What is a systematic review?
Vitamin pills ‘can increase the risk of early death’

Pope tells of his shame

I mean to continue, insists bruised Brown

Bad science

Celebs decry evidence on vitamin pills

Ben Goldacre

Review said vitamin pills may increase risk of dying Photograph: Fiona Hanson/PA
Antioxidant supplements for prevention of mortality in healthy participants and patients with various diseases (Review)

Bjelakovic G, Nikolova D, Gluud LL, Simonetti RG, Gluud C

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2010, Issue: 1

http://www.thecochranelibrary.com
**Systematic review - Wikipedia, the free encyclopedia**
en.wikipedia.org/wiki/Systematic_review

A **systematic review** is a literature review focused on a research question that tries to identify, appraise, select and synthesize all high quality research evidence ...

**Characteristics** - Cochrane Collaboration - Strengths and weaknesses - See also

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Cochrane Database of **Systematic Reviews**, Issue 11 of 12, Nov 2012 | ... Other Reviews (DARE) Issue 4 of 4, Oct 2012. Methods Studies Issue 4 of 4, Oct 2012 ...

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About Cochrane **Systematic Reviews** and Protocols What is a systematic review A **systematic review** attempts to identify, appraise and synthesize all the ...

**Systematic Reviews - NIHR**
www.nihr.ac.uk › Home › Research

**Systematic reviews** identify, evaluate, combine and summarise the findings of all relevant individual studies and, when carried out well, provide decision-makers ...

**Systematic Reviews**
www.systematicreviewsjournal.com/

**Systematic Reviews** encompasses all aspects of the design, conduct and reporting of **systematic reviews**. The journal aims to publish high quality systematic ...

**[PDF] What is a systematic review? - Medical Sciences Division ...**
www.medicine.ox.ac.uk/bandolier/painres/download/.../syst-review.p...

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by P Hemingway - Related articles

research evidence. ○ **Systematic reviews** attempt to bring the same level of rigour to ...

one review it is called a mixed-method **systematic review**. ○ Systematic ...
Where do I find the best evidence?

The Literature

• Information overload
• 2 million articles published a year
• 20,000 biomedical journals
• 500 dental journals
• Unpublished studies
• Language
Where do I find the best evidence?

Textbooks/Reviews

- Written by “experts”
- Quickly out of date
Where do I find the evidence?

- Ask someone
- Look in filing cabinet
- Consult a text book
- Search an electronic database
  - Bibliographic- *Medline, Embase, Lilacs*
  - Secondary publications- *Cochrane, Database of Systematic Reviews*
Where do I find the best evidence?  
Electronic Databases

- Identify <50% of available relevant articles
- Most missed citations are on Medline
- Indexing is poor
- Title, abstract and ‘key words’
- Structured abstracts
Where do I find the best evidence?

Hand Searching

• Only reliable way to identify all relevant articles
• Boring, tedious and time consuming
• Must try to avoid duplication of effort
One solution to this problem is using systematic reviews of the evidence.
What are systematic reviews?

- A systematic review is the process of systematically locating, appraising and synthesising evidence from scientific studies in order to obtain a reliable overview.
Terminology: systematic review & meta analyses

Systematic reviews

Meta-analyses
How are Systematic Reviews different?

**Traditional reviews**
- Individual opinions based on haphazardly selected data rather than comprehensive systematic assessment
- Inconsistent, prone to error and unconvincing

**Systematic reviews**
- Prepared as methodically and as carefully as a piece of primary research
- Describe how trials were identified, selected and evaluated
- Checked and verified
Why are they important?

- Reduce large quantities of information into manageable portions
- Formulate policy and develop guidelines
- Efficient use of resources
- Increased power/precision
- Limit bias and improve accuracy
Antman 1992 examined the treatment of acute myocardial infarction and compared:

- Recommendations in textbooks and reviews
- Results of meta analysis (if they had been done)
A. Thrombolytic Therapy (clot-busters)

Odds Ratio (Log Scale)

<table>
<thead>
<tr>
<th>Year</th>
<th>RCT</th>
<th>Pts</th>
</tr>
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<tbody>
<tr>
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<td>1</td>
<td>23</td>
</tr>
<tr>
<td>1965</td>
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<td>5767</td>
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<td>1985</td>
<td>33</td>
<td>6571</td>
</tr>
<tr>
<td>1990</td>
<td>70</td>
<td>48154</td>
</tr>
</tbody>
</table>

Favors Treatment  Favors Control

Textbook/Review Recommendations

<table>
<thead>
<tr>
<th>Routine</th>
<th>Specific</th>
<th>Rare/Never</th>
<th>Experimental</th>
<th>Not Mentioned</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>21</td>
<td>8</td>
<td>110</td>
<td>2</td>
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<td>1</td>
<td>2</td>
<td>1</td>
<td></td>
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<tr>
<td></td>
<td>2</td>
<td>8</td>
<td>7</td>
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<td>1</td>
<td>7</td>
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<td>5</td>
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<td>2</td>
<td></td>
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<tr>
<td></td>
<td>15</td>
<td>8</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Results

• Discrepancies between meta-analysis and recommendations by reviewers

• Review articles failed to mention important new advances and delayed recommending effective preventive measures

• Harmful treatments continued to be recommended by experts
Systematic review process

- Structured process involving several steps (all described in review protocol):

1. Well formulated question
2. Comprehensive data search
3. Unbiased selection and abstraction process
4. Assessment of papers
5. Synthesis of data
1. Well formulated question

How effective is flossing in addition to toothbrushing, as compared with toothbrushing alone, in the management of bleeding gums and tooth decay?
1. Well formulated question

- Participants
- Interventions (Exposure)
- Comparisons
- Outcomes
This question is...

• The lynchpin of a systematic review protocol

• Leads on to inclusion and exclusion criteria

• Helps build up a search strategy

• Gets authors thinking about what data to extract, and what quality criteria are important

• Allows authors to decide on their analysis now
Inclusion criteria | Specifics

• Participants
  – All ages? People with restricted dexterity? orthodontic patients?

• Interventions
  – Self performed (supervised)? Mouthrinses?

• Comparisons
  – Toothbrushing with out flossing- is rinsing OK

• Outcomes
  – number of bleeding sites, side effects? costs?
Hierarchy of evidence

- RCT
- Cohort
- Case-control
- Cross-sectional survey
- Case-series/report
- Expert opinion

STRONG

WEAK
Meta-analysis of association between β carotene intake and cardiovascular mortality

Egger 1998 BMJ
**Cohorts**
- Male health workers (United States)
- Male social insurance workers (Finland)
- Female social insurance workers (Finland)
- Male chemical workers (Switzerland)
- Hyperlipidaemic men (United States)
- Nursing home residents (United States)

**Trials**
- Male smokers (Finland)
- Patients with skin cancer (United States)
- Former smokers, asbestos workers (United States)
- Male physicians (United States)

**Relative risk (95% CI)**
Meta-analysis of association between β-carotene intake and cardiovascular mortality

• Results from observational studies show considerable benefit, whereas the findings from randomised controlled trials show an increase in the risk of death
Possible scenarios

• **Question not related to effectiveness of an intervention**
  – Associations between gum disease and risk of heart disease, low birth weight babies and stroke.

• **RCTs not feasible in area of study**
  – Water fluoridation

• **No/limited RCTs**
  – Effectiveness of physiotherapy, occupational therapy, and speech pathology for people with Huntington's disease.
2. Search strategy

• Needs to be as **comprehensive** as possible

• Consider:
  
  – Electronic databases (Cochrane Controlled Trials Register, Medline, Embase);
  
  – Reference lists;
  
  – Handsearching;
  
  – English language/non-English language;
  
  – Sources of ongoing and/or unpublished studies
Reporting biases

- Statistically significant ‘positive’ results are:
  - more likely to be published
    - publication bias
  - more likely to be published rapidly
    - time lag bias
  - more likely to be published in English
    - language bias
  - more likely to be cited by others
    - citation bias
Publication bias | an example

- Systematic review of reboxetine, a third-generation anti-depressant

- **13 trials**, published and unpublished data

- **74%** of patient data *previously unpublished*

- Reboxetine is “*overall an ineffective and potentially harmful antidepressant*”

- **Contradicts findings of previous reviews** which considered only published data

_Eyding et al, BMJ 2010_
Registered trials

- Trials registries
  - clinicaltrials.gov

- The Declaration of Helsinki states:
  
  "Every clinical trial must be registered in a publicly accessible database before recruitment of the first subject."

- International Committee of Medical Journal Editors (ICMJE)
Registered trials

- 50% of trials supporting drugs that are approved by the U.S. Food and Drug Administration (FDA) remain unpublished 5 years after drug approval

*Bourgeois et al, Ann Intern Med. 2010*
PRISMA 2009 Flow Diagram

Records identified through database searching (n = )

Additional records identified through other sources (n = )

Records after duplicates removed (n = )

Records screened (n = )

Records excluded (n = )

Full-text articles assessed for eligibility (n = )

Full-text articles excluded, with reasons (n = )

Studies included in qualitative synthesis (n = )

Studies included in quantitative synthesis (meta-analysis) (n = )
3. Unbiased selection and data extraction process

- Selection of relevant papers
- Data extraction using predefined data extraction form
- Process should be conducted independently by at least two reviewers
4. ‘Quality’ assessment of included studies

- Process should be conducted independently by at least two reviewers
- Results of the assessment should be reflected in the analysis
‘Quality’ assessment tools

• **Composite scales**
  
  – assign numerical value to individual items to provide overall estimate of quality – *problematic*

• **Component approach**
  
  – assesses relevant methodological aspects individually (*e.g.* randomisation, blinding, drop-outs) - *preferred*
Risk of bias assessment

• Bias determines the **extent to which results of studies can be believed**. A study conducted to the highest possible standards can still have risk of bias.

• **Direction of bias**: causes overestimation or underestimation of effect

• **Magnitude of bias**
<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation <em>(selection bias)</em></td>
<td>Unclear risk</td>
<td>&quot;Subjects were randomly assigned to one of the five test groups...&quot;</td>
</tr>
<tr>
<td>Allocation concealment <em>(selection bias)</em></td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding - Outcome assessors</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding - Participants</td>
<td>Unclear risk</td>
<td>Unclear</td>
</tr>
<tr>
<td>Incomplete outcome data <em>(attrition bias)</em></td>
<td>Low risk</td>
<td>Exact number of subjects lost to follow-up in each of the groups cannot be ascertained from the report. The total number of subjects lost to follow-up was 3 out of 161, so attrition seems low and therefore unlikely to affect the results.</td>
</tr>
<tr>
<td>Selective reporting <em>(reporting bias)</em></td>
<td>Low risk</td>
<td>No protocol available. All primary outcomes in the 'Methods' section were addressed in the 'Results'</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
<td>Compliance was not assessed, breakdown by gender not reported.</td>
</tr>
</tbody>
</table>
Risk of Bias

Summary Table

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding - Outcome assessors</th>
<th>Blinding - Participants</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogel 1975</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zimmer 2006</td>
<td>-</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

Summary Graph

- Green: Low risk of bias
- Yellow: Unclear risk of bias
- Red: High risk of bias
### 4.1.1 Manual flossing

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Mean (Flossing)</th>
<th>SD (Flossing)</th>
<th>Total</th>
<th>Mean (Control)</th>
<th>SD (Control)</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference (IV, Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finkelstein 1990</td>
<td>0.15</td>
<td>0.28</td>
<td>30</td>
<td>0.14</td>
<td>0.35</td>
<td>31</td>
<td>17.3%</td>
<td>0.01 [-0.15, 0.17]</td>
</tr>
<tr>
<td>Hague 2007</td>
<td>0.56</td>
<td>0.28</td>
<td>35</td>
<td>0.67</td>
<td>0.35</td>
<td>18</td>
<td>13.3%</td>
<td>-0.11 [-0.30, 0.08]</td>
</tr>
<tr>
<td>Jared 2005</td>
<td>1.29</td>
<td>0.7</td>
<td>29</td>
<td>1.56</td>
<td>0.64</td>
<td>32</td>
<td>4.5%</td>
<td>-0.27 [-0.61, 0.07]</td>
</tr>
<tr>
<td>Lobene 1982</td>
<td>0.65</td>
<td>0.17</td>
<td>85</td>
<td>0.84</td>
<td>0.18</td>
<td>33</td>
<td>49.1%</td>
<td>-0.19 [-0.26, -0.12]</td>
</tr>
<tr>
<td>Vogel 1975</td>
<td>0.16</td>
<td>0.28</td>
<td>6</td>
<td>0.22</td>
<td>0.35</td>
<td>6</td>
<td>4.0%</td>
<td>-0.06 [-0.42, 0.30]</td>
</tr>
<tr>
<td>Zimmer 2006</td>
<td>0.83</td>
<td>0.47</td>
<td>39</td>
<td>0.98</td>
<td>0.43</td>
<td>39</td>
<td>11.8%</td>
<td>-0.15 [-0.35, 0.05]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>224</strong></td>
<td></td>
<td></td>
<td><strong>159</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>-0.14 [-0.21, -0.06]</strong></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.00; \ Chi^2 = 6.01, \ df = 5 \ (P = 0.31); \ I^2 = 17\%$

Test for overall effect: $Z = 3.69 \ (P = 0.0002)$
THE COCHRANE COLLABORATION
Cochrane Collaboration

An international organisation that aims to help people make well-informed decisions about healthcare by preparing, maintaining and promoting the accessibility of systematic reviews of the effects of health care interventions.
The Cochrane Collaboration is an enterprise that rivals the Human Genome Project in its potential implications for modern medicine."

- The Lancet ¹
Further reading

- Cochrane Handbook (Higgins 2011)
  http://www.cochrane-handbook.org/


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