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Active Surveillance Methods Performance and Challenges: Lessons from the Observational Medical Outcomes Partnership

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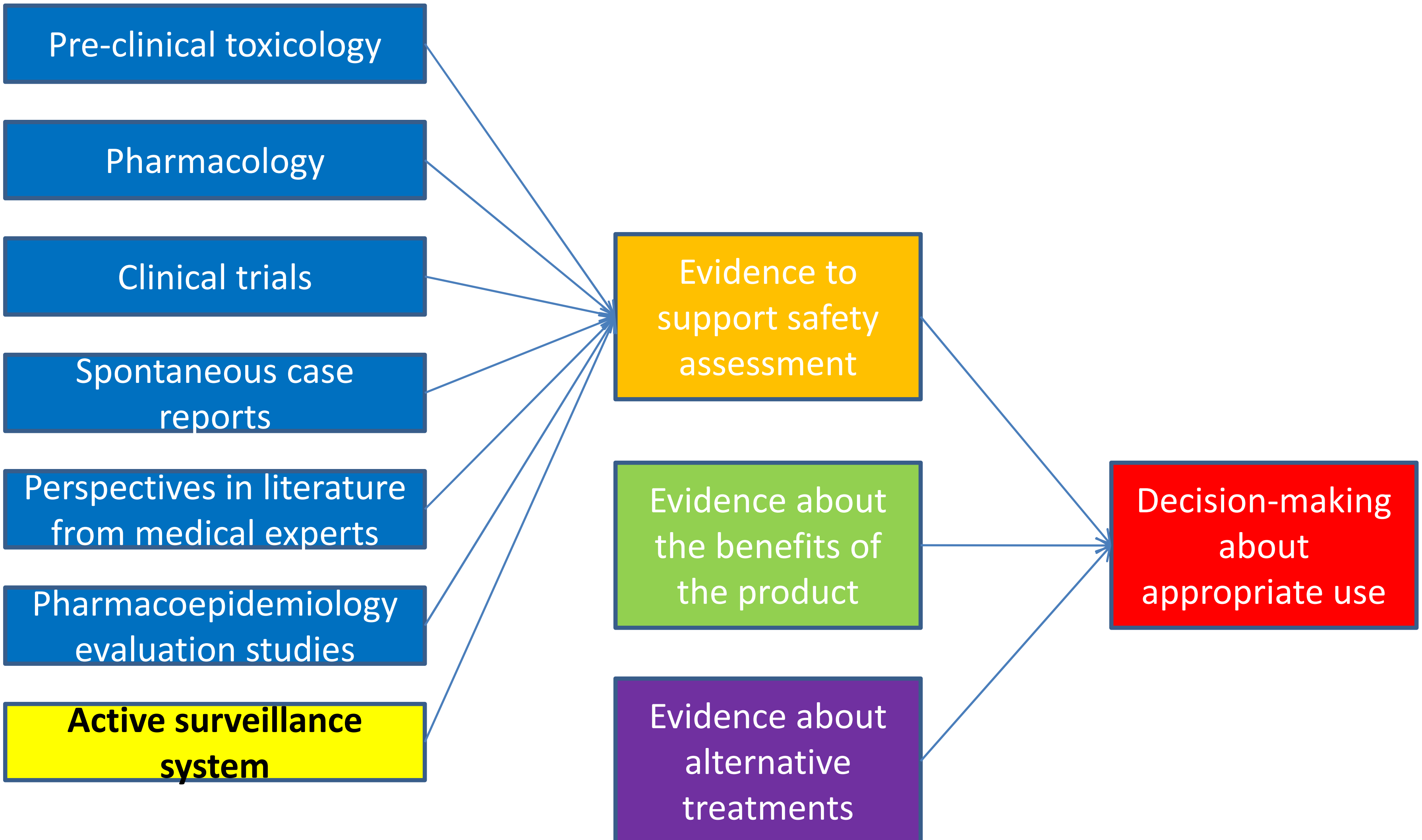
Active surveillance: One additional piece of evidence to inform medical decision-making



Methodological challenges for active surveillance

- A traditional pharmacoepidemiology study may conduct an analysis to estimate association of ONE drug and ONE outcome in ONE database at ONE point in time
- A national active surveillance system is envisioned to enable ONGOING monitoring of ANY medical product and ANY health outcome of interest across ALL databases in the network
- Methodological issues to be evaluated:
  - Precision
  - Accuracy
  - Value of information

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Observational Medical Outcomes Partnership

Established to inform the appropriate use of observational healthcare databases for active surveillance by:

- **Conducting methodological research** to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues
- **Developing tools and capabilities** for transforming, characterizing, and analyzing disparate data sources
- **Establishing a shared resource** so that the broader research community can collaboratively advance the science

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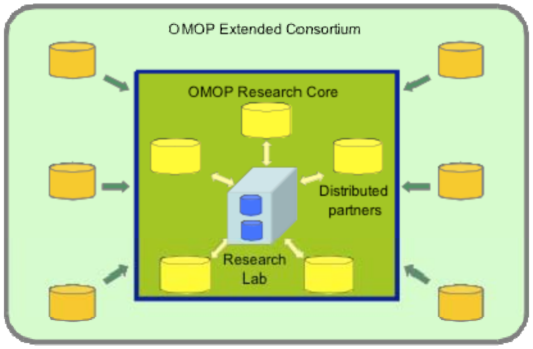
OMOP research experiment workflow

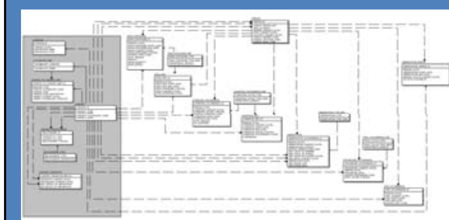


OMOP Methods Library

Method 1
Method 2
Method 3
Method 4

feasibility testing

Common Data Model



Drugs
- ACE Inhibitors
- Amphotericin B
- Antibiotics
- Antiepileptics
- Benzodiazepines
- Beta blockers
- Bisphosphonates
- Tricyclic antidepressants
- Typical antipsychotics
- Warfarin

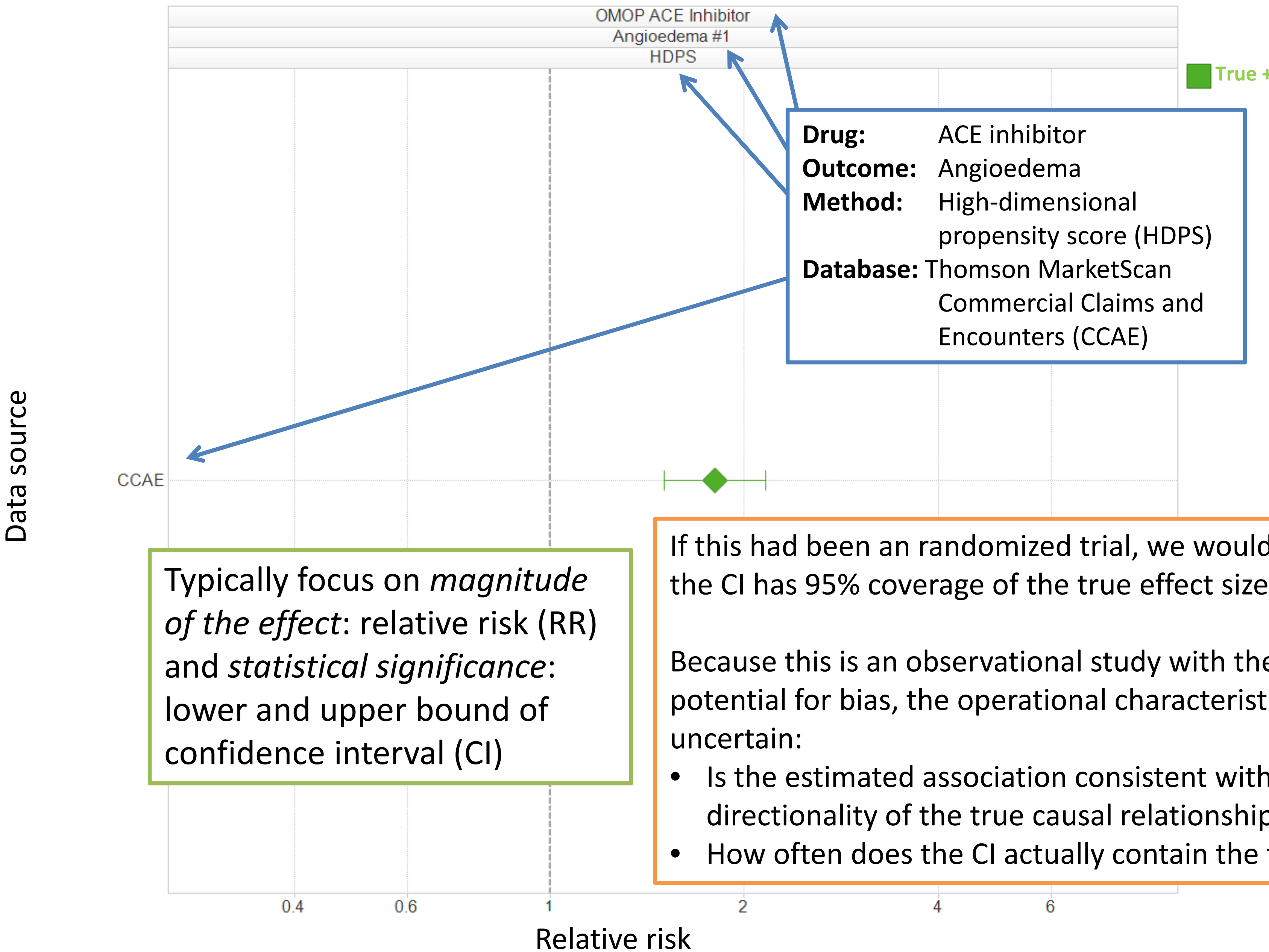
Health Outcomes of Interest
- Angioedema
- Aplastic Anemia
- Acute Liver Injury
- Bleeding
- GI Ulcer Hospitalization
- Hip Fracture
- Hospitalization
- Myocardial Infarction
- Mortality after MI
- Renal Failure

Non-specified conditions

-All outcomes in condition terminology

-'Labeled events' as reference
-Warning
-Precautions
-Adverse Reactions
-Postmarketing Experience

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)

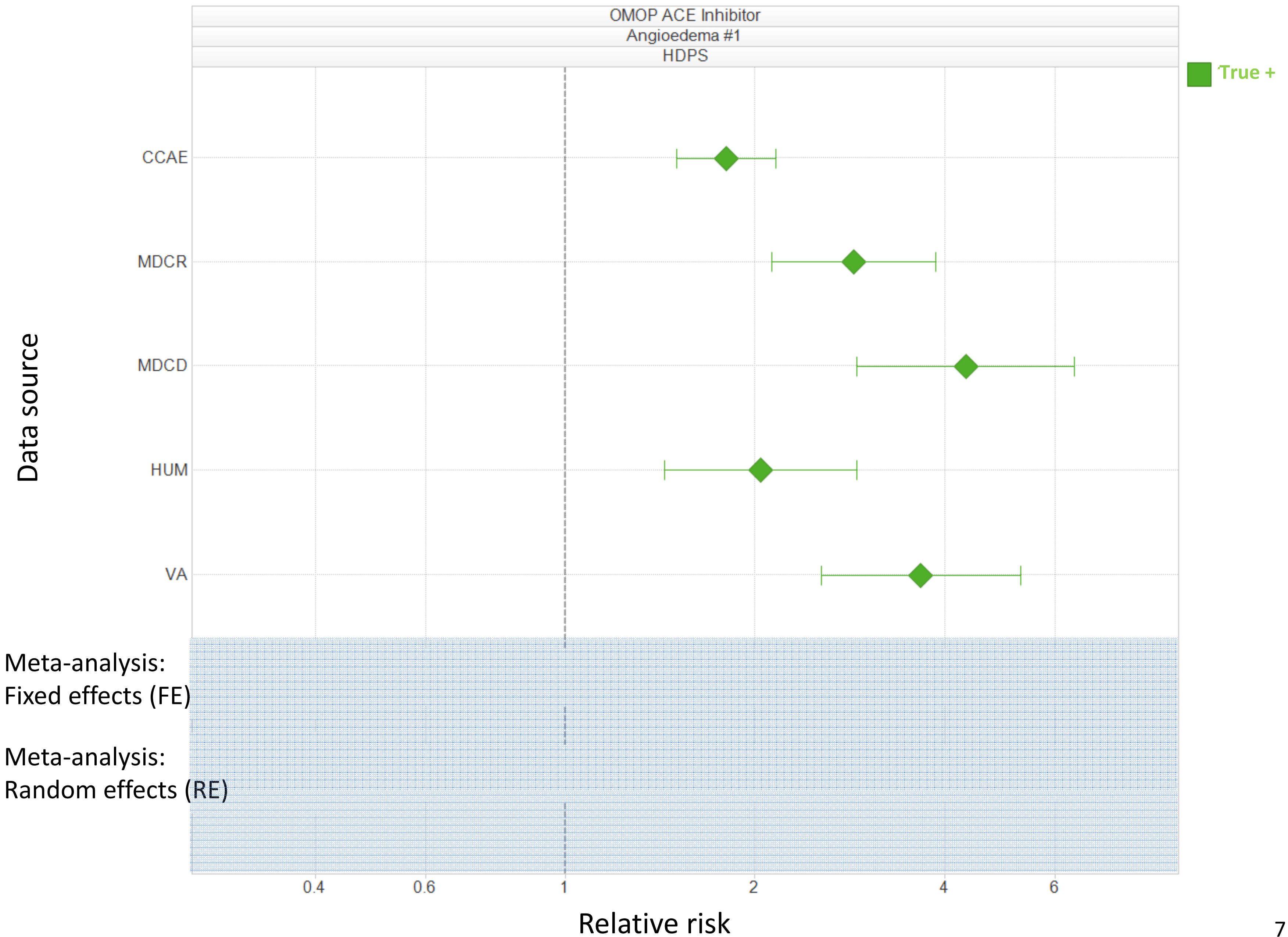
Typically focus on *magnitude of the effect*: relative risk (RR) and *statistical significance*: lower and upper bound of confidence interval (CI)

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?

Opportunity for an active surveillance system: Pooling estimates across a network of disparate data sources



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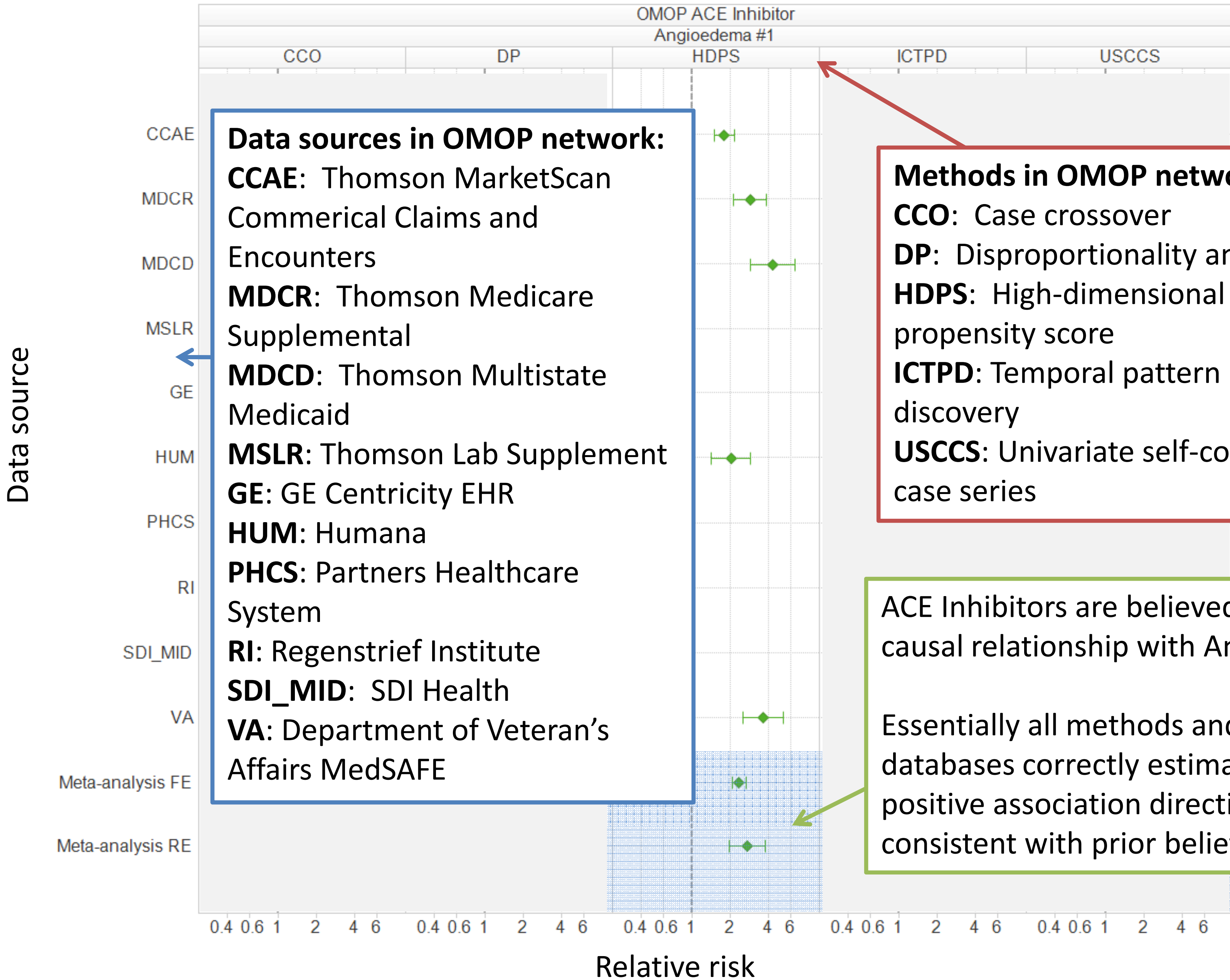
Systematic sensitivity analysis: Estimate the effect using multiple methods across the network of databases



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

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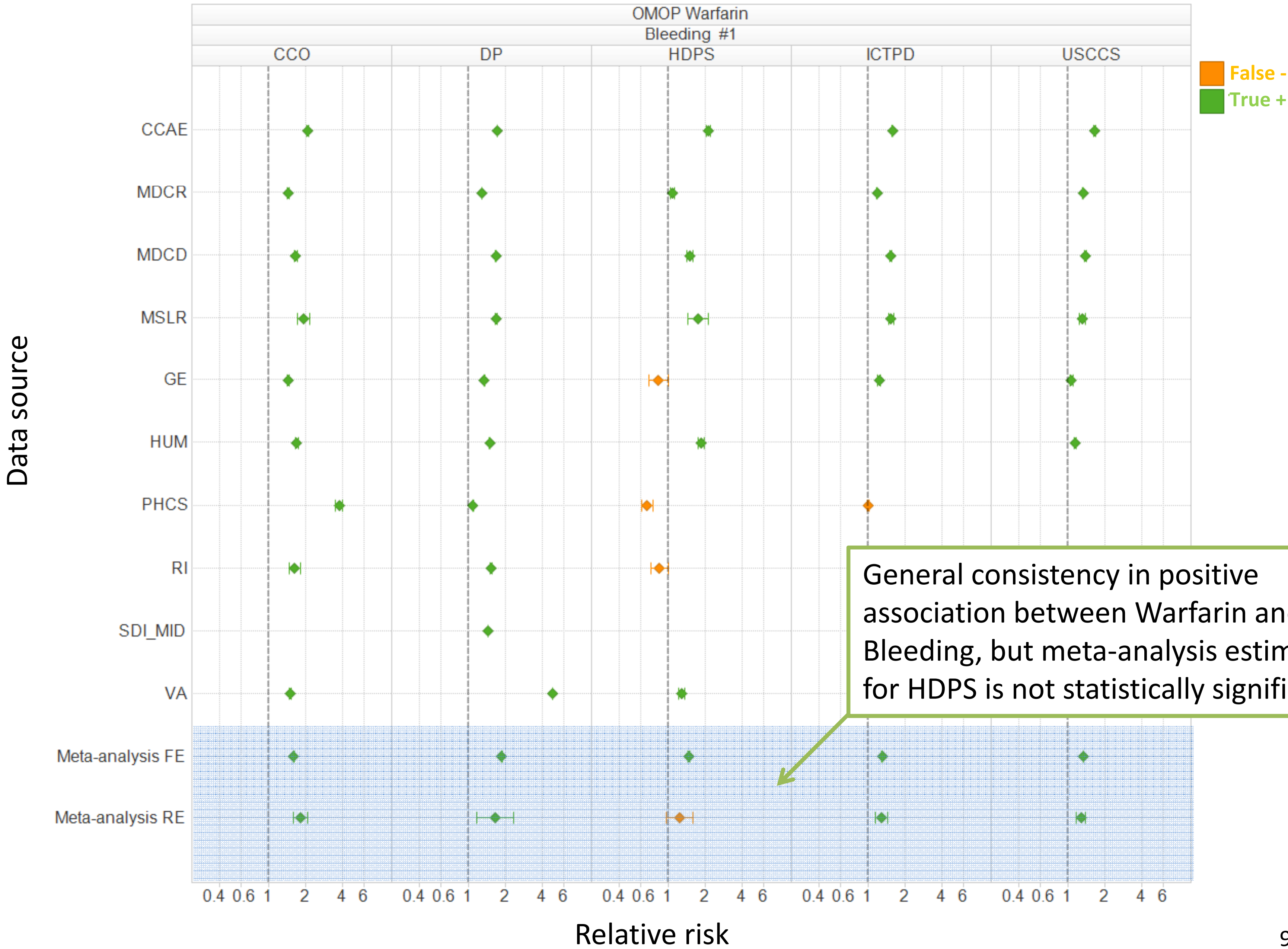
Evaluating the association between Warfarin and Bleeding



General consistency in positive association between Warfarin and Bleeding, but meta-analysis estimate for HDPS is not statistically significant

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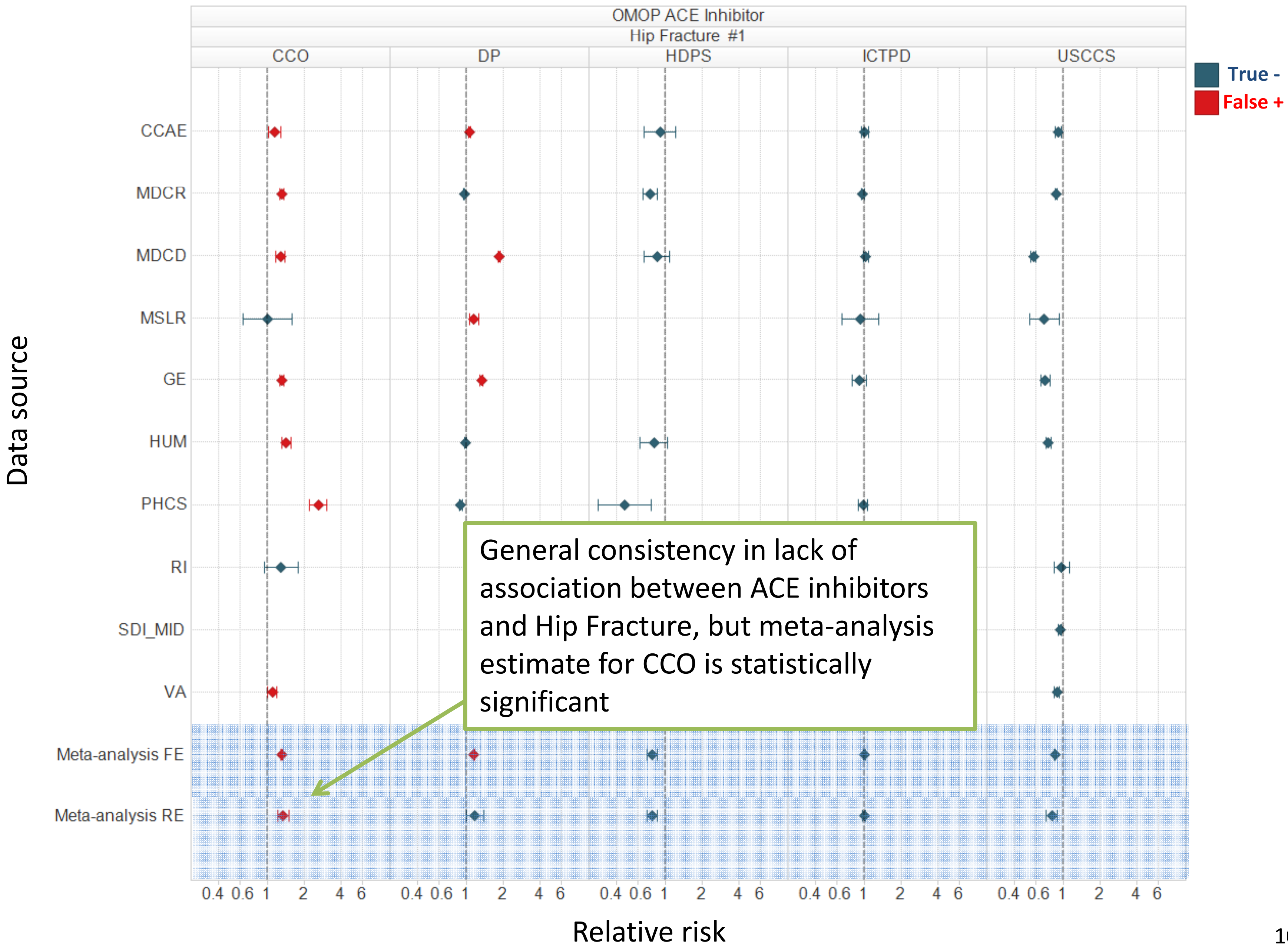
'True negative' observed for 'negative control' of ACE Inhibitors and Hip Fracture



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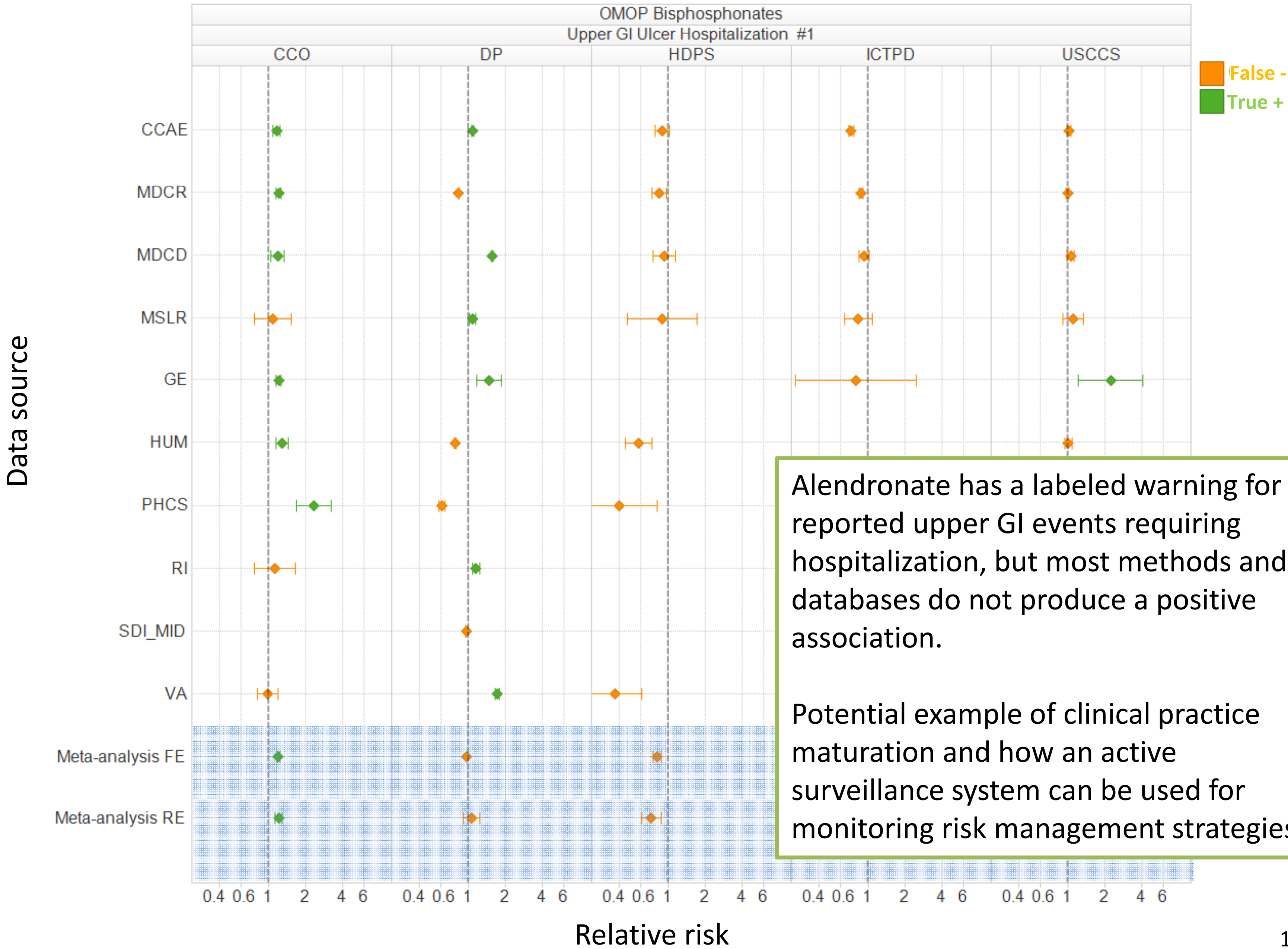
Consistent 'false negative' observed for 'true' association between Bisphosphonates and GI Ulcer Hospitalization



Alendronate has a labeled warning for reported upper GI events requiring hospitalization, but most methods and databases do not produce a positive association.

Potential example of clinical practice maturation and how an active surveillance system can be used for monitoring risk management strategies.

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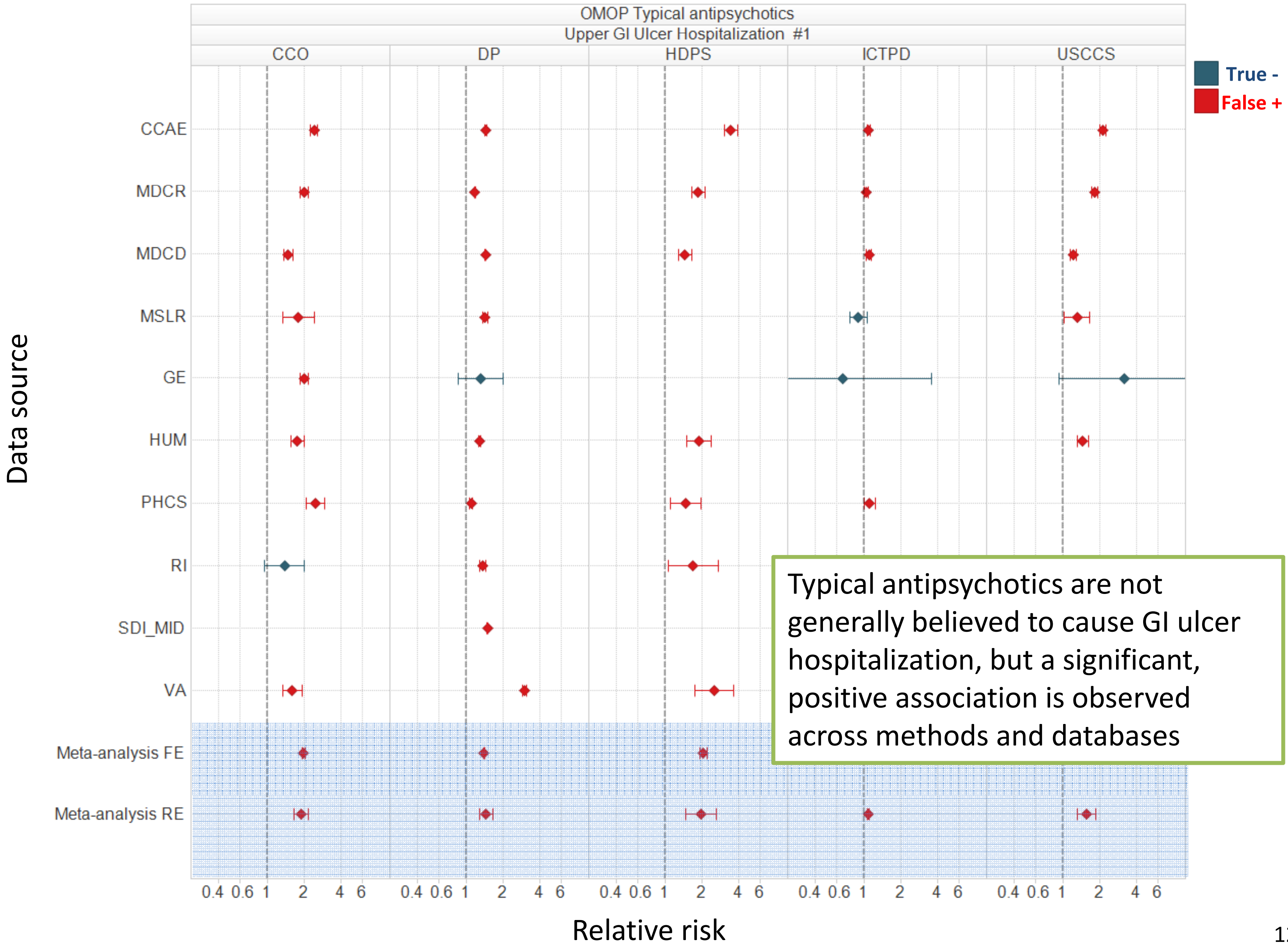
Consistent 'false positive' observed for 'negative control' of Typical antipsychotics and GI Ulcer Hospitalization



Typical antipsychotics are not generally believed to cause GI ulcer hospitalization, but a significant, positive association is observed across methods and databases

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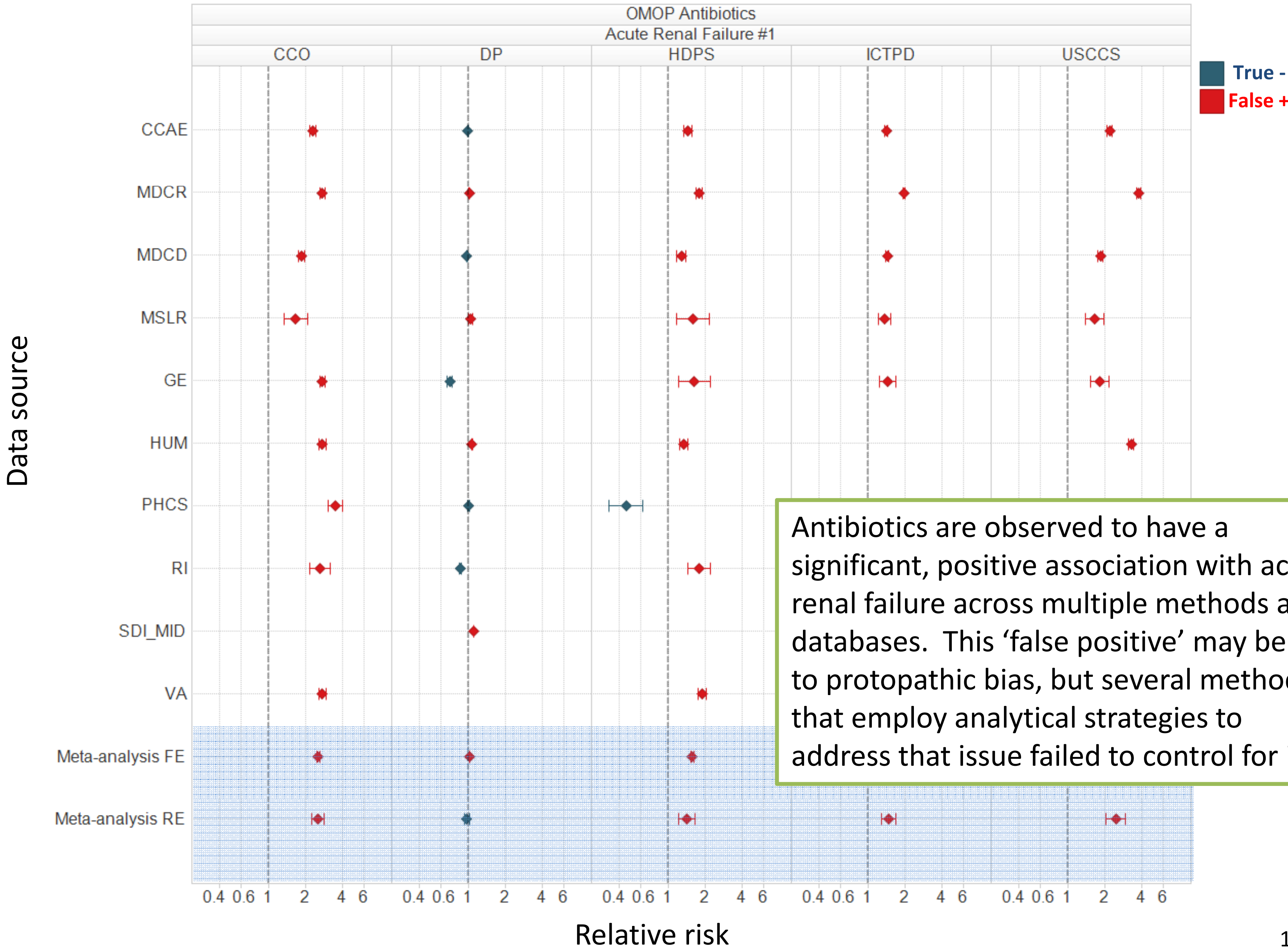
Consistent 'false positive' observed for 'negative control' of Antibiotics and Acute Renal Failure



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.

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Measuring method performance: Classifying the illustrative examples

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:** **ACE Inhibitors- Angioedema** **Warfarin- Bleeding**	**False positives:** **Typical antipsychotic- GI Ulcer hospitalization** **Antibiotics- Acute renal failure**
N	**False negatives:** **Bisphosphonates- GI Ulcer hospitalization**	**True negatives:** **ACE Inhibitors- Hip fracture**

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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?

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'Ground truth' assumed for Monitoring Health Outcomes of Interest

Outcome \ Drug	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'			Negative control'		True positive' risk
Hip Fracture	Negative control'	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

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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

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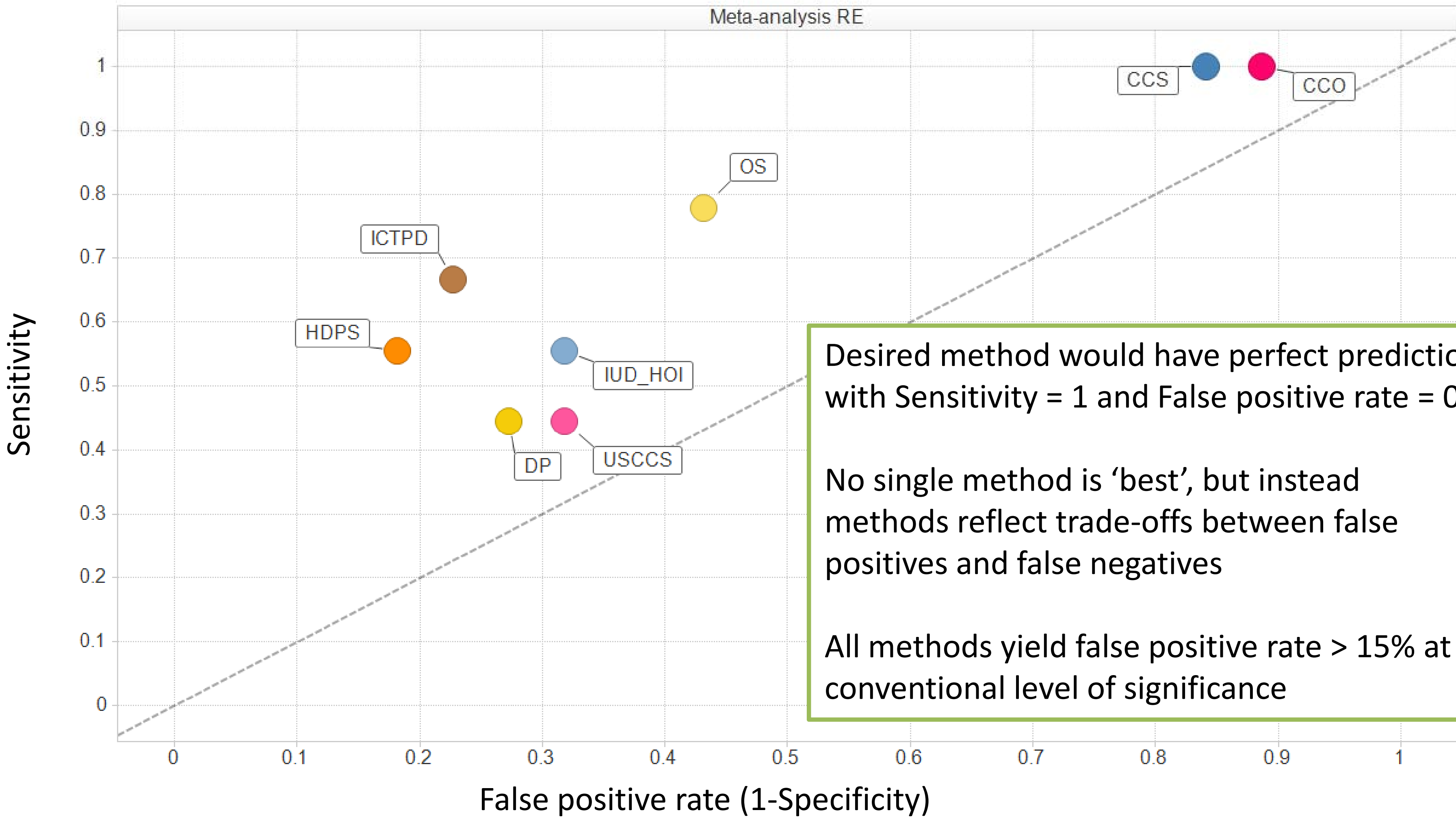
Active surveillance methods under evaluation in OMOP experiment

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)	Harvard Medical School / 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

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

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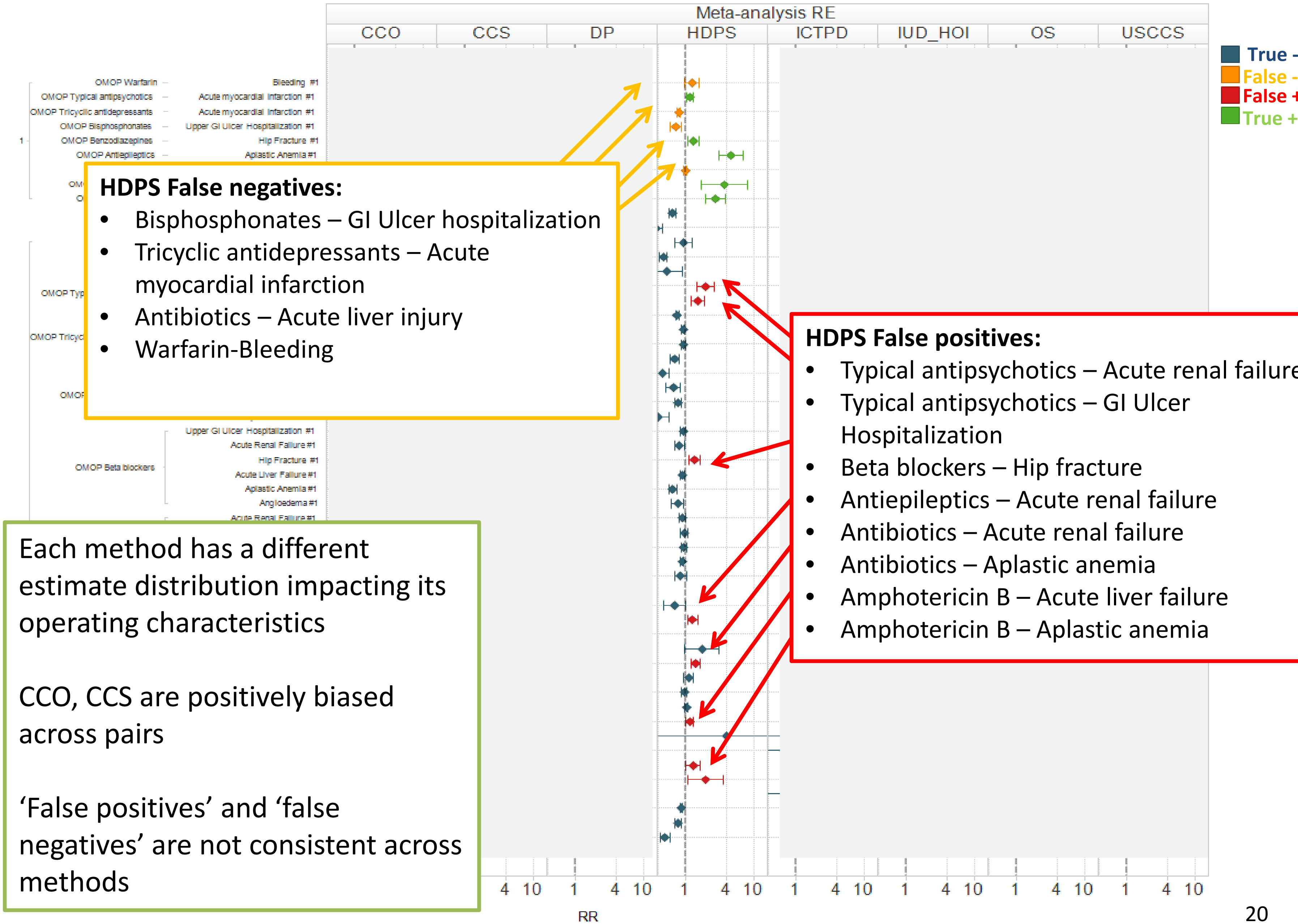
Distribution of estimates across all drug-outcome pairs



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

So given these operating characteristics, what can we expect to do in practice….

- Use case: An emerging safety concern is raised for a new medical product. The association between the drug and outcome could be estimated by running an OMOP active surveillance method across the network of observational databases
  - The method will produce a relative risk and standard error from each participating data source, which can then be pooled together in a meta-analytic framework
  - Hypothetical scenario: The random-effects meta-analysis yields an RR=2.0 with SE=0.06.
  - Question: what is the probability that there is a true causal relationship given this observed association?

- Bayes rule enables such calculation…
  - p(true|RR,SE) ~ p(RR,SE|true)*p(true)
  - p(true) is the prior probability of true association; consider a family of priors: skeptical (0.1), indifferent (0.5), enthusiastic (0.9)
  - p(RR,SE|true) can be estimated from empirical data (OMOP experimental results)

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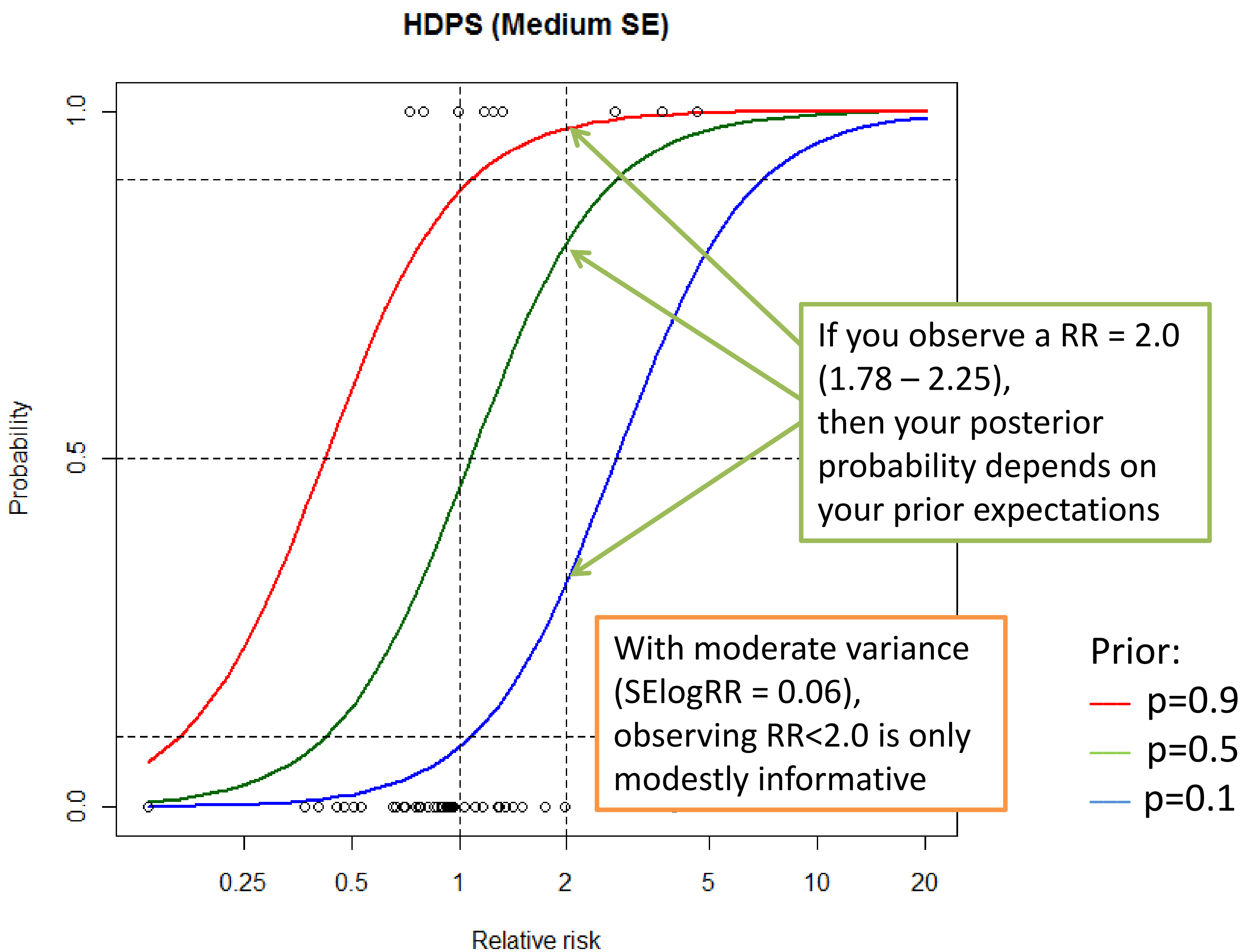
Revising prior expectations in light of new evidence from an active surveillance system



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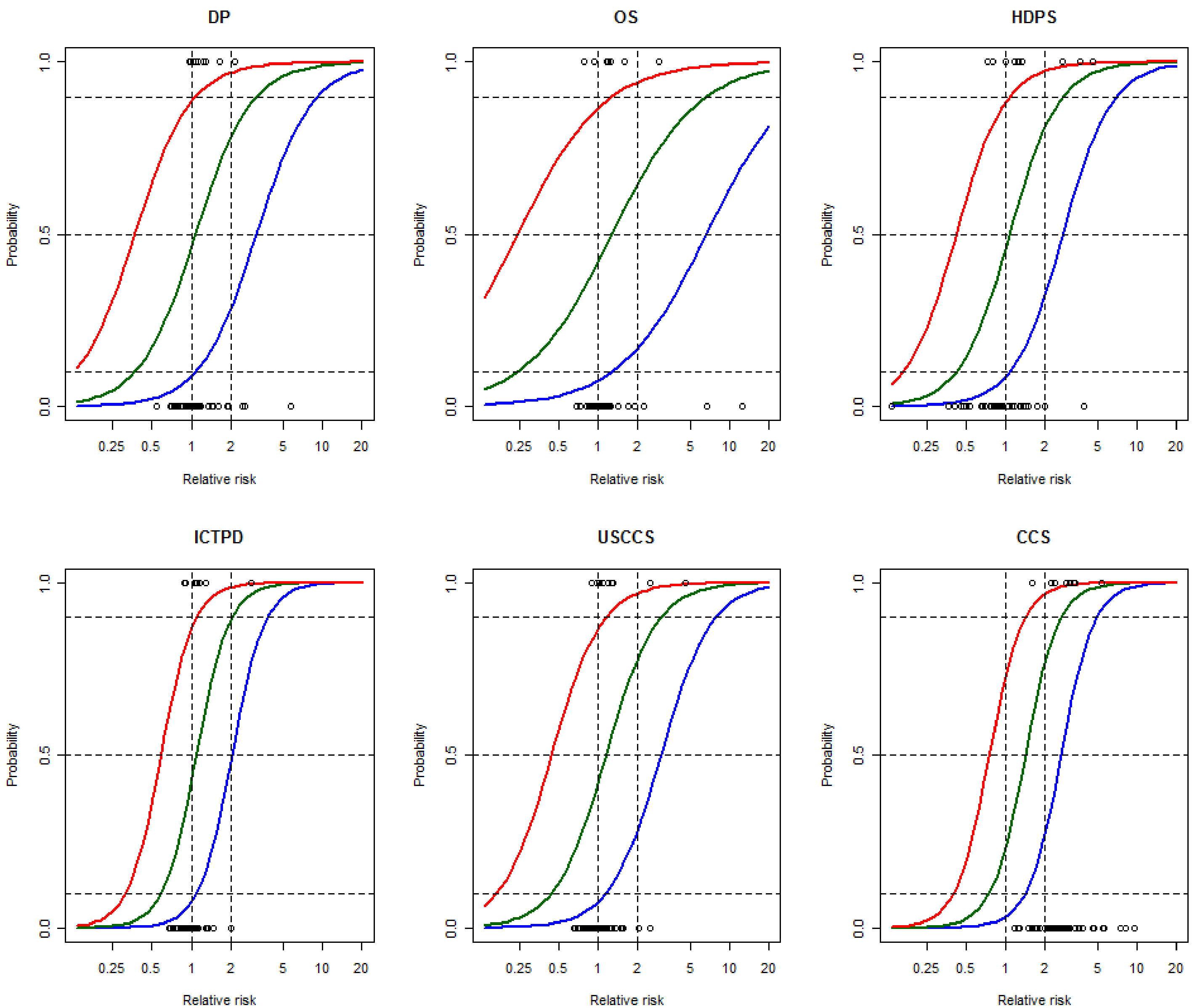
Revising prior expectations in light of new evidence from an active surveillance system: Impact of using estimates from different methods



Across all methods, observing a RR=2.0 with moderate variance (SElogRR = 0.06) does not increase a skeptical prior beyond indifference

Prior:
- p=0.9
- p=0.5
- p=0.1

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Concluding thoughts

- An active surveillance 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
- Systematic pharmacoepidemiology can achieve:
  - 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
- You need a relative risk > 2 to have confidence in result ….detecting effects smaller than 2 will incur higher risk of false positives

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