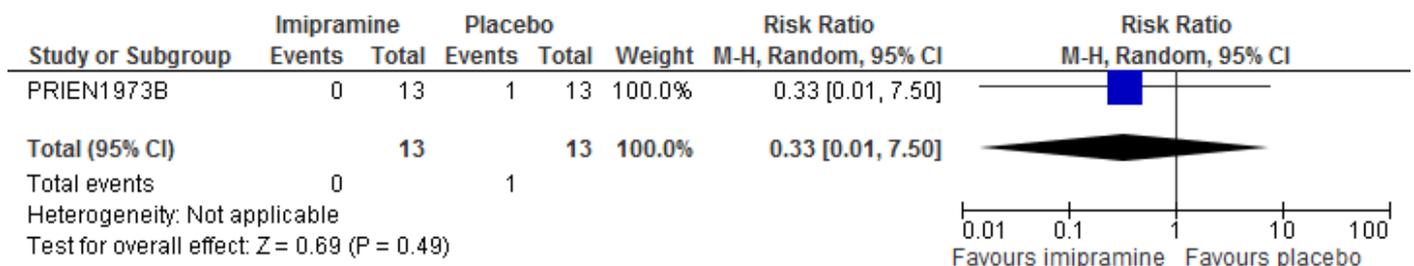
#### Number of participants who relapsed (depression)



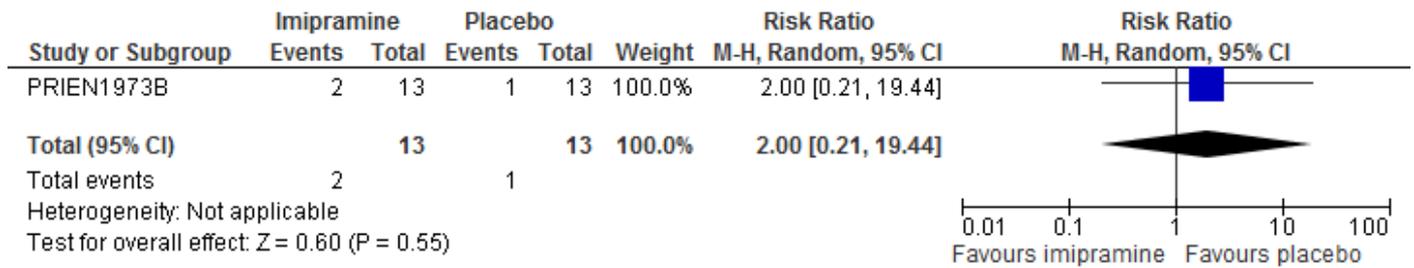
#### Number of participants discontinuing (for any reason)



#### Number of suicides

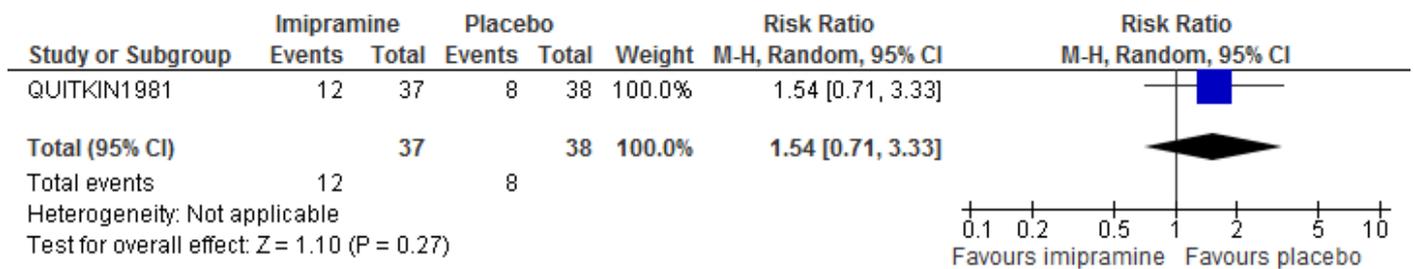


**Number of deaths**



**1.5.2 Outcomes for imipramine compared with placebo (all participants were taking lithium)**

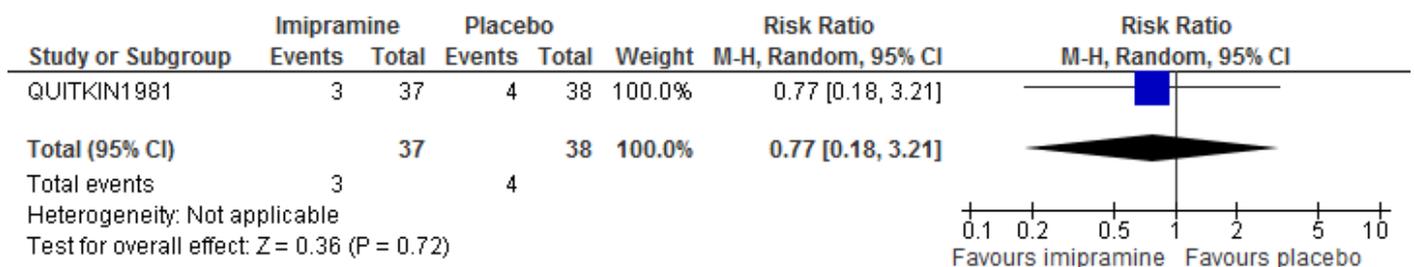
*Number of participants who relapsed (any type)*



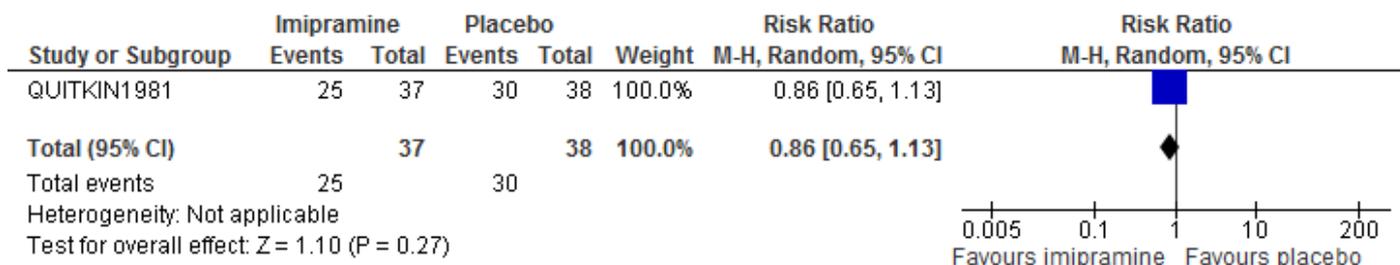
*Number of participants who relapsed (mania)*



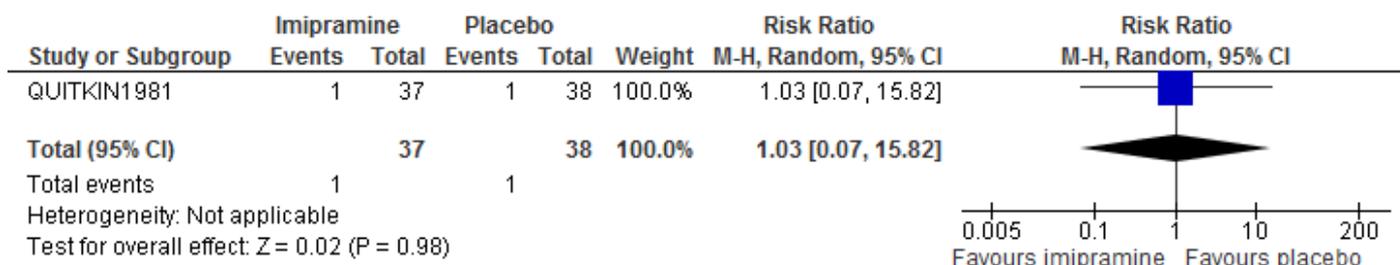
*Number of participants who relapsed (depression)*



**Number of participants discontinuing (for any reason)**

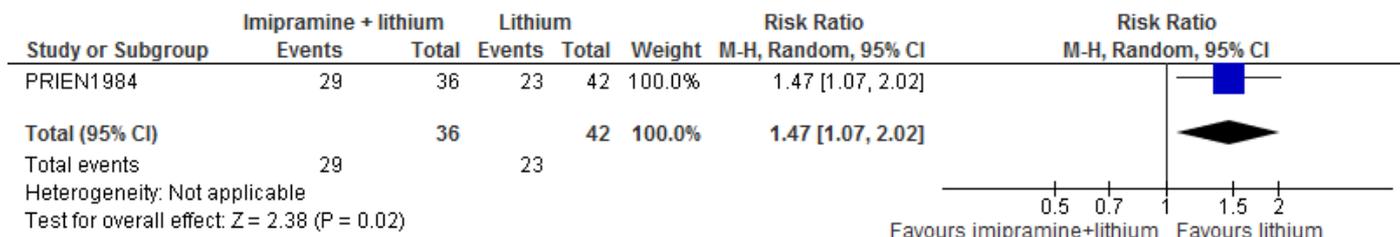


**Number of participants discontinuing due to side effects**

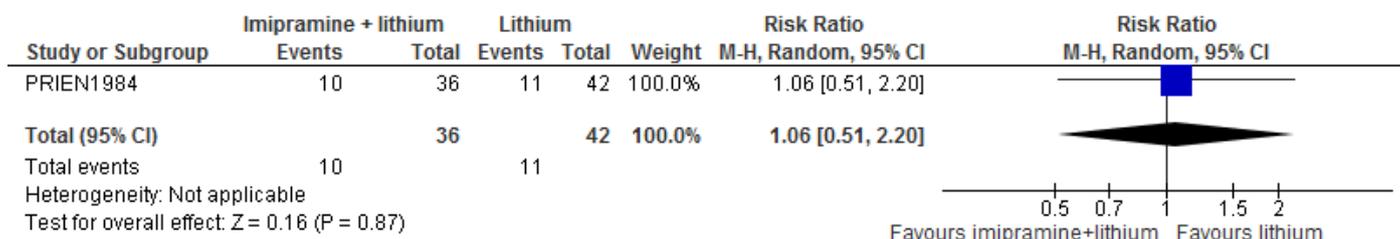


**1.5.3 Outcomes for imipramine and lithium combination compared with lithium**

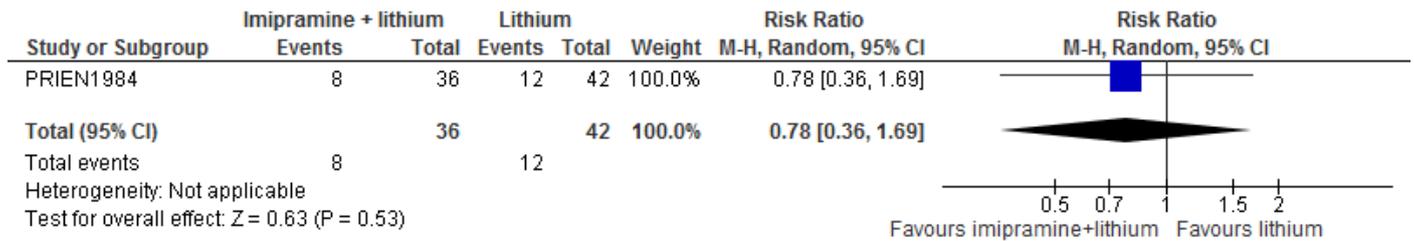
**Number of participants who relapsed (any type)**



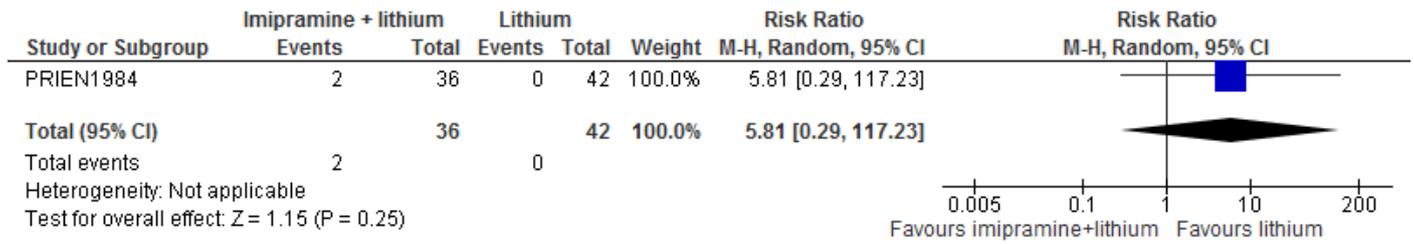
**Number of participants who relapsed (mania)**



**Number of participants who relapsed (depression)**



**Number of participants discontinuing (for any reason)**



## 1.6 DEFINITIONS OF RELAPSE IN STUDIES OF LONG-TERM MANAGEMENT

Comparison	N	K	Relapse (any)*	Definition†	Discontinuation (for any reason)*	Length of follow-up‡	References
<b>Pharmacological interventions</b>							
<b>Lithium</b>							
<i>Lithium (standard dose) compared with lithium (low dose)</i>	94	1	RR = 3.50 [1.55, 7.89]	Research diagnostic criteria or DSM-III criteria for mania or depression	RR = 0.46 [0.25, 0.83]	52	GELENBERG1989
<i>Lithium daily compared with lithium every other day)</i>	50	1	RR = 2.40 [0.99, 5.81]	Manic or depressive relapse was defined as the DSM-III-R criteria for mania or major depression and a BRMaS score $\geq 10$ or a BRMeS score $\geq 10$ , respectively	RR = 0.11 [0.01, 1.96]	56	JENSEN1995
<i>Lithium compared with placebo (participants were euthymic at study entry)</i>	92	2	RR = 0.41 [0.07, 2.43]	<i>Extra medication required to treat symptoms</i>	RR = 1.39 [0.58, 5.08]	121, 69	STALLONE1972, DUNNER1976
<i>Lithium compared with placebo (participants received open-label lamotrigine – alone or in combination with other psychotropic drugs – for 8-16 weeks and were randomised once euthymic)</i>	358	2	RR = 0.71 [0.47, 1.06]	<i>An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)</i>	RR = 1.38 [0.78, 2.45]	72, 76	CALABRESE2003, BOWDEN2003
<i>Lithium compared with placebo (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)</i>	185	1	RR = 0.80 [0.54, 1.20]	<i>A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms</i>	RR = 1.21 [0.86, 1.71]	52	BOWDEN2000

Interventions for long-term management – forest plots

Comparison	N	K	Relapse (any)*	Definition†	Discontinuation (for any reason)*	Length of follow-up‡	References
<i>Lithium compared with placebo (following remission of an acute manic episode and prior to discharge patients were stabilised on maintenance doses of lithium)</i>	205	1	RR = 0.53 [0.41, 0.67]	<i>Manic or depressive attack requiring hospitalisation or supplementary drugs</i>	RR = 0.42 [0.28, 0.62]	104	PRIEN1973
<i>Lithium compared with placebo (following remission from a depressive episode, patients were stabilised on lithium or imipramine)</i>	31	1	NR	<i>Manic or depressive attack requiring hospitalisation or supplementary drugs</i>	RR = 0.12 [0.02, 0.88]	104	PRIEN1973B
<i>Lithium compared with placebo (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)</i>	768 <sup>δ</sup>	1	NR	<i>One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania</i>	RR = 1.37 [1.06, 1.78]	104	WEISLER2011
<i>Lithium compared with carbamazepine (participants were euthymic and were ready to start prophylactic treatment)</i>	399	3	RR = 0.73 [0.56, 0.95]	Recurrence of an affective episode	RR = 0.75 [0.16, 3.54]  K = 2 ; N = 262	52, 104, 130	WOLF1997, HARTONG2003, KLEINDIENST2000
<i>Lithium compared with carbamazepine (participants were euthymic and all on stable doses of lithium)</i>	31	1	RR = 1.25 [0.57, 2.75]	Not defined	RR = 0.47 [0.05, 4.56 ]	52	COXHEAD1992
<i>Lithium compared with quetiapine (participants received open-label quetiapine for 4-24 weeks and were randomised once euthymic)</i>	768 <sup>δ</sup>	1	NR	<i>One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania;</i>	RR = 1.62 [1.23, 2.13]	104	WEISLER2011

Comparison	N	K	Relapse (any)*	Definition†	Discontinuation (for any reason)*	Length of follow-up‡	References
				<i>a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania</i>			
<i>Lithium compared with valproate (participants were randomised when euthymic and within 3 months of the onset of the index manic episode)</i>	278	1	RR = 1.28 [0.86, 1.91]	<i>A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms</i>	RR = 1.19 [0.89, 1.59]	52	BOWDEN2000
<i>Lithium compared with valproate (participants were randomised when euthymic and after 6 months of active treatment with lithium and valproate)</i>	60	1	RR = 1.13 [0.70, 1.82]	<i>Patients who met criteria for mania (a total YMRS score ≥ 20 for up to 8 weeks) or depression (a 24-item Hamilton depression scale score ≥ 20 for 8 weeks) were considered to have relapsed</i>	RR = 1.46 [0.61, 3.50]	80	CALABRESE2005C
<i>Lithium compared with valproate (participants were randomised whilst euthymic and after 4-8 weeks of active treatment with lithium and valproate)</i>	220 <sup>β</sup>	1	RR = 0.85 [0.70, 1.05]	<i>New intervention for an emerging mood episode (including drug treatment) or admission to hospital</i>	RR = 1.02 [0.78, 1.34]	104	GEDDES2010
<i>Lithium compared to lithium and valproate combination</i>	220 <sup>β</sup>	1	RR = 1.10 [0.87, 1.40]	<i>New intervention for an emerging mood episode (including drug treatment) or admission to hospital</i>	RR = 0.96 [0.74, 1.26]	104	GEDDES2010
<i>Valproate compared to lithium and valproate combination</i>	220 <sup>β</sup>	1	RR = 1.29 [1.04, 1.61]	<i>New intervention for an emerging mood episode (including drug treatment) or admission to hospital</i>	RR = 0.95 [0.72, 1.24]	104	GEDDES2010
<i>Olanzapine compared with lithium</i>	431	1	RR = 0.76 [0.56, 1.03]	<i>DSM-IV criteria for a depressive, manic or mixed episode</i>	RR = 0.79 [0.68, 0.93]	52	TOHEN2005

<b>Antipsychotics</b>							
<i>Aripiprazole compared with placebo (all participants taking lamotrigine)</i>	351	1	RR = 0.69 [0.49, 0.98]	<i>One or more of the following events: hospitalisation for a manic or mixed episode; a serious adverse event or worsening disease during the study; or discontinuation due to a lack of efficacy (as determined by the investigator). For the latter two criteria, patients also needed to have a YMRS total score <math>\geq 14</math> and a MADRS total score <math>\leq 16</math> for a relapse to a manic episode; a YMRS total score <math>\geq 14</math> and a MADRS total score <math>\geq 16</math> for a relapse to a mixed episode; and a YMRS total score <math>\leq 14</math> and a MADRS total score <math>\geq 16</math> for a relapse to a depressive episode</i>	RR = 0.92 [0.79, 1.06]	52	CARLSON2012
<i>Aripiprazole compared with placebo (all participants taking lithium or valproate)</i>	337	1	RR = 0.58 [0.38, 0.91]	<i>One or more of the following: hospitalisation for a manic, mixed or depressive episode; a serious adverse event of worsening disease accompanied by a YMRS total score <math>\geq 16</math> and/or a MADRS total score <math>\geq 16</math>; discontinuation due to lack of efficacy, as determined by the investigator, accompanied by a YMRS total score <math>\geq 16</math> and/or a MADRS total score <math>\geq 16</math></i>	RR = 0.82 [0.64, 1.05]	52	MARCUS2011
<i>Olanzapine compared with placebo (all participants taking lithium or valproate)</i>	68	1	RR = 0.66 [0.38, 1.15]	<i>YMRS total score <math>\geq 15</math>, symptomatic relapse of depression defined as an HRSD-21 total score <math>\geq 15</math></i>	RR = 0.77 [0.62, 0.94]	78	TOHEN2004
<i>Olanzapine compared with placebo</i>	278	1	RR = 0.42 [0.30, 0.59]	<i>(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score <math>\geq 12</math>, MADRS score <math>\geq 12</math>, or CGI-S scale score <math>\geq 4</math> at any visit</i>	RR = 1.10 [0.66, 1.85]	78	VIETA2012

Interventions for long-term management – forest plots

<i>Paliperidone compared with placebo</i>	300	1	RR = 0.83 [0.66, 1.06]	(1) YMRS $\geq$ 15 and CGI-BP-S for mania $\geq$ 4; YMRS $\geq$ 15, MADRS $\geq$ 16 and CGI-BP-S for depression $\geq$ 4; voluntary or involuntary hospitalisation for any mood symptoms; therapeutic intervention to prevent or treat an impending mood episode; another therapeutic measure; any other clinically relevant event suggestive of a recurrent mood episode	RR = 1.05 [0.78, 1.42]	129	BERWAERTS2012
<i>Quetiapine compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with quetiapine)</i>	585	1	RR = 0.59 [0.49, 0.76]	<i>One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 16 or 20, respectively; or discontinuation due to depression and/or mania or hypomania</i>	RR = 1.23 [1.05, 1.43]	52	YOUNG2012
<i>Quetiapine compared with placebo (participants were randomised when euthymic after 4-24 weeks of active treatment with quetiapine)</i>	808 <sup>δ</sup>	1	NR	<i>One or more of the following: initiation of any other medication to treat mania/hypomania or depression, including an antipsychotic, antidepressant mood stabilising agent, or anxiolytic other than lorazepam; hospitalisation for depression and/or mania or hypomania; a YMRS or MADRS total score of at least 20; or discontinuation due to depression and/or mania or hypomania</i>	RR = 0.85 [0.63, 1.14]	104	WEISLER2011
<i>Quetiapine compared with placebo (all participants were taking lithium or valproate)</i>	1,326	2	RR = 0.38 [0.29, 0.48]	<i>Initiation of any medication to treat mixed, manic, or depressive symptoms, including an antipsychotic, antidepressant, or mood-stabilising agent other than lithium or divalproex or an anxiolytic other than lorazepam; psychiatric hospitalisation; YMRS or MADRS total scores <math>\geq</math> 20 at two consecutive assessments; or discontinuation from the study because of a mood event (as determined by the investigator)</i>	RR = 1.53 [1.24, 1.89]	104	SUPPES2009, VIETA2008B

Interventions for long-term management – forest plots

Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 8 weeks of active treatment with risperidone)	273	1	RR = 0.69 [0.53, 0.90]	(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score $\geq$ 12, MADRS score $\geq$ 12, or CGI-S scale score $\geq$ 4 at any visit	RR = 1.33 [0.82, 2.17]	78	VIETA2012
Risperidone long-acting injectable compared with placebo (participants were randomised when euthymic after 3 weeks of active treatment with oral risperidone and 26 weeks of risperidone long-acting injectable)	303	1	RR = 0.63 [0.51, 0.77]	(1) Fulfilled DSM-IV-TR criteria for a manic, hypomanic, mixed, or depressive episode; (2) required treatment intervention with any mood stabiliser, antipsychotic medication (other than study drug), benzodiazepine (beyond the dosage allowed), or antidepressant medication; (3) hospitalisation for any bipolar mood episode; (4) had YMRS score $\geq$ 12, MADRS score $\geq$ 12, or CGI-S scale score $\geq$ 4 at any visit	RR = 0.89 [0.61, 1.32]	104	QUIROZ2010
Risperidone long-acting injectable compared with placebo injection (all participants received treatment as usual and were euthymic as randomisation following 16 weeks of active treatment with risperidone long-acting injectable)	124	1	RR = 0.50 [0.30, 0.85]	DSM-IV-TR criteria for an acute mood episode in the setting of adequate compliance with oral TAU. Additionally, at least one of the following three conditions was satisfied: (i) clinical worsening, with the addition of a new mood stabiliser, antidepressant or antipsychotic or a > 20% dose increase of existing oral TAU medication, and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score $\geq$ 4 or CGI-BP-C score $\geq$ 6 or GAF score decreased by > 10 points from baseline; (ii) hospitalisation for worsening of manic or depressive symptoms and meeting the following criteria: (a) YMRS score > 15 or MADRS score > 15 and (b) CGI-BP-S score $\geq$ 4 or CGI-BP-C score $\geq$ 6 or GAF score decreased by > 10 points from baseline; (iii) hospitalisation for worsening of manic or depressive symptoms and having significant suicidal ideation	RR = 1.27 [0.61, 2.64]	52	MACFADDEN2009

Interventions for long-term management – forest plots

Risperidone long-acting injectable in addition to treatment as usual compared with treatment as usual (all participants were rapid cyclers and not in an acute episode at randomisation)	50	1	NR	Occurrence of any of the following at any study visit: (1) a YMRS score >14 or a MADRS score >15; (2) 20% or greater increase in YMRS or MADRS scores from the previous study visit for patients with a MADRS score ≥ 10 or a YMRS score ≥ 8 at the current study visit; (3) urgent care visit/referral (psychiatric hospitalisation; emergency department visit; or referral for respite care, partial hospitalisation, or intensive outpatient treatment) due to worsening mood symptoms; (4) a CGI-S score ≥ 4; (5) syndromal relapse (DSM-IV-TR criteria for manic, hypomanic, major depressive, or mixed episode met); (6) withdrawal from the study due to inefficacy; and (7) necessary clinical medication adjustments	RR = 1.50 [0.63, 3.59]	52	BOBO2011b
<b>Anticonvulsants</b>							
Oxcarbazepine compared with placebo	55	1	RR = 0.50 [0.26, 0.94 ]	DSM-IV-TR criteria for a manic, hypomanic, mixed or depressive episode or scoring ≥ 12 in the YMRS or ≥ 20 in the MADRS	RR = 1.12 [0.55, 2.24 ]	52	VIETA2008
Gabapentin compared with placebo	25	1	NR	NR	RR = 1.08 [0.51, 2.30 ]	52	VIETA2006
Lamotrigine compared with placebo	471	2	RR = 0.82 [0.59, 1.14 ]	An intervention - addition of ECT or pharmacotherapy, including antidepressants, antipsychotics, anticonvulsants/mood stabilisers, or benzodiazepines (exceeding doses of rescue medication)	RR = 1.14 [0.64, 2.06 ]	76, 78	CALABRESE2003, BOWDEN2003
Valproate compared with placebo	281	1	RR = 0.63 [0.44, 0.90]	A manic episode was defined as one accompanied by an MRS score of 16 or more or requiring hospitalisation. A depressive episode was defined as one requiring antidepressant use or premature discontinuation from the study because of symptoms	RR = 1.02 [0.74, 1.40]	52	BOWDEN2000
<b>Antidepressants</b>							

Interventions for long-term management – forest plots

<i>Imipramine compared with placebo (all participants were taking lithium)</i>	75	1	RR = 1.54 [0.71, 3.33]	Research diagnostic criteria for mania or major depressive disorder	RR = 0.86 [0.65, 1.13]	129	QUITKIN1981
<i>Imipramine compared with placebo</i>	26	1	RR = 0.75 [0.36, 1.55]	<i>Manic or depressive attack requiring hospitalisation or supplementary drugs (that is, psychopharmacologic agents other than the patient's assigned treatment)</i>	RR = 1.17 [0.54, 2.53]	104	PRIEN1973b
<i>Imipramine and lithium combination compared with lithium</i>	78 <sup>u</sup>	1	RR = 0.68 [0.49, 0.93]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	RR <sup>o</sup> = 5.81 [0.29, 117.23]	104	PRIEN1984
<i>Imipramine and lithium combination compared with imipramine</i>	72 <sup>u</sup>	1	RR = 0.62 [0.43, 0.89]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	RR <sup>o</sup> = 5.81 [0.29, 117.23]	104	PRIEN1984
<i>Imipramine compared with lithium</i>	78 <sup>u</sup>	1	RR = 1.47 [1.07, 2.02]	A recurrence was declared if the clinical condition satisfied the research diagnostic criteria for definite major depressive disorder or mania and yielded a GAS rating of 60 or less	There was no discontinuation in either group.	104	PRIEN1984
<i>Antidepressants compared with placebo</i>	70	1	NR	NR	NR	52	GHAEMI2010

\* A relative risk (RR) of less than 1 favours the first treatment named.

† Definitions of relapse which do not meet the GDG's definition have been *italicised*.

‡ Length of follow-up reported in number of weeks.

<sup>o</sup>GEDDES2010 is a three-arm trial including lithium, valproate and the combination of lithium and valproate. The overall number of participants is 330. All three comparisons have been included in this table so the number of participants has been double-counted.

<sup>u</sup>WEISLER2011 is a three-arm trial including lithium, quetiapine and placebo. The overall number of participants is 1,172. All three comparisons have been included in this table so the number of participants has been double-counted.

<sup>u</sup>PRIEN1984 is a three-arm trial including imipramine, lithium and the combination of imipramine and lithium. The overall number of participants is 114. All three comparisons have been included in this table so the number of participants has been double-counted.

<sup>o</sup> Discontinuation due to side effects. No other reasons for discontinuation were reported.