Systematic review
and
Meta-analysis

衛生福利部雙和醫院
實證健康照護中心
譚家偉　主任

Mountin' Hopes
Therapeutic Riding Center
We Believe in the Healing Power of Horses

Immediate and Long-Term Effects of Hippotherapy on Symmetry of Adductor Muscle Activity and Functional Ability in Children With Spastic Cerebral Palsy

Conclusions: Hippotherapy can improve adductor muscle symmetry during walking and can also improve other functional motor skills.

A randomized controlled trial of the impact of therapeutic horse riding on the quality of life, health, and function of children with cerebral palsy

but there was weak evidence of a difference for KIDSCREEN (parent report). This study suggests that therapeutic horse riding does not have a clinically significant impact on children with CP. However, a smaller effect cannot be ruled out and

Systematic review and meta-analysis of the effect of equine assisted activities and therapies on gross motor outcome in children with cerebral palsy

Sung-Hui Tseng[1], Hung-Chou Chen[2] & Ka-Wai Tam[3]

Table IV. Summary of studies assessing effect of riding on postural control.

Study	Result
Therapeutic riding	
1988, Bertoti [30]	Significant change on BPAS post-TR ($p < 0.05$)
1995, MacKinnon [29]	No significant difference in change on BPAS between groups post-TR
Hippotherapy	
2007, Hamill [34]	None of the children made gains on SAS score post-HPOT
2009, Shurtleff [14]	Significant difference between Pre T and Post T_1 ($p < 0.05$) but no significant difference between Post T_1 and Post T_2 in head angles or movement variability
2010, Shurtleff [15]	Significant reduction of head angle and ant/post translation post-HPOT ($p < 0.05$)
2011, Kwon [17]	Significant change on PBS post- HPOT ($p < 0.05$)

TR, Therapeutic riding; HPOT, Hippotherapy; BPAS, Bertoti's Postural Assessment Scale; SAS, Sitting Assessment Scale; PBS, Pediatric Balance Scale.

"Blue Highways" on the NIH Roadmap
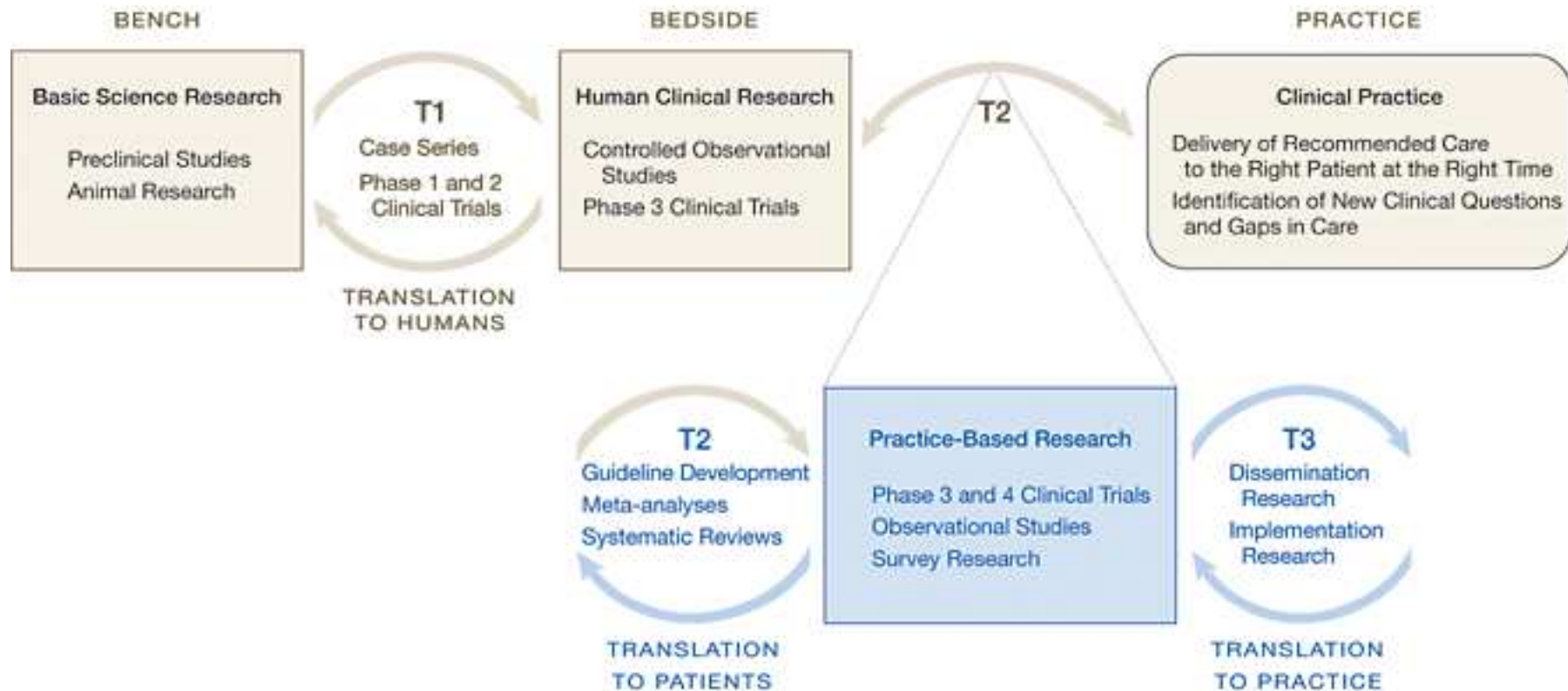
Westfall, J. M. et al. JAMA 2007;297:403-406

Identify the issue and determine the question

Write a plan for the review (protocol)

Search for studies

What authors DO

Sift and select studies
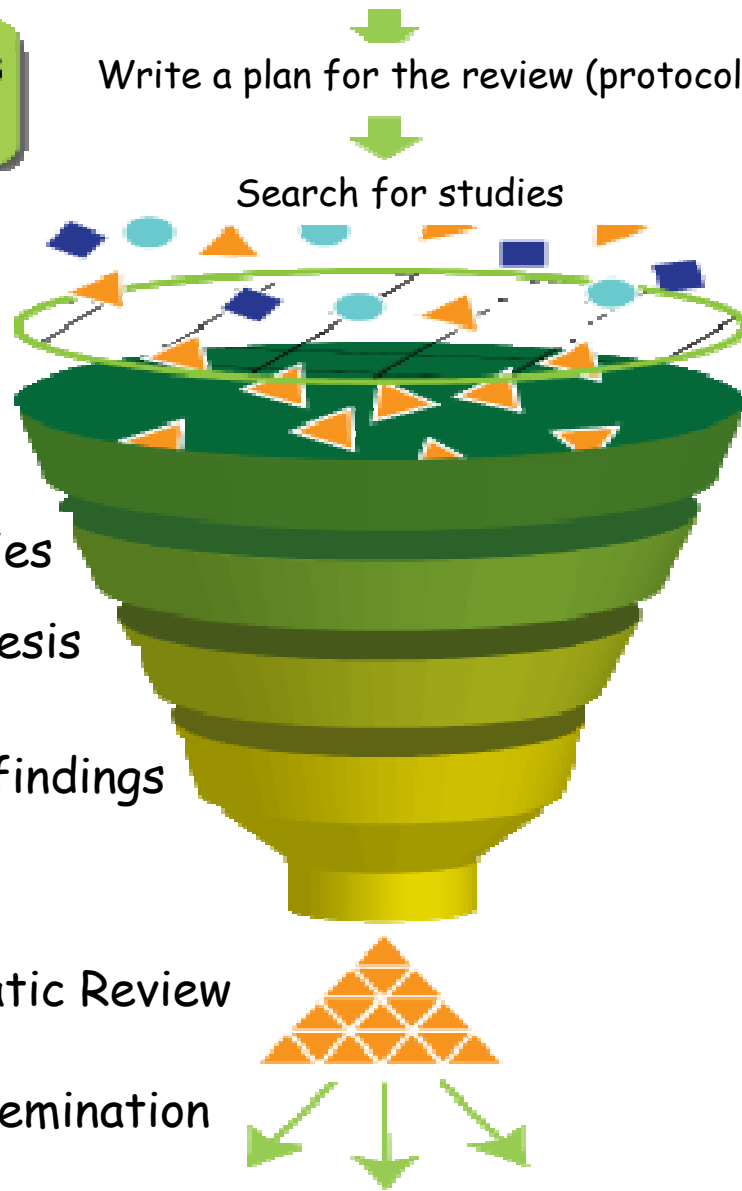
Extract data from studies

Assess the quality of the studies

Combine the data (synthesis or meta-analysis)

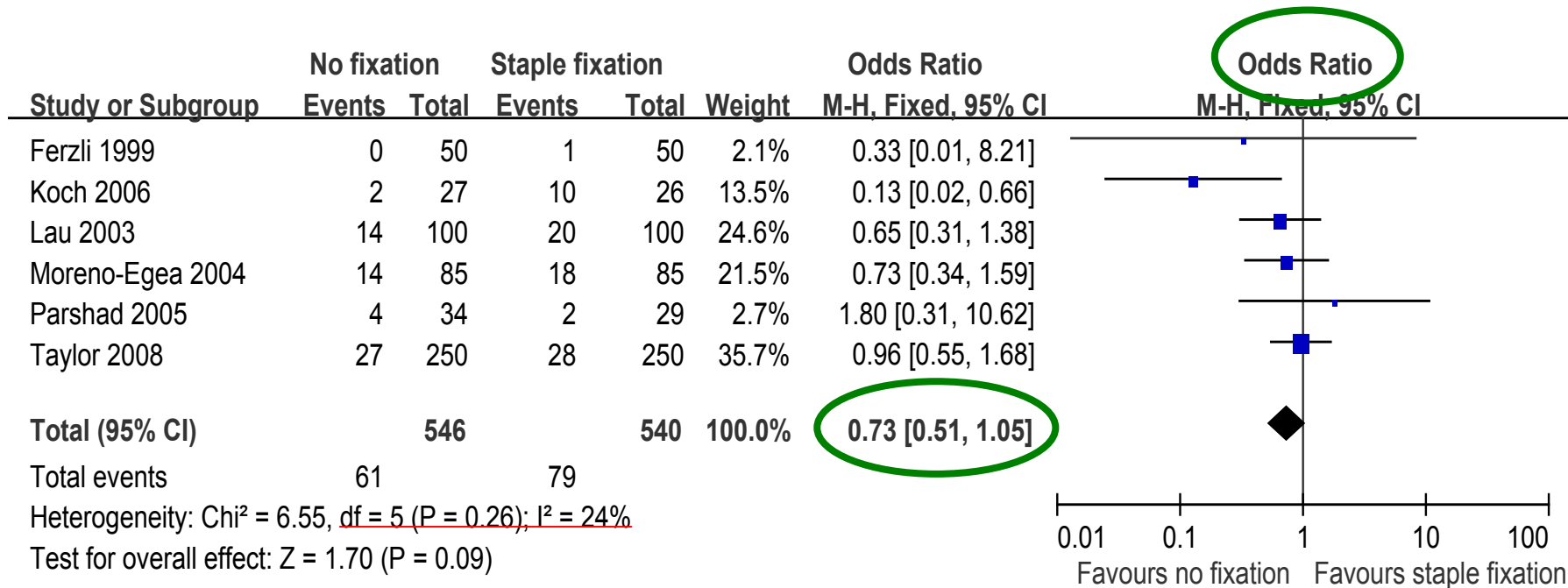Discuss and conclude overall findings

Systematic Review

Dissemination

Meta-Analysis

- Statistical procedure for combining data from multiple studies

- When treatment effect is consistent from one study to the next, meta-analysis can be used to identify this common effect

- When the effect varies from one study to the next, meta-analysis may be used to identify the reason for the variation

Forest plot: Morbidity

Study or Subgroup	No fixation Events	Total	Staple fixation Events	Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferzli 1999	0	50	1	50	2.1%	0.33 [0.01, 8.21]
Koch 2006	2	27	10	26	13.5%	0.13 [0.02, 0.66]
Lau 2003	14	100	20	100	24.6%	0.65 [0.31, 1.38]
Moreno-Egea 2004	14	85	18	85	21.5%	0.73 [0.34, 1.59]
Parshad 2005	4	34	2	29	2.7%	1.80 [0.31, 10.62]
Taylor 2008	27	250	28	250	35.7%	0.96 [0.55, 1.68]
Total (95% CI)		546		540	100.0%	**0.73 [0.51, 1.05]**
Total events	61		79			

Odds Ratio M-H, Fixed, 95% CI

Heterogeneity: Chi² = 6.55, df = 5 (P = 0.26); I² = 24%

Test for overall effect: Z = 1.70 (P = 0.09)

0.01 0.1 1 10 100

Favours no fixation   Favours staple fixation

Research

Primary

- Recruits patients for their data
- Screens patients for inclusion/ exclusion
- Records/ extracts patient data
- Statistical analysis on the data to compare the available data
- Explains its results in comparison to other published research

Secondary

- Recruits for patient data in evidence reports
- Screens evidence reports for inclusion/ exclusion
- Extracts data from evidence reports
- Statistical analysis on the data to compare the available data
- Explains not only its results, but also compares the heterogeneity of the included research

Differences between Narrative Reviews and Systematic Reviews

Feature	Narrative Review	Systematic Review
Question	Often broad in scope	Often a focused clinical question
Sources and search	Not usually specified, potentially biased	Comprehensive sources and explicit search strategy
Selection	Not usually specified, potentially biased	Criterion-based selection, uniformly applied
Appraisal	Variable	Rigorous critical appraisal
Synthesis	Often a qualitative summary	Quantitative summary*
Inferences	Sometimes evidence-based	Usually evidence-based

* A quantitative summary that includes a statistical synthesis is a meta-analysis.

Cook D J et al. Ann Intern Med 1997;126:376-380

Characteristic	Narrative Review	Meta-analysis
Selection criteria	None	Explicit
Publication bias	Yes; no way to assess/deal	Yes; can be assessed
Quality of included studies	Subjective assessment	Systematic assessment
Weighting of studies	Subjective; Variable (size/significance)	Explicit; Objective; Consistent
Heterogeneity	Cannot be assessed	Systematic assessment
Flaw identification	By experts	By experts

Introduction to Meta-Analysis
2009 John Wiley & Sons, Ltd

Perform a Meta-analysis

- Download software

- Focus a good question

- Selection criteria

- Search strategy

- Study selection and data extraction

- Assess methodological quality

- Statistical Analysis

- Discussion

Software

- Comprehensive meta-analysis
- Review Manager 5
- STATA

Focus a good question

- Foreground question

- Therapy/Diagnosis/Prognosis/Etiology/Harm

- Tips:
  - 從Therapeutic question開始第一篇SR
  - 當臨床上有不同意見時，就PubMed一下吧
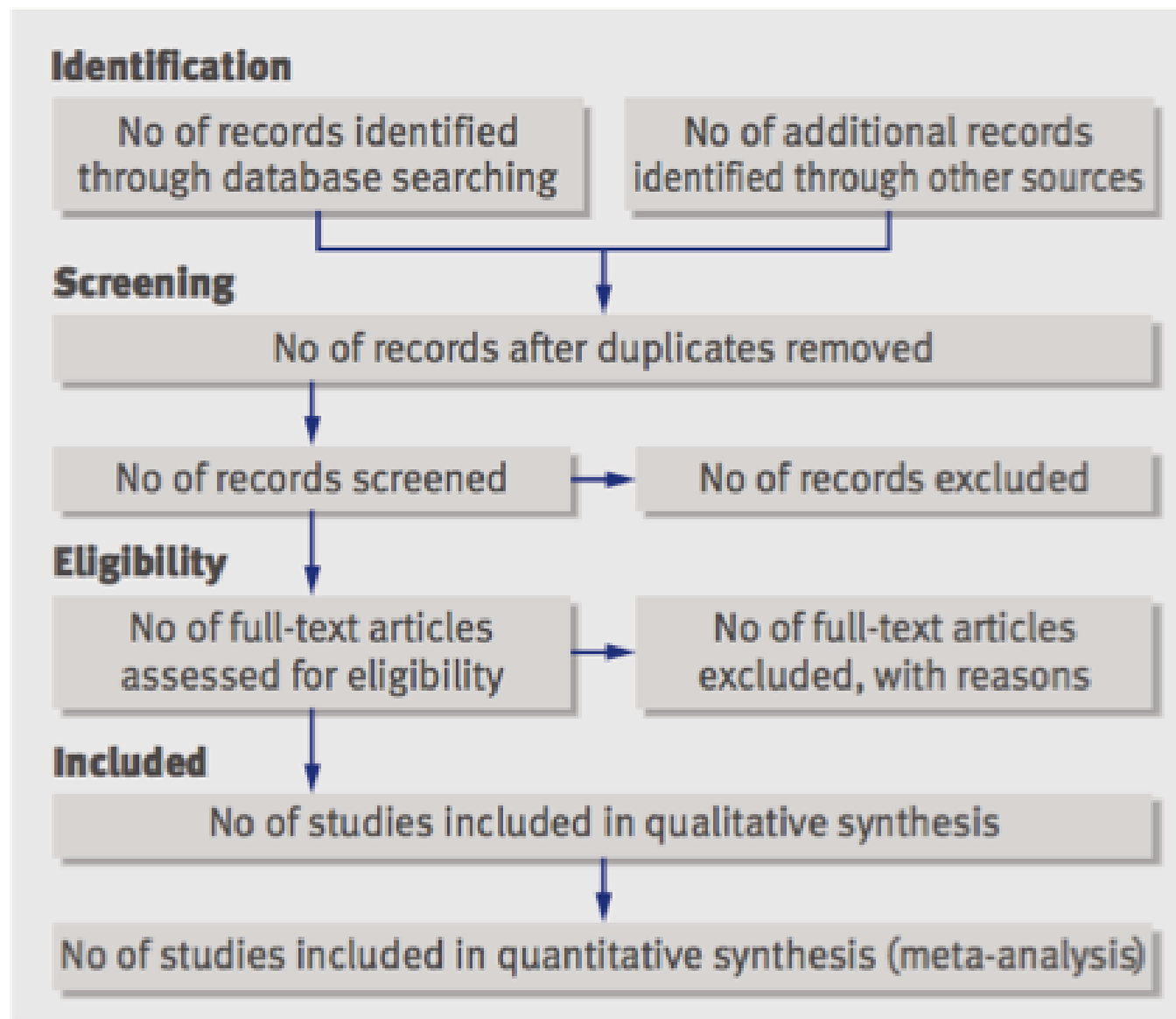 - 從小到大

Selection Criteria

Search strategy

- **Database:**
  - MEDLINE, PubMed, EMBASE, Cochrane databases, Others

- **Strategy:**
  - Randomized controlled trials
  - No language limitation
  - Last search: Date

Identification

No of records identified through database searching	No of additional records identified through other sources

Screening

No of records after duplicates removed

No of records screened	→	No of records excluded

Eligibility

No of full-text articles assessed for eligibility	→	No of full-text articles excluded, with reasons

Included

No of studies included in qualitative synthesis

No of studies included in quantitative synthesis (meta-analysis)

Flow of information through the different phases of a systematic review

Study selection and Data extraction

- **Two reviewers:**
  - Independent review (David, Peter) and then compare

- **Third reviewer:**
  - For any disagreements (Mary)

Table 1 Characteristics of the trials included in the meta-analysis

Study	Time of administration	Patients included in analysis (male/female)	Anesthetic technique	Co-intervention
Feroci 2010	20 mins before anesthesia	D 8 mg: 51 (16/35) versus P: 51 (17/34)	Propofol 2 mg/kg; fentanyl 2 μg/kg; vecurronium 0.1 mg/kg IV. Maintained with sevoflurane in oxygen.	Analgesia: Paracetamolo 1000 mg IV Q8H; ketorolac 30 mg IV Q12H prn. Antiemetics: Metoclopramide 10 mg IV; second line ondansetron 4 mg IV.
Fujii 2007	End of Surgery	D 8 mg: 25 (7/18) versus D 4 mg: 25 (6/19) versus P: 25 (7/18)	Propofol 2 mg/kg; fentanyl 2 μg/kg; vecurronium 0.1 mg/kg IV. Maintained with 1-3% sevoflurane in oxygen.	Analgesia: Indomethacin 50 mg rectally Antiemetics: Oral ranitidine 150 mg
Lee 2001	Before anesthesia	D 8 mg: 43 (0/43) versus D 5 mg: 45 (0/45) versus P: 44 (0/44)	Glycopyrrolate 0.2 mg ; fentanyl 2 μg/kg ; thiopental 5 mg/kg IV. Maintained with desflurane in oxygen.	Analgesia: Ketorolac 15 mg IV Q6H Antiemetics: Droperidol 1.25 mg IV
Wang 1999	1 min before anesthesia	D 10 mg: 38 (0/38) versus Do 1.25 mg: 40 (0/40) versus P: 38 (0/38)	Propofol 2-2.5 mg/kg; glycopyrrolate 0.2 mg; fentanyl 2 μg/kg IV. Maintained with isoflurane in oxygen.	Analgesia: Diclofenac 75 mg IM Q12H Antiemetics: Ondansetron 4 mg IV
Worni 2008	45 mins before anesthesia	D 8 mg: 37 (7/30) versus P: 35 (12/23)	Propofol/thiopental, atracurium, isofluran or sevofluran and fentanyl (5-10 μg/kg).	Analgesia: Acetaminophen 4g/day; second line metamizol or morphine 1 g. Antiemetics: Ondansetron 4 mg IV; second line droperidol 0.625 mg IV.

D, dexamethasone; Do, droperidol; M, morphine; P, placebo; IV, intravenous; IM, intramuscular.

Table 2 Methodological quality assessment of selected trials

Study	Country	Allocation generation	Allocation concealment	Blinding	Loss of follow-up (%)	Data analysis	Other biases
Agarwal *et al.*	India	Computer-generated	Adequate	Assessor blinded	2.5	PP	Obvious taste differences of experimental drugs
Gulas *et al.*	Turkey	Number table	Unclear	Triple	0	ITT	Unclear
Huang *et al.*	Taiwan	Unclear	Unclear	Triple	1	PP	Unclear
Hung *et al.*	Taiwan	Sealed envelopes	Adequate	Triple	11	PP	Unclear
Katı *et al.*	Turkey	Randomized sequence	Unclear	Triple	0	ITT	Unclear

ITT = intention-to-treat; PP = per-protocol

Statistical Analysis

- Review Manager version 5 (Cochrane Collaboration)
- Dichotomous (Mantel-Haenszel)
  - Odd ratio/Risk ratio
- Continuous (Inverse Variance)
  - weight mean difference/standard mean difference
- Generic Inverse Variance (Inverse Variance)
  - Hazard ratio
- Statistical heterogeneity: Cochran's Q statistic test and I^2 test

Pooling of Data

- Pain score:
  - Study 1: 0-10   VAS
  - Study 2: 0-100 VAS
  - Study 3: none / mild / moderate / severe

- Outcome after hernioplasty:
  - Study 1: Loss of sensation
  - Study 2: Loss of touch / Loss of pain
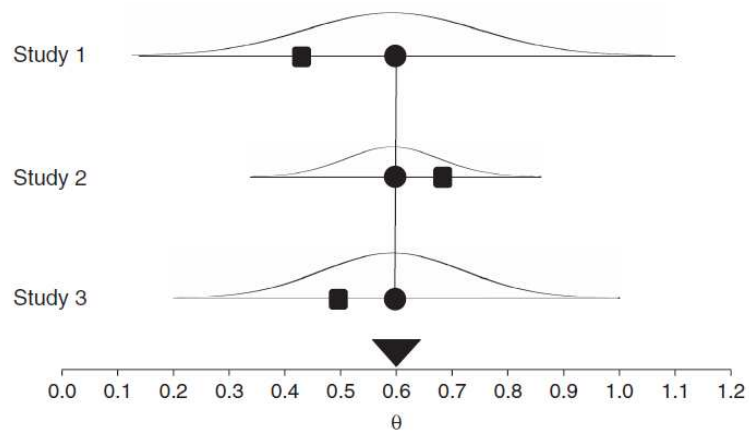
Statistic Analysis

- Fixed effect model
- Random effect model

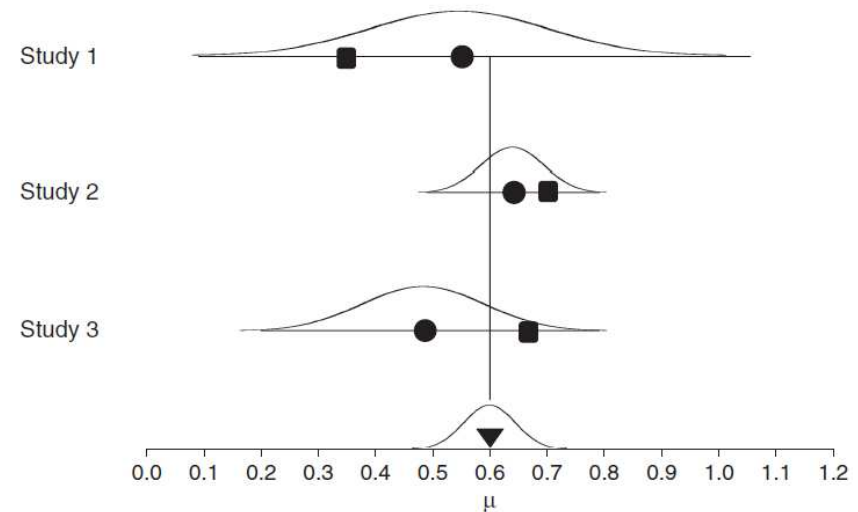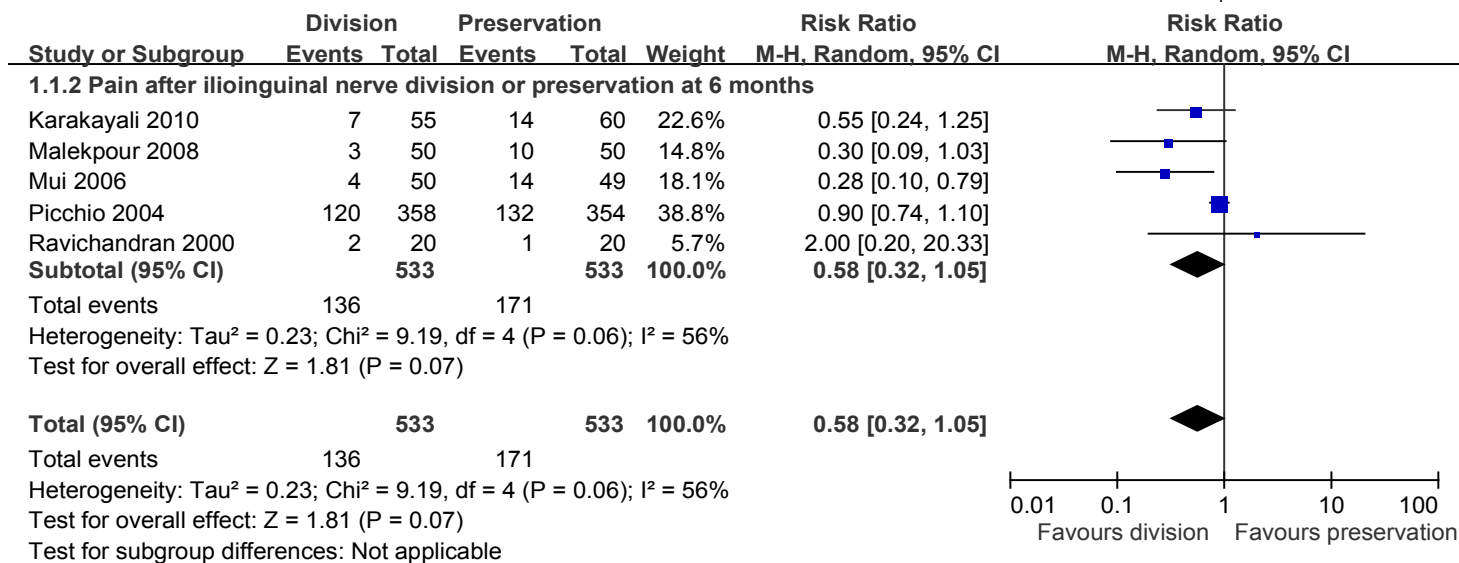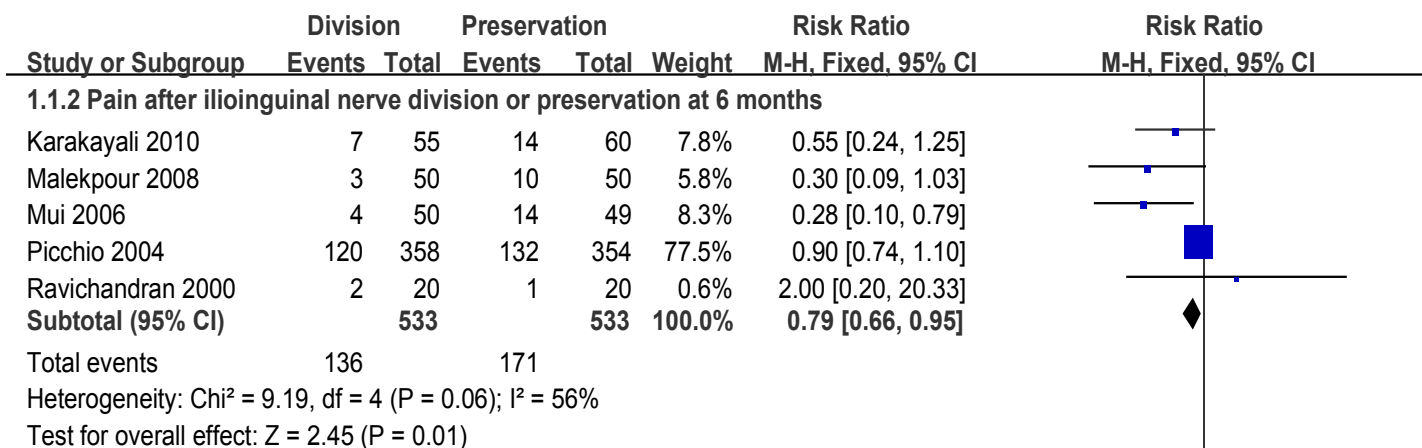Figure 11.3 Fixed-effect model – distribution of sampling error.

Figure 12.4 Random-effects model – between-study and within-study variance.
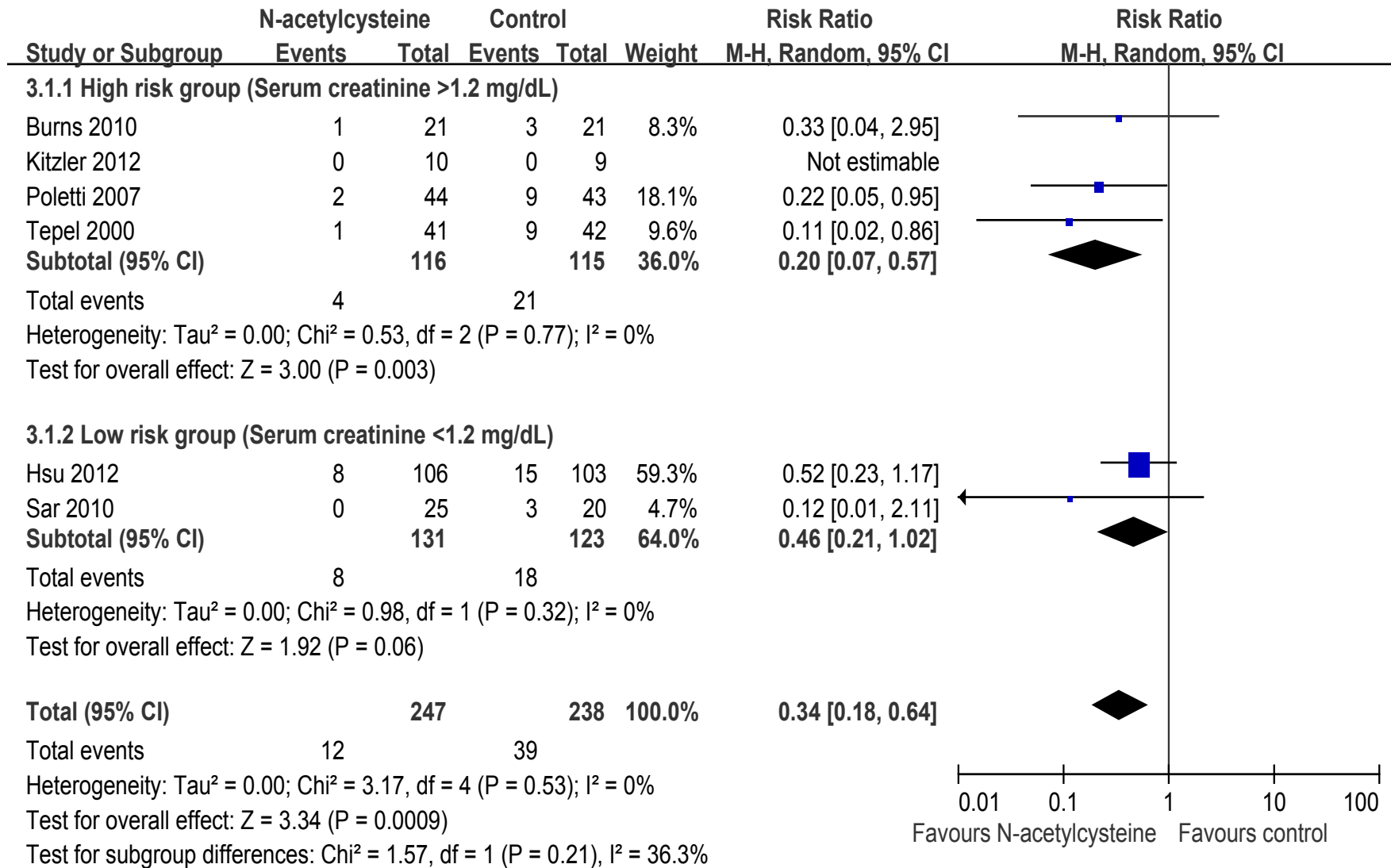
Fixed versus Random model

Study or Subgroup	Division Events	Total	Preservation Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.2 Pain after ilioinguinal nerve division or preservation at 6 months						
Karakayali 2010	7	55	14	60	7.8%	0.55 [0.24, 1.25]
Malekpour 2008	3	50	10	50	5.8%	0.30 [0.09, 1.03]
Mui 2006	4	50	14	49	8.3%	0.28 [0.10, 0.79]
Picchio 2004	120	358	132	354	77.5%	0.90 [0.74, 1.10]
Ravichandran 2000	2	20	1	20	0.6%	2.00 [0.20, 20.33]
Subtotal (95% CI)		**533**		**533**	**100.0%**	**0.79 [0.66, 0.95]**
Total events	136		171			

Heterogeneity: Chi² = 9.19, df = 4 (P = 0.06); I² = 56%

Test for overall effect: Z = 2.45 (P = 0.01)

Study or Subgroup	Division Events	Total	Preservation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.2 Pain after ilioinguinal nerve division or preservation at 6 months						
Karakayali 2010	7	55	14	60	22.6%	0.55 [0.24, 1.25]
Malekpour 2008	3	50	10	50	14.8%	0.30 [0.09, 1.03]
Mui 2006	4	50	14	49	18.1%	0.28 [0.10, 0.79]
Picchio 2004	120	358	132	354	38.8%	0.90 [0.74, 1.10]
Ravichandran 2000	2	20	1	20	5.7%	2.00 [0.20, 20.33]
Subtotal (95% CI)		**533**		**533**	**100.0%**	**0.58 [0.32, 1.05]**
Total events	136		171			

Heterogeneity: Tau² = 0.23; Chi² = 9.19, df = 4 (P = 0.06); I² = 56%

Test for overall effect: Z = 1.81 (P = 0.07)

Total (95% CI)		**533**		**533**	**100.0%**	**0.58 [0.32, 1.05]**
Total events	136		171			

Heterogeneity: Tau² = 0.23; Chi² = 9.19, df = 4 (P = 0.06); I² = 56%

Test for overall effect: Z = 1.81 (P = 0.07)

Test for subgroup differences: Not applicable

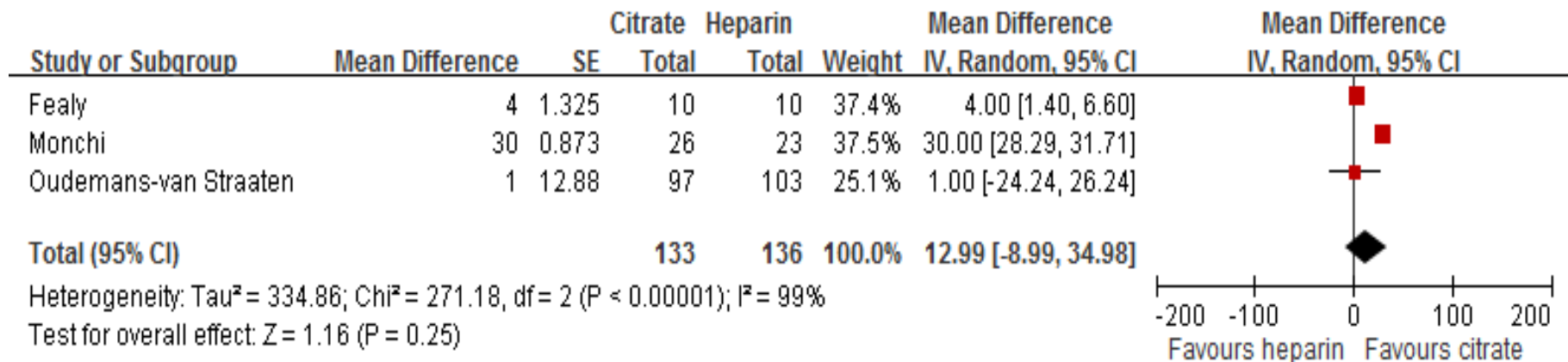Favours division   Favours preservation

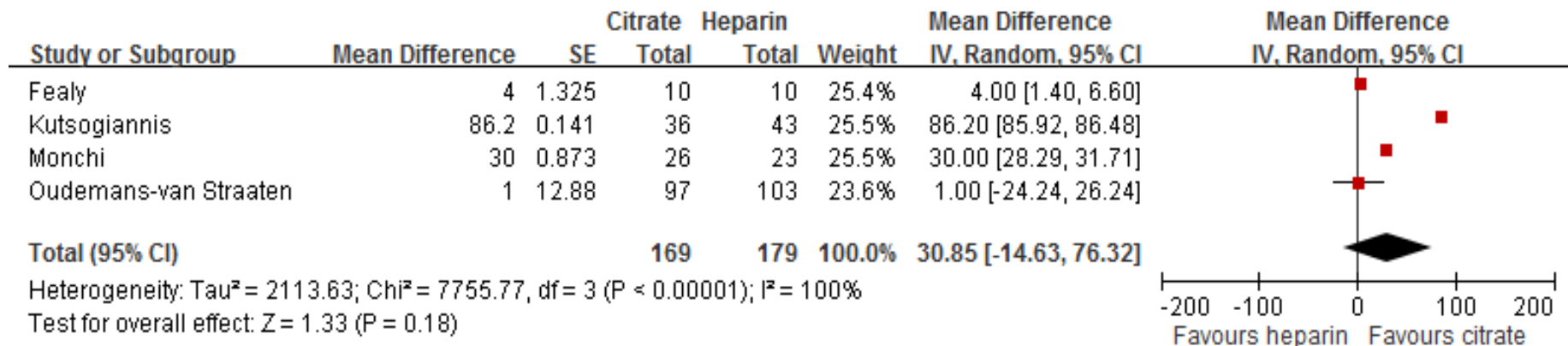# Heterogeneity

- Eyeball test
- Cochran chi-square (X^2: Cochran Q)
- $I^2 = (Q-df) / Q \times 100\%$

Subgroup analysis

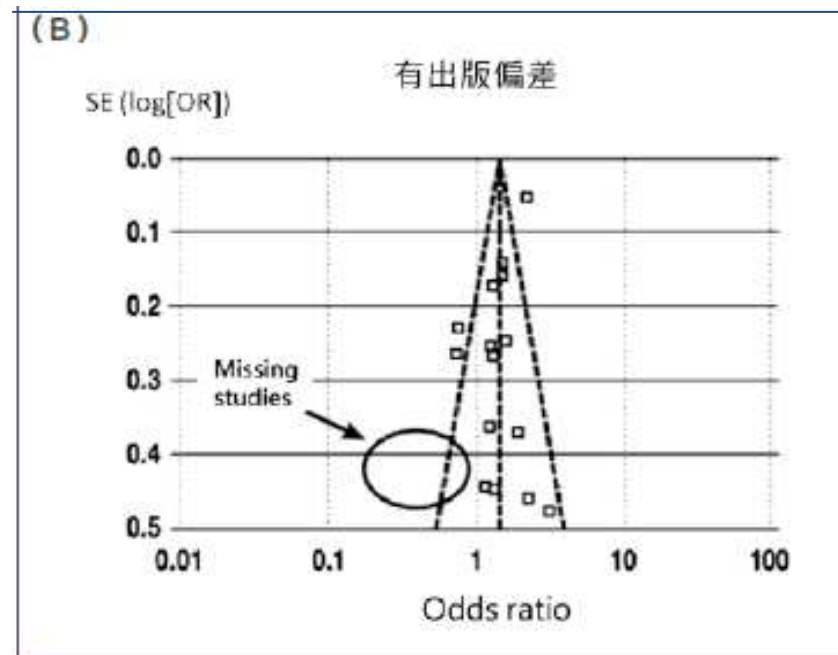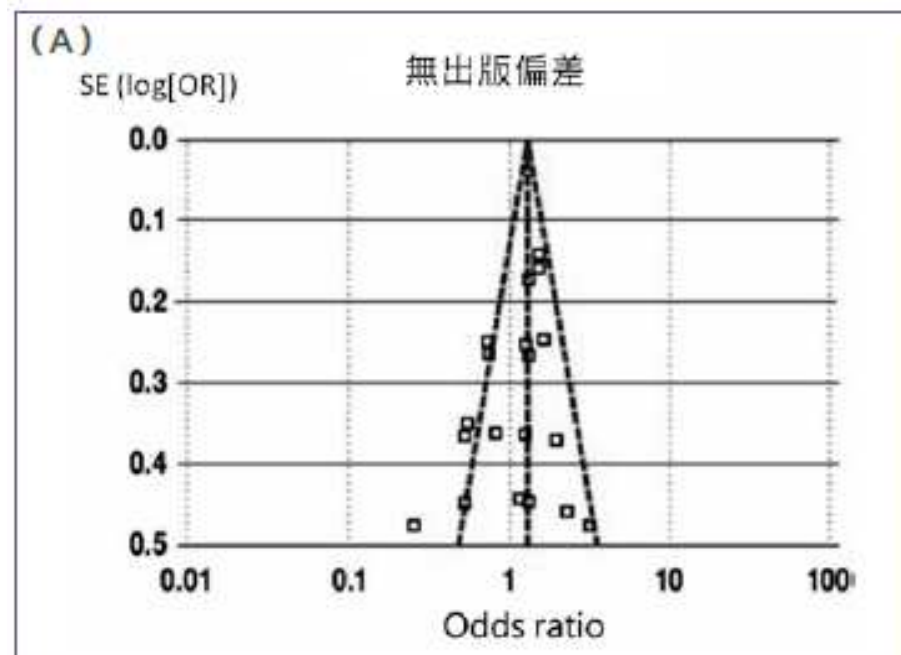| Study or Subgroup	N-acetylcysteine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 High risk group (Serum creatinine >1.2 mg/dL)						
Burns 2010	1	21	3	21	8.3%	0.33 [0.04, 2.95]
Kitzler 2012	0	10	0	9		Not estimable
Poletti 2007	2	44	9	43	18.1%	0.22 [0.05, 0.95]
Tepel 2000	1	41	9	42	9.6%	0.11 [0.02, 0.86]
Subtotal (95% CI)		**116**		**115**	**36.0%**	**0.20 [0.07, 0.57]**
Total events	4		21			

Heterogeneity: Tau² = 0.00; Chi² = 0.53, df = 2 (P = 0.77); I² = 0%

Test for overall effect: Z = 3.00 (P = 0.003)

Study or Subgroup	N-acetylcysteine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.2 Low risk group (Serum creatinine <1.2 mg/dL)						
Hsu 2012	8	106	15	103	59.3%	0.52 [0.23, 1.17]
Sar 2010	0	25	3	20	4.7%	0.12 [0.01, 2.11]
Subtotal (95% CI)		**131**		**123**	**64.0%**	**0.46 [0.21, 1.02]**
Total events	8		18			

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 1 (P = 0.32); I² = 0%

Test for overall effect: Z = 1.92 (P = 0.06)

Study or Subgroup	N-acetylcysteine Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)		**247**		**238**	**100.0%**	**0.34 [0.18, 0.64]**
Total events	12		39			

Heterogeneity: Tau² = 0.00; Chi² = 3.17, df = 4 (P = 0.53); I² = 0%

Test for overall effect: Z = 3.34 (P = 0.0009)

Test for subgroup differences: Chi² = 1.57, df = 1 (P = 0.21), I² = 36.3%

Risk Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100

Favours N-acetylcysteine   Favours control

Sensitivity analysis

Assessment of publication bias

- Egger test / Begg test
- Funnel plot

Discussion

- Summarize the main findings and the strength of evidence of each outcome

- Consider the relevant to the key groups

- Explain the heterogeneity of included studies

- Discuss limitations

- Provide conclusion of the results and implications for future research

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Tips of Writing Systematic Review

- 心動不如馬上行動
- Ask a focus clinical question
- 從小到大
- 從therapeutic study開始
- 到市場(PubMed)逛逛，再決定燒甚麼菜
- 關鍵是inclusion and exclusion criteria
- 優先建立table of characteristics of included trials與table of outcomes
- Extraction and pooling of data常是最有爭議的地方
- Discussion要有建設性，不離題
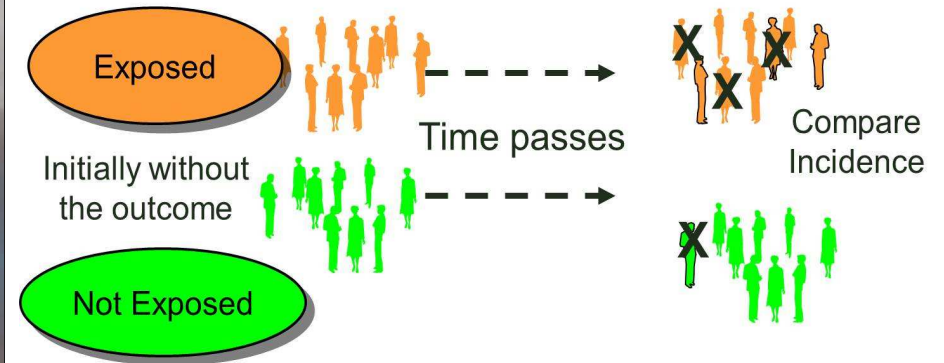- Systematic review是根基，meta-analysis是枝葉
- 快！快！快！

Meta-analysis

- 三大迷思：
  - Only about RCTs?
  - Results are similar, nothing news?
  - No study, no news?

- 一大爭議：
  - *Review* or *Original research*?

What authors DO

Identify the issue and determine the question

Write a plan for the review (protocol)

Search for studies

Sift and select studies

Extract data from the studies

Assess the quality of the studies

Combine the data (synthesis or meta-analysis)

Discuss and conclude overall findings

Systematic Review

Dissemination
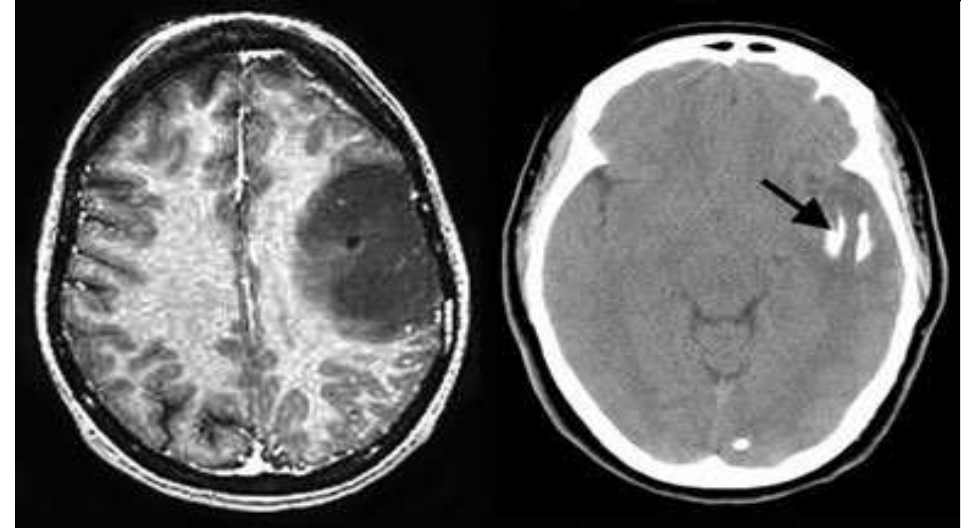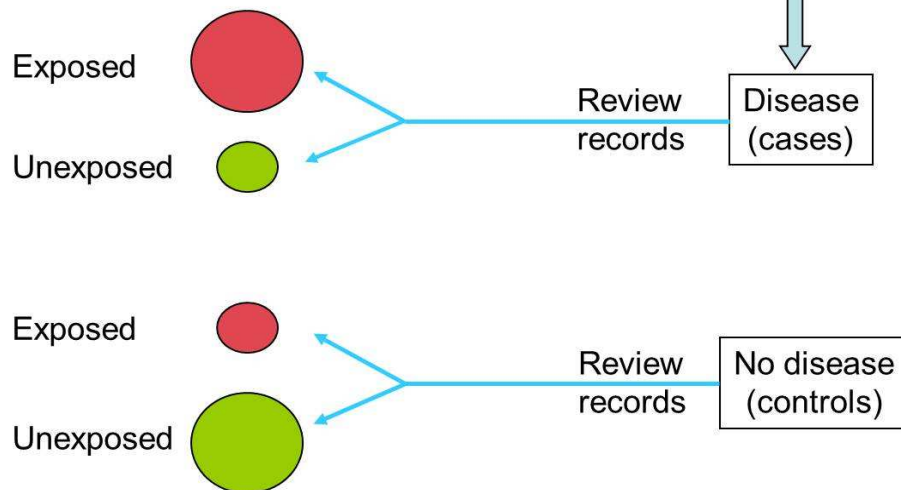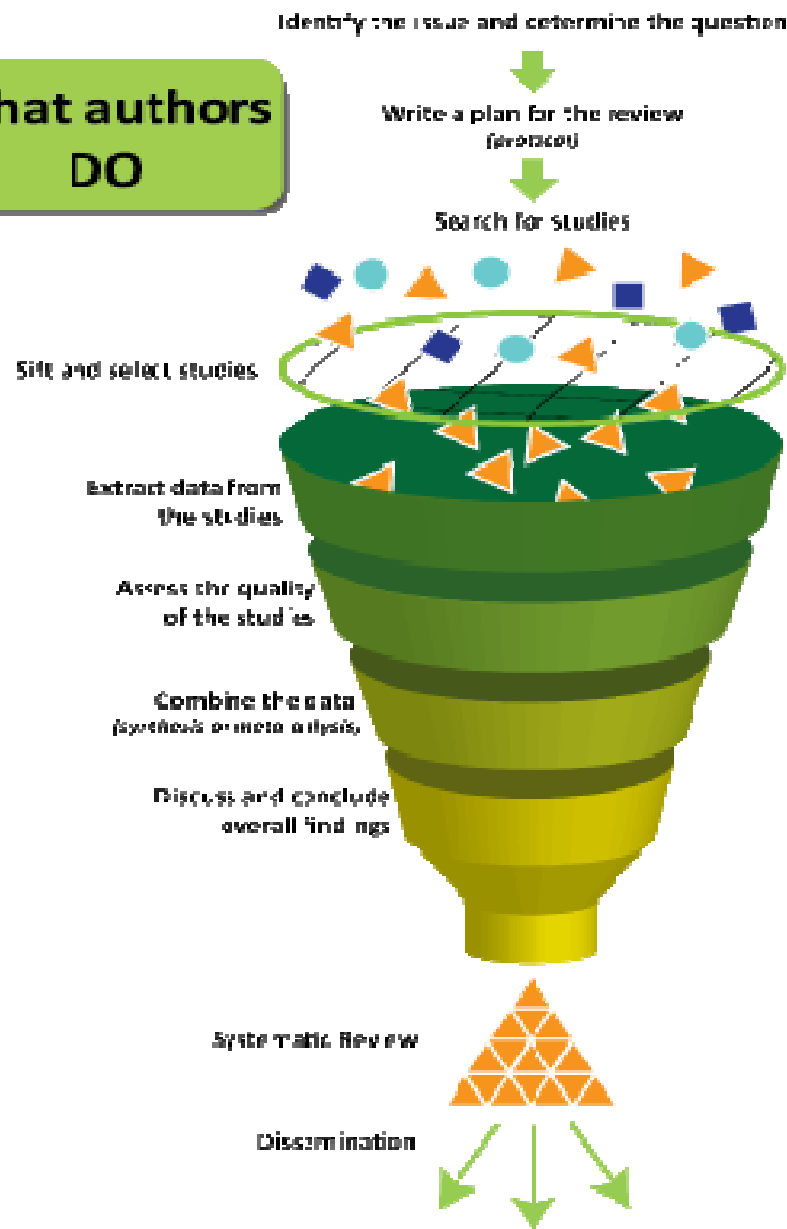
The Concept of a Systematic Review

Studies

Systematic review process

Systematic Review

Gastric cancer with C-spine metastasis

Patient positioning (mobilisation) and bracing for pain relief and spinal stability in metastatic spinal cord compression in adults (Review)

THE COCHRANE COLLABORATION®

Main results

One thousand, six hundred and eleven potentially relevant studies were screened. No studies met the inclusion criteria. Many papers identified the importance of mobilisation but no RCTs have been undertaken. No RCTs of bracing in MSCC were identified.

Authors' conclusions

There is lack of evidence based guidance around how to correctly position and when to mobilise patients with MSCC or if spinal bracing is an effective technique for reducing pain or improving quality of life. RCTs are required in this important area.

Meta-analysis

- *Review* or *Original research*?

Individual patient data

Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials

Early Breast Cancer Trialists' Collaborative Group (EBCTCG)*

Lancet 2011; 378:771-84
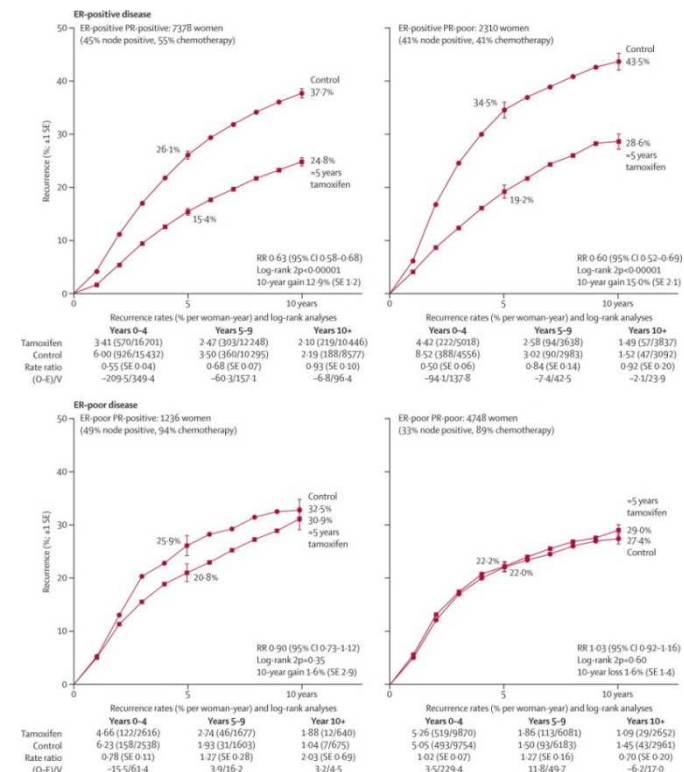
Network Meta-analysis

Effect of Noninsulin Antidiabetic Drugs Added to Metformin Therapy on Glycemic Control, Weight Gain, and Hypoglycemia in Type 2 Diabetes
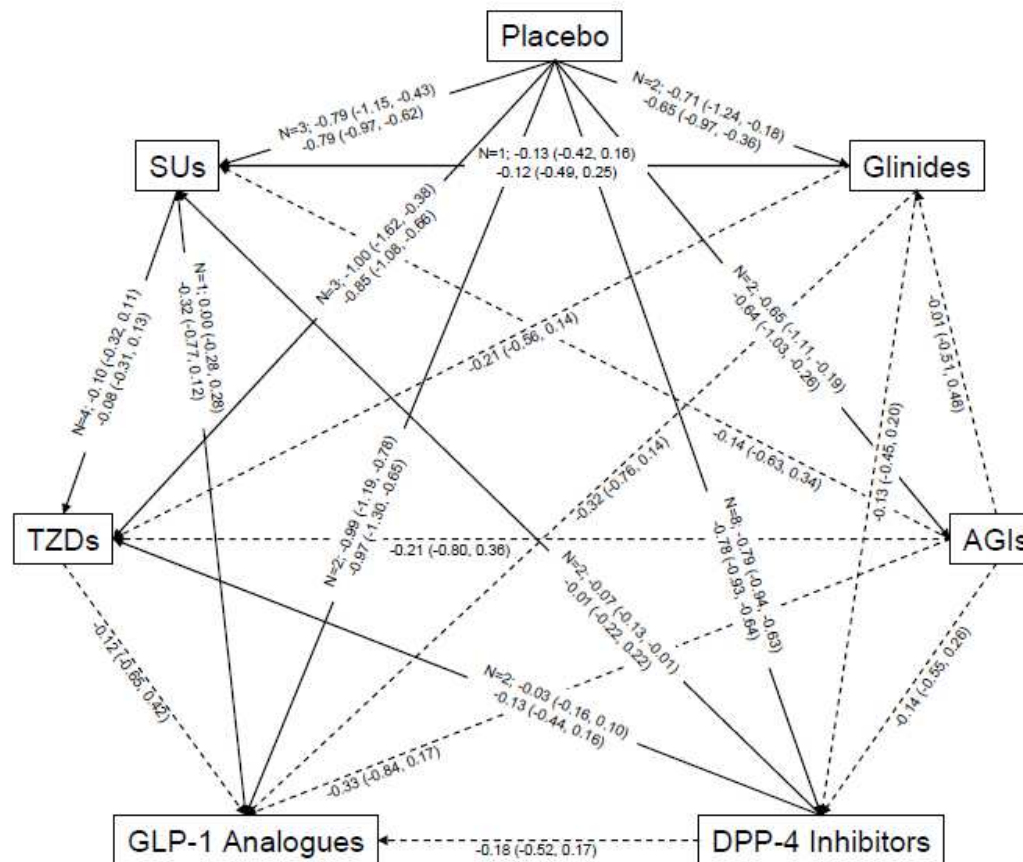
Different Types of Dry Laboratory

- Epidemiologic survey
- Database
  - National Health Insurance Research Database
- Systematic Review
- Others

Systematic Reviews *versus* Other Dry labs.

- Clinical-based
- More interesting
- Easily to obtain data
- Self-controlled
- Saving Money
- Quick
- Evidence-based practice

The paths from research to improved health outcomes
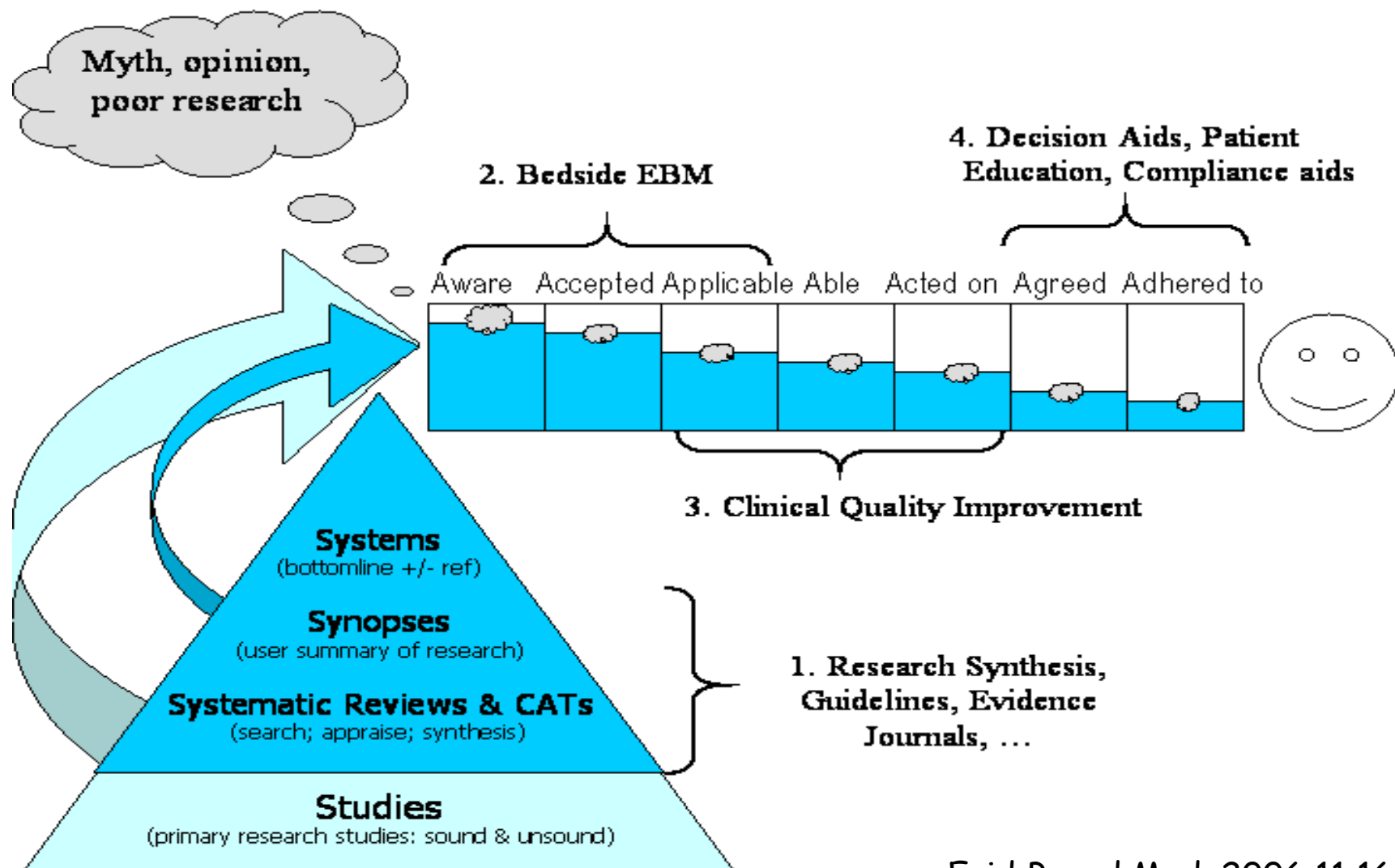
Bed rest for 8 hours?
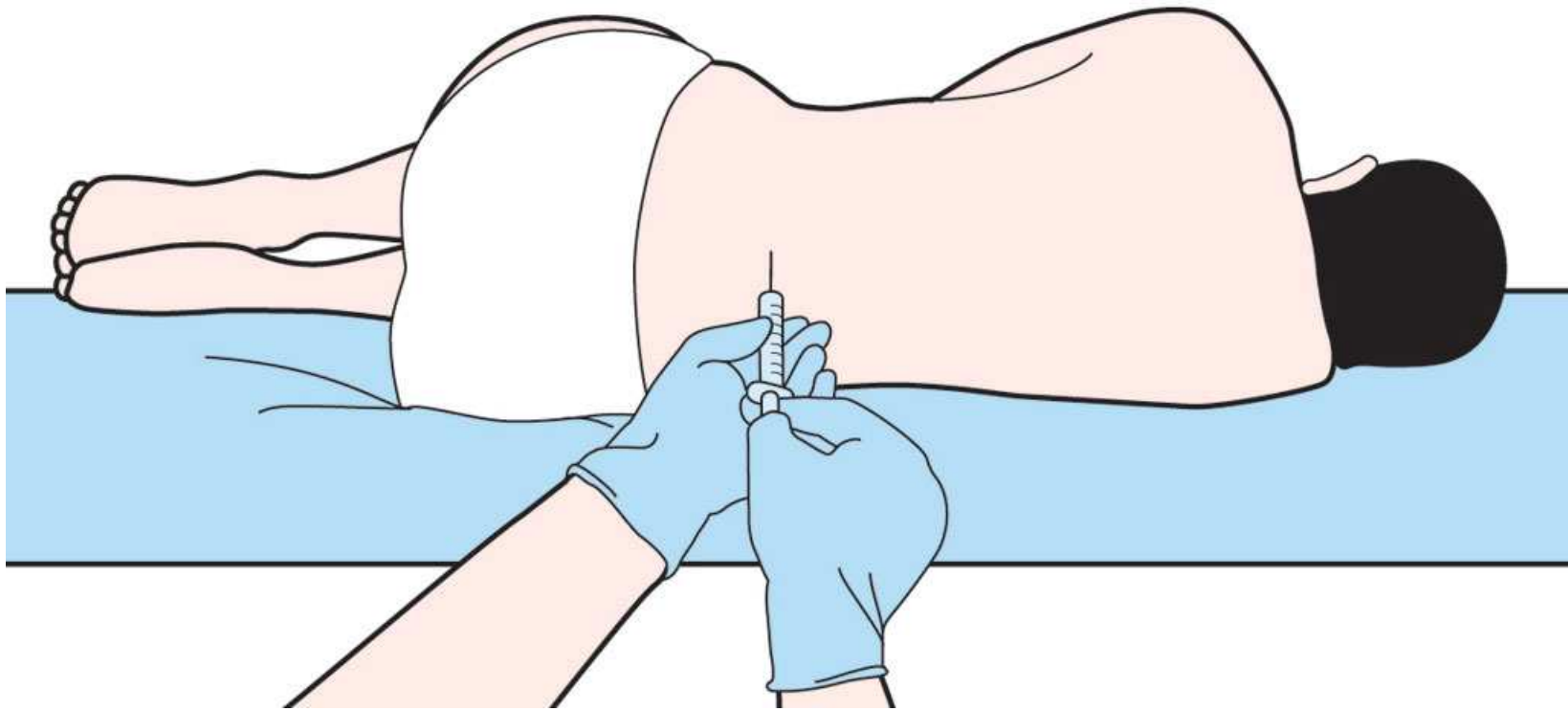
Does bed rest after cervical or lumbar puncture prevent headache?
A systematic review and meta-analysis

恢復室紀錄

病歷號碼：　床號：
姓　名：　性別：
出生日期：　年　月　日

　　　　年　月　日

進入時間	診斷		氧療法 ☐氣導管 ☐呼吸器 ☐面罩 ☐其他： ☐T-piece	恢復室醫師	恢復室護理師(士)
離開時間	手術名稱				

麻醉方式	麻醉後恢復指數	入	出			
☐GAET ☐EA				O₂ (L/min)		
☐GA Mask ☐TCI	意識			Fluid		
☐LMA#	清醒　　2			Blood		
☐IVG ☐Standby	嗜睡或煩躁 1 0			Drain		
☐Nerve block	無反應　　0			Urine		
☐SA Level	呼吸			Time		
入：	能深呼吸或咳嗽 2					
出：	淺快或深慢、喘鳴聲 1					
平躺到 ✕	呼吸暫停 0					
臥床	活動					
	移動四肢及軀體 2					
用儀器	移動兩肢　　1					
☐EKG+SpO₂	不能移動　　0					
☐NIBP	循環					
☐Bair-hugger	血壓在正常20%內 2					
☐烤燈	血壓在±21-49%內 1					
☐CVP	血壓超過±50% 0					
☐IBP	膚色					
☐其他	粉紅　　2					
OPD衛教	灰白　　1					
簽名	發紺　　0					
時間	*總分					

區域(半身)麻醉

1. 醫護人員會幫您接上基本監視器，包括心電圖、血壓計以及血氧飽和濃度測量儀器，以保障您的術中安全。

2. 麻醉醫師會依照您的情況給予適當的鎮定劑，以減輕您的焦慮或不適。

3. 醫護人員會協助您側睡，並將膝蓋及大腿盡量貼近腹部，把背拱出。

4. 麻醉醫師會從您的脊椎注入麻醉藥物。

5. 手術後請盡量平躺6-8小時，勿睡枕頭也不要將頭抬高及坐起，但可以左右側睡，以避免麻醉後發生頭痛。

Systematic review ???

Thank you for your attention!