Systematic review and meta-analysis
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Systematic review

- Review methodology
- Meta-analysis
What is a systematic review

• A review that has been conducted using a systematic approach in order to minimise biases and random error
Why do we need a systematic review

• Tool for health care practitioners, researchers, policy makers, and even consumers who want to keep up with the evidences that are accumulated in their area of interests
### Rationale

More objective appraisal of the evidence than traditional narrative reviews

#### Narrative review
- Subjective selection of studies
- Limitation of single or few studies
- Selection bias
- Unhelpful descriptions, e.g., no clear evidence
- A weak relationship, a strong relationship.

#### Systematic review
- Objective selection
- More transparent appraisal of evidence
- Allow reader to replicate
- Quantitative conclusion

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Rationale

• Meta-analysis:
  – Estimates treatment effects
  – Leading to reduces probability of false negative results (increase power of test)
  – Potentially to a more timely introduction of effective treatments.
Rationale

• Exploratory analyses:
  – Subgroups of patients who are likely to respond particularly well to a treatment (or the reverse)

• Systematic review may demonstrate
  – A lack of adequate evidence
  – A gap of knowledge
  – Thus, identify the area where further studies are needed
Review Methodology

• Good Rationale
• Clearly state research question
• Objective
• Identify relevant studies/locate studies
• Explicitly describe inclusion & exclusion criteria of studies
• Data extraction: study factor, outcome
• Quality assessment
• Statistical analysis
• Results
• Discussion
Rationale

• Why do we need to perform the review
• How were results of previous individual and review studies (if any)
  – Positive results
  – Negative results
• Methodological issues
  – Sample size/Power of test
  – Previous reviews
    • Narrative reviews?
      – Selective bias
      – Publication bias
      – Pooling effect sizes?
Rationale

• Previous systematic review/s with meta-analysis
  – Methods
    • Selection bias?
    • Pooling appropriately?
    • Number of studies?
    • Number of relevant outcomes?
    • Number of treatments?
  – Number of publications since previous published?
Management of Chronic Prostatitis/Chronic Pelvic Pain Syndrome
A Systematic Review and Network Meta-analysis

Magnitude of problem

• Prostatitis is a common condition, with an estimated prevalence in the community of about 9%,¹ and accounts for nearly 2 million ambulatory care encounters annually in the United States.²

• Symptoms of CP/CPPS can diminish quality of life and impair physical and psychological function.⁵
The etiology of CP/CPPS is uncertain but may include inflammatory or noninflammatory etiologies.\textsuperscript{6,7,8}

An inciting agent may cause inflammation or neurological damage in or around the prostate and lead to pelvic floor neuromuscular and/or neuropathic pain.

Predisposing factors for CP/CPPS may include heredity, infection, voiding abnormalities, hormone imbalance, intraprostatic reflux, immunological or allergic triggers, or psychological traits.
A wide variety of therapies including α-blockers, antibiotics, anti-inflammatory medications, and other agents (eg, finasteride, phytotherapy, and gabapentinoids) are routinely used.

**Rationale**

However, the efficacy of these treatments is controversial, partly because many clinical trials testing these therapies have been small, with little statistical power to detect treatment effects.

To date, only 1 systematic review and 1 meta-analysis of α-blockers vs placebo of which we are aware have been performed for treatment of CP/CPPS.
• We therefore performed a systematic review and network meta-analysis mapping all treatment regimens, with 2 aims.
  – To compare total symptom, pain, voiding, and quality-of-life scores at the end of therapy with α-blockers (the most commonly evaluated therapy for CP/CPPS), other active drugs, or placebo.
  – To compare rates of responses to therapies available for treating CP/CPPS.
Risk prediction models of breast cancer: a systematic review of model performances

Background & rationale

- Breast cancer is the most common cancer found in women across the world, accounting for 23% of all new cancers in women [1].
- Although around two-thirds of new cases are in developed countries, it is the most common cancer in women in developing countries.
- An early detection screening using mammography can improve the survival rate of patients using strong evidence suggested from a meta-analysis [3].
- The organized breast cancer screening programs using mammography have therefore been well established in developed countries in Europe and North America.
• In contrast, the majority of women living in developing countries have never had access to mammography because of
  – the severe shortage of human resources and
  – infrastructures that have been needed for a few decades to fill the gap.
• Screening to every woman is therefore not feasible in most developing countries
• But identifying target women with relatively higher risk of developing breast cancer looks to be a promising alternative
• The number of risk prediction models has been increasingly developed, for estimating about breast cancer in individual women.
• However, those model performances are questionable, i.e., poor to fair performances.
• We therefore have conducted a study with the aim to systematically review previous risk prediction models
  – How the models were constructed?
  – How many variables and what were they?
  – Study design?

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– Were those models validated?
  • Internal and external validations?
– Model’s performance
  • Calibration
  • Discrimination
  • The results from this review help to identify the most reliable model and indicate the strengths and weaknesses of each model for guiding future model development.
Flow diagram of review for conducting further study

Stage 1: Start research:
- Carry out/update systematic review & meta-analysis

Results conclusive?*
- Yes: Stop research
- No: Stage 2

Stage 2: Would further analysis of existing data assist in answering unresolved research questions?
- Yes: Consider carrying out an IPD meta-analysis
- No: Consider carrying out a mixed treatment comparison synthesis

Stage 3: Conduct (further) trials basing design on the current synthesis model (or the best available evidence in the first instance)

Part 1: Efficient analysis of the existing evidence base

Part 2: Designing future research more coherently
Research question

Treatments

• CP/CPPS
  – Is alpha-blocker is better in improving total symptom, pain, voiding, and quality of life than antibiotics in CP/CPPS patients?
  – Among active treatments, which treatment regimens are better in improving symptoms in CP/CPPS patients?
Research question

• Preeclampsia
  – Does calcium or vitamin D supplementation decrease risk of preeclampsia occurrence in pregnancy when compares to placebo?
  – Among calcium, vitamin D, and calcium plus vitamin D supplementations, which one is better in prevention of preeclampsia in pregnancy?
Research question

• Diagnostic studies
  – How are performances of Berlin and Stop-Bang questionnaires comparing with the standard polysomnography in screening obstructive sleep apnea in pregnancy

• Observational studies
  – Does sleep duration associate with type two diabetes and its progression in general adults?
  – Is there association between VDR and BMD/osteoporosis in women?
Good research question

- Evidence-base Medicine (EBM)
  - P Patient
  - I Intervention
  - C Comparator
  - O Outcome
  - PICO
Research question

• Is alpha-blocker is better in improving total symptom, pain, voiding, and quality of life than antibiotics in CP/CPPS patients?
• Is there association between VDR and BMD/osteoporosis in women?
  – To compare rates of osteoporosis in women with BB with bb genotypes
1. Defines source of database

- **MEDLINE**
  - Medical Literature Analysis and Retrieval System Online, or MEDLARS Online
  - Launched by the National Library of Medicine in 1964
  - Over 26 million references since 1950 to present
  - Completed references are added each day Tuesday through Saturday
  - Cover > 5200 worldwide journals in 40 languages
    - Uses medical subject heading (MeSH) for index
  - ~ 47% of journals covered are published in the US
    - PubMed available free of charge

Defines source of databases

Excerpta Medica Database (EMBASE)

- Over ~30 million records since from 1974 to present
- More than 900,000 records added annually
- Covers over 8,500 active peer-reviewed journals published in 90 countries
- 2,900+ journals that are not covered by MEDLINE
- uses EMTREE for indexing
- includes English abstracts for 80% of references
- daily update, within two weeks of receipt of the original journal
- Produced by Elsevier, no free version available
Defines source of databases

Scopus (launched in November 2004)

• Covers > 60 million records
  – 21,500 peer-reviewed journals (4,200 Open Access journals)
  – 36 trade publications
  – Coverage year, back to 2003 for all subject areas
  – 113,000 books plus 530 book series
  – 3.6 million conference papers (~10%) from proceedings and journals
    • Medical Science ~2.9%
    • Biological Science ~2.7%
    • Chemical Science ~1.9%
• 41 million records
  – 21 million records with references back to 1996
  – 20 million records 1823-1996
• 318 million scientific web pages
• 23 million patent records from five patent offices
  – World Intellectual Property Organization (WIPO)
  – European Patent Office
  – US Patent Office
  – UK Intellectual Property Office
• “Articles-in-Press” > 5,000 journals
  – Cambridge University Press
  – Elsevier
  – Springer / Kluwer
  – Karger Medical and Scientific Publishers
  – Nature Publishing Group (NPG)
  – The Institute of Electrical and Electronics Engineers (IEEE)
  – BioMed Central (BMC)
  – Lippincott, Williams & Wilkins (LWW)
Defines source of database

- The Cochrane Controlled Trials Register (CCTR)
- ClinicalTrials.gov
- HUGE NET Review
- Reference lists
- Personal communication with expert in the field
Gray literatures

- **Gray Source Index**
- **AHRQ** - agency for healthcare research and quality
- **World Health Organization** - providing leadership on global health matters, shaping the health research agenda, setting norms and standards, articulating evidence-based policy options, providing technical support to countries and monitoring and assessing health trends.
- **List Gray Literature Producing Organizations** - from the New York Academy of Medicine, includes government and private sector
Locate studies

2. Define the software & version used for searching
   - PubMed
   - Ovid
   - Scopus
- Search by topic, journal title or abbreviation, ISSN, or browse by **subject terms**.
- **Limit** searches to PubMed journals and/or currently indexed.
- Lists of all **Entrez journals** and those with **links to full-text web sites** are available.
   Association between SLE nephritis and polymorphic variants of the CRP and Fc gamma receptor IIIa genes.

   The combined genotypes of stimulatory and inhibitory Fc gamma receptors associated with systemic lupus erythematosus and periodontitis in Japanese adults.

3. Harley JB, Kelly JA, Kaufman KM.
   Unraveling the genetics of systemic lupus erythematosus.

   A novel single-nucleotide polymorphism of the Fc gamma receptor IIIa gene is associated with genetic susceptibility to systemic
3. Defines searching terms

- Combinations of search terms
  - Intervention: treatment/study factor
  - Outcome of interest
  - Comparator*
  - Patient
- Specify period of searching
- Plan for update searching
Example

- VDR & BMD/Osteoporosis (J Bone Miner Res. 2004;19(3):419-28.) Intervention/exposure
- P
  - Women
  - Females
- I/E
  - Vitamin D receptor
  - VDR
  - Genotype
  - Allele
  - Polymorphism
  - Locus
• **Outcome**
  
  – Bone mineral density
  – BMD
  – Bone density
  – Osteoporosis
  – Fracture
Example

• **VDR**: BMD/Osteoporosis (J Bone Miner Res. 2004;19(3):419-28.)

1. vitamin D receptor or VDR (MeSH)
2. genotype(s) or allele(s) or polymorphism(s) (MeSH)
3. bone mineral density or BMD or bone density (MeSH)
4. low bone mineral density or low density (textword)
5. osteoporosis (MeSH)
6. fracture (MeSH)
7. 1 and 2 and 3
8. 1 and 2 and 4
9. 1 and 2 and 5
10. 1 and 2 and 6
Selecting studies

• Clearly define inclusion & exclusion criteria

• Inclusion criteria
  – Type of subjects (P)
    • Children, adults
    • Specific type of disease
      – T2D, CKD, CP/CPPS IIIA
  - Treatment or exposure or gene (I)
  - Comparator (if needed)
  - Outcome
• General considerations
  – **Study design**
    • Randomized controlled trial,
    • Observational studies (cohort, case-control, cross-sectional studies)
  – **Languages**
    • English, French, others
  – **Full articles**
    • Multiple publications of the same studies, choose the recent one or the one has provided more completeness of data
Exclusion

– Incompleteness of information
  • Contact authors at least two times for incomplete data

Ineligibility criteria

– Not studied patients
– Not the outcome/intervention of interests
– Study design
  • Not comparative studies, no control group
  • Not RCTs
– Review studies
  • Narrative review, systematic review
Selecting studies

• Merge studies identified from databases using reference manager (e.g. Endnote)
  – Remove duplicates

• Two reviewers independently select studies
  – Screen title/abstract to remove non-relevant studies based on eligibility criteria
  – Access full papers
  – Computerize review results
– Examine other sources of studies
– Contact author if needed
– Final decision

• Perform searching every 1-3 months while doing a review
Figure 1. Flow of information through the different phases of a systematic review.

doi:10.1371/journal.pmed.1000097.g001

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Study selection

• Participants with CP/CPPS categories IIIA or IIIB
• Any pair of the following interventions:
  – α-blockers,
  – antibiotics,
  – steroidal and nonsteroidal anti-inflammatory drugs,
  – finasteride, glycosaminoglycans, phytotherapy, gabapentinoids, and placebo.
• Any of the following outcomes:
  – pain scores, voiding scores, quality-of-life scores, and total symptom scores.
• The full article could be retrieved
• Had sufficient data for extraction, including number of patients, means and standard deviations of continuous outcomes in each group, and/or numbers of patients per group for dichotomous outcomes.
• For trials with multiple publications, we selected the publication with the most complete information.
• Disagreements in selection were resolved by discussion and consensus.
1 Article identified from reference lists

327 Articles identified from database search
162 From MEDLINE
165 From EMBASE

66 Excluded (duplicate studies)

262 Potentially relevant articles identified for title and abstract review

232 Excluded
151 Non-CP/CPPS study
26 Other interventions
21 Non-English language
16 Review articles
9 Noncomparative studies
3 Observational studies
2 Abstracts only
1 Outcome not of interest
1 Systematic review

30 Articles identified for full review

5 Excluded
1 Non-CP/CPPS study
1 Review article
1 Noncomparative study
1 Protocol article
1 Duplicate study

25 Articles eligible for inclusion

2 Excluded (insufficient data)

23 Articles included in systematic review and network meta-analysis

Anothaisintawee, T. et al. JAMA 2011;305:78-86
Data extraction (DE)

- At least two reviewers
- Design DEF, pilot, & revise DEF
  - The article
    - Study ID,
    - Author,
    - Year & source of publication
  - The study characteristics
    - Type of studies subjects
      - ethnicity, setting
      - Adults vs children
      - Postmenopause, premenopause
    - Study design (RCT, CS, CC, CrS)
– Patients
  • Demographic and clinical features of study's participants that might affect outcomes
    – mean age, gender, BMI, smoking, underlying diseases
– Methods/criteria used for measuring outcomes
– Interventions
  • Treatments
    – Dosage/day
  • Scanners
    – Version
– Table of study factors/interventions versus outcomes
DE (cont.)

- **Dichotomous outcome**
  - Frequencies between study factor/intervention vs outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
<th>Yes</th>
<th>No</th>
<th>n</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx (Exp+)</td>
<td>Yes</td>
<td>a</td>
<td>b</td>
<td>n₁</td>
<td>a/n₁</td>
</tr>
<tr>
<td>Placebo (Exp-)</td>
<td>Yes</td>
<td>c</td>
<td>d</td>
<td>n₂</td>
<td>c/n₂</td>
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</tbody>
</table>

- OR (95% CI), RR (95% CI), HR (95% CI)
**Continuous outcome**

- \( n, \text{mean} (95\% \text{ CI}) \)

<table>
<thead>
<tr>
<th>Group</th>
<th>( n )</th>
<th>mean</th>
<th>SD</th>
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<tbody>
<tr>
<td>A</td>
<td>( n_1 )</td>
<td>mean(_1)</td>
<td>SD(_1)</td>
</tr>
<tr>
<td>B</td>
<td>( n_2 )</td>
<td>mean(_2)</td>
<td>SD(_2)</td>
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</tbody>
</table>
Risk of bias assessment

- Quality Assessment (QA)
- Consider internal & external validity
Risk Of Bias (cont.)

• RCT
  – The Cochrane Collaboration’s tool for assessing risk of bias 2009
  – Preferred reports of items for systematic review and meta-analysis-PRISMA guideline
<table>
<thead>
<tr>
<th>Domain</th>
<th>Description</th>
<th>Review authors’ judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sequence generation.</strong></td>
<td>Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.</td>
<td>Was the allocation sequence adequately generated?</td>
</tr>
<tr>
<td><strong>Allocation concealment.</strong></td>
<td>Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.</td>
<td>Was allocation adequately concealed?</td>
</tr>
<tr>
<td><strong>Blinding of participants, personnel and outcome assessors</strong></td>
<td>Assessments should be made for each main outcome (or class of outcomes).</td>
<td>Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.</td>
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<tr>
<td><strong>Incomplete outcome data</strong></td>
<td>Assessments should be made for each main outcome (or class of outcomes).</td>
<td>Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.</td>
</tr>
<tr>
<td>Selective outcome reporting.</td>
<td>State how the possibility of selective outcome reporting was examined by the review authors, and what was found.</td>
<td>Are reports of the study free of suggestion of selective outcome reporting?</td>
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<td>-----------------------------</td>
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<td>-----------------------------------------------------------------</td>
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<tr>
<td>Other sources of bias.</td>
<td>State any important concerns about bias not addressed in the other domains in the tool.</td>
<td>Was the study apparently free of other problems that could put it at a high risk of bias?</td>
</tr>
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<td></td>
<td>If particular questions/entries were pre-specified in the review’s protocol, responses should be provided for each question/entry.</td>
<td>Premature trial termination</td>
</tr>
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<td></td>
<td>Trial methodology</td>
<td>Post-randomization exclusion</td>
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<tr>
<td></td>
<td>Statistical analysis</td>
<td>Unbalance baseline characteristics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adequately describe methods of data analysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- use per-protocol analysis, modified ITT</td>
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</tbody>
</table>
## Risk of bias assessment

<table>
<thead>
<tr>
<th>Author</th>
<th>Adequate sequence generation</th>
<th>Adequate allocation concealment</th>
<th>Blinding</th>
<th>address incomplete outcome data</th>
<th>Selective outcome report</th>
<th>Free of other bias</th>
<th>Description of other bias</th>
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</table>
Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I)

• For intervention studies where interventions are not randomly allocated.
• Seven domains are considered
  – Before interventions
    • Confounding
    • Selection of patients into the study
  – At interventions
    • Classification of interventions
ROBINS-I
– After interventions
  • Deviation from intended interventions
  • Missing data
  • Measurements of outcomes
  • Selective outcome report
• The first three domains are totally different from assessments of RCT because randomisation can protect against bias before/at randomization
• The last four domains overlapped with RCT because randomization does not protect bias after randomisation
• Response options for each domain
  – Yes, Probably yes
  – No, Probably no
  – No information

• Overall risk of bias judgment
  – Low risk
    • All seven domains are low risk of bias
– Moderate risk
  • The study is judged to be low and moderate risks for all domains

– Serious risk
  • The study is judged to be serious risk of bias at least one of all domains

– Critical risk
  • The study is judged to be critical risk of bias at least one of all domains
Observational studies

- NEWCASTLE - OTTAWA QUALITY ASSESSMENT SCALE (NOS)
- Risk/association studies
- Cohort studies
  - Selection of cohorts
  - Comparability of cohorts
  - Assessment of outcome
- Items
  - Selection (4)
  - Comparability (1)
  - Exposure (3)

NOS

- Case-Control studies
  - Selection of case and controls
  - Comparability of cases and controls
  - Ascertainment of exposure

- Items
  - Selection (4)
  - Comparability (1)
  - Exposure (3)
Grading

• Grade ‘high’ quality as a ‘star’
• A maximum of one ‘star’ for each item within the ‘Selection’ and ‘Exposure/Outcome’ categories; maximum of two ‘stars’ for ‘Comparability’
• **Prognostic studies**
  – Quality in prognostic study (QUIPS)
  • Study participants
  • Study attrition
  • Prognostic factor measurement
  • Outcome measurement
  • Study confounding
  • Statistical analysis and report
  • Each domain is graded as low, moderate, and high risk of bias
<table>
<thead>
<tr>
<th>Variable</th>
<th>Bias Domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal study or characteristics of unbiased study</td>
<td>The study sample adequately represents the population of interest</td>
</tr>
<tr>
<td>Prompting items and considerations†</td>
<td>a. Adequate participation in the study by eligible persons</td>
</tr>
<tr>
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<td>b. Description of the source population or population of interest</td>
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<td>c. Description of the baseline study sample</td>
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<td>d. Adequate description of the sampling frame and recruitment</td>
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<td></td>
<td>e. Adequate description of the period and place of recruitment</td>
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<td></td>
<td>f. Adequate description of inclusion and exclusion criteria</td>
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</tbody>
</table>
## Bias Domains

<table>
<thead>
<tr>
<th>5. Study Confounding</th>
<th>6. Statistical Analysis and Reporting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important potential confounding factors are appropriately accounted for</td>
<td>The statistical analysis is appropriate, and all primary outcomes are reported</td>
</tr>
<tr>
<td><strong>a.</strong> All important confounders are measured</td>
<td><strong>a.</strong> Sufficient presentation of data to assess the adequacy of the analytic strategy</td>
</tr>
<tr>
<td><strong>b.</strong> Clear definitions of the important confounders measured are provided</td>
<td><strong>b.</strong> Strategy for model building is appropriate and is based on a conceptual framework or model</td>
</tr>
<tr>
<td><strong>c.</strong> Measurement of all important confounders is adequately valid and reliable</td>
<td><strong>c.</strong> The selected statistical model is adequate for the design of the study</td>
</tr>
<tr>
<td><strong>d.</strong> The method and setting of confounding measurement are the same for all study participants</td>
<td><strong>d.</strong> There is no selective reporting of results</td>
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<tr>
<td><strong>e.</strong> Appropriate methods are used if imputation is used for missing confounder data</td>
<td></td>
</tr>
<tr>
<td><strong>f.</strong> Important potential confounders are accounted for in the study design</td>
<td></td>
</tr>
<tr>
<td><strong>g.</strong> Important potential confounders are accounted for in the analysis</td>
<td></td>
</tr>
<tr>
<td>The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome</td>
<td>The reported results are very likely to be spurious or biased related to analysis or reporting</td>
</tr>
<tr>
<td>The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome</td>
<td>The reported results may be spurious or biased related to analysis or reporting</td>
</tr>
<tr>
<td>The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome</td>
<td>The reported results are unlikely to be spurious or biased related to analysis or reporting</td>
</tr>
</tbody>
</table>
Risk of bias assessment for genetic association studies

- Selection bias
- Information bias
- Confounding bias
- Multiple testing
- Selective reporting
- HWE

- Yes, low/no risk of bias; No, possible/high risk of bias; unclear

Statistical analysis

• Meta-analysis
  – Dichotomous outcome
    • Pool OR, RR, HR
  – Continuous outcome
    • Mean difference
Steps of data analysis

- Unit of analysis is study NOT subject
- Describe how data will be pooled
  - OR, RR, RD, HR
  - Mean difference
- **Estimate treatment effect for each study,**
  - Effect size, e.g., ORᵢ
  - Variance of ln(ORᵢ)
  - Weight = 1/varln(ORᵢ)
- **Pool treatment effect using the fixed effect model**
- Check heterogeneity
  - Forest plot
  - Cochrane Q test & I²
    - Presence, i.e., Q test significance OR I² ≥ 25%
• Chose appropriate pooling method
  – Fixed-effect model
    • MH, IV, Peto
  – Random
    • Der-Simonian-Laid
  – Explore possible sources if presence of heterogeneity
    – Graph
    – Meta-regression

• Subgroup analysis

• Assess reporting bias
  – Graph & test

• Sensitivity analysis
Register review proposal

- Establish that we are doing this review
- May reduce the risk of multiple reviews addressing the same question
- Increases potential communication with interested researchers
- Provide greater transparency when updating a systematic review
- Where to register
  - National Institute of Health (NIH)
  - Campbell Collaboration - produces systematic reviews of the effects of social interventions
    - [http://www.campbellcollaboration.org/](http://www.campbellcollaboration.org/)
  - Cochrane Collaboration - international organization, produces and disseminates systematic reviews of health care interventions
    - [http://www.cochrane.org/](http://www.cochrane.org/)
  - PROSPERO - international prospective register of systematic reviews
    - [http://www.crd.york.ac.uk/prospero/](http://www.crd.york.ac.uk/prospero/)
  - Human Genome Epidemiological Network (HuGeNet)
Pooling effect size

No variation between studies (Homogeneity)
• Fixed effect model
  – Mantel-Haenzel
  – Peto
  – Inverse variance

Variations between studies (Heterogeneity)
• Random effect model
  – Der-Simonian and Laird
  – Baysian method
• Effects
  – OR, RR, RD for dichotomous outcome
  – Un/standardised mean difference for continuous outcome
## Dichotomous outcome

<table>
<thead>
<tr>
<th>Group</th>
<th>Disease</th>
<th>Yes</th>
<th>No</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>A</td>
<td>b</td>
<td></td>
<td>n₁</td>
</tr>
<tr>
<td>Placebo</td>
<td>C</td>
<td>d</td>
<td></td>
<td>n₂</td>
</tr>
</tbody>
</table>
\[
\ln OR_{MH} = \frac{\sum_{i=1}^{k} w_i \theta_i}{\sum_{i=1}^{k} w_i}
\]

\[
\theta_i = \ln OR_i = \ln\left(\frac{a_i d_i}{c_i b_i}\right)
\]

\[
w_i = \frac{1}{\text{var}_i} = \frac{b_i c_i}{N_i}
\]
Inverse variance

\[
\ln \text{OR}_{iV} = \frac{\sum_{i=1}^{k} \hat{w}_i \ln \text{OR}_i}{\sum_{i=1}^{k} \hat{w}_i}
\]

\[
\ln \text{OR}_i = \ln \left( \frac{a_i d_i}{b_i c_i} \right)
\]

\[
\hat{w}_i = \frac{1}{\hat{\text{var}}(\ln \text{OR}_i)}
\]

\[
\hat{\text{var}}(\ln \text{OR}_i) = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}
\]
Pooled RR

\[
\ln \hat{RR}_{iv} = \frac{\sum_{i=1}^{k} w_i \ln \hat{RR}_i}{\sum_{i=1}^{k} w_i}
\]

\[
\ln RR_i = \ln \left(\frac{a_i / n_{1i}}{c_i / n_{2i}}\right)
\]

\[
w_i = \frac{1}{\text{var ln } \hat{RR}_i}
\]

\[
\text{var ln } \hat{RR}_i = \frac{1}{a_i} - \frac{1}{n_{1i}} + \frac{1}{c_i} - \frac{1}{n_{2i}}
\]
Heterogeneity test

\[ Q = \sum_{i=1}^{k} w_i (\hat{\theta}_i - \hat{\theta}_p)^2 \]

\[ \hat{\theta}_i = \ln \hat{OR}_i \text{ (or } \ln \hat{RR}_i, \ln \hat{HR}_i) \]

\[ \hat{\theta}_p = \ln \hat{OR}_{i,v} \]

\[ Q \sim \chi^2 \text{ with } df = k - 1 \]
Degree of heterogeneity

\[ I^2 = \frac{[Q-(k-1)]}{Q} \times 100 \]

- \(< 25\% = low\)
- \(25\% - 75\% = moderate\)
- \(> 75\% = high\)

- Declaring for heterogeneity
- \(Q\) test significance
  - \(I^2 = \) moderate or higher
Random-effect model
Der-Simonian and Laird

\[
\ln OR_{DL} = \frac{\sum_{i=1}^{k} \hat{w}_i \hat{\theta}_i}{\sum_{i=1}^{k} \hat{w}_i}
\]

\[
\ln OR_i = \ln\left(\frac{a_i d_i}{b_i c_i}\right)
\]

\[
\hat{w}_i^* = \frac{1}{\text{var}_i + \tau^2}
\]

\[
\text{var}_i = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}
\]
Between study variation (Tau²)

\[ \tau^2 = \frac{Q - (k - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}} \]
### Table 3. Treatment Response Rates for α-Blockers and Anti-inflammatory Drugs

<table>
<thead>
<tr>
<th>Source</th>
<th>Definition of Treatment Response</th>
<th>Active Treatment</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel et al.² 2008</td>
<td>4-point decrease in NIH-CPSI</td>
<td>68</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td>Tuğcu et al.¹⁰ 2007</td>
<td>50% decrease in NIH-CPSI</td>
<td>20</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Alexander et al.²¹ 2004</td>
<td>4-point decrease in NIH-CPSI</td>
<td>12</td>
<td>33</td>
<td>11</td>
</tr>
<tr>
<td>Nickel et al.²⁴ 2004</td>
<td>50% decrease in NIH-CPSI</td>
<td>9</td>
<td>18</td>
<td>5</td>
</tr>
<tr>
<td>Cheah et al.³³ 2003</td>
<td>50% decrease in NIH-CPSI</td>
<td>24</td>
<td>19</td>
<td>14</td>
</tr>
<tr>
<td>Mehik et al.³⁶ 2003</td>
<td>33% decrease in NIH-CPSI</td>
<td>13</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Pooled RR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assess heterogeneity

\[ H_0 : \ln RR_1 = \ln RR_2 = \ldots = \ln RR_k \]
### Figure 2. Treatment responsiveness in CP/CPPS patients: Alpha-blockers versus placebo

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>RR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehik A. (2003)</td>
<td>3.82 (1.53, 9.55)</td>
<td>4.06</td>
</tr>
<tr>
<td>Cheah P.Y. (2003)</td>
<td>1.63 (1.03, 2.57)</td>
<td>16.28</td>
</tr>
<tr>
<td>Nickel J.C. (2004)</td>
<td>2.00 (0.76, 5.23)</td>
<td>3.68</td>
</tr>
<tr>
<td>Alexander R.B. (2004)</td>
<td>1.09 (0.54, 2.21)</td>
<td>6.83</td>
</tr>
<tr>
<td>Tugcu V. (2007)</td>
<td>2.00 (1.14, 3.52)</td>
<td>10.64</td>
</tr>
<tr>
<td>Nickel J.C. (2008)</td>
<td>1.00 (0.79, 1.27)</td>
<td>58.51</td>
</tr>
<tr>
<td>Overall (I-squared = 64.2%, p = 0.016)</td>
<td>1.27 (1.06, 1.53)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

**Risk ratio**

Section for Clinical Epidemiology & Biostatistics, Faculty of Medicine Ramathibodi Hospital
Heterogeneity test

\[ H_0 : \ln RR_1 = \ln RR_2 = \ldots = \ln RR_k \]

\[ H_a : \text{At least one pair of } \, RR_j \, \text{is different} \]
### Meta-Analysis Results

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel J.C. (2004)</td>
<td>2.000</td>
<td>0.765</td>
<td>5.232</td>
</tr>
<tr>
<td>Tugcu V. (2007)</td>
<td>2.000</td>
<td>1.136</td>
<td>3.522</td>
</tr>
<tr>
<td>Nickel J.C. (2008)</td>
<td>1.000</td>
<td>0.786</td>
<td>1.273</td>
</tr>
</tbody>
</table>

I-V pooled RR

<table>
<thead>
<tr>
<th>I-V pooled RR</th>
<th>RR</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.270</td>
<td>1.056</td>
<td>1.527</td>
</tr>
</tbody>
</table>

**Heterogeneity**

- chi-squared = 13.95 (d.f. = 5) \( p = 0.016 \)
- \( I^2 = 64.2\% \)
- Test of RR=1 : \( z = 2.54 \) \( p = 0.011 \)
Pooling with a random effect model

```
metan res_al non_al res_pl non_pl, rr randomi label(namevar=author, yearvar=year)
    sortby(year) xlabel(0.5,1,1.57,3,5,10)
```

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nickel J.C. (2004)</td>
<td>2.000</td>
<td>0.765</td>
<td>5.232</td>
</tr>
<tr>
<td>Tugcu V. (2007)</td>
<td>2.000</td>
<td>1.136</td>
<td>3.522</td>
</tr>
<tr>
<td>Nickel J.C. (2008)</td>
<td>1.000</td>
<td>0.786</td>
<td>1.273</td>
</tr>
<tr>
<td>D+L pooled RR</td>
<td>1.571</td>
<td>1.073</td>
<td>2.300</td>
</tr>
</tbody>
</table>

Heterogeneity chi-squared = 13.95 (d.f. = 5) p = 0.016
I-squared (variation in RR attributable to heterogeneity) = 64.2%
Estimate of between-study variance Tau-squared = 0.1296
Test of RR=1 : z = 2.32 p = 0.020
Figure 3. Effects of alpha-blockers on treatment responsiveness: The random effect model

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>RR (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mehik A. (2003)</td>
<td>3.82 (1.53, 9.55)</td>
<td>10.87</td>
</tr>
<tr>
<td>Cheah P.Y. (2003)</td>
<td>1.63 (1.03, 2.57)</td>
<td>0.53</td>
</tr>
<tr>
<td>Nickel J.C. (2004)</td>
<td>2.00 (0.76, 5.23)</td>
<td>10.20</td>
</tr>
<tr>
<td>Alexander R.B. (2004)</td>
<td>1.09 (0.54, 2.21)</td>
<td>14.56</td>
</tr>
<tr>
<td>Tugcu V. (2007)</td>
<td>2.00 (1.14, 3.52)</td>
<td>17.74</td>
</tr>
<tr>
<td>Nickel J.C. (2008)</td>
<td>1.00 (0.79, 1.27)</td>
<td>6.10</td>
</tr>
<tr>
<td>Overall (I-squared = 64.2%, p = 0.016)</td>
<td>1.57 (1.07, 2.30)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.
Continuous outcome

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>$n_1$</td>
<td>$\text{mean}_1$</td>
<td>$\text{SD}_1$</td>
</tr>
<tr>
<td>Placebo</td>
<td>$n_2$</td>
<td>$\text{mean}_2$</td>
<td>$\text{SD}_2$</td>
</tr>
</tbody>
</table>
Methods of pooling

- **Standardised mean difference (SMD)**
  - Different scale of measurements
    - Pain (VAS vs WOMAC), depression score

- **Unstandardised mean difference (USMD)**
  - The same scale of measurements
\[ \hat{D} = \frac{\sum_{i=1}^{k} w_i d_i}{\sum_{i=1}^{k} w_i} \]

\[ w_i = \frac{1}{\text{var}(d_i)} \]

\[ d_i = \frac{x_{1i} - x_{2i}}{s_{d_i}} \]

\[ s_{d_i} = \sqrt{\frac{(n_{1i} - 1)s_{d_{1i}}^2 - (n_{2i} - 1)s_{d_{2i}}^2}{(n_{1i} + n_{2i} - 2)}} \]

\[ \text{var}(d_i) = \frac{n_i}{n_{1i}n_{2i}} + \frac{d_i^2}{2(n_i - 2)} \ldots \text{(Cohen' s method)} \]
\[ d_i = (\bar{x}_{1i} - \bar{x}_{2i}) \]

\[ \text{var}(d_i) = \frac{s d_{1i}^2}{n_{1i}} + \frac{s d_{2i}^2}{n_{2i}} \]
Heterogeneity test

Ho: $D_1 = D_2 = \ldots, D_k$

\[
Q = \sum_{i=1}^{k} w_i (d_i - \hat{D})^2
\]

\[
\hat{D} = \frac{\sum_{i=1}^{k} w_i d_i}{\sum_{i=1}^{k} w_i}
\]

\[
w_i = \frac{1}{\text{var}(d_i)}
\]
Example

- CP/CPPS
- Total symptom score between alpha-blocker versus placebo
<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Scale</th>
<th>Alpha-blockers</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evliyaoglu Y</td>
<td>2002</td>
<td>IPSS</td>
<td>30 10.47 4.44</td>
<td>30 16.17 5.7</td>
</tr>
<tr>
<td>Cheah PY</td>
<td>2003</td>
<td>NIH-CP/CPPS</td>
<td>43 10.8 9</td>
<td>43 17 12.1</td>
</tr>
<tr>
<td>Alexander RB</td>
<td>2004</td>
<td>NIH-CP/CPPS</td>
<td>45 20.2 12.18</td>
<td>45 21.6 9.84</td>
</tr>
<tr>
<td>Tugcu V</td>
<td>2006</td>
<td>NIH-CP/CPPS</td>
<td>30 10.7 1.3</td>
<td>30 21.9 1.2</td>
</tr>
<tr>
<td>Nickel JC</td>
<td>2008</td>
<td>NIH-CP/CPPS</td>
<td>138 16.7 14.92</td>
<td>134 18.6 14.05</td>
</tr>
</tbody>
</table>
metan  n_alpha  mean_total_al  sd_total_al  n_placebo  mean_total_pl  
sd_total_pl,  label(namevar=author,  yearid=year )  sortby(year)  cohen

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evliyaoglu Y(3)</td>
<td>-1.116</td>
<td>-1.661  -0.570</td>
<td>10.32</td>
</tr>
<tr>
<td>Cheah PY(1)</td>
<td>-0.581</td>
<td>-1.013  -0.150</td>
<td>16.47</td>
</tr>
<tr>
<td>Alexander RB(10)</td>
<td>-0.126</td>
<td>-0.540  0.287</td>
<td>17.94</td>
</tr>
<tr>
<td>Tugcu V(2)</td>
<td>-8.953</td>
<td>-10.659 -7.247</td>
<td>1.05</td>
</tr>
<tr>
<td>Nickel JC(5)</td>
<td>-0.131</td>
<td>-0.369  0.107</td>
<td>54.21</td>
</tr>
</tbody>
</table>

I-V pooled SMD      | -0.399 | -0.574  -0.224       | 100.00   |

Heterogeneity chi-squared = 110.43 (d.f. = 4) p = 0.000
I-squared (variation in SMD attributable to heterogeneity) = 96.4%
Test of SMD=0 : z= 4.46 p = 0.000
Figure 6. Pooling standardized mean difference using fixed effect model: Alpha-blockers versus placebo

<table>
<thead>
<tr>
<th>Author</th>
<th>SMD (95% CI)</th>
<th>%Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evliyaoglu Y</td>
<td>-1.12 (-1.66, -0.57)</td>
<td>10.32</td>
</tr>
<tr>
<td>Cheah PY</td>
<td>-0.58 (-1.01, -0.15)</td>
<td>16.47</td>
</tr>
<tr>
<td>Alexander RB</td>
<td>-0.13 (-0.54, 0.29 )</td>
<td>17.94</td>
</tr>
<tr>
<td>Tugcu V</td>
<td>-8.95 (-10.66, -7.25)</td>
<td>1.05</td>
</tr>
<tr>
<td>Nickel JC</td>
<td>-0.13 (-0.37, 0.11 )</td>
<td>54.21</td>
</tr>
<tr>
<td>Overall (I-squared = 96.4%, p = 0.000)</td>
<td>-0.40 (-0.57, -0.22)</td>
<td>100.00</td>
</tr>
</tbody>
</table>
metan  n_alpha mean_total_al sd_total_al n_placebo mean_total_pl sd_total_pl, randomi label(namevar=author) sortby(year)

<table>
<thead>
<tr>
<th>Study</th>
<th>SMD</th>
<th>[95% Conf. Interval]</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evliyaoglu Y(3)</td>
<td>-1.116</td>
<td>-1.661 -0.570</td>
<td>20.98</td>
</tr>
<tr>
<td>Cheah PY(1)</td>
<td>-0.581</td>
<td>-1.013 -0.150</td>
<td>21.42</td>
</tr>
<tr>
<td>Alexander RB(10)</td>
<td>-0.126</td>
<td>-0.540 0.287</td>
<td>21.48</td>
</tr>
<tr>
<td>Tugcu V(2)</td>
<td>-8.953</td>
<td>-10.659 -7.247</td>
<td>14.17</td>
</tr>
<tr>
<td>Nickel JC(5)</td>
<td>-0.131</td>
<td>-0.369 0.107</td>
<td>21.95</td>
</tr>
</tbody>
</table>

| D+L pooled SMD      | -1.683| -2.751 -0.615        | 100.00   |

Heterogeneity chi-squared = 110.43 (d.f. = 4) p = 0.000
I-squared (variation in SMD attributable to heterogeneity) = 96.4%
Estimate of between-study variance Tau-squared = 1.3372
Test of SMD=0 : z= 3.09 p = 0.002