Appendix

A) Appendix Table 1 Characteristics of 49 comparisons of interventions from 44 network meta-analyses.

Network	Journal	Title	Outcome	Number of studies in the network	Number of treatments	Comparison of greatest interest	Number of studies in the comparison of greatest interest	Type of evidence (direct / indirect)*	Justification	Side-splitting inconsistency factor and 95% confidence interval	Side-splitting P	Strong evidence using network meta-analysis	Number of studies published afterwards**	Strong evidence using pairwise meta-analysis
Buti 2013	Journal of Clinical Periodontology	Bayesian network meta-analysis of root coverage procedures: ranking efficacy and identification of best treatment.	Continuous	26	7	Coronally advanced flap and connective tissue graft ***vs*** Coronally advanced flap and enamel matrix derivative	1	both	(1)	0.24 (-0.92, 1.40)	0.69	No	NA	No
Dogliotti 2013	Heart	Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients	Binary	20	8	Vitamin K antagonists ***vs*** Apixaban	1	both	(2)	-0.06 (-0.76, 0.63)	0.86	No	NA	No
Naci 2013	Circulation: Cardiovascular Quality and Outcomes	Comparative Tolerability and Harms of Individual Statins: A Study-Level Network Meta-Analysis of 246 955 Participants From 135 Randomized, Controlled Trials	Binary	135	8	Atorvastatin ***vs*** Rosuvastatin	27	both	(3)	0.09 (-0.29, 0.46)	0.65	No	NA	No
Filippini 2013	Cochrane Database of Systematic Reviews	Immunomodulators and immunosuppressants for multiple sclerosis: a network meta-analysis (Review)	Binary	21	10	β-interferon-1a (Avonex) ***vs*** β-interferon-1a (Rebif)	1	both	(4)	-0.04 (-1.67, 1.59)	0.96	No	NA	No
Hon-Yen Wu 2013	British Medical Journal	Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in patients with diabetes: systematic review and bayesian network meta-analysis	Binary	62	11	Angiotensin receptor blockers ***vs*** Angiotensin converting enzyme inhibitors	7	both	(5)	-0.04 (-0.99, 0.90)	0.93	No	NA	No
Lin 2014	Journal of Dentistry	Primary molar pulpotomy: A systematic review and network meta-analysis	Binary	22	5	Ferric Sulphate ***vs*** Mineral trioxide aggregate	3	both	(6)	0.93	0.48	No	NA	No

										(-1.64, 3.50)				
Castellucci 2014	Journal of the American Medical Association	Clinical and Safety Outcomes Associated With Treatment of Acute Venous Thromboembolism A Systematic Review and Meta-analysis	Binary	45	8	Unfractionated heparin and vitamin K antagonist ***vs*** Low-molecular-weight heparin and vitamin K antagonist	22	both	(7)	-0.13 (-0.66, 0.39)	0.62	Yes	6	Yes
Myers 2014	BMC Musculoskeletal Disorders	The efficacy of duloxetine, non-steroidal anti-inflammatory drugs, and opioids in osteoarthritis: a systematic literature review and meta-analysis	Continuous	34	9	Celecoxib ***vs*** Tramadol	1	both	(8–11)	0.13 (-0.15, 0.42)	0.35	No	NA	No
Alfirevic 2014	British Medical Journal	Labour induction with prostaglandins: a systematic review and network meta-analysis	Binary	94	13	Vaginal misoprostol ***vs*** Vaginal prostaglandin E2	2	both	(12)	0.04 (-0.83, 0.92)	0.95	No	NA	No
Greco 2015	British Journal of Anaesthesia	A Bayesian network meta-analysis on the effect of inodilatory agents on mortality	Binary	46	5	Dobutamine ***vs*** Levosimendan	4	both	No guidelines***	-0.26 (-2.10, 1.59)	0.79	Yes	1	No
Greco 2015	British Journal of Anaesthesia	A Bayesian network meta-analysis on the effect of inodilatory agents on mortality	Binary	46	5	Dobutamine ***vs*** Milrinone	2	both	No guidelines***	0.90 (-1.54, 3.35)	0.47	No	NA	No
Walsem 2015	Arthritis Research & Therapy	Relative benefit-risk comparing diclofenac to other traditional non-steroidal anti-inflammatory drugs and cyclooxygenase-2 inhibitors in patients with osteoarthritis or rheumatoid arthritis: a network meta-analysis	Continuous	57	7	Diclofenac ***vs*** Celecoxib	3	both	(13,14)	-0.05 (-0.54, 0.45)	0.86	Yes	0	No
Singh 2015	Gastroenterology	Comparative Efficacy of Pharmacologic Interventions in Preventing Relapse of Crohn's Disease After Surgery: A Systematic Review and Network Meta-analysis	Binary	20	8	5-ASA ***vs*** Anti–tumor necrosis factor	1	both	(15)	0.99 (-1.37, 3.35)	0.41	Yes	0	No
Singh 2015	Gastroenterology	Comparative Efficacy of Pharmacologic Interventions in Preventing Relapse of Crohn's Disease After Surgery: A Systematic Review and Network Meta-analysis	Binary	20	8	Anti–tumor necrosis factor ***vs*** Placebo	1	both	(15)	0.22 (-3.29, 3.74)	0.90	Yes	0	No

Linde 2015	The Annals of Family Medicine	Efficacy and Acceptability of Pharmacological Treatments for Depressive Disorders in Primary Care: Systematic Review and Network Meta-Analysis	Binary	59	9	Selective serotonin reuptake inhibitors ***vs*** Tricyclic and tetracyclic antidepressants	18	both	(16)	-0.26 (-0.60, 0.08)	0.13	No	NA	No
Sun 2015	Diabetes Technology & Therapeutics	Gastrointestinal Adverse Events of Glucagon-Like Peptide-1 Receptor Agonists in Patients with Type 2 Diabetes: A Systematic Review and Network Meta-Analysis	Binary	60	26	Metformin ***vs*** Sitagliptin	1	both	(17)	0.25 (-1.43, 1.94)	0.77	Yes	0	No
Leucht 2013	Lancet	Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis	Continuous	167	16	Haloperidol ***vs*** Olanzapine	11	both	(18)	-0.02 (-0.21, 0.17)	0.85	Yes	0	No
Ke-Qing Shi 2013	European Journal of Clinical Investigation	Secondary prophylaxis of variceal bleeding for cirrhotic patients: a multiple-treatments meta-analysis	Binary	51	12	Endoscopic injection sclerotherapy ***vs*** Endoscopic banding ligation	1	both	(19)	-1.86 (-4.14, 0.43)	0.11	Yes	1	No
Stagg 2014	Annals of Internal Medicine	Treatment of Latent Tuberculosis Infection. A Network Meta-analysis	Binary	38	15	Isoniazid (six months) ***vs*** Rifampicin and isoniazid (three-four months)	6	both	(20)	-0.20 (-1.02, 0.63)	0.64	No	NA	No
Tadrous 2014	Osteoporosis International	Comparative gastrointestinal safety of bisphosphonates in primary osteoporosis: a network meta-analysis	Binary	46	5	Alendronate ***vs*** Risedronate	3	both	(21)	0.04 (-0.52, 0.61)	0.88	No	NA	No
Dong 2013	Thorax	Comparative safety of inhaled medications in patients with chronic obstructive pulmonary disease: systematic review and mixed treatment comparison meta-analysis of randomised controlled trials	Binary	41	6	Inhaled corticosteroids ***vs*** Long-acting β2 agonists - inhaled corticosteroids	7	both	(22)	0.04 (-0.57, 0.65)	0.90	No	NA	No
Stevens 2015	Diabetes Research and Clinical Practice	Preventing the progression to Type 2 diabetes mellitus in adults at high risk: A systematic review and network meta-analysis of lifestyle, pharmacological and surgical interventions	Time to event	30	20	Standard care or placebo ***vs*** Diet and exercise	11	both	(17)	-0.48 (-1.52, 0.57)	0.37	Yes	6	Yes
Lin 2012	Journal of Clinical Periodontology	In-office treatment for dentin hypersensitivity: a systematic review and network meta-analysis	Continuous	41	6	Chemical occlusion ***vs*** Physical occlusion	5	both	(23)	-1.16 (-3.10, 0.78)	0.71	No	NA	No

Fretheim 2012	BMC Medicine	Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis	Binary	26	9	Angiotensin converting enzyme inhibitors ***vs*** Calcium-channel blockers	2	both	(24)	-0.12 (-0.28, 0.05)	0.18	No	NA	No
Fretheim 2012	BMC Medicine	Comparative effectiveness of antihypertensive medication for primary prevention of cardiovascular disease: systematic review and multiple treatments meta-analysis	Binary	26	9	Angiotensin receptor blockers ***vs*** Calcium-channel blockers	2	both	(24)	0.03 (-0.21, 0.27)	0.81	No	NA	No
Liu 2012	Diabetes, Obesity and Metabolism	Effect of antidiabetic agents added to metformin on glycaemic control, hypoglycaemia and weight change in patients with type 2 diabetes: a network meta-analysis	Continuous	39	9	Thiazolidinediones ***vs*** Dipeptidyl peptidase-IV inhibitors	2	both	(17)	0.10 (-0.23, 0.42)	0.56	No	NA	No
Lori 2012	Cardiovascular Drugs and Therapy	Systematic Review and Meta-analysis of the Efficacy of Cardioversion by Vernakalant and Comparators in Patients with Atrial Fibrillation	Binary	20	11	Amiodarone (IV) ***vs*** Flecainide (IV)	1	both	(2)	-0.43 (-3.55, 2.69)	0.79	No	NA	No
Ara 2012	Health Technology Assessment	What is the clinical effectiveness and cost-effectiveness of using drugs in treating obese patients in primary care? A systematic review	Continuous	26	8	Orlistat ***vs*** Standard care	5	both	(25)	-0.92 (-6.75, 4.93)	0.76	Yes	4	Yes
Gray 2012	Obesity reviews	A systematic review and mixed treatment comparison of pharmacological interventions for the treatment of obesity	Continuous	28	8	Orlistat ***vs*** Lifestyle	6	both	(25)	-0.51 (-1.45, 0.44)	0.30	Yes	5	Yes
Chatterjee 2013	British Medical Journal	Benefits of β blockers in patients with heart failure and reduced ejection fraction: network meta-analysis	Binary	21	8	Metoprolol ***vs*** Bisoprolol	0	indirect	(26)	NE	NE	No	NA	NE
Mavranezouli 2013	PharmacoEconomics	The Cost Effectiveness of Pharmacological Treatments for Generalized Anxiety Disorder	Time to event	26	11	Sertraline ***vs*** Diazepam	0	indirect	(27)	NE	NE	No	NA	NE
Akshintala 2013	Alimentary Pharmacology and Therapeutics	Systematic review with network metaanalysis: pharmacological prophylaxis against post-ERCP pancreatitis	Binary	99	17	Nonsteroidal anti-inflammatory drugs ***vs*** Nafamostat	0	indirect	(28–30)	NE	NE	No	NA	NE

Bodalia 2013	British Journal of Clinical Pharmacology	Comparative Efficacy and Tolerability of Antiepileptic Drugs for Refractory Focal Epilepsy	Binary	41	11	Pregabalin ***vs*** Gabapentin	0	indirect	(31)	NE	NE	No	NA	NE
Kew 2014	Cochrane Database of Systematic Reviews	Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis (Review)	Continuous	25	5	Glycopyrronium bromide ***vs*** Budesonide	0	indirect	(22)	NE	NE	No	NA	NE
Windecker 2014	British Medical Journal	Revascularisation versus medical treatment in patients with stable coronary artery disease: network meta-analysis	Time to event	95	9	Everolimus eluting stent ***vs*** Coronary artery bypass grafting	0	indirect	(32)	NE	NE	No	NA	NE
Kriston 2014	Depression and Anxiety	Efficacy and acceptability of acute treatments for persistent depressive disorder: a network meta-analysis	Binary	45	10	Fluoxetine ***vs*** Escitalopram	0	indirect	(16)	NE	NE	No	NA	NE
Dong 2015	Medicine	Treatments for Shoulder Impingement Syndrome A PRISMA Systematic Review and Network Meta-Analysis	Continuous	26	17	Exercise and nonsteroidal anti-inflammatory drugs ***vs*** Exercise	0	indirect	(33)	NE	NE	Yes	NA	NE
Rotta 2013	Jama Dermatology	Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed treatment comparison meta-analysis involving 14 treatments.	Binary	60	15	Terbinafine ***vs*** Flutrimazole	0	indirect	(34)	NE	NE	No	NA	NE
Murad 2012	The Journal of Clinical Endocrinology & Metabolism	Comparative Effectiveness of Drug Treatments to Prevent Fragility Fractures: A Systematic Review and Network Meta-Analysis	Binary	40	11	Alendronate ***vs*** Denosumab	0	indirect	(35)	NE	NE	No	NA	NE
Ramsberg 2012	Plos One	Effectiveness and Cost-Effectiveness of Antidepressants in Primary Care: A Multiple Treatment Comparison Meta-Analysis and Cost-Effectiveness Model	Binary	87	17	Amitriptyline ***vs*** Fluoxetine	0	indirect	(16)	NE	NE	No	NA	NE
Haas 2012	British Medical Journal	Tocolytic therapy for preterm delivery: systematic review and network meta-analysis	Binary	55	17	Nifedipine ***vs*** Placebo	0	indirect	(36)	NE	NE	Yes	0	NE
Shamiliyan 2012	Agency for Healthcare Research and Quality	Migraine in Adults: Preventive Pharmacologic Treatments Preventive Pharmacologic Treatments	Binary	83	14	Candesortom ***vs*** Topiramate	0	indirect	(37)	NE	NE	Yes	0	NE

Shi 2013	European Journal of Clinical Investigation	Secondary prophylaxis of variceal bleeding for cirrhotic patients: a multiple-treatments meta-analysis	Binary	51	12	Endoscopic banding ligation ***vs*** Endoscopic banding ligation and endoscopic injection sclerotherapy	3	direct	(19)	NE	NE	No	NA	No
Dogliotti 2013	Heart	Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79 808 patients	Binary	20	8	Vitamin K antagonists ***vs*** Rivaroxaban	1	direct	(2)	NE	NE	No	NA	No
Pechlivanoglou 2013	Journal of Antimicrobial Chemotherapy	Mixed treatment comparison of prophyla xis against invasive fungal infections in n eutropenic patients receiving therapy for haematological malignancies: a systematic review	Rate	25	9	Posaconazole ***vs*** Fluconazole	1	direct	(38)	NE	NE	Yes	0	Yes
Yang 2014	Plos One	Efficacy and Safety of Therapies for Acute Ischemic Stroke in China: A Network Meta-Analysis of 13289 Patients from 145 Randomized Controlled Trials	Binary	145	5	Edaravone ***vs*** Placebo	41	direct	(39–42)	NE	NE	Yes	40	Yes
Zoccai 2014	International Journal of Cardiology	Nephropathy after administration of iso-osmolar and low-osmolar contrast media: Evidence from a network meta-analysis	Binary	33	7	Iopromide ***vs*** Iodixanol	9	direct	(43)	NE	NE	No	NA	No
Samarasekera 2013	British Journal of Dermatology	Topical therapies for the treatment of plaque psoriasis: system atic review and network meta-analyses.	Binary	34	14	Very potent corticosteroid ***vs*** Placebo	5	direct	(44)	NE	NE	Yes	3	Yes
Terasawa 2012	Cancer Treatment Reviews	Comparative efficacy of first-line therapies for advanced-stage chronic lymphocytic leukemia: A multiple-treatment meta-analysis	Time to event	25	10	Fludarabine-rituximab-based chemoimmunotherapies ***vs*** Fludarabine-based combination regimens	1	direct	(45)	NE	NE	No	NA	No

Treatment effects and inconsistency factors from the SIDE test are expressed as standardized mean difference, log odds ratios and log hazard ratios for continuous, binary and time to event data respectively. Heterogeneity is assumed equal to the median of the respective predictive distributions according to outcome and intervention characteristics. Efficacy boundaries are constructed using an alpha spending function, which resembles the O'Brien Flemming boundaries. Type I and type II errors were set throughout to be 5% and 10% respectively. We set the anticipated treatment effect to detect equal to the final estimate from network meta-analysis. See **B) References to guidelines used to select treatment comparisons** and

C) References to the included network meta-analyses. NE: non estimable; vs: versus; NA: non applicable.

* Type of evidence refers to the availability of direct alone, indirect alone or both direct and indirect evidence

** We present the number of direct studies addressing a comparison that were published after network meta-analysis provided strong evidence.

*** For Greco 2015 we could not identify any guidelines available.

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D) Appendix Table 2 Sensitivity analysis: estimated heterogeneity

Number of comparisons with strong evidence from conventional pairwise and network meta-analysis, with heterogeneity estimated at each step of the analysis separately for pairwise and network meta-analysis.

Strong evidence against the null hypothesis of treatment differences		**Network meta-analysis**		Total	*P* value of McNemar exact test
		Yes	No		
Pairwise meta-analysis	Yes	7 (14%)	0 (0%)	7 (14%)	0.008
	No	8 (16%)	34 (69%)	42 (86%)	
Total		15 (31%)	34 (69%)	49 (100%)	

Treatment effects are measured as standardized mean difference, log odds ratios and log hazard ratios for continuous, binary and time to event data respectively. Monitoring boundaries are constructed using an alpha spending function, which resembles the O'Brien Flemming boundaries. Type I and type II errors were set throughout to be 5% and 10% respectively. We set the anticipated treatment effect to detect equal to the final estimate from network meta-analysis.

E) Appendix Table 3 Sensitivity analysis: difference equal to final estimate from pairwise meta-analysis

Number of comparisons with strong evidence from conventional pairwise and network meta-analysis.

Strong evidence against the null hypothesis of treatment differences		**Network meta-analysis**		Total	*P* value of McNemar exact test
		Yes	No		
Pairwise meta-analysis	Yes	7 (14 %)	0 (0%)	7 (14 %)	0.004
	No	9 (18 %)	33 (67 %)	42 (86 %)	
Total		16 (33 %)	33 (67 %)	49 (100%)	

Treatment effects are measured as standardized mean difference, log odds ratios and log hazard ratios for continuous, binary and time to event data respectively. Monitoring boundaries are constructed using an alpha spending function, which resembles the O'Brien Flemming boundaries. Type I and type II errors were set throughout to be 5% and 10% respectively. We set the anticipated treatment effect to detect equal to the final estimate from pairwise meta-analysis when available; for the 13 comparisons where direct evidence was absent, we set the anticipated treatment effect to detect equal to the final estimate from network meta-analysis. Heterogeneity variance was imputed as the median value of the predictive distributions suggested for heterogeneity using empirical data.

F) Appendix Table 4 Number of comparisons with strong evidence from conventional pairwise and network meta-analysis according to the type of evidence informing the comparison of interest

Number of comparisons with strong evidence from conventional pairwise and network meta-analysis classified according to the type of evidence. In parentheses, we present the P values from the Exact McNemar test. For comparisons with both direct and indirect evidence, network meta-analysis is 24% more likely to provide strong evidence (95% CI 8% to 44%).

Comparisons with both direct and indirect evidence (P=0.016)				
Strong evidence against the null hypothesis of treatment differences		**Network meta-analysis**		Total
		Yes	No	
Pairwise meta-analysis	Yes	4 (14%)	0 (0%)	4 (14%)
	No	7 (24%)	18 (62%)	25 (86%)
Total		11 (38%)	18 (62%)	29 (100%)
Comparisons with indirect evidence only				
Strong evidence against the null hypothesis of treatment differences		**Network meta-analysis**		Total
		Yes	No	
Pairwise meta-analysis	Yes	-	-	-
	No	3 (23%)	10 (77%)	13 (100%)
Total		3 (23%)	10 (77%)	13 (100%)
Comparisons with direct evidence only				
Strong evidence against the null hypothesis of treatment differences		**Network meta-analysis**		Total
		Yes	No	
Pairwise meta-analysis	Yes	4 (57%)	0	4 (57%)
	No	0	3 (43%)	3 (43%)
Total		4 (57%)	3 (43%)	7 (100%)

A pairwise or network meta-analysis provided strong evidence against the null hypothesis when the accumulated information crossed the monitoring boundaries. Monitoring boundaries were constructed using an alpha spending function, with Type I and type II errors set at 5% and 10% respectively. We set the anticipated treatment effect to detect equal to the final estimate from network meta-analysis. Treatment effects were measured as standardized mean difference, log odds ratios and log hazard ratios for continuous, binary and time to event data respectively. Heterogeneity variance was imputed as the median value of the predictive distributions suggested for heterogeneity using empirical data.

G) Appendix Table 5 Number of comparisons with strong evidence from conventional pairwise and network meta-analysis according to medical field

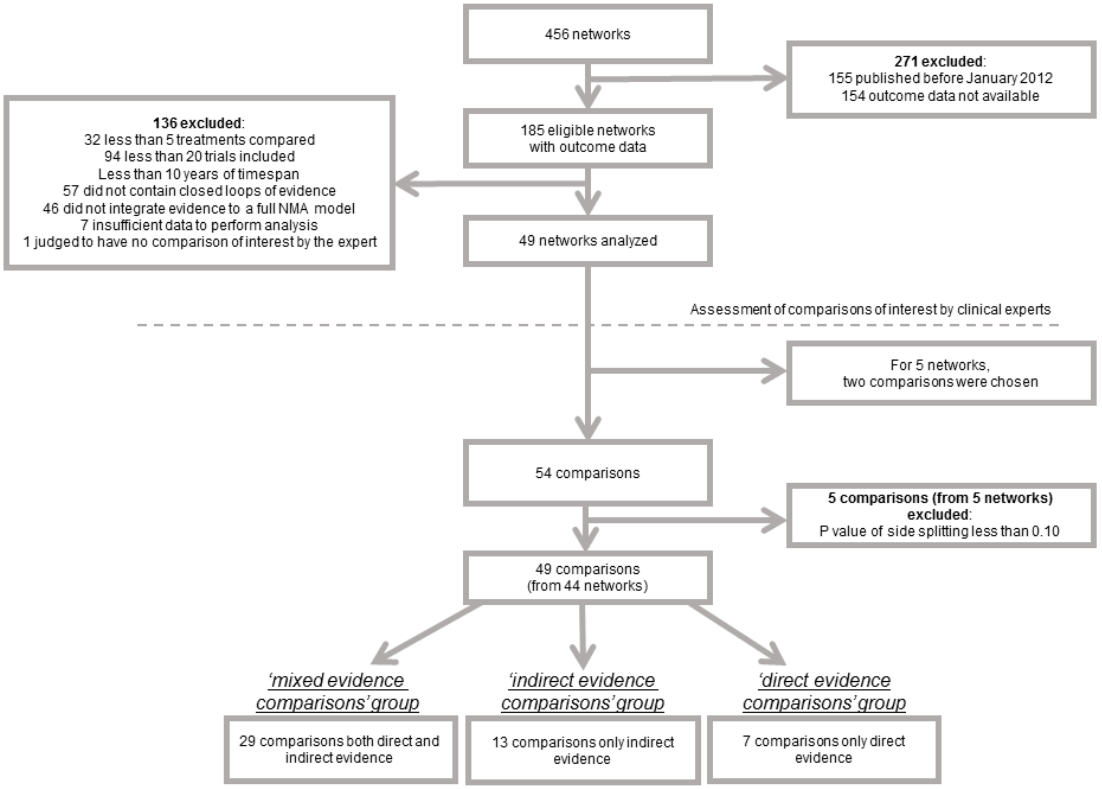
Number of comparisons with strong evidence from conventional pairwise and network meta-analysis classified according to the medical field.

Medical field	Strong evidence with pairwise meta-analysis	Strong evidence with network meta-analysis
Cardiology	2 out of 11 comparisons	2 out of 11 comparisons
Endocrinology	3 out of 6 comparisons	4 out of 6 comparisons
Psychiatry	0 out of 5 comparisons	1 out of 5 comparisons
Rheumatology	0 out of 5 comparisons	2 out of 5 comparisons
Neurology	0 out of 3 comparisons	1 out of 3 comparisons
Dentistry/periodontology	0 out of 3 comparisons	0 out of 3 comparisons
Pulmonology	0 out of 3 comparisons	0 out of 3 comparisons
Dermatology	1 out of 2 comparisons	1 out of 2 comparisons
Gastroenterology	0 out of 3 comparisons	2 out of 3 comparisons
Obstetrics	0 out of 2 comparisons	1 out of 2 comparisons
Oncology	1 out of 2 comparisons	1 out of 2 comparisons
Anesthesiology	0 out of 2 comparisons	1 out of 2 comparisons
Hepatology	0 out of 2 comparisons	1 out of 2 comparisons

A pairwise or network meta-analysis provided strong evidence against the null hypothesis when the accumulated information crossed the monitoring boundaries. Monitoring boundaries were constructed using an alpha spending function, with type I and type II errors set at 5% and 10% respectively. We assumed an anticipated treatment effect to detect equal to the final estimate from network meta-analysis. Treatment effects were measured as standardized mean difference, log odds ratios and log hazard ratios for continuous, binary and time to event data respectively. Heterogeneity variance was imputed as the median value of the predictive distributions suggested for heterogeneity using empirical data.

H) Appendix Figure 1 Flow chart of the identified networks of interventions.

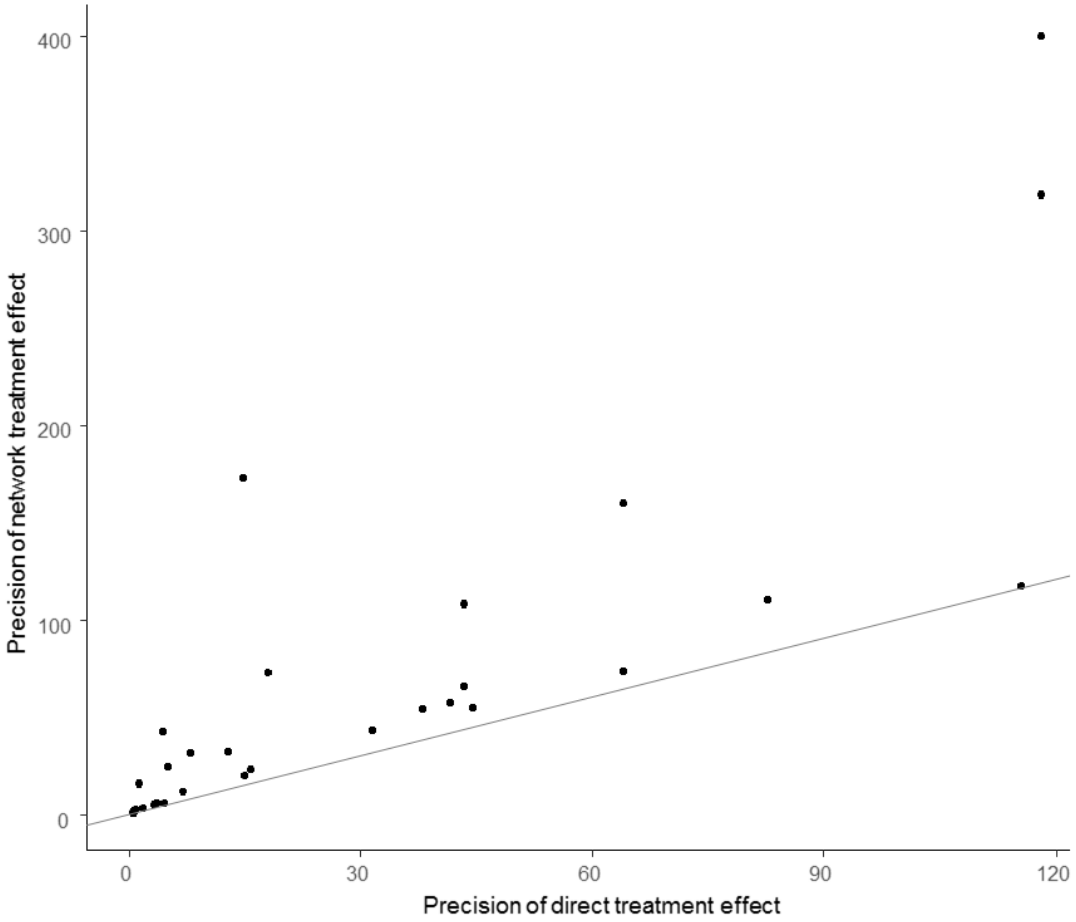
We excluded networks that did not integrate direct and indirect evidence in a full network meta-analysis model and networks that did not contain closed loops of evidence, or contained only loops formed by multi-arm studies only. We asked experts to provide a single comparison of highest interest; in the case that they reported two comparisons, we kept them both. We judged upon evidence of inconsistency using the SIDE approach (also called node-splitting) implemented in Stata using the *network sidesplit* command; network comparisons with a P value less than 0.10 were excluded. NMA: network meta-analysis.



I) Appendix Figure 2 Scatter plot of precision of final treatment effects

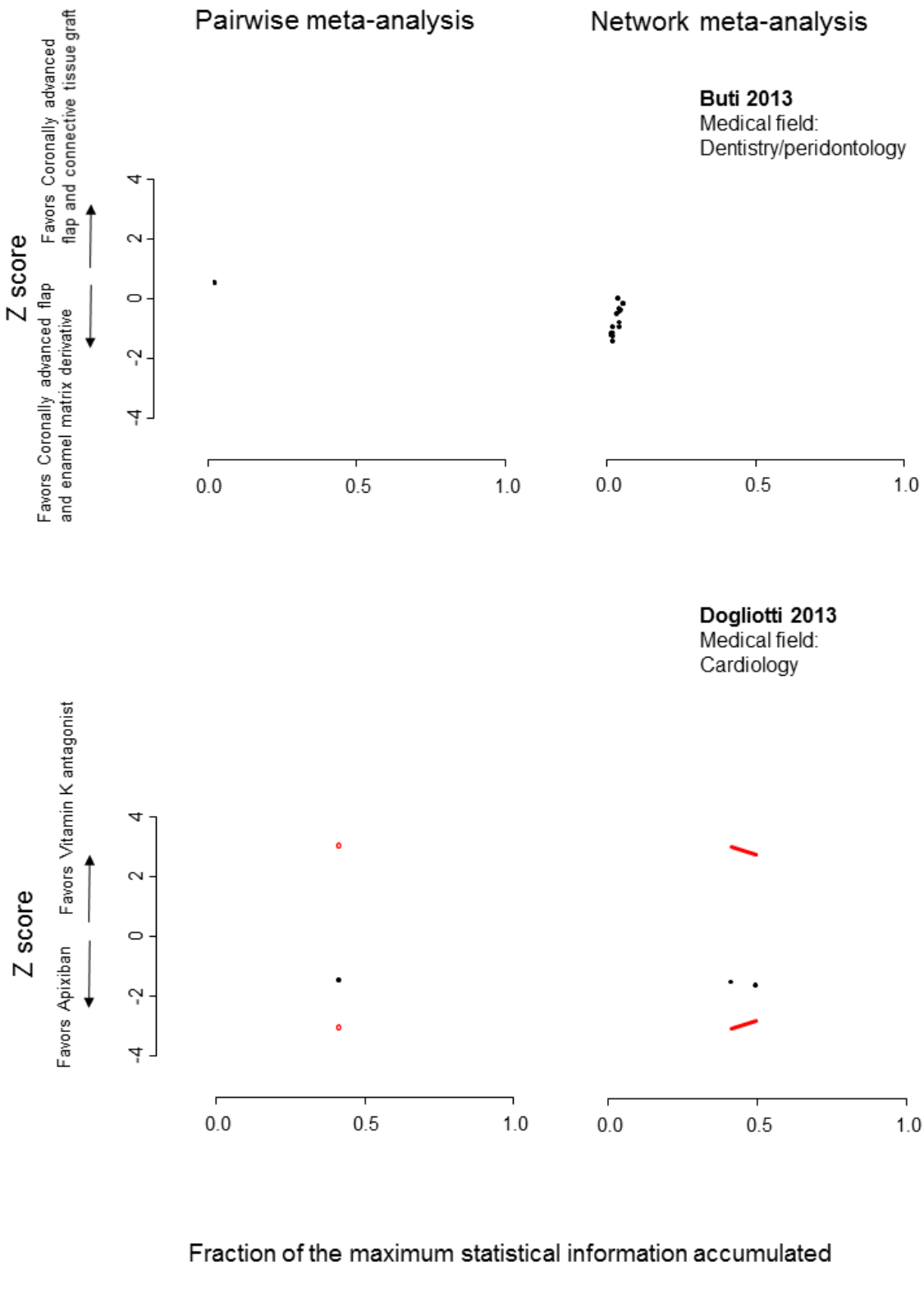
Scatter plot of precision of final treatment effects in mixed evidence comparisons (29 comparisons), measured as inverse of the variance of the meta-analytic estimate, using pairwise and network meta-analysis.

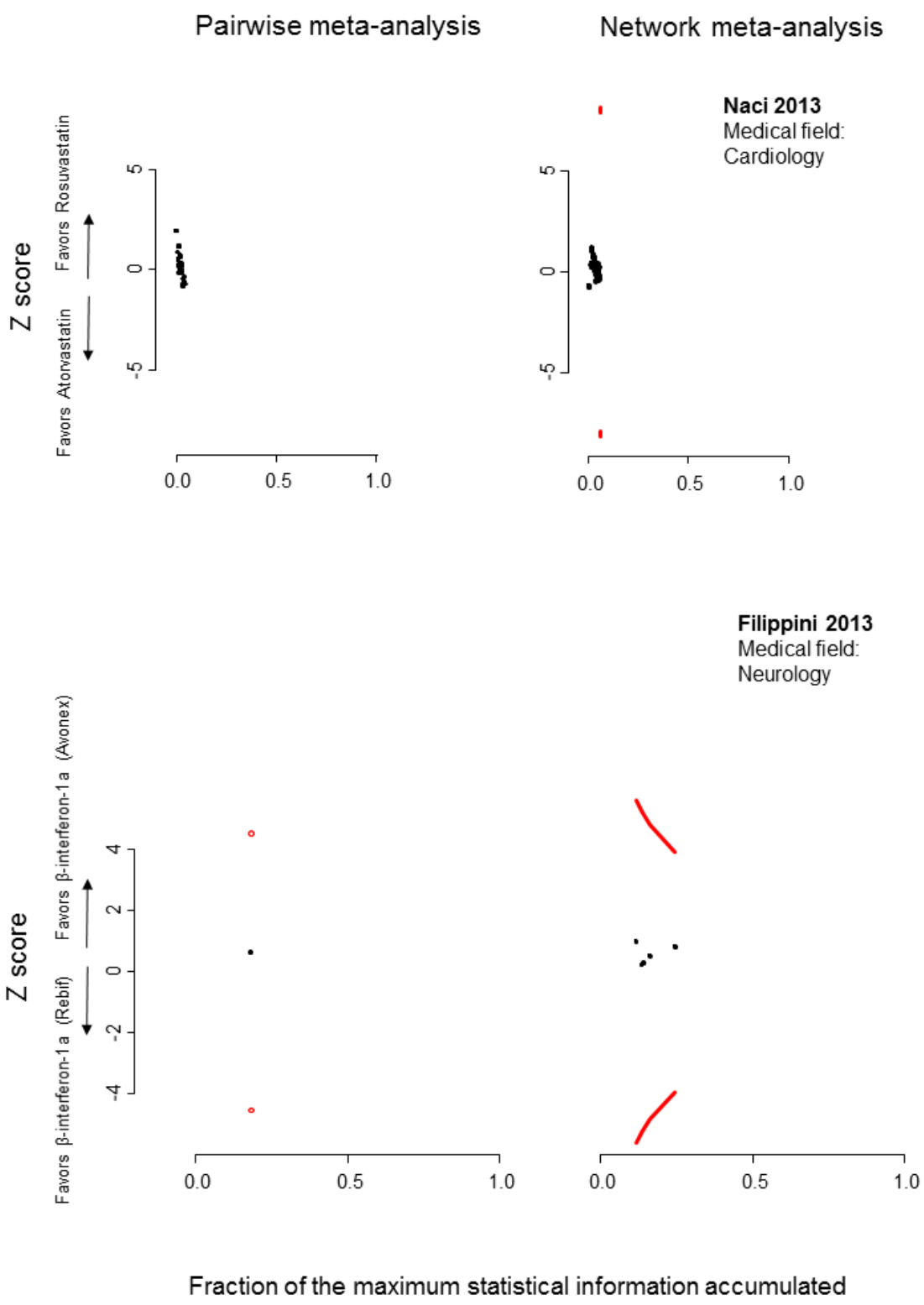
All circles are lying above the diagonal, indicating that network meta-analyses usually provide more precise results than pairwise meta-analysis.

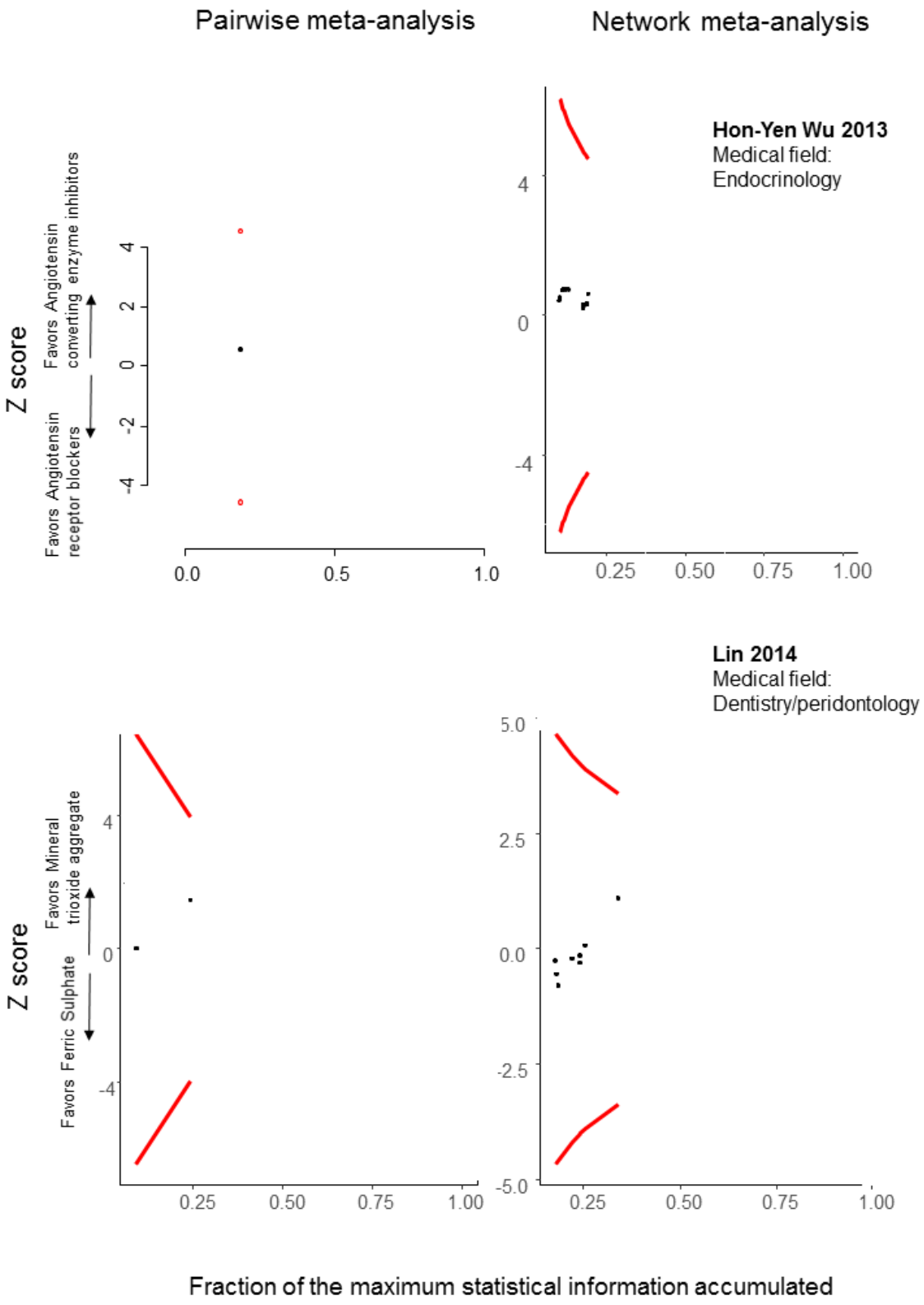


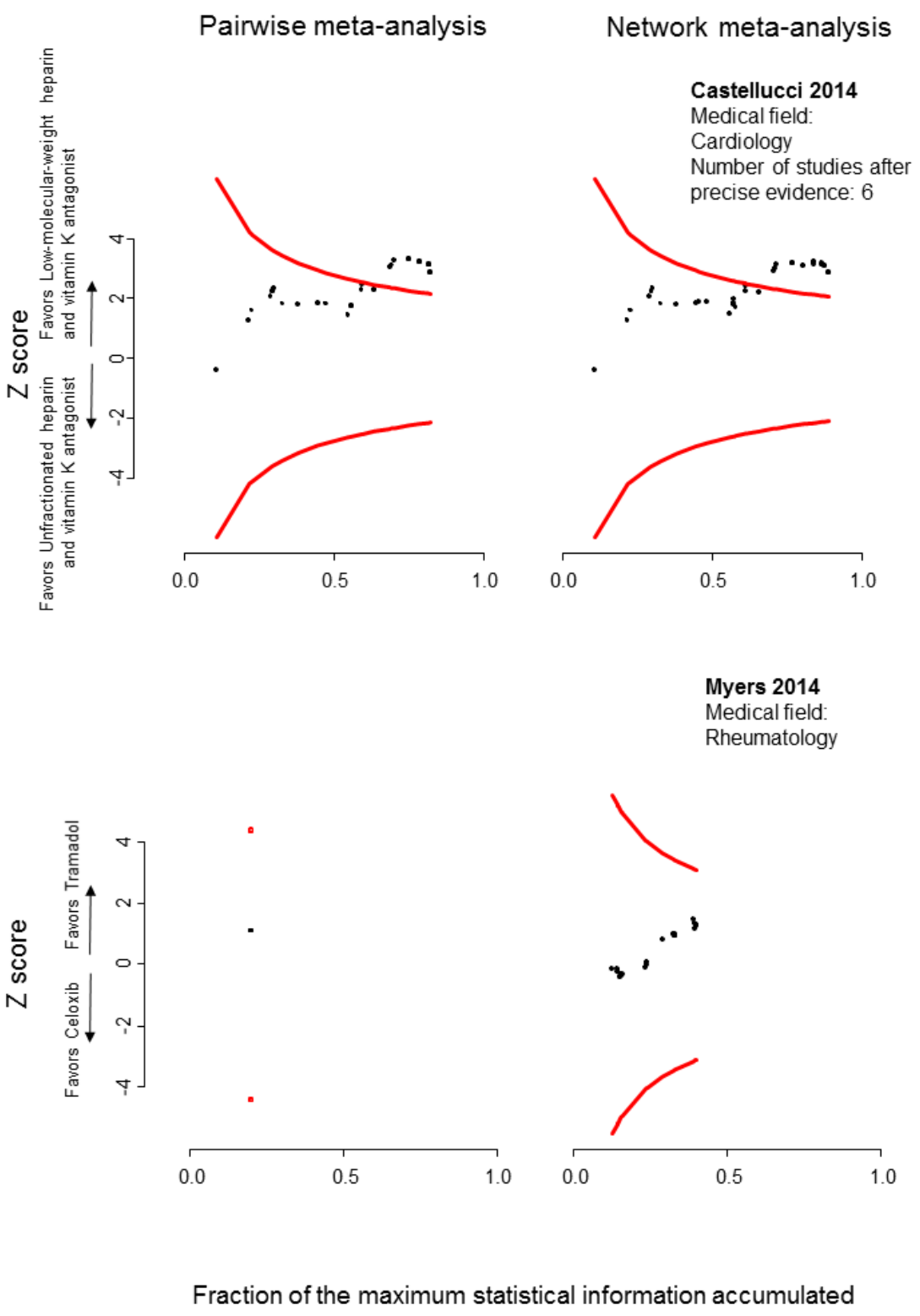
J) Appendix Figure 3 Z-scores and monitoring boundaries for all the comparisons of highest interest.

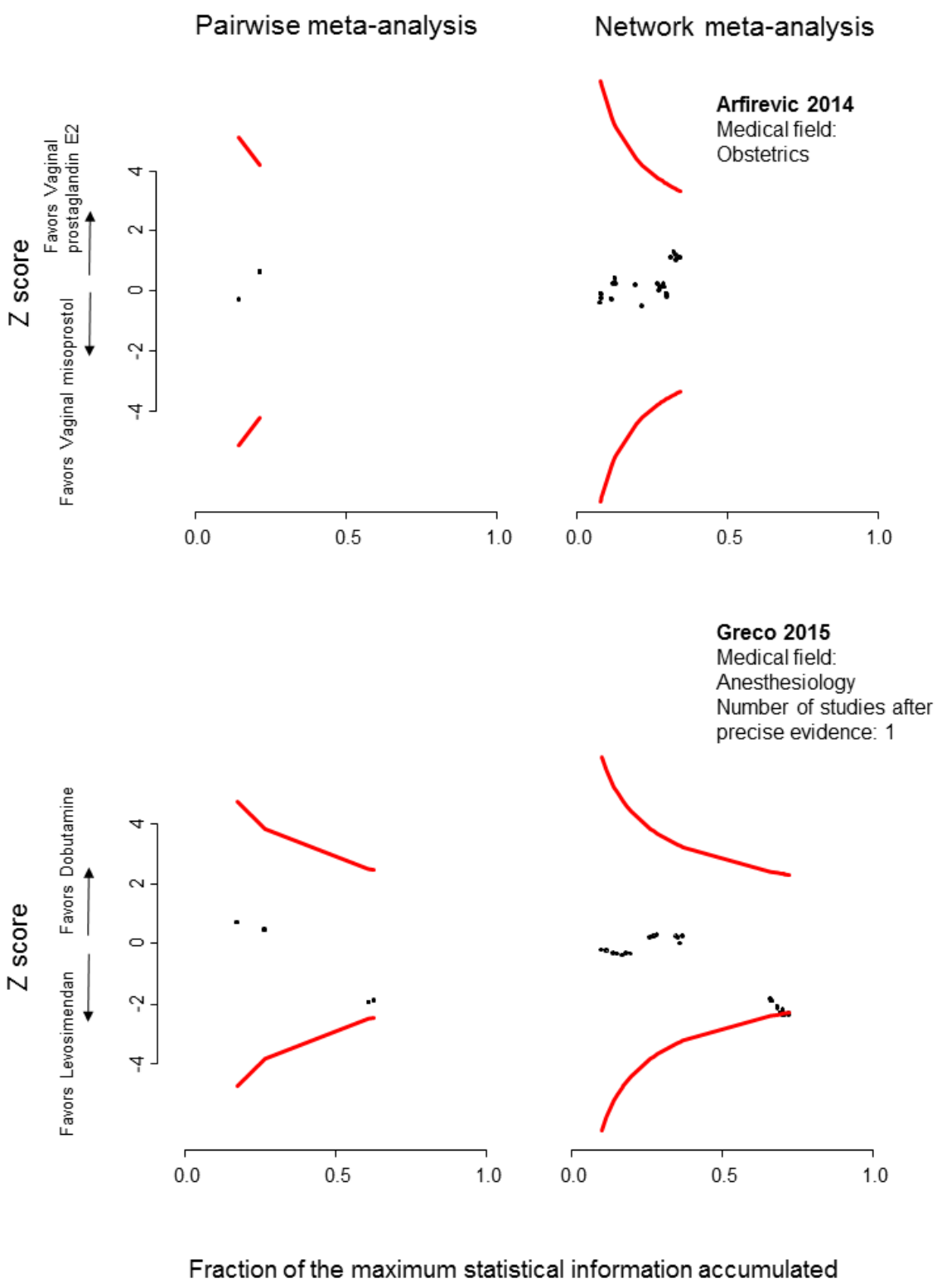
Monitoring boundaries were constructed using an alpha spending function with type I and type II errors fixed at 5% and 10%, respectively. The horizontal axis shows the statistical information that accumulated over time, compared to the maximum statistical information (the information in a single adequately powered study). Heterogeneity variance is assumed equal to the median of the respective predictive distributions. Monitoring boundaries are drawn for the range of estimated Z-scores and are displayed as red lines (or points when they can be estimated only for a single Z-score). When monitoring boundaries are not drawn, they are larger than the limits of the x-axis. When accumulated information is greater than the maximum statistical information from the first update (more than 1 in the horizontal axis), conventional boundaries of 1.96 are drawn. First author's name, year of publication, medical field and, when applicable, number of additional studies after strong evidence with network meta-analysis are also displayed.

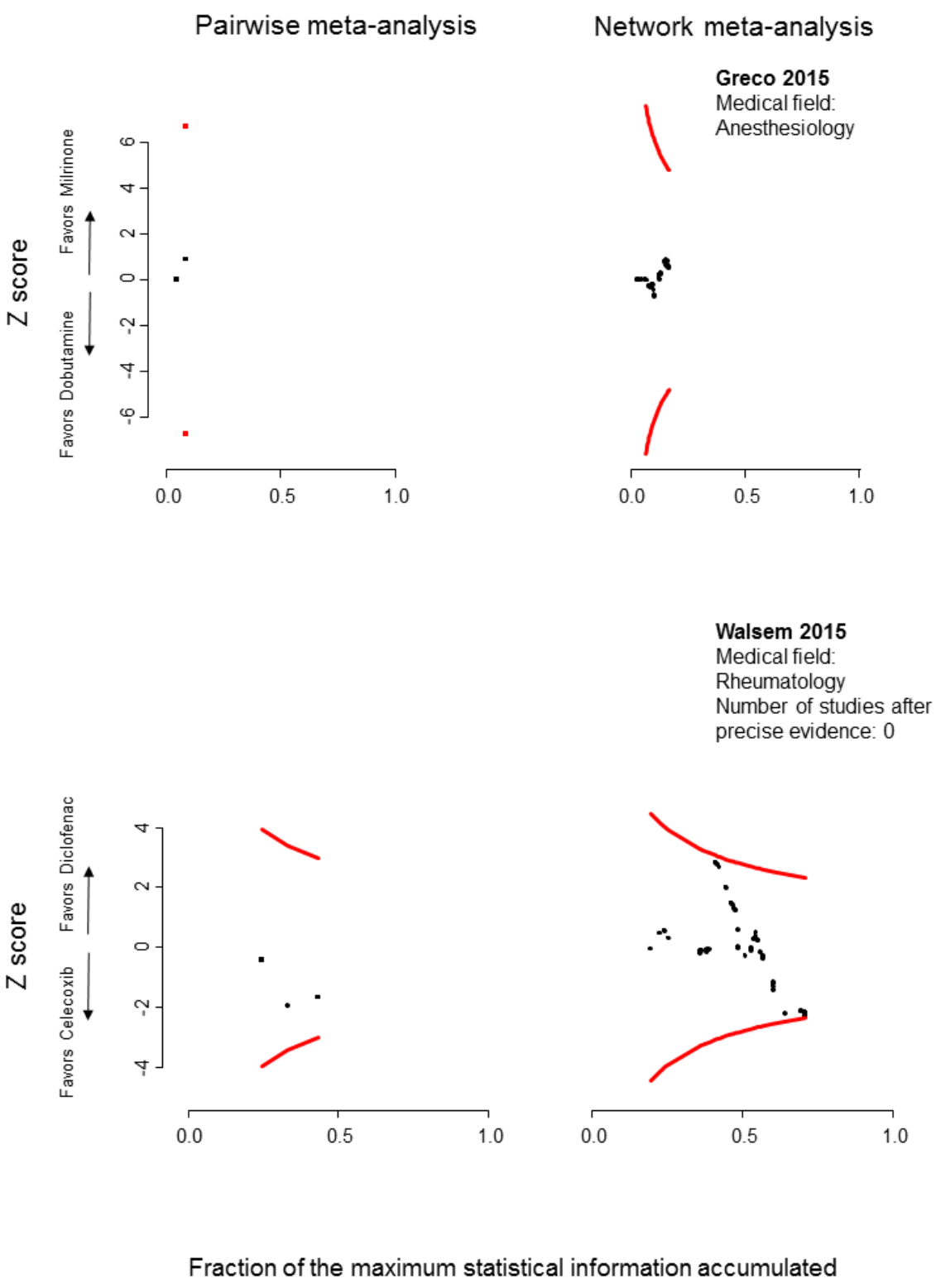

Pairwise meta-analysis
Network meta-analysis
Buti 2013
Medical field:
Dentistry/peridontology
Dogliotti 2013
Medical field:
Cardiology
Z score
Favors Coronally advanced flap and enamel matrix derivative
Favors Coronally advanced flap and connective tissue graft
Z score
Favors Apixiban
Favors Vitamin K antagonist
-4
-2
0
2
4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

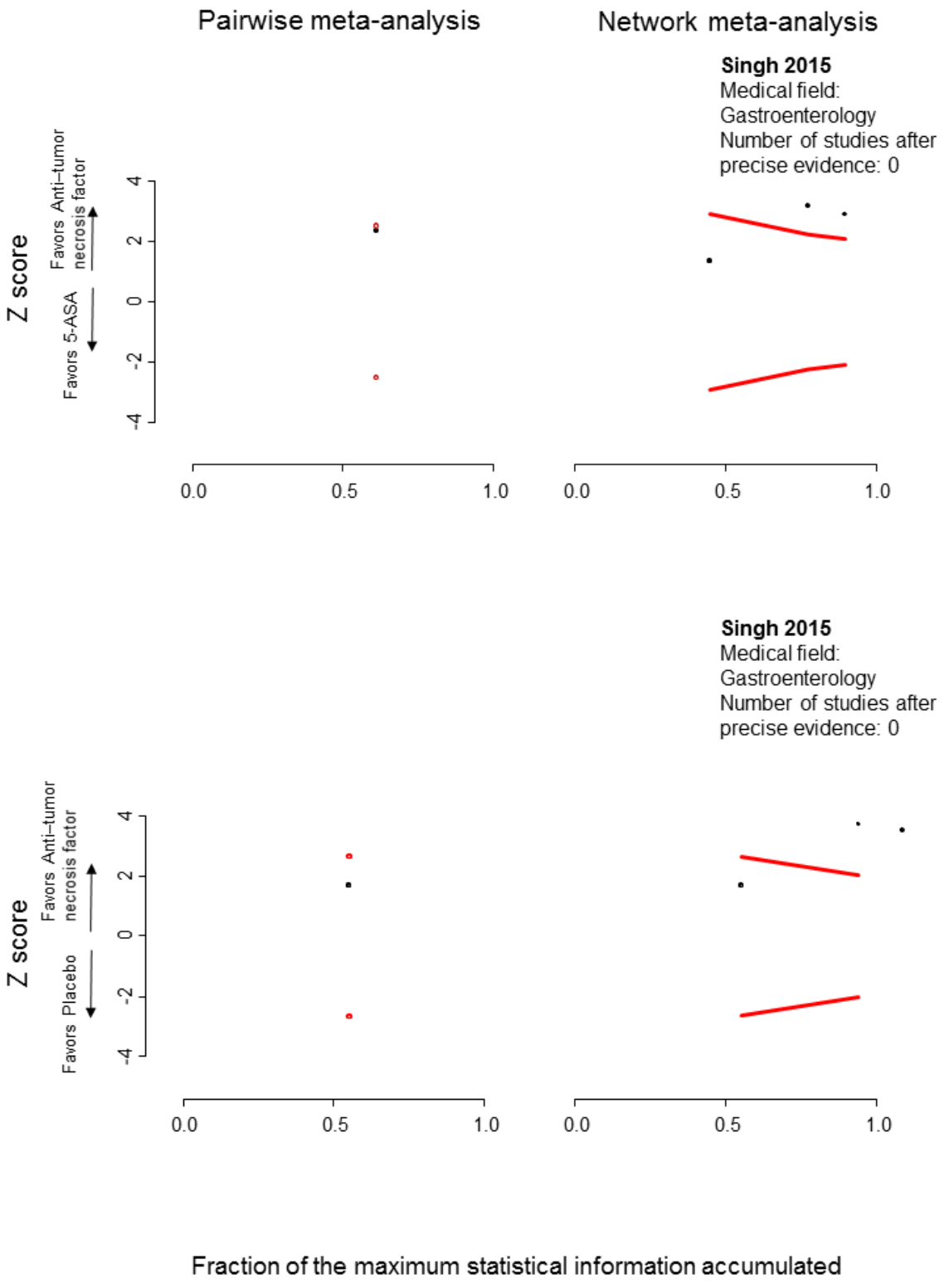

Pairwise meta-analysis
Network meta-analysis
Naci 2013
Medical field:
Cardiology
Z score
Favors Rosuvastatin
Favors Atorvastatin
5
0
-5
0.0
0.5
1.0
Filippini 2013
Medical field:
Neurology
Favors β-interferon-1a (Avonex)
Favors β-interferon-1a (Rebif)
4
2
0
-2
-4
Fraction of the maximum statistical information accumulated

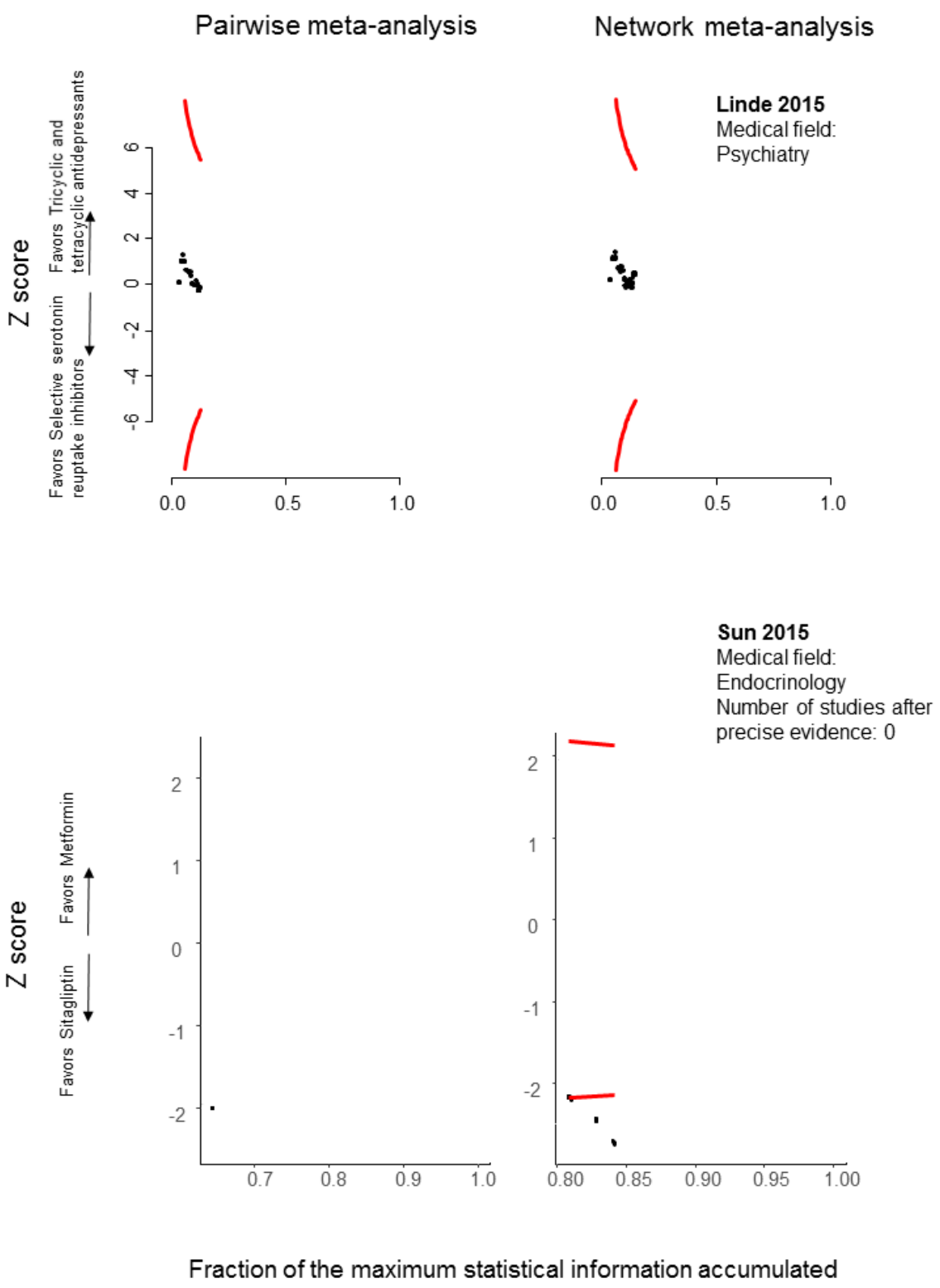

Pairwise meta-analysis
Network meta-analysis
Hon-Yen Wu 2013
Medical field:
Endocrinology
Lin 2014
Medical field:
Dentistry/peridontology
Z score
Favors Angiotensin converting enzyme inhibitors
Favors Angiotensin receptor blockers
Favors Mineral trioxide aggregate
Favors Ferric Sulphate
Fraction of the maximum statistical information accumulated

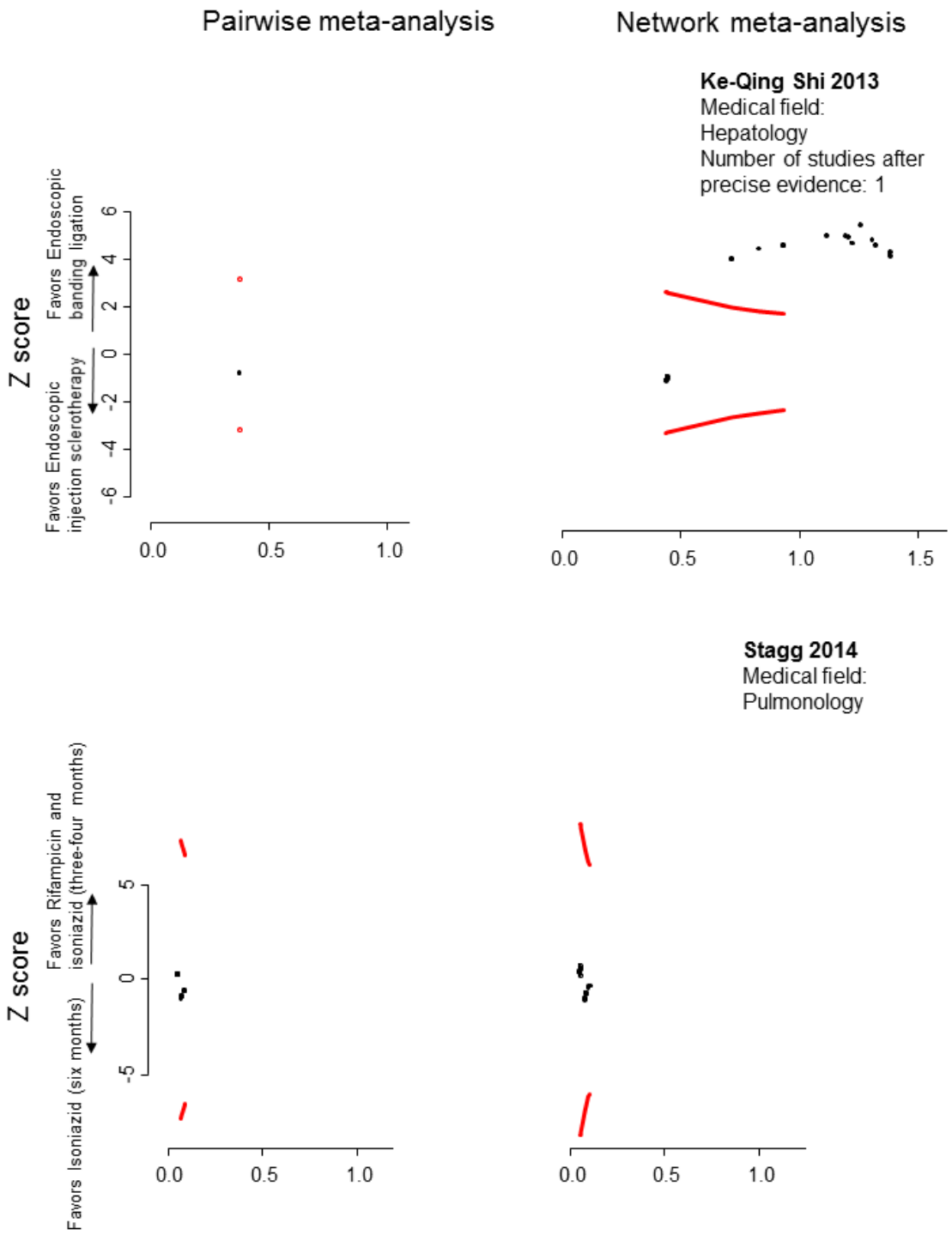

Pairwise meta-analysis
Network meta-analysis
Castellucci 2014
Medical field:
Cardiology
Number of studies after
precise evidence: 6
Myers 2014
Medical field:
Rheumatology
Z score
Favors Unfractionated heparin and vitamin K antagonist
Favors Low-molecular-weight heparin and vitamin K antagonist
Favors Celoxib
Favors Tramadol
-4
-2
0
2
4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

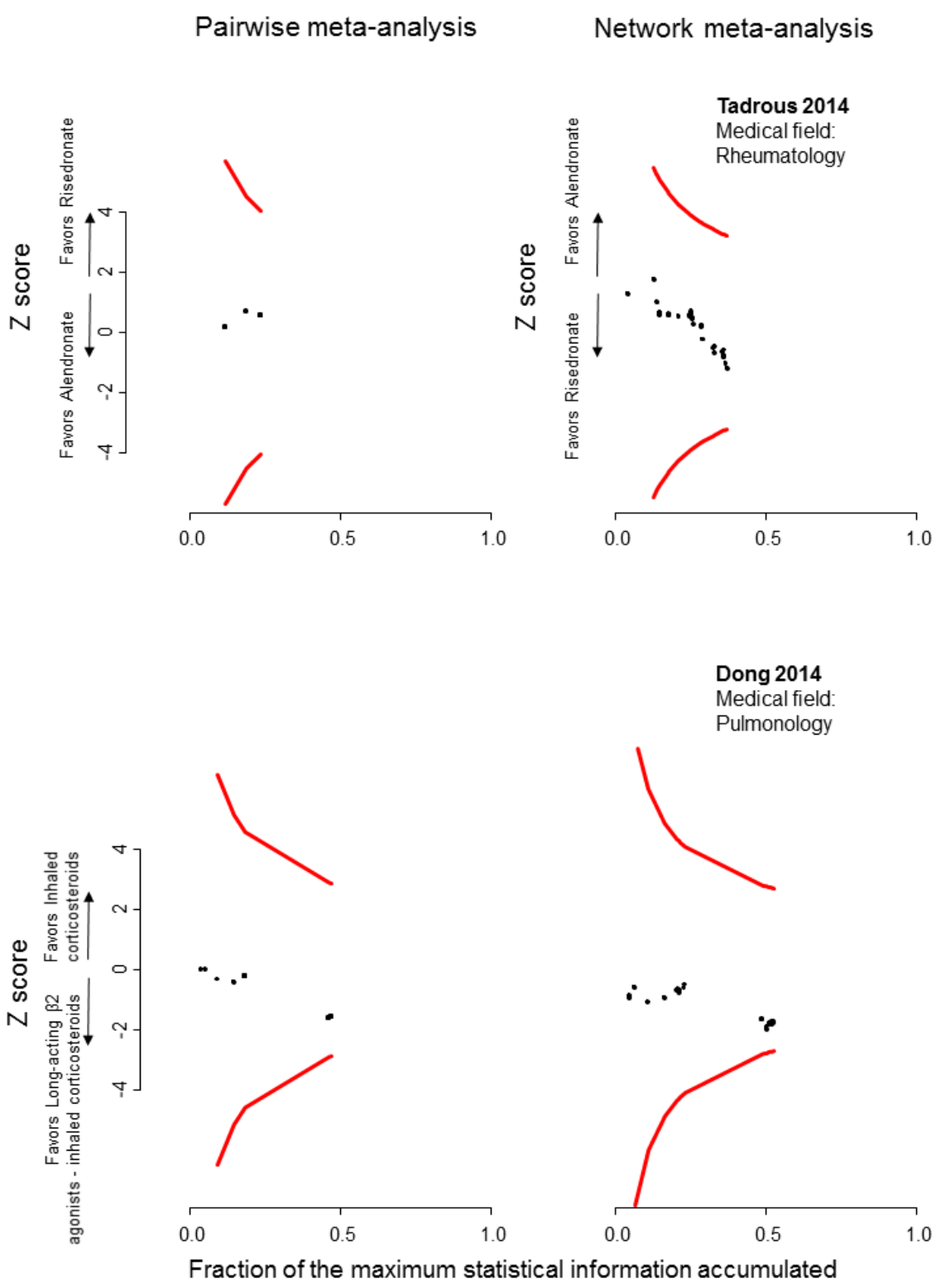

Pairwise meta-analysis
Network meta-analysis
Arfirevic 2014
Medical field:
Obstetrics
Z score
Favors Vaginal prostaglandin E2
Favors Vaginal misoprostol
4
2
0
-2
-4
0.0
0.5
1.0
Greco 2015
Medical field:
Anesthesiology
Number of studies after precise evidence: 1
Favors Dobutamine
Favors Levosimendan
Fraction of the maximum statistical information accumulated

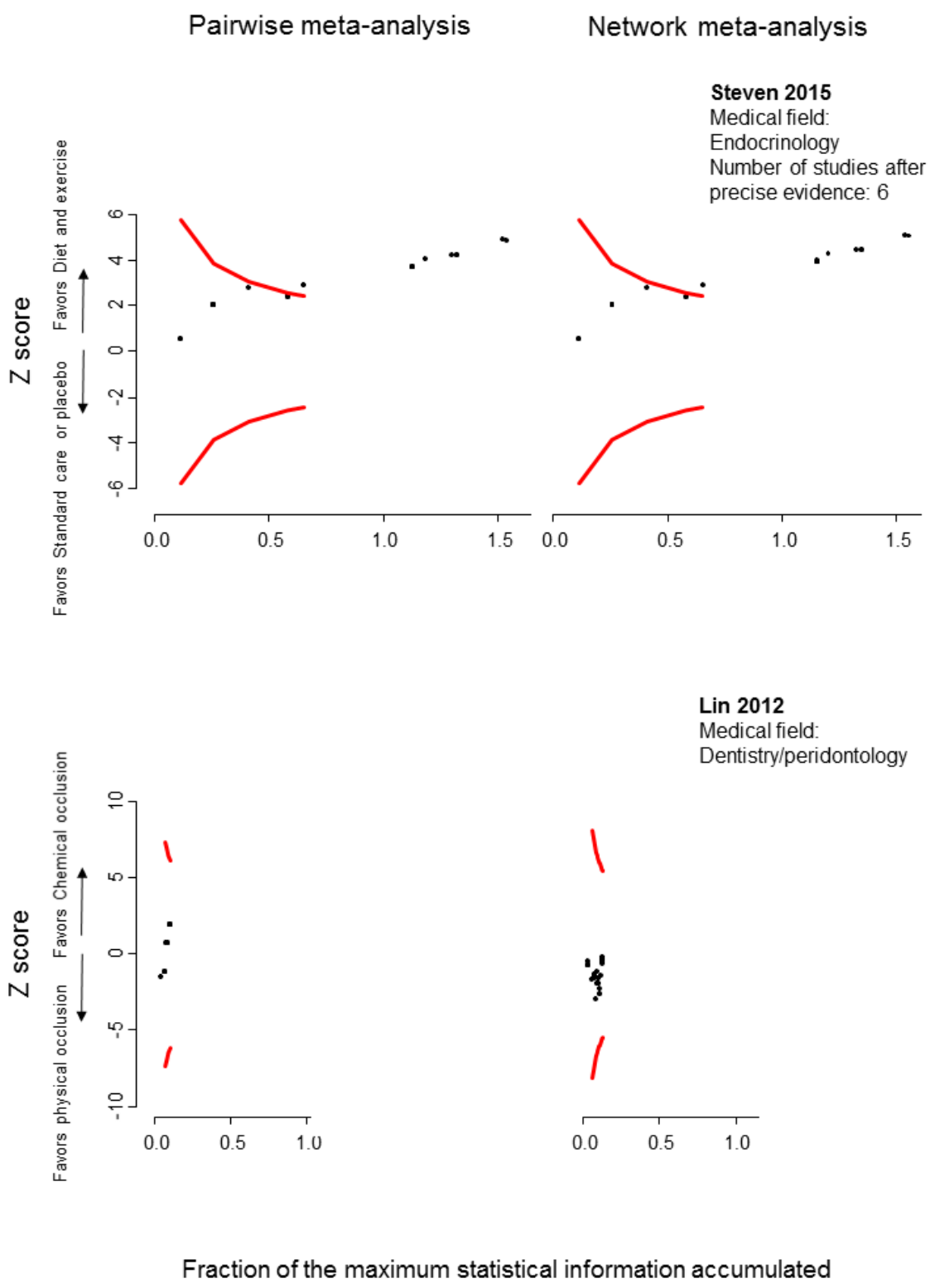

Pairwise meta-analysis
Network meta-analysis
Greco 2015
Medical field:
Anesthesiology
Z score
Favors Milrinone
Favors Dobutamine
6
4
2
0
-2
-4
-6
0.0
0.5
1.0
Walsem 2015
Medical field:
Rheumatology
Number of studies after
precise evidence: 0
Favors Diclofenac
Favors Celecoxib
4
2
0
-2
-4
Fraction of the maximum statistical information accumulated

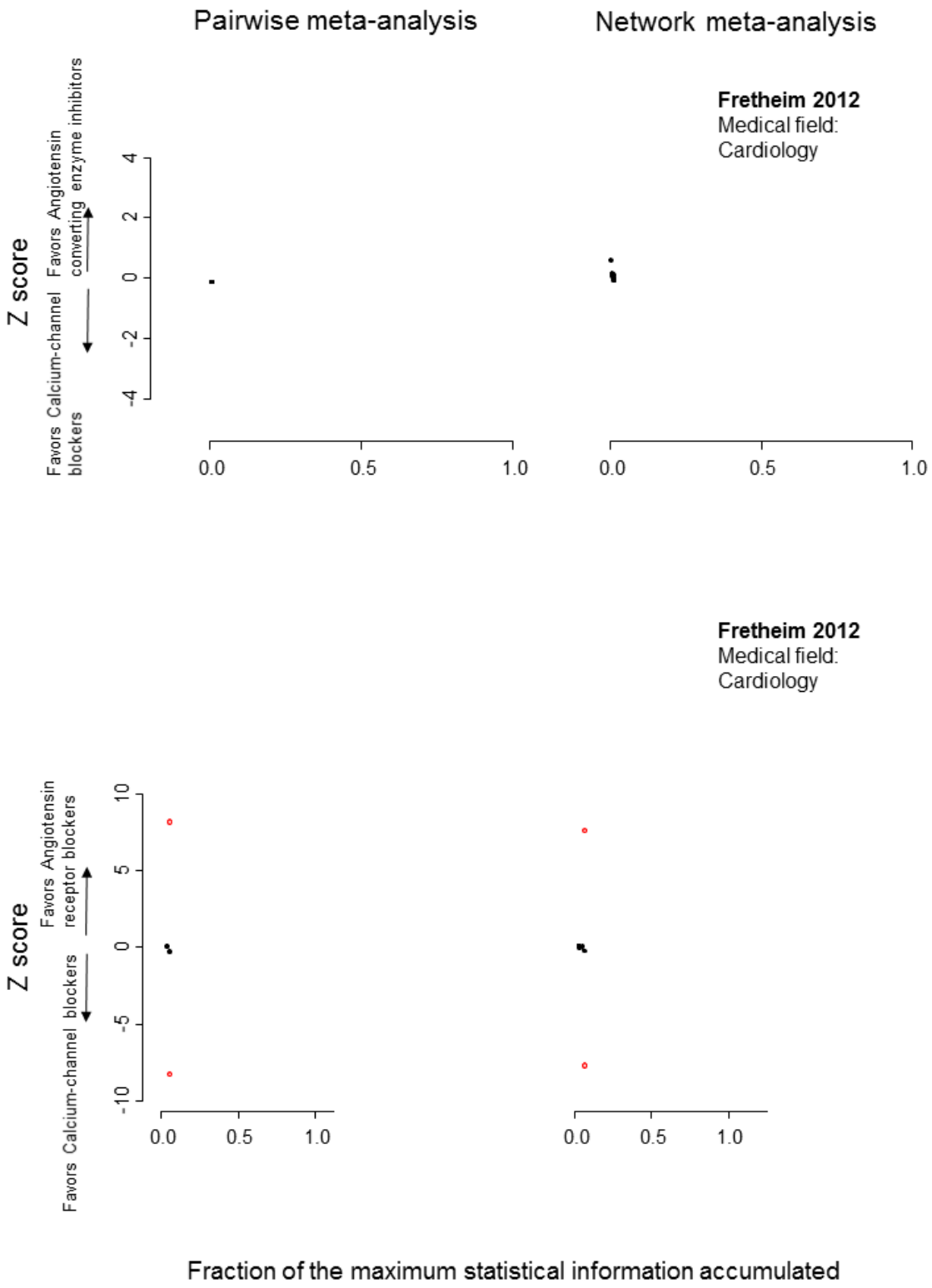

Pairwise meta-analysis
Network meta-analysis
Singh 2015
Medical field:
Gastroenterology
Number of studies after
precise evidence: 0
Z score
Favors Anti–tumor necrosis factor
Favors 5-ASA
4
2
0
-2
-4
0.0
0.5
1.0
Singh 2015
Medical field:
Gastroenterology
Number of studies after
precise evidence: 0
Z score
Favors Anti–tumor necrosis factor
Favors Placebo
Fraction of the maximum statistical information accumulated

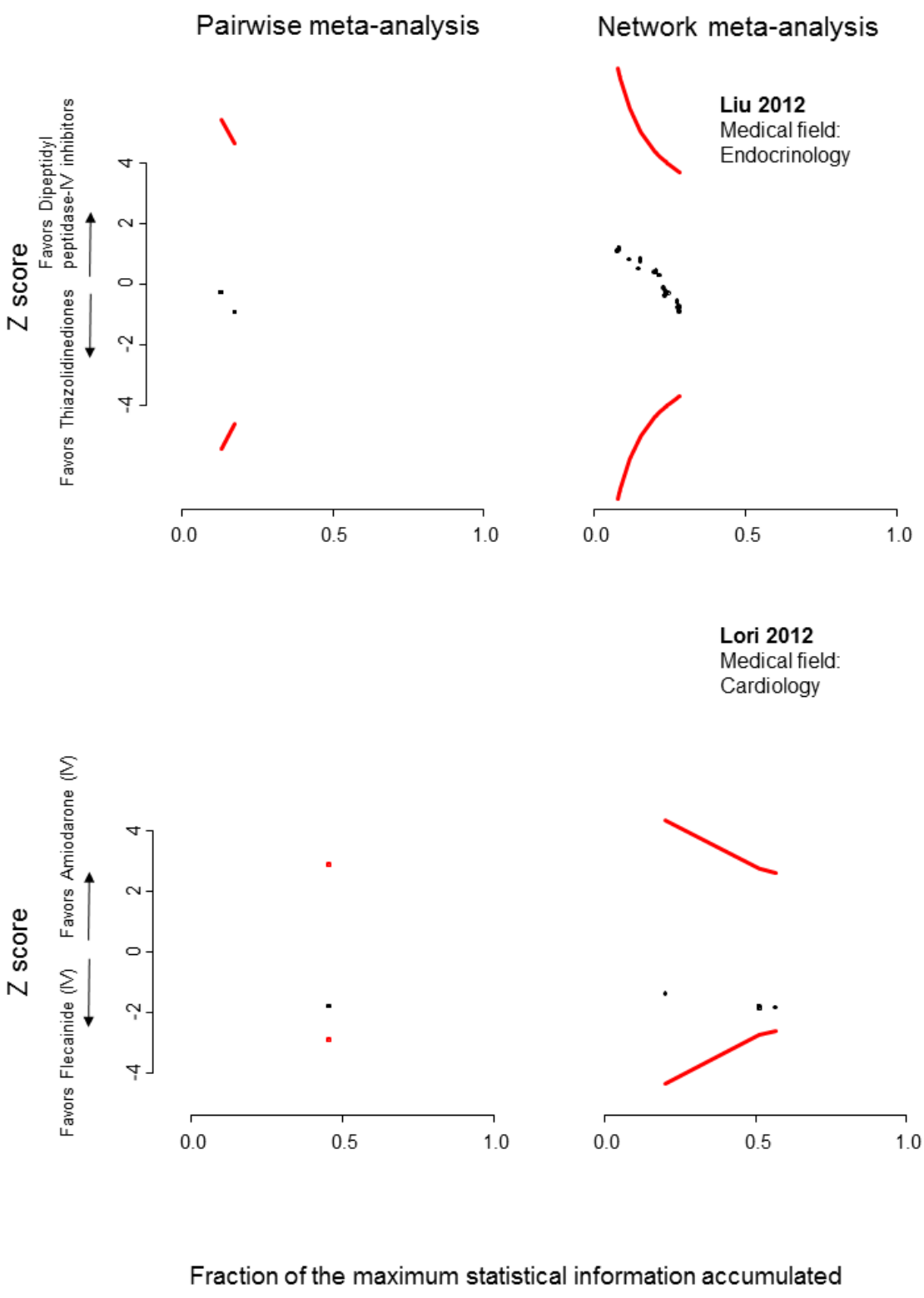

Pairwise meta-analysis
Network meta-analysis
Z score
Favors Tricyclic and tetracyclic antidepressants
Favors Selective serotonin reuptake inhibitors
6
4
2
0
-2
-4
-6
0.0
0.5
1.0
Linde 2015
Medical field: Psychiatry
Sun 2015
Medical field: Endocrinology
Number of studies after precise evidence: 0
Favors Metformin
Favors Sitagliptin
2
1
0
-1
-2
0.7
0.8
0.9
1.0
0.80
0.85
0.90
0.95
1.00
Fraction of the maximum statistical information accumulated

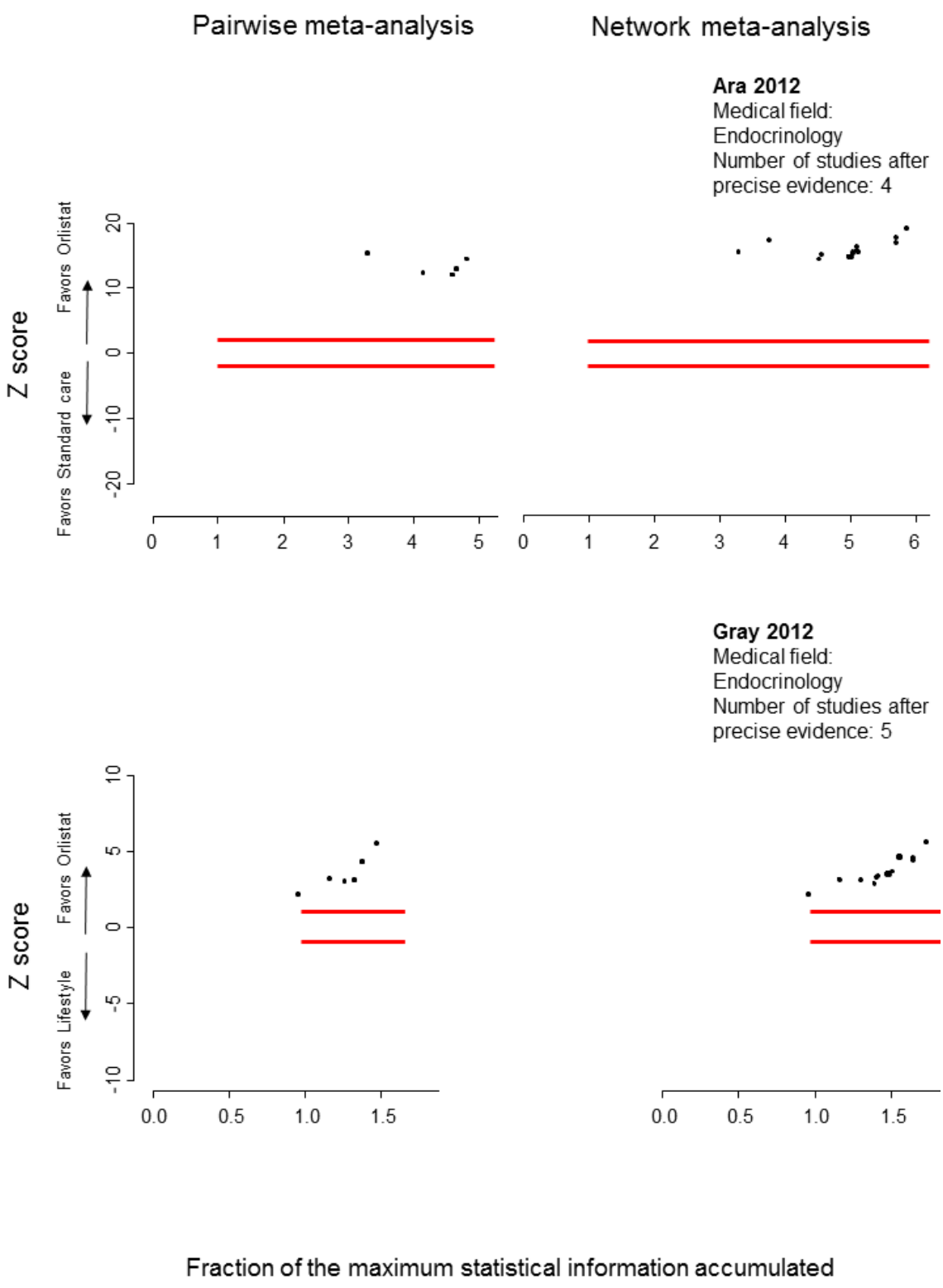

Pairwise meta-analysis
Network meta-analysis
Ke-Qing Shi 2013
Medical field:
Hepatology
Number of studies after
precise evidence: 1
Z score
Favors Endoscopic
banding ligation
Favors Endoscopic
injection sclerotherapy
6
4
2
0
-2
-4
-6
0.0
0.5
1.0
1.5
Stagg 2014
Medical field:
Pulmonology
Favors Rifampicin and
isoniazid (three-four months)
Favors Isoniazid (six months)
5
0
-5
Fraction of the maximum statistical information accumulated

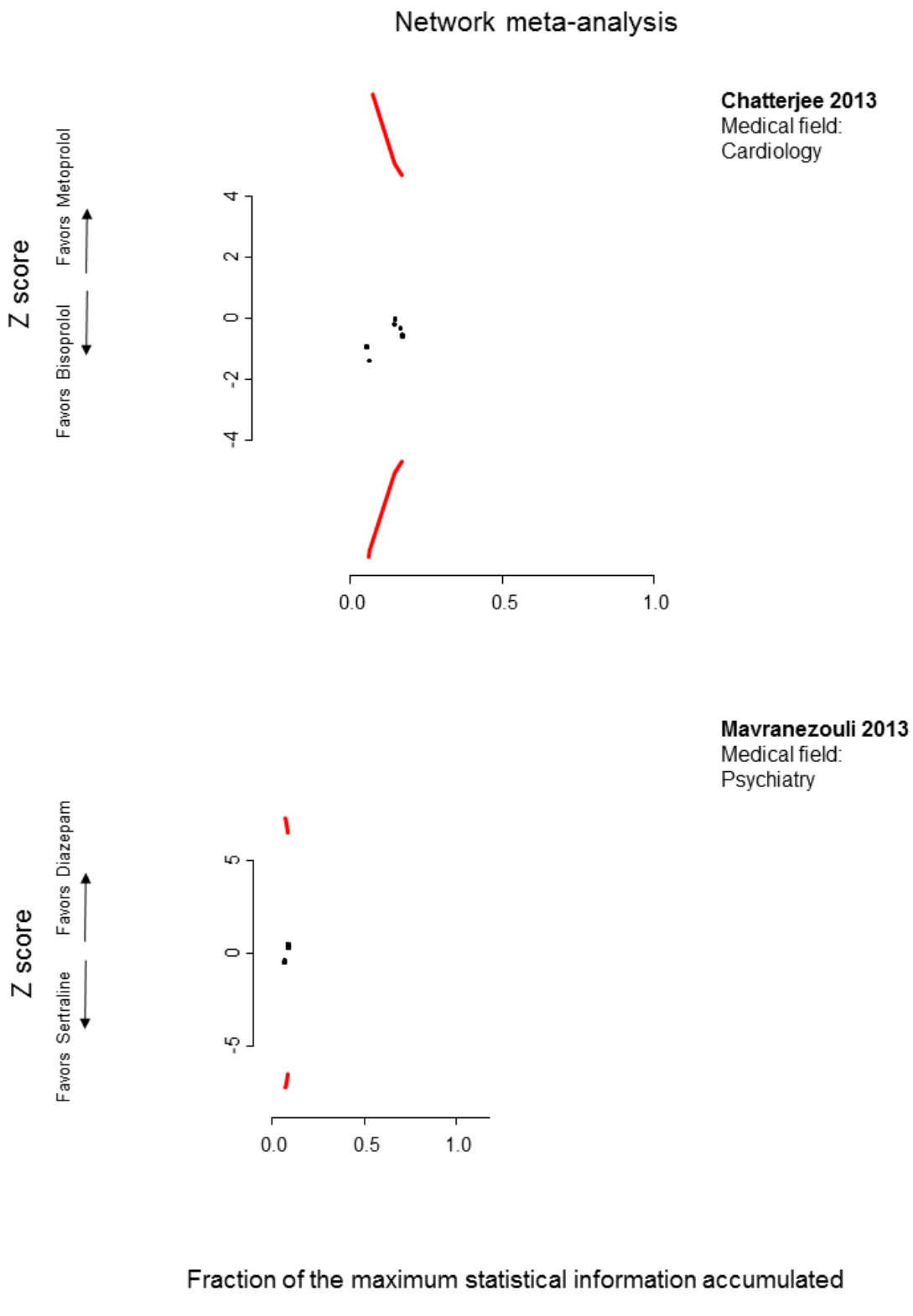

Pairwise meta-analysis
Network meta-analysis
Tadrous 2014
Medical field:
Rheumatology
Dong 2014
Medical field:
Pulmonology
Z score
Favors Alendronate
Favors Risedronate
Favors Long-acting β2 agonists - inhaled corticosteroids
Favors Inhaled corticosteroids
-4
-2
0
2
4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

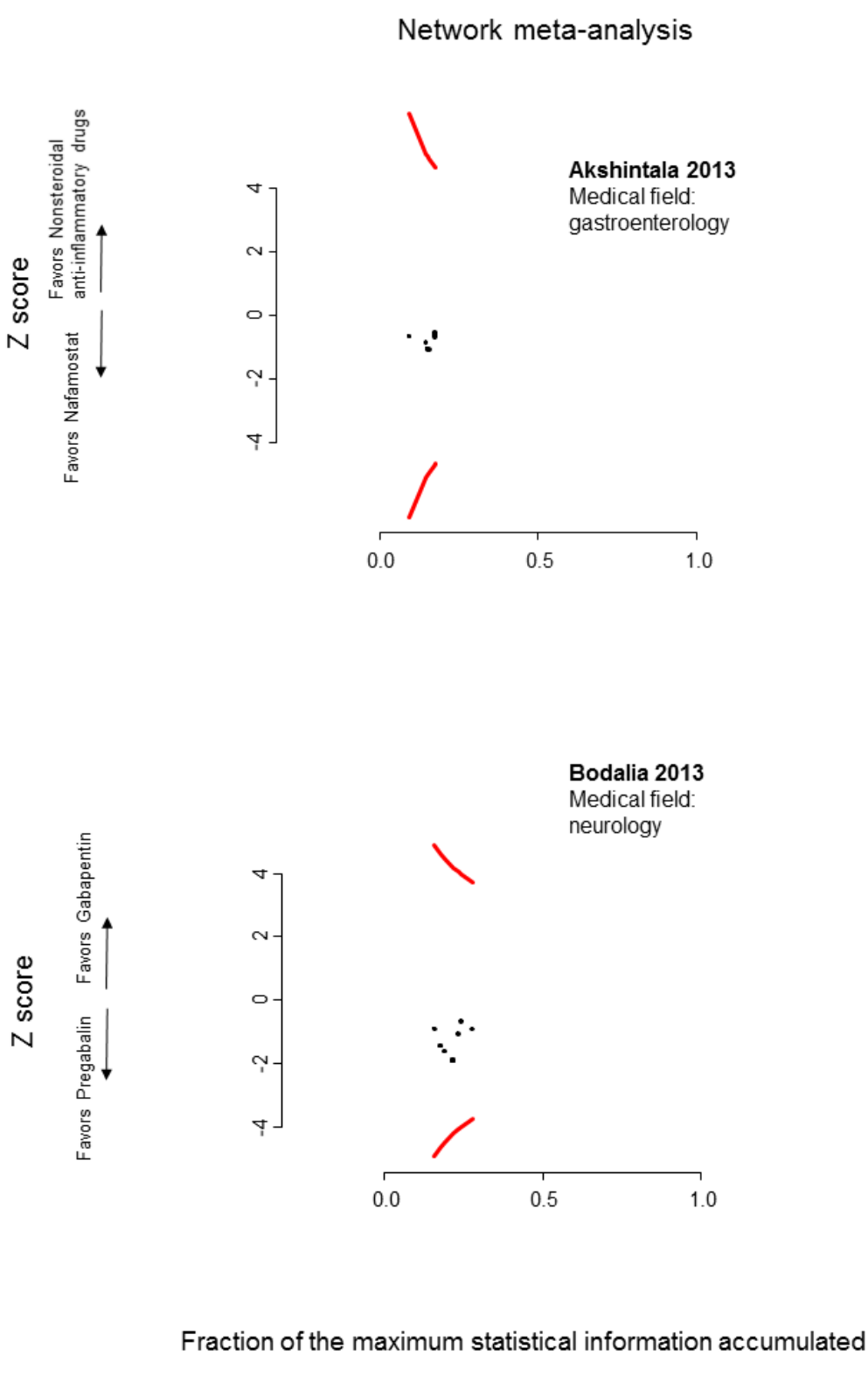

Pairwise meta-analysis
Network meta-analysis
Steven 2015
Medical field:
Endocrinology
Number of studies after
precise evidence: 6
Z score
Favors Standard care or placebo
Favors Diet and exercise
6
4
2
0
-2
-4
-6
0.0
0.5
1.0
1.5
Lin 2012
Medical field:
Dentistry/peridontology
Z score
Favors physical occlusion
Favors Chemical occlusion
10
5
0
-5
-10
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated


Pairwise meta-analysis
Network meta-analysis
Fretheim 2012
Medical field:
Cardiology
Z score
Favors Calcium-channel blockers
Favors Angiotensin converting enzyme inhibitors
-4
-2
0
2
4
0.0
0.5
1.0
Fretheim 2012
Medical field:
Cardiology
Z score
Favors Calcium-channel blockers
Favors Angiotensin receptor blockers
-10
-5
0
5
10
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated


Pairwise meta-analysis
Network meta-analysis
Z score
Favors Dipeptidyl peptidase-IV inhibitors
Favors Thiazolidinediones
4
2
0
-2
-4
0.0
0.5
1.0
Liu 2012
Medical field:
Endocrinology
Lori 2012
Medical field:
Cardiology
Favors Amiodarone (IV)
Favors Flecainide (IV)
Fraction of the maximum statistical information accumulated

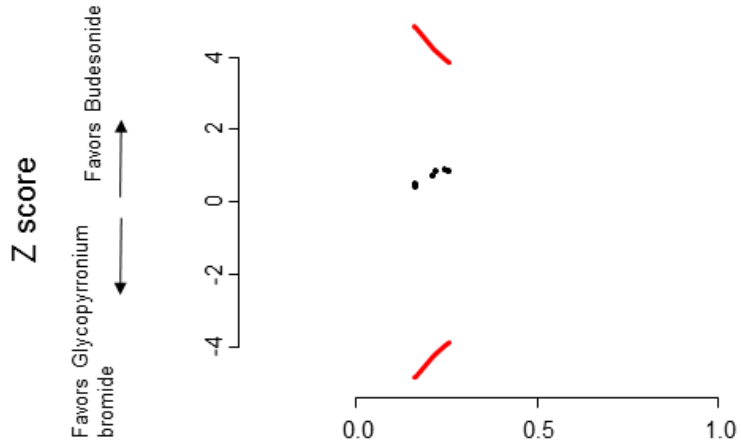

Pairwise meta-analysis
Network meta-analysis
Ara 2012
Medical field:
Endocrinology
Number of studies after
precise evidence: 4
Z score
Favors Orlistat
Favors Standard care
20
10
0
-10
-20
0
1
2
3
4
5
6
Gray 2012
Medical field:
Endocrinology
Number of studies after
precise evidence: 5
Z score
Favors Orlistat
Favors Lifestyle
10
5
0
-5
-10
0.0
0.5
1.0
1.5
Fraction of the maximum statistical information accumulated


Network meta-analysis
Chatterjee 2013
Medical field:
Cardiology
Z score
Favors Bisoprolol
Favors Metoprolol
-4
-2
0
2
4
0.0
0.5
1.0
Mavranezouli 2013
Medical field:
Psychiatry
Z score
Favors Sertraline
Favors Diazepam
-5
0
5
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

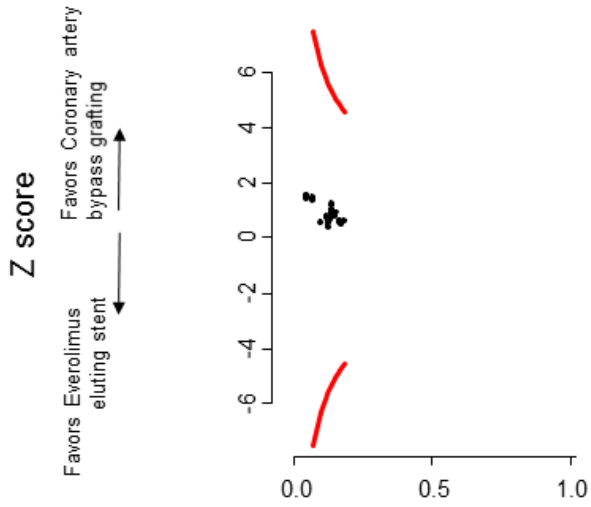

Network meta-analysis
Z score
Favors Nonsteroidal anti-inflammatory drugs
Favors Nafamostat
4
2
0
-2
-4
0.0
0.5
1.0
Akshintala 2013
Medical field:
gastroenterology
Z score
Favors Gabapentin
Favors Pregabalin
4
2
0
-2
-4
0.0
0.5
1.0
Bodalia 2013
Medical field:
neurology
Fraction of the maximum statistical information accumulated

Network meta-analysis

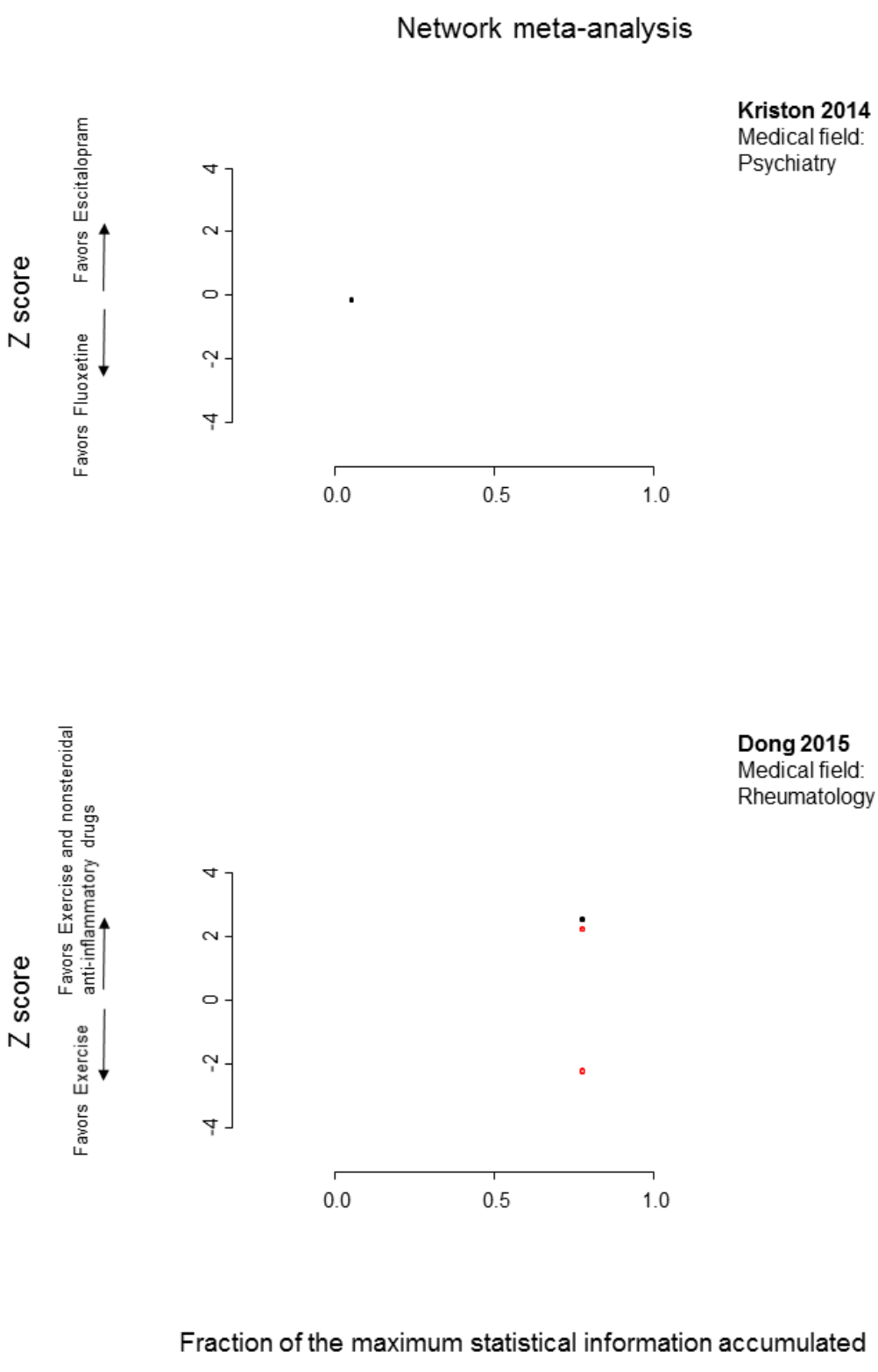
Kew 2014
Medical field:
Pulmonology

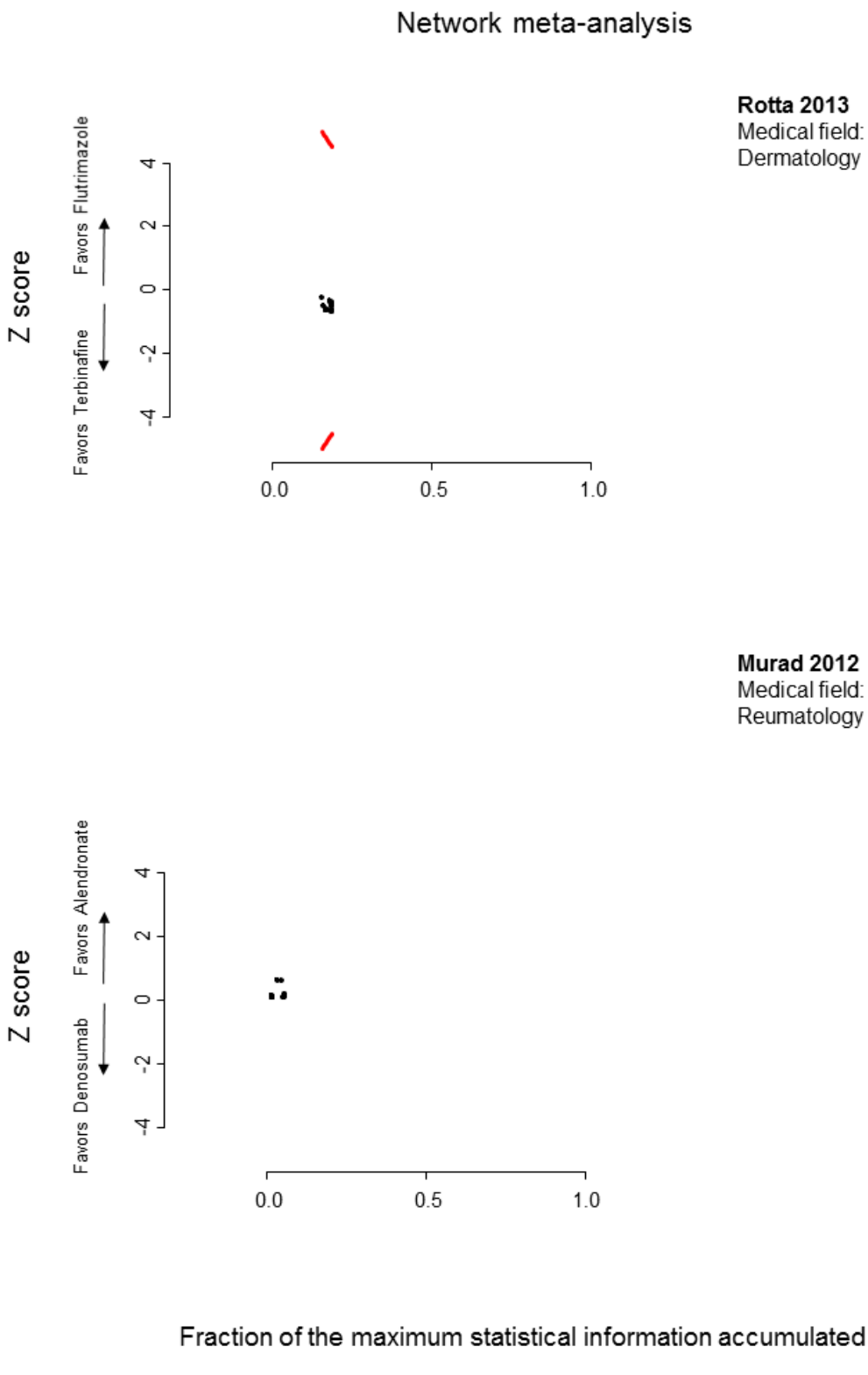


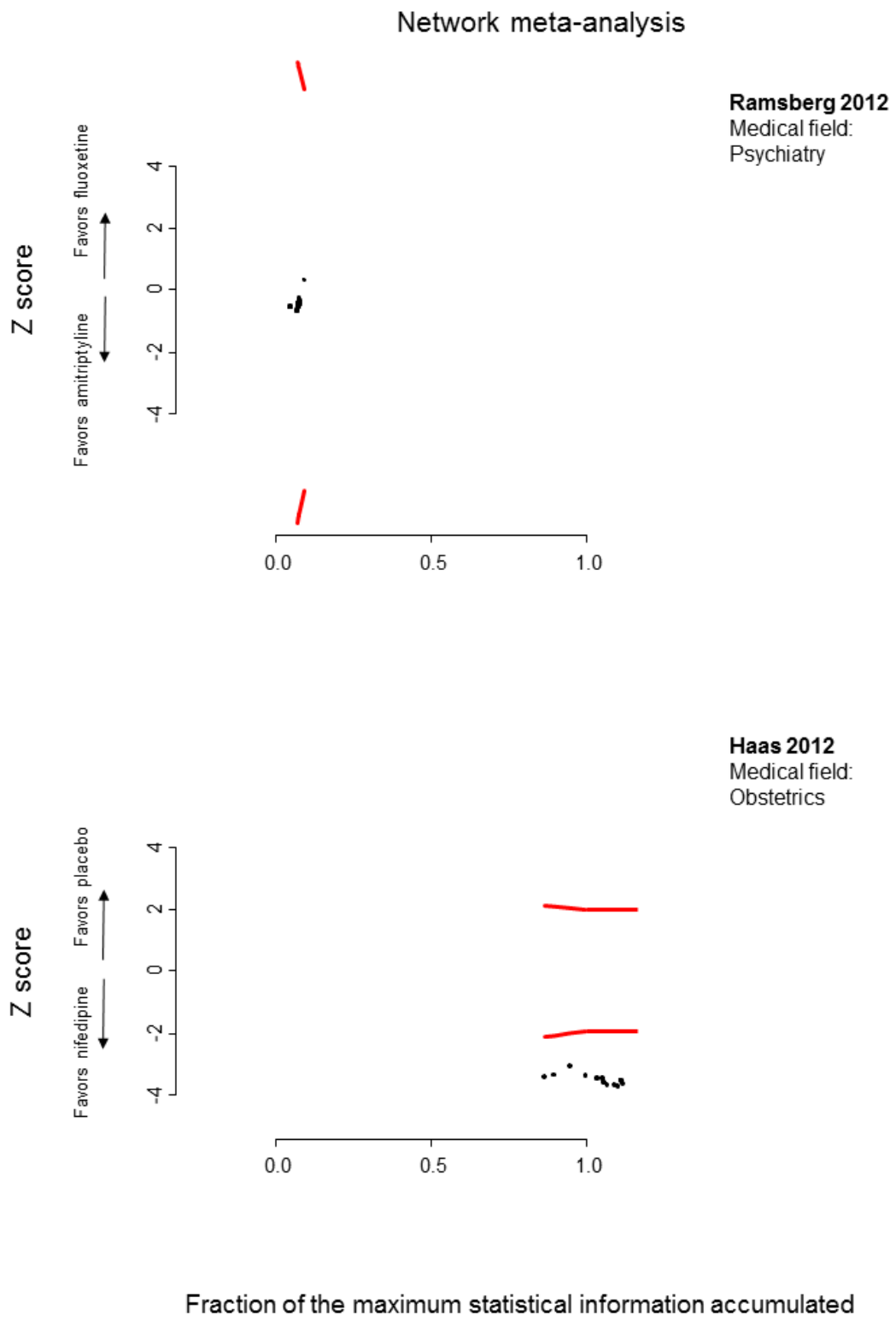
Windecker 2014
Medical field:
Cardiology

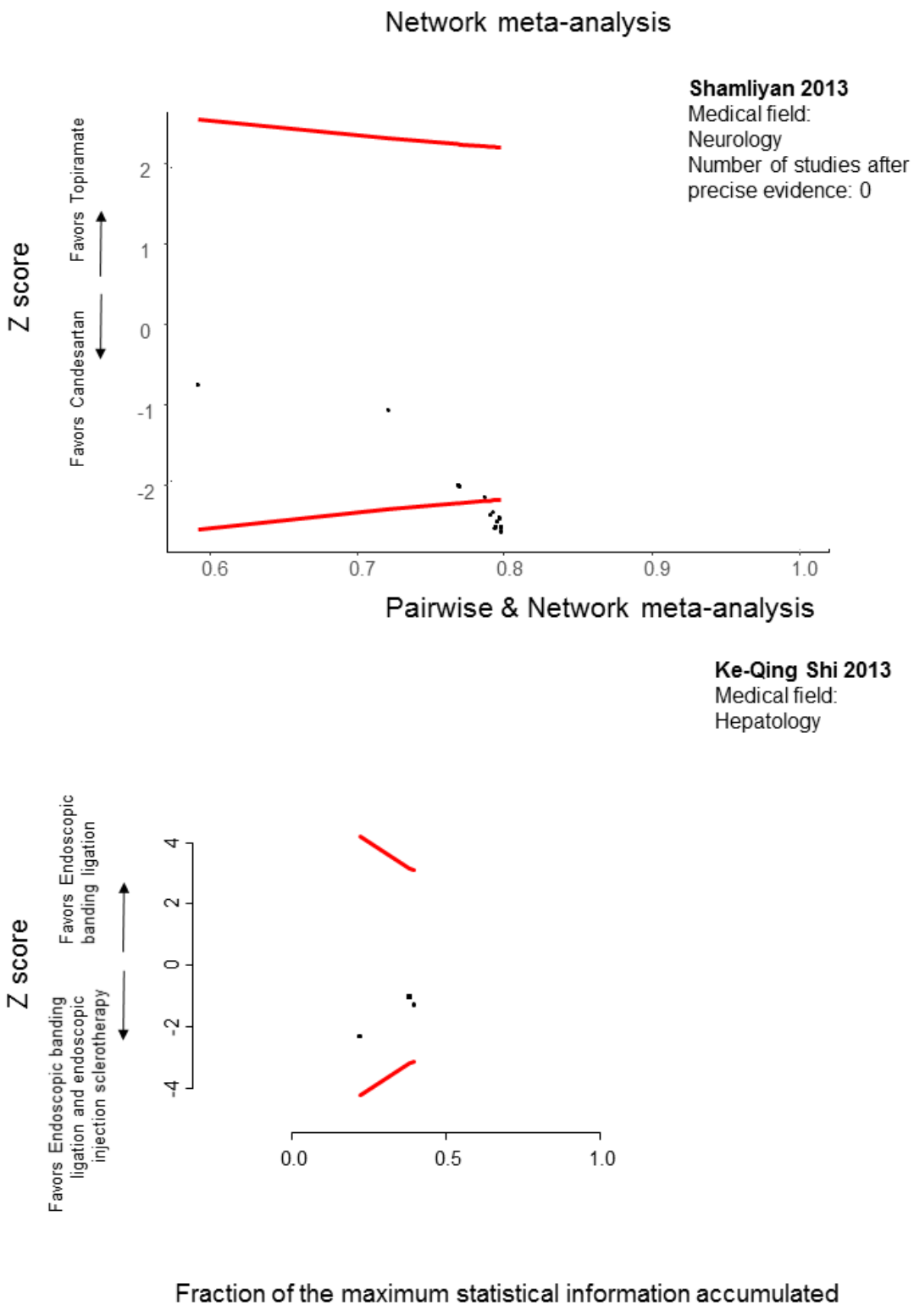


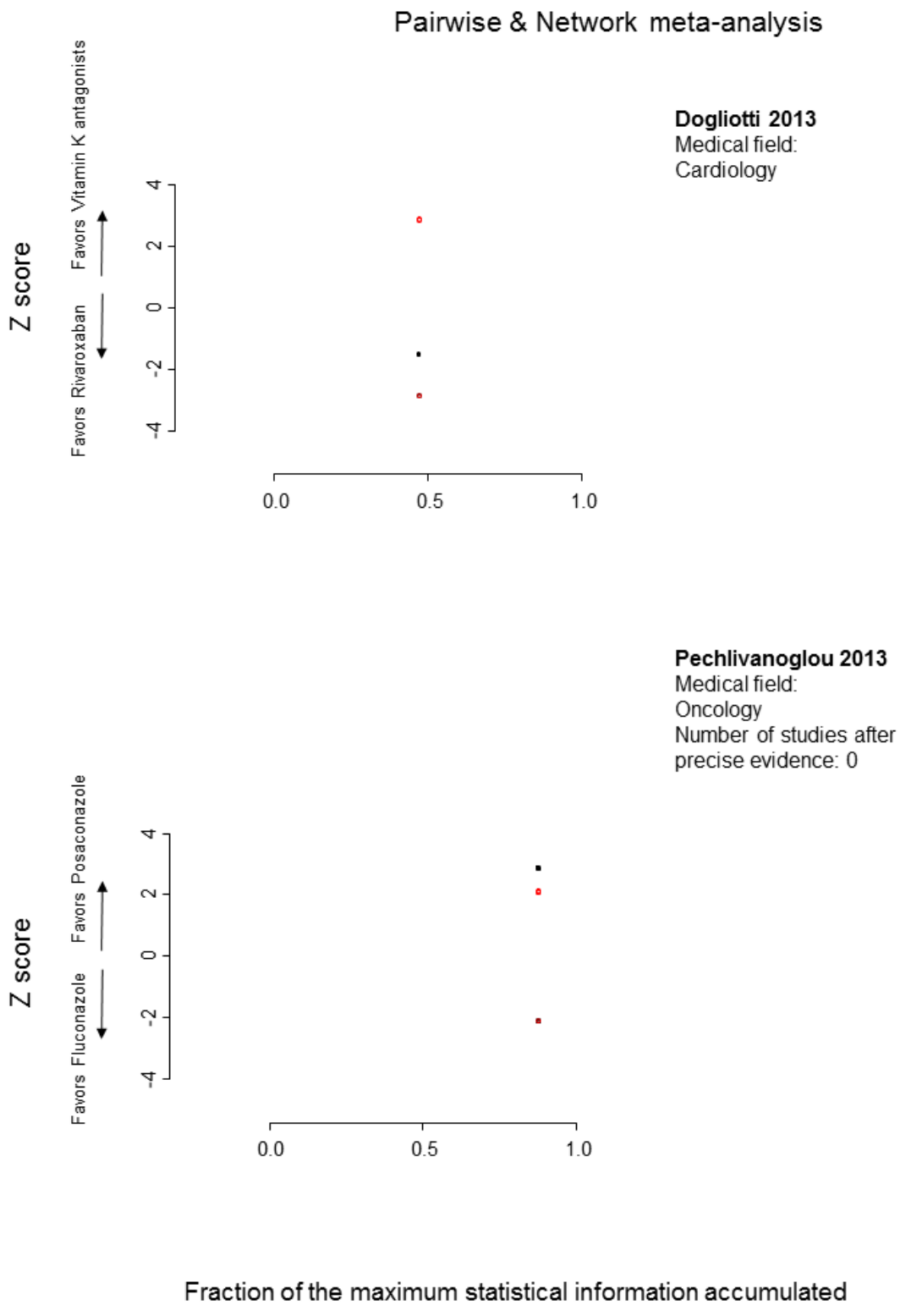
Fraction of the maximum statistical information accumulated


Network meta-analysis
Kriston 2014
Medical field:
Psychiatry
Z score
Favors Escitalopram
Favors Fluoxetine
4
2
0
-2
-4
0.0
0.5
1.0
Dong 2015
Medical field:
Rheumatology
Z score
Favors Exercise and nonsteroidal anti-inflammatory drugs
Favors Exercise
4
2
0
-2
-4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

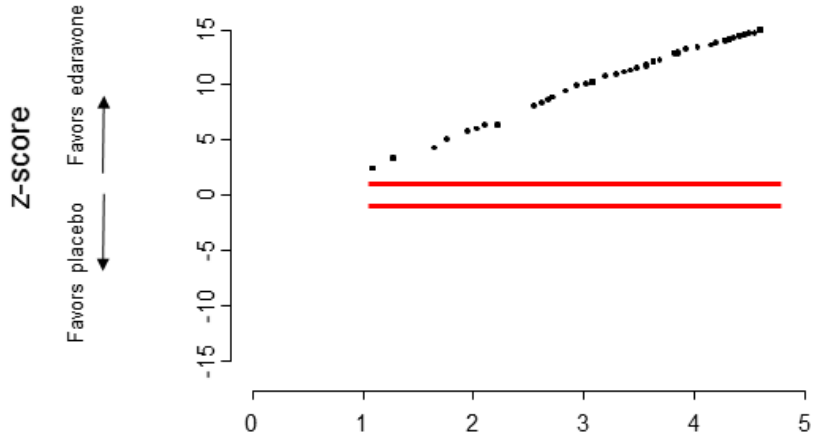

Network meta-analysis
Rotta 2013
Medical field:
Dermatology
Z score
Favors Flutrimazole
Favors Terbinafine
4
2
0
-2
-4
0.0
0.5
1.0
Murad 2012
Medical field:
Reumatology
Z score
Favors Alendronate
Favors Denosumab
4
2
0
-2
-4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated


Network meta-analysis
Ramsberg 2012
Medical field:
Psychiatry
Z score
Favors fluoxetine
Favors amitriptyline
4
2
0
-2
-4
0.0
0.5
1.0
Haas 2012
Medical field:
Obstetrics
Z score
Favors placebo
Favors nifedipine
4
2
0
-2
-4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

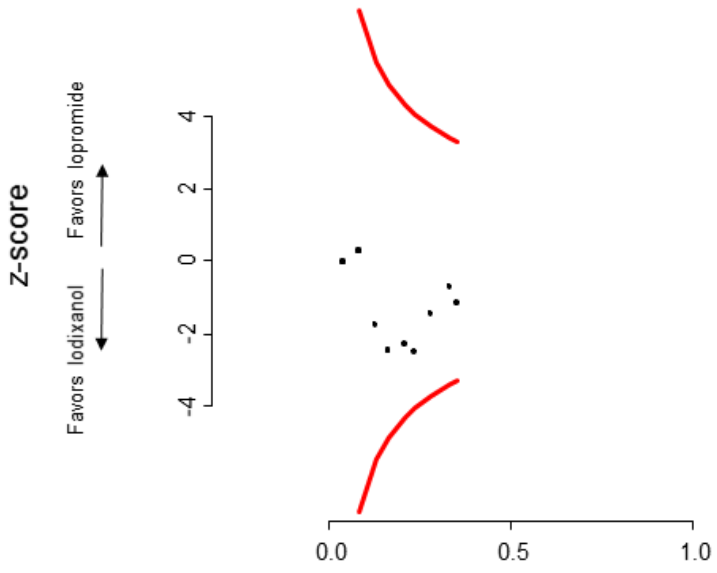

Network meta-analysis
Shamliyan 2013
Medical field:
Neurology
Number of studies after
precise evidence: 0
Z score
Favors Topiramate
Favors Candesartan
2
1
0
-1
-2
0.6
0.7
0.8
0.9
1.0
Pairwise & Network meta-analysis
Ke-Qing Shi 2013
Medical field:
Hepatology
Z score
Favors Endoscopic banding ligation
Favors Endoscopic ligation and endoscopic injection sclerotherapy
4
2
0
-2
-4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated


Pairwise & Network meta-analysis
Dogliotti 2013
Medical field:
Cardiology
Z score
Favors Vitamin K antagonists
Favors Rivaroxaban
4
2
0
-2
-4
0.0
0.5
1.0
Pechlivanoglou 2013
Medical field:
Oncology
Number of studies after precise evidence: 0
Z score
Favors Posaconazole
Favors Fluconazole
4
2
0
-2
-4
0.0
0.5
1.0
Fraction of the maximum statistical information accumulated

Pairwise & Network meta-analysis



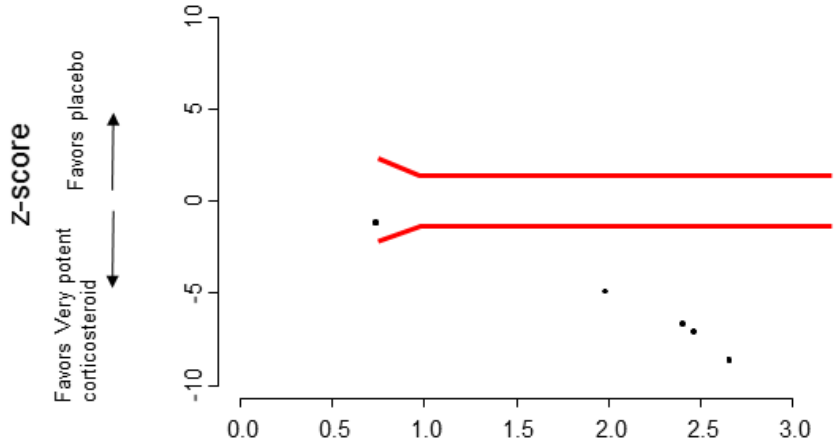
Yang 2014
Medical field:
Cardiology
Number of studies after precise evidence: 40



Biondi-Zoccai 2014
Medical field:
Cardiology

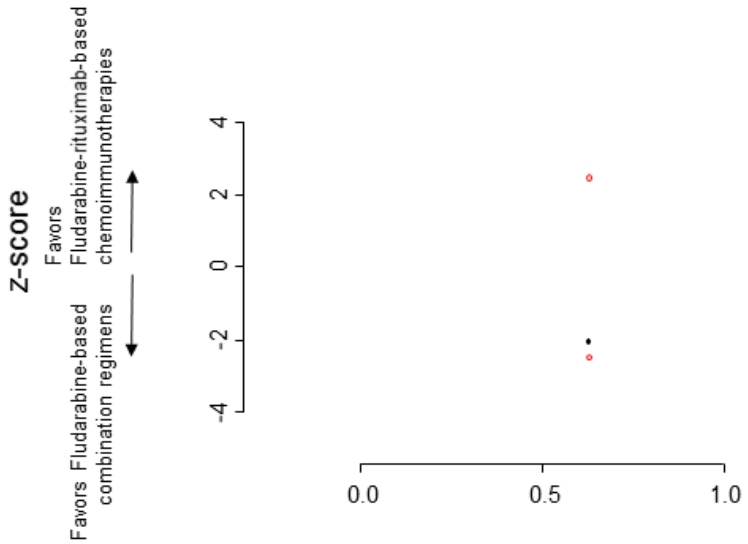
Fraction of the maximum statistical information accumulated

Pairwise & Network meta-analysis



Samarasekera 2013
Medical field:
Dermatology
Number of studies after precise evidence: 3

Terasawa 2012
Medical field:
Oncology



Fraction of the maximum statistical information accumulated

K) Technical details for the comparison between strength of evidence in meta-analysis versus network meta-analysis

The comparison of the numbers of treatment comparisons providing strong evidence with each method in any 2x2 table was performed using the McNemar test using the `exact2x2` R-package (*Fay MP (2010). Two-sided Exact Tests and Matching Confidence Intervals for Discrete Data. R Journal 2(1):53-58.*). The difference between the two paired ratios of strong evidence in any 2x2 table and the corresponding 95% CI were calculated using the `ExactCIdiff` package in R *(Guogen Shan and Weizhen Wang (2013). ExactCIdiff: Inductive Confidence Intervals for the difference between two proportions. R package version CRAN.R-project.org/package= ExactCIdiff)*

The estimation of the hazard ratio from the frailty model was performed using the command `stcox` in Stata and specifying the shared frailty using the `shared(varname)` option. The frailties are assumed to have gamma-distributed latent random effects.

The 95% confidence interval for difference between the median survival times between pairwise and network meta-analysis (4 years) was estimated using the `Hmisc` package in R (*Frank E Harrell Jr, with contributions from Charles Dupont and many others. (2017). Hmisc: Harrell Miscellaneous. R package version 4.0-3. CRAN.R-project.org/package= Hmisc*). Bootstrap Kaplan-Meier estimates of the median survivals were calculated using 10,000 bootstrap repetitions separately for pairwise and network meta-analysis. Then, the generic function `quantile` in R was used to produce a 95% confidence interval of their difference. Infinite values were not used in the computation of the quantiles.

L) Assumptions underlying continuous inferences on a living network meta-analysis

As described in 'Construction of monitoring boundaries and definition of strong evidence', the first step in a sequential (pairwise or network) meta-analysis is to decide upon the anticipated treatment effect (here equal to the final network estimate, standardized mean difference 0.13 in favor of olanzapine), type I and type II errors (5% and 10% respectively). Decisions on these quantities are of particular importance and need to be justified as they can considerably drive inferences. In a real-world living network meta-analysis, the anticipated treatment effect is unknown and its value should be selected in such a way that it reflects an effect size that is important to detect. As different perspectives may result in different judgments on the effects that are "important to detect", it is advisable that a sensitivity analysis is undertaken. However, a trade-off between capturing various perspectives and producing a pragmatic set of stopping decisions is warranted. We recommend that researchers make an effort to include patients' views and values; such efforts may involve multi-criteria decision analysis methods to determine the anticipated treatment effects taking into account patients' preferences related to e.g. discomfort or inconvenience.

Assumptions on heterogeneity and inconsistency need also to be made. As heterogeneity is typically unknown and ill-informed in the first steps of the analysis, we adopt a random effects network meta-analysis model where the heterogeneity parameters are informed by empirical data. We recommend regularly checking for potential inconsistencies in the network in the course of adding new studies in the evidence base. In case that evidence of inconsistency is found, an exploration of its potential sources should be undertaken and the continuation of living network meta-analysis should be carefully reconsidered.

M) Construction of repeated confidence intervals in a living network meta-analysis

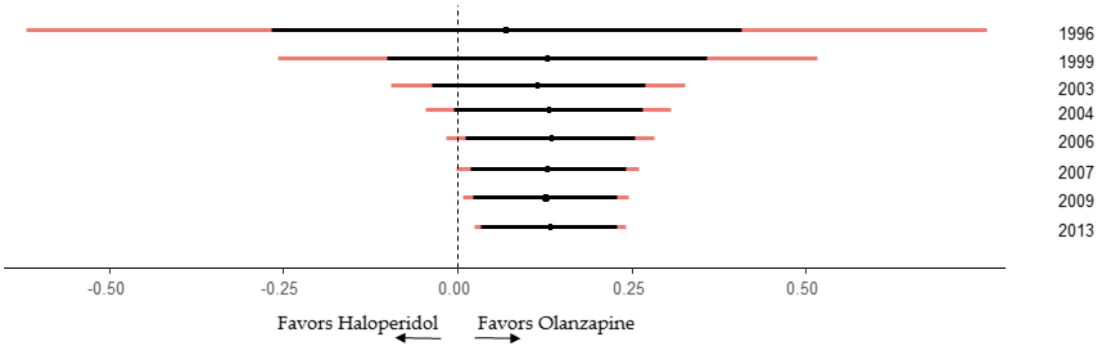
An alternative and equivalent to monitoring boundaries way to present the living network meta-analysis results is by using repeated confidence intervals. These are extensions to the confidence intervals that account for the sequential nature of the accumulated evidence in a way similar to that of constructing boundaries. Consider as an example the olanzapine versus haloperidol comparison for reducing symptoms in schizophrenia, measured as standardized mean difference. We subsequently describe the process only using network meta-analysis results; the respective pairwise meta-analysis quantities can be derived similarly.

After each study is included in network, we re-calculate the network meta-analysis treatment effect (on an additive scale) and its variance. Then, we calculate the repeated confidence interval in each step as

$$\mu \pm E\sqrt{var(\mu)}$$

where μ and $var(\mu)$ are the interim network meta-analysis treatment effect and its variance respectively and E is the Z-score of the constructed monitoring boundary. An indication of a comparison providing strong evidence would be made when the repeated confidence interval would exclude 0. Equivalence between inferences on repeated confidence intervals and boundaries can be seen as the repeated confidence interval would exclude 0 when the absolute value of the observed Z-score (calculated as $\mu/\sqrt{var(\mu)}$) would be greater than E.

The following figure shows the confidence (black lines) and the repeated confidence intervals (red lines) for the network meta-analysis treatment effect of 'olanzapine vs haloperidol' at eight steps of the analysis. While olanzapine is statistically significantly better than haloperidol from 2006 without adjusting for multiple testing, appropriately accounting for the inflation of type I error would lead to a precise statement in 2008.



N) The `sequentialnma` package: reproducing the monitoring boundaries

We will illustrate the reproduction of the monitoring boundaries using as example the comparison 'Long-acting β2 agonists - inhaled corticosteroids versus Inhaled corticosteroids' examined in Dong et al.; see reference 20 in section

C) References to the included network meta-analyses.

We set the anticipated treatment effect for the mortality outcome equal to the final network meta-analysis odds ratio (OR=1.26 favouring Long-acting β2 agonists - inhaled corticosteroids), a type I error of 5% and a type II error of 10%. The heterogeneity variance is assumed equal to 0.014 throughout the analysis; this value corresponds to the median of the predictive distribution for an objective outcome (mortality) and a pharmacological versus pharmacological intervention comparison type (*Turner RM et al. Int J Epidemiol. 2012*).

R codes for performing and presenting sequential pairwise and network meta-analysis can be found in the library https://github.com/esm-ispm-unibe-ch/sequentialnma. A brief description of the functions is given below.

sequentialnma: This function estimates cumulative pairwise and network meta-analysis treatment effects and calculates the monitoring boundaries. The methodology uses formal statistical monitoring initially suggested for clinical trials and pairwise meta-analysis using the alpha-spending functions. The method is described in detail in *Nikolakopoulou A et al. Stat Methods Med Res. 2016*. An object of class `sequentialnma` is returned.

plot.sequentialnma: This function takes as input an object of class `sequentialnma` and plots the Z scores and the monitoring boundaries for pairwise and network meta-analysis for a specific comparison.

repeatedCI: This function takes as input an object of class `sequentialnma` and plots the cumulative effect sizes with the repeated confidence intervals for pairwise and network meta-analysis for a specific comparison.

summary.sequentialnma: This function takes as input an object of class `sequentialnma` and gives a table with the accumulated information through the sequential network meta-analysis for a specific comparison.

The packages below need to be installed.

```
install.packages("plyr")
install.packages("devtools")
install.packages("ggplot2")
install.packages("grid")
library(devtools)
install_version("netmeta",version="0.9-5")
```

Then, we need to install the functions to perform sequential network meta-analysis from GitHub.

```
install_github("esm-ispm-unibe-ch/sequentialnma")
library(sequentialnma)
```

RE-ANALYSIS OF DONG ET AL. IN R USING THE `sequentialnma` PACKAGE

The outcome data for the Dong et al. example are in the library and can be downloaded as

```
data(Dong)
```

and viewed

```
head(Dong)
```

```
  year           study id        t    n   r
1 1998       Paggioaro 24      ICS  142   0
2 1998       Paggioaro 24  Placebo  139   2
3 1999         Pauwels 22      ICS  634   8
4 1999         Pauwels 22  Placebo  643  10
5 1999          Vestbo 23      ICS  145   4
6 1999          Vestbo 23  Placebo  145   5
7 2000           Burge 21      ICS  376  32
8 2000           Burge 21  Placebo  375  36
```

The command `sequentialnma` is the main function and takes the following arguments:

Arguments in `sequentialnma`

`data`: a dataset in which the following arguments can be found: `sortvar`, `studyid`, `t` (or `t1` and `t2`), `n` and `r` for binary outcomes, `y`, `sd` and `n` for continuous outcomes, `TE` and `seTE` for inverse variance data.
`perarm`: a logical value indicating whether data are given as one treatment arm per row. If TRUE the `pairwise` command in `netmeta` package is used to produce a dataset with one comparison per row.
`type`: a character value indicating the type of the measured outcome, e.g. "binary", "continuous".
`sm`: a character string indicating underlying summary measure, e.g. "OR", "RR", "RD", "MD", "SMD".
`tau.preset`: an optional value for the square-root of the between-study variance τ^2. If not specified, heterogeneity is re-estimated at each step.
`comb.fixed`: A logical value indicating whether a fixed effect meta-analysis should be conducted.
`comb.random`: A logical value indicating whether a random effects meta-analysis should be conducted.
`typeIerror`: the type I error to be used in the calculations of the sequential boundaries. Default value is 0.05.
`power`: the power to be used in the calculations of the sequential boundaries. Default value is 0.90.
`method`: the method to be approximated in the alpha spending function to construct the sequential boundaries, e.g. “BF” (O'Brien Fleming),"POC" (Pocock), "LIN" (Linear), "PFUN" (power function).

Then, the function performs sequential pairwise and network meta-analysis and returns an object of class `sequentialnma`.

```
dongseq <- sequentialnma(data=Dong, perarm=TRUE, type="binary", sm="OR",
studlab="id",sortvar="year", tau.preset = sqrt(0.014), comb.fixed=F,
comb.random=T)
```

The above command runs in 36 seconds (in a single core 2 GHz Intel Core i7 cpu) and an object of class `sequentialnma` is produced that can be used as argument in `plot`, `repeatedCI` and `summary` functions.

Output of `sequentialnma`

An object of class `sequentialnma`; a list containing the following components:

`sm`: a character string indicating the underlying summary measure.

`result`: a list of equal to the number of studies corresponding to the cumulative update of the meta-analysis. The following are included in `result` a) cumulative pairwise and network meta-analysis treatment effects b) standard errors c) confidence intervals d) repeated confidence intervals e) anticipated treatment effects f) Z-scores g) accumulated information h) fraction of accumulated information i) spent alpha and j) efficacy boundaries at each step of the analysis.

`studies`: the dataset used in the calculations of the sequential network meta-analysis.

`comparisons`: a vector of the comparisons in the network.

Summary of cumulative network meta-analysis treatment effects and sequential quantities

The command `sequentialnma` performs sequential meta-analysis for all comparisons in the network. To see the network meta-analysis monitoring for a particular comparison in all analysis steps you can use the function `summary.sequentialnma`. It takes the following arguments:

Arguments in `summary.sequentialnma`

`seqnmaobject`: An object of class `sequentialnma`.

`comparison`: A character string defining the comparison for which the summary is to be produced. It needs to be one of those listed in `seqnmaobject$comparisons`.

Here we will choose "ICS vs LABA-ICS" (abbreviation of 'Long-acting β2 agonists - inhaled corticosteroids versus Inhaled corticosteroids').

```
summary(dongseq,comparison="ICS:LABA-ICS")
```

Plotting the monitoring boundaries for sequential pairwise and network meta-analysis

The command `plot.sequentialnma` takes the following arguments:

Arguments in `plot. sequentialnma`

`seqnmaobject`: An object of class `sequentialnma`.

`comparison`: A character string defining the comparison for which the plot is to be produced. It needs to be one of those listed in `seqnmaobject$comparisons`.

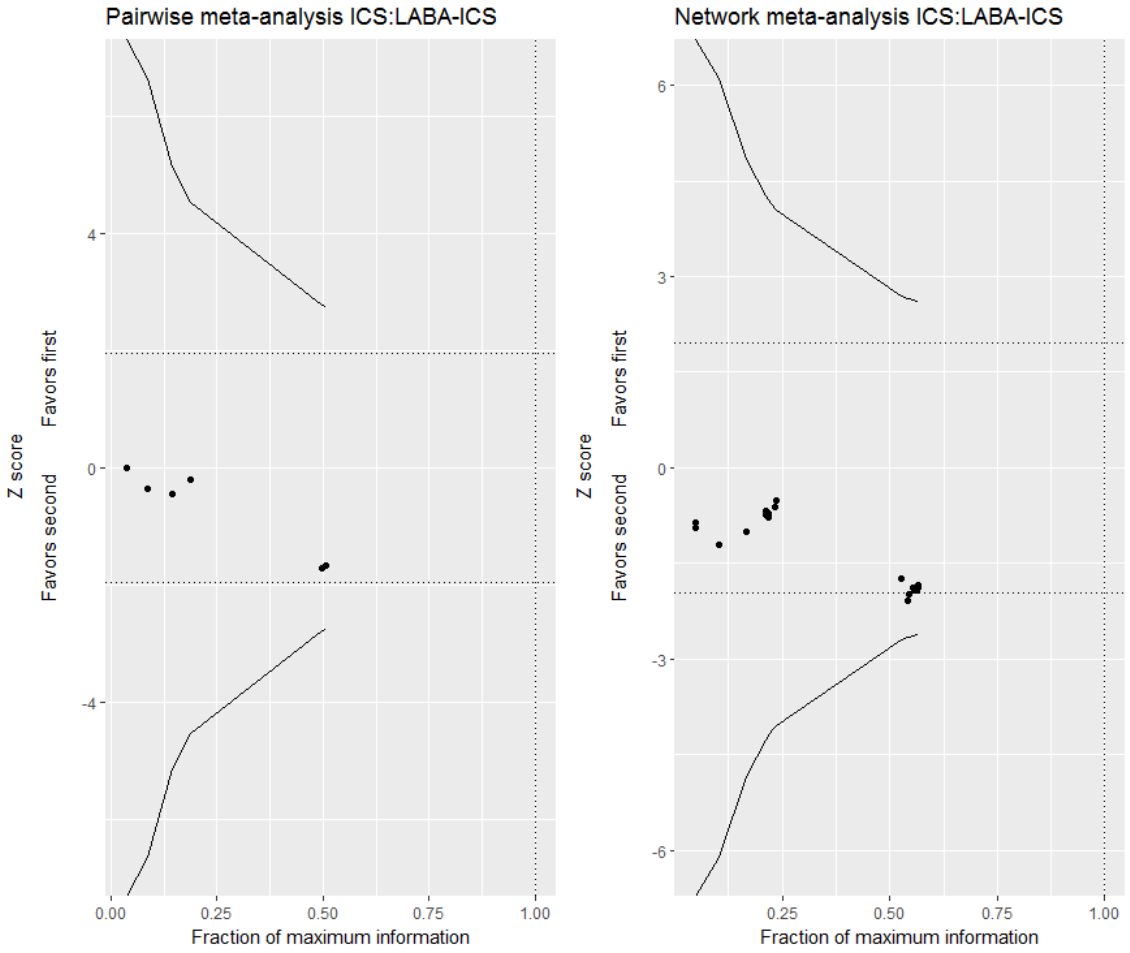
`evidence`: A character string to indicate whether the stopping framework should be drawn based on "pairwise", "network" or "both" evidence.

`small.values`: A character string specifying whether small outcome values indicate benefit ("good") or harm ("bad").

Then, the function produces the monitoring panels for pairwise and network meta-analysis either separately or together.

Using the following command, we produce the monitoring for both network and pairwise meta-analysis:

```
plot(seqnmaobject=dongseq,comparison="ICS:LABA-ICS",evidence="both",
small.values="good")
```



<u>Construction of forest plots with repeated confidence intervals for sequential pairwise and network meta-analysis</u>

In order to construct forest plots with the cumulative treatments effects along with confidence and repeated confidence intervals, we will use the command `repeatedCI` which takes the same arguments as the `plot` command.

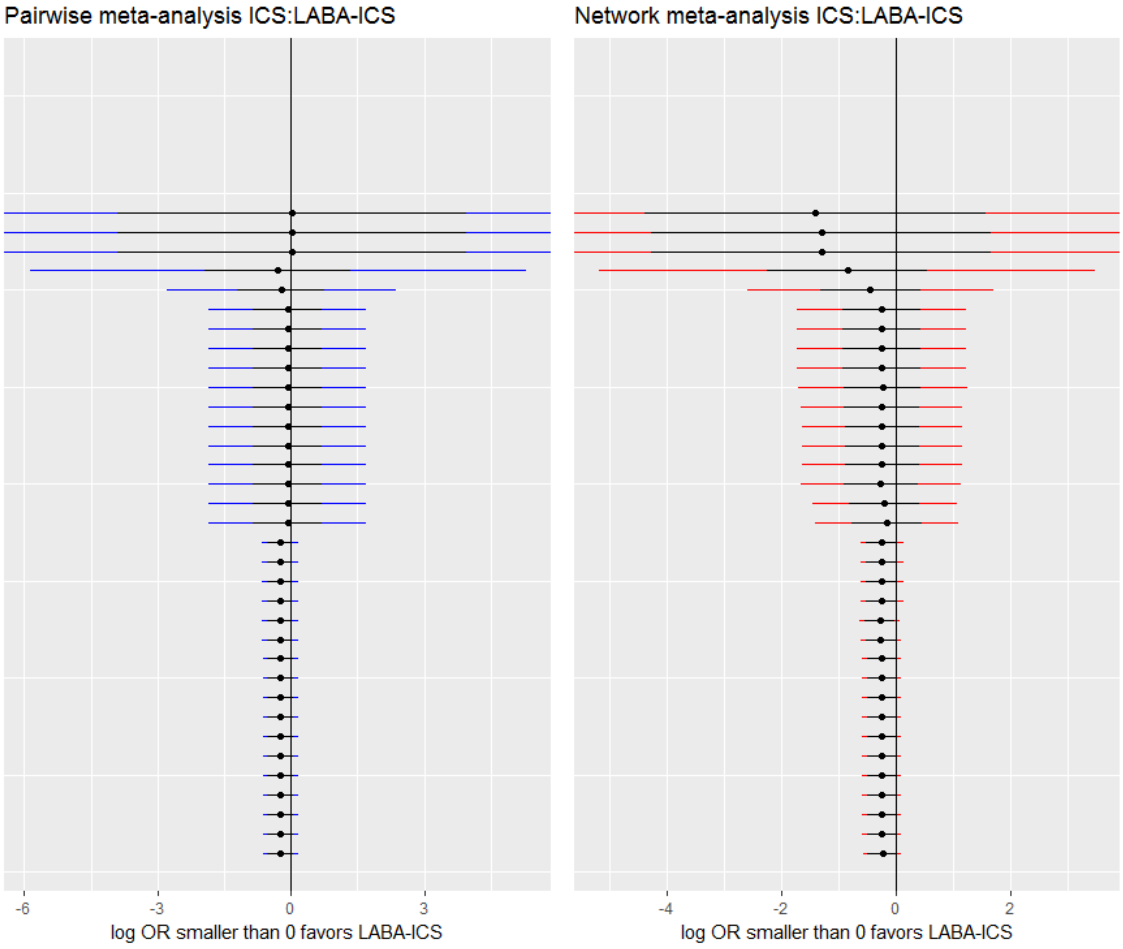
Arguments in `repeatedCI`
`seqnmaobject`: An object of class `sequentialnma`
`comparison`: A character string defining the comparison for which the forest plot is to be produced. It needs to be one of those listed in `seqnmaobject$comparisons`.
`evidence`: A character string to indicate whether the stopping framework should be drawn based on "pairwise", "network", "both.separate" or "both.together"; "both.separate" will draw two forest plots side by side where "both.together" will draw both pairwise and network meta-analysis results on the same forest plot.

`small.values`: A character string specifying whether small outcome values indicate benefit ("good") or harm ("bad").

We produce the forest plot with confidence intervals (black solid lines) and repeated confidence intervals (blue solid lines for pairwise meta-analysis and red solid lines for network meta-analysis).

With the following command we produce both forest plots side by side:

```
repeatedCI(seqnmaobject=dongseq,comparison="ICS:LABA-ICS",
evidence="both.separate", small.values="good")
```



RE-ANALYSIS OF LEUCHT ET AL. USING THE `sequentialnma` PACKAGE

The example of comparing the efficacy of olanzapine and haloperidol in patients with schizophrenia illustrated in Figure 1 of the main manuscript can also be reproduced. The command below takes 7.65 minutes (in a single core 2 GHz Intel Core i7 cpu).

```
data(Leucht)
```

```
leuchtseq <- sequentialnma(data=Leucht, perarm=FALSE, type="continuous", sm="SMD",
tau.preset = 0.2213594, comb.fixed=F, comb.random=T, studlab="id",sortvar="year",
TE="effect", seTE="se", t1="treat1", t2="treat2")
```

Then, sequential panels and forest plots with confidence and repeated confidence intervals can be drawn as

```
plot(seqnmaobject=leuchtseq,comparison="HAL:OLA",evidence="both",small.values="goo
d")
```

and

```
repeatedCI(seqnmaobject=leuchtseq,comparison="HAL:OLA",evidence="network",small.va
lues="good")
```