ANALYSIS | Diet research built on a 'house of cards'?

Nutrition studies depend on people telling the truth. But they don't.

By Kelly Crowe, CBC News Posted: Feb 24, 2015 1:07 PM ET | Last Updated: Feb 24, 2015 1:25 PM ET

Because humans are very bad at admitting or remembering what they ate, the self-reported methods in medical studies have shown evidence of bias that can lead to paradoxical nutritional findings. (Benjie Sanders/Arizona Daily Star/Associated Press)

Epi in the News: LINK

What is the primary source of bias outlined in this clip?

A. Random Error
B. Selection Bias
C. Measurement Bias
D. Confounding

What was suggested in this clip to potentially reduce this measurement error?

A. Strengthen external validity
B. Address issues of confounding
C. Incorporate the use of biomarkers
D. Keep using the dietary questionnaires

This clip indicates that nutritional studies based on self-reported dietary surveys are:

A. Lacking internal validity
B. Lacking external validity
C. Negatively influencing health policy
D. All of the above

Abstract ▾ Send to: ▾

Int J Obes (Lond). 2014 Nov 13. doi: 10.1038/ijo.2014.199. [Epub ahead of print]

Energy balance measurement: when something is not better than nothing.

Dhurandhar NV[1], Schoeller D[2], Brown AW[3], Heymsfield SB[4], Thomas D[5], Sørensen TI[6], Speakman JR[7], Jeansonne M[8], Allison DB[8]; the Energy Balance Measurement Working Group.

⊕ Author information

Abstract

Energy intake (EI) and physical activity energy expenditure (PAEE) are key modifiable determinants of energy balance, traditionally assessed by self-report despite its repeated demonstration of considerable inaccuracies. We argue here that it is time to move from the common view that self-reports of EI and PAEE are imperfect, but nevertheless deserving of use, to a view commensurate with the evidence that self-reports of EI and PAEE are so poor that they are wholly unacceptable for scientific research on EI and PAEE. While new strategies for objectively determining energy balance are in their infancy, it is unacceptable to use decidedly inaccurate instruments, which may misguide health-care policies, future research and clinical judgment. The scientific and medical communities should discontinue reliance on self-reported EI and PAEE. Researchers and sponsors should develop objective measures of energy balance.International Journal of Obesity advance online publication, 23 December 2014; doi:10.1038/ijo.2014.199.

Full Text Unavailable at this time – abstract online

METABOLOMICS IN THE IDENTIFICATION OF BIOMARKERS OF DIETARY INTAKE

Aoife O'Gorman [a,b], Helena Gibbons [a,b], Lorraine Brennan [a,b,*]

Abstract: Traditional methods for assessing dietary exposure can be unreliable, with under reporting one of the main problems. In an attempt to overcome such problems there is increasing interest in identifying biomarkers of dietary intake to provide a more accurate measurement. Metabolomics is an analytical technique that aims to identify and quantify small metabolites. Recently, there has been an increased interest in the application of metabolomics coupled with statistical analysis for the identification of dietary biomarkers, with a number of putative biomarkers identified. This minireview focuses on metabolomics based approaches and highlights some of the key successes.

MINI REVIEW ARTICLE

Introduction

In today's modern world nutrition research is focused on improving population and individual health through diet [1]. Nutrition and health related research are beginning to understand that in addition to their essential functions, nutrients and non-nutrient components of foods interact with numerous metabolic pathways and influence health reducing or increasing the risk of disease. Diet is considered one of the major factors contributing to the rapid increase in the incidence of metabolic disorders such as obesity, diabetes and cardiovascular disease [2].

Reliable dietary assessment methods are vital when attempting to understand the links between diet and chronic disease profiles. Conventional tools for collecting quantitative information on dietary exposure such as food diaries, 24-h recalls and food frequency questionnaires (FFQ) can be unreliable for characterising and quantifying eating behaviour and are all subject to possible reporting and other biases [3,4]. In addition, these methods are unreliable for certain groups such as the obese or elderly people, whose self-reported energy intakes tend to be underestimated, as assessed by energy expenditure measurements using the doubly labelled water method [5,6]. A full critical review of limitations associated with the current techniques is beyond the scope of the present review and the reader is referred to the following papers [3,4,7-9].

In an attempt to overcome the problems with measuring dietary exposure with self-reported methods, nutritional epidemiologists started examining biomarkers as measures of dietary intake and nutrient status [10,11]. The use of dietary biomarkers provides a more objective and accurate measure of intake in comparison to traditional questionnaires as they take into account the nutrient bioavailability and metabolism [12,13]. One of the main applications of these dietary biomarkers is to use them as reference measurements to assess the validity of dietary assessment measures [11,14,15]. So far ideal biomarkers exist for salt and protein intake (sodium/nitrogen measure in a 24 h urine sample) and energy expenditure (double labelled water technique) [11]. Other biomarkers exist that do not provide information on the exact dietary intake but which are highly correlated with intake for example the measurement of serum cartenoids and vitamin C as biomarkers of fruit and vegetable intake [16].

The development of robust food biomarkers will help in better classifying a person's dietary intake and in turn will improve the assessment of the relationship between diet and chronic disease [17]. In recent years there has been an increased interest in applying metabolomics for the discovery of biomarkers of dietary intake. This review will focus on metabolomics and its use in assessing dietary biomarkers.

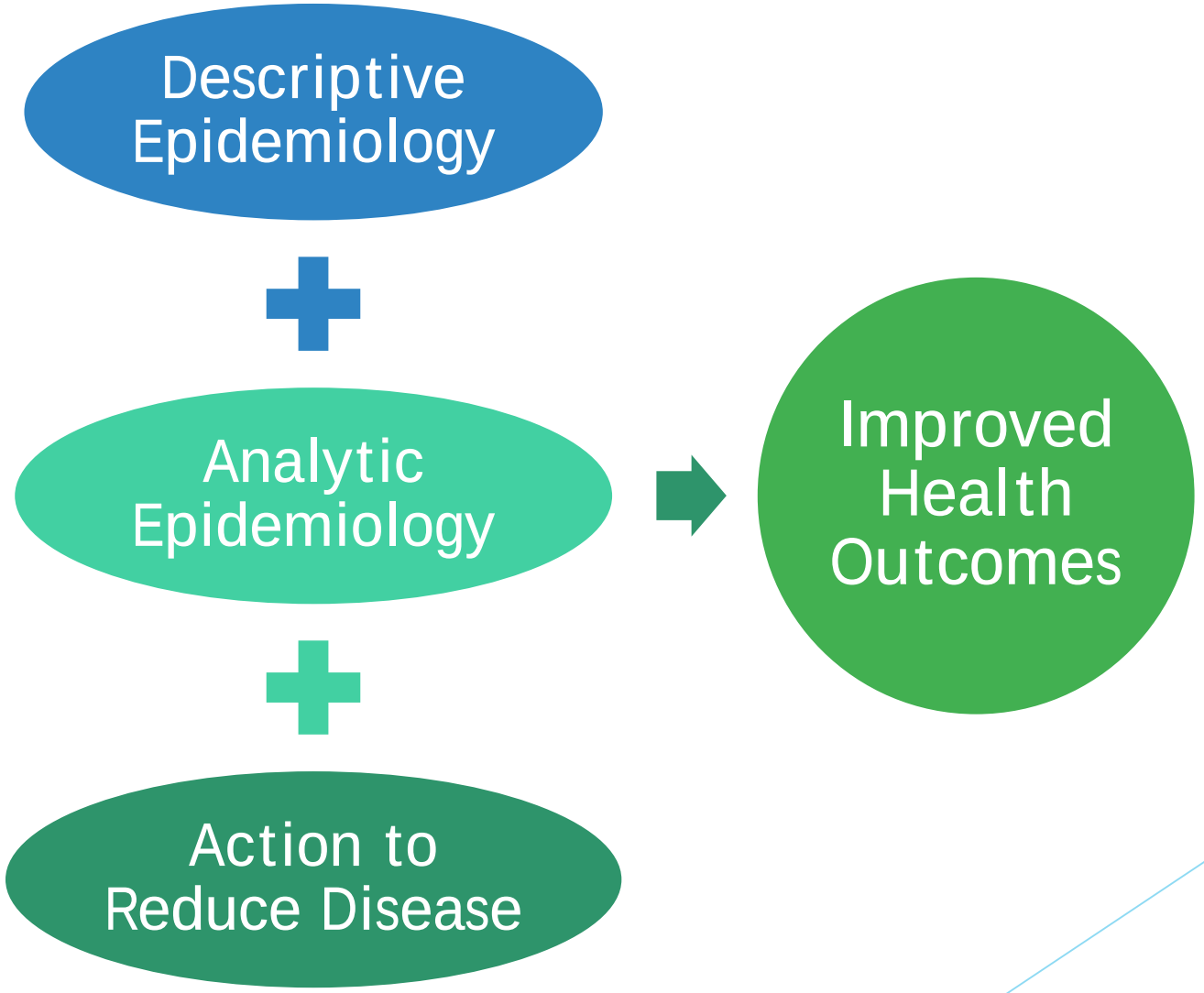
Metabolomic Technologies

Metabolomics refers to comprehensive and non-selective analytical chemistry approaches aiming to provide a global description of all metabolites present in a biofluid at a given time [18-21]. The two main approaches employed in metabolomics are nuclear magnetic resonance (NMR) spectroscopy and mass spectroscopy (MS). These techniques both have their advantages and disadvantages and at present there is no single analytical technique capable of measuring and identifying all metabolites in a single sample simultaneously and therefore comprehensive metabolomic data needs to be assessed by bringing together data from different platforms [22].

For instance, NMR spectroscopy uses an untargeted approach

LINK to article

Cycle in Epidemiologic Work – Outcomes depend on good work at all other levels

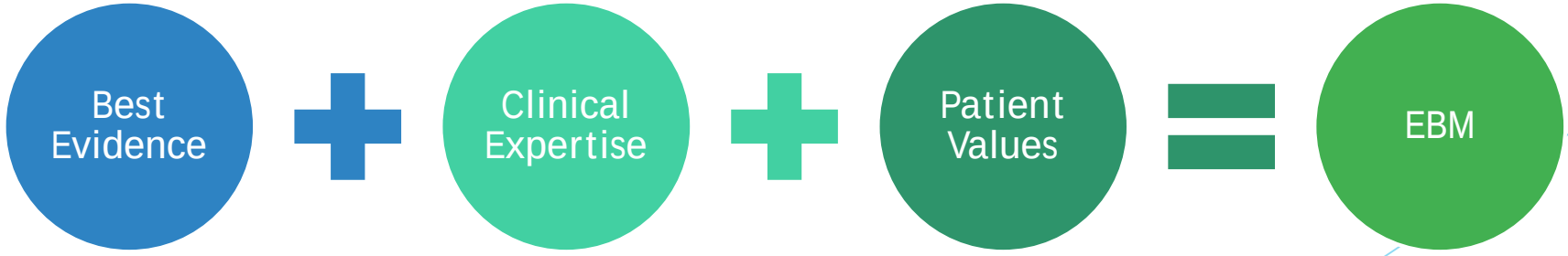


Evidence Based Medicine (EBM)

- The integration of best research evidence with clinical expertise and patient values for health care decision making

- EBM advocates that health professionals search primary research literature to find answers to their questions about clinical intervention and treatment

- Systematic Reviews help, by summarizing the results from a number of studies on the same topic



Class 13:

Systematic Reviews

HLSC 2003

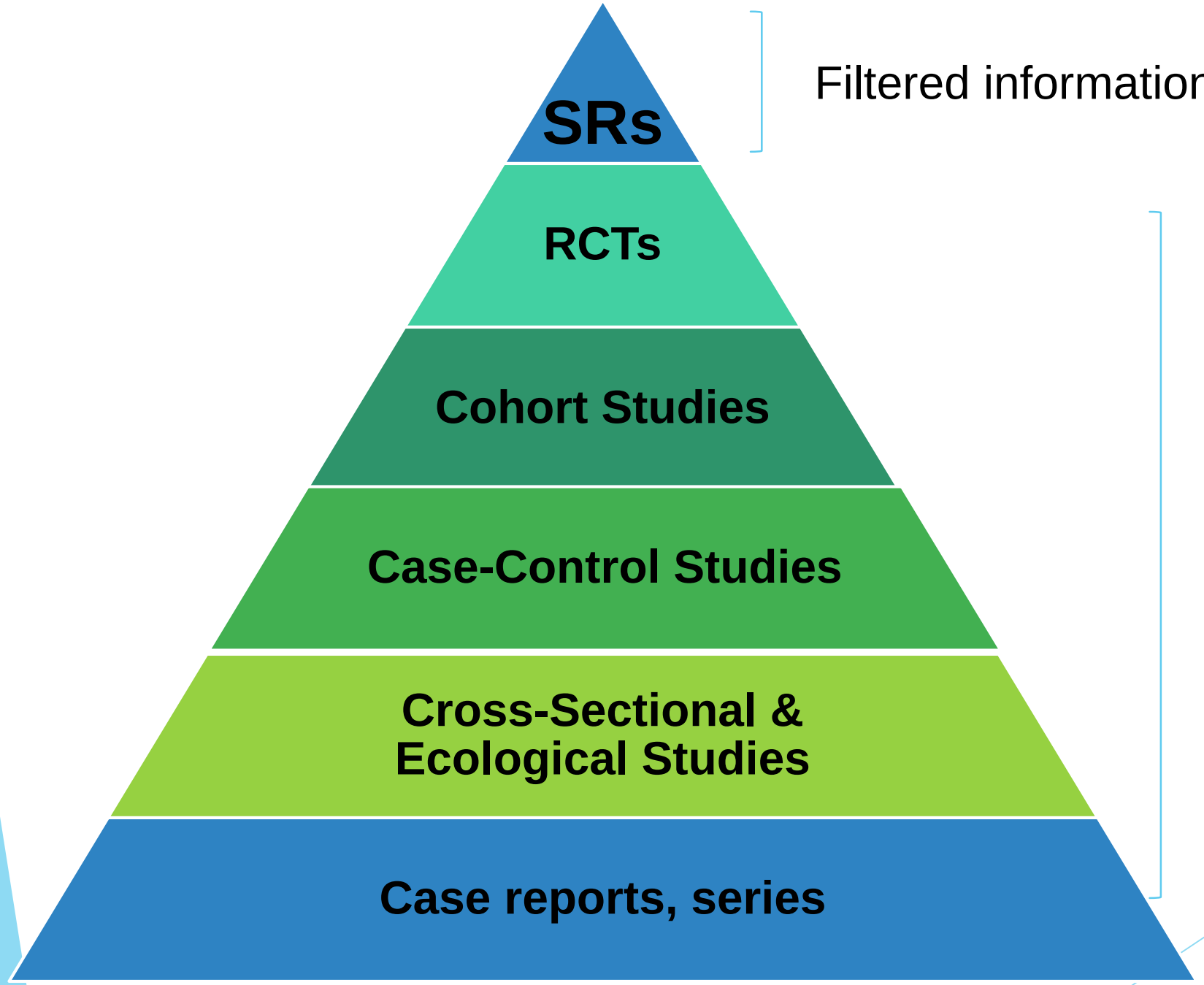
Faculty of Health Sciences

University of Lethbridge

Walker

Learning Objectives:

1. What is the structure and the stages of a SR?
2. What is a **meta-analysis** & a **pooled analysis**?
3. How do you **interpret SR results** using forest plots?
4. What is **publication bias** & why is it a concern in SRs?
5. What is **evidence-based medicine** & what are its challenges?


SRs
RCTs
Cohort Studies
Case-Control Studies
Cross-Sectional &
Ecological Studies
Case reports, series
Filtered information
Unfiltered

What is a Systematic Review (SR)?

- A comprehensive and unbiased review process which collates criteria-selected primary research on a particular research question. Throughout the review process, systematic reviews identify, select, synthesize, and appraise all high quality research evidence relevant to the question and draw conclusion to inform evidence based decisions.

-Cochrane Handbook of Systematic Reviews, 2011

Systematic Review vs. Narrative Review

The Challenge of EBM

Is it realistic to expect all medical practices to be based on SRs of RCTs?

Are SRs based on observational data acceptable in some cases?

- Link

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, professor and Jill P Pell, consultant

Additional article information

Abstract

Objectives To determine whether parachutes are effective in preventing major trauma related to gravitational challenge.

Conclusions As with many interventions intended to prevent ill health, the effectiveness of parachutes has not been subjected to rigorous evaluation by using randomised controlled trials. Advocates of evidence based medicine have criticised the adoption of interventions evaluated by using only observational data. We think that everyone might benefit if the most radical protagonists of evidence based medicine organised and participated in a double blind, randomised, placebo controlled, crossover trial of the parachute.

Systematic Reviews Can:

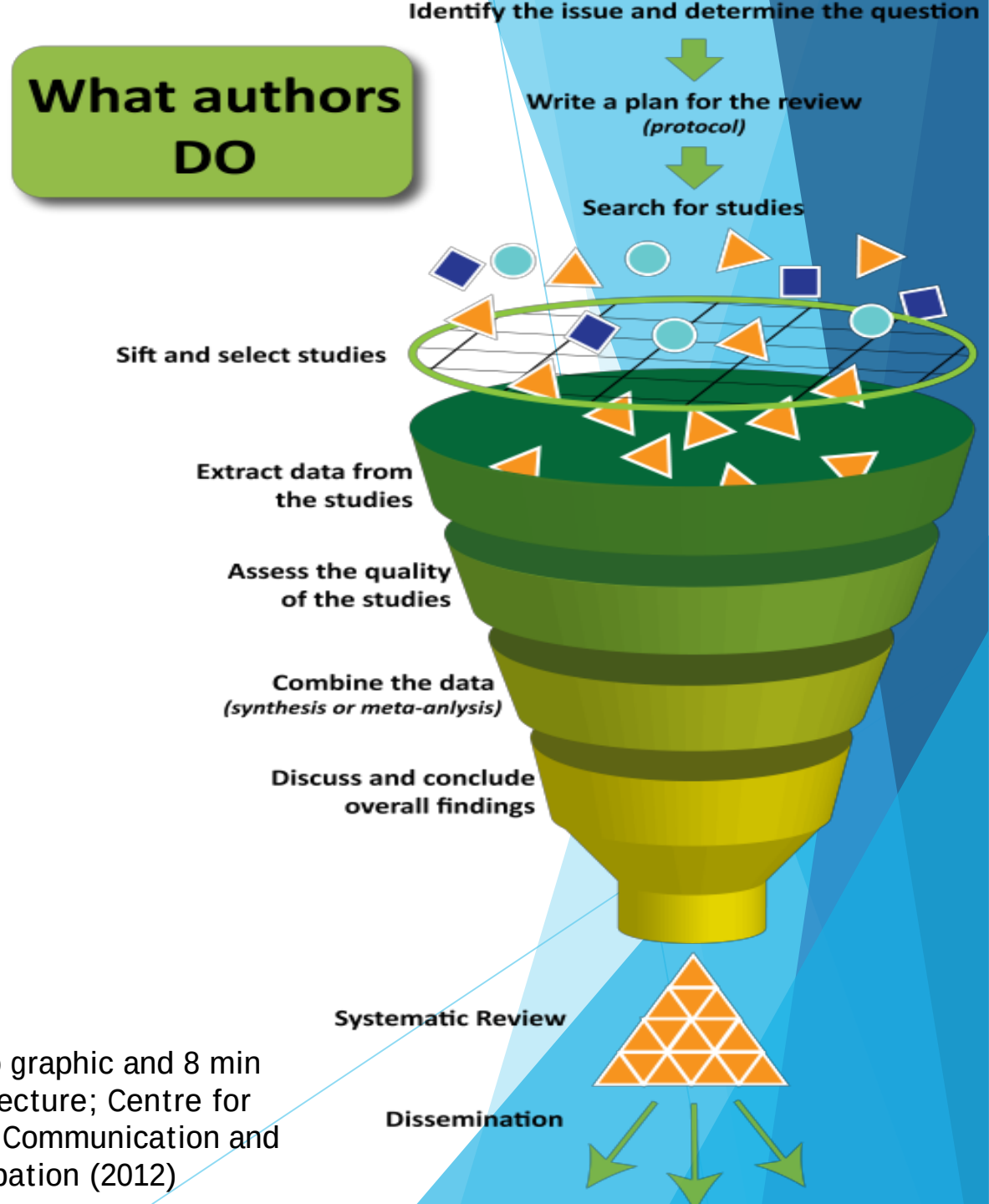
- End confusion
- Highlight where there is not enough evidence
- Yield new insights by combining findings from different studies
- Show that enough evidence has been produced
- Reduce the influence of flaws or errors in single studies

Structure of a SR:

- **Introduction** – What is the study objective? (question to be answered)
- **Methods** – How studies were searched, identified, selected, appraised, and the data extracted (clarification of the "systematic approach")
- **Results** – Patterns and differences in research highlighted in relation to research question.
- **Discussion** – Results are interpreted, threats to validity considered, comparison with other SRs, conclusions drawn, recommendations for practice or future research

Stages of SRs:

1. Formulate the research question
2. Define inclusion and exclusion criteria
3. Develop a search strategy
4. Select studies
5. Extract data
6. Assess study quality
7. Analyze and interpret results
8. Disseminate findings



LINK to graphic and 8 min audio lecture; Centre for Health Communication and Participation (2012)

1. Formulate the Review Question:

- Clearly define what question the review is trying to answer

"Do speed cameras reduce incidence of speeding, road traffic crashes, injury and death?" Link to Summary

"…outcomes across all studies show that speed cameras are a worthwhile intervention for reducing the number of road traffic injuries and deaths…mosre studies needed"

2. Define clear inclusion and exclusion criteria

- This criteria is determined a priori (prior to starting the review) and is often published before the review even takes place

- *Consider size of studies, types of studies, population age range, published or unpublished studies, language, type of intervention, outcomes, etc.*

Vaccines for preventing influenza in healthy adults...

LINK to full study
LINK to summary

Inclusion Criteria:

- RCT or quasi-RCT, observational studies
- Comparative non-randomized studies
- Healthy individuals aged 16-65
- Live, attenuated, or killed vaccines administered by any route
- Clinical outcomes
- Harms
- Secondary outcomes

3. Develop a Search Strategy and Select Studies for further review:

- Develop a list of key search terms
- Electronic biomedical data bases (MEDLINE, EMBASE, CINHAL) often used – choose databased depending on the research question
- May involve checking article reference lists, hand searching key journals, posting requests on listservs, *personal communication with experts in the field, conference abstracts…this will reduce PUBLICATION BIAS
- Select studies based on the title and abstract (based on criteria set forth in beginning)

Publication Bias

- A bias that occurs because **positive results**, that support a researchers hypothesis, are more likely to be published, are published earlier, and are published in more prestigious journals.
  - An important consideration that can **exaggerate the true magnitude of the effect** documented in an SR.
  - More **widespread** than the publication of deliberately falsified data (such as the Wakefield MMR study)
  - **Funnel Plots** can help to assess potential publication bias

Example:

- A study of **74 antidepressant studies** registered with the FDA found **97% of positive studies** were published.

- Only 39% of neutral/negative studies were published.
  - Of these, 8 in 10 were published in a way that conveyed the positive results while deemphasizing the negative findings.

- When only published literature was examined, the positive effects of antidepressant use were **exaggerated by 32%** compared to a more complete analysis of all RCTs (published & not published)

Turner EH. *NEJM* 2008;358:252-60.

Taking action on potential publication bias!

http://www.bmj.com/tamiflu

http://www.tamiflu.com/

OCT 31 2012

BMJ pushes Roche for raw data on Tamiflu trials

Posted by Gary Schwitzer in Drug industry, Journal practices

NO COMMENTS

BMJ journal editor Fiona Godlee this week published an open letter to Roche, makers of the flu drug Tamiflu. Background provided by BMJ: *Roche promised in 2009 to release full reports from clinical trials of oseltamivir in response to an investigation by the BMJ and the Cochrane Collaboration. In this open letter to John Bell, regius professor of medicine at Oxford University and a Roche board member, the BMJ's editor in chief further urges the company to disclose the full data.*

Excerpts of the letter (copy of letter pasted below):

Dear John

I am writing to you in your capacity as a member of the board of Roche. As you may be aware, the *BMJ* has been working with the Cochrane Collaboration in its efforts to get Roche to release the raw data on the effects of oseltamivir (Tamiflu) so that Cochrane can properly fulfil the UK government's commission for a systematic review of neuraminidase inhibitors based on clinical study reports.

...

The Cochrane reviewers now know that there are at least 123 trials of oseltamivir and that most (60%) of the patient data from Roche's phase III completed treatment trials remain unpublished. We have concerns on a number of fronts: the likely overstating of effectiveness and the apparent under-reporting of potentially serious adverse effects. Meanwhile, oseltamivir has just been added to the World Health Organization's List of Essential Medicines, alongside aspirin and β blockers.

On behalf of the Cochrane collaborators and public health decision makers around the world, I ask Roche to honour its publicly stated promise to make available the full clinical study reports. In order for the Cochrane collaborators to properly analyse these data they will need individual patient data in electronic format.

Oseltamivir has been a great commercial success for Roche. Billions of pounds of public money have been spent on it, and yet the evidence on its effectiveness and safety remains hidden from appropriate and necessary independent scrutiny. I am appealing to you, as an internationally respected scientist and clinician and a leader of clinical research in the United Kingdom, to bring your influence to bear on your colleagues on Roche's board. As company directors, responsibility for Roche's behaviour rests with

BMJ

BMJ 2012;345:e7304 doi: 10.1136/bmj.e7304 (Published 29 October 2012)

EDITORIALS

Clinical trial data for all drugs in current use

Must be made available for independent scrutiny

Fiona Godlee *editor in chief*

BMJ, London WC1H 9JR, UK

full article

The drug industry does many good things. It produces medicines that can improve health and save lives. It creates jobs and stimulates economic growth. Sadly it does bad things too. Persistently and systematically over decades it has withheld and misreported data from clinical trials.[1] As a result, a whole range of widely used drugs across all fields of medicine have been represented as safer and more effective than they are, endangering people's lives and wasting public money. Such wilful distortion is scientific misconduct.[2] It is not something we can forgive because of the good things drug companies do. As Ben Goldacre says in the introduction to his new book *Bad Pharma*, "Drug companies around the world have produced some of the most amazing innovations of the past fifty years, saving lives on an epic scale. But that does not allow them to hide data, mislead doctors, and harm patients."[3]

the exceptional tenacity of individual researchers and investigative journalists (Roche's oseltamivir)[8] to try to piece together the evidence on individual drugs?

Goldacre's book makes it clear that the reasons are complex and there are no simple solutions. But there is no doubt that medical journals could do more. Rather than no longer publishing industry funded trials, as some have suggested, they could leverage their power and publish only where there is a commitment to make the relevant anonymised patient level data available on reasonable request. The International Committee of Medical Journal Editors has so far declined to take such a step. The *BMJ* will require this commitment for all clinical trials of drugs and devices—whether industry funded or not—from January 2013.

The battle against publication bias...

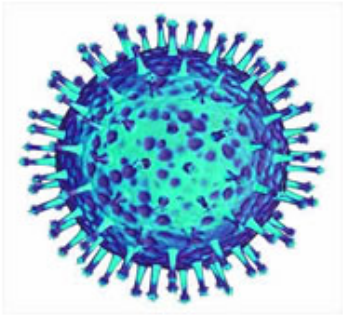
They're coming for you Tamiflu!

Timeline

Link to article

Tamiflu campaign

The *BMJ's* **open data campaign** aims to achieve appropriate and necessary independent scrutiny of data from clinical trials. Working with others, we seek to highlight the problems caused by lack of access to data, and we welcome any suggestions on how to take things further.



The Tamiflu story

Our first open data campaign initiative relates to a public promise Roche made in 2009 to release full clinical trial reports in response to an investigation by the *BMJ* and Cochrane collaborators Peter Doshi and Tom Jefferson. [1][2][3][4]

The bottom line:

- WHO recommends Tamiflu, but has not vetted the Tamiflu data.
- EMA approved Tamiflu, but did not review the full Tamiflu dataset.
- CDC and ECDC encourage the use and stockpiling of Tamiflu, but did not vet the Tamiflu data.
- The majority of Roche's Phase III treatment trials remain unpublished over a decade after completion.
- In Dec 2009, Roche publicly promised independent scientists access to "full study reports" for selected Tamiflu trials, but to date the company has not made even one full report available.

Releasing the trial reports would allow independent academics to answer questions about this globally stockpiled drug. To date, the full data set has not been provided.

This page links to others listing open correspondence with Roche, and the various bodies around the world which licence or recommend drugs. This open correspondence of letters offers readers the chance to witness attempts to compel greater accountability and responsibility in public health decision making and policy. The *BMJ* plans to launch other campaigns linked to its investigations in the future. Find out more about the background to Tamiflu and open data by reading this feature and accompanying editorial.

BMJ

BMJ 2014;348:g2545 doi: 10.1136/bmj.g2545 (Published 9 April 2014)

RESEARCH

Oseltamivir for influenza in adults and children: systematic review of clinical study reports and summary of regulatory comments

Tom Jefferson *reviewer*[1], Mark Jones *senior research fellow (biostatistics)*[2], Peter Doshi *assistant professor*[3], Elizabeth A Spencer *nutritional epidemiologist*[4], Igho Onakpoya *research fellow in evidence-based practice and pharmacovigilance*[4], Carl J Heneghan *professor*[4]

[1]Cochrane Acute Respiratory Infections Group, Via Puglie 23, 00187 Rome, Italy; [2]School of Population Health, University of Queensland, Brisbane, Australia; [3]Department of Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Baltimore, MD 21201, USA; [4]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

Abstract

Objective To describe the potential benefits and harms of oseltamivir by reviewing all clinical study reports (or similar document when no clinical study report exists) of randomised placebo controlled trials and regulatory comments ("regulatory information").

Design Systematic review of regulatory information.

Data sources Clinical study reports, trial registries, electronic databases, regulatory archives, and correspondence with manufacturers.

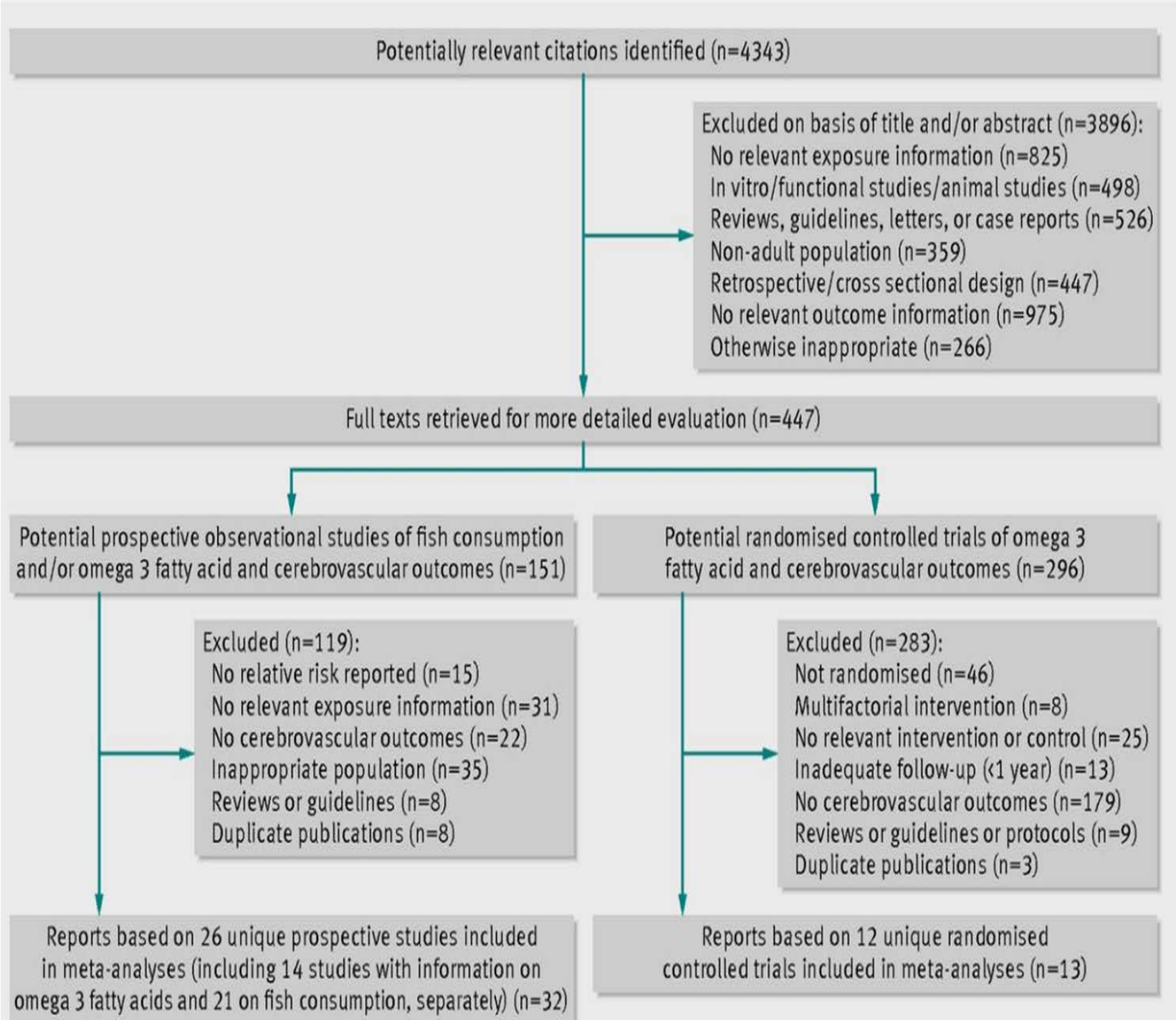
Eligibility criteria for selecting studies Randomised placebo controlled trials on adults and children who had confirmed or suspected exposure to natural influenza.

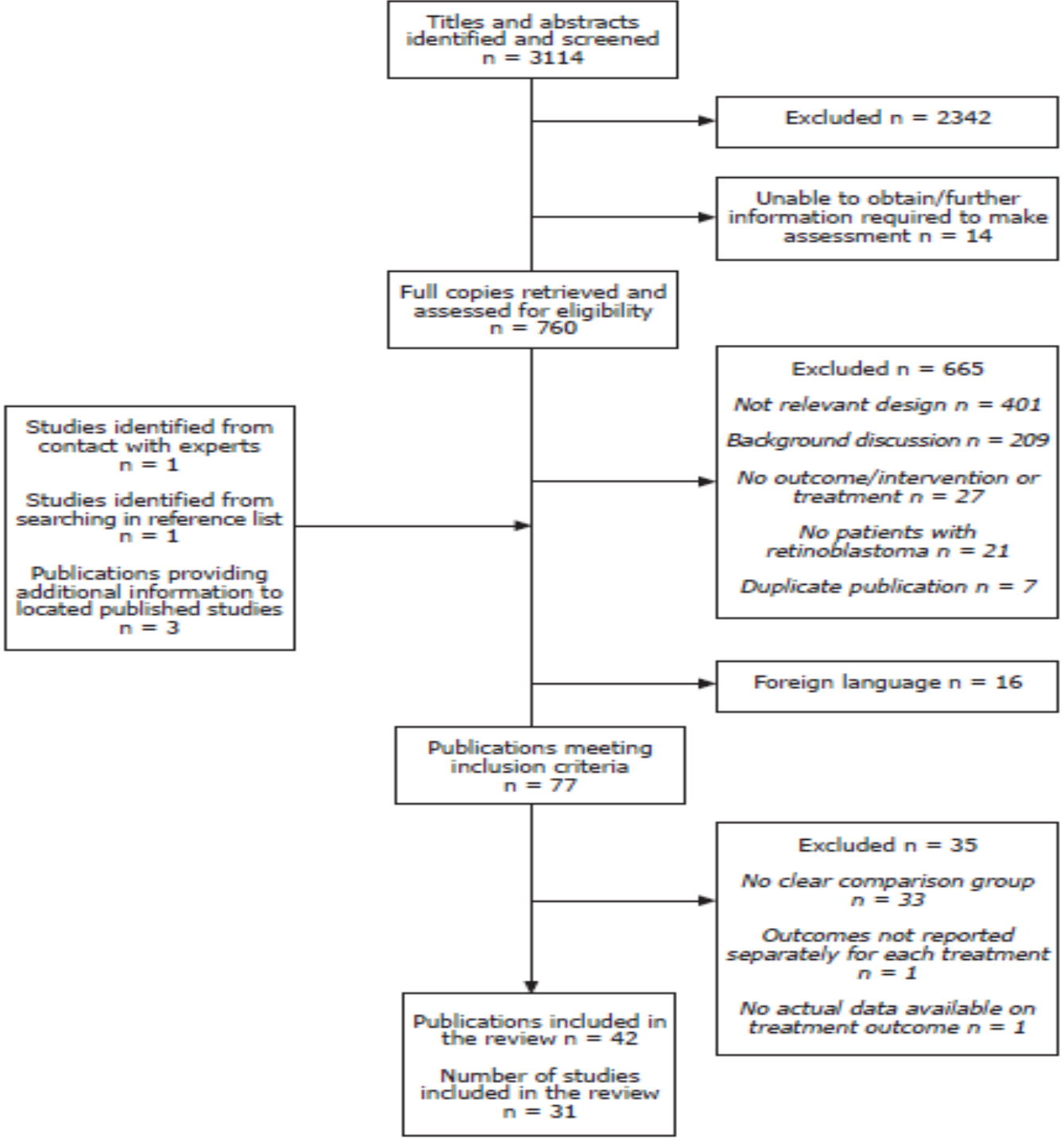
Main outcome measures Time to first alleviation of symptoms, influenza hours, 95% confidence interval 12 to 47 hours, P=0.001). In treatment trials there was no difference in admissions to hospital in adults (risk difference 0.15%, 95% confidence interval −0.91% to 0.78%, P=0.84) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference 1.00%, 0.22% to 1.49%; number needed to treat to benefit (NNTB) 100, 95% confidence interval 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for "pneumonia," and no clinical study reports reported laboratory or diagnostic confirmation of "pneumonia." The effect on unverified pneumonia in children and for prophylaxis was not significant. There was no significant reduction in risk of unverified bronchitis, otitis media, sinusitis, or any complication classified as serious or that led to

LINK to article

4/5. Select Studies to be included in the Review:

- Evaluate studies in full
- Each study should be evaluated by more than one reviewer
- Blinding reviewers to authors
- Document reasons for exclusion and inclusion
- Extract data from individual studies (Standard format)




Titles and abstracts identified and screened n = 3114
Excluded n = 2342
Unable to obtain/further information required to make assessment n = 14
Full copies retrieved and assessed for eligibility n = 760
Excluded n = 665
Not relevant design n = 401
Background discussion n = 209
No outcome/intervention or treatment n = 27
No patients with retinoblastoma n = 21
Duplicate publication n = 7
Studies identified from contact with experts n = 1
Studies identified from searching in reference list n = 1
Publications providing additional information to located published studies n = 3
Foreign language n = 16
Publications meeting inclusion criteria n = 77
Excluded n = 35
No clear comparison group n = 33
Outcomes not reported separately for each treatment n = 1
No actual data available on treatment outcome n = 1
Publications included in the review n = 42
Number of studies included in the review n = 31

6. Assess Individual Study Hierarchy and Quality (coding systems utilized)

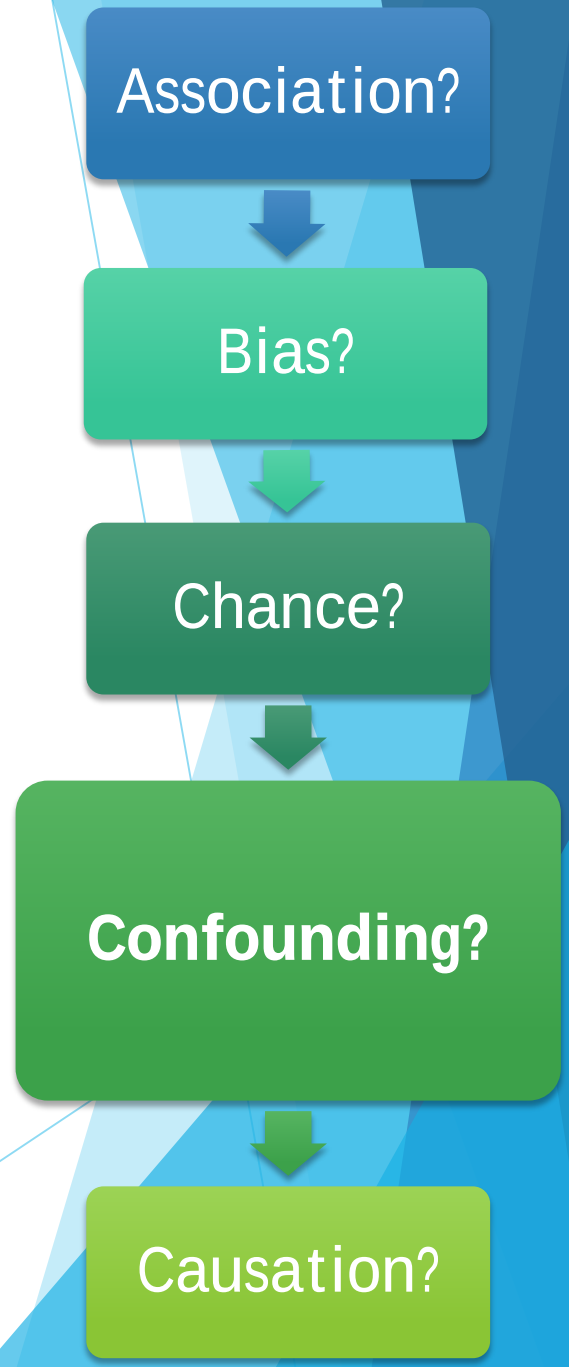
I	• Study is a randomized trial
II-1	• Study is a nonrandomized trial
II-2	• Study is a cohort or case-control study
II-3	• Study is a cross-sectional study
III	• Study is a case report or case series study

Assess quality of individual Study Design

I
- Quality of evidence is **GOOD**

II
- Quality of evidence is **FAIR**

III
- Quality of evidence is **POOR**



7. Analyze and Interpret Results

- Review all the data from the selected studies, then simplify their interpretations
- Look for consistency of effects, and possible differences, between studies (heterogeneity)
- Perform a *Meta-analysis* (where possible) and display on a *Forest Plot*

Meta-analysis:

- Combines the results from a number of different studies and aggregates the findings (OR, RR) into one numerical value
- A Pooled analysis goes one step further and takes all the raw data from all of the studies and re-analyzed them together
- Combining findings can result in small confidence intervals (giving a sense of greater precision), but cannot account for errors not properly addressed in individual studies

REMEMBR: Garbage is still garbage, even if it is gathered together in one neat and tidy location – importance of inclusion and exclusion criteria and study quality.

Combining the result of individual studies in a meta-analysis will:

A. Increase accuracy

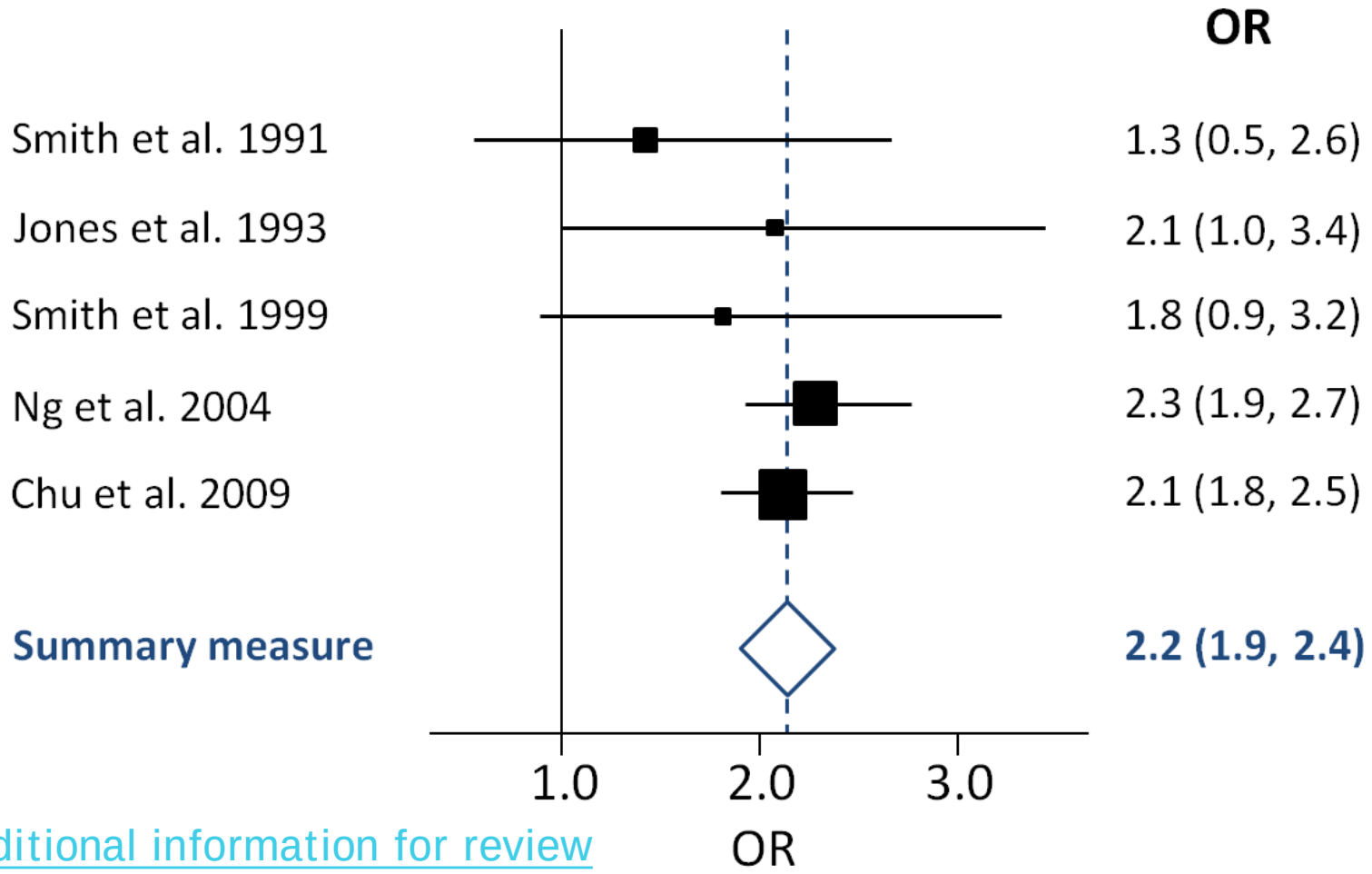
B. Increase power

C. Widen the confidence interval

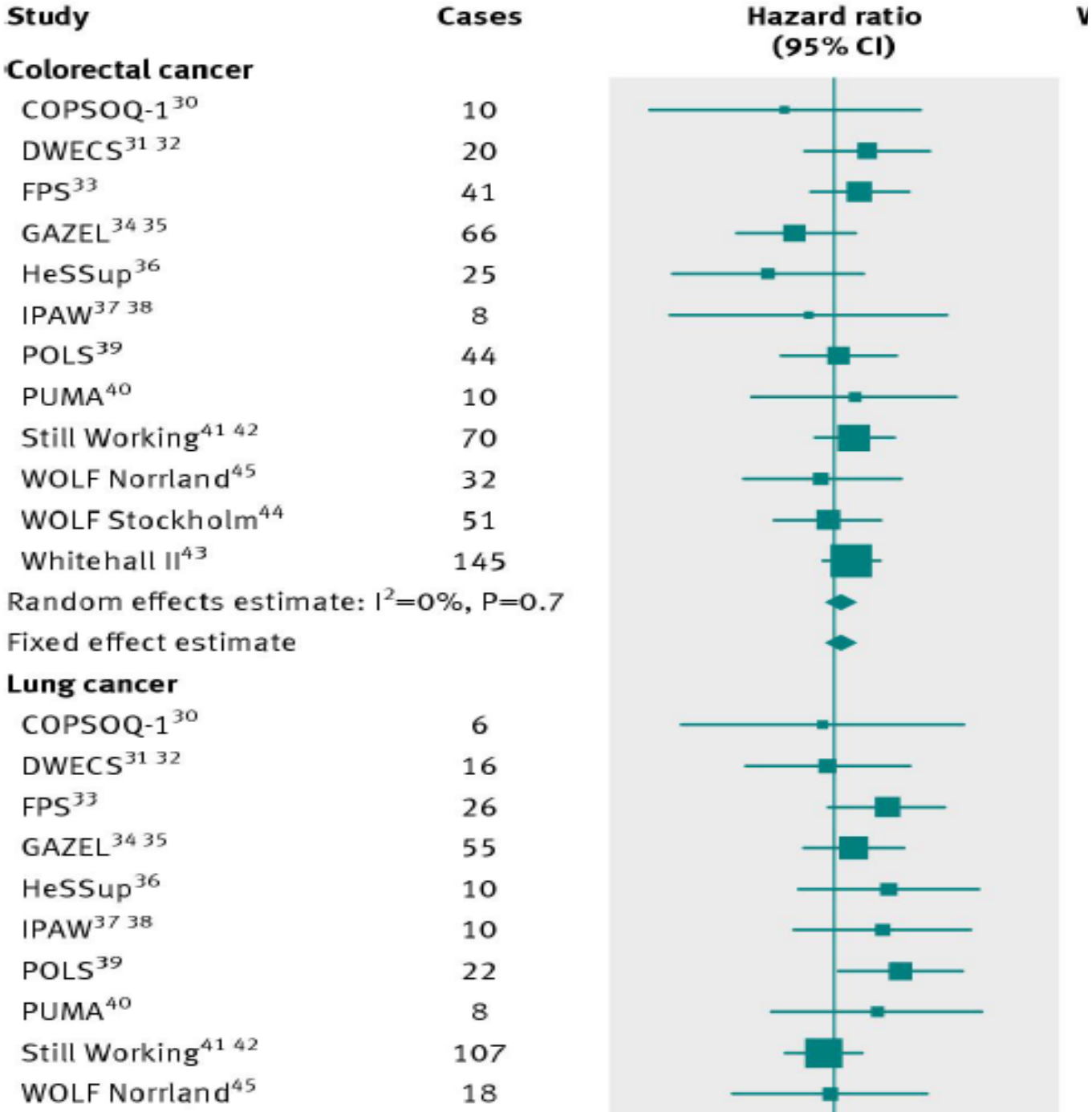
D. All of the above

Forest Plots:

- Graphical representation of a systematic review and/or meta-analysis



LINK to additional information for review



SR Results

Forest plot often used to summarize SRs and Meta-analysis

- ■ = OR, RR or HR
- Size of square = size of study
- Thin horizontal lines = 95% CIs
- ◆ = combined OR, RR or HR.
- Vertical line = OR, RR or HR of 1.0

Types of Systematic Reviews

Normal SR	• Findings across studies summarized (e.g., range of RRs)
Meta-Analysis SR	• Combine published RRs or ORs to create one average RR or OR
Pooled Analysis SR	• Obtain original data & re-analyze as one large study (e.g., one RR only)

iClicker Question

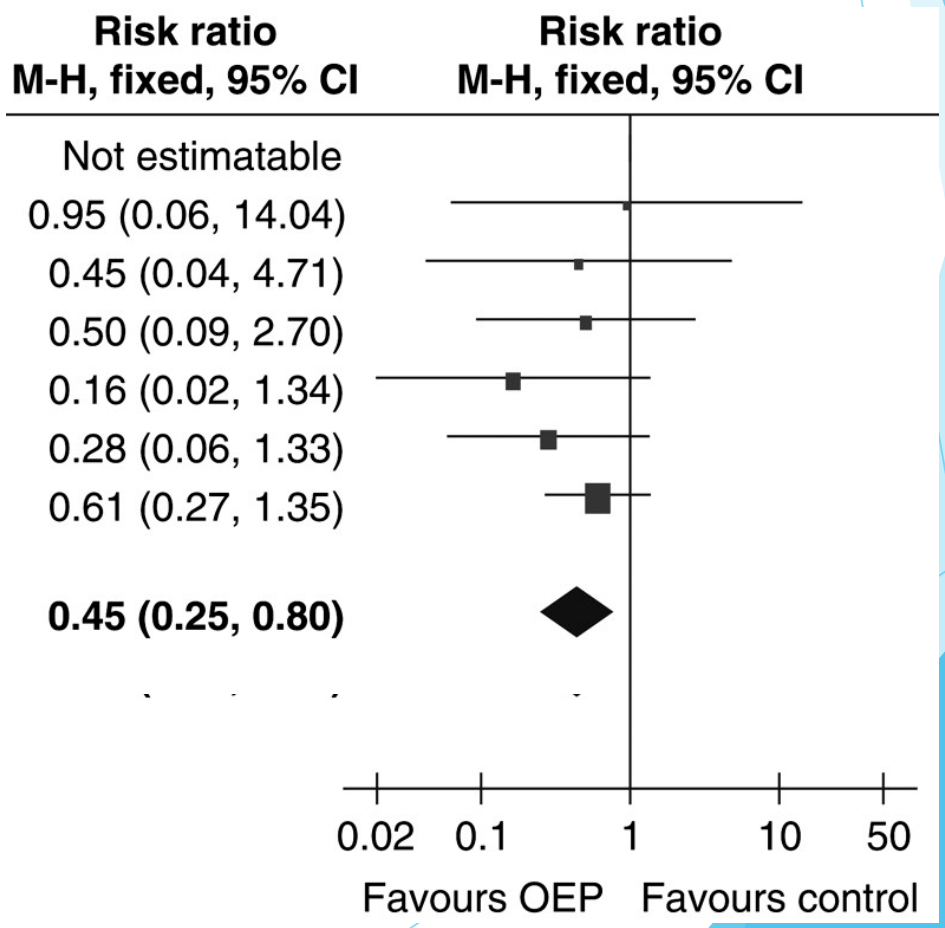
1. A systematic review examined whether the Otago exercise program (OEP) reduced falls in the elderly. What do the results suggest?

A. No association

B. OEP decreased falls

C. OEP *increased* falls

D. No pattern



iClicker Question

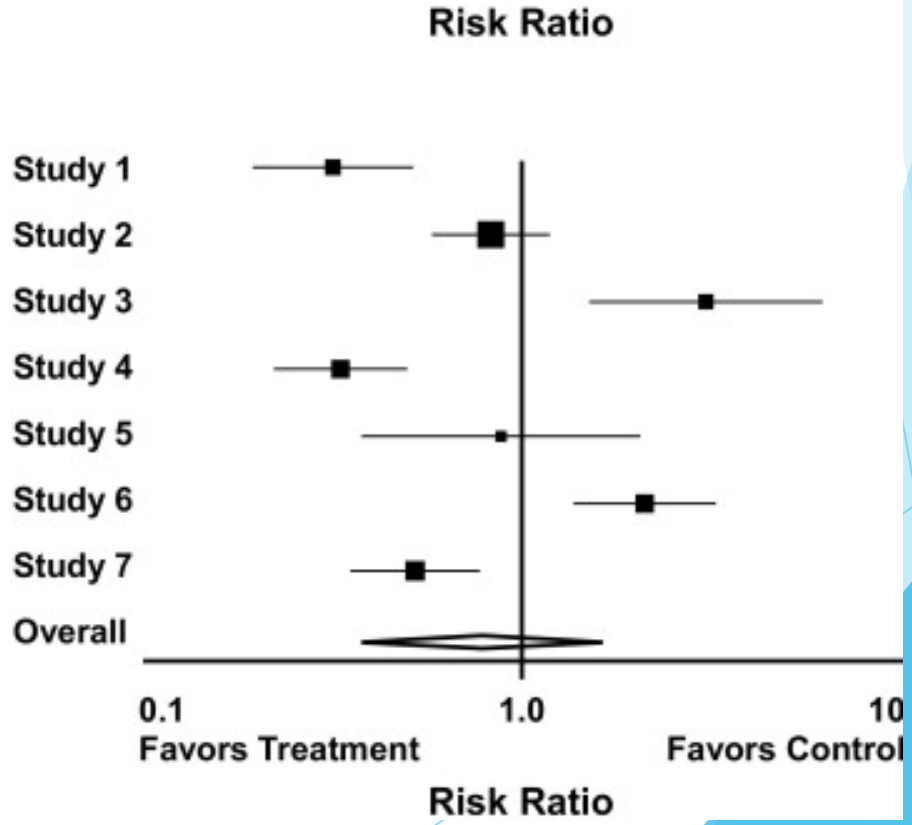
1. A systematic review examined whether Vitamin C was associated with arthritis symptoms. What do the results suggest?

A. No association

B. Vitamin C *reduced* arthritis symptoms

C. Vitamin C *increased* arthritis symptoms

D. No pattern



How can you find SRs?

CINAHL/PubMed

http://www.youtube.com/watch?v=kYg1sftDnj4

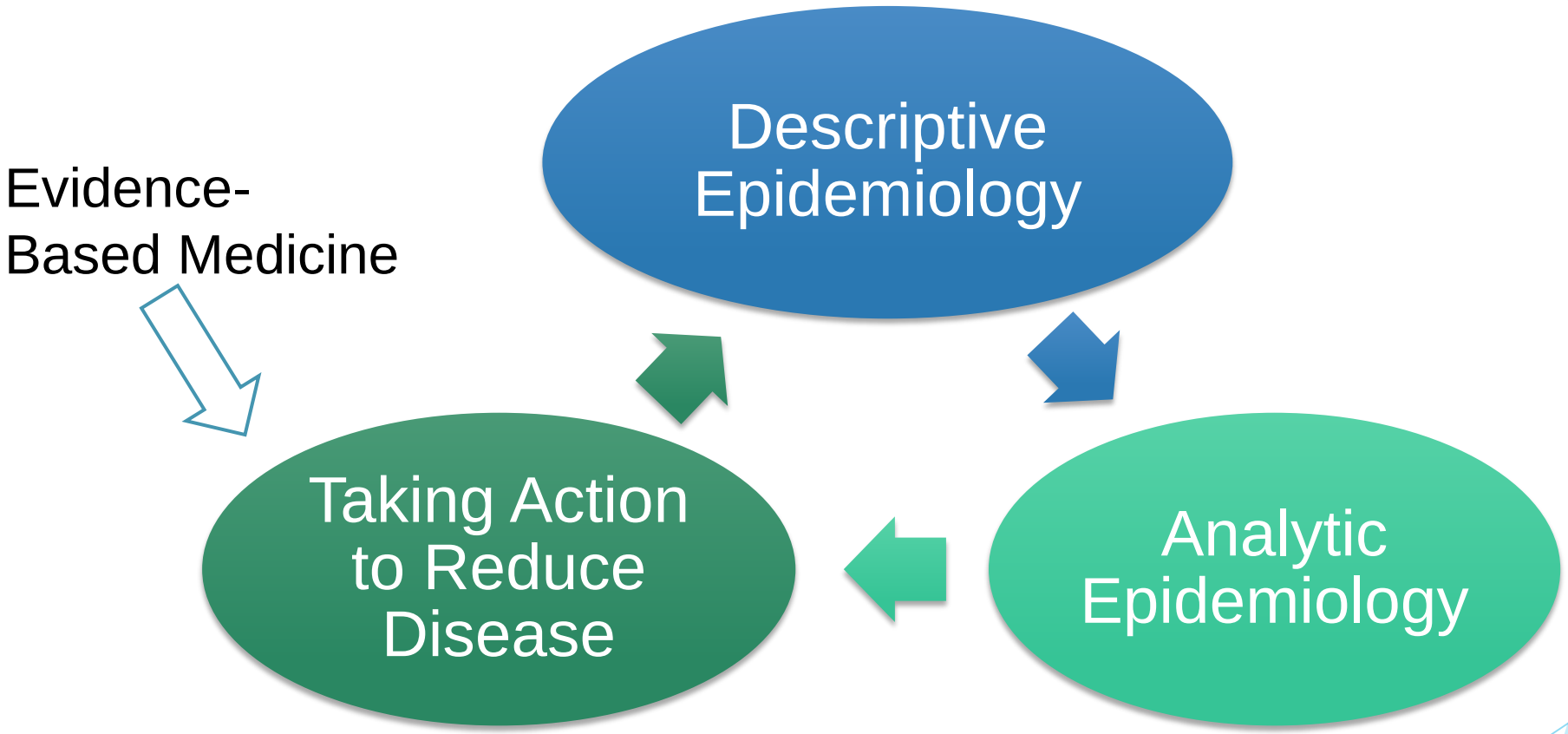
Cochrane Reviews

http://www.cochrane.org/cochrane-reviews

The Cochrane Collaboration

- International network that prepares systematic reviews of **healthcare interventions based on RCTs** (more than 5000 published so far!)
- Cochrane is **the gold standard** for high quality information about health care. It is independent (no ties to drug companies, etc.), no geographic boundaries – Sites all over the world.
- Important basis for evidence based medicine around the world: Cochrane website
- The Story of a Cochrane Review

Cycle in Epidemiologic Work



Are low-fat diets really better?

- Systematic review of **16,000 published studies** on healthy eating.

Mat vid fetma

En systematisk litteraturöversikt

September 2013

Link to report

SBU • Statens beredning för medicinsk utvärdering

Swedish Council on Health Technology Assessment

Low Carb Diet more effective for weight loss...

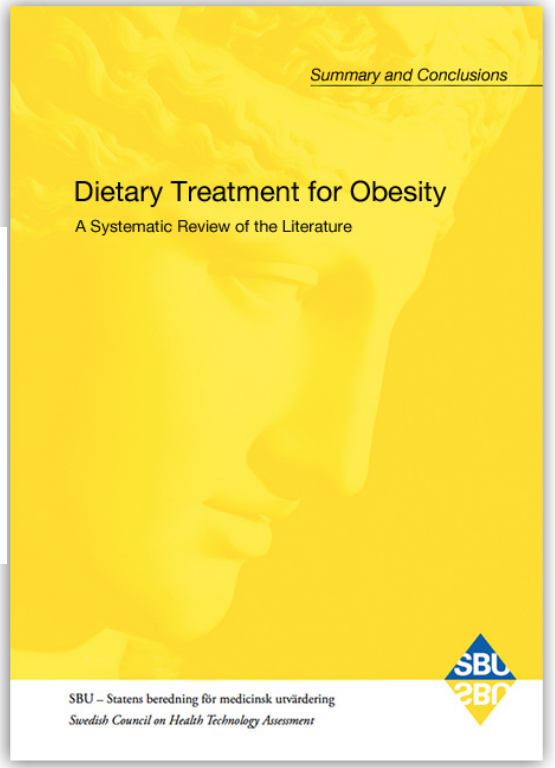
> *...a greater increase in HDL cholesterol ("the good cholesterol") without having any adverse affects on LDL cholesterol ("the bad cholesterol"). This applies to both the moderate low-carbohydrate intake of less than 40 percent of the total energy intake, as well as to the stricter low-carbohydrate diet, where carbohydrate intake is less than 20 percent of the total energy intake. In addition, the stricter low-carbohydrate diet will lead to improved glucose levels for individuals with obesity and diabetes, and to marginally decreased levels of triglycerides.*

Recent cautions on low-carbohydrate diets are at best based on statistical associations derived from food questionnaires from people who didn't (!) eat a low-carbohydrate diet. The SBU also dismisses these warnings:

> *Advice on a low-carbohydrate diet is however very rare, if we look at the practice survey. It's not clear how common it is to actively discourage patients from the strict low-carbohydrate diet. A low-carbohydrate diet, even the stricter form, will lead to a greater weight loss in the short term than the low-fat diet, and studies have indicated no adverse effects on blood lipids, provided that the weight stays low. One possible consequence of this report will therefore be an increased use of a strict low-carbohydrate diet for short-term weight reduction.*

It would be wonderful if the health care system started to apply the benefits of a low-carbohydrate diet, even before the outdated fear of butter has melted away everywhere.

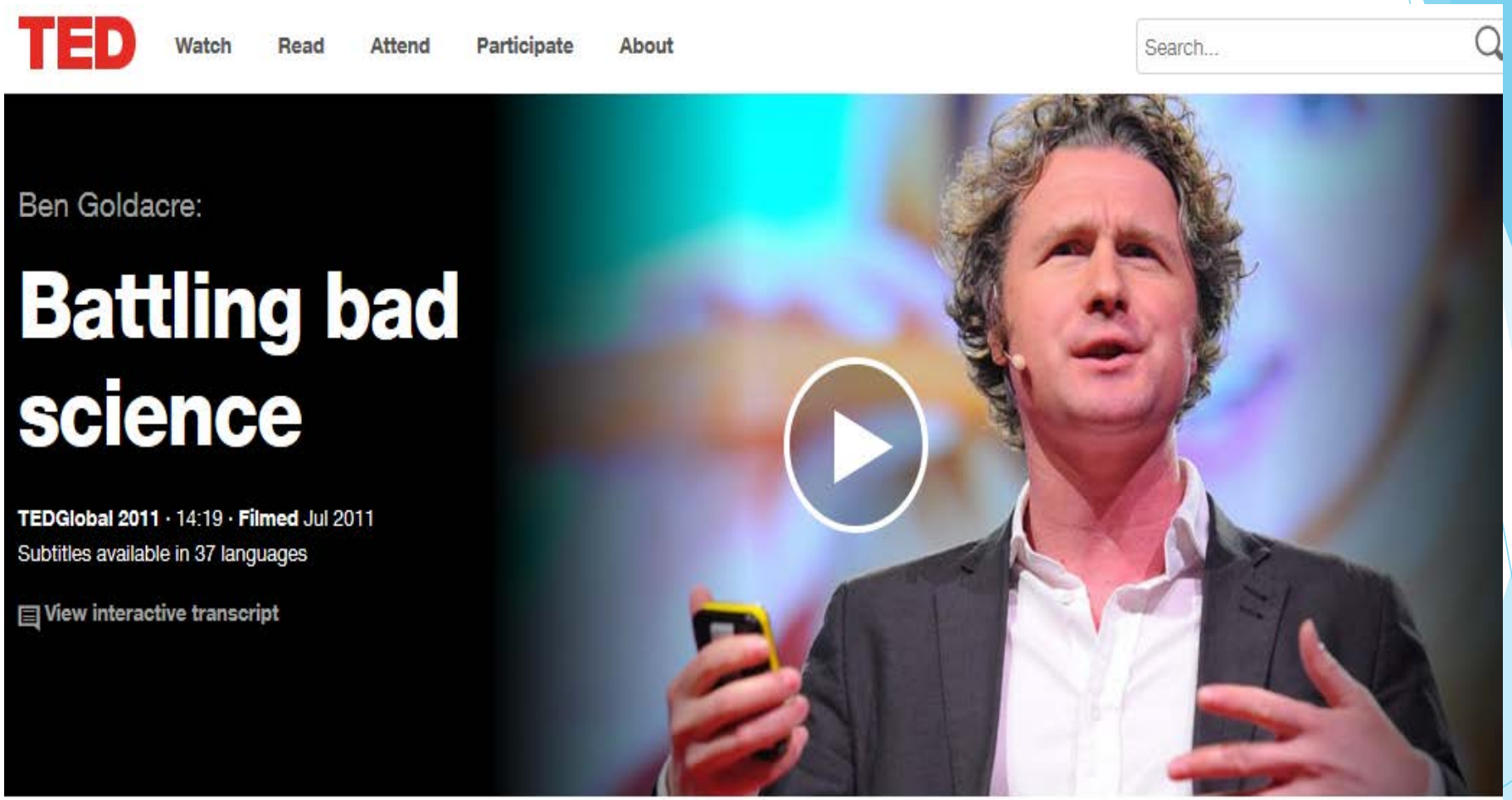
The SBU-report Dietary Treatment for Obesity is a gigantic step towards more effective dietary guidelines within the health care system. This is a historic day in Sweden.



LINK to Report

LINK to SBU "Dietary Treatment of Obesity"

LINK to Additional Commentary of interest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- During Mar 1st (or 3rd?) class period
- A bit longer than Quiz 1
- Bring a calculator
- Heavier weighting (25%)

Brief Review for Midterm Exam

- Observational and Experimental study designs
  - Design, strengths and weakness, common biases
- Measures of Association
  - 2X2 Tables
  - Odds ratios & Relative Risks
  - Difference Measures (attributable risk/fractions)
- Causation (Hills Postulates)
- Error (Chance, Systematic bias)
- Confounding
- Study Critique
- Systematic Reviews

Resources for Study:

- Assignments done in class (answers posted)
- Practice exercises on Moodle
- Additional readings posted