

**OBSERVATIONAL
MEDICAL
OUTCOMES
PARTNERSHIP**

**Lessons learned, Current Activities, and
Anticipated Needs for Methods
Research and Development:
OMOP Perspective**

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on behalf of OMOP Research Team
June 3, 2011

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Current practice in the use of observational healthcare databases to study the safety of medical products

Initiated at
any time by
any group
with access
to any data

- **Hypothesis:** Does ‘Drug X’ cause ‘Condition Y’?
- **Test:** Estimate the association between ‘Drug X’ exposure and incidence of ‘Condition Y’
- **Result:** Presentation at scientific conference, publication in peer-review journal, or report otherwise made available
- **Action:** Regulators, manufacturers, and medical community at large react to new information by integrating with existing knowledge to inform their decision-making

Example: ACE inhibitor-Angioedema

Angioedema Incidence in US Veterans Initiating Angiotensin-Converting Enzyme Inhibitors

One data source: VA

Donald R. Miller, Susan A. Oliveria, Dan R. Berlowitz, Benjamin G. Fincke, Paul Stang, David E. Lillienfeld

One method: cohort

Abstract—Angioedema is a rare but potentially serious complication of angiotensin-converting enzyme (ACE) inhibitor (ACE) use. We conducted a study to estimate incidence of ACE-related angioedema and explore its determinants in a large racially diverse patient population. We used linked medical and pharmacy records to identify all patients in the US Veterans Affairs Health Care System from April 1999 through December 2000 who received first prescriptions for antihypertensive medications. We studied 195 192 ACE initiators and 399 889 patients initiating other antihypertensive medications (OAH). New angioedema was identified by diagnosis codes using methods validated in a national sample of 869 angioedema cases. Confirmation for over 95% of cases. Overall incidence of ACE-related angioedema while on the medication and the incidence rate was 1.97 (1.77 to 2.17) per 100 person years. This compares with a rate of 0.51 (0.43 to 0.59) in OAH initiators and the adjusted rate was 3.56 (2.82 to 4.44). Fifty five percent of cases occurred within 90 days of first ACE use but 25% occurred with prolonged use, even beyond 1 year. We estimate that 58.3% of angioedema in patients starting antihypertensives was related to ACE. We also found that angioedema rates were nearly 4-fold higher in blacks, 50% higher in women, and 12% lower in those with diabetes. This study provides a reliable estimate of angioedema incidence associated with ACE use in a diverse nontrial patient population, confirming the low, but finding substantial variation by race, sex, and diabetes status. (*Hypertension*. 2008;51:1-2.)

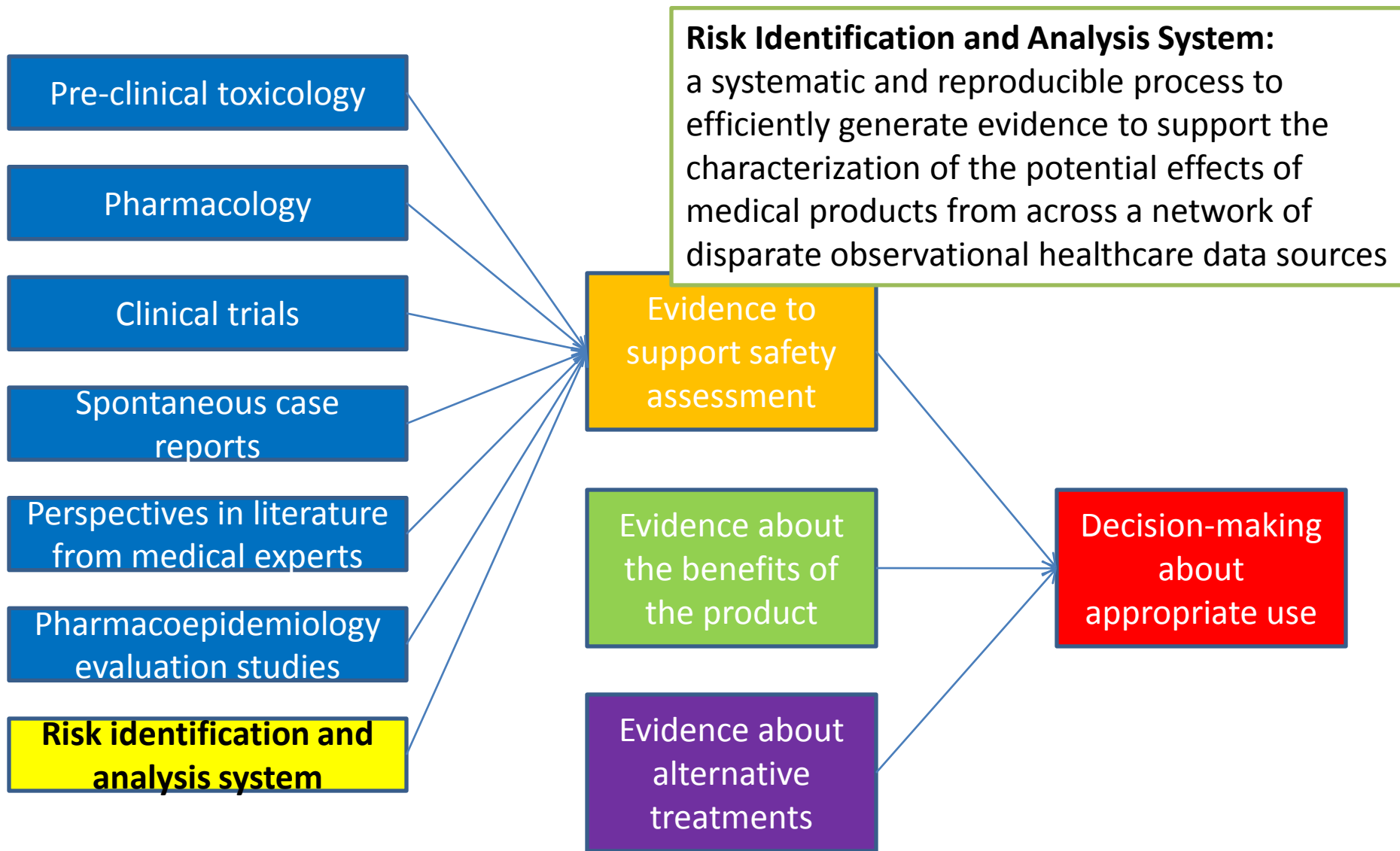
Temporality

One estimate: strength of association

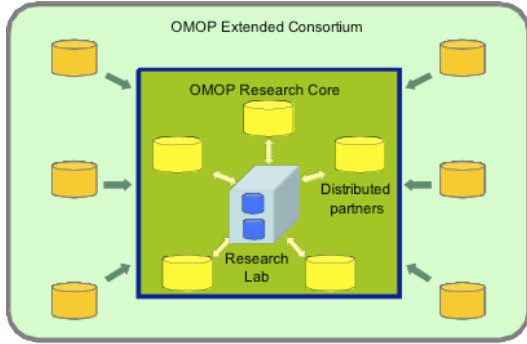
Risk factors

Key Words: angioedema ■ angiotensin-converting enzyme inhibitors ■ antihypertensive agents ■ adverse effects ■ pharmacoepidemiology ■ drug toxicity

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

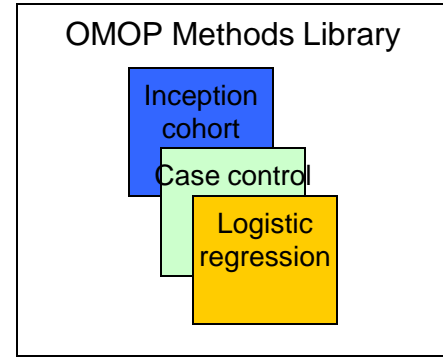
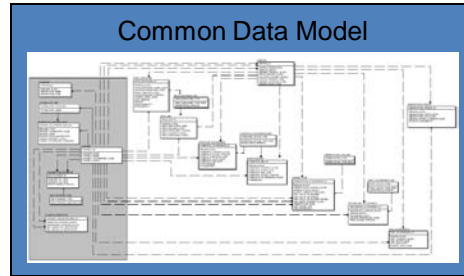


OMOP Research Experiment



- 10 data sources
- Claims and EHRs
- 200M+ lives
- Simulated data (OSIM)

- Open-source
- Standards-based
- OSCAR, NATHAN, GROUCH



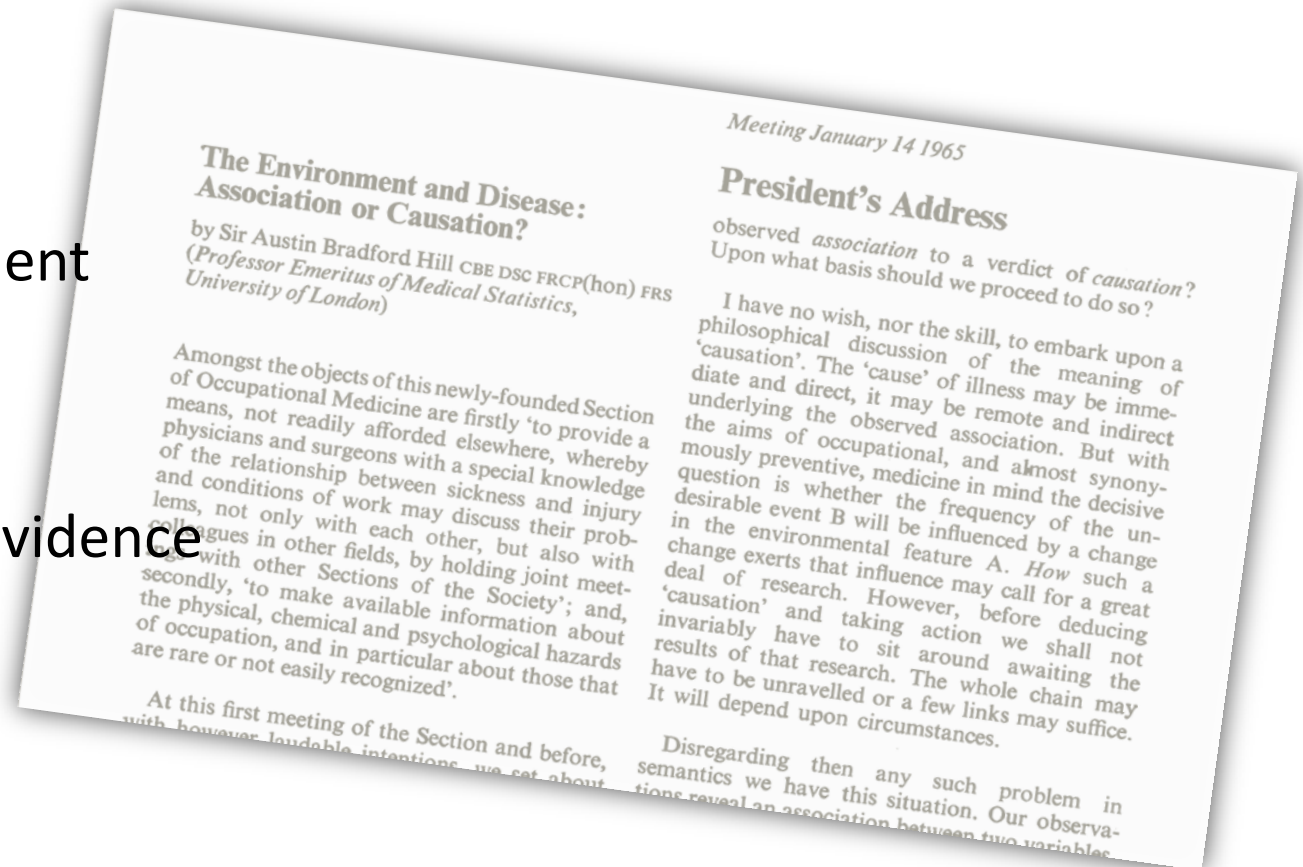
- 14 methods implemented as standardized procedures
- Full transparency with open-source code and documentation
- Epidemiology, statistical and machine learning designs

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

Hill's causality viewpoints

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



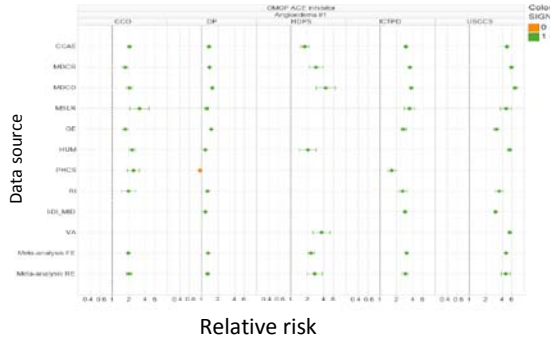
Austin Bradford Hill, "The Environment and Disease: Association or Causation?," *Proceedings of the Royal Society of Medicine*, 58 (1965), 295-300.

Vision for a risk identification and analysis system 'causal dashboard'

Drug Tricyclic antidepressants ▼

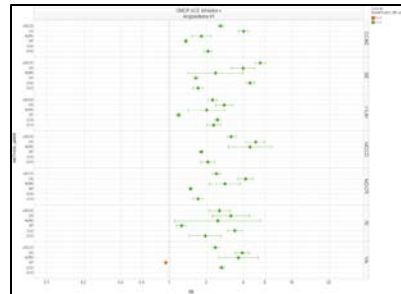
Outcome Acute myocardial infarction ▼

Strength of association

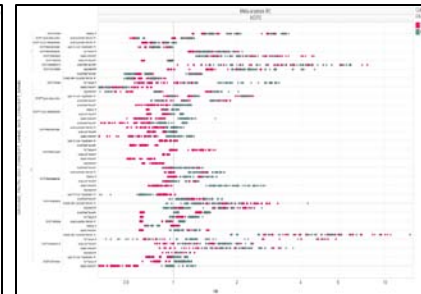


Consistency

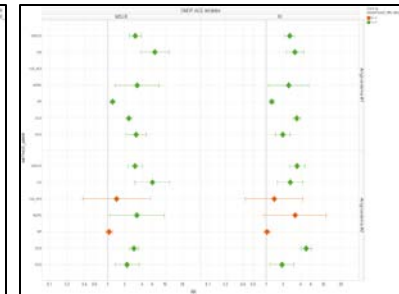
by data source



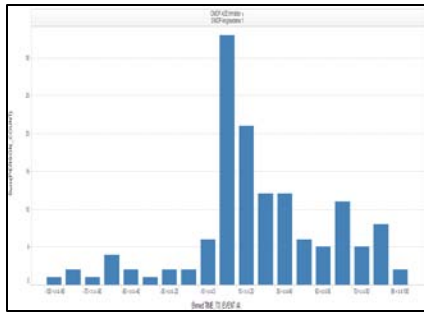
by method and parameters



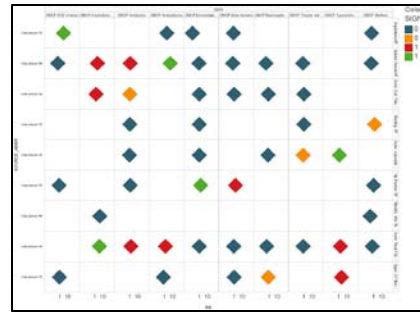
by outcome definition



Temporality

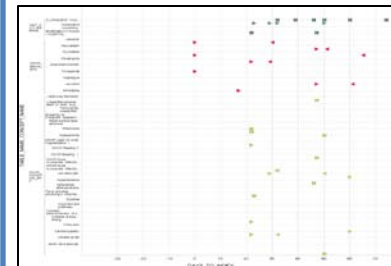


Specificity

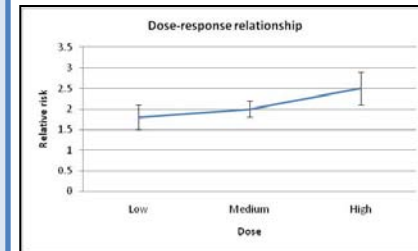


Plausibility

Interactive patient profiles



Biological gradient



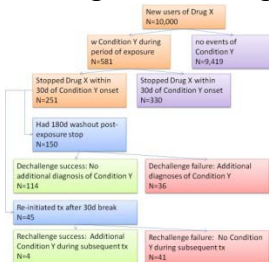
Analogy

Explore related conditions and treatments



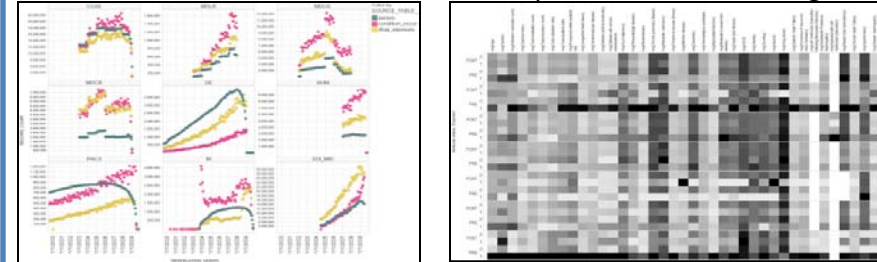
Experimental evidence

Dechallenge/Rechallenge



Coherence

Understand data and cohort to assess potential confounding



Observational analyses to support each causal consideration

- **Strength of association**

- Current focus: methods produce effect estimates (RR) of temporal association between exposure and outcome

- Consistency

- Specificity

- Temporality

- Biological gradient

- Plausibility

- Coherence

- Experimental evidence

- Analogy

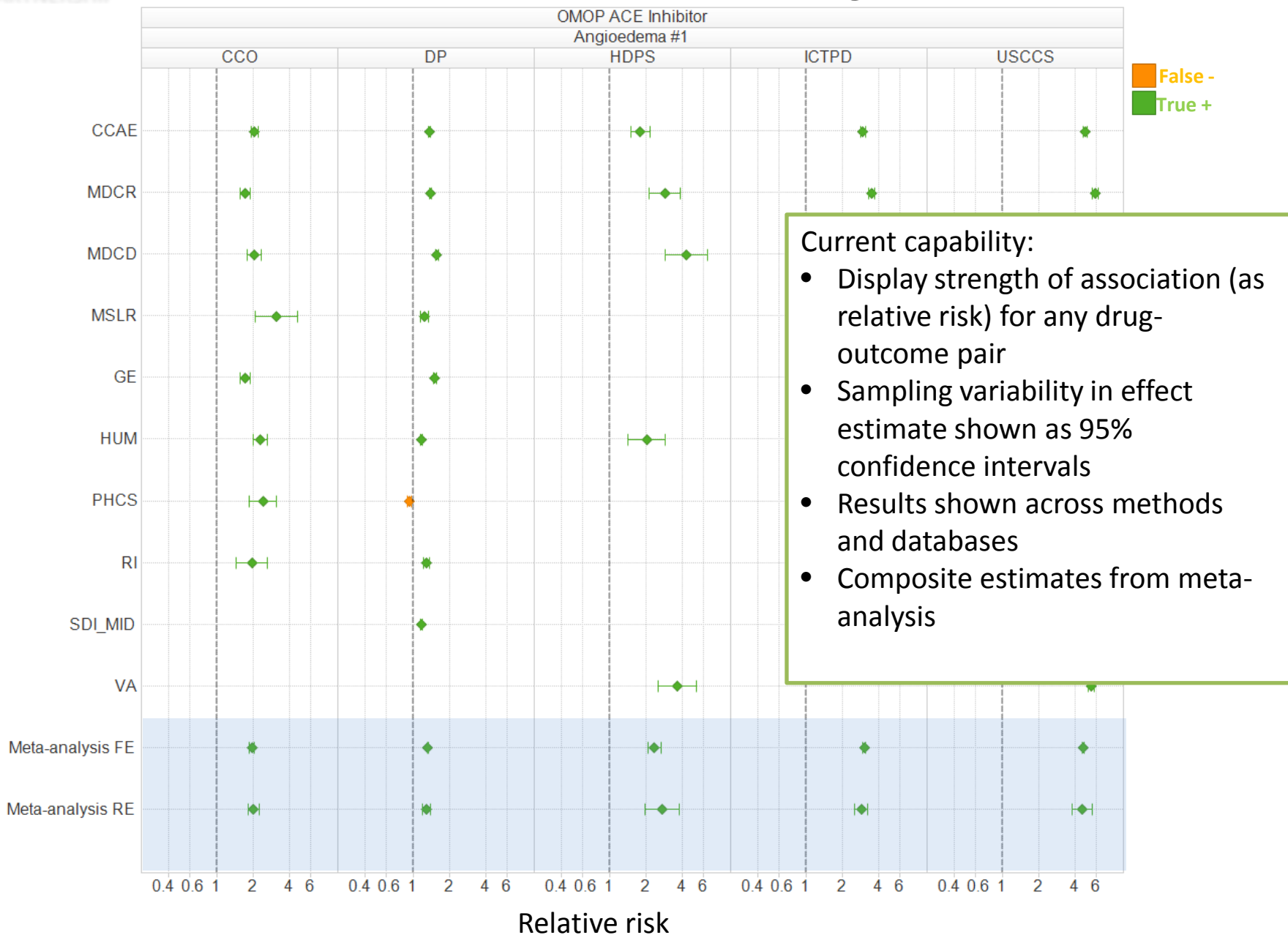


Initial prototype complete with two examples:

- **ACE inhibitors – Angioedema**
- **Antibiotics – Acute renal failure**

Strength of association: Ex 1: ACE inhibitor - Angioedema

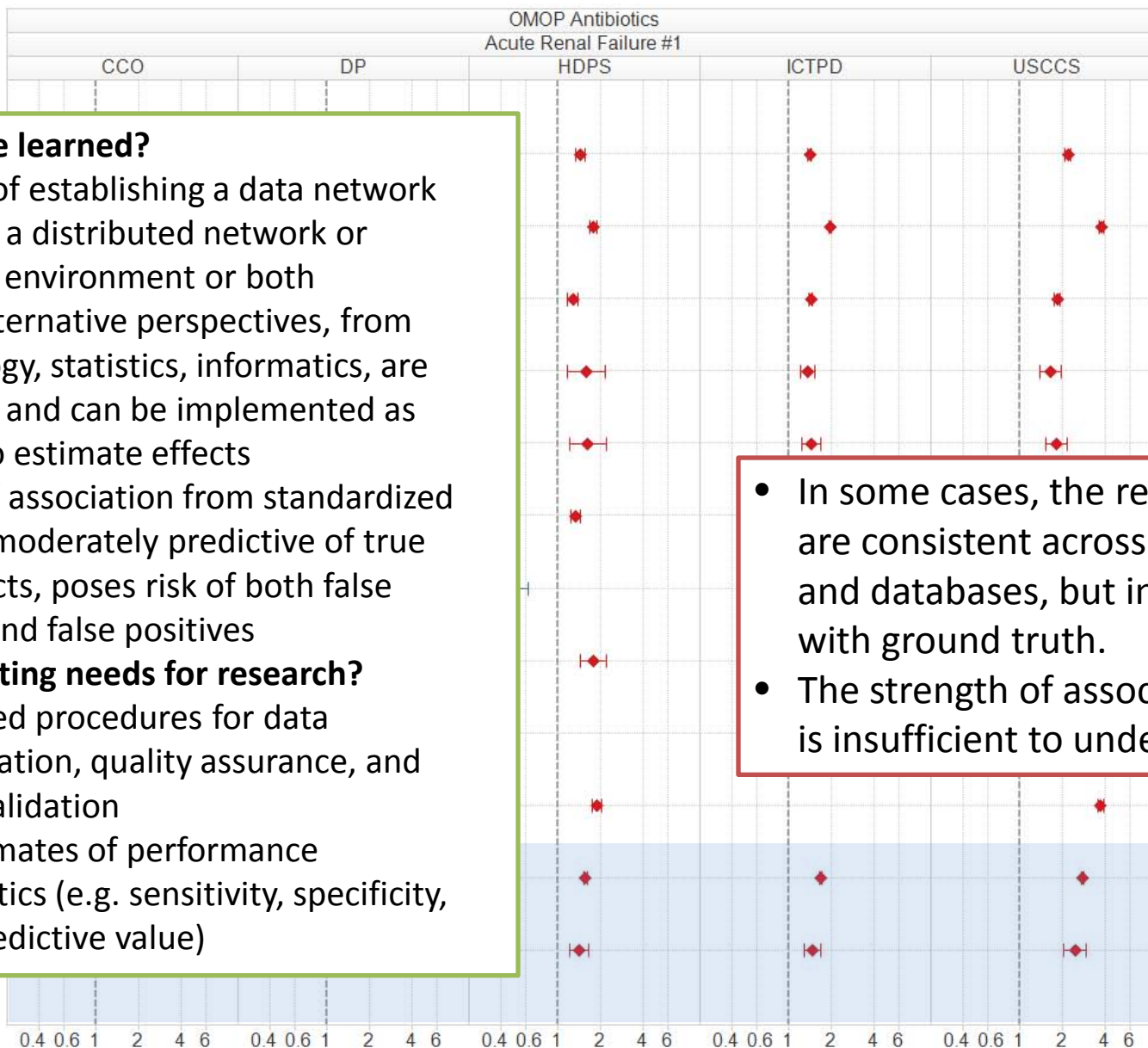
Data source



Current capability:

- Display strength of association (as relative risk) for any drug-outcome pair
- Sampling variability in effect estimate shown as 95% confidence intervals
- Results shown across methods and databases
- Composite estimates from meta-analysis

Strength of association: Ex 2: Antibiotics – Acute Renal Failure



What have we learned?

- Feasibility of establishing a data network with either a distributed network or centralized environment or both
- Multiple alternative perspectives, from epidemiology, statistics, informatics, are considered and can be implemented as methods to estimate effects
- Strength of association from standardized analysis is moderately predictive of true causal effects, poses risk of both false negatives and false positives

What are existing needs for research?

- Standardized procedures for data characterization, quality assurance, and software validation
- Better estimates of performance characteristics (e.g. sensitivity, specificity, positive predictive value)

- In some cases, the relative risks are consistent across methods and databases, but inconsistent with ground truth.
- The strength of association alone is insufficient to understand why

Observational analyses to support each causal consideration

- Strength of association
- **Consistency**
 - We currently consider four types of consistency:
 1. Consistency across different databases (including measures of heterogeneity)
 2. Consistency across different methods
 3. Consistency across parameters within method
 4. Consistency across different HOI definitions

- Specificity
- Temporality
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Initial prototype complete with two examples:

- **ACE inhibitors – Angioedema**
- **Antibiotics – Acute renal failure**

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

What have we learned?

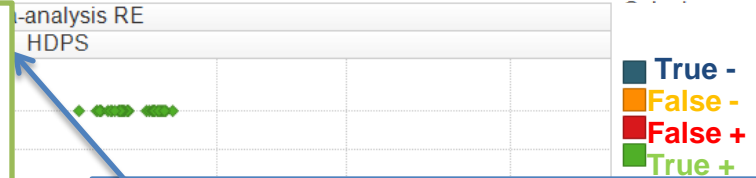
- Effect estimates are highly sensitive to study design decisions
- Substantial heterogeneity in estimates across data sources
- Comparable estimates across alternative standardized vocabularies (ICD9, SNOMED, MedDRA)
- Differential performance by alternative outcome definitions

What are existing needs for research?

- Methods for pooling results across sources
- Systematic process for defining and evaluating HOI definitions
- Explicit rules to map decisions that would be made during custom evaluations into standardized systematic process

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)



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

Relative risk

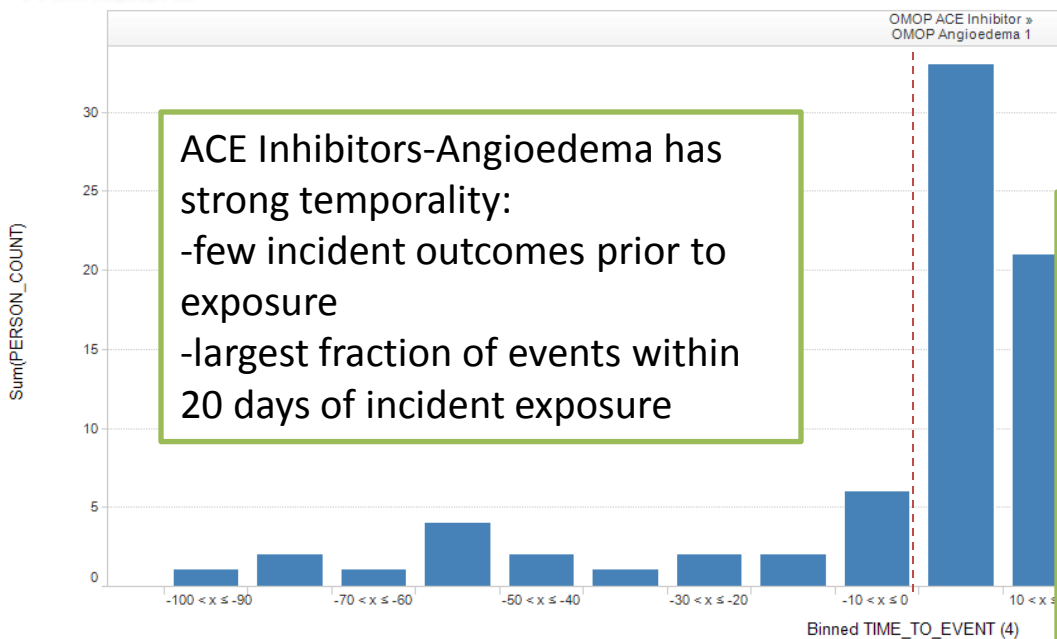
Observational analyses to support each causal consideration

- Strength of association
- Consistency
- Specificity
- **Temporality**
 - Evaluate time-to-event relationship between exposure and outcome
 - High incidence of events prior to exposure may suggest co-occurrence correlation without causal relationship
- Biological gradient
- Plausibility
- Coherence
- Experimental evidence
- Analogy



**Initial prototype complete:
Examples to follow**

Temporality



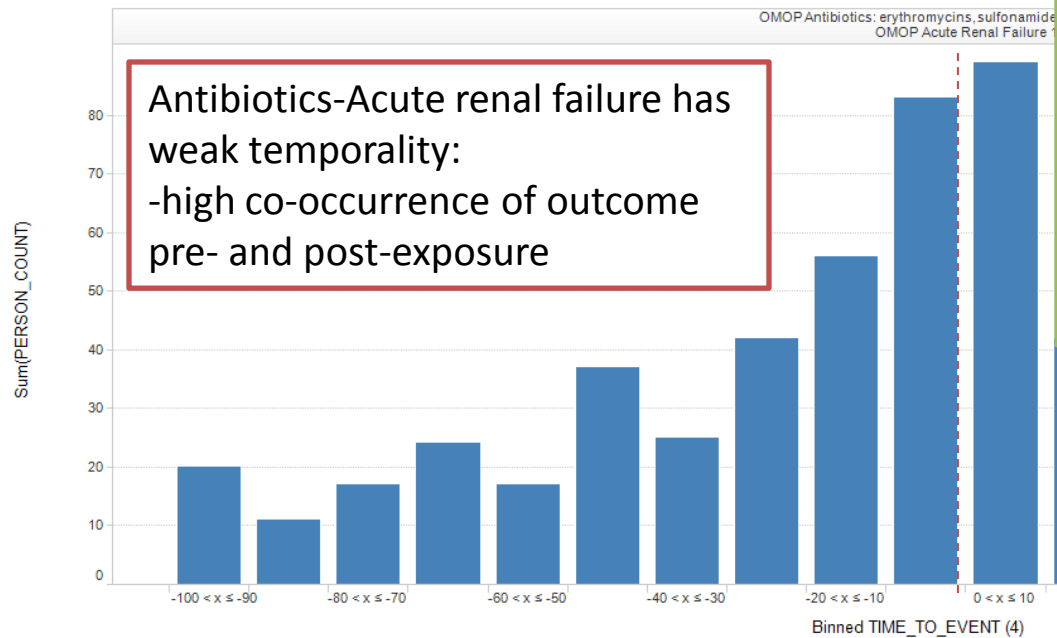
ACE Inhibitors-Angioedema has strong temporality:
-few incident outcomes prior to exposure
-largest fraction of events within 20 days of incident exposure

What have we learned?

- Other aspects of causal framework, beyond strength of association, can be operationalized and do contribute to better understanding of medical product effects

What are existing needs for research?

- Determine what customized analyses need to be implemented within systematic solution
- Standardize quantitative measures for each causal component to minimize subjectivity in assessment



Antibiotics-Acute renal failure has weak temporality:
-high co-occurrence of outcome pre- and post-exposure

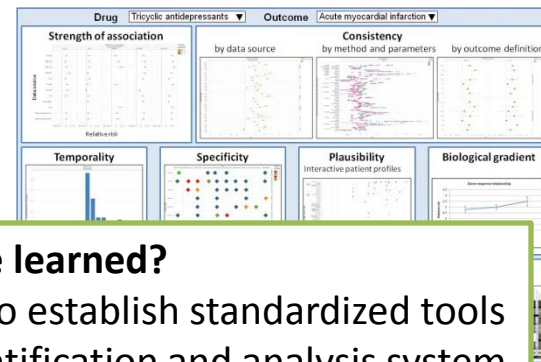
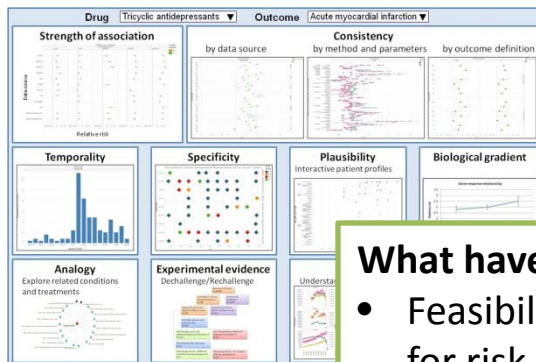
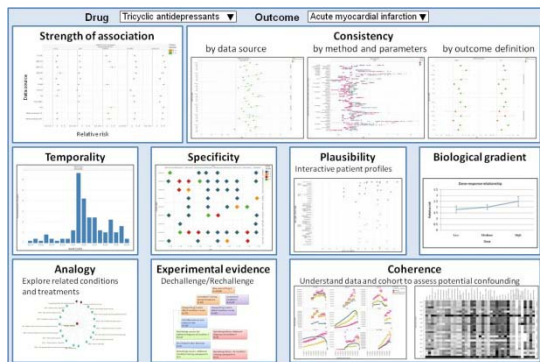
Exploratory framework for studying effects

Unstable angina

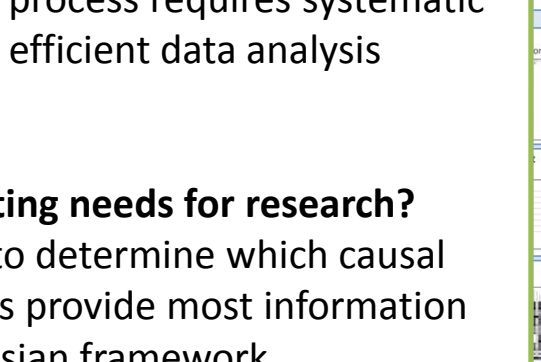
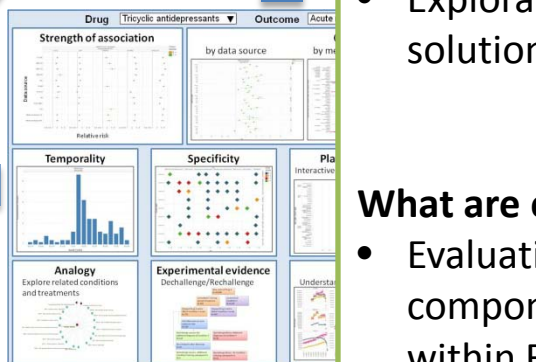
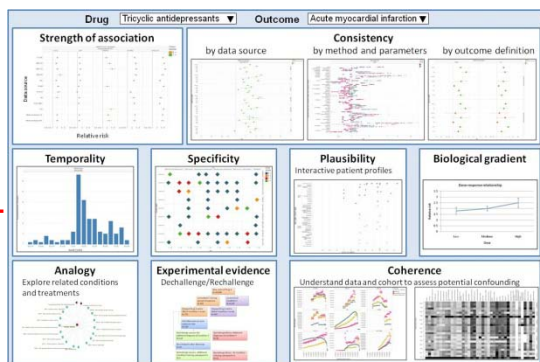
Acute myocardial infarction

Cerebrovascular accident

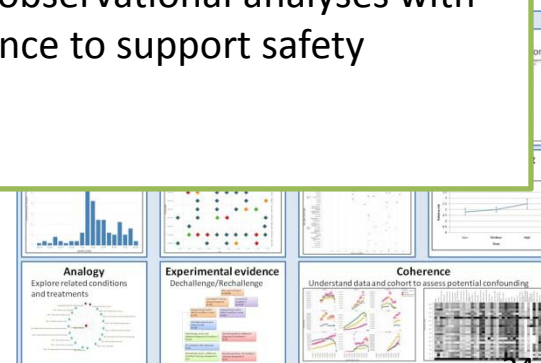
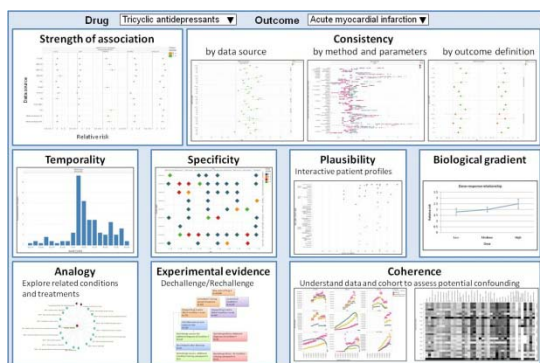
Amitriptyline



Tricyclic antidepressants



SSRIs



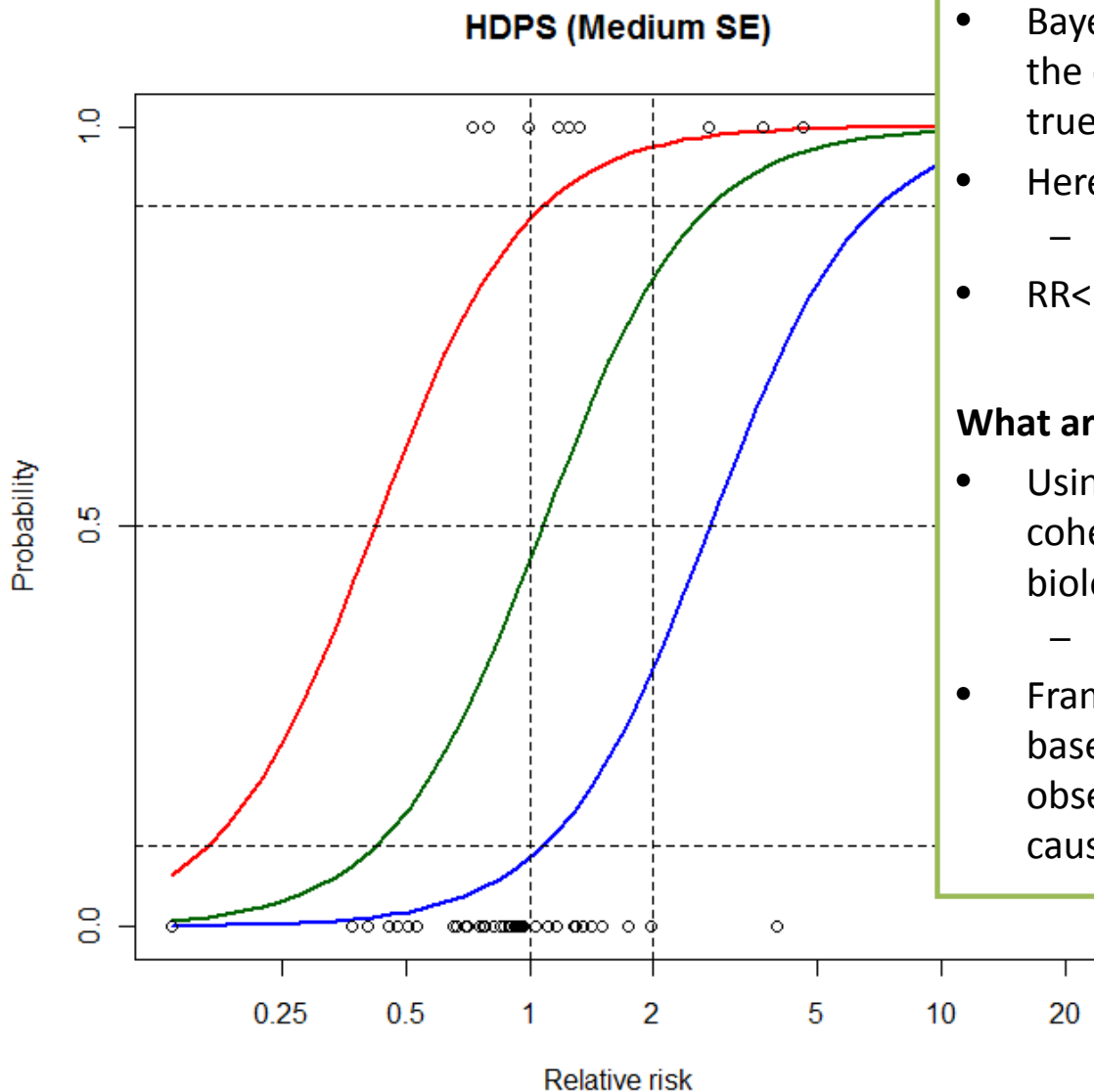
What have we learned?

- Feasibility to establish standardized tools for risk identification and analysis system
- Exploratory process requires systematic solution for efficient data analysis

What are existing needs for research?

- Evaluation to determine which causal components provide most information within Bayesian framework
- Integrating observational analyses with other evidence to support safety assessment

Quantitative framework for studying effects



What has been learned?

- Bayesian framework can answer: ‘in light of the data, what is our revised belief of a true causal effect?’
- Here, $p(\text{true} \mid \text{RR}, \text{SE})$
 - Logistic regression with 2 predictors
- $\text{RR} < 2$ are largely uninformative

What are existing needs for research?

- 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
- Framework rests on confidence in model, based on empirical evidence of how observational analyses correspond to true causal status

— $p=0.1$

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

