



SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10^a EDIZIONE

MODULI SPECIALISTICI - S1



VENERDÌ 8 - SABATO 9 MARZO 2024

NEGRAR DI VALPOLICELLA (VR)

Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Tipologia e obiettivi delle
Revisioni della Letteratura
Scientifica

Michela CINQUINI

Studio primario: qualunque studio in cui l'unità di analisi sia il paziente o gruppi di pazienti

Pubblicazioni secondarie: qualunque tipo di pubblicazione la cui unità di analisi siano gli studi primari

- Linee Guida

-Rapporti HTA

-Revisioni narrative

-**Revisioni sistematiche** su:

- **Efficacia trattamenti**

 - RCTs

 - studi osservazionali

- Efficacia programmi di screening

- Accuratezza test diagnostici

- Impatto dei test diagnostici su scelta terapia e salute paziente

- Fattori di rischio

- Fattori prognostici

- Frequenza eventi avversi

Revisioni narrative e sistematiche

- Non esiste un definizione ufficiale e riconosciuta né di revisione narrativa né di revisione sistematica
- Systematic reviews: “There is no standard definition of an SR. We counted a report as an SR if the authors’ stated objective was to summarize evidence from multiple studies and the article **described explicit methods**, regardless of the details provided”. (Moher 2007)

REVISIONI NARRATIVE

Narrative reviews are the traditional approach and usually do not include a section describing the methods used in the review. They are mainly based on the experience and subjectivity of the author, who is often an expert in the area.

(Cipriani. Epidemiologia e Psichiatria sociale 2003)

REVISIONI NARRATIVE

- A narrative review discusses and summarises the literature on a particular topic, without generating any pooled summary figures through meta-analysis. This type of review usually gives a **comprehensive overview of a topic**, rather than addressing a specific question such as how effective a treatment is for a particular condition. Narrative reviews **do not often report on how the search for literature was carried out or how it was decided which studies were relevant to include** (Glossary – NHS)

REVISIONI NARRATIVE

Rassegne descrittive di un certo numero di studi, presentazioni dei risultati (spesso senza i dati precisi) e conclusioni circa l'efficacia del trattamento

- La strategia di **ricerca bibliografica** per recuperare gli articoli **non è descritta**
- I **criteri usati per includere** gli studi **non sono specificati**
- **Descrivono studi senza dire che % sono** di tutti quelli esistenti su quell'argomento
- Spesso le caratteristiche degli studi primari sono descritte sommariamente: non è riportata la numerosità del campione, né i dati relativi all'efficacia
- **Non viene valutata la qualità metodologica** degli studi inclusi
- **Articoli non validi per trarre conclusioni affidabili circa l'efficacia di un trattamento**

Cosa è una revisione sistematica (RS)? (1)

Un tentativo di sintetizzare i risultati e le conclusioni di due o più pubblicazioni (articoli primari) su una determinata problematica sanitaria.

Vero e proprio progetto di ricerca

Cosa è una RS? (2)

Una valutazione *complessiva ed esaustiva*

- della qualità
- della rilevanza clinica e
- eterogeneità

Di tutte le informazioni disponibili su una determinata problematica sanitaria.

- Una revisione che è stata realizzata attraverso un approccio scientifico rigoroso, per ridurre gli errori sistematici e casuali, in un modo documentato nei materiali e metodi.
- Una revisione sistematica può includere, o meno, una metanalisi: un'analisi statistica dei risultati degli studi indipendenti che ha, generalmente, come obiettivo di produrre una singola stima numerica dell'effetto del trattamento.

Chalmers I and Altman DG, 1995

Una visione insiemistica



Principi di una meta-analisi

Una meta-analisi può:

- Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;
- Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

NB: una revisione sistematica non si conclude forzatamente con una meta-analisi.

Revisioni sistematiche vs Revisioni narrative

Le revisioni tradizionali vs le revisioni sistematiche

CARATTERISTICHE	REVISIONE TRADIZIONALE	REVISIONE SISTEMATICA
Domanda	Ampia	Focalizzata su un unico quesito clinico
Fonti e ricerca	Non specificate	Complete ed esplicita
Selezione	Solitamente non specificata	Basata su criteri specifici
Valutazione critica	Variabile	Rigorosa
Sintesi	Qualitativa	Qualitativa/quantitativa (meta-analisi)

Caratteristiche delle RS (1)

- Chiara definizione del titolo e dell'obiettivo;
- Strategia di ricerca esaustiva che risponda agli obiettivi della RS (studi rilevanti) per includere sia gli studi pubblicati che i non pubblicati;
- Criteri di inclusione/esclusione adottati esplicitati e motivati;
- Lista esaustiva di tutti gli studi identificati;
- Presentazione chiara delle caratteristiche di ogni studio incluso e analisi della loro qualità metodologica;
- Lista degli studi esclusi e motivazione dell'esclusione;
- Analisi trasparente dei risultati degli studi eleggibili utilizzando tecniche di sintesi statistica (meta-analisi) se appropriato e possibile;
- Analisi di sensibilità dei dati se appropriate e possibili;
- Stesura di un rapporto finale che presenti chiaramente l'obiettivo, descriva i materiali e metodi e riporti i risultati.

Perché sono necessarie le revisioni sistematiche?

- Perché il numero di pubblicazioni e di ricerche su un determinato argomento è troppo grande
- Perché considerare solo parte delle informazioni disponibili può determinare errori (publication bias)
- Perché la qualità metodologica degli studi è variabile
- Perché i risultati di studi diversi condotti sullo stesso argomento spesso differiscono tra loro

**Perché sono utili le
revisioni sistematiche?**

'In God we trust, all others (must) bring data'

W Edwards Deming

Situazioni di particolare utilità

- Quando risultati conflittuali si accumulano rapidamente con risultati incerti
- Quando una patologia è percepita in modo “drammatico” dalla popolazione
- Quando un trattamento potenzialmente efficace rischia di essere abbandonato
- Quando la ricerca clinica deve essere “ri-orientata”
- Quando bisogna esplicitare la limitazione delle informazioni scientifiche disponibili per le decisioni sanitarie
- Ogni volta che si deve costruire un progetto di ricerca

50c
50
66-48

DR. BENJAMIN SPOCK

BABY AND CHILD CARE



The
Spock
Book
FIRST
EDITION

The most widely recommended hand-
book for parents ever published—
Authoritative, illustrated, indexed

Over 19,000,000 copies sold

Benjamin McLane Spock (New Haven, 2 maggio 1903 – La Jolla, 15 marzo 1998) - pediatra statunitense

- fama con la pubblicazione del libro: ***Common Sense Book of Baby and Child Care.***

Il libro venne **pubblicato** per la prima volta nel **1946** e fu tradotto in tutte le principali lingue del mondo; fu uno dei **maggiori successi editoriali** dell'immediato dopoguerra, vendendo per circa un decennio un milione di copie all'anno e raggiungendo, **nel 2011**, un volume complessivo di vendite di circa **50 milioni** di copie. Spock aveva avuto l'abilità di trattare temi molto popolari (soprattutto presso le donne), come la gravidanza, il parto, l'alimentazione e le cure del bambino, con un linguaggio semplice e brillante, spregiudicato e anticonformista, presentando progressi e orientamenti della ginecologia e della pediatria come novità rivoluzionarie derivanti anche dalla sua esperienza professionale.

Scenario: 1970 – reparto di ostetricia

Madre primipara, spaventata dalla “**morte in culla**”, alla dimissione dal reparto dopo il parto, **chiede:**

Qual è la posizione migliore in cui porre il neonato durante il sonno ?

Il medico di stanza scrupoloso commissiona allo specializzando una **ricerca bibliografica ...**

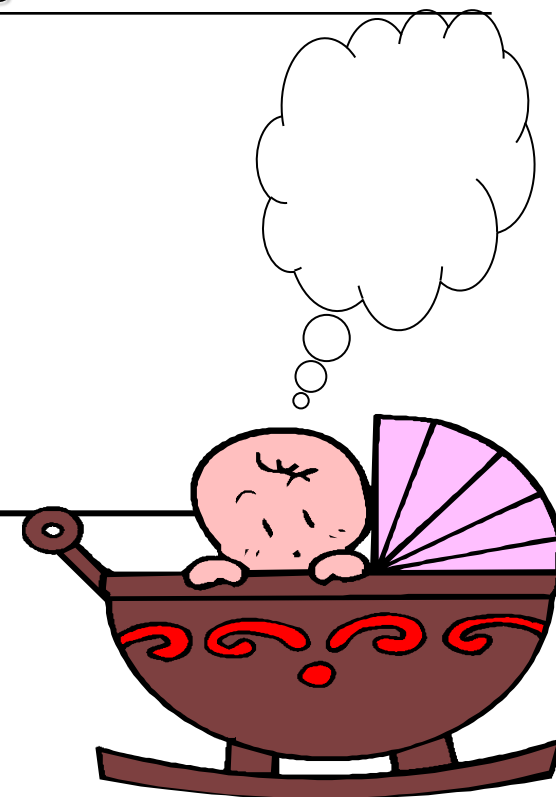


Scenario: 1970 – reparto di ostetricia

Ricerca Bibliografica:

Testo	Posizione consigliata
Mollon 1967 1° ed.	Supina
Potts 1967 1° ed.	Prona o fianco
Illingworth & Illingworth 1968 4° ed.	Indifferente
Illingworth 1968 4° ed.	Prona
Mollon 1968 2° ed.	Supina
Spock 1969 3° ed.	Prona

... nella lettera di dimissione, tra le raccomandazioni, viene riportato che *la posizione migliore del neonato nella culla, durante il sonno, è quella **prona (pancia in giù)***



...ancora sulla posizione del lattante:

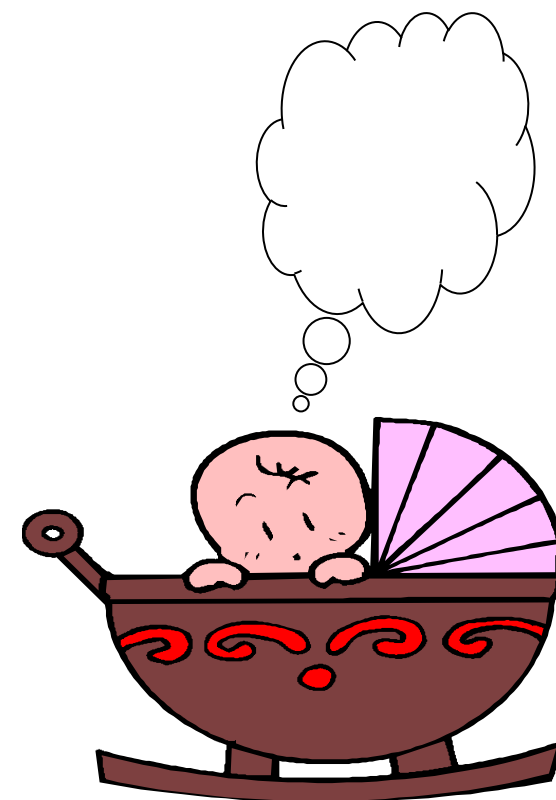
Facoltà di Medicina

Anni 90



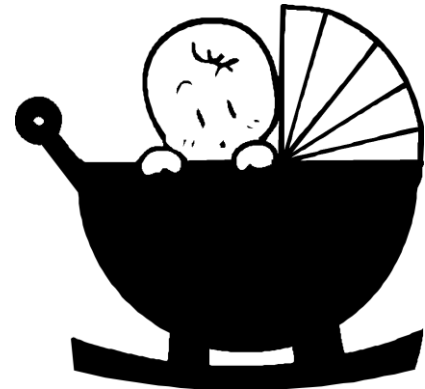
Dal testo consigliato per l'esame di pediatria

- Dalla edizione 1990 e dalla edizione 1997:
 - Sulla morte in culla: 5 (cinque) righe
 - Possibile causa: shock anafilattico da latte vaccino
 - 1-2 casi per 1000 nati vivi
 - Prima causa di morte tra 1 e 12 mesi
 - Sulla posizione dei lattanti nel sonno, riportata per terapia del reflusso gastroesofageo:
 - “Corretta posizione: prona e su un letto tenuto leggermente inclinato”



Alcune possibili conseguenze di
questo modo di procedere:

una strage silenziosa



Int. J. Epidemiol. Advance Access published April 20, 2005

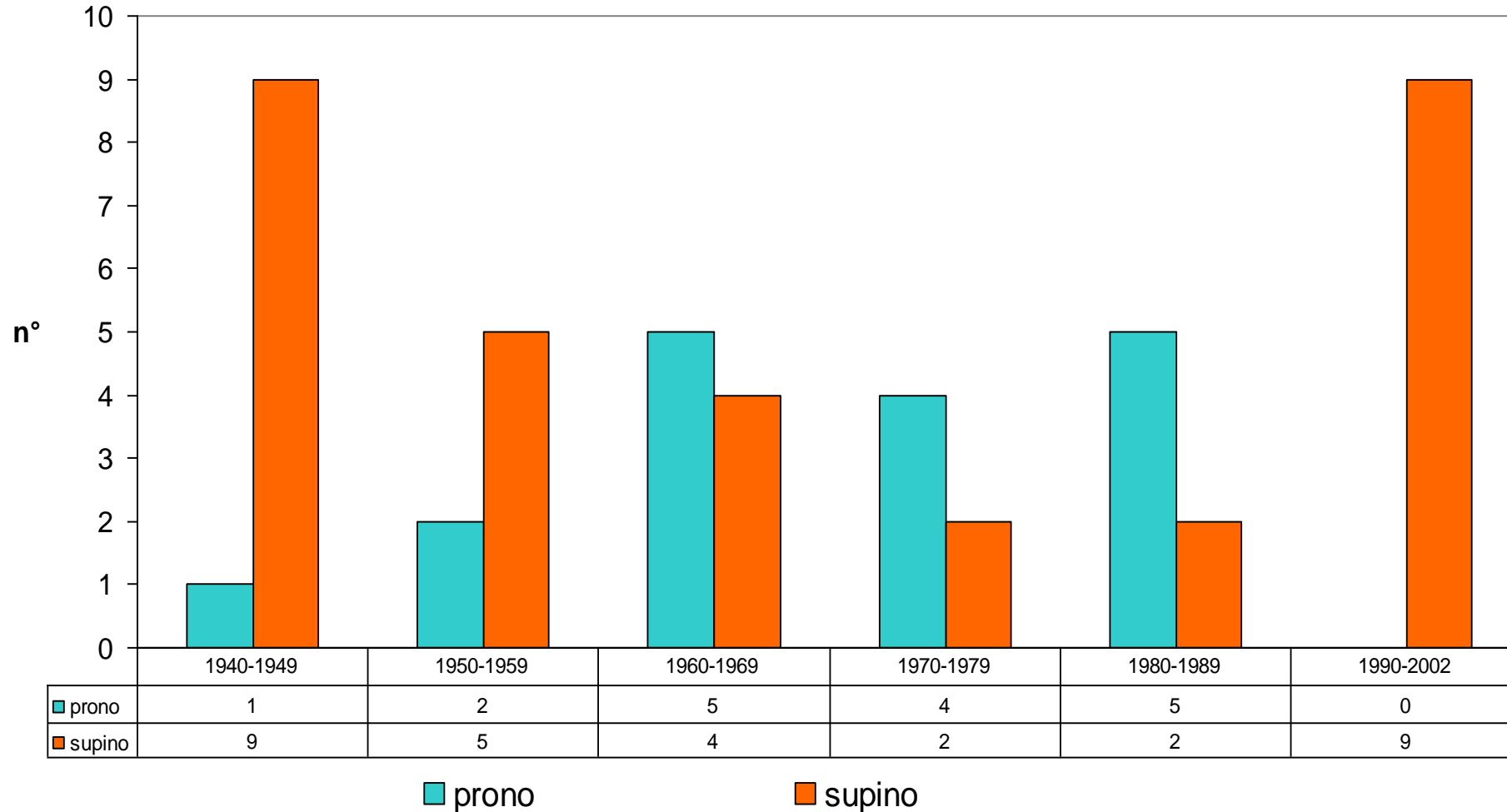
Published by Oxford University Press on behalf of the International Epidemiological Association
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International Journal of Epidemiology
doi:10.1093/ije/dy1888

Infant sleeping position and the sudden infant death syndrome: systematic review of observational studies and historical review of recommendations from 1940 to 2002

Ruth Gilbert,^{1*} Georgia Salanti,² Melissa Harden¹ and Sarah See^{1,3}

Raccomandazioni sulle posizioni del sonno nel lattante: letteratura inglese



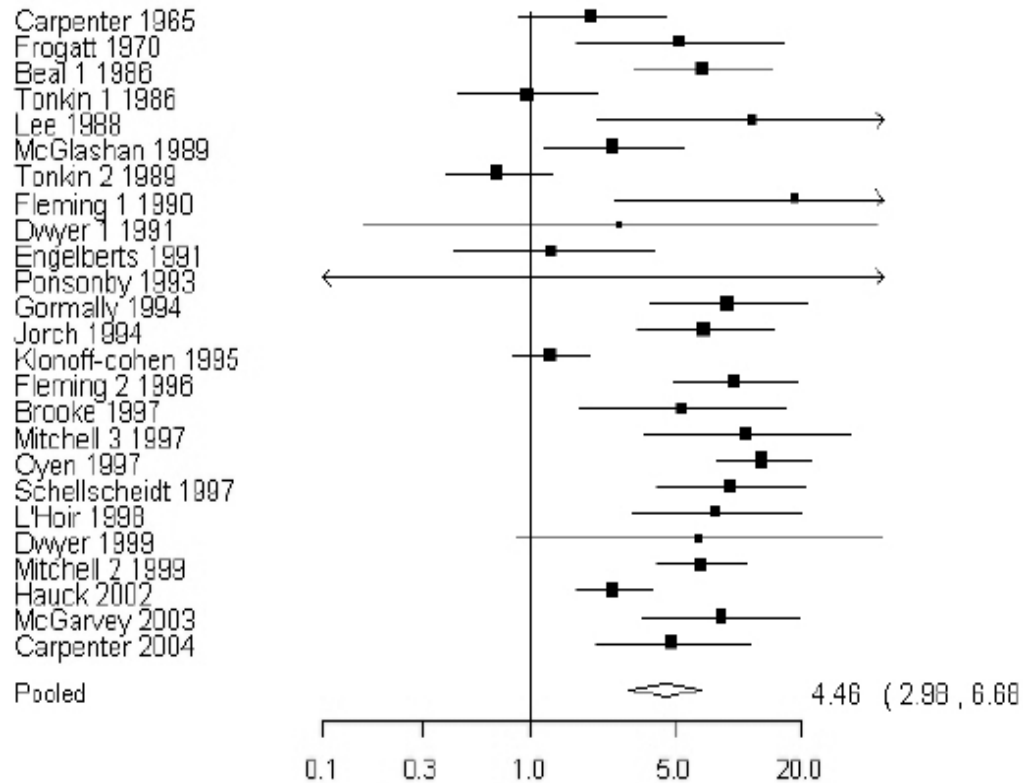
(Gilbert 2005)

Morte in culla

Metanalisi degli studi epidemiologici sulla posizione prona e rischio di morte del lattante nel sonno



(a) Study



(Gilbert 2005)

odds ratio

prone position better ← → prone position worse

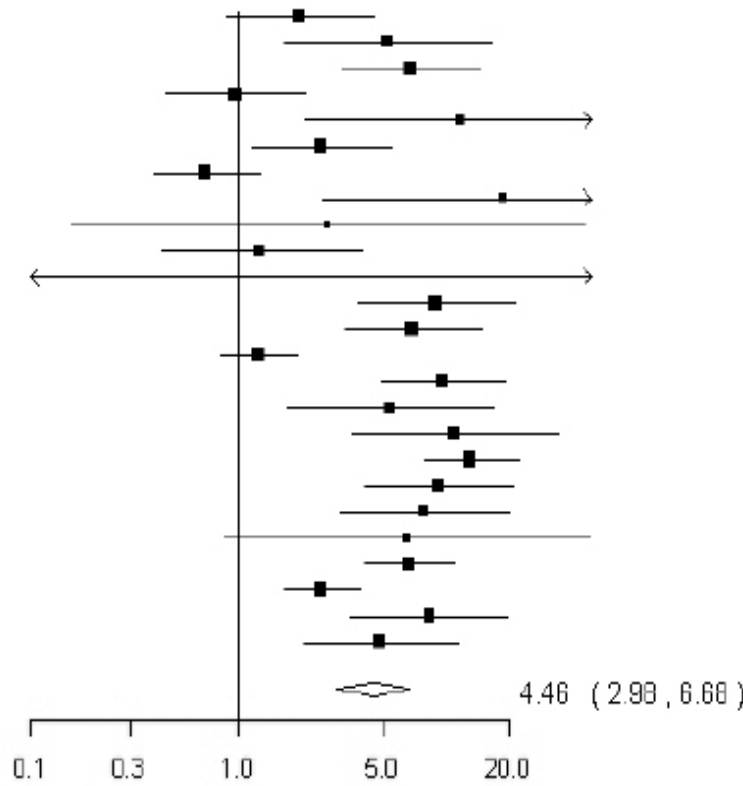
Morte in culla



Meta analisi CUMULATIVA

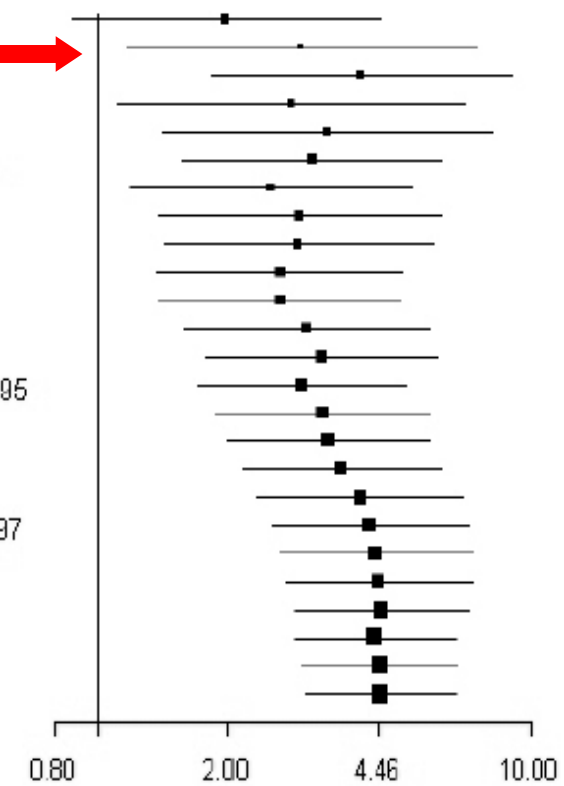
(a) Study

Carpenter 1965
 Frogatt 1970
 Beal 1 1986
 Tonkin 1 1986
 Lee 1988
 McGlashan 1989
 Tonkin 2 1989
 Fleming 1 1990
 Dwyer 1 1991
 Engelberts 1991
 Ponsonby 1993
 Gormally 1994
 Jorch 1994
 Klonoff-cohen 1995
 Fleming 2 1996
 Brooke 1997
 Mitchell 3 1997
 Oyen 1997
 Schellscheidt 1997
 L'Hoir 1998
 Dwyer 1999
 Mitchell 2 1999
 Hauck 2002
 McGarvey 2003
 Carpenter 2004



(b) Study

Carpenter 1965
 Frogatt 1970
 Beal 1 1986
 Tonkin 1 1986
 Lee 1988
 McGlashan 1989
 Tonkin 2 1989
 Fleming 1 1990
 Dwyer 1 1991
 Engelberts 1991
 Ponsonby 1993
 Gormally 1994
 Jorch 1994
 Klonoff-cohen 1995
 Fleming 2 1996
 Brooke 1997
 Mitchell 3 1997
 Oyen 1997
 Schellscheidt 1997
 L'Hoir 1998
 Dwyer 1999
 Mitchell 2 1999
 Hauck 2002
 McGarvey 2003
 Carpenter 2004



(Gilbert 2005)

prone position better ← → prone position worse

prone position better ← → prone position worse

Morte in culla

Gilbert 2005:



- La raccomandazione di **tenere il neonato in culla in posizione prona è proseguita per circa 50 anni** senza tener conto dell'**evidenza disponibile** già dal **1970** che la posizione prona era dannosa
- **Una revisione sistematica** dei fattori di rischio prevenibili per evitare la morte in culla avrebbe permesso a partire **dal 1970** di **conoscere** che la posizione prona era dannosa e avrebbe **evitato** più di **10.000** morti in **Gran Bretagna** e almeno **50.000** tra **Europa, Stati Uniti e Australia**.

Fasi di produzione di una LG

- Scelta dell'argomento
- Composizione di un gruppo multidisciplinare
- Definizione dei quesiti clinici
- **Revisione sistematica della letteratura**
- Valutazione critica dei risultati della ricerca (qualità dell'evidenza)
- Formulazione delle raccomandazioni
- Esplicitazione della forza delle raccomandazioni
- Peer review
- Diffusione e implementazione

CON CHI?

- Non da soli!
- Multidisciplinare
- Esperti dell'argomento bilanciati da 'ignari'
- Metodologi, epidemiologi clinici o statistici
- Un po' di esperienza e un po' di training non guastano (ecco perché siete qui)
- Coinvolgere pazienti/users (molto Cochrane)

Il protocollo di una revisione sistematica

Protocollo -contenuti

- Background
- Obiettivi della revisione
- Metodi
 - ✓ I criteri di inclusione degli studi
 - ✓ La strategia di ricerca bibliografica
 - ✓ I metodi con cui verranno estratti i dati
 - ✓ I criteri di valutazione di qualità metodologica degli studi che verranno usati
 - ✓ Il metodo usato per l'eventuale sintesi statistica
 - ✓ Eventuali analisi per sottogruppi
 - ✓ Metodo per valutare la qualità dell'evidenza (GRADE)

Protocollo

- Scriverlo: fondamentale
 - ✓ più revisori
 - ✓ avere idee chiare di quello che si vuole fare
 - ✓ evitare il reporting bias (solo i risultati significativi)
- Pubblicarlo: raccomandato

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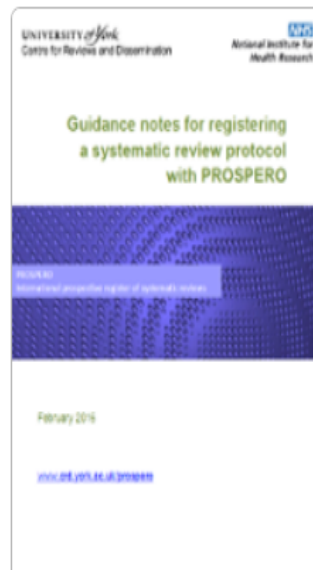
[What happens after submitting a form](#)

[Making changes, amendments and updating a published record](#)

[What to do after completing a review and after publishing the](#)

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Download the guidance notes for registering a systematic review on PROSPERO.



COSA VOGLIAMO FARE?

**Il Quesito/obiettivo della
vostra revisione sistematica
detta titolo e criteri di
inclusione/esclusione
(i.e. PICO)**

*A clearly defined, focused review begins with a well framed
question*



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Strutturazione del quesito clinico
e misure di associazione
Giovanni L. PAPPAGALLO

Defining the review question

A clearly defined, focused review begins with a well framed question.

The review question should specify:

- **types of population** (participants),
- **types of interventions** (and comparisons),
- **types of outcomes** that are of interest.

These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.



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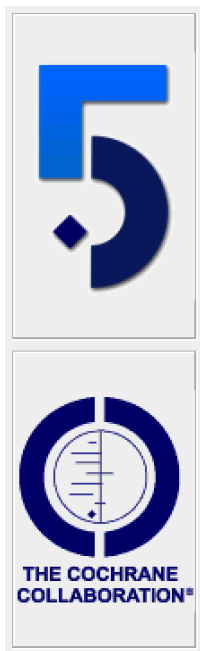
[Home](#) › [Online learning](#) › [Core software for Cochrane Reviews](#) › [RevMan](#)

Review Manager (RevMan)

There are two versions of Cochrane RevMan: RevMan Web (online) and RevMan 5 (desktop)



Cochrane RevMan



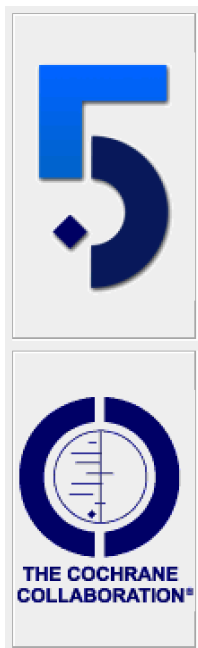
Review Manager 5.3

[Intervention] for [health problem]

Text of Review

- Intervention review
 - Title
 - Protocol information
 - Main text
 - Abstract
 - Plain language summary
 - Background
 - Objectives**
 - Methods
 - Results
 - Discussion
 - Authors' conclusions
 - Acknowledgements
 - Contributions of authors
 - Declarations of interest
 - Differences between protocol and review
 - Published notes
 - Tables
 - Studies and references
 - Data and analyses
 - Figures
 - Sources of support
 - Feedback
 - Appendices

- Objectives
- Methods
- Criteria for considering studies for this review
- Types of studies
- Types of participants
- Types of interventions
- Types of outcome measures
- Primary outcomes
- Secondary outcomes



Review Manager 5.3

New Review Wizard

What is the title of the review?

Title:

- [Intervention] for [health problem]
- [Intervention A] versus [intervention B] for [health problem]
- [Intervention] for [health problem] in [participant group/location]
- [Use if title does not fit any of the formats above]

Cancel < Back Next > Finish

The screenshot shows the 'New Review Wizard' dialog box in Review Manager 5.3. The title of the wizard is 'New Review Wizard'. The main question is 'What is the title of the review?'. Below this, there are four radio button options for the title format. The second option, '[Intervention A] versus [intervention B] for [health problem]', is selected. At the bottom, there are four buttons: 'Cancel', '< Back', 'Next >', and 'Finish'.

Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

OBJECTIVES

The **primary objective** of this review was to determine the **efficacy of screening men for prostate cancer** in reducing prostate cancer-specific and all-cause mortality.

The secondary objectives of this review were to:

- determine the impact of prostate cancer screening on quality of life and adverse effects; and
- document the costs of screening for prostate cancer.

Defining the review question

A clearly defined, focused review begins with a well framed question.

The review question should specify:

- **types of population** (participants),
- **types of interventions** (and comparisons),
- **types of outcomes** that are of interest.

These components of the question, with the additional specification of types of study that will be included, form the basis of the pre-specified eligibility criteria for the review.

The 'clinical question' should specify the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.

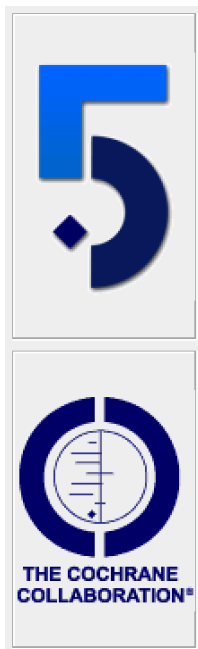
The acronym PICO (**P**articipants, **I**nterventions, **C**omparisons and **O**utcomes) helps to serve as a reminder of these.

P Population
Used to first develop the health care question

I Intervention

C Comparison

O Outcomes
Used to determine if the evidence found directly answers the health care question



Review Manager 5.3

[Intervention A] versus [intervention B] for [health problem]

Text of Review

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- Primary outcomes
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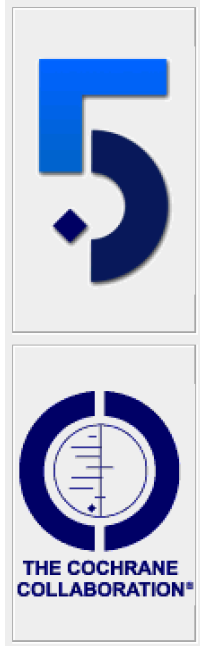
Screening for prostate cancer (Review)

Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of participants

All men enrolled in studies of prostate cancer screening were eligible for this review, with no exclusions based on ethnicity, age, or presence of lower urinary tract symptoms. Studies including men with a previous diagnosis and treatment of prostate cancer were excluded.



Review Manager 5.3

[Intervention A] versus [intervention B] for [health problem]

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Screening for prostate cancer (Review)

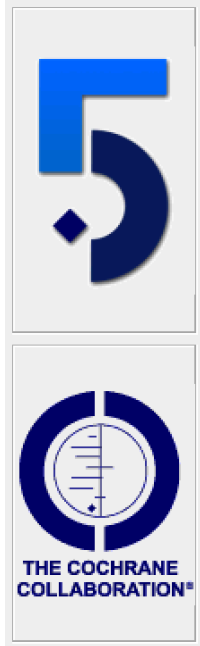
Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

Types of interventions

Studies that used any of the following screening procedures, individually or in combination, were included:

- digital rectal examination (DRE);
- prostate-specific antigen (PSA) test (including total, velocity, density, and percentage free and complex); and
- transrectal ultrasound (TRUS)-guided biopsy.



Review Manager 5.3

[Intervention A] versus [intervention B] for [health problem]

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Ilic D, Neuberger MM, Djulbegovic M, Dahm P

Cochrane Database of Systematic Reviews 2013, Issue 1.

Primary outcomes

Primary outcome measures for this review were prostate cancer-specific and all-cause mortality.

Secondary outcomes

Secondary outcome measures included:

- incident prostate cancers by stage and grade at diagnosis;
- metastatic disease at follow-up;
- quality of life;
- harms of screening (including both adverse outcomes from false-positive or false-negative results and their impact upon resulting treatment procedures); and
- costs associated with screening programs.



Outcomes

Should be
importance driven
NOT
evidence driven

Journal of Clinical Epidemiology 64 (2011) 395–400

GRADE guidelines: 2. Framing the question and deciding on important outcomes

Gordon H. Guyatt^{a,*}, Andrew D. Oxman^b, Regina Kunz^c, David Atkins^d, Jan Brozek^a, Gunn Vist^b, Philip Alderson^e, Paul Glasziou^f, Yngve Falck-Ytter^g, Holger J. Schünemann^a

If evidence is lacking for an important outcome, this should be acknowledged, rather than ignoring the outcome - that uncertainty may have a bearing on the ultimate recommendation.

Defining the review question

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New Outcome Wizard

What type of outcome do you want to create?

Data Type:

- Dichotomous
- Continuous
- O-E and Variance
- Generic Inverse Variance
- Other Data

Description:

Enter observed minus expected and its variance (e.g. calculated from individual patient data). Optionally enter number of participants with events and total number of participants in experimental and control groups.

Cancel < Back Next > Finish

variabili di risposta

New Outcome Wizard

Which analysis method do you want to use?

Statistical Method

- Peto
- Mantel-Haenszel
- Inverse Variance
- Exp[(O-E) / Var]

Analysis Model

- Fixed Effect
- Random Effects

Effect Measure

- Peto Odds Ratio
- Odds Ratio
- Risk Ratio
- Risk Difference
- Mean Difference
- Std. Mean Difference
- Name of Effect Measure:

Hazard Ratio

Cancel < Back Next > Finish

misure riassuntive di effetto

VARIABILI DI RISPOSTA:

- di tipo **qualitativo (nominale)**
 - esprime categorie di risposta del tipo successo / insuccesso (di un trattamento somministrato).
- di tipo **quantitativo (intervallare)**
 - assume uno spettro continuo di valori e viene misurata in riferimento a una scala a intervalli costanti.
- del tipo **“tempo a evento”**
 - rappresenta il tempo trascorso fino al verificarsi (o meno) di un evento.



New Outcome Wizard

What type of outcome do you want to create?

Data Type:

- Dichotomous
- Continuous
- O-E and Variance
- Generic Inverse Variance
- Other Data

Description:

Enter observed minus expected and its variance (e.g. calculated from individual patient data). Optionally enter number of participants with events and total number of participants in experimental and control groups.

Cancel < Back Next > Finish

variabili di risposta

New Outcome Wizard

Which analysis method do you want to use?

Statistical Method

- Peto
- Mantel-Haenszel
- Inverse Variance
- Exp[(O-E) / Var]

Analysis Model

- Fixed Effect
- Random Effects

Effect Measure

- Peto Odds Ratio
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Cancel < Back Next > Finish

misure riassuntive di effetto

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

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OS (overall survival) PFS (progression-free survival) DFS (disease-free survival) TTD (time to deterioration...)	tempo a evento	HR (hazard ratio) - - -	differenza tra mediane differenza tra stime al tempo t... RMST (restricted mean survival time) RD (risk difference)

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Risk and Odds

- **Risk** (proportion of persons with disease = cumulative incidence)

$$\frac{\text{number of new events during the specified period}}{\text{number of persons at risk during the specified period}}$$

Sintesi degli indicatori di effetto per variabili qualitative (nominali)...

Misure di
effetto relativo

Risk

$$70 \text{ risposte} / 100 \text{ pazienti} = 0.70$$

Risk Ratio

$$\frac{70 \text{ risposte} / 100 \text{ pazienti (braccio A)}}{30 \text{ risposte} / 100 \text{ pazienti (braccio B)}} = \frac{0.70}{0.30} = 2.33$$

Odds

$$65 \text{ risposte} / 35 \text{ non risposte} = 1.86$$

Odds Ratio

$$\frac{65 \text{ risposte} / 35 \text{ non risposte (braccio A)}}{25 \text{ risposte} / 75 \text{ non risposte (braccio B)}} = \frac{1.86}{0.33} = 5.63$$

Misura di
effetto assoluto

Risk Difference

$$0.70 - 0.30 = 0.40, \text{ ovvero: } 40 \text{ risposte } \textit{in pi\`u} \text{ ogni } 100 \text{ pazienti trattati}$$

NNT

$$1 / 0.40 = 2.5, \text{ ovvero: } \textit{una risposta } \textit{in pi\`u} \text{ ogni } 2.5 \text{ pazienti trattati}$$

Risk and Odds

- **Risk** (proportion of persons with disease = cumulative incidence)
 - **Risk Ratio** = ratio of 2 cumulative incidence estimates = Relative Risk

$$\frac{\text{Risk of event within experimental arm}}{\text{Risk of event within control arm}}$$

- Absolute difference of 2 cumulative
- Odds (probability of event will or will not be observed)
- Relative Odds

Sintesi degli indicatori di effetto per variabili qualitative (nominali)...

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Beneficio RELATIVO (RR, OR , HR) o ASSOLUTO (RD)?

WHY THE NUMBERS MATTER

RELATIVE RISK

**"New wonder drug
reduces heart
attack risk 50%"**



Beneficio RELATIVO (RR, OR , HR) o ASSOLUTO (RD)?

WHY THE NUMBERS MATTER

RELATIVE RISK

**"New wonder drug
reduces heart
attack risk 50%"**

ABSOLUTE RISK

**"New wonder drug
reduced heart attacks
from from 2 per 100
to 1 per 100"**

The absolute risk is more useful at conveying the true impact of an intervention, yet is often under-reported in the research and the news.



HEALTHNEWSREVIEW
YOUR HEALTH NEWS WATCHDOG

Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

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Risk and Odds

number of new events during
the specified period

number of non events during
the specified period

- **Odds** (the likelihood that an event will or will not be observed)
 - Odds Ratio = ratio of 2 odds

Sintesi degli indicatori di effetto per variabili qualitative (nominali)...

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- **Risk** (proportion of persons with disease = cumulative incidence)
 - Risk difference = absolute difference of 2 cumulative incidence estimates =
 - Risk Ratio = ratio of 2 cumulative incidence estimates
- **Odds** (the likelihood that an event will or will not be observed)
 - **Odds Ratio** = ratio of 2 odds

$$\frac{\text{Odds of event within experimental arm}}{\text{Odds of event within control arm}}$$

Sintesi degli indicatori di effetto per variabili qualitative (nominali)...

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Misura di
effetto assoluto

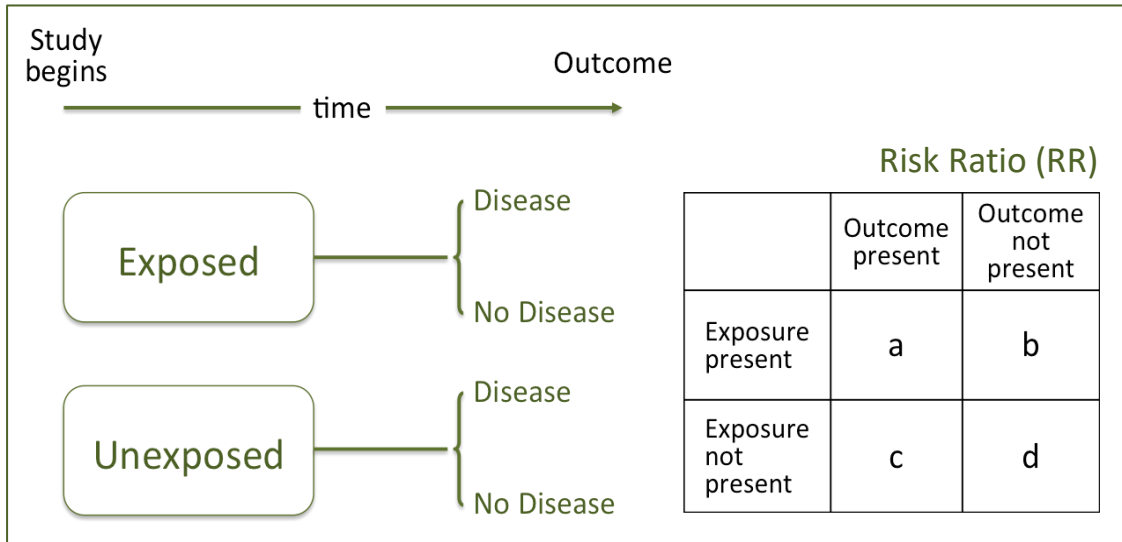
Risk Difference

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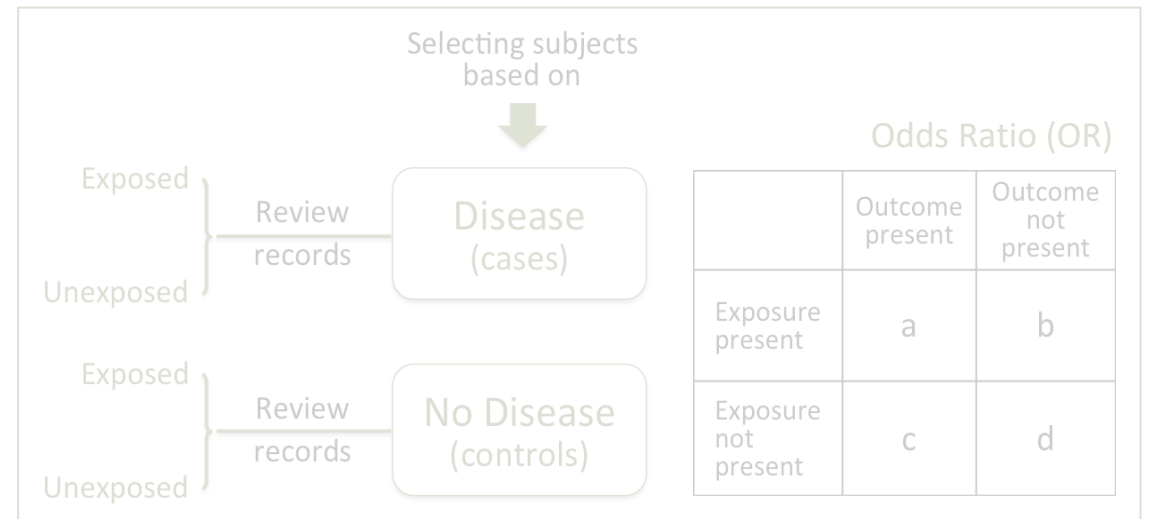
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$$1 / 0.40 = 2.5, \text{ ovvero: una risposta } \textit{in pi\`u} \text{ ogni } 2.5 \text{ pazienti trattati}$$

STUDI EPIDEMIOLOGICI

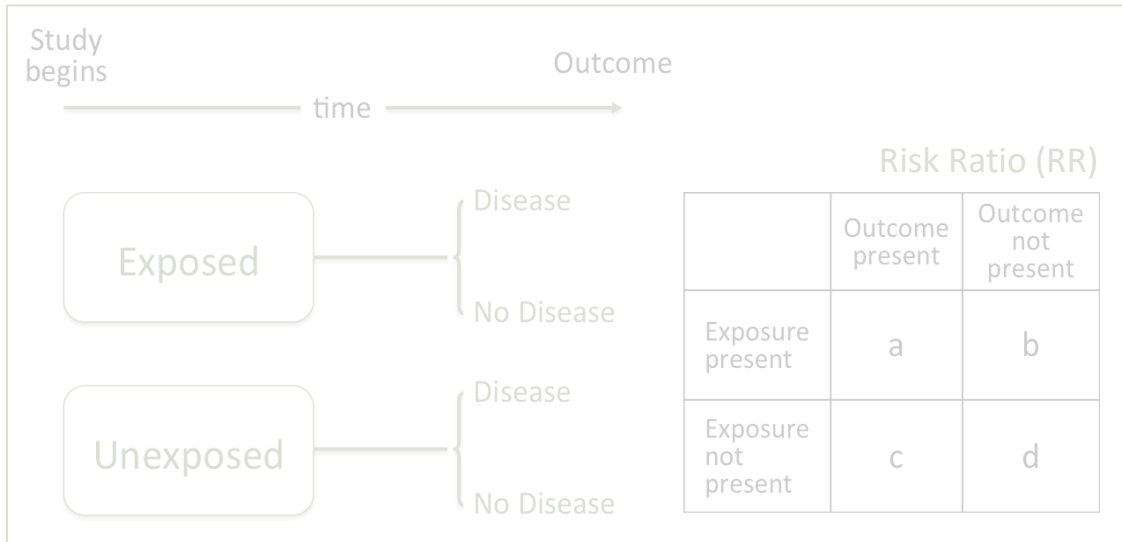


Studio di coorte
(prospettico)

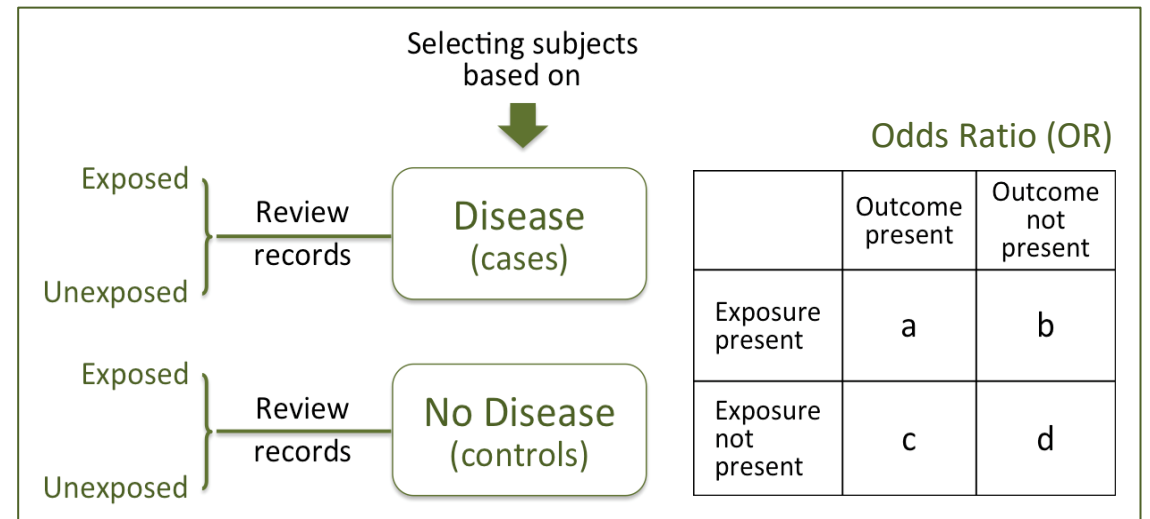


Studio caso-controllo
(retrospettivo)

STUDI EPIDEMIOLOGICI



Studio di coorte
(prospettico)



Studio caso-controllo
(retrospettivo)

VARIABILE DI RISPOSTA

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Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

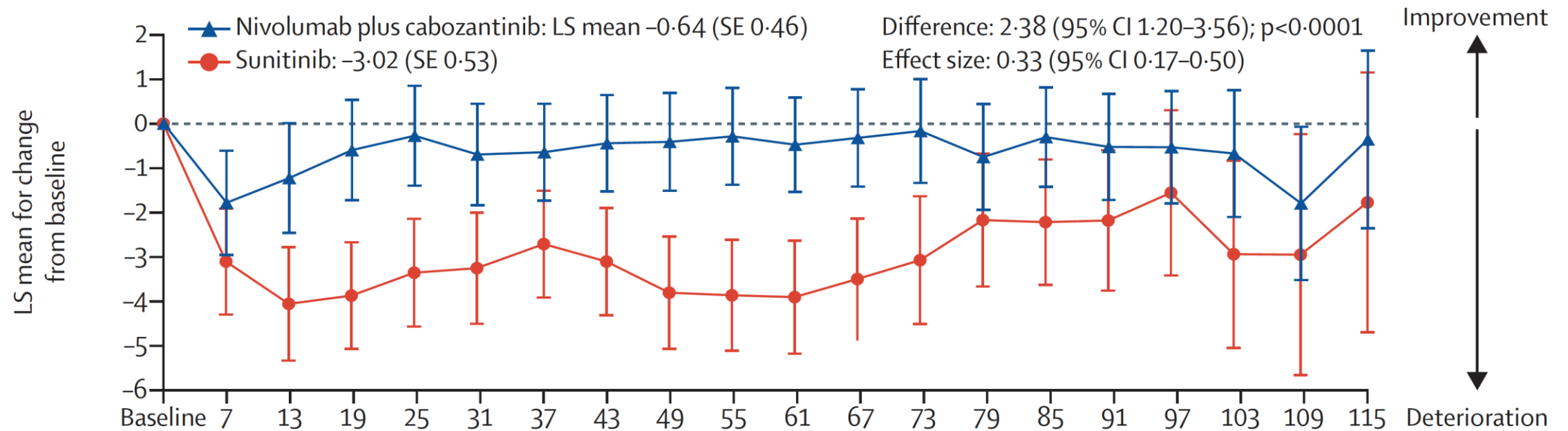
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Patient-reported outcomes with first-line nivolumab plus cabozantinib versus sunitinib in patients with advanced renal cell carcinoma treated in CheckMate 9ER: an open-label, randomised, phase 3 trial

David Cella*, Robert J Motzer*, Cristina Suarez, Steven I Blum, Flavia Ejzykowicz, Melissa Hamilton, Joel F Wallace, Burcin Simsek, Joshua Zhang, Cristina Ivanescu, Andrea B Apolo, Toni K Choueiri

Lancet Oncol 2022; 23: 292–303

A FKSI-19 total score



VARIABILE DI RISPOSTA

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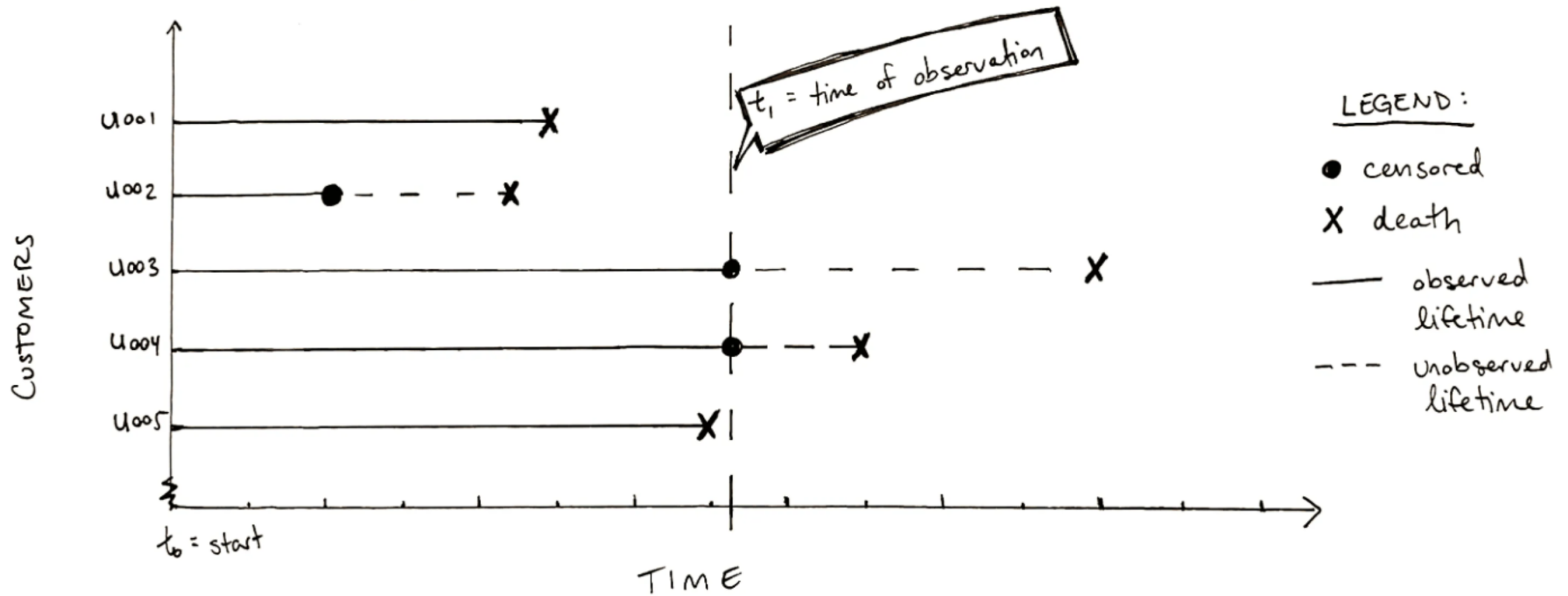
Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

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TIME TO EVENT ANALYSIS

SUBJECTS. OR WORSE DROPPING ALL CENSORED SUBJECTS CAN BIAS OUR RESULTS.

Observed customer lifetimes



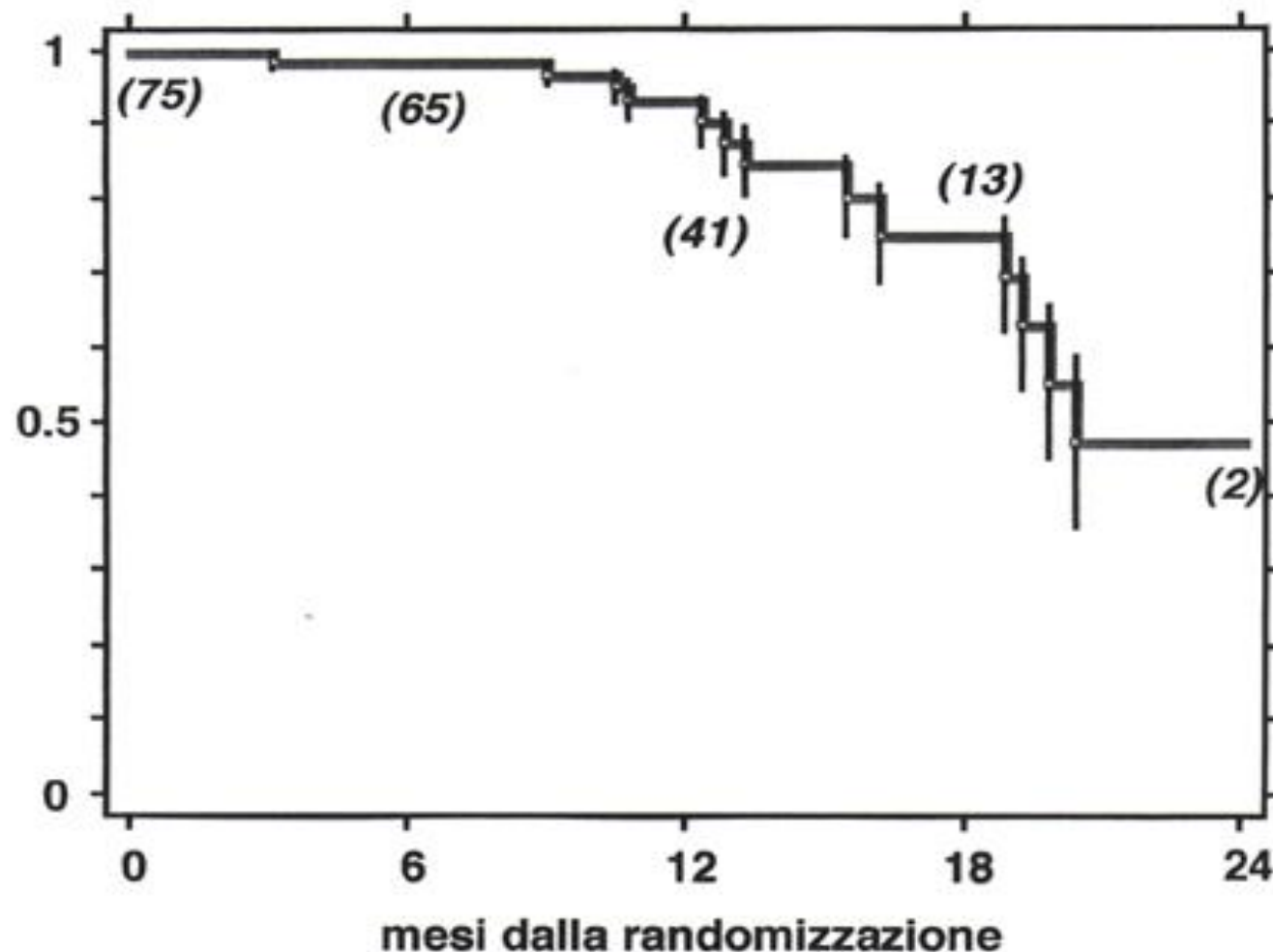
Variabile tempo-a-evento

- Apparentemente assimilabile a una variabile di tipo quantitativo (intervallare)...
- ...ma il verificarsi o meno di un evento la rende assimilabile a una variabile di tipo qualitativo (nominale)

Metodo di Kaplan-Meier

Stima della probabilità di sopravvivere in corrispondenza di ciascuno dei tempi in cui si verifica almeno un evento

CURVA DI SOPRAVVIVENZA



Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

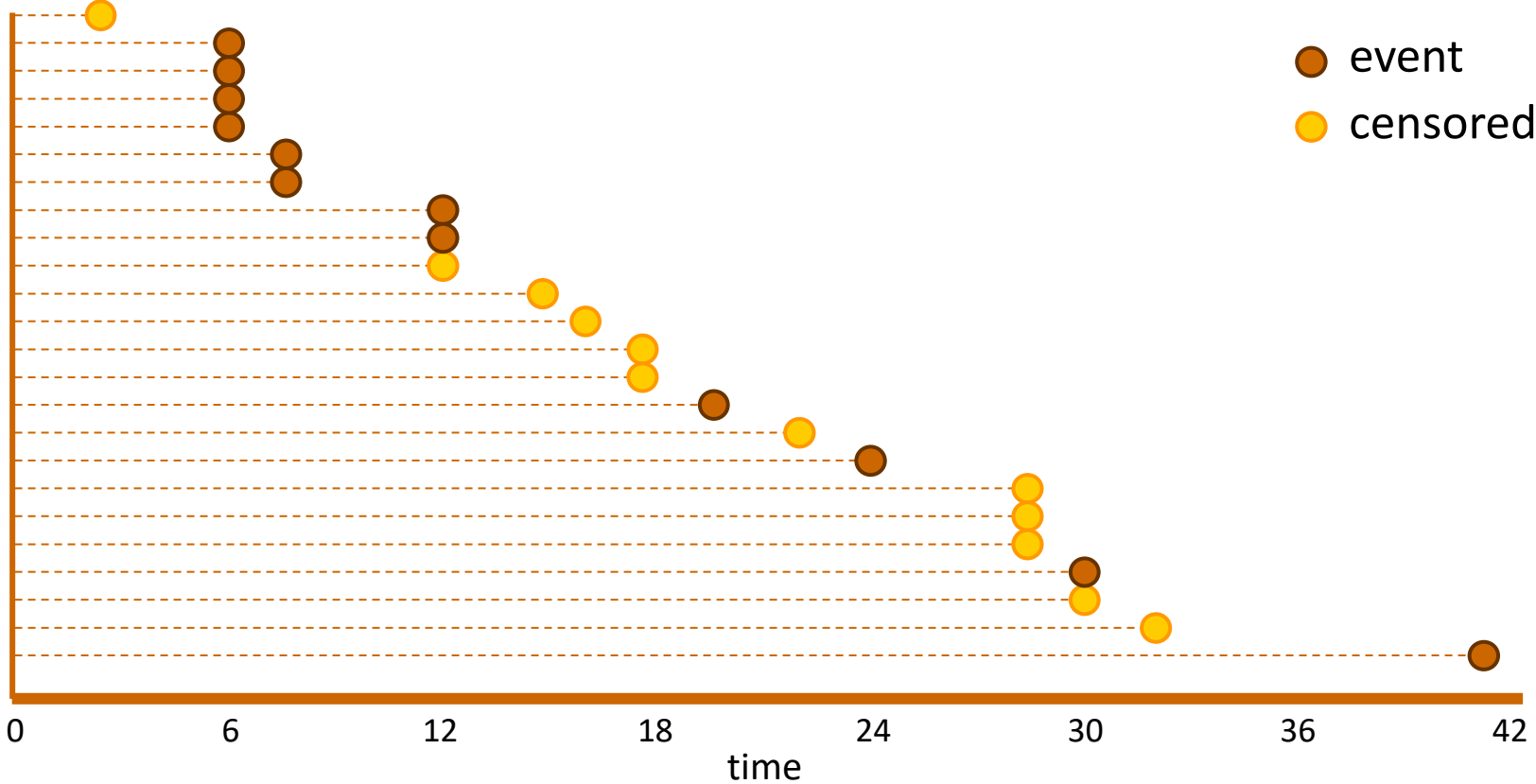
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Defining a Hazard Ratio (HR)

- Compares risk of event in two populations or samples
- The ratio of risk (*hazard rate*) in experimental group to risk (*hazard rate*) in control group
 - *The Hazard Rate (λ)* is the rate at which events happen
- Assumption: *proportional hazards (PH)*, i.e. the risk does not depend on time, that is, “risk is constant over time”

$$\lambda = \frac{d}{f + F}$$

d = number of events
 f = sum of follow-up times for patients with event
 F = sum of follow-up times for patients with no event (censored)



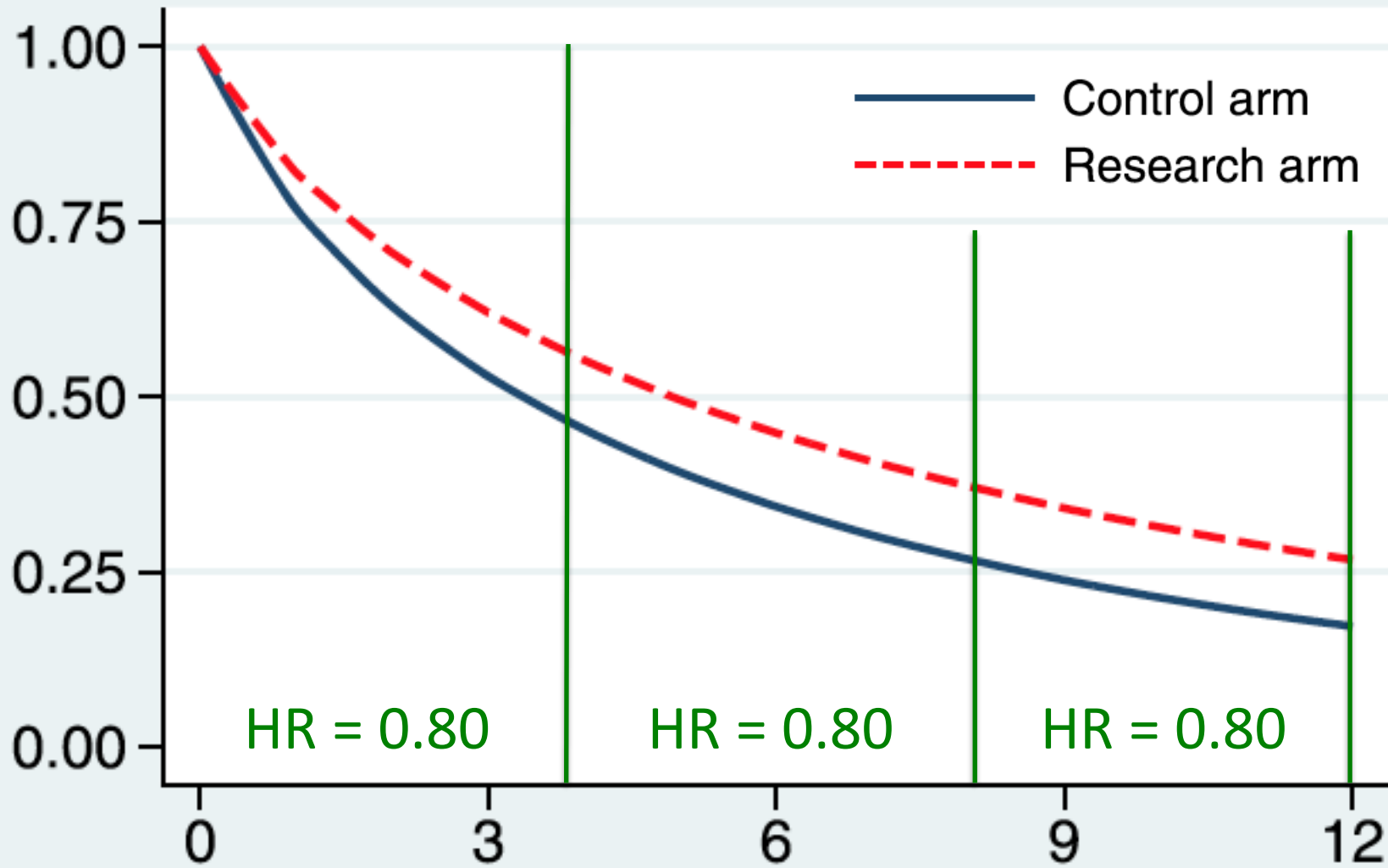
d = 12
 f = 6+6+6+6+8+8+12+12+20+24+30+42 = 180
 F = 3+12+15+16+18+18+22+28+28+28+30+33 = 251

$$\lambda = \frac{12}{431} = 0.0278$$

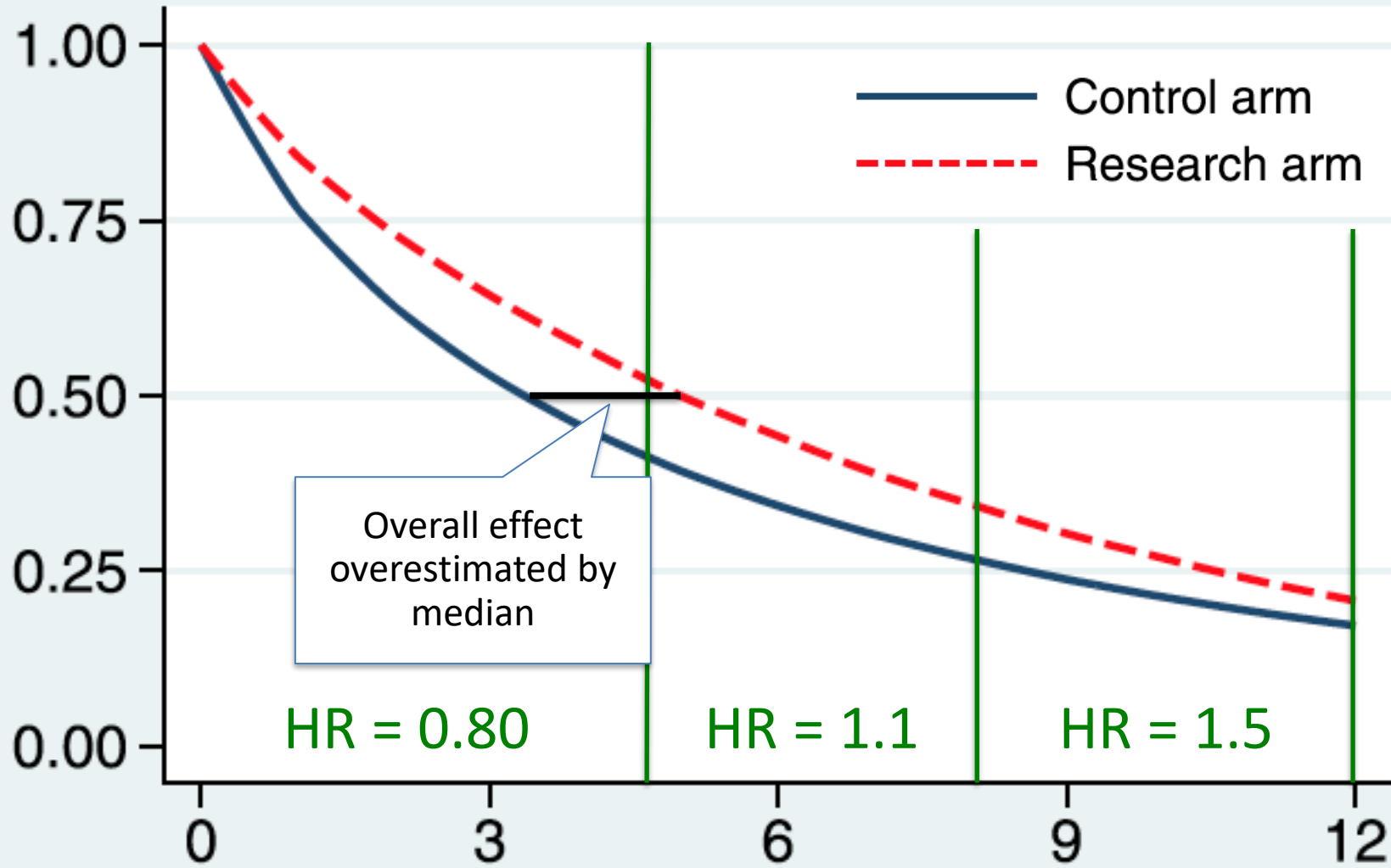
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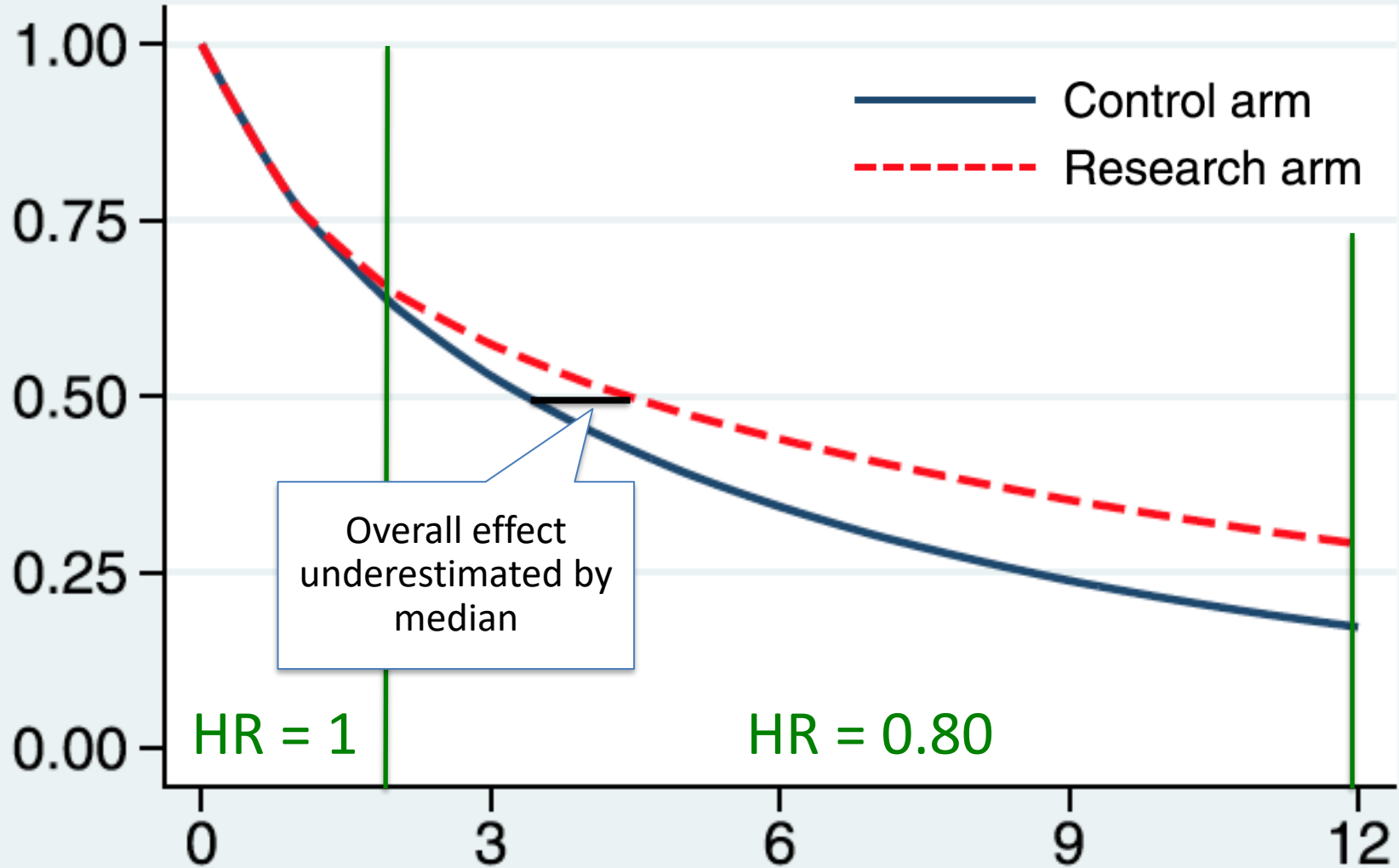
Proportional hazards



Decreasing treatment effect

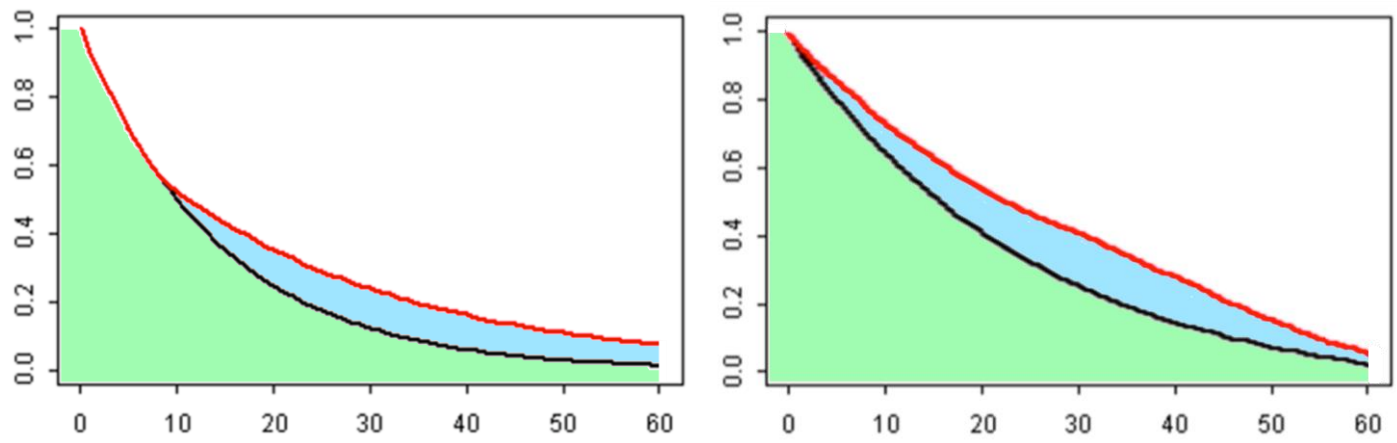
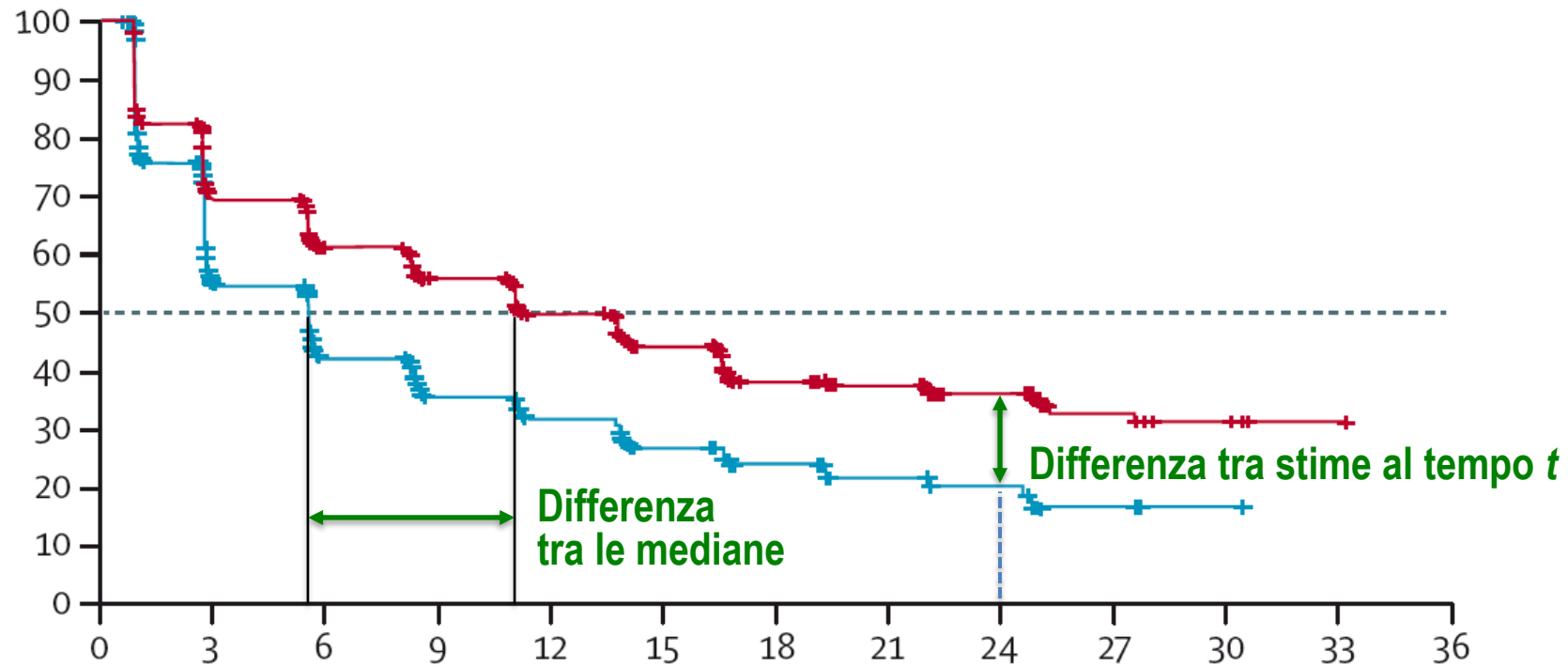


Increasing treatment effect



Variabili di comune riscontro negli studi clinici e indicatori comparativi di effetto

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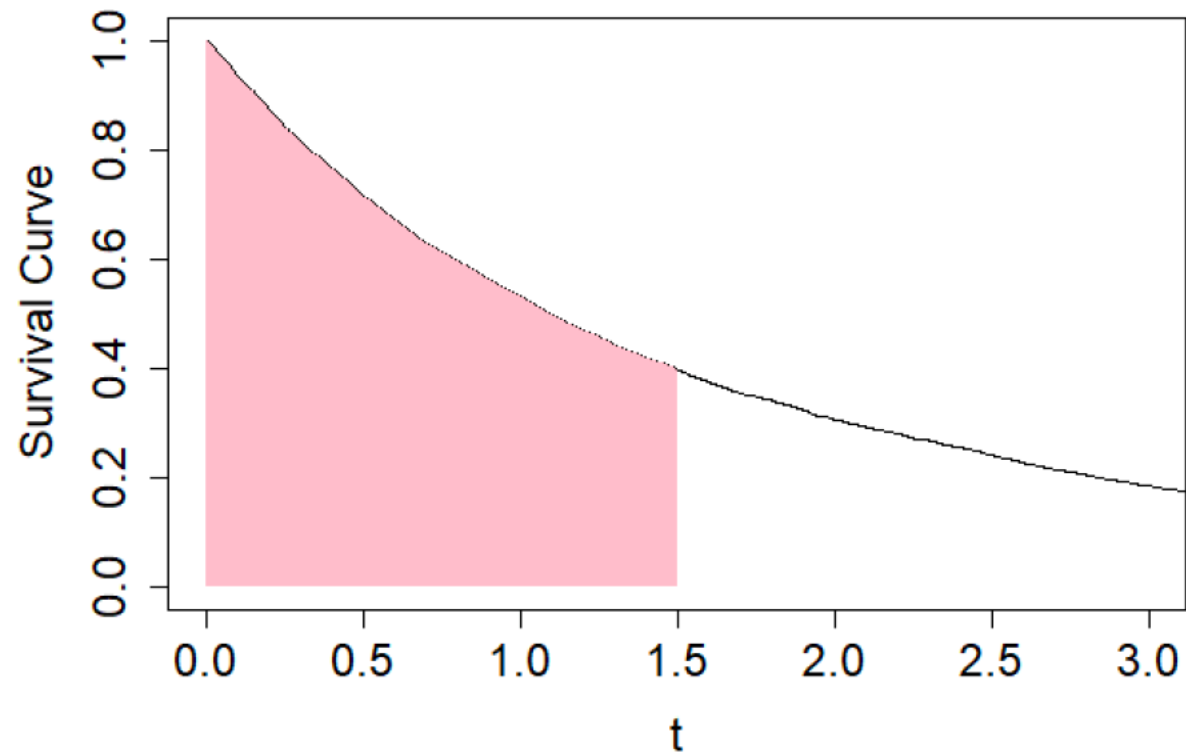
Restricted Mean Survival Time
(differenza tra le aree sotto la curva)

— Time to Event (control) — Time to Event (treatment) ■ RMST (control) ■ Additional RMST (treatment)

Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome

Patrick Royston* and Mahesh KB Parmar

BMC Medical Research Methodology 2013, **13**:152



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GRADE guidelines 27: how to calculate absolute effects for time-to-event outcomes in summary of findings tables and Evidence Profiles

Nicole Skoetz^{a,*}, Marius Goldkuhle^a, Elvira C. van Dalen^b, Elie A. Akl^c, Marialena Trivella^d,
Reem A. Mustafa^e, Artur Nowak^f, Philipp Dahm^g, Holger Schünemann^h,
Ralf Benderⁱ, GRADE Working Group

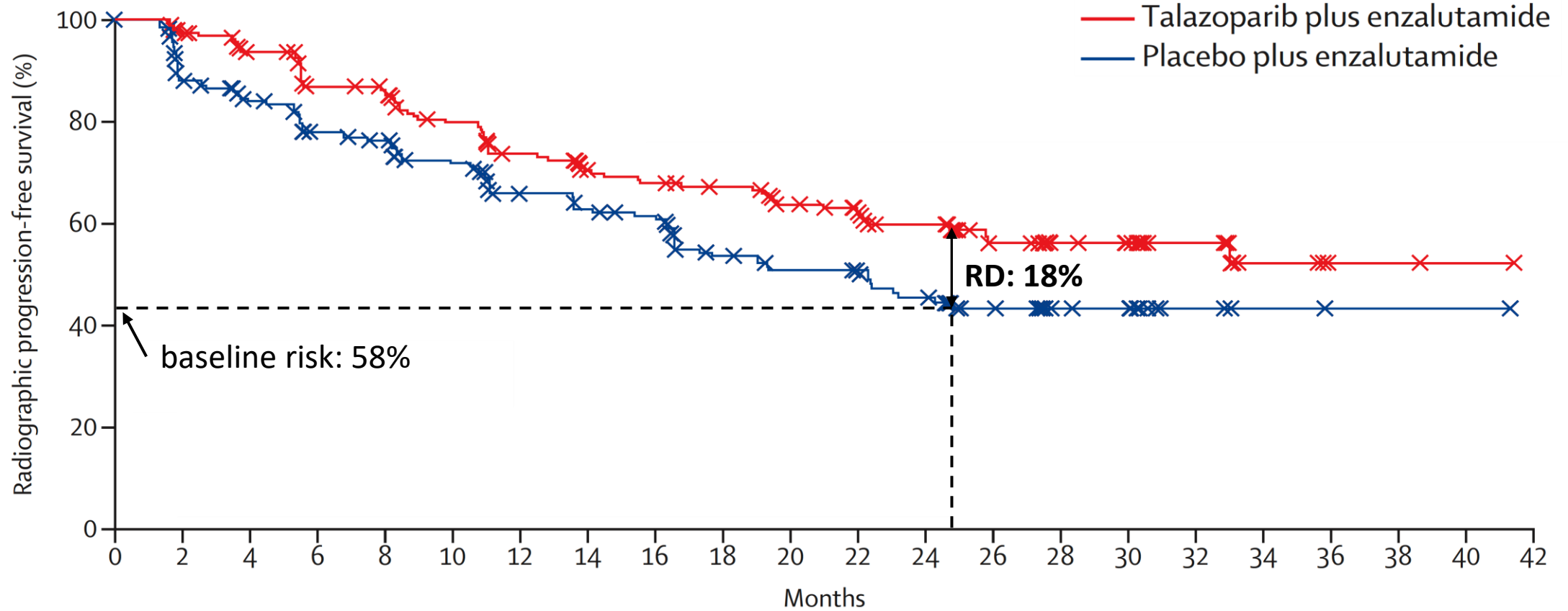
Absolute effect estimates (i.e., risk difference, the number needed to treat) provide important supplementary information to relative effect estimates by **considering the control event rate over a given time period**. As they take into account the underlying baseline risk for the event of interest in the study groups, absolute effect estimates **are less vulnerable to exaggerated effect interpretation than relative effect estimates** and allow a more appropriate assessment of the clinical relevance of effects.

...

Data from Kaplan-Meier survival curves from the control groups of the trials included in the analysis may be **used to estimate the baseline risk**.

Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial

Neeraj Agarwal*, Arun A Azad, Joan Carles, Andre P Fay, Nobuaki Matsubara, Daniel Heinrich, Cezary Szczylik, Ugo De Giorgi, Jae Young Joung, Peter C C Fong, Eric Voog, Robert J Jones, Neal D Shore, Curtis Dunshee, Stefanie Zschäbitz, Jan Oldenburg, Xun Lin, Cynthia G Healy, Nicola Di Santo, Fabian Zohren, Karim Fizazi*
Lancet 2023; 402: 291-303



Median follow-up for rPFS was 24.9 months (IQR 21.9–30.2) for the talazoparib group and **24.6 months (14.4–30.2) for the placebo group.**



SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10^a EDIZIONE

MODULI SPECIALISTICI - S1



VENERDÌ 8 - SABATO 9 MARZO 2024
NEGRAR DI VALPOLICELLA (VR)
Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

Database bibliografici
e ricerca delle informazioni
Veronica Andrea FITTIPALDO

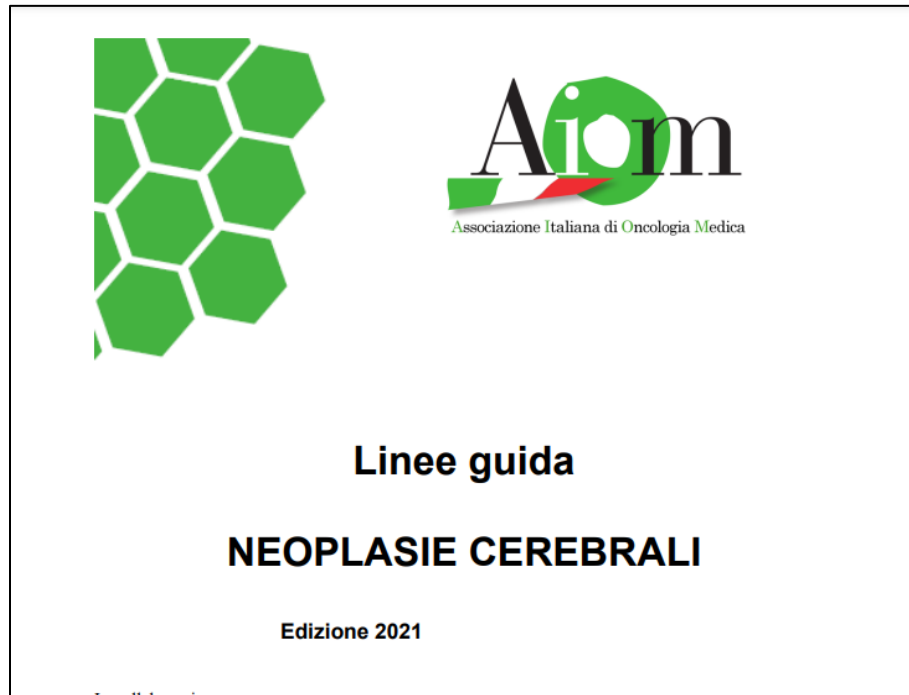
Ricerca sistematica della letteratura scientifica

Obiettivo Generale

Prendere decisioni nella pratica clinica
rispondendo a quesiti attraverso il reperimento
delle evidenze disponibili

Impostare una strategia di ricerca

Quesito clinico



Capitolo 9: Glioblastoma di nuova diagnosi

Q2: Nei pazienti con meno di 70 anni alla radioterapia (60 Gy/30 frazioni) dovrebbe essere associato un trattamento con temozolomide concomitante (75 mg/m²/die) ed adiuvante (150-200 mg/m² per 5 giorni, ogni 28)?

https://snlg.iss.it/wp-content/uploads/2021/10/LG_266_neoplasie_cerebrali_agg2021.pdf

Elaborazione del modello PICO

Articolare il quesito clinico col modello PICO
risulta molto efficace per ritrovare evidenze
cl clinicamente rilevanti in letteratura

Elaborazione del modello PICO

P = paziente o popolazione

I = intervento

C = confronto

O = outcome (esito)

Nei pazienti con meno di 70 anni alla radioterapia (60 Gy/30 frazioni) dovrebbe essere associato un trattamento con temozolomide concomitante (75 mg/m²/die) ed adiuvante (150-200 mg/m² per 5 giorni, ogni 28)?

Elaborazione del modello PICO

P = soggetti affetti di glioblastoma <70anni

I = radioterapia

C = temozolamide

Nei *pazienti affetti da glioblastoma di nuova diagnosi, con meno di 70 anni*, alla *radioterapia* deve essere associato un trattamento con *temozolomide* concomitante o adiuvante?

Linee guida «Neoplasie cerebrali». AIOM (Associazione Italiana Oncologia Medica) Edizione 2021.

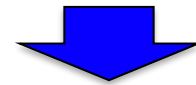
Creare la stringa di ricerca



Interrogare le diverse banche dati



Trovare gli studi randomizzati (RCT)



The image shows the PubMed.gov website homepage. At the top left is the NIH logo and the text "U.S. National Library of Medicine National Center for Biotechnology Information". At the top right is a "Log in" button. The main header features the "PubMed.gov" logo. Below the logo is a search bar with the placeholder text "Search PubMed" and a green "Search" button. Under the search bar, the word "Advanced" is written in a smaller font. A paragraph of text states: "PubMed® comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites." Below this text is a navigation menu with four categories: "Learn" (with a lightbulb icon), "Find" (with a magnifying glass icon), "Download" (with a download arrow icon), and "Explore" (with a globe icon). Each category has a list of sub-links. In the bottom right corner, there is a green "Feedback" button.

NIH U.S. National Library of Medicine
National Center for Biotechnology Information

Log in

PubMed.gov

Search PubMed Search

Advanced

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FTP
Batch Citation Matcher

Explore
MeSH Database
Journals

Feedback

<https://www.ncbi.nlm.nih.gov/pubmed/>

Pubmed: Banca dati bibliografica

- Archivio di **citazioni**, curato dal National Center of Biotechnology (NCBI) presso la National Library of Medicine di Bethesda e messo a disposizione gratuitamente nel 1996 tramite la piattaforma PubMed disponibile sul Web.
- L'Index Medicus, pubblicata dalla National Library of Medicine (NLM) nel 1879, ha indicizzato le principali riviste di medicina e di scienze biomediche, all'inizio negli Stati Uniti e dopo in tutto il mondo diventando il database ora conosciuto come MEDLINE®.

MEDLINE®

(Medical Literature Analysis and Retrieval System Online)

- Contiene più di 29 milioni di **citazioni** di riviste e abstract di letteratura biomedica da tutto il mondo.
- Medline contiene più di 5 mila journals indexati.
- Offre strumenti di ricerca attraverso parole chiavi su più campi (autore, titolo, abstract).
- Consente l'uso di operatori logici e la modalità di ricerca libera e con i termine MeSH.

Citazione bibliografica

- Ogni citazione bibliografica rappresenta un articolo di rivista.
- È composta da campi che forniscono informazioni sull'articolo.

I campi della citazione bibliografica

Rivista

Titolo citazione

Autori e affiliazione

> Oncotarget. 2017 Jul 4;8(27):44015-44031. doi: 10.18632/oncotarget.17054.

Survival benefit of glioblastoma patients after FDA approval of temozolomide concomitant with radiation and bevacizumab: A population-based study

Ping Zhu ^{1,2}, Xianglin L Du ¹, Guangrong Lu ², Jay-Jiguang Zhu ²

Affiliations + expand

PMID: 28467795 PMCID: PMC5546458 DOI: 10.18632/oncotarget.17054

Free PMC article

Abstract

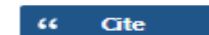
Few population-based analyses have investigated survival of glioblastoma patients treated with concomitant radiotherapy-temozolomide (RT-TMZ) and then bevacizumab (BEV) after Food and Drug Administration (FDA) approval. We aimed to explore the effects on survival with RT-TMZ of a population based on the Surveillance, Epidemiology, and End Results (SEER) databases. A total of 28933 GBM patients from Surveillance, Epidemiology, and End Results (SEER) databases (January 2000 to December 2013) were included. Patients were divided into three groups based on date of diagnosis: pre-RT-TMZ and pre-BEV (P1), RT-TMZ and pre-BEV (P2), and RT-TMZ and post-BEV (P3). The Kaplan-Meier method and Cox proportional hazards model were used to analyze overall survival (OS) across the three periods in both population-based and institutional-based analyses. The results showed that survival was significantly reduced during P2 and further decreased during P3. Comparison and validation analysis were performed. Consistent results were observed. We conclude that the survival of glioblastoma patients has been steadily improved from January 2000 to December 2013. The administration of RT and adjuvant TMZ for newly diagnosed GBM and then BEV for recurrent GBM after respective FDA approval.

Keywords: bevacizumab; cancer registry; glioblastoma (GBM); overall survival; temozolomide.

FULL TEXT LINKS



ACTIONS



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Conflict of interest statement

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Zhu P, Du XL, Lu G, Zhu JJ. Survival benefit of glioblastoma patients after FDA approval of temozolomide concomitant with radiation and bevacizumab: A population-based study. Oncotarget. 2017 Jul 4;8(27):44015-44031. doi: 10.18632/oncotarget.17054. PMID: 28467795; PMCID: PMC5546458.

Copy Download .nbib Format: NLM

Riassunto

PMID: 28467795

PMCID: [PMC5546458](https://pubmed.ncbi.nlm.nih.gov/PMC5546458/)

DOI: [10.18632/oncotarget.17054](https://doi.org/10.18632/oncotarget.17054)



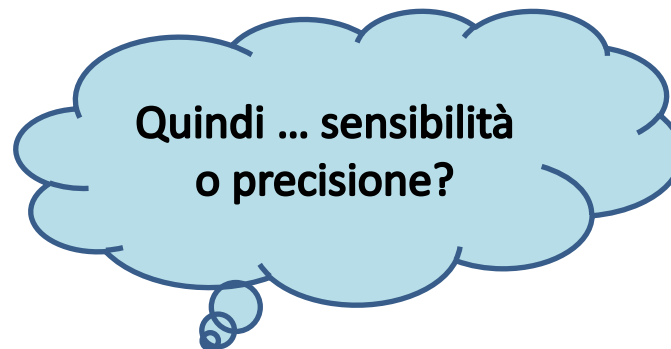
30 records utili su 3000
ritrovati su PubMed

- ✓ Ricerca completa
- X Alto numero di records non rilevanti alla nostra ricerca

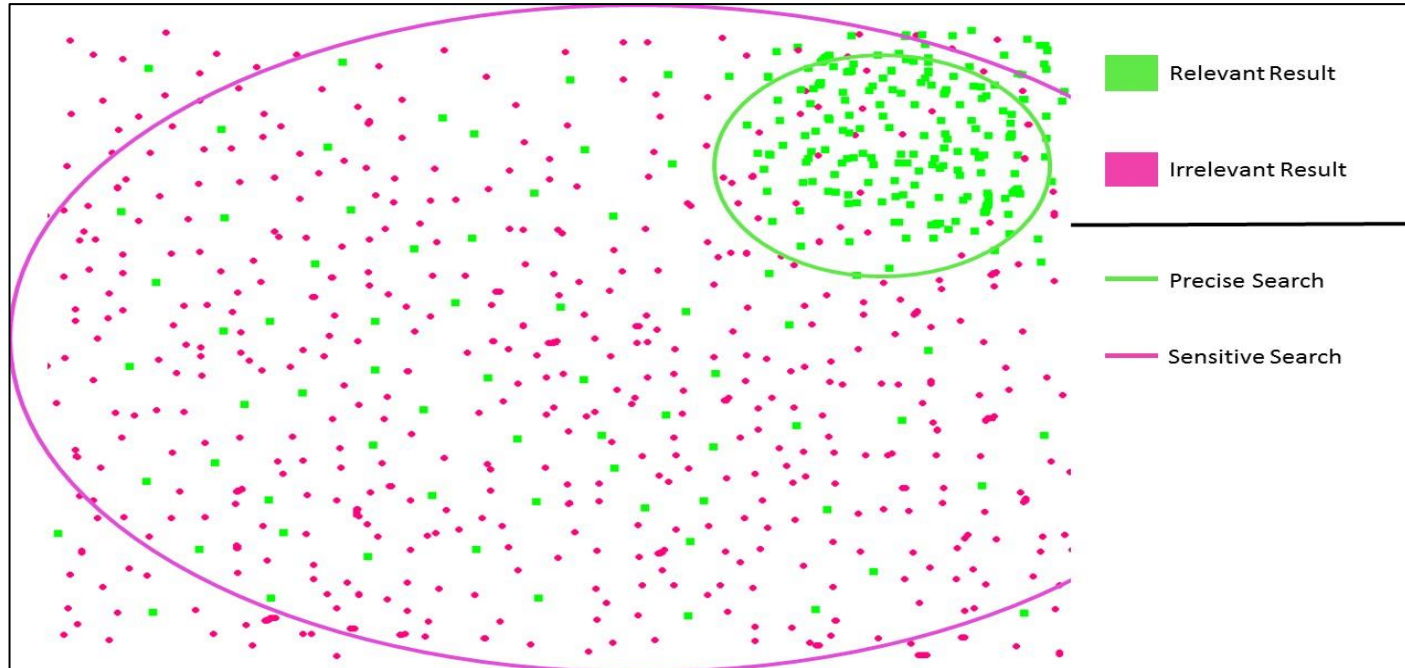


10 records utili su 30 ritrovati su
PubMed

- ✓ Trova i records rilevanti
- X Pericolo di perdere records, ricerca incompleta



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impossibile**



Fonte: University of Toronto <https://guides.library.utoronto.ca/c.php?g=577919&p=4304403>

Per fare una revisione sistematica



sensibilità

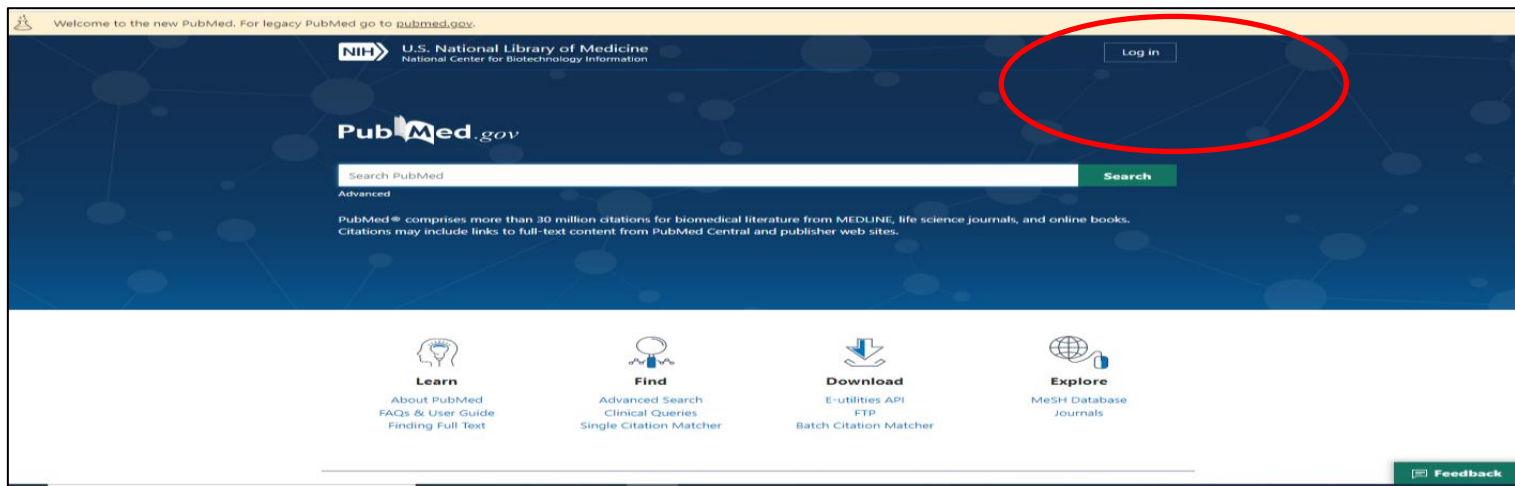
Per il clinico, che deve rispondere ad un quesito clinico



Precisione

Guida per una ricerca su PubMed

- Pubmed: Registrarsi e creare un account
- Ricerca libera
- Gli operatori booleani
- Creare una stringa di ricerca
- Mesh: utilizzo
- Risultati: conservazione e rilancio della ricerca
- Scaricare i risultati



1

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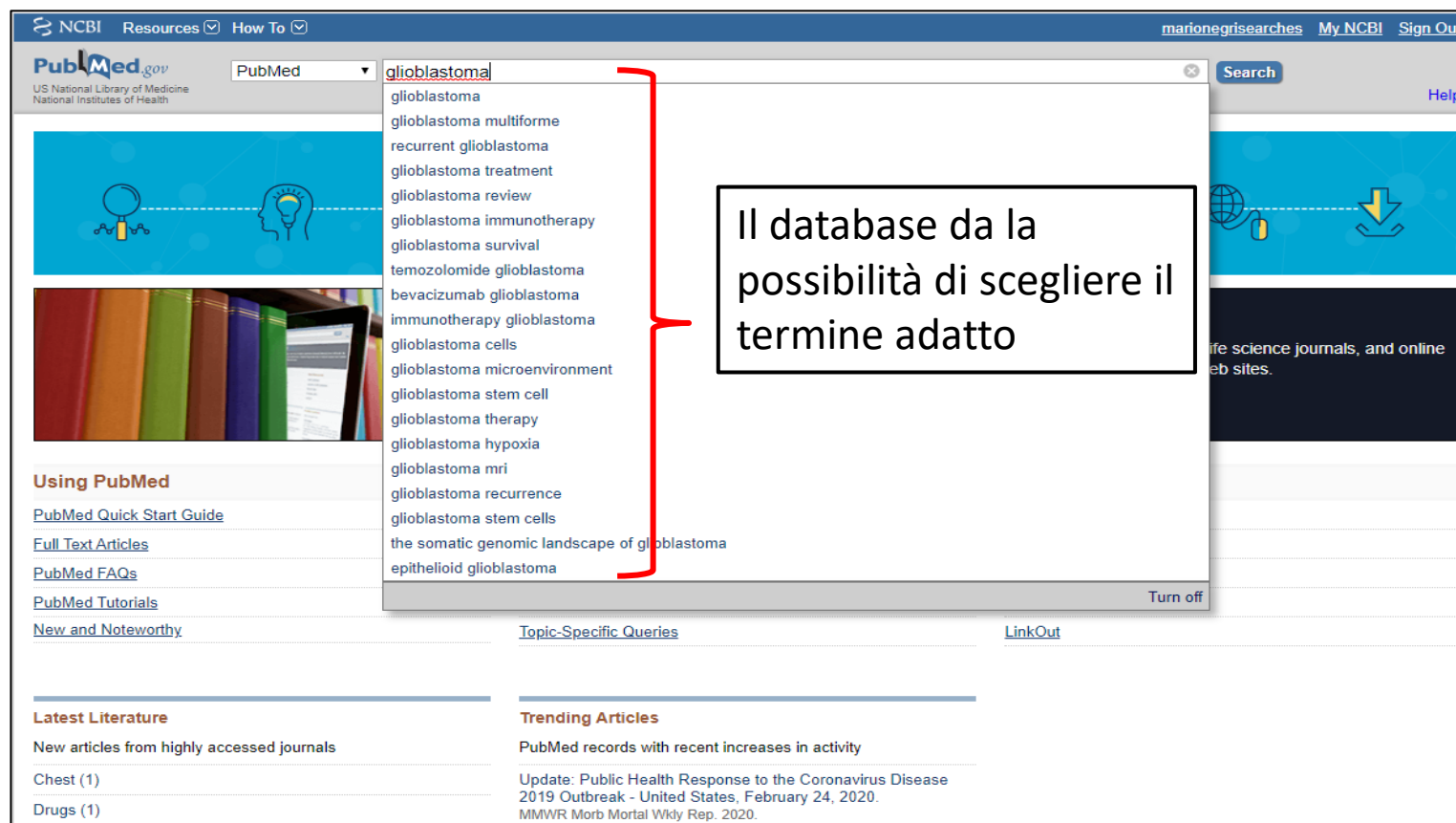
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2

Registrarsi sul sito di PubMed e creare una utenza permette di salvare le ricerche e richiamarli per aggiornarli.

Ricerca libera



The screenshot shows the PubMed website interface. At the top, there are navigation links for NCBI, Resources, and How To. The main search bar contains the text "glioblastoma". A dropdown menu is open, displaying a list of suggestions: glioblastoma, glioblastoma multiforme, recurrent glioblastoma, glioblastoma treatment, glioblastoma review, glioblastoma immunotherapy, glioblastoma survival, temozolomide glioblastoma, bevacizumab glioblastoma, immunotherapy glioblastoma, glioblastoma cells, glioblastoma microenvironment, glioblastoma stem cell, glioblastoma therapy, glioblastoma hypoxia, glioblastoma mri, glioblastoma recurrence, glioblastoma stem cells, the somatic genomic landscape of glioblastoma, and epithelioid glioblastoma. A red bracket highlights this list. A text box with a black border contains the text: "Il database da la possibilità di scegliere il termine adatto". Below the search bar, there are sections for "Using PubMed" with links to guides and FAQs, "Latest Literature" with a list of new articles, and "Trending Articles" with a list of recent activity.

Il database è formato da diversi campi: autore, data, nome del journal, ecc. Inserendo solo una parola chiave, in questo caso glioblastoma, la ricerca verrà fatta in tutti i campi, la chiamata “ricerca libera”

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PubMed.gov PubMed glioblastoma Search

US National Library of Medicine National Institutes of Health Create RSS Create alert Advanced Help

Click here to try the **New PubMed!**

An updated version of PubMed is now available. Come see the new improvements to the interface!

Article types: Clinical Trial, Review, Customize ...

Text availability: Abstract, Free full text, Full text

Publication dates: 5 years, 10 years, Custom range...

Species: Humans, Other Animals

Format: Summary Sort by: First Author Per page: 20

Send to Filters: Manage Filters

Sort by: Best match Most recent

Best matches for glioblastoma:

- [Glioblastoma](#)
Wirsching HG et al. Handb Clin Neurol. (2016)
- [Glioblastoma and other malignant gliomas: a clinical review](#)
Omuro A et al. JAMA. (2013)
- [Multidimensional communication in the microenvirons of glioblastoma](#)
Broekman ML et al. Nat Rev Neurol. (2018)

Switch to our new best match sort order

Results by year

Download CSV

Related searches: glioblastoma multiforme

Search results

Items: 1 to 20 of 39397

<< First < Prev Page 1 of 1970 Next > Last >>


**Più di 35.000 risultati e
1.790 pagine da controllare!**



La ricerca libera e semplice da fare ma il risultato ritrova un alto numero di records e, nella maggior parte dei casi, poco attinenti alla nostra ricerca.

MeSH: Medical Subject Headings

Welcome to the new PubMed. For legacy PubMed go to pubmed.gov.





 U.S. National Library of Medicine
National Center for Biotechnology Information [Log in](#)

PubMed.gov

Search PubMed [Search](#)

Advanced

PubMed® comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.

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---	--	--	--

[Feedback](#)

A large red arrow points from the bottom center of the page up to the 'MeSH Database' link in the 'Explore' section.

MeSH: Medical Subject Headings

The screenshot shows the PubMed website interface. At the top, there is a navigation bar with 'NCBI Resources' and 'How To' menus. The main header includes the 'PubMed.gov' logo and the text 'US National Library of Medicine National Institutes of Health'. A search bar contains the text 'glioblastoma' and a 'Search' button. A dropdown menu is open, showing 'Recent' items (PubMed, MeSH, Books) and 'All' items (All Databases, Assembly, Biocollections, BioProject, BioSample, BioSystems, Books, ClinVar, Conserved Domains, dbGaP, dbVar, Gene, Genome, GEO DataSets, GEO Profiles). A blue banner in the center reads 'Click here to try the New PubMed! An updated version of PubMed is now available. Come see the new improvements to the interface!'. Below this, a 'PubMed' section states: 'PubMed comprises more than 30 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites.' The page is divided into three columns: 'Using PubMed' (with links to Quick Start Guide, Full Text Articles, FAQs, Tutorials, and New and Noteworthy), 'PubMed Tools' (with links to Mobile, Single Citation Matcher, Batch Citation Matcher, Clinical Queries, and Topic-Specific Queries), and 'More Resources' (with links to MeSH Database, Journals in NCBI Databases, Clinical Trials, E-Utilities (API), and LinkOut). At the bottom, there are sections for 'Latest Literature' (New articles from highly accessed journals, including Chest and Drugs) and 'Trending Articles' (PubMed records with recent increases in activity, including an update on the Coronavirus Disease 2019 Outbreak).

Con il vocabolario controllato possiamo costruire una ricerca più mirata.

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MeSH MeSH glioblastoma Search

Create alert Limits Advanced Help

Summary 20 per page Send to: PubMed Search Builder

Search results
Items: 9

[Glioblastoma](#)

1. A malignant form of astrocytoma histologically characterized by pleomorphism of cells, nuclear atypia, microhemorrhage, and necrosis. They may arise in any region of the central nervous system, with a predilection for the cerebral hemispheres, basal ganglia, and commissural pathways. Clinical presentation most frequently occurs in the fifth or sixth decade of life with focal neurologic signs or seizures.
Year introduced: 1994

2. A TGF-beta subtype that was originally identified as a **GLIOBLASTOMA**-both helper and **CYTOTOXIC T LYMPHOCYTES**. It is synthesized as a p and TGF-beta2 latency-associated peptide. The association of the cleava must be activated to bind its receptor.
Year introduced: 2007(2000)
3. A malignant tumor arising from the nuclear layer of the retina that is the m tends to occur in early childhood or infancy and may be present at birth. T transmitted as an autosomal dominant trait. Histologic features include de calcification and necrosis. An abnormal pupil reflex (leukokoria); NYSTAG represent common clinical characteristics of this condition. (From DeVita,

NCBI Resources How To marionegrisearches My NCBI Sign Out

MeSH MeSH Search

Limits Advanced Help

Full Send to: PubMed Search Builder

"Glioblastoma"[Mesh]

Add to search builder AND Search PubMed

Glioblastoma

A malignant form of astrocytoma histologically characterized by pleomorphism of cells, nuclear atypia, microhemorrhage, and necrosis. They may arise in any region of the central nervous system, with a predilection for the cerebral hemispheres, basal ganglia, and commissural pathways. Clinical presentation most frequently occurs in the fifth or sixth decade of life with focal neurologic signs or seizures.
Year introduced: 1994

PubMed search builder options
[Subheadings:](#)

<input type="checkbox"/> analysis	<input type="checkbox"/> embryology	<input type="checkbox"/> physiopathology
<input type="checkbox"/> anatomy and histology	<input type="checkbox"/> enzymology	<input type="checkbox"/> prevention and control
<input type="checkbox"/> blood	<input type="checkbox"/> epidemiology	<input type="checkbox"/> psychology
<input type="checkbox"/> blood supply	<input type="checkbox"/> ethnology	<input type="checkbox"/> radiotherapy
<input type="checkbox"/> cerebrospinal fluid	<input type="checkbox"/> etiology	<input type="checkbox"/> rehabilitation
<input type="checkbox"/> chemically induced	<input type="checkbox"/> genetics	<input type="checkbox"/> secondary
<input type="checkbox"/> chemistry	<input type="checkbox"/> history	<input type="checkbox"/> statistics and numerical data
<input type="checkbox"/> classification	<input type="checkbox"/> immunology	<input type="checkbox"/> surgery
<input type="checkbox"/> complications	<input type="checkbox"/> metabolism	<input type="checkbox"/> therapy
<input type="checkbox"/> congenital	<input type="checkbox"/> microbiology	<input type="checkbox"/> transmission
<input type="checkbox"/> cytology	<input type="checkbox"/> mortality	<input type="checkbox"/> transplantation
<input type="checkbox"/> diagnosis	<input type="checkbox"/> nursing	<input type="checkbox"/> ultrastructure
<input type="checkbox"/> diagnostic imaging	<input type="checkbox"/> organization and administration	<input type="checkbox"/> urine
<input type="checkbox"/> diet therapy	<input type="checkbox"/> parasitology	<input type="checkbox"/> veterinary
<input type="checkbox"/> drug therapy	<input type="checkbox"/> pathology	<input type="checkbox"/> virology
<input type="checkbox"/> economics	<input type="checkbox"/> physiology	

Restrict to MeSH Major Topic.
 Do not include MeSH terms found below this term in the MeSH hierarchy.

Related information

PubMed

PubMed - Major Topic

Clinical Queries

NLM MeSH Browser

dbGaP Links

MedGen

Recent Activity Turn Off Clear

Glioblastoma MeSH

glioblastoma (9) MeSH

Il vocabolario controllato da la possibilità di scegliere il termine più attinente alla nostra ricerca

Sicuro | <https://www.ncbi.nlm.nih.gov/mesh/68005909>

Full ▾

Glioblastoma

A malignant form of astrocytoma histologically characterized by pleomorphism of cells, nuclear atypia, microhemorrhage, and necrosis. They may arise in any region of the central nervous system, with a predilection for the cerebral hemispheres, basal ganglia, and commissural pathways. Clinical presentation most frequently occurs in the fifth or sixth decade of life with focal neurologic signs or seizures.
Year introduced: 1994

PubMed search builder options
[Subheadings:](#)

<input type="checkbox"/> analysis	<input type="checkbox"/> embryology	<input type="checkbox"/> physiopathology
<input type="checkbox"/> anatomy and histology	<input type="checkbox"/> enzymology	<input type="checkbox"/> prevention and control
<input type="checkbox"/> blood	<input type="checkbox"/> epidemiology	<input type="checkbox"/> psychology
<input type="checkbox"/> blood supply	<input type="checkbox"/> ethnology	<input type="checkbox"/> radiotherapy
<input type="checkbox"/> cerebrospinal fluid	<input type="checkbox"/> etiology	<input type="checkbox"/> rehabilitation
<input type="checkbox"/> chemically induced	<input type="checkbox"/> genetics	<input type="checkbox"/> secondary
<input type="checkbox"/> chemistry	<input type="checkbox"/> history	<input type="checkbox"/> secretion
<input type="checkbox"/> classification	<input type="checkbox"/> immunology	<input type="checkbox"/> statistics and numerical data
<input type="checkbox"/> complications	<input type="checkbox"/> metabolism	<input type="checkbox"/> surgery
<input type="checkbox"/> congenital	<input type="checkbox"/> microbiology	<input type="checkbox"/> therapy
<input type="checkbox"/> cytology	<input type="checkbox"/> mortality	<input type="checkbox"/> transmission
<input type="checkbox"/> diagnosis	<input type="checkbox"/> nursing	<input type="checkbox"/> transplantation
<input type="checkbox"/> diagnostic imaging	<input type="checkbox"/> organization and administration	<input type="checkbox"/> ultrastructure
<input type="checkbox"/> diet therapy	<input type="checkbox"/> parasitology	<input type="checkbox"/> urine
<input type="checkbox"/> drug therapy	<input type="checkbox"/> pathology	<input type="checkbox"/> veterinary
<input type="checkbox"/> economics	<input type="checkbox"/> physiology	<input type="checkbox"/> virology

Restrict to MeSH Major Topic.
 Do not include MeSH terms found below this term in the MeSH hierarchy.

Tree Number(s): C04.557.465.625.600.380.080.335, C04.557.470.670.380.080.335, C04.557.580.625.600.380.080.335
MeSH Unique ID: D005909
Entry Terms:

PubMed Search Builder

"Glioblastoma"[Mesh]

Add to search builder AND ▾

Search PubMed

Related information

PubMed

PubMed - Major Topic

Clinical Queries

NLM MeSH Browser

dbGaP Links

MedGen

Recent Activity

Turn Off Clear

Glioblastoma MeSH

glioblastoma (9) MeSH

((((glioblastoma[Title/Abstract]) OR astrocytoma[Title/Abstrac... (299) PubMed

Glioblastoma OR astrocytoma AND (radiotherapy NOT temozolamide) /54 PubMed

Impostato il termine da cercare se inserisce nella maschera di ricerca

P = soggetti affetti di **glioblastoma** <70anni

I = radioterapia

C = temozolamide

Full ▾ Send to: ▾

Glioblastoma

A malignant form of astrocytoma histologically characterized by pleomorphism of cells, nuclear atypia, microhemorrhage, and necrosis. They may arise in any region of the central nervous system, with a predilection for the cerebral hemispheres, basal ganglia, and commissural pathways. Clinical presentation most frequently occurs in the fifth or sixth decade of life with focal neurologic signs or seizures.
Year introduced: 1994

PubMed search builder options
[Subheadings:](#)

<input type="checkbox"/> analysis	<input type="checkbox"/> embryology	<input type="checkbox"/> physiopathology
<input type="checkbox"/> anatomy and histology	<input type="checkbox"/> enzymology	<input type="checkbox"/> prevention and control
<input type="checkbox"/> blood	<input type="checkbox"/> epidemiology	<input type="checkbox"/> psychology
<input type="checkbox"/> blood supply	<input type="checkbox"/> ethnology	<input type="checkbox"/> radiotherapy
<input type="checkbox"/> cerebrospinal fluid	<input type="checkbox"/> etiology	<input type="checkbox"/> rehabilitation
<input type="checkbox"/> chemically induced	<input type="checkbox"/> genetics	<input type="checkbox"/> secondary
<input type="checkbox"/> chemistry	<input type="checkbox"/> history	<input type="checkbox"/> secretion
<input type="checkbox"/> classification	<input type="checkbox"/> immunology	<input type="checkbox"/> statistics and numerical data
<input type="checkbox"/> complications	<input type="checkbox"/> metabolism	<input type="checkbox"/> surgery
<input type="checkbox"/> congenital	<input type="checkbox"/> microbiology	<input type="checkbox"/> therapy
<input type="checkbox"/> cytology	<input type="checkbox"/> mortality	<input type="checkbox"/> transmission
<input type="checkbox"/> diagnosis	<input type="checkbox"/> nursing	<input type="checkbox"/> transplantation
<input type="checkbox"/> diagnostic imaging	<input type="checkbox"/> organization and administration	<input type="checkbox"/> ultrastructure
<input type="checkbox"/> diet therapy	<input type="checkbox"/> parasitology	<input type="checkbox"/> urine
<input type="checkbox"/> drug therapy	<input type="checkbox"/> pathology	<input type="checkbox"/> veterinary
<input type="checkbox"/> economics	<input type="checkbox"/> physiology	<input type="checkbox"/> virology

Restrict to MeSH Major Topic.
 Do not include MeSH terms found below this term in the MeSH hierarchy

Tree Number(s): C04.557.465.625.600.380.080.335, C04.557.470.670.380.080.335, C04.557.580.625.600.380.080.335
MeSH Unique ID: D005909

PubMed Search Builder

Add to search builder AND ▾
Search PubMed

YouTube Tutorial

Related information

PubMed

PubMed - Major Topic

Clinical Queries

NLM MeSH Browser

dbGaP Links

MedGen

Recent Activity

Turn Off Clear

Glioblastoma MeSH

glioblastoma (9) MeSH

(((((((glioblastoma[Title/Abstract]) OR astrocytoma[Title/Abstrac... (299) PubMed

I **subheadings**: restringono il campo ad un aspetto più specifico ed è possibile scegliere più di uno.

Restrict to MeSH Major Topic: con questa opzione i risultati ottenuti ricadranno sul termine MeSH cercato.

Do not include MeSH terms found below this term in the MeSH hierarchy: esplodere o no il termine, i risultati non includeranno i termini al di sotto della nostra parola chiave nella struttura ad albero.

Sicuro | <https://www.ncbi.nlm.nih.gov/mesh/68005909>

Entry Terms:

- Glioblastomas
- Astrocytoma, Grade IV
- Astrocytomas, Grade IV
- Grade IV Astrocytoma
- Grade IV Astrocytomas
- Glioblastoma Multifome
- Giant Cell Glioblastoma
- Giant Cell Glioblastomas
- Glioblastoma, Giant Cell
- Glioblastomas, Giant Cell

Entry terms: Sinonimi del termine

[All MeSH Categories](#)
[Diseases Category](#)
[Neoplasms](#)
[Neoplasms by Histologic Type](#)
[Neoplasms, Germ Cell and Embryonal](#)
[Neuroectodermal Tumors](#)
[Neoplasms, Neuroepithelial](#)
[Glioma](#)
[Astrocytoma](#)
Glioblastoma

[All MeSH Categories](#)
[Diseases Category](#)
[Neoplasms](#)
[Neoplasms by Histologic Type](#)
[Neoplasms, Glandular and Epithelial](#)
[Neoplasms, Neuroepithelial](#)
[Glioma](#)
[Astrocytoma](#)
Glioblastoma

Struttura ad albero

Q Glioblastoma OR astrocytoma AND (radiotherapy NOT temozolomide) (54 PubMed)
 Q (((glioblastoma[Title/Abstract]) OR astrocytoma[Title/Abstract])... (3451) PubMed
 See more...

Struttura ad albero: qui si vede a che punto dell'albero è il nostro termine di interesse

NCBI Resources How To marionegrisearches My NCBI Sign Out

PubMed.gov "Glioblastoma"[Mesh] Search

Format: Summary Sort by: Most Recent per page: 20

Search results

Items: 1 to 20 of 22445

1. CAR-T cells : indications actuelles en pédiatrie et perspectives de développement.
1. Dourthe MÉ, Yakouben K, Chaillou D, Lesprit E, Dalle JH, Baruchel A.
Bull Cancer. 2018 Dec;105 Suppl 2:S147-S151. doi: 10.1016/S0007-4551(19)30045-1. French.
PMID: 30686353
Similar articles

2. Papillary glioblastoma exhibiting a neuro-radiological cyst with a mural nodule: A case report.
2. Homma T, Hanashima Y, Maebayashi T, Nakanishi Y, Ishige T, Ohta T, Yoshino A, Hao H.
Medicine (Baltimore). 2019 Jan;98(2):e14102. doi: 10.1097/MD.00000000000014102.
PMID: 30633222 Free PMC Article
Similar articles

3. Conventionally fractionated stereotactic radiotherapy (CFRT) in combination with dose-dense
3. te
Qi
Me
PM
Sit

Results by year

Titles with your search terms

Drug combination using an injectable nanomedicine hydrogel for gli [Int J Pharm. 2019]

2D Phas... M... P... A... G... M... M... M...

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PubMed Home More Resources Help

PubMed Advanced Search Builder

Query #1 deleted.

Use the builder below to create your search

[Edit](#) [Clear](#)

Builder

All Fields [] Show index list

AND All Fields [] Show index list

Search or Add to history

History

Search	Add to builder	Query	Items found	Time
#6	Add	Search "Glioblastoma"[Mesh] Sort by: Author	24552	08:46:29

Cliccando su **Advanced** se accede alla pagina che ci permette di costruire una strategia di ricerca.

Operatori booleani

The top screenshot shows the PubMed Advanced Search Builder interface. The search query is: `("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract]`. The interface includes a search bar, an "Edit" button, a "Clear" button, and a "Builder" section with dropdown menus for "All Fields", "Title/Abstract", and "AND".

The bottom screenshot shows the search results history table. The table has columns for Search, Add to builder, Query, Items found, and Time.

Search	Add to builder	Query	Items found	Time
#8	Add	Search ("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract] Sort by: Author	39393	08:52:11
#7	Add	Search glioblastoma[Title/Abstract] Sort by: Author	33673	08:51:45
#6	Add	Search "Glioblastoma"[Mesh] Sort by: Author	24552	08:46:29
#2	Add	Search glioblastoma Sort by: Author	39397	08:24:22

Utilizzando gli operatori logici: OR – AND – NOT
si può stabilire una relazione tra i termini da ricercare.

NCBI Resources How To marionegrisearches My NCBI Sign Out

PubMed Home More Resources Help

PubMed Advanced Search Builder

YouTube Tutorial

("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract]

Edit Clear

Builder

All Fields "Glioblastoma"[Mesh] Show index list

OR All Fields glioblastoma[Title/Abstract] Show index list

AND All Fields Show index list

Search or Add to history

History Download history Clear history

Search	Add to builder	Query	Items found	Time
#8	Add	Search ("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract] Sort by: Author	39393	08:52:11

Con **OR** il database ricercherà i documenti che contengano la parola glioblastoma come termine MeSH o nei titoli e abstract.

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((("Radiotherapy"[Mesh] OR radiotherapy[Title/Abstract])) AND (("Temozolomide"[Mesh] OR ((temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract])))

[Edit](#) [Clear](#)

Builder

All Fields All Fields All Fields

AND AND AND

Search or [Add to history](#)

History [Download history](#) [Clear history](#)

Search	Add to builder	Query	Items found	Time
#17	Add	Search ("Temozolomide"[Mesh] OR ((temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract])) Sort by: Author	7498	09:03:27
#16	Add	Search (temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract]) Sort by: Author	7034	09:03:19
#15	Add	Search "Temozolomide"[Mesh] Sort by: Author	4420	09:02:45
#13	Add	Search ("Radiotherapy"[Mesh]) OR radiotherapy[Title/Abstract] Sort by: Author	286029	09:00:22
#12	Add	Search radiotherapy[Title/Abstract] Sort by: Author	176676	09:00:13
#11	Add	Search "Radiotherapy"[Mesh] Sort by: Author	182419	08:59:58
#8	Add	Search ("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract] Sort by: Author	39393	08:52:11
#7	Add	Search glioblastoma[Title/Abstract] Sort by: Author	33673	08:51:45
#6	Add	Search "Glioblastoma"[Mesh] Sort by: Author	24552	08:46:29

Con **AND** il database ricercherà i documenti che contengano le parole radiotherapy e temozolomide contemporaneamente.

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Search	Add to builder	Query	Items found	Time
#19	Add	Search (((("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract])) AND (((("Radiotherapy"[Mesh]) OR radiotherapy[Title/Abstract])) AND ((("Temozolomide"[Mesh]) OR ((temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract])))) Sort by: Author	1710	09:06:37
#18	Add	Search (((("Radiotherapy"[Mesh]) OR radiotherapy[Title/Abstract])) AND ((("Temozolomide"[Mesh]) OR ((temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR Methazolastone[Title/Abstract])))) Sort by: Author	2525	09:06:17
#17	Add	Search ("Temozolomide"[Mesh]) OR ((temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract])) Sort by: Author	7498	09:03:27
#16	Add	Search (temozolomide[Title/Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract]) Sort by: Author	7034	09:03:19
#15	Add	Search "Temozolomide"[Mesh] Sort by: Author	4420	09:02:45
#13	Add	Search ("Radiotherapy"[Mesh]) OR radiotherapy[Title/Abstract] Sort by: Author	288029	09:00:22
#12	Add	Search radiotherapy[Title/Abstract] Sort by: Author	178878	09:00:13
#11	Add	Search "Radiotherapy"[Mesh] Sort by: Author	182419	08:59:58
#8	Add	Search ("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract] Sort by: Author	39393	08:52:11
#7	Add	Search glioblastoma[Title/Abstract] Sort by: Author	33873	08:51:45
#6	Add	Search "Glioblastoma"[Mesh] Sort by: Author	24552	08:46:29
#2	Add	Search glioblastoma Sort by: Author	39397	08:24:22

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Search	Actions	Details	Query	Results	Time
#1	<ul style="list-style-type: none"> Add query Delete Save to MyNCBI 		<pre>((("Glioblastoma"[Mesh]) OR glioblastoma[Title/Abstract] AND (((("Radiotherapy"[Mesh]) OR radiotherapy[Title/Abstract]) AND ((("Temozolomide"[Mesh]) OR (temozolomid[Abstract] OR temodar[Title/Abstract] OR temodal[Title/Abstract] OR Methazolastone[Title/Abstract]))) AND (((((((("Randomized Controlled Trial"[Publication Type]) OR "Clinical Trial"[Publication Type]) OR "drug therapy"[Subheading]) OR ((random[Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract] OR groups)))) NOT (((("Animals"[Mesh]) OR NOT ("Animals"[Mesh]) AND "Humans"[Mesh]))))))))</pre>	1,125	09:55:31
#3			Search: "Glioblastoma"[Mesh]	24,552	09:51:20

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Precisione nella ricerca

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Search: (((\"Glioblastoma\"[Mesh]) OR glioblastoma[Title/Abstract])) AND (((\"Radiotherapy\"[Mesh]) OR radiotherapy[Title/Abstract])) AND temozolomide[Title/Abstract]

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Search results: Items: 1 to 20 of 1710

1. [Role of endolysosomes and pH in the pathogenesis and treatment of glioblastoma.](#)
Halcrow P, Datta G, Ohm JE, Soliman ML, Chen X, Geiger JD. *Cancer Rep.* 2019 Dec;2(6). doi: 10.1002/cnr2.1177. Epub 2019 May 6. PMID: 32095788 Free PMC Article [Similar articles](#)

2. [Delivery of temozolomide and N3-propargyl analog to brain tumors using an apoferritin nanocage.](#)
Bouzinab K, Summers H, Stevens MFG, Moody CJ, Thomas NR, Gershkovich P, Weston N, Ashford MB, Bradshaw TD, Turyanska L. *ACS Appl Mater Interfaces.* 2020 Feb 19. doi: 10.1021/acsami.0c01514. [Epub ahead of print] PMID: 32073826 [Similar articles](#)

3. [Superiority of temozolomide over radiotherapy for elderly patients with RTK II methylation class, MGMT promoter-methylated malignant astrocytoma.](#)
Wick A, Kessler T, Platten M, Meisner C, Bamberg M, Herrlinger U, Felsberg J, Weyerbrock A, Papsdorf K, Steinbach JP, Sabel M, Vesper J, Debus J, Meixensberger J, Ketter R, Hertler C, Mayer-Steinacker R, Weisang S, Bölting H, Reuss D, Reifenberger G, Sahm F, von Deimling A, Weller M, Wick W; NOA-08 Study Group of the Neurooncology Working Group (NOA) of the German Cancer Society. *Neuro Oncol.* 2020 Feb 17. pii: noaa033. doi: 10.1093/neuonc/noaa033. [Epub ahead of print] PMID: 32064499 [Similar articles](#)

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Search details: (\"Glioblastoma\"[Mesh] OR glioblastoma[Title/Abstract]) AND (\"Radiotherapy\"[Mesh] OR radiotherapy[Title/Abstract]) AND (\"Temozolomide\"[Mesh] OR temozolomide[Title/Abstract]) Search See more...

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P = soggetti affetti di glioblastoma <70anni

I = radioterapia

C = temozolamide

I filtri (limits) delimitano la nostra ricerca

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effects of radiotherapy with concomitants and adjuvant temozolomide

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Abstract

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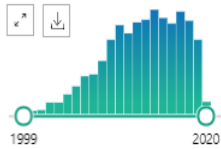
Full text

ARTICLE ATTRIBUTE

1 **Repurposing Disulfiram for Targeting of Glioblastoma Stem Cells: An In Vitro Study.**
Cite Zirjacks L, Stransky N, Klumpp L, Prause L, Eckert F, Zips D, Schleicher S, Handgretinger R, Huber SM, Ganser K.
Share Biomolecules. 2021 Oct 21;11(11):1561. doi: 10.3390/biom11111561. PMID: 34827559 [Free PMC article.](#)
Reportedly, DSF in combination with Cu(2+) ions exerts multiple tumoricidal, chemo- and radio-therapy-sensitizing **effects** in several tumor entities. The present study aimed to quantify these DSF **effects** in glioblastoma stem cells in vitro, regarding dependence on AL ...

2 **Survival benefit of glioblastoma patients after FDA approval of **temozolomide concomitant** with radiation and bevacizumab: A population-based study.**
Cite Zhu P, Du XL, Lu G, Zhu JJ.

E molto importante ricordarci che i limiti impostati vengono mantenuti in memoria nelle ricerche successive, quindi una volta finita la ricerca bisogna disattivarli.



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ARTICLE TYPE

- Books and Documents
- Clinical Trial
- Meta-Analysis
- Randomized Controlled Trial
- Review
- Systematic Reviews

PUBLICATION DATE

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- [Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma](#)
Stupp R, et al. N Engl J Med 2005 - *Clinical Trial*. Among authors: **Taphoorn MJ**. PMID 15758009 Free article.
In **this trial** we compared **radiotherapy** alone with **radiotherapy plus temozolomide**, given concomitantly with and after **radiotherapy**, in terms of efficacy and safety. ...The unadjusted hazard ratio for death in the **radiotherapy-plus-temozolomide group** was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). ...
“ Cite Share
- [Effect of Tumor-Treating Fields Plus Maintenance Temozolomide vs Maintenance Temozolomide Alone on Survival in Patients With Glioblastoma: A Randomized Clinical Trial.](#)
Stupp R, et al. JAMA 2017 - *Clinical Trial*. Among authors: **Tran D, Toms S, Taillibert S**. PMID 29260225 Free PMC article.
Adverse events were compared by **group**. RESULTS: Of the 695 **randomized** patients (median age, 56 years; IQR, 48-63; 473 men [68%]), 637 (92%) completed the **trial**. ...CONCLUSIONS AND RELEVANCE: In the final analysis of **this randomized clinical trial** of patients with **glioblastoma** who had received standard radiochemotherapy, the addition of **TFFields** to maintenance **temozolomide** chemotherapy vs maintenance **temozolomide** alone, resulted in statistically significant improvement in progression-free survival and overall survival. ...
“ Cite Share
- [Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma.](#)
Perry JR, et al. N Engl J Med 2017 - *Clinical Trial*. Among authors: **Tills M**. PMID 28296618 Free article.
METHODS: We conducted a **trial** involving patients 65 years of age or older with newly diagnosed **glioblastoma**. Patients were **randomly** assigned to receive either **radiotherapy** alone (40 Gy in 15 fractions) or **radiotherapy** with concomitant and adjuvant **temozolomide**. ...Quality of life was similar in the **two trial groups**. CONCLUSIONS: In elderly patients with **glioblastoma**, the addition of **temozolomide** to short-course **radiotherapy** resulted in longer survival than short-course **radiotherapy** alone. ...
“ Cite Share
- [Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter \(CeTeG/NOA-09\): a randomised, open-label, phase 3 trial.](#)
Herrlinger U, et al. Lancet 2019 - *Clinical Trial*. Among authors: **Tonn JC, Tzaridis T, Tabatabai G**. PMID 30782343
BACKGROUND: There is an urgent need for more effective **therapies** for **glioblastoma**. Data from a previous unrandomised phase 2 **trial** suggested that lomustine-**temozolomide** plus **radiotherapy** might be superior to **temozolomide** plus **radiotherapy** in newly diagnosed **glioblastoma** with

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Query #15 deleted.

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```
((((("Randomized Controlled Trial" [Publication Type] OR "Clinical Trial" [Publication Type] OR "drug therapy" [Subheading])) OR ((random* [Title/Abstract] OR placebo[Title/Abstract] OR trial[Title/Abstract] OR groups OR)))) NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans" [Mesh]))
```

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Troncare le parole con l'asterisco (*): verranno ricercate tutte le varianti che iniziano con la stessa radice.

random* (randomized, randomizes, randomizing, randomization, randomised, randomises, randomising and randomisation)

Le **parentesi** stabiliscono un ordine di priorità nei termini da cercare, in questo caso il database non cercherà gli studi sugli animali e neanche quelli su umani e animali

... NOT (("Animals"[Mesh]) NOT ("Animals"[Mesh] AND "Humans"[Mesh]))

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"Randomized Controlled Trial"[Publication Type]

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Builder

Publication Type "Randomized Controlled Trial" [Show index list](#)

AND

Search

History

Search

#20

#19

#18

Query

Items found

Time

5129984 09:19:05

1710 09:10:38

2525 09:06:17

Sort by: Author

"Clinical Trial" [Publication Type] OR "Randomized Controlled Trial" [Publication Type]

Ricerca per frase: Inserendo più termini nella maschera di ricerca, il database cercherà ogni singolo termine combinandolo con l'operatore AND.

Se invece si vuole trovare un risultato come frase, i termini devono essere racchiusi tra virgolette.

Risultati

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(((("Complex Regional Pain Syndromes"[Mesh]) OR ("Complex Regional Pain S

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RESULTS BY YEAR

Complex regional pain syndrome: An updated comprehensive review.
1 Kessler A, Yoo M, Calisoff R.
Cite NeuroRehabilitation. 2020;47(3):253-264. doi: 10.3233/NRE-208001.
PMID: 32986618 Review.
Share Complex regional pain syndrome (CRPS) is a **complex** disorder that can have a significant impact on the quality of life of a person with this syndrome. ...Ultimately, more research is needed to identify the exact etiology of CRPS in order to help target

Dalle tendine si può scegliere sia il formato che l'ordine da dare all'elenco dei risultati

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1: Kessler A, Yoo M, Calisoff R. Complex regional pain syndrome: An updated comprehensive review. *NeuroRehabilitation*. 2020;47(3):253-264. doi: 10.3233/NRE-208001. PMID: 32986618.

2: Sdrulla AD, Guan Y, Raja SN. Spinal Cord Stimulation: Clinical Efficacy and Potential Mechanisms. *Pain Pract*. 2018 Nov;18(8):1048-1067. doi: 10.1111/papr.12692. Epub 2018 Apr 23. PMID: 29526043; PMCID: PMC6391880.

3: Smart KM, Wand BM, O'Connell NE. Physiotherapy for pain and disability in adults with complex regional pain syndrome (CRPS) types I and II. *Cochrane Database Syst Rev*. 2016 Feb 24;2(2):CD010853. doi: 10.1002/14651858.CD010853.pub2. Update in: *Cochrane Database Syst Rev*. 2022 May 17;5:CD010853. PMID: 26905470; PMCID: PMC8646955.

4: Rock AK, Truong H, Park YL, Pilitsis JG. Spinal Cord Stimulation. *Neurosurg Clin N Am*. 2019 Apr;30(2):169-194. doi: 10.1016/j.nec.2018.12.003. Epub 2019 Feb 18. PMID: 30898269.

5: O'Connell NE, Wand BM, McAuley J, Marston L, Moseley GL. Interventions for treating pain and disability in adults with complex regional pain syndrome. *Cochrane Database Syst Rev*. 2013 Apr 30;2013(4):CD009416. doi: 10.1002/14651858.CD009416.pub2. PMID: 23633371; PMCID: PMC6469537.

6: Lee JW, Lee SK, Choy WS. Complex Regional Pain Syndrome Type 1: Diagnosis and Management. *J Hand Surg Asian Pac Vol*. 2018 Mar;23(1):1-10. doi: 10.1142/S2424835518300013. PMID: 29409405.

7: Méndez-Rebolledo G, Gatica-Rojas V, Torres-Cueco R, Albornoz-Verdugo M, Cordero-Muñoz E. Update on the Effects of medical water immersion and winter therapy...

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Search: ("Complex Regional Pain Syndromes"[Mesh]) OR ("Complex Regional Pain S...
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RESULTS BY YEAR
1969 2022

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Complex regional pain syndrome: An updated comprehensive review.
1 Kessler A, Yoo M, Calisoff R.
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3

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Books and Documents

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1 Kessler A, Yoo M, Calisoff R.
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3 Smart KM, Wand BM, O'Connell NE.
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13-May-2022	MeSH	record	Clinical Trials_Phase IV as Topic
13-May-2022	MeSH	record	Clinical Trials_Phase III as Topic
13-May-2022	MeSH	record	Clinical Trials_Phase II as Topic
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SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10^a EDIZIONE

MODULI SPECIALISTICI - S1



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*Study flow, entità dell'effetto,
eterogeneità, reporting*

Michela CINQUINI

In pratica..

1. Ottenere una unica lista di referenze

- I risultati della ricerca di ogni database vanno importati su un programma di gestione delle referenze (endnote, excel)
- Eliminare i doppioni (stesso articolo indicizzato su più di una banca dati e quindi trovato più volte)

2. Selezionare gli articoli potenzialmente rilevanti da acquisire in full text

- Scriversi su un foglio i criteri di inclusione sotto forma di PICOS
- Valutare ogni titolo e abstract rispetto al PICOS

3. Obiettivo è non perdere nulla

- Fare il lavoro in due in modo indipendente
- In caso di dubbio, disaccordo o mancanza di abstract il titolo si seleziona lo stesso

4. Procurarsi i full text

5. Rivalutare ogni articolo leggendo il full text rispetto al PICOS

- Fare il lavoro in due in modo indipendente
- Confrontarsi sui risultati
- In questa fase vanno presi solo gli articoli realmente pertinenti In caso di differenze:
 - Risolvere il disaccordo tramite discussione
 - Rivolgersi a terzo revisore

6. Fare lista di studi esclusi

- Indicare ragione dell'esclusione sempre in base al PICOS
- Es: studi esclusi perché partecipanti non nei criteri di inclusione, intervento non nei criteri di inclusione, disegno di studio non nei criteri di inclusione
- Questo lavoro va fatto solo sui full text, non per gli studi esclusi sulla base dell'abstract

7. Fare lista finali di studi inclusi

- Se presenti più record di un articolo tenerli per eventuali dati
Es: diversi periodi di follow up, analisi di sottogruppi; doppie pubblicazioni (stesso studio pubblicato più volte su riviste diverse con titolo diverso e/o diverso ordine degli autori)

8. Fare flow chart (es: PRISMA)

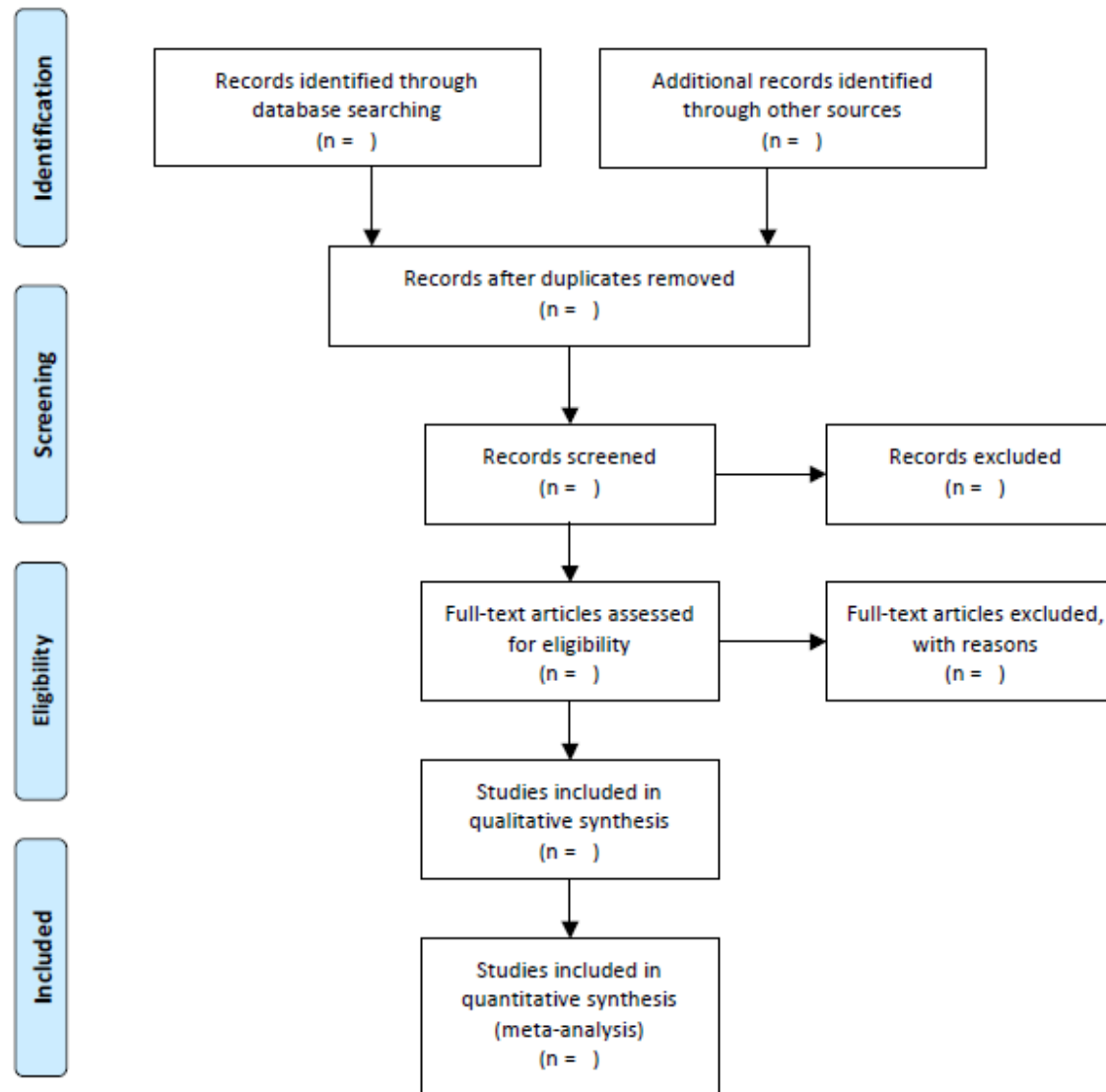
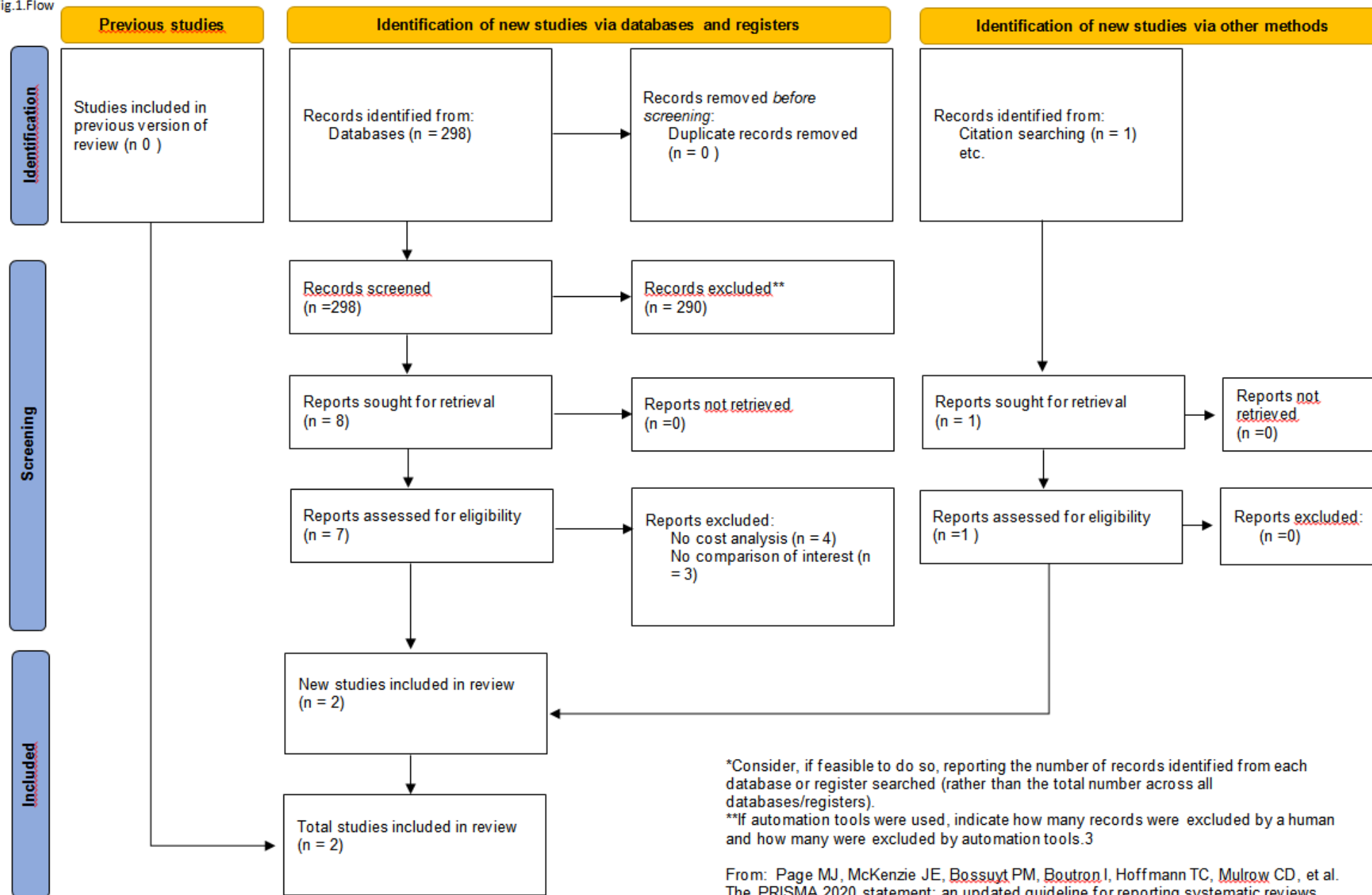


Fig.1.Flow



9. Estrazione dei dati dai singoli studi

- A seconda del tipo di esito che si sta considerando (RR, OR, HR, medie, mediane, ecc.) bisognerà estrarre tutti gli elementi che servono per effettuare la meta-analisi
- Ad es. se esito dicotomico, sintetizzabile con RR, i dati da estrarre o ricalcolare sono n. eventi exp, N totale exp, n. eventi ctrl, N totale ctrl
- Ad es. se esito continuo: media e SD exp, media e SD ctrl

• 10. Fare le meta-analisi

Principi di una meta-analisi

Una **meta-analisi** può:

- Combinare i risultati dei singoli studi per ottenere una stima complessiva dell'effetto del trattamento;
- Esplorare l'eterogeneità tra gli studi (e le relative fonti di eterogeneità).

E' efficace?

Author(s)
Teo et al

Reference
Effects of intravenous magnesium in suspected acute myocardial infarction. BMJ 1991;303:1499-50

Outcome object
Mortality

Unit
Event

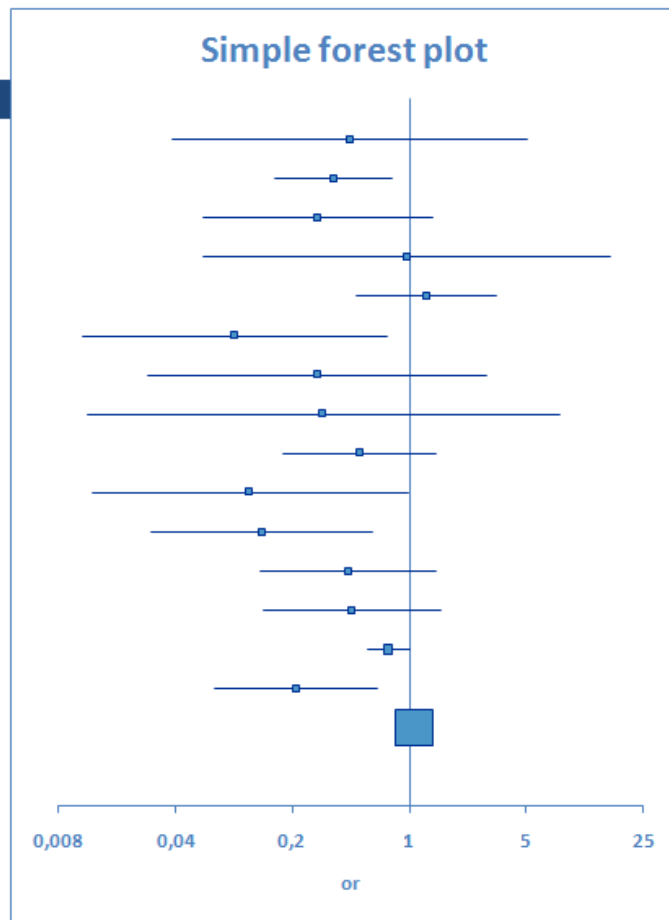
Intervention (e)
Intravenous magnesium

Control (c)
Control

Study ID	Ref #	n[e]	n[e](E=1)	n[c]	n[c](E=1)	Study date	-
Morton	1	40	1	36	2	1984	
Rasmussen	2	135	9	135	23	1986	
Smith	3	200	2	200	7	1986	
Abraham	4	48	1	46	1	1987	
Feldstedt	5	150	10	148	8	1988	
Schechter	6	59	1	56	9	1989	
Ceremuzynski	7	25	1	23	3	1989	
Bertschal	8	22	0	21	1	1989	
Singh	9	76	6	75	11	1990	
Pereira	10	27	1	27	7	1990	
Schechter 1	11	89	2	80	12	1991	
Golf	12	23	5	33	13	1991	
Thogersen	13	130	4	122	8	1991	
LIMIT-2	14	1159	90	1157	118	1992	
Schechter 2	15	107	4	108	17	1995	
ISIS-4	16	29011	2216	29039	2103	1995	

Forest plot (meta-graph) analitico

author	year	n[I]	N[I]	n[C]	N[C]	Weight
Morton	1984	1	40	2	36	0,06%
Rasmussen	1986	9	135	23	135	0,54%
Smith	1986	2	200	7	200	0,14%
Abraham	1987	1	48	1	46	0,05%
Feldstedt	1988	10	150	8	148	0,39%
Schechter	1989	1	59	9	56	0,08%
Ceremuzynsk	1989	1	25	3	23	0,07%
Bertschat	1989	0	22	1	21	0,03%
Singh	1990	6	76	11	75	0,32%
Pereira	1990	1	27	7	27	0,08%
Schechter 1	1991	2	89	12	80	0,15%
Golf	1991	5	23	13	33	0,24%
Thogersen	1991	4	130	8	122	0,24%
LIMIT-2	1992	90	1159	118	1157	4,33%
Schechter 2	1995	4	107	17	108	0,28%
ISIS-4	1995	2216	29011	2103	29039	92,99%



or	ci-	ci+	p
0,44	0,04	5,02	0,51
0,35	0,15	0,78	0,01
0,28	0,06	1,36	0,11
0,96	0,06	15,77	0,98
1,25	0,48	3,26	0,65
0,09	0,01	0,74	0,02
0,28	0,03	2,88	0,28
0,30	0,01	7,88	0,47
0,50	0,17	1,43	0,19
0,11	0,01	0,97	0,05
0,13	0,03	0,60	0,01
0,43	0,13	1,44	0,17
0,45	0,13	1,54	0,21
0,74	0,56	0,99	0,04
0,21	0,07	0,64	0,01
1,06	1,00	1,13	0,07

META-ANALYSIS

General

Number of studies	16
Number of participants	62607 (62607)

OR (MH) - Fixed effect model

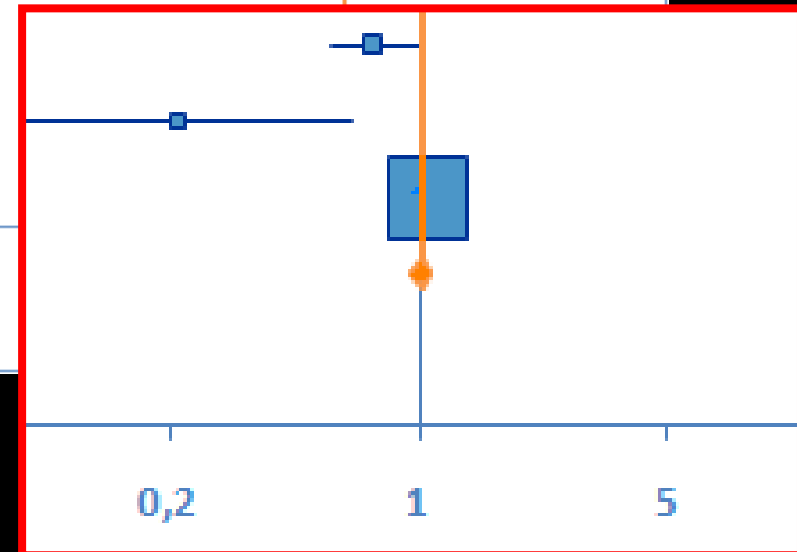
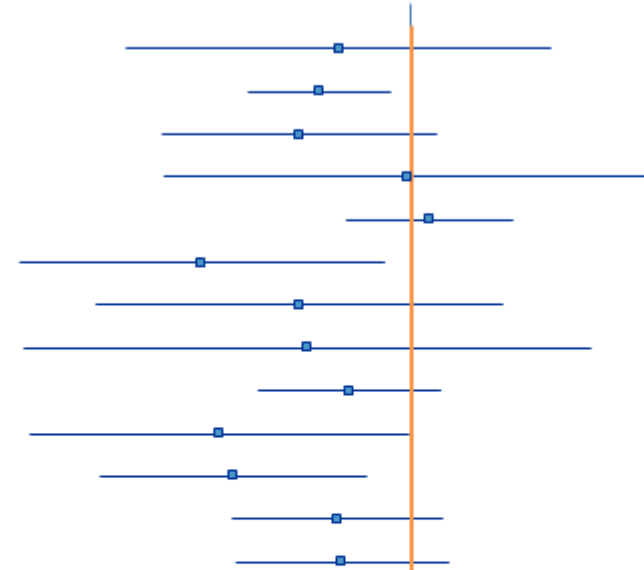
Meta-analysis outcome	1,0063
95% CI lower limit	0,9482
95% CI upper limit	1,068
z	0,2073
p-value (two-tailed)	0,8358

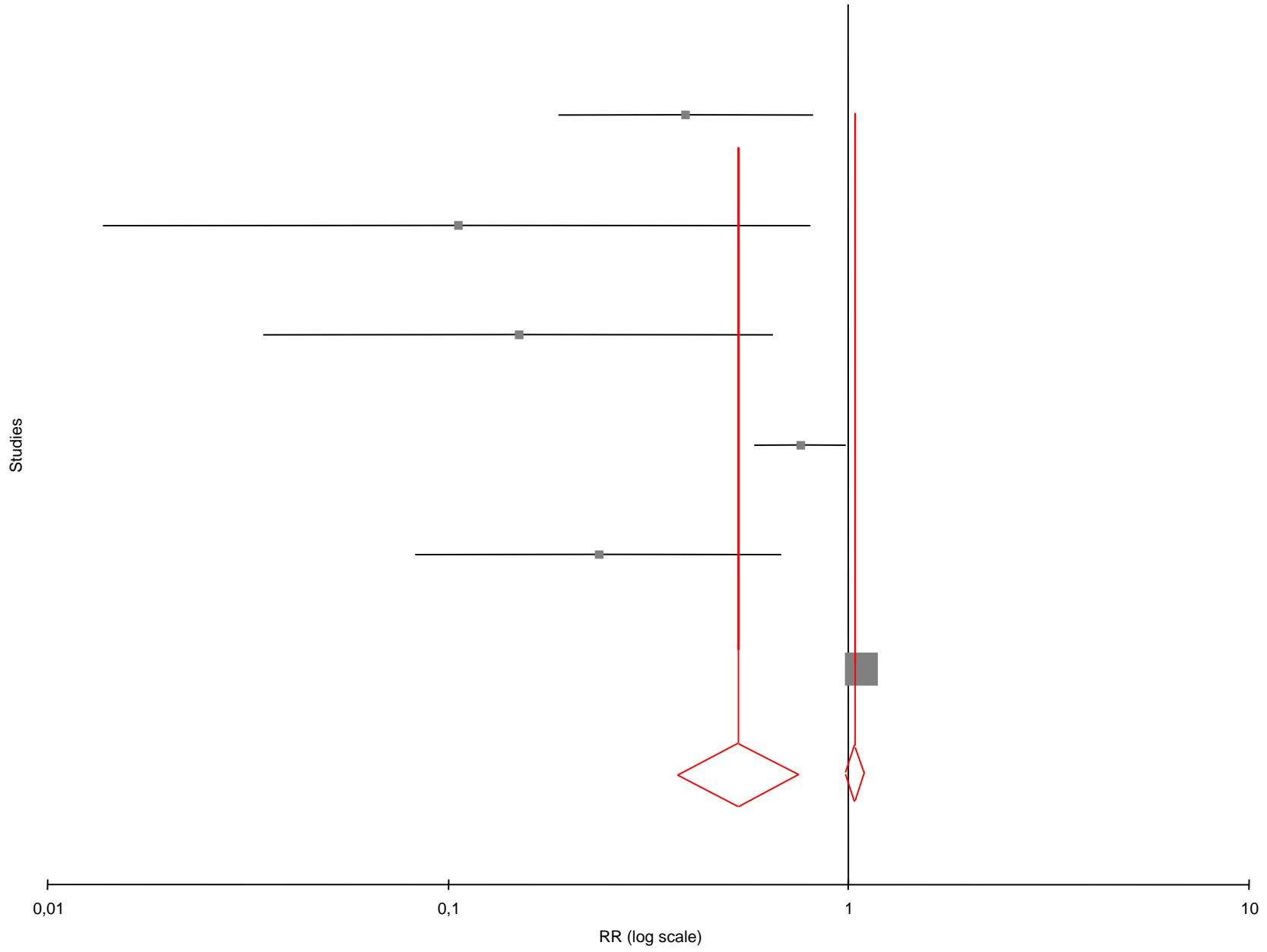
Heterogeneity

Q	47,1363
p-value (two-tailed)	< 0,0001

I ²	68,18%
95% CI lower limit	46,53%
95% CI upper limit	81,06%

Synthesis forest plot





Come si decide quanto pesa uno studio?

- Il peso è proporzionale al contributo informativo dello studio alla capacità di effettuare una stima
- Studi di ampie dimensione e/o con molti eventi potrebbero contribuire di più
- In gergo sono quelli più precisi

- Ma tutto è relativo ... tutti gli studi stanno misurando lo stesso effetto?

What is heterogeneity?

- Heterogeneity is variation between the studies' results

What is **heterogeneity**?

Differences between studies with respect to:

Clinical heterogeneity (clinical diversity)

- *Participants*
 - e.g. conditions under investigation, eligibility criteria for trials, geographical variation
- *Interventions*
 - e.g. intensity / dose / duration, sub-type of drug, mode of administration, experience of practitioners, nature of the control (placebo/none/standard care)
- *Outcomes*
 - e.g. definition of an event, follow-up duration, ways of measuring outcomes, cut-off points on scales

What is **heterogeneity**?

Differences between studies with respect to:

Methodological heterogeneity (methodological diversity)

- *Design*
 - e.g. randomised vs non-randomised, crossover vs parallel group vs cluster randomised, pre-test and long follow up
- *Conduct*
 - e.g. allocation concealment, blinding etc, approach to analysis, imputation methods for missing data

What is heterogeneity?

What do we do if there *is* statistical heterogeneity?

- Variation in the *true effects* underlying the studies
- ...which may manifest itself in **more observed variation than expected by chance alone**
- May be due to **clinical diversity** (different treatment effects) or **methodological diversity** (different biases)

Come si misura questa
eterogeneità?

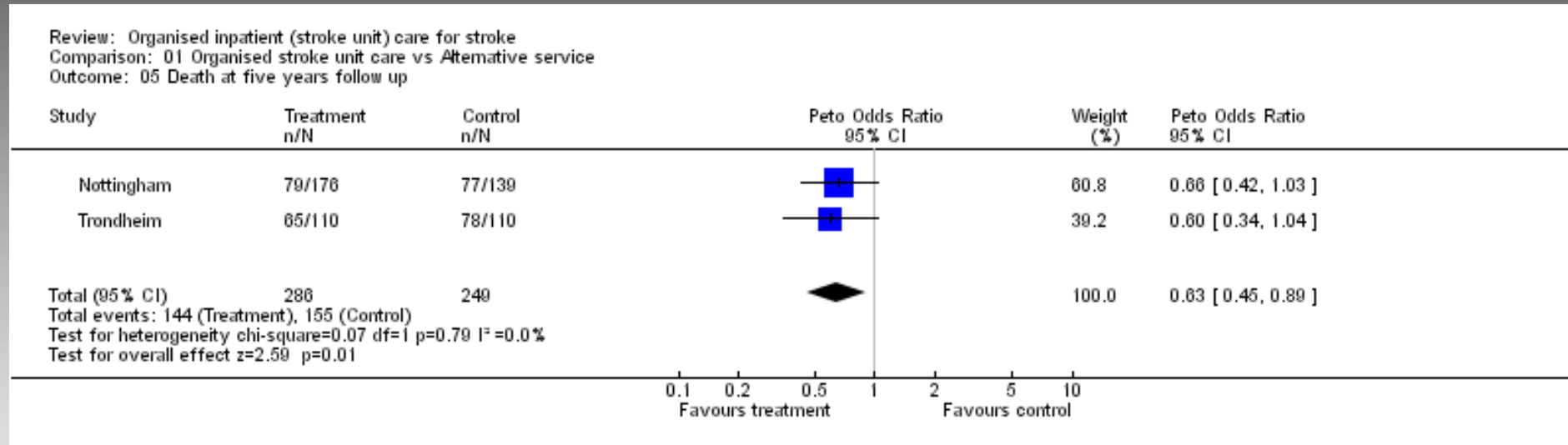
**KEEP
CALM**

e fà

**BALA'
L'OEUCC!**

- Confidence interval overlapping **Eyeball test**
- **Cochran's Q**: to assess whether observed differences in results are compatible with change alone
 χ^2 distribution; low power (small number of studies, small sample size)
 $p < 0.10$ (heterogeneity)
- **I²** quantifying heterogeneity (describes the percentage of variation across studies that is due to heterogeneity rather than chance)
0-40% might not be important
30-60% may represent moderate heterogeneity
50-90% may represent substantial heterogeneity
75-100% considerable heterogeneity
- Tau....

Esempio di Metaview



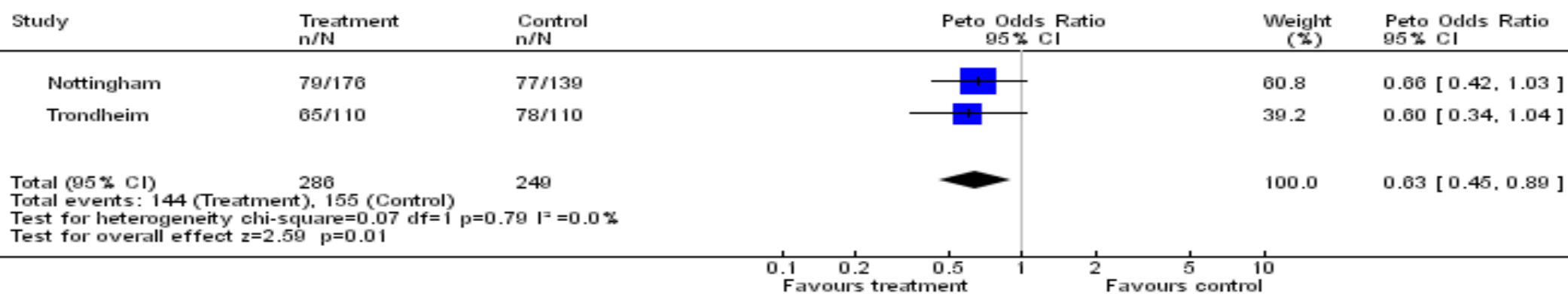
How to deal with heterogeneity

1. Do not pool at all
2. Ignore heterogeneity: use *fixed effect model*
3. Allow for heterogeneity: use *random effects model*
4. Explore heterogeneity: subgroups analysis or meta-regression (tricky)

Un diamante è «per sempre» ma dipende da molti aspetti

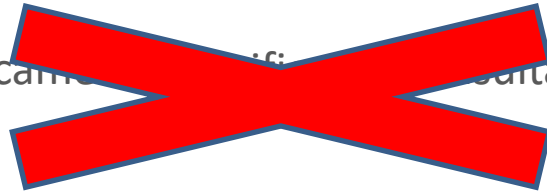
- *P.I.C.O.*
- *Disegno di studio*
- *Esito considerato*
- *Misura di effetto (RR, OR, HR, MD, SMD)*
- *Peso degli studi inclusi (modello effetti fissi o random)*
- *Eterogeneità e sue fonti (sottogruppi)*
- *Bias*

Review: Organised inpatient (stroke unit) care for stroke
 Comparison: 01 Organised stroke unit care vs Alternative service
 Outcome: 05 Death at five years follow up

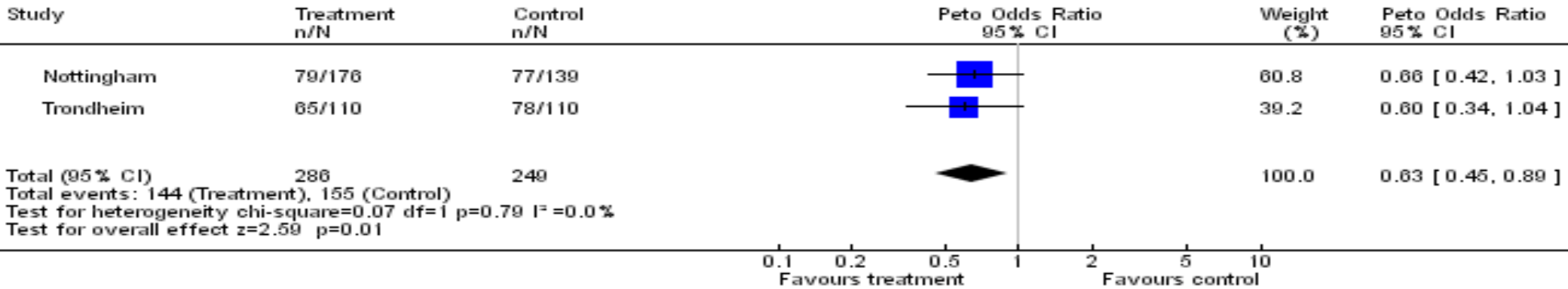


Miti da sfatare (1)

Se combino studi con risultati non statisticamente significativi, il risultato della meta-analisi sarà non significativo



Review: Organised inpatient (stroke unit) care for stroke
Comparison: 01 Organised stroke unit care vs Alternative service
Outcome: 05 Death at five years follow up



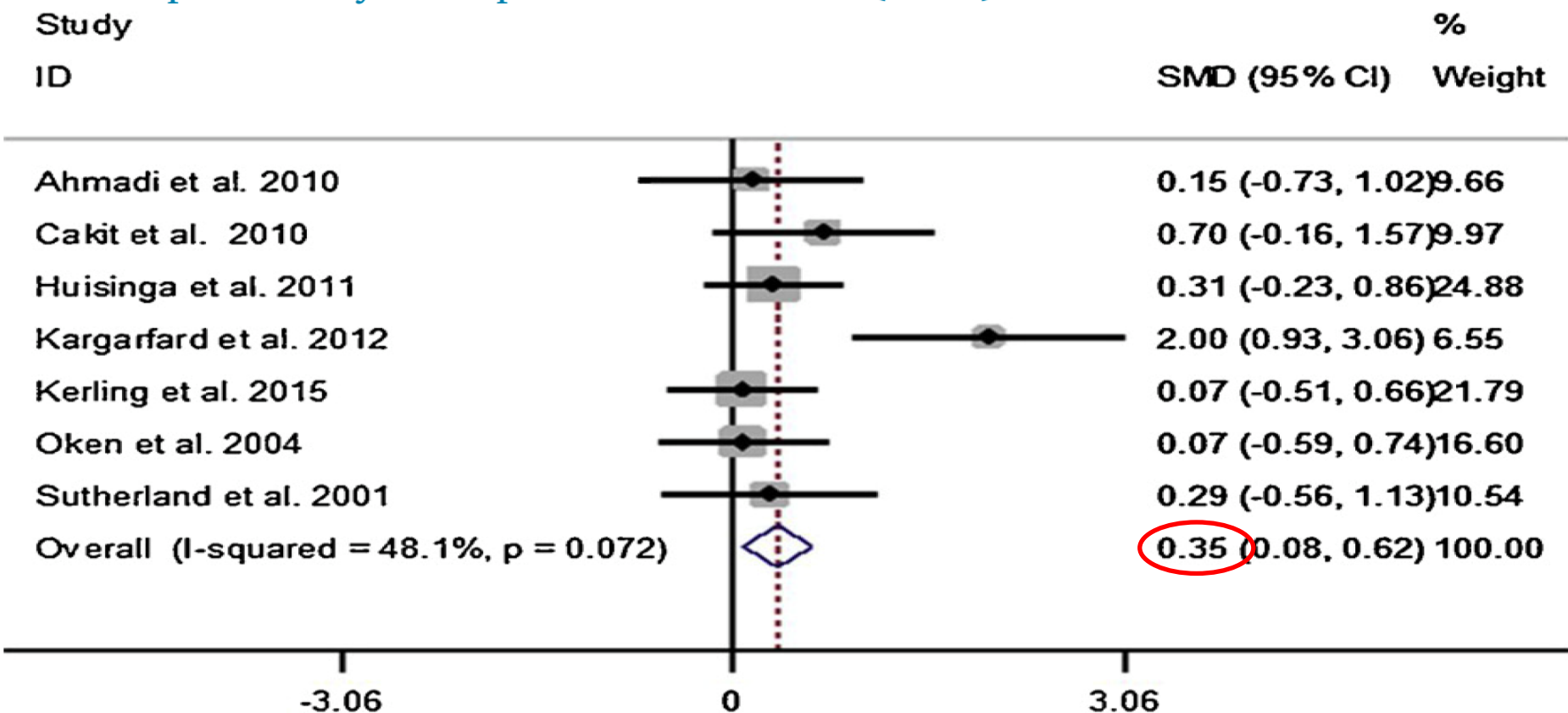
Miti da sfatare (2)

Se il risultato della meta-analisi è statisticamente significativo, allora il risultato è clinicamente rilevante

The effect of exercise, yoga and physiotherapy on the quality of life of people with multiple sclerosis: Systematic review and meta-analysis

Khrisha B. Alphonsus^{a,*}, Yingying Su^a, Carl D'Arcy^{a,b}

Complementary Therapies in Medicine 43 (2019) 188–195



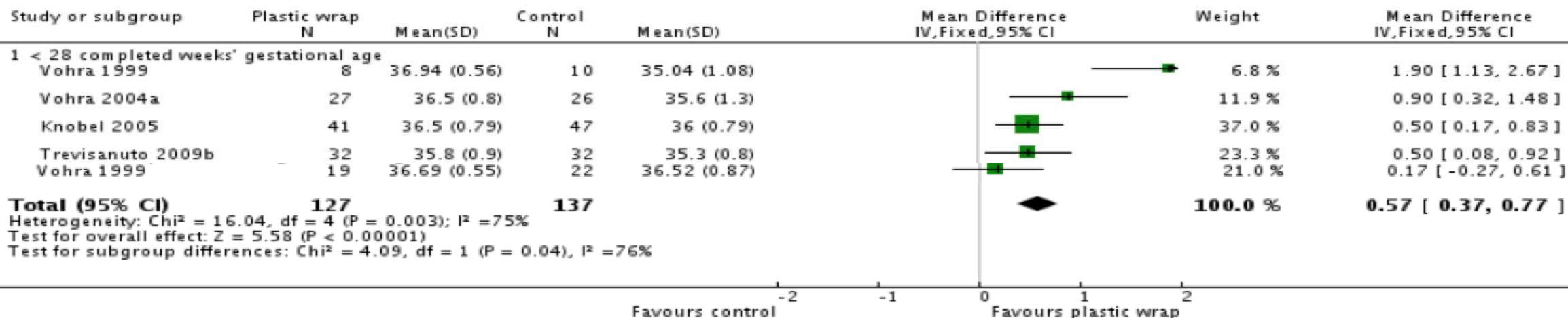
Cohen effect size 0.2 small effect
0.5 medium effect
0.8 large effect

Miti da sfatare (3)

Se trovo elevata eterogeneità tra gli studi inclusi, la meta-analisi non ha senso (si mettono insieme mele e pere)

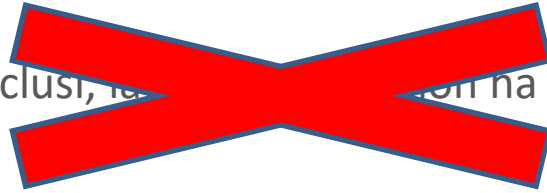
Esito: Temperatura corporea

Review: Interventions to prevent hypothermia at birth in preterm and/or low birthweight infants
 Comparison: 1 Plastic wrap versus routine care
 Outcome: 1 Core body temperature (°C) on admission to NICU or up to 2 hours after birth



Miti da sfatare (3)

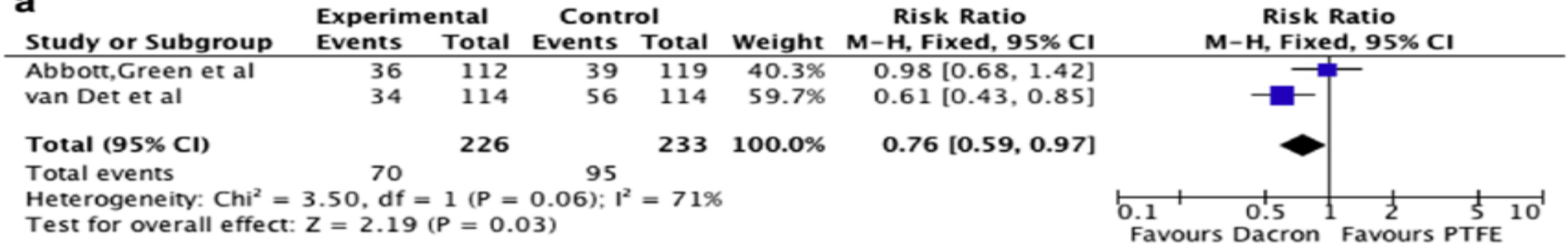
Se trovo elevata eterogeneità tra gli studi inclusi, ~~non~~ non ha senso (si mettono insieme mele e pere)



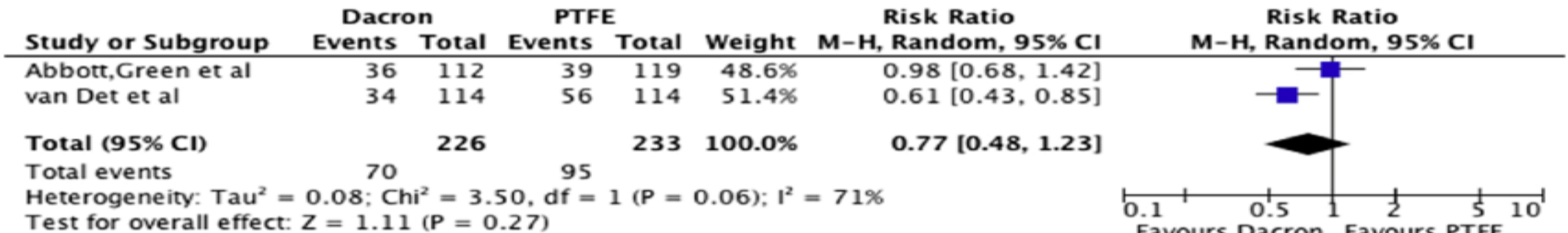
- Dipende dal quesito: se il quesito fosse sulla frutta?
- Dipende dal peso degli studi che «creano» eterogeneità
- Dipende dalla direzione e non dalla magnitudo dell'effetto dei singoli studi
- Dipende dal fatto di poterla spiegare (analisi per sottogruppi)

Un diamante è per sempre ma dipende da molti aspetti

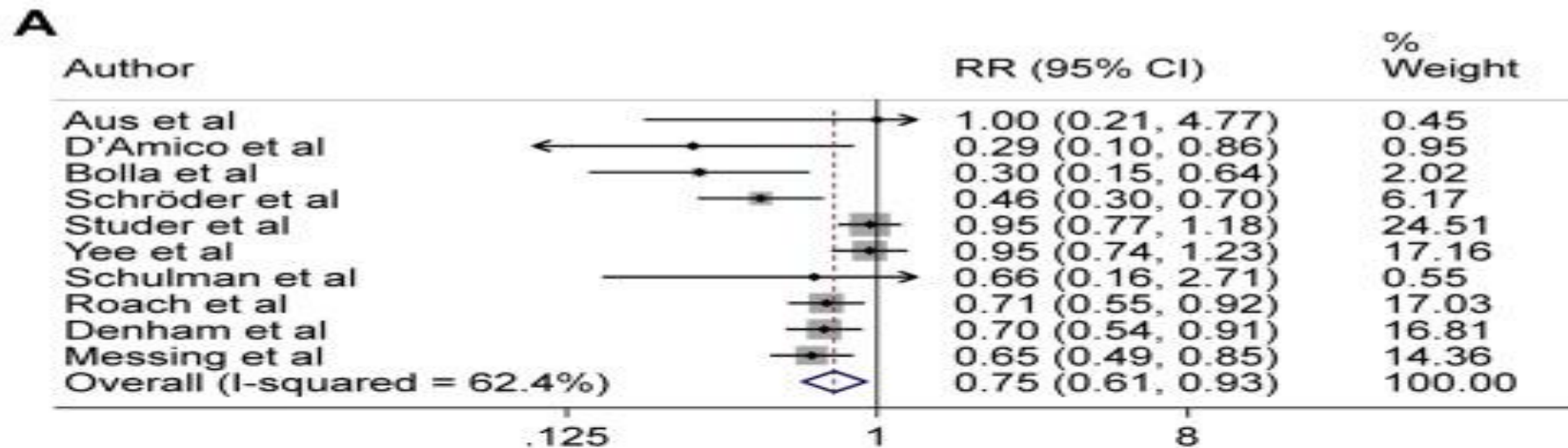
a



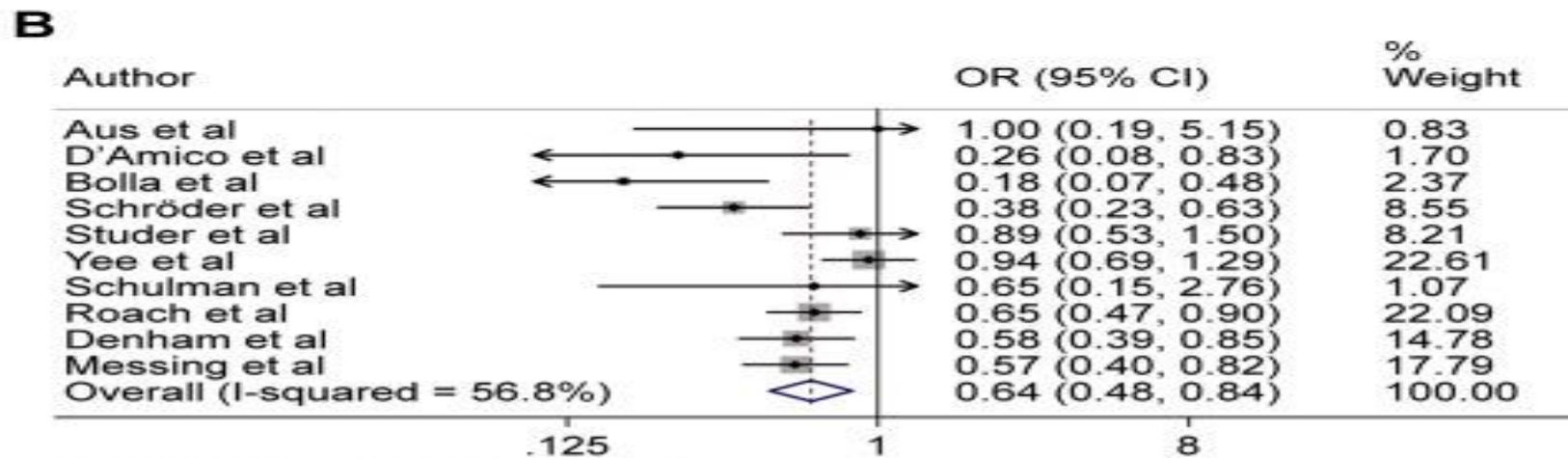
b



Un diamante è per sempre ma dipende da molti aspetti



NOTE: Weights are from Doi's IVHet model



NOTE: Weights are from Doi's IVHet model

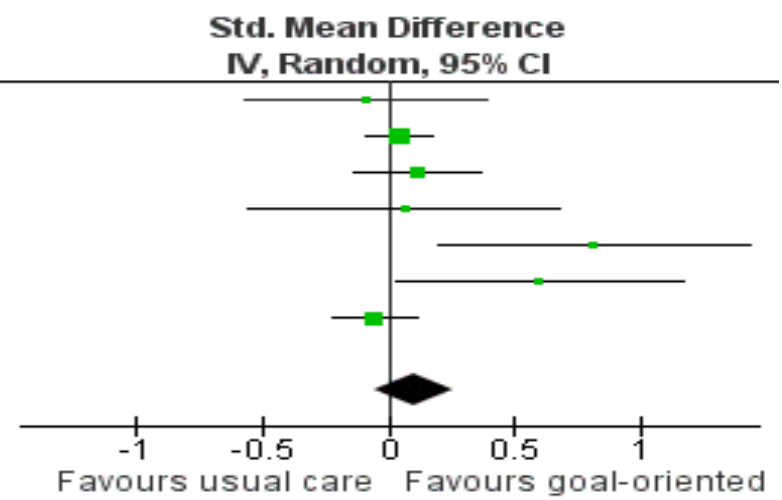
Miti da sfatare (4)

Garbage in, garbage out

Esito: QoL

Study or Subgroup	goal-oriented care			usual care			Weight	Std. Mean Difference IV, Random, 95% CI
	Mean	SD	Total	Mean	SD	Total		
Barley 2014	32.4	10.7	32	33.3	9.2	37	8.5%	-0.09 [-0.56, 0.38]
Blom 2016	6.82	1.34	276	6.76	1.39	1044	29.2%	0.04 [-0.09, 0.18]
Ell 2017	38.3	0.8	122	38.2	0.9	122	19.0%	0.12 [-0.13, 0.37]
Ford 2019	0.56	0.25	18	0.54	0.34	23	5.6%	0.06 [-0.55, 0.68]
Garvey 2015	65.7	20.2	22	50.5	16.3	22	5.5%	0.81 [0.20, 1.43]
Park 2014	-2.8	0.6	25	-3.3	1	25	6.4%	0.60 [0.03, 1.16]
Verdoorn 2019	0.73	0.2	266	0.74	0.18	261	25.7%	-0.05 [-0.22, 0.12]
Total (95% CI)			761			1534	100.0%	0.10 [-0.06, 0.26]

Heterogeneity: Tau² = 0.02; Chi² = 11.44, df = 6 (P = 0.08); I² = 48%
 Test for overall effect: Z = 1.25 (P = 0.21)



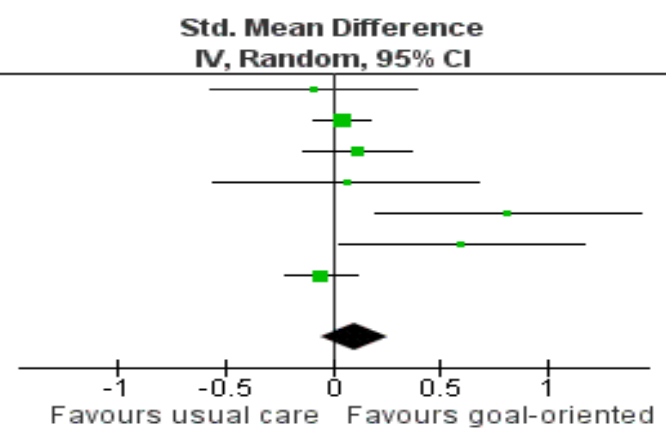
Miti da sfatare (4)

Garbage in, garbage out

Esito: QoL

Study or Subgroup	goal-oriented care			usual care			Weight	Std. Mean Difference	
	Mean	SD	Total	Mean	SD	Total		IV, Random, 95% CI	95% CI
Barley 2014	32.4	10.7	32	33.3	9.2	37	8.5%	-0.09	[-0.56, 0.38]
Blom 2016	6.82	1.34	276	6.76	1.39	1044	29.2%	0.04	[-0.09, 0.18]
Eli 2017	38.3	0.8	122	38.2	0.9	122	19.0%	0.12	[-0.13, 0.37]
Ford 2019	0.56	0.25	18	0.54	0.34	23	5.6%	0.06	[-0.55, 0.68]
Garvey 2015	65.7	20.2	22	50.5	16.3	22	5.5%	0.81	[0.20, 1.43]
Park 2014	-2.8	0.6	25	-3.3	1	25	6.4%	0.60	[0.03, 1.16]
Verdoorn 2019	0.73	0.2	266	0.74	0.18	261	25.7%	-0.05	[-0.22, 0.12]
Total (95% CI)			761			1534	100.0%	0.10	[-0.06, 0.26]

Heterogeneity: Tau² = 0.02; Chi² = 11.44, df = 6 (P = 0.08); I² = 48%
 Test for overall effect: Z = 1.25 (P = 0.21)



Risk of Bias										
A	B	C	D	E	F	G	H	I	J	
+	?	-	-	?	?	?	?	-	+	
-	-	-	-	-	-	-	-	-	-	
+	?	-	-	?	?	?	?	-	+	
+	+	-	-	?	?	?	?	?	+	
+	+	-	-	-	-	?	?	?	+	
+	?	-	-	?	?	?	?	?	-	

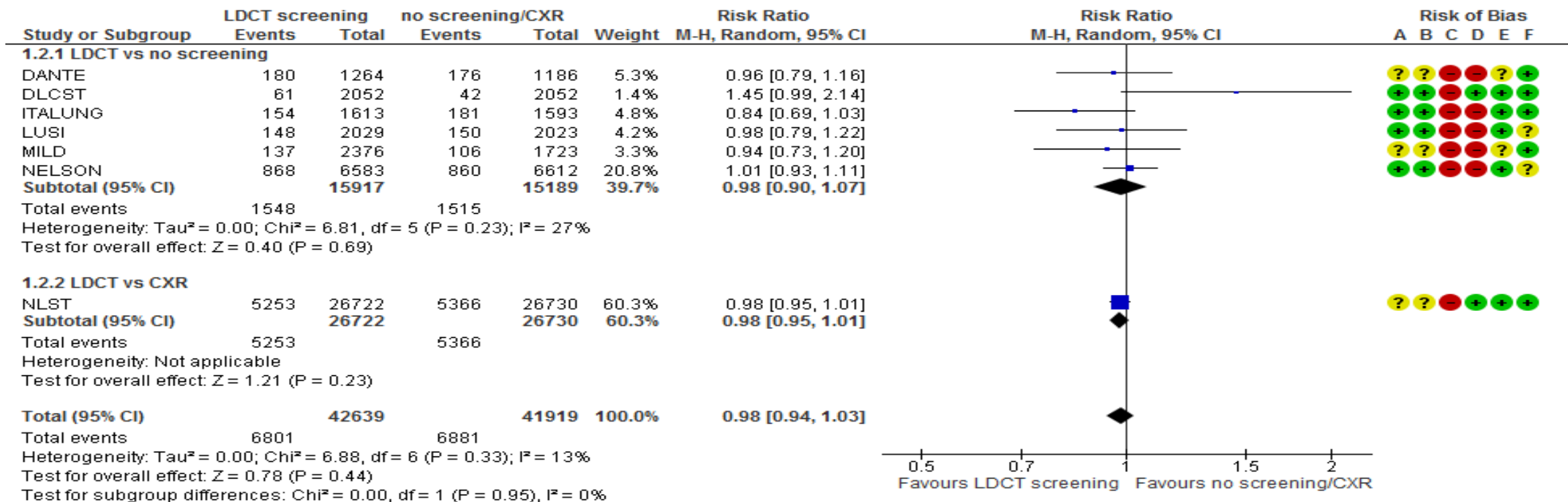
Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (Quality of life)
- (E) Blinding of outcome assessment (Social Functioning)
- (F) Blinding of outcome assessment (patient's satisfaction)
- (G) Blinding of outcome assessment (Hospital admission)
- (H) Blinding of outcome assessment (Caregiver burden)
- (I) Incomplete outcome data (attrition bias)
- (J) Selective reporting (reporting bias)

Miti da sfatare (4)

Garbage in, garbage out

Esito: Overall mortality



Risk of bias legend

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)

Miti da sfatare (5)

La lettura dei sottogruppi

Forest plot

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
1.2.1 ≤ 6 months				
Buzdar	0	0		Not estimable
FinHer	-0.6	0.36	4.9%	0.55 [0.27, 1.11]
Subtotal (95% CI)			4.9%	0.55 [0.27, 1.11]
Heterogeneity: Not applicable Test for overall effect: Z = 1.67 (P = 0.10)				
1.2.2 > 6 months				
NOAH	-0.48	0.3	7.1%	0.62 [0.34, 1.11]
BCIRG006	-0.46	0.13	37.7%	0.63 [0.49, 0.81]
HERA	-0.46	0.17	22.0%	0.63 [0.45, 0.88]
B31 (1)	-0.4	0.17	22.0%	0.67 [0.48, 0.94]
PACS-04	0.24	0.32	6.2%	1.27 [0.68, 2.38]
Subtotal (95% CI)			95.1%	0.67 [0.57, 0.80]
Heterogeneity: Tau ² = 0.00; Chi ² = 4.41, df = 4 (P = 0.35); I ² = 9% Test for overall effect: Z = 4.52 (P < 0.00001)				
Total (95% CI)			100.0%	0.66 [0.57, 0.77]
Heterogeneity: Tau ² = 0.00; Chi ² = 4.70, df = 5 (P = 0.45); I ² = 0% Test for overall effect: Z = 5.16 (P < 0.00001) Test for subgroup differences: Chi ² = 0.30, df = 1 (P = 0.58), I ² = 0% (1) B31+N9831				

0.2 0.5 1 2 5
Favours experimental Favours control

Add as Figure Cancel

Footnote:

General Assumptions in Subgroup Analysis

- Hypotheses tested usually address an overall or ‘average’ treatment effect in the study population
- No assumption of homogeneity of effect across subgroups - **interaction**
- Direction, not magnitude, of the treatment effect is expected be the same in subgroups

*• Only one thing is worse than doing subgroup analyses---
believing the results*

R. Peto

AMSTAR CHECKLIST

- Valuta il **QUALITY OF CONDUCT**: la misura in cui la revisione è esente da errori sistematici
- Per aiutare chi legge a capire se la SR è affidabile e valida
- Composta di 11 items
- [Shea BJ et al.](#) Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007 Feb 15;7:10.

AMSTAR – a measurement tool to assess the methodological quality of systematic reviews.

1. Was an 'a priori' design provided?

The research question and inclusion criteria should be established before the conduct of the review.

- Yes
- No
- Can't answer
- Not applicable

Note: Need to refer to a protocol, ethics approval, or pre-determined/a priori published research objectives to score a "yes."

2. Was there duplicate study selection and data extraction?

There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.

- Yes
- No
- Can't answer
- Not applicable

Note: 2 people do study selection, 2 people do data extraction, consensus process or one person checks the other's work.

3. Was a comprehensive literature search performed?

At least two electronic sources should be searched. The report must include years and databases used (e.g., Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized

- Yes
- No

AMSTAR CHECKLIST II

- *“... The original AMSTAR instrument did not include an assessment of the risk of bias in non-randomised studies included in a review, which is a key issue given the diversity of designs that such studies may use and the biases that may affect them”.*
- [Shea BJ et al.](#) AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017 Sep 21;358:j4008
- 16 items

ROBIS: A new tool to assess risk of bias in systematic reviews was developed

Penny Whiting^{a,b,c,*}, Jelena Savović^{a,b}, Julian P.T. Higgins^{a,d}, Deborah M. Caldwell^a, Barnaby C. Reeves^e, Beverley Shea^f, Philippa Davies^{a,b}, Jos Kleijnen^{c,g}, Rachel Churchill^a, the ROBIS group

^aSchool of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK

^bThe National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West at University Hospitals Bristol NHS Foundation Trust, 9th Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT

^cKleijnen Systematic Reviews Ltd, Unit 6, Escrick Busi

^dCentre for Reviews and Dissemination, I

^eSchool of Clinical Sciences, University of Bristol, Bristol Royal Infirmary

^fCommunity Information and Epidemiological Technologies Institute of Popula

^gSchool for Public Health and Primary Care (CAPHRI), Maastrich

Accepted 5 June 2015; Publ

Abstract

Objective: To develop ROBIS, a new tool for assessing the risk
Study Design and Setting: We used four-stage approach to develo
face meeting, and refine the tool through piloting.

ROBIS QUALITY OF CONDUCT Checklist

Phase 2: Identifying concerns with the review process

DOMAIN 1: STUDY ELIGIBILITY CRITERIA

Describe the study eligibility criteria, any restrictions on eligibility and whether there was evidence that objectives and eligibility criteria were pre-specified:

1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	Y/PY/PN/N/NI
1.2 Were the eligibility criteria appropriate for the review question?	Y/PY/PN/N/NI
1.3 Were eligibility criteria unambiguous?	Y/PY/PN/N/NI
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Y/PY/PN/N/NI
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Y/PY/PN/N/NI

Concerns regarding specification of study eligibility criteria LOW/HIGH/UNCLEAR

Rationale for concern:

DOMAIN 2: IDENTIFICATION AND SELECTION OF STUDIES

Describe methods of study identification and selection (e.g. number of reviewers involved):

2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	Y/PY/PN/N/NI
2.2 Were methods additional to database searching used to identify	Y/PY/PN/N/NI

PRISMA Statement

OPEN ACCESS Freely available online

PLoS MEDICINE

Guidelines and Guidance

Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement

David Moher^{1,2*}, Alessandro Liberati^{3,4}, Jennifer Tetzlaff¹, Douglas G. Altman⁵, The PRISMA Group[¶]

1 Ottawa Methods Centre, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, **2** Department of Epidemiology and Community Medicine, Faculty of Medicine, University of Ottawa, Ottawa, Ontario, Canada, **3** Università di Modena e Reggio Emilia, Modena, Italy, **4** Centro Cochrane Italiano, Istituto Ricerche Farmacologiche Mario Negri, Milan, Italy, **5** Centre for Statistics in Medicine, University of Oxford, Oxford, United Kingdom



<http://www.prisma-statement.org/>

PRISMA

- Pubblicato nel 2009, evoluzione del QUOROM statement (guida, pubblicata nel 1999, per migliorare il reporting di meta-analisi di RCT).
- Valuta il ***QUALITY OF REPORTING***
- Pubblicato in Annals of Internal Medicine, PLoS Medicine, Open Medicine, the British Medical Journal and the Journal of Clinical Epidemiology.

KEY DOCUMENTS

- [PRISMA Statement](#)
- [PRISMA Checklist](#)
- [PRISMA flow diagram](#)
- [PRISMA E&E](#)

PRISMA Checklist

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria; participants; and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases) with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ² for each meta-analysis).	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome, consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed.0060097

For more information, visit: www.prisma-statement.org

Style and Format

File format

Length

Font

Headings

Layout

Page and line numbers

Footnotes

Submission Guidelines

PLOS Medicine publishes original research articles of outstanding medical importance. We will consider manuscripts of any length; we encourage the submission of both substantial full-length bodies of work and shorter manuscripts that report novel findings that might be based on a more limited range of experiments.

The writing style should be concise and accessible, avoiding jargon so that the paper is understandable for readers outside a specialty or those whose first language is not English. Editors will make suggestions for how to achieve this, as well as suggestions for deletions or additions that could be made to the article to strengthen the argument. Our aim is to make the editorial process rigorous and consistent, but not intrusive or overbearing. Authors are encouraged to use their own voice and to decide how best to present their ideas, results, and conclusions.

Systematic reviews and meta-analyses

Reports of systematic reviews and meta-analyses must adhere to the [PRISMA Statement](#) or alternative guidelines appropriate to the study design, and include the completed checklist and flow diagram to accompany the main text. Authors must complete the appropriate reporting checklist not only with page references, but also with sufficient text excerpted from the manuscript to explain how they accomplished all applicable items.



Download blank templates of the checklist and flow diagram from the [EQUATOR web site](#).

Abstracts should follow [PRISMA for Abstracts](#), using the PLOS abstract format. Authors must also state within the Methods section of their paper whether a protocol exists for their systematic review, and if so, provide a copy of the protocol as supporting information.

Esempio

PLOS ONE

Efficacy of muscle exercise in patients with muscular dystrophy: a systematic review showing a missed opportunity to improve outcomes

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	done
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Structured abstract done
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page #2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page #2
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	None
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page #2-3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page #3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page #3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page #3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page #4

<http://www.equator-network.org/>



Enhancing the **QUALITY** and
Transparency Of health Research



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[Systematic reviews](#)

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[Quality improvement studies](#)

[CONSORT](#) [Extensions](#)

[STROBE](#) [Extensions](#)

[PRISMA](#) [Extensions](#)

[SPIRIT](#) [PRISMA-P](#)

[STARD](#) [TRIPOD](#)

[CARE](#) [Extensions](#)

[AGREE](#) [RIGHT](#)

[SRQR](#) [COREQ](#)

[ARRIVE](#)

[SQUIRE](#)

Researching
BIOMARKERS?
Make sure you use
REMARK
to report every
important detail!



Example of bad reporting

[Hip Int.](#) 2012 Jul-Aug;22 Suppl 8:S19-24. doi: 10.5301/HIP.2012.9566.

Value of debridement and irrigation for the treatment of peri-prosthetic infections. A systematic review.

Abstract

Debridement and irrigation has been proposed as a salvage procedure for early post-operative and late acute haematogenous periprosthetic hip and knee infections, however the effective ability of this procedure to avoid recurrent infection is still debated. In this systematic review of the literature we reviewed full-text papers published from 1970 through 2011, that reported the success rate of infection eradication after debridement and irrigation with prosthesis retention for the treatment of early septic complications (within six weeks from surgery) or late acute haematogenous infections after hip or knee prosthesis. In all, 14 original articles, reporting the results of 710 patients were retrieved. The average success rate has been, respectively, 45.9% and 52% after a single or repeated debridement and irrigation procedures, at a mean follow-up of 53.3 months. The methodological limitations of this study and the heterogeneous material in the reviewed papers notwithstanding, this systematic review shows that debridement and irrigation procedure is associated with a rather poor outcome, even in a population of patients selected on the basis of symptoms' duration and patients should be adequately informed prior to undergo this salvage procedure.

- ✓ **ABSTRACT NON STRUTTURATO IN INTRODUZIONE, OBIETTIVI, RISORSE RICERCA, CRITERI DI ELIGIBILITA', INTERVENTI, CRITICAL APPRISAL, SINTESI DEI METODI, RISULTATI, LIMITAZIONI CONCLUSIONI, IMPLICAZIONI**
- ✓ **SYSTEMATIC REVIEW REGISTRATION NUMBER**
- ✓ **MANCANO BANCHE DATI**

Example of good reporting

Virtual Reality Therapy for Adults Post-Stroke: A Systematic Review and Meta-Analysis Exploring Virtual Environments and Commercial Games in Therapy

Abstract

Background: The objective of this analysis was to systematically review the evidence for virtual reality (VR) therapy in an adult post-stroke population in both custom built virtual environments (VE) and commercially available gaming systems (CG).

Methods: MEDLINE, CINAHL, EMBASE, ERIC, PSYCInfo, DARE, PEDro, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were systematically searched from the earliest available date until April 4, 2013. Controlled trials that compared VR to conventional therapy were included. Population criteria included adults (>18) post-stroke, excluding children, cerebral palsy, and other neurological disorders. Included studies were reported in English. Quality of studies was assessed with the Physiotherapy Evidence Database Scale (PEDro).

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ABSTRACT STRUTTURATO IN INTRODUZIONE, OBIETTIVI, RISORSE RICERCA, CRITERI DI ELIGIBILITA', INTERVENTI, CRITICAL APPRISAL, SINTESI DEI METODI, RISULTATI, LIMITAZIONI CONCLUSIONI, IMPLICAZIONI, SYSTEMATIC REVIEW REGISTRATION NUMBER

VR
VE
32,
all

Discussion: VR rehabilitation moderately improves outcomes compared to conventional therapy in adults post-stroke. Current CG interventions have been too few and too small to assess potential benefits of CG. Future research in this area should aim to clearly define conventional therapy, report on participation measures, consider motivational components of therapy, and investigate commercially available systems in larger RCTs.

Trial Registration: Prospero CRD42013004338



SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10^a EDIZIONE

MODULI SPECIALISTICI - S1



VENERDÌ 8 - SABATO 9 MARZO 2024

NEGRAR DI VALPOLICELLA (VR)

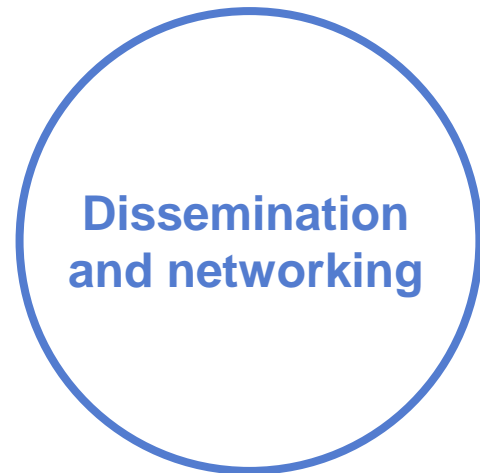
Centro Formazione IRCCS "Sacro Cuore - Don Calabria"

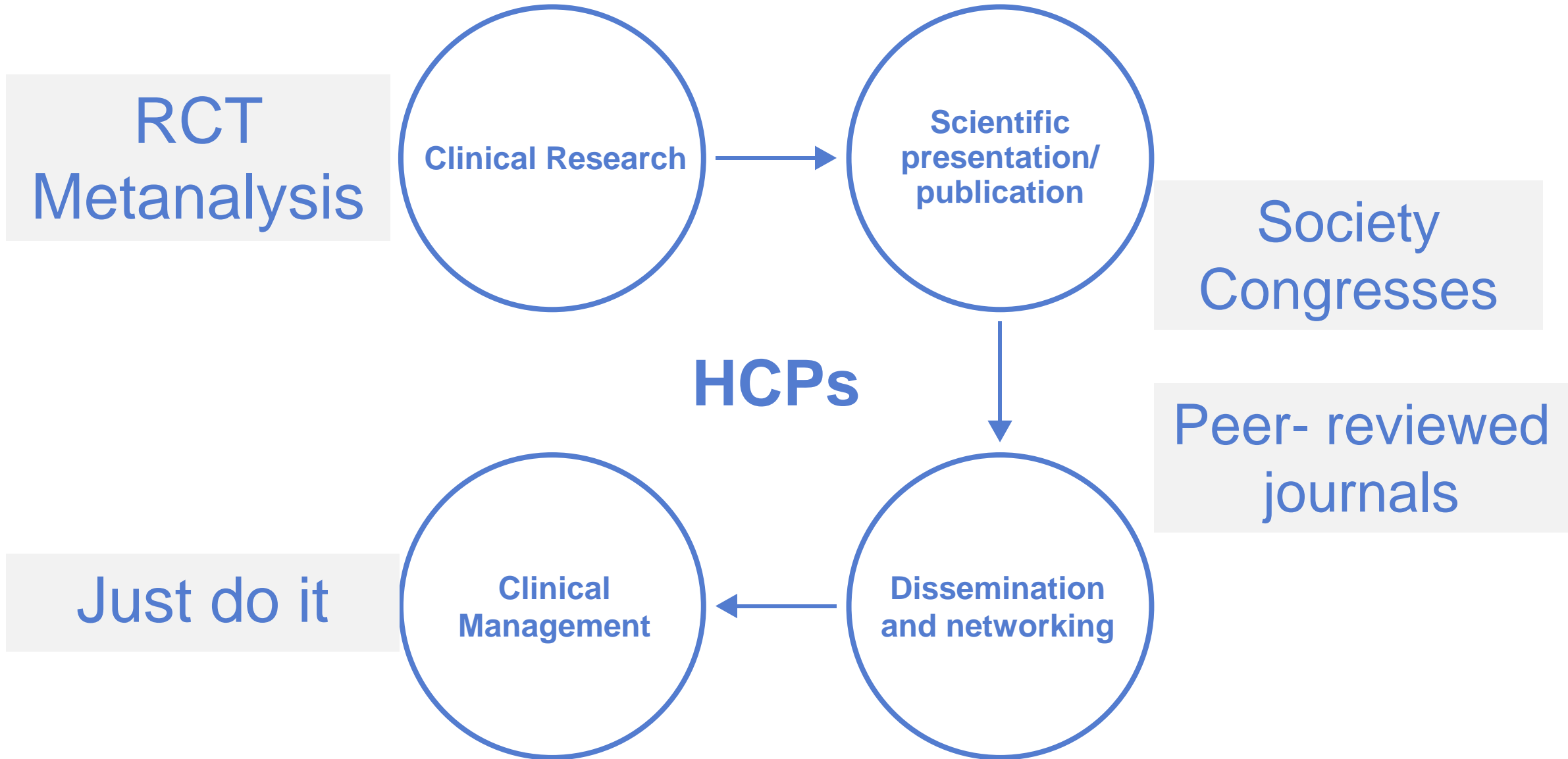
Metodi di valutazione di autori
e riviste scientifiche: indici
bibliometrici classici e
innovativi

Giulio ZUANETTI



HCPs





RCT
Metanalysis

Clinical Research

Scientific
presentation/
publication

Society
Congresses

HCPs

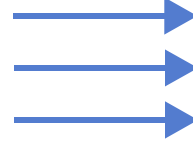
Peer- reviewed
journals

Just do it

Clinical
Management

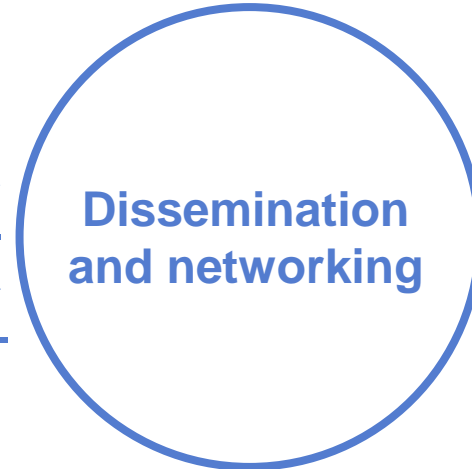
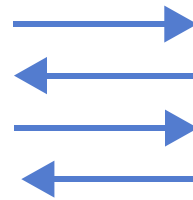
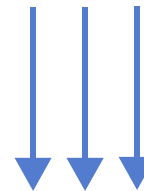
Dissemination
and networking

RCT, RWE,
NetworkMet,
AI...

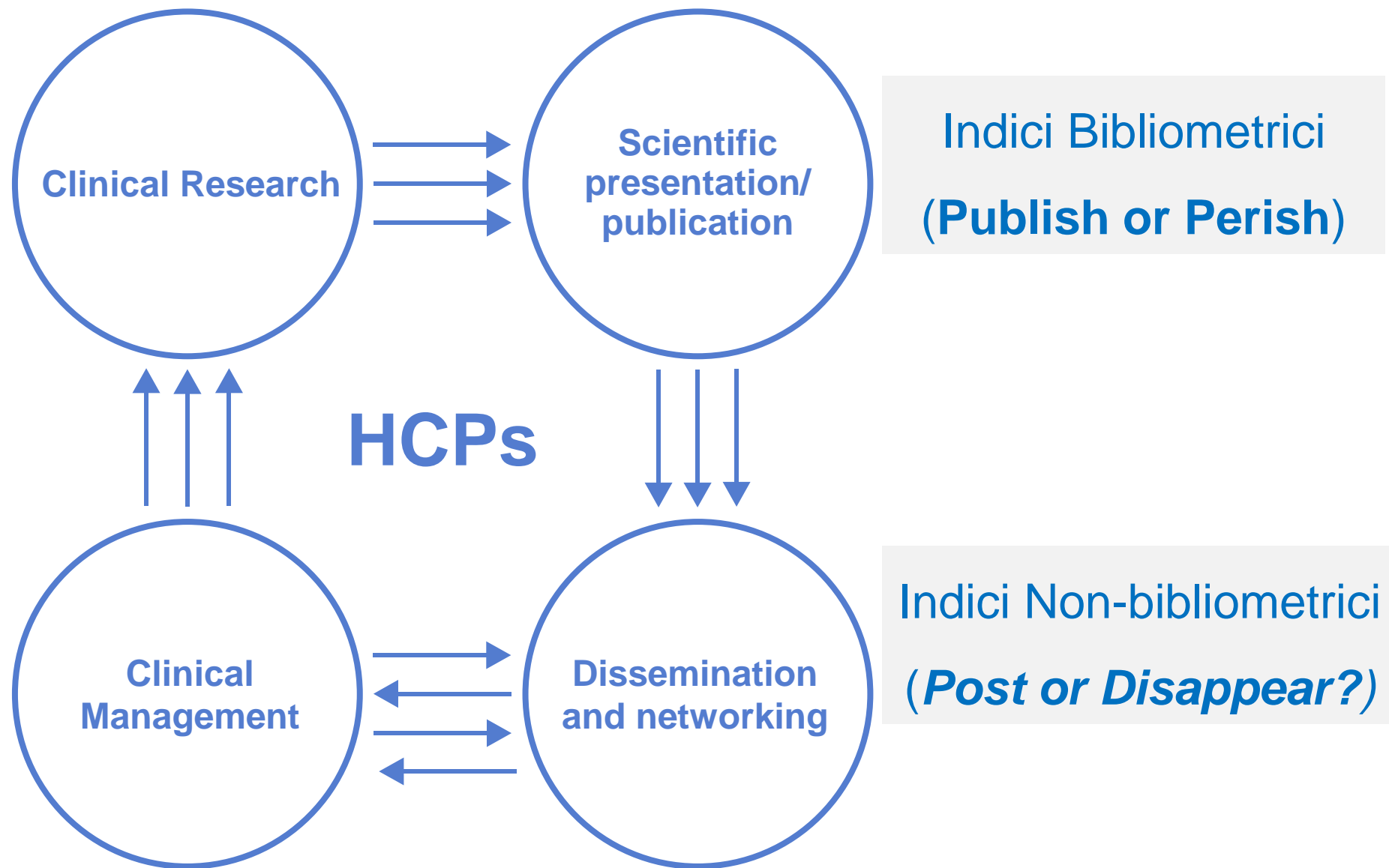


Congresses,
PeerRev Journals,
PrePrints,
Media & Events,
Forums,
Social networks,
AI...

HCPs



*Do it &
tell about it*



Publish or perish

(Top)

From Wikipedia, the free encyclopedia

[Origin](#)

[Advantages](#)

[Disadvantages](#)

[Variants](#)

[See also](#)

[Notes](#)

[References](#)

[External links](#)

"**Publish or perish**" is an [aphorism](#) describing the pressure to [publish academic work](#) in order to succeed in an [academic career](#).^{[1][2][3]} Such institutional pressure is generally strongest at [research universities](#).^[4] Some researchers have identified the publish or perish environment as a contributing factor to the [replication crisis](#).

Successful publications bring attention to scholars and their sponsoring institutions, which can help continued funding and their careers. In popular academic perception, scholars who publish infrequently, or who focus on activities that do not result in publications, such as instructing [undergraduates](#), may lose ground in competition for available tenure-track positions. The pressure to publish has been cited as a cause of poor work being submitted to [academic journals](#).^[5] The value of published work is often determined by the prestige of the academic journal it is published in. Journals can be measured by their [impact factor \(IF\)](#), which is the average number of citations to articles published in a particular journal over the last two years.^[6]

Publicare bene è molto importante per il percorso professionale



Tú

Vorrei sapere quali sono i criteri per diventare professore associato in Oncologia in Italia, quali indici bibliometrici vengono utilizzati



ChatGPT

In Italia, il percorso per diventare professore associato in ambito universitario, inclusa l'area dell'Oncologia o qualsiasi altro campo accademico, è regolamentato da criteri specifici che includono valutazioni basate su indici bibliometrici. Questi criteri sono stabiliti dal Ministero dell'Università e della Ricerca (MUR) e possono variare nel tempo con l'aggiornamento delle normative. Di seguito, sono elencati i principali passaggi e requisiti, inclusi gli indici bibliometrici comunemente utilizzati:

1. Abilitazione Scientifica Nazionale (ASN)

Per diventare professore associato, è necessario ottenere l'Abilitazione Scientifica Nazionale alla funzione di professore di seconda fascia. L'ASN valuta l'idoneità dei candidati basandosi su pubblicazioni, esperienza di ricerca, e contributi scientifici.

2. Pubblicazioni e Indici Bibliometrici

Le pubblicazioni sono valutate in termini di qualità e impatto nel campo di riferimento. Gli indici bibliometrici utilizzati per valutare le pubblicazioni includono:

- **H-index (Indice di Hirsch):** Misura sia la produttività che l'impatto citazionale dei lavori pubblicati di un ricercatore. Un h-index elevato indica che il ricercatore ha pubblicato molti lavori che sono stati citati frequentemente da altri.
- **Citations (Citazioni):** Il numero totale di citazioni ricevute può essere considerato un indicatore dell'impatto della ricerca.
- **Impact Factor (Fattore di Impatto)** delle riviste in cui si è pubblicato: Anche se non è un indice bibliometrico personale, pubblicare su riviste con un alto Impact Factor è spesso considerato indicativo della qualità della ricerca.

3. Contributo Scientifico e Didattico

Oltre agli indici bibliometrici, sono valutati il contributo scientifico del candidato nel suo campo di specializzazione, l'esperienza didattica, l'abilità di attrarre finanziamenti per la ricerca, e il contributo allo sviluppo del dipartimento di appartenenza.

4. Concorso Universitario

Dopo aver ottenuto l'ASN, il candidato può partecipare a concorsi banditi dalle università italiane per posti di professore associato. Questi concorsi valutano il merito scientifico, l'esperienza didattica e le competenze professionali dei candidati.

5. Valutazione da Parte di Una Commissione

Una commissione accademica valuta i candidati attraverso l'esame del curriculum, delle pubblicazioni, e spesso mediante colloqui o lezioni prova. La commissione può basarsi sugli indici bibliometrici, ma considera anche altri aspetti della carriera accademica e professionale.

Gli indici di valutazione scientifica bibliometrici:

Riviste

Articoli Scientifici

Autori



Activity and safety of enobosarm, a novel, oral, selective androgen receptor modulator, in androgen receptor-positive, oestrogen receptor-positive, and HER2-negative advanced breast cancer (Study G200802): a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial

Carlo Palmieri, Hannah Linden, Stephen N Birrell, Sally Wheelwright, Elgene Lim, Lee S Schwartzberg, Amy R Dwyer, Theresa E Hickey, Hope S Kugo, Patrick Cobb, Joyce A O'Shaughnessy, Stephen Johnston, Adam Brufsky, Wayne D Tilley*, Beth Overmeyer*

Summary
Background The androgen receptor is a tumour suppressor in oestrogen receptor-positive breast cancer. The activity and safety of enobosarm, an oral selective androgen receptor modulator, was evaluated in women with oestrogen receptor (ER)-positive, HER2-negative, and androgen receptor (AR)-positive disease.

Methods Women who were postmenopausal (aged ≥ 18 years) with previously treated ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled in a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial done at 35 cancer treatment centres in nine countries. Participants were stratified on the setting of immediately preceding endocrine therapy and the presence of bone-only metastasis and randomly assigned (1:1) to 9 mg or 18 mg oral enobosarm daily using an interactive web response system. The primary endpoint was clinical benefit rate at 24 weeks in those with centrally confirmed AR-positive disease (ie, the evaluable population). This trial is registered with ClinicalTrials.gov (NCT02463032).

Findings Between Sept 10, 2015, and Nov 28, 2017, 136 (79%) of 172 patients deemed eligible were randomly assigned to 9 mg (n=72) or 18 mg (n=64) oral enobosarm daily. Of these 136 patients, 102 (75%) patients formed the evaluable population (9 mg, n=50; 18 mg, n=52). The median age was 60·5 years (IQR 52·3–69·3) in the 9 mg group and 62·5 years (54·0–69·3) in the 18 mg group. The median follow-up was 7·5 months (IQR 2·9–14·1). At 24 weeks, 16 (32%, 95% CI 20–47) of 50 in the 9 mg group and 15 (29%, 17–43) of 52 in the 18 mg group had clinical benefit. Six (8% of 75 patients who received 9 mg and ten (16% of 61 patients who received 18 mg had grade 3 or grade 4 drug-related adverse events, most frequently increased hepatic transaminases (three [4%] of 75 in the 9 mg group and two [3%] of 61 in the 18 mg group), hypercalcaemia (two [3%] and two [3%]), and fatigue (one [1%] and two [3%]). Four deaths (one in the 9 mg group and three in the 18 mg group) were deemed unrelated to the study drug.

Interpretation Enobosarm has anti-tumour activity in patients with ER-positive, HER2-negative advanced breast cancer, showing that AR activation can result in clinical benefit, supporting further clinical investigation of selective AR activation strategies for the treatment of AR-positive, ER-positive, HER2-negative advanced breast cancer.

Funding GTX.

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Articles



Lancet Oncol 2024; 25: 317–25
Published Online
February 8, 2024
[https://doi.org/10.1016/S1470-2045\(24\)00004-4](https://doi.org/10.1016/S1470-2045(24)00004-4)
See Comment page 269
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(Prof H Linden MD); Wollond Health/Burnside War Memorial Hospital, Torrak Gardens, SA, Australia (S N Birrell MBBS PhD); Dana-Farber Cancer Research Laboratories, Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia (S N Birrell, A R Dwyer PhD, T E Hickey PhD, Prof W D Tilley PhD); Sussex Health Outcomes Research & Education in Cancer (SHORE-CL), University of Sussex, Falmer, Brighton, UK

Carlo Palmieri,



Gli indici di valutazione scientifica bibliometrici

Riviste



Ci sono pochi database fondamentali dove le riviste sono indicizzate, una di gestione pubblica USA, le altre invece di società private:

Web of Science,
ESCI



Medline/
Pubmed

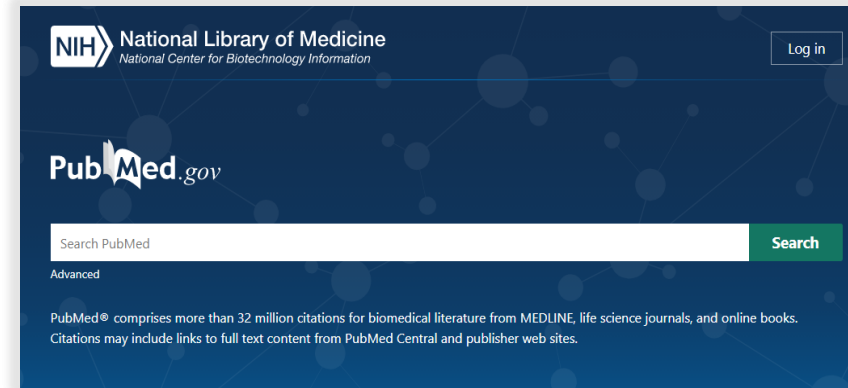


Embase,
Scopus

ELSEVIER

La presenza di un articolo in uno o più di questi database è un elemento di garanzia sulla qualità del lavoro, **tuttavia i confini sono ora meno definiti rispetto al passato.**

...oggi i ricercatori, in particolare i giovani, non cercano solo su PubMed...



<https://pubmed.ncbi.nlm.nih.gov/>

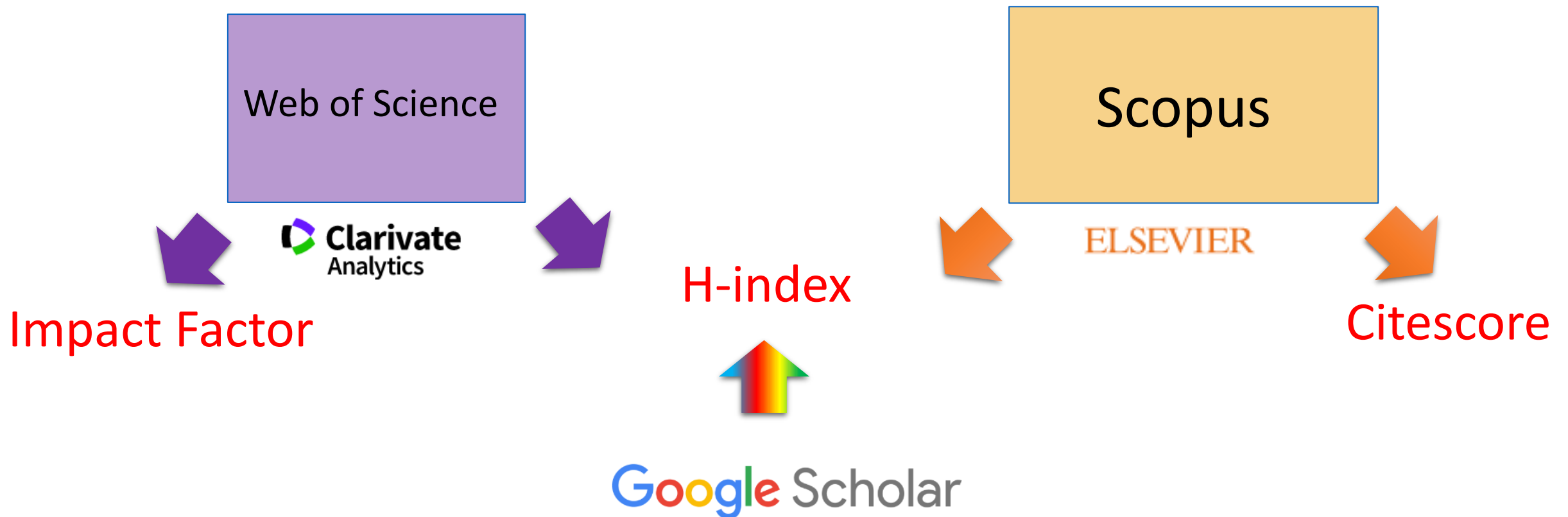
Google Scholar

Articles Case law

Stand on the shoulders of giants

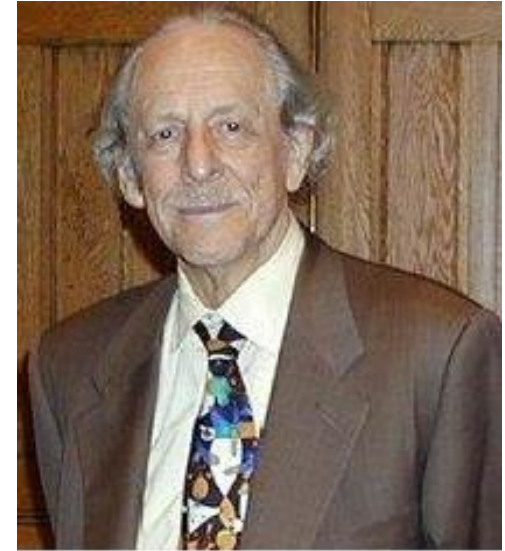
..ma sempre più utilizzano motori di ricerca che si basano su algoritmi propri dei motori di ricerca generalisti...

Le società private hanno sviluppato degli indicatori di performance delle riviste: questi sono indici **bibliometrici** (quindi basati sul numero di citazioni) che vengono ottenuti analizzando i dati da due dei loro databases.



L'Impact Factor non è un indice molto recente

Eugene Garfield è il creatore dell'Impact Factor.



Citation Indexes for Science

A New Dimension in Documentation
through Association of Ideas

Eugene Garfield

Mr. Garfield is a documentation consultant with
offices at 1530 Spring Garden St., Philadelphia
1, Pa.

1955 SCIENCE, VOL. 122

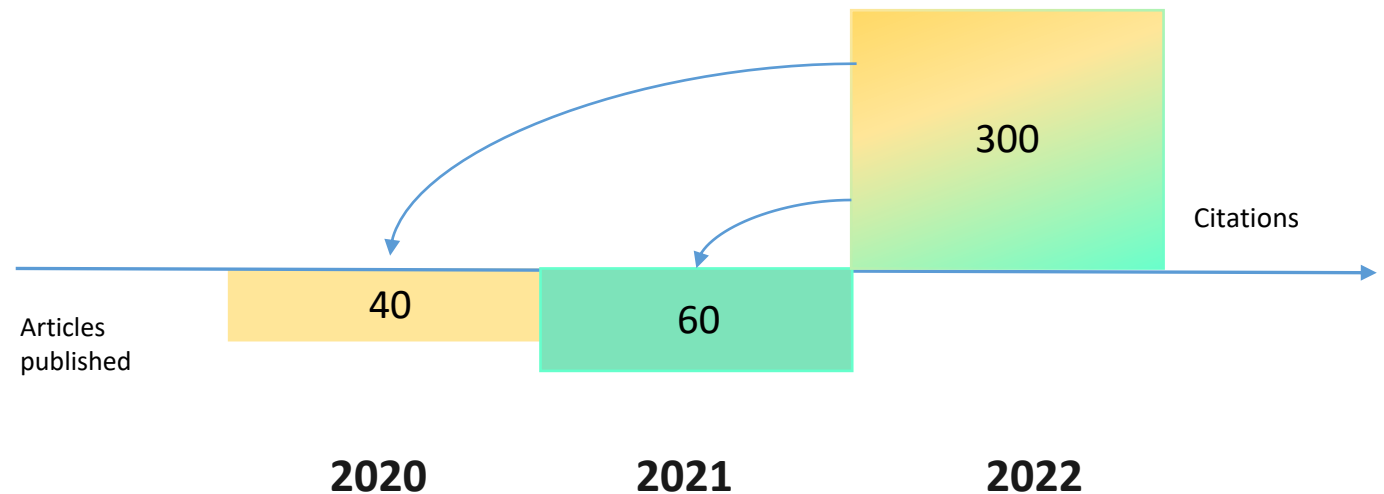
Il lavoro su cui si basa il calcolo dell'indice è stato pubblicato nel **1955**, anche se ufficialmente l'anno in cui si è iniziato a calcolare l'Impact Factor è il **1975**

Il calcolo dell'Impact Factor

Alla data del Corso (Marzo 2024), l'ultimo IF è quello pubblicato nel Giugno **2023** che si basa sulle **citazioni** totali nell'anno **2022** dei **lavori** pubblicati nel **2020** e **2021**

È definito come il **rapporto** tra numero complessivo di citazioni da parte di qualsiasi rivista presente in Web of Science, pertinenti ad articoli della rivista in esame pubblicati nei due anni precedenti, **diviso** il numero totale degli articoli della rivista in esame pubblicati sempre nei due anni precedenti.

Esempio



$$\mathbf{2023\ IF} = \frac{300}{40 + 60} = 3.0$$

L'IF non deve essere utilizzato per la valutazione degli autori

Gli autori di un articolo con zero citazioni possono fare il claim di aver pubblicato su una rivista “impattata” o di essere “**autori impattati**” senza aver avuto neanche una citazione del loro articolo, solo perchè l'IF di una rivista è stato spinto da un articolo citato moltissimo

- L'IF è un indicatore (con diversi limiti) della “bontà” di una rivista ma sicuramente NON degli autori che pubblicano sulla stessa.
- Il fatto che l'IF si riferisca sempre ad articoli pubblicati da 2 a 3 anni prima della valutazione la rende poco “attuale”

→ Il problema è che non abbiamo comunque niente di veramente meglio dell'IF....

Il Competitor dell'IF: CiteScore di Elsevier

- I dati sono disponibili a tutti, non soltanto agli abbonati al JCR come nel caso dell'IF
- Solo gli articoli peer-reviewed sono inclusi nel numeratore e nel denominatore
- Si contano tutti gli articoli e tutte le citazioni presenti andando indietro fino a 4 anni.
- Il CiteScore può essere calcolato anche dopo un solo anno di pubblicazione della rivista



CiteScore non sta riuscendo a scalzare l'IF
come indice di riferimento

I Competitor dell'IF: Le bufale

- Cite Factor
- Cosmos Impact Factor
- Directory of Indexing and Impact Factor
- General Impact Factor
- Global Impact Factor
- Global Science Citation Impact Factor
- Impact Factor Services for International Journals
- International Journal Impact Factor
- Journal Impact Factor
- Journals Impact Factor
- Research Journal Impact Factor
- Science Impact Factor
- Scientific Journal Impact Factor
- Systematic Impact Factor
- Technical Impact Factor
- Universal Impact Factor

I predatory publishers



The definition (Nature, dicembre 2019)

“Predatory journals and publishers are entities that prioritize self-interest at the expense of scholarship and are characterized by **false or misleading information, deviation from best editorial and publication practices**, a lack of transparency, and/or the **use of aggressive and indiscriminate solicitation practices.**”

Fanno
soliciting
sistematico
verso
potenziali
autori

From: Applied Medical Research <medicalresearch@onlinescientificresearch.info>

Sent: Tuesday, 20 February 2024 12:28 pm

To: Giulio Zuanetti <Giulio.Zuanetti@aboutpharma.com>

Subject: Reg: Your Excellency Research Work

Importance: High

Dear Dr. Giulio Zuanetti,

Greetings from the Journal!

It's glad to inform you that with the continues support from the Scholars, Viewers and Great Potential authors like you our **Applied Medical Research** got improved by Classification, with the **Impact Factor 3.182***, **Volume 11** and the Citations value has been increased and indexed in **ISI**.

We would like to invite for your article to publish in this upcoming issue for a better development of the Journal.

We would appreciate receiving your submission on or before **March 05, 2024**.

Awaiting your Submission

With regards,

Joyson K

Applied Medical Research

ISSN: 2149-2018

Impact Factor: 3.182(ISI)*



Abstracting and Indexing



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ISSN: 2149-2018

Applied Medical Research, 2024
VOL 11, NO. 1, PAGE 1 – 4
DOI: doi.org/10.47363/AMR/2024(11)234



 Open Access

RESEARCH ARTICLE

Effectiveness of the Feldenkrais Method on Self-Perception of Anxiety, Fatigue and Depression in Fibromyalgic Patients

Giorgio Mandala^{1*}, Valentina La Mantia¹, Cataldo Pietro³, Marco Mirabella³, Umberto Pandolfo T², Marianna Bellafiore³, Daniela Smirni³ and Caterina Forte T²

¹UOC of Physical and Rehabilitation Medicine Buccheri La Ferla Fatebenefratelli Hospital Palermo, Italy

²Studio Forte Feldenkrais, Milano/Palermo, Italy

³Department of Psychology, educational science and human movement, University of Palermo, Italy

ABSTRACT

The diagnosis and clinical characteristics of fibromyalgia are controversial and the therapeutic possibilities are increasingly of growing interest. Little is known about the effects of Feldenkrais method on symptoms of these patients. Therefore, we conducted a randomized pilot study on a small group of fibromyalgia patients, using the Feldenkrais method as a specific physical exercise, to evaluate the changes in fatigue, anxiety and depression self-perceived. Self-completion questionnaires were administered at the beginning and at the end of a 24-week trial period. The results are favorable for a reduction in fatigue and depression in patients with fibromyalgia.

Introduction

ARTICLE HISTORY

Received December 28, 2023

Accepted January 11, 2024

Published January 31, 2024

KEYWORDS

Fibromyalgia Syndrome,
Body Awareness Therapy,
Feldenkrais Method,
Posture, Neuromuscular
Re-Education

Pubblicare su un predatory journal

- Fa perdere tempo
- Determina un eventuale danno economico
- Rende impossibile o comunque molto difficile ripubblicare i dati del lavoro su una rivista “seria”
- Aiuta un dark system che contribuisce alla disseminazione di fake-news credibili

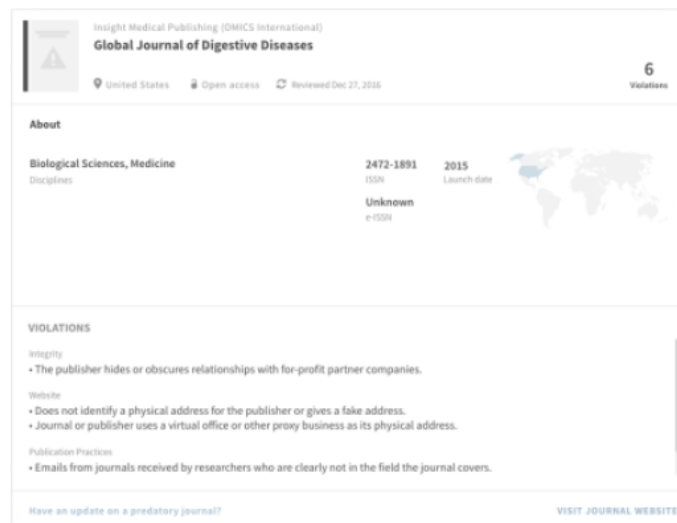


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- Open Access:** Yes
- Reviewed:** Dec 27, 2016
- About:**
 - Disciplines:** Biological Sciences, Medicine
 - ISSN:** 2472-1891
 - Launch date:** 2015
 - e-ISSN:** Unknown
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I publishers Open Access non
considerati predatory ma sicuramente
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Gli indici di valutazione scientifica bibliometrici

Autori

Carlo Palmieri,



H-index

Indice molto più “giovane” dell’Impact Factor, creato nel 2005

a scientist has an index h if h of their papers have at least h citations each, and their other papers have no more than h citations each



Hirsch, Jorge (2005) PNAS 46: 16569
[arXiv:physics/0508025](https://arxiv.org/abs/physics/0508025)

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H-index

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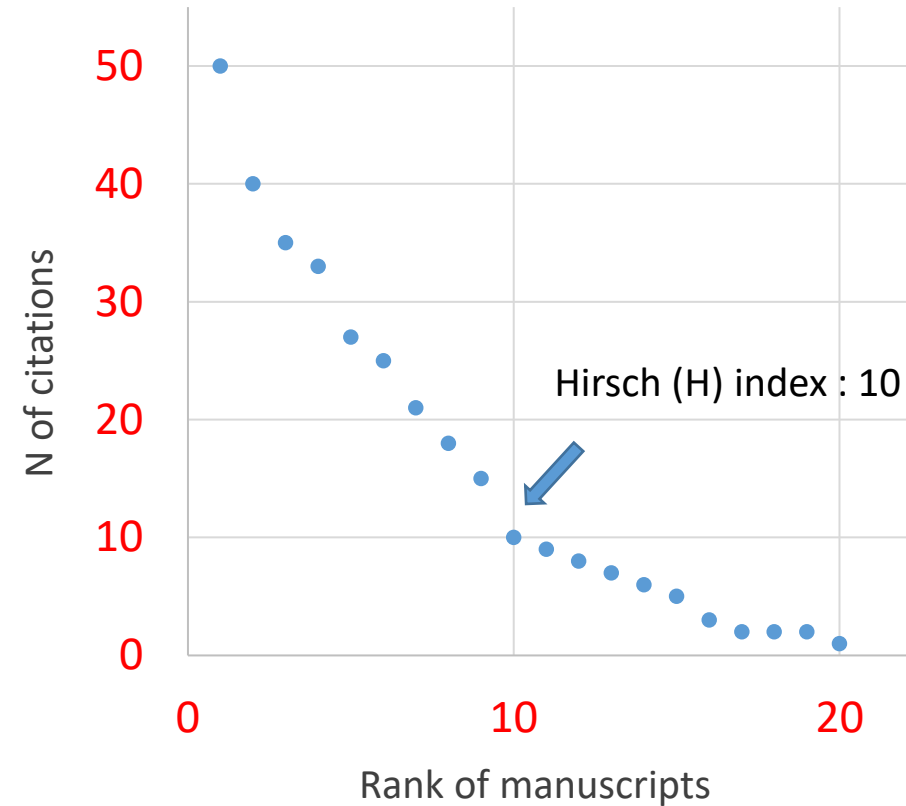
Article	Citations
A	18
B	25
C	9
D	35
E	2
F	6
G	3
H	50
I	15
L	40
M	7
N	2
O	1
P	33
Q	8
R	27
S	21
T	10
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V	2



Si mettono gli articoli in ordine decrescente

Article	Rank	Citations
H	1	50
L	2	40
D	3	35
P	4	33
R	5	27
B	6	25
S	7	21
A	8	18
I	9	15
T	10	10
C	11	9
Q	12	8
M	13	7
F	14	6
U	15	5
G	16	3
E	17	2
N	18	2
V	19	2
O	20	1

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H-index

- ✓ Diversi databases, tra cui Web of Science, Scopus, Google Scholar e altri, calcolano automaticamente l'H-index
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H-index di Google Scholar può essere manipolato

Google Scholar is manipulatable

Hazem Ibrahim,^{1,2,‡} Fengyuan Liu,^{1,3,‡} Yasir Zaki^{1,*} Talal Rahwan^{1,*}

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²Tandon School of Engineering, New York University, New York, USA

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[‡] Joint first authors

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Citations are widely considered in scientists' evaluation. As such, scientists may be incentivized to inflate their citation counts. While previous literature has examined self-citations and citation cartels, it remains unclear whether scientists can purchase citations. Here, we compile a dataset of ~1.6 million profiles on Google Scholar to examine instances of citation fraud on the platform. We survey faculty at highly-ranked universities, and confirm that Google Scholar is widely used when evaluating scientists. Intrigued by a citation-boosting service that we unravelled during our investigation, we contacted the service while undercover as a fictional author, and managed to purchase 50 citations. These findings provide conclusive evidence that citations can be bought in bulk, and highlight the need to look beyond citation counts.

- Citation metrics in Google Scholar **can be and are being manipulated**
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 - Even ***post hoc* screening fails to eliminate the problem**, as Google Scholar indexes and then caches citations that may appear for only a short while before being taken down
 - Google Scholar misses **obvious instances of citation manipulation**
- Google Scholar is **more widely used** for faculty evaluation than previously documented

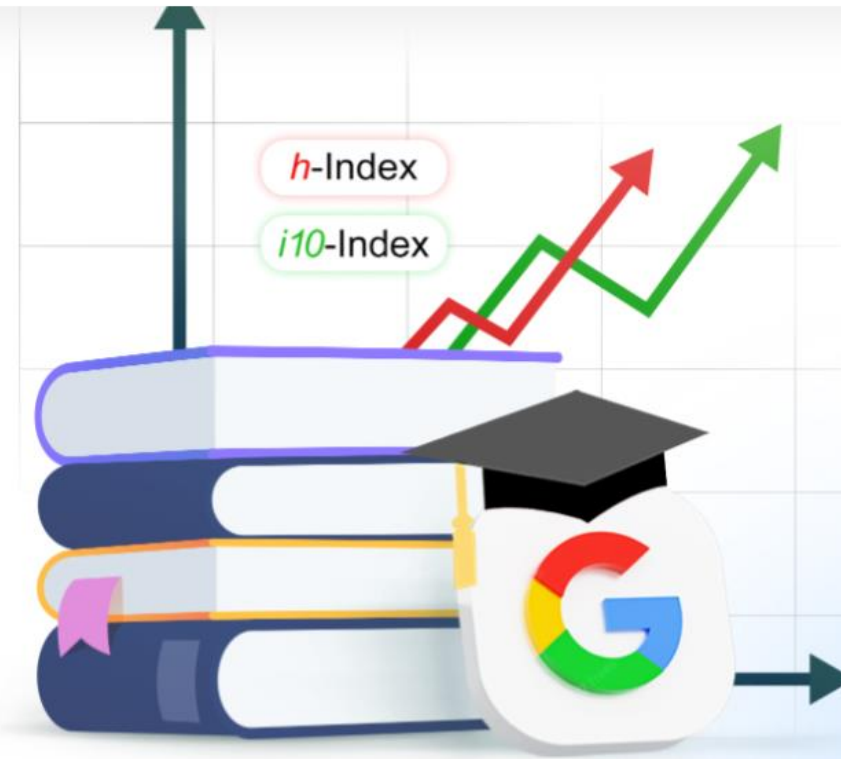
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Author Beamplots

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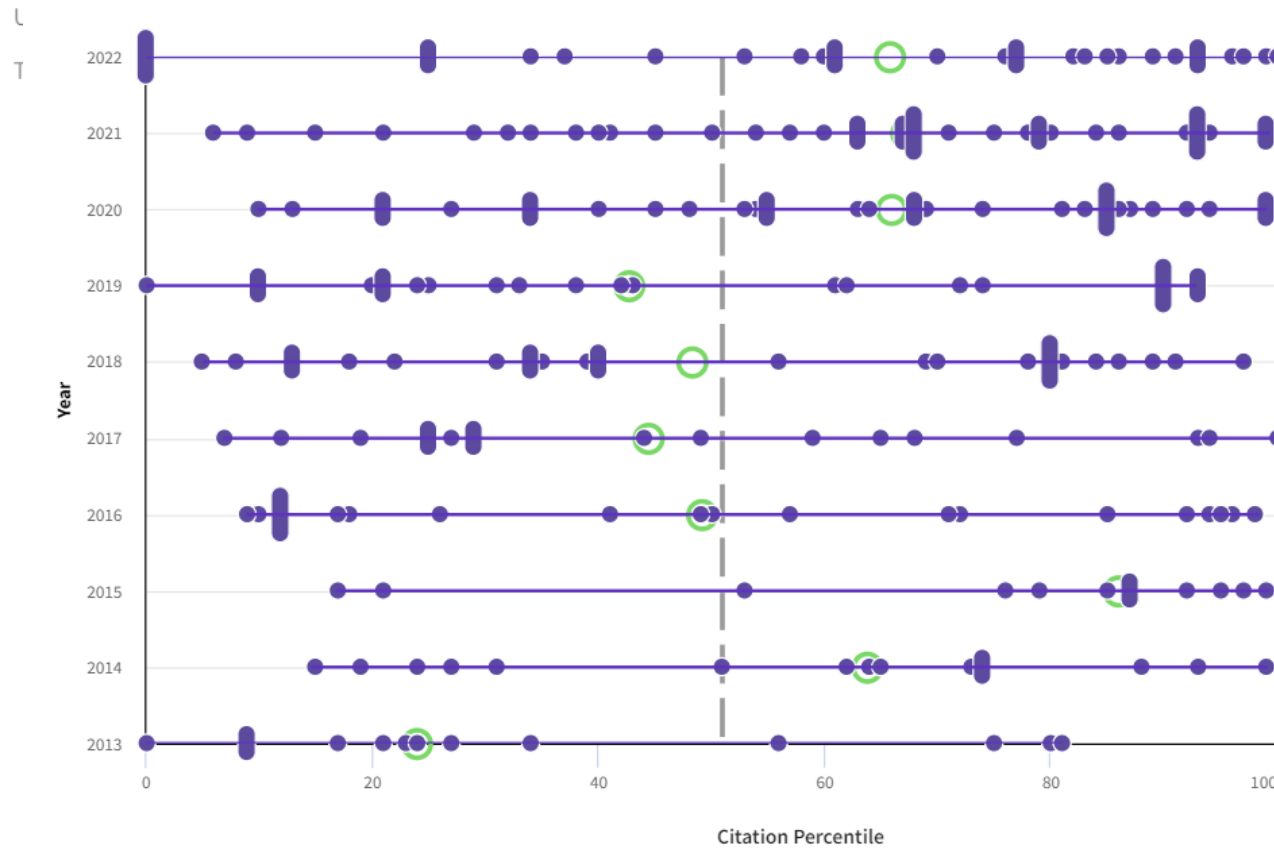
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Di Maio, Massimo *This is an algorithmically generated author record* ⓘ

(Mai, Massimo Di)

Open Filters >



● Citation percentile ○ Annual citation percentile — Overall citation percentile median

Profile summary

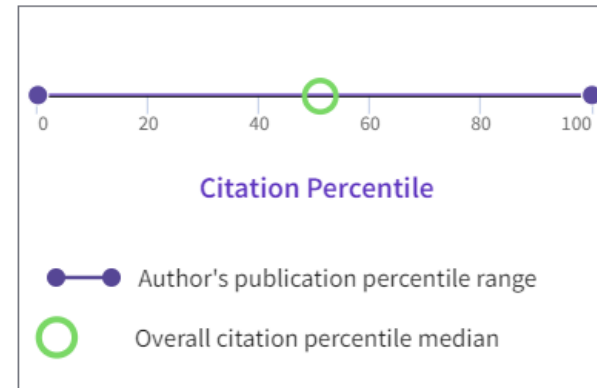
- 604 Total documents
- 603 Web of Science Core Collection publications
- 1 Preprint

Web of Science Core Collection metrics

56 H-Index	603 Total Publications
11,425 Sum of Times Cited	10,374 Citing Articles

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Percentile range displays for authors from 1980 to 2022. View all publications in full beamplot.

Gli indici di valutazione scientifica bibliometrici

Articoli Scientifici

Activity and safety of enobosarm, a novel, oral, selective androgen receptor modulator, in androgen receptor-positive, oestrogen receptor-positive, and HER2-negative advanced breast cancer (Study G200802): a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial

Carlo Palmieri, Hannah Linden, Stephen N Birrell, Sally Wheelwright, Elgme Lim, Lee S Schwartzberg, Amy R Dwyer, Theresa E Hickey, Hope S Rugo, Patrick Cobb, Joyce A O'Shaughnessy, Stephen Johnston, Adam Brofsky, Wayne D Tilley*, Beth Overmeyer*

Summary

Background The androgen receptor is a tumour suppressor in oestrogen receptor-positive breast cancer. The activity and safety of enobosarm, an oral selective androgen receptor modulator, was evaluated in women with oestrogen receptor (ER)-positive, HER2-negative, and androgen receptor (AR)-positive disease.

Methods Women who were postmenopausal (aged ≥ 18 years) with previously treated ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an Eastern Cooperative Oncology Group performance status of 0–2 were enrolled in a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial done at 35 cancer treatment centres in nine countries. Participants were stratified on the setting of immediately preceding endocrine therapy and the presence of bone-only metastasis and randomly assigned (1:1) to 9 mg or 18 mg oral enobosarm daily using an interactive web response system. The primary endpoint was clinical benefit rate at 24 weeks in those with centrally confirmed AR-positive disease (ie, the evaluable population). This trial is registered with ClinicalTrials.gov (NCT02463032).

Findings Between Sept 10, 2015, and Nov 28, 2017, 136 (79%) of 172 patients deemed eligible were randomly assigned to 9 mg ($n=72$) or 18 mg ($n=64$) oral enobosarm daily. Of these 136 patients, 102 (75%) patients formed the evaluable population (9 mg, $n=50$; 18 mg, $n=52$). The median age was 60.5 years (IQR 52.3–69.3) in the 9 mg group and 62.5 years (54.0–69.3) in the 18 mg group. The median follow-up was 7.5 months (IQR 2.9–14.1). At 24 weeks, 16 (32%, 95% CI 20–47) of 50 in the 9 mg group and 15 (29%, 17–43) of 52 in the 18 mg group had clinical benefit. Six (8% of 75 patients who received 9 mg and ten (16%) of 61 patients who received 18 mg had grade 3 or grade 4 drug-related adverse events, most frequently increased hepatic transaminases (three [4%] of 75 in the 9 mg group and two [3%] of 61 in the 18 mg group), hypercalcaemia (two [3%] and two [3%]), and fatigue (one [1%] and two [3%]). Four deaths (one in the 9 mg group and three in the 18 mg group) were deemed unrelated to the study drug.

Interpretation Enobosarm has anti-tumour activity in patients with ER-positive, HER2-negative advanced breast cancer, showing that AR activation can result in clinical benefit, supporting further clinical investigation of selective AR activation strategies for the treatment of AR-positive, ER-positive, HER2-negative advanced breast cancer.

Funding GTS.

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Articles



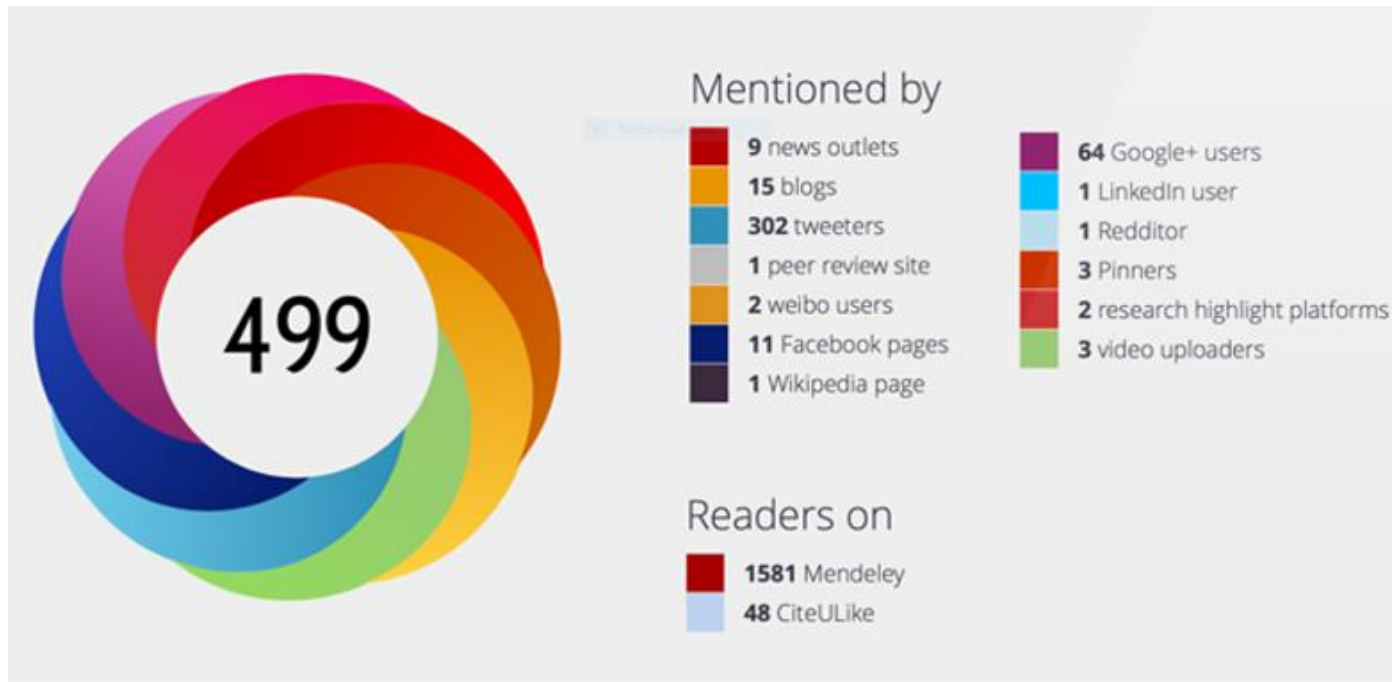
oa

Lancet Oncol 2024; 25: 117–25
Published Online
February 9, 2024
[https://doi.org/10.1016/S1473-2045\(24\)00004-4](https://doi.org/10.1016/S1473-2045(24)00004-4)
See Comment page 269
*Correspondence

The Clatterbridge Cancer Centre NHS Foundation Trust, Liverpool, UK
(Prof C Palmieri, MBBS PhD); Department of Molecular and Clinical Cancer Medicine, Institute of Systems, Molecular, and Integrative Biology, The University of Liverpool, Liverpool, UK (Prof C Palmieri); Division of Hematology and Oncology, Fred Hutchinson Cancer Center/University of Washington, Seattle, WA, USA (Prof H Linden MD); Welland Health/Burnside War Memorial Hospital, Toorak Gardens, SA, Australia (S N Birrell MBBS PhD); Dame Roma Mitchell Cancer Research Laboratories, Adelaide Medical School, University of Adelaide, Adelaide, SA, Australia (S N Birrell, A E Dwyer PhD, T E Hickey PhD, Prof W D Tilley PhD); Sussex Health Outcomes Research & Education in Cancer (SHORE-CL), University of Sussex, Falmer, Brighton, UK

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I colori che formano i “donuts” riflettono il mix delle fonti che determinano lo score, azzurro per Twitter (ora X), giallo per i blog etc etc

Altmetric rappresenta forse l’elemento più *disruptive* nella misurazione dell’impatto degli articoli scientifici su una audience fatta di addetti ai lavori ma non solo, grazie anche all’adozione sempre più larga dell’open access.

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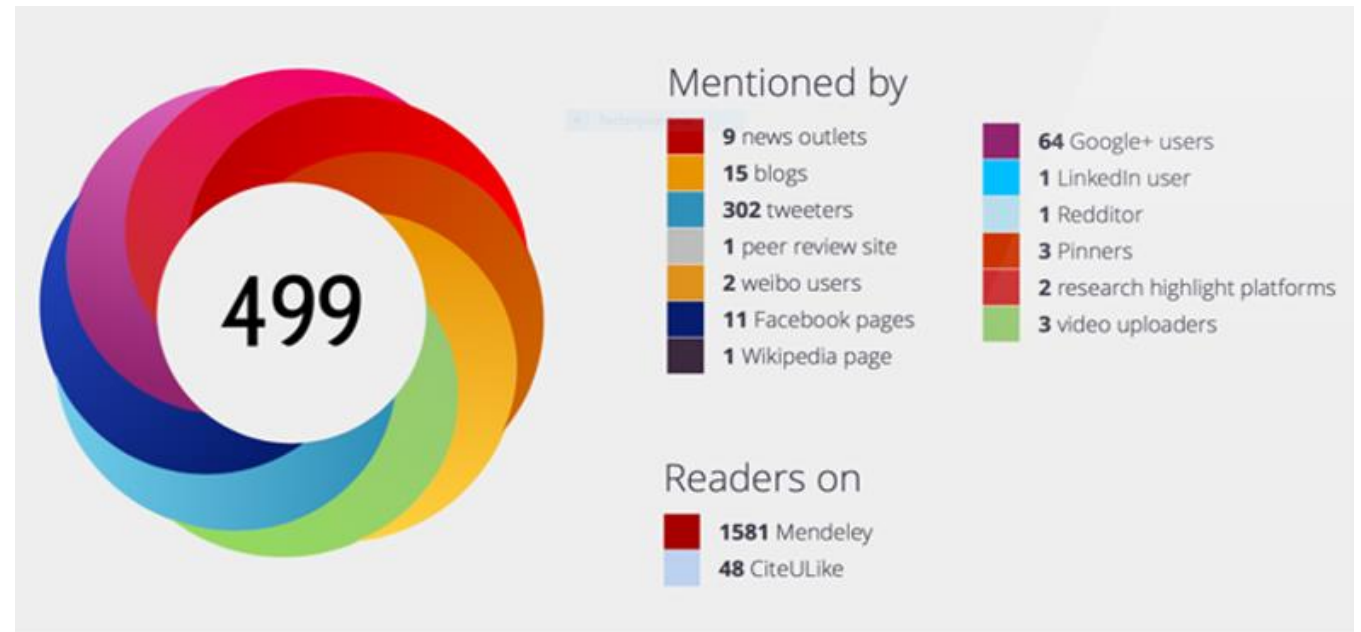
Altmetric: l'Attention Score

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ARTICLES | VOLUME 25, ISSUE 3, P317-325, MARCH 2024

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Activity and safety of enobosarm, a novel, oral, selective androgen receptor modulator, in androgen receptor-positive, oestrogen receptor-positive, and HER2-negative advanced breast cancer (Study G200802): a randomised, open-label, multicentre, multinational, parallel design, phase 2 trial

Prof Carlo Palmieri, MBBS PhD • Prof Hannah Linden, MD • Stephen N Birrell, MBBS PhD • Sally Wheelwright, PhD • Prof Elgene Lim, MBBS PhD • Prof Lee S Schwartzberg, MD • et al. [Show all authors](#) •

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Open Access • Published: February 08, 2024 • DOI: [https://doi.org/10.1016/S1470-2045\(24\)00004-4](https://doi.org/10.1016/S1470-2045(24)00004-4) •

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Impact Factor

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Numero di citazioni

Autori



H-index

Indici bibliometrici classici e innovativi

Riviste



Impact Factor

Journal Citation Indicator

Articoli Scientifici



Numero di citazioni

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Autori

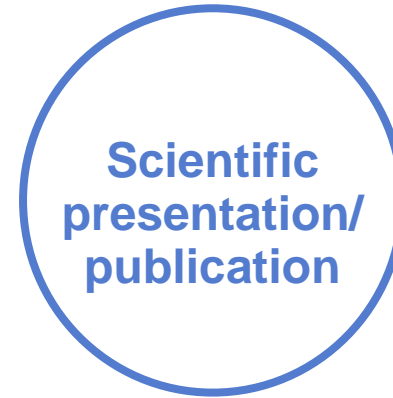


H-index

Author Beamplots

Take Home Messages

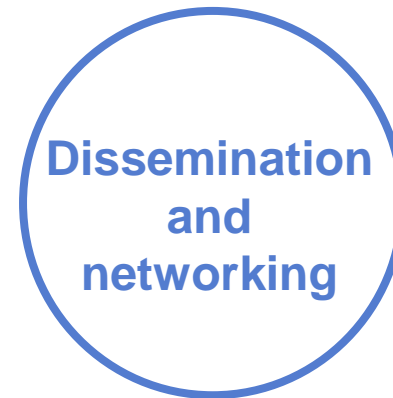
Fare buona
ricerca è
molto
importante



Saper scrivere
e pubblicare
bene è
altrettanto
importante

HCPs

Contribuire a
una cura
ottimale dei
pazienti è la
soddisfazione
più importante



Saper districarsi
nella giungla di
informazioni e
disseminare
bene è sempre
più importante



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Valutazione del rischio di bias
negli studi selezionati
Ivan MOSCHETTI

VALIDITA' INTERNA

La misura in cui uno studio riesce a cogliere la relazione «vera» fra due variabili

ERRORE CASUALE

ERRORE SISTEMATICO (BIAS)

ERRORE CASUALE

Errore che si verifica per effetto del caso

Replicazioni multiple della stessa misurazione producono differenti risultati in tutte le direzioni per variazioni casuali ma la media dà il risultato corretto

ERRORE SISTEMATICO

Errore che si verifica per la presenza di un fattore che distorce sistematicamente le osservazioni nella stessa direzione

Es: mancanza di cecità e dati self report; pazienti diversi per fattori prognostici nei due gruppi a confronto

Replicazioni multiple della stessa misurazione producono risultati sempre nella stessa direzione e “sbagliati”

Bias

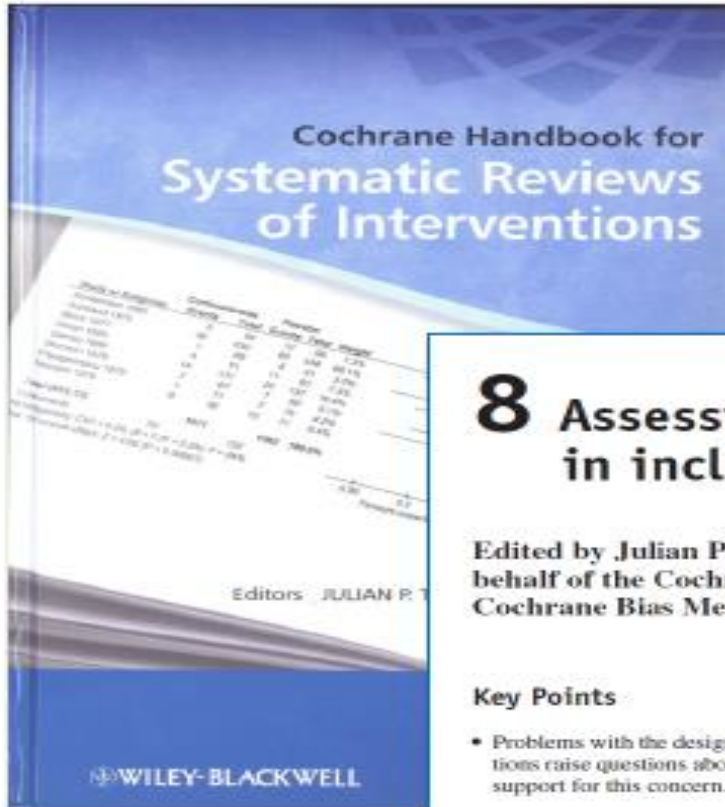
Systematic distortion of the estimated intervention effect away from the truth, caused by **inadequacies** in the **design, conduct,** or **analysis** of a trial , or in the **publication of its results**. In other words, in a biased trial, the results observed reflect other factors in addition to (or, in extreme cases, instead of) the effect of the tested therapeutic procedure alone.

Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med* 2001;134:663–94

Errore sistematico e validità interna di uno studio

- I risultati di uno studio sono tanto più validi (probabilmente veri) quanto meno esso è affetto da errori sistematici
- Gli errori sistematici vanno previsti ed evitati o ridotti in fase di disegno dello studio

Dove approfondire



8 Assessing risk of bias in included studies

Edited by Julian PT Higgins and Douglas G Altman on behalf of the Cochrane Statistical Methods Group and the Cochrane Bias Methods Group

Key Points

- Problems with the design and execution of individual studies of healthcare interventions raise questions about the validity of their findings; empirical evidence provides support for this concern.
- An assessment of the validity of studies included in a Cochrane review should emphasize the risk of bias in their results, i.e. the risk that they will overestimate or underestimate the true intervention effect.
- Numerous tools are available for assessing methodological quality of clinical trials. We recommend against the use of scales yielding a summary score.
- The Cochrane Collaboration recommends a specific tool for assessing risk of bias in each included study. This comprises a description and a judgement for each item in a 'Risk of bias' table, where each entry addresses a specific feature of the study. The judgement for each entry involves answering a question, with answers 'Yes' indicating low risk of bias, 'No' indicating high risk of bias, and 'Unclear' indicating either lack of information or uncertainty over the potential for bias.

RESEARCH METHODS & REPORTING

The Cochrane Collaboration's tool for assessing risk of bias in randomised trials

Julian P T Higgins,¹ Douglas G Altman,² Peter C Gøtzsche,³ Peter Jüni,⁴ David Moher,^{5,6} Andrew D Oxman,⁷ Jelena Savović,⁸ Kenneth F Schulz,⁹ Laura Weeks,⁹ Jonathan A C Sterne,⁸ Cochrane Bias Methods Group, Cochrane Statistical Methods Group

Flaws in the design, conduct, analysis, and reporting of randomised trials can lead to biased estimates of treatment effects. Until recently, Cochrane

Methodological Expectations of Cochrane Intervention Reviews (MECIR)

Standards for the conduct and reporting of new Cochrane Intervention Reviews, reporting of protocols and the planning, conduct and reporting of updates

Julian PT Higgins, Toby Lasserson, Jackie Chandler, David Tovey and Rachel Churchill

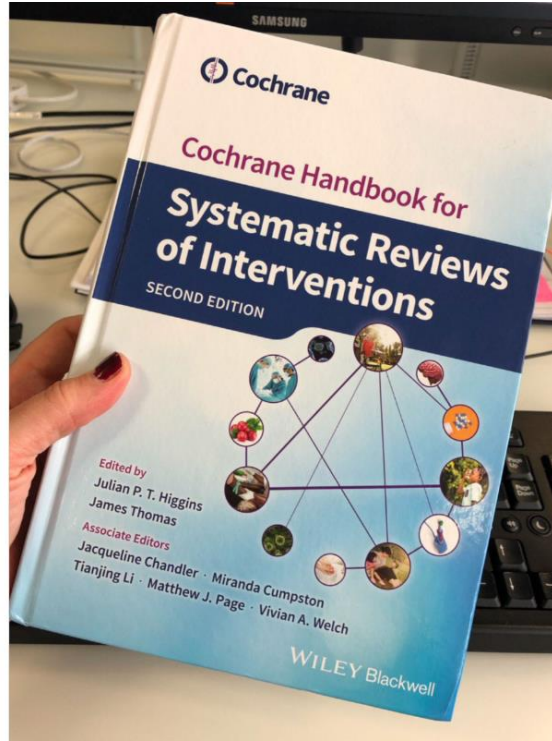
Collaboration's methods groups strategy for assessing the quality of randomised trials, and the process by which it was developed and evaluated.

Risk assessment tool

Methodologists, statisticians, epidemiologists, and review authors met for a three day meeting to develop the new tool. JPTH and DGA compiled an extensive list of sources of bias in clinical trials. These were divided into seven areas: generation of the trial; concealment of the allocation sequence; concealment and exclusions; other generic biases specific to the trial design (such as selection bias in randomised trials); and biases that are specific to a clinical specialty. For each of the seven areas, a meeting participant prepared a review of the literature, a discussion of specific issues and a proposed set of criteria for assessing the risk of bias as adequate, inadequate, or unclear.

Decisions were made by informal consensus of items that were truly potential biases of heterogeneity or imprecision. Potential biases were divided into domains, and strategies for assessing them were agreed, again by informal consensus. A new tool for assessing potential biases was developed, and participants also discussed how to summarise across domains, how to illustrate assessments in analyses, and how to incorporate assessments into analyses. Minutes of the meeting were transcribed and discussed in conjunction with written notes. Several pairs of authors developed detailed descriptions of each item in the tool and guidance for assessing the risk of bias. Documents were shared and discussed with the whole working group (including those who did not attend the meeting). Several email discussions, which also incorporated feedback from review authors, led to proposed guidance at various meetings of the Cochrane Collaboration and from

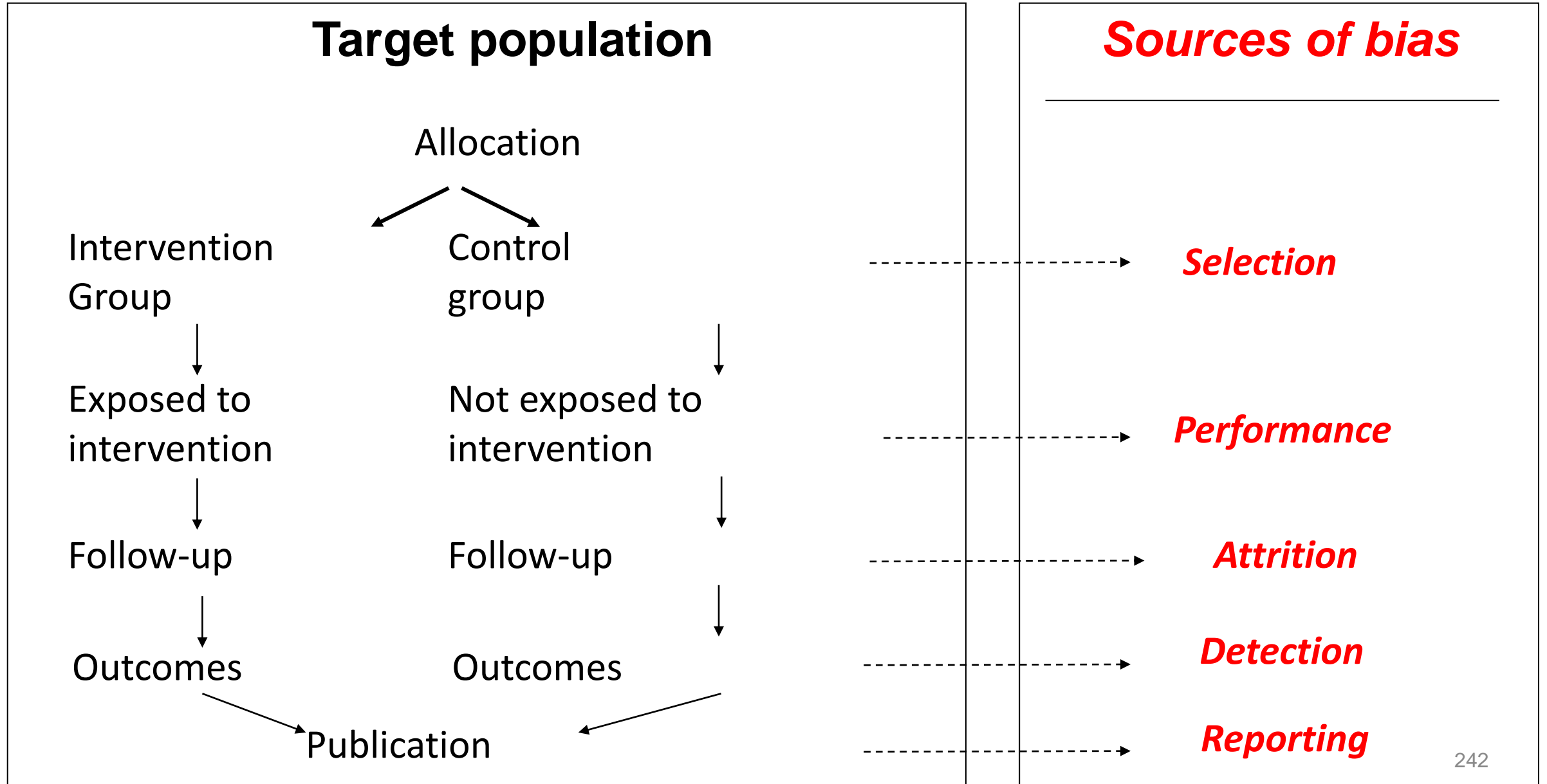
New Cochrane Handbook for Systematic Reviews of Interventions



Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y / PY / PN / N / NI	[Description]
	1.2 Was the allocation sequence concealed until participants were recruited and assigned to interventions?	Y / PY / PN / N / NI	[Description]
	1.3 Were there baseline imbalances that suggest a problem with the randomization process?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias arising from the randomization process?		[Rationale]
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.2. Were carers and trial personnel aware of participants' assigned intervention during the trial?	Y / PY / PN / N / NI	[Description]
	2.3. <u>If Y/PY/NI to 2.1 or 2.2:</u> Were there deviations from the intended intervention beyond what would be expected in usual practice?	NA / Y / PY / PN / N / NI	[Description]
	2.4. <u>If Y/PY to 2.3:</u> Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome?	NA / Y / PY / PN / N / NI	[Description]
	2.5 Were any participants analysed in a group different from the one to which they were assigned?	Y / PY / PN / N / NI	[Description]
	2.6 <u>If Y/PY/NI to 2.5:</u> Was there potential for a substantial impact (on the estimated effect of intervention) of analysing participants in the wrong group?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to deviations from intended interventions?		[Rationale]
Bias due to missing outcome data	3.1 Were outcome data available for all, or nearly all, participants randomized?	Y / PY / PN / N / NI	[Description]
	3.2 <u>If N/PN/NI to 3.1:</u> Are the proportions of missing outcome data and reasons for missing outcome data similar across intervention groups?	NA / Y / PY / PN / N / NI	[Description]
	3.3 <u>If N/PN/NI to 3.1:</u> Is there evidence that results were robust to the presence of missing outcome data?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to missing outcome data?		[Rationale]
Bias in measurement of the outcome	4.1 Were outcome assessors aware of the intervention received by study participants?	Y / PY / PN / N / NI	[Description]
	4.2 <u>If Y/PY/NI to 4.1:</u> Was the assessment of the outcome likely to be influenced by knowledge of intervention received?	NA / Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to measurement of the outcome?		[Rationale]
Bias in selection of the reported result	Are the reported outcome data likely to have been selected, on the basis of the results, from...		
	5.1 ... multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Y / PY / PN / N / NI	[Description]
	5.2 ... multiple analyses of the data?	Y / PY / PN / N / NI	[Description]
	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the predicted direction of bias due to selection of the reported result?		[Rationale]
Overall bias	Risk of bias judgement	Low / High / Some concerns	[Support]
	Optional: What is the overall predicted direction of bias for this outcome?		[Rationale]

Our vision is that healthcare decision-making throughout the world will be informed by high quality, timely research evidence

Trial as a flow



randomizzazione

- attribuzione casuale di ogni paziente al gruppo in trattamento sperimentale oppure al gruppo di controllo
- Se è affettutata correttamente, ogni soggetto ha la stessa probabilità di essere assegnato al gruppo sperimentale o al gruppo di controllo
- assicura che tutti i fattori prognostici - **sia noti che sconosciuti** - si distribuiscano omogeneamente nel gruppo sperimentale e in quello di controllo.

Se la randomizzazione non è eseguita in maniera corretta è possibile introdurre un bias di selezione anche negli studi randomizzati

Selection bias: due componenti

RANDOMIZZAZIONE

```
graph TD; A[RANDOMIZZAZIONE] --> B[Generazione della lista di randomizzazione]; A --> C[Nascondimento della sequenza di randomizzazione (allocation concealment)];
```

Generazione della lista di randomizzazione
metodi per generare la lista di randomizzazione

Nascondimento della sequenza di randomizzazione
(allocation concealment)
metodi per implementare e nascondere la lista di randomizzazione fino all'assegnazione del paziente

Generazione lista di randomizzazione

- **Basso rischio di bias.** Uso di metodi realmente casuali come ad esempio: tavole di numeri random, sistemi computerizzati, lancio di una moneta o di un dado, sorteggio.
- **Alto rischio di bias.** Uso di metodi **NON** realmente casuali come ad esempio: giorno di nascita o di ammissione in ospedale, giudizio del medico, preferenze del paziente, risultati di test di laboratorio, disponibilità del trattamento, alternanza
- **Rischio incerto.** Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Nascondimento della sequenza di randomizzazione*

- **Basso rischio di bias.** Sperimentatori che arruolano i pazienti non possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: randomizzazione centralizzata (telefonica, via web, o gestita da personale esterno alla sperimentazione - farmacista, statistico); buste chiuse e opache.
- **Alto rischio di bias.** Sperimentatori che arruolano i pazienti possono prevedere in quale gruppo verrà inserito il paziente perché si usa uno dei seguenti metodi: liste di randomizzazione, buste aperte o non opache, alternanza, data di nascita, numero di cartella, ect.
- **Rischio incerto.** Non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Blinding

- Sperimentatori e partecipanti non conoscono gruppo di allocazione (*performance bias*)
- Valutatori degli esiti non conoscono gruppo di allocazione (*detection bias*)

Singolo cieco

i pazienti inclusi nello studio non conoscono il gruppo al quale sono stati assegnati

Doppio cieco

i pazienti e gli sperimentatori non conoscono il gruppo al quale (i pazienti) sono stati assegnati

Triplo cieco

i pazienti, gli sperimentatori e i valutatori degli esiti non conoscono il gruppo di allocazione

...

Non sempre il significato è questo ... è sempre bene valutare chi è davvero in cieco!

Performance bias

Si verifica quando i partecipanti allo studio (sperimentatori o pazienti) modificano i loro comportamenti perché sanno a quale gruppo è assegnato un dato paziente

Esempi:

Lo sperimentatore controlla la presenza di effetti avversi più frequentemente nei pazienti assegnati al gruppo di trattamento.

Un paziente nel gruppo placebo assume altri farmaci, fa più (o meno) visite di controllo.

Detection bias

Si verifica quando la valutazione degli esiti dello studio viene influenzata dalla conoscenza del gruppo al quale è assegnato un dato paziente

Esempi:

Interpretazione di esiti radiologici, risoluzione dei sintomi, valutazione delle ricadute di malattia diversa nei pazienti assegnati al trattamento e al controllo

Performance&Detection bias

- Derivano da comportamenti consci o non consci
- Sovrastimano/sottostimano l'effetto dell'intervento
- La distorsione potenziale è tanto maggiore quanto più soggettivo è l'esito misurato
- Si limitano se pazienti, sperimentatori, valutatori degli esiti dello studio non sono a conoscenza del trattamento che il paziente sta effettivamente ricevendo

Performance bias

Cecità di pazienti e sperimentatori

- **Basso rischio di bias.** Pazienti e sperimentatori non conoscono l'assegnazione dei pazienti al gruppo di controllo o di trattamento oppure è poco probabile che la mancanza di cecità influenzi la performance di pazienti e sperimentatori
- **Alto rischio di bias.** Pazienti e sperimentatori conoscono l'assegnazione dei pazienti o, durante lo studio, diventa chiaro a quale gruppo di trattamento sono allocati (rottura del cieco). Studi definiti come “open label”
- **Rischio incerto.** Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Conduzione dello studio in cieco

Trattamento sperimentale = controllo (ad esempio, capsule identiche nell'aspetto, forma, colore, sapore).

Non sempre si può fare (ad esempio confronto tra farmaci con profili di tossicità specifici, interventi fisioterapici, educativi, chirurgici, ecc).

Non basta pianificarlo. E' importante garantire che, durante lo studio, sperimentatori e pazienti non "scoprono" il gruppo di allocazione (ad esempio perché un trattamento ha effetti collaterali particolari).

Detection bias

Cecità del valutatore degli esiti dello studio (outcome)

- **Basso rischio di bias.** L'esito dello studio è valutato senza conoscere l'assegnazione dei pazienti al gruppo di controllo o di intervento; oppure è poco probabile che la mancanza di cecità influenzi la valutazione
- **Alto rischio di bias.** L'esito dello studio è valutato conoscendo l'assegnazione dei pazienti al gruppo di controllo o di intervento ed è probabile che la mancanza di cecità influenzi la valutazione
- **Rischio incerto.** Quando non sono disponibili sufficienti informazioni per definire il rischio (bassa qualità del reporting)

Valutazione esiti in cieco

- Gli esiti di uno studio possono essere valutati dai pazienti stessi (diari, questionari), dagli sperimentatori, oppure da valutatori indipendenti
- Visite di follow up effettuate da uno sperimentatore diverso
- Non sempre si può fare (ad esempio esiti riferiti dal paziente in uno studio in aperto)
- Tanto più l'esito è soggettivo (dolore, qualità della vita, ecc.) tanto più il rischio di detection bias è alto se la valutazione non avviene in cieco.
- Anche esiti apparentemente oggettivi, non sempre lo sono (imaging, morte/causa)

Performance and detection bias

- Impatto diverso su outcome **soggettivi** e **oggettivi** (quindi la valutazione va fatta separatamente)
- Se studio su **farmaco in doppio cieco** e dice che tutti gli operatori erano all'oscuro dell'assegnazione è probabile che sia in cieco anche l'outcome assessor, anche se non espressamente detto
- Se studio su **interventi che non possono essere in doppio cieco** (psicosociali, educativi, chirurgici, riabilitativi) importante che sia in cieco l'outcome assessor e deve essere specificato
 - Performance: high risk per outcomes soggettivi sempre
 - Detection: low risk se c'è blinding of outcome assessor anche per outcomes soggettivi

Allocation concealment

≠

Blinding

- It prevents **selection bias** in intervention assignment by protecting the allocation sequence **before and until** assignment
- It can always be successfully implemented regardless of the study topic

- It seeks to prevent **performance and detection bias** by protecting the sequence **after** assignment
- Not always feasible – for example, in trials comparing surgical with medical interventions

Attrition bias

- Quando non tutti i soggetti randomizzati completano lo studio
- i soggetti non escono a caso dallo studio: è possibile che quelli che escono siano sistematicamente diversi da quelli che non escono: i gruppi non sono più randomizzati
- **Validità esterna** : es: escono tutti i più giovani, o i meno gravi, o i maschi: posso trarre conclusioni solo su quelli che rimangono
- **Validità interna (Bias)**: se la probabilità di uscire dallo studio è legata all'intervento o all'outcome, cioè se quelli che escono hanno sistematicamente probabilità più alte o più basse di avere l'outcome di quelli che restano

Attrition bias

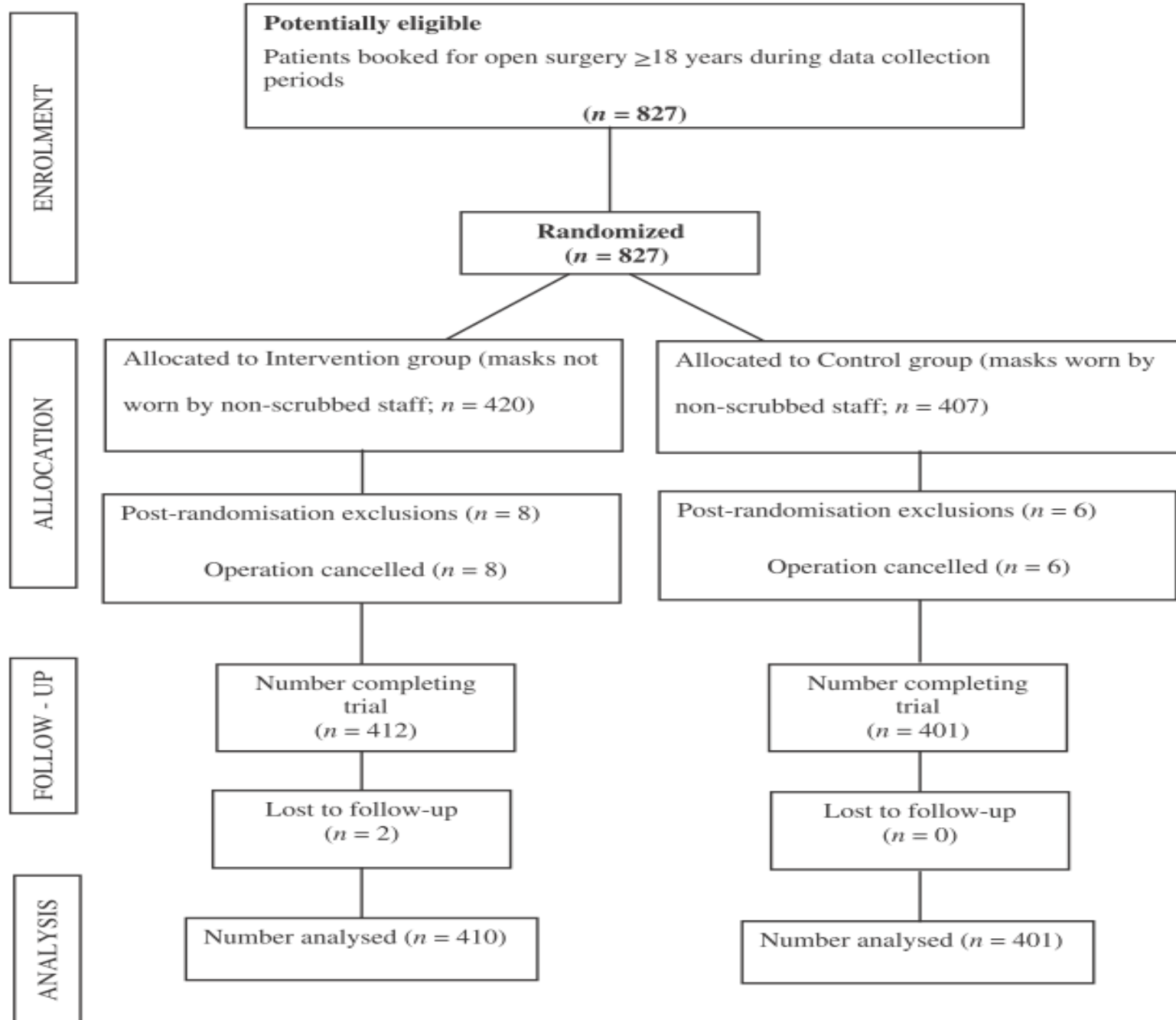
Low risk of bias

- No missing outcome data;
- the **proportion of missing outcomes** compared with observed event risk **not enough** to have a relevant impact on the intervention effect;
- Missing outcome data **balanced in numbers across intervention** groups, with similar reasons across groups;
- Missing data **imputed using appropriate methods**
- All patients analysed in the group they were allocated to by randomisation irrespective of non-compliance and co-interventions (**intention to treat**)

High risk of bias:

- the **proportion of missing outcomes** compared with observed event risk **enough** to induce relevant bias in intervention effect estimate
- Reason for missing outcome data likely to be related to true outcome, with either **imbalance in numbers or reasons** for missing data across intervention groups;

A total of 811 (98.1%) patients were enrolled and 811 (98.1%) patients completed the trial in the Intervention group and 410 No Mask group (Fig. 1).



What is publication bias (1)?

- Definition

“Publication bias refers to the greater likelihood that studies with positive results will be published”

What is publication bias (2)?

- An alternative definition:

Publication bias is the selective or *multiple* publication or *suppression* of trial results so that the scientific record is distorted

Extension: applied to trial parts - outcomes, subgroups, adverse events REPORTING BIAS

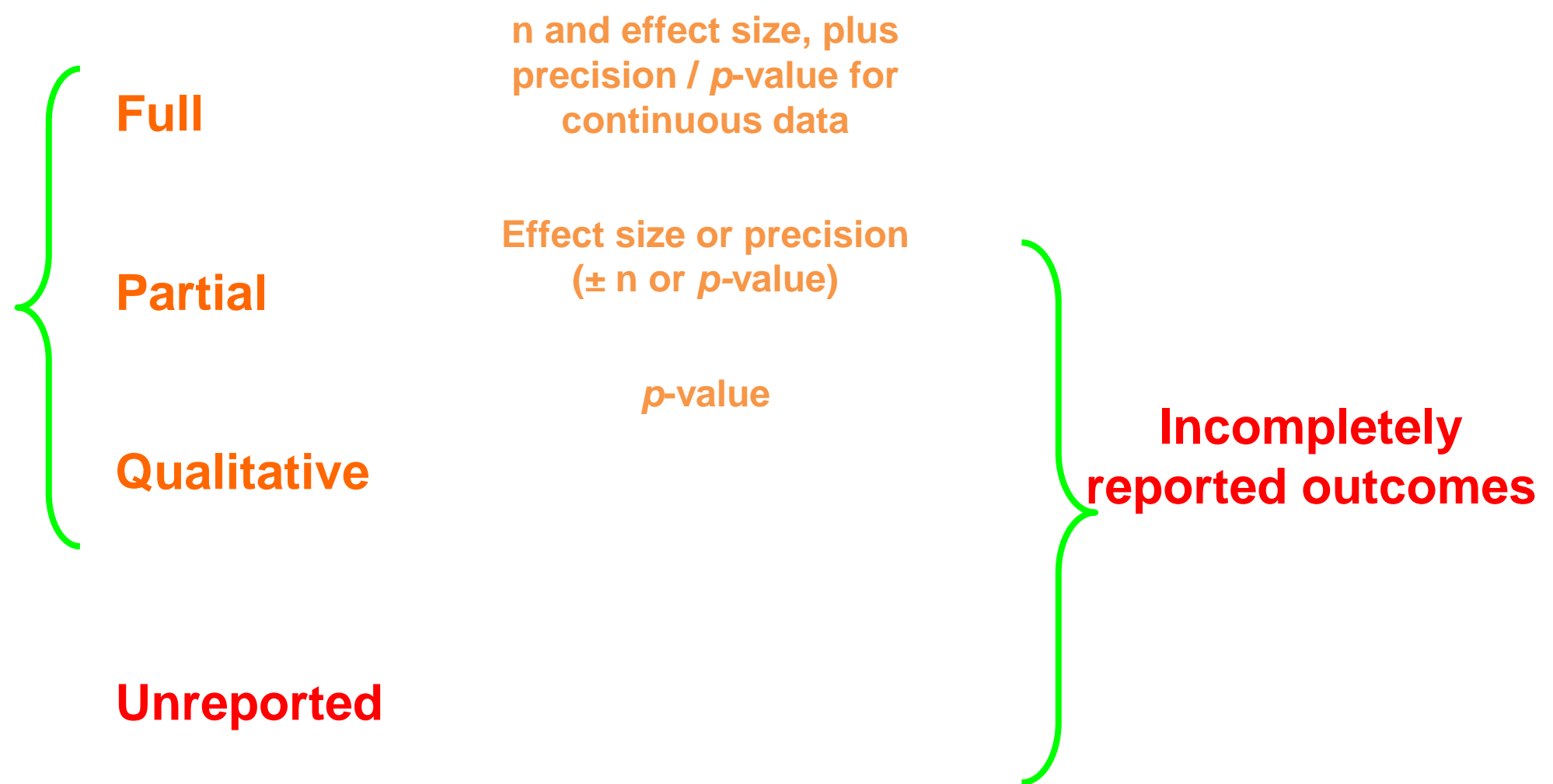
The likelihood of finding studies is related to the results of those studies (positive vs negative/detrimental)

Why does it matter?

- Distorts the scientific record
 - Hides the “truth”
 - Influences doctors’ decision making
 - Misleads policy makers
 - Causes harm to patients
 - Costly for the health service
 - A form of scientific and research misconduct
-
- TO U: It will matter if the studies you don’t find differ systematically from the ones you have found
 - You might arrive at different answers, or even
THE WRONG ANSWER

Reporting bias is selection bias

- Reporting bias is perhaps the greatest source of selection bias
- Originally defined as the publication or non-publication of studies depending on the direction and statistical significance of the results
- Is a complex phenomenon



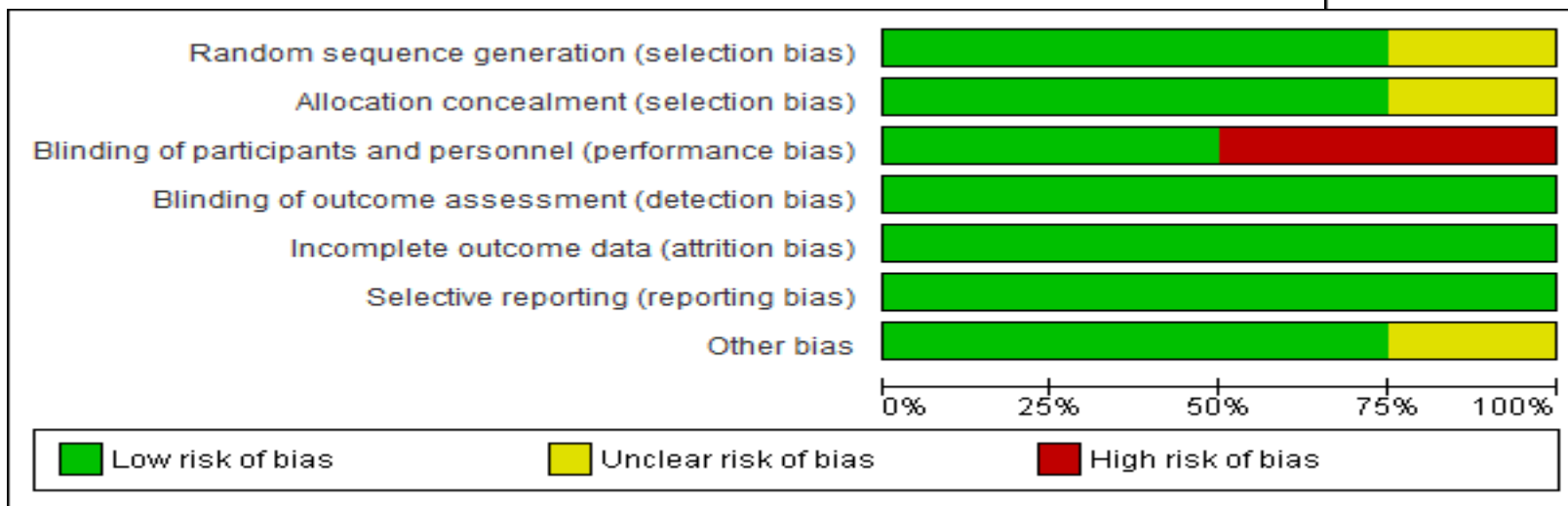
Risk of bias in one study



☐ Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk ▼	NR
Allocation concealment (selection bias)	Unclear risk ▼	NR
Blinding of participants and personnel (performance bias)	High risk ▼	open label
Blinding of outcome assessment (detection bias)	Low risk ▼	An independent blinded endpoint committee adjudicated all reported bleeding and efficacy events
Incomplete outcome data (attrition bias)	Low risk ▼	ITT. all patients followed up
Selective reporting (reporting bias)	Low risk ▼	
Other bias	Low risk ▼	

Risk of bias across studies/domains



	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
2011	+	+	+	+	+	+	+
LE-J	?	?	-	+	+	+	+
2011	+	+	-	+	+	+	?
MI 48	+	+	+	+	+	+	+
2012	?	?	+	+	+	+	+
2009	+	+	-	+	+	+	+
2011	+	+	+	+	+	+	+
YAMASHITA 2012	+	+	-	+	+	+	?



SCUOLA DI METODOLOGIA DELLA RICERCA CLINICA

2024 - 10^a EDIZIONE

MODULI SPECIALISTICI - S1



VENERDÌ 8 - SABATO 9 MARZO 2024
NEGRAR DI VALPOLICELLA (VR)
Centro Formazione IRCCS “Sacro Cuore - Don Calabria”

Summary of Findings Tables
(S.O.F. / Tabelle Sinottiche delle
Evidenze)

Ivan MOSCHETTI

Cos'è la Summary Of Findings

- **Summary of findings:** tabular presentation of key information about relevant outcomes of alternative health care interventions. It presents information about the body of evidence, key numerical results, and **summary judgment about the certainty of underlying evidence** for each outcome. SoF table has been chosen by the Cochrane Collaboration to present main findings of a **systematic review**.

Evidence profile: summary of evidence for a given question; it represents relevant information about the body of evidence, key numerical results, and with a **detailed quality assessment** and an explicit judgment of each factor that determines the quality. Used by guideline producers

PICO

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management¹

Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕○ moderate ²	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was 0.53 lower (0.96 to 0.1 lower)		144 (2)	⊕⊕○○ low ^{3,4}	Lower score indicates improvement
Number and severity of exacerbations ⁵	See comment	See comment	Not estimable ⁵	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	Low risk population ⁶		OR 0.64 (0.47 to 0.89)	966 (8)	⊕⊕⊕○ moderate ⁷	
	10 per 100	7 per 100 (5 to 9)				
	High risk population ⁶					
	50 per 100	35 per 100 (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was 0.1 higher (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕○ moderate ⁴	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 visits per	The mean Doctor and nurse visits in the intervention groups was 0.02 higher (1 lower to 1 higher)		629 (8)	⊕⊕⊕○ moderate ⁸	

Primary outcomes – up to 7

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- Choose primary outcomes early – avoid reporting bias
- Choose patient important outcomes
- Include primary outcomes – even if no information
- Describe the outcome – scale, follow-up

Results – Baseline risks (Assumed Risk)

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- From meta-analysis
- Needs to be representative of population
- Can present mean, range, low risk, moderate risk, high risk

Results – Risk with intervention (Corresponding Risk)

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- Calculated using the Relative Effect or Mean Differences
- Confidence intervals provided

Results – Relative effects

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- From meta-analysis
- Relative Risks, Odds ratios, Hazard ratios, etc.

Results – Number of Participants/studies

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Intervention: self management¹

Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	usual care	self management				
Quality of Life St George's Respiratory Questionnaire. Scale from: 0 to 100. (follow-up: 3 to 12 months)	The mean quality of life ranged across control groups from 38 to 60 points	The mean Quality of Life in the intervention groups was 2.58 lower (5.14 to 0.02 lower)		698 (7)	⊕⊕⊕⊖ moderate ²	Lower score indicates better quality of life. A change of less than 4 points is not shown to be important to patients.
Dyspnoea Borg Scale. Scale from: 0 to 10. (follow-up: 3 to 6 months)	The mean dyspnoea ranged across control groups from 1.2 to 4.1 points	The mean Dyspnoea in the intervention groups was 0.53 lower (0.96 to 0.1 lower)		144 (2)	⊕⊕⊖⊖ low ^{3,4}	Lower score indicates improvement
Number and severity of exacerbations ⁵	See comment	See comment	Not estimable ⁵	591 (3)	See comment	Effect is uncertain
Respiratory-related hospital admissions (follow-up: 3 to 12 months)	Low risk population ⁶		OR 0.64 (0.47 to 0.89)	966 (8)	⊕⊕⊕⊖ moderate ⁷	
	10 per 100	7 per 100 (5 to 9)				
	High risk population ⁶					
	50 per 100	35 per 100 (27 to 46)				
Emergency department visits for lung diseases (follow-up: 6 to 12 months)	The mean emergency department visits for lung diseases ranged across control groups from 0.2 to 0.7 visits per person per year	The mean Emergency department visits for lung diseases in the intervention groups was 0.1 higher (0.2 lower to 0.3 higher)		328 (4)	⊕⊕⊕⊖ moderate ⁴	
Doctor and nurse visits (follow-up: 6 to 12 months)	The mean doctor and nurse visits ranged across control groups from 1 to 5 visits per	The mean Doctor and nurse visits in the intervention groups was 0.02 higher (1 lower to 1 higher)		629 (8)	⊕⊕⊕⊖ moderate ⁸	

- From meta-analysis
- Or when no meta-analysis from individual studies

Results

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management¹

Comparison: usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
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- Describes the score on a scale (38 to 60 points)
- Describes change on the scale with intervention (2.58 points lower)

Results – Outcomes not reported / not measured / not pooled

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management¹

Comparison: usual care

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- Outcomes without data are still presented
- Outcomes not pooled are still presented and graded

Comments

Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

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- More description
- E.g. relevance of findings, notes when no data, no meta-analysis, or meta-analysis plus studies not in meta-analysis

SoF: Quando e Perché?

- Nelle revisioni Cochrane è obbligatorio (si parla di *Summary of Findings*)
- Per concludere una revisione sistematica per sintetizzare i risultati e la loro qualità (si parla di *Summary of Findings*)
- Come materiale di base per la elaborazione di Linee Guida per la pratica clinica (si parla di *Evidence Profile*)

2. Scegliere quali *outcomes* per la SoF

Di interesse per i pazienti e decisori

Utili per prendere decisioni cliniche

E' possibile riportarne al **massimo 7** (desiderabili e indesiderabili)

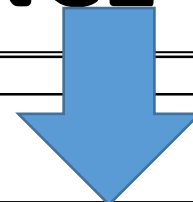
In genere solo gli **outcomes primari** della revisione

Dovrebbero essere definiti nel protocollo

Outcomes

Should be
importance driven
NOT
evidence driven

QUALITY OF EVIDENCE



Self management for patients with chronic obstructive pulmonary disease

Patient or population: patients with chronic obstructive pulmonary disease

Settings: primary care, community, outpatient

Intervention: self management¹

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Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GDT

Rate quality of evidence for each outcome

Randomization raises initial quality
RCTs: high
Observational: low

P
I
C
O

Outcome Critical
 Outcome Critical
 Outcome Important
 Outcome Not important



Summary of findings & estimate of effect for each outcome

Outcome	Limitations	Resource use	Indirectness	Imprecision	Other considerations	Quality assessment	Summary of findings	Importance
						GRADE	Relative risk	
1. Mortality	No serious limitations	No serious resource use	No serious indirectness	No serious imprecision	No other considerations	High	RR 0.85 (95% CI 0.75 to 0.95)	CRITICAL
2. Quality of life	No serious limitations	No serious resource use	No serious indirectness	No serious imprecision	No other considerations	High	RR 0.85 (95% CI 0.75 to 0.95)	CRITICAL
3. Adverse events	No serious limitations	No serious resource use	No serious indirectness	No serious imprecision	No other considerations	High	RR 0.85 (95% CI 0.75 to 0.95)	CRITICAL
4. Health-related quality of life	No serious limitations	No serious resource use	No serious indirectness	No serious imprecision	No other considerations	High	RR 0.85 (95% CI 0.75 to 0.95)	CRITICAL

High
 Moderate
 Low
 Very low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Opposing bias & Confounders

Grade overall quality of evidence
 across outcomes based on lowest quality of **critical** outcomes

Evidence synthesis (SR, HTA)

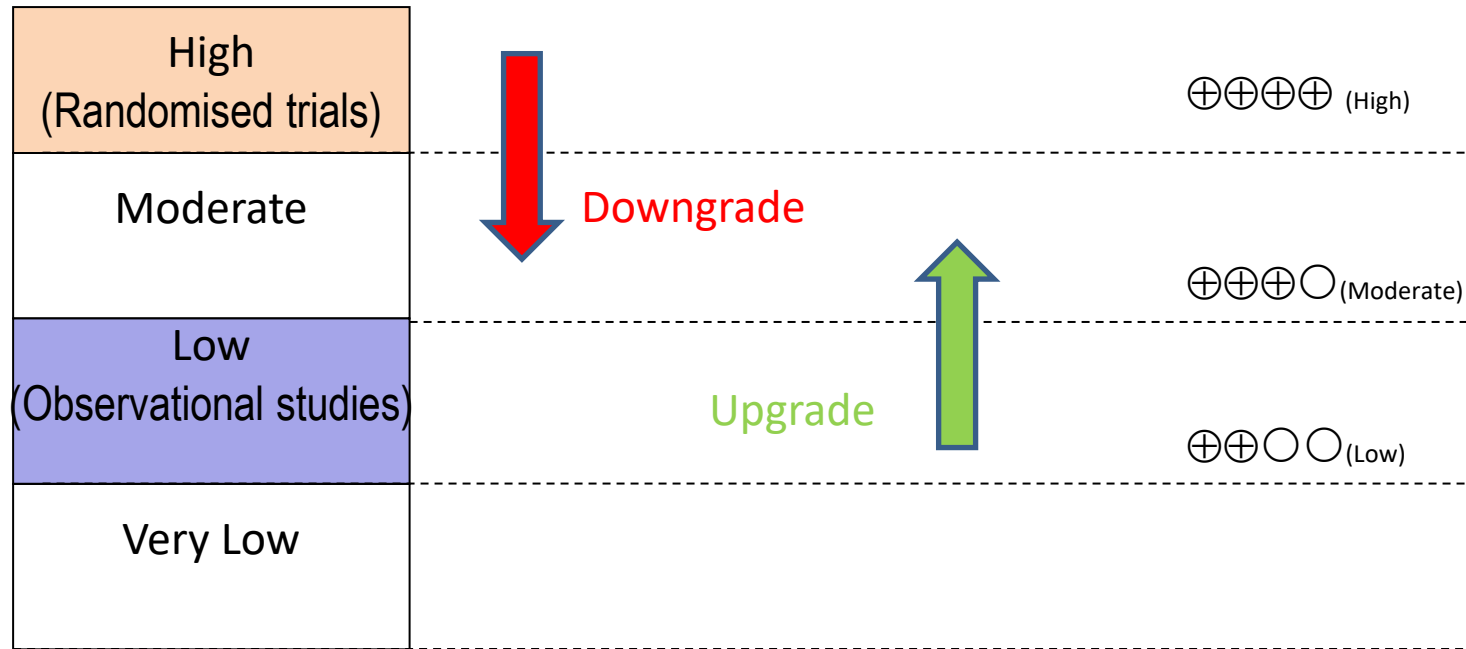
Quality of evidence

- **GRADE is “outcome centric”**: rating is made for each outcome, and quality **may differ** -indeed, is likely to differ - **from one outcome to another within a single study and across a body of evidence**
- E.g: subjective outcomes are prone to performance and detection bias, while objective outcomes are not
- E.g. one outcome within a review could have imprecision in the pooled estimate of the effect, while another could have not
- E.g. one outcome could have high attrition bias (use of substance) while another could have not (drop out)



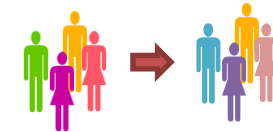
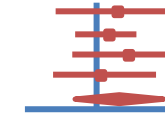
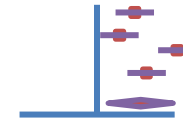
Rating quality of evidence

GRADE's approach begins with the study design. Randomized controlled trials (RCTs) start as high-quality evidence and observational studies as low-quality evidence supporting estimates of intervention effects



Determinants of quality/certainty of a body of evidence

- **RCTs** ⊕⊕⊕⊕
- **observational studies** ⊕⊕○○
- **5 factors that can lower quality**
 1. limitations in detailed study design and execution (*risk of bias criteria*)
 2. Inconsistency (*or heterogeneity*)
 3. Indirectness (*PICO and applicability*)
 4. Imprecision
 5. Publication bias
- **3 factors can increase quality**
 1. large magnitude of effect
 2. opposing plausible residual bias or confounding
 3. dose-response gradient



1. Study limitations (risk of bias)

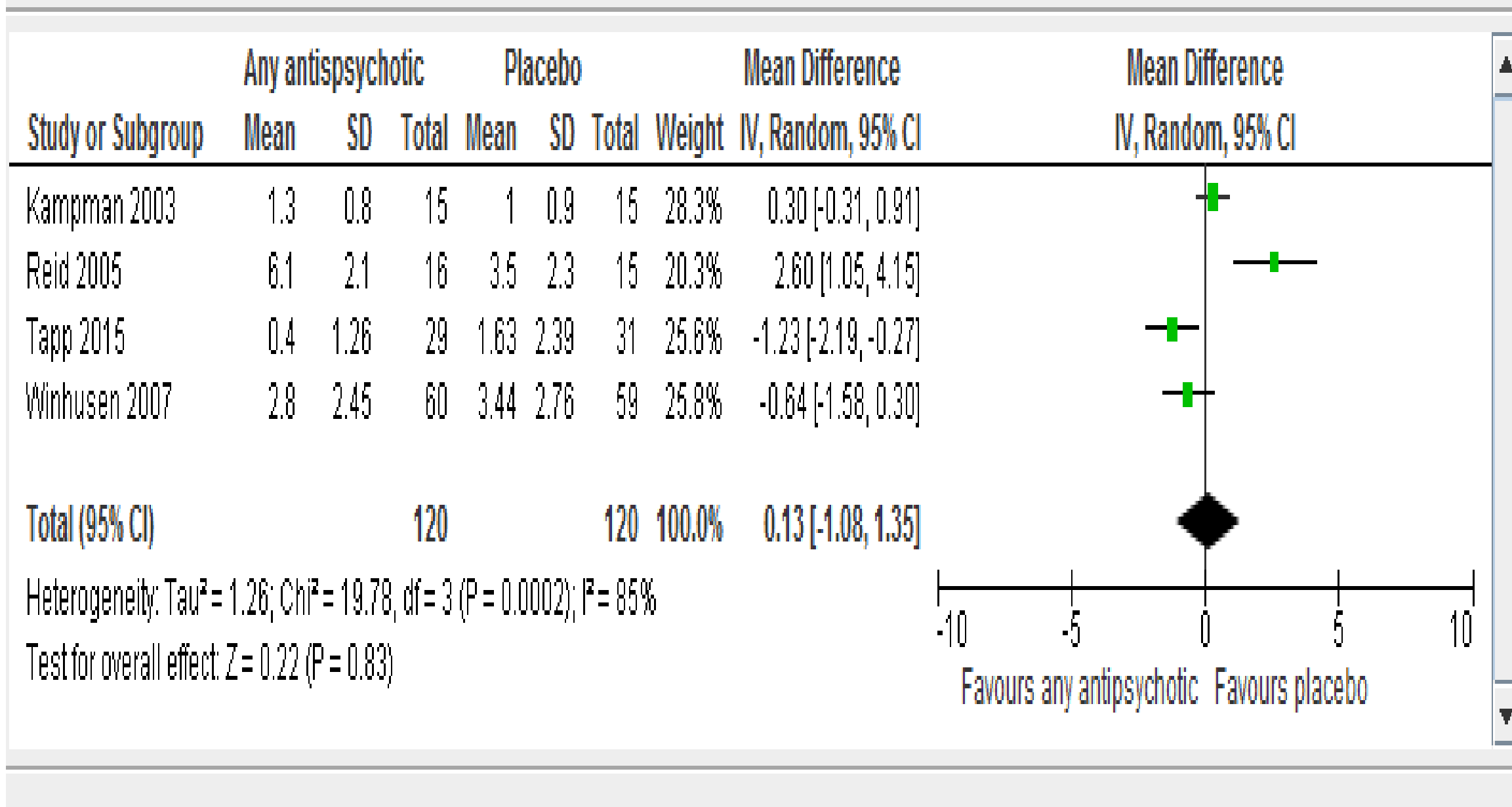
	Adequate sequence generation?	Allocation concealment?	Blinding?	Incomplete outcome data addressed?	Free of other bias?
Altinbas 2004	?	?	+	?	?
Kakkar 2004	+	+	+	+	+
Klerk 2005	+	+	+	-	+
Lebeau 1994	?	+	+	+	+
Sideras 2006	?	+	+	?	+

Risk of bias

- Outcome specific
- Do not average risk quality across the studies
- Evaluate the extent to which each trial contributes toward the estimate of magnitude of effect. This contribution will usually reflect **study sample size** and **number of outcome events** -larger trials with many events will contribute more, much larger trials with many more events will contribute much more (**look at the weight of each study in the forest plot**)

2. Inconsistency (heterogeneity) between studies results

- Variation in size of effect (**Point estimates vary widely** across studies)
- **Confidence intervals** (CIs) show minimal or **no overlap**
- The statistical test for heterogeneity which tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effect shows a low **P-value** (< 0.05)
- The **I^2** which quantifies the proportion of the variation in point estimates due to among-study differences ($< 40\%$: low, 30 e 60% : moderate, **60 e 90% : substantial, 75 e 100% : considerable**)
- All statistical approaches have limitations, and their results should be seen in the context of a subjective examination of the variability in point estimates and the overlap in CIs.



3. Directness of Evidence generalizability, transferability, applicability

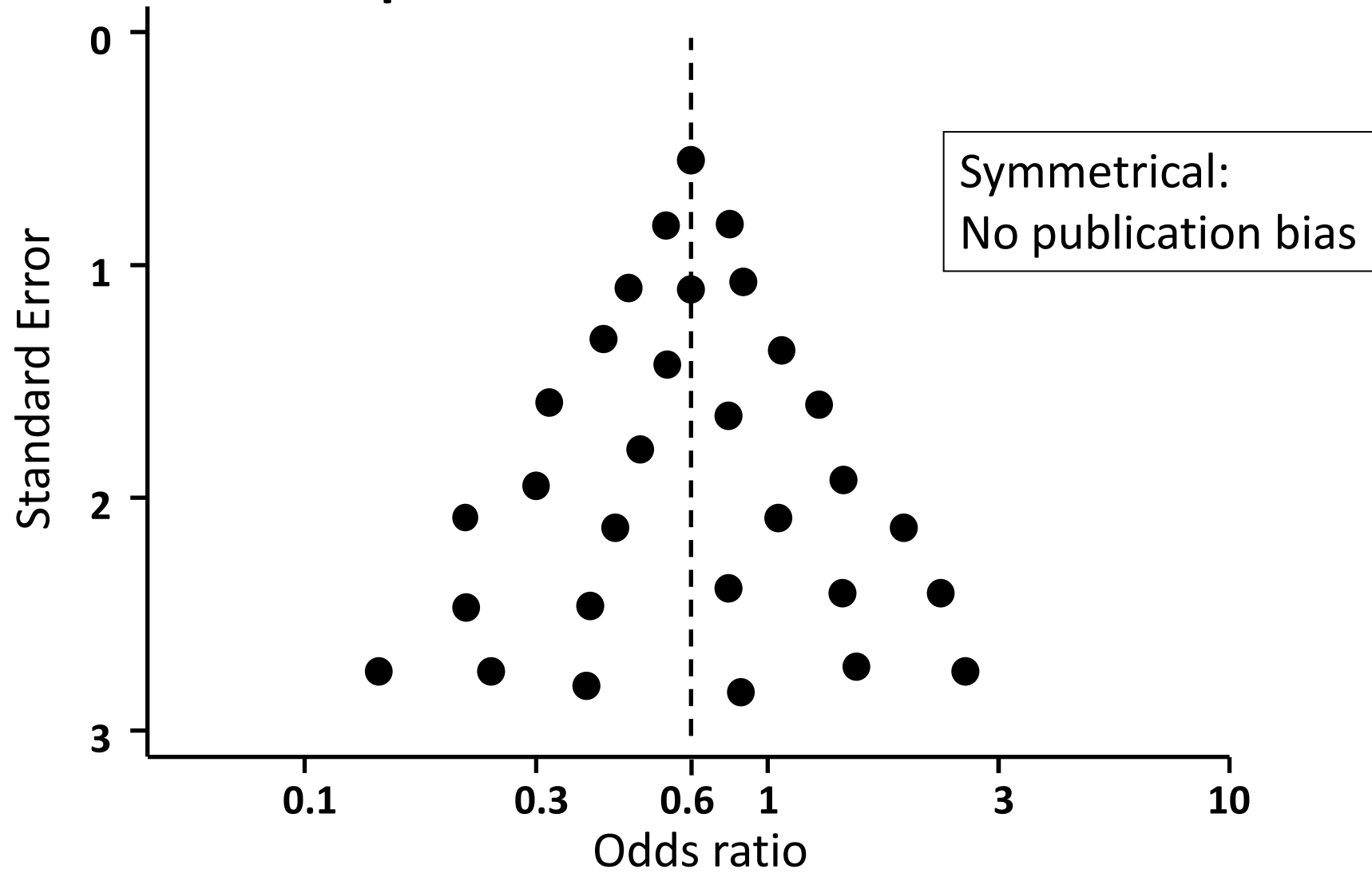
- differences between PICO and available evidence in
 - **populations**/patients (interested in children but found adults population)
 - **interventions** (interested in high dosage but found low dosage, interested in long treatment but found short, etc)
 - **outcomes** (interested in important but we found surrogate; e.g hip fracture vs bone density; interested in long term but found short term results)
- indirect **comparisons**
 - interested in A versus B
 - found A versus C and B versus C

4. Publication Bias

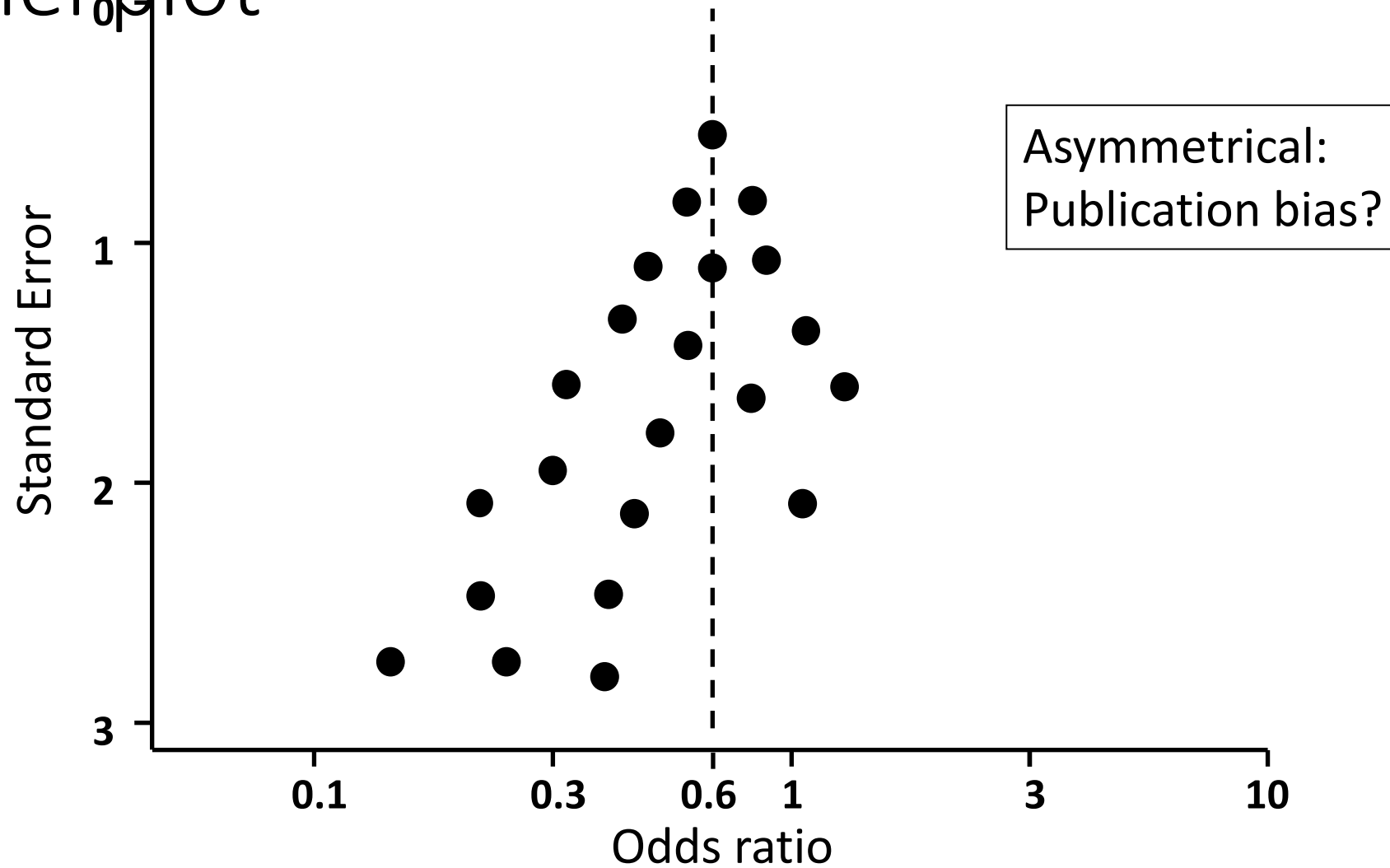
Consider rating down if:

- You find **systematic reviews performed early, when only few initial studies are available**, that will overestimate effects when “negative” studies face delayed publication. Early positive studies, particularly if small in size, are suspect.
- You find **only small “positive” studies, mainly if sponsored by industry**
- **Funnel plot showing asymmetry** but
- Funnel plot should be seen as a generic means of displaying small-study effects – a tendency for the intervention effects estimated in smaller studies to differ from those estimated in larger studies (Sterne 2000). Small-study effects may be due to reasons other than publication bias (low methodological quality, chance, patients characteristics).
- **Funnel plot should be used only when there are at least 10 studies** included in the meta-analysis, because when there are fewer studies the power of the tests is too low to distinguish chance from real asymmetry

Funnel plot



Funnel plot



5. Imprecision of the overall estimate: CI approach

What is new?

Key findings

- In systematic reviews and guidelines The Grading of Recommendations Assessment, Development and Evaluation (GRADE) now suggests aligning approach that relies on thresholds and CIs of the absolute effect (i.e., CI approach) as a primary criterion for imprecision rating.
- Using the CI approach, when the CI is wide and considerably cross the threshold(s) of interests (i.e., one or both boundaries of CIs suggest inferences appreciably different from point estimate), one should consider rating down two levels for imprecision, and when the CI is very wide that the two boundaries of CI suggest very different inferences, one should consider rating down three levels for imprecision.
- Using the OIS approach, for dichotomous outcomes, one should consider rating down two levels for imprecision, when the ratio of the upper to the lower boundary of the CI is more than 2.5 for odds ratio or three for risk ratio; for continuous outcomes, when the sample size is smaller than 30–50% of the OIS.
- When the baseline risk is very low, GRADE suggests being more restrained in rating down for imprecision.

Box 1 Possible threshold(s) of interest and target of certainty rating in minimally, partially, or fully contextualized approach

Using a minimally contextualized approach (typically in systematic reviews), authors consider only one outcome at a time. Authors rate their certainty in relation to the null—rating their certainty that an effect is truly present—or in relation to a minimally important difference (MID)—rating their certainty that an important effect is truly present.

Using a partially contextualized approach, authors rate their certainty that the true effect falls in a range representing a trivial, small, moderate, or large effects for one outcome at a time.

In a fully contextualized approach (typically used in guidelines), authors simultaneously consider multiple outcomes (i.e., trading off desirable vs. undesirable health effects of an intervention) and set a decision threshold above which they would recommend in favor of an intervention and below which they would recommend against it.

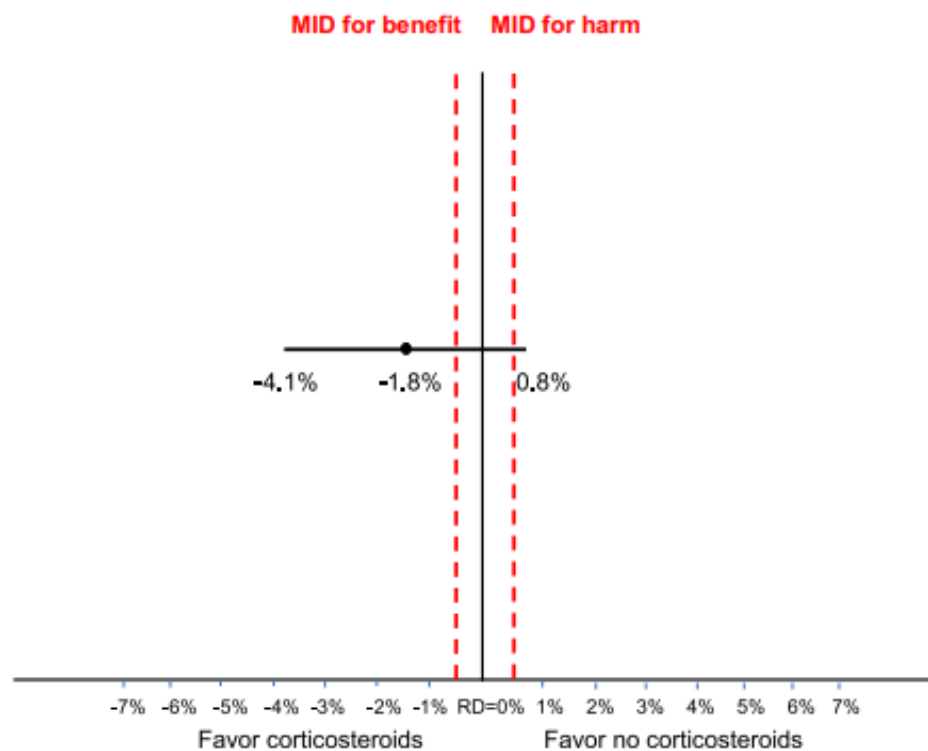


Fig. 2. Effect of corticosteroids vs. no corticosteroids in death at short term for patients with sepsis. *Abbreviations:* MID, minimally important difference.

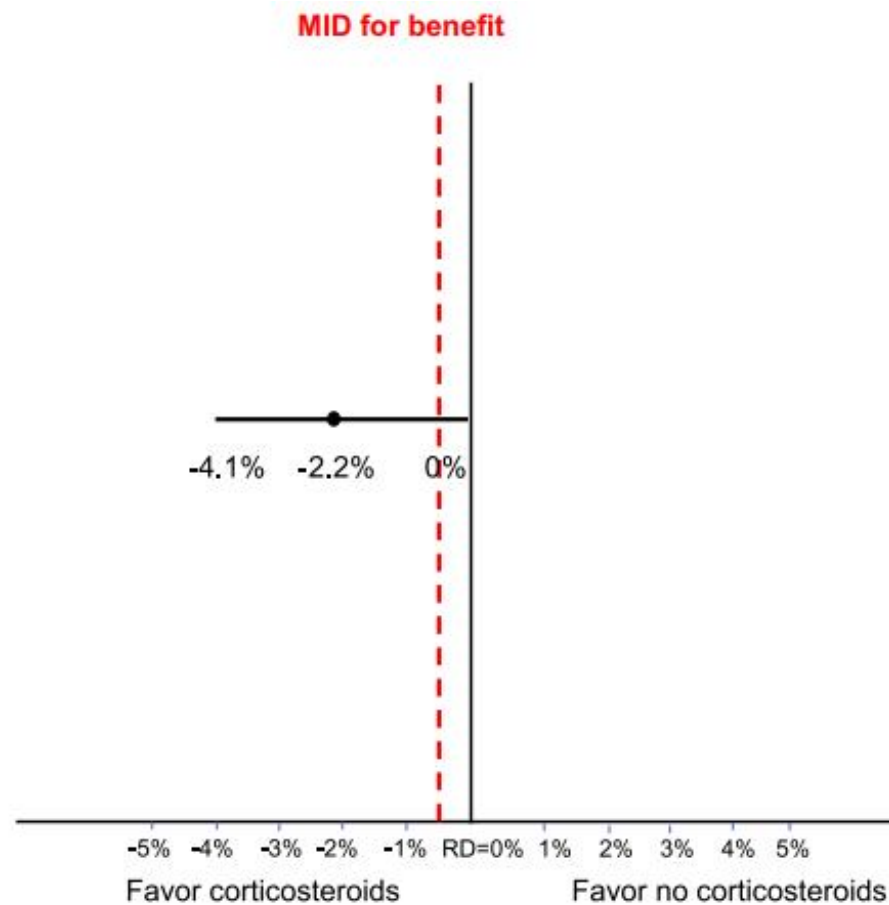


Fig. 1. Effects of corticosteroids vs. no corticosteroids in death for patients with sepsis. *Abbreviations:* MID, minimally important difference.

Box 4 Circumstances when one should consider rating down two levels for imprecision based on confidence interval approach using a minimally contextualized approach

Rating certainty in relation to an minimally important difference threshold when point estimate suggests an important effect (circumstance 1–2)

1. When rating the certainty that there is a true important benefit, the point estimate reflects an important benefit, and the boundary of the CI least favorable to the intervention includes the possibility of harm, particularly important harm (Example 1).
2. When rating the certainty that there is a true important harm, the point estimate reflects an important harm, and the boundary of the CI most favorable to the intervention includes the possibility of benefit, particularly important benefit (Example 2).

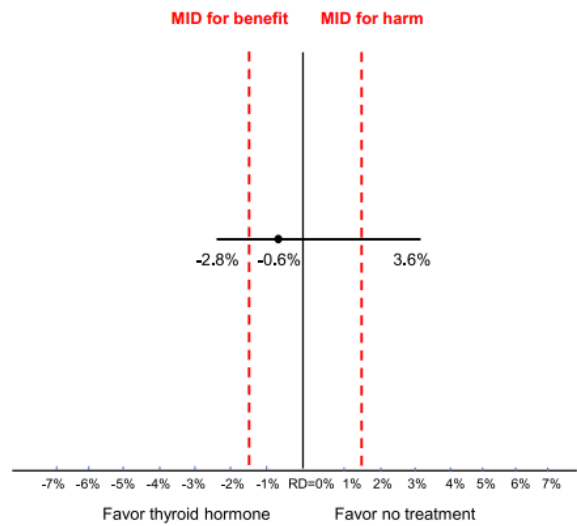


Fig. 4. Effect of thyroid hormone treatment vs. no treatment in cardiovascular event for patients with subclinical hypothyroidism. *Abbreviations:* MID, minimally important difference.

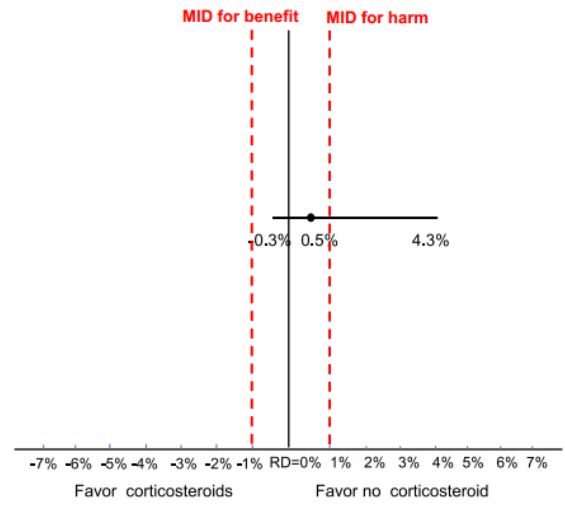


Fig. 5. Effect of corticosteroids vs. no corticosteroids in stroke for patients with sepsis. *Abbreviations:* MID, minimally important difference.

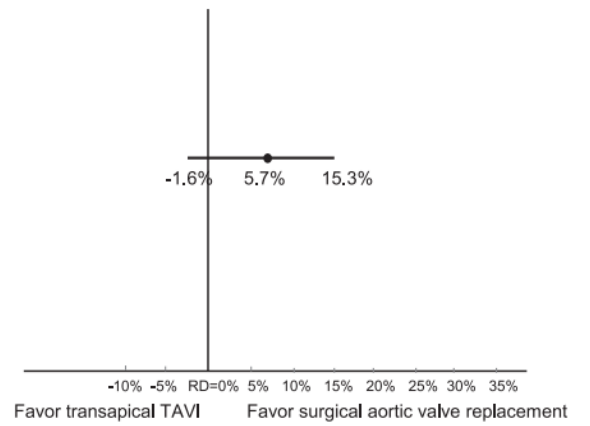


Fig. 3. Effect of transapical TAVI vs. surgical aortic valve replacement in mortality for patients with severe aortic stenosis. *Abbreviations:* TAVI, transcatheter aortic valve implantation.

Rating certainty in relation to minimally important difference thresholds when point estimate suggests a trivial effect (circumstance 3–5)

3. When rating the certainty that the true effect is a trivial or no effect, the point estimate is consistent with a trivial effect, and the CI includes the possibility of both important benefit and important harm (Example 3).
4. When rating the certainty that the true effect is a trivial or no effect, the point estimate is consistent with a trivial effect, and the CI includes the possibility of substantial (possibly large) important harm (Example 4).
5. When rating the certainty that the true effect is a trivial or no effect, the point estimate is consistent with a trivial effect, and the CI includes the possibility of substantial (possibly large) important benefit. (Example 5).

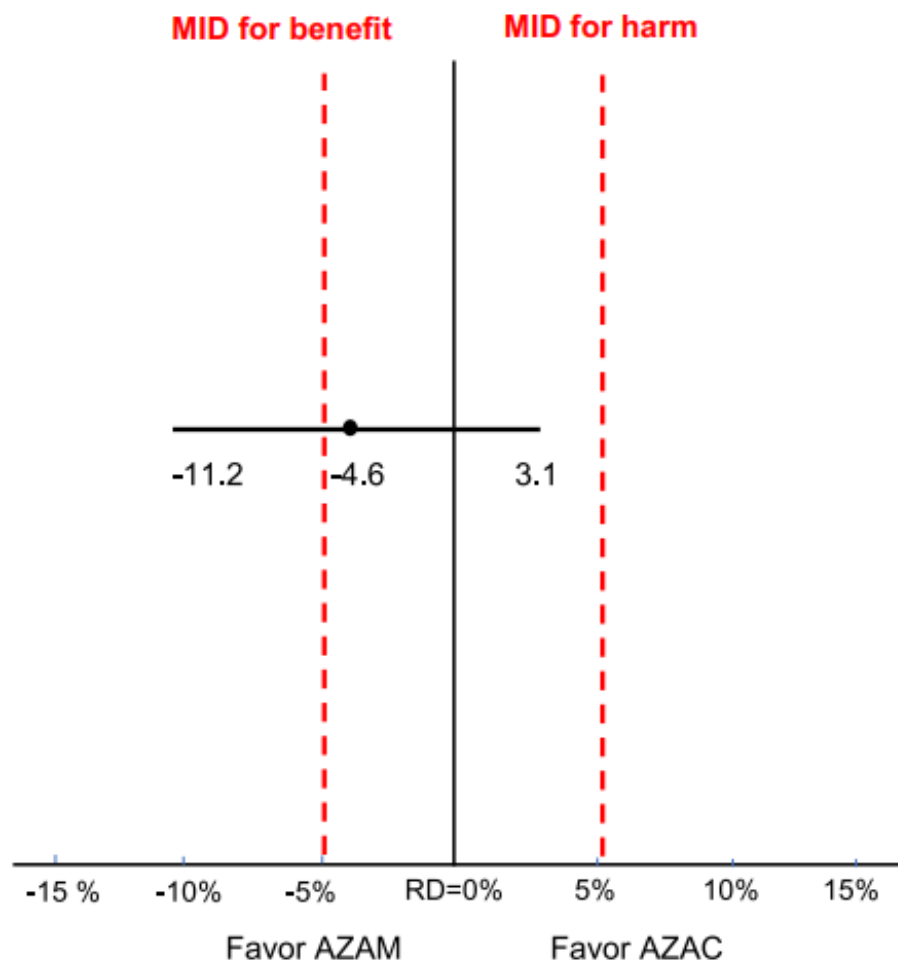


Fig. 6. Effect of azacitidine monotherapy (AZAM) vs. azacitidine combination (AZAC) in thrombocytopenia for patients with acute myeloid leukemia. *Abbreviations:* MID, minimally important difference.

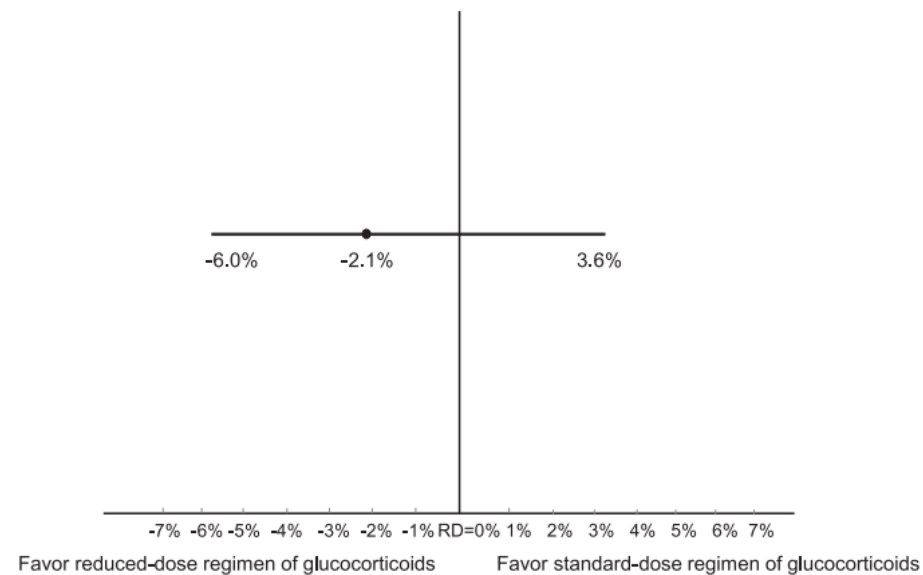
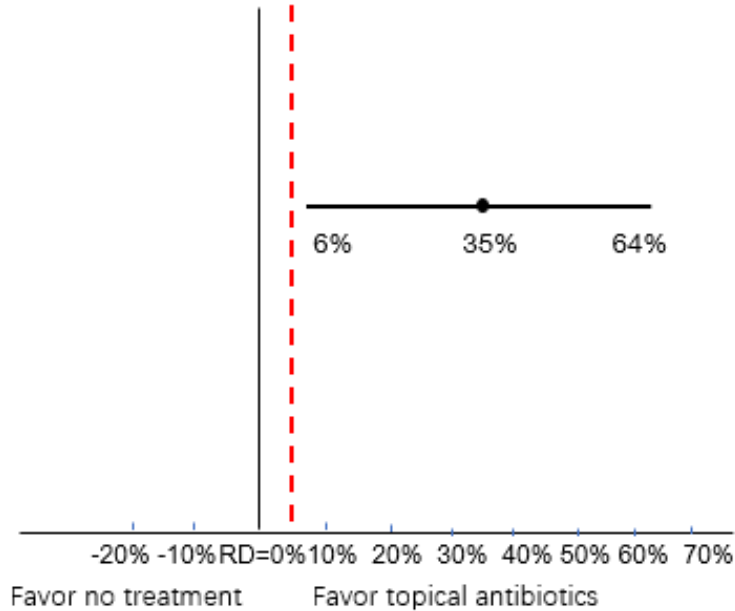


Fig. 7. Effect of reduced-dose regimen vs. standard-dose regimen of glucocorticoids in mortality for patients with vasculitis.

Rating certainty in relation to the null effect threshold (circumstance 6–7)

6. When rating the certainty of nonzero benefit, the point estimate suggests benefit, and the CI includes the possibility of important harm (Example 6).
7. When rating the certainty of nonzero harm, the point estimate suggests harm, and the CI includes the possibility of important benefit (Example 7).

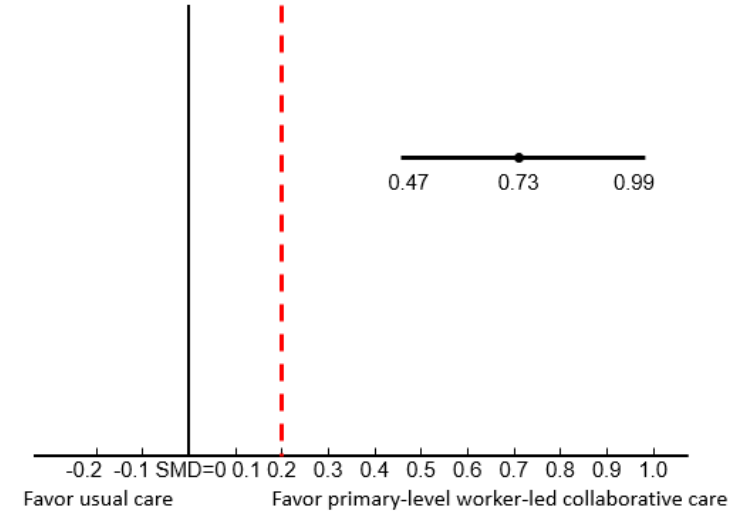
MID for benefit



Box 5 Circumstances when one should consider rating down two levels for imprecision based on optimal information size calculation using a minimally contextualized approach

1. For dichotomous outcomes, when the ratio of the upper to the lower boundary of the CI is more than 2.5 for odds ratio or three for risk ratioR (Appendix A, Example 1).
2. For continuous outcomes, when the total sample size of a meta-analysis is smaller than 30–50% of the OIS (Appendix A, Example 2).

MID for benefit



Example 3 [When the baseline risk is very low, GRADE suggests being more restrained in rating down for imprecision]

When the baseline risk is very small (how small of a baseline risk is very small depends on the importance of the outcome), the absolute estimates of effect used for decision-making are unlikely to change importantly regardless of how much new evidence is added. Therefore, when facing situations in which the baseline risk is very small, authors should not rate down certainty of evidence for imprecision around relative effect but rate the overall certainty of baseline risk.

What can raise quality?

1. **large magnitude of effect** can upgrade (**RRR 50%/RR 2**)
 - very large two levels (**RRR 80%/RR 5**) ; modeling studies suggests that **confounding** (from nonrandom allocation) alone **is unlikely to explain associations with a relative risk (RR) greater than 2** (or less than 0.5), and very unlikely to explain associations with an RR greater than 5 (or less than 0.2)
 - Es: relationship between infant sleeping position and sudden infant death syndrome (SIDS) found an odds ratio (OR) of 4.1 (95% confidence interval [CI]: 3.1, 5.5) of SIDS occurring with front vs. back sleeping positions

What can raise quality?

2. dose response relation

- higher INR – increased bleeding
- childhood lymphoblastic leukemia
 - risk for CNS malignancies 15 years after cranial irradiation
 - no radiation: 1% (95% CI 0% to 2.1%)
 - 12 Gy: 1.6% (95% CI 0% to 3.4%)
 - 18 Gy: 3.3% (95% CI 0.9% to 5.6%)

Residual confounding

- 3. all plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed (underestimate of the treatment effect)
- Es: effect of condom use on HIV infection among men who have sex with men RR: 0.34 [0.21, 0.54] (RRR: 66%) in favor of condom use compared with no condom use. Condom users were more likely to have more partners (but studies did not adjust for this confounding factor in their analyses). Considering the number of partners would, if anything, strengthen the effect estimate in favor of condom use.

Assessing Certainty in the Evidence by Outcome

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

Study design	Initial confidence in an estimate of effect
Randomized trials →	High confidence
Observational studies →	Low confidence

2.
Consider lowering or raising
level of confidence

Reasons for considering lowering or raising confidence	
↓ Lower if	↑ Higher if*
Risk of Bias Inconsistency Indirectness Imprecision Publication bias	Large effect Dose response All plausible confounding & bias <ul style="list-style-type: none"> would reduce a demonstrated effect would suggest a spurious effect if no effect was observed

3.
Final level of
confidence rating

Confidence in an estimate of effect across those considerations
High ⊕⊕⊕⊕
Moderate ⊕⊕⊕○
Low ⊕⊕○○
Very low ⊕○○○

*upgrading criteria are usually applicable to observational studies only.



Lowering certainty in RCTs

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	Higher*	
Randomized trials →	High confidence	<ul style="list-style-type: none"> Risk of Bias Inconsistency Indirectness Imprecision Publication Bias 	<ul style="list-style-type: none"> Large effect Dose response All plausible confounding & bias would reduce demonstrated effect or would suggest spurious effect if no effect was observed 	<ul style="list-style-type: none"> High (++++) Moderate (+++) Low (++) Very low (+)
Observational studies →	Low confidence			

*upgrading criteria are usually applicable to observational studies only.



Altering certainty in observational studies

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	Higher*	
Randomized trials →	High confidence	Risk of Bias	Large effect	High ++++
		Inconsistency	Dose response	Moderate +++
		Indirectness	All plausible confounding & bias would reduce demonstrated effect or would suggest spurious effect if no effect was observed	Low ++
Observational studies →	Low confidence	Imprecision		Very low +
		Publication bias		

*upgrading criteria are usually applicable to observational studies only.

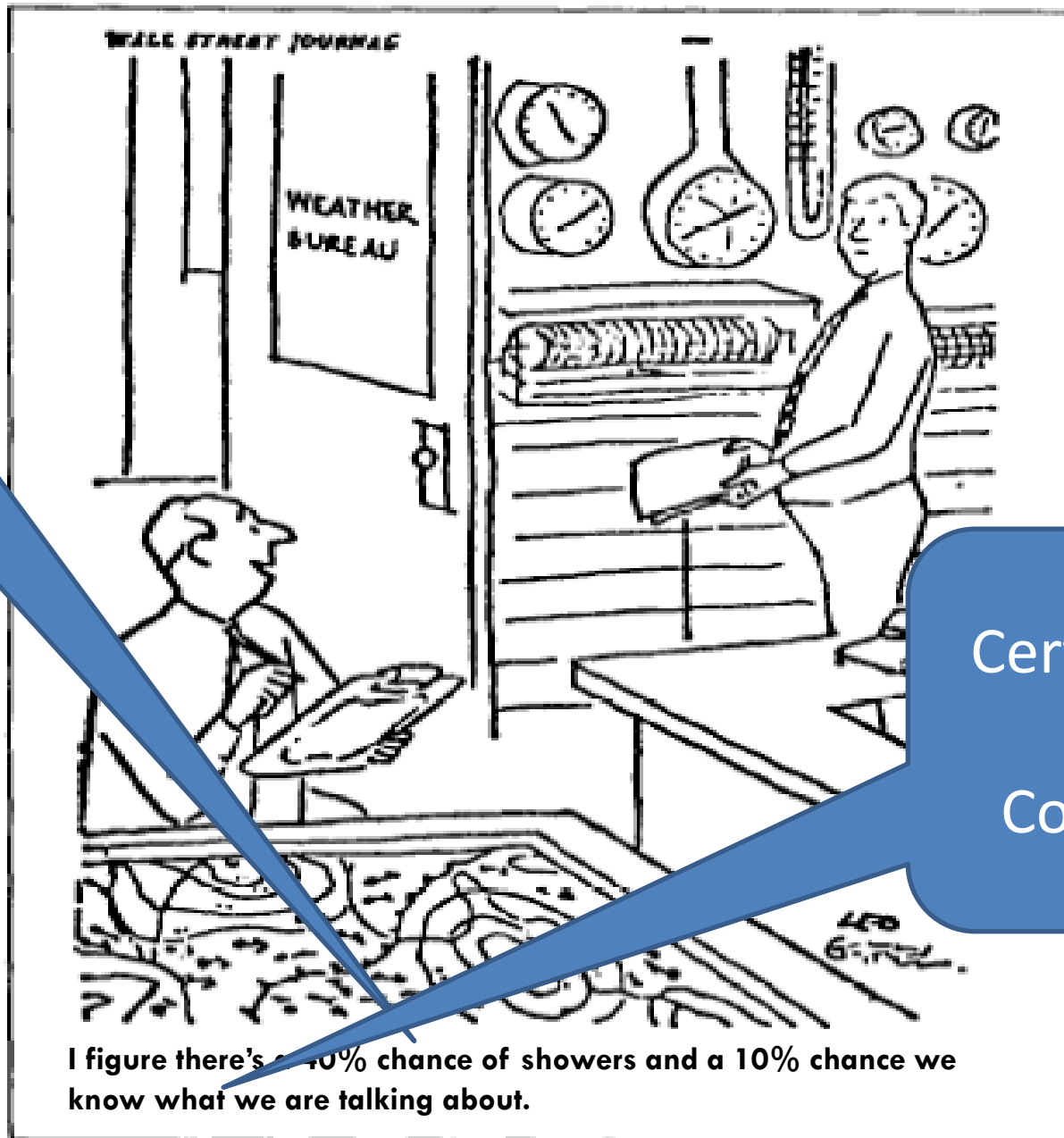
Grades of evidence and Interpretation

Symbol	Quality	Interpretation
⊕⊕⊕⊕	High	We are very confident that the true effect lies close to that of the estimate of the effect
⊕⊕⊕○	Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
⊕⊕○○	Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
⊕○○○	Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

grades of evidence and Interpretation

Quality of evidence = certainty of the results

Magnitude of Effect



Likelihood of and certainty in the evidence or effect

Certainty or Quality of evidence
Confidence in effect