Large-scale observational research
What is the quality of the current evidence from observational analyses?

August 2010: “Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer.”

Sept 2010: “In this large nested case-control study within a UK cohort [General Practice Research Database], we found a significantly increased risk of oesophageal cancer in people with previous prescriptions for oral bisphosphonates.”
Distribution of possible results for one hypothesis

Stat signif > 1

OR

Databases

Methods
Distribution of possible results for one hypothesis

OR

Stat signif > 1

Databases

Methods
Distribution of possible results for one hypothesis

OR

Stat signif > 1

Stat signif < 1

Databases

Methods
Distribution of possible results for one hypothesis

OR

JAMA  BMJ

Study #3

Methods

Databases
Distribution of possible results for one hypothesis

OR

Databases

Methods

OR
Take a scientific approach to science

1. **Database heterogeneity:**
   Holding analysis constant, different data may yield different estimates
     “Evaluating the Impact of Database Heterogeneity on Observational Study Results”

2. **Parameter sensitivity:**
   Holding data constant, different analytic design choices may yield different estimates

3. **Empirical performance:**
   Most observational methods do not have nominal statistical operating characteristics
   - Ryan PB, Stang PE, Overhage JM et al, Drug Safety, 2013:
     “A Comparison of the Empirical Performance of Methods for a Risk Identification System”

4. **Empirical calibration can help restore interpretation of study findings**
   - Schuemie MJ, Ryan PB, DuMouchel W, et al, Statistics in Medicine, 2013:
     “Interpreting observational studies: why empirical calibration is needed to correct p-values”
Open science

• Admit that there is a problem
• Study it scientifically
  – Define that surface and differentiate true variation from confounding ...
• Total description of every study
• Research into new methods

• Show work by Schuemie, Suchard, Ryan, Madigan, Hripcsak, ...
Standard error vs effect size

Statistically significant
Observational research results in literature

85% of exposure-outcome pairs significant

29,982 estimates
11,758 papers
Observational research results in literature

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