L’evoluzione della ricerca epidemiologica basata sugli archivi sanitari: uno sguardo al futuro

Pavia, 24-25 novembre 2016
Collegio Fratelli Cairoli

Il metodo: norme di buona pratica della ricerca osservazionale con banche dati sanitarie

Giovanni Corrao

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Healthcare Research & Pharmacoepidemiology

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Società Italiana di Statistica Medica ed Epidemiologia Clinica

Clinical review

BMJ
1996;**312**:1215-8

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

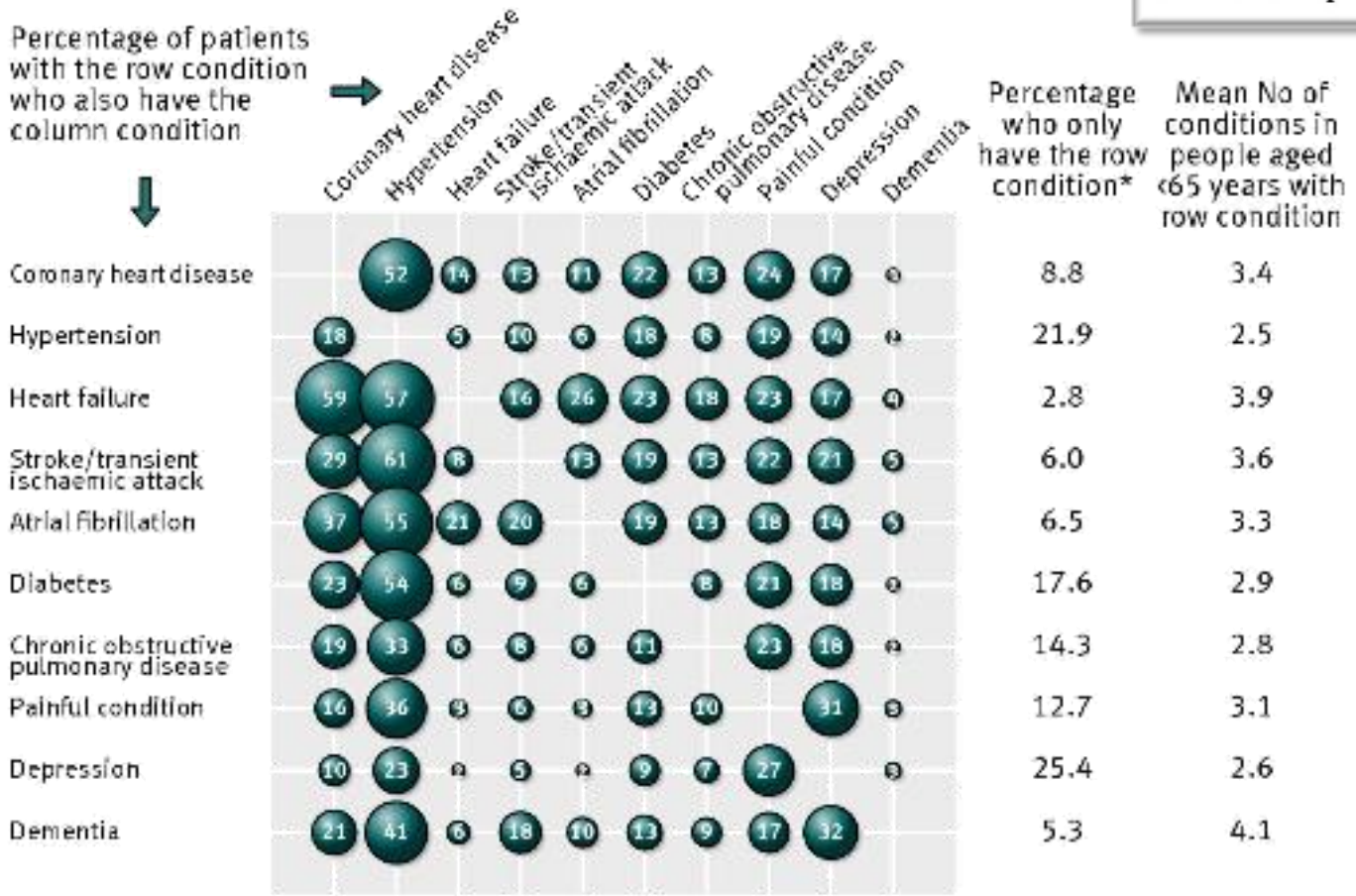
Background
(What are we talking about?)

Data availability
(National Health Service and RWD)

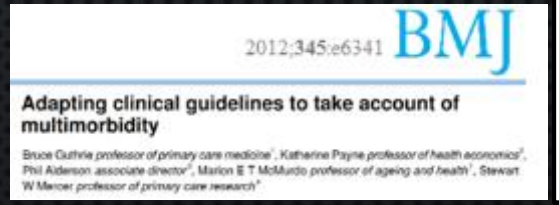
Generating evidence
(From RWD to RWE)

Critical issues and cautiousness
(How to ensure credibility to RWE?)

Take home messages
(What have we learned?)



Comorbidity of 10 common conditions among UK primary care patients[2]



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Characteristics of patients with metastatic colorectal cancer included in the pivotal randomised controlled trial (RCT) and those observed in clinical practice

	RCT [1]	Clinical practice
Age (median yrs)	59	68
Life expectancy	>= 3 month	About 20% died in the first 3 months of observation
Hematologic, hepatic and renal function	Required to be adequate	No restrictions
Clinically significant cardiovascular disease	Exclusion criteria	About 10% of patients have CVD at baseline
NSAID use	Exclusion criteria	>10% of patients reported past use of NSAID
Regular use of aspirin	Exclusion criteria	About 5% of patients reported past use of aspirin
Clinically detectable ascites	Exclusion criteria	No restrictions
Pregnancy or lactation	Exclusion criteria	No restrictions
Pre-existing bleeding diatheses	Exclusion criteria	No restrictions
Central nervous system metastases	Exclusion criteria	No restrictions

1. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42

From RCT

… to clinical practice

1. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42

Monitoraggio e valutazione dei percorsi diagnostico-terapeutici

Aderenza alle raccomandazioni

	Lombardia	Sicilia
Emoglobina glicata [1]	49.4%	34.9%
Profilo lipidico [2]	64.8%	72.0%
Microalbuminuria [2]	44.0%	27.6%
Creatininemia [2]	74.4%	57.2%
Visita oculistica [2]	21.3%	14.2%
Terapia farmacologica [3]	53.9%	31.4%

[1] almeno 2 controlli / anno
[2] almeno 1 controllo / anno
[3] aderenza (MPR) ≥ 75%

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Monitoraggio e valutazione dei percorsi diagnostico-

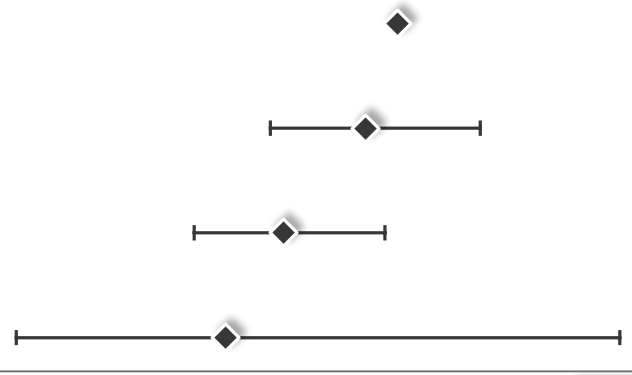
Impatto dell'aderenza alle raccomandazioni

IMPATTO

↓↓↓

FE = 25%

N. raccomandazioni alle quali il paziente aderisce	%	HR [(b)] (95% CI)
0-1	25,0	1,00 (rif.)
2-3	39,4	0,95 (0,80-1,13)
4-5	33,9	0,82 (0,68-0,98)
6	1,7	0,73 (0,40-1,35)



$p_{trend} = 0,019$

(a) Esito composito: Scompenso cardiaco, Infarto miocardico, Patologia cerebrovascolare, Aritmia, Vasculopatia periferica; Complicanze arti inferiori, Procedure di rivascolarizzazione; Diabete con complicanze renali, oculari, neurologiche, circolatorie periferiche, altre complicanze specificate e non

(b) Hazard ratio (e 95% CI) stimato interpolando un modello di Cox. Il modello include come covariate genere, età, cotrattamenti (statine, anti-ipertensivi, anticoagulanti, antiaritmici, nitrati, antidepressivi) and comorbidità (cardiovascolare, cerebrovascolare, renale, respiratoria, tumori, indice di comorbosità di Charlson)

Perspective
June 5, 2014

The NEW ENGLAND JOURNAL of MEDICINE

Learning from Big Health Care Data

Sebastian Schneeweiss, M.D., Sc.D.

Dobbiamo realizzare un sistema di auto-apprendimento che, basato sulle esperienze passate, sia in grado di «**orientare le scelte**» sul miglior trattamento dei pazienti che vedremo nel futuro

Ministero della Salute

FRAME

flussi regionali automatizzati per il monitoraggio dell'assistenza e la generazione di evidenze scientifiche di indirizzo per le politiche sanitarie

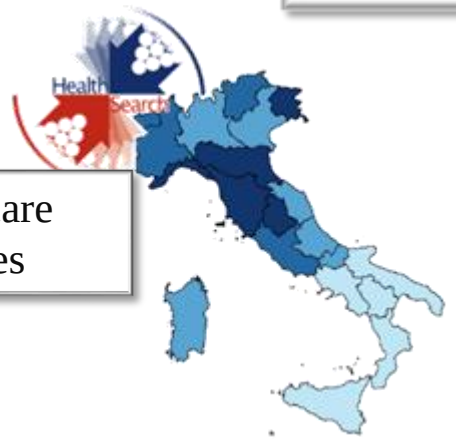
Censimento dei DB «linkabili» in 8 Regioni italiane

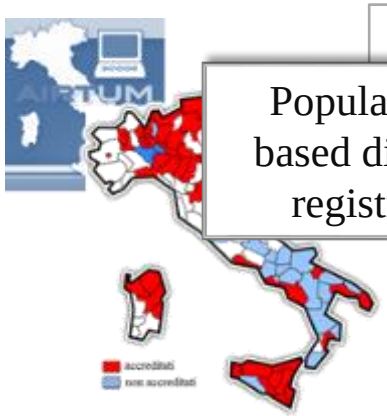
	ABR	FVG	LOMB	MAR	SARD	SIC	TRN	UMB
Registry of NHS beneficiaries	1996	1982	1997	2005	2005	2010	1995	1987
Hospital discharge diagnoses	2003	1986	2000	1996	2001	2001	1995	1987
Emergency room diagnoses	2011	2000	2011	2011	2012	2008	1995	2009
Outpatients services	2008	1998	2000	1998	2009	2003	1995	1996
Outpatients drug prescriptions	2008	1995	2004	2003	2009	2007	1995	1993
Inpatients drugs dispensed	2010	2007	2004	2007	2009	2005	2006	2008
Certificates of Delivery Assistance	2003	1989	2003	2011	2009	2007	1995	2001

Regione Lombardia | Provincia di Trento | Regione Friuli VG | Regione Marche | Regione Umbria | Regione Abruzzo | Regione Sicilia | Regione Sardegna

Healthcare utilization databases

Primary care databases





Population-based disease registries

Drugs submitted to monitoring

AIFA

Value in Health

2007;**10**:326-35

Using Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report

Louis P. Garrison Jr., PhD (cochair),[1] Peter J. Neumann, ScD (cochair),[2] Pennifer Erickson, PhD,[3] Deborah Marshall, PhD,[4] C. Daniel Mullins, PhD[5]

The notion was that "data" conjures the idea of simple factual information, whereas "evidence" connotes the organization of the information to inform a conclusion

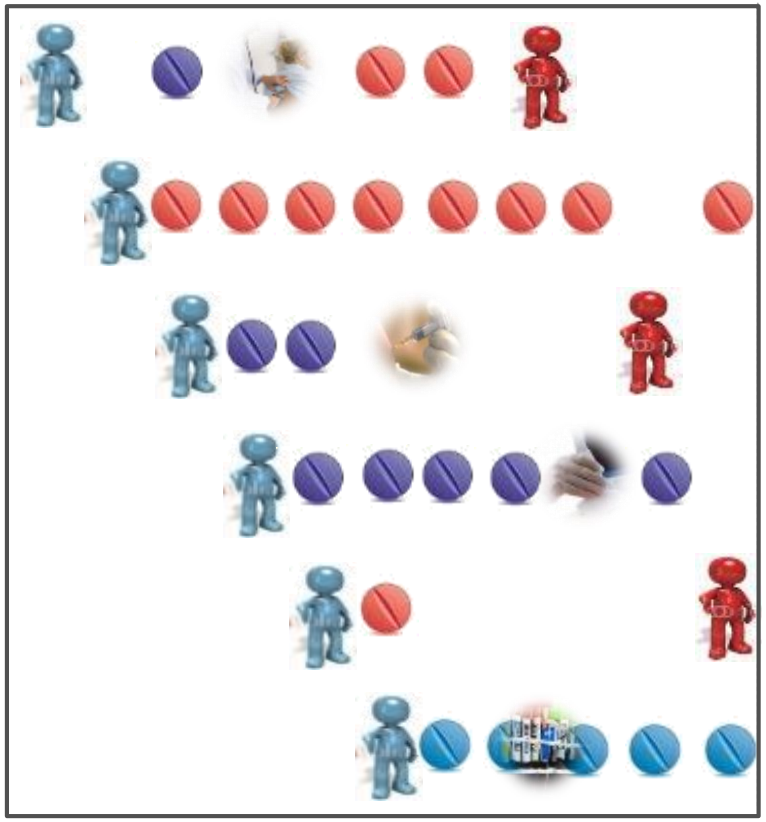
Evidence is generated according to a research plan and interpreted accordingly, whereas data is but one component of the research plan.

dence is shaped, while data simply are raw materials and alone are noninformative.

American Heart Association. Hypertension 2015;65:490-8

Corrao G, Mancia G. Generating evidence from computerized healthcare utilization databases

Il piano osservazionale di riferimento



Tempo

Presa in carico

Terapie

Accertamenti diagnostici / Visite ambulatoriali / Altre forme di assistenza

Esito

PDTA

Spesa

Efficacia*

Sicurezza

Aderenza, appropriatezza

Costo - efficacia

Sicurezza-efficacia

Strengths

Data availability

Large and unselected populations

Use and impact of healthcare in the clinical practice

Strengths

Data availability

Large and unselected populations

Use and impact of healthcare in the clinical practice

designed for healthcare management rather than for healthcare research and assessment

Concerns

Data accessibility

Evidence credibility

Vulnerabilità dell'approccio osservazionale

Editorials — BMJ

Evidence based medicine: what it is and what it isn't — 1996;312:71

David L Sackett, William M C Rosenberg, J A Muir Gray, R Brian Haynes, W Scott Richardson

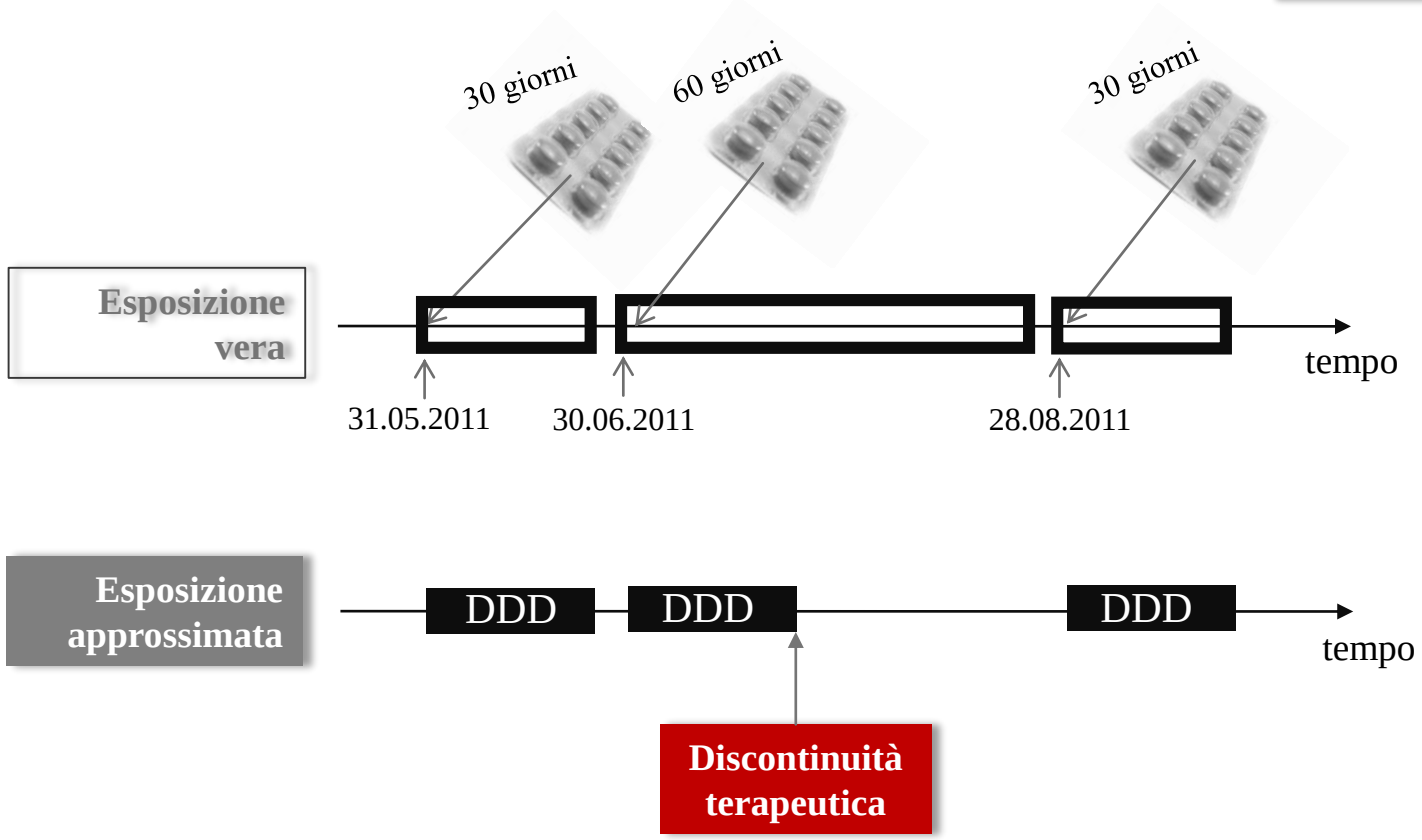
"... If you find that a study was not randomized, we'd suggest that you stop reading it and go to the next article ..."

Carenza di dati clinici

Misclassificazione dell'esposizione

Misclassificazione dell'esito

Confondimento da indicazione



DDD: defined daily dose

Mesi coperti dalla terapia con antidiabetici orali durante il primo anno dalla diagnosi in base alla dose prescritta (PDD) e a quella stimata (DDD)

PDD → **7.1 mesi**

DDD → **5.3 mesi**

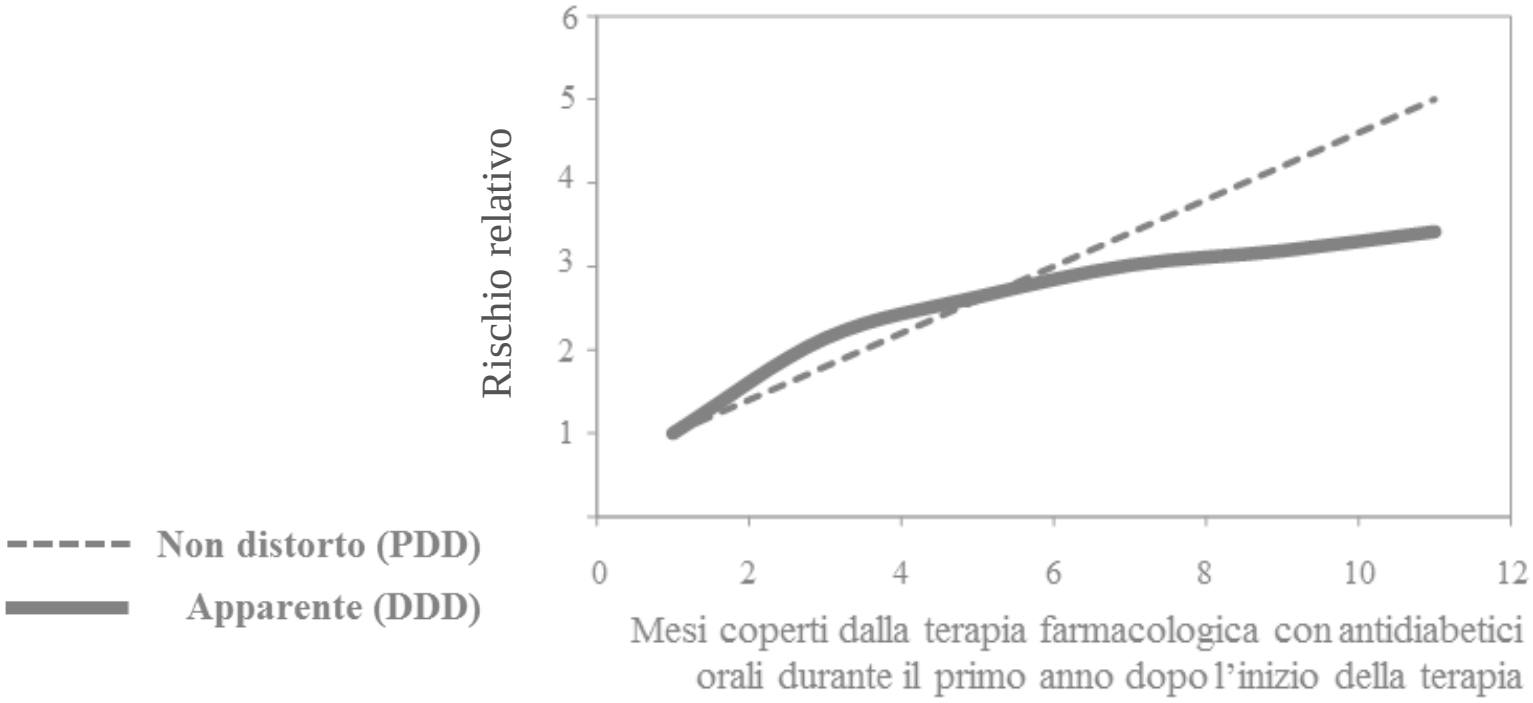
DDD \ PDD	0	2	4	6	8	10	12
0	65%	25%	6%	2%	1%	1%	
2	3%	30%	25%	16%	11%	17%	
4		3%	25%	24%	27%	21%	
6		1%	5%	25%	25%	44%	
8			2%	8%	44%	46%	
10				3%	17%	80%	
12							


PDS Pharmacoepidemiology & Drug Safety
2016 Sep 4. doi: 10.1002/pds.4093. [Epub ahead of print]
Pharmacoepidemiology and Drug Safety

A probabilistic bias analysis for misclassified categorical exposures, with application to oral anti-hyperglycaemic drugs

Andrea Arfè, Federica Nicotra, Arianna Ghirardi, Monica Simonetti, Francesco Lapi, Miriam Sturkenboom, Giovanni Corrao

Distorsione introdotta dalle DDD per la stima della relazione tra durata della terapia e rischio di un certo esito

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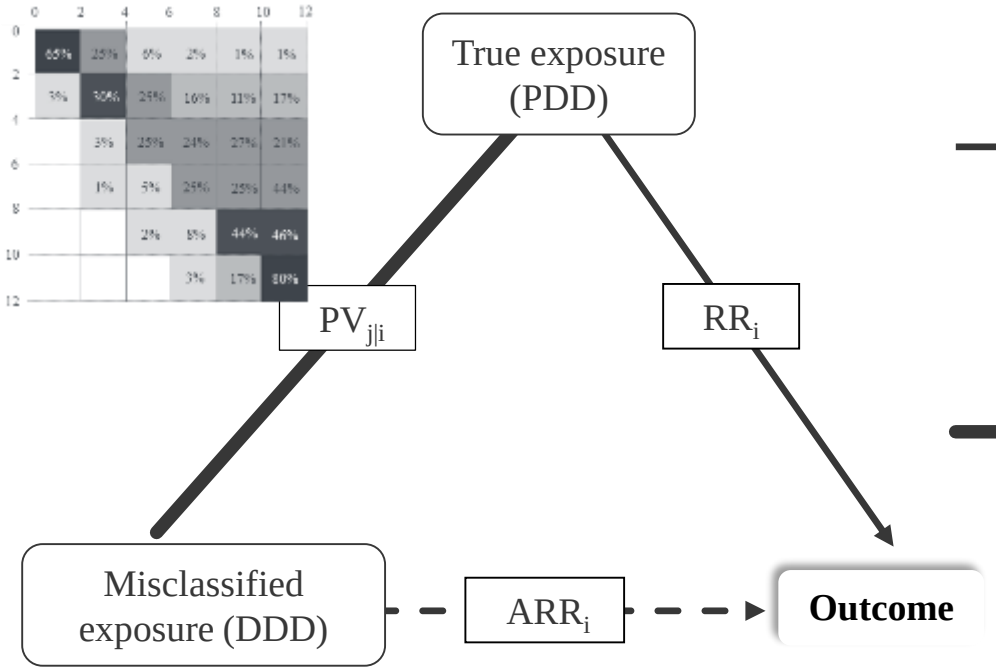

True exposure - disease association

Key quantities: True/adjusted risk ratio (RR_i)

Misclassified exposure - disease association

Key quantities: apparent risk ratio (ARR_i)

True exposure – misclassified exposure association

Key quantities: predictive values ($PV_{j|i}$)

$$\mathbf{RR} = 1 + (\mathbf{PV} - \mathbf{ARR} \cdot \mathbf{PV}_0^{\mathrm{T}})^{-1} \cdot (\mathbf{ARR} - 1)$$


PDS Pharmacoepidemiology & Drug Safety
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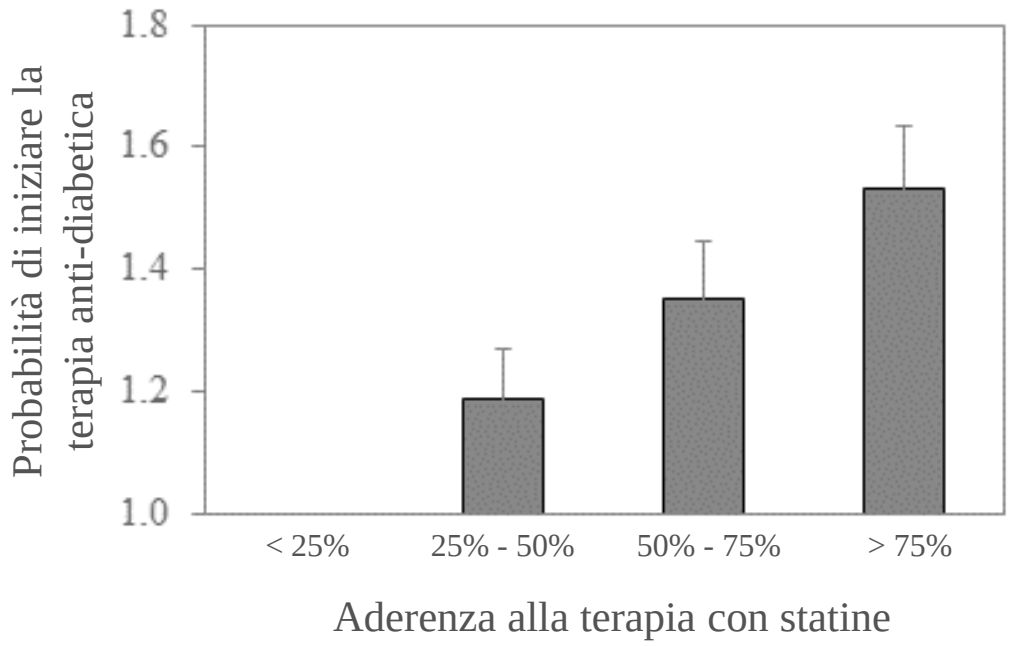
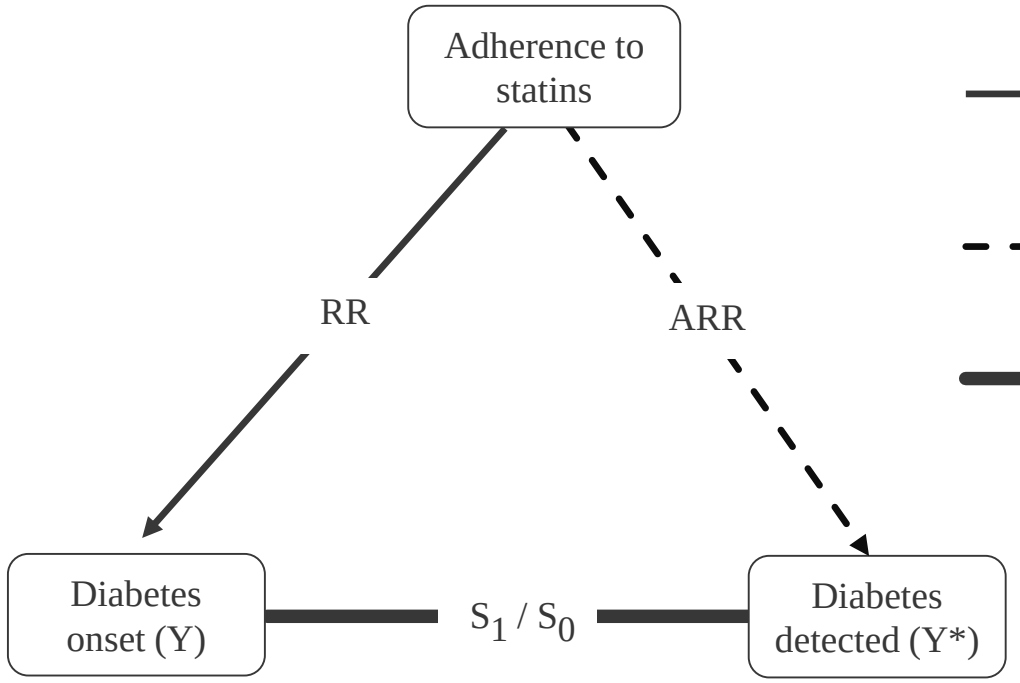
Associazione tra aderenza alla terapia con statine e inizio della terapia anti-diabetica



American Diabetes Association. Diabetes Care. 2014;37:2225-32

Corrao G, Ibrahim B, Nicotra F, et al. Statins and risk of diabetes: evidence from a large population-based cohort study



True (exposure – disease) association

Key quantities: True/adjusted risk ratio (*RR*).

Misclassified (exposure – disease) association

Key quantities: apparent risk ratio (*ARR*)

True – misclassified outcome association

Key quantities: between sensitivities ratio (S_0/S_1)

$S_1 = Pr(Y^*=1 \mid Y=1, E=1)$

$S_0 = Pr(Y^*=1 \mid Y=1, E=0)$

$RR = ARR\ (S_0 / S_1)$


JCE
JOURNAL OF CLINICAL EPIDEMIOLOGY
May 2016 Volume 68, Issue 5, Pages 480–488

Tutorial: Strategies addressing detection bias were reviewed and implemented for investigating the statins–diabetes association

Anima Arfè, Giovanni Corrao

Department of Statistics and Quantitative Methods, Division of Biostatistics, Epidemiology and Public Health, Laboratory of Healthcare Research and Pharmacoepidemiology, University of Milano-Bicocca, Via Bicocca degli Arcimboldi 8, Building U7, 20126 Milan, Italy

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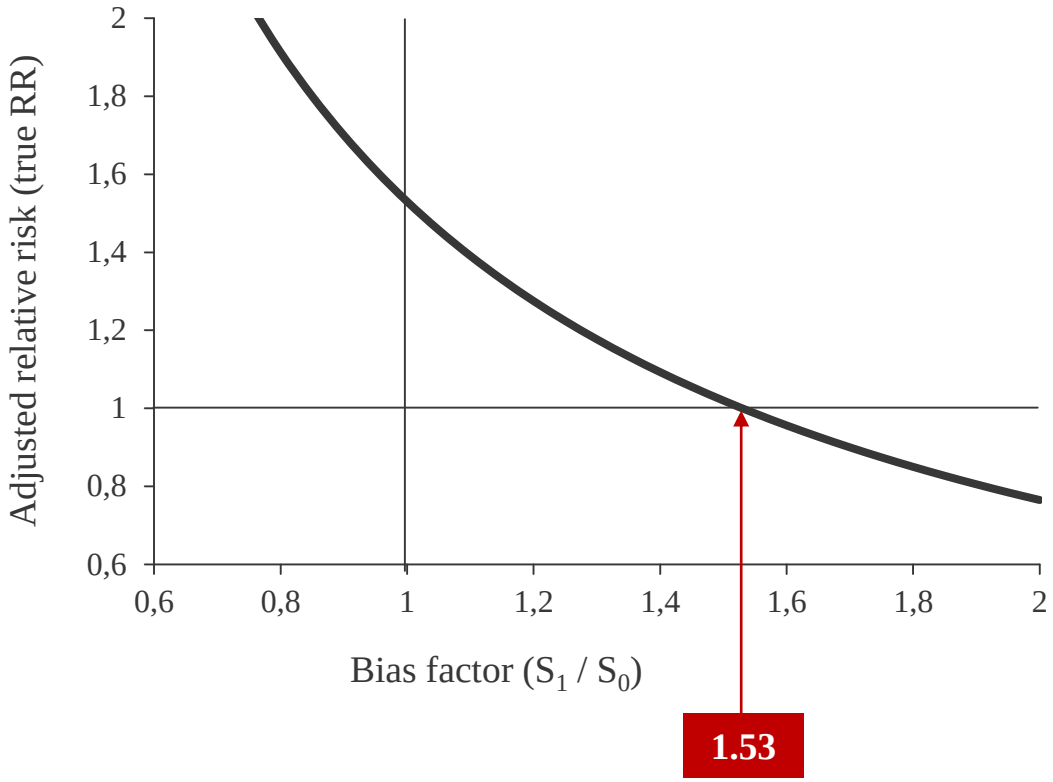
Healthcare Research
& Pharmacoepidemiology

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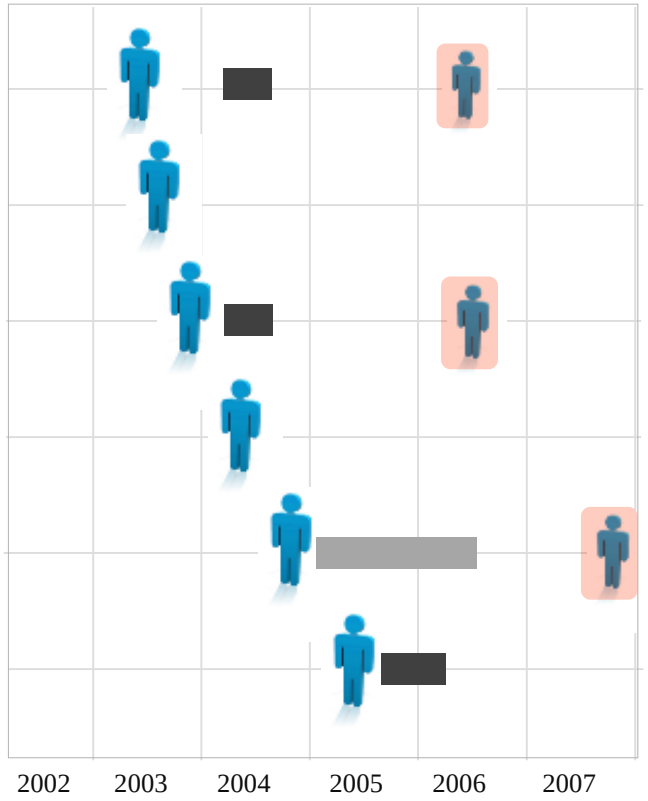
L'uso di bifosfonati per la prevenzione secondaria delle fratture ossee

AIFA

BEST Project: Assessing the risk/benefit profile of bisphosphonates therapy in the secondary prevention of osteoporotic fractures



First hospital admission for fracture — 47,022 patients

Starting with bisphosphonates therapy — 4,275 patients (9%)

Re-hospitalization for fracture — 1,796 patients (4%)

PDS Pharmacoepidemiology & Drug Safety
2014;23:859-67

Corrao G, Ghirardi A, et al. User-only design for assessing drug effectiveness in clinical practice

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BEST Project: Assessing the risk/benefit profile of bisphosphonates therapy in the secondary prevention of osteoporotic fractures

Use of bisphosphonates	OR_{adj}	IC 95%
No	1.00	Rif
Yes	1.20	1.01 to 1.44

Odds ratio (and 95% CI) was modelled by conditional logistic regression. Confounding effect of measured covariates was taken into account by including selected covariates into the model. Considered covariates were co-treatments (with lipid-lowering agents, anticoagulants, corticosteroids, glucocorticoids, proton pump inhibitors and antidepressant) and comorbidities (orthostatic hypotension, cerebrovascular disease, balance disorders, Parkinson disease, dementia, epilepsy, and blindness)

PDS Pharmacoepidemiology & Drug Safety
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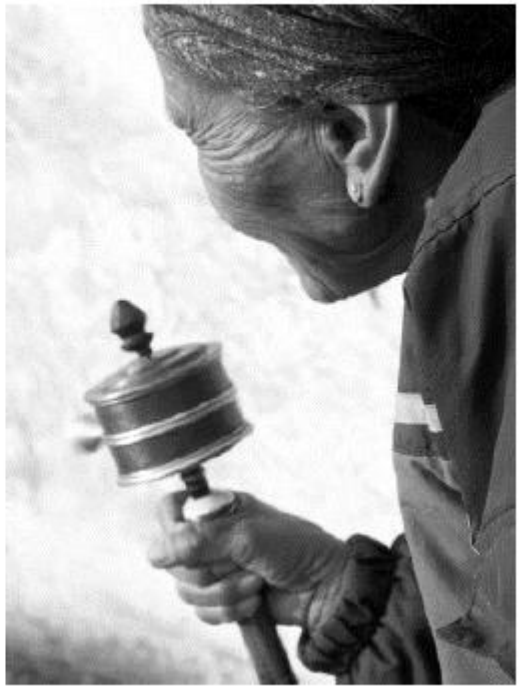
Corrao G, Ghirardi A, et al. User-only design for assessing drug effectiveness in clinical practice

The Mantra of Trialists:

Non-randomized studies are inherently biased due to patient selection into treatment groups



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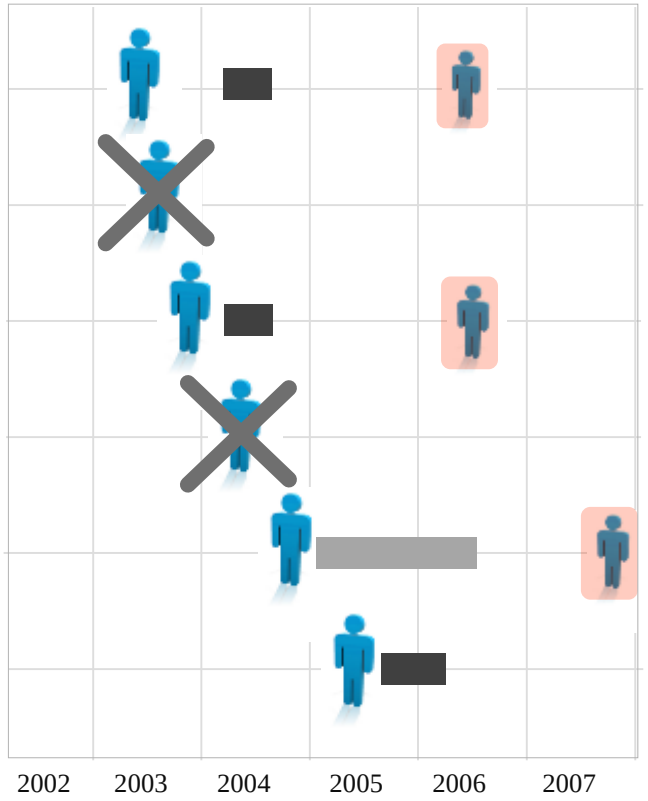

First hospital admission for fracture — ~~47,022 patients~~

Starting with bisphosphonates therapy — 4,275 patients (9%)

Re-hospitalization for fracture — 214 patients (5%)

PDS Pharmacoepidemiology & Drug Safety
2014;23:859-67

Corrao G, Ghirardi A, et al. User-only design for assessing drug effectiveness in clinical practice

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L'uso di bifosfonati per la prevenzione secondaria delle fratture ossee

AIFA

BEST Project: Assessing the risk/benefit profile of bisphosphonates therapy in the secondary prevention of osteoporotic fractures

INAPPROPRIATEZZA

Uso di bifosfonati	%	OR
< 6 mesi	42	1.00
da 6 mesi a 1 anno	15	0.73
≥ 1 anno	43	0.64

IMPATTO

↓↓↓

FE = 17%

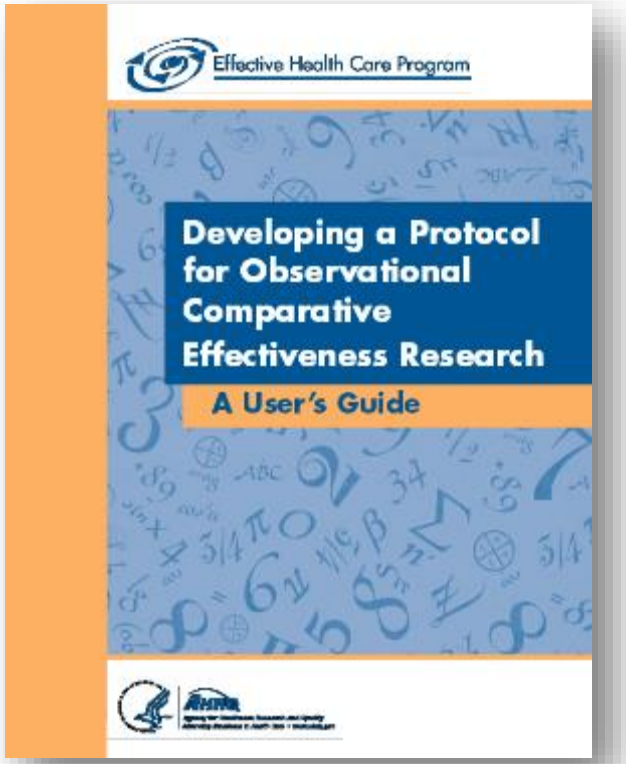
Odds ratio (and 95% CI) was modelled by conditional logistic regression. Confounding effect of measured covariates was taken into account by including these covariates into the model. Considered covariates were co-treatments (with lipid-lowering agents, anticoagulants, corticosteroids, glucocorticoids, proton pump inhibitors and antidepressant) and comorbidities (orthostatic hypotension, cerebrovascular disease, balance disorders, Parkinson disease, dementia, epilepsy, and blindness)

PDS Pharmacoepidemiology & Drug Safety
2014;23:859-67

Corrao G, Ghirardi A, et al. User-only design for assessing drug effectiveness in clinical practice

Per generare evidenze credibili:

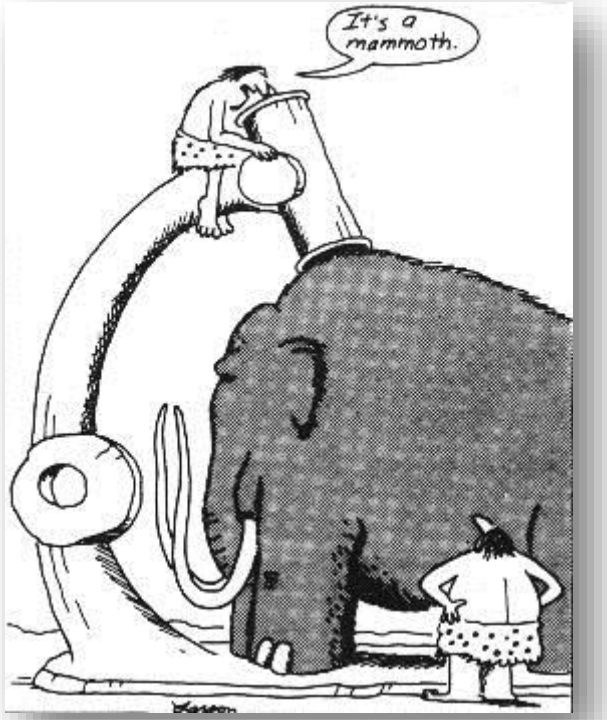
… bisognerebbe adottare e diffondere norme condivise per la buona pratica della ricerca osservazionale con fonti secondarie …



Per orientare le politiche:

… bisognerebbe incentivare la ricerca epidemiologica traslazionale [a] purché «genuina», pertinente e rigorosa …

[a] trasferimento delle evidenze tratte dalla vita reale alla pratica della sanità pubblica



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(How to ensure credibility to RWE?)

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(What have we learned?)

Healthcare Research

& Pharmacoepidemiology

Statuto – Art. 2

Il Centro intende proporsi come:
«…organismo scientifico di riferimento per istituzioni, operatori e ricercatori che … hanno interesse verso i temi dell'utilizzo, dell'appropriatezza, dell'efficacia, dell'efficienza e dell'equità degli interventi medici … attraverso … la messa a punto e la diffusione di metodi scientificamente validi e la generazione di evidenze…»

WELCOME
TO THE REAL WORLD