# Real World Evidence: why should you care?

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Prof of Pharmaco-epidemiology
Oxford University

# AGENDA

- Preface: Why bother?
- Mitigating confounding
- Collaboration is the new competition
- Hacking COVID-19
- And then we got the vaccines!
- The future (of RWE) is here
- Key learnings

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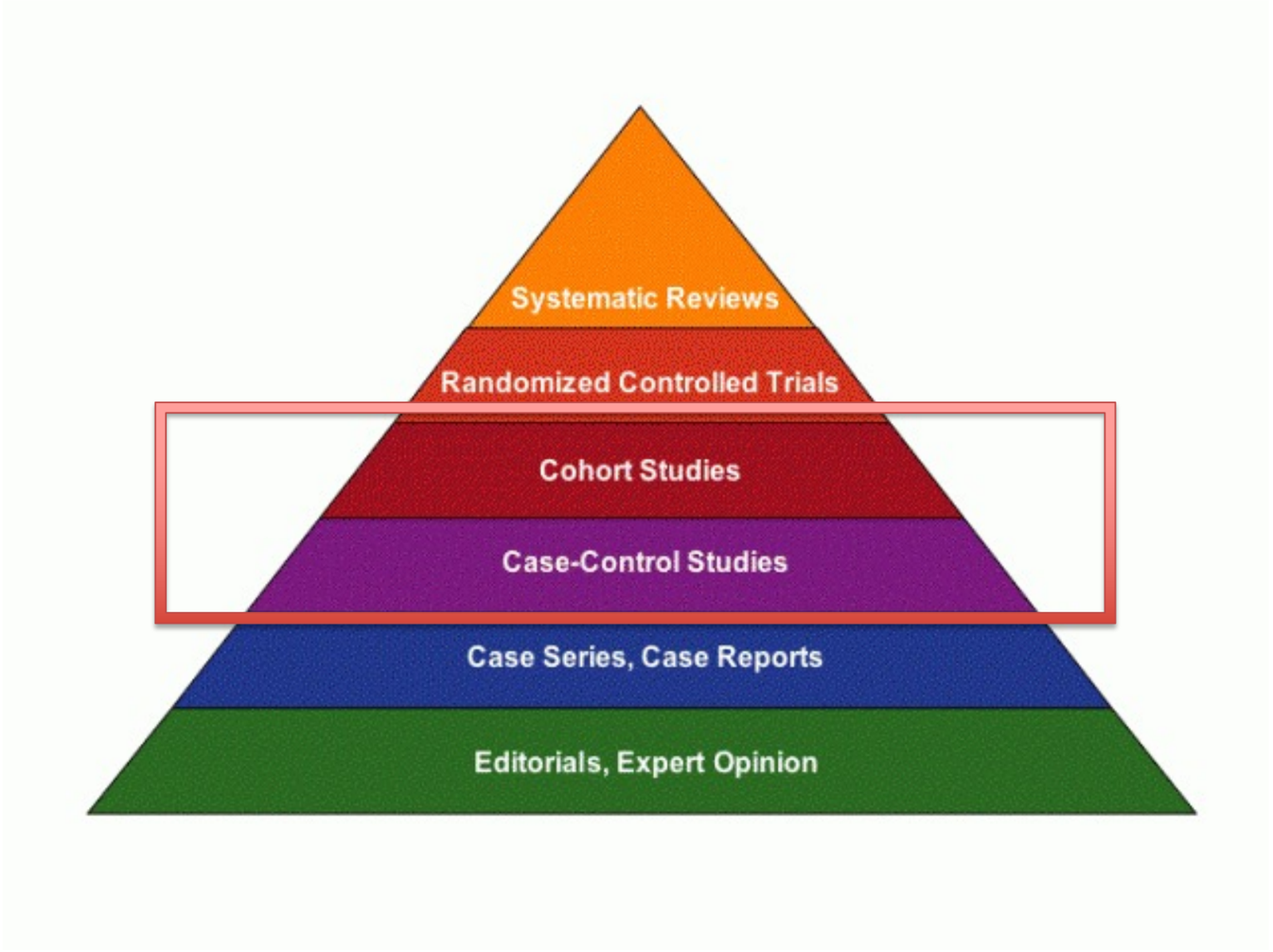
# Why RWE?


Systematic Reviews
Randomized Controlled Trials
Cohort Studies
Case-Control Studies
Case Series, Case Reports
Editorials, Expert Opinion

# Why ‘real world’ data?
# 1.RCTs are not always possible …

Hazard

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

*BMJ 2003*

Gordon C S Smith, Jill P Pell

**What this study adds**

No randomised controlled trials of parachute use have been undertaken

The basis for parachute use is purely observational, and its apparent efficacy could potentially be explained by a “healthy cohort” effect

**The medicalisation of free fall**

It is often said that doctors are interfering monsters obsessed with disease and power, who will not be satisfied until they control every aspect of our lives (*Journal*

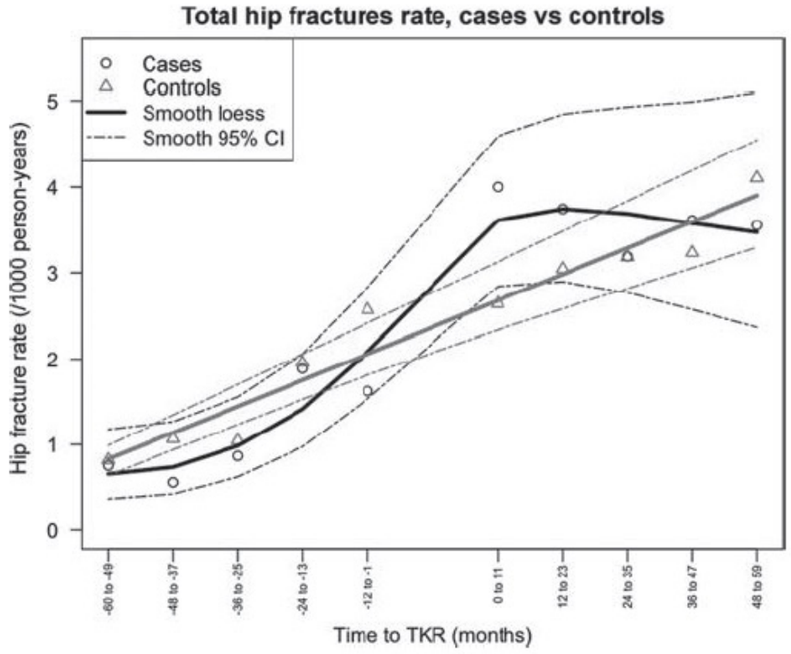
**# OF RCTs = 0**

# Why ‘real world’ data?

# 2.The data is out there … and this enables replication studies

Changes in hip fracture rate before and after total knee replacement due to osteoarthritis: a population-based cohort study

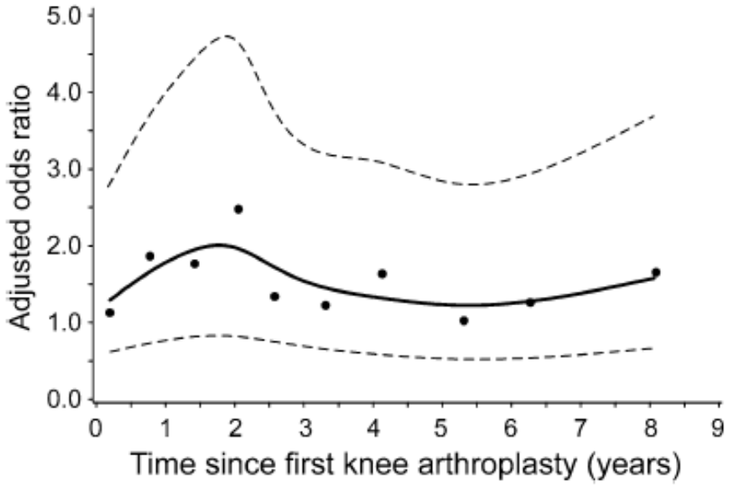
Daniel Prieto-Alhambra,[1–3] M Kassim Javaid,[1] Joe Maskell,[1,4] Andrew Judge,[1] Michael Nevitt,[5] Cyrus Cooper,[1,4] Nigel K Arden[1,4]




Prieto-Alhambra D et al. Ann Rheum Dis 2011

**Knee Arthroplasty and Risk of Hip Fracture: A Population-Based, Case–Control Study**

Arief Lalmohamed · Frans Opdam · Nigel K. Arden · Daniel Prieto-Alhambra · Tjeerd van Staa · Hubertus G. M. Leufkens · Frank de Vries




Prieto-Alhambra D et al. CTI 2012

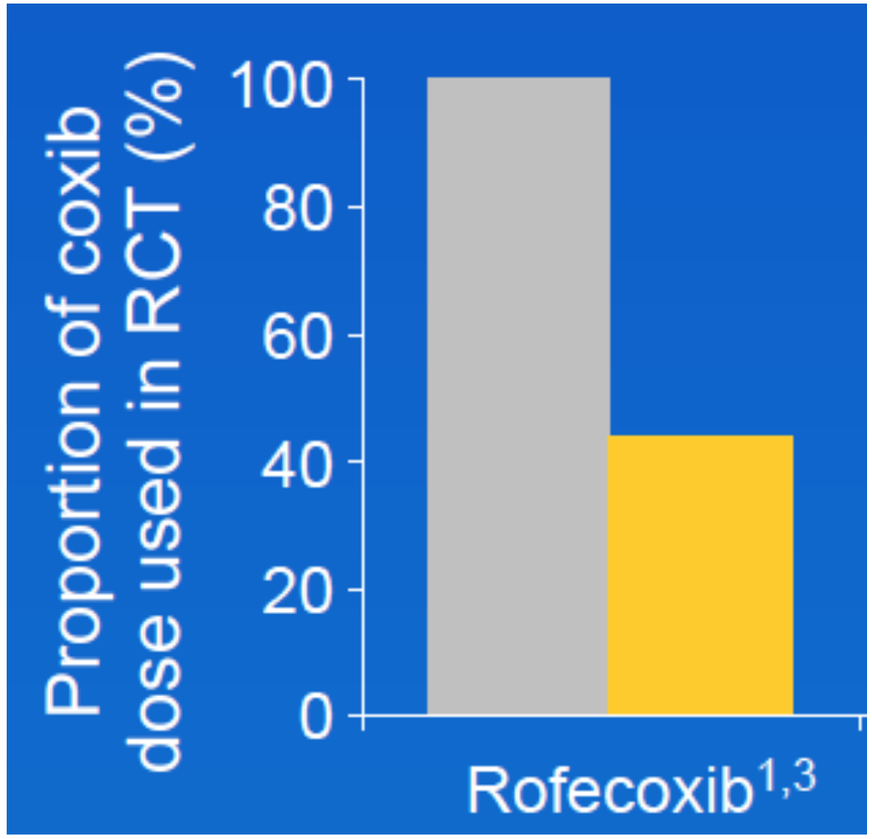
# Why ‘real world’ data?
# 3.Generalizability

**Table 1** Comparison of the exclusion criteria in the FIT trial with the incident users of alendronate in the SIDIAP and DHR database

| FIT exclusion criteria[a] | Operational definition/ICD-10 Codes | Incident users of Alendronate[d] | |
|---|---|---|---|
| | | SIDIAP $N = 14{,}316$ (%) | DHR $N = 21{,}214$ (%) |
| Men | Sex according to administrative data | 3818 (26.7 %) | 3885 (18.3 %) |
| Age <55 years old | Age at first ALD dispensation | 1844 (12.9 %) | 1654 (7.8 %) |
| Age >80 years old | Age at first ALD dispensation | 2347 (16.4 %) | 5275 (24.9 %) |

C Reyes et al. Osteoporos Int 2014

# Why ‘real world’ data?
# 4.Efficacy vs Effectiveness …



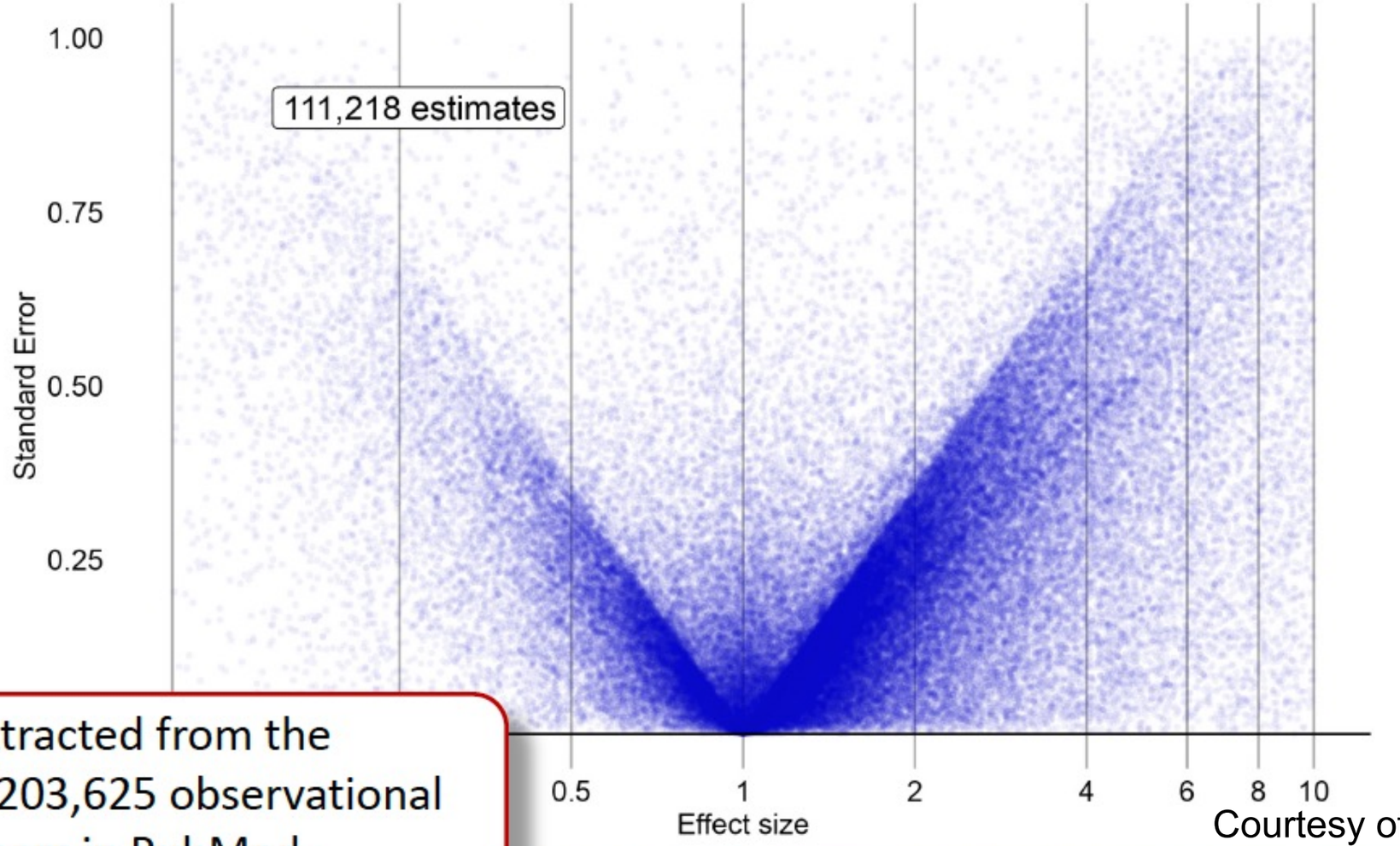

**Adherence in RCT (Vigor study) vs “real life”**

**Rofecoxib users in CPRD**

*[TV Staa PLoS One ‘09]*

# BUT… RWE also has problems…

# 1. P-hacking




Estimates extracted from the abstracts of 203,625 observational research papers in PubMed.

Courtesy of M Schuemie

# 2. Fraud is still an issue

Science Contents News Careers Journals

Two papers relying on hospital records of COVID-19 patients have been retracted because the company that purportedly analyzed the raw data won't allow their validity to be independently validated. AP PHOTO/MANU FERNANDEZ

## Two elite medical journals retract coronavirus papers over data integrity questions

By Charles Piller, Kelly Servick | Jun. 4, 2020 , 5:30 PM

Science Contents News Careers Journals

E. PETERSEN/*SCIENCE*

## Who's to blame? These three scientists are at the heart of the Surgisphere COVID-19 scandal

By Charles Piller | Jun. 8, 2020 , 7:00 PM

***Science*'s COVID-19 reporting is supported by the Pulitzer Center.**

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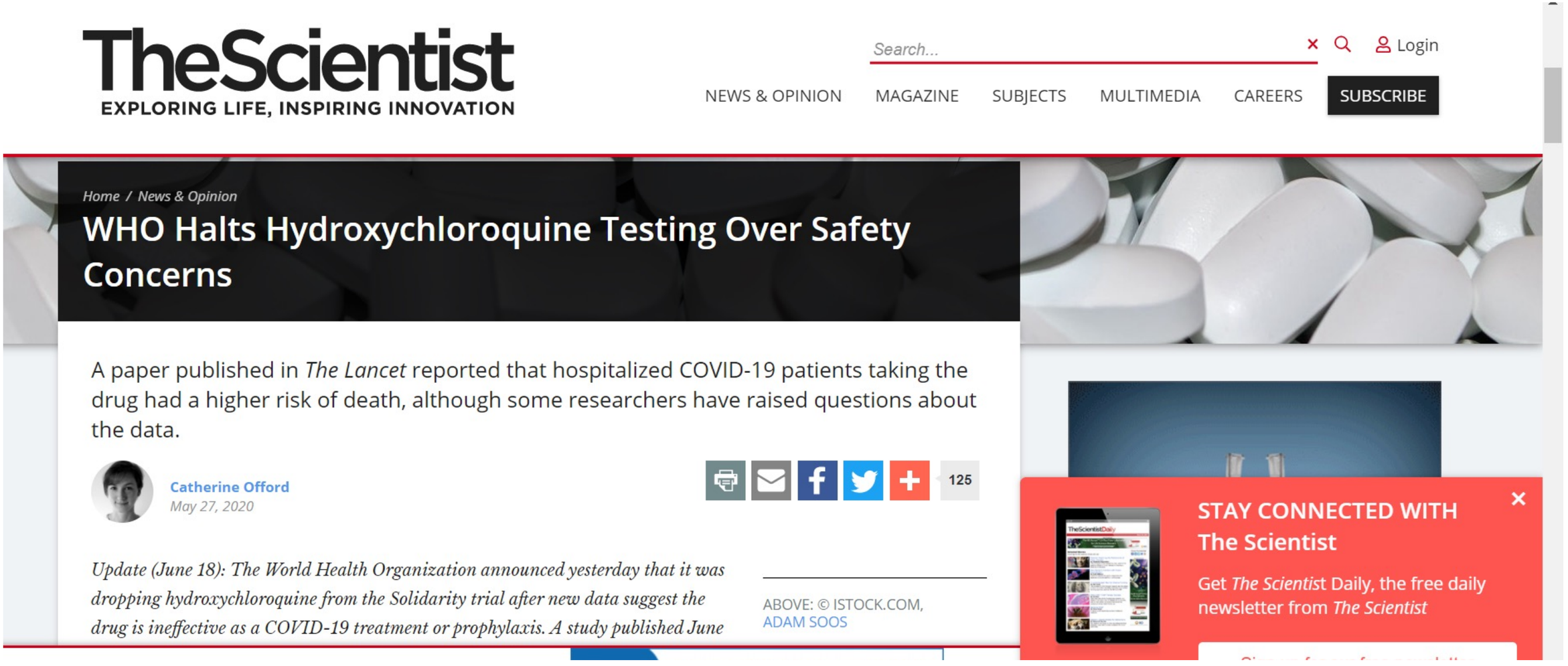
Three unlikely collaborators are at the heart of the fast-moving COVID-19 research scandal, which led to **retractions last week by *The Lancet* and *The New England Journal of Medicine*** (*NEJM*), and the withdrawal of an online preprint, after the trove of patient data they all relied on

# 3. And bad data can harm



# 4.VALIDITY

## *TKA/THA in CPRD vs linked HES*

**Total Hip Replacement**

| | | HES: Positive | HES: Negative | HES: Total |
|---|---|---|---|---|
| CPRD | Positive | 7,383 | 2,458 | 9,841 |
| CPRD | Negative | 1,398 | 13,048 | 14,446 |
| CPRD | Total | 8,781 | 15,506 | 24,287 |

**Total Knee Replacement**

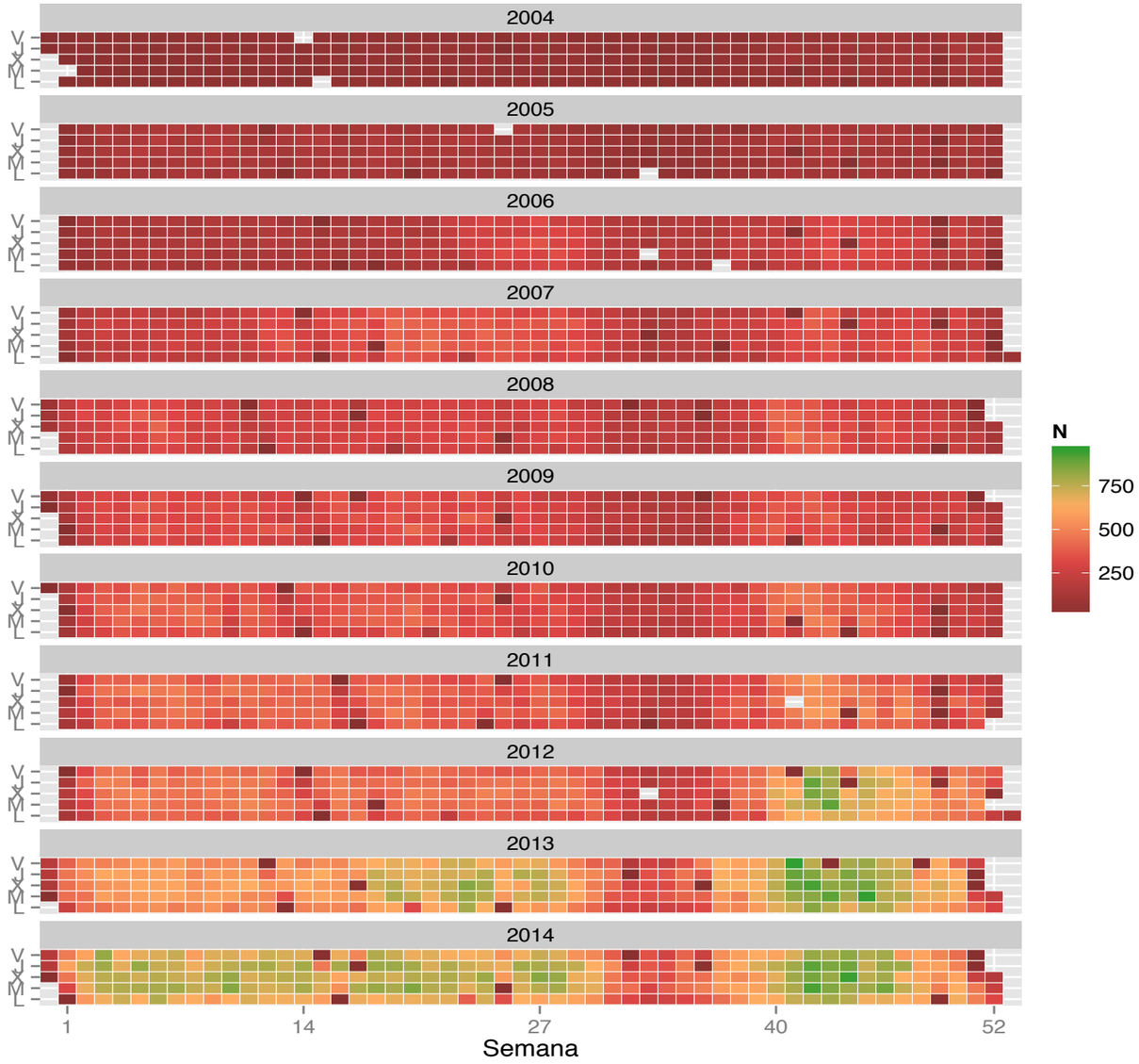
| | | HES: Positive | HES: Negative | HES: Total |
|---|---|---|---|---|
| CPRD | Positive | 6,742 | 2,013 | 8,755 |
| CPRD | Negative | 1,153 | 41,470 | 42,623 |
| CPRD | Total | 7,895 | 43,483 | 51,378 |

# 4.VALIDITY

## *Not 100% .. but not that bad!*

| | Sensitivity | Specificity |
|---|---|---|
| **Rheumatoid arthritis** | | |
| THR | 80.5 | 98.6 |
| TKR | 83.6 | 98.4 |
| **Hip Osteoarthritis** | | |
| THR | 84.1 | 84.1 |
| **Knee Osteoarthritis** | | |
| TKR | 85.4 | 95.4 |

# 5.COMPLETENESS
## *(i.e. missing data)*




**Mini-mental test**:

- Routinely collected by GPs
- Primary care EMR Spain
- Screening cognitive imp.

# AND 6. CONFOUNDING

Open Access Research

BMJ open

Oral bisphosphonates may not decrease hip fracture risk in elderly Spanish women: a nested case–control study

Juan Erviti,[1] *

PLOS ONE

RESEARCH ARTICLE

Use of Oral Bisphosphonates in Primary Prevention of Fractures in Postmenopausal Women: A Population-Based Cohort Study

Jordi Real[1,2*‡], Gisela Galindo[1,3‡], Leonardo Galván[4‡], María Antonia Lafarga[5‡], María Dolors Rodrigo[5‡], Marta Ortega[6‡]

*“Causality, the c word”*

≠

Cochrane Library

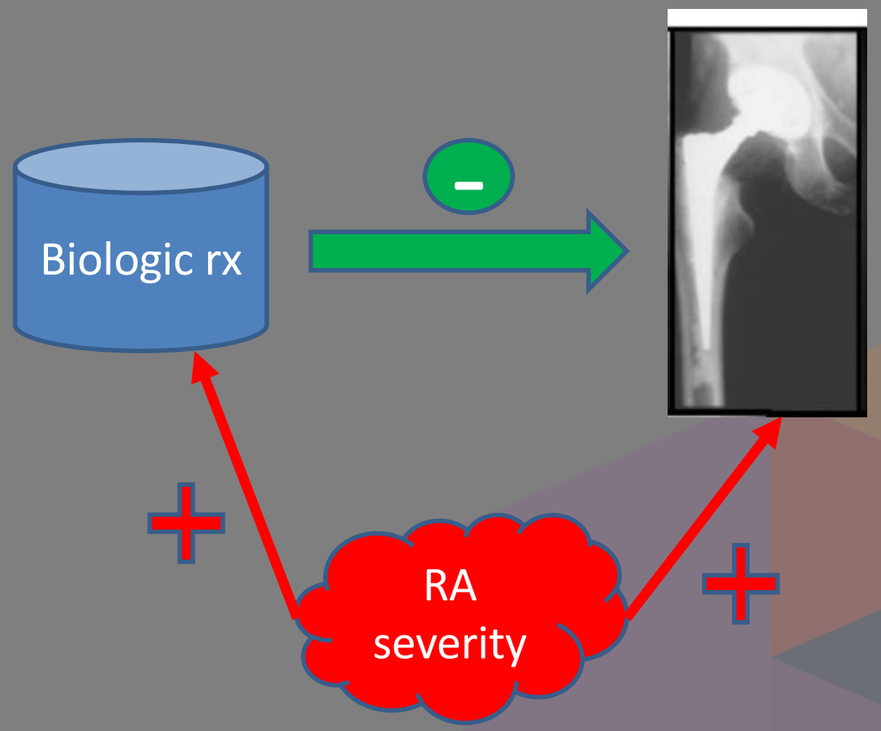
Cochrane Database of Systematic Reviews

**Alendronate for the primary and secondary prevention of osteoporotic fractures in postmenopausal women**

Cochrane Systematic Review - Intervention | Version published: 23 January 2008 see what's new

# Confounding …(by indication)

- We spare costly therapies for more severe patients …
- And + severe disease leads to worse outcomes.. (that is why we treat ☺)
- Things will get messy …



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- Chapter 2: Hacking COVID-19
- Chapter 3: And then we got the vaccines!
- Chapter 4: The future (of RWE) is here
- Epilogue: The learnings

# Robust causal inference methods for observational data analyses

- Self-controlled methods
- Cohort analyses with propensity scores, IPW, etc..
- Keep it safe: diagnostics

# SELF-CONTROLLED METHODS (e.g. SCCS)

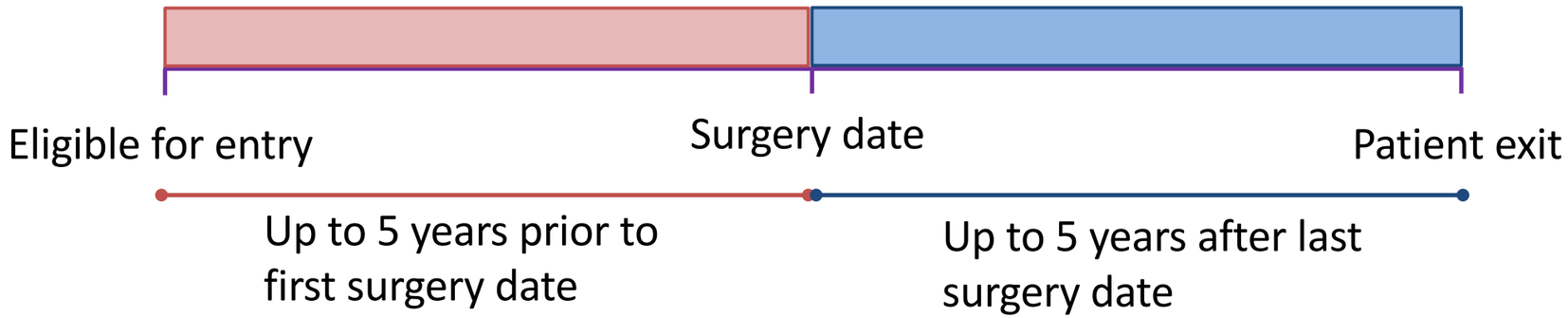
ORIGINAL ARTICLE

JBMR®

**Bariatric surgery increases the rate of major fracture: self-controlled case series study in UK Clinical Practice Research Datalink**

Danielle E. Robinson,[1] Ian Douglas,[2] Garry D. Tan,[3,4] Antonella Delmestri,[1] Andrew Judge,[1,5] Cyrus Cooper,[1,6,7,8] M. Kassim Javaid,[1,6] Victoria Y. Strauss,[1] and Daniel Prieto-Alhambra[1,9]

- Method which controls for time consistent confounding
- Compares a patient to their previous self

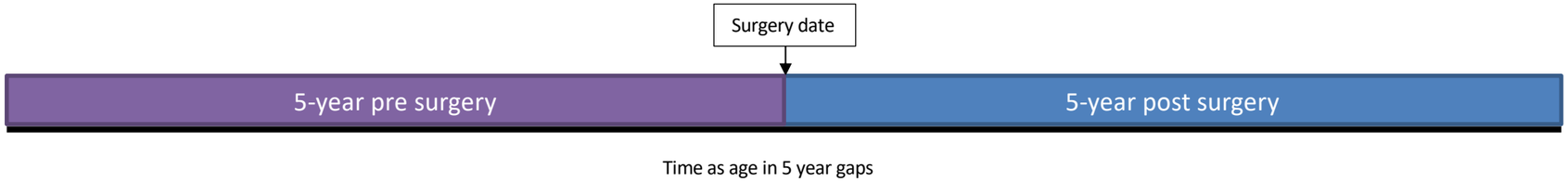



- Only includes patients who have the outcome at least once in the time window of interest
- Popular in drug and specially in vaccine safety research

DE Robinson et al. JBMR 2021

# SCCS – Bariatric surgery and fracture/s

| Outcome | Events | Duration (med, IQR) | IRR (95% CI) |
|---|---|---|---|
| "Any" (primary) | 272 | 4.6 (2.4, 5.0) | 1.17 (0.86, 1.60) |
| Major | 80 | 4.9 (2.4, 5.0) | **2.70 (1.31, 5.57)** |
| Peripheral | 135 | 4.6 (2.3, 5.0) | 0.92 (0.60, 1.42) |

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# Propensity score methods

- PS = The probability of treatment based on the patients' observed baseline characteristics
- Can be used to match, weight, regress, stratify…

**Table 1.** Baseline Characteristics Before and After Matching for CPRD and SIDIAP

| | CPRD | | | | SIDIAP | | | |
|---|---|---|---|---|---|---|---|---|
| | Before matching, after imputation | | After matching | | Before matching, after imputation | | After matching | |
| Category | Non-BP (*n* = 53,986) | BP (*n* = 2613) | Non-BP (*n* = 8931) | BP (*n* = 2447) | Non-BP (*n* = 40,800) | BP (*n* = 1408) | Non-BP (*n* = 6547) | BP (*n* = 1399) |
| Age (years), mean (SD) | 77.6 (9.8) | 80.6 (8.8) | 80.3 (9.1) | 80.4 (8.8) | 78.9 (10.0) | 78.8 (7.7) | 78.7 (10.0) | 78.8 (7.7) |
| Sex (male), *n* (%) | 23,280 (43.1) | 595 (22.8) | 2669 (29.9) | 584 (23.9) | 15,366 (37.7) | 314 (22.3) | 1609 (24.6) | 314 (22.4) |
| Socioeconomic deprivation, *n* (%) | | | | | | | | |
| 1 (least deprived) | 11,949 (22.1) | 637 (24.4) | 2127 (23.8) | 587 (24.0) | 5325 (13.1) | 211 (15.0) | 935 (14.3) | 210 (15.0) |
| 2 | 12,649 (23.4) | 620 (23.7) | 2089 (23.4) | 585 (23.9) | 5318 (13.0) | 194 (13.8) | 944 (14.4) | 193 (13.8) |
| 3 | 11,539 (21.4) | 550 (21.0) | 1881 (21.1) | 517 (21.1) | 5342 (13.1) | 170 (12.1) | 816 (12.5) | 169 (12.1) |
| 4 | 10,771 (20.0) | 480 (18.4) | 1654 (18.5) | 452 (18.5) | 4967 (12.2) | 161 (11.4) | 734 (11.2) | 161 (11.5) |
| 5 (most deprived) | 7078 (13.1) | 326 (12.5) | 1180 (13.2) | 306 (12.5) | 4789 (11.7) | 181 (12.9) | 792 (12.1) | 178 (12.7) |
| Urban (deprivation level undefined) | N/A | N/A | N/A | N/A | 4879 (12.0) | 201 (14,3) | 934 (14.3) | 200 (14.3) |
| Rural | | | | | 10,180 (25.0) | 290 (20.6) | 1392 (21.3) | 288 (20.6) |
| BMI, mean (SD)[a] | 27.6 (5.5) | 26.7 (5.2) | 26.9 (5.4) | 26.8 (5.3) | 29.1 (5.2) | 29.1 (5.1) | 29.1 (5.4) | 29.1 (5.1) |
| Smoking category, *n* (%)[b] | | | | | | | | |
| No | 28,093 (52.0) | 1423 (54.5) | 4784 (53.6) | 1329 (54.3) | 30,904 (75.7) | 1159 (82.3) | 5324 (81.3) | 1150 (82.2) |
| Ex | 19,910 (36.9) | 966 (37.0) | 3295 (36.9) | 906 (37.0) | 6515 (16.0) | 158 (11.2) | 776 (11.9) | 158 (11.3) |
| Yes | 5983 (11.1) | 224 (8.6) | 852 (9.5) | 212 (8.7) | 3381 (8.3) | 91 (6.5) | 447 (6.8) | 91 (6.5) |
| [illegible] | [illegible] | [illegible] | [illegible] | [illegible] | NA | NA | NA | NA |
| eGFR category (mL/min/1.73 m$^2$), *n* (%) | | | | | | | | |
| 0–4.9 | 67 (0.1) | <5 (<0.1) | 5 (0.1) | <5 (<0.1) | 74 (0.2) | <5 (<0.1) | 8 (0.1) | <5 (<0.1) |
| 5–9.9 | 362 (0.7) | 16 (0.6) | 60 (0.7) | 16 (0.7) | 388 (1.0) | 7 (0.5) | 51 (0.8) | 7 (0.5) |
| 10–14.9 | 616 (1.1) | 29 (1.1) | 116 (1.3) | 29 (1.2) | 785 (1.9) | 15 (1.1) | 114 (1.7) | 15 (1.1) |
| 15–19.9 | 1278 (2.4) | 81 (3.1) | 263 (2.9) | 73 (3.0) | 1568 (3.8) | 37 (2.6) | 207 (3.2) | 37 (2.6) |
| 20–24.9 | 2541 (4.7) | 164 (6.3) | 537 (6.0) | 149 (6.1) | 2814 (6.9) | 99 (7.0) | 425 (6.5) | 98 (7.0) |
| 25–29.9 | 4665 (8.6) | 327 (12.5) | 996 (11.2) | 299 (12.2) | 4983 (12.2) | 172 (12.2) | 759 (11.6) | 172 (12.3) |
| 30–34.9 | 8417 (15.6) | 542 (20.7) | 1709 (19.1) | 498 (20.4) | 7741 (19.0) | 272 (19.3) | 1126 (17.2) | 269 (19.2) |
| 35–39.9 | 14,415 (26.7) | 704 (26.9) | 2378 (26.6) | 657 (26.8) | 10,830 (26.5) | 399 (28.3) | 1807 (27.6) | 397 (28.4) |
| 40–44.9 | 21,625 (40.1) | 749 (28.7) | 2867 (32.1) | 725 (29.6) | 11,617 (28.5) | 406 (28.8) | 2050 (31.3) | 403 (28.8) |

ORIGINAL ARTICLE

JBMR®

**Safety of Oral Bisphosphonates in Moderate-to-Severe Chronic Kidney Disease: A Binational Cohort Analysis**

Danielle E Robinson,[1†] M Sanni Ali,[1,2,3†] Natalia Pallares,[4] Cristian Tebé,[4,5] Leena Elhussein,[1] Bo Abrahamsen,[6,7,8] Nigel K Arden,[9] Yoav Ben-Shlomo,[10] Fergus J Caskey,[10,11] Cyrus Cooper,[6,12] Daniel Dedman,[13] Antonella Delmestri,[1] Andrew Judge,[1,12,14] María José Pérez-Sáez,[15] Julio Pascual,[15] Xavier Nogues,[16,17] Adolfo Diez-Perez,[16] Victoria Y Strauss,[1] M Kassim Javaid,[6‡] and Daniel Prieto-Alhambra[1,18‡]

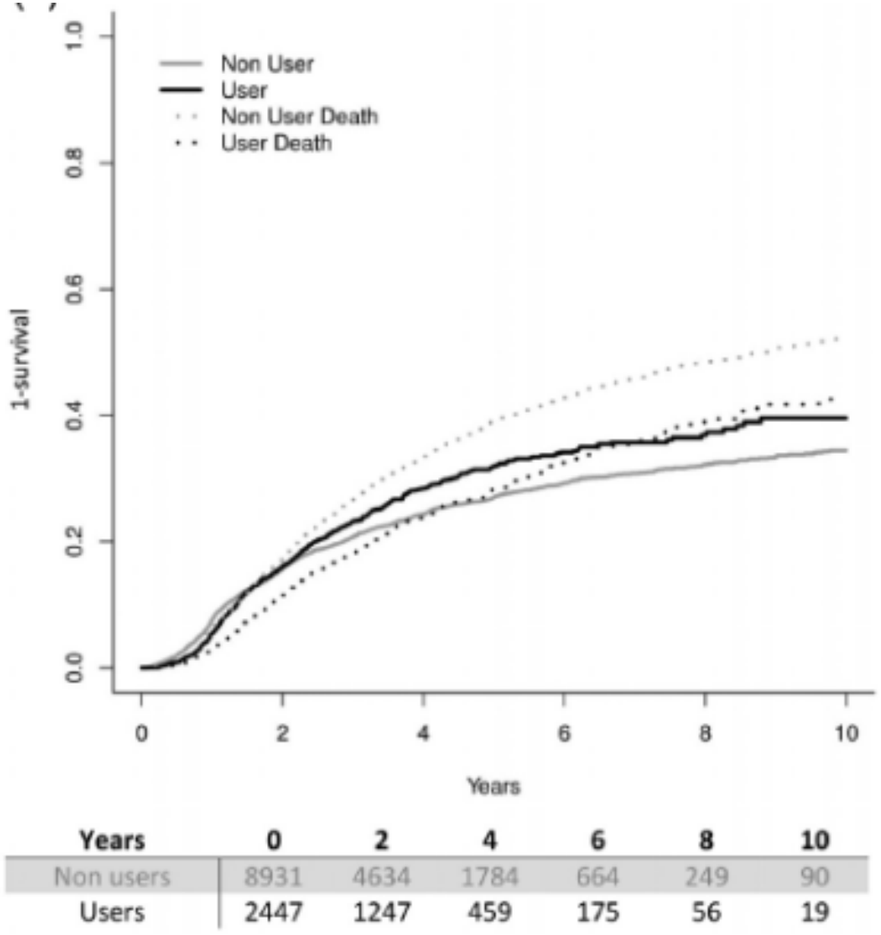
DE Robinson et al. JBMR 2021 (2)

# PS methods (2): clinical example

**Table 2.** Numbers of Events, Incidence Rates, and Hazard Ratios per 1000 person-years for All Analyses

| | | CPRD | | SIDIAP | | |
|---|---|---|---|---|---|---|
| | | BP | Non-BP | BP | Non-BP | Combined |
| Chronic kidney disease progression | Unmatched no. events | 614 | 15,411 | 471 | 13,462 | |
| | Unmatched incidence rates | 90.8 (83.9, 98.3) | 73.3 (72.1, 74.4) | 119.0 (108.5,130.2) | 104.7 (102.9,106.5) | |
| | Unadjusted HR | **1.25 (1.15, 1.36)** | | **1.13 (1.03, 1.23)** | | **1.19 (1.12, 1.27)** |
| | Fully adjusted HR | **1.18 (1.08, 1.29)** | | **1.19 (1.08, 1.31)** | | **1.18 (1.11, 1.26)** |
| | PS-matched no. events | 576 | 1996 | 467 | 2015 | |
| | PS-matched incidence rates | 89.1 (82.1, 96.7) | 85.6 (82.0, 89.5) | 118.4 (107.9,129.6) | 100.0 (95.7,104.5) | |
| | PS-matched sub-HR | **1.14 (1.04, 1.26)** | | **1.15 (1.04, 1.27)** | | **1.14 (1.07, 1.23)** |
| Acute kidney injury | Unmatched no. events | 83 | 2,739 | 101 | 3,203 | |
| | Unmatched incidence rates | 11.7 (9.5, 14.6) | 11.2 (10.8, 11.6) | 19.8 (16.1, 24.0) | 19.6 (18.9, 20.3) | |
| | Unadjusted HR | 1.11 (0.89, 1.38) | | 1.01 (0.83, 1.23) | | 1.05 (0.91, 1.22) |
| | Fully adjusted HR | 0.84 (0.66, 1.05) | | 1.07 (0.88, 1.31) | | 0.97 (0.83, 1.12) |
| | PS-matched no. events | 80 | 402 | 99 | 498 | |
| | PS-matched incidence rates | 15.2 (13.8, 16.8) | 12.0 (9.7, 14.9) | 19.5 (15.9, 23.8) | 19.6 (17.9, 21.4) | |
| | PS-matched sub-HR | 0.86 (0.67, 1.09) | | 0.97 (0.78, 1.21) | | 0.92 (0.78, 1.08) |
| Gastrointestinal event | Unmatched no. events | 38 | 1294 | 10 | 338 | |
| | Unmatched incidence rates | 5.3 (3.9, 7.3) | 5.3 (5.0, 5.6) | 1.9 (0.9, 3.5) | 2.0 (1.8, 2.2) | |
| | Unadjusted HR | 0.97 (0.71, 1.35) | | 0.97 (0.52, 1.82) | | 0.97 (0.73, 1.29) |
| | Fully adjusted HR | 1.00 (0.71, 1.41) | | 1.18 (0.62, 2.22) | | 1.04 (0.77, 1.40) |
| | PS-matched no. events | 37 | 160 | 10 | 49 | |
| | PS-matched incidence rates | 5.5 (4.0, 7.5) | 6.4 (5.5, 7.4) | 1.9 (0.9, 3.5) | 1.9 (1.4, 2.5) | |
| | PS-matched sub-HR | 0.96 (0.67, 1.39) | | 0.99 (0.50, 1.96) | | 0.97 (0.70, 1.33) |
| Hypocalcemia | Unmatched no. events | <5 | 155 | <5 | 14 | |
| | Unmatched incidence rates | 0.3 (0.1, 1.1) | 0.6 (0.5, 0.7) | 0.2 (0.0, 1.1) | 0.1 (0.0, 0.1) | |
| | Unadjusted HR | 0.45 (0.11, 1.82) | | NA | | NA |
| | Fully adjusted HR | 0.28 (0.07, 1.17) | | NA | | NA |
| | PS-matched no. events | <5 | 26 | <5 | 6 | |
| | PS-matched incidence rates | 0.3 (0.1, 1.2) | 1.1 (0.8, 1.6) | 0.2 (0, 1.1) | 0.2 (0.1, 0.5) | |
| | PS-matched sub-HR | 0.34 (0.08, 1.43) | | NA | | NA |

BP = bisphosphonate; CPRD = Clinical Practice Research Datalink; HR = hazard ratio; PS = propensity score; SIDIAP = Information System for the Development of Research in Primary Care; NA = analysis not undertaken due to lack of events.



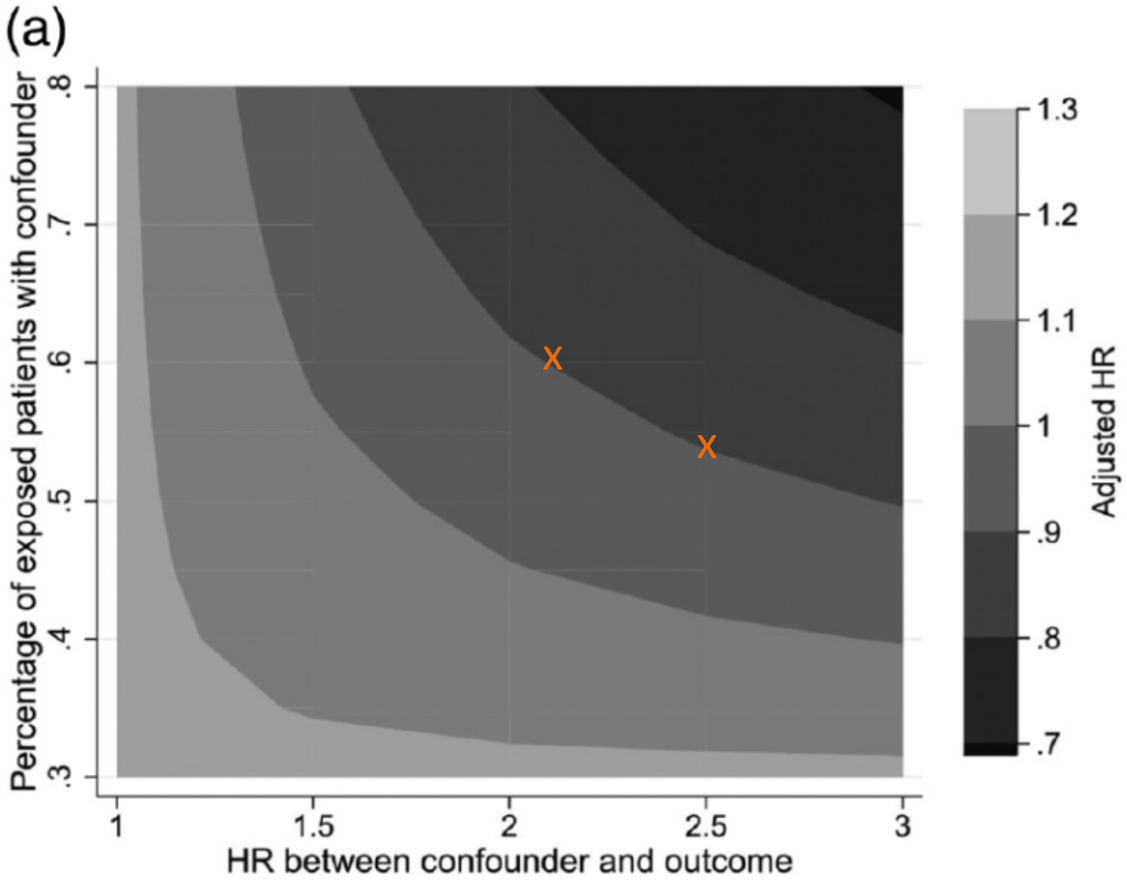

| Years | 0 | 2 | 4 | 6 | 8 | 10 |
|---|---|---|---|---|---|---|
| Non users | 8931 | 4634 | 1784 | 664 | 249 | 90 |
| Users | 2447 | 1247 | 459 | 175 | 56 | 19 |

DE Robinson et al. JBMR 2021 (2)

# Probabilistic bias analyses

- How strong and common would a confounder need to be to “attenuate” or “reverse” the observed effect?

- E.g. with a HR of approx. 1.20 …
  - A confounder w HR 2 and prevalence 60%
  - Or HR 2.5 and prevalence 55% …
  - would take our HR to 1



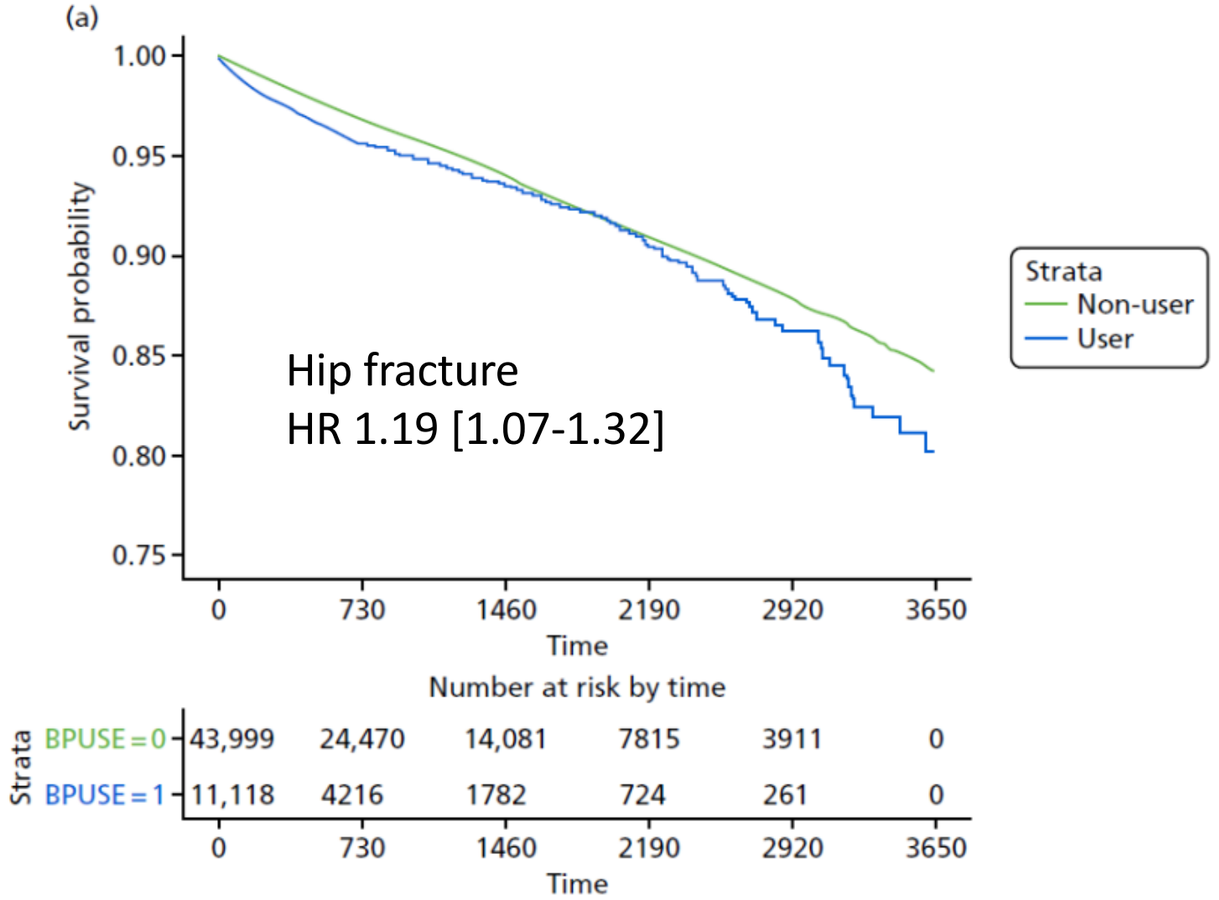

DE Robinson et al. JBMR 2021 (2)

# Negative exposure

NIHR | National Institute for Health Research
Journals Library
Check for updates
Health Technology Assessment
Volume 25 • Issue 17 • March 2021
ISSN 1366-5278

Bisphosphonates to reduce bone fractures in stage 3B+ chronic kidney disease: a propensity score-matched cohort study

- A time window when no effect should be seen
  - 10d after 1st covid vaccine
  - 3 or 6m after starting bp rx
- Here, we looked at the anti-fracture effectiveness of BP in CKD Stage 3b+
- Despite PS matching, HR suggests increased risk w BP

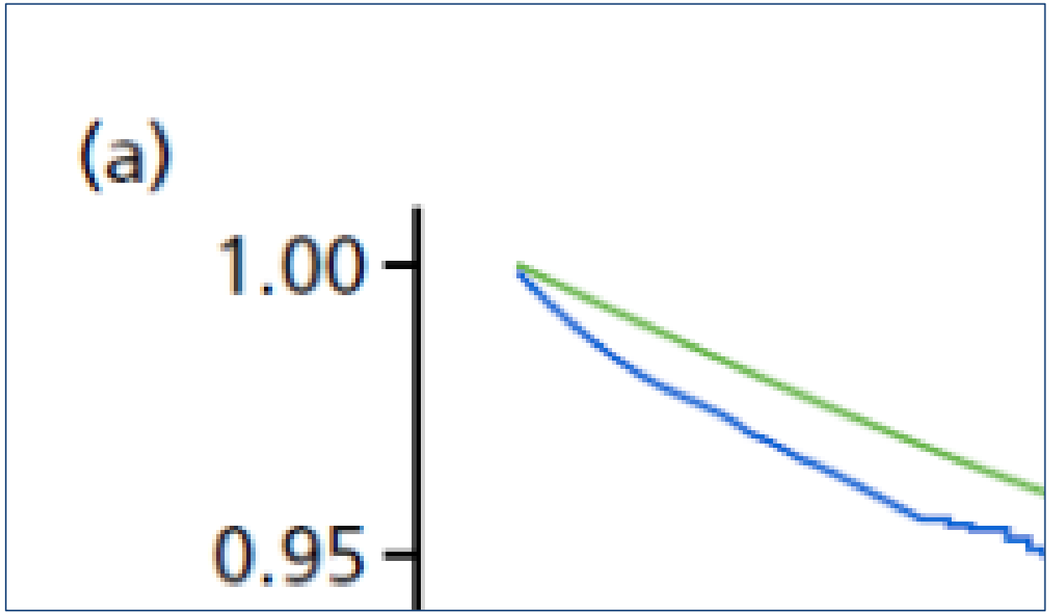



DE Robinson et al. HTA 2021

# Negative exposure time

- A time window when no effect should be seen
  - 10d after 1st covid vaccine
  - 3 or 6m after starting bp rx

- Here, we looked at the anti-fracture effectiveness of BP in CKD Stage 3b+
- Despite PS matching, HR suggests increased risk w BP



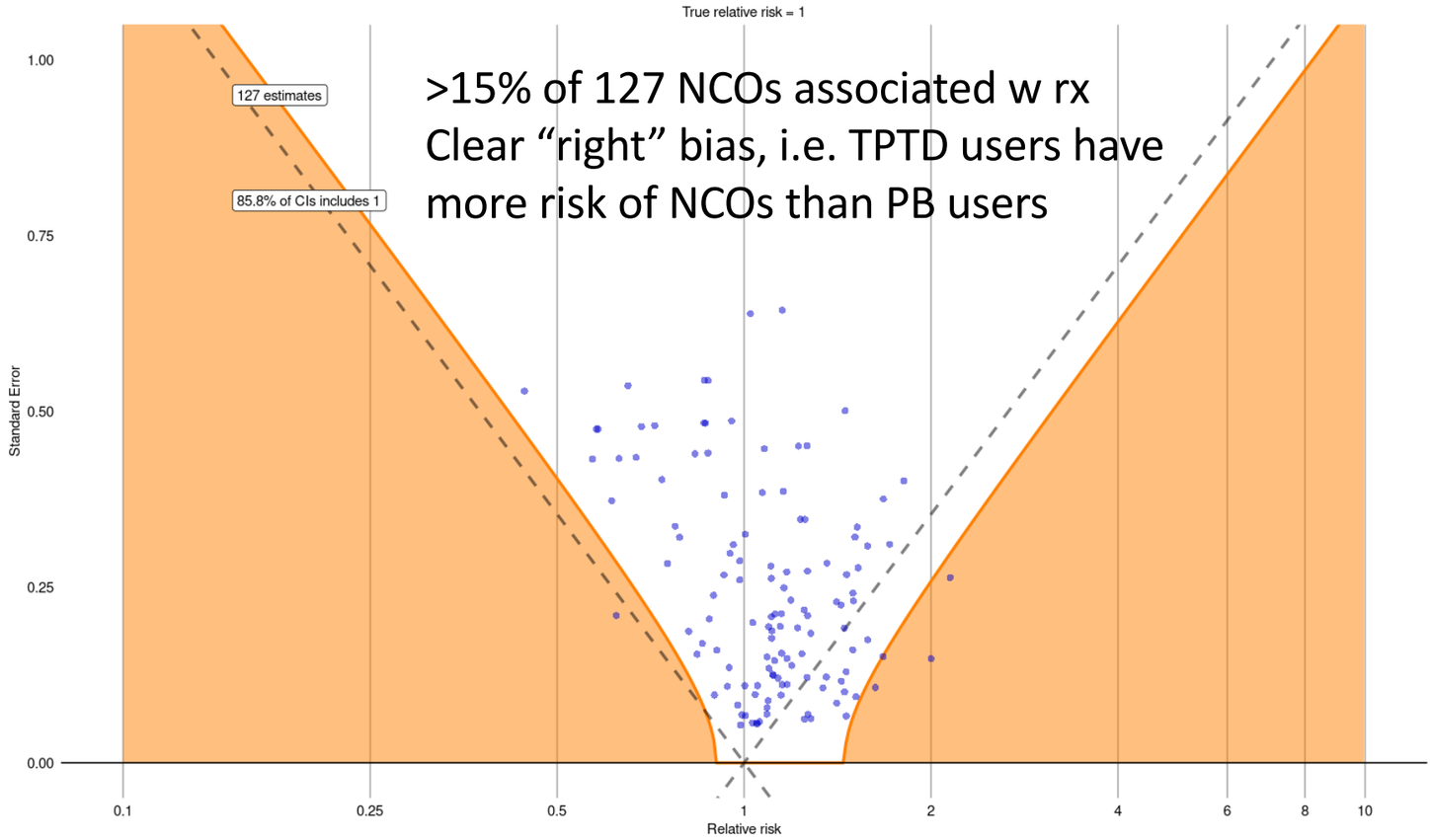

Hip fracture (overall)
HR 1.19 [1.07-1.32]

**Hip fracture (6 months)**
**HR 1.91 [1.57-2.33]**

DE Robinson et al. HTA 2021

# Negative control outcomes

- Outcomes not associated with the exposure
  - E.g. covid vaccine vs hip fx
  - E.g. bp vs thyroiditis
- Clinical example:
  - TPTD vs BP in MDCR, PS match
  - Hip FX HR 1.03 [0.85-1.24]
  - Vert FX HR 1.11 [0.92-1.32]




Rekkas A et al. Unsubmitted

# AGENDA

- Preface: Why bother?
- Mitigating confounding
- Collaboration is the new competition
- Hacking COVID-19
- And then we got the vaccines!
- The future (of RWE) is here
- Key learnings

# Collaboration…

- Who has all the data we need?
  - Registry
  - Electronic medical records
  - Genomics, …
- And all the expertise?
  - Epidemiology/biostats
  - Data sciences
  - Informatics, …

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

#OHDSICOVID19

# OHDSI COVID-19 International Study-A-Thon

Follow our COVID19 Updates

www.ohdsi.org/covid-19-updates

/OHDSI

/company/ohdsi

#JoinTheJourney

**Collaborating to design and execute observational research and generate real-world evidence to inform the global pandemic**

March 26-29, 2020

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

OHDSI

OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

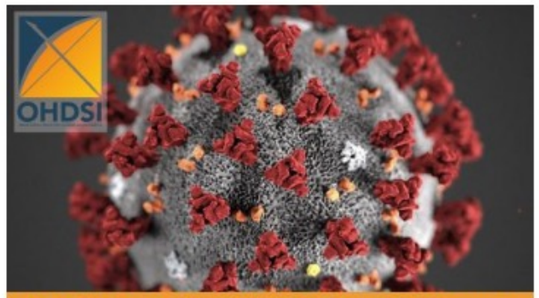
Who We Are | Latest News | Standards | Software Tools | Methods | Book of OHDSI | Research | Resources | Join the Journey

The Journey Newsletter | Past Events | Upcoming Events

Home › COVID-19 Updates Page

## COVID-19 Updates Page

The Observational Health Data Sciences and Informatics (OHDSI) international community will host a COVID-19 virtual study-a-thon this week (March 26-29) to inform healthcare decision-making in response to the current global pandemic.




OHDSI Kicks Off COVID-19 Research Agenda With 4-Day International Virtual Study-A-Thon

**Day 4**

**Early Call:** Video
**Global Call:** Video
**FINAL CALL:** Use This Link To Watch Live (regardless of whether you registered)

Please take a look at the early calls, but we're going to save the exciting study-a-thon updates for our final call tonight! This link will work for anybody, regardless of whether you registered for the study-a-thon. We are so excited to share our studies and early results with the world. Please share this link with people in your networks, so they can see the power of global collaboration in the OHDSI community.

**Day 3 Updates**

EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

# What have we done?

# In only **88** hours, we did:

- Convene **351** participants from **30** countries
- Hold **12** Global Huddles, **>100** collaborator calls, **>13,000** chat messages
- Engage **15** concurrent channels
- Review **>10,000** publications
- Draft **9** study protocols
- Release **13** study packages
- Design **355** cohort definitions
- Assemble a distributed data network with **37** partners signed on to execute studies

https://www.ohdsi.org/covid-19-updates/

# 4 things that we did in 4 days that nobody had ever done before

1. First large-scale intl phenotyping of COVID
2. First externally validated prediction model
3. Largest study ever on the safety of HCQ…
4. And a MASSIVE NETWORK for research

# EHDEN-OHDSI COVID-19 RWE Collaboration

OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

| EUROPE (9) | | |
|---|---|---|
| CPRD (EHR) | 3,864 | NR |
| IQVIA DA Germany (EHR) | 11,500 | NR |
| HM Hospitales (Hospital Billing) | NR | 2,544 |
| Hospital del Mar (EHR) | NR | 2,686 |
| Integrated Primary Care Information (EHR) | 3,306 | 60 |
| IQVIA LPD France (EHR) | 23,592 | NR |
| IQVIA LPD Italy (EHR) | 4,816 | NR |
| Information System for Research in Primary Care (SIDIAP) (EHR) | 124,305 | 18,369 |
| SIDIAP-H (EHR Hospital linkage) | 43,441 | 7,197 |

- > 4.5 m tested+
- > 1.2 m hospitalized
- 9 EU countries
- 13 US, 3 Asian nodes

| USA (13) | | |
|---|---|---|
| Columbia University Irving Medical Center (EHR) | 10,437 | 3,439 |
| Department of Veterans Affairs (EHR) | 57,937 | 10,951 |
| HealthVerity (Claims with diagnostic testing) | 587,683 | 22,887 |
| IQVIA Open Claims (Claims) | 2,875,812 | 533,997 |
| IQVIA Hospital Charge Data (Hospital Billing) | 153,477 | 57,062 |
| Optum EHR (EHR) | 217,772 | 36,717 |
| Optum SES (EHR with socio-economic data) | 7,863 | 4,336 |
| Oregon Health & Sciences University (EHR) | 11,187 | 627 |
| Premier (Hospital Billing) | 417,650 | 156,187 |
| Stanford University (EHR) | 4,788 | 744 |
| Tufts Medical Center (EHR) | 1,250 | 326 |
| University of Colorado Anschutz Medical Campus-Health Data Compass(EHR) | 9,481 | 1,874 |
| University of Washington School of Medicine (EHR) | 3,245 | 733 |

| ASIA-PACIFIC (3) | | |
|---|---|---|
| Health Insurance Review & Assessment Service (Claims) | NR | 7,599 |
| Daegu Catholic University Medical Center (EHR) | 559 | 46 |
| Nanfang Hospital (EHR) | 403 | 304 |

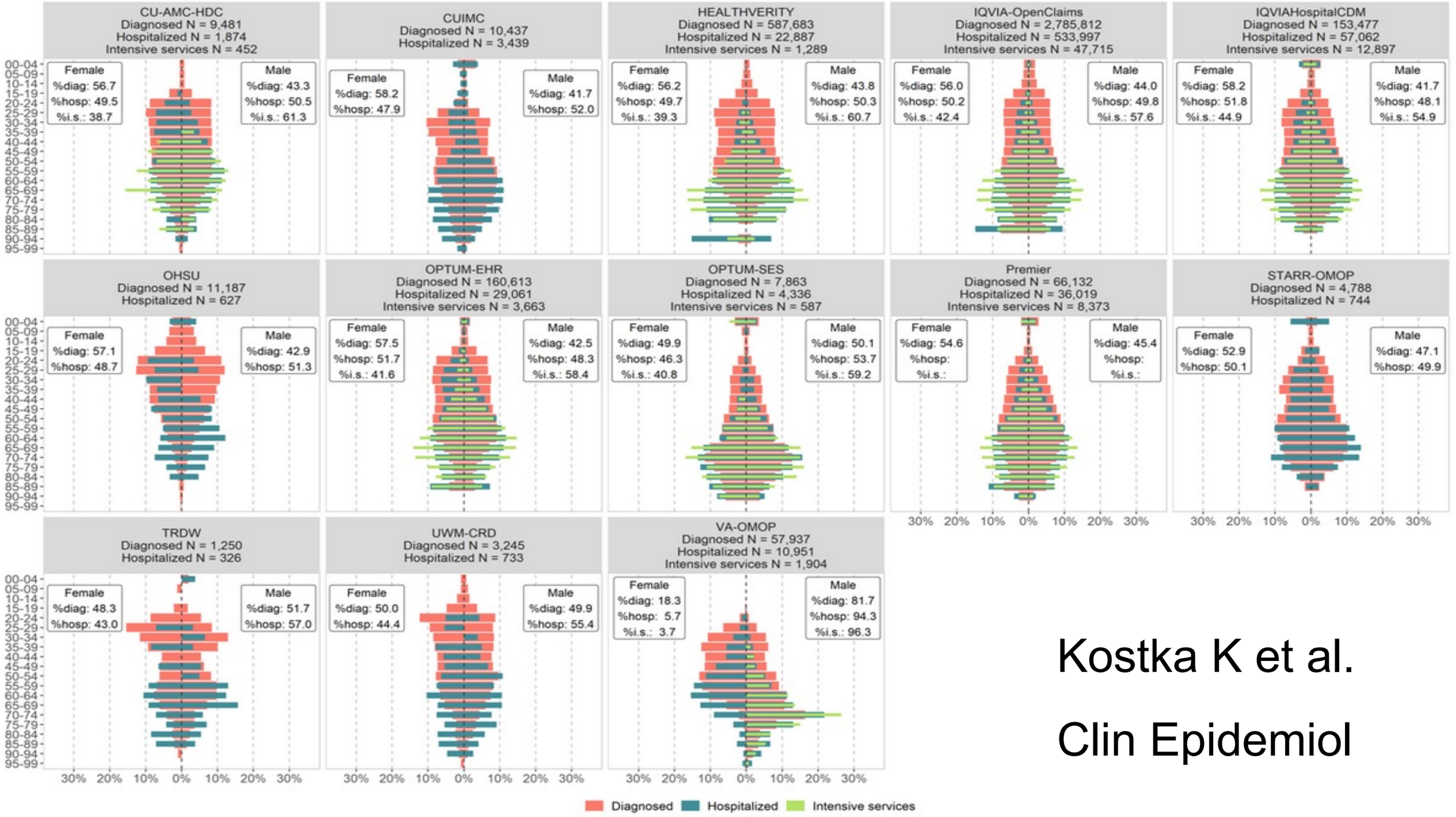
KEY

Persons diagnosed with COVID-19 or lab confirmed tested positive (no prior observation required)

Persons hospitalized with diagnosed with COVID-19 or lab confirmed tested positive (no prior observation required)

NR = Not Reported

Kostka K et al. Clin Epidemiol ‘22



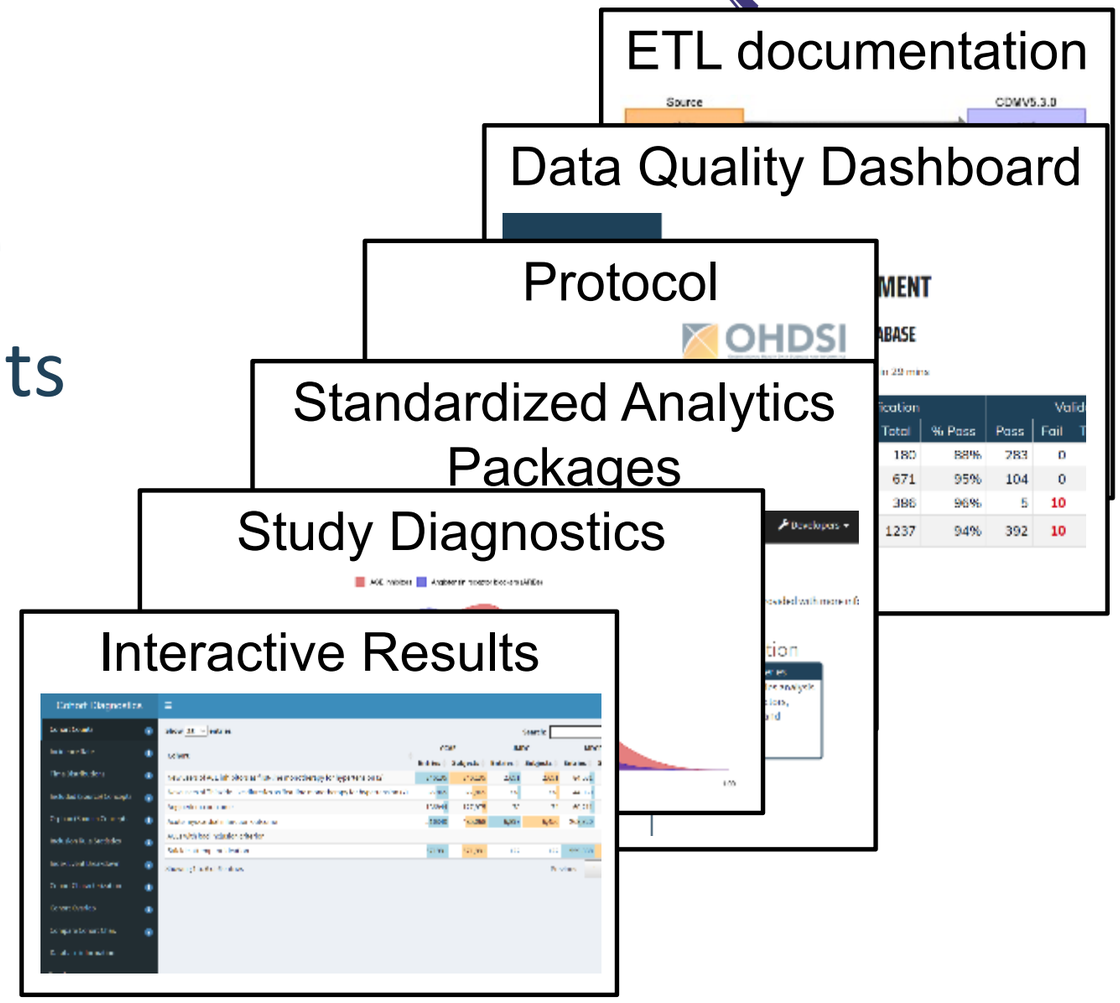

Kostka K et al.

Clin Epidemiol

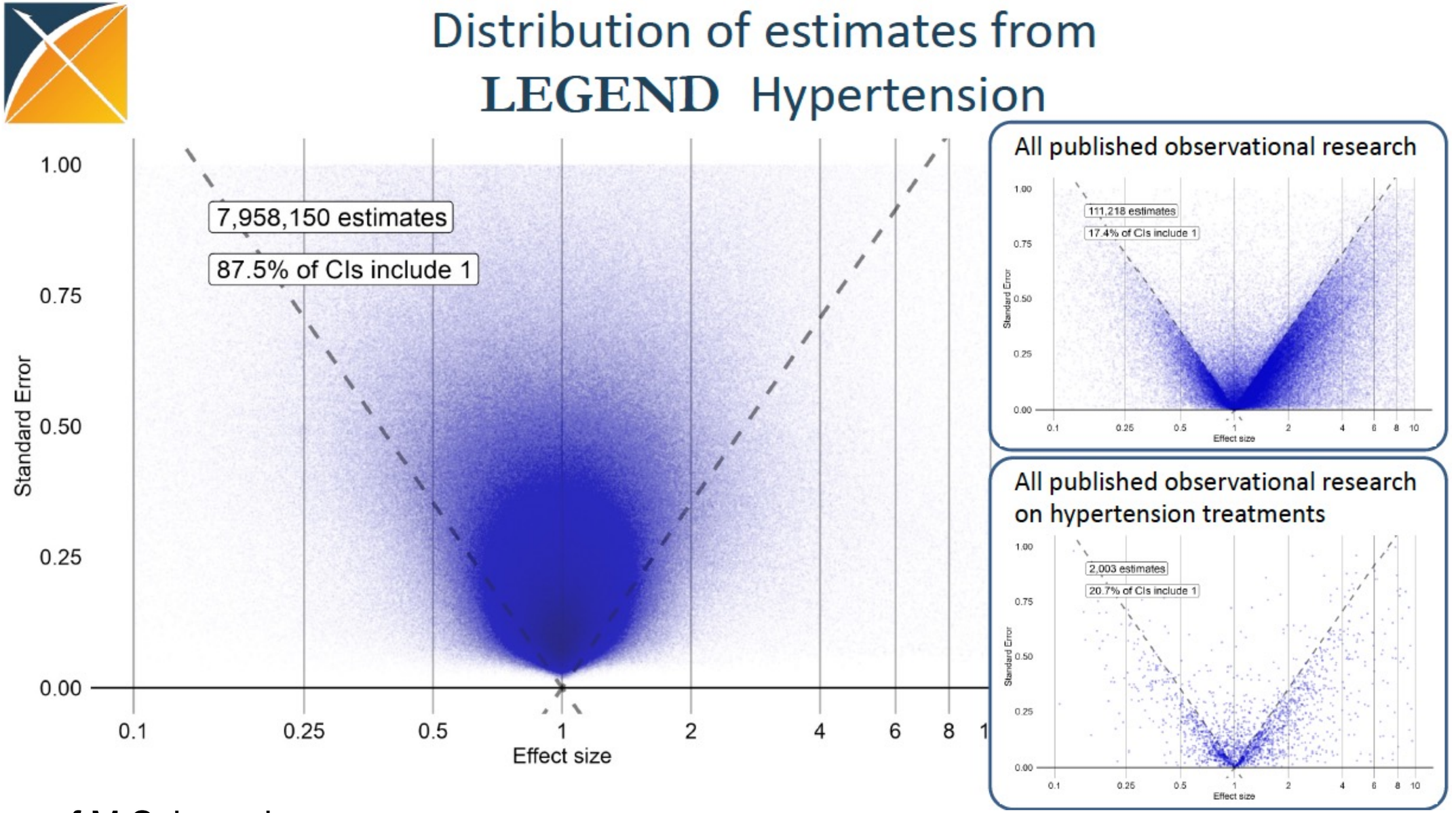
# OPEN SCIENCE principles!

- We need to declare a protocol
- We need to share ALL our code
- We need to share ALL our results

- Transparency is key to
  - **Reproducibility**
  - **Interpretability**
  - **Trustworthiness**



# Here is the result!

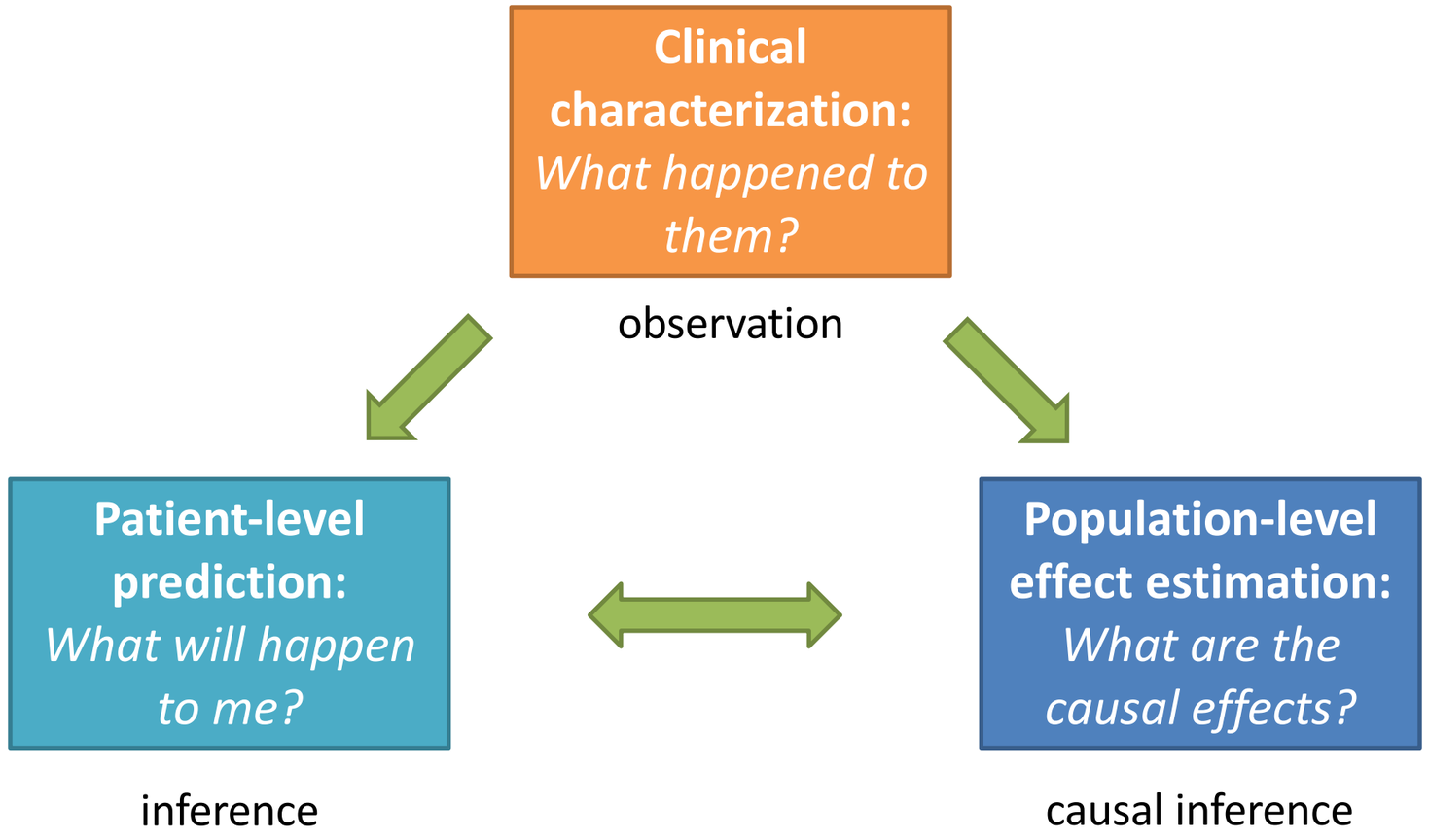



Courtesy of M Schuemie

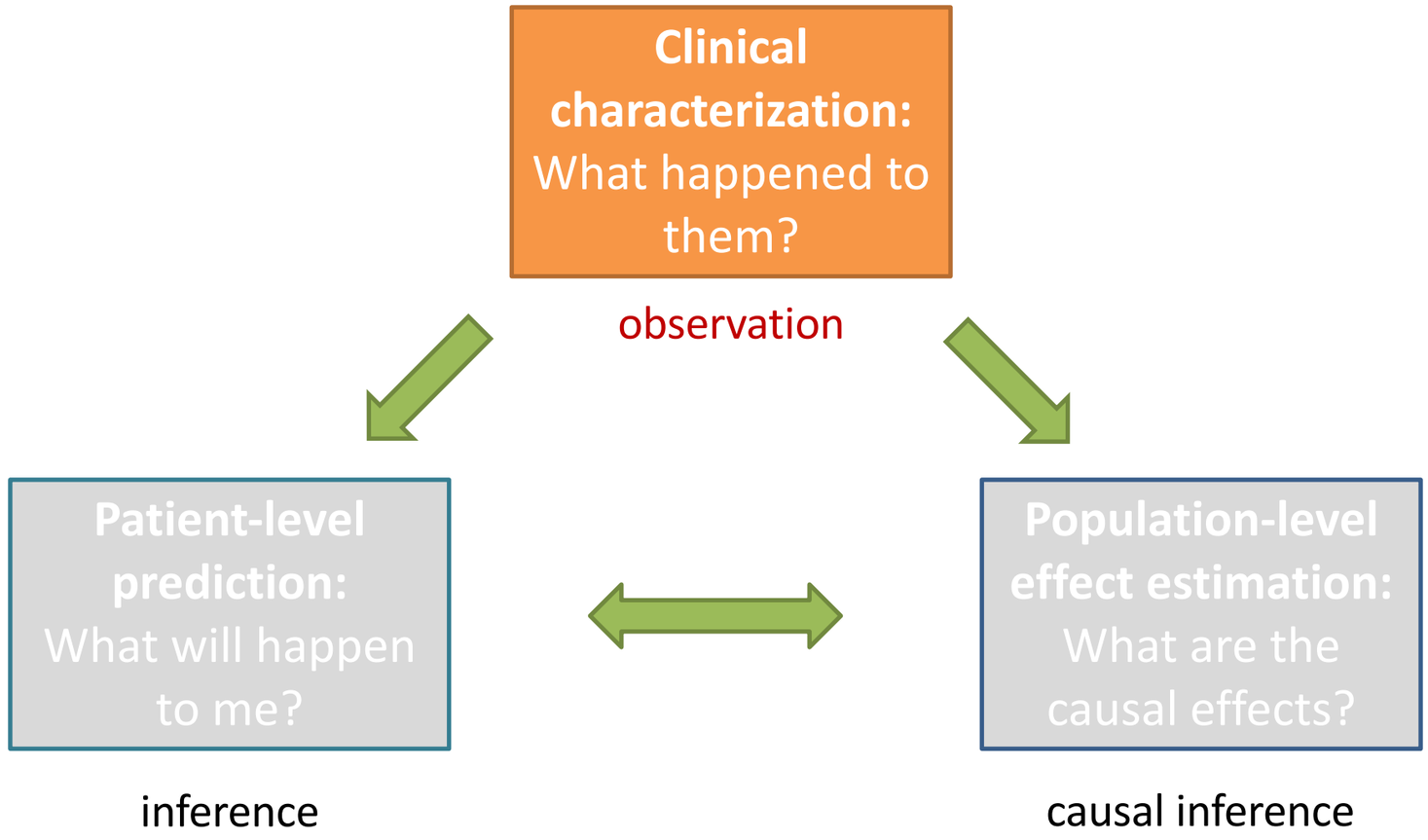
# AGENDA

- Preface: Why bother?
- Mitigating confounding
- Collaboration is the new competition
- Hacking COVID-19
- And then we got the vaccines!
- The future (of RWE) is here
- Key learnings

# How could RWE help?



# Complementary evidence to inform the patient journey



# Back in March 2020, when we were a bit too clever..

- “Take it in the chin”
- “COVID is like the flu”

# What is COVID-19? In RWE data

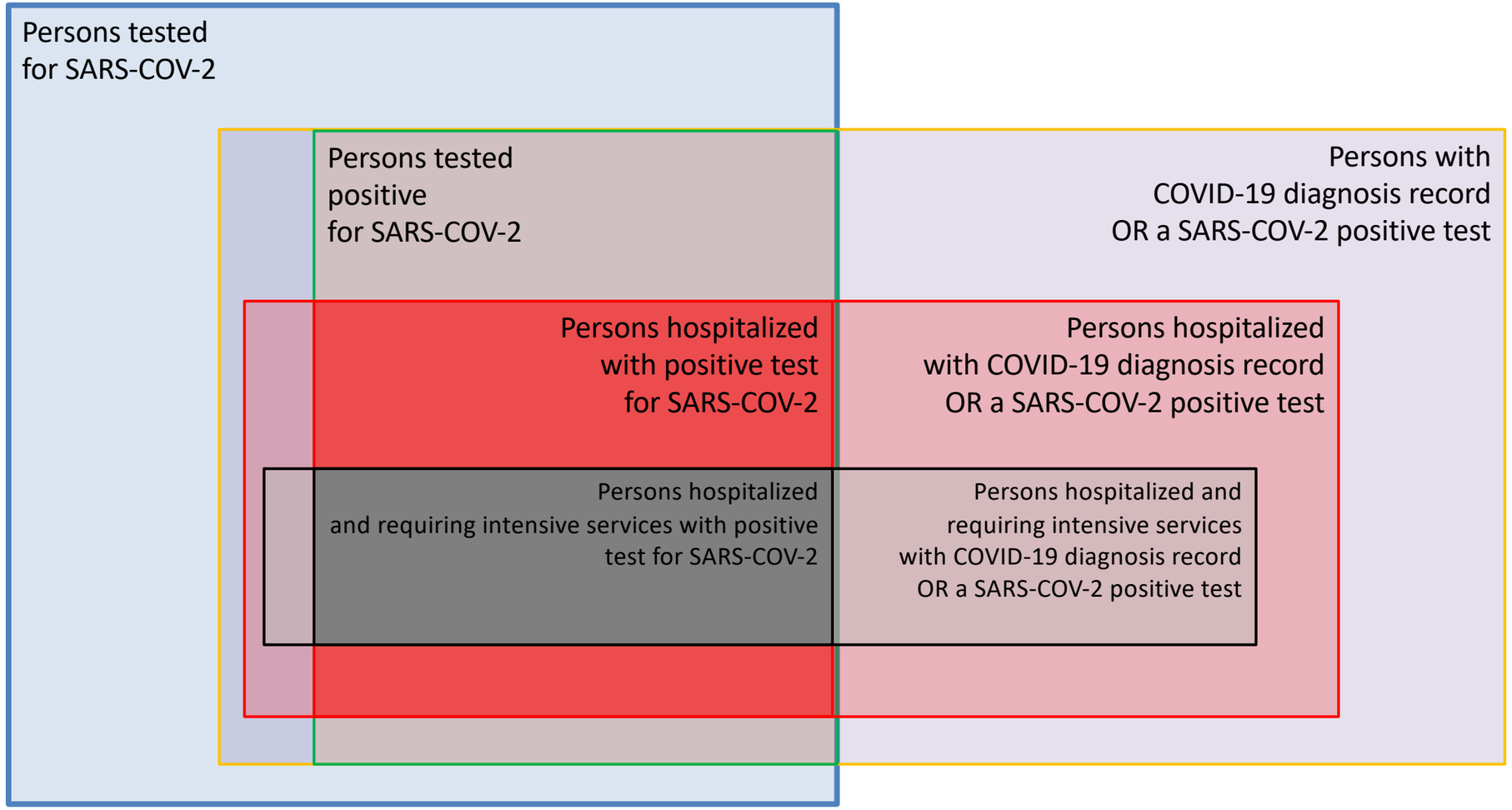
- Clinically relevant
- Actionable/interoperable for different types of data
- Sensitive
- … and specific
- FEASIBLE ?!

# What is COVID-19?
## Possible definitions

- Tested positive in RT-PCR for SARS-CoV-2
- Clinically diagnosed with COVID-19
- Hospitalized with a recorded diagnosis of COVID-19
- Admitted in ICU with a diagnosis of COVID-19
- Death with COVID-19
- … [add your preferred one here]

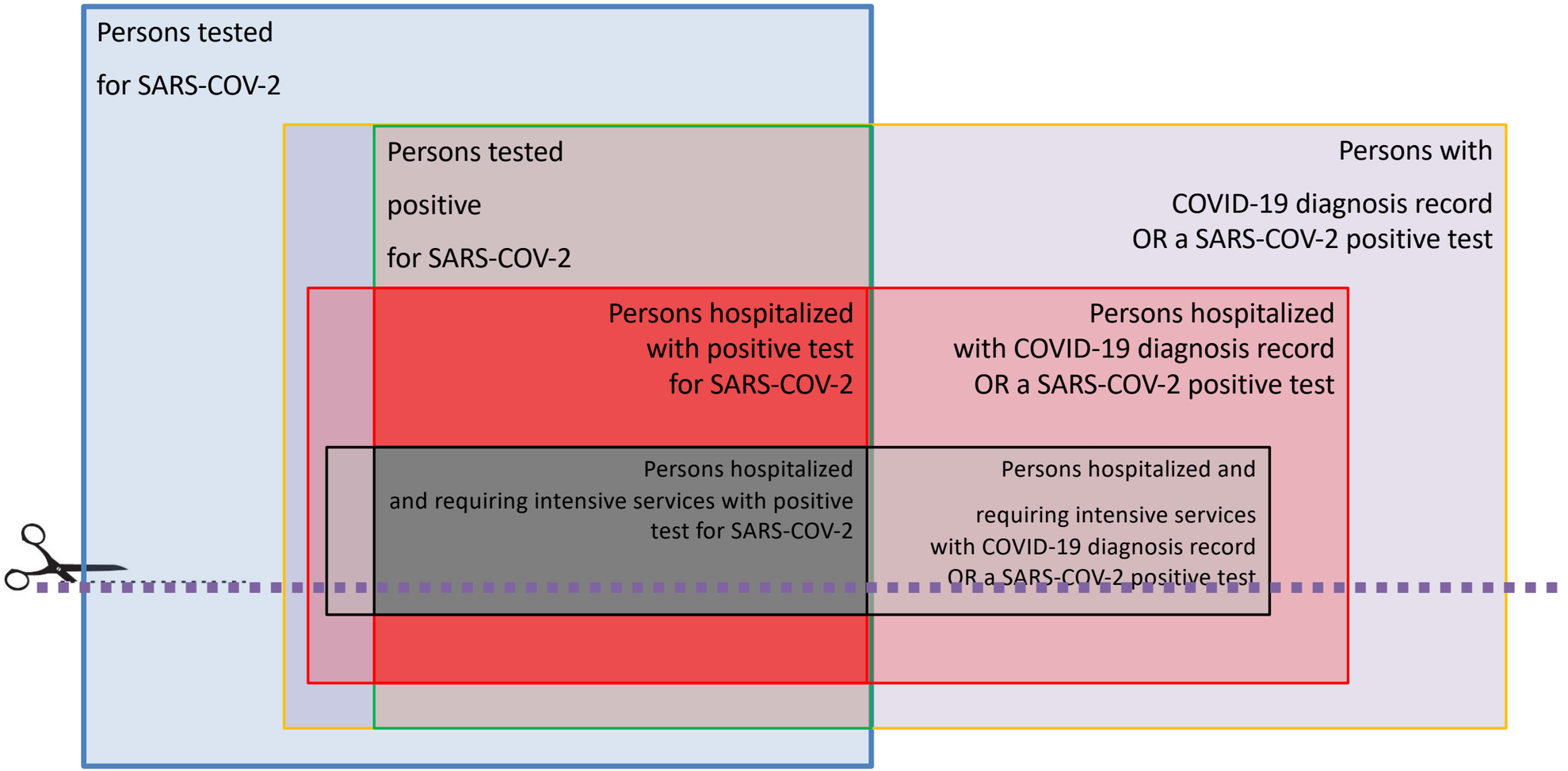
Characterization

# CHARYBDIS target cohorts



Characterization

# CHARYBDIS subgroup cohorts

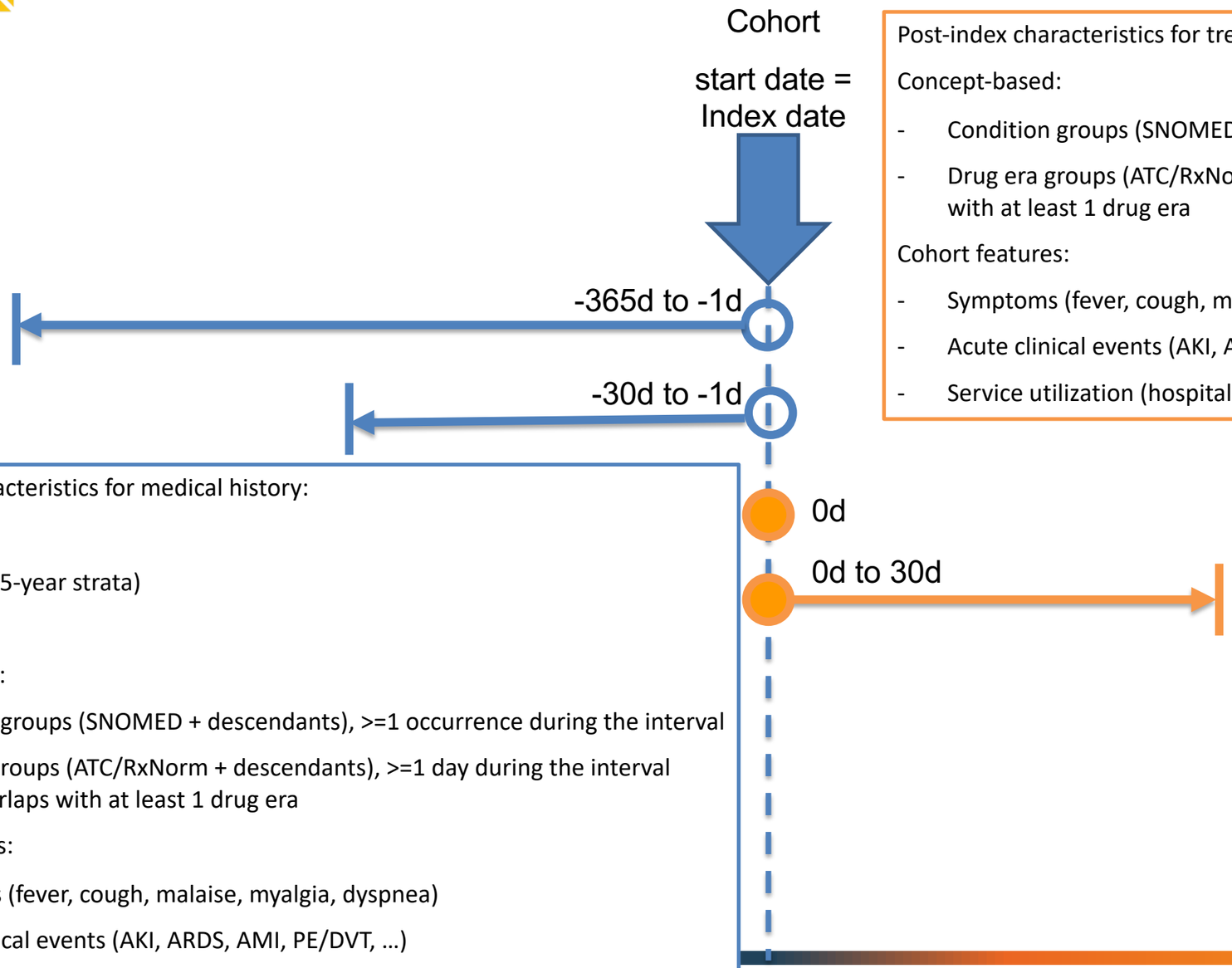



Stratification cohorts:

- Age: <18, >65
- Gender: Female/Male
- Race: Black/White
- Index month
- Hypertension
- Type 2 Diabetes
- Heart disease
- Obesity
- Asthma
- COPD
- Chronic kidney disease
- End stage renal disease
- Cancer
- Autoimmune conditions
- Dementia
- HIV
- Pregnant women

Characterization

# CHARYBDIS time windows




Post-index characteristics for treatments and outcomes:

Concept-based:

- Condition groups (SNOMED + descendants), >=1 occurrence during the interval
- Drug era groups (ATC/RxNorm + descendants), >=1 day during the interval which overlaps with at least 1 drug era

Cohort features:

- Symptoms (fever, cough, malaise, myalgia, dyspnea)
- Acute clinical events (AKI, ARDS, AMI, PE/DVT, …)
- Service utilization (hospitalization, ventilation, tracheostomy, ECMO, dialysis)

Pre-index characteristics for medical history:

Demographics:

- Age group (5-year strata)
- Sex

Concept-based:

- Condition groups (SNOMED + descendants), >=1 occurrence during the interval
- Drug era groups (ATC/RxNorm + descendants), >=1 day during the interval which overlaps with at least 1 drug era

Cohort features:

- Symptoms (fever, cough, malaise, myalgia, dyspnea)
- Acute clinical events (AKI, ARDS, AMI, PE/DVT, …)
- Service utilization (hospitalization, ventilation, tracheostomy, ECMO, dialysis)

# Unravelling COVID-19 in March'20

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18849-z OPEN

Deep phenotyping of 34,128 adult patients hospitalised with COVID-19 in an international network study

Edward Burn et al.#

RESEARCH



Use of repurposed and adjuvant drugs in hospital patients with covid-19: multinational network cohort study

Albert Prats-Uribe,[1] Anthony G Sena,[2,3] Lana Yin Hui Lai,[4] Waheed-Ul-Rahman Ahmed,[5,6] Heba Alghoul,[7] Osaid Alser,[8] Thamir M Alshammari,[9] Carlos Areia,[10] William Carter,[11] Paula Casajust,[12] Dalia Dawoud,[13,14] Asieh Golozar,[15,16] Jitendra Jonnagaddala,[17] Paras P Mehta,[18] Mengchun Gong,[19] Daniel R Morales,[20,21] Fredrik Nyberg,[22] Jose D Posada,[23] Martina Recalde,[24,25] Elena Roel,[24,25] Karishma Shah,[5] Nigam H Shah,[23] Lisa M Schilling,[11] Vignesh Subbian,[26] David Vizcaya,[27] Lin Zhang,[28,29] Ying Zhang,[19] Hong Zhu,[30] Li Liu,[30] Jaehyeong Cho,[31] Kristine E Lynch,[32] Michael E Matheny,[33,34] Seng Chan You,[35] Peter R Rijnbeek,[3] George Hripcsak,[36] Jennifer CE Lane,[5] Edward Burn,[1,24] Christian Reich,[37] Marc A Suchard,[38] Talita Duarte-Salles,[24] Kristin Kostka,[37,39] Patrick B Ryan,[2,40] Daniel Prieto-Alhambra[1]

For numbered affiliations see end of the article.

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2021;373:n1038 http://dx.doi.org/10.1136/bmj.n1038

**ABSTRACT**

**OBJECTIVE**

To investigate the use of repurposed and adjuvant drugs in patients admitted to hospital with covid-19 across three continents.

**DESIGN**

Multinational network cohort study.

**SETTING**

in Spain), azithromycin (from 15 (4.9%) in China to 1473 (57.9%) in Spain), combined lopinavir and ritonavir (from 156 (<2%) in the VA-OMOP US to 2,652 (34.9%) in South Korea and 1285 (50.5%) in Spain), and umifenovir (0% in the US, South Korea, and Spain and 238 (78.3%) in China). Use of adjunctive drugs varied greatly, with the five most used treatments being enoxaparin, fluoroquinolones, ceftriaxone, vitamin D, and corticosteroids. Hydroxychloroquine

# Open science = FULL transparency **in every step** of the research process

- Protocol and analysis source code freely available and directly downloadable: https://github.com/ohdsi-studies/Covid19HospitalizationCharacterization
- Phenotype definitions are both human-readable and computer-executable using ATLAS against any OMOP CDM: https://atlas.ohdsi.org/
- Manuscript posted on Medrxiv while awaiting peer-review: https://www.medrxiv.org/content/10.1101/2020.04.22.20074336v1
- All analysis results available for public exploration through interactive R shiny application: http://evidence.ohdsi.org/Covid19CharacterizationHospitalization/

# KEY FINDINGS

- 34,128 participants from 3 continents:
  - North America (US) 8,362
  - Asia (South Korea) 7,341
  - Europe (Spain) 18,425

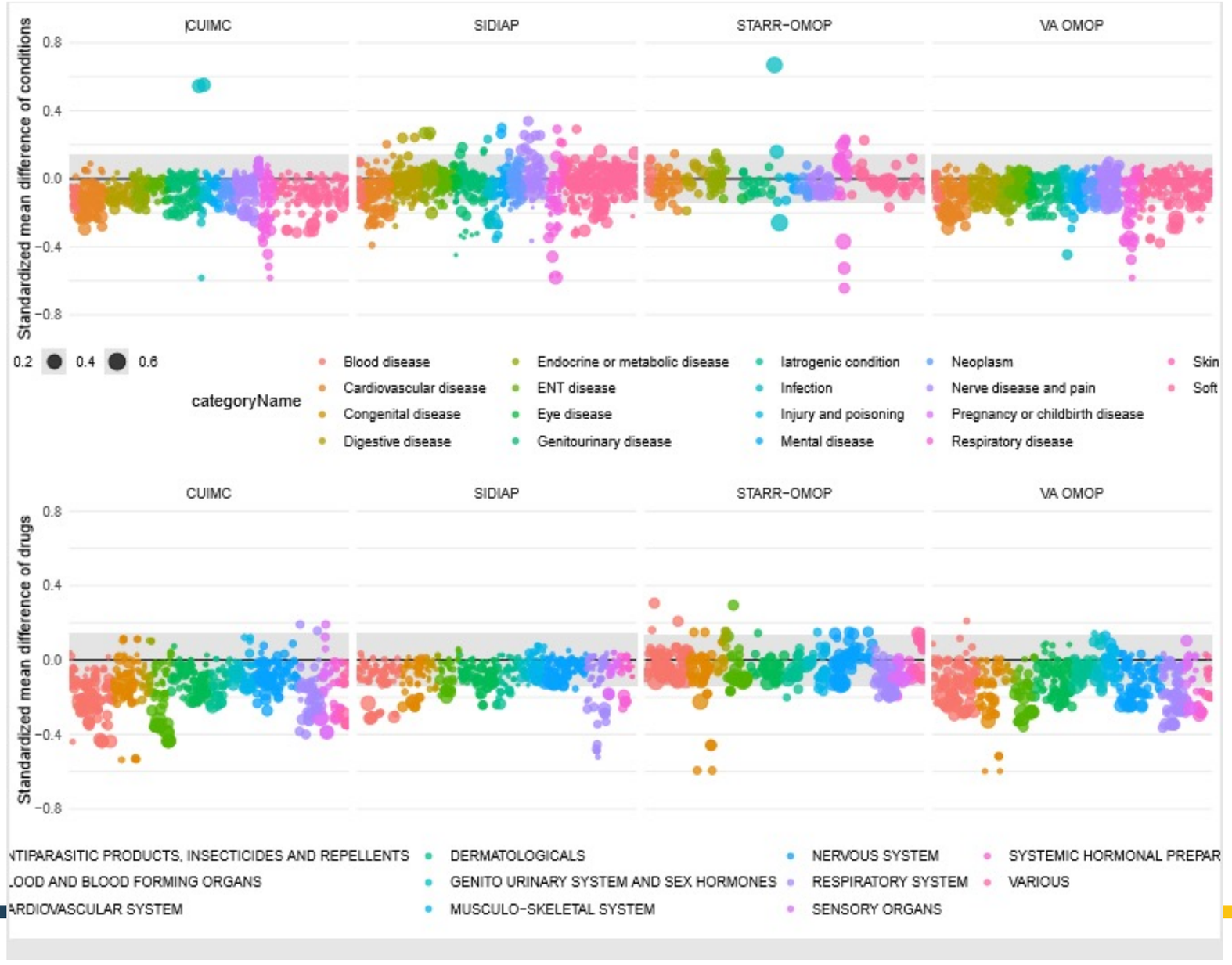
- 81,596 influenza ‘controls’ as benchmark

- 4,811 to 11,643 features extracted and summarised in an interactive web app

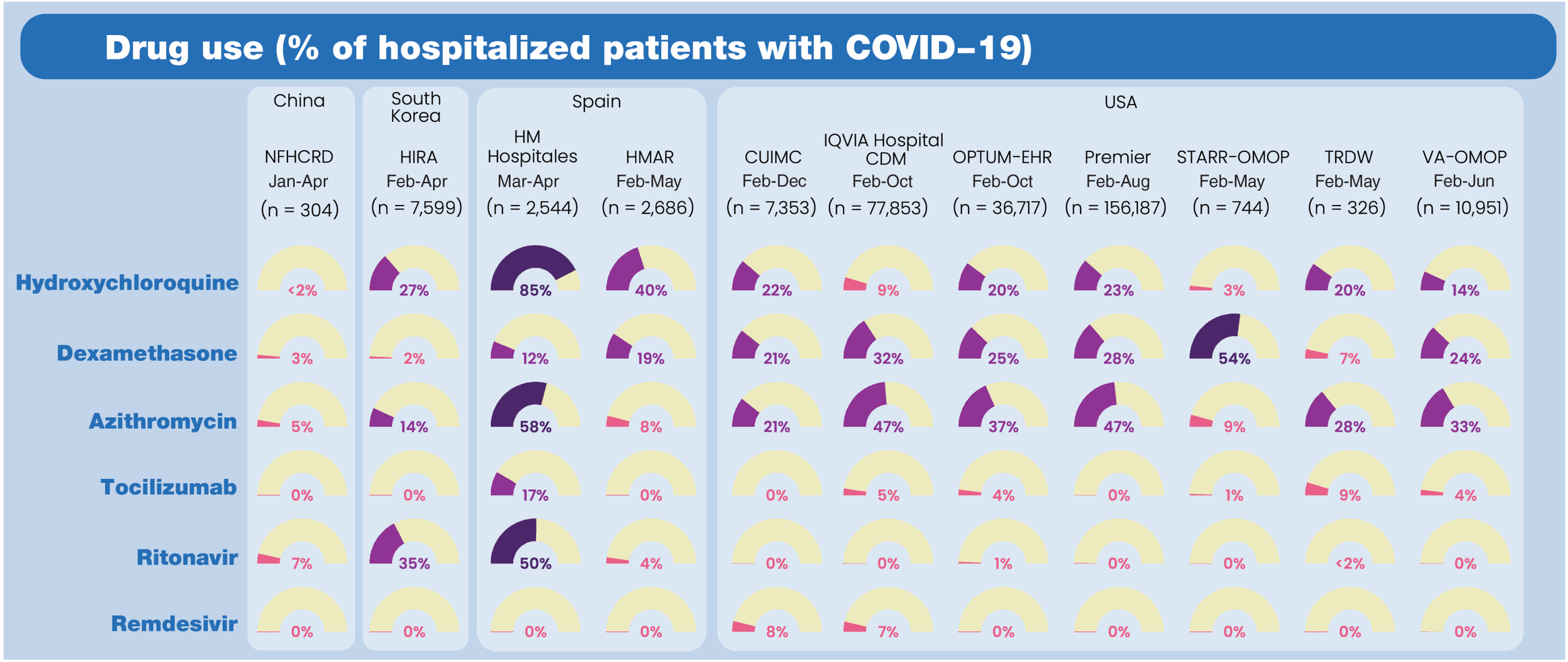
- Preprint available in MedRXiv on 22nd April 2020

# KEY FINDINGS (2)

- COVID is no flu
- Healthier
- Less drug usage
- Exceptions incl. obesity OR diabetes



# Drug Utilisation within 30d of hosp.




A Prats-Uribe et al. BMJ 2021

# The rise and fall of HCQ … -> before trials

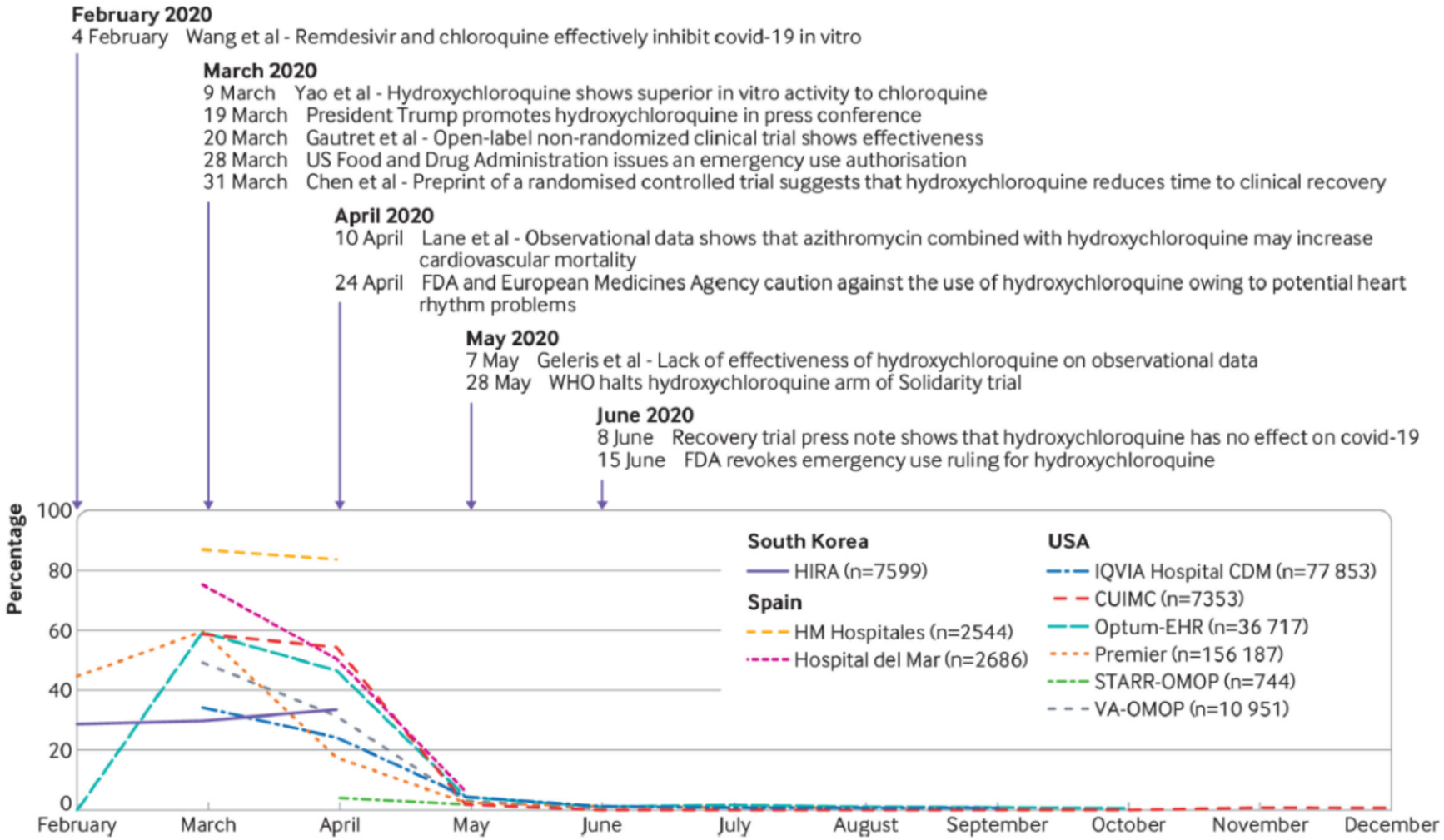
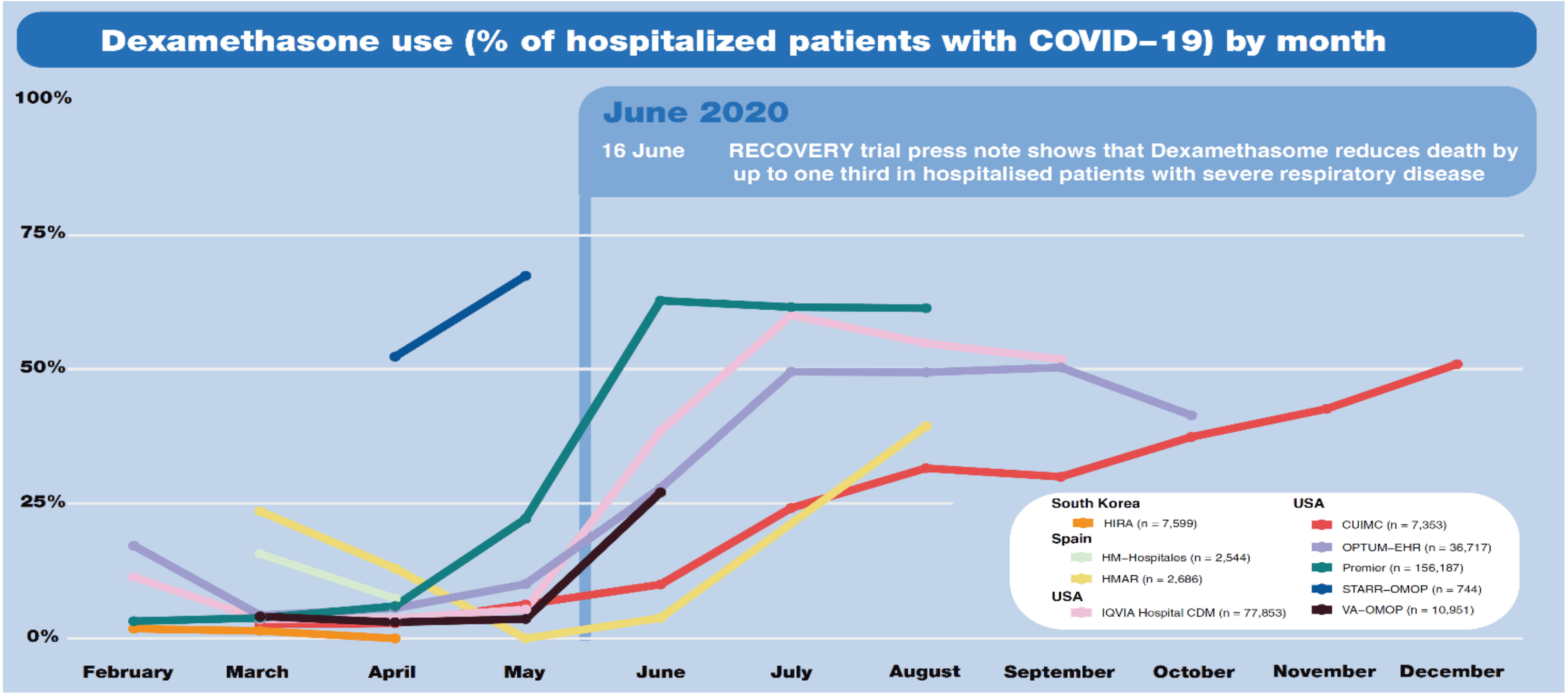



Fig 4 | Time trends in hydroxychloroquine use on days 0 to 30 after hospital admission in patients with a positive test result for or diagnosis of covid-19 by month. CUIMC=Columbia University Irving Medical Center; HIRA=Health Insurance Review and Assessment; OMOP=Observational Medical Outcomes Partnership; Optum-EHR=Optum deidentified electronic health record dataset; STARR=STAnford medicine Research data Repository; TRDW=Tufts Research Data Warehouse; VA=Veterans Affairs

A Prats-Uribe et al. BMJ 2021

# And the winner is … Dexamethasone (after trials)




A Prats-Uribe et al. BMJ 2021

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- Mitigating confounding
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# DAY ~90 AFTER THE START OF GLOBAL VACCINATION CAMPAIGNS…

## PHARMACOVIGILANCE

- So … it looks like we're seeing more reports of blood clots post-vaccine than we expect
- (based on comparisons vs other vaccines/medicines)

## EPIDEMIOLOGY

- Well, but how many did you expect?
- (based on a "comparable" unvaccinated population)

# Background rates:

# Preparing for the arrival of COVID vaxx

RESEARCH: SPECIAL PAPER

OPEN ACCESS

Check for updates

FAST TRACK

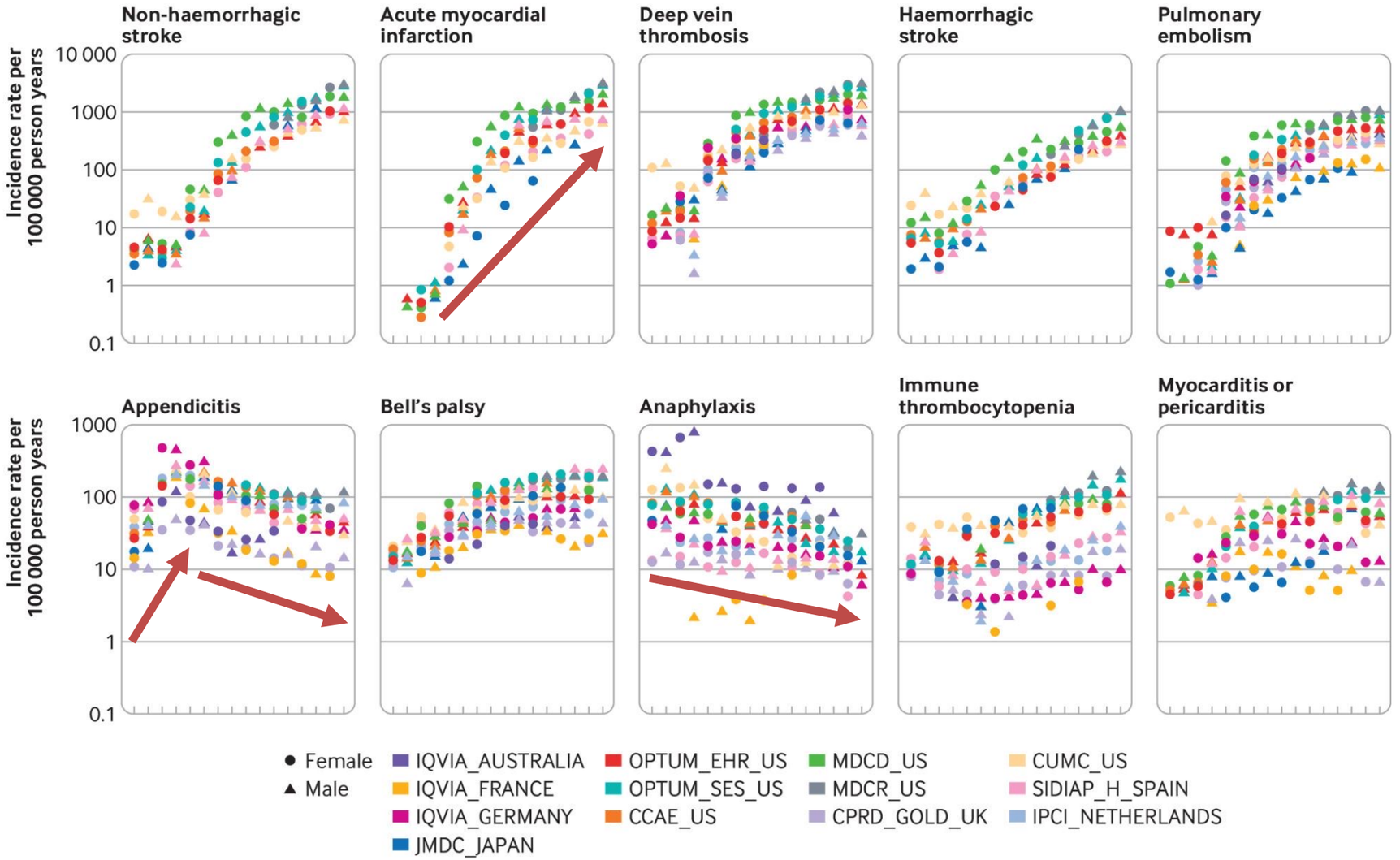
## Characterising the background incidence rates of adverse events of special interest for covid-19 vaccines in eight countries: multinational network cohort study

Xintong Li,[1] Anna Ostropolets,[2] Rupa Makadia,[3] Azza Shoaibi,[3] Gowtham Rao,[3] Anthony G Sena,[3,6] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Katia Verhamme,[6,7] Peter R Rijnbeek,[6] Talita Duarte-Salles,[5] Marc A Suchard,[8,9] Patrick B Ryan,[2,3] George Hripcsak,[2] Daniel Prieto-Alhambra[1,6]

thebmj

**Xintong Li et al. BMJ 2021**

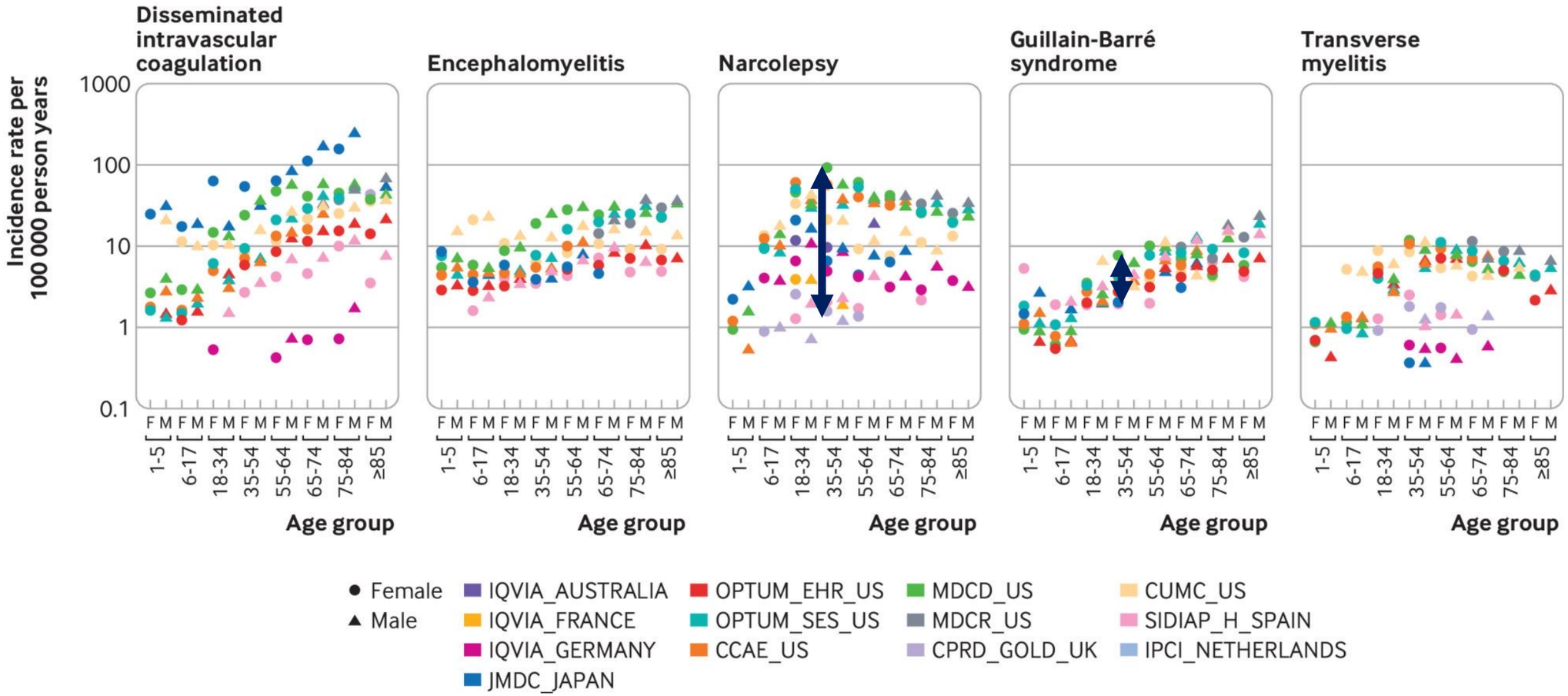
# Age and sex stratified incidence rates for 15 AESI






Xintong Li et al. BMJ 2021;373:bmj.n1435

# Age and sex stratified incidence rates for 15 AESI






Xintong Li et al. BMJ 2021;373:bmj.n1435

# Age-sex IRs 2017-2019

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**CIOMS Frequency classification**

| |
|---|
| Very rare: <1/10,000 |
| Rare: >1/10,000 AND <1/1,000 |
| Uncommon: >1/1,000 AND <1/100 |
| Common: >1/100 AND <1/10 |
| Very common: >1/10 |

**Incidence rate (per 100,000 person-years) by age group**

| Outcome | Sex | 1 - 5 | 6 - 17 | 18 - 34 | 35 - 54 | 55 - 64 | 65 - 74 | 75 - 84 | 85+ |
|---|---|---|---|---|---|---|---|---|---|
| Non-hemorrhagic stroke | Female | 4 (2-9) | 4 (1-12) | 18 (4-86) | 83 (11-617) | 217 (25-1882) | 413 (77-2198) | 874 (197-3884) | 1523 (320-7239) |
| | Male | 6 (2-20) | 5 (2-10) | 17 (4-75) | 119 (21-664) | 370 (67-2046) | 612 (145-2578) | 1063 (242-4662) | 1495 (260-8607) |
| Acute myocardial infarction | Female | <1 (<1-1) | <1 (<1-1) | 6 (1-49) | 54 (7-430) | 171 (24-1235) | 312 (76-1280) | 617 (184-2069) | 1144 (313-4184) |
| | Male | <1 (<1-1) | 1 (1-1) | 16 (4-72) | 172 (40-740) | 467 (135-1611) | 653 (214-1994) | 934 (290-3013) | 1514 (356-6432) |
| Deep vein thrombosis | Female | 12 (3-50) | 18 (8-40) | 140 (66-298) | 306 (117-797) | 428 (150-1224) | 683 (257-1820) | 975 (360-2642) | 1206 (407-3572) |
| | Male | 14 (4-55) | 14 (6-32) | 80 (28-228) | 272 (88-836) | 499 (194-1289) | 695 (250-1931) | 831 (254-2720) | 1003 (278-3616) |
| Hemorrhagic stroke | Female | 7 (2-28) | 5 (2-16) | 13 (4-47) | 36 (7-175) | 77 (15-389) | 124 (29-527) | 249 (56-1108) | 412 (85-1986) |
| | Male | 8 (2-43) | 8 (3-24) | 19 (5-76) | 51 (10-268) | 115 (23-562) | 178 (49-650) | 312 (73-1340) | 506 (86-2961) |
| Pulmonary embolism | Female | 1 (<1-36) | 3 (1-13) | 38 (11-124) | 81 (21-309) | 125 (33-470) | 217 (77-611) | 358 (135-951) | 427 (154-1184) |
| | Male | 1 (<1-24) | 2 (<1-12) | 20 (5-80) | 80 (20-318) | 171 (59-497) | 256 (96-683) | 349 (119-1030) | 398 (124-1277) |
| Appendicitis | Female | 32 (12-84) | 154 (55-430) | 134 (69-260) | 85 (42-172) | 66 (28-156) | 53 (20-143) | 40 (13-124) | 35 (12-98) |
| | Male | 38 (17-85) | 194 (101-372) | 146 (81-266) | 88 (49-159) | 65 (32-132) | 57 (23-144) | 47 (15-152) | 45 (14-143) |
| Bells palsy | Female | 15 (9-27) | 25 (12-51) | 44 (23-84) | 61 (26-140) | 76 (31-184) | 86 (29-256) | 101 (31-330) | 92 (31-274) |
| | Male | 15 (10-24) | 21 (13-34) | 43 (29-64) | 68 (37-125) | 86 (43-172) | 94 (35-252) | 92 (29-291) | 100 (34-292) |
| Anaphylaxis | Female | 49 (16-150) | 50 (16-154) | 39 (16-95) | 34 (13-91) | 35 (14-85) | 29 (11-76) | 23 (7-73) | 12 (4-36) |
| | Male | 74 (26-209) | 56 (18-175) | 29 (14-63) | 24 (11-53) | 25 (11-53) | 24 (9-68) | 18 (7-49) | 10 (2-50) |
| Immune thrombocytopenia | Female | 12 (8-19) | 9 (4-21) | 14 (6-36) | 15 (5-43) | 18 (6-53) | 25 (8-82) | 30 (8-110) | 36 (11-118) |
| | Male | 17 (12-23) | 8 (3-19) | 8 (2-23) | 10 (3-35) | 19 (6-57) | 30 (9-105) | 41 (10-170) | 56 (15-210) |
| Myocarditis pericarditis | Female | 6 (1-25) | 7 (2-21) | 16 (8-32) | 22 (9-53) | 31 (13-72) | 35 (12-97) | 39 (11-138) | 34 (8-143) |
| | Male | 7 (1-32) | 11 (5-24) | 37 (16-88) | 37 (16-87) | 45 (20-102) | 49 (17-139) | 54 (15-193) | 41 (9-193) |
| Disseminated intravascular coagulation | Female | 2 (<1-104) | 2 (<1-48) | 4 (<1-99) | 5 (<1-75) | 10 (1-89) | 14 (2-97) | 19 (4-94) | 16 (3-82) |
| | Male | 3 (<1-137) | 2 (<1-44) | 4 (<1-31) | 5 (1-56) | 12 (1-120) | 17 (2-154) | 23 (4-152) | 24 (5-126) |
| Encephalomyelitis | Female | 5 (2-15) | 5 (2-16) | 5 (2-19) | 6 (1-44) | 9 (1-61) | 11 (2-62) | 12 (2-77) | 14 (2-100) |
| | Male | 5 (2-12) | 5 (2-14) | 5 (2-17) | 7 (1-55) | 12 (3-58) | 16 (3-73) | 18 (3-101) | 16 (1-180) |
| Narcolepsy | Female | 1 (<1-5) | 7 (3-17) | 15 (4-52) | 11 (2-55) | 9 (2-42) | 10 (2-46) | 8 (1-49) | 9 (2-42) |
| | Male | 1 (<1-5) | 6 (2-18) | 13 (4-40) | 10 (2-47) | 11 (3-44) | 10 (2-50) | 10 (2-68) | 10 (2-60) |
| Guillain-Barre syndrome | Female | 1 (<1-8) | 1 (<1-2) | 3 (1-5) | 3 (1-11) | 5 (1-18) | 6 (2-19) | 6 (3-16) | 7 (2-22) |
| | Male | 2 (<1-18) | 1 (<1-3) | 2 (1-4) | 4 (2-7) | 7 (4-14) | 8 (3-25) | 11 (3-40) | 12 (2-68) |
| Transverse myelitis | Female | 1 (<1-3) | 1 (<1-3) | 3 (1-8) | 4 (1-12) | 4 (2-13) | 4 (2-13) | 4 (1-11) | 2 (1-9) |
| | Male | 1 (<1-2) | 1 (<1-3) | 2 (1-6) | 3 (1-10) | 4 (1-10) | 4 (1-11) | 4 (1-13) | 4 (1-11) |

# CONCLUSIONS

- #SorryNotSorry - I cannot give you “one number” …
- If really necessary, we need to adjust/standardize by age & sex
- Please use the same data for obs & exp rates (next sections)

# Historical comparison/s and SCCS:

# Monitoring vaccine safety

RESEARCH

OPEN ACCESS

Check for updates

## Association between covid-19 vaccination, SARS-CoV-2 infection, and risk of immune mediated neurological events: population based cohort and self-controlled case series analysis

Xintong Li,[1] Berta Raventós,[2,3] Elena Roel,[2,3] Andrea Pistillo,[2] Eugenia Martinez-Hernandez,[4] Antonella Delmestri,[1] Carlen Reyes,[2] Victoria Strauss,[1] Daniel Prieto-Alhambra,[1,5] Edward Burn,[1,2] Talita Duarte-Salles[2]

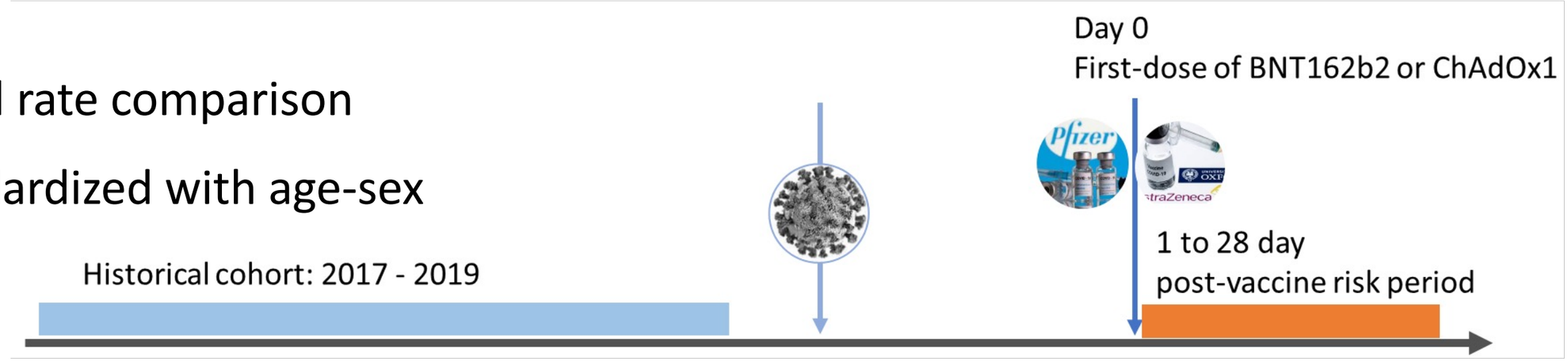
thebmj

**Xintong Li et al. BMJ 2022**

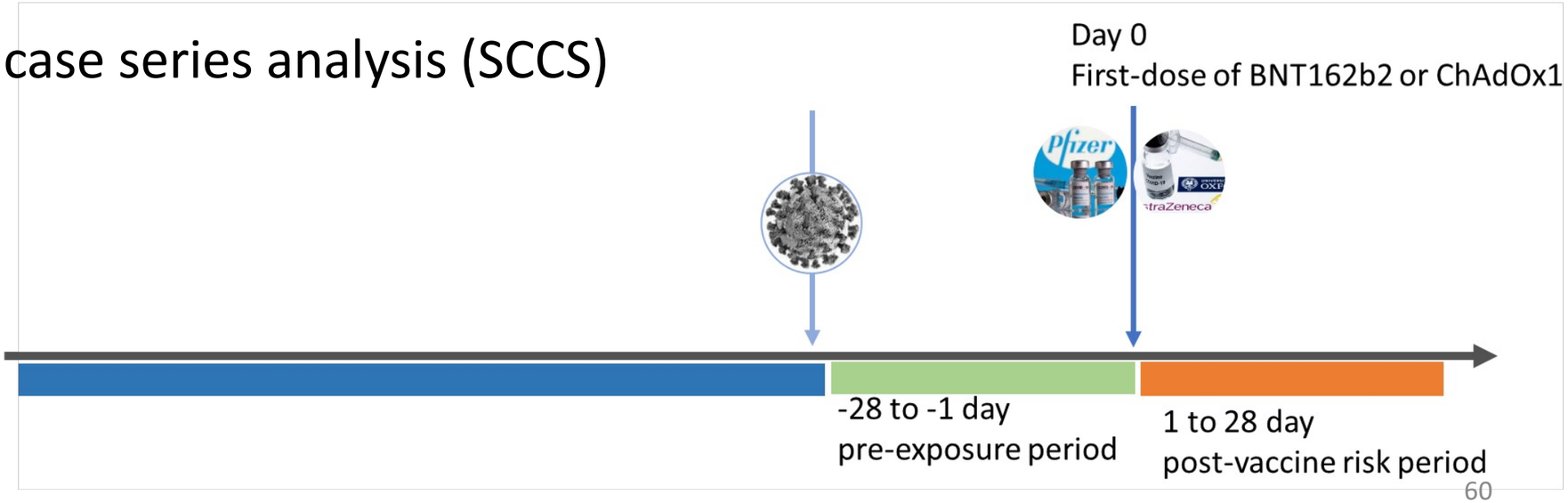
# Adverse events after Covid-19 vaccine: Methods

Analysis:

- Historical rate comparison
  - standardized with age-sex




- Self-controlled case series analysis (SCCS)



# Methods

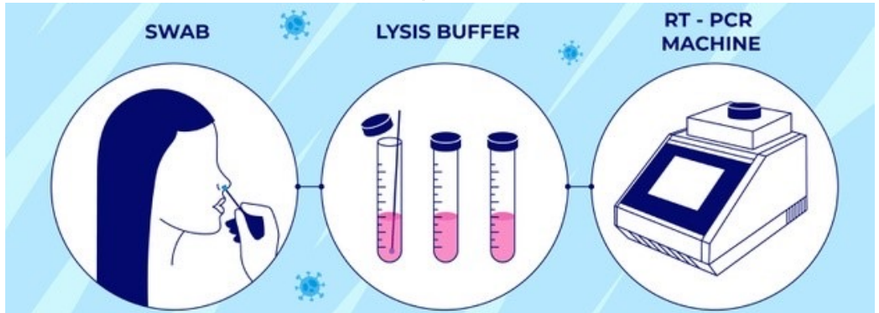
## Exposure:

### Vaccine cohort

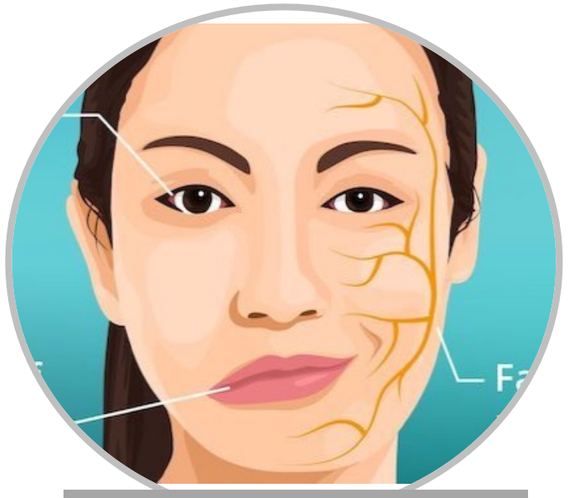




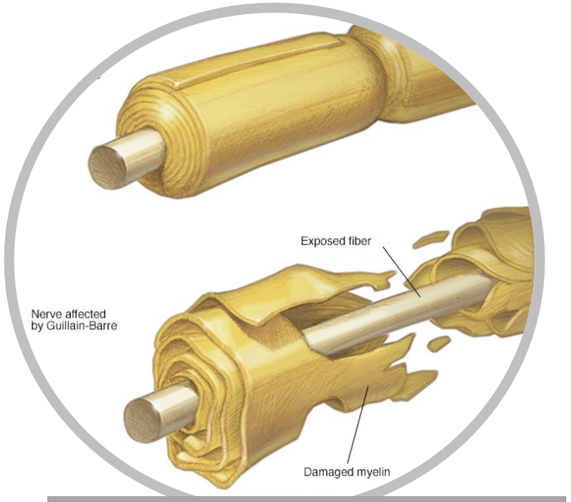
### SARS-CoV-2 PCR positive cohort



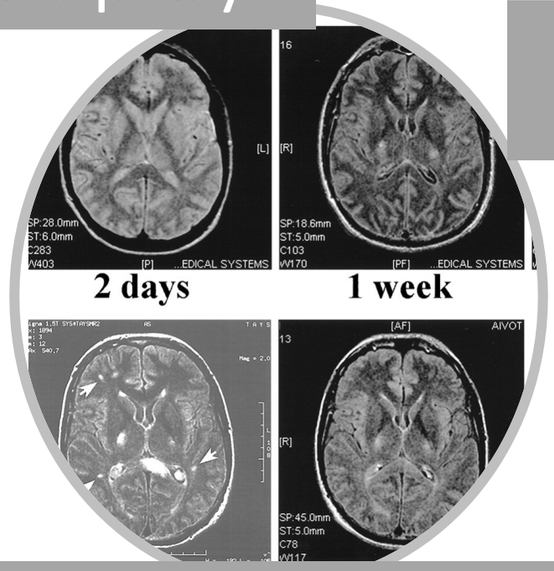

## Outcome:



Bell's palsy



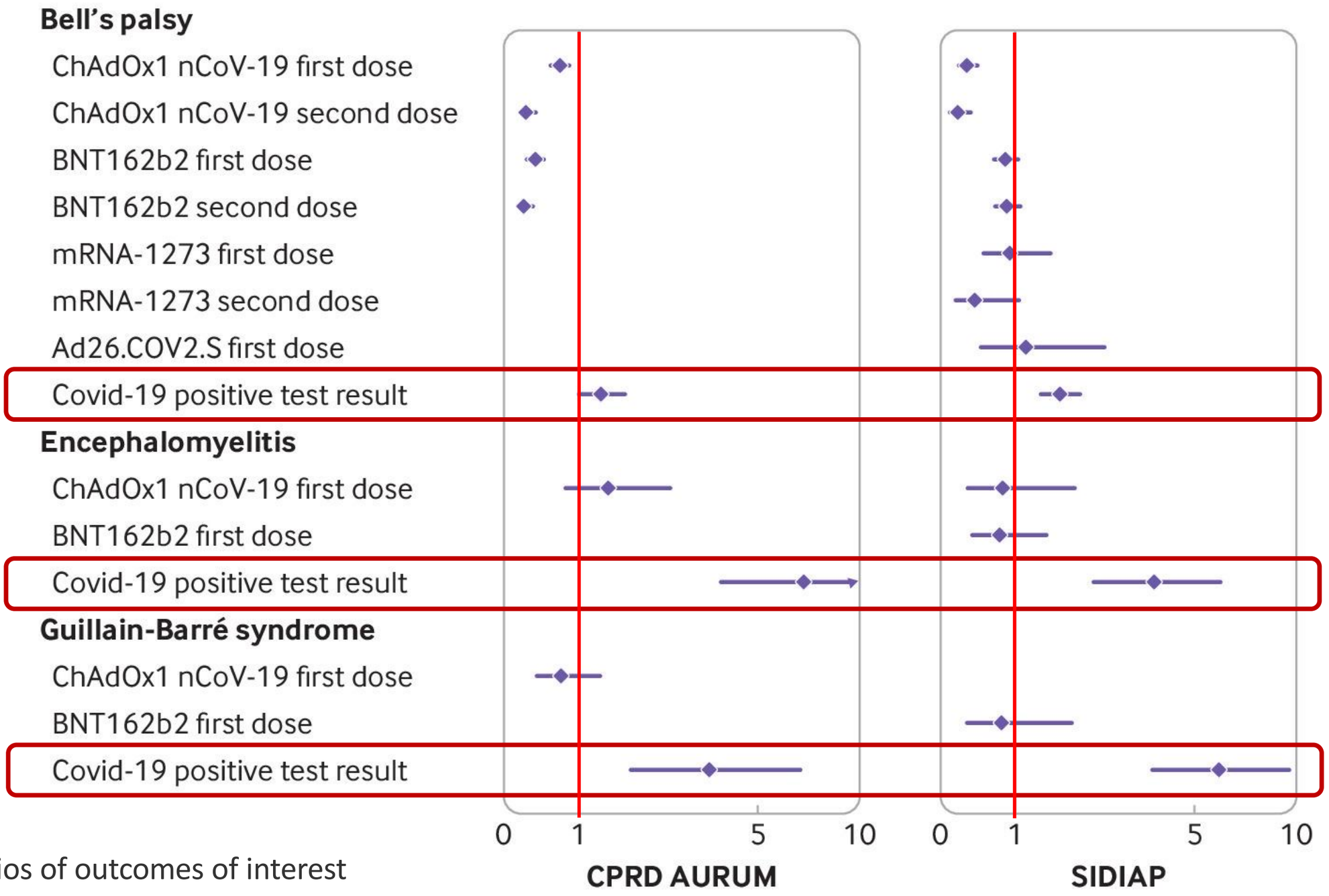

Guillain-Barré syndrome




Encephalomyelitis

NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS, RHEUMATOLOGY AND MUSCULOSKELETAL SCIENCES
UNIVERSITY OF OXFORD

# Results




Standardised incidence ratios of outcomes of interest

# Conclusion

No safety signal was observed between covid-19 vaccines and the Bell’s palsy, encephalomyelitis, and Guillain-Barré syndrome.

An increased risk observed for people with SARS-CoV-2 infection.

# Cohort studies:

# Comparative safety

RESEARCH

OPEN ACCESS

Check for updates

## Comparative risk of thrombosis with thrombocytopenia syndrome or thromboembolic events associated with different covid-19 vaccines: international network cohort study from five European countries and the US

Xintong Li,[1] Edward Burn,[1,2] Talita Duarte-Salles,[2] Can Yin,[3] Christian Reich,[3] Antonella Delmestri,[1] Katia Verhamme,[4] Peter Rijnbeek,[4] Marc A Suchard,[5,6] Kelly Li,[5] Mees Mosseveld,[4] Luis H John,[4] Miguel-Angel Mayer,[7] Juan-Manuel Ramirez-Anguita,[7] Catherine Cohet,[8] Victoria Strauss,[1] Daniel Prieto-Alhambra[1,4]

thebmj

**Xintong Li et al. BMJ 2022**

# AIMS & METHODS



- **Objective**: To quantify the comparative risk of thrombosis +/- thrombocytopenia associated with adenovirus- vs mRNA-based COVID vaccination

- **Design**: International active comparator cohort study incl data from DE, ES, FR, NL, UK, and USA

- **Analysis**:
  1. Large-scale PS matching
  2. Incidence rate ratios 28-d post-each dose
  3. Meta-analysis across databases (where I2<40%)

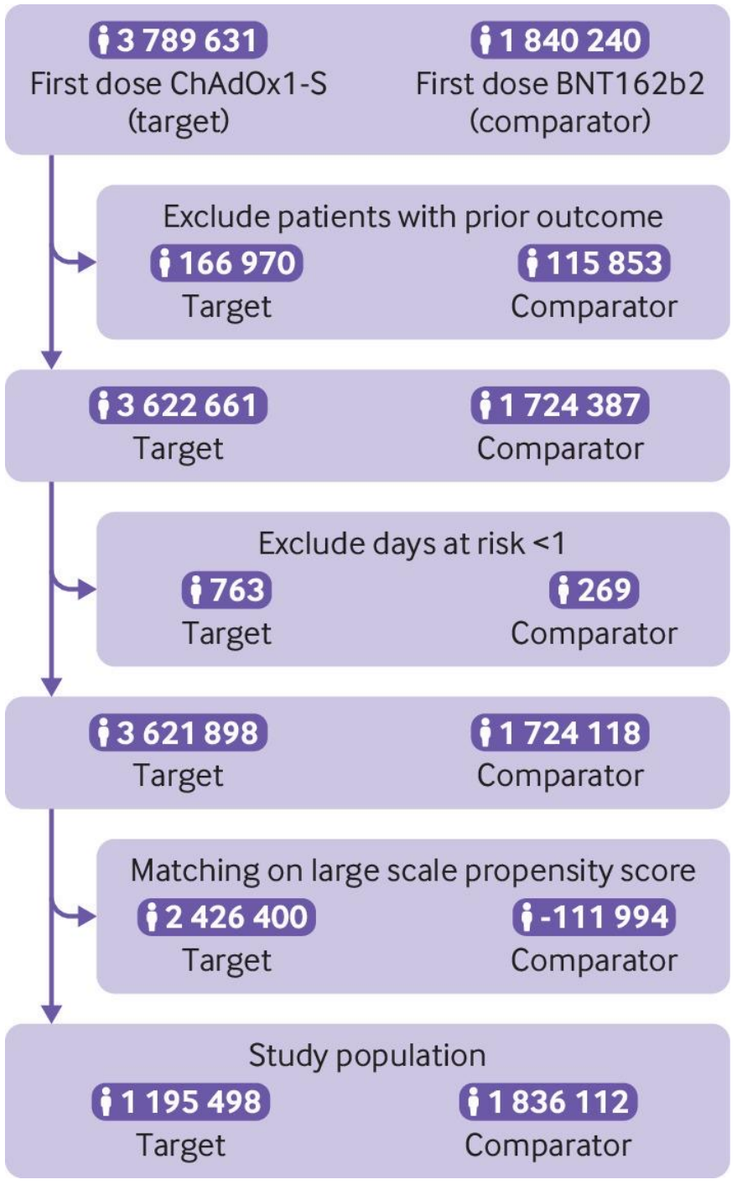
# CONTRIBUTING DATA SOURCES/PARTNERS

**Table 1 | Descriptions of medical records databases used in study**

| Database full (short) names | Country | Active size of database (by mid-2021; No of people) | Latest data available time | Key data available | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Covid-19 vaccines | Hospital treatments | Hospital outcomes | Outpatient treatments | Platelet counts |
| Clinical Practice Research Datalink Aurum (UK CPRD) | UK | 13m | May 2021 | Complete | No | Incomplete | Yes | Yes |
| Information System for Research in Primary Care with minimum basic set of hospital discharge data (CMBD-HA; Spain SIDIAP) | Spain | 6m | June 2021 | Complete | No | Linked | Yes | Yes |
| Integrated Primary Care Information (Netherlands IPCI) | The Netherlands | 2m | June 2021 | Incomplete | No | Incomplete | Yes | Yes |
| IQVIA Longitudinal Patient Data France (France LPD) | France | 2.3m | September 2021 | Incomplete | No | Incomplete | Yes | Yes |
| IQVIA Disease Analyser Germany (Germany DA) | Germany | 8.5m | August 2021 | Incomplete | No | Incomplete | Yes | Yes |
| Medical and Institutional Claims (US Open Claims) | US | 187m | September 2021 | Incomplete | Incomplete | Incomplete | Yes | Yes |
| Charge Data Master (US Hospital CDM) | US | 30m | July 2021 | Incomplete | Yes | Yes | Incomplete | Incomplete |

# RESULTS (I)

**Study cohort selection flowchart.** Illustrative example of cohort participants for the study of post-vax thrombocytopenia in UK CPRD AURUM

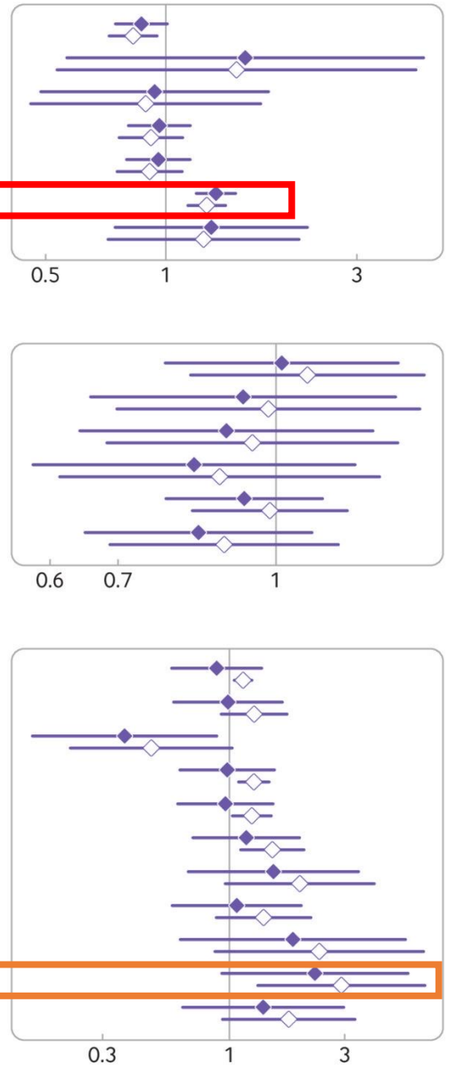



Xintong Li et al. BMJ 2022;379:bmj-2022-071594

# RESULTS (II)

## Meta-analytical estimates

| Outcome | Calibrated incidence rate ratio (95% CI) | $I^2$ | UK CPRD | Germany DA | Netherlands IPCI | France LPD |
|---|---|---|---|---|---|---|
| **ChAdOx1-S first dose *v* BNT162b2 first dose** | | | | | | |
| Arterial thromboembolism | 0.87 (0.75 to 1.01) | 0 | X | X | X | X |
| Deep vein thrombosis | 1.58 (0.56 to 4.42) | 0.86 | X | X | X | |
| Ischemic stroke | 0.94 (0.48 to 1.81) | 0.51 | X | X | X | |
| Myocardial infarction | 0.96 (0.8 to 1.15) | 0 | X | X | X | X |
| Pulmonary embolism | 0.96 (0.79 to 1.15) | 0 | X | X | X | |
| Thrombocytopenia | 1.33 (1.18 to 1.5) | 0 | X | X | X | X |
| Venous thromboembolism | 1.3 (0.75 to 2.26) | 0.65 | X | X | X | X |
| **ChAdOx1-S second dose *v* BNT162b2 second dose** | | | | | | |
| Arterial thromboembolism | 1.01 (0.78 to 1.32) | 0 | X | X | X | |
| Deep vein thrombosis | 0.93 (0.66 to 1.31) | 0 | X | | X | |
| Myocardial infarction | 0.89 (0.64 to 1.25) | 0 | X | X | X | |
| Pulmonary embolism | 0.83 (0.58 to 1.2) | 0 | X | X | | |
| Thrombocytopenia | 0.93 (0.78 to 1.11) | 0 | X | X | X | |
| Venous thromboembolism | 0.84 (0.65 to 1.09) | 0 | X | X | X | |
| **Ad26.COV2.S *v* BNT162b2 first dose** | | $I^2$ | Germany DA | Spain SIDIAP | Netherlands IPCI | US Open Claims |
| Arterial thromboembolism | 0.89 (0.58 to 1.37) | 0 | X | X | X | X |
| Deep vein thrombosis | 0.99 (0.58 to 1.67) | 0.14 | X | X | | X |
| Intestinal infarction | 0.37 (0.15 to 0.89) | 0 | | X | | X |
| Ischemic stroke | 0.99 (0.63 to 1.55) | 0 | X | X | | X |
| Myocardial infarction | 0.97 (0.61 to 1.53) | 0 | X | X | X | X |
| Pulmonary embolism | 1.17 (0.7 to 1.97) | 0.06 | X | X | | X |
| Splanchnic and visceral thrombosis | 1.52 (0.67 to 3.47) | 0 | | X | | X |
| Thrombocytopenia | 1.08 (0.58 to 1.99) | 0.78 | X | X | | X |
| TTS Deep vein thrombosis | 1.83 (0.62 to 5.38) | 0 | | X | | X |
| TTS Venous thromboembolism | 2.26 (0.93 to 5.52) | 0 | | X | | X |
| Venous thromboembolism | 1.38 (0.64 to 2.99) | 0.73 | X | X | | X |




Xintong Li et al. BMJ 2022; 379:bmj-2022-071594

# Conclusions

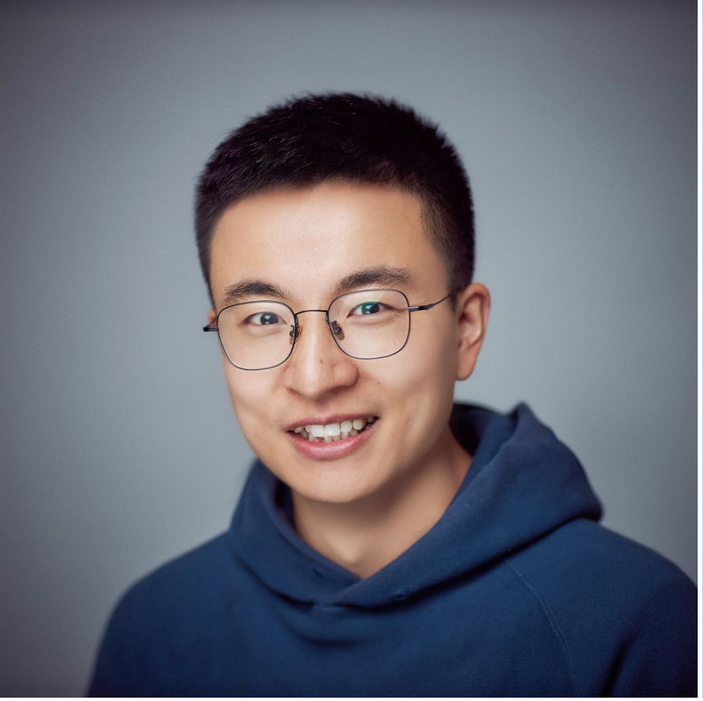
No differential risk of ‘common’ thromboembolic events, venous or arterial

A 30% increased risk of thrombocytopenia

A trend towards an increased risk of TTS-VTE

# AGENDA

- Preface: Why bother?
- Mitigating confounding
- Collaboration is the new competition
- Hacking COVID-19
- And then we got the vaccines!
- The future (of RWE) is here
- Key learnings



# Genetics of post-COVID VTE:

## Does COVID-19 also cause blood clots?

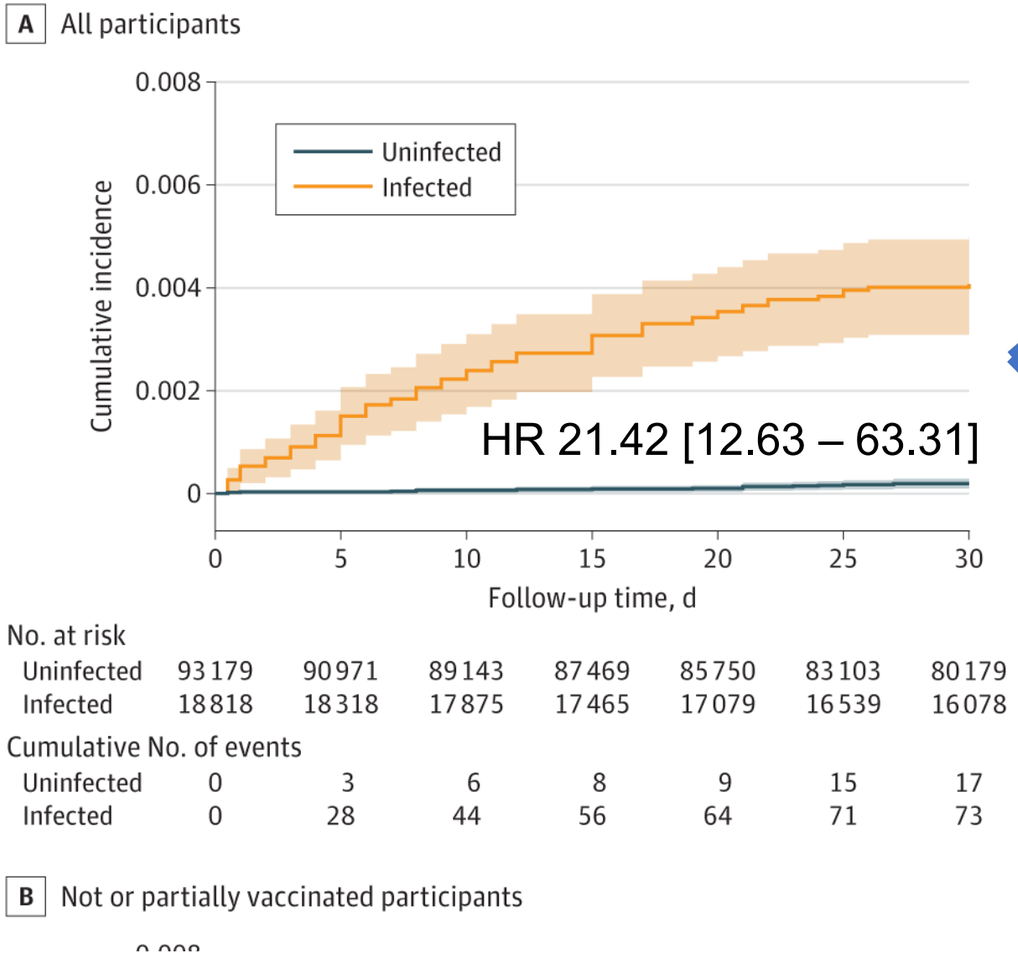
Research

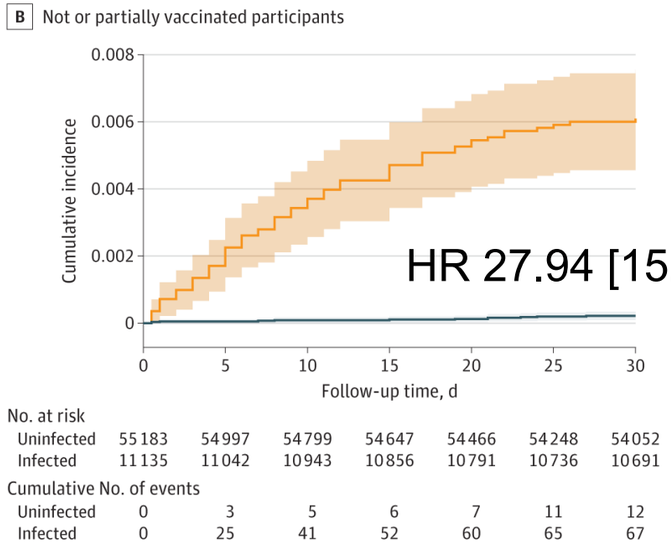
JAMA Internal Medicine | Original Investigation

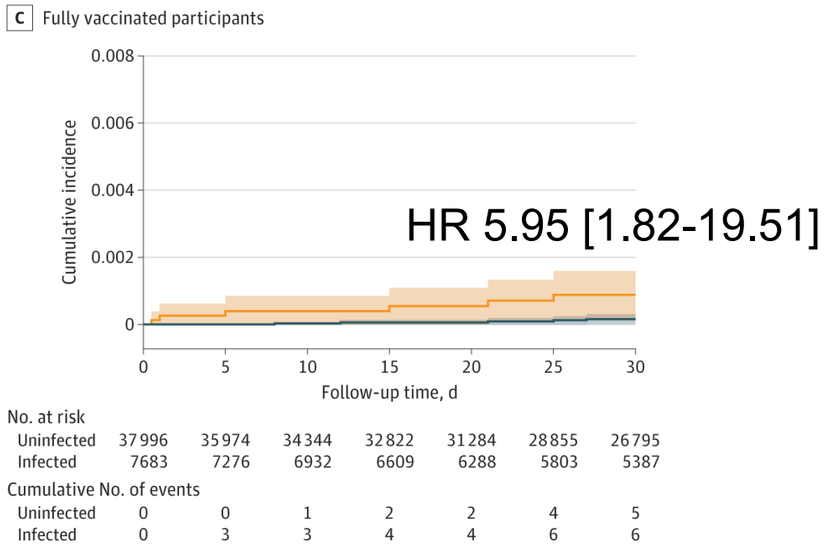
## Clinical and Genetic Risk Factors for Acute Incident Venous Thromboembolism in Ambulatory Patients With COVID-19

JunQing Xie, BSMed, MSc; Albert Prats-Uribe, DPhil; QI Feng, PhD; YuniHe Wang, MSc; Dipender Gill, MD, PhD; Roger Paredes, MD, PhD; Dani Prieto-Alhambra, MD, PhD

# COVID-19 increases (dramatically) the risk of venous blood clots (VTE)

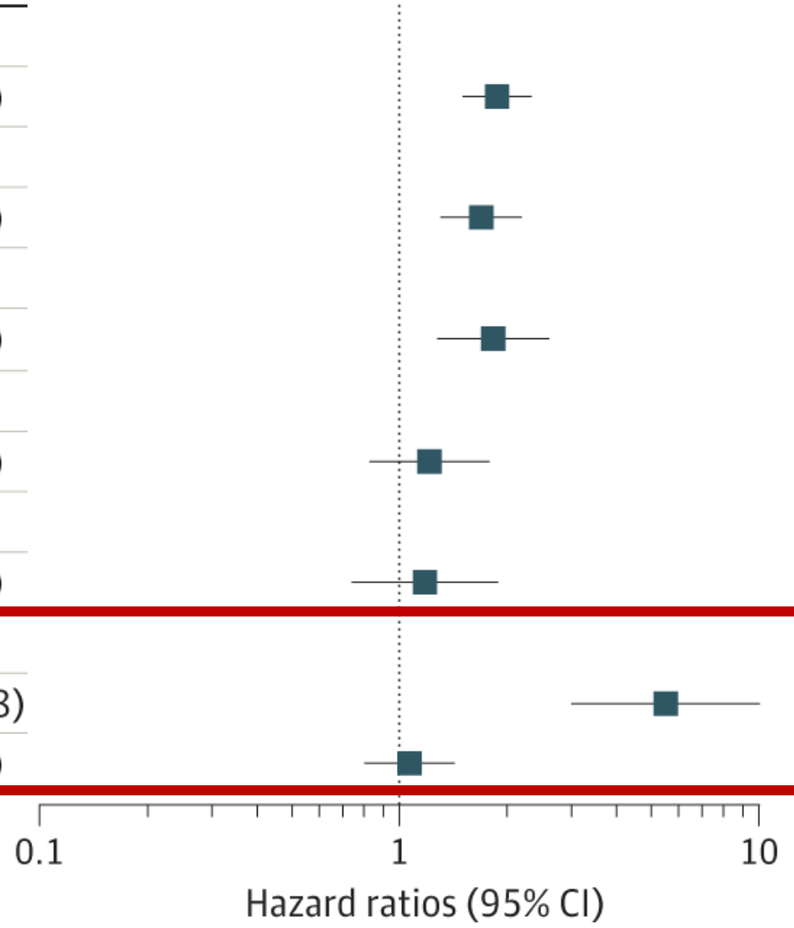


# Vaccination leads to a reduced risk of post-COVID VTE (beautifully, it does not protect vs other VTE, a NCO)

| Variable | Hazard ratios (95% CI) |
|---|---|
| Age (per 10-y increase) | |
| Infection-related VTE | 1.87 (1.50-2.33) |
| Sex (male vs female) | |
| Infection-related VTE | 1.69 (1.30-2.19) |
| Obesity (BMI ≥30 vs <30) | |
| Infection-related VTE | 1.83 (1.28-2.61) |
| Socioeconomic status (higher 50% IMD vs lower 50%) | |
| Infection-related VTE | 1.21 (0.83-1.78) |
| Ethnicity (other ethnic vs White) | |
| Infection-related VTE | 1.18 (0.74-1.88) |
| Vaccination status (not or partial vs full) | |
| Infection-related VTE | 5.50 (3.00-10.08) |
| Other VTE | 1.07 (0.80-1.42) |



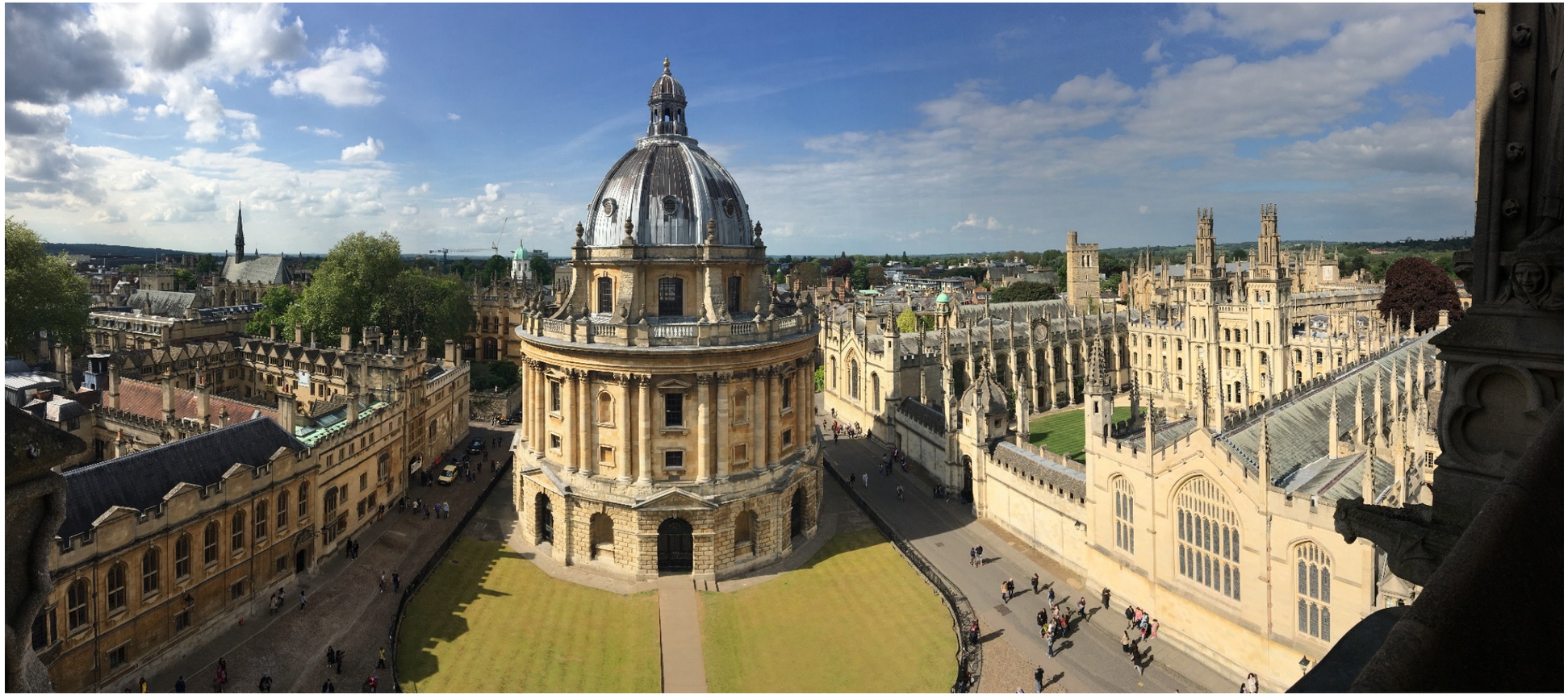
# AGENDA

- Preface: Why bother?
- Mitigating confounding
- Collaboration is the new competition
- Hacking COVID-19
- And then we got the vaccines!
- The future (of RWE) is here
- Key learnings

# 1. Pandemics SUCK!
# (but they exist,
# and we need to prepare)


# 2. Team work ROCKS!

# AND 3. Data and collaboration can make a difference

# QUESTIONS?

@prieto_alhambra