Best Practices in Writing a Systematic Review

Elsevier Health

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Agenda

- Definition and Importance of Systematic Reviews
- Overview and Key Requirements of the Systematic Review Process
- Identifying the Topic and Framing a Research Question
- Writing the *Protocol*, *Data Synthesis* and *Discussion/ Conclusion* Sections
- Audience Discussion & Closing

Common Reasons for Manuscript Rejection

The research process

1. Identify the research topic (acquire)
2. Review the literature to identify the knowledge gap (appraise)
3. Formulate specific research question/s, objectives and hypothesis
4. Choose study type (obs vs. interv.) and decide on type of data, methods, statistical tests
5. Write the study protocol (research proposal)
6. Conduct the study
7. Process and analyze the data
8. Write the article
9. Submit for publication

Further Reading: Writing a better research paper: Advice for young authors

Types of published research

Original Article
Written by the person or team that conducted the experiment or observations → Primary Source

Review Article
Summarizes the current state of understanding on a topic within a certain discipline → Secondary Source

Case Report
Unexpected or novel occurrence is described in a detailed report of findings, clinical course, and prognosis of an individual patient

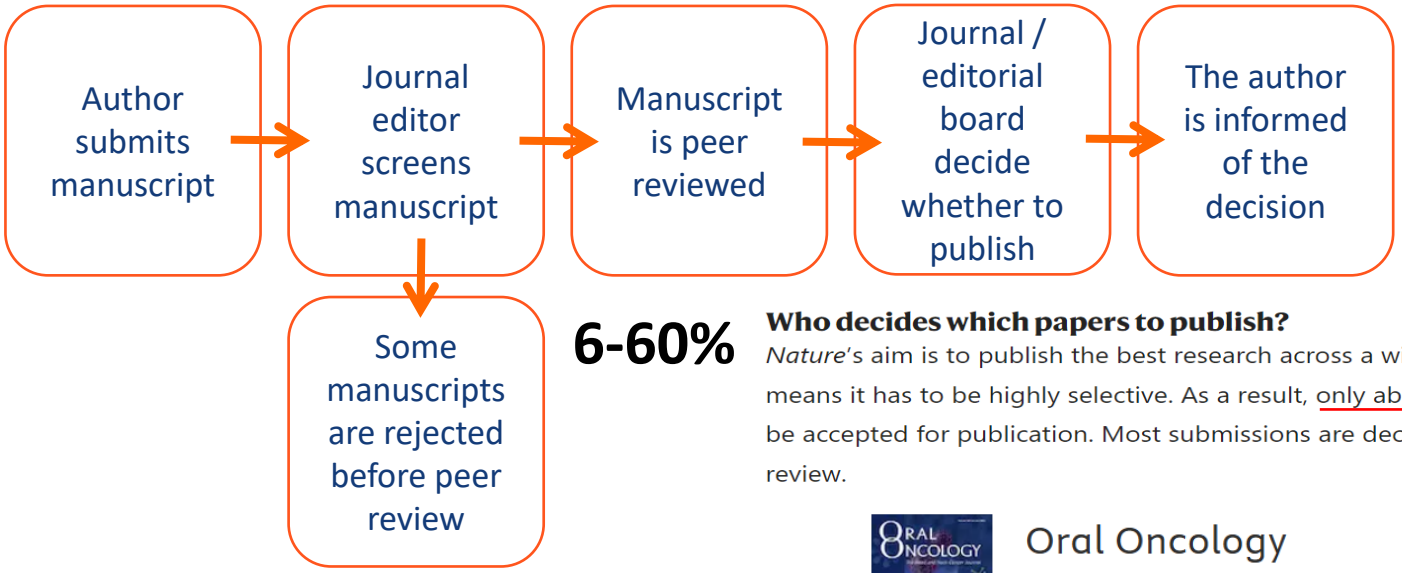
Letter to the Editor
Basic letter addressing core issues that the sender wishes to highlight. Comment on a previous article

Methodologies
A new experimental method, test or procedure. The method described may either be completely new or may offer a better version

Source: https://www.springer.com/gp/authors-editors/authorandreviewertutorials/writing-a-journal-manuscript/types-of-journal-articles/10285504

Neither Do You Want This....

Snapshot of the peer review and editorial process



6-60%

Who decides which papers to publish?

Nature's aim is to publish the best research across a wide range of scientific fields, which means it has to be highly selective. As a result, only about 8% of submitted manuscripts will be accepted for publication. Most submissions are declined without being sent out for peer review.

Source: http://www.editage.com/insights/peer-review-process-and-editorial-decision-making-at-journals; https://www.nature.com/nature/for-authors/edito criteria-and-processes

Oral Oncology

Save journal

Impact Factor	CiteScore	Time to 1st decision	Time to acceptance	Acceptance rate
4.0	8.7	4 days	35 days	14%

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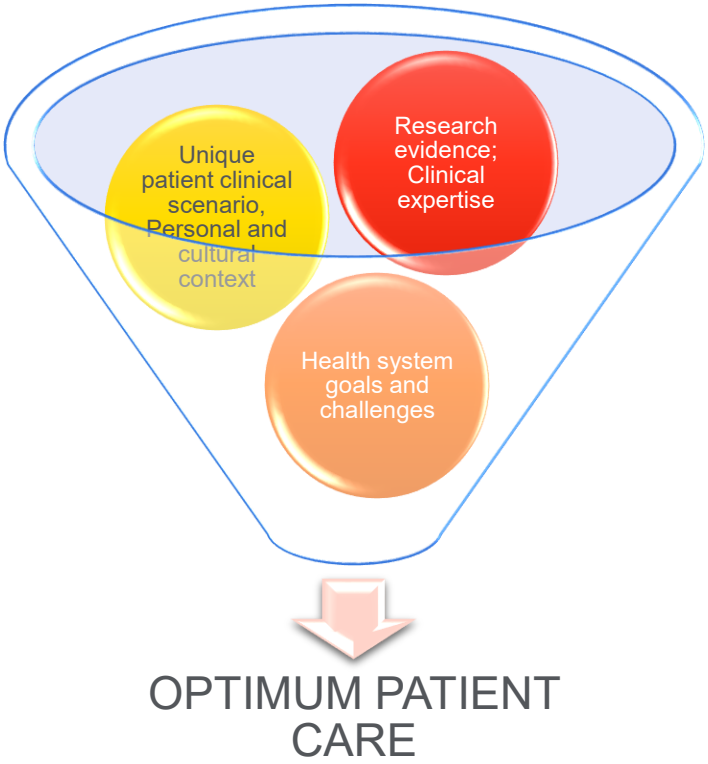
Definition & Importance of Systematic Reviews

What is Evidence-Based Medicine?

Applying the full-body of medical (and scientific) knowledge, collated via robust research, to clinical decision making



Why is it important?

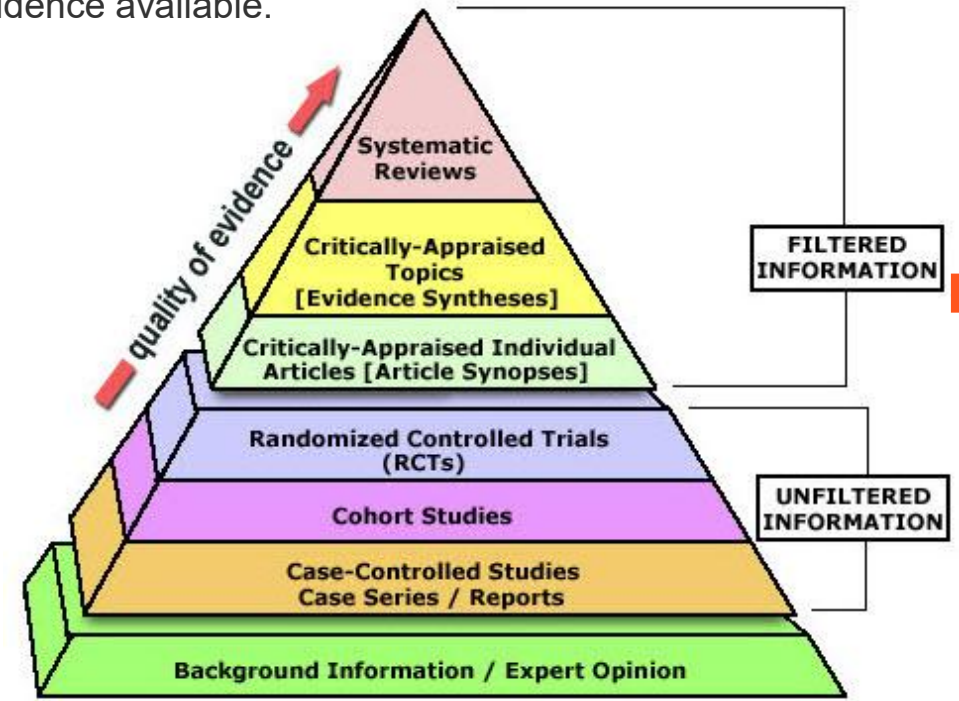
- Medical literature grows and changes every day
- Yet new clinical questions constantly emerge and may need/ deserve to be answered
- Practicing EBM means creating a life-long learning mindset
- Contextualizing medical literature to patient needs

Benefits of EBM

- Care standardization
- Improvement in patient care for individuals and for communities
- Optimizing and equalizing care, social justice and policy making

Levels of Evidence

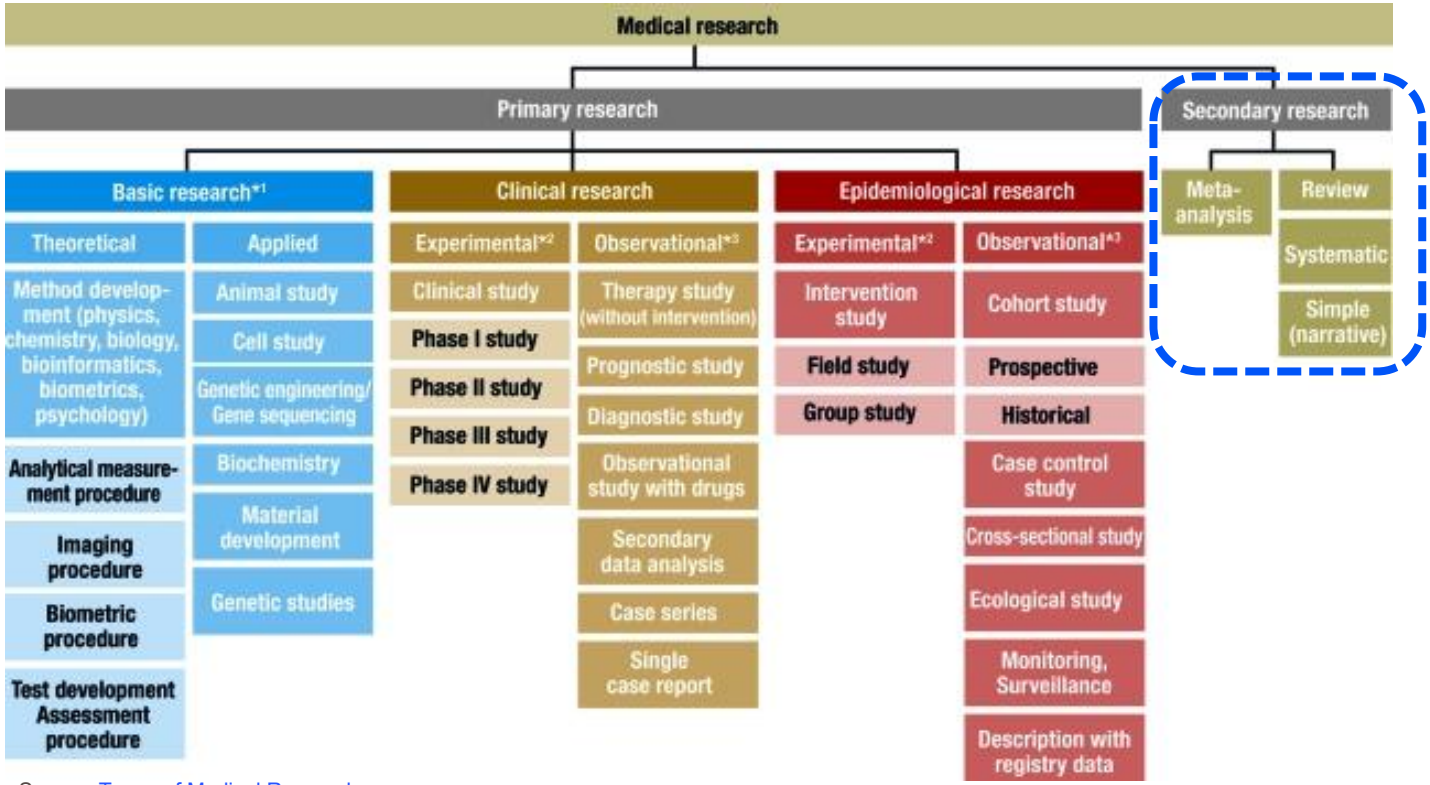
The levels of evidence pyramid provides a way to visualize both the quality of evidence and the amount of evidence available.



Appraise the quality of study and make recommendations on practice.

Source: https://academicguides.waldenu.edu/library/healthevidence/evidencepyramid

Types of Medical Research



Source: Types of Medical Research

Definitions

Systematic Review

A type of *Secondary Research* that methodically analyzes all available research/ evidence and synthesizes opinions and findings based on it in a scientific, structured manner.

Meta Analysis

Analysis of a systematic review can be conducted quantitatively by statistically combining the results from multiple studies. This type of analysis is called Meta-Analysis

Systematic Review vs Literature Review

Systematic Review is:

- Repeatable – and it should be regularly replicated
- Structured protocol
- Reduces bias

Overview and Key Requirements of a Systematic Review

Direct Impact on Patient Outcomes and Healthcare Cost

Wasted research when systematic reviews fail to provide a complete and up-to-date evidence synthesis: the example of lung cancer

Perrine Créquit, Ludovic Trinquart ✉, Amélie Yavchitz & Philippe Ravaud

BMC Medicine **14**, Article number: 8 (2016) | Cite this article

Results

We identified 77 trials (28,636 patients) assessing 47 treatments with 54 comparisons and 29 systematic reviews (13 published after 2013). From 2009 to 2015, the evidence covered by existing systematic reviews was consistently incomplete: 45 % to 70 % of trials; 30 % to 58 % of patients; 40 % to 66 % of treatments; and 38 % to 71 % of comparisons were missing. In the cumulative networks of randomized evidence, 10 % to 17 % of treatment comparisons were partially covered by systematic reviews and 55 % to 85 % were partially or not covered.

https://www.clinicalkey.com/#!/content/journal/1-s2.0-S147020452200540X?scrollTo=%23hl0002393;
https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-016-0555-0

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Need for a Thorough Literature Review

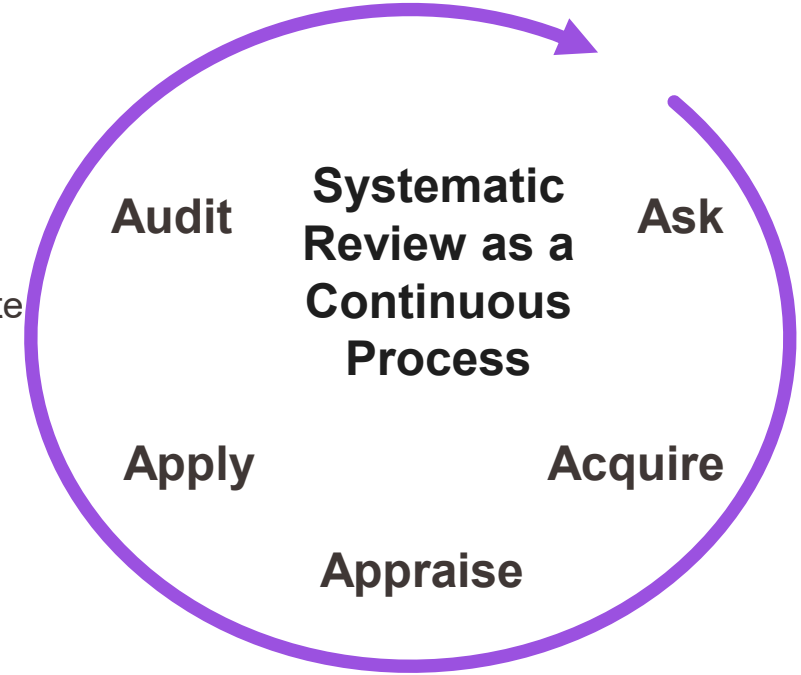
Table 1

Features to consider in appraising whether clinical research is useful.

Feature	Questions to Ask
Problem base	Is there a health problem that is big/important enough to fix?
Context placement	Has prior evidence been systematically assessed to inform (the need for) new studies?
Information gain	Is the proposed study large and long enough to be sufficiently informative?
Pragmatism	Does the research reflect real life? If it deviates, does this matter?
Patient centeredness	Does the research reflect top patient priorities?
Value for money	Is the research worth the money?
Feasibility	Can this research be done?
Transparency	Are methods, data, and analyses verifiable and unbiased?

Ioannidis JP. Why Most Clinical Research Is Not Useful. PLoS Med. 2016 Jun 21;13(6):e1002049. doi: 10.1371/journal.pmed.1002049. PMID: 27328301; PMCID: PMC4915619.

High-Level Approach to Systematic Reviews

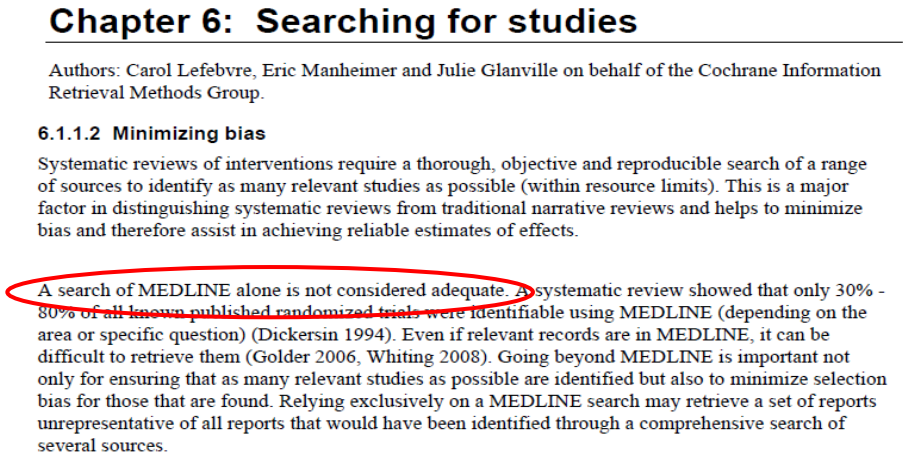


1. Convert information need into an answerable clinical question
2. Identify the best evidence for answering the question
3. Critically appraise the evidence for validity, impact & applicability
4. Report findings and discuss implications
5. Review over a period of time and in comparison to practice and update

Preparing for a Systematic Review

The ***Cochrane Handbook*** outlines eight general steps for preparing a systematic review:

1. Defining the review question(s) and developing criteria for including studies
2. **Searching for studies (Requires access to published literature)**
3. Selecting studies and collecting data
4. Assessing risk of bias in included studies
5. Analyzing data and undertaking meta-analyses
6. Addressing reporting biases
7. Presenting results and "summary of findings" tables
8. Interpreting results and drawing conclusions



Chapter 6: Searching for studies

Authors: Carol Lefebvre, Eric Manheimer and Julie Glanville on behalf of the Cochrane Information Retrieval Methods Group.

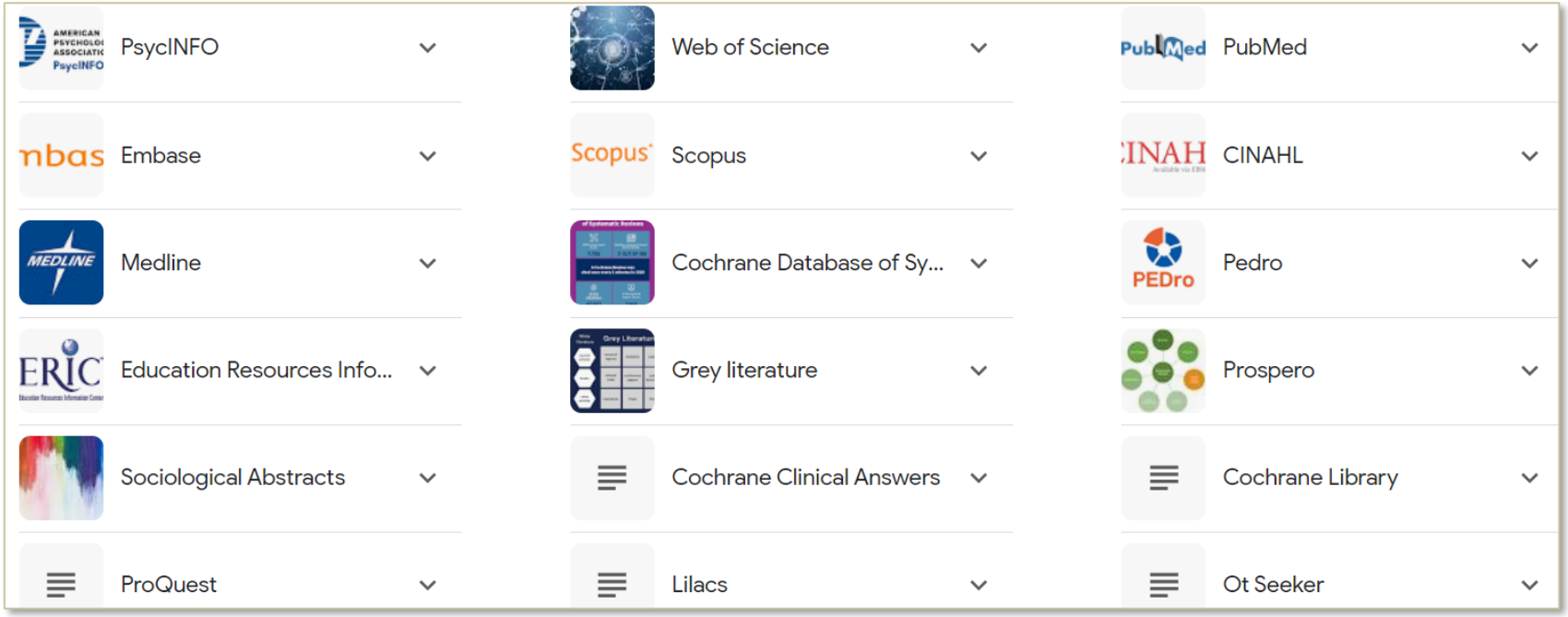
6.1.1.2 Minimizing bias

Systematic reviews of interventions require a thorough, objective and reproducible search of a range of sources to identify as many relevant studies as possible (within resource limits). This is a major factor in distinguishing systematic reviews from traditional narrative reviews and helps to minimize bias and therefore assist in achieving reliable estimates of effects.

A search of MEDLINE alone is not considered adequate. A systematic review showed that only 30% - 80% of all known published randomized trials were identifiable using MEDLINE (depending on the area or specific question) (Dickersin 1994). Even if relevant records are in MEDLINE, it can be difficult to retrieve them (Golder 2006, Whiting 2008). Going beyond MEDLINE is important not only for ensuring that as many relevant studies as possible are identified but also to minimize selection bias for those that are found. Relying exclusively on a MEDLINE search may retrieve a set of reports unrepresentative of all reports that would have been identified through a comprehensive search of several sources.

Source: Cochrane Handbook

Resources for Published Literature



Resources Needed

- A team of **at least 3 researchers**
- An advisory group of 5-6 experience researchers or KOLs in the subject
- Bibliographic, word-processing and statistical analysis software
- Citation Manager
- Time

Identifying a Topic and Framing a Research Question

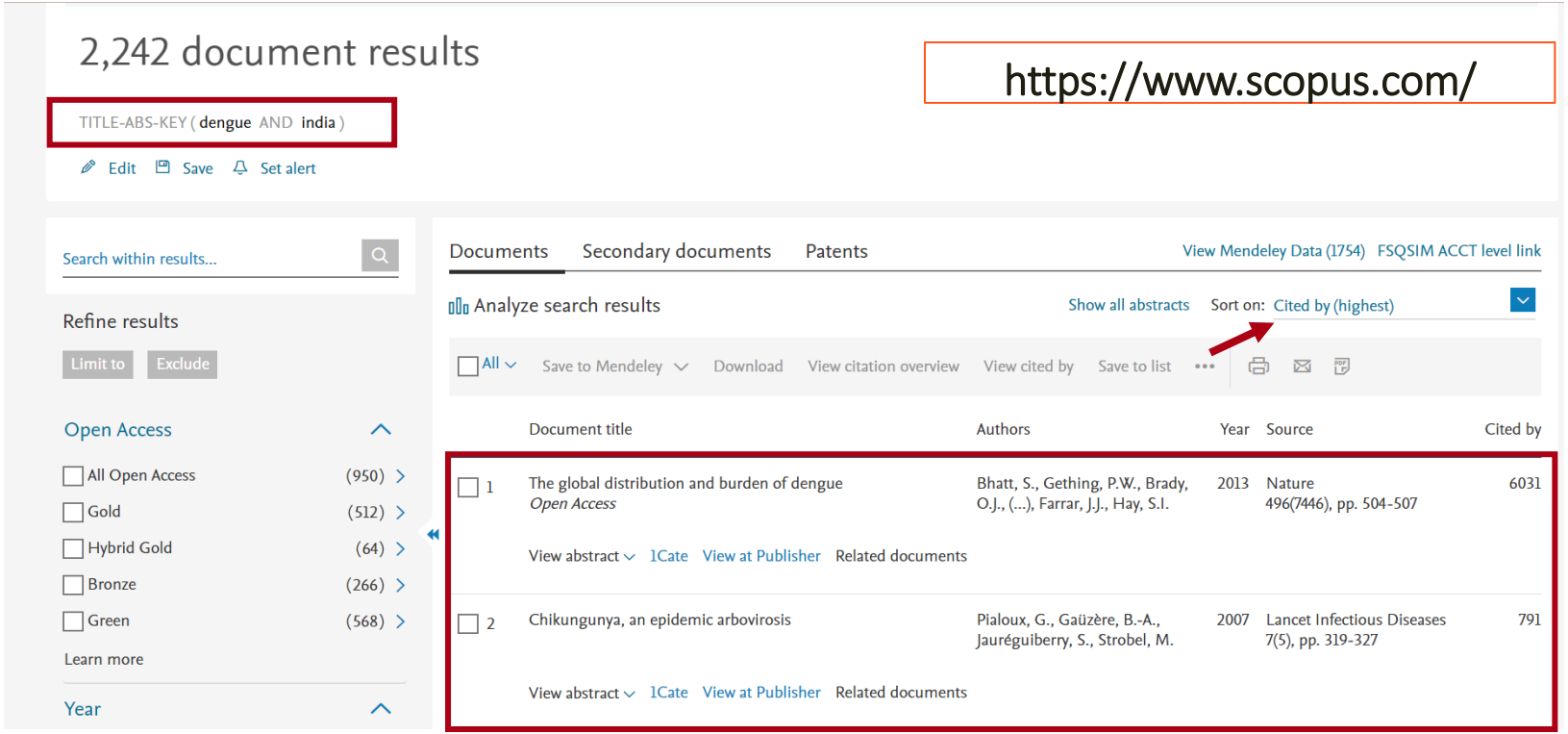
Sources of Ideas/ Inspiration

- Identify the problems in the industry
- Identify unique challenges that government/ health ministry or your institution is focusing on
- **Literature review – what is known and unknown? Thoroughly read the "Recommendations" and "Limitations"**
- Attend conferences – presentations, roundtable discussions
- Attend dissertation presentations if possible
- Leverage on academic network
- Conduct brainstorming sessions
- Observe changes in the external environment and build them into your topic

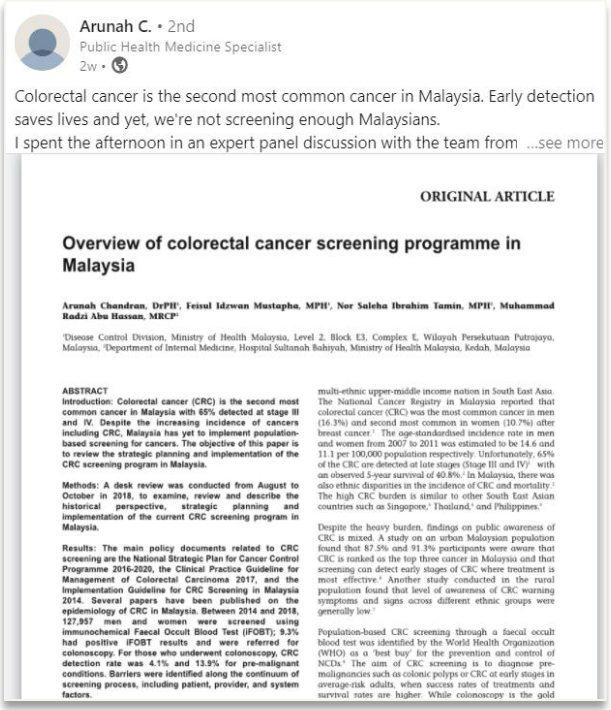
Topic is interesting to you

Topic is interesting to your Supervisor

Use Highly Cited Papers



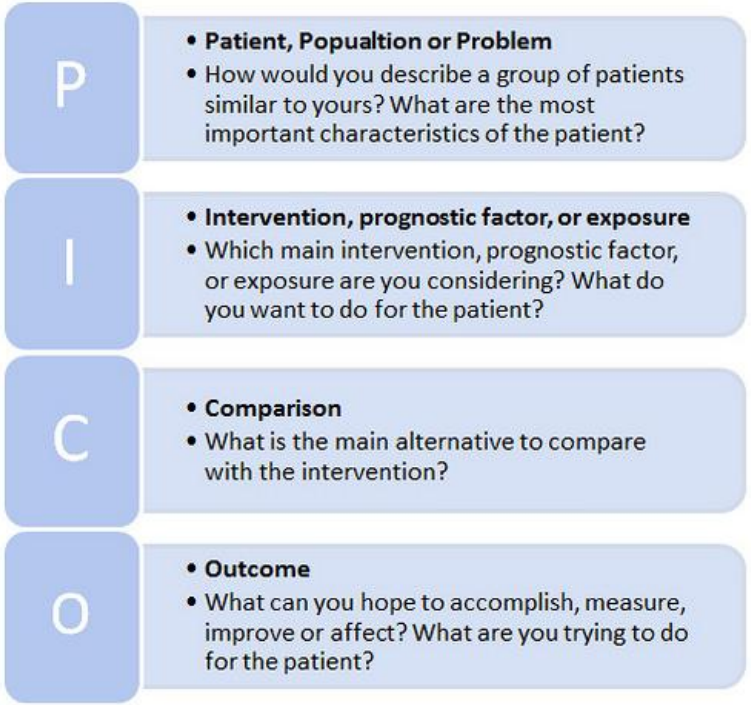
Leverage Social Media



Frameworks for Research Question

FINER Criteria for a Good Research Question		
F	Feasible	• Adequate number of subject • Adequate technical expertise • Affordable in time and money • Manageable in scope
I	Interesting	• Getting the answer intrigues the investigator, peers, and community
N	Novel	• Confirms, refutes, or extends previous findings
E	Ethical	• Amenable to a study that Institutional Review Board will approve
R	Relevant	• To scientific knowledge • To clinical and health policy • To future research

Frameworks for Research Question



A 2-year-old boy presents in an outpatient clinic with fever and severe pain in his right ear. He has a history of recurrent ear infections, and his mother expresses a concern that he has been on the antibiotic amoxicillin for the past few weeks. She is worried about the consequences of the long-term antibiotic use. She is also concerned about the outcome associated with recurrent ear infections. She wants to know if the prescribed amoxicillin is effective, or it can be substituted with another antibiotic because of its side effects such as frequent diarrhea.

- What is the background question?
- What is the foreground question?
- What is the PICO question?

Frameworks for Research Question

S	Sample	The group you are focusing on.
P of I	Phenomenon of interest	The behaviour or experience your research is examining.
D	Design	How the research will be carried out?
E	Evaluation	What are the outcomes you are measuring?
R	Research type	What is the research type you are undertaking?

S	Setting	The setting or the context
P	Population or perspective	Which population or perspective will the research be conducted for/from
I	Intervention	The intervention been studied
C	Comparison	Is there a comparison to be made?
E	Evaluation	How well did the intervention work, what were the results?

Source: https://plymouth.libguides.com/systematicreviews/question;

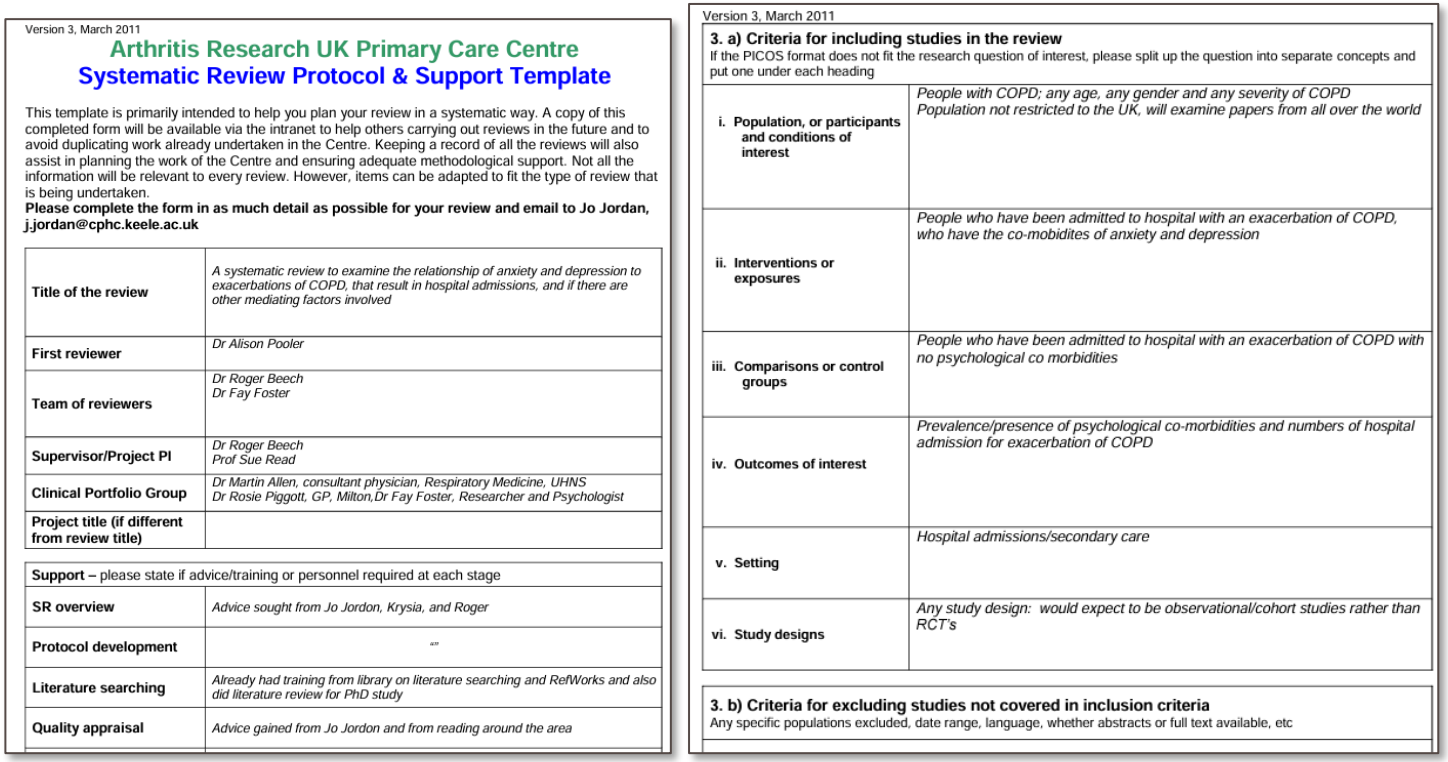
Writing the *Protocol*, *Data Synthesis*, *Discussion/ Conclusion* Sections

Developing a Protocol

- **Protocol** – a document that defines your step-by-step research plan, which enables you to be methodical, scientific and efficient. It includes:
  - Research background – currently known information, knowledge gap, need for study
  - Research objective – research question rephrased as the objective
  - Methodology – study selection criteria; search strategy; analysis
- Get approval on the protocol from the IRB prior to conducting the study. An approved protocol should only be modified if there is a valid need to revise in order to more effectively answer the research question.
- Advisable to register the protocol on PROSPERO

Additional Reading: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s13643-021-01877-1; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802597/

Protocol Template



Version 3, March 2011

Arthritis Research UK Primary Care Centre

Systematic Review Protocol & Support Template

This template is primarily intended to help you plan your review in a systematic way. A copy of this completed form will be available via the intranet to help others carrying out reviews in the future and to avoid duplicating work already undertaken in the Centre. Keeping a record of all the reviews will also assist in planning the work of the Centre and ensuring adequate methodological support. Not all the information will be relevant to every review. However, items can be adapted to fit the type of review that is being undertaken.

Please complete the form in as much detail as possible for your review and email to Jo Jordan, j.jordan@cphc.keele.ac.uk

Title of the review	*A systematic review to examine the relationship of anxiety and depression to exacerbations of COPD, that result in hospital admissions, and if there are other mediating factors involved*
First reviewer	*Dr Alison Pooler*
Team of reviewers	*Dr Roger Beech* *Dr Fay Foster*
Supervisor/Project PI	*Dr Roger Beech* *Prof Sue Read*
Clinical Portfolio Group	*Dr Martin Allen, consultant physician, Respiratory Medicine, UHNS* *Dr Rosie Piggott, GP, Milton,Dr Fay Foster, Researcher and Psychologist*
Project title (if different from review title)	

Support – please state if advice/training or personnel required at each stage	
SR overview	*Advice sought from Jo Jordon, Krysia, and Roger*
Protocol development	""
Literature searching	*Already had training from library on literature searching and RefWorks and also did literature review for PhD study*
Quality appraisal	*Advice gained from Jo Jordon and from reading around the area*

Version 3, March 2011

3. a) Criteria for including studies in the review

If the PICOS format does not fit the research question of interest, please split up the question into separate concepts and put one under each heading

i. Population, or participants and conditions of interest	*People with COPD; any age, any gender and any severity of COPD* *Population not restricted to the UK, will examine papers from all over the world*
ii. Interventions or exposures	*People who have been admitted to hospital with an exacerbation of COPD, who have the co-mobidites of anxiety and depression*
iii. Comparisons or control groups	*People who have been admitted to hospital with an exacerbation of COPD with no psychological co morbidities*
iv. Outcomes of interest	*Prevalence/presence of psychological co-morbidities and numbers of hospital admission for exacerbation of COPD*
v. Setting	*Hospital admissions/secondary care*
vi. Study designs	*Any study design: would expect to be observational/cohort studies rather than RCT's*

3. b) Criteria for excluding studies not covered in inclusion criteria

Any specific populations excluded, date range, language, whether abstracts or full text available, etc

Source: https://www.crd.york.ac.uk/PROSPEROFILES/3611_STRATEGY_20130031.pdf

Search Strategy

- Databases – Advisable to use multiple databases. Pubmed and Scopus are some popular options. EMBASE is great for creating the query string and health/ life sciences research.
- Handsearching – databases can be the primary source. However, also need to scan relevant journals and conference proceedings. Review reference lists of relevant studies.
- Gray Literature – Publications by governments, universities and other institutions that are typically not published by traditional publishers. Includes thesis and registries.
- Expert Advice – Take advice from the Advisory Group on sources.
- Query String:
  - Clearly defined query string that is approved *a priori*
  - Can be created in 1 database and then replicated in others
  - Includes Boolean operators and structured text
  - Studies sourced using this string within a defined period of time

Source: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323810388000110?scrollTo=%23hl0000362; https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323567114000079?scrollTo=%23hl0000229;

Search Strategy

2 Methods

This systematic review was conducted following the CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies (CHARMS) (Moons et al., 2014) and the guidance by Debray et al. (Debray et al., 2017) for reviews of prediction model studies. The protocol for this review was registered at the PROSPERO International Prospective Register of Systematic Reviews Website (registration number CRD42021286576).

2.1 Literature search

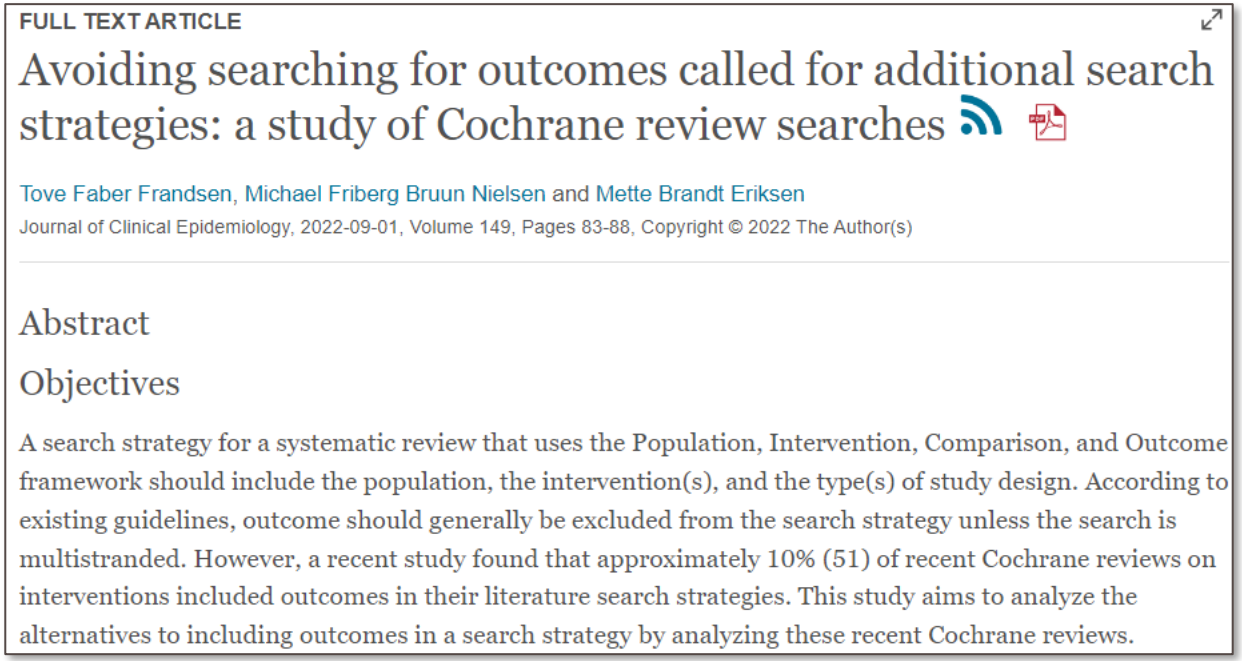
We systematically searched PubMed, EMBASE and PsycINFO from the inception of each database to January 20, 2022, for prediction models developed to predict the risk of developing MDD among older adults aged 60 years or older. Additionally, we manually reviewed the reference lists of included studies. The search strategy consisted of three concepts (1) prediction models, (2) older adults, and (3) major depression and related derivatives. We created the search algorithm according to the previous guidance of the search method for systematic reviews of prediction model studies (Bellou et al., 2019; Debray et al., 2017; Geersing et al., 2012). A complete list of search terms can be found in **Appendix A .**

2.2 Search strategy

One researcher (SK) searched for eligible RCTs in MEDLINE, ISI Web of Science (WoS) and Cochrane Central Register of Controlled Trials (CENTRAL) plus appropriate systematic reviews and meta-analyses in the Cochrane Database of Systematic Reviews (CDSR) and Kleijnen Systematic Reviews (KSR) Evidence from inception to January 18, 2022. The search strings shown in Supplementary table 3 were conceived by two researchers (SK and BS) and reviewed by a specialist for systematic bibliographic searches at the Central Library of the German Cancer Research Center (Andrea Heppert). SK searched for ongoing or completed RCTs with unpublished data in the WHO's International Clinical Trials Research Portal (ICTRP) and clinicaltrials.gov via CENTRAL. Reference lists of eligible studies were scanned to yield relevant articles via cross-referencing. No restrictions regarding time of publication, language, settings, or geographical locations were applied.

Source: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S156816372300082X?scrollTo=%23hl0000716; https://www.clinicalkey.com/#!/content/journal/1-s2.0-S1568163722002458

Should Outcomes be included in search (PIC O?)



FULL TEXT ARTICLE

Avoiding searching for outcomes called for additional search strategies: a study of Cochrane review searches

Tove Faber Frandsen, Michael Friberg Bruun Nielsen and Mette Brandt Eriksen

Journal of Clinical Epidemiology, 2022-09-01, Volume 149, Pages 83-88, Copyright © 2022 The Author(s)

Abstract

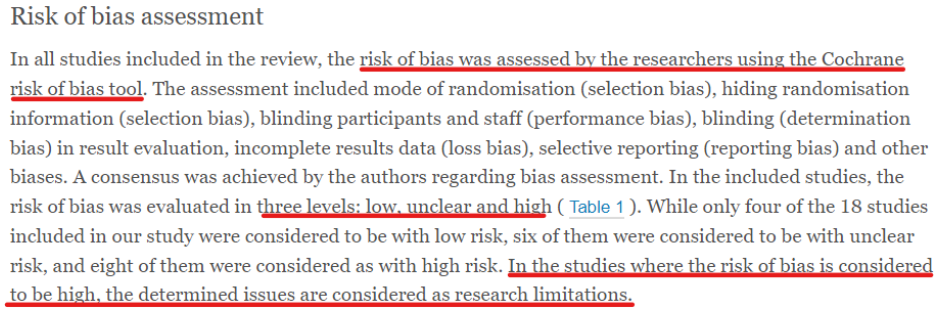
Objectives

A search strategy for a systematic review that uses the Population, Intervention, Comparison, and Outcome framework should include the population, the intervention(s), and the type(s) of study design. According to existing guidelines, outcome should generally be excluded from the search strategy unless the search is multistranded. However, a recent study found that approximately 10% (51) of recent Cochrane reviews on interventions included outcomes in their literature search strategies. This study aims to analyze the alternatives to including outcomes in a search strategy by analyzing these recent Cochrane reviews.

Additional Reading: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S0895435622001378?scrollTo=%23top

Study Selection

- Use a reference manager like Mendeley, Zotero or End Note
- Min 3 members – two to select and 1 to arbitrate
- Ensure everyone fully understands the selection criteria. Selection criteria directly comes from your PICO question.
- Level 1 selection – based on title and abstract
- Level 2 selection – based on full-text
- Must state inclusion criteria and exclusion criteria. Also a good idea to state how Risk of Bias was addressed.



Risk of bias assessment

In all studies included in the review, the risk of bias was assessed by the researchers using the Cochrane risk of bias tool. The assessment included mode of randomisation (selection bias), hiding randomisation information (selection bias), blinding participants and staff (performance bias), blinding (determination bias) in result evaluation, incomplete results data (loss bias), selective reporting (reporting bias) and other biases. A consensus was achieved by the authors regarding bias assessment. In the included studies, the risk of bias was evaluated in three levels: low, unclear and high (Table 1). While only four of the 18 studies included in our study were considered to be with low risk, six of them were considered to be with unclear risk, and eight of them were considered as with high risk. In the studies where the risk of bias is considered to be high, the determined issues are considered as research limitations.

Source: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S2530018022000956?scrollTo=%23hl0000873

Another example of study selection

FULL TEXT ARTICLE

Efficacy of vitamin D $_3$ supplementation on cancer mortality: Systematic review and individual patient data meta-analysis of randomised controlled trials

Sabine Kuznia, Anna Zhu, Taisuke Akutsu, Julie E. Buring, Carlos A. Camargo Jr, Nancy R. Cook, Li-Ju Chen, Ting-Yuan David Cheng, Sari Hantunen, I.-Min Lee, JoAnn E. Manson, Rachel E. Neale, Robert Scragg, Aladdin H. Shadyab, Sha Sha, John Sluyter, Tomi-Pekka Tuomainen, Mitsuyoshi Urashima, Jyrki K. Virtanen, Ari Voutilainen, Jean Wactawski-Wende, Mary Waterhouse, Hermann Brenner and Ben Schöttker

Ageing Research Reviews, 2023-06-01, Volume 87, Article 101923, Copyright © 2023 Elsevier B.V.

2.3 Inclusion and exclusion criteria for meta-analysis

2.3.1 Study type

Double-blind RCTs with parallel-group designs were included. Single-arm studies, observational studies (e.g., cohort and case-control studies) and other records (e.g., narrative reviews, dissertations, editorials, study protocols, clinical guidelines, commentaries, correspondences, and letters) were excluded.

2.3.2 Participants

Studies were included if they were conducted in the general population or in a population suffering from any specific chronic disease (e.g., HIV patients). Special populations such as pregnant or lactating women, infants, and COVID-19 patients were excluded. No other age restrictions were applied.

2.3.3 Interventions

Trials that used vitamin D $_3$ and bioequivalent substances (e.g., calcitriol (i.e., 1,25(OH) $_2$ D), alfacalcidol, calcifediol (i.e., 25(OH)D) in any dose and any regimen (e.g., daily/weekly/monthly intake) for at least six months were included. Co-administration with other medications or dietary supplements (e.g., calcium or chemotherapy) was allowed if all arms received the same therapy. Studies not permitting personal/private use of vitamin D $_3$ supplements were included as well. Trials were excluded if vitamin D $_3$ was supplied via fortified foods, or if vitamin D $_2$ or bioequivalent substances were used because it was already found not to affect mortality in a previous meta-analysis (Bjelakovic et al., 2014).

2.3.4 Comparators

Studies that used placebo as the comparator were included. Studies were excluded if they were designed as open-label trials, used no treatment as control or administered an active control (e.g., standard of care or lower vitamin D $_3$ doses than the intervention dose) instead of a placebo.

2.3.5 Outcomes

Studies required at least one cancer death per arm to be eligible and were included if risk ratios for cancer mortality or cancer survival were published. Results of the intention-to-treat approach were used, including all participants randomised, when both intention-to-treat and per-protocol results were given. We prioritized unadjusted summary estimates over adjusted estimates since studies adjusted for different covariates. Published results including a subsequent follow-up were used in the meta-analyses only when results covering solely the intervention period were not available. If studies reported cancer incidence or all-cause mortality as a primary outcome or in the framework of serious adverse events, the authors were contacted to obtain unpublished data on cancer outcomes. Studies were excluded if no data on at least one of the outcomes of interest were obtainable.

Source: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S156816372300082X?scrollTo=%23hl0000716

Data Extraction

- Systematically collect/ tabulate/ categorize data from the included studies.
- Use a form for data extraction. Include the form in Appendix or Supplementary Material. You can develop your own forms or use templates like The Registry of Methods and Tools for Evidence-Informed Decision Making and the Grading of Recommendations, Assessment, Development and Evaluations Working Group.
- Data points to capture will depend on your research question. Common items are study design, sample size, context, research findings and conclusions.
- If working on a meta-analysis there may be further stringent criteria on study selection and data extraction.

Source: https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323810388000110?scrollTo=%23hl0000362; https://www.clinicalkey.com/#!/content/book/3-s2.0-B9780323567114000079?scrollTo=%23hl0000229;

Data Extraction

2.4 Data extraction

Two researchers (JT and CXNM) independently extracted data. A standardized data extraction form (**Appendix B**) was developed and piloted using the CHARMS checklist (Moons et al., 2014) for collecting relevant data items from eligible studies. Some studies reported more than one model, and some models were analyzed in various studies (external validation studies). The unit of this review was a model within a study unless with other specifications. For the articles that developed more than one prediction model within a study, we only extracted data from the model with the best prediction performance. If it was unclear which model was the best, data from all models would then be extracted. We extracted data including the first author, year, journal of publication, study type, data source, study setting, study population, geographical location, the definition of depression, size of study population and number of depression episodes, candidate and included predictors, and predictive pe

To analyze each model's predictive ability, we extracted discrimination, calibration, classification, and overall performance of included models (Collins et al., 2015). A prediction model's discrimination refers to the model's ability to differentiate people who may develop an outcome of interest from those who do not (Damen et al., 2016 ; Harrell et al., 1996) and is frequently measured by the concordance (C) statistics (C-statistics) (Debray et al., 2017). The C-statistics lays between 0.50 and 0.59, 0.60–0.69, 0.70–0.79, 0.80–0.89 and 0.90 or over, indicating poor discrimination, moderate discrimination, good discrimination, very good discrimination, and excellent discrimination, respectively (Hanley and McNeil, 1982; Yourman et al., 2012). Concordance refers to the area under the receiver operating characteristics curve (AUC) in logistic regression models (Debray et al., 2017). A prediction model's calibration refers to the model's agreement between predicted and observed numbers of events (Damen et al., 2016; Royston and Altman, 2013). Calibration is often measured by calibration intercept and calibration slope (Bedogni et al., 2009). It might be challenging to summarize estimates of calibration performance, given that calibration plots are usually absent, and studies often reported different forms of summary statistics in the calibration (Bouwmeester et al., 2012; Collins et al., 2013). Potential classification indicators include sensitivity, specificity, accuracy, and positive and negative predictive value. Potential overall performance was demonstrated by the value of R^2 and Brier score (Steyerberg, 2019; Steyerberg et al., 2010).

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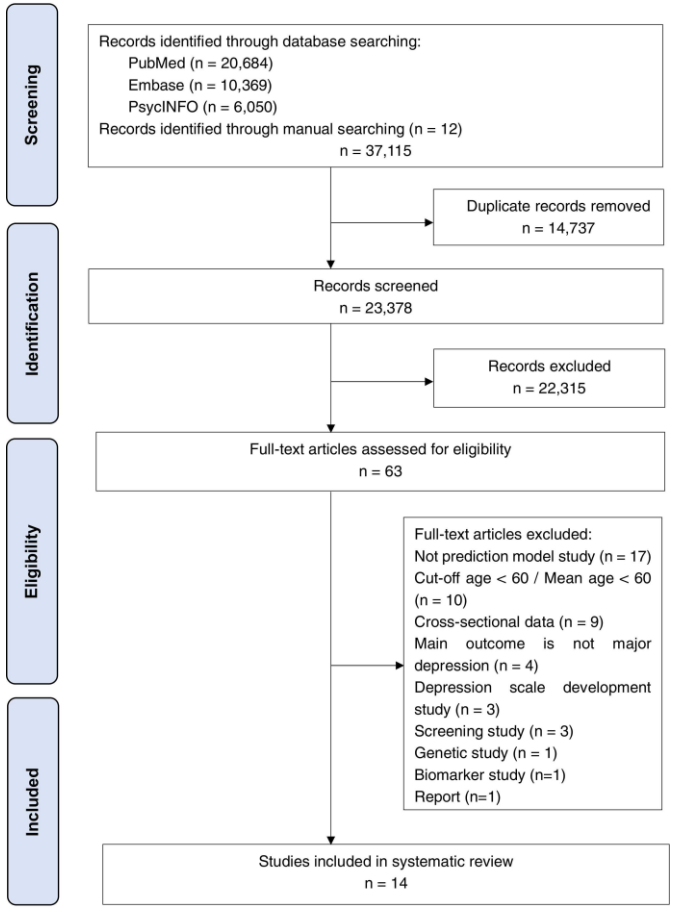
Synthesis and Results

- Bring together all the information and analysis you collected into a single, cohesive, unbiased story. It can be narrative or quantitative. In the quantitative meta-analysis pool and analyze data across comparable study using statistical methods.
- Always a good idea to conduct a systematic review and meta-analysis together when possible. If a quantitative analysis is not possible, include a justification.
- Results:
  - Good idea to open the section with a summary of total studies, selected studies and further groupings based on inclusion, if not already done so.
  - Report other key findings directly relevant to the PICO question, such as, description of the populations found, details of the interventions captures, impact of controls and outcomes implications
  - Comment on Risk of Bias

Synthesis and Results in PRISMA

- PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020 Statement, PRISMA Flow Diagrams, PRISMA Checklist)
- PRISMA Extensions:
- PRISMA-P – for developing review protocols was published in January 2015 in Systematic Reviews
- PRISMA-IPD – individual patient data
- PRISMA-NMA – network meta-analyses



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Synthesis and Results in PRISMA

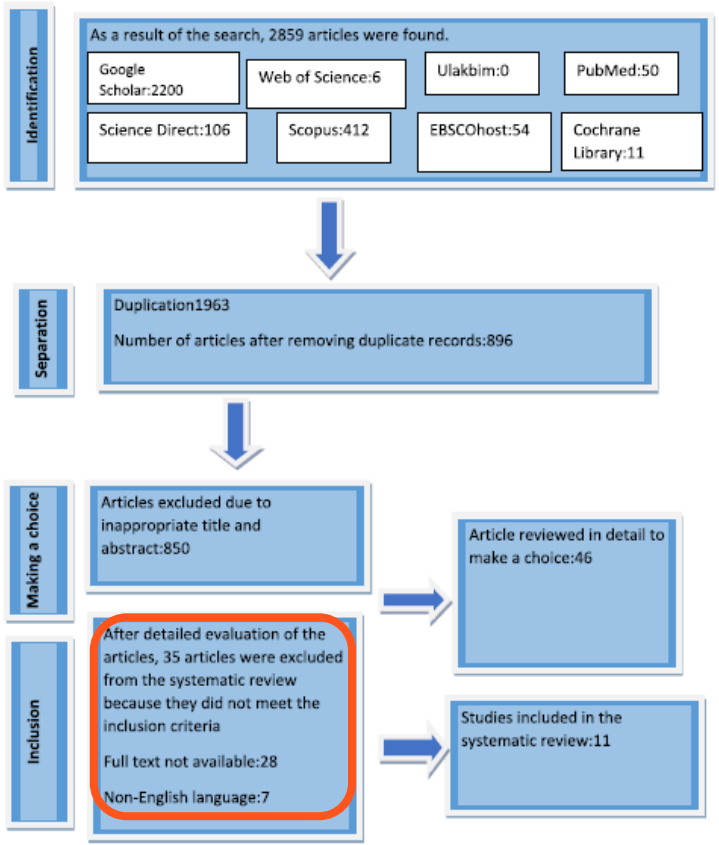

Fig. 1. Flowchart of studies included in the systematic review (PRISMA-P Flowchart).

Discussion

- It is the **most important** (and **hardest**) section to write.
- Many articles are **rejected** because the discussion is **weak**.

"I won't know why I should care about your experiment until you tell me why I should".
https://www.nature.com/articles/d41586-018-02404-4

Discussion

- Are my results clinically and scientifically relevant? The reader must be remineded of the importance of what he/she just read.
- What is the **NEW KNOWLEDGE gained**? How does it impact various stakeholders – patients, providers, policy makers, community, anyone else?
- What is the impact of my results on the current body of knowledge?
- Include clear recommendations and limitations from flagship studies that align with your findings. Reference key studies as well as other reviews from key authors or institutions.
- Use short phrases (30-35 words).
- Use transitional words such as “therefore”, “however”, “thus”, “conversely”, “consistent with”, “in contrast to”...
- Finish with the study limitations and a conclusion.
- Read systematic reviews especially those related to your overall subject area to get inspiration.

Discussion

4 Discussion

4.1 Summary of main findings

This systematic review and IPD meta-analysis observed that, overall, vitamin D $_3$ supplementation resulted in a statistically non-significant 6% reduction of cancer mortality in the general population, 5% improved overall survival of cancer patients and 7% improved cancer-specific survival of cancer patients. The relationship with cancer mortality was stronger and statistically significant when the analysis was restricted to trials with a daily vitamin D $_3$ dosing regimen (reduction by 12%). Subgroup analysis with IPD of trials with daily vitamin D $_3$ treatment revealed statistically significant efficacy for cancer mortality among adults aged ≥ 70 years, males, non-Hispanic Whites, and participants free of cancer at initiation of treatment. However, tests for interaction by these factors were not significant and these results must be interpreted with caution because they were post-hoc analyses and confidence intervals overlapped (see below).

4.2 Comparison with other systematic reviews

Previous meta-analyses reporting statistically significant effects of vitamin D $_3$ supplementation on cancer mortality did not include the recently published D -Health trial (Neale et al., 2022), which applied a bolus dosing regime, had a negative finding and contributed 23.6% of the weight to our meta-analysis of all trials (Bjelakovic et al., 2014; Guo et al., 2022; Keum et al., 2019; Zhang et al., 2019; Zhang et al., 2020). Our non-significant pooled effect estimate of all trials (RR [95% CI]: 0.94 [0.86; 1.02]) is comparable to the most recent systematic review by Zhang et al. (RR [95% CI]: 0.96 [0.80–1.16]), which also included the D -Health trial but not the WHI trial because of co-administration of calcium (Zhang et al., 2022). Thus, their result is similar to our sensitivity analysis excluding trials with co-administration of calcium (HR [95% CI]: 0.97 [0.86; 1.08]). However, it is debatable whether it is necessary to exclude the WHI trial because it is unclear whether calcium supplementation has an impact on cancer mortality. A meta-analysis of RCTs found no effect of calcium on cancer mortality at trial-level (HR [95%CI]: 0.96 [0.74; 1.24]) or patient-level (HR [95%CI]: 0.98 [0.74; 1.29]) and, moreover, no biologically plausible explanation is currently available for an effect of calcium supplementation on cancer mortality (Bristow et al., 2013; Yang et al., 2016).

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Discussion

4.7 Strengths and limitations

This is the first systematic review and meta-analysis on the efficacy of vitamin D_3 supplementation for cancer mortality and survival using IPD. All major trials contributed IPD except a single older one (Trivedi et al., 2003), making the IPD analyses representative for the overall available evidence in this field. Furthermore, the acquisition of previously unpublished data is a strength of this systematic review, as it reduced selective reporting biases that were listed as limitations in previous systematic reviews. The final number of 14 RCTs included in meta-analyses for the endpoint "cancer mortality" involved 104,727 randomised participants including 1928 cancer deaths, which led to a high statistical power and precision of the pooled effect estimates, and allowed the conduction of subgroup analyses, which were nonetheless underpowered. No signs of heterogeneity or publication bias were detected.

A further strength of our systematic review is that we included exclusively double-blind and placebo-controlled randomised trials. We meticulously followed guidelines such as the PRISMA-IPD statement (supplementary table 2), registered the systematic review before any data collection occurred, published a protocol (Schöttker et al., 2021), recorded all deviations to ensure transparency (supplementary table 1), and evaluated the strength of evidence according to the GRADE approach. Moreover, data extraction, risk assessment and all statistical analyses were performed by two independent researchers.

However, our systematic review and IPD meta-analysis also has limitations. As anticipated in the protocol, the sample size was limited for certain subgroup analyses, such as non-White ethnicities, baseline 25(OH)D levels, cancer stage and cancer sites, and sometimes the studies contributed not to all subgroup meta-analyses for the same factor (e.g. if only women were included in the trial, the study could not contribute to the subgroup analysis on males), making it challenging to draw firm c

Despite the high response rate and excellent collaboration with authors from around the globe, we lacked replies from 30 studies and did not find an appropriate contact for ten studies. In most cases, these were studies that dated back more than 15 years and whose authors had moved on or retired, or whose data were stored in inaccessible archives. Thus, selective reporting bias cannot be completely excluded, but it is likely negligible because the results of the additional trial data obtained were equally distributed and did not all point into either a favourable or unfavourable direction for vitamin D.

Source: https://www.clinicalkey.com/#!/content/journal/1-s2.0-S1568163

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Conclusion

- Direct answer to the PICO question
- Emphasize on the relevance to practice

5 Conclusions

The conclusion of the main meta-analysis of all RCTs is that vitamin D $_3$ supplementation did not reduce cancer mortality because the 6% reduction of cancer mortality was not statistically significant: HR 0.94 (95% CI: 0.86; 1.02). However, we believe that the arguments for an efficacy of daily (as compared to bolus) vitamin D treatment regimens are convincing. Indeed, restricting the IPD meta-analysis to trials with daily dosing regimen yielded a statistically significant 13% cancer mortality reduction and 11% increased cancer-specific survival. As these effect estimates are based on untargeted vitamin D $_3$ supplementation of individuals with and without vitamin D insufficiency, the potential in a situation where only patients with low vitamin D status are treated is likely to be substantially underestimated. Furthermore, our findings suggest that, for the health outcome "cancer survival", starting vitamin D $_3$ treatment before or at least shortly after a cancer diagnosis could be beneficial, which was not done for all cancer patients in the large trials, which recruited from the general population. Considering the very likely

s in the currently available trials by not focussing on subjects with low
D self-medication to the control group, the almost negligible risk of
lementation at reasonable doses and the very low treatment costs, we
ised medication for cancer patients and should be considered for use
apy when low serum 25(OH)D levels justify its use.

5 Conclusions

We found 20 prediction models to predict the risk of developing MDD among older adults, and they all reported moderate to excellent discrimination. Nevertheless, all models had a high or unclear ROB due to methodological defects. Therefore, their reported predictive performance is probably overestimated and can't represent the target population (Wolff et al., 2019). We cannot advocate any of the existing prediction models to be put into practice at present. Subsequent prediction modeling studies for geriatric depression risk should primarily deal with the problems raised, and also should follow the methodological guidance of prediction modeling studies, since unreliable predictions may lead to more harm than benefit when guiding medical practice (Wynants et al., 2020). Meanwhile, future studies in this area should also concentrate on assessing model applicability and generalizability and conducting a cost-effectiveness analysis to estimate the most effective model for use in practice.

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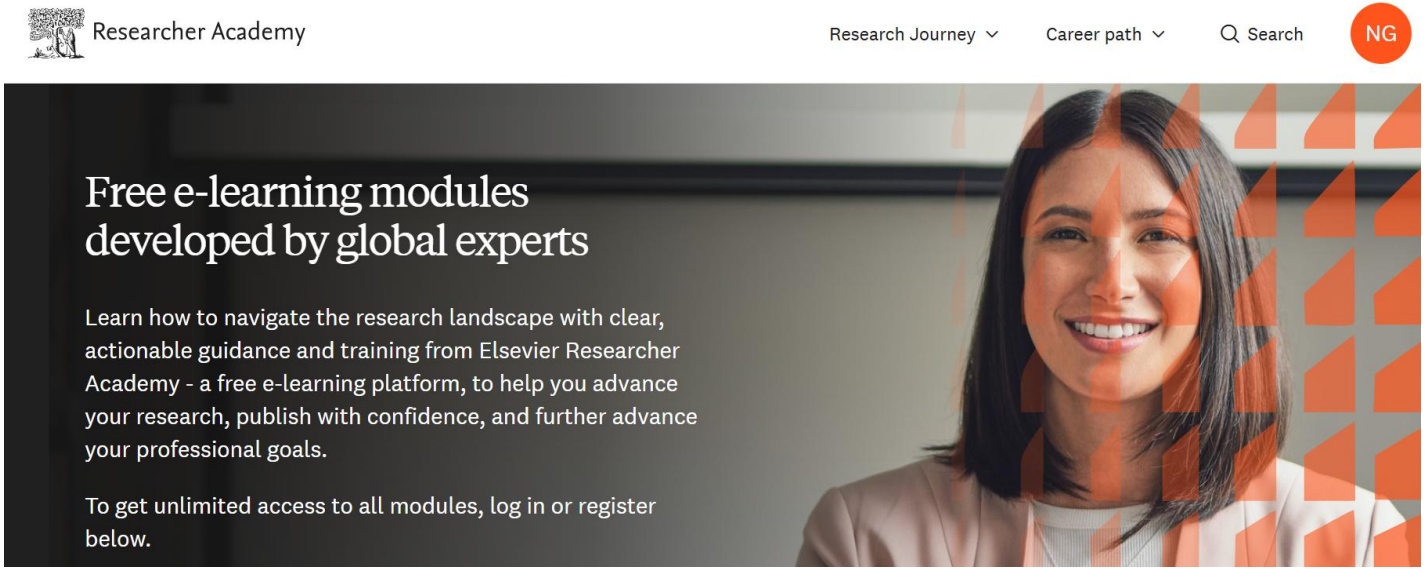

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