Learning from observational databases: Lessons from OMOP and OHDSI

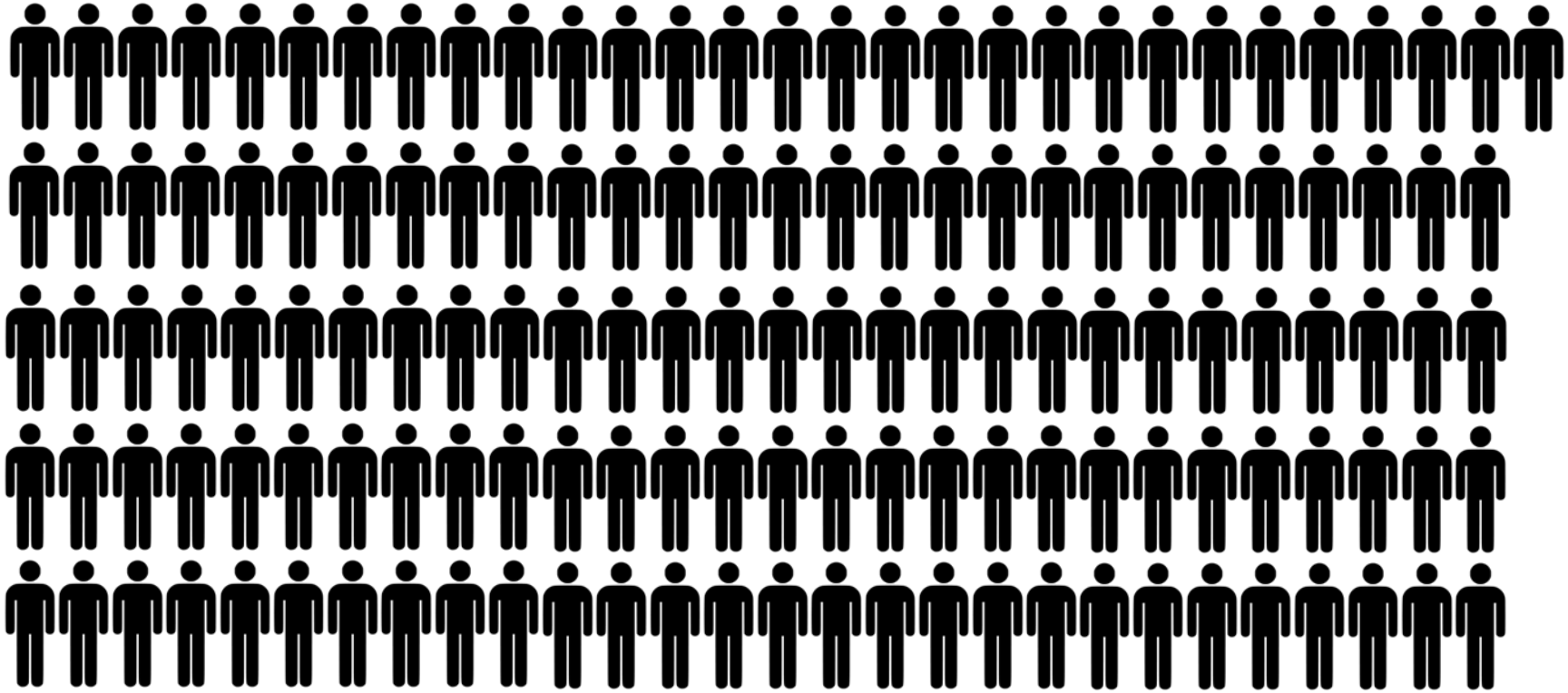
Patrick Ryan
Janssen Research and Development
David Madigan
Columbia University

http://www.omop.org
http://www.ohdsi.org

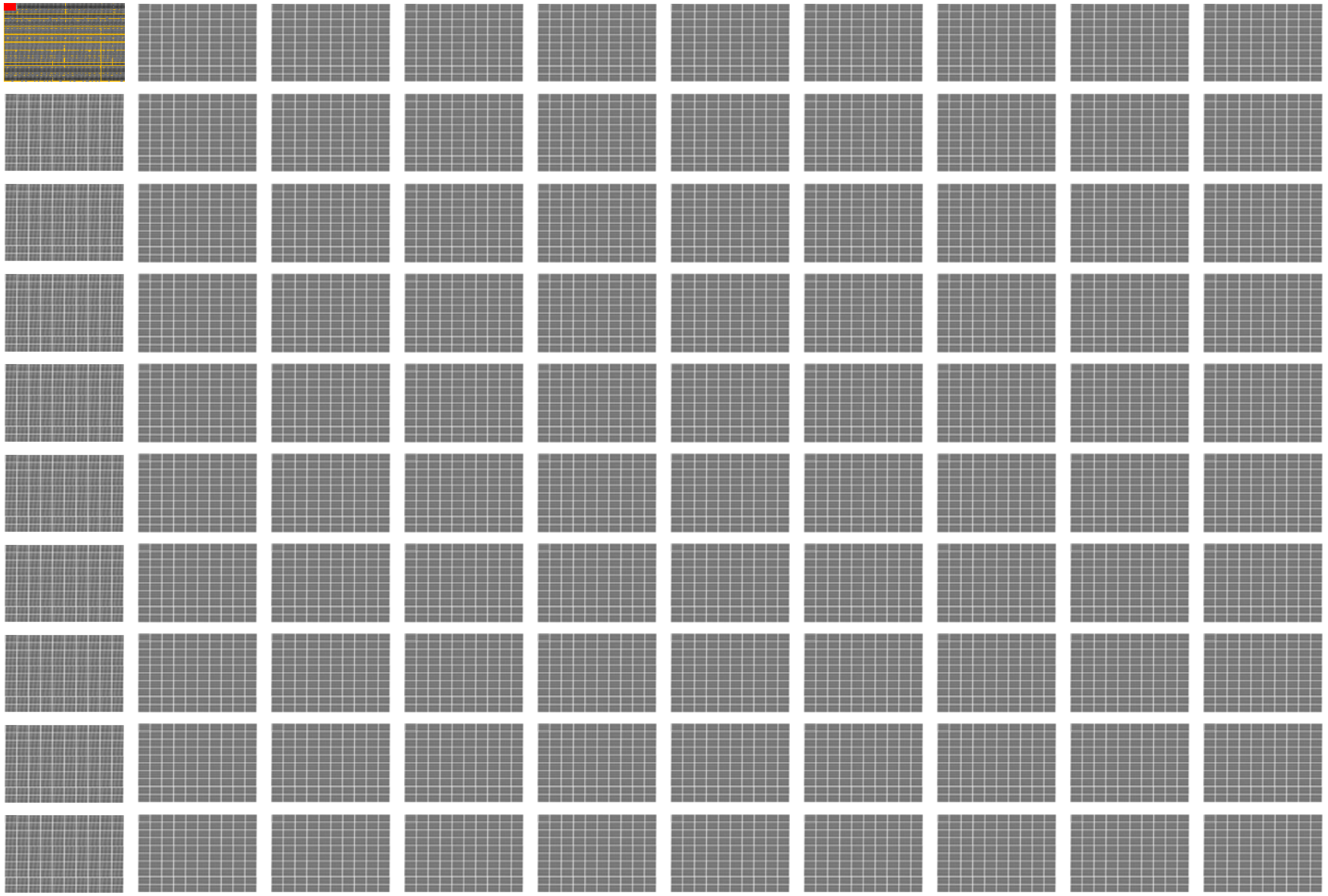
"The sole cause and root of almost every defect in the sciences is this: that whilst we falsely admire and extol the powers of the human mind, we do not search for its real helps."

— Novum Organum: Aphorisms [Book One], 1620, Sir Francis Bacon

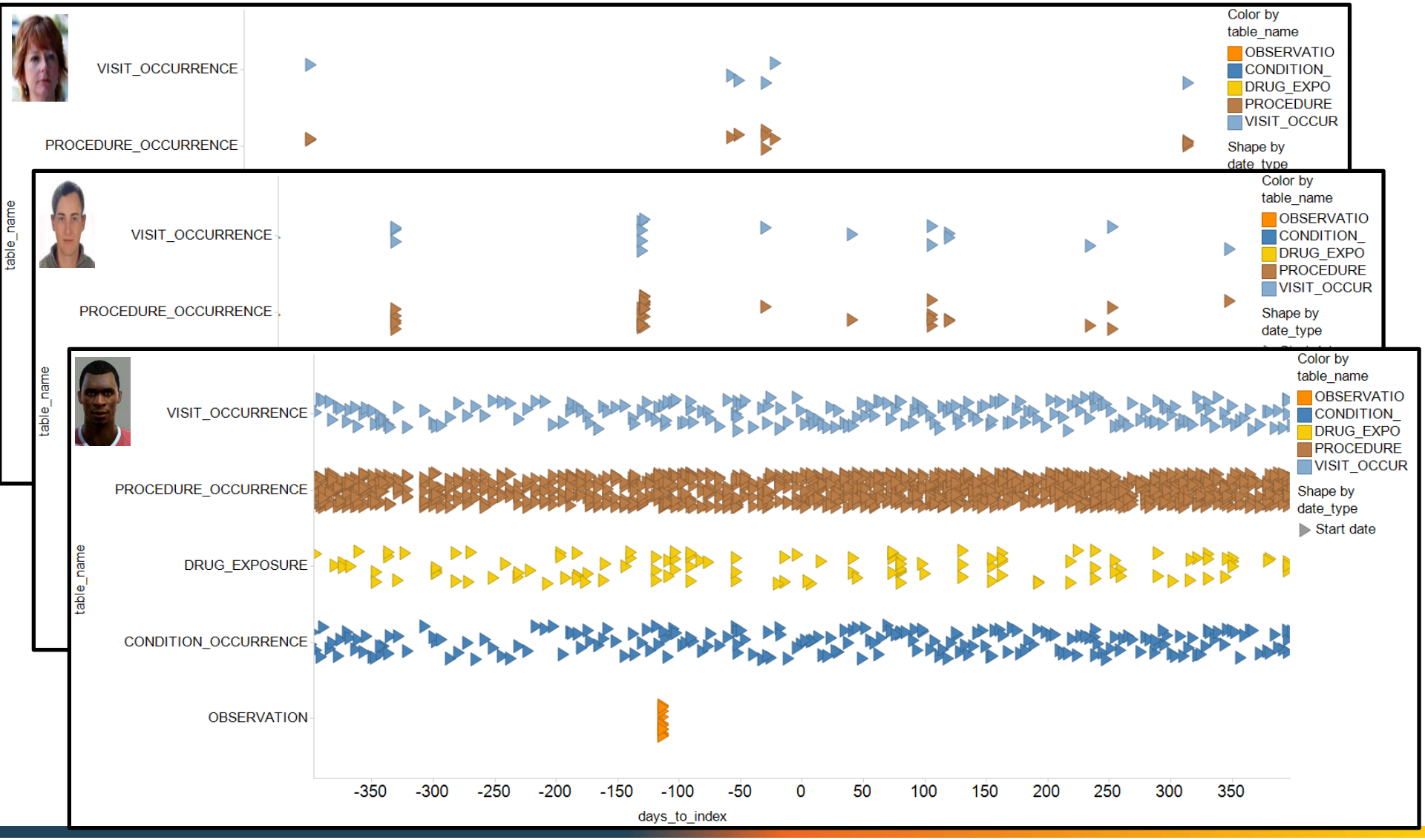
141 patients exposed in pivotal randomized clinical trial for metformin



>1,000,000 new users of metformin in one administrative claims database



Patient profiles from observational data



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

ORIGINAL CONTRIBUTION

JAMA®

Exposure to Oral Bisphosphonates and Risk of Esophageal Cancer

Chris R. Cardwell, PhD
Christian C. Abnet, PhD
Marie M. Cantwell, PhD
Liam J. Murray, MD

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

Objective To investigate the association between bis

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"

cause serious esophagitis in some users.[4,5] Crystalline material that resembles 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.[6] Reflux esophagitis is an established risk factor for esophageal cancer through the Barrett pathway.[7-9] 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 alen-

there were 41 826 members in each cohort (81% w
11.4) years). One hundred sixteen esophageal or gas
occurred in the bisphosphonate cohort and 115 (72
cohort. The incidence of esophageal and gastric cancer
person-years of risk in both the bisphosphonate and c
of esophageal cancer alone in the bisphosphonate a
and 0.44 per 1000 person-years of risk, respectively. T
of esophageal and gastric cancer combined between
phonate use (adjusted hazard ratio, 0.96 [95% confid
risk of esophageal cancer only (adjusted hazard ratio,
val, 0.77-1.49]). There also was no difference in risk of
by duration of bisphosphonate intake.

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

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

Large studies with appropriate comparison groups, adequate follow-up, ro- termine wi crease esor

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]

idemiology Unit, of Oxford, Oxford
s and Healthcare Regulatory Agency, epidemiology Research on SW8 5NQ
dence to: J Green @ceu.ox.ac.uk

: *BMJ* 2010;341:c4444 /bmj.c4444

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-

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

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"

not vary by age, sex, smoking, alcohol intake, or body from primary and secondary care, referrals to outpati-

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

ORIGINAL CONTRIBUTION

JAMA

Oral Fluoroquinolones an of Retinal Detachment

Mahyar Etminan, PharmD, MSc (epi)
Farzin Forooghian, MD, MSc, FRCSC
James M. Brophy, MD, PhD, FRCPC
Steven T. Bird, PharmD
David Maberley, MD, MSc, FRCSC

Context Fluoroquinolon
numerous case reports of
ocular safety, particularly
Objective To examine th
risk of developing a retina
Design, Setting, and Pa
in British Columbia, Cana

April2012: "Patients taking oral fluoroquinolones were at a higher risk of developing a retinal detachment"

sociated with a wide array of adverse events such as dysglycemia,[1] cardiac arrhythmia,[2] and neuropsychiatric events.[3] Fluoroquinolones also have been linked to several forms of ocular toxicity such as corneal perforations,[4] optic neuropathy,[5] and retinal hemorrhages.[6] In 2011, the label for gemifloxacin was updated to include hemorrhage,[6] which includes retinal hemorrhage that was reported during postmarketing surveillance. A class-wide warning for fluoroquinolones also has been issued for tendon rupture,[7] which raises concerns for the effect of these drugs on connective tissue in the eye. Animal studies also provide evidence for retinal degeneration with use

a higher risk of developing
adjusted rate ratio [ARR], 4
vs 0.2% of controls; ARR,
6.1% of controls; ARR, 1.
tachment. The absolute in
person-years (number nee
lones). There was no evide
tachment and β-lactam ar
β-agonists (ARR, 0.95 [95
Conclusion Patients tak
ing a retinal detachment c
condition was small.
JAMA. 2012;307(13):1414-1419

through the destructive
drugs on collagen and
tissue.[11] Collagen fibers
role in the structure a

Research

JAMA

Original Investigation

Association Between Oral Fluoroquinolone Use and Retinal Detachment

Björn Pasternak, MD, PhD; Henrik Svanström, MSc; Mads Melbye, MD, DrMedSci; Anders Hviid, MSc, DrMedSci

Editorial page 2151
JAMA Patient Page 2212
Supplemental content at jama.com

IMPORTANCE A recent study of ophthalmologic patients found a strong association between fluoroquinolone use and retinal detachment. Given the prevalent use of fluoroquinolones, this could, if confirmed in the general population, translate to many excess cases of retinal detachment that are potentially preventable.

l fluoroquinolone use is associated with an increased risk of

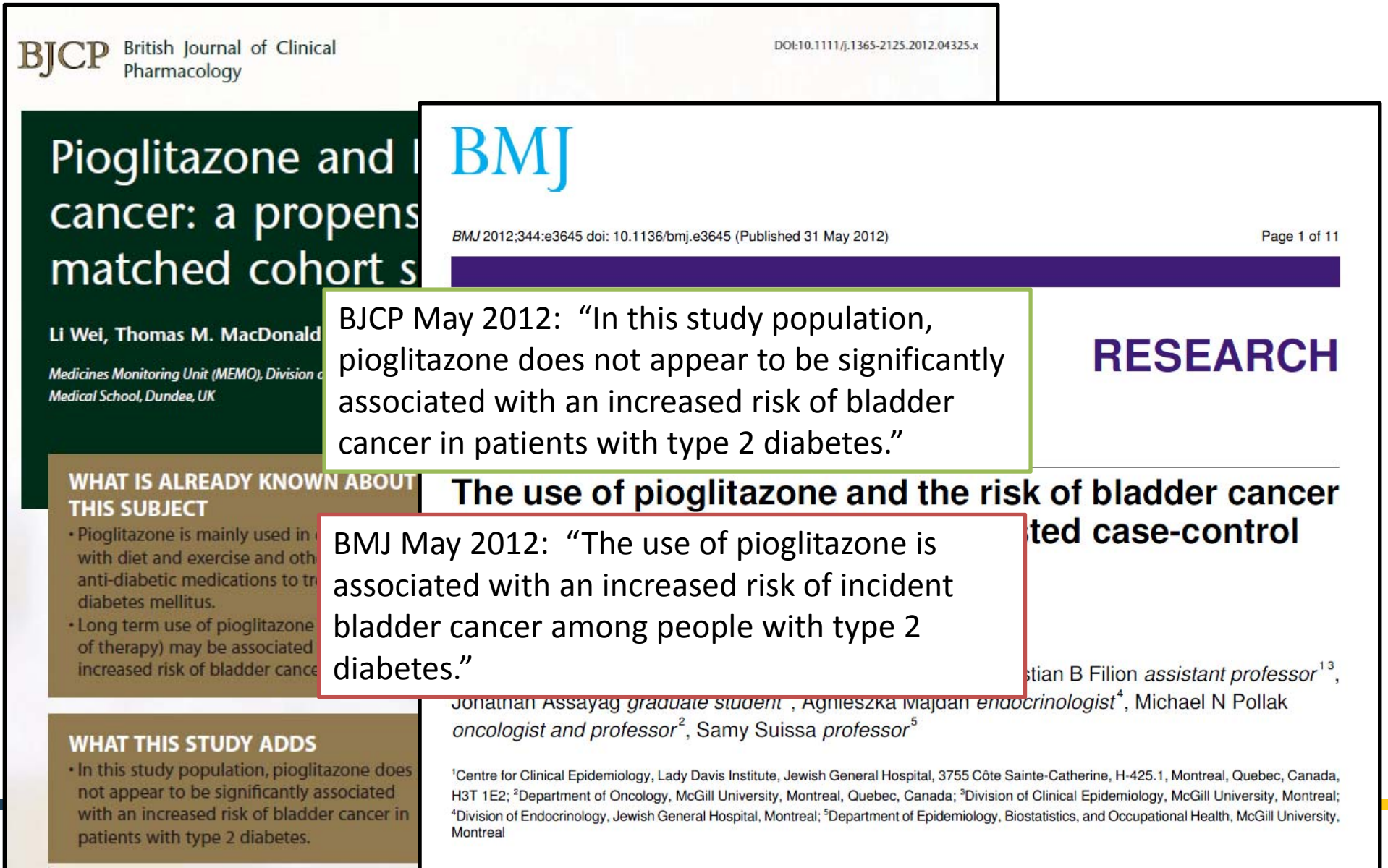
PANTS A nationwide, register-based cohort study in Denmark linked data on participant characteristics, filled prescriptions, nt with surgical treatment (scleral buckling, vitrectomy, or pneumatic retinopexy). The cohort included 748 792 episodes of fluoroquinolone use (660 572 [88%

Dec2013: "Oral fluoroquinolone use was not associated with increased risk of retinal detachment"

MAIN OUTCOME
for incident reti
variables. The r
recent use (day

RESULTS A total of 566 cases of retinal detachment occurred, of which 465 (82%) were rhegmatogenous detachments; 72 in fluoroquinolone users and 494 in control nonusers. The crude incidence rate was 25.3 cases per 100 000 person-years in current users, 18.9 in recent users, 26.8 in past users, and 24.8 in distant users compared with 19.0 in nonusers. Compared with nonuse, fluoroquinolone use was not associated with a significantly increased risk of retinal detachment: the adjusted RRs were 1.29 (95% CI, 0.53 to 3.13) for current use;

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



BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2012.04325.x

Pioglitazone and
cancer: a propens
matched cohort s

Li Wei, Thomas M. MacDonald

Medicines Monitoring Unit (MEMO), Division o
Medical School, Dundee, UK

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Pioglitazone is mainly used in
with diet and exercise and oth
anti-diabetic medications to tr
diabetes mellitus.
- Long term use of pioglitazone
of therapy) may be associated
increased risk of bladder cance

WHAT THIS STUDY ADDS

- In this study population, pioglitazone does not appear to be significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes.

BJCP May 2012: "In this study population, pioglitazone does not appear to be significantly associated with an increased risk of bladder cancer in patients with type 2 diabetes."

BMJ

BMJ 2012;344:e3645 doi: 10.1136/bmj.e3645 (Published 31 May 2012)

Page 1 of 11

RESEARCH

The use of pioglitazone and the risk of bladder cancer
ted case-control

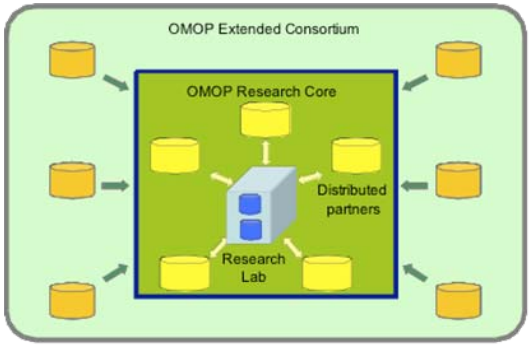
BMJ May 2012: "The use of pioglitazone is associated with an increased risk of incident bladder cancer among people with type 2 diabetes."

stian B Filion *assistant professor*[1 3],
Jonathan Assayag *graduate student*[1], Agnieszka Majdan *endocrinologist*[4], Michael N Pollak
oncologist and professor[2], Samy Suissa *professor*[5]

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte Sainte-Catherine, H-425.1, Montreal, Quebec, Canada, H3T 1E2; [2]Department of Oncology, McGill University, Montreal, Quebec, Canada; [3]Division of Clinical Epidemiology, McGill University, Montreal; [4]Division of Endocrinology, Jewish General Hospital, Montreal; [5]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal

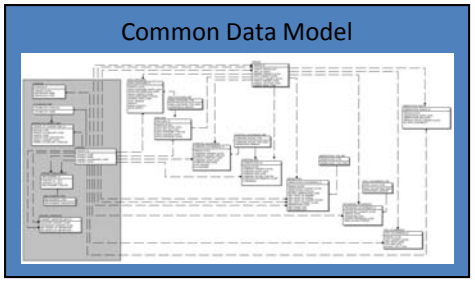
- Unknown operating characteristics
- Type 1 error rate? “95%” confidence interval?
- Like early days of lab testing – “trust me, I measured it myself”

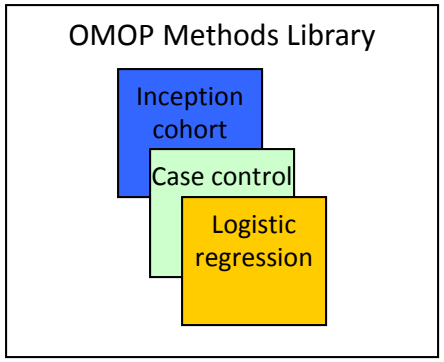
2010-2013 OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 200M+ lives

- Open-source
- Standards-based

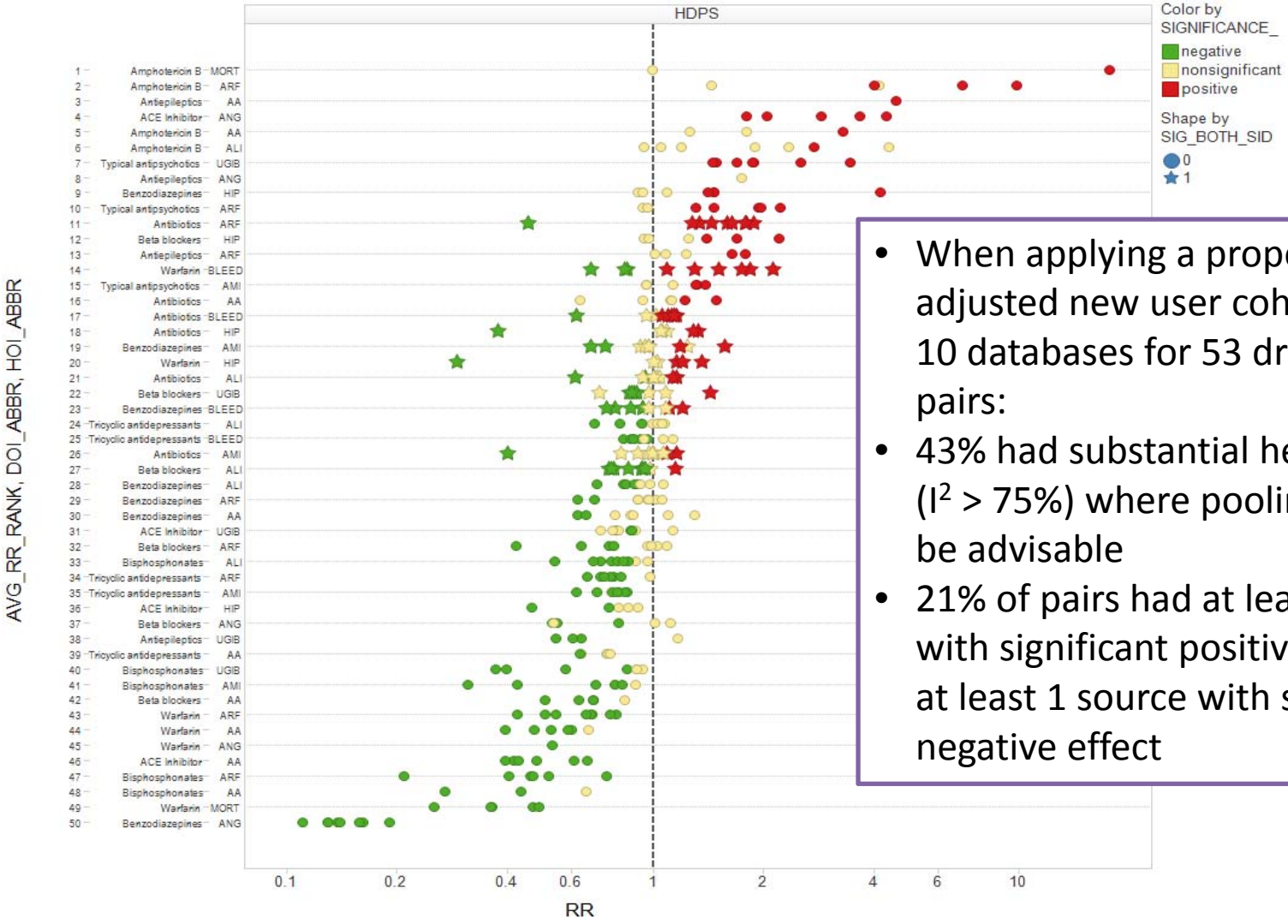




- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data

Outcome \ Drug	ACE Inhibitors	Amphotericin B	Antibiotics: erythromycins, sulfonamides, tetracyclines	Antiepileptics: carbamazepine, phenytoin	Benzodiazepines	Beta blockers	Bisphosphonates: alendronate	Tricyclic antidepressants	Typical antipsychotics	Warfarin
Angioedema										
Aplastic Anemia										
Acute Liver Injury										
Bleeding										
Hip Fracture										
Hospitalization										
Myocardial Infarction										
Mortality after MI										
Renal Failure										
GI Ulcer Hospitalization										

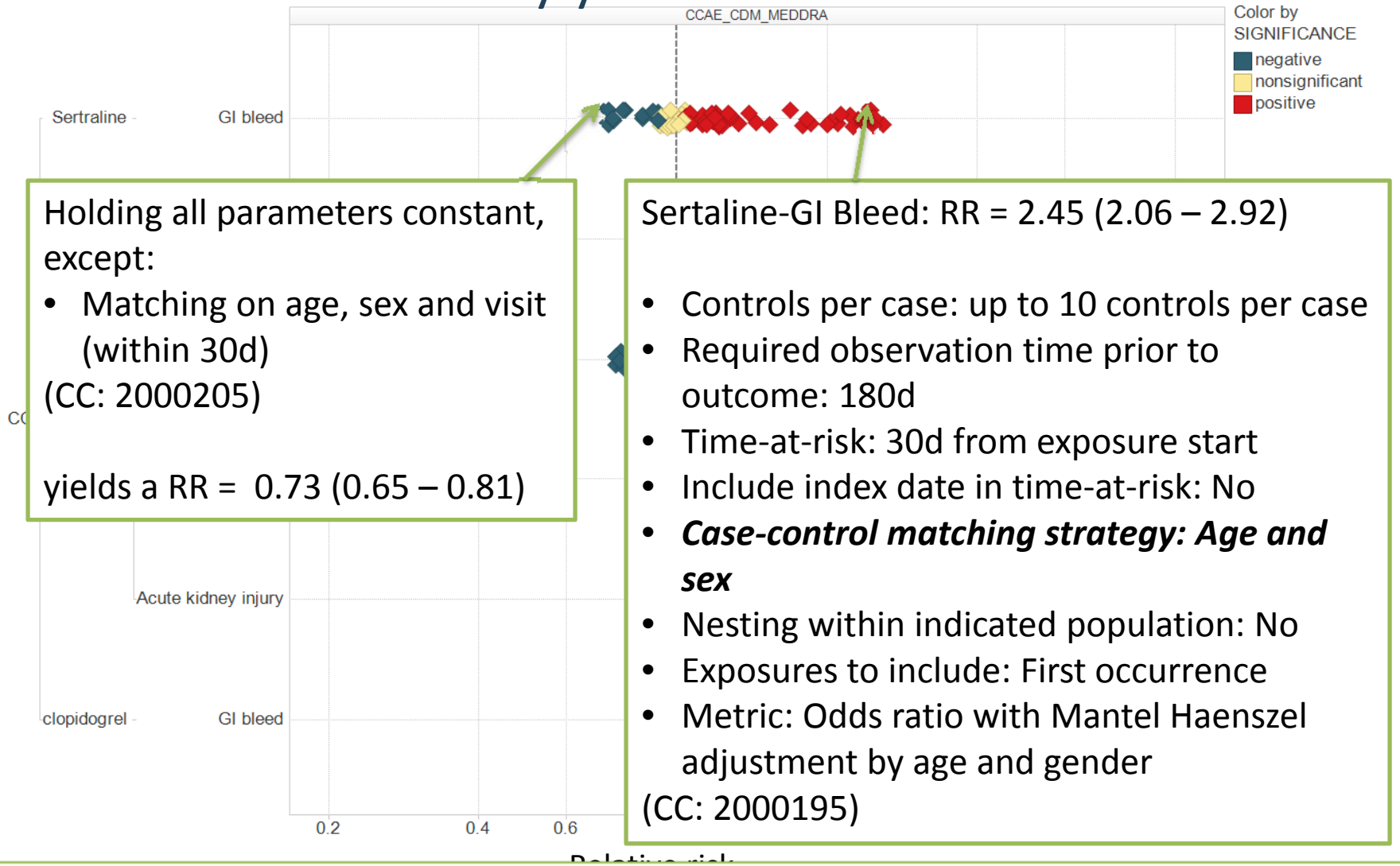
Lesson 1: Database heterogeneity: Holding analysis constant, different data may yield different estimates



- When applying a propensity score adjusted new user cohort design to 10 databases for 53 drug-outcome pairs:
- 43% had substantial heterogeneity ($I^2 > 75\%$) where pooling would not be advisable
- 21% of pairs had at least 1 source with significant positive effect and at least 1 source with significant negative effect

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

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



Holding all parameters constant, except:

- Matching on age, sex and visit (within 30d)

(CC: 2000205)

yields a RR = 0.73 (0.65 – 0.81)

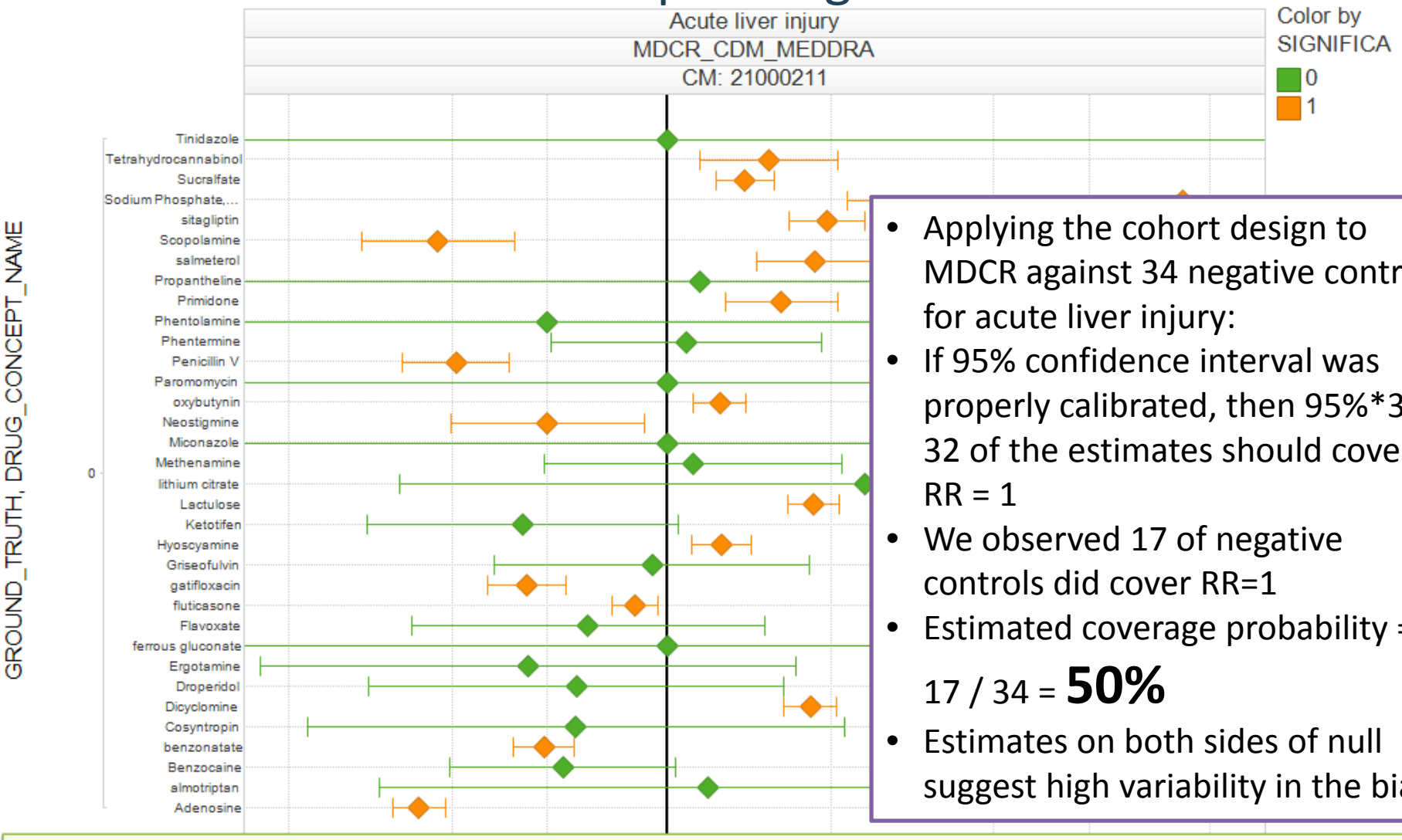
Sertaline-GI Bleed: RR = 2.45 (2.06 – 2.92)

- Controls per case: up to 10 controls per case
- Required observation time prior to outcome: 180d
- Time-at-risk: 30d from exposure start
- Include index date in time-at-risk: No
- ***Case-control matching strategy: Age and sex***
- Nesting within indicated population: No
- Exposures to include: First occurrence
- Metric: Odds ratio with Mantel Haenszel adjustment by age and gender

(CC: 2000195)

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

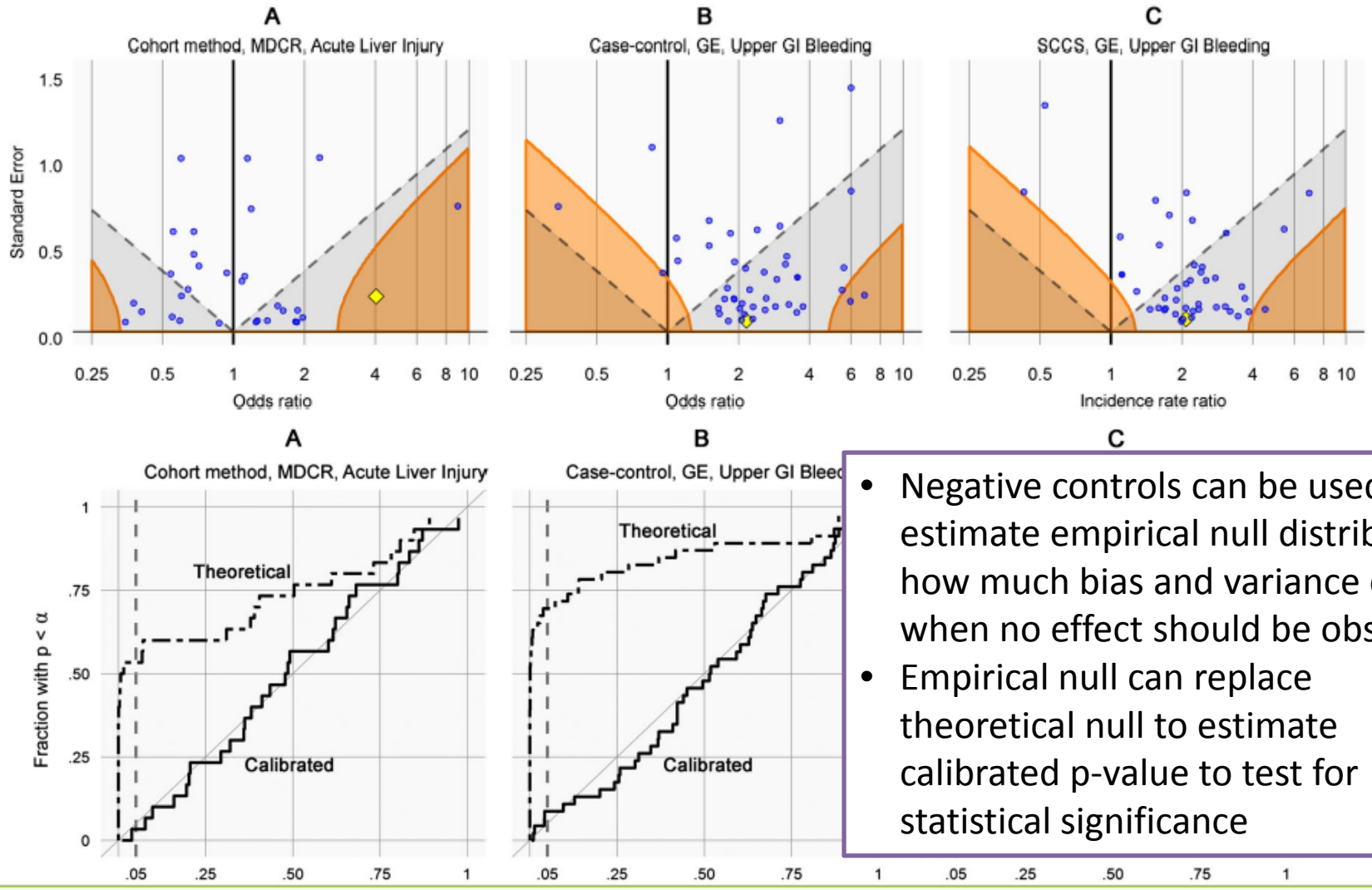
Lesson 3: Empirical performance: Most observational methods do not have nominal statistical operating characteristics



- Applying the cohort design to MDCR against 34 negative controls for acute liver injury:
- If 95% confidence interval was properly calibrated, then 95%*34 = 32 of the estimates should cover RR = 1
- We observed 17 of negative controls did cover RR=1
- Estimated coverage probability = 17 / 34 = **50%**
- Estimates on both sides of null suggest high variability in the bias

Ryan PB, Stang PE, Overhage JM et al, Drug Safety, 2013:
"A Comparison of the Empirical Performance of Methods for a Risk Identification System"

Lesson 4: Empirical calibration can help restore interpretation of study findings

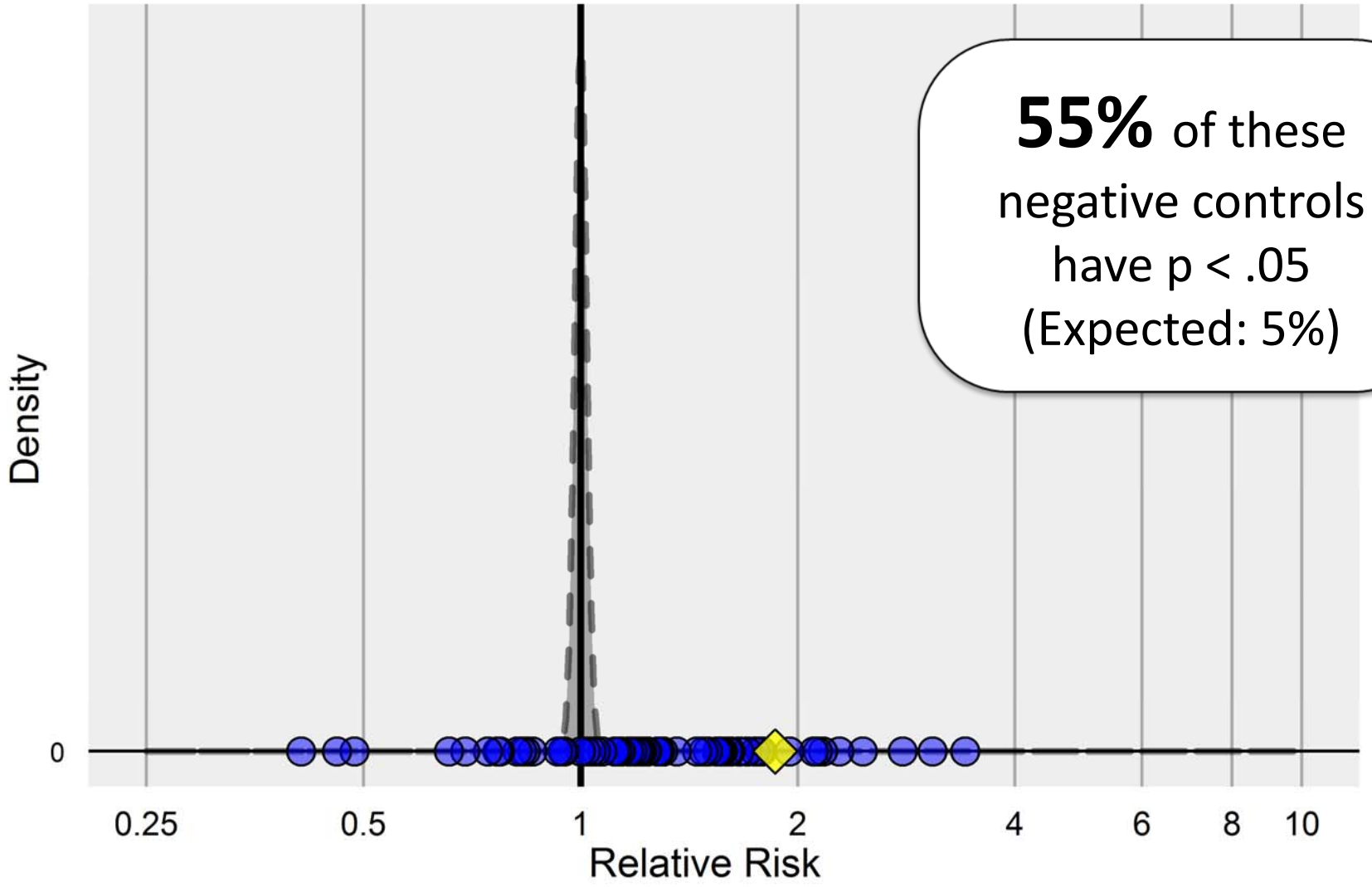


- Negative controls can be used to estimate empirical null distribution: how much bias and variance exists when no effect should be observed
- Empirical null can replace theoretical null to estimate calibrated p-value to test for statistical significance

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

Negative controls & the null distribution

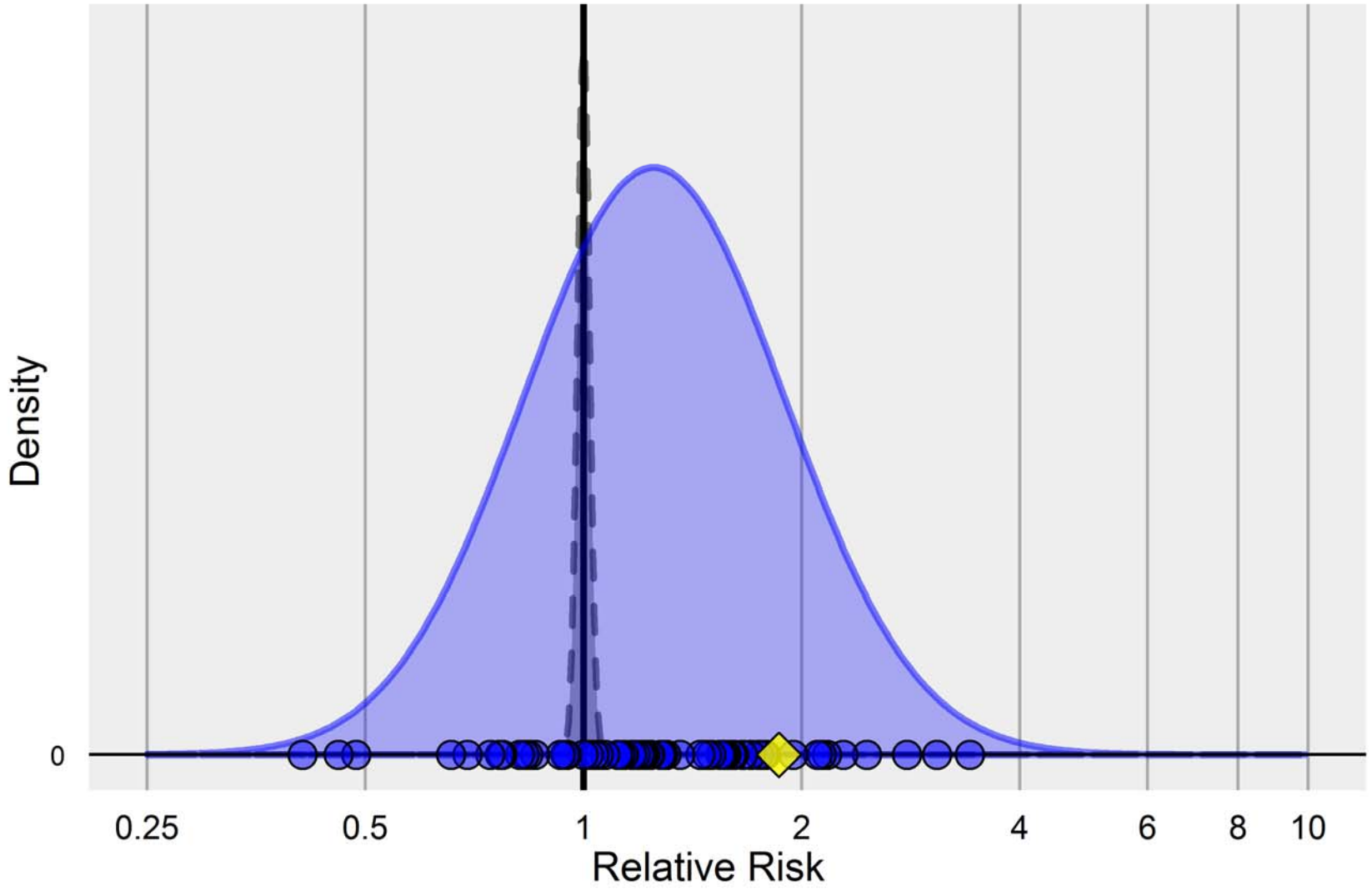
CC: 2000314, CCAE, GI Bleed



55% of these negative controls have p < .05 (Expected: 5%)

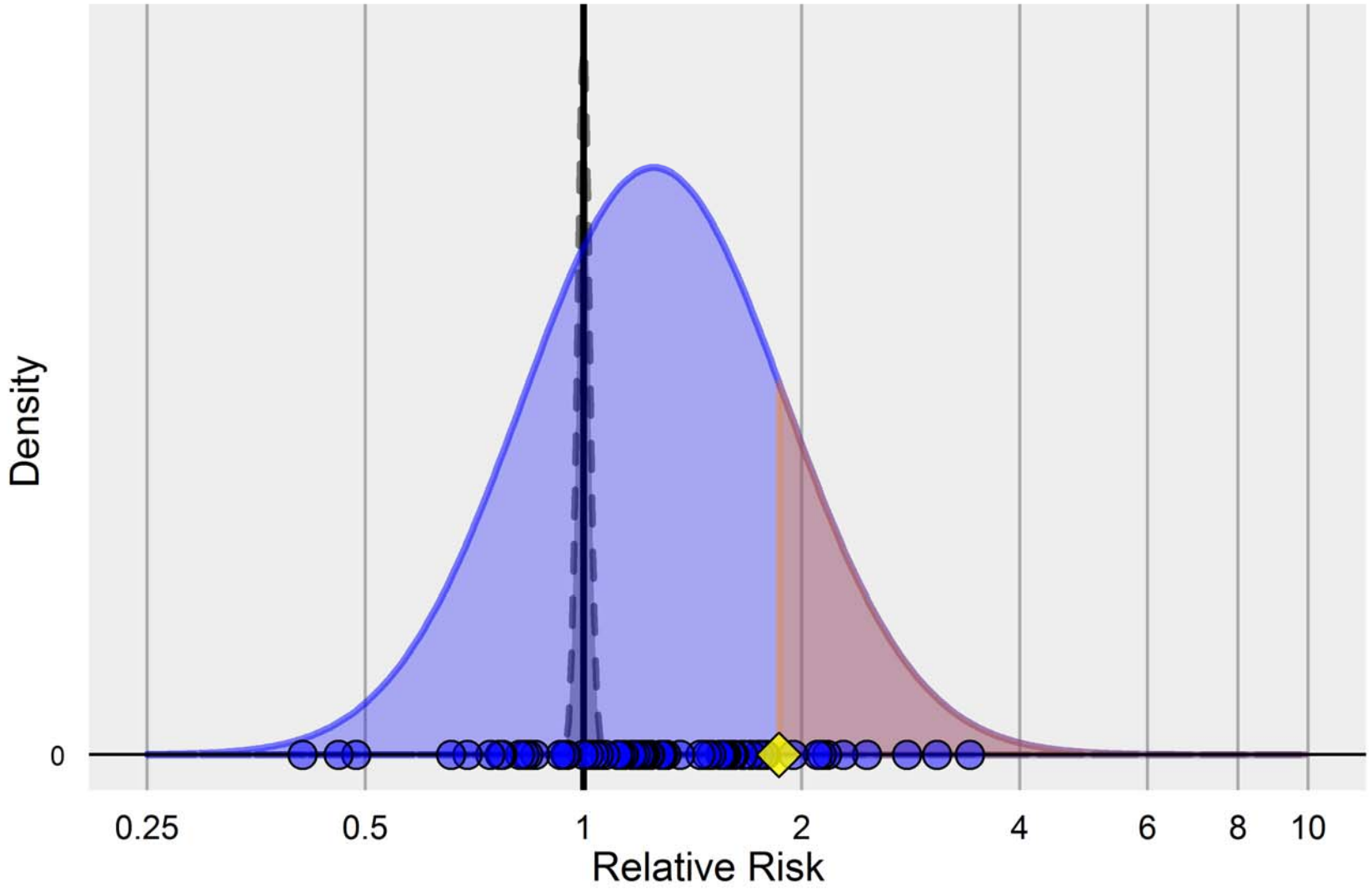
Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed



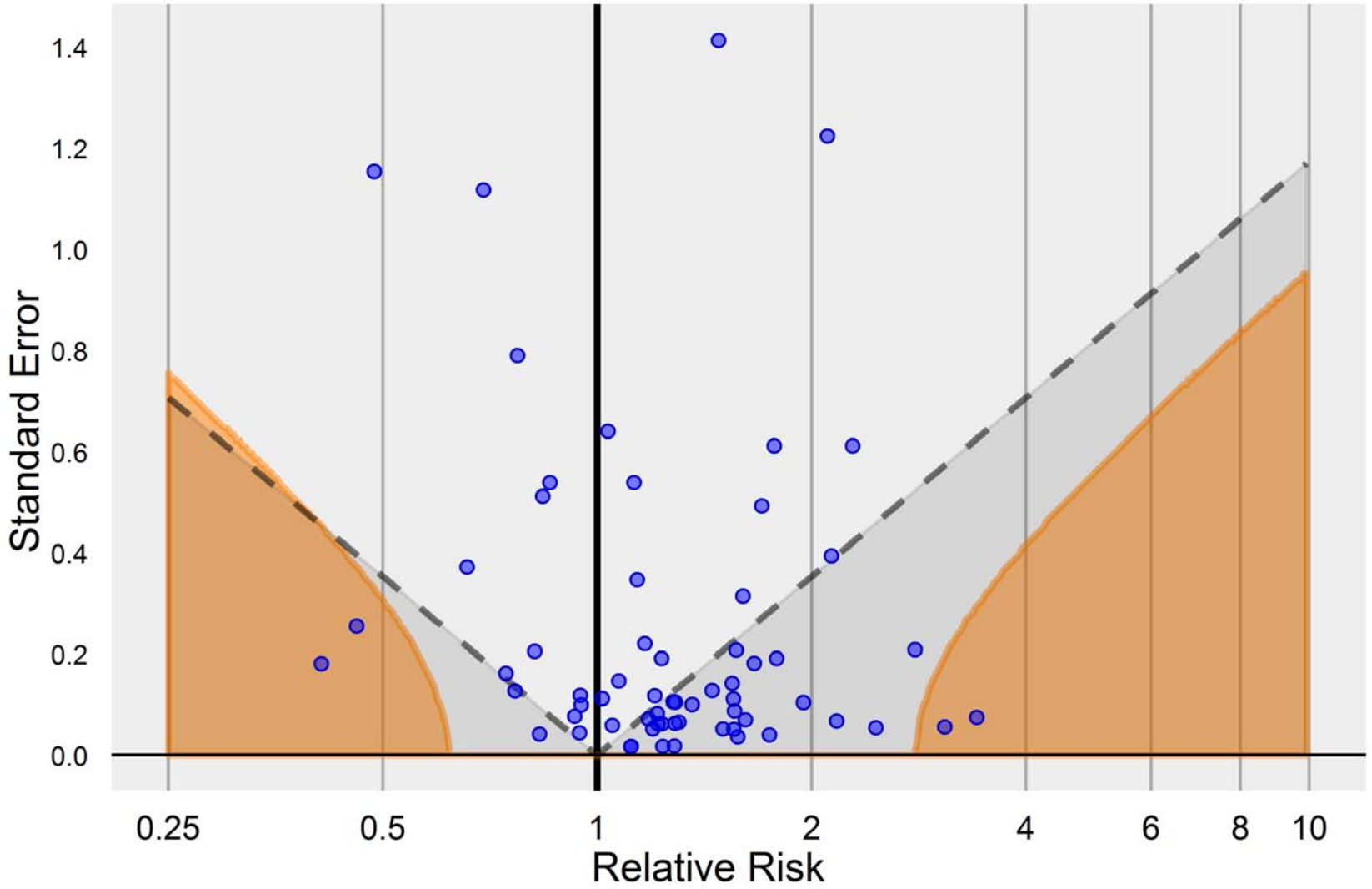
Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed



p-value calibration plot

CC: 2000314, CCAE, GI Bleed



Clear path forward: systematic evaluation and calibration

Drug Safety

Drug Saf (2013) 36 (Suppl 1):S143–S158
DOI 10.1007/s40264-013-0108-9

ORIGINAL RE

A Compari
for a Risk

Patrick B. Ryan ·
Marc A. Suchard
Christian G. Reic

© Springer Internatio

Abstract
Background Obse
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Statistics in Medicine

Research Article

Received 12 November 2012, Accepted 3 July 2013 Published online in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.5925

Interpreting observational studies: why empirical cal
correct *p*-val

Martijn J. Schuemie
William DuMouchel

ANNUAL REVIEWS
A NONPROFIT SCIENTIFIC PUBLISHER

A Systematic Statistical Approach to Evaluating Evidence from Observational Studies

David Madigan,[1,2] Paul E. Stang,[2,3] Jesse A. Berlin,[4]

ANNUAL REVIEWS Further

CPT: Pharmacometrics & Systems Pharmacology

Citation: CPT: Pharmacometrics & Systems Pharmacology (2013) 2, e76; doi:10.1038/psp.2013.52
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www.nature.com/psp

ORIGINAL ARTICLE

Medication-Wide Association Studies

PB Ryan[1], D Madigan[2], PE Stang[1], MJ Schuemie[1,3] and G Hripcsak[4]

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utes of
m,
iemens.com
California,

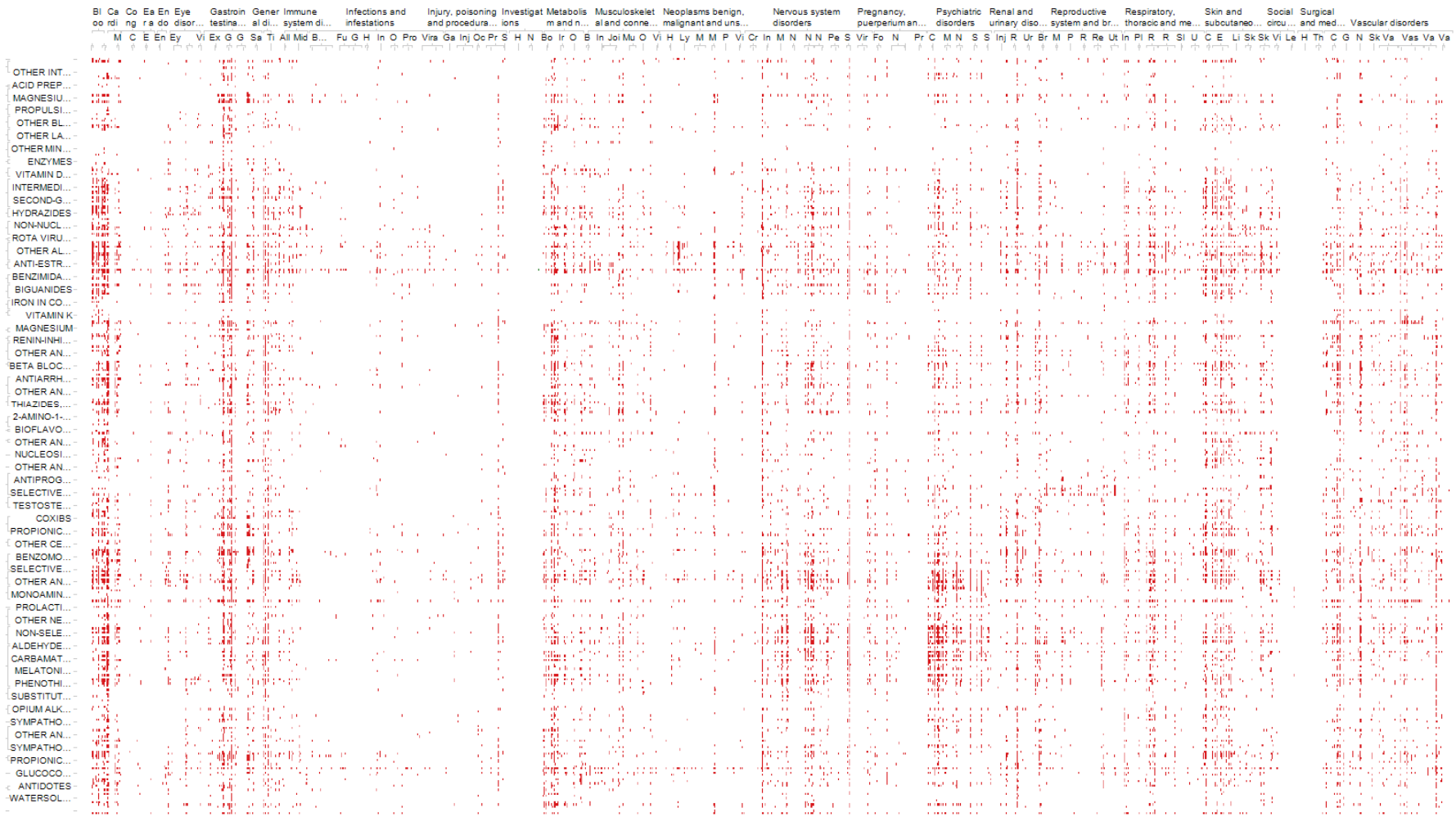
Introducing OHDSI

- The Observational Health Data Sciences and Informatics (OHDSI) program is a multi-stakeholder, interdisciplinary collaborative to create open-source solutions that bring out the value of observational health data through large-scale analytics
- OHDSI has established an international network of researchers and observational health databases with a central coordinating center housed at Columbia University

Why large-scale analysis is needed in healthcare

All health outcomes of interest

All drugs



What is large-scale?

- Millions of observations

  Need for performance in handling relational structure with millions of patients and billions of clinical observations, focus on optimization to analytical use cases.

- Millions of covariates

  No analytics software in the world can fit a regression with >1m observations and >1m covariates on typical hardware… but CYCLOPS can!

- Millions of questions

  Systematic solutions with massive parallelization should be designed to run efficiently for one-at-a-time AND all-by-all

Questions OHDSI seeks to answer from observational data

- Clinical characterization:
  - Natural history: Who are the patients who have diabetes? Among those patients, who takes metformin?
  - Quality improvement: what proportion of patients with diabetes experience disease-related complications?
- Population-level estimation
  - Safety surveillance: Does metformin cause lactic acidosis?
  - Comparative effectiveness: Does metformin cause lactic acidosis more than glyburide?
- Patient-level prediction
  - Given everything you know about me and my medical history, if I start taking metformin, what is the chance that I am going to have lactic acidosis in the next year?

OHDSI Communities

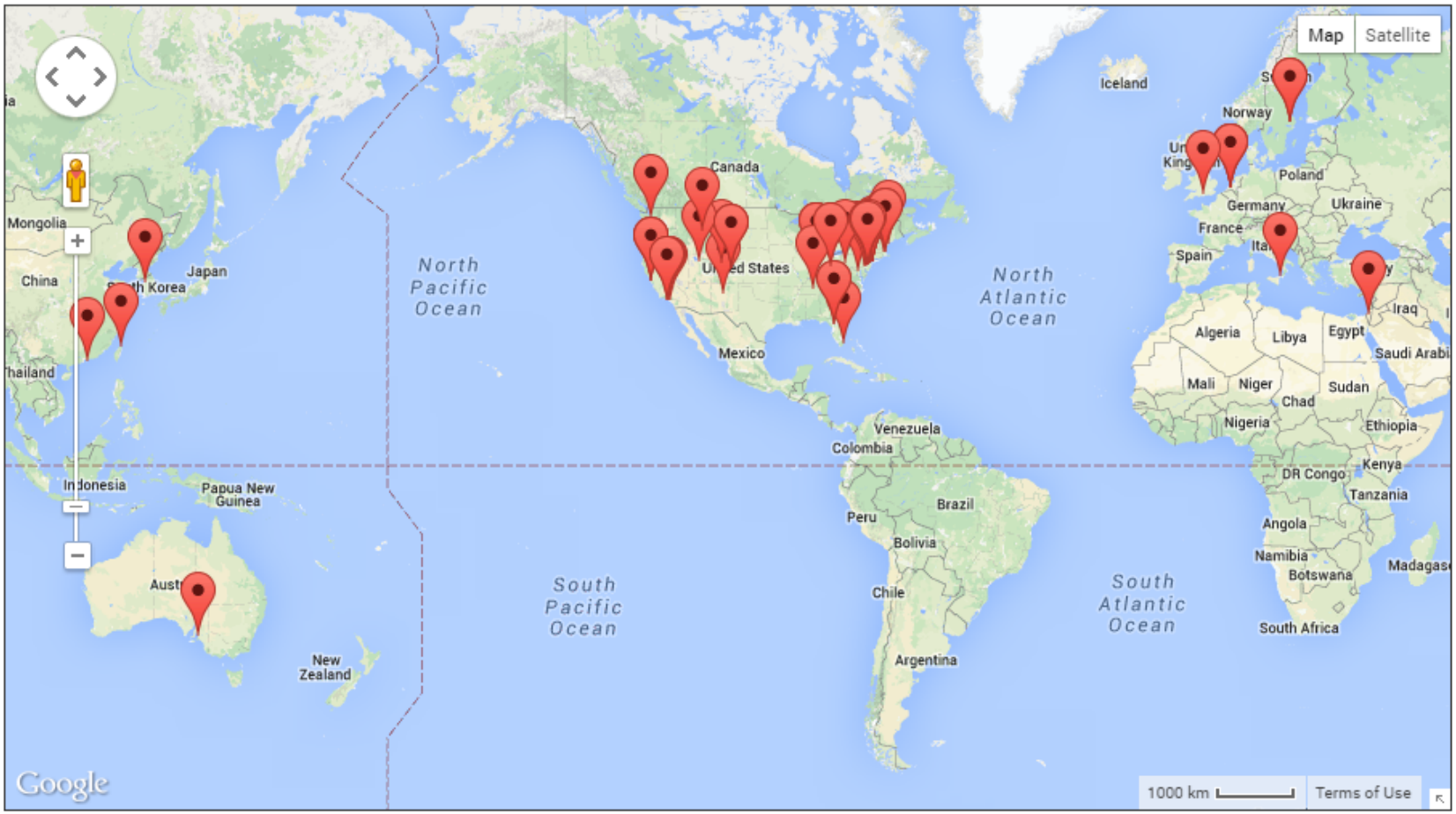
Community: a social unit of any size that shares common values

--http://en.wikipedia.org/wiki/Community

OHDSI's communities:

- Research
- Open-source software development
- Data network

OHDSI's global research community



- >120 collaborators from 11 different countries
- Experts in informatics, statistics, epidemiology, clinical sciences
- Active participation from academia, government, industry, providers

http://ohdsi.org/who-we-are/collaborators/

Data network accomplishments, 2014

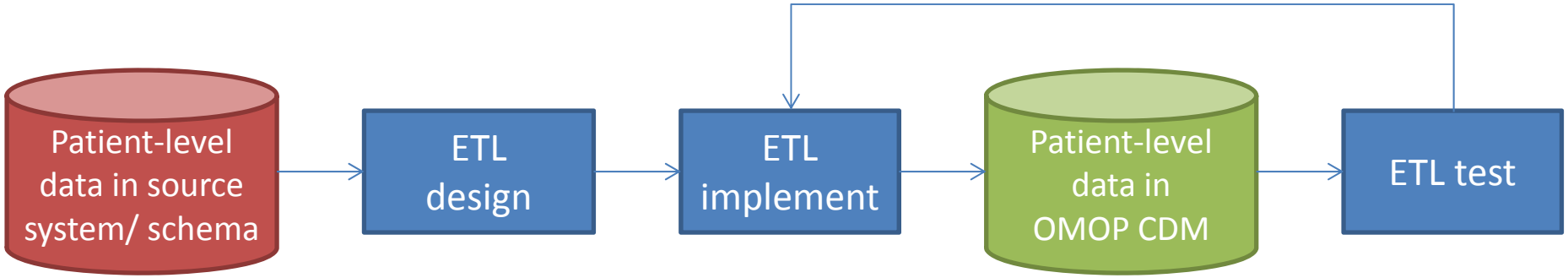
- Databases in OMOP CDM
  - 58 databases reported in progress or completed
  - Types: Administrative claims, electronic health records, health information exchanges, hospital billing data, clinical registries, national surveys
  - 9 countries: US, UK, Italy, Germany, Netherlands, Korea, Taiwan, Hong Kong, Japan
  - >682 million patients covered across sources

The odyssey to evidence generation

Patient-level data in source system/ schema

evidence

Preparing your data for analysis



OHDSI tools built to help

WhiteRabbit: profile your source data

RabbitInAHat: map your source structure to CDM tables and fields

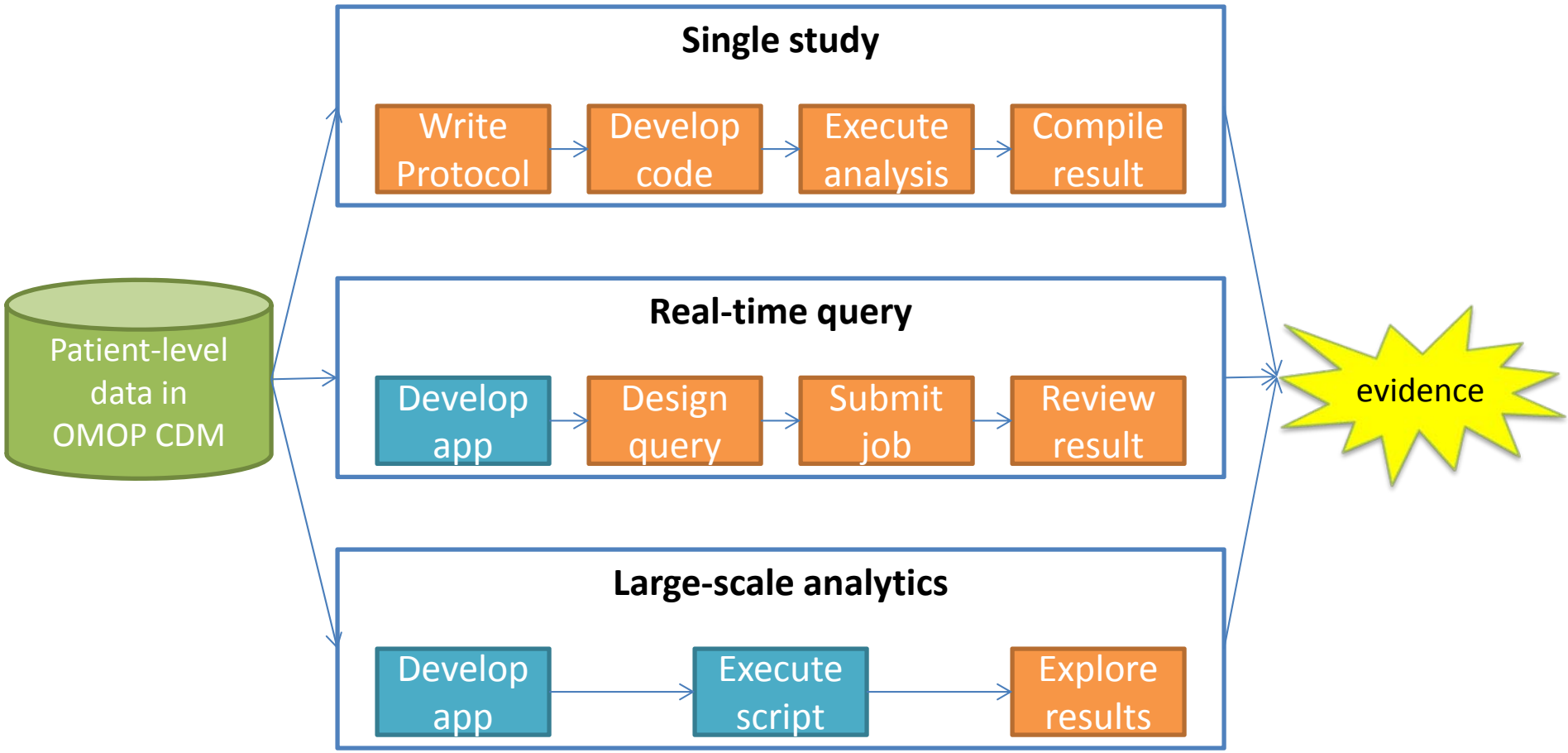
Usagi: map your source codes to CDM vocabulary

CDM: DDL, index, constraints for Oracle, SQL Server, PostgresQL; Vocabulary tables with loading scripts

ACHILLES: profile your CDM data; review data quality assessment; explore population-level summaries

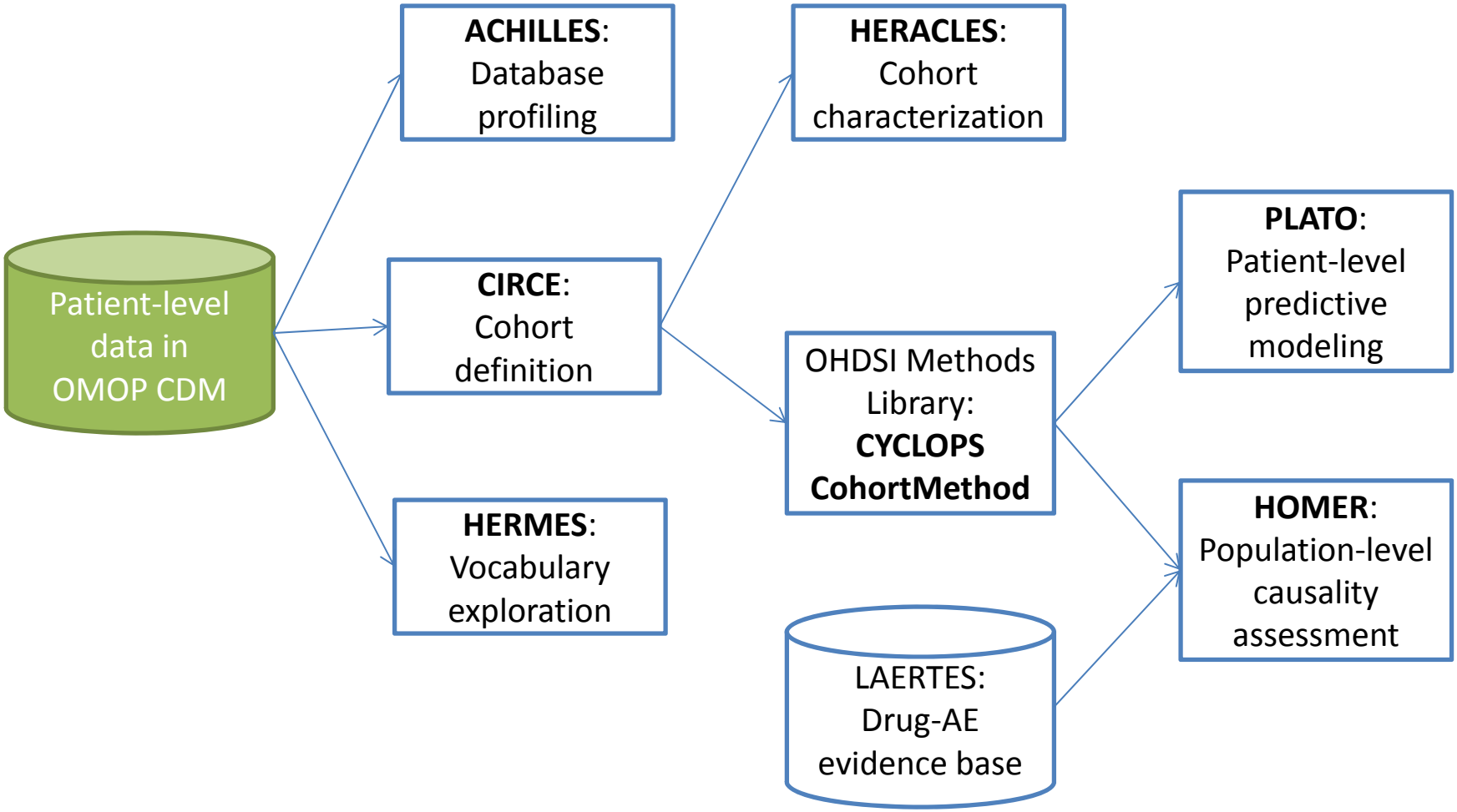
OHDSI Forums:
Public discussions for OMOP CDM Implementers/developers

~~Data~~ Evidence sharing paradigms



One-time Repeated

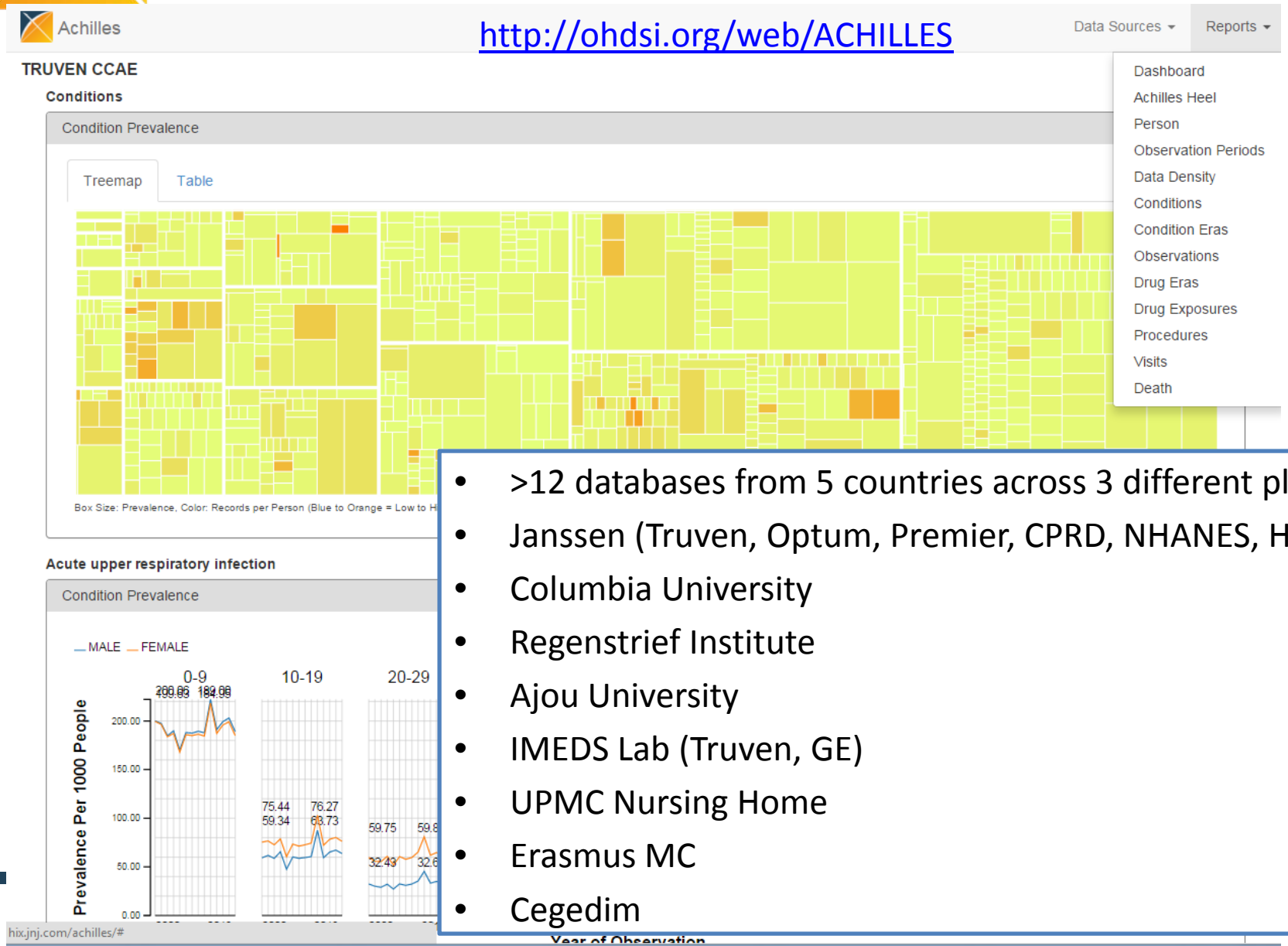
Standardized large-scale analytics tools under development within OHDSI



http://github.com/OHDSI

Large-scale analytics example: ACHILLES

http://ohdsi.org/web/ACHILLES



- >12 databases from 5 countries across 3 different platforms:
- Janssen (Truven, Optum, Premier, CPRD, NHANES, HCUP)
- Columbia University
- Regenstrief Institute
- Ajou University
- IMEDS Lab (Truven, GE)
- UPMC Nursing Home
- Erasmus MC
- Cegedim

Single study example: Treatment pathways

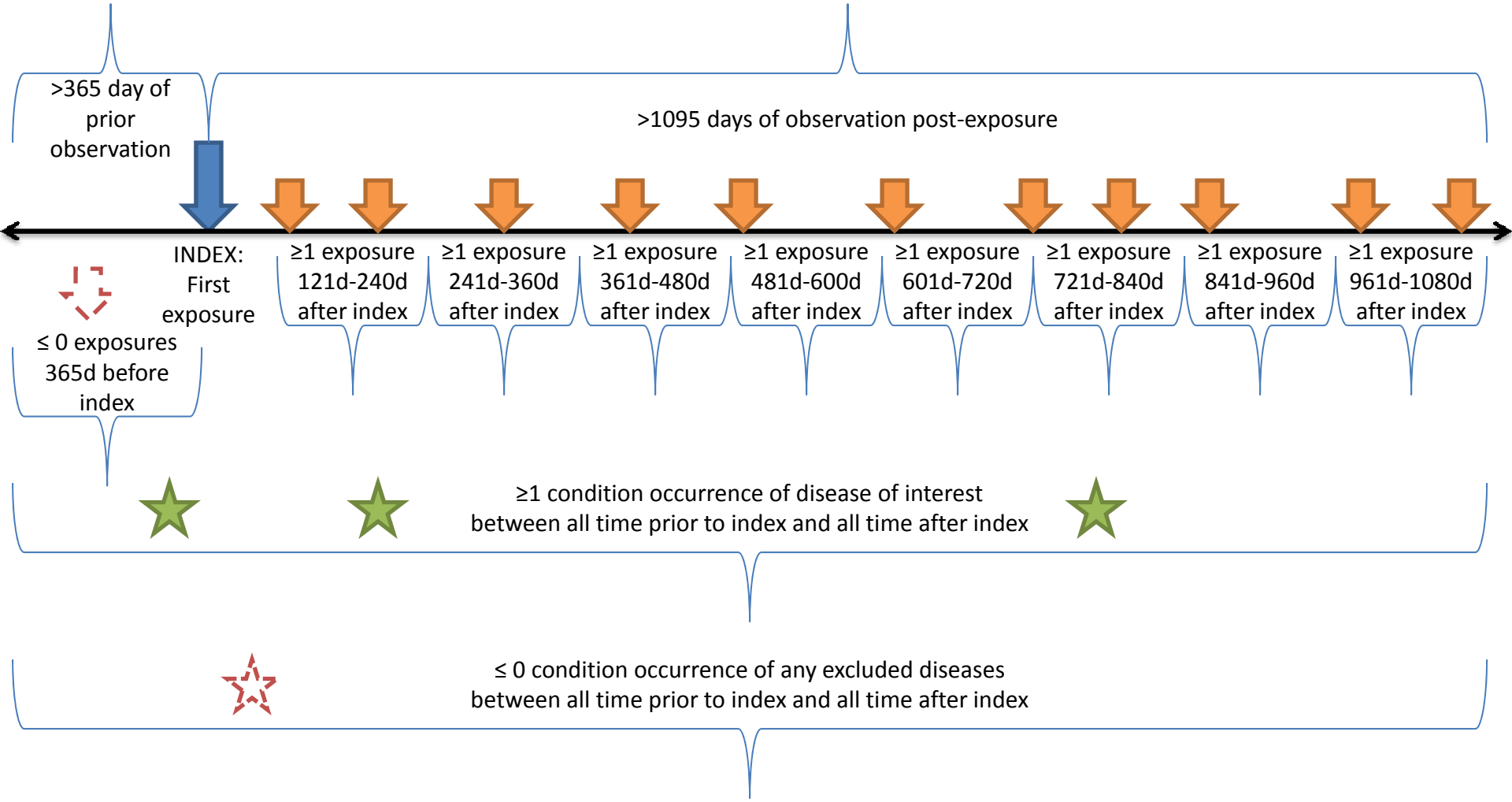
Open-source process:

- Write protocol: http://www.ohdsi.org/web/wiki/doku.php?id=research:studies
- Program analysis: https://github.com/ohdsi
- Execute code on CDM and centrally share results
- Collaboratively explore statistics and jointly publish findings

Treatment pathway example:

- Conceived at AMIA 15Nov2014
- Protocol written, code written and tested at 2 sites 30Nov2014
- Analysis submitted to OHDSI network 2Dec2014
- Results submitted for 7 databases by 5Dec2014, other databases awaiting IRB approval
- Preview of findings now…

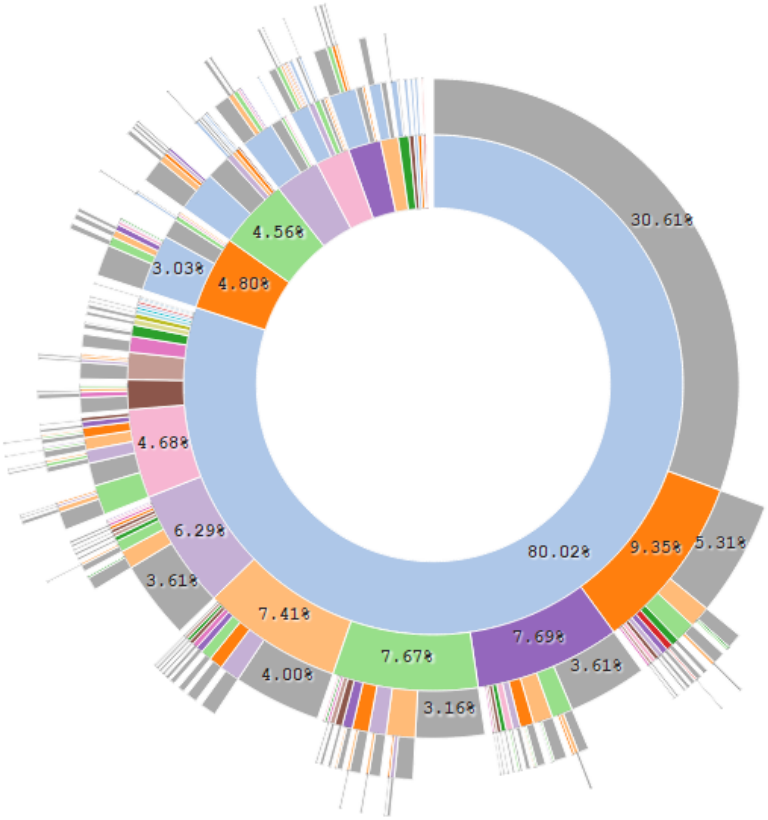
Treatment pathway protocol



http://www.ohdsi.org/web/wiki/doku.php?id=research:treatment_pathways_in_chronic_disease

Treatment pathway results

Disease: T2DM; Year: All; Source: CCAE

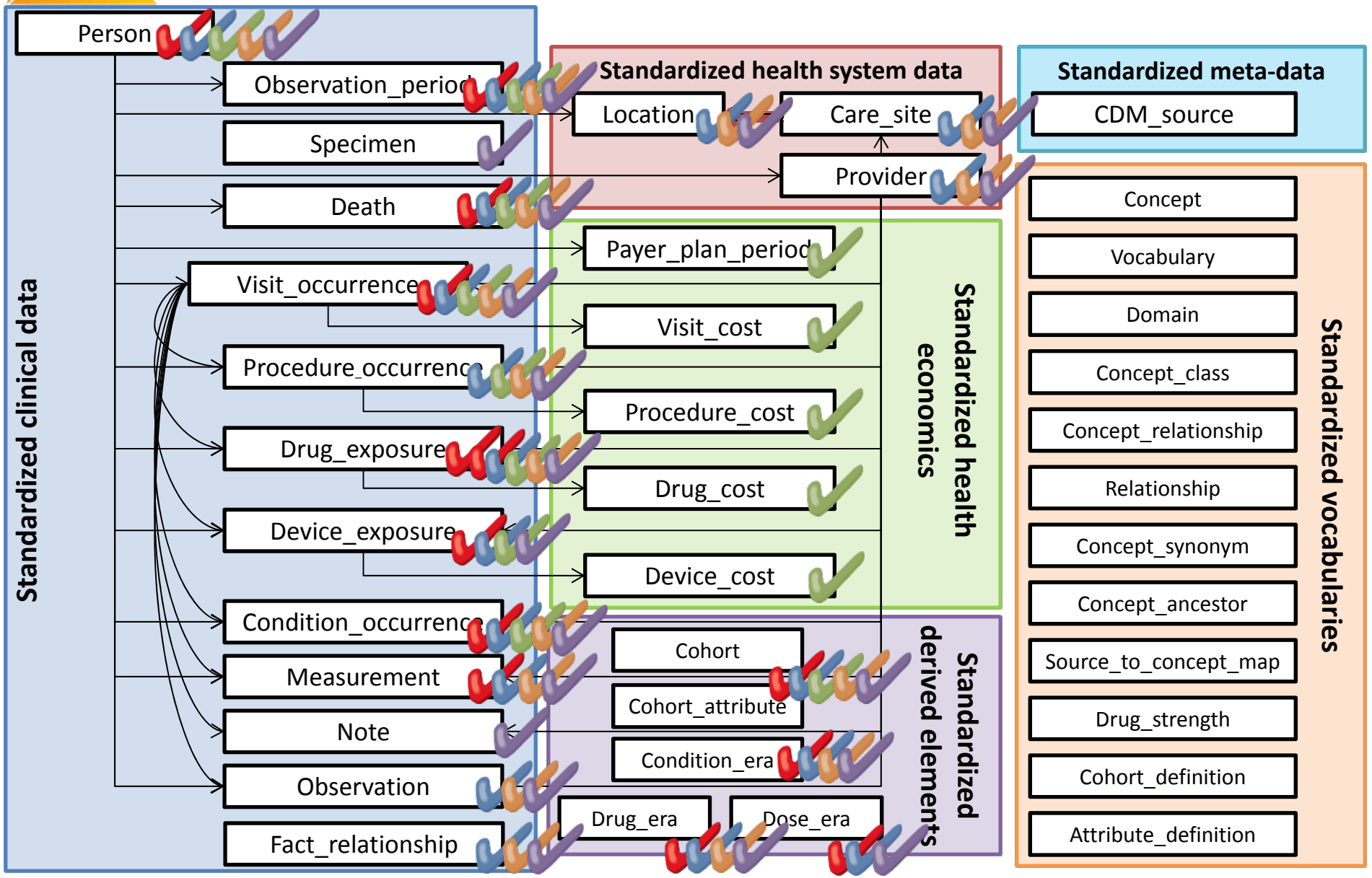


- Pramlintide
- canagliflozin
- Chlorpropamide
- Glipizide
- saxagliptin
- glimepiride
- nateglinide
- rosiglitazone
- Glyburide
- repaglinide
- Glucose
- Glucagon
- Insulin, Regular, Human
- Tolazamide
- Insulin, Aspart, Human
- Acarbose
- sitagliptin
- Insulin, Glulisine, Human
- Insulin, Isophane, Pork
- Insulin, Lispro, Human
- insulin, tetradecanoyl-Lys(B29)-des-Ala(B30)-
- exenatide
- Bromocriptine
- liraglutide
- Insulin, Extended Zinc, Beef-Pork
- Metformin
- Diazoxide
- Insulin, Glargine, Human
- Insulin, Isophane, Human
- miglitol
- Linagliptin
- alogliptin
- pioglitazone

Concluding thoughts

- An international community and global data network can be used to generate real-world evidence in a secure, reliable and efficient manner
- Multiple evidence sharing paradigms can and should be used, but all require systematic approaches enabled by a common data model
- Statisticians can and should play a leading role throughout the journey from data to evidence

One model, multiple use cases



Revisiting clopidogrel & GI bleed (Opatrny, 2008)

Agent	Cases ($n = 4028$)	Controls ($n = 40\,171$)	Crude rate ratio	Adjusted rate ratio*	95% confidence interval
Antidepressants					
SSRI	335 (8.3%)	1780 (4.4%)	1.97	1.33	1.09, 1.62
TCA	262 (6.5%)	1764 (4.4%)	1.52	1.04	0.83, 1.30
Venlafaxine	56 (1.4%)	229 (0.6%)	2.48	1.85	1.34, 2.55
Anticoagulant					
Warfarin	281 (7.0%)	1130 (2.8%)	2.64	2.17	1.82, 2.59
Clopidogrel	160 (4.0%)	532 (1.3%)	3.16	2.07	1.66, 2.58

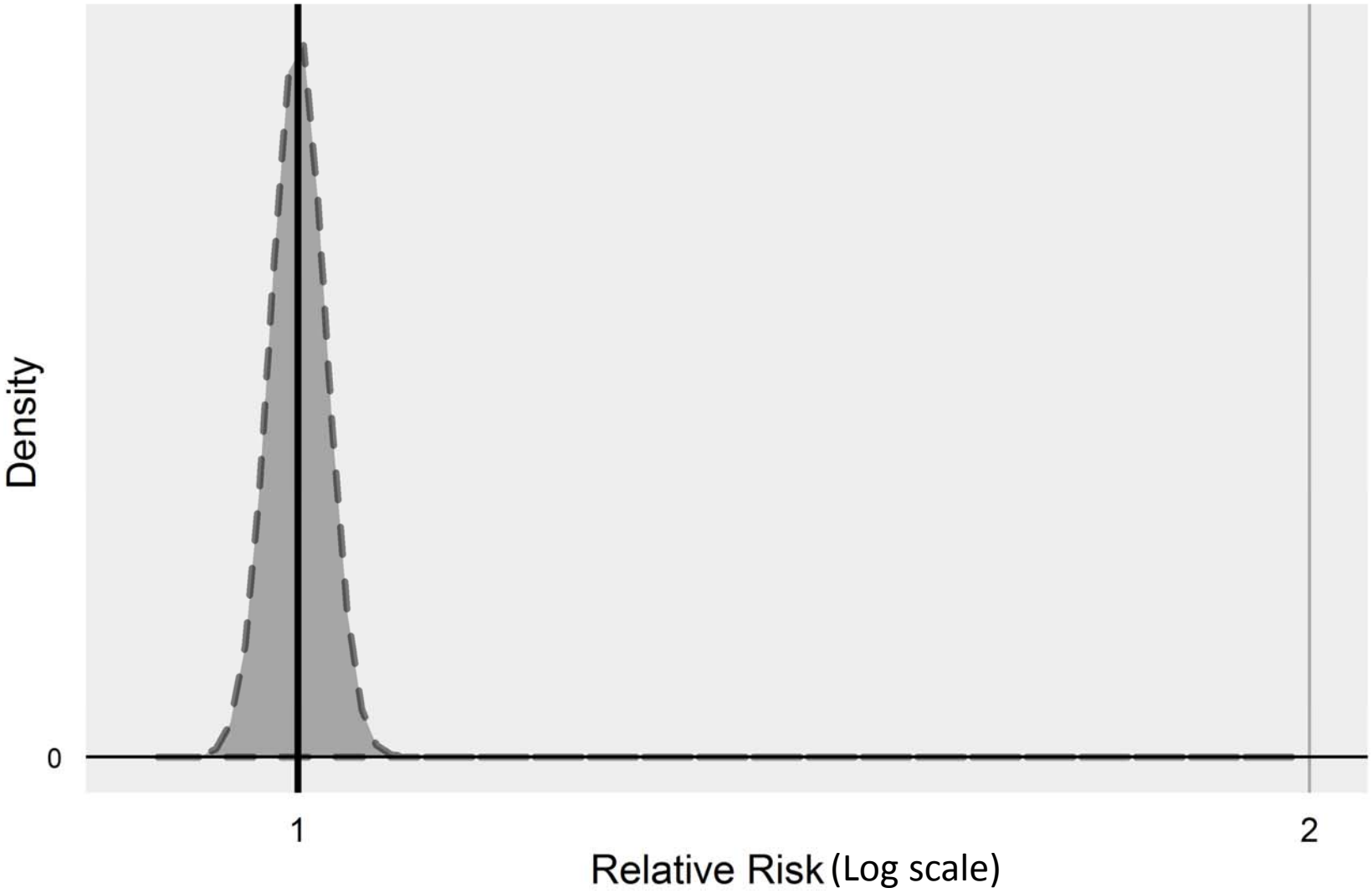
OMOP, 2012 (CC: 2000314, CCAE, GI Bleed)

Relative risk: 1.86, 95% CI: 1.79 – 1.93

Standard error: 0.02, p-value: <.001

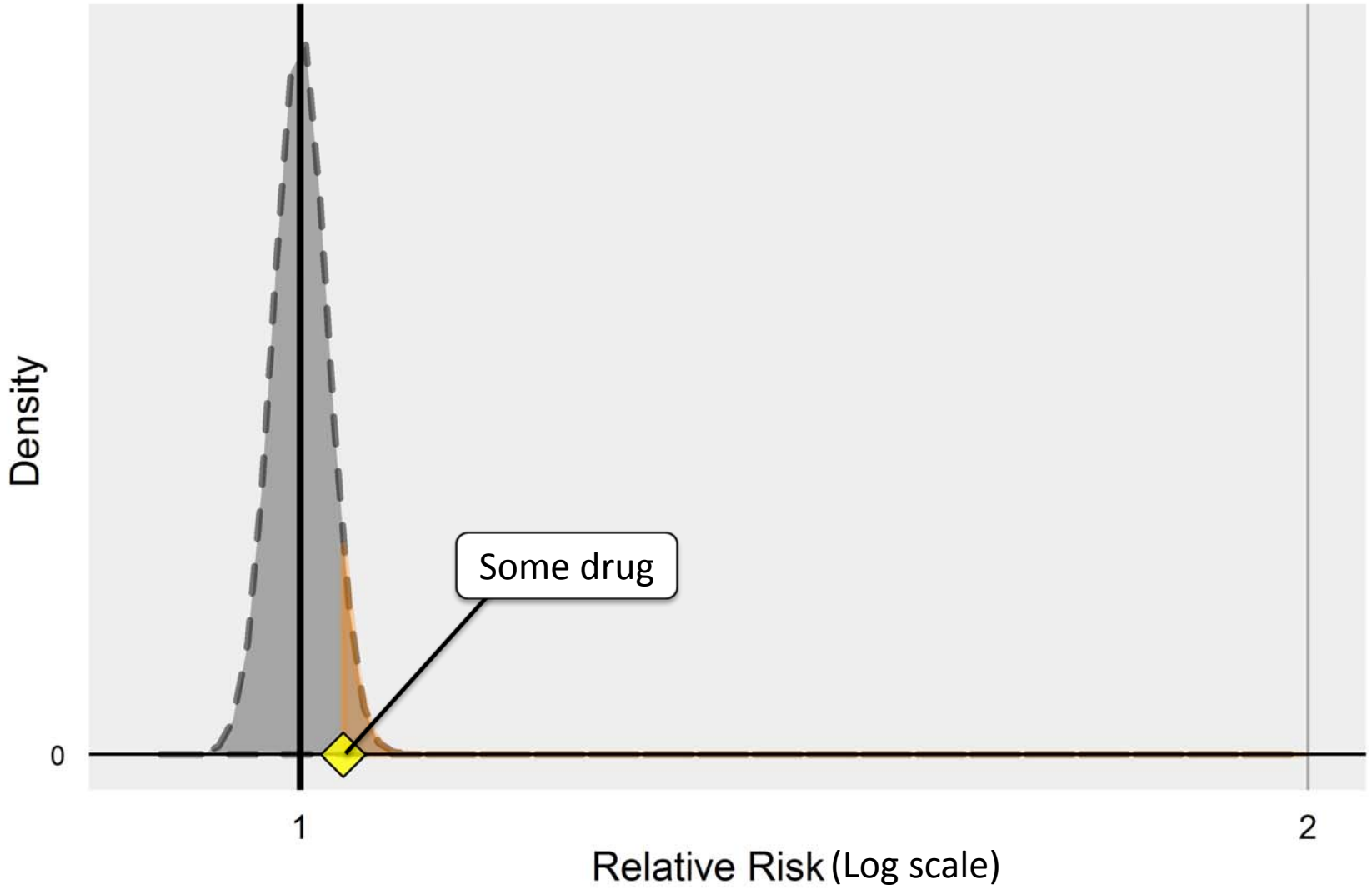
Null distribution

CC: 2000314, CCAE, GI Bleed



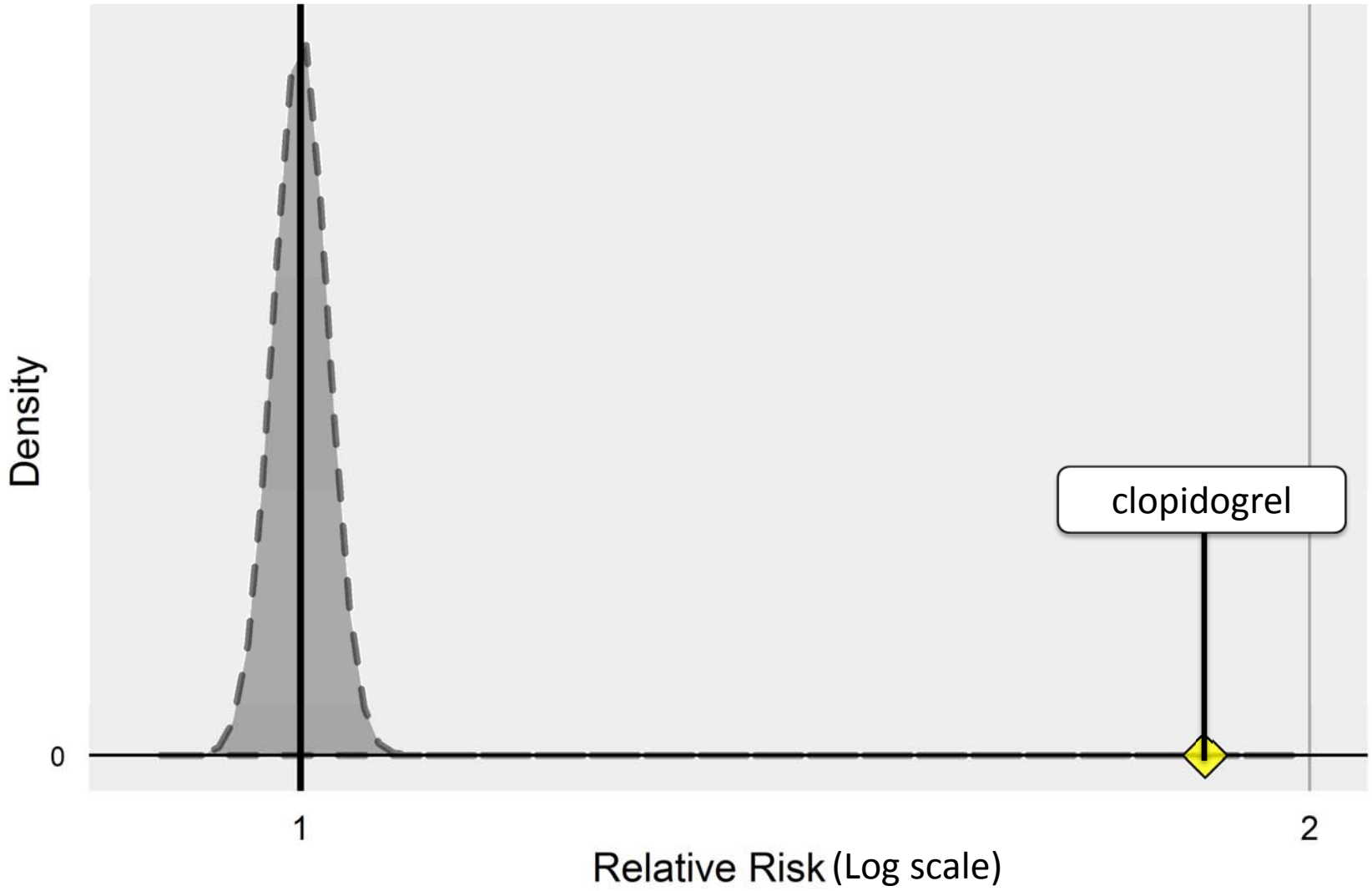
Null distribution

CC: 2000314, CCAE, GI Bleed



Null distribution

CC: 2000314, CCAE, GI Bleed



Evaluating the null distribution?

- Current p-value calculation assumes that you have an unbiased estimator (which means confounding either doesn't exist or has been fully corrected for)

- Traditionally, we reject the null hypothesis at $p<.05$ and we assume this threshold will incorrectly reject the null hypothesis 5% of time. Does this hold true in observational studies?

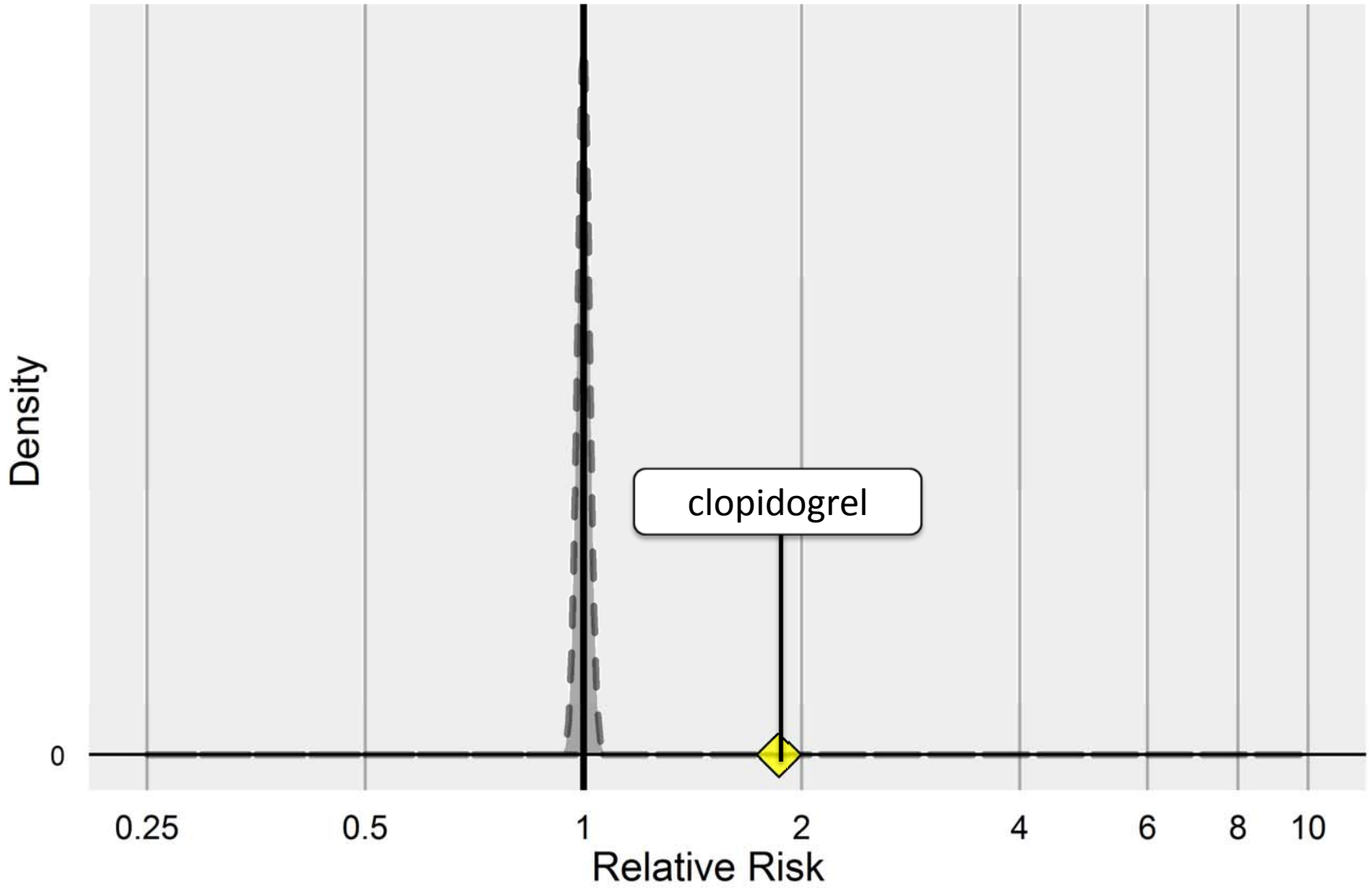
- We can test this using our negative controls

Ground truth for OMOP 2011/2012 experiments

	Positive controls	Negative controls	Total
Acute Liver Injury	81	37	118
Acute Myocardial Infarction	36	66	102
Acute Renal Failure	24	64	88
Upper Gastrointestinal Bleeding	24	67	91
Total	165	234	399

Criteria for negative controls:

- Event not listed anywhere in any section of active FDA structured product label
- Drug not listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Literature review identified no evidence of potential positive association

Negative controls & the null distribution

CC: 2000314, CCAE, GI Bleed