Observational studies made easy!

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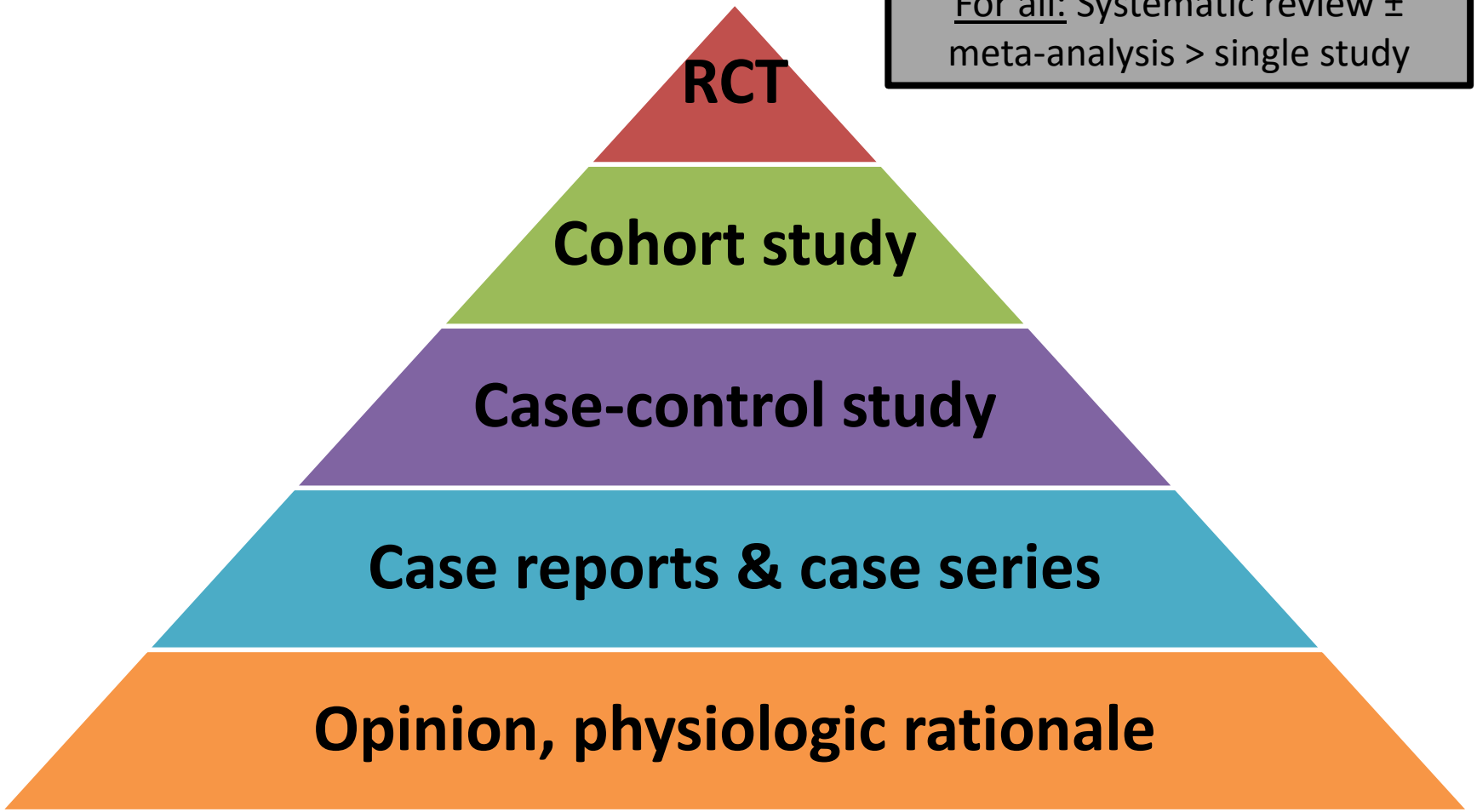
Disclosures

I have no real or perceived conflict of interest to declare.

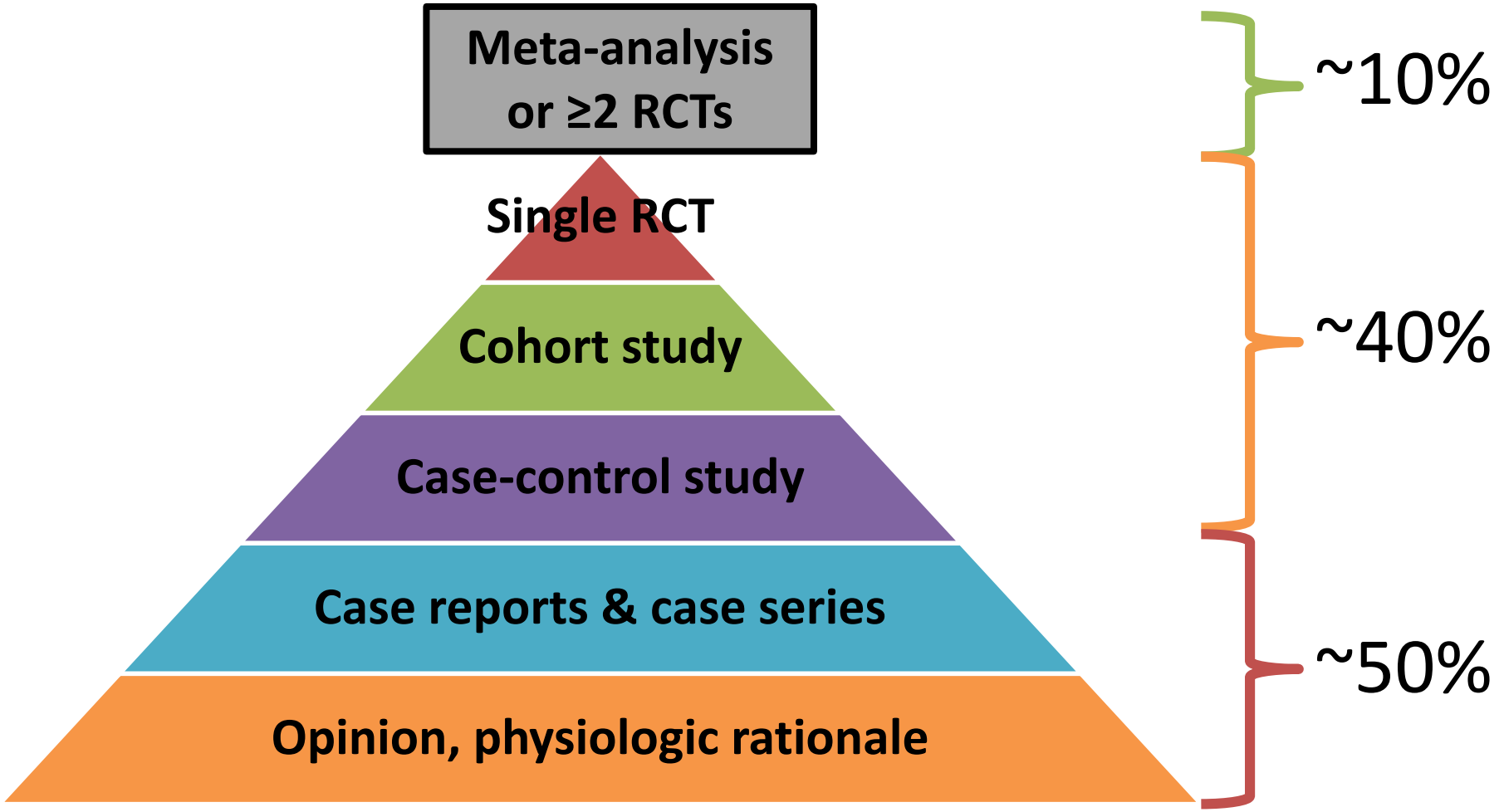
I created NERDCAT-Obs, the observational study critical appraisal tool that we will demonstrate today.

The Evidence Pyramid

For all: Systematic review ± meta-analysis > single study



Cardiology Guideline Recommendations



JAMA 2009;301:831-41

Most Medical Research is OBSERVATIONAL

PubMed search of “atrial fibrillation AND warfarin” (in 2010) – 2175 articles

- Review, opinion, irrelevant (62.7%)
- RCT (0.3%)
- **Cohort (17%)**
- **Case-control (11%)**
- Case report (9%)

http://www.cebm.net/ocebm-levels-of-evidence/

Observational Studies Can MISLEAD

Well-done RCTs often refute or fail to confirm findings of observational studies

Observational Studies Can MISLEAD

"Hormone-replacement therapy reduces risk of cardiovascular events in post-menopausal women"

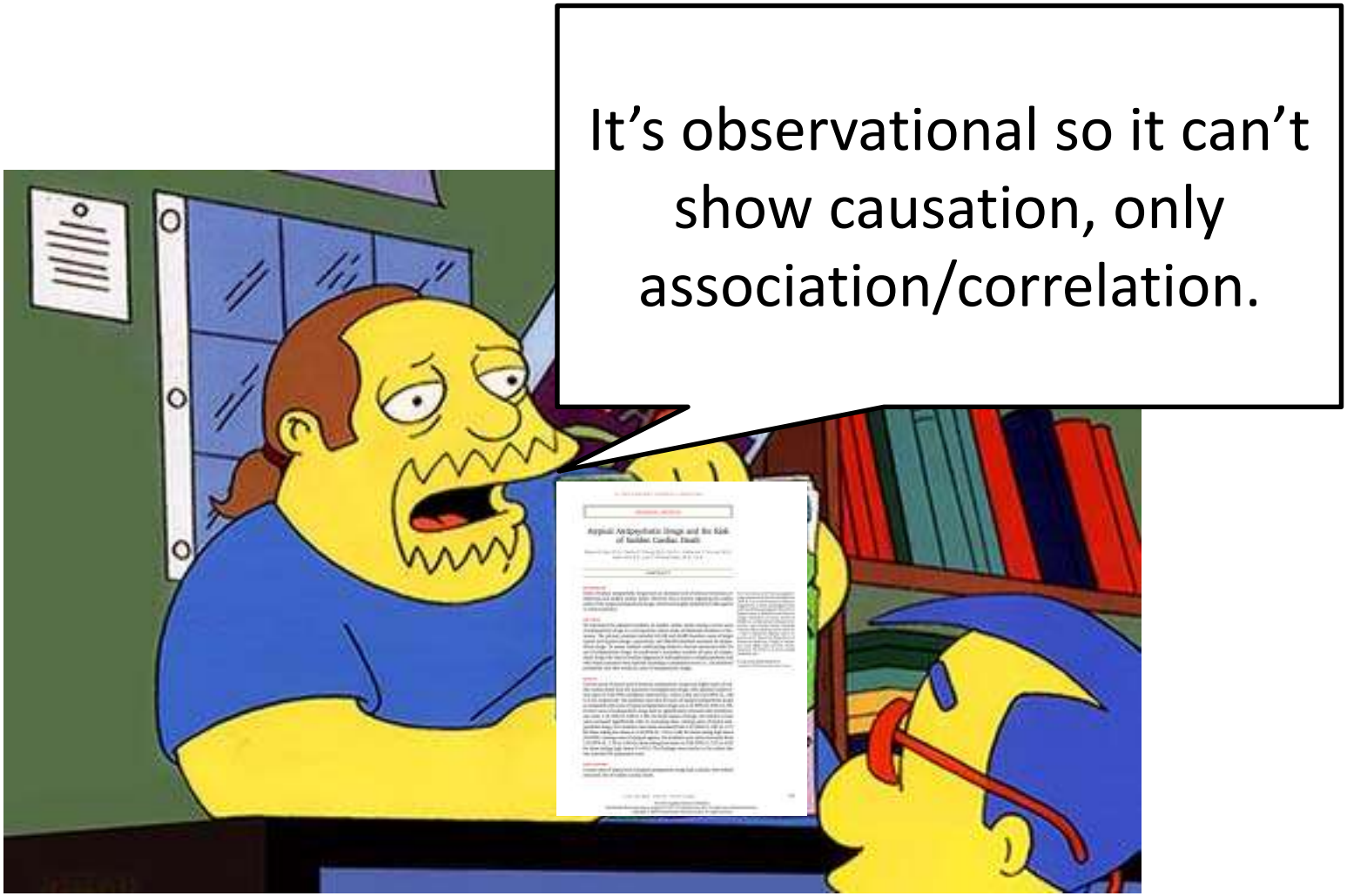
Observational Studies Can MISLEAD

“Diuretics increase cardiovascular deaths in diabetics”

Observational Studies Can MISLEAD

"Omeprazole decreases effectiveness of clopidogrel, pantoprazole doesn't"

It's Easy to do This, But It's Not Productive



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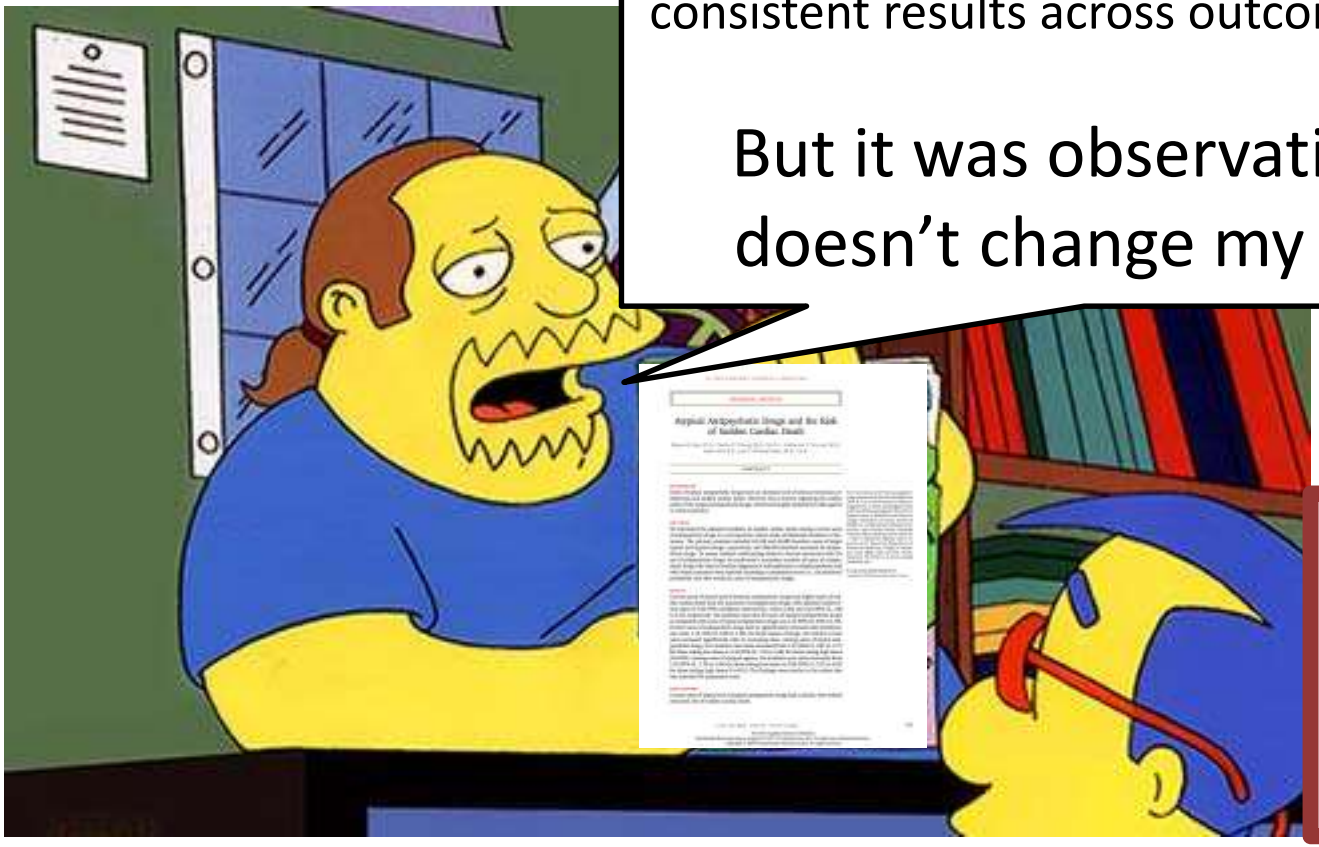
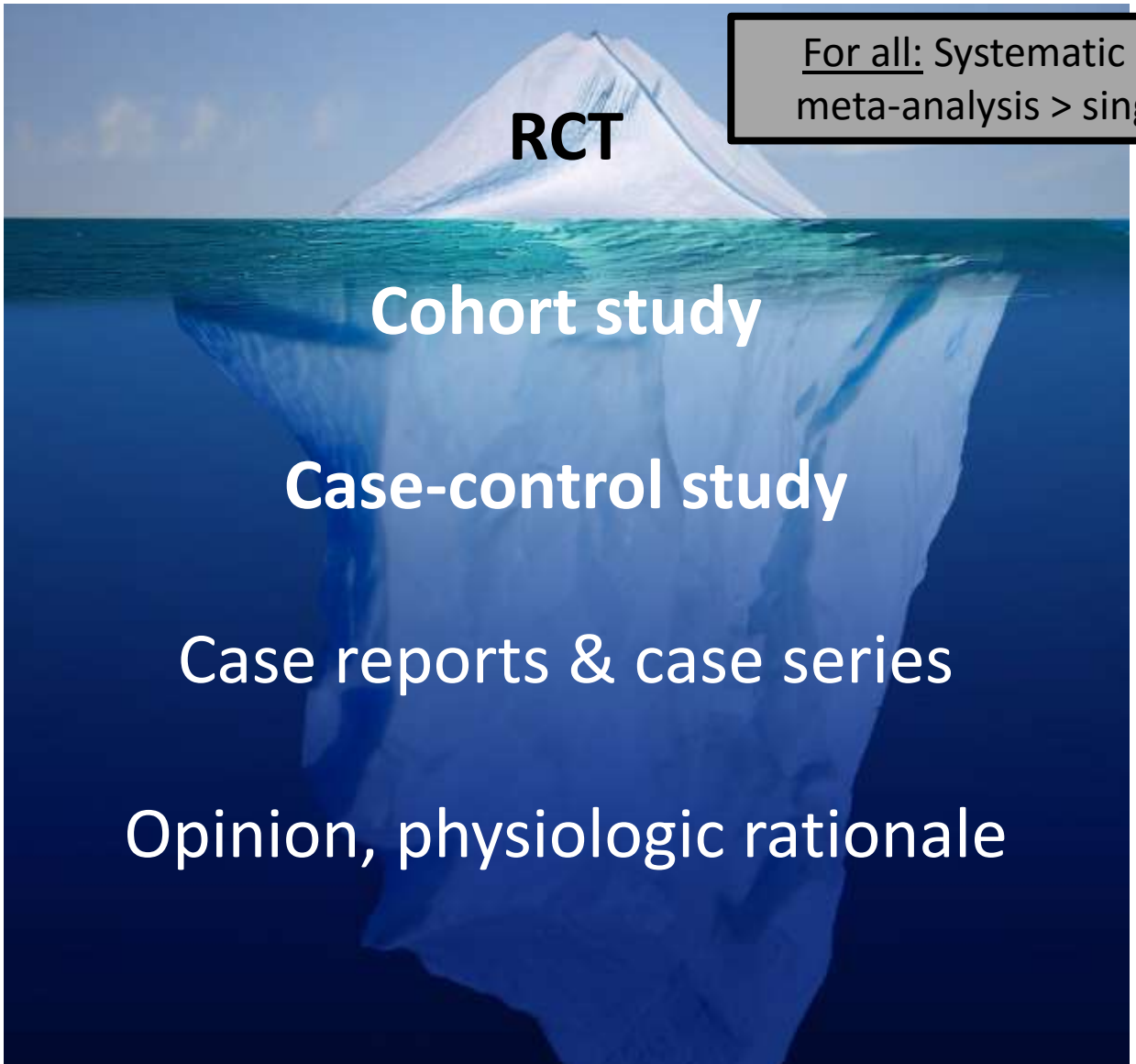


*Which is based on pathophysiologic rationale/ expert opinion

The Evidence ~~Pyramid~~ Iceberg



For all: Systematic review ± meta-analysis > single study

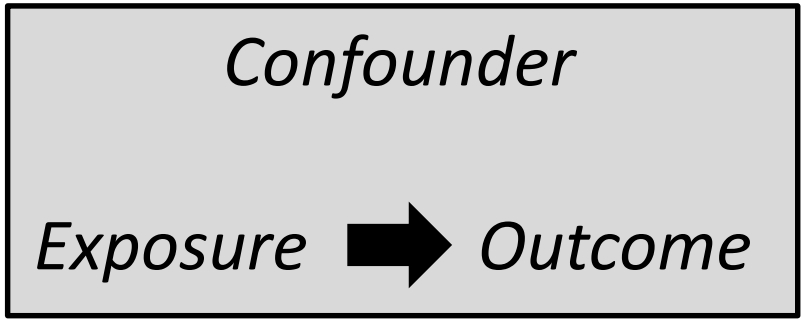
Learning Objectives

1. Review fundamentals of clinical studies
2. Describe data sources for observational studies
3. Explain biases & confounding relevant to observational studies
4. Describe ways to minimize bias & confounding
5. Incorporate a structured approach to reading & appraising observational studies (NERDCAT-Obs)

1. Review fundamentals of clinical studies

What Are the 4 Possible Explanations for a Study Result?

1. Chance
2. Confounding
3. Bias
4. True cause-effect relationship



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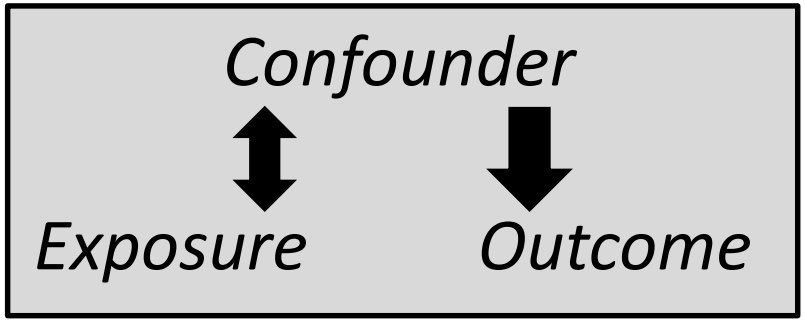


Why is the RCT the Gold Standard for Establishing a Cause-Effect Relationship?

1. ~~Chance~~ **Statistical testing**

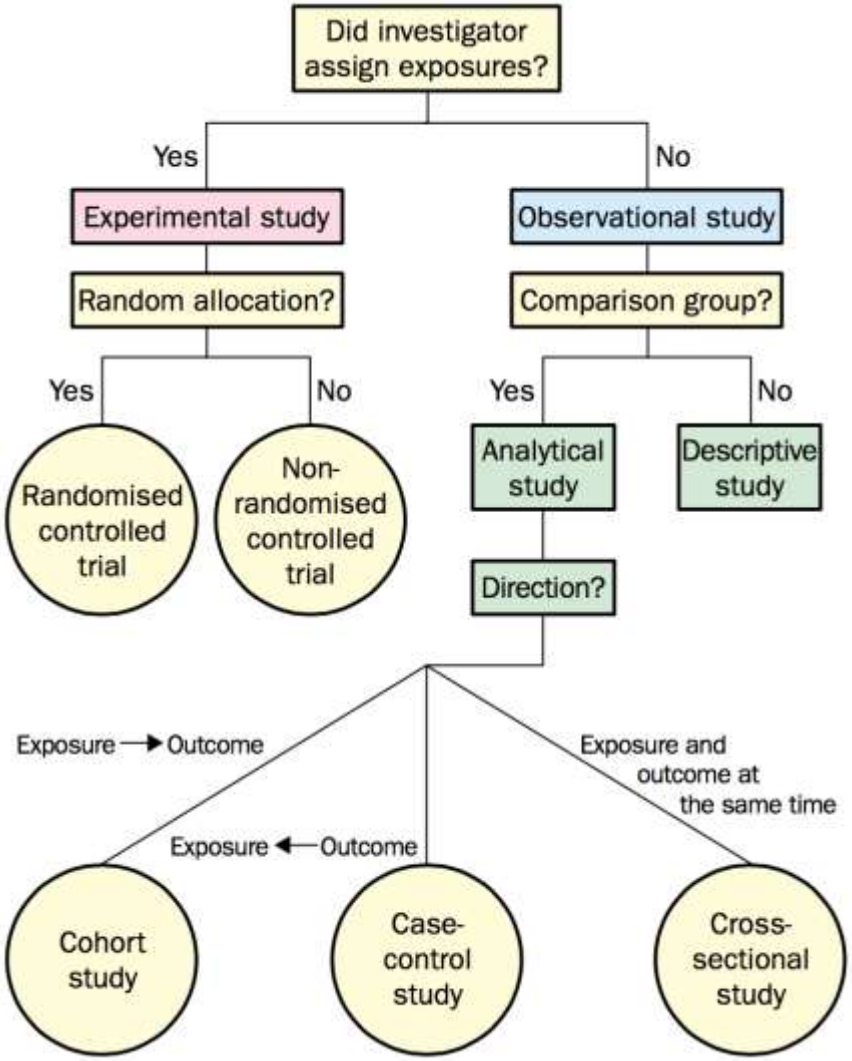
2. ~~Confounding~~

3. ~~Bias~~

} **Randomization, concealed allocation & double blinding**

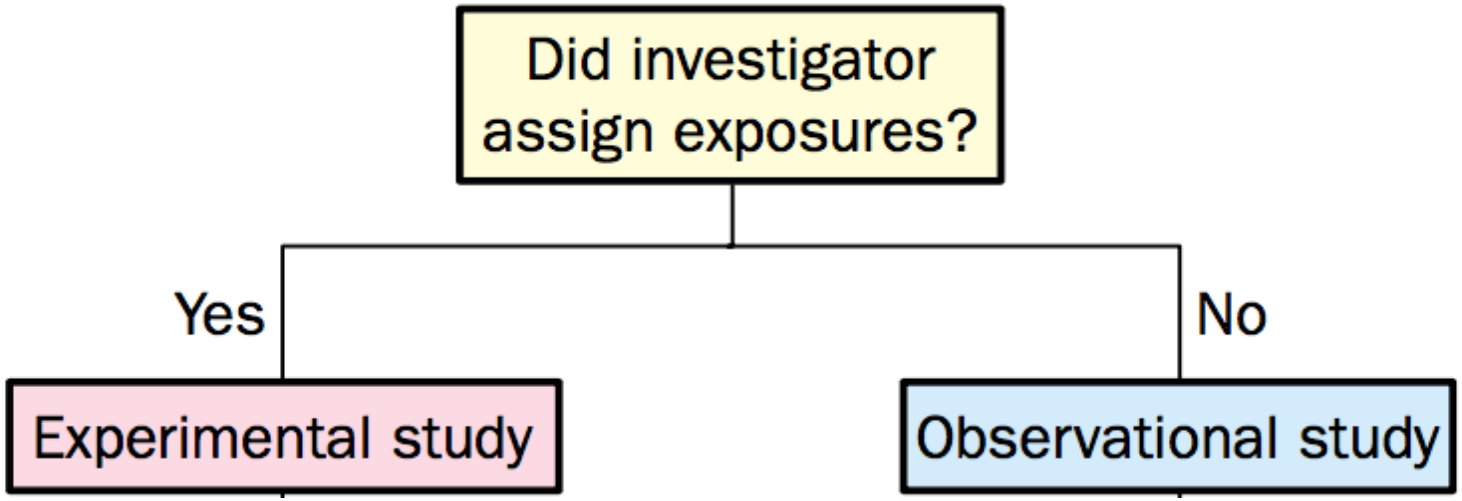
4. **True cause-effect relationship**

Taxonomy of Clinical Research



Lancet 2002;359:57-61

Taxonomy of Clinical Research



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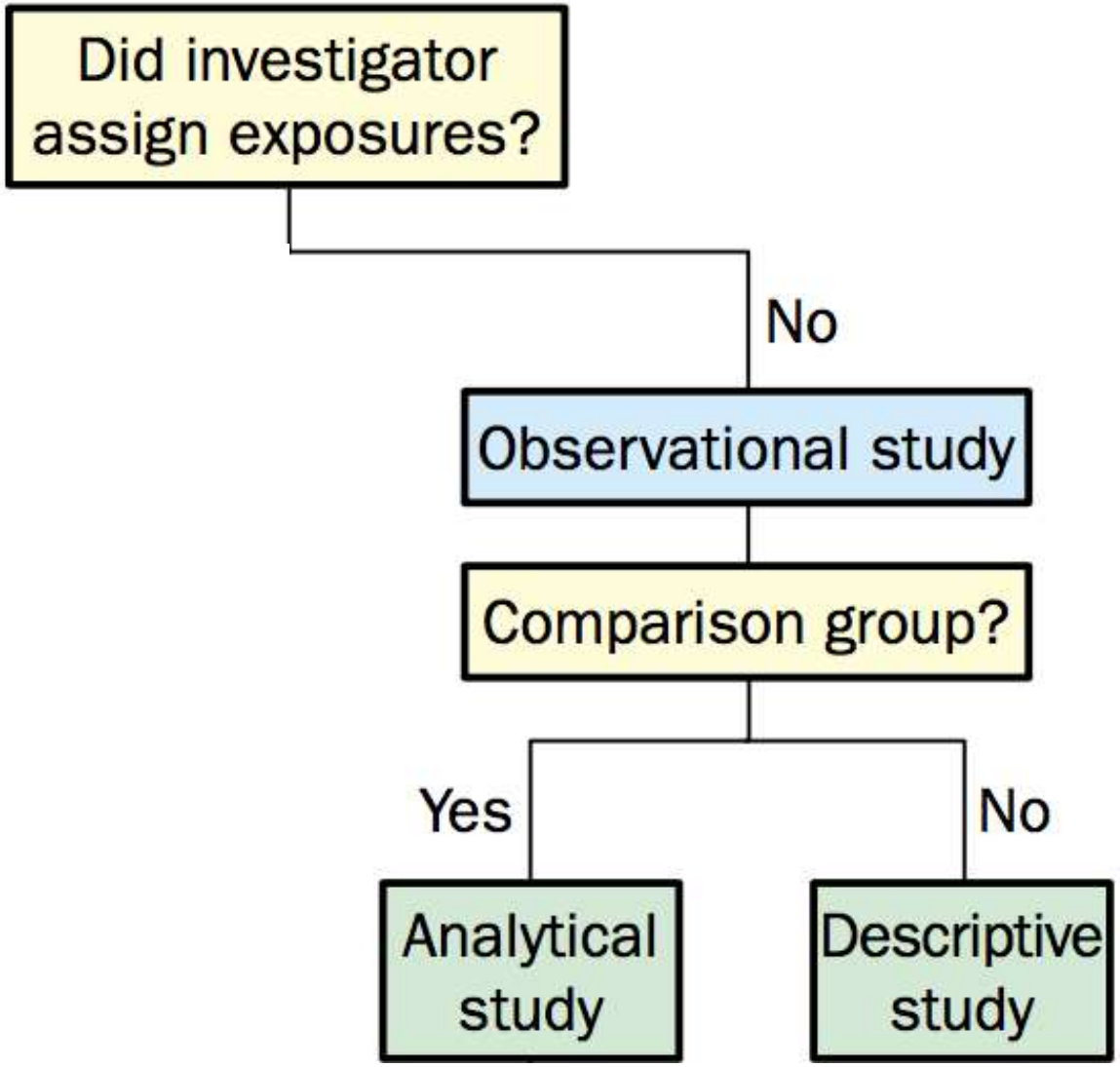

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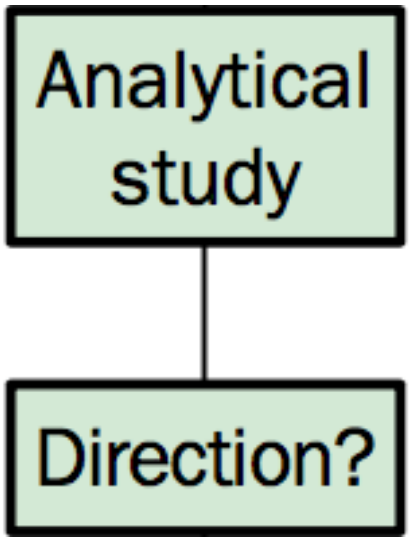
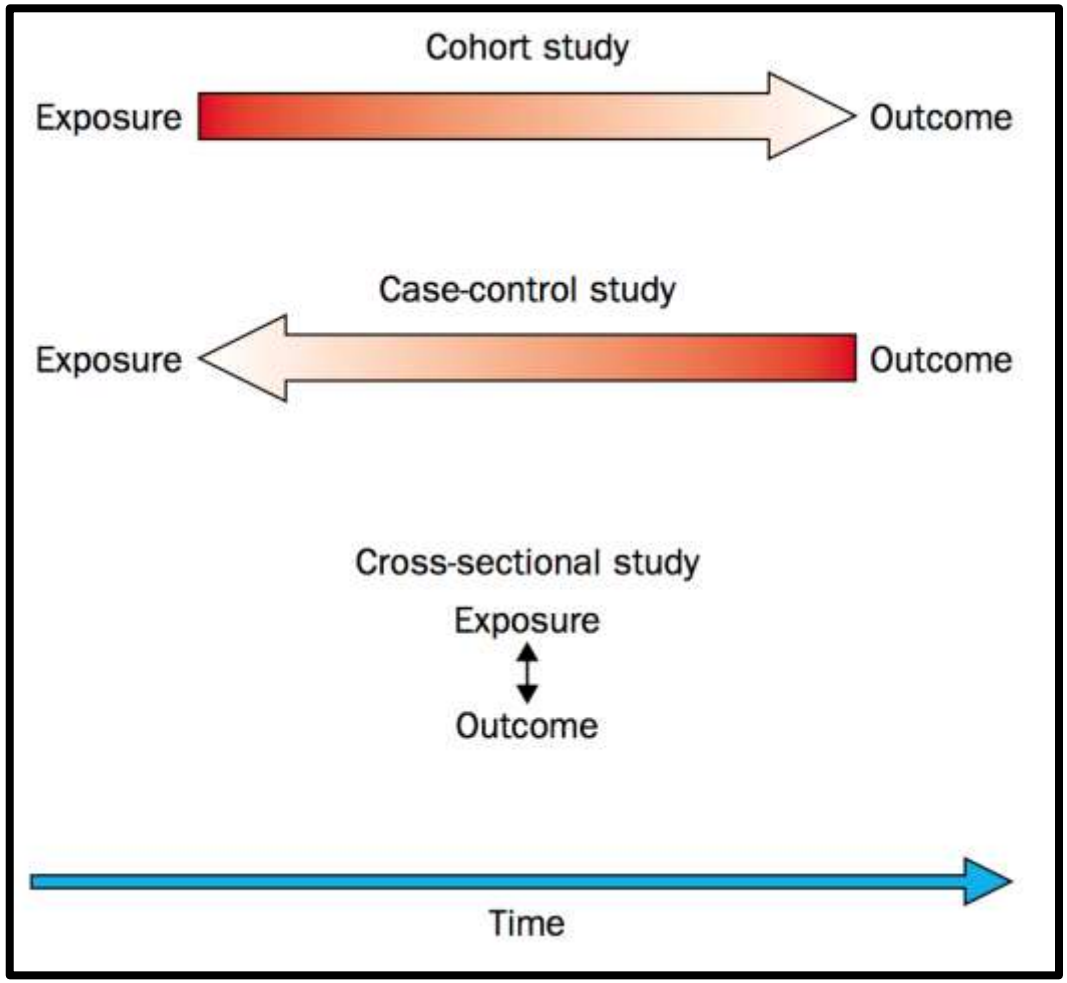




2. Describe data sources for observational studies

Data Sources: Too Complex to Label

- Choice of data source impacts study validity
- "Prospective" vs "retrospective" = useless

1982: RCT of ASA to reduce death in MI

Prospective or retrospective?

Years later: Use RCT data to answer "does having diabetes increase risk of death after an MI?"

Data Sources: Some Considerations

Factors that increase internal validity:

- Complete data recording
- Accurate measurement or surrogate for
  - Exposure
  - Possible confounders for outcome
  - Outcome
- Blinded data collection &/or adjudication

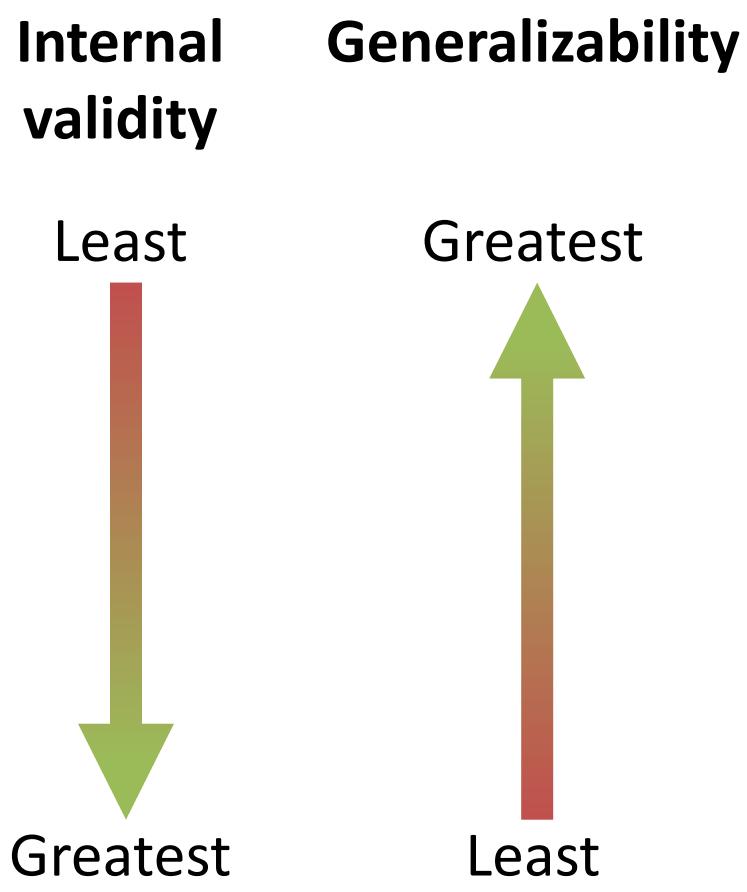
Data Sources: Non-Exhaustive List

Survey

Health records (“chart review”)

Database

- Administrative/billing
- Clinical registry
- RCT



3. Explain biases & confounding relevant to observational studies

Name That Confounder!

Confounding
by indication

D: Cohort of administrative data

P: Elderly Ontarians (all)

I: Celecoxib

C: Non-selective NSAIDs

O (“case” definition): GI bleed

Problem: Study did not account for history of prior GI bleed in design/analysis

Name That Bias!

Protopathic bias (i.e. reverse causation)

D: Cohort of administrative data

P: Elderly Americans

I: PPI

C: No PPI

O: Acute coronary syndrome @ 90 days

Problem: Misdiagnosis of intermittent stable angina as heartburn

Misclassification

Random

- Subjects in both groups have equal opportunity to be misclassified
- **Causes imprecision**

Biased

- Subjects in 1 group are more likely to be misclassified
- **Exaggerates or attenuates estimate of association**

Misclassification: Random or Biased?

Random misclassification

D: Cohort of administrative data (pre-2005)

P: Individuals without CVD

I: Statin

C: No statin

O: Diabetes identified by ICD-10 code

Problem: ~1/3 patients with diabetes are undiagnosed

Misclassification: Random or Biased?

Biased misclassification

D: Cohort using health records

P: Hospitalized medical patients

I: Heparin-based VTE prophylaxis

C: Mechanical VTE prophylaxis

O: DVT/PE confirmed by imaging

Problem: Mechanical VTE prophylaxis perceived to be less effective, increasing vigilance & frequency of imaging

4. Describe ways to minimize bias & confounding

Minimization of Bias & Confounding in Observational Studies

Design

1. Data source
2. Exposure & outcome definitions
3. Restriction
4. Matching

Analysis

1. Stratification
2. Multivariable regression (i.e. statistical adjustment)
3. Active control / tracer

Both: Propensity score

Minimization Strategies: Design

Data source

- Can minimize all sources of bias & confounding
  - More detail = better use of other strategies

Exposure & outcome definitions

- Clear, valid & reproducible
- Minimizes misclassification, immortal-time bias

Minimization Strategies: Design

Restriction (i.e. inclusion/exclusion criteria)

- Minimize confounding by indication by excluding or including only patients with “the indication”
- Can also minimize performance bias

Matching

- Select controls with same/similar key characteristics likely to cause substantial confounding (e.g. age, smoking status)
- Minimizes baseline differences & thus confounding

Minimization Strategies: Analysis

Can only account for *measured* confounders

Stratification

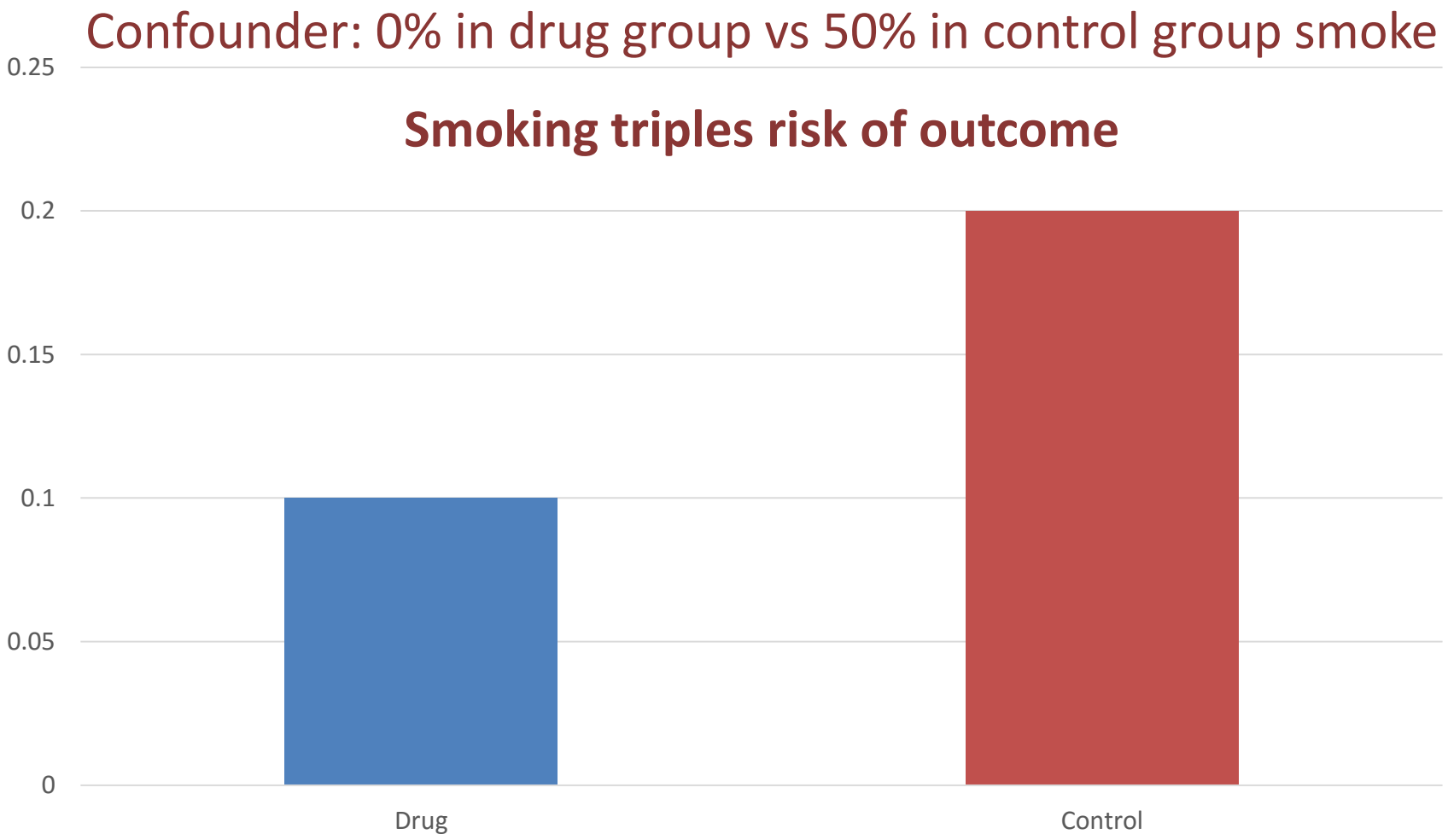
- Type of subgroup analysis
  - Tests whether exposure-outcome association related to characteristic of interest
- Pro: Simple
- Con: # of strata/co-variables limited by sample size

Minimization Strategies: Analysis

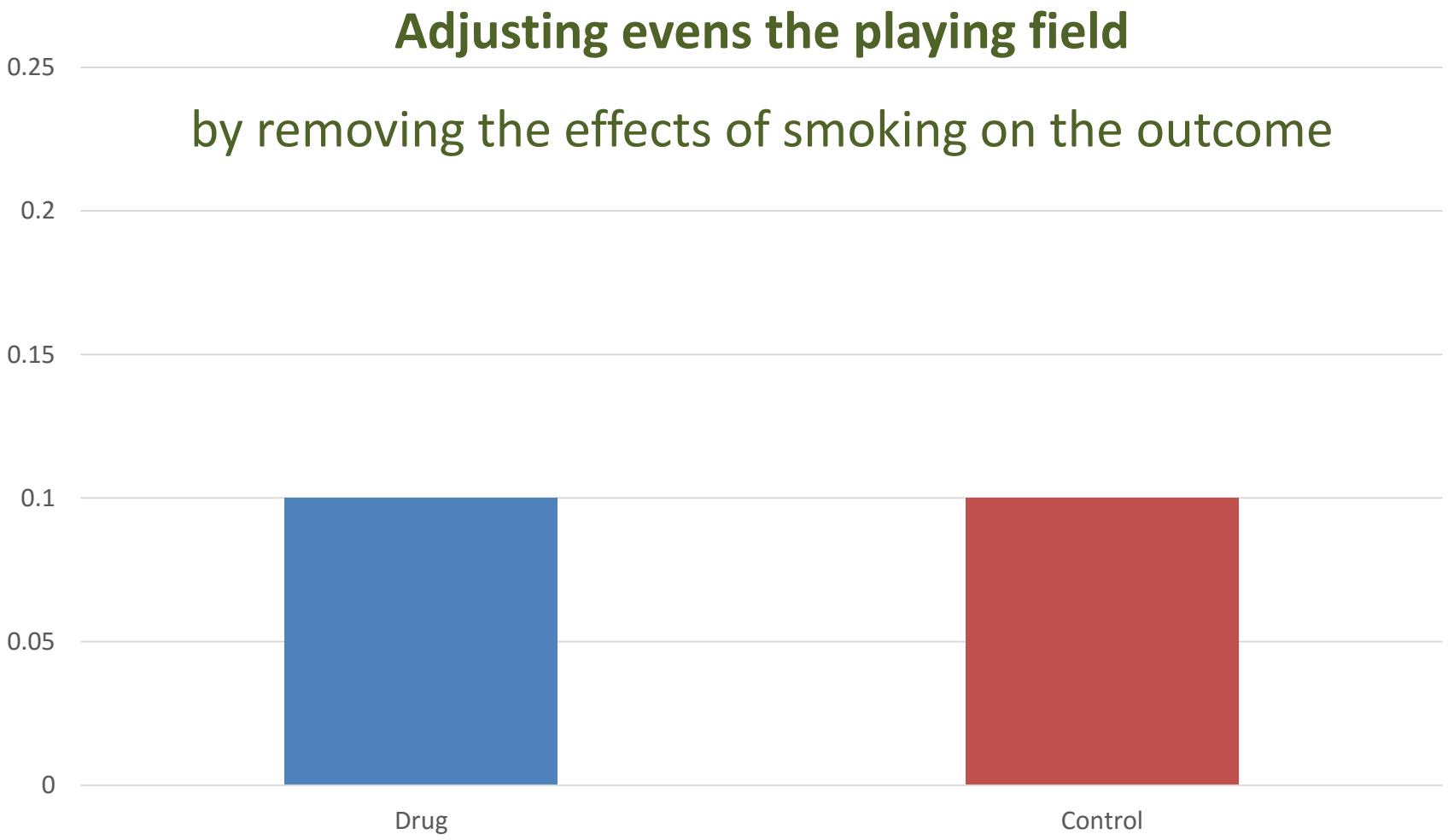
Multivariable regression (i.e. statistical adjustment)

- Mathematically removes effect of known confounders on outcome
- Pros vs stratification: Can account for multiple confounders at once

Minimization Strategies: Analysis



Minimization Strategies: Analysis



Minimization Strategies: Analysis

Further minimize confounding

- Active control
  - Control group exposed to alternate intervention
- Tracer
  - Repeat analysis replacing exposure with similar intervention not expected to be associated with outcome

Minimization Strategies: Propensity Score

- Especially useful for minimizing confounding by indication
- Answers “probability that patient would get exposed given combination of known baseline variables”
  - Score 0-100% calculated with multivariable regression
- Score can then be used as variable in design or analysis, most commonly **matching (best use of it)** or **regression**

Propensity Score: Simplified Example

"Propensity" for patient to receive statin:

1. 35 y/o female, no FHx CVD, SBP 110, LDL 1.4 **~0%**
2. 45 y/o male, T2DM, SBP 140, LDL 3.0 (Framingham ~15%) **~60%**
3. 50 y/o female, smoker, SBP 150, LDL 2.5 (Framingham ~15%) **~60%**
4. 65 y/o male, smoker, T2DM, MI treated with drug-eluting stent 7 months ago **≤100%**

Why NERDCAT-Obs?

Numerous other methods/tools, e.g.

- Users' Guides to the Medical Literature questions
  - & derivative checklists including those from "CASP"
- STROBE checklist *(for reporting standards)*
- Newcastle-Ottawa Scale *(superficial numerical rating scale)*

Why NERDCAT-Obs?

Issues with existing checklists

- Too superficial or complex
- Insufficient guidance for interpretation (i.e. what's good/bad)
- Not focused on bias/confounding & their minimization
- Not focused on clinical implementation of evidence
  - Don't help your answer "so what do I do with this…?

NERDCAT-Obs:

A clinician's guide to appraising observational studies (cohort & case-control studies)

NERDCAT-Obs: Sections

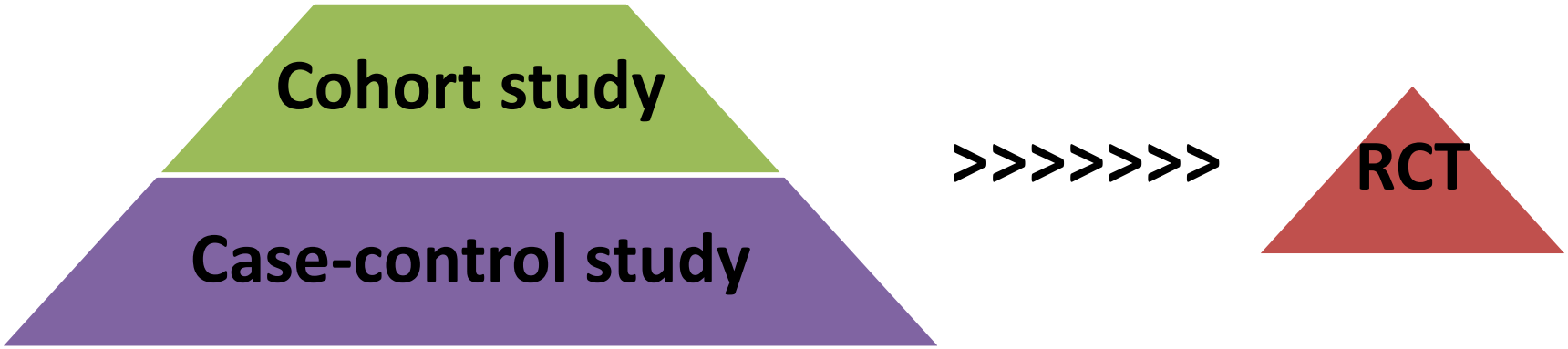
1. Clinical question (PICO)
2. Generalizability
3. Internal validity
4. Results
5. Interpretation

Interpretation: Put it all together

- Generalizability: Who does this apply to?
- Internal validity:
  - What's the likelihood/degree of residual bias/confounding?
  - What impact is this to have on the magnitude & direction of effect?
- Results
  - Best case vs worst case scenario (+/- residual bias/confounding)
  - Translate to absolute values; clinically important?

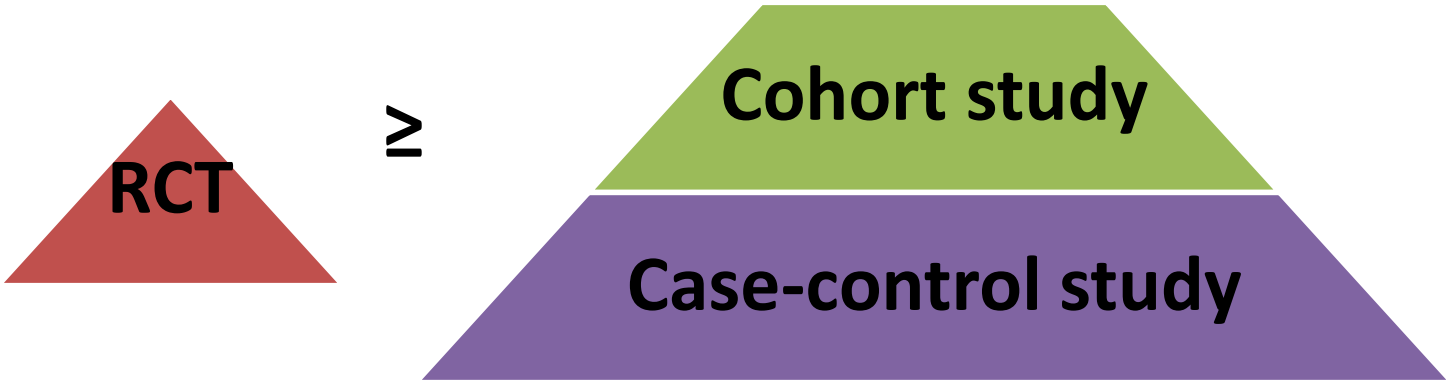
Session Summary

1. In quantity



Session Summary

2. In value/reliability



Session Summary

3. Prospective cohort > retrospective cohort

Cohort > case-control

Does the data source allow for sufficient minimization of misclassification, bias & confounding?

Session Summary

4. Use of NERDCAT-Obs or other appraisal tools can help turn
   - X “it’s observational, so it doesn’t change my practice” to
   - √ “these results in context of these limitations allow me to make the following changes to my practice…”

General References

NERDCAT-Obs & other critical appraisal tools

- Most recent version always available from https://nerdlmps.wordpress.com/critical-appraisal-tools/)

Books

- Clinical Epidemiology: How to Do Clinical Practice Research, 3rd Edition (2005).
- Users' Guides to the Medical Literature, 2nd Edition (2008).