PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium

Outcomes of studies for six adverse event-drug pairs and five databases: what did we learn?

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Outline

- Drug-AE pairs and designs
- Selected results
- Practical considerations/lessons learned
- Methodological conclusions
- Recommendations

Drug-AE pairs and designs

Drug-AE pair	Descriptive	Cohort	Nested case control	Case crossover	Self-Controlled case series*
AB-ALI	All Databases	CPRD BIFAP	CPRD BIFAP	CPRD	CPRD
AED-Suicidality	All Databases	CPRD DKMA			
AD- Hip	All Databases	THIN Mondriaan BIFAP	THIN Mondriaan BIFAP	THIN Mondriaan	THIN Mondriaan
BZP-Hip	All Databases	CPRD BIFAP Mondriaan	CPRD BIFAP Mondriaan	CPRD BIFAP	CPRD BIFAP
B2A-AMI	All Databases	CPRD Mondriaan			
CCB-Cancer	All Databases	CPRD			

AD/BZD and Hip Fracture

Eligibility
- Patients >= 18 years
- Registered for at least 12 months at GP practice
- Use during 2001 to 2009
- Initiators (no use 6 m prior to inclusion)
- No hip fracture 12 m prior to inclusion

Cohort study
- Current, recent use vs. past use
- Follow up until event, eos, leaving GP practice

Self-controlled case series
- Also including cases of HF occurring prior to initiating AD use
- Follow up until eos, leaving GP practice

Nested case-control study
- 1:4 matching (age, gender, time from inclusion)
- Matching including/excluding GP practice

Case-crossover study
- Case moment matched with 4 control moments (-3, -6, -9 and -12 months from case date)

Methods

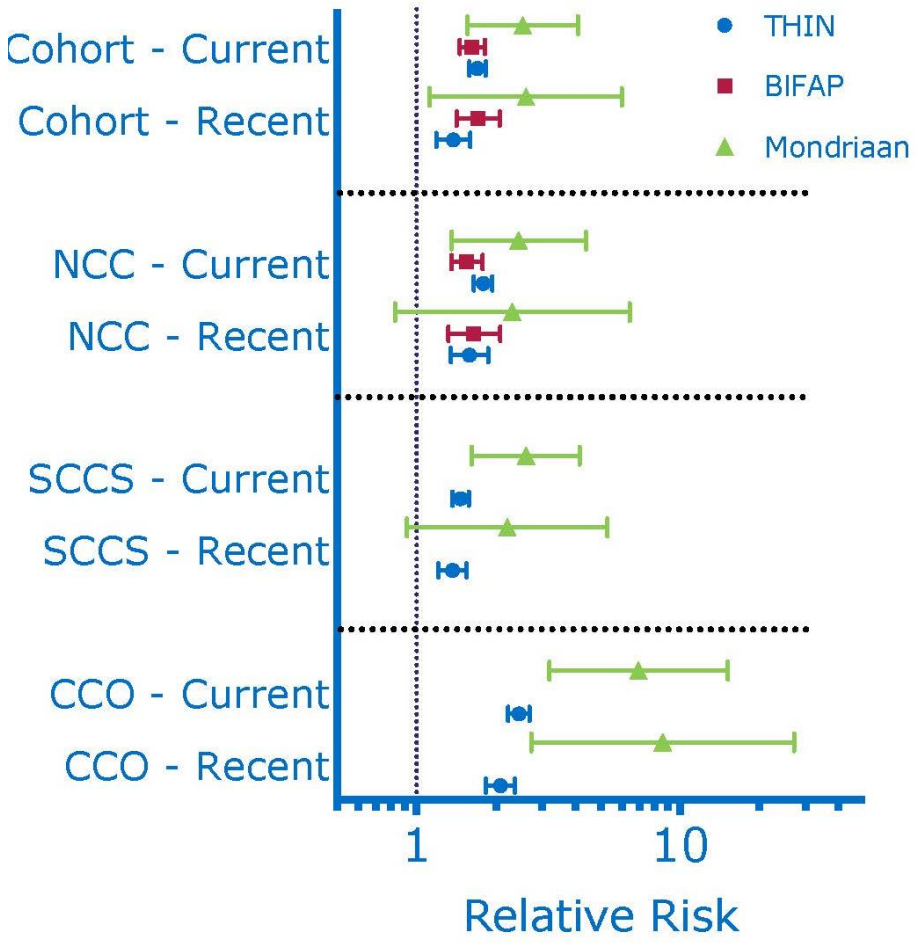
- Data
  - Bifap (Spain), Mondriaan (NL), THIN (UK, AD), CPRD (UK, BZD)
- Exposure to AD/BZD
  - Construction of treatment episodes - Current, recent & past use
- Outcome – hip fracture
- Analytical models
  - Model 1: age & sex
  - Model 2: Model 1 + Well established risk factors, glucocorticoid use (systemic) , +/- Life-style factors (BMI, smoking, alcohol use)
  - Model 3: Model 2 + Risk factors immediately related to outcome: history of osteoporosis or other bone diseases, use of bisphosphonate or other bone protecting drugs
  - Model 4: Model 3 + Other co-morbidities and co-medication use

Results – Patient disposition and cohort definition

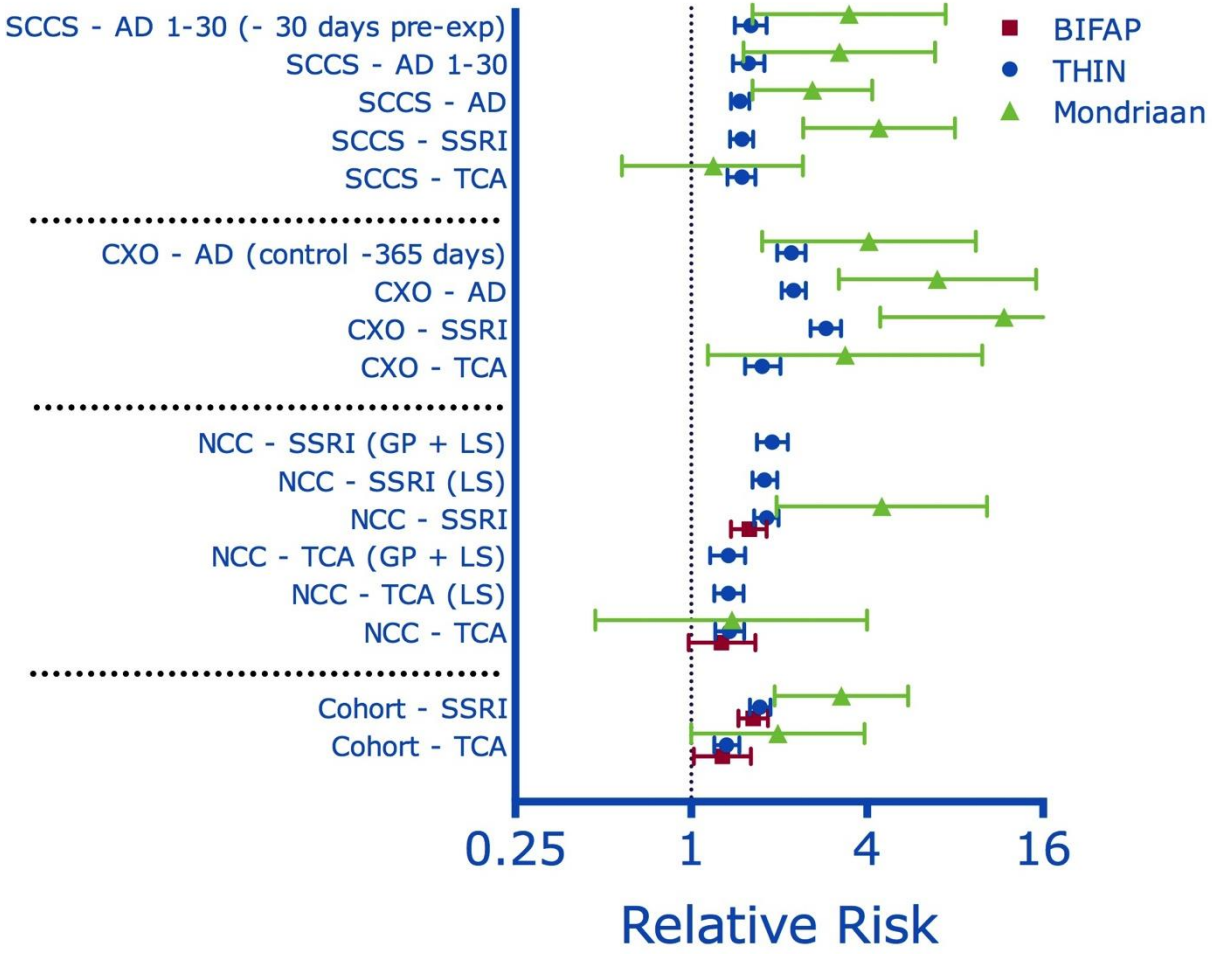
	BZD cohort			AD cohort		
	Bifap	**Mondriaan**	**CPRD**	**Bifap**	**Mondriaan**	**THIN**
Subjects initially identified*	674,100	78,813	744,049	304,861	31,319	894,150
Included in analysis	**557,066 (82.6%)**	**50,464 (64.0%)**	**669,835 (90.0%)**	**252,203 (82.7%)**	**22,954 (73.3%)**	**587,637 (65.7%)**
Cases of hip fracture	2459 (0.4%)	151 (0.3%)	4,469 (0.7%)	1535 (0.6%)	82 (0.4%)	3756 (0.6%)
Age mean (SD)	55.1 (18.7)	48.7 (16.6)	51.1 (18.4)	50.9 (16.9)	48.8 (17.2)	49.7 (17.0)
Female, %	65.5%	57.7%	60.5%	72.7%	63.6%	63.7%

* Received an AD/BZD prescription within the study period, =>18 years, at least 1 year enrollment prior to entry

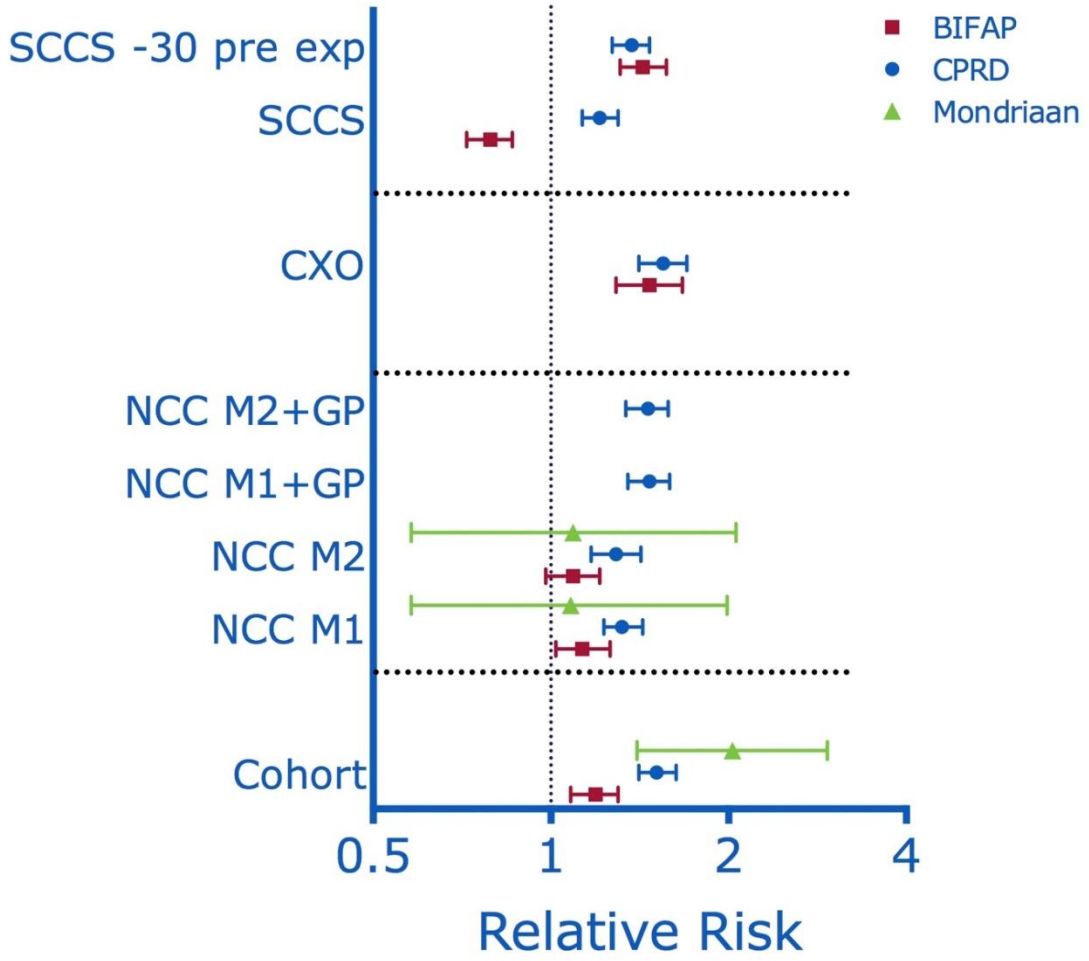
Antidepressants and risk of Hip Fracture



Antidepressants and risk of Hip Fracture



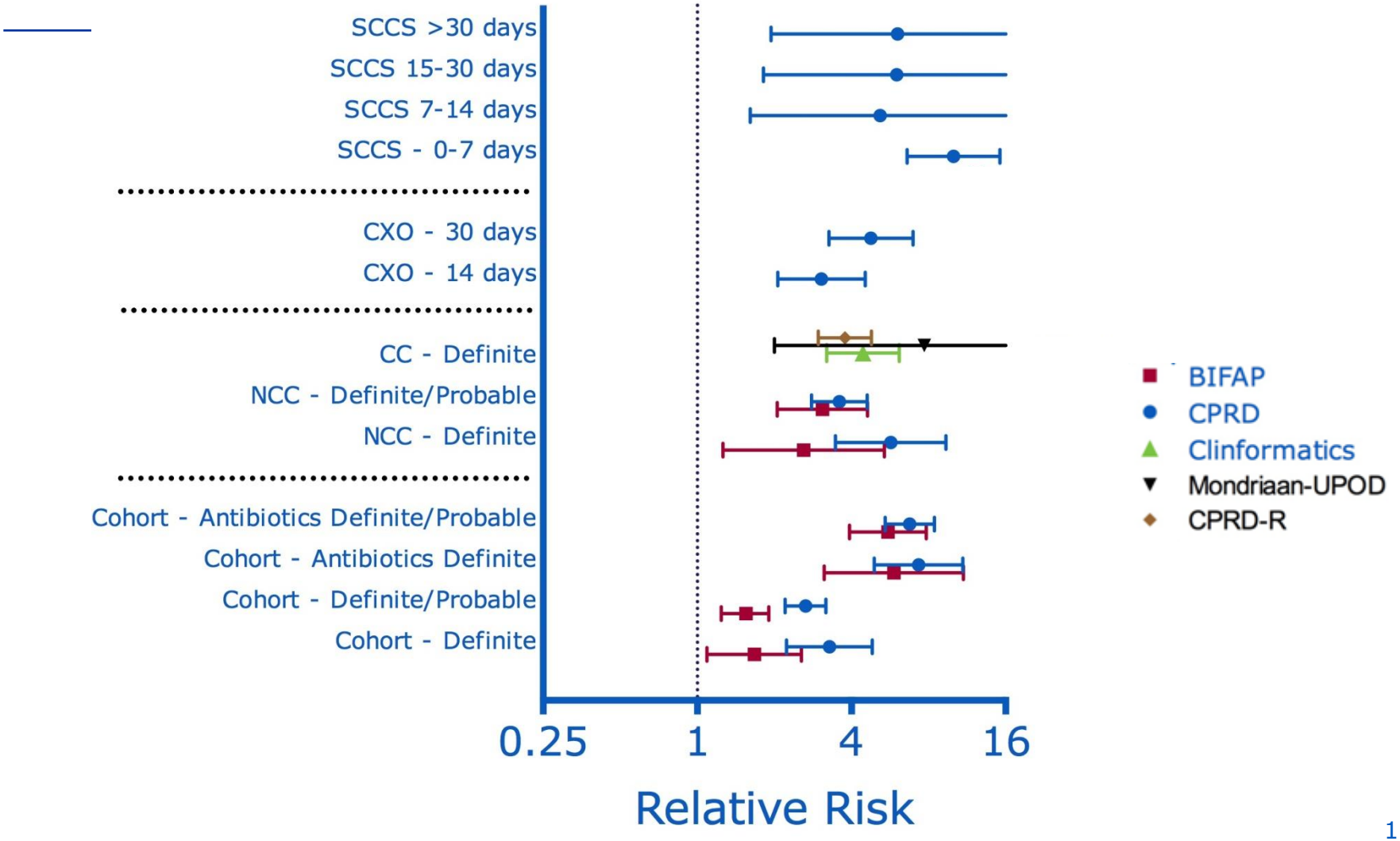
Benzodiazepines and risk of Hip Fracture



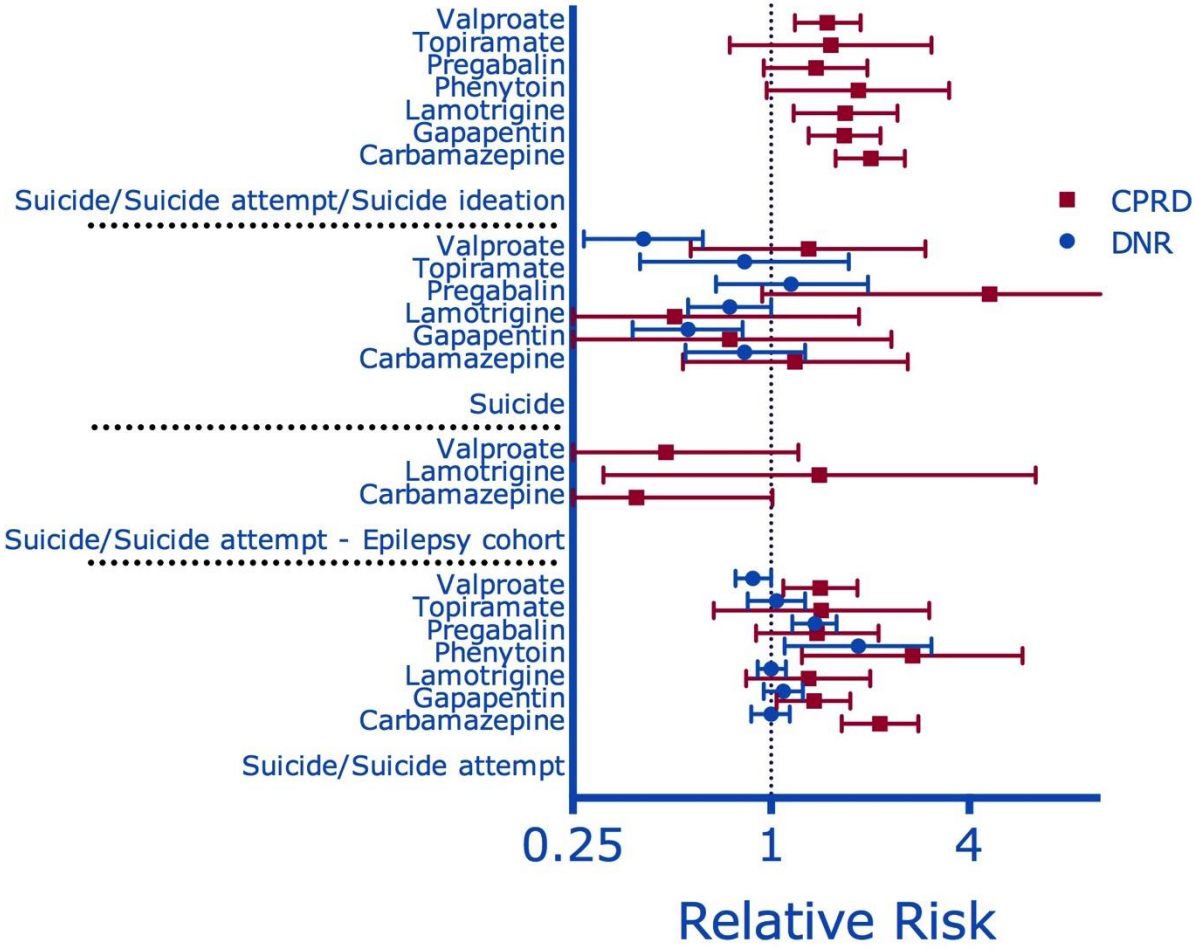
Conclusions AD/BZD and Hip fracture

- Applying different design in varying databases shows consistently increased risk of HF associated with AD and BZD use, although size estimates vary
- Age and gender the most influential confounders, other such as co-medication, life-style and GP practice of less influence

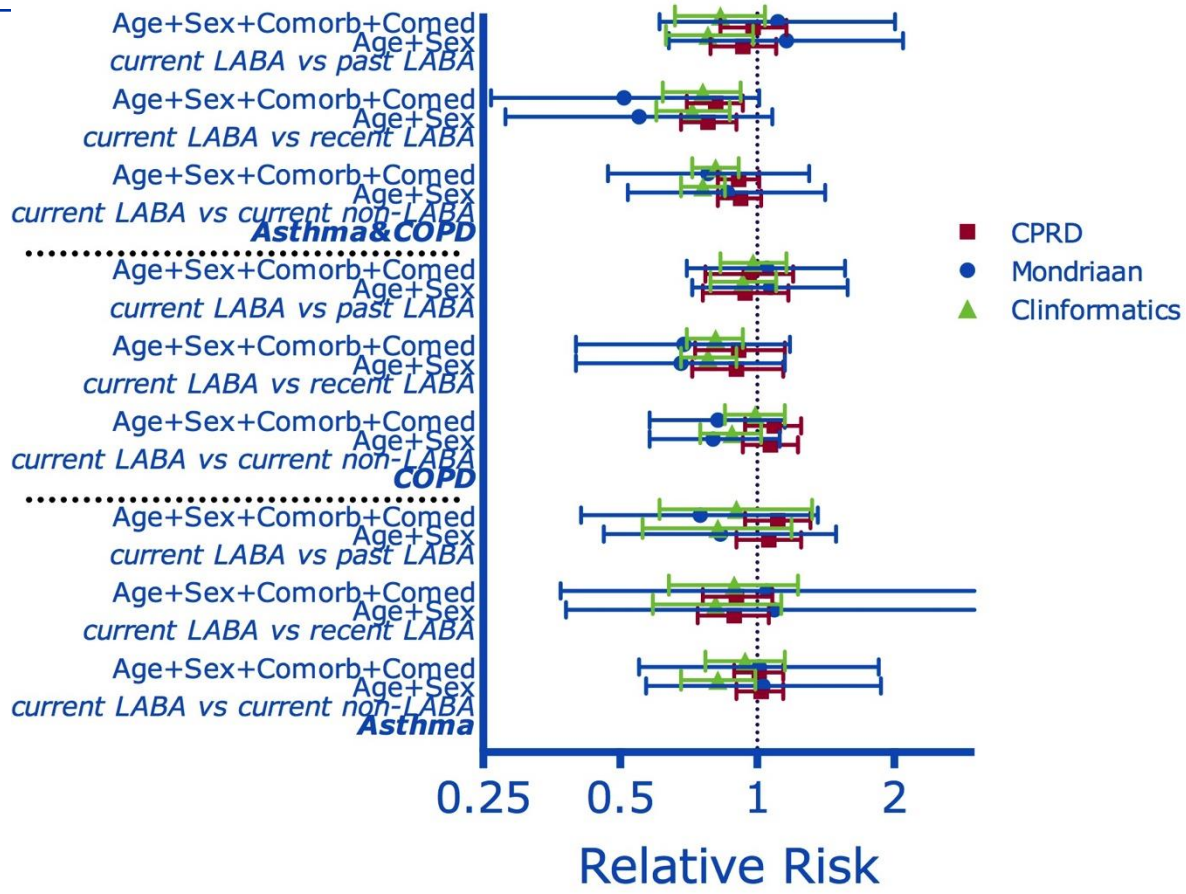
AB/ALI All DBs/Designs

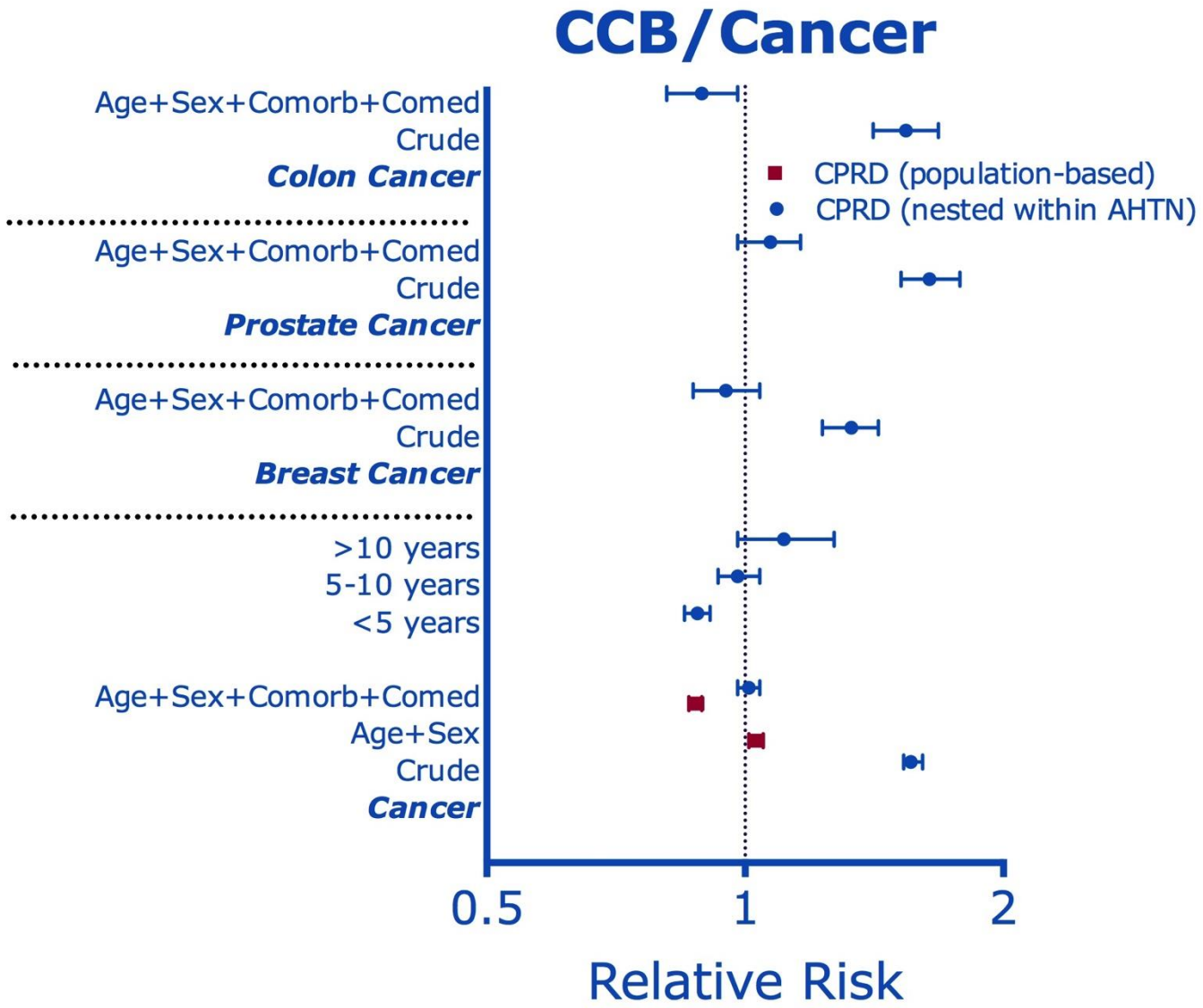


AED/Suicide All DBs



LABA and risk of MI




CCB/Cancer
Age+Sex+Comorb+Comed
Crude
Colon Cancer
Age+Sex+Comorb+Comed
Crude
Prostate Cancer
Age+Sex+Comorb+Comed
Crude
Breast Cancer
>10 years
5-10 years
<5 years
Age+Sex+Comorb+Comed
Age+Sex
Crude
Cancer
CPRD (population-based)
CPRD (nested within AHTN)
0.5
1
2
Relative Risk

Practical considerations/lessons learned

- Substantial time (+/-1 year) needed to reach agreement on common protocol between different research centres and stakeholders (regulator, industry, academia)
  - Consensus/buy-in on approach between stakeholders!
- Registration of protocols at ENCePP to guarantee transparency
- Blinding of centres for in-parallel analysis and replication analysis
  - -stepwise unblinding after completion of each design
- Research question determined choice of database and design of data collection
  - Acute Liver Injury only feasible in CPRD and BIFAP (and for replication in Clinformatics and Mondriaan-UPOD)
  - Suicide only feasible in CPRD and DNR
  - Cancer only feasible in DBs with long observation periods
  - CXO and SCCS only feasible for acute transient events

Practical considerations/lessons learned

- **Detailed data-specification** documents are needed to harmonize procedures and analyses
  - Coding of exposure, outcome, confounders
  - Programming of data-analytical datasets
  - Different statistical packages may have different default settings and may cause variation in results

- **Frequent communication** between research centres to reduce variation in "interpretation" of protocol

- During programming and analysis phase it becomes apparent that despite detailed data-specification **further clarification** is required and needs documentation

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Methodological determinants of drug-AE associations (1)

- **Study design**
  - Case-only estimates > Cohort/NCC/CC estimates
- **Databases**
  - Some variation in size of estimate, direction consistent for AB/ALI, AD-BZD/HIP, LABA/AMI
  - Large variation in size and direction of estimate for databases (AED/SUI)
- **Study population**
  - Impact of AED users versus epilepsy, population based versus nested (AB, CCB)
  - No impact of indication (asthma, copd)

Methodological determinants of drug-AE associations (2)

- **Outcome definition**
  - Small impact on AB/ALI associations
  - Large impact on AED/SUI associations

- **Exposure definition**
  - Impact of individual/classes of compounds (AB, AD, AED, BZD)
  - Impact of dosage (BZD), duration (AB), reference group (LABA)
  - No impact of duration (BZD, AD, CCB).

Methodological determinants of drug-AE associations (3)

- **Methods to adjust for <u>observed</u> confounding**

  - Control for confounding factors (e.g. +/- comborbidity/comedication/lifestyle), matching algorithm, matching on GP practice had little impact on associations between:
    - AB-ALI
    - BZD/AD-Hip
    - LABA/AMI
    - AED/SUI (CPRD, DNR)

  - Control for confounding factors had large impact on:
    - CCB-Cancer (CPRD)

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Recommendations

- Develop common protocol with great detail to reduce methodological differences and "interpretation" by researchers
- Solid infrastructure for communication/collaboration
- Conduct analysis in parallel in multiple DBs versus "a priori" pooling of DBs
  - Cherish heterogeneity and explore its sources

Recommendations

- To test robustness of findings conduct multiple sensitivity analyses:
  - Multiple designs ?
  - Exposure (e.g. Individual AEDs), outcome (e.g SUI), confounding adjustment

- Replication needed if parallel analysis consistent?

What's next ?

- Network for observational safety and effectiveness studies
  - Common protocol in multiple databases may increase confidence in investigations
  - Testing of existing network
    - New safety signals
    - Platform for methods development and testing
  - Further development of network infrastructure
    - Library of codes/programs
    - Governance of network
    - Structure for collaboration/communication
    - Collaboration with other networks

VIEWPOINT

When are observational studies as credible as randomised trials?

Jan P Vandenbroucke

Cartoon deriding chronic disease epidemiology, for randomly generating fears by investigating seemingly unrelated risk factors and diseases

This cartoon contains a grain of truth: observational research is at its methodological best in discovering unexpected adverse effects.

Lancet 2004; **363:** 1728–31

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