Observational Studies vs. Randomized Controlled Trials

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(1) The relevance of observational data as compared to clinical data for the purposes of identifying relevant endpoints and developing dose-response relationships for establishing recommended intakes for generally healthy persons

(2) Relevant confounders for data interpretation from the perspective of major and minor confounders or even such factors as obesity and physical activity

(3) The state of knowledge for vitamin D, as compared to other nutrients of current and past interest such as vitamin E or beta-carotene (i.e., whether the plausibility for vitamin D is stronger than for other micronutrients)
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Randomized Trials (RCTs) vs. Observational Data

- Dose
- Compliance
- Duration
- Confounding
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Common assumption:
Dose-response is only addressable in RCTs.

Is this always true?
Ranges in RCTs have not always tested the dose-response relation implied in the observational data.

Examples: $\beta$-carotene

Vitamin D
Range in Observational Studies

Plasma Beta-Carotene (ng/L)

- 0.29
- 0.10

Range in RCT (ATBC)

- 3.00
- 0.18
Plasma 25(OH) Vitamin D and Colorectal Cancer Nurses’ Health Study

Multivariable OR

P trend = 0.02

Feskanich D. et al., CEBP 2004
Compliance

e.g. dietary fat
Example

Studies of dietary fat:

In iso-caloric studies, low dietary fat increases plasma triglycerides.
There is no good biomarker of total fat intake, but as % of energy from fat increases, serum triglyceride levels go down.
Women’s Health Initiative (Year 3, mean)

Plasma Triglycerides

Intervention Group: 161.2
Placebo Group: 159.6

Beresford S., et al., JAMA 2006
≤ 20% Energy  ≥ 40% Energy

Fat Intake

Plasma Triglyceride

Nurses Health Study and Health Professionals Follow-Up Study

* Adjusted for age, BMI, physical activity

Unpublished
For chronic diseases, such as cancer, the relevant exposure may occur over decades or could be relevant much longer before the diagnosis.

Examples: aspirin vitamin D
• Observational data consistently suggest that aspirin intake lowered risk of colorectal cancer, especially after 10-15 years of use

• Initial RCTs did not show an association
RR and 95% CI of Colorectal Cancer According to Years of Aspirin Use
Nurses Health Study

Giovannucci et al., *NEJM* 1995
<table>
<thead>
<tr>
<th>Study</th>
<th>0-9 Years</th>
<th>10-19 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK-TIA Trial</td>
<td>1.14 (0.49-2.61)</td>
<td>0.51 (0.25-1.00)</td>
</tr>
<tr>
<td>British Doctors Aspirin Trial</td>
<td>0.82 (0.45-1.49)</td>
<td>0.64 (0.42-0.97)</td>
</tr>
<tr>
<td>Pooled</td>
<td>0.92 (0.56-1.49)</td>
<td>0.60 (0.42-0.87)</td>
</tr>
</tbody>
</table>

Flossmann et al., *Lancet* 2007
### Nurses’ Health Study

**Colorectal Cancer**

<table>
<thead>
<tr>
<th>Vitamin D Intake</th>
<th>RR High vs. Low</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Assessment</td>
<td>0.84</td>
<td>0.16</td>
</tr>
<tr>
<td>~ 10 years</td>
<td>0.77</td>
<td>0.11</td>
</tr>
<tr>
<td>~ 20 years</td>
<td>0.33</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Martinez E. et al., JNCI 1996
Case-Control Study of Breast Cancer

Knight J. et al. CEBP 2007

- Multivariable RR
- Outdoor Activities

- 45-54 yrs old
  - P trend = 0.59
  - RR: 1.01

- 10-19 yrs old
  - P trend <0.0006
  - RR: 0.81

Low ——— High

Knight J. et al. CEBP 2007
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Confounding

- Key factor to consider in observational studies.
- Attempt to control for it through multivariate analysis
- In nutritional studies, particularly difficult to isolate a micronutrient

For example, does:
- Beta-carotene = fruits and vegetables?
- Lycopene = tomato products?
- Calcium = dairy products?
Confounding: Vitamin D

- Qualitatively different from nutritional studies
- Diet contributes about 10-15% of total vitamin D
- Correlation between vitamin D intake and 25(OH)D levels are modest and easily controllable
- Arguably, the most important potential confounders to consider are physical activity and body mass index (BMI)
Interrelationship Among Risk Factors for Colon Cancer

BMI

Physical Activity

Colon Cancer Incidence

Colon Cancer Mortality

25(OH)D

Davis CD & Dwyer JT, JNCI 2009
Empirically use an outcome clearly associated with BMI and physical activity, but not vitamin D, to address if physical activity and BMI could be controlled for in the Health Professionals Follow-Up Study.
BMI

Physical Activity

25 (OH) Vitamin D

Resting Heart Rate
BMI

Physical Activity

Resting Heart Rate

25 (OH) Vitamin D

€ 11 bpm

€ 0.88 bpm, P=0.008*
€ 0.37 bpm, P=0.27**

* unadjusted – per 10 ng/mL decrement in 25(OH)D
** adjusted for BMI and physical activity
A modest spurious association was induced between low 25 (OH) D and resting pulse due to confounding by BMI and physical activity.

This spurious association was entirely removed when adjusted for BMI and physical activity.

This finding suggests that BMI and physical activity can be controlled for in studies of 25(OH)D.
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Vitamin D vs. Micronutrients

- Confounding issues entirely different
- Vitamin D is part of a well established endocrine / paracrine / autocrine system with strong biologic effects
- At least some of the purported benefits of vitamin D are seen in RCTs (e.g. reduction in fractures, falls, PTH levels)
- Conceptually different, addressing “deficiency” vs. “mega-dose” supplementation
Relative Concentrations

RCT Dose (3 ng/L)

High “Natural” Diet (0.3 ng/L)

“Natural” Sun Exposure (50 ng/L)

Deficient (10 ng/L)

Beta-Carotene

Vitamin D