



EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

EHDEN and the Oxford Study-a-thon

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¹Erasmus MC The Netherlands

²Oxford University, UK



OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS



EHDEN: VISION AND MISSION



Vision

The European Health Data & Evidence Network (EHDEN) aspires to be the trusted observational research ecosystem to enable better health decisions, outcomes and care

Mission

Our mission is to provide a new paradigm for the discovery and analysis of health data in Europe, by building a large-scale, federated network of data sources standardised to a common data model



EHDEN CONSORTIUM

Innovative Medicines Initiative (IMI) Project

www.imi.europe.eu



Start date: 1 Nov 2018

End date: 30 Apr 2024

Duration: 66 months



22 partners



Almost €29 million

Universities, public bodies and research organisations



Academic
coordinator



Small to medium-sized companies



ODYSSEUS
DATA SERVICES INC

Non-for-profit organisations



EFPIA & Associated partners



EFPIA Lead



EHDEN IS ABOUT ...

FEDERATION

Creation of an EU-wide architecture for federated analyses of real world data

HARMONISATION

Harmonise more than 100 million anonymised health records to the OMOP common data model



COMMUNITY

Establish a self-sustaining open science collaboration in Europe, supporting academia, industry, regulators, payers, government, NGOs and others

OUTCOMES

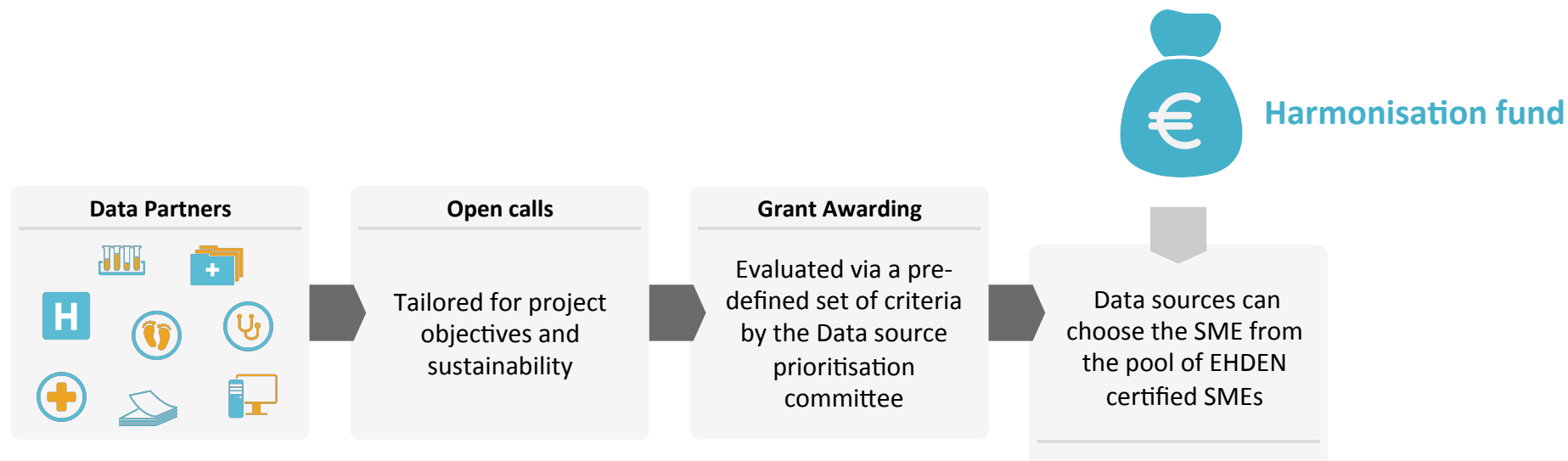
Enabling outcomes driven healthcare at a European level

EDUCATION

The establishment of an EHDEN Academy, webinars and face-to-face training sessions to train all stakeholders



CALL PROCESS FOR DATA PARTNERS AND SMALL TO MEDIUM-SIZED ENTERPRISE (SMEs)





Aim

To develop an **e-learning** environment **to train all stakeholders** in the project in the use of the tools and processes that are being adopted in EHDEN and OHDSI



Collaboration

Course development on the OMOP Common Data Model and the rich set of OHDSI tools are developed in collaboration with the **OHDSI community**



Infrastructure

The EHDEN Academy is developed in **Moodle** and is hosted in the **Amazon AWS cloud**

- Academy Pilot running with approx.50 users
- Planned to be opened to full OHDSI community end of this year!



SME CERTIFICATION

Goal: to provide the SME all the skills to perform the data standardisation task to the OMOP-CDM and train them on the installation of the analytical infrastructure

- 28 SMEs signed up from X countries
- 11 currently following the e-learning curriculum



Training

- 1) EHDEN Foundation: Introduction to IMI, EHDEN, OHDSI
- 2) OHDSI-IN-A-BOX Virtual Machine
- 3) OMOP CDM and Standardized Vocabularies
- 4) Extract, Transform and Load
- 5) Analytical Infrastructure



Certification

- Final certification will contain a two days face-to-face meeting at the Erasmus MC in Rotterdam with all SMEs in the current batch. Multiple persons per SME can participate.
- Final assessment will contain a mapping exercise and installation of the Analytical Infrastructure.

More course will be added in the EHDEN Academy in the near future.

Course overview

Course overview interface showing a list of courses with filters and sorting options.

Filters: Sort by:

Course Name	Icon/Logo
Academy Support	EHDEN Academy logo
EHDEN Foundation	EHDEN logo
Extract, Transform and Load	ETL diagram icon
OHDSI-In-A-Box Virtual Machine	OHDSI and AWS logos





OPEN CALL FOR DATA PARTNERS

- Draft Call Description has been made available on the website for public review since July. Pilot call opened Sept 1st and closed Sept 15th. Multiple Calls during the project for a total amount of 17 Million Euro financial support.
- Different types of grants (max 100.000 Euro):
 - Create new Data Transformation and Analytical Infrastructure
 - Revise Existing Data Transformation and Analytical Infrastructure
 - Inspect Completed Data Transformation and Analytical Infrastructure
- Data Partners from EU Member States and H2020 countries can apply through online application portal.

- X Data Partners showed interest in mapping
- X Applications Submitted
- X Countries
- Inpatient, Outpatient, Registry, etc.
- X number of patient records

For more information about the Open Calls see the EH DEN website: www.ehden.eu



WORK PACKAGE STRUCTURE

WP1: Evidence Workflow Development

Incorporating the use cases for supporting development and validation of the EHDEN socio-technical approach, inclusive of BD4BO projects

WP2: Outcome Driven Healthcare

Related to all activities specific to e.g. BD4BO projects outcome focus, and ICHOM standards incorporation

WP3: Personalized Medicine

Focusing on the support of outcomes/value based healthcare, inclusive of clinical prediction models, with the incorporation of 'novel' patient data

WP4: Technical Implementation

Key priority is socio-technical development of the EHDEN federated framework and relevant services

WP5: Data Workflow Implementation & Service Deployment

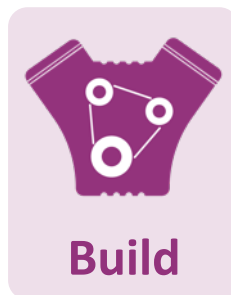
Development, oversight and evaluation of the ecosystem development from SME qualification/certification to data source engagement, OMOP CDM mapping and evaluation

WP6: Outreach and Sustainability

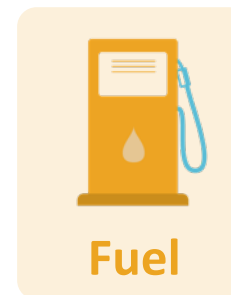
Ensuring the development of value propositions for key stakeholders, and developing the sustainable operational model for EHDEN during and post IMI phase

WP7: Project Management and Dissemination

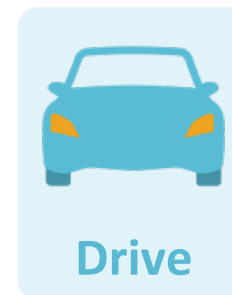
Concentrating on intra-project project management, internal communications and external dissemination, and responding to IMI deliverables



Build



Fuel



Drive



QUICK UPDATES

- Data Quality Tool Development
- Portal Development to bring together multiple tools, e.g. Database Catalogue, Arachne Central, Atlas, EHDEN Academy
- Database Catalogue containing extrinsic and intrinsic meta data and visualisation on Database and Network level (**see Forum Post**)
- QueryLibrary developments for community training (200+ queries):
<https://github.com/OHDSI/QueryLibrary>
- Tantalus vocabulary comparison tool:
<https://github.com/OHDSI/Tantalus>
- Mapping of the Article 57th Database of European Medicines Agency (X % of codes currently mapped)
- Methods Research, e.g. Heterogeneity of Treatment Effect Package: <https://github.com/OHDSI/XXXX> (see poster and Shiny App)

ADD SCREENSHOTS



EHDEN

EUROPEAN HEALTH DATA & EVIDENCE NETWORK

Oxford Study-a-thon

EHDEN and OHDSI in Action



OHDSI
OBSERVATIONAL HEALTH DATA SCIENCES AND INFORMATICS

The Oxford Study-Athon

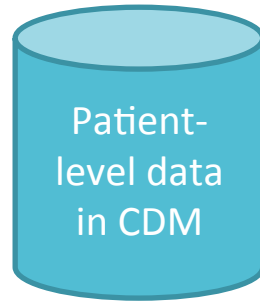
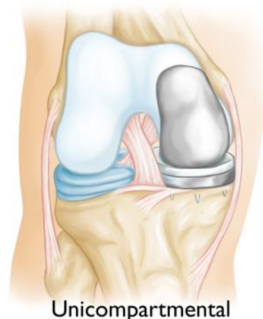
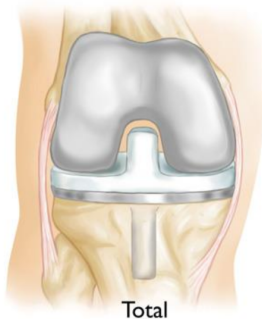
(based on true events)



Our journey with OHDSI and EHDEN to real-world useful evidence



Important
clinical
question



Data partners
standardized to
OMOP CDM:
Iqvia
Janssen



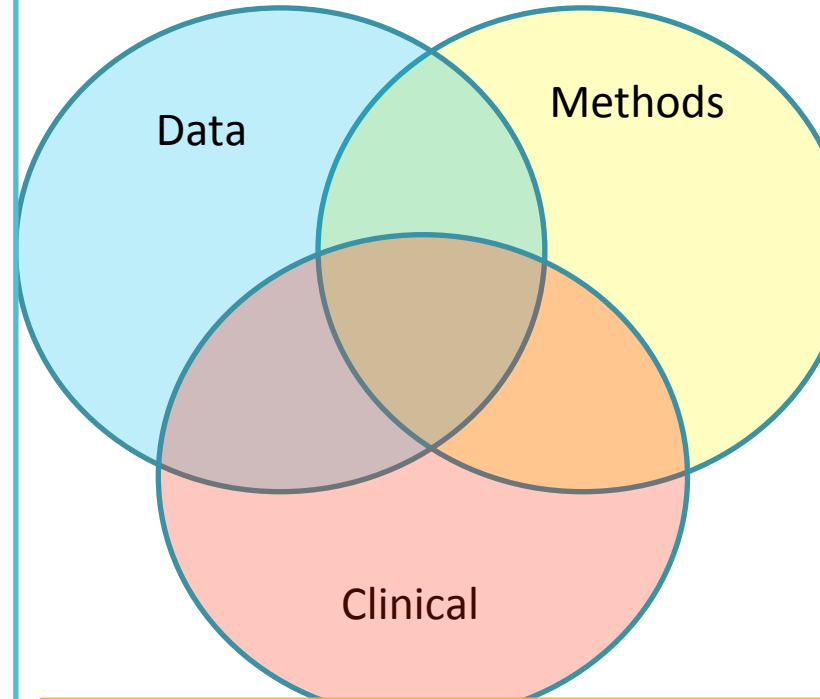
Standardized
analysis tools
from OHDSI



Valuable clinical
answers
disseminated to
medical decision-
makers

What we needed in the mix ...

Hands-on knowledge of 1+ data source/s, including its structure and content, the provenance of the underlying population and data capture process, data quality issues and temporal variability, so that you can responsibly use the data to generate reliable evidence and recognize its limitations



Hands-on knowledge in designing studies and executing statistical methods to generate aggregate summary statistics from patient-level data. Different expertise required for clinical characterization, patient-level prediction, and population-level effect estimation

Direct knowledge of the diagnosis, treatment, and management of severe knee OA, including healthcare delivery, natural history and patient prognosis

Expertise required

- Clinical knowledge in knee oa/arthroplasty?
- UK electronic health records (THIN)?
- US claims (MarketScan, Optum, PharMetrics)?
- OHDSI tools?
- R programming?
- Literature review?
- Publication writing?

Who has all of these prerequisites?

“To compare the risk of post-operative complications (infection, venous thrombo-embolism, mortality) and long-term implant revision between unicompartmental vs total knee replacement.”

What we knew before we started ...

- N = 60 acceptable quality studies
- From 1998 to 2018 (20 years of research!!)
- Reduced risk of VTE with UKR

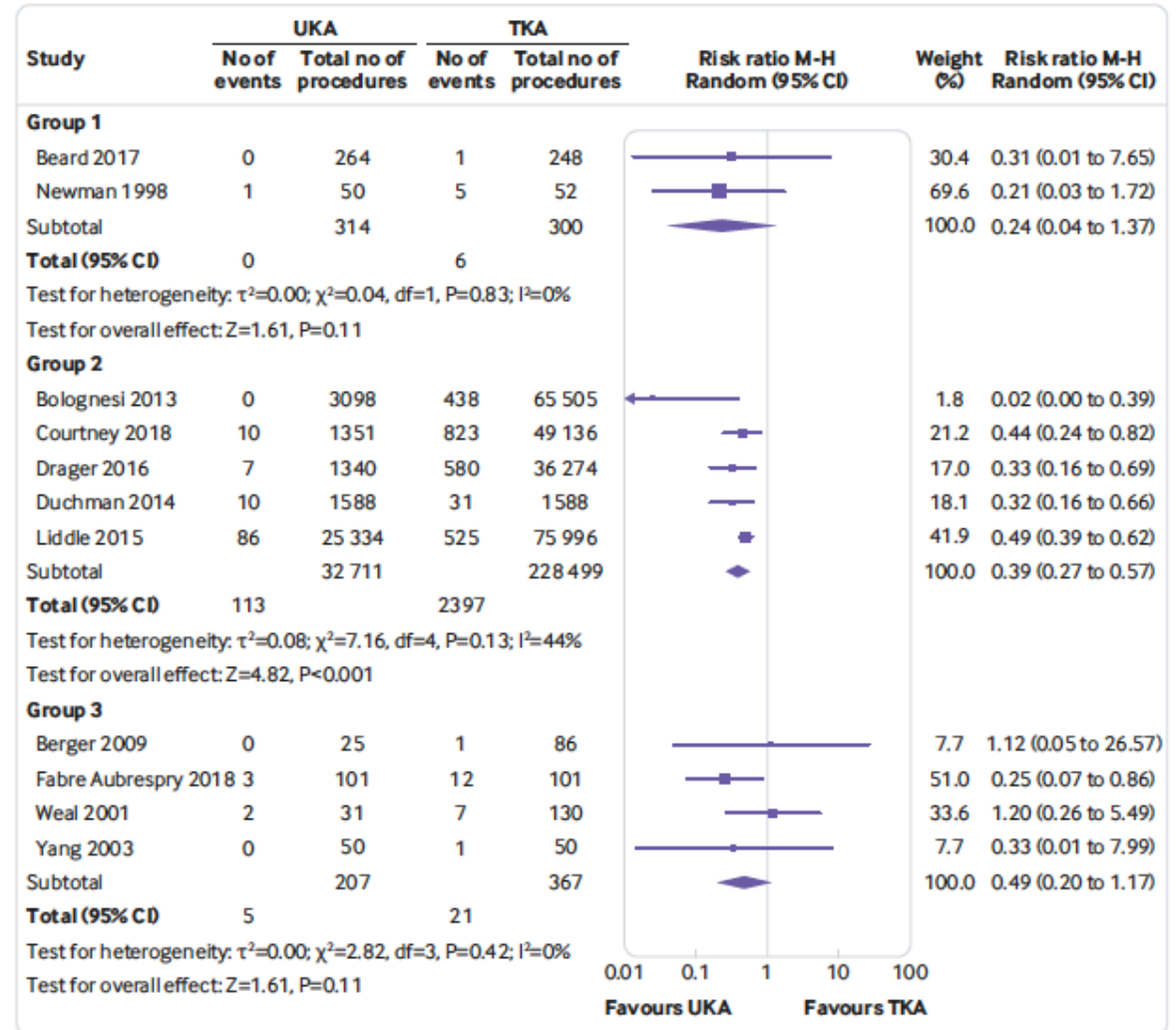


Fig 3 | Forest plot comparing risk of venous thromboembolism after unicompartmental (UKA) versus total knee replacement (TKA). Also appears in the supplementary material as supplementary figure 5. M-H=Mantel-Haenszel test

What we knew before we started (2) ...

- Possibly a reduction in post-operative mortality ...
- [although little data available on this]

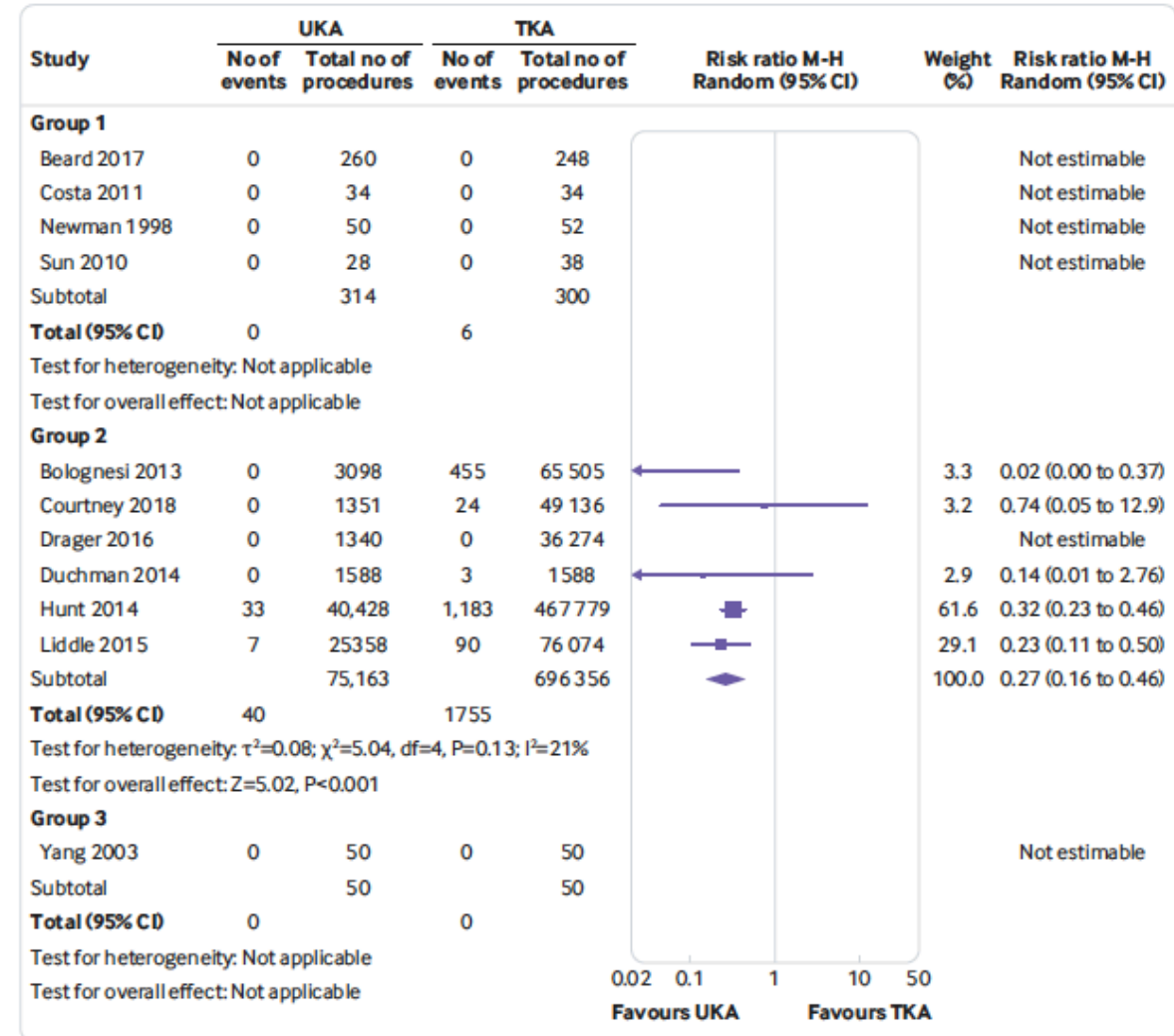


Fig 4 | Forest plot comparing risk of early mortality (at 45 days) after unicompartmental (UKA) versus total knee replacement (TKA). Also appears in the supplementary material as supplementary figure 7. M-H=Mantel-Haenszel test

What we knew before we started (3) ...

- Loads of data on pain and function and PROMs
- Most pointing towards a further improvement with UKR vs TKR

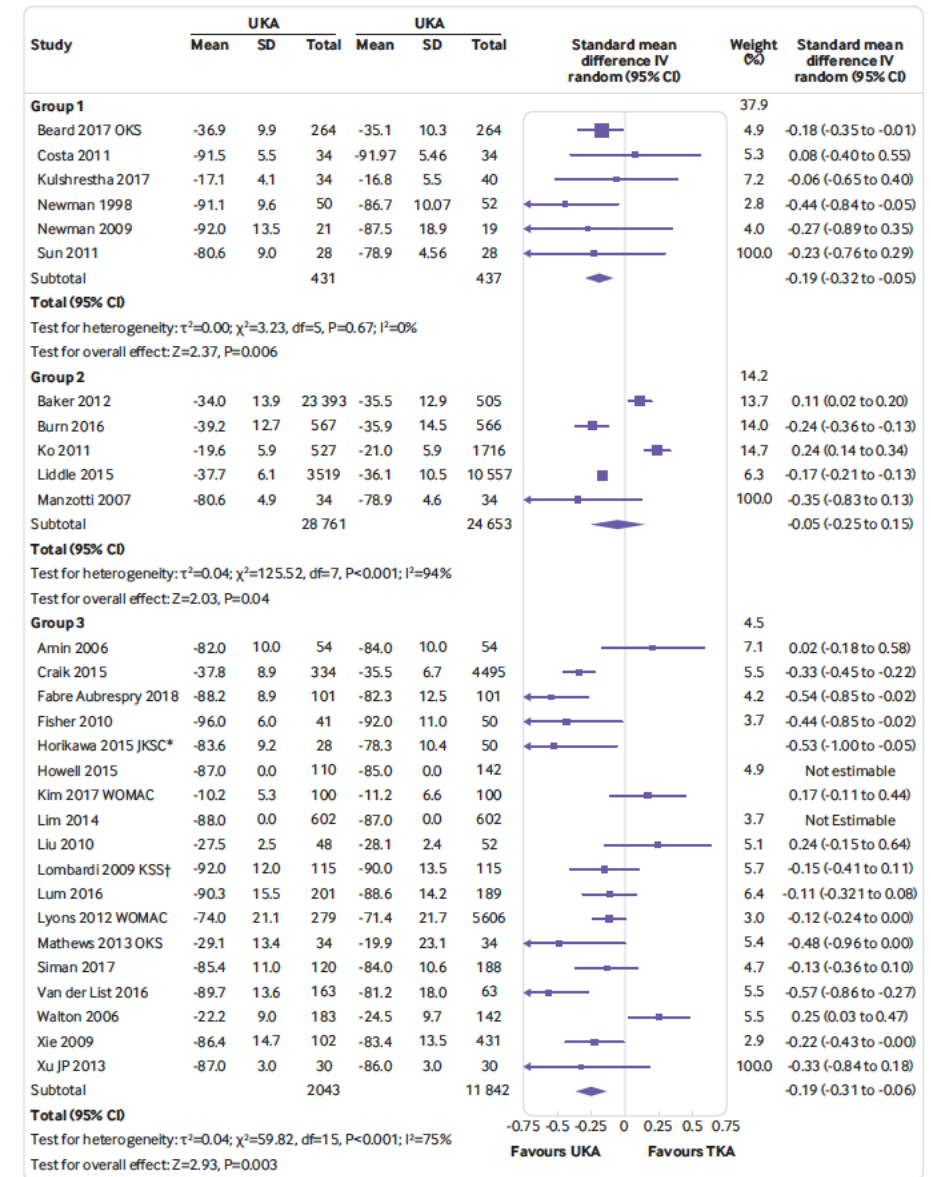


Fig 5 | Forest plot comparing combined pain and function measured using knee specific patient reported outcome measures after unicompartmental (UKA) versus total knee replacement (TKA). Also appears in the supplementary material as supplementary figure 10. IV=inverse variance weighting; OKS=Oxford knee score; JKSC=Japanese knee osteoarthritis score; WOMAC=Western Ontario McMaster Universities osteoarthritis index; KSS=Knee Society Score; JOA=Japanese orthopaedic association score

What we knew before we started (4) ...

- ... BUT
- An increase in long-term revision risk

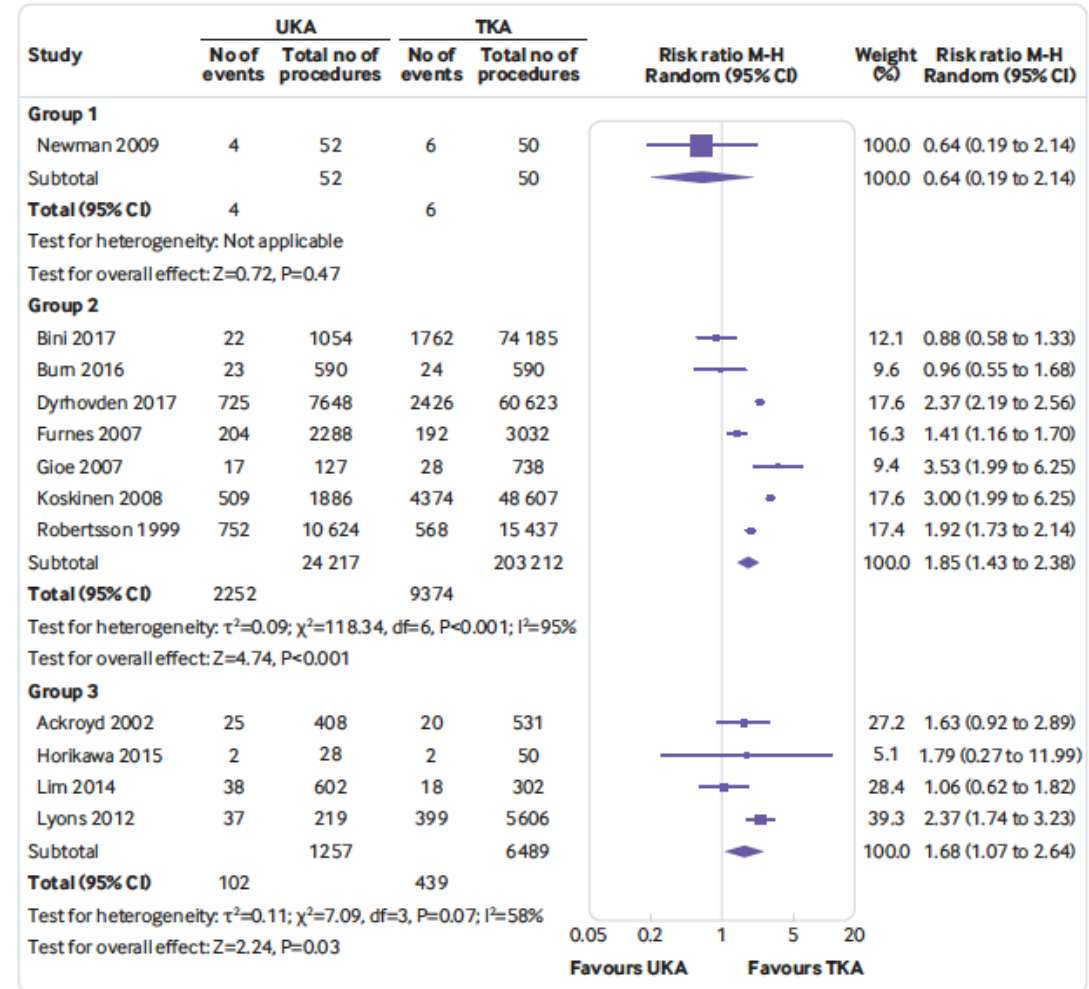


Fig 7 | Forest plot comparing incidence of revision at 10 years after unicompartmental (UKA) versus total knee replacement (TKA). Also appears in the supplementary material as supplementary figure 16. M-H=Mantel-Haenszel test

What we knew before we started (5) ...

- Caveats with quality of these 60 papers (and 20y) of data (mostly observational and from different sources)
- NIHR UK-funded
 - 1 surgical RCT (TOPKAT)
 - 1 observational study (UTMOST)



The clinical and cost-effectiveness of total versus partial knee replacement in patients with medial compartment osteoarthritis (TOPKAT): 5-year outcomes of a randomised controlled trial



David J Beard, Loretta J Davies, Jonathan A Cook, Graeme MacLennan, Andrew Price, Seamus Kent, Jemma Hudson, Andrew Carr, Jose Leal, Helen Campbell, Ray Fitzpatrick, Nigel Arden, David Murray, Marion K Campbell, for the TOPKAT Study Group*

HTA - 15/80/40

Risk-benefit and costs of unicompartmental (compared to total) knee replacement for patients with multiple co-morbidities: a non-randomised study, and different novel approaches to minimise confounding.

Project title: Risk-benefit and costs of unicompartmental (compared to total) knee replacement for patients with multiple co-morbidities: a non-randomised study, and different novel approaches to minimise confounding.

Call to action: 15/80 15/80 HTA Efficient Study Designs

Research type: Primary Research

Chief investigator: [Professor Daniel Prieto-Alhambra](#)  orcid.org/0000-0002-3950-6346

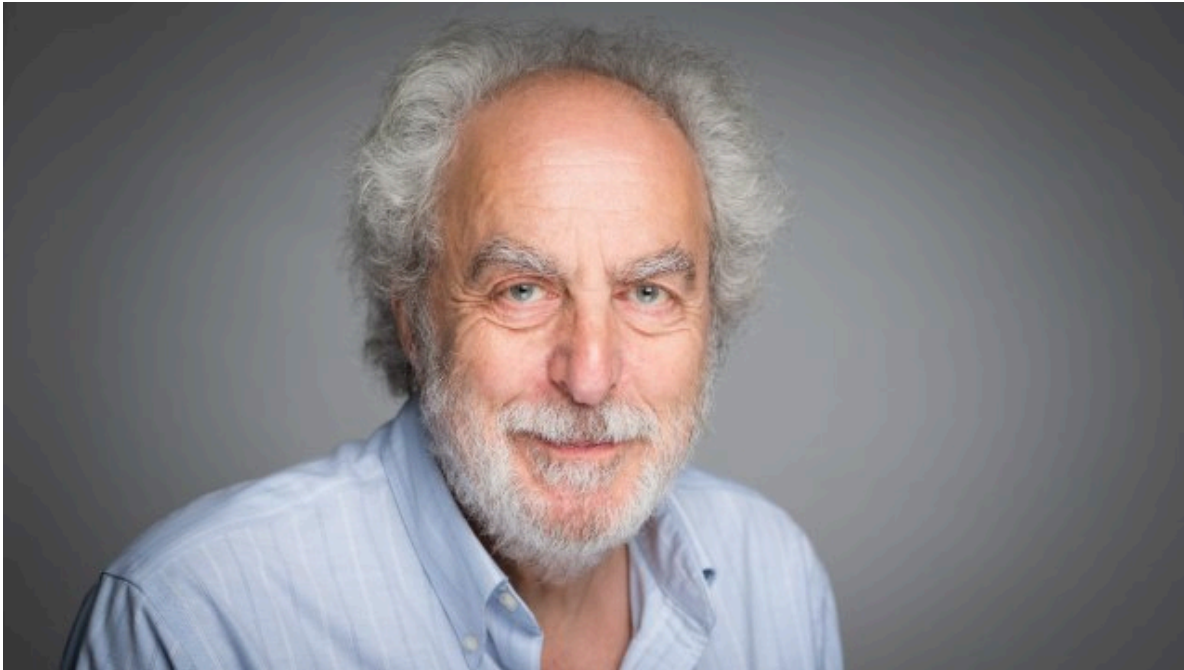
Contractor: [University of Oxford](#)

Cost: £268,076.76

Co-investigators: [Dr Irene Petersen](#), [Dr Rafael Pinedo-Villanueva](#), [Ms Susan Thwaite](#), [Professor Alan Silman](#), [Professor Andrew Carr](#), [Professor Andrew Judge](#), [Professor David Beard](#), [Professor David Murray](#), [Professor Ian Douglas](#), [Professor Jeremy Wilkinson](#), [Professor Jose M Valderas](#), [Professor Nigel Arden](#), [Professor Sarah Lamb](#).

Started: June 2017 | **Status:** Research in progress

MOTIVATION



“We need less research, better research,
And research done for the right reasons”

Ie, CAN WE DO IN A WEEK AND 1 STUDY WHAT HAS
TAKEN SO FAR 20+ YEARS, 60+ PAPERS AND LOADS OF
CASH?

Intended for healthcare professionals

thebmj



Editorials

The scandal of poor medical research

BMJ 1994 ; 308 doi:

<https://doi.org/10.1136/bmj.308.6924.283>

(Published 29 January 1994)

Cite this as: *BMJ* 1994;308:283

Linked Opinion

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Article

Related

Metrics

Responses

D G Altman

We need less research, better research, and
research done for the right reasons

RATIONALE

- **Surgical/Device RCTs are rare, costly, and difficult:**
 - *Logistics (eg “blinding”)*
 - *Ethics (placebo/sham surgery)*
 - *Not always required (by regulators)*
- **New US and EU regulation will increase the need for observational data in this field**

RATIONALE (2)

- **Methodological challenges in the area of surgery/device observational research**
 - *Confounding due to patient characteristics*
 - *... but also due to **surgeon/centre features***
 - *Modelling difficulties (propensity score building to include surgeon/hospital characteristics)*
- **Little experience/investment to date ...**
- **EHDEN provides an unprecedented opportunity**

BACKGROUND – UKR vs TKR

- **UKR** is a less invasive, partial replacement, of the knee
- **TKR** is an established procedure with excellent results in terms of safety and effectiveness
- **(Some) surgeons prefer UKR in younger, fit patients**

BACKGROUND (2) – UKR vs TKR

- But research to date suggests UKR leads to:
 - Less complications
 - More revision/s
- So maybe best for **older patients with complex medical history**

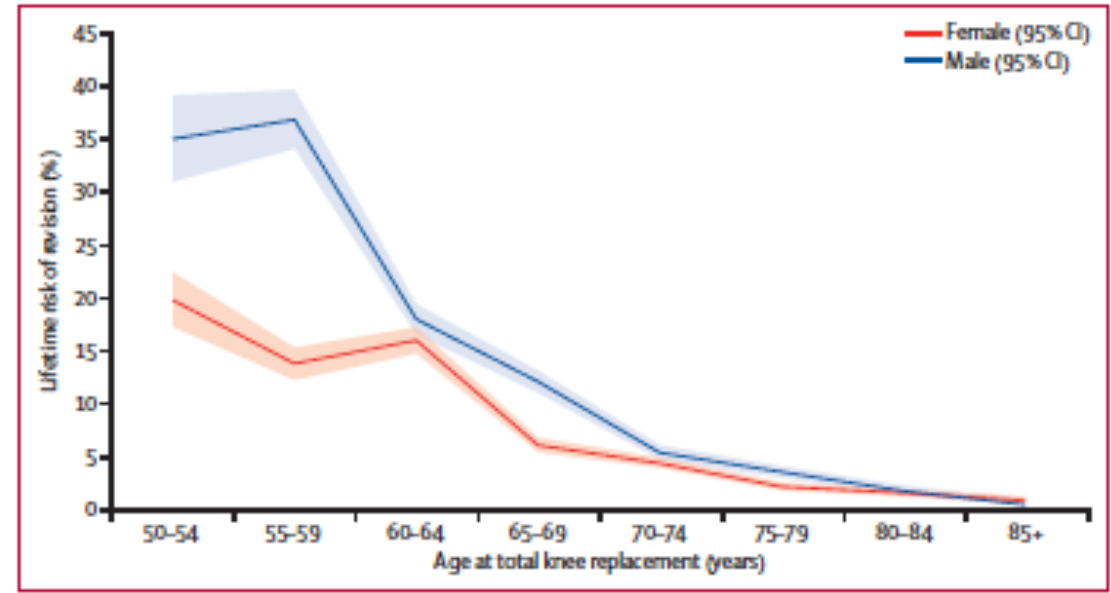


Figure 3: Lifetime risk of revision after total knee replacement
Plot showing estimates of lifetime risk of total knee replacement revision against age at the time of primary total knee replacement surgery (in 5-year age bands) and stratified by sex (results adjusted for lost and censored population).

BACKGROUND (3) – UKR vs TKR

- An on going surgical RCT comparing UKR vs TKR is reporting 5-year data published **NOW in the Lancet!!! [Beard D et al. Lancet]**
- As usual in RCTs, they have excluded old complex patients with co-morbidity etc (ASA 3+) ...
- Also as usual, they are not powered for safety (complications)
- And the trial will be run in specialized treatment centres ...

OUR AIMS!

- **Can we ‘predict’ the TOPKAT results (on complications) before they publish?**
- **And more:**
 - **can we report on the results of UKR (vs TKR) in the older, more complex patients, excluded from TOPKAT?**
 - **Can we predict who is likely to have a post-operative complication following knee replacement surgery**



WE CAN DO THIS IN ONE WEEK (STUDY-A-THON)??

“To compare the **risk** of post-operative **complications** and **mortality** between unicompartmental vs total knee replacement.”

Monday

Group consensus on the **problem**
Draft cohort definitions

Wednesday

Review patient-level prediction results
Externally validate prediction model

Friday

Review of results
Plan for completing **publications**

Tuesday

Review clinical characterisation
Draft patient-level prediction design

Thursday

Draft population-level effect estimation design
Review population-level effect estimation diagnostics

First OHDSI-EHDEN Study-Athon!

Our final (refined) research question!!

“To compare the risk of post-operative complications (infection, revision, and venous thrombo-embolism) and mortality between unicompartmental vs total knee replacement.”

Let's start collaborating!

- Open the shared group notes:

<https://docs.google.com/document/d/17Valb33sl64laDq307PpoMZd4drIsVoja0zpYE6ZXe8/edit?usp=sharing>

- Ground rules:
 - During group exercises, take all your notes here together
 - During breakout exercises, assign one person in your team to make sure notes are recorded so other groups can learn from our experience
-

Let's start writing our papers!

- Patient-Level Prediction:

<https://docs.google.com/document/d/13GIkdulRmU2nbrqM58G2neWPV0U4PoTh8w13UihLgLc/edit?usp=sharing>

- Population-Level Effect Estimation:

<https://docs.google.com/document/d/1BC6-cBR1by0GNeRc4zatzdSkOOmtvWfMpZrePIn0XaE/edit?usp=sharing>

Let's start learning ATLAS!

- Public version from OHDSI (v2.6, simulated data), go to:
<http://ohdsi.org/web/ATLAS>
 - Private version from Iqvia (v2.4, THIN data), go to:
<https://training.atlasplus.imshealth.com>
-

SO WHAT DID WE LEARN (by Friday!!)

- Population-level effect estimation:

<http://data.ohdsi.org/UkaTkaSafetyEffectiveness/>

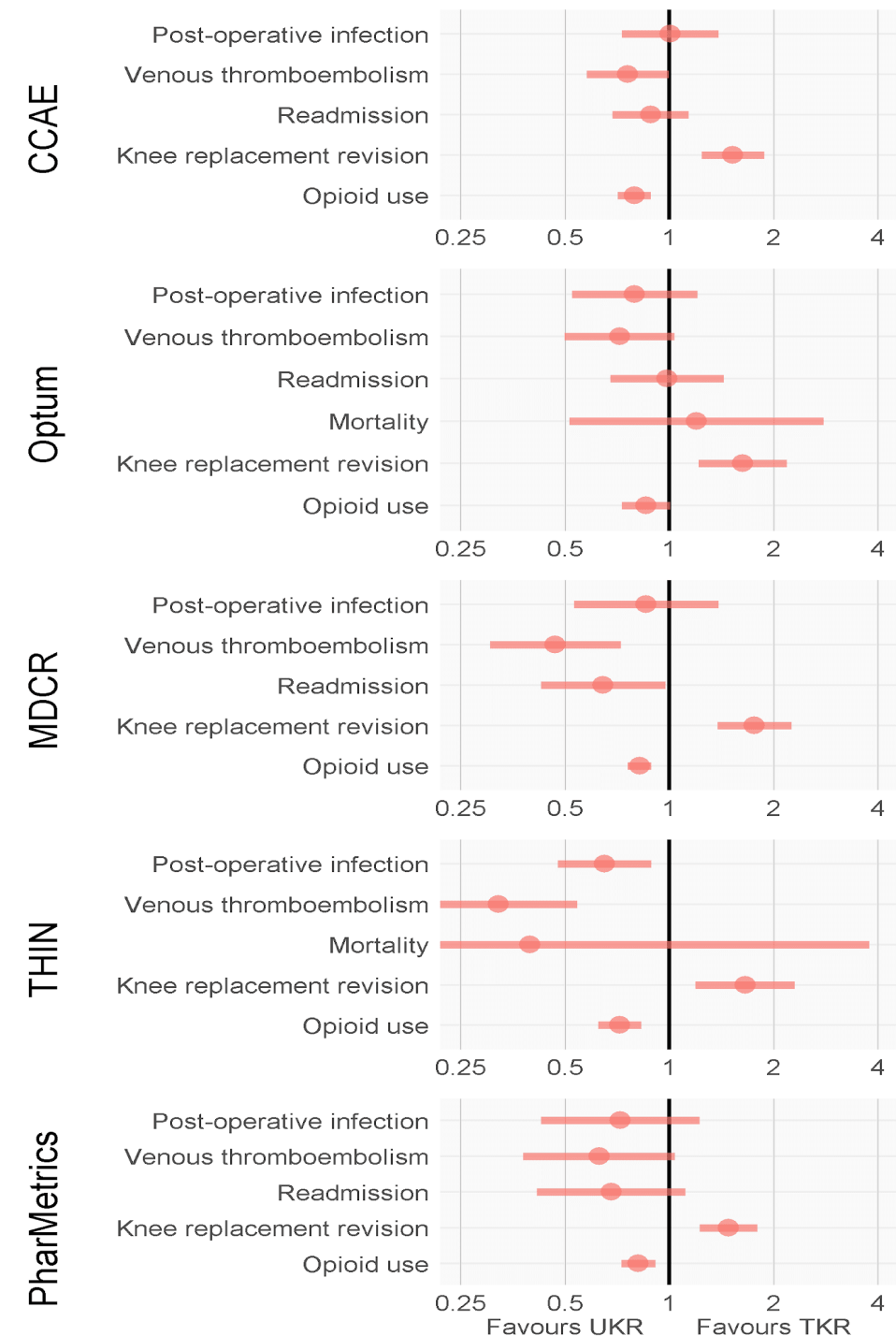
- Patient-level prediction

<http://data.ohdsi.org/oxfordMortalityExternalValidation/>

OUR WEEK vs 20y of research

OX Study-a-thon vs BMJ Syst Rev

- VTE
 - RR 0.49 [0.20 to 1.17] (20 y)
 - vs HR 0.62 [0.36-0.96] (1 week)
- Long-term revision
 - RR 1.68 [1.07 to 2.64] (20y)
 - vs HR 1.51 to 2.16 (1 week)



OUR WEEK vs a £3m trial

[D Beard et al. Lancet 2019]

- Small improvement in pain/function with UKR in TOPKAT vs Small reduction in opioid/s use in Study-a-thon
- No power for safety in TOPKAT vs findings compatible w 20y of data in Study-a-thon
- ... Yet revision not significantly increased!! [vs all previous papers]
 - **WAS IT ALL A WASTE???**

Intended for healthcare professionals

thebmj



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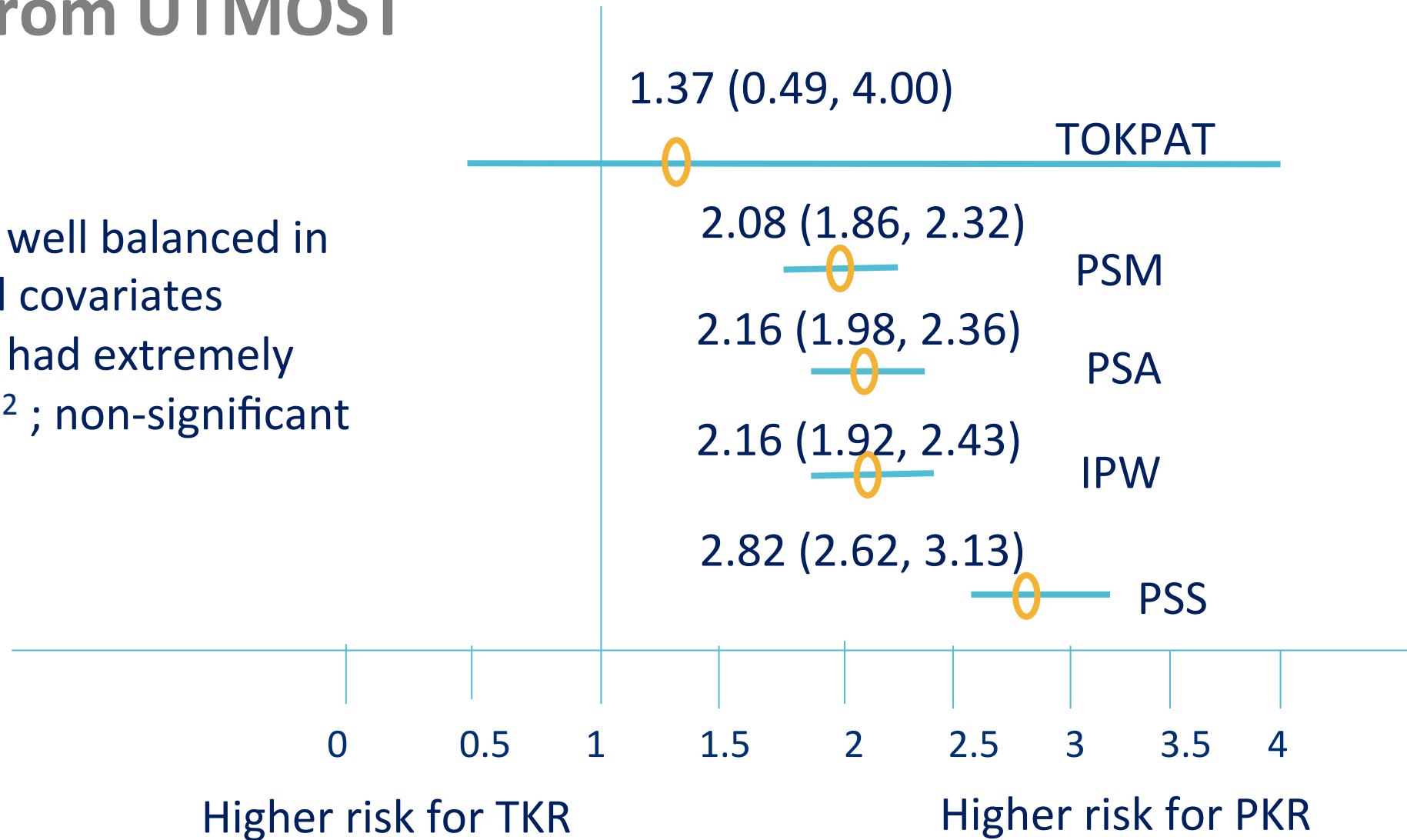
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We need less research, better research, and research done for the right reasons

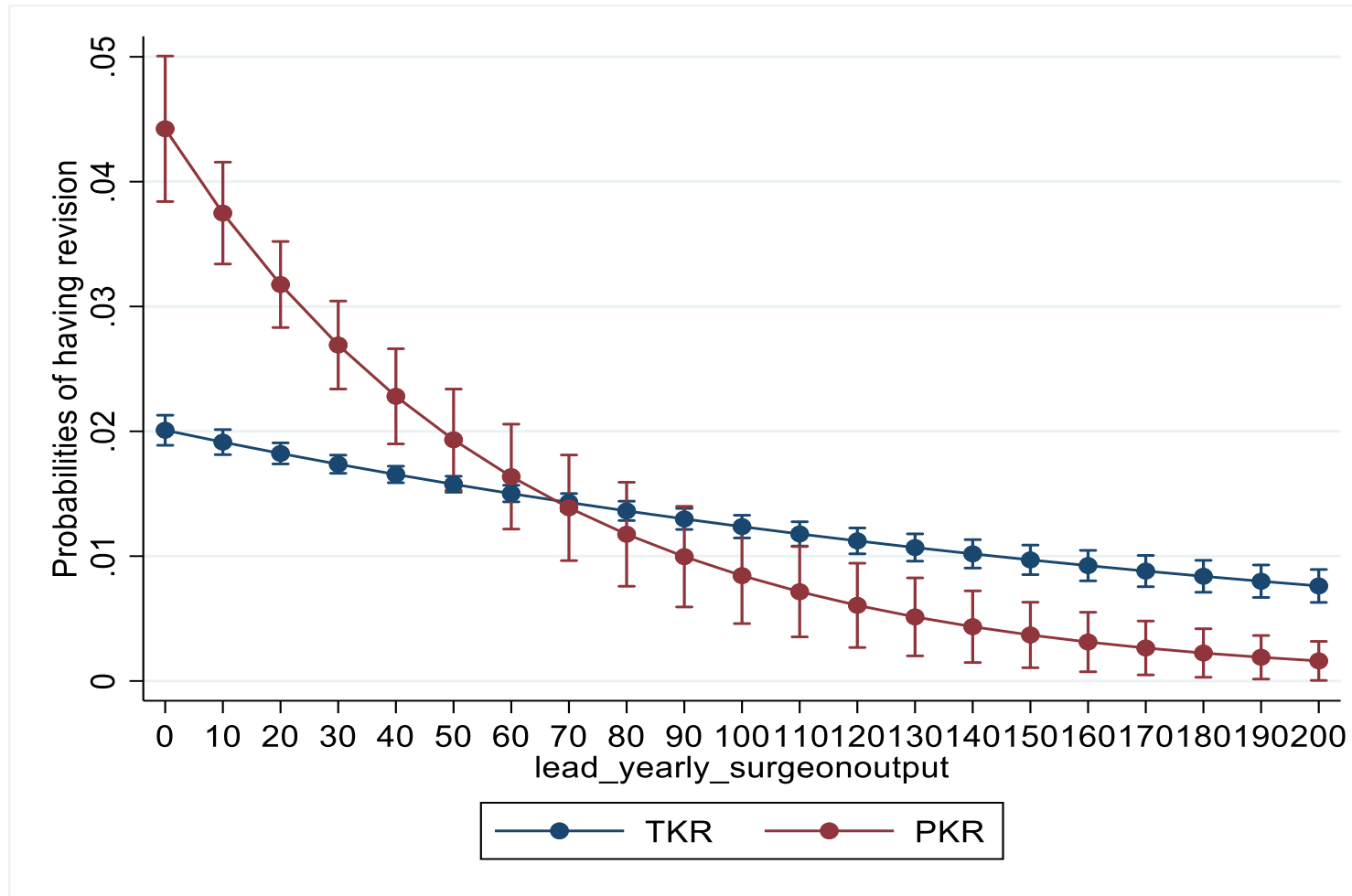
Revision risk: confused vs confounding

Insights from UTMOST

- All methods well balanced in patient-level covariates
- All methods had extremely small τ^2 & I^2 ; non-significant p-values

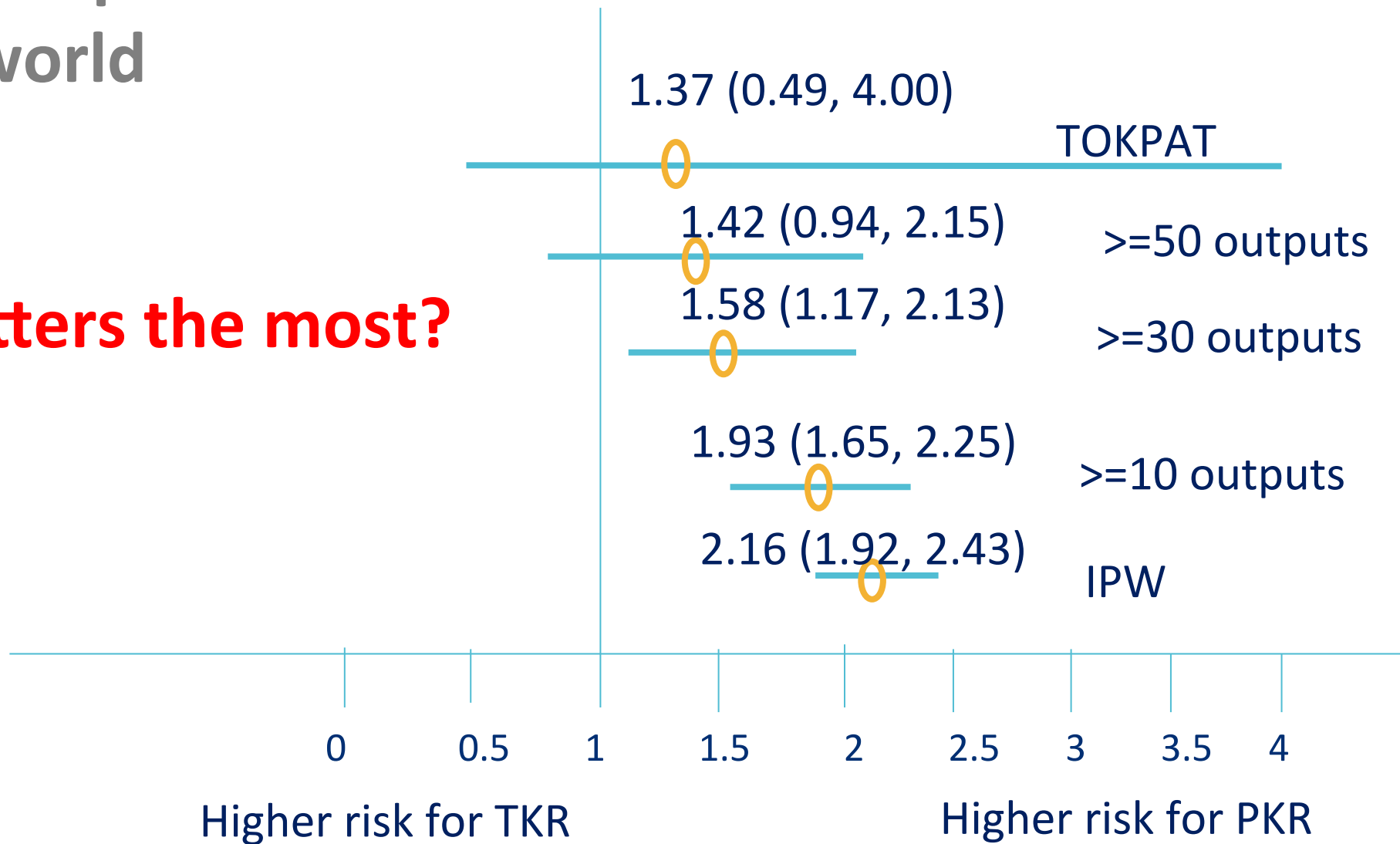


Surgeons' experience (1): effect modifiers



Surgeons' experience in trials vs The real world

What matters the most?



Prediction...

Predicting post-op mortality

← → ↻ ⓘ Not Secure data.ohdsi.org/TKROutcomesExplorer/ ☆ 🌐 🌐 🌐

Apps EUADRSharePoint EU-ADR Home EMIF EMIF Catalogue AppsSIDIAP Revalidation AEMPS-CIMA NHS_e_Learning Variables SIDIAP »

Multiple PLP Viewer ☰

Summary

Performance

Model

Log

Help

Filters

Development Database

Optum

Validation Database

All

Target Cohort

Oxford studyathon Day2 Patients with total knee replacement

Outcome Cohort

Oxford studyathon Mortality

Time-at-risk start:

0

Results Model Settings Population Settings Covariate Settings

Show 10 entries Search:

Analysis	Dev	Val	T	O	Model	TAR start	TAR end	AUC	AUPRC	T Size	O Count	O Incidence (%)
Analysis_1	Optum	Optum	Oxford studyathon Day2 Patients with total knee replacement	Oxford studyathon Mortality	Lasso Logistic Regression	0	90	0.78136	0.01252	38166	88	0.23057
Analysis_1	Optum	ambemr	Oxford studyathon Day2 Patients with total knee replacement	Oxford studyathon Mortality	Lasso Logistic Regression	0	90	0.47702	0.00025	77950	10	0.01283
Analysis_1	Optum	CUMC	Oxford studyathon Day2 Patients with total knee replacement	Oxford studyathon Mortality	Lasso Logistic Regression	0	90	0.8576	0.0133	1853	6	0.3238
Analysis_1	Optum	STARR	Oxford studyathon Day2 Patients	Oxford studyathon Mortality	Lasso Logistic	0	90	0.76257	0.00829	2306	7	0.30356

3.Prediction...

Predicting post-op mortality

THE MODEL

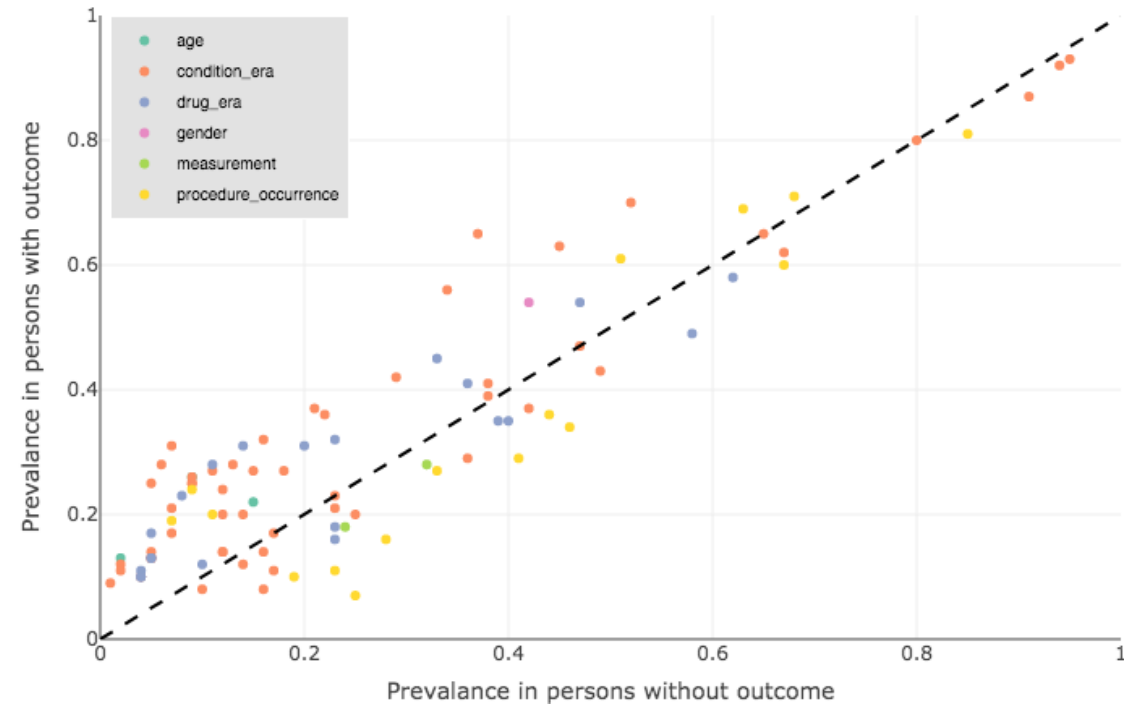
Model Table

Download Model

Show 10 entries

Search:

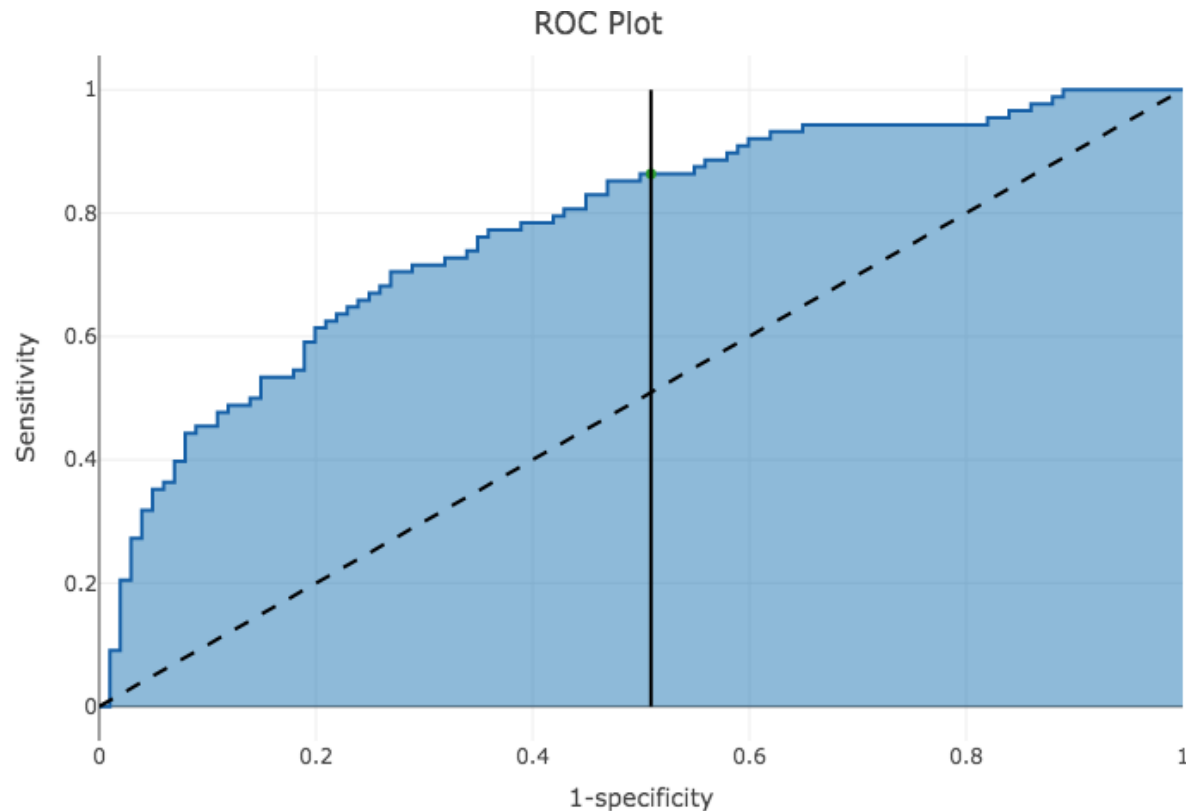
	Covariate Name	Value	Outcome Mean	Non-outcome Mean
1	index month: 1	0	0.1	0.1
2	Charlson index - Romano adaptation	0	3.81	2.16
3	Diabetes Comorbidity Severity Index (DCSI)	0	3.71	1.96
4	CHADS2	0	2.54	1.57
5	CHADS2VAsC	0	4.18	2.94
6	visit_occurrence concept count during day -1095 through -1 concept_count relative to index	0	71.99	50.13
7	visit_occurrence concept count during day -365 through -1 concept_count relative to index	0	32.46	24.26
8	index month: 2	0	0.1	0.08
9	index month: 3	0	0.1	0.09
10	index month: 4	0	0.08	0.08



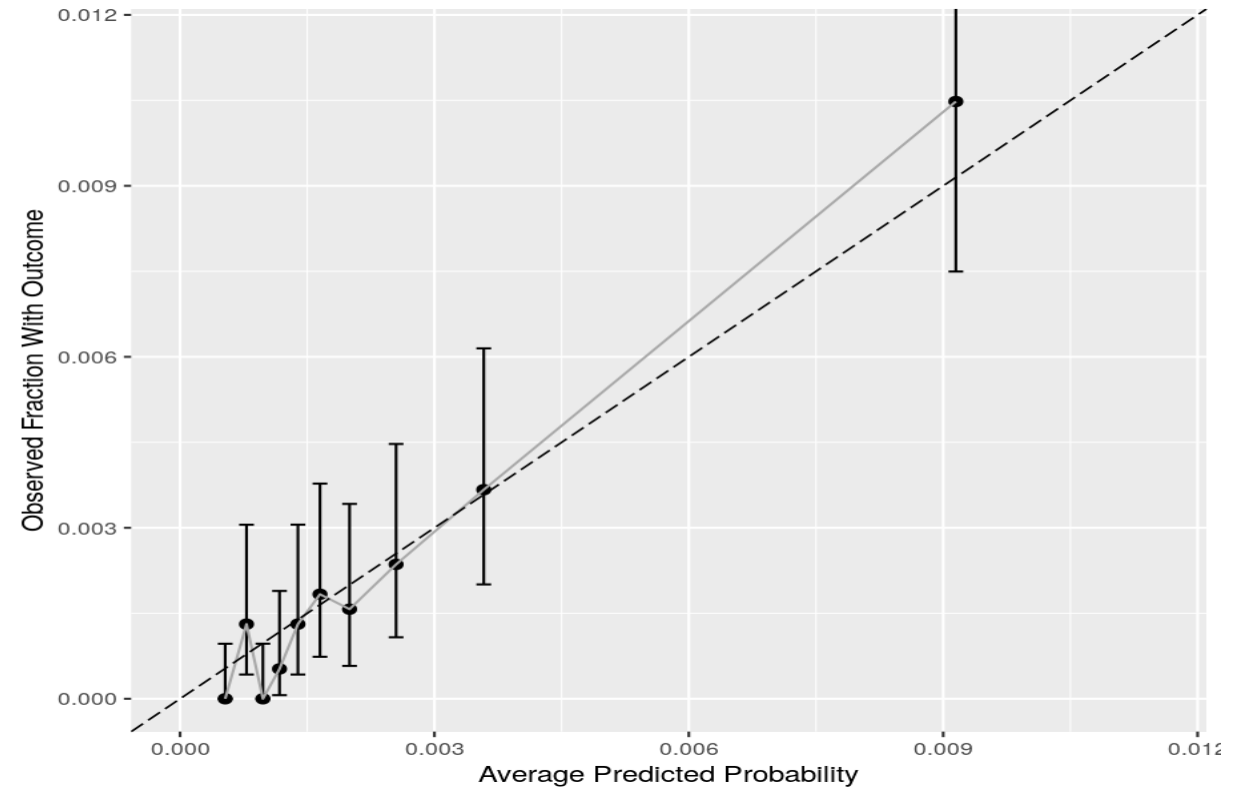
3.Prediction...

Predicting post-op mortality

DISCRIMINATION



CALIBRATION



AND WHAT DID I LEARN (by Friday too!!)



The Oxford Study-Athon

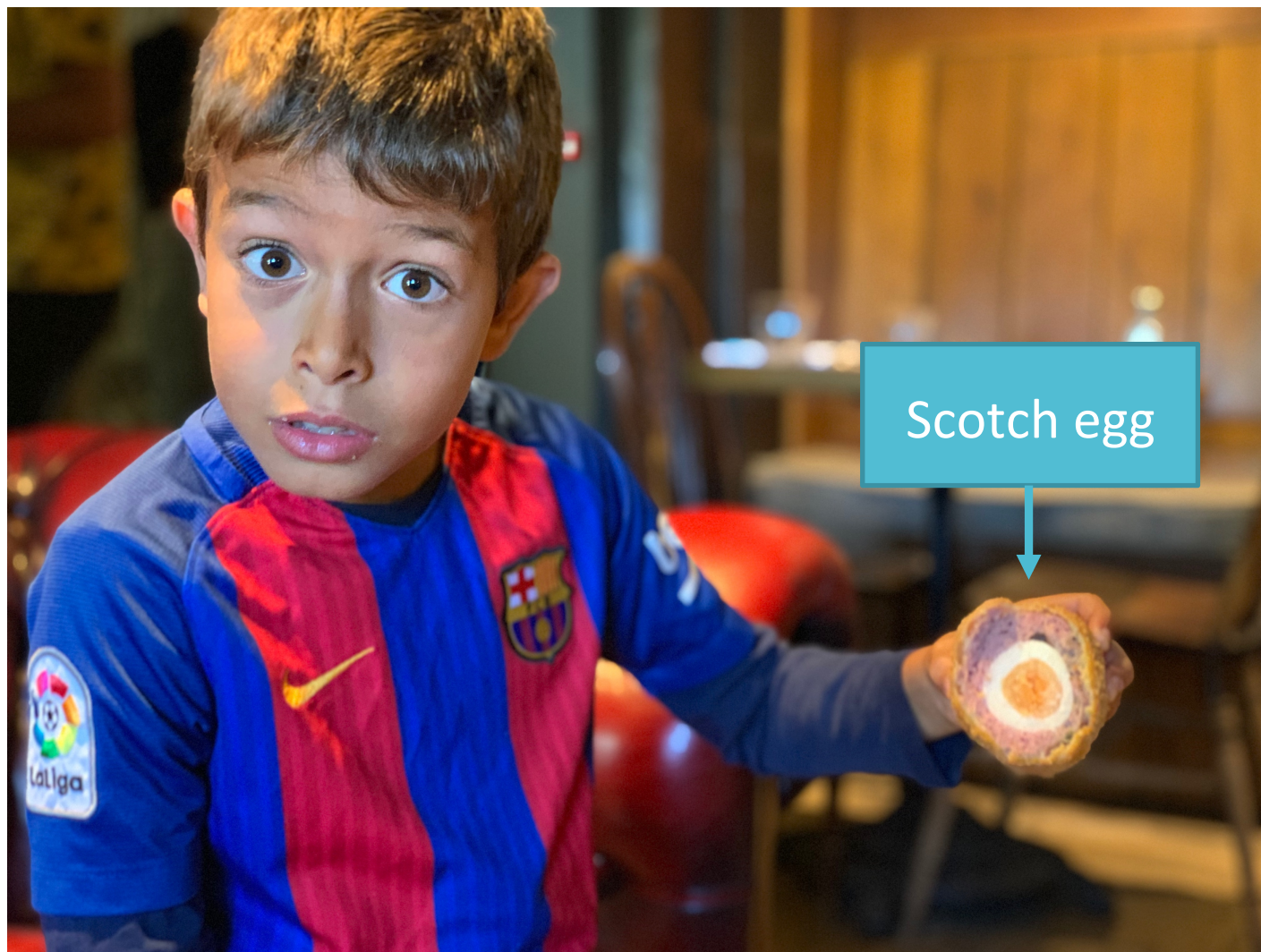
*“Why had we not
joined the
journey earlier?”*

Finished in 1430

Finished in the 1600s



Tradition?



Or laziness?

Or maybe we're not
as good as some think..

Family & Education

Oxford top of global university rankings

By Sean Coughlan

BBC News family and education correspondent

11 September 2019



Oxford University has been ranked first in an international league table for the fourth year in a row.

The annual Times Higher Education world

Or maybe we're not as good as some think..

BBC Home News More

NEWS

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News › Politics

Students at Boris Johnson's former Oxford college launch petition to have him banned from campus

SEAN MORRISON | 2 days ago |



Like Click to follow
The Evening Standard



The petition calls on Balliol College to publicly condemn the Prime Minister for suspending Parliament /

It's always hard to start a journey ...



But once you find a good boat ...



*“As you set out for Ithaka
hope your road is a long one,
full of adventure, full of discovery...”*

Ithaka, by G Cavafis



AN EXCITING JOURNEY AHEAD

The uptake of the OMOP-CDM and success of OHDSI enables the EHDEN project to build the European eco-system that brings reliable evidence quicker to our patients.

Expanding the Data Network, Community, and the support system with SMEs, will drive the sustainability of the eco-system.

The EHDEN project will continue the collaboration with OHDSI and will invest in further development of the CDM, Vocabularies, ETL tools, analytical tools, DQ tools.





NEED MORE INFORMATION?

All this work would not have been possible without the contribution of many collaborators in EHDEN and OHDSI

Thanks for this great adventure!



enquiries@ehden.eu



www.ehden.eu



[@IMI_EHDEN](https://twitter.com/IMI_EHDEN)



[IMI_EHDEN](https://www.linkedin.com/company/IMI_EHDEN)



github.com/EHDEN



This project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement No 806968. The JU receives support from the European Union's Horizon 2020 research and innovation programme and EFPIA.