ISTITUTO DI RICERCHE FARMACOLOGICHE

MARIO NEGRI

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Unità di Farmacoepidemiologia
Dipartimento di Salute Pubblica

WORKSHOP

LA *DRUG UTILIZATION*
ATTRAVERSO
I DATABASE AMMINISTRATIVI

Milano, 27 novembre 2012

sismec
Società Italiana di Statistica
Medica ed Epidemiologia Clinica

Database amministrativi e

OUTCOME

Giovanni Corrao

UNIVERSITÀ DEGLI STUDI DI MILANO
BICOCCA

giovanni.corrao@unimib.it

OUTCOME

AGENDA

Premessa (di cosa stiamo parlando?)

Fonti di incertezza (è questo un campo promettente?)

Nuove sfide (cosa stiamo facendo?)

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OUTCOME

- Premessa
- Fonti di incertezza
- Nuove sfide

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Milano, 27 novembre 2012

BMJ 1996;312:1215-8

Clinical review

Why we need observational studies to evaluate the effectiveness of health care

Nick Black

The view is widely held that experimental methods (randomised controlled trials) are the "gold standard" for evaluation and that observational methods (cohort and case control studies) have little or no value. This ignores the limitations of randomised trials, which may prove unnecessary, inappropriate, impossible, or inadequate. Many of the problems of conducting randomised trials could often, in theory, be overcome, but the practical implications for researchers and funding bodies mean that this is often not possible. The false conflict between those who advocate randomised trials in all situations and those who believe observational data provide sufficient evidence needs to be replaced with mutual recognition of the complementary roles of the two approaches. Researchers should be united in their quest for scientific rigour in evaluation, regardless of the method used.

What work well in pharmacological research may not work in the messier world of clinical care

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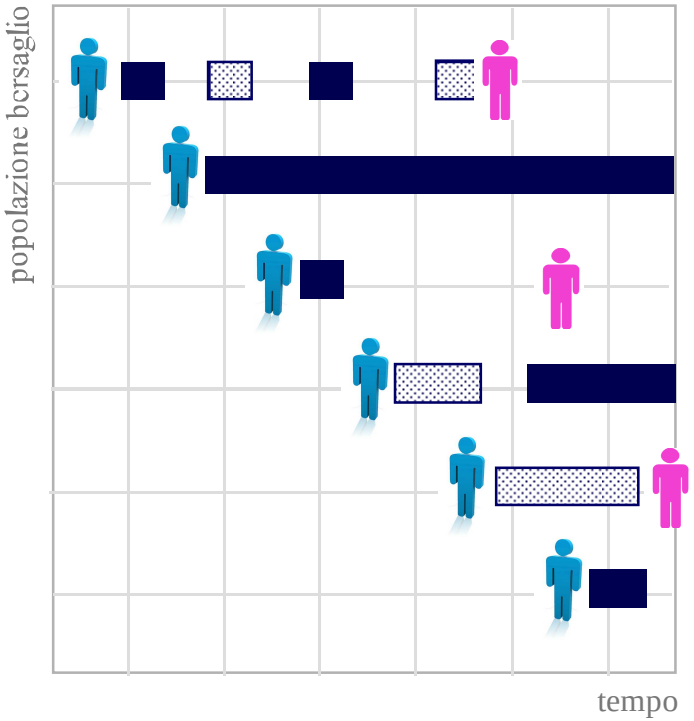
Il disegno osservazionale di riferimento

OUTCOME



Uso

Spesa

Efficacia *

Sicurezza

Uso e impatto clinico ed economico delle prestazioni sanitarie nel mondo reale

* Comparative effectiveness

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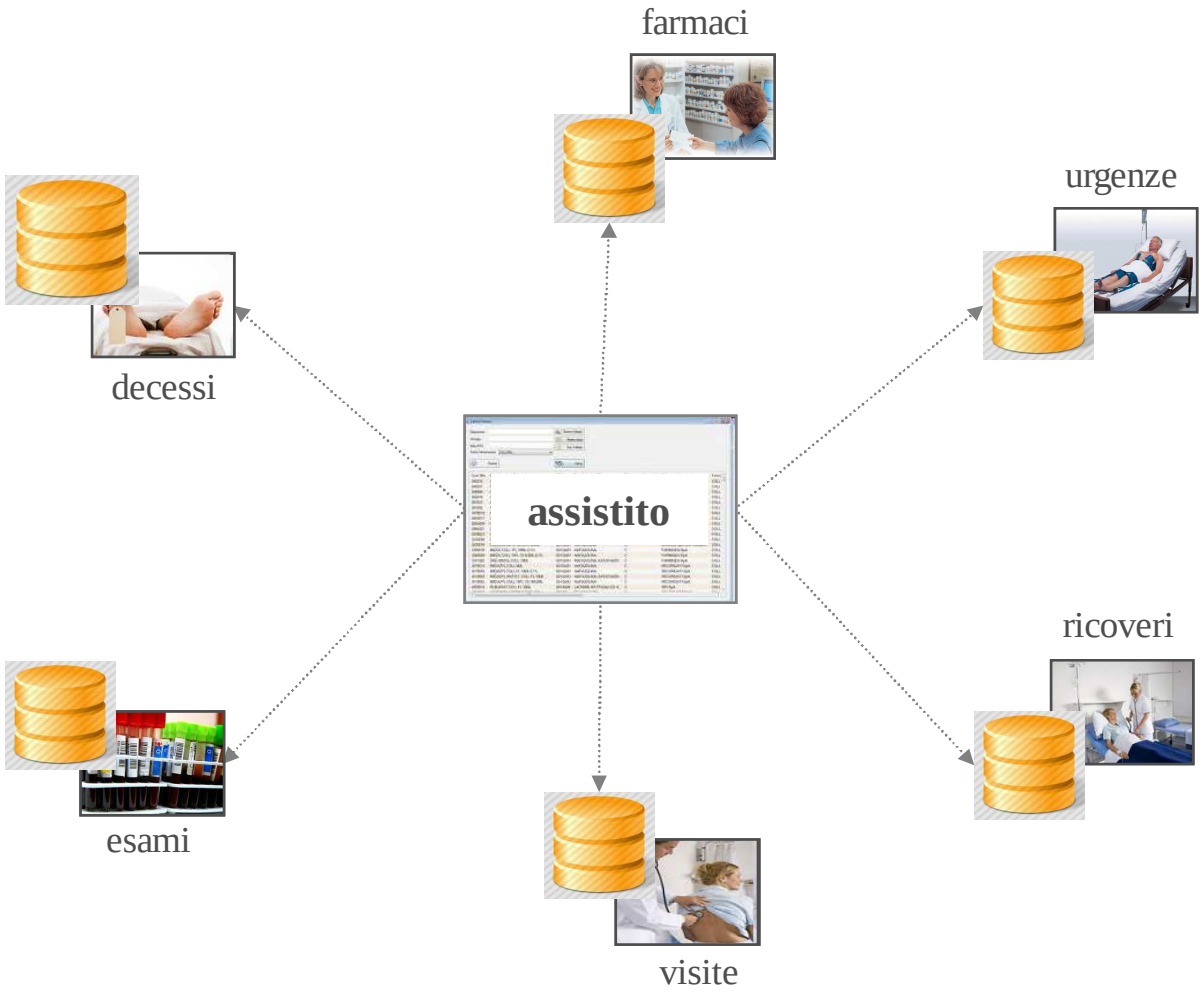
Il monitoraggio dei percorsi assistenziali

OUTCOME

- **Premessa**
- Fonti di incertezza
- Nuove sfide



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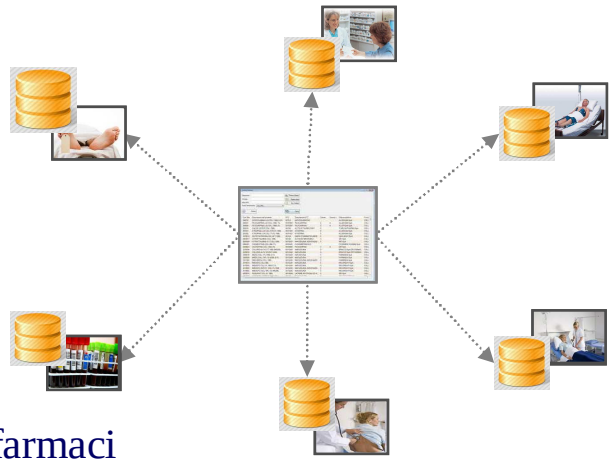
OUTCOME

FORZA

- Dati disponibili
- Popolazioni ampie e ben definite
- Uso e impatto dei farmaci nella pratica clinica corrente



DEBOLEZZA

- Solo farmaci in classe A
- Incerta qualità dei dati
- Carenza di dati sui pazienti

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FONTI DI INCERTEZZA SISTEMATICA (due esempi)

Misclassificazione dell'esposizione

Confondimento non misurato

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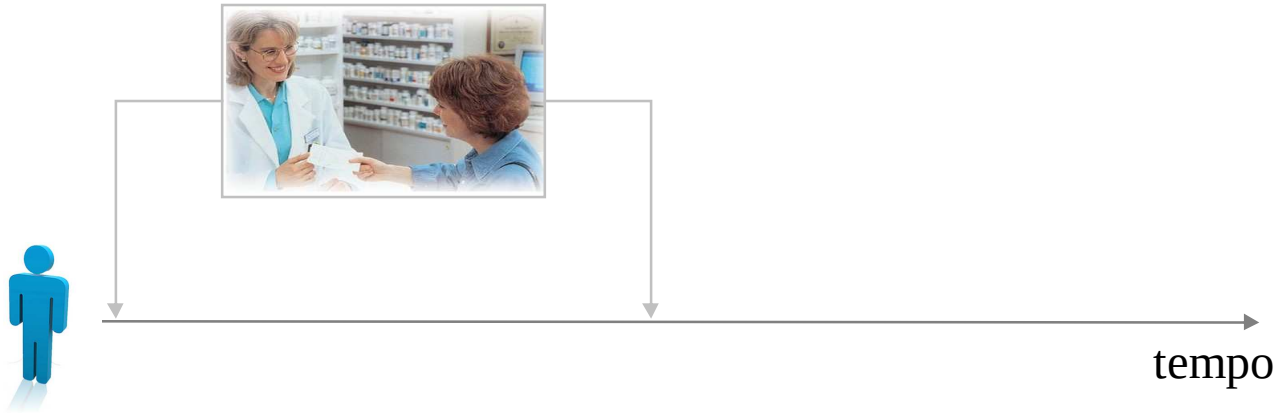
OUTCOME

Come misuriamo l'esposizione?



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Misclassificazione dell'esposizione?

OUTCOME

Journal of Clinical Epidemiology

2004;57:973-7

Misclassification of exposure is high when interview data on drug use are used as a proxy measure of chronic drug use during follow-up

Annette B. Beiderbeck[a,b], Miriam C.J.M. Sturkenboom[b], Jan W.W. Coebergh[b], Hubert G.M. Leufkens[a], Bruno H.Ch. Stricker[b,*]

Validity of interview-based exposure measurement for the assessment of exposure to CCBs

		User status, pharmacy		
		User	Nonuser	Total
User status, interview	User	203	3	206
	Nonuser	354	1,927	2,281
	Total	557	1,930	2,487

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OUTCOME

Come misuriamo la durata dell'esposizione?

DDD: defined daily dose

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Come misuriamo la durata dell'esposizione?

OUTCOME

WHO Collaborating Centre for Drug Statistics Methodology

- News
- ATC/DDD Index
- ATC/DDD methodology
- ATC
- DDD
  - Definition and general considerations
  - Application for DDD
  - Application for DDD alterations
  - Application form
  - Lists of new ATC/DDDs and alterations
  - List of DDDs combined products
- ATC/DDD alterations, cumulative lists

Definition and general considerations

Definition and introduction
The basic **definition** of the defined daily dose (DDD) is:

The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults.

A DDD will only be assigned for drugs that already have an ATC code.

It should be emphasised that the defined daily dose is a unit of measurement and does not necessarily reflect the recommended or Prescribed Daily Dose.

will often differ from the DDD and will necessarily have to be based on individual characteristics (e.g. age and weight) and pharmacokinetic considerations.

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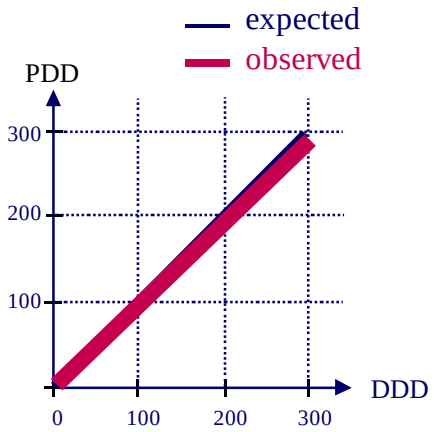
Misclassificazione dell'esposizione?

OUTCOME

	N. observations	Beta estimates
Indometacin	7324	1.261
Sulindac	876	1.64
Diclofenac	239201	0.978
Aceclofenac	1,557	1.043
Diclofenac, combination	35045	1.001
Piroxicam	13,537	1.002
Tenoxicam	55	1.295
Meloxicam	18,647	1.482
Ibuprofen	199505	1.218
Naproxen	139,784	0.713
Ketoprofen	2662	0.941
Flurbiprofen	473	1.214
Tiaprofenic acid	2163	1.545
Dexibuprofen	481	1.013
Dexketoprofen	75	1.451
Celecoxib	2,934	1.099
Rofecoxib	12636	1.343
Valdecoxib	132	0.406
Etoricoxib	2317	0.879
Nabumetone	12,093	0.947



$RR_{obs} = RR$

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SOS
SAFETY OF NSAIDs

PHARMO
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Misclassificazione dell'esposizione?

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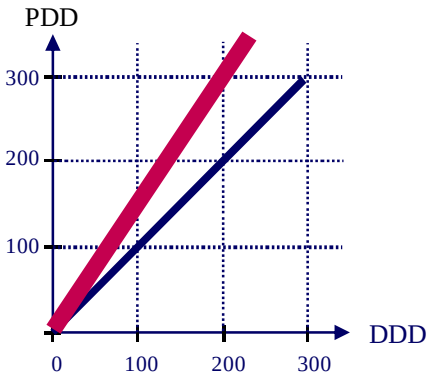

$RR_{obs} > RR$

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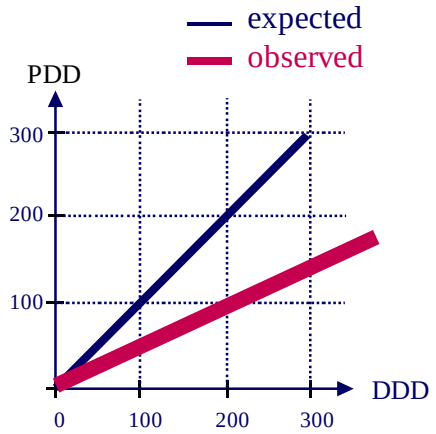

$RR_{obs} < RR$

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Correzione della misclassificazione dell'esposizione: regression calibration

OUTCOME

Il metodo

Regression calibration method for correcting measurement error bias in nutritional epidemiology[1–3]

Donna Spiegelman, Aidan McDermott, and Bernard Rosner

The American Journal of Clinical Nutrition

1997;**65**(suppl):1179S-86S

$$RR = RR_{obs} / \beta$$

$$RR_{obs} = f(DDD) \neq RR$$

Studio principale

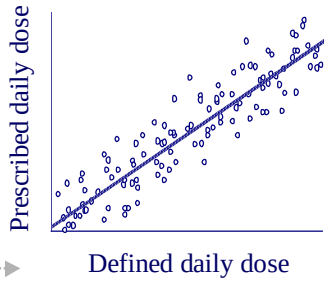
(DB amministrativi)

$$PDD = \beta\ DDD + \varepsilon$$

Studio secondario

(di validazione)

La fonte



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OUTCOME

DUE FONTI DI INCERTEZZA SISTEMATICA (esempi)

Misclassificazione dell'esposizione

Confondimento non misurato

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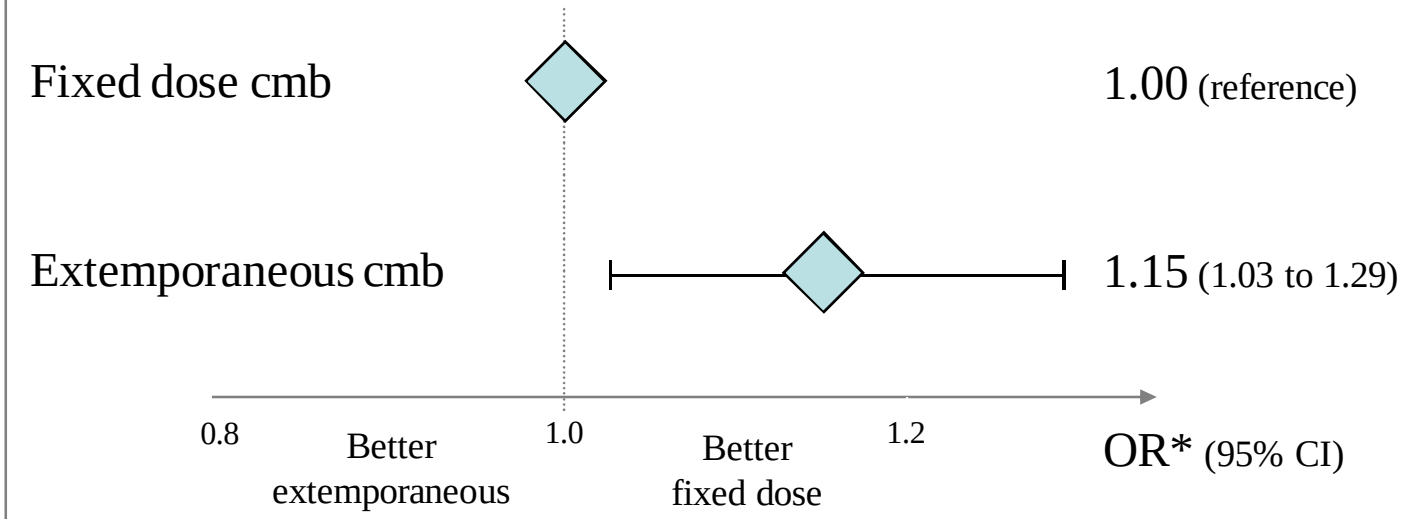
OUTCOME

Trattamento anti-ipertensivo

Patients who started on fixed dose combination had lower CV risk than those who started on extemporaneous combination



* Adjusted for BP-lowering drug therapy during follow-up, and concomitant use of other drugs

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Milano, 27 novembre 2012

Journal of Clinical Epidemiology

2012;**65**:1190-9

External adjustment for unmeasured confounders improved drug–outcome association estimates based on health care utilization data

Giovanni Corrao[a,*], Federica Nicotra[a,b], Andrea Parodi[a], Antonella Zambon[a], Davide Soranna[a], Franca Heiman[c], Luca Merlino[d], Giuseppe Mancia[e]

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Trattamento anti-ipertensivo

Patients who started on fixed dose combination had better clinical profile than those who started on extemporaneous combination

OUTCOME

	Fixed dose cmb	Extemporaneous cmb
Severity of hypertension		
Moderate	83.3%	79.8%
Severe	16.7%	20.1%
Chronic disease score		
0	74.5%	65.7%
1	21.8%	26.6%
2	3.8%	7.7%

Journal of Clinical Epidemiology

2012;**65**:1190-9

External adjustment for unmeasured confounders improved drug–outcome association estimates based on health care utilization data

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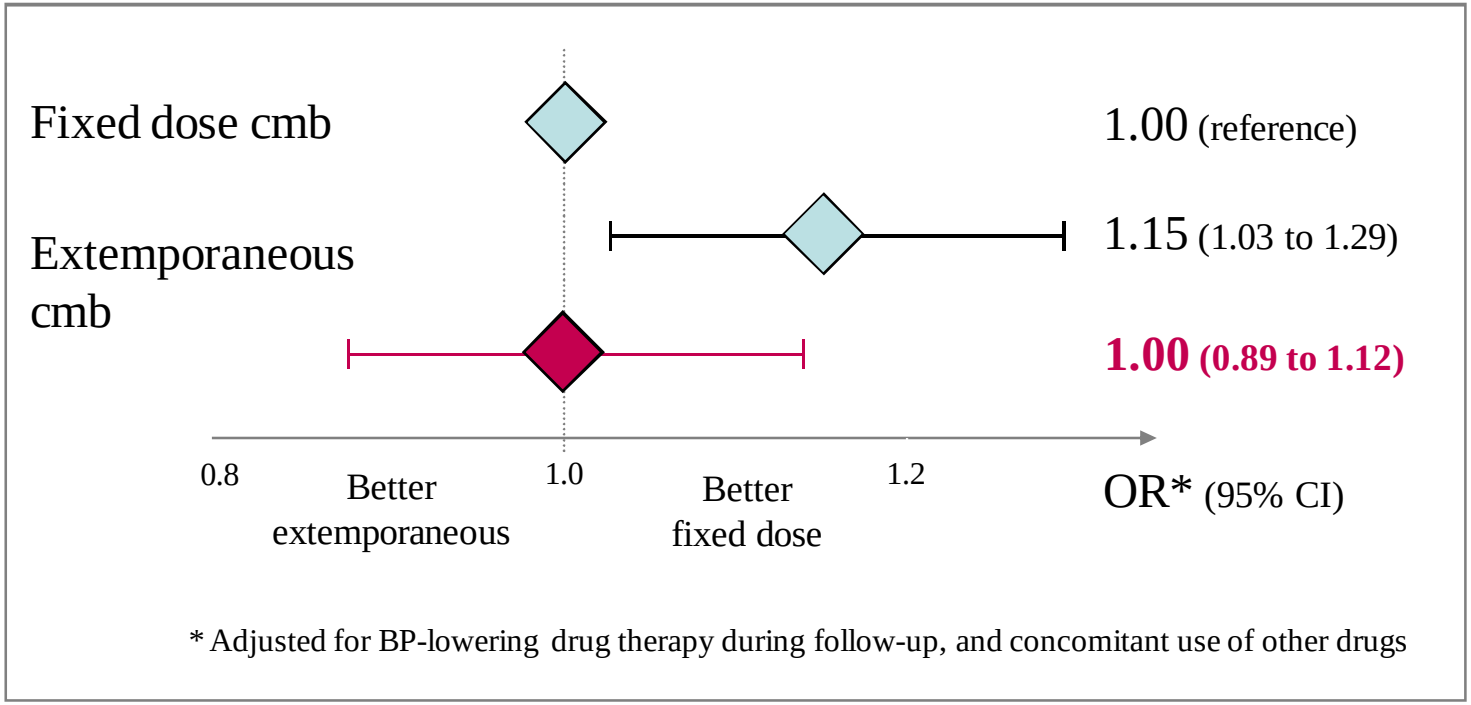
Correzione del confondimento non misurato:
aggiustamento esterno secondo Greenland

Confondimento non misurato

OUTCOME

La fonte



* Adjusted for BP-lowering drug therapy during follow-up, and concomitant use of other drugs

Il metodo

PDS Pharmacoepidemiology & Drug Safety

2006;**15**:291-303

Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics†

Sebastian Schneeweiss MD, ScD*

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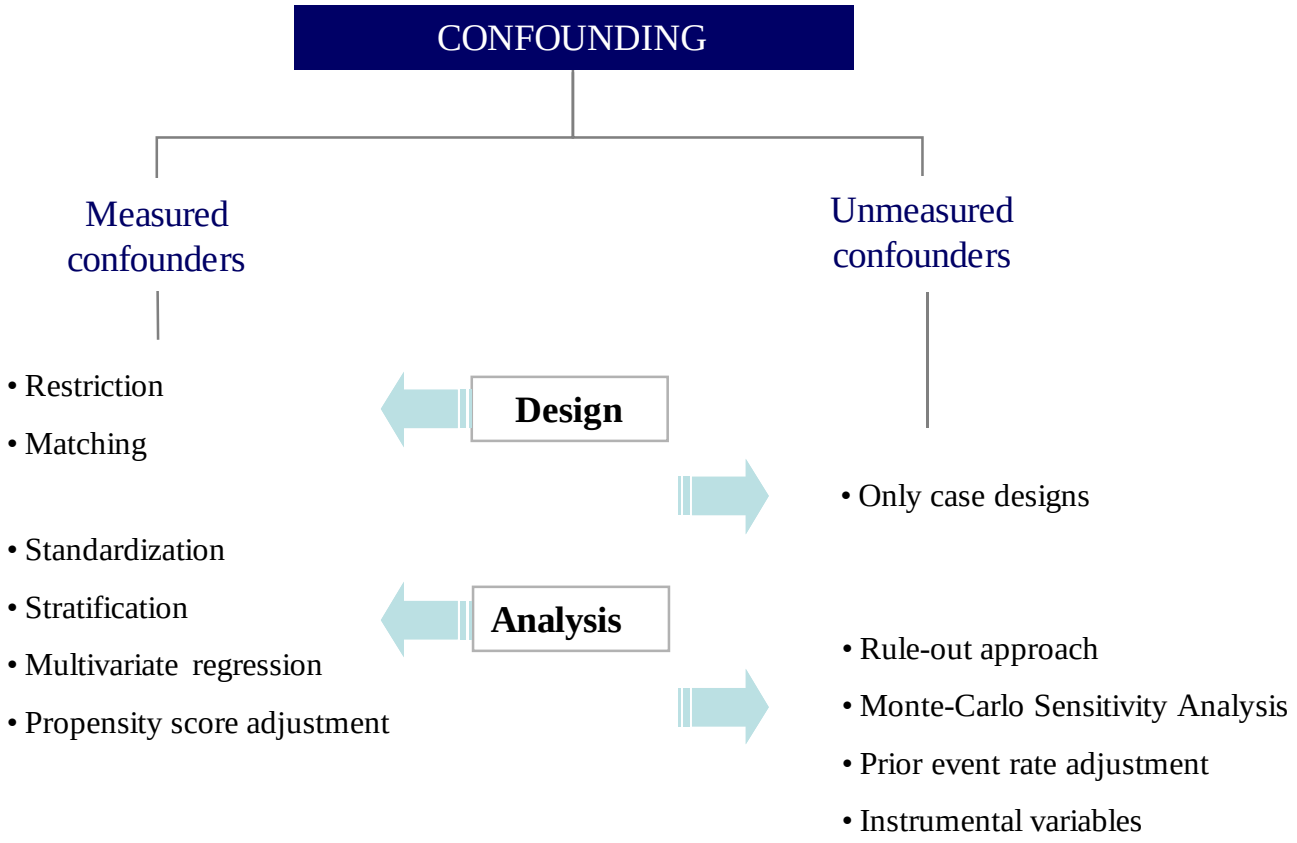
OUTCOME

Come affrontare il problema della vulnerabilità al confondimento?



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PDS Pharmacoepidemiology & Drug Safety
2006;**15**:291-303

Sensitivity analysis and external adjustment for unmeasured confounders in epidemiologic database studies of therapeutics†

Sebastian Schneeweiss MD, ScD*

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Controlling for unmeasured confounders in observational studies

OUTCOME

Annals of Internal Medicine 2008;149:380-90

Risk for Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease

Todd A. Lee, PharmD, PhD; A. Simon Pickard, PhD; David H. Au, MD, MS; Brian Bartle, MPH; and Kevin B. Weiss, MD, MPH, MS

JAMA® The Journal of the American Medical Association 2009;302:1782-9

Cardiovascular and Noncardiovascular Mortality Among Patients Starting Dialysis

Dinanda J. de Jager, MSc; Diana C. Grootendorst, PhD; Kitty J. Jager, MD, PhD; Paul C. van Dijk, PhD; Lonneke M. J. Tomas; David Ansell, PhD; Frederic Collart, MD, PhD; Patrik Finne, MD, PhD; James G. Heaf, MD, DMSc; Johan De Meester, MD, PhD; Jack F. M. Wetzels, MD, PhD; Frits R. Rosendaal, MD, PhD; Friedo W. Dekker, PhD

ARCHIVES OF INTERNAL MEDICINE 2008;168:2081-7

Preadmission Use of Statins and Outcomes After Hospitalization With Pneumonia

Population-Based Cohort Study of 29 900 Patients

Reimar W. Thomsen, MD, PhD; Anders Riis, MSc; Jette B. Kornum, MD; Steffen Christensen, MD; Søren P. Johnsen, MD, PhD; Henrik T. Sørensen, MD, DMSc

The NEW ENGLAND JOURNAL of MEDICINE 2009;360:1815-26

Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival

Mari M. Kitahata, M.D., M.P.H., Stephen J. Gange, Ph.D., Alison G. Abraham, Ph.D., Barry Merriman, M.A., Michael S. Saag, M.D., Amy C. Justice, M.D., Ph.D., Robert S. Hogg, Ph.D., Steven G. Deeks, M.D., Joseph J. Eron, M.D., John T. Brooks, M.D., Sean B. Rourke, Ph.D., M. John Gill, M.R., Ch.B., Ronald J. Bosch, Ph.D., Jeffrey N. Martin, M.D., M.P.H., Marina B. Klein, M.D., Lisa P. Jacobson, Sc.D., Benigno Rodriguez, M.D., Timothy R. Sterling, M.D., Gregory D. Kirk, M.D., Ph.D., Sonia Napravnik, Ph.D., Anita R. Rachlis, M.D., Lviana M. Calzavara, Ph.D., Michaela. Horberg, M.D., Michael J. Silverberg, Ph.D., Kelly A. Gebo, M.D., M.P.H., James J. Goedert, M.D., Constance A. Benson, M.D., Ann C. Collier, M.D., Stephen E. Van Rompaey, Ph.D., Heidi M. Crane, M.D., M.P.H., Rosemary G. McKaig, Ph.D., Bryan Lau, Ph.D., Aimee M. Freeman, M.A., and Richard D. Moore, M.D., for the NA-ACCORD Investigators*

THE AMERICAN JOURNAL of MEDICINE® 2009;122:647-55

Effect of Statin Adherence on Cerebrovascular Disease in Primary Prevention

Sylvie Perreault, BPharm, PhD,[a] Laura Ellia, MSc,[a] Alice Dragomir, MSc,[a] Robert Côté, MD, FRCPC,[b] Lucie Blais, PhD,[a] Anick Bérard, PhD,[a] Lyne Lalonde, BPharm, PhD[a]

BMJ 2011;342:d1672

Statin treatment for primary prevention of vascular disease: whom to treat? Cost-effectiveness analysis

JP Greving, research fellow in clinical epidemiology,[1] PJ Visseren, internist and professor of vascular medicine,[2] GA de Wit, associate professor of health technology assessment,[1,3] A Algra, professor of clinical epidemiology[1,4]

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OUTCOME

Cosa abbiamo imparato?

La biostatistica e la metodologia epidemiologica offrono un'ampia gamma di modelli e disegni volti ad affrontare le insidie insite nel metodo osservazionale senza per questo ostacolarne la versatilità e la capacità di adattarsi a un vasto spettro di obiettivi

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OUTCOME

A scientific alliance for

Carry out a **R**epository for **A**dministrative and **C**linical data **K**notting

Evaluating the management of chronic conditions in real world clinical practice

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John Lennon, 1971

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