Interoperability between Registries and Health Systems

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In this is my first visit to Australia and Adelaide, I want to acknowledge the Kaurna people as traditional owners of this beautiful land

I also want to pay my respects to their elders past and present

AGENDA

- Real world data sources and linkage
- Interoperability: centralised vs federated
- From data standardisation to standardised analytics
- Use case 1: vaccine and public health data for COVID19
- Use case 2: registries and EMR/claims for trial emulation
- Use case 3: UKBB and pharmacogenomics

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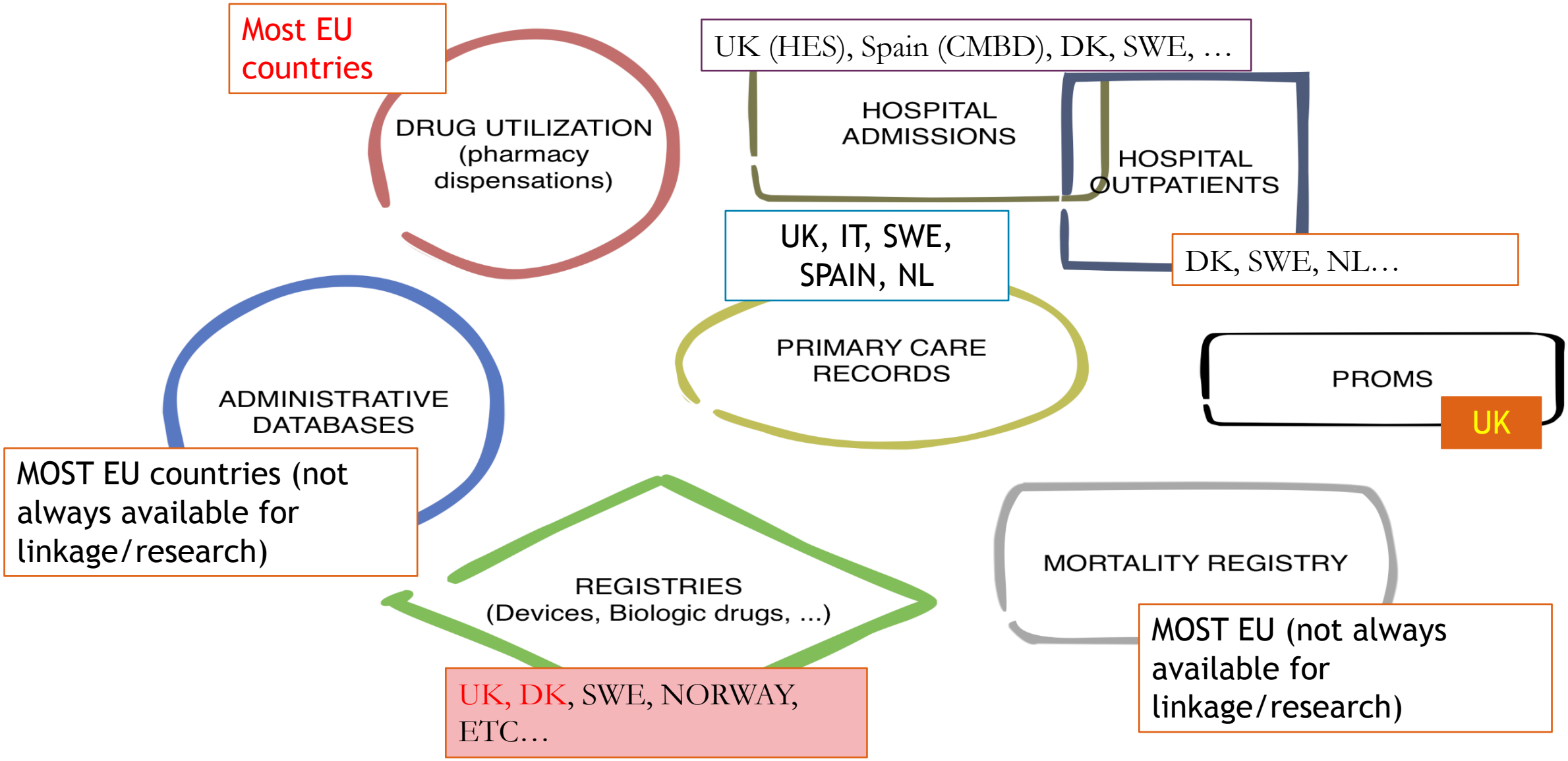
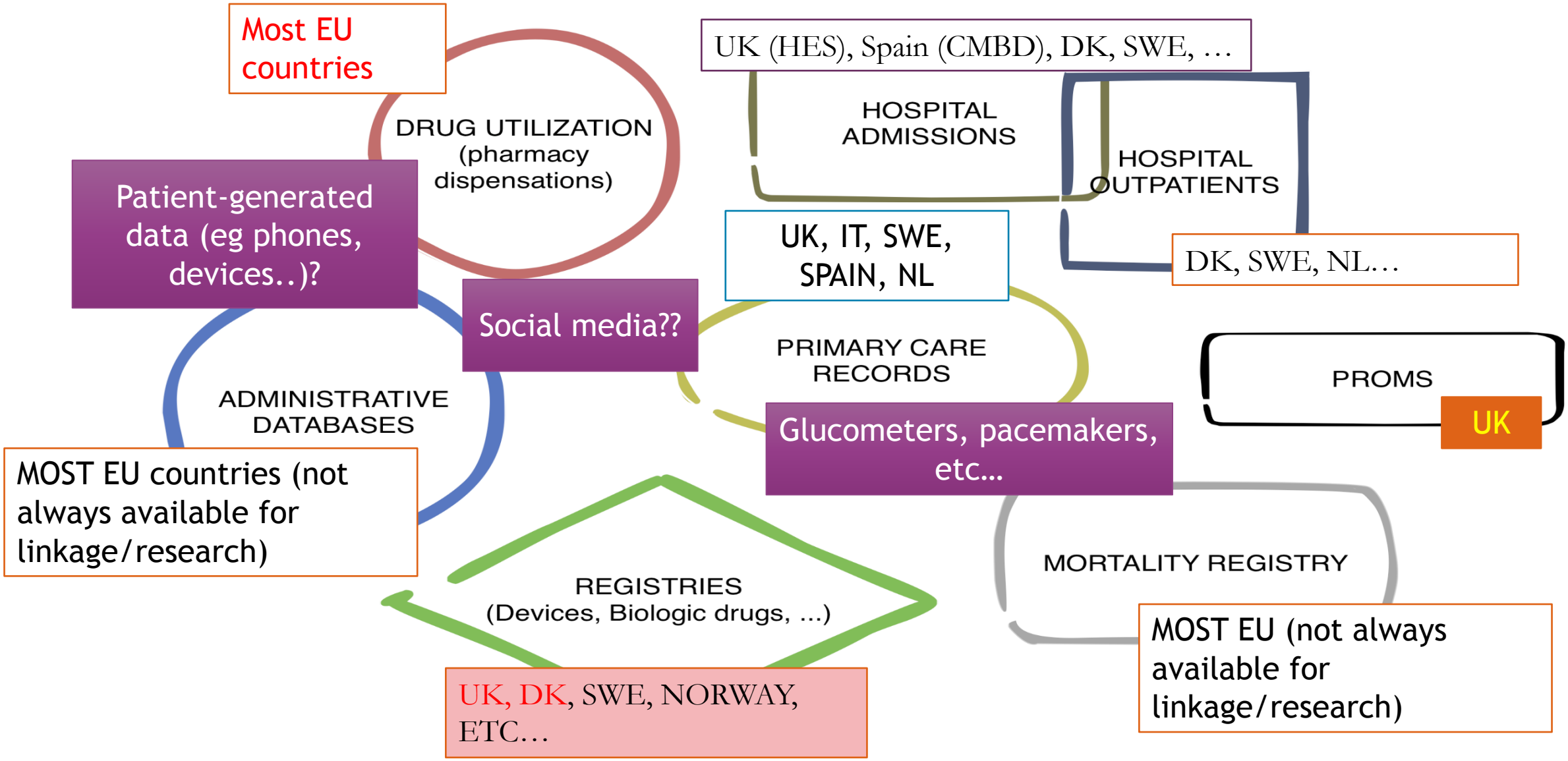
Desirable attributes of reliable RWE
Why we need linked interoperable data

Desired attribute	Question	Researcher	Data	Analysis		Result
Repeatable	Identical	Identical	Identical	Identical	=	Identical
Reproducible	Identical	Different	Identical	Identical	=	Identical
Replicable	Identical	Same or different	Similar	Identical	=	Similar
Generalizable	Identical	Same or different	Different	Identical	=	Similar
Robust	Identical	Same or different	Same or different	Different	=	Similar

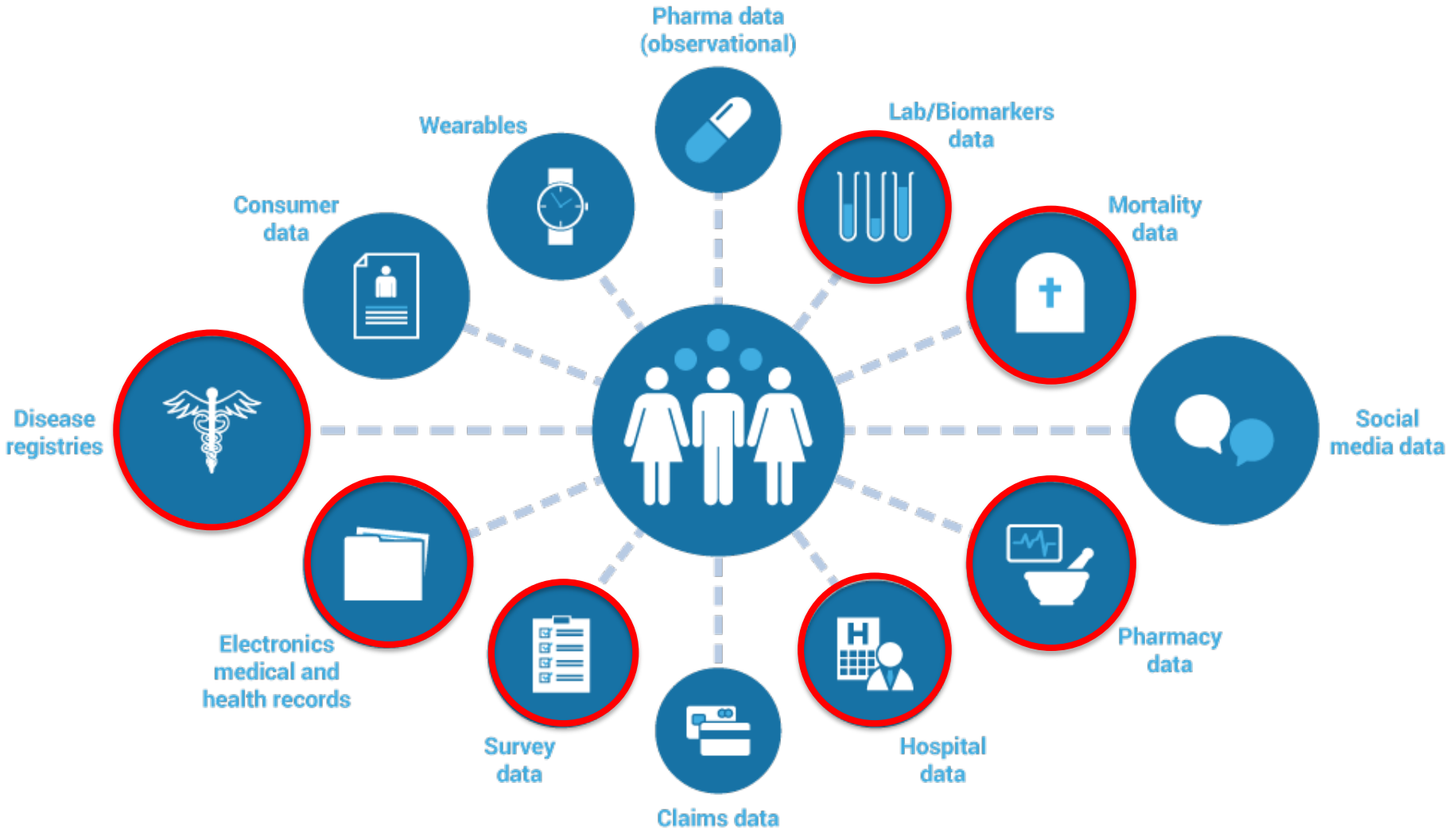
RWE Data Sources in Europe



Adding in patient-generated data



Data linkage: the whole journey!!



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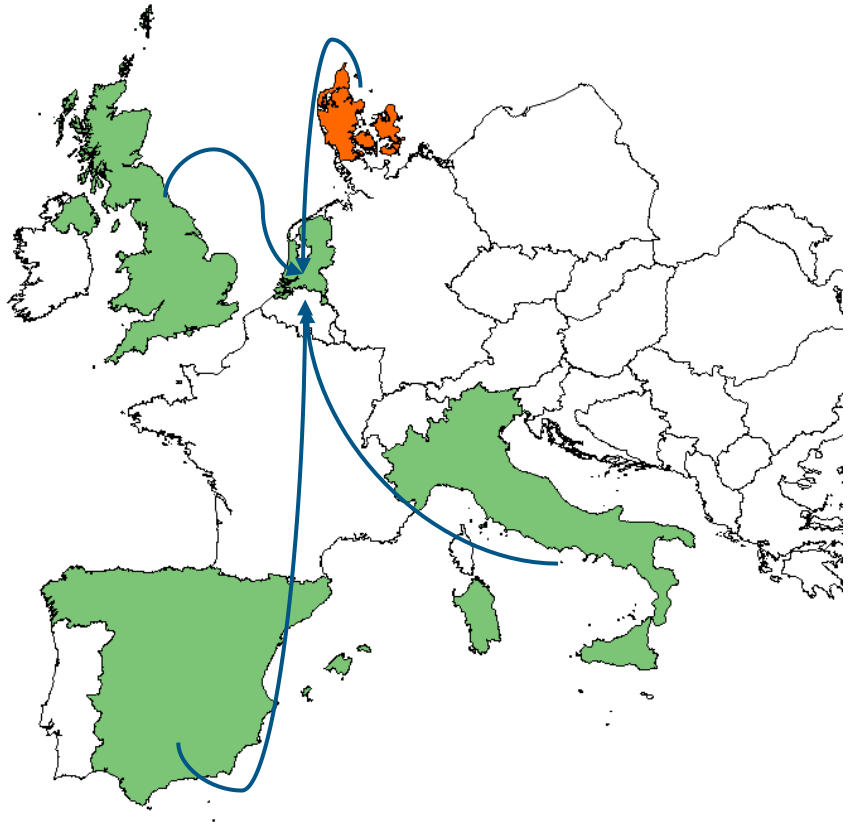
The EU-ADR Alliance

An example of centralised interoperability

Data sources

	Italy		Netherlands	UK	Denmark	Spain	
	HSD	PEDIANET	IPCI	THIN	Aarhus	SIDIAP	SIDIAP PEDIATRICS
Type of datasource	Electronic medical record	Pediatrician records	Electronic medical record	Electronic medical record	Record linkage	Electronic medical record + pharmacy invoice	Electronic medical record + pharmacy invoice
Period covered	From 1998	From 2002	From 1996	From 1990	From 1998	From 2005	From 2006
Population	1.5 million (active)	200.000 (active), pediatric	1.1 million (active)	3.5 million (active) 9 million total	1.8 million (active)	5.1 million (active)	826,940 (active)
Setting	Primary care	Outpatient care	Primary care	Primary care	Dynamic cohorts	Primary care linked to hospital admissions data	Primary care pediatrics linked to hospital admissions data
Type of diagnoses	Outpatient	Outpatient	In-outpatient	In-outpatient	In-outpatient	In-outpatient	Outpatient
Causes of death	Incomplete	Yes	Yes	Yes	Yes	Yes (linked with mortality register)	Yes (linked with mortality register)
Vaccinations	Yes	for now partially	Yes (to be linked)	Yes	Yes (selected)	Yes	Yes
Drugs	Prescriptions	Prescriptions	Prescriptions	Prescriptions	Prescriptions	Prescriptions and Community pharmacy dispensings	Prescriptions and Community pharmacy dispensings
Laboratory values	Yes	Yes	Yes	Yes	Yes	Yes (primary care labs)	Yes (primary care labs)
Frequency of updates	Every 6 months	Continuous	Every 6 months	Every 3 months	Every 12 months	Every 12 months	Every 12 months

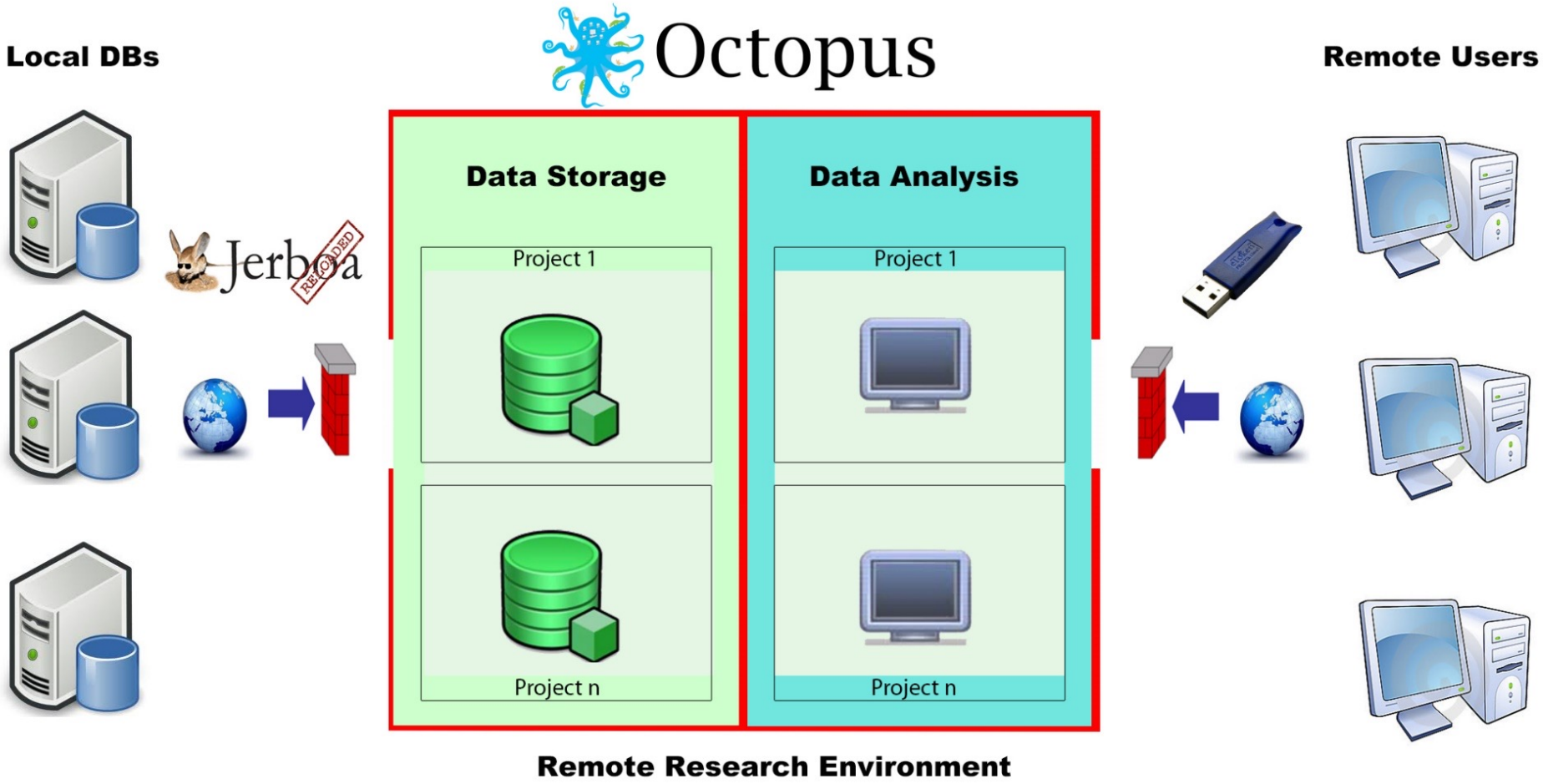
- Honest broker
- Stable, structured, multi-national, multi-database
- Setting:
  - hospital discharge registry (orange)
  - primary care databases (green), some linked to inpatient data
- Data Management:
  - Per protocol minimal common data model
  - Jerboa, Octopus [1]



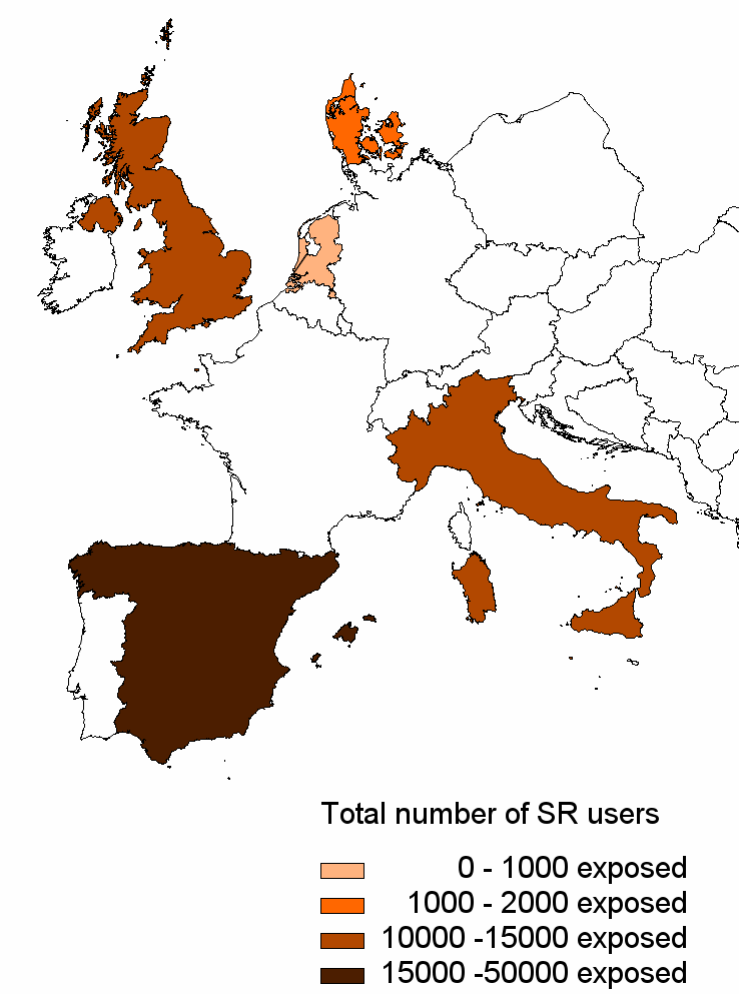
K Berencsi et al. ICPE 2018

'Per protocol' minimum common dataset

Centralized interoperability



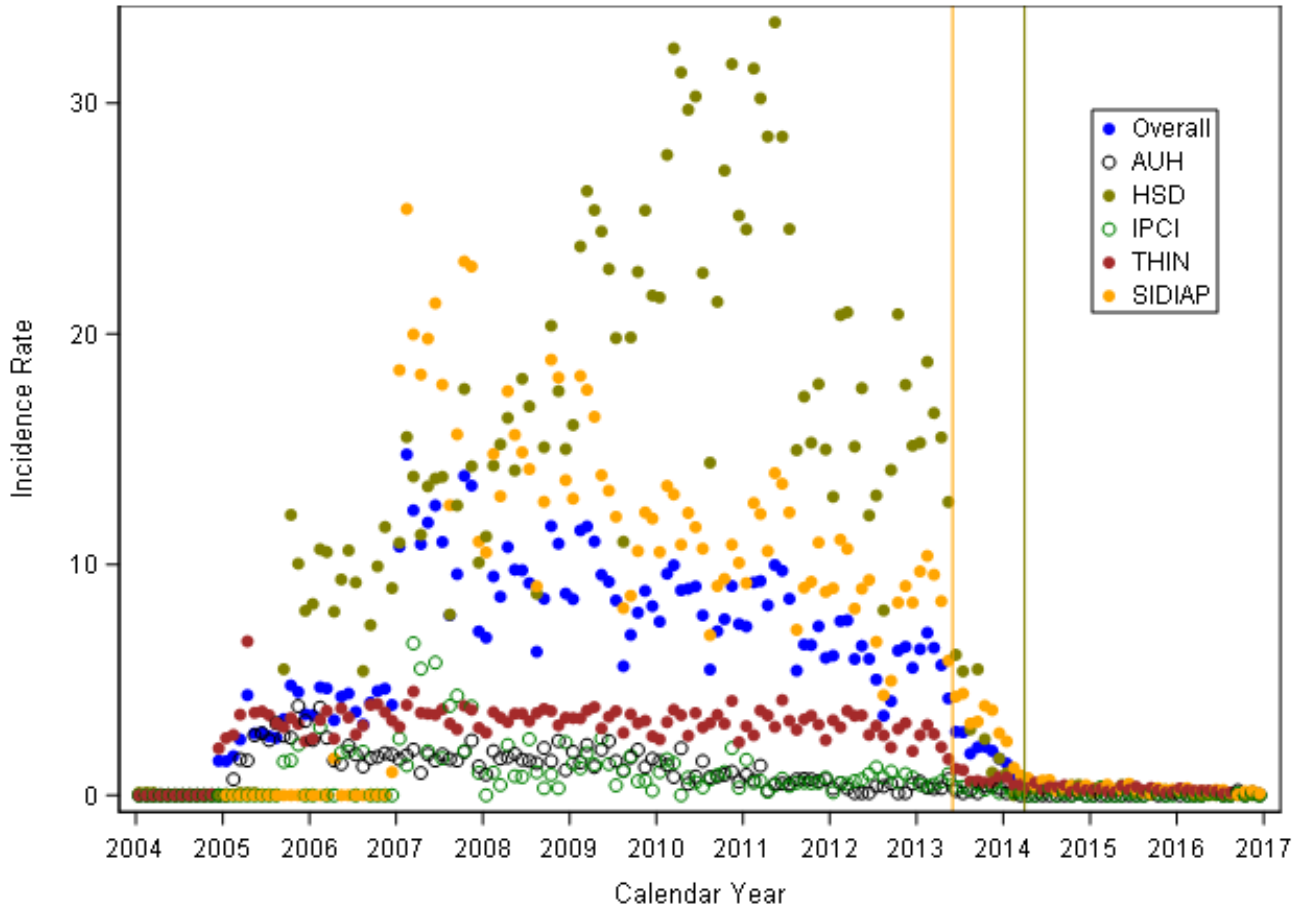
Database	Person-time	Exposed individuals
HSD	14 million	~ 14 300
IPCI	8 million	~ 600
AUH	14 million	~ 1 300
THIN	49 million	~ 12 000
SIDIAP	57 million	~ 49 100
Total	144 million	~ 77 300



K Berencsi et al. ICPE 2018

An example
Population Level SR DUS (2)

Monthly IR (10,000 PY) of SR use overall and in each



EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Federated analytics

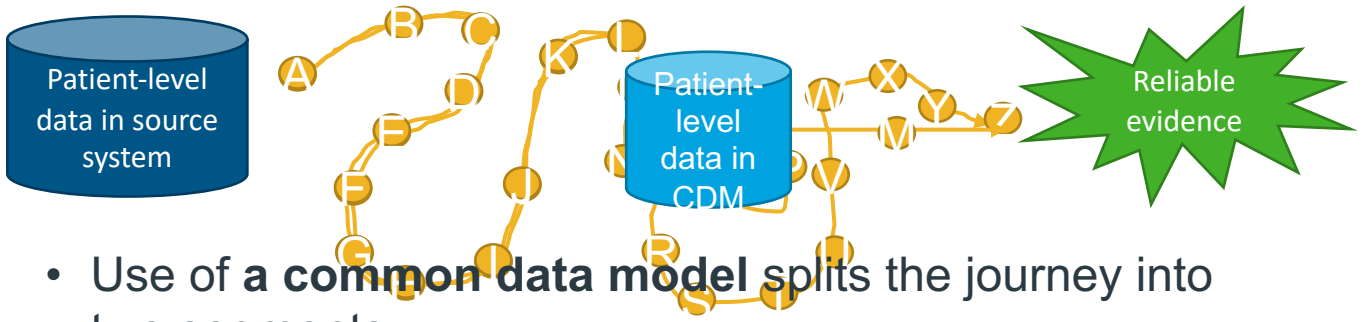
The journey to real-world evidence: a fully reproducible data flow

- Complete documented specification that fully describes all data manipulations and statistical procedures
- Full analysis code that executes end-to-end (from source to results) without manual intervention

GOAL: to implement a **large sustainable** data **network** (+100m records) in Europe to generate **reliable evidence** for patient care that is **transparent** and fully **reproducible**

OHDSI

A Common Data Model and Standardized Vocabularies



- Use of **a common data model** splits the journey into two segments:
  - 1) data standardization/curation,
  - 2) data analysis

- **CDM** creates opportunity for re-use of data curation and analysis steps and pipelines

HOW TO START – The EHDEN journey

Data Sources

SMEs

EHDEN Portal

Open Calls

- Series of in-project calls across the EU
- Tailored for project objectives and sustainability

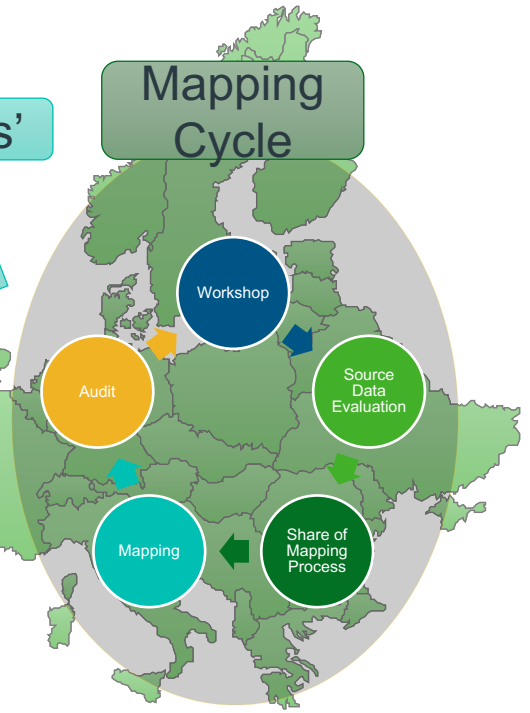
Open Calls

- Continuous open call across the EU
- Focusing on SME representation to support mapping and sustainability

Review

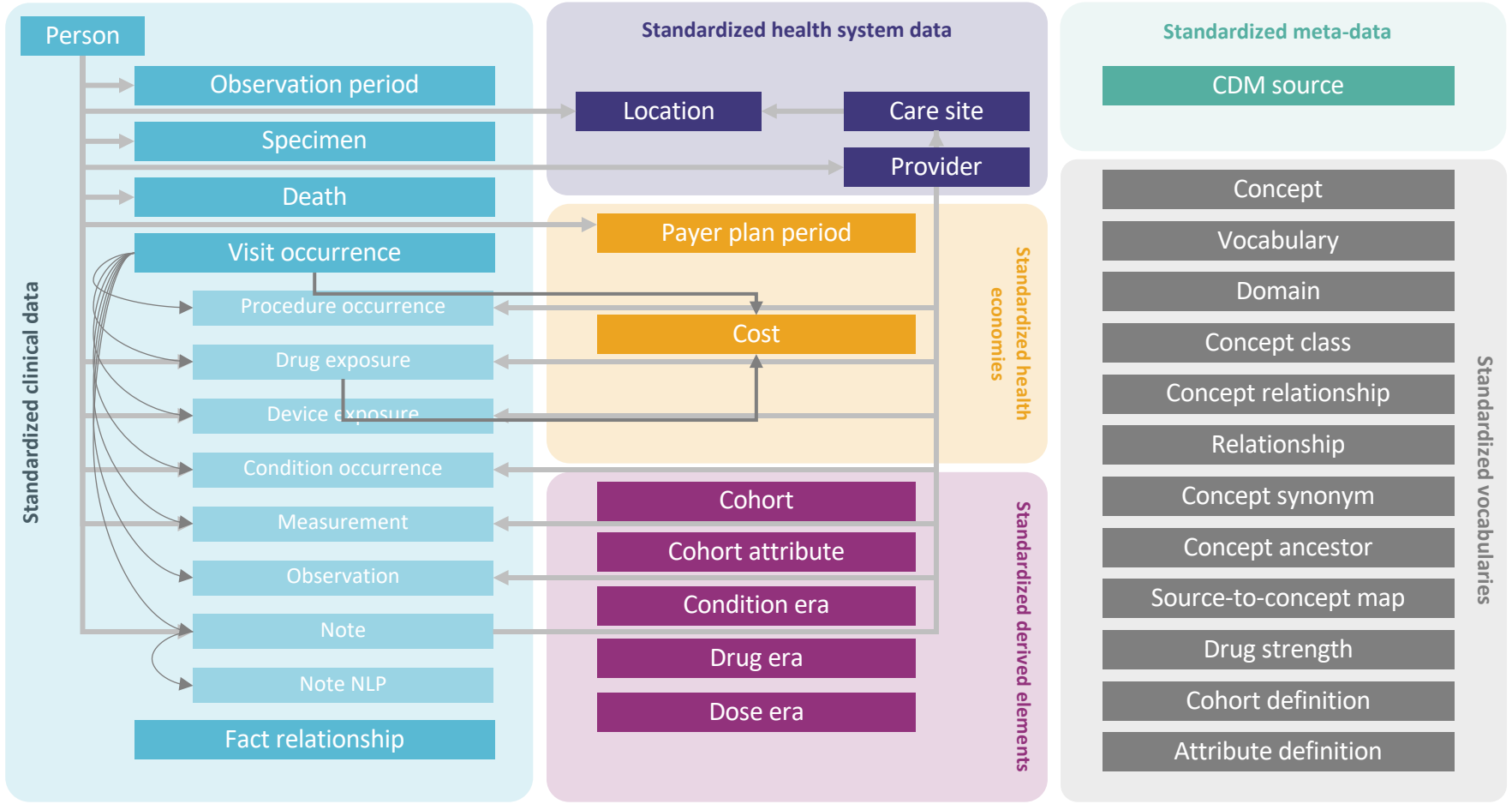
‘Grants’

Training/ Certification



- ‘Grants’ are provided via milestone payments to Data Sources
- SMEs will support Mapping Cycle and be paid via the Data Source ‘grant’, following certification by EHDEN

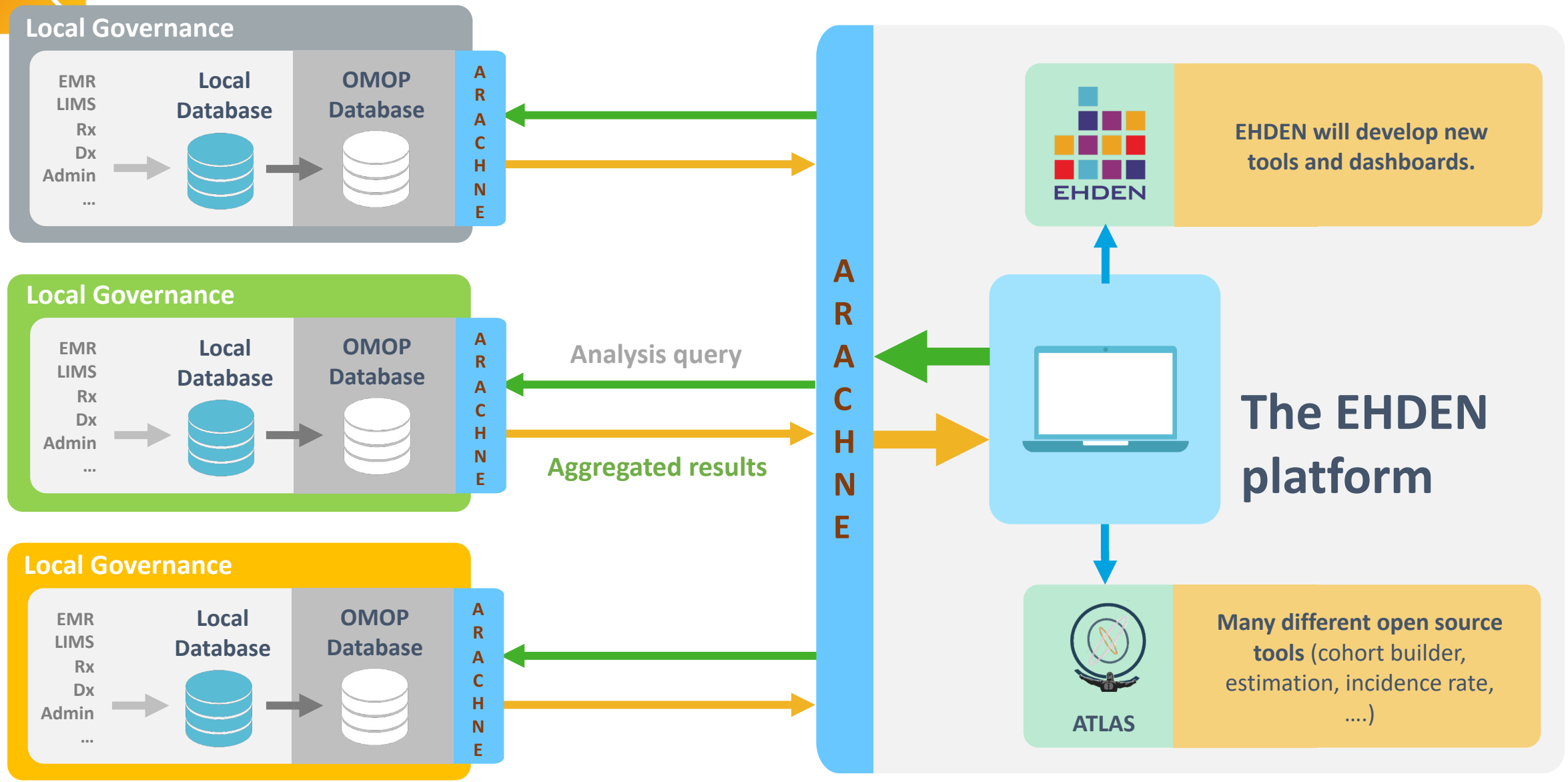
The OMOP common data model



- Patient-centric
- Tabular
- Extendable
- Built for analytics
- Relational design

v 5.0.1

Federated Analytics



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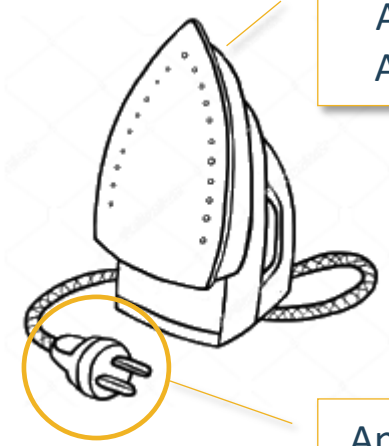
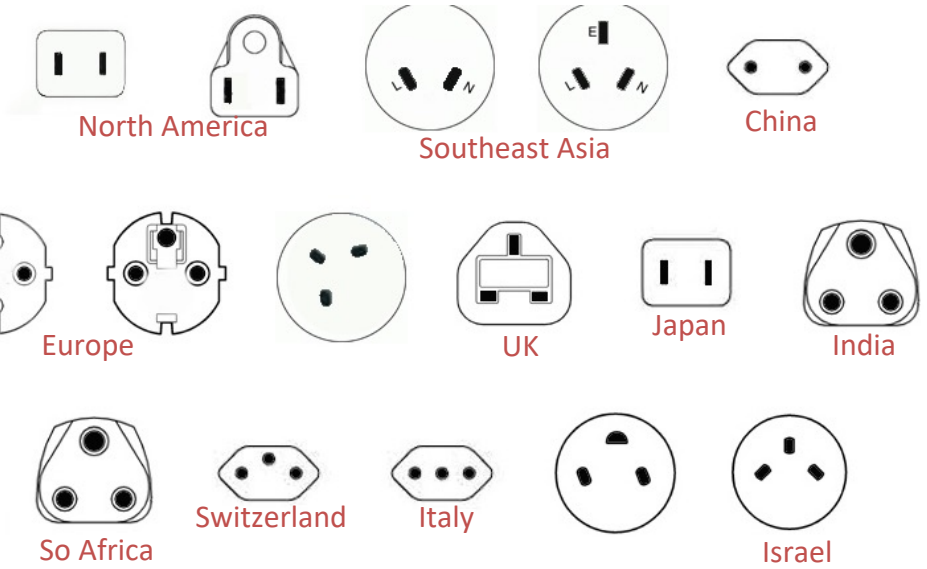
Current Approach: “One Study – One Script“

"What's the adherence to my drug in the data assets I own?"

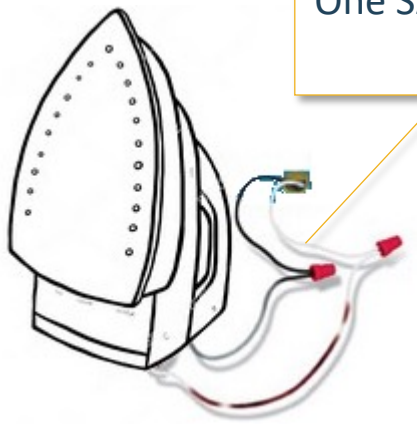


Analytical method:
Adherence to Drug

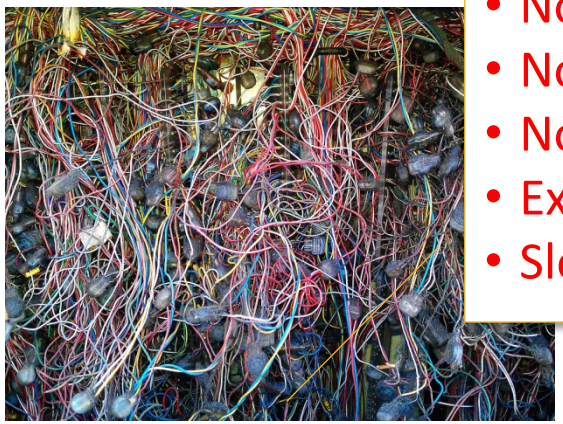
Application to data



Current solution:

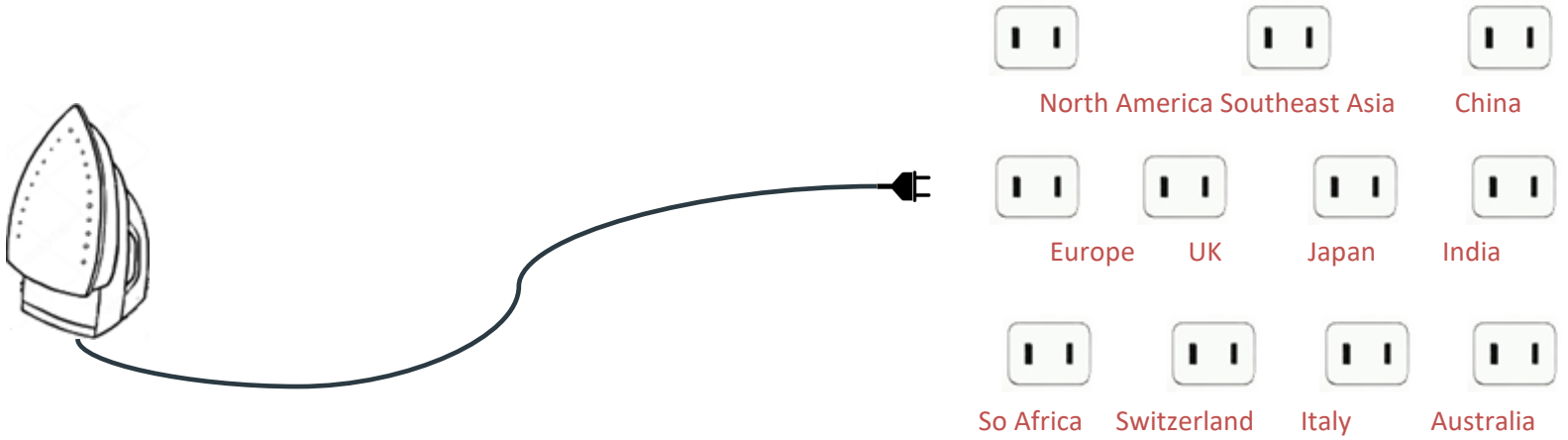


One SAS or R script for each study



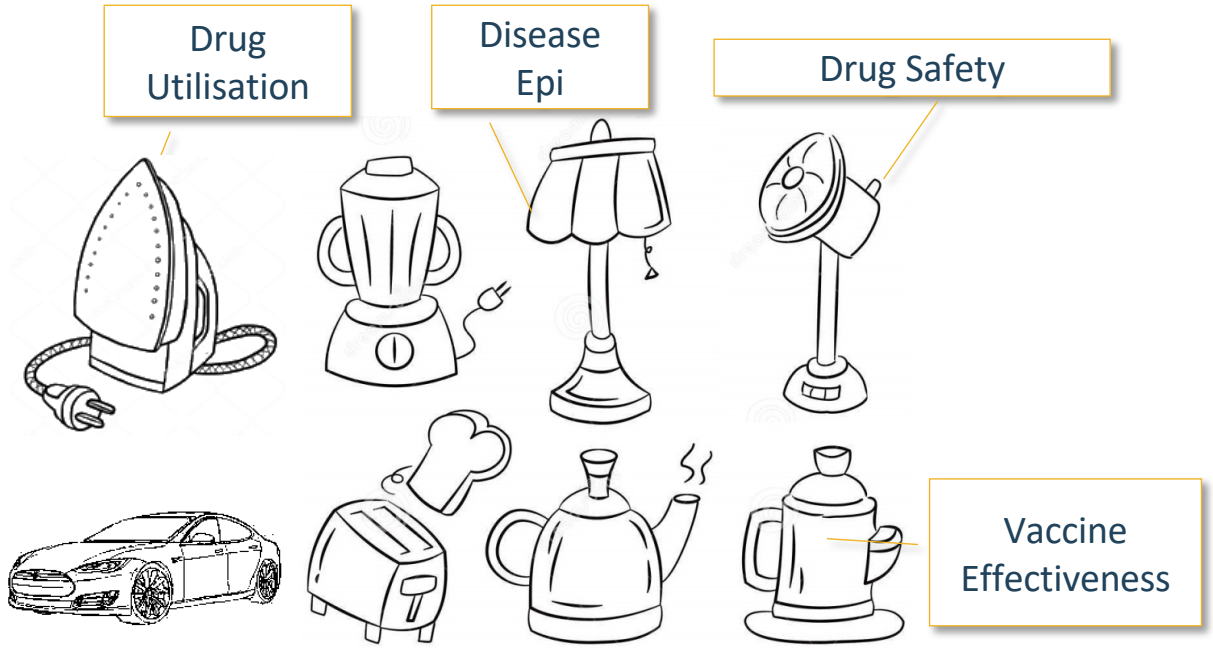
- Not scalable
- Not transparent
- Not reproducible
- Expensive
- Slow

Scaling up the evidence



- No patient-level data transfer -> Privacy “by design”
- Reproducibility, Repeatability
- Preserve Desirable Heterogeneity
- Federated analyses -> Collaboration and cross-fertilisation
- Standardised Data <- <- <- Standardised Analytics

From Data Standardization To Standardised Analytics



Standardized analytics → Standardized data

Desirable attributes of reliable RWE

Desired attribute	Question	Researcher	Data	Analysis		Result
Repeatable	Identical	Identical	Identical	Identical	=	Identical
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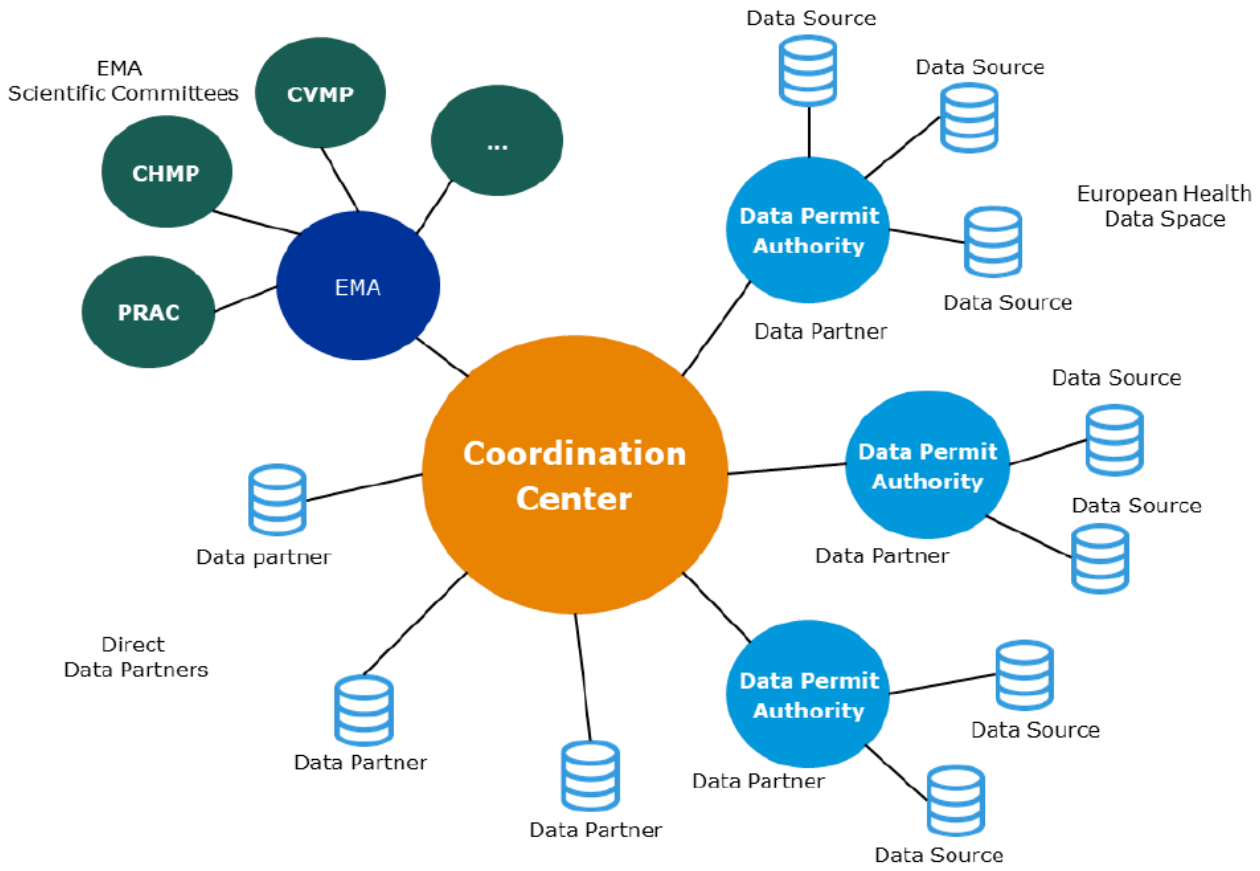
CDM and standardized analytics

Network studies

Sensitivity analyses

Scaling up regulatory evidence in Europe: DARWIN EU

DARWIN EU® is a federated **network** of **data**, **expertise** and **services** that supports better decision-making throughout the product lifecycle by generating reliable **evidence from real world healthcare data**



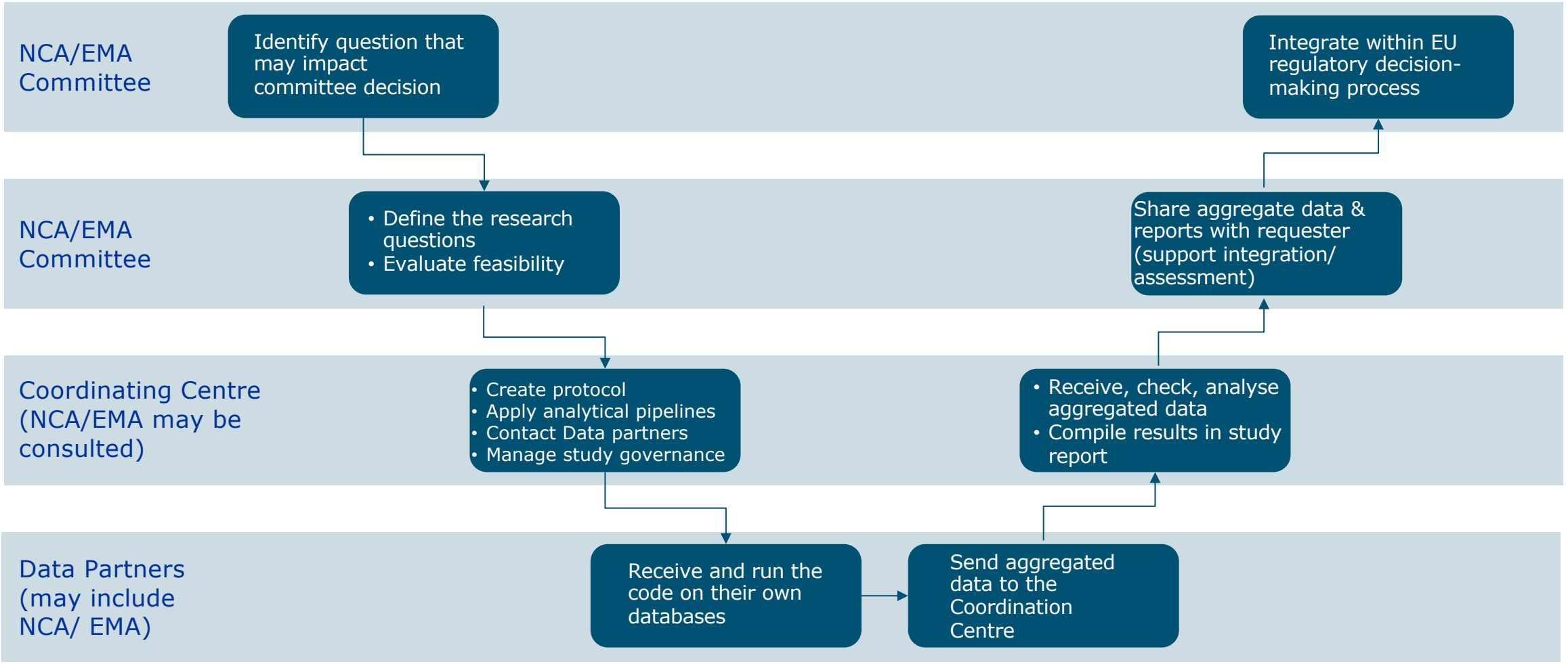
FEDERATED NETWORK PRINCIPLES

- Data stays **local**
- **Use of Common Data Model** to perform studies in a timely manner and increase consistency of results

What analyses and studies will DARWIN EU® deliver?

Category of observational analyses and studies	Description
Off-the-shelf studies	Studies for which a generic protocol is adapted to a research question
Complex Studies	Studies requiring development or customisation of specific study designs, protocols, phenotypes, etc
Routine repeated analyses	Routine analyses based on Off-The-Shelf or Complex Studies (see above), repeated periodically with a pre-specified regularity (e.g. yearly)
Very Complex Studies	Studies which cannot rely only on electronic health care databases, or which would require complex and/or novel methodological work

What is the DARWIN EU® process for conducting studies?



Draft Catalogue of Standard Analyses:
Off-the-shelf studies and examples

Standard Analysis	Regulatory example
Population-level disease epidemiology	• Prevalence of rare disease/s • Background rates of AESI or DMEs
Patient-level disease epidemiology	• Natural history/prognosis • Current practice/treatment patterns
Population-level DUS	• Incidence and prevalence of use of medicine/s over time
Patient-level DUS	• Describing indication/s for drug/s • Treatment duration, cumulative use

Data Partners – Phase I

UK

1. Clinical Practice Research Datalink (CPRD GOLD)

Belgium

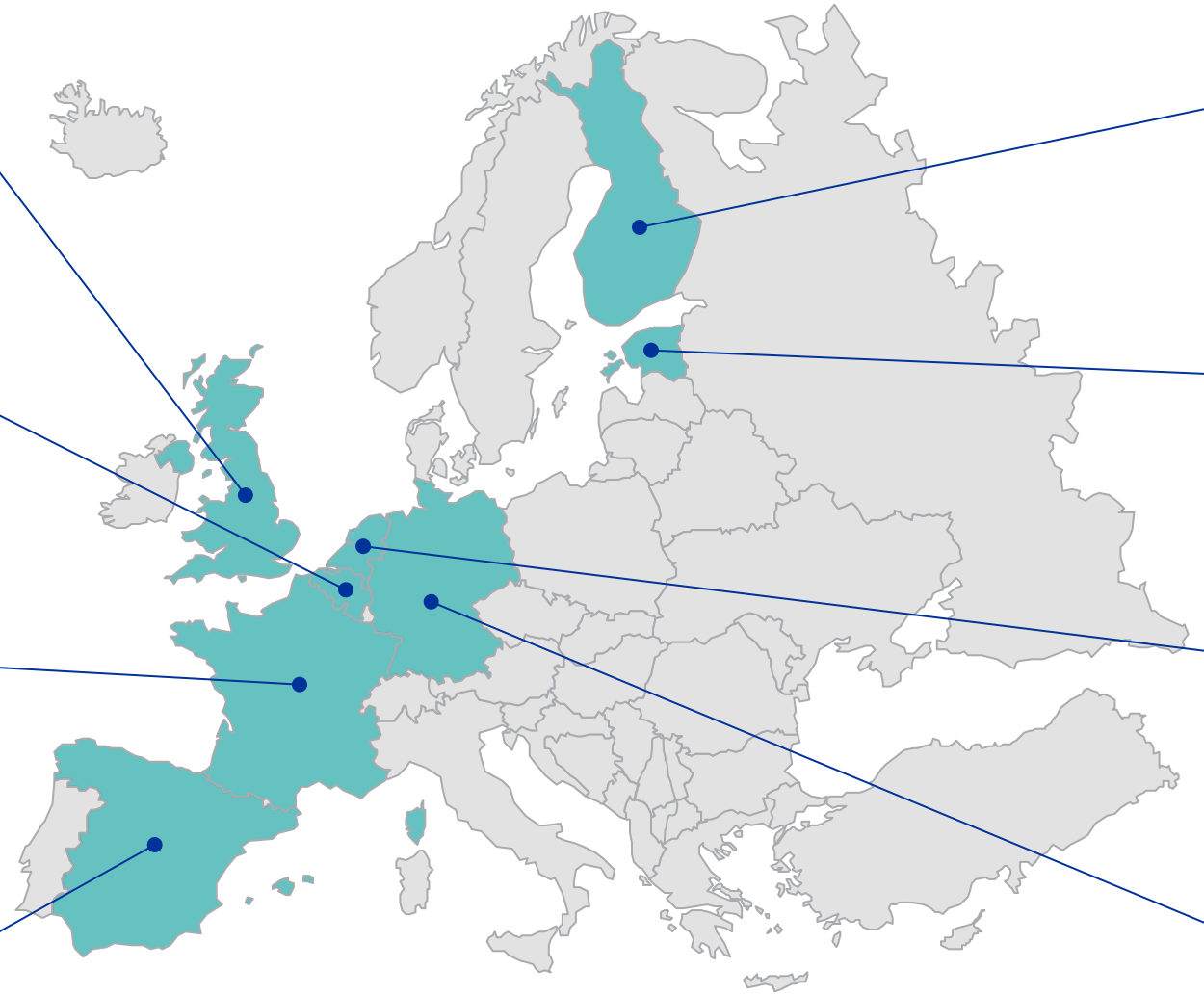
2. IQVIA Belgium Longitudinal Patient Data

France

3. Bordeaux University Hospital

Spain

4. IDIAPJGol
5. Parc Salut Mar Barcelona, Hospital del Mar (IMIM)



Finland

6. Auria Clinical Informatics at Hospital District of Southwest Finland (HDSF)

Estonia

7. University of Tartu (EE Biobank)

Netherlands

8. Integrated Primary Care Information
9. Netherlands Comprehensive Cancer Organisation

Germany

10. IQVIA Germany Disease Analyser

~26 million active patients

DARWIN EU® Studies – Phase I

Type	Studies	Data Partners	Planned RWE use	Committee	
OTS	**Population level epidemiology** study on prevalence of **rare blood cancers** from 2010.	NL, ES, UK, BE, DE	Support COMP in orphan designation decision making	COMP	Complete
OTS	Patient level **drug utilisation** study of **valproate-containing medicinal products** in women of childbearing potential from 2010	NL, ES, UK, BE, DE, FI	Assess the use of valproate after safety referral	PRAC	
OTS	Patient level **drug utilisation** study of **antibiotics** on the Watch list of the WHO AWaRe classification, 2010-2021	NL, FR, ES, DE, UK	Inform PRAC/CHMP decision making	PRAC – CHMP AMR strategy	
Com plex	Background all-cause **mortality rates in patients with severe asthma aged ≥12 years** old		Support CHMP evaluation and post-authorisation informing future decision making	CHMP	Ongoing

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Linking vaccine registries to public health data to monitor COVID vax 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]

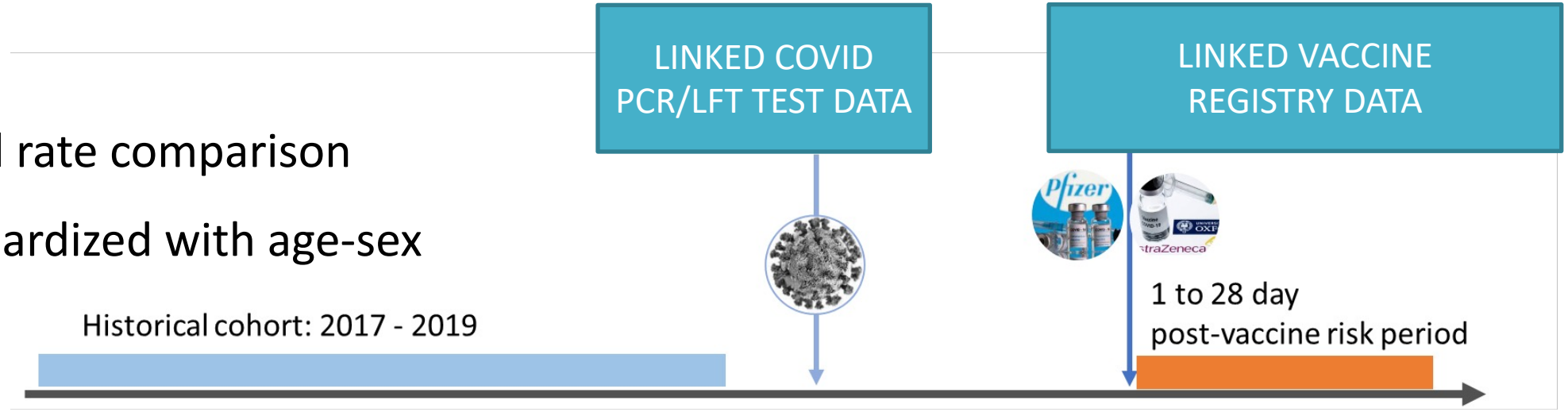
thebmj

Xintong Li et al. BMJ 2022

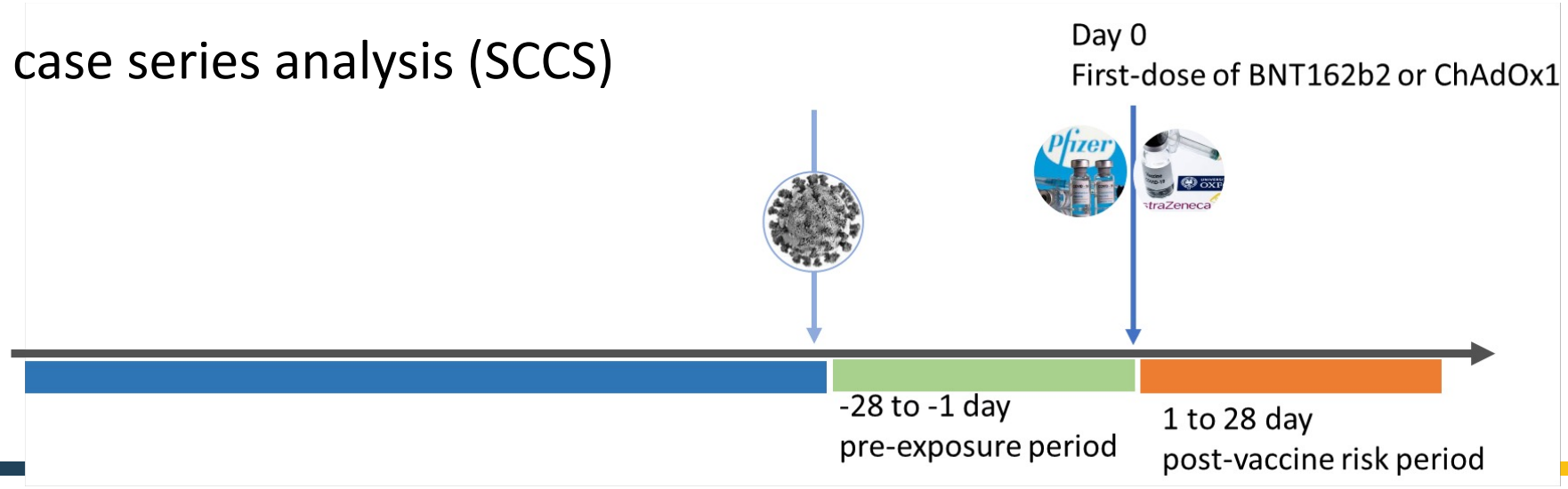
OBS/EXP AND SCCS METHODS
REQUIRE COMPLETE VAX AND COVID19 DATA -> LINKAGE

Analysis:

- Historical rate comparison
  - standardized with age-sex



- Self-controlled case series analysis (SCCS)



POTENTIAL CONTRIBUTING PARTNERS

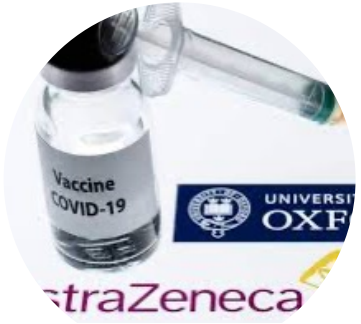
Table 1 | Descriptions of medical records databases used in study

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

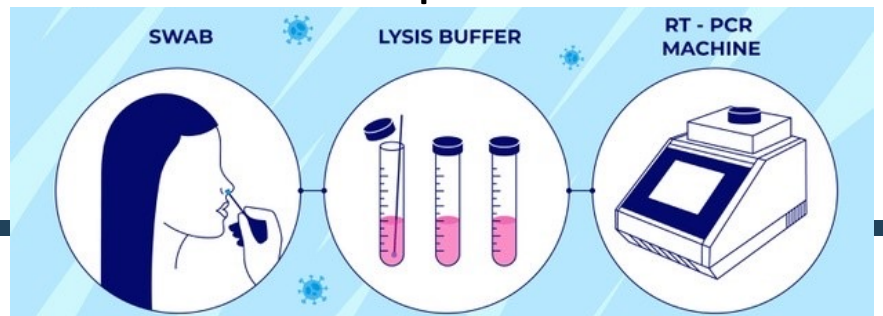
Methods

Exposures:

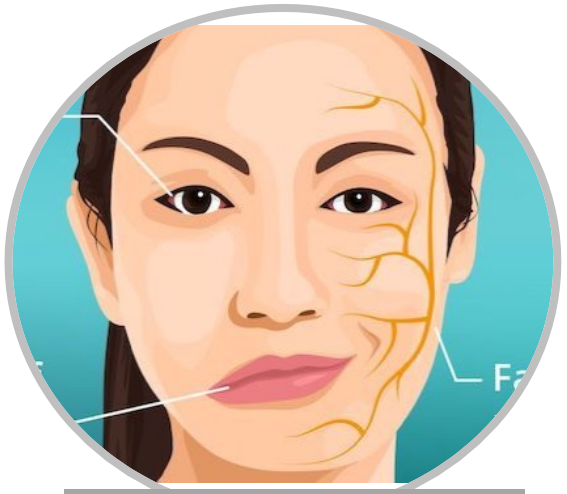
Vaccine cohort



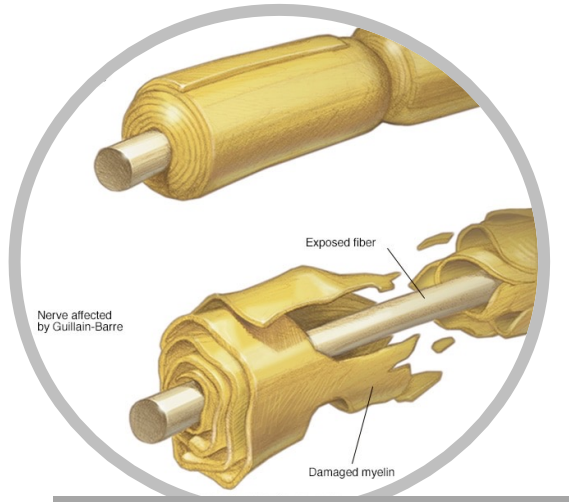
SARS-CoV-2 PCR positive cohort



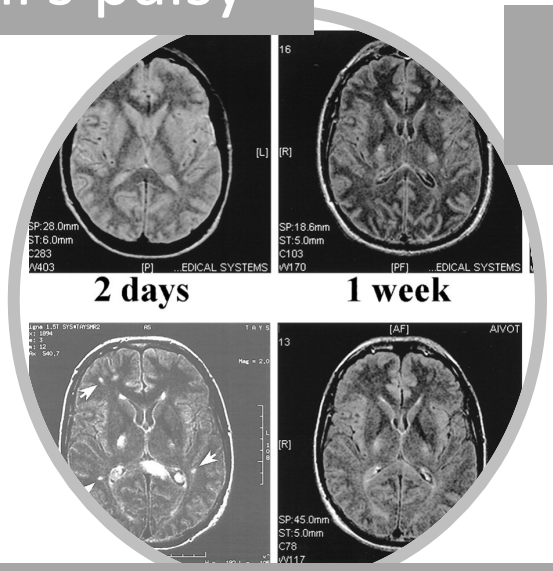
Outcomes:



Bell's palsy



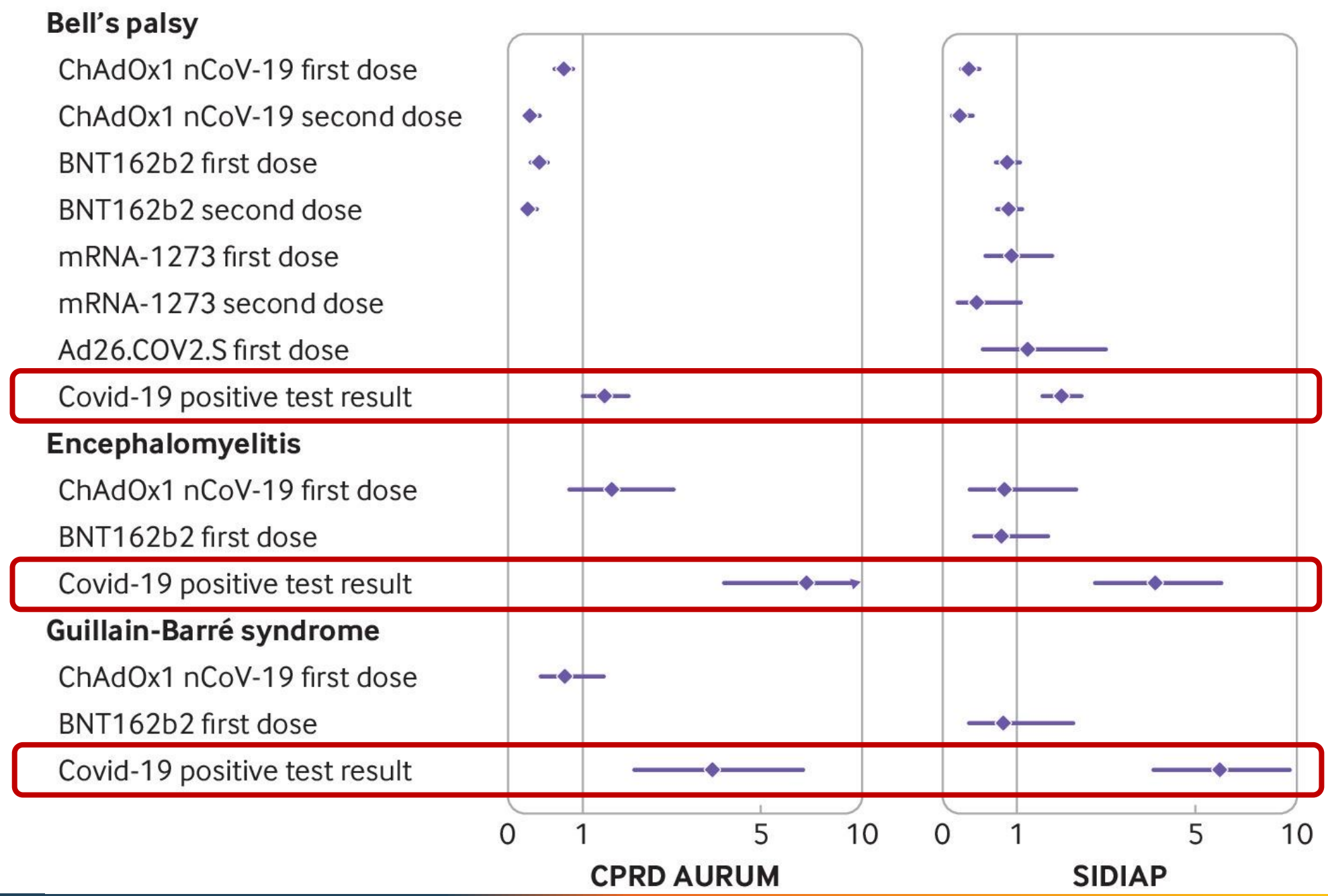
Guillain-Barré syndrome



Encephalomyelitis

NDORMS
NUFFIELD DEPARTMENT OF ORTHOPAEDICS,
UNIVERSITY OF OXFORD

Results



Standardised incidence ratios of outcomes of interest

Conclusion

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

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

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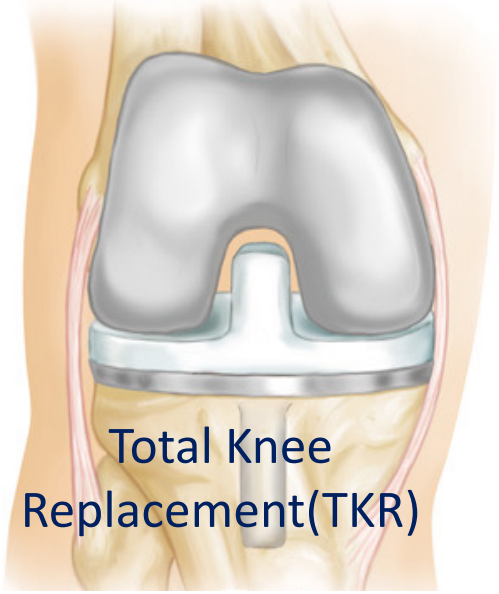
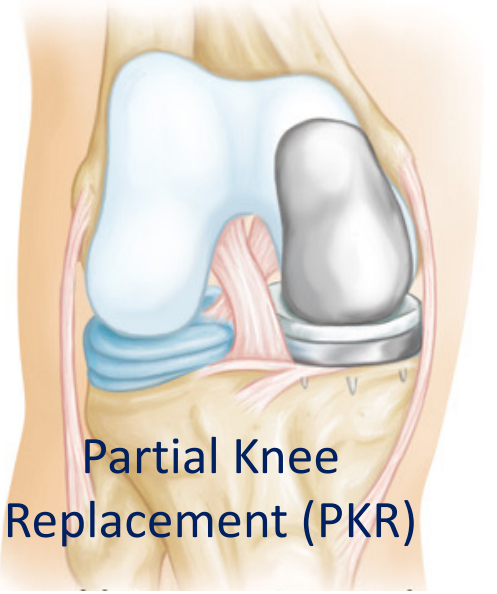
Emulating a device/surgery RCT

- The TOPKAT trial is a multi-centre, pragmatic and expertise-based surgical RCT, evaluating the clinical and cost-effectiveness of PKR with TKR

- We linked data from the UK NJR and HES to replicate the TOPKAT trial using observational data





Data sources

HES:
UK Hospital Inpatient Data

Patient-level measured covariates

Gender, age, rural index, IMD, Charlson comorbidity, other joint problem, mental health, respiratory disease, CVD, thyroid problems, foot, hip and spine pain, co-arthrosis, neurological disorders, other arthrosis, poly arthrosis & spondylosis

Up to 3y prior

Exposure/comparator eligible to TOPKAT
TKR / PKR

NJR:
UK National Joint Registry (from 2009 to 2016)

Surgeon-level measured covariate:
surgeon experience

Secondary outcomes:
Revision, mortality, 90 day risk of venous thromboembolism, MI, and joint infection

Pre and post-operative

PROMS:
Patient Reported Outcome Measures

Patient-level measured covariates:
Pre-operative EQ5D, general health, OKS

Primary outcome:
Oxford Knee Scores (OKS)

Statistical analysis: creating comparable treatment groups

- Propensity Score (PS): logistic regression on 18 patient-level covariates
  - PS matching with up to 1:5 ratio, a caliper of 0.2, and without replacement
  - Inverse probability weighting
  - PS stratification (10 strata)
  - PS adjustment

- Comparability assessed using standardized mean difference

Statistical analysis: Assessing outcome

- Primary outcome (continuous):
  - post-operative Oxford Knee Score (OKS; PROM)
  - multilevel mixed-effects generalized linear model (level 1: lead surgeon and level 2: patients) with Robust SE

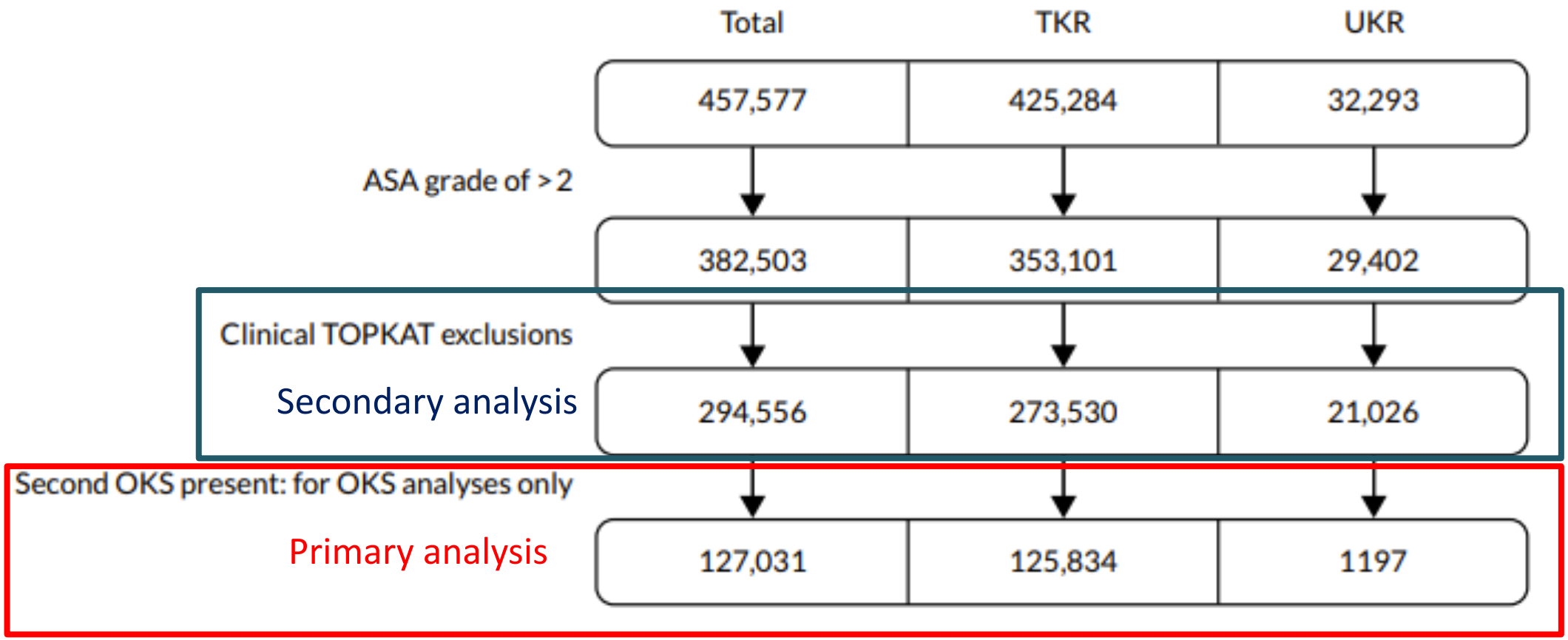
- Secondary outcomes (binary):
  - 5-years revision recorded in NJR
  - multilevel mixed-effects Poisson model (level 1: lead surgeon and level 2: patients) with Robust SE

Comparing results with TOPKAT

Criteria for results to be comparable with TOPKAT

- Chi square test p-value <0.05 (indicating statistical heterogeneity)
- Large tau^2
- Large I^2 >40% (more heterogeneity)
- Effect size overlap
- Statistical significance agreement
- Minimally clinically significant difference of <4

Participant flow diagram: Stages 1



Achieving comparable treatment groups

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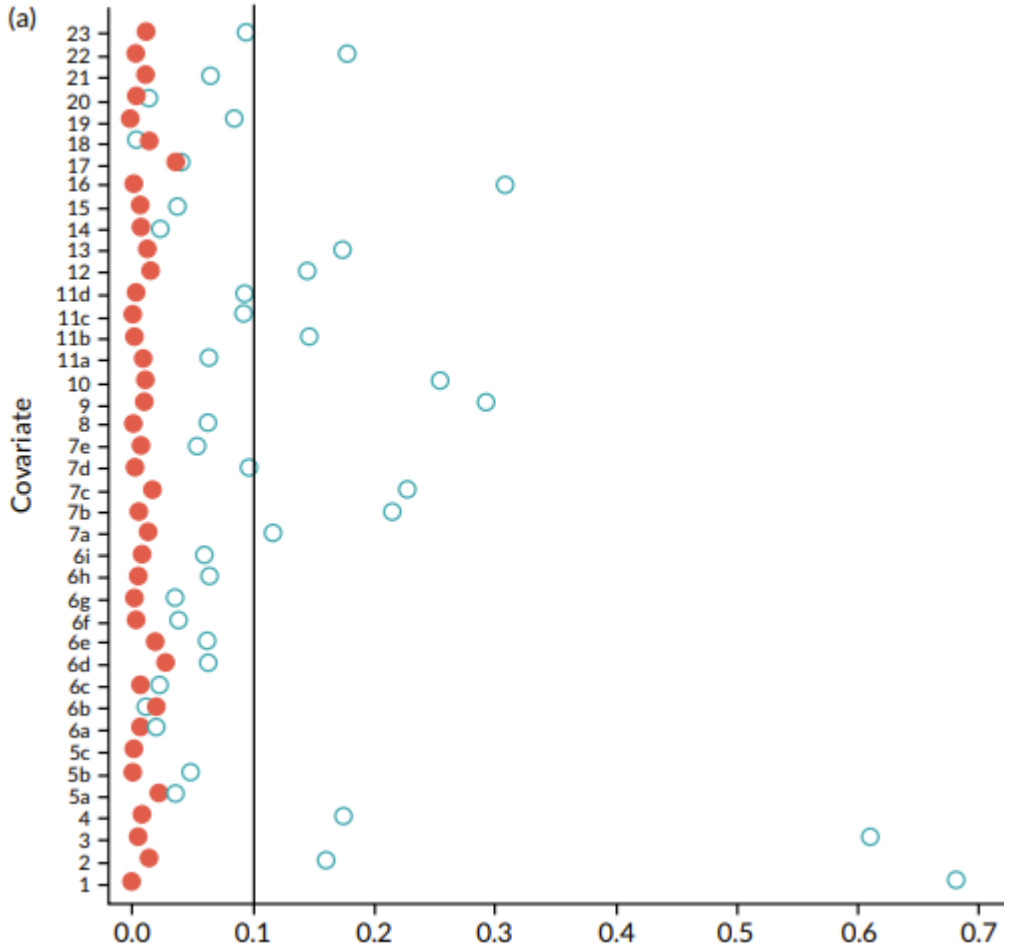
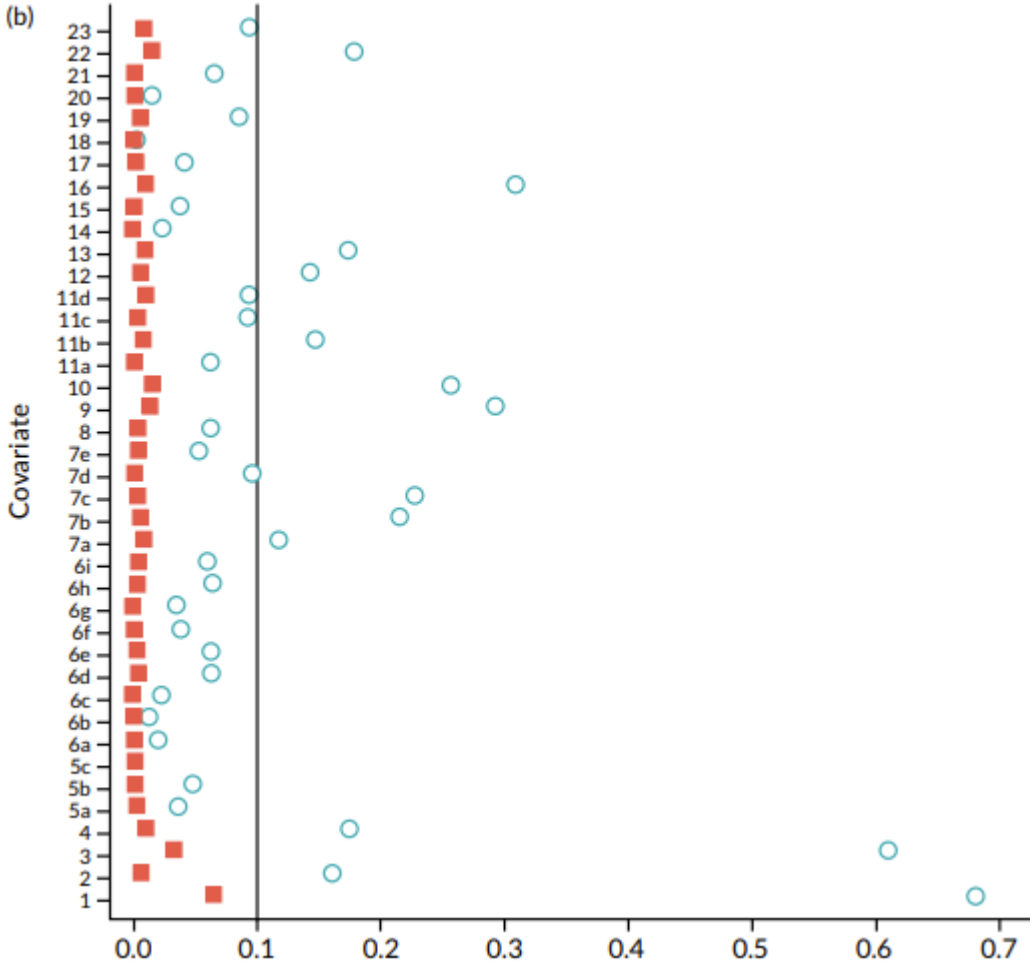
PS Matching



PS Stratification (exp)



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Achieving comparable treatment groups

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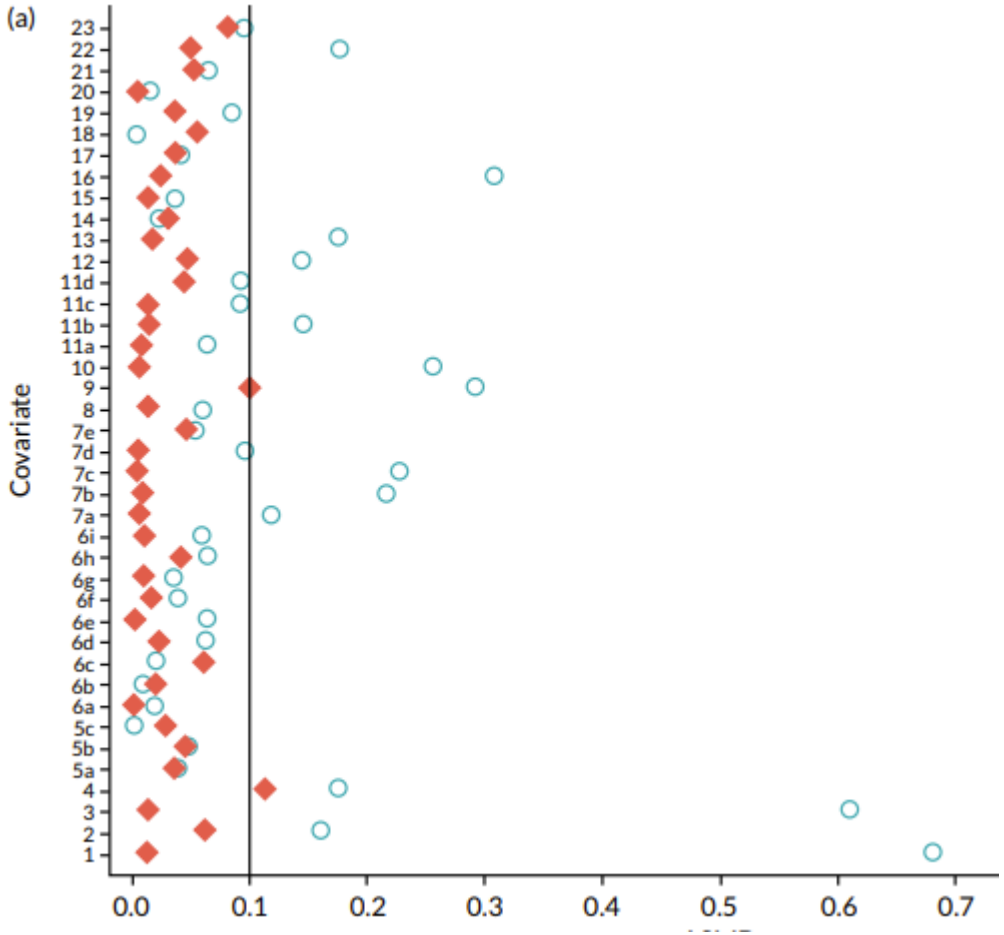
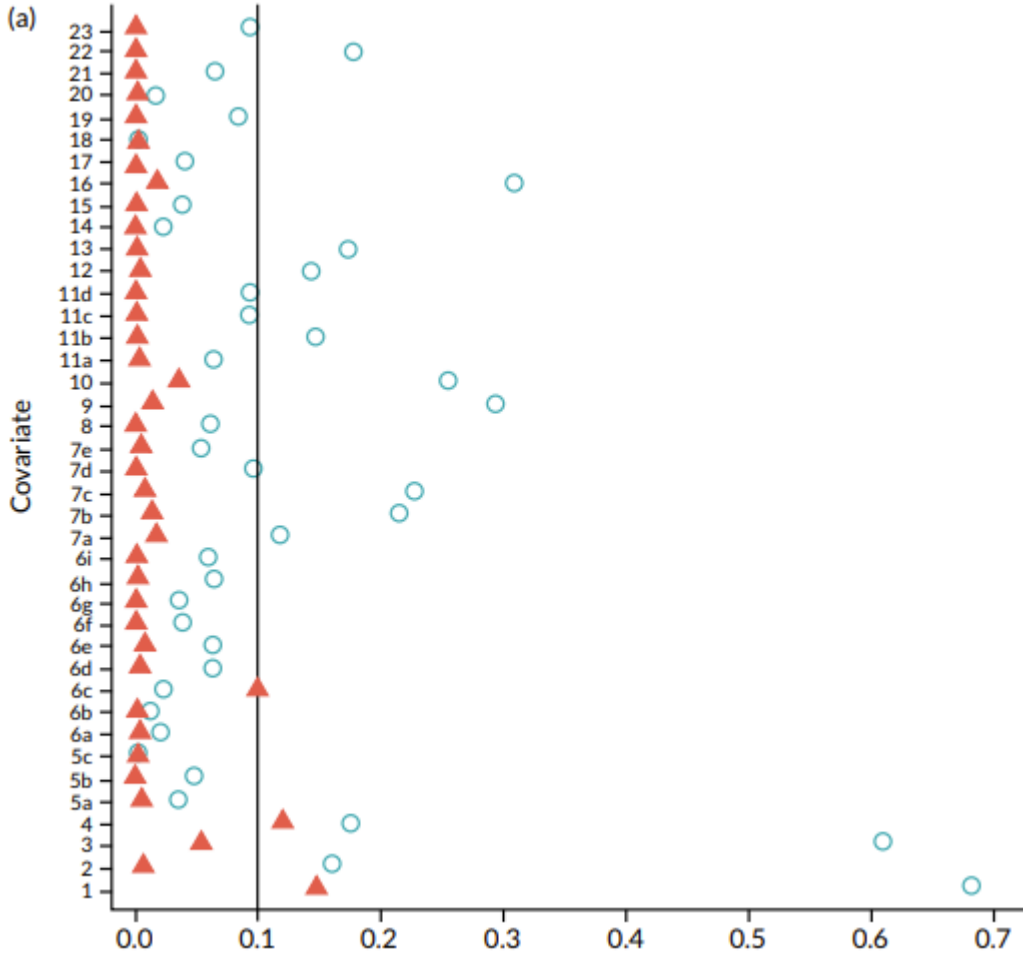
PS Weighting



PS Stratification (whole)



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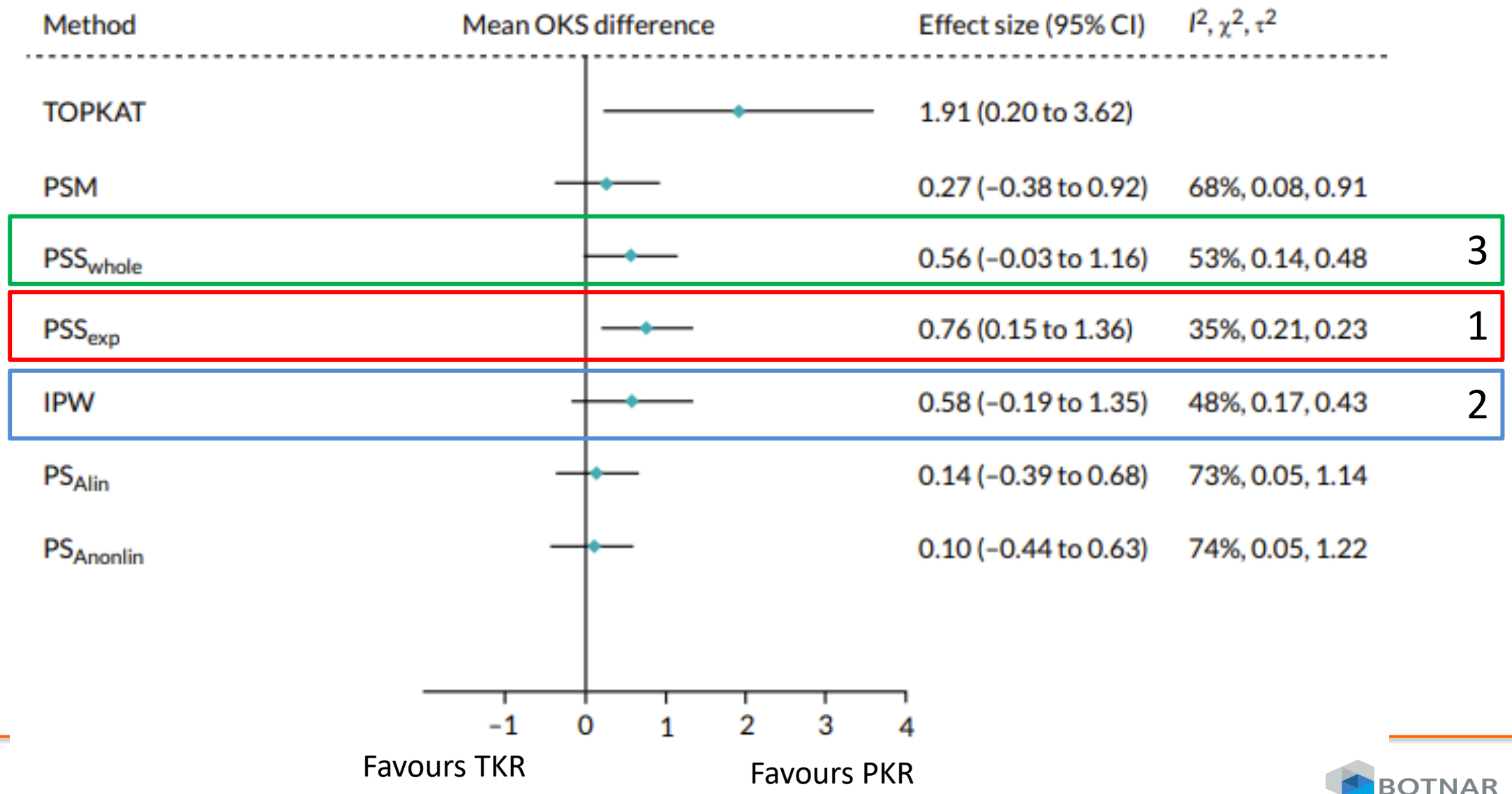
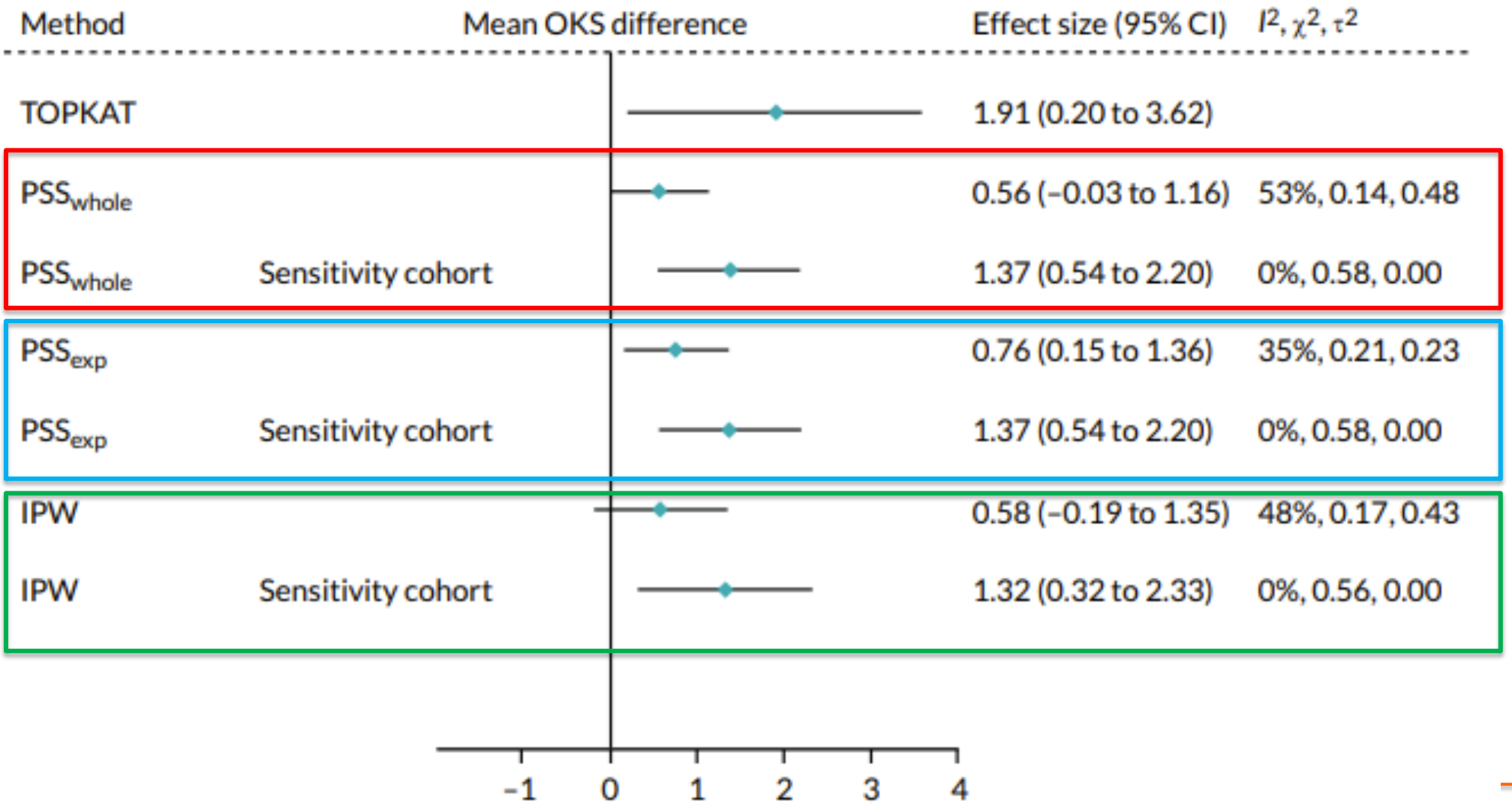
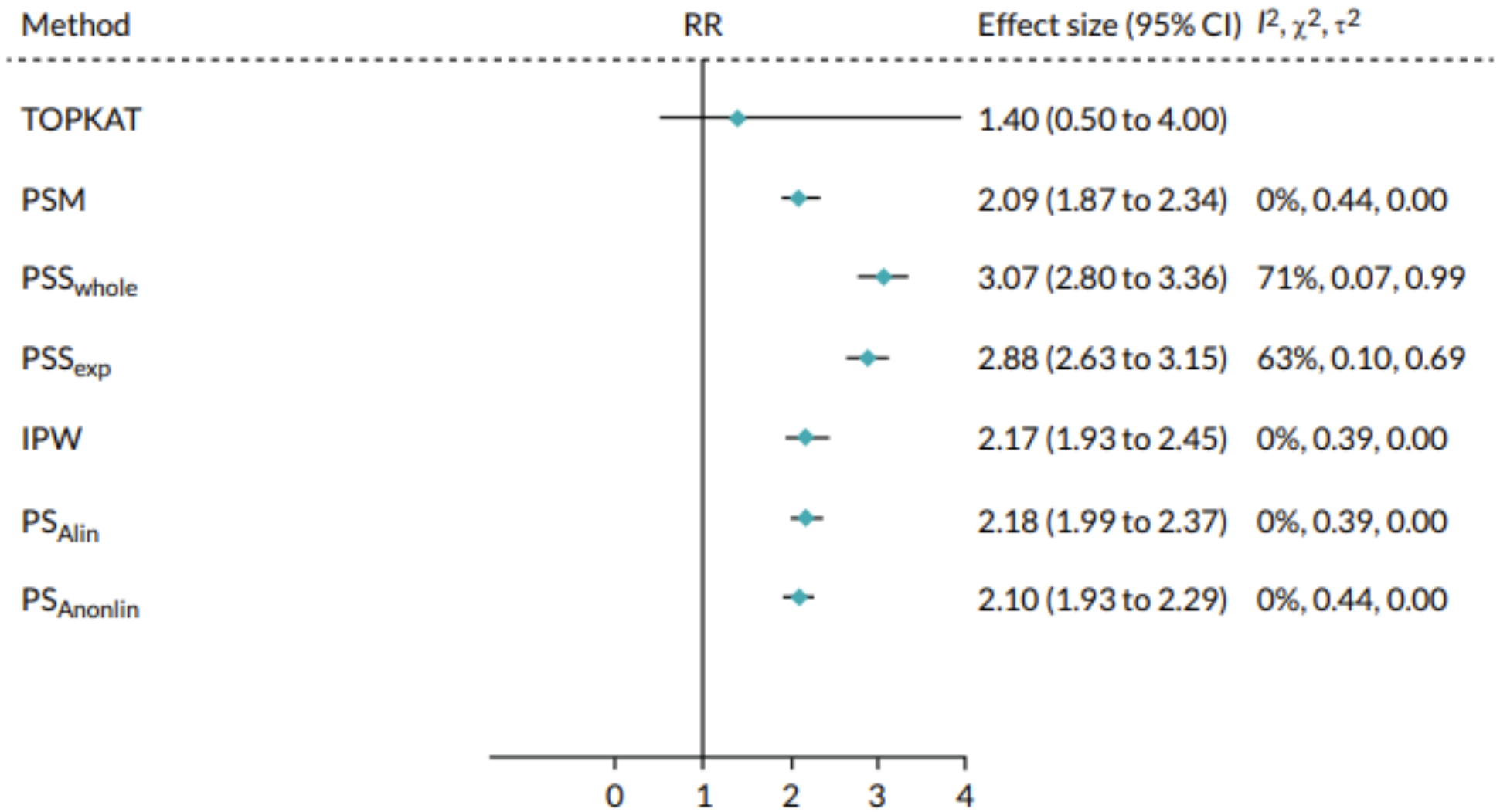
Primary outcome analysis



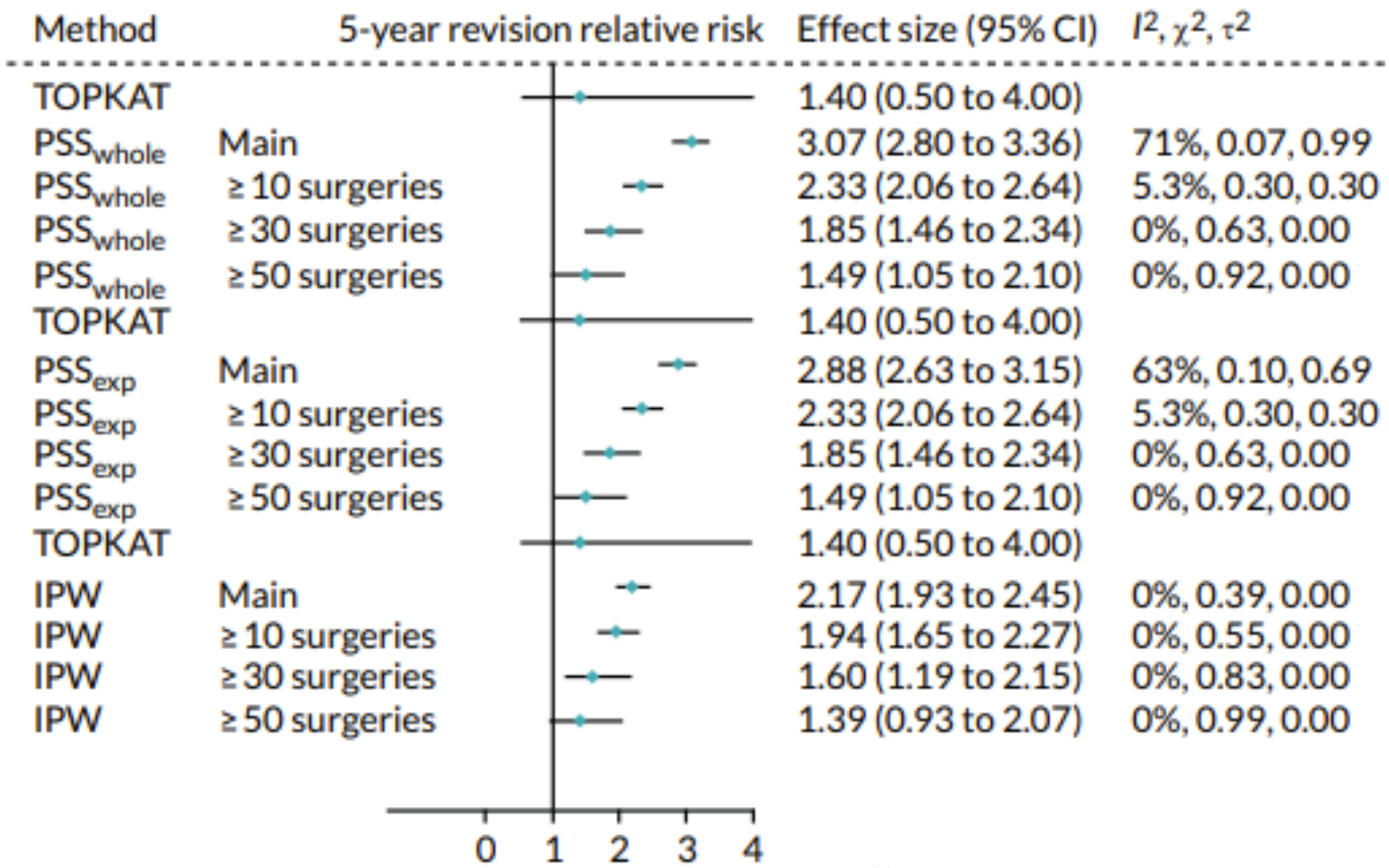
Primary outcome analysis: restricted by surgeon experience



Secondary outcome analysis: Five year revision surgery



Sensitivity analysis: impact of surgeon experience



Stage 2: Studying patients ineligible for the TOPKAT trial (ASA ≥3)

Safety data

	Revision surgery	Mortality	Venous thromboembolism	MI	Prosthetic joint infection
PSS whole	2.70 (2.15, 3.38)	0.64 (0.55, 0.75)	0.33 (0.15, 0.74)	0.73 (0.36, 1.45)	0.85 (0.33, 2.19)
PSS exp	2.70 (2.15, 3.38)	0.64 (0.55, 0.75)	0.33 (0.15, 0.74)	0.73 (0.36, 1.45)	0.85 (0.33, 2.19)
IPW	2.60 (1.94, 3.47)	0.83 (0.67, 1.03)	0.39 (0.16, 0.96)	0.73 (0.36, 1.45)	0.55 (0.18, 1.71)

Conclusions

- We demonstrate the usefulness of linking registry data to other routinely collected datasets, including EMR, HRQoL, mortality, and hospital claims

- By doing this, we could account for more and more granular information on confounders, both at the patient and surgeon/hospital level

- All PS methods replicated the TOPKAT trial findings after restricting to eligible (experienced) surgeons

Conclusions

- Observational studies and RCTs are mutually complementary in evaluating effectiveness and safety

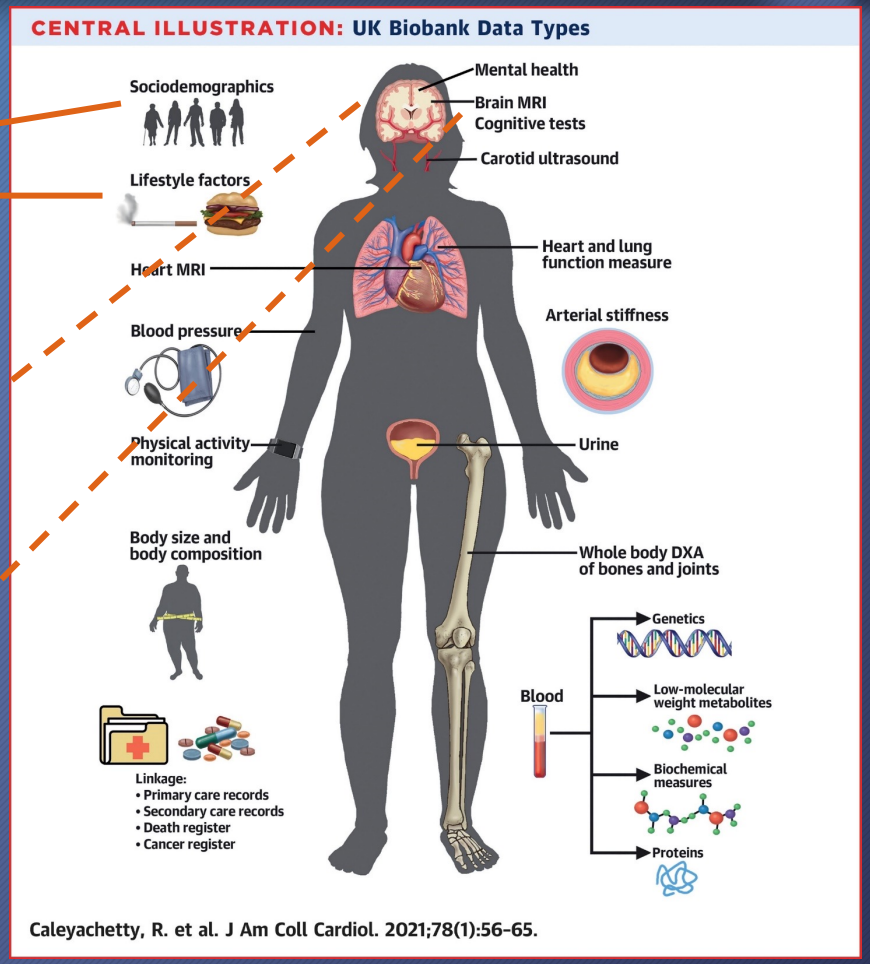
- Here, our study was able to quantify effectiveness and safety of PKR in patients who were ineligible for the TOPKAT trial:
  - PKR was more effective and safer than TKR for patients with severe comorbidity and should be considered the first option for suitable patients

AGENDA

- Real world data sources and linkage
- Interoperability: centralised vs federated
- From data standardisation to standardised analytics
- Use case 1: vaccine and public health data for COVID19
- Use case 2: registries and EMR/claims for trial emulation
- Use case 3: HRQoL for HTA
- Use case 4: UKBB and pharmacogenomics

UK Biobank: The ultimate linkage
(i) Baseline visit and survey

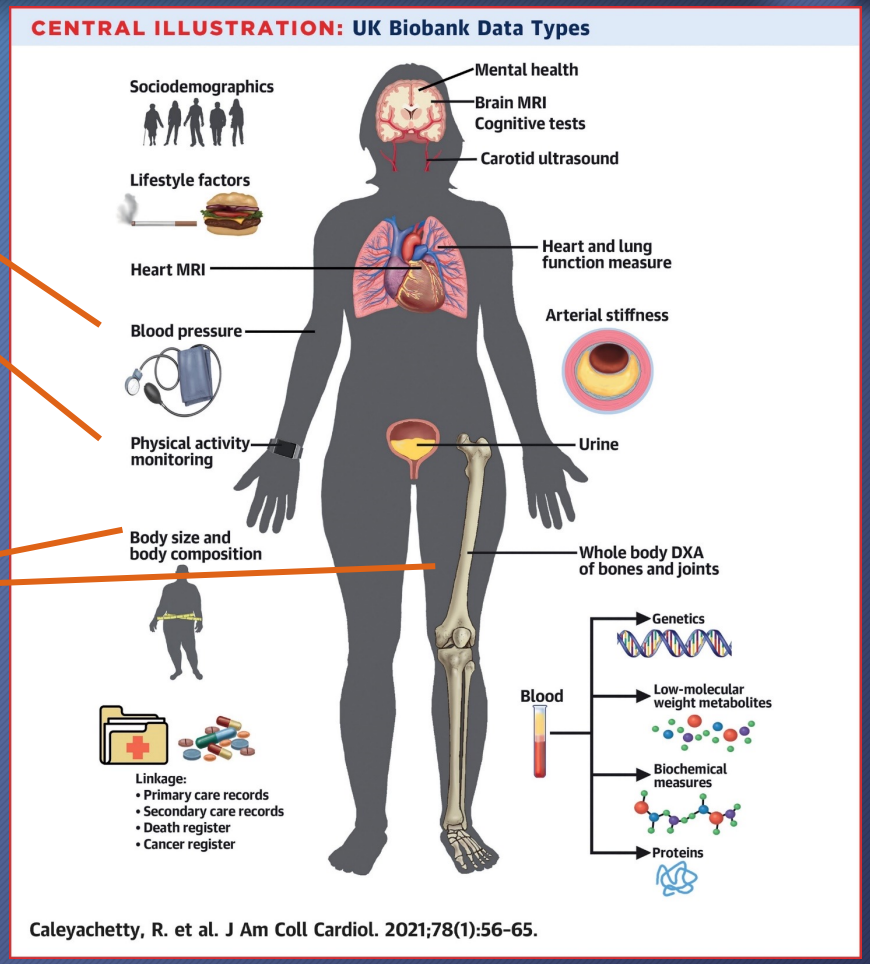
Touchscreen questionnaire and computer-assisted verbal interview	
Sociodemographic	Ethnicity, education, employment, household information, Townsend deprivation index (socioeconomic status)
Lifestyle	Smoking; alcohol consumption; physical activity; diet; sleep
Environmental factors	Current address; current (or last) occupation; domestic heating and cooking fuel; housing; means of travel; shift work; mobile phone use; sun exposure
Early life factors	Birthplace, birth weight, breastfed, childhood body size and height, maternal smoking, handedness, adopted, and part of multiple birth
Family history	Illnesses of father/mother/siblings, age of parents, age parents died, and number of siblings
Psychosocial factors	Social support, bipolar/major depression, anxiety, nerves, psychological traits, and mood
Health and medical history	Medical conditions, medications, operations, cancer screening, pain, oral health, eyesight, hearing, and general health
Sex-specific factors	Male specific—first facial hair, age voice broke, hair/balding pattern, children fathered; female specific—hormone replacement therapy, contraception, pregnancy, menstruation, menopause, and cervical test
Cognitive function	Pairs matching; reaction time; prospective memory[a]; fluid intelligence[a]; numeric memory[b]
Hearing tests	Speech reception threshold[a]



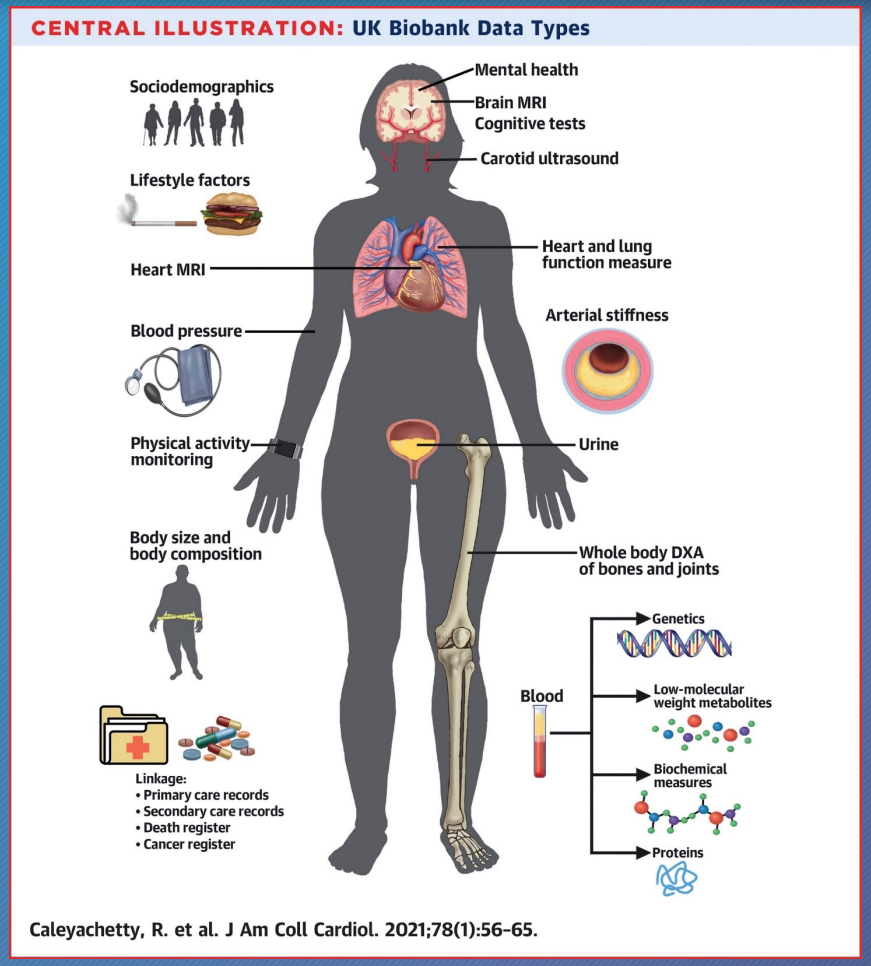
UK Biobank: The ultimate linkage
(ii) Measurements / anthropometrics

Physical measures	
Blood pressure and heart rate	Two automated measures taken 1 min apart
Arterial stiffness[c]	Pulse wave velocity using infrared sensor at the finger
Grip strength	Right- and left-hand isometric grip strength

Anthropometrics	Standing/sitting height, waist/hip circumference, weight body mass index, and whole-body bioimpedance measures



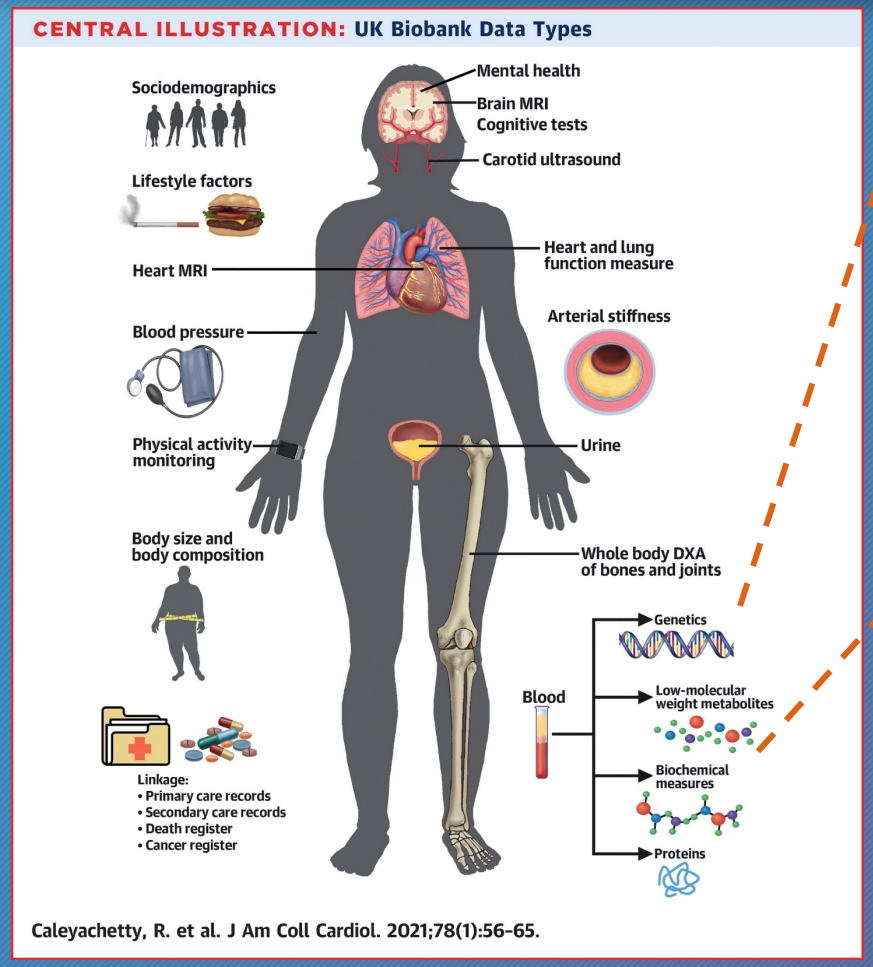
UK Biobank: The ultimate linkage
(iii) Imaging



Imaging data

- MR images of the brain
- MR images of the heart
- MR images of the body
- Full body DXA scans
- Carotid ultrasound images

UK Biobank: The ultimate linkage
(iv) Biomarkers and Genetics

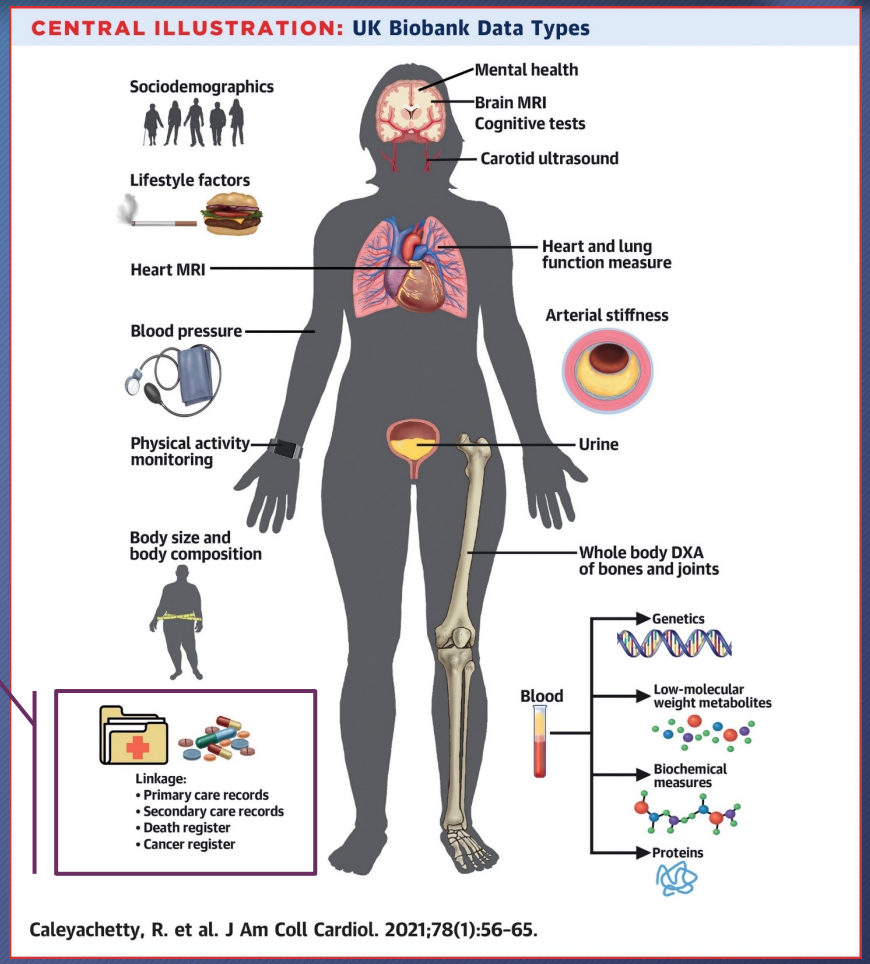


Data Type	Details	Date of Data Acquisition	Data First Available
Genetic			
Genotype	Genome-wide genotyping was performed on all UK Biobank participants using the UK Biobank Axiom Array. Approximately 850,000 variants were directly measured, with >90 million variants imputed using the Haplotype Reference Consortium and UK10K + 1000 Genomes reference panels.	2013–2015	Q3 2017
Whole-exome sequencing	Exome sequencing for 50,000 participants was undertaken by Regeneron and GlaxoSmithKline. A further consortium (comprising Regeneron, AbbVie, Alnylam Pharmaceuticals, AstraZeneca, Biogen, Pfizer, Takeda and Bristol Myers Squibb) are undertaking exome sequencing on the remaining 450,000 participants.	2017–2021	Q1 2019 (50,000 participants) Q4 2020 (200,000 participants)
Whole-genome sequencing	The Medical Research Council provided funding for a pilot project (the Vanguard) to perform whole-genome sequencing on 50,000 participants, undertaken by the Wellcome Sanger Institute, Cambridge. A consortium of government (UK Research and Innovation [UKRI]), industry (Amgen, AstraZeneca, GlaxoSmithKline, and Johnson & Johnson) and charity (The Wellcome Trust) have funded whole-genome sequencing of the remaining 450,000 participants.	2020–	Expected Q3 2021 (200,000 participants)
Biomarkers			
Telomere length	Leucocyte telomere length measured in all 500,000 participants.	2015–2020	Expected Q1 2021
Biochemical measures	34 biomarkers assayed in the plasma, serum, red blood cells, and urine samples. Chosen based on their scientific relevance for studying a wide range of diseases, and included established risk factors for disease (eg, lipids for vascular disease, sex hormones for cancer), diagnostic measures (eg, HbA_{1c} for diabetes and rheumatoid factor for arthritis) or markers of phenotypes that were not otherwise well assessed (eg, renal and liver function).	2006–2010 2012–2013	Urinary biomarkers Q4 2016 Blood biomarkers Q1 2019
Plasma metabolites	Nightingale Health: NMR-metabolomics assay from blood samples collected at baseline assessment and at the first repeat assessment visit for all 500,000 participants. The platform measures over 200 metabolites, which will provide detailed data on circulating lipids, lipoprotein subclasses, fatty acid composition and various other low-molecular metabolites.	2020–	Expected Q1 2021 (120,000 participants)
Plasma proteins	Measurement of 1,500 plasma proteins using Olink's assay in 50,000 participants. Study funded by an industrial consortium including Amgen, AstraZeneca, Biogen, Bristol Myers Squibb, Genentech (a member of the Roche Group), GlaxoSmithKline (GSK), the Janssen Pharmaceutical Companies of Johnson & Johnson, Pfizer Inc, Regeneron and Takeda Pharmaceutical Co. Ltd.	2021–	Pending

UK Biobank: The ultimate linkage
(v) Prospective linked data collection

Linkage to routinely health databases

- ✓ Primary care
- ✓ Secondary care / Hospital admissions
- ✓ Cancer register
- ✓ Death register
- ✓ COVID-19 tests and results (PHE-UKHSA)



Pharmacogenomics:
From promise to reality

EHDEN
EUROPEAN HEALTH DATA & EVIDENCE NETWORK

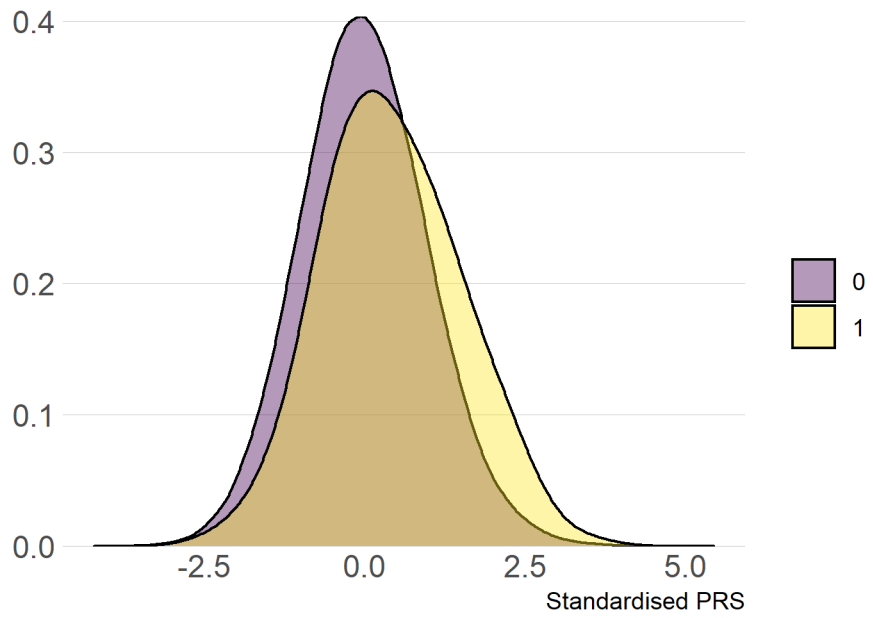
jth journal of thrombosis and haemostasis®

Genetic risk and incident venous thromboembolism in middle-aged and older adults following COVID-19 vaccination

Junqing Xie, Albert Prats-Uribe, Maria Gordillo-Marañón, Victoria Y. Strauss, Dipender Gill, Daniel Prieto-Alhambra

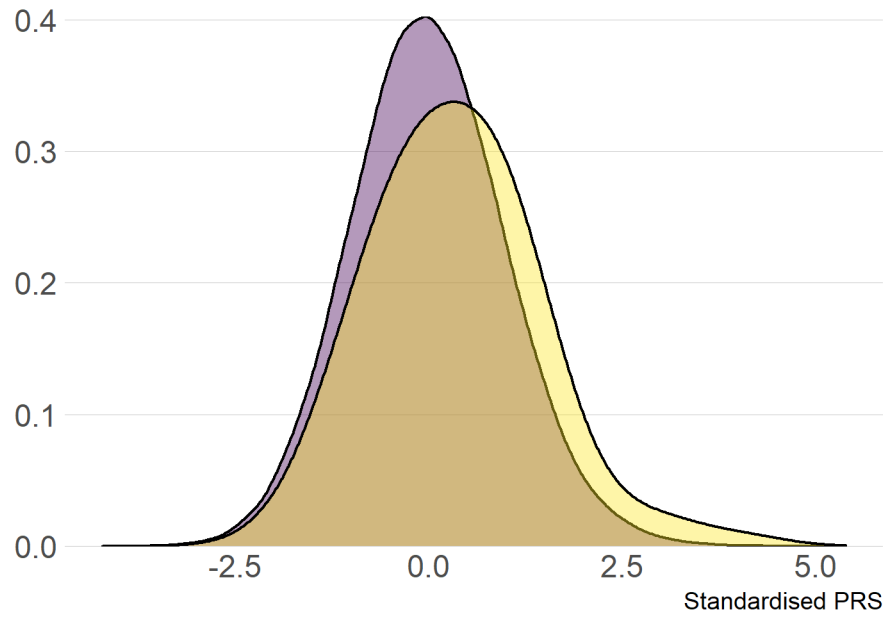
Genetic risk score (PRS) for VTE in UKBB

2019 cases (whole UK Biobank)



446614 *UKBB people survived in 2019-01-01*
727 *cases occurred in the year 2019*

Post vaccination cases

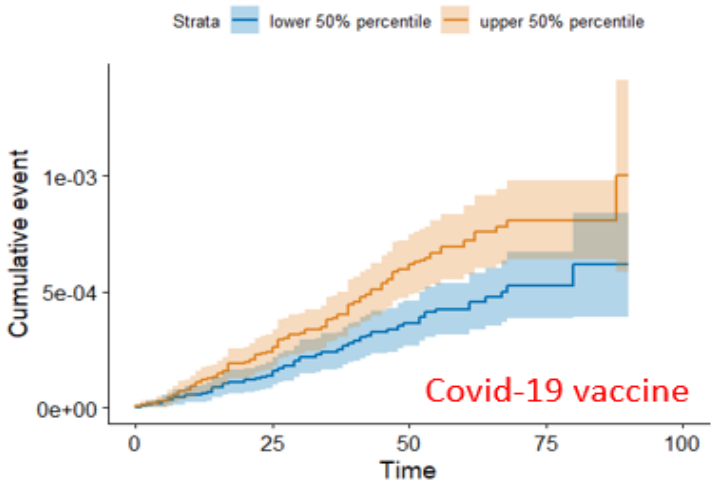


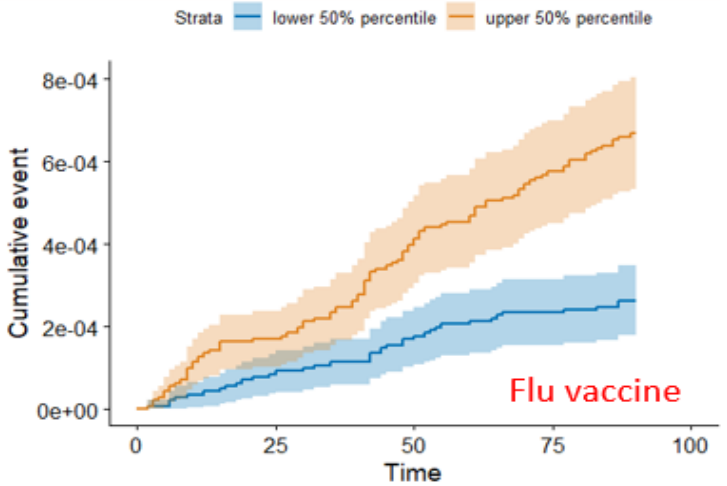
354897 *UKBB people vaccinated with 1-dose end march*
80 *cases occurred on the first up to 28 d after vaccination*

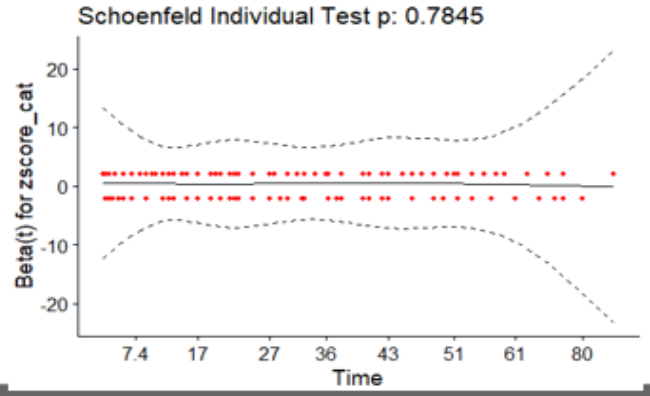
Hazard ratios for incident VTE events following Covid-19 and influenza vaccine

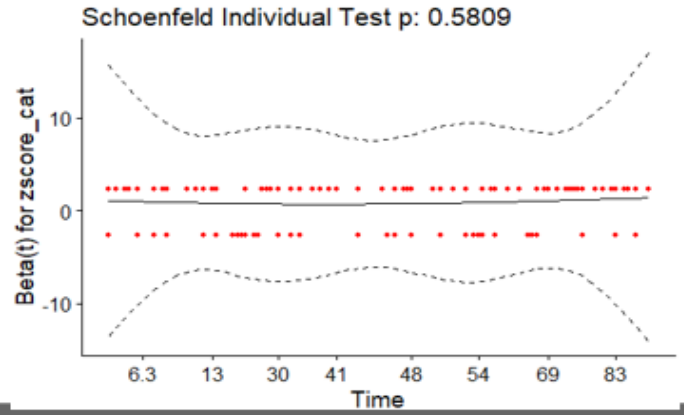
EMIS + TPP

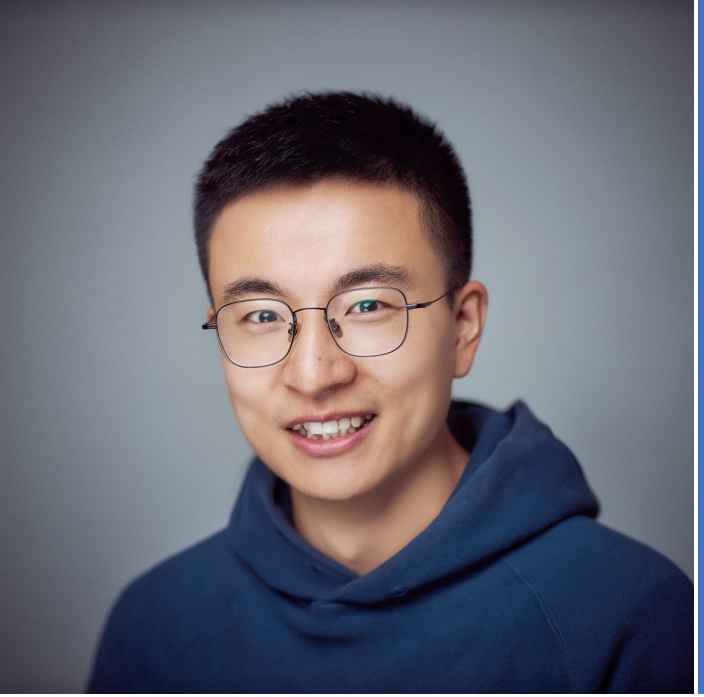
Follow-up periods	N	Cases	HRs (continuous)
Entire vaccinated cohort			Per SD increase
28 days (Covid-19 vaccine)	354879	80	1.37 (1.11 – 1.70)*
28 days (Flu vaccine)	281623	39	1.36 (1.01 – 1.85)*
90 days (Covid-19 vaccine)	354879	168	1.41 (1.21 – 1.63)*
90 days (Flu vaccine)	281623	131	1.57 (1.33 – 1.85)*











Vaccination reduces post-COVID *thromboembolic complications*

Research

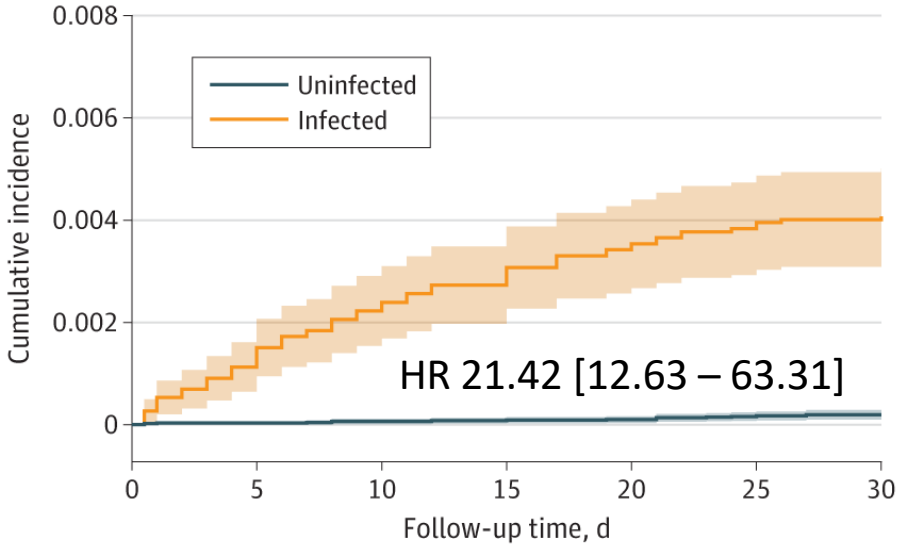
JAMA Internal Medicine | Original Investigation

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; YunHe 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)

A All participants



No. at risk

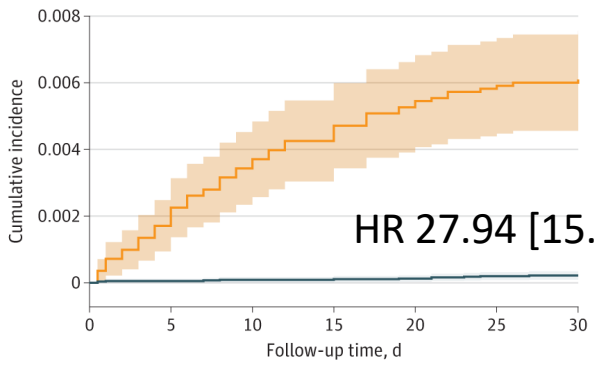
Uninfected	93 179	90 971	89 143	87 469	85 750	83 103	80 179
Infected	18 818	18 318	17 875	17 465	17 079	16 539	16 078

Cumulative No. of events

Uninfected	0	3	6	8	9	15	17
Infected	0	28	44	56	64	71	73

B Not or partially vaccinated participants

B Not or partially vaccinated participants



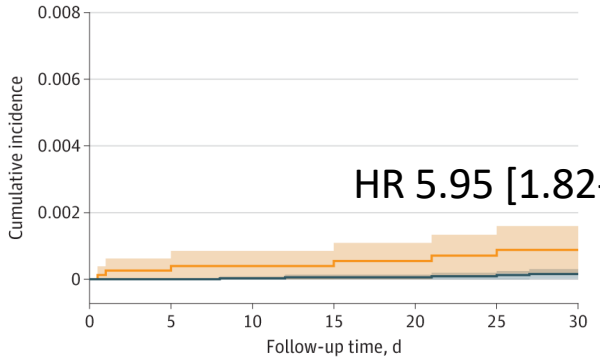
No. at risk

Uninfected	55 183	54 997	54 799	54 647	54 466	54 248	54 052
Infected	11 135	11 042	10 943	10 856	10 791	10 736	10 691

Cumulative No. of events

Uninfected	0	3	5	6	7	11	12
Infected	0	25	41	52	60	65	67

C Fully vaccinated participants



No. at risk

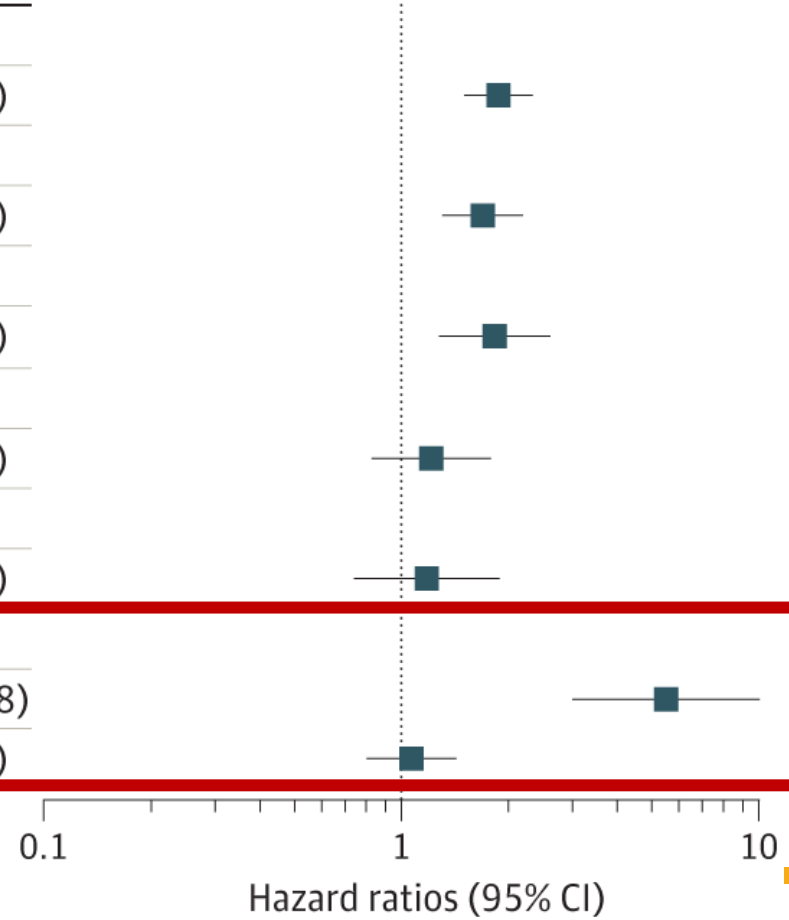
Uninfected	37 996	35 974	34 344	32 822	31 284	28 855	26 795
Infected	7683	7276	6932	6609	6288	5803	5387

Cumulative No. of events

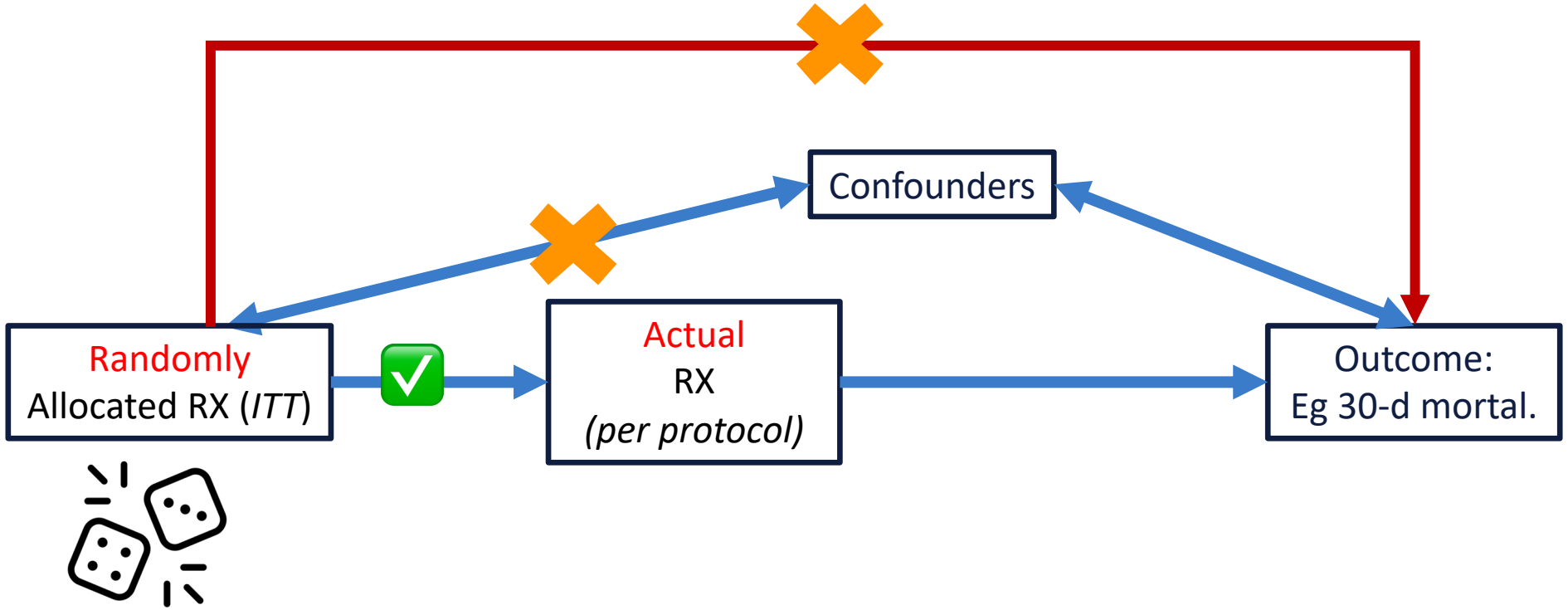
Uninfected	0	0	1	2	2	4	5
Infected	0	3	3	4	4	6	6

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

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)



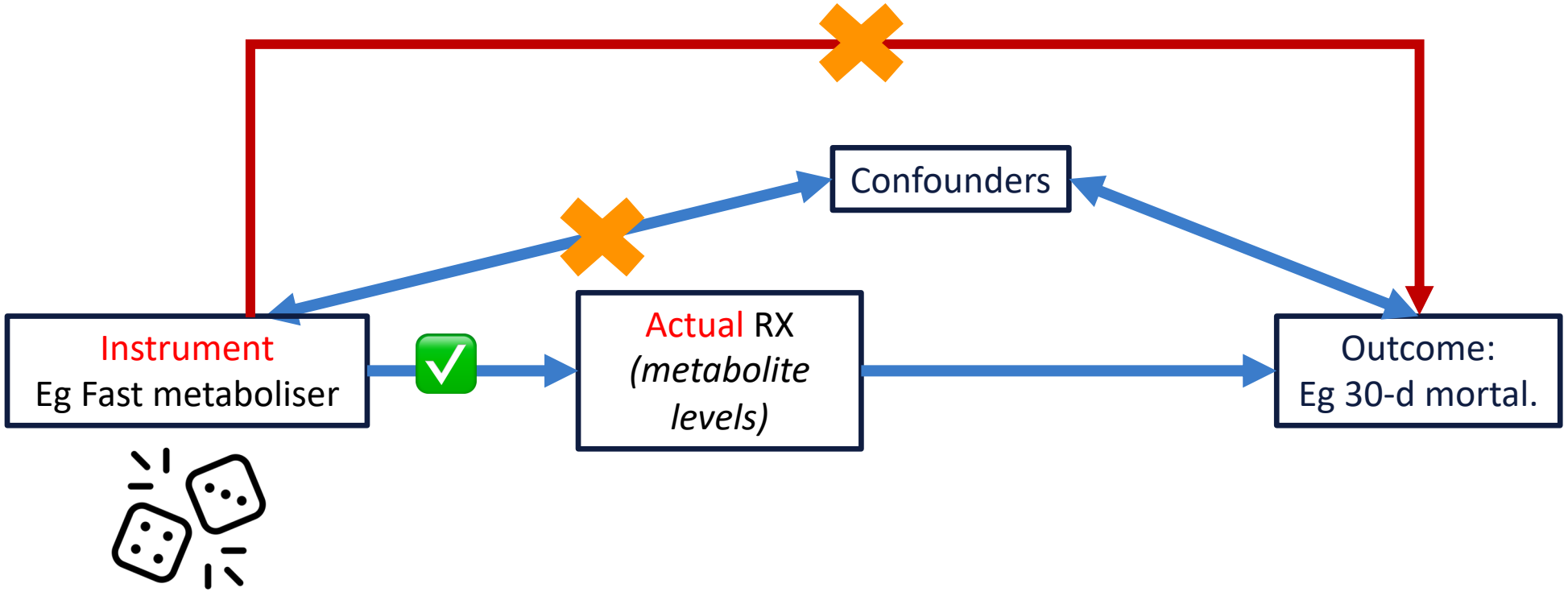
Watch this space: MR studies
Instrumental Variables vs RCT



1. Strong association with treatment (ie Rx A vs Rx B)
2. No association with outcome (other than through treatment)
3. No association with potential confounders

Watch this space: MR studies

Instrumental Variables vs RCT



1. Strong association with treatment (ie Fast metaboliser-> more drug)
2. No association with outcome (other than through treatment)
3. No association with confounders (Mendelian laws)

JAMA | Original Investigation

Association of Tramadol vs Codeine Prescription Dispensation With Mortality and Other Adverse Clinical Outcomes

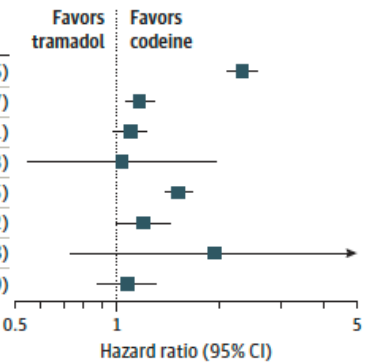
Junqing Xie, BSMed, MSc; Victoria Y. Strauss, PhD; Daniel Martinez-Laguna, MD, PhD; Cristina Carbonell-Abella, MD, PhD; Adolfo Diez-Perez, MD, PhD; Xavier Nogues, MD, PhD; Gary S. Collins, PhD; Sara Khalid, PhD; Antonella Delmestri, PhD; Aleksandra Turkiewicz, PhD, CStat; Martin Englund, MD, PhD; Mina Tadrous, PharmD, PhD; Carlen Reyes, MD, PhD; Daniel Prieto-Alhambra, MD, PhD

Limitations

This study has several limitations. First, although tramadol and codeine have been widely indicated for managing moderate to severe pain, confounding by indication could have affected the study findings. For example, codeine is often prescribed to control coughs, and a higher prevalence of cough has been observed among patients with codeine prescription dispensation (9.1%) than among patients with tramadol prescription dispensation (6.0%) before matching. However, the

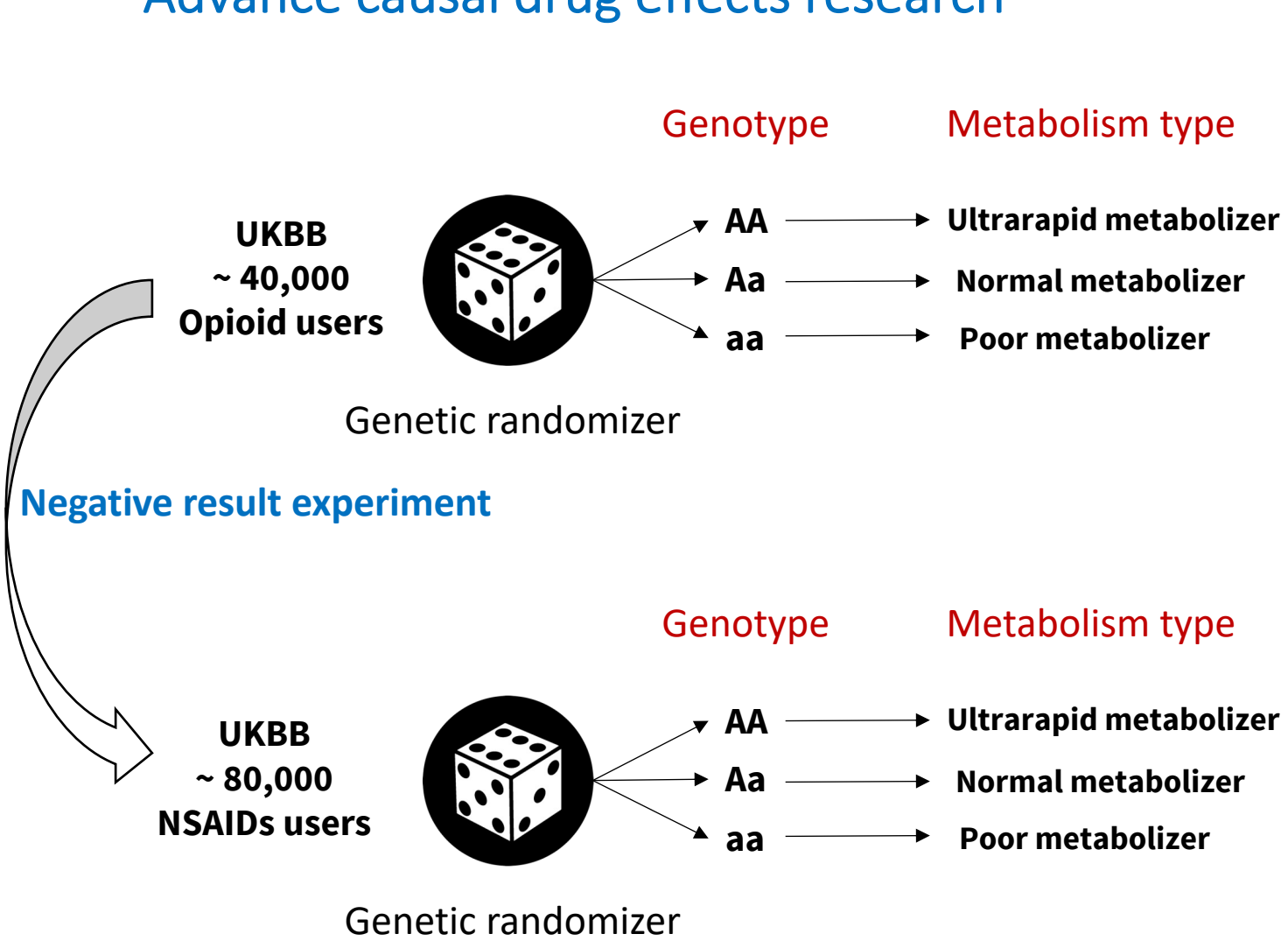
Figure 3. Event Counts, Incidence Rates, Absolute Rate Differences, and Adjusted Hazard Ratios for 8 Study Outcomes Within 1 Year in the Matched Cohort

	Tramadol (n = 184 480)		Codeine (n = 184 480)			
Outcome	No. of Events	Incidence rate per 1000 person-years	No. of Events	Incidence rate per 1000 person-years	Rate difference (95% CI) per 1000 person-years	Hazard ratio (95% CI)
All-cause mortality	2307	13.00	999	5.61	7.37 (6.09 to 8.78)	2.31 (2.08 to 2.56)
Cardiovascular events	1772	10.03	1536	8.67	1.36 (0.45 to 2.36)	1.15 (1.05 to 1.27)
Constipation	1234	6.98	1137	6.41	0.56 (-0.17 to 1.39)	1.08 (0.97 to 1.21)
Delirium	38	0.21	37	0.20	0.00 (-0.09 to 0.18)	1.02 (0.54 to 1.93)
Fractures	2160	12.26	1442	8.13	4.10 (3.02 to 5.29)	1.50 (1.37 to 1.65)
Falls	488	2.75	413	2.32	0.43 (-0.02 to 0.98)	1.18 (0.98 to 1.42)
Opioid abuse/dependence	23	0.12	12	0.06	0.05 (-0.01 to 0.24)	1.91 (0.72 to 5.08)
Sleep disorders	394	2.22	371	2.08	0.13 (-0.26 to 0.62)	1.06 (0.87 to 1.29)

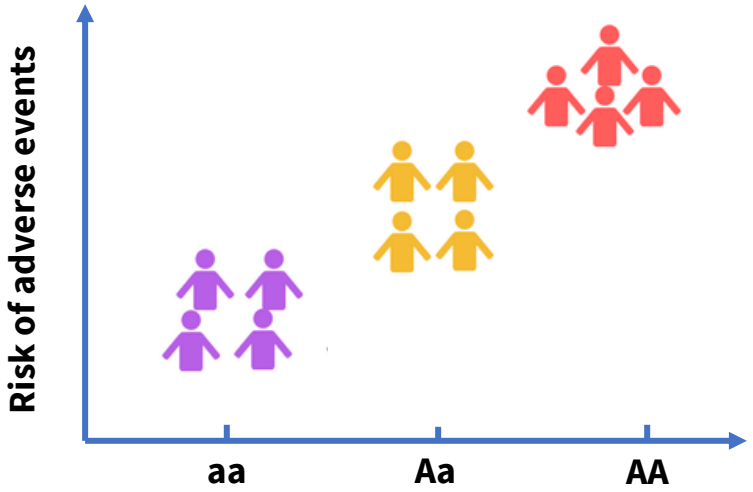


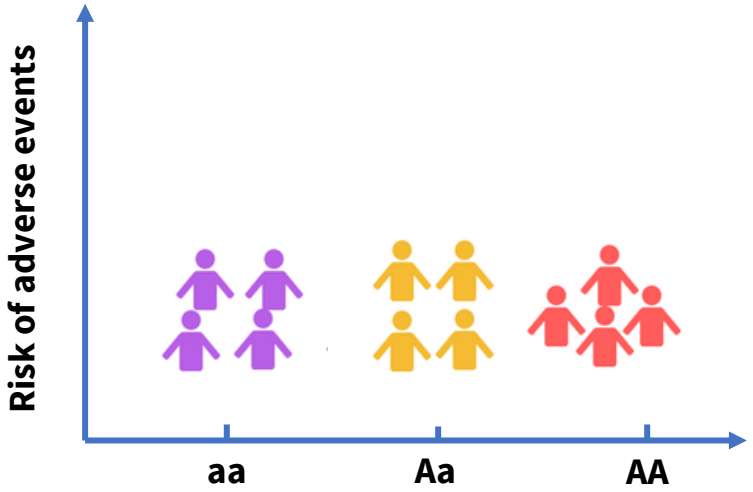
Watch this space: Mendelian Randomisation

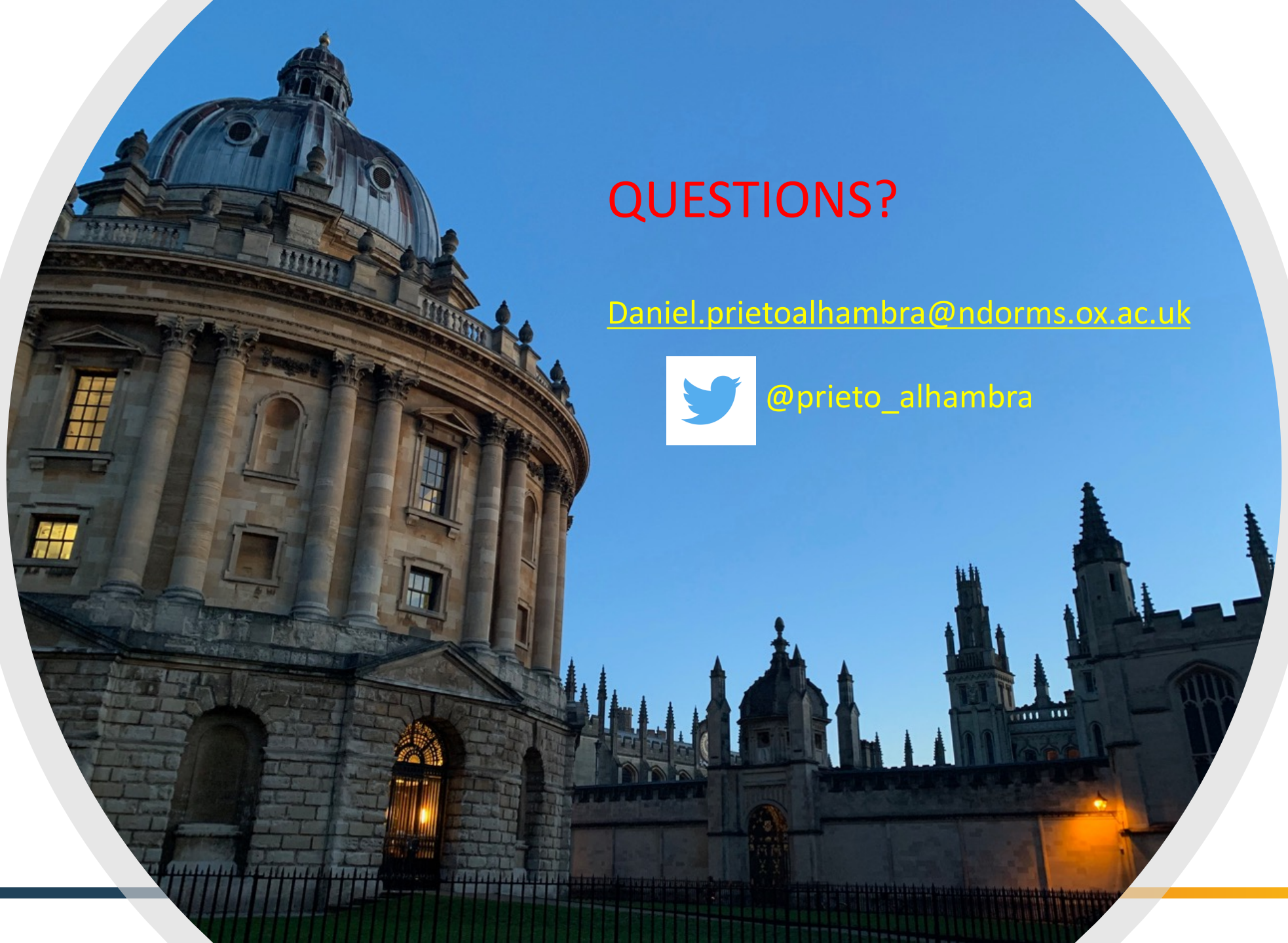
Advance causal drug effects research



E.g.: CVDs, fracture, death







QUESTIONS?

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