



Medicines & Healthcare products
Regulatory Agency



Data-Rich Phenomena - Modelling, Analysing & Simulation Using Partial Differential Equations:

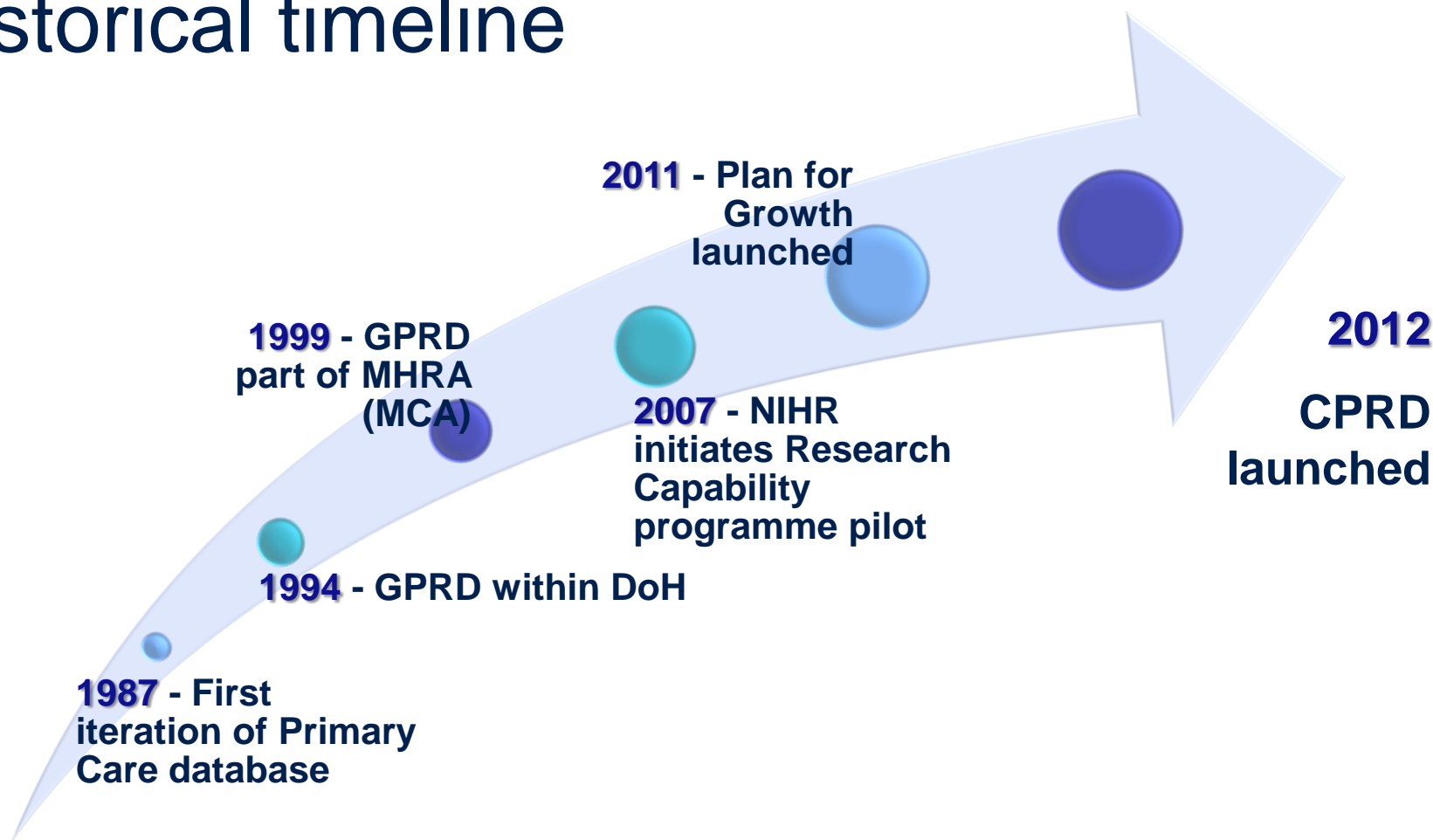
Anonymised Electronic Health Record Data: Uses, Strengths and Weaknesses

Tim Williams, CPRD, 14th December 2015



The Clinical Practice Research Datalink

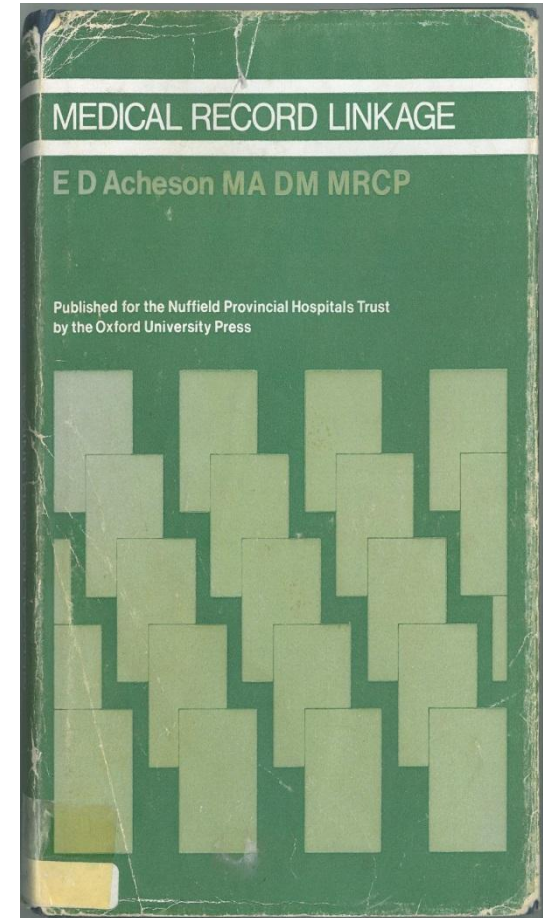
Historical timeline



Potential of using health records in research

NHS 'cradle to grave cohort' of UK population

- Enables research at scale not otherwise possible
- Linkage across health records and other datasets
- Real world settings
- Answer questions needing large datasets
 - Rare conditions
 - Replicate smaller research studies
- Retrospective and prospective
- Long term follow up – added value
- Cost effective



What is CPRD?

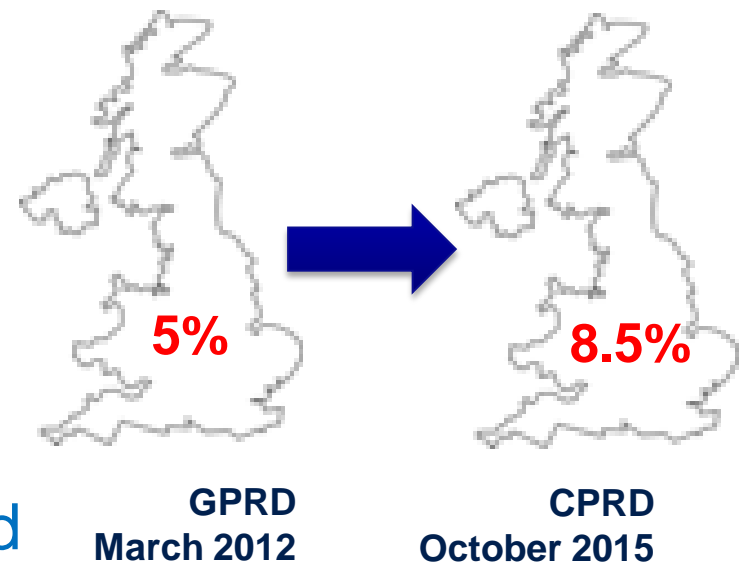
- A longitudinal database of anonymised primary care records linked to other health data sets
- UK Government funded - MHRA and NIHR
- England, Scotland, Wales and NI

28 years of data collection

Total >20 million lives

Current data collection

>5 million patients currently registered
with 620 GP practices



Data collected from primary care record

1.8 billion consultations including

- Drug exposure
- Diagnoses and symptoms
- Referrals
- Laboratory tests
- Vaccination history
- Demographic data
- Full coded record
- No free text
- Patient identifiers removed at source

Pharmacy Stamp
Age
Title, Forename, Surname & Address
NHS Number
Signature of Pharmacist
Date
NHS 69723945556 FP10SS0608

Page 1.
Patient ID : 6002
Mrs. Mistle Mouse
141 Breckfield Road North Liverpool

PLEASE TICK BOX FOR THE MEDICINE YOU REQUIRE AND POST IN THE BOX KEPT AT THE RECEPTION PLEASE FOLLOW 2 WORKING DAYS BEFORE COLLECTION
WE DO NOT ACCEPT TELEPHONE REQUEST FOR PRESCRIPTIONS
Usual Doctor
Date Printed : 10/08/2007

Mat Continus M/R Tablets 60mg
ONE TO BE TAKEN TWICE A DAY
QUANT : 60 tablets (s)
NEXT Issue Due : 16.08.2007

glyceryl Trinitrate Cofree Pump Spray
400 micrograms
AS REQUIRED
QUANT : 1 spray (s)
NEXT Issue Due : 11.12.2005

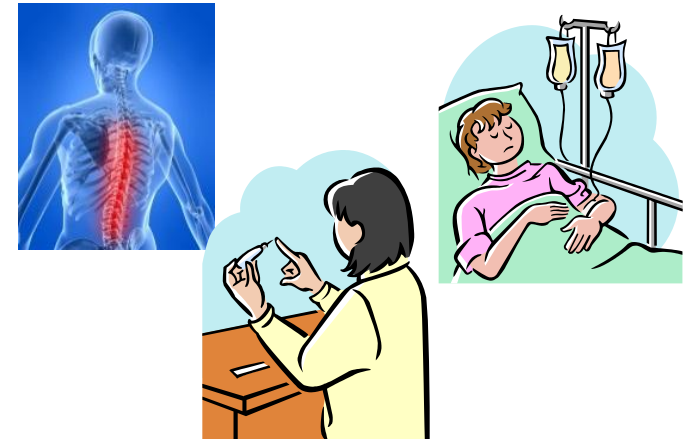
Cereasone Tablets 75 micrograms
ONE TO BE TAKEN DAILY
QUANT : 4 tablets (s)
NEXT Issue Due : 13.11.2007

Aspirin Tablets 75 mg
ONE TO BE TAKEN FOUR TIMES A DAY
QUANT : 450 tablets (s)
NEXT Issue Due : 05.02.2008

Cloprazole Capsules (Gastro-Resistant) 20 mg
1 ONCE DAILY
QUANT : 28 capsule
NEXT Issue Due :

Review Date : 11/12/2007
****REVIEW OVERDUE****

PATIENTS - please read the notes overleaf



Data linkage

National datasets regularly linked to primary care data

- Mortality
- Hospital Episode Statistics (HES)
 - Inpatient, Outpatient and A&E data
- National Cancer Registry
- Diagnostic Imaging Dataset (DIDs)
- Townsend score
- Index of Multiple Deprivation (IMD)

Bespoke data linkage for individual studies

- Eg The Million Women Study, ALSPAC

Research Applications of EHRs

- Drug usage and patterns – Pharmacoepidemiology
- Drug safety – Pharmacovigilance
- Effectiveness and cost effectiveness
- Epidemiology – risks, incidence, prevalence
- Public health - immunisation, disease surveillance
- Health services – quality of care, resource planning, clinical decisions
- Locate potentially eligible patients for clinical trials
- Policy evaluation

Pubic health impact

2 CPRD studies in the shortlisted final 5 for the BMJ UK Research Paper of the Year 2014



thebmj



ORIGINAL ARTICLE

Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation

René Schade, M.D., Frank Andersohn, M.D., Samy Suissa, Ph.D., Wilhelm Haverkamp, M.D., Ph.D., and Edeltraut Garbe, M.D.,

PULSE

At the heart of general practice since 1960

Wednesday 28 January 2015

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One in seven GP-prescribed antibiotic courses fails, study finds

26 September 2014 | By Caroline Price

Submit your questions for RCGP chair Dr Maureen Baker



THE LANCET

Volume 364, Issue 9438, 11–17 September 2004, Pages 963–969

MMR vaccination and pervasive developmental disorders: a case-control study

Medscape MULTISPECIALTY ▾

News & Perspective

Drugs & Diseases

CME & Education

Medscape Medical News > Neurology

Mega Hypertension Study Defines Risk for 12 CVD Outcomes

Sue Hughes

June 11, 2014

NICE

 National Institute for Health and Care Excellence

Suspected cancer Clinical Guidance

For some cancers exclusively drew evidence from CPRD research

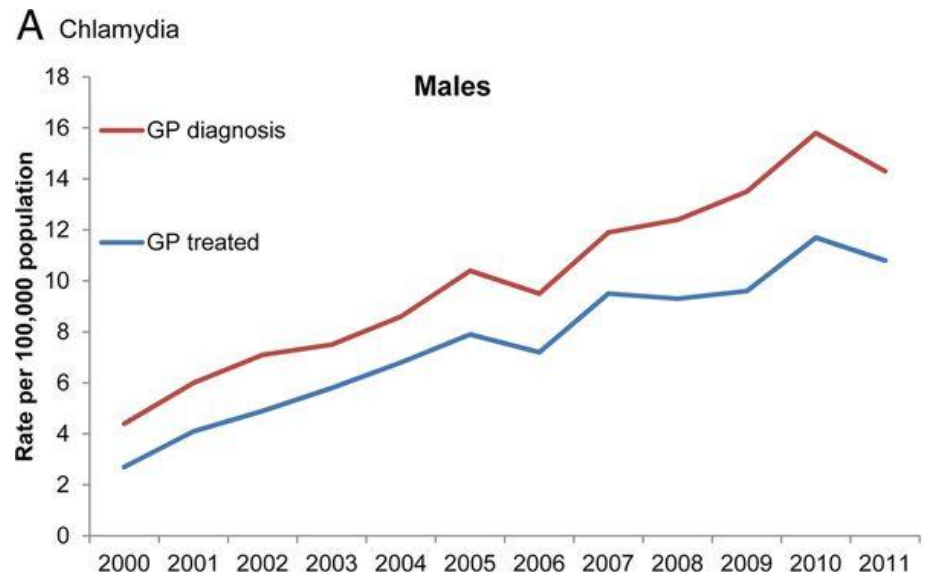
Diagnosis & Treatment of bacterial STIs

Question: Contribution of GPs to the diagnosis and management of STIs, & whether treatment complied with national guidelines

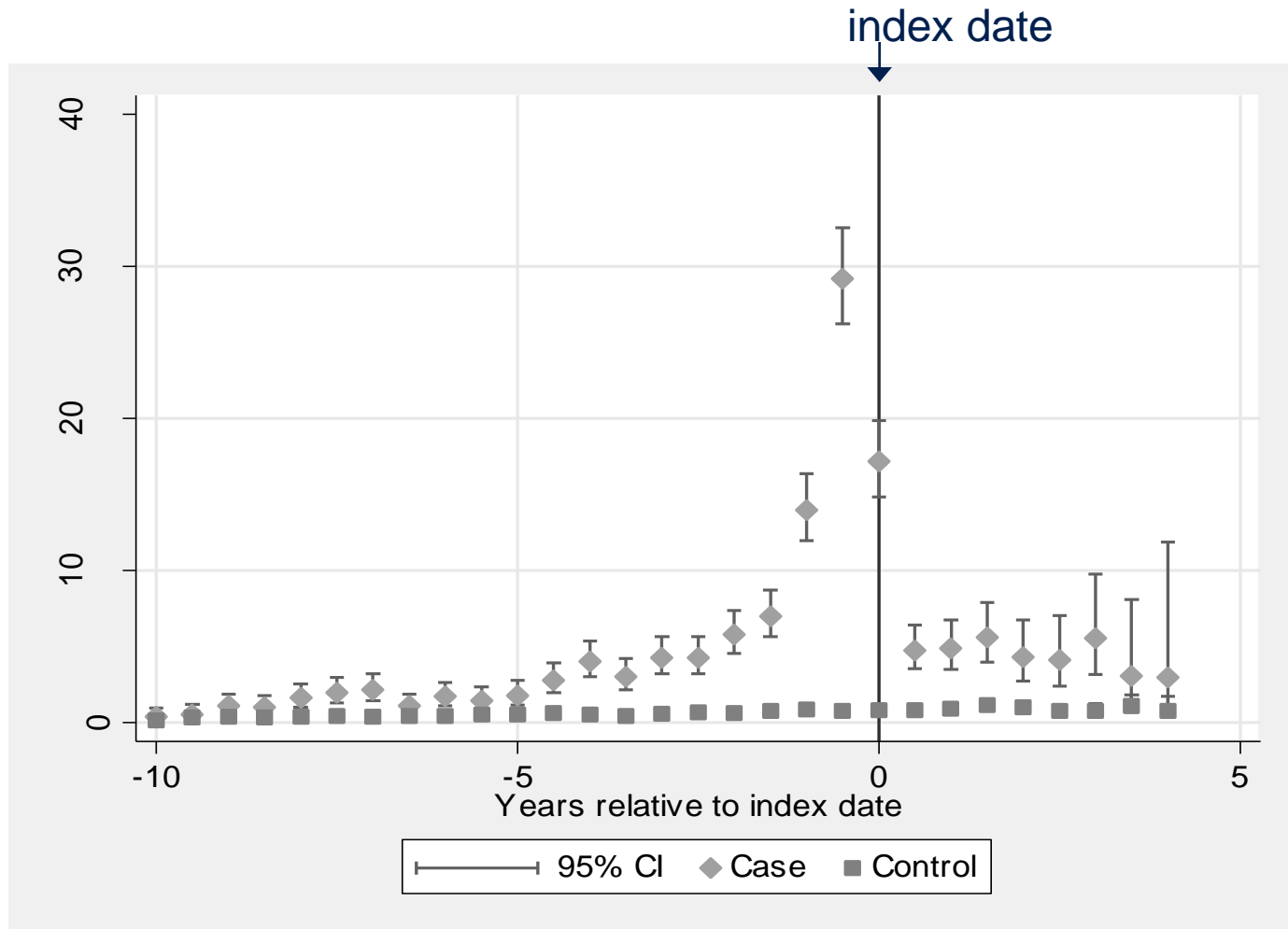
Data used: over 200,000 EHRs from 2000-2011 patients with chlamydia or gonorrhoea, compared to >1.3m records from GU clinics

Result: ~50% of gonorrhoea patients were treated with antibiotic no longer recommended by guidelines.

Wetten et al, BMJ Open 2015;5:e007776



Rate of referral to rheumatology: Fibromyalgia cases and matched controls



CPRD Real World studies across drug development pipeline



Epidemiology, incidence / prevalence

Drug utilisation & prescribing

Standard of care delivery

Pharmacovigilance, Pharmacoepidemiology

Patient referral for intervention studies and clinical trials

Post marketing pragmatic studies

Clinical trials feasibility – patient eligibility

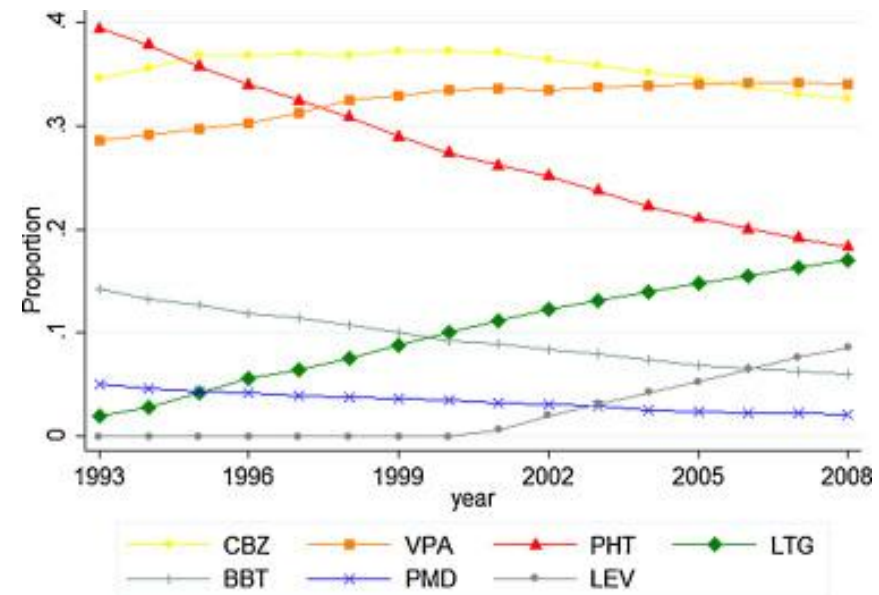
Antiepileptic Drugs utilisation over 15 years

Utilisation trends in UK 1993-2008

Cohort of 63,586 patients - total 361,207 person-years data

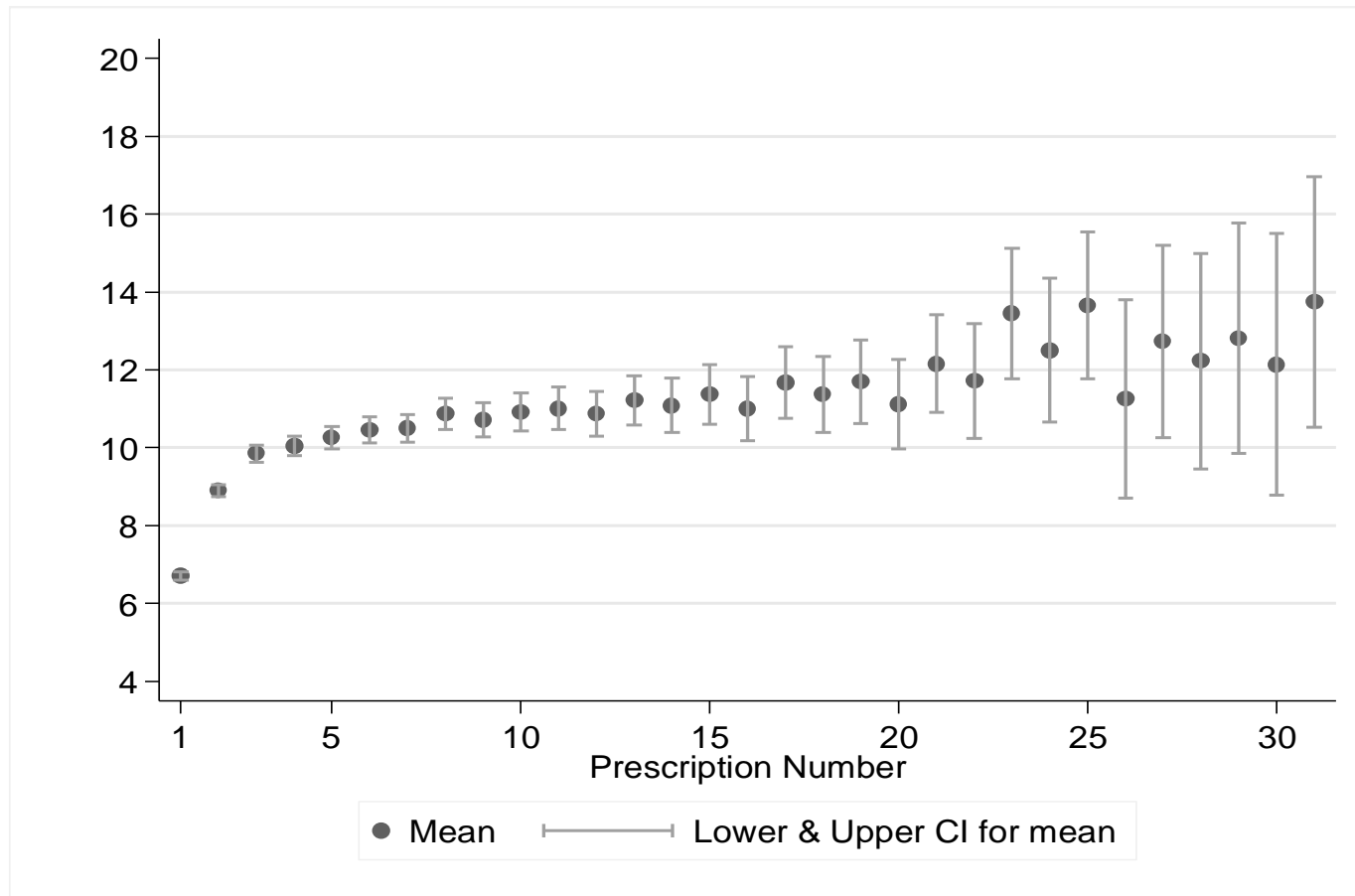
Trends for 21 different medicines
Accuracy of prescription records

Changes generally consistent with national recommendations for prescribing in epilepsy current during this period.



Dose titration

Mean prescription strength over time in a group of patients using buprenorphine patches for chronic pain



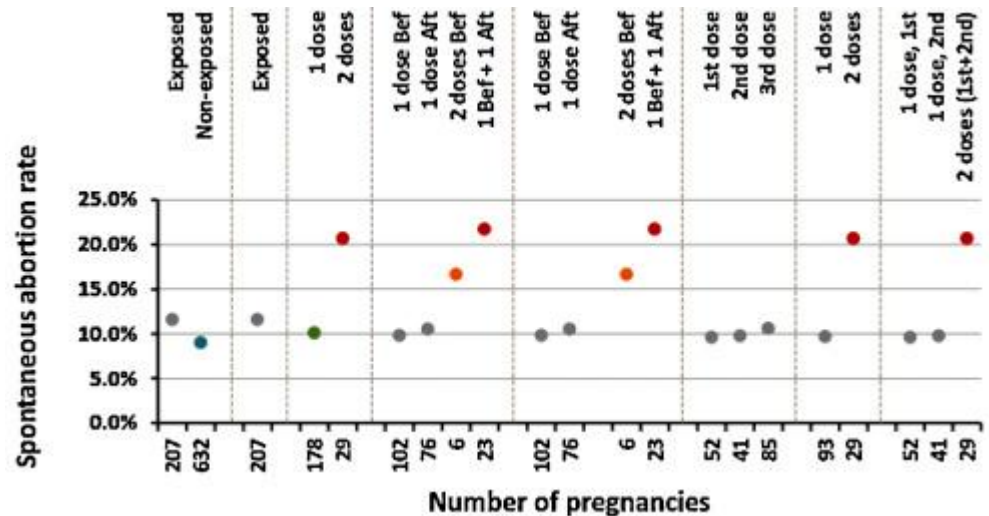
Exposure to HPV-16/18-vacc & spontaneous abortion

- HPV-16/18-vaccine indicated for women (15-25yo) for prevention of cervical cancer
- Analysis of clinical trial data suggested increased risk of spontaneous abortion when LMP occurred -30 to +45 days from exposure

CPRD primary care data for 1,046 HPV-vaccinated women 15-25yo, 09/2008-06/2011.

Results: Increased HR (one or two doses) vs non-exposed, not significantly

- No overall increase in spontaneous abortion in women inadvertently vaccinated
- Women who are pregnant / trying to get pregnant advised to postpone vaccination

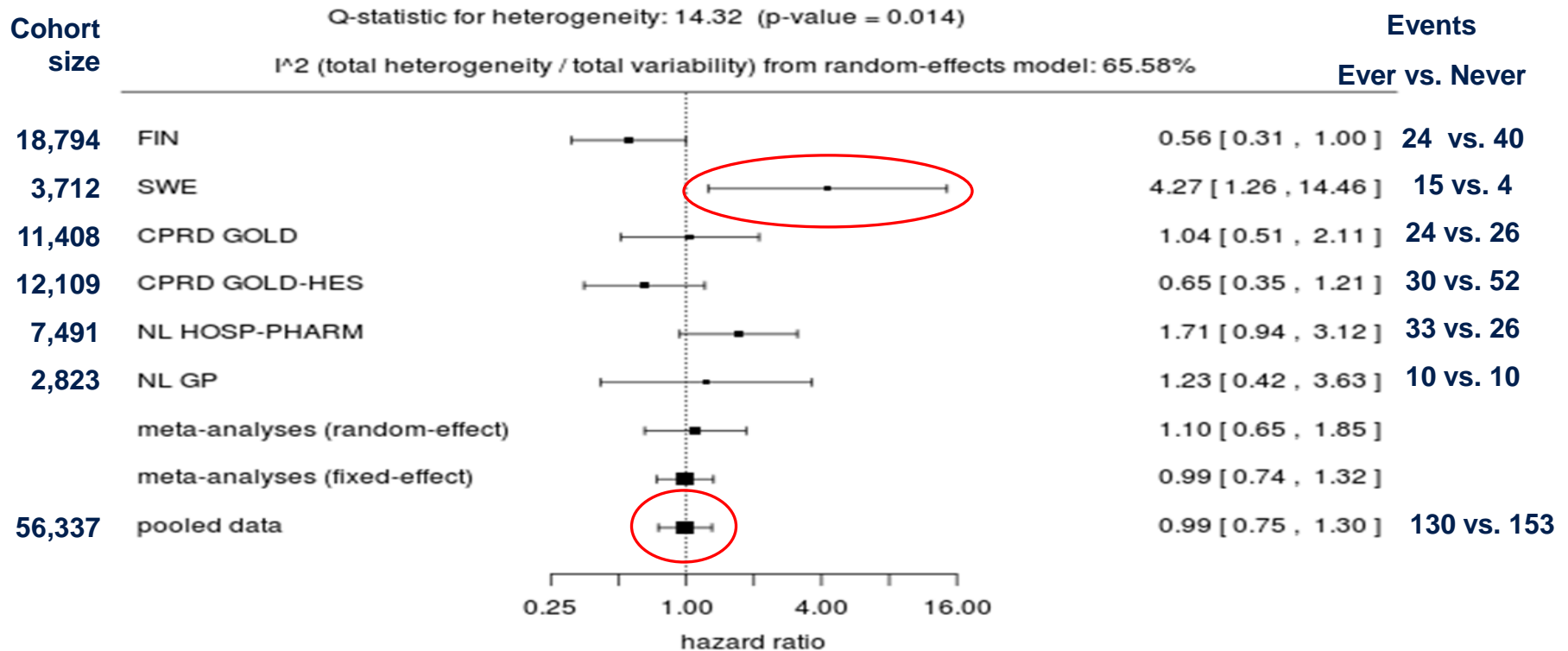


Pioglitazone safety study



Bladder cancer risk in T2DM patients on pioglitazone

Bladder cancer risk for never vs. ever exposed to Pioglitazone



Risk of Mortality and Major Cardiovascular Events in Antipsychotics

Data: Primary care, HES, ONS death data and free-text.

Cohort: 183,392 antipsychotic users, 544,726 general population controls, and 193,920 psychiatric nonusers. Outcomes included all cause mortality, cardiac mortality and sudden cardiac death.

Results:

Outcome	Exposure	Age & sex adjusted Relative Risk [95% CI]	Fully adjusted Relative Risk [95% CI]
All Cause Mortality	General population	Reference	Reference
	Current use	2.98 [2.93-3.03]	2.72[2.67-2.77]
	Psychiatric non-users	Reference	Reference
	Current use	2.15[2.10-2.21]	1.75[1.64-1.87]
Cardiac Mortality	General population	Reference	Reference
	Current use	2.01[1.90-2.10]	1.83[1.74-1.93]
	Psychiatric non-users	Reference	Reference
	Current use	1.62 1.52 -1.74]	1.72[1.42-2.07]

Conclusion: Antipsychotic users are at increased risk of cardiac mortality, all-cause mortality, and SCD compared to a psychiatric nonuser cohort.

Trial feasibility & protocol optimisation

Test Trial Heart disease and diuretics

1,841,139	1,841,139	53,462	31,533	29,809	23,159	14,968	12,716
Search Details	Stack #1	Stack #2	Stack #3	Stack #4	Stack #5	Stack #6	Stack #7
	<ul style="list-style-type: none"> NYHA Class II... Structural Hea... 	<ul style="list-style-type: none"> QOF Heart Fai... QOF LVSD C... 	<ul style="list-style-type: none"> Diuretics BNF ... Diuretics BNF ... 	<ul style="list-style-type: none"> Myocardial Inf... CABG 	<ul style="list-style-type: none"> hgb<10g/dl BMI>40 Severe Obesity 	<ul style="list-style-type: none"> SBP<80 SBP>=140 Hypertension Hypotension 	<ul style="list-style-type: none"> Hyperkalemia Hyperkalemia...

Search Details + 12,716

Patient Demographics

Year of Birth: Before 1960
 Selected Gender: Female, Male

Options: [Modify](#)

Search Results

Patient Count : 15,816 found

North East: 128 found

North West: 3,136 found

Yorkshire & The Humber: 350 found

East Midlands: 410 found

West Midlands: 1,522 found

East of England: 1,604 found

South West: 629 found

South Central: 1,444 found

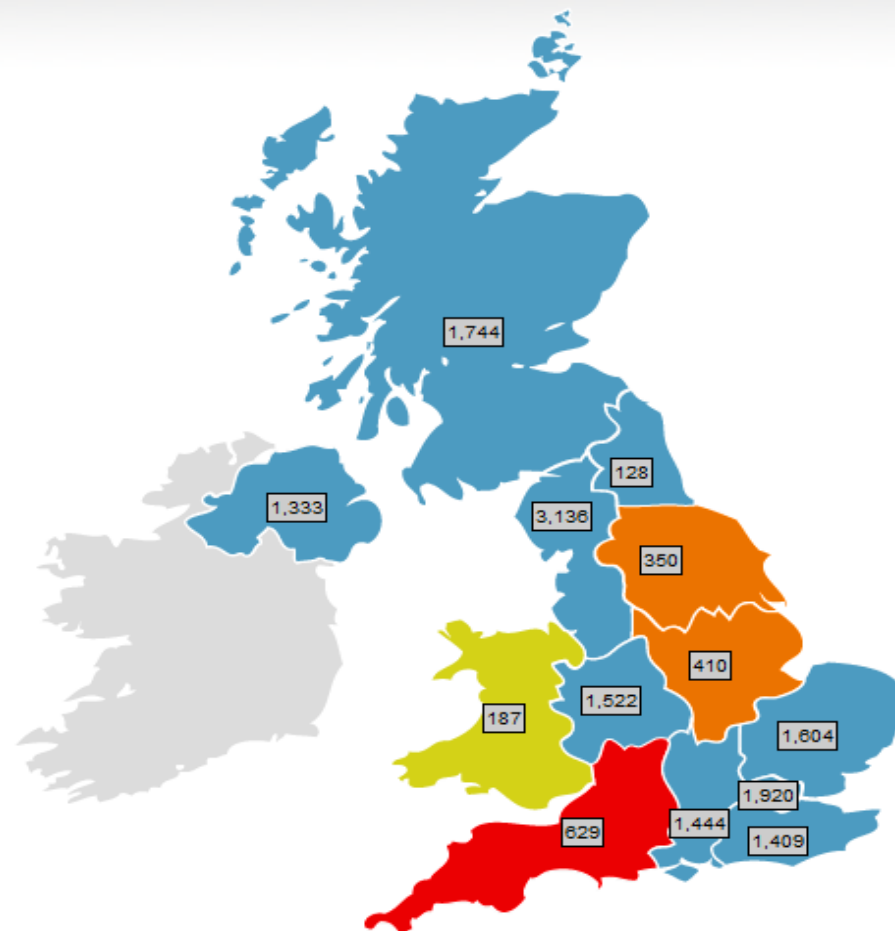
London: 1,920 found

South East Coast: 1,409 found

Northern Ireland: 1,333 found

Scotland: 1,744 found

Wales: 187 found



Actions:

[Recruitment Enquiry](#)[Patient Visualiser](#)[Back To Search](#)

Save Search To:

New Patient Card [Save](#)

“Explanatory” vs “Pragmatic” trials

Explanatory	Pragmatic
“Can this intervention work under ideal conditions?”	“Does this intervention work under usual conditions?”
Maximise internal validity	Maximise external validity
Selective recruitment: high risk, highly responsive patients with high compliance	Not selective: include all patients with condition of interest
Intervention: tightly controlled, applied by highly trained trial personnel and carefully monitored	Flexible: intervention applied by usual range of providers and settings
Control intervention: carefully designed to maximise change of detecting benefit of experimental intervention	Comparison is with normal standard of care
Follow-up: intensive visit schedule, extensive data collection, shorter duration, all patients	No formal follow-up. Use routine data(bases) to detect outcomes (including adverse)
Adherence & protocol deviations: closely monitored	Minimal monitoring.
Analysis: additional per protocol and subgroup analyses to identify maximum achievable treatment effect	Intention to treat analysis only

J Clin Epidemiol 2009;65;464-75



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Challenges of pharmacoepidemiology with databases

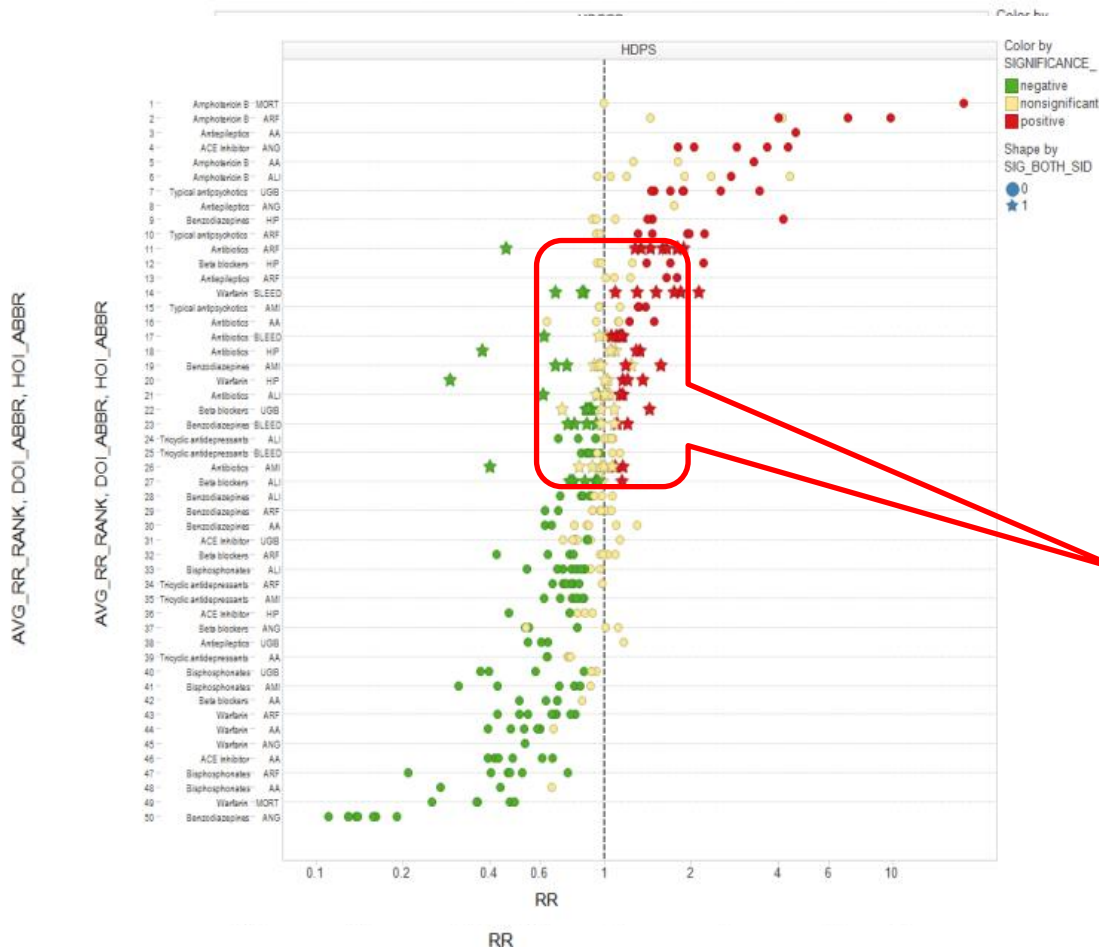


Same database (CPRD), different answers: Statins and fracture risk

	[1] Meier <i>et al</i> Adjusted OR (95% CI) Selected population	[2] van Staa <i>et al</i> Adjusted OR (95% CI) Entire population
Any fracture	0.55 (0.44-0.69)	1.01 (0.88-1.16)
Femur/hip	0.12 (0.04-0.41)	0.59 (0.31-1.13)
Vertebral	0.14 (0.02-0.88)	1.15 (0.62-2.14)

[1] JAMA 2000;283:3205-10. [2] JAMA 2001;285:1850-55

Same study design: different databases

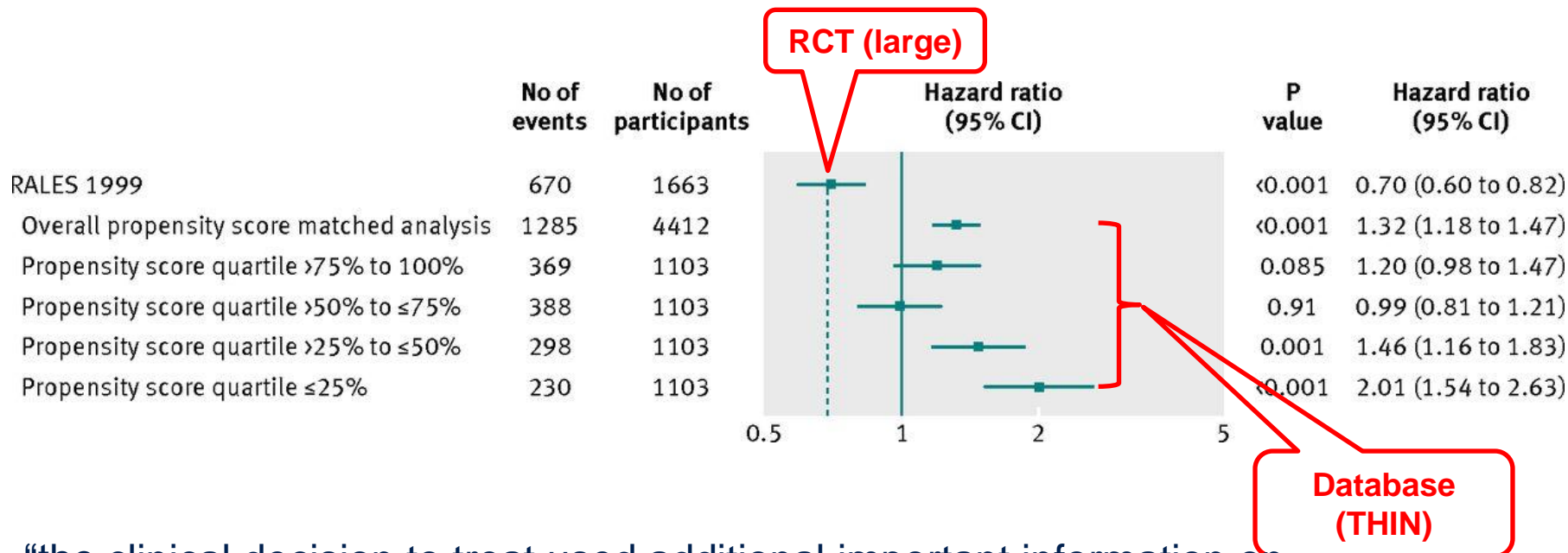


- 53 drug-outcome pairs
- 10 different US databases: insurance claims, and integrated EHRs from different settings and populations.
- Standard method for each database (self controlled case series)
- RESULTS: 19 (35%) drug-outcome pairs had significant increased AND significant decreased risk
- only 5 (9%) drug-outcome pairs had consistent findings across databases

Evaluating the Impact of Database Heterogeneity on Observational Study Results.

Madigan D et al. Am. J. Epidemiol. 2013; 178(4): 645-651.

Database study fails to replicate RCT findings: Spironolactone in heart failure: effect on mortality



“the clinical decision to treat used additional important information on severity of heart failure that the propensity score did not capture”

“The challenge of a latent function such as confounding by indication is that it (by definition) cannot be measured directly but only tangentially through its effects, if it is recognised at all.”

Nick Freemantle et al. BMJ 2013;347:bmj.f6409

Bias and Confounding

- Confounding by indication can occur if some unmeasured variable is associated with both the outcome *and* with the study treatment
- Measuring disease severity can be challenging, and lead to confounding if study treatment is preferentially given to patients with more (or less) severe disease

Summary

- The CPRD and other EHR databases - key resource for generating evidence on:
 - Disease epidemiology and Drug utilisation
 - Drug safety / Adverse drug reactions
 - Health outcomes and resource utilisation
 - Health service planning
- As with any non-randomised study, observational studies using databases are susceptible to bias and confounding.
- Large scale randomised studies embedded within EHR databases combine some of the advantages of each study types