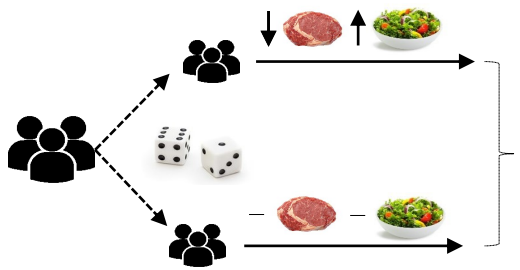
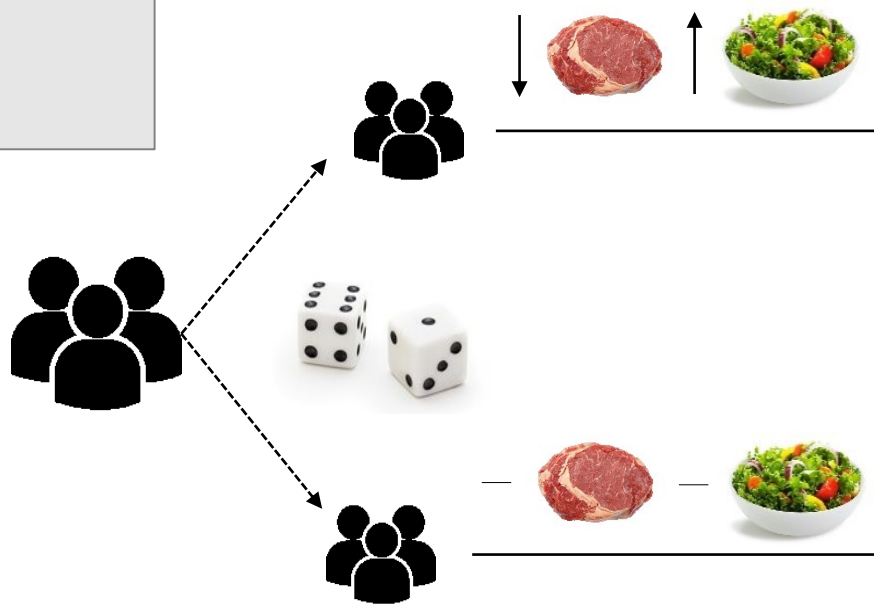
To make decisions you need to know what works and what doesn't (=causal effects)

Intervention studies



To answer a causal question, you need to do an RCT

Some challenges:
- Blinding?
- Placebo?
- Solution = pragmatic trial?



Risk of heart failure
~ 10 years

But!
- Recruiting participants?
- Adherence?
- Loss to follow-up?
- Costs?
- Timely?
- Ethical?

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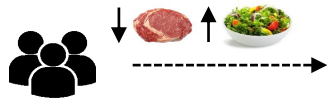
To make decisions you need to know what works and what doesn't (=causal effects)

Observational studies



Outline of a Target-Trial Protocol: Specification and Emulation Using Observational Data.

Protocol Component	Description	Example: Antiretroviral Therapy Initiation in HIV-Positive Persons[1]	
		Specification	Emulation Using Observational HIV Cohorts
Eligibility criteria	Who will be included in the study?	HIV-positive persons ≥18 yr of age with no prior use of antiretroviral therapy and no history of AIDS	Same as for specification *Required data for each person: age, history of therapy use, history of AIDS diagnosis*
Treatment strategies	What interventions will eligible persons receive?	Initiation of antiretroviral therapy: 1. Immediately 2. When CD4 cell count drops below 500 cells per cubic millimeter	Same as for specification *Required data: date of therapy initiation, clinical measurements of CD4 cell count*
Treatment assignment	How will eligible persons be assigned to the interventions?	Eligible persons will be randomly assigned to one strategy and will be aware of which strategy they were assigned to.	Eligible persons will be assigned to the strategies with which their data were compatible at the time of eligibility.
Outcomes	What outcomes in eligible persons will be compared among intervention groups?	Death	Same as for specification *Required data: date of death during the study*
Follow-up	During which period will eligible persons be followed in the study?	From treatment assignment until death, loss to follow-up, or administrative end of follow-up, whichever occurs first	Same as for specification *Required data: date of loss to follow-up*
Causal estimand	Which counterfactual contrasts will be estimated using the above data?	Intention-to-treat effect (effect of being assigned to treatment) Per-protocol effect (effect of receiving treatment as indicated in the protocol)	Observational analogue of the per-protocol effect
Statistical analysis	How will the counterfactual contrasts be estimated?	Intention-to-treat analysis Per-protocol analysis (requires adjustment for preassignment and postassignment confounders)	Same as per-protocol analysis *Required data: preassignment and postassignment confounders*

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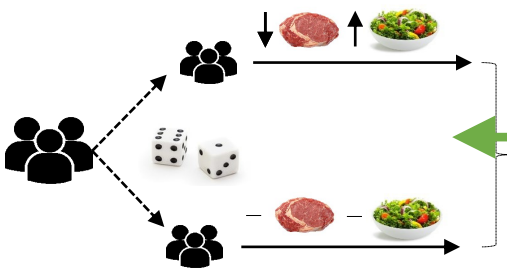
Some central points

- Using target trial approach improves transparency
- Helps you articulate clear questions
- If you do not have good data on confounders, the method will not fix it
- You cannot emulate a trial that is not pragmatic
- Having a benchmark is highly valuable for comparison – improves confidence
- Can solve problems with selection bias / immortal time-bias by properly allocate person-time
- Is problematic when there could be confounding by indication
- Using negative controls is recommended

Intervention studies



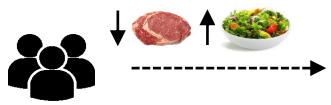
Target trial

TABLE 2 Emulation of a target trial of dietary interventions using observational data from the Health Professionals Follow-up Study, Nurses' Health Study, and Nurses' Health Study II

	Target trial specification	Target trial emulation
Eligibility criteria	Age ≥25 y, no history of diabetes, cardiovascular disease, and cancer.	Same. We also required complete questions on diet and covariates and report plausible energy intake (800 to 4200 kcal/d in men; 500 to 3500 kcal/d in women) at prebaseline and baseline questionnaires. • Baseline is defined as the date of return of the second dietary questionnaire (1990 for HPFS, 1986 for NHS, and 1995 for NHS II) to allow for adjustment for prebaseline diet.
Dietary strategies	Each individual would be assigned to 1 of 14 following strategies: • No intervention (usual diet) • Joint intervention on all 6 food-based components of the AHA 2020 Dietary Goals • Intervention on only 1 of the components (6 separate strategies) • Joint intervention on 5 of the 6 components (6 strategies, leaving 1 component out under each strategy) Each strategy is followed for 20 y. Fish interventions apply to nonvegetarians only. Participants assigned to a dietary strategy are expected to maintain their dietary intake within the range prespecified by the corresponding intervention.	Same. We assumed that each 4-y dietary questionnaire accurately reflects *1*) the average diet during the previous 4-y period; and 2) the intended diet (under no intervention) that the individual would have reported at the start of the 4-y period.
Assignment	Individuals are randomly assigned to a dietary strategy.	We attempted to emulate randomized assignment by adjusting for prebaseline or baseline covariates: baseline age at enrollment; family history of myocardial infarction before 60 y; smoking index; aspirin use; menopausal status (NHS/NHS II); menopausal hormone therapy (NHS/NHS II); baseline diagnosis of hypertension or hypercholesterolemia; and prebaseline values of fruits and vegetables, whole grains, processed meat, fish, sugar- sweetened beverages, legumes/nuts/seeds, and alcohol; and total energy intake.
Outcome	Primary outcome: 20-y risk of all-cause mortality. Secondary outcomes: 20-y risk of death from CVD, cancer, and other causes.	Same.
Follow-up	Starts at baseline and ends at death, incomplete follow-up, or 20 y after baseline, whichever occurs first.	Same. Incomplete follow-up is defined as questionnaire nonresponse or incomplete responses to dietary questions.
Causal contrast	Intention-to-treatment effect. Per-protocol effect.	Observational analog of per-protocol effect.
Statistical analysis	Intention-to-treat analysis. Per-protocol analysis: Apply g-formula to compare 20-y risk of death between groups receiving each treatment strategy with adjustment for pre- and postbaseline prognostic factors associated with adherence to strategies and loss to follow-up.	Same as per-protocol analysis.

Abbreviations: AHA, American Heart Association; CVD, cardiovascular disease; HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; NHS II, Nurses' Health Study II.

Observational studies



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