Epidemiologia II

Fabrizio Stracci

Epidemiologia

- Eziologica

Finalizzata alla identificazione delle cause di malattia e del benessere delle popolazioni

- Clinica e valutativa

Finalizzata alla identificazione di determinanti dei risultati dei trattamenti e,in generale, del decorso della malattia nelle popolazioni dei malati

Susser

- ‘insofar as epidemiology is a science that aims to discover the causes of health states, the search includes **all determinants of a health outcome**’
- Susser M. *What is a cause and how do we know one? A grammar for pragmatic epidemiology. Am J Epidemiol 1991;133:635-48.*

Tentativi di definizione

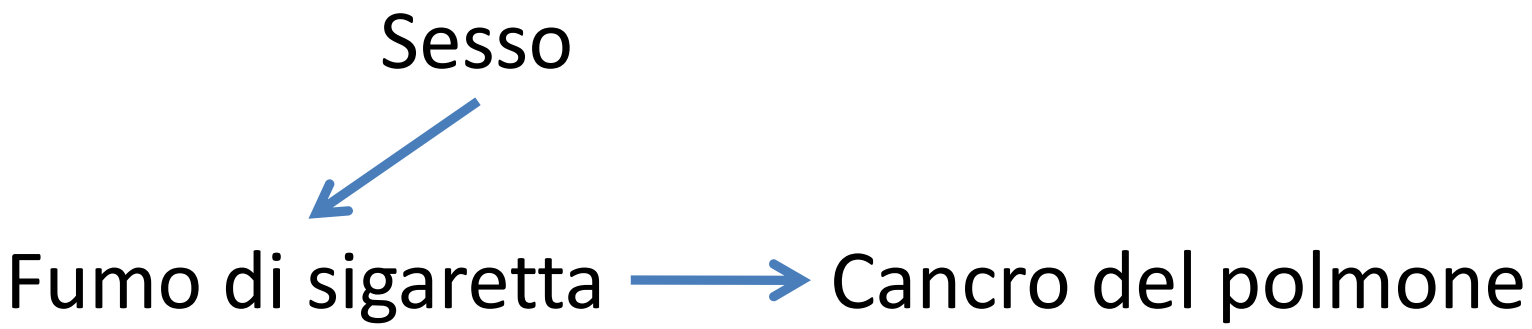
Table 1
Definitions of causation from the epidemiologic literature (modified from Parascandola and Weed 2001).

Definition	Main criticism
A cause is something that produces or creates an effect.	Tautological because " production" and "creation" are synonyms of "causation"
A cause is a condition without which the affect cannot occur.	Only very few diseases could then have a cause [a]
A cause is a condition with which the affect must occur.	Again, only few diseases could then have a cause [b]
A cause is made up of several components, no single one of which is sufficient of its own, which taken together must lead to the effect.	Introduces unnecessary complexity in cases of simple dose response and in cases of interaction between components
A cause is a condition that increases the probability of occurrence of the affect.	Does not distinguish between an association and a "cause" [c]
A cause is a condition that, if present, makes a difference in (the probability of) the outcome.	Is, in the strict sense, unprovable because there is only one world and one cannot observe it twice-once with once without the condition

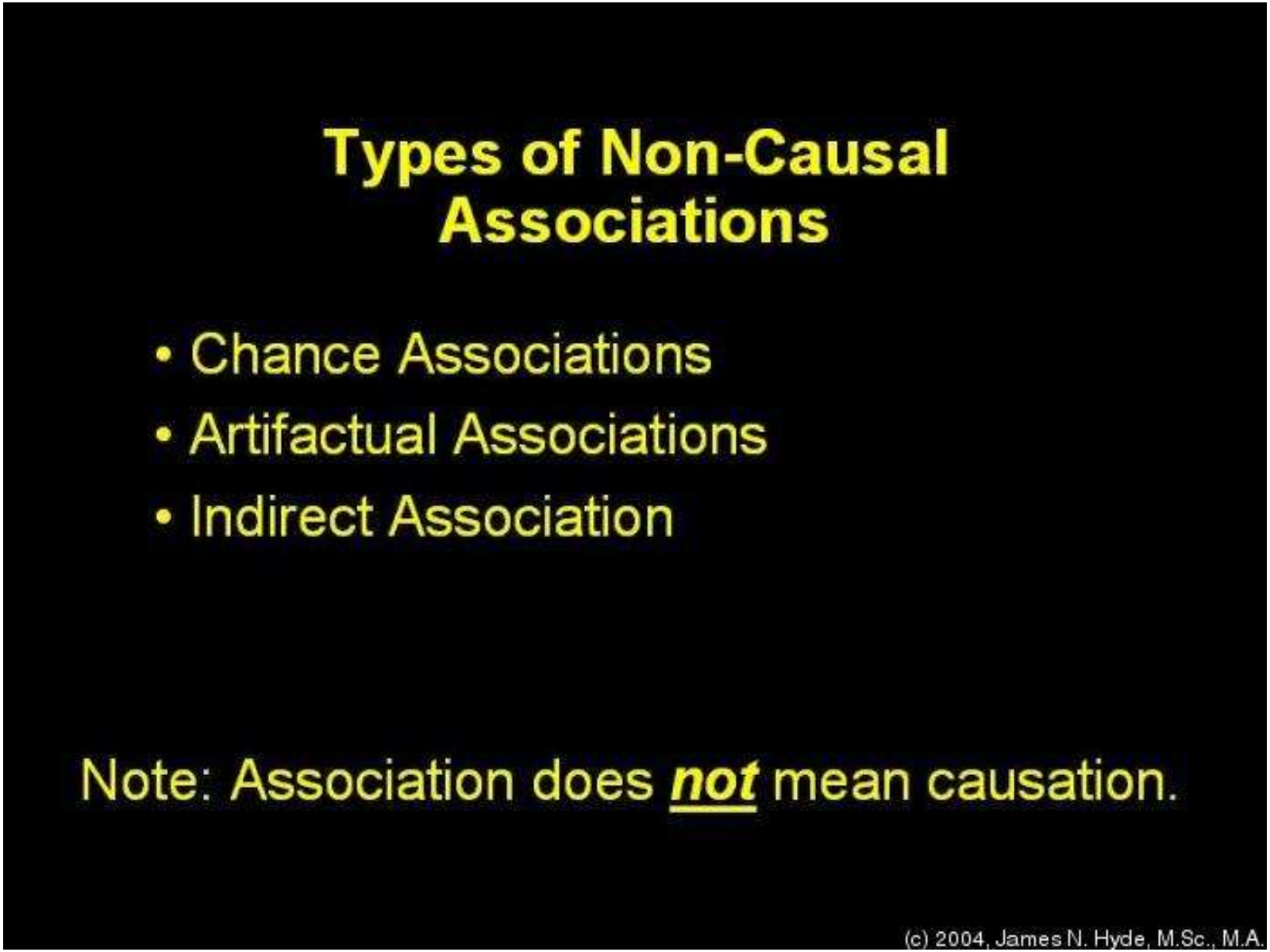
[a] Many disease definitions already include a cause(e.g., AIDS is a clinical syndrome in the presence of HIV infection of CD4 cells), but this must not be confused with a necessary cause. All clinical symptoms that occur in AIDS patients can have a variety of other" "causes".[b] For example, falling from the 27th floor onto the pavement is not necessary cause for breaking the skull because many other processes can lead to this effect; however, it can be seen as a sufficient cause. Except for injuries due to extreme physical or chemical conditions and exposure to extremely contagious infectious agents that lead to death (e.g., rabies)or do not result in immunity(e.g., gonorrhea),there are no sufficient causes in this strict sense.[c] Following this definition, male sex would be a cause of lung cancer.

Differenze

- Fattore (condizione) di rischio o protettivo non equivale a causa
- Associazione e correlazione non equivalgono a relazione causale; per associazione si intende una relazione misurata mediante un indice statistico tra due o più variabili


Sesso
Fumo di sigaretta
Cancro del polmone

Associazione e causalità

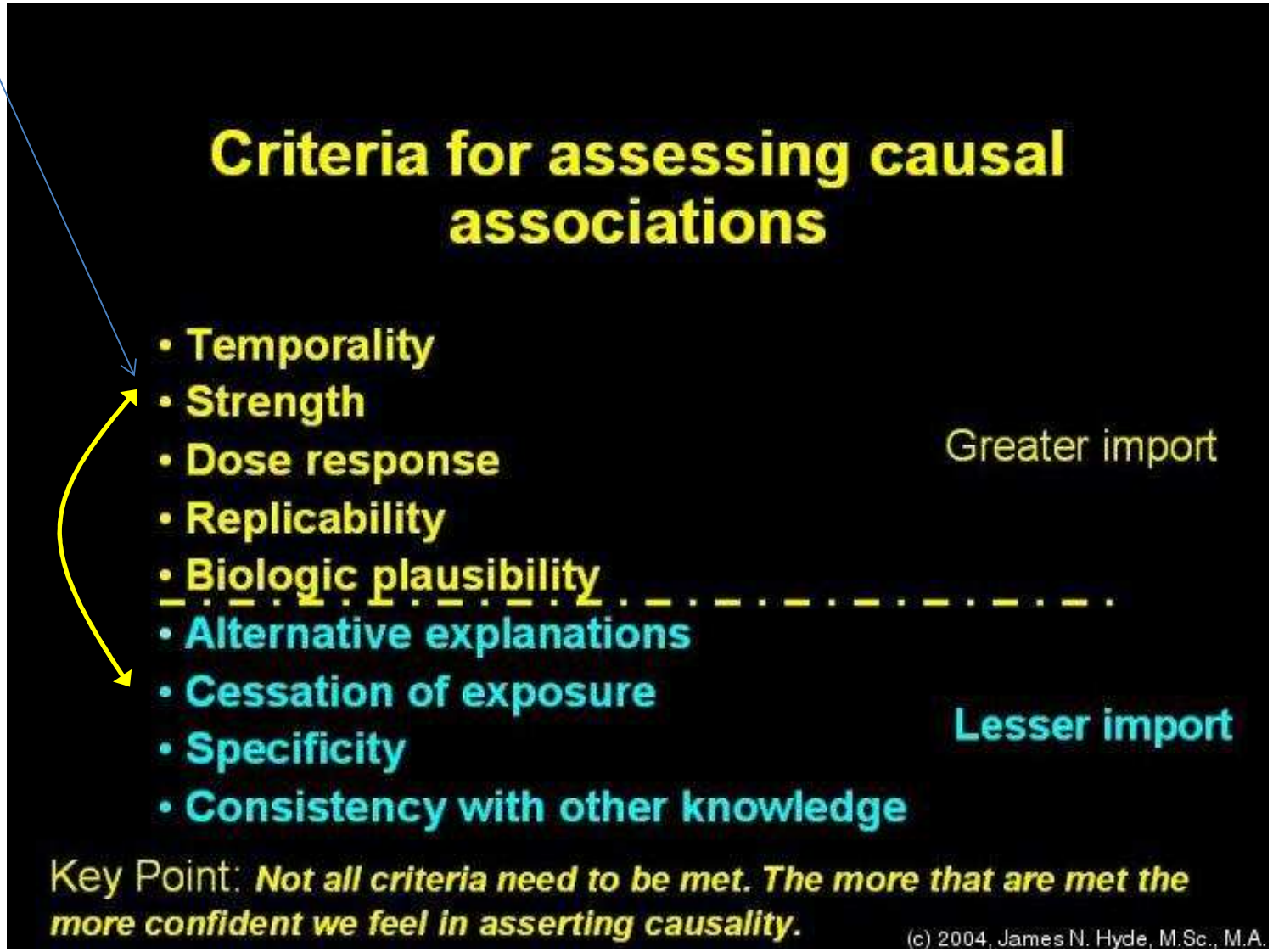


I criteri di Hill

(1) Strength ,
(2) Consistency [*among study types and over time*],
(3) Specificity [*wrong*],
(4) **Temporality** ,
(5) Biological gradient ,
(6) Plausibility ,
(7) Coherence [similar to plausibility],
(8) **Experimental evidence** [*best evidence in humans but seldom available*], and
(9) Analogy [very weak].

Semplifica lo studio

Priorità



Dalla associazione alla causalità

- Forza dell'associazione

  [*valori di RR ed OR: i fattori eziologici con valori dei parametri più elevati sono più facili da identificare*]
- Relazione dose-risposta
- Consistenza dell'associazione

Causalità

Table 2–3. Criteria Used to Test Causal Hypotheses

1. The hypothesized cause should be distributed in the population in the same manner as the disease.
2. The incidence of the disease should be higher in those exposed to the hypothesized cause than in those not so exposed. (The cause may be present in the external environment or as a defect in host responses.)
3. Exposure to the hypothesized cause should be more frequent among those with the disease than in controls without the disease, when all other risk factors are held constant.
4. Temporally, the disease should follow exposure to the hypothesized causative agent.
5. The greater the dose or length of exposure, the greater the likelihood of occurrence of the disease.
6. For some diseases, a spectrum of host responses should follow exposure to the hypothesized agent along a logical biologic gradient from mild to severe.
7. The association between the hypothesized cause and disease should be found in various populations when different methods of study are used.
8. Other explanations for the association should be ruled out.
9. Elimination or modification of the hypothesized cause or of the vector carrying it should decrease the incidence of the disease (e.g., control of polluted water, removal of tar from cigarettes).
10. Prevention or modification of the host's response on exposure to the hypothesized cause should decrease or eliminate the disease (e.g., immunization, drugs to lower cholesterol, specific lymphocyte transfer factor in cancer).
11. When possible, in experimental settings the disease should occur more frequently in animals or humans appropriately exposed to the hypothesized cause than in those not so exposed; this exposure may be deliberate in volunteers, experimentally induced in the laboratory, or demonstrated in a controlled regulation of natural exposure.
12. All of the relationships and findings should make biologic and epidemiologic sense.

Cause di malattia: il modello di Rothman

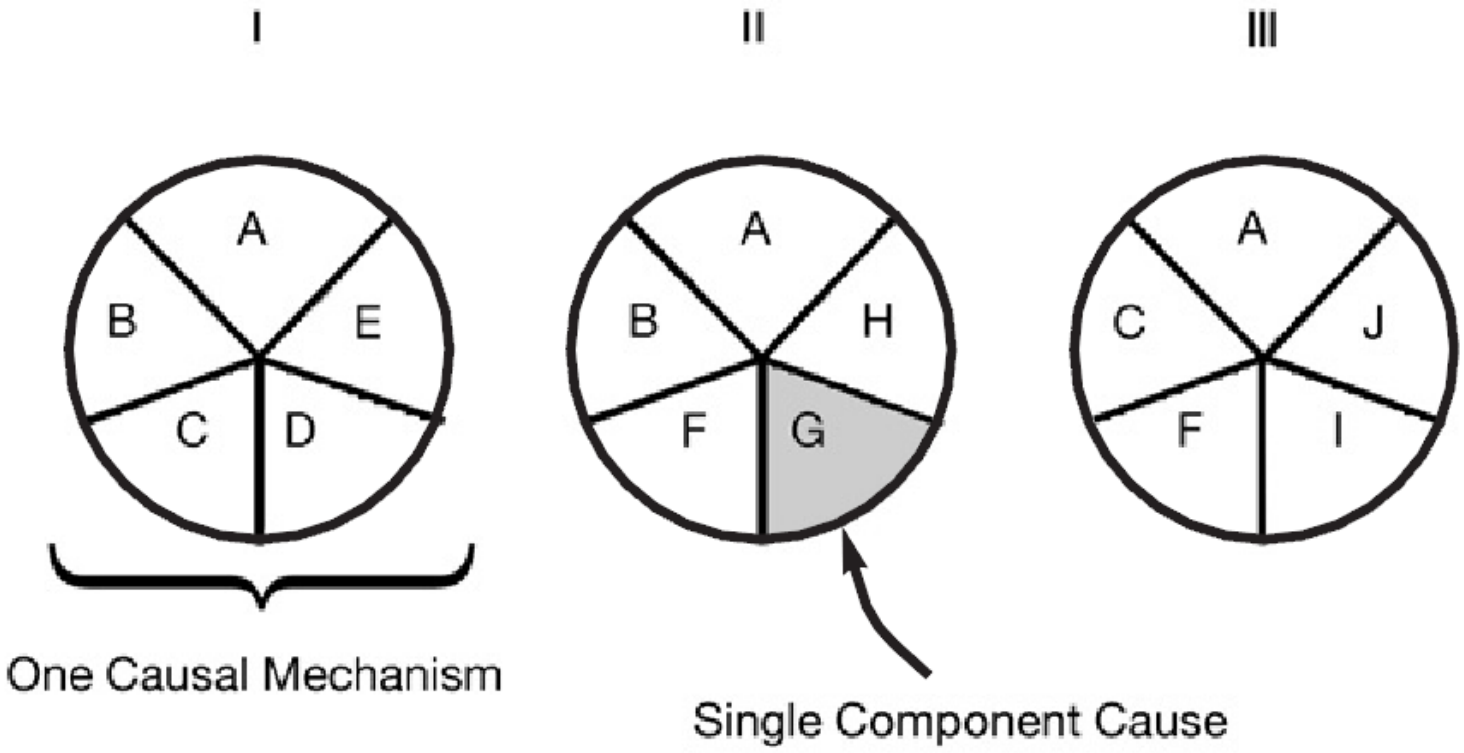


FIGURE 1—Three sufficient causes of disease.

Cause di malattia: il modello di Rothman

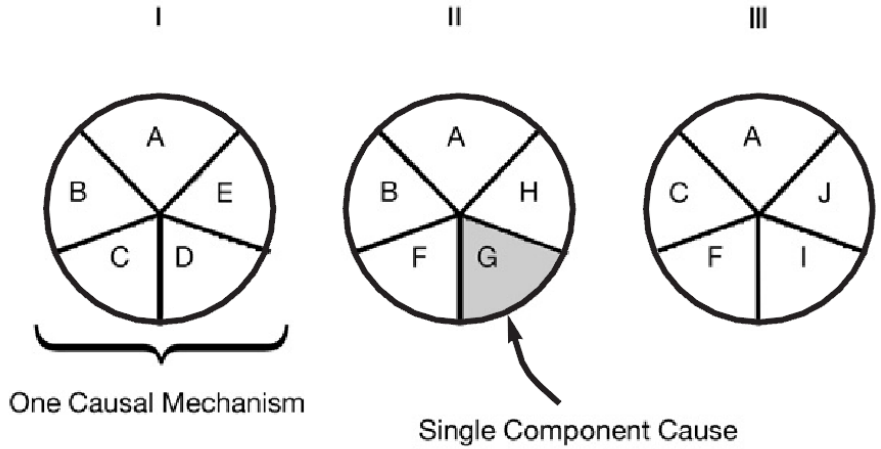
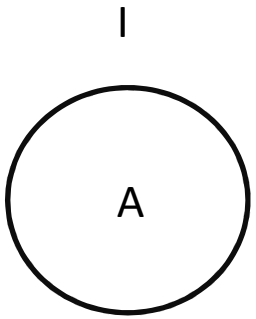


FIGURE 1—Three sufficient causes of disease.



Malattia che può essere determinata da un singolo agente e che si manifesta in tutti gli esposti: l'agente è causa necessaria e sufficiente della malattia x

Controfattuale

- Possiamo definire Causa un oggetto , seguito da un altro, dove, se il primo oggetto non avesse avuto luogo, il secondo non sarebbe mai esistito (Hume)
- implica il criterio maggiore della causalità : la direzione e consequenzialità temporale
- La causa rappresenta la differenza tra l'effetto attuale e quello che si sarebbe verificato se la causa fosse rimossa (controfattuale)

Formalismo di Neyman: il modello degli esiti potenziali

- Abbiamo N unità sperimentali
- Esperimento consiste nell'assegnazione di K+1 trattamenti $x_0, x_1, \ldots, x_K$ (di solito x_0 corrisponde a nessun trattamento o standard)
- Per l'unità i consideriamo la variabile di risposta Y_i
- L'effetto causale del trattamento xk con k>=1 rispetto a x_0, è $y_{ik}-y_{i0}$ (o per Y_i positive y_{ik}/y_{i0} o $\log y_{ik} - \log y_{i0}$)

A parole

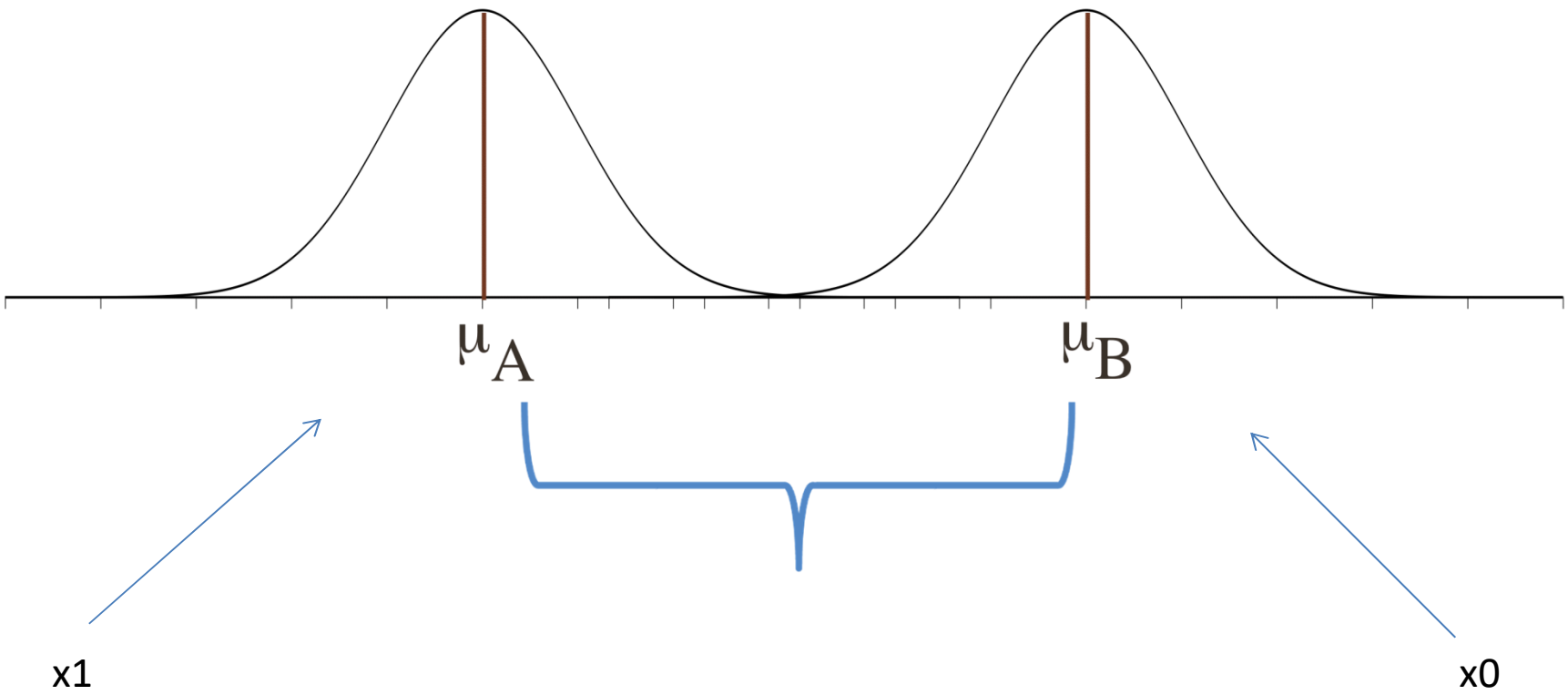
- L'effetto causale corrisponde per una singola unità al contrasto tra gli esiti (y_{ik} e y_{i0}), le risposte, corrispondenti a differenti possibilità di trattamento (x_k e il riferimento x_0)

- In termini probabilistici per una popolazione con distribuzione F(y), l'effetto può essere considerato come la risposta media per una popolazione esposta a diversi trattamenti o come differenza tra le distribuzioni marginali $F(y_0)$,…, $F(y_k)$

Il parametro μ

- Supponiamo che la popolazione A possa essere esposta ad un fattore x_1,
- μ assumerà valore μ_{A1} per A esposta e μ_{A0} se non esposta (fattore x_0)
- L'effetto causale di x_1 rispetto a x_0 sarà dato da $\mu_{A1} - \mu_{A0}$ (o μ_{A1}/μ_{A0}) non osservabile
- Se assumiamo che per una qualche popolazione B non esposta (di controllo o di riferimento), $\mu_{B0} = \mu_{A0}$, siamo in grado di stimare l'effetto come $\mu_{A1} - \mu_{B0}$

Effetto $\Delta\mu$ di una causa su una variabile normalmente distribuita



Non equivalenza

- La nostra stima di $\mu_{A1} - \mu_{A0}$ è distorta (biased) se $\mu_{B0} \neq \mu_{A0}$
- Questo accade se vi è uno squilibrio nelle popolazioni A e B tra i fattori o covariate che influiscono su μ
- Tuttavia distribuzioni diverse di fattori non necessariamente producono bias dal momento che influenze opposte possono annullarsi

Esiti non osservabili

- Negli studi sperimentali: equivalenza della suscettibilità a rispondere in seguito alla eguale probabilità di assegnazione ai diversi trattamenti
- Negli studi osservazionali : assunti di assenza di confondimento o correzione per variabili confondenti misurate
- Ricerca di esperimenti naturali (assunto) : situazione in cui il fattore x risulto assegnato a caso tra i soggetti in circostanze naturali

Controllo della distorsione

- Mediante disegno dello studio
  - Restrizione (criteri di inclusione)
  - Appaiamento (matching , difficile per numerose variabili)
  - Assegnazione casuale (equivalenza probabilistica tra A e B)
- Mediante ‘aggiustamento’, correzione, in fase di analisi dei dati
  - Stratificazione
  - Propensione al trattamento
  - Modello di regressione

Possiamo evidenziare relazioni causali

- For example, epidemiological studies demonstrating strong causal connections between smoking and lung cancer and asbestos exposure and mesothelioma have strengthened our resolve that we can discover causes of disease states.
- Consideriamo valida una teoria eziologica in base alle evidenze disponibili e fino alla comparsa di evidenze contrarie

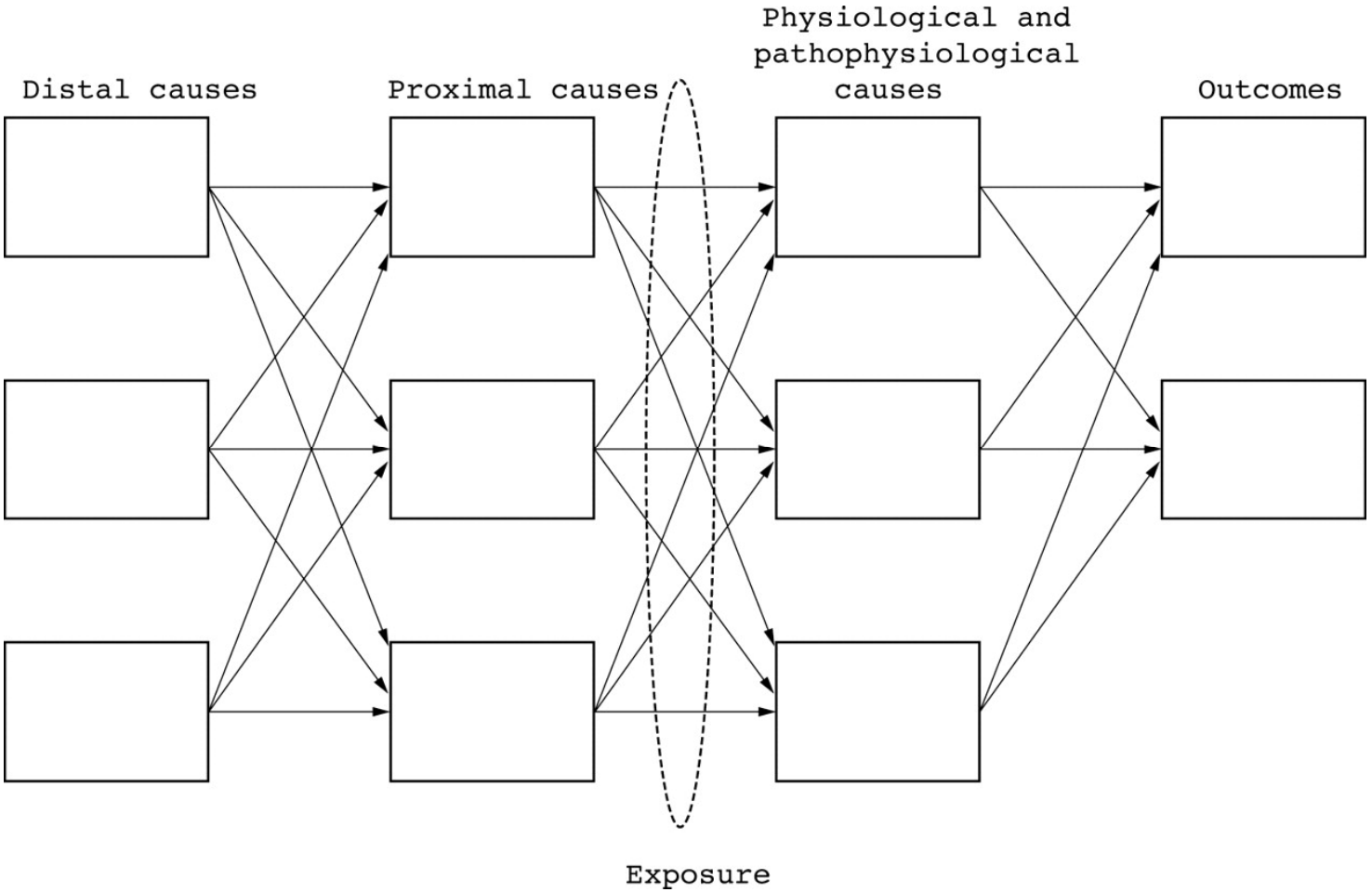
In base al problema in studio la ricerca eziologica presenta diversi livelli di difficoltà

- Exp amianto -> malattia caratteristica: mesotelioma (difficoltà :tempo di latenza)
- Exp inquinamento atmosferico -> cancro del polmone (difficoltà: confondenti come il fumo, misura dell'esposizione individuale, tempo di latenza, variabilità composizione e attività miscela)

Complicazione delle cause

- “Factors at multiple levels, including biological, behavioural, group and macro-social levels, all have implications for the production and distribution of health”
- “these factors frequently influence one another and, in addition, are sometimes influenced by the health indicators of interest.”
- Galea S, Riddle M, Kaplan GA. Causal thinking and complex system approaches in epidemiology. Int J Epidemiol. 2010 Feb;39(1):97-106.

Rete delle cause



Cause indirette

- One might argue that factors that are at higher levels of influence and exert their influence indirectly by way of other factors are not truly ‘causes’.
- In accordo con la relazione tra epidemiologia, sanità pubblica e prevenzione, è preferibile considerare i diversi livelli dei fattori eziologici in relazione alla possibilità di modificare i determinanti per produrre effetti desiderati

Adattamento

- Possiamo complicare ulteriormente questo modello se consideriamo che le relazioni tra le cause e tra cause ed effetti spesso prevedono influenze reciproche e adattamenti retroattivi cosicché
- le relazioni sono complesse e può essere difficoltoso isolare una causa

Evidenze eziologiche

- In base alle evidenze disponibili, si può passare da fattore associato ad agente eziologico
- Tuttavia la nostra attribuzione del ruolo di agente causale non è assoluta e acquisita, ma valida fintantoché essa non venga smentita o corretta da ulteriori evidenze

Risultati degli studi

- Validità: capacità di uno studio di fornire una informazione vera
- Interna: capacità di misurare ciò che lo studio è stato costruito per misurare
- Esterna: applicabilità dei risultati di uno studio internamente valido ad un contesto differente

- La validità interna è prerequisito della validità esterna
- Il fatto che uno studio sia internamente valido non implica la generalizzabilità al di fuori del contesto

Tipo di studio e validità

- Internal and external validity entail important tradeoffs.
- For example, randomised controlled trials are more likely than observational studies to be free of bias, but,
- because they usually enroll selected participants, external validity can suffer.

Minacce alla validità interna

Bias o distorsione:

- Fattore sistematico
- Determina mancanza di validità della stima

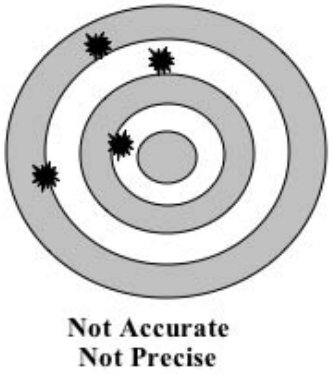
Errore casuale o mancanza di precisione

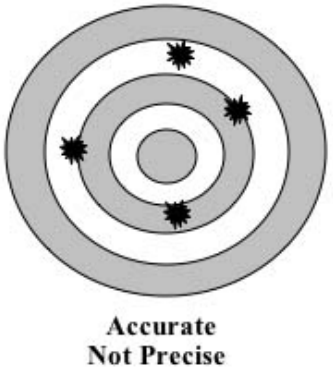
- Variabilità tra le unità sperimentali (rispetto alla informazione disponibile)
- Determina incertezza rispetto alla stima del parametro

Bias

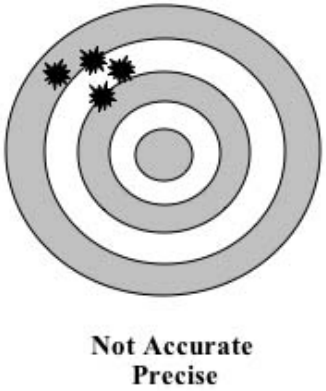
- Deviazione sistematica dal vero dei risultati o delle inferenze derivate da una ricerca
- vuol dire nell'accezione comune "pregiudizio" in qualche modo è un errore che pregiudica lo studio e lo condanna a non poter esplorare la verità

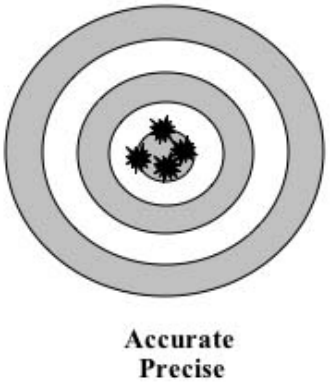
La metafora del bersaglio





Variabilità casuale (errore) elevata





Fattore sistematico

4 categorie

Feinstein AR. Clinical epidemiology: the architecture of clinical research. Philadelphia: WB Saunders Company, 1985.

- That arise sequentially during research: susceptibility, performance, detection, and transfer.
- **Susceptibility** bias refers to differences in baseline characteristics,
- **Performance** bias to different proficiencies of treatment,
- **Detection** bias to different measurement of outcomes, and
- **Transfer** bias to differential losses to follow-up.

Conseguenze dei bias

- Biases can be **classified by the direction** of the change they produce in a parameter (for example, the odds ratio (OR)).
- **Toward the null bias** or negative bias yields estimates closer to the null value (for example, lower and closer OR to 1),
- whereas **away from the null bias** produces the opposite, higher estimates than the true ones.
- these biases can induce a **switchover bias**, or change of the direction of association (for example, a true OR .1 becomes >1).

Classificazione dei Bias

Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research. Belmont, CA: Lifetime Learning Publications, 1982.

- Bias di **selezione**
- Bias di **informazione**
- **Confondimento**

- Modifica di effetto (non un bias)

Table 1 Alphabetical list of biases, indicating their type and the design where they can occur

Specific name of bias	Group of bias	Subgroup of bias (next level to specific name)	Type of design affected
Allocation of intervention bias	Execution of an intervention		Trial
Apprehension bias	Information bias	Observer bias	All studies
Ascertainment bias	Selection bias	Inappropriate definition of the eligible population	Observational study
Berkson's bias	Selection bias	Inappropriate definition of the eligible population	Hospital based case-control study
Centripetal bias	Selection bias	Healthcare access bias	Observational study
Citation bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
Competing risks	Selection bias	Ascertainment bias	All studies
Compliance bias	Execution of an intervention		Trial
Confounding by group	Confounding		Ecological study
Confounding by indication	Confounding		Case-control study, cohort study
Contamination bias	Execution of an intervention		Trial, mainly community trials
Detection bias	Selection bias	Uneven diagnostic procedures in the target population	Case-control study
Detection bias	Information bias	Misclassification bias	Cohort study
Diagnostic/treatment access bias	Selection bias	Healthcare access bias	Observational study
Diagnostic suspicion bias	Selection bias	Detection bias	Case-control study
Diagnostic suspicion bias	Information bias	Detection bias	Cohort study
Differential maturing			Trial
Differential misclassification bias	Information bias	Misclassification bias	All studies
Dissemination bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
Ecological fallacy	Information bias		Ecological study
Exclusion bias	Selection bias	Inappropriate definition of the eligible population	Case-control study
Exposure suspicion bias	Information bias	Recall bias	Case-control study
Family aggregation bias	Information bias	Reporting bias	Observational study
Friend control bias	Selection bias	Inappropriate definition of the eligible population	Case-control study
Hawthorne effect	Information bias		Trial
Healthcare access bias	Selection bias	Ascertainment bias	Observational study
Healthy volunteer bias	Selection bias	Non-response bias	Observational study
Healthy worker effect	Selection bias	Inappropriate definition of the eligible population	Cohort study (mainly retrospective)
Incidence-prevalence bias (synonym of Neyman bias)			
Inclusion bias	Selection bias	Inappropriate definition of the eligible population	Hospital based case-control study
Lack of intention to treat analysis			Randomised trial
Language bias	Selection bias	Inappropriate definition of the eligible population	Systematic review/meta-analysis
Lead-time bias	Information bias		Screening study
Length biased sampling	Selection bias	Ascertainment bias	Cross sectional study, screening
Losses/withdrawals to follow up	Selection bias	During study implementation	Cohort study, trial
Mimicry bias	Selection bias	Detection bias	Case-control study
Mimicry bias	Information bias	Detection bias	Cohort study
Misclassification bias	Information bias		All studies
Missing information in multivariable analysis	Selection bias	During study implementation	All studies (mainly retrospective)
Mode for mean bias	Information bias	Reporting bias	All studies
Neyman bias	Selection bias	Ascertainment bias	Cross sectional study, case-control study with prevalent cases
Non-differential misclassification bias	Information bias	Misclassification bias	All studies
Non-random sampling bias	Selection bias	Lack of accuracy of sampling frame	Observational study
Non-response bias	Selection bias	During study implementation	Observational study
Obsequiousness bias	Information bias	Reporting bias	All studies
Observer expectation bias	Information bias	Observer bias	All studies
Observer/interviewer bias	Information bias	Misclassification bias	All studies
Overmatching	Selection bias	Inappropriate definition of the eligible population	Case-control study
Participant expectation bias	Information bias	Recall bias	Trial
Popularity bias	Selection bias	Healthcare access bias	Observational study
Post hoc analysis	Selection bias	Publication bias	Systematic review/meta-analysis
Protopathic bias	Information bias		Observational study
Publication bias	Selection bias	Lack of accuracy of sampling frame	Systematic review/meta-analysis
Purity diagnostic bias	Selection bias	Spectrum bias	Validity of diagnostic tests
Recall bias	Information bias	Misclassification bias	All studies
Referral filter bias	Selection bias	Healthcare access bias	Observational study
Regression dilution bias	Information bias	Regression to the mean	Cohort study, trial
Regression to the mean	Information bias		Cohort study, trial
Relative control bias	Selection bias	Inappropriate definition of the eligible population	Case-control study
Reporting bias	Information bias	Misclassification bias	All studies
Rumination bias	Information bias	Recall bias	Case-control study, retrospective cohort study
Selective survival bias (synonym of Neyman bias)			
Sick quitter bias	Information bias	Protopathic bias	Observational study
Spectrum bias	Selection bias	Ascertainment bias	Validity of diagnostic tests (mainly case-control study)
Survivor treatment selection bias	Selection bias	Ascertainment bias	Cohort study (mainly retrospective)
Susceptibility bias (synonym of confounding)			
Telephone random sampling bias	Selection bias	Non-random sampling bias	Observational study
Temporal ambiguity	Information bias		Cross sectional study, ecological study
Unacceptable disease/exposure	Information bias	Reporting bias	Observational study
Underreporting bias	Information bias	Reporting bias	Observational study
Unmasking—detection signal—bias	Selection bias	Detection bias	Case-control study
Verification bias (synonym of work up bias)			
Will Rogers phenomenon	Information bias		Prognostic (mainly cohort) study
Work up bias	Information bias		Validity of diagnostic test (retrospective study)

Una lista di bias da Delgado-Rodríguez M, Llorca J. **Bias**. J Epidemiol Community Health. 2004; 58:635-41.

1. Bias di selezione

- I due gruppi a confronto differiscono per aspetti rilevanti diversi dalla esposizione
- Nel caso di studi retrospettivi, il bias di selezione origina dalla scelta di controlli non rappresentativi della popolazione che ha dato origine ai casi per quanto riguarda l'esposizione in studio

Bias di selezione

- Diversi bias vengono definiti di selezione

(può essere difficoltosa la distinzione da confondimento e bias di informazione)

- inappropriate selection of controls in case-control studies
- differential loss-to-follow up
- incidence–prevalence bias
- healthy-worker bias,
- **volunteer bias**
- and **non response bias**

Non-response bias

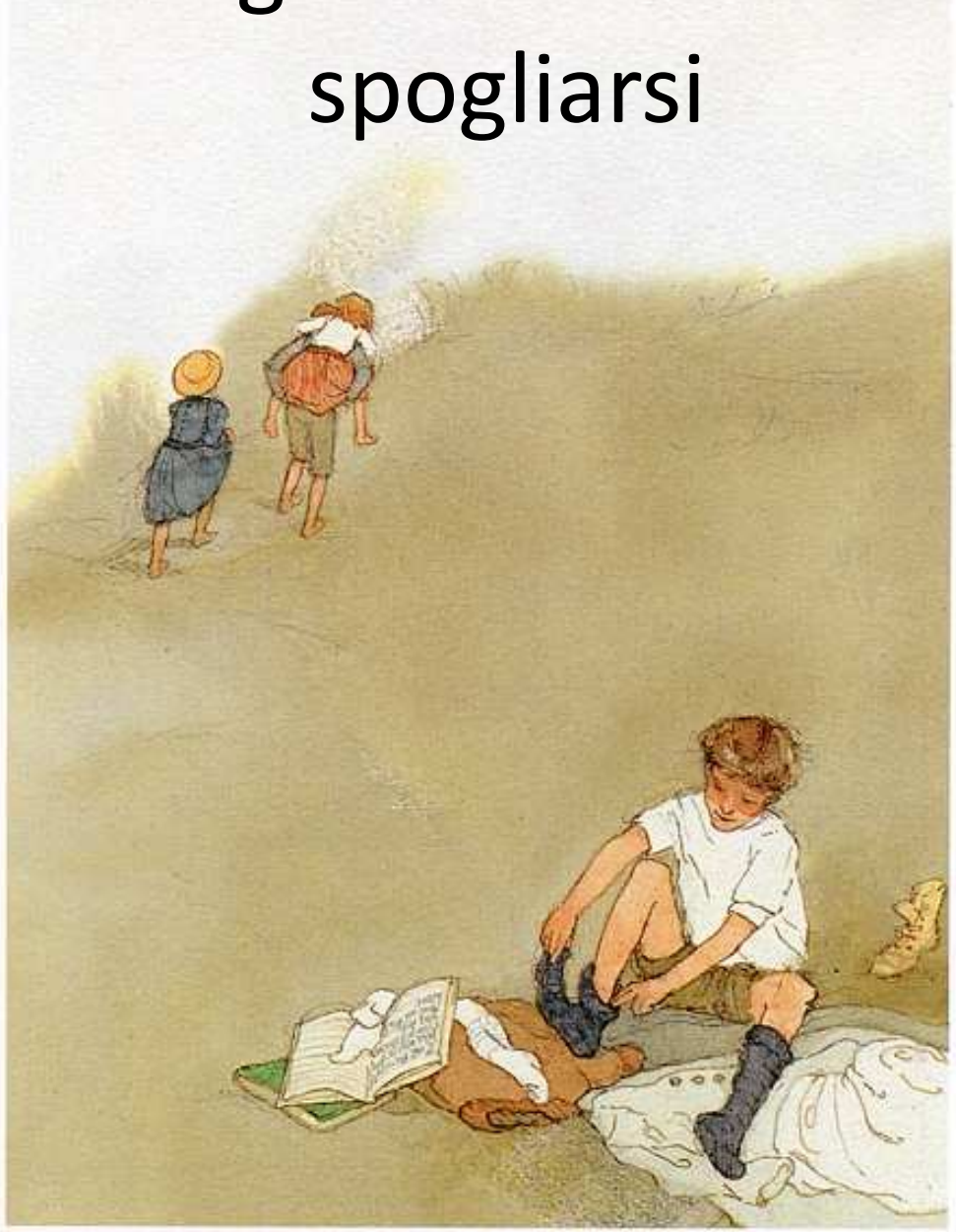
- Non-response bias: when participants differ from nonparticipants
- The healthy volunteer effect is a particular case: when the participants are healthier than the general population.
- This is particularly relevant when a diagnostic manoeuvre, such as a screening test, is evaluated in the general population,
- producing an away from the null bias; thus the benefit of the intervention is spuriously increased.

[*Delgado-Rodríguez M et al.2004]*

Quantificare bias di selezione

- Di solito non disponiamo di informazioni relative alle unità sperimentali escluse
- Possono essere presenti variabili informative sui dati mancanti in altre variabili presenti nella base dati (imputazione multipla)
- In alcuni casi vengono raccolte informazioni ulteriori, specifiche, relativamente ai non partecipanti nel complesso o ad un campione di essi
- L'identificazione di un bias e la correzione in uno studio osservazionale non è garanzia dell'assenza di ulteriori e diversi bias
- Immagine semplificata della realtà formata in base a elementi biologici e risultati di studi
- La complessità del modello può essere molto variabile

La storia dei giovani che non volevano spogliarsi



Obiettivi

Fornire una descrizione dei seguenti parametri nella popolazione studiata:

BMI

Circonferenza vita

Soddisfazione

Strategie di controllo del peso

Attività fisica

Casi e metodi

Disegno:

studio trasversale di popolazione

Casi:

iscritti alle medie superiori nel territorio della USL1 dell'Umbria (4564); la presente analisi è limitata a 4275 ragazzi (2070 femmine, 48.4%) in età tra 14 e 18 anni.

Misure antropometriche:

peso (svestito) e altezza sono stati misurati da personale addestrato. L'indice di massa corporea (BMI) è stato calcolato secondo la formula peso(kg)/(altezza(m))^2. La circonferenza vita è stata misurata a metà tra cresta iliaca e decima costa.

Studi di prevalenza o trasversali (*cross-sectional*)

- Descrittivi : a. definire la prevalenza di una patologia in una popolazione; b. definire la prevalenza di fattori di rischio/eziologici noti

- Analitici (eziologici) : misurazione ad un tempo dello stato di malattia e della esposizione ai fattori sospetti

Vantaggi e svantaggi degli studi trasversali

+ Spesso sono condotti su base di popolazione o su un campione rappresentativo
+ Sono realizzabili in tempo breve rispetto agli studi di coorte e senza sorveglianza degli eventi quindi meno costosi
- Difficile attribuire ruolo eziologico in assenza della sequenza temporale
- “In generale è importante tenere a mente che lo stato di esposizione nel momento dell’indagine può avere poco a che fare con l’esposizione all’inizio del processo patologico” *Kelsey JL et al eds Ch. 10 Cross-sectional and other types of studies . Methods in Observational Epidemiology*
- Bias di prevalenza: i casi prevalenti comprendono in maggior misura quelli con lungo decorso

Misura dell’esposizione

- Non variabile : HLA
- Obesità artrosi del ginocchio

- Difficoltà di ricostruire esposizioni pregresse (bias di memoria)

Classificazione:

la qualifica di sovrappeso e obeso è stata attribuita utilizzando i limiti età e sesso specifici internazionali proposti da Cole et al. I limiti corrispondono al prolungamento retrogrado dei percentili corrispondenti ai limiti adottati per gli adulti.

Questionario:

un semplice questionario è stato somministrato durante l'orario scolastico per raccogliere informazioni su istruzione e professione dei genitori, soddisfazione e strategie per modificare il peso, tipo e durata di attività fisica e occupazioni sedentarie

Overweight and obesity among Umbria USL1 males by age

Age	n.	**Overweight**	95%IC	*Celi et al.*	**Obese**	95%IC	*Celi et al.*
14	450	**21.6**	18.0-25.6	*20.6 (18.4-22.7)*	**9.8**	7.4-12.9	*5.1 (4.0-6.3)*
15	477	**21.6**	18.1-25.5	*19.3 (17.1-21.5)*	**8.0**	5.9-10.7	*5.2 (3.9-6.4)*
16	449	**20.7**	17.2-24.7	*15.0 (13.0-17.0)*	**7.3**	5.3-10.1	*5.1 (3.8-6.3)*
17	431	**14.2**	11.2-17.8	*15.0 (12.7-17.2)*	**5.3**	3.6- 7.9	*4.3 (3.0-5.6)*
18	319	**18.5**	14.6-23.1	-	**3.8**	2.2- 6.5	-
all	*2126*	***19.4***	*17.8-21.2*	-	***7.1***	*6.0-8.2*	-

Overweight and obesity among Umbria USL1 females by age

Age	n.	Overweight	95%IC	Celi et al.	Obese	95%IC	Celi et al.
14	357	**17.6**	14.0-21.9	***19.6*** *(17.3-21.8)*	**4.8**	3.0-7.5	***3.5*** *(2.6-4.7)*
15	401	**15.2**	12.0-19.1	***16.6*** *(14.3-18.9)*	**3.5**	2.1-5.8	***3.5*** *(2.5-4.8)*
16	397	**12.8**	9.9-16.5	***12.5*** *(10.3-14.7)*	**2.8**	1.6-4.9	***3.4*** *(2.4-4.8)*
17	406	**12.3**	9.5-15.9	***11.1*** *(9.0-13.3)*	**2.5**	1.3-4.5	***3.0*** *(2.1-4.4)*
18	296	**9.8**	6.9-13.7	-	**2.4**	1.2-4.8	-
all	*1857*	***14.1***	*12.6-15.8*	-	***3.2***	*2.5-4.1*	-

Non partecipazione allo studio

Il 6.8% degli studenti ha opposto un rifiuto alla misurazione del peso.

Il rifiuto è stato più frequente da parte delle femmine (10.3%) che dei maschi (3.6%)

Il personale dello studio ha classificato soggettivamente in sovrappeso e normali coloro che rifiutavano la misura

Il 20% dei maschi che hanno rifiutato la misurazione antropometrica sono stati considerati sovrappeso dal personale dello studio. Nelle femmine questa percentuale è risultata del 44%.

Nei maschi, il calcolo della prevalenza che include anche gli studenti privi di misure antropometriche in base alla classificazione del personale dello studio non modifica la prevalenza

A comparison between prevalence for measured cases and prevalence adjusted for overweight assigned by study personnel

Age	n.	**unadjusted**	95%IC	n.	**adjusted**	95%IC
14	450	**31.3**	27.2-35.8	461	**31.7**	27.6-36.1
15	477	**29.6**	25.6-33.8	491	**28.9**	25.1-33.1
16	449	**28.1**	24.1-32.4	474	**27.6**	23.8-31.8
17	431	**19.5**	16.0-23.5	444	**19.6**	16.2-23.5
18	319	**22.3**	18.0-27.1	335	**21.8**	17.7-26.5
all	*2126*	***26.5***	*24.6-28.4*	*2205*	***26.3***	*24.5-28.1*

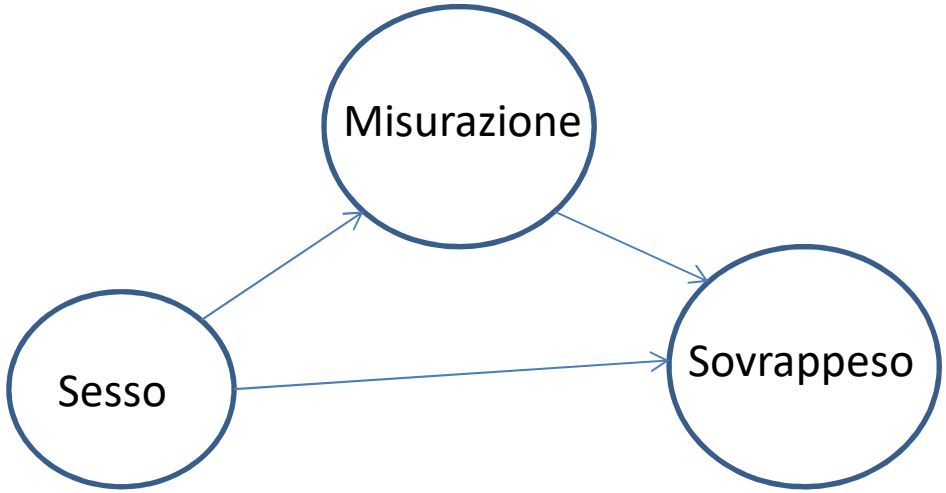
Nelle femmine la correzione per distribuzione del sovrappeso tra coloro che hanno rifiutato le misure antropometriche modifica la prevalenza in misura maggiore rispetto ai maschi.

A comparison between prevalence for measured cases and prevalence adjusted for overweight assigned by study personnel

Age	n.	**unadjusted**	95%IC	n.	**adjusted**	95%IC
14	357	23.5	19.4-28.2	407	27.3	23.2-31.8
15	401	18.7	15.2-22.8	435	21.8	18.2-26.0
16	397	16.6	13.3-20.6	436	20.4	16.9-24.4
17	406	15.0	11.9-18.8	456	16.4	13.3-20.1
18	296	12.2	9.0-16.4	336	14.3	10.9-18.4
all	*1857*	*17.3*	*15.7-19.1*	*2070*	*20.2*	*18.5-22.0*

Bias di selezione

- Il rapporto tra prevalenze M/F si riduce da 1.5 a 1.3
- L'Odds ratio di prevalenza da 1.7 a 1.4



Partecipazione e bias: caso 2

- Se vi fosse diversa partecipazione in base alla esposizione ma non in relazione alla malattia, gli indicatori non sarebbero distorti e avremmo solo perdita di potenza dello studio

- Nel nostro esempio: se vi fosse stata minore partecipazione nel sesso femminile ma indipendente dal rischio di sovrappeso

Partecipazione e bias: caso 3

- Se vi fosse partecipazione diversa in relazione alla malattia ma non alla esposizione avremmo una distorsione dell'indicatore prevalenza di sovrappeso ma non dell'associazione (PRR o POR)

Fattori associati a obesità

(i) endogenous factors such as genes and factors influencing their expression;

(ii) individual-level factors such as behaviours (size of food portions, dietary habits, exercise, television-viewing patterns), education, income;

(iii) neighbourhood-level factors such as availability of grocery stores, suitability of the walking environment, advertising of high caloric foods;

(iv) school-level factors such as availability of high-caloric foods and beverages and health education;

(v) district or state-level policies that regulate marketing of high caloric foods;

(vi) national-level surplus food programmes, other food distribution programmes and support for various agricultural products; and

(vii) from a lifecourse perspective history of breastfeeding, maternal health and parental obesity

Relazione attività fisica - IMC

- Going back to our obesity example, even though individual exercise patterns are linked to the risk of obesity

[DiPietro L. Physical activity, body weight and adiposity: an epidemiologic perspective. Exerc Sport Sci Rev 1995;23:275–303],

- obesity is also a determinant of individual exercise patterns

[Trost S, Owen N, Bauman AE, Sallis JP, Brown W. Correlatees of adults' participation in physical activity: review and update. Med Sci Sports Exerc 2002;34: 1996–2001.].

Determinanti della partecipazione ad attività fisica o a sport competitivi

	1) Non competitive sport*			2) Competitive sport*		
Factor	RRR	*95%IC*	*p*	RRR	*95%IC*	*p*
Age	0.91	*(0.85-0.96)*	0.002	0.79	*(0.74-0.84)*	0.000
Gender	2.00	*(1.45-2.70)*	0.000	10.85	*(7.67-15.3)*	0.000
Father's job	1.11	*(1.01-1.21)*	0.02	1.32	*(1.18-1.47)*	0.000
Gender* Father's job	0.89	*(0.78-1.01)*	0.07	0.79	*(0.69-0.91)*	0.001
Mother's job	1.05	*(0.97-1.14)*	0.2	1.14	*(1.05-1.24)*	0.003
Mother's education	1.14	*(1.03-1.26)*	0.008	1.21	*(1.09-1.34)*	0.000
Father's education	1.13	*(1.03-1.24)*	0.009	1.04	*(0.95-1.15)*	0.4
BMI	**1.04**	***(1.02-1.07)***	**0.000**	1.00	*(0.97-1.03)*	0.9

Selezione: Healthcare access bias

- Healthcare access bias: when the patients admitted to an institution do not represent the cases originated in the community. This may be due:
- to the own institution if admission is determined by the interest of health personnel on certain kind of cases (***popularity bias***),
- To the patients if they are attracted by the prestige of certain clinicians (***centripetal bias***),
- to the healthcare organisation if it is organised in increasing levels of complexity (primary, secondary, and tertiary care) and ‘‘difficult’’ cases are referred to tertiary care (***referral filter bias***),
- to a web of causes if patients by cultural, geographical, or economic reasons show a differential degree of access to an institution (***diagnostic/treatment access bias***)

Length-bias

- Length-bias sampling: cases with diseases with long duration are more easily included in surveys. This series may not represent the cases originated in the target population. These cases usually have a better prognosis.
- È uno dei bias che caratterizzano la coorte dei casi con diagnosi mediante screening in oncologia assieme al precedente (Access)

La storia del caffè e del cancro del pancreas

Preferenza per il tè

- “According to some reports, after this study came out, MacMahon stopped drinking coffee and replaced coffee with tea in his office” (Pai M, Kaufman JS. Bias File 2. Should we stop drinking coffee? The story of coffee and pancreatic cancer)

MacMahon B, Yen S, Trichopoulos D, et al: Coffee and cancer of the pancreas. N Engl J Med 304:630-633,1981

We questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee. There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea. A strong association between coffee consumption and pancreatic cancer was evident in both sexes. The association was not affected by controlling for cigarette use. For the sexes combined, there was a significant dose-response relation (P approximately 0.001); after adjustment for cigarette smoking, the relative risk associated with drinking up to two cups of coffee per day was 1.8 (95% confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7). This association should be evaluated with other data; if it reflects a causal relation between coffee drinking and pancreatic cancer, coffee use might account for a substantial proportion of the cases of this disease in the United States

Individuazione dei controlli

To assemble a control series, the interviewers also attempted to question all other patients who were under the care of the same physician in the same hospital at the time of an interview with a patient with pancreatic cancer. Either before the interview (if the information was known) or afterward, patients with diseases of the pancreas or hepatobiliary tract or diseases known to be associated with smoking or alcohol consumption were excluded. The principal diagnostic categories excluded (in addition to diseases of the biliary tract or pancreas) were cardiovascular disease, diabetes mellitus, respiratory or bladder cancer, and peptic ulcer. From a total of

Table 1. Distribution of Cases and Controls According to Cigarette-Smoking Habits and Estimates of Risk Ratios.

Sex	Category	Never Smoked	Ex-Smokers	Current Smokers		Total *
				<1 pack/day	>1 pack/day	
Men	Cases (no.)	40	99	22	57	218
	Controls (no.)	74	122	35	75	306
	Adjusted relative risk †	1.0	1.4	1.1	1.4	1.4
	95% confidence interval	—	0.9–2.3	0.5–2.2	0.9–2.4	0.9–2.2
Women	Cases (no.)	62	41	20	26	149
	Controls (no.)	160	86	36	55	337
	Adjusted relative risk †	1.0	1.3	1.5	1.6	1.5
	95% confidence interval	—	0.8–2.2	0.8–2.8	0.9–2.9	1.0–2.2

*Adjusted relative risks and 95 per cent confidence intervals in this column are for consumers of any amount (including ex-consumers) as compared with nonconsumers.

†Mantel–Haenszel estimates of risk ratios, adjusted over categories of age in decades. In all comparisons, the referent category was subjects who had never smoked. Chi-square (Mantel extension) with equally spaced scores, adjusted over age in decades: 1.2 for men, 4.1 for women.

Aggiustato per fumo

Table 5. Estimates of Relative Risk of Cancer of the Pancreas Associated with Use of Coffee and Cigarettes.*

Cigarette Smoking	Coffee Drinking (Cups per Day)			Total †
	0	1–2	≥3	
Never	1.0	2.1	3.1	1.0
Ex-smokers	1.3	4.0	3.0	1.3 (0.9–1.8)
Current smokers	1.2	2.2	4.6	1.2 (0.9–1.8)
Total †	1.0	1.8 (1.0–3.0)	2.7 (1.6–4.7)	

*The referent category is the group that uses neither cigarettes nor coffee. Estimates are adjusted for sex and for age in decades.

†Values are adjusted for the other variable, in addition to age and sex, and are expressed in relation to the lowest category of each variable. Values in parentheses are 95 per cent confidence intervals of the adjusted estimates.

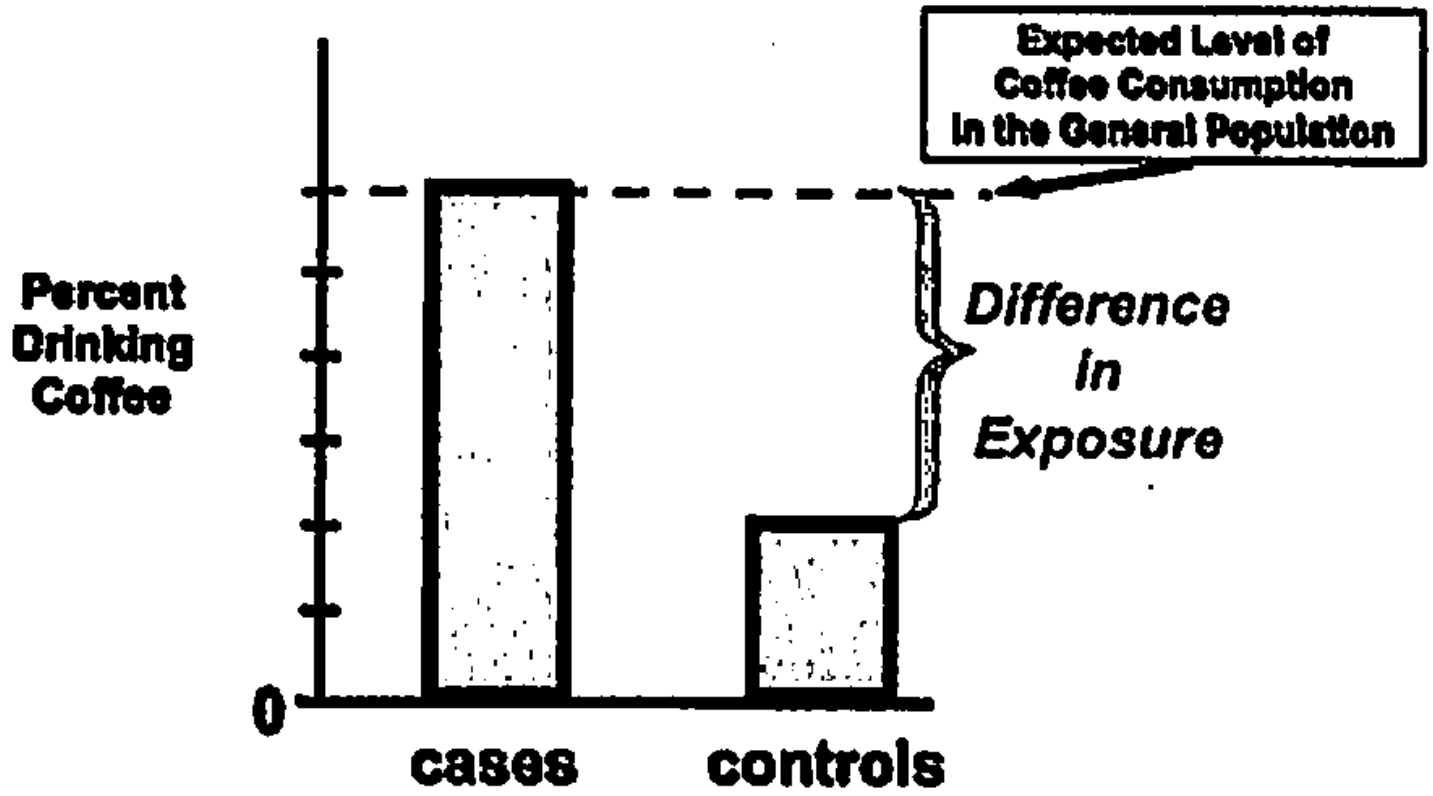
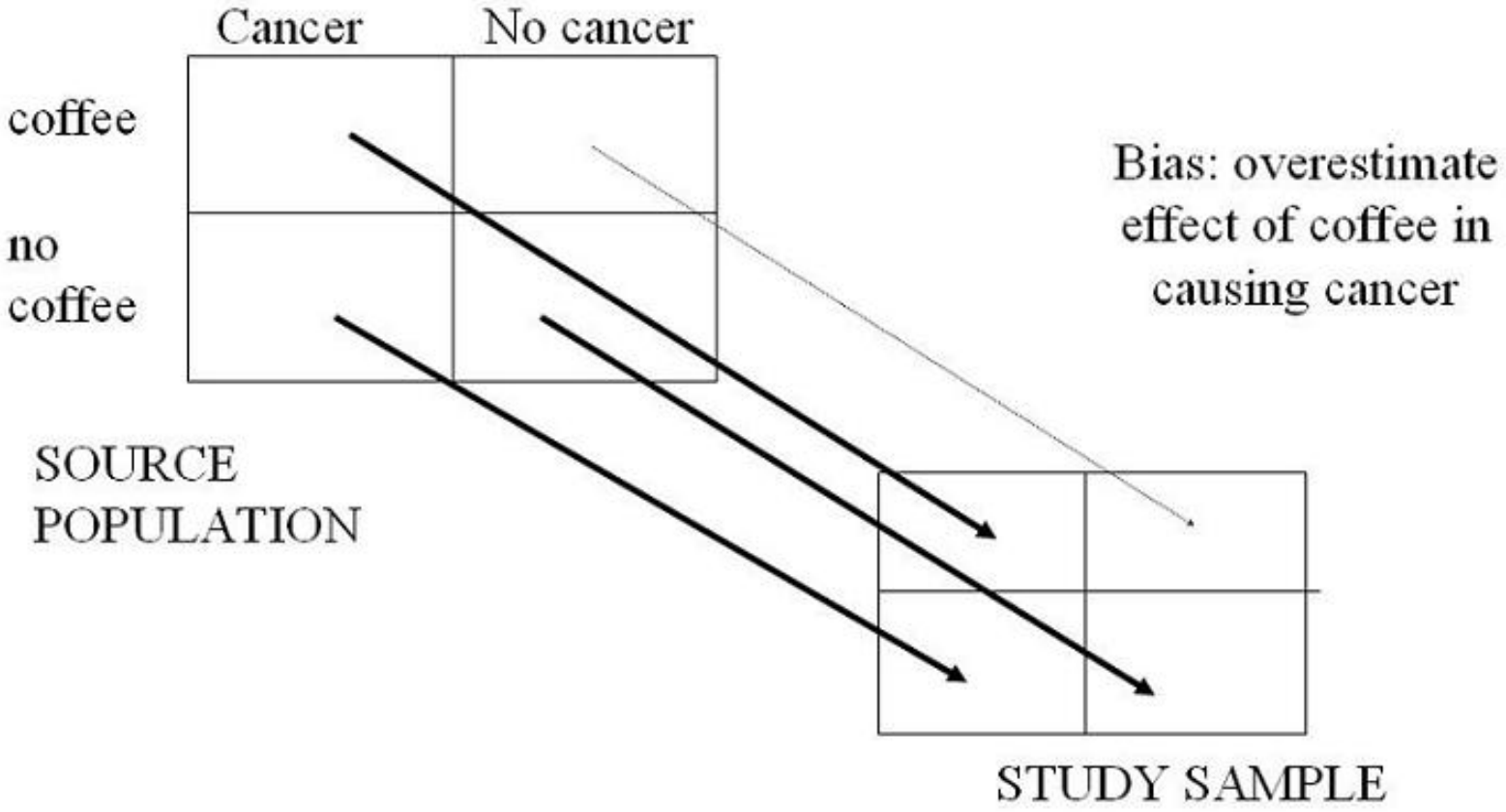


Figure 10-5. Interpreting the results of case-control studies: Is the higher level the expected level of exposure?

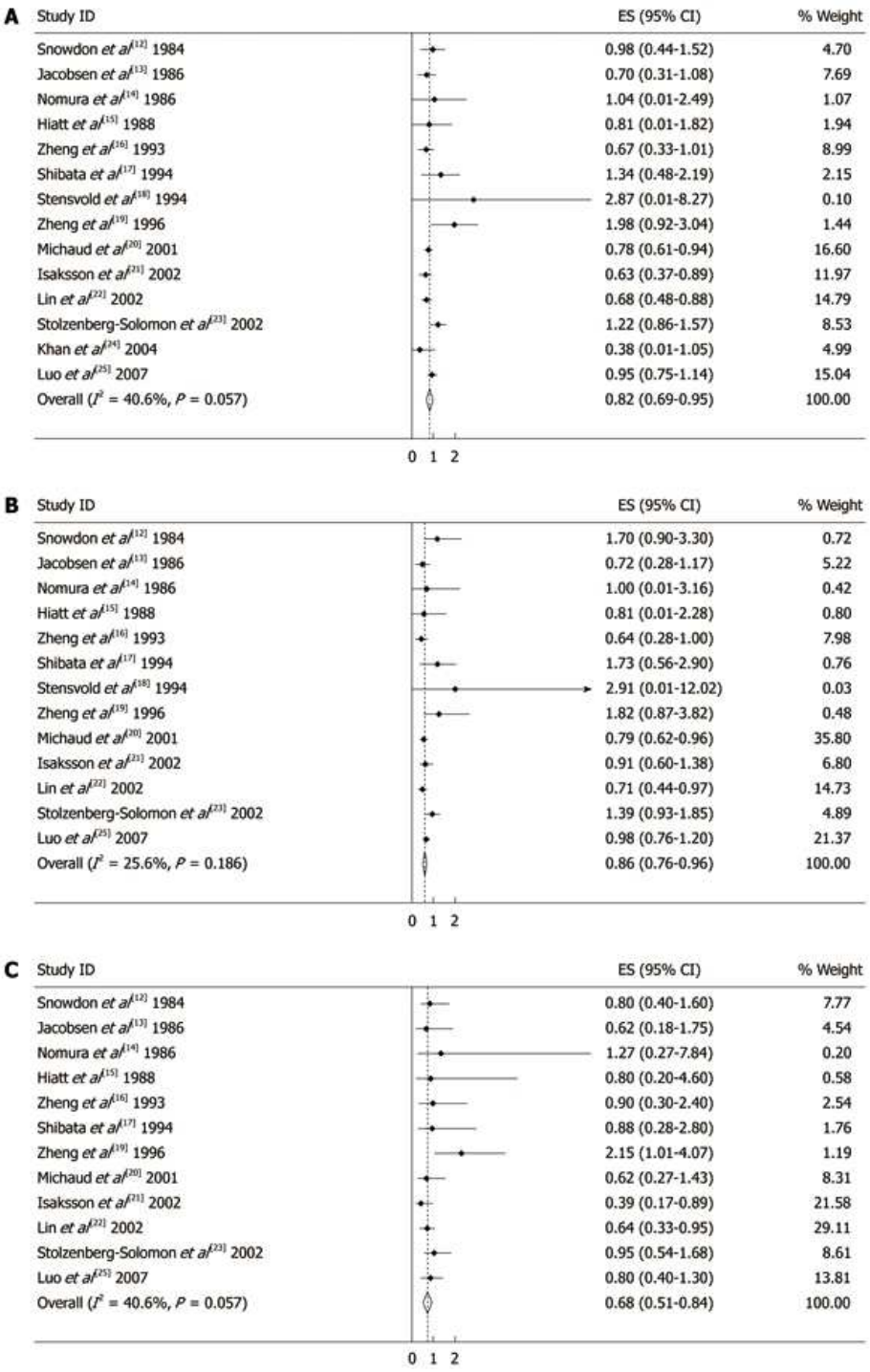
I controlli inclusi tendono a consumare meno caffè rispetto alla base dello studio



Conclusioni beffarde

Compared with individuals who did not drink or seldom drank coffee per day, the pooled RR of pancreatic cancer was 0.82 (95% CI: 0.69-0.95) for regular coffee drinkers, 0.86 (0.76-0.96) for low to moderate coffee drinkers, and 0.68 (0.51 0.84) for high drinkers.

Findings from this meta-analysis **suggest that there is an inverse relationship between coffee drinking and risk of pancreatic cancer** [Dong J 2011]



Cohort Studies

Cohort studies are frequently conducted in selected populations, with the study subjects either self-selected or selected according to some pre-specified criteria. The consequence of this selection process on the internal validity of the exposure –outcome associations has been defined as selection bias, or a special case of confounding

Information Bias

- An information bias occurs during data collection.
- Also known as observation, classification, or measurement bias
- Results from incorrect determination of exposure or outcome, or both
- The most important types of information bias are:
- a. misclassification bias
- b.ecological fallacy

Bias di misclassificazione

- ***Differential misclassification bias***: when misclassification is different in the groups to be compared; for example, in a case-control study the recalled exposure is not the same for cases and controls (**recall bias**). The estimate is biased in either direction, toward the null or away from the null.
- ***Non-differential misclassification bias (ie, noise in the system)****:* when the misclassification is the same across the groups to be compared, for example, exposure is equally misclassified in cases and controls. For binary variables the estimate is biased toward the null value

Observer bias, also called ascertainment bias or detection bias

- Might be especially important when outcome assessors have strong predispositions and when outcomes are subjective
- The knowledge of the hypothesis, the disease status, or the exposure status (including the intervention received) can influence data recording (observer expectation bias).
- The means by which interviewers can introduce error into a questionnaire include administering the interview or helping the respondents

Cieco

- To minimise information bias, detail about exposures in case-control studies should be gathered by people who are unaware of whether the respondent is a case or a control.
- Similarly, in a cohort study with subjective outcomes, the observer should be unaware of the exposure status of each participant.

Blinding in randomised trials: hiding who got what

Schulz KF, Grimes DA. Lancet. 2002; 359:696-700.

Panel 1: **Potential benefits accruing dependent on those individuals successfully blinded**

Individuals blinded	Potential benefits
Participants	Less likely to have biased psychological or physical responses to intervention More likely to comply with trial regimens Less likely to seek additional adjunct interventions Less likely to leave trial without providing outcome data, leading to lost to follow-up
Trial investigators	Less likely to transfer their inclinations or attitudes to participants Less likely to differentially administer co-interventions Less likely to differentially adjust dose Less likely to differentially withdraw participants Less likely to differentially encourage or discourage participants to continue trial
Assessors	Less likely to have biases affect their outcome assessments, especially with subjective outcomes of interest

Cieco e Doppio-cieco

Observer bias in randomised clinical trials

- Many trials use blinded outcome assessors to avoid bias, though
- use of non-blinded outcome assessors is also common

Observer bias in randomised clinical trials with binary outcomes: systematic review of trials with both blinded and non-blinded outcome assessors (BMJ 2012;344:e1119**)**

- Objective To evaluate the impact of non-blinded outcome assessment on estimated treatment effects in randomised clinical trials with binary outcomes.
- Design Systematic review of trials with both blinded and non-blinded assessment of the same binary outcome.
- For each trial we calculated the **ratio of the odds ratios**—the odds ratio from non-blinded assessments relative to the corresponding odds ratio from blinded assessments.

Ricerca bibliografica

- We searched standard databases (PubMed, Embase, PsycINFO, CINAHL*, Cochrane Central Register of Controlled Trials) and full text databases (HighWire Press and Google Scholar).
- Our core search string was: random* AND (“blind* and unblind*” OR “masked and unmasked”) with variations according to the specific database

* CINAHL (Cumulative Index to Nursing and Allied Health Literature)

Criteri di esclusione

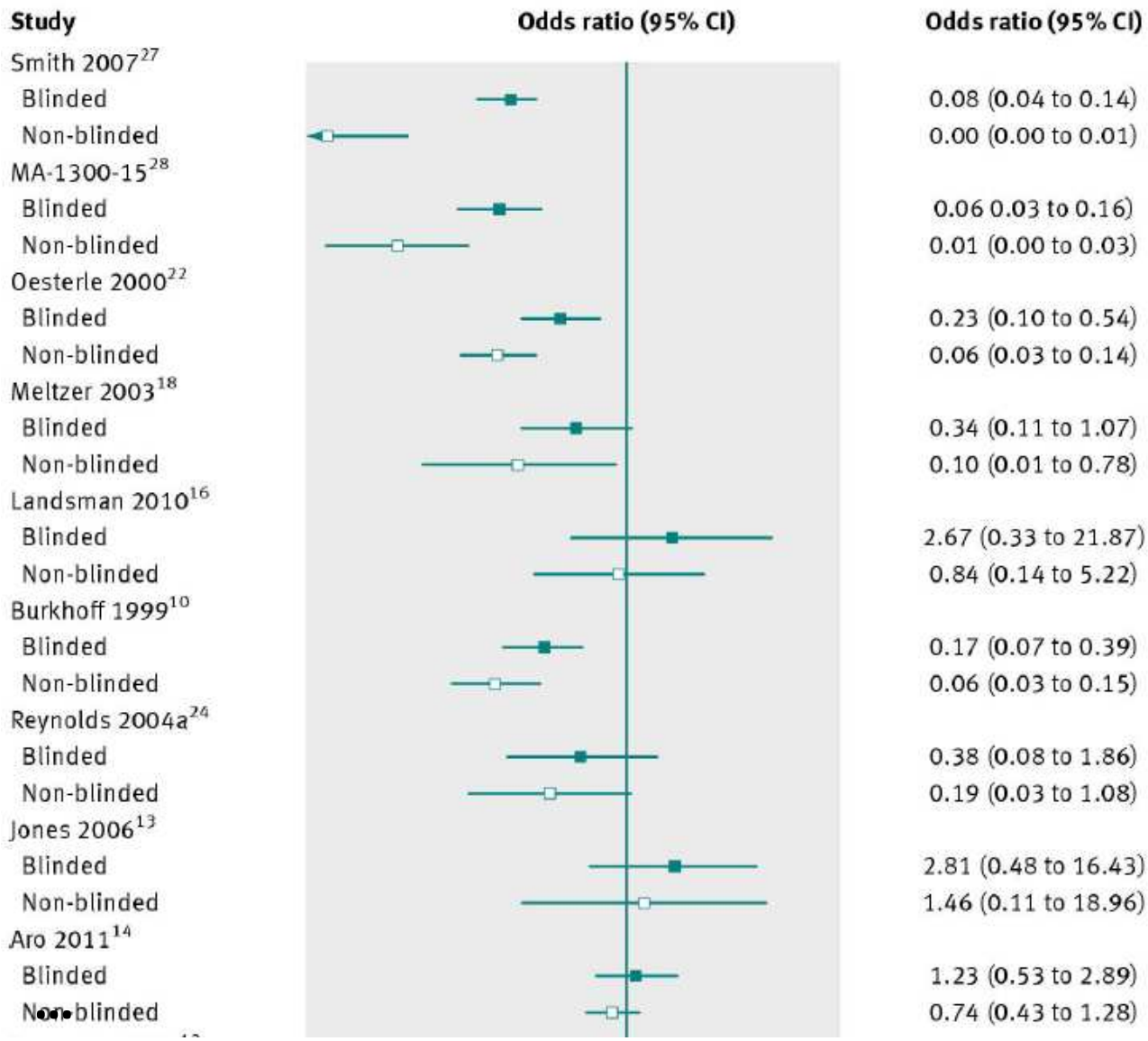
- For each trial, we evaluated five pre-specified potential confounders in the comparison between blinded and non-blinded outcome assessments:
- a considerable time difference between these two assessments,
- different types of assessors (such as nurses *vs physicians),*
- *different types of procedures (such as* direct visual assessment of wounds *vs assessment of photographs* of wound),
- a substantial risk of ineffective blinding procedure, and
- non-identical groups of patients assessed (such as a few patients evaluated only by the blinded outcome assessor).

Esito dell'analisi

- We calculated the odds ratio for failures (such as an unhealed wound) in each trial for both the blinded and non-blinded assessments.
- An odds ratio under 1 indicates a beneficial effect of the experimental intervention.
- For each trial we summarised the impact of non-blinded outcome assessment as the ratio of the odds ratios ($OR_{non\text{-}blind}$ / OR_{blind}).
- A ratio <1 indicates that non-blinded assessments are more optimistic.

Più sofisticato

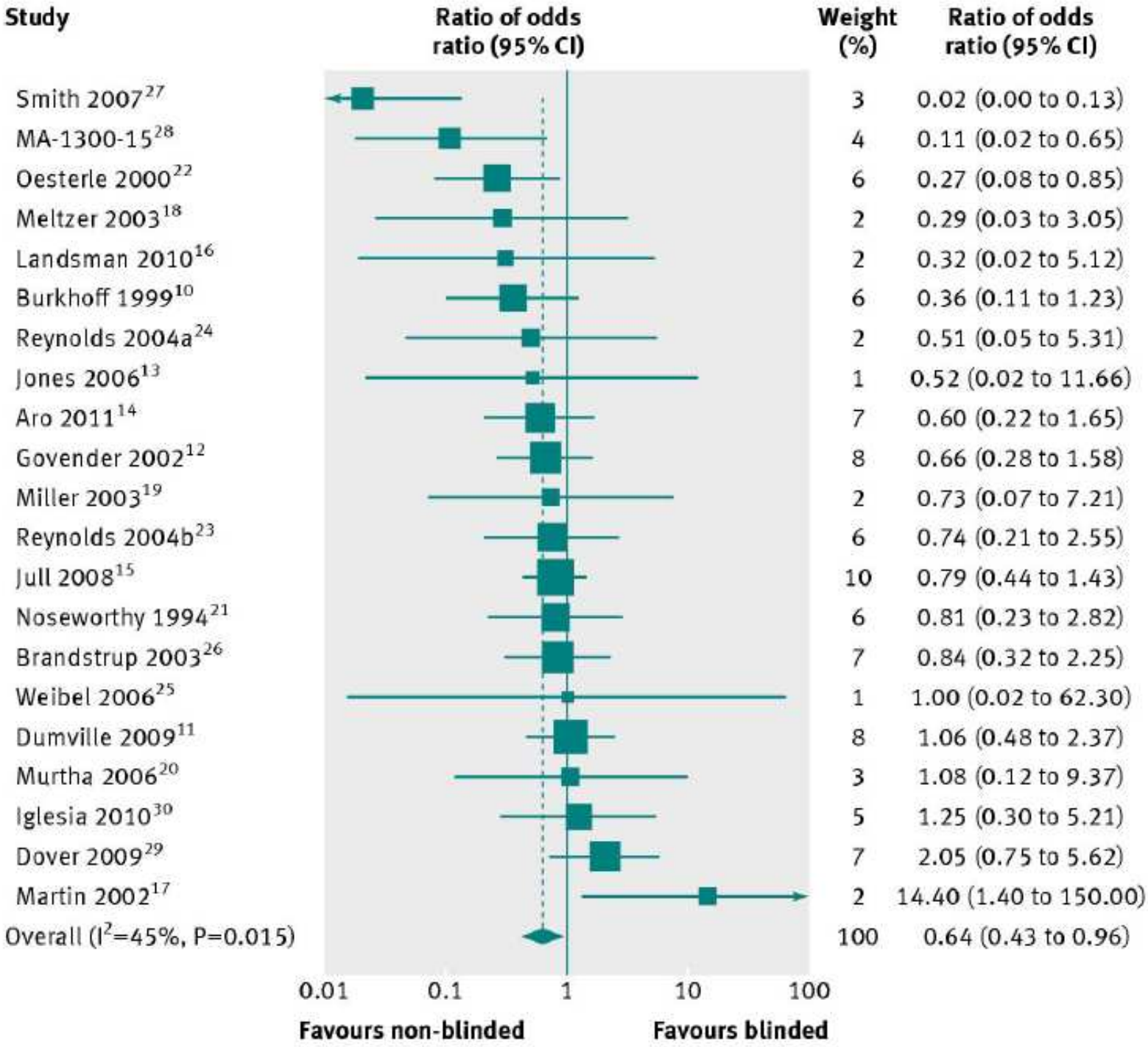
- We meta-analysed the individual trial ratio of odds ratios with inverse variance methods using random-effects models.
- The standard error of the ratio of odds ratios used for the main analysis disregarded the dependency between blinded and non-blinded assessments.
- The statistical software we used was Stata 11.



Estimated intervention effect according to blinded or non-blinded outcome assessor

Non-blinded verso Blinded

- The odds ratio point estimate was more optimistic when based on the non-blinded assessors in 15 trials (out of 21)


Study
Ratio of odds ratio (95% CI)
Weight (%)
Ratio of odds ratio (95% CI)
Smith 2007[27] 3 0.02 (0.00 to 0.13)
MA-1300-15[28] 4 0.11 (0.02 to 0.65)
Oesterle 2000[22] 6 0.27 (0.08 to 0.85)
Meltzer 2003[18] 2 0.29 (0.03 to 3.05)
Landsman 2010[16] 2 0.32 (0.02 to 5.12)
Burkhoff 1999[10] 6 0.36 (0.11 to 1.23)
Reynolds 2004a[24] 2 0.51 (0.05 to 5.31)
Jones 2006[13] 1 0.52 (0.02 to 11.66)
Aro 2011[14] 7 0.60 (0.22 to 1.65)
Govender 2002[12] 8 0.66 (0.28 to 1.58)
Miller 2003[19] 2 0.73 (0.07 to 7.21)
Reynolds 2004b[23] 6 0.74 (0.21 to 2.55)
Jull 2008[15] 10 0.79 (0.44 to 1.43)
Noseworthy 1994[21] 6 0.81 (0.23 to 2.82)
Brandstrup 2003[26] 7 0.84 (0.32 to 2.25)
Weibel 2006[25] 1 1.00 (0.02 to 62.30)
Dumville 2009[11] 8 1.06 (0.48 to 2.37)
Murtha 2006[20] 3 1.08 (0.12 to 9.37)
Iglesia 2010[30] 5 1.25 (0.30 to 5.21)
Dover 2009[29] 7 2.05 (0.75 to 5.62)
Martin 2002[17] 2 14.40 (1.40 to 150.00)
Overall (I^2=45%, P=0.015) 100 0.64 (0.43 to 0.96)
0.01
0.1
1
10
100
Favours non-blinded
Favours blinded

Conclusions

- On average, non-blinded assessors of subjective binary outcomes generated substantially biased effect estimates in randomised clinical trials, exaggerating odds ratios by 36%.

- This bias was compatible with a high rate of agreement between blinded and non-blinded outcome assessors and driven by the misclassification of few patients:
- A surprisingly small number of misclassified patients was needed to generate this bias. The median number of patients needed to be reclassified to neutralise bias in a trial was 2.5 or 3% of the assessed patients

Mechanisms of observer bias

- The pattern of misclassifications underlying the observer bias can be characterised by “optimism error” and “intervention preoccupation.”
- The non-blinded assessors detected fewer failures than blinded assessors. This optimism error, however, was much more pronounced in the intervention group than in the control group.
- Thus, the non-blinded outcome assessor did not “under-rate” patients in the control group and “over-rate” patients in the intervention group.
- Both groups were over-rated but the intervention group considerably more so.

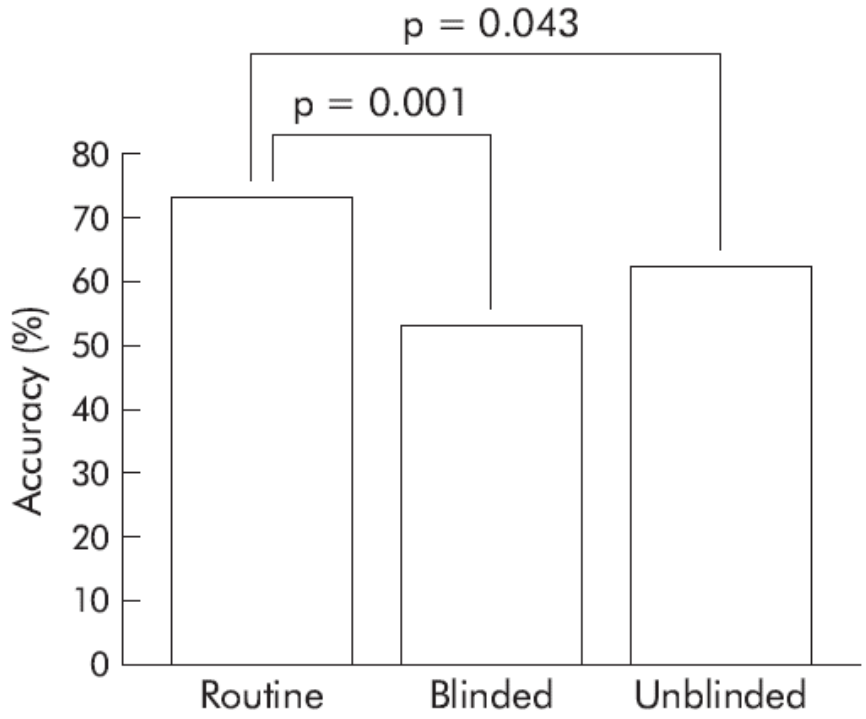
Difficile da predire

- Observer bias is caused by the predispositions of the observers, which might vary unpredictably from trial to trial
- Thus, in any individual trial it is not possible to safely predict neither the direction nor the size of any bias

You get what you expect? A critical appraisal of imaging methodology in endosonographic cancer staging

A Meining, et al. Gut 2002;50:599–603

After an initial period of excellent results with newly introduced imaging procedures, the accuracy of most imaging methods declines in later publications



Well documented videotapes of EUS examinations of 101 patients with resected tumours of the oesophagus (n=32), stomach (n=33), or pancreas (n=36) were evaluated

Gruppi a confronto

(1) *Routine analysis. A retrospective analysis of the T staging* results from the EUS reports produced at the initial EUS examinations in routine clinical conditions.

(2) Blinded analysis. The videotapes recorded at the initial examination were re-evaluated by one of the main investigators (TR). Patients were mixed, and their names were concealed.

(3) *Unblinded analysis. A minimum of a further 18 months* after the blinded re-evaluation, the investigator was not blinded, and was allowed to review the corresponding endoscopy tapes before the EUS assessment (for oesophagogastric cancers) or to read the CT reports (for pancreatic cancers).

cT EUS verso pT

- The results obtained using all three assessment methods were compared with the histopathological findings for the resected tumours, which served as the **gold standard**.

Conclusions

Table 1 Overall accuracy of T staging, stratified according to the location of the cancer

	All patients (n=101)	Oesophageal cancer (n=32)	Gastric cancer (n=33)	Pancreatic cancer (n=36)
Routine analysis	73.3%	81.3%	66.7%	72.2%
Blinded	52.5%**	50.0%**	45.5%*	61.1%
Unblinded	62.4%*	71.9%	39.4%**	75.0%

*p<0.05, **p<0.01 compared with "routine analysis" (McNemar test).

The accuracy of EUS for T staging in clinical practice appears to be lower than has previously been reported.

In addition, blinded analysis produced significantly poorer results, which improved when another test was added.

It may be speculated that better results with routine EUS obtained in a clinical setting are due to additional sources of information.

Validity and predictors of BMI derived from self-reported height and weight among 11- to 17-year-old German adolescents from the KiGGS study

Brettschneider AK et al. *BMC Research Notes* 2011, 4:414

Background: For practical and financial reasons, self-reported instead of measured height and weight are often used.

The aim of this study is to evaluate the validity of self-reports and to identify potential predictors of the validity of body mass index (BMI) derived from self-reported height and weight.

Findings: Self-reported and measured data were collected from a sub-sample (3,468 adolescents aged 11-17) from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). BMI was calculated from both reported and measured values, and these were compared in descriptive analyses.

Linear regression models with BMI difference (self-reported minus measured) and logistic regression models with weight status misclassifications as dependent variables were calculated.

Height was overestimated by 14- to 17-year-olds. Overall, boys and girls under-reported their weight. On average, BMI values calculated from self-reports were lower than those calculated from measured values.

This underestimation of BMI led to a bias in the prevalence rates of under- and overweight which was stronger in girls than in boys.

Based on self-reports, the prevalence was 9.7% for underweight and 15.1% for overweight. However, according to measured data the corresponding rates were 7.5% and 17.7%, respectively. Linear regression for BMI difference showed significant differences according to measured weight status: BMI was overestimated by underweight adolescents and underestimated by overweight adolescents. When weight status was excluded from the model, body perception was statistically significant: Adolescents who regarded themselves as 'too fat' underestimated their BMI to a greater extent. Symptoms of a potential eating disorder, sexual maturation, socioeconomic status (SES), school type, migration background and parental overweight showed no association with the BMI difference, but parental overweight was a consistent predictor of the misclassification of weight status defined by self-reports.

Conclusions: The present findings demonstrate that the observed discrepancy between self-reported and measured height and weight leads to inaccurate estimates of the prevalence of under- and overweight when based on self-reports. The collection of body perception data and parents' height and weight is therefore recommended in addition to self-reports.

Use of a correction formula seems reasonable in order to correct for differences between self-reported and measured data.

Table 2 Mean, standard deviation (SD), *p*-value, Cohen's *d* and 95% CI of measured and self-reported data

Boys	11-13 years (n = 802)					14-17 years (n = 990)				
	Mean	SD	p^1	d^2	95% CI	Mean	SD	p^1	d^2	95% CI
Difference between self-reported and measured data										
Height (cm)	**-0.04**	4.82	0.825	0.00	-0.37-0.30	**0.29**	4.07	0.025	0.03	0.04-0.54
Weight (kg)	**-0.92**	3.41	0.000	0.07	-1.15-(-0.68)	**-0.28**	4.37	0.041	0.02	-0.56-(-0.01)
BMI (kg/m^2)	**-0.32**	1.85	0.000	0.09	-0.45-(-0.19)	**-0.15**	1.84	0.008	0.04	-0.27-(-0.04)

Girls	**11-13 years** (n = 728)					**14-17 years** (n = 948)				
	Mean	SD	p^1	d^2	95% CI	**Mean**	SD	p^1	d^2	95% CI
Difference between self-reported and measured data										
Height (cm)	**-0.33**	4.80	0.060	0.04	-0.68-0.01	**1.18**	2.70	0.000	0.18	1.01-1.35
Weight (kg)	**-1.07**	4.08	0.000	0.09	-1.37-(-0.77)	**-0.64**	2.45	0.000	0.06	-0.80-(-0.48)
BMI (kg/m^2)	**-0.33**	2.00	0.000	0.08	-0.48-(-0.18)	**-0.54**	1.23	0.000	0.14	-0.62-(-0.47)

[1] paired samples t-test for difference from zero

[2] Cohen's d value calculated as effect size

Although the bias in mean BMI differences was small, self-reports resulted in a considerable underestimation of BMI and thus a lower prevalence of overweight and a higher prevalence of underweight, especially in girls. The identified main predictors of the validity of the BMI self-reports in adolescents were gender, age, weight status, and body perception

Fallacia ecologica

- Two types of correlation ecological and individual.
- The former is obtained for a ***group*** of people, while
- the latter is estimated for indivisible units, such as ***individuals***

- The **ecological fallacy** consists in thinking that **relationships observed for groups necessarily hold for individuals**

Studio ecologico

- An **ecologic or aggregate study** focuses on the **comparison of groups**, rather than individuals.
- The underlying reason for this focus is that individual-level data are missing on the joint distribution of at least two and perhaps all variables within each group
- Although ecologic studies are easily and inexpensively conducted, the results are often difficult to interpret

Ecologic measures

Ecologic measures may be classified into three types:

1. **Aggregate measures** are summaries (e.g. means or proportions) of observations derived from individuals in each group (e.g. the proportion of smokers or median family income).
2. **Environmental measures** are physical characteristics of the place in which members of each group live or work (e.g. air-pollution level or hours of sunlight). Note that each environmental measure has an analogue at the individual level, and these individual exposures, or doses, usually vary among members of each group, though they may remain unmeasured.
3. **Global measures** are attributes of groups or places for which there is no distinct analogue at the individual level. unlike aggregate and environmental measures (e.g. population density, level of social disorganization. or the existence of a specific law)

Studi ecologici

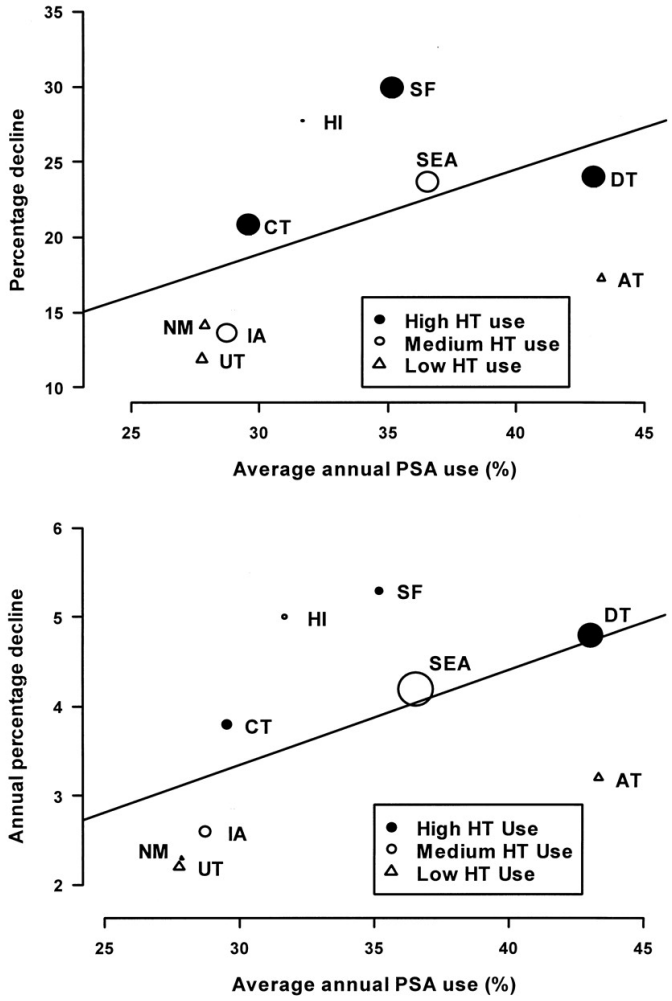
- **Completely ecologic analysis**, all variables (exposure, disease, and covariates) are ecologic measures, so the unit of analysis is the group (e.g. region, worksite, school, demographic stratum, or time interval).
- Thus, within each group, we do not know the joint distribution of any combination of variables at the individual level (e.g. the frequencies of exposed cases, unexposed cases, exposed noncases, and unexposed noncases); all we know is the marginal distribution of each variable (e.g. the proportion exposed and the disease rate
- In a **partially ecologic analysis** of three or more variables, we have additional information on certain joint distributions; for example, in an ecologic study of cancer incidence by county, the joint distribution of age (a covariate) and disease status within each county might be obtained from the census and a population tumor registry.

An Ecologic Study of Prostate-specific Antigen Screening and Prostate Cancer Mortality in Nine Geographic Areas of the United States

Shaw PA et al. *Am. J. Epidemiol*. 2004;160:1059-1069

Ecologic studies of cancer screening examine cancer mortality rates in relation to use of population screening. These studies can be confounded by treatment patterns or influenced by choice of outcome and time horizon. Interpretation can be complicated by uncertainty about when mortality differences might be expected. The authors examined these issues in an ecologic analysis of prostate-specific antigen (PSA) screening and prostate cancer mortality across nine cancer registries in the United States. Results suggested a weak trend for areas with greater PSA screening rates to have greater declines in prostate cancer mortality; however, the magnitude of this trend varied considerably with the time horizon and outcome measure. A computer model was used to determine whether divergence of mortality declines would be expected under an assumption of a clinically significant survival benefit due to screening. Given a mean lead time of 5 years, the model projected that differences in mortality between high- and low-use areas should be apparent by 1999 in the absence of other factors affecting mortality. The authors concluded that modest differences in PSA screening rates across areas, together with additional sources of variation, could have produced a negative ecologic result. Ecologic analyses of the effectiveness of PSA testing should be interpreted with caution.

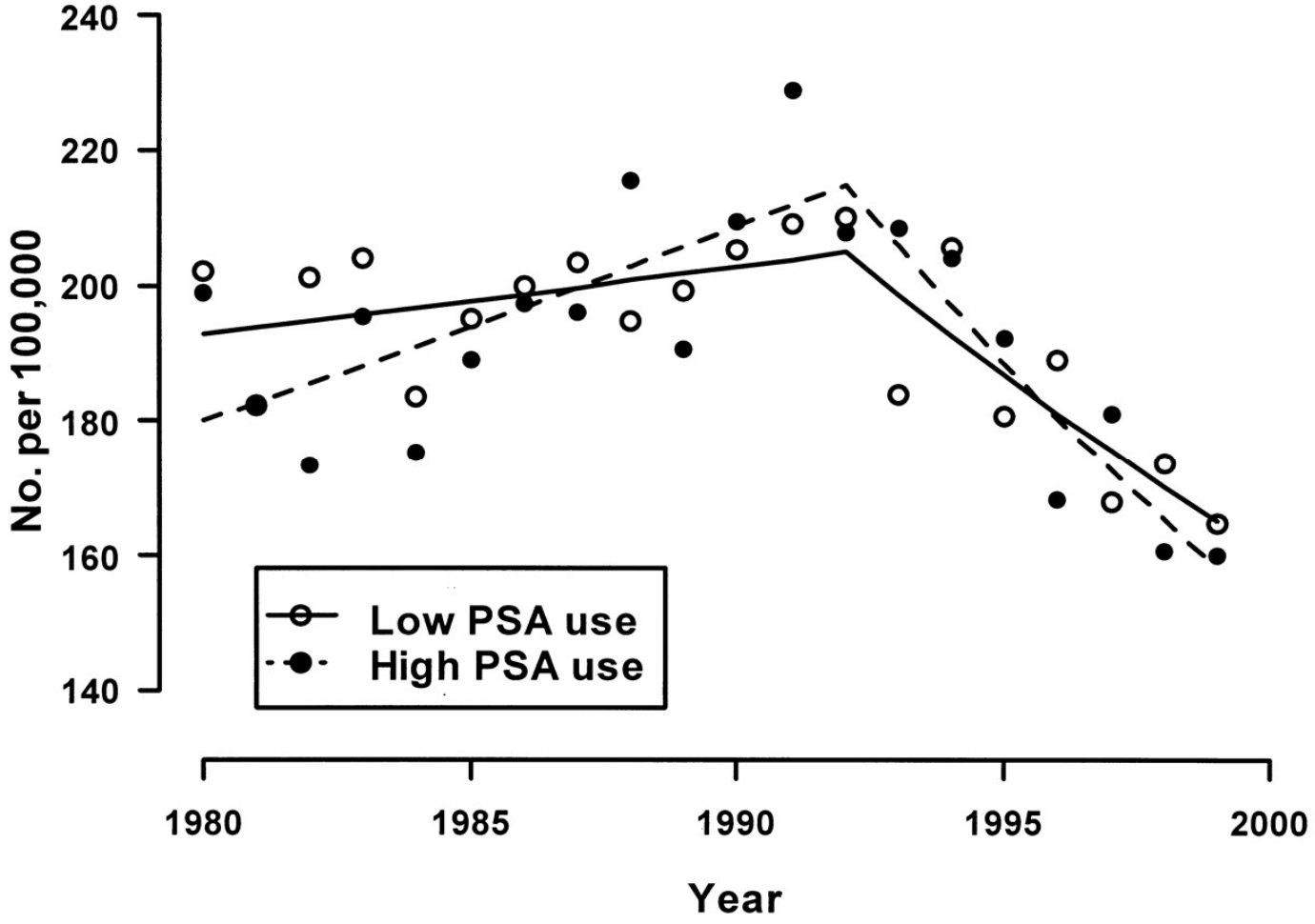
FIGURE 4. Decline in age-adjusted prostate cancer mortality rates vs. average prostate-specific antigen (PSA) screening use.



Shaw P A et al. Am. J. Epidemiol. 2004;160:1059-1069

American Journal of
EPIDEMIOLOGY

FIGURE 5. Age-adjusted prostate cancer mortality rates by registry of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute for White men aged 65–84 years, grouped by high vs. low use of prostate-specific antigen (PSA) screening.



Shaw P A et al. Am. J. Epidemiol. 2004;160:1059-1069

American Journal of EPIDEMIOLOGY

Ecological or cross-level bias

- If different conclusions are drawn from the analysis of data upon their aggregations into units of different sizes (e.g., from individuals to townships and regions),
- these differences are commonly referred to as ‘‘ecological fallacy’’
- In epidemiology, these differences are also known as ecological or cross-level bias

Ecologic bias

Ecologic bias can arise from three sources when using simple linear regression to estimate the crude exposure effect: The first may operate in any type of study; the latter two are unique to ecologic studies (i.e. cross-level bias), but are defined in terms of individual-level associations.

1. Within-group bias The exposure effect within groups may be biased by confounding, selection methods, or misclassification. Thus, for example, if there is positive net bias in every group, we would expect the ecologic estimate to be biased as well.
2. **Confounding by group** Ecologic bias may result if the background rate of disease in the unexposed population varies across groups, specifically if there is a nonzero ecologic (linear) correlation between mean exposure level and the background rate.
3. **Effect modification by group** Ecologic bias may also result if the rate difference for the exposure effect at the individual level varies across groups.

Tasso di suicidi e % di popolazione Protestante

- Durkheim's study of religion and suicide used data from four groups of Prussian provinces between 1883 and 1890.
- The groups were formed by ranking 13 provinces according to the proportion (X) of the population that was Protestant.
- Durkheim found that suicide rates (Y) were highest in provinces that were heavily Protestant.
- He concluded that stronger social control among Catholics resulted in lower suicide rates.

Tasso di suicidi e % di popolazione Protestante

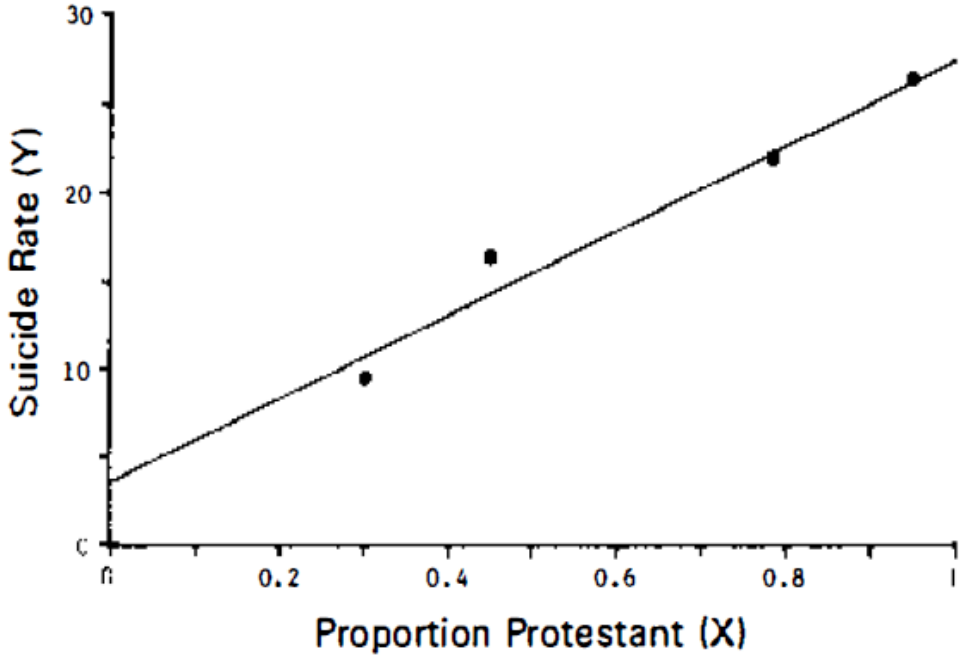


Figure 2 Suicide rate (Y, per 10^5/year) by proportion Protestant (X) for four groups of Prussian provinces, 1883–90. The four observed points (X, Y) are (0.30, 9.56), (0.45, 16.36), (0.785, 22.00), and (0.95, 26.46); the fitted line is based on unweighted least-squares regression [Source: Adapted from Durkheim (16)].

Using ordinary least-squares linear regression, we estimate the suicide rate ($\hat{Y}$, per 10^5/year) in each group to be 3.66 + 24.0(X).

2 vs 8

- The estimated rate ratio of 7.6 was probably not because suicide rates were nearly 8 fold higher in Protestants than in non-Protestants.
- Rather, because none of the regions was entirely Protestant or non-Protestant, it may have been non-Protestants (primarily Catholics) who were committing suicide in predominantly Protestant provinces.
- It is plausible that members of a religious minority might have been more likely to commit suicide than were members of the majority
- Durkheim compared the suicide rates at the individual level for Protestants, Catholics and Jews living in Prussia, and from his data, the rate was about twice as great in Protestants as in other religious groups.
- Thus, when the rate ratios are compared (2 vs 8), there appears to be substantial ecological bias using the aggregate level data.

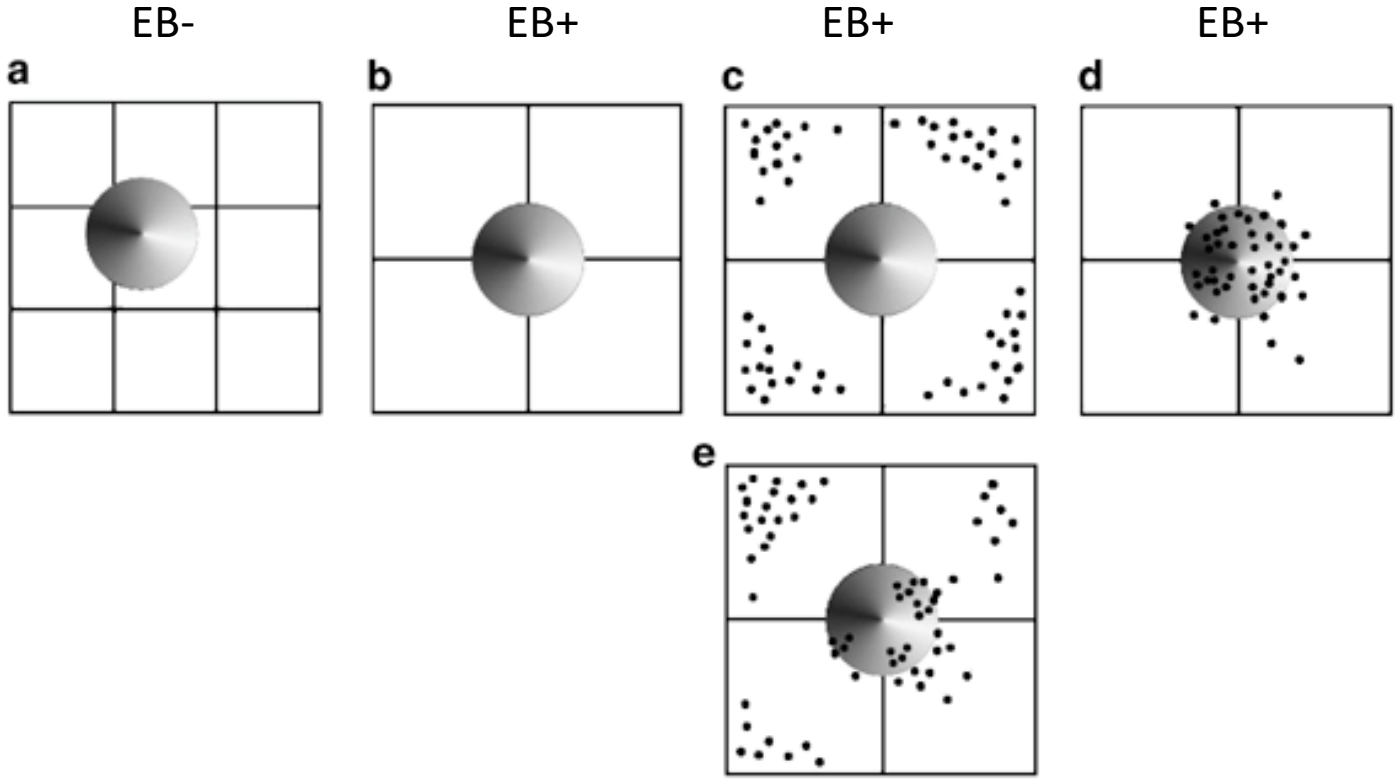
Stima del RR

- Using ordinary least-squares linear regression, we estimate the suicide rate ($\hat{Y}$, per 10^5/year) in each group to be 3.66 + 24.0(X).
- Therefore, the estimated rate ratio, comparing Protestants with other religions, is 1 + (24.0/3.66) = 7.6.
- Note in Figure 2 that the fit of the linear model is excellent (R^2 = 0.97)

Stima del RR dalla retta

- $\hat{Y} = B_0 + B_1X$, where B_0 and B_1 are the estimated intercept and slope, using ordinary least-squares methods.
- The estimated biologic effect of the exposure (at the individual level) can be derived from the regression results . The predicted disease rate ($\hat{Y}$) in a group that is entirely exposed is $B_0 + B_1(1) = B_0 + B_1$, and the predicted rate in a group that is entirely unexposed is $B_0 + B_1(0) = B_0$.
- Therefore, the estimated rate difference is B_1 and the estimated rate ratio is $1 + B_1/B_0$.
- Note that this ecologic method of effect estimation requires rate predictions be extrapolated to both extreme values of the exposure variable (i.e. X = 0 and 1), which are likely to lie well beyond the observed range of the data. It is not surprising, therefore, that different model forms (e.g. log-linear vs linear) can lead to very different estimates of effect. Fitting a linear model, in fact, may lead to negative, and thus meaningless, estimates of the rate ratio.

Bias ecologico derivante dalla analisi per area

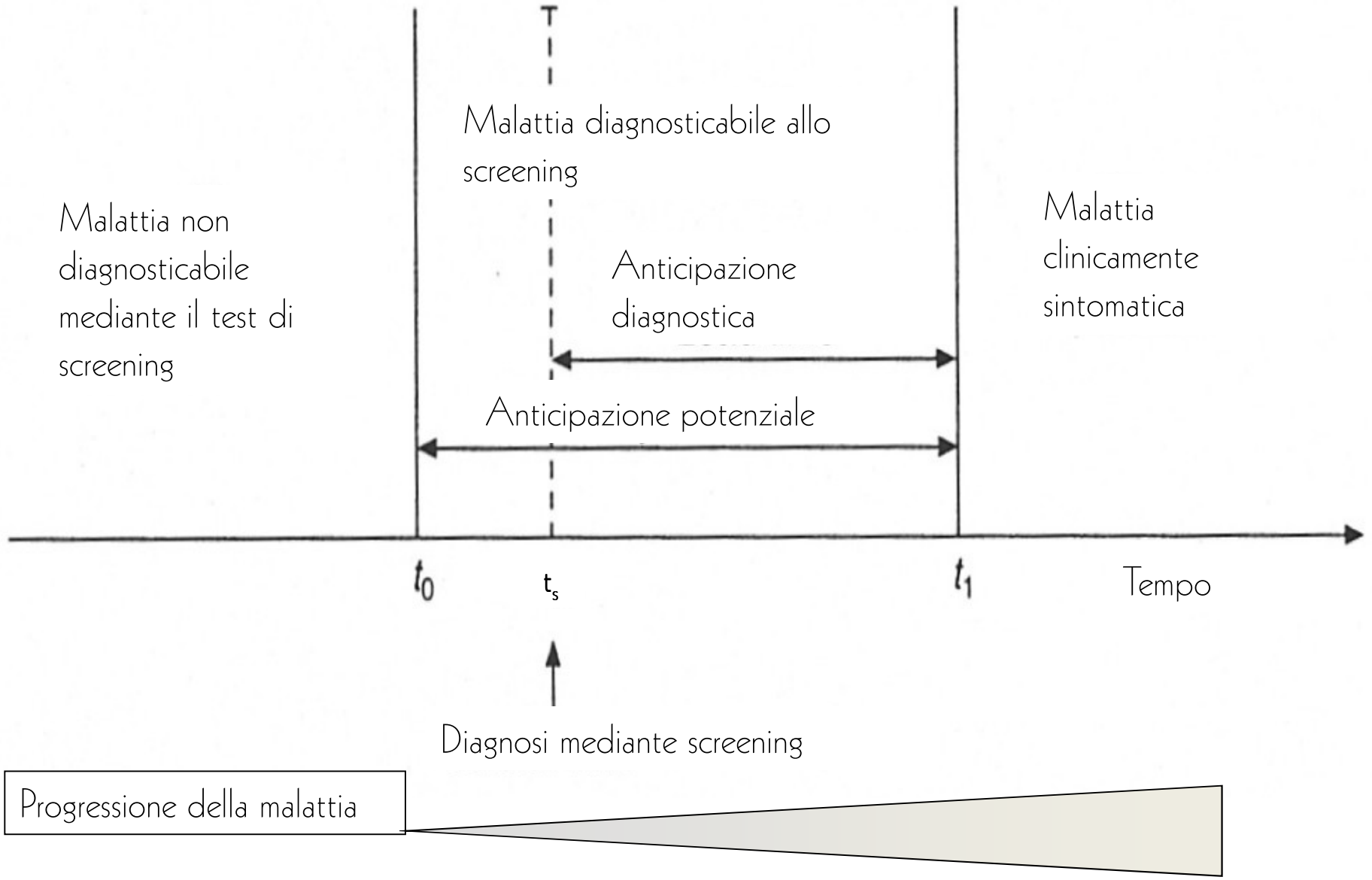


Altri bias di informazione

- Hawthorne effect: described in the 1920s in the Hawthorne plant of the Western Electric Company (Chicago, IL).
- It is an increase in productivity—or other outcome under study—in participants who are aware of being observed

Lead time: anticipazione diagnostica

- Lead time bias: the added time of illness produced by the diagnosis of a condition during its latency period.
- This bias is relevant in the evaluation of the efficacy of screening, in which the cases detected in the screened group has a longer duration of disease


T
Malattia diagnosticabile allo screening
Malattia non diagnosticabile mediante il test di screening
Anticipazione diagnostica
Malattia clinicamente sintomatica
Anticipazione potenziale
t_0
t_s
t_1
Tempo
Diagnosi mediante screening
Progressione della malattia

Will Rogers

- Will Rogers phenomenon: named in honour of the philosopher Will Rogers by Feinstein et al.
- The improvement in diagnostic tests refines disease staging in diseases such as cancer.
- This produces a stage migration from early to more advances stages and an apparent higher survival.
- This bias is relevant when comparing cancer survival rates across time or even among centres with different diagnostic capabilities

Control for confounding

- When selection bias or information bias exist in a study, irreparable damage results.

David A Grimes, Kenneth F Schulz Bias and causal associations in observational research. Lancet 2002