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The ROB-MEN tool to evaluate the risk of bias due to missing evidence in network meta-analysis

Virginia Chiocchia

Institute of Social and Preventive Medicine, University of Bern

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Outline

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1. Introduction & overview of the ROB-MEN
2. Live demo: antipsychotics for schizophrenia NMA
3. Final remarks & updates

Introduction

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Why ROB-MEN?

Reporting bias in NMA

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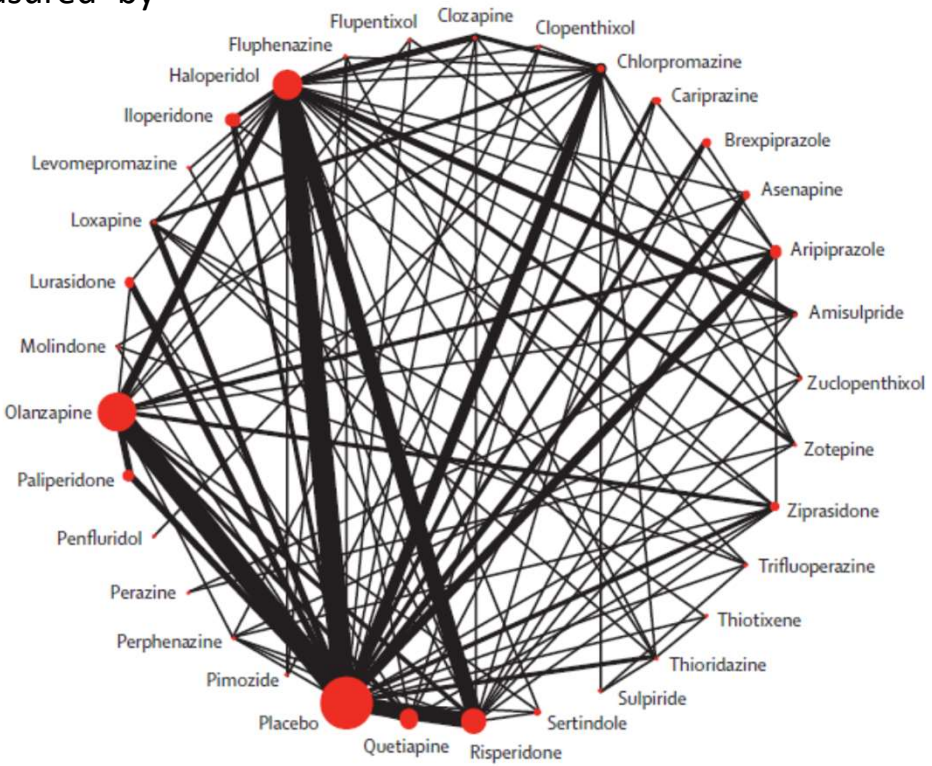
Network of placebo-controlled studies of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia.

Outcome: overall efficacy, symptoms of schizophrenia as measured by rating scales.



(Huhn et al, *Lancet* 2019; 394: 939–51)

❖ Direct comparison → Pairwise MA reporting bias methods

❖ NMA estimate: contribution from direct and indirect evidence

❖ **Risk of bias:** low, some, high ?

✓ ROB-MEN tool

✓ CINeMA framework

CINeMA Reporting Bias domain - before

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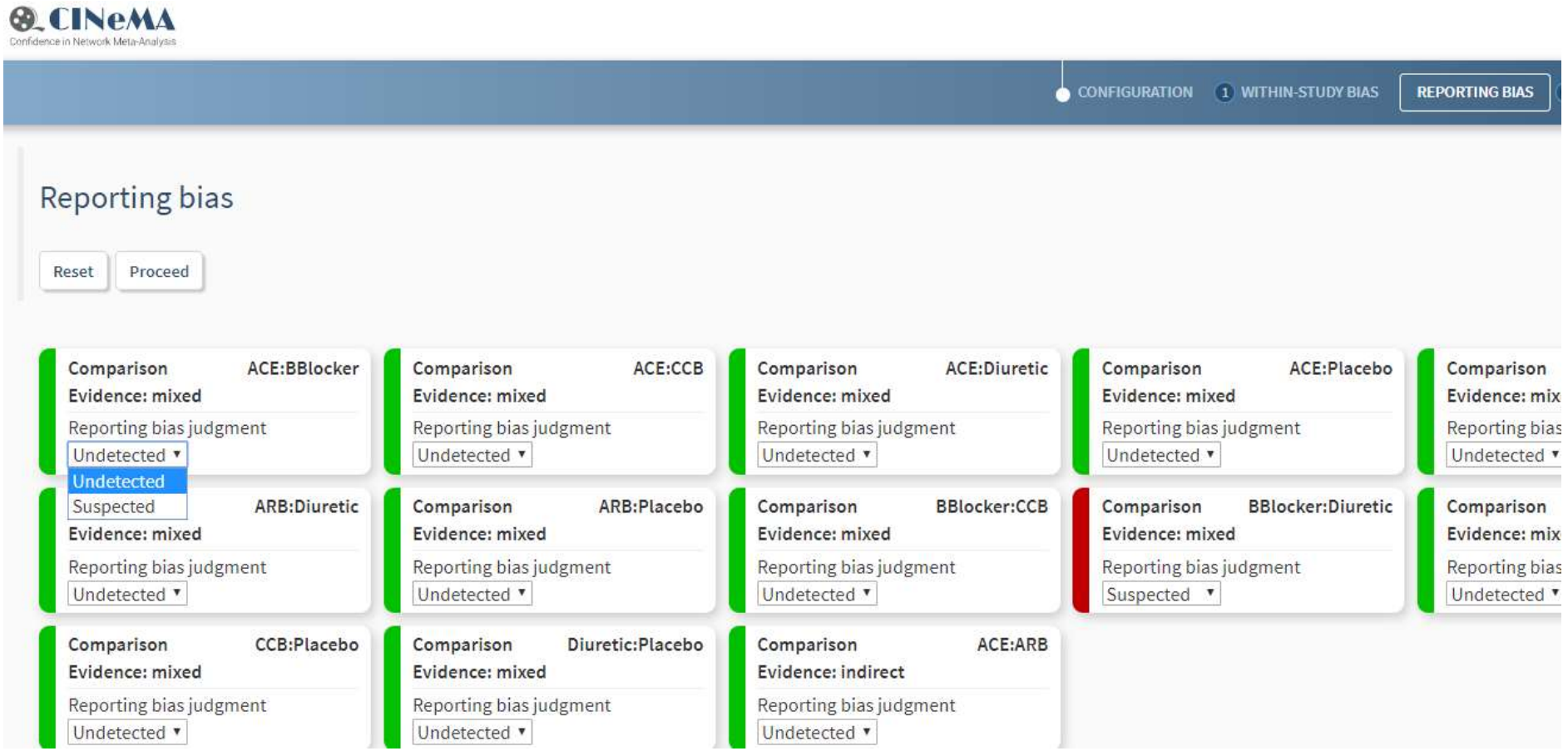
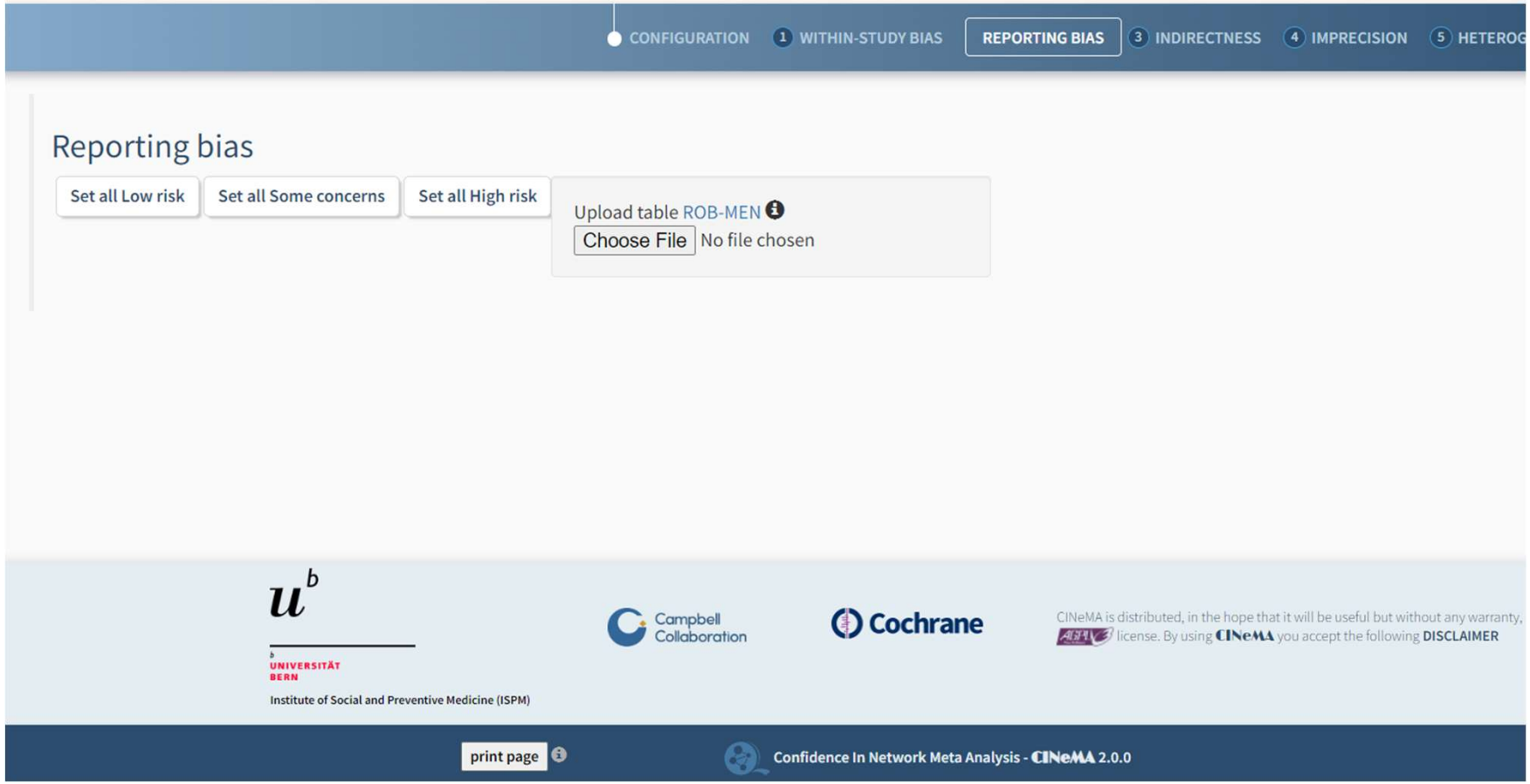


CINeMA Reporting Bias domain - now



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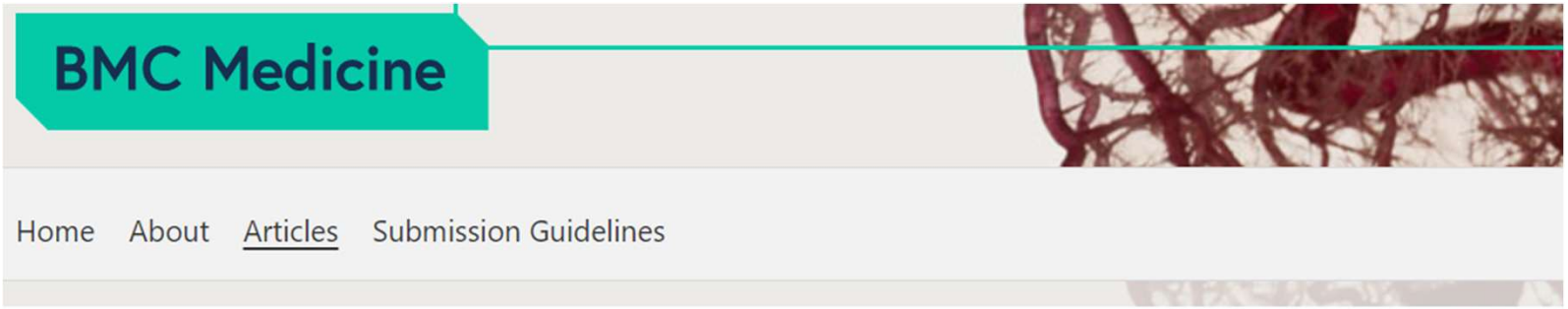

Guideline | Open Access | Published: 23 November 2021

ROB-MEN: a tool to assess risk of bias due to missing evidence in network meta-analysis

Virginia Chiocchia, Adriani Nikolakopoulou, Julian P. T. Higgins, Matthew J. Page, Theodoros Papakonstantinou, Andrea Cipriani, Toshi A. Furukawa, George C. M. Siontis, Matthias Egger & Georgia Salanti

BMC Medicine **19**, Article number: 304 (2021) | Cite this article

ROB-MEN app

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ROB-MEN: Risk Of Bias due to Missing Evidence in Network meta-analysis

Load data | Data analysis | Pairwise Comparison Table | ROB-MEN Table

Summary measure
- SMD

Smaller outcome values are
- Desirable

Synthesis model
- Random effects

Choose the reference treatment
- Placebo

Parameters for the Bayesian network meta-regression

Burn In

1000

Iterations

10000

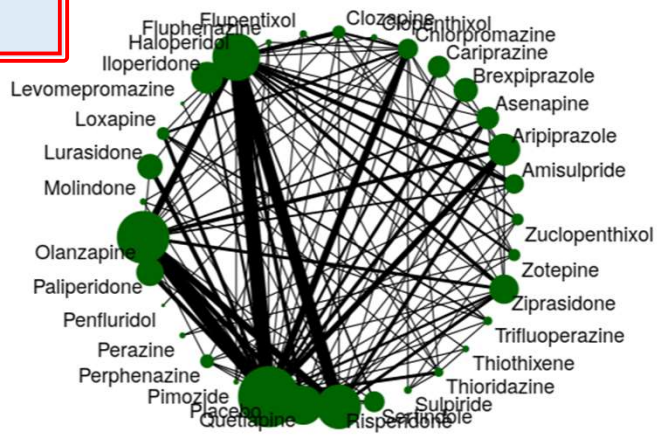
Assumption for treatment-specific interactions
- Exchangeable/related treatment-specific interactions

Data Summary | Bayesian network meta-analysis | Bayesian network meta-regression

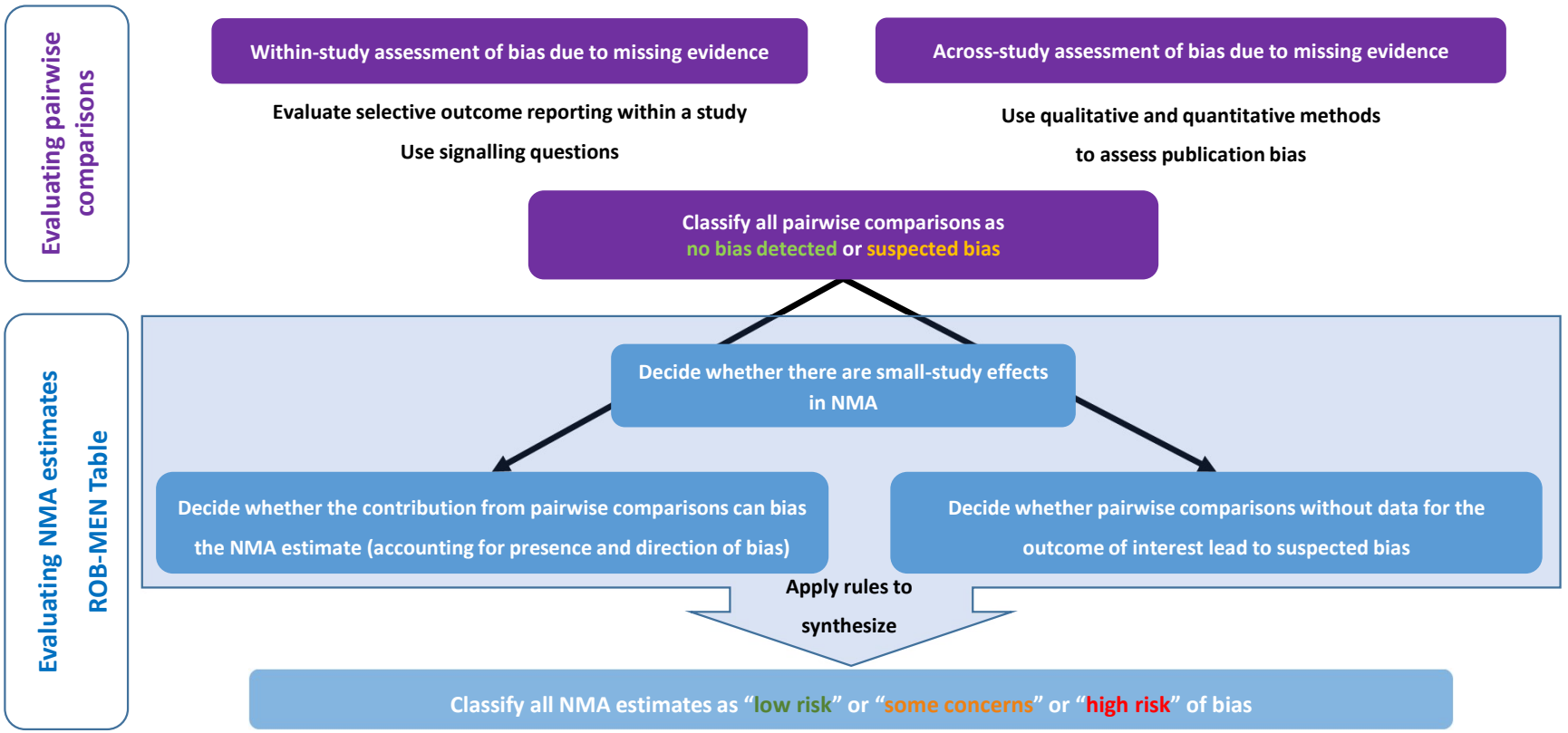
Funnel plots and test for small-study effects | Contribution matrix

ROB-MEN Shiny app
cinema.ispm.unibe.ch/rob-men/

Network graph



Overview of ROB-MEN



Within-study assessment of bias

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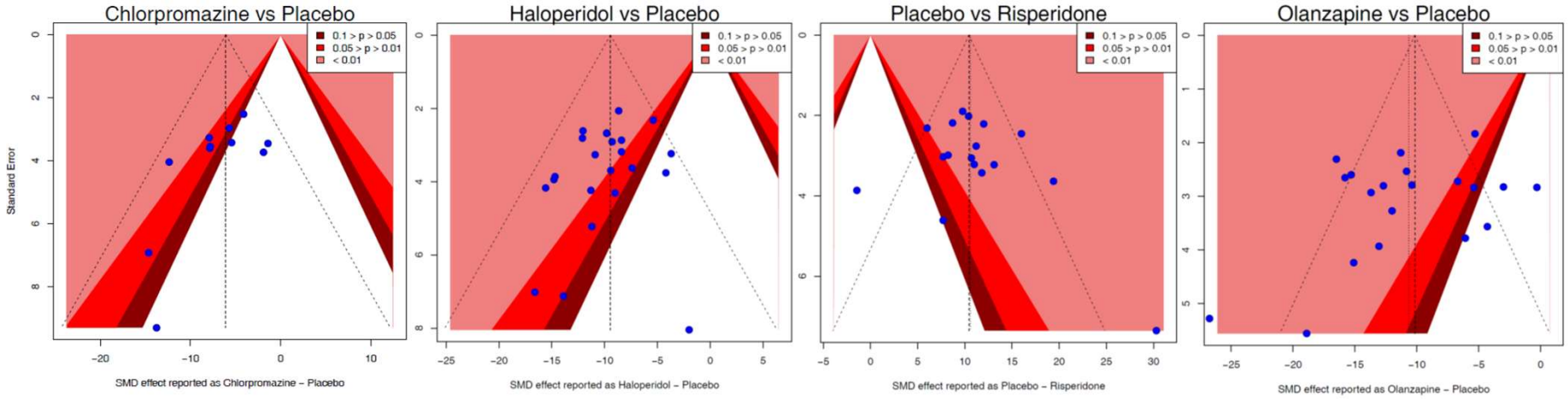
- ROB-ME (https://www.riskofbias.info/welcome/rob-me-tool)
- ORBIT classification (https://www.outcome-reporting-bias.org/)

Signalling question	**Responses for each comparison (groups A and B only)**		
Was there any eligible study for which results for the outcome of interest were unavailable, likely because of the *p*-value, magnitude or direction of the result generated?	Yes	Yes	No
(If Yes to the previous question) Was the amount of information omitted from the synthesis sufficient to have a notable effect on the magnitude of the synthesised result?	Yes	No	-
Overall judgement	*Suspected bias (favouring X)*	*No bias detected*	*No bias detected*

Across-study assessment of bias



	comparison	bias	p.value	interpretation
1	Chlorpromazine vs Placebo	-1.89	0.06	Small studies favour 1st intervention
2	Haloperidol vs Olanzapine	-1.06	0.14	Small studies favour 1st intervention
3	Haloperidol vs Placebo	-0.8	0.24	Small studies favour 1st intervention
4	Haloperidol vs Risperidone	1.4	0.1	Small studies favour 2nd intervention
5	Olanzapine vs Placebo	-2.2	0.2	Small studies favour 1st intervention
6	Olanzapine vs Risperidone	-0.44	0.44	Small studies favour 1st intervention
7	Placebo vs Risperidone	1.2	0.38	Small studies favour 2nd intervention
8	Quetiapine vs Risperidone	-0.17	0.77	Small studies favour 1st intervention

ROB-MEN app – Pairwise Comparison Table

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		Number of studies in each comparison		Within-study assessment of bias	Across-study assessment of bias	Overall bias
View data	wise comparison	Reporting this outcome (sample size)	Total identified in the SR (total sample size)	Evaluation of selective reporting within studies using signalling questions	Qualitative and quantitative assessment of publication bias	Overall judgement
Group A: observed for this outcome						
10	Aripiprazole:Placebo	9 (1814)	9 (1814)	No bias detected	No bias detected	No bias detected
17	Asenapine:Placebo	6 (1711)	6 (1711)	No bias detected	No bias detected	No bias detected
20	Brexpiprazole:Placebo	5 (1942)	5 (1942)	No bias detected	No bias detected	No bias detected
22	Cariprazine:Placebo	4 (1610)	4 (1610)	No bias detected	No bias detected	No bias detected
33	Chlorpromazine:Placebo	11 (442)	34 (1923)	Suspected bias favouring Chlorpromazine	No bias detected	Suspected bias favouring Chlorpromazine
41	Clopenthixol:Placebo	1 (29)	2 (65)	No bias detected	Suspected bias favouring Clopenthixol	Suspected bias favouring Clopenthixol
44	Clozapine:Placebo	1 (24)	1 (24)	No bias detected	Suspected bias favouring Clozapine	Suspected bias favouring Clozapine
49	Flupentixol:Placebo	1 (30)	1 (30)	No bias detected	Suspected bias favouring Flupentixol	Suspected bias favouring Flupentixol
52	Fluphenazine:Placebo	1 (41)	1 (41)	No bias detected	Suspected bias favouring Fluphenazine	Suspected bias favouring Fluphenazine
60	Haloperidol:Placebo	23 (2831)	28 (2996)	No bias detected	No bias detected	No bias detected
69	Iloperidone:Placebo	4 (1565)	4 (1565)	No bias detected	No bias detected	No bias detected
73	Loxapine:Placebo	6 (253)	6 (253)	No bias detected	No bias detected	No bias detected
78	Lurasidone:Placebo	7 (2075)	7 (2075)	No bias detected	No bias detected	No bias detected
80	Molindone:Placebo	1 (29)	1 (29)	No bias detected	Suspected bias favouring Molindone	Suspected bias favouring Molindone
84	Olanzapine:Placebo	20 (3702)	21 (4002)	No bias detected	No bias detected	No bias detected
89	Paliperidone:Placebo	7 (2120)	7 (2120)	No bias detected	No bias detected	No bias detected
92	Perphenazine:Placebo	1 (48)	2 (121)	No bias detected	Suspected bias favouring Perphenazine	Suspected bias favouring Perphenazine
97	Placebo:Quetiapine	9 (2532)	10 (2541)	No bias detected	No bias detected	No bias detected
98	Placebo:Risperidone	17 (3376)	18 (3401)	No bias detected	No bias detected	No bias detected
99	Placebo:Sertindole	3 (603)	3 (603)	No bias detected	No bias detected	No bias detected
100	Placebo:Thioridazine	5 (150)	8 (243)	Suspected bias favouring Thioridazine	No bias detected	Suspected bias favouring Thioridazine
101	Placebo:Thiothixene	2 (96)	3 (116)	No bias detected	Suspected bias favouring Thiothixene	Suspected bias favouring Thiothixene

ROB-MEN app – Pairwise Comparison Table

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56	Haloperidol:Loxapine	2 (98)	3 (148)	No bias detected	No bias detected	No bias detected
57	Haloperidol:Lurasidone	1 (213)	1 (213)	No bias detected	Suspected bias favouring Lurasidone	Suspected bias favouring Lurasidone
58	Haloperidol:Olanzapine	11 (3200)	14 (3396)	No bias detected	No bias detected	No bias detected
59	Haloperidol:Pimozide	1 (29)	3 (71)	No bias detected	No bias detected	No bias detected
60	Haloperidol:Placebo	23 (2831)	28 (2996)	No bias detected	No bias detected	No bias detected
61	Haloperidol:Quetiapine	6 (1039)	8 (1119)	No bias detected	No bias detected	No bias detected
62	Haloperidol:Risperidone	19 (1842)	27 (2192)	No bias detected	No bias detected	No bias detected
63	Haloperidol:Sertindole	3 (893)	3 (893)	No bias detected	No bias detected	No bias detected
64	Haloperidol:Thioridazine	1 (16)	2 (102)	No bias detected	No bias detected	No bias detected
65	Haloperidol:Trifluoperazine	2 (56)	4 (92)	No bias detected	No bias detected	No bias detected
66	Haloperidol:Ziprasidone	6 (1105)	8 (1838)	Suspected bias favouring Ziprasidone	No bias detected	Suspected bias favouring Ziprasidone
67	Haloperidol:Zotepine	4 (262)	5 (379)	No bias detected	No bias detected	No bias detected
68	Haloperidol:Zuclopenthixol	4 (244)	5 (259)	No bias detected	No bias detected	No bias detected
Group B: observed for other outcomes						
128	Haloperidol:Molindone	NA (NA)	1 (30)	No bias detected	No bias detected	No bias detected
129	Haloperidol:Perazine	NA (NA)	2 (82)	No bias detected	No bias detected	No bias detected
130	Haloperidol:Sulpiride	NA (NA)	2 (150)	No bias detected	No bias detected	No bias detected
Group C: Unobserved						
221	Brexpiprazole:Haloperidol	NA (NA)	NA (NA)		No bias detected	No bias detected
247	Cariprazine:Haloperidol	NA (NA)	NA (NA)		No bias detected	No bias detected
316	Flupentixol:Haloperidol	NA (NA)	NA (NA)		No bias detected	No bias detected
356	Haloperidol:Paliperidone	NA (NA)	NA (NA)		Suspected bias favouring Paliperidone	Suspected bias favouring Paliperidone
357	Haloperidol:Penfluridol	NA (NA)	NA (NA)		No bias detected	No bias detected

View data

ROB-MEN overall bias algorithm

Low risk	There is no substantial contribution from evidence with suspected bias favouring one of the two treatments, OR There is substantial contribution from evidence at suspected bias but it is split more or less equally between evidence with bias favouring one of the treatments and evidence with bias favouring the other treatment **AND** There is no evidence of small-study effects favouring one of the two treatments OR [For indirect estimates only] There is no suspected bias favouring one of the two treatments from the assessment of indirect evidence.
Some concerns	All other combinations
High risk	There is substantial contribution from evidence with suspected bias favouring one of the two treatments, say X **AND** There is evidence of small-study effects favouring the same treatment X OR [For indirect estimates only] There is suspected bias favouring that treatment X from the assessment of indirect evidence.

ROB-MEN app – ROB-MEN Table

	NMA estimate	% contribution of evidence from pairwise comparisons with suspected bias		Evaluation of contribution from evidence with suspected bias	Bias assessment for indirect evidence	NMA treatment effect	NMR treatment effect at the smallest observed variance	Evaluation of small-study effects	Overall risk of bias
		Favouring first treatment	Favouring second treatment						
mixed/only direct									
10	Aripiprazole:Placebo	0	0	No substantial contribution from bias	No bias detected	-8.08 (-9.78 to -6.43)	-7.12 (-9.02 to -5.23)	No evidence of small-study effects	Low risk
17	Asenapine:Placebo	0	0	No substantial contribution from bias	No bias detected	-7.23 (-9.60 to -4.83)	-6.40 (-8.98 to -3.91)	No evidence of small-study effects	Low risk
20	Brexpiprazole:Placebo	0	0	No substantial contribution from bias	No bias detected	-5.96 (-8.54 to -3.29)	-5.26 (-7.95 to -2.59)	No evidence of small-study effects	Low risk
22	Cariprazine:Placebo	0	0	No substantial contribution from bias	No bias detected	-6.43 (-9.30 to -3.55)	-5.80 (-8.66 to -2.91)	No evidence of small-study effects	Low risk
33	Chlorpromazine:Placebo	38	0	Substantial contribution from bias favouring Chlorpromazine	Suspected bias favouring Chlorpromazine	-6.34 (-8.14 to -4.58)	-5.19 (-7.32 to -3.13)	No evidence of small-study effects	Some concerns
41	Clopenthixol:Placebo	19	0	Substantial contribution from bias favouring Clopenthixol	Suspected bias favouring Clopenthixol	-6.75 (-11.22 to -2.32)	-5.61 (-10.22 to -0.98)	No evidence of small-study effects	Some concerns
44	Clozapine:Placebo	17	0	Substantial contribution from bias favouring Clozapine	Suspected bias favouring Clozapine	-13.22 (-15.65 to -10.87)	-11.79 (-14.46 to -8.95)	No evidence of small-study effects	Some concerns
49	Flupentixol:Placebo	56	0	Substantial contribution from bias favouring Flupentixol	Suspected bias favouring Flupentixol	-4.69 (-8.84 to -0.50)	-4.05 (-8.19 to 0.09)	No evidence of small-study effects	Some concerns
52	Fluphenazine:Placebo	24	0	Substantial contribution from bias favouring Fluphenazine	Suspected bias favouring Fluphenazine	-4.58 (-9.65 to 0.39)	-3.28 (-8.53 to 1.98)	No evidence of small-study effects	Some concerns
60	Haloperidol:Placebo	0	0	No substantial contribution from bias	No bias detected	-8.74 (-9.85 to -7.66)	-7.64 (-9.06 to -6.21)	No evidence of small-study effects	Low risk
69	Iloperidone:Placebo	0	0	No substantial contribution from bias	No bias detected	-6.19 (-8.51 to -3.91)	-5.28 (-7.68 to -2.89)	No evidence of small-study effects	Low risk
73	Loxapine:Placebo	0	0	No substantial contribution from bias	No bias detected	-6.80 (-9.51 to -4.07)	-5.28 (-8.26 to -2.26)	No evidence of small-study effects	Low risk
78	Lurasidone:Placebo	4	0	No substantial contribution from bias	No bias detected	-7.27 (-9.73 to -4.80)	-6.31 (-8.89 to -3.73)	No evidence of small-study effects	Low risk
80	Molindone:Placebo	27	0	Substantial contribution from bias favouring Molindone	Suspected bias favouring Molindone	-5.68 (-10.25 to -1.07)	-4.29 (-8.95 to 0.36)	No evidence of small-study effects	Some concerns
84	Olanzapine:Placebo	0	0	No substantial contribution from bias	No bias detected	-10.93 (-12.06 to -9.82)	-9.87 (-11.24 to -8.42)	No evidence of small-study effects	Low risk
89	Paliperidone:Placebo	0	0	No substantial contribution from bias	No bias detected	-9.82 (-11.96 to -7.66)	-8.91 (-11.17 to -6.64)	No evidence of small-study effects	Low risk

Final remarks

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- ROB-MEN first tool to evaluate bias due to missing evidence in NMA
- The ROB-MEN app simplify the assessment process
- Part of CINeMA framework (https://cinema.ispm.unibe.ch/)

- Not published in journal ≠ reporting bias
- Missing data problem

- Run the NMA before using the ROB-MEN app
- Follow the instructions in the app and guidelines in the paper

Future updates

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- New version of the app
- Update documentation
- Tutorial paper in draft

virginia.chiocchia@ispm.unibe.ch

@VirgieGinny

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ROB-MEN collaborators

Alex Holloway

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