중재 연구에 관한 체계적 고찰 관점에서의 메타분석

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Meta-analysis in a Systematic Review for Interventional Studies

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Contents

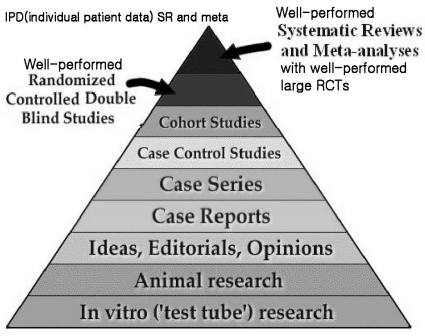
2

EBM과 SR

- **Evidence-based decision making**
  - 적절하고 신뢰할만한 연구결과들을 이용
    - 더 나은 public policy 및 decision making 보장
    - 이에 관한 measures를 개발하기 위한 international interest 증가
- **Evidence-based medicine (EBM)**
  - 각 환자에게 필요한 치료를 결정할 때 '최신'의, 그리고 '최상'의 "근거"를 '면밀' 하고 '명료'하며 '사려 깊게' 사용하자.
  - Execution: 아래 두 근거를 종합하여 결정
    - 내적 근거: 각 의사들의 '전문가적 지식' / 외적 근거: '체계적 문헌고찰' 결과
- **Evidence-based healthcare (EBH)**
  - EBM 전략을 healthcare delivery 측면으로 확대한 새로운 개념
  - Current best evidence, 즉, 여러 형태의 healthcare policy들의 relevant하고 valid한 결과들을 up-to-date 한 information을 활용
- **Evidence-based nursing (EBN)**
  - Nursing decisions 결정 시, patient preferences 및 clinical experience 등과 더불어, research로 부터 얻어지는 best available evidence를 사용
    - Cullum et al. Implementing evidence-based nursing: some misconceptions [editorial] Evidence-Based Nursing 1998;1:38-40.

3

Evidence level of researches



4

EBM / EBH strategy

- 권고(지침, guideline)의 범위 결정
- 핵심질문 (key question) 도출
- 문헌 검색 / 문헌 선택
  - ✓ 문헌의 inclusion/exclusion criteria 설정
  - ✓ 문헌 찾기, 문헌 선별
- 문헌 평가 및 근거 종합
  - ✓ 편향위험도(연구의 질) 평가
  - ✓ 자료 추출
  - ✓ 결과 종합
- 등급화(grading) 및 권고안 도출(recommendation)

Meta-analysis (MA) ⊂ Systematic review (SR) ⊂ EBM, EBN, EBH

- Sackett DL et al. Evidence based medicine: what is it and what it isn't. BMJ 1996;312:71-72

5

10 Steps in conducting a Systematic Review

Step 1. Review의 필요성(need) 확인	- CDSR / HTA	Preparing the review
Step 2. 연구계획서(protocol) 준비	- Estimate efforts - Prepare a proposal (protocol)	
Step 3. Review question을 구체화	- PICOTS	
Step 4. 관련 논문들 탐색 (locating)	- CCTR / other DB / references / hand search / personal contact	Conducting the review
Step 5. 관련 논문들 선택 (selection)	- More than one observer - Develop strategy for disagreement - Log for exclusion and its reasons	
Step 6. Risk of bias (study quality)평가	- More than one observer - Domain evaluation / Checklists (?)	
Step 7. 자료 추출 (data extraction)	- Design & pilot data extraction form - More than one observer - Consider blinding of observers	
Step 8. 자료 합성 (pooling)	- Tabulate and pooling results - Check small study effects (publication bias) - Explore heterogeneity / subgroups - Perform sensitivity analyses	
Step 9. 결과 해석 및 보고 (reporting)	- Strength and limitations - Strength of evidence / applicability - Economic implications	Reporting and dissemination
Step 10. Evidence를 practice에 적용	- Clinical practice implication - Future research implication	

6

An example paper (1)

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Meta-Analysis

Meng Lee, MD; Bruce Ovbiagele, MD, MS; Keun-Sik Hong, MD; Yi-Ling Wu, MS;
Jing-Er Lee, MD, PhD; Neal M. Rao, MD; Wayne Feng, MD; Jeffrey L. Saver, MD

Background and Purpose—Elevated blood pressure is common in acute stage of ischemic stroke and the strategy to manage this situation is not well established. We therefore conducted a meta-analysis of randomized controlled trials comparing active blood pressure lowering and control groups in early ischemic stroke.
Methods—Pubmed, EMBASE, and Clinicaltrials.gov from January 1966 to March 2015 were searched to identify relevant studies. We included randomized controlled trials with blood pressure lowering started versus control within 3 days of ischemic stroke onset. The primary outcome was unfavorable outcome at 3 months or at trial end point, defined as dependency or death, and the key secondary outcome was recurrent vascular events. Pooled relative risks and 95% confidence intervals were calculated using random-effects model.
Results—The systematic search identified 13 randomized controlled trials with 12 703 participants comparing early blood pressure lowering and control. Pooling the results with the random-effects model showed that blood pressure lowering in early ischemic stroke did not affect the risk of death or dependency at 3 months or at trial end point (relative risk, 1.04; 95% confidence interval, 0.96–1.13; P=0.35). Also, blood pressure lowering also had neutral effect on recurrent vascular events, as well as on disability or death, all-cause mortality, recurrent stroke, and serious adverse events.
Conclusions—This meta-analysis suggested blood pressure lowering in early ischemic stroke had a neutral effect on the prevention of death or dependency. (***Stroke*. 2015;46:1883-1889. DOI: 10.1161/STROKEAHA.115.009552.**)

7

An example paper (2)

BMJ 2010;341:c5702 **RESEARCH**

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials

Markus Schürks, instructor of medicine,[1] Robert J Glynn, associate professor of medicine and biostatistics,[1,3] Pamela M Rist, doctoral student in epidemiology,[1,2] Christophe Tzourio, senior director of research,[4,5] Tobias Kurth, director of research[1,2,4,5]

Objective To evaluate the effect of vitamin E supplementation on incident total, ischaemic, and haemorrhagic stroke.
Design Systematic review and meta-analysis of randomised, placebo controlled trials published until January 2010.

8

Step 1. Identify the need for a review

- Originality 확인
  - To avoid duplication of efforts, search for published and ongoing SR's including key databases:
    - CDSR (Cochrane Database of Systematic Review)
    - DARE (Database of Abstracts of Review Effects)
    - NICE (National Institute for Health and Clinical Excellence)
    - NIHR / HTA (National Institute for Health Research Health Technology Assessment)
    - Key journals in your specific area
- Consider biologic and scientific reasoning

너무나 정명한 분체에 기본 공은 소식을 드리면 더욱 기본 계몽이 있었을 것 같므데..
저 I am writing to you in regard to manuscript # bmjopen-2015-010220, "Serum uric acid and the development of metabolic syndrome: A dose-
응 response meta-analysis of 16 cohort studies" which you submitted to BMJ Open. Your manuscript has been evaluated and has been declined
그 for publication in BMJ Open.

J Clin Endocrinol Metab. 2015 Aug 26:jc20152527. [Epub ahead of print]
Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-analysis of Prospective Studies.
Sci Rep. 2015 Sep 23;5:14525. doi: 10.1038/srep14525.
Yuan H[1], Yu C[2,3], Li X[1], Sun L[1], **Dose-response Relationship of Serum Uric Acid with Metabolic Syndrome and Non-alcoholic Fatty Liver Disease Incidence: A Meta-analysis of Prospective Studies.**
Liu Y[1,2,3], Qiao S[4], Zhou L[1,2,3], Zheng S[1,2,3]

9

Identify the need for a review

- Biological reasoning 'and/or' research reasoning

Effect of Blood Pressure Lowering in Early Ischemic Stroke
***Stroke*. 2015;46:1883-1889**

Elevated blood pressure is common in acute stage of ischemic stroke, occurring in two thirds to three quarters of patients.[1,2] The early hypertension that follows ischemic stroke often reflects undiagnosed or undertreated hypertension as well as neuroendocrine response to physiological stress.[3] Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke.[4] The best strategy to manage this early elevation of blood pressure in patients with ischemic stroke is not well established.[4] On one

Accordingly, randomized controlled trials (RCTs) are needed to clarify optimum blood pressure management regimens in early ischemic stroke. A systematic review and meta-analysis through 2008 identified 12 small RCTs, which

3 days of stroke onset. Several large trials have been published in the interval since the most recent meta-analysis[5] and offer more evidence on this issue. We therefore conducted a sys-

10

Step 2. Prepare a protocol for a review

- Protocol
  - A written document
    - Including background information, the specific research question, and the methodology of the review
- Systematic reviews
  - Range widely in complexity and the amount of work involved
- Need to estimate efforts
  - Roughly estimate the number of studies that can be expected by searching one database
    - The Cochrane Controlled Trial Register (CCTR)
    - General database (e.g. MEDLINE, EMBASE)

11

Box 2.2.a: Sections of a protocol for a Cochrane review

Title*
Protocol information:
- Authors*
- Contact person*
- Dates
- What's new
- History

The protocol:
- Background*
- Objectives*
- Methods:
  - Criteria for selecting studies for this review:
    - Types of studies*
    - Types of participants*
    - Types of interventions*
    - Types of outcome measures*
  - Search methods for identification of studies*
  - Data collection and analysis*
- Acknowledgements
- References:
  - Other references:
    - Additional references
    - Other published versions of this review
- Tables and figures:
  - Additional tables
  - Figures

Supplementary information:
- Appendices
- Feedback:
  - Title
  - Summary
  - Reply
  - Contributors

About the article:
- Contributions of authors
- Declarations of interest*
- Sources of support:
  - Internal sources
  - External sources
- Published notes

12

Step 3. Formulate a review question

- ***The most important part of the review!***
  - Important to think carefully in advance
  - Determines the IC/EC for the review
  - Helps design the search strategy
  - One way to avoid bias
- 구조화된 핵심질문 through **PICO(TS)**
  - Population
    - For which group do we need information?
  - Intervention (or Exposure)
    - What event do we need to study the effect for?
  - Comparison
    - What group do we want to compare an effect of intervention?
  - Outcomes
    - What is the effect of the intervention?
  - Time frame
  - Study design

13

An example for PICOTS

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

S, C (1) Randomised, placebo controlled design with a follow-up of ≥1 year

I, O (2) Investigating the effect of vitamin E on stroke incidence (total stroke or stroke subtypes)

P (3) Trial participants must be selected on clinical grounds

14

Step 4. Locating studies

- 문헌 검색 (literature searches)

NO SINGLE DATABASE is likely to contain all published studies on a given subject
- Zvi M, Chung KC. "Systematic Reviews: A Primer for plastic Surgery Research." PRS Journal. 120/7(2007)

  - 목적
    - 평가질문에 대한 답을 할 수 있는 적절한 문헌 찾기
  - 과정
    - 현재까지 동일한 주제로 출판된 SR 검색 →
    - 관련 문헌의 양을 추정하기 위한 준비검색 →
    - 평가질문에서 도출된 개념어를 조합한 시범검색 →
    - 관련분야 전문가 협의 후, 전략 결정
- COSI model

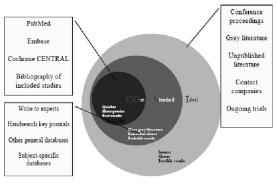


Fig. 1. 검색의 범위.

15

Search engines / terms

- Search Engines
  - All English and non-English articles!
  - Librarian!
  - *Cochrane Controlled Trials Register / CENTRAL*
  - *MEDLINE* (MEDlars onLINE) / PubMed
  - *EMBASE*
  - Specific journals (CINAHL, PsycLit, etc.)
  - Internet (portal): *Google scholar*
  - Searching reference lists
  - Contacting experts, Searching abstracts (gray literatures)
- Search terms
  - Medline: MeSH (Medical Subject Heading) terms
  - EMBASE: EMTREE terms
- Search tips
  - Develop strategies first for MEDLINE, then EMBASE, then CENTRAL
  - Peek Cochrane library (similar topics)
  - Focus on **P**, **I**, (**O**), **T**, **S** (maybe not for (**O**), **C**)

16

An example for DB's

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Data Sources and Searches
We systematically searched PubMed, EMBASE, and the clinical trial registry maintained at Clinicaltrials.gov from 1966 to March 10, 2015

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

METHODS
Data sources and searches
We followed the guidelines for reports of meta-analyses of randomised controlled trials according to the PRISMA statement.[21] Two investigators (MS and TK) independently searched Medline and Embase (from inception to January 2010) as well as the Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2010), combining text terms and,

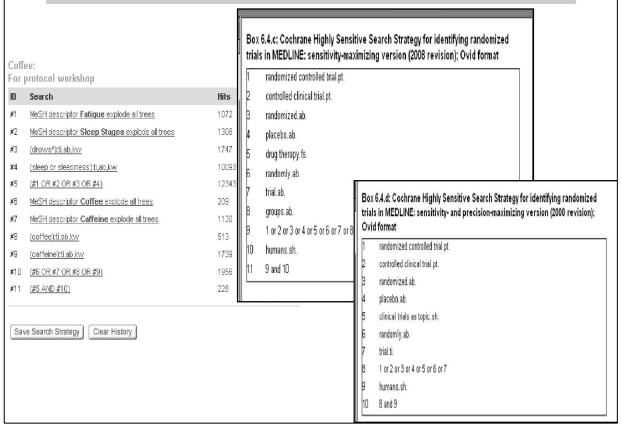
17

Searches in Medline & an example

- Some MeSH terms
  - exp = exploded MeSH
  - $ = any character(s)
  - tw = text word
  - pt = publication type
  - sh = MeSH
  - adj = adjacent
  - mp = title, original title, abstract, name of substance word, subject heading word
- Search strategy for alcohol and breast cancer
- MEDLINE
  - Exp alcoholic beverages OR Alcoholic intoxication OR Alcohol drinking OR Alcoholism OR Ethanol OR Alcohol consumption.tw
  - Breast neoplasms
  - 1 AND 2
  - Limit 3 to human
- EMBASE
  - Alcohol OR alcohol abuse OR alcoholic beverage# OR alcohol consumption OR alcohol intoxication OR alcoholism
  - Breast cancer
  - 1 AND 2
  - Limits: human

18

Search term example / Cochrane search strategy for RCTs in OVID Medline



Search term and search examples

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

using the following search terms: stroke or cerebrovascular disease or cerebrovascular attack or cerebral ischemia or brain infarct or transient ischemic attack AND antihypertensive therapy or blood pressure lowering or blood pressure reduction or thiazide or β-antagonists or α-antagonist or angiotensin-converting enzyme inhibitors or angiotensin antagonists or angiotensin inhibitors or calcium channel blockers AND acute or early or immediate or rapid. We restricted our search to human beings and clinical trials. There were no language restrictions. We also reviewed the introduction and discussion sections of retrieved trials and prior meta-analysis[3] to identify additional trials. Some data not provided by original articles but published in the latest Cochrane Review were also used.[7]

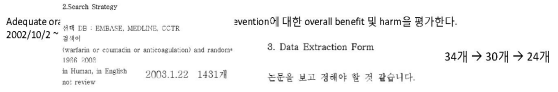
Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

where appropriate, MeSH terms for vitamin E ("vitamin E" or "alpha tocopherol") and stroke ("cerebrovascular disorders" or "cerebrovascular disease" or "stroke" or "intracranial hemorrhage" or "brain hemorrhage"). The search terms were combined with the "explode" feature. We limited our search to humans, clinical trials, randomised controlled trials, meta-analyses, and systematic reviews. We did not apply language restrictions. We also searched the reference lists of the identified articles.

20

Step 5. Selecting studies

- **Documentation!**
  - **Record** each step of your selection process and reasons for exclusion !!! (Keep a "log")
  - **What** we searched
    - Which databases, conference proceedings etc.
  - **When** we searched
    - Start and finish dates for the databases used, years of conference proceedings searched
  - **How** we searched
    - Database search strategies, keywords used in handsearch



21

Study selection example

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Study Selection

studies were selected when they met the following entry criteria: (1) studies were RCTs; (2) all participants in the study or in a separately reported subgroup were patients with ischemic stroke confirmed by brain computed tomography or magnetic resonance imaging; (3) the active treatment consisted of blood pressure lowering intervention. We included trials in which baseline antihypertensive were stopped in the control arm, whereas the intervention arm consisted of a trial-specific regimen (eg, The Scandinavian Candesartan Acute Stroke

tervention arm. (4) Reported outcome included dependency or death (modified Rankin Scale, 3–6 or nearest equivalent) or recurrent vascular events at 3 months or at the trial end point. All data from eligible

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

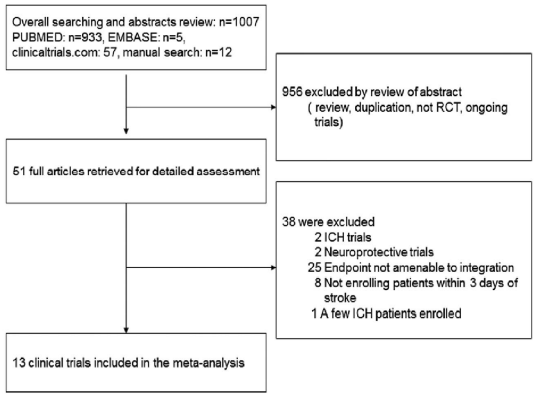
Study selection

A priori, we defined the following inclusion criteria:
(1) Randomised, placebo controlled design with a follow-up of ≥1 year
(2) Investigating the effect of vitamin E on stroke incidence (total stroke or stroke subtypes)
(3) Trial participants must be selected on clinical grounds
(4) If multiple papers reported on a trial, we chose either the original report or the report that was most informative with regard to stroke and stroke subtypes.
We did not include trials of multivitamins or fixed vitamin combinations.

Two investigators [MS and TK] screened the titles and abstracts and identified and excluded all papers not meeting any of the prespecified criteria by consensus. The same investigators evaluated the remaining studies as full papers. Studies were excluded if they did not meet all criteria.

22

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889



23

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

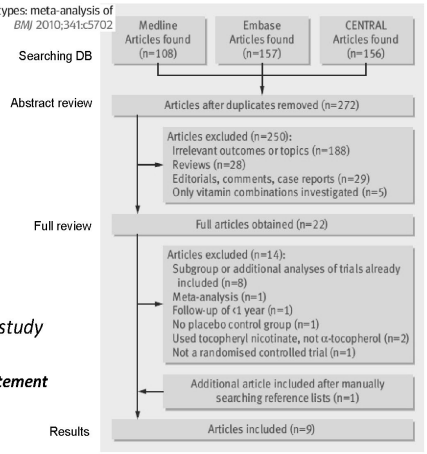


Fig 1| Flow chart of identifying and including trials

- *Flow diagram of study selection*
  - ***The PRISMA statement***

Step 6. Assessing risk of bias (RoB): Study quality

- Synthesis 시 research quality를 평가하는 문제
  - Poor quality 결과들을 결합 → biased misleading pooled estimates
    - 정교한 분석방법: poor data의 한계점을 극복하지는 못함 (Thacker, 1988)
  - Study quality와 study result 간에 일정한 관련이 있다는 증거 없다.
  - But, quality assessment는
    - 메타분석 수행할 때 가장 간과할 수 없는 형태의 bias 평가 (Greenland, 1994)
  - Schulz, et al (1995), an empirical study, large number of RCTs
    - 부적절한 방법론의 사용(incorrect randomization, unblinding, 특별히 poor allocation concealment)은 bias된 결과를 초래
- 자주 사용되는 평가도구/방법
  1. Quality scoring system (scaling)의 사용
     - Chalmers scale (1981) / Jadad (1996) scale 자주 사용 (RCTs)
  2. Check list
     - Observational study에 대한 평가도구들 개발
  3. Domain 측면에서 RoB를 평가 (Cochrane recommendation)

25

Quality assessment examples

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Study Quality Assessment

Jadad score was used to assess study quality because all included studies were RCTs.[12] This 5-point scoring system evaluates the randomization process (2 questions), blinding (2 questions), and the description of withdrawals and dropouts (1 questions).

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

The following limitations of our meta-analysis

Second, we considered randomised controlled trials irrespective of blinding and morbidity status of participants. This approach increases the total sample size and thus the power to detect a potential effect of vitamin E on stroke subtypes and also allows for greater flexibility at the analysis level by performing sensitivity analyses. Methodological quality is an important consideration when combining trials in a meta-analysis.[29] For example, larger effects have been reported in trials that were not double blinded compared with those that were double blinded.[30] Although quality scales for clinical trials are available, they are not generally recommended to assess quality in systematic reviews.[29] Meta-regression may be a better tool to investigate if metho-

26

Bias의 종류와 평가 영역

종류	무작위 연구	비무작위 (관찰) 연구
선택 편향 (selection bias)	• 무작위번호 생성 • 무작위배정 은폐	• 대상군 선정 • 교란변수처리
수행 편향 (performance bias)	• 눈가림 • Validity에 대한 다른 잠재적 위험	• 노출측정
탈락(마모) 편향 (attrition bias)	• 결과 변수에 관한 부적절한 자료	• 결과변수에 관한 부적절한 자료
탐지 편향 (detection bias)	• 눈가림 • Validity에 대한 다른 잠재적 위험	• 눈가림
보고 편향 (reporting bias)	• 결과에 관한 선택적 reporting	• 결과에 관한 선택적 reporting

27

DAMI (study design algorithm for medical literature of intervention) – NECA (한국보건의료연구원)

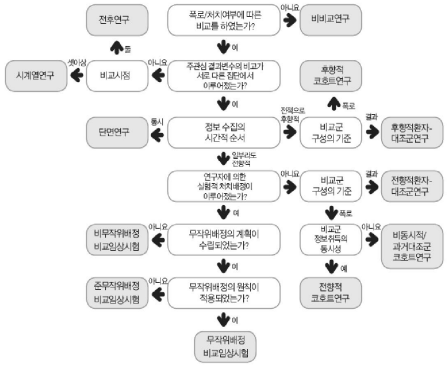


그림 9. 문헌의 분류도구, DAMI

28

Study quality: A scale approach (old version)

- 장점
  - Quality에 관한 overall quantity estimate를 제공
- 단점
  - 현존하는 scale들 중 많은 것들의 타당성은 의심됨
  - 많은 scale들
    - 실제로 quality를 측정하는 것이 아니라 reporting의 적절성이나 일반화 가능성과 관련된 외부 요인들에 조점
  - 최소한 RCT의 경우, 어떤 scale을 사용하느냐에 따라 결과가 많이 달라질 수 있음
    - Juni, et al., 1999; Moher, et al., 1996, 1999
- 메타분석에서 study quality를 다루는 최적의 방법이 무엇인지에 대해서는 논란이 많지만,
- Quality assessment가 항상 실시되어야 한다는 점에 대해서는 일반적으로 의견의 일치

29

Study quality assessment scale의 예

Jadad's quality assessment scale

- Jadad, et al., 1996
- Item: 5개
- Score range: 0-5점

A. Randomization
- Randomize 되었다고 묘사되었는가?
- Allocation sequence는 적절하게 generate 되었는가?

B. Blinding
- Double blind라고 묘사되었는가?
- Control treatment (예: placebo)는 구별되지 않게끔 묘사되었는가?

C. Patient attrition
- (lost 되었거나 exclude 된 patients의 수 및 그 이유가 포함된) 각 group 에 대한 attrition이 묘사되었는가?

30

Jadad scale (5 points in total)

	Yes	No
• Was the study described as randomized?	1	0
• Was the study described as double blind?	1	0
• Was there a description of withdrawals and dropouts?	1	0

Points +, if	Yes
• The method of randomization was described in the paper, and that method was appropriate	+1
• The method of blinding was described, and it was appropriate	+1

Points -, if	Yes
• The method of randomization was described, but was inappropriate	-1
• The method of blinding was described, but was inappropriate	-1

31

Others

- 이 외에도 약 23가지 정도의 scale system 존재

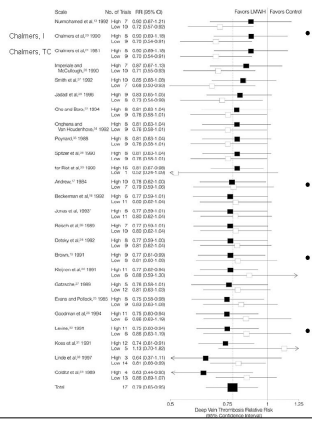
Table 5.2 Characteristics of 25 scales for quality assessment of clinical trials identified by Moher *et al.** Total number of items, range of possible scores, threshold scores for definition of "high quality", and weight allocated to methodological domains most relevant to the control of bias.

Scale	No. of items	Scoring range	Threshold score for definition of "high" quality (%)*	Weight of methodological domain (%)*		
				Randomisation†	Blinding‡	Attrition
Andrew	11	0–22	73	9	9	9
Beckerman	24	−3–25	52	4	12	16
Brown	6	0–21	81	14	5	–
Chalmers I	3	0–9	67	33	33	33
Chalmers TC	30	0–100	–	13	20	7
Cho	24	0–49	–	14	8	8
Colditz	7	0–7	–	29	–	14
Detsky	14	0–15	–	20	7	–
Evans	33	0–100	–	3	4	11
Gooderham	34	1–5	60	3	3	6
Gotzsche	16	0–16	–	6	13	13
Imperiale	5	0–5	80	–	–	–
Jadad	3	0–5	60	40	40	20
Jonas	18	0–36	76	11	11	6
Kleijnen	7	0–100	55	20	20	–
Koes	17	0–100	50	4	20	12
Levine	29	0–100	60	3	3	3
Linde	7	0–7	71	29	29	29
Normohamed	8	0–8	88	13	13	13
Oxghma	10	−10–100	–	5	10	5
Poynard	14	−2–26	50	8	23	15
Reisch	34	0–34	–	6	6	3
Smith	8	0–40	50	–	25	13
Spitzer	32	0–32	–	3	3	9
ter Riet	18	0–100	50	12	15	5

* Threshold scores and weights expressed as per cent of maximum score. No thresholds were described for nine scales.
† Generation of random sequences and/or concealment of allocation.
‡ Blinding of patients and/or outcome assessors.

32

Comparison



- Combined results for 17 trials
  - Low molecular vs. standard heparin
  - Dividing trials in "high" and "low quality" strata
    - Using 25 different quality assessment scales.
- Black squares
  - Estimates from "high quality" trials
- White squares
  - Estimates from "low quality" trials
- Modified from Juni, et al. JAMA 1999;282:1054-1060

33

Possible use of "study quality" in MA

1. Quality score에 근거한 forest plot 확인
2. Quality score에 근거한 cumulative meta analysis 수행
   - Quality score가 가장 높은 것부터 시작해서 descending order 로 실시
   - Study가 하나 추가될 때마다 pooled estimate 계산
   - 이 graph를 통해 quality가 outcome에 미치는 영향을 분류
3. Regression model의 사용
4. Weighting
5. Excluding studies
6. Sensitivity analysis
   - 메타분석 결과의 robustness 평가

34

The Cochrane recommendation

- Describe the following for each study in detai
  - **Six domains**
  1. Random sequence generation (무작위배정표 생성)
  2. Allocation concealment (무작위배정 은폐)
  3. Blinding (눈가림)
  4. Incomplete outcome data (불완전한 결과 자료)
  5. Selective outcome reporting (선택적 결과 보고)
  6. Other potential problems (기타 잠재적 문제점들)
- Empirical research shows that
  - These components can have a significant effect on results, often leading to exaggerated effects
- For each domain
  - A judgment regarding risk of bias will be encouraged
  - **'high risk', 'low risk' or 'unknown risk'**

35

Risk of Bias 평가 (NECA guidance)

평가	무작위배정 번호 생성
예	• 난수표, 컴퓨터를 이용한 random number 생성 • 기타 random number 임이 보장되는 수행과정을 확인할 수 있는 배정
아니오	• 무작위배정 방법 미시행, 부적절한 시행 • 등록번호 / 병록번호 등을 사용 • 생년월일 / 내원일 등을 사용 • 연구자나 배정자의 임의판단에 의한 배정 • 환자 선호도에 따라 배정 • 검사 결과 순에 따라 배정 • 약제 준비 순에 따라 배정 등
불확실	• 언급이 없거나 모호

평가	무작위배정 은폐
예	• 적절한 은폐로 연구자가 배정내용을 모름 • 독립적인 중앙관리 • 봉투양한 밀봉 일련번호 봉투 사용
아니오	• 은폐방법 미시행, 부적절한 방법 사용 • 공개된 난수(표) • 밀봉되지 않은 일련번호 봉투를 사용 • 교대로 할당 • 성별, 병록번호 등을 사용
불확실	• 언급이 없거나 모호 • 일련번호(?), 밀봉(?), 봉투명(?)

평가	눈가림
예	• 편향(bias)을 최소화 할 수 있는 눈가림법 저택. 그러고 임상시험 수행 시 피험자 및 연구자의 눈가림이 깨지지 않았다는 확신 • 결과평가자에 대한 눈가림으로 결과측정과 평가에 bias 없음 • 눈가림이 영향을 미치지 않는 의료장치 등에 의한 측정
아니오	• 눈가림이 결과측정에 영향을 미침에도 불구하고 미시행 • 부적절한 눈가림으로 결과 측정에 영향을 미침 • 눈가림의 시도에도 불구하고 실제 눈가림이 이루어지지 않았음
불확실	• 눈가림에 대한 정보 불충분

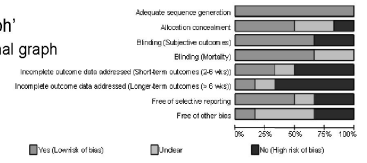
평가	불완전한 결과 자료
예	• 결측치 없음 • 결측치가 결과에 영향을 미치지 않음 • 결측치 발생 원인과 결측치 분포가 군 간에 유사 • 적절한 통계기법을 이용하여 결측치 대체를 실시했음
아니오	• 군 간의 결측치가 존재 • 결측치의 존재가 실제 결과에 영향을 미칠 수 있음 • 결측치 발생 원인, 분포 등이 군 간에 차이가 있음 • 부적절한 방법으로 결측치를 대체했음
불확실	• 제외/탈락에 대한 보고 내용이 불충분한 경우 (예: 결측 이유에 대한 언급 없음)

평가	선택적 결과 보고
예	• 연구 프로토콜이 존재, 연구에서 미리 정의한 일, 이차 결과변수가 미리 정해진 대로 다루어졌음 • 연구 프로토콜은 없으나 보고를 통해 결과가 사전에 예정된 대로 수행되었음을 확신할 수 있음
아니오	• 미리 정해진 결과변수였음에도 결과보고에서 누락된 경우 • 미리 정하지 않은 분석, 소집단분석 등이 존재하고 이 같은 분석에 대한 이유가 설명되어 있지 않음 • 급여의 필요한 적심 결과변수에 대한 보고가 누락되었음
불확실	• 예/아니오 판단을 할 수 있는 정보가 충분치 않음

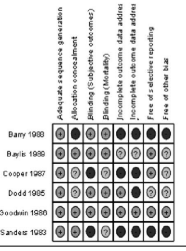
평가	편향 위험을 높일 수 있는 다른 문제들
예	• Bias 발생과 관련된 다른 원인은 없는 것으로 보임
아니오	• 아래의 예가 있을 경우, 추가 bias 위험 있는 것으로 판단 • 연구설계와 관련된 추가 bias 위험 • 결과의 방향에 따라 연구가 조기 중단 • 피험자들의 baseline characteristics에 심각한 불균형 존재 • 연구 부정(fraud)의 주장 제기 여부
불확실	• 추가 bias 가능성에 대한 여지가 있으나 이를 평가할 충분한 근거나 정보가 없음

How to report?

- A "Risk of bias graph'
  - Single-dimensional graph



- A "Risk of bias summary figure'
  - Two-dimensional graph



37

관찰연구(비무작위 연구) 평가도구

- 아래와 같은 영역들에 대한 평가 필요
  1. 대상군 선정
  2. 교란변수(confounding)의 처리
  3. 노출(exposure)에 대한 측정
  4. 결과 평가에 대한 눈가림 여부
  5. 자료의 불완전성
  6. 선택적 결과 보고
  7. 기타 편향(bias) 위험들
- Scale
  1. Newcastle-Ottawa
     - 8개 항목 / 비교적 간단 / 연구설계 형태에 따라 문항수정 필요
  2. Downs and Black
     - 27개 항목 / 전문성, 시간 요구됨 / 환자-대조군 질평가에 부적절
  3. MINORS
- Checklist
  1. RoBANS

38

MINORS

- Methodological Index for NOn-Randomized Studies
  - Slim, et al. Methodological index for non-randomized studies (minors): development and validation of a new instrument. ANZ J Surg 2003;73:712-716
    - 비무작위 연구를 평가하기 위해 개발. 12개 항목 (항목 당 0, 1, 2점)
      1. 분명한 목적이 있는가?
      2. 환자가 연속적으로 포함되었는가?
      3. 데이터가 전향적으로 수집되었는가?
      4. 연구목적에 적절한 결과인가?
      5. 연구결과가 편향(bias)없이 평가되었는가?
      6. 추적기간은 적절했는가?
      7. 탈락이 5% 미만인가?
      8. 연구크기가 전향적으로 계산되었는지 등의 공통항목이 있는가?
      9. 적절한 대조군이 있었는가?
      10. 두 군의 모집이 동시적이었는가?
      11. 두 군의 기저 상태가 유사한가?
      12. 적절한 통계분석이 이루어졌는가?
    - 대조군이 없는 비무작위 연구
      - 1-8번까지 공통항목 8개 평가 (16점 만점)
    - 대조군이 있는 비무작위 연구
      - 9-12번까지 4개 추가 (24점 만점)
    - 주요 단점
      - 비무작위 연구의 주된 bias 중 하나인 교란변수(confounder) 보정 여부를 다루지 않음

39

MINORS

Table 2. Methodological items for non-randomized studies.

Methodological items for non-randomized studies (MINORS)	Score*
1. **A clearly stated** aim: the question addressed should be precise and relevant in the light of available literature	
2. **Inclusion of consecutive patients:** all patients potentially fit for inclusion (satisfying the criteria for inclusion) have been included in the study during the study period (no exclusion or details about the reasons for exclusion)	
3. **Prospective collection of data:** data were collected according to a protocol established before the beginning of the study	
4. **Endpoints appropriate to the aim of the study:** unambiguous explanation of the criteria used to evaluate the main outcome which should be in accordance with the question addressed by the study. Also, the endpoints should be assessed on an intention-to-treat basis.	
5. **Unbiased assessment of the study endpoint:** blind evaluation of objective endpoints and double-blind evaluation of subjective endpoints. Otherwise the reasons for not blinding should be stated	
6. **Follow-up period appropriate to the aim of the study:** the follow-up should be sufficiently long to allow the assessment of the main endpoint and possible adverse events	
7. **Loss to follow up less than 5%:** all patients should be included in the follow up. Otherwise, the proportion lost to follow up should not exceed the proportion experiencing the major endpoint	
8. **Prospective calculation of the study size:** information of the size of detectable difference of interest with a calculation of 95% confidence interval, according to the expected incidence of the outcome event, and information about the level for statistical significance and estimates of power when comparing the outcomes	
Additional criteria in the case of comparative study	
9. **An adequate control group:** having a gold standard diagnostic test or therapeutic intervention recognized as the optimal intervention according to the available published data	
10. **Contemporary groups:** control and studied group should be managed during the same time period (no historical comparison)	
11. **Baseline equivalence of groups :** the groups should be similar regarding the criteria other than the studied endpoints. Absence of confounding factors that could bias the interpretation of the results	
12. **Adequate statistical analyses:** whether the statistics were in accordance with the type of study with calculation of confidence intervals or relative risk	

*The items are scored 0 (not reported), 1 (reported but inadequate) or 2 (reported and adequate).
The global ideal score being 16 for non-comparative studies and 24 for comparative studies.

40

RoBANS

- Risk of Bias Assessment tool for Non-randomized Study
  - Checklist 형식의 도구
    - 2009, NECA (한국보건의료연구원) 개발
  - 비무작위 연구에서 발생할 수 있는 bias 위험을 평가 영역으로 정의
    - 비무작위배정 비교임상시험, 코호트 연구, 사례-대조 연구, 전후 연구 등의 평가에 사용
    - "bias 위험 높음", "bias 위험 높음", "bias 위험 불확실" 판정
  - Grade를 쉽게 적용할 수 있다는 장점
    - 체계적 문헌고찰 매뉴얼 (NECA, 한국보건의료연구원)

표 6-4. RoBANS 도구

영역	설명	비뚤림 위험	판단근거 (논문에서 그대로 인용함)
대상군 선정	부적절한 대상군 선정으로 인해 발생한 선택 비뚤림	□ 낮음 □ 높음 □ 불확실	
교란변수	교란변수 확인과 고려가 부적절해서 발생한 선택비뚤림	□ 낮음 □ 높음 □ 불확실	
중재노출 측정	부적절한 중재노출(측정)으로 인해 발생한 오류 비뚤림	□ 낮음 □ 높음 □ 불확실	
결과 평가에 대한 눈가림	부적절한 결과 평가 눈가림으로 인해 발생한 결과 확인 비뚤림	□ 낮음 □ 높음 □ 불확실	
불완전한 자료	불완전한 자료를 부적절하게 다루어 발생한 탈락 비뚤림	□ 낮음 □ 높음 □ 불확실	
선택적 결과 보고	선택적 결과 보고 때문에 발생한 보고 비뚤림	□ 낮음 □ 높음 □ 불확실	

41

Step 7. Extracting data

- Two readers가 독립적으로 data를 extraction
- 해당 주제에 대한 appropriate data extraction form 함께 생성
  - What variables do you want to extract?
- 자료 추출은 개별적으로 시행
- Extraction 시 발생한 차이에 대해 토론
  - What were the differences?
  - How would you have modified the data extraction form?
  - 만일 disagreements가 발생하면
    - With adjudication by a third reader (recommended)
    - With a discussion
- General info.
  - Extraction date / Study identifier / Reviewer identifier
- Specific info.
  - Eligibility / Pt. char. / Methodological quality / Intervention / Outcomes / Analytics etc…

42

Data extraction example

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

cular events at 3 months or at the trial end point. All data from eligible trials were independently abstracted by 2 investigators (M.L. and K.-S.H.) according to standard protocol. Discrepancies were resolved by discussion with a third investigator (Y.-L.W.) and by referencing the original report.

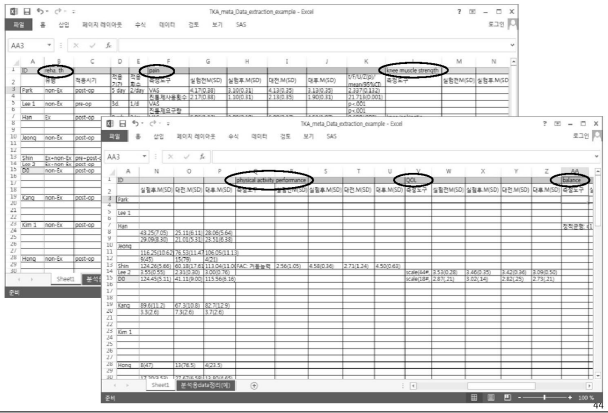
Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

Data extraction

Two investigators (MS and PMR) independently extracted data and entered them in a customised database. Disagreements were resolved by consensus. Extracted data included authors and title of study, year of publication, country of origin, blinding strategy, participant age at enrolment and sex, inclusion criteria, treatment dose, method of statistical analysis, duration and completeness of follow-up, number of participants, and number of outcome events in each of the treatment groups. All data were extracted from the published papers; we did not contact the authors to collect further information.

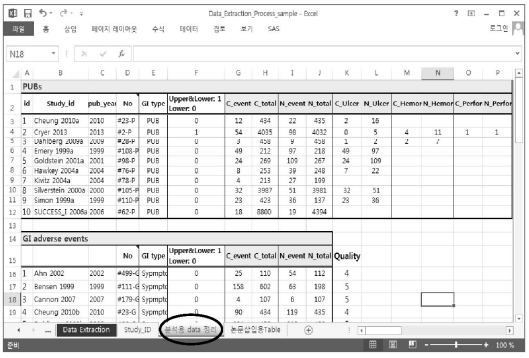
43

Data extraction (step 1)



44

Data extraction (step 2)



45

Data extraction at minimum

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Table 1. Characteristics of Included Trials

Trial, Publication Year, Country	Population	Patients Enrolled for This Meta-Analysis	Median or Mean Time From Stroke Onset to Randomization, h	Sample Size (% men)	Percentage of Patients Receiving Thrombolytic Therapy	Mean Age, y	Percentage Taking Antihypertensive Medication at Baseline	Intervention	Control
ACCESS,[14] 2003, Germany	Ischemic stroke with a motor deficit, SBP≥200 mm Hg, and DBP ≥110 mm Hg, within 36 h of admission	All trial patients	30	339 (51)	NA	68	NA	Candesartan for 7 d	Placebo for 7 d
CATIS,[15] 2014, China	Ischemic stroke within 48 h of symptom onset, SBP between 140 and 220 mm Hg	All trial patients	15	4071 (64)	0	62	49	Antihypertensive treatment during hospitalization	No antihypertensive treatment during hospitalization

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

Characteristics of the nine randomised controlled trials of vitamin E on stroke outcomes

Trial	Study design	Participant details: Total No	Age at enrolment (years)	Sex	Health status	Type of prevention	Vitamin E dose (source)	Follow-up details: Duration (years)	Completeness	Available data for stroke outcomes
CHAOS 1996 (GBI)[7]	Double blind RCT	2 002	Mean: 61.8	Mixed	Patients with angiographically proved coronary atherosclerosis	Secondary	400 or 800 IU daily (natural)	Median 1.4*	98%	Total (only fatal)
GISSI 1999 (Italy)[33]	Open label RCT	11 324	No limit	Mixed	MI within 3 months	Secondary	300 mg daily (synthetic)	3.4†	99.9%	Total
SPACE 2000 (Israel)[20]	Double blind RCT	196	40–75	Mixed	Haemodialysis patients with history of CVD events	Secondary	800 IU daily (natural)	Median 1.4*	Not stated	Ischaemic
HOPE 2000 (International)[34]	Double blind RCT	9 541	≥55	Mixed	High risk for CVD including previous CVD events, vascular disease, or diabetes	Secondary	400 IU daily (natural)	Mean 4.5	99.9% (mortality)	Total, haemorrhagic

46

Step 8. Synthesizing data

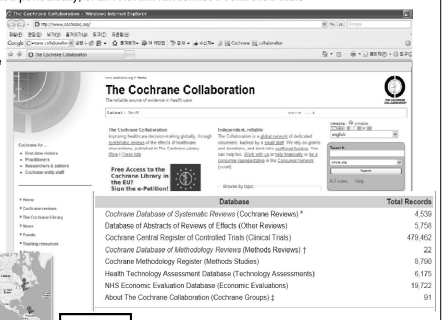
- Meta-analysis
  - "Meta-analysis refers to the analysis of analyses… the statistical analysis of a large collection of analysis results from individual studies for the purpose of integrating findings. It connotes a rigorous alternative to the casual, narrative discussions of research studies which typify our attempts to make sense of the rapidly expanding literature…"
    - Glass GV (1976). Primary, secondary, and meta-analysis of research. Edu. Researcher 5:3-8
  - "Statistical analysis of the results of independent studies, which generally aims to produce a single effect estimate"
    - BMJ book (2001)
  - "The statistical combination of results from two or more separate studies"
    - Cochrane handbook ver. 5.0.1 (2008)

47

Archie Cochrane (1979)
- The British physician and epidemiologist
- "People who want to make informed decisions about health care do not have ready access to reliable reviews of the available evidence"
-"It is surely a great criticism of our profession that we have not organised a critical summary, by specialty or subspecialty, adapted periodically, of all relevant randomised controlled trials"

1980th
- Becoming popular in medicine
- Cardiovascular dz, oncology, perinatal care, etc.

1990th
- Getting popular in public health, nursing
- Many initiatives through **the Cochrane Collaboration**
- The Cochran Library
  - CDSR / CCTR (CENTRAL) etc.

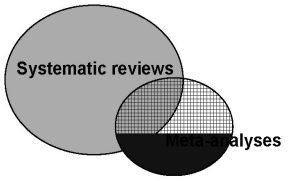


- A use of corticosteroid to prevent a premature delivery
- 7 RCT ('72-'80)
- SR ('89)
- Reduce 30-50% odds for complication deaths

48

Does SR differ from MA?

- Systematic reviews
  - May or may not include *a statistical synthesis of the data* (meta-analysis)
- A systematic review can be useful
  - Even when statistical synthesis of results of studies is not appropriate
- Meta-analysis is an ***optional*** part of a SR



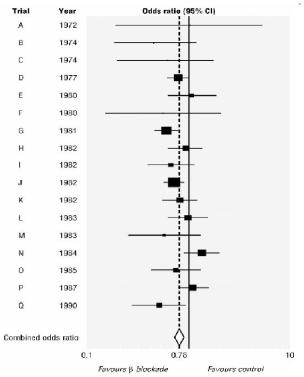
49

Meta-analysis

- **Not** be expected to ***reduce bias*** *(increase validity, accuracy)* **but** only to ***reduce imprecision*** *(increase reliability, precision)*
  - 하나 이상의 연구결과들을 양적으로 결합(pooling)
- Review process의 일부분을 차지
  - Primary research에서 추출된 자료들을 평가, 결합(pooling)해서 key question에 관한 결합 추정값(pooled estimate)을 도출
    - Fixed-effects model (고정효과 모형) vs. Random-effects model (변량효과 모형)
  - 결합하는데 사용된 결과들의 이질성(heterogeneity)을 탐색
    - Subgroup analysis (부집단 분석) 실시
    - meta-regression method (메타회귀) 사용
  - 결합추정값의 타당도(validity) 평가
    - Publication bias 평가, study quality (risk of bias) 평가
    - Sensitivity analysis (민감도 분석) 실시

50

예: meta analysis 결과 – forest plot



Egger M. et al. BMJ 1997;315:1533-1537

Total mortality from trials of ß-blockers in secondary prevention after myocardial infarction.

- The black square and horizontal line correspond to OR and 95% CI for each trial

- The size of the black square reflects the weight of each trial

- The diamond represents the combined OR and 95% CI, showing 22% a reduction in the odds of death

51

Statistical analysis

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Statistical Analysis

The primary outcome was unfavorable outcome at 3 months or at trial end point, defined as dependency or death (modified Rankin Scale, 3–6 or nearest equivalent) if measured. The key secondary outcome was recurrent vascular events at 3 months or at trial end point. Additional outcomes of interest were disability or death (modified Rankin Scale, 2–6), death from any cause, and recurrent stroke at 3 or 6 months. We also looked at death or dependency, death or disability, all-cause mortality, and serious adverse events at 2 weeks or 1 month.

Data were analyzed according to the intention-to-treat principle. A random-effect estimate based on the Mantel–Haenszel method was computed when ≥2 studies provided sufficient data for a given outcome. Statistical heterogeneity was assessed using a χ^2 and the I^2 statistics. Study-level estimates were considered heterogeneous if either the χ^2 test was significant at the P=0.10 level or the I^2 statistic was >50%. Publication bias was assessed by visual examination of funnel plots. The Cochrane Collaboration's Review Manager Software Package (RevMen 5.2) was used for this meta-analysis.

Data synthesis and analysis

Within each study, we calculated the risk ratio as a measure for the relative risk and 95% confidence interval for total stroke, ischaemic stroke, and haemorrhagic stroke based on the reported events in the treatment and placebo groups.

We used a fixed effects model (Mantel-Haenszel method) and random effects model (DerSimonian and Laird method) to investigate the effect of vitamin E on stroke across the trials and calculated pooled relative risks and 95% confidence intervals.[22] We performed the Q test for heterogeneity[23] and also calculated the I^2 statistic.[24] We used meta-regression to evaluate to which extent heterogeneity between study results is related to blinding strategy (open label *v* double blind), morbidity status of participants (primary *v* secondary prevention), and vitamin E dose (≤200 mg/day *v* >200 mg/day; <200 mg/day *v* ≥200 mg/day; 50 mg/day *v* >50 mg/day). We used Galbraith plots to visually examine the impact of individual studies on the overall homogeneity test statistic.[25] We formally tested for small study effects (such as publication bias) by using Harbord's test.[26]

We considered a two tailed P value <0.05 as significant. All analyses were performed with Stata 10.1 (Stata, College Station, Texas, USA). Since we used only previously published data, we did not need approval of an ethics committee.

52

A. Data synthesis (pooling)

A. Non-quantitative synthesis
- Tabulation and/or
- Graphical display of characteristics and results of individual studies

B. Quantitative synthesis if appropriate
- Calculation of summary results
  - Pooled estimate and its C.I.
  - By a statistical analysis of variation in study results

53

Non-quantitative synthesis

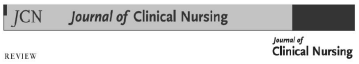
- An example (laparoscopy vs. open surgery)

Table 1 Characteristics of included studies in meta-analysis

Study	Study design	Tumor location	Patients enrolled			Mean follow-up (months)		Neoadjuvant therapy	Patients analyzed in recurrence and survival		
			LS (n)	OS (n)	AJCC stage	LS	OS		LS (n)	OS (n)	AJCC stage
Araujo 2003 [27]	RCT	Rectum	13	15	I–IV	47.3	47.3	Y	13	13	I–III
Braga 2007 [28]	RCT	Rectum	83	85	I–IV	53.6	53.6	Y	83	85	I–IV
Jayne 2007 [5]	RCT	Rectum	253	128	I–IV	36.8	36.8	NR	253	128	I–IV
Lujan 2009 [29]	RCT	Rectum	101	103	I–IV	32.8	34.1	Y	97	96	I–IV
Ng 2008 [31]	RCT	Low rectum	51	48	I–IV	87.2 (median)	90.1	NR	40	36	I–III
Ng 2009 [30]	RCT	Upper rectum	76	77	I–IV	112.5	108.8	NR	60	70	I–III

RCT randomized controlled trial, *LS* laparoscopic-assisted surgery, *OS* open surgery, *AJCC* American Joint Committee on Cancer, *Y* yes, *NR* no record

- Another example


JCN Journal of Clinical Nursing

REVIEW

A qualitative meta-synthesis of adult children of parents with a mental illness

Gillian Murphy, Kath Peters, Debra Jackson and Lesley Wilkes

54

Quantitative synthesis

- Calculation of summary results
  - An weighted average using, usually, an inverse of SE (standard error, 표준오차) as a weight
- Statistical models
  - Fixed-effects model
  - Random-effects model
  - Bayesian model, etc.

$$SE(\bar{X}) = \frac{SD}{\sqrt{n}} \qquad 1/SE \uparrow \ as \ SD \downarrow \qquad 1/SE \uparrow \ as \ n \uparrow$$

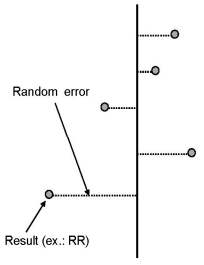
$$ex)\ SE(\ln OR) = \sqrt{\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d}}$$

- 메타분석 결과를 extrapolate하고자 하는 population 종류 및
- Effect의 특성에 대한 assumptions에 따라 구분되는 모형들

55

Fixed-effects model (고정효과모형)

- 모든 study들은 동일한 처리효과 (same treatment effect)를 가지고 있고, 따라서 연구결과들 간 variation이 관찰되는 이유는 단지 표본추출 변동 (sampling variation, random error) 때문이라고 가정
- 결합: 가중평균(weighted average)
  - 가중값
    - Sample size (Not recommended)
    - Inverse variance of effect size
- (자주 사용되는) 방법
  - Continuous outcome variable
    - Inverse-variance weighted (IVW) method
  - Binary outcome variable
    - Inverse-variance weighted (IVW) method
    - Mantel-Haenszel (MH) method
    - Peto method



$$y_i \sim N(\theta, s_i^2) \quad i = 1, \cdots, k$$

$$E(y_i) = \theta, \quad Var(y_i) = s_i^2$$

56

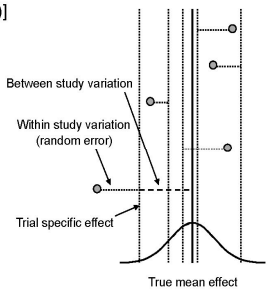
Comparisons of FE methods

- MH method is preferable
  - Pooling할 study 수는 많지만 within-study sample size는 작은 경우
- IVW method is preferable
  - Pooling할 study 수는 작지만 within-study sample size가 큰 경우
- Peto's method is under strong criticism
  - May produce seriously biased OR and SE
    - 특별히 두 집단의 수가 severely imbalance 되어 있을 때
  - Possibly biased when the estimated OR is far from 1
- Trial arm 내에 zero events가 있는 경우
  - For MH, a study with zero total events is completely excluded
    - 그러나 a continuity correction (add .5 to each cell)을 사용할 수도 있음
  - Peto method outperforms MH or IVW
    - 2×2 tables의 하나 이상의 cell들에서 event 수가 작을 때
- Important to report precisely what methods we used

57

Random-effects model

- 각 연구들은 [일정한 규칙(예, 정규분포)] 하에 어떤 평균적인 처리효과 (average treatment effect)를 중심으로 흩어져 있는 모집단 내 연구들로부터 무작위로 추출된 연구들이라고 가정
- 따라서 연구결과들 간에 variation이 관찰되는 이유는 표본추출 변동(within-study variation) 과 더불어 연구들 간의 변동(between-study variation)이 함께 나타났기 때문으로 간주
  - 즉, 연구결과들 간의 변동 원인을 추가적으로 더 인정
- (자주 사용되는) 방법
  - Continuous / Binary outcome variables
    - "DerSimonian-Laired method"



$$y_i \mid \theta_i \sim N(\theta_i, s_i^2) \quad i = 1, \cdots, k$$

$$E(y_i) = \theta_i, \quad Var(y_i \mid \theta_i) = s_i^2$$

$$\theta_i \sim N(\theta, \tau^2)$$

58

Methods of random-effects model

- Methods
  - Weighted least squares (WLS) method
    - DerSimonian and Laird, Controlled Clin Trials 1986;7:177-188
    - Called "DerSimonian-Laired (D-L) method"
  - Unweighted least squares (UWLS)
  - Maximum likelihood (ML)
  - Restricted maximum likelihood (REML)
  - Bayesian method
- Comparison
  - D-L와 REML은 항상 ML보다 약간 큰 between-study variation estimate를 제공
  - UWLS는 D-L, ML, REML과 다른 결과를 제공
  - Comparability나 simplicity 등을 고려할 때 일반적으로 D-L method 사용 추천

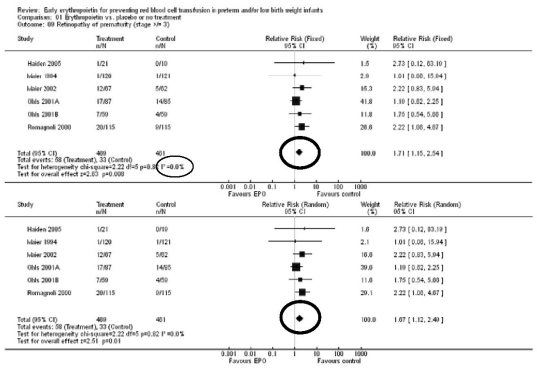
59

Fixed or Random?

- RE meta-analysis
  - **Identical** to FE meta-analysis
    - When there is no clear heterogeneity
  - **Similar** to FE meta-analysis but with wider C.I.
    - When there is some heterogeneity
      - RE model considers (allows) more variation between studies
  - **Different** from FE meta-analysis
    - When a bias introduced in the SR (ex., publication bias)
      - RE model gives relatively more weight to smaller studies

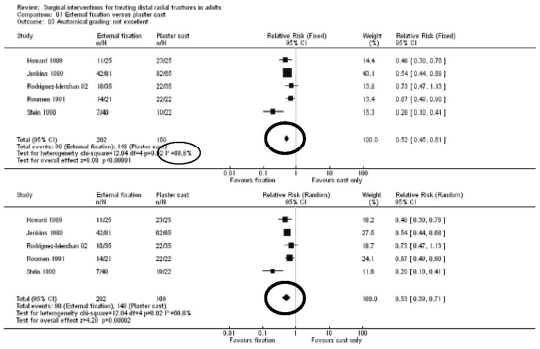
60

No clear heterogeneity



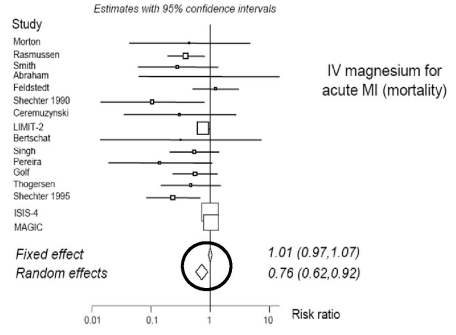
61

Some heterogeneity



62

Large heterogeneity



- Why? Bias?

63

Pooling에 관한 Summary

- When we use random-effects model?
  - Random-effects model
    - Between study heterogeneity 인정하면서 study들을 combining하는 방법
  - Study들 간에 unexplainable heterogeneity가 존재한다는 근거가 있을 때
  - 비록 test of heterogeneity 결과는 non-significant 하지만, study들이 true homogeneity하다는 가정을 할 수 없을 때
    - Because the heterogeneity test lacks power (i.e., studies may be regarded as homogeneous when in fact there is a degree of heterogeneity)

64

B. Heterogeneity

- Study 간 결과 차이: statistical heterogeneity
  - 즉, individual estimates of treatment effect will vary by chance
  - 문제는…
    - Variation이 by chance alone에 의해 기대되는 차이보다 더 큰가
  - An excessive variation other than that by chance alone is called
    - "Statistical heterogeneity", or simply "heterogeneity"
- Statistical heterogeneity의 이유
  - Clinically and methodologically heterogeneous 하기 때문

65

A variety of varieties

- **Clinical heterogeneity**
  - Clinical differences in the studies to do with the participants, interventions and outcomes
    - Study location and setting
    - Age, sex, diagnosis, and disease severity of participants
    - Intervention received
    - Dose and intensity of the intervention
    - Definitions of outcomes
- **Methodological heterogeneity**
  - Differences between how the studies were executed
    - Design: Parallel design or cross-over design
    - Execution: Randomization by cluster, by individual
    - Study quality: (ex., allocation concealment, blinding etc.)
    - Analysis: (Ex., ITT analysis / FAS analysis / PP analysis)
- The distinction between them
  - Not always clear-cut

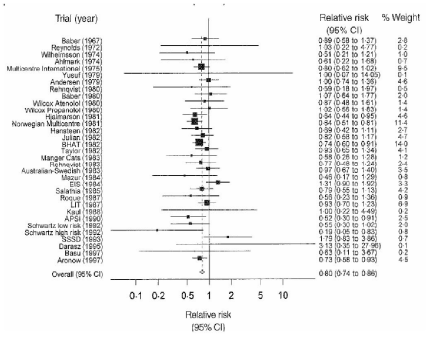
66

Identifying statistical heterogeneity

- Three main ways (other sophisticated statistical methods available)
  - Graphical way
    - A visual check of a forest plot
    - To see how well the CI overlap
    - If CI's do not overlap, should suspect heterogeneity
  - By performing a statistical tests
    - Heterogeneity χ^2-test (Cochran's Q-test)
    - Low power with few studies
      - Guided to use p<0.1
    - Too much power with lots of studies
      - Detect significant heterogeneity even if it is clinically trivial
    - Not answered for "how much heterogeneity is there?"
  - A statistical measure
    - Higgins I^2-statistic (Higgin's H-test)
      - Answers an amount of heterogeneity

67

Homogeneous or heterogeneous?



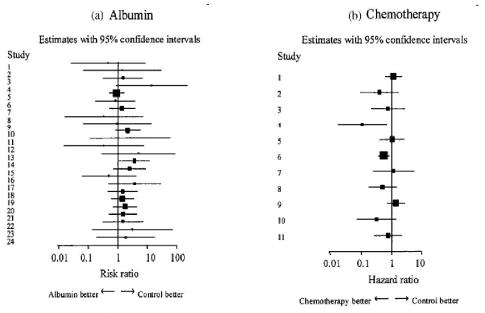
- Total mortality from trials of beta-blockers in secondary prevention after MI
- Trial clusters between a RR of 0.5 and 1.0 with widely overlapping CI's

68

Examples for heterogeneity

- Homogeneous set of trials

Moderately heterogeneous



- Higgins and Thompson, Stat. Med. 2002;21:1539-1558

69

Examples for heterogeneity

- Heterogeneous set

Outlying trial

Extreme heterogeneity

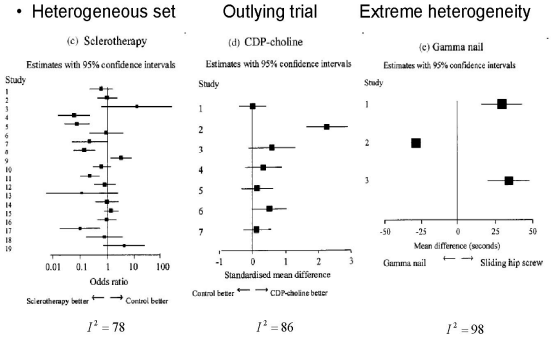


Figure 1. Confidence interval plots for four example data sets: (*a*) 24 trials of albumin versus placebo [5]; (*b*) 11 trials of adjuvant chemotherapy [7]; (*c*) 19 trials of sclerotherapy versus control [8]; (*d*) 7 trials of CDP-choline versus control [9]; (*e*) 3 trials of gamma nail versus sliding hip screws [10].

70

Identifying heterogeneity

1. Cochran's Q-test (이질성 존재 여부 평가)

θ_i = *the underlying true treatment effects*

$H_0 : \theta_1 = \theta_2 = \cdots = \theta_k$ (*i.e., true treatment effects are homogeneous*)

- Q-통계량

$$Q = \sum_{i=1}^{k} w_i (Y_i - \overline{Y}_\bullet)^2 \underset{H_0}{\rightarrow} \chi^2_{k-1}$$

- Limitation
  - Low statistical power (in general)
    - 실제로 heterogeneity가 존재하는 상황에서도 Q값은 일반적인 유의수준 (예: 0.05) 하에서 유의하지 않은 결과를 제시하게 됨
  - High rejection probability (in special)
    - 각 study들의 sample size가 크다면, 개별 effect size 값들이 서로 다르지 않은 경우에도 H_0 기각 가능
  - Difficult implication
    - Publication bias 혹은 design flaw가 개입된 경우, 검정 결과의 해석 어려움
  - 메타분석의 경우 α= 0.1 사용을 추천, 아니면 diagnostic tool only

71

Identifying heterogeneity

2. Higgin's I^2 (heterogeneity 존재여부 평가)

$$I^2 = \frac{Q - df}{Q} \times 100(\%)$$

- ***The proportion of total variation across studies due to heterogeneity rather than chance***
- Rough guide to levels of heterogeneity
  - Higgins, et al. BMJ. 2003;327:557-560
    - $I^2 \approx 25\%$ (low) / $I^2 \approx 50\%$ (medium) / $I^2 \approx 75\%$ (high)
  - Cochrane handbook ver. 5.0.1
    - 0-40% (not important)
    - 30-60% (moderate)*
    - 50-90% (substantial)*
    - 75-100% (considerable)

* The importance of the observed value of I^2 depends on
- Magnitude and direction of effects
- Strength of evidence for heterogeneity

72

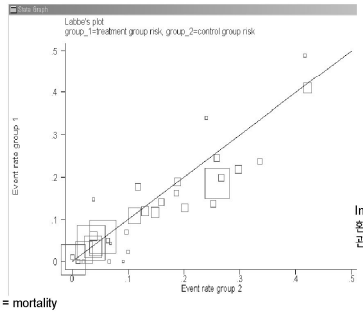
Evaluation of Between Study Heterogeneity
- A fundamental issue in meta analysis -

- Estimates of effect size for each of trials
  - Heterogeneity may exist
    1. When the results of trials are *in different directions*, or
    2. When they are *same direction but the size differs*
  - Need to investigate potential sources of heterogeneity
    - An important component of carrying out a meta-analysis
    - Clinical and/or methodological heterogeneity across the studies is likely to lead to some degree of statistical heterogeneity
    - Graphical methods
      - L`abbe plot, Galbraith plot
    - Often used statistical strategies other than graphs
      - Subgroup analysis (부집단 분석)
      - Meta-regression analysis (메타회귀분석)

73

(1) L'Abbe's plot

- Plot $Treatment\ group\ risk\left(=\frac{a}{a+b}\right)$ vs. $Control\ group\ risk\left(=\frac{c}{c+d}\right)$
  - An example: Total mortality data from 34 RCTs
    - The effect of cholesterol lowering interventions



Intervention effectiveness는 환자들의 underlying risk와 관련이 있는 듯 → meta-reg.

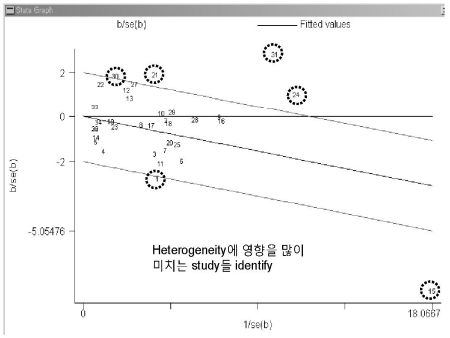
참고: event rate = mortality

74

(2) Galbraith's plot (Radial plot)

- Plot $\frac{Effect\ size}{SE}$ vs. $\frac{1}{SE}(=weight)$

- drug vs. diet trials
- Primary vs. secondary preventions



Heterogeneity에 영향을 많이 미치는 study들 identify

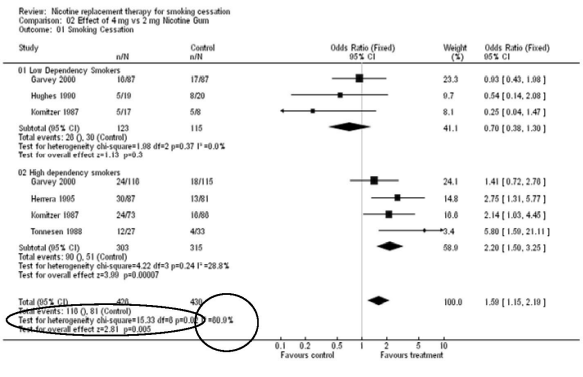
75

(3) Subgroup analysis

- A stratified analysis
  - Separate meta-analyses of different subsets of the studies
- Suspect, in advance, that certain features may alter the effect of an intervention
  - Participants
    - Ex) severity of condition
  - Interventions
    - Ex) intensity, dose, duration, type of intervention
  - Outcomes
    - Ex) timing of follow-up

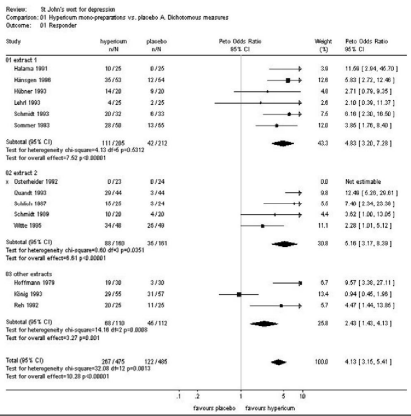
76

Subgroup analysis: Participants
- low dependency vs. high dependency smokers -



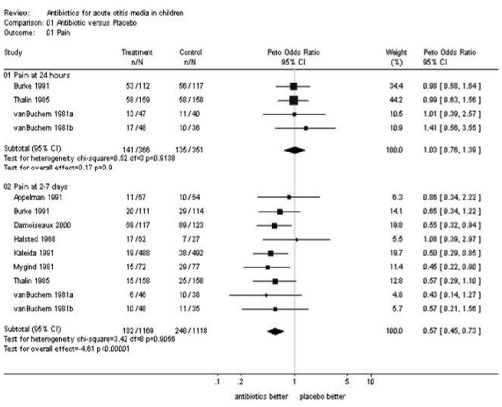
77

Subgroup analysis: Intervention
- extract formulation of St. John's wort vs. placebo -



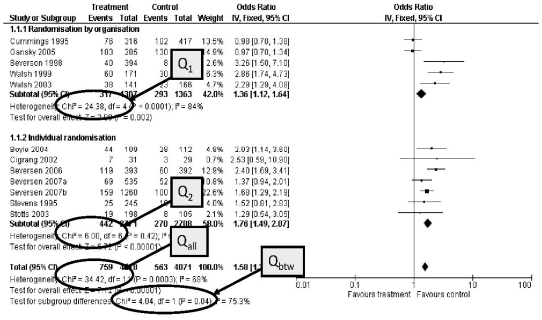
78

Subgroup analysis: Outcome
- Antibiotics to reduce pain: 24 hours vs. 2-7 days -



79

Subgroup analyses: Test for differences



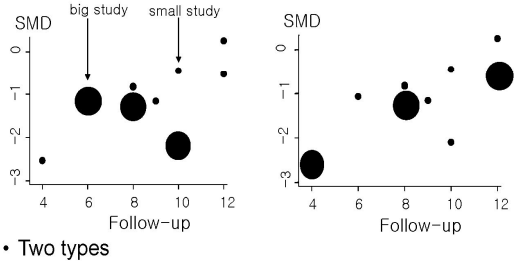
- Heterogeneity explained by differences between subgroups

$$Q_{btw} = Q_{all} - (Q_1 + \ldots + Q_m),\ df = m-1$$

80

(4) Meta-regression analysis

- Use a weighted linear regression
  - Just as in meta-analysis, the studies are different sizes, and should have different influences on the analysis



- Two types
  - Fixed-effects meta-regression / random-effects meta-regression

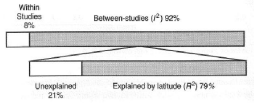
81

Proportion of heterogeneity explained by the use of meta-regression

- Compare
  - Heterogeneity variance from random-effects meta-analysis (τ_a^2) with
  - Heterogeneity variance from random-effects meta-regression (τ_b^2)
    - Allows more variation between studies due to covariates (slopes)
- % reduction in true variance by using covariate(s)
  - Proportion of variance explained

$$100\% \times \frac{\tau_a^2 - \tau_b^2}{\tau_a^2}$$

  - Analogous to the coefficient of determination (R^2) used in primary studies



82

An example

- BCG vaccine for the prevention of TB?
  - Non-vaccinated group과 비교한 13 RCT들을 SR
  - (log) Relative Risk (RR) is used
    - 1-RR을 사용해 vaccine의 protective effect를 직접 계산하기 위해

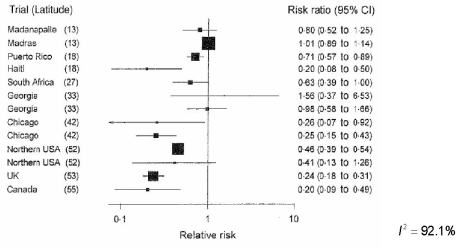


Figure 2.3 Forest plot of trials of BCG vaccine to prevent tuberculosis. Trials are ordered according to the latitude of the study location, expressed as degrees from the equator. No meta-analysis is shown. Adapated from Colditz *et al.*[32]

83

An example: The vaccine trial

- Random-effects model

```
. metan vaccine_dz vaccine_ndz novaccine_dz novaccine_ndz, rr randomi

        Study |        RR   [95% Conf. Interval]    % Weight
--------------+-------------------------------------------------
1             |  .410939     .134302     1.2574       5.03686
2             |  .204868     .086297     .486352      6.34761
3             |   .25974     .073443     .918609      4.41241
4             |  .236561     .179281     .312141      9.71734
5             |   .80449     .516293     1.25356      8.875527
6             |  .455611     .387132     .536203      10.1207
7             |  .197221     .078357     .498919      6.00822
8             |  1.01202     .894572      1.1449      10.2159
9             |  .625366     .392576     .996196      8.74833
10            |  .253765     .149421     .430976      8.36824
11            |  .712227     .572514     .886035      9.94717
12            |  1.56192     .373689     6.52837      3.79808
13            |  .985587     .583262     1.66399       8.4039
--------------+-------------------------------------------------
  D+L pooled RR |  .489736     .344987     .695219
--------------+-------------------------------------------------
  Heterogeneity chi-squared = 152.27 (d.f. = 12) p = 0.000
  Estimate of between-study variance Tau-squared =  0.3088
  Test of RR=1 : z= 3.99 p = 0.000
```

RE model 사용 후에도 some amount of heterogeneity가 여전히 존재: $\hat{\tau}_\theta^2 = 0.3088$

84

An example: The vaccine trial

- Dependence of BCG vaccine efficacy on study latitude

```
. metareg logrr centered, wsvar(varlogrr) bs(mm)

Meta-analysis regression                          No. of studies =  13
                                                  tau^2 method   =  mm
                                                  tau^2 estimate =  .0635

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    centered |  -.0292955   .0062989    -4.34   0.000    -.0416433   -.0169478
       _cons |  -.7183326   .1013561    -7.09   0.000    -.9169987   -.5196783
------------------------------------------------------------------------------
```

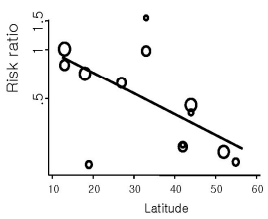
$$\log(\hat{RR}) = -0.7183 - 0.0292 \times l_{center}$$
$$= -0.7183 - 0.0292 \times (l - 33.4615)$$

$$RR_{\beta_1} = e^{\beta_1} = 0.97 \ [0.96,\ 0.99]$$

$\hat{\tau}_\theta^2 = 0.0635$

%variance explained by a distance from the latitude = $\frac{0.3088 - 0.0635}{0.3088} \times 100 = 79.4\%$

그러나 wide CI를 볼 때 아직 some unexplained heterogeneity 존재



85

Another example: Trial year and stroke recurrent rate

Declining Stroke and Vascular Event Recurrence Rates in Secondary Prevention Trials Over the Past 50 Years and Consequences for Current Trial Design

Keun-Sik Hong, MD; Sharon Yegiaian, MD; Meng Lee, MD; Juneyoung Lee, PhD; Jeffrey L. Saver, MD

Statistical Analyses

This was a study-level rather than an individual, patient-level systematic review, and each study was treated as a unit. Trends over time of annual event rates and the association of individual clinical characteristics with annual event rates were analyzed by restricted maximum likelihood fitting of univariable linear mixed meta-regression models for reported event rates. In these models, the effects of predictors were considered as fixed, studies varied additionally by normally distributed random effects, and event rates were weighted inversely to their estimated variances assuming that the numbers of events followed Poisson distributions.[9] For multivariable random-effects meta-regression analyses to explore the influence of changes in clinical characteristics on the secular trends of annual recurrent stroke rates, we selected variables (1) that were associated

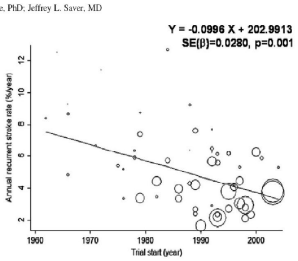


Figure. Trends over time of the event rates of recurrent stroke, fatal stroke, and major vascular events. The size of each circle on the graph indicates the weight of each trial, which was derived by the inverse of variance of the event rate of each trial. SE(β) indicates standard error of β-coefficient; CV, cardiovascular.

Conclusions—Recurrent stroke and vascular event rates have declined substantially over the last 5 decades, with improved blood pressure control and more frequent use of antiplatelet therapy as the leading causes. Considerably larger sample sizes are now needed to demonstrate incremental improvements in medical secondary prevention. (*Circulation*. 2011;123:2111-2119.)

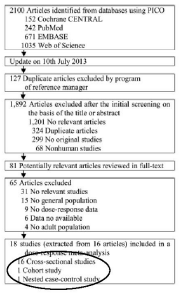
86

Another example: Blood vit. D status vs. MS

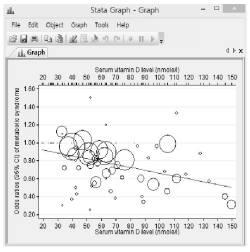
Blood Vitamin D Status and Metabolic Syndrome in the General Adult Population: A Dose-Response Meta-Analysis (*J Clin Endocrinol Metab* 99: 1053–1063, 2014)

Sang Yhun Ju, Hyun Suk Jeong, and Do Hoon Kim

Department of Family Medicine (S.Y.J.), Yeouido St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 150-713, Korea; Department of Preventive Medicine (H.S.J.), Seoul St Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul 137-701, Korea; and Department of Family Medicine (D.H.K.), Korea University Anam Hospital, Korea University College of Medicine, Seoul 136-705, Korea



We performed a 2-stage random-effects dose-risk meta-analysis to examine a nonlinear dose-response relationship between blood 25(OH)D levels and metabolic syndrome. After modeling the 25(OH)D levels using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) of the distribution (24–26), we used a generalized least-squares method and a multivariate maximum likelihood method to estimate a summary nonlinear dose-response relationship, while taking random effects into account (27). A *P* value for nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline was equal to 0. We also performed a linear regression model with weights, based on the inverse of variances (28).



87

Heterogeneity에 관한 summary

- Heterogeneity is inevitable
  - Extent of heterogeneity can be difficult
  - Pooling heterogeneous studies: long debate
- Furberg & Morgan(1987)
  - "combining apples and oranges and the occasional lemon"
- Study results variation이 얼마일 때까지 결합하는 것이 타당한가?
  - 정확한 가이드라인은 없음
  - 해당 주제의 context에 대한 이해 + 통계적 고려에 달려있다!
- Heterogeneity를 처리하는 best strategy는 없음
  - 그러나 이질성을 탐색, 검증, 원인 탐구: 연구자의 기본
    - Pooling은 clinical/methodological heterogeneity가 combine이 필요 없을 정도로 크지는 않다는 확신이 있는 경우에만 진행한다는 자세가 필요
- 탐색 후에도 여전히 상당한 양의 설명 불가능한 이질성이 존재?
  - 연구 결과들을 결합하는 것이 과연 적절한지 심사숙고
- 결합하기로 한다면 FE model과 RE model 중 어느 것을 사용할 것인지, 이로부터 어떤 결론을 유도할 것인지 결정해야.
  - 결국 이를 위해서는 상당한 양의 subjectivity가 필요할 수밖에 없다!
  - 중요한 것은 heterogeneity의 원인을 탐색하겠다는 자세!

88

C. Potential biases in MA

- Publication bias
  - Publication depends on the nature and direction of the results
- Time-lag bias
  - More likely to be published rapidly
- Multiple publication bias (duplication bias)
  - Sig. trial / SIT: more likely to be published more than once
- Citation bias
  - Positive trials : more likely to be cited by others
- Language bias
  - Positive trials : more likely to be published in English
- Outcome reporting bias
  - Selective reporting of some outcomes
- Biased inclusion criteria for the review

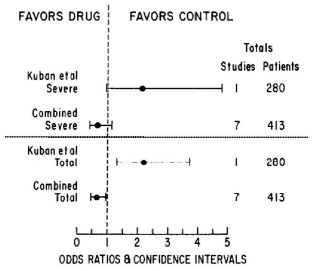
89

Publication bias (출판 편향, 출판 비뚤림)

- Unbiased된 결론에 도달?
  - 해당 연구 주제에 관한 대부분의 primary study들이 포함되어야
- 통계적으로 유의한 결과들을 보인 연구들
  - More likely to be submitted, published, published more rapidly
  - Leads to a preponderance of false-positive results than false-neg.
- Published bias
  - Combining only the identified published studies uncritically leads to an incorrect, over-optimistic conclusion

90

Suspected publication bias



Comparison of meta-analysis of 7 small RCTs of phenobarbital in the treatment of neonatal intracranial hemorrhage with one large co-operative study (3 institutions). Endpoints are total infants with hemorrhage and totals with severe hemorrhage (Grades III-IV) only. *Stat Med* 6(3): 321, 1987.

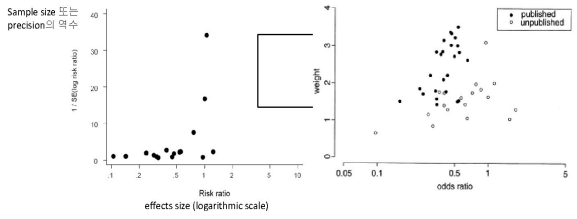
Meta-analyzed studies are small

91

Publication bias 확인 방법들

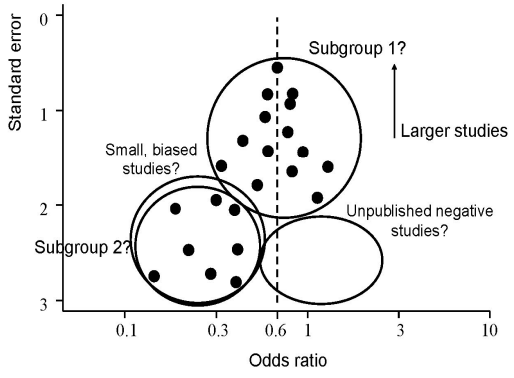
1. **The funnel plot / Contour-enhanced funnel plot**
2. Rank correlation test (Begg and Mazumdar, 1994) - lack of power
3. Linear regression test (Egger et al., 1997) – lack of power
4. **Harbord test (Harbord et al., 2006)**
5. Rosenbaum's fail-safe N (The file drawer problem)
6. The trim-and-fill method, selection model, etc.

(1) Funnel plot (깔때기 그림): Skewed if (publication) bias presents



92

Asymmetric funnel plot



93

Asymmetry? Small study effects!

- Publication bias detection: funnel plot의 **한계점**
  - Useful 그러나 다양한 sizes를 가진 다수의 study들이 필요
  - Informal method
    - 따라서 동일한 plot에 대해 사람마다 해석이 다를 수 있음
  - 다른 원인으로 인해 skewed 된 plot이 얻어질 수도 있음
    - Selection bias (biased inclusion criteria)
    - Study quality가 study size에 따라 다른 경우
    - Intervention 강도의 차이
    - Underlying risk 차이
    - Small study의 poor design
    - Inadequate analysis
    - True heterogeneity

94

(2) Contour-enhanced funnel plots

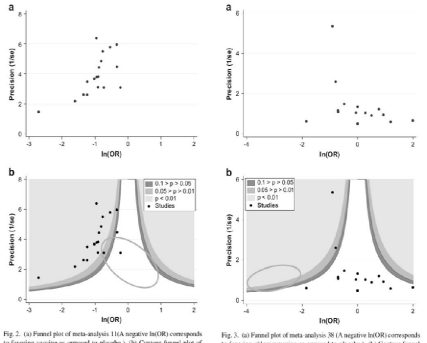


Fig. 2. (a) Funnel plot of meta-analysis 11(A negative ln(OR) corresponds to favoring vaccine as opposed to placebo.). (b) Contour-funnel plot of meta-analysis 11 (the ellipse indicates likely areas where "missing" studies are expected).

Publication bias is suspected based on statistical significance

Fig. 3. (a) Funnel plot of meta-analysis 38 (A negative ln(OR) corresponds to favoring chlorpromazine as opposed to placebo.). (b) Contour-funnel plot of meta-analysis 38 (the ellipse indicates likely areas where "missing" studies are expected).

May not be due to publication bias based on statistical significance

95

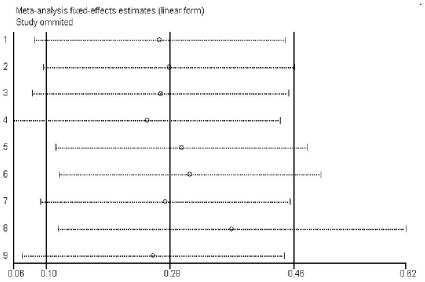
D. Sensitivity analysis (민감도 분석)

- 메타분석 결과가 분석에 사용된 특정 방법들이나 각 연구에서 얻어진 결론들에 얼마나 robust 한지를 평가
- 민감도 분석을 통해 "결과가 쉽게 변화되지 않는다"고 판단 되면 해당 메타분석 결과에 더 자신감을 가질 수 있을 것
- Oxman (1996):
  - Review 결과가 review를 수행하는 과정에서 행해진 key decision 들이나 assumption 들에 대해 얼마나 robust 한지를 검사하는 것
  - Reviewer는 문제가 될 소지가 있고 결과에 영향을 미칠 수 있는 key decision 들과 assumption 들을 identify 해 주어야
- Sensitivity analysis의 목적
  - 메타분석 결과가
    - Robust to the choice of the statistical methods?
    - Robust to the exclusion of trials of lesser quality (higher risk of bias)?
    - Robust to the exclusion of trials terminated early?
    - Distorted findings by publication bias?

96

An example

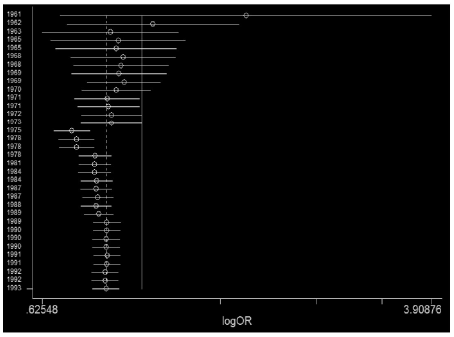
- MA: sodium fluoride (NaF) vs.h sodium monoflouorophos-phate (SMFP)
  - In terms of differences from baseline in DMFS
  - Using fixed-effects model



97

Another example

- Cumulative meta-analysis (by pub. year / baseline risk)



The trial in 1975

98

An example of sensitivity analysis

- Effect of homeopathy vs. placebo effect
  - Linde, et al., Lancet 1997:350;834-843

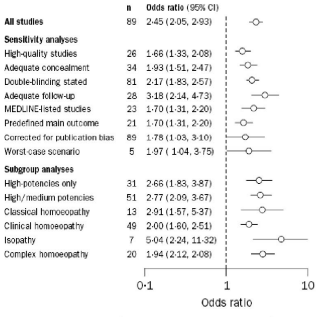


Table 3: **Pooled odds ratios and 95% CI (random-effects model)**

99

Meta-analysis

Effect of Blood Pressure Lowering in Early Ischemic Stroke
Stroke. 2015;46:1883-1889

Pooling the results from 12 trials with the random-effects model showed that blood pressure lowering in early ischemic stroke did not affect the risk of death or dependency at 3 months or at trial end point (relative risk, 1.04; 95% confidence interval, 0.96–1.13; P=0.35). There was significant heterogeneity among studies (I^2=51%; P for heterogeneity=0.02; Figure 2). The funnel plots showed no major asymmetry (Figure 3).

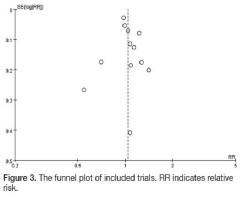


Figure 3. The funnel plot of included trials. RR indicates relative risk.

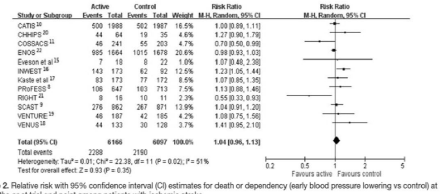


Figure 2. Relative risk with 95% confidence interval (CI) estimates for death or dependency (early blood pressure lowering vs control) at 3 months or at trial end point among patients with ischemic stroke.

100

Meta-analysis

Effects of vitamin E on stroke subtypes: meta-analysis of randomised controlled trials *BMJ* 2010;341:c5702

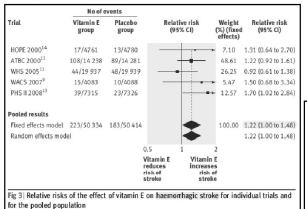


Fig 3| Relative risks of the effect of vitamin E on haemorrhagic stroke for individual trials and for the pooled population

1000 treated people of 0.6 fewer total strokes, 0.8 more haemorrhagic strokes, and 2.1 fewer ischaemic strokes. In other words, for every 1250 individuals taking vitamin E, one haemorrhagic stroke occurs; whereas one ischaemic stroke is prevented for every 476 individuals treated. NNH = 1/ARI = (1/0.8)*1000 = 1250
NNT = 1/ARR = (1/2.1)*1000 = 476

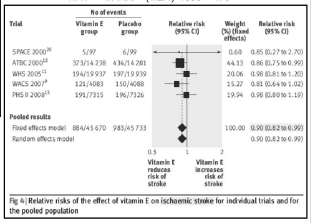


Fig 4| Relative risks of the effect of vitamin E on ischaemic stroke for individual trials and for the pooled population

Sensitivity analyses
By visually examining Galbraith plots, we did not identify trial results that fell outside the margins set by two standard deviations from the mean for all evaluated outcomes. For the analysis on ischaemic stroke, we excluded the trial that did not specify if the analysis was performed according to the intention to treat method.[37] This did not change the results (fixed effects model, relative risk 0.90 (0.82 to 0.99), P=0.02).

DISCUSSION
This meta-analysis of randomised controlled trials of vitamin E treatment reporting on stroke outcomes indicates that the risk of haemorrhagic stroke is significantly increased by 22% whereas the risk of ischaemic stroke is significantly reduced by 10%. These associations are obscured when total stroke is evaluated as the outcome.

101

Step 9. Reporting

- Points-to-consider in reporting
  - Strengths and limitations of study
  - Discussion of individual trials
  - Potential biological mechanisms
  - Implications for clinical practice
  - Directions for future research
- Guidelines for reporting meta-analyses
  - QUality Of Reporting Of Meta-analyses (QUOROM guideline)
    - To address standards for improving quality of reporting of meta-analyses of RCTs
    - Moher, et al. Lancet 1999;354:1896-1900
  - Meta-analysis Of Observational Studies in Epidemiology (MOOSE guideline)
    - Stroup, et al. JAMA 2000;283:2008-2012
  - Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA statement)
    - Liberati, et al. Ann Intern Med. 2009;151:W65-W94
    - Moher, et al. Ann Intern Med. 2009;151:264-269
    - Moher, et al. J Clin Epidemiol. 2009;62:1006-1012

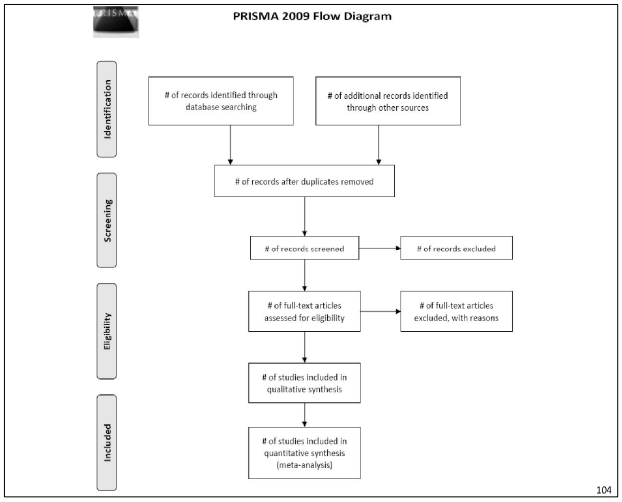
102

PRISMA 2009 Checklist

Section/topic	#	Checklist item
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 revie registration infor
Eligibility criteria	6	Specify study ch language, public
Information sources	7	Describe all infor additional studies
Search	8	Present full electr repeated.
Study selection	9	State the process included in the m
Data collection process	10	Describe method for obtaining and
Data items	11	List and define al simplifications m
Risk of bias in individual studies	12	Describe method done at the study
Summary measures	13	State the principa
Synthesis of results	14	Describe the met (e.g., I2 for each

PRISMA 2009 Checklist

Section/topic	#	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.



104

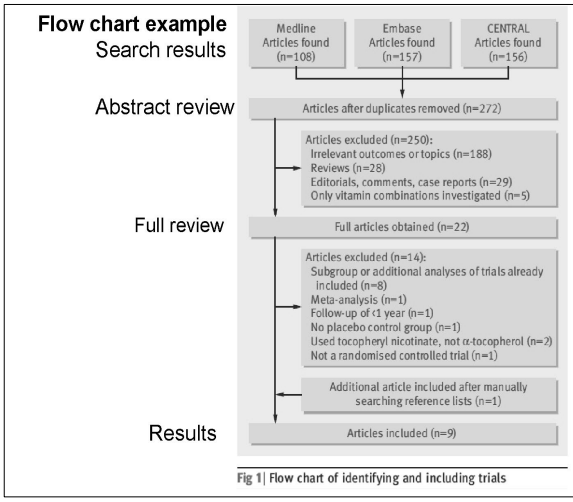


Fig 1| Flow chart of identifying and including trials

105

Step 10. From evidence to practice

- 해당 research question의 nature에 따라 적절성 여부를 결정
  - Are there direct public health or clinical applications?
  - Does apply to etiological research questions

In conclusion, this meta-analysis of completed clinical trials suggested blood pressure lowering in early ischemic stroke had a neutral effect on the prevention of death or dependency. Further studies with an appropriately phenotyped population that is recruited in the hyperacute phase of ischemic stroke are warranted.

Conclusion

In this meta-analysis of randomised trials, we found that vitamin E increased the risk for haemorrhagic stroke by 22% and reduced the risk of ischaemic stroke by 10%. Using total stroke as the outcome obscures these harms and benefits. However, given the relatively small reduction in risk of ischaemic stroke and the generally more severe outcome of haemorrhagic stroke, indiscriminate widespread use of vitamin E should be cautioned against.

106

Merits and limitations of SR / MA

- 장점
  - Bias의 minimization
    - 논문의 content 확인, 명확한 IC/EC 기준 사용
  - 신뢰성 있고 정확한 결론 제공
  - 대규모 정보들의 신속한 흡수
  - Small sized effect intervention 평가의 유일한 대안
    - Large sample size
  - Generalizability 확보
  - 새로운 가설 설정에 도움
    - Subgroup analysis
  - 결과의 정확도 향상
    - 정량적인 체계적 고찰 방법론 (메타분석) 사용
- 논란점
  - Garbage in, garbage out
    - A meta-analysis is only as good as the studies in it
  - 'mixing apples with oranges'
  - 임상적 논리 확증에는 도움. 그러나 이를 대체할 수는 없다
  - 'A new ***bete noire***', statistical alchemy for the 21st century
  - Meta-analysis / Mega-silliness / A weapon

107

An observational nature of SR / MA

- RCT들을 SR한다 하더라도 review 그 자체는 하나의 관찰연구에 해당
  - 따라서 potentially subject to the same biases inherent in observational studies
  - Comparison of results of RCTs with different characteristics is not a randomized comparison and can be confounded
  - As in primary studies, subgroup analyses in meta-analyses increase the likelihood of chance findings

→ Data selection과 analysis plan에 관한 protocol 필요

→ Pre-planned
  - Study report에 a priori 결과인지, data-driven 결과인지에 대한 명확한 구분 필요 (pre-planned)

108

메타분석 프로그램들

- Software info.
  - http://www.prw.le.ac.uk/epidemio/personal/ajs22/meta/index.html
- Commercial
  - STATA (http://www.stata.com), SAS, S+, R
  - Comprehensive meta-analysis (http://www.meta-analysis.com)
  - Metawin (http://www.metawinsoft.com)
  - WEasyMA (http://www.weasyma.com)
- Freeware
  - Review-Manager (RevMan v.5) (http://www.cc-ims.net/revman)
  - Sinergy (http://www.e-biometria.com/ebiometria/sinergy/sinergy.htm)
  - Epi-meta (http://www.cdc.gov/epo/dpram/epimeta/epimeta.htm)
  - MetaDISc ver 1.4 (http://meta-disc.software.informer.com/1.4/)
  - Meta, Meta-Analyst, Meta-Test

109

* Further topics

- Missing data
  - Types of missing data
  - General principles for dealing with missing data
  - ***Missing SD for changes***
- ITT (intention-to-treat) issues
- Cluster randomized trials
- Cross-over trials
- Indirect comparisons and multiple treatments meta-analysis
- Multiplicity and the play of chance
- Bayesian and hierarchical approaches to meta-analysis
- Handling rare events (including zero frequencies)
- Handling relative risks across multiple categories
- Meta-analysis for Diagnostic Test Accuracy (DTA)
- Meta-analysis with Survival data

110

나가며...

- Systematic review
  - Up-to-date relevant and valid information 제공
- Meta-analysis
  - Quantitative relationship에 관한 indication을 제공하게 될 것
- 장점
  - Bias의 minimization
    - 논문의 content 확인, 명확한 기준을 사용한 논문 exclusion
  - 신뢰성 있고 정확한 결론 제공
  - 대규모 정보들의 신속한 흡수
  - 새로운 가설 설정에 도움
    - 이질적인 결과들에 대한 subgroup analysis
  - 결과의 정확도 향상
    - 정량적인 체계적 문헌고찰 방법론(메타분석)의 사용
- 한계점
  - 임상/보건학적 논리를 확실히 하는데 도움
  - 그러나 대체할 수는 없다.
  - 체계적 고찰결과의 무비판적 수용 및 무감각한 적용은 피해야 할 것!
  - (지식)+(경험)+(가치관)+(근거) 등이 통합된 의사결정이 이루어져야!
  - 이러한 인식 하에서 SR / MA 실시

Ref.: Cook et al. (1997) Systematic reviews: Synthesis of best evidence for clinical decisions. Ann.Int.Med. 126:376-380.

111