Opportunities and challenges of using systematic reviews to summarize knowledge about “what works” in disease prevention & health promotion

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Rockville, Maryland
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Kay Dickersin’s declaration of interests

- Grants and contracts from agencies:
  - NIH-Cochrane Eyes and Vision
  - PCORI-Influence of multiple sources of data on meta-analysis
  - PCORI-Engagement of consumers
  - PCORI-Consumer Summit with G-I-N North America
  - AHRQ-Consumers United for Evidence-based Healthcare Conference Grant
  - FDA-Centers for Excellence in Regulatory Science Innovation (GC Alexander, PI)

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Reviews are necessary in health and healthcare

• Systematic reviews of existing research scientifically summarize “what works” at any point in time.

• Reasons for summarizing what works vary (e.g., understanding priorities for research, pursuing answers where there are knowledge gaps, or setting guidelines for care)
What is a systematic review?

• A review of existing knowledge that uses explicit, scientific methods.

• Systematic reviews may also combine results quantitatively (“meta-analysis”)
Types of review articles

- Systematic reviews with meta-analyses
- Systematic reviews
- Individual patient data (IPD) meta-analyses
- Reviews that are not systematic (traditional, narrative reviews)

Steps in a systematic review

Step 1 – Gather together your team (content and methods experts)
Step 2 - Write a protocol
  – Question, eligibility criteria, search, data abstraction, quality assessment, qualitative and quantitative (if appropriate) synthesis
Step 3 – Collect data (search)
Step 4 – Appraise
Step 4 – Synthesize (qualitative)
Step 6 – Analyze (quantitative)
Step 5 – Interpret data and assess limitations
Step 6 – Update review
What meta-analysis can help you do

– Assess strength of evidence
  • To determine whether an effect exists in a particular direction

– Combine results quantitatively
  • To obtain a single summary result

– Investigate heterogeneity
  • To examine reasons for different results among studies
Presentation of a meta-analysis: the forest plot

Estimates with 95% confidence intervals

- Kennedy 1997
- Locke 1952A
- Lopes 1997
- Reynolds 1998
- Seiberth 1994

Line of no effect

Estimate and confidence interval for each study

Estimate and confidence for the meta-analysis (optional)

Scale (effect measure)

Direction of effect

Risk ratio

Favours LR  ➡️  Favours control
Many reports summarizing knowledge are “reviews”, but are they systematic reviews?
A genome-wide association study of intra-ocular pressure suggests a novel association in the gene *FAM125B* in the TwinsUK cohort

Abhishek Nag¹, Cristina Venturini², Kerrin S. Small¹, International Glaucoma Genetics Consortium†, Terri L. Young³, Ananth C. Viswanathan⁴, David A. Mackey⁵, Pirro G. Hysi¹

Glaucoma is a major cause of blindness in the world. To date, common genetic variants associated with glaucoma only explain a small proportion of its heritability. We performed a genome-wide association study of intra-ocular pressure (IOP), an underlying endophenotype for glaucoma. The discovery phase of the study was carried out in the TwinsUK cohort (*N* = 2774) analyzing association between IOP and single nucleotide polymorphisms (SNPs) imputed to HapMap2. The results were validated in 12 independent replication cohorts of European ancestry (combined *N* = 22 789) that were a part of the International Glaucoma Genetics Consortium. Expression quantitative trait locus (eQTL) analyses of the significantly associated SNPs were performed using data from the Multiple Tissue Human Expression Resource (MuTHER) Study. In the TwinsUK cohort, IOP was significantly associated with a number of SNPs at 9q33.3 (*P* = 3.48 × 10⁻⁸ for rs2286885, the most significantly associated SNP at this locus), within the genomic sequence of the *FAM125B* gene. Independent replication in a composite panel of 12 cohorts revealed consistent direction of effect and significant association (*P* = 0.003, for fixed-effect meta-analysis). Suggestive evidence for an eQTL effect of rs2286885 was observed for one of the probes targeting the coding region of the *FAM125B* gene. This gene codes for a component of a membrane complex involved in vesicular trafficking process, a function similar to that of the Caveolin genes (*CAV1* and *CAV2*) which have previously been associated with primary open-angle glaucoma. This study suggests a novel association between SNPs in *FAM125B* and IOP in the TwinsUK cohort, though further studies to elucidate the functional role of this gene in glaucoma are necessary.
Why bother with a systematic review?

Many nonsystematic methods are used to synthesize knowledge; most use fewer resources, and in a given field experts believe they know the literature sufficiently to avoid the investment. For example:

- Integrative review
- Realist review
- Narrative review
- Scoping review
- Mixed methods review
- Rapid review

Many ways of summarizing what is known

Fig. 2. Word cloud for most frequent knowledge synthesis methods.

2016 Tricco et al J Clin Epi 73: 19e28
There are published standards on how to conduct and how to report a systematic review.
IOM - Standards for Systematic Reviews and Guidelines

Finding What Works in Health Care

Standards for Systematic Reviews

Clinical Practice Guidelines We Can Trust
Why bother with doing or commissioning a systematic review?

What would you feel is acceptable to omit?
Steps in a systematic review

Step 1 – Gather together your team (content and methods experts)

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Step 6 – Analyze (quantitative)

Step 5 – Interpret data and assess limitations

Step 6 – Update review
Risk of bias in systematic reviews

• Bias in the methods used in the included studies
• Bias in the methods used in the systematic review
Sources of bias in an RCT

**Bias**
- **Selection**
  - Random sequence generation & allocation concealment protect against selection bias
- **Information**
  - Masking of patient, carer, outcome assessors protects against information bias
- **Analysis**
  - Intention to treat analysis of pre-defined outcomes protects against bias resulting from analysis

**Target Population**
- Random Allocation
  - Intervention group
  - Control group

**Outcome assessment**
- Outcome assessment

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Methodological quality of observational studies

• Selection bias
  – Definitions of exposed/unexposed
  – Choice of cases/controls

• Information bias
  – Definition exposure
  – Definition outcome
  – How information obtained

• Analysis
Risk of bias in systematic reviews

- Bias in the methods used in the included studies
- **Bias in the methods used in the systematic review (metabias)**

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**Annals of Internal Medicine**

**Metabias: A Challenge for Comparative Effectiveness Research**

Comparative effectiveness research encompasses both individual primary research studies and syntheses of the primary research, typically systematic reviews and meta-analyses. Before accepting the results of either form of study, decision makers must critically assess their methods to identify sources of potential bias.

For primary research, critical appraisal involves close examination of research methods, including design, data, execution, analysis, and interpretation. For meta-analyses, individual studies are examined in the same way, but the collection of studies is also examined for heterogeneity. Studies are deemed heterogeneous if their methods or results differ from one another so much that the studies cannot be regarded as addressing the same scientific question. Factors that produce heterogeneity are typically not regarded as producers of bias, but rather of differences in effect due to variations in populations, interventions, comparisons, outcomes, or settings. Although heterogeneity is related to the characteristics of the individual studies, it is research have led to heightened concern about these studies, both from journals and systematic reviewers (8–10). This has led some to explore whether industry sponsorship by itself should be considered a bias, or by our criteria, a metabias (11–13).

Reporting biases can be regarded as a mix of procedural biases for individual studies and metabiases. They often elude detection through even the closest examination of an individual study report. They can be found only by comparing study protocols with a published study report or tracking ultimate publication status of an inception cohort of studies. Governments, funders, and the research community have responded to this recognized threat to validity. The most far-reaching remedy to date has been clinical trial registries (14–16). These registries, together with mandates from funders to register trials and protocols before trial onset, allow persons conducting evidence syntheses to detect nonpublication or deviations from pre-specified plans for study conduct or analysis (17–18).
Reporting biases - our biggest challenge in doing a systematic review

Reporting biases introduce selection bias into a systematic review

- **Publication bias** - unpublished studies have different results from published studies
- **Selective outcome reporting** – unpublished outcomes have different results from published outcomes
  - Selective reporting of an entire study outcome (e.g., adverse events);
  - Selective reporting of a specific outcome (e.g., selected timepoints or follow-up intervals),
  - Incomplete reporting of a specific outcome (e.g., incomplete reporting of nonsignificant p values, such as p>0.05).
Sources of trial information

- **Public**
  - Short report (e.g., conference abstract)
  - Journal article (about one or more trials)
  - Results on trial registry (e.g. ClinicalTrials.gov)
  - Information from regulators (e.g. FDA review, label)
  - Trial registration (e.g. ClinicalTrials.gov)
  - Study protocol / statistical analysis plan (e.g., PROSPERO)

- **Non-public (hidden)**
  - Unpublished manuscript (e.g. clinical study report)
  - Individual participant data
  - Grant proposal
  - IRB submission
  - Case report form
  - Metadata (e.g., codebooks, memos)
The Neurontin Story: Selective outcome reporting

- Recognizing that Neurontin earnings were limited with epilepsy, Pfizer did marketing assessment for other applications:
  - Migraine
  - Bipolar disorders
  - Neuropathic pain
  - Nociceptive pain

- Marketing assessments uniformly recommended a “publication strategy” over an “indication strategy”

Number of primary outcomes in research protocols and published reports for 12 clinical trials of off-label uses of gabapentin (bipolar, migraine, neuropathic pain)

21 Primary outcomes in protocols of 12 published trials (includes those described with no distinction from secondary outcomes)

11 Were reported with no changes (includes those described with no distinction from secondary outcomes)

4 Were reported as secondary outcomes

6 Were not reported in publication

12 New primary outcomes in publication (includes those described with no distinction from secondary outcomes)

5 Protocol-defined secondary outcomes (reported with no distinction from primary outcomes in publication)

28 Primary outcomes in publications (includes those described with no distinction from secondary outcomes)

P Values for Protocol-Defined Primary Outcome in Internal Research Report and in Main Publication

P Values for Protocol-Defined Primary Outcome in Internal Research Report and in Main Publication

Development of core outcome measures could help
Who is doing systematic reviews?

- Independent authors
- Cochrane Collaboration
- Groups interested in policy (professional societies, governments, payers)
  - US: US Preventive Services Task Force, CDC, AHRQ, EPCs, Blue Cross
  - UK: NICE, Health Technology Assessments
  - Germany: IQWiG
  - Oz: NHMRC
- Funders (next slide)
- Businesses: Hayes, ECRI (contracting to pharma and others)
Knowledge translation: From clinical research to practice decisions

Evidence generation → Cochrane Collaboration, others → Clinical trials, observational studies → Evidence-based healthcare

Professional Societies, others

Application of policy: Evidence
Clinician expertise
Patient values

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Do funders require applicants (primary research) to refer to systematic reviews of existing evidence?

<table>
<thead>
<tr>
<th>Organization</th>
<th>Requirement</th>
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<tbody>
<tr>
<td>NIHR (UK)</td>
<td>Yes – It only funds research with a systematic review of existing evidence.</td>
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<tr>
<td>NHMRC (Australia)</td>
<td>No</td>
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<tr>
<td>CIHR (Canada)</td>
<td>Partial - It encourages (but does not require) conduct of a systematic review in proposals for clinical trials.</td>
</tr>
<tr>
<td>NIH (US)</td>
<td>Partial - It encourages a ‘check of the literature to verify that the proposed project has not been done before’, but it doesn’t specify whether it has to be a systematic review.</td>
</tr>
<tr>
<td>MRC (UK)</td>
<td>No - The major grant opportunities do not require a systematic review; the global health clinical trial programme encourages the conduct of a systematic review before request for large-scale clinical trials.</td>
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Elevated Risk for HIV Infection among Men Who Have Sex with Men in Countries 2000–

**Abstract**

Recent reports indicate that the risk of HIV transmission is higher among men who have sex with men (MSM) in Asia, Africa, and South America than among MSM in the United States. This systematic review of prevalence data analyzed the published data on HIV among MSM from these regions from 2000 to 2007. The results indicate that the proportion of MSM who are HIV-positive is significantly higher in Asia, Africa, and South America than in the United States, with a risk of transmission that is twice that observed in the United States. The findings suggest that targeted interventions are needed to reduce the risk of HIV transmission among MSM in these regions.
Association of All-Cause Mortality With Overweight and Obesity Using Standard Body Mass Index Categories

A Systematic Review and Meta-analysis

Katherine M. Flegal, PhD
Brian K. Kit, MD
Heather Orpana, PhD
Barry I. Graubard, PhD

The topic of the mortality differences between weight categories has sometimes been described as controversial. The appearance of controversy

Importance Estimates of the relative mortality risks associated with normal weight, overweight, and obesity may help to inform decision making in the clinical setting.

Objective To perform a systematic review of reported hazard ratios (HRs) of all-cause mortality for overweight and obesity relative to normal weight in the general population.

Data Sources PubMed and EMBASE electronic databases were searched through September 30, 2012, without language restrictions.

Study Selection Articles that reported HRs for all-cause mortality using standard body mass index (BMI) categories from prospective studies of general populations of adults were included. Articles reporting HRs from studies of clinical populations, repeated BMI measurements, or BMI categories not consistent with international definitions were excluded.
Interventions to improve inhaler technique for people with asthma

Rebecca Normansell, Kayleigh M Kew

First published: 14 July 2016

Editorial Group: Cochrane Airways Group

DOI: 10.1002/14651858.CD012286  View/save citation

Cited by: 0 articles  Check for new citations

Cited by: 1 article  Refresh  Citing literature
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Title: Interventions Designed to Improve Financial Capability by Improving Financial Behavior and Financial Access: A Systematic Review
Authors: Julie Birkenmaier, Brandy R Maynard
Published: 01.07.2016
Group: Social Welfare
Evidence for What Works in Education

We review the research on the different programs, products, practices, and policies in education.

Then, by focusing on the results from high-quality research, we try to answer the question “What works in education?”

Our goal is to provide educators with the information they need to make evidence-based decisions.
The EPA’s IRIS Program is using systematic reviews.

IRIS Process

Notice

[11/12] EPA announced a public stakeholders meeting to hear comments on the IRIS Process and Program.


The IRIS process consists of the development of a draft Toxicological Review for a chemical; internal and external scientific reviews of the draft document; EPA responses to review comments; and development and posting of an IRIS Summary and final Toxicological Review to EPA’s web site. EPA announced revisions to the IRIS process in May 2009 and further revisions in 2011.

2012 Updates

On June 5, 2012, EPA released an IRIS Progress Report to Congress. This report, delivered to Congress on April 20, 2012, provides Congress, stakeholders, and the public with an update on the IRIS Program and EPA’s progress toward implementing the recommendations from the National Research Council (NRC), received in April 2011, for improving the development of IRIS assessments.

IRIS 2012 Progress Report to Congress

- IRIS Progress Report to Congress – June 2012 (PDF) (29 pp, 1.34MB, about PDF)
- Fact Sheet: Path Forward for IRIS - 2012 (PDF) (2 pp, 54.8 KB, about PDF)
- IRIS Blog post by Becki Clark (Acting Center Director) May 2012
Who is using SRs?

- **Clinicians** – Underuse and inappropriate use of interventions, prognosis, etiology
- **Public health practitioners** – Health policy
- **Government** – Policy (eg, environmental exposures)
- **Guidelines producers** – Health and healthcare
- **Epidemiologists** – Incidence, prevalence, etiology
- **Payers, purchasers** – Especially new health technologies
- **Consumers** – Appropriate interventions
- **Legislators** - Public health policy
- **Journalists** – New results in context
- **Educators** – Implementation of what works
Ensuring the quality of published systematic reviews

Instructions for Authors

Systematic Reviews and Meta-analyses

Systematic reviews seek to collect and critically assess all evidence that fits pre-specified criteria to answer a clinical question pertaining to the cause, diagnosis, prognosis, prevention, or therapy for a condition. A systematic review may contain a meta-analysis, which uses statistical methods to combine results from similar but independent studies.

Features of a systematic review include: a clearly stated set of objectives with pre-defined eligibility criteria for studies; an explicit, reproducible methodology; a systematic search that attempts to identify all studies that would meet the eligibility criteria; an assessment of the validity of the findings of the included studies, for example through the assessment of risk of bias; and a systematic presentation, and synthesis of the characteristics and findings of the included studies (Higgins JPT, Green S (editors). Chapter 1. Cochrane...
A Model to Set CER Priorities

Step 1
Derived 45 clinical questions from the guideline
Classified 9 clinical questions as high priority using a Delphi survey

Step 2
Identified 39 existing systematic reviews
Classified 13 systematic reviews as “reliable”
• Based on characteristics of participants and interventions examined
• One review could be mapped to more than one clinical question

Step 3
Map systematic reviews with prioritized CER research questions
Interpret findings from reliable systematic reviews
Propose a research agenda

Cochrane Editorial Unit

Cochrane Priority Review List 2015-16

We are pleased to announce the publication of the first Cochrane-wide Priority Review List. The creation of this list represents the achievement of a key milestone for Target 1.1 Prioritisation, a part of Cochrane’s Strategy to 2020. In this target we set out a plan to identify about 200 Cochrane reviews, either new titles or reviews requiring updates, that best meet the needs of healthcare and health policy decision makers. The Cochrane Editorial Unit approached this task in two ways: firstly encouraging Cochrane Review Groups to engage with their stakeholders to identify priority reviews in their area, and secondly, identifying a list of research recommendations from national and international organisations in Australia, Canada, Spain, Switzerland, the United Kingdom, and the United States. We hope that publicising the list will act as a stimulus to encourage funders to support production of the reviews.

The level of engagement on this project was high, with about 300 priority review recommendations received from 50 Cochrane Review Groups – significantly more titles than we had hoped to gather. Many of the groups have undertaken engagement activities with external stakeholders, including consumers and health professional groups, so the list reflects those evidence needs. Other titles have been derived from the published research priorities of organisations such as research funders, patient advocacy groups and guideline developers.

This is the first time Cochrane has set priorities across all areas, and we will monitor our success in delivering the reviews. In addition, we recognise that the priority list will need to be refreshed regularly over time, and we will use the learning we have gained through this exercise to ensure that the process is as user-focused and inclusive as possible in future.

If you would like to contribute in any way to our goal of delivering the reviews through to publication, please contact the Editor in Chief, David Tovey (dtovey@cochrane.org). Please be aware that all titles in the priority list have author teams in place, except for those which have been highlighted.

Download the final Cochrane Priority Review list for 2015-16 (spreadsheet)

Ruth Foxlee, Information Specialist

David Tovey, Editor in Chief
Everybody needs training!

- Free courses
  - MOOCs
  - Cochrane
  - US Cochrane
  - Etc
- Paid courses
  - Johns Hopkins
  - Columbia
  - Etc

Send questions to prevention@mail.nih.gov
Use @nihprevents & #nihmtg on Twitter
MOOC (Massive Open Online Course) - free

Introduction to Systematic Review and Meta-Analysis

Starts Jul 11: Pre-enroll to get early access to videos, readings, and more.

About this course: We will introduce methods to perform systematic reviews and meta-analysis of clinical trials. We will cover how to formulate an answerable research question, define inclusion and exclusion criteria, search for the evidence, extract data, assess the risk of bias in clinical trials, and perform a meta-analysis.

Created by: Johns Hopkins University
• Everybody needs formal training and mentoring
• Systematic reviews are transparent and good ones adhere to standards endorsed by the IOM and others
• A lot of groups and individuals are doing systematic reviews but many are doing a “shorter” version that has not undergone scrutiny
• Systematic reviews are used for many things, including priority setting, policy making, clinical practice and public health guidelines
• Cochrane is an international collaboration of over 30,000 contributors from >100 countries producing up-to-date and reliable systematic reviews in prevention, treatment, health promotion, and other topics.
• 2016 NIH funding and support for US Cochrane groups
  – National Eye Institute (Johns Hopkins)
  – National Institute of Child Health and Human Development (University of Vermont)
  – National Center for Complementary and Integrative Health (University of Maryland)