Why network studies are necessary to improve trust in evidence

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

What is reliable evidence?

It's 2025: let's just ask a LLM!

"Reliable evidence" according to Gemini

"In medicine, reliable evidence is information derived from rigorous scientific research that minimizes bias and can be reproduced or replicated. The most trustworthy evidence comes from study types ranked highest on the "hierarchy of evidence" and published in authoritative, peer-reviewed medical and scientific literature.

The hierarchy of evidence

The hierarchy of evidence, often depicted as a pyramid, organizes different study types based on their methodological rigor. The studies at the top are the most reliable because they are designed to reduce the risk of bias.

Highest levels of evidence (Filtered/Pre-appraised):

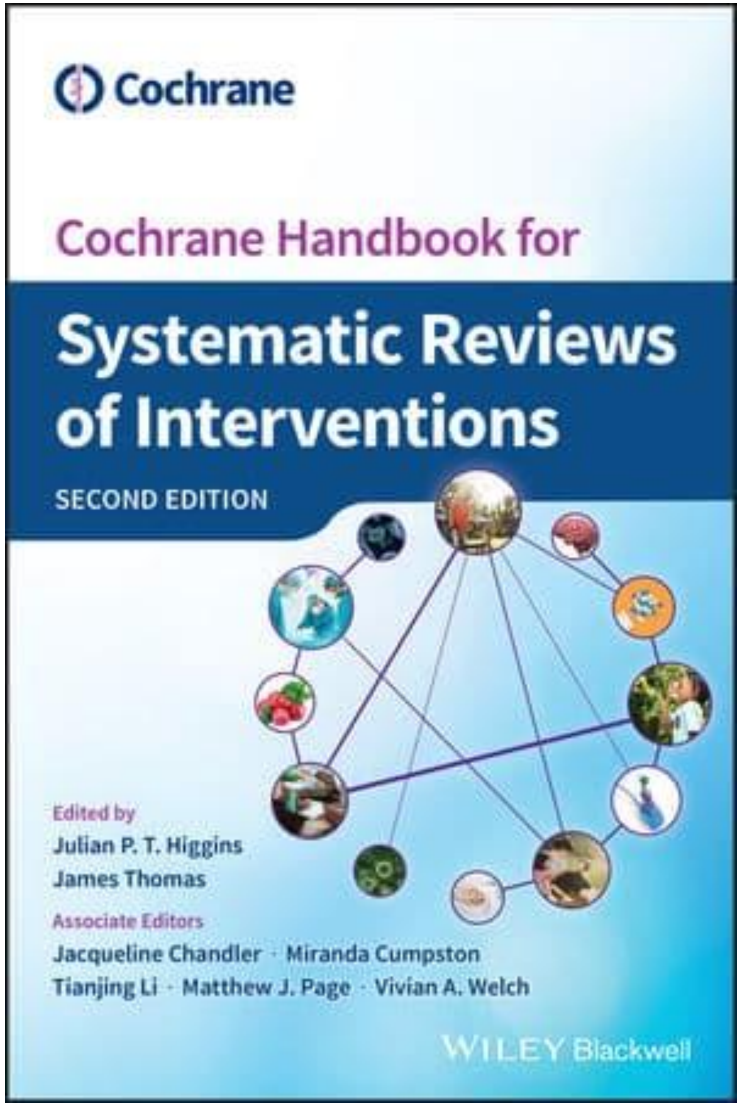
- **Systematic reviews and meta-analyses:** Considered the strongest evidence, these studies use rigorous, systematic methods to identify, appraise, and summarize all relevant studies on a specific clinical question. A meta-analysis goes a step further by statistically combining the results of multiple studies for a more precise estimate of an effect.

High levels of evidence (Primary/Unfiltered):

- **Randomized controlled trials (RCTs):** Often called the "gold standard" for evaluating interventions, RCTs randomly assign participants to an experimental group (e.g., receiving a new drug) or a control group (e.g., receiving a placebo). Randomization minimizes bias by ensuring the groups are comparable at the start of the trial.
- **Cohort studies:** In these observational studies, researchers follow a group of people over time to see what factors are linked to a specific outcome. They are useful for understanding risk factors.

…"

To be the best, you got to learn from the best



A working definition of ‘reliable evidence’

- ‘Reliable evidence’ = accurate, precise, and consistent estimate of average treatment effect of an exposure in the population of interest
  - Accurate = low probability and small magnitude of bias
  - Precise = high certainty around effect estimate
  - Consistent = little heterogeneity in estimates across network

Why network studies?

In OHDSI's population-level estimation use case, a distributed network study is the application of rigorous, systematic methods to estimate causal relationship between an exposure and an outcome within a population of interest:

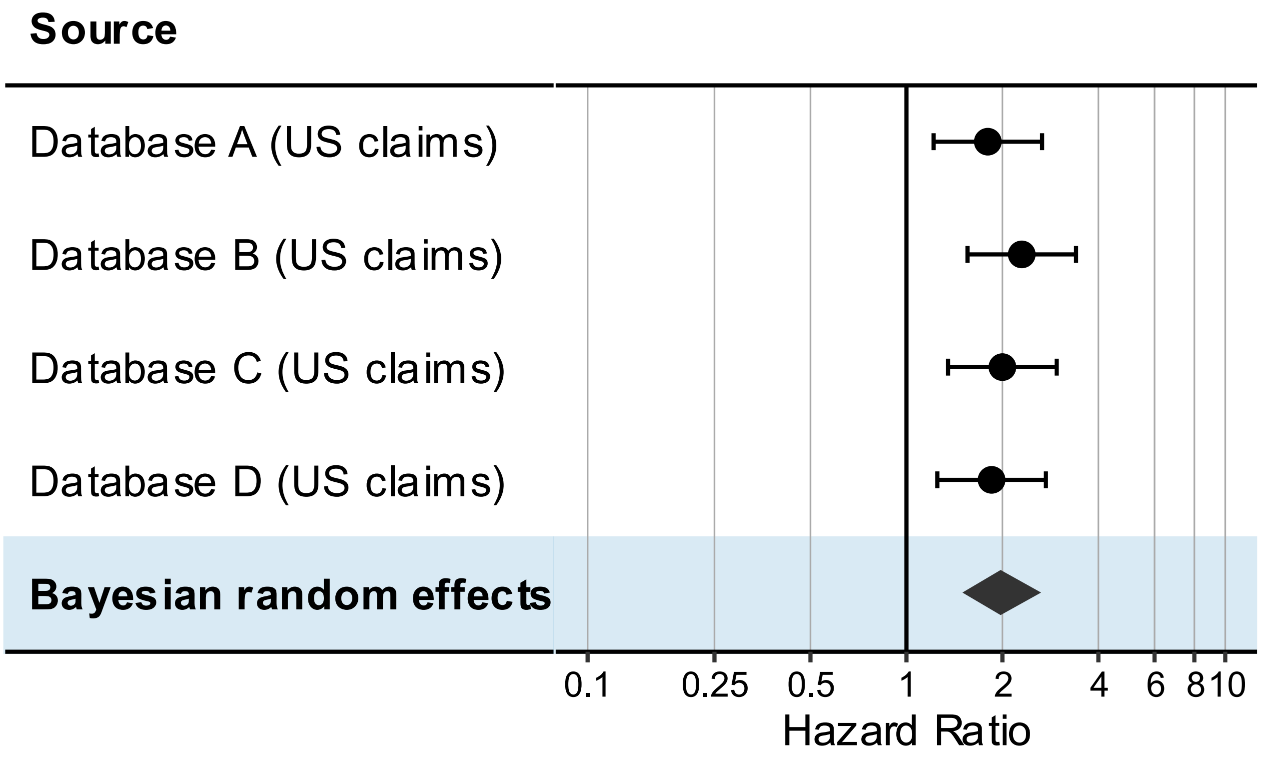
- A study protocol is collaboratively developed to define the research question and pre-specify all analytic design decisions
    - Target Exposure, Comparator(s), Outcome definition(s), Time-at-risk window(s), Statistical modeling parameters, Diagnostics and unblinding decision criteria
- A study package is developed that implements the study protocol specification using standardized analytics tools
- Participating sources execute the study package against their standardized patient-level data to generate a collection of standardized aggregate summary statistics
- A study coordinator compiles the aggregate summary results centrally from across the distributed data network
- A meta-analysis is performed to combine results from the network and synthesize the evidence into a more precise estimate of the effect
- The study team collaboratively interprets, summarizes and disseminates the evidence

Since our OHDSI Eye Care and Vision Research WG is so active, today we will run a refraction test...

- You will be presented results from two hypothetical studies, both conducted to answer the same research question

Each study will have estimates from one or more databases, each will have a description (country and data type)

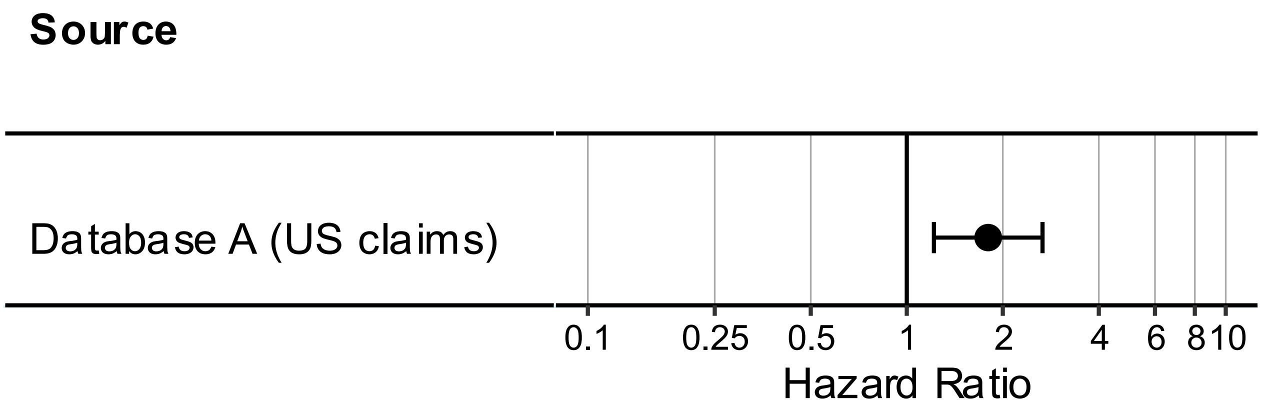
Each study will have a random-effects meta-analysis



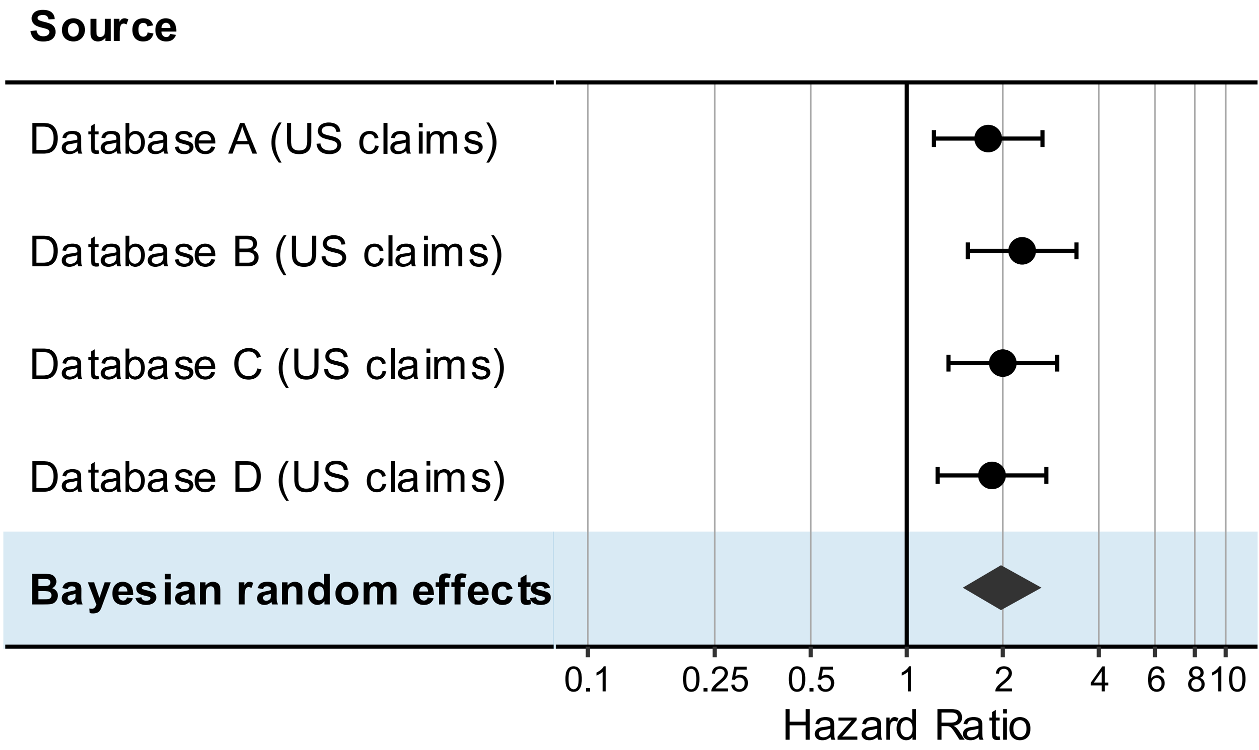
You will be asked to compare two studies and answer the question: “Which study do you think provides more reliable evidence?”

Which study do you think provides more reliable evidence?

Study 1



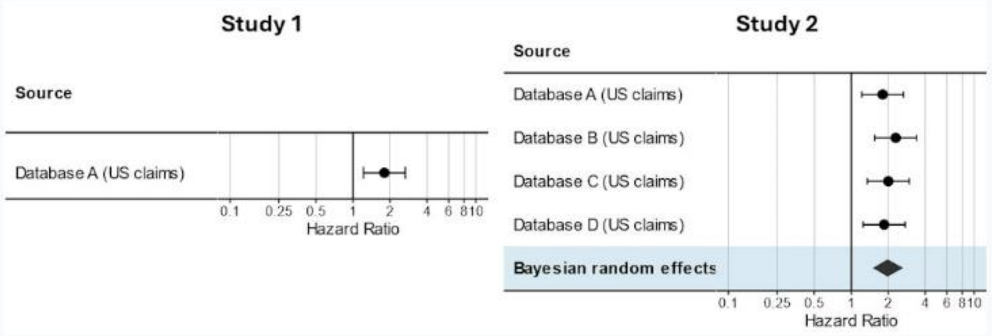
Study 2



Join by Web **PollEv.com/patrickryan800** Join by Text Send **patrickryan800** to **22333**

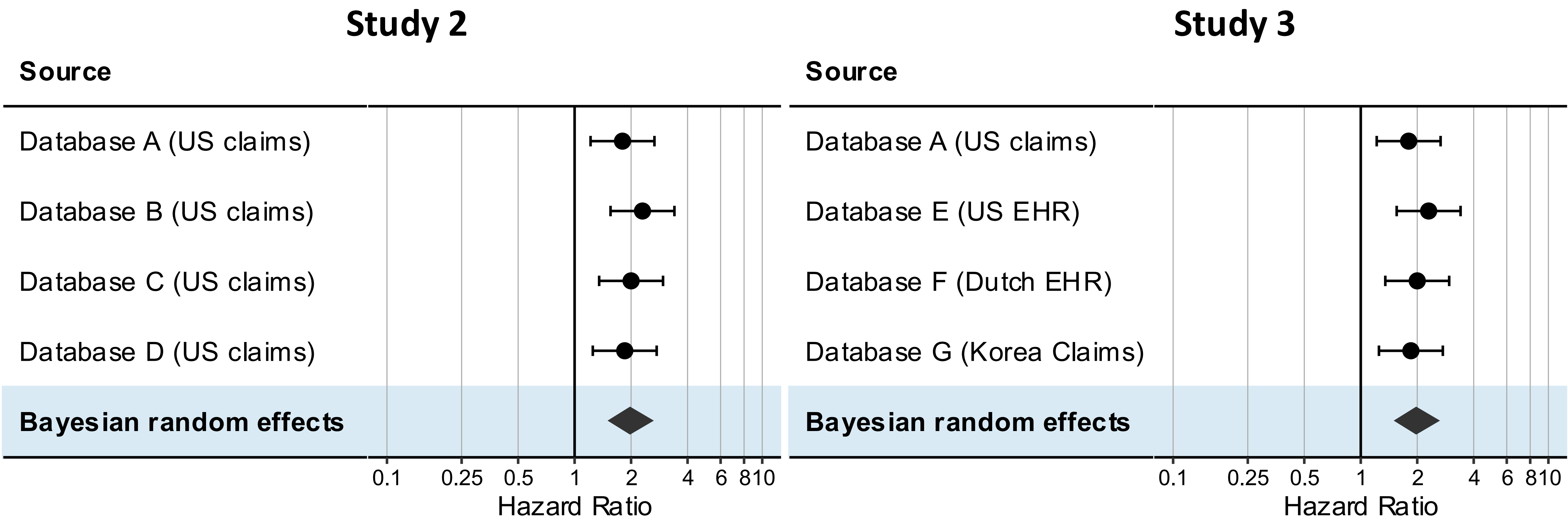
Which study do you think provides more reliable evidence?

0



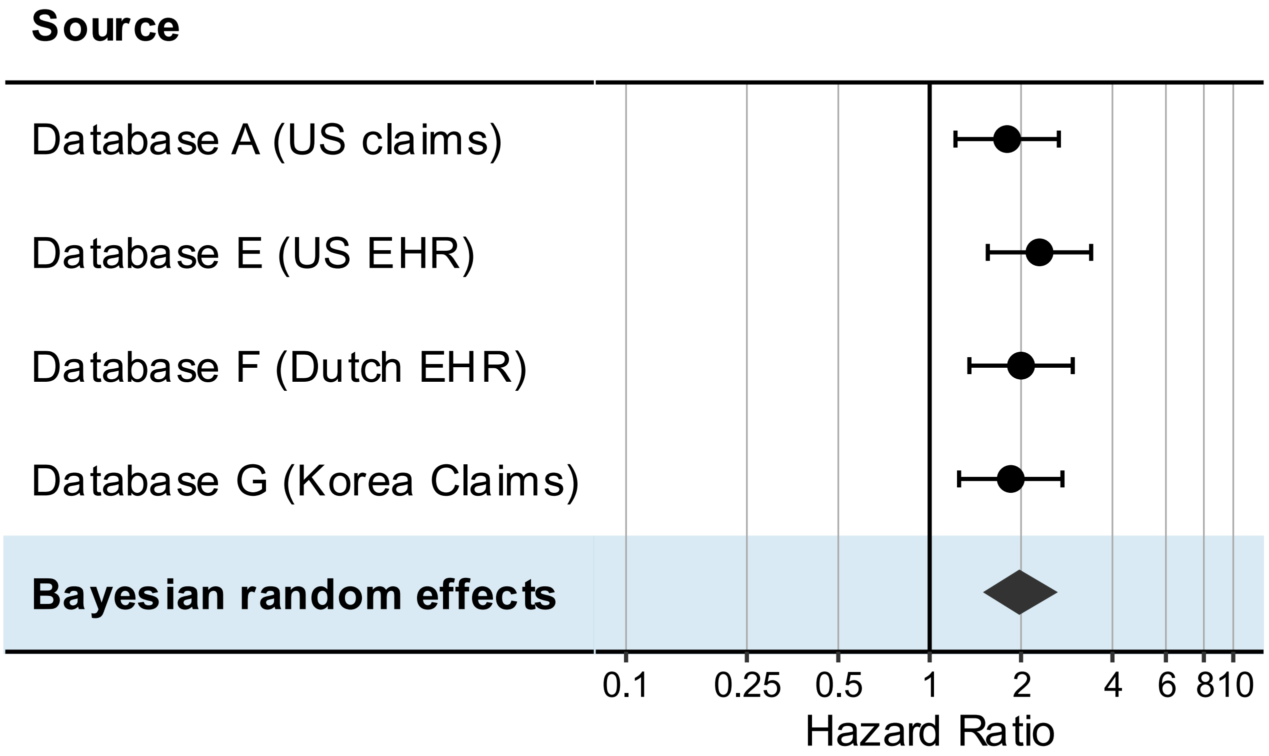
- Study 1 is more reliable than Study 2 **(A)**
- Study 1 is equally reliable as Study 2 **(B)**
- Study 1 is less reliable than Study 2 **(C)**

Which study do you think provides more reliable evidence?

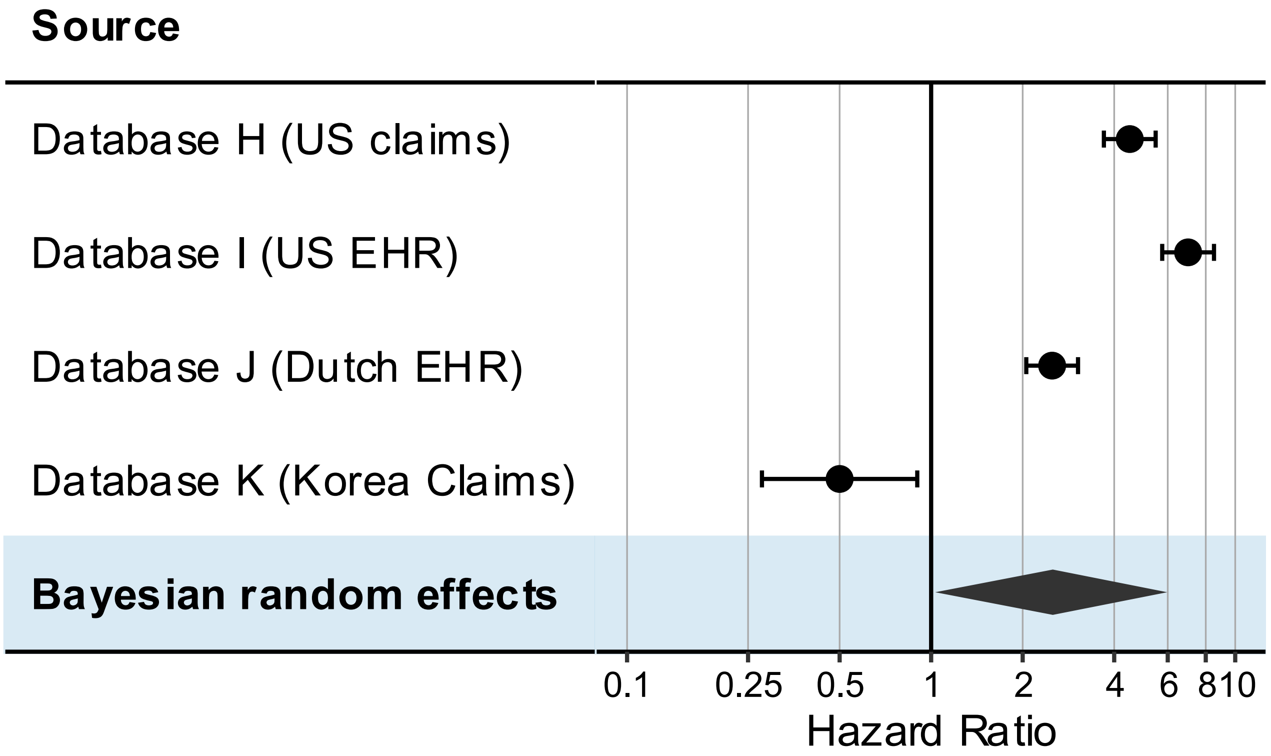


Which study do you think provides more reliable evidence?

Study 3

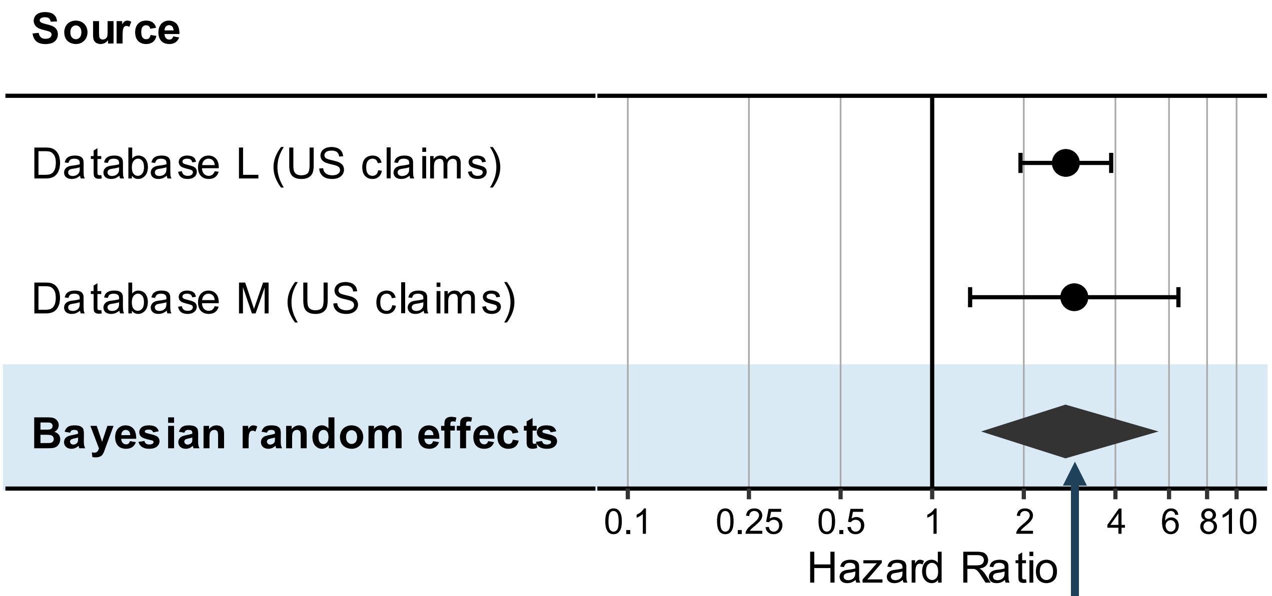


Study 4

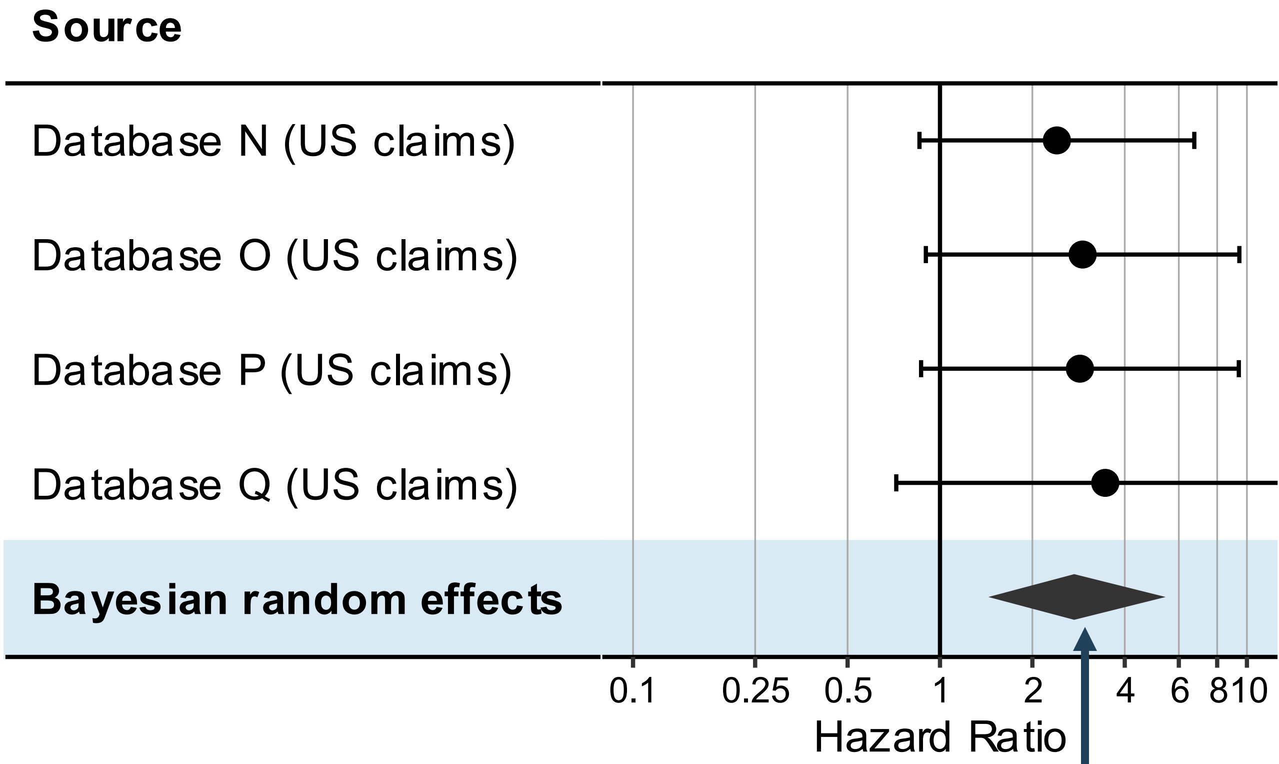


Which study do you think provides more reliable evidence?

Study 5



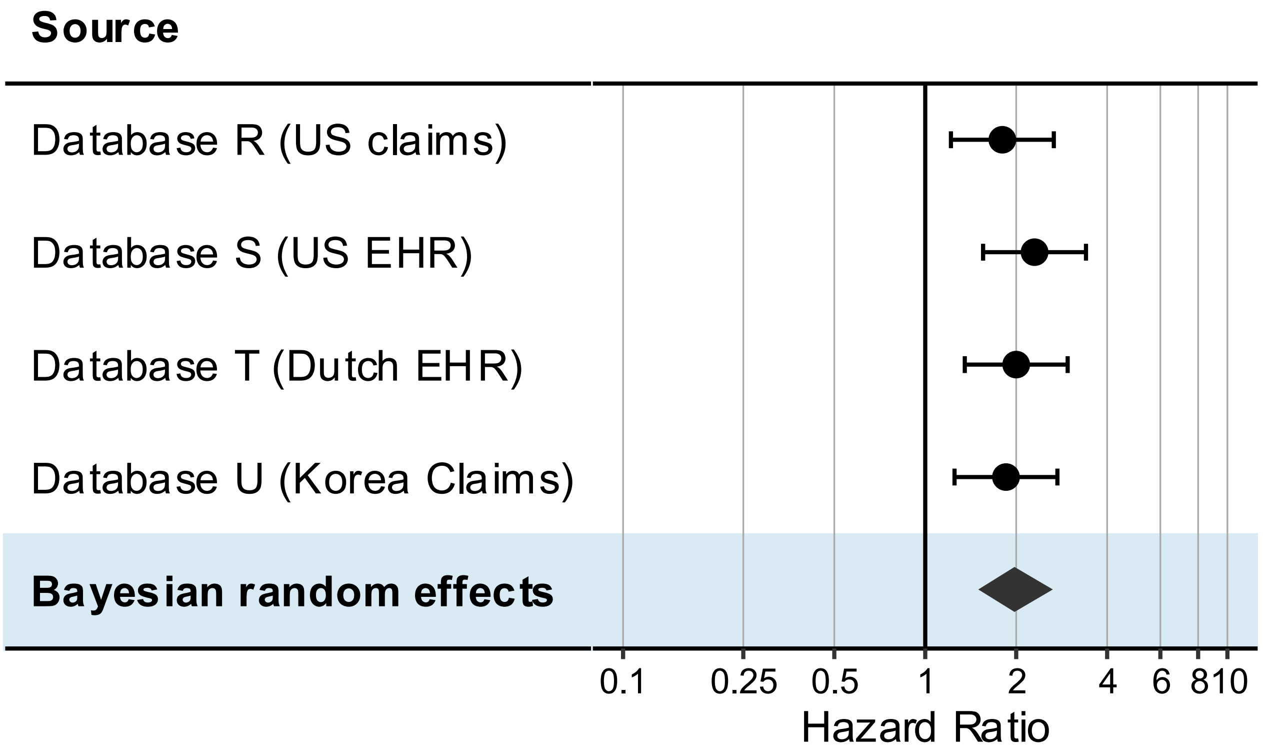
Study 6



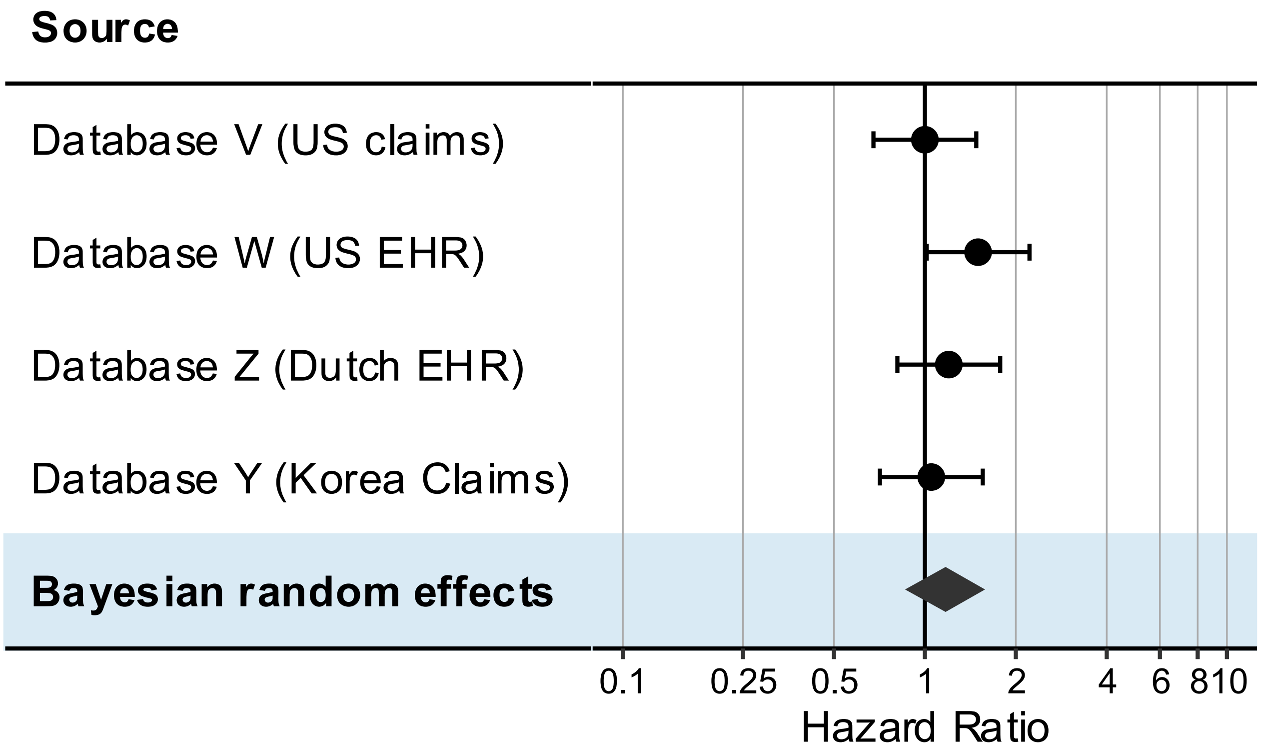
Identical estimates

Which study do you think provides more reliable evidence?

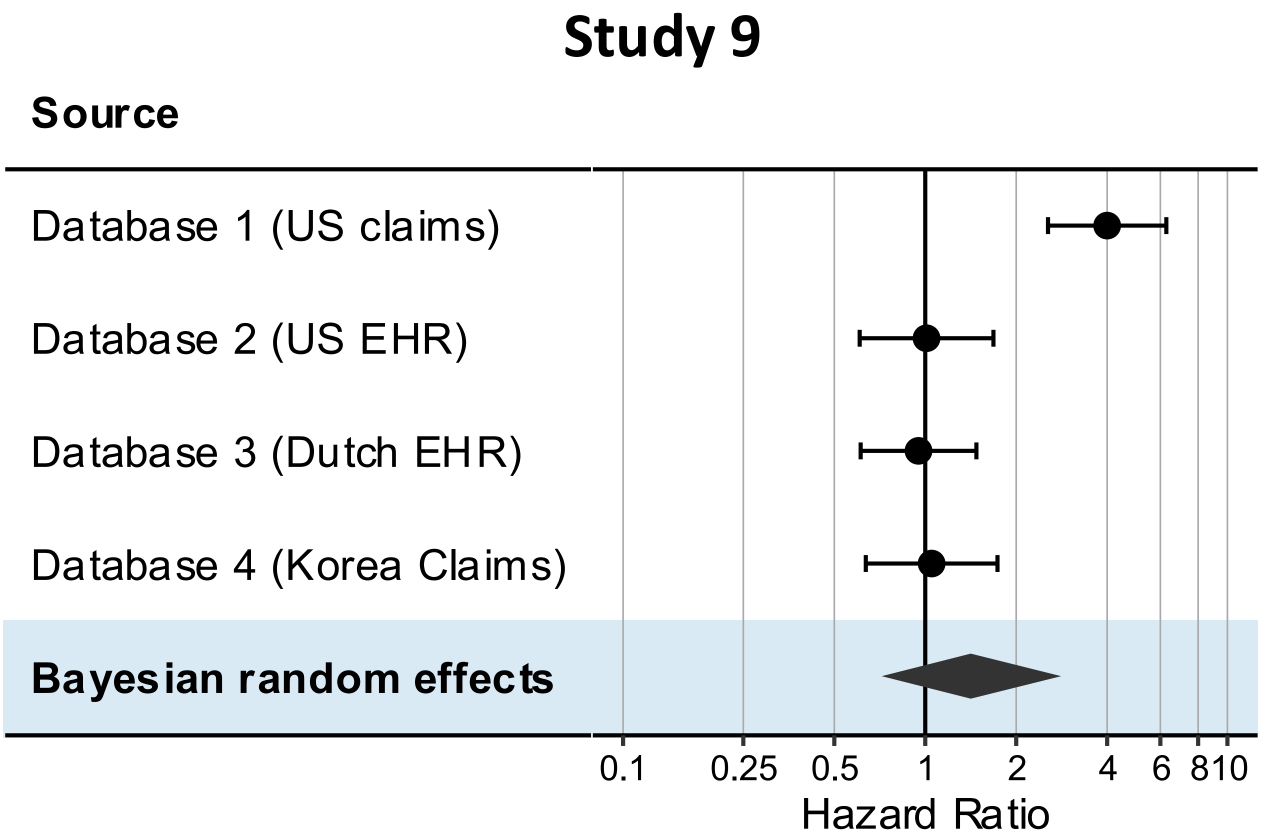
Study 7

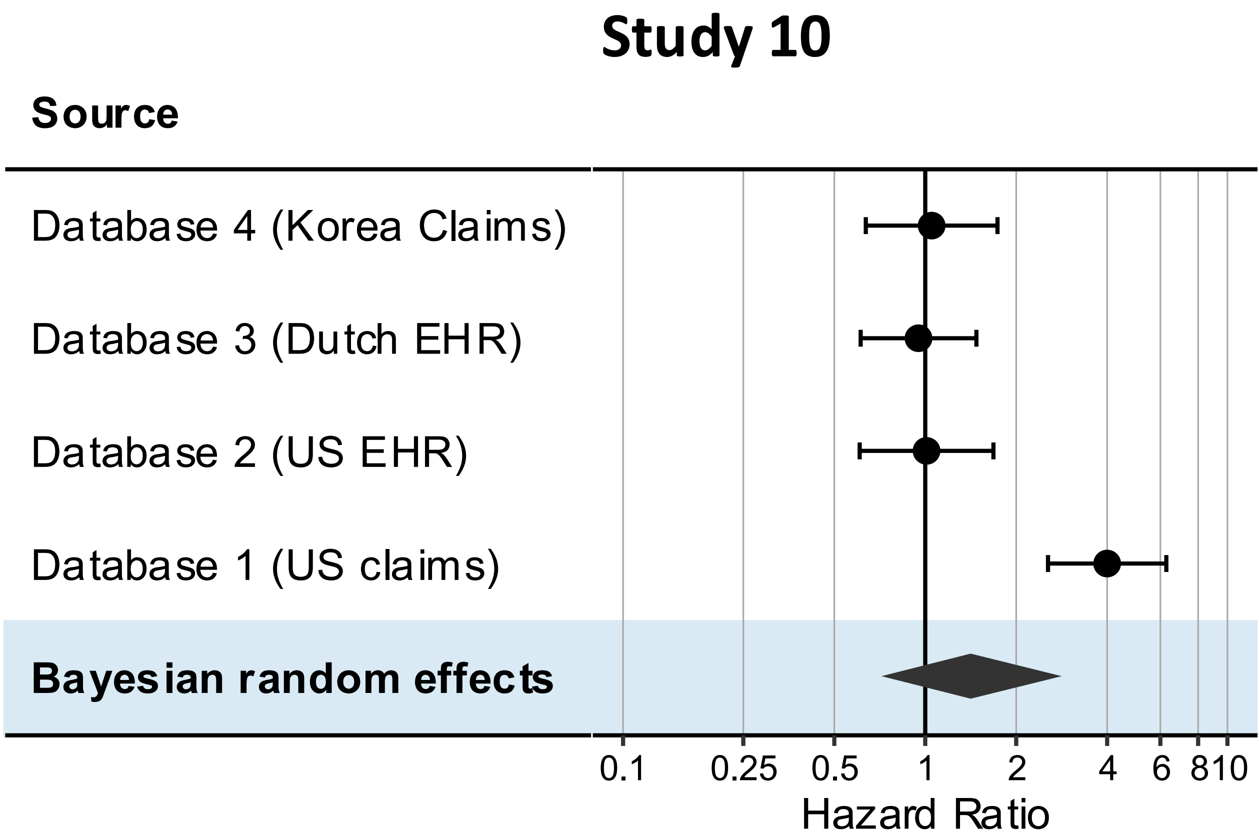


Study 8



Which study do you think provides more reliable evidence?





Value of a network study

Properties of evidence

- **Accuracy**: Extent to which our estimates are unbiased (systematic error)
- **Precision**: Magnitude of statistical power (random error, expressed as the width of confidence intervals)
- **Consistency**: Level of agreement of estimates across different populations (heterogeneity of treatment effects) and designs (sensitivity analyses)

Properties of evidence within and across databases

We will discuss each property as it applies to a single database, and across a network of databases

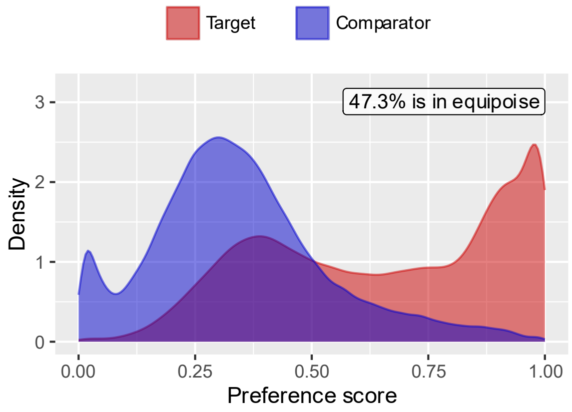
	Accuracy	Precision	Consistency
Within a database			
Across databases			

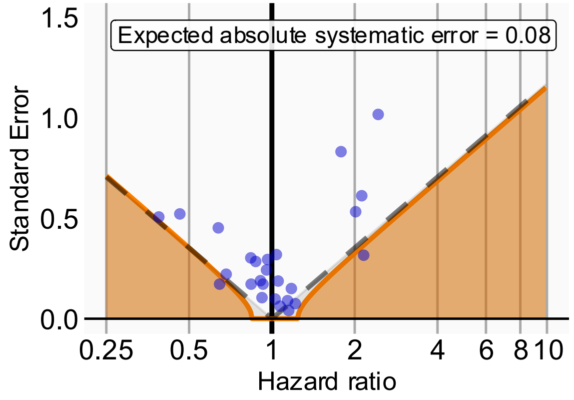
	Accuracy	Precision	Consistency
Within a database			
Across databases			

Accuracy within a database

We have done much to improve accuracy

- Advanced methods to minimize bias
  - Large-scale propensity scores (LSPS)
  - Self-controlled case series with spline adjustments
- Objective diagnostics to detect and blind biased results





Balance

Equipoise

Negative controls

We have done much to improve accuracy

- Advanced methods to minimize bias
  - Large-scale propensity scores (LSPS)
  - Self-controlled case series with spline adjustments
- Objective diagnostics to detect and blind biased results
- Empirical calibration to account for residual bias

	Accuracy	Precision	Consistency
Within a database			
Across databases			

Precision within a database

Precision in a single database

- Precision is expressed by the width of our confidence intervals
- We also compute the minimum detectable relative risk (MDRR)
- We agree with Hernán that even ‘underpowered’ studies can inform on the magnitude of the effect
- Precision is fixed, because our data has already been collected

ELSEVIER

Check for updates

Journal of Clinical Epidemiology 144 (2022) 203–205

Journal of Clinical Epidemiology

COMMENTARY

Causal analyses of existing databases: no power calculations required

Miguel A. Hernán[a,b,*]

[a] CAUSALab, Harvard T.H. Chan School of Public health, Boston, MA 02115, USA

[b] Departments of Epidemiology and Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA 02115, USA

Received 30 July 2021; Received in revised form 18 August 2021; Accepted 23 August 2021; Available online 27 August 2021

Abstract

	Accuracy	Precision	Consistency
Within a database	✓	✓	🔍
Across databases			

Consistency within a database

Consistency within a database

- Consistency across **subgroups**
  – heterogeneity of treatment effects
- Consistency across **design variants**
  – sensitivity analyses (robustness)

Evaluating consistency across subgroups

- Several OHDSI efforts to understand heterogeneity of treatment effects
- Here, consistency between subgroups is neither good nor bad


Journal of Diabetes and Its Complications 39 (2025) 109114

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: www.elsevier.com/locate/jdiacomp

Heterogeneity of treatment effects of glucose-lowering drug classes for type 2 diabetes: LEGEND-T2DM network real-world evidence

David M. Dávila-García [a,b,*], Thomas Falconer [a,1], Nicole Pratt [c,2], Karthik Natarajan [a,1], George Hripcsak [a,1]

[a] Department of Biomedical Informatics, Columbia University Irving Medical Center, New York, NY, United States
[b] Institute for Informatics, Data Science & Biostatistics, Washington University School of Medicine in Saint Louis, Saint Louis, MO, United States
[c] Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, Australia

ARTICLE INFO

ABSTRACT

npj | digital medicine

www.nature.com/npjdigitalmed

identification of relevant databases; (3) development of a prediction model for the outcome(s) of interest; (4) estimation of relative and absolute treatment effect within strata of predicted risk, after adjusting for observed confounding; (5) presentation of the results. We demonstrate our framework by evaluating heterogeneity of the effect of thiazide or thiazide-like diuretics versus angiotensin-converting enzyme inhibitors on three efficacy and nine safety outcomes across three observational databases. We provide a publicly available R software package for applying this framework to any database mapped to the Observational Medical

Go see Hsin Yi (Cindy)'s Lightning talk in Session 2!

Evaluating consistency across design variants

- We often run multiple design variants to answer the same question
  - CohortMethod vs SelfControlledCaseSeries
  - Different times at risk
  - Etc.
- We are assured when estimat
- We become wary when differ different estimates
  - They can’t all be right. Are som

Go see Shounak’s poster!
(poster 210)

	Accuracy	Precision	Consistency
Within a database	✓	✓	✓
Across databases			🔍

Consistency across databases

Between-database consistency

Evaluating consistency between databases

- Provides new opportunities to test the reliability of our evidence
  - Observing the same effect in all databases increases its credibility and generalizability
- But results could be inconsistent for different reasons

Reasons for between-database inconsistency

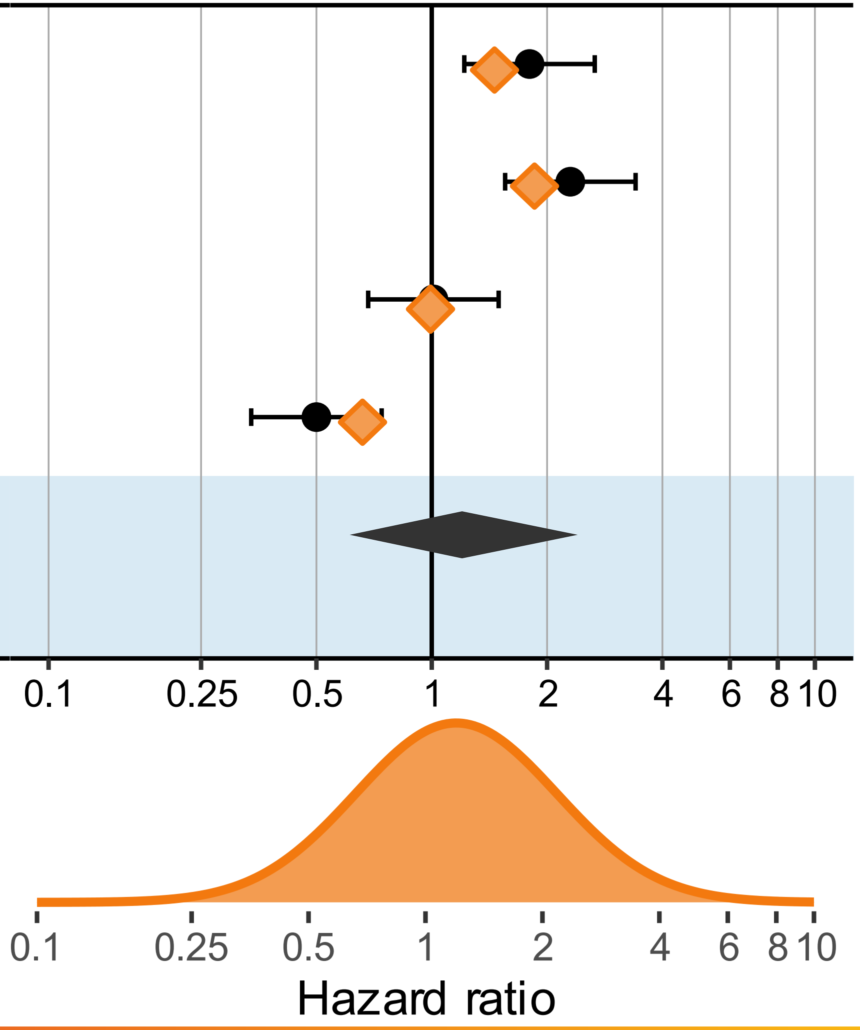
1. If populations are different, the treatment effect could be different
   - Example: Comparing MDCD vs MDCR when the effect differs by age
   - Could be due to unknown effect modifiers that we may not even be able to observe
2. If data capture processes and health care systems are different, systematic error could be different
   - Example: One database might have more measurement error in the outcome
   - Example: Prescribing behavior may differ between databases, causing different confounding by indication
   - Could have unknown causes that we don't observe

We often cannot distinguish between these two causes

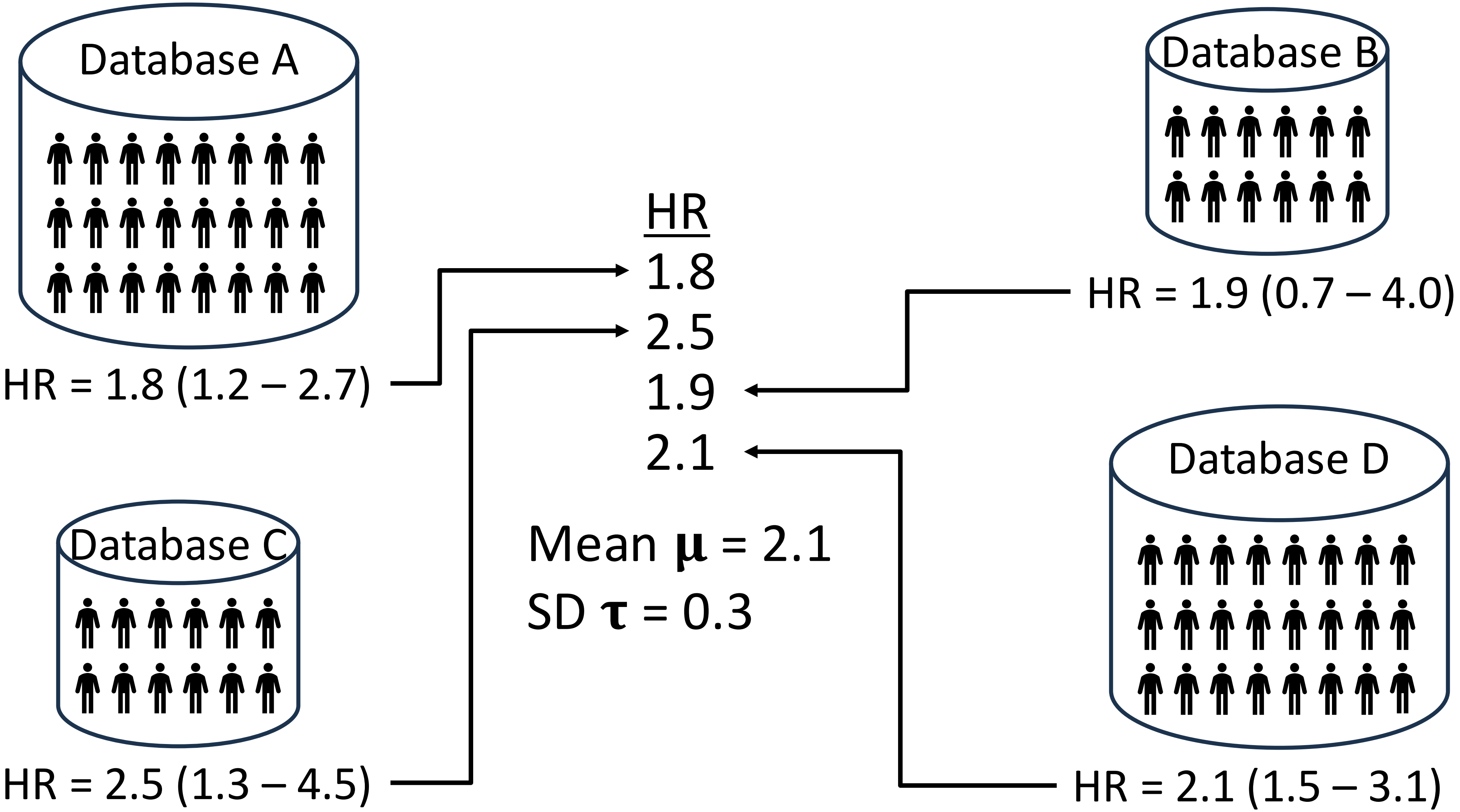
If we know with certainty consistency is high, both reasons must be absent

Quantifying between-database consistency using random-effects meta-analysis

Source	Hazard Ratio (95% CI)
Database A (US claims)	1.80 (1.22 - 2.66)
Database H (US EHR)	2.30 (1.55 - 3.40)
Database I (Dutch EHR)	1.01 (0.68 - 1.49)
Database J (Korea Claims)	0.50 (0.34 - 0.74)
Bayesian random effects τ = 0.60	**1.20 (0.61 - 2.40)**

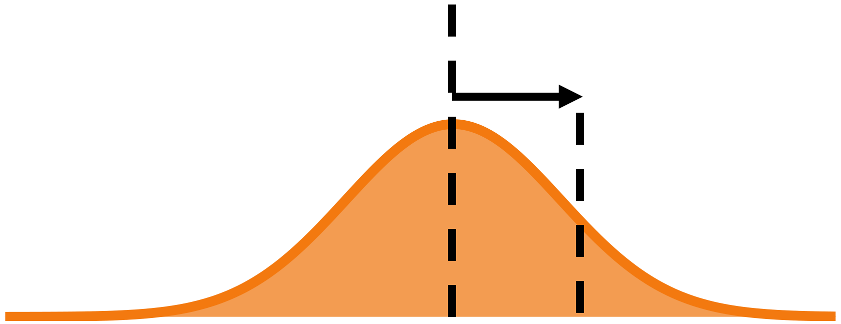


Network study as a sample of estimates



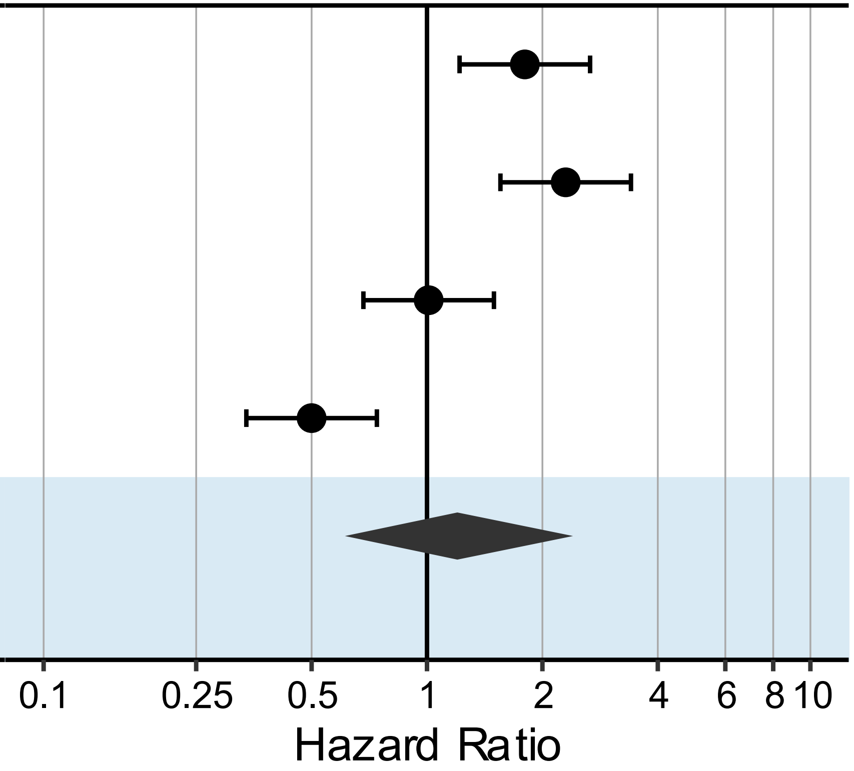
Random effects meta-analysis

- Assumes true effects draw from a distribution with
  - Mean ($\boldsymbol{\mu}$)
  - Standard deviation ($\boldsymbol{\tau}$)
- Interpretation:
  - $\boldsymbol{\mu}$ tells us the average effect across databases
  - $\boldsymbol{\tau}$ informs us on the heterogeneity (the inverse of consistency)



Random effects meta-analysis

Source	Hazard Ratio (95% CI)
Database A (US claims)	1.80 (1.22 - 2.66)
Database H (US EHR)	2.30 (1.55 - 3.40)
Database I (Dutch EHR)	1.01 (0.68 - 1.49)
Database J (Korea Claims)	0.50 (0.34 - 0.74)
Bayesian random effects τ = 0.60	**1.20 (0.61 - 2.40)**

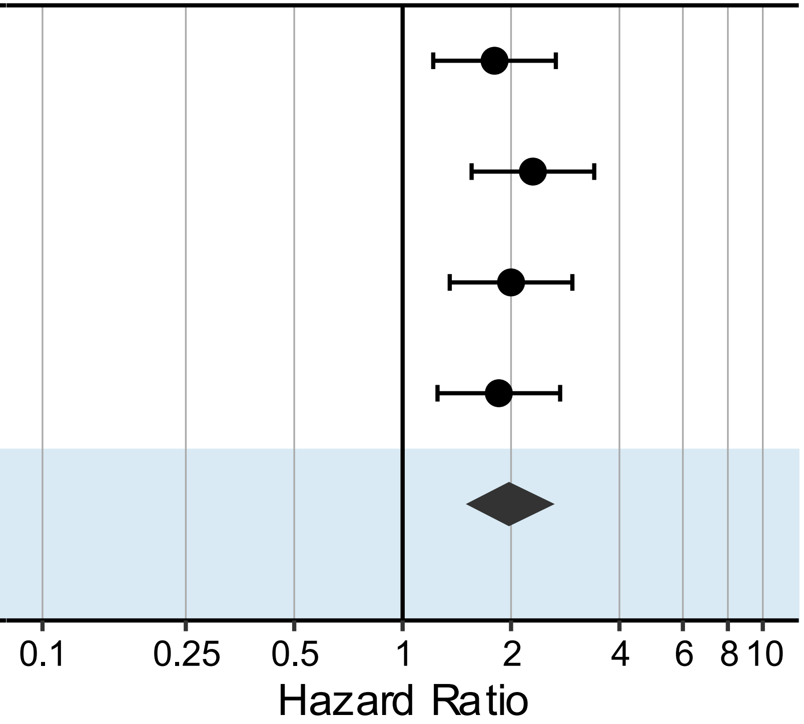


Here τ is high

(I^2 is the proportion of total variance explained by τ. I^2 will increase as power goes up, so we prefer τ)

Random effects meta-analysis

Source	Hazard Ratio (95% CI)	
Database A (US claims)	1.80	(1.22 - 2.66)
Database B (US claims)	2.30	(1.55 - 3.40)
Database C (US claims)	2.00	(1.35 - 2.96)
Database D (US claims)	1.85	(1.25 - 2.74)
Bayesian random effects τ = 0.12	**1.97**	**(1.50 - 2.64)**



Higher consistency, so lower **τ**

LEGEND Hypertension & **LEGEND** T2DM

Large-scale Evidence Generation and Evaluation across a Network of Databases (**LEGEND**) studies

- Compare all treatments for an indication
- For a large set of safety and effectiveness outcomes
- Across a network of databases
- Following OHDSI best practices

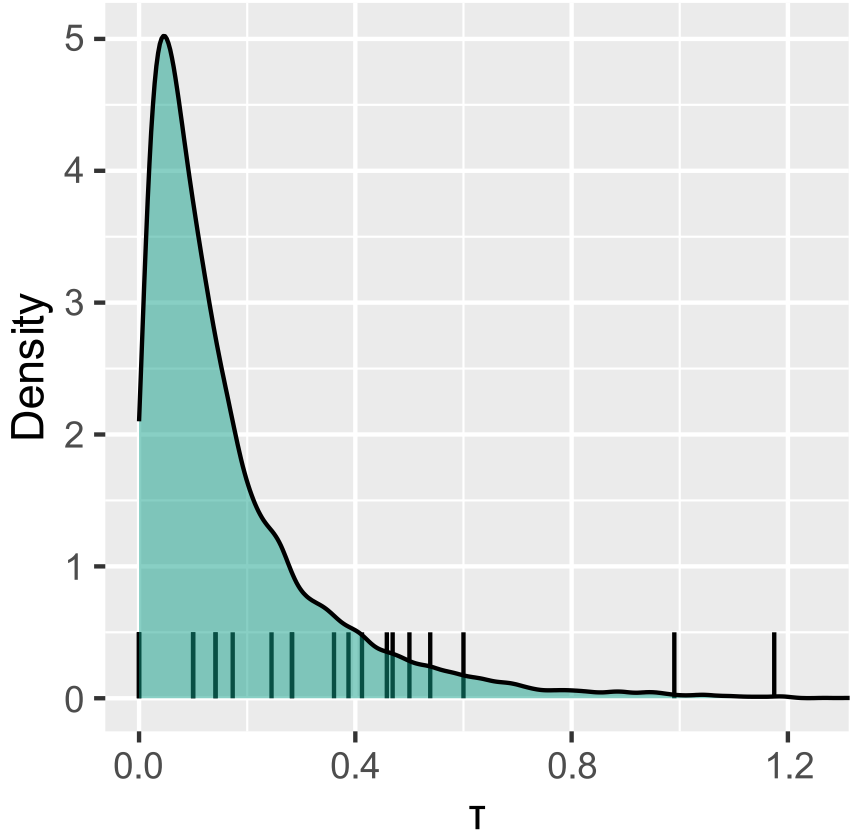
We will use the results of these studies to explore questions around network studies

Computing τ in LEGEND

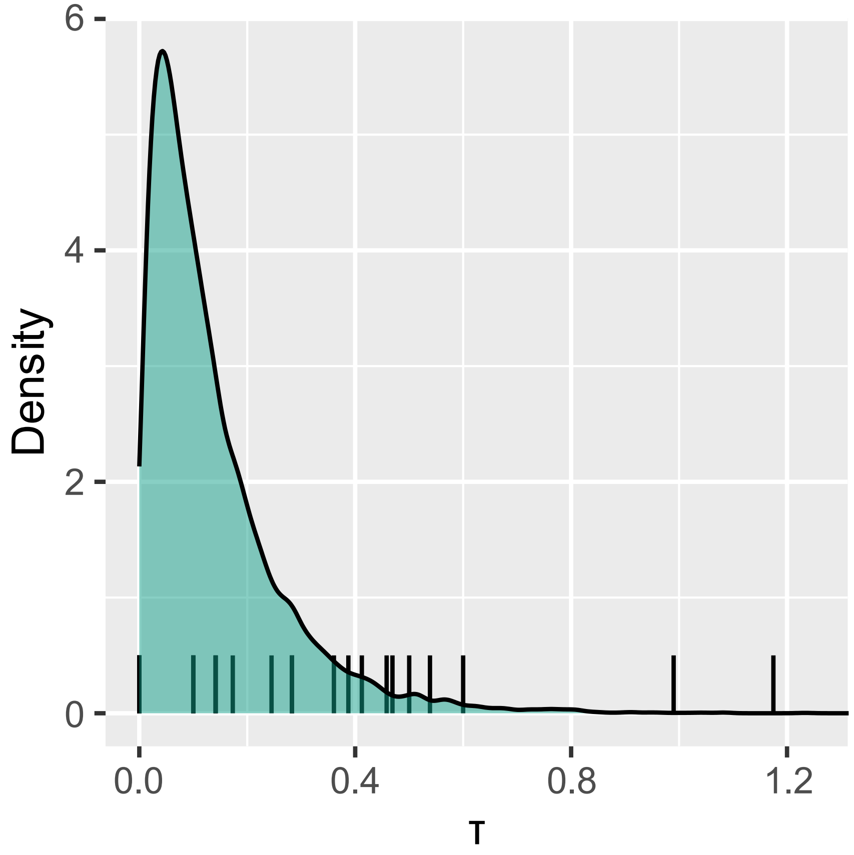
- LEGEND Hypertension:
  - 20,053 target-comparator-outcomes (class level)
  - 9 databases
- LEGEND T2DM:
  - 746 target-comparator-outcomes (class level)
  - 14 databases
- Remove estimates failing diagnostics
- Restricted to studies with 6 (Hypertension) or 9 (T2DM) databases passing diagnostics
- Perform meta-analysis across databases for each TCO
- Take estimated τ (posterior) from each meta-analysis
- Average across τs

Heterogeneity in LEGEND

LEGEND Hypertension



LEGEND T2DM

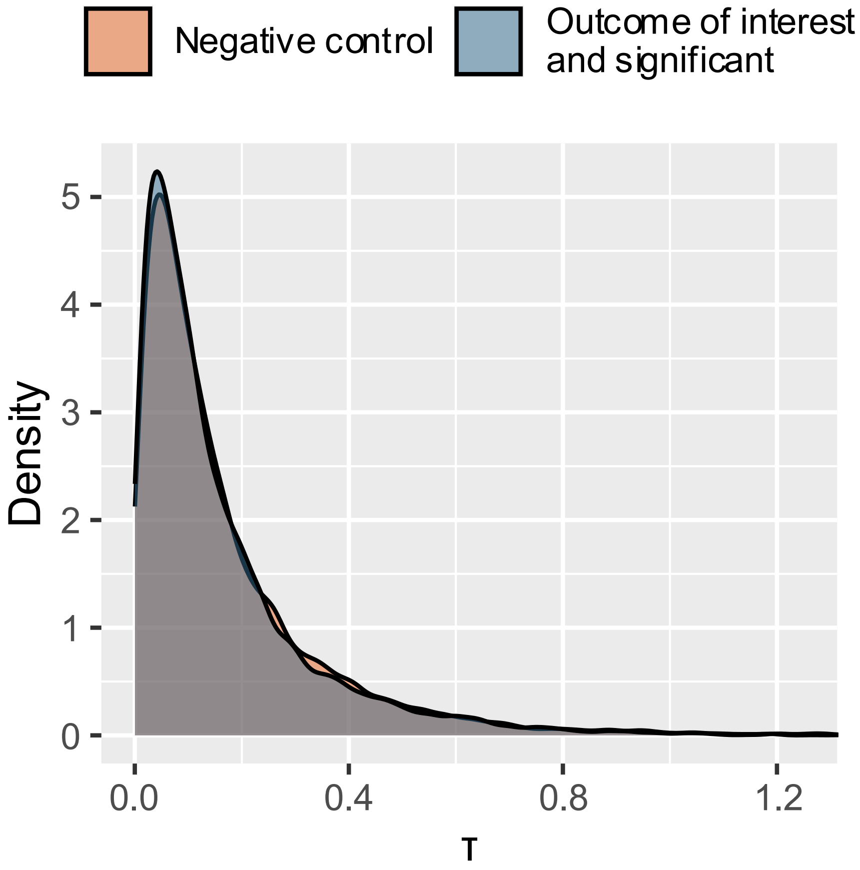


Overall, **τ** seems to be low, at around 0.05 (95% of effects are within ±10% from the mean)

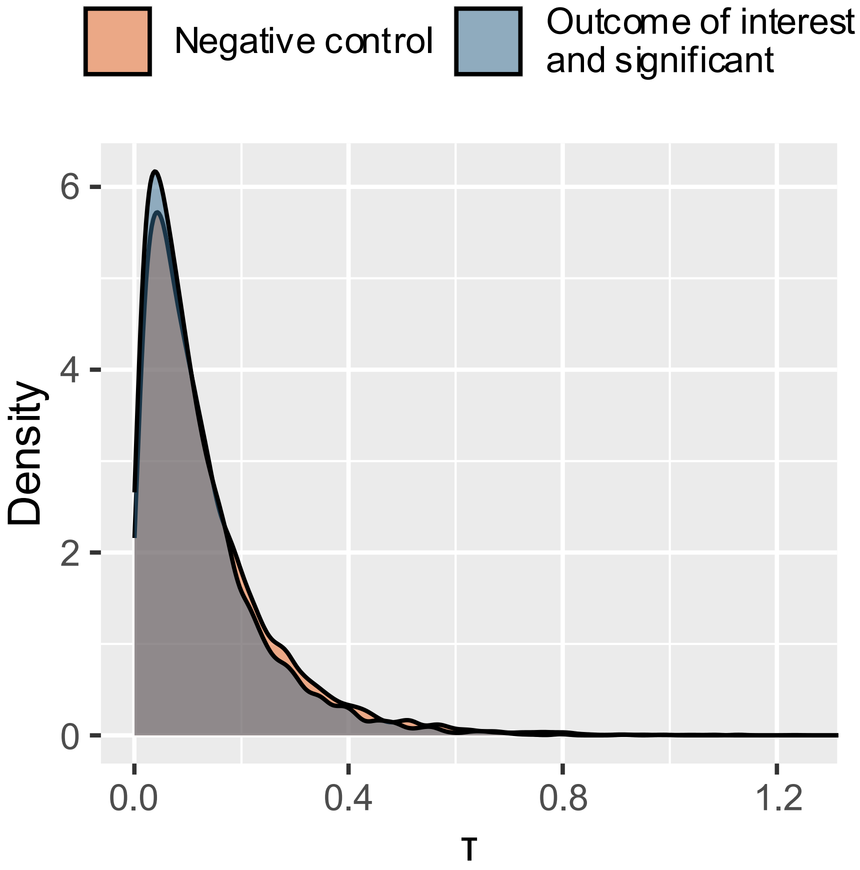
Vertical lines are **τ** estimates from Cochrane studies

Heterogeneity in LEGEND

LEGEND Hypertension



LEGEND T2DM



For negative controls there is no true effect, so also no effect heterogeneity. Only systematic error can cause heterogeneity.

To contrast, we select outcomes of interest where the meta-analyses rejects the null. Here we may expect a true effect and true effect heterogeneity

Interestingly, both have identical τ distributions, suggest there is little effect heterogeneity

	Accuracy	Precision	Consistency
Within a database	✓	✓	✓
Across databases		🔍	✓

Precision across databases

OHDSI

Observational Health Data Sciences and Informatics

Increasing precision

- With a single database precision is fixed
- In a network study we can increase precision by including more databases
  – Prospectively plan your network study to have sufficient power

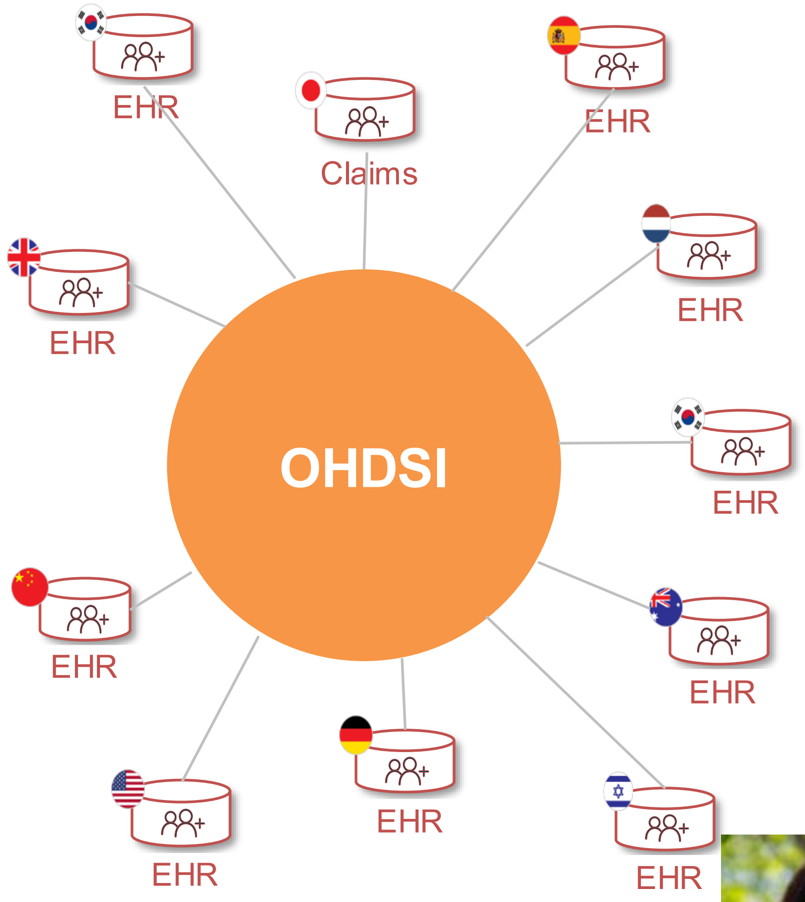
OHDSI Evidence Network

A community effort to facilitate collaborative research efforts and ensure the quality and integrity of data across the OHDSI network

Resource comprised of summary statistics of databases within the OHDSI network
- Held securely at the OHDSI Coordinating Center
- Used to inform network studies

Patient level data does not leave participating site

Compliance with privacy and IRB regulations



OHDSI Evidence Network

Data Source	Country	Data type	Care Level	Patient Count
Ajou University School of Medicine	Korea	EHR	IP,OP,ER	2.7M
Clinical Hospital Center Zvezdara	Serbia	EHR	IP,OP,ER	618K
Columbia University Irving Medical Center	USA	EHR	IP,OP,ER	7M
Emory University	USA	EHR	IP,OP,ER	6.5M
GUSTO Singapore Cohort	Singapore	Registry	OP	2.6K
HealthPartners Institute	USA	EHR	IP,OP,ER	3.2M
IMRD EMIS	UK	EHR	IP,OP	5.1M
IQVIA Australia EMR	Australia	EHR	OP	2.7M
IQVIA Belgium LPD	Belgium	EHR	OP	1.1M
IQVIA France DA	France	EHR	OP	6.2M
IQVIA France LPD	France	EHR	OP	17.4M
IQVIA Germany DA	Germany	EHR	OP	40.8M
IQVIA LPD Spain	Spain	EHR	OP	2.7M
IQVIA PharMetrics Plus	USA	Claims	IP,OP,ER	170.2M
IQVIA US Hospital	USA	EHR	IP,OP,ER	113.1M
IQVIA US Open Claims	USA	EHR	IP,OP,ER	330M
JMDC	Japan	Claims	IP,OP	17.6M
Johns Hopkins University	USA	EHR	IP,OP,ER	2.2M
Lancashire Teaching Hospitals NHS Trust	UK	EHR	IP,OP,ER	1.5M
Merative CCAE	USA	Claims	IP,OP,ER	172.2M
Merative MDCD	USA	Claims	IP,OP,ER	36.1M
Merative MDCR	USA	Claims	IP,OP,ER	11.3M

Data Source	Country	Data type	Care Level	Patient Count
Optum ClinFormatics	USA	Claims	IP,OP,ER	99.3M
Optum EHR	USA	EHR	IP,OP,ER	114.4M
Optum Market Clarity	USA	EHR	IP,OP,ER	90M
Papageorgiou General Hospital	Greece	EHR	IP,OP	1.4M
Penn State Health	USA	EHR	IP,OP,ER	8.7M
Premier	USA	Other	IP,OP,ER	300M
Semmelweis University	Hungary	EHR	IP,OP	1.9M
Seoul National University Bundang Hospital	Korea	EHR	IP,OP,ER	2.1M
Seoul National University Hospital	Korea	EHR	IP,OP,ER	2.1M
SMG-SNU Boramae Medical Center	Korea	EHR	IP,OP,ER	1M
Stanford University	USA	EHR	IP,OP,ER	3.8M
SUS Nexus Precision Data	Brazil	EHR	IP,OP	8.7M
Taipei Medical University	USA	EHR	IP,OP,ER	3.6M
Tufts University	USA	EHR	IP,OP,ER	3.9M
University of Colorado Anschutz MC	USA	EHR	IP,OP,ER	4.8M
University of Massachusetts Chan MC	USA	EHR	IP,OP,ER	3.4M
University of Texas Southwestern	USA	EHR	IP,OP,ER	5.5M
USC Keck Medical	USA	EHR	IP,OP,ER	883K
Veteran's Affairs	USA	EHR	IP,OP,ER	26.5M
Yonsei University Hospital	Korea	EHR	IP,OP,ER	6.4M

Quantifying power in the OHDSI Evidence Network

- 4,911 ingredient concepts (across all indications) appear in at least two databases
- For each database, we know the number of patients exposed to each drug.
- From this we can approximate the minimum detectable relative risk (MDRR) at power = 80% and alpha = 0.05
  - Given the prevalence of the outcome
  - Assuming we have a comparator of equal size

Computing minimum detectable relative risk

Tirzepatide

	Patients	MDRR
Database 21	4,730	6.18
Database 30	15,580	2.73
Entire network	2,617,400	1.08

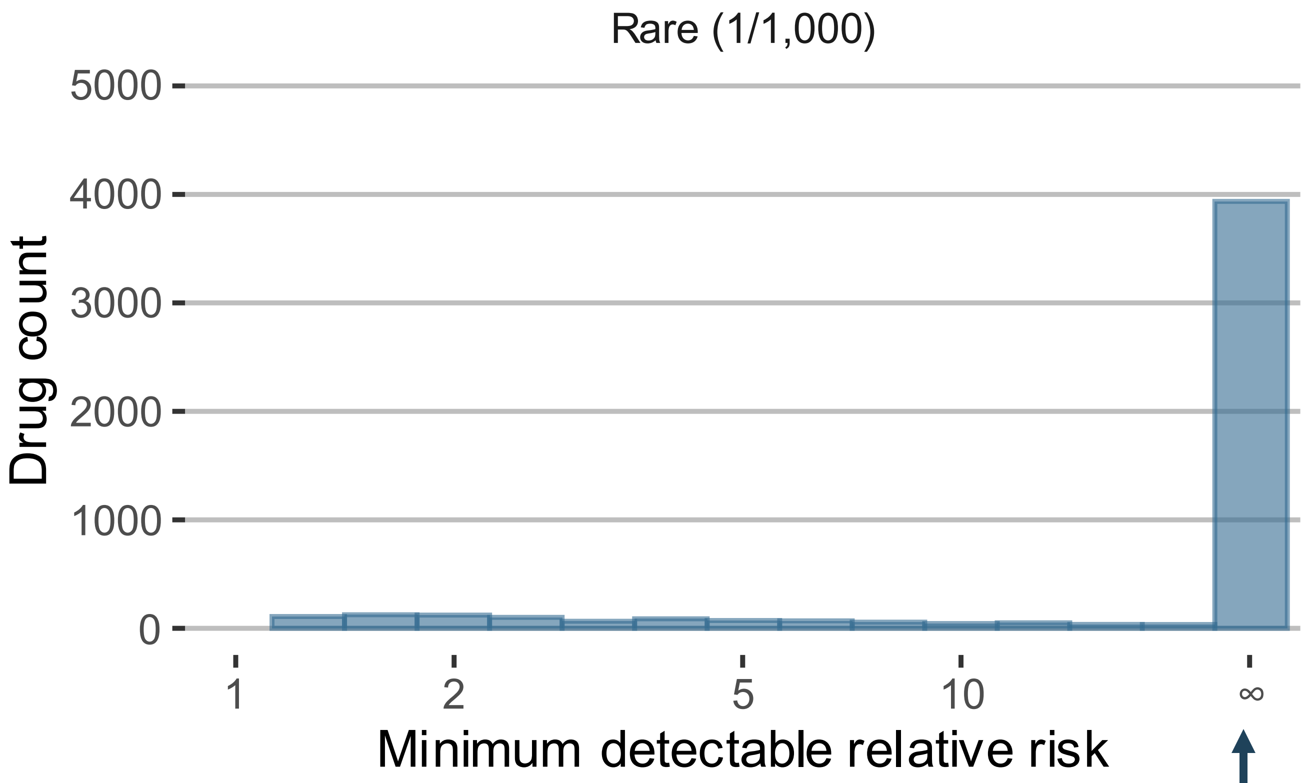
Empagliflozin

	Patients	MDRR
Database 21	21,600	2.35
Database 30	102,190	1.48
Entire network	10,295,190	1.04

Assuming the outcome is rare (1/1,000)

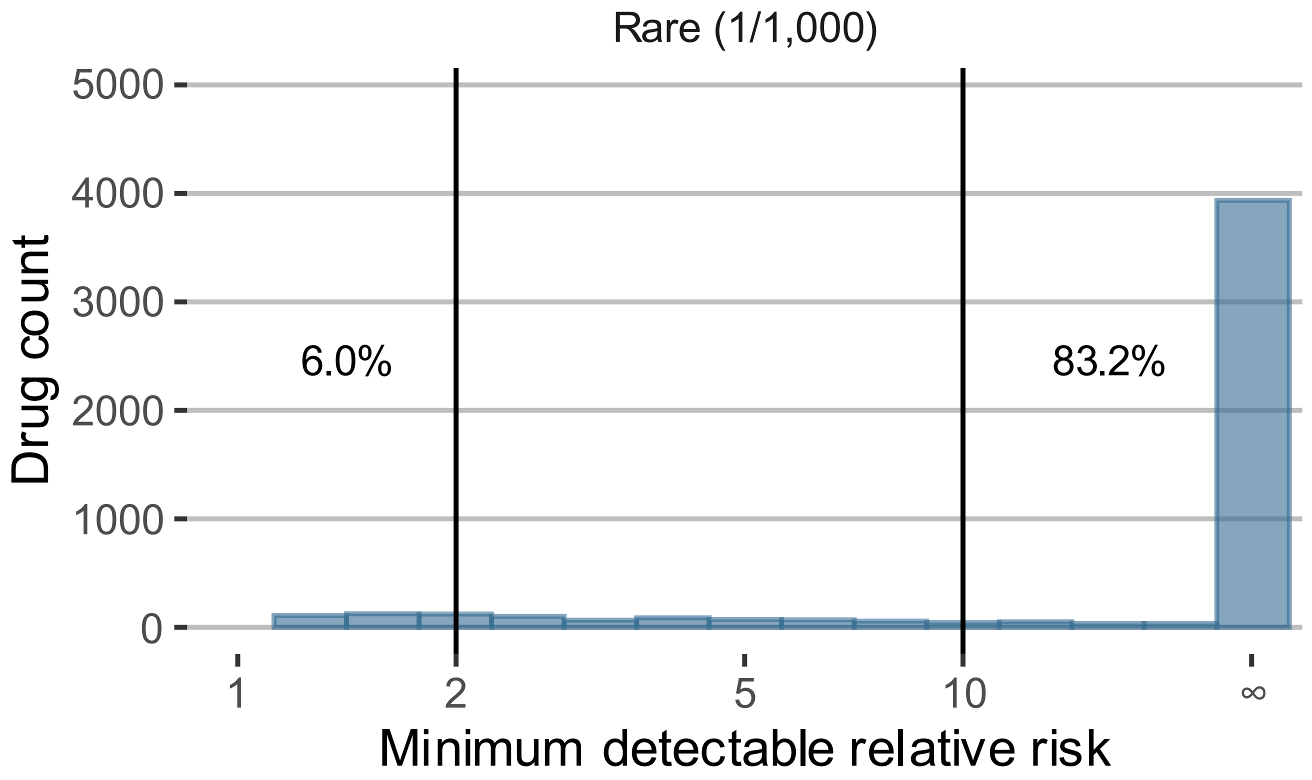
Computed this for all drugs and all databases

Distribution of MDRRs in a medium-sized database



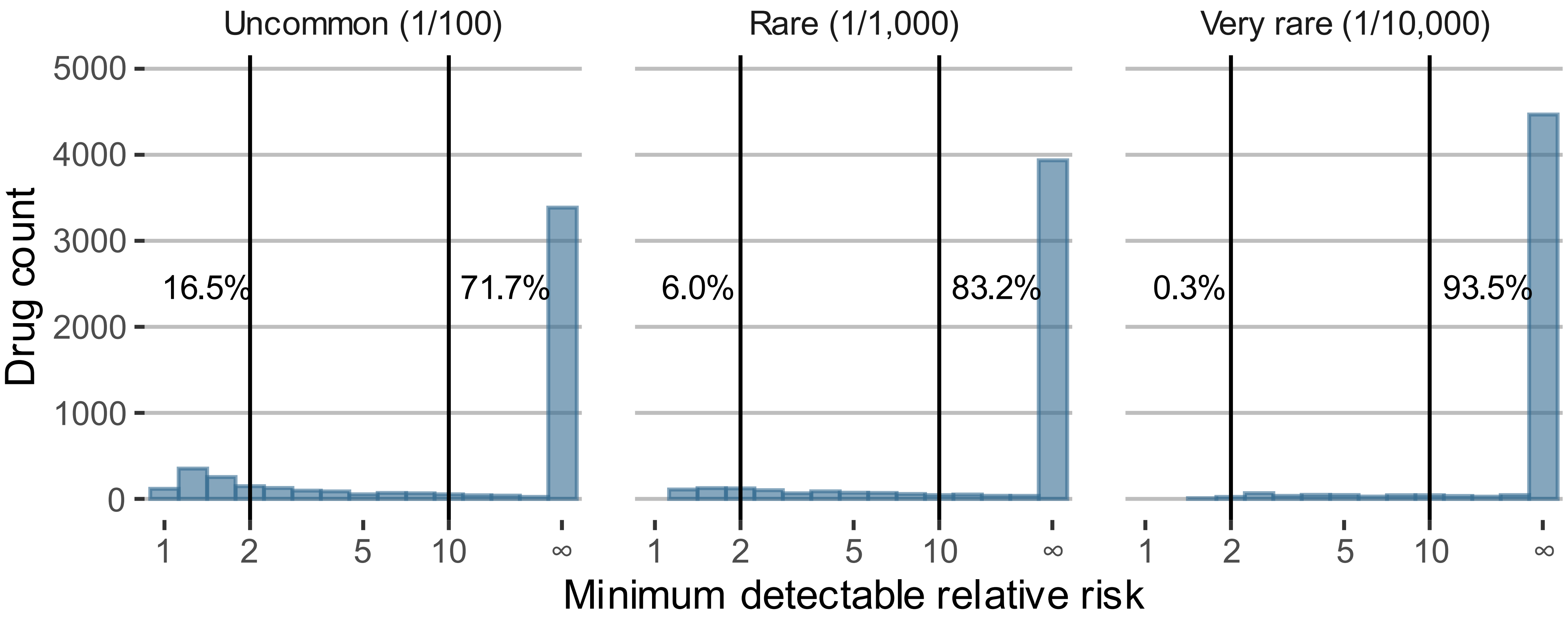
No data on most drugs

Distribution of MDRRs in a medium-sized database

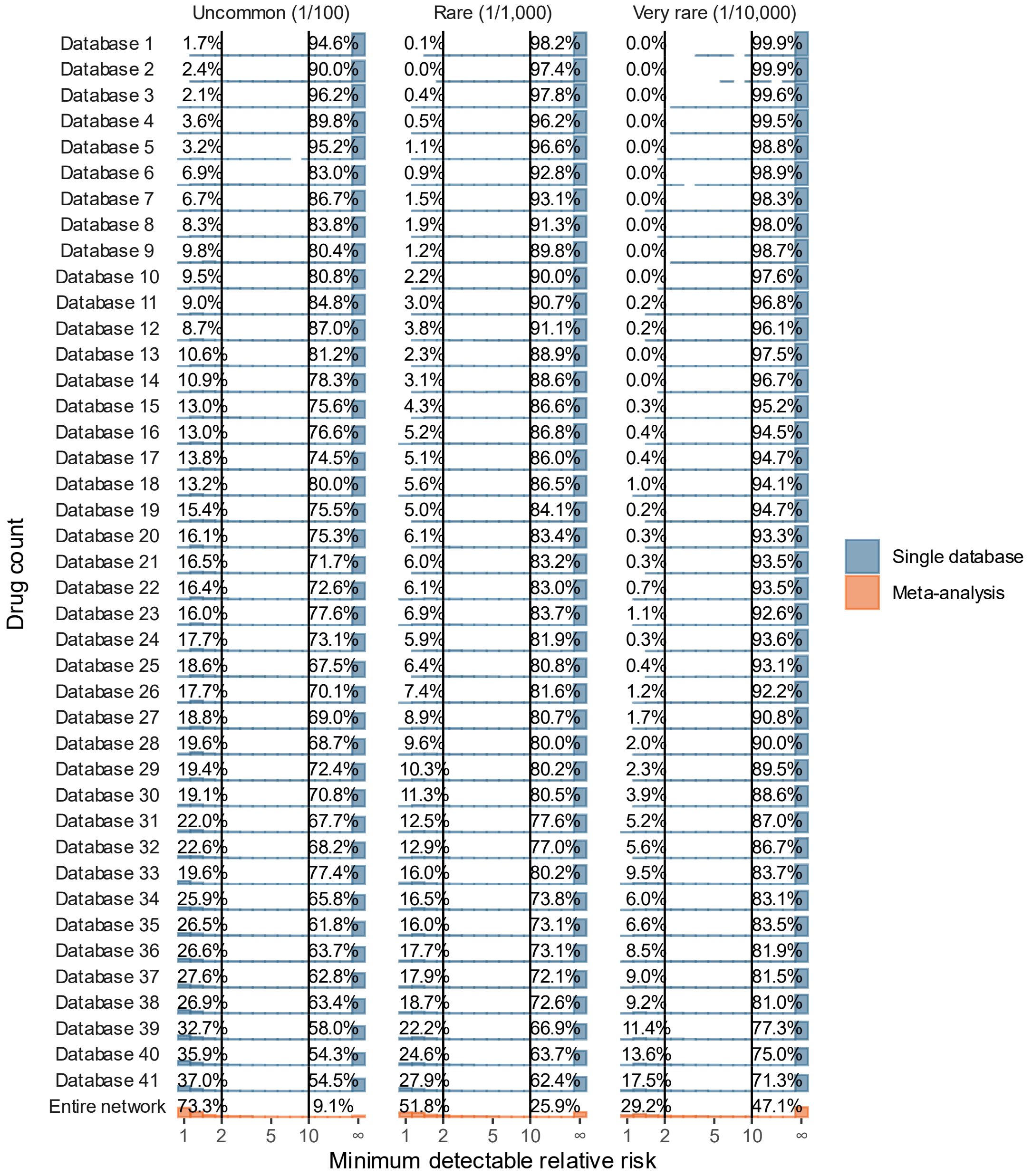


MDRR < 2: can probably show clinically relevant effects
MDRR > 10: likely not informative

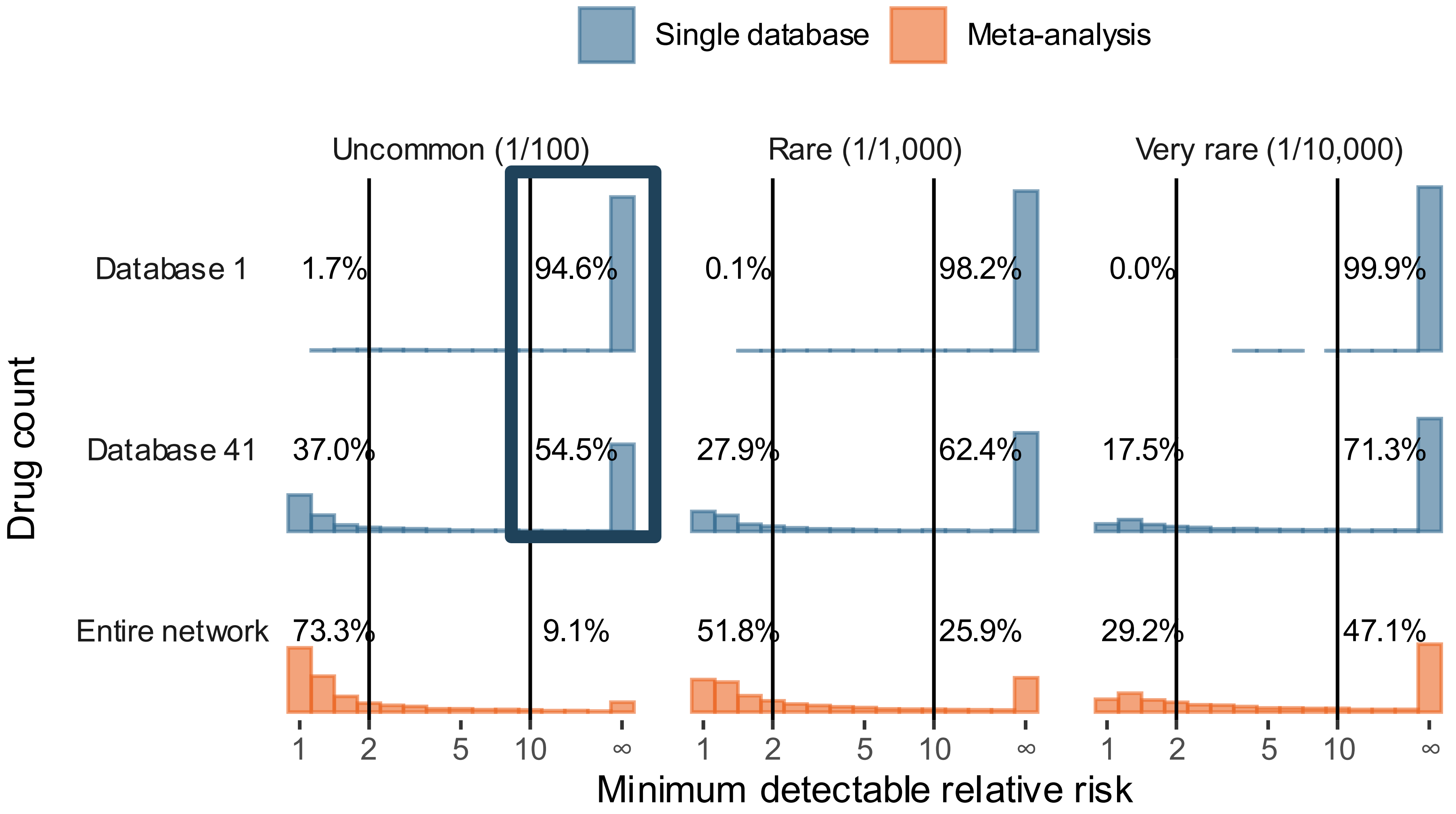
Distribution of MDRRs in a medium-sized database



Combining evidence across the network

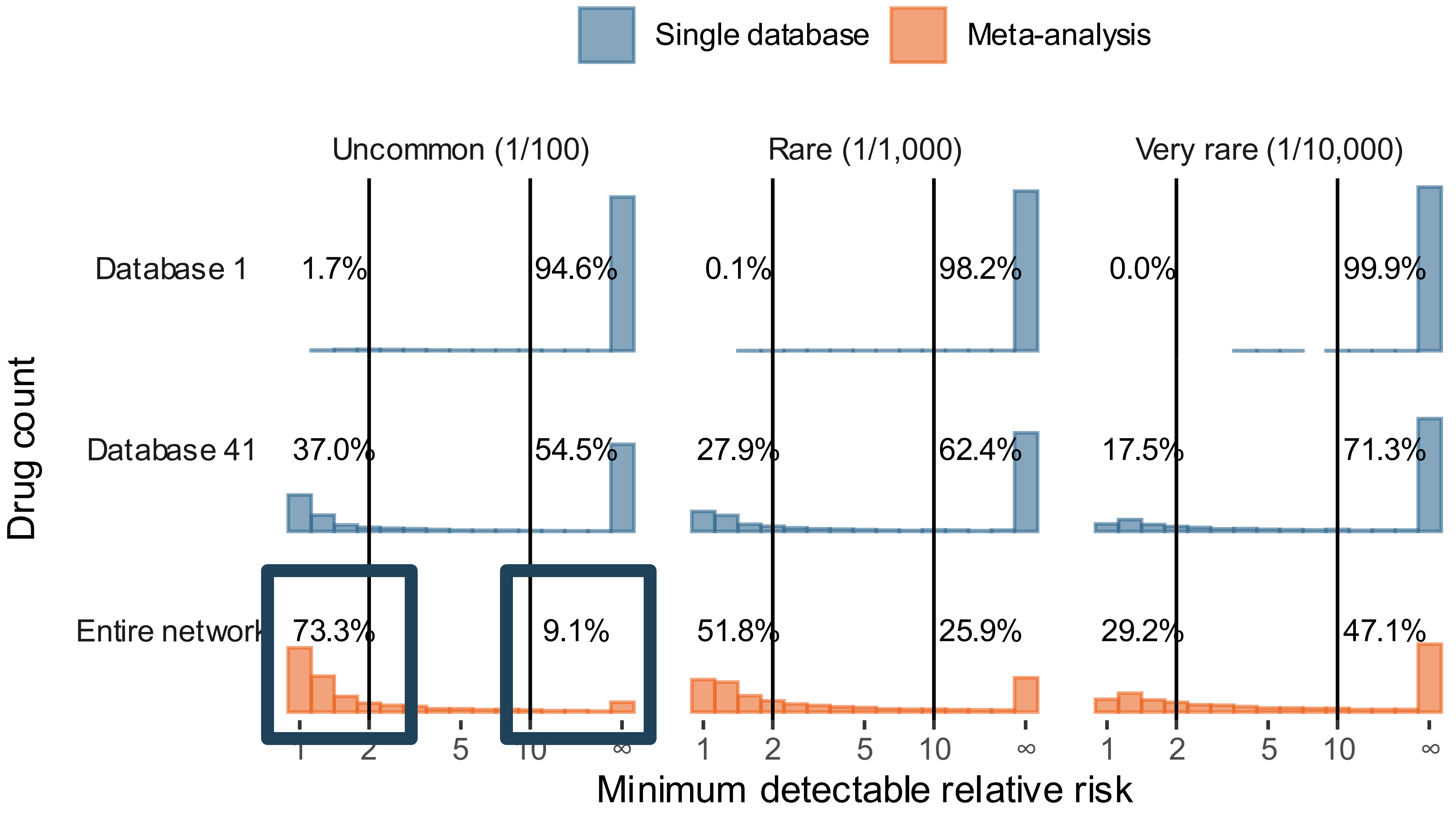


MDRR in the smallest and largest database



Most database cannot study most drugs on their own, even when the outcome occurs 1/100

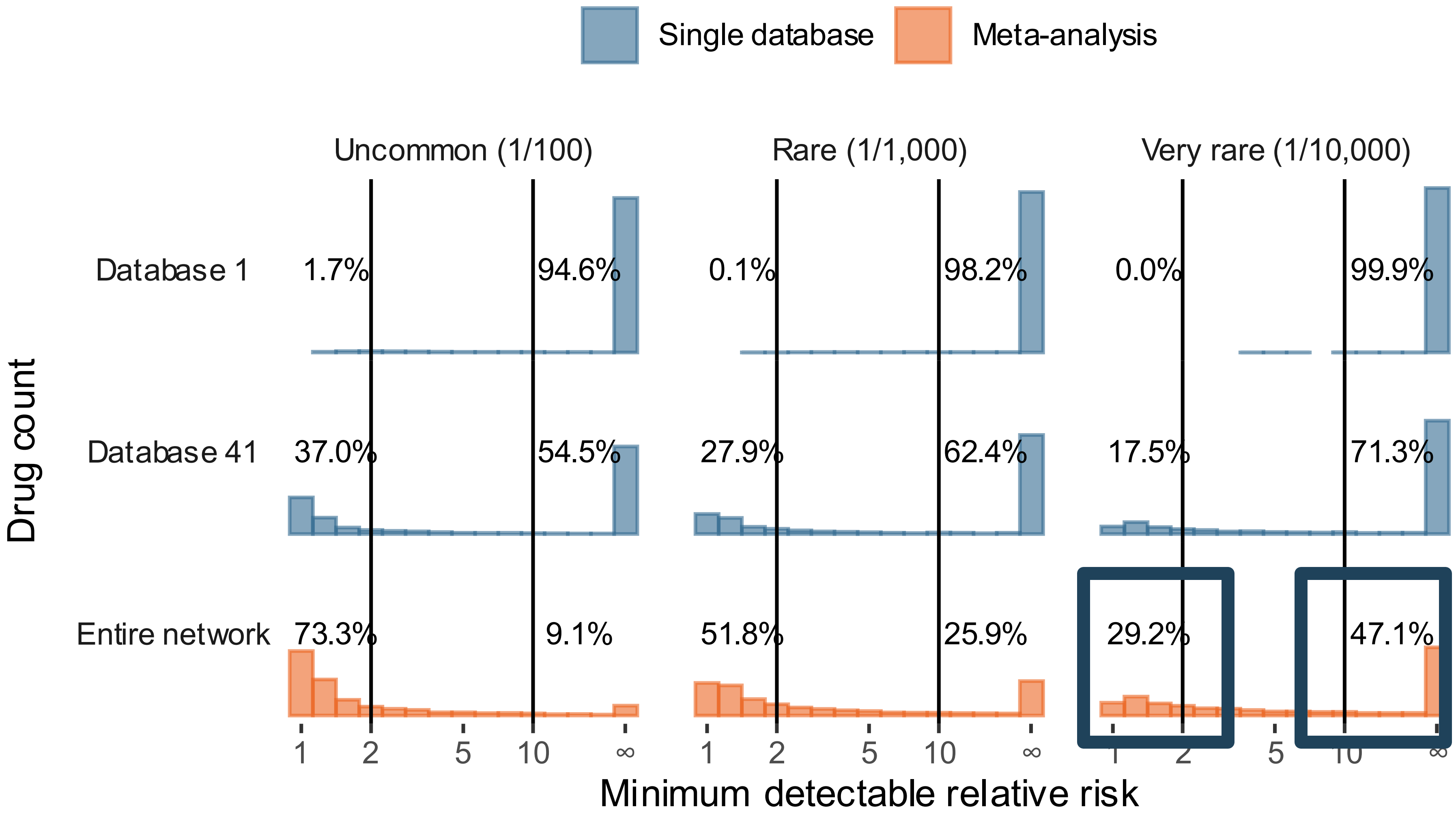
MDRR in the smallest and largest database



When combining evidence, many more drugs can be studied

We also have high power for more drugs

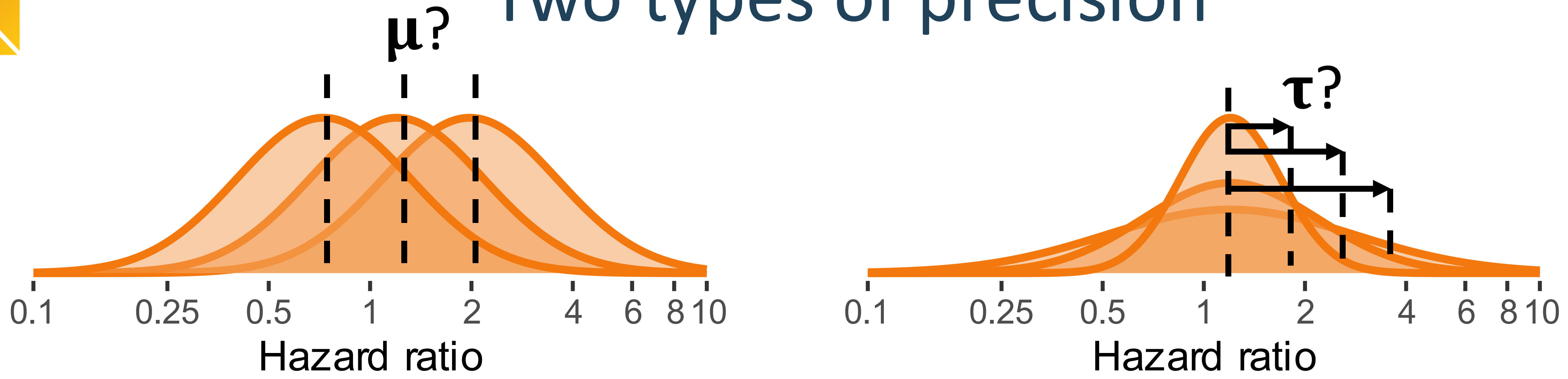
MDRR in the smallest and largest database



If the outcome is very rare, even the entire network is not enough to study many drugs

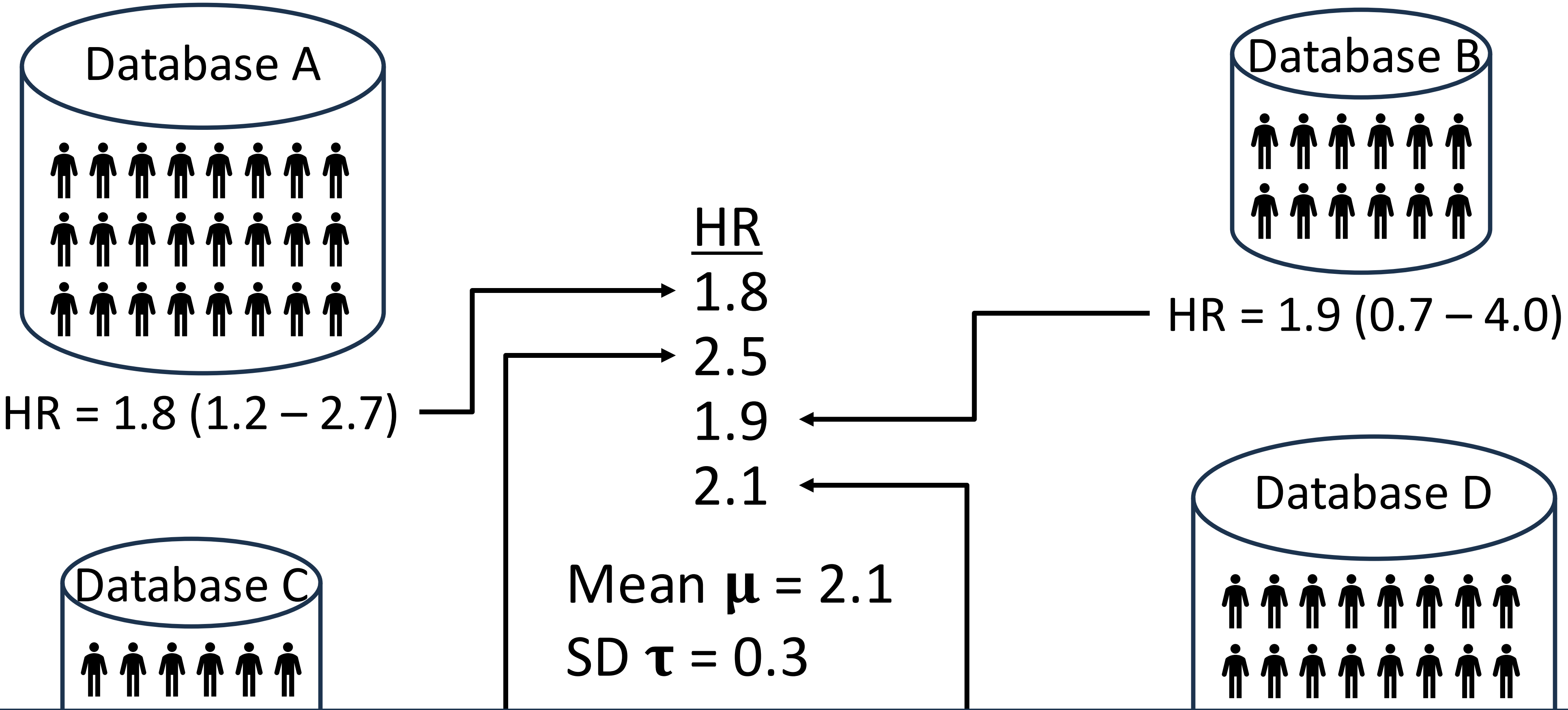
We need a bigger network!

Two types of precision



- Both meta-analytic estimate **μ** (the estimate of the effect) and **τ** (the estimate of consistency) will have uncertainty
  - Uncertainty around **μ** is essentially determined by the total number of people in the study
  - Uncertainty around **τ** is mostly driven by the number of databases

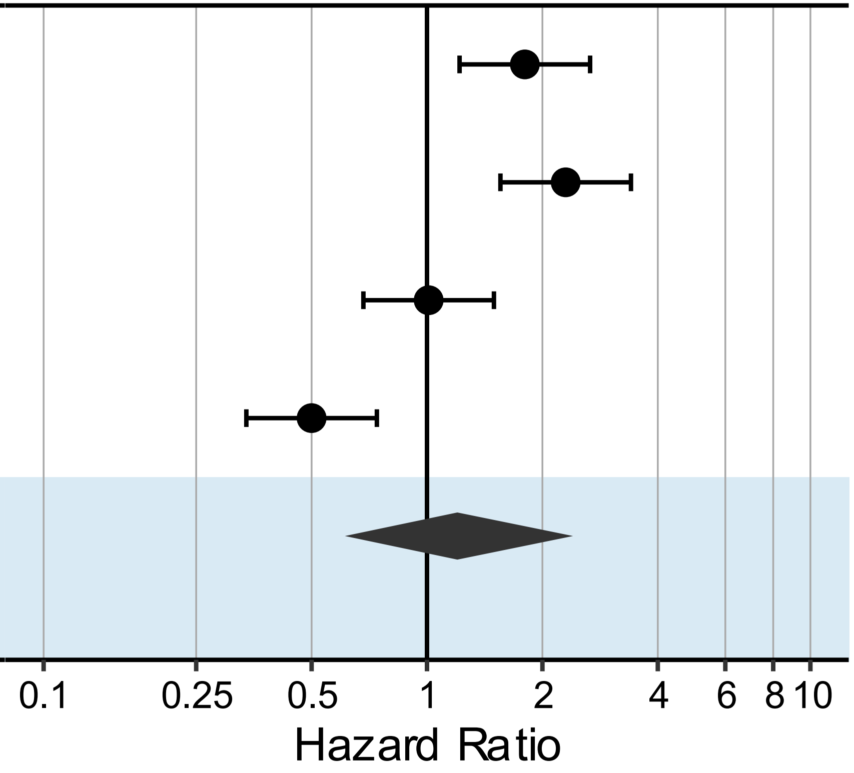
Uncertainty when sample is small



How certain are we about the mean and standard deviation when we only have a sample of 4? (Also, each has uncertainty of itself)

Random effects meta-analysis

Source	Hazard Ratio (95% CI)
Database A (US claims)	1.80 (1.22 - 2.66)
Database H (US EHR)	2.30 (1.55 - 3.40)
Database I (Dutch EHR)	1.01 (0.68 - 1.49)
Database J (Korea Claims)	0.50 (0.34 - 0.74)
Bayesian random effects τ = 0.60 (0.27 - 1.07)	**1.20 (0.61 - 2.40)**



Uncertainty around μ and τ are expressed as credible intervals

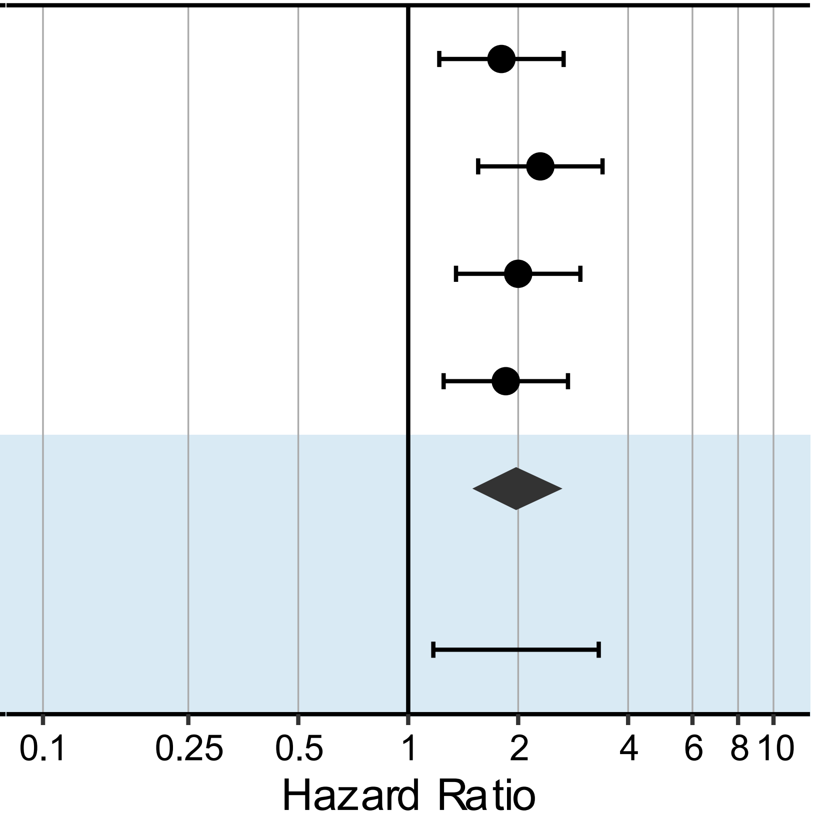
Integrating $\boldsymbol{\mu}$ and $\boldsymbol{\tau}$ and their uncertainty: the prediction interval

- The term 'prediction interval' relates to the use of this interval to **predict the possible underlying effect in a new study** that is similar to the studies in the meta-analysis.*
- Simplistically, it is centered on $\boldsymbol{\mu}$ and has $\mathrm{SD} = \sqrt{\boldsymbol{\tau}^2 + SE(\boldsymbol{\mu})^2}$
- Includes the uncertainty around $\boldsymbol{\mu}$ (number of persons) and $\boldsymbol{\tau}$ (number of databases)

* Cochrane handbook

Prediction interval examples

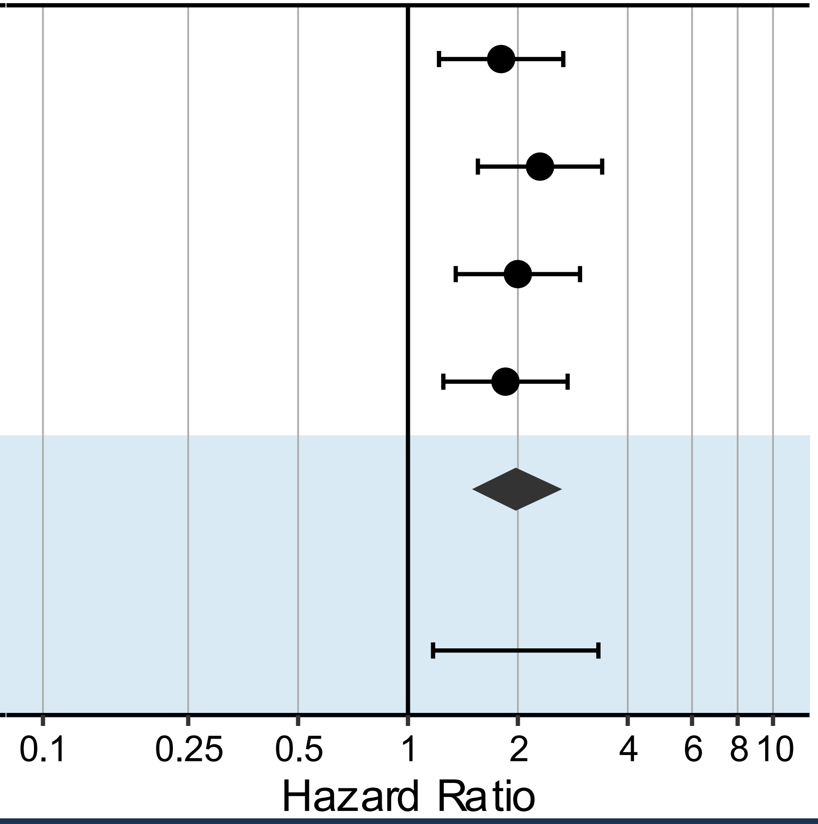
Source	Hazard Ratio (95% CI)	
Database A (US claims)	1.80	(1.22 - 2.66)
Database B (US claims)	2.30	(1.55 - 3.40)
Database C (US claims)	2.00	(1.35 - 2.96)
Database D (US claims)	1.85	(1.25 - 2.74)
Bayesian random effects τ = 0.12 (0.00 - 0.44)	**1.97**	**(1.50 - 2.64)**
Prediction interval		**(1.17 - 3.32)**



High consistency, high precision, so narrow prediction interval

Prediction interval examples

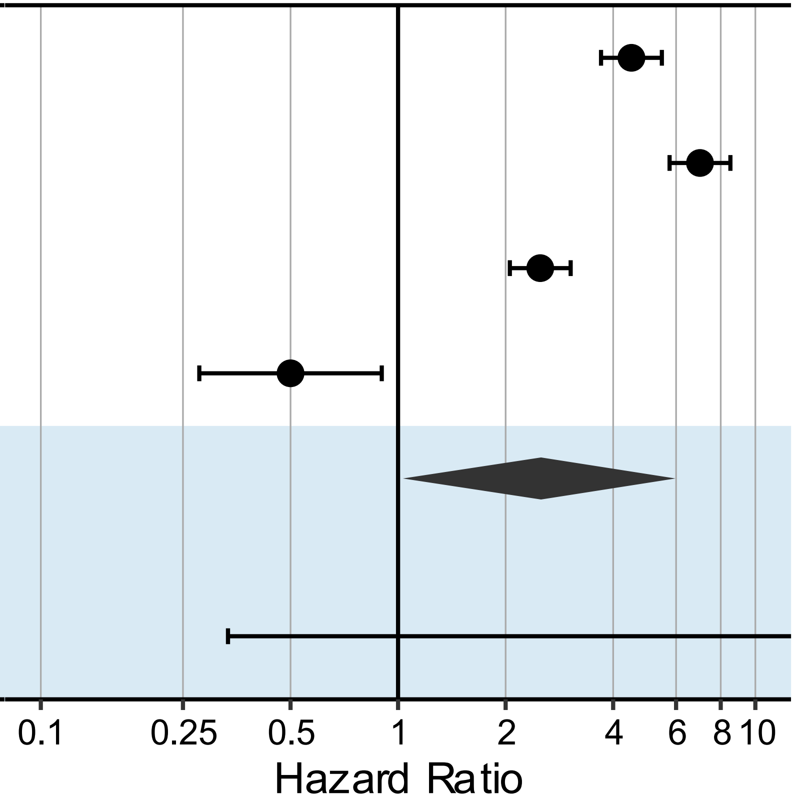
Source	Hazard Ratio (95% CI)	
Database A (US claims)	1.80	(1.22 - 2.66)
Database B (US claims)	2.30	(1.55 - 3.40)
Database C (US claims)	2.00	(1.35 - 2.96)
Database D (US claims)	1.85	(1.25 - 2.74)
Bayesian random effects τ = 0.12 (0.00 - 0.44)	**1.97**	**(1.50 - 2.64)**
Prediction interval		**(1.17 - 3.32)**



Both the prediction interval and meta-analytic estimate agree there is an effect, meaning a future study is predicted to agree.

Prediction interval examples

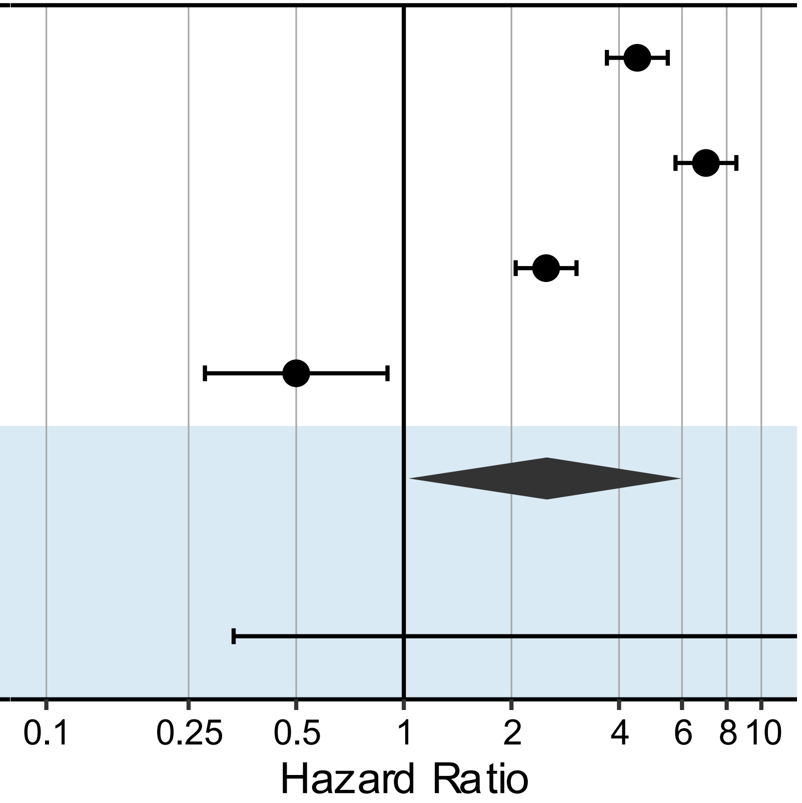
Source	Hazard Ratio (95% CI)	
Database H (US claims)	4.50	(3.70 - 5.47)
Database I (US EHR)	7.00	(5.75 - 8.52)
Database J (Dutch EHR)	2.50	(2.06 - 3.04)
Database K (Korea Claims)	0.50	(0.28 - 0.90)
Bayesian random effects τ = 0.84 (0.47 - 1.30)	**2.51**	**(1.03 - 5.98)**
Prediction interval		**(0.33 - 18.45)**



Low consistency so wide prediction interval

Prediction interval examples

Source	Hazard Ratio (95% CI)	
Database H (US claims)	4.50	(3.70 - 5.47)
Database I (US EHR)	7.00	(5.75 - 8.52)
Database J (Dutch EHR)	2.50	(2.06 - 3.04)
Database K (Korea Claims)	0.50	(0.28 - 0.90)
Bayesian random effects τ = 0.84 (0.47 - 1.30)	**2.51**	**(1.03 - 5.98)**
Prediction interval		**(0.33 - 18.45)**



The meta-analytic estimate shows an increased risk, but the prediction interval suggests we're uncertain what a next study might show, which could even be a decreased risk!

The value of the prediction interval

- When we have a tight prediction interval, we expect that any conclusion we draw from the prediction interval would not be changed by the next study. In other words: we expect **high replicability**
- When the prediction interval is wide, we may have learned something, but are less confident the result can be replicated
- You can get a tight prediction interval by having high precision of $\boldsymbol{\mu}$ (many patients), high precision of $\boldsymbol{\tau}$ (many databases), and low $\boldsymbol{\tau}$ (consistency)
- If there is inconsistency that mostly stems from residual systematic error, simulations show the prediction interval has better coverage than the confidence interval
- We should always report the prediction interval

	Accuracy	Precision	Consistency
Within a database	✓	✓	✓
Across databases	🔍	✓	✓

Accuracy across databases

Ensuring accuracy across databases

- OHDSI best practices aim to reduce bias within each database as much as possible
- When estimates are consistent across databases, it is unlikely there are database-specific residual biases
- This evidence becomes stronger when the databases are more diverse
  - Observing consistency across US claims databases is less informative than observing consistency across claims, EHRs, and different countries

Diversity across the OHDSI Evidence Network

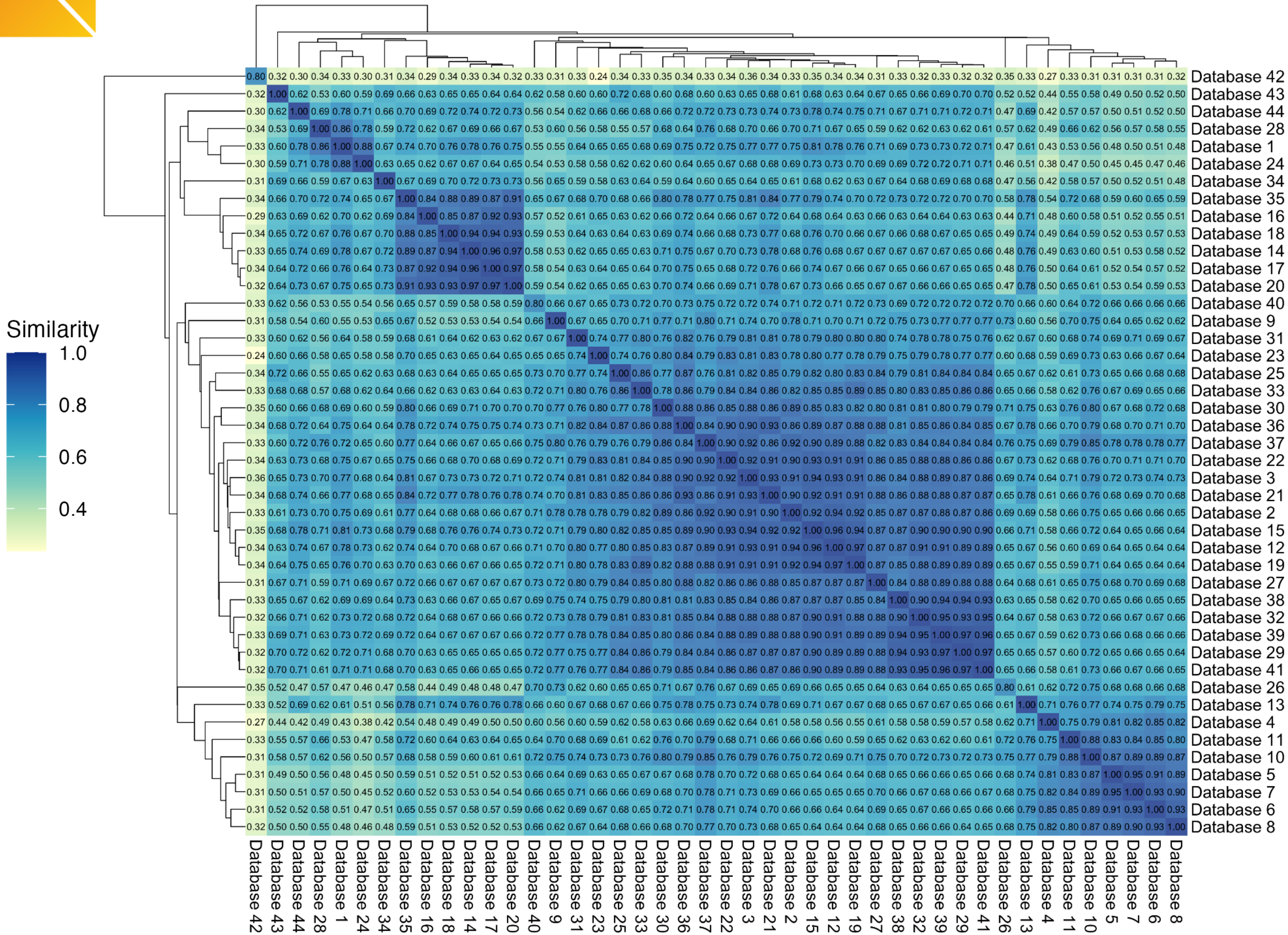
Data Source	Country	Data type	Care Level	Patient Count
Ajou University School of Medicine	Korea	EHR	IP,OP,ER	2.7M
Clinical Hospital Center Zvezdara	Serbia	EHR	IP,OP,ER	618K
Columbia University Irving Medical Center	USA	EHR	IP,OP,ER	7M
Emory University	USA	EHR	IP,OP,ER	6.5M
GUSTO Singapore Cohort	Singapore	Registry	OP	2.6K
HealthPartners Institute	USA	EHR	IP,OP,ER	3.2M
IMRD EMIS	UK	EHR	IP,OP	5.1M
IQVIA Australia EMR	Australia	EHR	OP	2.7M
IQVIA Belgium LPD	Belgium	EHR	OP	1.1M
IQVIA France DA	France	EHR	OP	6.2M
IQVIA France LPD	France	EHR	OP	17.4M
IQVIA Germany DA	Germany	EHR	OP	40.8M
IQVIA LPD Spain	Spain	EHR	OP	2.7M
IQVIA PharMetrics Plus	USA	Claims	IP,OP,ER	170.2M
IQVIA US Hospital	USA	EHR	IP,OP,ER	113.1M
IQVIA US Open Claims	USA	EHR	IP,OP,ER	330M
JMDC	Japan	Claims	IP,OP	17.6M
Johns Hopkins University	USA	EHR	IP,OP,ER	2.2M
Lancashire Teaching Hospitals NHS Trust	UK	EHR	IP,OP,ER	1.5M
Merative CCAE	USA	Claims	IP,OP,ER	172.2M
Merative MDCD	USA	Claims	IP,OP,ER	36.1M
Merative MDCR	USA	Claims	IP,OP,ER	11.3M

Data Source	Country	Data type	Care Level	Patient Count
Optum ClinFormatics	USA	Claims	IP,OP,ER	99.3M
Optum EHR	USA	EHR	IP,OP,ER	114.4M
Optum Market Clarity	USA	EHR	IP,OP,ER	90M
Papageorgiou General Hospital	Greece	EHR	IP,OP	1.4M
Penn State Health	USA	EHR	IP,OP,ER	8.7M
Premier	USA	Billing	IP,OP,ER	300M
Semmelweis University	Hungary	EHR	IP,OP	1.9M
Seoul National University Bundang Hospital	Korea	EHR	IP,OP,ER	2.1M
Seoul National University Hospital	Korea	EHR	IP,OP,ER	2.1M
SMG-SNU Boramae Medical Center	Korea	EHR	IP,OP,ER	1M
Stanford University	USA	EHR	IP,OP,ER	3.8M
SUS Nexus Precision Data	Brazil	EHR	IP,OP	8.7M
Taipei Medical University	USA	EHR	IP,OP,ER	3.6M
Tufts University	USA	EHR	IP,OP,ER	3.9M
University of Colorado Anschutz MC	USA	EHR	IP,OP,ER	4.8M
University of Massachusetts Chan MC	USA	EHR	IP,OP,ER	3.4M
University of Texas Southwestern	USA	EHR	IP,OP,ER	5.5M
USC Keck Medical	USA	EHR	IP,OP,ER	883K
Veteran's Affairs	USA	EHR	IP,OP,ER	26.5M
Yonsei University Hospital	Korea	EHR	IP,OP,ER	6.4M

Measuring diversity in the OHDSI evidence network

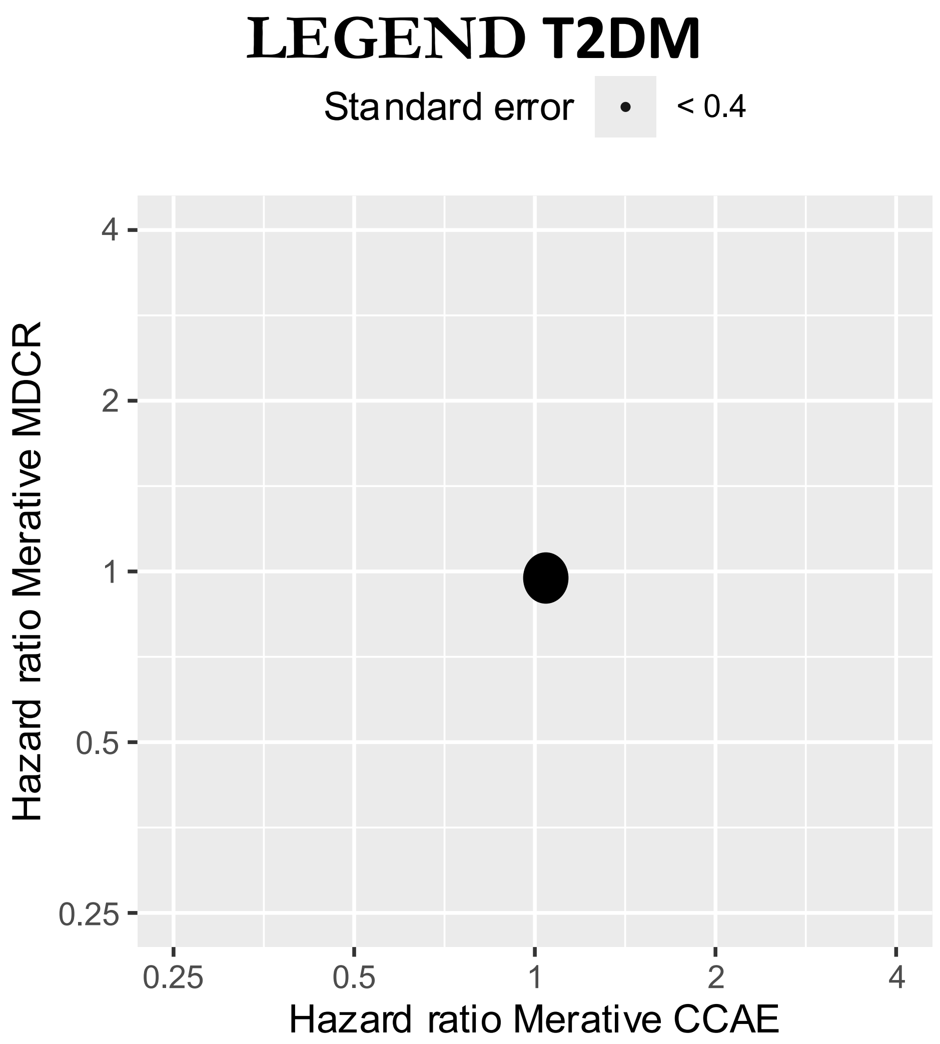
- Computing average similarity based on aggregate statistics:
  - demographics: age/sex
  - longitudinality (observation period length)
  - visit composition (inpatient/outpatient/emergency room)
  - condition prevalence
  - drug era prevalence
- This can be computed from data collected for Database Diagnostics
- These were collected for all databases in the **OHDSI Evidence Network**

Database similarity in the OHDSI Evidence Network



Does this similarity correspond to similar biases?

Measure bias similarity by comparing unadjusted estimates

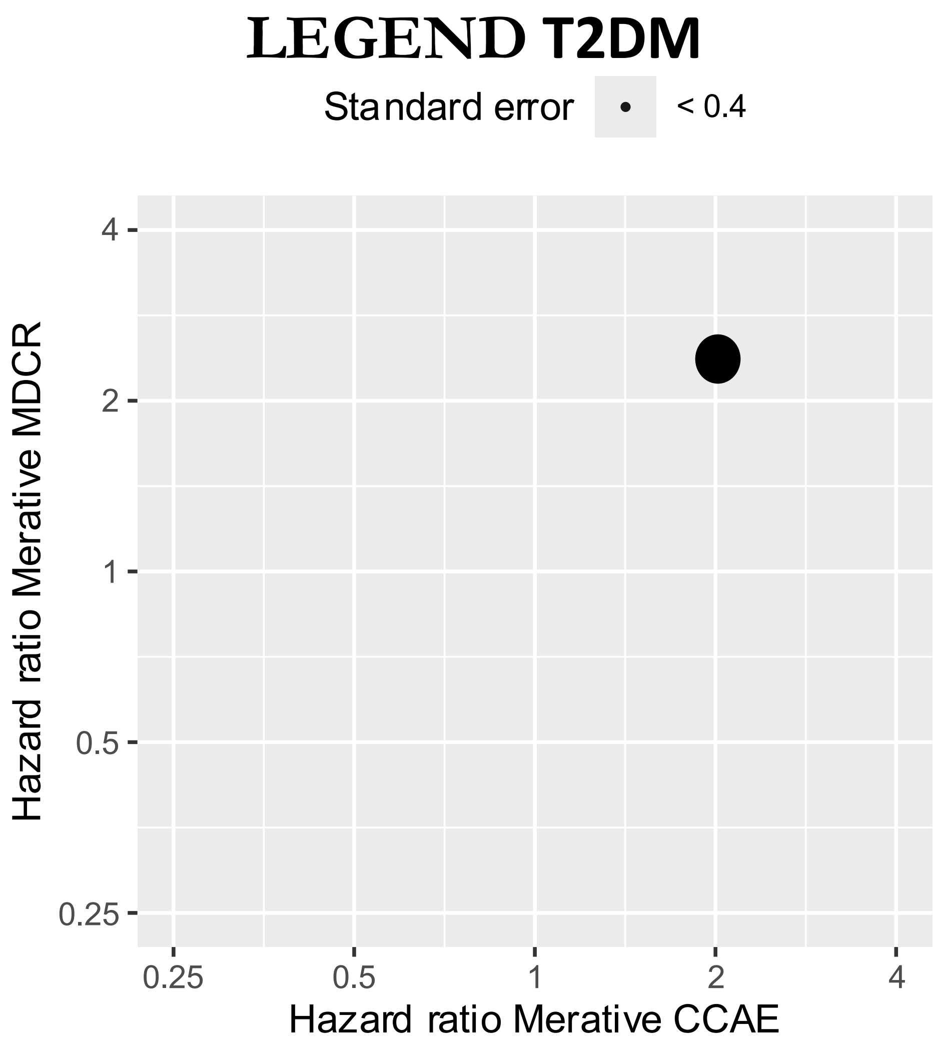


Target: DPP4I
Comparator: SU
Outcome: Ingrowing nail

Merative CCAE: HR = 1.02 (0.93-1.13)
Merative MDCR: HR = 0.98 (0.85-1.13)

Unadjusted estimates, so reflecting biases in each database

Measure bias similarity by comparing unadjusted estimates

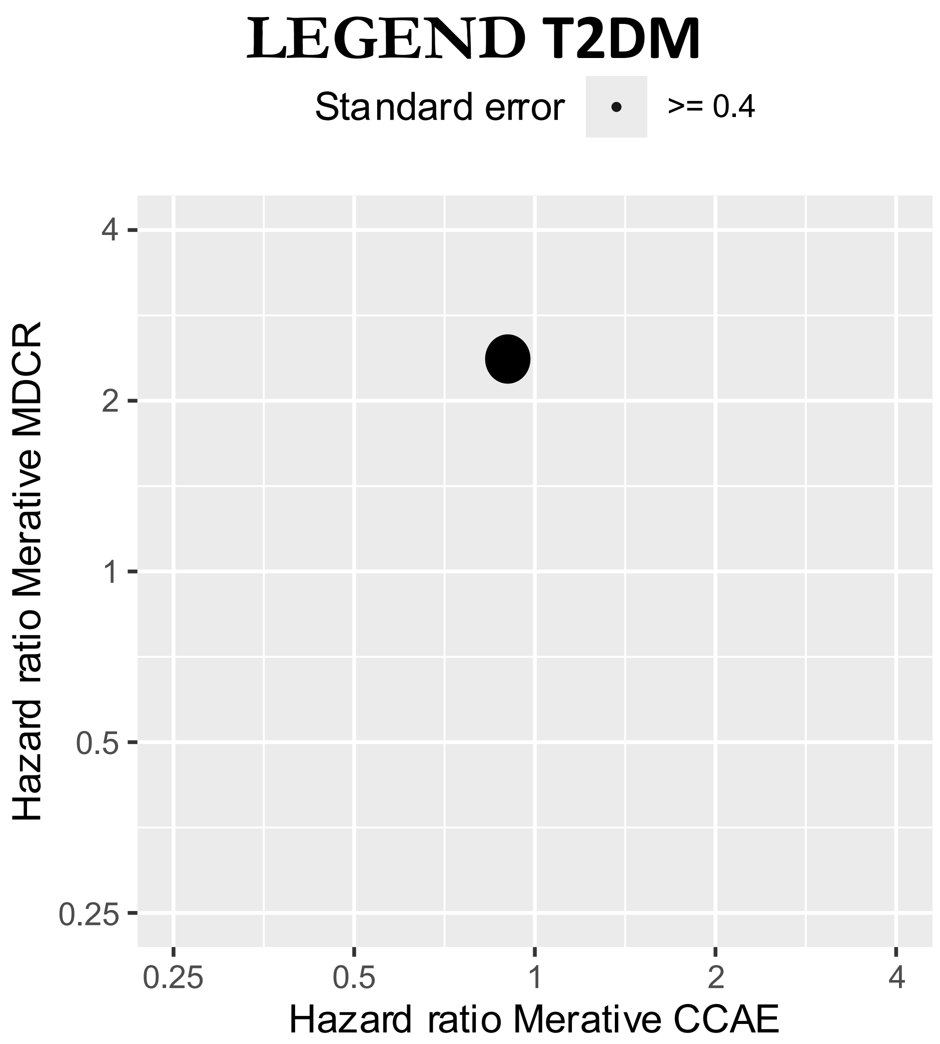


Target: GLP1RA
Comparator: SU
Outcome: Melena

Merative CCAE: HR = 2.00 (1.59-2.51)
Merative MDCR: HR = 2.35 (1.26-4.39)

Unadjusted estimates, so reflecting biases in each database

Measure bias similarity by comparing unadjusted estimates

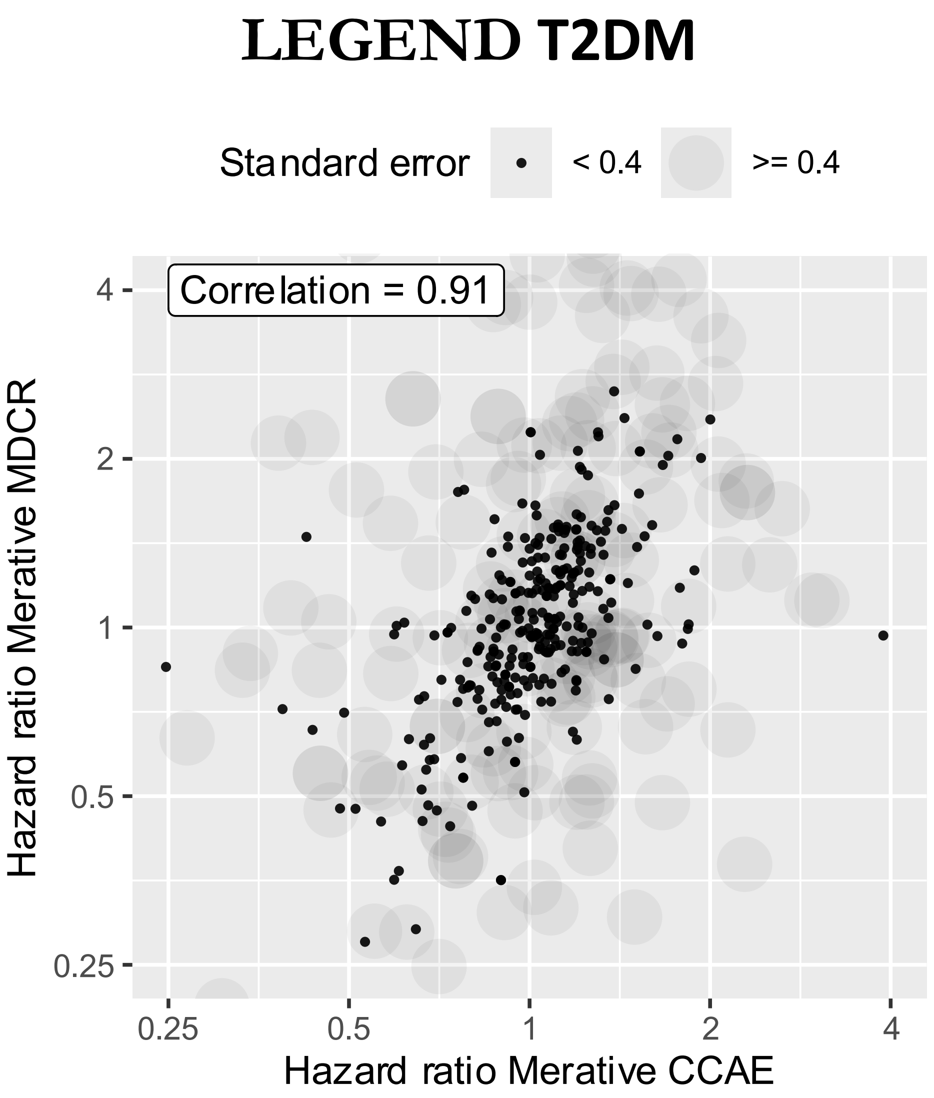


Target: GLP1RA
Comparator: SGLT2I
Outcome: Nicotine dependence

Merative CCAE: HR = 0.89 (0.74-1.06)
Merative MDCR: HR = 2.38 (1.04-5.46)

Unadjusted estimates, so reflecting biases in each database

Computing bias correlation



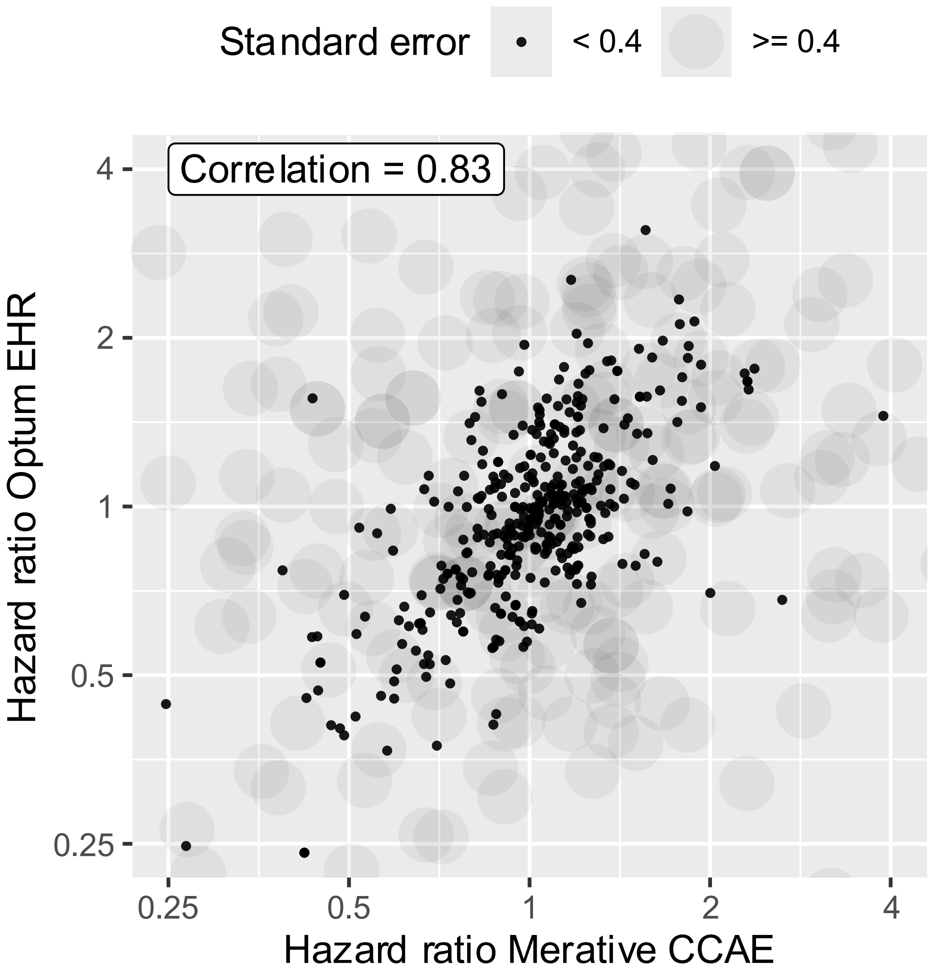
We can compute the correlation between unadjusted estimates to estimate bias similarity

We use a correlation measure that accounts for the uncertainty (standard error) of each estimate

Here we see high correlation between two US claims databases

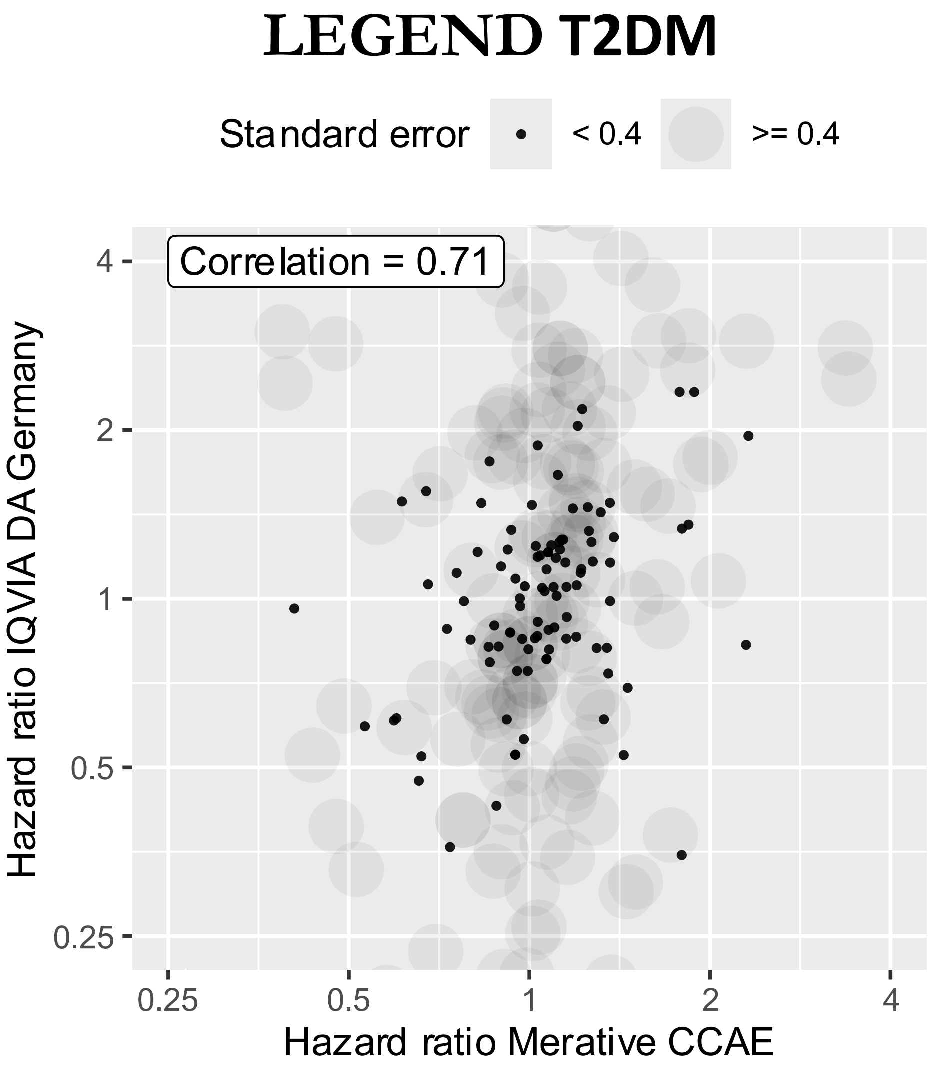
Understanding heterogeneity

LEGEND T2DM



We see slightly lower correlation between a US claims and a US EHR database

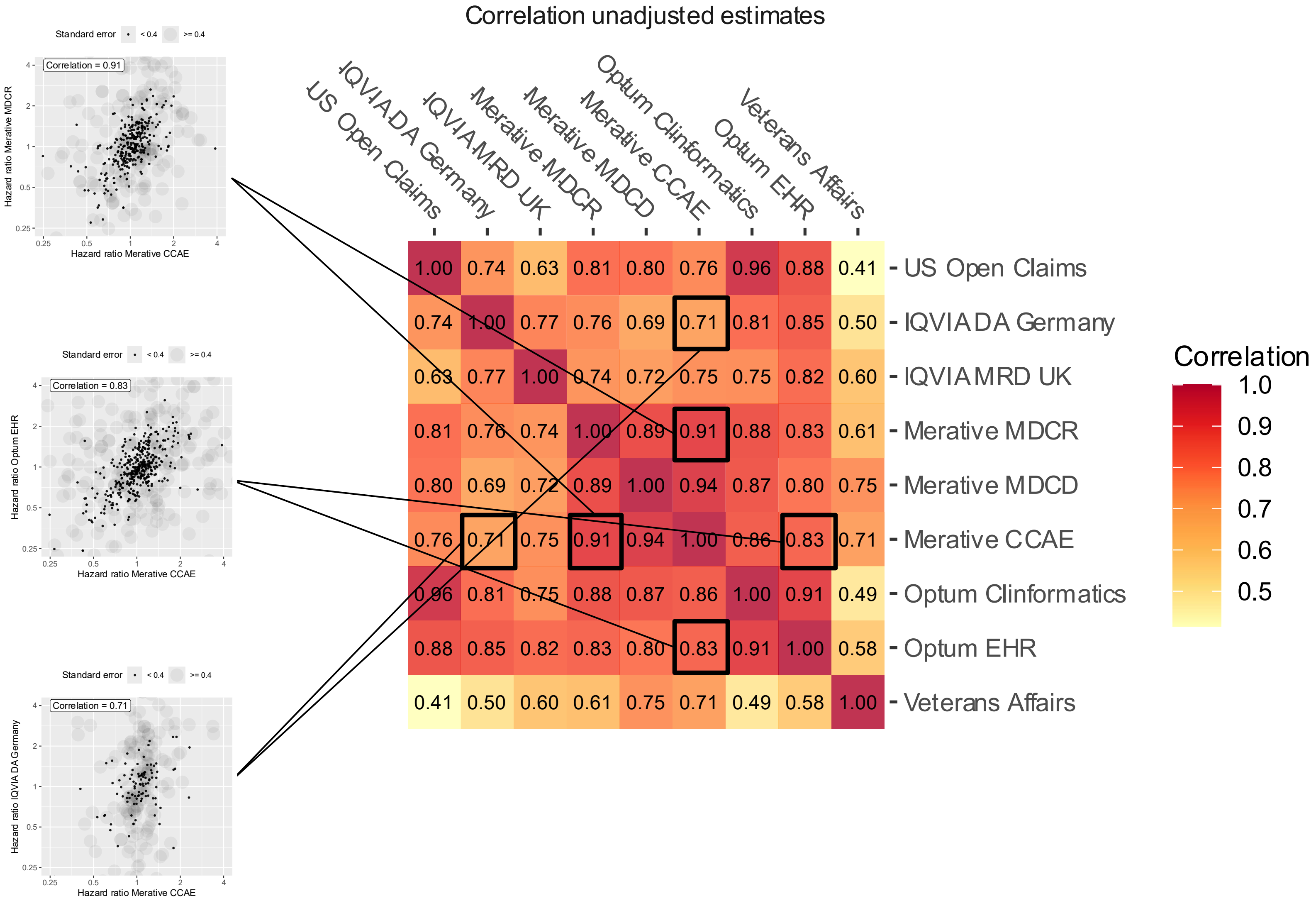
Understanding heterogeneity



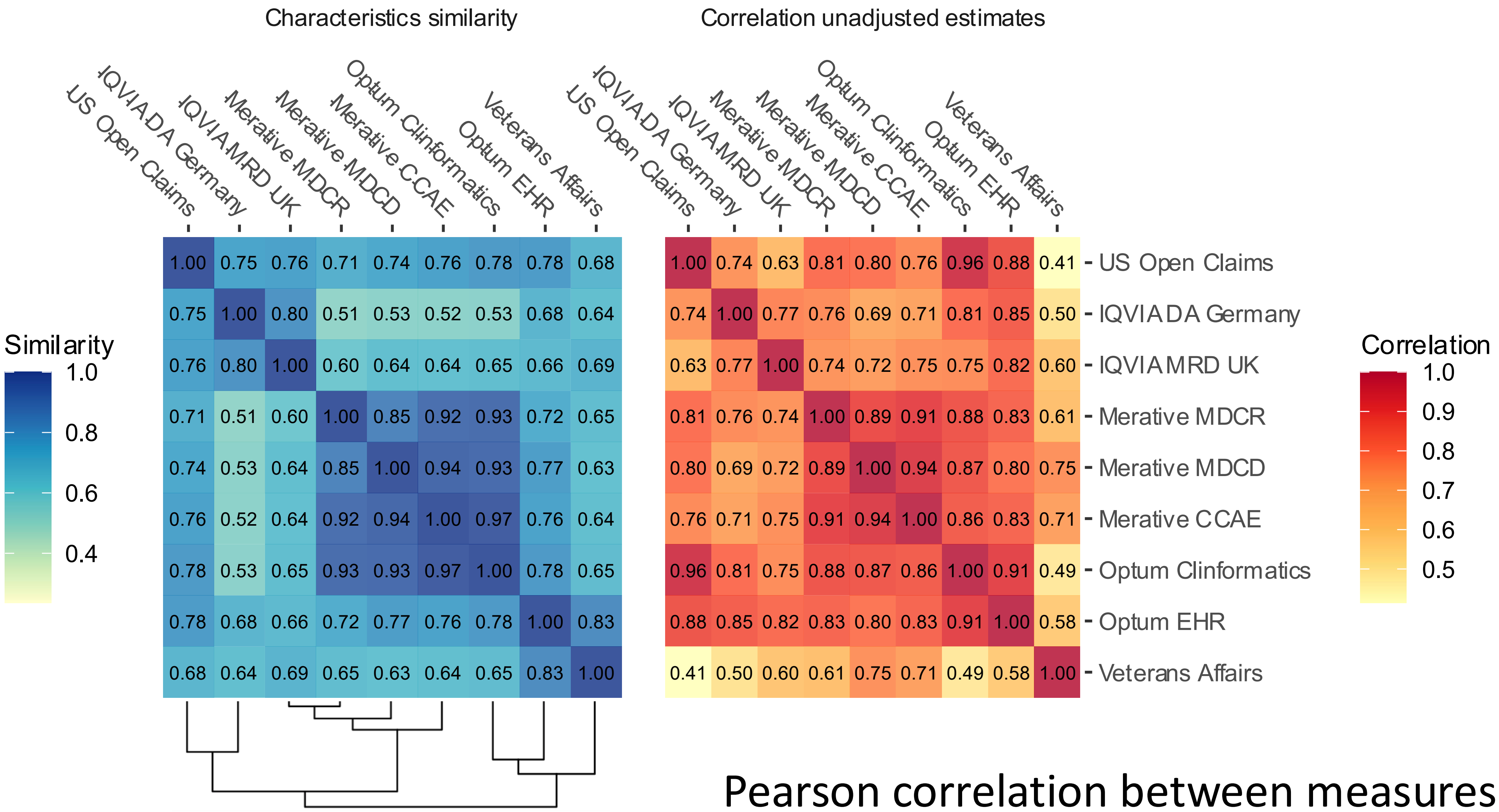
We see even lower correlation between a US claims and a German EHR database

It seems databases with similar characteristics have more similar effect estimates

Computing a bias similarity matrix

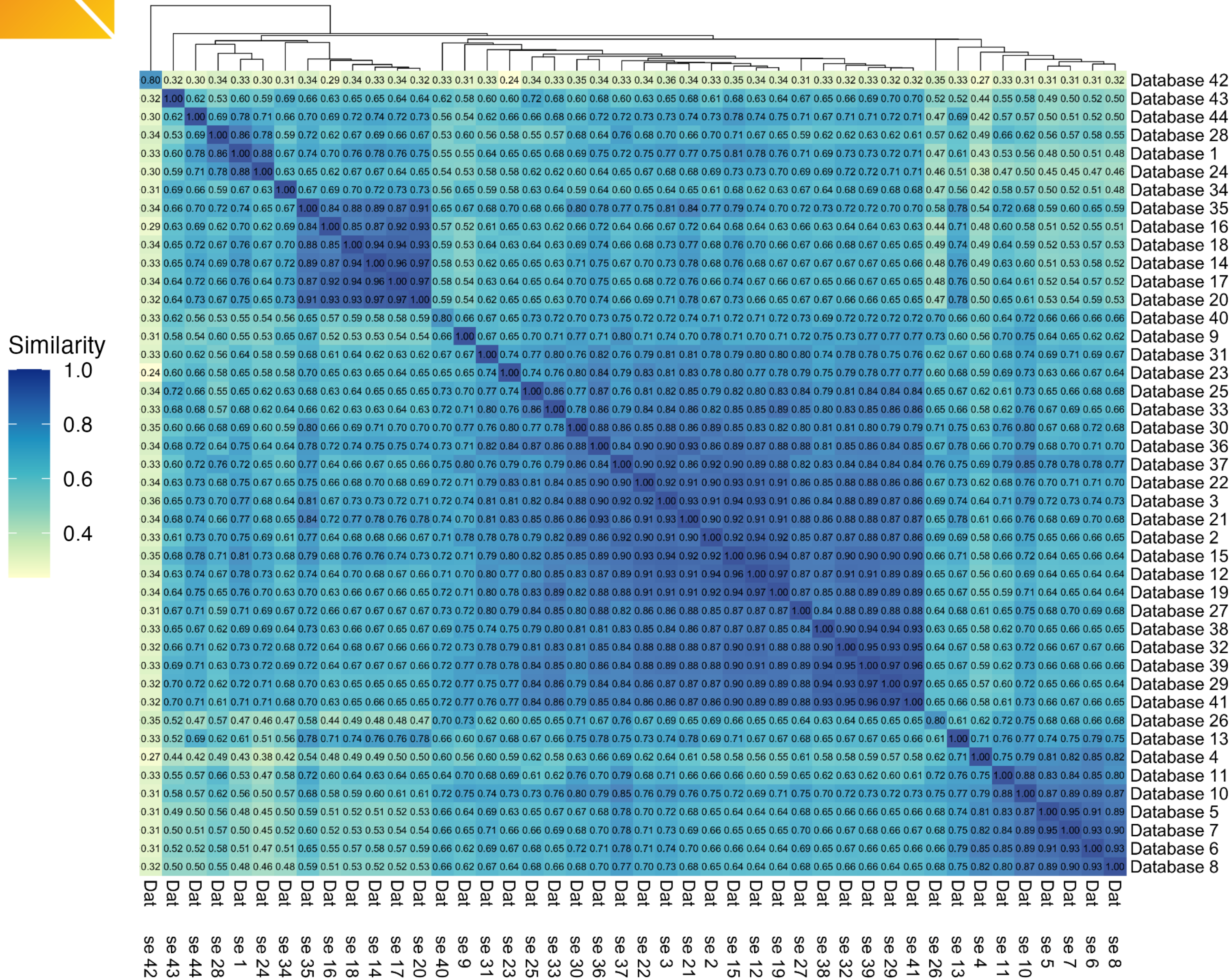


Comparing characteristic similarity to effect estimate similarity

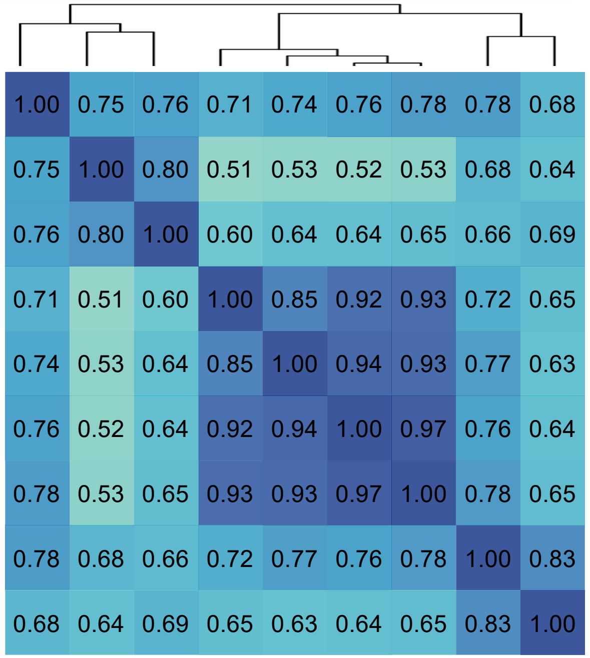


Pearson correlation between measures: 0.46

How diverse was LEGEND T2DM?



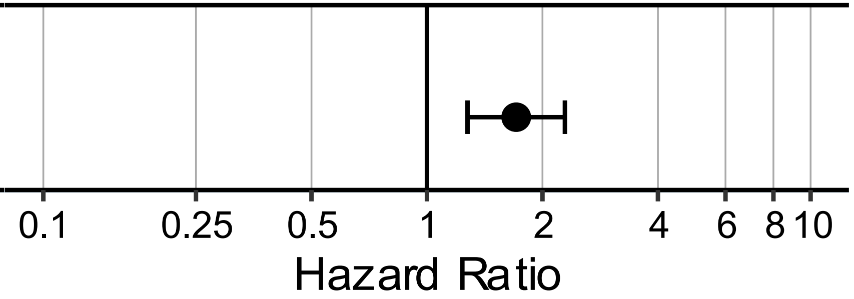
LEGEND T2DM



Trust the network

GLP1RA vs SU for Hypotension

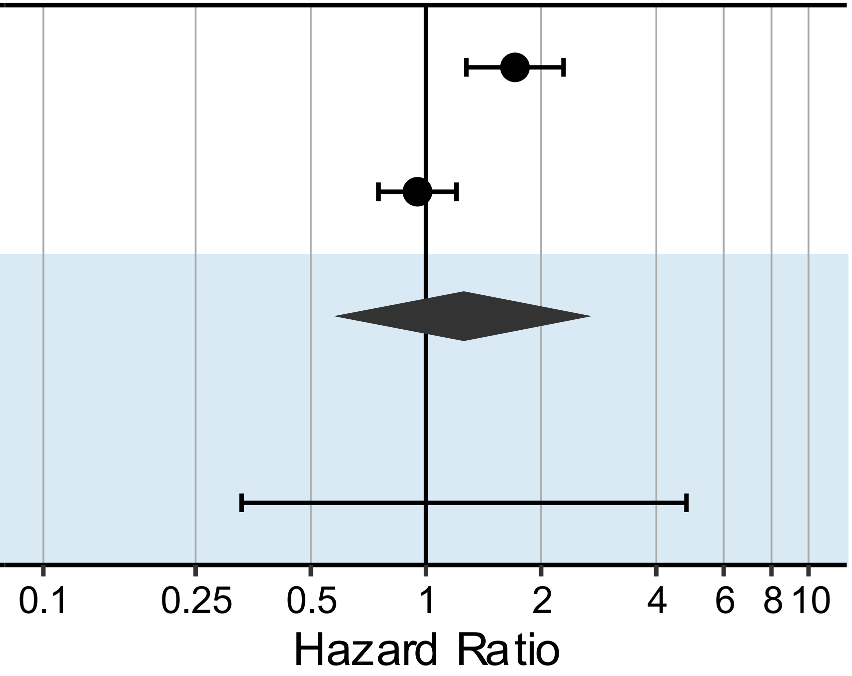
Source	Hazard Ratio (95% CI)
Optum EHR	1.71 (1.28 - 2.29)



Trust the network

GLP1RA vs SU for Hypotension

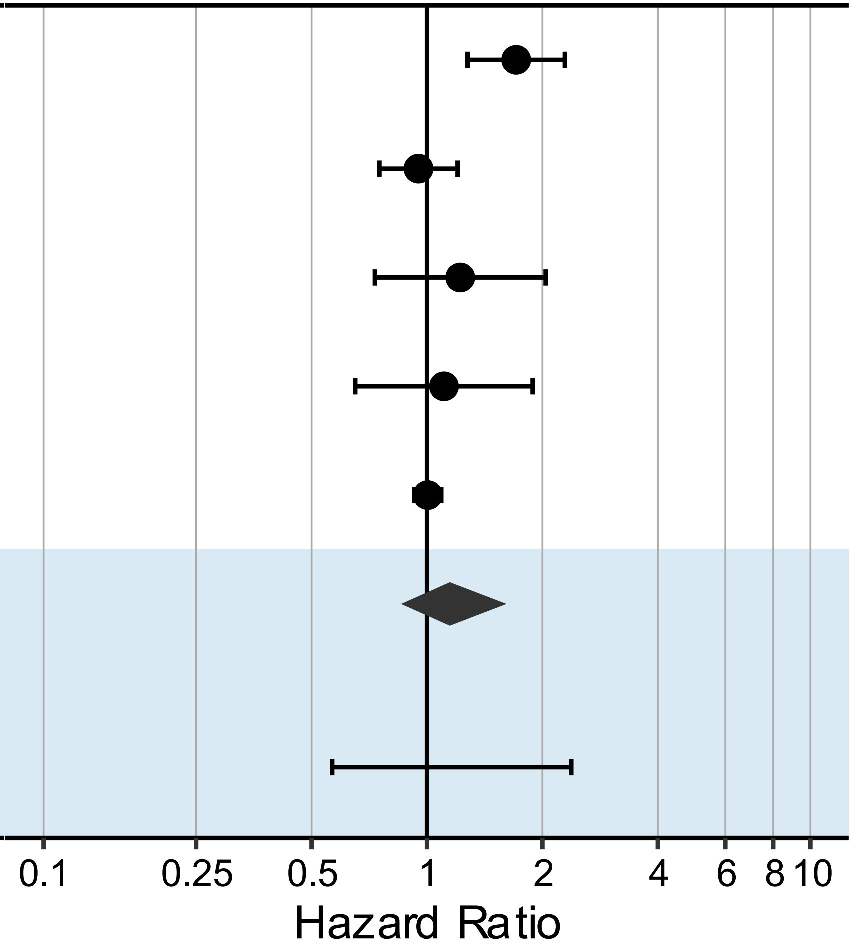
Source	Hazard Ratio (95% CI)	
Optum EHR	1.71	(1.28 - 2.29)
Optum Clinformatics	0.95	(0.75 - 1.20)
Bayesian random effects τ = 0.42 (0.05 - 0.94)	**1.26**	**(0.57 - 2.71)**
Prediction interval		**(0.33 - 4.80)**



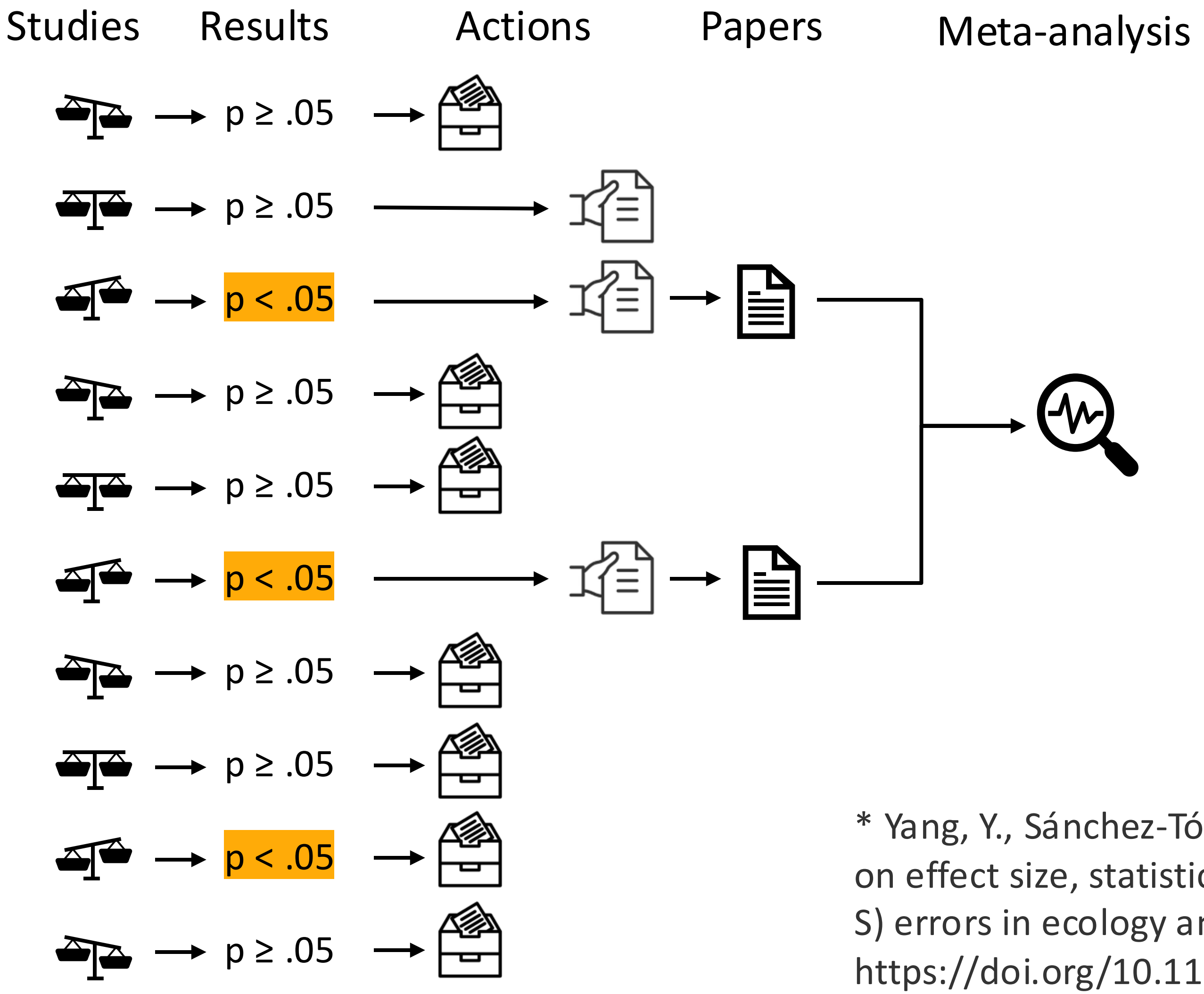
Trust the network

GLP1RA vs SU for Hypotension

Source	Hazard Ratio (95% CI)	
Optum EHR	1.71	(1.28 - 2.29)
Optum Clinformatics	0.95	(0.75 - 1.20)
Merative MDCD	1.22	(0.73 - 2.04)
Merative MDCR	1.11	(0.65 - 1.89)
US Open Claims	1.00	(0.93 - 1.09)
Bayesian random effects τ = 0.24 (0.03 - 0.57)	**1.15**	**(0.86 - 1.61)**
Prediction interval		**(0.57 - 2.38)**



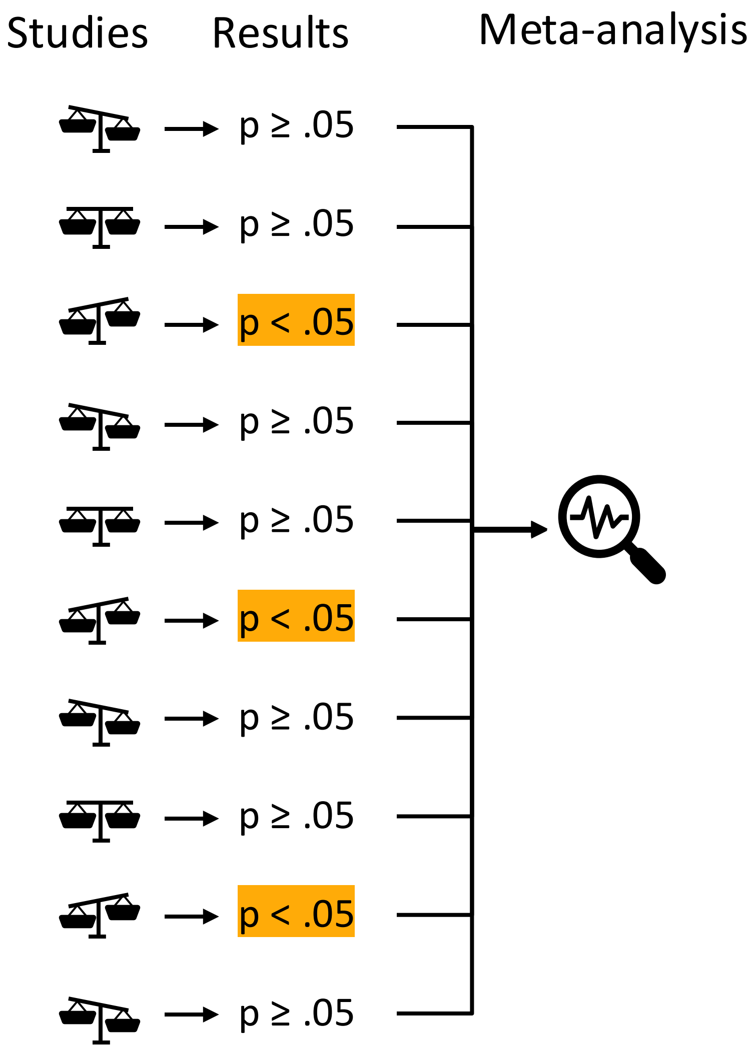
Meta-analysis of literature



66% of significant meta-analysis estimates become non-significant when adjusting for publication bias*

* Yang, Y., Sánchez-Tójar, A., O'Dea, R.E. *et al.* Publication bias impacts on effect size, statistical power, and magnitude (Type M) and sign (Type S) errors in ecology and evolutionary biology. *BMC Biol* **21**, 71 (2023). https://doi.org/10.1186/s12915-022-01485-y

Meta-analysis of a network study

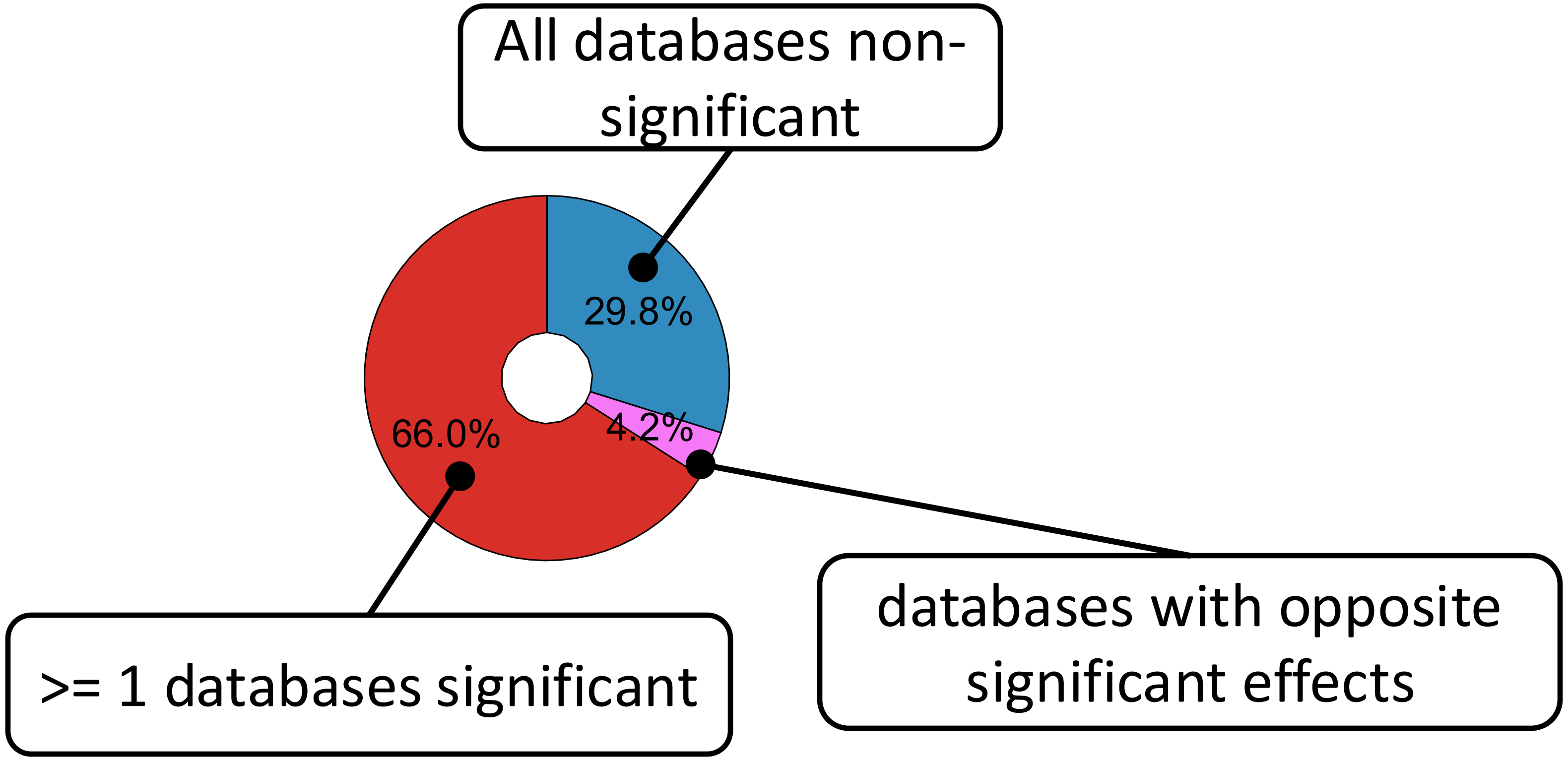


A network study is more likely to incorporate null findings from individual database

This suggests a more unbiased (accurate) estimate

Trust the network

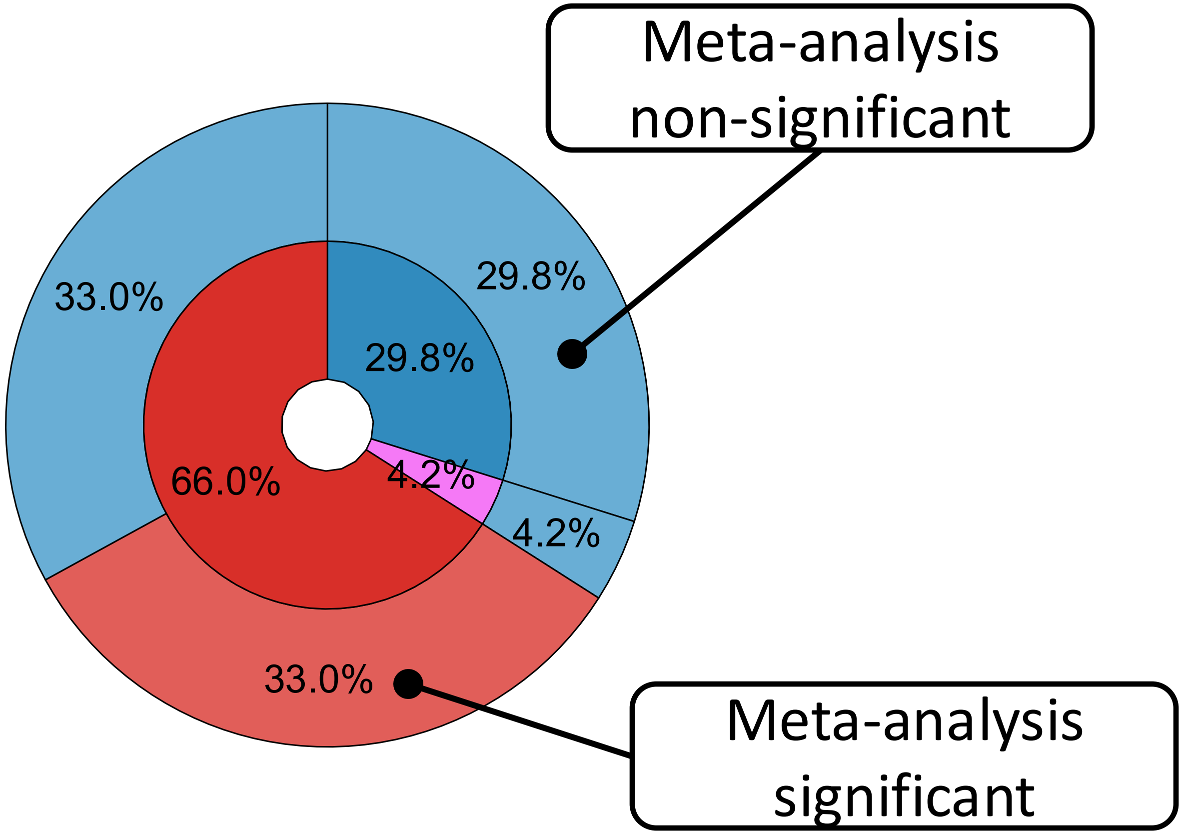
LEGEND T2DM



Based on 191 of 746 TCOs that have >= 2 databases passing diagnostics

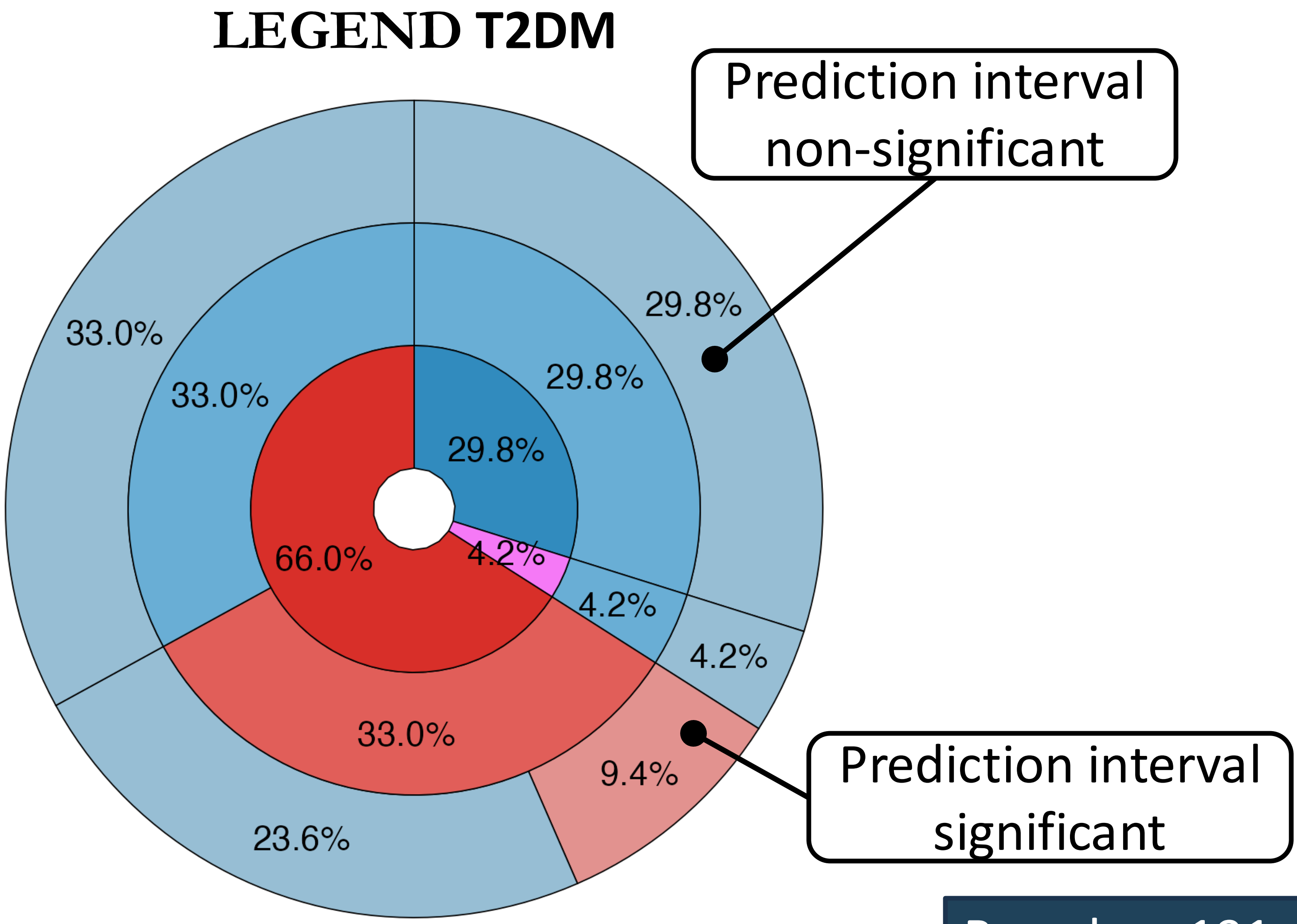
Trust the network

LEGEND T2DM



Based on 191 of 746 TCOs that have >= 2 databases passing diagnostics

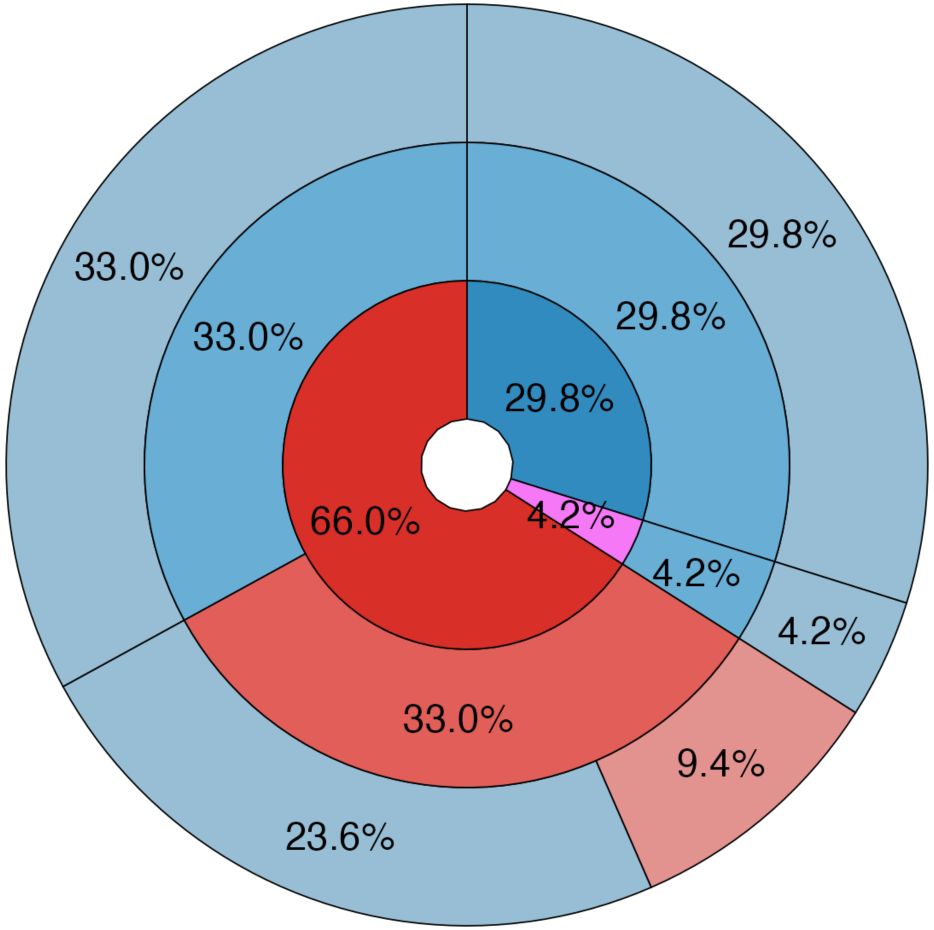
Trust the network



Based on 191 of 746 TCOs that have >= 2 databases passing diagnostics

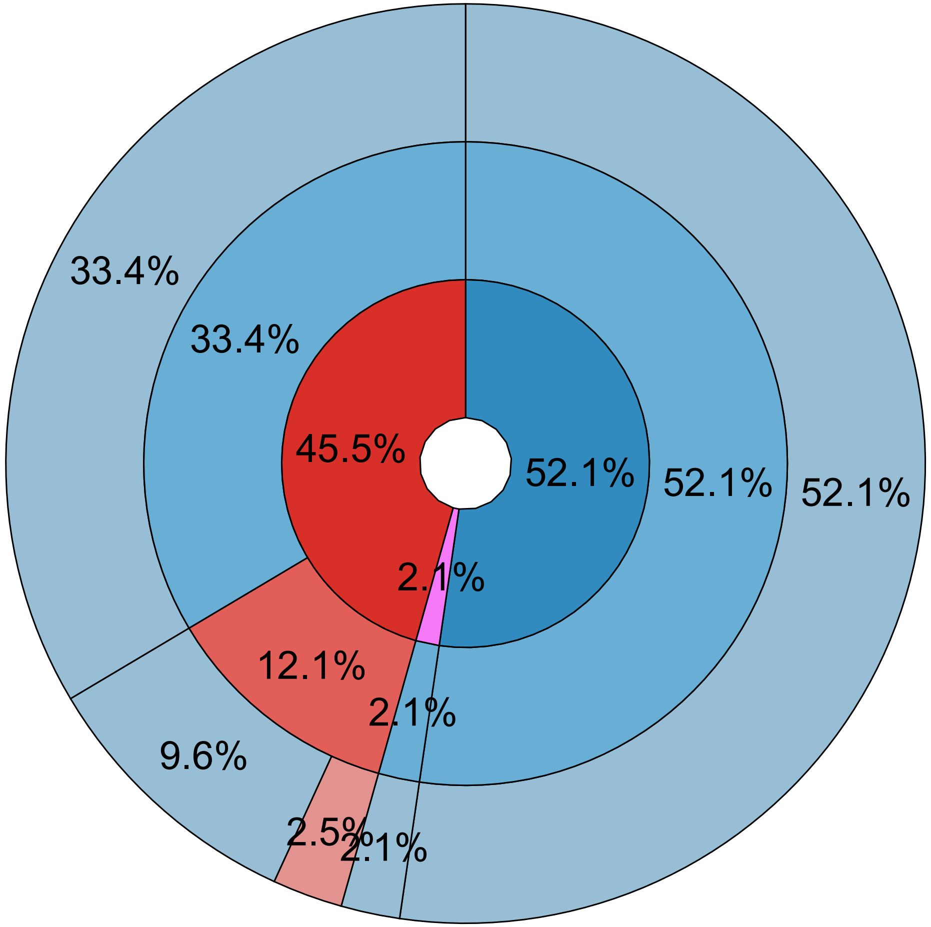
Trust the network

LEGEND T2DM



Based on 191 of 746 TCOs that have >= 2 databases passing diagnostics

LEGEND Hypertension



Based on 2,231 of 20,053 TCOs that have >= 2 databases passing diagnostics

	Accuracy	Precision	Consistency
Within a database	✓	✓	✓
Across databases	✓	✓	✓

Summary

Summary

Network studies add value in 3 dimensions:

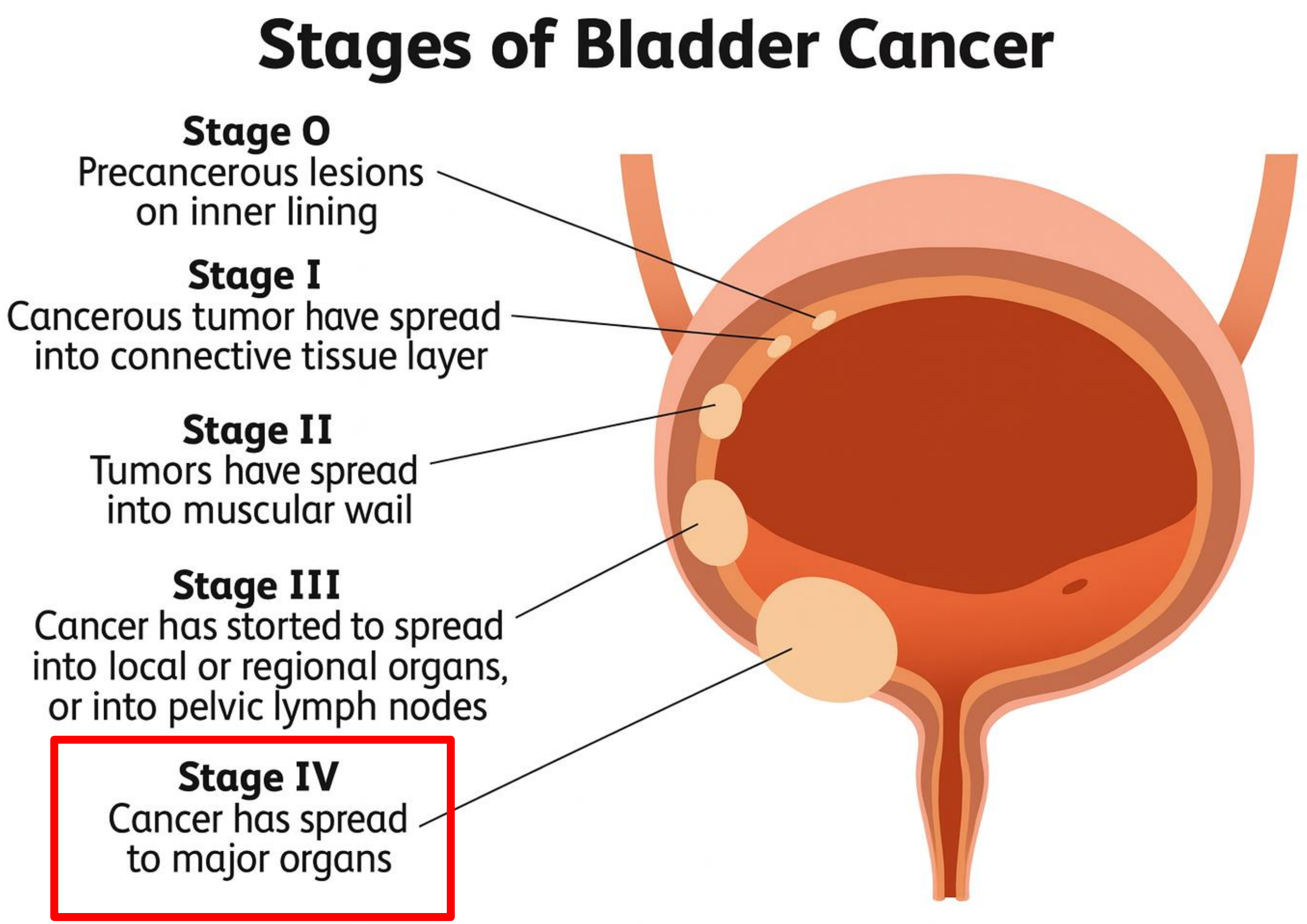
- Consistency
  - We can quantify consistency as $\boldsymbol{\tau}$, which comprises effect heterogeneity and differential systematic error
  - A consistent estimate is often more reliable
- Precision
  - To increase precision around $\boldsymbol{\mu}$ and $\boldsymbol{\tau}$ we need more patients and more databases
  - The prediction interval can summarize $\boldsymbol{\mu}$ and $\boldsymbol{\tau}$ and their uncertainties
- Accuracy
  - Observing consistency in a more diverse database network strengthens our belief that the result is accurate
  - Often a single database will disagree with the meta-analysis, so we should focus on the meta-analysis

What it takes to do cancer RWE

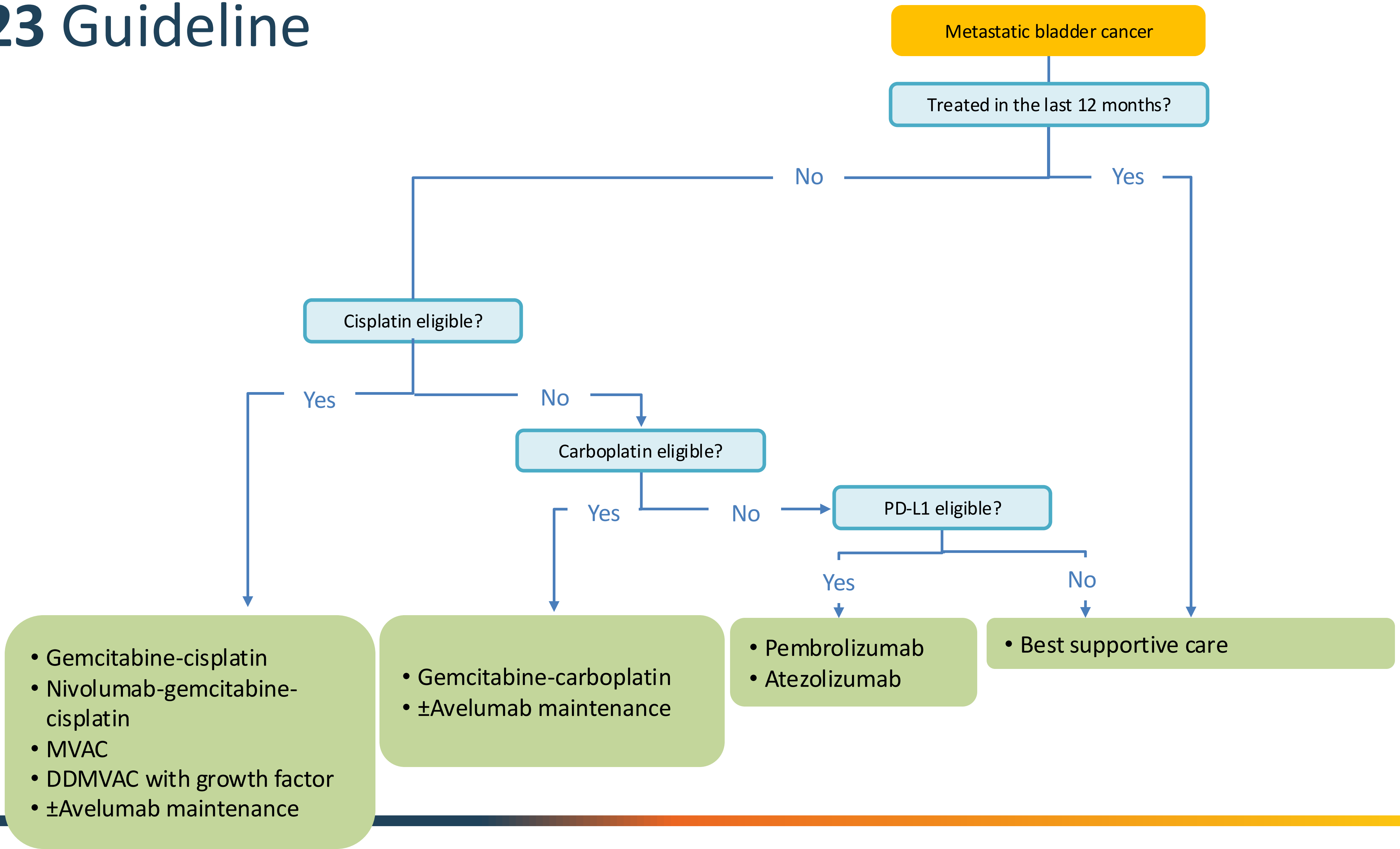
Evidence for the treatment of metastatic bladder cancer

Asieh Golozar
Nemesis Health

How do we treat ..



European Association of Urology
2023 Guideline



Treatment recommendations are based on decades of RCT research

- J Clin Oncol 1992
- J Clin Oncol 1990
- J Clin Oncol 2000
- J Clin Oncol 2001
- J Clin Oncol 2004
- Cancer 2004
- J Clin Oncol 2005

- Gemcitabine-cisplatin
- Nivolumab-gemcitabine-cisplatin
- MVAC
- DDMVAC with growth factor
- ±Avelumab maintenance

- J Clin Oncol 2009
- N Engl J Med 2020

- Gemcitabine-carboplatin
- ±Avelumab maintenance

- Lancet 2017
- Lancet Onc 2017

- Pembrolizumab
- Atezolizumab

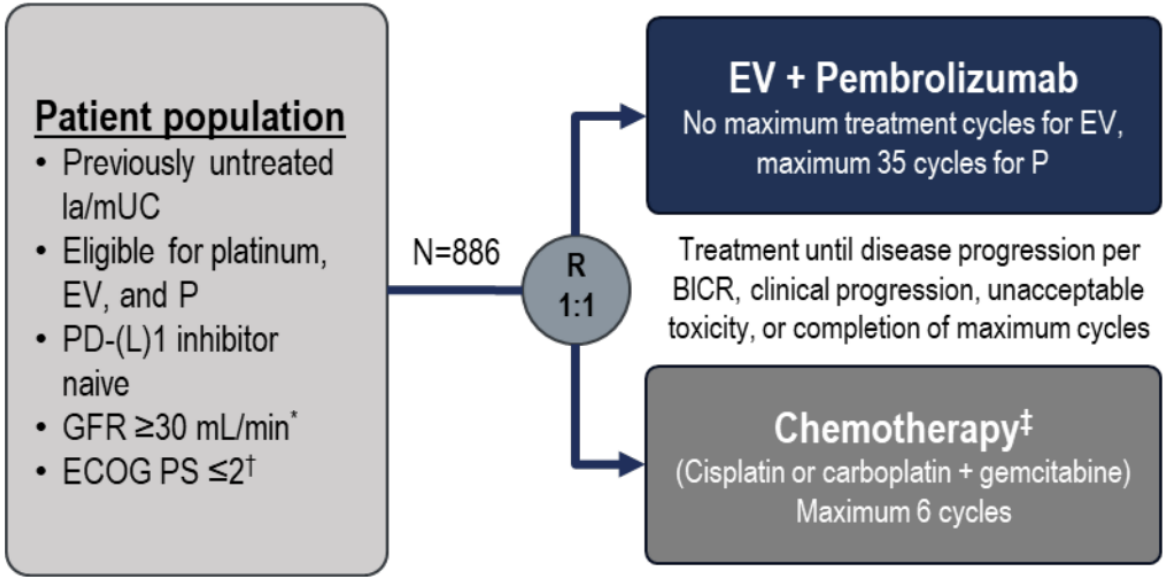
Pivotal Study for New Regimen

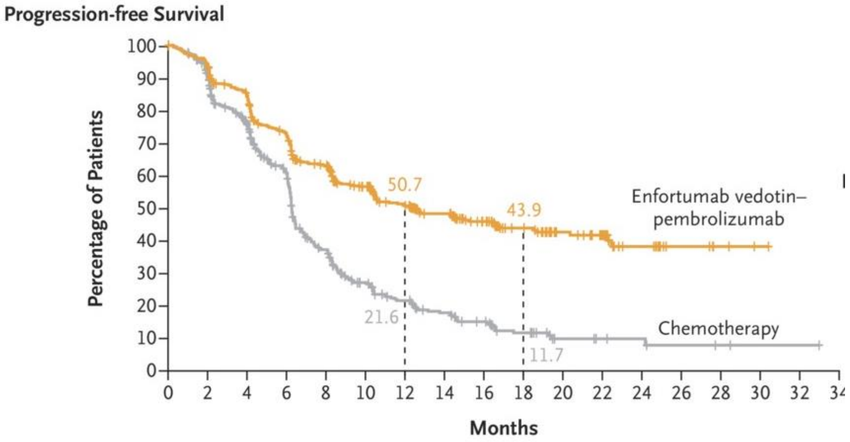
The NEW ENGLAND JOURNAL of MEDICINE

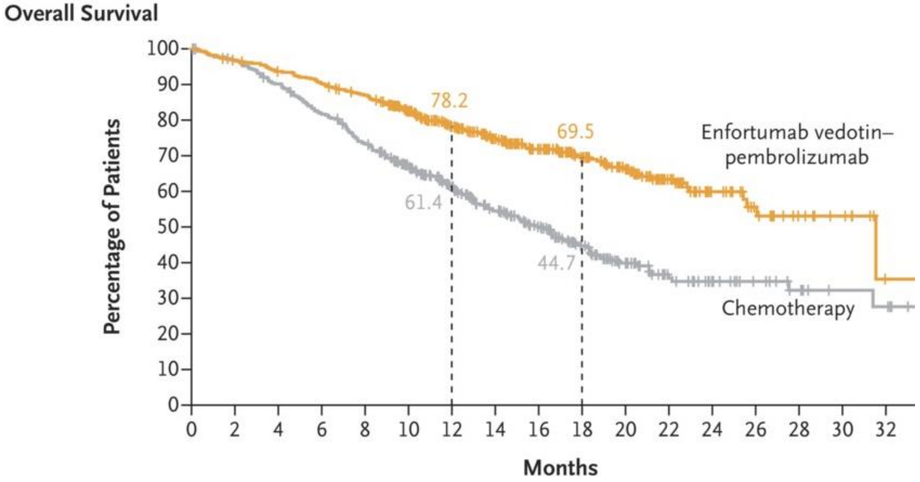
ORIGINAL ARTICLE

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

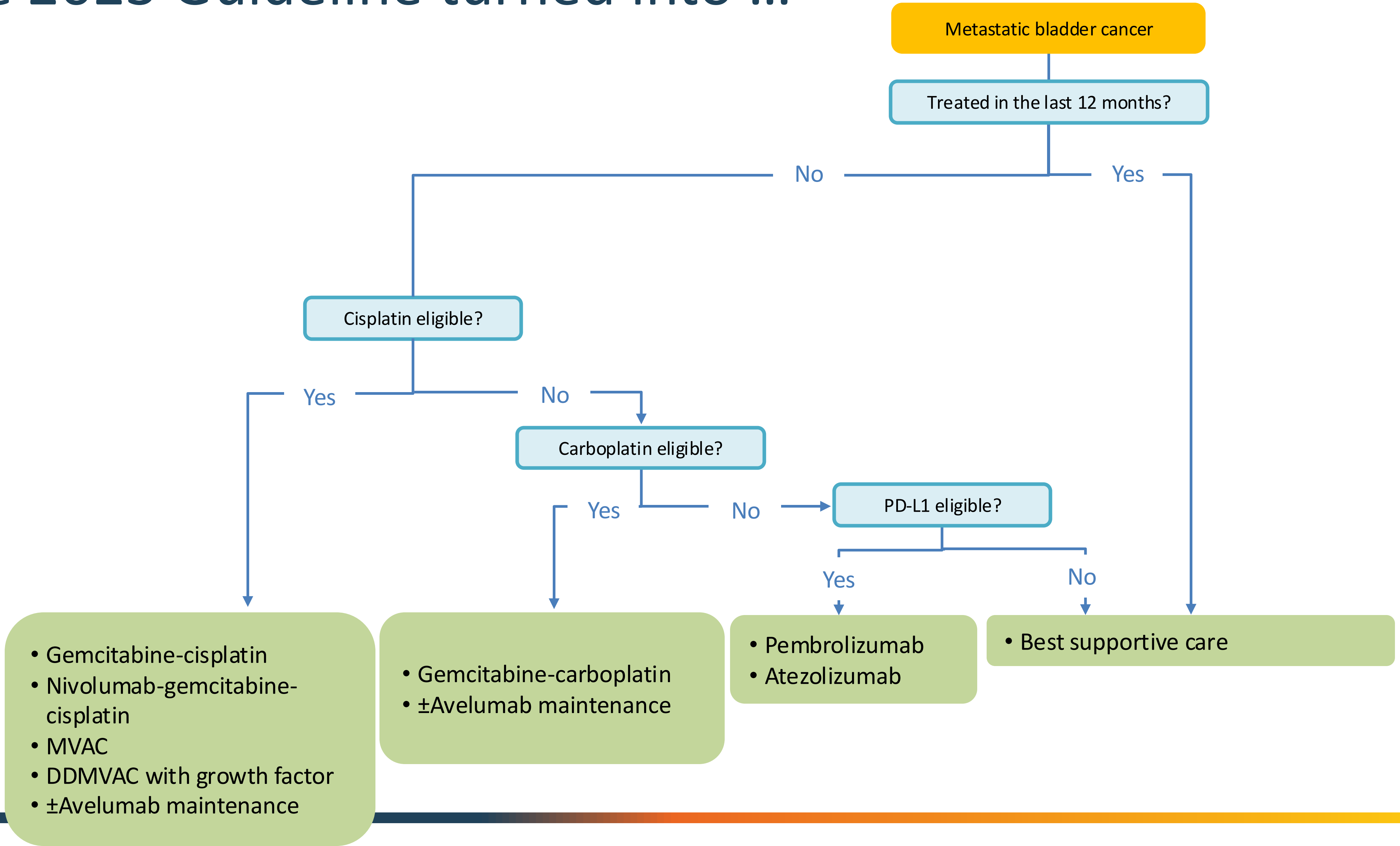
Published March 6, 2024





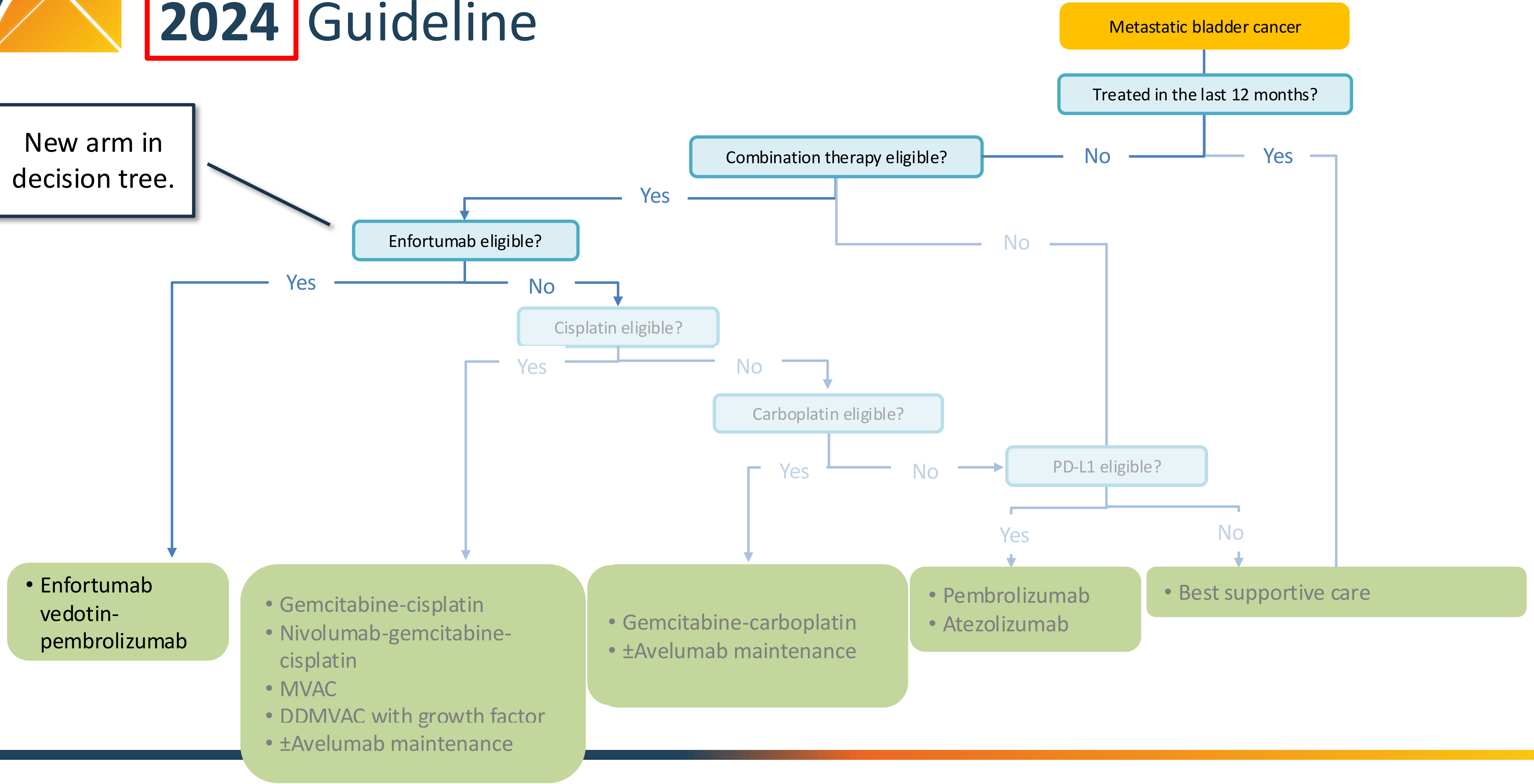


The 2023 Guideline turned into …



European Association of Urology 2024 Guideline

New arm in decision tree.



But that is not enough:

Metastatic bladder cancer

Treated in the last 12 months?

No

Combination therapy eligible?

Yes

Enfortumab eligible?

Yes

- Enfortumab vedotin-pembrolizumab

7.7.2 ***First-line systemic therapy for metastatic disease***

In general, patients with untreated metastatic UC can be divided into two broad categories: eligible for combination therapies or ineligible for combination therapies. The distinction between the two groups is currently based on the eligibility criteria for the pivotal trial EV-302/KEYNOTE 39A and is likely to undergo changes in the near future based on results from real-world evidence investigations.

European Association of Urology

What are the questions?

Dr. Elizabeth Heath, Mayo Clinic:

“This is timely because the combination is new, and we don’t know who benefits from it and should receive it.”

EAU Guideline office

“We have little information on the eligibility criteria and treatment sequencing after progression.”

The guideline asks for evidence from RWE to refine the treatment decision.

We should be answering!

Population size in the RCT treatment arm used to generate evidence

Metastatic bladder cancer

Treated in the last 12 months?

No

Combination therapy eligible?

Yes

Enfortumab eligible?

Yes

- Enfortumab vedotin-pembrolizumab

The NEW ENGLAND JOURNAL of MEDICINE

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

420 patients

Typical US Cancer Center's population size

Metastatic bladder cancer

Treated in the last 12 months?

No

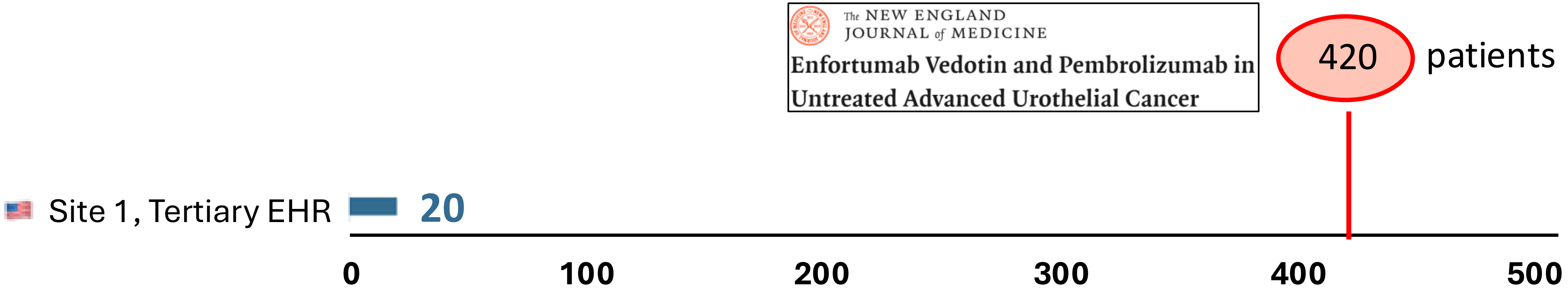
Combination therapy eligible?

Yes

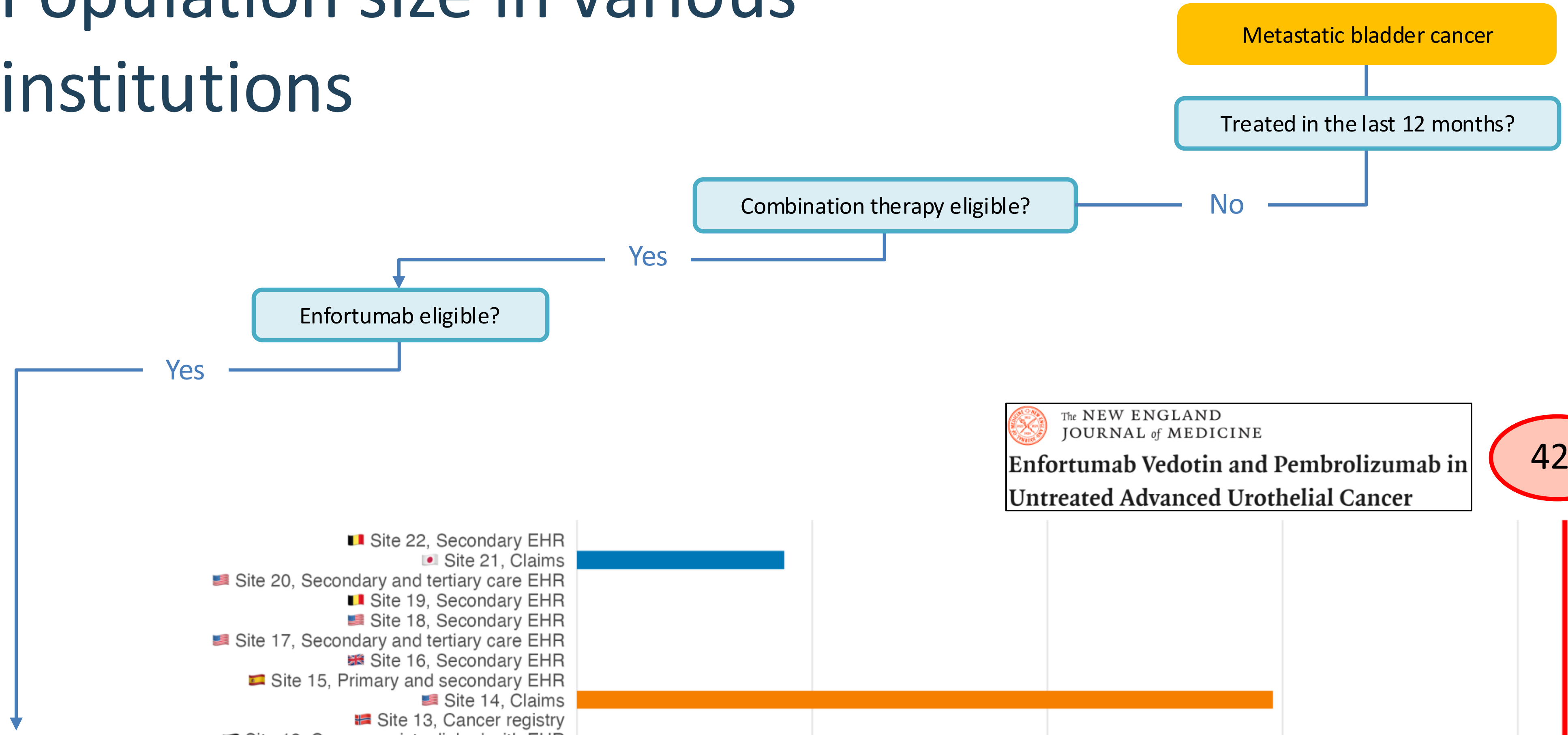
Enfortumab eligible?

Yes

- Enfortumab vedotin-pembrolizumab



Population size in various institutions

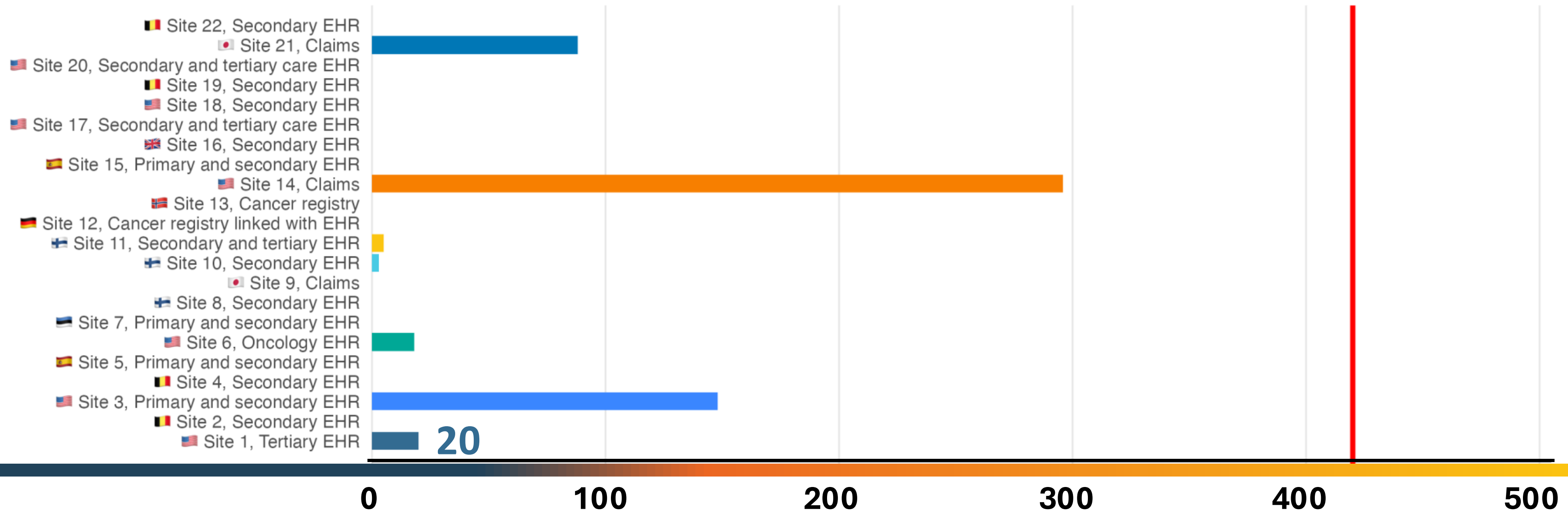


- Enfortumab vedotin-pembrolizumab

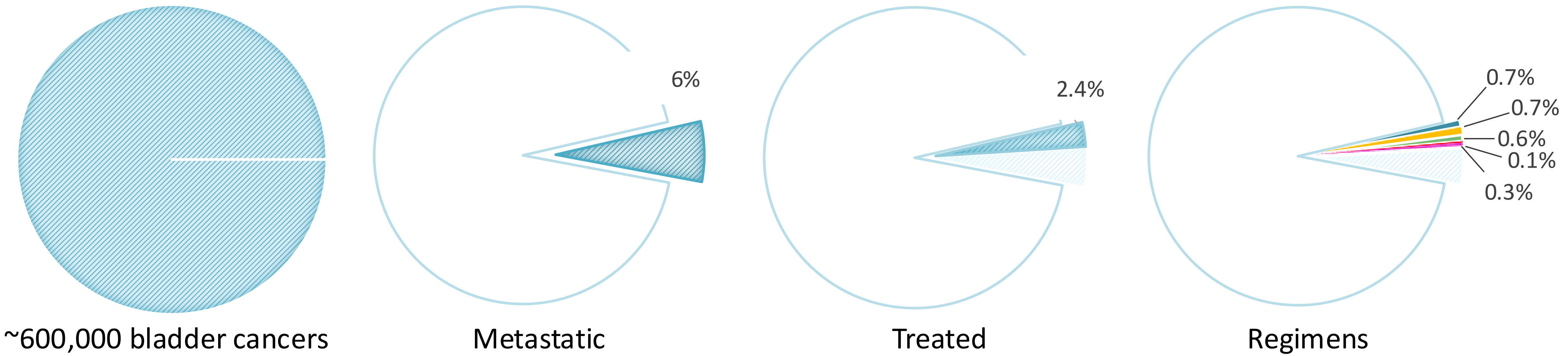
The NEW ENGLAND JOURNAL of MEDICINE

Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer

420 patients



Where are the patients?



→ Cancer is a **rare disease**

We need a network!

Population size available to generate evidence if we work together as a network

Metastatic bladder cancer

Treated in the last 12 months?

No

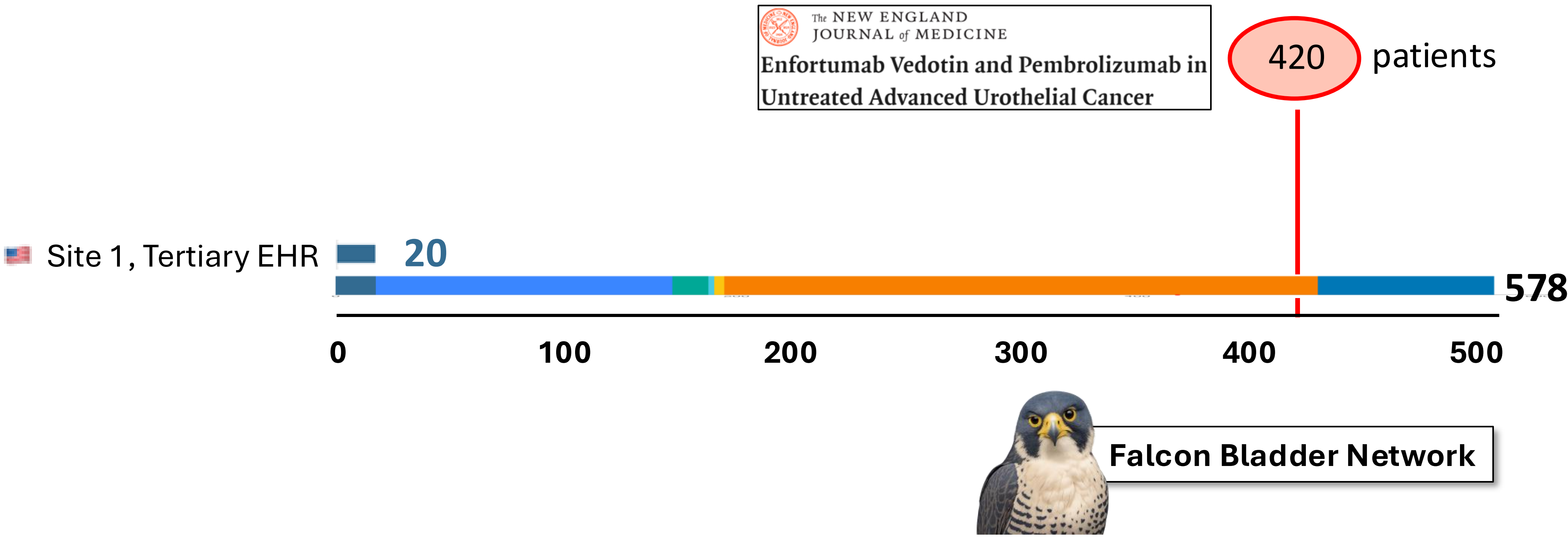
Combination therapy eligible?

Yes

Enfortumab eligible?

Yes

- Enfortumab vedotin-pembrolizumab



What about the other treatment groups? Any better?

Cisplatin containing regimens

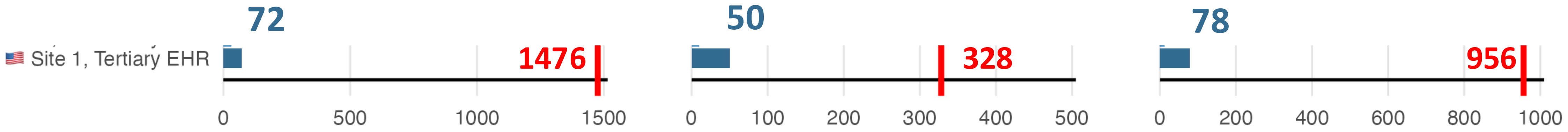
- Gemcitabine-cisplatin
- Nivolumab-gemcitabine-cisplatin
- MVAC
- DDMVAC with growth factor
- ±Avelumab maintenance

Carboplatin containing regimens

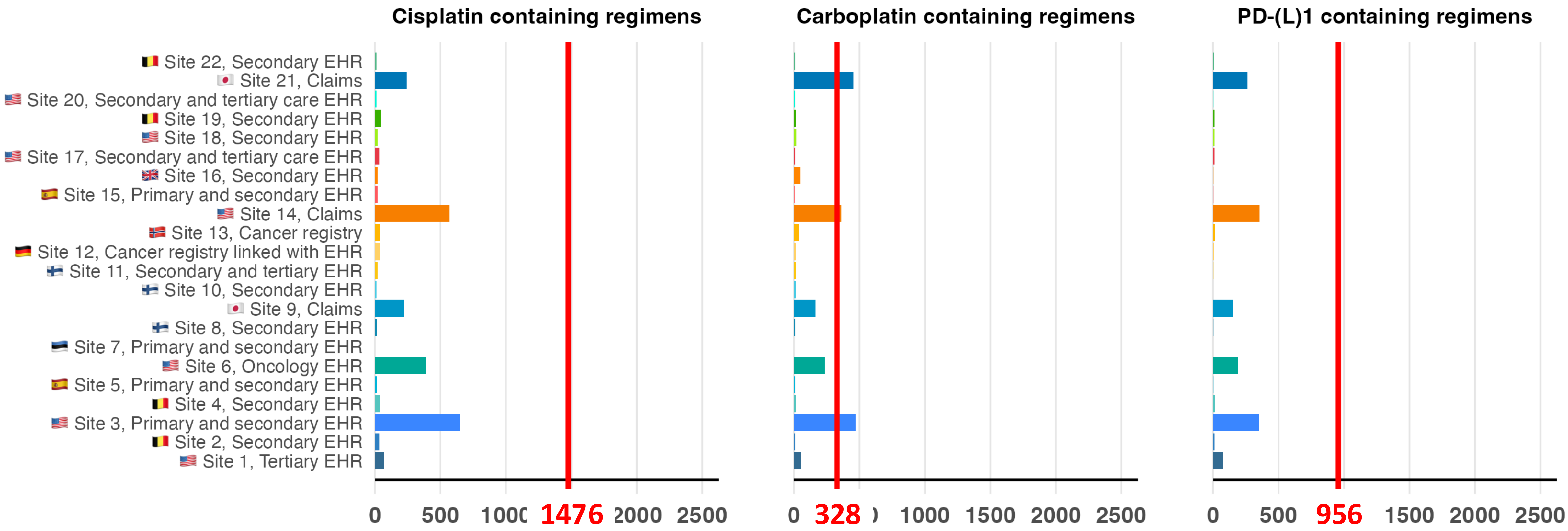
- Gemcitabine-carboplatin
- ±Avelumab maintenance

PD-(L)1 containing regimens

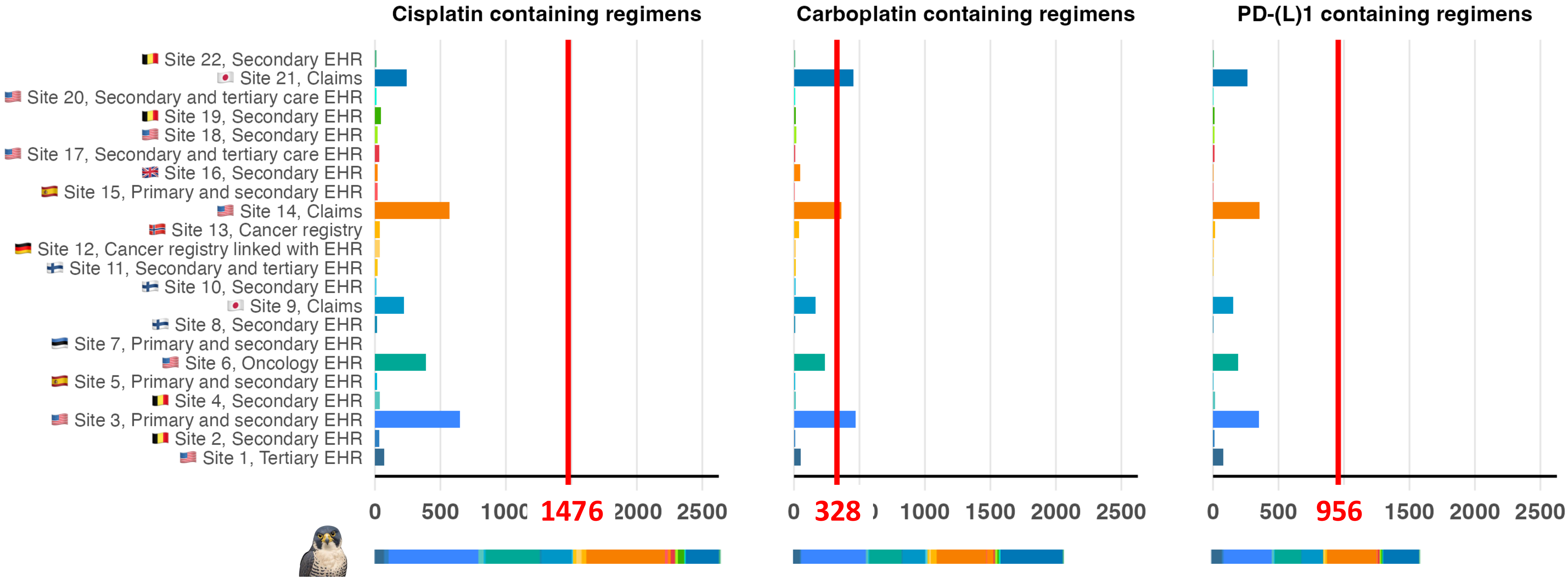
- Pembrolizumab
- Atezolizumab



And the other institutions?



And Falcon



Cisplatin containing regimens
Carboplatin containing regimens
PD-(L)1 containing regimens
Site 22, Secondary EHR
Site 21, Claims
Site 20, Secondary and tertiary care EHR
Site 19, Secondary EHR
Site 18, Secondary EHR
Site 17, Secondary and tertiary care EHR
Site 16, Secondary EHR
Site 15, Primary and secondary EHR
Site 14, Claims
Site 13, Cancer registry
Site 12, Cancer registry linked with EHR
Site 11, Secondary and tertiary EHR
Site 10, Secondary EHR
Site 9, Claims
Site 8, Secondary EHR
Site 7, Primary and secondary EHR
Site 6, Oncology EHR
Site 5, Primary and secondary EHR
Site 4, Secondary EHR
Site 3, Primary and secondary EHR
Site 2, Secondary EHR
Site 1, Tertiary EHR
0 500 1000 1476 2000 2500
0 328 1000 1500 2000 2500
0 500 956 1500 2000 2500

Summary

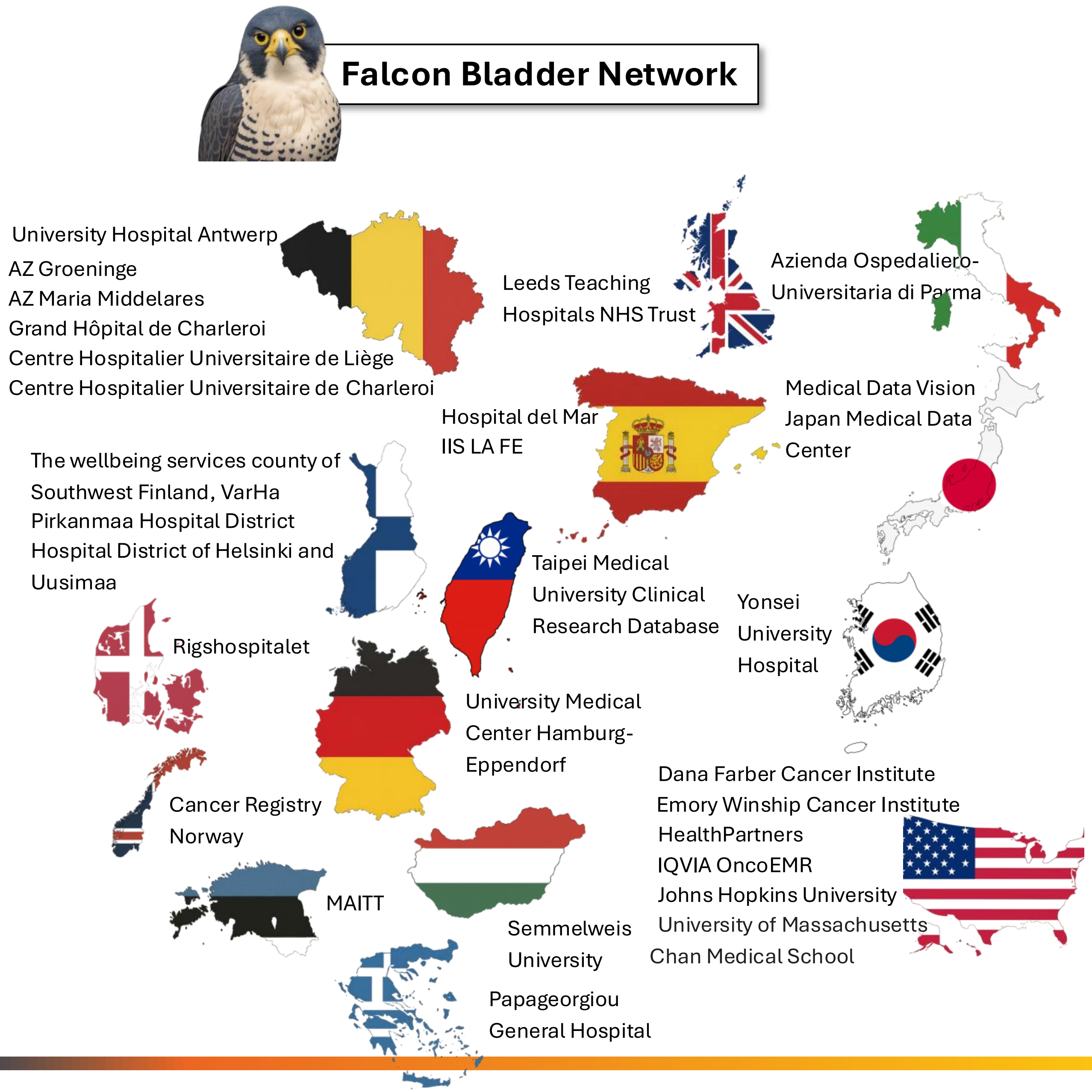
We must produce cancer RWE based on systematic analysis

- E.g. from guidelines

But

- No individual data center is even close to having enough data
- Only in a network can we have an impact

[Join the Journey]()



Cindy

Semaglutide and NAION

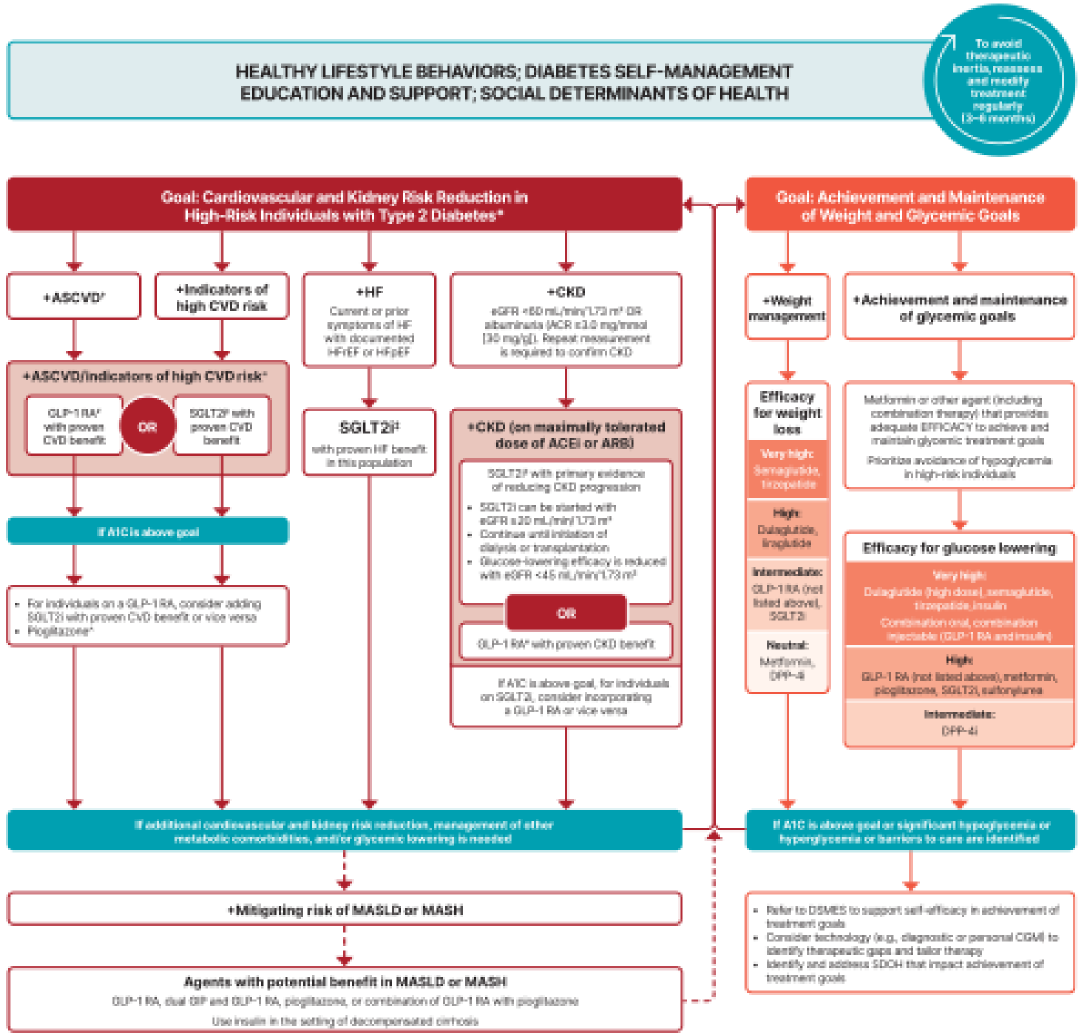
Cindy X. Cai, MD
The Jonathan and Marcia Javitt Rising Professor
Assistant Professor of Ophthalmology, Retina Division, The Wilmer Eye Institute
Assistant Professor of Medicine, Biomedical Informatics and Data Science, Division of General Internal Medicine, Department of Medicine
Johns Hopkins University School of Medicine

OHDSI
Observational Health Data Sciences and Informatics

Semaglutide

- Glucagon-like peptide 1 receptor agonist (GLP-1 RA)
- Benefits in reducing cardiovascular and kidney complications
- Recommended by the ADA as one of the preferred treatments of patients with T2DM and: atherosclerotic cardiovascular disease, chronic kidney disease, or obesity

Use of Glucose-Lowering Medications in the Management of Type 2 Diabetes

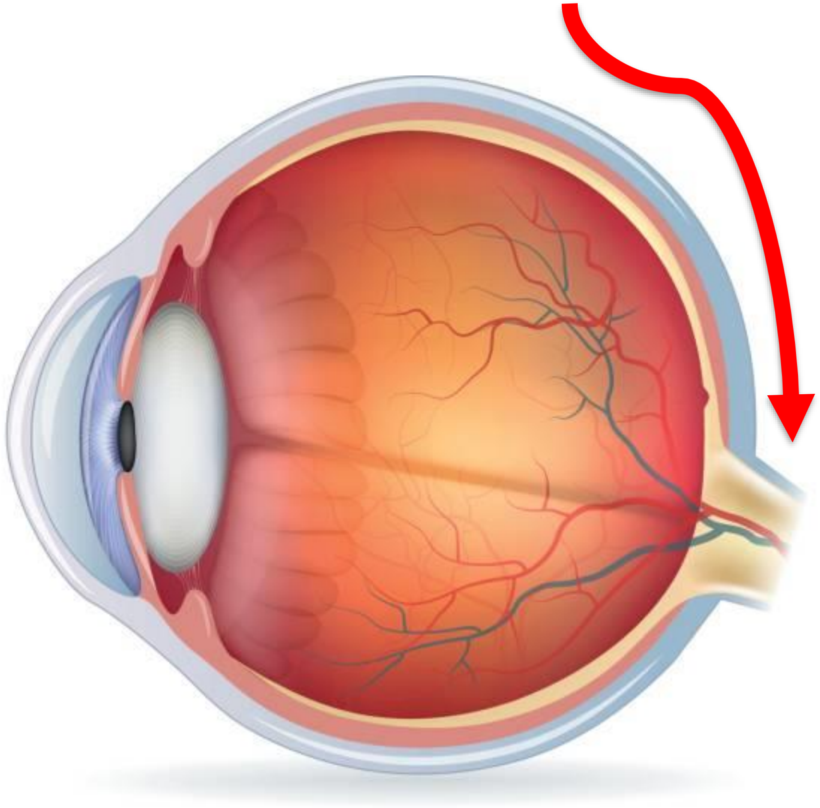


Committee ADAPP, ElSayed NA, McCoy RG, et al. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2025. *Diabetes Care*. 2024;48(Supplement_1):S181-S206.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

- Leading cause of acute optic neuropathy in the elderly
- Significant cause of blindness: 1 in 4 eyes with 20/200 or worse vision
- No definitive treatments

NAION = stroke of the optic nerve



JAMA Ophthalmology | Original Investigation

Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

Jimena Tatiana Hathaway, MD, MPH; Madhura P. Shah, BS; David B. Hathaway, MD; Seyedeh Maryam Zekavat, MD, PhD; Drenushe Krasniqi, BA; John W. Gittinger Jr, MD; Dean Cestari, MD; Robert Mallery, MD; Bardia Abbasi, MD; Marc Bouffard, MD; Bart K. Chwalisz, MD; Tais Estrela, MD; Joseph F. Rizzo III, MD

Published online July 3, 2024

EMA definition "common" (between 1 in 10 and 1 in 100 people)

- Cumulative incidence of NAION for the semaglutide and non–GLP-1 RA cohorts over 36 months was **8.9%** (95% CI, 4.5-13.1%) and 1.8% (95% CI, 0-3.5%), respectively
  - In year 1: cumulative incidence of NAION in semaglutide cohort 6.5% (95% CI, 2.7-10.2%)
- Hazard Ratio of NAION **4.28** (95% CI: 1.62 – 11.29, P < .001) (compared with non-GLP-1 RA)

Limitations: single academic institution, major referral center for NAION

"The best approaches to **confirm, refute, or refine** our findings would be to conduct a **much larger, retrospective, multicenter population-based cohort study**; a prospective, randomized clinical study; or a postmarket analysis of all GLP-1 RA drugs."

Ophthalmology Times | News | Media | Conferences | Events | More | Subscribe

Choose Specialty | Spotlight - Retina

News | Articles | July 9, 2024

Study suggests potential link between semaglutide and risk of no[n-arteritic ischemic optic] neuropathy

Author(s) Lynda Charters

Prescriptions with semaglutide (Wegovy, Ozempic, Novo Nordisk) are FDA approved to treat obesity

Boston researchers led by first author Jimena Tatiana Hathaway, MD, MPH, reported that there is a potential risk of the development of non-arteritic ischemic optic neuropathy (NAION)[1] associated with prescriptions for semaglutide (Wegovy, Ozempic, Novo Nordisk). Prescriptions with semaglutide are FDA approved to treat obesity and type 2 diabetes, respectively.

Hathaway is from the Harvard T.H. Chan School of Public Health, and the Department of Ophthalmology, and Neuro-Ophthalmology Service Massachusetts Eye and Ear, Harvard Medical School, all in Boston.

The authors cited anecdotal experience that suggested that semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1 RA), the use of which has been rapidly increasing, may be associated with the development of NAION.

They recognized that this association may be important considering that the weekly new-to-b[rand] ... other GLP-1 RA drugs have increased by about 60% from 2021 to 2023.[2]

CNN Health | Subscribe | Sign in

Popular weight loss and diabetes drugs linked to increased risk of rare form of blindness

By Deidre McPhillips, CNN

5 min read · Updated 12:00 PM EDT, Wed July 3, 2024

Risk of rare condition that causes blindness may be elevated for people with diabetes or obesity who take Ozempic or Wegovy, study suggests. Mario Tama/Getty Images

Medscape | News & Perspective | Tools & Reference | CME/CE | More

MEDBRIEF

Semaglutide Linked to Cause of Vision Loss

Edited by Jake Remaly
July 03, 2024

10 | 1319

TOPLINE:

Patients with type 2 diabetes, overweight, or obesity taking the glucagon-like peptide 1 receptor agonist (GLP-1 RA) semaglutide appear to have an increased risk for an uncommon condition that can cause vision loss.

METHODOLOGY:

- Researchers conducted a retrospective study of 16,827 patients at Massachusetts Eye and Ear in Boston.
- Their analysis focused on 710 patients with type 2 diabetes (194 of whom had been prescribed semaglutide) and 979 patients with overweight or obesity (361 prescribed semaglutide).

The Guardian | The whole picture | US

News | Opinion | Sport | Culture | Lifestyle

US news | US politics | World | Climate crisis | Middle East | Ukraine | US immigration | Soccer | Business | Envi...

Medical research

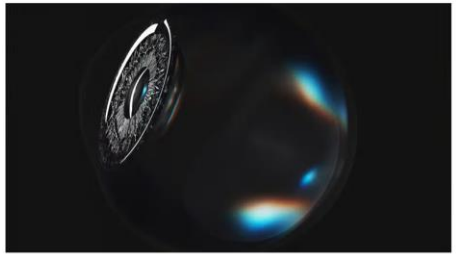
This article is more than **1 year old**

Weight-loss jabs may be linked to condition that can cause blindness, study finds

People with diabetes on semaglutide, found in Wegovy and Ozempic, four times more likely to be diagnosed with disease of optic nerve

MedicalNewsToday | Health Conditions | Health Products | Discover | Tools | Conn...

Drugs like Ozempic, Wegovy linked to eye condition causing vision loss



Are popular semaglutide drugs linked to a rare and aggressive eye condition? Image credit: Serg Myshkovsky/Getty Images.

https://www.ophthalmologytimes.com/view/study-suggests-potential-link-between-semaglutide-and-risk-of-non-arteritic-ischemic-optic-neuropathy, https://www.medscape.com/viewarticle/semaglutide-linked-cause-vision-loss-2024a1000cd7?form=fpf, https://www.theguardian.com/science/article/2024/jul/03/study-possible-link-weight-loss-jabs-wegovy-ozempic-and-naion-condition-blindness, https://www.cnn.com/2024/07/03/health/ozempic-wegovy-blindness-rare-risk, https://www.medicalnewstoday.com/articles/drugs-like-ozempic-wegovy-linked-to-eye-condition-causing-vision-loss

AAO and NANOS Public Statement

American Academy of Ophthalmology and North American Neuro-Ophthalmology Society

July 8, 2024

All the patients included in the study were **seen at the same large eye hospital**, which treats most of the region's NAION patients, making it hard to determine if this association is true of all people taking semaglutide.

At this time, we **do not recommend** that people stop taking semaglutide.

https://www.aao.org/newsroom/news-releases/detail/weight-loss-drug-and-eye-health

OHDSI Community Address Limitations of Hathaway Study

Analytic use case	Type	Structure	Example
Clinical characterization	**Disease Natural History**	Amongst patients who are diagnosed with **<insert your favorite disease>**, what are the patient's characteristics from their medical history?	Amongst patients with **rheumatoid arthritis**, what are their demographics (age, gender), prior conditions, medications, and health service utilization behaviors?
	Treatment utilization	Amongst patients who have **<insert your favorite disease>**, which treatments were patients exposed to amongst **<list of treatments for disease>** and in which sequence?	Amongst patients with **depression**, which treatments were patients exposed to **SSRI, SNRI, TCA, bupropion, esketamine** and in which sequence?
	Outcome incidence	Amongst patients who are new users of **<insert your favorite drug>**, how many patients experienced **<insert your favorite known adverse event from the drug profile>** within **<time horizon following exposure start>**?	Amongst patients who are new users of **methylphenidate**, how many patients experienced **psychosis** within **1 year of initiating treatment**?
Population-level effect estimation	**Safety surveillance**	Does exposure to **<insert your favorite drug>** increase the risk of experiencing **<insert an adverse event>** within **<time horizon following exposure start>**?	Does exposure to **ACE inhibitor** increase the risk of experiencing **Angioedema** within **1 month after exposure start**?
	Comparative effectiveness	Does exposure to **<insert your favorite drug>** have a different risk of experiencing **<insert any outcome (safety or benefit) >** within **<time horizon following exposure start>**, relative to **<insert your comparator treatment>**?	Does exposure to **ACE inhibitor** have a different risk of experiencing **acute myocardial infarction** while **on treatment**, relative to **thiazide diuretic**?
Patient level prediction	**Disease onset and progression**	For a given patient who is diagnosed with **<insert your favorite disease>**, what is the probability that they will go on to have **<another disease or related complication>** within **<time horizon from diagnosis>**?	For a given patient who is **newly diagnosed with atrial fibrillation**, what is the probability that they will go onto to have **ischemic stroke** in **next 3 years**?
	Treatment response	For a given patient who is a new user of **<insert your favorite chronically-used drug>**, what is the probability that they will **<insert desired effect>** in **<time window>**?	For a given patient **with T2DM who start on metformin**, what is the probability that they will **maintain HbA1C<6.5%** after **3 years**?
	Treatment safety	For a given patient who is a new user of **<insert your favorite drug>**, what is the probability that they will experience **<insert adverse event >** within **<time horizon following exposure>**?	For a given patients who is a **new user of warfarin**, what is the probability that they will have **GI bleed** in **1 year**?

Does exposure to semaglutide have a different risk of experiencing NAION while on treatment, relative to other non-GLP-1 RA T2DM medications?

Research

JAMA Ophthalmology | Original Investigation

Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

Cindy X. Cai, MD, MS; Michelle Hribar, PhD; Sally Baxter, MD, MSc; Kerry Goetz, MS; Swarup S. Swaminathan, MD; Alexis Flowers, MD; Eric N. Brown, MD, PhD; Brian Toy, MD; Benjamin Xu, MD, PhD; John Chen, MD, PhD; Aiyin Chen, MD; Sophia Wang, MD, MS; Cecilia Lee, MD, MS; Theodore Leng, MD, MS; Joshua R. Ehrlich, MD, MPH; Andrew Barkmeier, MD; Karen R. Armbrust, MD, PhD; Michael V. Boland, MD, PhD; David Dorr, MD, MS; Danielle Boyce, MPH, DPA; Thamir Alshammari, PhD; Joel Swerdel, PhD, MS, MPH; Marc A. Suchard, MD, PhD; Martijn Schuemie, PhD; Fan Bu, PhD; Anthony G. Sena, BA; George Hripcsak, MD, MS; Akihiko Nishimura, PhD; Paul Nagy, PhD; Thomas Falconer, MS; Scott L. DuVall, PhD; Michael Matheny, MD; Benjamin Viernes, PhD; William O'Brien, MS; Linying Zhang, PhD; Benjamin Martin, PhD; Erik Westlund, PhD; Nestoras Mathioudakis, MD, MHS; Ruochong Fan, MA; Adam Wilcox, PhD; Albert Lai, PhD; Jacqueline C. Stocking, PhD, RN; Sahar Takkouche, MD, MBA; Lok Hin Lee, DPhil; Yangyiran Xie, BS; Izabelle Humes, PT, DPT; David B. McCoy, BA; Mohammad Adibuzzaman, PhD; Raymond G. Areaux Jr, MD; William Rojas-Carabali, MD; James Brash, PhD; David A. Lee, MD, MS; Nicole G. Weiskopf, PhD; Louise Mawn, MD; Rupesh Agrawal, MD; Hannah Morgan-Cooper, Msc; Priya Desai, Msc; Patrick B. Ryan, PhD

Published online February 20, 2025

OHDSI Community Address Limitations of Hathaway Study

- Multiple databases
- Multiple outcomes
- Multiple study design
  - Included sensitivity analyses

Indication Cohort

- T2DM exclude T1DM

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 84, NO. 10, 2024

Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes

A Multinational, Federated Analysis of LEGEND-T2DM

Rohan Khera, MD, MS,[a,b,c] Arya Aminorroaya, MD, MPH,[a] Lovedeep Singh Dhingra, MBBS,[a] Phyllis M. Thangaraj, MD, PhD,[a] Aline Pedroso Camargos, PhD,[a] Fan Bu, PhD,[d] Xiyu Ding, MS,[e] Akihiko Nishimura, PhD,[e] Tara V. Anand, BS,[f] Faaizah Arshad, BS,[g] Clair Blacketer, MPH,[h] Yi Chai, PhD,[i] Shounak Chattopadhyay, PhD,[g] Michael Cook, BSc,[e] David A. Dorr, MD, MS,[j] Talita Duarte-Salles, PhD,[k,l] Scott L. DuVall, PhD,[m,n] Thomas Falconer, MS,[f] Tina E. French, RN, CPHQ,[o,p] Elizabeth E. Hanchrow, RN, MSN,[o,p] Guneet Kaur, MS,[q] Wallis C.Y. Lau, BSc, PhD,[r,s,t,u] Jing Li, MS,[v] Kelly Li, BS,[g] Yuntian Liu, MPH,[a,b] Yuan Lu, ScD,[a] Kenneth K.C. Man, BSc, MPH, PhD,[r,s,t,u] Michael E. Matheny, MD, MS, MPH,[o,p] Nestoras Mathioudakis, MD, MHS,[w] Jody-Ann McLeggon, MPH,[f] Michael F. McLemore, RN,[o,p] Evan Minty, MD, MSc,[x] Daniel R. Morales, MD,[q] Paul Nagy, PhD,[w] Anna Ostropolets, MD, PhD,[h] Andrea Pistillo, MSc,[k] Thanh-Phuc Phan, MBA,[y] Nicole Pratt, PhD,[z] Carlen Reyes, MD, PhD,[k] Lauren Richter, MD,[f] Joseph S. Ross, MD, MHS,[b,aa] Elise Ruan, MD,[f] Sarah L. Seager, BS,[bb] Katherine R. Simon, AA,[o,p] Benjamin Viernes, PhD,[m,n] Jianxiao Yang, MS,[cc] Can Yin, MS,[dd] Seng Chan You, MD, PhD,[ee,ff] Jin J. Zhou, PhD,[g,gg] Patrick B. Ryan, PhD,[f] Martijn J. Schuemie, PhD,[hh] Harlan M. Krumholz, MD, SM,[a,b,ii] George Hripcsak, MD, MS,[f] Marc A. Suchard, MD, PhD[g,m,jj,kk]

Khera R, Aminorroaya A, Dhingra LS, et al. Comparative Effectiveness of Second-Line Antihyperglycemic Agents for Cardiovascular Outcomes A Multinational, Federated Analysis of LEGEND-T2DM. *J Am Coll Cardiol*. 2024;84(10):904-917.

Drug Exposures

Semaglutide (GLP-1 RA)	Dulaglutide (GLP-1 RA)	Exenatide (GLP-1 RA)	Empagliflozin (SGLT2 inhibitor)	Sitagliptin (DPP4 inhibitor)	Glipizide (sulfonylurea)

GLP-1 RA

Non-GLP-1 RA

Outcome

- Lack of structured diagnosis codes for NAION
  – 40% of cases coded of ION are not NAION

"Sensitive" NAION -require 1 ION condition	"Specific" NAION -require 2 ION condition

ION diagnosis codes, diagnosis date adjustments (visual field defect, optic disc disorder, optic neuritis, optic disc edema), exclude patients with GCA (x2), exclude patients with traumatic optic neuropathy

Hathaway JT, Shah MP, Hathaway DB, et al. Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide. *JAMA Ophthalmol*. 2024;142(8).

Study Design

- Active-Comparator New-User Cohort Analysis
- Self-Controlled Case-Series Analysis

Active-Comparator New-User Cohort Analysis

Objective:
Estimate the risk of NAION (Non-Arteritic Anterior Ischemic Optic Neuropathy) associated with semaglutide use compared to other diabetes medications.

Exposure groups:
- Target: Semaglutide (GLP-1RA)
- Comparators:
  - Other GLP-1RAs: Dulaglutide, Exenatide.
  - Non-GLP-1RAs: Empagliflozin, Sitagliptin, Glipizide.

Semaglutide

LSPS

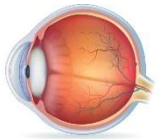
Dulaglutide
Exenatide
Empagliflozin
Sitagliptin
Glipizide

Timeline

Pre-treatment time

Follow-up time

Outcomes:
- “Sensitive” NAION
- “Specific” NAION



Study Population: New users of semaglutide and comparators (study period: 12/1/2017-12/31/2023)

Inclusion Criteria:
- Adults with T2DM on metformin monotherapy.
- At least 1 year of prior observation.
- No prior exposure to comparator diabetes medications.
- No more than 30 days of prior insulin use.

Analysis plan:
- Confounding adjustment:
  - Large-scale propensity score (LSPS)
  - 1:1 PS matching
- Hazard ratio estimation:
  - Cox proportional hazards model
- Meta-analysis:
  - Bayesian random-effects model

Slide courtesy of Linying Zhang

Self-Controlled Case-Series Analysis

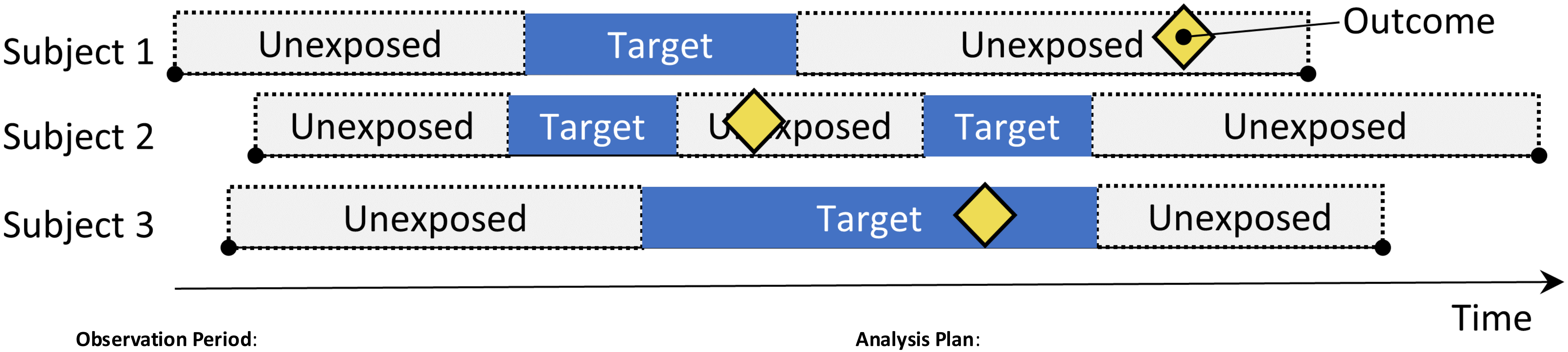
Objective:

Estimate the incidence rate ratio (IRR) for NAION during semaglutide exposure compared with non-exposure time

Exposure groups:

- Target: semaglutide
- Similarly for each of the other medications: dulaglutide, exenatide, empagliflozin, sitagliptin, glipizide

No comparator group: Individuals act as their own control.



Observation Period:

- Period when patients had T2DM
- Excluded first 365 days (improve detection of incident NAION)

Pre-Exposure Control:

- 30 days prior to treatment initiation

Analysis Plan:

- Conditional Poisson Regression
- Adjusted for seasonality: spline functions of calendar month
- Control period adjustment: pre-exposure time window
- Meta-analysis

Figure source: The Book of OHDSI

Study Diagnostics / Negative Controls / Meta-Analysis

Study Diagnostics for Cohort Method

- Empirical equipoise
  - Assess the similarity between target and comparator groups
- Covariate balance
  - Absolute standardized mean difference (ASMD)
  - Unbalanced covariates -> residual bias
- Expected absolute systematic error (EASE)
  - 97 negative control outcomes
  - Assess residual bias
- Minimum detectable relative risk (MDRR)

Study Diagnostics for SCCS

- Time trend diagnostic
  - Detects time trend in the outcome rate.
- Pre-exposure diagnostic
  - The outcome increases the probability of having the exposure ("reverse causality")
  - Detects increased rate of outcome just before the exposure
- Expected absolute systematic error (EASE)
- Minimum detectable relative risk (MDRR)

Only databases that passed all diagnostics were included in the Bayesian random effects meta-analysis

Results

- 14 OHDSI network databases were included.
  - All 14 were included in the NAION incidence analysis.
  - 8 were included in the active-comparator new-user cohort analysis.
  - 10 were included in the self-controlled case-series analysis.

Administrative Claims Databases (6)
Merative MarketScan Medicare Supplemental and Coordination of Benefits Database (MDCR)
Merative MarketScan Commercial Claims and Encounters Database (CCAE)
Merative MarketScan Multi-State Medicaid Database (MDCD)
IQVIA Open Claims (IQVIA)
Optum Clinformatics Data Mart - Extended Data Mart – Socioeconomic Status (Optum Extended SES)
PharMetrics Plus

Electronic Health Record Databases (8)
Optum de-identified Electronic Health Record data set (Optum EHR)
Johns Hopkins Medical Enterprise (JHME)
Department of Veterans Affairs (VA)
Columbia University Medical Center (CUMC)
Keck Medical Center of University of Southern California (USC)
Oregon Health & Science University (OHSU)
Stanford University (STARR)
Washington University (WashU)

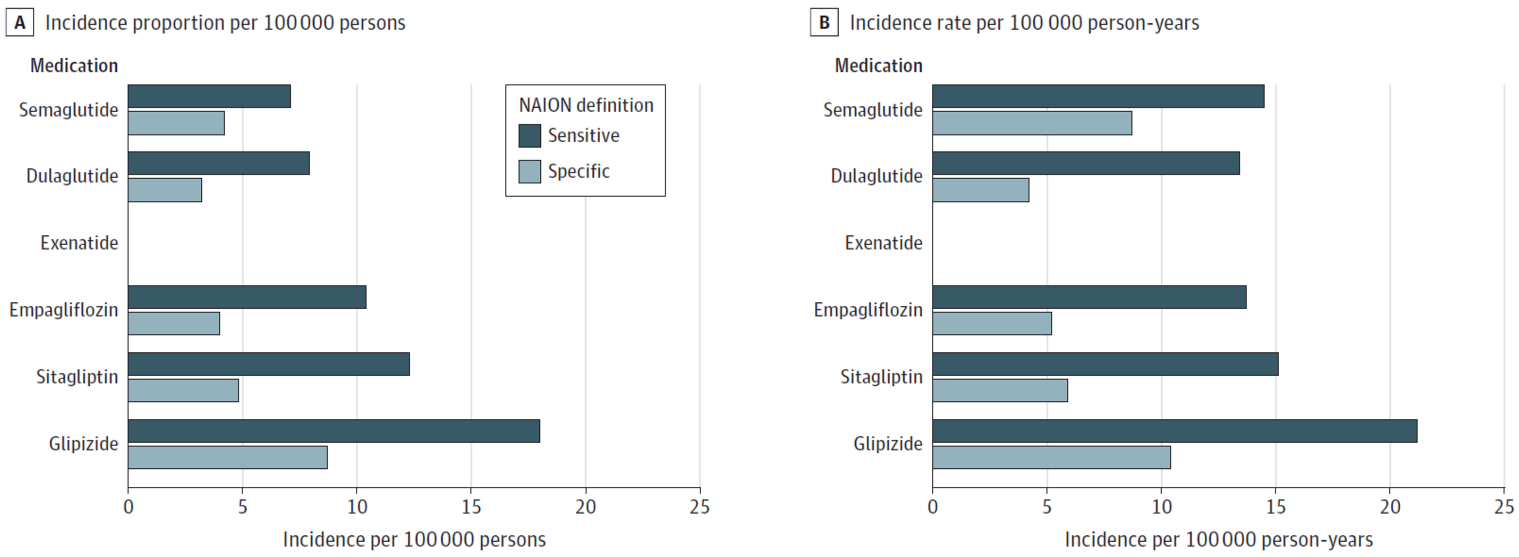
Results

	T2DM	Semaglutide (GLP-1 RA)
Sample Size	37.1M	810390
Incidence Rate (per 100K person-years)	41 / 16.8	14.5 / 8.7

Sensitive NAION

Specific NAION

Figure 1. Incidence of Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) Among Patients With Type 2 Diabetes



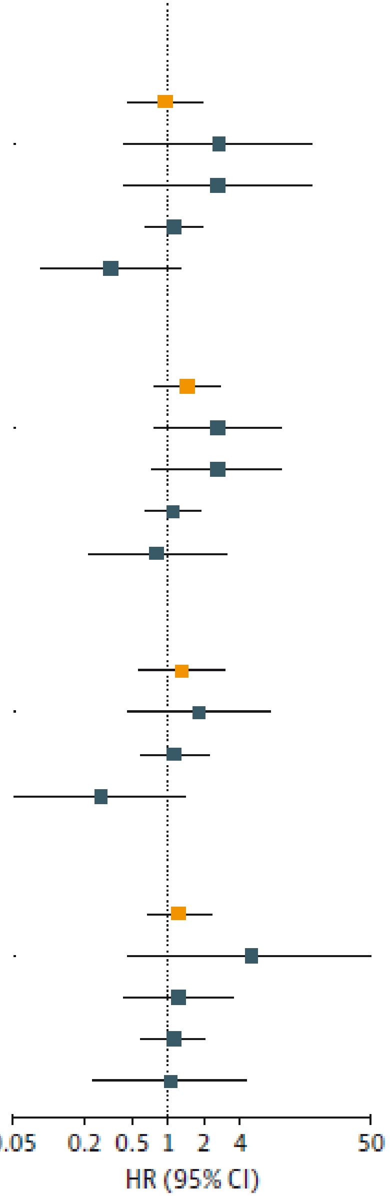
Historically, 2.3 to 11.4 (as high as 82) per 100,000 person-years

Active-Comparator New-User Cohort Analysis

Figure 2. Forest Plot for the Active-Comparator New-User Cohort Analysis

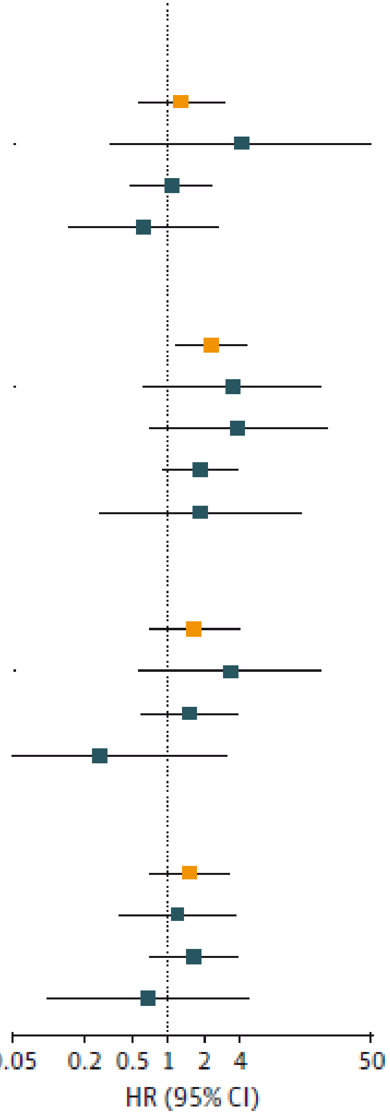
A Sensitive NAION

Study	HR (95% CI)	P value
Semaglutide vs dulaglutide (n = 553 662)		
Meta-analysis	0.93 (0.46-1.91)	.85
CCAE	2.63 (0.43-16.07)	.29
Clinformatics	2.57 (0.42-15.63)	.31
IQVIA	1.12 (0.65-1.93)	.69
PharMetrics	0.33 (0.09-1.25)	.10
Semaglutide vs empagliflozin (n = 768 608)		
Meta-analysis	1.44 (0.78-2.68)	.25
CCAE	2.60 (0.76-8.84)	.13
Clinformatics	2.58 (0.74-8.99)	.14
IQVIA	1.10 (0.66-1.84)	.71
PharMetrics	0.81 (0.22-3.02)	75
Semaglutide vs sitagliptin (n = 418 066)		
Meta-analysis	1.30 (0.56-3.01)	.54
Clinformatics	1.80 (0.46-7.13)	.40
IQVIA	1.13 (0.59-2.18)	.71
PharMetrics	0.27 (0.05-1.41)	.12
Semaglutide vs glipizide (n = 601 394)		
Meta-analysis	1.23 (0.66-2.28)	.51
CCAE	4.98 (0.46-54.28)	.19
Clinformatics	1.23 (0.43-3.52)	.70
IQVIA	1.12 (0.61-2.05)	.73
PharMetrics	1.04 (0.24-4.54)	.95



B Specific NAION

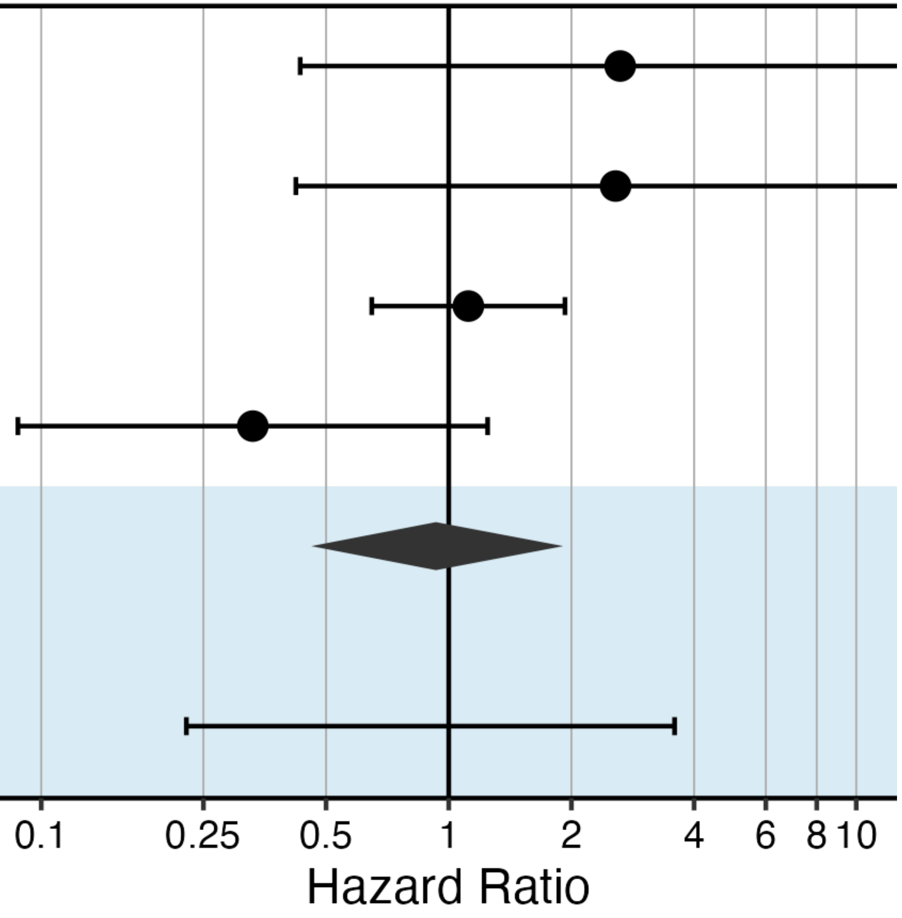
Study	HR (95% CI)	P value
Semaglutide vs dulaglutide (n = 553 982)		
Meta-analysis	1.28 (0.57-2.88)	.55
CCAE	4.13 (0.33-51.99)	.27
IQVIA	1.06 (0.49-2.33)	.88
PharMetrics	0.62 (0.14-2.61)	.51
Semaglutide vs empagliflozin (n = 769 136)		
Meta-analysis	2.27 (1.16-4.46)	.02
CCAE	3.43 (0.63-18.84)	.16
Clinformatics	3.82 (0.70-20.93)	.12
IQVIA	1.87 (0.92-3.83)	.09
PharMetrics	1.85 (.27-12.58)	.53
Semaglutide vs sitagliptin (n = 418 336)		
Meta-analysis	1.64 (0.69-3.90)	.27
Clinformatics	3.31 (0.58-19.05)	.18
IQVIA	1.48 (0.58-3.75)	.41
PharMetrics	0.27 (0.02-3.08)	.29
Semaglutide vs glipizide (n = 575 356)		
Meta-analysis	1.50 (0.70-3.21)	.29
Clinformatics	1.18 (0.38-3.67)	.77
IQVIA	1.64 (0.70-3.84)	.26
PharMetrics	0.67 (0.10-4.63)	.68



Semaglutide v Dulaglutide (GLP-1 RA)

Sensitive NAION

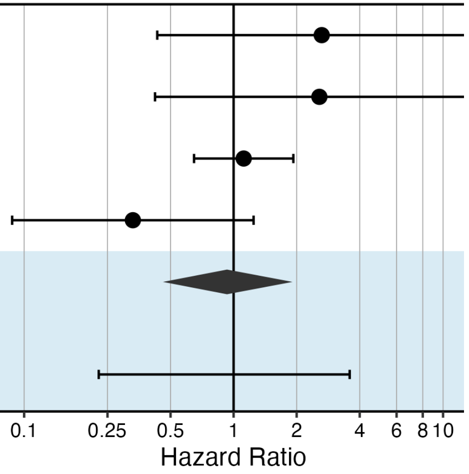
Source	Hazard Ratio (95% CI)
CCAE	2.63 (0.43 - 16.07)
Clinformatics	2.57 (0.42 - 15.63)
IQVIA	1.12 (0.65 - 1.93)
PharMetrics	0.33 (0.09 - 1.25)
Bayesian random effects τ = 0.42 (0.00 - 1.00)	**0.93 (0.46 - 1.91)**
Prediction interval	**(0.23 - 3.58)**



Semaglutide v Dulaglutide (GLP-1 RA)

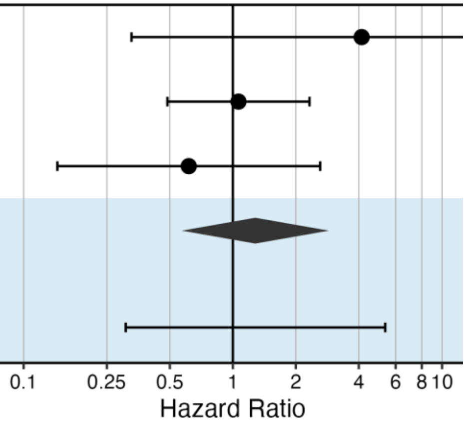
Sensitive NAION

Source	Hazard Ratio (95% CI)
CCAE	2.63 (0.43 - 16.07)
Clinformatics	2.57 (0.42 - 15.63)
IQVIA	1.12 (0.65 - 1.93)
PharMetrics	0.33 (0.09 - 1.25)
Bayesian random effects τ = 0.42 (0.00 - 1.00)	**0.93 (0.46 - 1.91)**
Prediction interval	**(0.23 - 3.58)**



Specific NAION

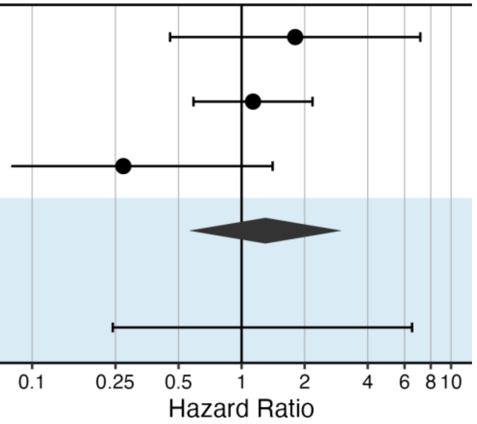
Source	Hazard Ratio (95% CI)
CCAE	4.13 (0.33 - 51.99)
IQVIA	1.06 (0.49 - 2.33)
PharMetrics	0.62 (0.14 - 2.61)
Bayesian random effects τ = 0.40 (0.01 - 1.03)	**1.28 (0.57 - 2.88)**
Prediction interval	**(0.31 - 5.35)**



Semaglutide v Sitagliptin (DPP4 inhibitor)

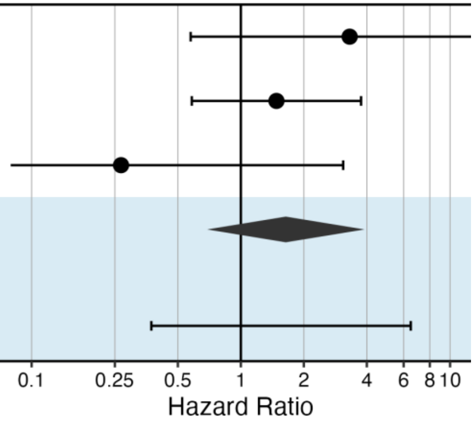
Sensitive NAION

Source	Hazard Ratio (95% CI)
Clinformatics	1.80 (0.46 - 7.13)
IQVIA	1.13 (0.59 - 2.18)
PharMetrics	0.27 (0.05 - 1.41)
Bayesian random effects τ = 0.53 (0.00 - 1.16)	**1.30 (0.56 - 3.01)**
Prediction interval	**(0.24 - 6.51)**



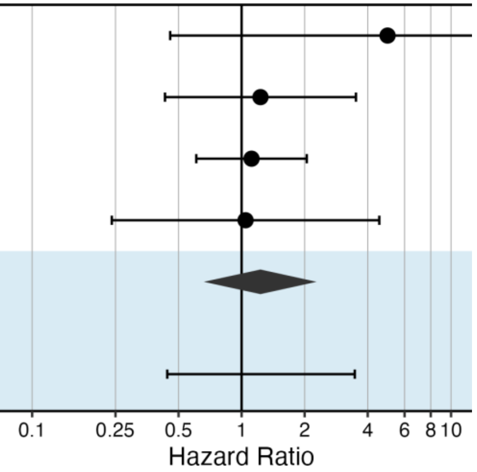
Specific NAION

Source	Hazard Ratio (95% CI)
Clinformatics	3.31 (0.58 - 19.05)
IQVIA	1.48 (0.58 - 3.75)
PharMetrics	0.27 (0.02 - 3.08)
Bayesian random effects τ = 0.37 (0.01 - 1.01)	**1.64 (0.69 - 3.90)**
Prediction interval	**(0.37 - 6.49)**

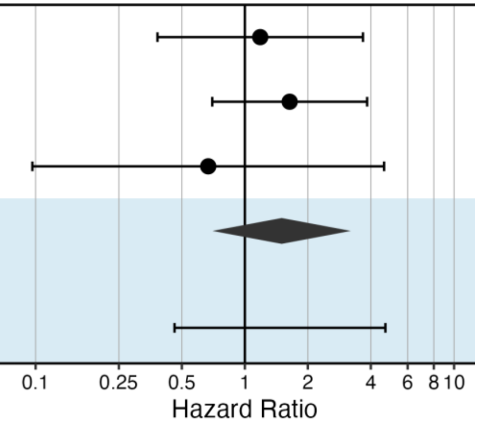


Semaglutide v Glipizide (sulfonylurea)

Source	Hazard Ratio (95% CI)
CCAE	4.98 (0.46 - 54.28)
Clinformatics	1.23 (0.43 - 3.52)
IQVIA	1.12 (0.61 - 2.05)
PharMetrics	1.04 (0.24 - 4.54)
Bayesian random effects τ = 0.26 (0.00 - 0.76)	**1.23 (0.66 - 2.28)**
Prediction interval	**(0.44 - 3.47)**



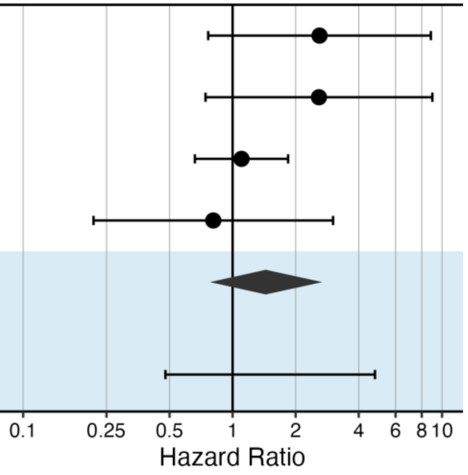
Source	Hazard Ratio (95% CI)
Clinformatics	1.18 (0.38 - 3.67)
IQVIA	1.64 (0.70 - 3.84)
PharMetrics	0.67 (0.10 - 4.63)
Bayesian random effects τ = 0.28 (0.00 - 0.83)	**1.50 (0.70 - 3.21)**
Prediction interval	**(0.46 - 4.70)**



Semaglutide v Empagliflozin (SGLT2 inhibitor)

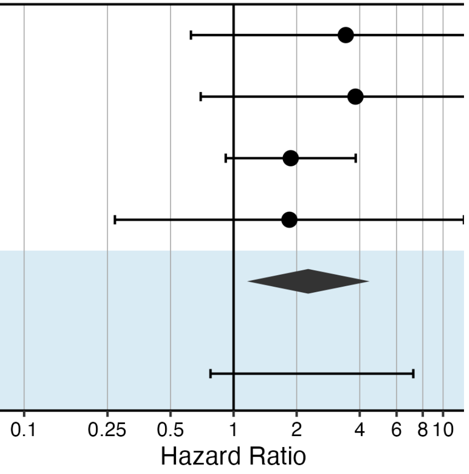
Sensitive NAION

Source	Hazard Ratio (95% CI)	
CCAE	2.60	(0.76 - 8.84)
Clinformatics	2.58	(0.74 - 8.99)
IQVIA	1.10	(0.66 - 1.84)
PharMetrics	0.81	(0.22 - 3.02)
Bayesian random effects τ = 0.33 (0.00 - 0.87)	**1.44**	**(0.78 - 2.68)**
Prediction interval		**(0.48 - 4.78)**



Specific NAION

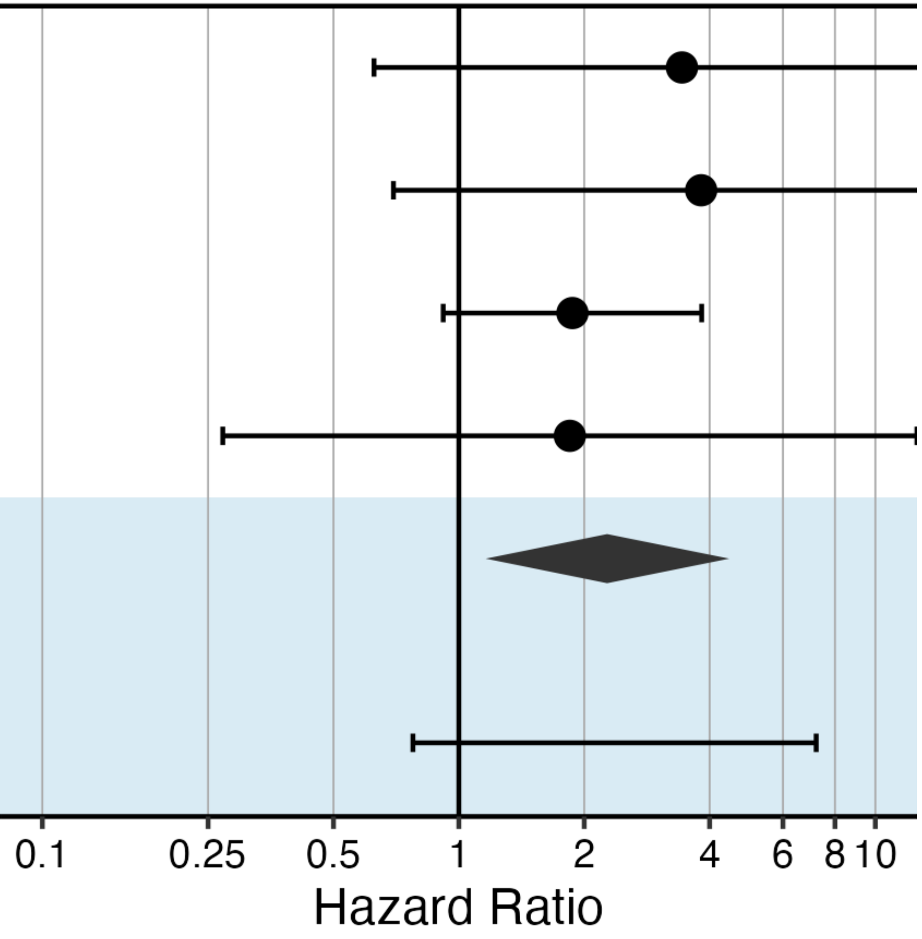
Source	Hazard Ratio (95% CI)	
CCAE	3.43	(0.63 - 18.84)
Clinformatics	3.82	(0.70 - 20.93)
IQVIA	1.87	(0.92 - 3.83)
PharMetrics	1.85	(0.27 - 12.58)
Bayesian random effects τ = 0.29 (0.00 - 0.80)	**2.27**	**(1.16 - 4.46)**
Prediction interval		**(0.78 - 7.21)**



Semaglutide v Empagliflozin (SGLT2 inhibitor)

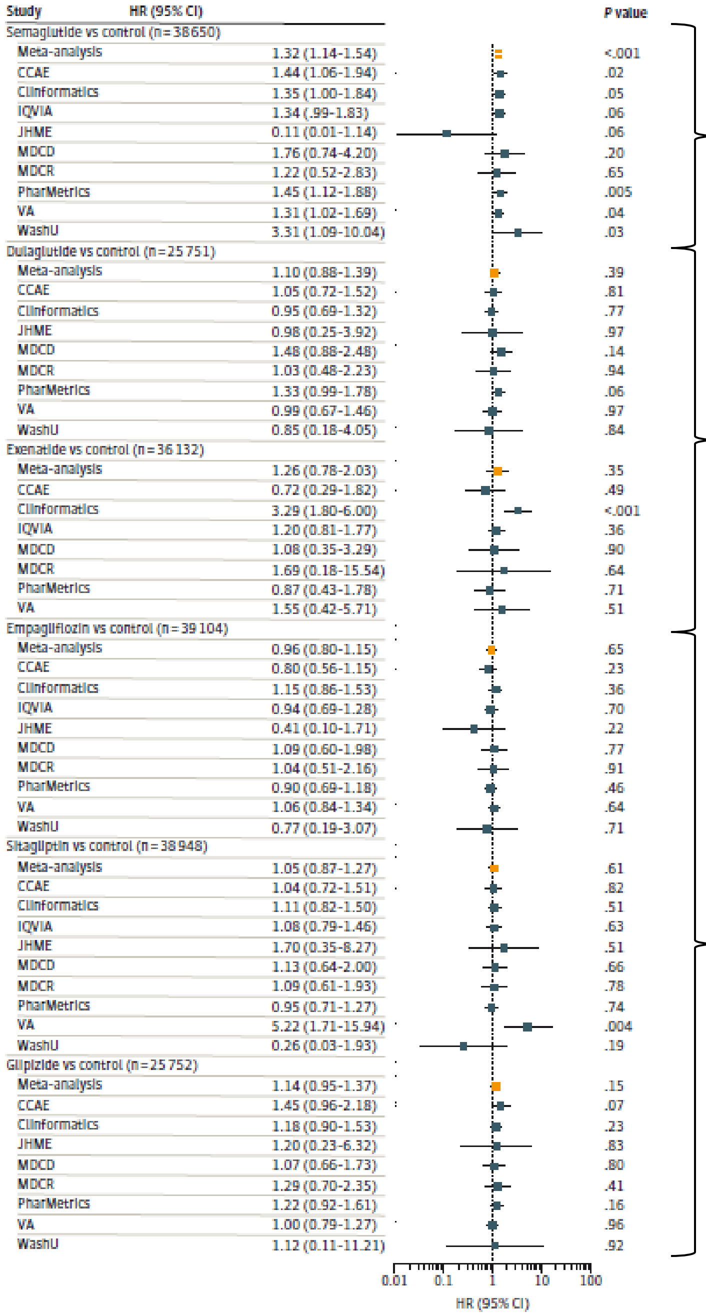
Specific NAION

Source	Hazard Ratio (95% CI)
CCAE	3.43 (0.63 - 18.84)
Clinformatics	3.82 (0.70 - 20.93)
IQVIA	1.87 (0.92 - 3.83)
PharMetrics	1.85 (0.27 - 12.58)
Bayesian random effects τ = 0.29 (0.00 - 0.80)	**2.27 (1.16 - 4.46)**
Prediction interval	**(0.78 - 7.21)**



Self-Controlled Case-Series Analysis

Figure 3. Forest Plot for the Self-Controlled Case Series Analysis, Sensitive Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) Definition[a] Sensitive NAION

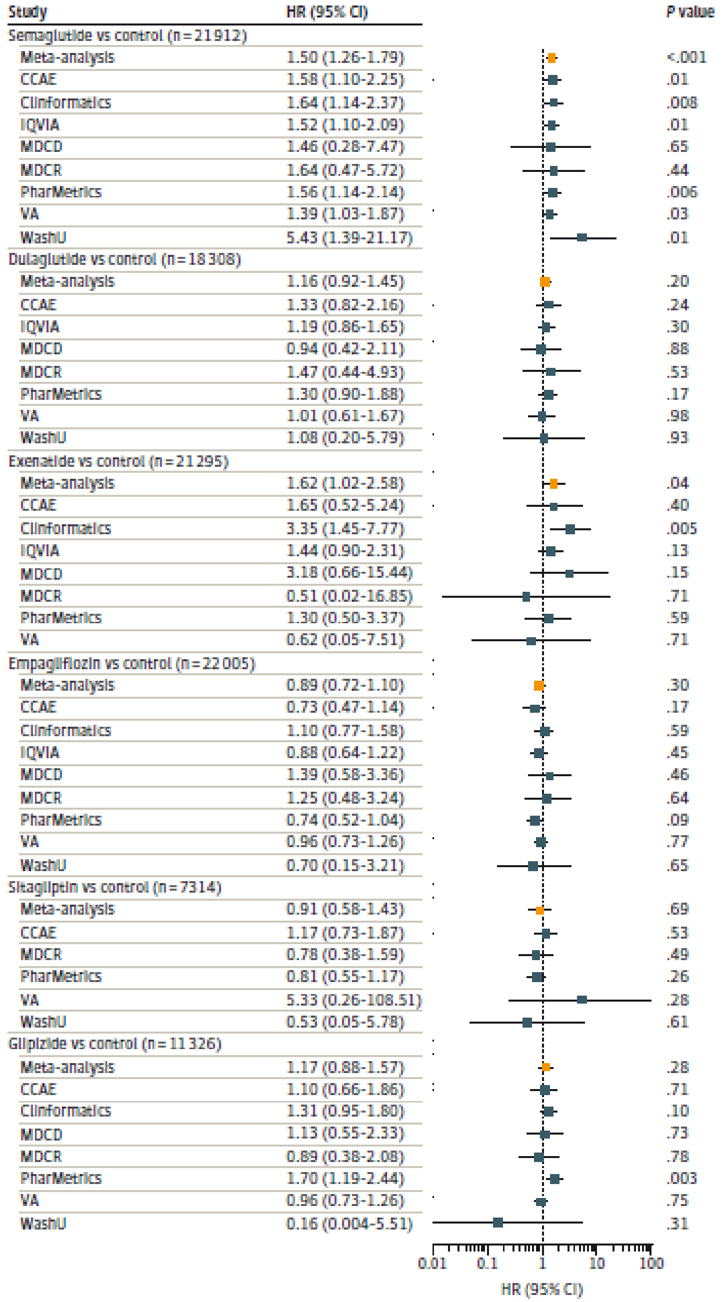


Semaglutide

Other GLP-1 RAs

Non-GLP-1 RAs

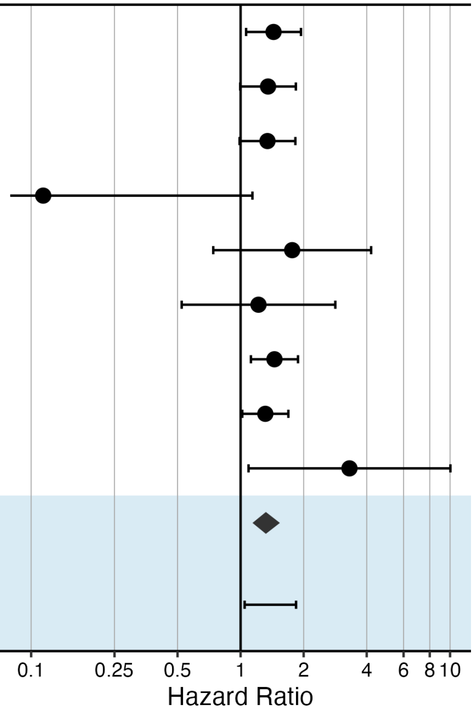
Figure 4. Forest Plot for the Self-Controlled Case Series Analysis, Specific Nonarteritic Anterior Ischemic Optic Neuropathy (NAION) Definition[a] Specific NAION



Self-Controlled Case Series: Semaglutide

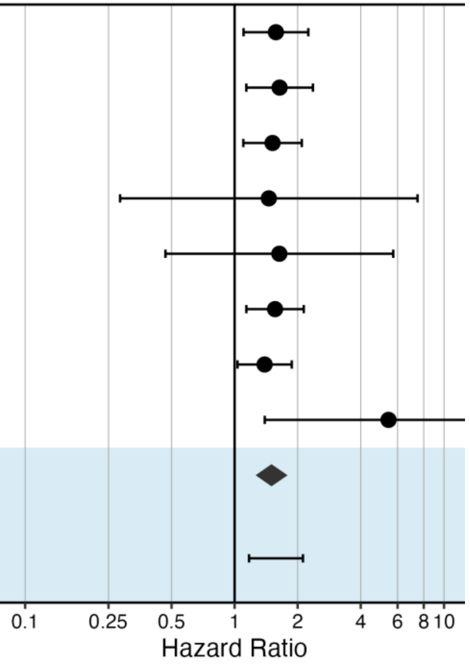
Sensitive NAION

Source	Hazard Ratio (95% CI)
CCAE	1.44 (1.06 - 1.94)
Clinformatics	1.35 (1.00 - 1.84)
IQVIA	1.34 (0.99 - 1.83)
JHME	0.11 (0.01 - 1.14)
MDCD	1.76 (0.74 - 4.20)
MDCR	1.22 (0.52 - 2.83)
PharMetrics	1.45 (1.12 - 1.88)
VA	1.31 (1.02 - 1.69)
WashU	3.31 (1.09 - 10.04)
Bayesian random effects τ = 0.07 (0.00 - 0.25)	**1.32 (1.14 - 1.54)**
Prediction interval	**(1.05 - 1.84)**



Specific NAION

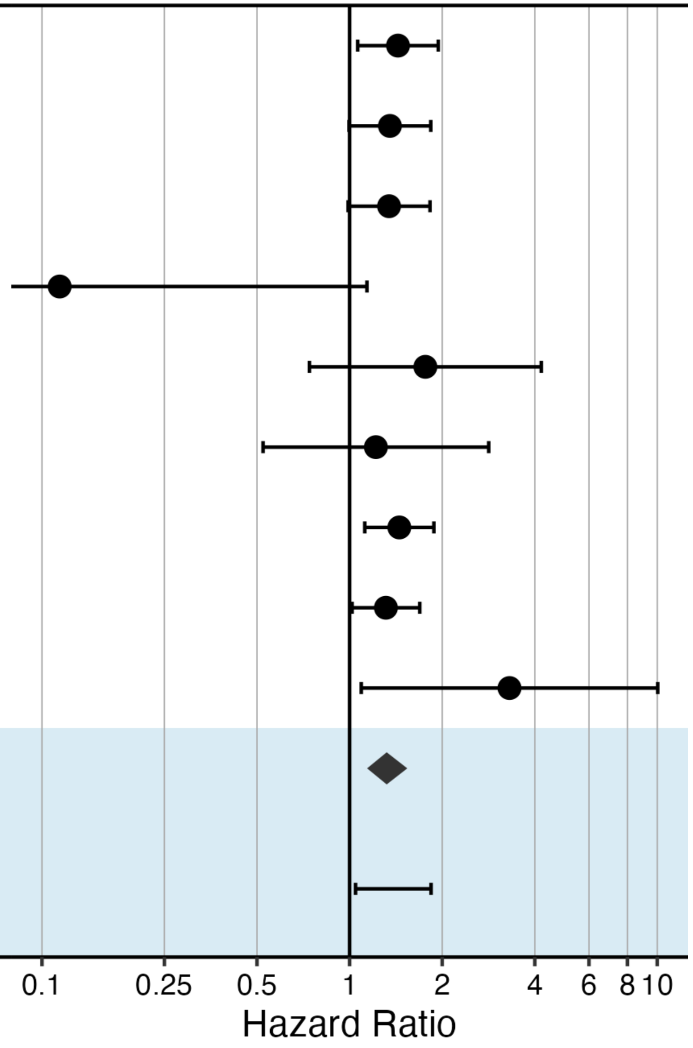
Source	Hazard Ratio (95% CI)
CCAE	1.58 (1.10 - 2.25)
Clinformatics	1.64 (1.14 - 2.37)
IQVIA	1.52 (1.10 - 2.09)
MDCD	1.46 (0.28 - 7.47)
MDCR	1.64 (0.47 - 5.72)
PharMetrics	1.56 (1.14 - 2.14)
VA	1.39 (1.03 - 1.87)
WashU	5.43 (1.39 - 21.17)
Bayesian random effects τ = 0.07 (0.00 - 0.25)	**1.50 (1.26 - 1.79)**
Prediction interval	**(1.17 - 2.12)**



Self-Controlled Case Series: Semaglutide

Sensitive NAION

Source	Hazard Ratio (95% CI)
CCAE	1.44 (1.06 - 1.94)
Clinformatics	1.35 (1.00 - 1.84)
IQVIA	1.34 (0.99 - 1.83)
JHME	0.11 (0.01 - 1.14)
MDCD	1.76 (0.74 - 4.20)
MDCR	1.22 (0.52 - 2.83)
PharMetrics	1.45 (1.12 - 1.88)
VA	1.31 (1.02 - 1.69)
WashU	3.31 (1.09 - 10.04)
Bayesian random effects τ = 0.07 (0.00 - 0.25)	**1.32 (1.14 - 1.54)**
Prediction interval	**(1.05 - 1.84)**



Our OHDSI Network Study Conclusions

- Small increased risk of NAION among T2DM patients exposed to semaglutide
  - Much smaller than previously reported
  - HR of 1.32 or 1.50 versus 4.28

- Incidence rate of NAION among T2DM patients exposed to semaglutide
  - Much smaller than previously reported
  - 14.5 or 8.7/100,000 person-years versus 6.5/100 person-years

Strengths of OHDIS Network Study

- Multiple databases
- Multiple outcomes
- Multiple study design
  - Included sensitivity analyses

Generalizability, replicability, and robustness

Invited Commentary

Semaglutide and Risk of NAION—Additional Insights

Joseph F. Rizzo III, MD; Jimena Tatiana Hathaway, MD, MPH

"…**should be congratulated** on conducting a **thoughtful and well-designed study** that advances our knowledge about a relatively small risk associated with semaglutide, at least among patients with T2D."

Rizzo JF, Hathaway JT. Semaglutide and Risk of NAION—Additional Insights. *JAMA Ophthalmol*. 2025;143(4).

Explosion of Conflicting Observational Studies in Literature

Letter to the Editor

Real-World Evidence Assessment of the Risk of Nonarteritic Anterior Ischemic Optic Neuropathy in Patients Prescribed Semaglutide

Journal of Diabetes Science and Technology
1–2
© 2024 Diabetes Technology Society
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/19322968241268050
journals.sagepub.com/home/dst
Sage

David C. Klonoff, MD, FACP, FRCP (Edin), Fellow AIMBE[1], Gavin Hui, MD[2], and Saurabh Gombar, MD, PhD[2,3]

Klonoff: GLP1 RA v non-GLP-1 RA, no difference in risk

The Effect of Semaglutide and GLP-1 RAs on Risk of Nonarteritic Anterior Ischemic Optic Neuropathy

NADIA J. ABBASS, RAYA NAHLAWI, JACQUELINE K. SHAIA, KEVIN C. ALLAN, DAVID C KAELBER, KATHERINE E. TALCOTT, AND RISHI P. SINGH

Abbass: semaglutide v non-GLP-1R RA, no difference in risk

ORIGINAL ARTICLE — WILEY

Use of semaglutide and risk of non-arteritic anterior ischemic optic neuropathy: A Danish–Norwegian cohort study

Emma Simonsen MD[1] | Lars Christian Lund PhD[1] | Martin Thomsen Ernst MSc[1] | Vidar Hjellvik PhD[2] | Laszlo Hegedüs DMSc[3,4] | Steffen Hamann PhD[5,6] | Øystein Kalsnes Jørstad PhD[7,8] | Hanne Løvdal Gulseth PhD[2] | Øystein Karlstad PhD[2] | Anton Pottegård DMSc[1]

Simonsen: semaglutide v SGLT2i, HR 2.81

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Association between Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy

A Multinational Population-Based Study

Chien-Chih Chou, MD, PhD,[1,2,3] Ssu-Yu Pan, MD,[1,2] Yi-Jing Sheen, MD, PhD,[1,3,4,5] Jun-Fu Lin, MS,[6] Ching-Heng Lin, PhD,[6,7,8,9] Hsu-Ju Lin, MD, PhD,[10,11] I-Jong Wang, MD, PhD,[12,13] Chien-Hsiang Weng, MD, MPH[14,15]

Chou: semaglutide v non-GLP-1 RA, no difference in risk

RESEARCH — Open Access

Once-weekly semaglutide doubles the five-year risk of nonarteritic anterior ischemic optic neuropathy in a Danish cohort of 424,152 persons with type 2 diabetes

Jakob Grauslund[1,2,3*†], Andreas Abou Taha[1,2†], Laleh Dehghani Molander[1], Ryo Kawasaki[2,4], Sören Möller[2,5], Kurt Højlund[2,3] and Lonny Stokholm[2,5]

Grauslund: semaglutide v non-exposure, HR 2.19

Research

JAMA Ophthalmology | Original Investigation

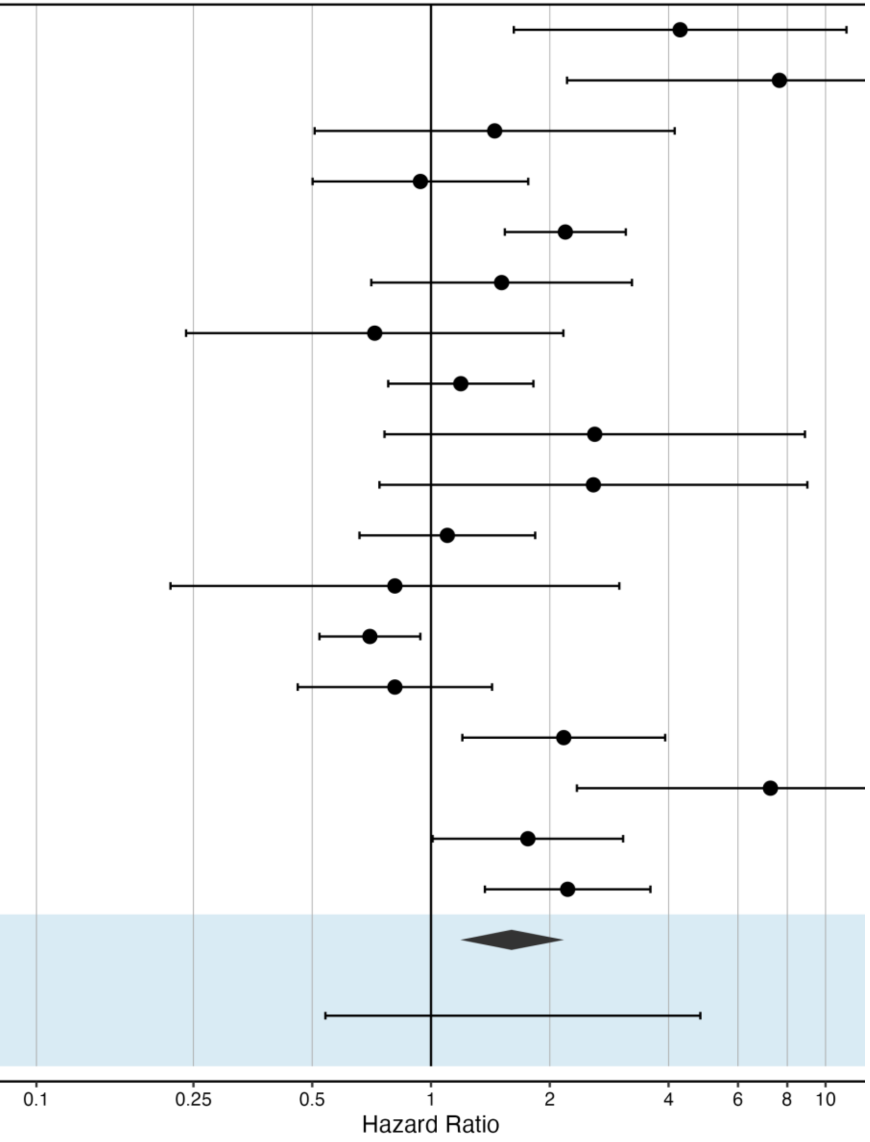
Semaglutide and Nonarteritic Anterior Ischemic Optic Neuropathy Risk Among Patients With Diabetes

Alan Y. Hsu, MD; Hou-Ting Kuo, MD; Yu-Hsun Wang, MS; Chun-Ju Lin, MD; Yi-Ching Shao, MD; Chun-Chi Chiang, MD, PhD; Ning-Yi Hsia, MD; Chun-Ting Lai, MD; Hsin Tseng, MD; Bing-Qi Wu, MD; Huan-Sheng Chen, MD; Yi-Yu Tsai, MD, PhD; Min-Yen Hsu, MD, PhD; James Cheng-Chung Wei, MD, PhD

Hsu: semaglutide v non-GLP-1 RA, HR 1.33-2.99

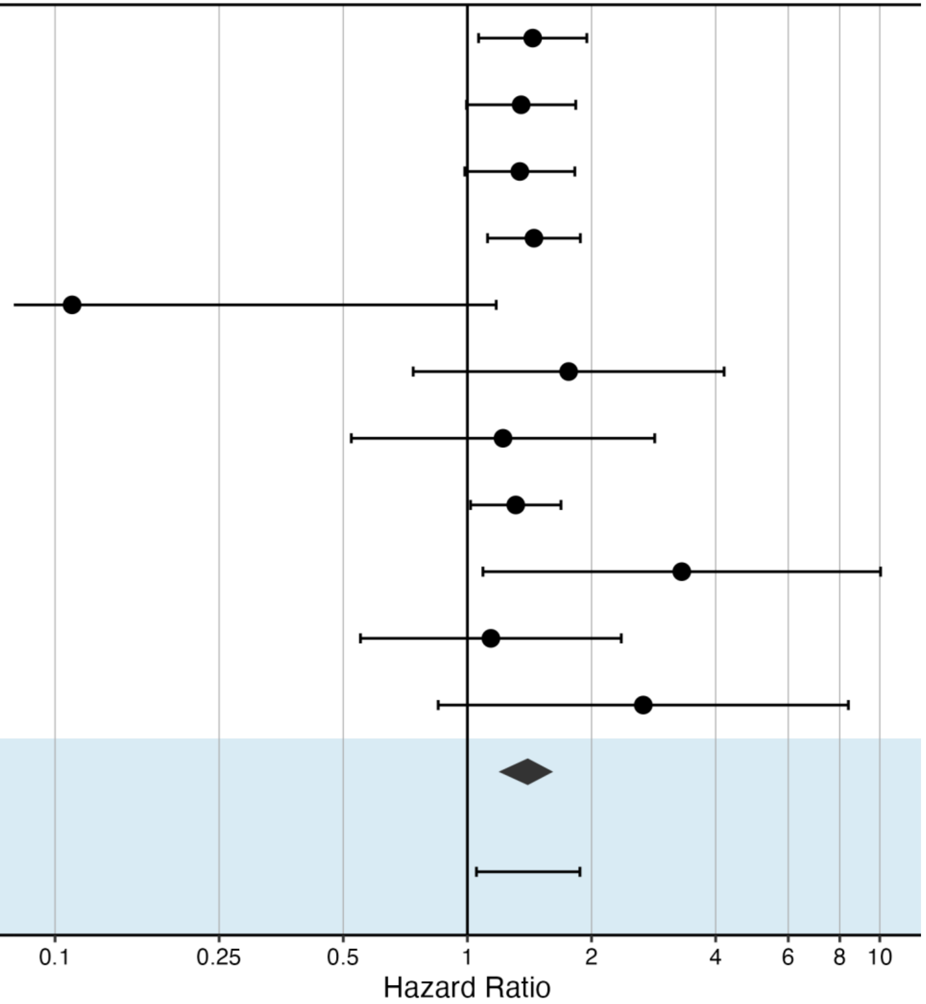
Meta-Analysis of Literature: Cohort Analysis

Source	Hazard Ratio (95% CI)	
Hathaway et al.; Mass Eye and Ear (US EHR); unexposed	4.28	(1.62 - 11.30)
Hathaway et al.; Mass Eye and Ear (US EHR); unexposed	7.64	(2.21 - 26.39)
Klonoff et al.; Arcadia (US EHR and claims); non-GLP1	1.45	(0.51 - 4.15)
Klonoff et al.; Stanford; non-GLP1	0.94	(0.50 - 1.76)
Grauslund et al.; Denmark National Registry; unexposed	2.19	(1.54 - 3.12)
Chou et al.; TriNetx (EHR data network); non-GLP1RA	1.51	(0.71 - 3.23)
Chou et al.; TriNetx (EHR data network); non-GLP1RA	0.72	(0.24 - 2.16)
Chou et al.; TriNetx (EHR data network); non-GLP1RA	1.19	(0.78 - 1.82)
Cai et al.; CCAE (US claims); empagliflozin	2.60	(0.76 - 8.87)
Cai et al.; Optum Clinformatics (US claims); empagliflozin	2.58	(0.74 - 8.99)
Cai et al.; Iqvia Open Claims (US claims); empagliflozin	1.10	(0.66 - 1.84)
Cai et al.; PharMetrics (US claims); empagliflozin	0.81	(0.22 - 3.00)
Abbass et al.; TriNetx (EHR data network); non-GLP1RA	0.70	(0.52 - 0.94)
Abbass et al.; TriNetx (EHR data network); non-GLP1RA	0.81	(0.46 - 1.43)
Simonsen et al.; Denmark National Registry; SGLT2i	2.17	(1.20 - 3.92)
Simonsen et al.; Norway National Registry; SGLT2i	7.25	(2.34 - 22.43)
Wang et al.; Trinetx global; other	1.76	(1.01 - 3.07)
Hsu et al.; Trinetx US; non-GLP1RA	2.22	(1.37 - 3.60)
Bayesian random effects τ = 0.49 (0.27 - 0.78)	**1.60**	**(1.19 - 2.17)**
Prediction interval		**(0.54 - 4.82)**

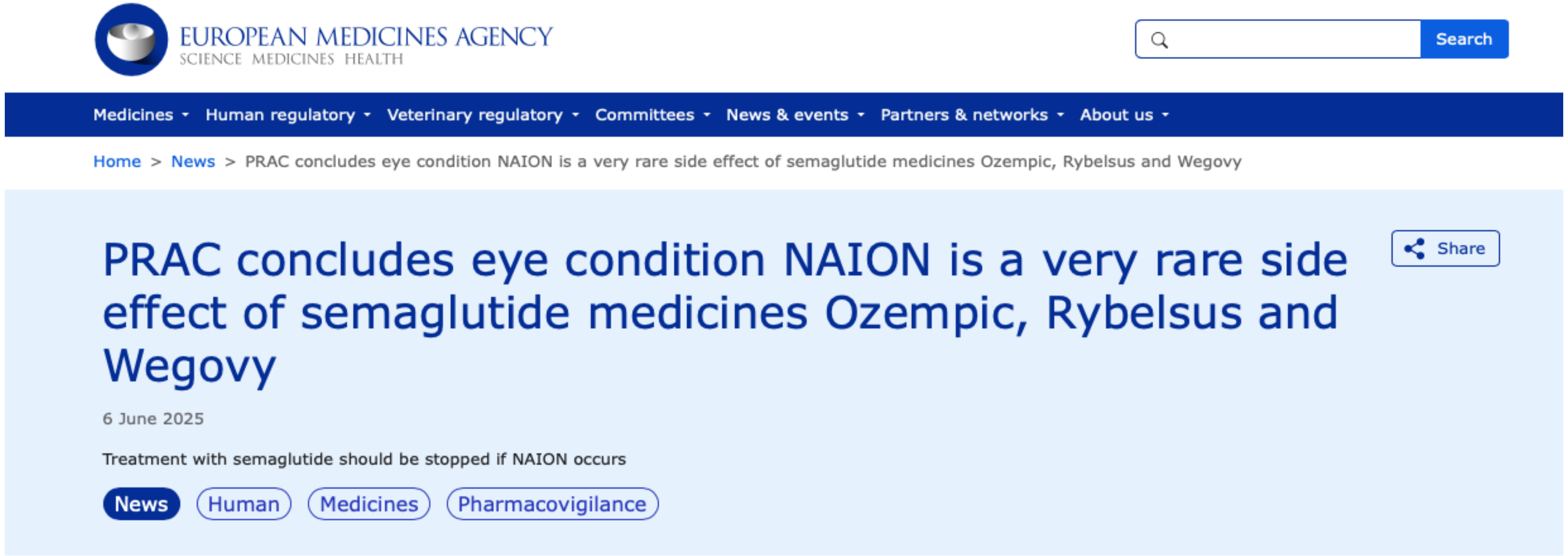


Meta-Analysis of Literature: Self-Controlled Case Series

Source	Hazard Ratio (95% CI)	
Cai et al.; CCAE (US claims)	1.44	(1.06 - 1.95)
Cai et al.; Optum Clinformatics (US claims)	1.35	(1.00 - 1.83)
Cai et al.; Iqvia Open Claims (US claims)	1.34	(0.99 - 1.82)
Cai et al.; PharMetrics (US claims)	1.45	(1.12 - 1.88)
Cai et al.; JHME (US EHR)	0.11	(0.01 - 1.17)
Cai et al.; MDCD (US claims)	1.76	(0.74 - 4.19)
Cai et al.; MDCR (US claims)	1.22	(0.52 - 2.85)
Cai et al.; VA (US EHR)	1.31	(1.02 - 1.69)
Cai et al.; WashU (US EHR)	3.31	(1.09 - 10.05)
Simonsen et al.; Denmark National Registry	1.14	(0.55 - 2.36)
Simonsen et al.; Norway National Registry	2.67	(0.85 - 8.39)
Bayesian random effects τ = 0.07 (0.00 - 0.24)	**1.40**	**(1.19 - 1.61)**
Prediction interval		**(1.05 - 1.87)**



EMA’s safety committee


EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Search

Medicines · Human regulatory · Veterinary regulatory · Committees · News & events · Partners & networks · About us

Home > News > PRAC concludes eye condition NAION is a very rare side effect of semaglutide medicines Ozempic, Rybelsus and Wegovy

Share

PRAC concludes eye condition NAION is a very rare side effect of semaglutide medicines Ozempic, Rybelsus and Wegovy

6 June 2025

Treatment with semaglutide should be stopped if NAION occurs

News | Human | Medicines | Pharmacovigilance

EMA has therefore recommended that the product information for semaglutide medicines is updated to include NAION as a side effect with a frequency of ‘very rare’ (up to 1/10,000 person-years)

EMA side effect frequency categories: very common, common, uncommon, rare, very rare

https://www.ema.europa.eu/en/news/prac-concludes-eye-condition-naion-very-rare-side-effect-semaglutide-medicines-ozempic-rybelsus-wegovy

AAO and NANOS Recommendation

American Academy of Ophthalmology and North American Neuro-Ophthalmology Society

July 7, 2025

American Academy of Ophthalmology and the North American Neuro-Ophthalmology Society **do not support a blanket recommendation for all patients to immediately stop taking semaglutide if they develop NAION**.

Instead, we recommend that patients who develop NAION while on semaglutide engage in a shared decision-making process with their physicians, including their ophthalmologist, neurologist, primary care physician, or endocrinologist. This discussion should consider the individual's overall health, risk factors, and therapeutic options to make an informed decision about whether to continue or discontinue semaglutide.

https://www.aao.org/newsroom/news-releases/detail/should-you-stop-taking-glp-1-drugs-like-ozempic

Amazing Community

Thank you!

ccai6@jhmi.edu

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Why network studies are necessary to improve trust in evidence

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

Why network study is better than single database study

	Accuracy	Precision	Consistency
Network study	Designed to provide unbiased sample of databases, each providing unbiased estimates of effect	Planned to have sufficient power to detect effect, accounting for within-source random error and across-source random error	Evaluate both within-database consistency across designs, and between-database consistency across populations
Single database study	Accuracy is always worse than network study: • Diversity is greater in network study	Precision is always worse than network study in both dimensions: • Sample of persons greater in network study • Sample of databases greater in network study	Cannot evaluate between-database consistency with only one database

Why meta-analysis of the published literature may be better than a network study

	Accuracy	Precision	Consistency
Network study	Designed to provide unbiased sample of databases, each providing unbiased estimates of effect	Planned to have sufficient power to detect effect, accounting for within-source random error and across-source random error	Evaluate both within-database consistency across designs, and between-database consistency across populations
Meta-analysis of published literature	Results from randomized clinical trials (RCTs) and other non-interventional studies with prospective data collection may be less biased than retrospective database analyses	Can summarize all evidence across study designs	Evaluate consistency across study designs and interpretations from different organizations

Why network study may be better than a meta-analysis of the published literature

	Accuracy	Precision	Consistency
Network study	Designed to provide unbiased sample of databases, each providing unbiased estimates of effect	Planned to have sufficient power to detect effect, accounting for within-source random error and across-source random error	Evaluate both within-database consistency across designs, and between-database consistency across populations
Meta-analysis of published literature	Within-study bias can be appraised, but not corrected: - "Problems with the design and execution of individual studies ... raise questions about the internal validity of their findings" Across-study meta-analysis results subject to risk of "non-reporting bias"	Power determined by the number of publications identified and the samples available within each study	Different studies targeting the same research question may use different design choices (ex: comparator, outcome definition, adjustment strategy, time-at-risk) so more possible reasons for inconsistency

Recommendations for Network Studies

	Design and pre-specification	Transparent reporting and interpretation
Accuracy	• Apply objective diagnostics with pre-specified unblinding decision criteria to each source • Ensure your network study has a diverse sample of data sources, collectively reflective of the target population of interest	• Report all diagnostics results (passes and fails), including sources that remain blinded • Summarize network diversity of resulting unblinded sources
Precision	• Plan for adequate statistical power on two dimensions: number of persons and number of data sources. • Calculate Minimum Detectable Relative Risk for Network Prediction Interval	• Report estimates from all sources plus meta-analytic summary, but focus on prediction interval to reflect uncertainty around estimate • Sufficient precision: no more replications needed

Consistency	• Define multiple analytic design variants to assess sensitivity analysis robustness
	• Pre-define subgroups to enable exploration of heterogeneity of treatment effects
		• Evaluate consistency (τ) to recommend next steps when there is insufficient precision:
		    • Low τ: more replications would be helpful
		    • High τ: test new hypotheses to explain the heterogeneity