

Weighing Scientific Evidence

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Disclosure/Disclaimer

§ No financial conflicts

§ Outside activity: editor-in-chief, JNCI

- No connection with the NCI or Federal government

§ Opinions are mine, not official positions of the Federal Government or National Institutes of Health

“A wise man proportions his belief
to the evidence.”

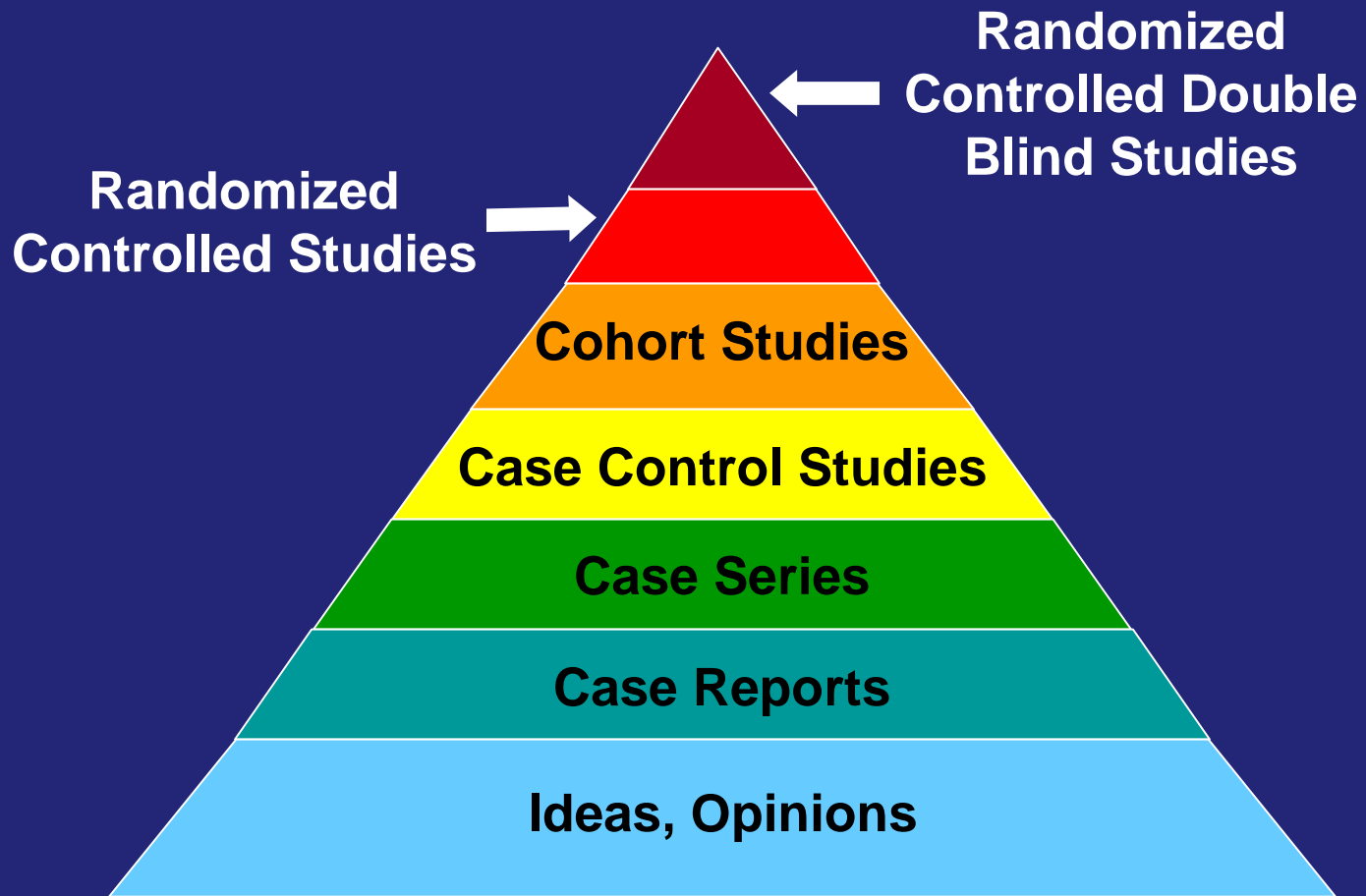
David Hume, Scottish philosopher, 1711-1776

Questions to Ask About Medical Research

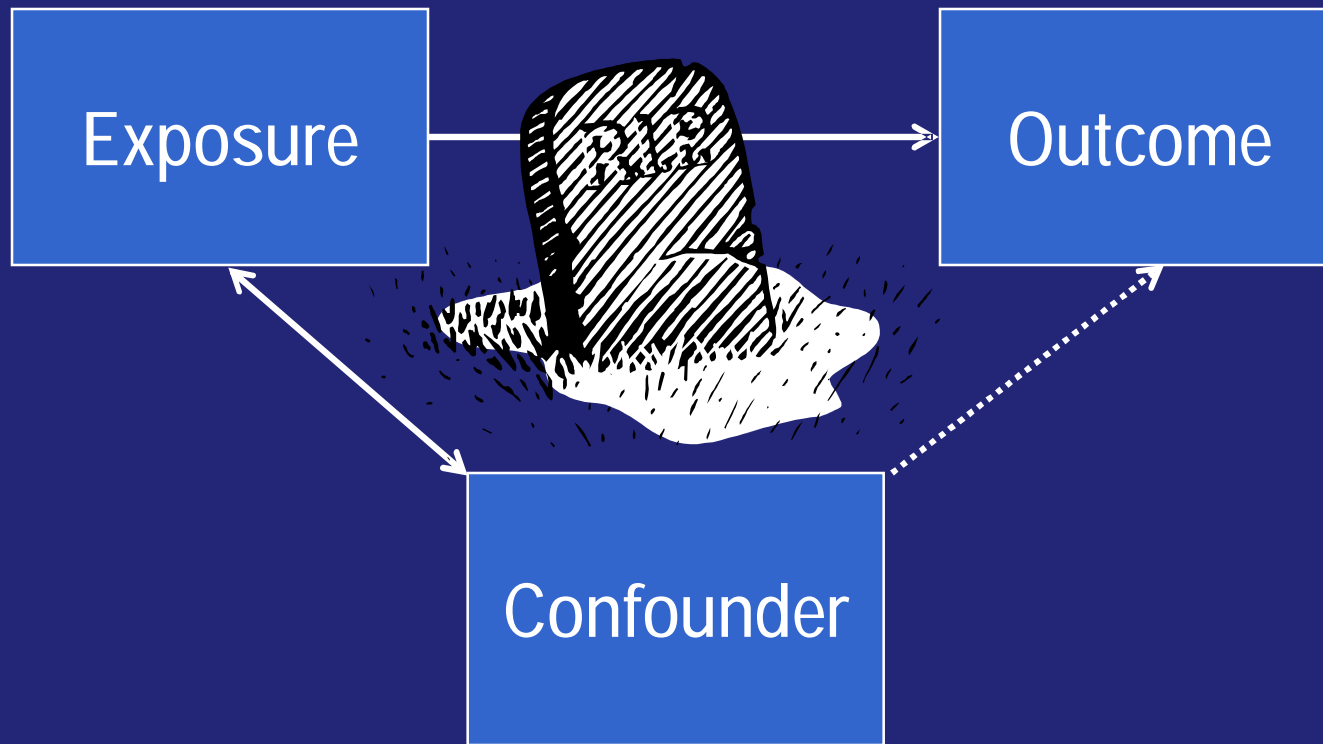
1. What is the exposure and what is the outcome?
2. How certain is it that exposure causes outcome?
3. How important is the outcome?
4. How big is the effect?
5. To whom does it apply?

Levels of Decision Making

- Level I:** *“Would you have this done for yourself or for someone else in your immediate family?”*
Influenced by one’s personal experience with the disease and capacity to deal with risk.
Affects few people.
- Level II:** *“What would I recommend to my patient/client?”*
Physician making a recommendation for his/her patients. Influenced by prior experience, but the scientific evidence may play a greater role.
Affects possibly hundreds of people.
- Level III:** *“What would I recommend to the nation, the world?”*
Across-the-board recommendations for a population. Must be based on rigorous assessment of the scientific evidence.
Affects hundreds of thousands, even millions of people.

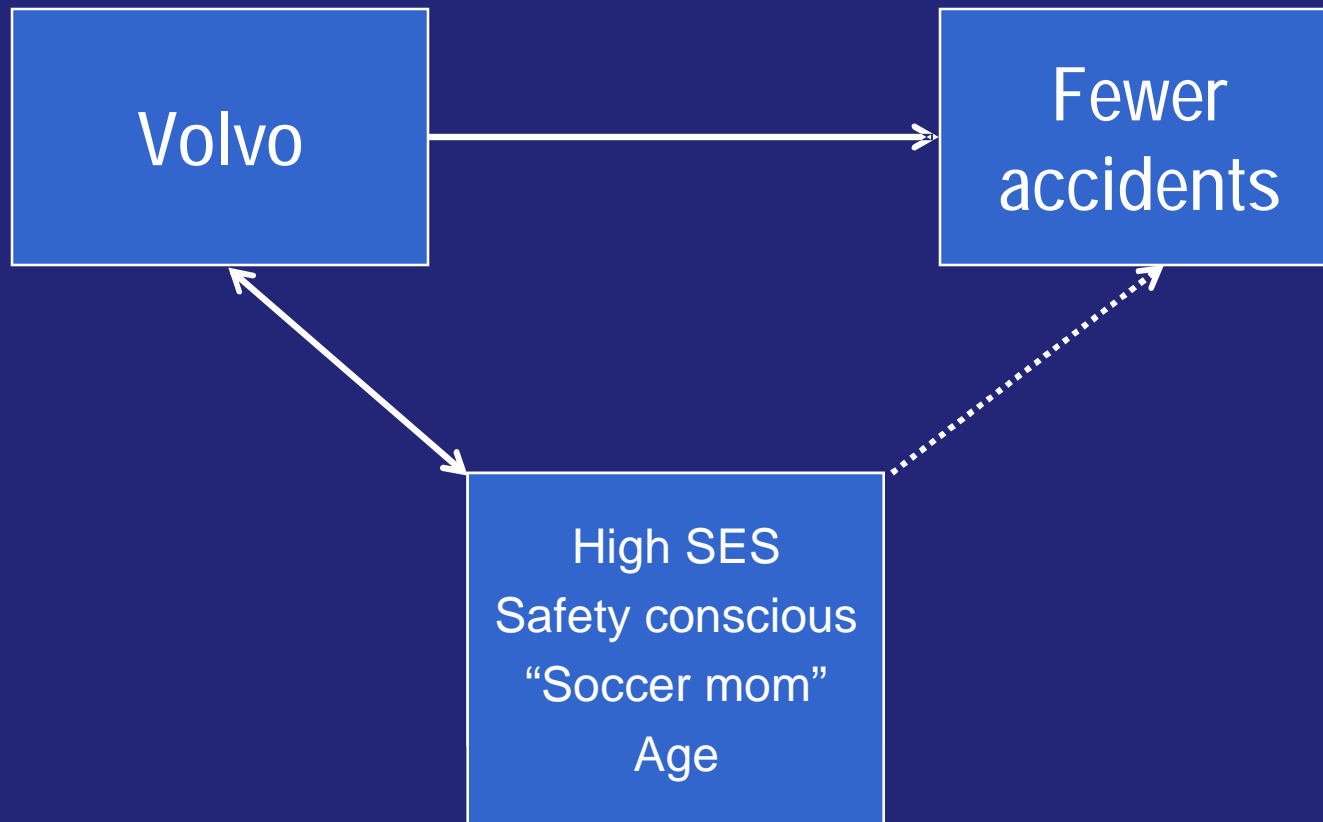


Confounding Variables

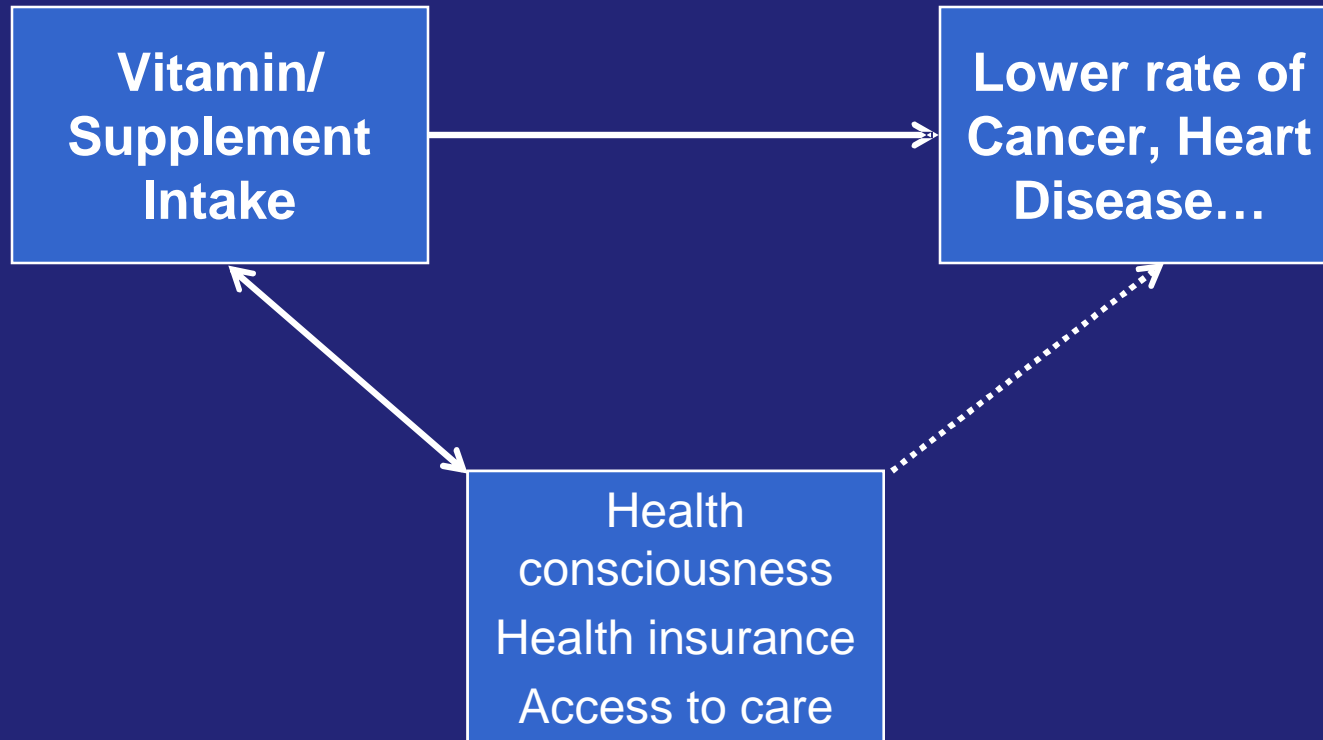


Confounding is the death of any study!

Confounding Variables



Confounding Variables



Confounding is a concern in any observational study!

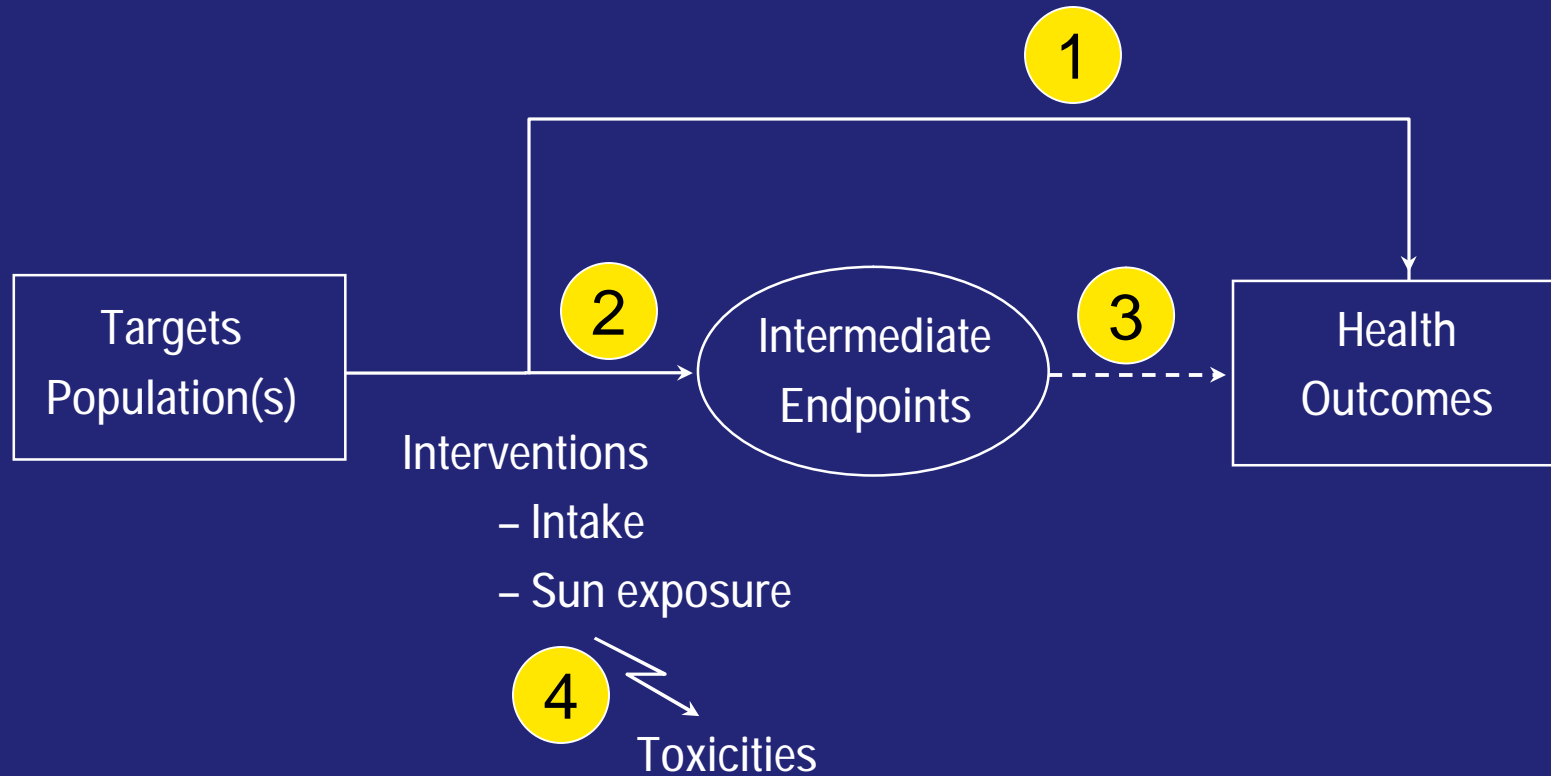
**Confounding is more likely when
someone's choice (patient, doctor, etc.)
determined who was in the exposed and
unexposed group**

Observational Studies

"...are guilty until proven innocent."

David Ransohoff, M.D., JNCI, 2006

Vitamin D Analytic Framework



Vitamin D: Potential Target Populations

- Children
- Women of reproductive age
- Elderly women
- Elderly men
- Different ethnic groups, skin pigmentation
- Populations at different latitudes (above 37° North in winter)

Vitamin D: “Interventions”

- Dietary intake/fortified foods
- Dietary supplements
- Exclusive breastfeeding
- Sun exposure (UVB light): the main source worldwide
 - Avoidance to protect against skin cancer
 - Sunscreen
 - Protective clothing

Biomarkers/Surrogate Endpoints for Optimal Vitamin D Status

Potential Surrogate Outcomes

- Blood levels
- Bone mineral density
- Polyps
- PTH levels

None validated

- None can substitute for health outcomes

Health Outcomes of Sun/UV Exposure or Vitamin D Intake

- Bone collagen matrix mineralization
 - Fracture
 - Rickets
 - Falls
- Cancers
 - Skin: melanoma, non-melanoma
 - Colorectal
 - Prostate
 - Breast
- Cardiovascular disease
- Autoimmune disease

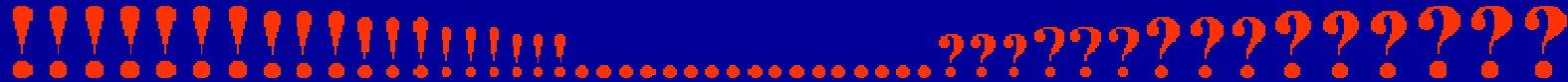
A Closer Look at Outcomes

Health Outcomes

Very important

Surrogate Endpoints

Unclear importance



Fewer
deaths,
period

Fewer
deaths
due to
specific
disease

Fewer
compli-
cations
of disease

Fewer
diagnoses
of
disease

Better
test
results

Change
in risk
factor

Discordance Between Surrogate Endpoint Biomarkers and Health Outcomes

Intervention	Effect on Surrogate Endpoint	Effect on Health Outcome
High vs. std. dose Paclitaxel	↑ RR & PFS	↔ Mortality (no effect) ↑ Toxicity
Encainide, flecainide	↓ Cardiac arrhythmias (PVCs)	↑ Sudden Death
Postmenopausal Estrogen + Progestin	↓ Cholesterol ↓ LDL ↑ HDL	↑ Coronary heart disease

Discordance Between Surrogate Endpoint Biomarkers and Health Outcomes (2)

Intervention	Effect on Surrogate Endpoint	Effect on Health Outcome
Low fat, high vegetable diet (Women's Health Initiative)	↓ Polyps	↔ Colon Cancer
Torcetrapib	↑ HDL cholesterol	↑ Deaths, heart failure

“Level of Evidence” for Cancer Prevention Physician Data Query (PDQ)

- Definition: certainty of the editorial board’s estimate of the health effects of implementing an intervention
- Steps
 - I. Description of the evidence (5 Domains)
 - II. Summary assessment for both benefits and harms

Description of Evidence in PDQ: Five Domains

1. Study design: ranked by design strength
2. Internal validity: “quality” of execution within study design (good, fair, poor)
3. Consistency (coherence)/volume of evidence
 - One vs. multiple studies
 - Small vs. large studies
 - Consistent direction of outcomes
4. Magnitude of effects: prefer absolute vs. relative effects
 - Change from 1% to 0.5%, or from 4/1000 to 2/1000 [Not: 50% decrease]
5. External validity (good, fair, poor)
 - Applicability in usual practice with same effect?

Internal Validity Criteria for Randomized Controlled Trials (RCTs) and Cohort Studies

Initial assembly of comparable groups:

- For RCTs: adequate randomization, including concealment
- For cohort studies: consideration of potential confounders with adjustment in the analysis

Maintenance of comparable groups (attrition, crossovers, adherence, contamination)

Low rates of loss to follow-up (and non-differential)

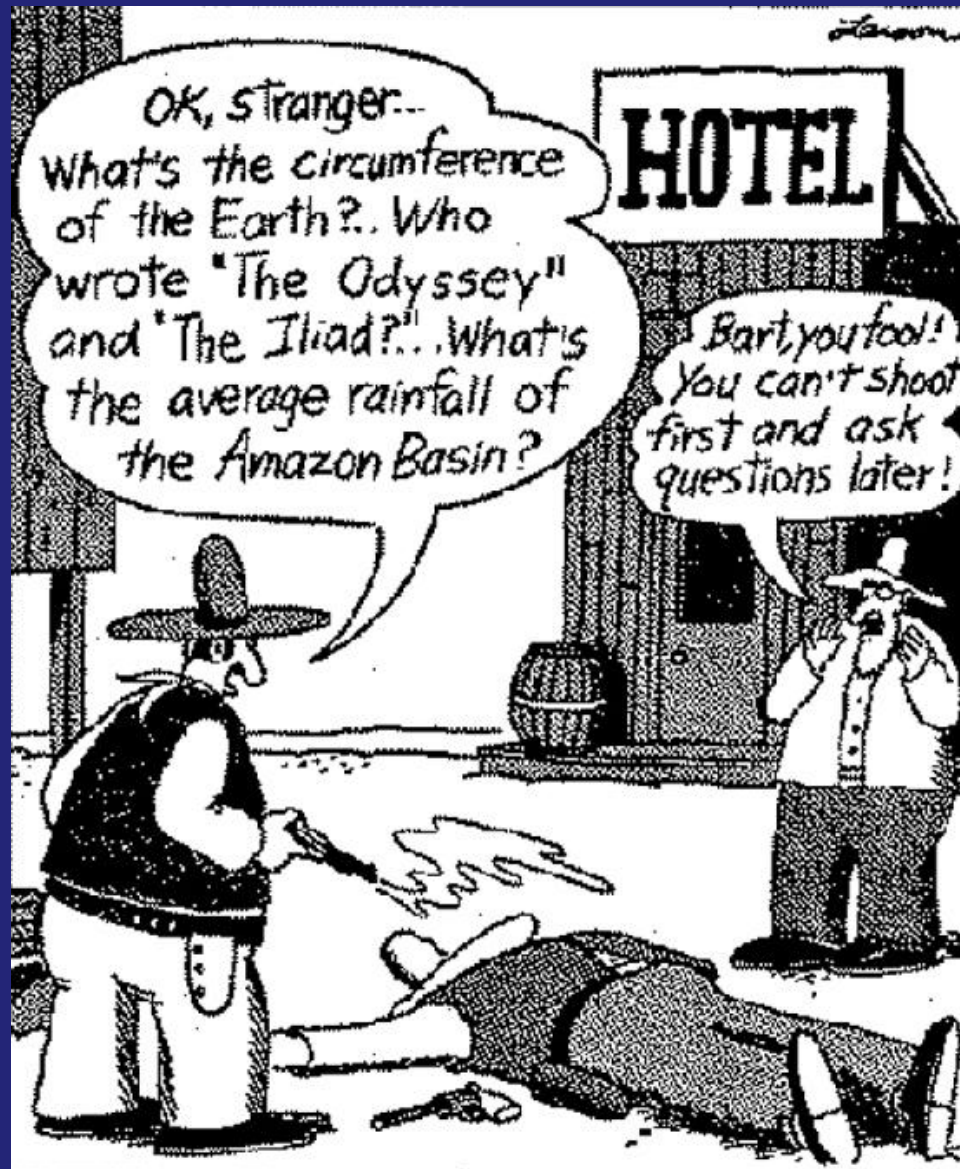
Outcome measurements: equal, reliable, and valid (includes masking)

Clear definition of interventions

All important outcomes considered

Physician Data Query (PDQ) Summary of Evidence for Cancer Prevention with Vitamins

- **Rationale:** Many different mechanistic pathways for anticancer effects have been invoked.
- **Benefits:** Evidence is insufficient to support the use of multivitamin and mineral supplements or single vitamins or minerals to prevent cancer.
- **Harms:** Two prospective placebo-controlled trials found that smokers and former smokers who received beta carotene supplements had increased lung cancer incidence and mortality.
- **Implications:** Research into the potential anticancer properties of vitamin and mineral supplements is ongoing.



OK, stranger...
What's the circumference
of the Earth?. Who
wrote "The Odyssey"
and "The Iliad?". What's
the average rainfall of
the Amazon Basin?

HOTEL

Bart, you fool!
You can't shoot
first and ask
questions later!

Illusions of knowledge are the
obstacles to discovery.

Daniel Boorstin, 1983