Large-scale observational research

What is the quality of the current evidence from observational analyses?

ORIGINAL CONTRIBUTION

JAMA®

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

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Context Use of oral bisphosphonates has increased dr
and elsewhere. Esophagitis is a known adverse effect o
cent reports suggest a link between bisphosphonate us
this has not been robustly investigated.

Objective To investigate the association between bis
ageal cancer.

Design, Setting, and Participants Data were ex

Conclusion Among patients in the UK General Practic
of oral bisphosphonates was not significantly associate
gastric cancer.

JAMA. 2010;304(6):657-663

August2010: "Among patients in the UK General Practice Research Database, the use of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer"

BMJ

RESEARCH

Oral bisphosphonates and risk of cancer of oesophagus, stomach, and colorectum: case-control analysis within a UK primary care cohort

Jane Green, clinical epidemiologist,[1] Gabriela Czanner, statistician,[1] Gillian Reeves, statistical epidemiologist,[1] Joanna Watson, epidemiologist,[1] Lesley Wise, manager, Pharmacoepidemiology Research and Intelligence Unit,[2] Valerie Beral, professor of cancer epidemiology[1]

ABSTRACT

Objective To examine the hypothesis that risk of oesophageal, but not of gastric or colorectal, cancer is increased in users of oral bisphosphonates.

Design Nested case-control analysis within a primary care cohort of about 6 million people in the UK, with prospectively recorded information on prescribing of bisphosphonates.

Setting UK General Practice Research Database cohort.

Participants Men and women aged 40 years or over—2954 with oesophageal cancer, 2018 with gastric cancer, and 10 641 with colorectal cancer, diagnosed in 1995-2005; five controls per case matched for age, sex, general practice, and observation time.

Main outcome measures Relative risks for incident invasive cancers of the oesophagus, stomach, and colorectum, adjusted for smoking, alcohol, and body mass index.

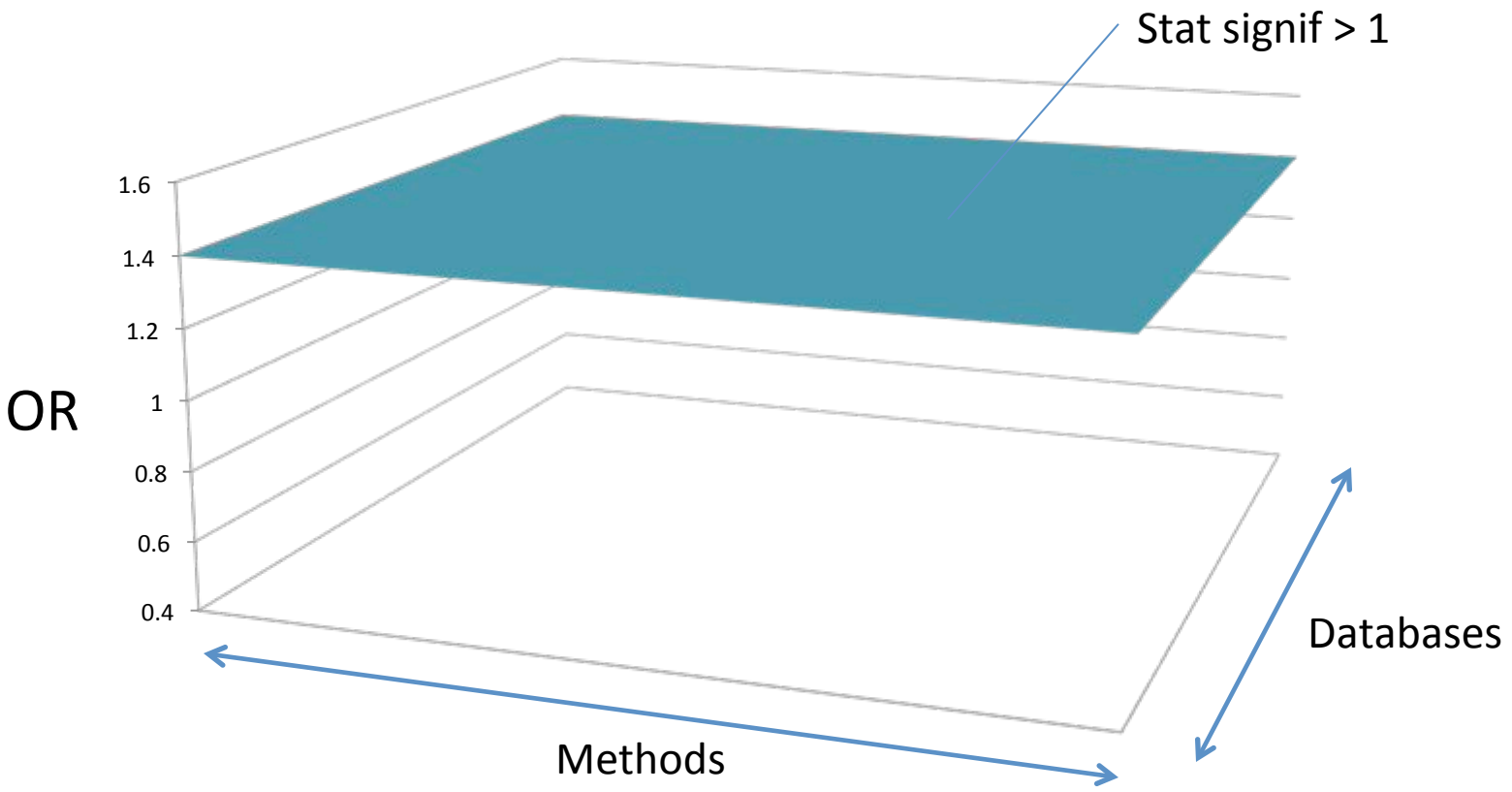
Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period. In Europe and North America, the incidence of oesophageal cancer at age 60-79 is typically 1 per 1000 population over five years, and this is estimated to increase to about 2 per 1000 with five years' use of oral bisphosphonates.

INTRODUCTION

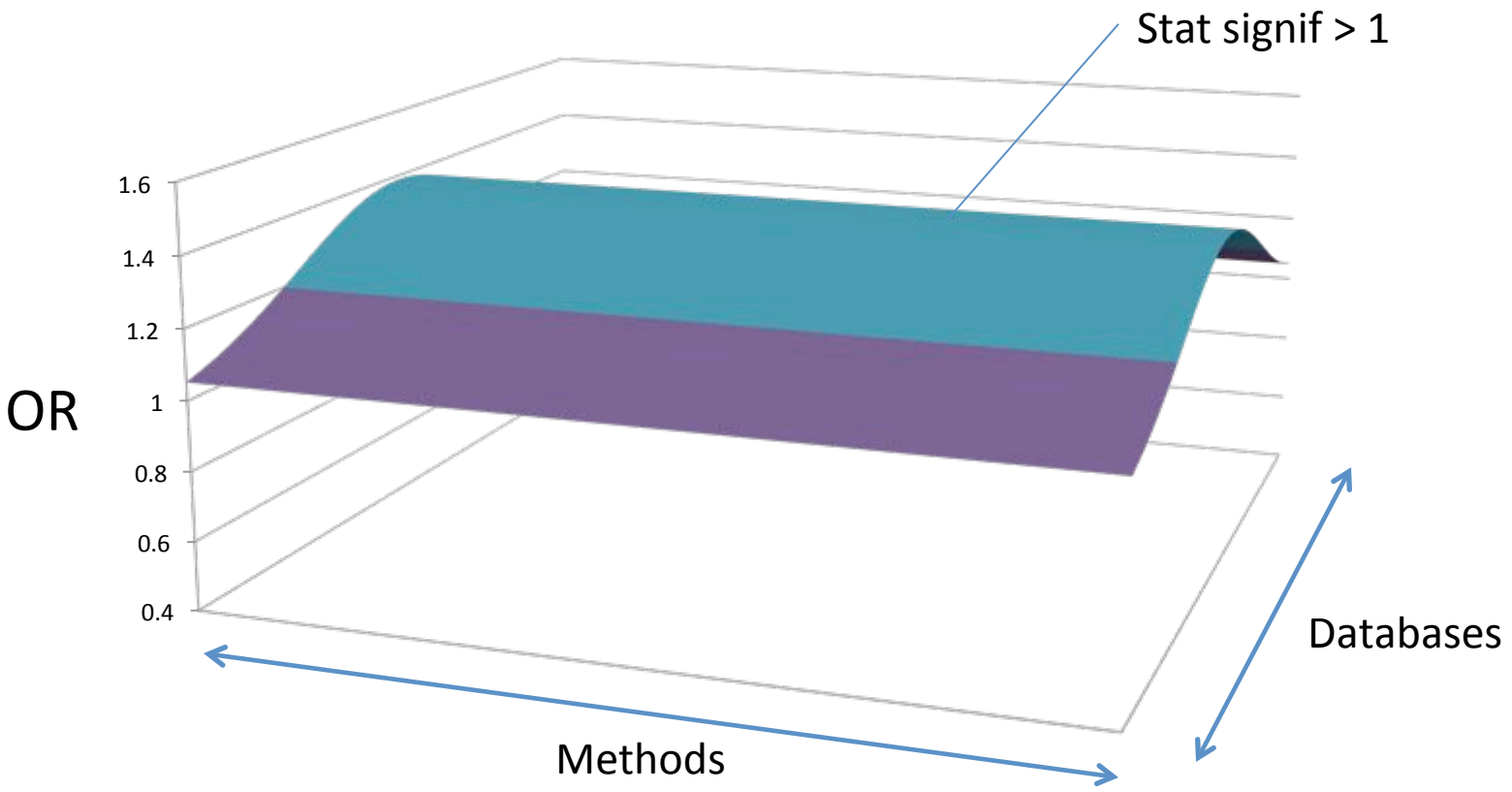
Adverse gastrointestinal effects are common among people who take oral bisphosphonates for the prevention and treatment of osteoporosis; they range from dyspepsia, nausea, and abdominal pain to erosive oesophagitis and oesophageal ulcers.[1] Recent case reports have suggested a possible increase in the risk of oesophageal cancer with use of such bisphosphonate preparations.[2] We report here on the relation between prospectively recorded prescribing information for

Sept2010: "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



Distribution of possible results for one hypothesis



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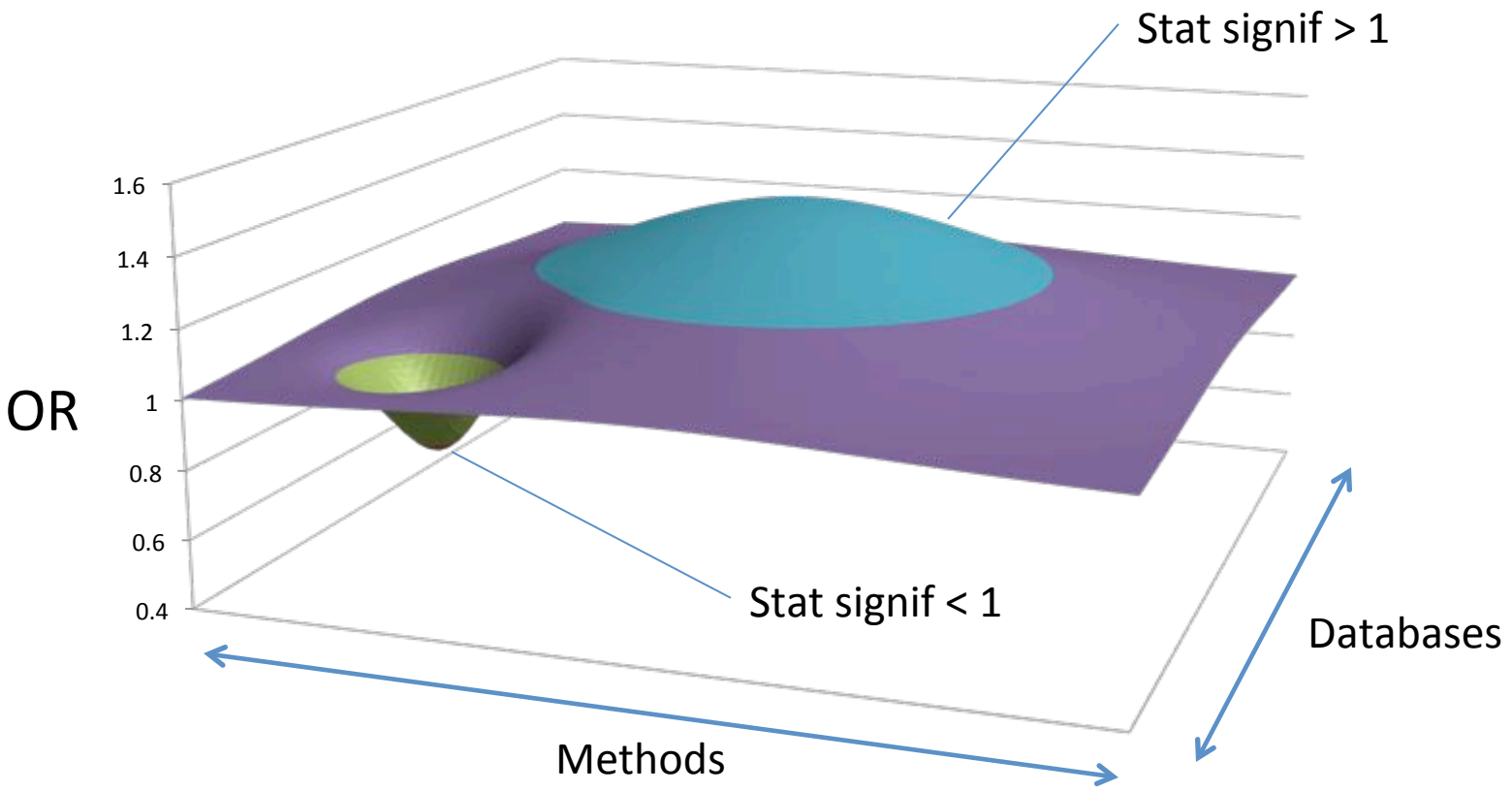

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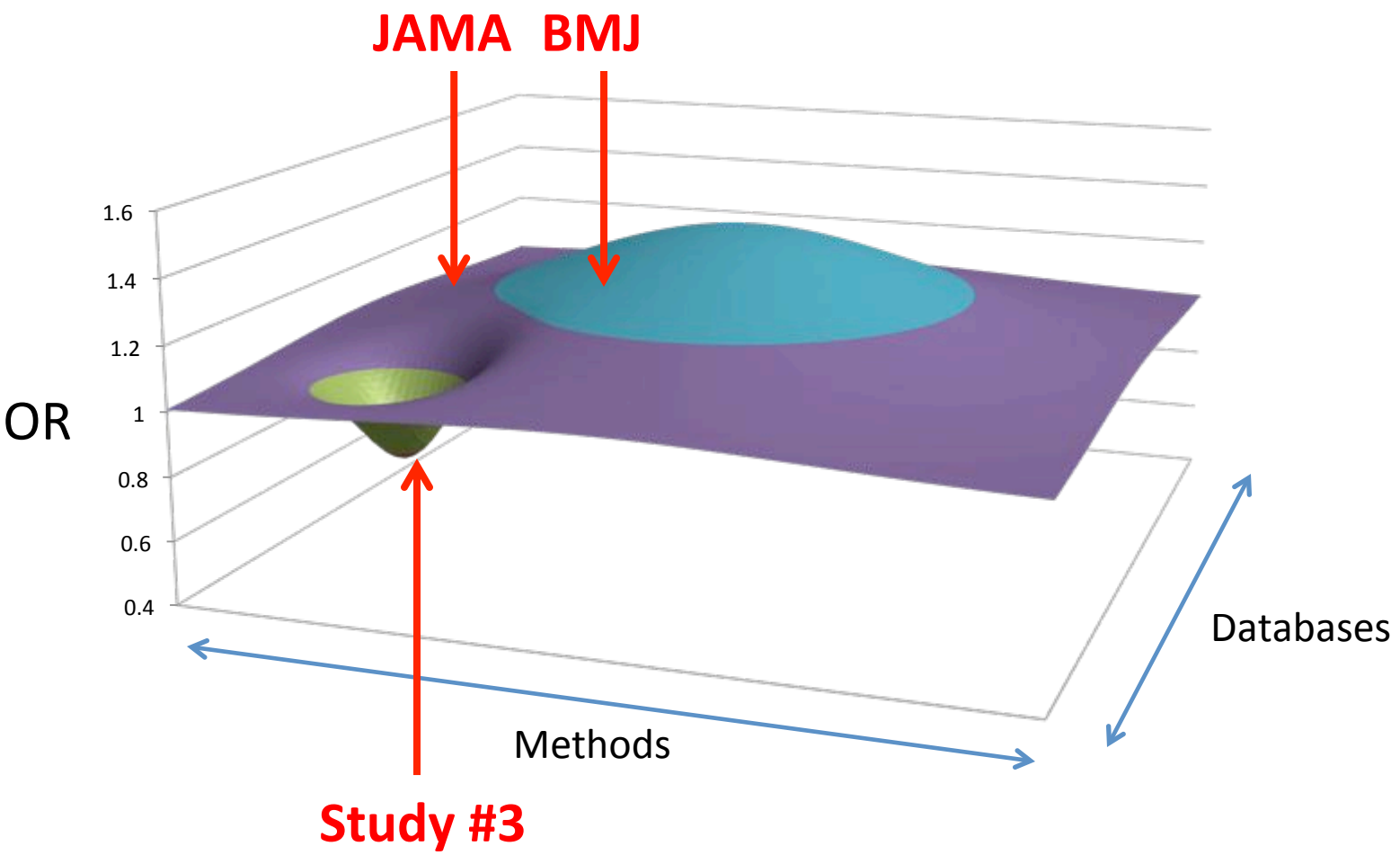

Distribution of possible results for one hypothesis

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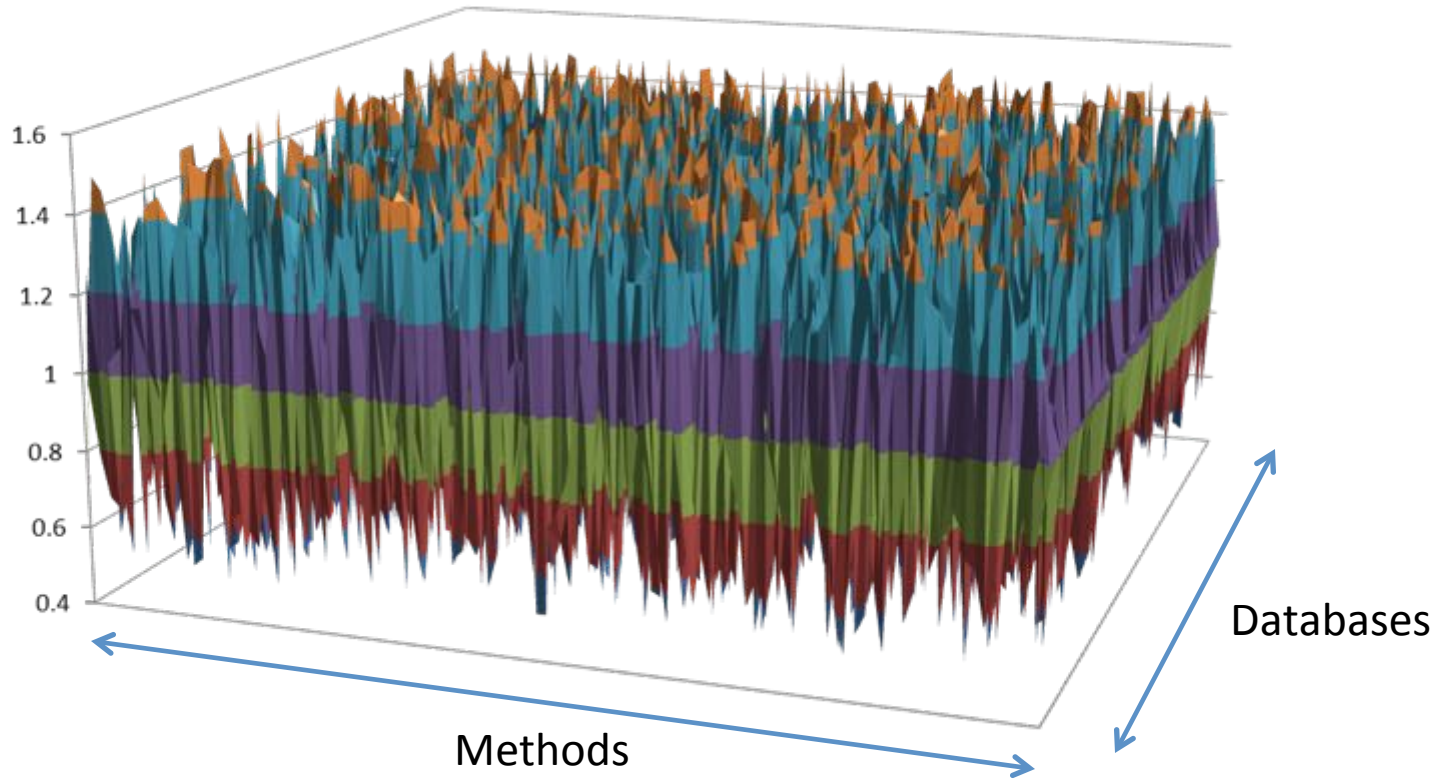


Take a scientific approach to science

1. Database heterogeneity:
   Holding analysis constant, different data may yield different estimates

Madigan D, Ryan PB, Schuemie MJ et al, American Journal of Epidemiology, 2013
"Evaluating the Impact of Database Heterogeneity on Observational Study Results"

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

Madigan D, Ryan PB, Schuemie MJ, Therapeutic Advances in Drug Safety, 2013: "Does design matter? Systematic evaluation of the impact of analytical choices on effect estimates in observational studies"

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

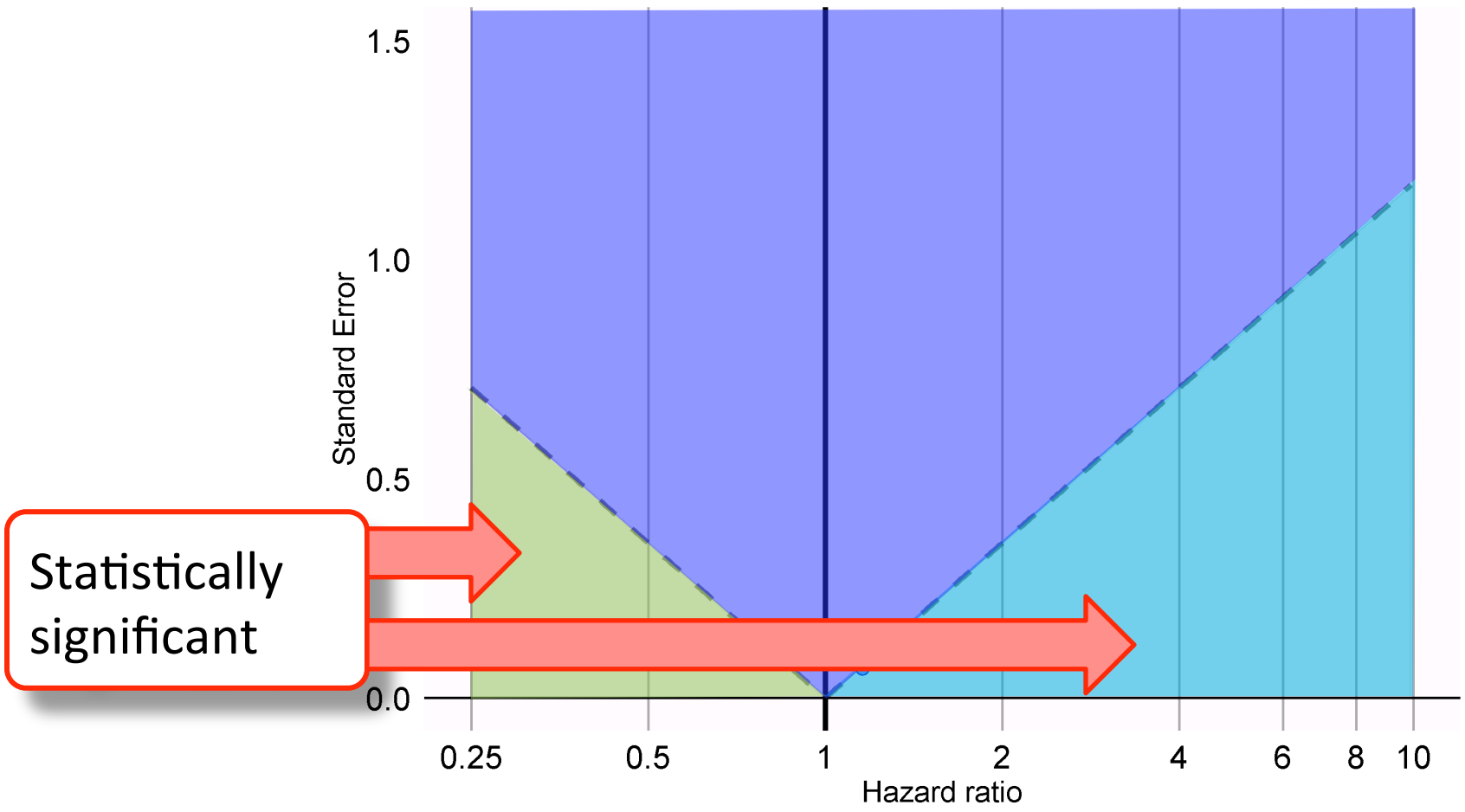
Schuemie MJ, Ryan PB, DuMouchel W, et al, Statistics in Medicine, 2013:
"Interpreting observational studies: why empirical calibration is needed to correct p-values"

Open science

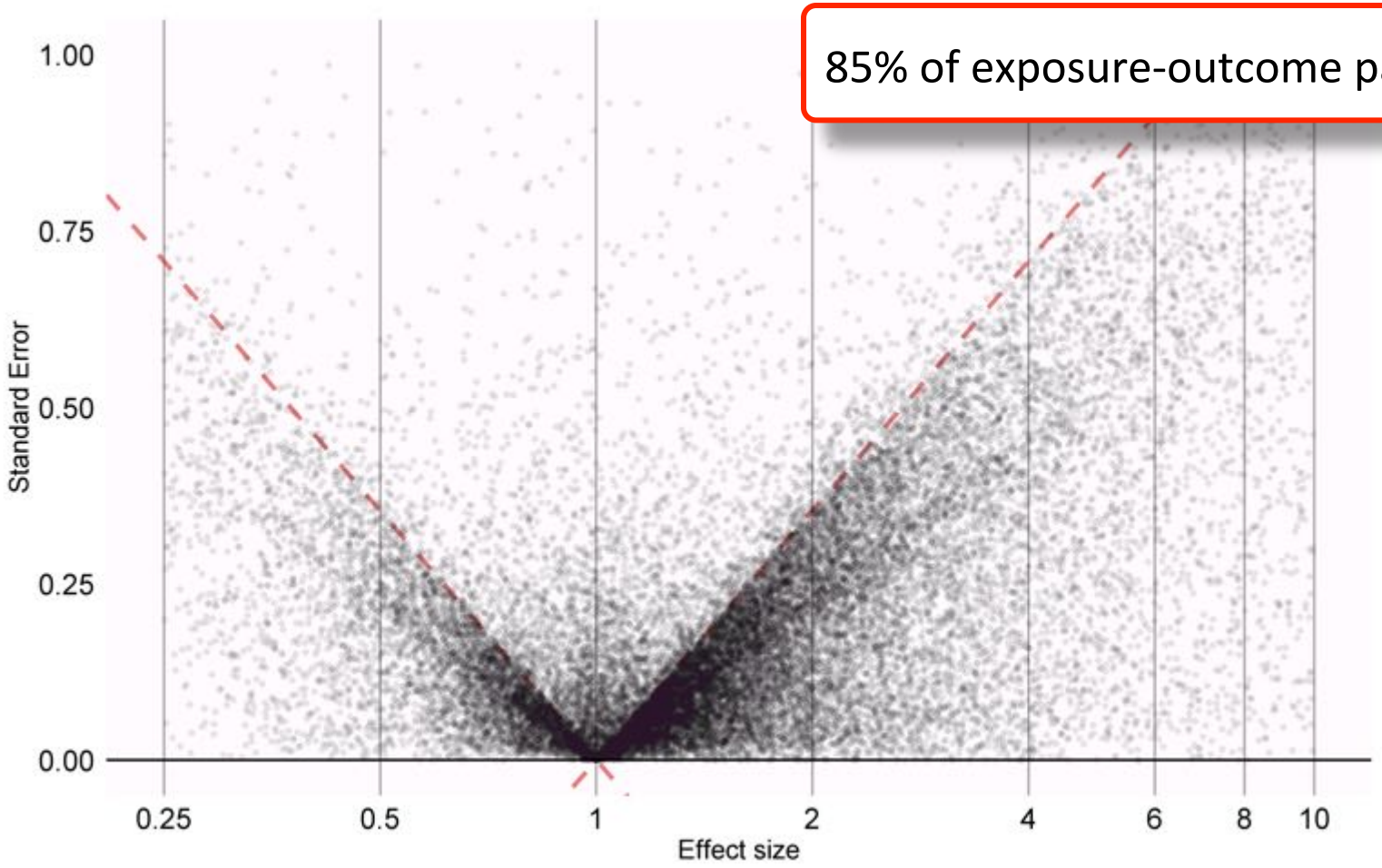
- Admit that there is a problem
- Study it scientifically
  - Define that surface and differentiate true variation from confounding …
- Total description of every study
- Research into new methods

- Show work by Schuemie, Suchard, Ryan, Madigan, Hripcsak, …

Standard error vs effect size



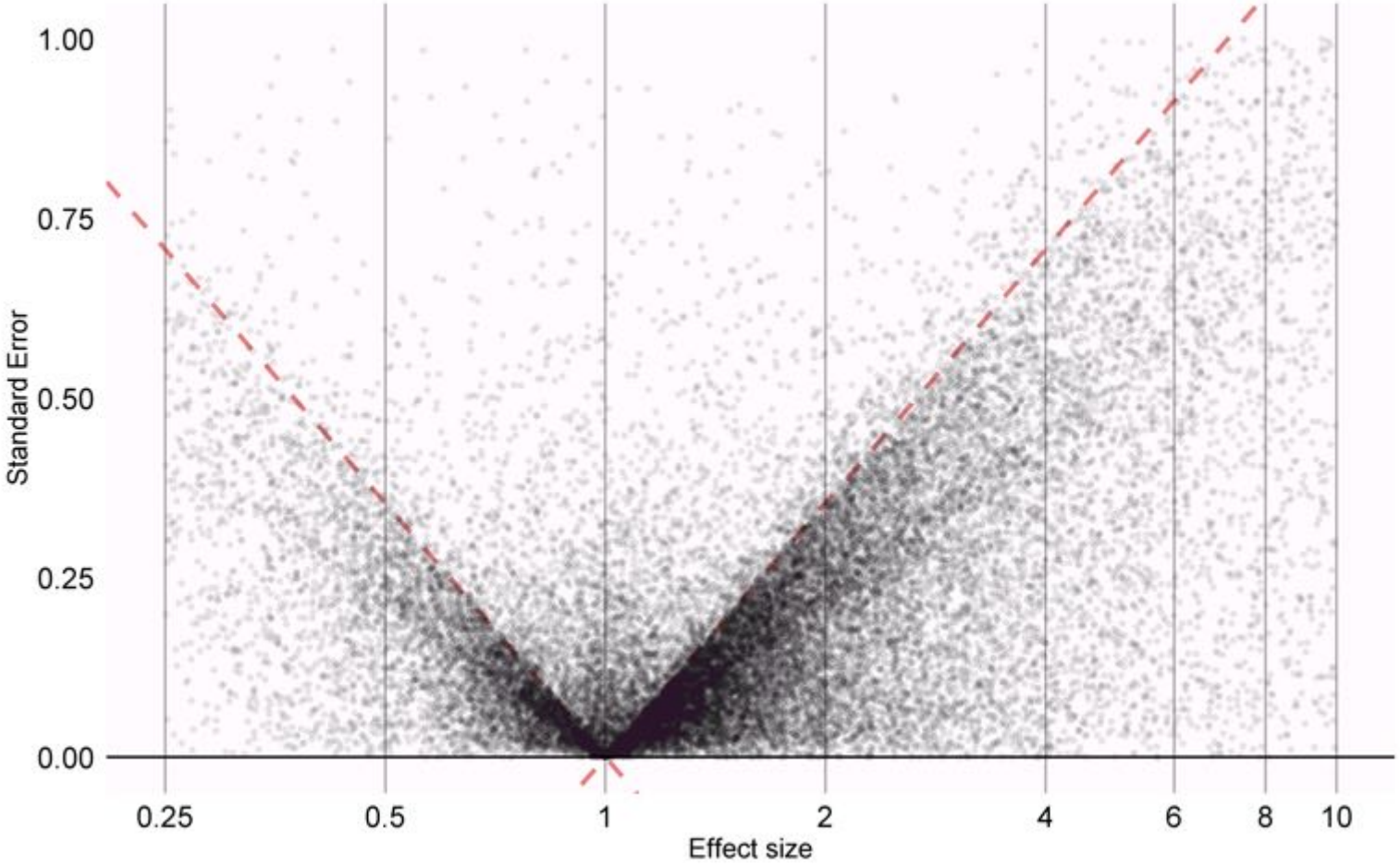
Observational research results in literature



85% of exposure-outcome pairs significant

29,982 estimates
11,758 papers

Observational research results in literature



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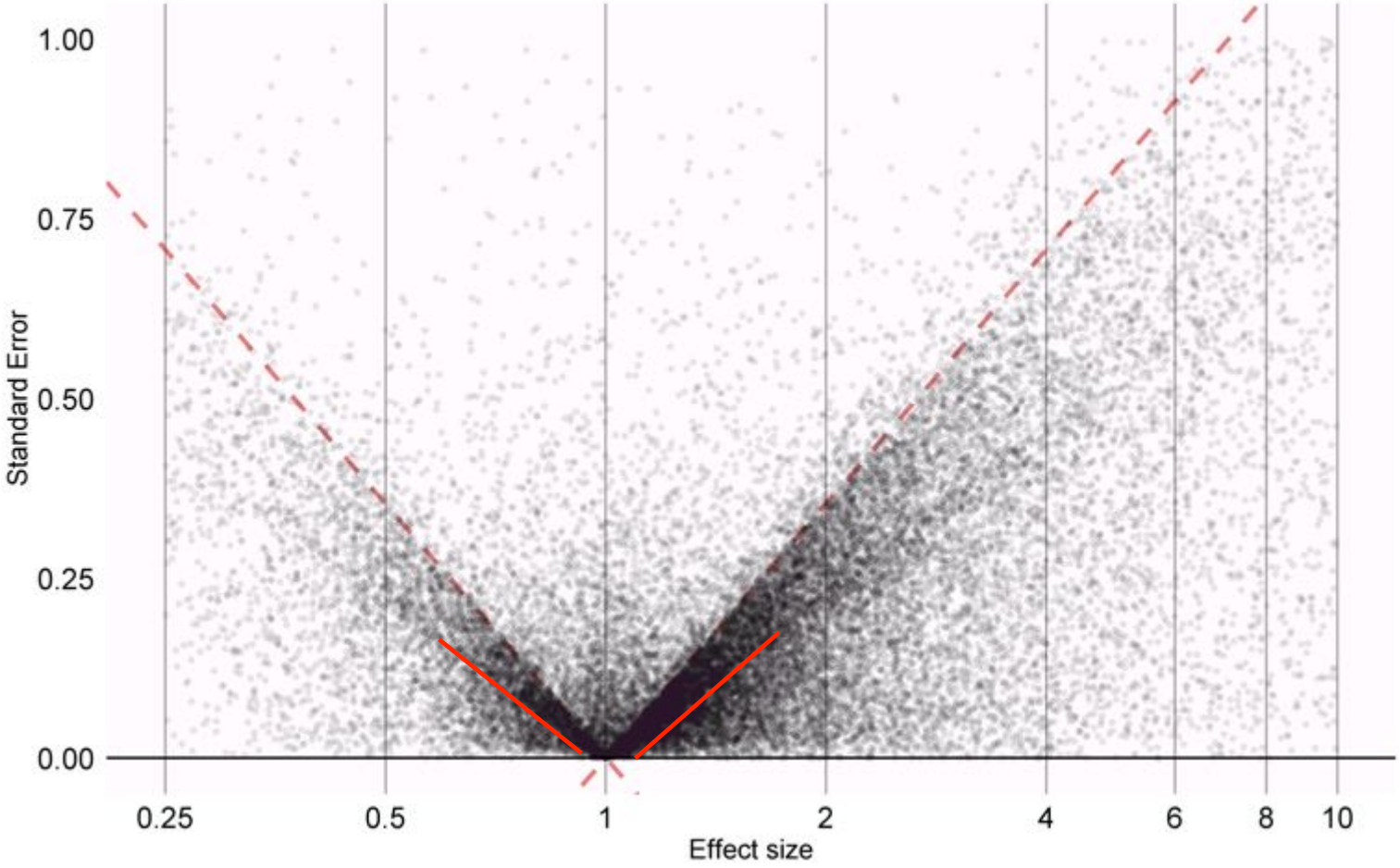

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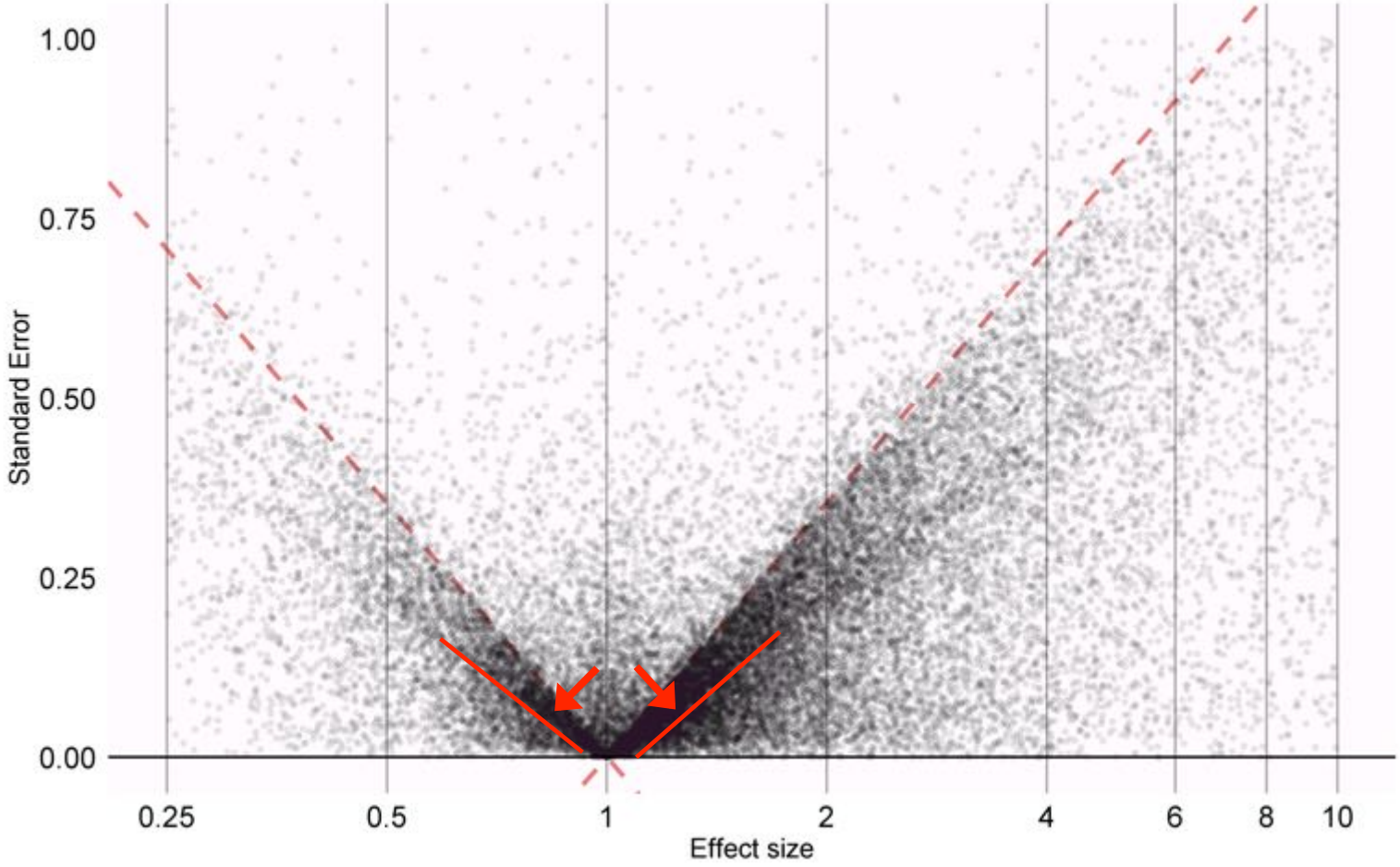

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