



# 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 dramatically and elsewhere. Esophagitis is a known adverse effect of these drugs, and recent reports suggest a link between bisphosphonate use and esophageal cancer; this has not been robustly investigated.

**Objective** To investigate the association between bisphosphonate use and esophageal cancer.

**Design, Setting, and Participants** Data were extracted from the UK General Practice Research Database (GPRD) between 1995 and 2008. The study included 1,000,000 patients with a history of bisphosphonate use.

**D**ISPHOSPHONATES INHIBIT OSTEOCLAST-MEDIATED BONE RESORPTION AND INCREASE BONE DENSITY.

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”

sembles ground alendronate tablets has been found on biopsy in patients with bisphosphonate-related esophagitis, and follow-up endoscopies have shown that abnormalities remain after the esophagitis heals.<sup>6</sup> Reflux esophagitis is an established risk factor for esophageal cancer through the Barrett pathway.<sup>7-9</sup> It is not known whether bisphosphonate-related esophagitis can also increase esophageal cancer risk. However, the US Food and Drug Administration recently reported 23 cases of esophageal cancer (between 1995 and 2008) in patients using the bisphosphonate alendronate and a further 31 cases in patients using bisphosphonates in Europe.

cohort. The incidence of esophageal and gastric cancer per person-years of risk in both the bisphosphonate and control groups was 0.44 and 0.44 per 1000 person-years of risk, respectively. The risk of esophageal and gastric cancer combined between bisphosphonate use (adjusted hazard ratio, 0.96 [95% confidence interval, 0.77-1.49]). There was no difference in risk of cancer by duration of bisphosphonate intake.

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

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

Large studies with appropriate comparison groups, adequate follow-up, robust characterization of bisphosphonate use, and appropriate outcome definitions are needed to determine whether bisphosphonate use increases esophageal cancer risk. We undertook a

## BMJ

## RESEARCH

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

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DOI: 10.1136/bmj.2010.244444

#### 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.

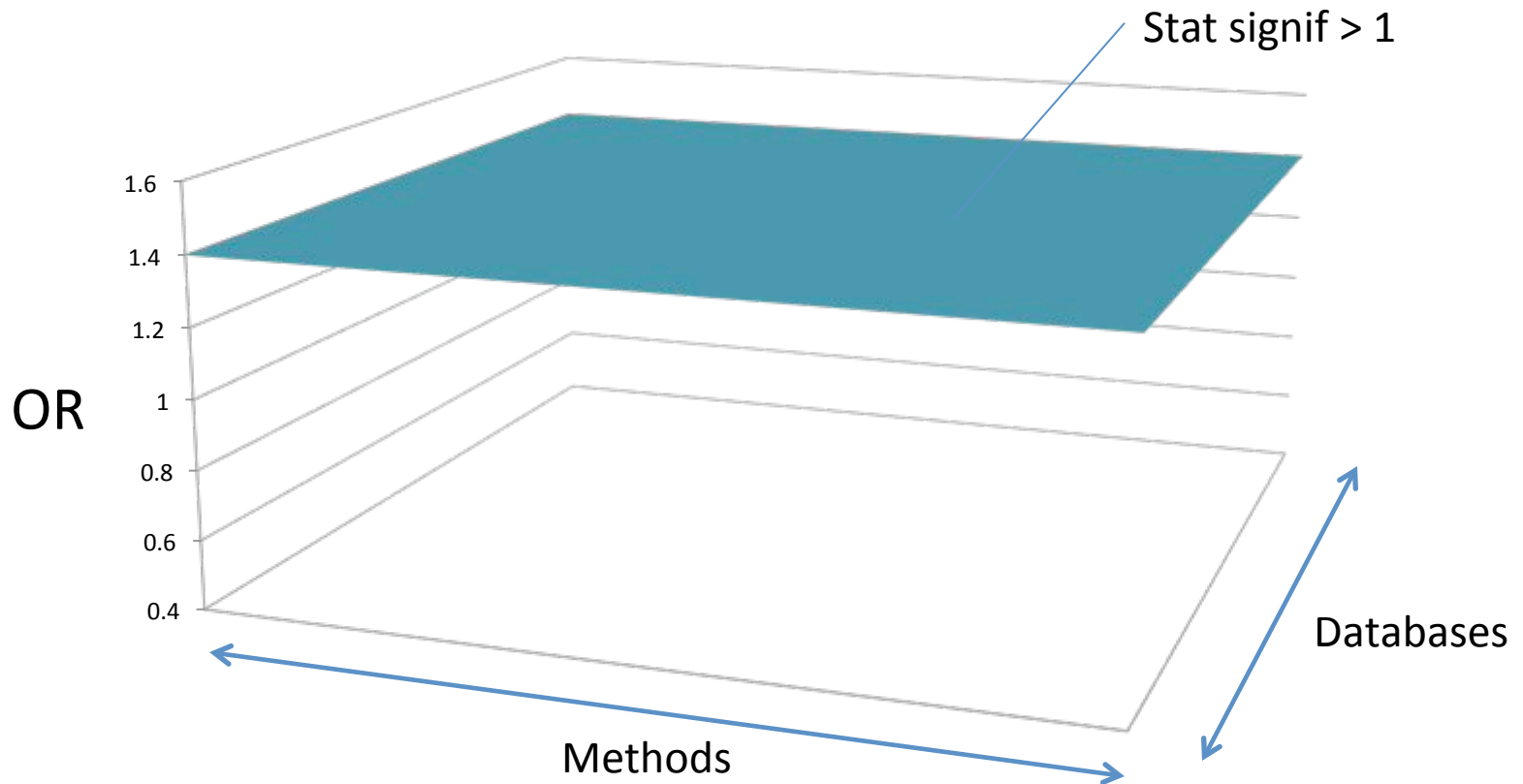
#### INTRODUCTION

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.<sup>1</sup> Recent case reports have suggested a possible increase in the risk of oesophageal cancer with use of such bisphosphonate preparations.<sup>2</sup> We report here on the relation between prospectively recorded prescribing information for

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”

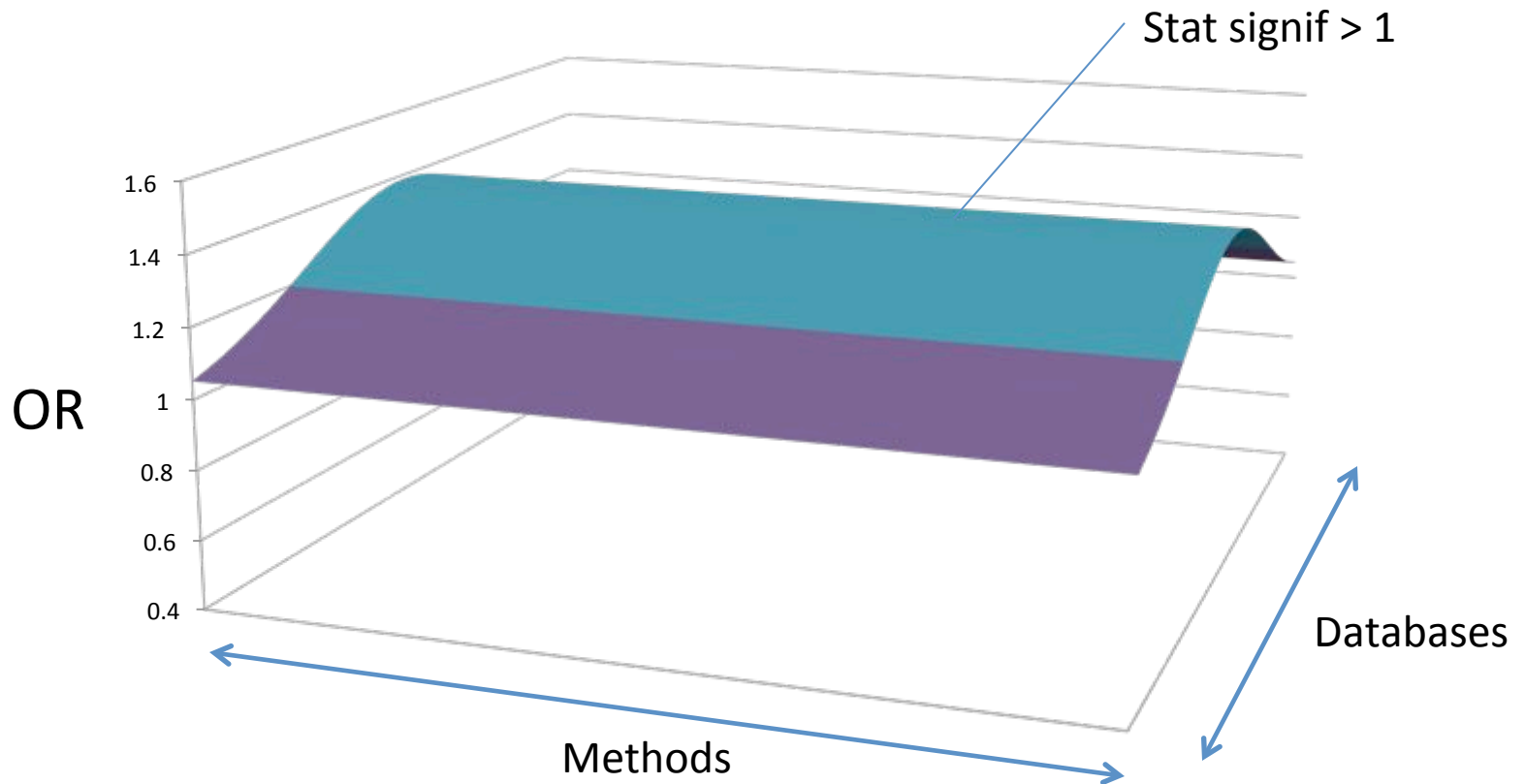


# Distribution of possible results for one hypothesis



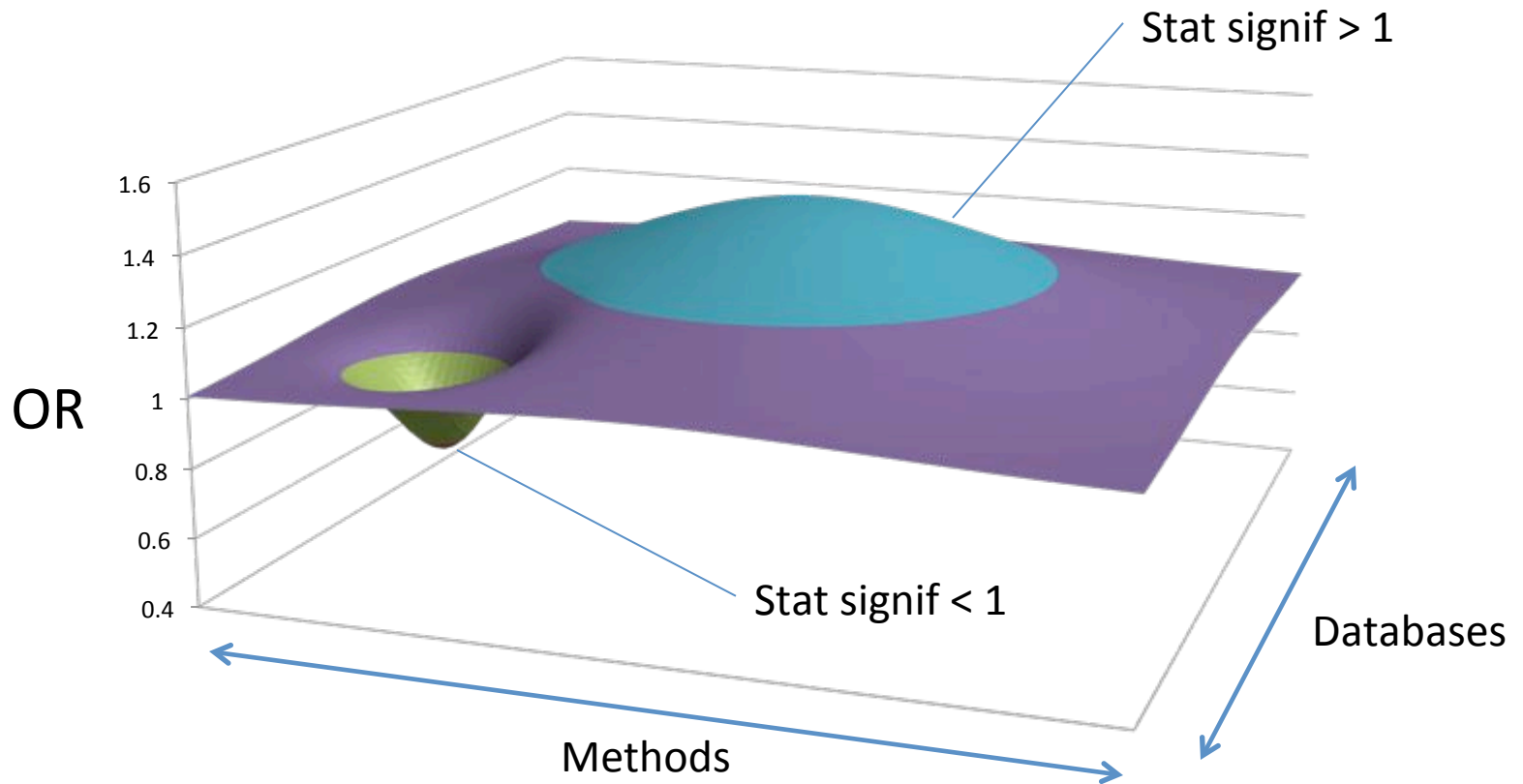


# Distribution of possible results for one hypothesis



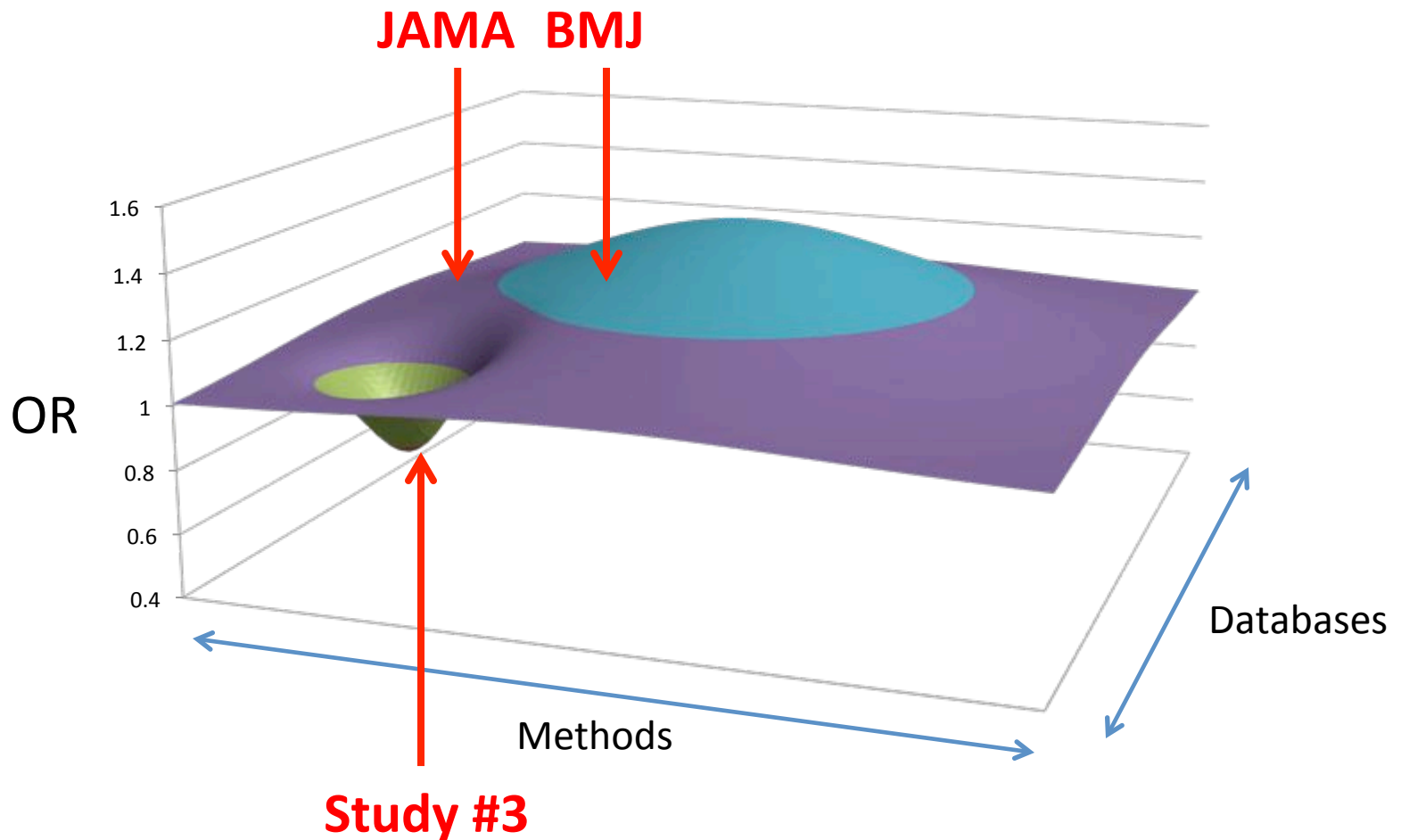


# Distribution of possible results for one hypothesis



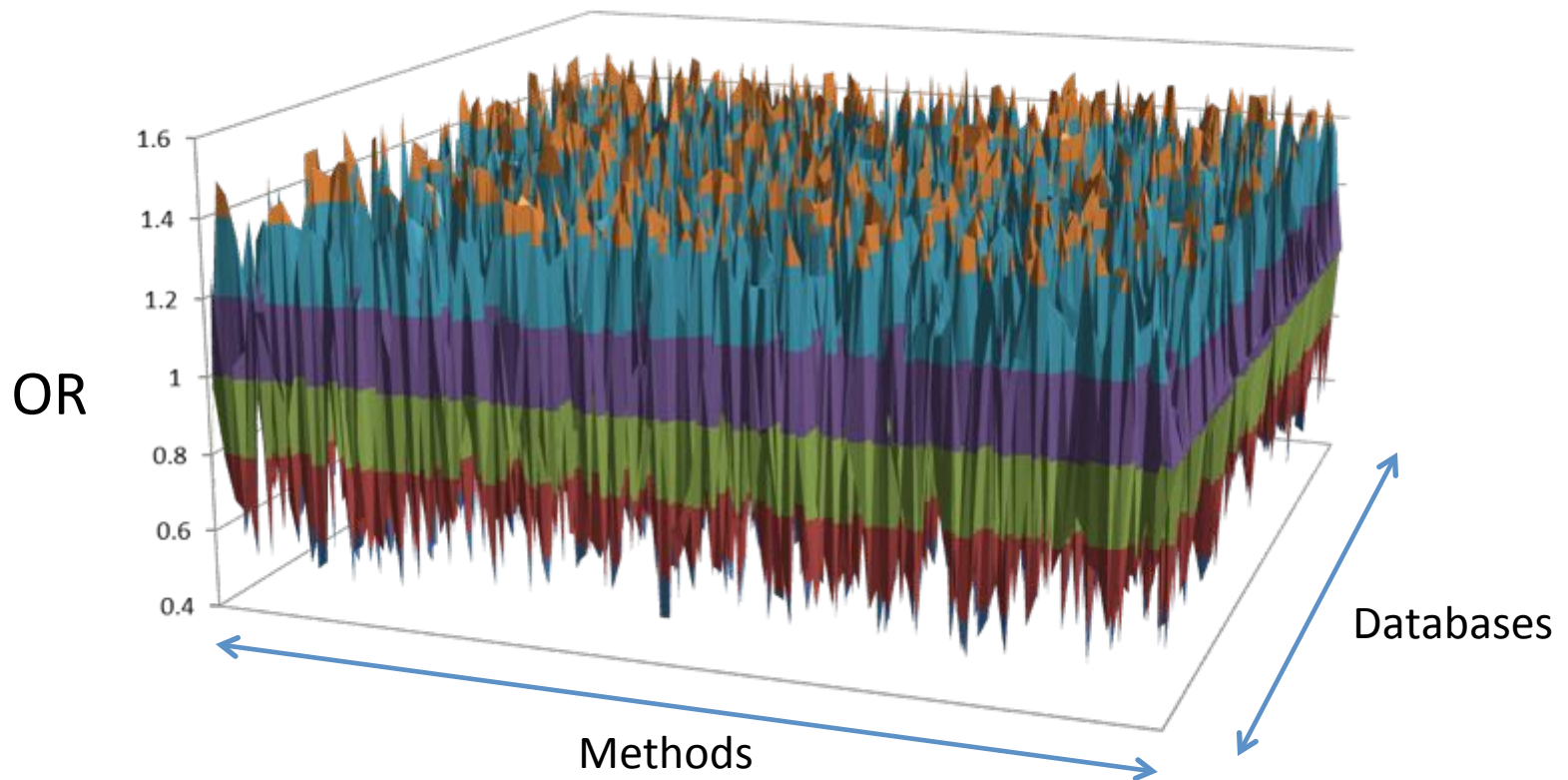


# Distribution of possible results for one hypothesis





# Distribution of possible results for one hypothesis







# 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”



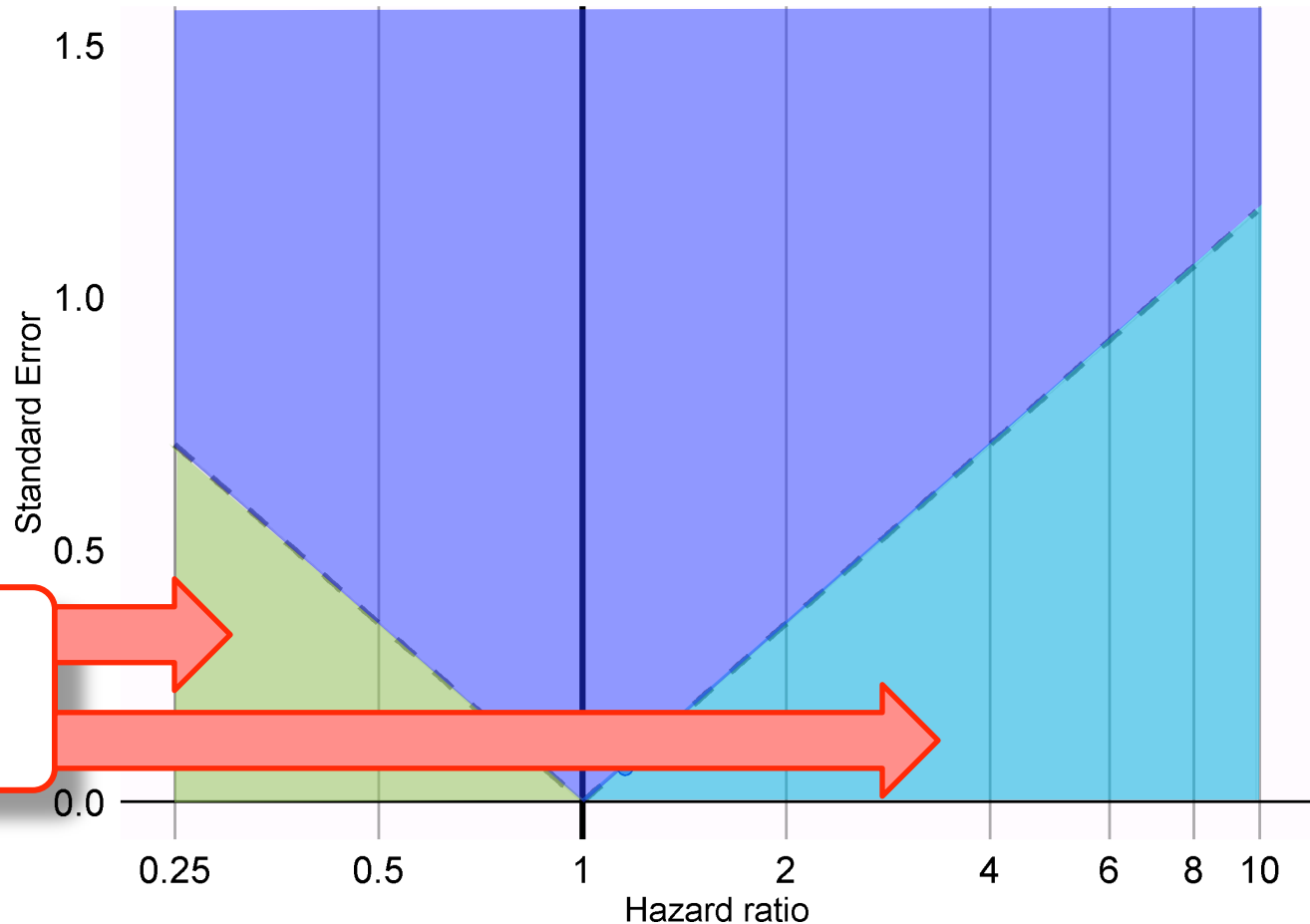


# Open science

- 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, ...
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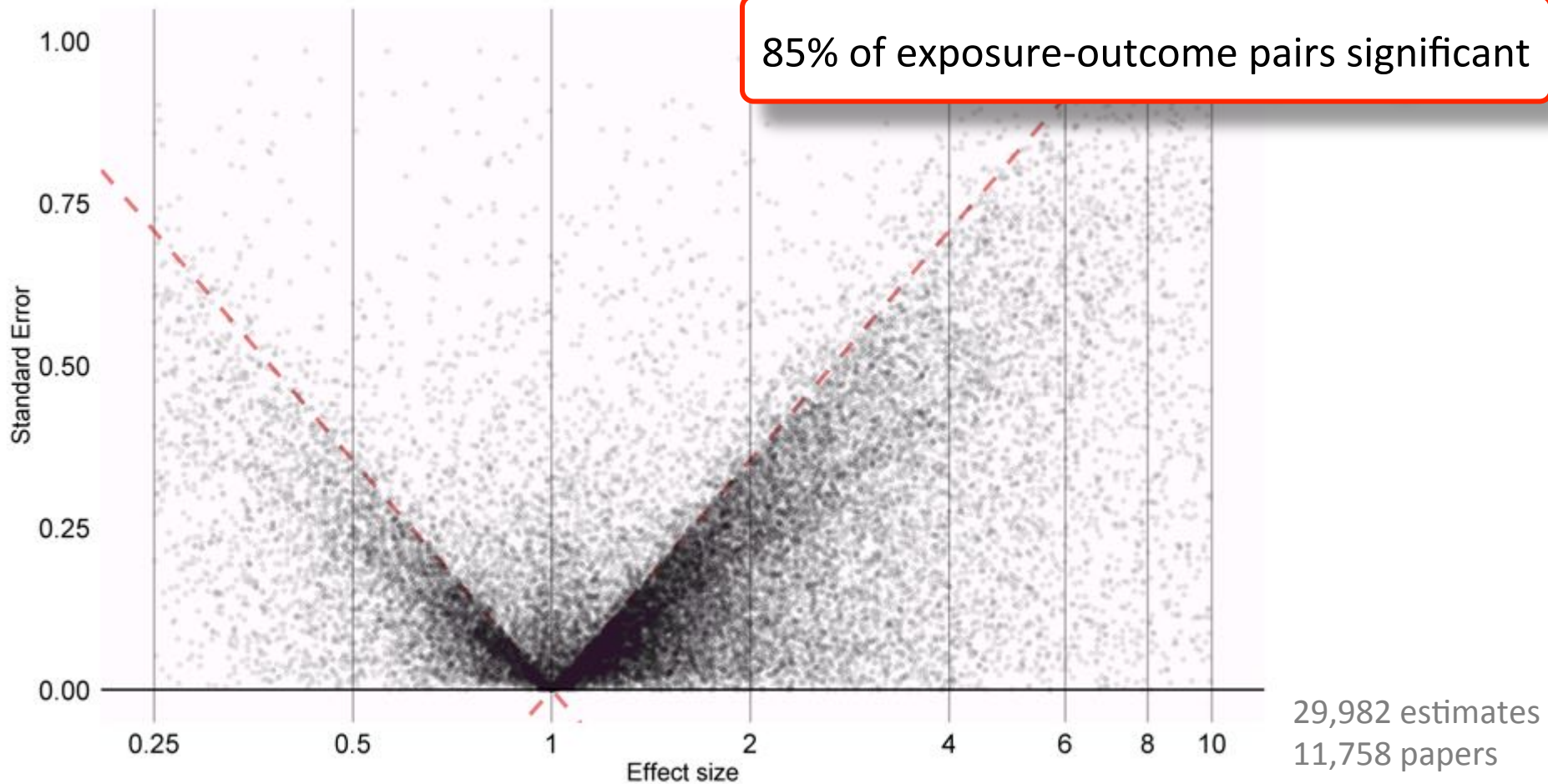
# Standard error vs effect size



Statistically significant

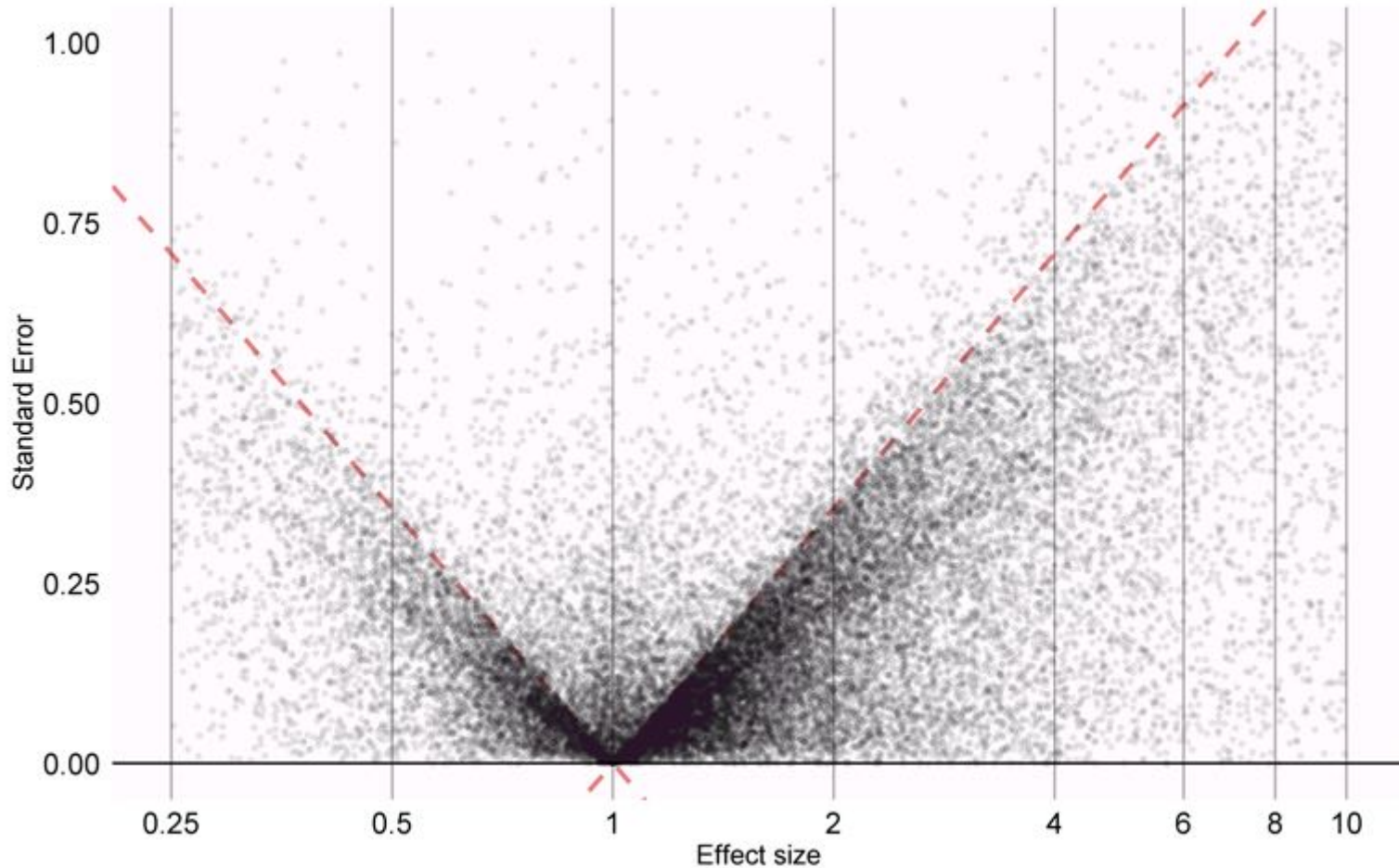


# Observational research results in literature





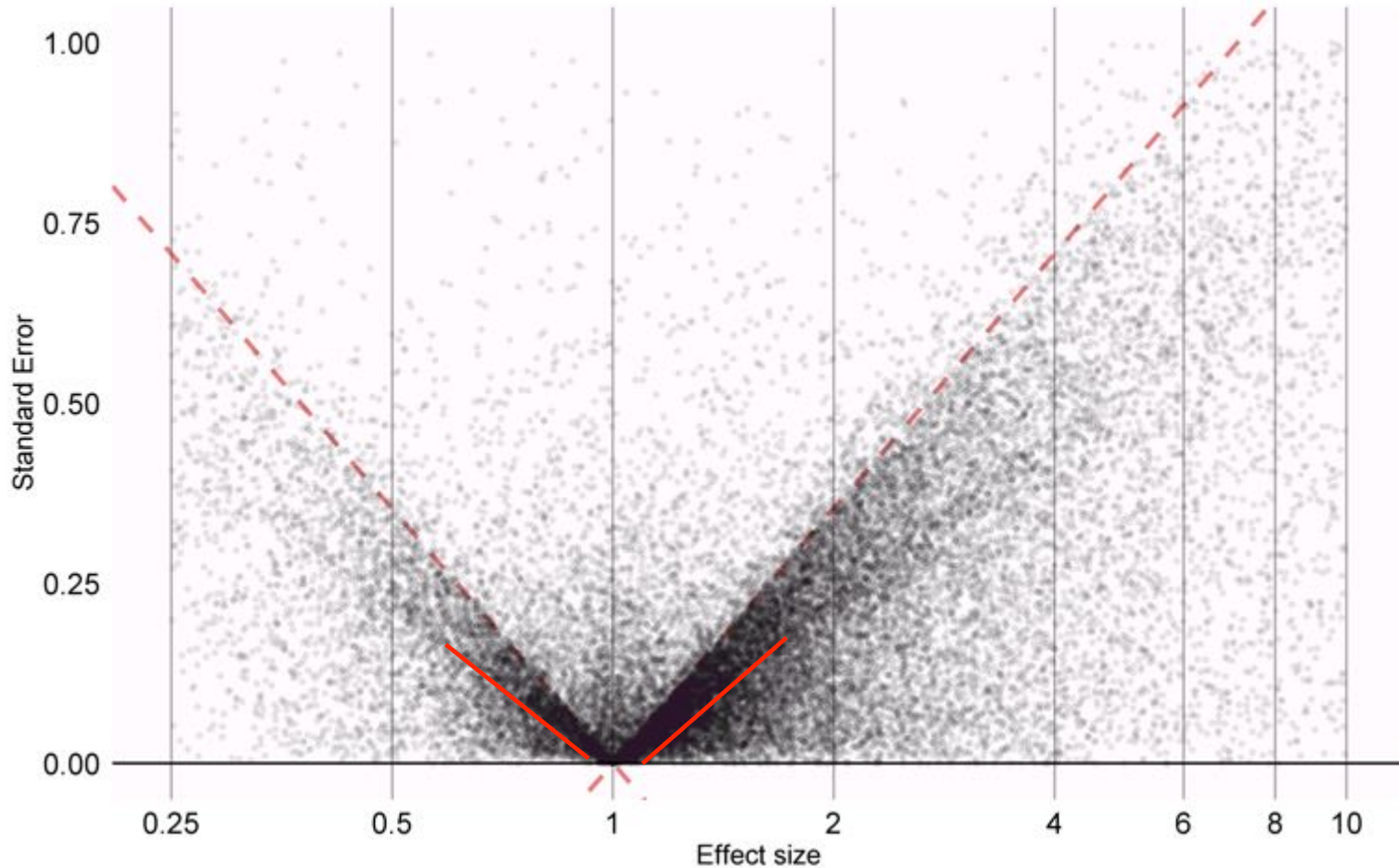
# Observational research results in literature



29,982 estimates  
11,758 papers



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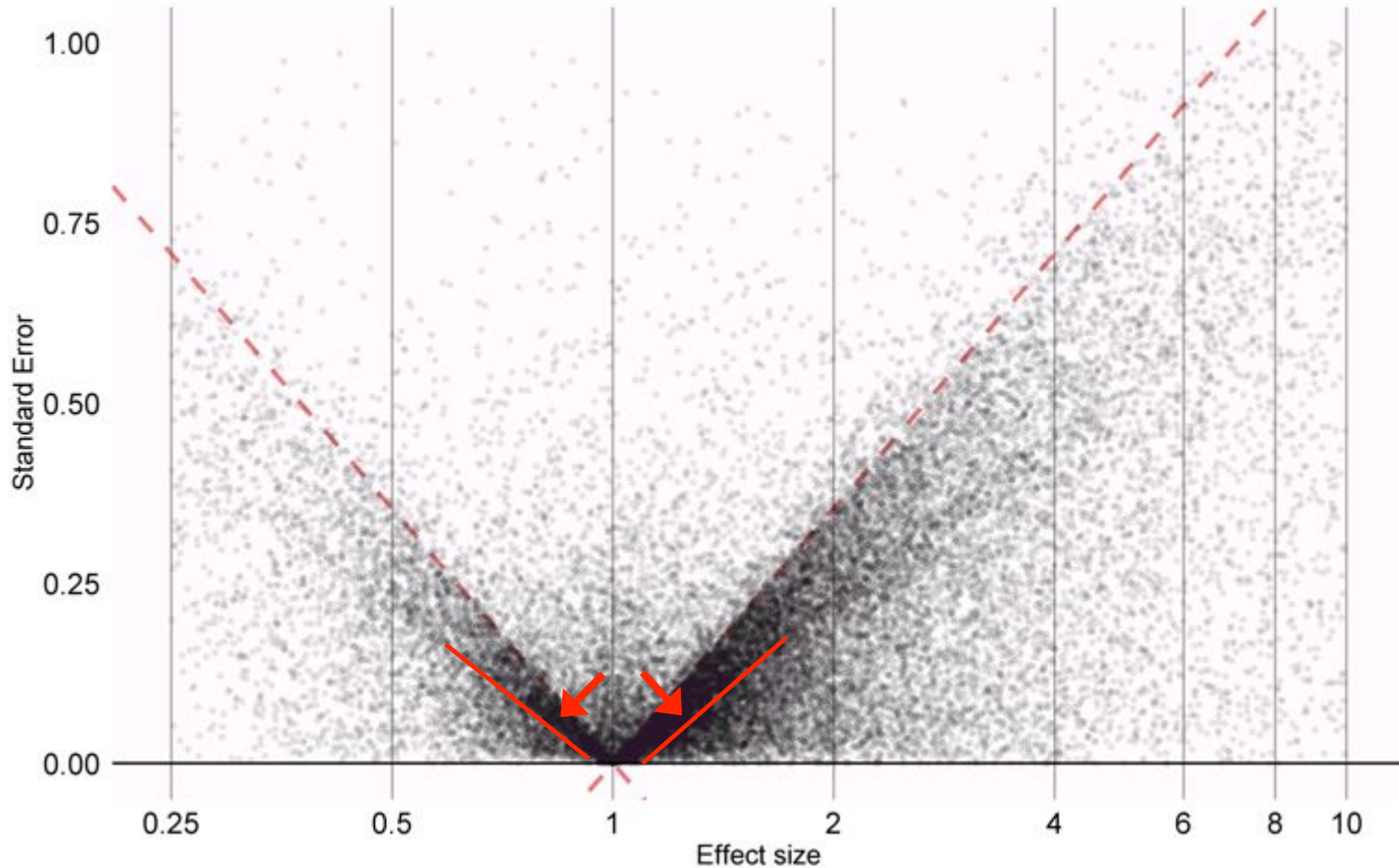


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