LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

STRengthening Analytical Thinking for Observational Studies: STRATOS initiative:

Study Design

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Acknowledgments & Conflicts of Interest

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European Commission appointed independent Member of Pharmacovigilance & Risk Assessment Committee of EU at the European Medicines Agency

Member of CIOMS Working Group on Meta-analysis for safety

LSHTM (but not SE) funded by several pharmaceutical companies

Member of expert working groups at the UK Medicines & Healthcare Products Regulatory Agency (MHRA)

All remarks are a personal viewpoint and have not been approved by other members of TG5

STRATOS

- STROBE has provided guidance on *Reporting*
- STRATOS is an attempt to improve conduct
  - ENCePP has guidance on methods-http://www.encepp.eu/standards_and_guidances/documents/ENCePPGuideofMethStandardsinPE_Rev4.pdf
- Guidance on reporting is like lighting up a room-not saying if it is clean
- Critical appraisal is saying if it is clean enough-
  - Operating theatre or coal shed?
- Guidance on conduct is to make sure the room is clean enough


Communication
Report Writing
Analysis
Execution
Planning
Design
Objectives

Some principles

- single observational studies rarely definitive (or perfect!)
- Assessing epidemiologic evidence -> a process of triangulation across studies, aim to contribute to the pool of knowledge
- different populations, variety of designs, investigators, and methods,
- often involving meta-analysis (not “top of the hierarchy”) & integration of data from variety of sources and study types
- obtain valid effect estimates in a particular population during a particular risk period

Purposes

1. Descriptive
   - Disease oriented
   - Intervention oriented
     - Intervention utilisation
       - E.g. Compliance with Summary of Product Characteristics (label)
     - Risk factor distribution
     - Spontaneous reports of adverse drug reactions
2. Comparative
   - Causal effects; benefits, comparative effectiveness, harms

Comparative studies

The main focus of epidemiology

- They will usually want to estimate causal effects; {Safety- demonstrated absence of harm}
  - Usually they focus on harms, but may also look at-
    - Benefits (often reduction in harm), comparative effectiveness,
  - Moves towards formal decision making for risk/benefit
    - Will require confirmation of benefit from RCTs in practice

Main Comparative designs

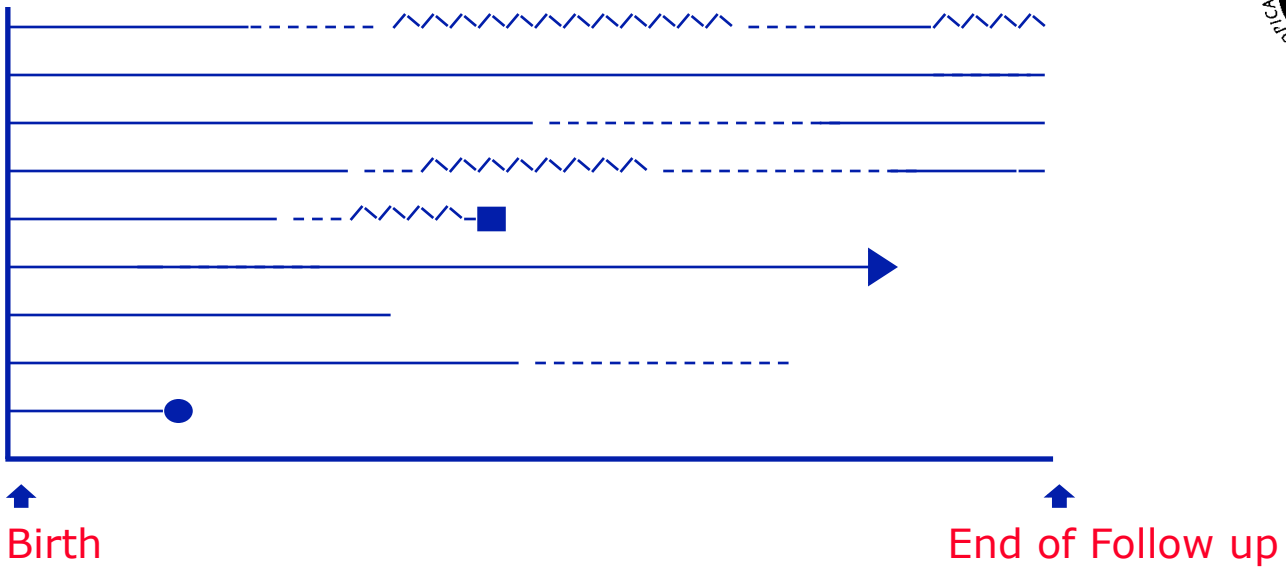
- Randomised Controlled Trials (RCTs)
  - Systematic reviews (SRs) of RCTs
- Cohort Studies
  - "Field" studies; registry-based; databases
- Case-control studies
  - "Field" studies; registry-based/aided; databases
- Distinguish incidence and prevalence in each

Time has only one direction

- In some senses all studies are based on a cohort
- RCTs have random allocation to treatment, then follow-up
- Observational studies have non-random allocation and follow-up (though if totally deterministic, then extra information outside study or strong, untestable, assumptions required to interpret them)
- The issues are
  - what is the source population?
  - what is the outcome?
    - (Incidence or prevalence)
  - How is the sampling done?

Study Design Options

- All epidemiological studies are (or should be) based on a particular population (the ***source population***) followed over a particular period of time (the ***risk period***)
- The different study design options differ only in how the source population is defined and how information is drawn from this population and time period



- Death
- other death
- lost to follow up
- "non-diseased"
- symptoms
- severe disease

Cohort studies

- define a source population - exposed & unexposed
  - follow-up (FU) to event
- Not just in databases or even in large longitudinal cohort studies (ALSPAC, National Cohorts, 1958, 1970)
  - Some cohort studies (often registry-based) have no valid comparative groups)
- `Self-Controlled Case Series' is a special case
- Case-cohort design {sample <100% non-cases}

Incidence and Prevalence

- ***Incidence*** is the number of new cases of the condition over a specified period of time
- ***Prevalence*** is the number of cases of the condition at a particular point in time

A Hypothetical Incidence Study

	Exposed	Non-exposed	Ratio
Cases	1,813	952	
Non-cases	8,187	9,048	
Total	10,000	10,000	
Person-years	90,635	95,163	
Incidence rate	0.0200	0.0100	2.00
Incidence proportion (risk)	0.1813	0.0952	1.90
Incidence odds	0.2214	0.1052	2.11

A Hypothetical Case-Control Study

	Exposed	Non-exposed	Odds
Cases	1,813	952	1,813/952
Controls	1,313	1,452	1,313/1,452
Odds	1,813/1,313	952/1,452	
Odds ratio			2.11

Odds Ratio

- OR=(1813/1313)/(952/1452) = 2.11
- This ***incidence case-control study*** yields the same estimate as would have been obtained by an incidence study but with a much smaller number of participants because we include ***all*** of the cases but only a ***sample*** of the non-cases

Methods of Sampling Controls

- From ***survivors*** (non-cases at end of follow-up) = cumulative sampling
- From ***source population*** = case-cohort sampling
- From ***person-years*** = density sampling

Methods of Sampling Controls

	Exposed	Non-exposed	Odds ratio
Cases	1,813	952	
Controls			
from survivors	1,313	1,452	2.11
from source population	1,383	1,383	1.90
from person-year	1,349	1,416	2.00

Misconceptions re: Case-Control Studies

- Proceeds from effect (disease) to cause (exposure), i.e. reverse causality
- Inherently more prone to bias than cohort studies
- Odds ratio only approximately estimates the relative risk
- Depends on a "rare disease" assumption
- book by Keogh & Cox for modern views (Cambridge UP 2014)

Prevalence Case-Control Studies

This ***prevalence case-control study*** yields the same estimate as would have been obtained by a prevalence study but with a much smaller number of participants because we include ***all*** of the prevalent cases but only a ***sample*** of the non-cases

Study Design Options

		Sampling on outcome	
		No	Yes
Study outcome	Incidence	Incidence studies	Incidence case-control studies
	Prevalence	Prevalence studies	Prevalence case-control studies

Strengths & weaknesses - RCTs

- RCTs strong for causal inference (but not perfect)
  - confounders not usually relevan t{but see Williamson et al Stat Med. 2014; 33(5): 721–737}
  - Might be done in registries or databases
  - Staa TP et al. Pragmatic randomised trials using routine electronic health records: putting them to the test. BMJ. 2012;344:e55. also Pharmacoepidemiology session
  - New NEJM paper: http://www.nejm.org/doi/pdf/10.1056/NEJMoa1308789
- Weaknesses
  - Many biases can arise – selective publication worst for pepi
  - Costly in time & resources; unrepresentative?
  - Short FU; small sample size for clinical harms (& benefits?)
  - Elderly, pregnant, co-morbidity & co-prescription limited

Observational Medical Outcomes Partnership
Third Annual Symposium

A Public Private Partnership of
THE FOUNDATION
FOR THE NATIONAL
INSTITUTES OF HEALTH

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These slides are a selection from the OMOP symposium in June 2012

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See also special issue of *Drug Safety* 2013;36 Suppl 1:S3-4.

Ground truth for OMOP 2011/2012 experiments

isoniazid

fluticasone

indomethacin

clindamycin

	Positive controls	Negative controls	Total
Acute Liver Injury	81	37	118
Acute Myocardial Infarction	36	66	102
Acute Renal Failure	24	64	88
Upper Gastrointestinal Bleeding	24	67	91
Total	165	234	399

ibuprofen

loratadine

sertraline

pioglitazone

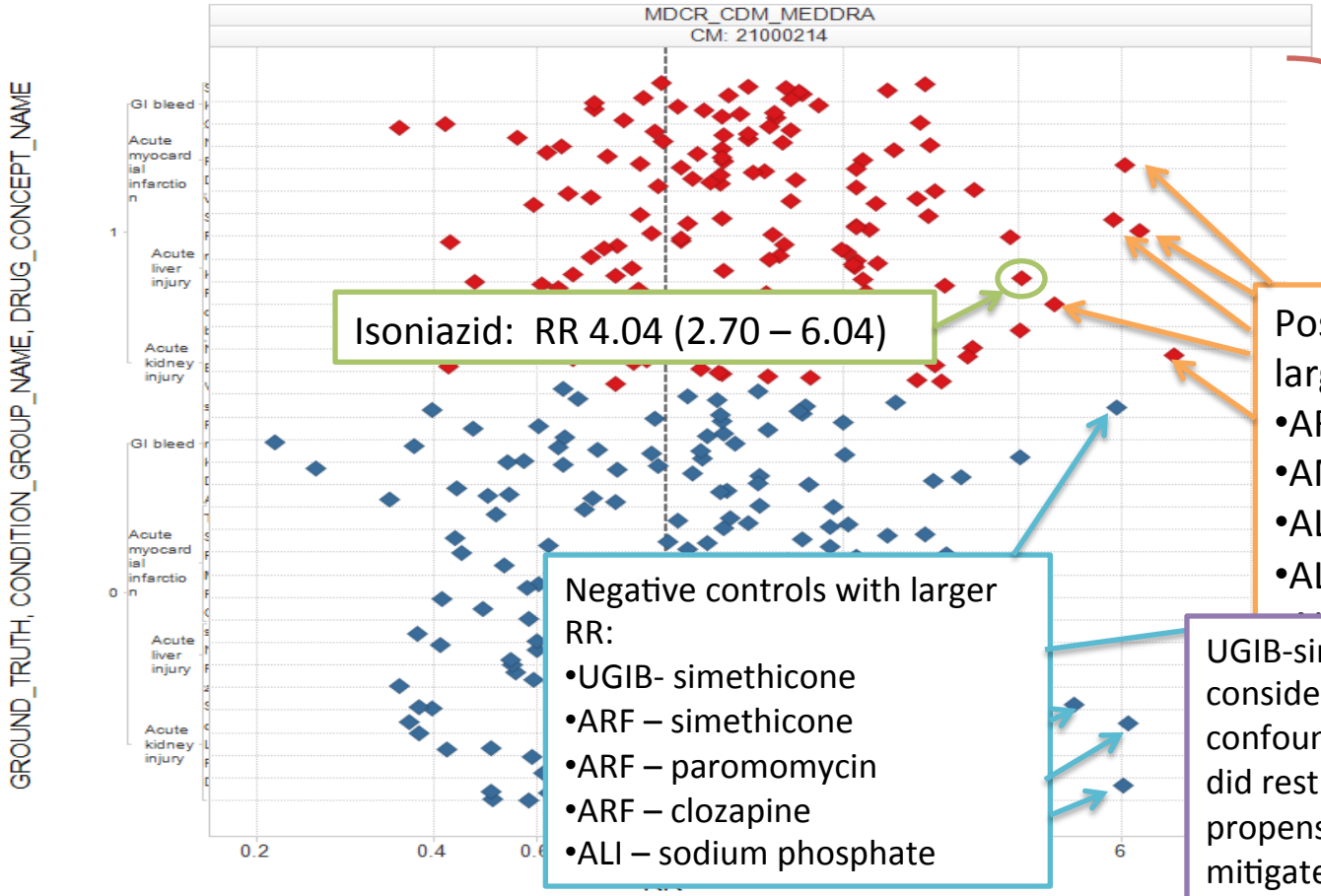
Criteria for positive controls:

- Event listed in Boxed Warning or Warnings/Precautions section of active FDA structured product label
- Drug listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Li

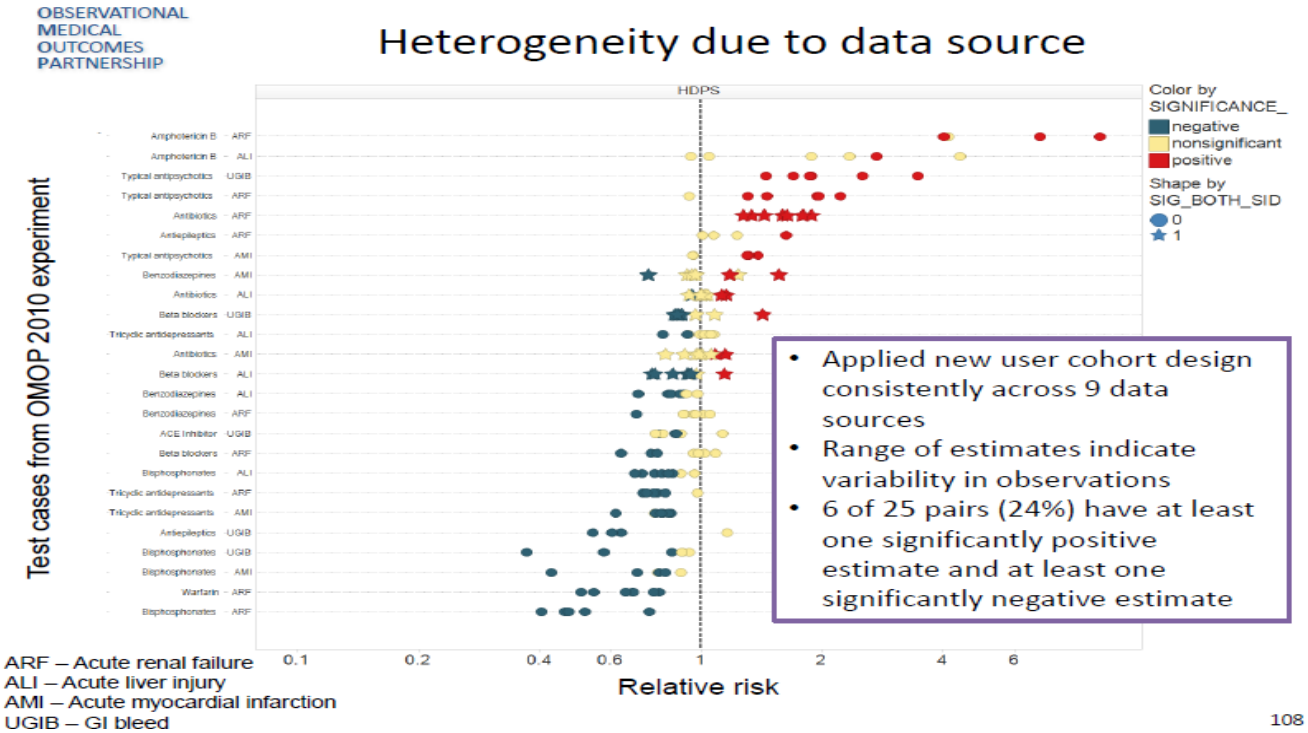
Criteria for negative controls:

- Event not listed anywhere in any section of active FDA structured product label
- Drug not listed as 'causative agent' in Tisdale et al, 2010: "Drug-Induced Diseases"
- Literature review identified no powered studies with evidence of potential positive association

New user cohort design applied to all test cases



New user cohort from OMOP (*Drug Safety* 2013)



Protocols

- Must have research question and objectives
- Should be registered e.g- http://www.encepp.eu/encepp/studiesDatabase.jsp
  - Declaration of Helsinki requires registration
- Design specified in detail in protocol
- Statistical analysis plan should be included

Aspects of Design for comparison

- Structure
  - Baker MA et al. A vaccine study design selection framework ...*rapid.. monitoring. Am J Epidemiol.* 2015;181:608-18
- Designs described- case-control , self-controlled risk interval, self-controlled case series method, case-crossover
- All used for vaccine safety surveillance
- Exploratory designs (& analysis) should be clearly described as exploratory

Selection criteria

- Perrio et al (2007) *Pharmacoepidem. Drug Safe.*, 16: 329–336.
- Showed exclusion criteria widely used in pharmacoepidemiology but not well studied.
  - Exclusion criteria relating to data quality and validation were the most commonly applied (87% of publications), followed by patient characteristics (75%), disease-related (69%), exposure-related (38%) and miscellaneous (3%)

Is there a crisis in epidemiology?

- Stan Young "Any claim coming from an observational study is most likely to be wrong." Young, S. S. and Karr, A. (2011), Deming, data and observational studies. *Significance*, 8: 116–120.
- John Ioannidis- 2015. Video of lecture can be watched through this website-. www.lshtm.ac.uk/newsevents/events/2015/07/24th-bradford-hill-memorial-lecture
- Replication of studies is not done often enough
  - Open data less likely in epidemiology
    - Alsheikh-Ali AA et al. Public availability of published research data in high-impact journals. PLoS ONE 6, e24357 (2011).

STRATOS

- The challenge is to bring statistical *thinking* into observational research including design
- We cannot write a textbook on observational research
- We may have to look at where investigators go wrong but show how we can do it well