Introduction to Systematic Reviews

Dr. Tina Jafari

MD-PhD of clinical nutrition

Aims of the workshop….

- Outline what a systematic review is
- Knowing the difference between the "*systematic review*" and "*narrative review*"
- To discuss scope and the formulation of a review question
- The purpose and format of a protocol
- Systematic searching/screening of studies
- Data extraction/quality appraisal and intro to evidence synthesis

What is a systematic review?

- ***SYSTEMATIC:*** Done or acting according to a *fixed plan or system*: methodical

- ***REVIEW:*** A critical appraisal of a book, play or other work

"A systematic review is a review in which there is a *comprehensive search* for *relevant studies* on a *specific topic*,

and those identified are then appraised and synthesized according to a predetermined and explicit method."

(*Klassen et al. Guides for reading and interpreting systematic reviews. Arch Pediatr Adolesc Med ۱۹۹۸;۱۵۲:۷۰۰-۷۰۴.)

- A systematic review attempts to collate all *empirical evidence* that fits pre-specified eligibility criteria in order to answer a specific research question.

- It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made (Antman ١٩٩٢, Oxman ١٩٩٣)

Why systematic reviews are needed?

- Minimise the impact of bias/errors
- Can help to end confusion
- Highlight where there is not sufficient evidence
- Combining findings from different studies can highlight new findings
- Can mitigate the need for further trials
- Facilitate rational decision making

Health care providers, researchers and policy makers are inundated with unmanageable amounts of information

- Over ٢٠ million citations in PubMed
- Approx. ٧٥ to ١٠٠ RCTs published daily
- Usually impossible to consider all relevant individual primary research studies in a decision making context

- Systematic reviews enable practitioners to keep up to date with evidence accumulating in field and to practice evidence-based medicine

What is the difference…
between Literature Review and Systematic Review

- Systematic reviews generally answer very focused, PICO-based questions.
- *Systematic reviews have a protocol in place prior to the literature review beginning, including:*

- *The clinical question*
- *Specific inclusion and exclusion criteria*
- *Methods for assessing bias*
- *Methods for combining the data (e.g., via a meta-analysis)*

- A systematic review literature search is pre-specified and designed to find all relevant materials;
- difference is a literature review does not follow a pre-specified protocol, nor does it need to be truly “comprehensive”.
- Systematic reviews are often the basis for a meta-analysis, where the data from the materials fitting the pre-specified criteria are pooled and statistically analyzed.
- Traditional literature reviews do not apply additional statistical methods to the materials found.

….*A* is a drug.

It seems to be useful for the disease *B*.

Studies represent different results on *A* for *B*….

arrative review

There are ١٠ studies on A for B:

٦ studies reported that A has beneficial effects for B.

٤ studies reported that A did not have significant effects for B…

o

The authors concluded that A is useful for B

Or

An expert in this field concluded that

A is useful for B or,

A is not useful for B because….

Sometimes

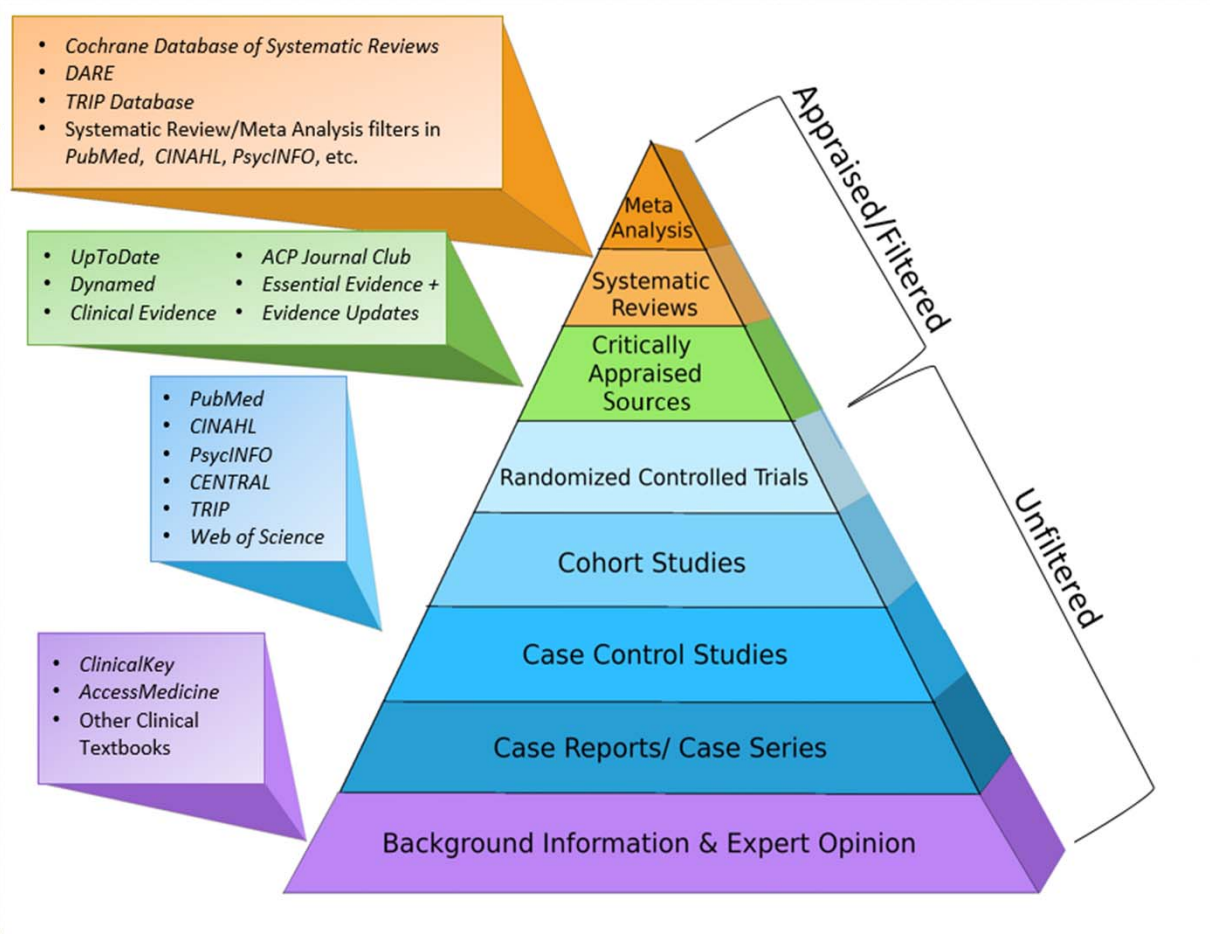
- ***Narrative conducted by expert(s).***

- ***Systematic review conducted by students.***

Why not traditional reviews

- ‘Unscientific’ rarely pre-specify or make methods explicit
- Rarely transparent or reproducible
- Usually qualitative, subjective, opinions of individual
- Often incomplete, filing cabinet or MEDLINE review
- Difficult to make sense across groups of studies, especially when conflicting based on qualitative reading alone

Hierarchy of evidence



Who undertakes systematic reviews?

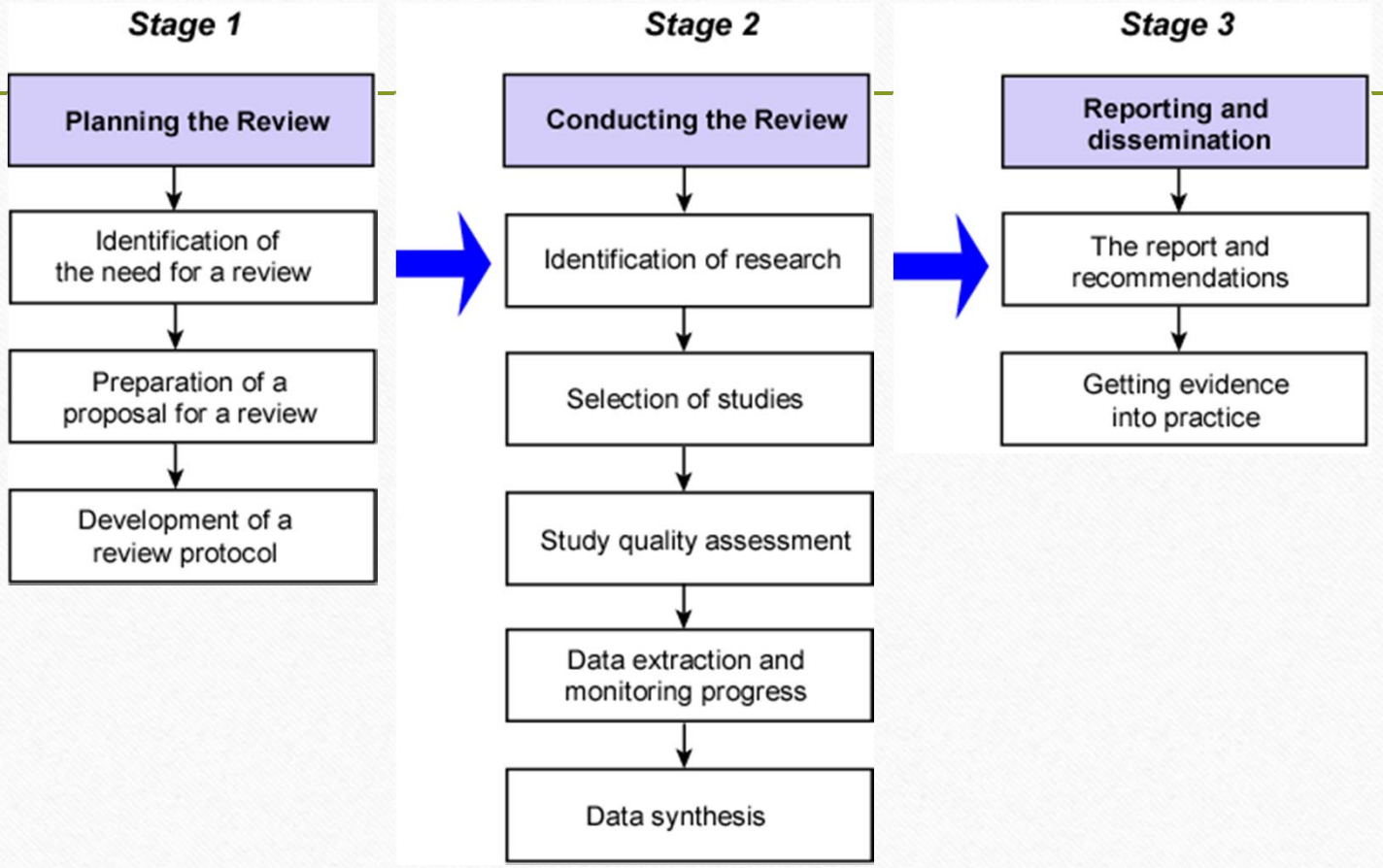
- Cochrane/Campbell Collaboration
- NICE (National Institute for Health and Care Excellence)
- Health Technology Assessment
- Academics/researchers/Clinicians
- MSc/PhD students

Who undertakes systematic reviews?

- *Multidisciplinary teams*
  - Clinicians
  - Health services researchers
  - Information scientists
  - Statisticians
  - Health Economists
  - Patient and public involvement – particularly for guidelines

Stages in a Systematic Review- the process

Conducting systematic reviews

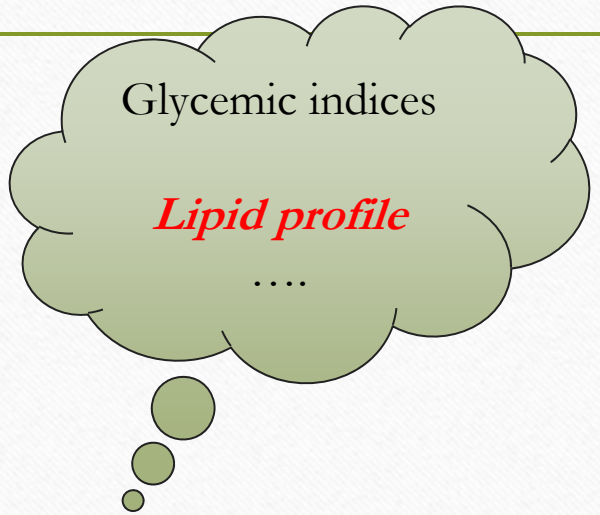


Identification of research/review question

- Questions may be broad or narrow Well-formulated questions will guide many aspects of the review process
  - Searching strategy
  - Inclusion/exclusion criteria
  - Data extraction
  - Choice of synthesis method
  - Presentation/dissemination of findings

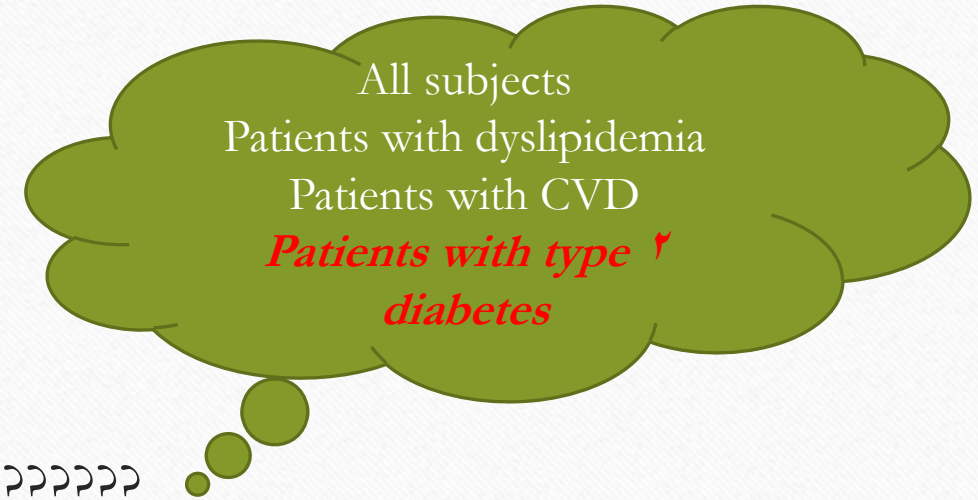
Example

Vitamin D for metabolic profile….



Metabolic profile

Vitamin D for ***lipid profile***


All subjects
Patients with dyslipidemia
Patients with CVD
Patients with type ۲ diabetes

Subjects??????

Vitamin D for ***lipid profile in patients with type ٢ diabetes***

Clinical Nutrition 35 (2016) 1259–1268

Contents lists available at ScienceDirect

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alyses

s of vitamin D on serum lipid profile in patients with type 2 es: A meta-analysis of randomized controlled trials

ari [a, b, *], Aziz A. Fallah [c], Afshin Barani [d]

of Biochemistry and Nutrition, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
nts Research Center, Shahrekord University of Medical Sciences, Sharhekord, Iran
of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord 34141, Iran
of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Urmia University, Urmia, Iran

- "To assess the effects of [*intervention or comparison*] for [*health problem*] in [*types of people, disease or problem, and setting if specified*]."

Question formulation

- Determining the scope is a decision dependent upon multiple factors:
  - *Perspectives regarding a question's relevance and potential impact;*
  - *Supporting theoretical, biologic and epidemiological information;*
  - *The potential generalizability and validity of answers to the questions;*
  - *Available resources;*

The wider literature base – has a recent high-quality SR been conducted?

Advantages and disadvantages to both broad and narrow question

- The validity of very broad question may be criticized for ‘mixing apples and pears’;

- but advantages might include
  - Comprehensive summary of the evidence
  - Generalizability of findings

Research

Original Investigation

Effect of Vitamin D Supplementation on Blood Pressure
A Systematic Review and Meta-analysis Incorporating Individual Patient Data

Louise A. Beveridge, MB, ChB; Allan D. Struthers, MD; Faisel Khan, PhD; Rolf Jorde, PhD; Robert Scragg, MBBS, PhD; Helen M. Macdonald, PhD; Jessica A. Alvarez, PhD, RD; Rebecca S. Boxer, MD, MS; Andrea Dalbeni, MD; Adam D. Gepner, MD; Nicole M. Isbel, MBBS, PhD; Thomas Larsen, MD, PhD; Jitender Nagpal, MBBS, MD; William G. Petchey, BM, PhD; Hans Stricker, MD; Franziska Strobel, MD; Vin Tangpricha, MD, PhD; Laura Toxqui, PhD; M. Pilar Vaquero, PhD; Louise Wamberg, MD, PhD; Armin Zittermann, PhD; Miles D. Witham, BM, BCh, PhD; for the D-PRESSURE Collaboration

IMPORTANCE Low levels of vitamin D are associated with elevated blood pressure (BP) and future cardiovascular events. Whether vitamin D supplementation reduces BP and which patient characteristics predict a response remain unclear.

OBJECTIVE To systematically review whether supplementation with vitamin D or its analogues reduce BP.

DATA SOURCES We searched MEDLINE, CINAHL, EMBASE, Cochrane Central Register of

Supplemental content at jamainternalmedicine.com

International Journal for Vitamin and Nutrition Research

Vitamin D ameliorates systolic but not diastolic blood pressure in type 2 diabetic patients: a meta-analysis of randomized controlled trials

--Manuscript Draft--

Manuscript Number:	IJVNR-D-16-00072R3
Full Title:	Vitamin D ameliorates systolic but not diastolic blood pressure in type 2 diabetic patients: a meta-analysis of randomized controlled trials
Article Type:	Review
Keywords:	Vitamin D; Type 2 Diabetes; blood pressure; meta-analysis
Corresponding Author:	Tina Jafari, Ph.D. Shahrekord University of Medical Science Shahrekord, IRAN (ISLAMIC REPUBLIC OF)
Corresponding Author Secondary Information:	
Corresponding Author's Institution:	Shahrekord University of Medical Science
Corresponding Author's Secondary	

Subject: ***"effect of vitamin D on lipid profile"***

Advantage & disadvantage???

- Most obvious advantage of narrow focus is clarity of objectives and ease of reading;

- but disadvantages might include
  - Sparse evidence may limit findings/usefulness
  - Generalizability of findings??

Subject: ***"effect of vitamin D on lipid profile in obese postmenopausal women"***

Advantage & disadvantage???


WE HAVE
ANSWERS

Effectiveness:

- Does the intervention work/not work?
- Who does it work/not work for?

Other important questions:

- How does the intervention work?
- Is the intervention appropriate?
- Is the intervention feasible?

- ?

Asking an answerable question

Answerable questions

EFFECTIVENESS

A description of the populations ***P***

An identified intervention ***I***

An explicit comparison ***C***

Relevant outcomes ***O***

AND

In a particular time OR, Type of the studies ***T***

A PICO question

Time-consuming question:

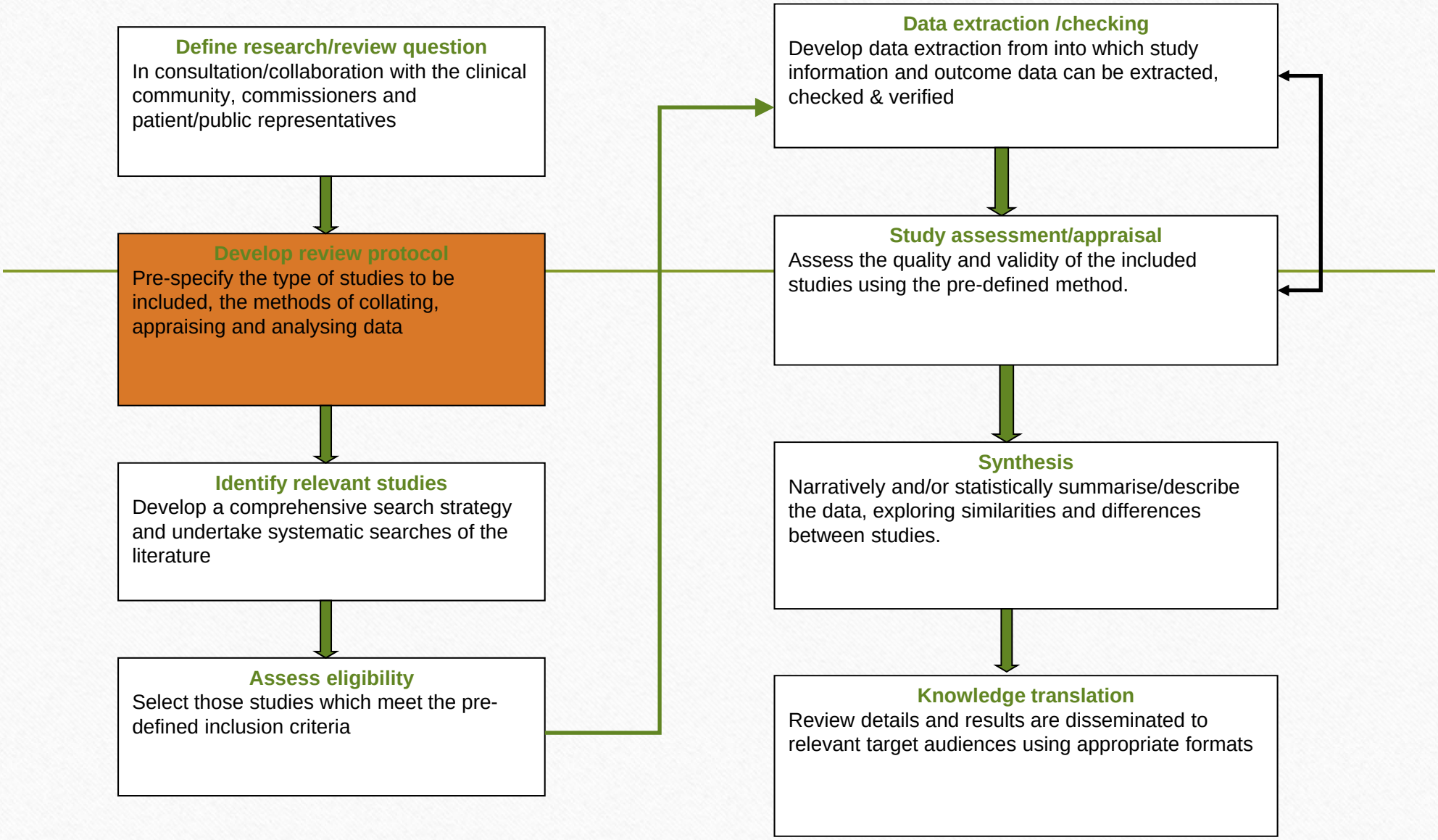
What is the best strategy to prevent smoking in young people?

An answerable question

Q. Are mass media *(or school-based or community-based)* interventions effective in preventing smoking in young people?

The PICO(T) chart

Problem, population	Intervention	Comparison	Outcome	Types of studies
Young people under ٢٥ years of age	a) Television b) Radio c) Newspapers d) Bill boards e) Posters f) Leaflets g) Booklets	a) School-based interventions b) No intervention	a) objective measures of smoking (saliva thiocyanate levels, alveolar CO) b) self-reported smoking behaviour c) Intermediate measures (intentions, attitude, knowledge, skills) d) Media reach	a) RCT b) Controlled before and after studies c) Time series designs


Define research/review question
In consultation/collaboration with the clinical community, commissioners and patient/public representatives
Develop review protocol
Pre-specify the type of studies to be included, the methods of collating, appraising and analysing data
Identify relevant studies
Develop a comprehensive search strategy and undertake systematic searches of the literature
Assess eligibility
Select those studies which meet the pre-defined inclusion criteria
Data extraction /checking
Develop data extraction from into which study information and outcome data can be extracted, checked & verified
Study assessment/appraisal
Assess the quality and validity of the included studies using the pre-defined method.
Synthesis
Narratively and/or statistically summarise/describe the data, exploring similarities and differences between studies.
Knowledge translation
Review details and results are disseminated to relevant target audiences using appropriate formats

Protocol Development

- A protocol is an essential component of the systematic review process
- Helps to ensure careful *a priori* planning
  - Consistency
  - Transparency
  - Integrity

- *Protocol development is one of the features that distinguish a systematic review from a narrative review*

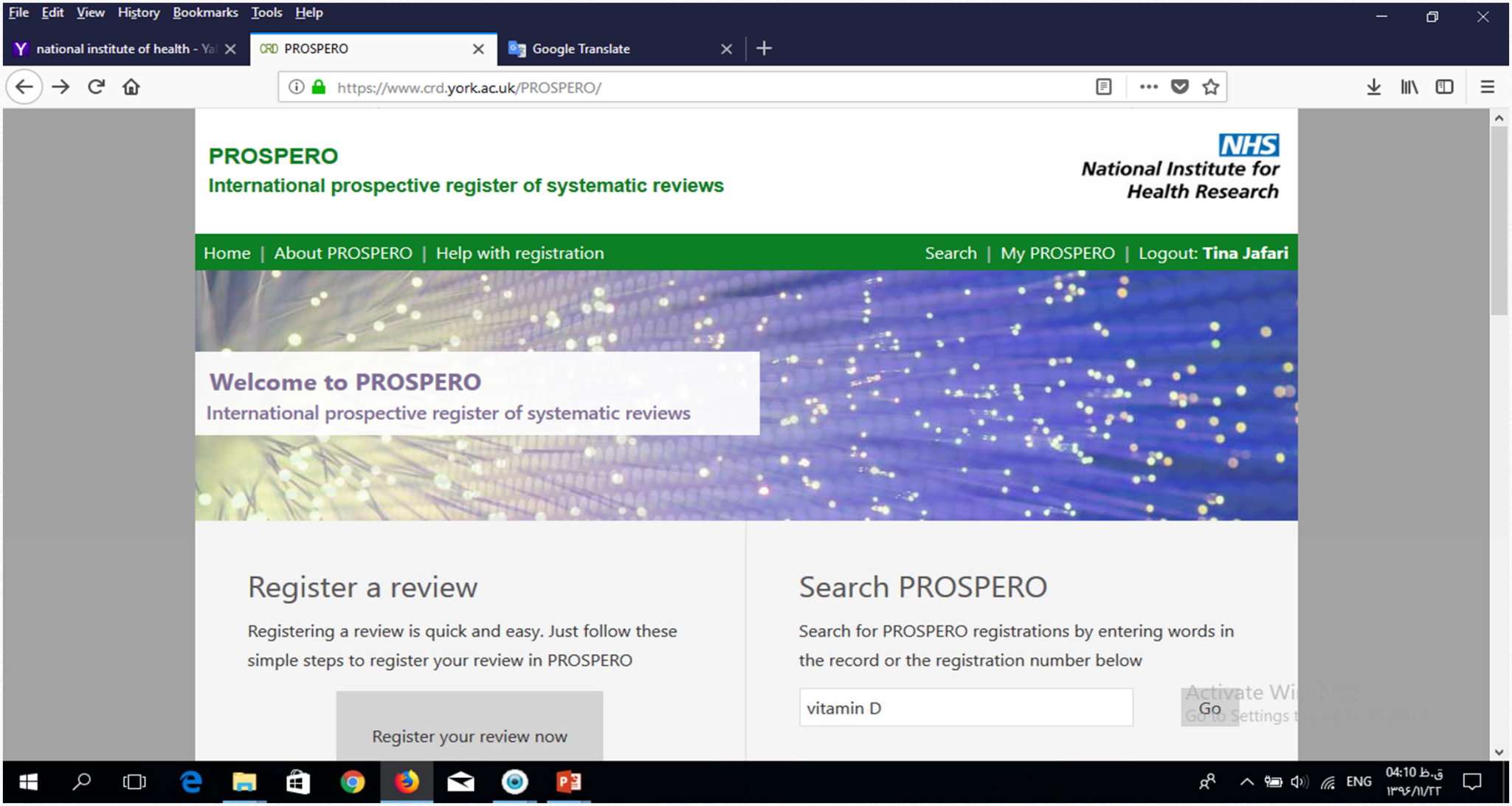
Pre-specification of criteria

- Inclusion
- Exclusion
- Methods
- Outcomes to be synthesised
- Etc.

- Types of
  - Studies (RCTs, non-RCTs, cohort/case-controlled)
  - Population and setting
  - Interventions
  - Outcome measures

Researchers need to….

- Search for existing current reviews
- Register their planned review online
- Publish protocol online
- Update record on Prospero website as the review progresses
- Avoids duplication of reviews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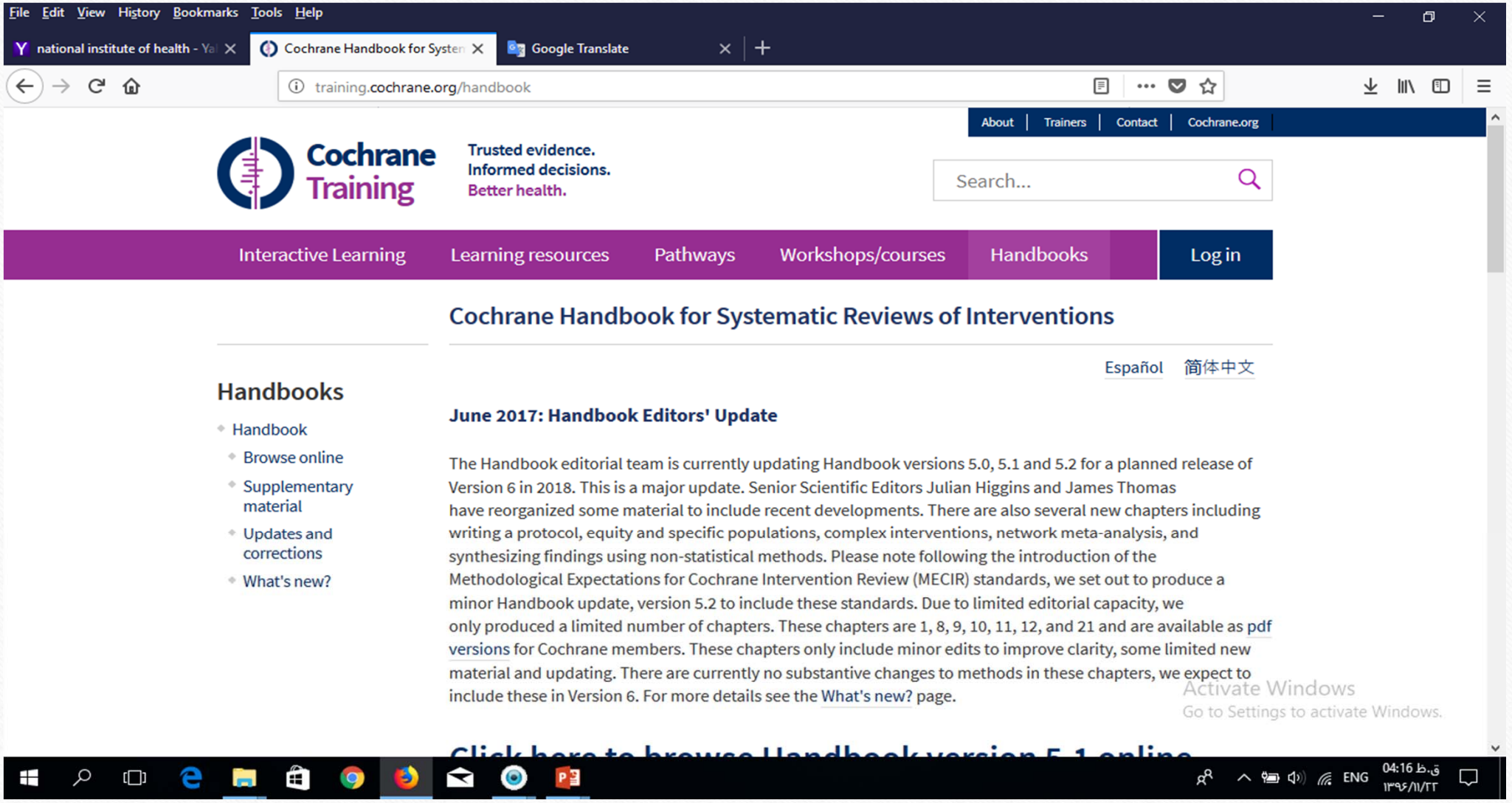
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What's new?
June 2017: Handbook Editors' Update
The Handbook editorial team is currently updating Handbook versions 5.0, 5.1 and 5.2 for a planned release of Version 6 in 2018. This is a major update. Senior Scientific Editors Julian Higgins and James Thomas have reorganized some material to include recent developments. There are also several new chapters including writing a protocol, equity and specific populations, complex interventions, network meta-analysis, and synthesizing findings using non-statistical methods. Please note following the introduction of the Methodological Expectations for Cochrane Intervention Review (MECIR) standards, we set out to produce a minor Handbook update, version 5.2 to include these standards. Due to limited editorial capacity, we only produced a limited number of chapters. These chapters are 1, 8, 9, 10, 11, 12, and 21 and are available as pdf versions for Cochrane members. These chapters only include minor edits to improve clarity, some limited new material and updating. There are currently no substantive changes to methods in these chapters, we expect to include these in Version 6. For more details see the What's new? page.
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- *www.york.ac.uk/inst/crd/pdf/**Systematic Reviews**.pdf*
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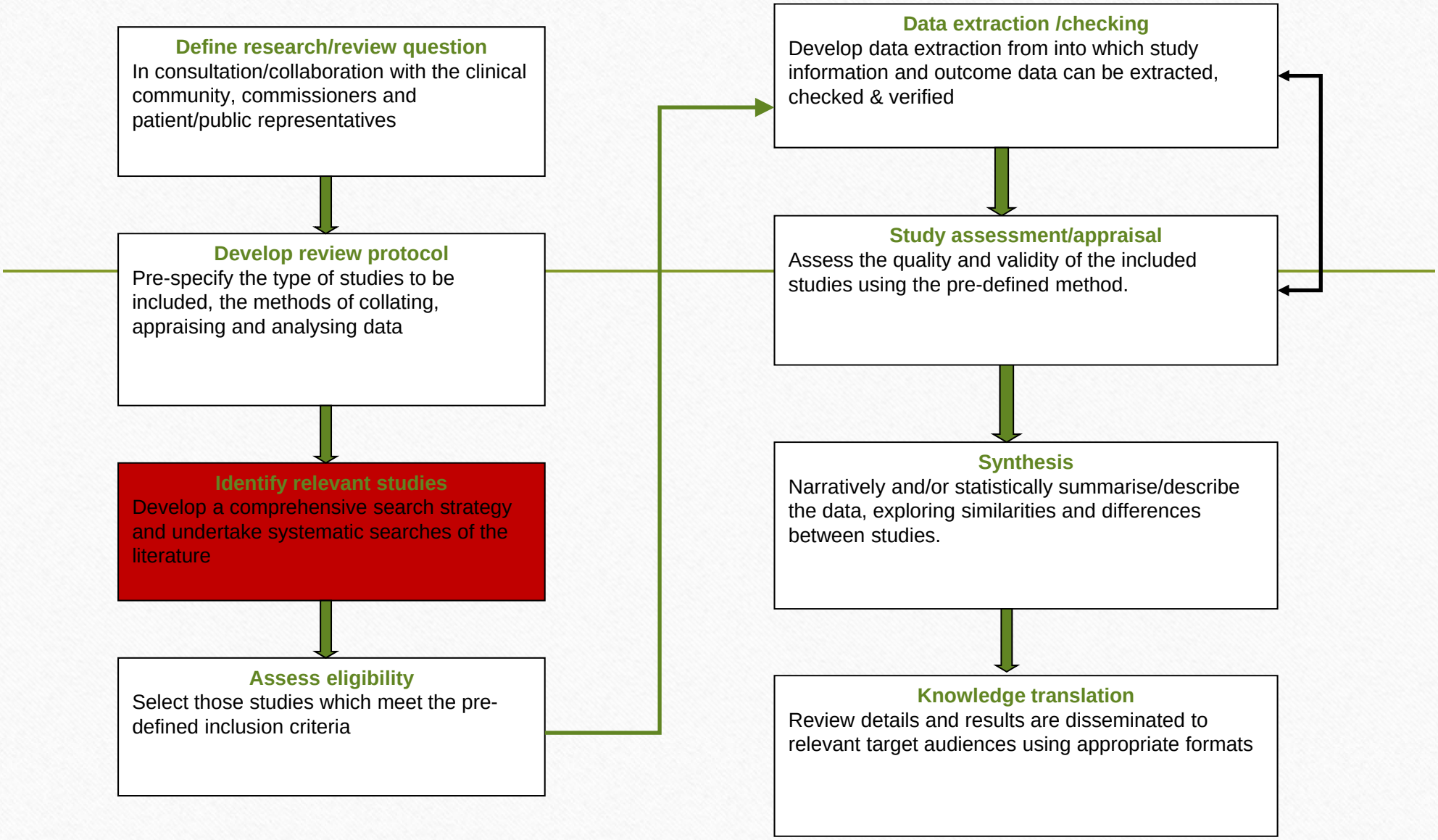
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Searching for Information

- ***MESH*** terms and key words/synonyms
  - *Medical Subject Heading*

  young; adoles*; teen*; child*.....

  *end of the 'stem' of the word it will automatically search for all the endings for that word stem

- Child* will also return children, childbearing, childbirth and so on…

Word variants

- ***AIDS***
  - acquired immunodeficiency syndrome
  - acquired immuno-deficiency syndrome
  - acquired immune deficiency syndrome
  - acquired immune-deficiency syndrome

- Synonyms e.g. Newborn: infant, toddler, baby, etc.
- Plurals e.g. child : children OR teenager : teenagers
- Spelling variants (UK vs US) e.g. randomise/randomize

Where to search?

- Electronic databases:

Pubmed

Embase

Cochrane

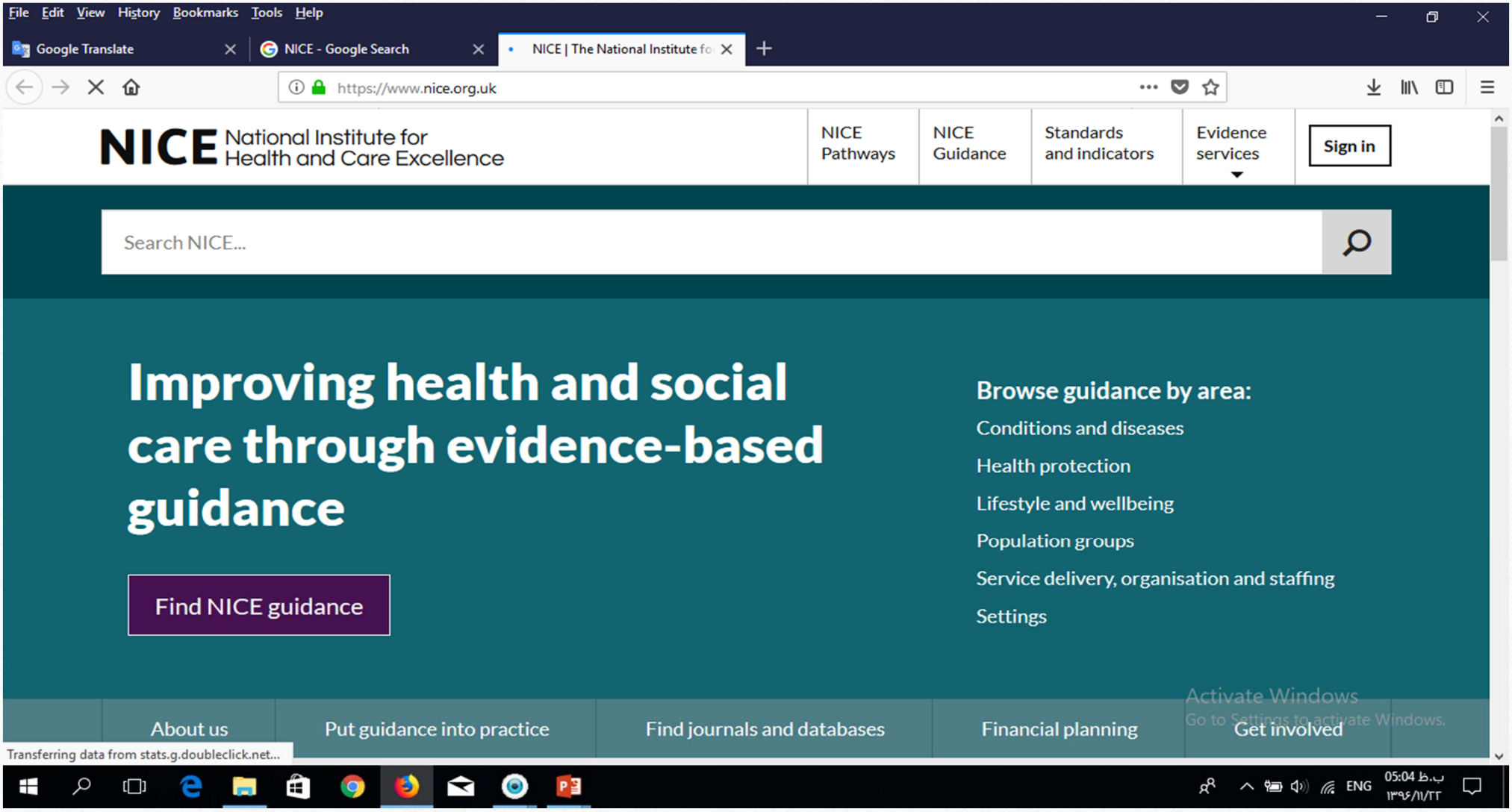
Scopus

Web of Science

etc.

- Grey literature, dissertations, theses, conference proceedings, national bodies (NICE, HTA), PROSPERO, clinical trial database (www.clincialtrails.gov/ AND IRCT.IR)

- Look at the databases own guidance for searching they vary!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NICE National Institute for Health and Care Excellence
NICE Pathways
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Improving health and social care through evidence-based guidance
Find NICE guidance
Browse guidance by area:
Conditions and diseases
Health protection
Lifestyle and wellbeing
Population groups
Service delivery, organisation and staffing
Settings
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Put guidance into practice
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Financial planning
Get involved
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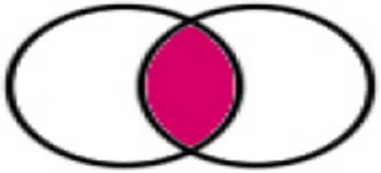
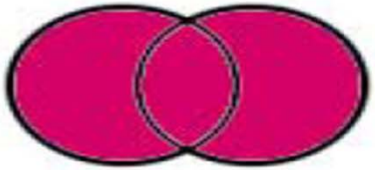
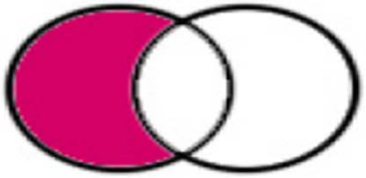
Boolean operators

Operator	Symbols	Example search	The search will find…	Venn diagrams – results are the shaded areas
AND	+	dogs AND cats	items containing both dogs and cats	
OR	/	dogs OR cats	items containing either dogs or cats or both	
NOT	-	dogs NOT cats	items containing dogs but not cats – *caution,* its easy to exclude relevant items	

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Clinical Nutrition xxx (2017) 1–10

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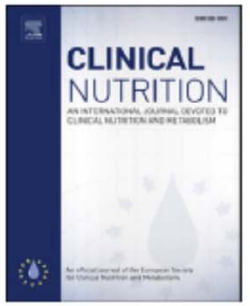

a-analyses

ect of *Chlorella* supplementation on cardiovascular risk factors: meta-analysis of randomized controlled trials

z A. Fallah [a], Elham Sarmast [a], Saied Habibian Dehkordi [b], Javad Engardeh [c], a Mahmoodnia [d], Arsalan Khaledifar [e], Tina Jafari [f, g, *]

- Five electronic databases (PubMed, ISI Web of Science, Google Scholar, Cochrane Central Register of Controlled Trials, and MagIran) were systematically searched to find relevant studies until ۱۵ January ۲۰۱۷.

- The following terms were used to search PubMed: (“Chlorella” OR “microalgae”) AND (“Intervention Studies” [MESH] OR “intervention” [tiab] OR “controlled trial” [tiab] OR “randomized” [tiab] OR “randomised” [tiab] OR “random” [tiab] OR “randomly” [tiab] OR “placebo” [tiab] OR “assignment” [tiab] OR “clinical trial” [All Fields] OR “trial” [All Fields]).

- The search terms for ISI Web of Science were: (“Chlorella” OR “microalgae”) AND (“Intervention Studies” OR “intervention” OR “controlled trial” OR “randomized” OR “randomised” OR “random” OR “randomly” OR “placebo” OR “assignment” OR “clinical trial” OR “trial”).
- The other databases were searched as follows: “Chlorella” AND (“clinical study” OR “clinical trial” OR “trial”).

Meta-analyses

Parenteral immunonutrition in patients with acute pancreatitis: A systematic review and meta-analysis

Mina Jafari [a,*], Awat Feizi [b,c], Gholamreza Askari [a], Aziz A. Fallah [d]

Department of Community Nutrition, School of Nutrition and Food Science, Isfahan University of Medical Sciences, Isfahan, Iran
Department of Epidemiology and Biostatistics, School of Public Health, Isfahan University of Medical Sciences, Isfahan, Iran
Integrative Functional Gastroenterology Research Center, Isfahan University of Medical Sciences, Isfahan 81745-319, Iran
Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord 34141, Iran

- The search strategy for PubMed was: (“acute pancreatitis”[tiab] OR “pancreatitis”[tiab] OR “acute necrotizing pancreatitis”[tiab]) AND (“nutritional support”[tiab] OR” dietary supplementation”[tiab] OR “parenteral nutrition”[tiab] OR “total parenteral nutrition”[tiab] OR “parenteal nutrition solutions”[tiab] OR “immunonutrition”[tiab]) AND (“Fatty Acids, Omega-٣”[Mesh] OR “Fish oil”[tiab] OR “glutamine”[tiab] OR “glutamine dipeptides”[tiab] OR “L-glutamine”[tiab] OR “glutamine supplementation”[tiab]).

- We decided to search other databases with the key words: “parenteral nutrition” AND “acute pancreatitis”.

- Three authors evaluated the total identified articles separately through study of the titles, abstracts, and if necessary, full texts.
- An additional search was done on the references of the probable related literature to avoid missing articles.
- The eligibility criteria for articles to be selected were parallel-group RCTs in which a parenteral immunonutrition solution was compared with standard form in patients with acute pancreatitis.

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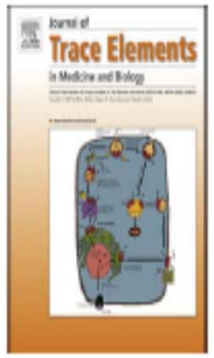
Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb



Nutrition

The association between mercury levels and autism spectrum disorders: A systematic review and meta-analysis

Tina Jafari[a,b,*], Noushin Rostampour[c], Aziz A. Fallah[d], Afshin Hesami[a]

[a] Clinical Biochemistry Research Center, Shahrekord University of Medical Sciences, Sharhekord, Iran
[b] Department of Biochemistry and Nutrition, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[c] Department of Internal Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran
[d] Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord 34141, Iran

- A systematic search was performed in several databases including PubMed, ISI Web of Science, Cochrane register of controlled trials, Google Scholar, Scopus, and MagIran until ۲۵ June ۲۰۱۷.

- The search strategy was as follow: PubMed was searched by keywords: “Mercury”[Mesh] OR “Mercury Compounds”[Mesh] OR “Mercury Isotopes”[Mesh]) AND (“Autism” OR “Autistic Disorder”[Mesh] OR “Autism Spectrum Disorder”[Mesh]);

- ISI Web of Science and Cochrane register of control trials were searched by keywords: “Mercury” OR “Mercury Compounds” OR “Mercury Isotopes”) AND (“Autism” OR “Autistic Disorder” OR “Autism Spectrum Disorder”;

- Scopus and Google Scholar was searched by keywords: “mercury” AND (“autism” OR “autistim spectrum disorder” OR “autistic disorder”).

- Magiran; was searched by keywords: Mercury AND (Autism OR “Autistic Disorder”).
- Search on the databases was separately performed by all of the authors.

Journal of Trace Elements in Medicine and Biology 29 (2015) 195–201

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Journal of Trace Elements in Medicine and Biology

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NUTRITION

The association between serum selenium and gestational diabetes mellitus: A systematic review and meta-analysis

Gholamreza Askari[a], Bijan Iraj[b], Amin Salehi-Abargouei[c,d], Aziz A. Fallah[e], Tina Jafari[a,*]

Food Security Research Center and Department of Community Nutrition, School of Nutrition and Food Sciences, Isfahan University of Medical Sciences, Isfahan, Iran
Isfahan Endocrine and Metabolism Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Department of Nutrition, Faculty of Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Nutrition and Food Security Research Center, Shahid Sadoughi University of Medical Sciences, Yazd, Iran
Department of Food Hygiene and Quality Control, Faculty of Veterinary Medicine, Shahrekord University, Shahrekord 34141, Iran

Designing a systematic review

- *Subject:*

  Vitamin D for lipid profile

Vitamin D ameliorates lipid profile in patients with dyslipidemia

Intervention *Population*

Comparison???? *Placepo or anti other*

- Is the subject valuable for conducting a SR?

….our knowledge and experience will answer

- Are there any SR or meta-analysis on this subject?

If yes, how old is it????

- Search vitamin D AND lipid profile in Pubmed…..

The result; ۶۵۵ article….

IS it OK?

Lets build KEYWORD

Dose “vitamin D” have MeSH term?

Lets see the Mesh for “vitamin d” in Pubmed….

Search details in PubMed

- "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND (("lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]) AND profile[All Fields])

Vitamin D

- *Our previous knowledge tells us that*
- ("Cholecalciferol"[Mesh] OR "Calcitriol"[Mesh] OR "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR “vitamin D۲”[tiab] OR “vitamin D۳”[tiab] OR “vitamin D-“)

Search result = ۷۶۷۰۸

Search details in PubMed

- "vitamin d"[MeSH Terms] OR "vitamin d"[All Fields] OR "ergocalciferols"[MeSH Terms] OR "ergocalciferols"[All Fields]) AND (("lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]) AND profile[All Fields])

- Dose “lipid” have MeSH term?

Lets see the PubMed…..

- ("Cholecalciferol"[Mesh] OR "Calcitriol"[Mesh] OR "Vitamin D"[Mesh] OR "Ergocalciferols"[Mesh] OR “vitamin D٢”[tiab] OR “vitamin D٣”[tiab] OR “vitamin D-“) AND (("lipids"[MeSH Terms] OR "lipids"[All Fields] OR "lipid"[All Fields]) AND profile[All Fields])

The result =٦٦١ studies

Some Example search strategies

- The effect of Whole grain on fasting blood glucose: a systematic review and meta-analysis

- **("Cereals"[Mesh] OR "wheat"[tiab] OR "cereal"[tiab] OR "brown rice"[tiab] OR "oat"[tiab] OR "whole grain"[tiab] OR "grain"[tiab] OR "bran"[tiab]) AND ("Intervention Studies"[MESH] OR "intervention"[tiab] OR "controlled trial"[tiab] OR "randomized"[tiab] OR "randomised"[tiab] OR "random"[tiab] OR "randomly"[tiab] OR "placebo"[tiab] OR "assignment"[tiab] OR "clinical trial"[All Fields] OR "trial"[All Fields])**

۱. Databases for publications

- Pubmed (Medline)
- ISI web of science
- Scopus
- EMBASE
- Google scholar

Local databases

- SID
- Iranmedex
- Magiran
- Local databases for other countries

- **Need to develop search strategy for each database**

۲. Unpublished literature

- Not all known published trials are identifiable in Medline (depending on topic)
- Only ۲۵% of all medical journals in Medline
- Non-English language articles are under-

represented in Medline (and developing countries)

- Publication bias – tendency for investigators to submit manuscripts and of editors to accept them, based on strength and direction of results (Olsen ۲۰۰۱)

٢. Unpublished literature

- Hand searching of key journals and conference proceedings
- Scanning bibliographies/reference lists of primary studies and reviews
- Contacting individuals/agencies/ academic institutions

Neglecting certain sources may result in reviews being biased

Librarians are your friends!

Selection of Studies

- Reference manager software package
  - Endnote – RevMan – ProCite – Mendeley

- Import results and screen
  - Assess titles/abstracts against your predetermined criteria
  - If in doubt include
  - Retrieve full text articles of initial selections

- Assess full text for inclusion
  - Requires judgement (>١ reviewer)
  - Check reviewer agreement (٣rd review to resolve)
  - Use a selection form to ensure consistency and record decisions

Data Extraction

- Be clear what information you want from the studies:
  - Study details
  - Data for your analysis

- Information will need to be collected relating to:
  - *Population*
  - *Interventions being compared*
  - *Outcomes evaluated*
  - *Methodology*

How much to extract??

- Level of judgement is required
  - *Sufficient to describe studies*
  - *Sufficient to allow you to undertake the planned analysis*
  - *Sufficient so you do not need to return to the full text papers*

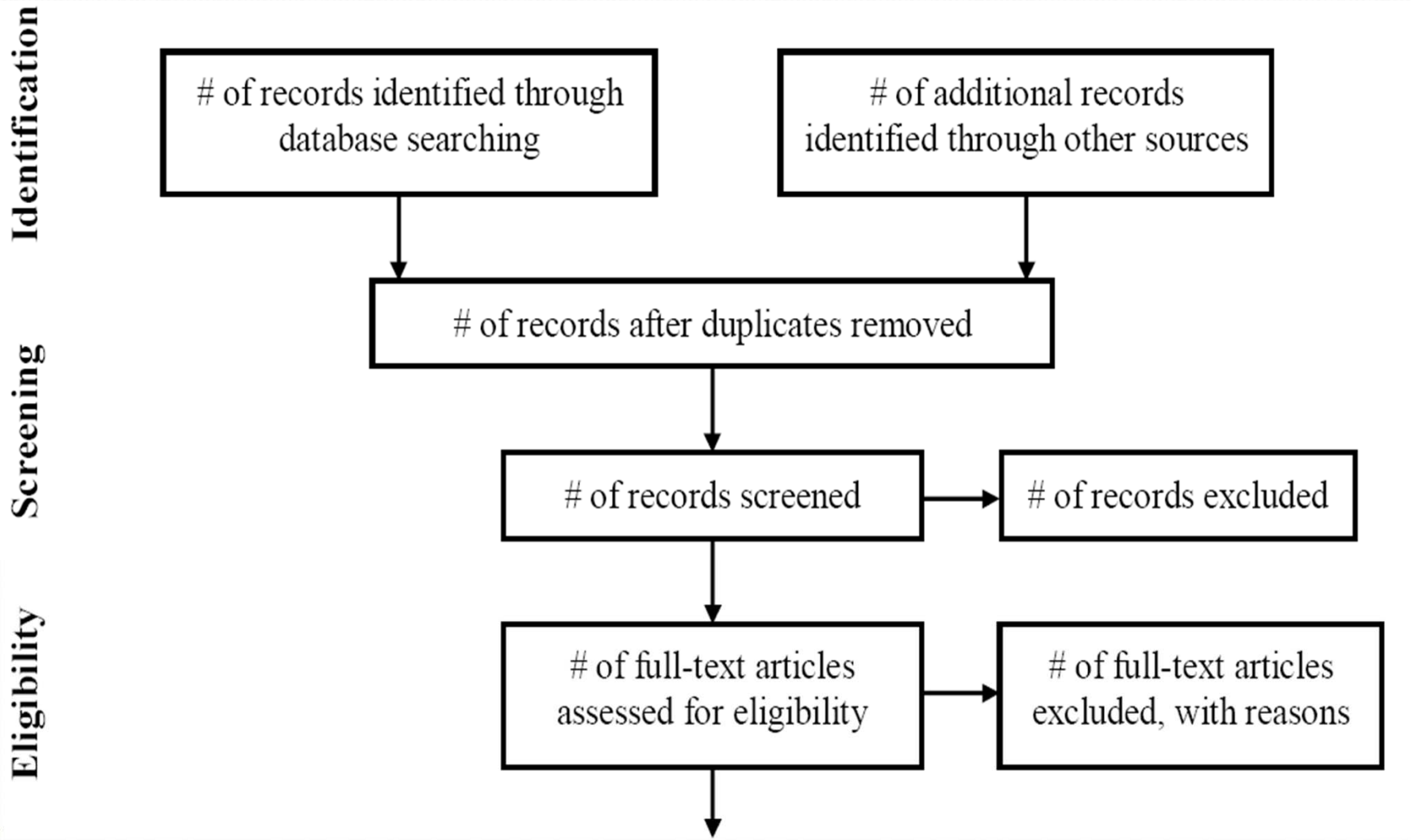
Data extraction software?

- There is a wide selection of software to choose from
- Selection depends on a number of factors
- Main considerations are probably
  - *What are you are familiar with?*
  - *What package best suits your data?*
  - *How many included studies do you have?*

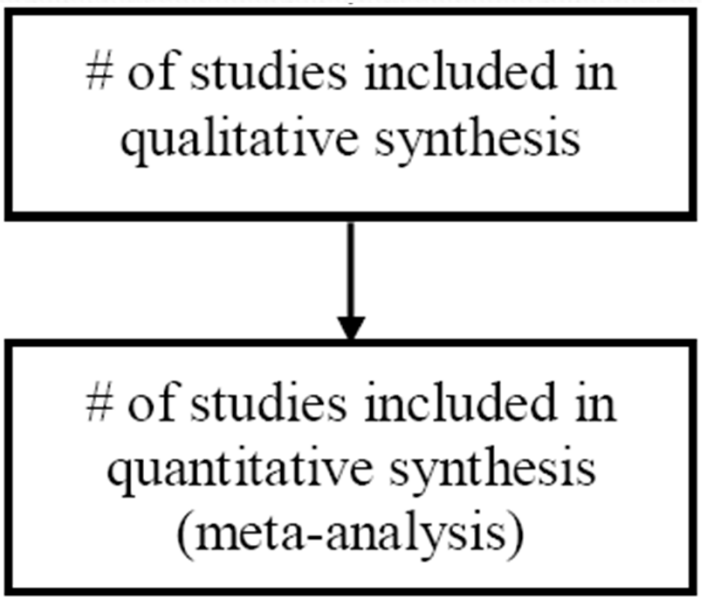
Which software?

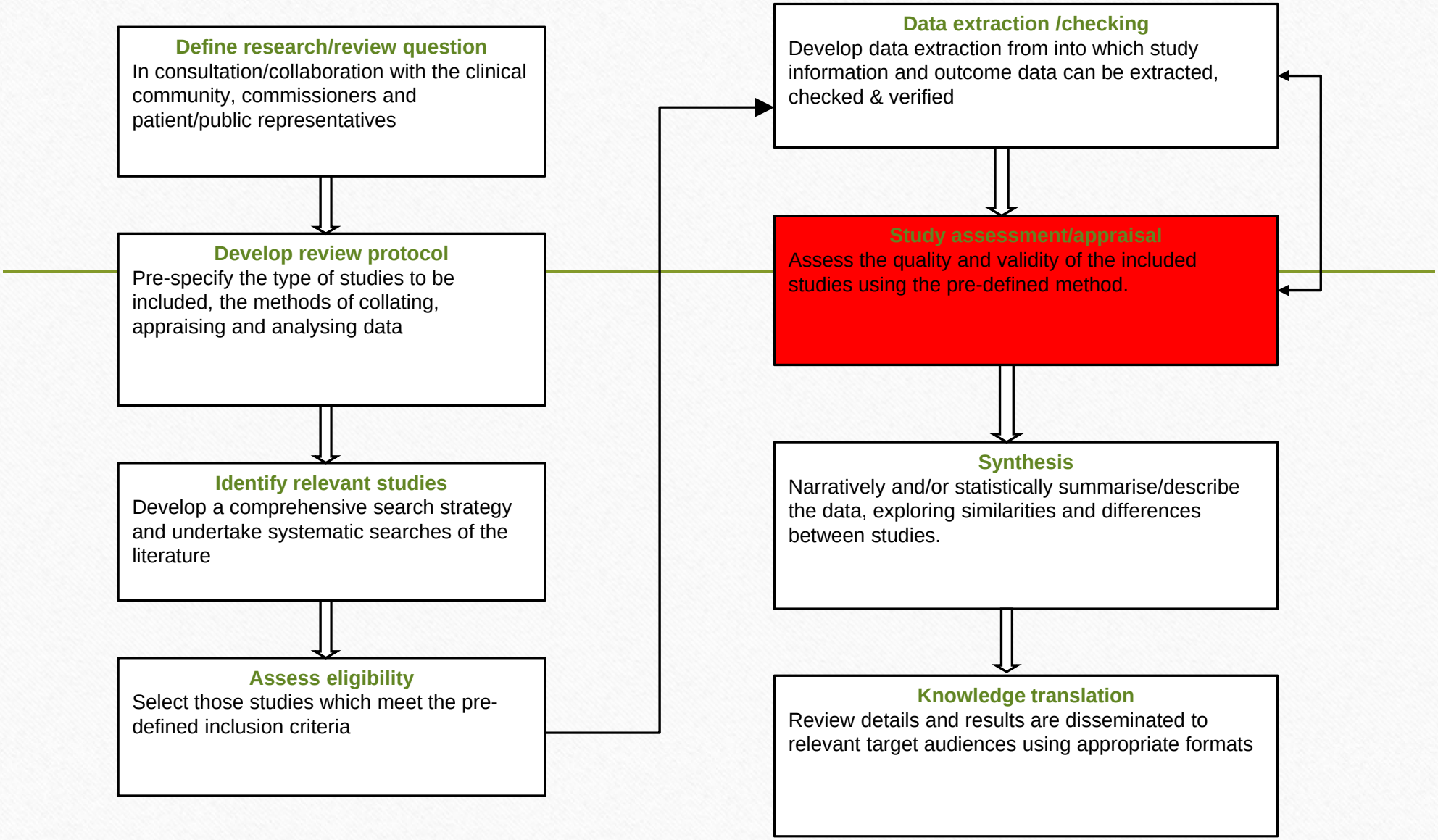
- *Word*
- *Excel*
- *Access*
- *SPSS*
- *EPPI reviewer*
- *COEVIDENCE*
- *REVMAN*
- *????*

PRISMA flow diagram



Included


# of studies included in qualitative synthesis
# of studies included in quantitative synthesis (meta-analysis)


Define research/review question
In consultation/collaboration with the clinical community, commissioners and patient/public representatives
Develop review protocol
Pre-specify the type of studies to be included, the methods of collating, appraising and analysing data
Identify relevant studies
Develop a comprehensive search strategy and undertake systematic searches of the literature
Assess eligibility
Select those studies which meet the pre-defined inclusion criteria
Data extraction /checking
Develop data extraction from into which study information and outcome data can be extracted, checked & verified
Study assessment/appraisal
Assess the quality and validity of the included studies using the pre-defined method.
Synthesis
Narratively and/or statistically summarise/describe the data, exploring similarities and differences between studies.
Knowledge translation
Review details and results are disseminated to relevant target audiences using appropriate formats

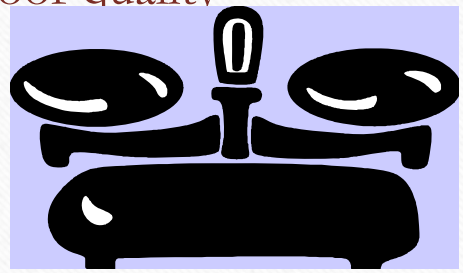
Principles of critical appraisal

Critical appraisal

The process of ***systematically*** *examining research evidence to assess its* ***validity, results*** *and* ***relevance*** *before using it to inform a decision.*

Weighting of studies

- Articles may be rejected in a systematic review due to their poor quality



- Alternatively, studies are assigned weights in relation to their assessed validity
  - Studies that are more valid will have more influence on the review's final results
  - Based on methodological quality, width of the confidence intervals, and external validity

Bias – quality assessment tool

١. Selection bias
٢. Allocation bias
٣. Confounding
٤. Blinding (detection bias)
٥. Data collection methods
٦. Withdrawals and drop-outs
٧. Statistical analysis
٨. Intervention integrity

Jadad score

- **Assessing the Quality of Reports of Randomized** Clinical **Trials: Is Blinding Necessary?**

Newcastle-Ottawa scale for non-RCTs

Table S1 Assessment of study quality with Newcastle-Ottawa scale

Study ID	Year	Selection				Comparability		Exposure			No. of star
		S1	S2	S3	S4	C1	C2	E1	E2	E3	
Chariyalertsak S	1994	★	★	★		★		★	★		6
Kim JS	1997		★	★		★	★	★	★		6
Kim JH	2009	★		★	★	★	★	★	★	★	8
Marx AH	2009		★	★	★	★			★		5
Kim JY	2010			★		★	★	★	★		5
Kim MA	2011	★	★			★			★	★	5
Geng YT	2011			★	★	★	★	★	★	★	7
Bozzetti C	2011	★	★	★	★	★			★		6
Zhang YL	2012		★			★		★	★	★	5
Tsapralis D	2012			★	★	★	★	★	★		6
Fassan M	2012	★	★	★		★	★	★	★		7
Asioli S	2012		★		★	★		★	★		5
Shinozaki E	2013		★			★		★	★		4
Pagni F	2013	★			★	★	★		★	★	6
Kochi M	2013	★	★	★	★	★		★	★		7
Fusco N	2013	★	★		★	★	★	★	★	★	8
Cho EY	2013	★	★	★	★	★		★	★		7
Geng Y	2014	★		★	★	★	★		★		6

Selection contains four criteria: S1, is the case definition adequate? S2, representativeness of the cases; S3, selection of controls; S4, definition of controls. Comparability means: C1, comparability of cases; C2, controls on the basis of the design or analysis. Exposure contains three criteria: E1, ascertainment of exposure; E2, same method of ascertainment for cases and controls; E3, non-response rate.

Interpretation of results

Structure of review articles

- Should conform to the anatomy of a typical scholarly article
  - i.e., Abstract, Introduction, Methods, Results, Discussion, and References
- Literature reviews are in reality a type of research
  - However, conclusions are derived from original sources of information

Structured Abstract

- ***Objective***
  - The author should clearly state the purpose of the article
- ***Background***
  - A description of what prompted the review
  - Presentation of a context for the review
- ***Methods***
  - A description of the methods used

Structured Abstract (cont.)

- Discussion
  - The implication and relevance of the information the review presents
- Conclusion
  - Summary of what the review contributes to the literature
  - What new conclusion can be drawn as a result of the synthesis of the literature

Introduction

- Presents the background and context of the problem that inspired review
- A description of the course of the disease, common outcomes and treatment options
- The importance and need for the review

Introduction (cont.)

- A focused and well-constructed question should be present
  - Provides direction for the review
  - Assists readers in determining if the review is applicable to their individual clinical circumstances
  - Should help establish the review's inclusion criteria

Methods

- Describes the search process and strategies involved, including:
  - Databases searched
  - Search terms
  - Search limits
    - e.g., publication years, languages, ages, etc.
- Should include enough detail to enable others to replicate the search

Methods should include

- The criteria that were used to include or exclude studies
  - For example, exclude surgery related studies or drug trials
- A description of how studies were appraised
  - Rating instruments are typically used
  - However, the reliability of these instruments varies considerably
  - Design
  - Randomization
  - ……for example type of **calorie restriction**!!!!
- Information about
  - How the relevance of primary studies was ascertained

Results

- The outcome of the search process is presented
- Including information on
  - The number of articles retrieved
  - How many articles were excluded from the review and which of the inclusion criteria they failed to meet
    - Look for evidence of selective referencing

Results (cont.)

- **The characteristics of the included studies may be described and contrasted in this section**
- Often presented in **tables**
- **Important points about selected studies must be addressed.**

Discussion

- The findings of all of the articles in the review are synthesized to generate a conclusion
  - *There may or may not be a separate Conclusions section*
- Information about the etiology, pathophysiology, diagnosis, treatment, and prognosis of the condition at issue is often provided
- Comparison of our results with other published reviews

Discussion (cont.)

- Presents a new perspective on the topic that is usually more reliable than any of the individual articles in the review

- **Caution –** authors have the leeway to defend articles that support their viewpoint and challenge those that do not
  - Systematic methods control for much of this subjectivity, but it is still possible in the best types of reviews

Discussion (cont.)

- **Appraisal of current review**
  - **Limitations**
  - **Strengths**

Discussion (cont.)

- The conclusion should be in agreement with the evidence presented in the review
- Authors should emphasize what new information can be gained
- The conclusion should not merely repeat what was previously written

References

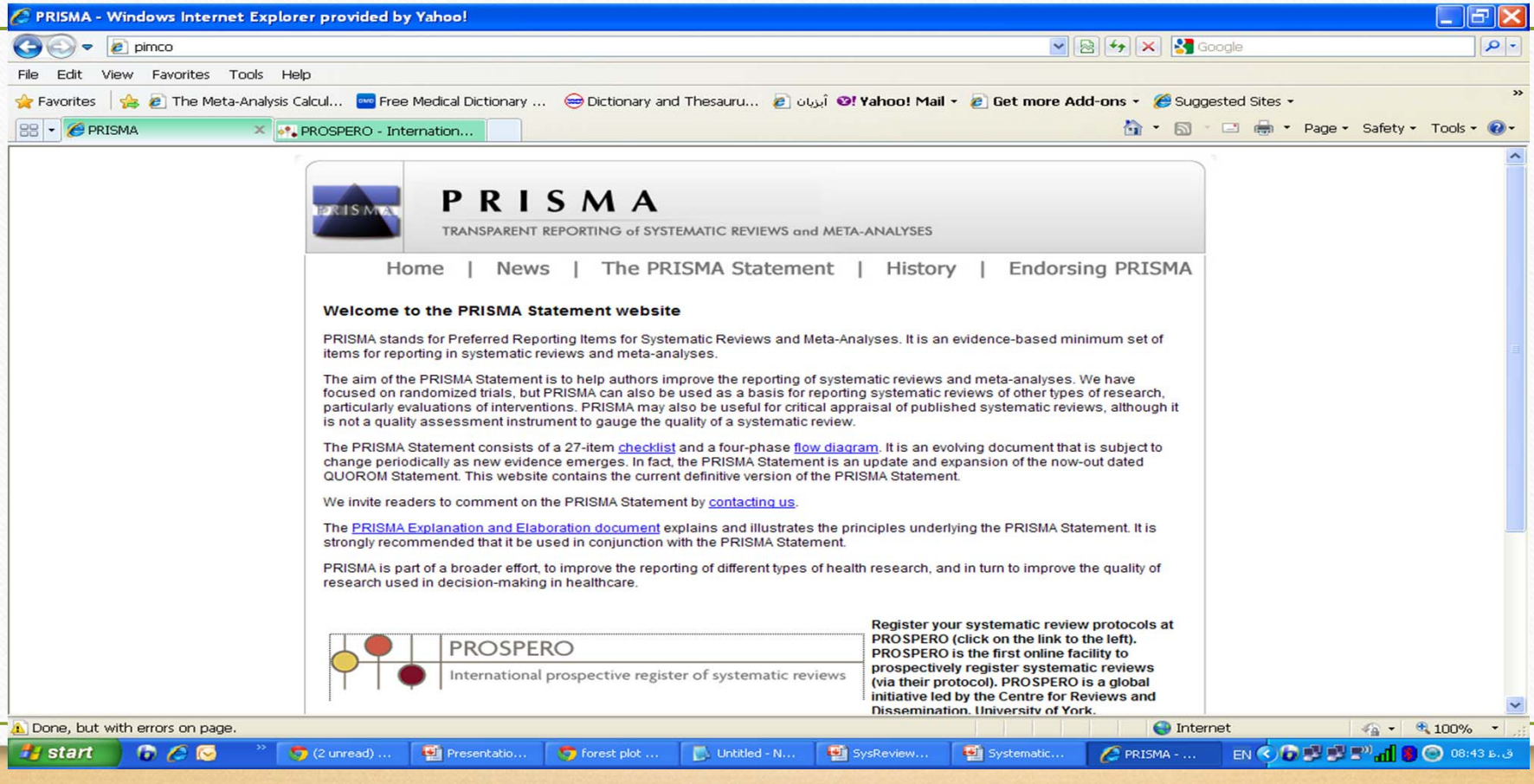
- Should be comprehensive and cite all articles included in the review

- Derived almost entirely from peer-reviewed journals
  - But may include conference proceedings, textbooks, and government documents

  - Unpublished works too; but keep in mind, they have not been peer-reviewed

PRISMA statement

http://www.prisma-statement.org/



Checklist of items to include when reporting a systematic review or meta-analysis

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).

METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.

RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome-level assessment (see Item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group and (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., health care providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

What is the "GRADE" system?

- Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system

Thank you