Exploring the Types of Evidence Behind Diet and Chronic Disease Individual Level: Clinical Trials, Alternatives

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"To navigate proof, we must reach into a thicket of errors and biases. We must confront monsters and embrace uncertainty, balancing — and rebalancing —our beliefs. We must seek out every useful fragment of data, gather every relevant tool, searching wider and climbing further. Finding the good foundations among the bad. Dodging dogma and falsehoods. Questioning. Measuring. Triangulating. Convincing. Then perhaps, just perhaps, we'll reach the truth in time."—Adam Kucharski—Proof: The Uncertain Science of Certainty

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My starting point is this:

For almost half a century the basics of a healthy diet that is associated with longer life and better functional status has been relatively constant with several twist and turns.

Eating more vegetables, fruits, whole grains, lean proteins, dairy, nutrient dense foods and healthy fats and avoiding excess salt, sugar, saturated fat are common findings of many randomized and observational studies over the decades and form the basis of current recommendations

The degree to which processing and ultraprocessing in its many forms has an effect over and above the basics is question that needs to be addressed (for example, pasteurization is processing)

More specific or extreme claims about particular diets and supplements have enriched proponents, sold books and led to cyclical levels of enthusiasm, but have never been shown to improve longevity, function or quality of life in adequate and well controlled clinical studies with the exception of specific nutritional deficiencies that can be corrected through replacement therapy,

Those advocating for a specific diet for the general population or for parts of the population based on phenotype should adhere to the standard:

“In God we trust, all others must bring data”.

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A Tough Problem

- For the most part the effect of food on health is the sum of many small effects over the course of a lifetime
- Impact of biological effect of a particular diet and impact of promotion of eating behavior to favor that diet are related, but not the same
- Effects of nutrition in an otherwise healthy person are different than food as medicine for a person with an inborn deficiency of an essential element of nutrition
- Eating a meal is like taking a gazillion microdoses of a medication all at the same time
- Reductionism for separating the impact of biology, behavior, social interaction and environment has value, but needs to be alongside integrative understanding of how these elements fit into ultimate outcome—better health of individuals and populations-–in the real world
- We need to develop methods to measure long term effects of the interactions of the individual with the food environment

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Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease

Authored by the Committee on Qualification of Biomarkers and Surrogate Endpoints in Chronic Disease
Edited by Christine M. Micheel and John R. Ball

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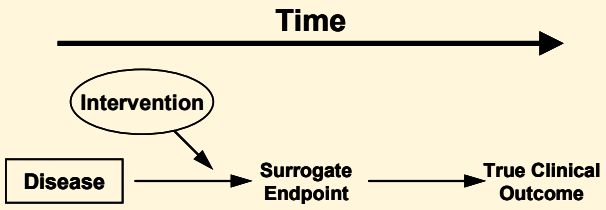
"Even in the best of circumstances, it is possible for surrogate endpoints to be misleading by either overestimating or underestimating an intervention's effect on clinical outcomes."



Fleming, T. R., and D. L. DeMets. 1996. Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine* 125(7):605–613.

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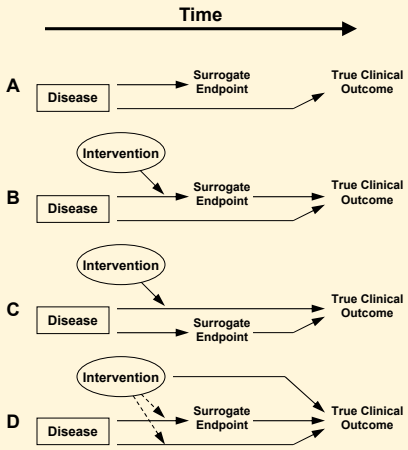
Failures of Surrogate Endpoints



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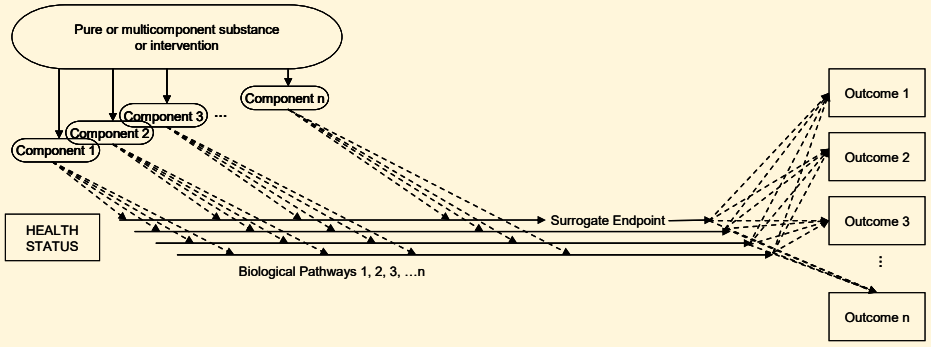
Biological Complexity Leads to Many Opportunities for Error



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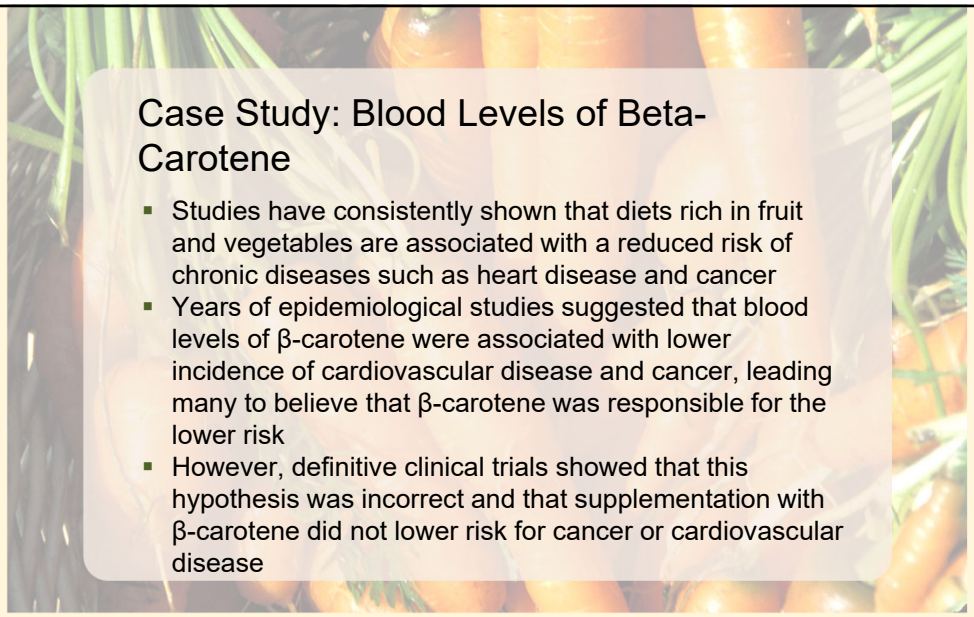

Case Study: Blood Levels of Beta-Carotene

- Studies have consistently shown that diets rich in fruit and vegetables are associated with a reduced risk of chronic diseases such as heart disease and cancer
- Years of epidemiological studies suggested that blood levels of β-carotene were associated with lower incidence of cardiovascular disease and cancer, leading many to believe that β-carotene was responsible for the lower risk
- However, definitive clinical trials showed that this hypothesis was incorrect and that supplementation with β-carotene did not lower risk for cancer or cardiovascular disease

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Lessons from RCTs of Drugs and Devices

- Important to have an inception cohort (characterize people at the inception point of the trial)
- Important to measure whether the intervention has been delivered
  - Real issue with measurement of what people eat
  - Big improvements in digital measurement of food intake/grocery carts, etc.
  - Food ingredient databases
- Adherence to protocol is important issue to understand
  - For efficacy studies adherence is essential
  - For effectiveness studies the degree of adherence is important
- Critical importance of difference between a biomarker, a putative, unvalidated surrogate and a validated surrogate
- Outcomes should be carefully defined
  - Feel, function, survive
- Completeness of follow-up essential—missingness is not random!
- Length of trial is important—early hazard; cumulative benefits and risks

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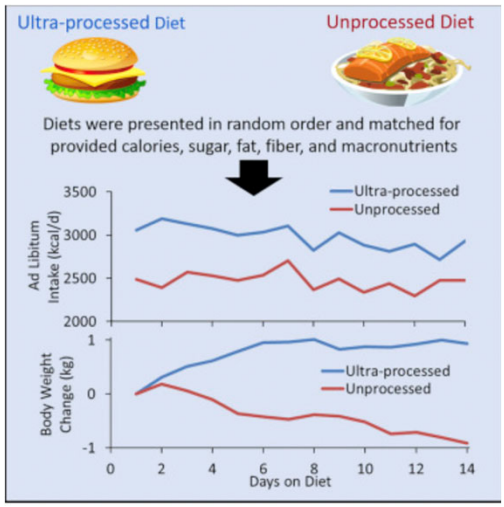

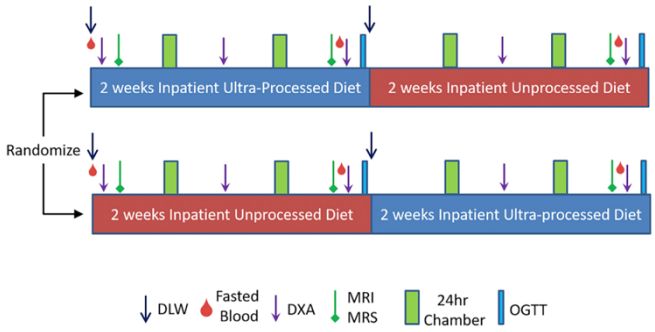

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Ultra-Processed Diets Cause Excess Calorie Intake and Weight Gain: An Inpatient Randomized Controlled Trial of *Ad Libitum* Food Intake

Kevin D. Hall [1,5] · Alexis Ayuketah [1] · Robert Brychta [1] · … · Peter J. Walter [1] · Shanna Yang [2] · Megan Zhou [1] …
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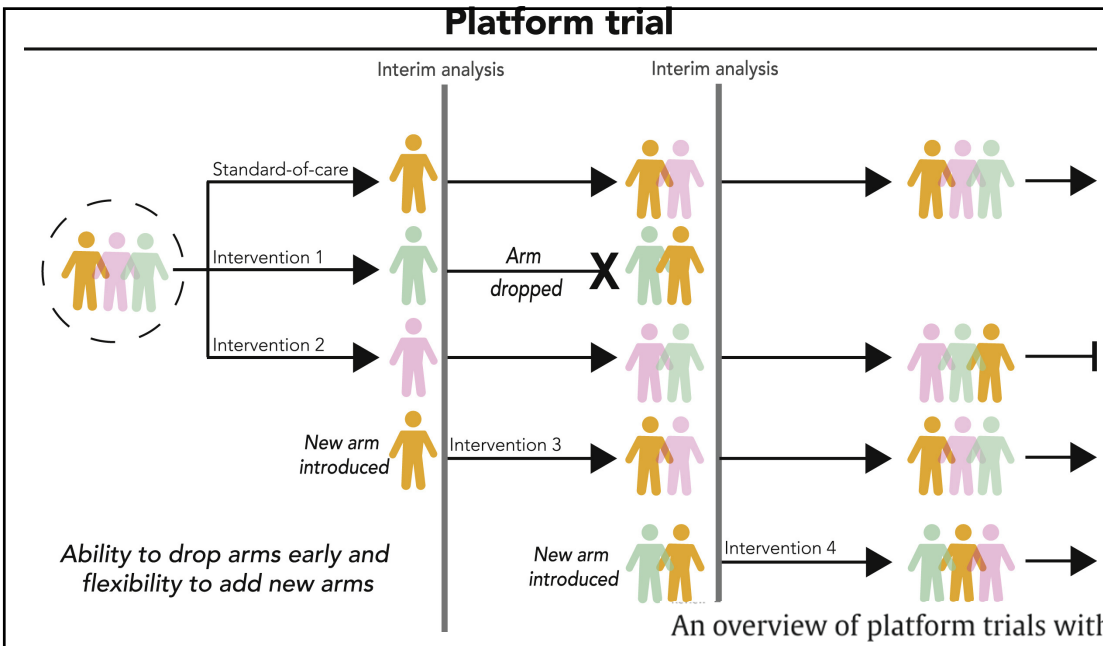

An overview of platform trials with a checklist for clinical readers

Jay J.H. Park [a,b], Ofir Harari [b,c], Louis Dron [b,c], Richard T. Lester [a], Kristian Thorlund [b,c],

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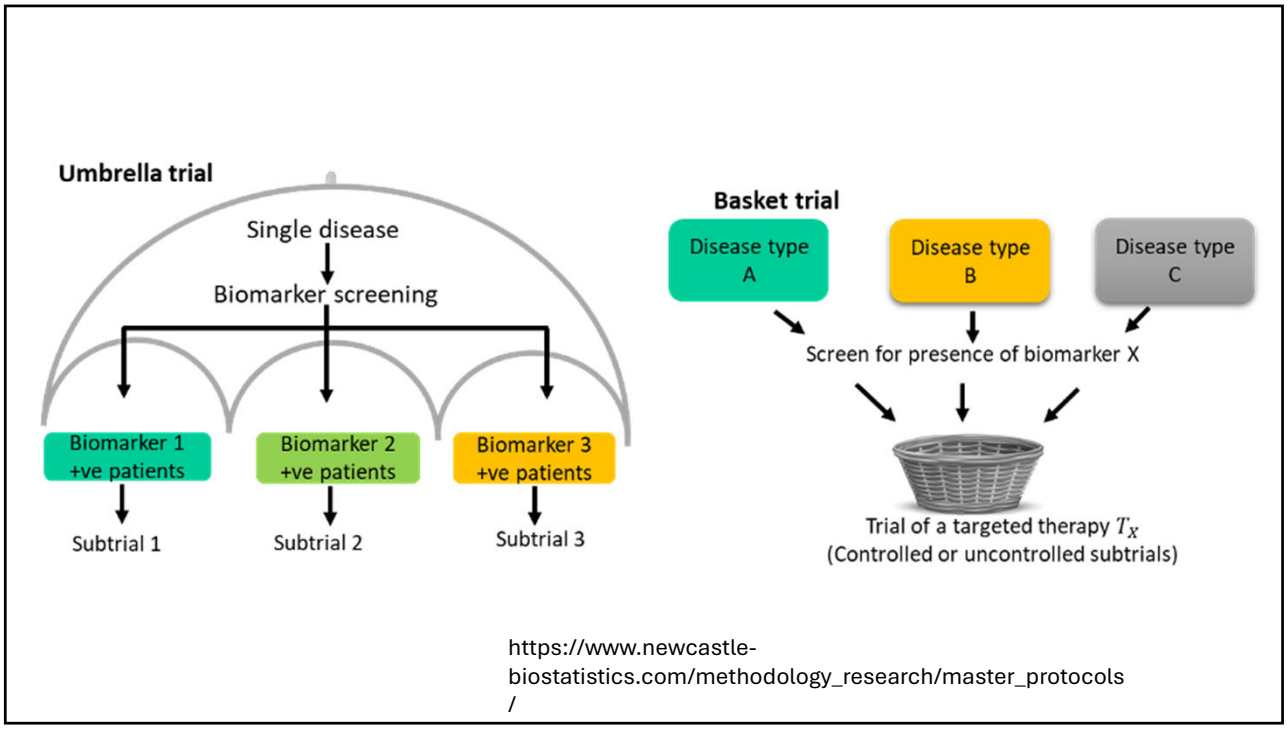

https://www.newcastle-biostatistics.com/methodology_research/master_protocols/

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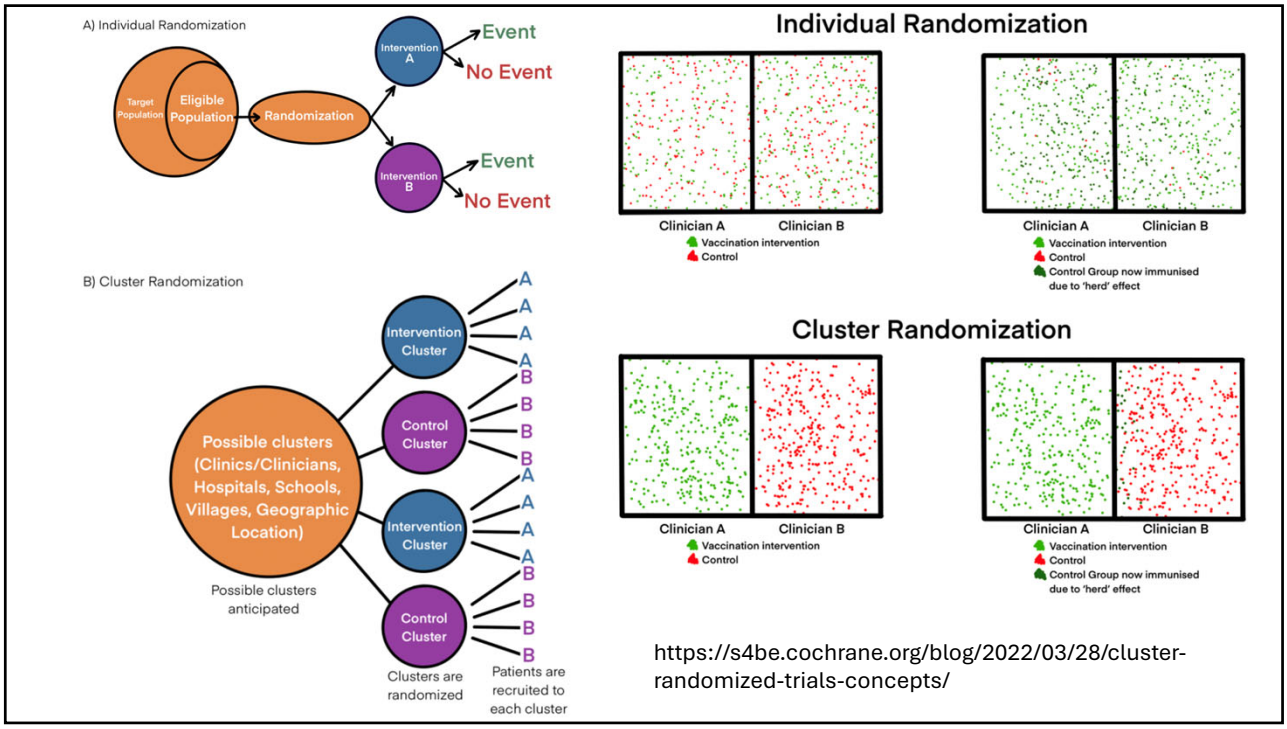

https://s4be.cochrane.org/blog/2022/03/28/cluster-randomized-trials-concepts/

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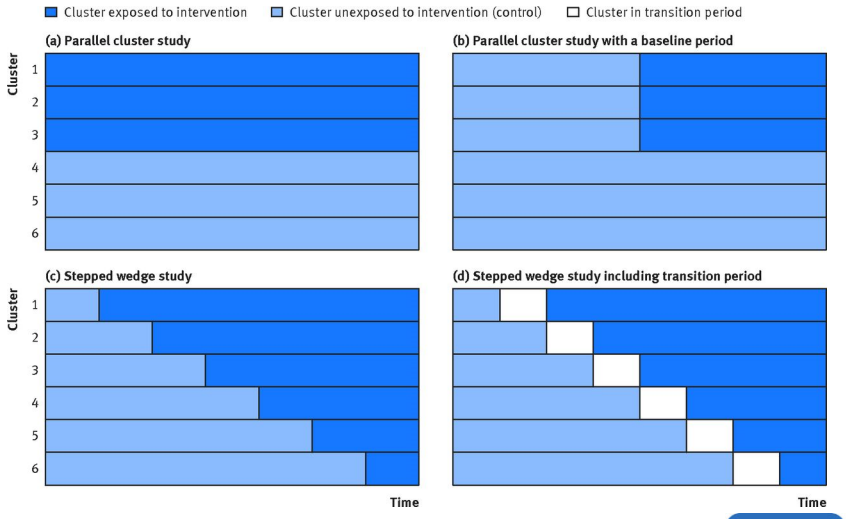
Fig 1 Schematic illustration of the conventional parallel cluster study (with variations) and the stepped wedge study.



K Hemming et al. BMJ 2015;350:bmj.h391

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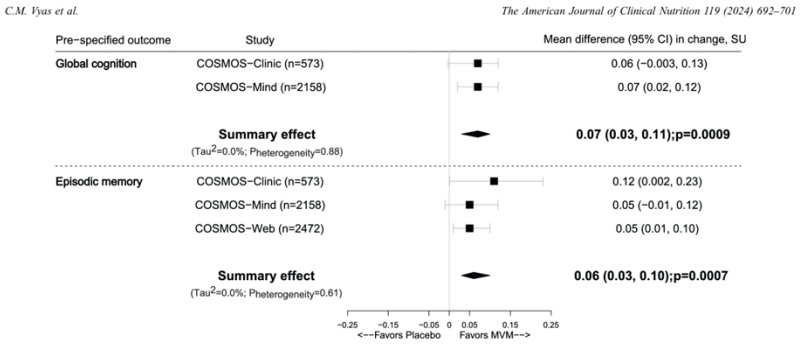
Dietary Supplements

- US market size > $150B per year; growing at 7-8% per year
  - PMCID: PMC10421343 PMID: 37571258
- Perfectly amenable to standard individual RCTs with long term followup
- Multivitamins and cognitive function



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Chemicals Added to Food

- Effects likely quite small, but accrete over many years
- No obvious RCT approach that could work here
- One topic of interest may be quasi-experimental analysis related to chemicals that will be banned with the more ”precautionary principle’ approach
- This should be a hot topic for methods development with clear public record of modeling and assumptions

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Summary

- No simple solution to trial design
- Traditional randomization
  - Supplements
  - Short term unraveling of biology
  - ? Dietary advice
- Umbrella and basket trials
  - Could be useful for “precision nutrition” based on biomarker predictions
- Cluster and Stepped Wedge Designs
  - Policies
  - Longer term outcomes of real world strategies
- No single design is perfect for the common question: “What should I eat?

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“To navigate proof, we must reach into a thicket of errors and biases. We must confront monsters and embrace uncertainty, balancing — and rebalancing —our beliefs. We must seek out every useful fragment of data, gather every relevant tool, searching wider and climbing further. Finding the good foundations among the bad. Dodging dogma and falsehoods. Questioning. Measuring. Triangulating. Convincing. Then perhaps, just perhaps, we'll reach the truth in time.”—Adam Kucharski
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