Mahidol University
Faculty of Medicine Ramathibodi Hospital
Section for Clinical Epidemiology and Biostatistics

Systematic Review and Meta-analysis International College of Public Health, Chulalongkorn University March, 11th 2019

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Outline of talk

- Review methodology
  - Identifying studies
  - Selection of studies
  - Risk of bias assessment
  - Data extractions
  - Statistical analysis plan
  - Protocol registration
- Meta-analysis
  - Dichotomous outcome
  - Continuous outcome

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,
  - 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
- Include identified studies as many as possible, less bias
- More transparent appraisal of evidence
- Allow reader to replicate
- Quantitative conclusion

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 gab of knowledge
  - Thus, identify the area where further studies are needed

Review proposal

- Introduction & background & rationale
- Research question/objective
- Review methods
  - Locate studies
  - Select studies
    - Inclusion/exclusion criteria
  - Data extraction
  - Risk of bias assessment
  - Statistical analysis plan
  - Time frame
  - Budget

Introduction

- Background
  - Prevalence/incidence
  - Burden
  - Treatment managements or risk factors if observational studies
- 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?
        - Selection 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?

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The association between oral hygiene and periodontitis: a systematic review and meta-analysis.

Lertpimonchai A[1,2], Rattanasiri S[1], Arj-Ong Vallibhakara S[1], Attia J[3,4], Thakkinstian A[1].
Int Dent J. 2017 Dec;67(6):332-343

Background and rationale

- Periodontitis is the most common oral disease worldwide, with an age-standardized prevalence of 11.2%
- It is a multi-factorial disease with risk factors such as age, gender, diabetes mellitus (DM), smoking, and, most directly, oral hygiene (OH).
- Dental plaque and calculus are usually caused by improper tooth brushing technique, ignoring interdental cleaning and irregular dental visits.
- It predictably results in the gingival inflammation.

- Persistent gingivitis is a key risk-predictor for breakdown of periodontal attachment.
- Despite the fact that poor OH is well accepted as an important risk factor of periodontitis, the magnitude of OH associated with periodontitis, to date, has not been explored in a meta-analysis.
- Therefore, we conducted a systematic review and meta-analysis aiming to estimate the effects of OH measured by the oral hygiene index (OHI), plaque index (PI) and plaque score (PSc) on periodontitis. In addition, we secondarily aimed to pool the magnitude of association between oral care habits (i.e., regular tooth brushing, interdental cleaning and dental visit) and periodontitis.

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The efficacy of antibiotic treatment versus surgical treatment of uncomplicated acute appendicitis: Systematic review and network meta-analysis of randomized controlled trial

Poprom N, Numthavaj P, Wilasrusmee C, Rattanasiri S, Attia J, McEvoy M, Thakkinstian A.

Am J Surg. 2018 Oct 9. doi: 10.1016/j.amjsurg.2018.10.009

- Appendicitis,
  - Most common urgent condition in general surgery,
  - An incidence ~100/100,000/year, and higher prevalence in men than women (8.6% versus 6.7%).
- Standard treatment
  - Appendectomy
    - Intra and post-operative morbidities
      - Post-operative complication rate ranges from 2% to 23%
      - Vascular injuries, urinary tract complications, hematomas, colonic fistulas, surgical site infections, adhesions, bowel obstructions, and significant length of hospital stay
  - Conservative treatment is use of antibiotics
      - failure is ~ 13% higher, but lower complications

Previous evidences and rationale

- 3 systematic reviews in children
- 13 adults
  - 10 included only RCTs; N ranged from 3-6
  - published during 1995–2015
- 1 mixed children and adults
- Antibiotics:
  - 3rd generation of cephalosporin, metronidazole, penicillin, and beta-lactamase
  - These were collapsed into one category
- We therefore conducted a systematic review and network meta-analysis to assess both the efficacy and safety between individual antibiotics and appendectomy. Probabilities of being the best treatment option, i.e., high efficacy and safety, were estimated and ranked.

Good research question

- Evidence-base Medicine (EBM)
  - Patient/Population
  - Intervention/Exposure
  - Comparator
  - Outcome
  - PICO

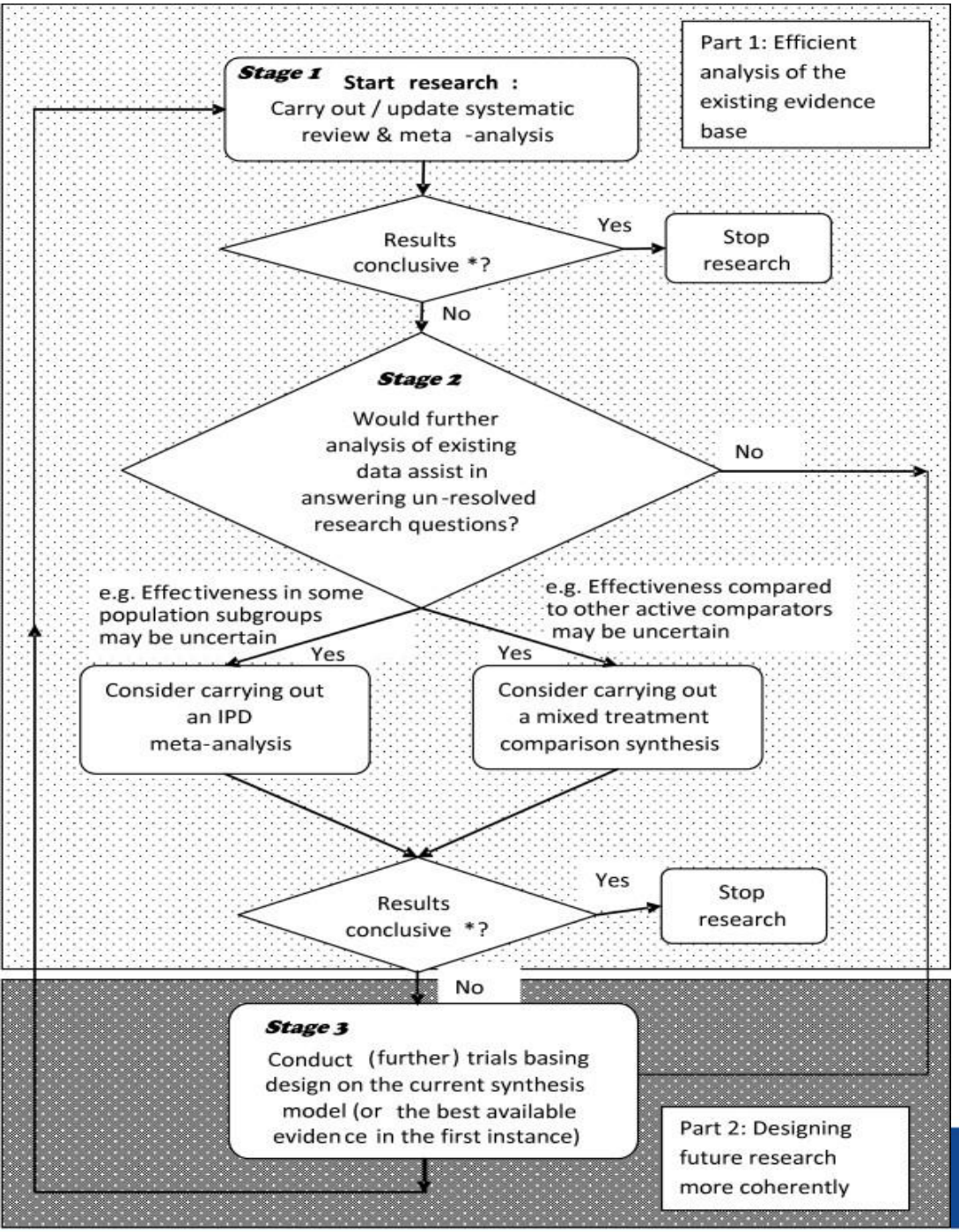
Research question

Treatments

- Is individual antibiotic better in lowering complication than open surgery in uncomplicated appendicitis?
- Among antibiotics, which regimens are better in success rate and lowering complications

Research question

- Observational studies
  - **Is there association between oral hygiene and periodontitis?**
  - Does sleep duration associate with type two diabetes and its progression in general adults?
  - Is there association between VDR and BMD/osteoporosis in women?



Flow diagram of applying systematic review & meta-analysis for conducting further study

From BMC medical research methodology. 2009;9:29.

Locate studies

1. Defines source of database
   - MEDLINE
     - 1949to present
     - Over 16 million references
     - Completed references are added each day from Tuesday through Saturday
     - Cover 5200 worldwide journals in 40 languages
     - Uses medical subject heading (MeSH) for index
     - Includes biomedicine and health science journals
       - English abstracts for 79% on references
       - 90% are English language articles
       - 47% of journals covered are published in the US
     - PubMed available free of charge

From http://www.nlm.nih.gov/pubs/factsheets/medline.html

Defines source of databases

EMBASE

- Over 12 million records from 1974-present
- More than 600,000 records added annually
- Covers over 4,800 active peer-reviewed journals published in > 70 countries/ 30 languages
- 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)

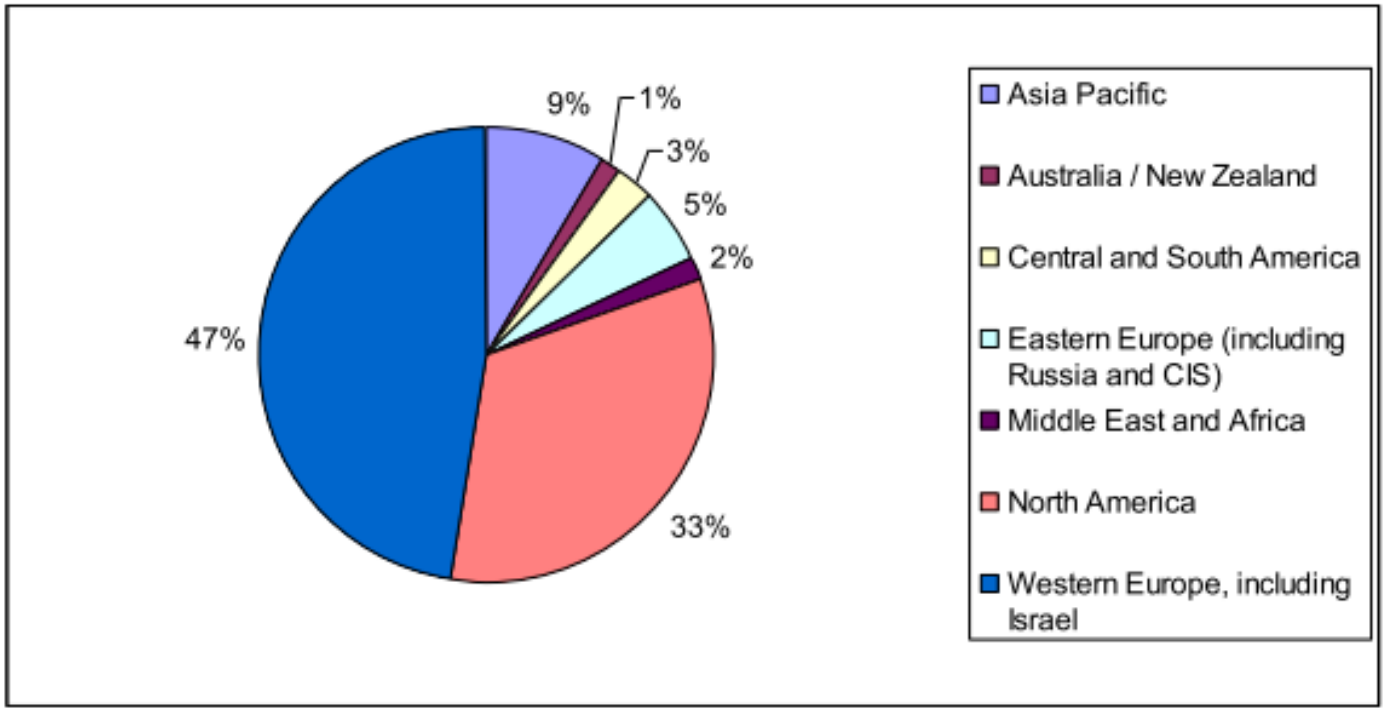
- 18,000 titles
  - 16,500 peer-reviewed journals (1,200 Open Access journals)
  - 600 trade publications
  - 350 book series
  - 3.6 million conference papers (~10%) from proceedings and journals
    - Medical Science ~2.9%
    - Biological Science ~ 2.7%
    - Chemical Science ~ 1.9%

- 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
  - Japanese Patent Office
  - UK Intellectual Property Office

- "Articles-in-Press" from over 3,000 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)

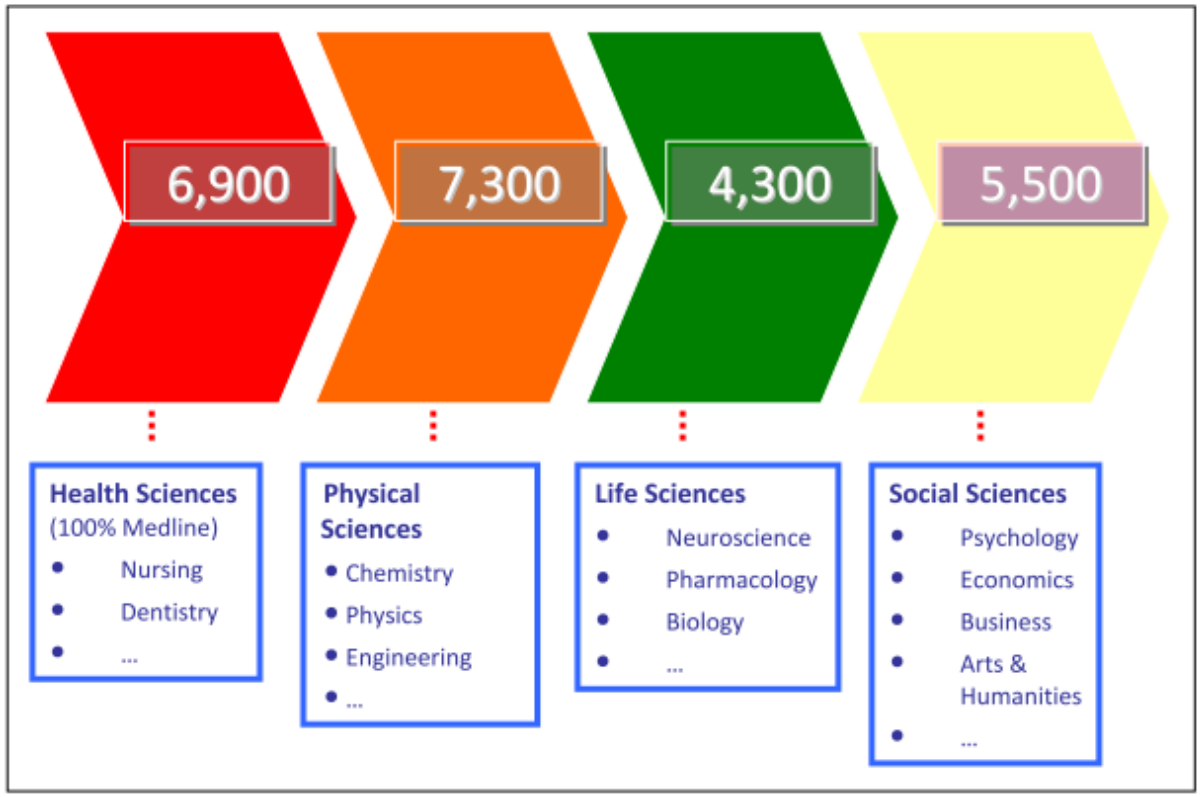
Coverage by region

Number of Scopus titles by geographical region (October 2009)



Percentage of journals in Scopus based on geographical regions (January 2010)

Coverage across subject areas



Number of journal titles by broad subject area.
Note: Journal titles may belong to more than one subject area.

Defines source of database

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

Define source of database

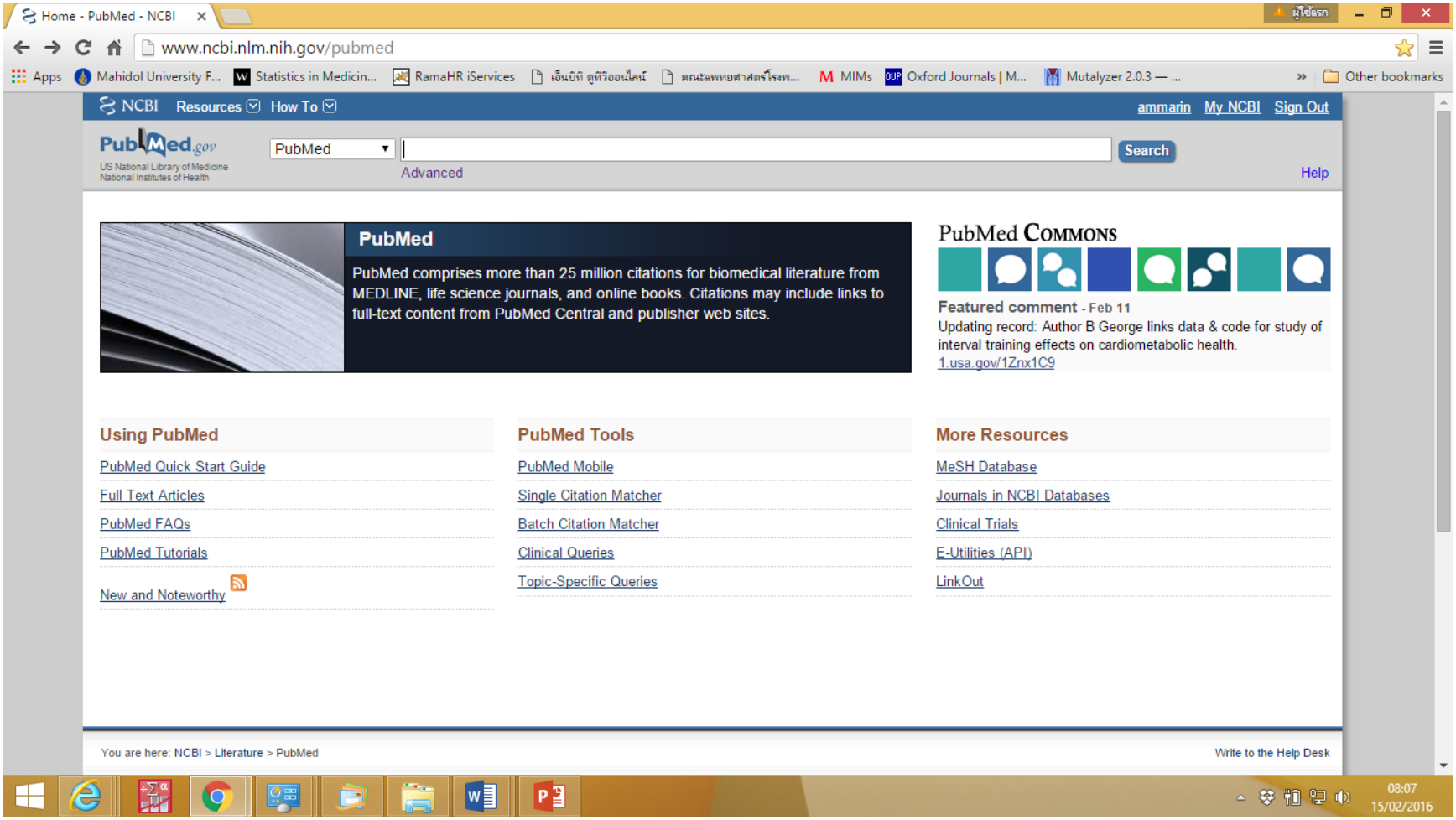
- Gray literatures
  - Information that falls outside the mainstream of published journal and monograph literature, not controlled by commercial publishers
- Sources from NSH library: http://nihlibrary.campusguides.com/content.php?pid=252593&sid=2085946)
  - WorldCat - 1.5 billion items in this collection of library catalogs
  - Google Scholar - Search scholarly literature across many disciplines and sources, including theses, books, abstracts and articles.

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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PubMed Commons
Featured comment - Feb 11
Updating record: Author B George links data & code for study of interval training effects on cardiometabolic health.
1.usa.gov/1Znx1C9
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PubMed Quick Start Guide
Full Text Articles
PubMed FAQs
PubMed Tutorials
New and Noteworthy
PubMed Tools
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Single Citation Matcher
Batch Citation Matcher
Clinical Queries
Topic-Specific Queries
More Resources
MeSH Database
Journals in NCBI Databases
Clinical Trials
E-Utilities (API)
LinkOut
You are here: NCBI > Literature > PubMed
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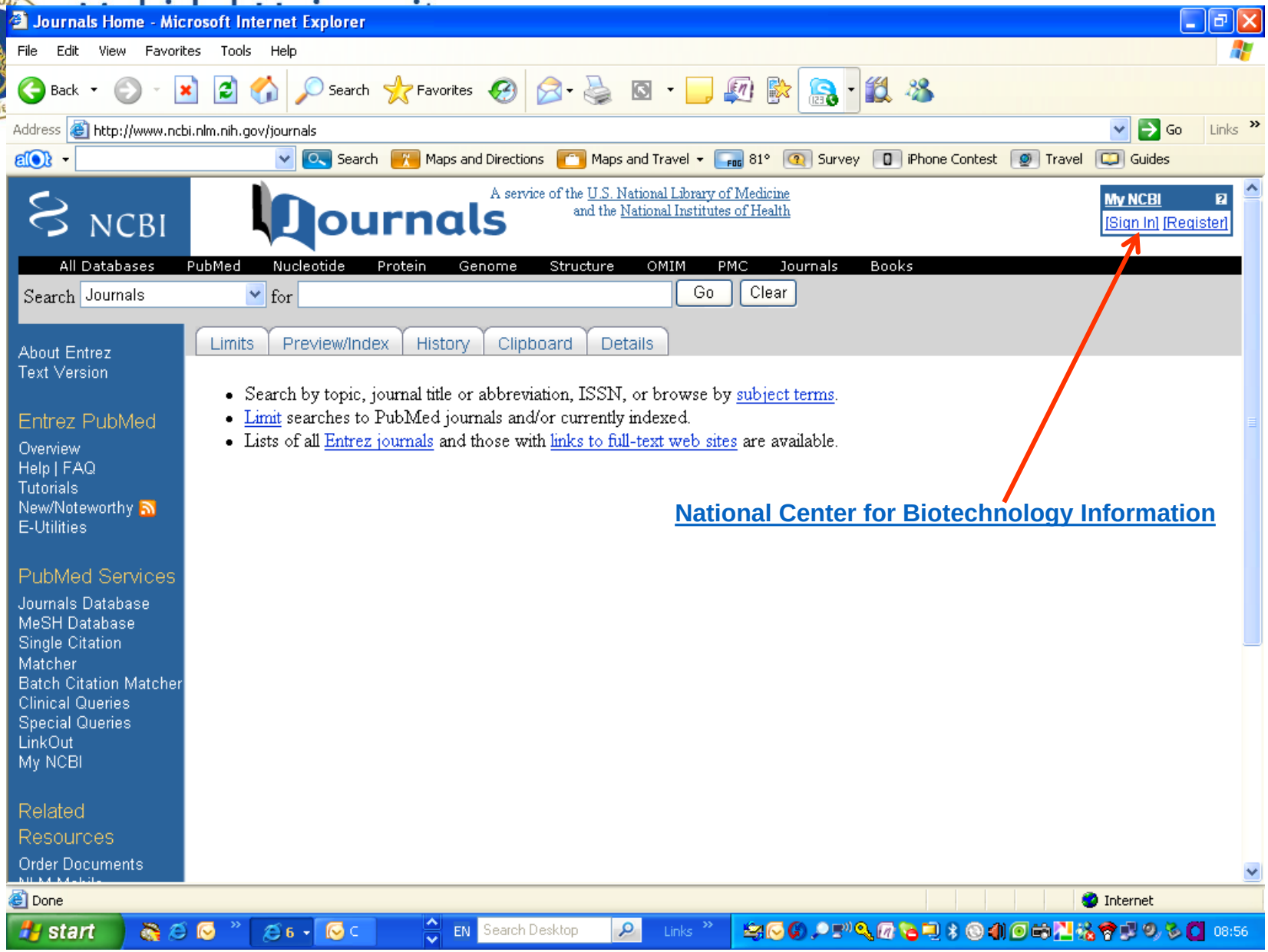
15/02/2016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Search by topic, journal title or abbreviation, ISSN, or browse by subject terms.
Limit searches to PubMed journals and/or currently indexed.
Lists of all Entrez journals and those with links to full-text web sites are available.
National Center for Biotechnology Information
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Session Results

Save | Delete | Print | Email | Export | Combine using And Or Basic | Advanced | Change View

Search Query	Results	Actions	Alerts
#1 'genotype'/exp OR genotype	192,526	View | Edit	

Save | Delete | Print | Email | Export | Change View

Refine Search BETA

- Journal Title
- Publication Type
- Publication Year

Apply Limits

192,526 Search Results

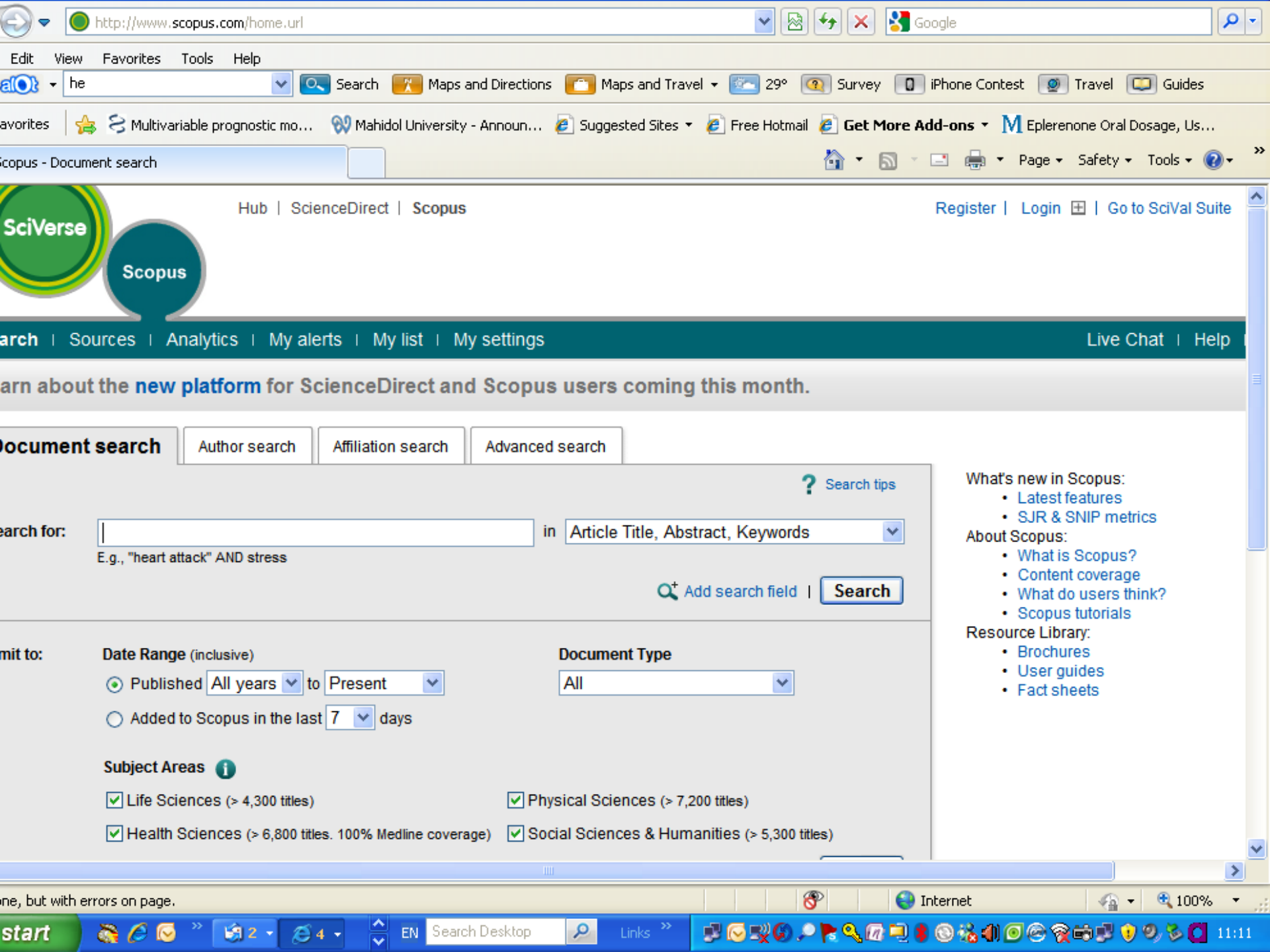
Search Details - Open

View | Print | Export | Email | Order | Add to Clipboard 1-25 next

Sort by: Relevance Publication Year Entry Date Selected: 0 (clear), or select first: 100 500 5000

1 Role of LINGO1 polymorphisms in Parkinson's disease
Haubenberger D., Hotzy C., Pirker W., Katzenschlager R., Brücke T., Zimprich F., Auff E., Zimprich A.
Movement Disorders 2009 **24**:**16** (2404-2407)
Embase MEDLINE Abstract Index Terms View Full Text

2 Relationship between glucose-6-phosphate dehydrogenase gene mutations and neonatal jaundice in Naning, Guangxi
Zhong D.-N., Gao Z.-Y., Liu Y.-N., Liu Y., Wei L.-M.
Chinese Journal of Contemporary Pediatrics 2009 **11**:**12** (970-972)
Embase MEDLINE Abstract Index Terms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Hub | ScienceDirect | Scopus
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11:11

3. Defines searching terms

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

Oral hygiene and Periodontitis

- Databases
  - Medline via PubMed
  - Scopus
- Period
  - Since inception to May 2016
- Search terms based on three domains
  - Oral hygiene
  - Periodontitis
  - General aspects

Item	Domains	Terms
1	Periodontitis	Periodontitis
2		Periodontal
3		Periodontitis [MesH]*
4		1 OR 2 OR 3
5	Oral hygiene	Poor oral hygiene
6		Plaque index
7		Dental plaque index [MeSH]*
8		Oral hygiene index
9		Oral hygiene index [MeSH]*
10		Plaque score
11		5 OR 6 OR 7 OR 8 OR 9 OR 10
12	General	Risk factor
13		Association
14		Relation
15		Correlation
16		12 OR 13 OR 14 OR 15
17		4 AND 11 AND 16

Selecting studies

- Clearly define inclusion & exclusion criteria
- Inclusion criteria base on PICO
  - 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 criteria

- Study design
  - randomized controlled trial
  - observational studies (cohort, case-control, cross-sectional studies)
- Full paper Languages
  - English, French, others
- 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

Design coding for 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 base 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**

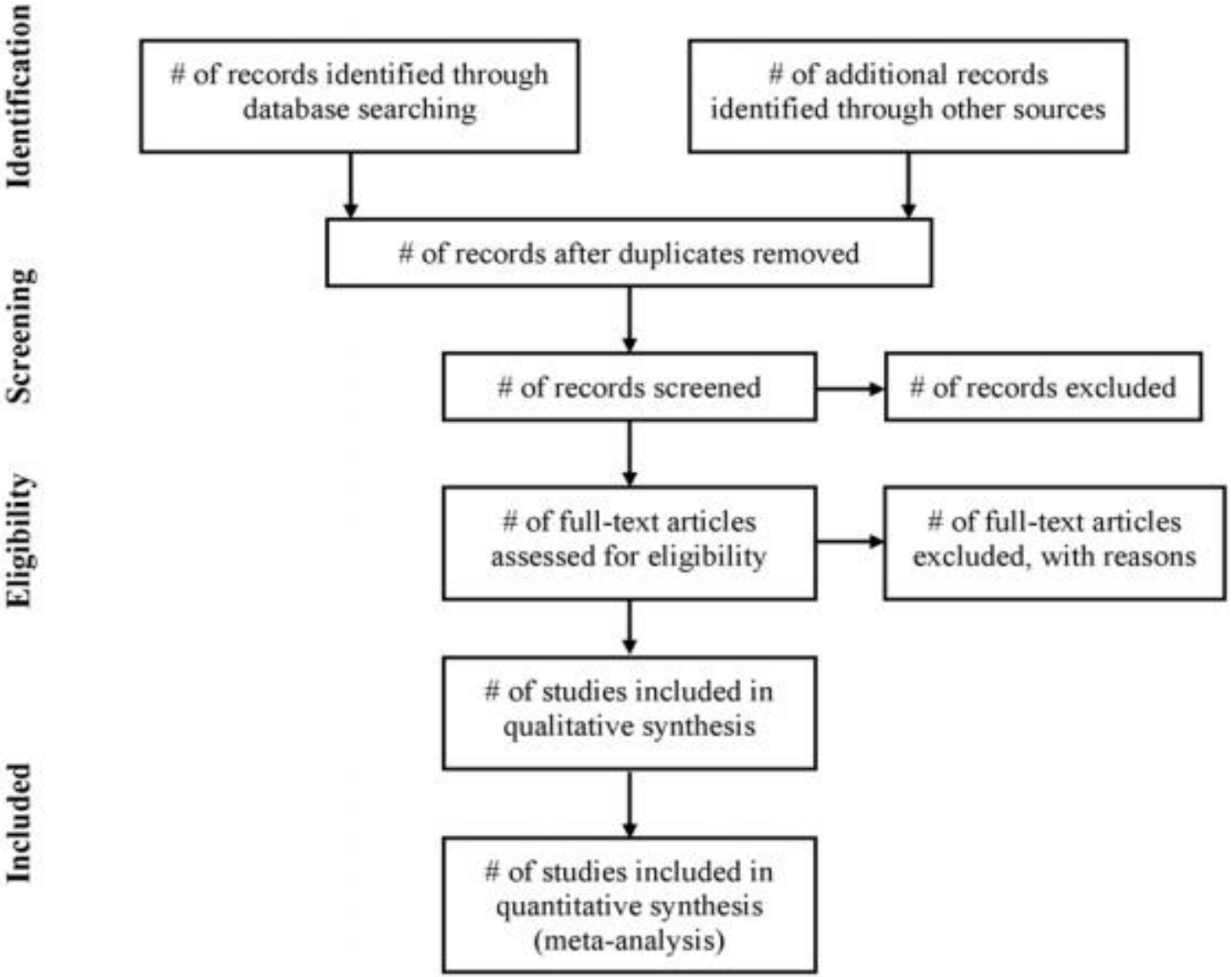


Figure 1. Flow of information through the different phases of a systematic review.
doi:10.1371/journal.pmed.1000097.g001

Example: Selection of studies

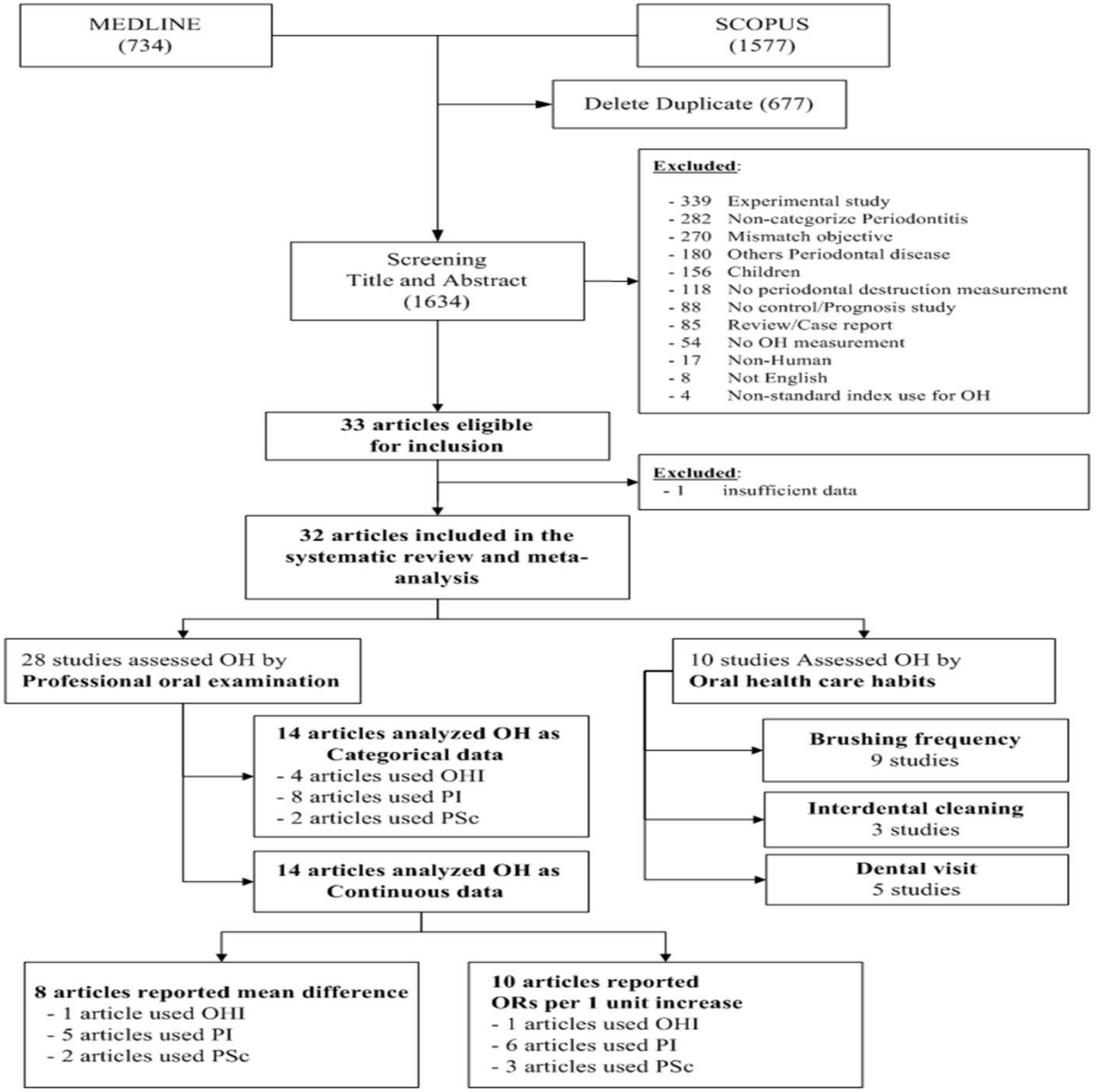
Any observational study, published in English, was included if it met the following criteria:

- Studied in general or specific types of adult populations
- Assessed OH by standard tools
  - the Oral Hygiene Index (OHI) or
  - Simplified Oral Hygiene Index (OHI-S),
  - Plaque Index (PI),
  - Plaque control record / Plaque Score (PSc), or
  - a questionnaire including frequency of brushing, interdental cleaning and dental visits and

Int Dent J. 2017 Dec;67(6):332-343.

Selection of studies (cont.)

- Had at least 2 groups of outcome, periodontitis versus non-periodontitis, or mild, moderate, severe periodontitis versus normal periodontium
- Studies were excluded if they had insufficient data for pooling after contacting authors for additional data.



Int Dent J. 2017 Dec;67(6):332-343.

Data extraction (DE)

- At least two reviewers
- Design DEF, pilot, & revise DEF
- General characteristics of article
    - Study ID,
    - First Author's & corresponder's surnames
    - Year & source of publication
- Characteristics of studies
    - Setting/country
    - Study design (RCT, CS, CC, CrS)
    - Type of studied patients
        - Ethnicity, setting
        - Children, adults, pregnancy
        - Postmenopause, premenopause

- Patients
  - Demographic and clinical features
    - mean age, gender, BMI, smoking, underlying diseases
- Methods/criteria/definition used for measurement
  - Outcome
  - Studied factor
- Interventions/exposure/test
  - Treatments
    - Dosage/day, period of treatments, course of treatments, route
  - Scanners
    - Version
  - Lab tests
  - Questionnaire & cutoff

Data for pooling

- Frequency data
  - Contingency table of studied factors/interventions versus outcomes (rxc)

Treatment groups	Disease			
	Yes	No	n	Incidence
Rx (Exp+)	A	b	n_1	a/n_1
Placebo (Exp-)	c	d	n_2	c/n_2

- Summary statistic data
  - OR (95% CI), RR (95% CI), HR (95% CI)

Data for pooling

- Continuous outcome
  - Summary data
    - n, mean, SD

Group	n	mean	SD
A	n_1	$mean_1$	SD_1
B	n_2	$mean_2$	SD_2

  - Summary statistic data
    - Mean difference & 95% CI

Risk of bias in individual studies

- 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
    - RoB 2.0 : https://sites.google.com/site/riskofbiastool/

Domain	Description	Review authors' judgement
Sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated?
Allocation concealment.	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.	Was allocation adequately concealed?

Domain	Description	Review authors' judgement
Blinding of participants, personnel and outcome assessors *Assessments should be made for each main outcome (or class of outcomes).*	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.	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes).*	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.	Were incomplete outcome data adequately addressed?

Domain	Description	Review authors' judgement
Selective outcome reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry. Trial methodology Statistical analysis	Was the study apparently free of other problems that could put it at a high risk of bias? Premature trial termination Post-randomization exclusion Unbalance baseline characteristics Adequately describe methods of data analysis -use per-protocol analysis, modified ITT

Risk of bias assessment

Author	Adequate sequence generation	Adequate allocation concealment	Blinding	address incomplete outcome data	Selective outcome report	Free of other bias	Description of other bias

Risk Of Bias

- **Non-RCT**
  - Intervention studies where interventions are not randomly allocated.
  - Non-randomised Studies-of Interventions (ROBINS-I)
    - https://sites.google.com/site/riskofbiastool/welcome/home
  - Seven domains are considered
    - Before interventions
      - Confounding
      - Selection of patients into the study

the bmj | BMJ 2016;355:i4919 | doi: 10.1136/bmj.i4919

ROBINS-I

- At interventions
  - Classification of interventions
- After interventions
  - Deviation from intended interventions
  - Missing data
  - Measurements of outcomes
  - Selective outcome report

- Before/at intervention domians are totally different from assessments of RCT because randomisation can protect against bias before/at randomisation
- The last four domains for after interventions overlapped with RCT because RCT could not protect bias after randomisation

ROBINS-I

- 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)

Wells G, Shea B, O'Connell J, Robertson J, Peterson V, Welch V, et al.
The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomized Studies in Meta-Analysis.
Available from: http://www.evidencebasedpublichealth.de/download/Newcastle_Ottowa_Scale_Pope_Bruce.pdf.

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 h item within the ‘Selection’ and ‘Exposure/Outcome’ categories; maximum of two ‘stars’ for ‘Comparability’

- Prognostic studies
  - Quality in prognostic study (QUIPS)

  Ann Intern Med. 2013;158:280-286
    - 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

Variable	Bias Domains			
	1. Study Participation	2. Study Attrition	3. Prognostic Factor Measurement	4. Outcome Measurement
Optimal study or characteristics of unbiased study	The study sample adequately represents the population of interest	The study data available (i.e., participants not lost to follow-up) adequately represent the study sample	The PF is measured in a similar way for all participants	The outcome of interest is measured in a similar way for all participants
Prompting items and considerations†	a. Adequate participation in the study by eligible persons	a. Adequate response rate for study participants	a. A clear definition or description of the PF is provided	a. A clear definition of the outcome is provided
	b. Description of the source population or population of interest	b. Description of attempts to collect information on participants who dropped out	b. Method of PF measurement is adequately valid and reliable	b. Method of outcome measurement used is adequately valid and reliable
	c. Description of the baseline study sample	c. Reasons for loss to follow-up are provided	c. Continuous variables are reported or appropriate cut points are used	c. The method and setting of outcome measurement is the same for all study participants
	d. Adequate description of the sampling frame and recruitment	d. Adequate description of participants lost to follow-up	d. The method and setting of measurement of PF is the same for all study participants	
	e. Adequate description of the period and place of recruitment	e. There are no important differences between participants who completed the study and those who did not	e. Adequate proportion of the study sample has complete data for the PF	
	f. Adequate description of inclusion and exclusion criteria		f. Appropriate methods of imputation are used for missing PF data	

Bias Domains

5. Study Confounding	6. Statistical Analysis and Reporting
Important potential confounding factors are appropriately accounted for	The statistical analysis is appropriate, and all primary outcomes are reported
a. All important confounders are measured	a. Sufficient presentation of data to assess the adequacy of the analytic strategy
b. Clear definitions of the important confounders measured are provided	b. Strategy for model building is appropriate and is based on a conceptual framework or model
c. Measurement of all important confounders is adequately valid and reliable	c. The selected statistical model is adequate for the design of the study
d. The method and setting of confounding measurement are the same for all study participants	d. There is no selective reporting of results

e. Appropriate methods are used if imputation is used for missing confounder data	
f. Important potential confounders are accounted for in the study design	
g. Important potential confounders are accounted for in the analysis	
The observed effect of the PF on the outcome is very likely to be distorted by another factor related to PF and outcome	The reported results are very likely to be spurious or biased related to analysis or reporting
The observed effect of the PF on outcome may be distorted by another factor related to PF and outcome	The reported results may be spurious or biased related to analysis or reporting
The observed effect of the PF on outcome is unlikely to be distorted by another factor related to PF and outcome	The reported results are unlikely to be spurious or biased related to analysis or reporting

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

Thakkinstian et al, Am J Epidemiol. 2011 Jun 15;173(12):1365-79

Domain	Item	Low risk of bias
Selection bias	Representativeness of cases	
	A. Consecutive/randomly selected from cases population with clearly defined random frame	Yes Yes
	B. Consecutive/randomly selected from cases population without clearly defined random frame or with extensive inclusion criteria	No
	C. Spectrum of diseases Select on advance (atrophy or neovascular) or mild AMD	
	A. Not describe method of selection	
	Representativeness of controls	
	A. Controls were consecutive/randomly drawn from area (ward/community) as cases with the same criteria	Yes No
	B. Controls were consecutively/randomly drawn from different areas as cases	No
	C. Not describe	
	Differential participation in case and control	
	Non-participant rate is small (< 10%) and similar (to rates?) between case and control groups	Yes
	Incomplete participant rates are different	NO
	- Refusal or inability to provide data	
	- Refusal or inability to provide biological specimens	
	- Insufficient amount quality of data/ quality of DNA	

Information bias	Ascertainment of AMD	
	- Clearly described objective criteria of diagnosis of AMD	Yes
	- Not describe/unclear definition	No
	Ascertainment of control	
	- Controls were non-case that proved by ocular examination	Yes
	- Just mentioned that controls were subjects who did not have AMD without ocular examination	No
	- Not describe	No
	Ascertainment of genotyping examination	
	- Genotyping done under "blind" condition of case and control specimens	Yes
	- Genotyping of cases & controls were performed together	Yes
	- Genotyping error rate < 5%	Yes
	- Quality control procedure e.g., reanalysis of random specimens, using different genotyping methods for analysis, analysis if replicate sample	Yes
	- Unblind or	No
	- Not mention what was done	No
	- No quality control check	No

Confounding bias	Population stratification	
	- No difference in ethnic origin between cases and controls	Yes
	- Use of controls who were not related to cases	Yes
	- Use of some controls who came from the same familywhat was done	No No
	- Other confoun	Yes
	- Use of genomic controls	No
	- Not report ding bias	
	- Controls for confounding variables (e.g., age, gender, smoking) in analysis	
	- Not controlled /not mentioned (or, no control/ no mention)	
Multiple testing & Selective reporting (for replication studies)	How many polymorphisms have been studied	
	- Adjustment for multiple tests	Yes
	- Report results of all polymorphisms mentioned in objectives, non-significant or not	Yes No
	- Report results of only significant polymorphisms	
HWE	- HWE in control group	Yes
	- HW disequilibrium in control group	No
	- Not check HWE	No

Statistical analysis plan

- **Describe what and how to pool data**
- What's to pool
  - Dichotomous outcome
    - Pool OR, RR, HR
  - Continuous outcome
    - Unstandardised mean difference
    - Standardised mean difference
- Pooling methods
  - Fixed-effect model
  - Random-effect model

- Check heterogeneity
- Explore sources
    - Factors
    - Graph
    - Meta-regression
- Subgroup analysis
- Assess reporting bias
    - Graph & test
- Sensitivity analysis
- Statistical software & level of significance

SAP: Oral hygiene and periodontitis

- Data analysis will be performed separately by categorical and continuous data of OH
- For categorical OH
  - Odds ratio (OR) of having periodontitis for fair versus good OH (OR_1), and poor versus good OH (OR_2) along with their variances will be estimated for each study.
  - A multivariate random-effect meta-analysis will be applied for pooling ORs taking into account for within-study variation using Riley's method.
  - For those studies where OH was divided into more than 2 groups and reported ORs without frequency data, the variance-covariance will be assumed to be zero.

- For continuous data,
  - Standardized mean difference (SMD) in OH scores between periodontitis and non-periodontitis groups will be estimated
  - Then SMDs will be pooled across studies
  - If mean and standard deviation (SD) were not reported, but correlation coefficients of logistic model were reported instead, the beta coefficients were then pooled using pooling mean method.

- Heterogeneity
  - Will be assessed by Cochrane's Q test and I^2 statistic.
  - Heterogeneity is present
    - Q test < 0.1 or $I^2 \geq 25\%$
- A random-effect model (Dersimonian & Laird) will be used, otherwise a fixed-effect model with inverse variance method will be applied.
- Sources of heterogeneity
  - Will be explored using a Galbraith plot to identify outlier studies.
  - Co-variables including type of population, age, gender, smoking, DM, periodontitis definitions will be then fitted one by one into a meta-regression model
  - If there is a suggested association, a sensitivity analysis excluding the outlier studies and/or a subgroup analysis will be performed.

- Publication bias will be assessed using
  - The Egger test
  - A funnel plot
  - If any of these indicated asymmetry, a contour enhanced funnel plot will be constructed to identify the cause of asymmetry.
- All analyses will be performed using STATA software version 14.
- Two-sided $P < 0.05$ will be considered statistically significant except for the heterogeneity test, in which $P < 0.10$ will be used.

Time plan

Activities	Time									
	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct
Develop review proposal	→									
Register proposal		→								
Select studies		→	→							
Data extraction			→	→						
RBA			→	→						
Data management				→	→					
Data analysis					→	→				
Writing manuscript							→	→	→	
Submission										→

Register review proposal

Why do we need to register

- Establish that we are doing this review
- May reduce the risk of multiple reviews addressing the same question
- Increases potential communication with interested researchers
- Promote transparency of the methods
- Allows your peers to review how you will extract data for quantitative poolings
- Serve as a road map for our review

- What do we need in hands for registration
  - Research questions & specific objectives
  - Review methods,
    - How to identify studies
    - Selection of studies
    - Data extractions & risk of bias assessment
    - Interventions/Exposure
    - Outcomes of primary interest
    - Statistical analysis plan
    - Time schedule

Where to register

- National Institute of Health (NIH):

  http://nihlibrary.campusguides.com/content.php?pid=252593&sid=2085601

  - Campbell Collaboration - produces systematic reviews of the effects of social interventions
    - http://www.campbellcollaboration.org/
  - Cochrane Collaboration - international organization, produces and disseminates systematic reviews of health care interventions
    - http://www.cochrane.org/
  - PROSPERO -international prospective register of systematic reviews
    - http://www.crd.york.ac.uk/PROSPERO/

Network

- Cochrane collaboration
  - RCT
  - Diagnostic studies
- Human Genome Epidemiology Network
  - https://www.cdc.gov/genomics/about/index.htm

Pooling effect size by Meta-analysis

- **Select effect size**
  - OR, RR, RD for dichotomous outcome
  - Un/standardised mean difference for continuous outcome
- **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

Dichotomous outcome

Group	Disease		
	Yes	No	n
Treatment	A	b	n_1
Placebo	C	d	n_2

Mantel-Haenzel

$$\ln \hat{OR}_{MH} = \frac{\sum_{i=1}^{k} w_i \hat{\theta}_i}{\sum_{i=1}^{k} w_i}$$

$$\theta_i = \ln \hat{OR}_i = \ln\left(\frac{a_i d_i}{c_i b_i}\right)$$

$$w_i = \frac{1}{\text{var}_i} = \frac{b_i c_i}{N_i}$$

Inverse variance

$$\widehat{\ln OR}_{iv} = \frac{\sum_{i=1}^{k} w_i \widehat{\ln OR}_i}{\sum_{i=1}^{k} w_i}$$

$$\widehat{\ln OR}_i = \ln\left(\frac{a_i d_i}{b_i c_i}\right)$$

$$w_i = \frac{1}{\widehat{\mathrm{var}}(\ln OR_i)}$$

$$\widehat{\mathrm{var}}(\ln OR_i) = \frac{1}{a_i} + \frac{1}{b_i} + \frac{1}{c_i} + \frac{1}{d_i}$$

Pooled RR

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

$$\ln \hat{RR}_i = \ln\left(\frac{a_i / n_{1i}}{c_i / n_{2i}}\right)$$

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

$$\text{var} \ln \hat{RR}_i = \frac{1}{a_i} - \frac{1}{n_{1i}} + \frac{1}{c_i} - \frac{1}{n_{2i}}$$

Heterogeneity test

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

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

$$\hat{\theta}_p = \ln \hat{OR}_{iv}$$

$$Q \sim \chi^2 \ with \ df = k - 1$$

Degree of heterogeneity

$I^2 = [Q-(k-1)]/Qx100$

< 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

$$\ln \hat{OR}_{DL} = \frac{\sum_{i=1}^{k} w_i^* \hat{\theta}_i}{\sum_{i=1}^{k} w_i^*}$$

$$\ln \hat{OR}_i = \ln\left(\frac{a_i d_i}{b_i c_i}\right)$$

$$w_i^* = \frac{1}{\mathrm{var}_i + \tau^2}$$

$$\mathrm{var}_i = \frac{1}{a} + \frac{1}{\mathrm{b}} + \frac{1}{\mathrm{c}} + \frac{1}{\mathrm{d}}$$

Between study variation (Tau^2)

$$\tau^2 = \frac{Q - (k - 1)}{\sum w_i - \frac{\sum w_i^2}{\sum w_i}}$$

Example: CP/CPPS

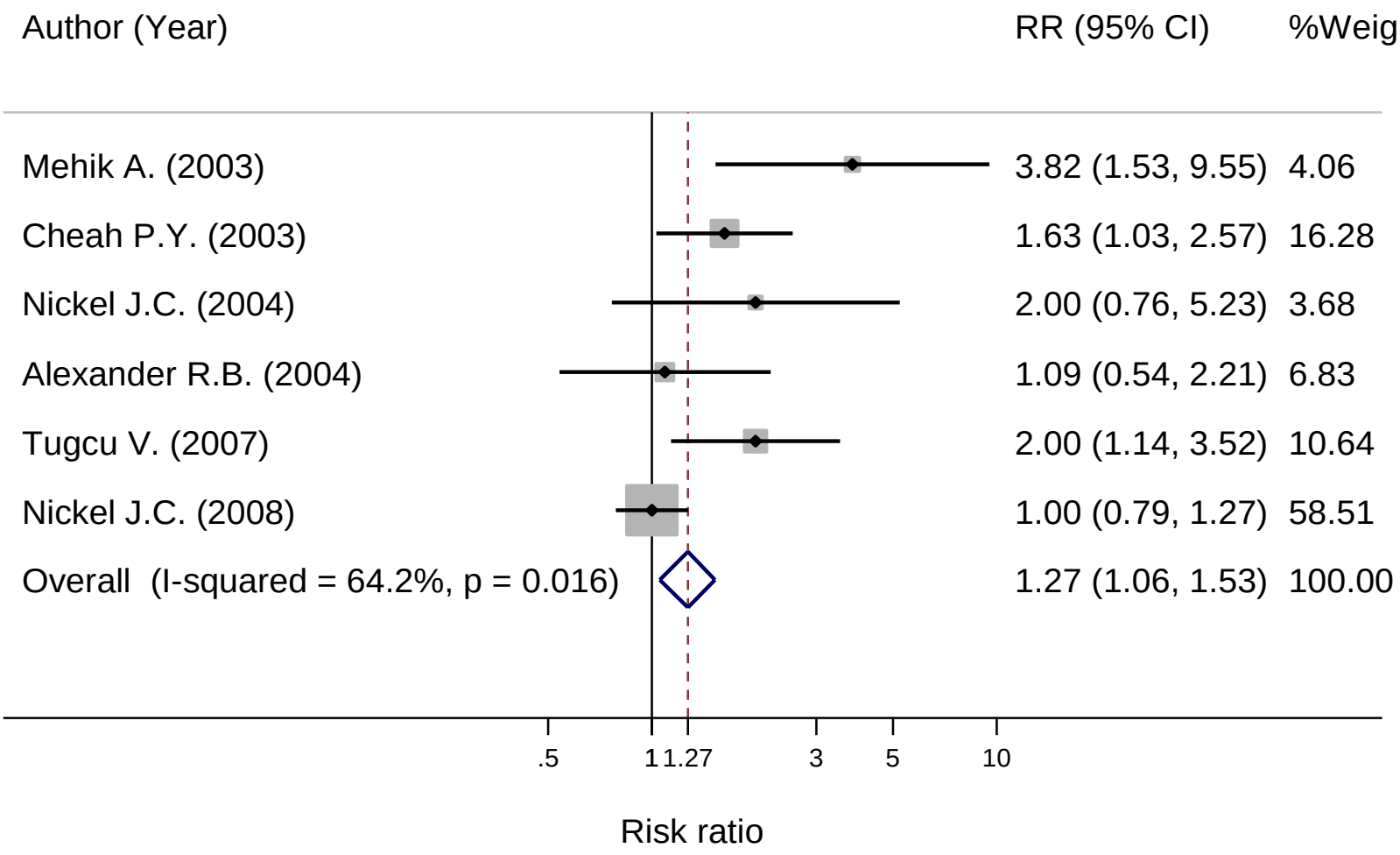
Table 3. Treatment Response Rates for α-Blockers and Anti-inflammatory Drugs

Source	Definition of Treatment Response	Active Treatment		Placebo		RR (95% CI)
		No. of Responses	No. of Nonresponses	No. of Responses	No. of Nonresponses	
α-Blockers						
Nickel et al,[9] 2008	4-point decrease in NIH-CPSI	68	70	66	68	1.0 (0.8-1.3)
Tuğcu et al,[10] 2007	50% decrease in NIH-CPSI	20	10	10	20	2.0 (1.4-3.5)
Alexander et al,[21] 2004	4-point decrease in NIH-CPSI	12	33	11	34	1.1 (0.5-2.3)
Nickel et al,[24] 2004	50% decrease in NIH-CPSI	9	18	5	25	2.0 (0.8-5.2)
Cheah et al,[33] 2003	50% decrease in NIH-CPSI	24	19	14	29	1.6 (1.0-2.6)
Mehik et al,[38] 2003	33% decrease in NIH-CPSI	13	4	4	16	2.5 (1.4-4.5)
Pooled RR						1.6 (1.1-2.3)

Assess heterogeneity

$$H_0 : \ln RR_1 = \ln RR_2 = ,..., = \ln RR_k$$

Figure 2. Treatment responsiveness in CP/CPPS patients: Alpha-blockers versus placebo



Heterogeneity test

$$H_o : \ln RR_1 = \ln RR_2 = \ldots = \ln RR_k$$

$$H_a : \text{At least one pair of } RR_j \text{ is different}$$

```
metan res_al non_al res_pl non_pl, fixedi rr label(namevar=author,
  yearvar=year) sortby(year)
```

Study	RR	[95% Conf.	Interval]	% Weight
Mehik A. (2003)	3.824	1.531	9.550	4.06
Cheah P.Y. (2003)	1.625	1.029	2.567	16.28
Nickel J.C. (2004)	2.000	0.765	5.232	3.68
Alexander R.B. (2004	1.091	0.538	2.210	6.83
Tugcu V. (2007)	2.000	1.136	3.522	10.64
Nickel J.C. (2008)	1.000	0.786	1.273	58.51
I-V pooled RR	1.270	1.056	1.527	100.00

```
  Heterogeneity chi-squared =  13.95 (d.f. = 5) p = 0.016
  I-squared (variation in RR attributable to heterogeneity) =  64.2%
  Test of RR=1 : z=   2.54 p = 0.011
```

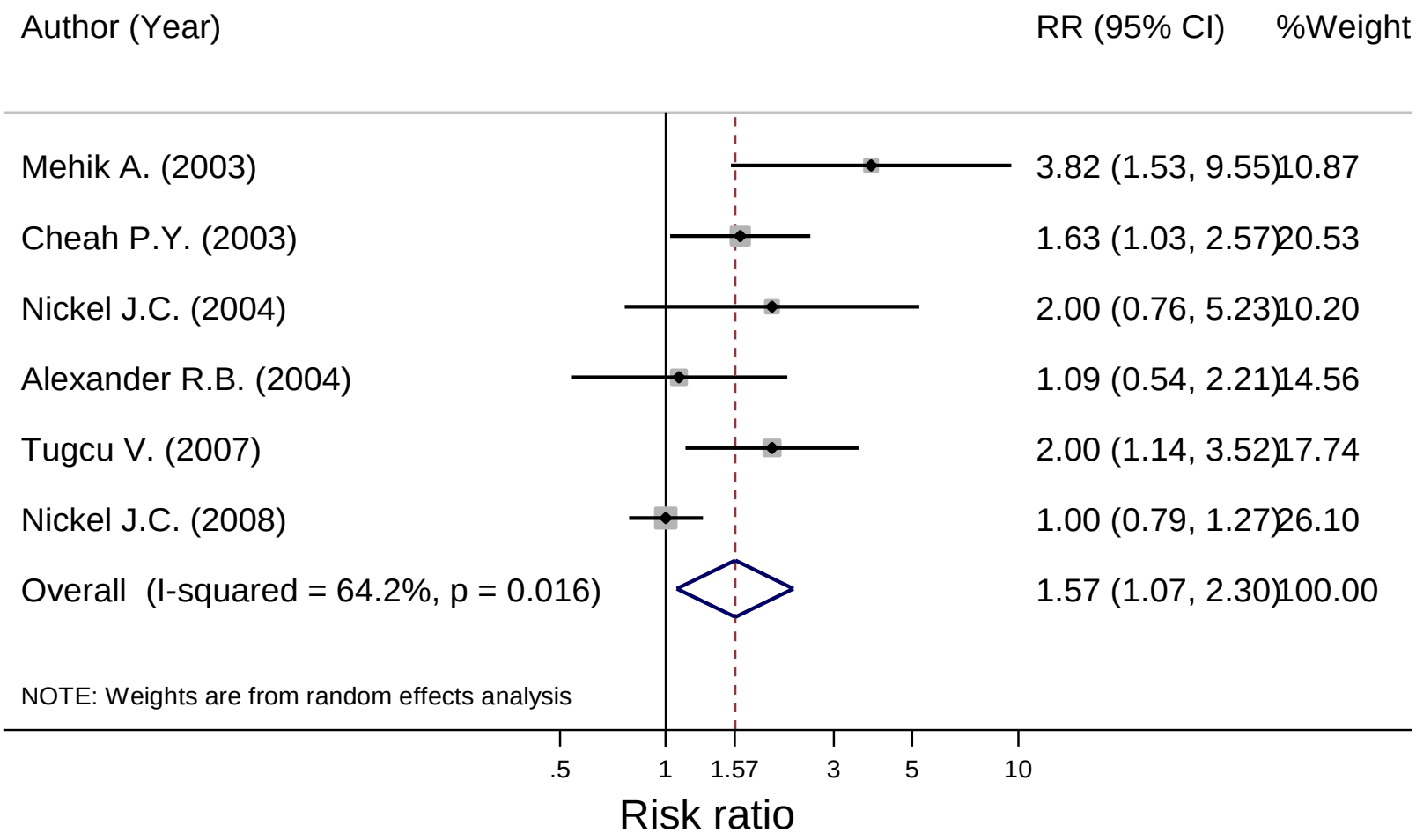
Pooling with a random effect model

```
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)
```

Study	RR	[95% Conf.	Interval]	% Weight
Mehik A. (2003)	3.824	1.531	9.550	10.87
Cheah P.Y. (2003)	1.625	1.029	2.567	20.53
Nickel J.C. (2004)	2.000	0.765	5.232	10.20
Alexander R.B. (2004	1.091	0.538	2.210	14.56
Tugcu V. (2007)	2.000	1.136	3.522	17.74
Nickel J.C. (2008)	1.000	0.786	1.273	26.10
D+L pooled RR	1.571	1.073	2.300	100.00

```
  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



Continuous outcome

Groups	n	mean	SD
Treatment	n_1	$mean_1$	SD_1
Placebo	n_2	$mean_2$	SD_2

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

SMD

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

$$w_i = \frac{1}{\mathrm{var}(d_i)}$$

$$d_i = \frac{\bar{x}_{1i} - \bar{x}_{2i}}{sd_i}$$

$$sd_i = \sqrt{\frac{(n_{1i}-1)sd_{1i}^2 - (n_{2i}-1)sd_{2i}^2}{(n_{1i}+n_{2i}-2)}}$$

$$\mathrm{var}(d_i) = \frac{n_i}{n_{1i}n_{2i}} + \frac{d_i^2}{2(n_i-2)} \ldots (\text{Cohen's method})$$

USMD

$$d_i = (\bar{x}_{1i} - \bar{x}_{2i})$$

$$\text{var}(d_i) = \frac{sd_{1i}^2}{n_{1i}} + \frac{sd_{2i}^2}{n_{2i}}$$

Heterogeneity test

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

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

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

$$w_i = \frac{1}{\mathrm{var}(d_i)}$$

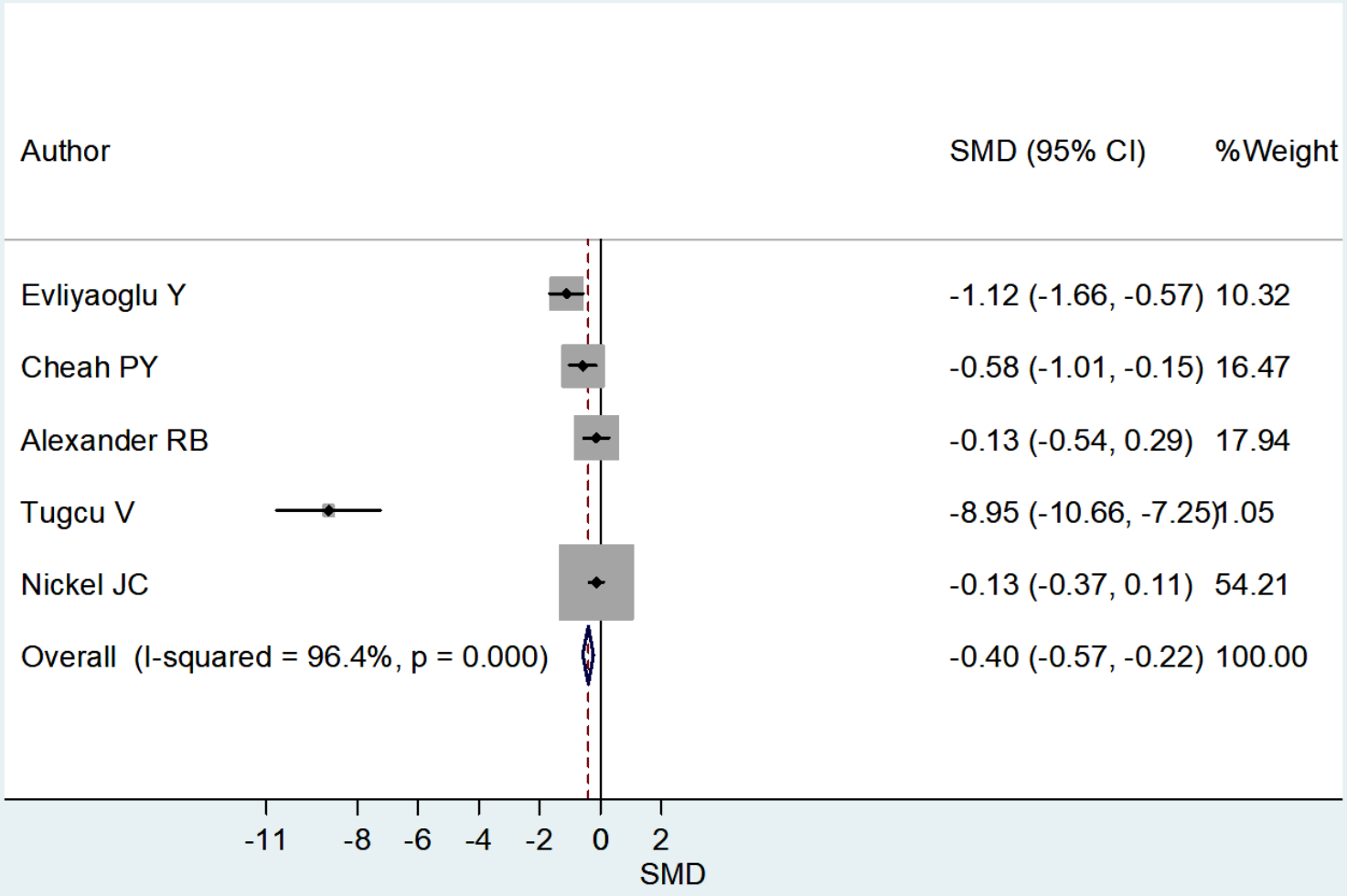
Example

- CP/CPPS
- Total symptom score between alpha-blocker versus placebo

			Alpha-blockers			Placebo		
Author	Year	Scale	N	Mean	SD	N	Mean	SD
Evliyaoglu Y	2002	IPSS	30	10.47	4.44	30	16.17	5.7
Cheah PY	2003	NIH-CP/CPPS	43	10.8	9	43	17	12.1
Alexander RB	2004	NIH-CP/CPPS	45	20.2	12.18	45	21.6	9.84
Tugcu V	2006	NIH-CP/CPPS	30	10.7	1.3	30	21.9	1.2
Nickel JC	2008	NIH-CP/CPPS	138	16.7	14.92	134	18.6	14.05

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



```
metan  n_alpha mean_total_al sd_total_al n_placebo mean_total_pl sd_total_pl,
  randomi label(namevar=author) sortby(year)
```

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