Finnish Institute of Occupational Health

Four of kind Combining studies: from heterogeneity to similarity

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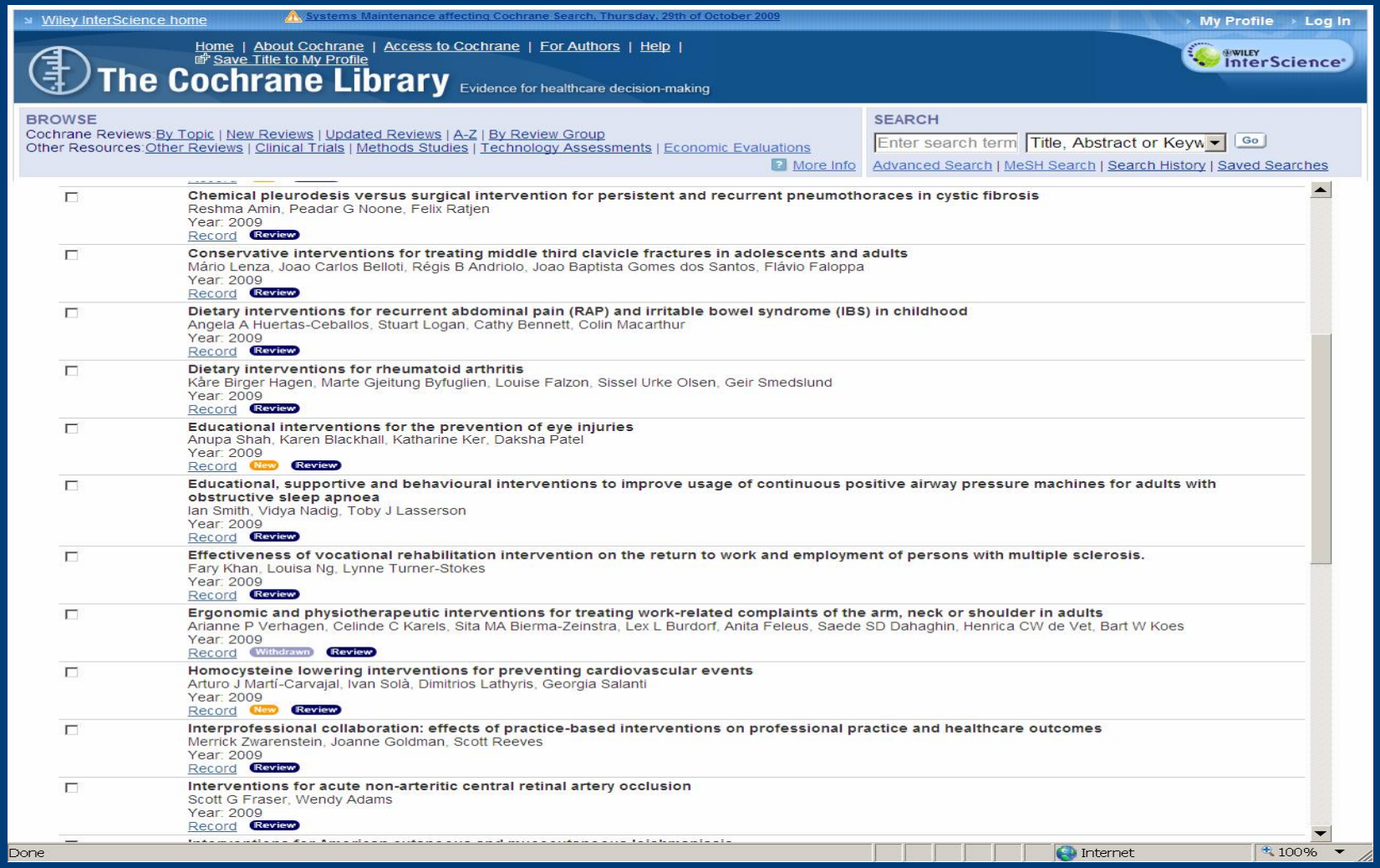
A systematic review

1. Well-formulated question (PICO)
2. Thorough search
3. Objective selection of studies
4. Critical assessment of methodological quality
5. Objective data extraction
6. Synthesis of the data
   a) appropriate comparisons of interventions and controls
   b) meta-analysis per comparison
7. Conclusions for practice and research

Scope of a review

- Interventions for.....
  - Cochrane Library
    - intervention* NOT pharmacological in title
      - 411 reviews and 261 protocols
- Resulting in a variety of interventions
  - non-drug
  - complex interventions
    - multi-faceted
    - multi-component
    - behavioural
    - team based
    - community-based
    - rehabilitation
    - exercises for..
    - educational

Example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Advanced Search | MeSH Search | Search History | Saved Searches
Chemical pleurodesis versus surgical intervention for persistent and recurrent pneumothoraces in cystic fibrosis
Reshma Amin, Peadar G Noone, Felix Ratjen
Year: 2009
Record Review
Conservative interventions for treating middle third clavicle fractures in adolescents and adults
Mário Lenza, Joao Carlos Belloti, Régis B Andriolo, Joao Baptista Gomes dos Santos, Flávio Faloppa
Year: 2009
Record Review
Dietary interventions for recurrent abdominal pain (RAP) and irritable bowel syndrome (IBS) in childhood
Angela A Huertas-Ceballos, Stuart Logan, Cathy Bennett, Colin Macarthur
Year: 2009
Record Review
Dietary interventions for rheumatoid arthritis
Kåre Birger Hagen, Marte Gjeitung Byfuglien, Louise Falzon, Sissel Urke Olsen, Geir Smedslund
Year: 2009
Record Review
Educational interventions for the prevention of eye injuries
Anupa Shah, Karen Blackhall, Katharine Ker, Daksha Patel
Year: 2009
Record New Review
Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines for adults with obstructive sleep apnoea
Ian Smith, Vidya Nadig, Toby J Lasserson
Year: 2009
Record Review
Effectiveness of vocational rehabilitation intervention on the return to work and employment of persons with multiple sclerosis.
Fary Khan, Louisa Ng, Lynne Turner-Stokes
Year: 2009
Record Review
Ergonomic and physiotherapeutic interventions for treating work-related complaints of the arm, neck or shoulder in adults
Arianne P Verhagen, Celinde C Karels, Sita MA Bierma-Zeinstra, Lex L Burdorf, Anita Feleus, Saede SD Dahaghin, Henrica CW de Vet, Bart W Koes
Year: 2009
Record Withdrawn Review
Homocysteine lowering interventions for preventing cardiovascular events
Arturo J Martí-Carvajal, Ivan Solà, Dimitrios Lathyris, Georgia Salanti
Year: 2009
Record New Review
Interprofessional collaboration: effects of practice-based interventions on professional practice and healthcare outcomes
Merrick Zwarenstein, Joanne Goldman, Scott Reeves
Year: 2009
Record Review
Interventions for acute non-arteritic central retinal artery occlusion
Scott G Fraser, Wendy Adams
Year: 2009
Record Review
Done
Internet
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How to deal with heterogeneity?

- Usual text in Cochrane Protocol Method Section
  - We will assess clinical heterogeneity by examining types of participants, interventions, and outcomes in each study
  - We will pool data from studies judged to be clinically homogeneous with RevMan 5 software.
- When you are going to look for heterogeneity you will probably find it and then it will be difficult to pool studies
- Better to state we will look for *similarity* between

Heterogeneity? Similarity?

- In the review “Interventions for preventing noise-induced hearing loss in workers” you find the following 7 studies. How are they similar assuming that study designs are all similar?

1. Ear muffs vs plugs for reducing noise levels in construction workers
2. Ear plugs vs other ear plugs for reducing hearing loss in farmers
3. Legislation versus no legislation for reducing noise exposure in mines
4. Worker training in ear plug use vs no training for preventing hearing loss in metal sheet workers
5. Subsidies for employers vs no subsidies for reducing noise exposure in offshore oil platforms
6. Information campaign vs no campaign for preventing hearing loss in construction workers
7. Magnesium vs placebo for preventing hearing loss in noise-exposed workers

Too heterogeneous for meta-analysis?

- Cochrane Systematic Review, Rehabilitation for older people in long-term care, CD004294
- Objective: to evaluate physical rehabilitation interventions directed at improving physical function among older people in long-term care.
- ..From these, 49 studies fulfilled the eligibility criteria and are included in this review.
- ..The included studies are heterogeneous. They examine different types of intervention, and evaluate them with a wide battery of outcome measures. *Such variety made a meta-analysis unfeasible.*
- *Are the authors correct?*

Solutions for heterogeneity 1: focus

1. Narrow down the scope of the review

2. When few studies expected, formulate on beforehand which comparisons will be judged sufficiently similar to be combined.

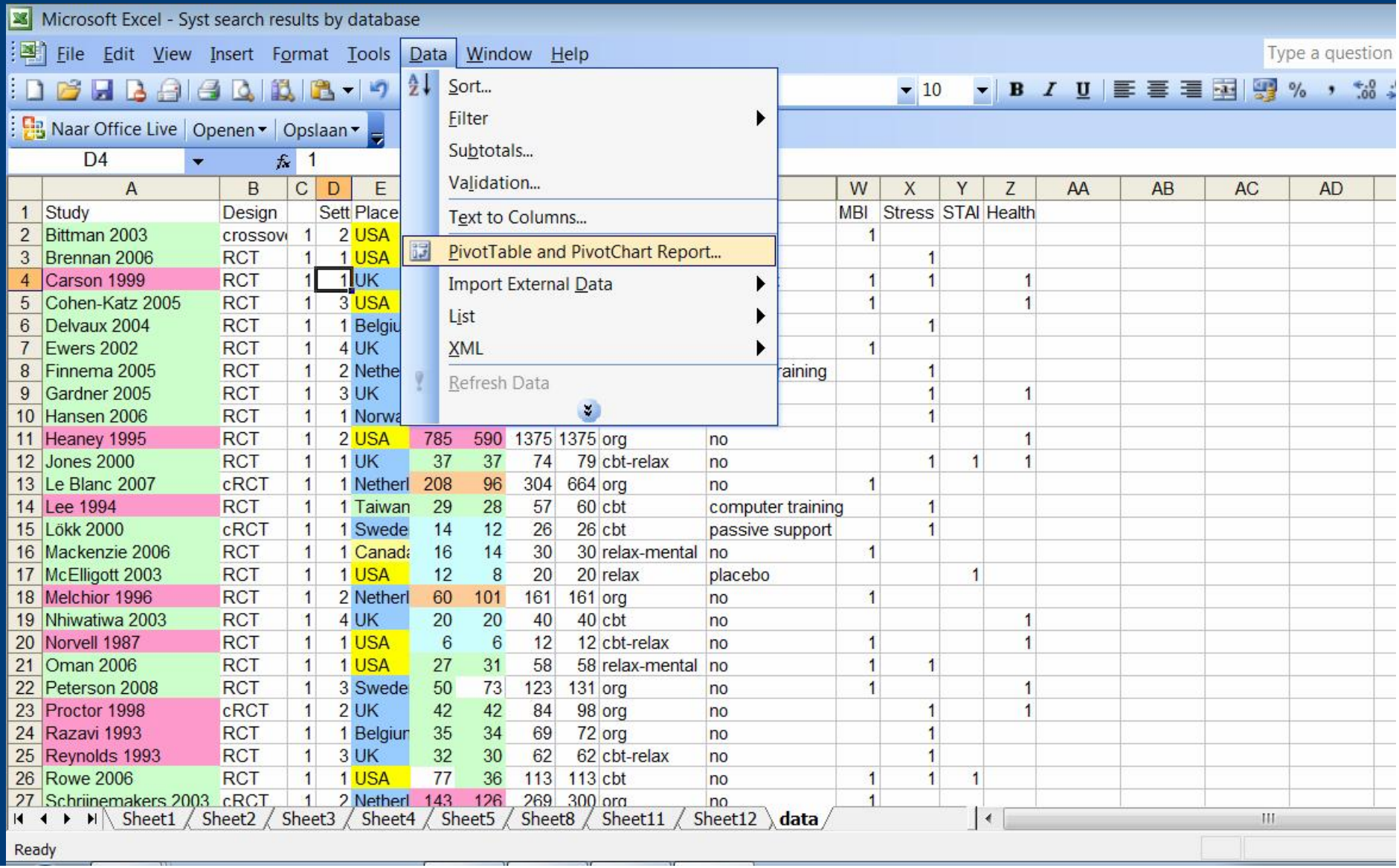
Need for intervention classification

- Preferably classification should…
  - be mechanism based
  - have a practical meaning
  - have consequences in resource use

Criteria for intervention classification

- Outcome
  - that the intervention aims to reduce
  - exposure, worker behaviour, occupational disease, disability, injury
- Mode of action
  - environmental, behavioural, clinical
- Level or point of action
  - individual, group, societal level (legal)
- Complexity
  - simple, multi-component, multi-actor
- Target Group
  - workers, students, specific occupations
- Place of delivery or setting
  - hospital, primary care, workplace
- Moment of application
  - preventive (without request for help), treatment
- Mode of delivery
  - verbal, written, web-based, media

Use Excel Pivot Table



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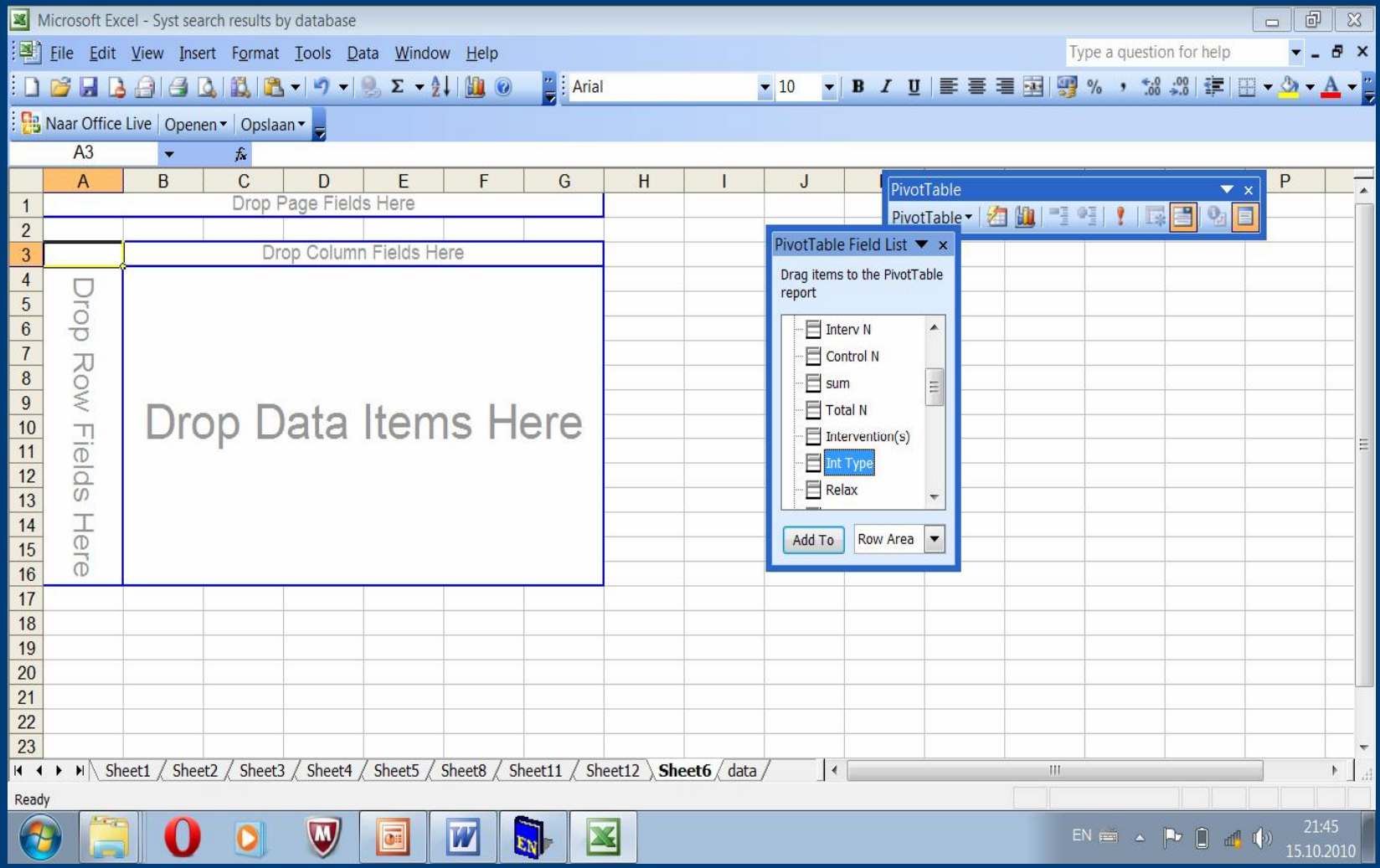

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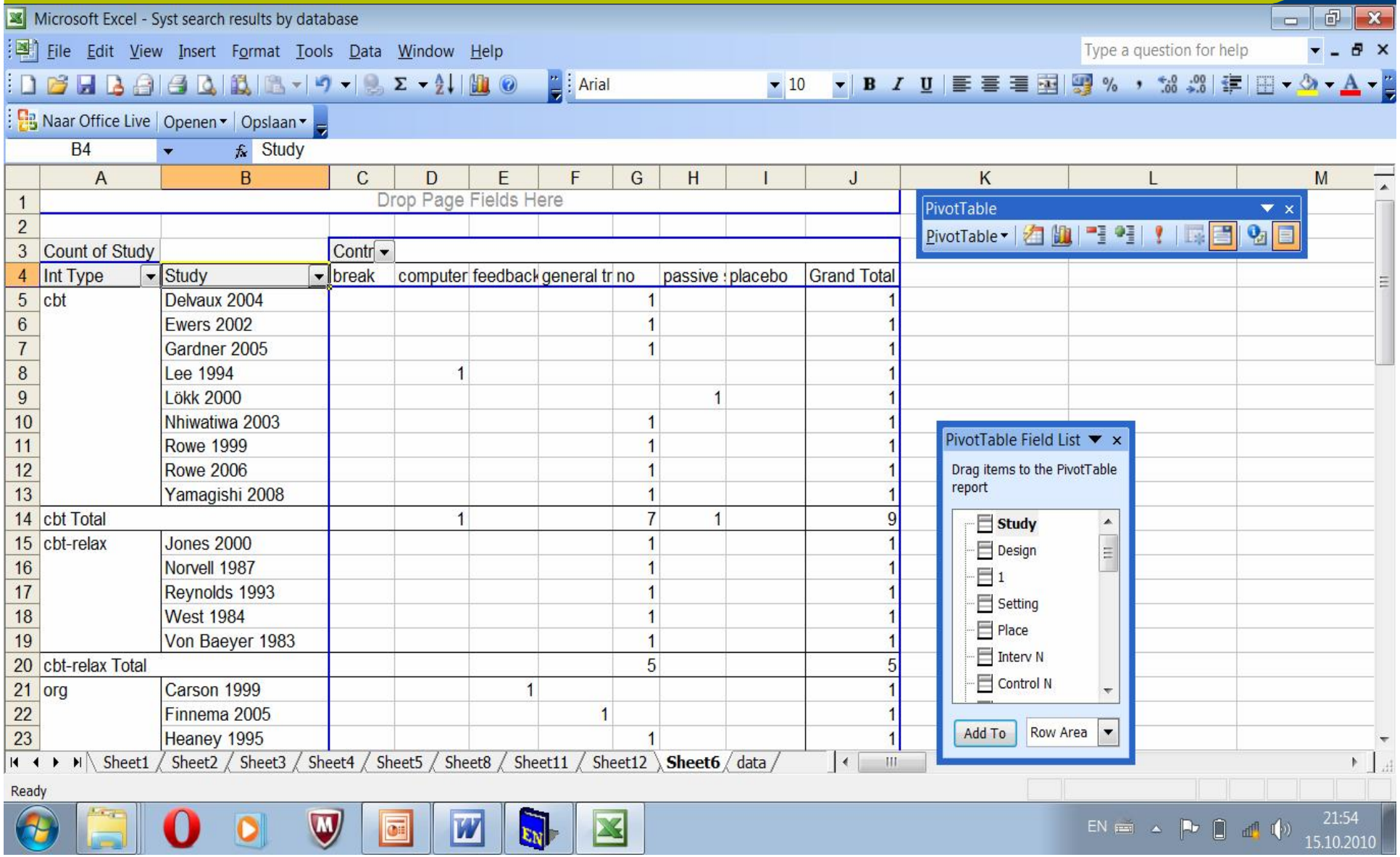
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Alternatives for dealing with heterogeneity?

- Because the studies were too heterogeneous to combine them in a meta-analysis we used a levels of evidence synthesis (best evidence synthesis) to combine them
- Data synthesis: The selected studies were very heterogeneous in types of interventions, types of complaints, study population and outcomes measures, and therefore meta-analyses were not performed. Findings were reported narratively.
- *Levels of evidence:* For a more qualitative approach to synthesise the findings from included studies, so-called 'levels of evidence' were used (Ostelo 2002; Van Tulder 1997; Van Tulder 2001).
- Levels of evidence:
  1. Good evidence - provided by generally consistent findings in two or more high-quality studies
  2. Moderate evidence - provided by generally consistent findings in one high-quality study and one or more low-quality studies, or by generally consistent findings in two or more low-quality studies
  3. Limited or conflicting evidence - only one study (either high or low quality), or inconsistent findings in two or more studies
  4. No evidence - no studies. (Henken 2007)
- Are the authors correct?

Too heterogeneous to combine thus..

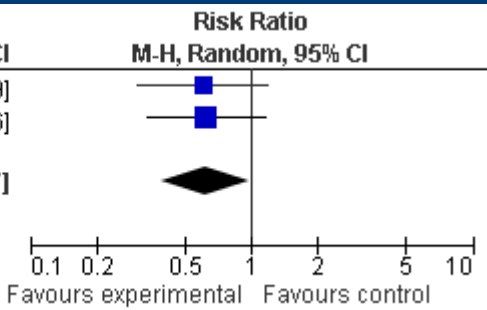
- Worker training to prevent injuries
- Outcome: Reported Injuries
  - Peterson 2001 found after one year follow-up:
    - intervention: 15 injuries / 450 workers
    - control: 19 injuries / 370 workers
    - RR 0.61 (95% CI 0.3 to 1.2)
    - author's conclusions: non-significant outcome
  - Hansson 2004 found after one year follow-up:
    - intervention: 15 injuries / 402.000 working hours
    - control 23 injuries / 386.000 working hours
    - RR 0.63 (95% CI 0.3 to 1.2)
    - author's conclusions: non-significant outcome
- No quantitative analysis possible we combined studies qualitatively:
  - conclusion: based on two studies with a non-significant outcome we found no evidence of effectiveness

Solution to heterogeneity 2: recalculate

- Recalculate all outcomes on similar scale
  - 2000 working hours = 1 working year (US)
- Combine in meta-analysis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hansson 2004	14	450	19	370	45.6%	0.61 [0.31, 1.19]
Peterson 2001	15	200	23	192	54.4%	0.63 [0.34, 1.16]
Total (95% CI)		**650**		**562**	**100.0%**	**0.62 [0.39, 0.97]**
Total events	29		42			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 2.07 (P = 0.04)



- Review Conclusion:
  - the intervention reduces injuries with 38%

Solution to heterogeneity 3: narrative synthesis

- Studies used different outcomes and interventions and therefore we did not combine them but described them in a narrative way.

- How would you perform a narrative synthesis?

Narrative synthesis

- Rodgers et al 2009:
  - developing a theory of how the intervention works, why and for whom;
  - developing a preliminary synthesis;
  - exploring relationships within and between studies;
  - assessing the robustness of the synthesis product.

Narrative synthesis

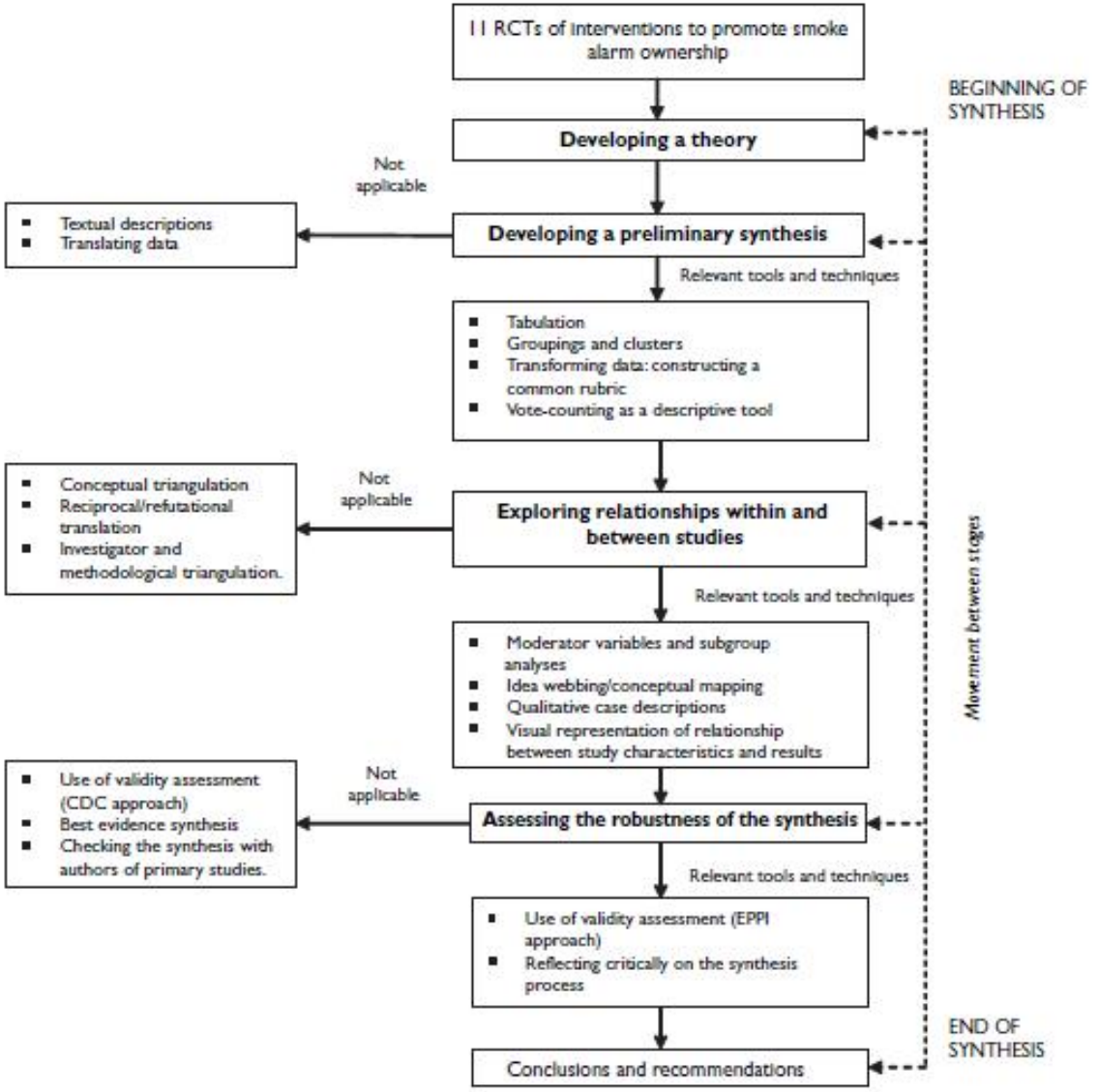


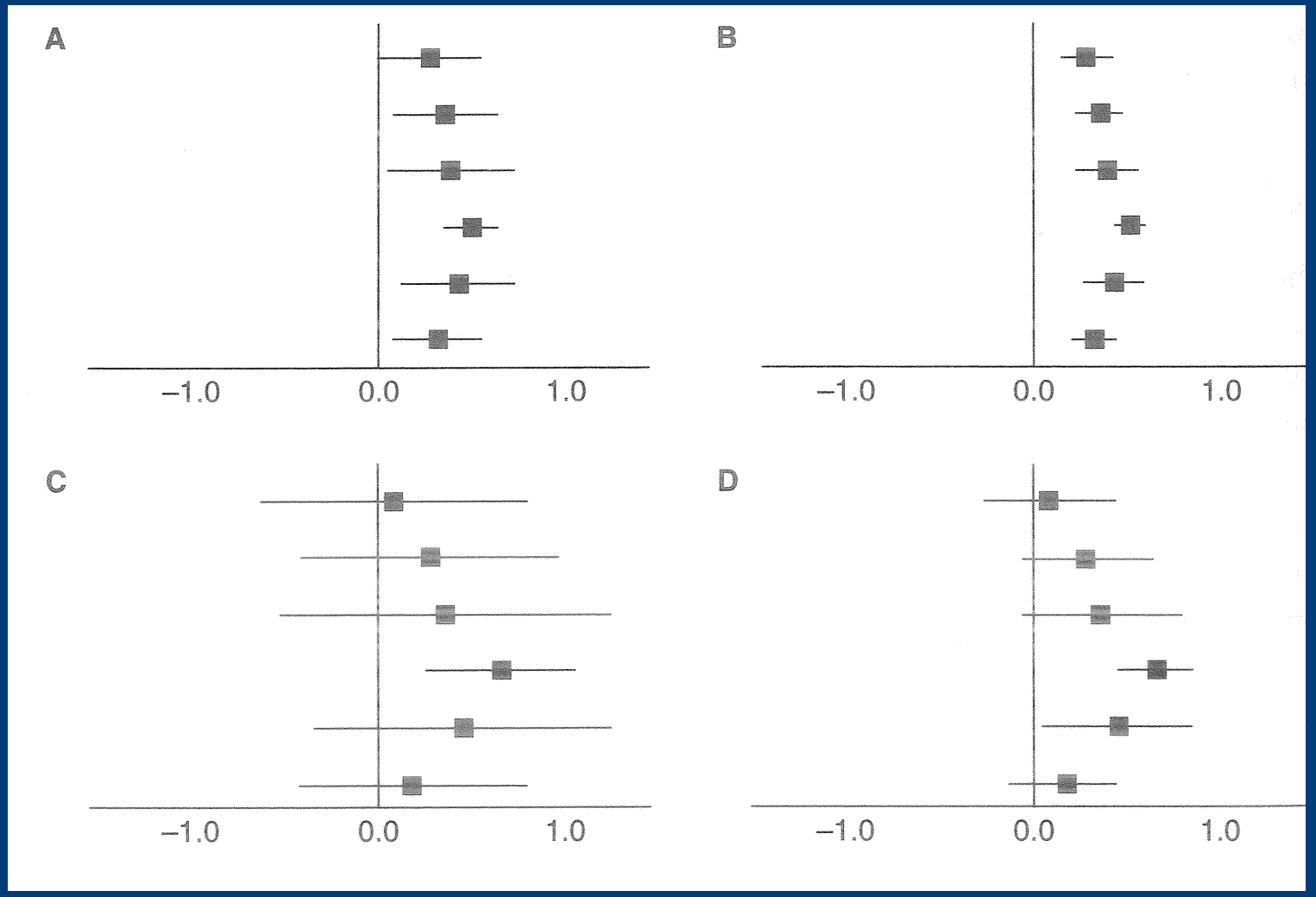
Figure 1. Synthesis Process

Narrative synthesis

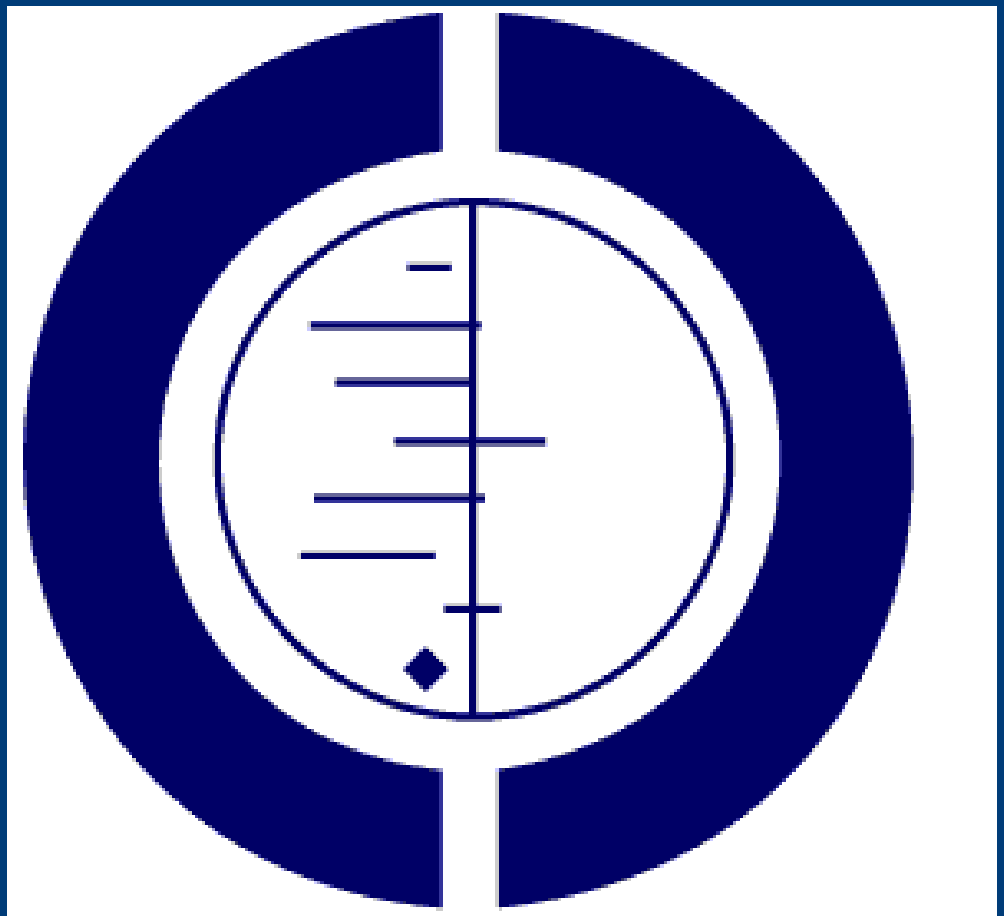
- Rodgers et al. Evaluation 2009 (15) 47-79

- Guidance-led narrative synthesis against a meta-analysis of the same study data.
  - The conclusions of the two syntheses were broadly similar.
  - However, conclusions about the
    - impact of moderators of effect appeared stronger when derived from the meta-analysis,
    - whereas implications for future research appeared more extensive when derived from the narrative synthesis.

Statistical heterogeneity



Statistical heterogeneity



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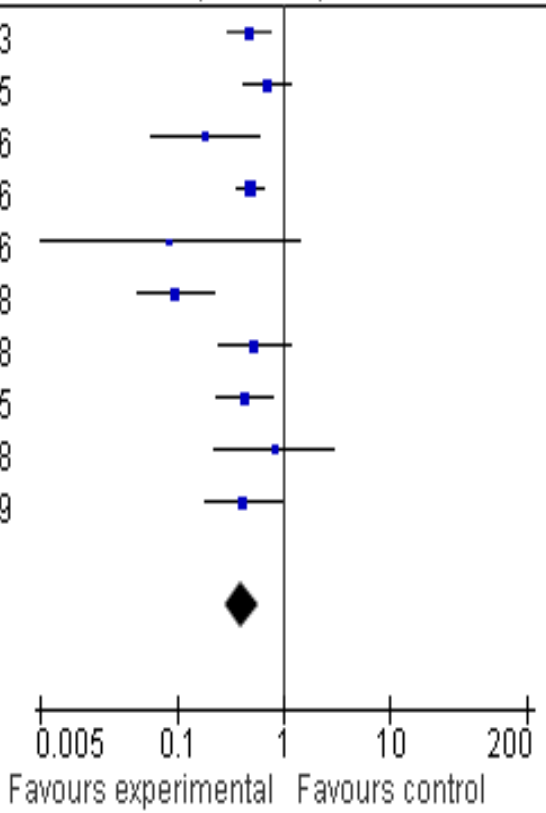
Statistical heterogeneity

Study or Subgroup	Blunted needles Events	Total	Sharp needles Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Wright 1993	18	76	31	62	14.4%	0.47 [0.29, 0.76]	1993
Thomas 1995	14	40	20	40	13.7%	0.70 [0.41, 1.18]	1995
Hartley 1996	3	46	14	39	6.3%	0.18 [0.06, 0.59]	1996
Mingoli 1996	49	390	102	392	16.9%	0.48 [0.35, 0.66]	1996
Rice 1996	0	36	10	64	1.5%	0.08 [0.01, 1.39]	1996
Botet 1998	6	200	63	200	9.7%	0.10 [0.04, 0.21]	1998
Ablett 1998	9	104	15	91	10.2%	0.53 [0.24, 1.14]	1998
Nordkam 2005	12	100	28	100	12.3%	0.43 [0.23, 0.79]	2005
Wilson 2008	4	217	5	221	5.5%	0.81 [0.22, 2.99]	2008
Sullivan 2009	7	97	17	97	9.5%	0.41 [0.18, 0.95]	2009
Total (95% CI)		**1306**		**1306**	**100.0%**	**0.40 [0.28, 0.57]**	
Total events	122		305				

Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 23.42$, df = 9 (P = 0.005); $I^2 = 62\%$

Test for overall effect: Z = 5.00 (P < 0.00001)



Statistical heterogeneity

Study or Subgroup	Blunted needles Events	Total	Sharp needles Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
14.1.1 Perforations per operation							
Thomas 1995	14	40	20	40	14.2%	0.70 [0.41, 1.18]	1995
Rice 1996	0	36	10	64	0.5%	0.08 [0.01, 1.39]	1996
Hartley 1996	3	46	14	39	2.8%	0.18 [0.06, 0.59]	1996
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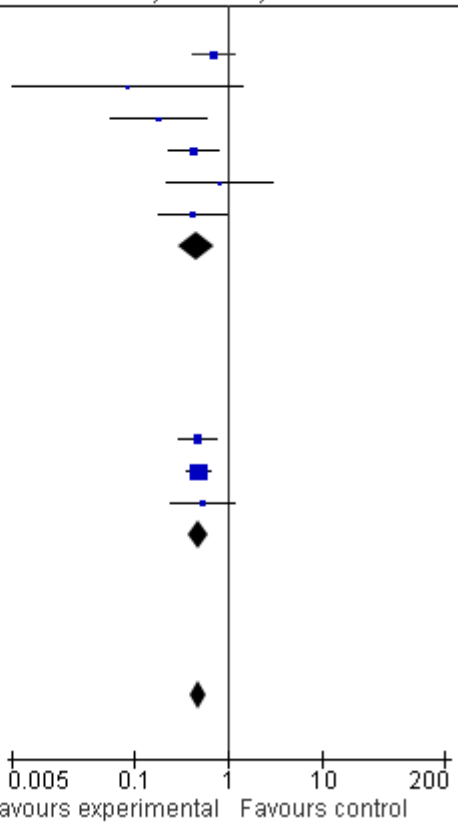
Wilson 2008	4	217	5	221	2.3%	0.81 [0.22, 2.99]	2008
Sullivan 2009	7	97	17	97	5.6%	0.41 [0.18, 0.95]	2009
Subtotal (95% CI)		**536**		**561**	**35.7%**	**0.46 [0.29, 0.72]**	
Total events	40		94				
Heterogeneity: Tau² = 0.10; Chi² = 7.52, df = 5 (P = 0.18); I² = 33%							
Test for overall effect: Z = 3.40 (P = 0.0007)							
14.1.2 Perforations per number of gloves							
Wright 1993	18	76	31	62	17.4%	0.47 [0.29, 0.76]	1993
Mingoli 1996	49	390	102	392	40.5%	0.48 [0.35, 0.66]	1996
Ablett 1998	9	104	15	91	6.5%	0.53 [0.24, 1.14]	1998
Subtotal (95% CI)		**570**		**545**	**64.3%**	**0.48 [0.38, 0.62]**	
Total events	76		148				
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 2 (P = 0.98); I² = 0%							
Test for overall effect: Z = 5.77 (P < 0.00001)							
Total (95% CI)		**1106**		**1106**	**100.0%**	**0.49 [0.40, 0.59]**	
Total events	116		242				
Heterogeneity: Tau² = 0.00; Chi² = 7.24, df = 8 (P = 0.51); I² = 0%							
Test for overall effect: Z = 7.13 (P < 0.00001)							



Meta-regression

- Linear regression model
  - Dependent variable:
    - effect size (SMD, ln OR)
  - Independent variables
    - any study characteristic (‘subgroup’)
- Tests for differences between ‘subgroups’
- Needs at least 10 studies
- Can be best performed in Stata

Flowchart

List of included studies

Check the conceptual similarity of the items 1 to 7 and in that order

1. Interventions / Exposure
2. Control condition
3. Participants
4. Study Design
5. Outcome
6. Follow-up time
7. Effect Size (RR, MD)

Transform ES if necessary

Perform Meta-Analysis

Check / Explain Statistical Heterogeneity

1. If a little dissimilar, consider making subgroups
2. If quite dissimilar consider narrative synthesis
3. If very dissimilar consider describing studies separately
4. Always report and pool different study designs separately