The Observational Medical Outcomes Partnership: Overview of experimental results

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OMOP Research Team
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Observational
Medical
Outcomes
Partnership

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Full results and audio presentations from OMOP Symposium available at:
http://omop.fnih.org/OMOP2011Symposium

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Risk identification and analysis system: One additional piece of evidence to inform medical decision-making

“Drug safety active surveillance systems exploit large repositories of automated healthcare data to identify and examine drug safety issues…Active surveillance systems use sophisticated statistical methods to actively search for patterns in prescription, outpatient, and inpatient data systems that might suggest the occurrence of an adverse event, or safety signal, related to drug therapy.”
Woodcock J, Behrman RE, Dal Pan GJ, Annu. Rev. Med. 2011

- Pre-clinical toxicology
- Pharmacology
- Clinical trials
- Spontaneous case reports
- Perspectives in literature from medical experts
- Pharmacoepidemiology evaluation studies
- **Risk identification and analysis system**

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Risk Identification and Analysis System:

a systematic and reproducible process to efficiently generate evidence to support the characterization of the potential effects of medical products from across a network of disparate observational healthcare data sources

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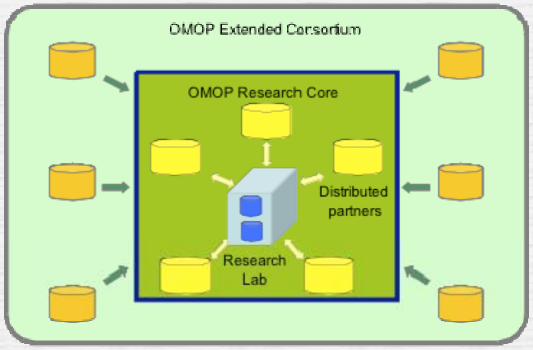
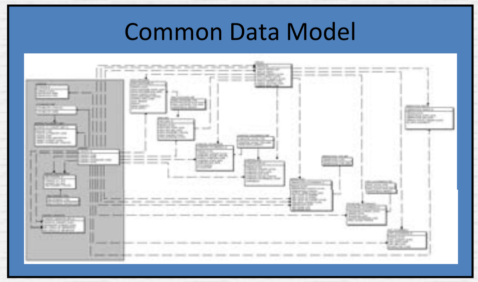
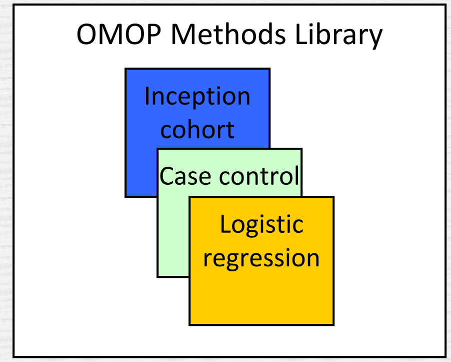
Evidence about alternative treatments

OMOP Research Experiment



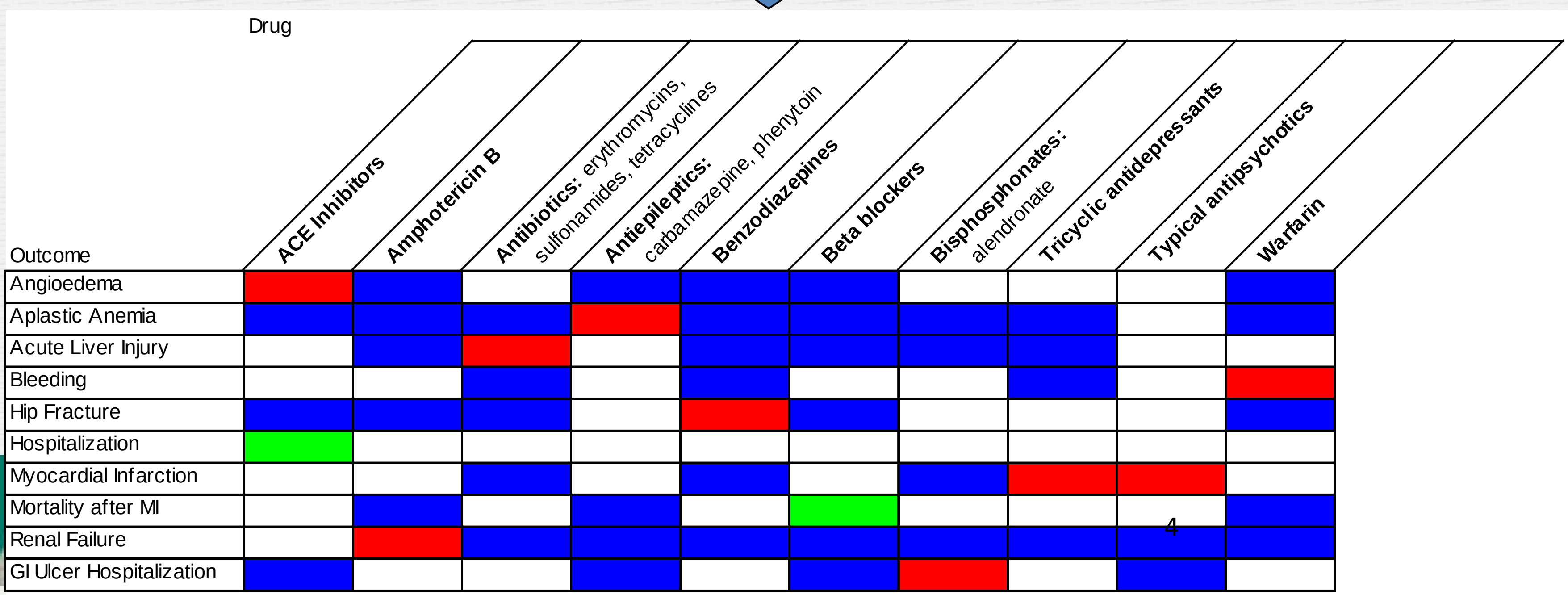
- Open-source
- Standards-based



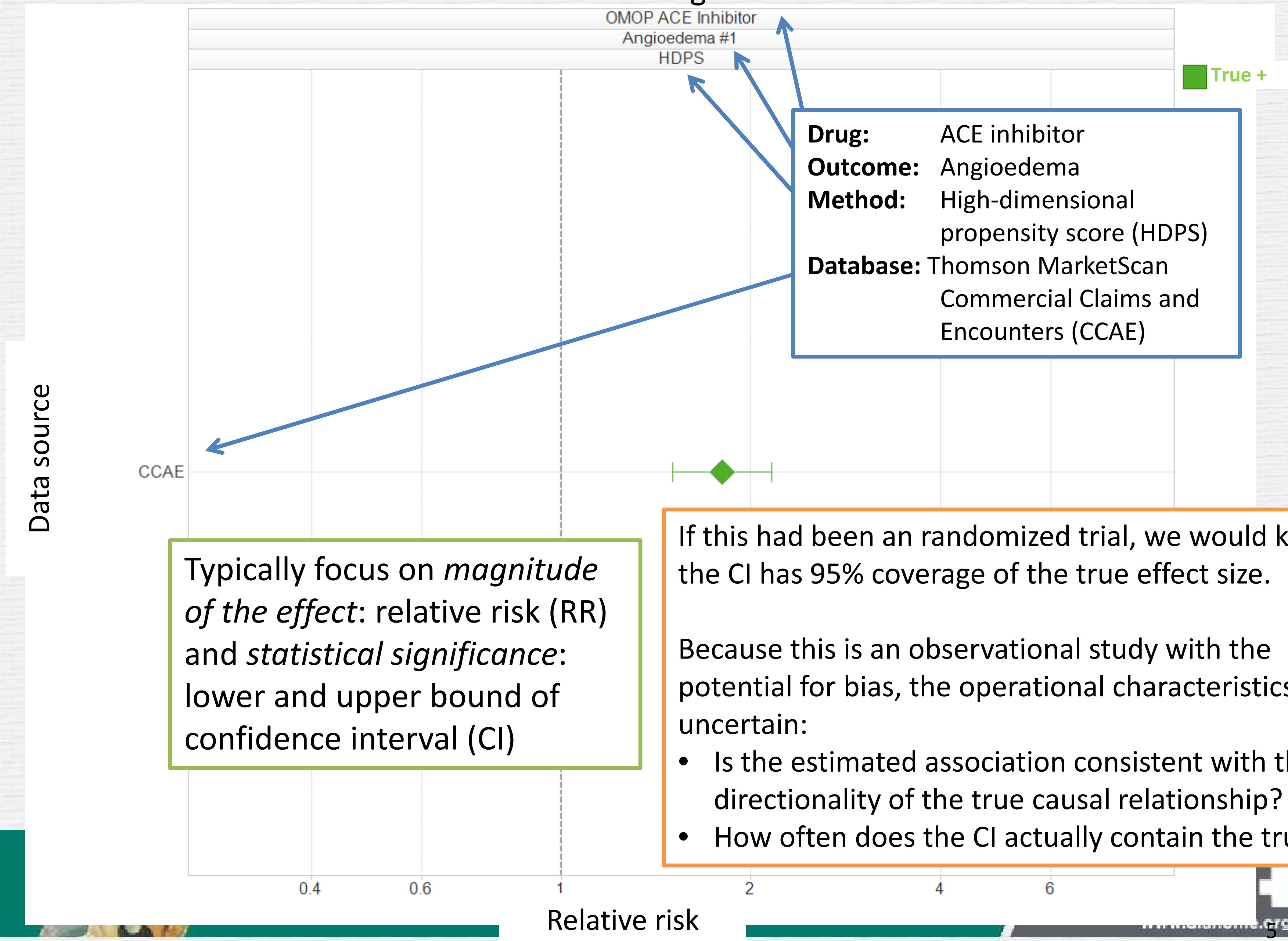


- 10 data sources
- Claims and EHRs
- 200M+ lives

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



Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



Drug: ACE inhibitor
Outcome: Angioedema
Method: High-dimensional propensity score (HDPS)
Database: Thomson MarketScan Commercial Claims and Encounters (CCAE)

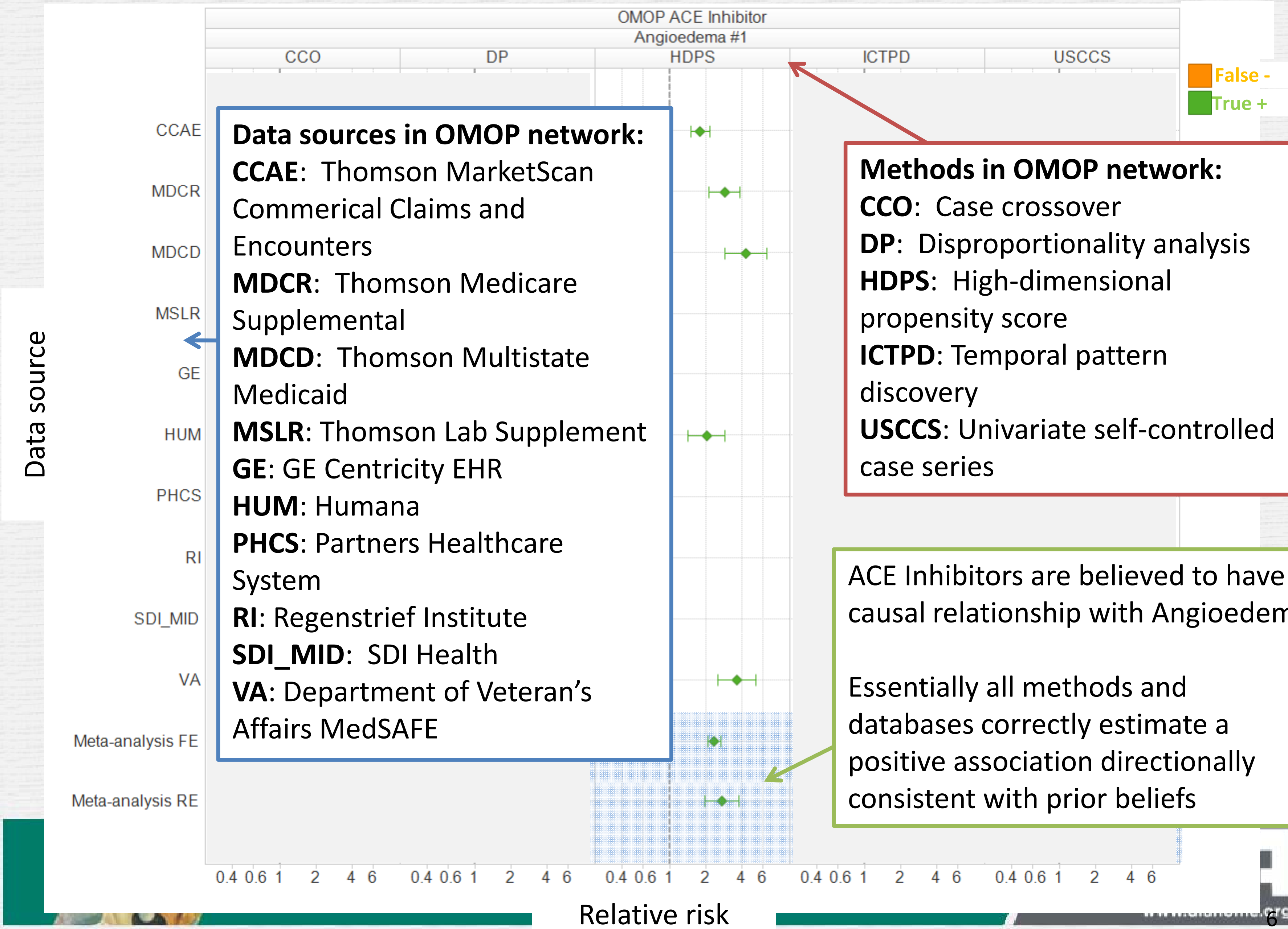
Typically focus on *magnitude of the effect*: relative risk (RR) and *statistical significance*: lower and upper bound of confidence interval (CI)

If this had been an randomized trial, we would know the CI has 95% coverage of the true effect size.

Because this is an observational study with the potential for bias, the operational characteristics are uncertain:

- Is the estimated association consistent with the directionality of the true causal relationship?
- How often does the CI actually contain the truth?

Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



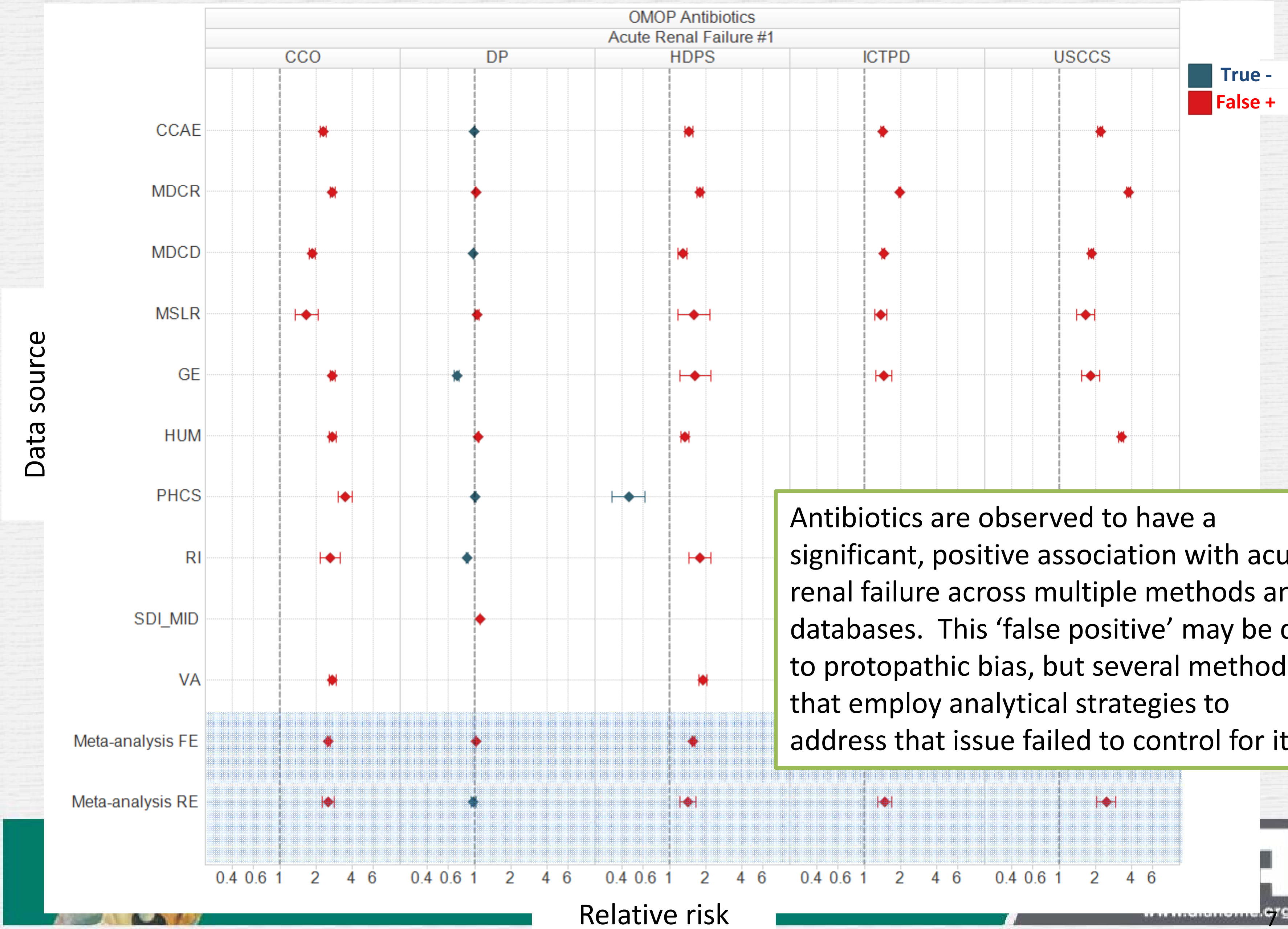
Data sources in OMOP network:
CCAE: Thomson MarketScan Commerical Claims and Encounters
MDCR: Thomson Medicare Supplemental
MDCD: Thomson Multistate Medicaid
MSLR: Thomson Lab Supplement
GE: GE Centricity EHR
HUM: Humana
PHCS: Partners Healthcare System
RI: Regenstrief Institute
SDI_MID: SDI Health
VA: Department of Veteran's Affairs MedSAFE

Methods in OMOP network:
CCO: Case crossover
DP: Disproportionality analysis
HDPS: High-dimensional propensity score
ICTPD: Temporal pattern discovery
USCCS: Univariate self-controlled case series

ACE Inhibitors are believed to have a causal relationship with Angioedema

Essentially all methods and databases correctly estimate a positive association directionally consistent with prior beliefs

Consistent 'false positive' observed for 'negative control' of Antibiotics and Acute Renal Failure



Antibiotics are observed to have a significant, positive association with acute renal failure across multiple methods and databases. This 'false positive' may be due to protopathic bias, but several methods that employ analytical strategies to address that issue failed to control for it.

Measuring method performance

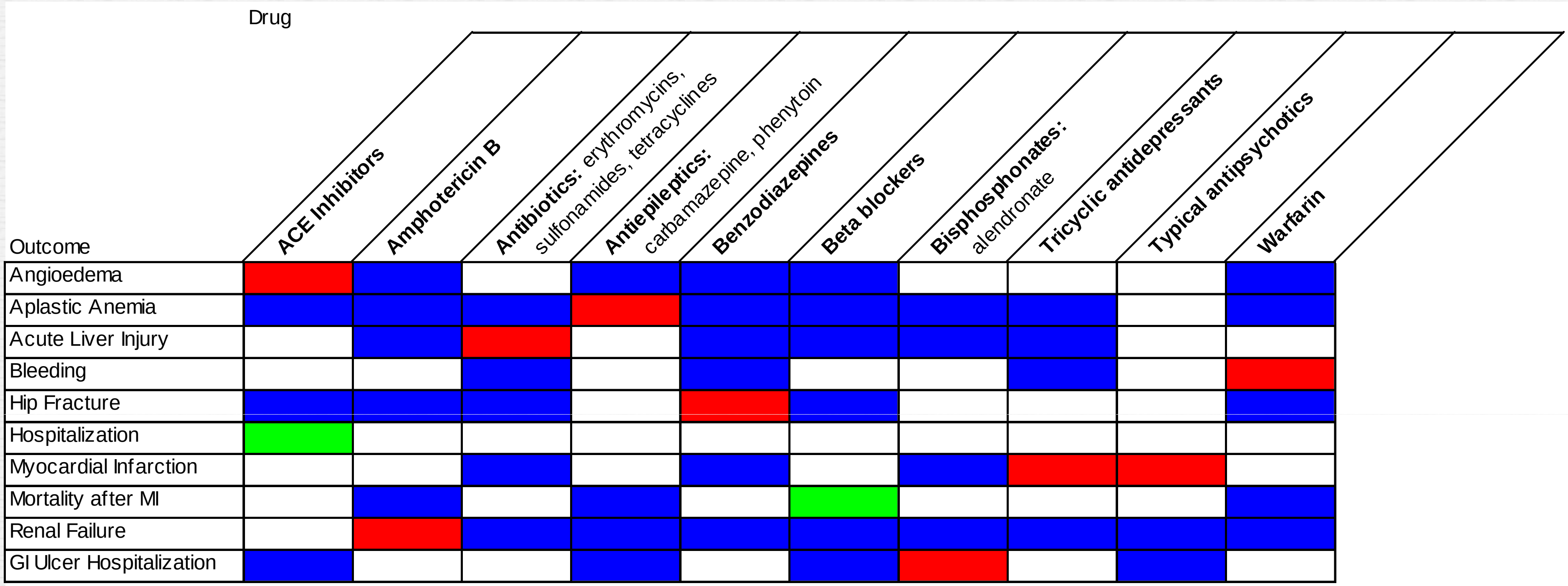
Drug-condition association status
Y – 'true association',
N – 'negative control'

Method prediction: Drug-condition pair met a specific threshold

	Y	N
Y	**True positives**	**False positives**
N	**False negatives**	**True negatives**

Question: For any method applied to any data source, what are the expected operating characteristics?

‘Ground truth’ assumed for Monitoring Health Outcomes of Interest



Legend	Total
True positive' benefit	2
True positive' risk	9
Negative control'	44

Measuring method performance example: Random-effect meta-analysis of estimates from High-dimensional propensity score

Drug-condition association status
Y – ‘true association’,
N – ‘negative control’

Method prediction: Drug-condition pair met a specific threshold: (LB 95% CI > 1)		Y	N	
	Y	True positives: 5	False positives: 8	Positive predictive value = precision = TP / (TP+FP) = 5 / (5+8) = 0.38
	N	False negatives: 4	True negatives: 36	Negative predictive value = TN / (FN+TN) = 36 / (4+36) = 0.90

Sensitivity
= Recall
= TP / (TP+FN)
= 5 / (5+4) = 0.56

Specificity
= TN / (FP+TN)
= 36 /(8+36) = 0.82

False positive rate
= 1 – 0.82 = 0.18

Accuracy
= (TP+TN) /
(TP+TN+FP+FN)
=(5+36)/(9+44) = 0.77

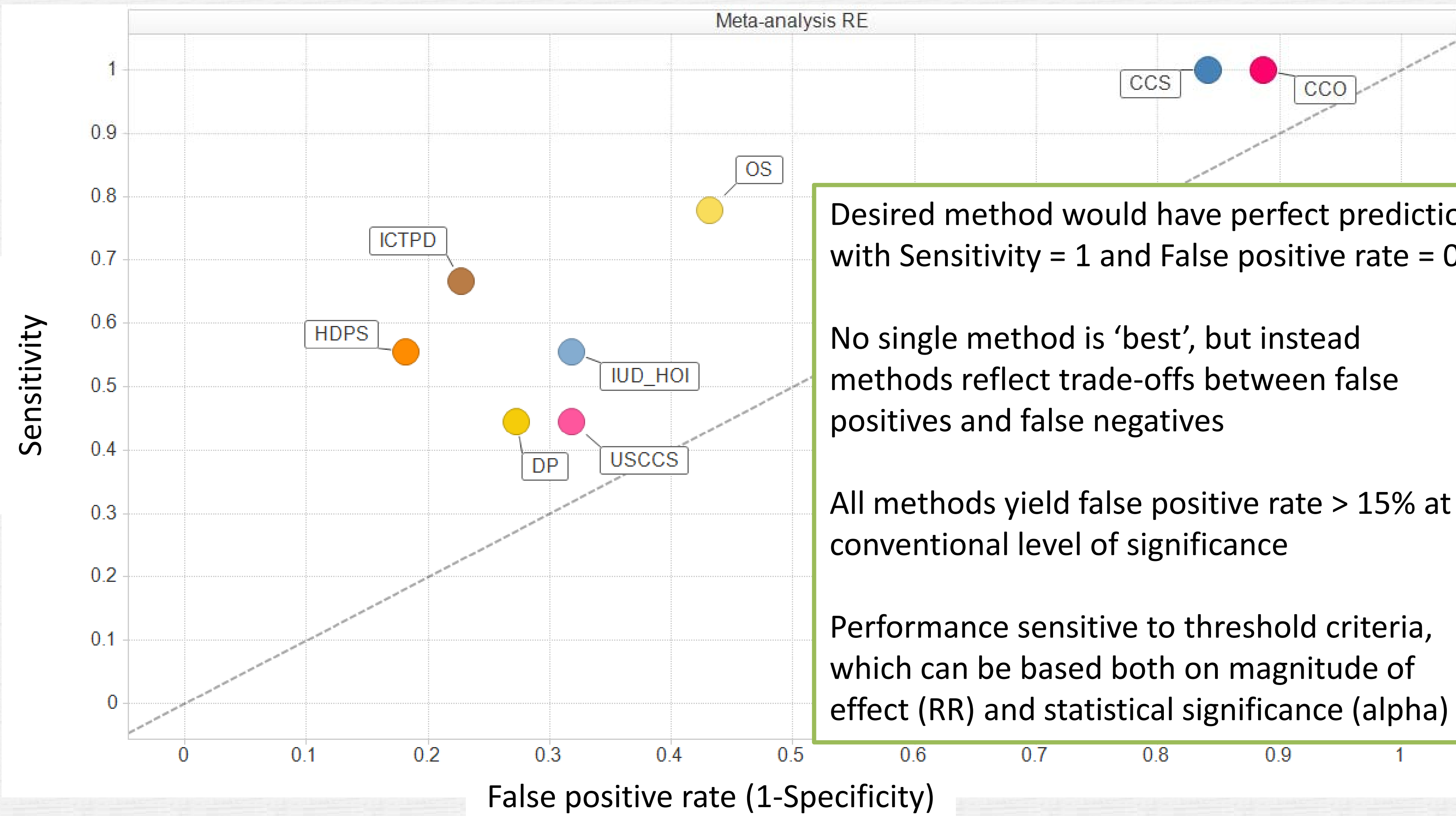
Risk identification methods under evaluation in OMOP experiment

Method name	Contributor	Release date
Disproportionality analysis		
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10
Case-based methods		
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10
Case-control surveillance (CCS)	Lilly	2-May-10
Case-crossover (CCO)	University of Utah	1-Jun-10
Exposure-based methods		
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10
High-dimensional propensity score (HDPS)	Columbia	6-Aug-10
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10
Sequential testing methods		
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10

In what follows, we have chosen one parameter combination for each method that performs best for the meta-analysis estimates

http://omop.fnih.org/MethodsLibrary

Comparing methods by sensitivity and specificity at alpha=0.05



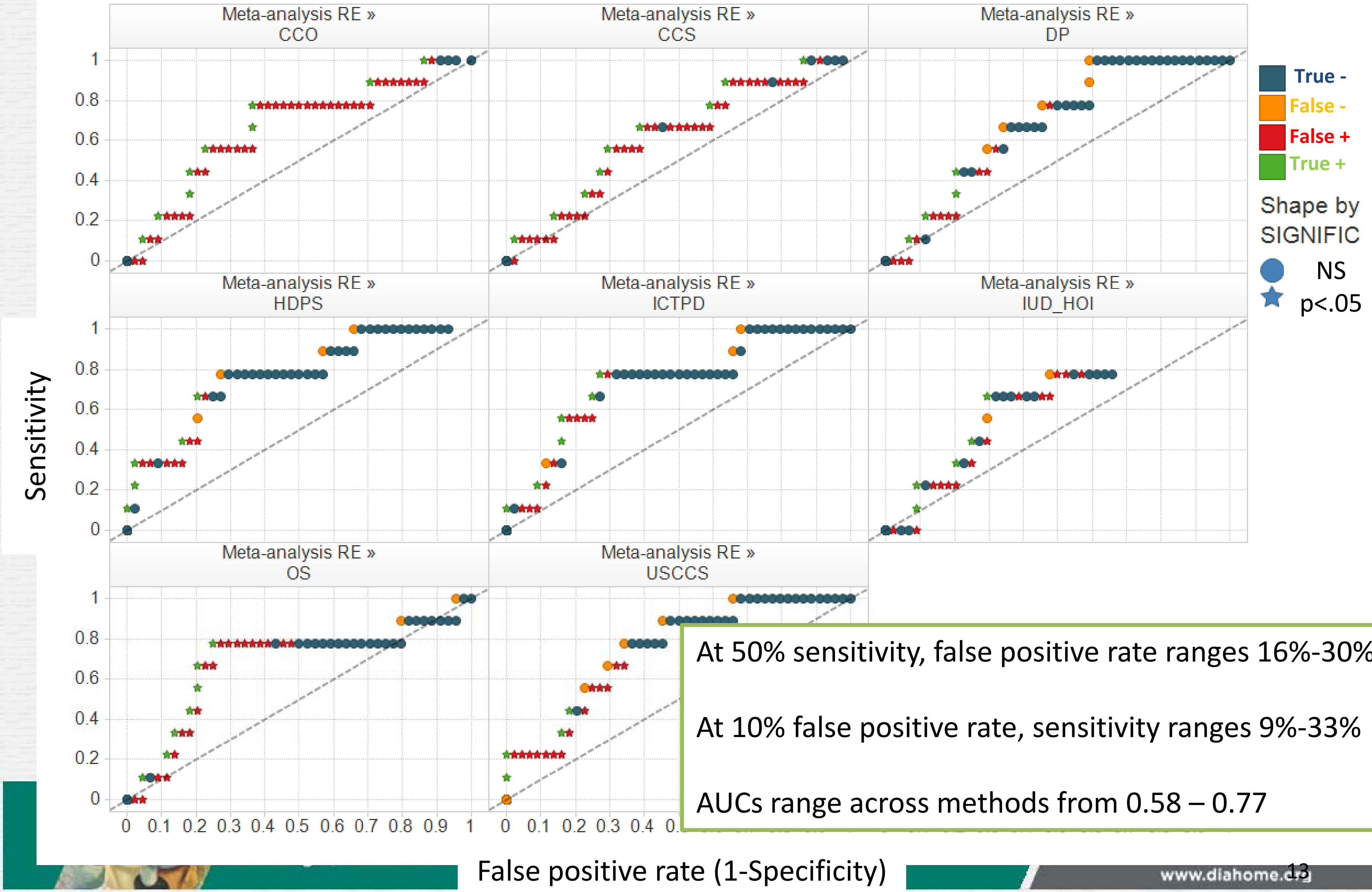
Desired method would have perfect prediction with Sensitivity = 1 and False positive rate = 0

No single method is ‘best’, but instead methods reflect trade-offs between false positives and false negatives

All methods yield false positive rate > 15% at conventional level of significance

Performance sensitive to threshold criteria, which can be based both on magnitude of effect (RR) and statistical significance (alpha)

ROC curves of random-effects meta-analysis estimations for all methods

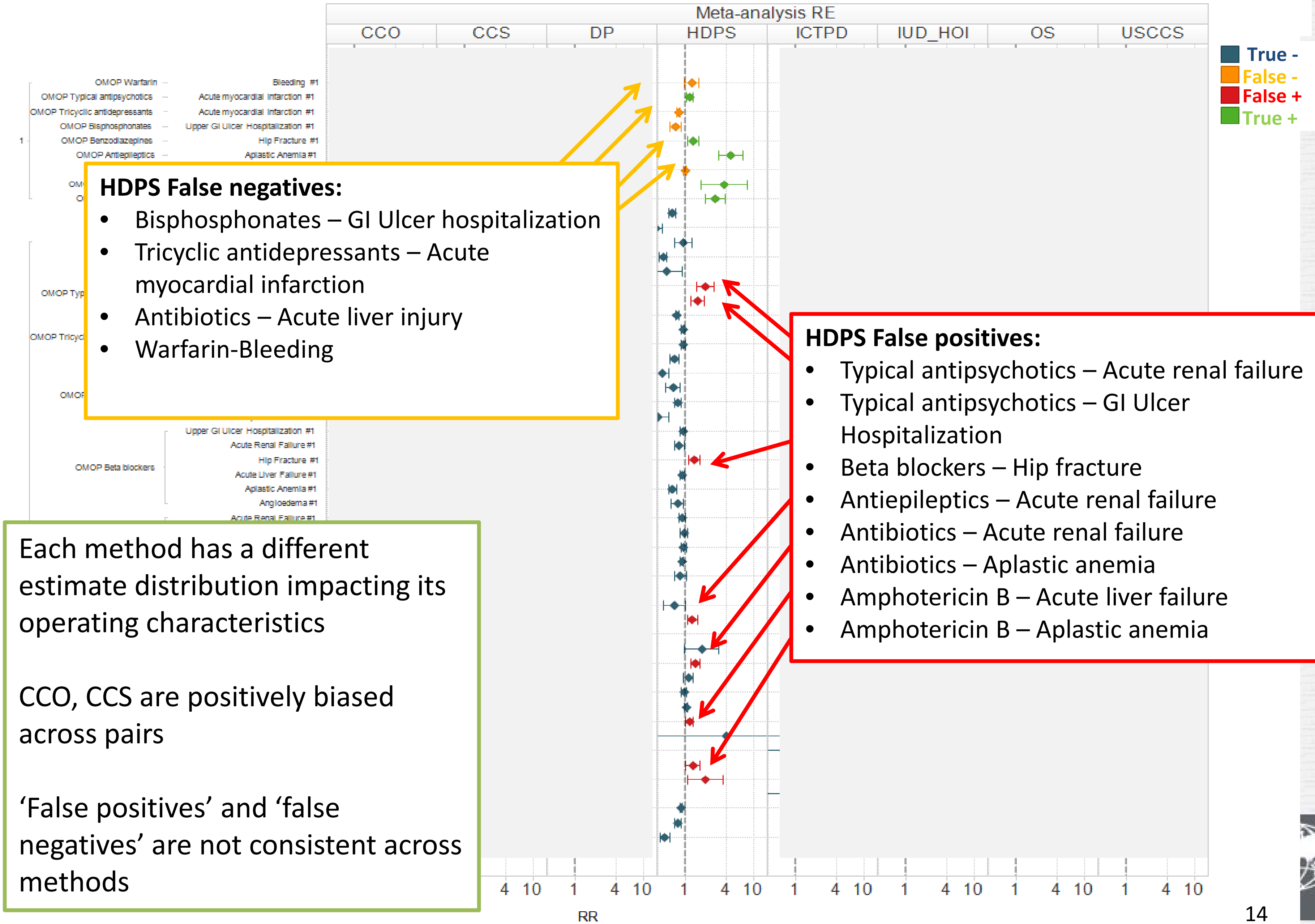


At 50% sensitivity, false positive rate ranges 16%-30%

At 10% false positive rate, sensitivity ranges 9%-33%

AUCs range across methods from 0.58 – 0.77

Distribution of estimates across all drug-outcome pairs



HDPS False negatives:

- Bisphosphonates – GI Ulcer hospitalization
- Tricyclic antidepressants – Acute myocardial infarction
- Antibiotics – Acute liver injury
- Warfarin-Bleeding

HDPS False positives:

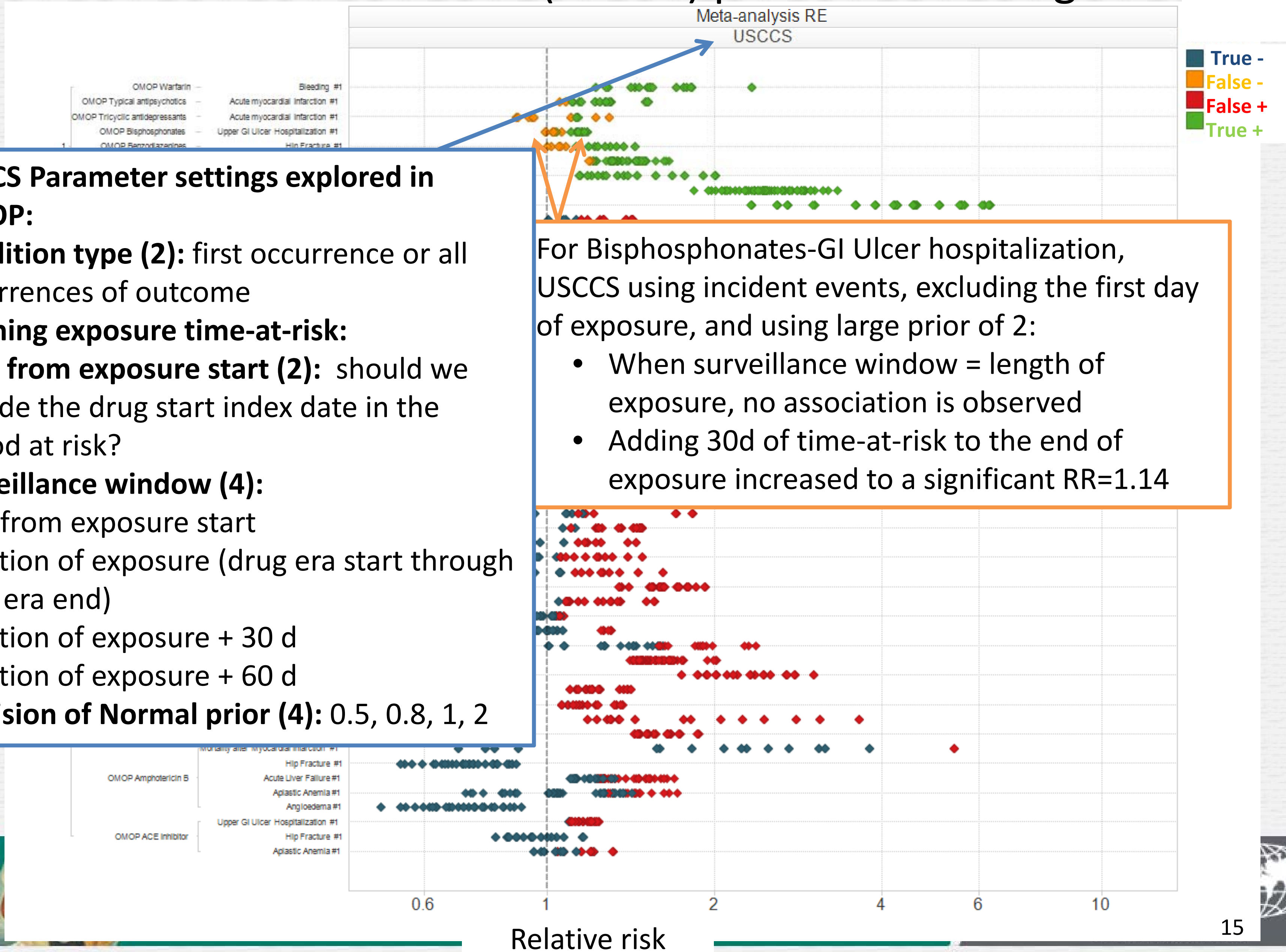
- Typical antipsychotics – Acute renal failure
- Typical antipsychotics – GI Ulcer Hospitalization
- Beta blockers – Hip fracture
- Antiepileptics – Acute renal failure
- Antibiotics – Acute renal failure
- Antibiotics – Aplastic anemia
- Amphotericin B – Acute liver failure
- Amphotericin B – Aplastic anemia

Each method has a different estimate distribution impacting its operating characteristics

CCO, CCS are positively biased across pairs

'False positives' and 'false negatives' are not consistent across methods

Range of estimates across univariate self-controlled case series (USCCS) parameter settings

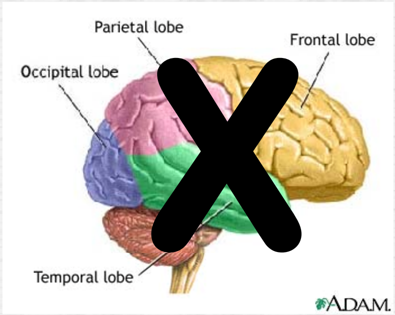


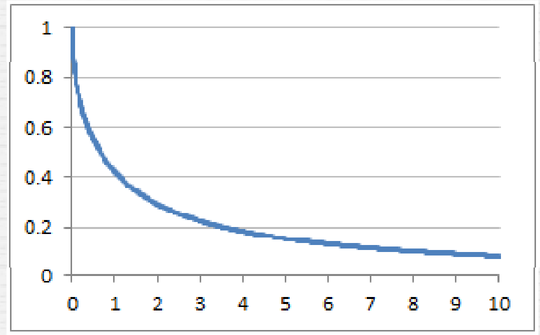
USCCS Parameter settings explored in OMOP:
Condition type (2): first occurrence or all occurrences of outcome
Defining exposure time-at-risk:
Days from exposure start (2): should we include the drug start index date in the period at risk?
Surveillance window (4):
30 d from exposure start
Duration of exposure (drug era start through drug era end)
Duration of exposure + 30 d
Duration of exposure + 60 d
Precision of Normal prior (4): 0.5, 0.8, 1, 2

For Bisphosphonates-GI Ulcer hospitalization, USCCS using incident events, excluding the first day of exposure, and using large prior of 2:

- When surveillance window = length of exposure, no association is observed
- Adding 30d of time-at-risk to the end of exposure increased to a significant RR=1.14

Bayesian Learning paradigm





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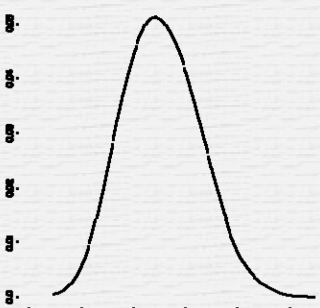
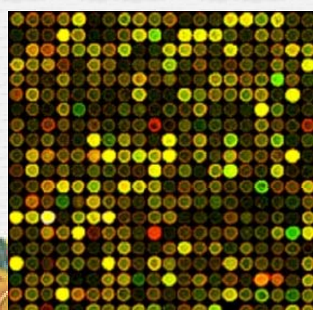


prior

Bayes' Rule

Name	Thread pitch (mm)	Minor diameter tolerance	Nominal diameter (mm)	Head shape	Price for 50 screws	Available at factory outlet?	Number in stock	Flat or Phillips head?
M4	0.7	4g	4	Pan	$10.08	Yes	276	Flat
M5	0.8	4g	5	Round	$13.89	Yes	183	Both
M6	1	5g	6	Button	$10.42	Yes	1043	Flat
M8	1.25	5g	8	Pan	$11.98	No	298	Phillips
M10	1.5	6g	10	Round	$16.74	Yes	488	Phillips
M12	1.75	7g	12	Pan	$18.26	No	998	Flat
M14	2	7g	14	Round	$21.19	No	235	Phillips
M16	2	8g	16	Button	$23.57	Yes	292	Both
M18	2.1	8g	18	Button	$25.87	No	664	Both
M20	2.4	8g	20	Pan	$29.09	Yes	486	Both
M24	2.55	9g	24	Round	$33.01	Yes	982	Phillips
M28	2.7	10g	28	Button	$35.66	No	1067	Phillips
M36	3.2	12g	36	Pan	$41.32	No	434	Both
M50	4.5	15g	50	Pan	$44.72	No	740	Flat

data



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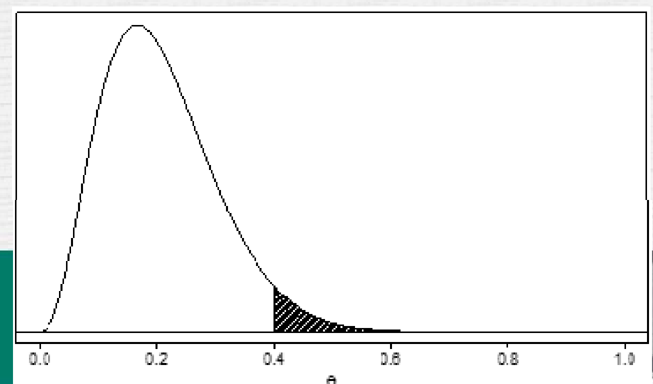
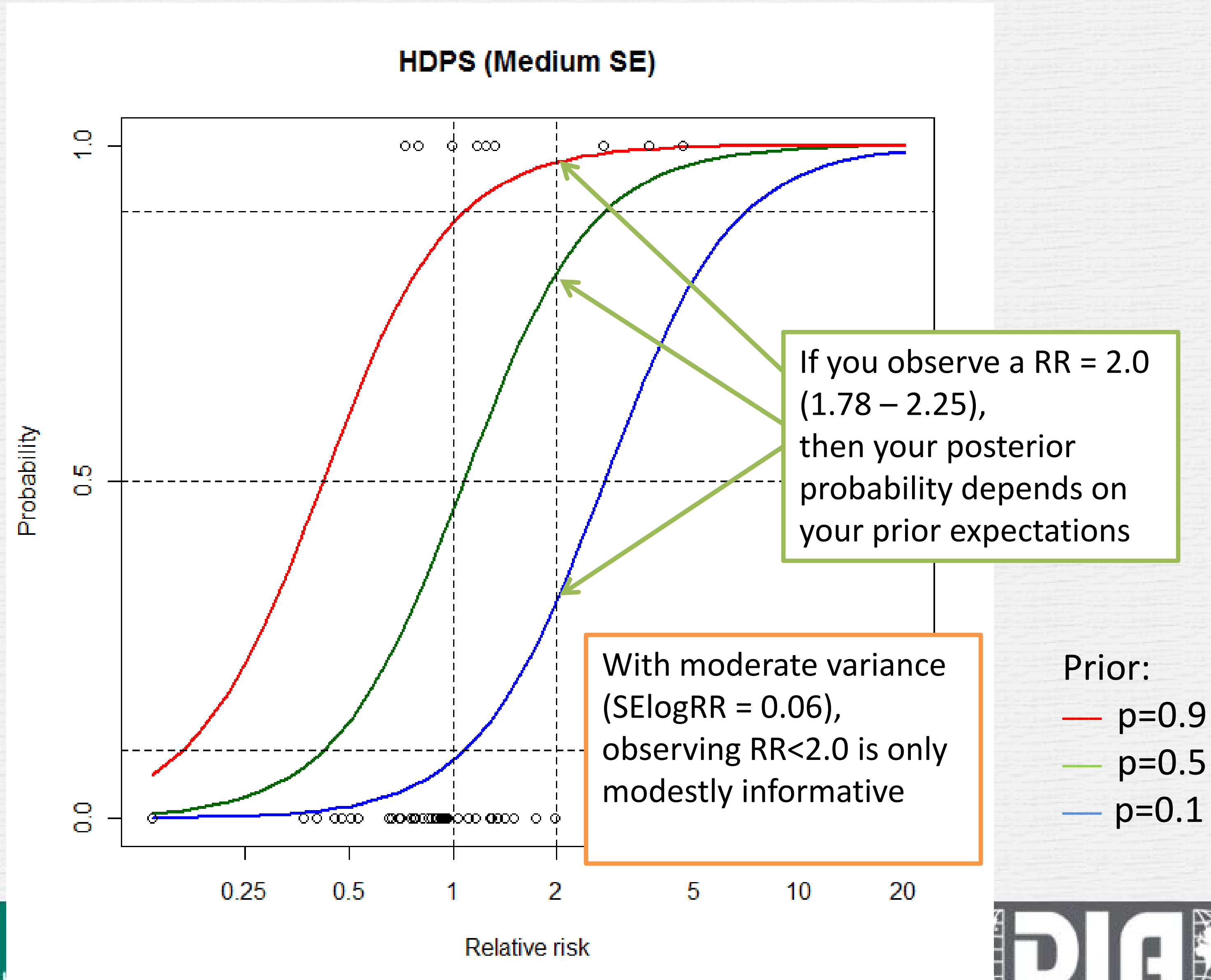
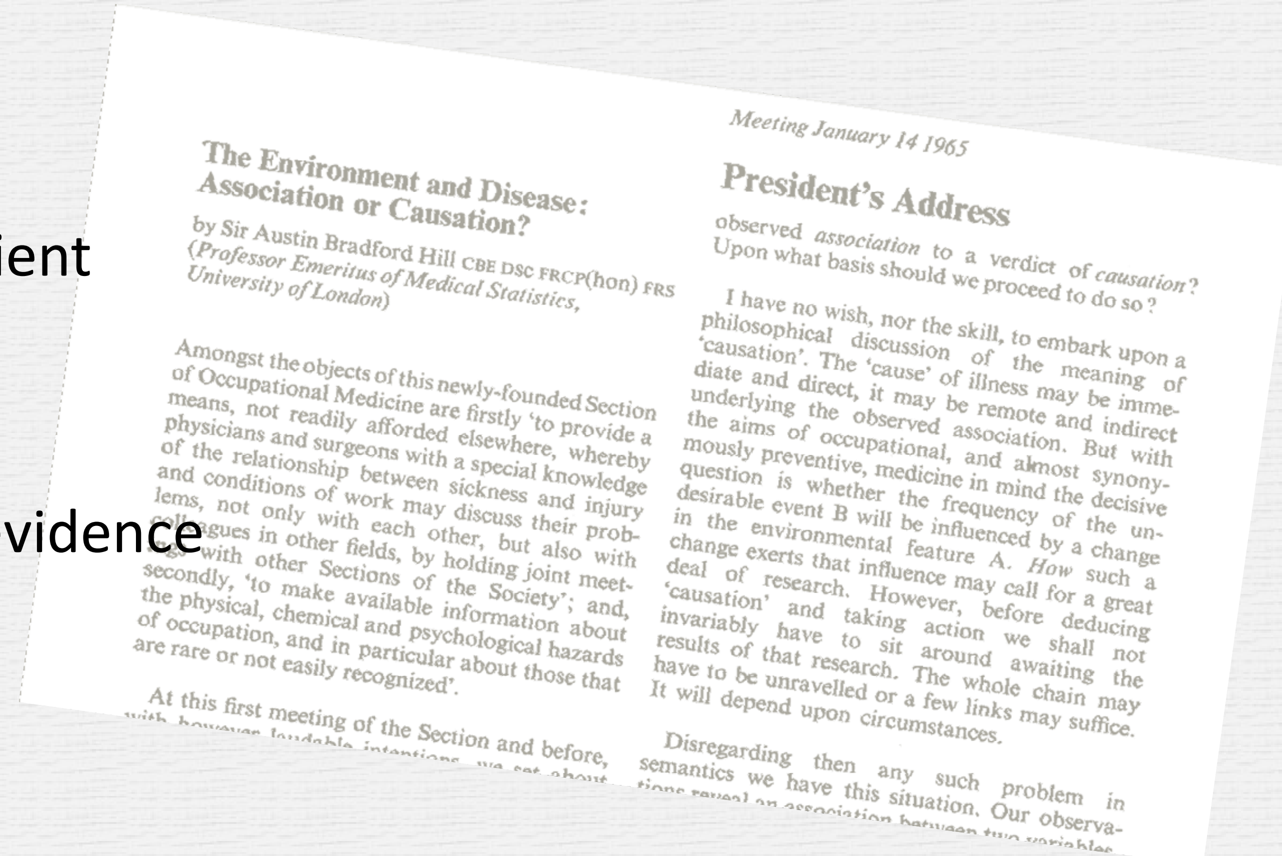


Revising prior expectations in light of new evidence from a risk identification system



Hill’s causality viewpoints

- Strength of association
- Consistency
- Specificity
- Temporality
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy



Meeting January 14 1965

The Environment and Disease: Association or Causation?

by Sir Austin Bradford Hill CBE DSC FRCP(hon) FRS
(Professor Emeritus of Medical Statistics, University of London)

Amongst the objects of this newly-founded Section of Occupational Medicine are firstly ‘to provide a means, not readily afforded elsewhere, whereby physicians and surgeons with a special knowledge of the relationship between sickness and injury and conditions of work may discuss their problems, not only with each other, but also with colleagues in other fields, by holding joint meetings with other Sections of the Society’; and, secondly, ‘to make available information about the physical, chemical and psychological hazards of occupation, and in particular about those that are rare or not easily recognized’.

At this first meeting of the Section and before,

President’s Address

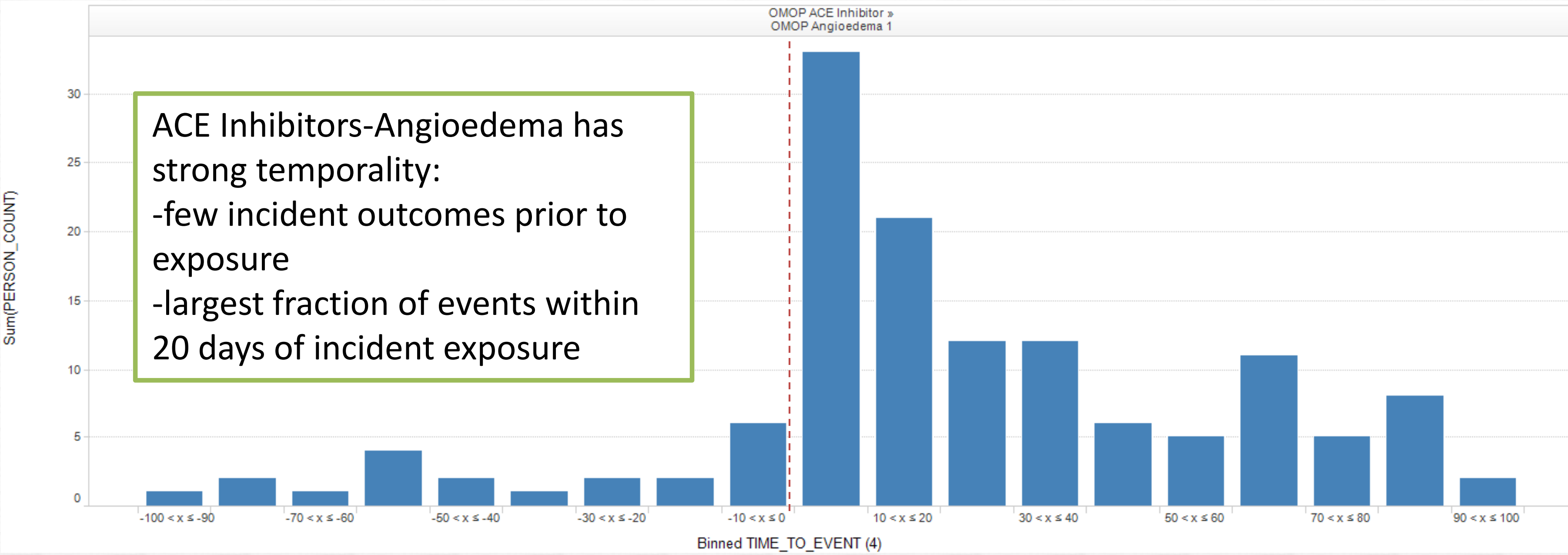
observed *association* to a verdict of *causation*? Upon what basis should we proceed to do so?

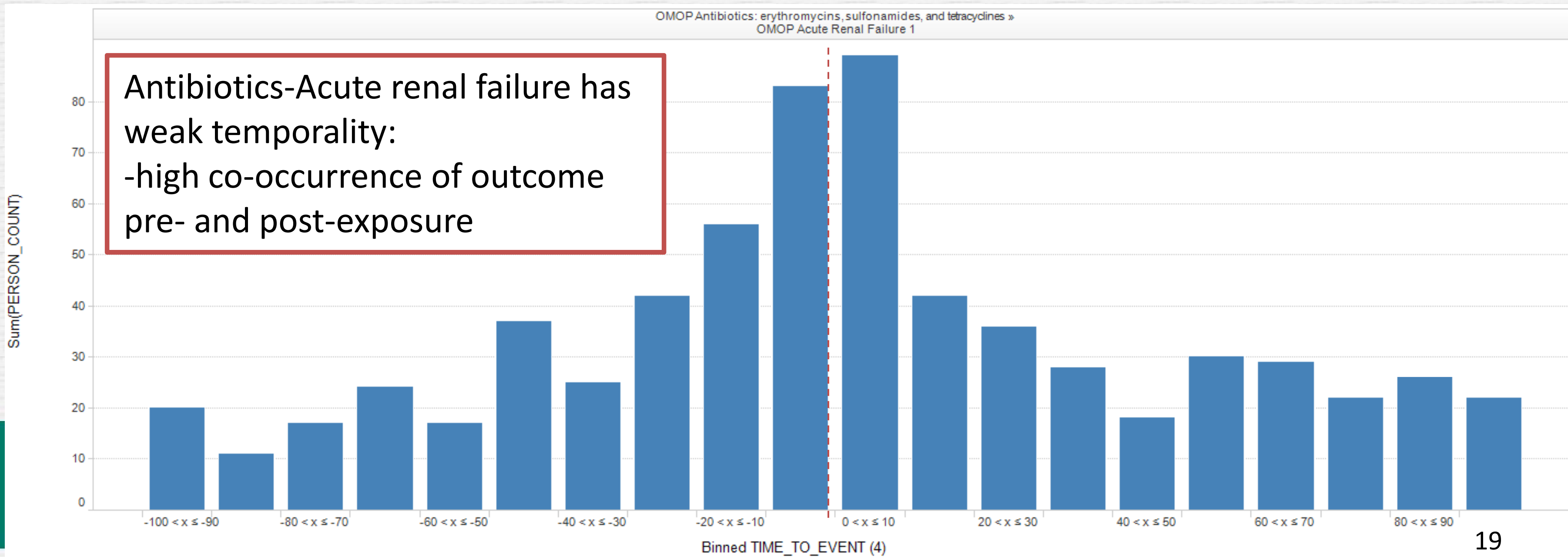
I have no wish, nor the skill, to embark upon a philosophical discussion of the meaning of ‘causation’. The ‘cause’ of illness may be immediate and direct, it may be remote and indirect underlying the observed association. But with the aims of occupational, and almost synonymously preventive, medicine in mind the decisive question is whether the frequency of the undesirable event B will be influenced by a change in the environmental feature A. *How* such a change exerts that influence may call for a great deal of research. However, before deducing ‘causation’ and taking action we shall not invariably have to sit around awaiting the results of that research. The whole chain may have to be unravelled or a few links may suffice. It will depend upon circumstances.

Disregarding then any such problem in semantics we have this situation. Our observa-

Austin Bradford Hill, “The Environment and Disease: Association or Causation?,” *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

Temporality

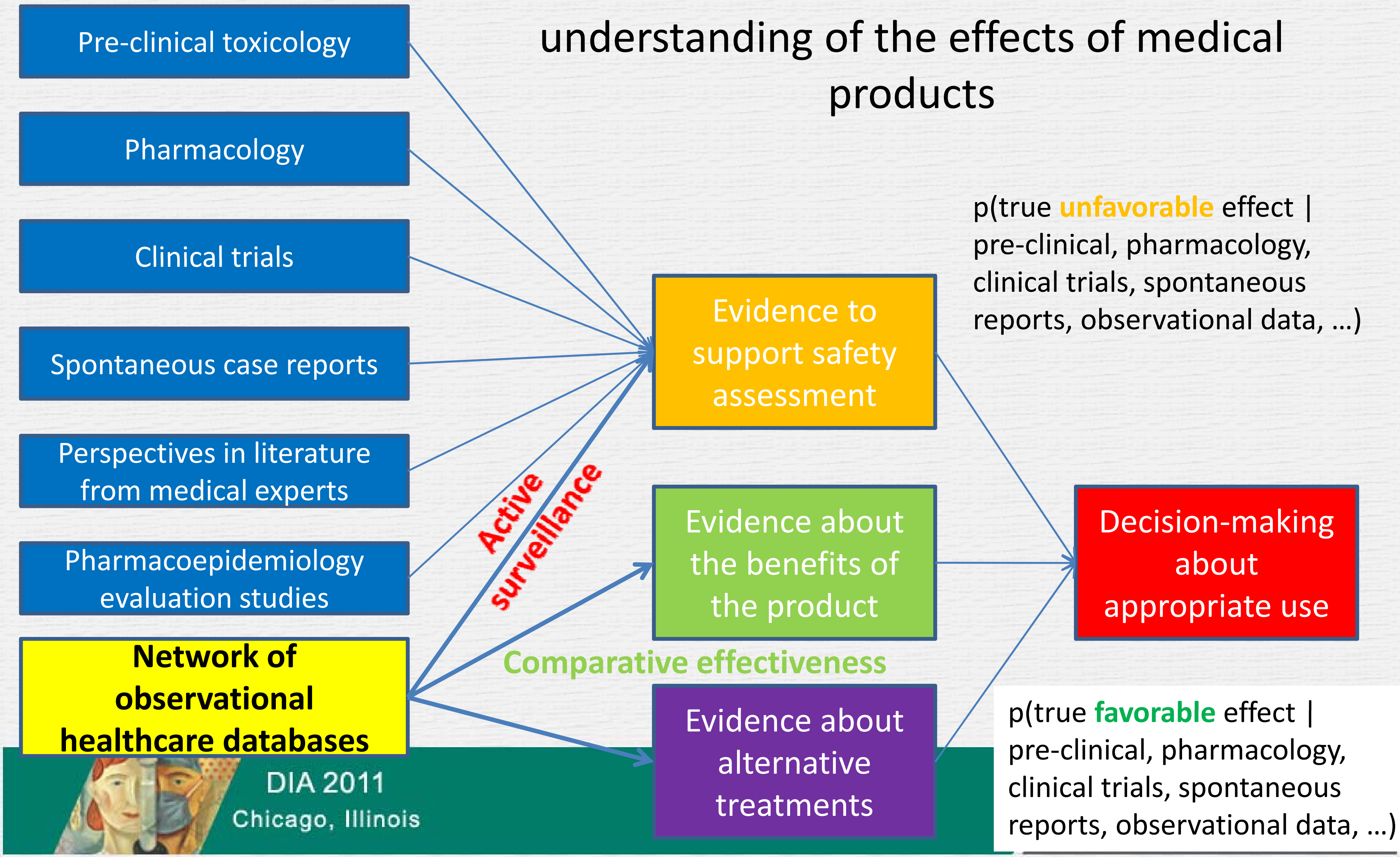




Harnessing Hill

- Previously p(true | RR, SE)
  - Logistic regression with 2 predictors
- Using Hill: p(true | RR, SE, temporality, coherence, consistency, plausibility, biological gradient, specificity, etc.)
  - Logistic regression with many predictors
- Thus we have a framework to formally integrate diverse evidence into the causal judgment

Opportunities for a coordinated system that leverages a network of observational healthcare databases to enhance our understanding of the effects of medical products



Conclusions

- Observational healthcare data can be used to efficiently generate evidence about the potential effects of medical products
- The confidence in that evidence needs to be based on the operating characteristics of observational analyses
- The risk identification and analysis system will be only one piece of information that needs be to integrated with all other existing evidence to provide a more comprehensive safety assessment
- Safety assessments always need to be put into broader context with evidence about benefits and alternative treatments, incorporating stakeholder perspectives to guide medical decision-making