Can real world data emulate RCT findings and address common RCT limitations?

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Disclosures

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- The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

Conflicts of Interest

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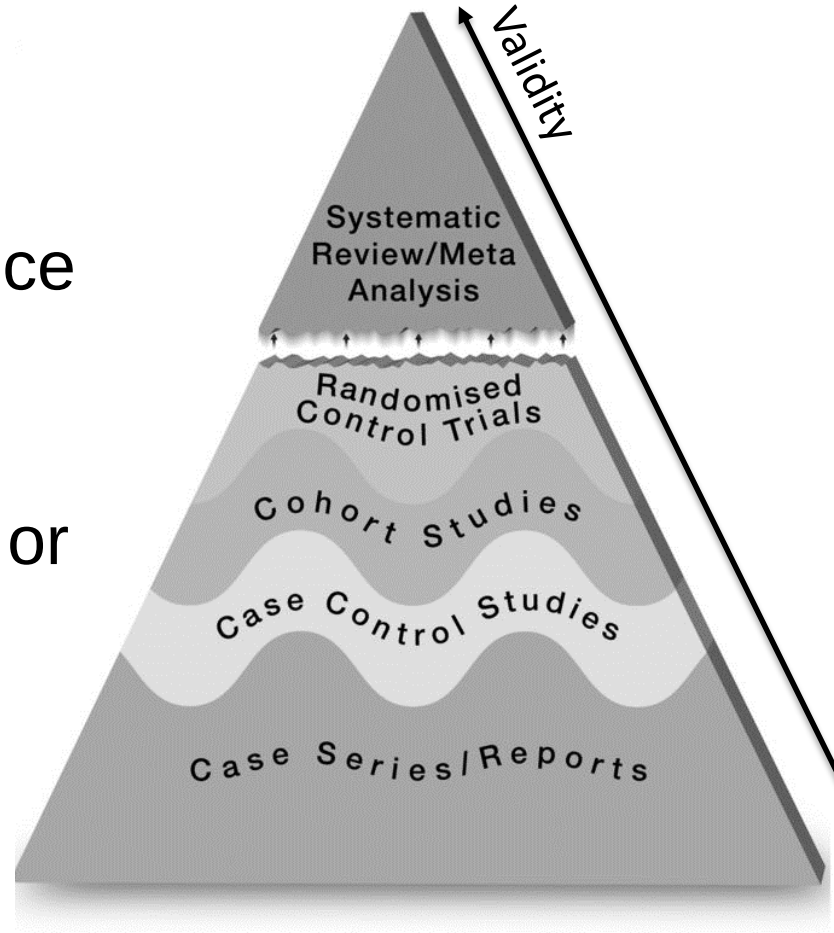
Overview

- Why do we need large population-based observational data?
  - limitations of RCTs
  - benefits and limitations of observational data

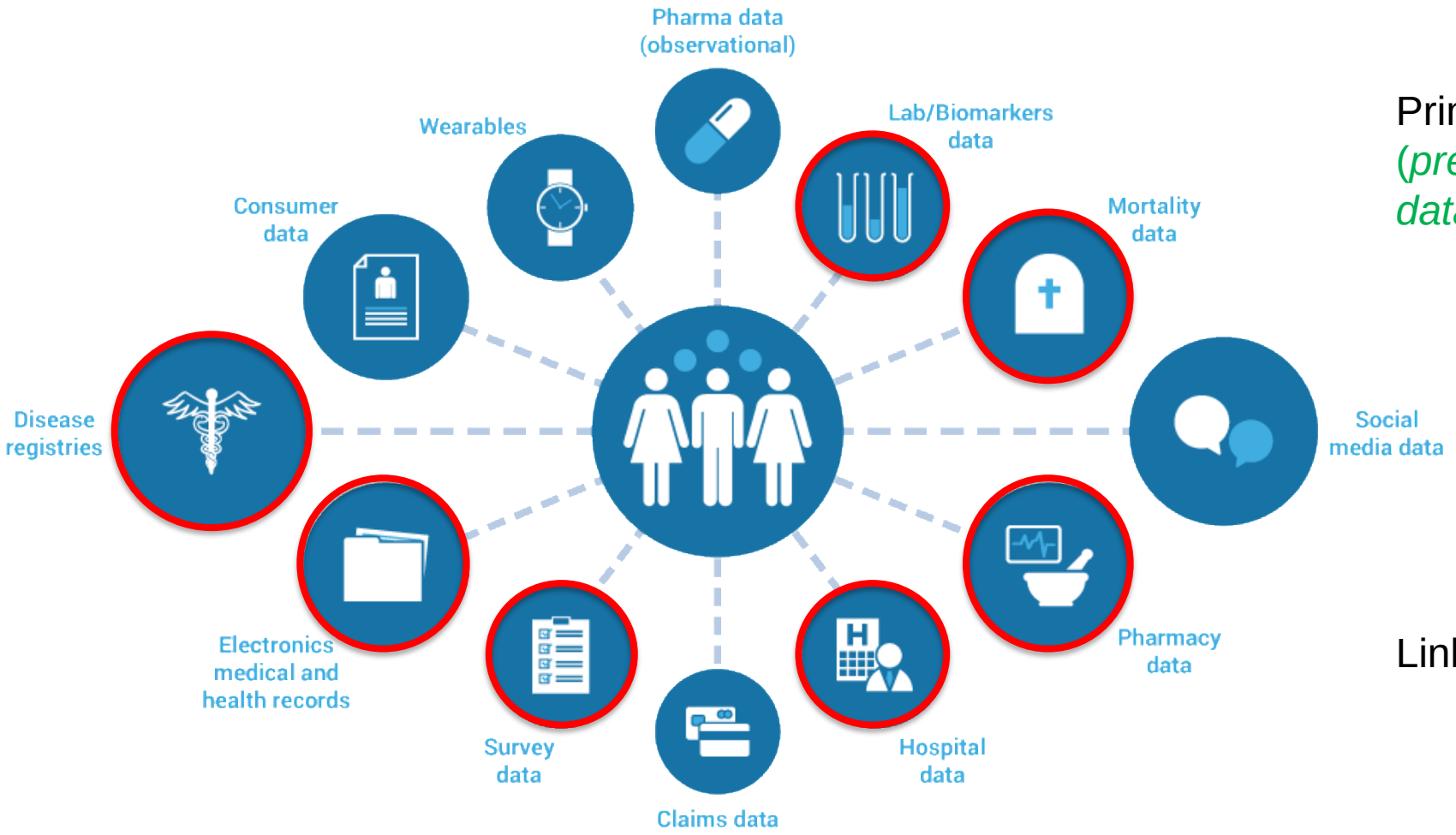
- Can observational data replicate trial findings?
  - effectiveness of partial vs. total knee replacement using routinely collected data: a trial emulation
  - comparison of various statistical methods

Pitfalls of RCTs

- Randomisation may not be feasible or ethical
- Tend to have strict/er exclusion and inclusion criteria
  - may exclude the elderly / very sick
- Strict monitoring which does not reflect clinical practice
  - participant behaviour
  - treatment adherence
- RCTs are not often designed/powered to detect rare or unexpected adverse events
- Short follow-up
- Limited sample size (vs routinely collected data)
- Resource intensive



Routinely collected observational data



Primary care medical records *(prescription, consultation, measurement data)*

- UK, Clinical Practice Research Datalink (CPRD)
- Spain, Information System for Research in Primary Care (SIDIAP)
- *Netherlands, The Integrated Primary Care Information (IPCI)*
- *USA, Medicare data*
- *Italy, France, Germany, IQVIA* Longitudinal Patients Database (LPD)

Linkage to other databases

- Hospital data *(diagnoses and procedures)*
- Mortality data *(date and cause of death)*

Benefits of observational data

BMJ. 2011 Dec 6;343:d7222. doi: 10.1136/bmj.d7222.

Association between bisphosphonate use and implant survival after primary total arthroplasty of the knee or hip: population based retrospective cohort study

Daniel Prieto-Alhambra [1], M Kassim Javaid, Andrew Judge, David Murray, Andy Carr, Cyrus Cooper, Nigel K Arden

Objectives: To test whether bisphosphonate use is related to improved implant survival after total arthroplasty of the knee or hip.

Design: Population based retrospective cohort study.

Setting: Primary care data from the United Kingdom.

Participants: All patients undergoing primary total arthroplasty of the knee (n = 18,726) or hip (n = 23,269) in 1986-2006 within the United Kingdom's General Practice Research Database. We excluded patients with a history of hip fracture before surgery or rheumatoid arthritis, and individuals younger than 40 years at surgery.

Intervention: Bisphosphonate users were classified as patients with at least six prescriptions of bisphosphonates or at least six months of prescribed bisphosphonate treatment with more than 80% adherence before revision surgery.

Outcome measures: Revision arthroplasties occurring after surgery, identified by READ and OXMIS codes. Parametric survival models were used to determine effects on implant survival with propensity score adjustment to account for confounding by indication. Results Of 41 995 patients undergoing primary hip or knee arthroplasty, we identified 1912 bisphosphonate users, who had a lower rate of revision at five years than non-users (0.93% (95% confidence interval 0.52% to 1.68%) v 1.96% (1.80% to 2.14%)). Implant survival was significantly longer in bisphosphonate users than in non-users in

Benefits of observational data

- Routinely collected medical record data (using data from several countries and data sources)
  - can quickly identify a diverse range of safety issues
- COVID-19 vaccinations
  - they have been shown to be protective against COVID-19
  - thrombosis, hypersensitivity, Guillain-Barre syndrome

Using observational data to infer causality

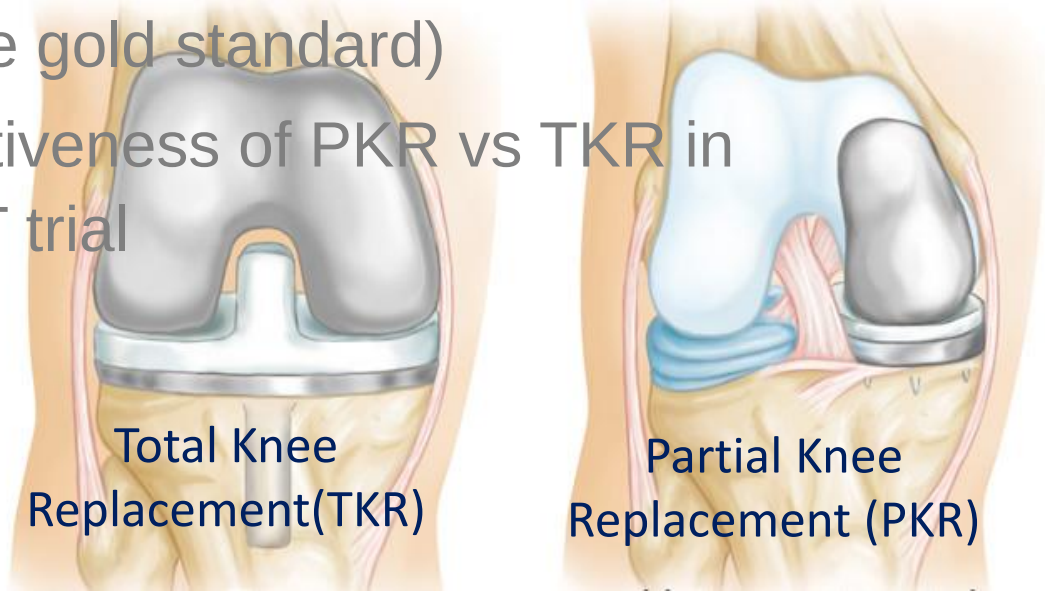
- Lack of randomisation
  - treatment groups are not comparable/exchangeable
  - typically those on treatment (vs no treatment) have worse health and more likely to have poor outcome
    - *appears treatment is detrimental*
- Ideally to mimic a RCT, want to separate study design and analysis

(1) Ensure treatment groups are comparable

(2) Estimate effect of treatment

Emulating a RCT, an example

- The TOPKAT trial is a multi-centre, pragmatic and expertise-based surgical RCT, evaluating the clinical and cost-effectiveness of PKR with TKR[Beard DJ et al. 2019, Lancet]
- The UTMoST study replicated the TOPKAT trial using observational data[Prats-Uribe et al. 2021, Health Technol Assess]
  - Stage 1: To assess the validity of various statistical methodologies to replicate findings from the TOPKAT trial (considered the gold standard)
  - Stage 2: Assess safety, clinical and cost effectiveness of PKR vs TKR in patients who were excluded from the TOPKAT trial



Real world 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 & safety 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 Score (OKS)
6-12 months post-op

Statistical analysis

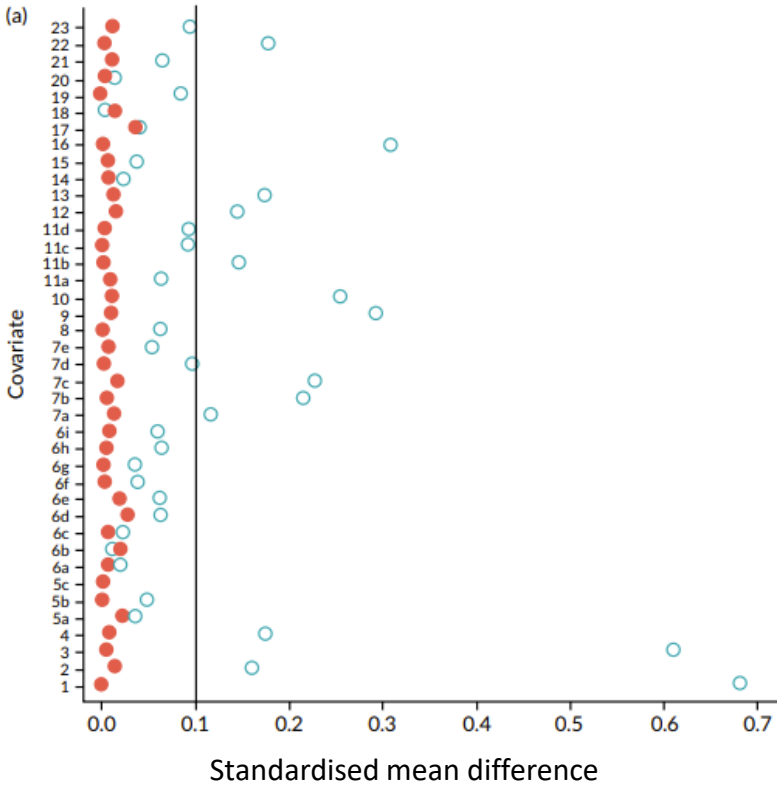
- Create comparable groups: Propensity Score (PS) analysis
  - PS matching with up to 1:5 ratio
  - inverse probability weighting
  - PS stratification (10 strata)
  - PS adjustment
- Comparing outcome results with TOPKAT
  - heterogeneity (Chi square test, Small I^2 <40%, Small tau^2)
  - effect size overlap
  - statistical significance agreement
  - minimally clinically significant difference of <4

Results: Baseline characteristics

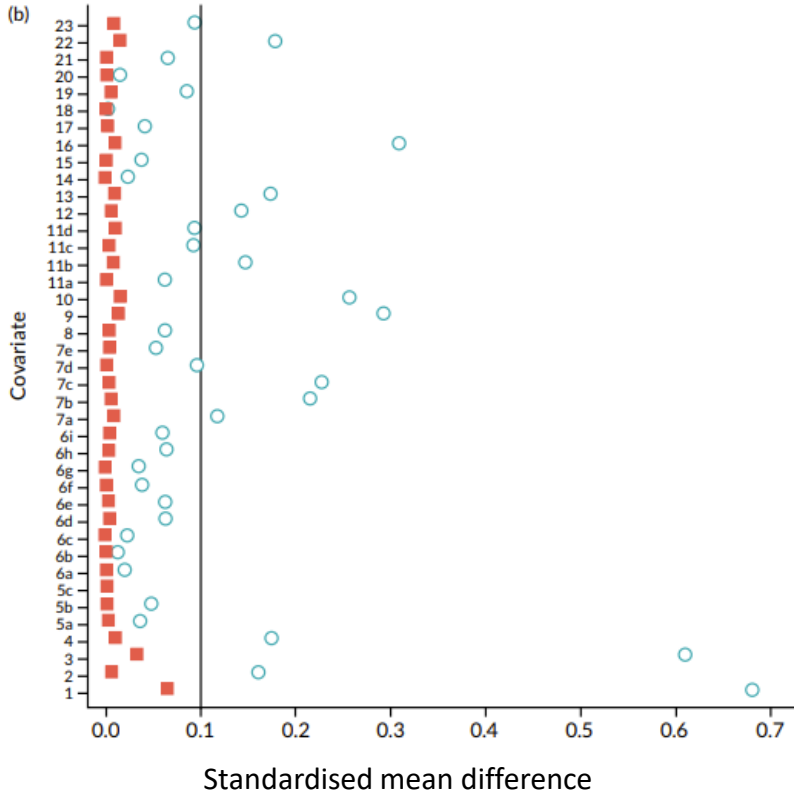
n(%) or mean (SD)*	OKS cohort (primary analysis)			
	TKR n=125,834	%/SD	PKR n=1,197	%/SD
Female	70,671	56	576	48
Age*	70.4	8.6	64.9	9.4
ASA - Mild disease not incapacitating	115,624	89	995	80
Charlson Comorbidity				
0	86,474	69	915	76
1	26,733	21	224	19
2	8,357	7	41	3
3+	4,270	3	17	1
GI disease	25,142	20	174	15
OA & Other joint problems	23,578	19	174	12
CVD	73,382	58	515	43
Pre-operative OKS*	19.7	7.6	21.9	7.5

Achieving comparable treatment groups

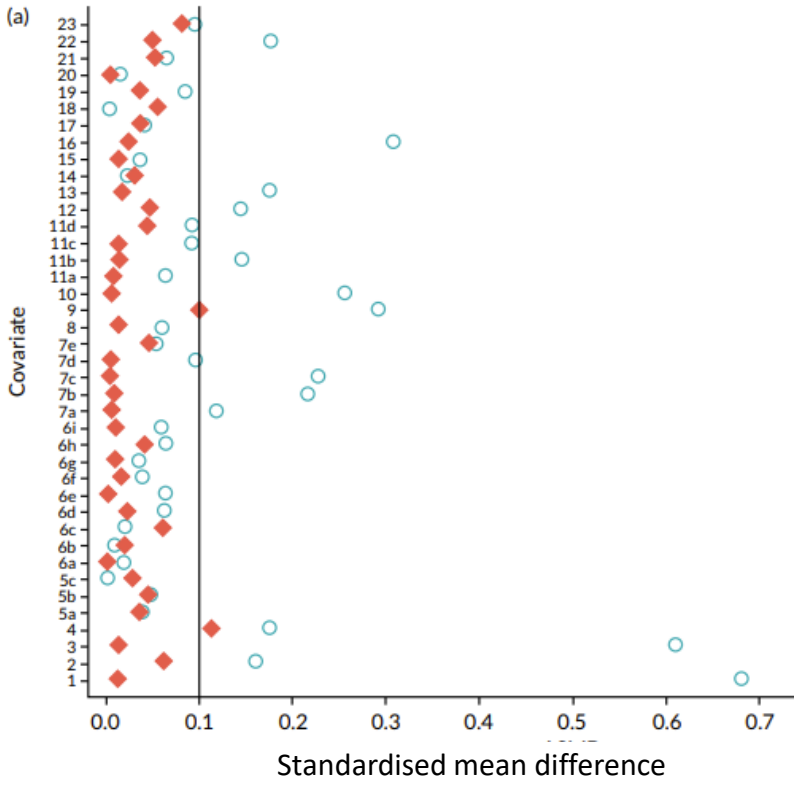
PS Matching



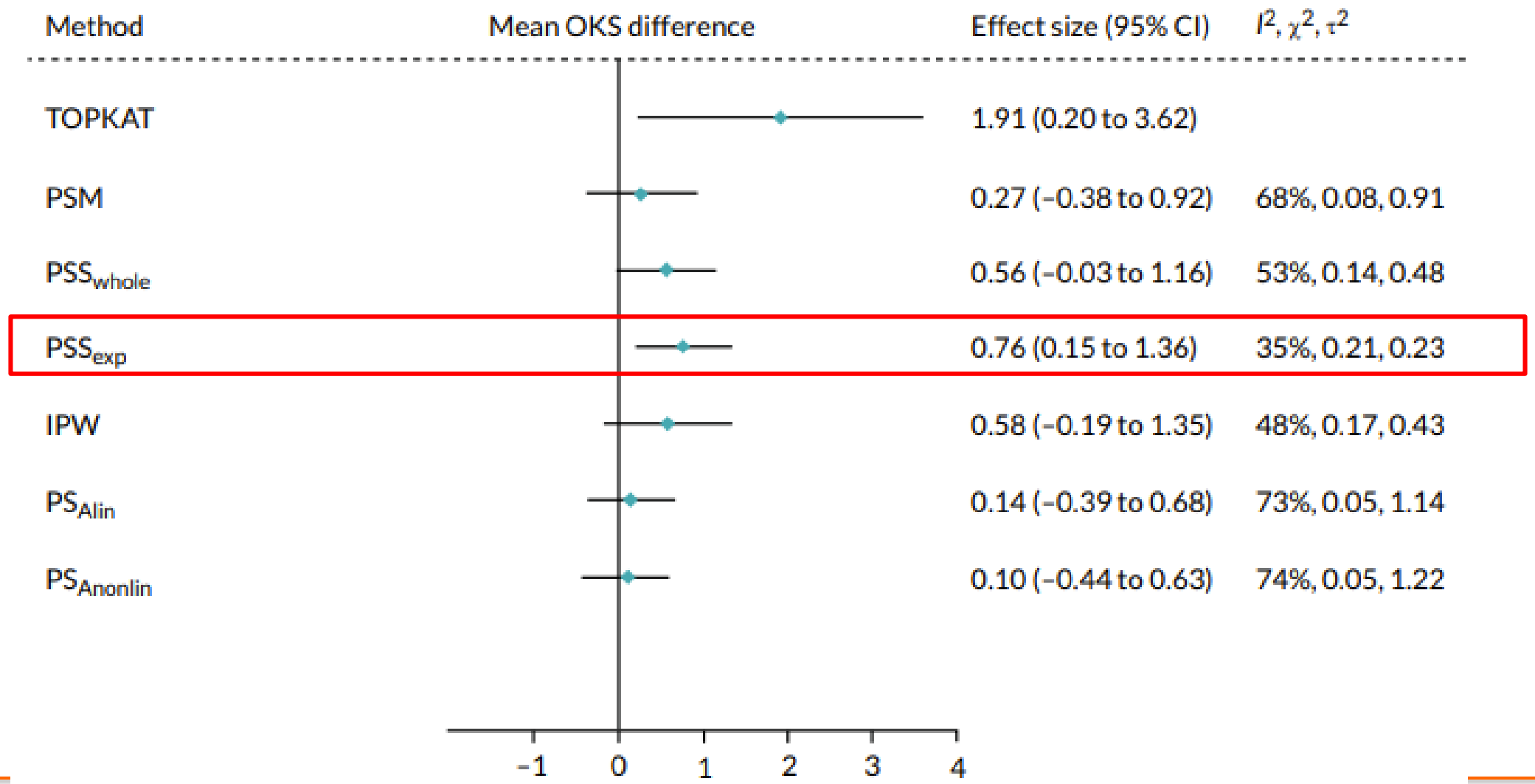
PS Stratification (exp)



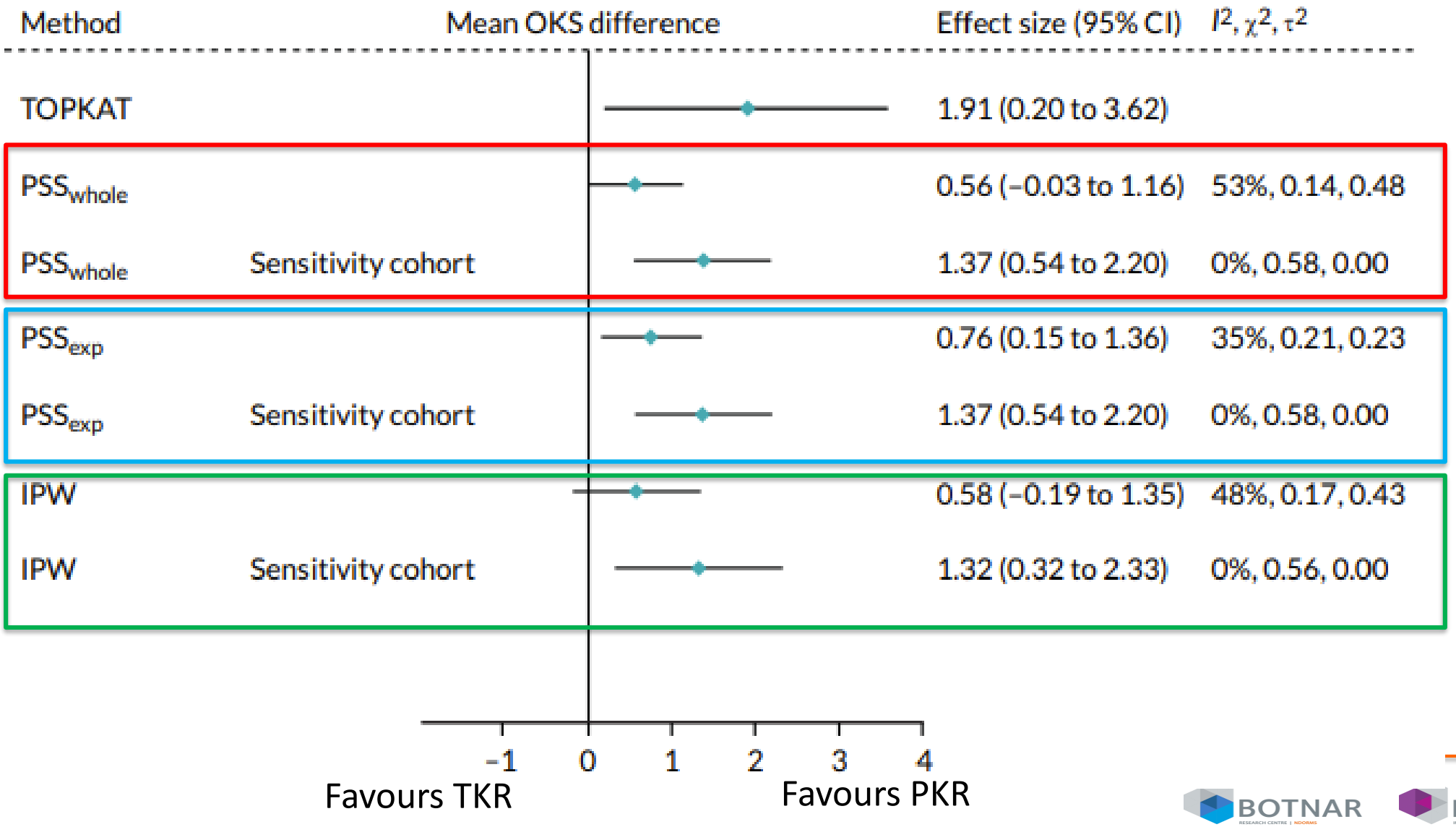
PS Weighting



Primary outcome analysis



Primary outcome analysis: restricted by surgeon experience



Stage 2: Effectiveness & safety for patients with multiple comorbidities (ASA ≥3)

OKS cohort (n=23,489) : mean difference (95% CI)

Comparability of treatment groups in stage 2	Stage 2	Stage 1
Overall covariate balance achieved via PS stratification	1.83 (0.10, 3.56)	0.76 (0.15, 1.36)

Safety cohort (n=59,938): relative risk HR (95% CI)

Comparability of treatment groups in stage 2	5 year mortality	Venous thromboembolism (90 days)	MI (90 days)	Prosthetic joint infection (90 days)
Overall covariate balance achieved via PS stratification	0.64 (0.55, 0.75)	0.33 (0.15, 0.74)	0.73 (0.36, 1.45)	0.85 (0.33, 2.19)

Conclusions

- Using routinely collected observational data from the national joint registry, findings replicated TOPTAK trial findings
- Some PS methods were successful in replicating TOPKAT trial findings
  - PS stratification based on the exposed (PKR) cohort for the primary outcome analysis
  - in addition, PS stratification based on the whole cohort and IPW for the primary outcome analysis when the analysis was restricted to patients operated on by surgeons with sufficient experience to have been eligible for TOPKAT
- 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.

Conclusions

- Observational studies and RCTs are mutually complementary in evaluating effectiveness of treatment
- Although observational studies have lower internal validity compared to RCTs
  - evaluate effectiveness of treatment in practice conditions
  - contributes information in subgroups of patients where RCT evidence is not available

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