

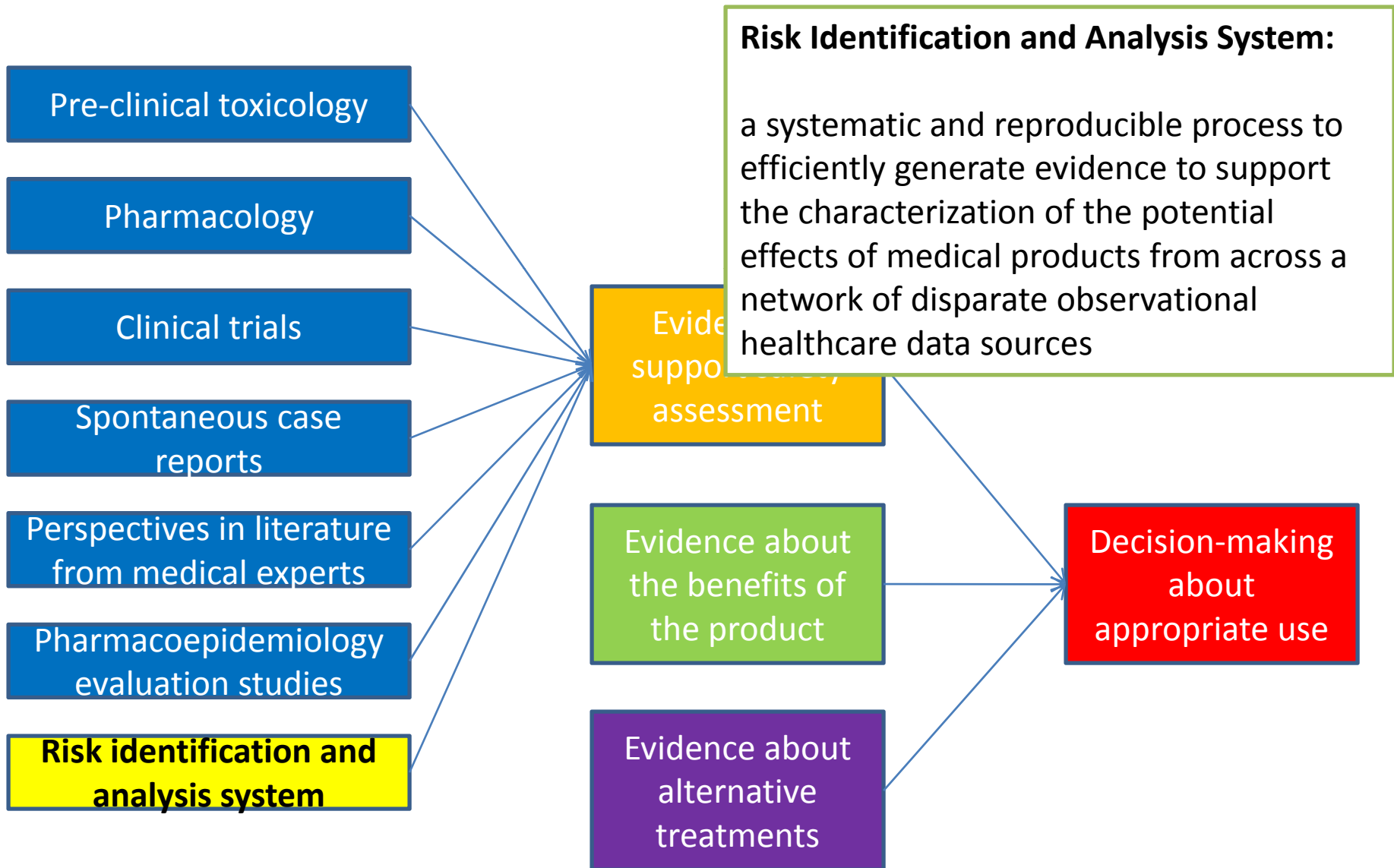
OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

The Observational Medical Outcomes Partnership: Overview of experimental results

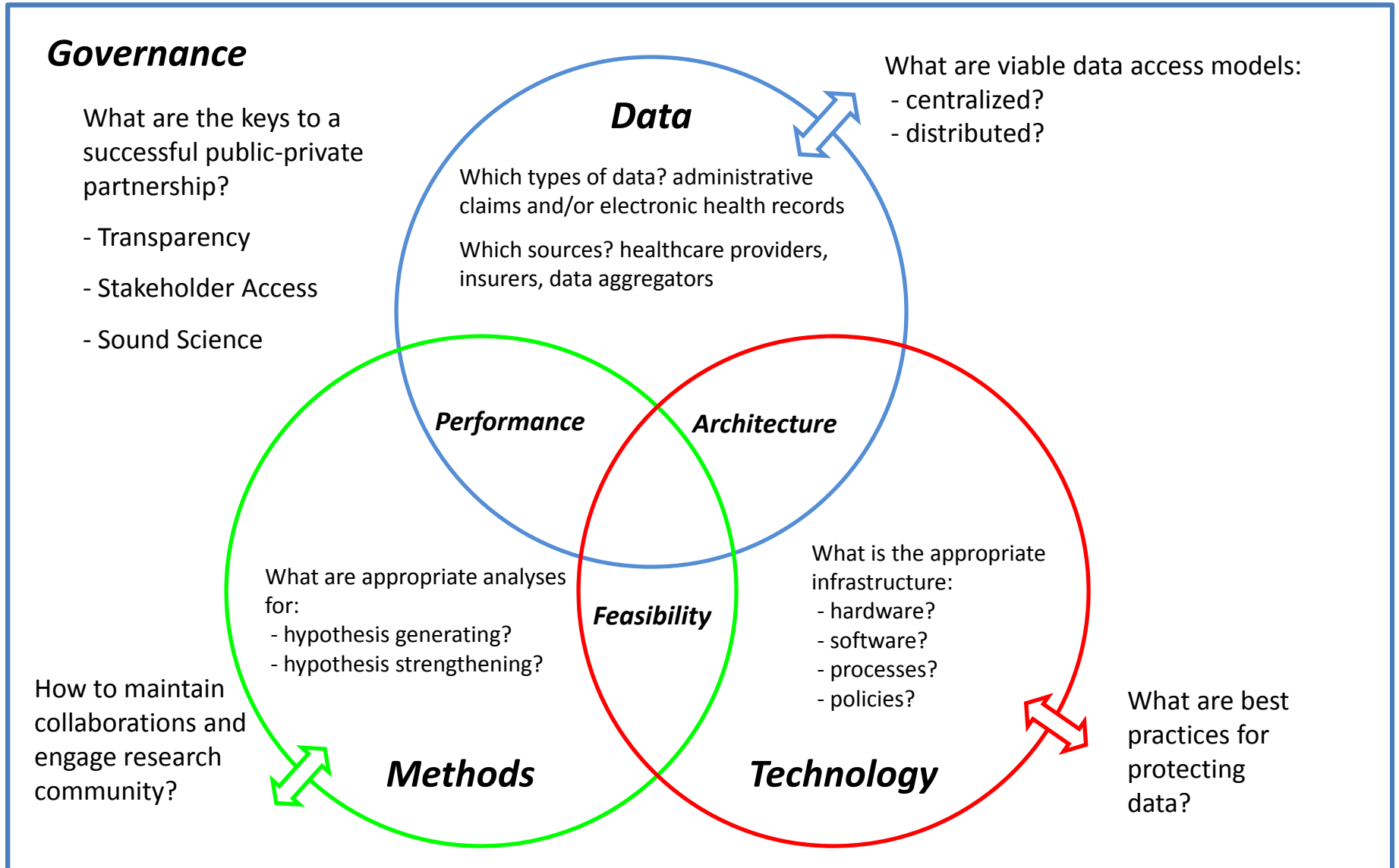
Patrick Ryan
on behalf of OMOP Research Team
June 8, 2011

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

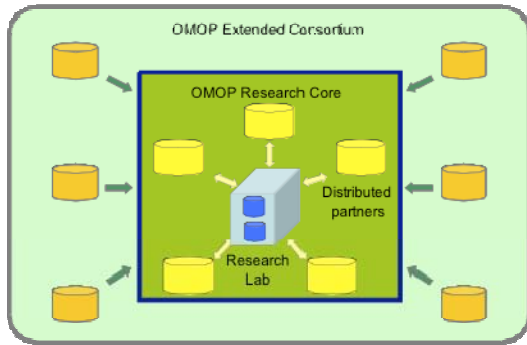
Risk identification and analysis system: One additional piece of evidence to inform medical decision-making



Outstanding Questions For Active Surveillance

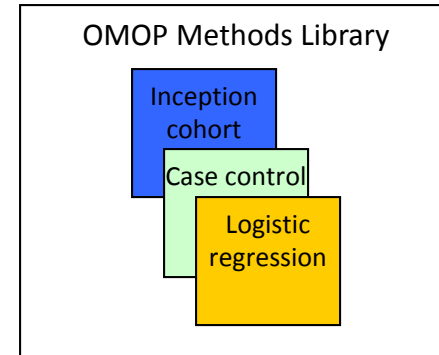
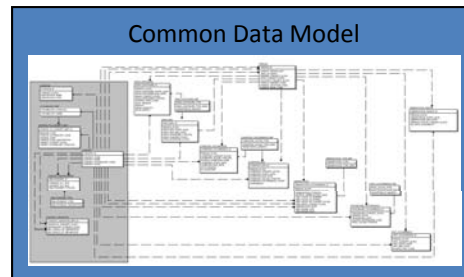


OMOP Research Experiment



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

- Open-source
- Standards-based



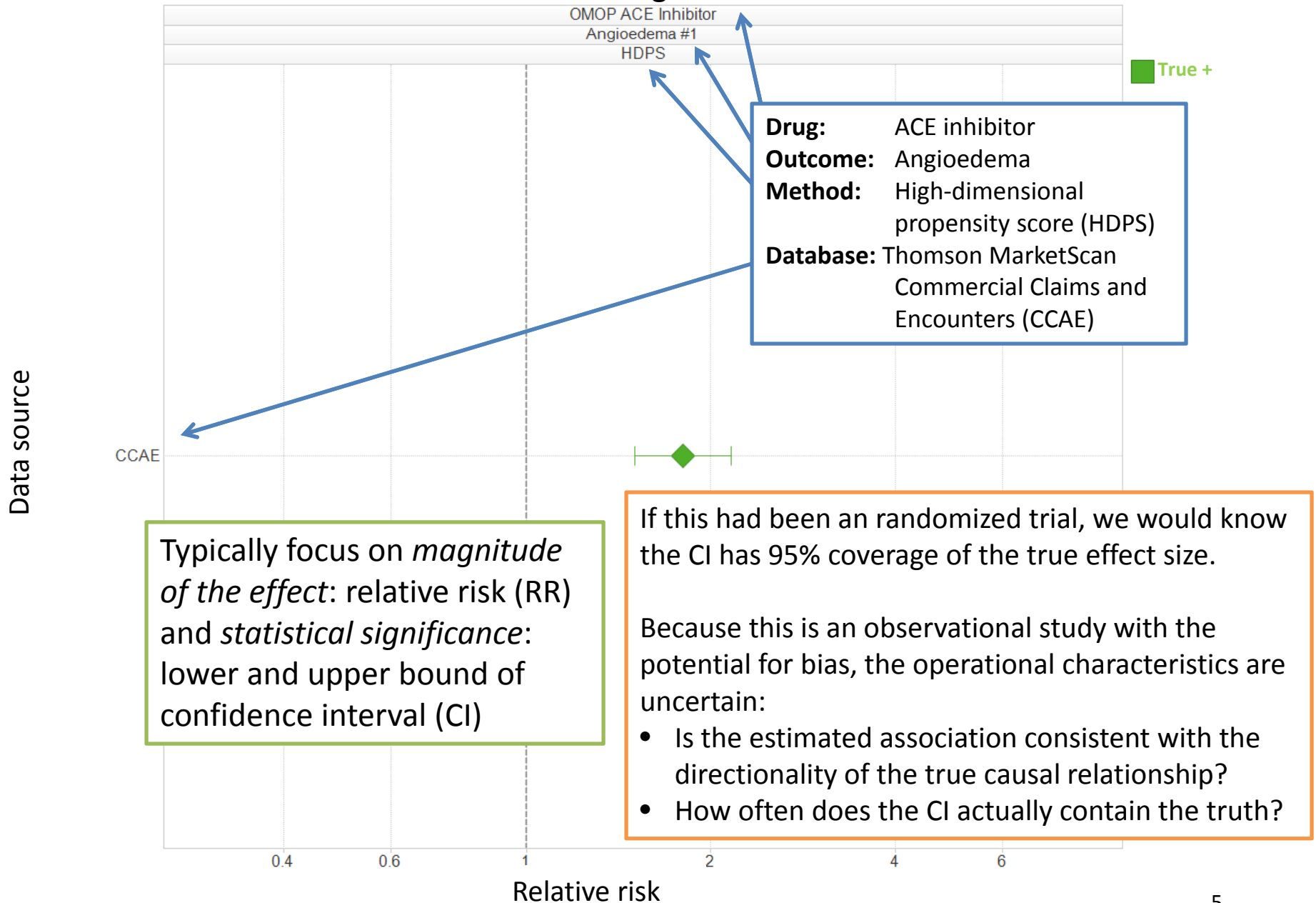
- 14 methods
- Epidemiology designs
- Statistical approaches adapted for longitudinal data



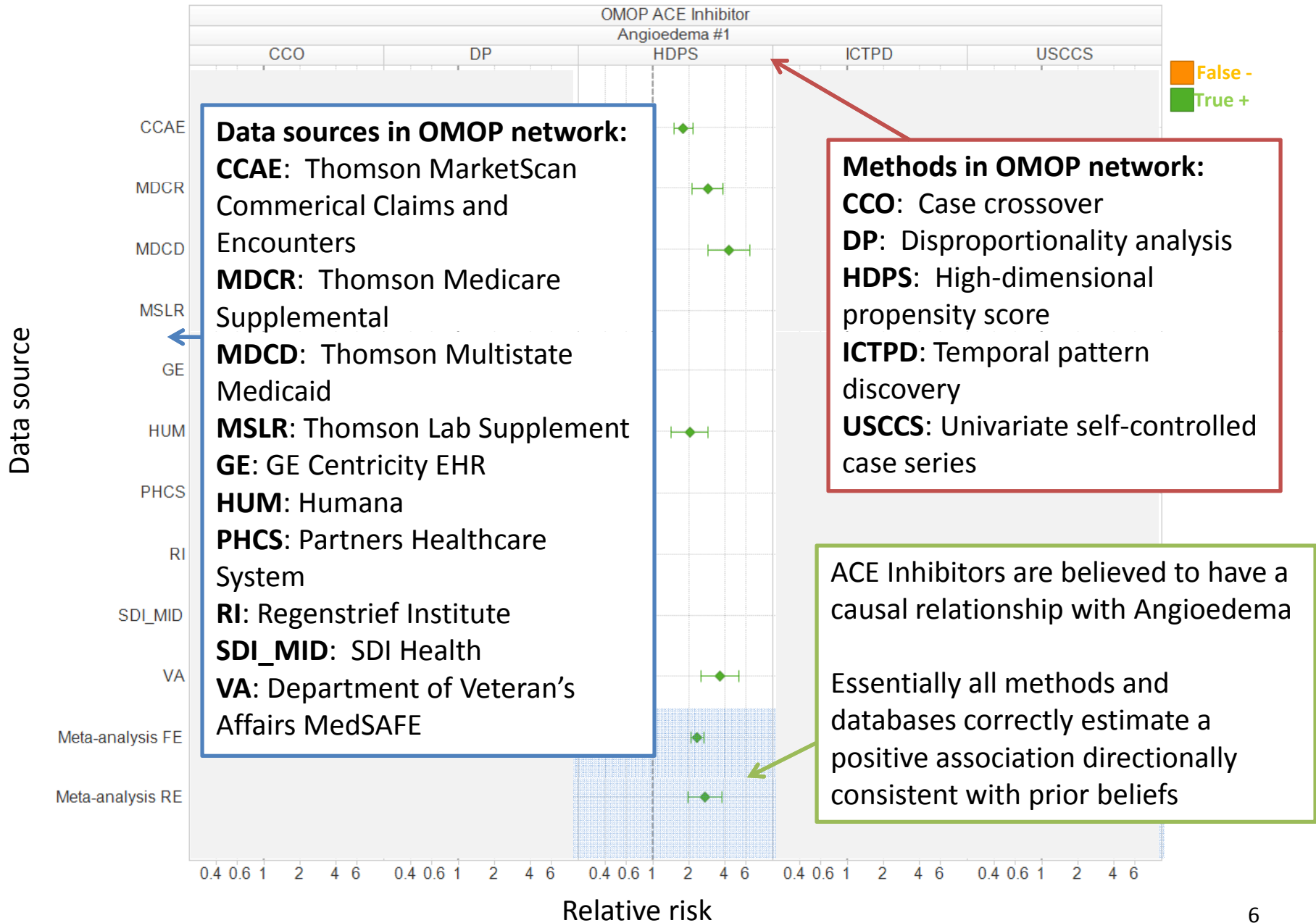
Drug

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

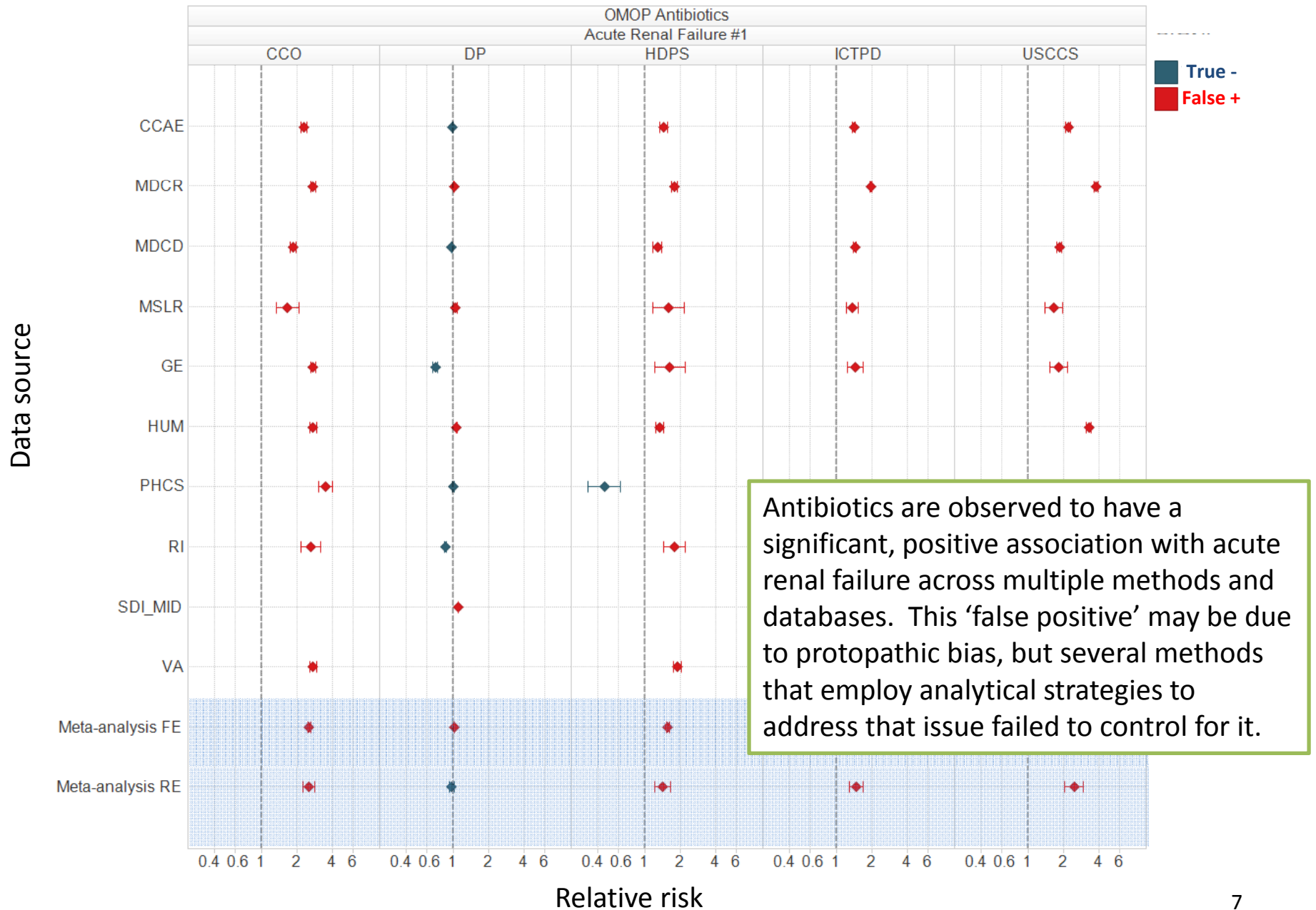
Typical scenario: Estimate the effect of one drug on one outcome using one method against one database



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



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



Measuring method performance

Drug-condition association status

Y – ‘true association’,

N – ‘negative control’

Y

N

Method prediction:
Drug-condition
pair met a
specific
threshold

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

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

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’

Y

N

Method prediction:
Drug-condition pair met a specific threshold:
(LB 95% CI > 1)

Y

N

True positives: 5	False positives: 8
False negatives: 4	True negatives: 36

Positive predictive value
= precision
= $TP / (TP+FP)$
= $5 / (5+8) = 0.38$

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

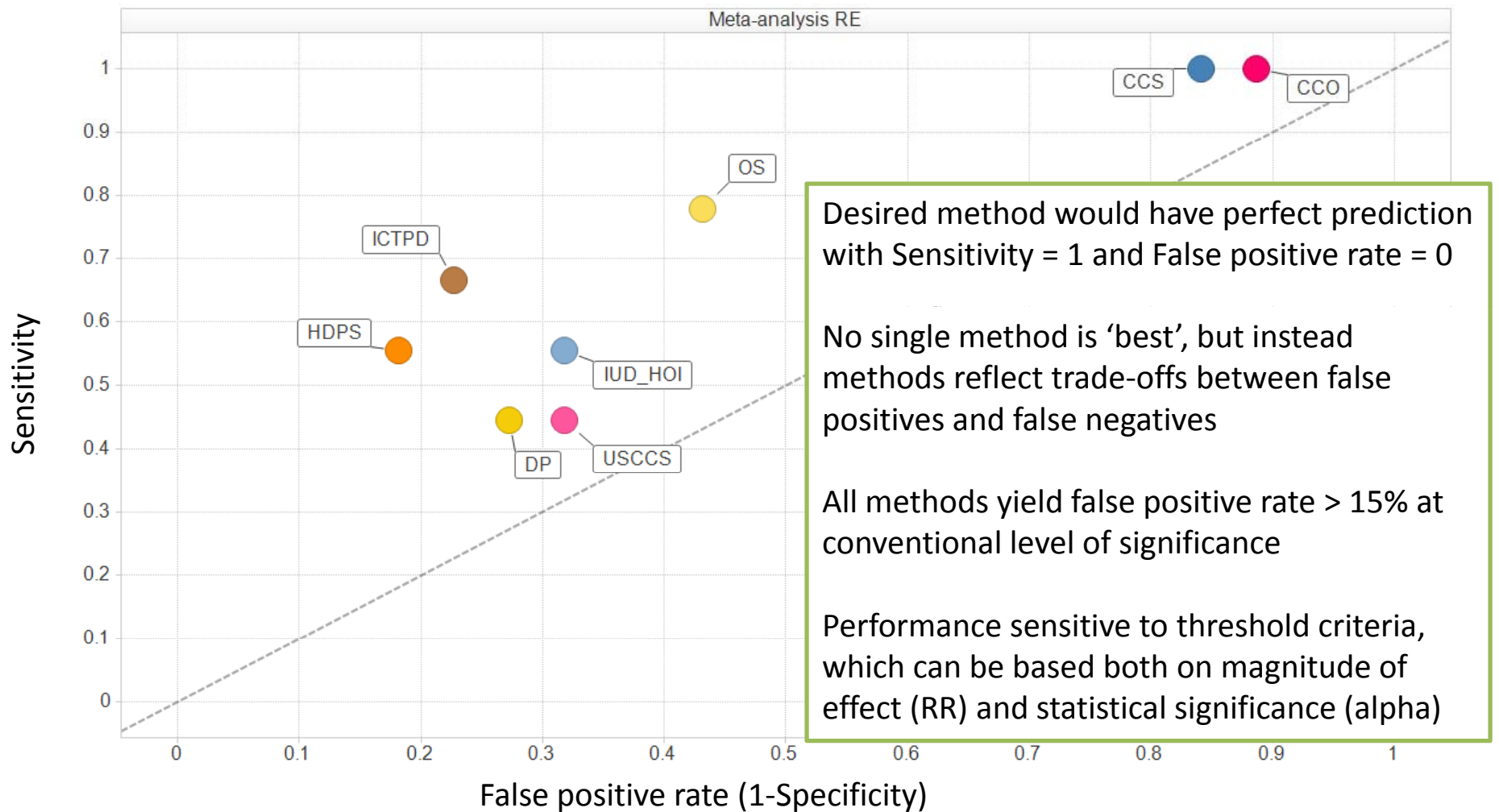
Risk identification methods under evaluation in OMOP experiment

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

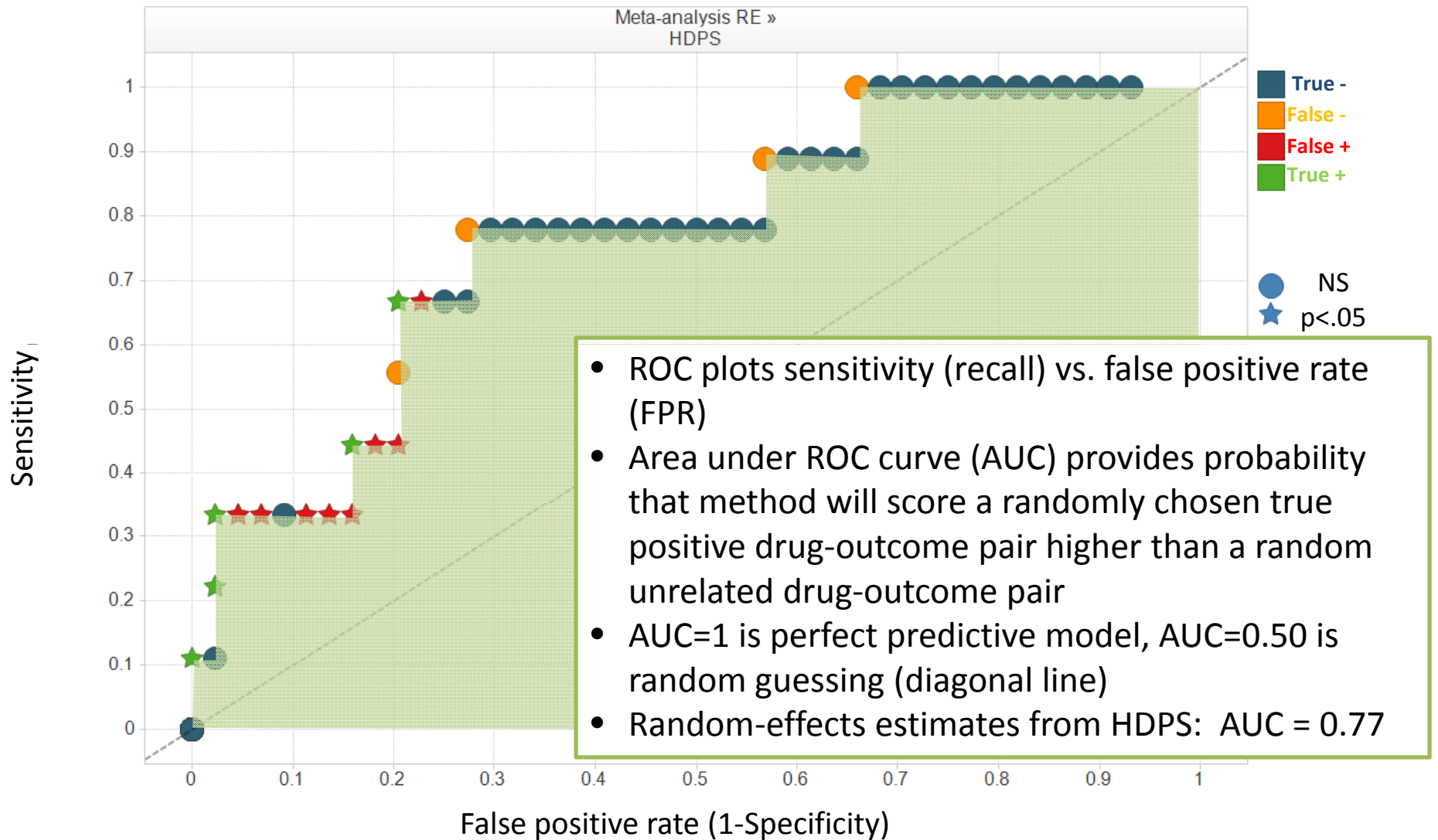
In what follows, we have chosen one parameter combination for each method that performs best for the meta-analysis estimates

<http://omop.fnih.org/MethodsLibrary>

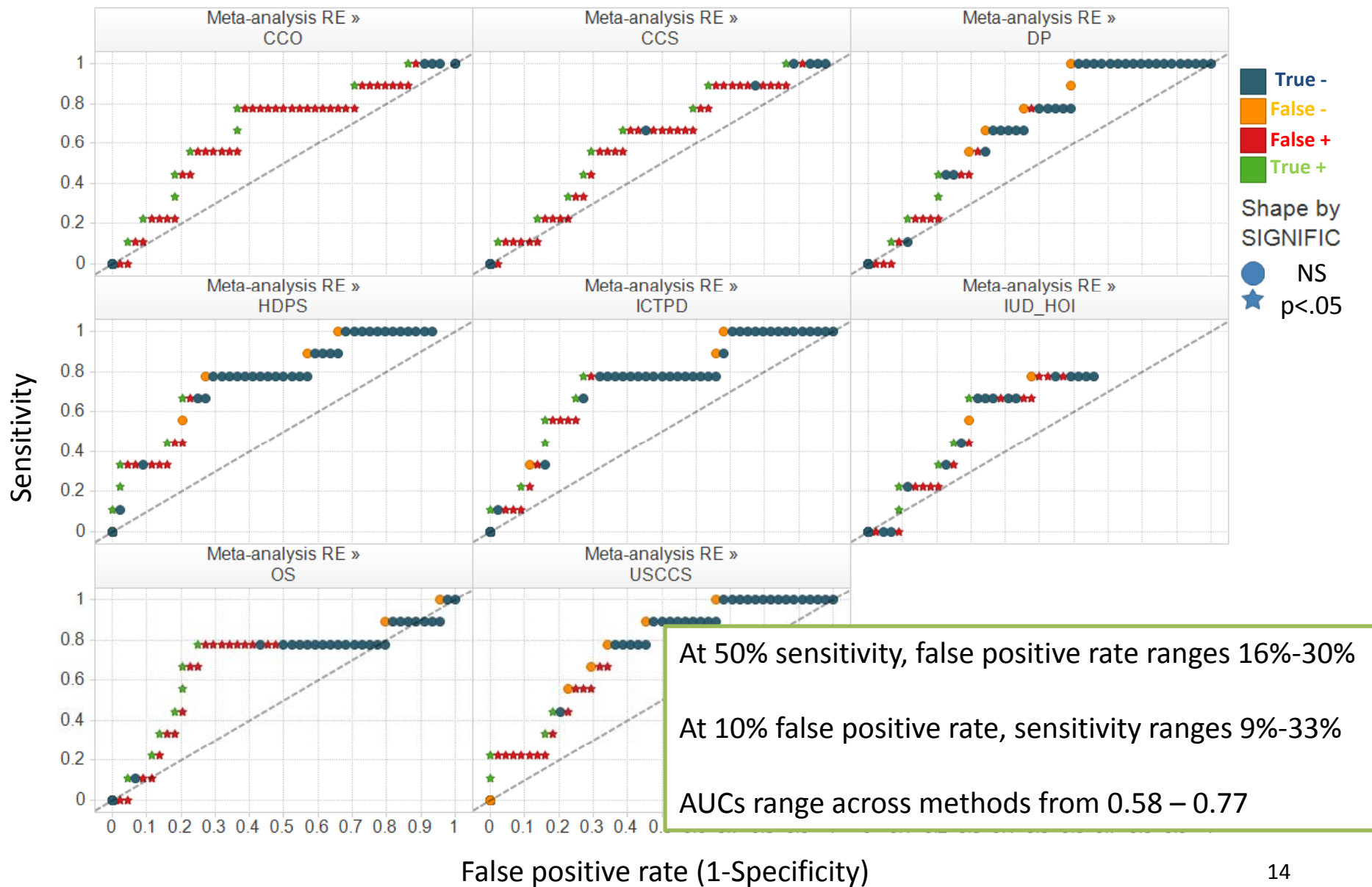
Comparing methods by sensitivity and specificity at alpha=0.05



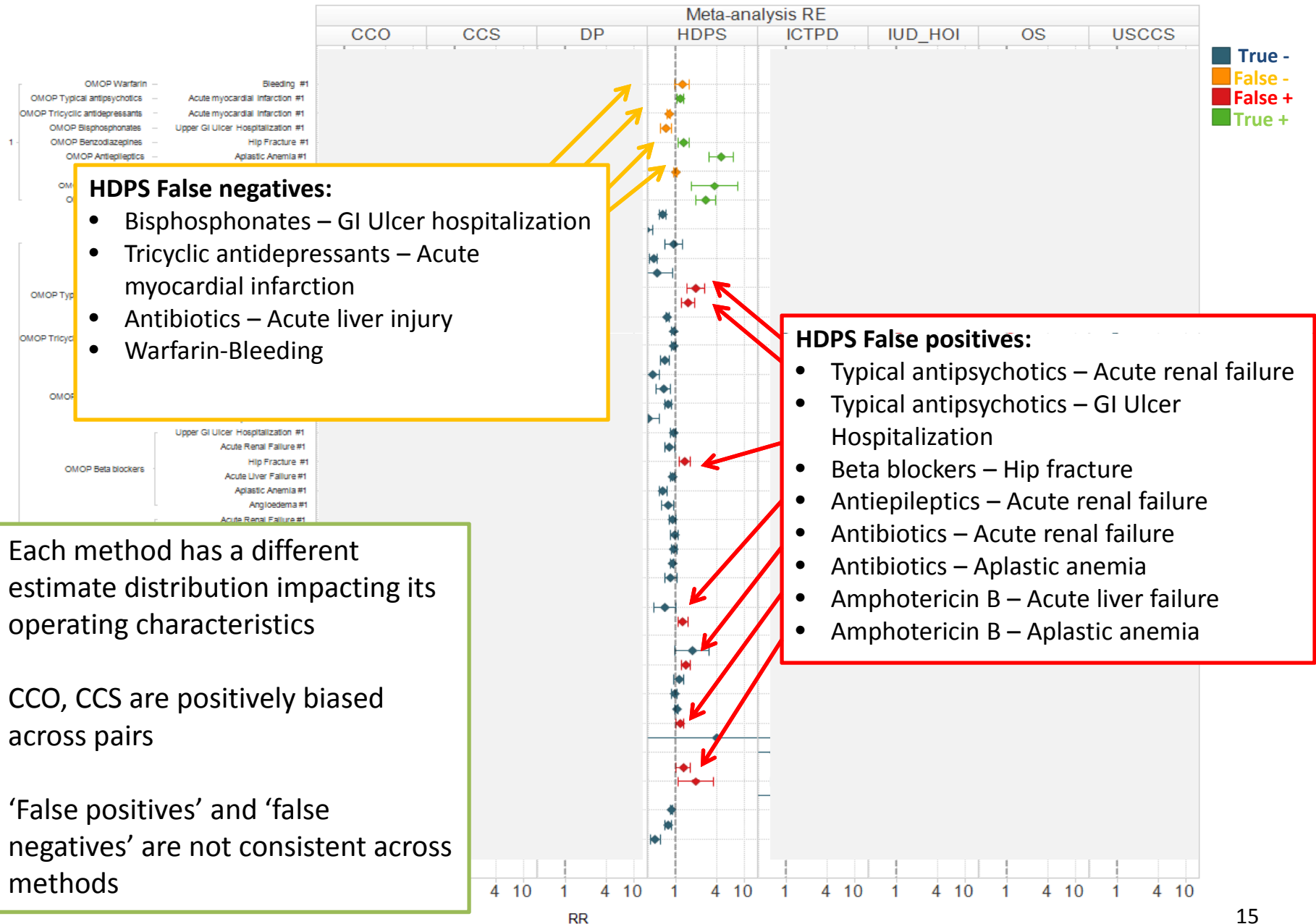
Receiver Operating Characteristic (ROC) curve



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



Distribution of estimates across all drug-outcome pairs



Concluding thoughts

- A risk identification system can complement current practice by providing evidence to support a comprehensive safety assessment
- No one clear 'best' method, as it depends on tolerance for false positives vs. false negatives
- In this experiment, active surveillance methods achieved:
 - At 50% sensitivity, false positive rate ranges 16%-30%
 - At 10% false positive rate, sensitivity ranges 9%-33%
- Need to be cautious in interpreting results from single method in single database
 - Replication does not necessarily provide complete confidence
- Further empirical research needed to have more complete understanding of operating characteristics before widespread adoption

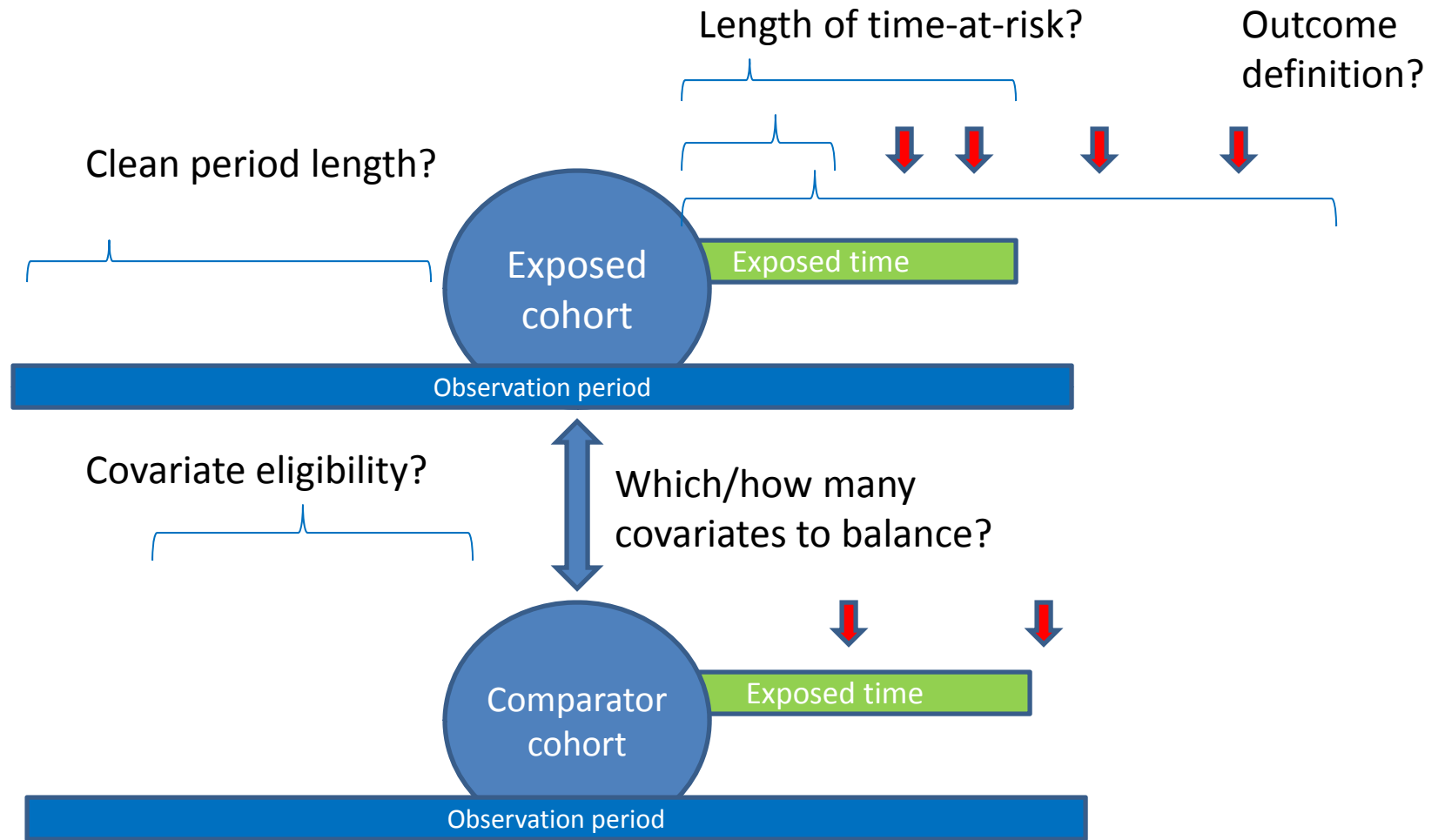
**OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP**

Impact of Observational Analysis Design

Risk identification methods under evaluation in OMOP experiment

Method name	Contributor	Release date	Parameter combinations
Disproportionality analysis			
Disproportionality analysis (DP)	Columbia / Merck	15-Mar-10	112
IC Temporal Pattern Discovery (ICTPD)	Uppsala Monitoring Centre	23-May-10	84
HSIU cohort method (HSIU)	Regenstrief / Indiana University	8-Jun-10	6
Case-based methods			
Univariate self-controlled case series (USCCS)	Columbia	2-Apr-10	64
Multi-set case control estimation (MSCCE)	Columbia / GlaxoSmithKline	16-Apr-10	32
Bayesian logistic regression (BLR)	Rutgers / Columbia	21-Apr-10	24
Case-control surveillance (CCS)	Lilly	2-May-10	48
Case-crossover (CCO)	University of Utah	1-Jun-10	48
Exposure-based methods			
Observational screening (OS)	ProSanos / GlaxoSmithKline	8-Apr-10	162
High-dimensional propensity score (HDPS)	Columbia	6-Aug-10	144
Incident user design (IUD-HOI)	University of North Carolina	26-Oct-10	160
Sequential testing methods			
Maximized Sequential Probability Ratio Test (MSPRT)	Harvard Pilgrim / Group Health	25-Jul-10	144
Conditional sequential sampling procedure (CSSP)	Harvard Pilgrim / Group Health	30-Aug-10	144

Exploration of test cases within inception cohort design



Exclusion criteria:
Indications
Contraindications

Which active
comparator?

Propensity score adjustment strategy?
Stratification
Multivariate adjustment

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 epidemiology¹

BMJ 2010; 341:c4444

Conclusions The risk of oesophageal cancer increased with 10 or more prescriptions for oral bisphosphonates and with prescriptions over about a five year period.

BMJ study design choices

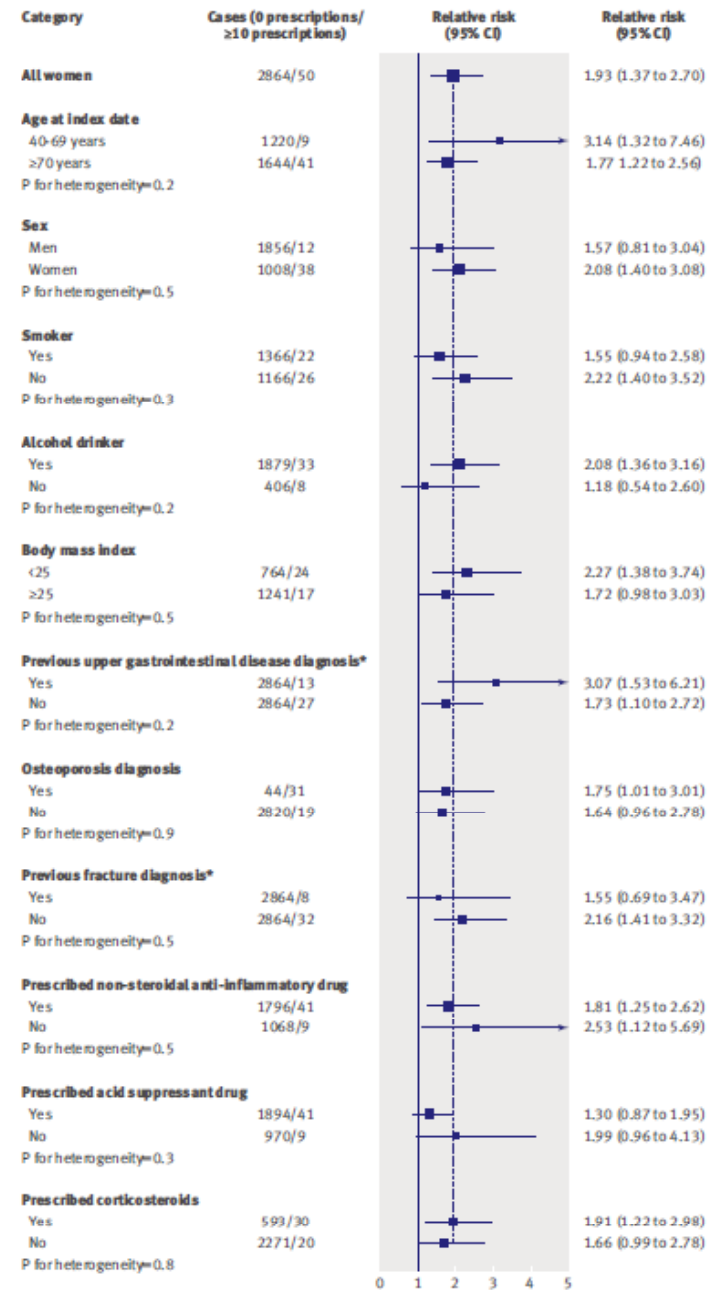
- Data source: General Practice Research Database
- Study design: Nested case-control
- Inclusion criteria: Age > 40
- Case: cancer diagnosis between 1995-2005 with 12-months of follow-up pre-diagnosis
- 5 controls per case
- Matched on age at index date, sex, practice, observation period prior to index
- Exposure definition: ≥ 1 prescription during observation period
- “RR” estimated with conditional logistic regression
- Covariates: smoking, alcohol, BMI before *outcome* index date
- Sensitivity analyses:
 - exposure = 2+ prescriptions
 - covariates not missing
 - time-at-risk = >1 yr post-exposure
- Subgroup analyses:
 - Short vs. long exposure duration
 - Age, Sex, smoking, alcohol, BMI
 - Osteoporosis or osteopenia
 - Fracture pre-exposure
 - Prior diagnosis of Upper GI dx pre-exposure
 - NSAID, corticosteroid, H2blocker, PPI utilization pre-exposure

BMJ Results

Table 2 | Relative risks (RRs) and 95% confidence intervals (CIs) for bisphosphonates

Oral bisphosphonates	Oesophagus		RR† (95% CI)
	Prescriptions*	Cases/controls	
Not prescribed	NA	2864/14 376	1.00
Prescribed	13.6/2.4	90/345	1.30 (1.02 to 1.66)
No of prescriptions:			
1-9	3.6/1.0	40/214	0.93 (0.66 to 1.31)
≥10	21.6/3.5	50/131	1.93 (1.37 to 2.70)
Estimated duration of use‡:			
≤1 year	4.9/0.3	31/155	0.98 (0.66 to 1.46)
1-3 years	13.0/2.0	26/114	1.12 (0.73 to 1.73)
≥3 years	22.2/4.6	33/76	2.24 (1.47 to 3.43)

NA=not applicable.
*Prescriptions of bisphosphonates in cases; reported as mean number/mean year
†All relative risks adjusted for smoking status, alcohol intake, and body mass index
‡Time between first and last prescription.



Relative risks of incident oesophageal cancer in people with ≥10 prescriptions for oral bisphosphonates, compared with those with no prescriptions, by various factors. Relative risks adjusted for smoking status, alcohol intake, and body mass index, as appropriate. *Diagnosis before prescription of bisphosphonates: analyses restricted to those with ≥12 months' observation before first bisphosphonate prescription

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 dramatically in the United States and elsewhere. Esophagitis is a known adverse effect of bisphosphonate use, and recent reports suggest a link between bisphosphonate use and esophageal cancer, but this has not been robustly investigated.

Objective To investigate the association between bisphosphonate use and esoph-

JAMA 2010; 304(6): 657-663

Conclusion

of oral bisphosphonates was not significantly associated with incident esophageal or gastric cancer. the use

JAMA study design choices

- ✓ Data source: General Practice Research Database
- ✗ Study design: Cohort
- ✓ Inclusion criteria: Age > 40
- ✗ Exclusion criteria: Cancer diagnosis in 3 years before index date
- ✓ Exposed cohort: Patients with ≥ 1 prescription between 1996-2006 **1995-2005 in BMJ**
- ✗ “Unexposed” cohort: 1-to-1 match with exposed cohort **Match exposure vs.**
- ✓ Matched on year of birth, sex, practice **Not observation length outcome status; not 5-to-1**
 - “HR” estimated with Cox proportional hazards model
- ✗ Time-at-risk: >6mo from index date **Time-at-risk is ‘between’ two definitions used in BMJ: All time post-exposure and >1yr after index**
- ✓ Covariates: **Different index date**
 - Smoking, alcohol, BMI before *exposure* index date **BMJ didn’t stratify by hormone therapy**
 - Hormone therapy, NSAIDs, H2blockers, PPIs
- Sensitivity analyses:
 - Excluding people that were in both exposed and unexposed cohorts
 - Exclude patients with missing confounders (not reported)
- Subgroup analyses:
 - Low vs. medium vs. high use, based on defined daily dose
 - Alendronate vs. nitrogen-containing bisphosphonates vs. non-nitrogen-containing bisphosphonates

JAMA Results

Table 3. Esophageal (Only) Cancer Incidence in the Bisphosphonate and Matched Control Cohorts

Bisphosphonate Category	Bisphosphonate		Control		Risk			
	Cases	Person-Years	Cases	Person-Years	Unadjusted		Adjusted ^a	
					HR (95% CI)	P Value	HR (95% CI)	P Value
Any bisphosphonate Prescribed	79	165 400	72	163 480	1.08 (0.79-1.49)	.63	1.07 (0.77-1.49)	.67
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
183	51	104 676	49	104 104	1.04 (0.70-1.53)	.86	1.05 (0.70-1.57)	.82
365	31	73 364	35	73 170	0.88 (0.55-1.43)	.62	0.92 (0.56-1.51)	.74
730	22	40 326	22	40 492	1.00 (0.56-1.81)	.99	0.98 (0.53-1.81)	.95
1095	15	22 813	14	22 891	1.08 (0.52-2.23)	.84	1.01 (0.48-2.12)	.99
Total bisphosphonate intake during follow-up (in DDDs/d) ^c								
Low (0-<0.24)	35	62 922	27	63 648	1.31 (0.80-2.17)	.29	1.24 (0.74-2.09)	.41
Medium (≥0.24-<0.89)	24	58 162	23	55 334	0.98 (0.55-1.74)	.94	1.03 (0.57-1.86)	.92
High (≥0.89)	20	44 316	22	44 497	0.91 (0.50-1.67)	.78	0.90 (0.48-1.68)	.74
Nitrogen-containing bisphosphonates								
First prescribed	44	106 480	47	106 412	0.94 (0.62-1.41)	.75	0.96 (0.63-1.47)	.86
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
365	30	70 251	34	69 935	0.88 (0.54-1.44)	.61	0.93 (0.56-1.54)	.78
730	22	39 022	22	39 187	1.01 (0.56-1.82)	.99	0.98 (0.53-1.80)	.95
Alendronate								
First prescribed	33	81 369	42	80 837	0.78 (0.50-1.23)	.29	0.77 (0.48-1.23)	.27
Incidence after cumulative prescriptions greater than (in DDDs) ^b								
365	22	52 308	31	51 741	0.70 (0.41-1.21)	.20	0.68 (0.39-1.19)	.18
730	19	28 898	21	28 904	0.91 (0.49-1.68)	.75	0.85 (0.45-1.61)	.62
Non-nitrogen-containing bisphosphonates								
First prescribed	35	58 920	25	57 068	1.35 (0.81-2.25)	.25	1.25 (0.73-2.12)	.37

Abbreviations: CI, confidence interval; DDD, defined daily dose; HR, hazard ratio.

^aAdjusted for body mass index, alcohol, smoking, hormone therapy prescription (before index date), nonsteroidal anti-inflammatory drug prescription (before index date), Barrett esophagus diagnosis (before index date), gastroesophageal reflux disease diagnosis (before index date), H₂ receptor antagonist prescription (before index date), and proton pump inhibitor prescription (before index date).

^bPerson-years and cancer cases occurring after the date of specified prescriptions received for each bisphosphonate cohort member and their matched control. Daily divided dose equivalents: 183 DDDs are equivalent to a 6-month supply; 365 DDDs to a 1-year supply; 730 DDDs to a 2-year supply; and 1095 DDDs to a 3-year supply.

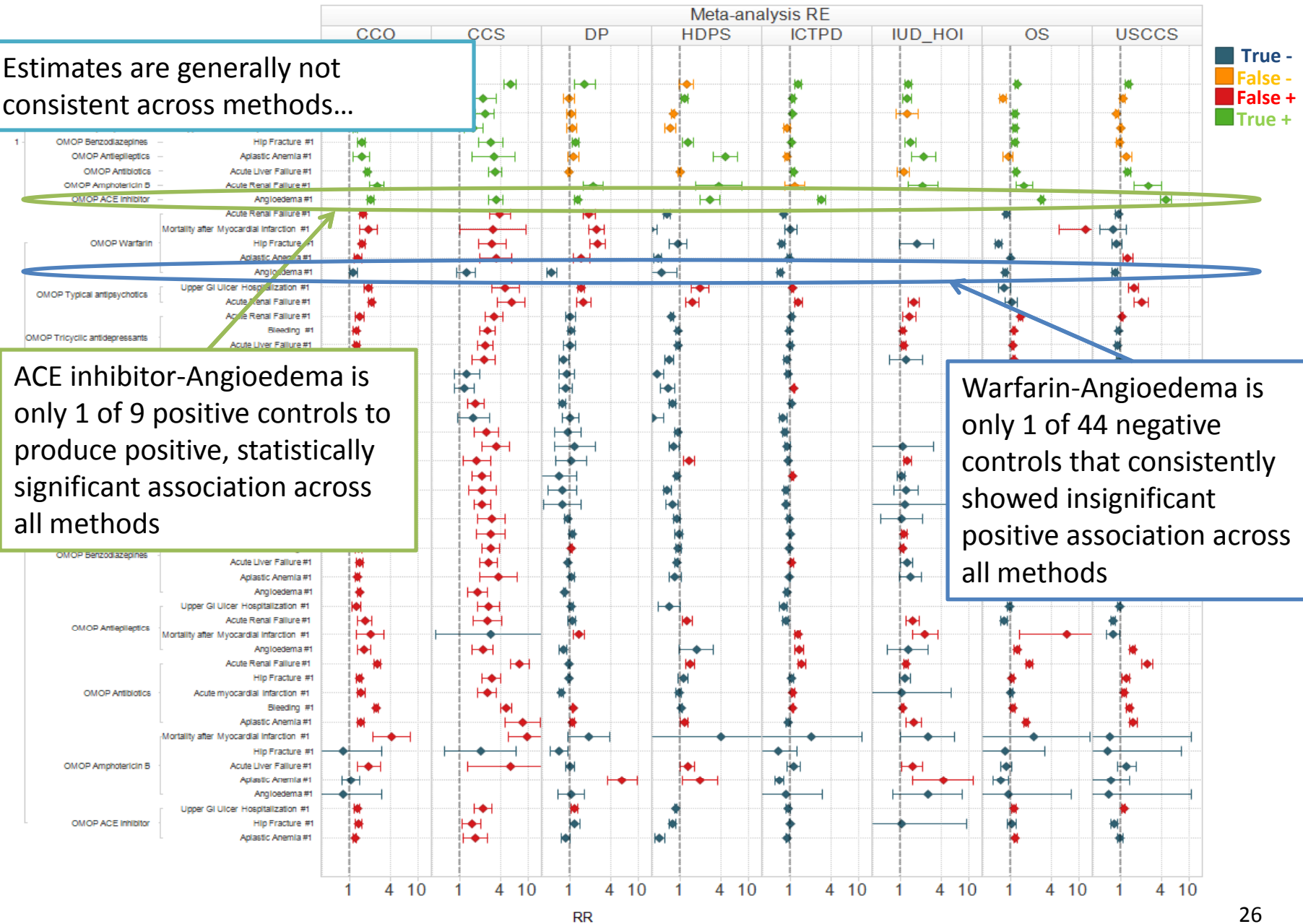
^cIn bisphosphonate cohort (see "Methods" for details of selection of cohorts).

Distribution of estimates across all drug-outcome pairs

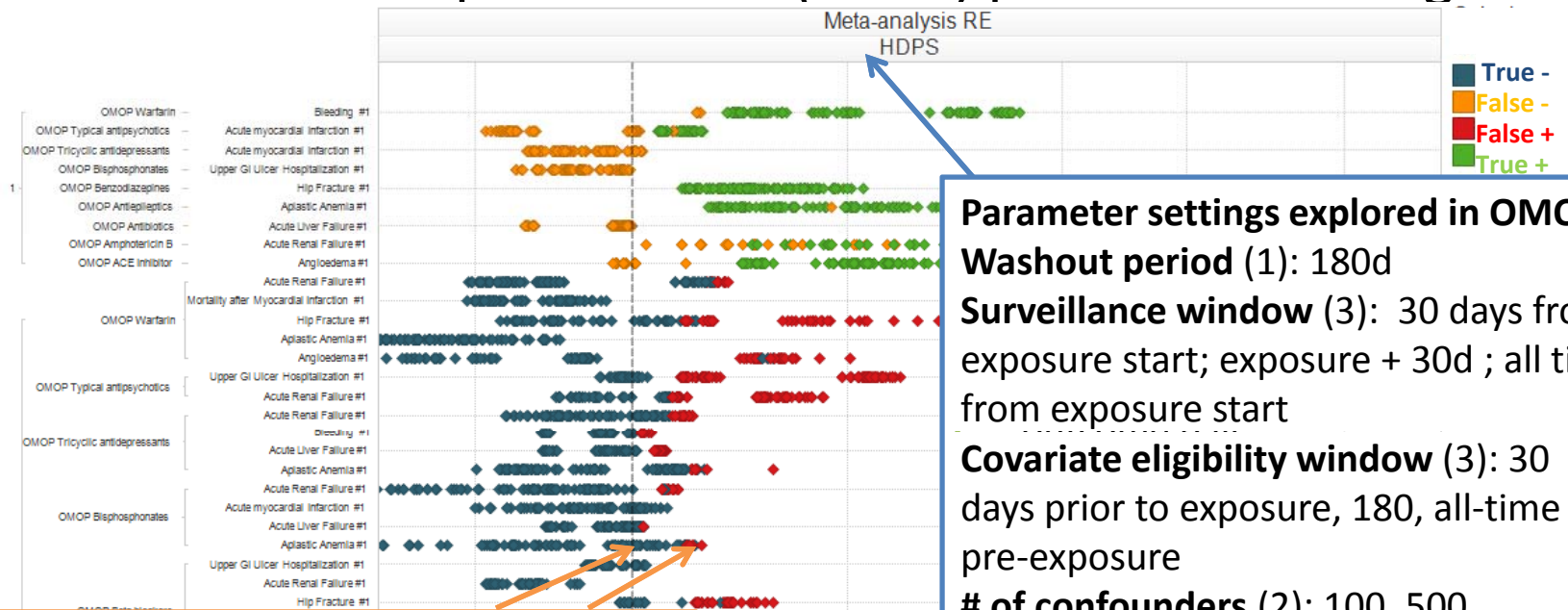
Estimates are generally not consistent across methods...

ACE inhibitor-Angioedema is only 1 of 9 positive controls to produce positive, statistically significant association across all methods

Warfarin-Angioedema is only 1 of 44 negative controls that consistently showed insignificant positive association across all methods



Range of estimates across high-dimensional propensity score inception cohort (HDPS) parameter settings



Parameter settings explored in OMOP:

- Washout period (1):** 180d
- Surveillance window (3):** 30 days from exposure start; exposure + 30d ; all time from exposure start
- Covariate eligibility window (3):** 30 days prior to exposure, 180, all-time pre-exposure
- # of confounders (2):** 100, 500 covariates used to estimate propensity score
- Propensity strata (2):** 5, 20 strata
- Analysis strategy (3):** Mantel-Haenszel stratification (MH), propensity score adjusted (PS), propensity strata adjusted (PS2)
- Comparator cohort (2):** drugs with same indication, not in same class; most prevalent drug with same indication, not in same class

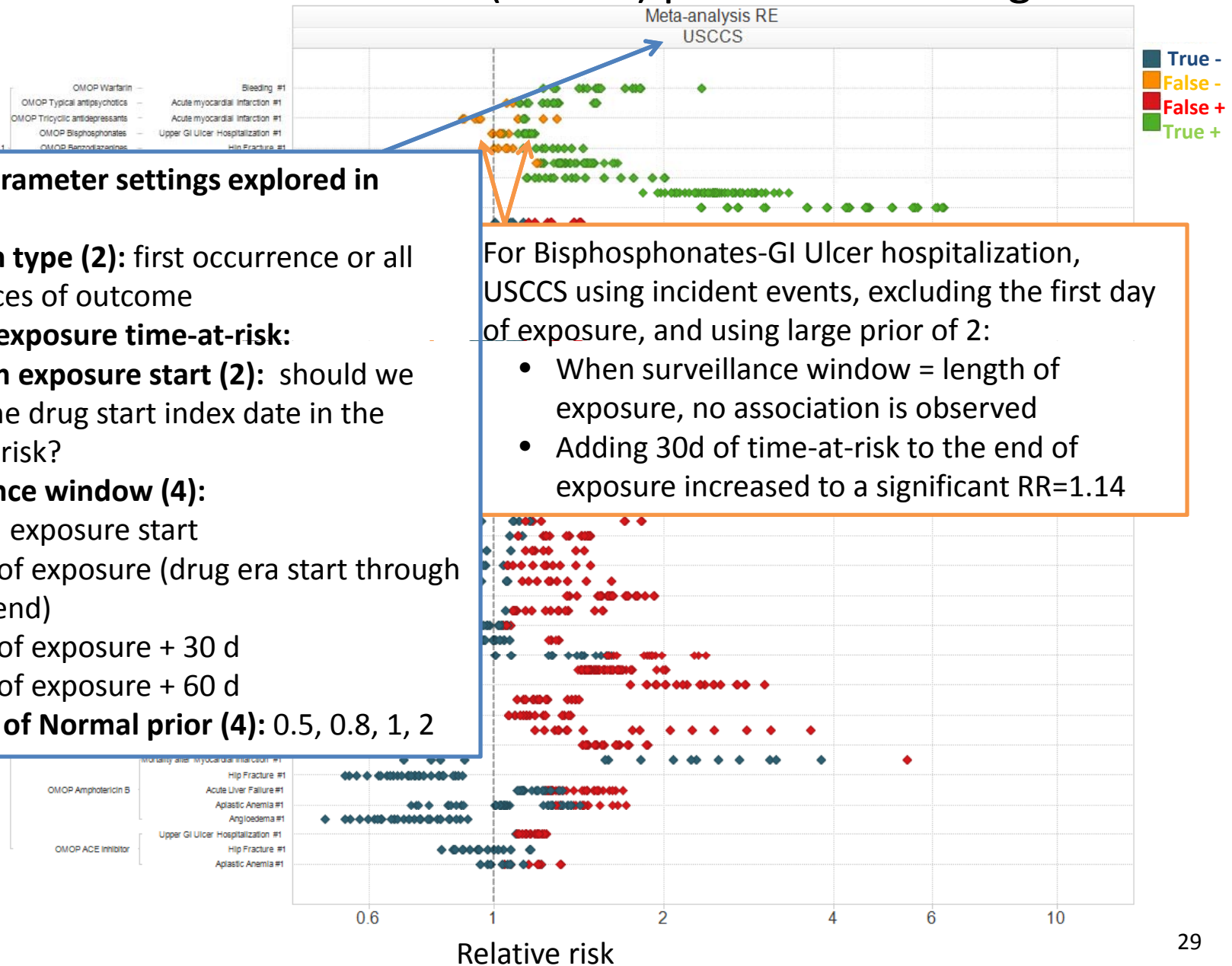
- When using all-time pre-exposure as covariate eligibility window, 100 confounders, propensity stratification with 20 strata, and comparator class of all drugs with same indication not in same class...
- HDPS produces significant, positive effect for bisphosphonates-aplastic anemia when surveillance window is 'all time post-exposure' (RR=1.25)...
- ...but shows no effect when time-at-risk defined by exposure length + 30 days (RR=1)

Relative risk

HDPS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Time-at-risk surveillance window (30d from exposure start, exposure length + 30d, all time post-exposure start)
 - Choice of comparator (all drugs with same indication but in different class, one drug with same indication but different class)
- Effect estimates are less sensitive for:
 - Covariate eligibility window (30d, 180d, all time pre-exposure)
 - Number of covariates (100, 500)
 - Propensity score adjustment strategy (stratification with 5 or 20 strata, multivariate regression with strata categories, regression with PS as covariate)

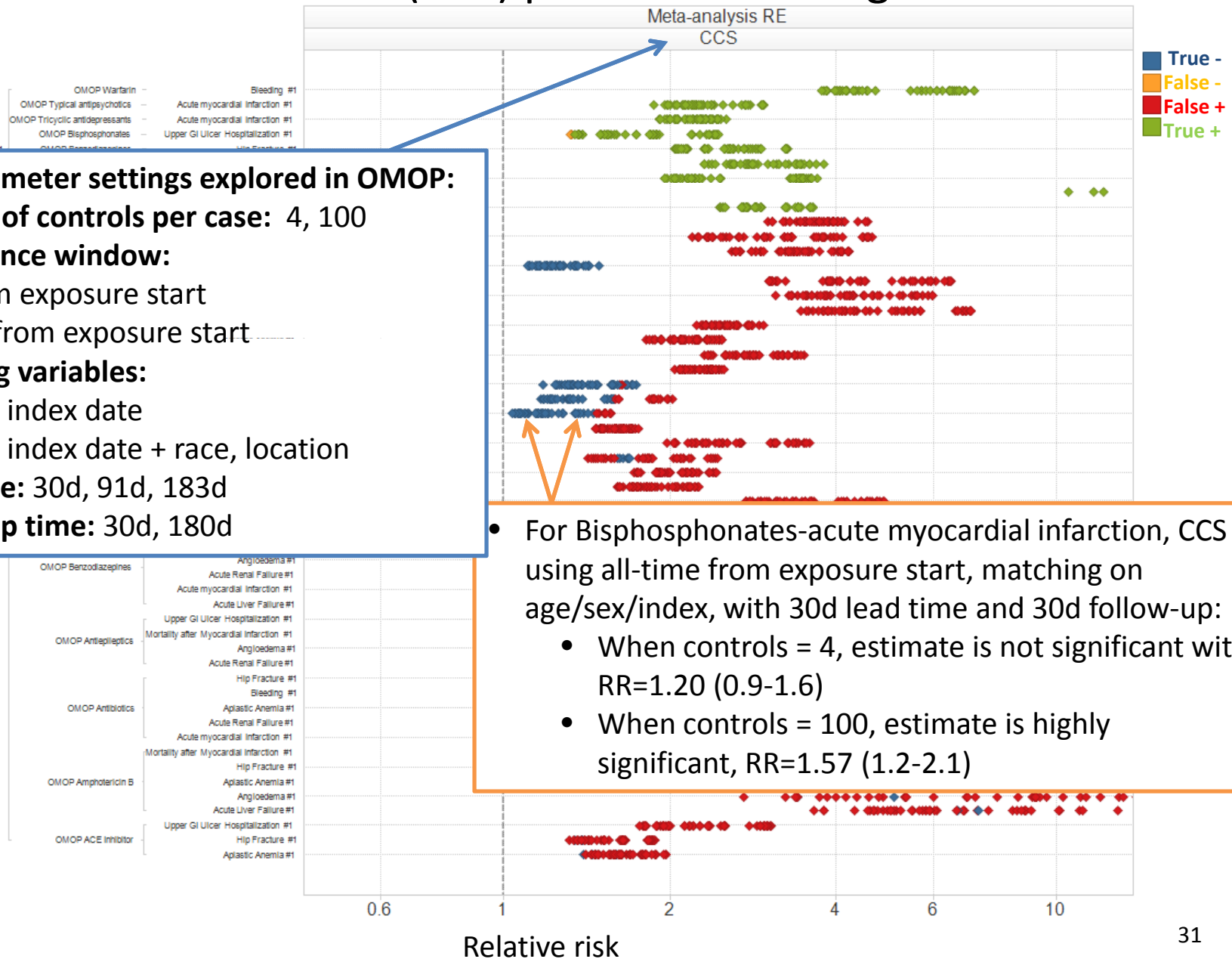
Range of estimates across univariate self-controlled case series (USCCS) parameter settings



USCCS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Whether to include the exposure start date as exposed time-at-risk: including day 0 produced higher estimates than excluding day 0 for many pairs
 - Exposed time-at-risk surveillance window
 - Length of exposure
 - Length of exposure + 30d
 - Length of exposure + 60d
 - 30d from exposure start
 - NOTE: Time ‘unexposed’ = Total observation period – time exposed
- Effect estimates are less sensitive for:
 - Use of first occurrence vs. all occurrences of events
 - Precision of the prior (0.5, 0.8, 1, 2)

Range of estimates across case-control surveillance (CCS) parameter settings



CCS Parameter settings explored in OMOP:

Number of controls per case: 4, 100

Surveillance window:

30 d from exposure start

All time from exposure start

Matching variables:

Age, sex, index date

Age, sex, index date + race, location

Lead time: 30d, 91d, 183d

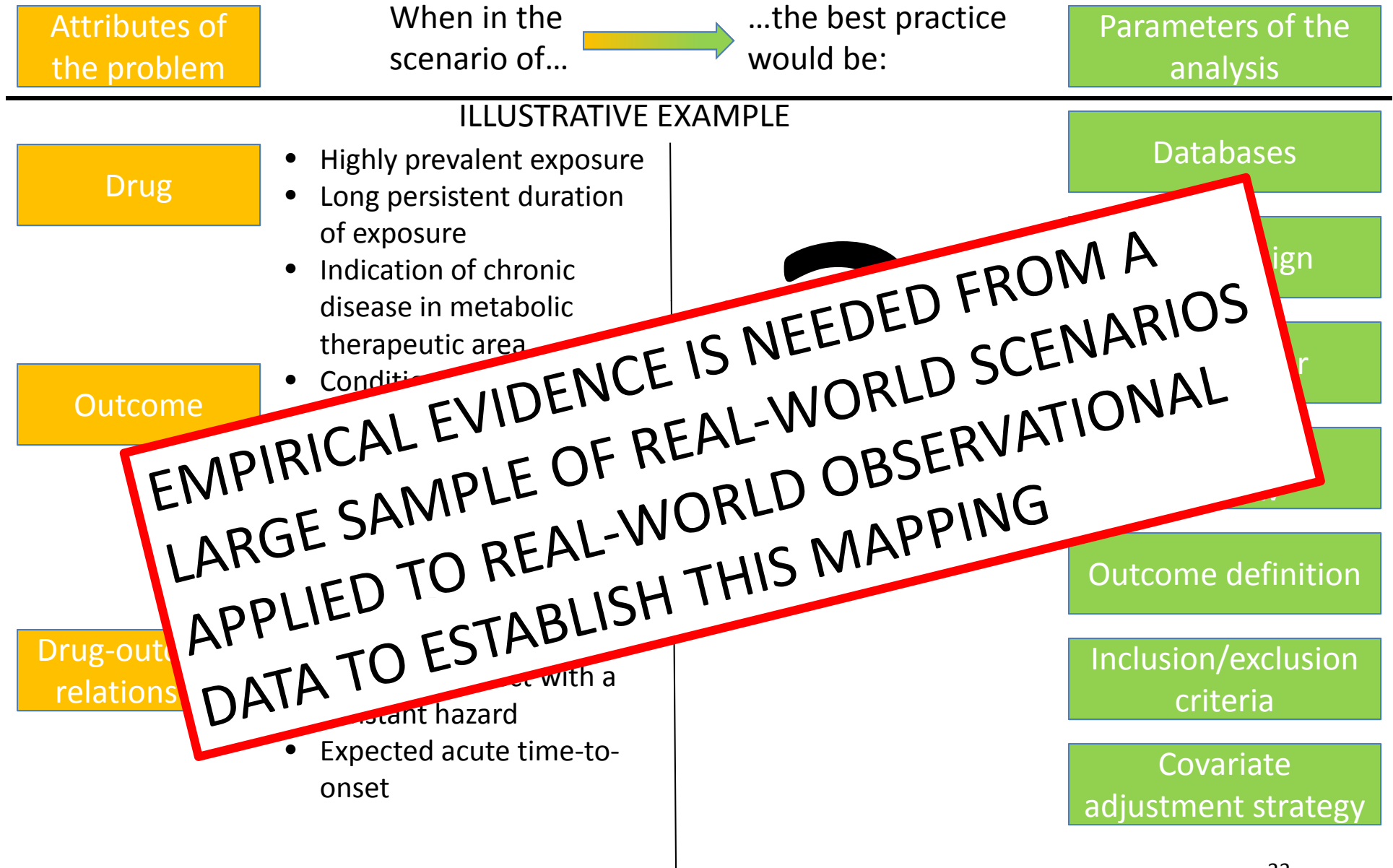
Follow-up time: 30d, 180d

- For Bisphosphonates-acute myocardial infarction, CCS using all-time from exposure start, matching on age/sex/index, with 30d lead time and 30d follow-up:
 - When controls = 4, estimate is not significant with RR=1.20 (0.9-1.6)
 - When controls = 100, estimate is highly significant, RR=1.57 (1.2-2.1)

CCS parameter sensitivity

- No single parameter completely separates ‘true’ vs. ‘false’ findings for drug-outcome pairs
- Effect estimates are more sensitive to:
 - Number of controls per case (4, 100)
 - 100 controls generated higher estimates than 4 controls for many drug-outcome pairs
 - Whether to match on race and location
 - Matching on race and location generated lower estimates than not matching for many drug-outcome pairs
 - Time-at-risk surveillance window (30d post-exposure, all-time post-exposure start)
 - 30d post-exposure generated higher estimates than all-time post-exposure for many drug-outcome pairs
- Effect estimates are less sensitive:
 - Lead time (30d, 91d, 183d)
 - Follow-up time (30d, 180d)

Mapping clinical problems to analytical solutions



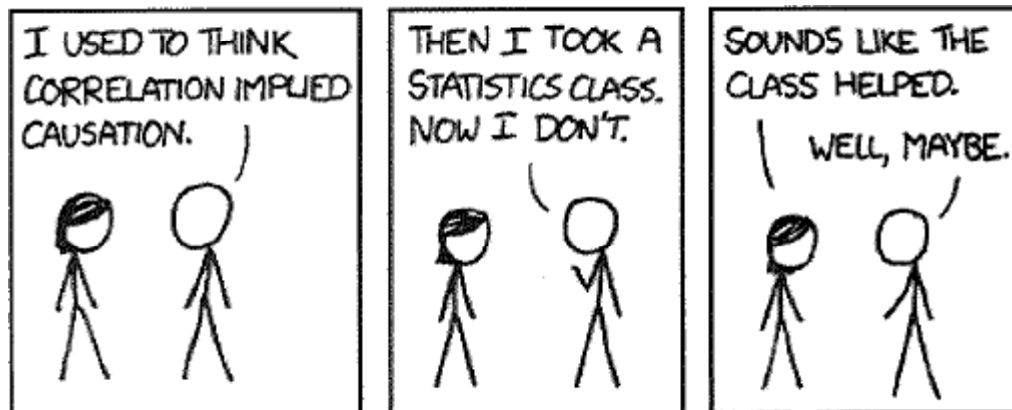
EMPIRICAL EVIDENCE IS NEEDED FROM A LARGE SAMPLE OF REAL-WORLD SCENARIOS APPLIED TO REAL-WORLD OBSERVATIONAL DATA TO ESTABLISH THIS MAPPING

Establishing robust practice through empirical research

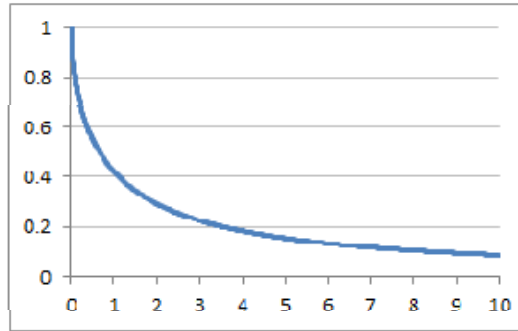
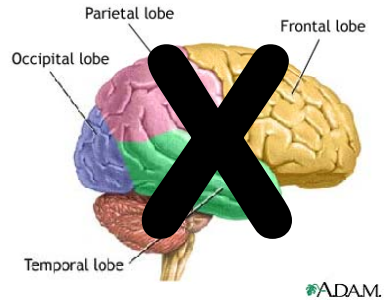
- For ‘risk identification’, many of the attributes of drug-outcome relationship may not be known a priori, so systematic analysis requires comprehensive exploratory framework
- Current data suggest need for systematic sensitivity analysis across all variables that have not been empirically demonstrated to be stable in the scenario
- A viable best practice may be:
“Don’t use observational data for this scenario, due to lack of evidence that a reliable estimate can be obtained”
- Further empirical research needed to have more complete understanding of operating characteristics and sensitivities before widespread adoption

OBSERVATIONAL MEDICAL OUTCOMES PARTNERSHIP

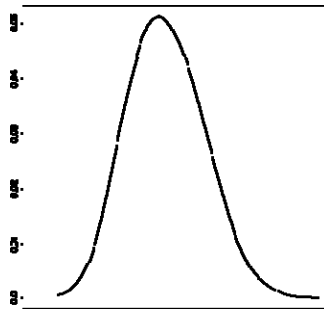
Integrating evidence from disparate sources: A learning paradigm for drug safety



Bayesian Learning paradigm



prior



posterior

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

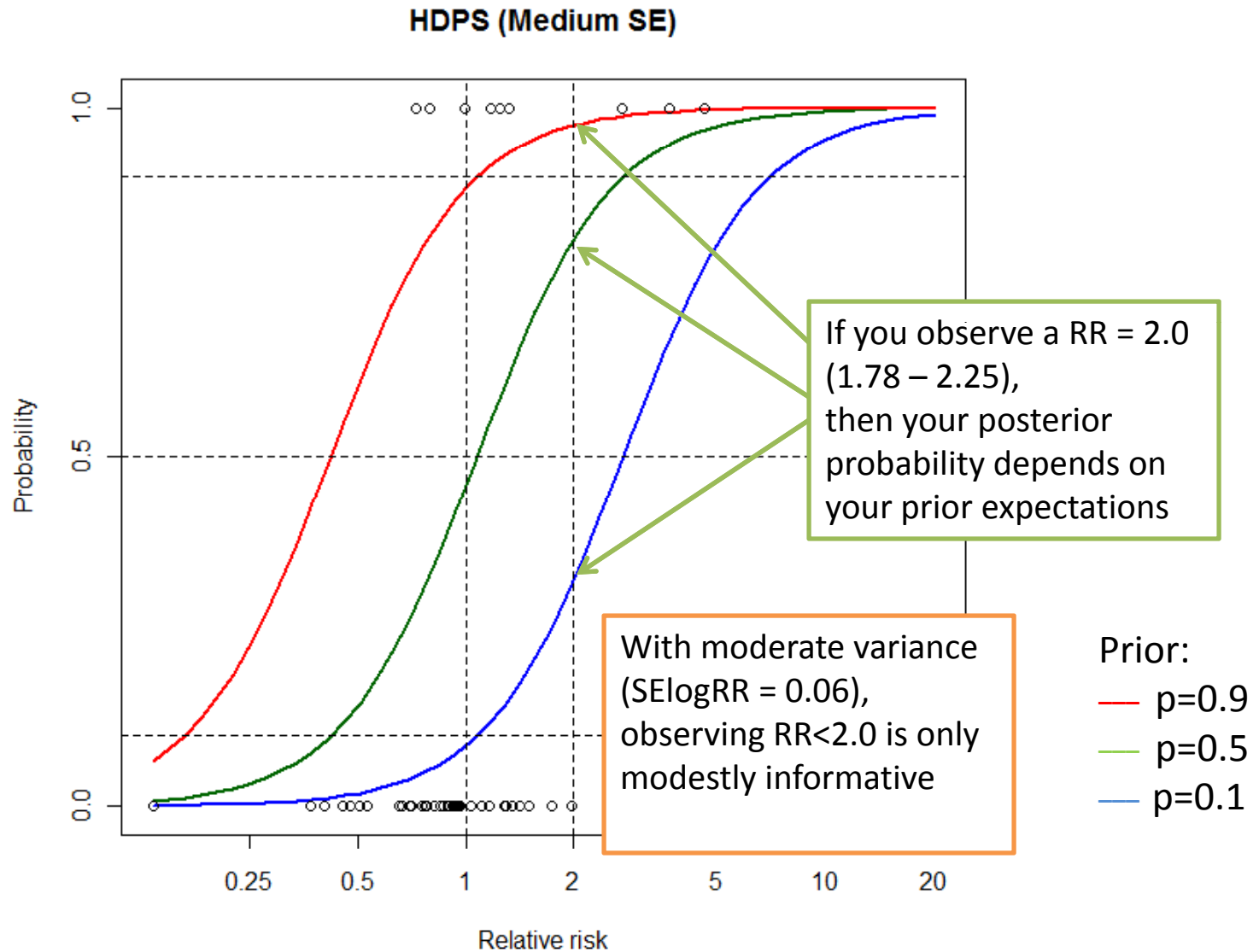
data

“Data”:

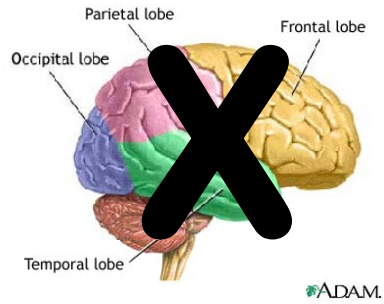
Effect estimates from one method against one database across an array of drug-outcome pairs

Effect estimates of HDPS against CCAE (RR, SE)	Angioedema #1	Aplastic Anemia #1	Acute Liver Failure #1	Bleeding #1	Acute myocardial Infarction #1	Hip Fracture #1	Mortality after Myocardial Infarction #1	Acute Renal Failure #1	Upper GI Ulcer Hospitalization #1
OMOP ACE Inhibitor	1.80 (0.15)	0.40 (0.05)				0.91 (0.12)			0.87 (0.03)
OMOP Amphotericin B		3.30 (0.99)	1.05 (0.24)					4.01 (0.99)	
OMOP Antibiotics		1.22 (0.08)	1.00 (0.01)	1.14 (0.01)	1.06 (0.03)	1.05 (0.09)		1.44 (0.06)	
OMOP Antiepileptics	1.74 (0.38)	4.60 (0.80)						1.63 (0.21)	0.54 (0.05)
OMOP Benzodiazepines	0.13 (0.01)	1.10 (0.06)	0.98 (0.01)	1.11 (0.01)	1.18 (0.03)	1.41 (0.12)		1.06 (0.05)	
OMOP Beta blockers	0.81 (0.07)	0.63 (0.06)	0.95 (0.02)			1.69 (0.19)		0.78 (0.04)	0.88 (0.03)
OMOP Bisphosphonates		0.27 (0.05)	0.85 (0.03)		0.82 (0.07)			0.40 (0.04)	0.90 (0.06)
OMOP Tricyclic antidepressants		0.63 (0.07)	1.02 (0.02)	0.96 (0.01)	0.80 (0.04)			0.82 (0.06)	
OMOP Typical antipsychotics					0.96 (0.08)			1.97 (0.16)	3.46 (0.21)
OMOP Warfarin	0.53 (0.11)	0.47 (0.04)		2.13 (0.04)		1.2 (0.09)	0.49 (0.07)	0.76 (0.05)	

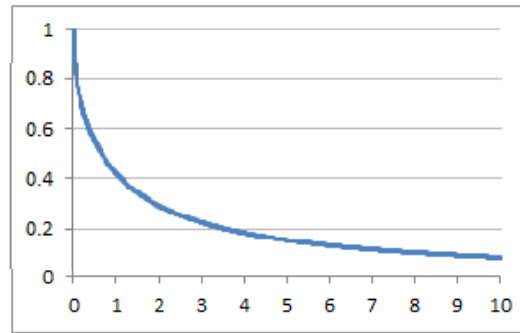
Revising prior expectations in light of new evidence from a risk identification system



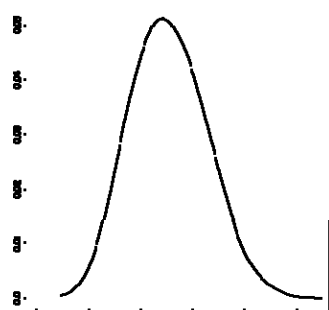
OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP



Bayesian Learning paradigm



prior

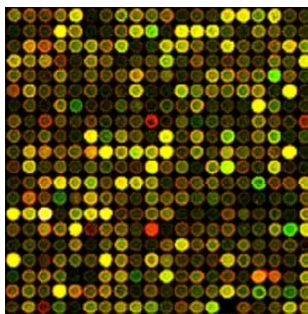


prior

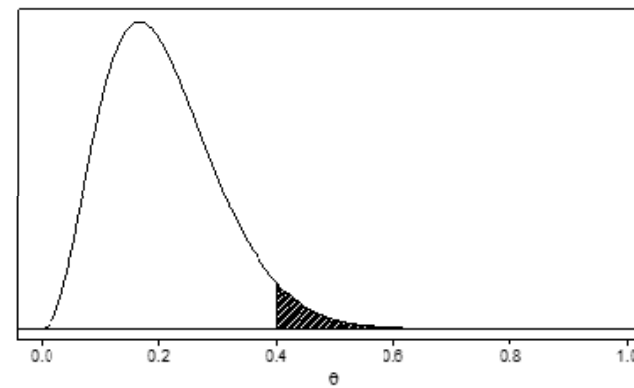
Bayes' Rule

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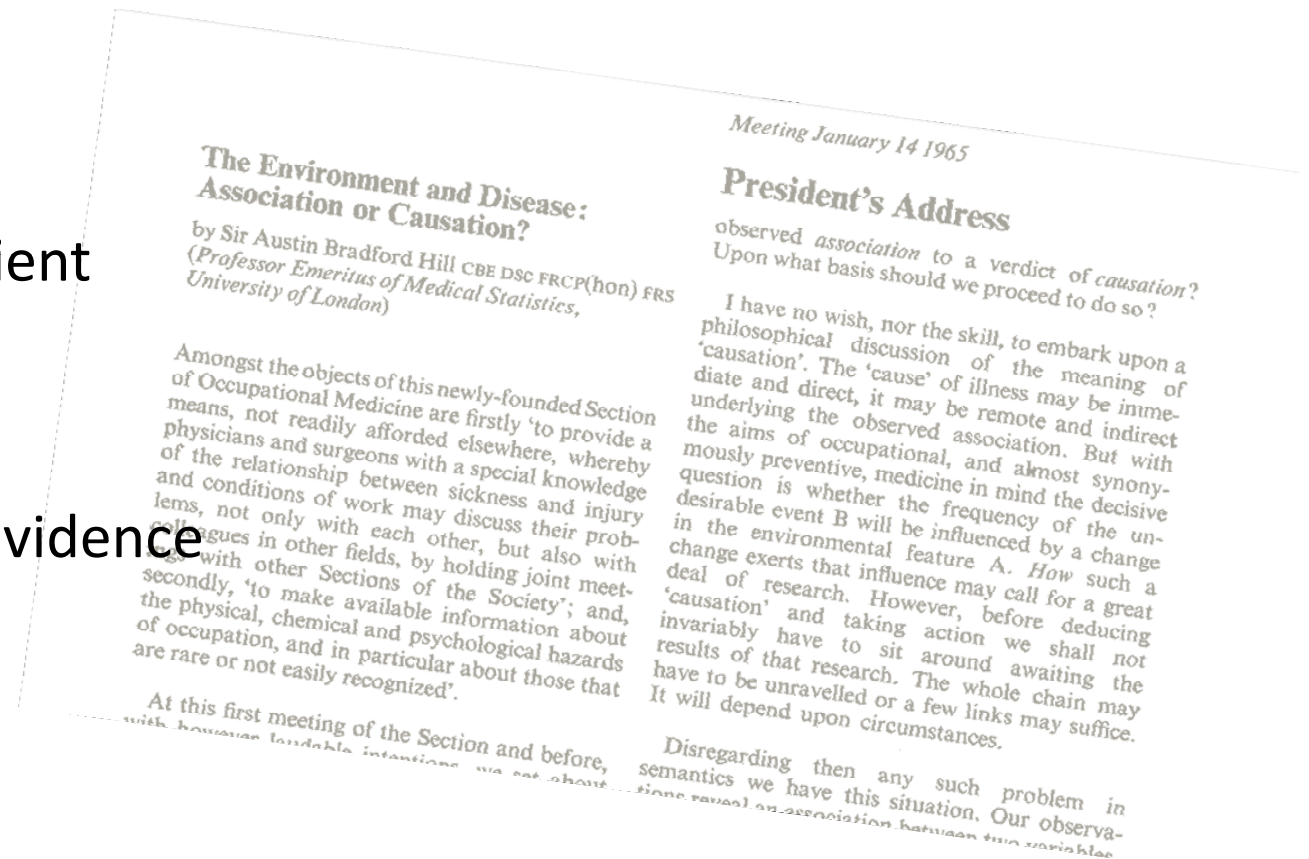


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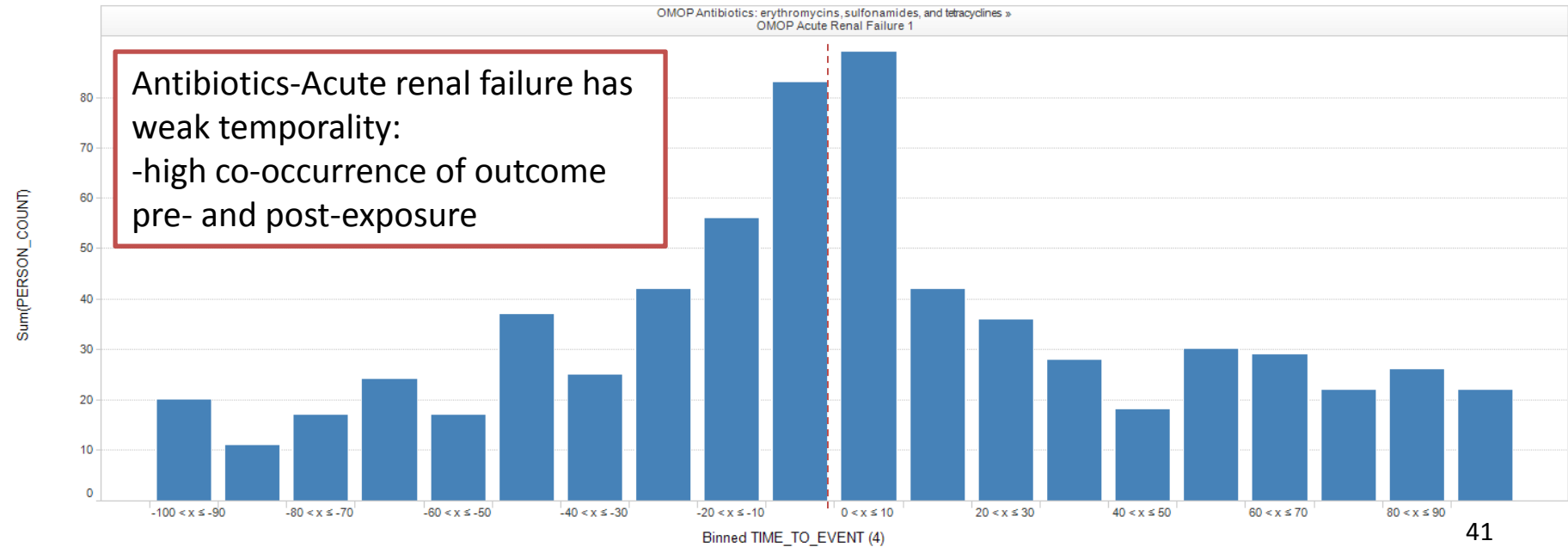
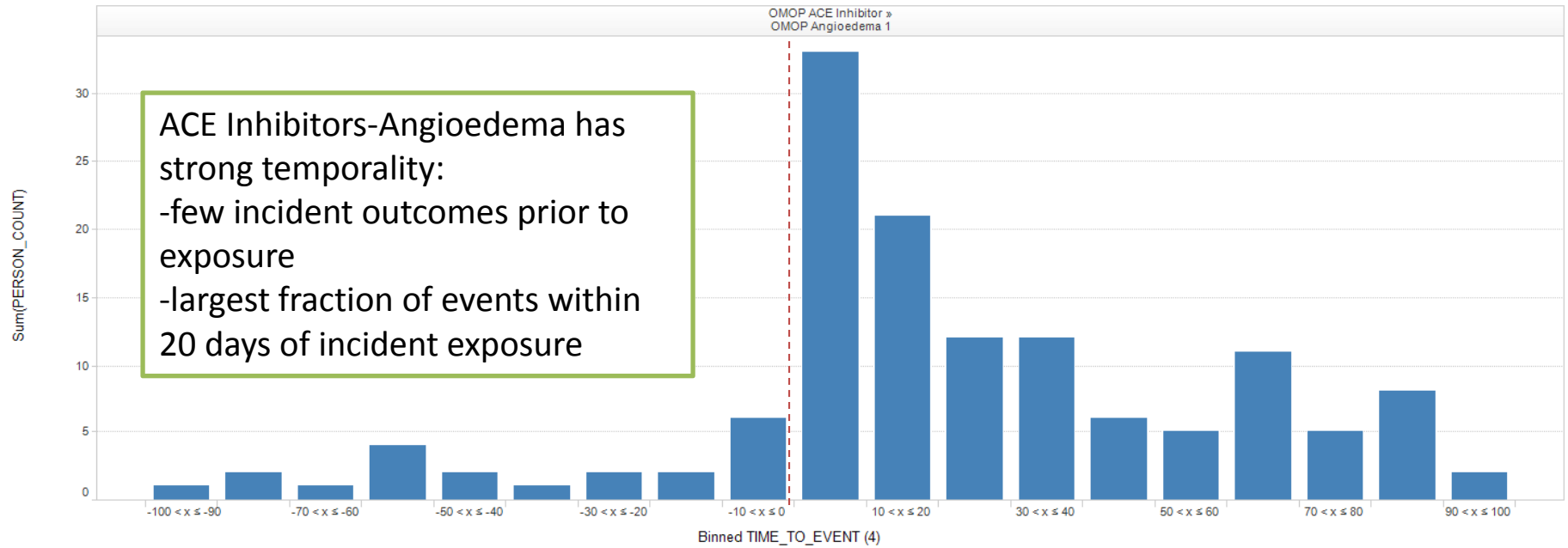
Hill's causality viewpoints

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



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

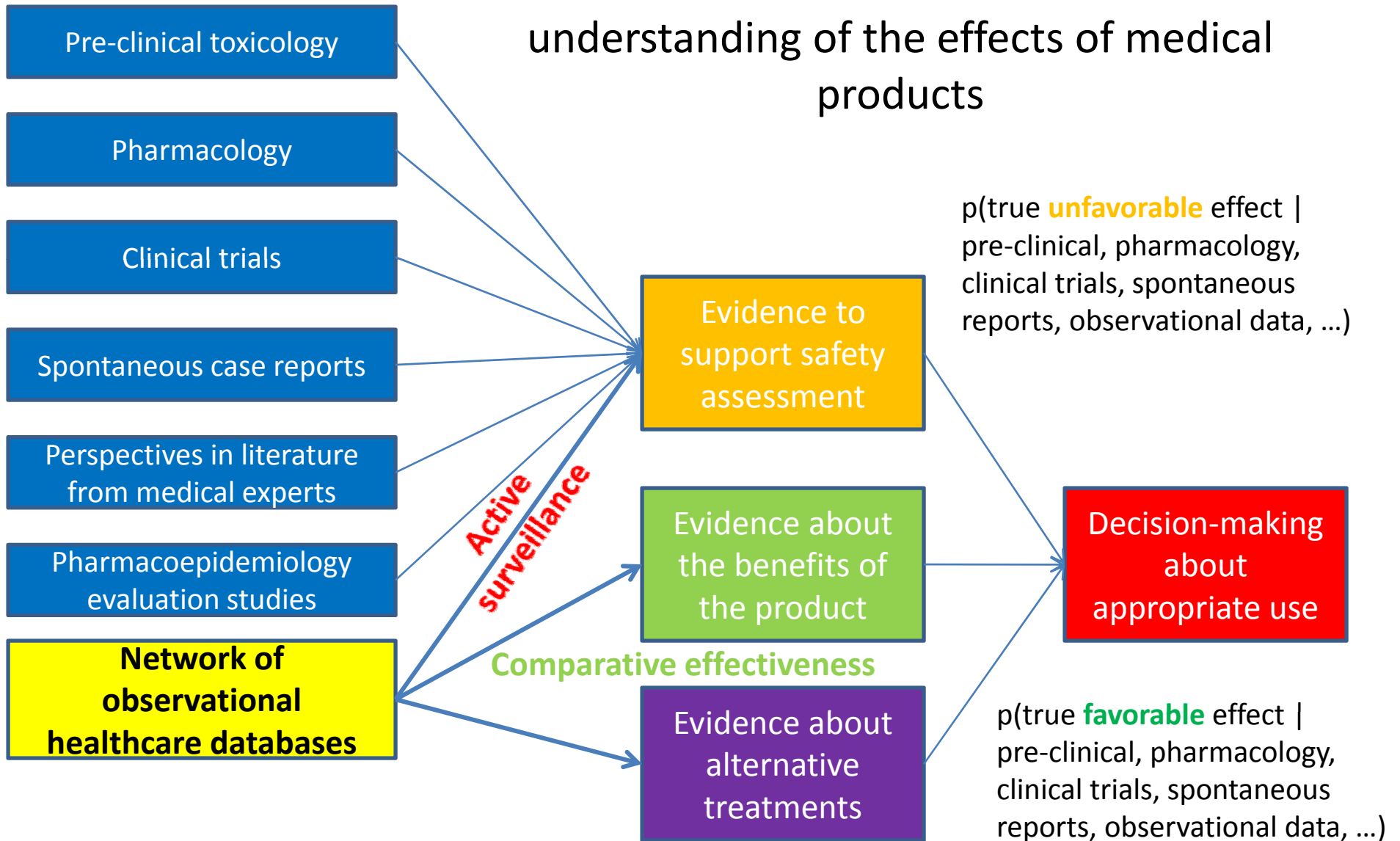
Temporality



Harnessing Hill

- Previously $p(\text{true} \mid \text{RR}, \text{SE})$
 - Logistic regression with 2 predictors
- Using Hill: $p(\text{true} \mid \text{RR}, \text{SE}, \text{temporality}, \text{coherence}, \text{consistency}, \text{plausibility}, \text{biological gradient}, \text{specificity}, \text{etc.})$
 - 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 to be 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