



Generating Reliable Evidence from Real-World Data : Lessons from the Observational Health Data Sciences and Informatics

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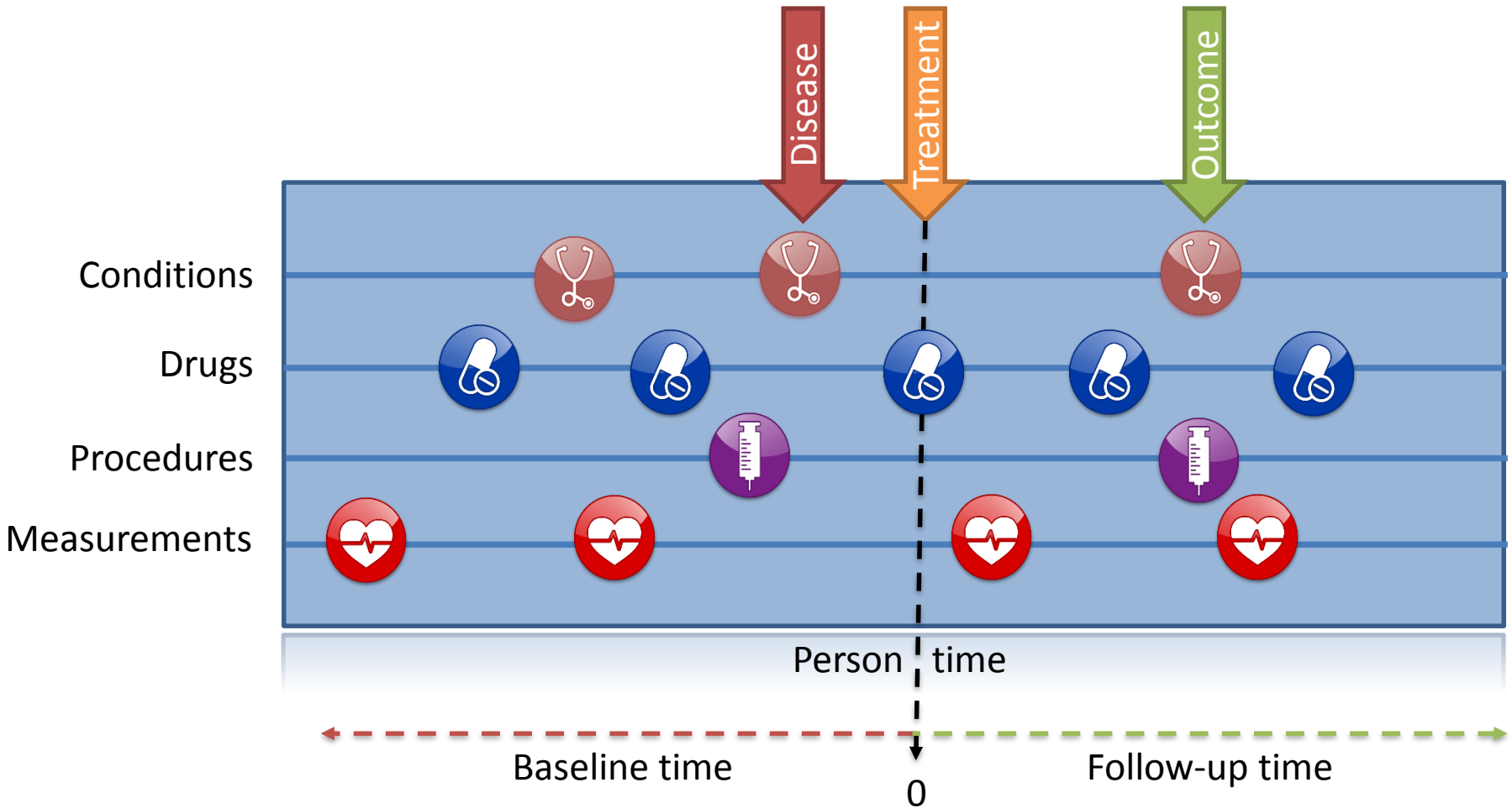


Introducing OHDSI

- 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

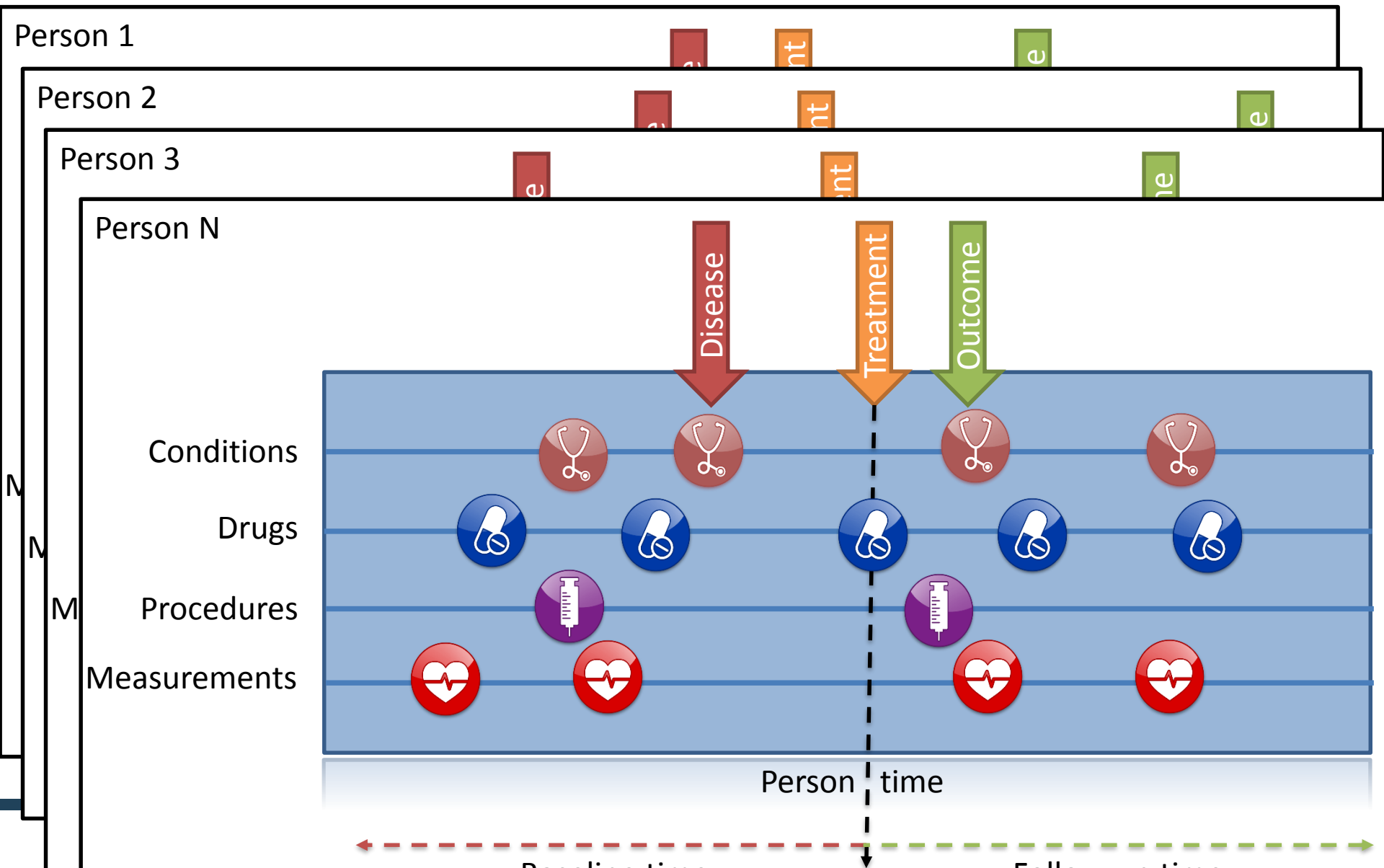


A caricature of the patient journey



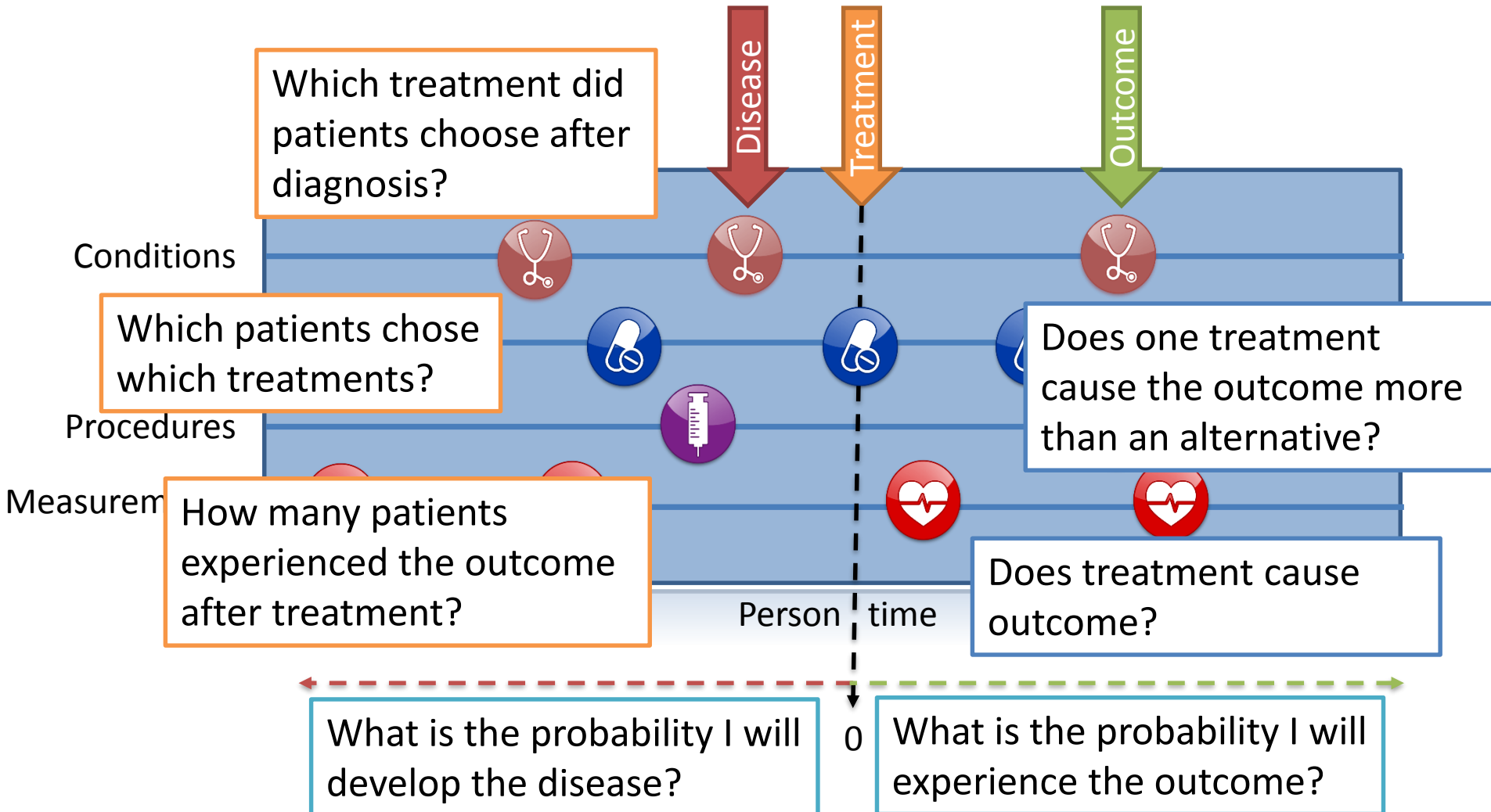


Each observational database is just an (incomplete) compilation of patient journeys





Questions asked across the patient journey



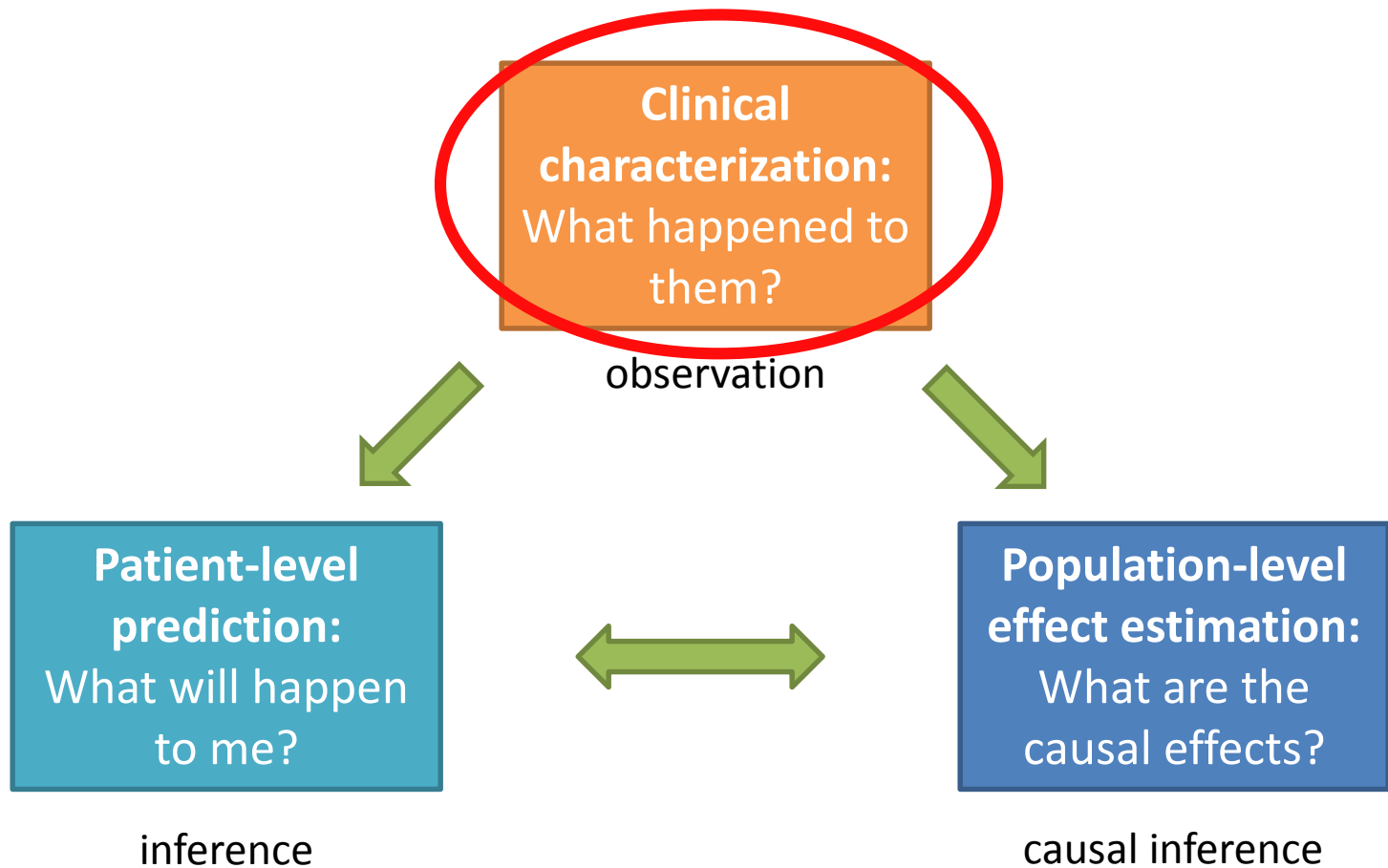


Classifying questions across the patient journey

- **Clinical characterization:** What happened to them?
 - What treatment did they choose after diagnosis?
 - Which patients chose which treatments?
 - How many patients experienced the outcome after treatment?
- **Patient-level prediction:** What will happen to me?
 - What is the probability that I will develop the disease?
 - What is the probability that I will experience the outcome?
- **Population-level effect estimation:** What are the causal effects?
 - Does treatment cause outcome?
 - Does one treatment cause the outcome more than an alternative?



Complementary evidence to inform the patient journey





How *should* patients with major depressive disorder be treated?

Treating Major Depressive Disorder

A Quick Reference Guide



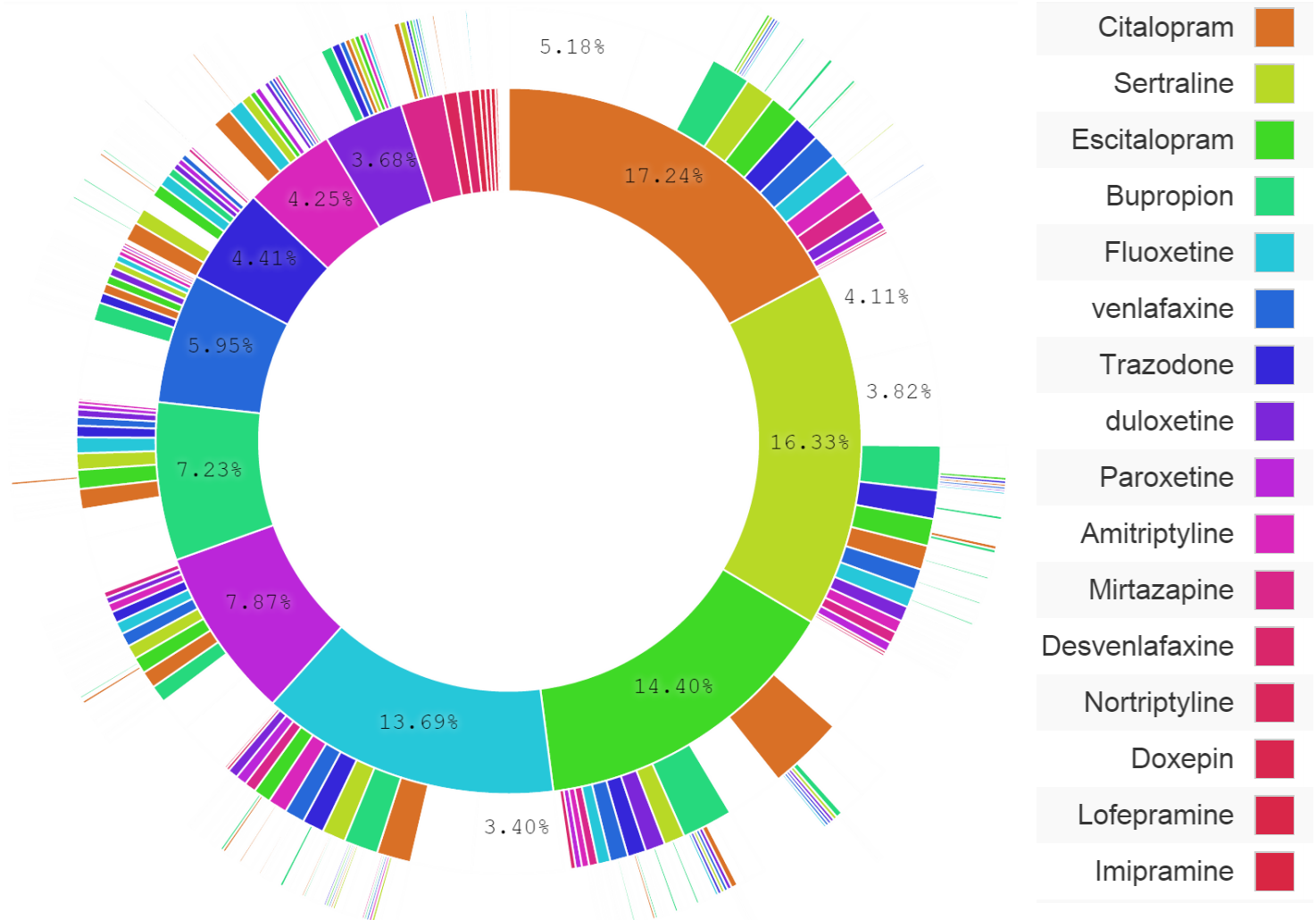
Pharmacotherapy

- The effectiveness of antidepressant medications is generally comparable between and within classes of medications, including selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), bupropion, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Therefore, choose a medication largely based on the following:
 - Patient preference
 - Nature of prior response to medication
 - Safety, tolerability, and anticipated side effects
 - Co-occurring psychiatric or general medical conditions
 - Pharmacological properties of the medication (e.g., half-life, actions on cytochrome P450 enzymes, other drug interactions; consult the full guideline or a current drug database)
 - Cost
- For most patients, a SSRI, a SNRI, mirtazapine, or bupropion is optimal.
- In general, the use of MAOIs should be restricted to patients who do not respond to other treatments.

Based on *Practice Guideline for the Treatment of Patients With Major Depressive Disorder*, Third Edition, originally published in October 2010. A guideline watch, summarizing significant developments in the scientific literature since publication of this guideline, may be available.



How are patients with major depressive disorder *ACTUALLY* treated?

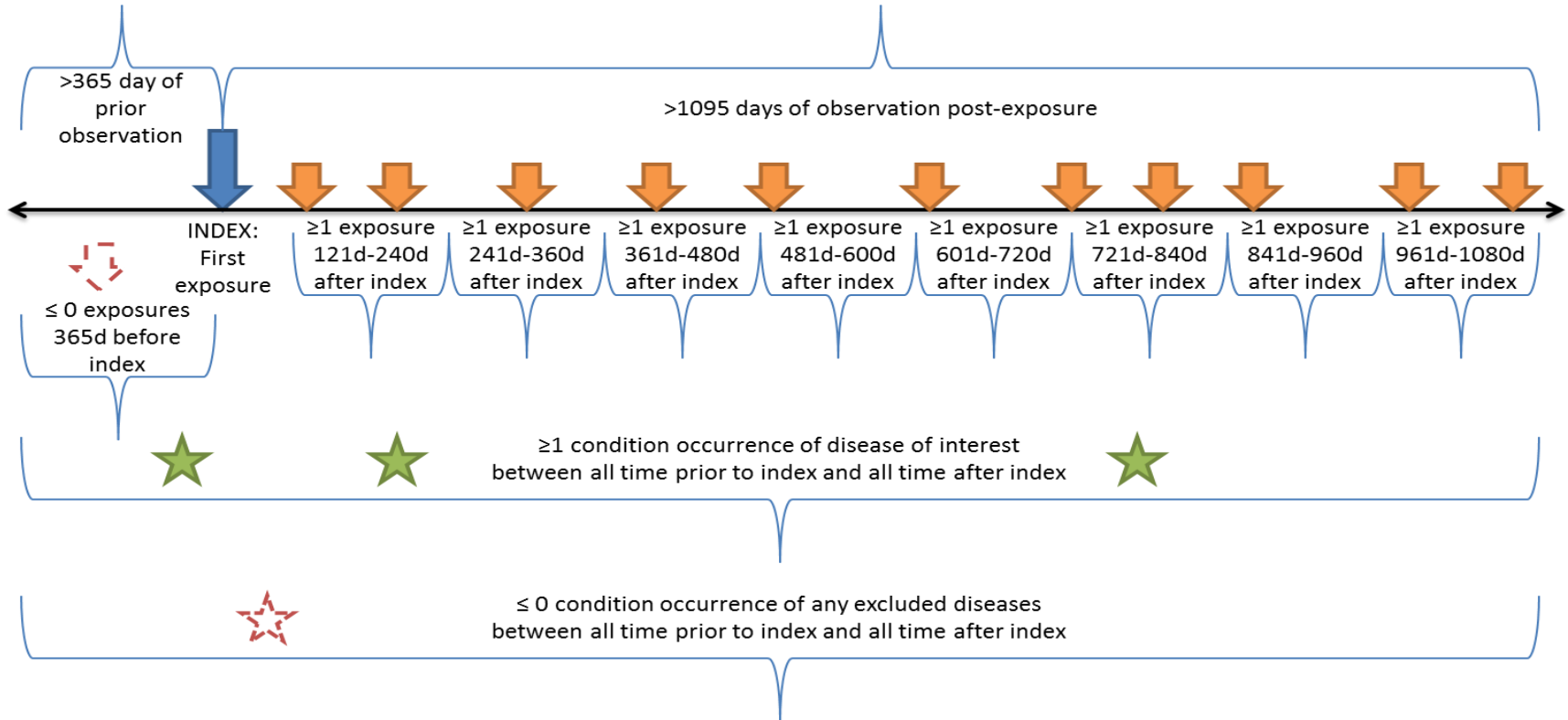




OHDSI participating data partners

Code	Name	Description	Size (M)
AUSOM	Ajou University School of Medicine	South Korea; inpatient hospital EHR	2
CCAE	MarketScan Commercial Claims and Encounters	US private-payer claims	119
CPRD	UK Clinical Practice Research Datalink	UK; EHR from general practice	11
CUMC	Columbia University Medical Center	US; inpatient EHR	4
GE	GE Centricity	US; outpatient EHR	33
INPC	Regenstrief Institute, Indiana Network for Patient Care	US; integrated health exchange	15
JMDC	Japan Medical Data Center	Japan; private-payer claims	3
MDCD	MarketScan Medicaid Multi-State	US; public-payer claims	17
MDCR	MarketScan Medicare Supplemental and Coordination of Benefits	US; private and public-payer claims	9
OPTUM	Optum ClinFormatics	US; private-payer claims	40
STRIDE	Stanford Translational Research Integrated Database Environment	US; inpatient EHR	2
HKU	Hong Kong University	Hong Kong; EHR	1

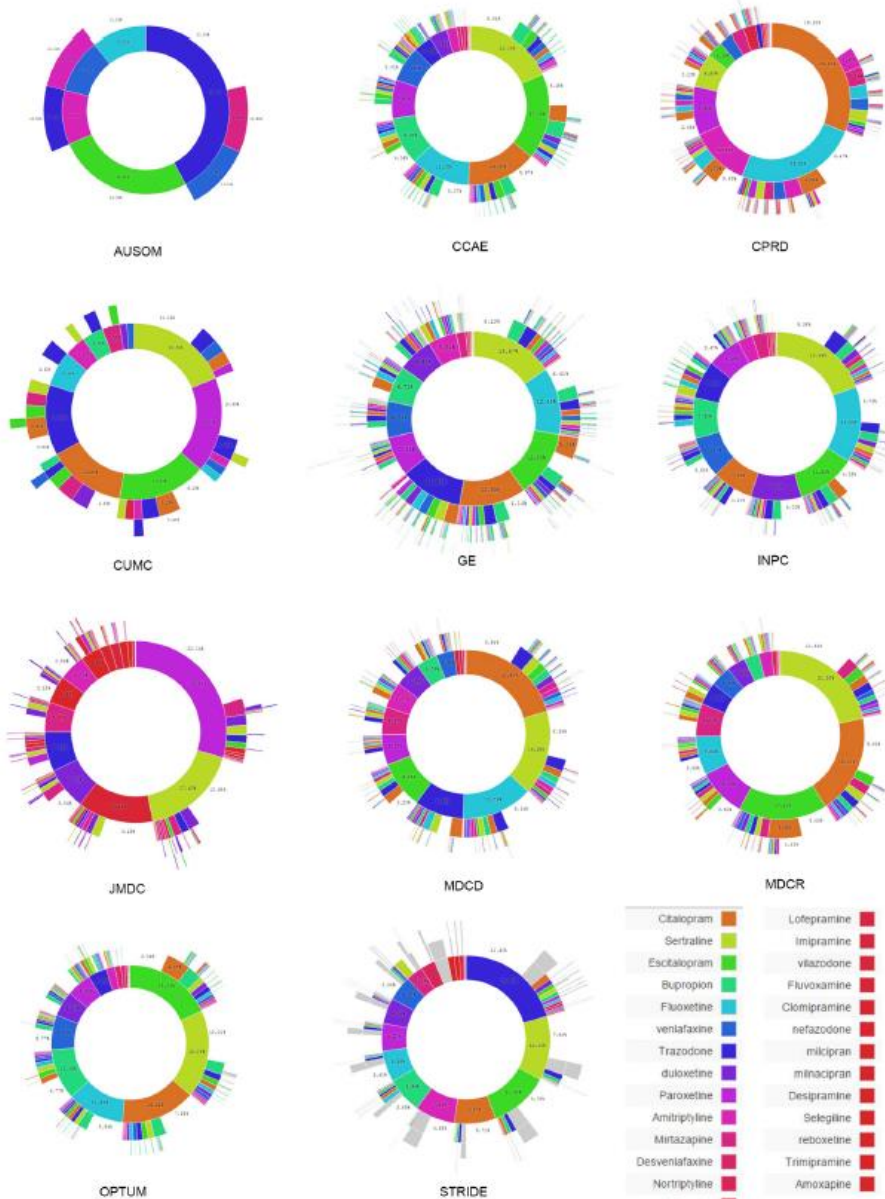
Treatment pathway study design



- >250,000,000 patient records used across OHDSI network
- ≥ 4 years continuous observation
- ≥ 3 years continuous treatment from first treatment
- N=264,841 qualifying patients with depression



How are patients with major depressive disorder ACTUALLY treated?



- Substantial variation in treatment practice across data sources, health systems, geographies, and over time
- Consistent heterogeneity in treatment choice as no source showed one preferred first-line treatment
- 11% of depressed patients followed a treatment pathway that was shared with no one else in any of the databases

Hripcsak et al, PNAS, 2016



Use case: Using real-world experience to inform clinical trial design

- Observational data can be used for clinical trial feasibility, evaluating the impact of inclusion criteria on study recruitment
- Proactively identifying restrictive criteria can allow for changing design prior to costly protocol amendments, or simply having context to be prepared for recruitment challenges
- Understanding trial feasibility also sheds light on the generalizability of your RCT to the real-world population



39 studies found for: [Interventional Studies](#) | [depression](#) | [sertraline](#) | [Phase 3](#)

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Only show open studies

Rank **Status** **Study**

1 **Completed** [Sertraline Compared With Hypericum Perforatum \(St.John's Wort\) in Treating Depression](#)
Conditions: Depression; Unspecified Adult Solid Tumor, Protocol Specific
Interventions: Drug: Zoloft 50 mg; Dietary Supplement: St. John's Wort 600 mg

2 **Completed** [Sertraline for the Prevention of Recurrent Postpartum Depression](#)
Condition: Depression
Intervention: Drug: Sertraline

3 **Completed**
Has
Results [Quetiapine XR Versus Sertraline in Acute Bipolar Depression as add-on Therapy](#)
Conditions: Bipolar Disorder; Bipolar Depression
Interventions: Drug: Extended release quetiapine (quetiapine XR); Drug: Sertraline;
Drug: adequate mood stabilizer

4 **Completed** [A Randomised Trial of Sertraline, Cognitive Behaviour Therapy & Combined Therapy for Postnatal Depression](#)
Conditions: Depression; Anxiety
Interventions: Drug: Sertraline; Behavioral: Cognitive Behavioural Therapy

5 **Completed** [Bipolar II Depression: Lithium, SSRI, or the Combination](#)
Conditions: Bipolar Disorder; Depression
Interventions: Drug: Sertraline; Drug: Lithium carbonate

6 **Terminated** [Depression and Health Outcomes in Refractory Epilepsy](#)
Conditions: Depression; Epilepsy
Interventions: Drug: sertraline; Behavioral: cognitive behavior therapy

7 **Recruiting** [A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients With Depression \(ASCEND\)](#)
Conditions: Depression; End Stage Renal Disease
Interventions: Behavioral: Engagement Interview; Behavioral: Cognitive Behavioral Therapy;
Drug: Antidepressant Drug Therapy

Try our beta test site

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► Eligibility

Home > Find Studies >

Ages Eligible for Study: 21 Years and older (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Age \geq 21 years;
2. Undergoing thrice-weekly maintenance HD for \geq 3 months;
3. Able to speak either English or Spanish;
4. BDI-II score \geq 15; and
5. Meets diagnostic criteria for either current major depressive episode or dysthymia on the MINI.

Exclusion Criteria:

1. Active suicidal intent;
2. Ongoing psychotherapy or current treatment with certain anti-depressant drugs;
3. Evidence of cognitive impairment on Mini-Cog;
4. Present or past psychosis or bipolar disorder I or II on the MINI;
5. Alcohol or substance abuse diagnosed on the MINI or history of such abuse in the past three months;
6. Life expectancy $<$ 3 months, in the judgment of the site principal investigator;
7. Anticipated to receive living related donor kidney transplantation within 3 months;
8. Pregnancy, or lactation, or women of childbearing age not willing to use adequate birth control;
9. Clinical and/or laboratory evidence of chronic liver disease;
10. History of significant active bleeding in the past three months, such as hospitalization for gastrointestinal bleeding;
11. Current use of class I anti-arrhythmic medications (e.g., propafenone, flecainide), pimozide, monoamine oxidase inhibitors, wort; and
12. Known hypersensitivity to sertraline.

A Trial of Sertraline

This study is current

Verified May 2016 by Ur

Sponsor:

University of Washin

Collaborators:

University of Texas
University of New Mex
Patient-Centered Outc

Information provided b

Rajnish Mehrotra, Univ

- Home
- Data Sources
- Vocabulary
- Concept Sets
- Cohorts
- Incidence Rates
- Profiles
- Estimation
- Jobs
- Configuration
- Feedback

Cohort

RCT feasibility for "A Trial of Sertraline vs. CBT for End-stage Renal Disease Patients With Dep

Save Close Copy

- Definition
- Concept Sets
- Generation
- Reporting
- Explore
- Export

Cohort definition: A cohort is defined as the set of persons satisfying one or more inclusion criteria for a duration of time. One person may qualify for one cohort multiple times during non-overlapping time intervals. Cohorts are constructed in ATLAS by specifying cohort entry criteria and cohort exit criteria. Cohort entry criteria involve selecting one or more initial events, which determine the start date for cohort entry, and optionally specifying additional inclusion criteria which filter to the qualifying events. Cohort exit criteria are applied to each cohort entry record to determine the end date when the person's episode no longer qualifies for the cohort.

NCT02358343

- All
- Cohort Entry Criteria
- Cohort Exit Criteria

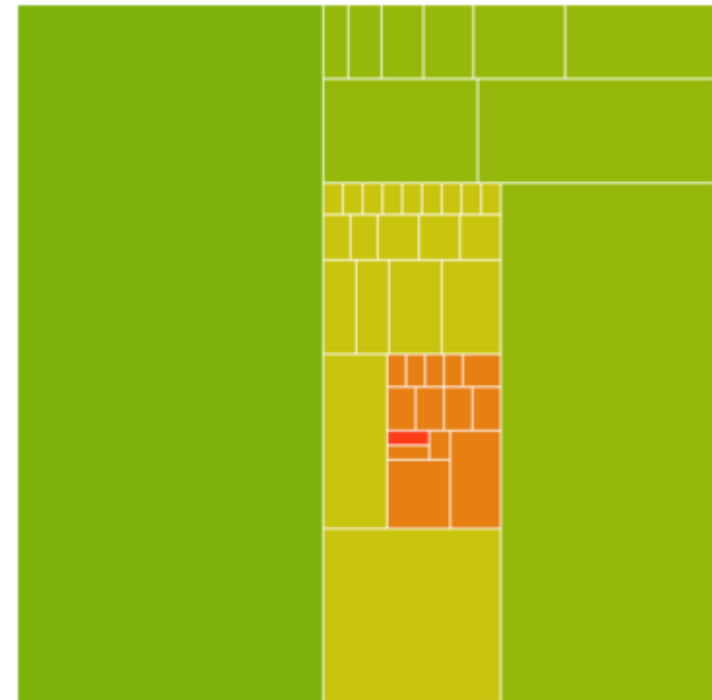
Initial event cohort: Events are recorded time-stamped observations for the persons, such as drug exposures, conditions, procedures, measurements and visits. All events have a start date and end date, though some events may have a start date and end date with the same value (such as procedures or

Inclusion Report for Truven MDCCD

	Match Rate	Matches	Total
Summary Statistics:	43.84%	345	787
Inclusion Rule	N	% Satisfied	% To-Gain
1. Age >= 21 yo	778	98.86%	0.51%
2. No active suicidal intent	762	96.82%	0.76%
3. No ongoing psychotherapy	740	94.03%	2.29%
4. No present or past psychosis of bipolar disease	485	61.63%	22.87%
5. No alcohol or substance abuse in the past 3 months	746	94.79%	1.40%
6. No kidney transplantation	771	97.97%	0.64%
7. No pregnancy	784	99.62%	0.38%
8. No clinical evidence of chronic liver disease	658	83.61%	5.08%
9. No significant active bleeding in the past three months, such as hospitalization for gastrointestinal bleeding	732	93.01%	3.30%

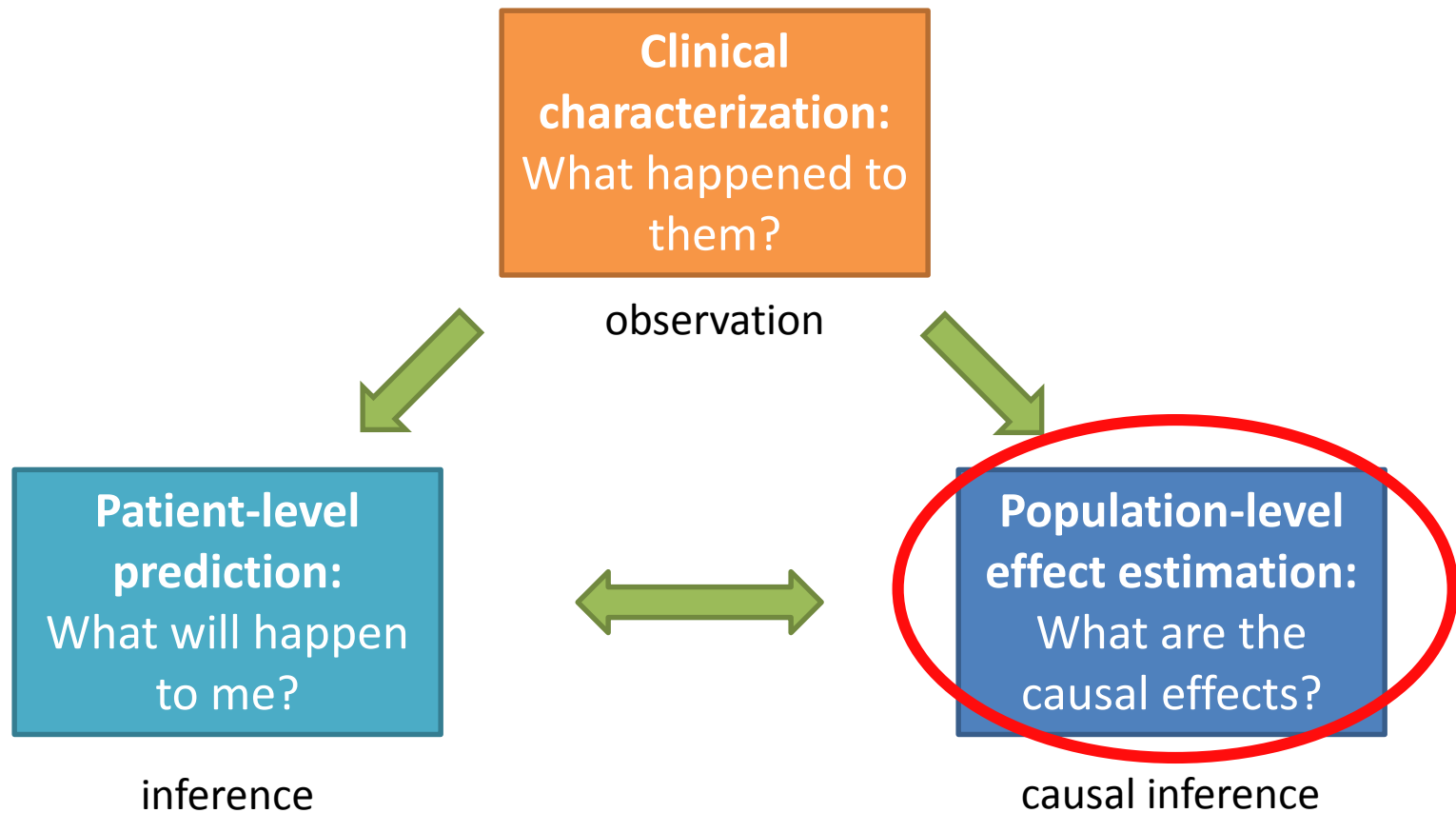
Population Visualization

[Switch to attrition view](#)





Complementary evidence to inform the patient journey





Comparison of the Effects of Serotonin-Norepinephrine Reuptake Inhibitors Versus Selective Serotonin Reuptake Inhibitors on Cerebrovascular Events

Yen-Chieh Lee, MD^{a,†}; Chin-Hsien Lin, MD, PhD^{b,†}; Min-Shung Lin, MD^a;
Yun Lu, MSc^c; Chia-Hsueh Chang, MD, ScD^{c,d,*}; and Jou-Wei Lin, MD, PhD^e

ABSTRACT

Background: Use of selective serotonin reuptake inhibitors (SSRIs) has been associated with an increased risk of intracranial hemorrhage. However, little is known about cerebrovascular risk in users of serotonin-norepinephrine reuptake inhibitors (SNRIs). Our aim was to determine the differential risk of cerebrovascular events between SSRIs and SNRIs.

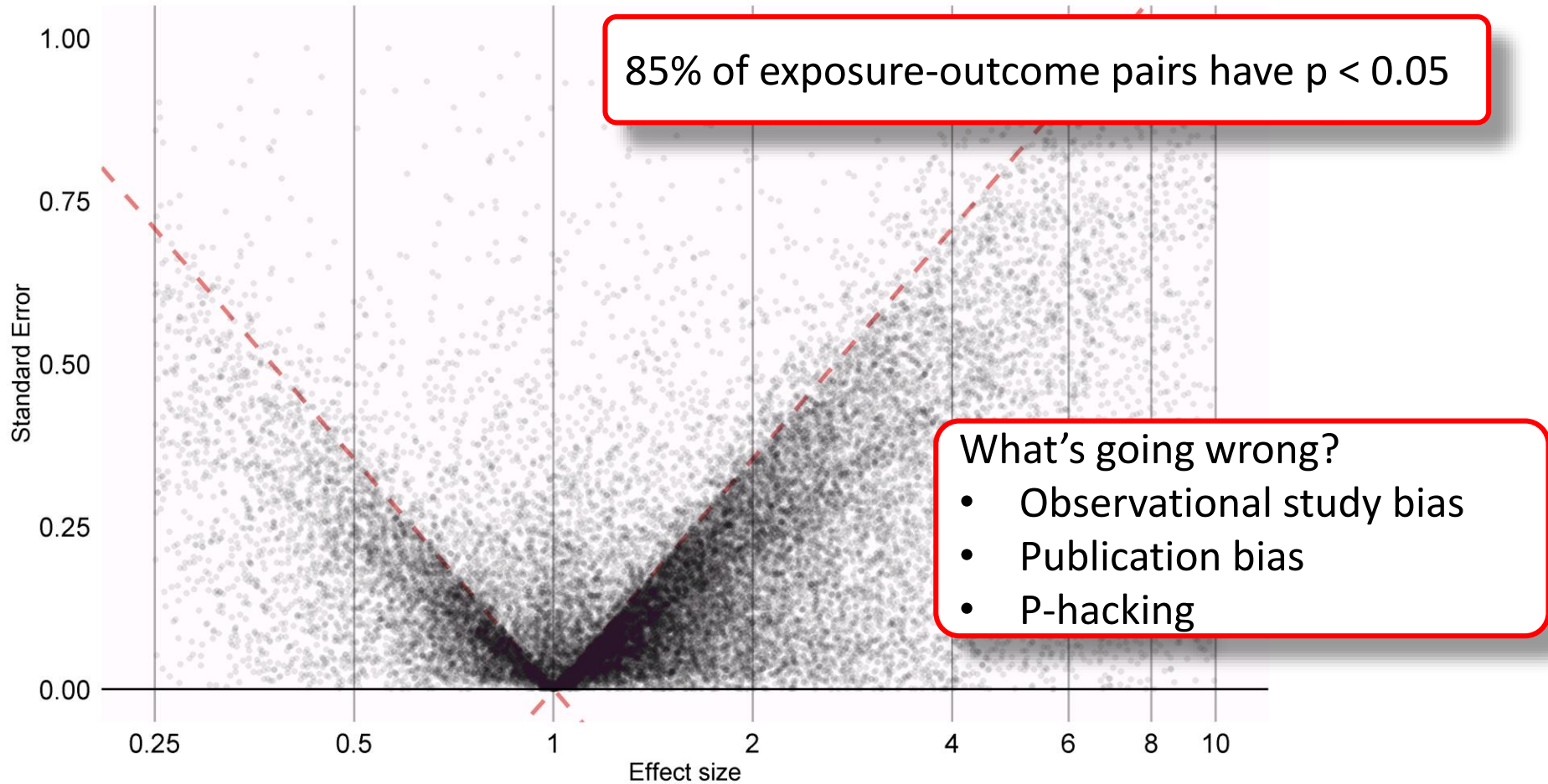
Method: A nationwide population-based cohort study was conducted in adult patients who started taking SSRIs or SNRIs during the time period 2005 through 2009. The outcome of interest was defined by the first hospitalization diagnosis for ischemic stroke (ICD-9-CM codes 433, 434, 436) or intracranial hemorrhage (ICD-9-CM codes 430, 431, 432). We used a Cox regression model with time-varying medication use and adjusted for stroke risk factors to estimate the hazard ratios (HRs) of ischemic stroke and intracranial hemorrhage associated with SNRI use, using SSRI use as a reference.

Results: Among 582,650 SSRI and 76,920 SNRI initiators with an average follow-up period of 3.2 years, there was a nonsignificantly increased trend toward intracranial hemorrhage (adjusted HR=1.24 [95% CI, 0.97–1.58]) in SNRI users compared to SSRI users. The risk of ischemic stroke was comparable between the 2 treatment groups (adjusted HR=1.01 [0.90–1.12]). Similar results were obtained in sensitivity analyses, considering a dose-response relation, allowance of a 7-day grace period between study drug discontinuation and outcome occurrence, and restriction to exclusive users, who remained on the initial treatment. In the subgroup analysis, there was an increased incidence of intracranial hemorrhages in SNRI users compared to SSRI users in patients without prior depression (adjusted HR=1.63 [1.14–2.32]).

Conclusions: Use of SNRIs is not associated with an increased risk of either ischemic stroke or intracranial hemorrhage as compared to use of SSRIs in adult patients with depression or anxiety. However, SNRIs should be used cautiously in patients without depression.

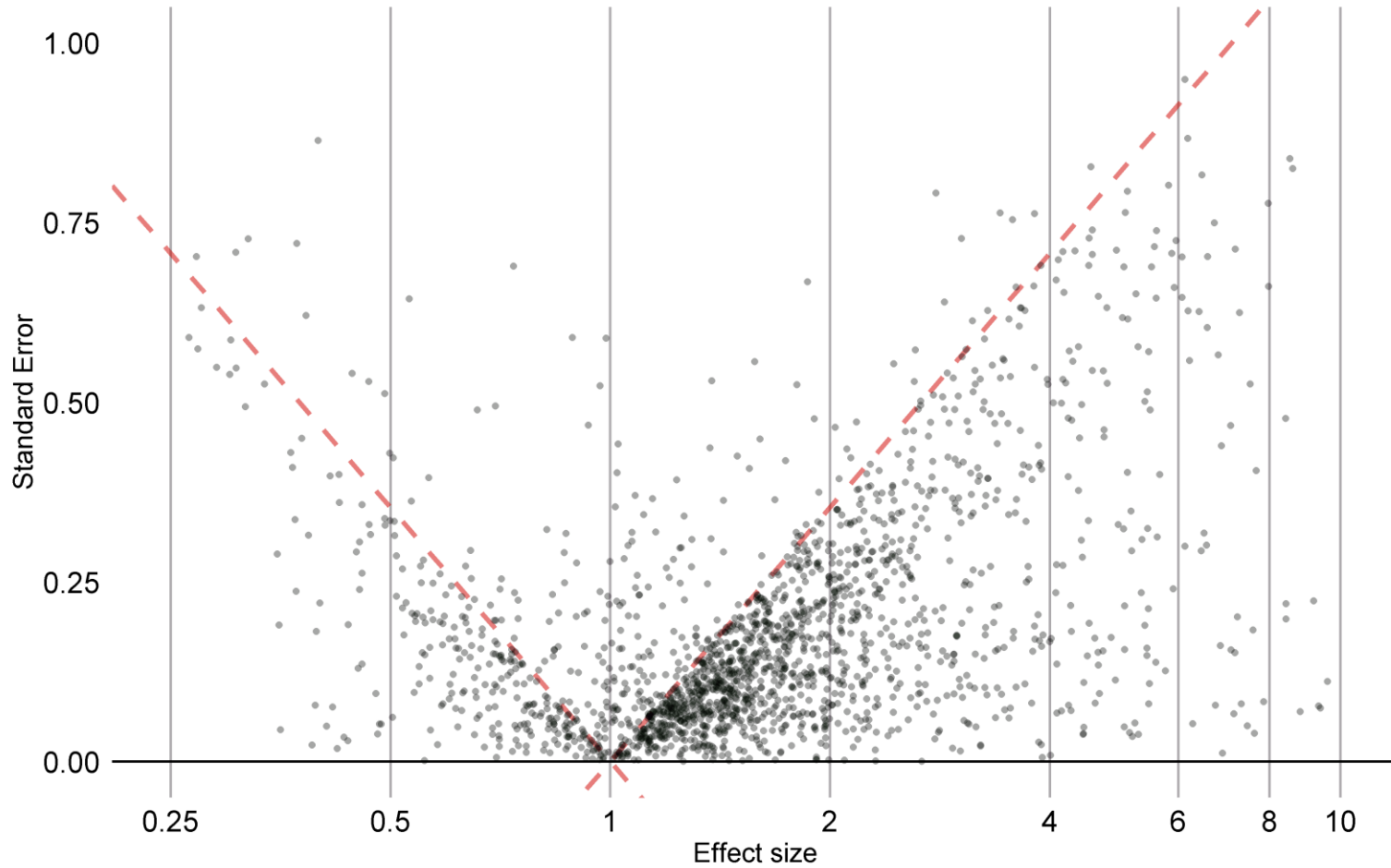


Observational research results in literature





Observational research in depression





What if we considered all outcomes?

Duloxetine vs. Sertraline for these 22 outcomes:

Acute liver injury	Hypotension
Acute myocardial infarction	Hypothyroidism
Alopecia	Insomnia
Constipation	Nausea
Decreased libido	Open-angle glaucoma
Delirium	Seizure
Diarrhea	Stroke
Fracture	Suicide and suicidal ideation
Gastrointestinal hemorrhage	Tinnitus
Hyperprolactinemia	Ventricular arrhythmia and sudden cardiac death
Hyponatremia	Vertigo



What if we consider all treatments?

Type	Class	Treatment
Drug	Atypical	Bupropion
Drug	Atypical	Mirtazapine
Procedure	ECT	Electroconvulsive therapy
Procedure	Psychotherapy	Psychotherapy
Drug	SARI	Trazodone
Drug	SNRI	Desvenlafaxine
Drug	SNRI	duloxetine
Drug	SNRI	venlafaxine
Drug	SSRI	Citalopram
Drug	SSRI	Escitalopram
Drug	SSRI	Fluoxetine
Drug	SSRI	Paroxetine
Drug	SSRI	Sertraline
Drug	SSRI	vilazodone
Drug	TCA	Amitriptyline
Drug	TCA	Doxepin
Drug	TCA	Nortriptyline



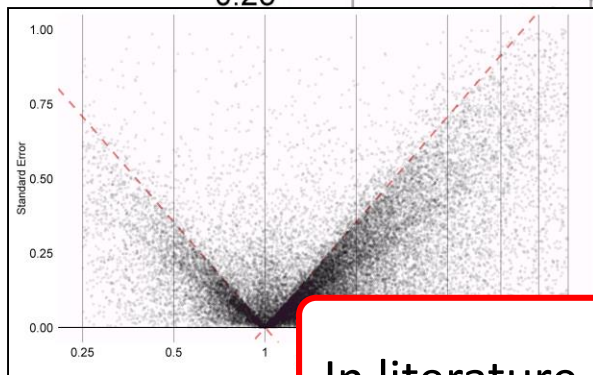
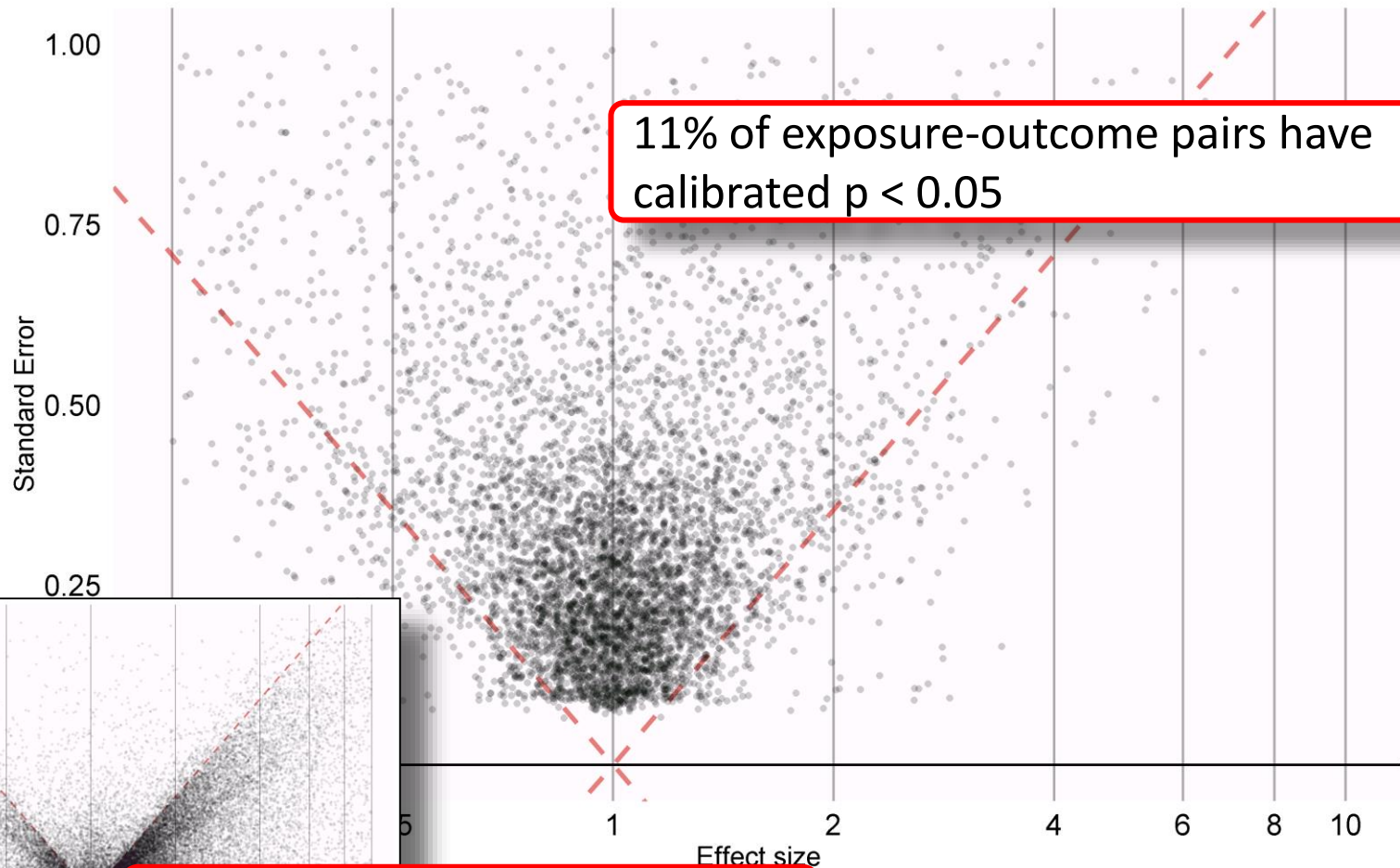
Large-scale estimation for depression

- **17 treatments**
- $17 * 16 = 272$ comparisons
- **22 outcomes**
- $272 * 22 = 5,984$ effect size estimates
- **4 databases** so far (Truven CCAE, Truven MDCCD, Truven MDCCR, Optum)
- $4 * 5,984 = \mathbf{23,936}$ estimates

NOT DATA MINING - Each analysis following best practice in causal inference



Estimates are in line with expectations



In literature, 85% have $p < 0.05$



How well can we do?



Comparative Benefits and Harms of Second-Generation Antidepressants for Treating Major Depressive Disorder

An Updated Meta-analysis

Gerald Gartlehner, MD, MPH; Richard A. Hansen, PhD, RPh; Laura C. Morgan, MA; Kylie Thaler, MD, MPH; Linda Lux, MPA; Megan Van Noord, MSIS; Ursula Mager, PhD, MPH; Patricia Thieda, MA; Bradley N. Gaynes, MD, MPH; Tania Wilkins, MSc; Michaela Strobelberger, MA; Stacey Lloyd, MPH; Ursula Reichenpfader, MD, MPH; and Kathleen N. Lohr, PhD

Background: Second-generation antidepressants dominate the management of major depressive disorder (MDD), but evidence on the comparative benefits and harms of these agents is contradictory.

Purpose: To compare the benefits and harms of second-generation antidepressants for treating MDD in adults.

Data Sources: English-language studies from PubMed, Embase, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts from 1980 to August 2011 and reference lists of pertinent review articles and gray literature.

Study Selection: 2 independent reviewers identified randomized trials of at least 6 weeks' duration to evaluate efficacy and observational studies with at least 1000 participants to assess harm.

Data Extraction: Reviewers abstracted data about study design and conduct, participants, and interventions and outcomes and rated study quality. A senior reviewer checked and confirmed extracted data and quality ratings.

Data Synthesis: Meta-analyses and mixed-treatment comparisons of response to treatment and weighted mean differences were

conducted on specific scales to rate depression. On the basis of 234 studies, no clinically relevant differences in efficacy or effectiveness were detected for the treatment of acute, continuation, and maintenance phases of MDD. No differences in efficacy were seen in patients with accompanying symptoms or in subgroups based on age, sex, ethnicity, or comorbid conditions. Individual drugs differed in onset of action, adverse events, and some measures of health-related quality of life.

Limitations: Most trials were conducted in highly selected populations. Publication bias might affect the estimates of some comparisons. Mixed-treatment comparisons cannot conclusively exclude differences in efficacy. Evidence within subgroups was limited.

Conclusion: Current evidence does not warrant recommending a particular second-generation antidepressant on the basis of differences in efficacy. Differences in onset of action and adverse events may be considered when choosing a medication.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2011;155:772-785.

For author affiliations, see end of text.

www.annals.org

Table 3. Comparative Adverse Events: Findings and Strength of Evidence

Outcome	Strength of Evidence*	Comparative Risk for Harms
General tolerability		
Adverse events profiles	High	Adverse events profiles are similar among second-generation antidepressants. Differences exist in the incidence of specific adverse events.
Nausea and vomiting	High	Meta-analysis of 15 fair-quality studies indicates that venlafaxine has a higher rate of nausea and vomiting than SSRIs as a class.
Diarrhea	Moderate	Evidence from multiple fair-quality studies indicates that sertraline has a higher incidence of diarrhea than bupropion, citalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, and venlafaxine.
Weight change	Moderate	Seven fair-quality trials indicate that mirtazapine causes greater weight gain than citalopram, fluoxetine, paroxetine, and sertraline.
Somnolence	Moderate	Six fair-quality studies provide evidence that trazodone has a higher rate of somnolence than bupropion, fluoxetine, mirtazapine, paroxetine, and venlafaxine.
The discontinuation syndrome	Moderate	A good-quality systematic review provides evidence that paroxetine and venlafaxine have the highest rates of the discontinuation syndrome; fluoxetine has the lowest.
Discontinuation rates	High	Meta-analyses of efficacy trials indicate that overall discontinuation rates are similar among second-generation antidepressants. Venlafaxine has a higher rate of discontinuation due to and a lower rate of discontinuation due to lack of efficacy than SSRIs as a class.
Serious adverse events		
Suicidality	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for suicidality.
Sexual adverse events	High	Five fair-quality trials and a pooled analysis of 2 identical randomized, controlled trials provide evidence that bupropion causes significantly less sexual dysfunction than escitalopram, fluoxetine, paroxetine, and sertraline.
Cardiovascular adverse events	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for cardiovascular adverse events. Insufficient evidence indicates that venlafaxine might cause an increased risk for cardiovascular adverse events.
Hyponatremia	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for hyponatremia.
Seizures	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for seizures. Insufficient evidence indicates that bupropion might increase risk for seizures.
Hepatotoxicity	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for hepatotoxicity. Insufficient evidence indicates that nefazodone might have an increased risk for hepatotoxicity.
The serotonin syndrome	Insufficient	Evidence from existing studies is insufficient to draw conclusions about the comparative risk for the serotonin syndrome. Observational studies indicate no differences in risk among second-generation antidepressants.

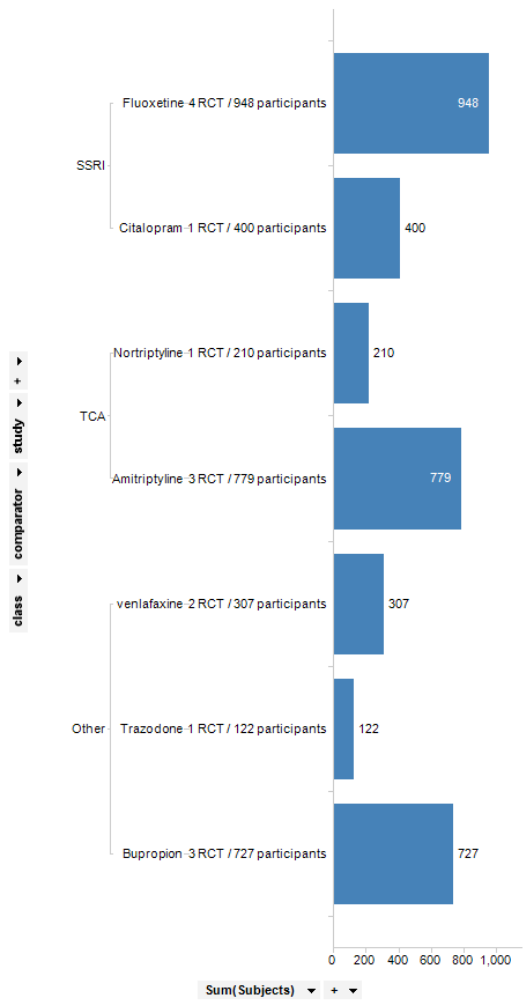
SSRI = selective serotonin reuptake inhibitor.

* High strength of evidence indicates high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. Moderate strength of evidence indicates that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. Low strength of evidence indicates that the evidence reflects the true effect. Further research is likely to change both the confidence in the estimate of effect and the estimate. Insufficient strength of evidence indicates that evidence is either unavailable or does not permit a conclusion.

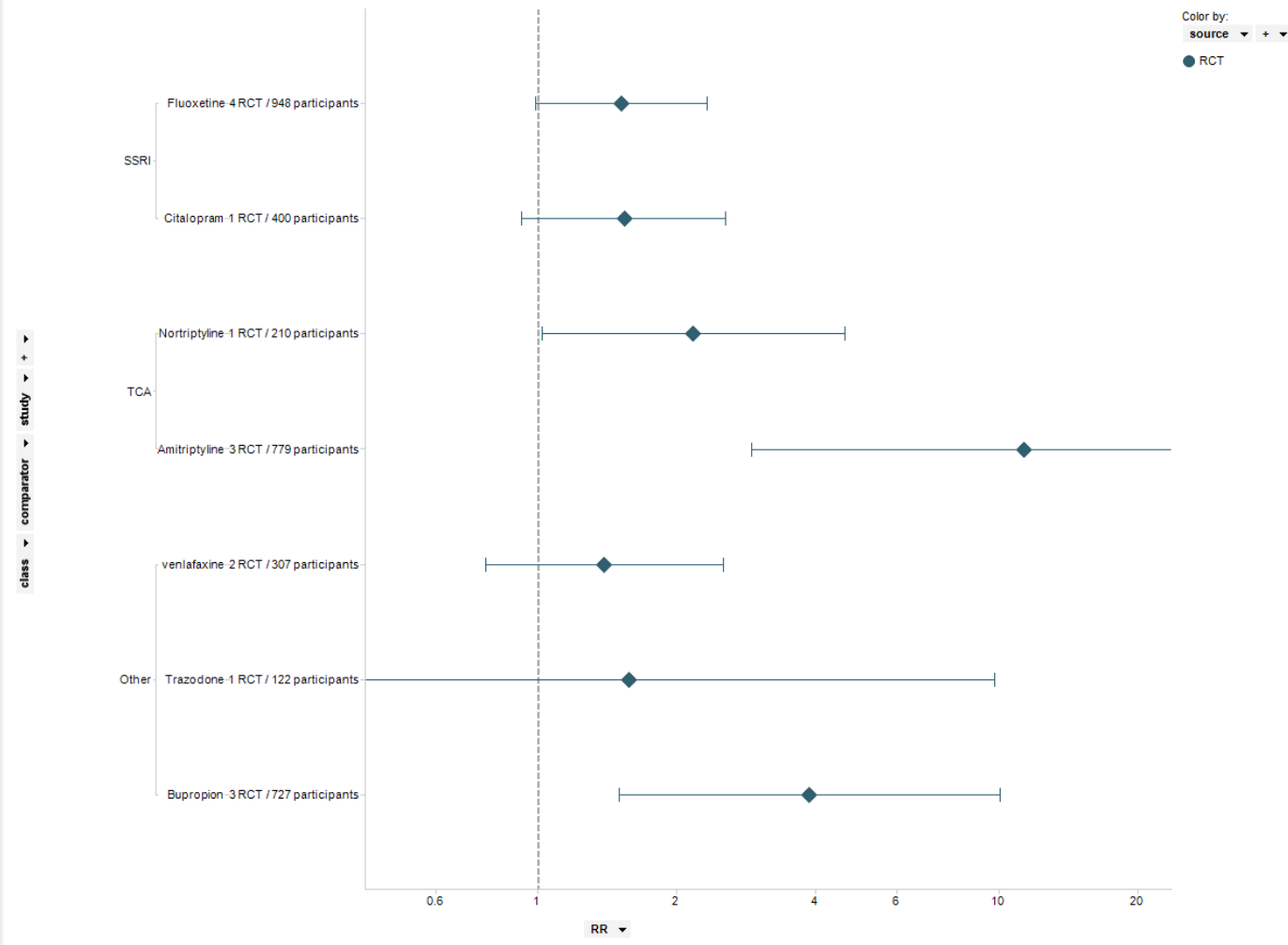


RCT results for effects of sertraline on diarrhea

Study population sizes (Target=Sertraline)



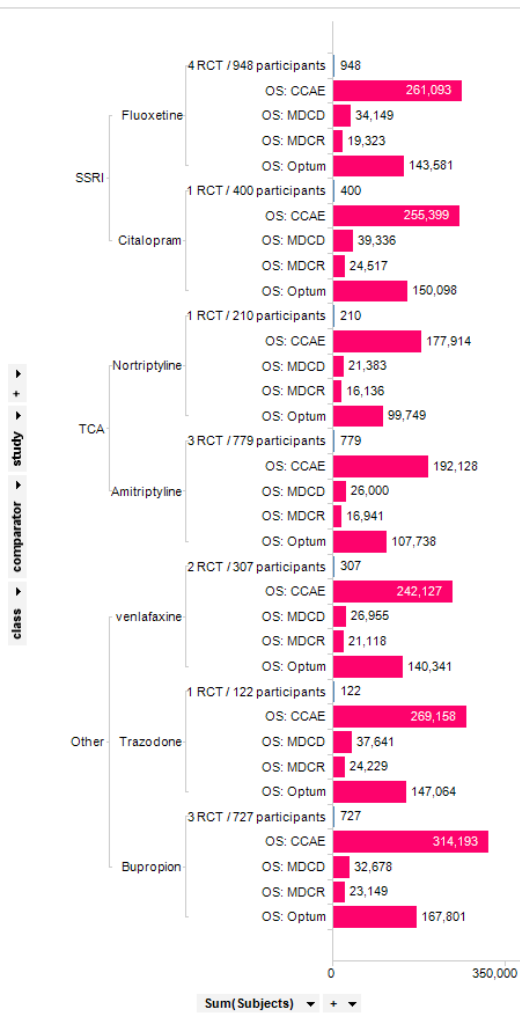
Population-level effect estimates (Target=Sertraline, Outcome=Diarrhea)



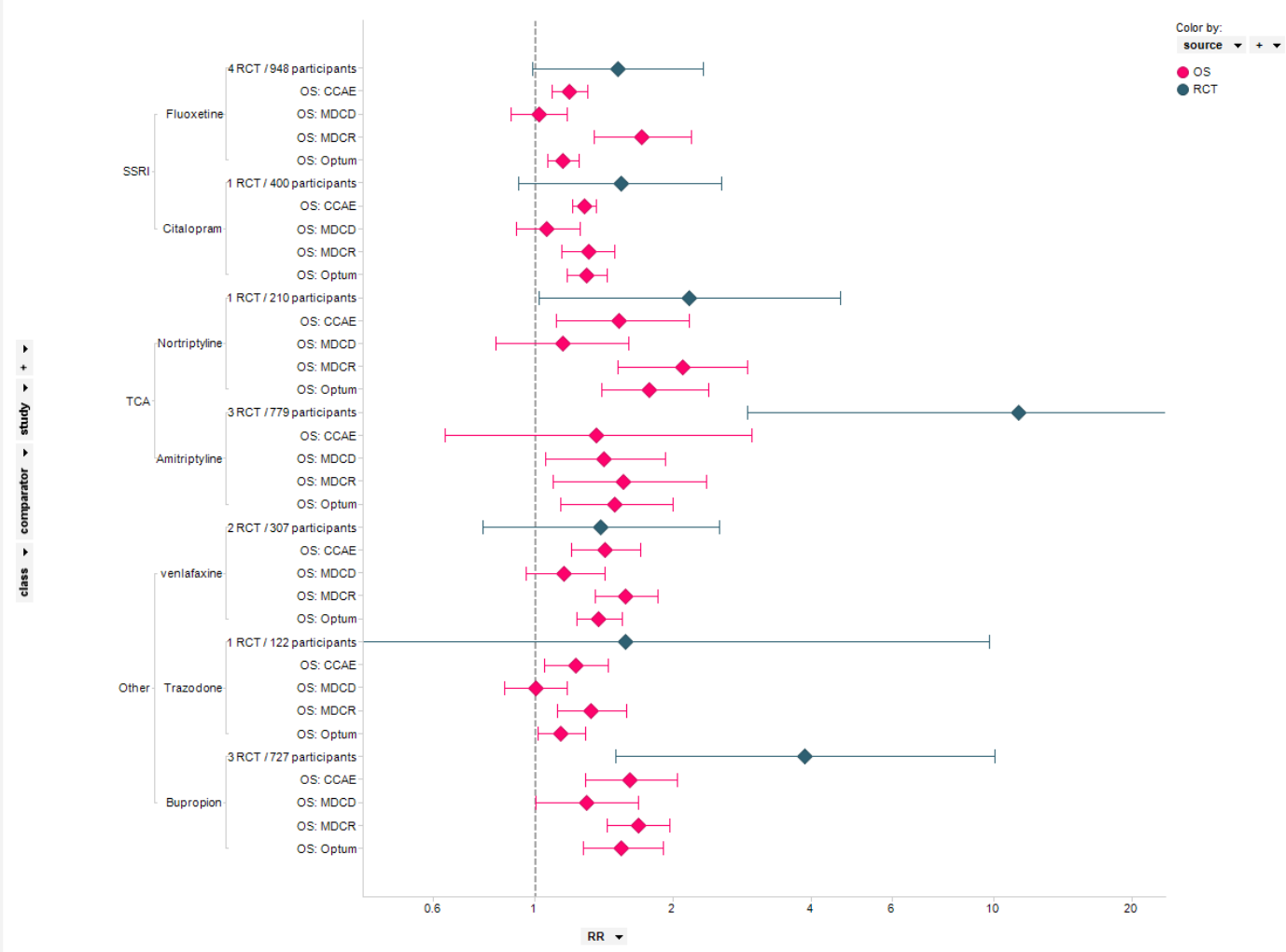


Comparing RCT and observational results for effects of sertraline on diarrhea

Study population sizes (Target=Sertraline)



Population-level effect estimates (Target=Sertraline, Outcome=Diarrhea)





Comparative effectiveness hypotheses from Gartleher et al

- Sertraline has higher risk of diarrhea than comparators
- Venlafaxine has higher risk of nausea than SSRI
- No difference in nausea between duloxetine and paroxetine or fluoxetine
- Paroxetine has higher rate of sexual dysfunction than fluoxetine and sertraline.
- Bupropion has lower incidence of sexual dysfunction than fluoxetine, paroxetine, and sertraline.



OHDSI's recommended best practices for population-level effect estimation

Evidence Generation

- Write and share protocol
- Open source study code
- Use validated software
- Replicate across databases

Evidence Evaluation

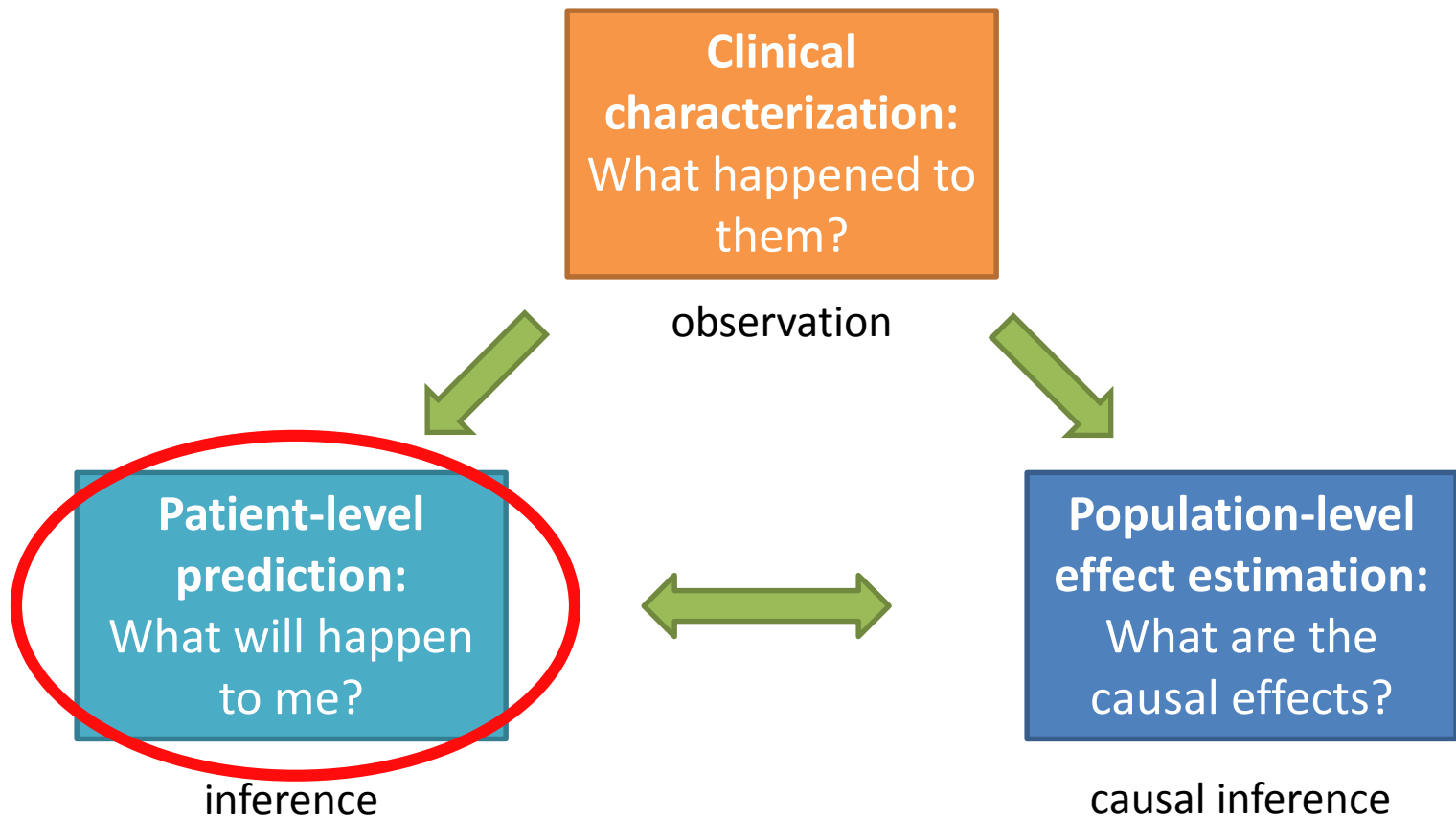
- Produce standard diagnostics
- Include negative controls
- Create positive controls
- Calibrate confidence interval and p-value

Evidence Dissemination

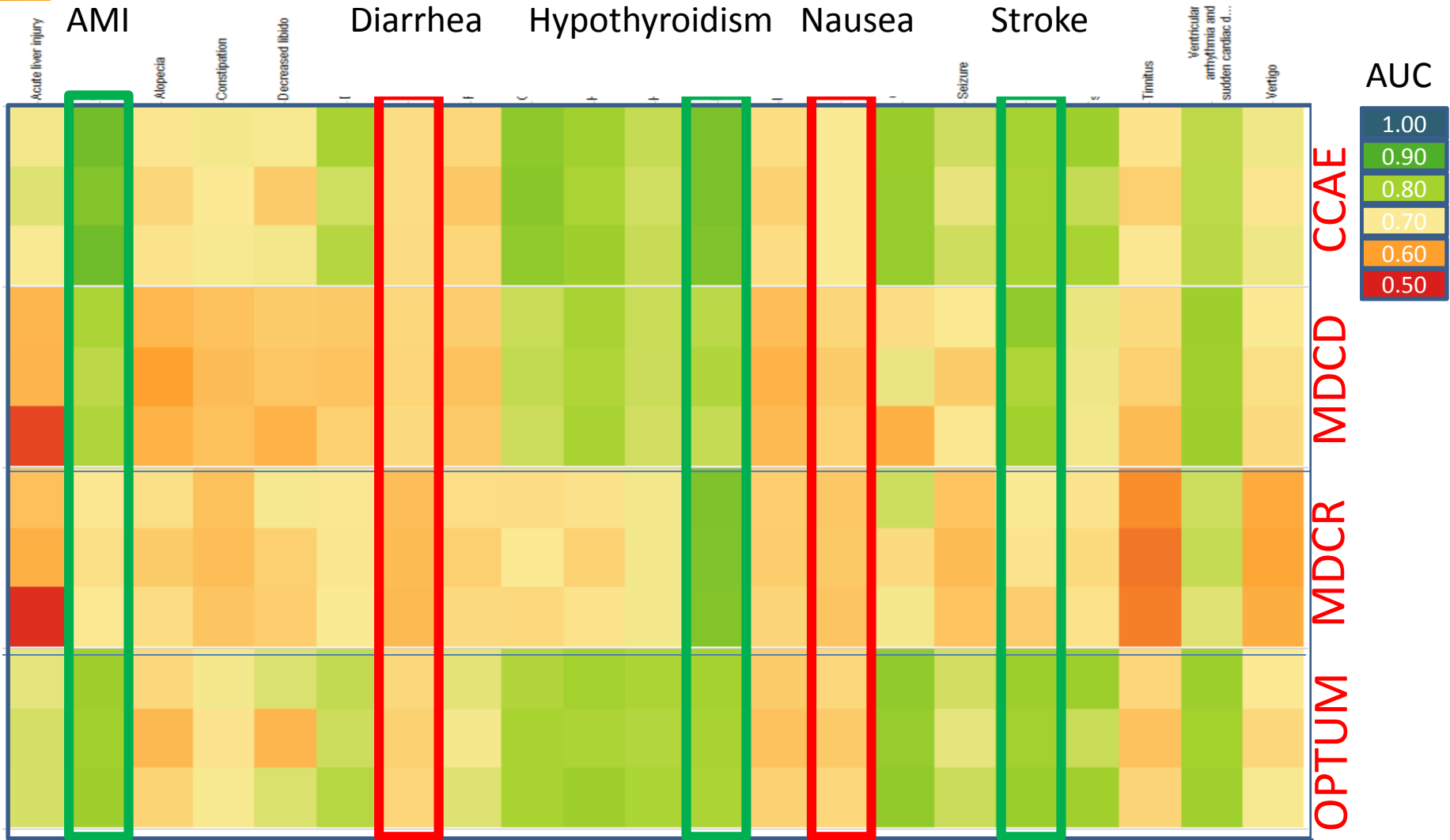
- Don't provide only the effect estimate
- Also share protocol, study code, diagnostics and evaluation
- Produce evidence at scale



Complementary evidence to inform the patient journey



Populations can be used to accurately predict outcomes for individuals





Building the LHC of observational research?





Join the journey

- Discussion / questions / comments

ryan@ohdsi.org
