Roma, 4 Novembre 2013

Seminario satellite di Farmacoepidemiologia – Associazione Italiana di Epidemiologia

Nuovi approcci per controllare il confondimento tramite acquisizione di dati clinici: Esperienze nazionali ed internazionali

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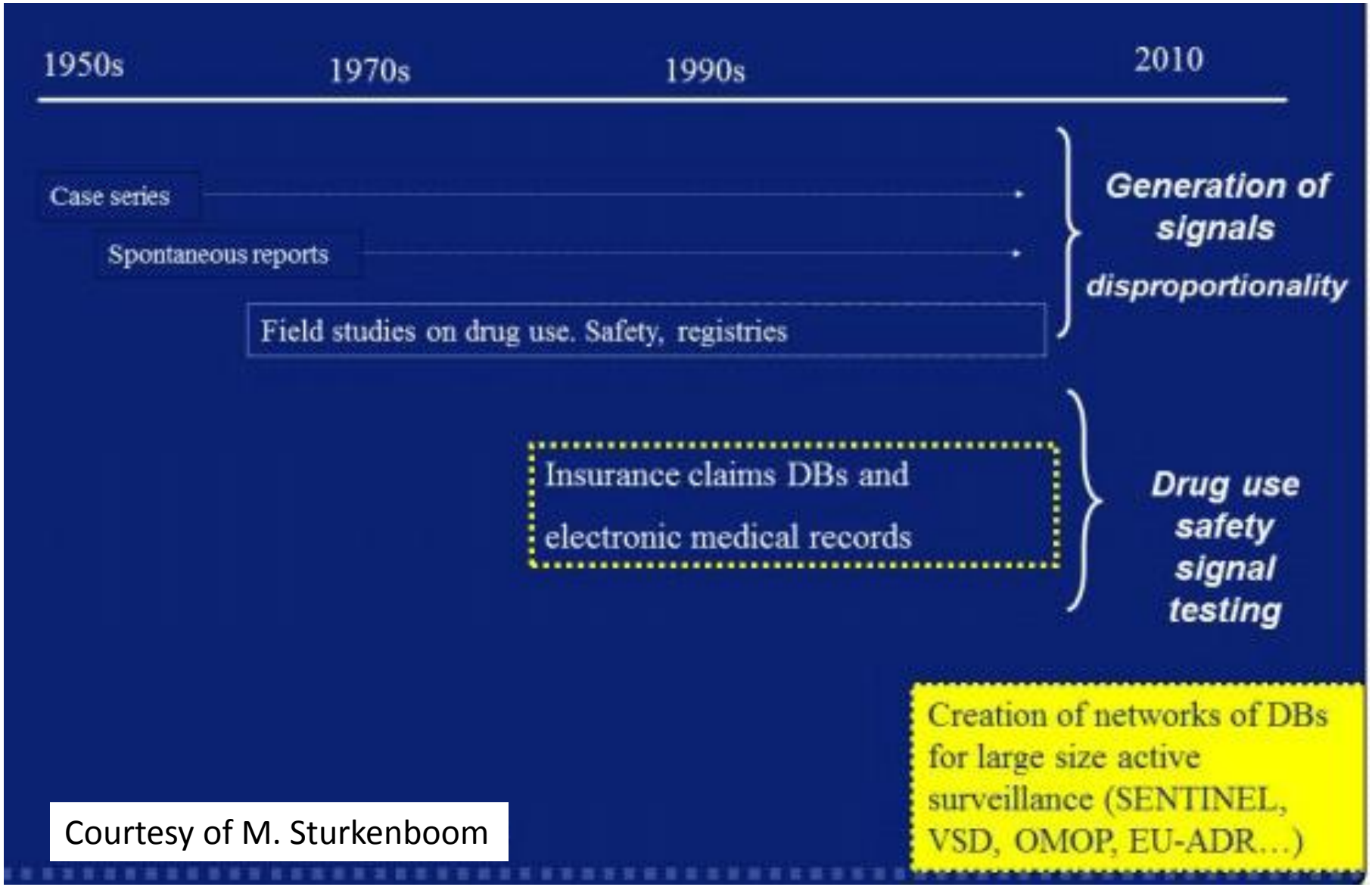
Outline

- Come è cambiata la ricerca in farmacoepidemiologia?
- Acquisizione di dati clinici in studi su banche dati:
  - Perché?
  - Quali dati?
  - Quali tecniche di *confounding adjustment*?
- In prospettiva…

Come è cambiata la ricerca in farmacoepi?



Courtesy of M. Sturkenboom

Large consortia of multi-DB safety studies

US
- VSD
- Sentinel
- OMOP

Canada
- CNODES

EU
- EU-ADR: www.euadr-project.org
- ARITMO: www.aritmo-project.org
- SAFEGUARD www.safeguard-diabetes.org
- PROTECT: www.imi-protect.eu
- VAESCO: www.vaesco.net
- EMIF: www.imi.europa.eu/content/emif

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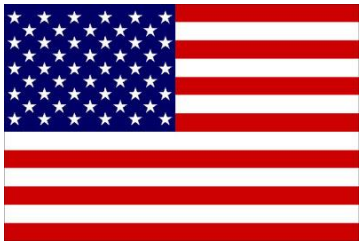
Global
- GRIP: www.grip-network.org



Looking into the future!

Trifirò G, et al. Journal of Internal Medicine. *In press*

Does only size matter?

Family Matters
By Bonnie Rochman

OBESITY

Smaller Dishes Could Cut Childhood Obesity

By Bonnie Rochman @brochman | April 08, 2013 | 32 Comments

Smaller plates, fewer calories? The latest study shows one way to fight childhood obesity may be to shrink the size of the dinner plate.

According research published in the journal *Pediatrics*, first-graders served themselves more and downed more calories when they used a large plate instead of a smaller one.

Simply advising parents — and kids — to eat less and exercise more hasn't turned the childhood obesity

Acquisizione di dati clinici in studi su banche dati

Perché?

Le informazioni nelle banche dati sanitarie

Fattore	Presente	Assente	Problema
Outcome	Registrazione evento come visita MMG, accesso in PS, causa di morte, ospedalizzazione	Data inizio sintomi/segni; validazione (miscoding); stadiazione	**Outcome misclassification - bias**
Esposizione	N. pezzi prescritti o dispensati, data prescrizione	Dose prescritta, compliance del paziente, OTC, farmaci di classe C, farmaci ospedalieri, integratori alimentari	**Exposure miscl. and residual confunding – bias**
Covariate	Comorbidità, farmaci rimborsati dal SSN e talvolta altre informazioni (esami lab., stili di vita, schede geriatriche, etc.)	**Farmaci**: vedi sopra **Patologie**: vedi sopra, severità patologia, esami laboratorio **Stili di vita:** dieta, fumo, alcol, esercizio fisico **Status socio-economico**	**Residual confunding - bias**

Acquisizione di dati clinici in studi su banche dati

Quali dati?

Outcome

Is outcome misclassification an issue when using EHR?

Common approach
when using EHR

Common approach
In SRS when using SRS
(e.g. broad SMQ)

The EU-ADR experience

Aim

Primary objective

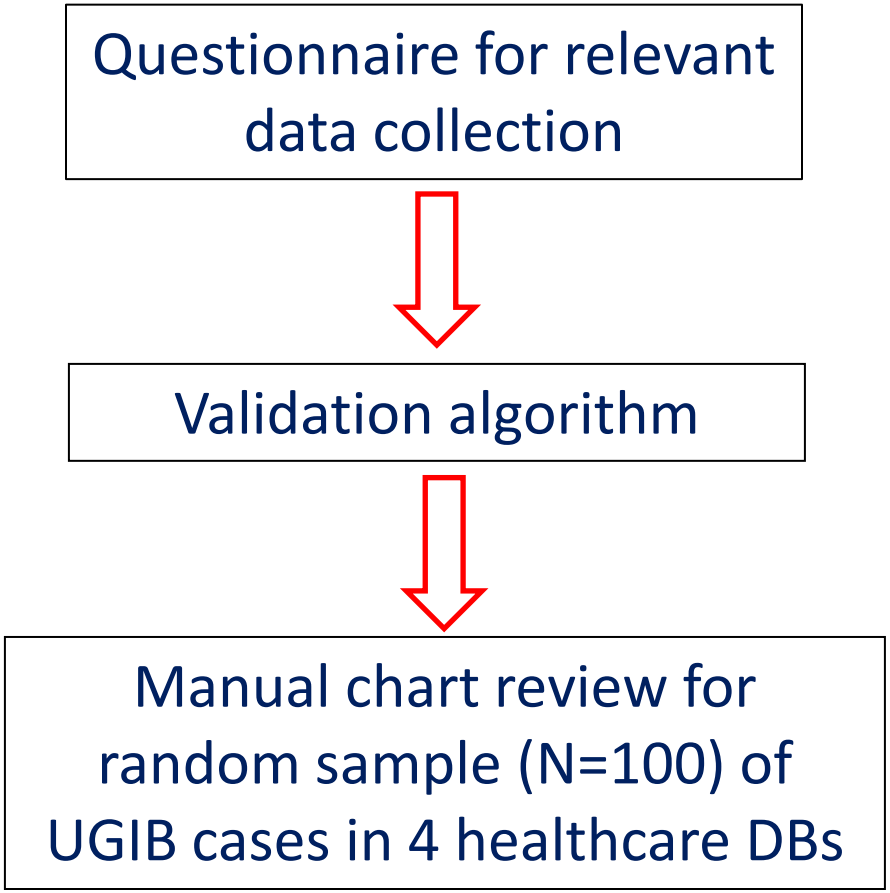
To explore the effect of outcome misclassification for the signal detection concerning Upper GastroIntestinal Bleeding (UGIB) in EU-ADR

Secondary objective

When using EHRs for drug safety signal detection, to evaluate the need of validation of automatically extracted events

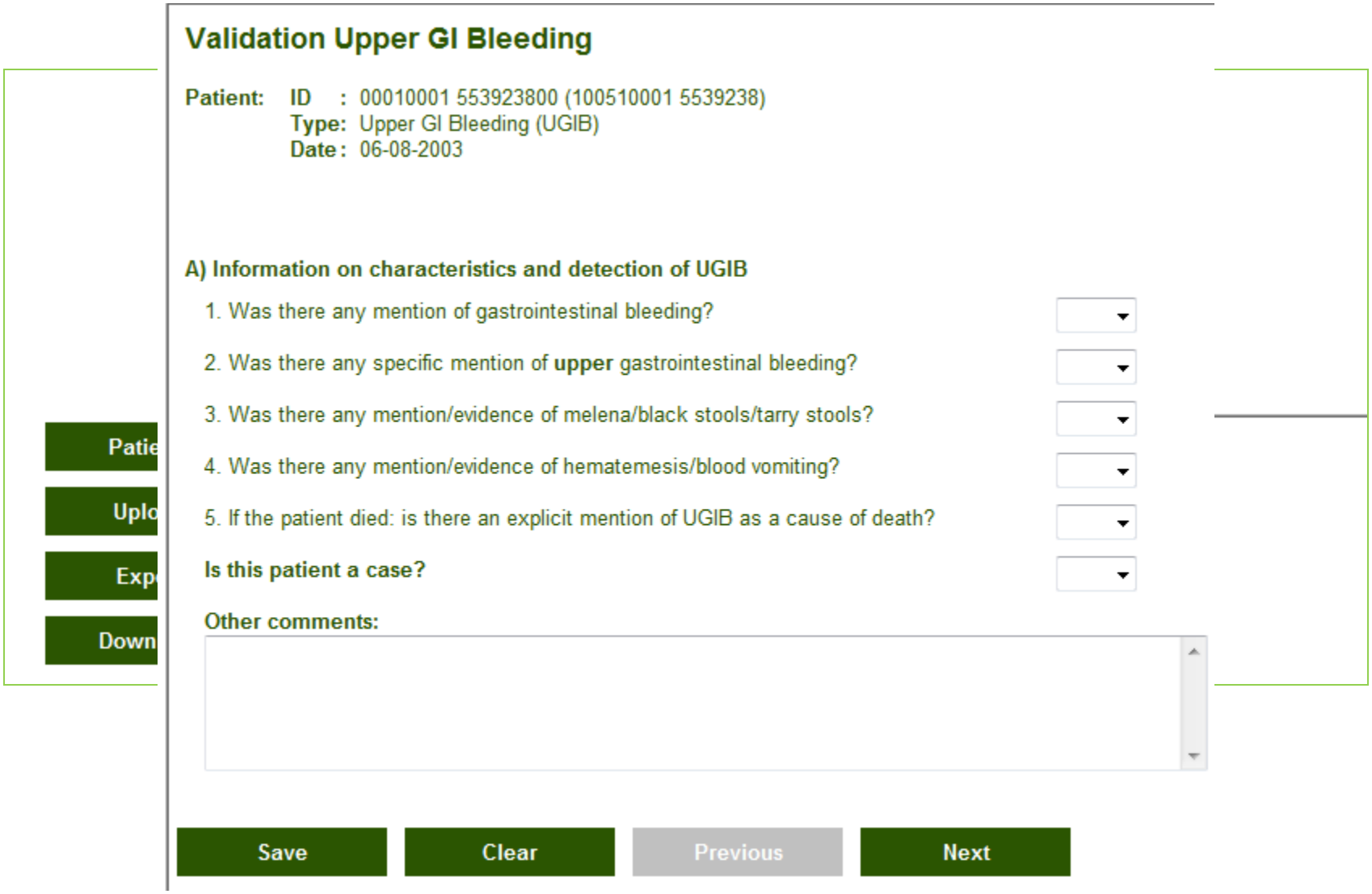
The EU-ADR experience

Methodology - 1



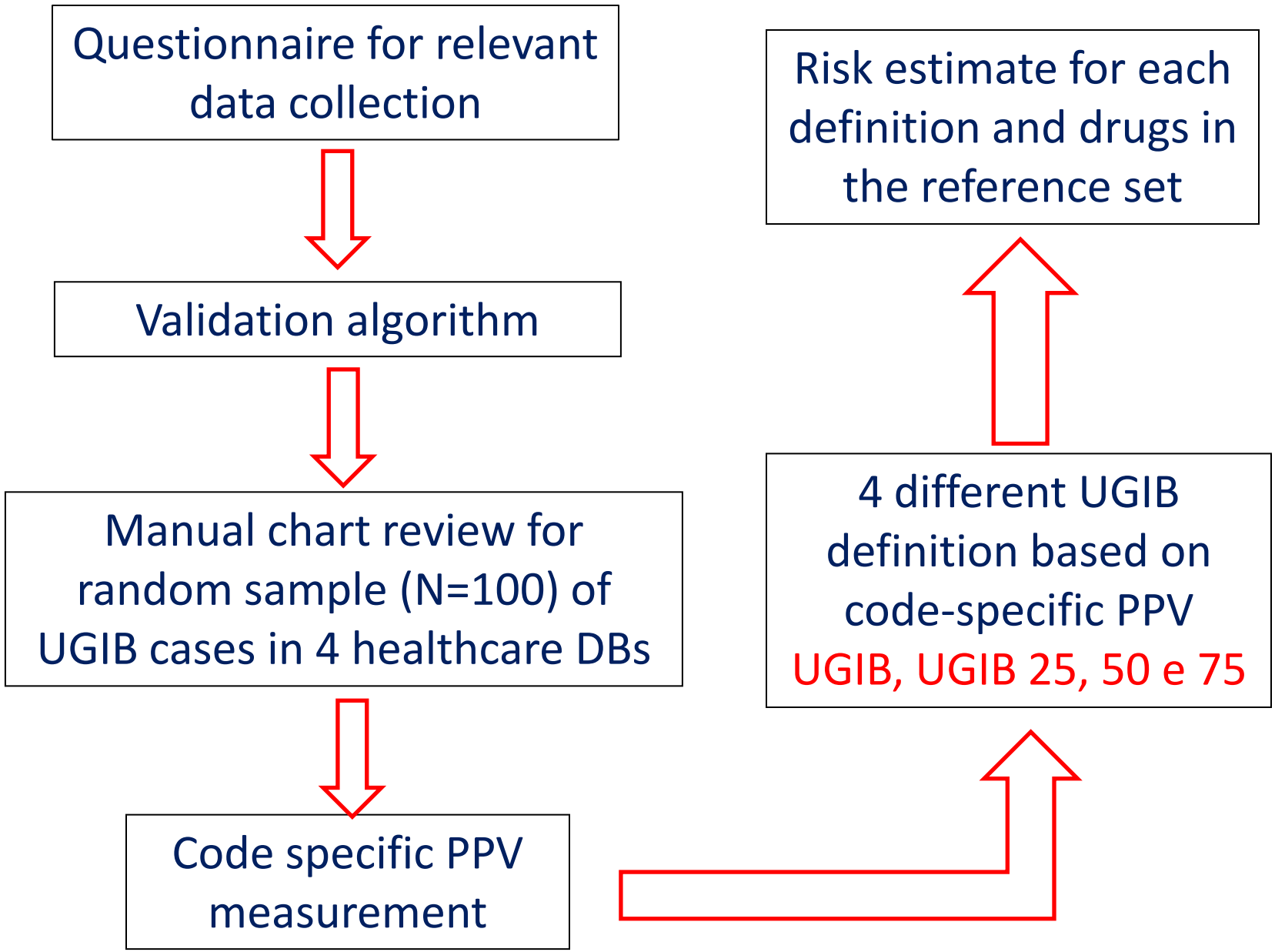
Electronic tool for event validation

Chameleon



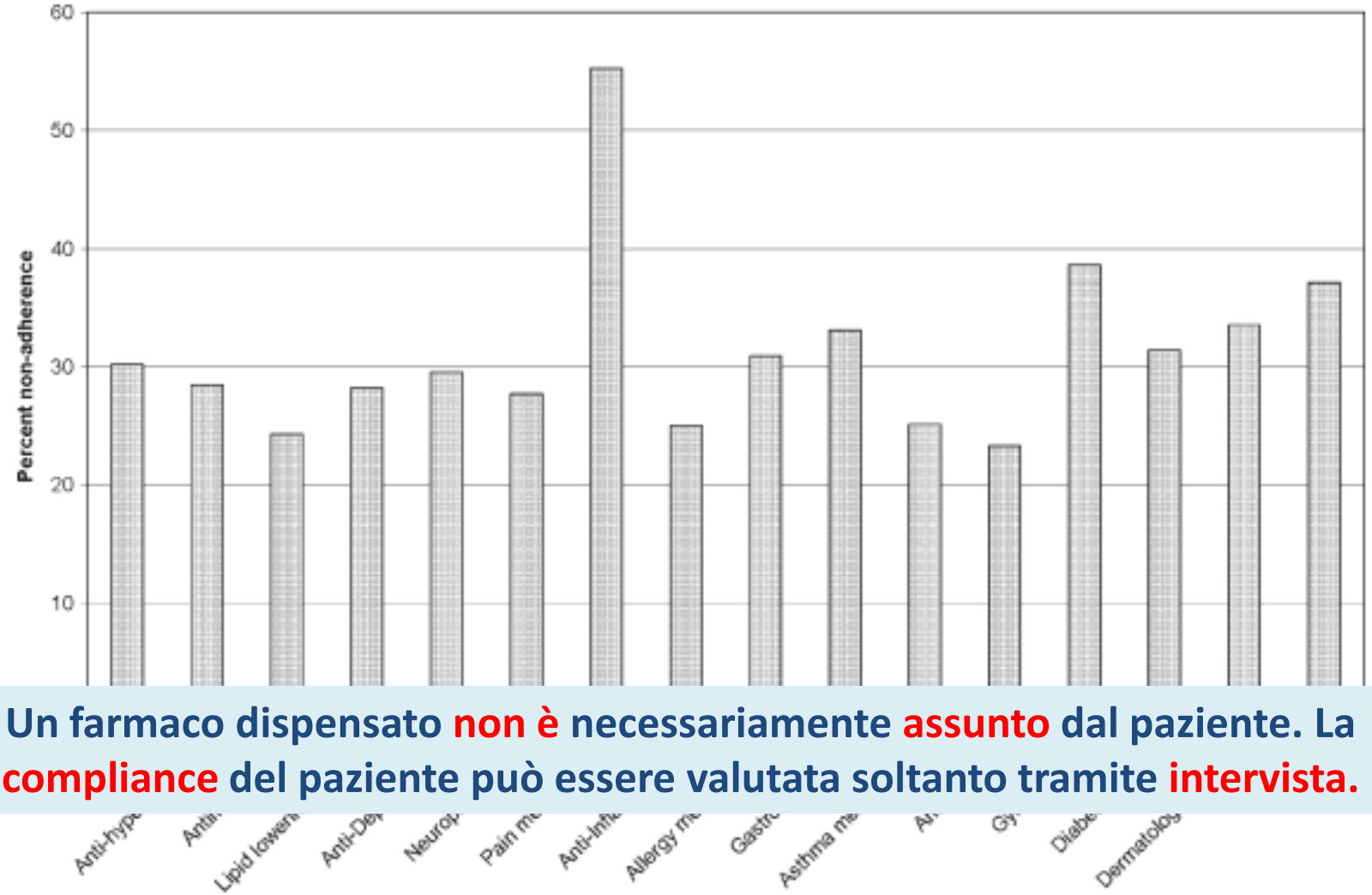
The EU-ADR experience

Methodology - 2



Esposizione

Prescription vs. Dispensing



Un farmaco dispensato non è necessariamente assunto dal paziente. La compliance del paziente può essere valutata soltanto tramite intervista.

Figure 1. Primary non-adherence to newly prescribed medications. Patients aged 19 and over.

J Gen Intern Med. 2010;25:284-90

Overexposure to NSAIDs as OTC

	Rheumatoid arthritis	Osteoarthritis
Patients' number	546	508
NSAIDs overusers (%)	216 (39.5)	240 (47)
Mean age (years) ± SD	65 ± 8 §	67 ± 11 £
Females/males	2.2	1.7
Reasons for NSAIDs overuse		
headhache (%)	111 (19.5)	56 (11)
dental pain (%)	24 (4.5)	48 (9)
other reasons (%)	0 (0)	10 (2)
Not reported (%)	24 (4.5)	78 (16)
more than 1 reason (%)	57 (10)	48 (9)
Associated NSAIDs		
Prescribing NSAIDs (%)	111 (20.5)	160 (31)
Total OTC (%)	105 (19)	80 (16)
OTC ibuprofen (%)	81 (15)	60 (12)
OTC diclofenac (%)	24 (4)	20 (4)

Stimare % misclassificazione per farmaci in studio e valutare effetti su stime di rischio

Int J Immunopathol Pharmacol. 2013; 26:279-81

Covariate

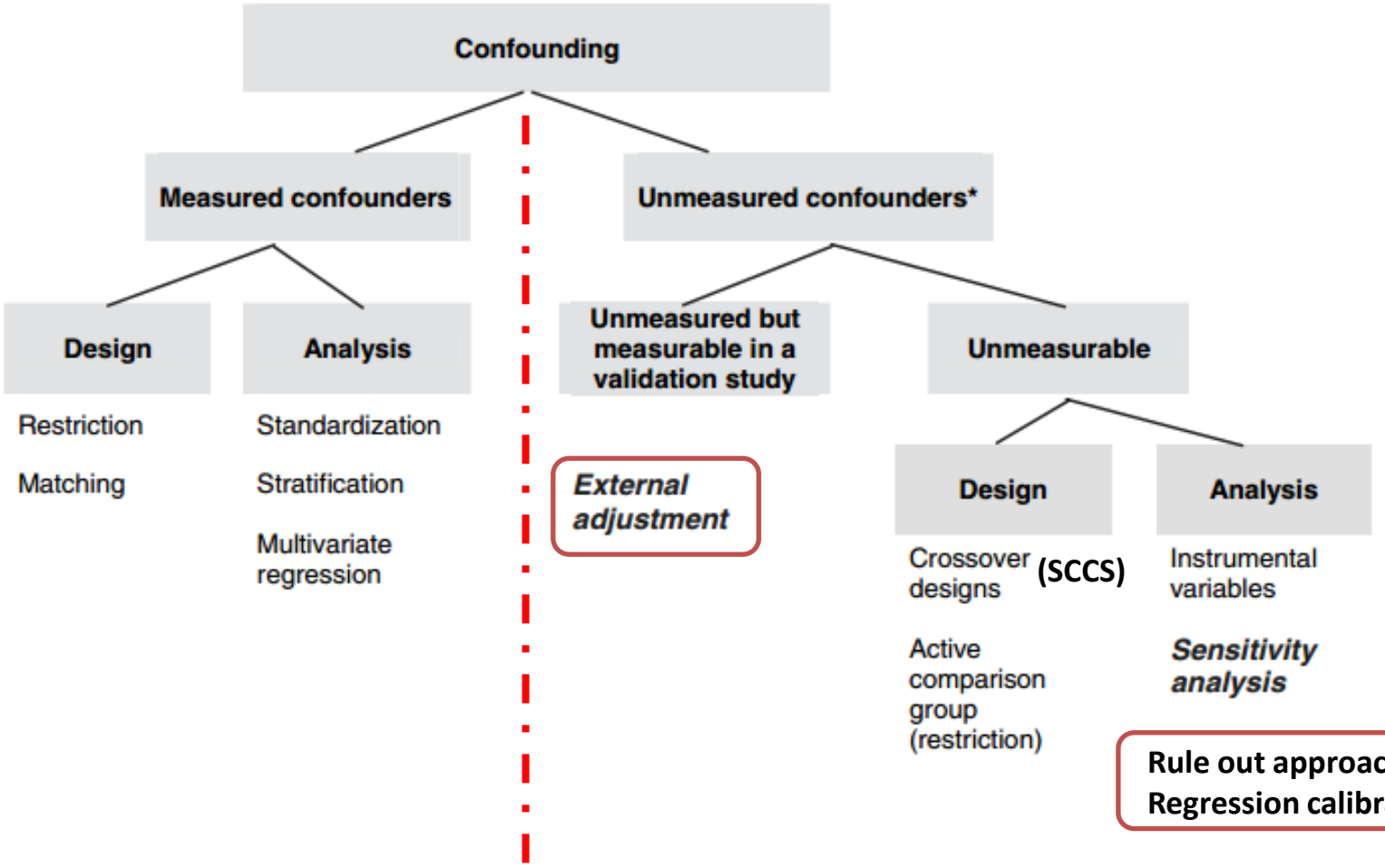
Misclassificazione

Unmeasured confounder
Unmeasurable confounder

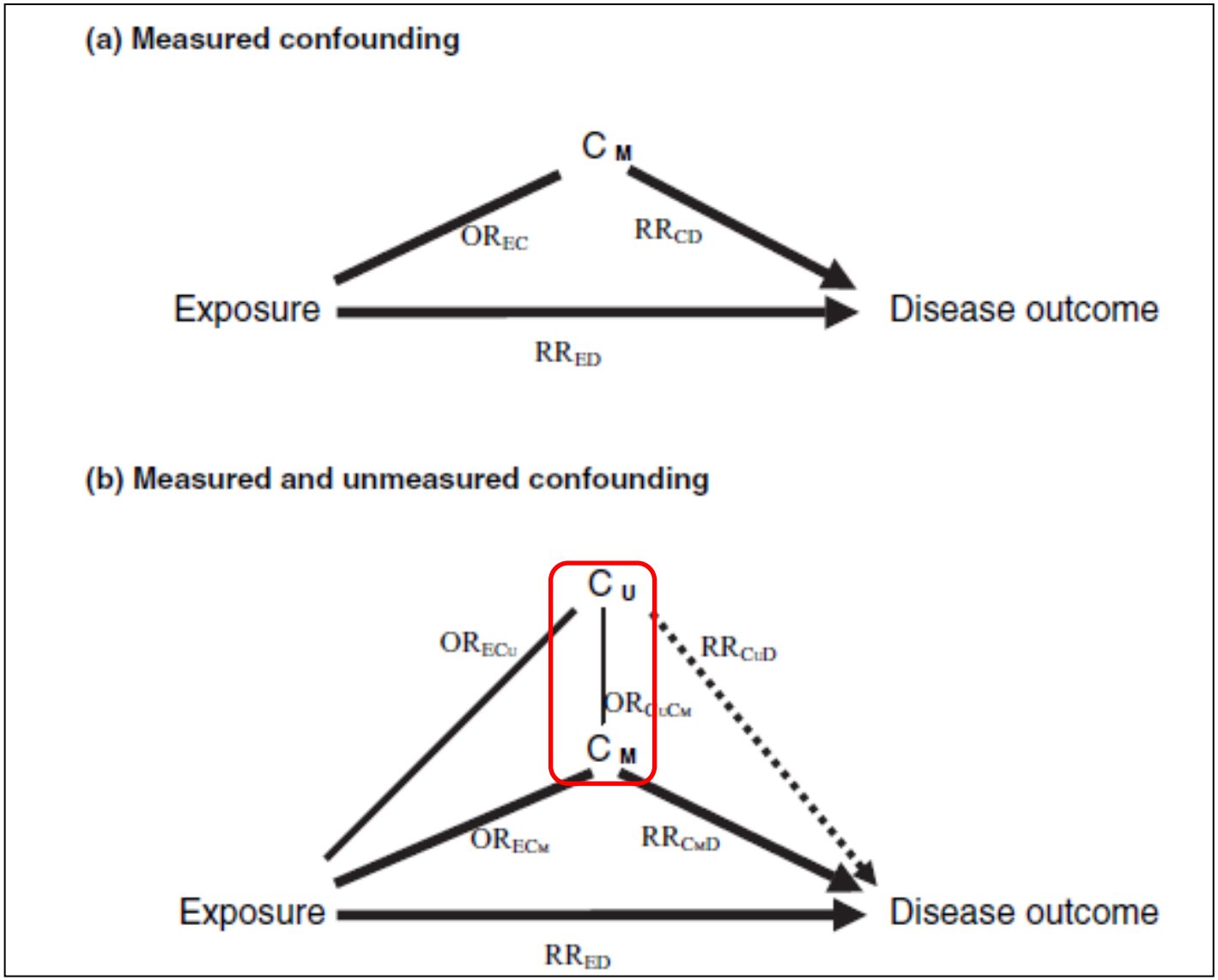
Residual Confounding

Acquisizione di dati clinici in studi su banche dati

Quali tecniche di *confounding adjustment*?



Pharmacoepidemiol DS 2006;15:291-303

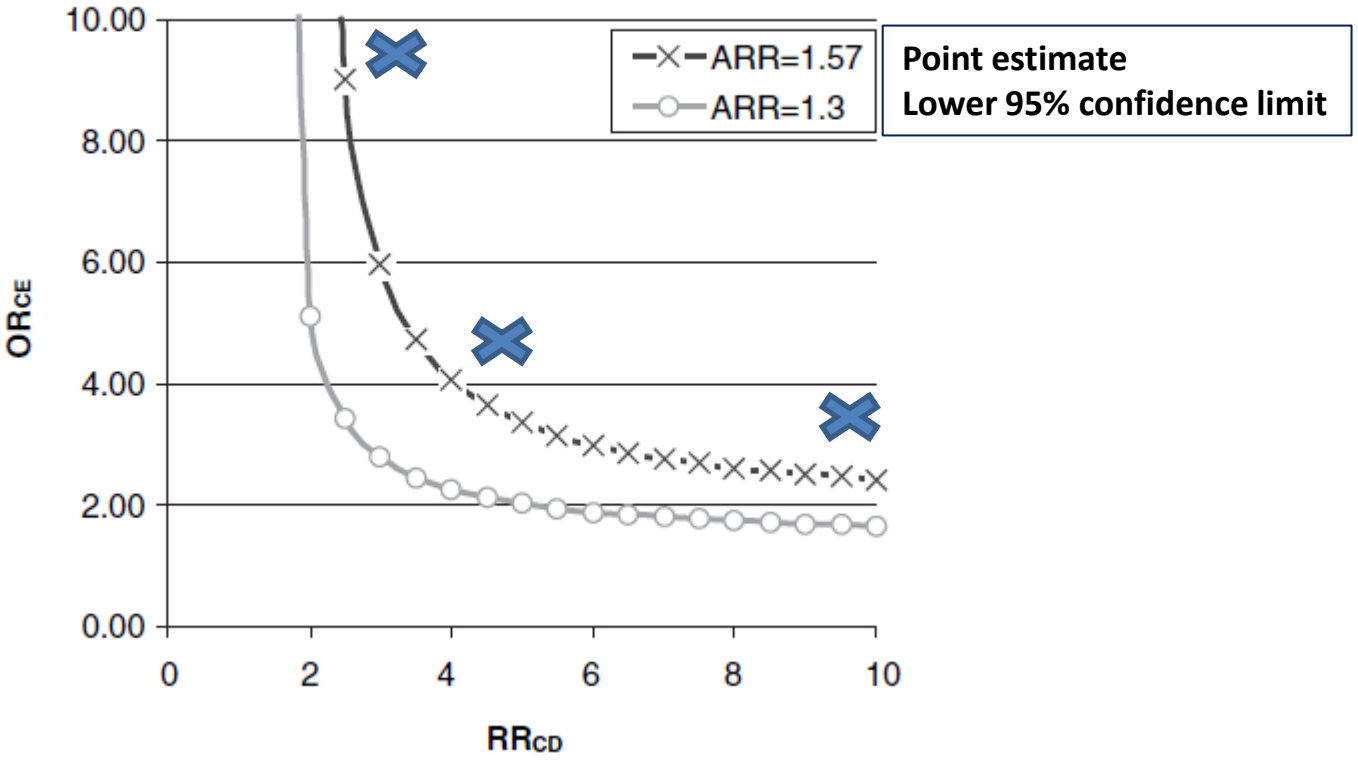


Pharmacoepidemiol DS 2006;15:291-303

Rule out approach

(a) P_E is constant at 0.01 and P_C is constant at 0.2:*

Apparent RR= True RR* Bias



1. To find all combinations of ORec and RRcd necessary to move the observed point estimate of RR to1
2. To rule out a number of possible unmeasured confounders as they cannot be strong enough confounders to explain the observation

J Am Geriatr Soc 1999; 47: 749-754

External adjustment - 1

- If additional information is available (e.g. survey in a sample of the main database study), adjustment for confounders unmeasured in the main study is possible;
- If internal validation study is not feasible, external data sources can be used under certain assumptions.
- Given estimates of ORec and RRcud for each of the unmeasured confounder, adjustment for these factors can be achieved;
- Due to limited size of validation studies, confounder-outcome association (RRcud) can be rarely evaluated, but can be abstracted from the literature.

External adjustment - 2

Table 3. COX2 external adjustment: quantitative assessment of confounding bias in relative risk estimates of the association between the selective COX-2 inhibitor rofecoxib and myocardial infarction compared with naproxen

Potential confounder Data source:	RR_{CD} literature	P_C MCBS	OR_{EC}* MCBS	RR assumed	P_E MCBS	ARR†	Percent bias‡
Obesity (BMI $\geq$30 kg/m^2 versus <30 kg/m^2)	1.7	0.20	1.00	1.00	0.51	1.000	0.01
Aspirin use (use versus non-use)	0.7	0.10	1.60	1.00	0.51	0.987	−1.28
Smoking (current versus former/never)	3.1	0.07	0.95	1.00	0.51	0.994	−0.61
Educational Attainment (≤high school versus >high school)	2.1	0.70	0.64	1.00	0.51	0.944	−5.61
Income status (≤$20,000 versus >$20,000)	2.1	0.51	0.63	1.00	0.51	0.922	−7.78
Net confounding							
Sum of all negative biases:							−15.3
Weighted average:							−5.10
Sum of all positive biases:							0.01

*Age- and sex-adjusted.
†Apparent relative risk between exposure (COX-2 use) and MI outcome if the potential confounder was not controlled, under the assumption that the fully adjusted relative risk RR equals 1.0.
‡Bias = [(ARR − RR)/RR] × 100.

The **joint distribution** of umeasured confounder can rarely be assessed with this approach because stable literature estimates are usually **not available** for several **confounding combinations**. A practical solution is to **sum biases estimates** of all confounders **weighted by the prevalence of each confounder** in the validation sample

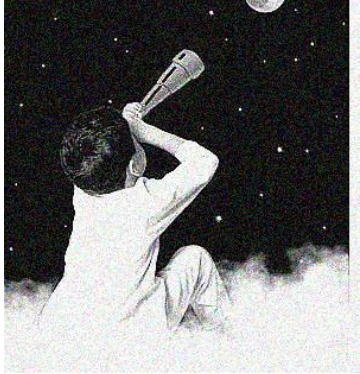
Pharmacoepidemiol DS 2006;15:291-303

Regression Calibration

- When external data are available on multiple unmeasured confounders, the method of propensity score calibration may be used to adjust estimates.
- Regression calibration is a statistical method for adjusting point and interval estimates of effect obtained from regression models for bias due to measurement error in assessing specific variables.
- Regression calibration is appropriate when a gold standard is available in a validation study and a linear measurement error with constant variance applies.

Am J Clin Nutr l997:65(suppl):1179
Stat Med. 1989; 8: 1051-1069.

In prospettiva…



- Armonizzazione a livello Europeo della legge su tutela privacy faciliterà uso secondario delle banche dati!?!
- Comprendere ed accettare i limiti delle banche dati per valorizzarne al meglio le potenzialità;
- Scegliere con attenzione disegni di studio e tecniche di *confounding adjustment, e se* necessario e possibile, acquisire dati clinici aggiuntivi;
- Integrazioni di banche dati non solo con dati clinici, ma anche con "i clinici"!

"Il pessimista vede delle difficoltà in ogni opportunità. L'ottimista vede delle opportunità in ogni difficoltà"

Winston Churchill

Grazie per la vostra attenzione

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