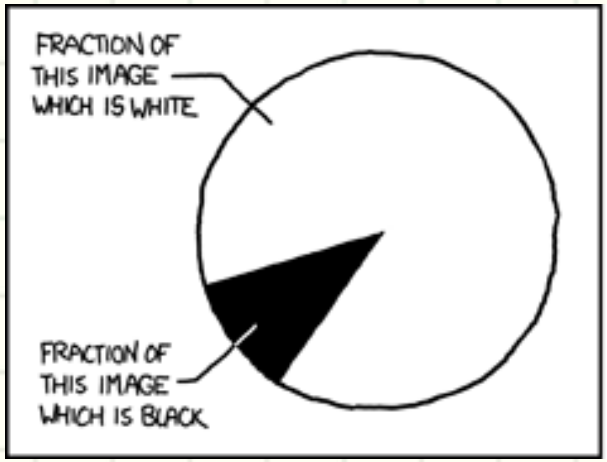
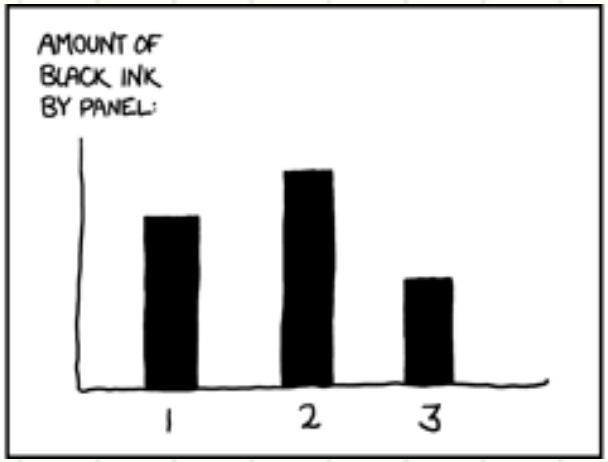
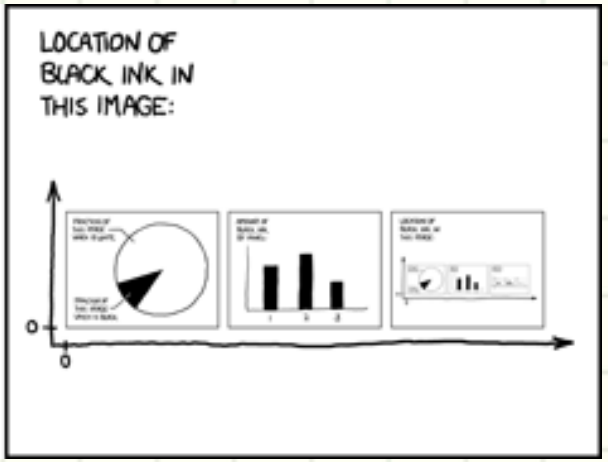
La statistica che serve - modificato

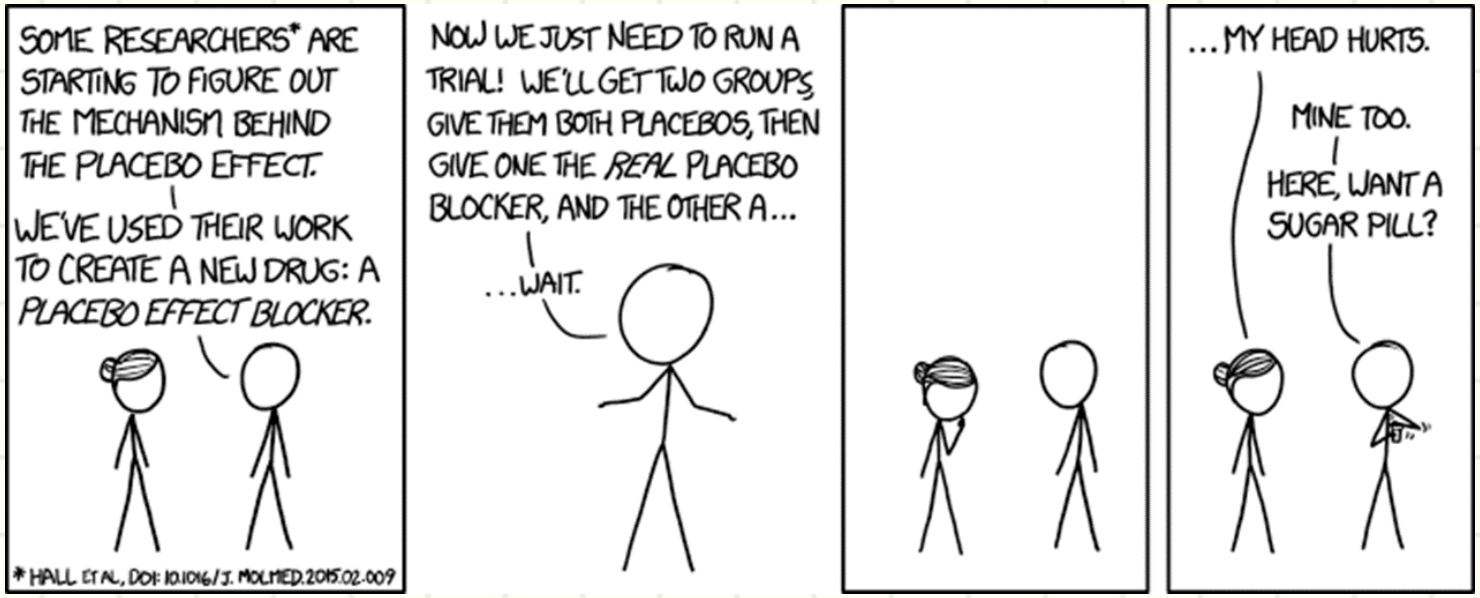
Prof. Fabrizio Stracci

Dip.to Medicina Sperimentale– Sez. Sanità Pubblica- Università di Perugia









Statistiche semplici

Genetics and the placebo effect: the placebome.

Hall KT et al. Trends Mol Med. 2015; 21:285-94.

Abstract

- Placebos are indispensable controls in randomized clinical trials (RCTs), and placebo responses significantly contribute to routine clinical outcomes.
- Recent neurophysiological studies reveal neurotransmitter pathways that mediate placebo effects.
- Evidence that genetic variations in these pathways can modify placebo effects raises the possibility of using genetic screening to identify placebo responders and thereby increase RCT efficacy and improve therapeutic care.
- Furthermore, the possibility of interaction between placebo and drug molecular pathways warrants consideration in RCT design. The study of genomic effects on placebo response, 'the placebome', is in its infancy. Here, we review evidence from placebo studies and RCTs to identify putative genes in the placebome, examine evidence for placebo-drug interactions, and discuss implications for RCTs and clinical care.

Table: GRADE's approach to rating quality of evidence (aka confidence in effect estimates)

For each outcome based on a systematic review and across outcomes (lowest quality across the outcomes critical for decision making)

1. Establish initial level of confidence		2. Consider lowering or raising level of confidence		3. Final level of confidence rating
Study design	*Initial confidence in an estimate of effect*	*Reasons for considering lowering or raising confidence*		*Confidence in an estimate of effect across those considerations*
		↓ Lower if	↑ Higher if*	
Randomized trials →	High confidence	Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias • would reduce a demonstrated effect or • would suggest a spurious effect if no effect was observed	High ⊕⊕⊕⊕
				Moderate ⊕⊕⊕◯
Observational studies →	Low confidence			Low ⊕⊕◯◯
				Very low ⊕◯◯◯

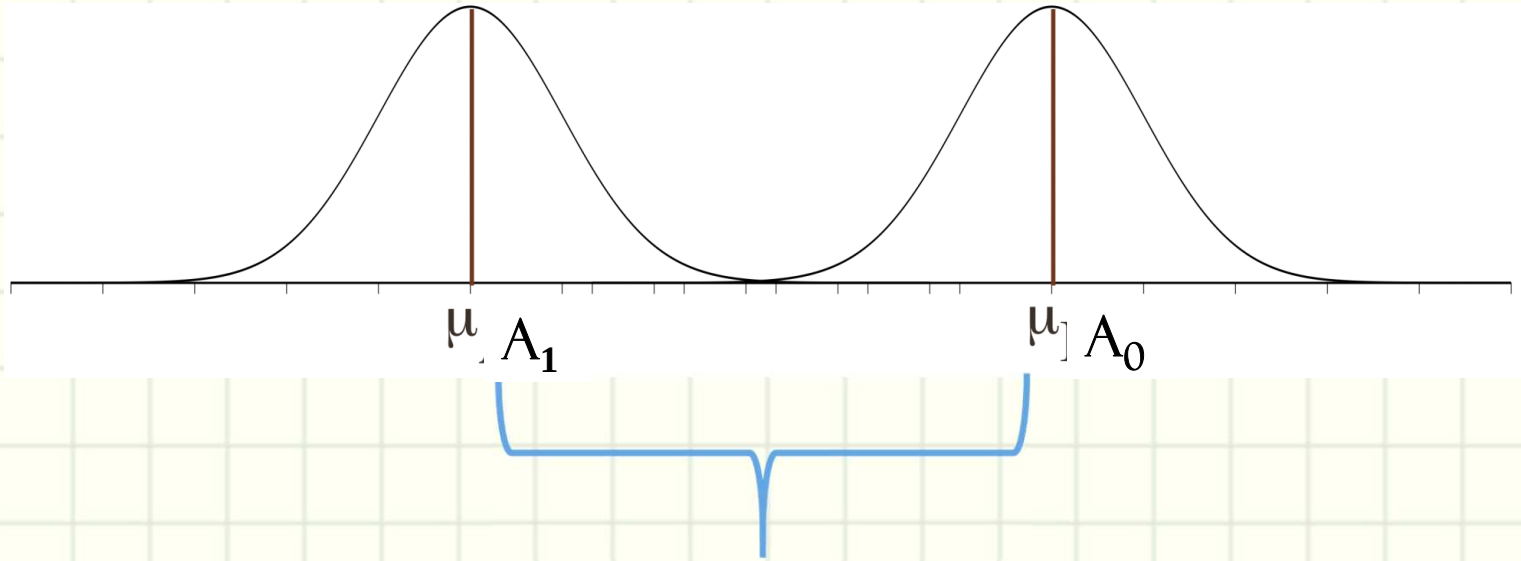
*upgrading criteria are usually applicable to observational studies only.

We want to measure an effect comparing the same individuals with and without the intervention

Suppose that μ will equal μ_{A1} if x_1 is applied to population A, and will equal μ_{A0} if x_0 is applied to that population; the causal effect of x_1 relative to x_0 is defined as the change from μ_{A0} to μ_{A1}, which could be measured by $\mu_{A1} - \mu_{A0}$ (or by μ_{A1}/μ_{A0} if μ is strictly positive). If A is observed under treatment x_1, μ will equal μ_{A1}, which is observable or estimable, but μ_{A0} will be unobserved. Suppose, however, we expect μ_{A0} to equal μ_{B0}, where μ_{B0} is the value of the outcome μ observed or estimated for a population B that was administered treatment x_0. The latter population is sometimes called a *control* or *reference* population. We say *confounding* is present if, in fact, $\mu_{A0} \neq \mu_{B0}$, for then there must be some difference between populations A and B (other than treatment) that is responsible for the discrepancy between μ_{A0} and μ_{B0}.

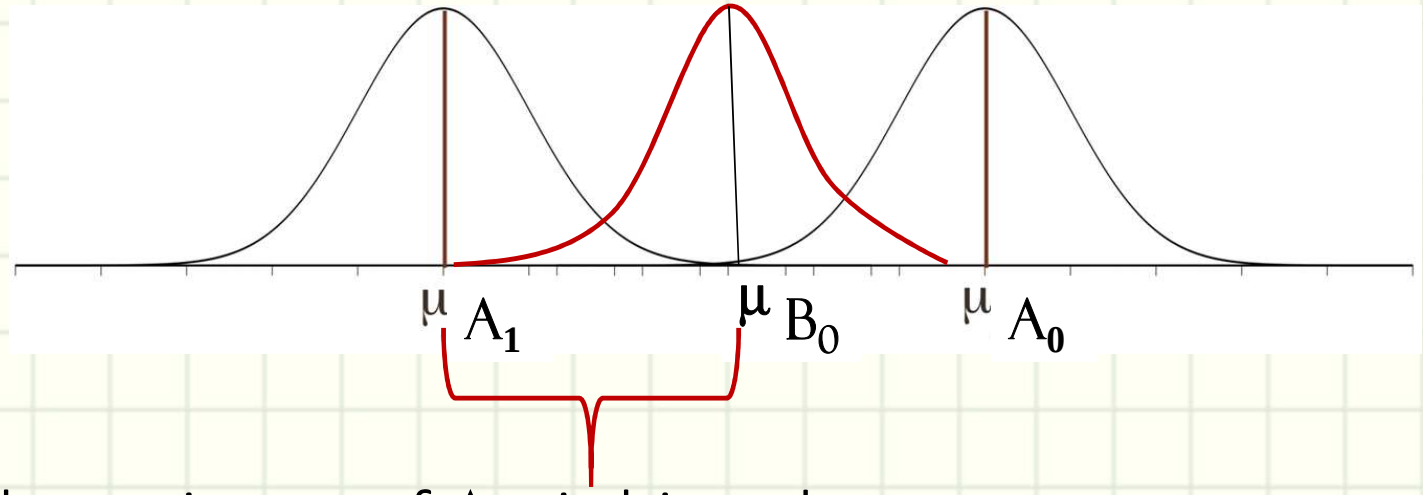
Confounding and Collapsibility in Causal Inference Greenland S, Pearl J, Robins JM Stat. Sci. 1999

$$\Delta\mu = \mu A_1 - \mu A_0$$

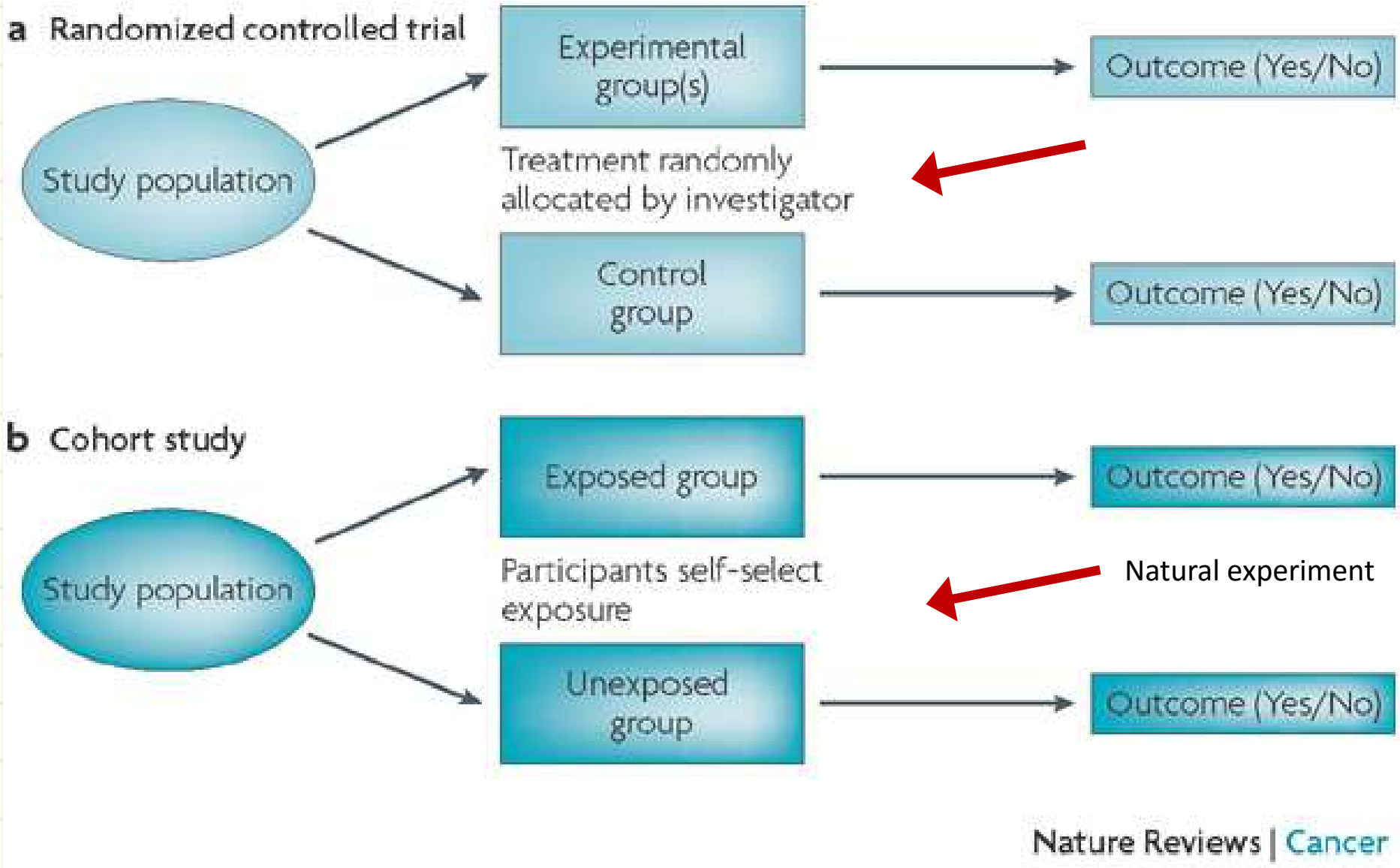


Since μA1-μA0 is not observable, we need a substitute for A0

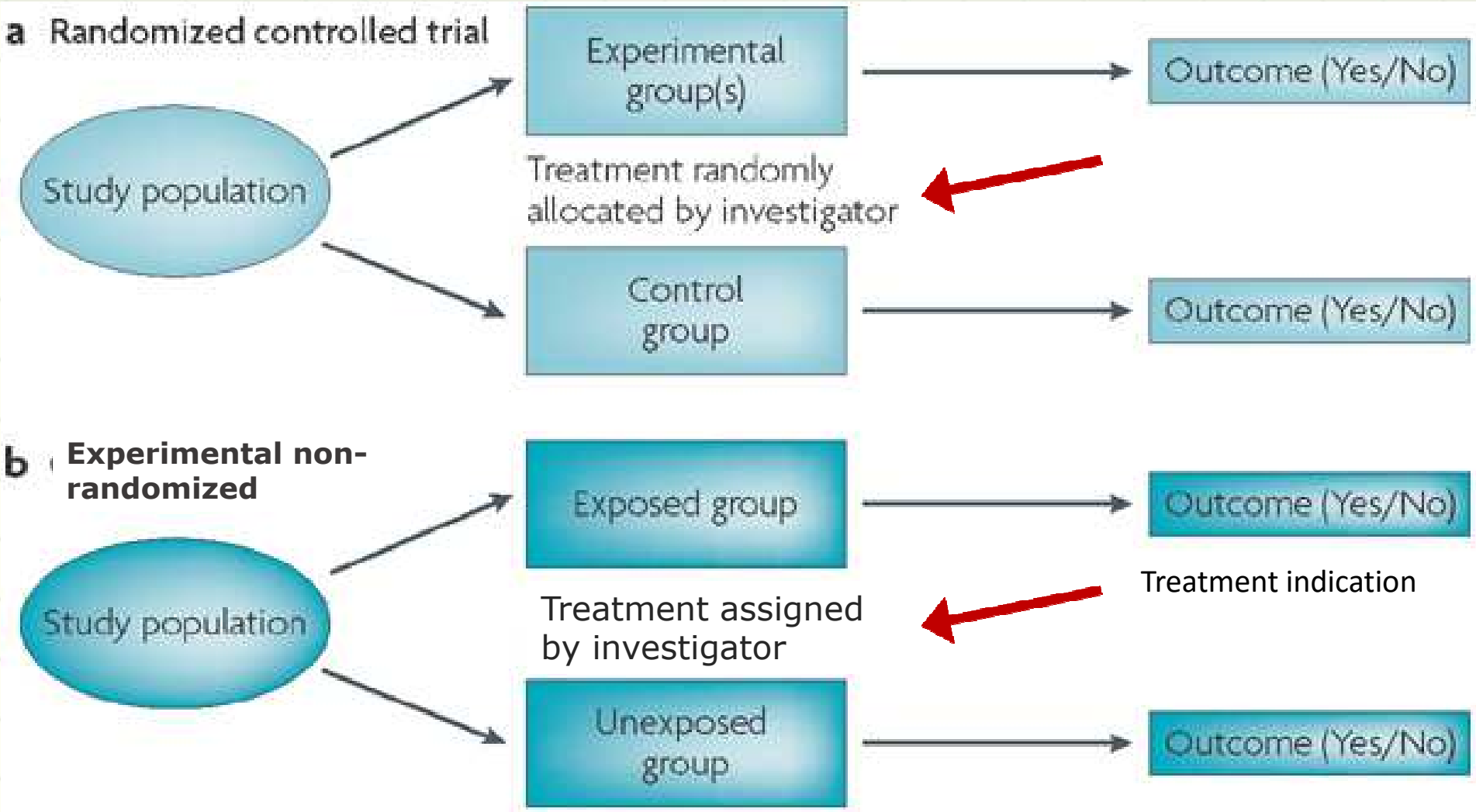
$\mu B_0 = \mu A_0$: the estimate of $\Delta\mu$ is unbiased



$\mu B_0 \neq \mu A_0$: the estimate of $\Delta\mu$ is biased



Martínez ME, Marshall JR, Giovannucci E. Diet and cancer prevention: the roles of observation and experimentation. Nat Rev Cancer. 2008



The term observational refers to study without intervention of the investigator (i.e. natural experiments)

Nature Reviews | Cancer

Randomization is not the same as bias free

- this solution is only probabilistic and subject to severe practical constraints. For example, protocol violations (e.g. noncompliance) and loss to follow-up may produce systematic covariate imbalances between the groups (and consequent confounding), and
- random imbalances may be severe, **especially if the study size is small**

Successful randomization

simply ensures that the difference, $\mu A0 - \mu B0$, and hence the bias due to confounding, has expectation zero and converges to zero under the randomization distribution; it also provides a permutation distribution for causal inferences

Greenland S, Morgenstern H. Confounding in health research. Annu Rev Public Health. 2001;22:189-212.

Randomization

- any **bias due to confounding is random* with a known distribution**; therefore, randomization permits derivation of statistical procedures for estimating treatment effects

- In addition, it can be argued that randomization should lead us to use the **entire (treated plus untreated) study group as the target population**, rather than just the treated (exposed) group

Greenland S, Morgenstern H. Confounding in health research. Annu Rev Public Health. 2001;22:189-212.

* *The statement that confounding (i.e. a systematic error) is random is weird*

Large trials

1. Poor statistical power increases the proportion of false positive findings (Ioannidis, 2005; Wacholder et al., 2004)…
2. Small studies have poor precision of estimated effects and will produce type-1 errors with relatively large effect sizes. This is because small studies have relatively more noise in data.
3. Small studies tend to report inflated effect sizes.
4. *Potential detection of "trivial" effects in large RCTs with incomplete reporting*

Ingre M. Neuroimage 2013

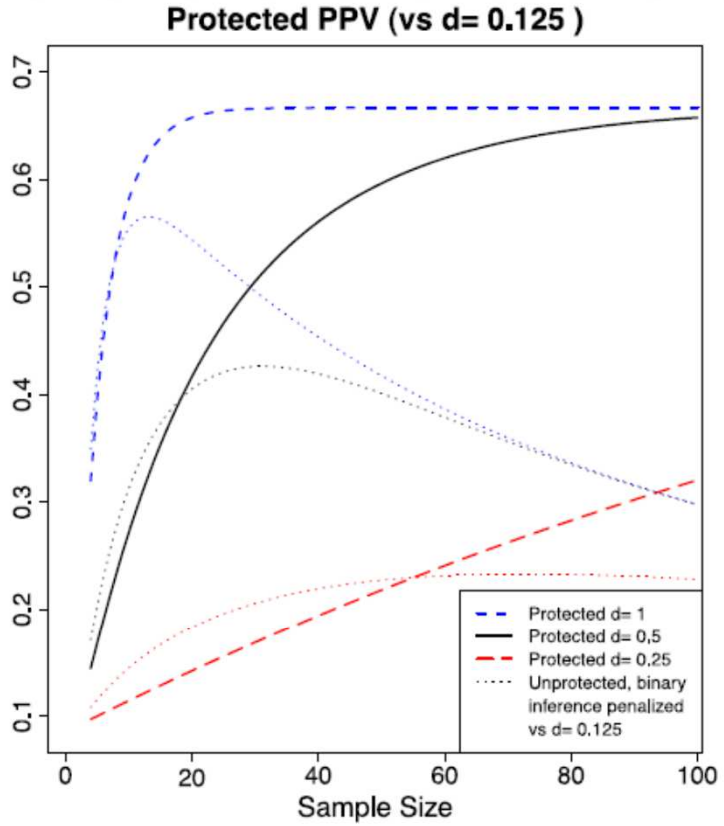


Fig. 3. Positive predictive values (PPV) indicating the probability of a significant finding to show a true effect rather than a type-1 error (Eq. (1)), protected against inferences of trivial (d = .125) effect sizes (thick lines). Dotted lines show PPV for unprotected binary inference penalized by substituting α for statistical power of trivial effects (d = .125). The plot assume α = .05, one-sample t-tests and R = .1 true effects (d = 1, d = .5 or d = .25) for every trivial effect (d = .125) present in data. These assumptions differ slightly from, e.g. Friston's (2012) loss-function, who assumes an even (R = 1) distribution of large effects (d = 1) and trivial effects (d = .125) in data, and will give more accurate estimates in many situations where true effects are less common (see Ioannidis, 2005, for a discussion of plausible priors/R in research). Readers are encouraged to model different distributions of effect sizes, R and alpha/p-values, using the attached R-code, to study how the function adapts to a situation suitable for their specific problem.

Criticism

(1) **they are too expensive** and difficult;

(2) their findings are too broad (*average treatment effect not representative of benefit for any given individual*) and too narrow (*trial population and setting not representative of general practice*);

(3) *randomizing patients can make patients and physicians uncomfortable, especially when comparing different types of existing care*; and

(4) **there are often long delays before RCT results diffuse into practice**.

…

Angus Dc. Fusing Randomized Trials With Big DataThe Key to Self-learning Health Care Systems? JAMA

The Design of Randomized Clinical Trials in Critically Ill Patients*

Chest. 2002;121(4):1290-1300. doi:10.1378/chest.121.4.1290

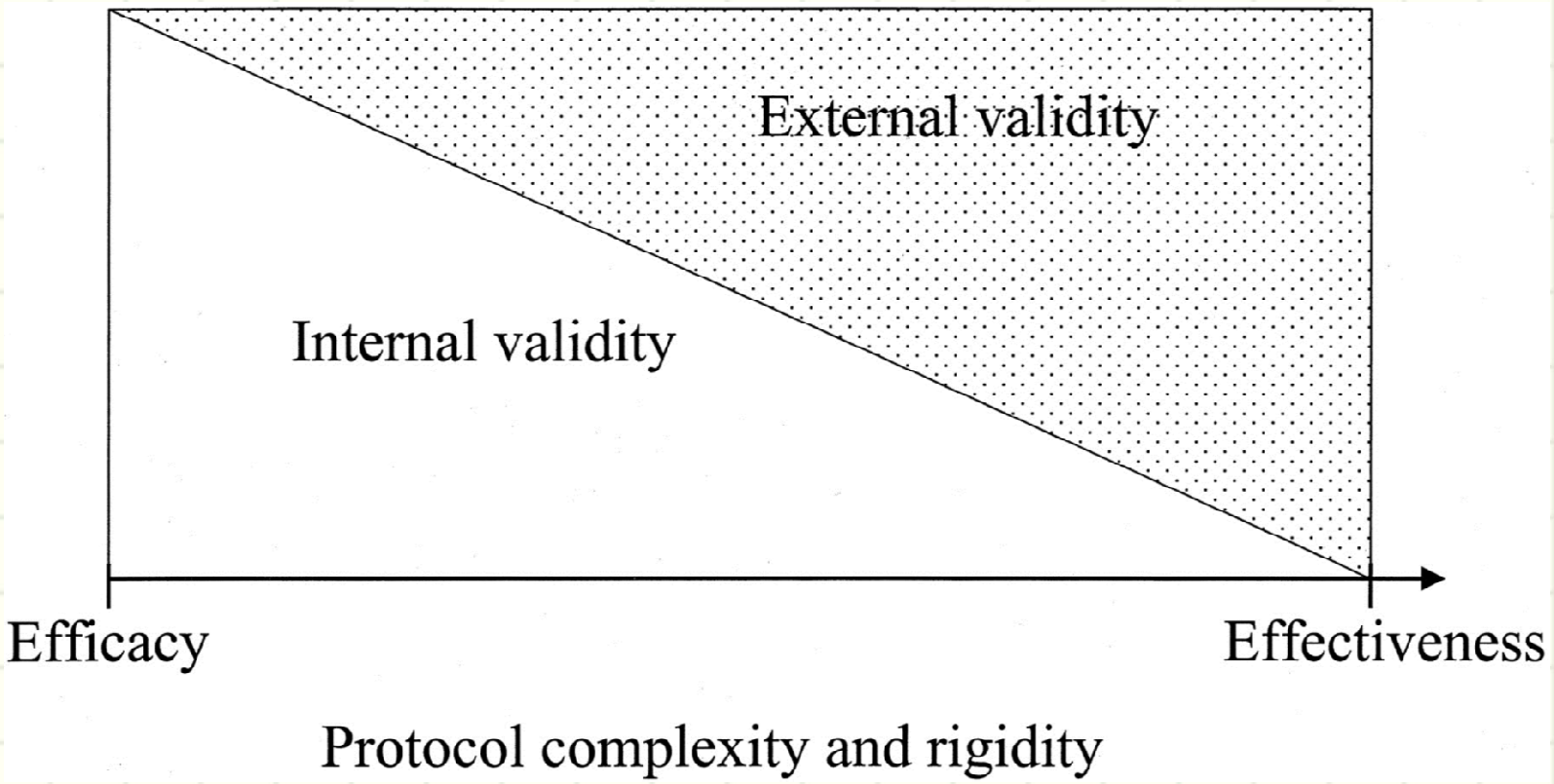
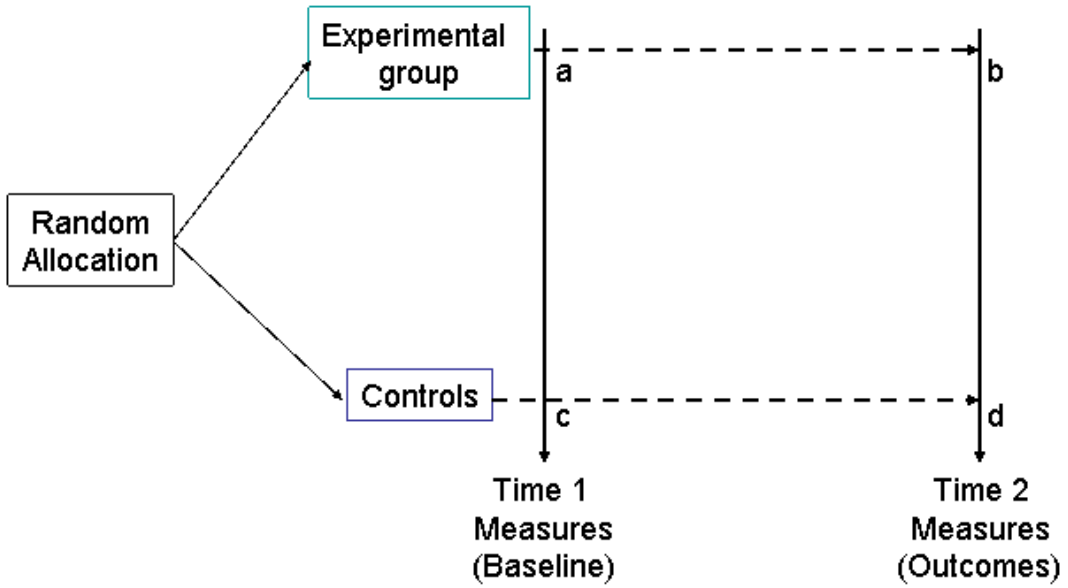


Figure Legend:

Implication of design approaches on internal and external validity.

Studio sperimentale randomizzato e controllato



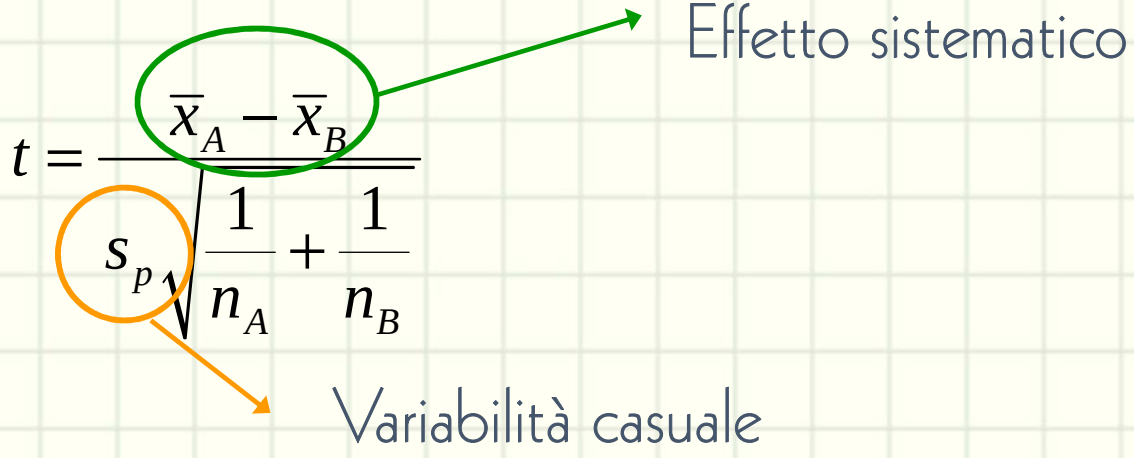
Effect measurement: (b - a) – (d - c)

Note:
random allocation should make a = c, but these are included in analysis to correct for any minor differences.

The types of statistical methods used in RCTs depend on the characteristics of the data

- For **continuous outcome** data, analysis of covariance tests the effects of predictor variables.
- For **dichotomous (binary) outcome** data, logistic regression and other methods can be used.
- For **time-to-event outcome** data that may be censored, survival analysis (e.g., Kaplan–Meier estimators and Cox proportional hazards models) is appropriate

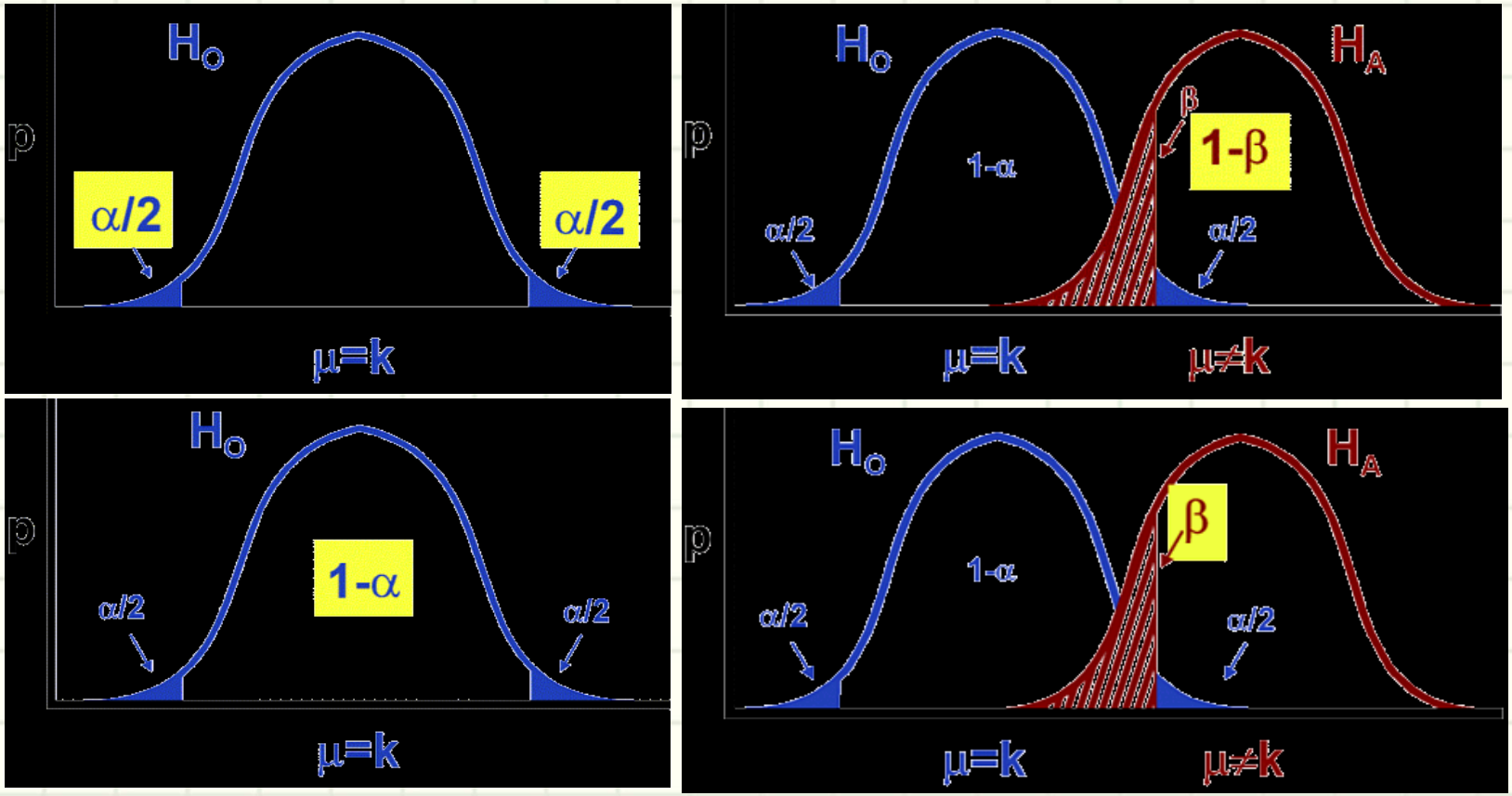
Un esempio: il test t di Student per il confronto di due gruppi

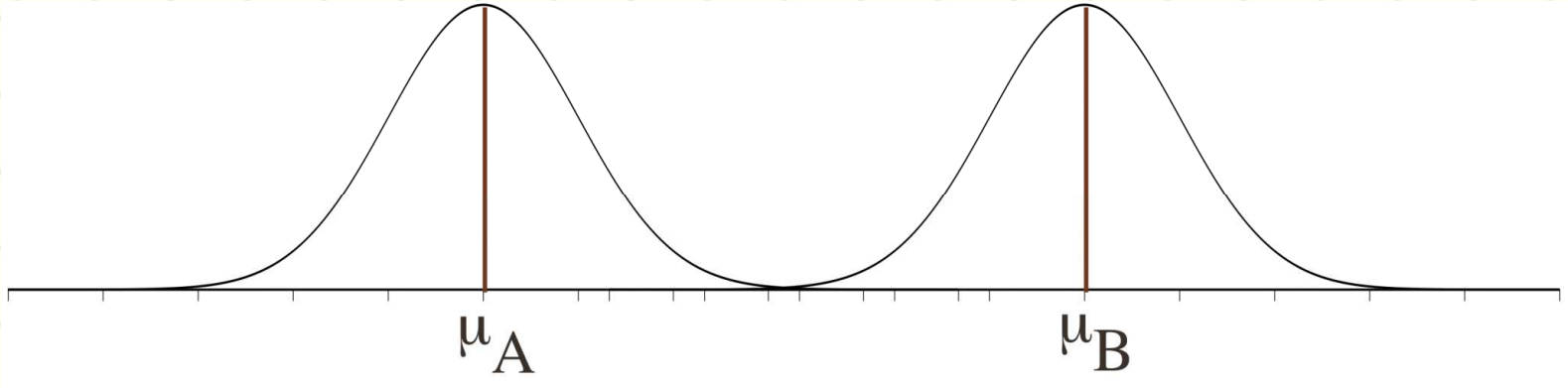


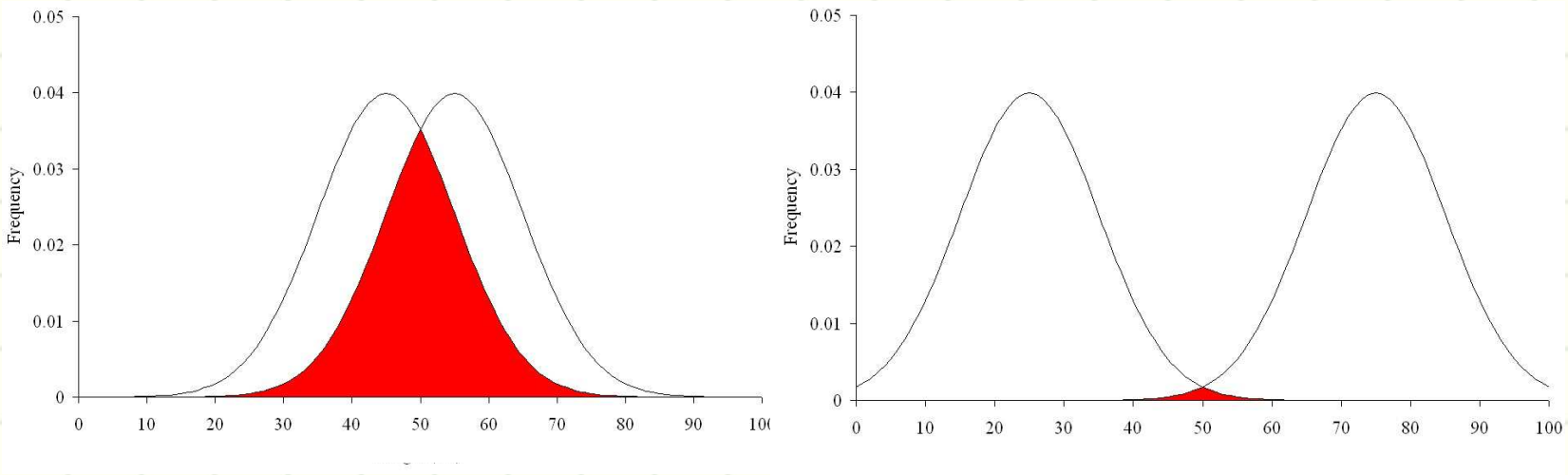
Se alcuni assunti sono verificati, possiamo calcolare s_p come:

$$s_p = \sqrt{\frac{dev_A + dev_B}{n_A + n_B - 2}}$$

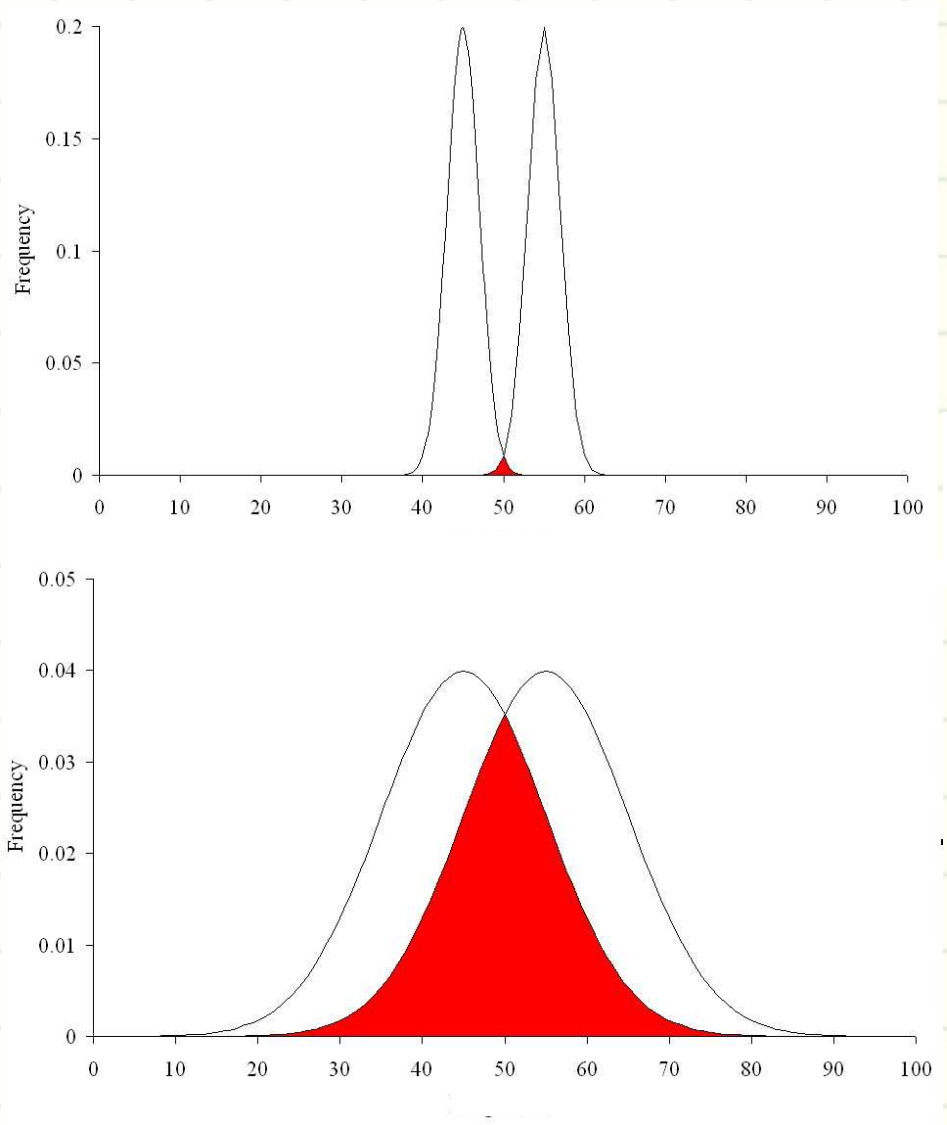
Possibilities:		Actual Situation	
		H_o is True	H_o is False
Decision	Reject H_o	Type I Error	Correct decision II
	Do not reject H_o	Correct decision II	Type II Error







Ignoriamo quale sia il valore effettivo del parametro $\Delta = \mu_A - \mu_B$



Ignoriamo quale sia la variabilità σ_A, σ_B

Risultato del test

- **Punti critici**. Utilizzando apposite tabelle o software, possiamo confrontare il valore sperimentale del test con il valore tabulare corrispondente all'errore alfa prescelto

- **Valore *p*.** Possiamo ottenere direttamente da un programma la probabilità del nostro risultato sotto l'ipotesi nulla: se tale probabilità $p < \alpha$ il test è significativo

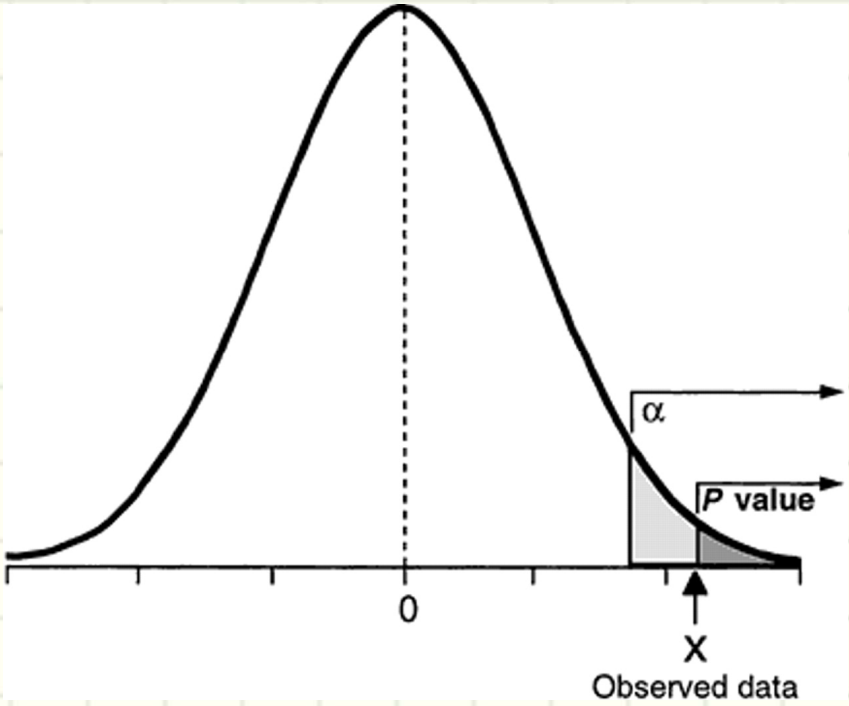
Il valore *p*

- A differenza di alfa, il valore *p* dipende dai dati
- *p* corrisponde alla probabilità di osservare un valore sperimentale del test come quello osservato o più improbabile sotto l'ipotesi nulla
- Quindi se l'errore alfa è

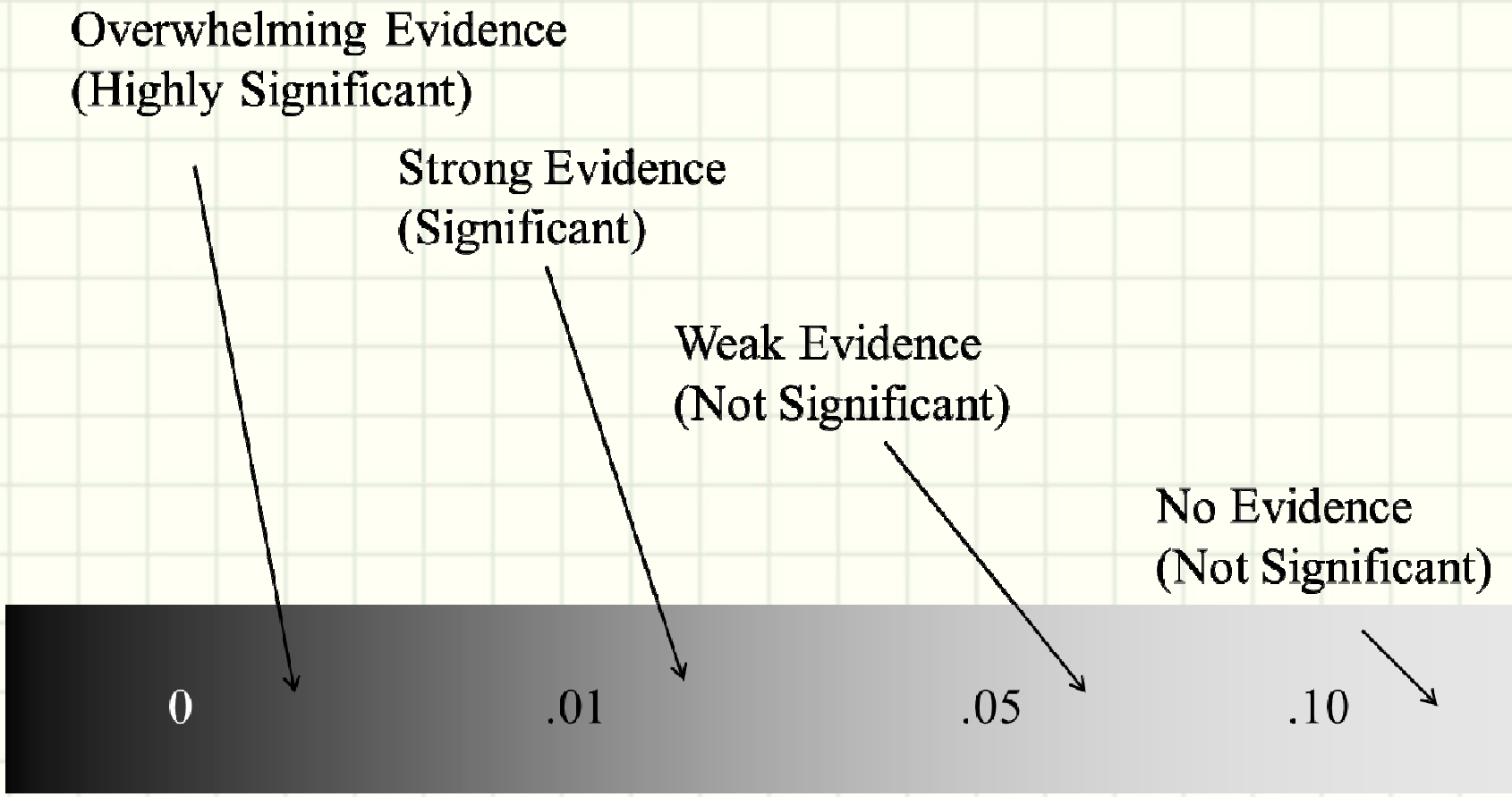
quello consueto, valori

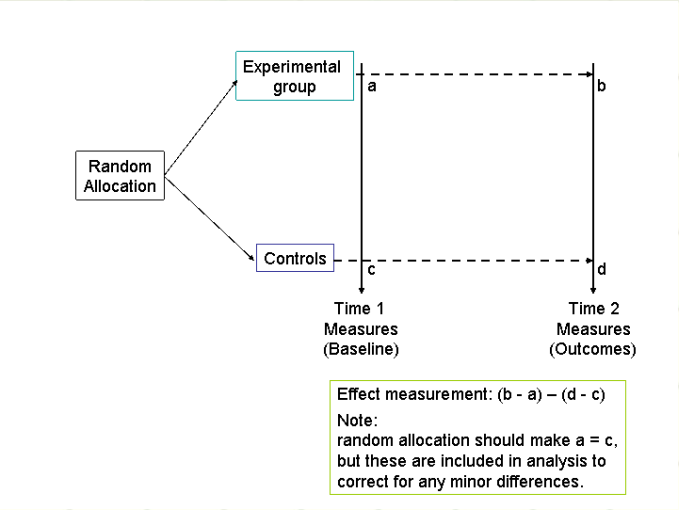
$p<0.05$ indicano un test

significativo



Interpreting the p-value





ANCOVA

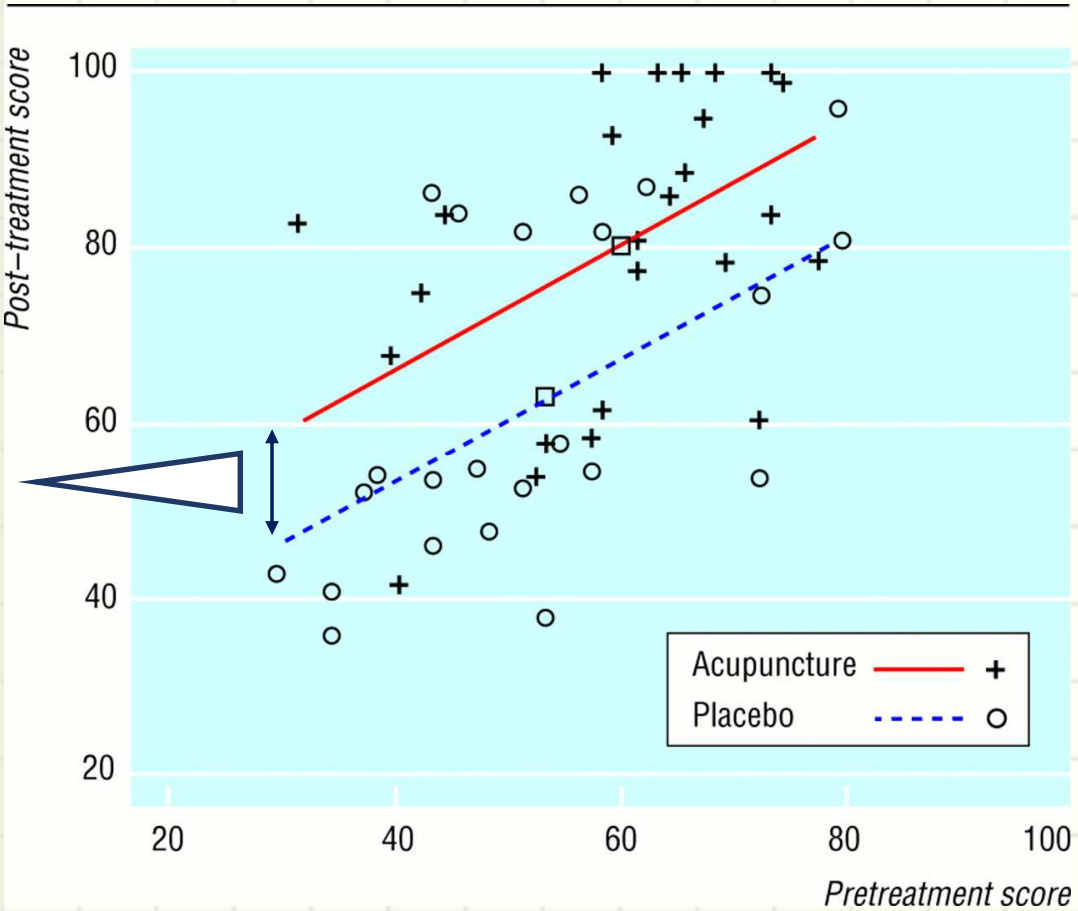
In many randomized trials researchers measure a continuous variable at baseline and again as an outcome assessed at follow up.

- to take account of chance imbalances at baseline between the treatment groups.
- use analysis of covariance (ANCOVA), which, despite its name, is a regression method. In effect two parallel straight lines (linear regression) are obtained relating outcome score to baseline score in each group
- An additional advantage of analysis of covariance is that it generally has greater statistical power to detect a treatment effect than the other methods

Analysing controlled trials with baseline and follow up measurements BMJ 2001

Pretreatment and post-treatment scores in each group showing fitted lines.

Effetto
(differenza tra gruppi)



Andrew J Vickers, and Douglas G Altman BMJ 2001;323:1123-1124

Il valore finale dipende da punteggio iniziale e gruppo (trattamento: variabile dicotomica)

$Y(\text{follow up score}) = a + b_1 * x_1(\text{baseline score}) + \mathbf{b_2} * x_2(\mathbf{treatment})$

Results of trial of acupuncture for shoulder pain

	Pain scores (mean and SD)			
	Placebo group (n=27)	**Acupuncture group (n=25)**	**Difference between means (95% CI)**	**P value**
Baseline	**53.9** (14)	**60.4** (12.3)	**6.5**	
Analysis				
Follow up	**62.3** (17.9)	**79.6** (17.1)	**17.3** (7.5 to 27.1)	**0.0008**
Change score*	***8.4*** *(14.6)*	***19.2*** *(16.1)*	***10.8*** *(2.3 to 19.4)*	***0.014***
ANCOVA			**12.7** (4.1 to 21.3)	**0.005**

"pain and function score improved by an estimated 12.7 points more on average in the treatment group than in the control group."

Test di Wilcoxon

Alternativa non parametrica al t test per confrontare due campioni indipendenti (si utilizza in caso di distribuzioni non normali)

Si basa sulla trasformazione in ranghi dei dati osservati nei due campioni

Di seguito l'approssimazione normale valida per n_A e n_B entrambi maggiori di 10:

$$\mathrm{pr}(W_A \geq w_A) \approx \mathrm{pr}(Z \geq z), \quad \text{where } z = \frac{w_A - \mu_A}{\sigma_A}$$

$$\mu_A = \frac{n_A(n_A + n_B + 1)}{2} \quad \text{and} \quad \sigma_A = \sqrt{\frac{n_A n_B (n_A + n_B + 1)}{12}}.$$

diametro	SLN
1.3	micro
2.3	micro
1.6	micro
1.9	micro
1.6	micro
1	micro
2.8	micro

diametro	SLN
2.3	macro
1.2	macro
3.3	macro
1.7	macro
1.9	macro
1.8	macro
5.5	macro

diametro	SLN	RANGO.MEDIA(Num;Rif;[Ordine])
1.3	micro	12
2.3	micro	4.5
1.6	micro	10.5
1.9	micro	6.5
1.6	micro	10.5
1	micro	14
2.8	micro	3
2.3	macro	4.5
1.2	macro	13
3.3	macro	2
1.7	macro	9
1.9	macro	6.5
1.8	macro	8
5.5	macro	1

Somma dei ranghi

W_{mic}=61

W_{mac}=44

=N(N+1)/2 – W_{mic} =(14*15/2) – 61=105 – 61

Ranghi

diametro	SLN	Rango	
5.5	macro	1	
3.3	macro	2	
2.8	micro	3	
2.3	micro	4.5	(4+5)/2
2.3	macro	4.5	(4+5)/2
1.9	micro	6.5	
1.9	macro	6.5	
1.8	macro	8	
1.7	macro	9	
1.6	micro	10.5	
1.6	micro	10.5	
1.3	micro	12	
1.2	macro	13	
1	micro	14	

Stata: ranksum diametro, by(sln)

Two-sample Wilcoxon rank-sum (Mann-Whitney) test

sln	obs	rank sum	expected
macro	7	61	52.5
micro	7	44	52.5
combined	14	105	105

unadjusted variance	61.25
adjustment for ties	-0.40
---	
adjusted variance	60.85

Ho: diametro(sln=macro) = diametro(sln=micro)

z = **1.090**

Prob > z = 0.28

Misure epidemiologiche

Frequenza

- *Frequenza assoluta*
- Rischio / probabilità
- Tasso

Associazione

- Rapporto (Rischio relativo, rapporto tra tassi)
- Differenza (tra rischi, tra tassi)
- Rapporto tra odds o odds ratio

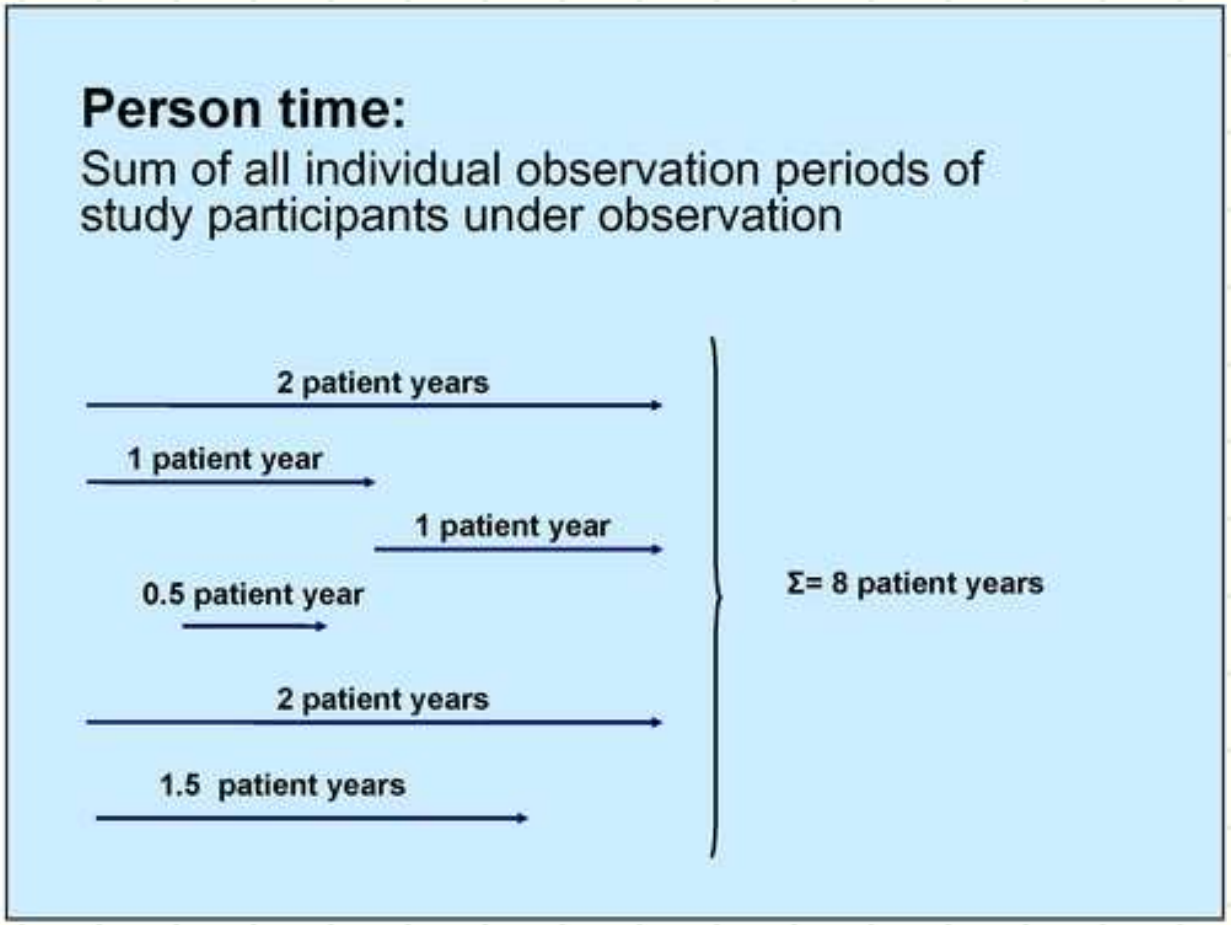
Impatto

- Rischio attribuibile

Tasso

- Misura la velocità di comparsa di un evento definito in una popolazione per unità di tempo
- Richiede:
  - la definizione di un evento misurabile e relativa enumerazione
  - La scelta di una popolazione di riferimento rispetto alla quale intendiamo misurare la comparsa dell'evento
  - La misurazione del tempo di osservazione (esposizione a rischio) per ogni componente della popolazione

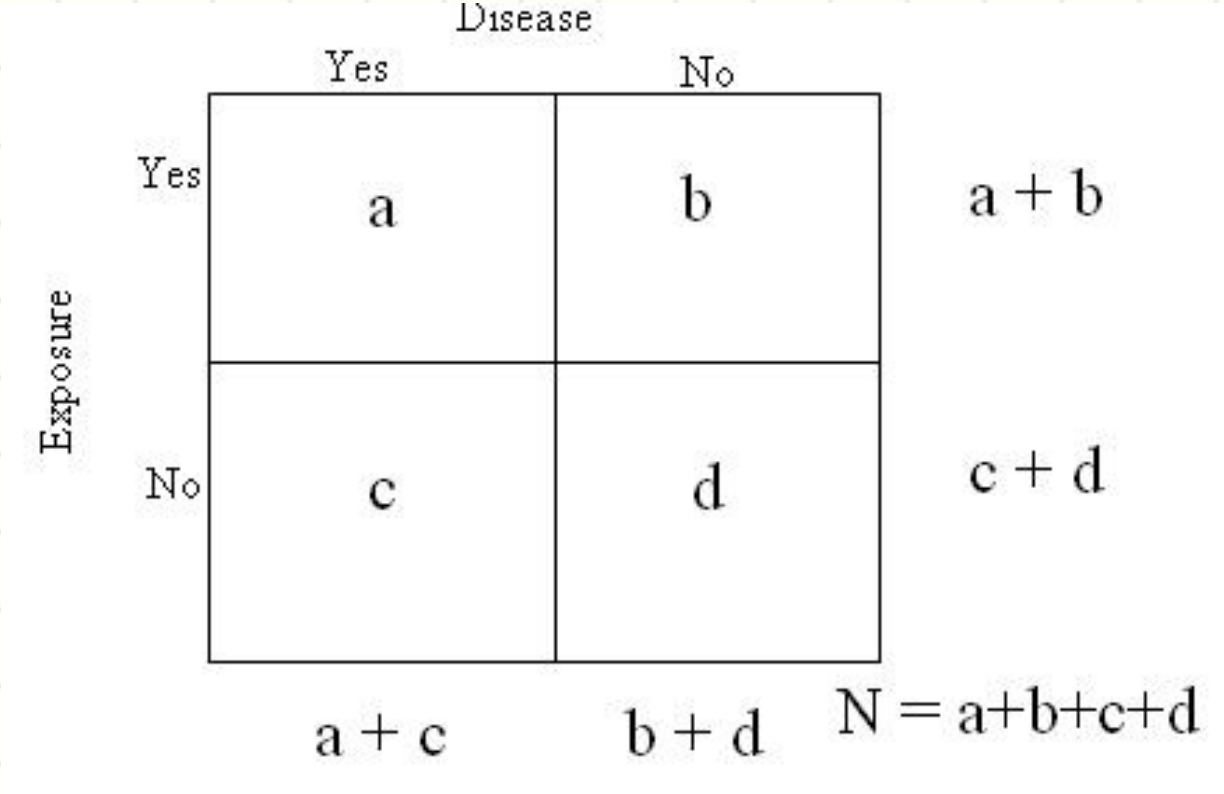
Tempo (anni) -persona

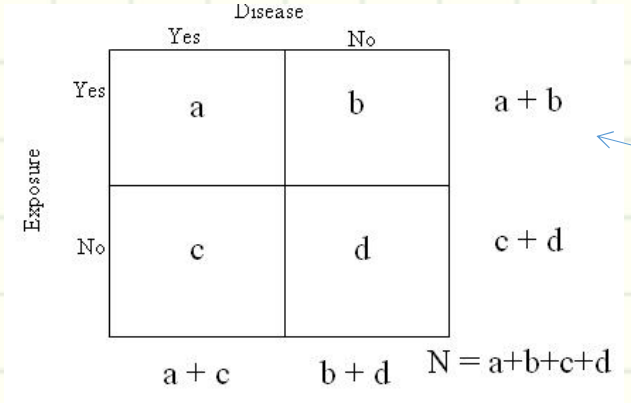


Misure relative o rapporti

- Vengono spesso chiamate complessivamente rischi relativi
- Si calcolano come rapporto tra misure di associazione
- Distinguiamo:
  - Rischio relativo (relative risk) o rapporto tra rischi (risk ratio)
  - Rapporto tra tassi (rate ratio)
  - Odds ratio o rapporto tra odds

Tabella 2x2





Margini della tabella
o valori marginali

- Rischio tra gli esposti

$$p(malattia \mid \exp^{+}) = R(\exp^{+}) = \frac{a}{a+b}$$

- Rischio tra i non esposti

- Rischio relativo $$p(malattia \mid \exp^{-}) = R(\exp^{-}) = \frac{c}{c+d}$$

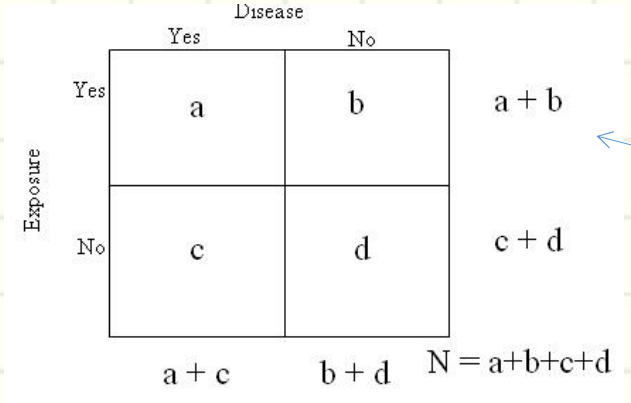
$$RR = \frac{R(\exp^{+})}{R(\exp^{-})}$$

Differenza tra rischi (*RD risk difference*) o riduzione assoluta del rischio (*ARR absolute risk reduction*)

- Al contrario dei rapporti rischio relativo e odds ratio, dipende dal livello di rischio
- *[ad esempio se il rischio negli esposti è 2% e nei non esposti 1% RR=2 ARR=1%; se i rischi fossero 20% e 10% avremmo RR=2 ma ARR=10%]*
- Viceversa una variazione del rischio di una data percentuale si traduce in diversi valori delle misure relative a parità di ARR
- Ha come valore corrispondente alla ipotesi di non effetto lo 0

Quanti trattamenti per prevenire un evento? *(NNT number needed to treat)*

- Nel caso di una esposizione nociva l'equivalente è NNH (*number needed to harm*)
- Si ottiene semplicemente calcolando il reciproco della differenza tra rischi (1/ARR)
- Esprime appunto quante persone devono essere sottoposte ad un intervento (terapeutico o preventivo) per evitare un evento (decesso o malattia)



Margini della tabella
o valori marginali

- Rischio tra gli esposti

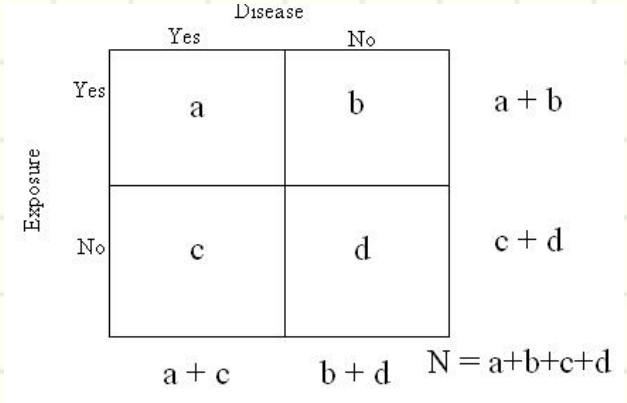
$$p(malattia \mid \exp^{+}) = R(\exp^{+}) = \frac{a}{a+b}$$

- Rischio tra i non esposti

$$p(malattia \mid \exp^{-}) = R(\exp^{-}) = \frac{c}{c+d}$$

- Riduzione assoluta del rischio

$$ARR = R(\exp^{+}) - R(\exp^{-})$$



- Gli odds

$$Odds(\exp^{+}) = \frac{a/a+b}{b/a+b} = \frac{p(malattia^{+} \mid \exp^{+})}{p(malattia^{-} \mid \exp^{+})} = \frac{p(malattia^{+})}{1 - p(malattia^{+})} = \frac{a}{b} = \frac{eventi}{non\_eventi}$$

$$Odds(\exp^{-}) = \frac{c/c+d}{d/c+d} = \frac{p(malattia^{+} \mid \exp^{-})}{p(malattia^{-} \mid \exp^{-})} = \frac{p(malattia^{+})}{1 - p(malattia^{+})} = \frac{c}{d} = \frac{eventi}{non\_eventi}$$

- L'odds ratio

$$OR = \frac{a/b}{c/d} = \frac{a*d}{b*c}$$

Odds e probabilità

- Sono simili se l'evento è raro
- È possibile calcolare la probabilità dagli odds:

  P= odds /1+odds
- Gli odds sono meno intuitivi e quindi più difficili da comprendere rispetto alla probabilità ma egualmente leciti come misure epidemiologiche
- Un modello di analisi multivariabile molto utilizzato per variabili di risposta dicotomiche, la regressione logistica, produce come risultato log odds di evento per le variabile esplicative

Rapporto tra tassi di incidenza

- Il rapporto tra tassi (rate ratio)
- Confronta incidenza, mortalità o in generale la velocità di comparsa di un evento tra esposti e non esposti in uno studio di coorte
- Al denominatore dei tassi c'è la somma del tempo trascorso nel corso dello studio a rischio di subire l'evento per ciascuna delle unità sperimentali
- IL RATE RATIO è spesso INDICATO come RISCHIO RELATIVO (Relative Risk RR)

COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. *Ray WA 2002 Lancet. 2002*

- Results of premarketing and post-marketing trials have raised doubts about the **cardiovascular safety** of the non-steroidal anti-inflammatory drug (NSAID) **rofecoxib**, especially **at doses greater than 25 mg**. Between Jan 1, 1999, and June 30, 2001, **we did a retrospective cohort study** of individuals on the expanded Tennessee Medicaid programme (TennCare), in which we assessed occurrence of serious coronary heart disease (CHD) in non-users (n=202 916) and in users of rofecoxib and other NSAIDs (rofecoxib n=24 132, other n=151 728). Participants were aged 50–84 years, lived in the community, and had no life threatening non-cardiovascular illness.
- Users of high-dose rofecoxib were 1·70 (95% CI 0·98–2·95, p=0·058) times more likely than non-users to have CHD; **among new users this rate increased to 1·93 (1·09–3·42, p=0·024).** By contrast, there was no evidence of raised risk of CHD among users of rofecoxib at doses of 25 mg or less or among users of other NSAIDs.

Table 2. Study events by NSAID*

	Person-years	Events	Rate/1000	Adjusted IRR (95% CI)	p
Non-user	237 975	3085	13·0	1·00	..
Former user	125208	1403	11·2	0·97 (0·90–1·03)	0·294
Current user					
Ibuprofen	16330	190	11·6	0·91 (0·78–1·06)	0·216
Naproxen	21093	245	11·6	0·93 (0·82–1·06)	0·304
Celecoxib	5643	74	13·1	0·96 (0·76–1·21)	0·192
Rofecoxib ≤25 mg	4037	55	13·6	1·03 (0·78–1·35)	0·299
Rofecoxib >25 mg	618	13	21·0	1·70 (0·98–2·95)	0·058
New user during study					
Ibuprofen	4319	52	12·0	1·01 (0·77–1·33)	0·954
Naproxen	6489	72	11·1	0·92 (0·73–1·16)	0·481
Celecoxib	4509	55	12·2	0·88 (0·67–1·16)	0·361
Rofecoxib ≤25 mg	3430	47	13·7	1·02 (0·76–1·37)	0·888
Rofecoxib >25 mg	500	12	24·0	1·93 (1·09–3·43)	0·024

* Does not include 16 872 person years of follow-up and 251 events for other or multiple non-selective NSAIDs.

Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial.

Shahzad A, Kemp I, Mars C,et al.
Lancet. 2014 Nov 22;384(9957):1849-58. Erratum in: Lancet. 2014 Nov 22;384(9957):1848.

- primary percutaneous coronary intervention (PPCI). We aimed to compare antithrombotic therapy with bivalirudin or unfractionated heparin during this procedure
- The **primary efficacy outcome** was a composite of all-cause mortality, cerebrovascular accident, reinfarction, or unplanned target lesion revascularisation. The **primary safety outcome** was incidence of major bleeding

Statistical analysis

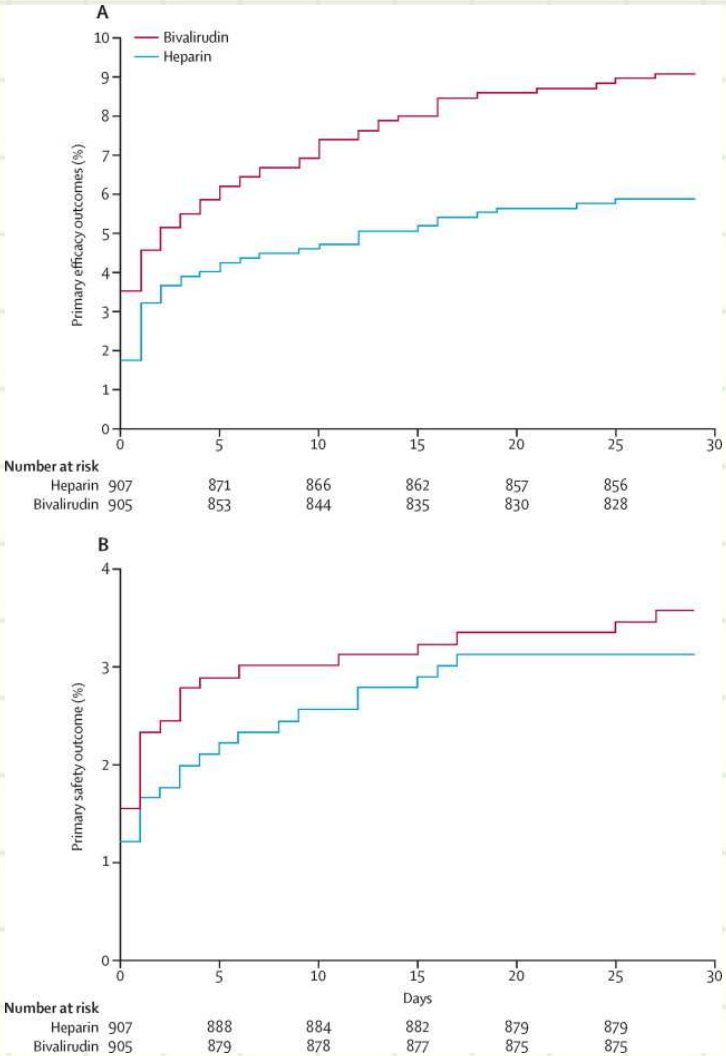
- We did all analyses according to intention to treat and patient data are reported and analysed in the two trial groups as allocated at randomisation.
- We compared categorical data with the χ^2 test (or Fisher's exact test when the absolute number of observed events in any group was five or less). We compared continuous data with the *t* test (or the Wilcoxon test in the case of non-normal data).

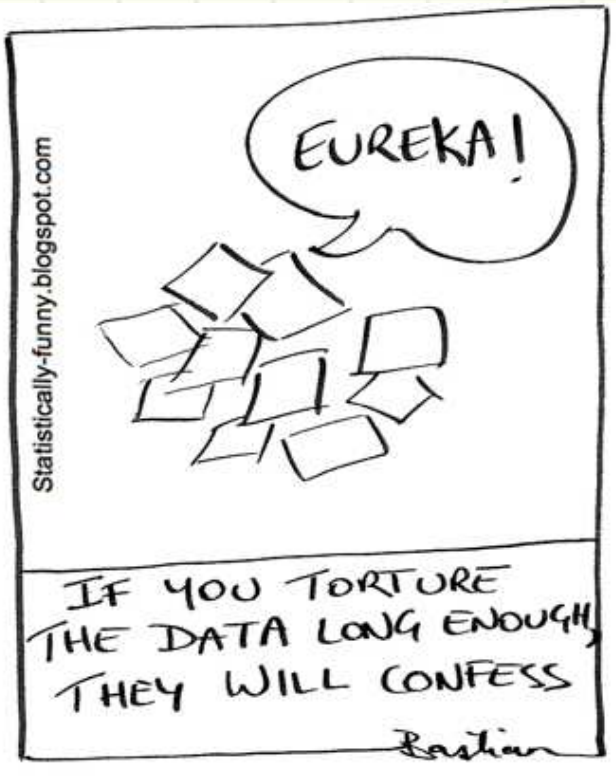
Table 3. Clinical outcomes at 28 days

	Bivalirudin group (n=905)	Heparin group (n=907)	Absolute risk difference (95% CI)	Relative risk (95% CI)	p value
Primary efficacy outcomes measures	79/905 (8·7%)	52/907 (5·7%)	**3·0** (0·6 to5·4)	**1·52** (1·09 to 2·13)	**0·01**
Death	46/905 (5·1%)	39/907 (4·3%)	**0·8** (-1·2 to2·8)	**1·18** (0·78 to 1·79)	0·43
Cerebrovascular accident	15/905 (1·6%)	11/907 (1·2%)	**0·4** (-0·7 to 1·6)	**1·37** (0·63 to 2·96)	0·43
New myocardial infarction or reinfarction	24/905 (2·7%)	8/907 (0·9%)	**1·8** (0·6 to 3·1)	**3·01** (1·36 to 6·66)	**0·004**
Additional unplanned target lesion revascularisation	24/905 (2·7%)	6/907 (0·7%)	**2·0** (0·8 to 3·3)	**4·01** (1·65 to 9·76)	**0·001**
Major bleed (primary safety outcome measure)*	32/905 (3·5%)	28/907 (3·1%)	**0·4** (-1·2 to 2·1)	**1·15** (0·70 to 1·89)	0·59

Conclusions

We showed that use of heparin, rather than bivalirudin, confers significant advantage in the avoidance of major adverse events—principally acute stent thrombosis and associated reinfarction events, with no difference in bleeding.





Gli studi non randomizzati

Role of non-randomized studies

Exclusive non-controversial

- Provide evidence for interventions that cannot be randomized
- Prognostic models; improvements of interventions (e.g. diagnostic technologies)
- Surveillance of rare outcomes

Complementary to RCTs

- Conducted in settings that more closely resemble clinical practice, evaluation of effectiveness
- Address questions of external validity
- Indicate the opportunity of RCTs

Evidence of efficacy of interventions - disputed

- *Evaluation of clinical benefit (i.e. non-randomized experimental studies)*

RCTs vs experimental non-randomized studies

- Concerns about potential bias inherent to nonexperimental studies, particularly due to baseline differences between groups
- Indeed without randomization, even after proper adjustment for relevant confounders, it is not posssible to rule out the presence of bias due to unknown- and thus unmeasured,- confounders
- **Confounding by indication** is a cause of concern: it arises when doctors assign different treatment plans to patients based on perceived patient risk or prognosis

Salas M, Hofman A, Stricker BH. Confounding by indication: an example of variation in the use of epidemiologic terminology. American Journal of Epidemiology 1999; 149 (11):981–983

Confounding by indication remains an often intractable threat to validity in observational studies

Del Bosco J et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. J Clin Epidemiol 2010

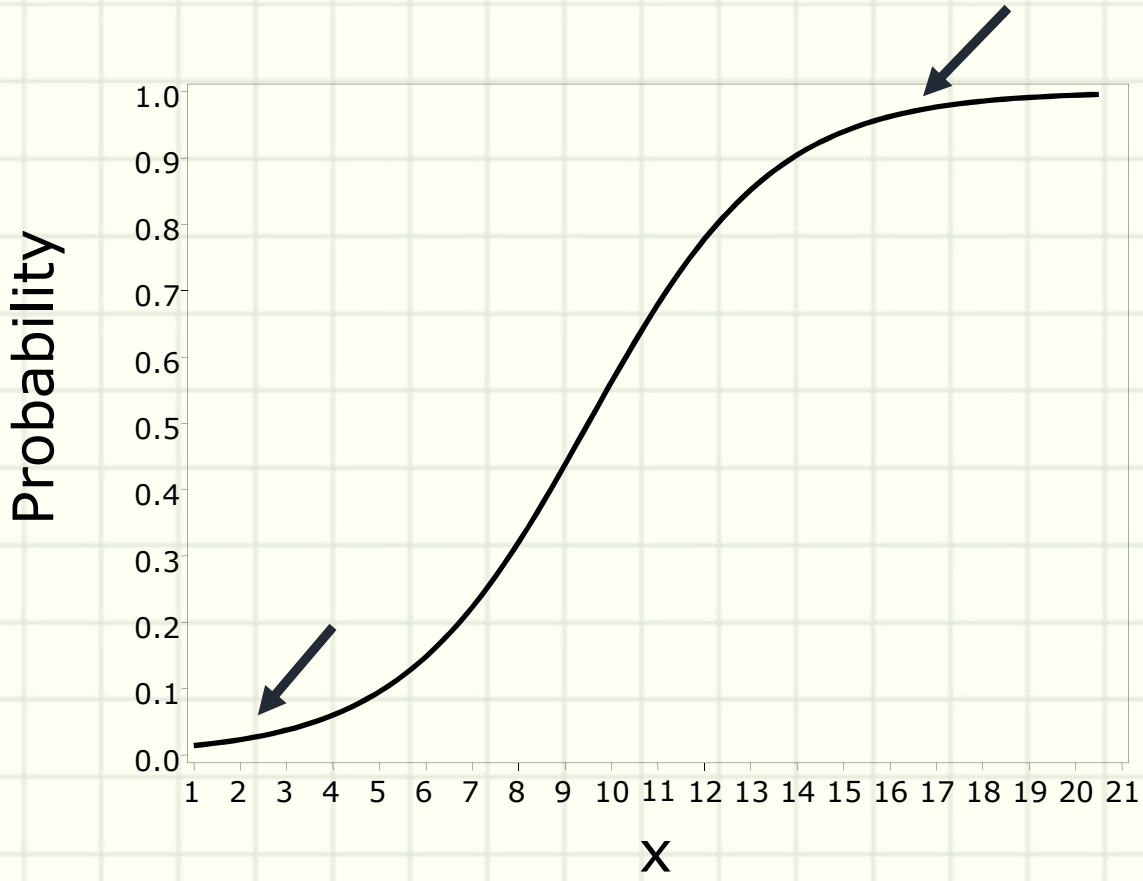
Logistic Regression

- "This is the most important model for categorical response data" – Agresti (Categorical Data Analysis, 2nd Ed.)
- Binary Response
- Predicting Probability (related to the Probit model)
- Assume (the usual):
  - Independence
  - NOT Homoscedasticity or Normal Errors
  - Linearity (in the Log Odds)
  - Also….adequate cell sizes.

Logistic Regression

- The Model
  - $\Pr(y = 1|x) = \frac{e^{\alpha+\beta x}}{1+e^{\alpha+\beta x}}$
    - In terms of probability of success π(x)
  - $\log \frac{\Pr(y = 1|x)}{1-\Pr(y = 1|x)} = \alpha + \beta x$
    - In terms of Logits (Log Odds)
    - Logit transform gives us a linear equation

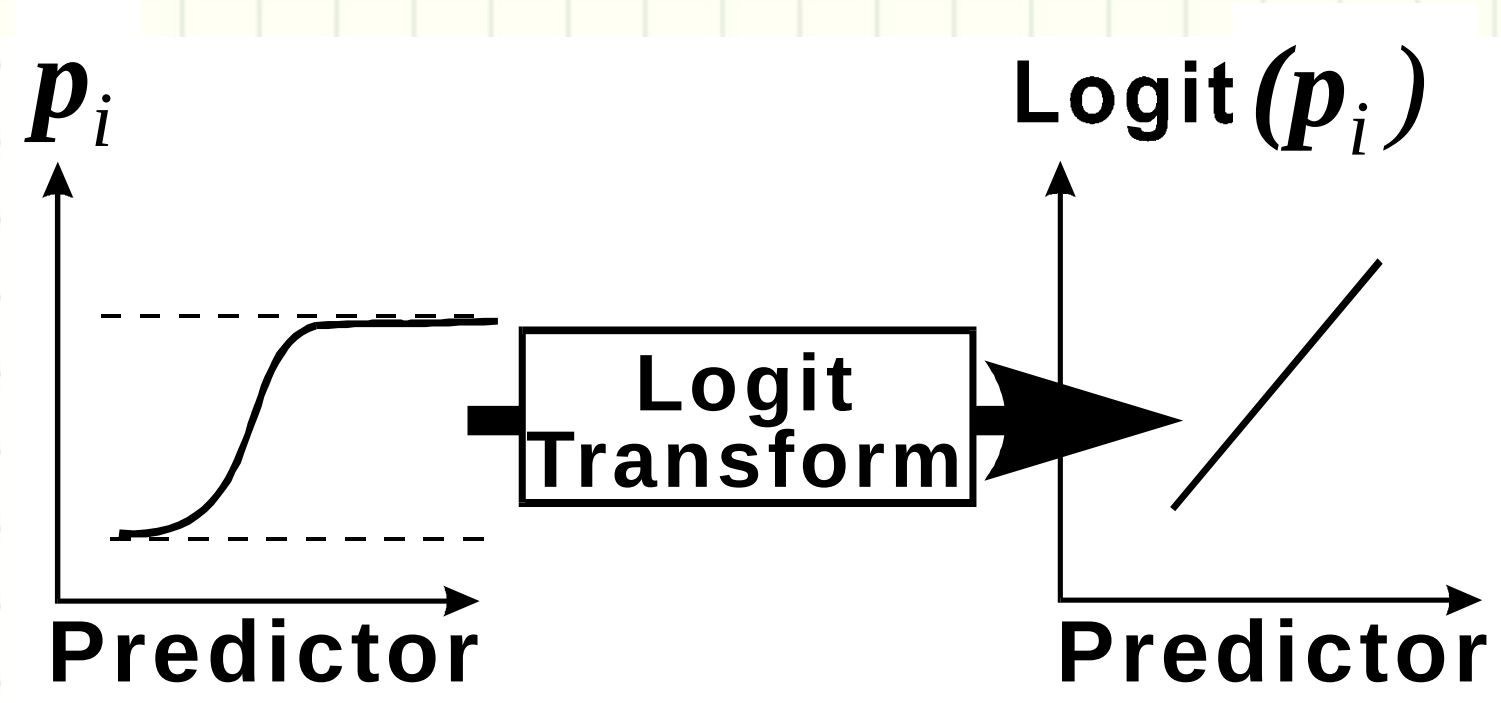
Logistic Regression Curve



This is a nonlinear model:

A given change in x will often have less impact when Pr(y=1|x) is close to the extremes (0 or 1) compared to middle values

Log-lineare



Colorectal cancer surgery 30 day mortality

- Mortality after surgical resection for colorectal cancer.
- Description: Proportion of patients with colorectal cancer who die within 30 days of emergency or elective surgical resection
- Much variation exists in the way CRC is managed
- Thirty-day mortality has conventionally been used to reflect perioperative outcome. Published 30-day and 1-year mortality rates after colorectal surgery range from 3·0 to 4·9 per cent (UK), and from 8·8 to 12·4 per cent, respectively

Methods

- Of the 5,979 cases, all the variables have a low number of missing, not higher than 3.9% as in marital status. Analysis restricted to patients with complete data would have allowed postoperative mortality to be assessed in 5,497 (91.9%) patients, preventing trust-level comparisons. Such estimates would also be at risk of bias with inflated standard errors. Missing data for tumor' stage, SED index and grading category were imputed using a multivariate imputation by chained equations (MICE in Stata Version 14) approach to handle missing values.
- The logistic regression models ware estimated using the imputed datasets according to Rubin's rule and used to investigate the associations of sociodemographic, tumour and treatment characteristics with 30-day mortality.

Odds ratios of death at 30 day – person variables

	Unadjusted		Sociodemographic		Complete		Complete (- screening)	
	OR	95% IC	OR	95% IC	OR	95% IC	OR	95% IC
Age								
<65	Ref.		Rif.		Rif.		Rif.	
65-74	**1.65**	(1.30 - 2.08)**	**1.56**	(1.25-1.93)**	**1.53**	(1.22-1.92)**	**1.65**	(1.21-2.26)**
75-84	**5.46**	(4.90 - 6.08)**	**4.73**	(4.27-5.23)**	**4.46**	(4.02-4.94)**	**4.59**	(3.75-5.62)**
>85	**17.65**	(14.04 - 22.19)**	**13.69**	(10.74-17.46)**	**12.19**	(9.05-16.42)**	**12.62**	(8.50-18.72)**
CCI								
0	Ref.		Rif.		Rif.		Rif.	
1	1.60	(1.21 - 2.11)**	1.30	(0.90-1.86)	1.27	(0.97-1.67)	1.16	(0.88-1.54)
2	1.23	(1.00 - 1.52)	1.00	(0.73-1.38)	0.96	(0.73-1.26)	0.93	(0.75-1.15)
≥3	**2.98**	(2.67 - 3.32)**	**1.90**	(1.74-2.07)**	**1.82**	(1.68-1.97)**	**1.77**	(1.64-1.90)**
Marital Status								
Married	Ref.		Rif.		Rif.		Rif.	
Single	**2.07**	(1.40 - 3.07)**	**1.51**	(1.04-2.21)*	**1.44**	(0.98-2.13)	**1.46**	(0.97-2.19)
SED								
1(Most affluent)	Ref.		Rif.		Rif.		Rif.	
2	1.17	(0.90 - 1.54)	1.38	(1.00-1.90)	1.38	(1.02-1.87)*	**1.46**	(1.09-1.94)*
3	1.10	(0.87 - 1.39)	1.27	(1.06-1.51)**	1.27	(1.03-1.58)*	**1.38**	(1.09-1.74)**
4(Most deprived)	1.32	(1.02 - 1.71)*	**1.54**	(1.25-1.89)**	**1.48**	(1.27-1.73)**	**1.57**	(1.29-1.91)**

Marginal probability of 30-day mortality by age class

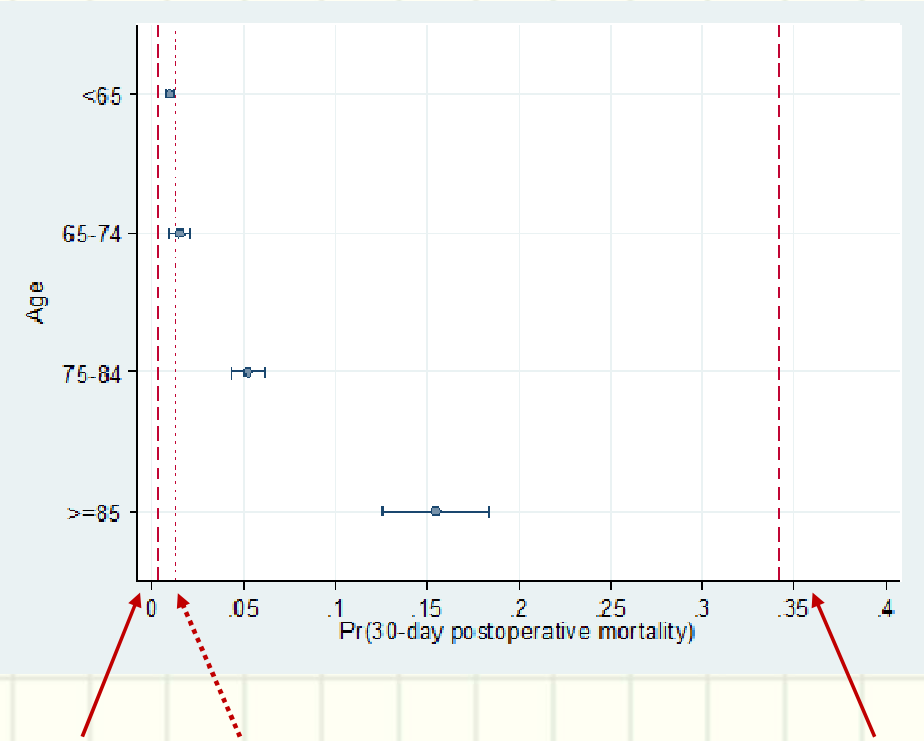
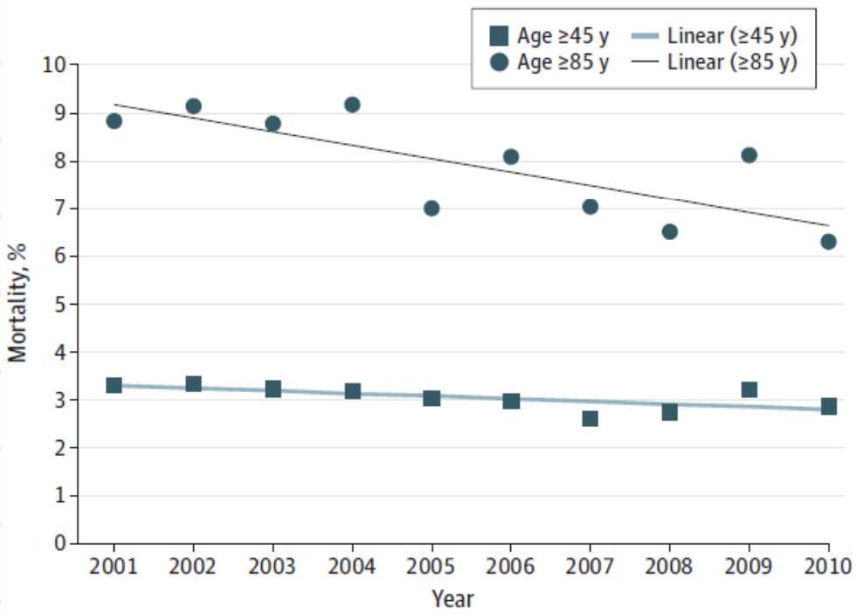


Figure 2. Improved Mortality in the Elderly



Decrease in mortality rates as demonstrated by the linear line comparing patients in the group 85 years and older with the control group (aged 45-64 years).

Colorectal Cancer Resections in the Aging US Population

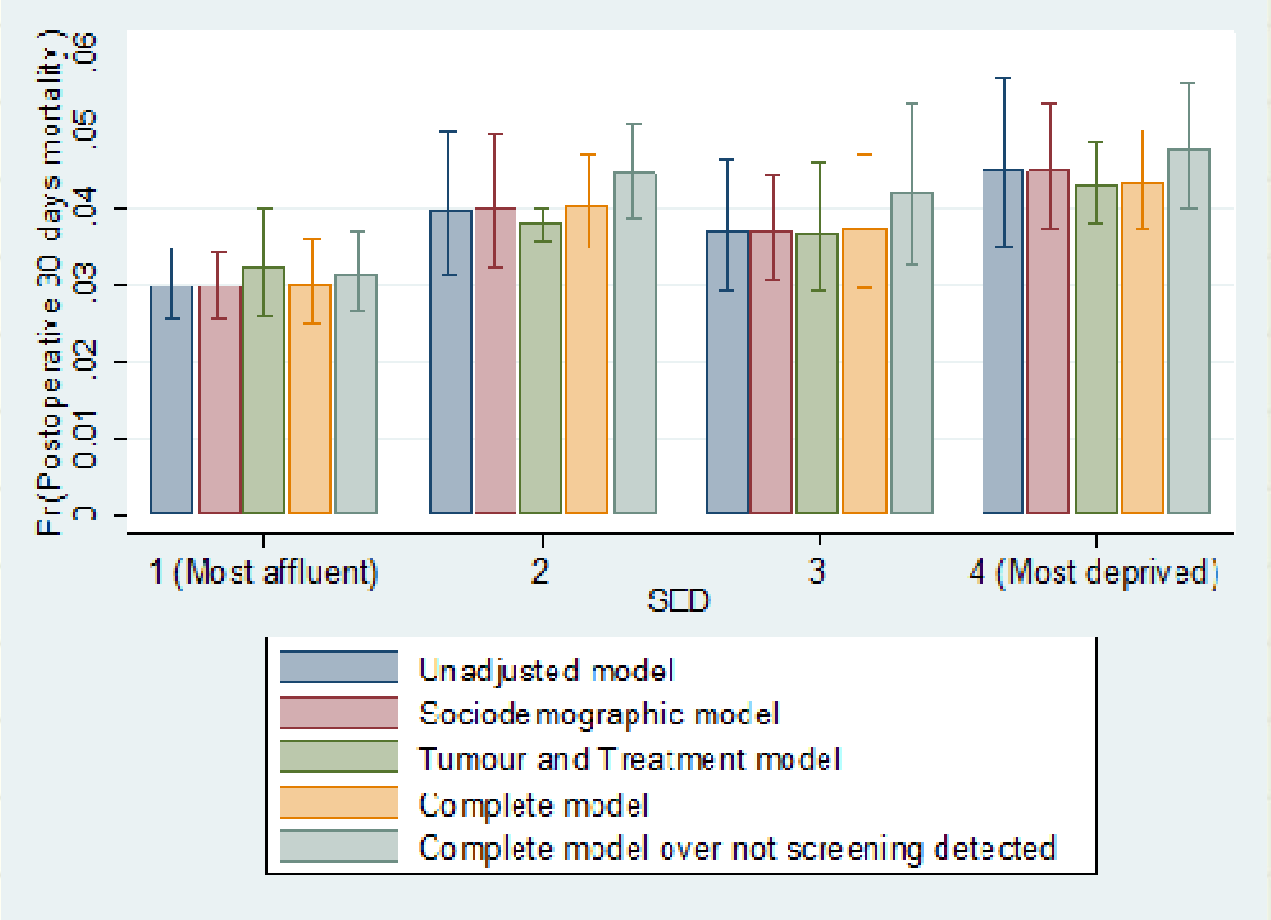
Jafari MD et al. JAMA Surg. 2014;149:557-564

Table 3. Postoperative Outcomes of Patients Undergoing Colorectal Resection in the United States From January 1, 2001, Through December 31, 2010[a]

	Age Group, y					
Outcome	45-64 (n = 377 129)	65-69 (n = 132 807)	70-74 (n = 143 132)	75-79 (n = 154 433)	80-84 (n = 128 686)	≥85 (n = 106 921)
Mortality	1.3	2.0[c]	2.9[c]	3.7[c]	4.9[c]	8.0[c]

A multivariate logistic regression was used to compare in-hospital mortality and morbidity between individual groups of patients 65 years and older and those aged 45 to 64 years while controlling for sex, comorbidities, procedure type, diagnosis, and hospital status

Marginal probability of 30-day mortality by socioeconomic status



Association between socioeconomic status, surgical treatment and mortality in patients with colorectal cancer.

Dik VK et al. Br J Surg. 2014;101:1173-82.

- BACKGROUND: High socioeconomic status is associated with better survival in colorectal cancer (CRC). This study investigated whether socioeconomic status is associated with differences in surgical treatment and mortality in patients with CRC.
- METHODS: Patients diagnosed with stage I-III CRC between 2005 and 2010 in the Eindhoven Cancer Registry area in the Netherlands were included. Socioeconomic status was determined at a neighbourhood level by combining the mean household income and the mean value of the housing.
- RESULTS: Some 4422 patients with colonic cancer and 2314 with rectal cancer were included. **Patients with colonic cancer and high socioeconomic status were operated on with laparotomy** (70·7 versus 77·6 per cent; P = 0·017), had laparoscopy converted to laparotomy (15·7 versus 29·5 per cent; P = 0·008) and developed anastomotic leakage or abscess (9·6 versus 12·6 per cent; P = 0·049) less frequently than patients with low socioeconomic status. These differences remained significant after adjustment for patient and tumour characteristics. In rectal cancer, patients with high socioeconomic status were more likely to undergo resection (96·3 versus 93·7 per cent; P = 0·083), but this was not significant in multivariable analysis (odds ratio (OR) 1·44, 95 per cent confidence interval 0·84 to 2·46). **The difference in 30-day postoperative mortality in patients with colonic cancer and high and low socioeconomic status (3·6 versus 6·8 per cent; P < 0·001) was not significant after adjusting for age, co-morbidities, emergency surgery, and anastomotic leakage or abscess formation (OR 0·90, 0·51 to 1·57)**.
- CONCLUSION: Patients with CRC and high socioeconomic status have more favourable surgical treatment characteristics than patients with low socioeconomic status. The lower 30-day postoperative mortality found in patients with colonic cancer and high socioeconomic status is largely explained by patient and surgical factors.

Table 5 Unadjusted and adjusted odds ratios for 30-day postoperative mortality in patients with colonic cancer

	Odds ratio				
Socioeconomic status	Unadjusted	Adjusted for patient variables*	Adjusted for tumour variables†	Adjusted for surgical variables†§	Adjusted for patient, tumour and surgical variables*†‡§
Low	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Intermediate	0·54 (0·39, 0·76)	0·70 (0·50, 0·99)	0·54 (0·39, 0·76)	0·55 (0·33, 0·91)	0·72 (0·43, 1·21)
High	0·51 (0·35, 0·73)	0·71 (0·49, 1·04)	0·51 (0·35, 0·74)	0·63 (0·37, 1·09)	0·90 (0·51, 1·57)

Values in parentheses are 95 per cent confidence intervals. *Adjusted for age and number of co-morbidities. †Adjusted for disease stage. ‡Adjusted for emergency surgery and anastomotic leak and/or abscess formation. §Includes only patients from 2008.

Table 6 Unadjusted and adjusted odds ratios for 30-day postoperative mortality in patients with rectal cancer

	Odds ratio				
Socioeconomic status	Unadjusted	Adjusted for patient variables*	Adjusted for tumour variables†	Adjusted for surgical variables‡	Adjusted for patient, tumour and surgical variables*†‡
Low	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)	1·00 (reference)
Intermediate	0·67 (0·34, 1·29)	0·95 (0·48, 1·88)	0·67 (0·34, 1·28)	0·55 (0·23, 1·36)	0·86 (0·33, 2·18)
High	0·68 (0·34, 1·35)	1·00 (0·49, 2·04)	0·68 (0·34, 1·36)	0·39 (0·14, 1·10)	0·60 (0·21, 1·76)

Values in parentheses are 95 per cent confidence intervals. *Adjusted for age and number of co-morbidities. †Adjusted for disease stage. ‡Adjusted for anastomotic leak and/or abscess formation.

Odds ratios of death at 30 day – disease variables

	Unadjusted		Tumour and Treatment		Complete		Complete - screening	
	OR	95% IC	OR	95% IC	OR	95% IC	OR	95% IC
Tumour stage								
I	Ref.		Rif.		Rif.		Rif.	
II	2.08	(1.36 - 3.19)**	1.90	(1.33-2.71)**	**1.37**	(1.05-1.79)*	1.24	(0.93-1.65)
III	2.05	(1.36 - 3.10)**	1.83	(1.38-2.45)**	**1.53**	(1.16-2.02)**	1.42	(1.10-1.82)**
IV	2.24	(1.44 - 3.47)**	1.67	(1.23-2.26)**	**1.79**	(1.35-2.36)**	1.60	(1.21-2.11)**
Grading								
1	Ref.		Rif.		Rif.		Rif.	
2	1.18	(0.57 - 2.44)	1.16	(0.66-2.02)	1.01	(0.57-1.79)	1.01	(0.58-1.77)
3	1.81	(1.17 - 2.82)**	1.69	(1.31-2.19)**	**1.40**	(1.08-1.82)*	1.33	(0.98-1.80)
Laterality								
Right Colon	Ref.		Rif.		Rif.		Rif	
Rectum	1.10	(0.88 - 1.37)	1.05	(0.87-1.27)	1.32	(1.17-1.49)**	1.38	(1.19-1.61)**
Left Colon	0.84	(0.81 - 0.86)**	0.86	(0.71-1.04)	1.22	(0.96-1.56)	1.18	(0.93-1.48)

Odds ratios of death at 30 day – treatment variables

	Unadjusted		Tumour and Treatment		Complete		Complete - screening	
	OR	95% IC	OR	95% IC	OR	95% IC	OR	95% IC
Lymph nodes examined								
1-6	2.32	(1.69 - 3.17)**	2.81	(1.74-4.53)**	**2.06**	(1.28-3.32)**	1.98	(1.19-3.30)**
7-11	0.97	(0.69.-1.37)	1.05	(0.70-1.57)	0.83	(0.56-1.23)	0.82	(0.54-1.24)
12+	Ref.		Ref.		Ref.		Ref.	
Operation Type								
Elective	Ref.		Ref.		Ref.		Ref.	
Urgency	1.78	(1.38 - 2.30)**	1.44	(1.11-1.88)**	**1.38**	(1.26-1.51)**	**1.37**	(1.23-1.53)**
Surgical Methods								
Laparoscopy	Ref.		Ref.		Ref.		Ref.	
Laparothomy	**3.65**	(1.90 - 6.99)**	**3.06**	(1.57-5.94)**	**2.28**	(1.28-4.04)**	**2.20**	(1.21-3.98)**
Surgery Type								
Total colectomy	3.06	(1.59 - 5.88)**	2.88	(1.44-5.76)**	**3.08**	(1.75-5.44)**	2.80	(1.67-4.67)**
Partial resection	Ref.		Ref.		Ref.		Ref.	
Transverse resection	1.59	(1.37 - 1.86)**	1.10	(0.87-1.40)	1.43	(0.84-2.47)	1.49	(0.85-2.60)

Comparative effectiveness of laparoscopy vs open colectomy among nonmetastatic colon cancer patients: an analysis using the National Cancer Data Base.

Zheng Z et al. J Natl Cancer Inst. 2015;107(3). pii: dju491

BACKGROUND: Randomized clinical trials showed that laparoscopic colectomy (LC) is superior to open colectomy (OC) in short-term surgical outcomes; however, the generalizability among real-world patients is not clear.

METHODS: The National Cancer Data Base was used to identify stage I-III colon cancer patients age 18 to 84 years in 2010 and 2011. A propensity score analysis with 1:1 matching (PS) was used to avoid the effect of treatment selection bias. Patients were clustered at the hospital level for multilevel regression analyses. The main outcomes measured were 30-day mortality, unplanned readmissions, length of stay (LOS), and initiation of adjuvant chemotherapy among stage III patients. All statistical tests were two-sided.

RESULTS: A total of 45 876 patients were analyzed, 18 717 (41%) LC and 27 159 (59%) OC. After PS matching, there were 18 230 patients in both groups and they were well balanced on their covariables. **Compared with OC, LC showed consistent benefits in 30-day mortality (1.3% vs 2.3 %, odds ratio [OR] = 0.59, 95% confidence interval [CI] = 0.49 to 0.69, P < .001)** and LOS (median 5 vs 6 days, incident rate ratio = 0.83, 95% CI = 0.8 to 0.84, P < .001). LC was also associated with a higher rate of adjuvant chemotherapy use in stage III patients (72.3% vs 67.0%, P < .001). LC was more likely to be performed by high-volume surgeons in high-volume hospitals, but there was no significant effect of the hospital/surgeon volume on short-term outcomes.

CONCLUSION: **In routine clinical practice, laparoscopic colectomy is associated with lower 30-day mortality,** shorter length of stay, and greater likelihood of adjuvant chemotherapy initiation among stage III colon cancer patients when compared with open colectomy.

Propensity Score Analysis

- We anticipated that comparison of the two treatment groups would demonstrate statistical differences by factors (eg, age, comorbidity status, and payer type)
- that were likely to be associated with both the treatment assignment and our outcomes of interest.
- We therefore performed a PS analysis based on all potential predictor variables for LC vs OC and identified two PS matched (1:1) cohorts for the primary comparisons.
- Following PS matching, the distribution of the covariables was fully balanced with 18 230 patients in each group, LC and OC

Table 2. Unmatched and PS matched multilevel regression adjusted outcomes between LC and OC*

	Unmatched				PS Matched			
Outcome	LC (n = 18 717)	OC (n = 27 159)	OR/IRR§ (95%CI)	P†	LC (n = 18 230)	OC (n = 18 230)	OR/IRR (95%CI)	P
Stage I-III patients								
30-day mortality No. (%)	244 (1.30)	766 (2.82)	0.54 (0.47 to 0.63)	<.001	243 (1.33)	420 (2.30)	0.59 (0.49 to 0.69)	<.001
30-day readmission No. (%)	899 (4.80)	1498 (5.52)	0.87 (0.79 to 0.96)	.003	881 (4.83)	412 (5.11)	0.90 (0.81 to 1.00)	.052
LOS, median (IQR)	5 (3 to 6)	6 (4 to 8)	0.82 (0.80 to 0.83)	<.001	5 (3 to 6)	6 (4 to 8)	0.83 (0.80 to 0.84)	<.001
Stage III patients only	LC (n = 6450)	OC (n = 10 529)	---	P	LC (n = 6395)	OC (n = 6454)	---	P
Adjuvant chemotherapy initiation No. (%)	4669 (72.39)	6828 (64.85)	---	<.001	4,622 (72.27)	4324 (67.00)	---	<.001
Initiated within 8 wks No. (%)	3661 (56.76)	4937 (46.89)	---	<.001	3,623 (56.65)	3199 (49.57)	---	<.001

* All statistical tests were two-sided. Full details of all other patient-level variables results from the multilevel regression are available in tables 3 and 4. CI = confidence interval; IQR = interquartile range; IRR = incident rate ratio; LC = laparoscopic colectomy; OC = open colectomy; OR = odds ratio; PS = propensity score.
† P values derived from adjusted multilevel regressions.
§ Referent = OC.

Propensity score

- First analysis uses treatment assignment as outcome
- A predicted propensity score is calculated for all experimental units
- The second analysisis is carried out on the study health outcomes :

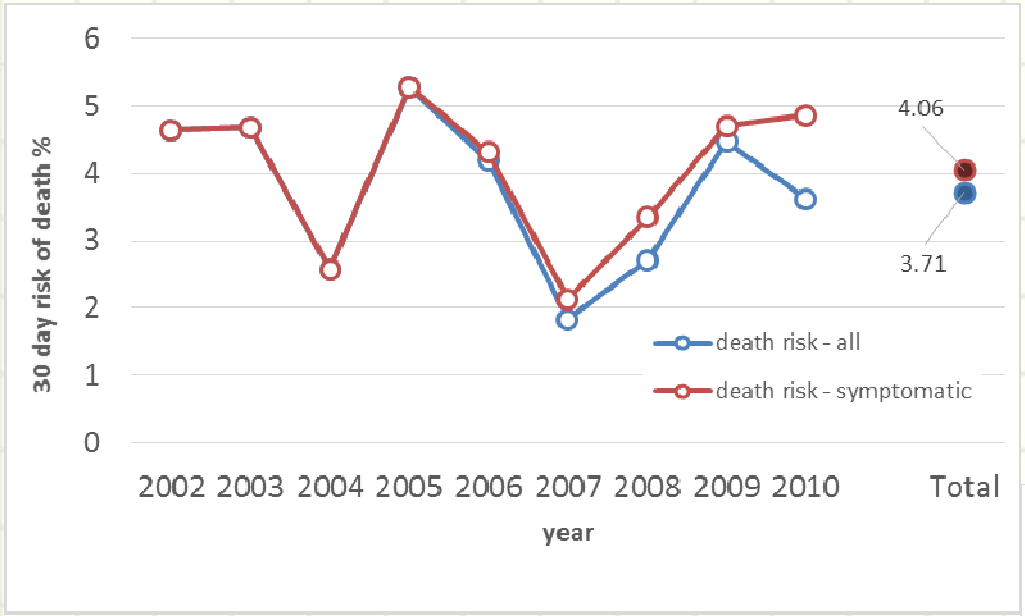
Three different possibilities:

- Propensity stratified
- Propensity adjusted
- **Propensity matched**

Laparoscopy for rectal cancer is oncologically adequate: a systematic review and meta-analysis of the literature. Arezzo A. et al. Surg Endosc. 2015

- BACKGROUND:
- This review of cancer outcomes is based on key literature searches of the medical databases and meta-analysis of short-term benefits of laparoscopy in rectal cancer treatment.
- METHODS:
- We carried out a systematic review of randomized clinical trials (RCTs) and prospective non-randomized controlled trials (non-RCTs) published between January 2000 and September 2013 listed in the MEDLINE and EMBASE databases (PROSPERO Registration number: CRD42013005076). The primary endpoint was clearance of the circumferential resection margin. Meta-analysis was performed using a fixed-effect model, and sensitivity analysis by a random-effect model; subgroup analysis was performed on subsets of patients with extraperitoneal cancer of the rectum. Relative risk (RR) and mean difference (MD) were used as outcome measures.
- RESULTS:
- Twenty-seven studies (10,861 patients) met the inclusion criteria; eight were RCTs (2,659 patients). The RCTs reported involvement of the circumferential margin in 7.9 % of patients who underwent laparoscopic and in 6.9 % of those undergoing open surgery; the overall RR was 1.00 (95 % confidence interval 0.73-1.35) with no heterogeneity. Subgroup analysis of patients with extraperitoneal cancer showed equivalent involvement of the circumferential margin in the two treatment groups. Although significantly more lymph nodes were retrieved in the surgical specimen after open surgery, the MD of -0.56 was of marginal clinical significance. The sensitivity and subgroup analyses revealed no other significant differences between laparoscopic and open surgery in the rate of R0 resections, distal margin clearance, mesorectal fascia integrity, or local recurrence at 5 years.
- CONCLUSIONS:
- **Based on the evidence from RCTs and non-RCTs,** the short-term benefit and oncological adequacy of laparoscopic rectal resection appear to be equivalent to open surgery, with some evidence potentially pointing to comparable long-term outcomes and oncological adequacy in selected patients with primary resectable rectal cancer.

Mortalità a 30 g in Umbria, 2002-2010

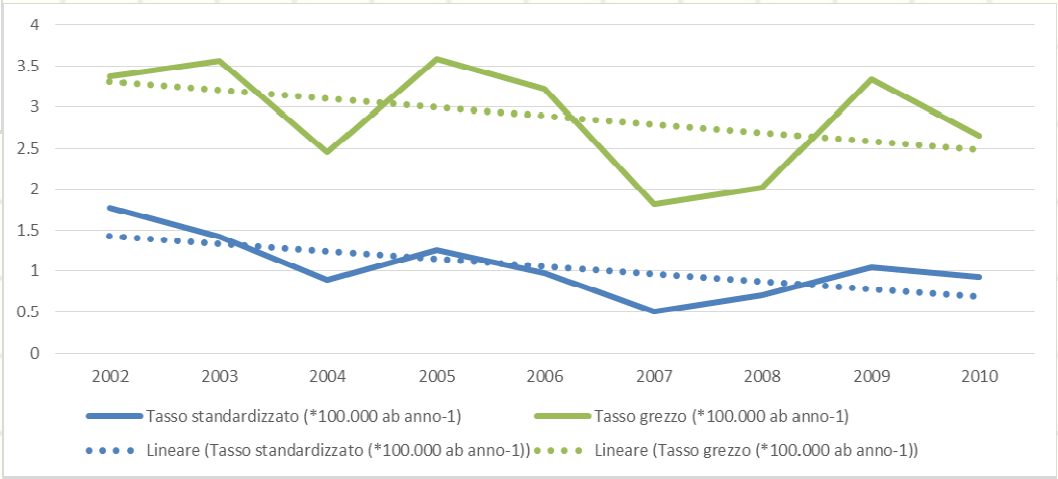


Rischio

- Solo sintomatici
- Tutti

Tasso

- Grezzo
- Standardizzato

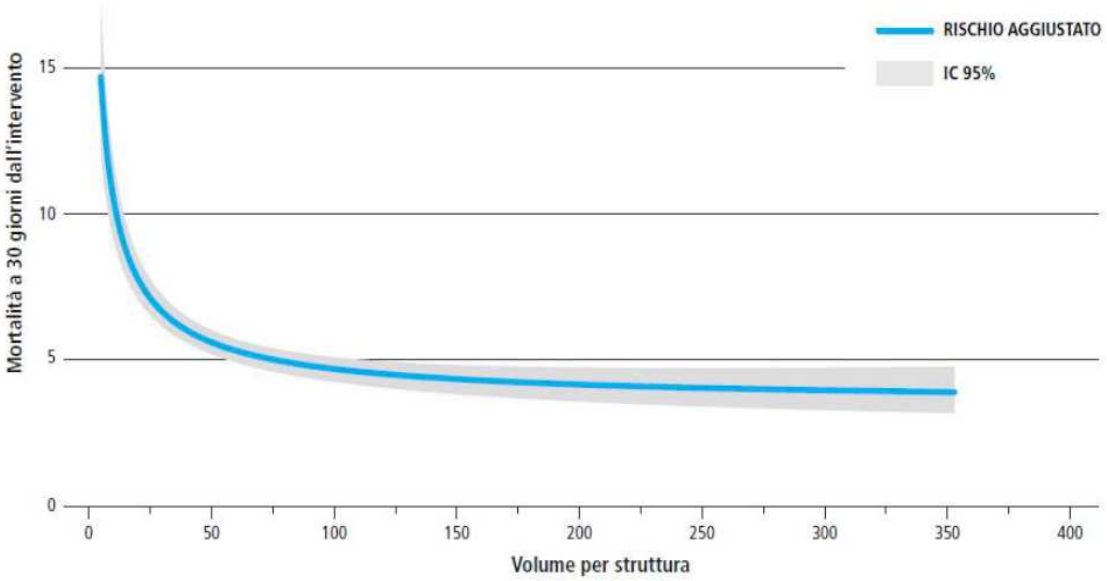


PIANO NAZIONALE ESITI

INTERVENTO CHIRURGICO PER TM COLON: VOLUME DI RICOVERI

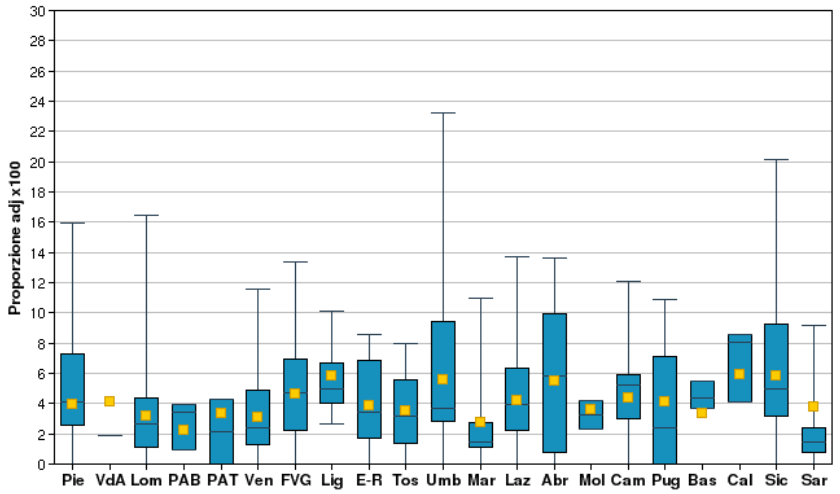
CHIRURGIA DEL CANCRO AL COLON.

ANALISI DELL'ASSOCIAZIONE TRA MORTALITÀ A 30 GIORNI E VOLUME DI ATTIVITÀ PER STRUTTURA

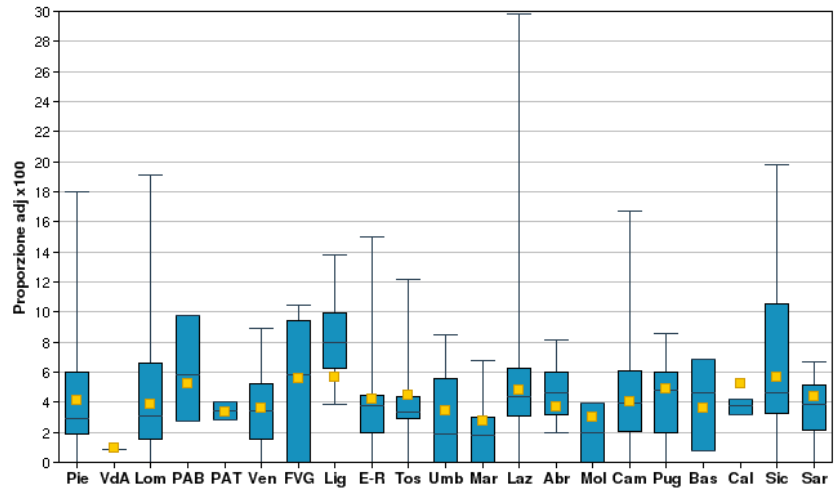


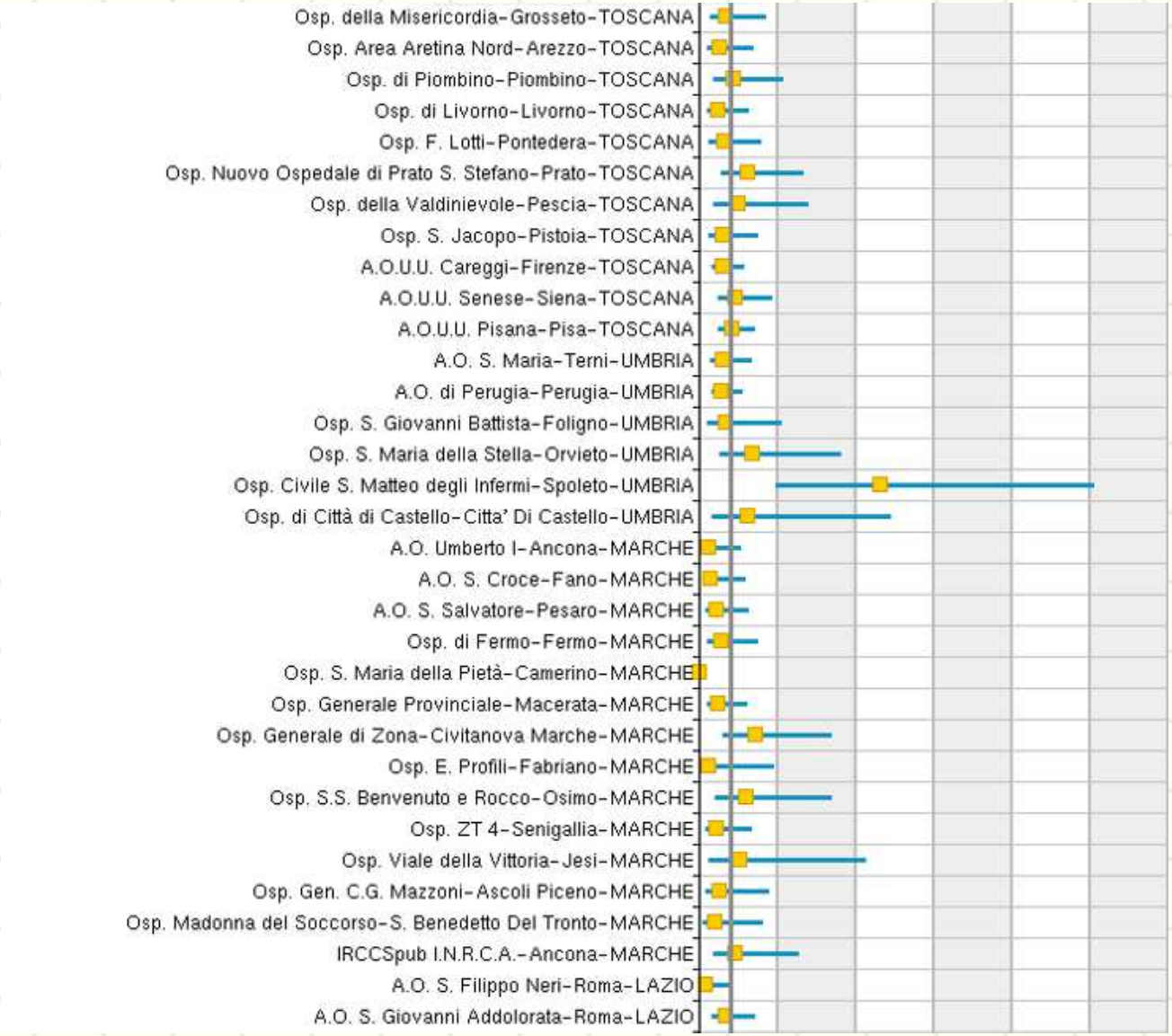
La mortalità a 30 giorni dopo l'intervento diminuisce decisamente fino a raggiungere circa 50-70 interventi/anno e continua a diminuire lievemente all'aumentare del volume di attività.

2014



2011




Osp. della Misericordia-Grosseto-TOSCANA
Osp. Area Aretina Nord-Arezzo-TOSCANA
Osp. di Piombino-Piombino-TOSCANA
Osp. di Livorno-Livorno-TOSCANA
Osp. F. Lotti-Pontedera-TOSCANA
Osp. Nuovo Ospedale di Prato S. Stefano-Prato-TOSCANA
Osp. della Valdinievole-Pescia-TOSCANA
Osp. S. Jacopo-Pistoia-TOSCANA
A.O.U.U. Careggi-Firenze-TOSCANA
A.O.U.U. Senese-Siena-TOSCANA
A.O.U.U. Pisana-Pisa-TOSCANA
A.O. S. Maria-Terni-UMBRIA
A.O. di Perugia-Perugia-UMBRIA
Osp. S. Giovanni Battista-Foligno-UMBRIA
Osp. S. Maria della Stella-Orvieto-UMBRIA
Osp. Civile S. Matteo degli Infermi-Spoleto-UMBRIA
Osp. di Città di Castello-Citta' Di Castello-UMBRIA
A.O. Umberto I-Ancona-MARCHE
A.O. S. Croce-Fano-MARCHE
A.O. S. Salvatore-Pesaro-MARCHE
Osp. di Fermo-Fermo-MARCHE
Osp. S. Maria della Pietà-Camerino-MARCHE
Osp. Generale Provinciale-Macerata-MARCHE
Osp. Generale di Zona-Civitanova Marche-MARCHE
Osp. E. Profili-Fabriano-MARCHE
Osp. S.S. Benvenuto e Rocco-Osimo-MARCHE
Osp. ZT 4-Senigallia-MARCHE
Osp. Viale della Vittoria-Jesi-MARCHE
Osp. Gen. C.G. Mazzoni-Ascoli Piceno-MARCHE
Osp. Madonna del Soccorso-S. Benedetto Del Tronto-MARCHE
IRCCSpub I.N.R.C.A.-Ancona-MARCHE
A.O. S. Filippo Neri-Roma-LAZIO
A.O. S. Giovanni Addolorata-Roma-LAZIO

Volumi ed esiti

VOLUME DI ATTIVITÀ OSPEDALIERA

ESITO		MORTALITÀ OSPEDALIERA O A 30 GIORNI	SOPRAVVIVENZA TOTALE E A 2/5 ANNI
n. studi (n. partecipanti)		19 (871.976)	7 (206.945)
n. studi con associazione positiva (n. partecipanti)		10 (577.259)	4 (154.276)
Cut-off ad alto volume (casi/anno)	range:	62-668 *	86-138 **
	media:	196	110,6
	mediana:	117	110
Metanalisi		Archampong 2012	Archampong 2012
n. studi (n. partecipanti)		8 (569.997)	2 (10.572)
Odds Ratio (IC95%)		0,90 (0,79-1,03)	0,97 (0,77-1,22)
Cut-off ad alto volume (casi/anno)		62	40
Metanalisi		Van Gijn 2010	Van Gijn 2010
n. studi (n. partecipanti)		5 (252.973)	4 (141.666)
Odds Ratio (IC95%)		0,88 (0,71-1,09)	0,91 (0,87-0,96)
Cut-off ad alto volume (casi/anno)		126	85
Metanalisi		Gruen 2009	Iversen 2006
n. studi (n. partecipanti)		13 (575.235)	3 (28.080)
Odds Ratio (IC95%)		0,90 (0,88-0,92)	1,22 (1,16-1,28)
Cut-off ad alto volume (casi/anno)		175	18
Metanalisi		Iversen 2006	
n. studi (n. partecipanti)		9 (271.836)	
Odds Ratio (IC95%)		0,64 (0,55-0,73)	
Cut-off ad alto volume (casi/anno)		41	

* Dato mancante per 9 studi / *Missing data from 9 studies*
** Dato mancante per 2 studi / *Missing data from 2 studies*

Epidemiol Prev 2013; 37(2-3) suppl 1: 1-100

CHIRURGIA DEL CANCRO AL COLON.
ANALISI DELL'ASSOCIAZIONE TRA MORTALITÀ A 30 GIORNI E VOLUME DI ATTIVITÀ PER STRUTTURA

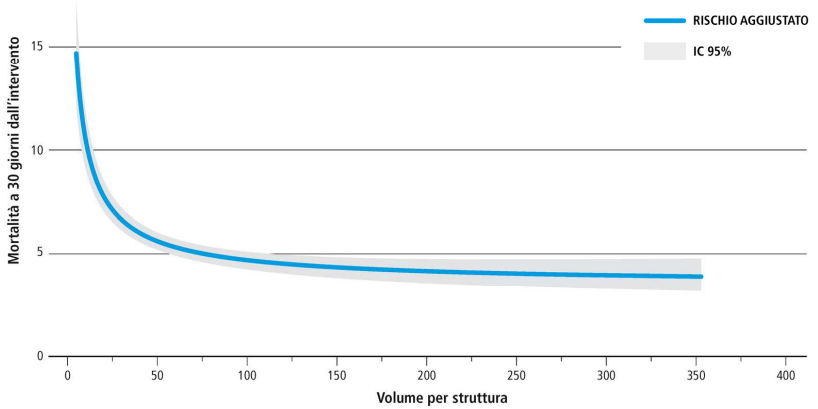


Tabella 7. Chirurgia del cancro al colon; risultati della revisione sistematica.
Table 7. Surgery for colon cancer; systematic review results.

Risk factors for relapse after conservative treatment in T1–T2 breast cancer with one to three positive axillary nodes: results of an observational study

C. Aristei[1,2*], C. Leonardi[3], F. Stracci[4], I. Palumbo[1,2], A. Luini[5], G. Viale[6,7], E. G. Cristallini[8], A. Cavaliere[9,2] & R. Orecchia[3,7]

[1]Department of Surgical, Radiological and Odontostomatological Sciences, Radiation Oncology Section, University of Perugia, Perugia; [2]Ospedale Santa Maria della Misericordia, Perugia; [3]Radiation Oncology, European Institute of Oncology, Milano; [4]Department of Surgical and Medical Specialties and Public Health, University of Perugia, Perugia; [5]Division of Senology, European Institute of Oncology, Milano; [6]Division of Senology, European Institute of Oncology, Milano; [7]University of Milano, Milano; [8]Division of Pathological Anatomy, Ospedale San Giovanni Battista, Foligno; [9]Department of Experimental Medicine and Biochemical Sciences, Institute of Pathological Anatomy, University of Perugia, Perugia, Italy

Received 23 July 2010; accepted 26 July 2010

Background: As few data are available on irradiation of the draining nodes after conservative surgery (CS), this study was designed to identify patients with T1–T2 breast cancer and one to three positive axillary nodes who needed regional radiotherapy (RT).

Patients and methods: Five hundred seventy-five patients were treated between 1988 and 2001 with CS and RT to the breast. All but three received adjuvant chemotherapy and/or hormone therapy. Risk factors for and the relationships between local, nodal and distant relapses were analyzed.

Results: At a median follow-up of 7.3 years, the 10-year probability of survival free of local relapse, nodal relapse and distant metastases were 92.8%, 94.0% and 84.9%, respectively. Independent predictors of local relapse were the positive/excised node ratio, margin status and age. Predictors of nodal relapse were tumor grade, hormone receptor and margin status. Significant risk factors for distant metastases were tumor stage, grade, hormone receptor and margin status. Local and nodal relapses were related significantly with distant metastases. Only local and distant relapses were linked by temporal sequence ($P = 0.03$).

Conclusions: Overall relapse rates were low in these patients and different mechanisms appeared to underlie local, nodal or distant relapse.

Statistical analysis

- Unadjusted and multivariate analyses were carried out using the Cox regression model. The effect of each factor was expressed as hazard ratio (HR) with 95% confidence intervals (CIs).
- To deal with missing data and make the best of available information, a regression switching approach to multiple imputation (MI) was used [25, 26]. MI relies on the assumption that missing values depend on other variables in the dataset [missing at random (MAR)]. MI encompasses estimating of n complete datasets and pooling in one easy-to-use procedure. Hazard rates were estimated on 10 imputed complete datasets.
- Data were also analyzed by complete cases and missing indicator models [27].

Factor	Distant		
	HR	95% CI L–U	*P*
Tumor stage			
T2	1.9	1.2–3.2	0.009
Tx	0.97	0.13–7.0	0.97
Histology			
Ductal G3	3.0	1.8–4.9	0.000
Carcinoma NOS	1.8	0.64–5.2	0.26
EIC			
Present	1.4	0.84–2.4	0.2
Not assessed	2.6	1.1–6.2	0.03
Multifocality			
Present	1.3	0.61–2.5	0.6
Not assessed	2.3	1.04–5.1	0.04
Lymphovascular invasion			
Present	1.8	1.1–2.9	0.03
Hormonal receptor status			
At least one positive type	0.31	0.18–0.51	0.000
Undetermined	0.62	0.24–1.6	0.33
Resection margin status			
Positive or close	2.2	1.15–4.2	0.02
Age	0.98	0.95–0.99	0.03
Nodal ratio[c]	1.004	1.0–1.01	0.07

Table 5. Cox model fitted to imputed data for distant metastasis

Outcome distant metastases		HR	95% CI L–U	*P*
Tumor grade	(ref. G1–G2)			
G3		2.1	1.3–3.6	0.005
Hormonal receptor status	(ref. both negative)			
ER+ and/or PR+		0.43	0.24–0.77	0.004
Resection margins	(ref. negative)			
Positive or close		2.6	1.3–5.0	0.007
Tumor stage	(ref. T1)			
T2		1.8	1.2–2.8	0.003

CI, confidence interval; HR, hazard ratio; L, lower limit; U, upper limit; ER, estrogen receptor; PR, progesterone receptors.

- Questo modello assume che le covariate non dipendano dal tempo
- Il rischio $\lambda(t)$ dipende sia dal tempo che dalle covariate, ma attraverso 2 fattori separati:
  - $\lambda_0(t)$ è una funzione del solo tempo; è arbitraria, ma è la stessa per tutti i soggetti
  - $\exp(\beta' \mathbf{x}_i)$ dipende dalle K covariate individuali unicamente attraverso il vettore β' dei coefficienti di regressione
- Non è un modello totalmente parametrico in quanto non viene specificata la forma del rischio basale $\lambda_0(t)$
  - Questo è un vantaggio, se non sono possibili assunzioni ragionevoli circa la forma del rischio basale

- Siano due individui con vettori di covariate **x** e **0**: $\lambda_0(t)$ può essere considerato il **rischio basale**

$$\frac{\lambda(t,x)}{\lambda(t,0)} = \frac{\lambda_0(t)\exp(\beta' x)}{\lambda_0(t)} = \exp(\beta' x)$$

- $\exp(\beta' x)$ rappresenta il rischio relativo di presentare l'evento terminale per un soggetto con covariate **x** rispetto ad un soggetto con covariate nulle, sotto l'ipotesi di rapporto dei rischi costante nel tempo

- Le assunzioni sono legate alla formulazione del modello
  - Rischi **proporzionali**: per 2 individui qualsiasi il rapporto dei rischi è costante nel tempo - analogamente, la differenza del logaritmo dei rischi è costante nel tempo
    - $\exp(\beta x)$ non è una funzione del tempo
  - Le covariate hanno un effetto **moltiplicativo** sul rischio
    - $\exp(\beta x)$ è il fattore moltiplicativo; oppure il log del rischio basale aumenta di un valore costante ad ogni aumento di 1 unità della covariata

Multiple Imputation model

- In our cohort, multivariate analysis using the MI approach seems better than complete case analysis and indicator missing method [27], which are commonly used when a low percentage of data is missing.
- MI solved the perfect separation problem that was present in the missing indicator model and
- included hormone receptor status among significant predictors that was not included in the complete case analysis for distant metastases.

Definitions: Types of Missing Data

- Missing completely at random (MCAR): The probability of having a missing value is unrelated to the respondent's other characteristics

- Missing at random (MAR): The probability of having a missing value is conditional on the respondent's other observed characteristics

- Missing not at random (MNAR): The probability of having a missing value depends on the respondent's other unobserved characteristics

Mancanti benigni e mancanti selvaggi

There are **many types of missing data and different reasons for data being missing**. Both issues affect the analysis. Some examples are:

- (1) In a postal questionnaire survey not all the selected individuals respond;
- (2) In a randomised trial some patients are lost to follow-up before the end of the study;
- (3) In a multicentre study some centres do not measure a particular variable;
- (4) In a study in which patients are assessed frequently some data are missing at some time points for unknown reasons;
- (5) Occasional data values for a variable are missing because some equipment failed;
- (6) Some laboratory samples are lost in transit or technically unsatisfactory;
- (7) In a magnetic resonance imaging study some very obese patients are excluded as they are too large for the machine;
- (8) In a study assessing quality of life some patients die during the follow-up period.

- an observation is missing is unrelated both to the unobserved value (and hence to patient outcome) and the data that are available this is called “missing completely at random.” Cases 5 and 6
- data are missing in a predictable way that does not depend on the missing value itself but which can be predicted from other data—as in case 3. Confusingly, this is known as “missing at random.”
- the missing data probably depend on unobserved values, called “missing not at random,” and hence their lack may lead to bias. Cases 1 and 2

Conventional methods and their failings

- Listwise deletion – If data are MCAR, estimates will be unbiased but we loose efficiency – If data are not MCAR, estimates may be biased

- Dummy indicator for missing data – Simulation studies have demonstrated that this method routinely provides biased estimates, even when data are MCAR

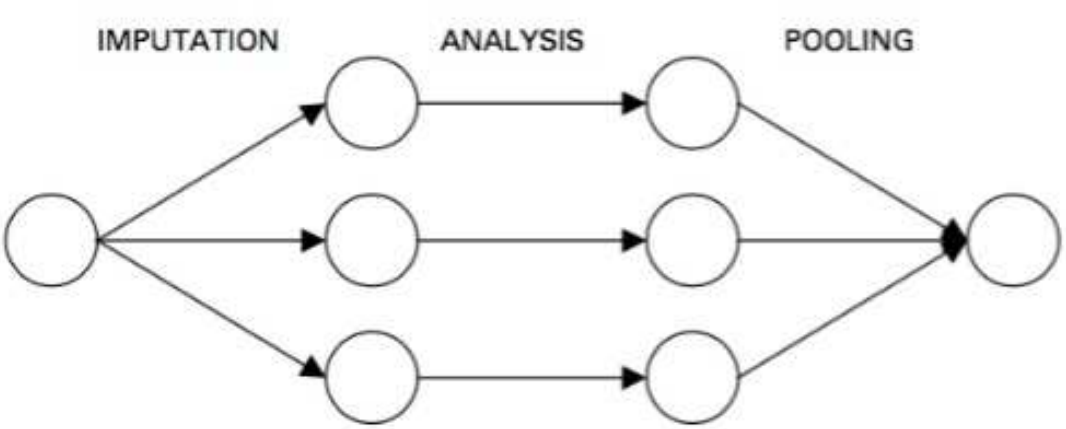
MI

- MI uses one model to create the multiple imputed data sets
  - MI models are iterative and stochastic models
- Each imputed value includes stochastic variation based on the variability in the posterior distribution of the estimate and the residuals
  - Thus, the imputed values vary across each of the MI data set
- MI relies on the MAR assumption; a weaker assumption than MCAR

Estimation requires a second model

- We estimate our substantive model using standard methods, in each data set
- Combine our results from each data set using standard methods

Schematizzazione del procedimento di imputazione



$f(\mathbf{Y}_{\text{mis}}|\mathbf{Y}_{\text{obs}})$ Impute based on missing data model

$f(Q|\mathbf{Y}_{\text{obs}}, \mathbf{Y}_{\text{mis}})$ Outcome model using complete data

$\int \mathrm{d}\mathbf{Y}_{\text{mis}}$ "Integrate" over imputed datasets

$f(Q|\mathbf{Y}_{\text{obs}})$ What you get

$$f(Q|\mathbf{Y}_{\text{obs}}) = \int f(Q|\mathbf{Y}_{\text{obs}}, \mathbf{Y}_{\text{mis}}) f(\mathbf{Y}_{\text{mis}}|\mathbf{Y}_{\text{obs}}) \mathrm{d}\mathbf{Y}_{\text{mis}}$$

Little 2002

Procedimento di imputazione

Observed					
Y	x1	xm	x3	…	xn
10	1	4.2	0		18
11	3	8	1		21
21	2	5	1		22
10	6		1		22.5
20	7		0		18

m(1)					
Y(imp)	xm	ximp 1	ximp 2	…	ximp n
10	4.2	1	0		18
11	8	3	1		21
21	5	2	1		22
10	**2**	6	1		22.5
20	**1.5**	7	0		18

m(2)					
Y(imp)	xm	ximp 1	ximp 2	…	ximp n
10	4.2	1	0		18
11	8	3	1		21
21	5	2	1		22
10	**3.2**	6	1		22.5
20	**2**	7	0		18

…

m(n)					
Y(imp)	xm	ximp 1	ximp 2	…	ximp n
10	4.2	1	0		18
11	8	3	1		21
21	5	2	1		22
10	**3.2**	6	1		22.5
20	**2**	7	0		18

Variabili utilizzate per predire i valore mancanti

MICE (Multiple Imputation by Chained Equation)

(White, I. R., P. Royston, and A. M. Wood. 2011. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine 30: 377—399.)

- In a large data set, missing values are often observed in more than one variable with an arbitrary pattern
- Two approaches to handle arbitrary missing values:
  - Joint modeling (JM): a multivariate normal distribution of all variables (parametric)
  - MICE (a.k.a. fully conditional specification): a series of conditional distributions, one for each missing variable (semi-parametric)

- MICE becomes popular due to the flexibility
  - Each missing variable is imputed based on its own imputation model

MICE Algorithm to Generate Multiply Imputed Data Sets

- Suppose a set of missing variables, *y1, …, yj*, where some of them are missing
- Fill in every missing value by a random draw from the observed values, which will serve as a placeholder
- For the first missing variable, say *y1*, return the placeholders to missing, and then construct an imputation model that regresses *y1*on the other variables, say *y2, …, yj*, only among individuals with the observed *y1*
- Replace every missing value in *y1* by a random draw from the posterior predictive distribution of the imputation model for *y1*

MICE Algorithm to GenerateMultiply Imputed Data Sets (cont.)

- For the second missing variable, say *y2*, return the placeholders to missing, and then construct an imputation model that regresses *y2*on the previously imputed variable(s) *y1*and the other variables *y3, … yj*, only among individuals with the observed *y2*.
- Replace every missing value in *y2* by a random draw from the posterior predictive distribution of the imputation model for *y2*.
- For all other missing variables, repeat Steps 4 and 5.
- To stabilize the results, repeat Steps 2 through 6 *l* times (e.g., 10 to 20), which produces one imputed data set.
- Repeat Steps 1 through 7 *m* times (e.g., 5 to 10) to generate *m* imputed data sets

MNAR

- Assumptions are addressed by performing such sensitivity analysis.
- In contrast, specific methods to address MNAR in the scientific literature are rare…
- it is necessary to either
- (i) describe the statistical relationship between the chance of seeing a variable and its (unseen) value or
- (ii) describe the difference in the distribution of patients with and without missing observations [5].
- Then, the key point of such approaches consists in modelling the missing mechanism.
- However, in clinical epidemiology, such mechanisms are rarely precisely known, and researchers prefer to include explanatory variables in the analyses as much as possible to make more plausible a MAR assumption and bet on the fact that relatively little information remains in the unseen data

Seasonal variation in the month of birth in patients with skin cancer

F La Rosa[1], A Liso[2], F Bianconi[1], E Duca[3] and F Stracci*[,1]

[1]Department of Experimental Medicine, Public Health Section, University of Perugia, 06126 Perugia, Italy; [2]Department of Medicine and Surgery, University of Foggia, 71122 Foggia, Italy and [3]Department of Health, Regional Government of Umbria, 06124 Perugia, Italy

Background: Month of birth influences the risk of developing several diseases. We investigated the influence of date of birth on melanoma skin cancer (MSC) and non-melanoma skin cancer (NMSC) incidence.

Methods: Enhanced cancer registry data were analysed including 1751 MSC and 15 200 NMSC.

Results: People born in February to April showed significantly elevated risks of NMSC compared with those born in summertime.

Conclusions: We demonstrated seasonality by date of birth for skin cancer incidence. Neonatal UV exposure may explain this finding.

Table 1. Negative binomial regression models for NMSC and MSC cancers by month of birth

	NMSC (C44)				MSC (C43)			
Variable	IRR	95% CI		*P*	IRR	95% CI		*P*
Months								
January	1.18	1.09	1.28	<0.001	1.41	1.12	1.77	0.003
February	1.29	1.19	1.39	<0.001	1.15	0.90	1.47	0.25
March	1.30	1.20	1.40	<0.001	1.36	1.09	1.71	0.007
April	1.31	1.21	1.41	<0.001	1.15	0.90	1.45	0.26
May	1.14	1.05	1.23	0.002	1.15	0.90	1.46	0.26
June	1.02	0.93	1.11	0.70	1.41	1.11	1.77	0.004
July[a]	Ref.				Ref.			
August	1.04	0.96	1.13	0.32	1.12	0.88	1.43	0.36
September	1.09	1.00	1.18	0.04	1.14	0.90	1.46	0.28
October	1.08	1.00	1.17	0.06	1.10	0.86	1.40	0.45
November	1.20	1.11	1.31	<0.001	1.12	0.87	1.43	0.37
December	1.11	1.02	1.21	0.01	0.93	0.72	1.21	0.61
Gender								
Males	Ref.				Ref.			
Females	0.66	0.64	0.68	<0.001	0.95	0.86	1.04	0.25

Abbreviations: CI = confidence interval; IRR = incidence rate ratio; MSC = melanoma skin cancer; NMSC = non-melanoma skin cancer; Ref. = reference category.

[a]reference category is the month with the lowest date of birth.

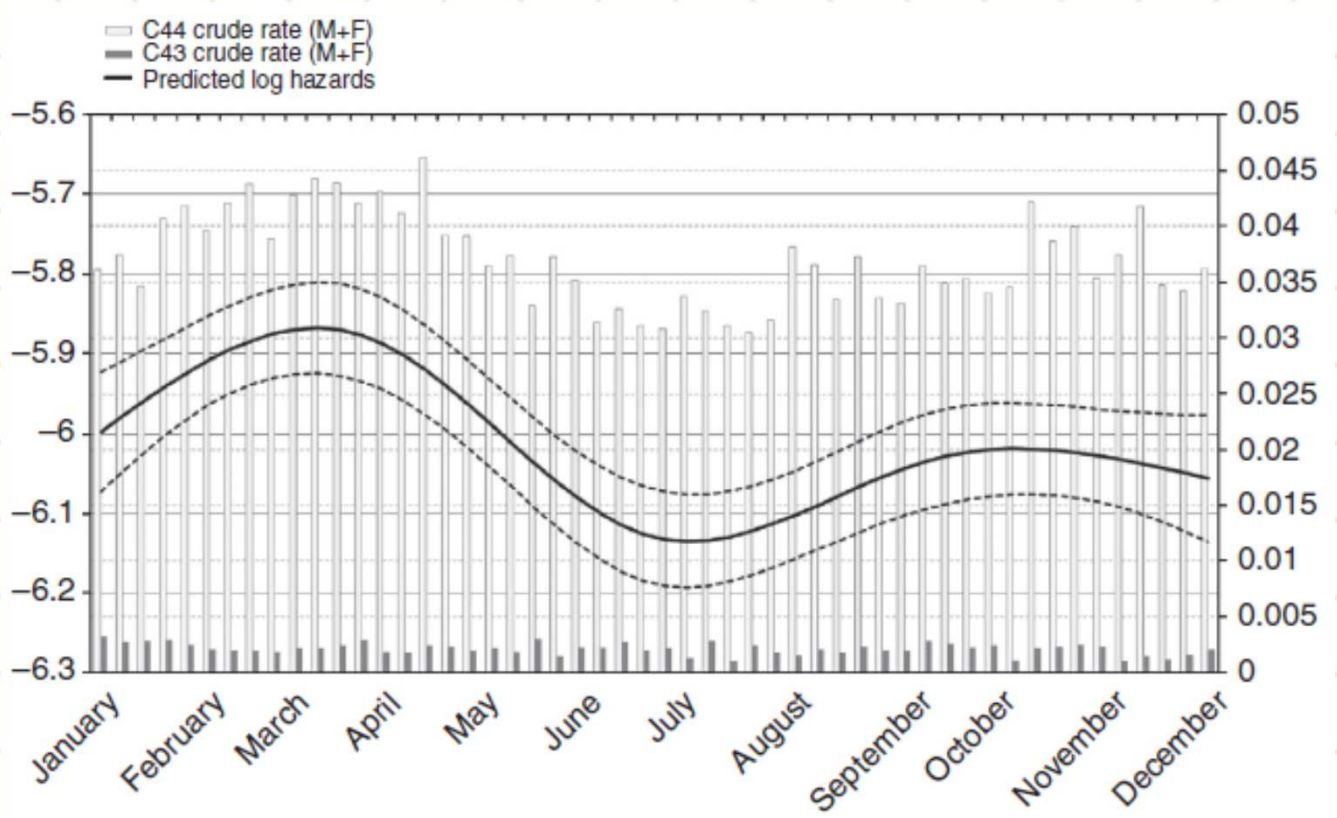
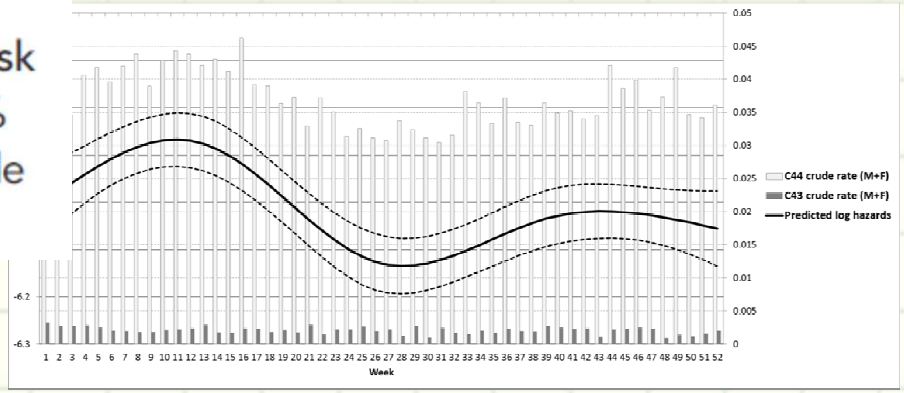
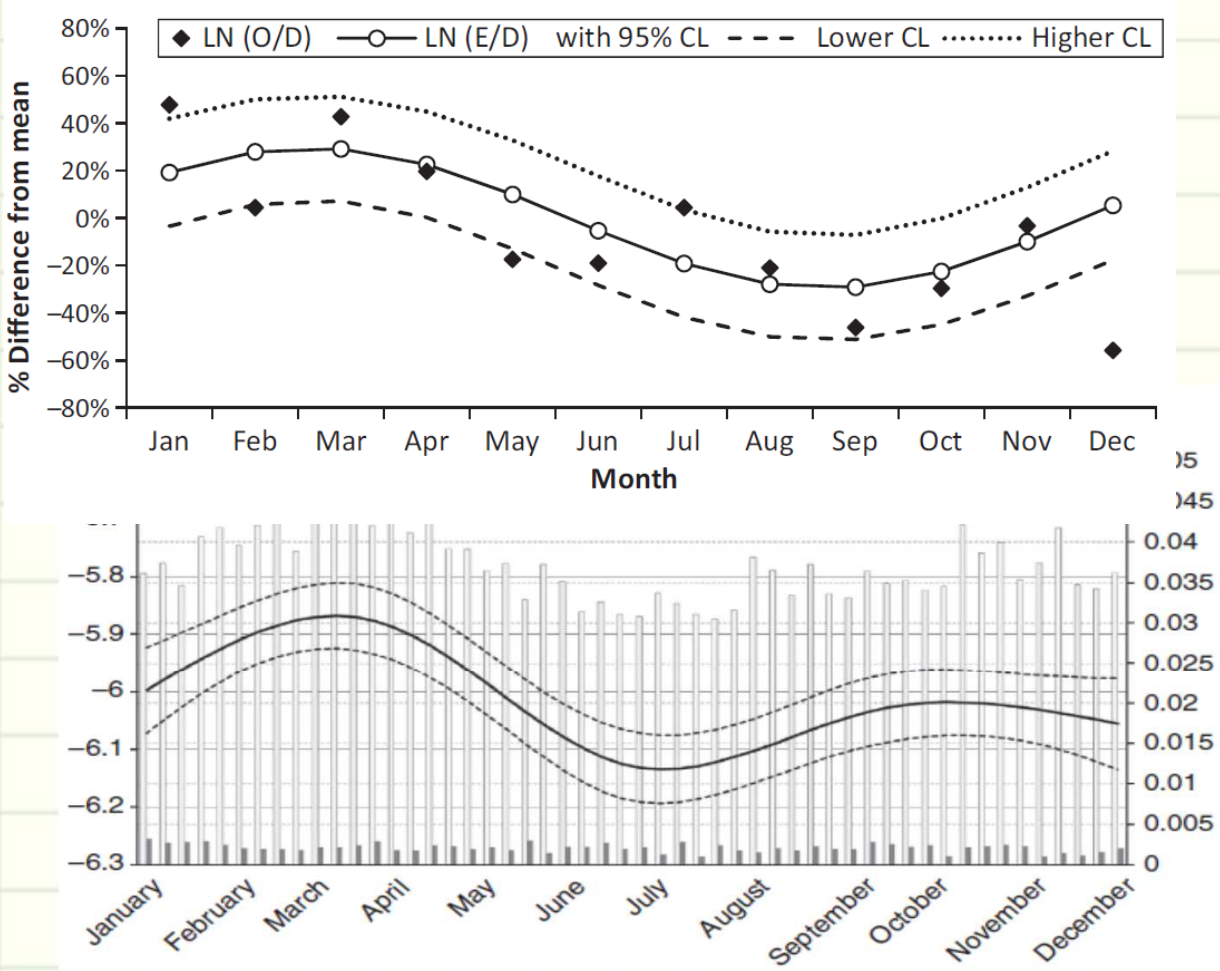


Figure 1. Weekly skin cancer risk. Curves represent skin cancer risk adjusted by gender, site and population at risk (dashed lines 95% confidence interval). Bars are MSC (solid) and NMSC (hollow) crude incidence rates.



Basta NO, James PW, Craft AW, McNally RJ. Seasonal variation in the month of birth in teenagers and young adults with melanoma suggests the involvement of early-life UV exposure. Pigment Cell Melanoma Res. 2011;24:250-3.



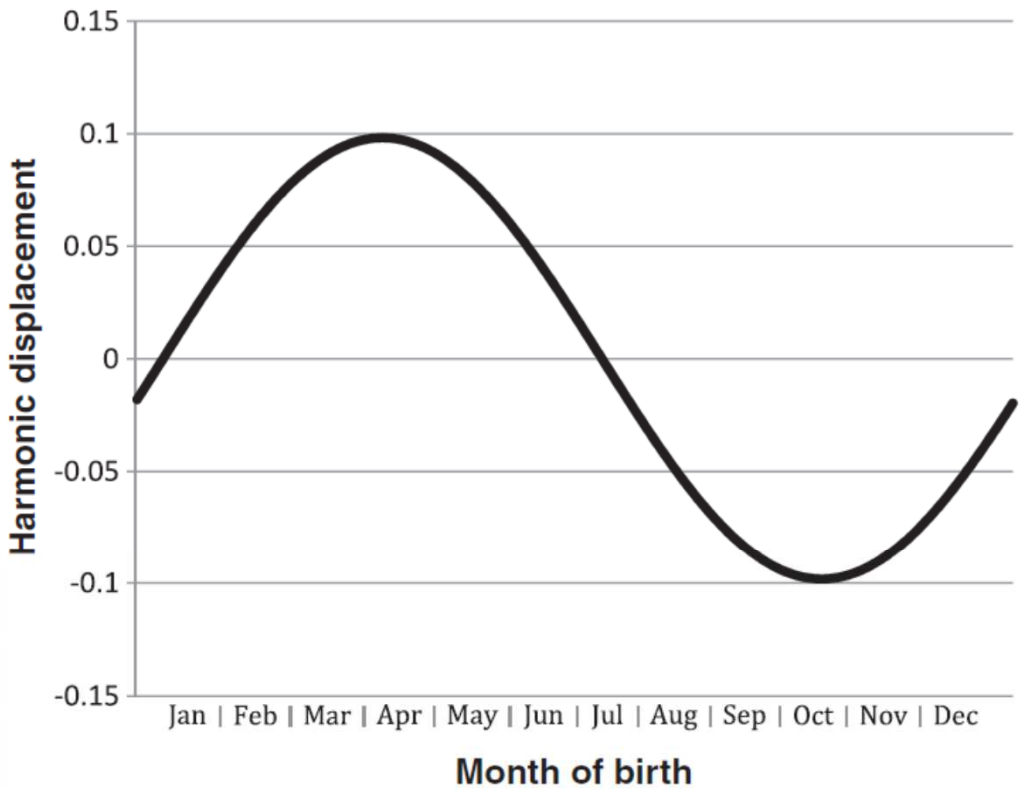


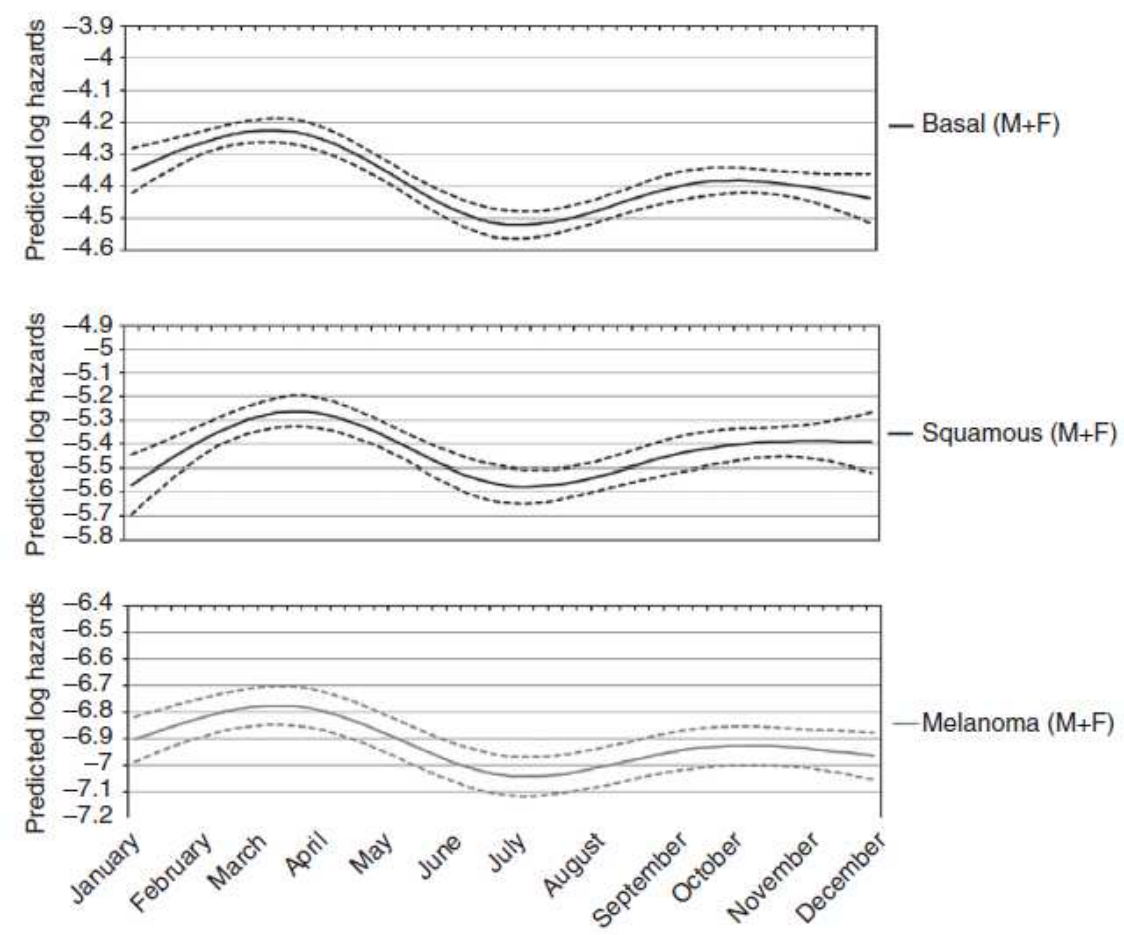
Figure 1. Sinusoidal logistic regression results for association between birth date and cutaneous malignant melanoma in childhood through young adulthood, adjusted for birth year ($P = 0.006$ for overall seasonal association). Harmonic displacement represents the log odds ratio for a given time point relative to the mean risk across the entire calendar year.

Methods: National **cohort study** of 3 571 574 persons born in Sweden in 1973–2008

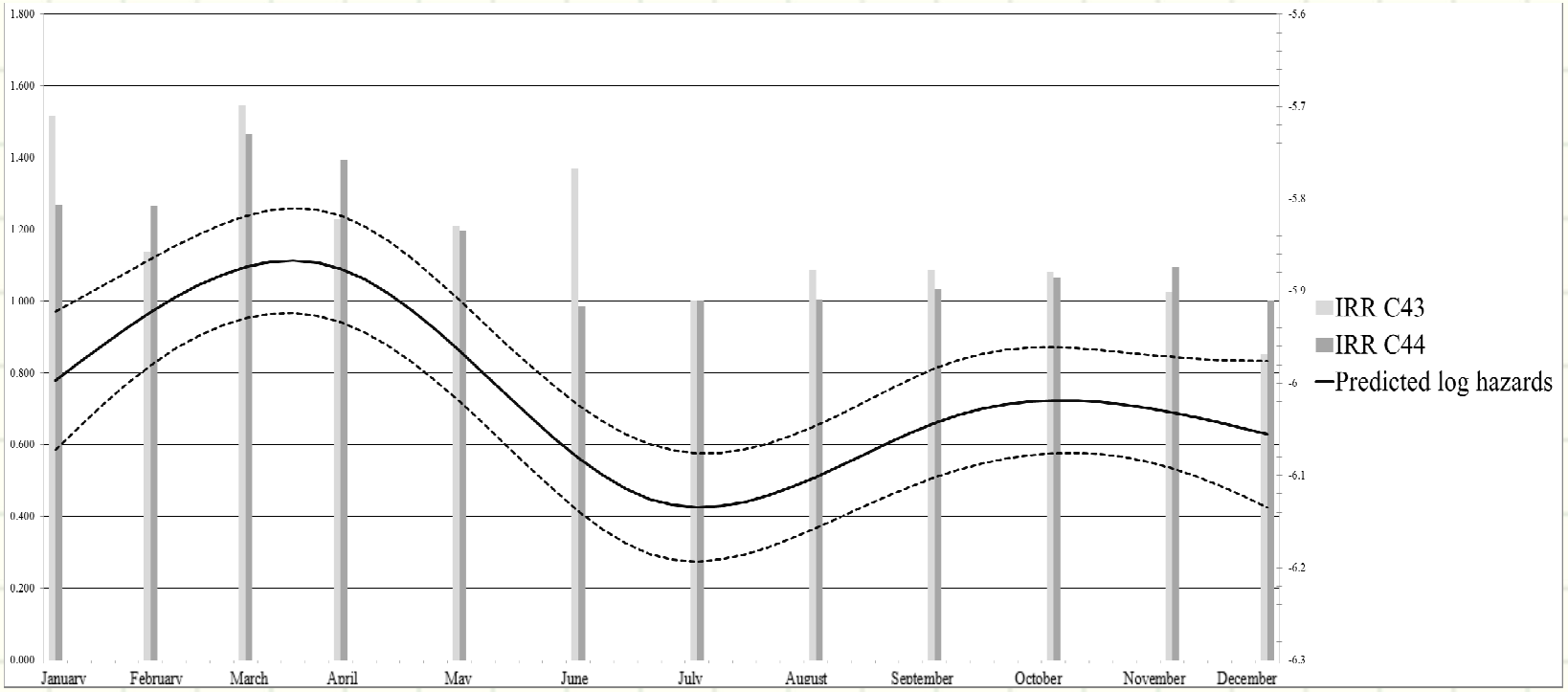
Crump C, et al. Season of birth and other perinatal risk factors for melanoma. Int J Epidemiol. 2014;43:793-801.

Rischio per periodo di nascita e morfologia

- Diversi tumori cutanei sono stati associati a modalità di esposizione differenti
- Le curve sono simili per cui i. il periodo di nascita è legato ad una suscettibilità ai tumori cutanei modulata dalle esposizioni ii. il rischio riflette l'azione di confondenti



Seasonal variation in the month of birth in patients with skin cancer: monthly RR vs spline



Count Models

- Two most common count models:
  - Poisson Regression Model
  - Negative Binomial Regression Model
- Both based on the Poisson distribution:
  - μ = expected count (and variance) Freese & Long 2006
    - Called lambda (λ) in some texts; y = observed count

$$P(y|\mu) = \frac{e^{-\mu}\mu^{y}}{y!}$$

Poisson Regression

- Strategy: Model log of μ as a function of Xs
  - Quite similar to modeling log odds in logit
  - Again, the log form avoids negative values

$$\ln(\mu) = \sum_{j=1}^{K} \beta_j X_{ji}$$

- Which can be written as:

$$\mu = e^{\sum_{j=1}^{K} \beta_j X_{ji}}$$

Poisson Model Assumptions

- Poisson regression makes a big assumption: variance of μ = μ ("equidisperson")
  - In other words, the mean and variance are the same
  - This assumption is often **not met** in real data
  - Dispersion is often greater than μ: **overdispersion**
- Consequence of overdispersion: Standard errors will be underestimated
  - Potential for overconfidence in results; rejecting H0 when you shouldn't!
  - Note: overdispersion doesn't necessarily affect predicted counts (compared to alternative models).

Negative Binomial Regression

- Strategy: Modify the Poisson model to address overdispersion
  - Add an "error" term to the basic model:

$$\mu = e^{\sum_{j=1}^{K} \beta_j X_{ji} + \varepsilon_i}$$

- Additional model assumptions:
  - Expected value of exponentiated error = 1 ($e^{\varepsilon} = 1$)
  - Exponentiated error is Gamma distributed

Negative Binomial Regression

- Full negative binomial model:

$$P(y \mid X) = \frac{\Gamma\left(y + \alpha^{-1}\right)}{y!\,\Gamma\left(\alpha^{-1}\right)} \left(\frac{\alpha^{-1}}{\alpha^{-1} + \mu} \right)^{\alpha^{-1}} \left(\frac{\mu}{\alpha^{-1} + \mu} \right)^{y}$$

- Note that the model incorporates a new parameter: α
  - Alpha represents the extent of overdispersion
  - If $\alpha = 0$ the model reduces to simple poisson regression

Negative Binomial Regression

- Question: Is alpha (α) = 0?
  - If so, we can use Poisson regression
  - If not, overdispersion is present; Poisson is inadequate
- Strategy: conduct a statistical test of the hypothesis: H0: $\alpha = 0$; H1: $\alpha > 0$
  - Stata provides this information when you run a negative binomial model:
  - Likelihood ratio test (G^2) for alpha
  - P-value < .05 indicates that overdispersion is present; negative binomial is preferred
  - If P>.05, just use Poisson regression
    - So you don't have to make assumptions about gamma dist….

Trattamento delle variabili continue

Categorizzazione

- A common occurrence is for the investigator to categorize a continuous variable before the model is developed.
- This is done because there may be uncertainty about the appropriate functional form for the continuous variable and the belief that discretizing it will impart robustness on the conclusion of the analysis.
- Furthermore it is generally easier to display and explain results with discrete, rather than continuous variables.

Dicotomizzazione

La trasformazione in variabile binaria è comune negli studi clinici ed epidemiologici (meno):

- Consente una semplice stratificazione del rischio in alto/basso
- Fornisce una indicazione rispetto alle scelte di trattamento
- Consente di indicare criteri diagnositci,
- Risulta più semplice da interpretare
- Evita l'assunto di linearità della relazione tra fattore ed esito
- …

Many Authors

- Many authors, particularly in areas of application, seem to believe the desirability of dichotomizing continuous variables.
- Apart from the throwing away of information, which is the topic of the current paper,
- this procedure produces a possibly scientifically unrealistic model where the effect has a sudden jump at the cut-off value, with all values below the cut-off having equal effect and all values below the cutoff having equal effect
- Bias and Efficiency Loss Due to Categorizing an Explanatory Variable

Taylor JMG J Multivariate Analysis 2002

Effetti nocivi della dicotomizzazione

Tuttavia la dicotomizzazione comporta:

- Perdita di informazione, in quanto non viene utilizzata la distribuzione entro ciascuna categoria
- Rischio di bias
- Perdita di potenza statistica
- Aumento degli errori di I e II tipo

Zhao LP, Kolonel LN. Efficiency loss from categorizing quantitative exposures into qualitative exposures in case–control studies. American Journal of Epidemiology 1992; 136:464–474.

MacCallum RC, Zhang S, Preacher KJ, Rucker DD. On the practice of dichotomization of quantitative variables. Psychological Methods 2002; 7:19–40.

Cohen J. The cost of dichotomization. Applied Psychological Measurement 1983; 7:249–253.

Ragland DR. Dichotomizing continuous outcome variables: dependence of the magnitude of association and statistical power on the cutpoint. Epidemiology 1992; 3:434–440.

Greenland S. Avoiding power loss associated with categorization and ordinal scores in dose–response and tread analysis. Epidemiology 1995; 6:450–454.

Austin PC, Brunner LJ. Inflation of the type I error rate when a continuous confounding variable is categorized in logistic regression analyses. Statistics in Medicine 23:1159–1178.

Vargha A, Rudas T, Delaney HD, Maxwell SE. Dichotomization, partial correlation, and conditional independence. Journal of Educational and Behavioral Statistics 1996; 21:264–282.

Maxwell SE, Delaney HD. Bivariate median splits and spurious statistical significance. Psychological Bulletin 1993; 113:181–190.

Streiner DL. Breaking up is hard to do: the heartbreak of dichotomizing continuous data. Canadian Journal of Psychiatry 2002; 47:262–266.

Cut-off

- Arbitrario
- Sulla base della distribuzione (ad esempio mediana)
- Sulla base dell'esito (*miglior cut-off associato ad un aumento dell'errore di I tipo, sovrastima dell'effetto, scarsa riproducibilità in studi successivi*)

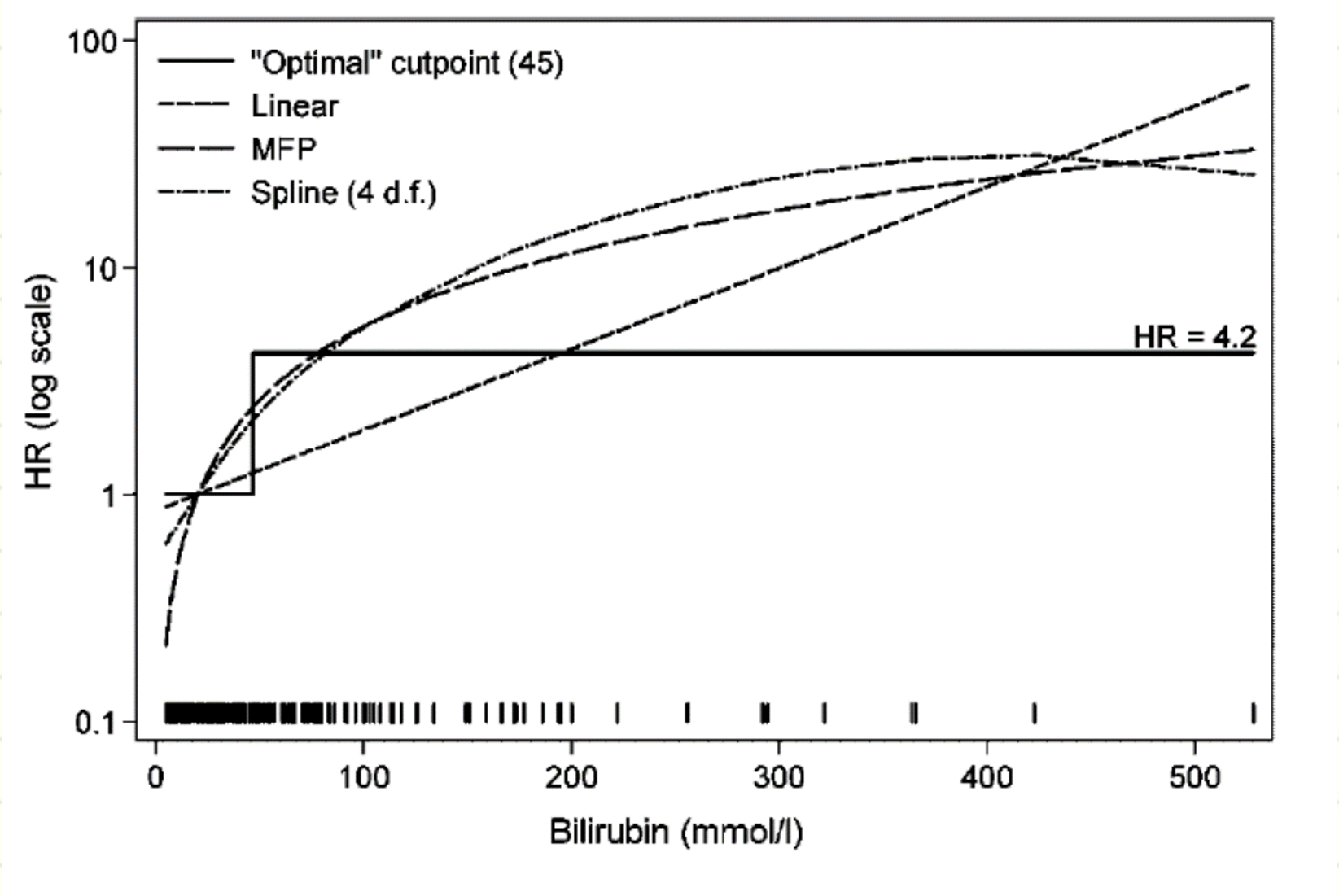
Dichotomizing continuous predictors in multiple regression: a bad idea.

Table I. Estimated treatment effect in PBC data using different confounder models.

Model no.	Adjustment for bilirubin	HR for treatment	95 per cent CI	*P*-value for treatment
1	None	0.83	0.57, 1.22	0.348
2	Median cutpoint	0.76	0.51, 1.12	0.170
3	'Optimal' cutpoint	0.72	0.49, 1.06	0.094
4	Four groups	0.67	0.45, 0.99	0.046
5	Eight groups	0.58	0.38, 0.87	0.009
6	Linear	0.61	0.41, 0.91	0.015
7	Quadratic	0.58	0.39, 0.86	0.007
8	FP1	0.61	0.41, 0.90	0.014
9	FP2	0.60	0.40, 0.89	0.011
10	Spline with 4 e.d.f.	0.59	0.39, 0.87	0.008
11	Multivariable (MFP)	0.61	0.41, 0.90	0.014

The strong prognostic factor bilirubin is handled differently in each model, whereas identical adjustment for age, cirrhosis and central cholestasis is applied. See text for details.

Royston P, Altman DG, Sauerbrei W. *Stat Med*. 2006; 25:127-41.


"Optimal" cutpoint (45)
Linear
MFP
Spline (4 d.f.)
HR = 4.2
HR (log scale)
100
10
1
0.1
0
100
200
300
400
500
Bilirubin (mmol/l)

Fractional polynomials

A fractional polynomial of degree m consists of m integer/fractional powers

$$fp(x) = a_0 + \sum_{j=1}^{m} a_j x^{(p_j)}$$

where the power (p_j) is generally chosen from a restricted set including

$$\{-2; -1; -0.5; 0; 0.5; 1; 2; 3\}$$

with

$$x^{(0)} = \log x$$

Algorithm to choose the most suitable model

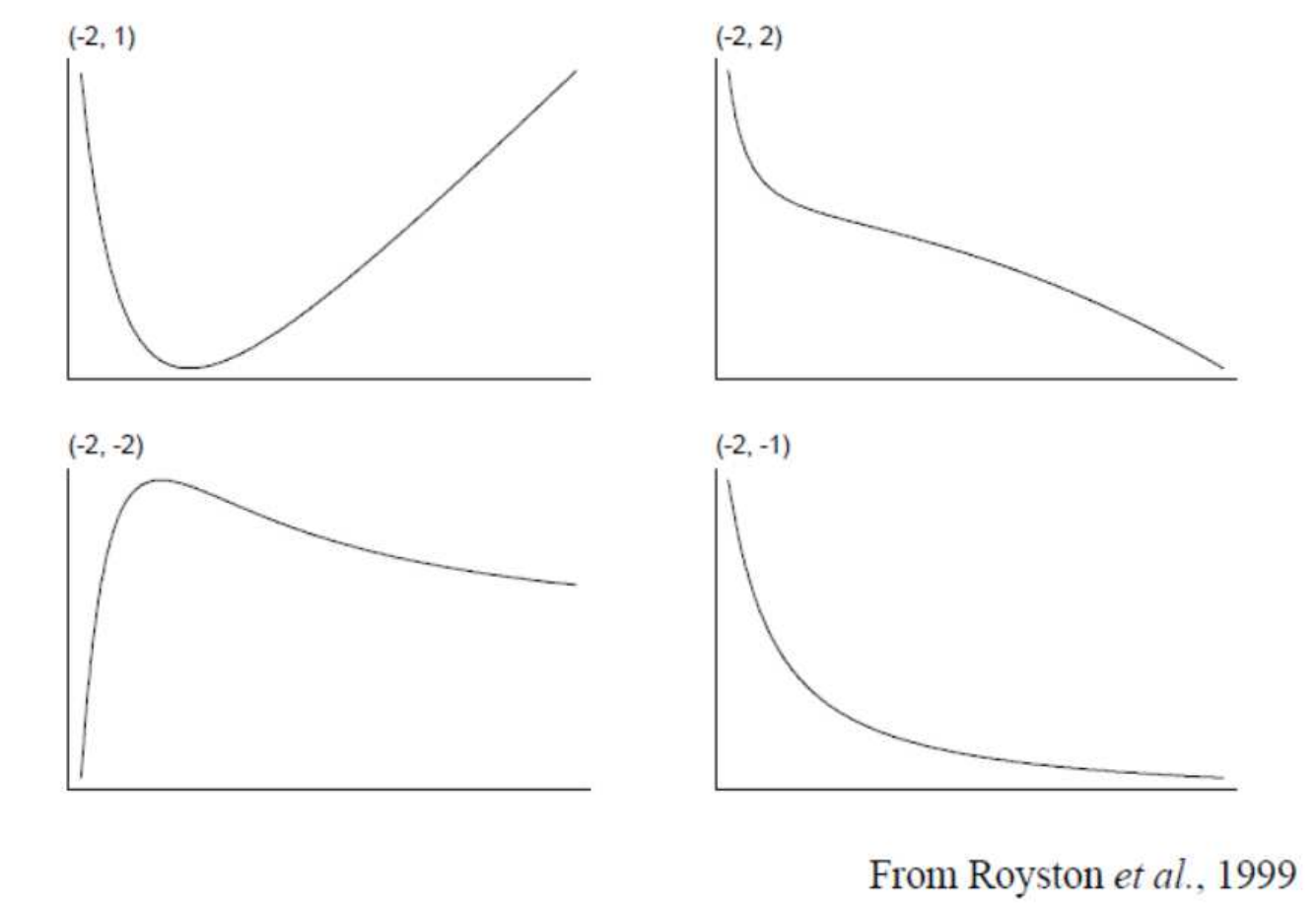
Sauerbrei W, Royston P. Journal of the Royal Statistical Society, Series A 1999; 162:71–94.

Implemented in Stata® command *mfp.ado* and adapted to *mvrs.ado*

Principles of the algorithm

1. Determine fitting order of co-variables from linear model
2. For each co-variable X:
   - Fit model with each combination of powers
   - Choose model with lowest deviance
   - Compare FPm with FP(m-1)
   - Functions for other X are fixed, but not their β's
3. Iterate step 2 until powers of FP functions do not change

Possible curve shapes with second-degree fractional polynomials



From Royston *et al.*, 1999

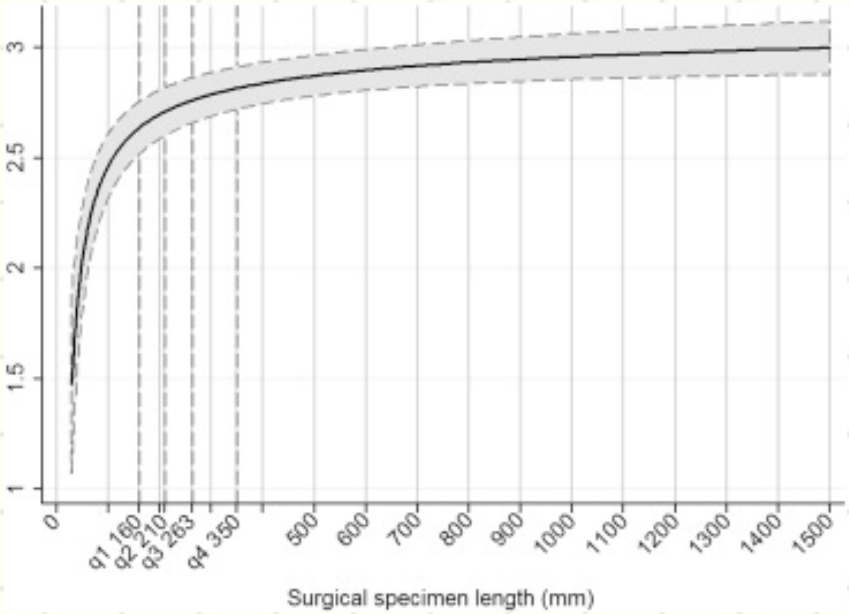


Figure 1. Relationship between surgical specimen length and number of examined lymph nodes.

F. Stracci, F. Bianconi, S. Leite, A. Liso, F. La Rosa, V. Lancellotta, C.J.H. van de Velde, C. Aristei

Linking surgical specimen length and examined lymph nodes in colorectal cancer patients

European Journal of Surgical Oncology (EJSO), Volume 42, Issue 2, 2016, 260–265

http://dx.doi.org/10.1016/j.ejso.2015.11.017

Splines

Excess hazard function $\lambda_c(t)$

$$\lambda_c(t) = \exp(f(t) + \beta(t)X(t))$$

with

$f(t)$ spline function and $\exp(f(t)) = \lambda_0(t)$

$\boldsymbol{\beta}(t)$ a vector of spline functions

Main broad classes

- regression or natural splines (incl. restricted, B-splines, …)
- smoothing splines
- *penalised splines*

Regression or natural splines

Linear combination of piecewise polynomial functions

+ linear combination of truncated functions

A k-degree polynomial function consists of $a_0 + a_1 t^1 + \ldots + a_k t^k$

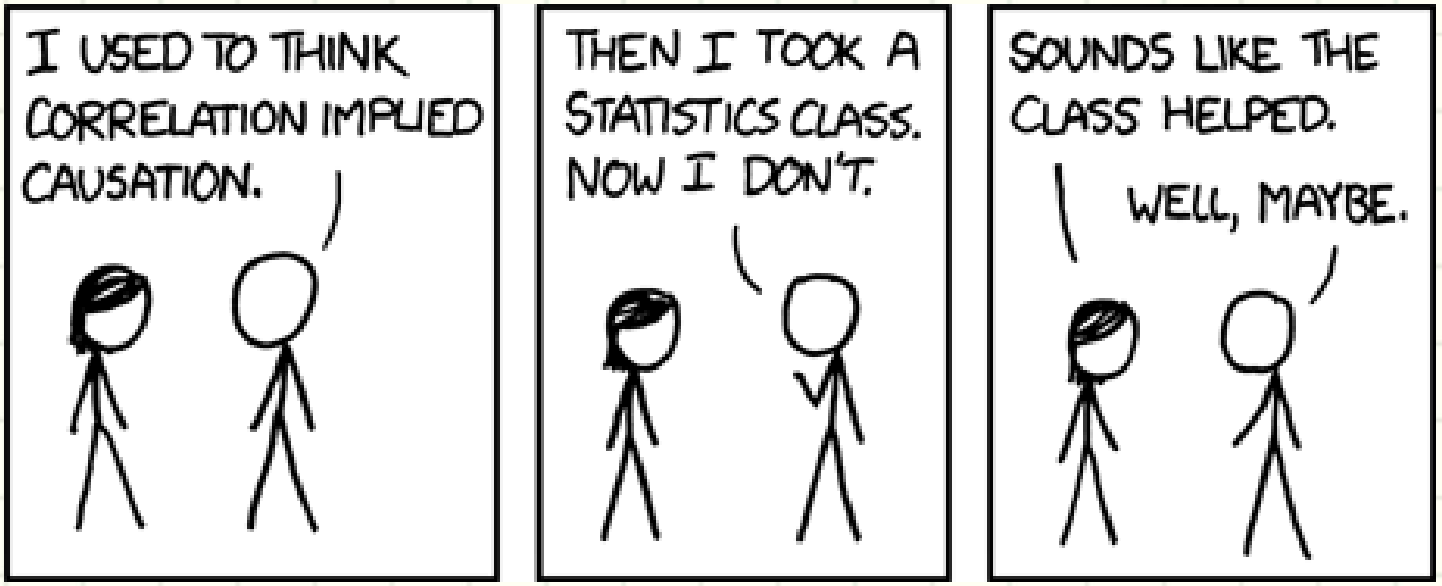
Interval-specific polynomials joined smoothly at distinct knots
(continuity of the function and the first two derivatives at the knots)

$$f(t) = a_0 + a_1 t^1 + \ldots + a_k t^k + \sum_{j=1}^{m} \theta_j \left(t - t_j\right)_+^k$$

where $u_+ = \max(0\ ,\ u)$ and $\{t_j\}_m$ are m knots

Regression splines

- Flexibility
  - Degree of the polynomial
    - cubic, quadratic …
  - Knots
  - sensitivity to their location and their number
- Degrees of freedom
  - number of internal knots + 1


I USED TO THINK CORRELATION IMPLIED CAUSATION.
THEN I TOOK A STATISTICS CLASS. NOW I DON'T.
SOUNDS LIKE THE CLASS HELPED.
WELL, MAYBE.

Grazie