Systematische Überprüfung der randomisierten kontrollierten Studien zur Homöopathie

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London, UK

June 2017

Systematic review of randomised controlled trials of homeopathy

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Plan of presentation

- **Summary of clinical research evidence in homeopathy**
  - Randomised controlled trials (RCTs)
    - Types of homeopathic intervention
    - Study design (placebo, etc.)
    - 'Vote counting' in evidence overviews
  - Systematic reviews (and meta-analyses) of RCTs
  - Limitations of evidence base
- **Programme of systematic reviews and meta-analysis of RCTs**
- **Implications for the future**

Hierarchy of clinical research evidence (World Health Organization)

Category of evidence	Source of evidence
Ia	**Systematic review** (with/without **meta-analysis**) of randomised controlled trials (RCTs)
Ib	At least one **RCT**
II	At least one **non-randomised, controlled, study** e.g. Parallel-group study
III	**Non-randomised, non-controlled, studies** e.g. Clinical outcomes (cohort) studies
IV	**Expert committee reports or opinions** and/or clinical experience of respected authorities

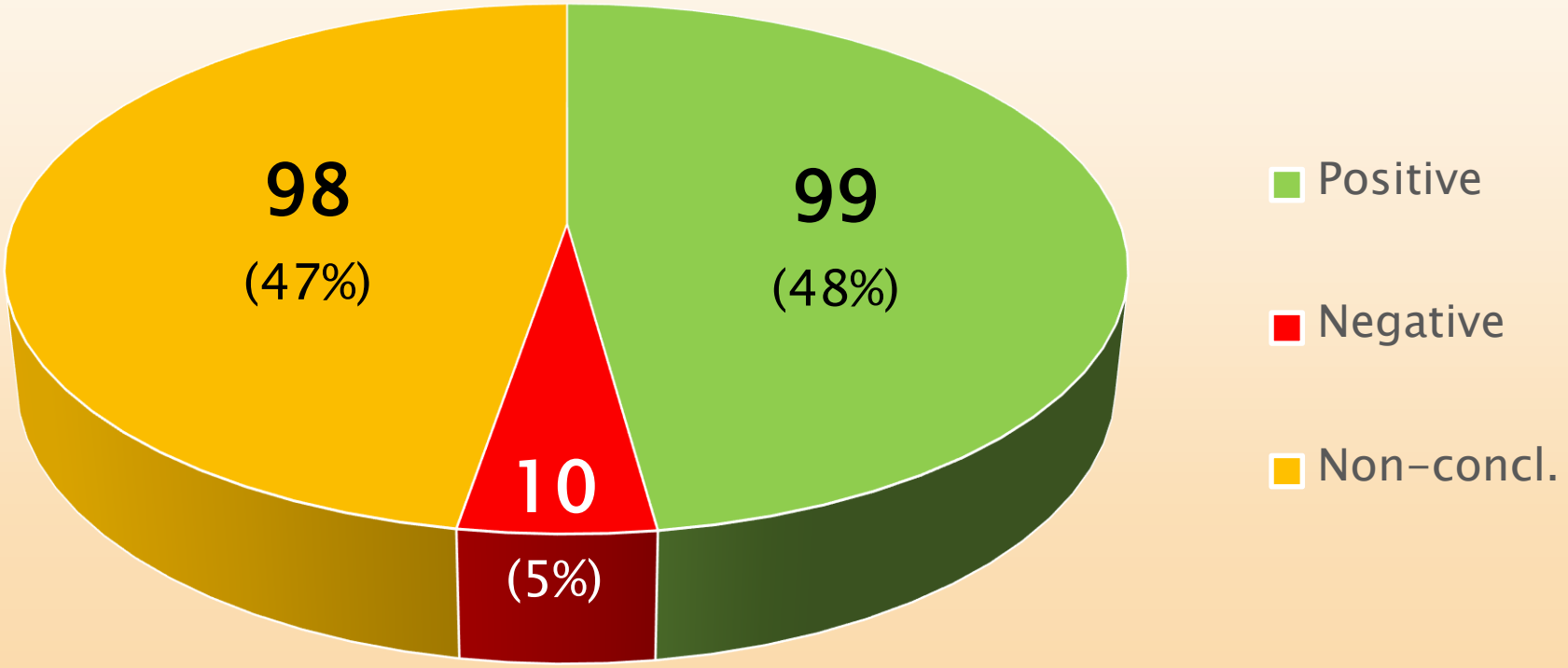
Category I evidence

- The RCT is the only method that enables clear inferences about cause and effect of an intervention
- Systematic review of RCTs in homeopathy provides (qualitative) overall view of evidence:
  - For a given medical condition
  - For a given homeopathic medicine
  - For a given mode of homeopathy
  - For all homeopathic interventions altogether
- Meta-analysis provides (quantitative) estimate of homeopathy's treatment effect size in a given category
  - With more than one RCT we increase..
    - the total sample size
    - the statistical power to detect any difference

Category Ib evidence: Randomised controlled trials (RCTs)

- Reported in peer-reviewed journals (to end of 2016):
  - Thorough, **systematic**, overview of literature
    - **Total=207 RCT papers of homeopathy**
      - **104 different medical conditions studied**
      - **All other medical conditions not studied**
  - 'Vote counting': *"Is there any evidence of an effect?"*
    - Numbers of homeopathy RCTs with statistically relevant results..
      - 'Positive' / 'Negative' / 'Non-conclusive'

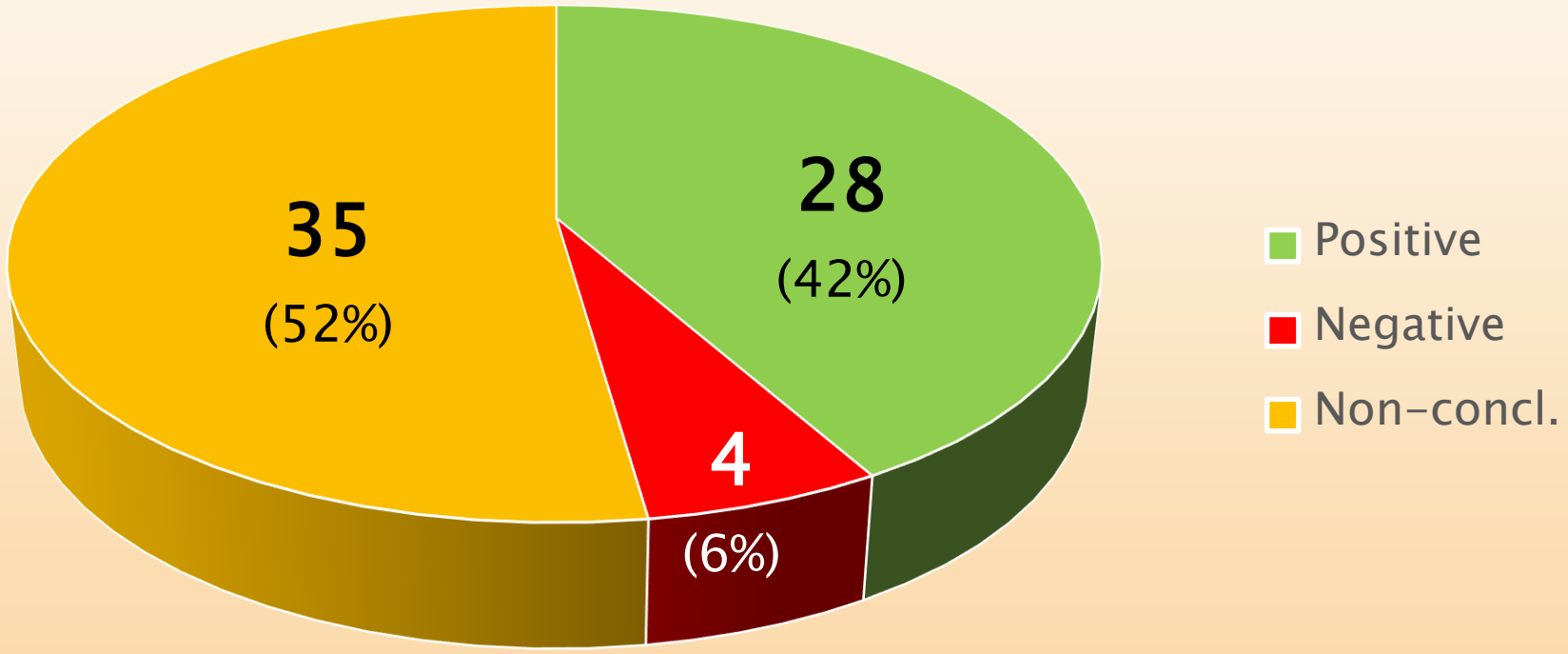
Evidence overall ('vote counting'): 207 RCTs of homeopathy



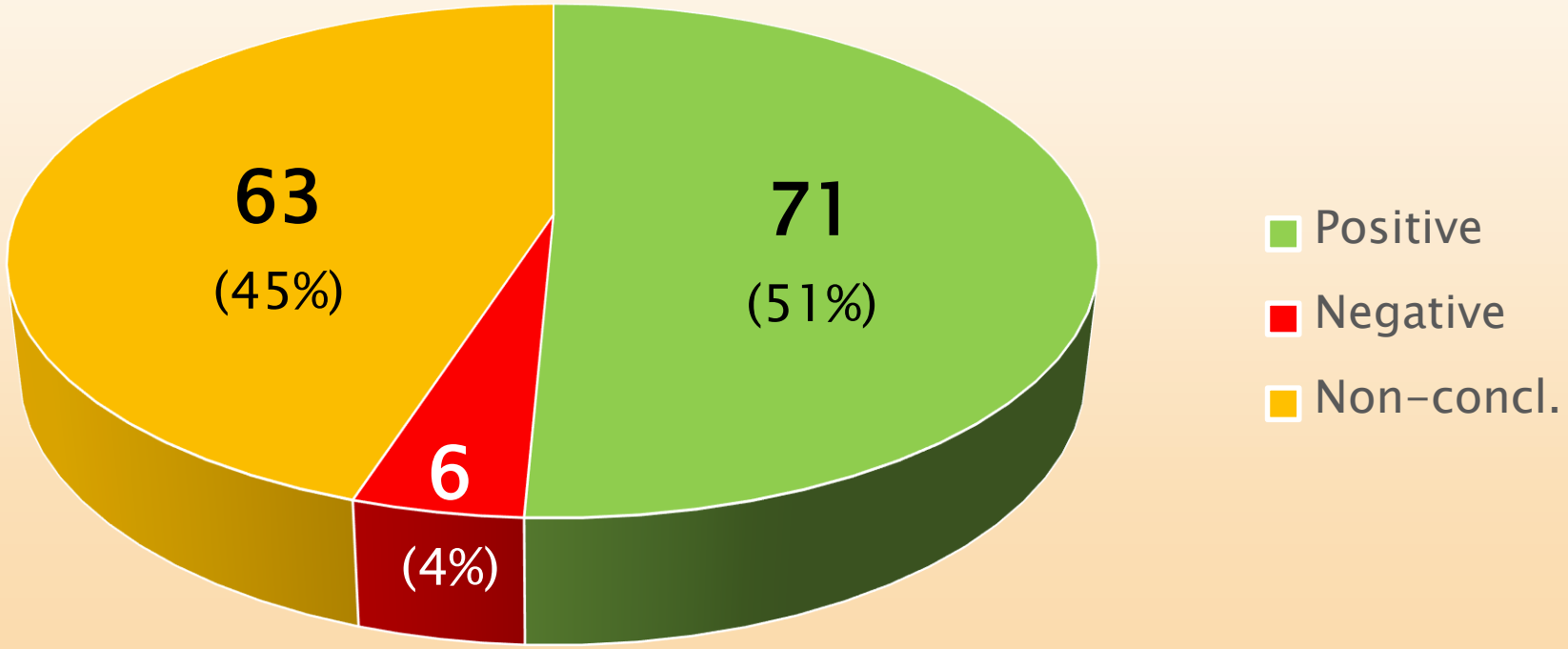
Different types of homeopathy in RCTs

- **Individualised homeopathy**
  - 'Classical homeopathy' ('Treatment by a homeopath')
  - Each patient in trial gets his/her simillimum
- **Non-individualised homeopathy**
  - Pre-selected homeopathic medicine for *typical* symptoms of a disease
  - Every patient gets the same medicine ('drug trial')
    - Single homeopathic medicine
    - Complex homeopathic medicine
      - Over-the-counter product
      - Research-related formulation
    - Isopathy

67 of 207 RCTs:
Individualised homeopathy



140 of 207 RCTs:
Non-individualised homeopathy



Interpretation of RCT findings

- ***Problems of 'vote counting'…***
  - Not fully systematic in approach
    - Merely asks: "Is there any evidence of an effect?"
  - No clear assessment of study quality
  - Loose definition of 'positive', 'negative'
    - Magnitude of treatment effect?

Table 1 Interpretation of original authors' conclusions from systematic reviews of homeopathy RCTs*

Review type	*Positive*	*Tentatively positive*	*Non-conclusive*	*Tentatively negative*	*Negative*
Comprehensive (all homeopathy)		Boissel 1996 [15] Cucherat 2000 [17] Kleijnen 1991 [2] Linde 1997 [16] †			Shang 2005 [18] ‡
Comprehensive (individualised homeopathy)		Linde & Melchart 1998 [20] Mathie 2014 [7]			
By group of diagnoses		Bellavite 2006a [27] Bellavite 2006b [28] Bornhöft 2006 [29] Davidson 2011 [30] Iannitti 2014 [31] Jonas 2000 [32]	**Kassab 2009** [12] Lüdtke & Hacke 2005 [38]	Altunç 2007 [44] Milazzo 2006 [45] Simonart 2011 [46]	Ernst & Pittler 1998 [47]
By single medical condition	Jacobs 2003 [24] Schneider 2005 [25] Taylor 2000 [26]	Barnes 1997 [33] Ernst 2011a [34] Boehm 2014 [35] **Mathie 2012** [13] **Peckham 2013** [14] Perry 2010 [36] Wiesenauer & Lüdtke 1996 [37]	Long & Ernst 2001 [39] **McCarney 2003** [8] **McCarney 2004** [10] Owen & Green 2004 [40] Pilkington 2005 [41] Pilkington 2006 [42] Saha 2013 [43]	**Smith 2003** [9]	Cooper & Relton 2010 [48] **Coulter & Dean 2007** [11] Ernst 1999 [49] Ernst 2011b [50] Ernst 2012 [51] Ernst & Barnes 1998 [52]

Entries arranged alphabetically, by first author name, per section.
A review comprising more than two authors is designated by its first author only. Cochrane reviews highlighted in **bold**.
* Summary description of a review's RCT evidence in homeopathy as 'positive', 'non-conclusive' or 'negative' is based on subjective interpretation of the original review authors' main conclusions, and reflecting key caveats that may have caused their conclusions to be expressed tentatively.
† Positive re placebo comparison; non-conclusive re specific medical conditions.
‡ Tentatively negative re specific effect of homeopathic medicines.

Most systematic reviews/meta-analyses on homeopathy had not adequately explored:

- **Intrinsic study quality**
  - **Internal validity (risk of bias)**
    - **Reliable evidence**
- **Size of 'treatment effect'**
  - May be small/difficult to detect?
- **Peer-reviewed** *vs.* **non-peer-reviewed** literature
- **Individualised** *vs.* **non-individualised** homeopathy
  - 'Whole system of medicine' *vs.* 'pre-selected drug'
- **Quality of homeopathic intervention / main outcome measure**
  - **Model validity**
- **Treatment** *vs.* **prophylaxis**
- **'Medical conditions'?**

Others' conclusions regarding 'placebo'

- **Linde, 1997**
  - "The results of our meta-analysis [of RCTs] are **not** compatible with the hypothesis that the clinical effects of homoeopathy are completely due to placebo"
- **Shang, 2005**
  - "The finding [from meta-analysis 'restricted to large RCTs of higher quality'] **is** compatible with the notion that the clinical effects of homoeopathy are placebo effects"
- **UK House of Commons S&T Committee, 2010**
  - "Homeopathic products perform **no better** than placebos"

Others' conclusions regarding 'conditions'

- **Linde, 1997**
  - "Insufficient [RCT] evidence…that homoeopathy is clearly efficacious for any single clinical condition"
- **Australian NHMRC report, 2015**
  - "There are no health conditions for which there is reliable [RCT] evidence that homeopathy is effective"

Our programme of systematic reviews focuses on…

- Individualised / non-individualised homeopathy
- Placebo-controlled / Other-than-placebo (OTP)-controlled trials
- Treatment / prophylaxis
- Study quality
  - **Internal validity** and **model validity**
- Peer-reviewed literature only
- Effect size (meta-analysis)

Homeopathy (2013) 102, 3–24
© 2012 The Faculty of Homeopathy
http://dx.doi.org/10.1016/j.homp.2012.10.002, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Randomised controlled trials of homeopathy in humans: characterising the research journal literature for systematic review

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Introduction: **A new programme of systematic reviews of randomised controlled trials (RCTs) in homeopathy will distinguish important attributes of RCT records, including: placebo controlled *versus* other-than-placebo (OTP) controlled; individualised *versus* non-individualised homeopathy; peer-reviewed (PR) *versus* non peer-reviewed (NPR) sources.**

Aims: **(a) To outline the methods used to search and categorise the RCT literature; (b) to report details of the records retrieved; (c) to compare our retrieved records with those reported in two previous systematic reviews (Linde *et al.*, 1997; Shang *et al.*, 2005).**

Methods: **Ten major electronic databases were searched for records published up to the end of 2011. A record was accepted for subsequent systematic review if it was a substantive report of a clinical trial of homeopathic treatment or prophylaxis in humans, randomised and controlled, and published in a PR or NPR journal.**

Results: **489 records were potentially eligible: 226 were rejected as non-journal, minor or repeat publications, or lacking randomisation and/or controls and/or a 'homeopathic' intervention; 263 (164 PR, 99 NPR) were acceptable for systematic review. The 263 accepted records comprised 217 (137 PR, 80 NPR) placebo-controlled RCTs, of which 121 were included by, 66 were published after, and 30 were potentially eligible for, but not listed by, Linde or Shang. The 137 PR records of placebo-controlled RCTs comprise 41 on individualised homeopathy and 96 on non-individualised homeopathy.**

Conclusion: **Our findings clarify the RCT literature in homeopathy. The 263 accepted journal papers will be the basis for our forthcoming programme of systematic reviews.**
Homeopathy (2013) **102**, 3–24.

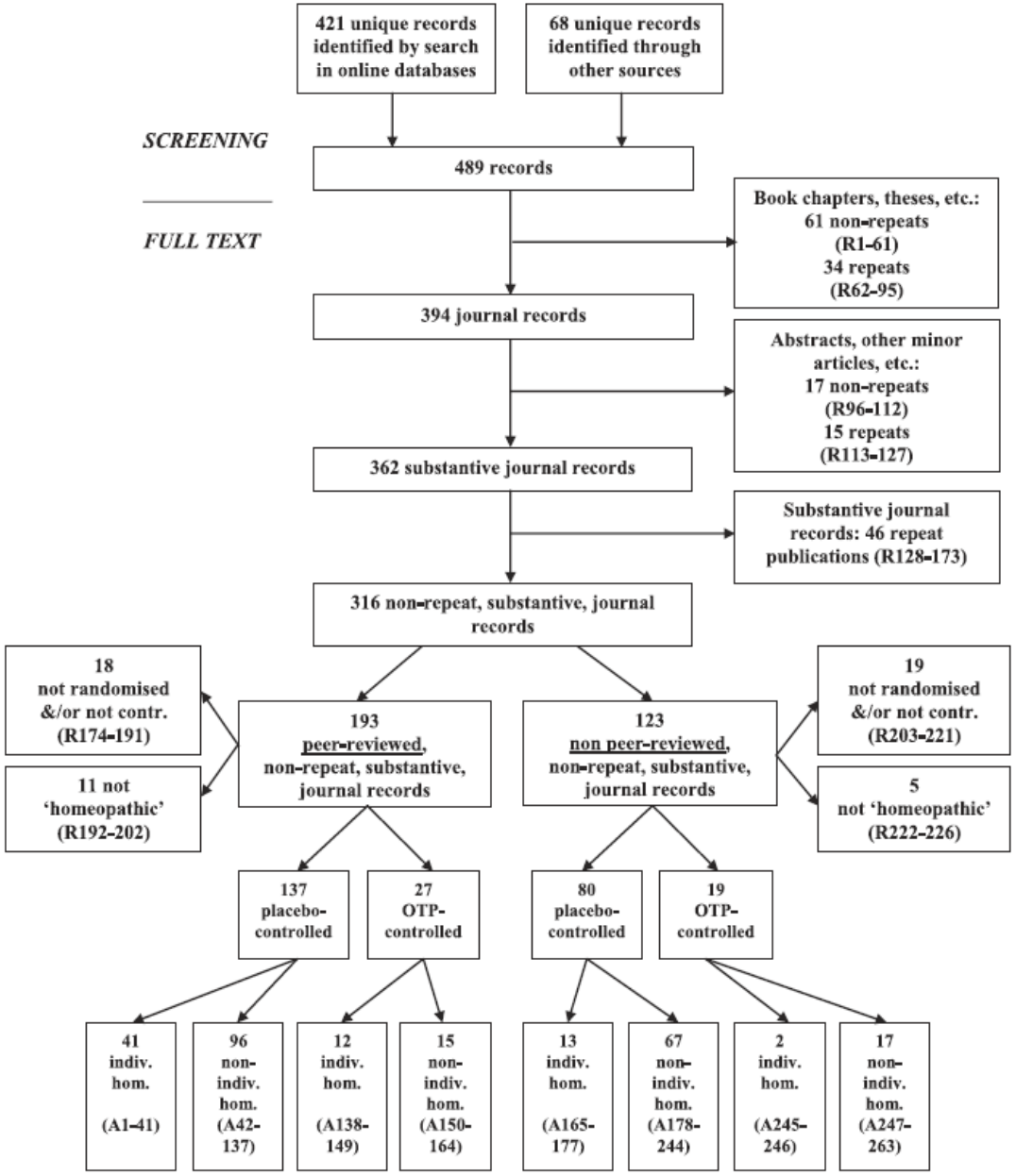


Figure 1 ***PRISMA*** **flowchart: inclusion and exclusion of records reporting RCTs in homeopathy.**
Key to abbreviations: Indiv. = individualised; OTP = other-than-placebo.

Phase 1:
Systematic review/meta-analysis, 2014

Hypothesis:

"For the spectrum of medical conditions that have been researched using relevant RCTs, the main clinical outcome of individually prescribed homeopathic medicines is distinguishable from that of corresponding placebos"

i.e. "Individually prescribed homeopathic medicines have specific effects"

Mathie et al. Systematic Reviews 2014, 3:142
http://www.systematicreviewsjournal.com/content/3/1/142

SYSTEMATIC REVIEWS

RESEARCH Open Access

Randomised placebo-controlled trials of individualised homeopathic treatment: systematic review and meta-analysis

Robert T Mathie[1*], Suzanne M Lloyd[2], Lynn A Legg[3], Jürgen Clausen[4], Sian Moss[5], Jonathan RT Davidson[6] and Ian Ford[2]

Abstract

Background: A rigorous and focused systematic review and meta-analysis of randomised controlled trials (RCTs) of individualised homeopathic treatment has not previously been undertaken. We tested the hypothesis that the outcome of an individualised homeopathic treatment approach using homeopathic medicines is distinguishable from that of placebos.

Methods: The review's methods, including literature search strategy, data extraction, assessment of risk of bias and statistical analysis, were strictly protocol-based. Judgment in seven assessment domains enabled a trial's risk of bias to be designated as low, undear or high. A trial was judged to comprise 'reliable evidence' if its risk of bias was low or was unclear in one specified domain. 'Effect size' was reported as odds ratio (OR), with arithmetic transformation for continuous data carried out as required; OR > 1 signified an effect favouring homeopathy.

Results: Thirty-two eligible RCTs studied 24 different medical conditions in total. Twelve trials were dassed 'uncertain risk of bias', three of which displayed relatively minor uncertainty and were designated reliable evidence; 20 trials were classed 'high risk of bias'. Twenty-two trials had extractable data and were subjected to meta-analysis; OR = 1.53 (95% confidence interval (CI) 1.22 to 1.91). For the three trials with reliable evidence, sensitivity analysis revealed OR = 1.98 (95% CI 1.16 to 3.38).

Conclusions: Medicines prescribed in individualised homeopathy may have small, specific treatment effects. Findings are consistent with sub-group data available in a previous 'global' systematic review. The low or unclear overall quality of the evidence prompts caution in interpreting the findings. New high-quality RCT research is necessary to enable more decisive interpretation.

Keywords: Individualised homeopathy, Meta-analysis, Randomised controlled trials, Systematic review

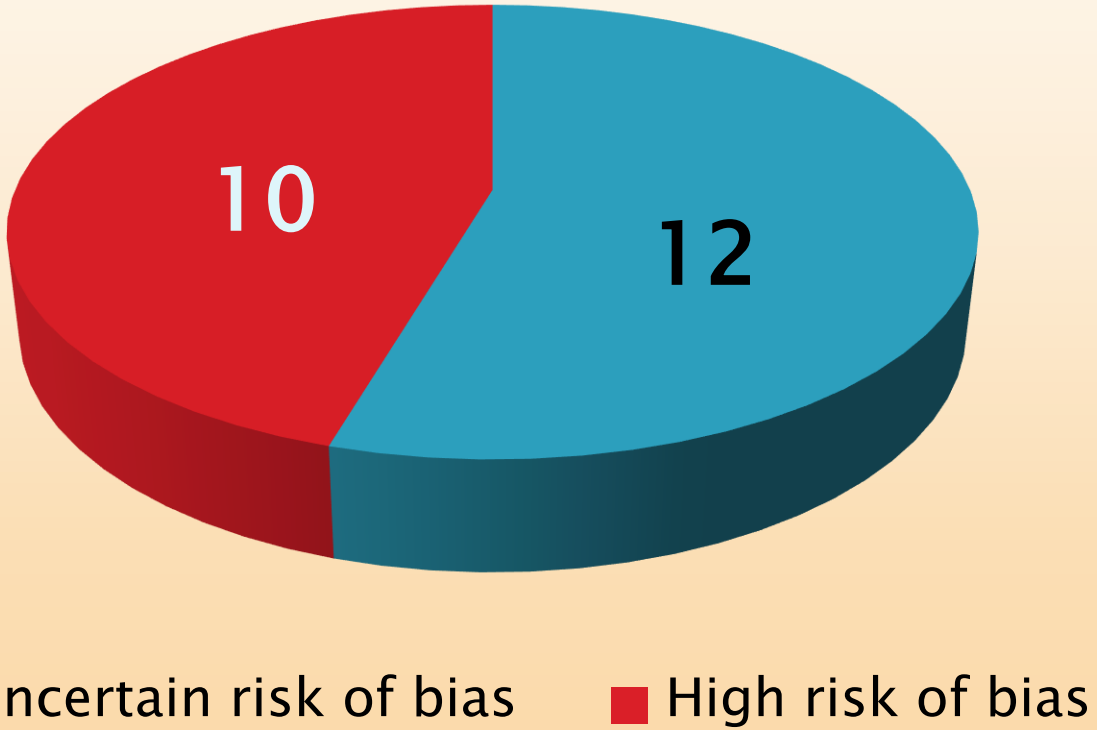
Studies included in systematic review

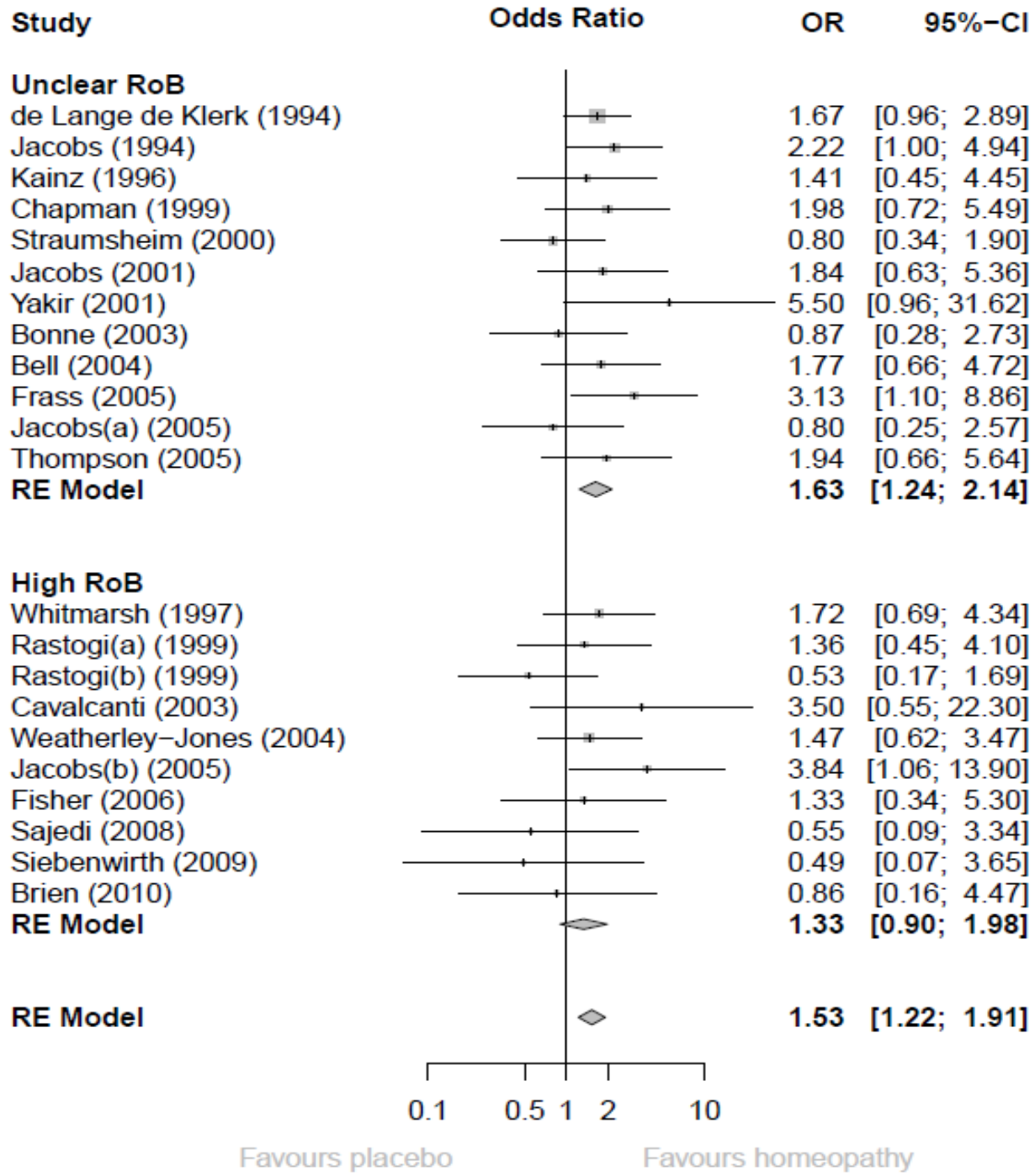
- **Eligible RCTs: 32**
  - Medical conditions: **24**
  - Main outcome measures: **28**
  - Measured endpoints: **12 hours** to **12 months**
- **RCTs with outcome data extractable for meta-analysis: 22**

Study quality of RCTs:
Internal Validity (Risk of Bias [RoB])

- **Seven domains of assessment (Cochrane)**:
  - **I. Sequence generation** (randomisation)
  - **II. Allocation concealment**
  - **IIIa. Blinding of participants and trial personnel**
  - **IIIb. Blinding of outcome assessors**
  - **IV. Incomplete outcome data** (drop-outs, missing data)
  - **V. Selective reporting of outcome measures**
  - **VI. Other sources of bias** (e.g. imbalanced baseline data)

N=22 RCTs suitable for meta-analysis: Risk of Bias

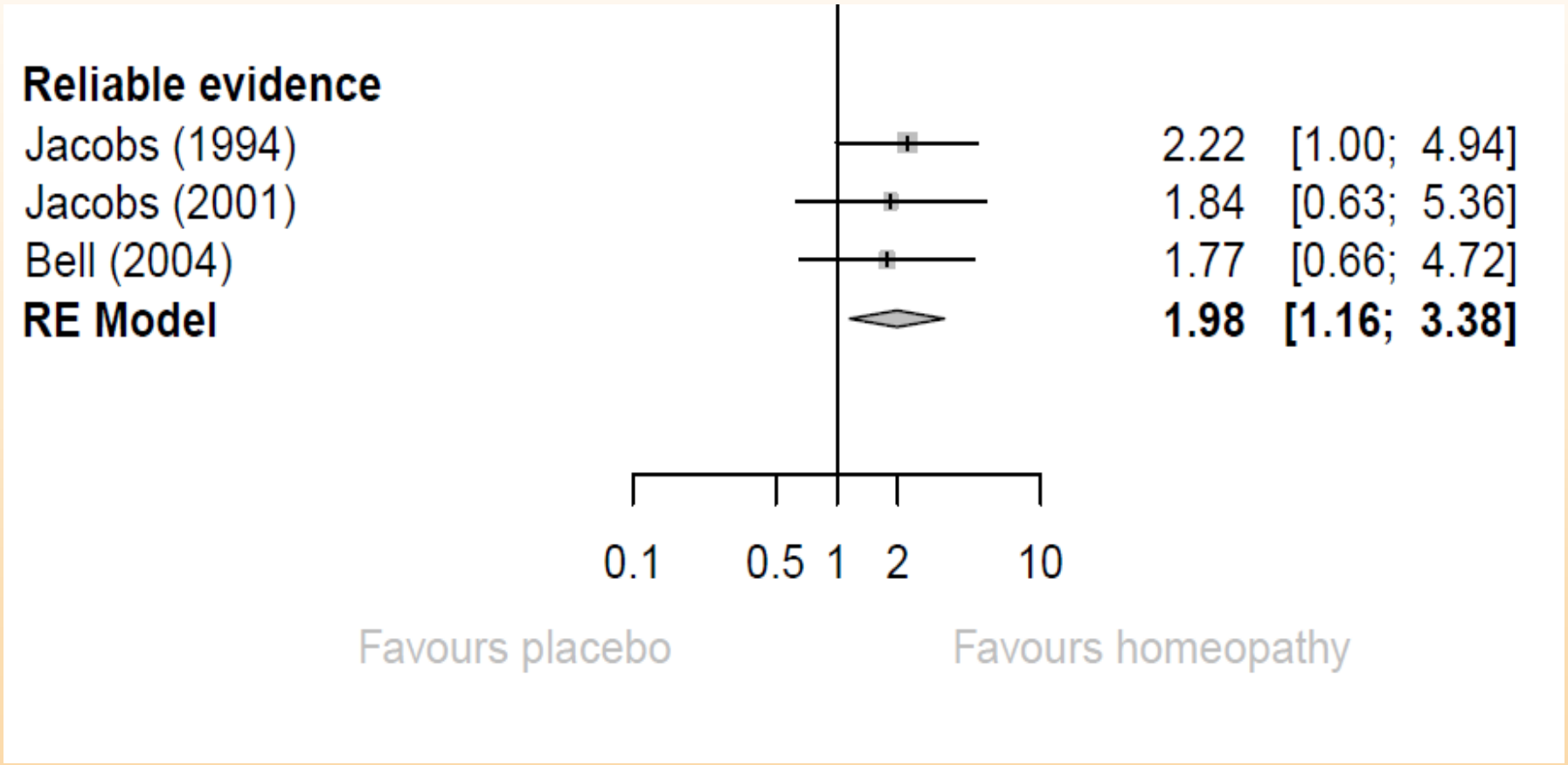



Study
Odds Ratio
OR
95%−CI
Unclear RoB
de Lange de Klerk (1994) 1.67 [0.96; 2.89]
Jacobs (1994) 2.22 [1.00; 4.94]
Kainz (1996) 1.41 [0.45; 4.45]
Chapman (1999) 1.98 [0.72; 5.49]
Straumsheim (2000) 0.80 [0.34; 1.90]
Jacobs (2001) 1.84 [0.63; 5.36]
Yakir (2001) 5.50 [0.96; 31.62]
Bonne (2003) 0.87 [0.28; 2.73]
Bell (2004) 1.77 [0.66; 4.72]
Frass (2005) 3.13 [1.10; 8.86]
Jacobs(a) (2005) 0.80 [0.25; 2.57]
Thompson (2005) 1.94 [0.66; 5.64]
RE Model 1.63 [1.24; 2.14]
High RoB
Whitmarsh (1997) 1.72 [0.69; 4.34]
Rastogi(a) (1999) 1.36 [0.45; 4.10]
Rastogi(b) (1999) 0.53 [0.17; 1.69]
Cavalcanti (2003) 3.50 [0.55; 22.30]
Weatherley−Jones (2004) 1.47 [0.62; 3.47]
Jacobs(b) (2005) 3.84 [1.06; 13.90]
Fisher (2006) 1.33 [0.34; 5.30]
Sajedi (2008) 0.55 [0.09; 3.34]
Siebenwirth (2009) 0.49 [0.07; 3.65]
Brien (2010) 0.86 [0.16; 4.47]
RE Model 1.33 [0.90; 1.98]
RE Model 1.53 [1.22; 1.91]
0.1
0.5
1
2
10
Favours placebo
Favours homeopathy

'Reliable evidence'

- Free of bias for at least **five domains** of assessment, which **must** include:
  - I: Randomisation
  - II: Allocation concealment
  - III: Blinding
- Uncertain risk of bias for **no (or for just one of the other)** domains of assessment:
  - IV: Outcome data
  - V: Selective reporting
  - VI: Other biases

Sensitivity analysis based on *reliable evidence*



Summary

- *22 RCTs were collectively positive:*
  - Mean odds ratio=**1.53**
- *3 RCTs **with reliable evidence** were **also** collectively positive*
  - Mean odds ratio=**1.98**
- i.e. Statistically positive result (N=22) is robust to sensitivity analysis based on reliable evidence

Conclusions

- Meta-analysis data (**N=22 RCTs**) are consistent with a small clinical effect due specifically to the medicines prescribed in individualised homeopathic treatment
- Overall high/unclear risk of bias in the RCT evidence prevents a decisive conclusion

Study quality of RCTs:
Model Validity (MV)

- *"MV is the extent to which a homeopathic intervention and the main measure of its outcome, as implemented in an RCT, reflect best clinical practice in homeopathy"*
- **Six domains of assessment (Mathie et al. 2012):**
  - **I. Rationale for homeopathic intervention**
  - **II. Principles of homeopathy**
  - **III. Practitioner input**
  - **IV. Outcome measure**
  - **V. Outcome sensitivity**
  - **VI. Follow-up duration**

'Acceptable model validity'

- Free of concern for four specific domains of MV assessment:
  - I: Rationale for homeopathic intervention
  - II: Principles of homeopathy
  - IV: Outcome measure
  - V: Outcome sensitivity
- Unclear concern for **no (or for just one of the other)** domains of MV assessment:
  - III: Practitioner input
  - VI: Follow-up duration

Homeopathy (2015) ■, 1–6
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http://dx.doi.org/10.1016/j.homp.2015.02.004, available online at http://www.sciencedirect.com

ORIGINAL PAPER

Model validity of randomised placebo-controlled trials of individualised homeopathic treatment

Robert T Mathie[1,*], Michel Van Wassenhoven[2], Jennifer Jacobs[3], Menachem Oberbaum[4], Helmut Roniger[5], Joyce Frye[6], Raj K Manchanda[7], Laurence Terzan[8], Gilles Chaufferin[8], Flávio Dantas[9] and Peter Fisher[5]

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Background: **Though potentially an important limitation in the literature of randomised controlled trials (RCTs) of homeopathy, the model validity of homeopathic treatment (MVHT) has not previously been systematically investigated.**

Objective: **As an integral part of a programme of systematic reviews, to assess MVHT of eligible RCTs of individualised homeopathic treatment.**

Methods: **From 46 previously identified papers in the category, 31 papers (reporting a total of 32 RCTs) were eligible for systematic review and were thus the subject of the**

Assessments per MV domain, and overall MV classification per trial

		MV domain of assessment						
No.	**First author** [ref]	***I***	***II***	***III***	***IV***	***V***	***VI***	**Classification**
A05	**Bell 2004**	Y	Y	Y	Y	Y	Y	**Acceptable MV**
A07	**Brien 2011**	Y	Y	Y	Y	Y	Y	
A20	**Jacobs 2001**	Y	Y	Y	Y	Y	Y	
A19	**Jacobs 1994**	Y	Y	Y	Y	Y	Y	
A21	**Jacobs 2000**	Y	Y	Y	Y	Y	Y	
A22	**Jacobs 2005b**	Y	Y	Y	Y	Y	Y	
A23	**Jacobs 2005a**	Y	Y	Y	Y	Y	Y	
A33	**Siebenwirth 2009**	Y	Y	Y	Y	Y	Y	
A36	**Thompson 2005**	Y	Y	Y	Y	Y	Y	
A38	**Weatherley-Jones 2004**	Y	Y	Y	Y	Y	Y	
A09	**Cavalcanti 2003**	Y	Y	U	Y	Y	Y	
A10	**Chapman 1999**	Y	Y	U	Y	Y	Y	
A13	**Fisher 2006**	Y	Y	Y	Y	Y	U	
A14	**Frass 2005**	Y	Y	U	Y	Y	Y	
A18	**Jacobs 1993**	Y	Y	U	Y	Y	Y	
A24	**Jansen 1992**	Y	Y	U	Y	Y	Y	
A31	**Rastogi (a) 1999**	Y	Y	U	Y	Y	Y	
A31	**Rastogi (b) 1999**	Y	Y	U	Y	Y	Y	
A41	**Yakir 2001**	Y	Y	U	Y	Y	Y	

Assessments per MV domain, and overall MV classification per trial

		MV domain of assessment						
No.	First author [ref]	*I*	*II*	*III*	*IV*	*V*	*VI*	Classification
A05	Bell 2004	Y	Y	Y	Y	Y	Y	Acceptable MV
A07	Brien 2011	Y	Y	Y	Y	Y	Y	
A20	Jacobs 2001	Y	Y	Y	Y	Y	Y	
A19	Jacobs 1994	Y	Y	Y	Y	Y	Y	
A21	Jacobs 2000	Y	Y	Y	Y	Y	Y	
A22	Jacobs 2005b	Y	Y	Y	Y	Y	Y	
A23	Jacobs 2005a	Y	Y	Y	Y	Y	Y	
A33	Siebenwirth 2009	Y	Y	Y	Y	Y	Y	
A36	Thompson 2005	Y	Y	Y	Y	Y	Y	
A38	Weatherley-Jones 2004	Y	Y	Y	Y	Y	Y	
A09	Cavalcanti 2003	Y	Y	U	Y	Y	Y	
A10	Chapman 1999	Y	Y	U	Y	Y	Y	
A13	Fisher 2006	Y	Y	Y	Y	Y	U	
A14	Frass 2005	Y	Y	U	Y	Y	Y	
A18	Jacobs 1993	Y	Y	U	Y	Y	Y	
A24	Jansen 1992	Y	Y	U	Y	Y	Y	
A31	Rastogi (a) 1999	Y	Y	U	Y	Y	Y	
A31	Rastogi (b) 1999	Y	Y	U	Y	Y	Y	
A41	Yakir 2001	Y	Y	U	Y	Y	Y	
A06	Bonne 2003	Y	U	Y	Y	Y	Y	Uncertain MV
A26	Katz 2005	Y	Y	Y	Y	U	Y	
A30	Naudé 2010	Y	Y	Y	Y	U	Y	
A35	Straumsheim 2000	Y	Y	Y	Y	U	Y	
A11	de Lange de Klerk 1994	Y	Y	Y	U	U	Y	
A37	Walach 1997	Y	Y	U	Y	Y	U	
A32	Sajedi 2008	U	Y	U	Y	U	Y	
A40	Whitmarsh 1997	Y	Y	Y	U	U	U	
A16	Gaucher 1994	U	Y	U	U	U	Y	
A01	Andrade 1991	Y	Y	Y	Y	N	Y	Inadequate MV
A39	White 2003	Y	Y	Y	U	N	Y	
A25	Kainz 1996	U	Y	U	U	N	U	
A34	Steinsbekk 2005	N	N	N	Y	U	U	

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Model validity and risk of bias in randomised placebo-controlled trials of individualised homeopathic treatment

Robert T. Mathie[a,*], Michel Van Wassenhoven[b], Jennifer Jacobs[c], Menachem Oberbaum[d], Joyce Frye[e], Raj K. Manchanda[f], Helmut Roniger[g], Flávio Dantas[h], Lynn A. Legg[i], Jürgen Clausen[j], Sian Moss[k], Jonathan R.T. Davidson[l], Suzanne M. Lloyd[m], Ian Ford[m], Peter Fisher[g]

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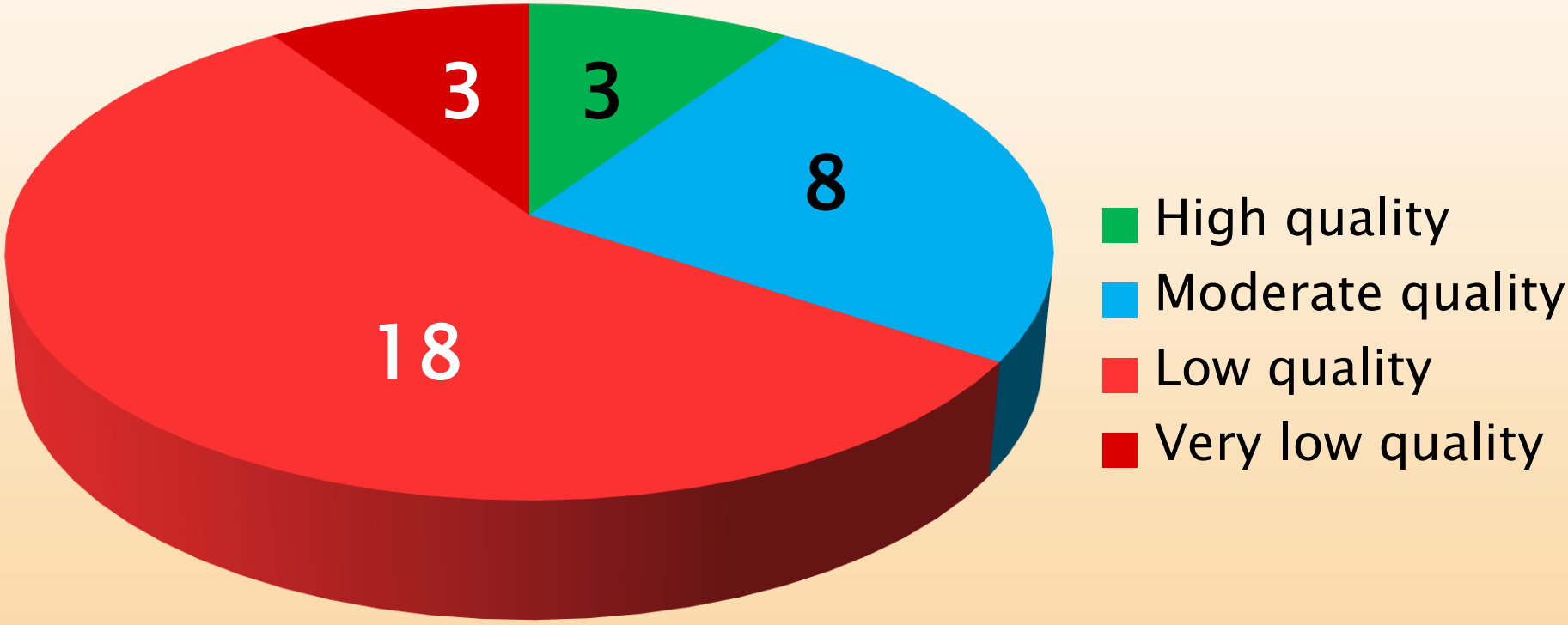
Method for merging RoB and MV into single overall designation of quality

Attribute of quality		Descriptive criteria	Overall designation
Risk of Bias	Model Validity		
Low risk (reliable evidence)	Acceptable	Neither attribute has important flaws	High quality
Uncertain risk	Acceptable	One attribute is 'uncertain'; the other attribute is 'uncertain' or better	Moderate quality
Uncertain risk	Uncertain		
Uncertain risk	Inadequate	One attribute has important flaws	Low quality
High risk	Acceptable		
High risk	Uncertain		
High risk	Inadequate	Both attributes have important flaws	Very low quality

N=32 RCTs:
Overall quality designation per RCT



Sensitivity analysis by overall quality designation

Ref.	First author	Year	Overall designation	Pooled OR [95% CI] for N trials		
A5	Bell	2004	High quality	1.53 [1.22, 1.91] (N = 22)	1.64 [1.24, 2.17] (N = 11)	1.98 [1.16, 3.38] (N = 3)
A19	Jacobs	1994	High quality			
A20	Jacobs	2001	High quality			
A10	Chapman	1999	Moderate quality			
A14	Frass	2005	Moderate quality			
A23	Jacobs	2005a	Moderate quality			
A36	Thompson	2005	Moderate quality			
A41	Yakir	2001	Moderate quality			
A6	Bonne	2003	Moderate quality			
A11	de Lange de Klerk	1994	Moderate quality			
A35	Straumsheim	2000	Moderate quality			
A7	Brien	2011	Low quality			
A9	Cavalcanti	2003	Low quality			
A13	Fisher	2006	Low quality			
A22	Jacobs	2005b	Low quality			
A31	Rastogi (a)	1999	Low quality			
A31	Rastogi (b)	1999	Low quality			
A33	Siebenwirth	2009	Low quality			
A38	Weatherley-Jones	2004	Low quality			
A32	Sajedi	2008	Low quality			
A40	Whitmarsh	1997	Low quality			
A25	Kainz	1996	Low quality			

Summary (including model validity)

- *22 RCTs were collectively positive:*
  - Mean odds ratio=**1.53**
- *3 RCTs **with high-quality evidence** were **also** collectively positive*
  - Mean odds ratio=**1.98**
- i.e. Statistically positive result (N=22) remains robust to sensitivity analysis based on high-quality evidence

Conclusions (including model validity)

- Meta-analysis data (**N=22 RCTs**) are consistent with a small clinical effect due specifically to the medicines prescribed in individualised homeopathic treatment
- Overall low/moderate quality of the RCT evidence prevents a decisive conclusion

Wider inferences

- **Our cautious positive conclusion (for individualised medicines) transcends condition-based interpretation**
- Contrast with:
  - *'Not clearly efficacious for any single clinical condition..'*
    - Linde 1997
  - *'No health conditions for which reliable evidence..'*
    - Australian NHMRC 2015

Phase 2:
Systematic review/meta-analysis, 2017

Hypothesis:

"Across the entire range of clinical conditions that have been researched [by RCTs], the main outcome of treatment using a non-individualised homeopathic medicine can be distinguished from that using a placebo"

> ***i.e. "A pre-selected homeopathic medicine, taken by every subject in a given trial, has a measurable effect on the typical symptoms of a given clinical condition"***

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Systematic Reviews

RESEARCH Open Access

Randomised, double-blind, placebo-controlled trials of non-individualised homeopathic treatment: systematic review and meta-analysis

Robert T. Mathie[1*], Nitish Ramparsad[2], Lynn A. Legg[3], Jürgen Clausen[4], Sian Moss[1], Jonathan R. T. Davidson[5], Claudia-Martina Messow[2] and Alex McConnachie[2]

Abstract

Background: A rigorous systematic review and meta-analysis focused on randomised controlled trials (RCTs) of non-individualised homeopathic treatment has not previously been reported. We tested the null hypothesis that the main outcome of treatment using a non-individualised (standardised) homeopathic medicine is indistinguishable from that of placebo. An additional aim was to quantify any condition-specific effects of non-individualised homeopathic treatment.

Methods: Literature search strategy, data extraction and statistical analysis all followed the methods described in a pre-published protocol. A trial comprised 'reliable evidence' if its risk of bias was low or it was unclear in one specified domain of assessment. 'Effect size' was reported as standardised mean difference (SMD), with arithmetic transformation for dichotomous data carried out as required; a negative SMD indicated an effect favouring homeopathy.

Results: Forty-eight different clinical conditions were represented in 75 eligible RCTs. Forty-nine trials were classed as 'high risk of bias' and 23 as 'uncertain risk of bias'; the remaining three, clinically heterogeneous, trials displayed sufficiently low risk of bias to be designated reliable evidence. Fifty-four trials had extractable data: pooled SMD was −0.33 (95% confidence interval (CI) −0.44, −0.21), which was attenuated to −0.16 (95% CI −0.31, −0.02) after adjustment for publication bias. The three trials with reliable evidence yielded a non-significant pooled SMD: −0.18 (95% CI −0.46, 0.09). There was no single clinical condition for which meta-analysis included reliable evidence.

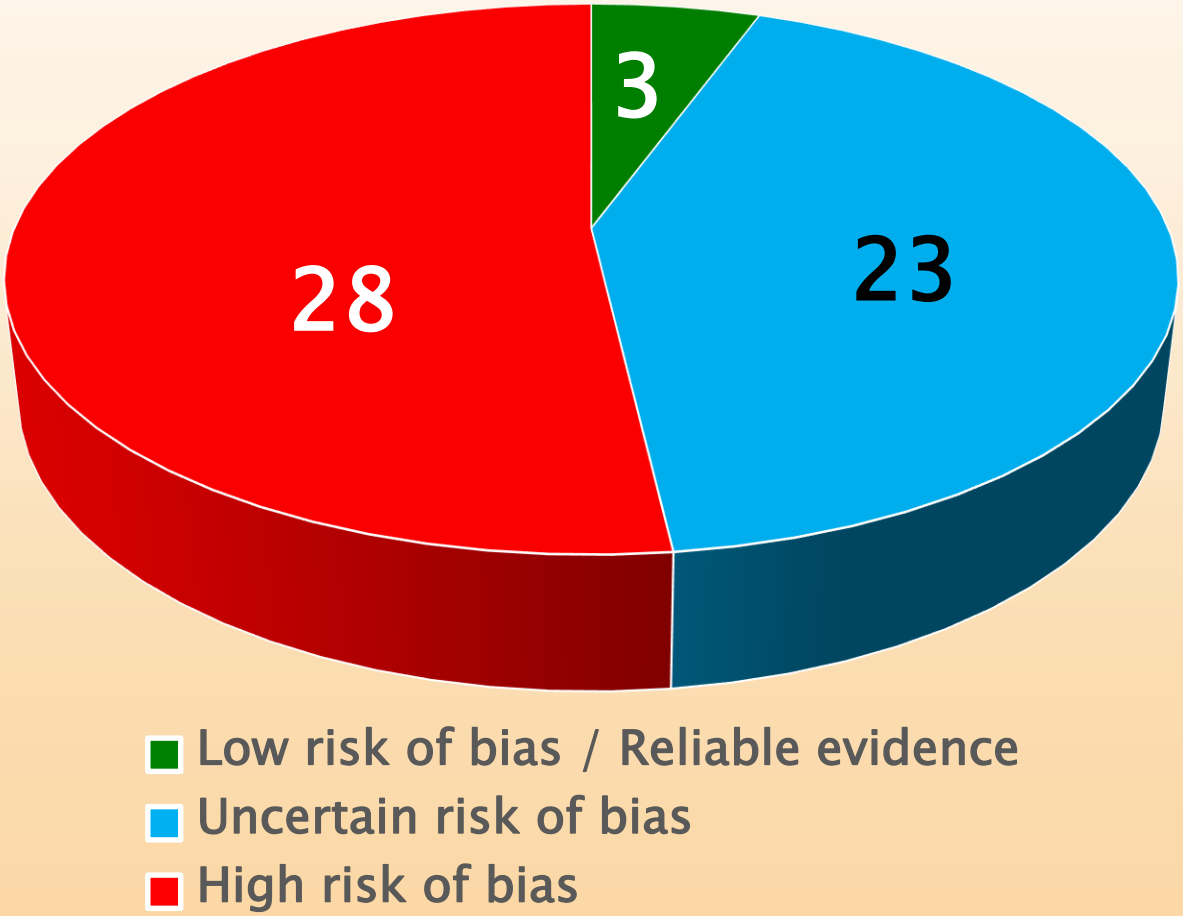
Conclusions: The quality of the body of evidence is low. A meta-analysis of all extractable data leads to rejection of our null hypothesis, but analysis of a small sub-group of reliable evidence does not support that rejection. Reliable evidence is lacking in condition-specific meta-analyses, precluding relevant conclusions. Better designed and more rigorous RCTs are needed in order to develop an evidence base that can decisively provide reliable effect estimates of non-individualised homeopathic treatment.

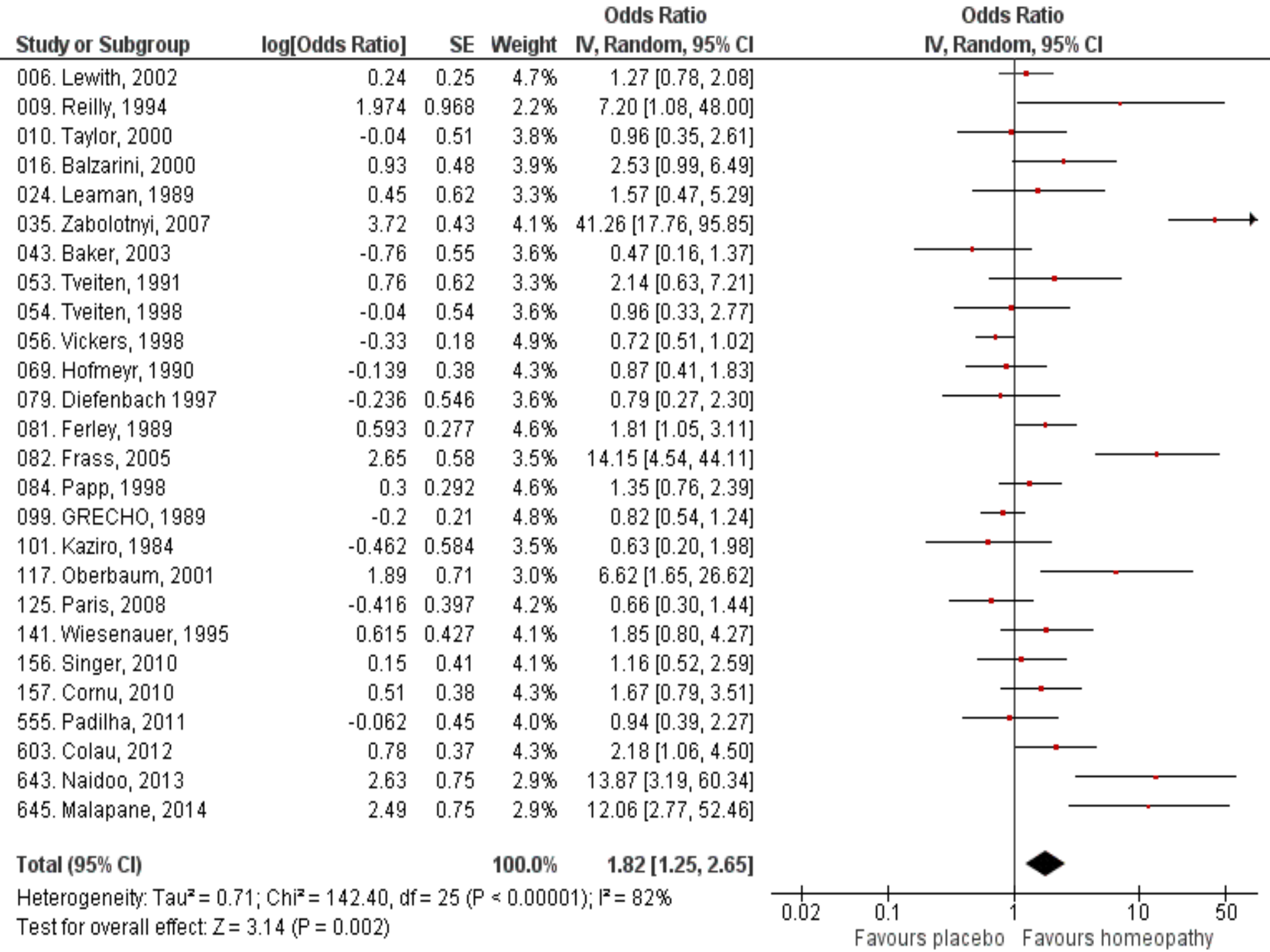
Keywords: Non-individualised homeopathy, Meta-analysis, Randomised controlled trials, Sensitivity analysis, Systematic review

Studies included in systematic review

- **Eligible RCTs: 75**
  - Clinical conditions: **48**
  - Main outcome measures: **45**
  - Measured endpoints: **6 hours** to **6 months**
- **RCTs with outcome data extractable for meta-analysis: 54**

N=54 RCTs suitable for meta-analysis: Risk of bias

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643. Naidoo, 2013 2.63 0.75 2.9% 13.87 [3.19, 60.34]
645. Malapane, 2014 2.49 0.75 2.9% 12.06 [2.77, 52.46]
Total (95% CI) 100.0% 1.82 [1.25, 2.65]
Heterogeneity: Tau² = 0.71; Chi² = 142.40, df = 25 (P < 0.00001); I² = 82%
Test for overall effect: Z = 3.14 (P = 0.002)
0.02
0.1
1
10
50
Favours placebo
Favours homeopathy

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
006. Lewith, 2002	0.24	0.25	0.0%	1.27 [0.78, 2.08]
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117. Oberbaum, 2001	1.89	0.71	0.0%	6.62 [1.65, 26.62]
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156. Singer, 2010	0.15	0.41	32.9%	1.16 [0.52, 2.59]
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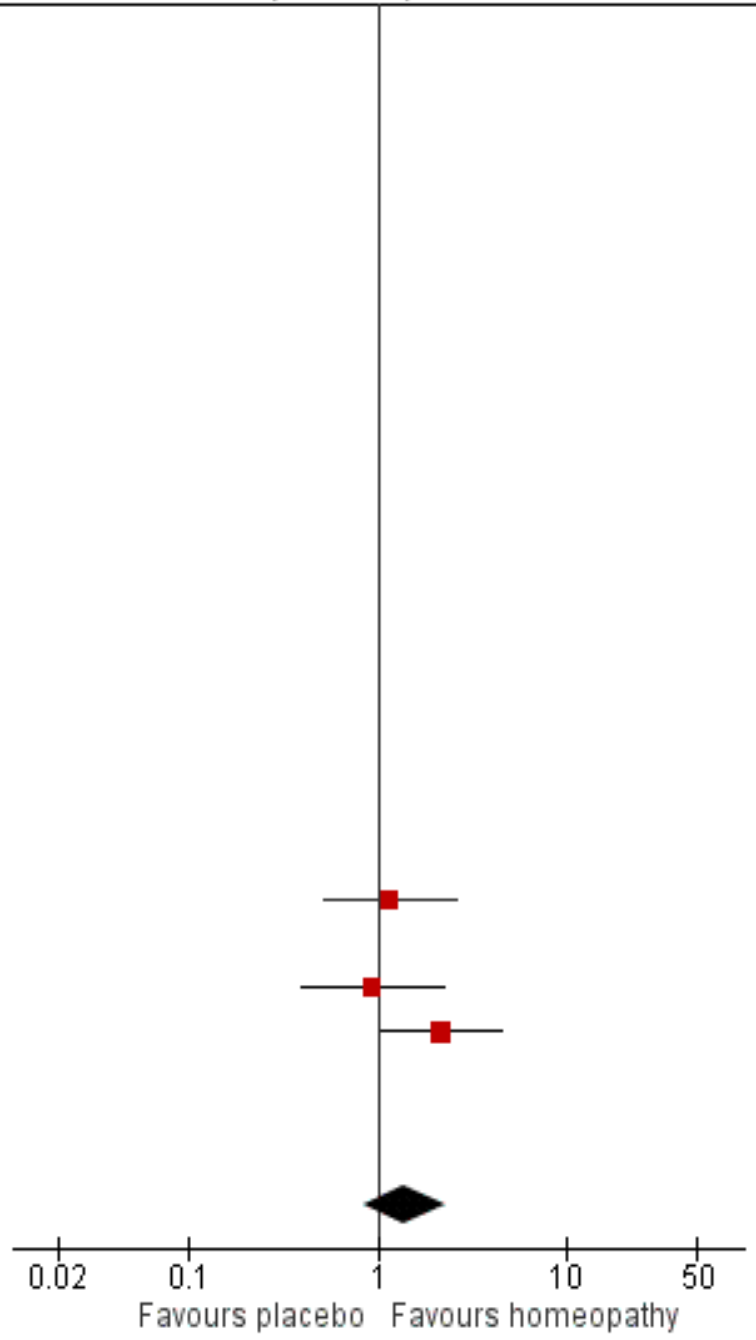
603. Colau, 2012	0.78	0.37	38.9%	2.18 [1.06, 4.50]
643. Naidoo, 2013	2.63	0.75	0.0%	13.87 [3.19, 60.34]
645. Malapane, 2014	2.49	0.75	0.0%	12.06 [2.77, 52.46]
Total (95% CI)			**100.0%**	**1.40 [0.84, 2.32]**

Heterogeneity: Tau² = 0.04; Chi² = 2.43, df = 2 (P = 0.30); I² = 18%

Test for overall effect: Z = 1.29 (P = 0.20)



Sensitivity analysis by risk of bias (reliability of evidence)

Ref.	First author	Year	Risk of bias (Reliability of evidence)	Pooled OR [95% CI] for N trials	
A272	Colau	2012	Reliable	1.82 [1.25 to 2.65] N=26 *P*=0.002	1.40 [0.84 to 2.32 N=3 *P* = 0.20
A103	Padilha	2011	Reliable		
A120	Singer	2010	Reliable		
A067	Frass	2005	Uncertain		
A093	Lewith	2002	Uncertain		
A112	Reilly	1994	Uncertain		
A123	Taylor	2000	Uncertain		
A126	Tveiten	1998	Uncertain		
A292	Malapane	2014	Uncertain		
A048	Balzarini	2000	Uncertain		
A135	Wiesenauer	1995	Uncertain		
A062	Diefenbach	1997	Uncertain		
A083	Kaziro	1984	Uncertain		
A125	Tveiten	1991	Uncertain		
A128	Vickers	1998	Uncertain		
A290	Naidoo	2013	Uncertain		
A075	GRECHO	1989	Uncertain		
A104	Papp	1998	Uncertain		
A137	Zabolotnyi	2007	Uncertain		
A064	Ferley	1989	Uncertain		
A079	Hofmeyr	1990	Uncertain		
A100	Oberbaum	2001	Uncertain		
A061	Cornu	2010	Uncertain		
A105	Paris	2008	Uncertain		
A092	Leaman	1989	Uncertain		
A047	Baker	2003	Uncertain		

Summary

- *26 RCTs were collectively positive:*
  - Mean odds ratio=**1.82** (*P*=0.002)
- *3 RCTs **with reliable evidence** were **not** collectively positive*
  - Mean odds ratio=**1.40** (*P*=0.20)
- i.e. Statistically positive result (N=26) is ***not robust to sensitivity analysis*** based on reliable evidence

Conclusions

- It is **not clear** whether meta-analysis data (**N=26 RCTs**) are consistent with pre-selected homeopathic medicines having a measurable effect in given clinical conditions
- Overall **unclear risk of bias** in the RCT evidence prevents a **decisive** conclusion

Research collaborators (MV):

Stephan Baumgartner, Jürgen Clausen,
Flávio Dantas, Jonathan Davidson, José Eizayaga,
Peter Fisher, Joyce Frye, Miek Jong,
Christien Klein-Laansma, Lynn Legg,
Alex McConnachie, Martina Messow, Ton Nicolai,
Nitish Ramparsad, Lex Rutten, Raj Manchanda,
Sian Moss, Menachem Oberbaum, Anna Pla i Castellsagué,
Helmut Roniger, Robbert van Haselen,
Michel van Wassenhoven

Consensus assessments per domain, with overall MVHT rating and classification per trial

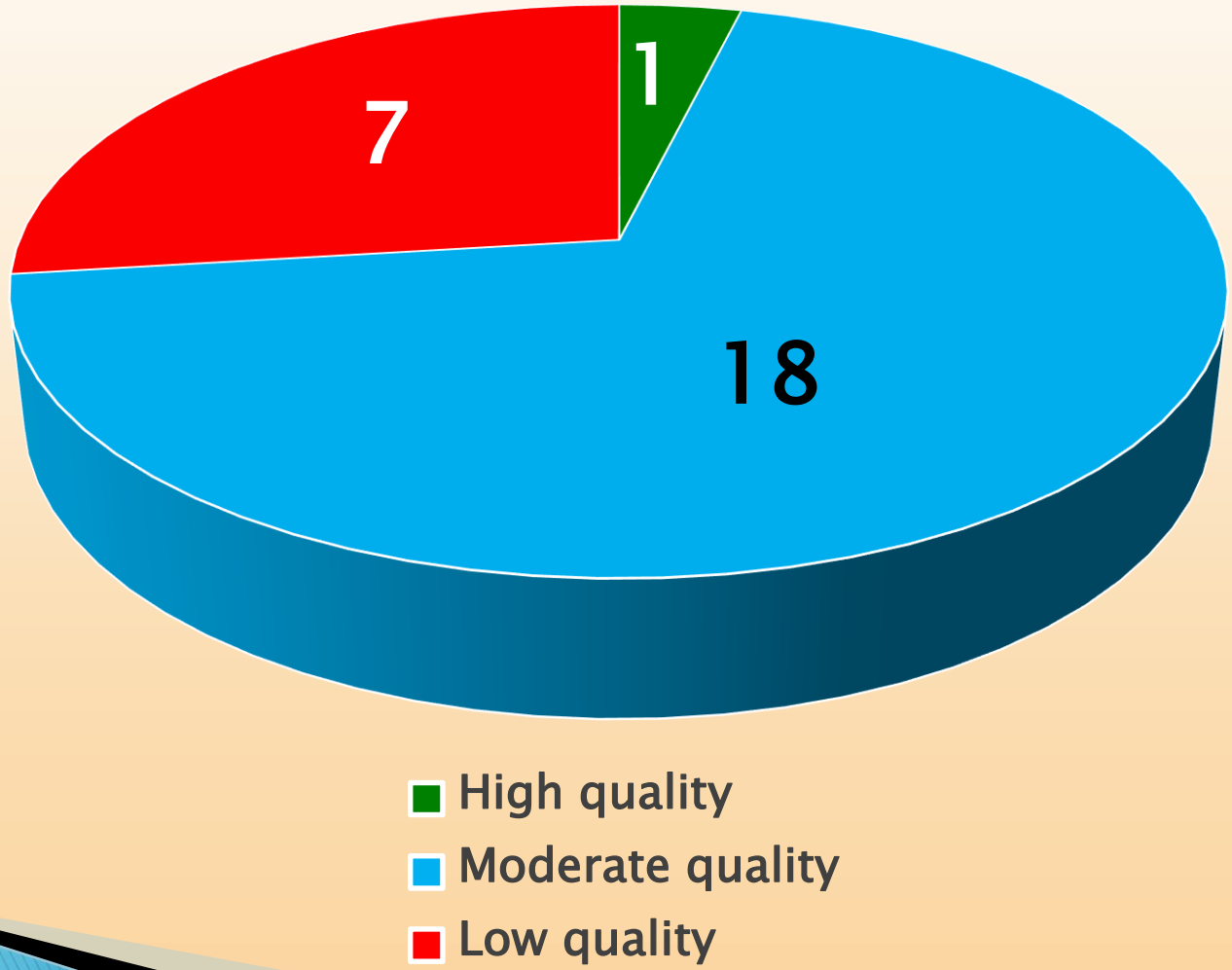
		Domain of assessment							
No.	First author	*I*	*II*	*III*	*IV*	*V*	*VI*	MVHT rating	Classification
A272	Colau	Y	Y	Y	Y	Y	Y	A	Acceptable MVHT
A067	Frass	Y	Y	Y	Y	Y	Y	A	
A093	Lewith	Y	Y	Y	Y	Y	Y	A	
A112	Reilly	Y	Y	Y	Y	Y	Y	A	
A123	Taylor	Y	Y	Y	Y	Y	Y	A	
A126	Tveiten	Y	Y	Y	Y	Y	Y	A	
A292	Malapane	Y	Y	Y	Y	Y	Y	A	
A048	Balzarini	Y	Y	U	Y	Y	Y	B1*	
A135	Wiesenauer	Y	Y	U	Y	Y	Y	B1*	
A062	Diefenbach	Y	Y	Y	Y	U	Y	B1	Uncertain MVHT
A083	Kaziro	U	Y	Y	Y	Y	Y	B1	
A125	Tveiten	Y	Y	Y	Y	U	Y	B1	
A128	Vickers	Y	Y	Y	Y	U	Y	B1	
A290	Naidoo	U	Y	Y	Y	Y	Y	B1	
A075	GRECHO	U	Y	U	Y	Y	Y	B2	
A104	Papp	U	U	Y	Y	Y	Y	B2	
A137	Zabolotnyi	U	U	Y	Y	Y	Y	B2	
A064	Ferley	U	U	U	Y	Y	Y	B3	
A079	Hofmeyr	Y	Y	U	Y	U	U	B3	
A100	Oberbaum	Y	N	Y	Y	Y	Y	C1.0	Inadequate MVHT
A120	Singer	Y	N	U	Y	Y	Y	C1.1	
A061	Cornu	U	N	Y	Y	U	Y	C1.2	
A105	Paris	Y	Y	Y	U	N	U	C1.2	
A103	Padilha	U	U	U	Y	U	N	C1.4	
A092	Leaman	U	N	U	N	Y	Y	C2.2	
A047	Baker	U	U	N	U	U	N	C2.4	
	No. of 'Y' per domain	16	17	17	23	18	22		
	No. of 'U' per domain	10	5	8	2	7	2		
	No. of 'N' per domain	0	4	1	1	1	2		

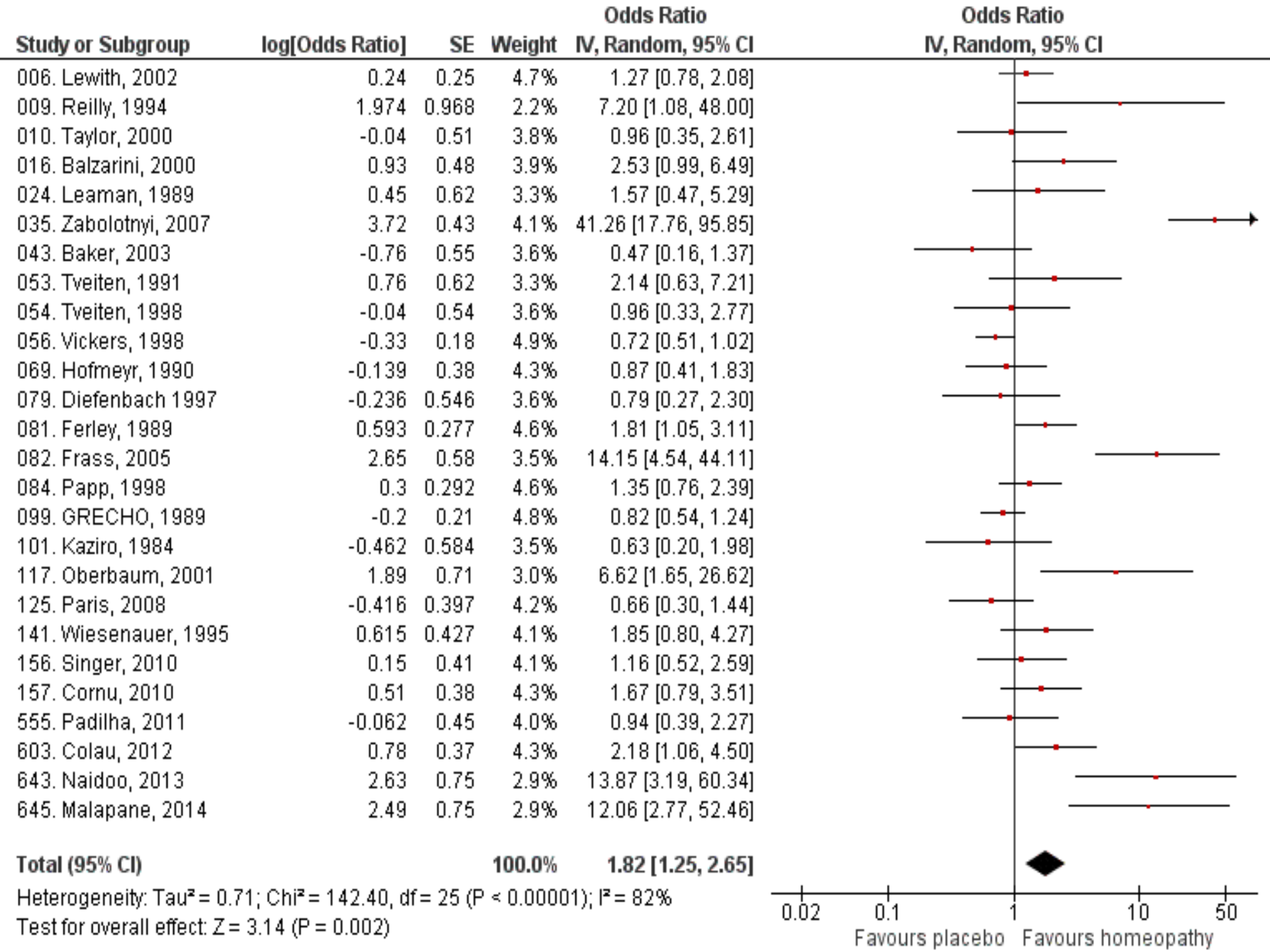
Table 4: Ordering of 26 trials by overall quality designation

Ref.	First author	MVHT	Risk of bias [9]	Downgrading	Overall designation
A272	**Colau**	Acceptable	Low risk **	0	High quality
A067	**Frass**	Acceptable	Uncertain risk	–1	Moderate quality
A093	**Lewith**	Acceptable	Uncertain risk	–1	Moderate quality
A112	**Reilly**	Acceptable	Uncertain risk	–1	Moderate quality
A123	**Taylor**	Acceptable	Uncertain risk	–1	Moderate quality
A126	**Tveiten**	Acceptable	Uncertain risk	–1	Moderate quality
A292	**Malapane**	Acceptable	Uncertain risk	–1	Moderate quality
A048	**Balzarini**	Acceptable	Uncertain risk	–1	Moderate quality
A135	**Wiesenauer**	Acceptable	Uncertain risk	–1	Moderate quality
A062	**Diefenbach**	Uncertain	Uncertain risk	–1	Moderate quality
A083	**Kaziro**	Uncertain	Uncertain risk	–1	Moderate quality
A125	**Tveiten**	Uncertain	Uncertain risk	–1	Moderate quality
A128	**Vickers**	Uncertain	Uncertain risk	–1	Moderate quality
A290	**Naidoo**	Uncertain	Uncertain risk	–1	Moderate quality
A075	**GRECHO**	Uncertain	Uncertain risk	–1	Moderate quality
A104	**Papp**	Uncertain	Uncertain risk	–1	Moderate quality
A137	**Zabolotnyi**	Uncertain	Uncertain risk	–1	Moderate quality
A064	**Ferley**	Uncertain	Uncertain risk	–1	Moderate quality
A079	**Hofmeyr**	Uncertain	Uncertain risk	–1	Moderate quality
A103	**Padilha**	Inadequate	Low risk **	–2	Low quality
A120	**Singer**	Inadequate	Uncertain risk **	–2	Low quality
A100	**Oberbaum**	Inadequate	Uncertain risk	–2	Low quality
A061	**Cornu**	Inadequate	Uncertain risk	–2	Low quality
A105	**Paris**	Inadequate	Uncertain risk	–2	Low quality
A092	**Leaman**	Inadequate	Uncertain risk	–2	Low quality
A047	**Baker**	Inadequate	Uncertain risk	–2	Low quality

** *Reliable evidence* (regarding risk of bias)

N=26 RCTs:
Overall quality designation per RCT

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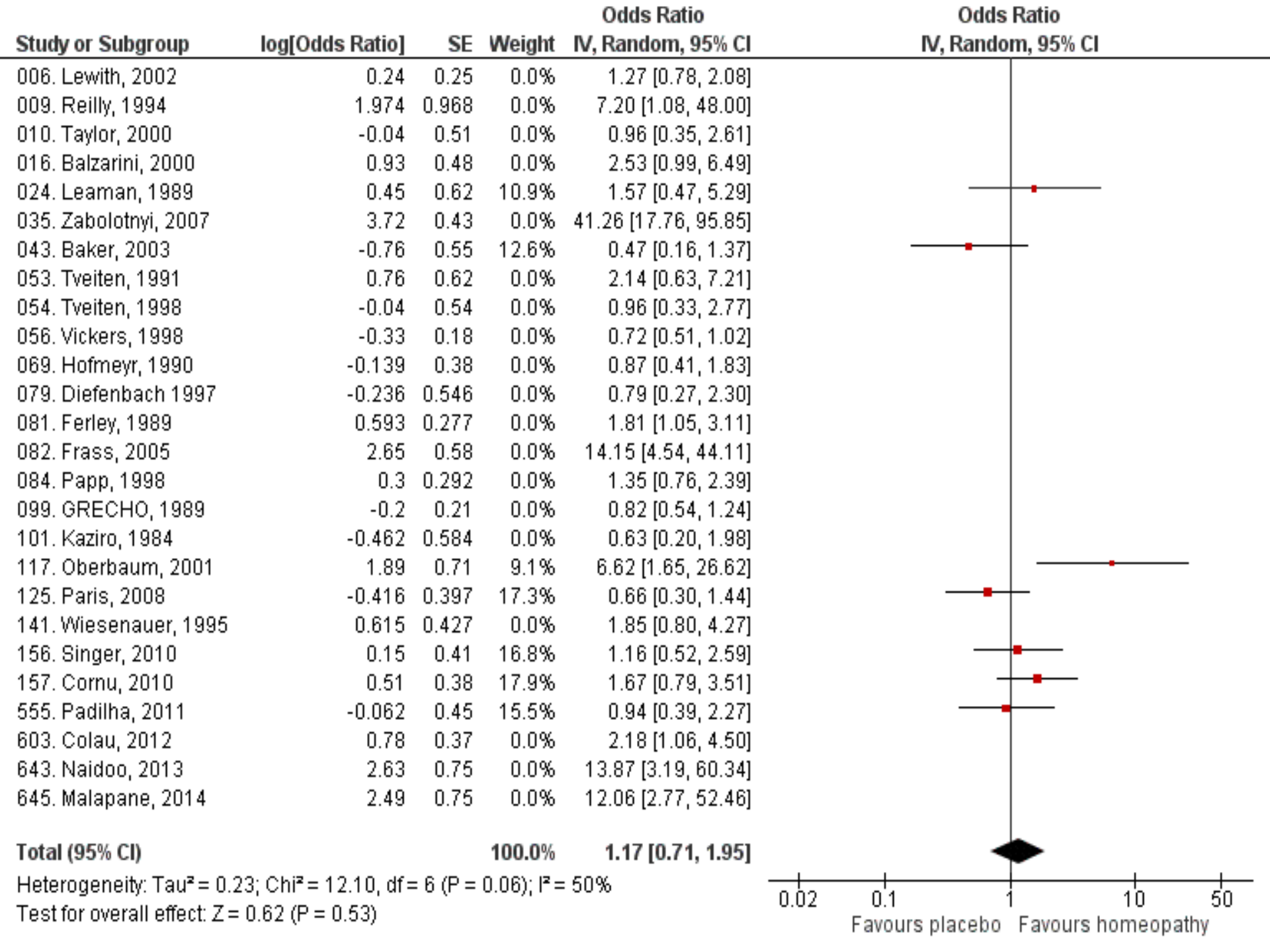
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603. Colau, 2012 0.78 0.37 0.0% 2.18 [1.06, 4.50]
643. Naidoo, 2013 2.63 0.75 0.0% 13.87 [3.19, 60.34]
645. Malapane, 2014 2.49 0.75 0.0% 12.06 [2.77, 52.46]
Total (95% CI) 100.0% 1.17 [0.71, 1.95]
Heterogeneity: Tau² = 0.23; Chi² = 12.10, df = 6 (P = 0.06); I² = 50%
Test for overall effect: Z = 0.62 (P = 0.53)
0.02
0.1
1
10
50
Favours placebo
Favours homeopathy

Study or Subgroup	log[Odds Ratio]	SE	Weight	Odds Ratio IV, Random, 95% CI
006. Lewith, 2002	0.24	0.25	6.3%	1.27 [0.78, 2.08]
009. Reilly, 1994	1.974	0.968	3.2%	7.20 [1.08, 48.00]
010. Taylor, 2000	-0.04	0.51	5.1%	0.96 [0.35, 2.61]
016. Balzarini, 2000	0.93	0.48	5.3%	2.53 [0.99, 6.49]
024. Leaman, 1989	0.45	0.62	0.0%	1.57 [0.47, 5.29]
035. Zabolotnyi, 2007	3.72	0.43	5.5%	41.26 [17.76, 95.85]
043. Baker, 2003	-0.76	0.55	0.0%	0.47 [0.16, 1.37]
053. Tveiten, 1991	0.76	0.62	4.6%	2.14 [0.63, 7.21]
054. Tveiten, 1998	-0.04	0.54	5.0%	0.96 [0.33, 2.77]
056. Vickers, 1998	-0.33	0.18	6.5%	0.72 [0.51, 1.02]
069. Hofmeyr, 1990	-0.139	0.38	5.8%	0.87 [0.41, 1.83]
079. Diefenbach 1997	-0.236	0.546	5.0%	0.79 [0.27, 2.30]
081. Ferley, 1989	0.593	0.277	6.2%	1.81 [1.05, 3.11]
082. Frass, 2005	2.65	0.58	4.8%	14.15 [4.54, 44.11]
084. Papp, 1998	0.3	0.292	6.1%	1.35 [0.76, 2.39]
099. GRECHO, 1989	-0.2	0.21	6.4%	0.82 [0.54, 1.24]
101. Kaziro, 1984	-0.462	0.584	4.8%	0.63 [0.20, 1.98]
117. Oberbaum, 2001	1.89	0.71	0.0%	6.62 [1.65, 26.62]
125. Paris, 2008	-0.416	0.397	0.0%	0.66 [0.30, 1.44]
141. Wiesenauer, 1995	0.615	0.427	5.5%	1.85 [0.80, 4.27]
156. Singer, 2010	0.15	0.41	0.0%	1.16 [0.52, 2.59]
157. Cornu, 2010	0.51	0.38	0.0%	1.67 [0.79, 3.51]
555. Padilha, 2011	-0.062	0.45	0.0%	0.94 [0.39, 2.27]
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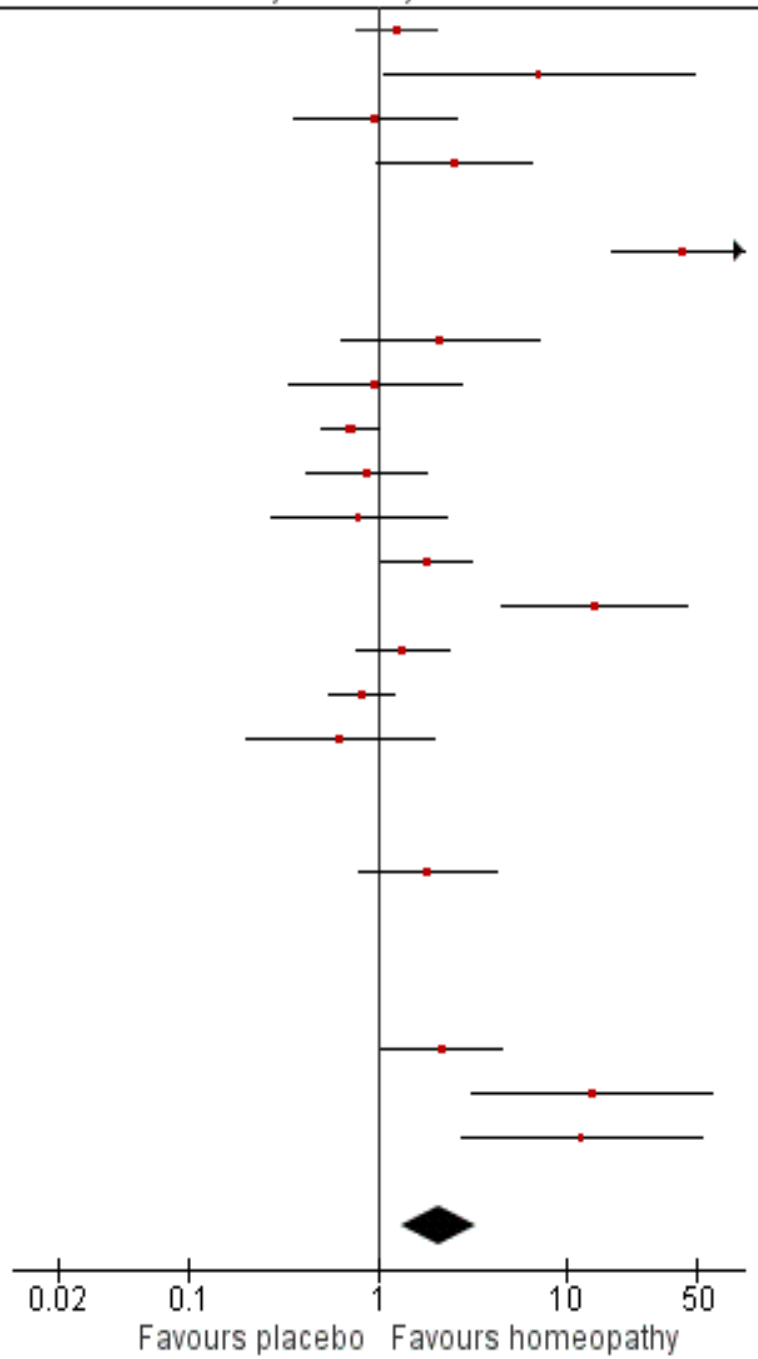
645. Malapane, 2014	2.49	0.75	4.0%	12.06 [2.77, 52.46]
Total (95% CI)			**100.0%**	**2.13 [1.34, 3.40]**

Heterogeneity: $Tau^2 = 0.84$; $Chi^2 = 128.95$, df = 18 ($P < 0.00001$); $I^2 = 86\%$

Test for overall effect: $Z = 3.18$ ($P = 0.001$)



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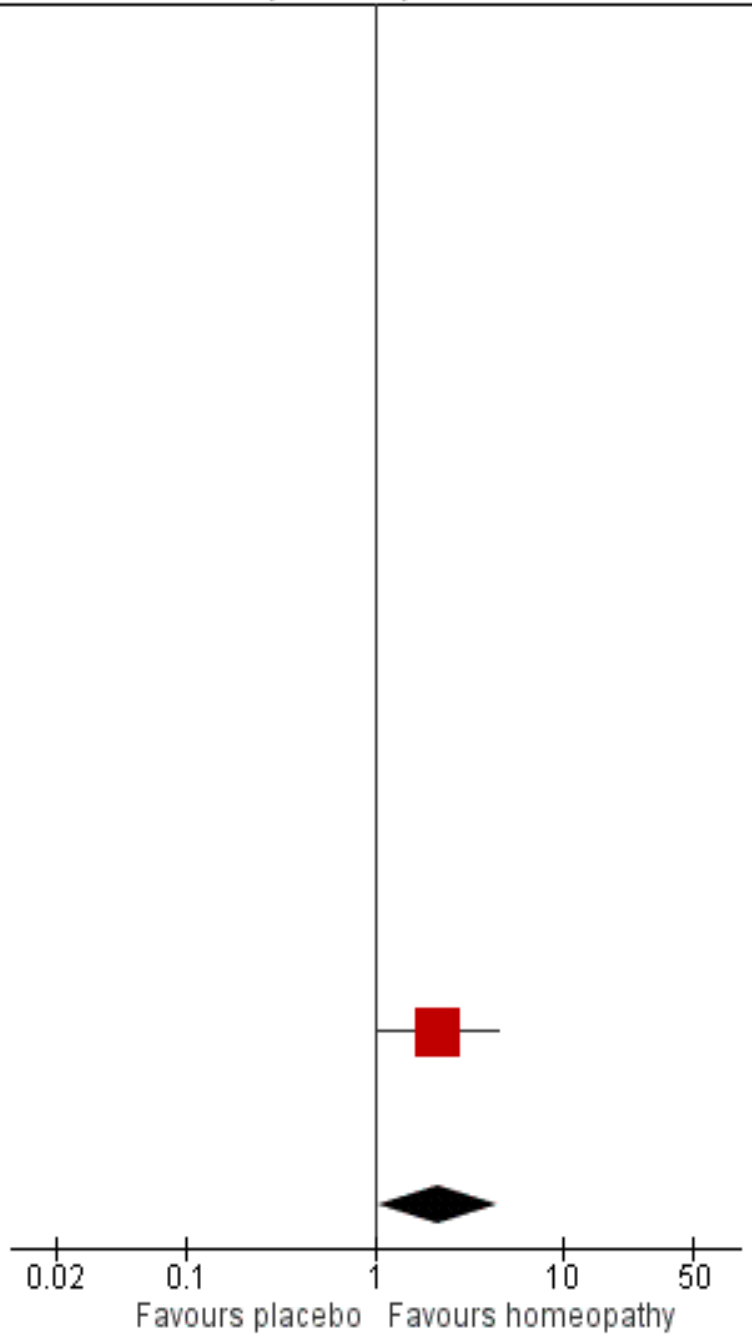
645. Malapane, 2014	2.49	0.75	0.0%	12.06 [2.77, 52.46]
Total (95% CI)			**100.0%**	**2.18 [1.06, 4.50]**

Heterogeneity: Not applicable

Test for overall effect: Z = 2.11 (P = 0.04)



Sensitivity analysis by overall quality designation

Ref.	First author	Year	Overall designation	Pooled OR [95% CI] for N trials		
A272	Colau	2012	High quality	1.82 [1.25 to 2.65] N=26 *P*=0.002	2.13 [1.34 to 3.40] N = 19 *P*=0.001	2.18 [1.06 to 4.50] N = 1 *P*=0.04
A067	Frass	2005	Moderate quality			
A093	Lewith	2002	Moderate quality			
A112	Reilly	1994	Moderate quality			
A123	Taylor	2000	Moderate quality			
A126	Tveiten	1998	Moderate quality			
A292	Malapane	2014	Moderate quality			
A048	Balzarini	2000	Moderate quality			
A135	Wiesenauer	1995	Moderate quality			
A062	Diefenbach	1997	Moderate quality			
A083	Kaziro	1984	Moderate quality			
A125	Tveiten	1991	Moderate quality			
A128	Vickers	1998	Moderate quality			
A290	Naidoo	2013	Moderate quality			
A075	GRECHO	1989	Moderate quality			
A104	Papp	1998	Moderate quality			
A137	Zabolotnyi	2007	Moderate quality			
A064	Ferley	1989	Moderate quality			
A079	Hofmeyr	1990	Moderate quality			
A103	Padilha	2011	Low quality			
A120	Singer	2010	Low quality			
A100	Oberbaum	2001	Low quality			
A061	Cornu	2010	Low quality			
A105	Paris	2008	Low quality			
A092	Leaman	1989	Low quality			
A047	Baker	2003	Low quality			

Summary (including model validity)

- *26 RCTs were collectively positive:*
  - Pooled odds ratio=**1.82**
- *There was only 1 RCT* ***of high quality overall:***
  - Odds ratio=**2.18**
- i.e. Statistically positive result (N=26) ***is robust to sensitivity analysis*** **based on high-quality evidence**
- *Difference from* Syst Rev (2017) *paper is due to two RCTs with inadequate model validity yet reliable internal validity*

Conclusions

- Accommodating MV into an overall RCT quality rating impacts meta-analysis findings in non-individualised homeopathy
- With just 1 high-quality RCT, it is unclear from meta-analysis data if the effect of a pre-selected homeopathic medicine on the typical symptoms of a given clinical condition is distinguishable from the effect of a placebo

Wider inferences

- Higher-quality RCT research on specified homeopathic medicines is required to enable more decisive interpretation about their efficacy for given clinical conditions or typical symptoms
- Future trialists need to minimise these studies' risk of bias in all domains, and to improve clarity of reporting
- Research might focus on non-individualised trial design where screening (not consultation) leads to including only the most positively matched subjects for the 'symptom picture' of the pre-specified homeopathic product
  - Large trials may therefore be needed to accommodate this 'sub-set' approach

Phase 3:
Systematic review and meta-analysis of OTP-controlled RCTs

- *Objectives*
  - For each study, to assess..
    - .. overall risk of bias
  - To evaluate effectiveness of individualised hom.
    - Compared with another treatment intervention
    - Adjunctively with another intervention, compared with the other intervention alone ('[A+B] versus B') ('Add-on')
    - (Compared with no other intervention)

Research collaborators:

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Lynn A Legg
E Rachel Roberts
Elizabeth S Baitson
Jonathan R T Davidson

Numbers per category of RCT

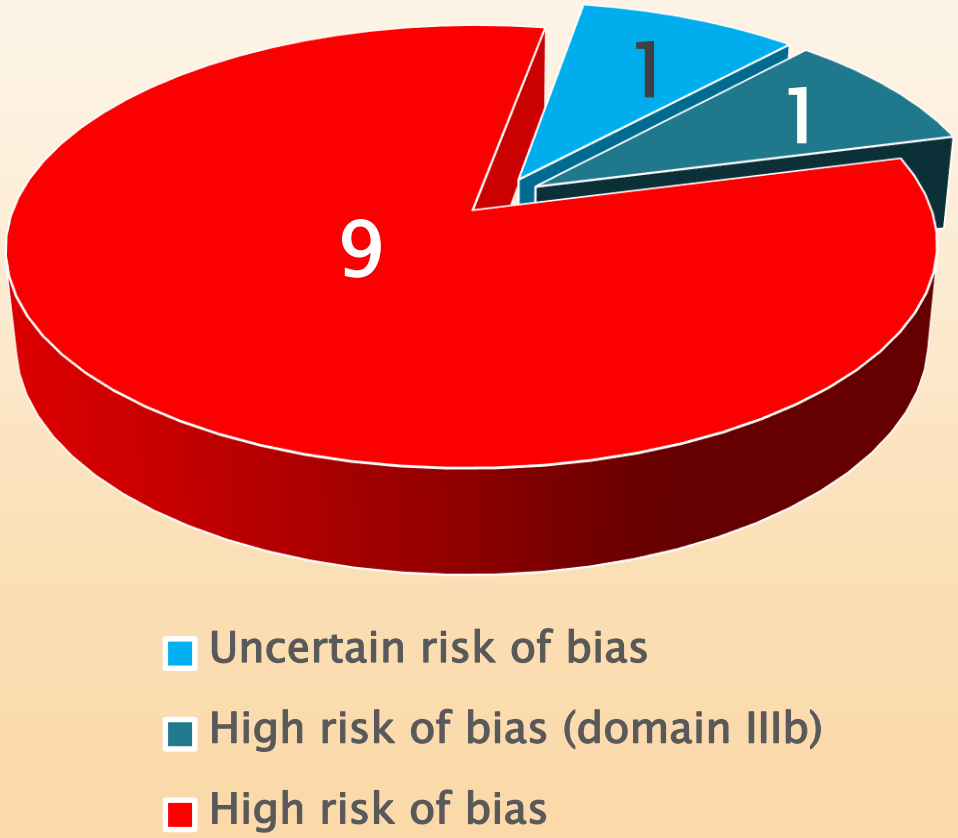
- N=217 peer-reviewed RCTs
  - N=171 placebo-controlled (79%)
  - N=46 OTP-controlled (21%)
    - N=26 non-individualised hom.
    - **N=20 individualised hom.**
      - N=9 ineligible for systematic review
      - N=11 eligible for systematic review
        - N=7 hom. compared with another intervention
        - N=4 *adjunctive hom.* compared with another intervention alone ('[A+B] versus B')

Studies included in systematic review

- **Eligible RCTs: 11**
  - Clinical conditions: **11**
  - Main outcome measures: **11**
  - Trial endpoint: **7 days** to **12 months**

- **RCTs with outcome data extractable for meta-analysis: 8**

N=11 RCTs eligible trials: Risk of bias

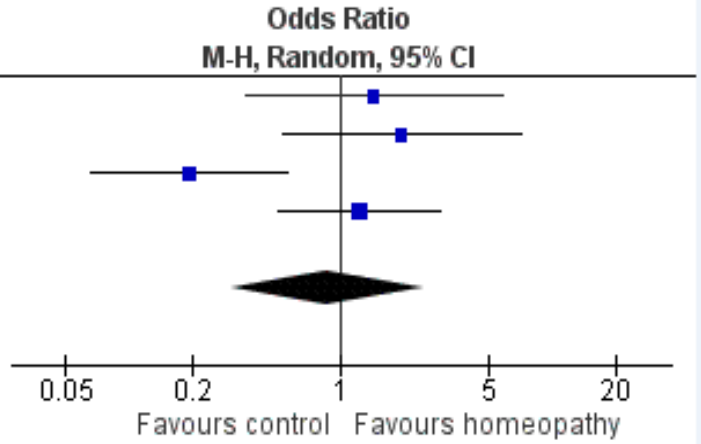


Individualised hom. compared with other intervention

Study or Subgroup	Homeopathy Events	Total	Control Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
A141. Harrison 1999 (1)	11	17	9	16	21.9%	1.43 [0.35, 5.79]
A148. van Erp 1996 (2)	25	30	18	25	23.2%	1.94 [0.53, 7.12]
A149. Witt 2009 (3)	9	23	37	48	26.1%	0.19 [0.07, 0.56]
A283. Sinha 2012 (4)	23	40	21	40	28.7%	1.22 [0.51, 2.96]
Total (95% CI)		**110**		**129**	**100.0%**	**0.87 [0.30, 2.48]**
Total events	68		85			

Heterogeneity: Tau² = 0.80; Chi² = 10.15, df = 3 (P = 0.02); I² = 70%

Test for overall effect: Z = 0.27 (P = 0.79)



Footnotes

(1) High risk of bias; Equally pragmatic and explanatory

(2) High risk of bias; Equally pragmatic and explanatory

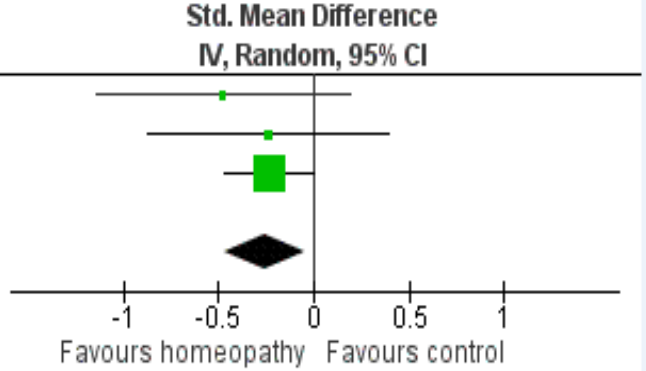
(3) High risk of bias; More explanatory than pragmatic

(4) Uncertain risk of bias; Equally pragmatic and explanatory

Adjunctive individualised hom. compared with other intervention alone ('[A+B] vs. B')

Study or Subgroup	Homeopathy Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
A144. Relton 2009 (1)	58.2	22.3	20	68.5	19.4	16	9.8%	-0.48 [-1.15, 0.19]
A296. Peckham 2014 (2)	210.4	112.4	12	237.3	110.2	51	11.0%	-0.24 [-0.87, 0.39]
A304. Frass 2015 (3)	-10.6	31.65	137	-3	33.48	145	79.3%	-0.23 [-0.47, 0.00]
Total (95% CI)			**169**			**212**	**100.0%**	**-0.26 [-0.47, -0.05]**

Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 2 (P = 0.79); I² = 0%
Test for overall effect: Z = 2.42 (P = 0.02)



Footnotes
(1) High risk of bias; More pragmatic than explanatory
(2) High risk of bias (domain IIIa only); Much more pragmatic than explanatory
(3) High risk of bias; More pragmatic than explanatory

Summary

- Internal validity is typically low
  - 9–10 trials assessed as *high risk of bias*
- Analysis by study design:
  - Individualised hom. vs. other intervention:
    - No significant effect (P=0.79)
  - Adjunctive individualised hom. vs. other intervention alone:
    - Significant effect favouring homeopathy (P=0.02)

Conclusions

- Comparative effectiveness of individualised hom. is uncertain
- *Adjunctive individualised hom.* may be comparatively more effective than another intervention alone
  - **But**:
    - Low intrinsic study quality
    - Only N=3 trials in this category

Currently in progress..

- Continuing programme of systematic reviews and meta-analyses of RCTs
  - Non-individualised homeopathy / OTP-controlled trials
  - Prophylaxis trials
- Considering implications for optimum RCT targets
  - Type of homeopathy
    - Individualised / Non-individualised
  - Study design
    - Placebo-controlled / OTP-controlled
  - Study quality
    - Internal validity / Model validity / External validity

The longer-term future…

- Where do we want homeopathy's research evidence to be in ~25 years' time?
  - Shown clearly to be effective for given *clinical conditions*?
    - Which type(s) of homeopathy?
    - Compared to placebo?
    - Compared to best conventional treatment?
    - As *adjunctive* treatment?
  - Shown clearly to be effective *per se*?
    - Analysis by 'clinical condition' may be secondary in importance to overarching results from **meta-analyses**
      - But highlight 'effectiveness gap' conditions in meta-analyses? (e.g. fibromyalgia, chronic fatigue, irritable bowel syndrome)
  - Shown clearly to be effective in *individual patients?*
    - Series of N-of-1 trials?