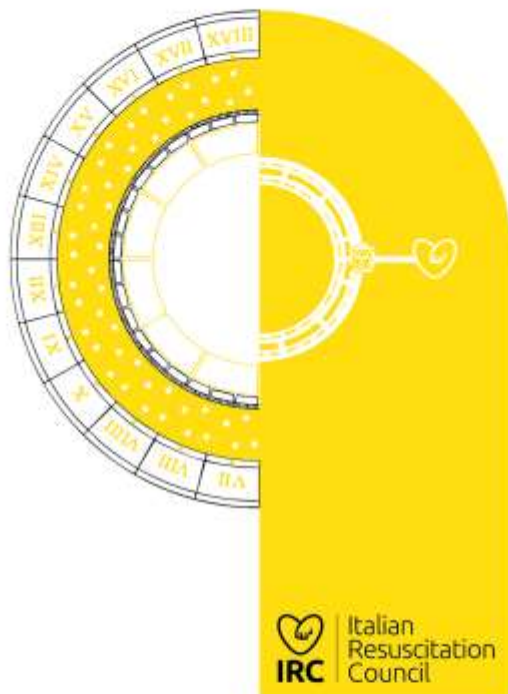




2025

DALLA RICERCA ALLA CLINICA:

IL PROCESSO DI SVILUPPO DELLE LINEE GUIDA
DELLA RIANIMAZIONE CARDIOPOLMONARE



Italian
Resuscitation
Council



Valutazione della qualità dell'evidenza: **GRADE**

Sonia D'Arrigo

Fondazione Policlinico Universitario A. Gemelli-IRCCS Roma

11 settembre 2025

GRADE

(Grading of Recommendations, Assessment, Development and Evaluations)

ILCOR utilizza il sistema **GRADE** per valutare:

- **Qualità dell'evidenza** (alta, moderata, bassa, molto bassa)
- **Forza delle raccomandazioni** (forte o debole)



Journal of Clinical Epidemiology 64 (2011) 393–394

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GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables

Gordon Guyatt^{a,b,*}, Andrew D. Oxman^c, Elie A. Akl^m, Regina Kunz^d, Gunn Vist^e, Jan Brozek^a, Susan Norris^e, Yngve Falck-Ytter^f, Paul Glasziou^g, Hans deBeer^h, Roman Jaeschke^h, David Rindⁱ, Joerg Meerpohl^{j,k}, Philipp Dahm^l, Holger J. Schünemann^{a,b}



Journal of Clinical Epidemiology 64 (2011) 395–400

Journal of
Clinical
Epidemiology

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



Journal of Clinical Epidemiology 64 (2011) 401–406

Journal of
Clinical
Epidemiology

GRADE guidelines: 3. Rating the quality of evidence

Howard Balshem^{a,*}, Mark Helfand^{a,b}, Holger J. Schünemann^c, Andrew D. Oxman^d, Regina Kunz^e, Jan Brozek^e, Gunn E. Vist^f, Yngve Falck-Ytter^g, Joerg Meerpohl^{h,i}, Susan Norris^j, Gordon H. Guyatt^c



Journal of Clinical Epidemiology 64 (2011) 407–415

Journal of
Clinical
Epidemiology

GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

Gordon H. Guyatt^{a,*}, Andrew D. Oxman^b, Gunn Vist^b, Regina Kunz^c, Jan Brozek^a, Pablo Alonso-Coello^d, Victor Montori^e, Elie A. Akl^f, Ben Djulbegovic^{g,h,i}, Yngve Falck-Ytter^j, Susan L. Norris^k, John W. Williams Jr.^l, David Atkins^m, Joerg Meerpohl^{n,o}, Holger J. Schünemann^a

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Journal of Clinical Epidemiology 64 (2011) 1277–1282

Journal of
Clinical
Epidemiology

GRADE SERIES - SHARON STRAUS, RACHEL CHURCHILL AND SASHA SHEPPERD, GUEST EDITORS

GRADE guidelines: 5. Rating the quality of evidence—publication bias

Gordon H. Guyatt^{a,b,*}, Andrew D. Oxman^c, Victor Montori^d, Gunn Vist^e, Regina Kunz^e, Jan Brozek^e, Pablo Alonso-Coello^f, Ben Djulbegovic^{g,h,i}, David Atkins^j, Yngve Falck-Ytter^k, John W. Williams Jr.^l, Joerg Meerpohl^{m,n}, Susan L. Norris^o, Elie A. Akl^p, Holger J. Schünemann^a



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IL PROCESSO DI SVILUPPO DELLE
LINEE GUIDA DELL'ARRESTO CARDIACO



Journal of Clinical Epidemiology 64 (2011) 1283–1293

Journal of
Clinical
Epidemiology

GRADE guidelines 6. Rating the quality of evidence—imprecision

Gordon H. Guyatt^{a,b,*}, Andrew D. Oxman^c, Regina Kunz^{d,e}, Jan Brozek^c, Pablo Alonso-Coello^f, David Rind^g, PJ Devereaux^h, Victor M. Montoriⁱ, Bo Freyschuss^j, Gunn Vist^c, Roman Jaeschke^b, John W. Williams Jr.^j, Mohammad Hassan Murad^b, David Sinclair^k, Yngve Falck-Ytter^l, Joerg Meerpohl^{m,n}, Craig Whittington^o, Kristian Thorlund^o, Jeff Andrews^p, Holger J. Schünemann^{a,b}



Journal of Clinical Epidemiology 64 (2011) 1303–1310

Journal of
Clinical
Epidemiology

GRADE guidelines: 8. Rating the quality of evidence—indirectness

Gordon H. Guyatt^{a,b,*}, Andrew D. Oxman^c, Regina Kunz^{d,e}, James Woodcock^f, Jan Brozek^g, Mark Helfand^h, Pablo Alonso-Coello^b, Yngve Falck-Ytter^{i,j}, Roman Jaeschke^b, Gunn Vist^c, Elie A. Akl^k, Piet N. Post^l, Susan Norris^m, Joerg Meerpohl^{n,o}, Vijay K. Shukla^p, Mona Nasser^q, Holger J. Schünemann^{a,b}, The GRADE Working Group[†]



Journal of Clinical Epidemiology 119 (2020) 126–135

SERIES

GRADE guidelines 26: informative statements to communicate the findings of systematic reviews of interventions

Nancy Santesso^{a,b}, Claire Glenton^b, Philipp Dahm^c, Paul Garner^d, Elie A. Akl^e, Brian Alper^{f,g}, Romina Brignardello-Petersen^h, Alonso Carrasco-Labra^h, Hans De Beer^b, Monica Hultcrantzⁱ, Ton Kuijpers^j, Joerg Meerpohl^k, Rebecca Morgan^l, Reem Mustafa^{m,n}, Nicole Skoetz^o, Shahnaz Sultan^o, Charles Wuysonge^{p,q,r,s}, Gordon Guyatt^{a,b}, Holger J. Schünemann^{a,b}, for the GRADE Working Group



Journal of Clinical Epidemiology 64 (2011) 1294–1302

Journal of
Clinical
Epidemiology

GRADE guidelines: 7. Rating the quality of evidence—inconsistency

Gordon H. Guyatt^{a,b,*}, Andrew D. Oxman^c, Regina Kunz^d, James Woodcock^e, Jan Brozek^f, Mark Helfand^g, Pablo Alonso-Coello^h, Paul Glasziou^b, Roman Jaeschke^b, Elie A. Aklⁱ, Susan Norris^j, Gunn Vist^c, Philipp Dahm^k, Vijay K. Shukla^l, Julian Higgins^m, Yngve Falck-Ytterⁿ, Holger J. Schünemann^{a,b}, The GRADE Working Group[†]



Journal of Clinical Epidemiology 64 (2011) 1311–1316

Journal of
Clinical
Epidemiology

GRADE guidelines: 9. Rating up the quality of evidence

Gordon H. Guyatt^{a,b,*}, Andrew D. Oxman^c, Shahnaz Sultan^d, Paul Glasziou^e, Elie A. Akl^f, Pablo Alonso-Coello^g, David Atkins^h, Regina Kunz^{i,j}, Jan Brozek^g, Victor Montori^k, Roman Jaeschke^b, David Rind^{l,m}, Philipp Dahmⁿ, Joerg Meerpohl^{o,p}, Gunn Vist^c, Elie Akl^q, Susan Norris^r, Yngve Falck-Ytter^s, M. Hassan Murad^k, Holger J. Schünemann^{a,b}, The GRADE Working Group[†]

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DALLA RICERCA
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METHODOLOGY

Understanding GRADE: an introduction

Gabrielle Goldet and Jeremy Howick

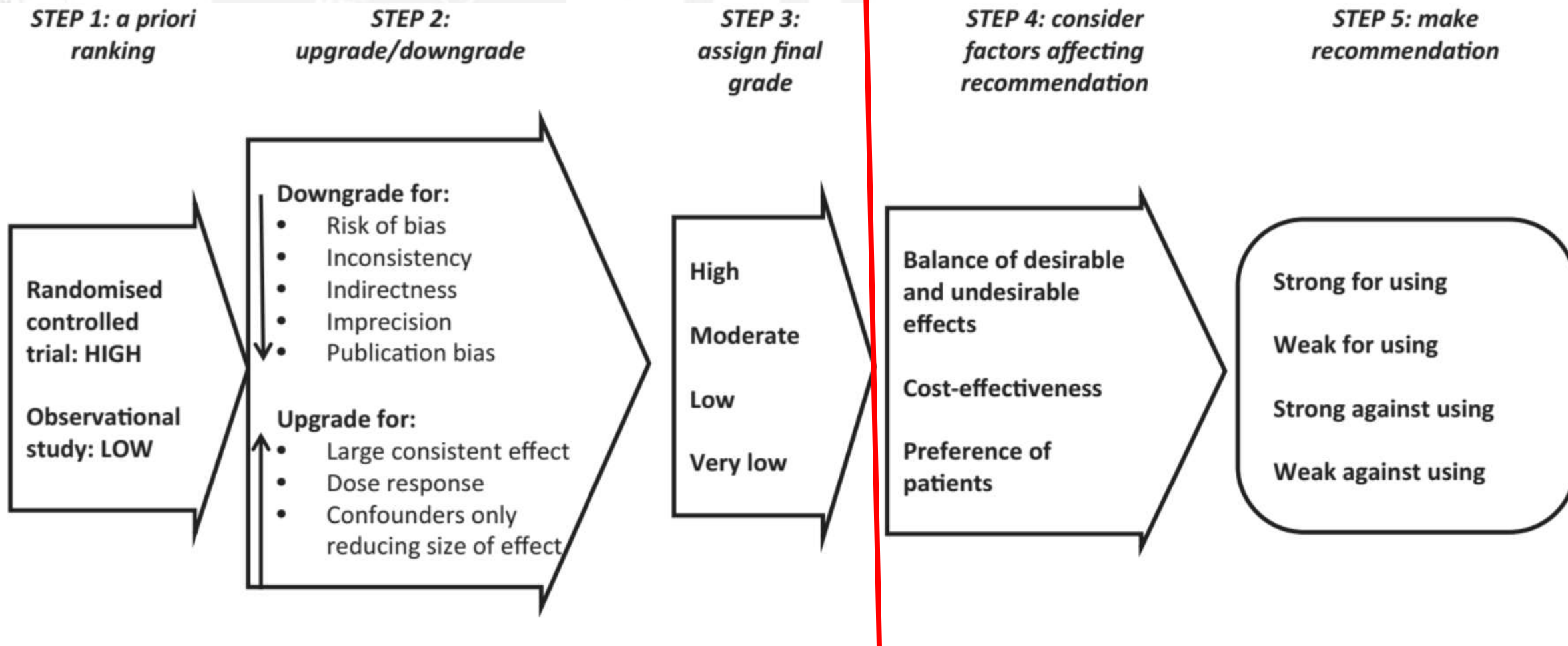


Figure 1 How GRADE is used to make recommendations; steps 1 to 3 are repeated for each critical outcome.

Fattori di **DOWNGRADE** (per abbassare la qualità)

1. Rischio di bias (study limitations)

Cosa significa: Errori sistematici nei metodi di conduzione o analisi degli studi.

Esempio pratico:

Uno studio RCT non descrive adeguatamente il metodo di randomizzazione né l'occultamento dell'allocazione. Questo potrebbe introdurre bias.



Downgrade di 1 livello.

GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias)

Gordon H. Guyatt^{a,*}, Andrew D. Oxman^b, Gunn Vist^b, Regina Kunz^c, Jan Brozek^d, Pablo Alonso-Coello^d, Victor Montori^e, Elie A. Akl^f, Ben Djulbegovic^{g,h,i}, Yngve Falck-Ytter^j, Susan L. Norris^k, John W. Williams Jr.^l, David Atkins^m, Joerg Meerpohl^{n,o}, Holger J. Schünemann^g

^aDepartment of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario L8N 3Z5, Canada

Risk of bias

(study limitations)



Per singolo lavoro

Table 1

Study limitations in randomized trials

1. Lack of allocation concealment

Those enrolling patients are aware of the group (or period in a crossover trial) to which the next enrolled patient will be allocated (major problem in “pseudo” or “quasi” randomized trials with allocation by day of week, birth date, chart number, etc)

2. Lack of blinding

Patient, care givers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated (or the medication currently being received in a crossover trial)

3. Incomplete accounting of patients and outcome events

Loss to follow-up and failure to adhere to the intention-to-treat principle in superiority trials; or in noninferiority trials, loss to follow-up, and failure to conduct both analyses considering only those who adhered to treatment, and all patients for whom outcome data are available

4. Selective outcome reporting bias

Incomplete or absent reporting of some outcomes and not others on the basis of the results

5. Other limitations

Stopping early for benefit

Use of unvalidated outcome measures (e.g., patient-reported outcomes)

Carryover effects in crossover trial

Recruitment bias in cluster-randomized trials

Fattori di **DOWNGRADE** (per abbassare la qualità)

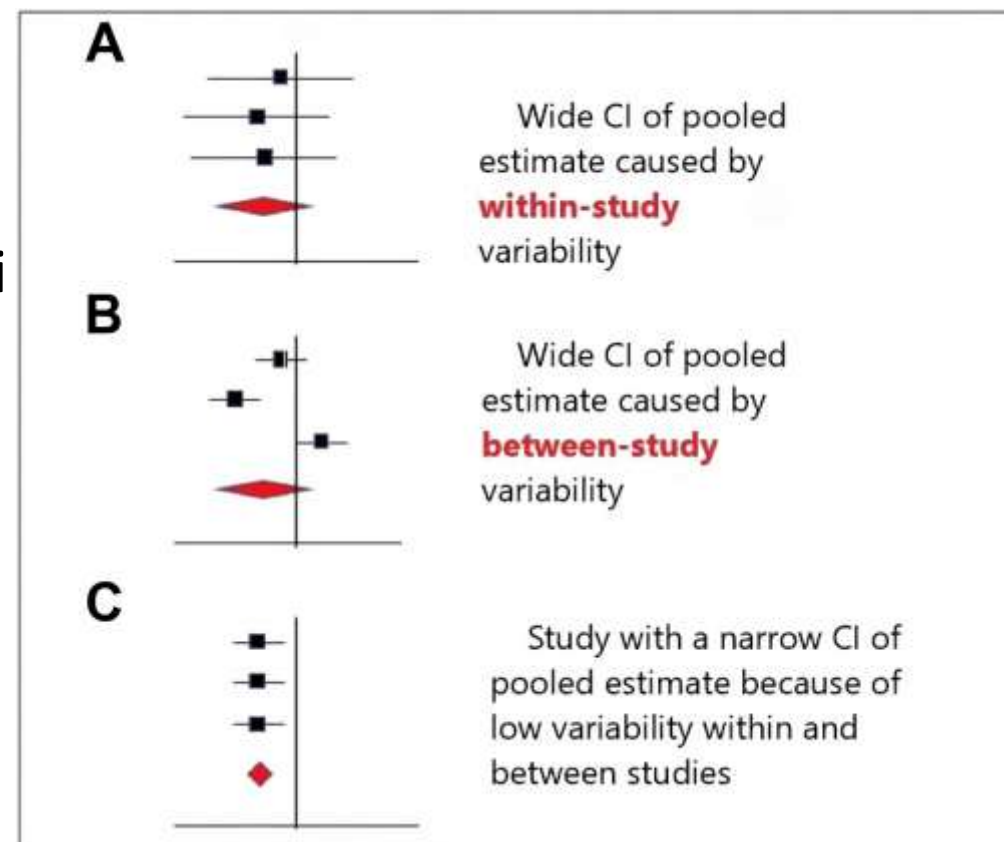
2. Inconsistency (heterogeneity in meta-analysis)

Cosa significa: Risultati molto eterogenei tra studi simili (alta variabilità).

Esempio pratico:
Tre RCT mostrano effetti molto diversi dello stesso farmaco, senza spiegazioni plausibili → alta eterogeneità ($I^2 > 75\%$).



Downgrade di 1 livello.



Fattori di **DOWNGRADE** (per abbassare la qualità)

3. Indirectness

Cosa significa: Lo studio non risponde esattamente alla domanda clinica (PICO) per popolazione, intervento, confronto o outcome.

Esempio pratico:

Studi su adulti quando la domanda riguarda bambini; uso di un farmaco simile ma non identico a quello di interesse.



Downgrade di 1 livello.

Fattori di **DOWNGRADE** (per abbassare la qualità)

4. Imprecision (small sample size, wide confidence interval)

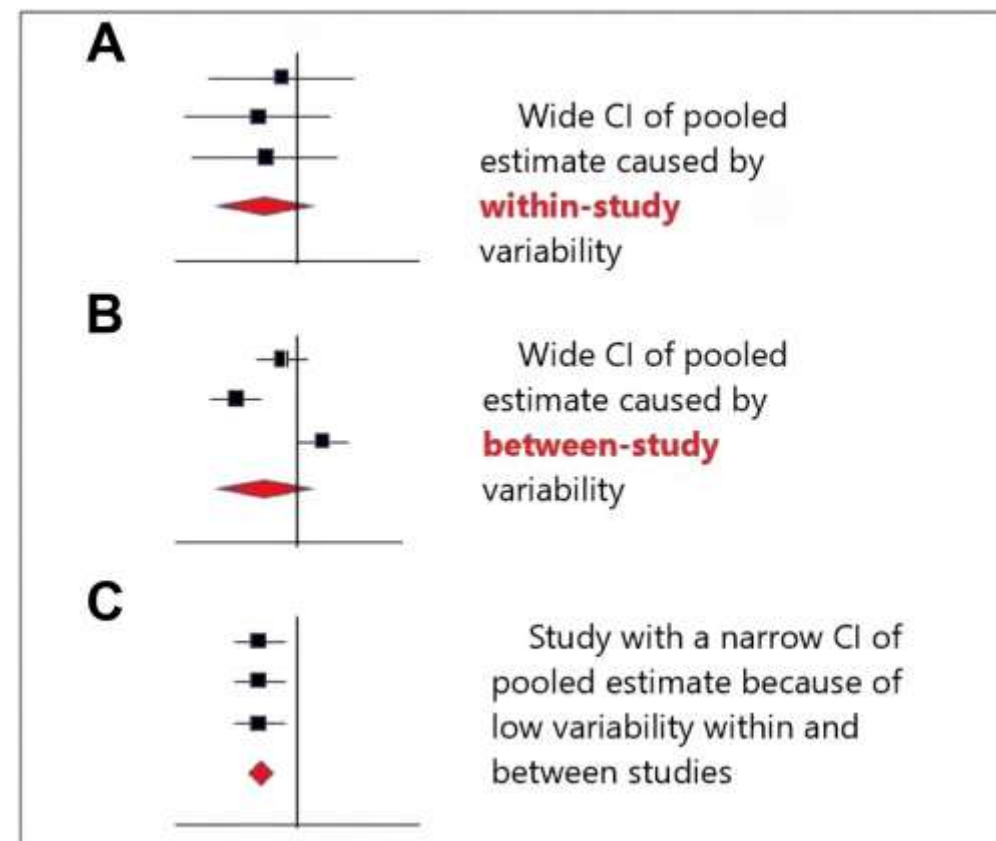
Cosa significa: Intervalli di confidenza (CI) molto ampi, pochi eventi o piccoli campioni → incertezza sul vero effetto.

Esempio pratico:

Un RCT mostra una riduzione della mortalità con $RR = 0.80$, ma $CI\ 95\% = 0.50-1.30$ → non è chiaro se l'effetto sia benefico o nullo.



Downgrade di 1 livello (o 2 se grave).



Fattori di **DOWNGRADE** (per abbassare la qualità)

5. Publication bias

Cosa significa: Studi con risultati negativi/non significativi non vengono pubblicati → rischio di sovrastimare l'effetto.

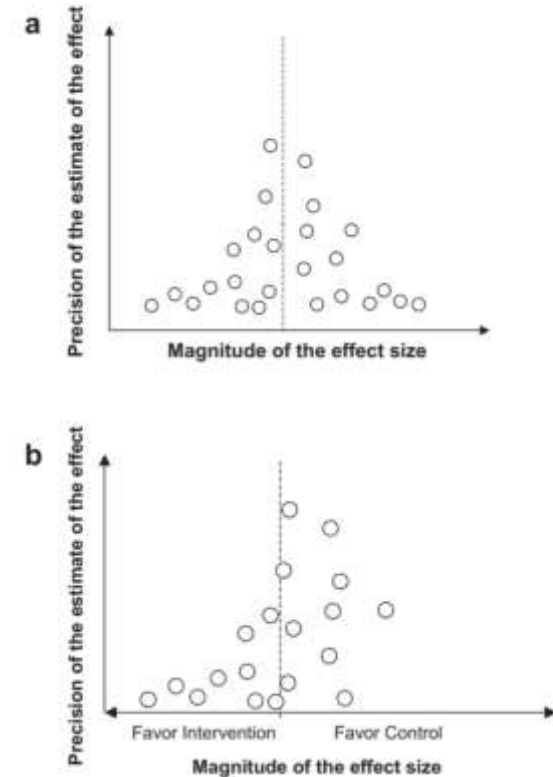
Esempio pratico:

Meta-analisi che include solo studi sponsorizzati da industrie, tutti con risultati positivi.



Downgrade di 1 livello.

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Fattori di **UPGRADE**

(per aumentare la qualità negli studi osservazionali)

1. Effetto molto grande

Uno studio osservazionale mostra che un farmaco riduce la mortalità del 70% ($RR = 0.3$), con CI stretto.

2. Relazione dose-risposta

Pazienti che ricevono dosi maggiori di un trattamento/aumentano il livello di esposizione migliorano più rapidamente → suggerisce causalità.

3. Tutti i bias plausibili ridurrebbero l'effetto osservato

Anche assumendo bias, l'effetto rimane forte o a favore del gruppo di controllo, quindi il beneficio reale potrebbe essere ancora maggiore.

Table 3

A summary of GRADE's approach to rating quality of evidence

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomized trials	High 	Risk of Bias -1 Serious -2 Very serious Inconsistency -1 Serious -2 Very serious Indirectness -1 Serious -2 Very serious Imprecision -1 Serious -2 Very serious Publication bias -1 Likely -2 Very likely	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient All plausible residual confounding +1 Would reduce a demonstrated effect +1 Would suggest a spurious effect if no effect was observed	High (four plus: ⊕ ⊕ ⊕ ⊕) Moderate (three plus: ⊕ ⊕ ⊕ ○) Low (two plus: ⊕ ⊕ ○ ○) Very low (one plus: ⊕ ○ ○ ○)
Observational studies	Low 			

Box 1 Final GRADE ranking

High we are very confident that the effect in the study reflects the actual effect.

Moderate we are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.

Low the true effect may differ significantly from the estimate.

Very low the true effect is likely to be substantially different from the estimated effect.



METHODOLOGY

Understanding GRADE: an introduction

Gabrielle Goldet and Jeremy Howick

STEP 1: a priori ranking

Randomised controlled trial: HIGH

Observational study: LOW

STEP 2: upgrade/downgrade

Downgrade for:

- Risk of bias
- Inconsistency
- Indirectness
- Imprecision
- Publication bias

Upgrade for:

- Large consistent effect
- Dose response
- Confounders only reducing size of effect

STEP 3: assign final grade

High

Moderate

Low

Very low

STEP 4: consider factors affecting recommendation

Balance of desirable and undesirable effects

Cost-effectiveness

Preference of patients

STEP 5: make recommendation

Strong for using

Weak for using

Strong against using

Weak against using

Figure 1 How GRADE is used to make recommendations; steps 1 to 3 are repeated for each critical outcome.

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