READ-It
Research, Evidence & Development Initiative

What's so special about systematic reviews?

Bhekisisa webinar 3

Jimmy Volmink, Solange Durao

11 September 2020

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Acknowledgements

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Webinar outline

1. Introductions

2. Why are systematic reviews important for policy and practice?

3. What's so special about systematic reviews and how to understand forest plots

4. Q&A session

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Learning objectives

1. Define ‘systematic review’

2. Outline the rationale for undertaking systematic reviews

3. Describe the difference between narrative and systematic reviews

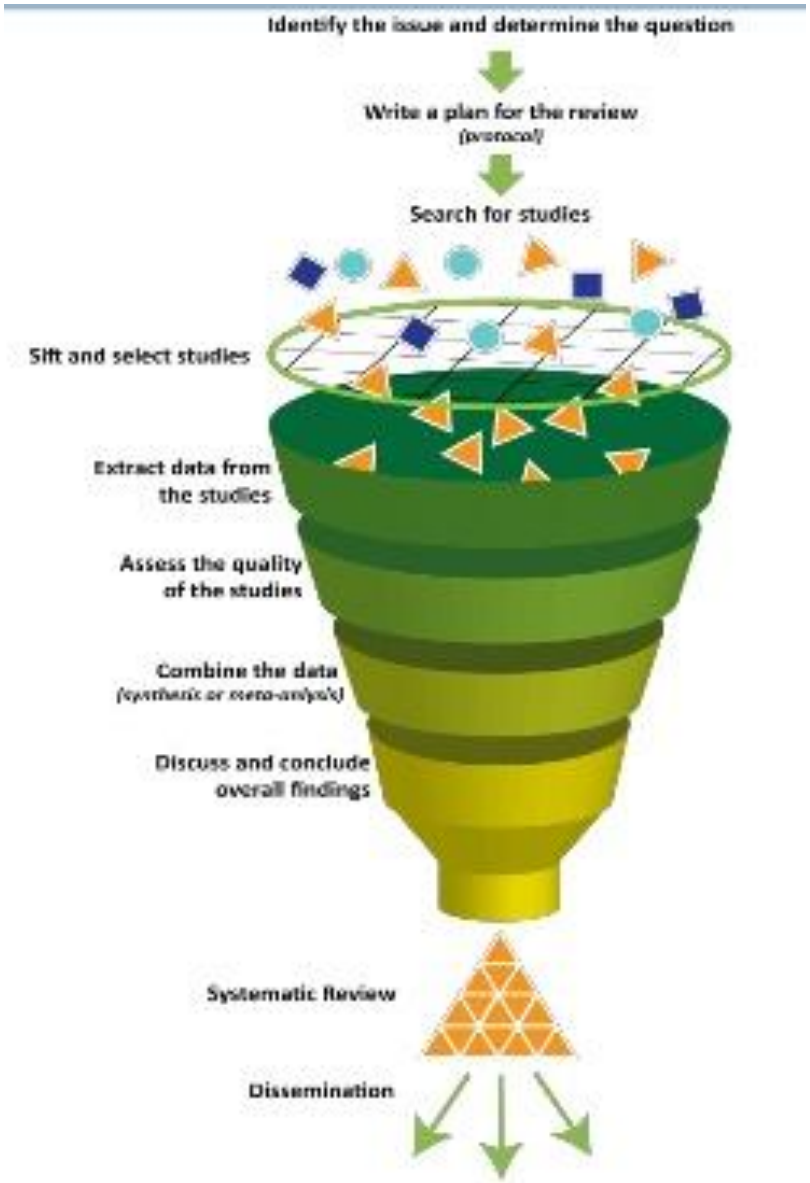
Evidence-informed decision-making

- Research Evidence
- Cost-effectiveness
- of intervention
- Patient Preference
- Ethical considerations
- litigation
- Knowledge of patient problem
- Resource
- constraints

Challenges of using evidence

Research synthesis

The process through which two or more research studies are assessed with the objective of summarising the evidence relating to a particular question



Why is research synthesis important?

- "The results of a particular research study cannot be interpreted with any confidence unless they have been considered together with the results of other studies addressing the same or similar questions."

Sir Iain Chalmers

- "The application of the principle that science is cumulative."

- Research synthesis allows us to evaluate the results of a given study <u>in context</u>

Why is research synthesis important?

- Making sense of research
  - Different/similar answers from different studies for the same question

Why is research synthesis important?

Coping with information overload

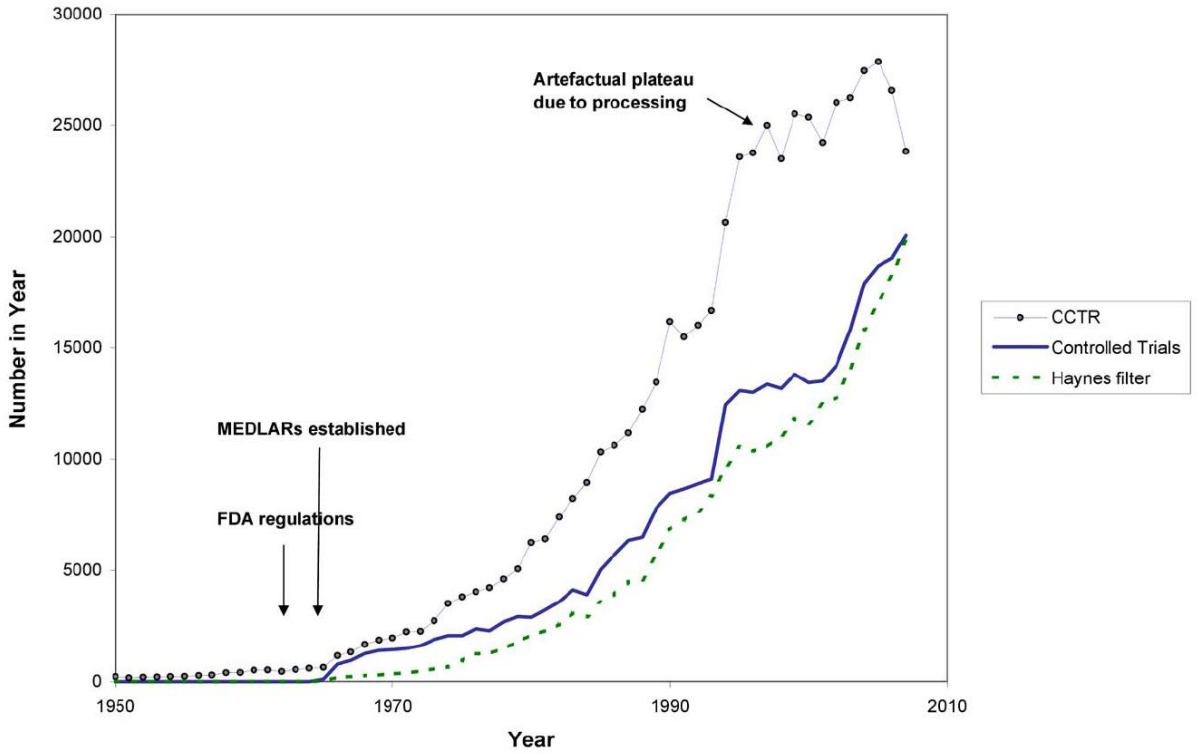


Figure 2. The number of published trials, 1950 to 2007. CCTR is the Cochrane Controlled Trials Registry; Haynes filter uses the "narrow" version of the Therapy filter in PubMed:ClinicalQueries; see Text S1.
doi:10.1371/journal.pmed.1000326.g002

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Why is research synthesis important?

- Justification of future research
  - What gaps in knowledge the proposed research intends to fill

Why is research synthesis important?

- Facilitating access to relevant research
  - Avoiding publication biases

Research synthesis

- Review (literature/traditional)
- Systematic review, Cochrane review, non-Cochrane systematic review
- Meta-analysis
- Pooled analysis
- Overview of systematic reviews
- Clinical/Public health guidelines

Traditional literature reviews

- Qualitative, narrative summary of evidence on a given topic
- Usually written by an expert in the field
- Typically, involves informal and subjective methods to collect and interpret information

Shortcomings of poorly conducted reviews

"Methodological research found that the traditional approach may be biased, leading to false conclusions and potentially serious consequences"

Antman et al, 1992

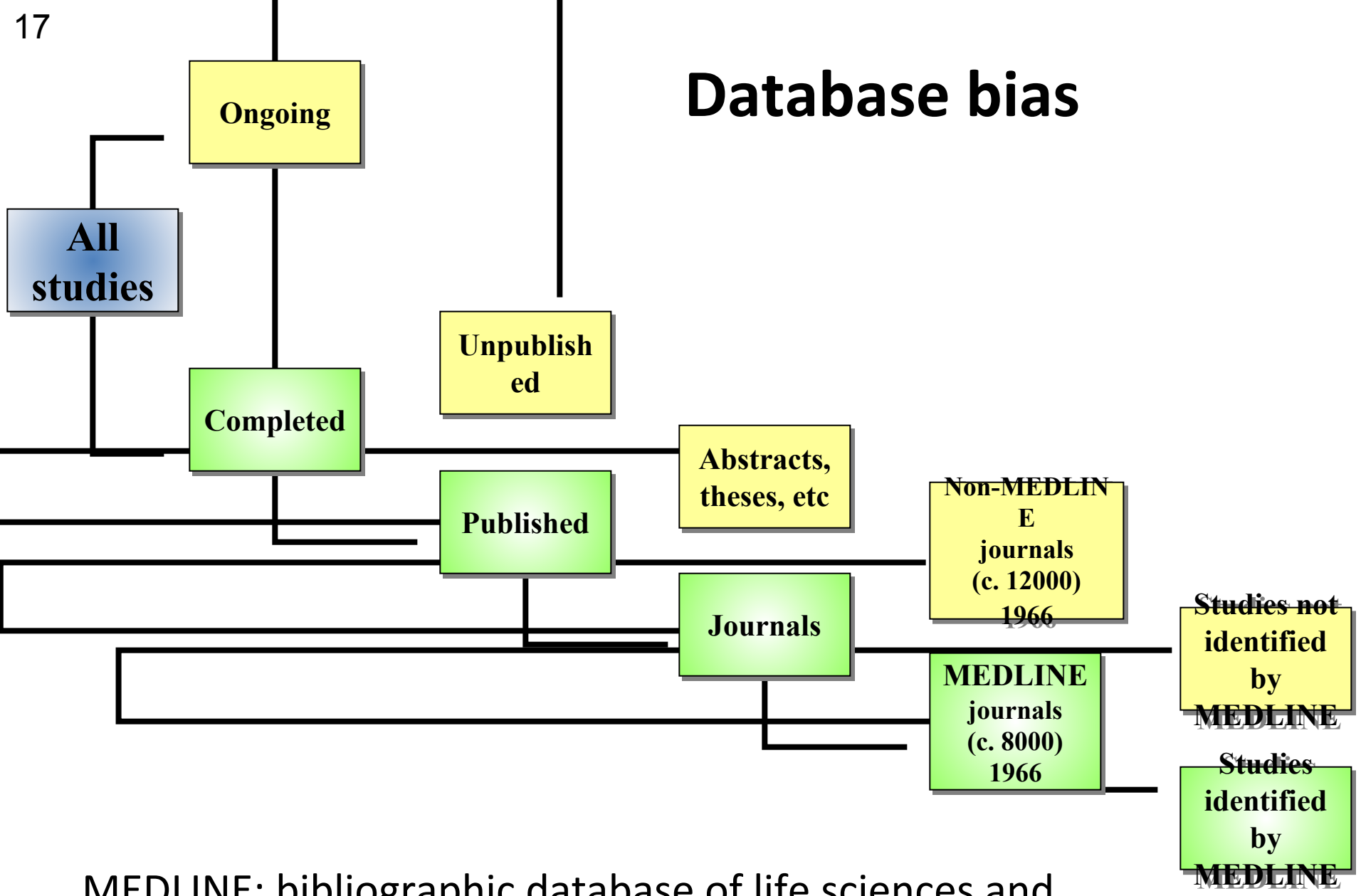
Personal (File Drawer) bias

Studies cited in reviews often reflect mainly the authors' perspectives, field, language and country

"The invited review? or, my field, from my standpoint, written by me using only my data and my ideas, and citing only my publications."

Caveman, Cell Sci 2000;113:3125-3126

Database bias



MEDLINE: bibliographic database of life sciences and biomedical information

Publication bias

Evidence from four "tracking" studies in the US, UK and Australia:

	Johns Hopkins University, Baltimore		Central Research Ethics Committee, Oxford	Royal Prince Alfred Hospital, Sydney
	Medicine	Public Health		
Reference	Dickersin *et al.*		Easterbrook *et al.*	Stern and Simes
Number approved	342 (100%)	172 (100%)	285 (100%)	321 (100%)
Period of approval	1980	1980	1984-87	1979-88
Years of followup	1988	1988	1990	1992
Published				
Full publication	230 (67%)	104 (61%)	138 (49%)	189 (59%)
Abstract only	36 (11%)	7 (4%)	69 (24%	n.a.
Other/unclear	11 (3%)	2 (1%)	0 (0%	0 (0%)
Unpublished	65 (19%)	59 (34%)	78 (27%)	132 (41%)

*n.a. = not assessed

Systematic Reviews in Health Care. Meta-analysis in Context.
M Egger, G Davey Smith, Doug Altman (eds). London: BMJ Books, 2001

Why are certain studies not published?

- Studies that have negative or disappointing results are less likely to be:
  - published in journals (Easterbrooke, Lancet 1991)
  - published in English (Egger, Lancet 1997)
  - published quickly (Stern, BMJ 1997)
  - published more than once (Tramèr, BMJ 1997)

Poor quality of research

- Fourth Congress on Peer Review in Biomedical Publication concluded that:
  - "Medical journals are full of serious methodological errors "
  - "Journal editors are giving no time, energy and thought to their craft"
  - "Studies are published that reach false conclusions"

BMJ, 22 September 2001:323

Methodological quality assessment = Crucial!

How can we make reviews more reliable?

Research synthesis

- Review (literature/traditional)
- Systematic review, Cochrane review, non-Cochrane systematic review
- Meta-analysis
- Pooled analysis
- Overview of systematic reviews
- Clinical/Public health guidelines

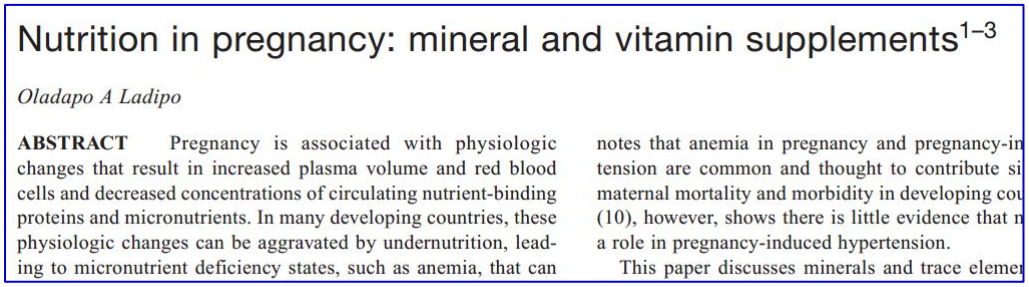
Systematic review

"A review in which bias has been reduced by the systematic identification, appraisal, synthesis, and, if relevant, statistical aggregation of all relevant studies on a specific topic according to a predetermined and explicit method"

Moher et al. Lancet 1999; 354: 1896-900

Key features of systematic reviews

- Clear set of objectives



Nutrition in pregnancy: mineral and vitamin supplements[1–3]

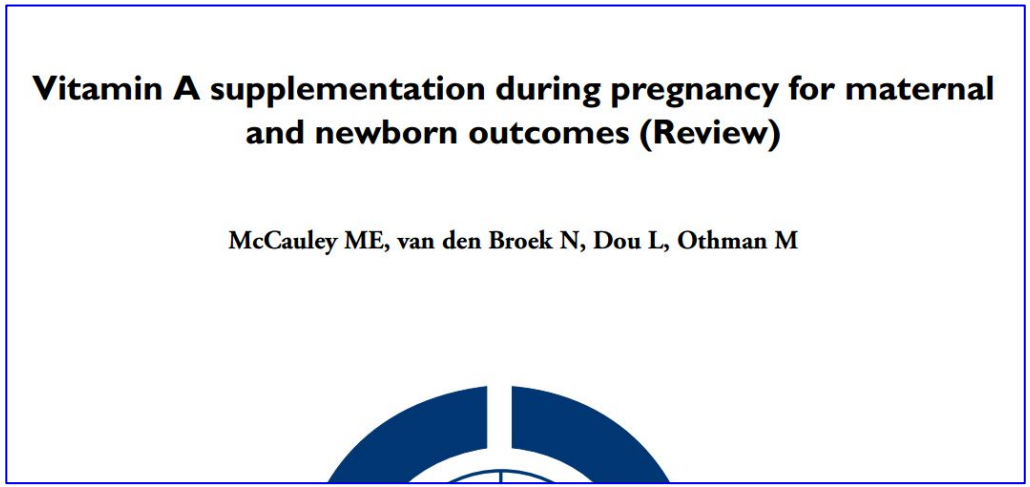
Oladapo A Ladipo

ABSTRACT Pregnancy is associated with physiologic changes that result in increased plasma volume and red blood cells and decreased concentrations of circulating nutrient-binding proteins and micronutrients. In many developing countries, these physiologic changes can be aggravated by undernutrition, leading to micronutrient deficiency states, such as anemia, that can

notes that anemia in pregnancy and pregnancy-in
tension are common and thought to contribute si
maternal mortality and morbidity in developing cou
(10), however, shows there is little evidence that n
a role in pregnancy-induced hypertension.

This paper discusses minerals and trace elemer

"This paper discusses minerals and trace elements as well as fat- and water-soluble vitamins in pregnancy—their concentrations, the requirements for them, the consequences of their deficiency, and the functional effects of supplementation with them."



Vitamin A supplementation during pregnancy for maternal and newborn outcomes (Review)

McCauley ME, van den Broek N, Dou L, Othman M

"To review the effects of supplementation of vitamin A, or one of its derivatives, during pregnancy, alone or in combination with other vitamins and micronutrients, on maternal and newborn clinical outcomes."

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Key features of systematic reviews

Explicit, reproducible methodology

- Predefined study eligibility criteria

METHODS

Criteria for considering studies for this review

Types of studies

Randomised or quasi-randomised controlled trials. Examp
quasi-random methods of assignment include alternation, c
birth, and medical record number. There were no restricti
language.

Types of participants

Current smokers, with no exclusions by age, gender, eth
language spoken or health status. We analyse stud
adolescents and young adults separately from the studies in
as both subgroups have particular needs which warrant se
investigation.

Types of interventions

We included studies evaluating Internet interventions

Types of outcome measures

The primary outcome is smoking cessation at least six months after the start of the intervention, and longer wherever the data were available. Where studies did not have follow-up of six months or longer, we report shorter-term outcomes narratively. We excluded trials with less than four weeks follow-up.We preferred sustained or prolonged cessation over point prevalence abstinence, but did not exclude studies which only reported the latter. We included studies that relied on self-reported cessation, as well as those that required biochemical validation of abstinence, but preferred biochemically-validated rates where available.

Taylor GMJ, Dalili MN, Semwal M, Civljak M, Sheikh A, Car J. Internet-based interventions for smoking cessation. *Cochrane Database of Systematic Reviews* 2017, Issue 9. Art. No.: CD007078. DOI: 10.1002/14651858.CD007078.pub5.

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Key features of systematic reviews

Explicit, reproducible me

- Comprehensive sear

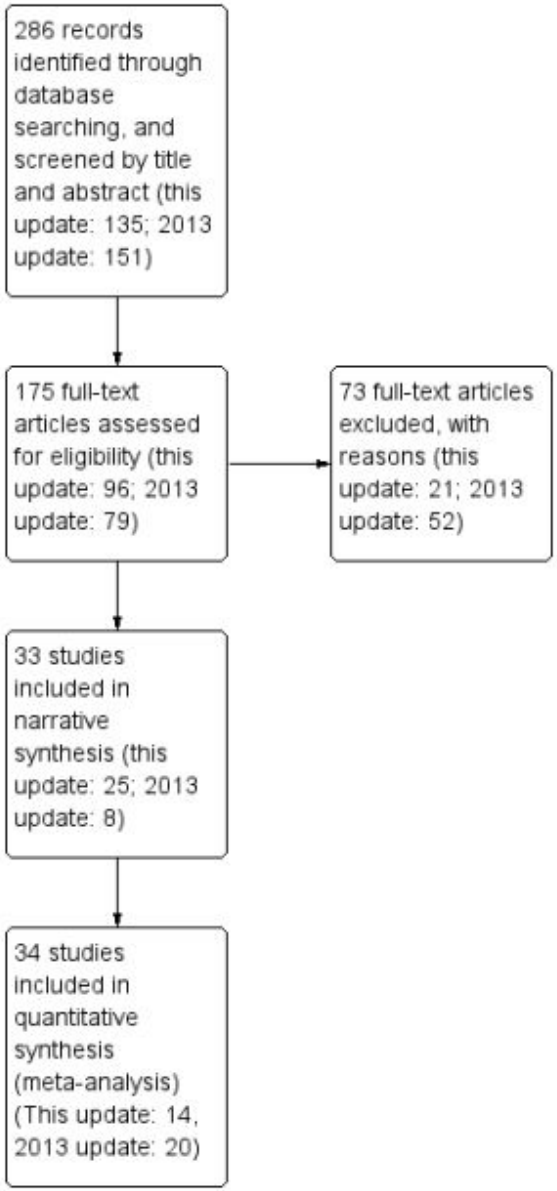
Search methods for identification of stu

Electronic Searches

We searched the specialised register of the Addiction Group for records including the 'www*' or 'web' or 'net' or 'online' , in th as keywords. The most recent search of the August 2016. At the time of the search th the results of searches of the Cochrane Controlled Trials (CENTRAL), issue 7, 2016; MED to update 20160729; Embase (through OVID PsycINFO (through OVID) to update 2016072 Addiction Group Module in the Cochrane Lib strategies and a list of other resources searche clinicaltrials.gov for records of relevant con studies.

Other Sources

We searched the reference lists of identified potentially relevant trials, and contacted autho field for unpublished work.



Key features of systematic reviews

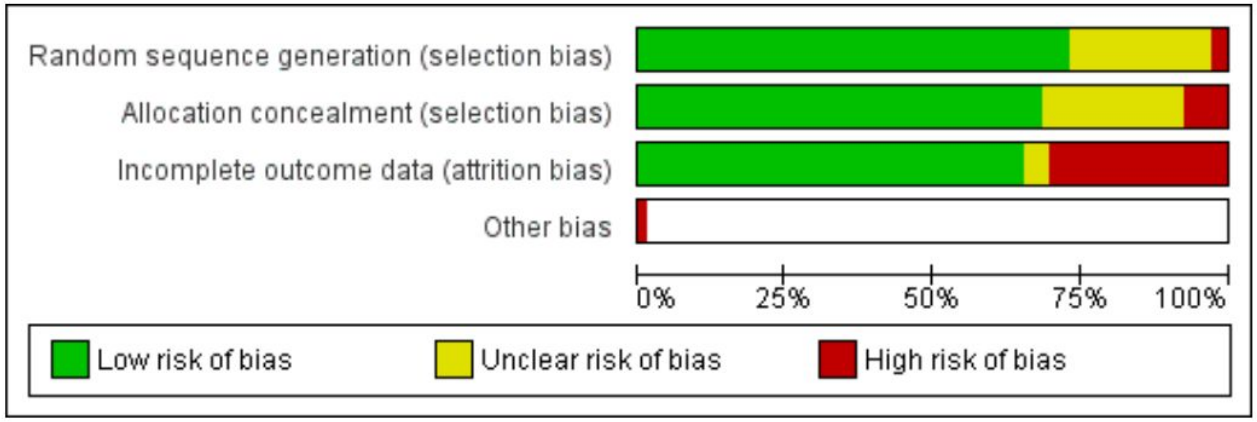
Explicit, reproducible methodology:

- Assessment of validity of study findings

Assessment of risk of bias in included studies

Two review authors independently assessed the risks of bias for each study, using the Cochrane 'Risk of bias' tool (Higgins 2011) for each study according to the presence and quality of the randomisation process, concealment of allocation, and description of withdrawals and dropouts.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



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Key features of systematic reviews

Explicit, reproducible methodology

- Appropriate quantitative and qualitative synthesis of findings

Data synthesis

We separated trials in adolescents from those in young adults and older adults. We distinguished between tailored or interactive and non-tailored, non-interactive interventions. In the five comparisons for which we judged meta-analysis to be appropriate, we pooled the weighted average of risk ratios, using a Mantel-Haenszel fixed-effect model, with a 95% confidence interval. Where there were 10 or more of studies we planned to use funnel plots to help identify possible publication bias, but there were not enough studies reporting any individual outcome for us to do this.

Sensitivity analysis

We used sensitivity analyses to investigate the impact of using data from complete cases (i.e. including only participants who were followed up) as compared to our primary ITT analysis which assumes that those who dropped out or who were lost to follow-up were continuing smokers.

Summary of findings table

We created a 'Summary of findings' table in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication

Key features of systematic reviews

Systematic, complete presentation of the findings

RESULTS

Description of studies

Across the updates we found 286 p through database searching, and scr abstract (this update: 135; 2013 updat spread across more than one record. articles for eligibility (this update: 9 excluded 73 full-text articles, with reas update: 52). A full list of these studi exclusion can be found in the Charact table. Sixty-seven studies met the inc

Effects of interventions

See: **Summary of findings for the main comparison** Internet-based interventions for adults who want to stop smoking

Smoking cessation

Internet intervention compared to non-active control

Trials in adults

We divided studies eligible for meta-analysis into three groups:

(1) Interactive and tailored Internet-based intervention (Haug 2011; Elfeddali 2012; Borland 2013; Emmons 2013; Harrington 2016; Skov-Ettrup 2016; Smit 2016; Yang 2016);
(2) Interactive but not tailored Internet-based intervention (McDonnell 2011);
(3) Neither interactive nor tailored Internet-based intervention (Humfleet 2013).

Five studies were lifestyle interventions (Oenema 2008; Epton 2014; Zullig 2014; Cameron 2015; Voncken-Brewster 2015), and four had follow-up of less than six months (Swartz 2006; Mehring 2014; Shuter 2014; Wittekind 2015).

Interactive and tailored Internet-based intervention

Pooled results demonstrated an effect in favour of the intervention (risk ratio (RR) 1.15, 95% confidence interval (CI) 1.01 to 1.30, Analysis 1.1, 8 studies, n = 6786). However, results should be interpreted with caution, as statistical heterogeneity was high (I^2 = 58%) and was unexplained despite perceived clinical homogeneity,

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Why are systematic reviews important?

- A readable summary of **ALL** the evidence
- Efficient way to access the body of research
  - saves time required for reading individual studies
  - critical appraisal
  - interpretation of results
- Explore differences between studies
- Reliable basis for decision making
  - unbiased selection of relevant information
  - useful for health care, policy, future research
- Transparent
- Up-to-date

Cochrane reviews

- A **systematic review** produced by the Cochrane
- Standardized format
- Extensive peer review
- Published electronically on the Cochrane Library (indexed in Medline)
- Invites comments and criticism
- Kept up-to-date
- Quality and reporting on average better than other systematic reviews

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- International non-profit organisation.

Vision

- A world of improved health where decisions about health and health care are informed by high-quality, relevant and up-to-date synthesised research evidence.

Mission

- To promote evidence-informed health decision making by producing high-quality, relevant, accessible systematic reviews and other synthesised research evidence.

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Steps of a Cochrane systematic review

1. Define the question → register title
2. Plan eligibility criteria
3. Plan methods → publish protocol
4. Search for studies
5. Apply eligibility criteria
6. Collect data
7. Assess studies for risk of bias
8. Analyse and present results
9. Interpret results and draw conclusions → publish review
10. Improve and update review → publish update

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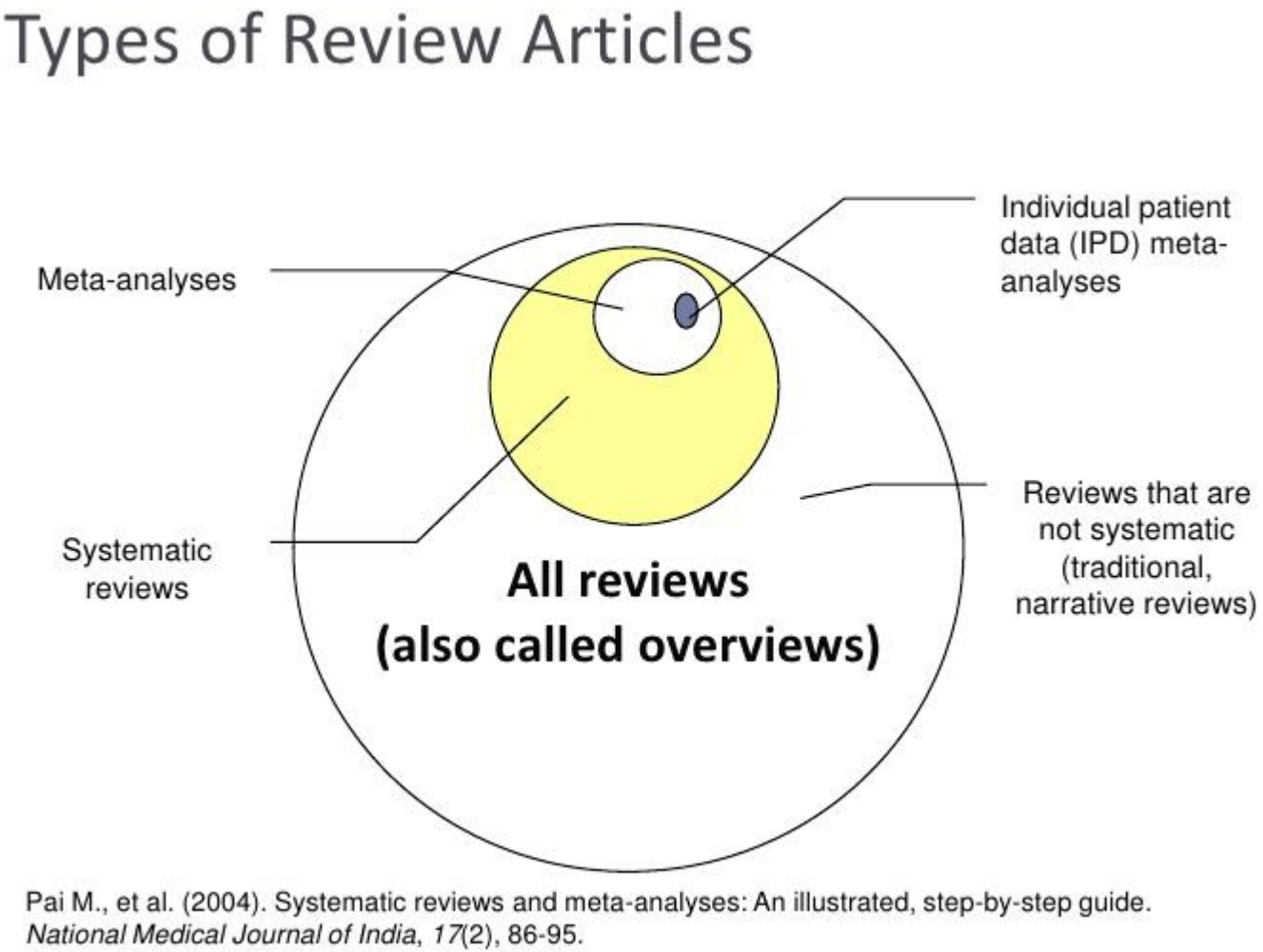
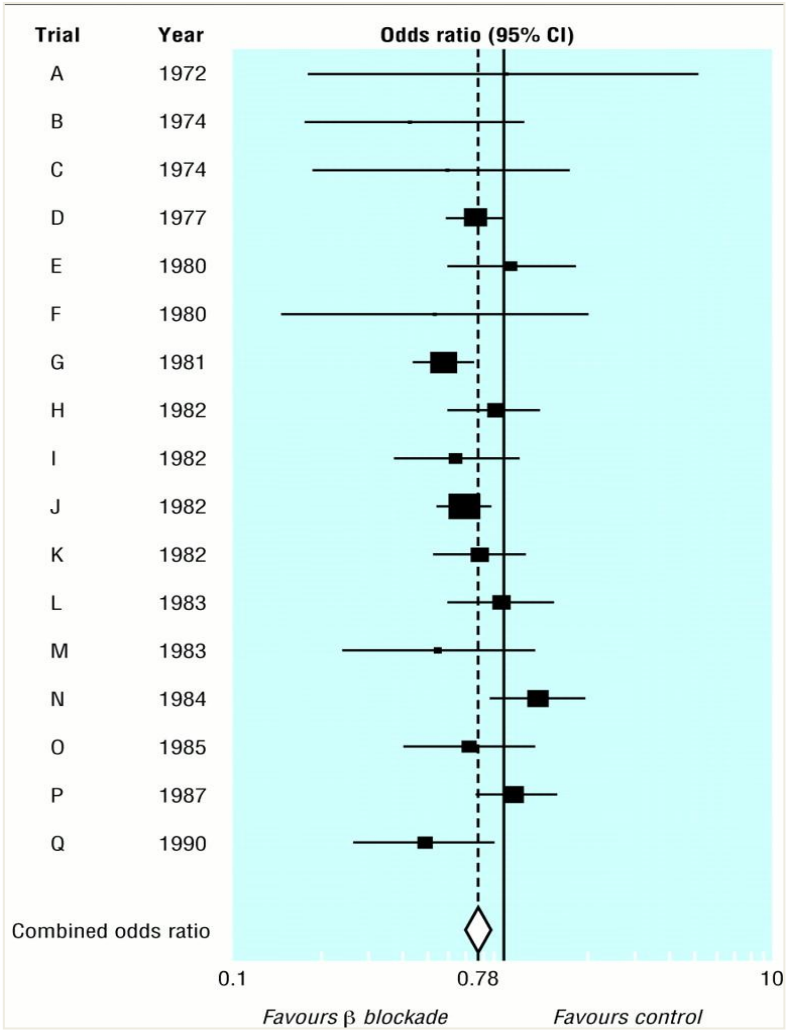
Meta analysis ≠ systematic review



Pai M., et al. (2004). Systematic reviews and meta-analyses: An illustrated, step-by-step guide. *National Medical Journal of India*, *17*(2), 86-95.

Systematic Review vs. meta-analysis

- A **meta-analysis** is *"a statistical procedure that integrates the results of several independent studies considered to be combinable."* Egger et al, BMJ 1997
- If appropriate, meta-analysis **can** be part of a systematic review
- Illustrated using a **forest plot**



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Internet-based interventions for smoking cessation (Review)

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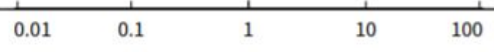
PICO of the review

Item	Description
Population	Current smokers, with no exclusions by age, gender, ethnicity, language spoken or health status.
Intervention	Internet interventions in all settings and from all types of providers interactive, tailored and non-interactive interventions that focused on standard approaches to information delivery.
Comparison	No treatment or other forms of treatment, such as self-help booklets.
Outcomes	Primary: smoking cessation at least six months after the start of the intervention

What is the comparison?

Analysis 3.1. Comparison 3 Internet plus behavioural support, Outcome 1 Smoking cessation at 6 months+ follow-up (adults) versus non-Internet-based non-active control.

Study or subgroup	Internet n/N	No Internet n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brendryen 2008a	29/144	10/146		11.76%	2.94[1.49,5.81]
Brendryen 2008b	44/197	26/199		30.62%	1.71[1.1,2.66]
Borland 2013	66/784	26/422		40.02%	1.37[0.88,2.12]
Burford 2013	11/80	1/80		1.18%	11[1.45,83.21]
Smit 2016	14/163	12/119		16.42%	0.85[0.41,1.77]
Total (95% CI)	**1368**	**966**		**100%**	**1.69[1.3,2.18]**
Total events: 164 (Internet), 75 (No Internet)					
Heterogeneity: $Tau^2=0$; $Chi^2=10.08$, df=4(P=0.04); $I^2=60.3\%$					
Test for overall effect: Z=3.99(P<0.0001)					



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What is the outcome?

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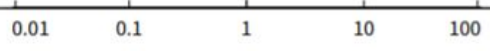

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How many studies included?

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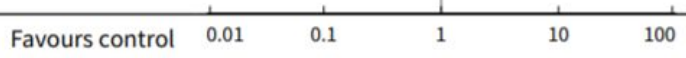

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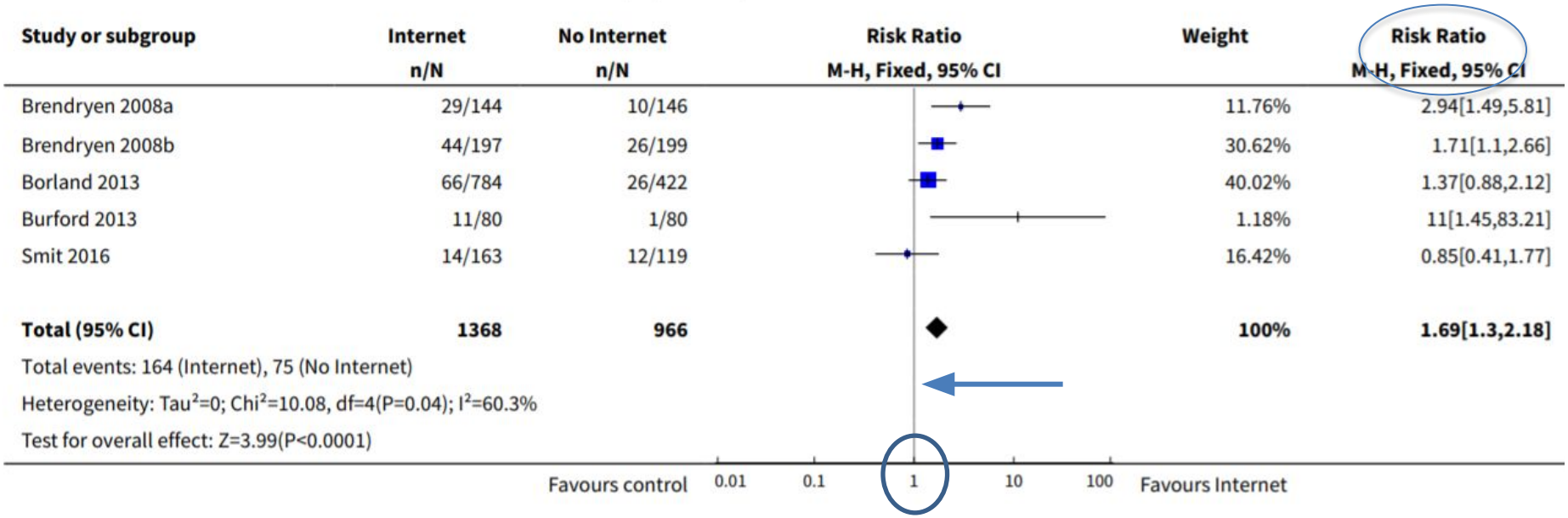
What is the effect measure?

Analysis 3.1. Comparison 3 Internet plus behavioural support, Outcome 1 Smoking cessation at 6 months+ follow-up (adults) versus non-Internet-based non-active control.



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Test for overall effect: Z=3.99(P<0.0001)					

What is the effect of the intervention?

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Brendryen 2008a	29/144	10/146		11.76%	2.94[1.49,5.81]

What was the Risk of smoking cessation in participants who received internet + behavioural support? 29/144 = 0.20 (20%)

What was the 'Risk' of smoking cessation in participants who received the control? 10/146 = 0.069 (6.9%)

What is the Risk Ratio of smoking cessation with internet + behavioral support compared to control? RR = 0.2/0.069 = 2.9

What does this mean? Internet + behavioural support increases the 'risk' of smoking cessation at 6months+ almost 3 fold compared to no intervention

Analysis 3.1. Comparison 3 Internet plus behavioural support, Outcome 1 Smoking cessation at 6 months+ follow-up (adults) versus non-Internet-based non-active control.

Study or subgroup	Internet n/N	No Internet n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brendryen 2008a	29/144	10/146		11.76%	2.94[1.49,5.81]

What is the Confidence Interval?

- 95% CI: 1.49 ; 5.81.

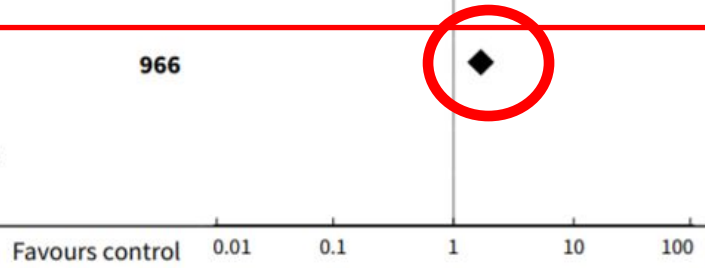
What does this mean?

- Internet + behavioural support interventions may increase the risk of smoking cessation by as little as 1.5 fold compared to not receiving supplements or by as much as much as 5.8 fold compared to not receiving an intervention
- The CI does not cross the line of no effect
- Statistically different effect of internet + behaviour support intervention on smoking cessation

What is the pooled effect?

Analysis 3.1. Comparison 3 Internet plus behavioural support, Outcome 1 Smoking cessation at 6 months+ follow-up (adults) versus non-Internet-based non-active control.

Study or subgroup	Internet n/N	No Internet n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Brendryen 2008a	29/144	10/146		11.76%	2.94[1.49,5.81]
Brendryen 2008b	44/197	26/199		30.62%	1.71[1.1,2.66]
Borland 2013	66/784	26/422		40.02%	1.37[0.88,2.12]
Burford 2013	11/80	1/80		1.18%	11[1.45,83.21]
Smit 2016	14/163	12/119		16.42%	0.85[0.41,1.77]
Total (95% CI)	**1368**	**966**		**100%**	**1.69[1.3,2.18]**
Total events: 164 (Internet), 75 (No Internet)					
Heterogeneity: $Tau^2=0$; $Chi^2=10.08$, df=4(P=0.04); $I^2=60.3\%$					
Test for overall effect: Z=3.99(P<0.0001)					



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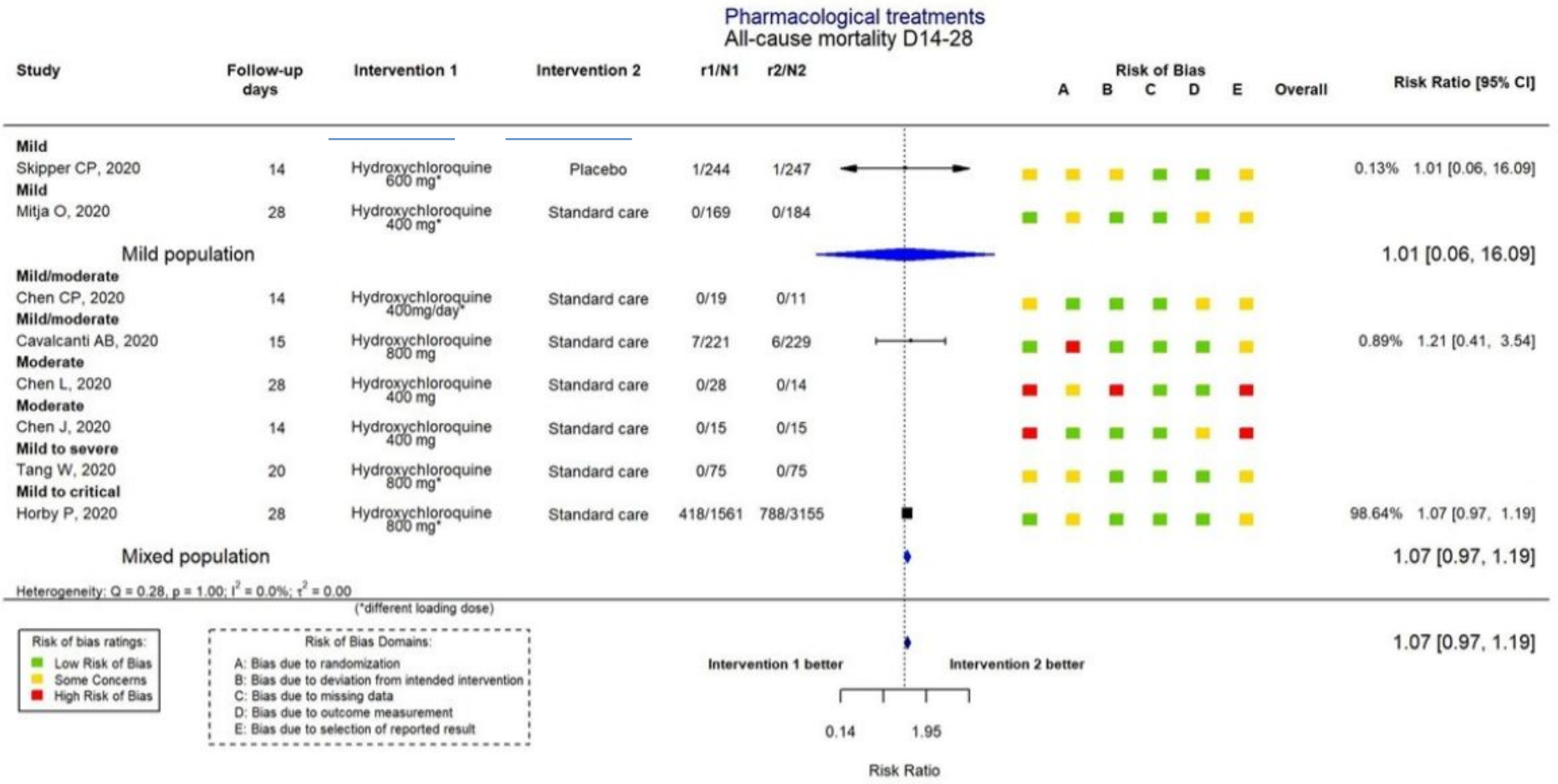
Hydroxychloroquine vs Standard Care/Placebo



https://covid-nma.com/living_data/index.php?comparison=3

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Other effect measures

- Dichotomous data
  - Risk Ratio (RR)
  - Odds Ratio (OR)
  - Risk Difference (RD)

- Continuous data
  - Mean difference (MD)
  - Standardised mean difference (SMD)

- Time to event data
  - Hazard ratios (HR)

Odds ratio

Mean difference

Analysis 1.5. Comparison 1 Macronutrient supplementation, Outcome 5 Mean weight gain.

Review: Nutritional supplements for people being treated for active tuberculosis

Comparison: 1 Macronutrient supplementation

Outcome: 5 Mean weight gain

Study or subgroup	Supplement N	Supplement Mean(SD)	No supplement N	No supplement Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 After 6 weeks							
Paton 2004 SGP (1)	19	2.57 (1.78)	15	0.84 (0.89)		100.0 %	1.73 [0.81, 2.65]
Subtotal (95% CI)	**19**		**15**			**100.0 %**	**1.73 [0.81, 2.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.69 (P = 0.00022)							
2 After 8 weeks							
Jeremiah 2014 TZA (2)	48	56.2 (12.7)	44	55.1 (9.4)		3.3 %	1.10 [-3.44, 5.64]
Martins 2009 TLS (3)	136	5.2 (6.2)	129	3.5 (6.3)		27.1 %	1.70 [0.19, 3.21]

Mean weight gain in supplement group? 5.2 kg

Mean weight gain in no supplement group? 3.5 kg

Mean difference in weight gain between groups: 5.2kg – 3.5kg = 1.7 kg

What does this mean?

Macronutrient supplementation results, on average, in weight gain of 1.7kg more compared to no supplementation

Analysis 1.5. Comparison 1 Macronutrient supplementation, Outcome 5 Mean weight gain.

Review: Nutritional supplements for people being treated for active tuberculosis

Comparison: 1 Macronutrient supplementation

Outcome: 5 Mean weight gain

Study or subgroup	Supplement N	Mean(SD)	No supplement N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
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Subtotal (95% CI)	**19**		**15**			**100.0 %**	**1.73 [0.81, 2.65]**
Heterogeneity: not applicable							
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Martins 2009 TLS (3)	136	5.2 (6.2)	129	3.5 (6.3)		27.1 %	1.70 [0.19, 3.21]

What about the confidence interval?

Macronutrient supplementation increases weight gain from 190 grams up to 3.21 kg.

MD does not cross line of no effect = statistically significant result

Test for overall effect: Z = 5.90 (P < 0.00001)

-4 -2 0 2 4

Favours no supplement Favours supplement

Analysis 1.5. Comparison 1 Macronutrient supplementation, Outcome 5 Mean weight gain.

Review: Nutritional supplements for people being treated for active tuberculosis

Comparison: 1 Macronutrient supplementation

Outcome: 5 Mean weight gain

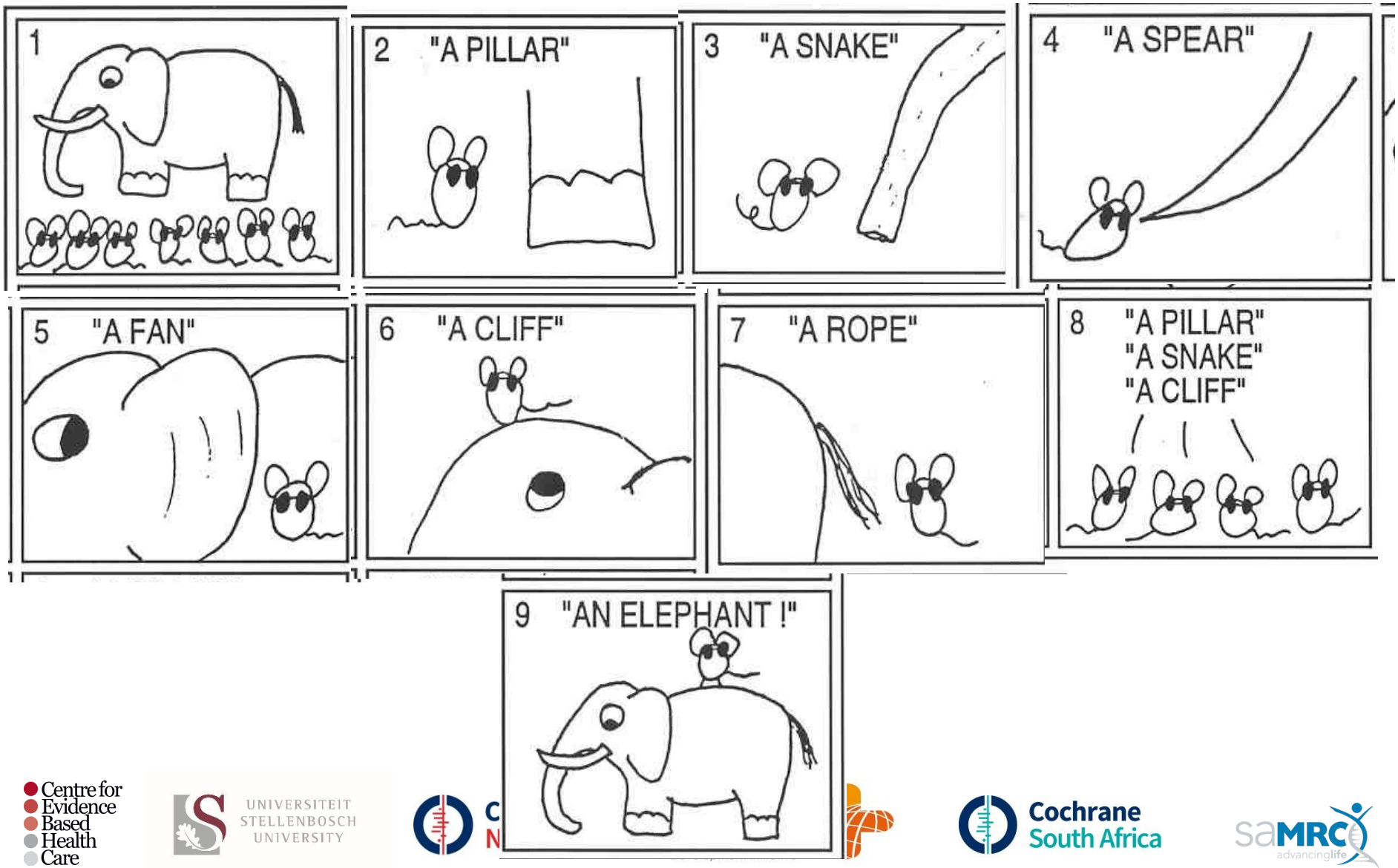
Study or subgroup	Supplement N	Mean(SD)	No supplement N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 After 6 weeks							
Paton 2004 SGP (1)	19	2.57 (1.78)	15	0.84 (0.89)		100.0 %	1.73 [0.81, 2.65]
Subtotal (95% CI)	**19**		**15**			**100.0 %**	**1.73 [0.81, 2.65]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.69 (P = 0.00022)							
2 After 8 weeks							
Jeremiah 2014 TZA (2)	48	56.2 (12.7)	44	55.1 (9.4)		3.3 %	1.10 [-3.44, 5.64]
Martins 2009 TLS (3)	136	5.2 (6.2)	129	3.5 (6.3)		27.1 %	1.70 [0.19, 3.21]
Praygod 2011b TZA (4)	166	2.9 (3.94)	166	2.5 (3.94)		69.6 %	0.40 [-0.45, 1.25]
Subtotal (95% CI)	**350**		**339**			**100.0 %**	**0.78 [-0.05, 1.60]**
Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 2.20$, $df = 2$ (P = 0.33); $I^2 = 9\%$							
Test for overall effect: Z = 1.83 (P = 0.067)							

What is the pooled effect for subgroup 2?

MD = 0.78

95% CI: -0.05, 1.6

Of Mice and Meta-Analysis
The Allegory of the Seven Blind Mice



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