Evidence-Based Evaluation of Benefits from Food Components

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Disclosures

• No financial conflicts
• ACSH Board of Scientific Advisors
• AJCN Associate Editor
establish causality (bias --)

randomised controlled studies

“It is shown that ...”

controlled longitudinal studies

“It is likely that ...”

uncontrolled longitudinal studies

“There are signs that ...”

cross-sectional studies and case studies

“Experts are of the opinion that ...”

expert opinions

generate hypotheses (bias ++)

[Diagram showing a hierarchy of research methods, starting from expert opinions at the bottom and ending with established causality at the top.]
<table>
<thead>
<tr>
<th></th>
<th>Number of articles (% of 525)</th>
<th>Number with causal language, (%)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Journal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AJCN</td>
<td>142 (27.0%)</td>
<td>23 (16.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IJO</td>
<td>174 (33.1%)</td>
<td>41 (23.6%)</td>
<td></td>
</tr>
<tr>
<td>JON</td>
<td>70 (13.3%)</td>
<td>39 (55.7%)</td>
<td></td>
</tr>
<tr>
<td>OBS</td>
<td>139 (26.5%)</td>
<td>58 (41.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>case control</td>
<td>18 (3.4%)</td>
<td>9 (50.0%)</td>
<td>0.0660**</td>
</tr>
<tr>
<td>cohort</td>
<td>241 (45.9%)</td>
<td>73 (30.3%)</td>
<td></td>
</tr>
<tr>
<td>cross sectional</td>
<td>266 (50.7%)</td>
<td>79 (29.7%)</td>
<td></td>
</tr>
<tr>
<td><strong>Manuscript primary result p-value</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘not significant’ (&gt;0.05)</td>
<td>69 (14.0%)</td>
<td>34 (49.3%)</td>
<td>0.0006</td>
</tr>
<tr>
<td>‘significant’ (≤0.05)</td>
<td>423 (86.0%)</td>
<td>121 (28.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Industry funding source</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>419 (79.8%)</td>
<td>125 (29.8%)</td>
<td>0.6774</td>
</tr>
<tr>
<td>not indicated</td>
<td>64 (12.2%)</td>
<td>21 (32.8%)</td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>42 (8.0%)</td>
<td>15 (35.7%)</td>
<td></td>
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</tbody>
</table>


*Chi-square comparison of number with causal language.

** Fisher’s exact test, p < 0.05 considered significant difference.
Limitations of Human Nutrition Studies

• RCTs are rare for chronic disease and results have been null
• Observational studies dominate
• Most rely on potentially biased self-reports
• FFQs are semi-quantitative
  – “Validation” is simply correlation against 24-hr recall
  – Not valid for energy or protein – A Schatzkin et al, Int J Epidemiol, 2003
  – When utrients are divided by invalid energy, no correct conclusion possible
  – Is this why diet patterns are replacing nutrients in health epidemiology?

• Baseline intake does not predict long-term diet
• Variability in nutrient content of foods is ignored
GRADE

• Grading of Recommendations Assessment, Development and Evaluation

• GH Guyatt et al, GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ 2008;336:924 and four other papers at same time; several since then.
  – Clear separation between quality of evidence and strength of recommendations
  – Explicit criteria for upgrading and downgrading quality of evidence ratings
  – RCTs begin as high quality and observational studies as low quality

• www.gradeworkinggroup.org
Rating the certainty of evidence for a causal association according to GRADE guidance

Certainty of the evidence is rated for each outcome, across studies

Randomized controlled trials with a high rating, observational studies with a low rating

<table>
<thead>
<tr>
<th>Rating is then modified downward:</th>
<th>Rating is then modified upward:</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Study limitations</td>
<td>✓ Large magnitude of effect</td>
</tr>
<tr>
<td>✓ Imprecision</td>
<td>✓ Dose response is observed</td>
</tr>
<tr>
<td>✓ Inconsistency of results</td>
<td>✓ Confounders likely minimize the effect</td>
</tr>
<tr>
<td>✓ Publication bias likely</td>
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</tbody>
</table>

Final rating for each outcome is ‘high’, ‘moderate’, or ‘low’

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease, NAP 2017
Traditional DRIs vs. DRIs for Chronic Disease

<table>
<thead>
<tr>
<th>Traditional DRIs</th>
<th>Chronic Disease DRIs</th>
</tr>
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<tbody>
<tr>
<td>DRIs for essential nutrients are needed because their deficiencies and toxicities:</td>
<td>Are not warranted unless sufficient evidence exists because:</td>
</tr>
<tr>
<td>a) will affect everyone, if intake is inadequate</td>
<td>a) risk to acquire CDs varies by individual</td>
</tr>
<tr>
<td>b) are caused by one nutrient</td>
<td>b) chronic diseases are often related to many risk factors (genetic, environmental)</td>
</tr>
<tr>
<td>c) are prevented by nutritional interventions</td>
<td>c) nutritional interventions will only partly ameliorate the risk of CD</td>
</tr>
</tbody>
</table>

Guiding Principles for Developing Dietary Reference Intakes Based on Chronic Disease, NAP 2017
Association Between Dietary Factors and Mortality From Heart Disease, Stroke, and Type 2 Diabetes in the United States

Renata Micha, RD, PhD; Jose L. Peñalvo, PhD; Frederick Cudhea, PhD; Fumiaki Imamura, PhD; Colin D. Rehm, PhD; Dariush Mozaffarian, MD, DrPH

**IMPORTANCE** In the United States, national associations of individual dietary factors with specific cardiometabolic diseases are not well established.

**OBJECTIVE** To estimate associations of intake of 10 specific dietary factors with mortality due to heart disease, stroke, and type 2 diabetes (cardiometabolic mortality) among US adults.
Cumulatively, 45% of deaths associated with suboptimal intake in abstract but this figure claims those deaths are attributable to dietary habits.
“Attributing Death to Diet. Precision Counts”

• Assumption that exposure-outcome relationship is causal
  – Strong evidence from randomized trials not available
  – Confounding bias could be substantial

• Are the 10 factors the right set?
  – Not included: trans fat, sugar, potassium

• How dietary factors are interrelated and modified by each other
  – Unreasonable to assume factors are all additive to affect 70% of deaths

• “The findings reported by Micha et al appear correct
  – But the reduction could be 30% to 70%.”

A core principle of good public health practice is to base all policy decisions on the highest-quality scientific data, openly and objectively derived. Determining whether data meet these conditions is difficult; uncertainty can lead to inaction by clinicians and public health decision makers. Although randomized, controlled trials (RCTs) have long been presumed to be the ideal source for data on the effects of treatment, other methods of obtaining evidence for decisive action are receiving increased interest, prompting new approaches to leverage the strengths and overcome the limitations of different data sources. In this article, I describe the use of RCTs and alternative (and sometimes superior) data sources from the vantage point of public health, illustrate key limitations of RCTs, and suggest ways to improve the use of multiple data sources for health decision making.
Divorce rate in Maine correlates with Per capita consumption of margarine

Correlation: 99.26% (r=0.992558)
Red Meat: 7 of 14 cohort studies
Processed Meat: 12 of 18 cohort studies

Carcinogenicity of consumption of red and processed meat

In October, 2015, 22 scientists from ten countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to evaluate the carcinogenicity of the consumption of red meat and processed meat. These assessments will be published in volume 114 of the IARC Monographs.

Red meat refers to unprocessed mammalian muscle meat—for example, beef, veal, pork, lamb, mutton, horse, or goat meat—including minced or frozen meat. It is usually consumed cooked. The Working Group analysed data from more than 200 g per person per day. Less information is available on the consumption of processed meat.

The Working Group assessed more than 800 epidemiological studies that investigated the association of cancer with consumption of red meat or processed meat in many countries, from several continents, with diverse ethnicities and diets. For the evaluation, the greatest weight was given to prospective cohort studies done in the general population. High-quality day of red meat and an 18% increase (95% CI 1.10–1.28) per 50 g per day of processed meat.

Data were also available for more than 15 other types of cancer. Positive associations were seen in cohort studies and population-based case-control studies between consumption of red meat and cancers of the pancreas and the prostate (mainly advanced prostate cancer), and between consumption of processed meat and some of the tumors.

Monograph with all data was to be published by IARC sometime in 2016.
Risk of Colon Cancer Associated with Meat Consumption

• **Absolute Risk**
  - Lifetime risk of colon cancer among vegetarians – 4.5%
  - Lifetime risk of colon cancer among people who eat two ounces of processed meat every day – 5.3%

• **IARC Identified hazard, not degree of risk**
  - Statistical significance in human studies was determined by RR!!
  - No systematic literature search
  - Quality of individual studies was not evaluated
  - No meta-analysis – Lancet Oncology summary cited a 2011 meta-analysis by one member not mentioned at working group meeting
  - Virtually no review of epidemiology studies by rest of working group
Meat Intake and Mortality NIH-AARP Study

RCTs and Colon Cancer

• Polyp Prevention Trial
  – ~950 subjects/group with polyp removed, 3 yr follow-up
  – Low meat diet high in F/V, whole grains, legumes
  – A Schatzkin et al, NEJM 342:1149-1152, 2000
  – RR of recurrence – 1.00 (95% CI, 0.90-1.12)

• Women’s Health Initiative
  – 19,500 on low fat, low meat diet; 29,000 on usual diet for up to 9 yr
  – RR of colon cancer – 1.08 (95% CI, 0.90-1.29)
When is a carcinogen not a carcinogen?
Lancet Oncology editorial, June 2016

A month rarely passes by without something being declared unhealthy or carcinogenic. Often, the WHO International Agency for Research on Cancer (IARC) is at the centre of such pronouncements and is duly rounded on to explain the consequences. IARC, however, is not the only agency with responsibility for determining carcinogenicity of products, compounds, or lifestyles,
These latest disputes regarding carcinogen classification highlight the problem of determining reliable findings when data are equivocal and where there are vested interests. They also highlight the difficulties of translating carcinogenicity research into appropriate health policies and recommendations for risk management. Furthermore, there is an equally clear need for a standardised, internationally agreed methodology for carcinogen assessment, alongside ways of presenting results that are easily understood and accepted by all interested parties. Until these objectives are met, carcinogen definition and regulation will continue to be the poor relation to other cancer preventative measures. ■ *The Lancet Oncology*
Key Takeaways

• Nutrition research will not earn the same respect as other hard science fields until we accept the same rigorous standards for reaching conclusions

• Grading of nutrition recommendations should be done with existing processes like systematic reviews, meta-analyses and GRADE

• Uncertainty factors point to the need for precision nutrition; targeting based on differences in genome, proteome, epigenome, metabolome, microbiome ...
  – Personalized nutrition sounds great but likely overpromises
  – One-size-fits-all approach is likely to fade away