FRENCH
COCHRANE CENTRE

Cochrane
Bias Methods Group
(BMG)

Other potential bias

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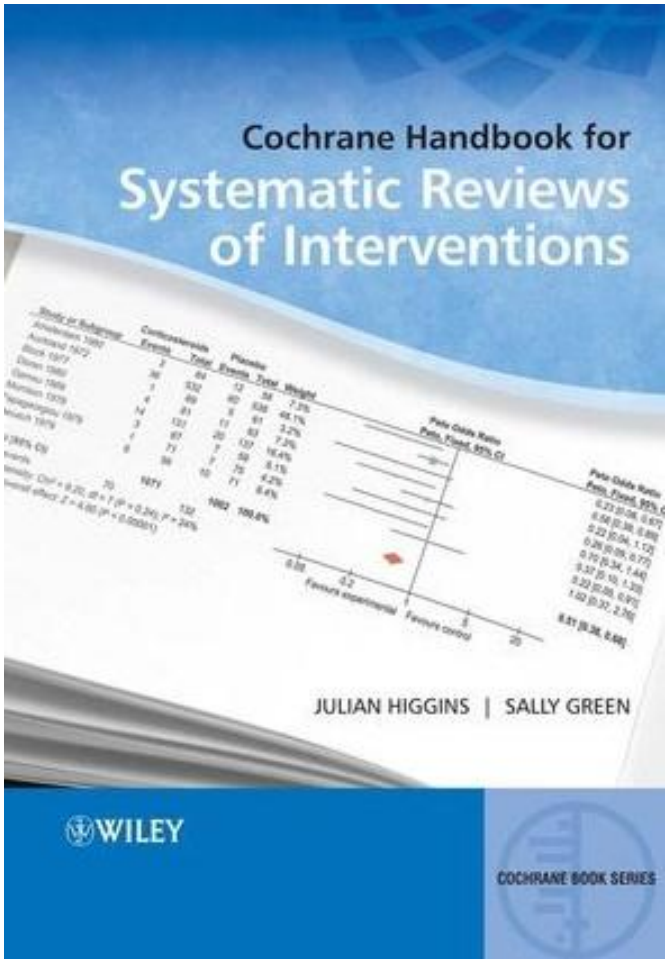
Outlines

- RoB tool for specific design
  - Cross over trial
  - Cluster randomized controlled trials

- Mono vs multicentric trials

The Risk of Bias Tool

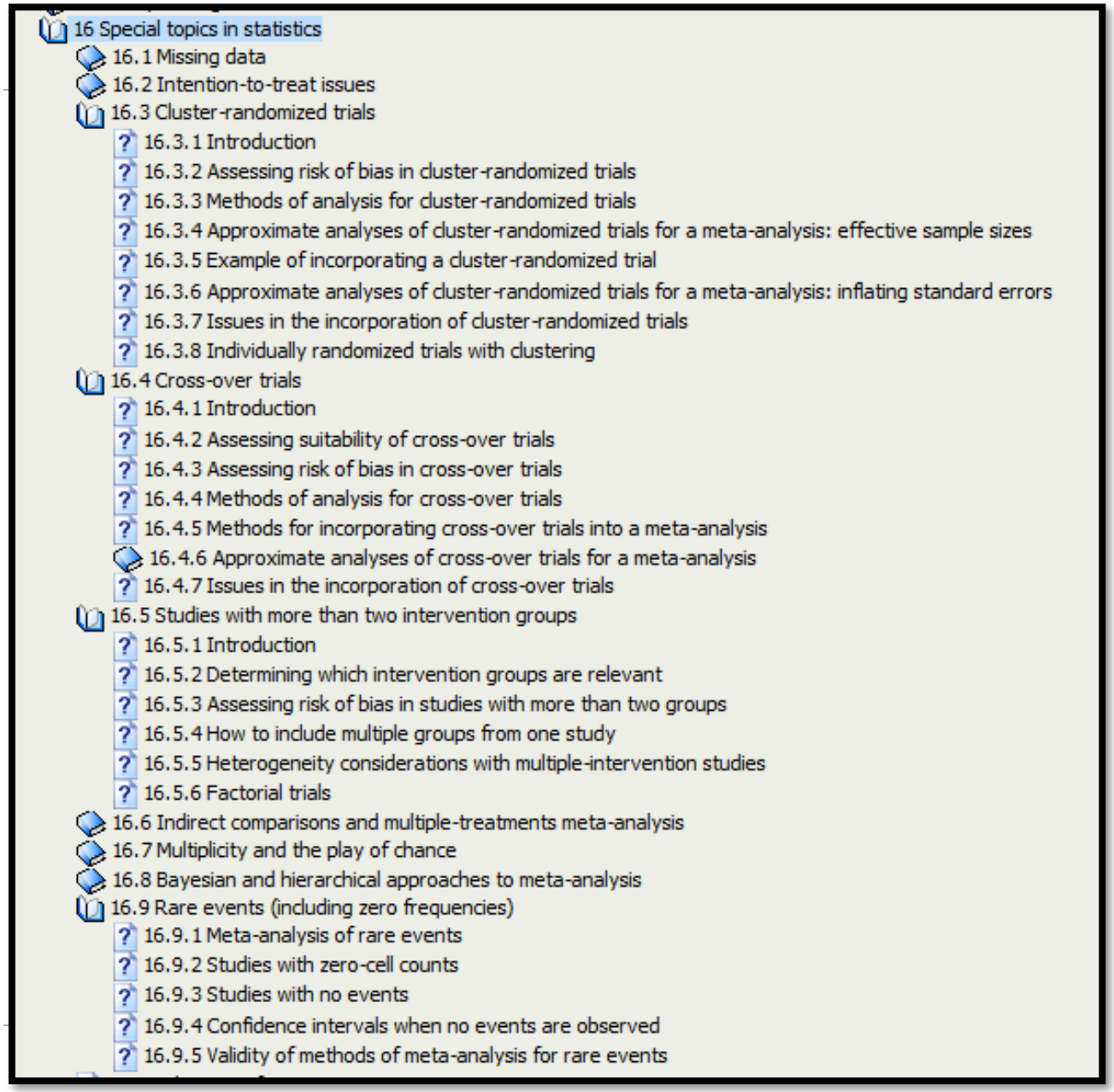


http://www.cochrane-handbook.org/

Other risk of bias

- Baseline imbalance
  - Imbalance in factors that are strongly related to outcome measures
- Blocked randomization in unblinded trials
- Differential diagnostic activity
  - Adverse event of the drug could lead to specific exams and differential diagnostic activities
- **Design-specific risks of bias**

Design-specific risks of bias



Cross over trials

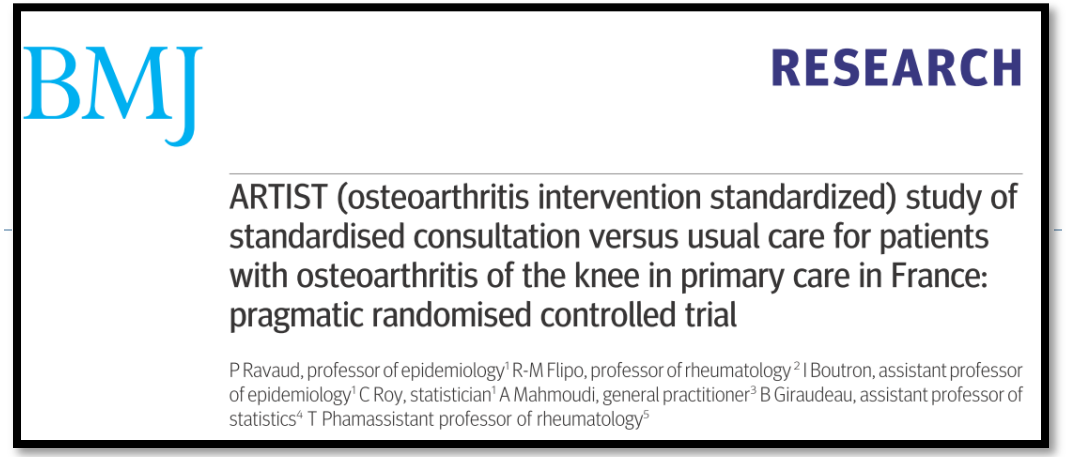
- Was use of a cross-over design appropriate?
  - Stable condition
- Is it clear that the order of receiving treatments was randomized?
- Can it be assumed that the trial was not biased from carry-over effects?
- Are unbiased data available?
  - Only first period data are available: High risk of bias

Cluster RCTs

- Recruitment bias
- Baseline imbalance
- Loss of clusters
- Incorrect analysis

Cluster RCTs

- Recruitment bias
  - Individuals are recruited to the trial after the clusters have been randomized
  - Knowledge of whether each cluster is an 'intervention' or 'control' cluster could affect the types of participants recruited
- Baseline imbalance related to the small number of clusters
- Loss of clusters
- Incorrect analysis
  - account for clustering in their analyses



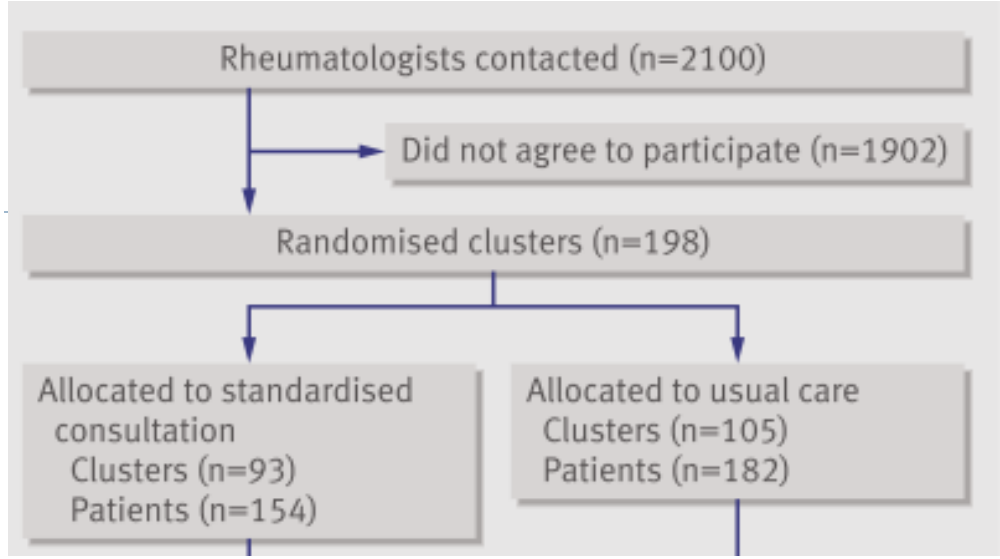
BMJ

RESEARCH

ARTIST (osteoarthritis intervention standardized) study of standardised consultation versus usual care for patients with osteoarthritis of the knee in primary care in France: pragmatic randomised controlled trial

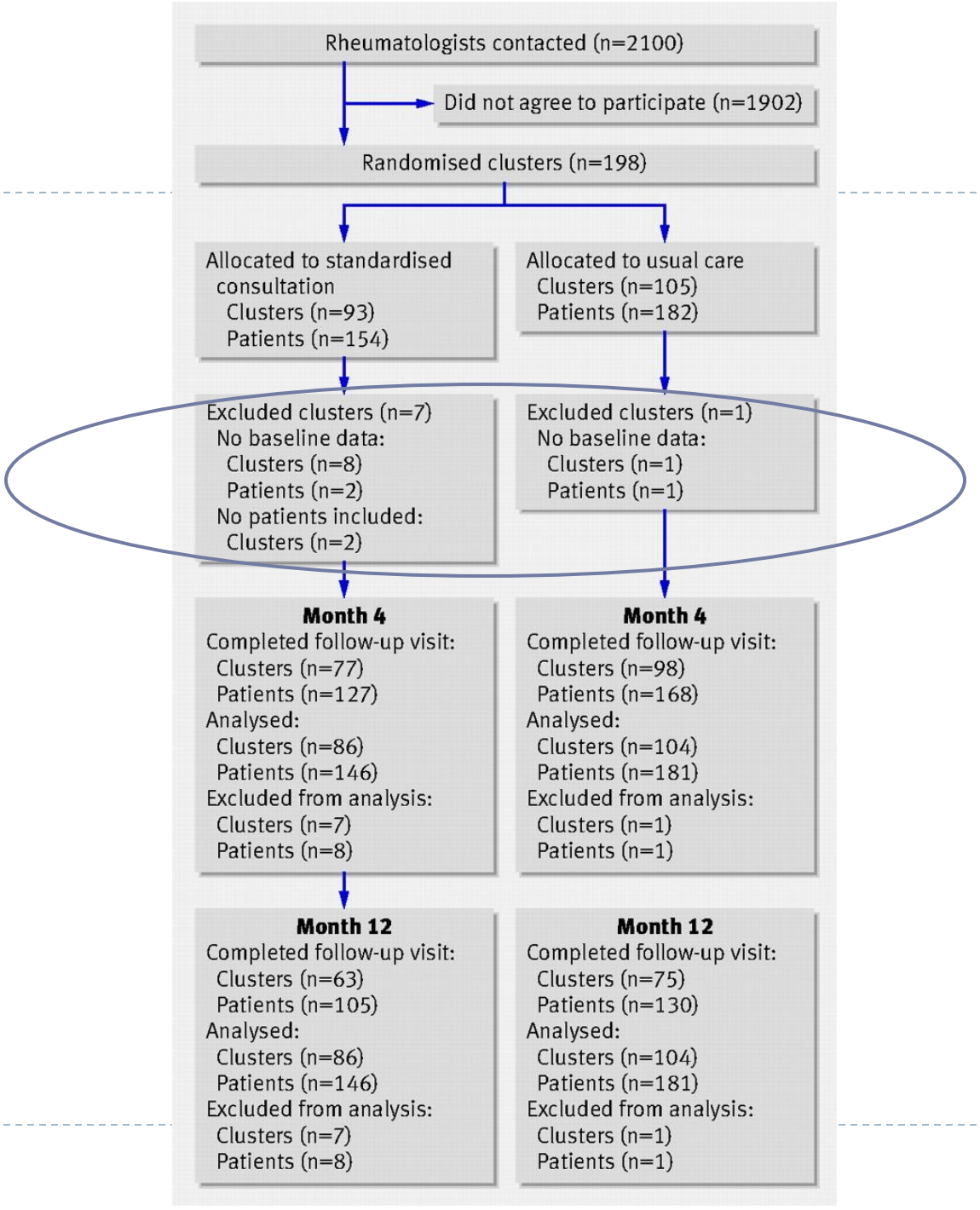
P Ravaud, professor of epidemiology[1] R-M Flipo, professor of rheumatology[2] I Boutron, assistant professor of epidemiology[1] C Roy, statistician[1] A Mahmoudi, general practitioner[3] B Giraudeau, assistant professor of statistics[4] T Phamassistant professor of rheumatology[5]

- Experimental treatment: Standardised consultation
  - Education on osteoarthritis and treatment management;
  - Information on physical exercises
  - Information on weight loss
- Comparator: usual care
- Outcome: Weight and physical activities
- Recruitment: Rheumatologists recruited patients after knowing the treatment assignment.



RECRUITMENT BIAS

- **Baseline data**
  - Standardised consultation: Weight (kg) = 84.1 (12.9)
  - Usual care: Weight (kg) = 81.4 (13.6)


Rheumatologists contacted (n=2100)
Did not agree to participate (n=1902)
Randomised clusters (n=198)
Allocated to standardised consultation
Clusters (n=93)
Patients (n=154)
Allocated to usual care
Clusters (n=105)
Patients (n=182)
Excluded clusters (n=7)
No baseline data:
Clusters (n=8)
Patients (n=2)
No patients included:
Clusters (n=2)
Excluded clusters (n=1)
No baseline data:
Clusters (n=1)
Patients (n=1)
Month 4
Completed follow-up visit:
Clusters (n=77)
Patients (n=127)
Analysed:
Clusters (n=86)
Patients (n=146)
Excluded from analysis:
Clusters (n=7)
Patients (n=8)
Month 4
Completed follow-up visit:
Clusters (n=98)
Patients (n=168)
Analysed:
Clusters (n=104)
Patients (n=181)
Excluded from analysis:
Clusters (n=1)
Patients (n=1)
Month 12
Completed follow-up visit:
Clusters (n=63)
Patients (n=105)
Analysed:
Clusters (n=86)
Patients (n=146)
Excluded from analysis:
Clusters (n=7)
Patients (n=8)
Month 12
Completed follow-up visit:
Clusters (n=75)
Patients (n=130)
Analysed:
Clusters (n=104)
Patients (n=181)
Excluded from analysis:
Clusters (n=1)
Patients (n=1)

Recent research results

Annals of Internal Medicine | Research and Reporting Methods

Single-Center Trials Show Larger Treatment Effects Than Multicenter Trials: Evidence From a Meta-epidemiologic Study

Agnes Dechartres, MD; Isabelle Boutron, MD, PhD; Ludovic Trinquart, MSc; Pierre Charles, MD; and Philippe Ravaud, MD, PhD

Background: A recent study suggested that results of single-center trials are frequently contradicted when similar trials are performed in multicenter settings.

Purpose: To perform a meta-epidemiologic study to evaluate whether estimates of treatment effect differ between single-center and multicenter randomized, controlled trials (RCTs)

log odds ratio to take publication bias into account. Forty-eight meta-analyses were selected, including 421 RCTs (223 were single-center and 198 were multicenter). Single-center RCTs showed a larger intervention effect than did multicenter RCTs (combined ROR, 0.73 [95% CI, 0.64 to 0.83]), with low heterogeneity across individual meta-analyses (I^2 = 12.0%; P = 0.24). Adjustment for

Ann Intern Med. 2011;155:39-51.

- Two previous studies suggested that the results of single-center and multicenter RCTs could be different:
  - In 1989, Berlin[1] suggested that single-center studies tended to show larger treatment effect on survival than did multicenter trials after adjustement for sample size
  - In 2009, Bellomo[2] highlighted the limits of single-center RCTs in the field of critical care medicine:
    - The results of many single-center RCTs have been contradicted when performed in multicenter setting

[1] Berlin and colleagues. *Journal of the American Statistical Association.* 1989.

[2] Bellomo and colleagues. *Crit Care Med.* 2009.

Methods

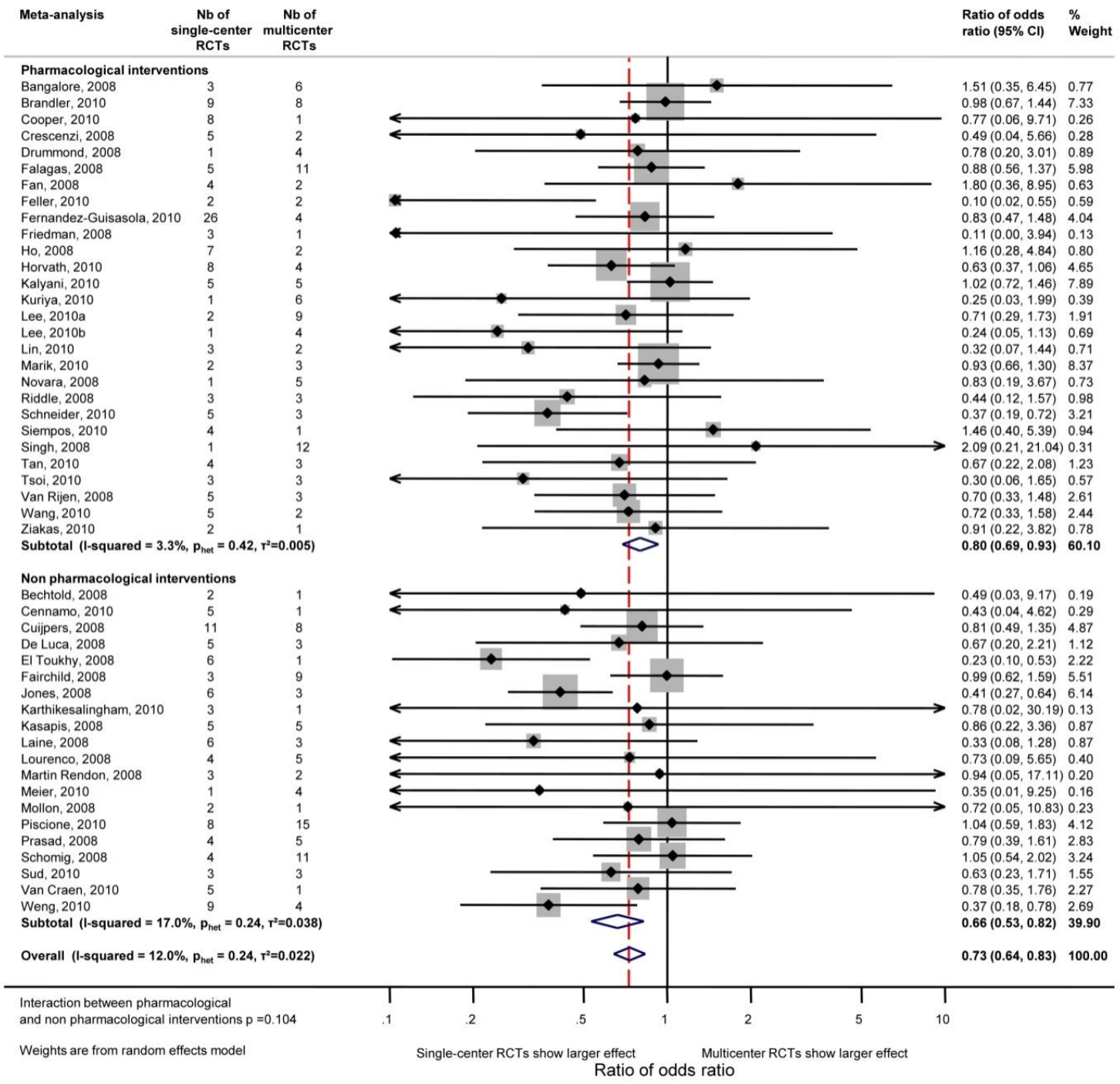
- Design
  - Meta-epidemiological study on a collection of meta-analyses of binary outcomes
- Data sources and searches
  - Meta-analyses of RCTs published in the Issue 4, 2008 of the Cochrane Collaboration and in Pubmed (high-impact factor journals)
- 48 Meta-analysis selected
  - 421 RCTs contributing to the analysis

Results

	Single-center RCTs N=223	Multicenter RCTs N=198
Interventions		
✓ Nonpharmacologic treatments	95 (43%)	86 (43%)
Funding source		
✓ Public	64 (29%)	56 (28%)
✓ Private	36 (16%)	102 (52%)
✓ Not reported	123 (55%)	40 (20%)
Sample size (Median [Q1-Q3]	90 [50-153]	243 [126-521]
Year of publication ✓ before 2000	98 (44%)	54 (27%)

Results

RoB tool	Single-center RCTs N=223	Multicenter RCTs N=198
Sequence generation		
✓Low risk of bias	75 (34%)	90 (45%)
Allocation concealment		
✓Low risk of bias	32 (14%)	68 (34%)
Blinding		
✓Low risk of bias	151 (68%)	157 (79%)
Incomplete outcome data		
✓Low risk of bias	68 (31%)	55 (28%)
Selective outcome reporting		
✓Low risk of bias	72 (32%)	134 (68%)
Overall risk of bias		
✓Low risk of bias	11 (5%)	17 (9%)
✓high risk of bias	39 (17%)	57 (29%)
✓Unclear	173 (78%)	124 (62%)

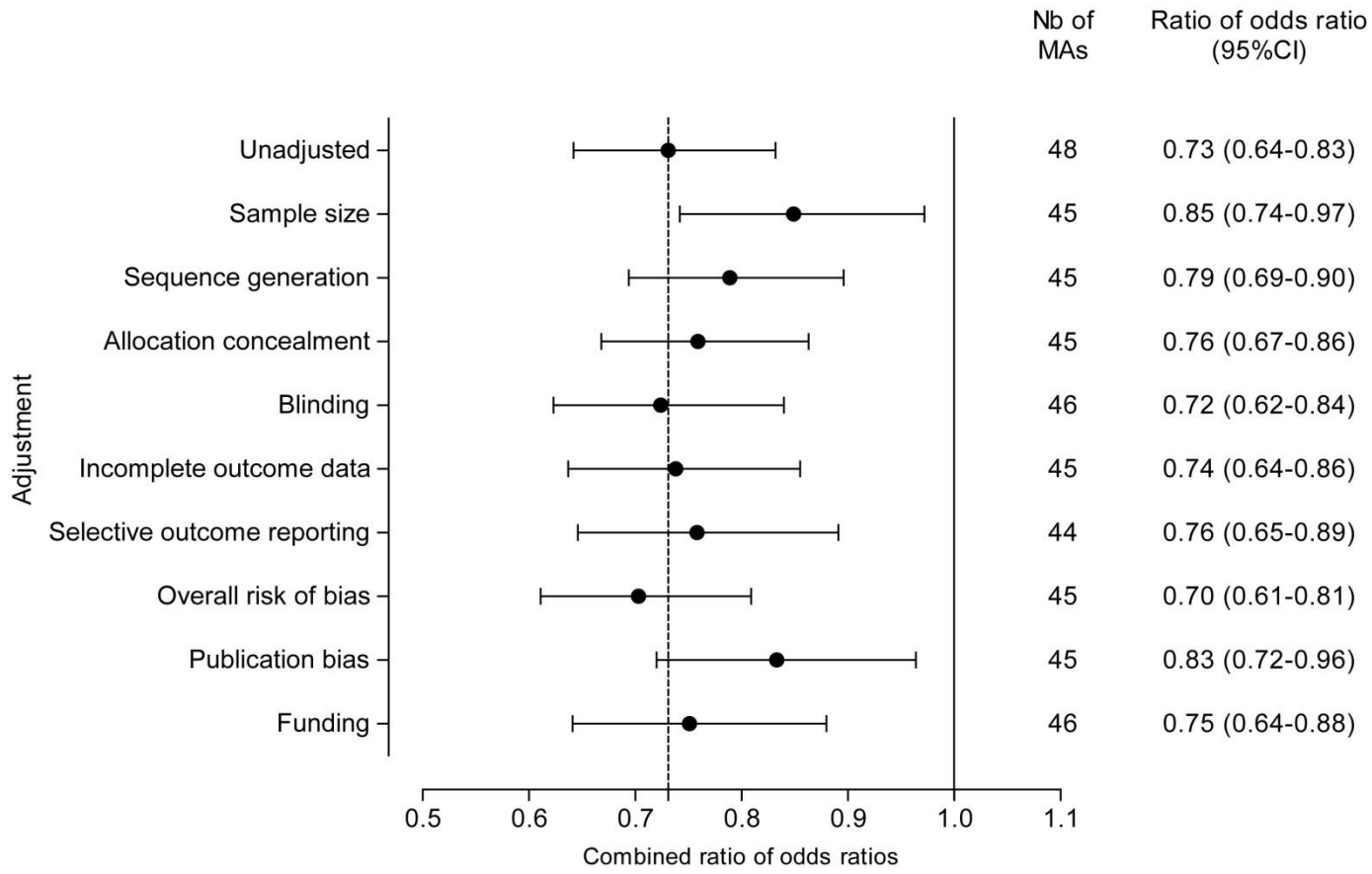

Meta-analysis
Nb of single-center RCTs
Nb of multicenter RCTs
Ratio of odds ratio (95% CI)
% Weight
Pharmacological interventions
Bangalore, 2008 3 6 1.51 (0.35, 6.45) 0.77
Brandler, 2010 9 8 0.98 (0.67, 1.44) 7.33
Cooper, 2010 8 1 0.77 (0.06, 9.71) 0.26
Crescenzi, 2008 5 2 0.49 (0.04, 5.66) 0.28
Drummond, 2008 1 4 0.78 (0.20, 3.01) 0.89
Falagas, 2008 5 11 0.88 (0.56, 1.37) 5.98
Fan, 2008 4 2 1.80 (0.36, 8.95) 0.63
Feller, 2010 2 2 0.10 (0.02, 0.55) 0.59
Fernandez-Guisasola, 2010 26 4 0.83 (0.47, 1.48) 4.04
Friedman, 2008 3 1 0.11 (0.00, 3.94) 0.13
Ho, 2008 7 2 1.16 (0.28, 4.84) 0.80
Horvath, 2010 8 4 0.63 (0.37, 1.06) 4.65
Kalyani, 2010 5 5 1.02 (0.72, 1.46) 7.89
Kuriya, 2010 1 6 0.25 (0.03, 1.99) 0.39
Lee, 2010a 2 9 0.71 (0.29, 1.73) 1.91
Lee, 2010b 1 4 0.24 (0.05, 1.13) 0.69
Lin, 2010 3 2 0.32 (0.07, 1.44) 0.71
Marik, 2010 2 3 0.93 (0.66, 1.30) 8.37
Novara, 2008 1 5 0.83 (0.19, 3.67) 0.73
Riddle, 2008 3 3 0.44 (0.12, 1.57) 0.98
Schneider, 2010 5 3 0.37 (0.19, 0.72) 3.21
Siempos, 2010 4 1 1.46 (0.40, 5.39) 0.94
Singh, 2008 1 12 2.09 (0.21, 21.04) 0.31
Tan, 2010 4 3 0.67 (0.22, 2.08) 1.23
Tsoi, 2010 3 3 0.30 (0.06, 1.65) 0.57
Van Rijen, 2008 5 3 0.70 (0.33, 1.48) 2.61
Wang, 2010 5 2 0.72 (0.33, 1.58) 2.44
Ziakas, 2010 2 1 0.91 (0.22, 3.82) 0.78
Subtotal (I-squared = 3.3%, p_{het} = 0.42, τ^2=0.005) 0.80 (0.69, 0.93) 60.10
Non pharmacological interventions
Bechtold, 2008 2 1 0.49 (0.03, 9.17) 0.19
Cennamo, 2010 5 1 0.43 (0.04, 4.62) 0.29
Cuijpers, 2008 11 8 0.81 (0.49, 1.35) 4.87
De Luca, 2008 5 3 0.67 (0.20, 2.21) 1.12
El Toukhy, 2008 6 1 0.23 (0.10, 0.53) 2.22
Fairchild, 2008 3 9 0.99 (0.62, 1.59) 5.51
Jones, 2008 6 3 0.41 (0.27, 0.64) 6.14
Karthikesalingham, 2010 3 1 0.78 (0.02, 30.19) 0.13
Kasapis, 2008 5 5 0.86 (0.22, 3.36) 0.87
Laine, 2008 6 3 0.33 (0.08, 1.28) 0.87
Lourenco, 2008 4 5 0.73 (0.09, 5.65) 0.40
Martin Rendon, 2008 3 2 0.94 (0.05, 17.11) 0.20
Meier, 2010 1 4 0.35 (0.01, 9.25) 0.16
Mollon, 2008 2 1 0.72 (0.05, 10.83) 0.23
Piscione, 2010 8 15 1.04 (0.59, 1.83) 4.12
Prasad, 2008 4 5 0.79 (0.39, 1.61) 2.83
Schomig, 2008 4 11 1.05 (0.54, 2.02) 3.24
Sud, 2010 3 3 0.63 (0.23, 1.71) 1.55
Van Craen, 2010 5 1 0.78 (0.35, 1.76) 2.27
Weng, 2010 9 4 0.37 (0.18, 0.78) 2.69
Subtotal (I-squared = 17.0%, p_{het} = 0.24, τ^2=0.038) 0.66 (0.53, 0.82) 39.90
Overall (I-squared = 12.0%, p_{het} = 0.24, τ^2=0.022) 0.73 (0.64, 0.83) 100.00
Interaction between pharmacological and non pharmacological interventions p =0.104
.1
.2
.5
1
2
5
10
Weights are from random effects model
Single-center RCTs show larger effect
Multicenter RCTs show larger effect
Ratio of odds ratio

Results

- Overall results
  - ROR = 0.73 [0.64-0.83]; I^2 = 12%

- Subgroup analysis
  - Non-pharmacologic treatments (NPT):
    ROR = 0.66 [0.53-0.82]; I^2 = 17%
  - Pharmacologic treatments (PT):
    ROR = 0.80 [0.69-0.93]; I^2 = 3.3%
  - Interaction between PT and NPT (p = 0.104)

Sensitivity analyses



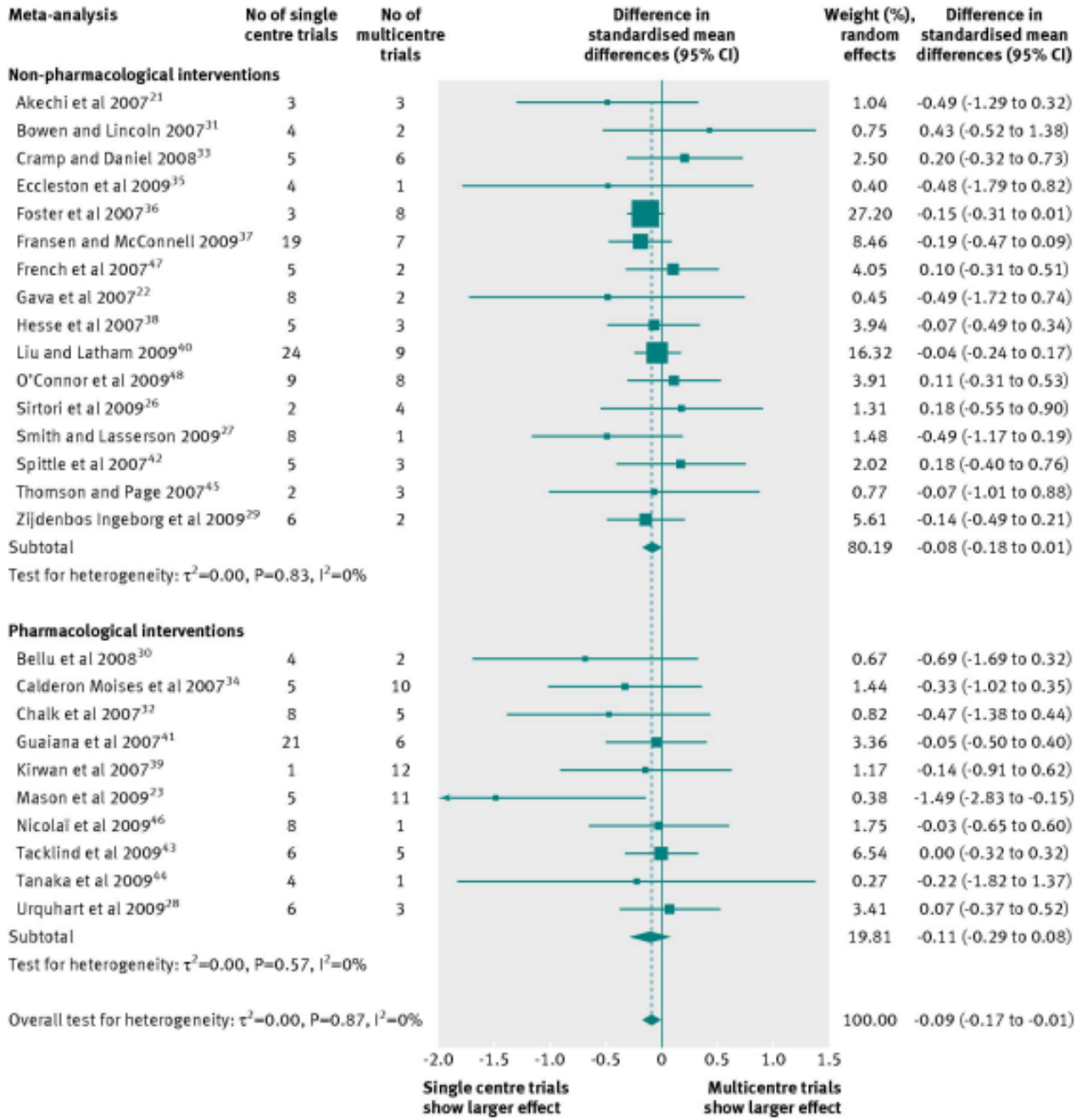
BMJ 2012;344:e813 doi: 10.1136/bmj.e813 (Published 14 February 2012)

RESEARCH

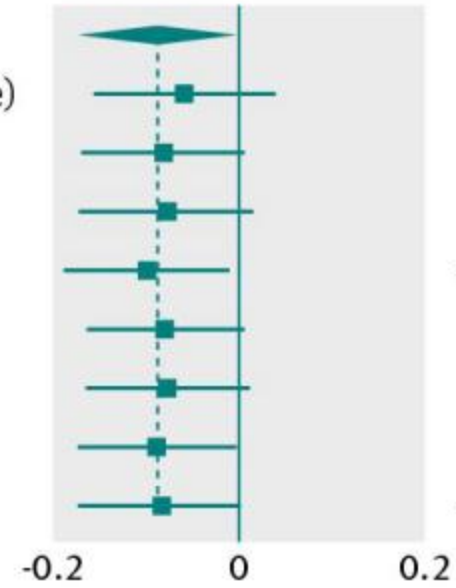
Impact of single centre status on estimates of intervention effects in trials with continuous outcomes: meta-epidemiological study

Aïda Bafeta *PhD student*[1], Agnes Dechartres *assistant professor of epidemiology*[1 2 3], Ludovic Trinquart *senior statistician*[4], Amélie Yavchitz *PhD student*[1], Isabelle Boutron *associate professor of epidemiology*[1 2 3 3], Philippe Ravaud *professor of epidemiology and director*[1 2 3 4]

- 26 meta-analysis (Cochrane)
- 292 RCTs


Meta-analysis
No of single centre trials
No of multicentre trials
Difference in standardised mean differences (95% CI)
Weight (%), random effects
Difference in standardised mean differences (95% CI)
Non-pharmacological interventions
Akechi et al 2007[21] 3 3 1.04 -0.49 (-1.29 to 0.32)
Bowen and Lincoln 2007[31] 4 2 0.75 0.43 (-0.52 to 1.38)
Cramp and Daniel 2008[33] 5 6 2.50 0.20 (-0.32 to 0.73)
Eccleston et al 2009[35] 4 1 0.40 -0.48 (-1.79 to 0.82)
Foster et al 2007[36] 3 8 27.20 -0.15 (-0.31 to 0.01)
Fransen and McConnell 2009[37] 19 7 8.46 -0.19 (-0.47 to 0.09)
French et al 2007[47] 5 2 4.05 0.10 (-0.31 to 0.51)
Gava et al 2007[22] 8 2 0.45 -0.49 (-1.72 to 0.74)
Hesse et al 2007[38] 5 3 3.94 -0.07 (-0.49 to 0.34)
Liu and Latham 2009[40] 24 9 16.32 -0.04 (-0.24 to 0.17)
O'Connor et al 2009[48] 9 8 3.91 0.11 (-0.31 to 0.53)
Sirtori et al 2009[26] 2 4 1.31 0.18 (-0.55 to 0.90)
Smith and Lasserson 2009[27] 8 1 1.48 -0.49 (-1.17 to 0.19)
Spittle et al 2007[42] 5 3 2.02 0.18 (-0.40 to 0.76)
Thomson and Page 2007[45] 2 3 0.77 -0.07 (-1.01 to 0.88)
Zijdenbos Ingeborg et al 2009[29] 6 2 5.61 -0.14 (-0.49 to 0.21)
Subtotal 80.19 -0.08 (-0.18 to 0.01)
Test for heterogeneity: τ^2=0.00, P=0.83, I^2=0%
Pharmacological interventions
Bellu et al 2008[30] 4 2 0.67 -0.69 (-1.69 to 0.32)
Calderon Moises et al 2007[34] 5 10 1.44 -0.33 (-1.02 to 0.35)
Chalk et al 2007[32] 8 5 0.82 -0.47 (-1.38 to 0.44)
Guaiana et al 2007[41] 21 6 3.36 -0.05 (-0.50 to 0.40)
Kirwan et al 2007[39] 1 12 1.17 -0.14 (-0.91 to 0.62)
Mason et al 2009[23] 5 11 0.38 -1.49 (-2.83 to -0.15)
Nicolaï et al 2009[46] 8 1 1.75 -0.03 (-0.65 to 0.60)
Tacklind et al 2009[43] 6 5 6.54 0.00 (-0.32 to 0.32)
Tanaka et al 2009[44] 4 1 0.27 -0.22 (-1.82 to 1.37)
Urquhart et al 2009[28] 6 3 3.41 0.07 (-0.37 to 0.52)
Subtotal 19.81 -0.11 (-0.29 to 0.08)
Test for heterogeneity: τ^2=0.00, P=0.57, I^2=0%
Overall test for heterogeneity: τ^2=0.00, P=0.87, I^2=0% 100.00 -0.09 (-0.17 to -0.01)
-2.0 -1.5 -1.0 -0.5 0 0.5 1.0 1.5
Single centre trials show larger effect
Multicentre trials show larger effect

Adjustment	Difference in standardised mean differences (95% CI)	Difference in standardised mean differences (95% CI)
Unadjusted		-0.09 (-0.17 to -0.01)
No of patients randomly assigned (continuous variable)		-0.06 (-0.16 to 0.04)
No of patients randomly assigned (binary variable)		-0.08 (-0.17 to 0.01)
Sequence generation		-0.08 (-0.17 to 0.01)
Allocation concealment		-0.10 (-0.19 to -0.01)
Blinding		-0.08 (-0.16 to 0.01)
Incomplete outcome data		-0.08 (-0.16 to 0.01)
Overall risk of bias		-0.09 (-0.17 to 0.00)
Funding		-0.09 (-0.18 to -0.01)



Discussion

- Possible explanations :
  - « Small study effect » but the results were consistent after adjustment for sample size
  - Publication bias:
    - Some studies suggested that single-center RCTs may be more prone to publication bias than multicenter trials

Sterne JA, et al JCE 2000
Sterne et al BMJ 1997

Discussion

- Possible explanations :
  - Lower methodological quality of single-center RCTs but the results were consistent after adjustment for risk of bias
  - Treatment effect really more important in single-center RCTs
    - Selection of a more homogeneous population
    - More standardized interventions in high skill units

Discussion

- Studies are needed to explore the different possible mechanisms
- The single-center or multicenter status is usually well reported in RCTs and simple to assess, so it could be used as a proxy measure when interpreting the results of meta-analysis