Global Systematic Reviews: How can it be done?

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Global Harmonization of Methodological Approach to Nutrient Intake Recommendations
FAO, Rome, Italy
Topics to be Discussed

- Importance of using systematic review (SR) and a harmonized protocol to review evidence
- A typical SR process
- Analytic framework to help identify SR questions
- An example of using an analytic framework to inform DRI development
- Tools for SR collaboration
- People needed in global SR collaboration
- Closing thoughts
My assumptions

• We have arrived at a stage in which the use and usefulness of systematic review (SR) to inform nutrition decisions is no longer debated
• Much of what has been learned (methods, processes) about SRs in the healthcare arena can be applied to the nutrition world
• Evidence is global, decision is local; the same evidence will be used to inform Nutrient Intake Recommendations
• Conducting a SR is laborious and requires a significant amount of resources (expertise, time, and money); thus it is desirable to minimize unnecessary replication of effort, and to collaborate and share resources
Discussion Paper 1: Lau J, Lichtenstein A. Evidence-based approach to nutrient hazard identification
• Growing international interest in the use of nutrient risk assessment to identify UL of intake for nutrient and related substances
• Need for a common approach
• Example: vitamin A reviews on bone effects
Different authoritative bodies came up with different Tolerable Upper Intake Level (UL) for vitamin A

- US – Institute of Medicine (IOM) (2001)
  - adults - 3000 ug/d
- EU – Scientific Committee on Food (SCF) (2002)
  - postmenopausal women should restrict their intake to 1500 ug/d
  - evidence base inadequate to establish a UL; total intake >1500 ug/d may be inappropriate
Table 2. Vitamin A and bone density—References cited by three reports, sorted according to the type of study (animal, in-vitro, human)

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Type</th>
<th>Specifics</th>
<th>Outcome</th>
<th>EU</th>
<th>EVM</th>
<th>IOM</th>
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<tr>
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<td>Histopathological changes</td>
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<td>A</td>
<td>Rats</td>
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<td>A</td>
<td>Monkey</td>
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<td>Lapadula</td>
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<td></td>
<td>A</td>
<td>12 exp rabbit 4 controls</td>
<td>Vitamin A induced osteoarthritis; histopathological changes</td>
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<td></td>
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<td>Rats</td>
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<td>Bone culture</td>
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<td></td>
<td>I</td>
<td>Mouse calvarial bones</td>
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<td>H</td>
<td>Clinical trial of Ca⁺⁺ supplement in 99 women</td>
<td>Vit A and BMD</td>
<td>X</td>
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<td>Case reports</td>
<td>H</td>
<td>Several children</td>
<td>Bone changes</td>
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<td>1990</td>
<td>? Cohort</td>
<td>H</td>
<td>Postmenopausal</td>
<td>Vit A intake, radial bone mass, fracture history</td>
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<td>No bone outcome</td>
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<td>1992</td>
<td>National osteoporosis register</td>
<td>H</td>
<td>MEDOS study group</td>
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<td>X</td>
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<td>Melton</td>
<td>1995</td>
<td>Book chapter</td>
<td>H</td>
<td>? original data</td>
<td>Hip fracture rates of N. Am vs. Scandinavia</td>
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<td>Cohort</td>
<td>H</td>
<td>66 women premenopausal</td>
<td>Vitamin A intake and BMD</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Theiler</td>
<td>1995</td>
<td>Case reports</td>
<td>H</td>
<td>3 cases</td>
<td>Vit A intoxication is related to osteoarthritis</td>
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<td>1998</td>
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<td>H</td>
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<td>NHANES</td>
<td>H</td>
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<td>Retinyl esters and BMD</td>
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<td>X</td>
<td>?</td>
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<td>Johansson</td>
<td>2001</td>
<td>H</td>
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<td>9 volunteers</td>
<td>Vit A and D interaction</td>
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<td>Kawahara</td>
<td>2002</td>
<td>RCT</td>
<td>H</td>
<td>40 men</td>
<td>7.6 mg vit A retinyl palmitate x 6 wks and bone turnover</td>
<td>X</td>
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<td>Feskanich</td>
<td>2002</td>
<td>Cohort</td>
<td>H</td>
<td>Nurses’s Health Study &gt;7,200 W</td>
<td>Vit A intake, hip fractures</td>
<td>X</td>
<td>X</td>
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<td>Promislow</td>
<td>2002</td>
<td>Cohort</td>
<td>H</td>
<td>570 W, 388 M</td>
<td>Retinol intake, BMD</td>
<td>?</td>
<td>X</td>
<td>?</td>
</tr>
</tbody>
</table>

A – animal; H – human; I – in-vitro; BMD – bone mineral density; ? – the report probably was completed prior to this publication.
Observations based on literature cited

• Different workgroups used different set of studies
• Unclear inclusion/exclusion criteria
• Unclear how included studies were used in supporting recommendations
Thoughts on how the three international groups arrived at different recommendations

- The lack of a predefined analytic framework affected the selection of specific outcomes to assess evidence.

- The lack of a common set of research questions and review criteria led to the selection of different studies.

- The use of different types (in-vitro, animal, human) of studies and the different emphasis placed on the evidence might have led to different interpretations of the data and characterization of the hazard.

- Composition of the workgroups might be different; different types of experts might weight evidence differently.
A typical systematic review process
Agency for Healthcare Research and Quality (AHRQ) evidence report

- Prepare topic:
  - Refine key questions
  - Develop analytic frameworks

- Search for and select studies:
  - Identify eligibility criteria
  - Search for relevant studies
  - Select evidence for inclusion

- Abstract data:
  - Extract evidence from studies
  - Construct evidence tables

- Analyze and synthesize data:
  - Assess quality of studies
  - Assess applicability of studies
  - Apply qualitative methods
  - Apply quantitative methods (meta-analyses)
  - Rate the strength of a body of evidence

- Present findings

Not shown on this slide are the steps of: identifying a SR team, forming a Technical Expert Panel (TEP), performing peer review of the draft report.
Also importantly, an evidence report does not constitute clinical or policy recommendations.
Timeline and tasks of a hypothetical systematic review
Analytic Framework

• A (visual) technique used to clarify and generate SR questions

• Relevant questions are formulated and organized into a model that analyzes all effects and interactions between intervention or exposure and outcomes
Generic Analytic Framework

effects or associations of nutrient with health outcomes

Arrow 1: Association of exposure with clinical outcomes of interest.

Arrow 2: Association of exposure with surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).

Arrow 3: Association of indicators of exposure to clinical outcomes.

Arrow 4: Association between exposure and indicators of exposure.

Arrow 5: Association of indicators of exposure to surrogate or intermediate outcomes (with good or possible evidence for linkage with clinical outcomes).

Arrow 6: Association between surrogate outcomes (with good or possible evidence for linkage) and clinical outcomes.
Values of Analytic Framework

- Help to define scope of evidence review, helps to construct evidence maps
- Uses experts efficiently
- The framework and process can be open to public review and provides transparency and minimizes biases
- Can help to highlight what aspects are known and unknown
- Can clarify what study designs may be best to address specific questions
- Facilitates future updates as new evidence emerges
Analytic Framework for Vitamin D and/or Calcium Health Outcomes

Vitamin D2, D3, 25(OH)D
Calcium

25(OH)D; 1,25(OH)D
Calcium balance

Hypertension
BMD, BMC

Bone health
CVD

Cancer
Muscle Function

Immune Outcomes

Pregnancy Outcomes
All cause mortality

Body weight, BMI; Growth

Blood Pressure
Breast milk or infant circulating levels

Cancer markers

UV exposure
Foods & supplements

Arrow 1
Arrow 2
Arrow 4
Arrow 5
Arrow 6
Key Question 1. What is the effect of vitamin D, calcium, or combined vitamin D and calcium intakes on clinical outcomes, including growth, cardiovascular diseases, weight outcomes, cancer, immune function, pregnancy or birth outcomes, mortality, fracture, renal outcomes, and soft tissue calcification?
Key Question 2. What is the effect of vitamin D, calcium or combined vitamin D and calcium intakes on surrogate or intermediate outcomes, such as hypertension, blood pressure, and bone mineral density?
Analytic Framework for Vitamin D and/or Calcium Safety-related (adverse) Outcomes

UV exposure

Vitamin D2, D3

Calciyum

Supplements

25(OH)D; 1,25(OH)D

Calcium balance

Renal Outcomes

Psoriasis

Soft tissue calcification

Cancer

All cause mortality
TEP specifies PICOS selection criteria
(partial list)

- **Population**
  - Generally healthy people with no known disorders
  - Studies enrolled <20% patients with common diseases
  - Any population for adverse effects of high intake

- **Intervention / Exposure**
  - Calcium intake, Vitamin D intake, or both
  - Observational studies: Serum 25(OH)D measurement

- **Comparator**
  - Different doses

- **Outcome**
  - 17 outcomes selected by technical expert panel

- **Study Design**
  - Experimental or observational, study duration
  - Excluded cross-sectional studies and studies that did not prospectively collect Vitamin D measurements before the outcome
Citations identified in MEDLINE and Cochrane Central database search for primary studies, published between 1969 and April 2009 (n=16,733)

Citations identified in MEDLINE, Cochrane Database of Systemic Reviews, and the Health Technology Assessments database search for systematic review articles published before December, 2008 (n=1,746)

Abstracts failed to meet criteria (n=17,825)

Primary study articles retrieved for full-text review (n=584)

Systematic review articles retrieved for full-text review (n=68)

Articles failed to meet criteria (n=476)

Primary study articles reviewed (n=165)
- 60 randomized, controlled trials
- 3 nonrandomized comparative studies
- 102 observational studies (either cohort or nested case-control studies)

Systematic reviews included (n=11)
Reporting of Evidence

• Evidence tables
  – detailed information about each study

• Summary tables
  – summary from each study that addresses a question (outcome, study design)

• Figures, graphs

• Meta-analyses (if appropriate)

• Narratives, highlight features and limitation of study in answering question

• Reminder: an evidence report in itself does not make recommendations
Resources available to facilitate global harmonization of methods

- Standards for conducting systematic reviews
  - AHRQ Methods Guide for Effectiveness and Comparative Effectiveness Reviews
  - Centre for Reviews and Dissemination (University of York)
  - Cochrane Handbook for Systematic Review of Interventions
  - Institute of Medicine (IOM) 2011 report
  - USDA – Nutrition Evidence Library (NEL)

- Standards for clinical practice guidelines
  - IOM 2012 report
  - WHO – 2005 series on Guidelines for guidelines

- Collaborative systematic review tools (web-based)
  - SRDR (Systematic Review Data Repository)
  - Cochrane Revman, Covidence
  - Abstrackr (abstract screening)
Standards for reporting systematic reviews and meta-analyses

- **PRISMA** – Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- **PRISMA-P** – . . . Protocols
- **STARD** - STAndards for the Reporting of Diagnostic accuracy studies
- **MOOSE** – Meta-analysis of Observational Studies in Epidemiology
- **EQUATOR (Enhancing the QUAlity and Transparency Of health Research) network** – Many other guidelines from international groups can be found at: www.equator-network.org
SRDR (Systematic Review Data Repository) srdr.ahrq.gov

- Disclosure: I am the director of this project since 2010
- Open-access collaborative systematic review tool
  - Creates data abstraction forms
  - Collects data, produces reports
  - Interfaces with other SR tools (e.g., Data Abstraction Assistant)
- Voluntary contribution and sharing of data used in SRs, so it could be reused for updates and to improve transparency of SRs
- Funded by US AHRQ
- Developed and maintained by Brown EPC
- Launched in June 2012
- International governance board
Some suggestions on structure to ensure high quality SR of evidence

• Based on the recently released National Academy of Medicine report on the Dietary Guidelines for Americans (DGA) process on SRs of evidence
• Oversight body to provide strategic directions (sponsor)
• Nutrient Intake Recommendation Committee(s) (NIRC) – makes recommendations informed by SRs, several members of this committee should be part of the TEP below
• Technical Expert panel (TEP) – assists the SR team refine key questions and help develop review criteria, but they do not participate in the SR
• Systematic review team(s) – carry out the SRs independently once protocol has been developed
• Peer reviewers
Systematic review team members
2011 IOM report on systematic review standards*

• Multidisciplinary team to include methodologist(s), content expert(s), librarian/information scientist, statistician, additional members (e.g., editor, research associate/assistant) as needed, and with appropriate expertise and experience [*Standard 2.1]

• Member should be free of conflict of interests [*Standard 2.2]

• Team leader
  – should be knowledgeable and experienced implementing SR protocol
  – open-minded about the topic
  – Detailed understanding of the scope
Closing thoughts

• Evidence is not static, nutrient intake recommendations may need to be updated. Thus, there is a need to monitor new evidence and to have a process to update SRs and nutrient intake recommendations.

• Different countries may need to convene its own expert panel to come up with nutrient intake recommendation, using the same SRs and framework and incorporating local dietary patterns and other factors. (globalize the evidence, localize the decisions)

• My talk focuses on evidence synthesis, not coming up with recommendations

• It is important to separate the tasks and to use separate expert groups to review evidence, interpret results to make recommendations, in order to minimize bias