Provincia Religiosa di San Pietro
dell'Ordine Ospedaliero di San Giovanni di Dio
Ospedale "Sacro Cuore di Gesù", Fatebenefratelli
UOC PEDIATRIA-NEONATOLOGIA-UTIN

JOURNAL CLUB of Pediatrics in Benevento

incontri monotematici ospedale - territorio per la elaborazione di linee guida comuni

Febbraio Dicembre 2015

Centro Congressi
Ospedale Sacro Cuore di Gesù
Fatebenefratelli, Benevento

Responsabili Scientifici:
Iride Dello Iacono
Maria Carmen Verga

CREDITI ECM 40,3

A.N.M.I.C.O.

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Società Italiana di Pediatria

Ordine Provinciale dei Medici Chirurghi e degli Odontoiatri di Benevento

Gastroenterologia

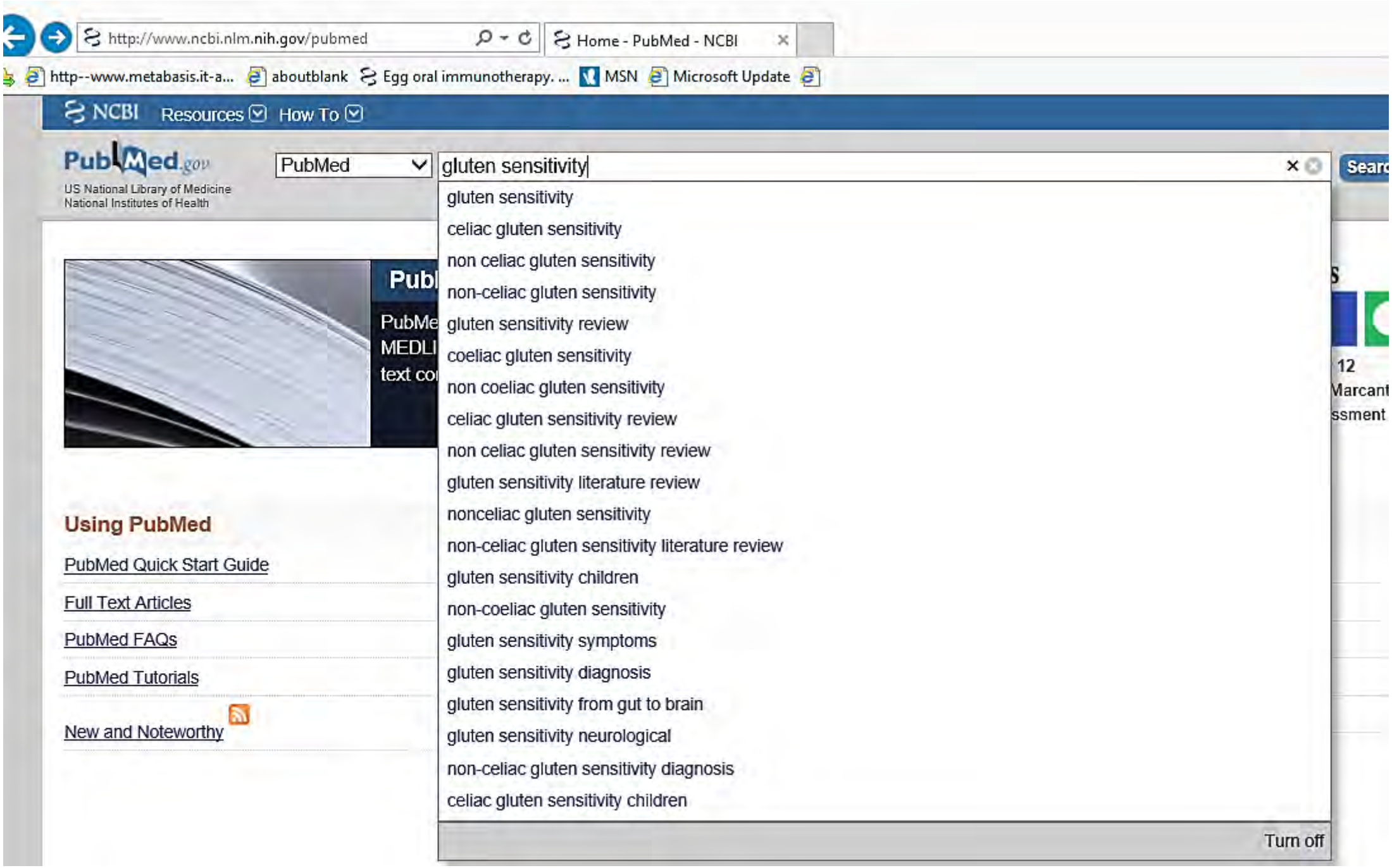
Pillola di EBM

Gluten-sensitive enteropathy
Revisioni o
Revisioni Sistematiche?

Marcello Bergamini
Maria Carmen Verga

14 marzo 2015

Perché le revisioni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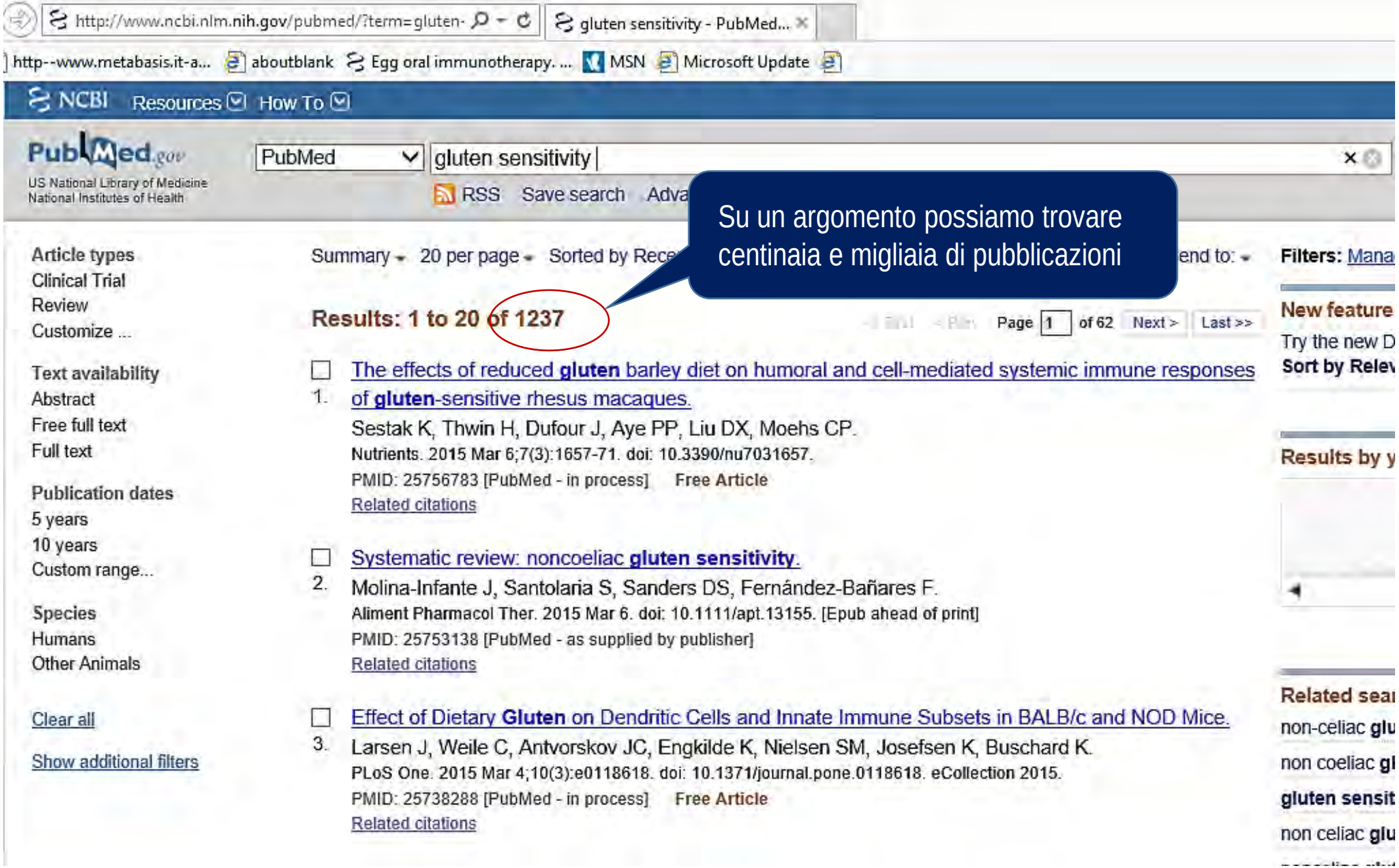
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Sestak K, Thwin H, Dufour J, Aye PP, Liu DX, Moehs CP.
Nutrients. 2015 Mar 6;7(3):1657-71. doi: 10.3390/nu7031657.
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Molina-Infante J, Santolaria S, Sanders DS, Fernández-Bañares F.
Aliment Pharmacol Ther. 2015 Mar 6. doi: 10.1111/apt.13155. [Epub ahead of print]
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PLoS One. 2015 Mar 4;10(3):e0118618. doi: 10.1371/journal.pone.0118618. eCollection 2015.
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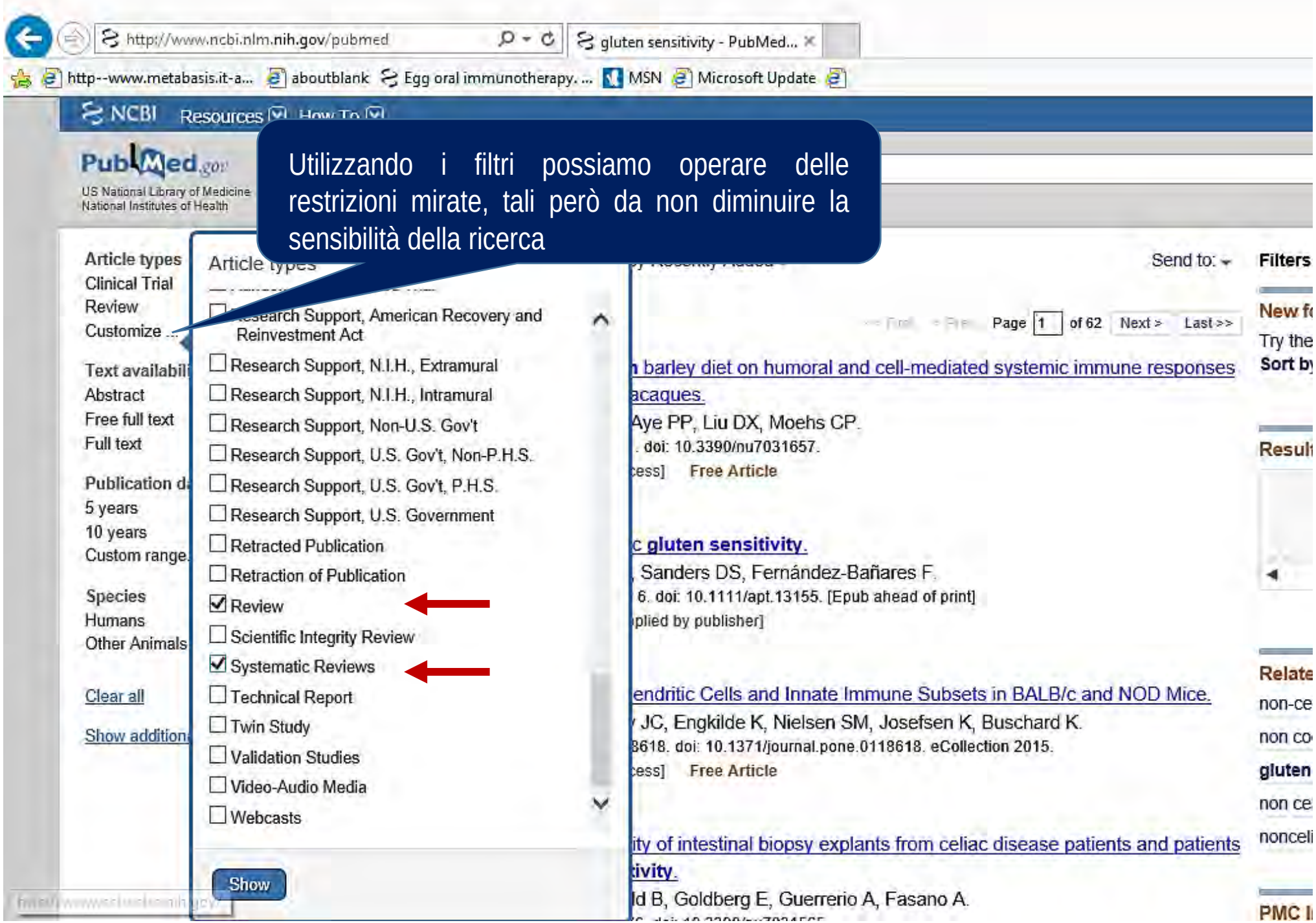
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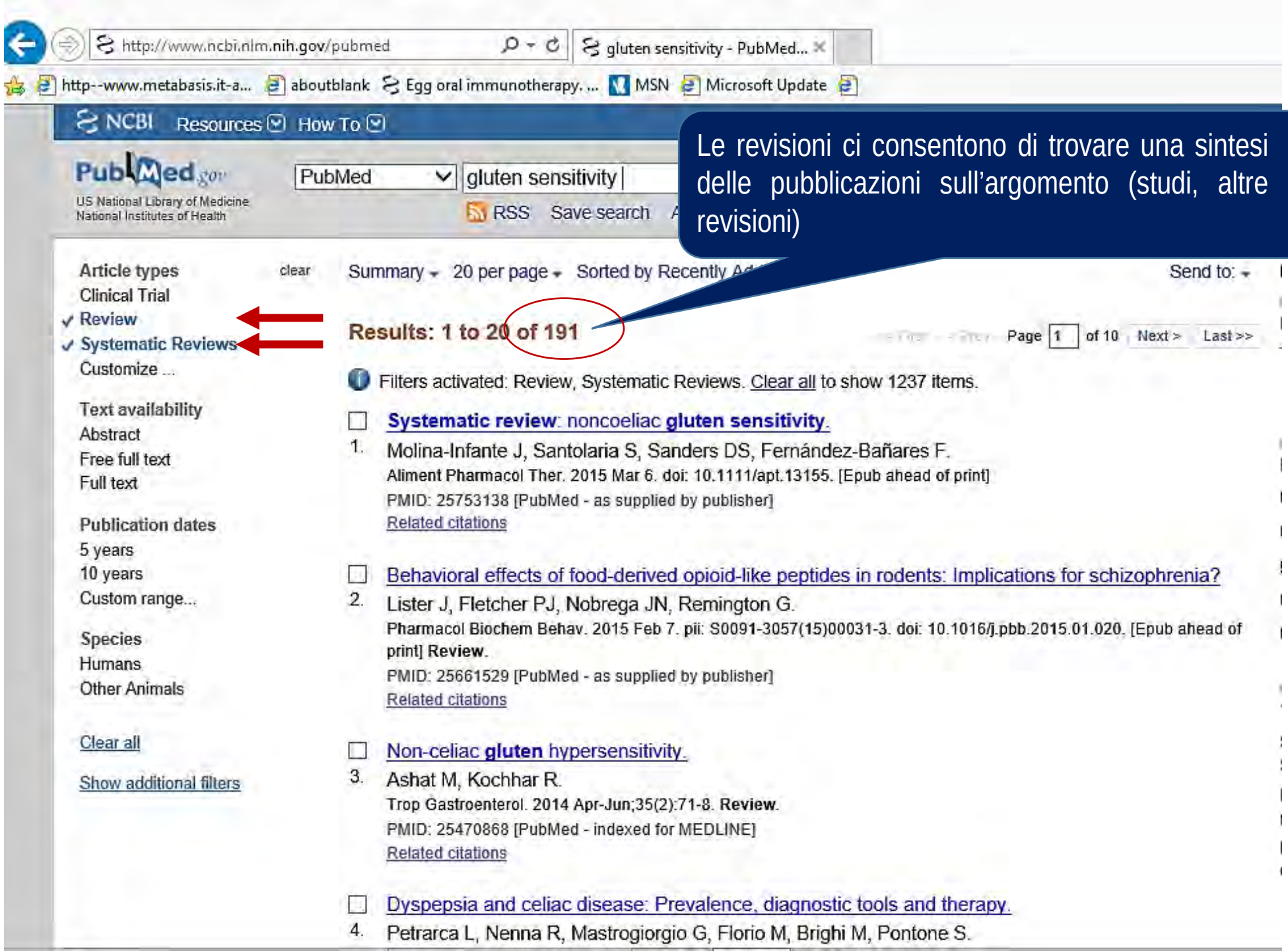
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Lister J, Fletcher PJ, Nobrega JN, Remington G.
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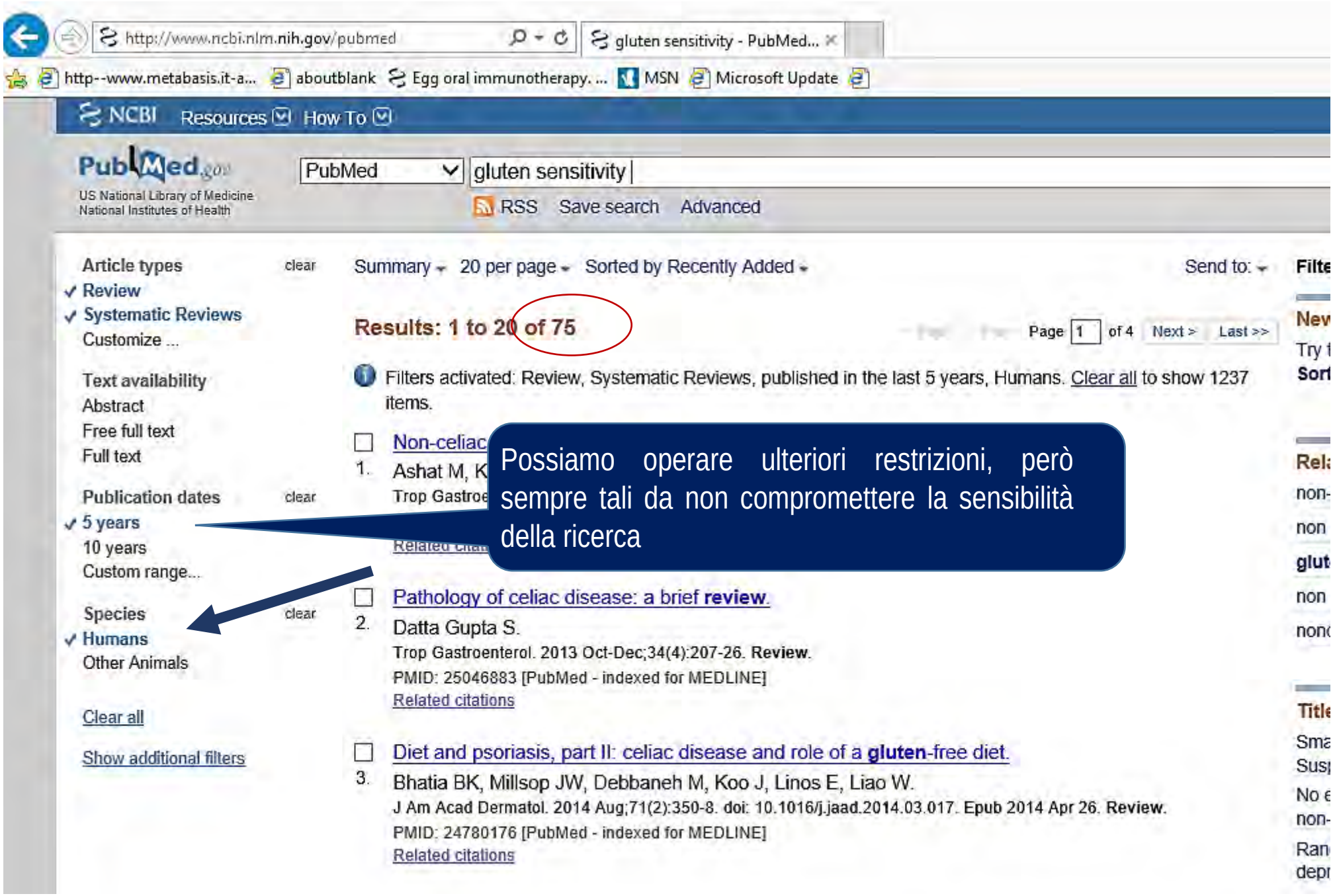
Petrarca L, Nenna R, Mastrogiorgio G, Florio M, Brighi M, Pontone S.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Pathology of celiac disease: a brief review.
2. Datta Gupta S.
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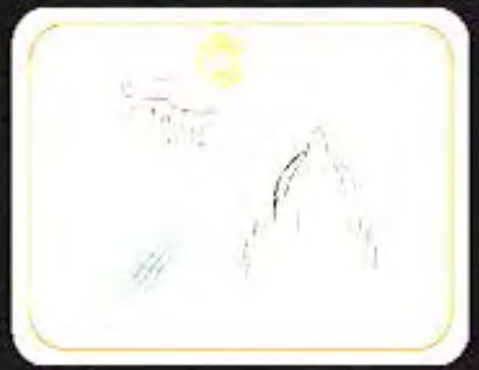
3. Bhatia BK, Millsop JW, Debbaneh M, Koo J, Linos E, Liao W.
J Am Acad Dermatol. 2014 Aug;71(2):350-8. doi: 10.1016/j.jaad.2014.03.017. Epub 2014 Apr 26. Review.
PMID: 24780176 [PubMed - indexed for MEDLINE]
Related citations

La ricerca di una revisione può essere fatta per aggiornare le nozioni di base, ma risulta particolarmente utile quando vogliamo rispondere ad uno specifico quesito con una sintesi delle relative evidenze

Qual è il rischio di contrarre un linfoma Non-Hodgkin in un paziente affetto da enteropatia gluten-sensitive?

Diari ver. 2.012

Nessun dorma



Roma, 25-27 Ottobre 2012

'O Fuori Corso (OFC)

APAL

Giovedì 25 Ottobre 2012, dalle 9 alle 13

Twitter sulla EBM

conduce Marina Macchiaiolo

Le domande imprescindibili e le risposte giuste per capire se uno studio clinico, una revisione sistematica, una linea guida vanno bene.
Sarete fulminati sulla Via della Pineta Sacchetti da

Marcello Bergamini, Giovanni Simeone, Maria Carmen Verga

MARCELLO BERGAMINI

Pediatra di Famiglia

Ferrara

25 Ottobre 2012

Revisioni Sistematiche: uno strumento necessario

Metanalisi: una risorsa potente … ma da prendere con le pinze

Io preferirei:

1. essere a conoscenza di **almeno 2** (o meglio ancora di più) studi che abbiano tentato di rispondere al mio quesito

2. prendendo in esame **quel tipo di intervento** (terapeutico o preventivo) o **quel tipo di fattore di rischio/prognostico**

3. magari stabilendo come **Indicatore d'Esito** proprio quello che interessa a me

Avrei bisogno allora di una sintesi delle migliori evidenze disponibili relative al mio preciso quesito clinico.

- Qualcun altro **si è già posto il Quesito** Clinico che mi interessa e …
- **ha fatto una completa (speriamo) revisione** della letteratura mirata alla sua risoluzione;
- **ha selezionato (speriamo) una popolazione analoga** a quella cui appartiene il mio paziente;
- **ha selezionato il tipo di disegno sperimentale più idoneo** ad indagare quel particolare aspetto (sicuramente meglio una serie di RCT ma, in loro mancanza, anche studi osservazionali di grandi dimensioni, possibilmente con stime dell'effetto importanti);
- **potrebbe aver selezionato, fra gli altri, proprio l'Indicatore d'Esito** la cui valutazione sperimentale mi aiuterebbe a risolvere il problema del mio paziente.

Qualcun altro, dunque, potrebbe aver fatto una Revisione (Review)

Ma come?? In maniera **narrativa?**

- **Quesiti:** Obiettivi molto ampi, generici. Non focalizzati

- **Fonti e strategie di ricerca**: non specificate >>> potenziale rischio di bias per ricerca non esaustiva

- **Selezione dei lavori**: Solitamente criteri non specificati >>> potenziale rischio di bias (es: preferenza per lavori che confermano le opinioni degli autori)

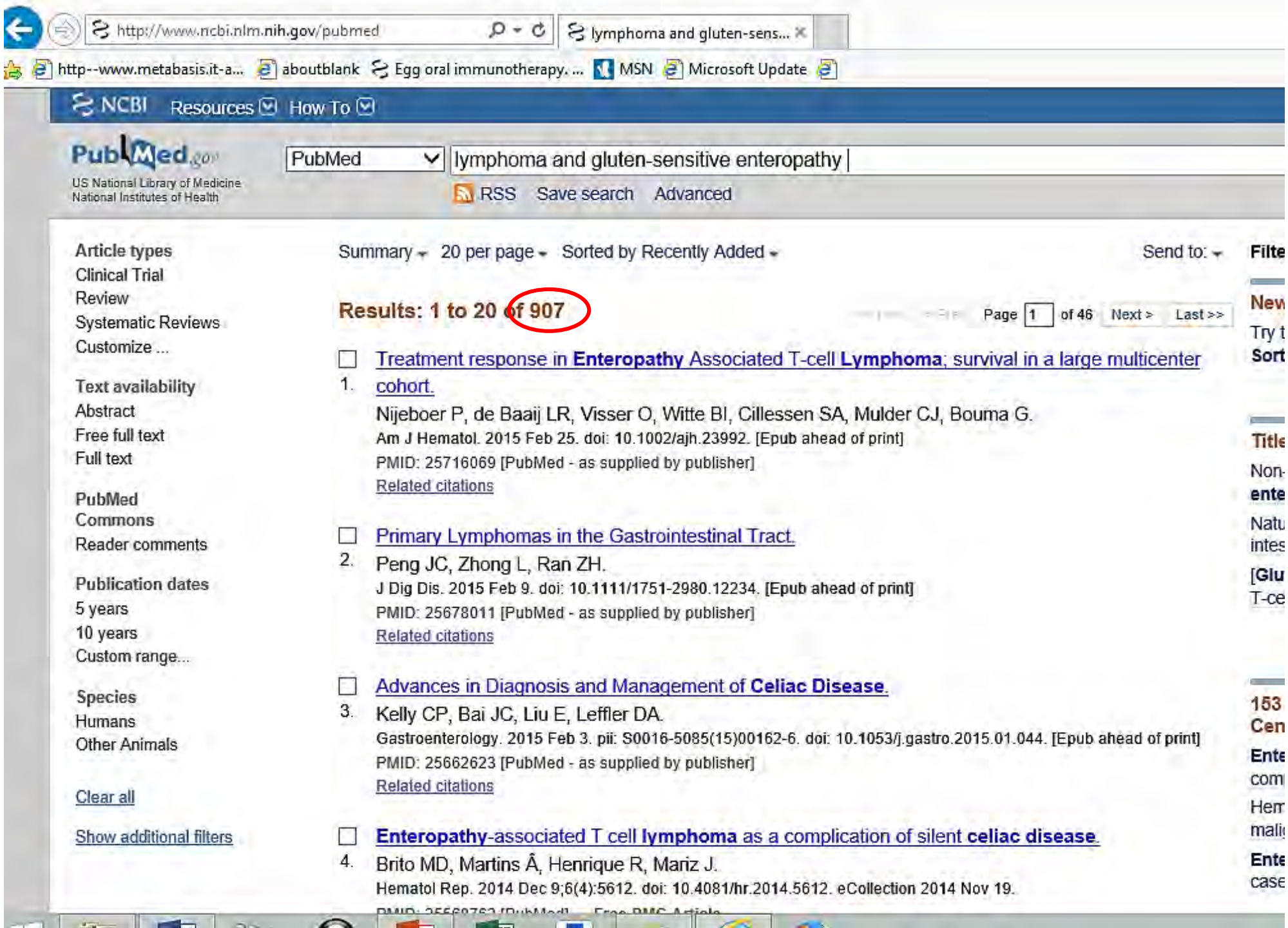
- **Valutazione della validità e della qualità** dei lavori: variabile

- **Sintesi**: Spesso solo qualitativa → descritti i risultati dei singoli lavori, nessun accorpamento dei dati

- **Conclusioni:** debole collegamento tra prove di efficacia e indicazioni per la clinica

La **Revisione Sistematica** invece **è:**

- una sintesi delle **migliori evidenze disponibili** relativamente a precisi **quesiti clinici**
- una vera **ricerca scientifica**
- come tale utilizza **metodologie esplicite** perché siano **riproducibili** (sistematicità)
- che **sintetizzano i risultati** degli studi originali
- minimizzando i **rischi di bias**
- fornisce dati su cui si possono basare **conclusioni (e decisioni)** meglio motivate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Nijeboer P, de Baaij LR, Visser O, Witte BI, Cillessen SA, Mulder CJ, Bouma G.
Am J Hematol. 2015 Feb 25. doi: 10.1002/ajh.23992. [Epub ahead of print]
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Peng JC, Zhong L, Ran ZH.
J Dig Dis. 2015 Feb 9. doi: 10.1111/1751-2980.12234. [Epub ahead of print]
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Kelly CP, Bai JC, Liu E, Leffler DA.
Gastroenterology. 2015 Feb 3. pii: S0016-5085(15)00162-6. doi: 10.1053/j.gastro.2015.01.044. [Epub ahead of print]
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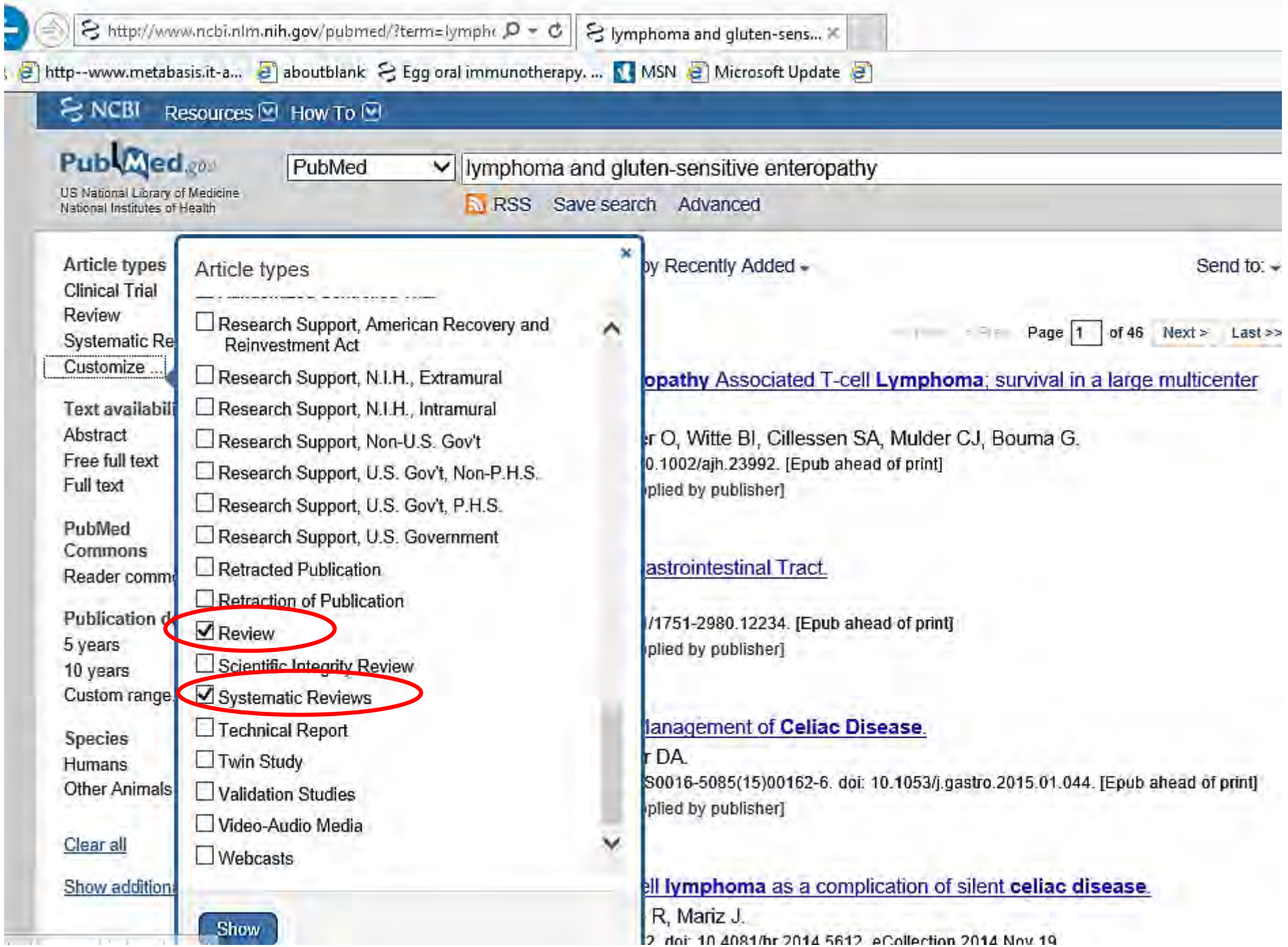
Brito MD, Martins Â, Henrique R, Mariz J.
Hematol Rep. 2014 Dec 9;6(4):5612. doi: 10.4081/hr.2014.5612. eCollection 2014 Nov 19.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REVISIONI E REVISIONI SISTEMATICHE

Gastroentérologie Clinique et Biologique (2010) 34, 590–605

CURRENT TREND

Enteropathy-associated T-cell lymphoma: A review on clinical presentation, diagnosis, therapeutic strategies and perspectives☆

Lymphomes T intestinaux associés à une entéropathie (maladie cœliaque et sprue réfractaire): présentation, diagnostic, prise en charge thérapeutique, pronostic et perspectives

M.-O. Chandesris[a], G. Malamut[b,c], V. Verkarre[c,d], B. Meresse[c],

Cancer Causes Control (2011) 22:1435–1444
DOI 10.1007/s10552-011-9818-4

ORIGINAL PAPER

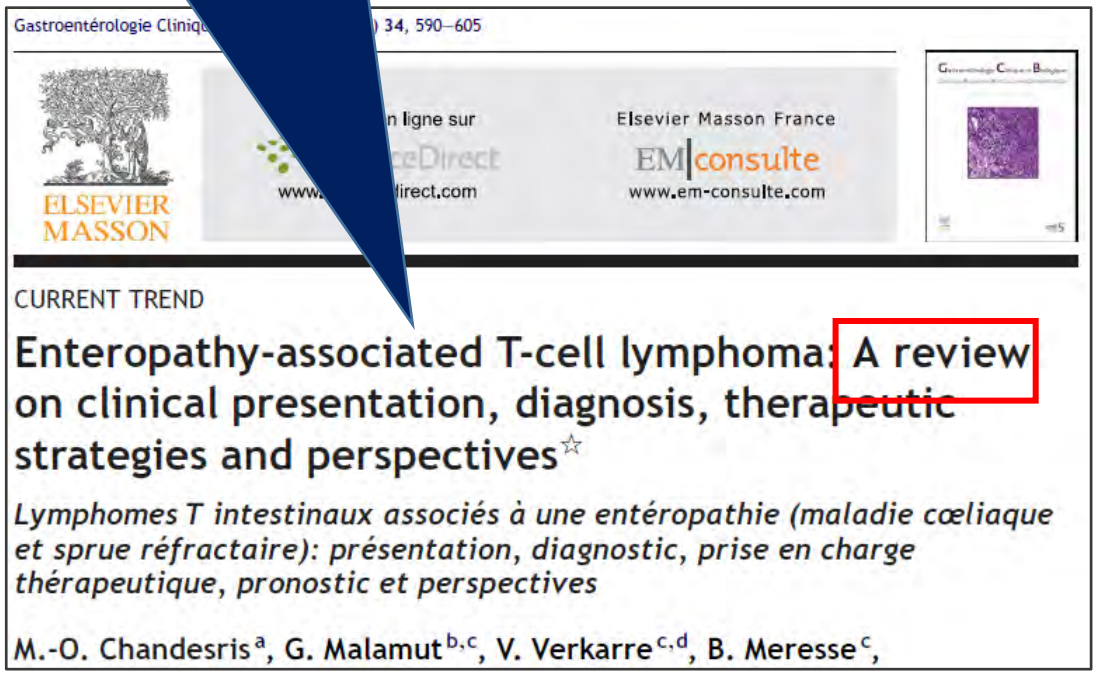
Non-Hodgkin lymphoma and gluten-sensitive enteropathy: estimate of risk using meta-analyses

Eleanor V. Kane · Rob Newton · Eve Roman

QUESITO

- **preciso**
- chiaramente **esplicitato** fin dall'inizio
- **clinico**
- rivolto alla valutazione delle **prove di efficacia**

Titolo generico: riporta i topics delle nozioni di base



Gastroentérologie Clinique) 34, 590–605

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CURRENT TREND

Enteropathy-associated T-cell lymphoma: A review on clinical presentation, diagnosis, therapeutic strategies and perspectives☆

Lymphomes T intestinaux associés à une entéropathie (maladie cœliaque et sprue réfractaire): présentation, diagnostic, prise en charge thérapeutique, pronostic et perspectives

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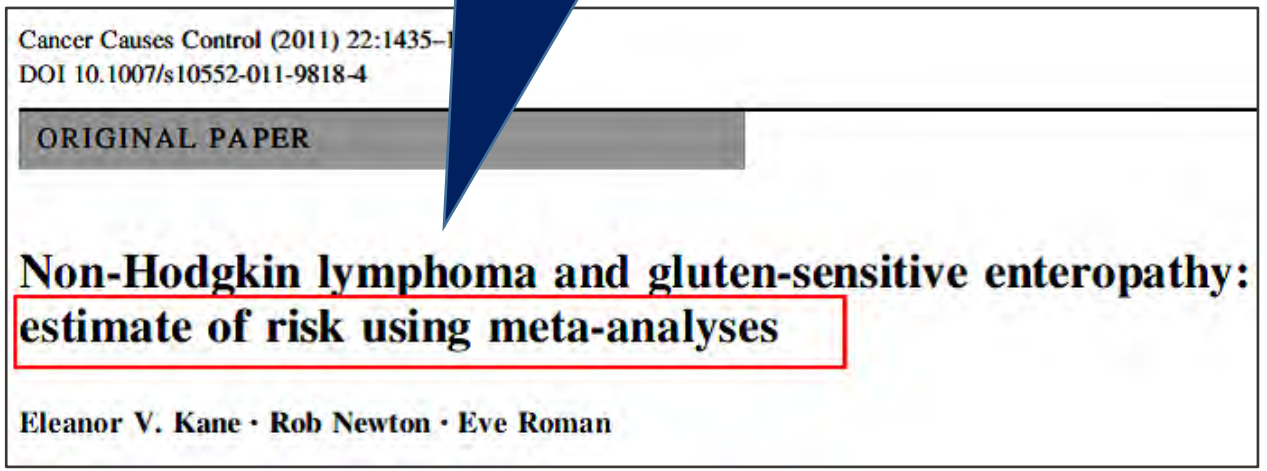
Titolo con specifico riferimento ad un quesito ed alle meta-analisi



Cancer Causes Control (2011) 22:1435–1

DOI 10.1007/s10552-011-9818-4

ORIGINAL PAPER

Non-Hodgkin lymphoma and gluten-sensitive enteropathy: estimate of risk using meta-analyses

Eleanor V. Kane · Rob Newton · Eve Roman

Objectives Gluten-sensitive enteropathy, including coeliac disease and dermatitis herpetiformis, is associated with non-Hodgkin lymphoma (NHL), and particularly enteropathy-associated T-cell lymphoma (EATCL). We conducted a meta-analysis to quantify the association.

The aim of this review, which is documented exclusively from a PubMed search, is to report on the published knowledge to date in the international literature with regard to pathophysiology, presentation, progression and especially therapeutic management by displaying the current results of CT and high-dose CT. EATL seems to distinctly

FONTI E STRATEGIE DI RICERCA

- Le fonti devono essere **multiple**, **esaustive**
- La strategia è **sistematica**
- La strategia è **esplicita**
- La strategia deve essere **riproducibile**

Più fonti, riportate parole chiave e restrizioni

The aim of this review, which is documented exclusively from a PubMed search, is to report on the published knowledge to date in the international literature with regard to pathophysiology, presentation, progression and especially therapeutic management by displaying the current results of CT and high-dose C[illegible] EATL seems to distinctly

Una sola fonte. Non sono riportate stringhe di ricerca e restrizioni

Methods

Articles were identified by searching Medline (1950–December 2010), PubMed (1865–December 2010), Web of Science (1899 to December 2010) and EMBASE (1980 to December 2010) using the keywords 'gluten-sensitive enteropathy', 'coeliac disease', 'dermatitis herpetiformis'; 'lymphoma', 'cancer', 'mortality', 'epidemiology', 'cohort' or 'case–control study'. To source additional papers, bibliographies of original and review publications were hand-searched, and studies of lymphoma and autoimmune conditions or medical histories were reviewed for relevant information. If the same study was reported more

Background

In 1855, Sir W. Gull made the first observation of a syndrome-like association between malabsorption and lymphoma [17]. Sometime later, in 1962, CD was found to be the cause of this malabsorption, carrying the risk of malignant transformation [18]. In 1978, the disease was defined as a "malignant histiocytosis of the intestine", with a histological description already very close to that currently used of infiltrating more or less stenosing and perforating involvement of the intestine by a polymorphic large cell NHL sometimes associating enteropathy) in the Revised European-American Lymphoma classification (REAL classification) [23–25]. Its origin in intraepithelial T-lymphocytes (IELs) of the intestinal mucosa was then recognised due to the HML1 immunostaining, currently named CD103, specifically distinguishing it from the other peripheral T-cell NHL [26]. EATL was only finally clearly identified later as part of the WHO classification of lymphomas in 2001. It was designated "enteropathy-type T-cell lymphoma" (ETCL), and then changed to the current designation of EATL in the more recent 2008 version [1,2,9,23,27]. It is in fact a separate T-cell NHL, as much in terms of its pathophysiology as in its progression and its prognosis.

More recently, refractory celiac disease (RCD) 2 was described as being a low-grade lymphoma restricted to the intraepithelial compartment that could be complicated by a more aggressive, more invasive and classic form of EATL [4,16,28]. Although the links of continuity between these transitional forms have now been well documented, it does not appear that RCD2 is an obligatory step.

Pathophysiology [29]

CD is a chronic inflammation of the small intestine secondary to gluten ingestion (wheat, rye, barley). The presence of

Nessun criterio esplicitato.
Nessun paragrafo sui metodi

SELEZIONE DEI LAVORI

- **Criteri di eligibilità definiti a priori**
- **Criteri di inclusione definiti a priori**
- **Criteri di esclusione definiti a priori**
- **Tutti i criteri vanno ESPLICITATI**

Eligibilità Inclusione Esclusione
Criteri riportati

papers, bibliographies of original and review publications were hand-searched, and studies of lymphoma and autoimmune conditions or medical histories were reviewed for relevant information. If the same study was reported more than once, the most recent publication was selected. Included studies reported relative risks of lymphoma following diagnosis of gluten-sensitive enteropathy with 95% confidence intervals or sufficient data to calculate these statistics. Where no cases were reported, risks were estimated by adding a half to each cell frequency. Non-English language articles and those reporting proportional risk estimates were excluded.

Initial searches identified 333 unique articles, and following review of titles and abstracts, 46 publications were

VALUTAZIONE DELLA QUALITA' DEI LAVORI

- **Critica**
- **Rigorosa**
- **Basata su metodi validati (Jadad score, «Assessment of Risk of Bias», altri)**

Valutati i criteri diagnostici ed i fattori di eterogeneità tra gli studi

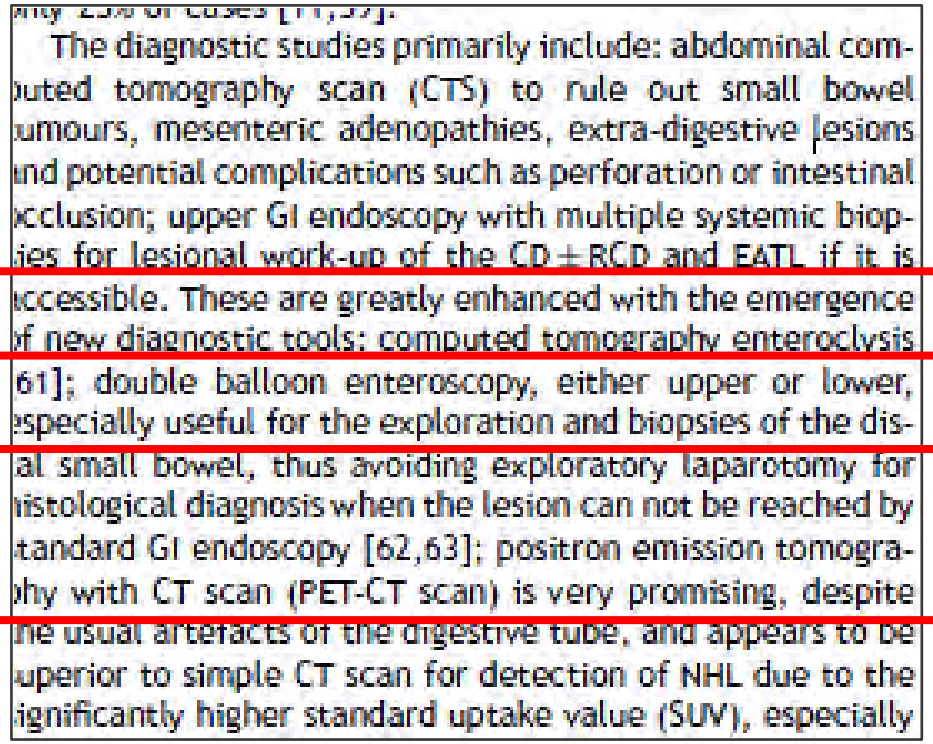
predictive intervals round the pooled risk estimate.

The meta-regression showed that risks were similar when diagnosis was by serology and biopsy, serology only or medical records (Supplementary Table 2). Compared to risks where diagnosis was by the current gold standard of serology then biopsy, biopsy only or diagnosis by a variety of methods or the method was unclear gave higher relative risks (relative risk estimate = 6.83, 95% CI 2.52–18.5; relative risk estimate = 3.79, 95% CI 1.22–11.7 respectively) while

One study was found to influence the heterogeneity where medical records were used [36], and another was the source of heterogeneity among studies where diagnostic methods were mixed or unclear [13] (Supplementary Table 3); no single study could explain heterogeneity in other strata including where diagnosis was by biopsy alone (data not shown). Removing these two studies gave pooled risks of around fourfold within their respective strata, comparable to pooled risks for serology alone or followed by biopsy. On this basis, the 31 studies using these four diagnostic methods were grouped for further analyses. The

SINTESI

- **Presentazione sistematica** dei risultati
- **Sintesi qualitativa** (in che direzione vanno i risultati di questo, quello e quell'altro lavoro, presi uno per uno?)
- **Sintesi «quantitativa»** attraverso le **METANALISI** (metodi statistico-matematici finalizzati ad accorpare correttamente i risultati di più lavori



The diagnostic studies primarily include: abdominal computed tomography scan (CTS) to rule out small bowel tumours, mesenteric adenopathies, extra-digestive lesions and potential complications such as perforation or intestinal occlusion; upper GI endoscopy with multiple systemic biopsies for lesional work-up of the CD ± RCD and EATL if it is accessible. These are greatly enhanced with the emergence of new diagnostic tools: computed tomography enteroclysis [61]; double balloon enteroscopy, either upper or lower, especially useful for the exploration and biopsies of the distal small bowel, thus avoiding exploratory laparotomy for histological diagnosis when the lesion can not be reached by standard GI endoscopy [62,63]; positron emission tomography with CT scan (PET-CT scan) is very promising, despite the usual artefacts of the digestive tube, and appears to be superior to simple CT scan for detection of NHL due to the significantly higher standard uptake value (SUV), especially

Among the homogeneous studies, five reported risks by sex [23, 25, 26, 31, 32]. Women with gluten-sensitive enteropathy were found to have similar risks of NHL to men (pooled risk estimate = 4.87, 95% CI 2.96–8.02, $I^2 = 4\%$, p(heterogeneity) = 0.39; pooled risk estimate = 4.43, 95% CI 2.91–6.74, $I^2 = 0\%$, p(heterogeneity) = 0.98, respectively). Where risks were estimated for gluten-sensitive enteropathy diagnosed more than a year before NHL [24, 25, 27, 32, 34], the pooled risk was similar (pooled risk estimate = 3.48, 95% CI 2.33–5.20, $I^2 = 35\%$, p(heterogeneity) = 0.19) to when data were not lagged (pooled risk estimate = 4.46, 95% 3.46–5.77, $I^2 = 0\%$, p(heterogeneity) = 0.94). Longer time periods

Nel momento cruciale della sintesi dei risultati dei singoli studi, la Revisione Sistematica ***può*** contenere una o più Metanalisi

Metanalisi = l'uso di metodi statistici per sommare fra loro, attraverso il cumulo dei pazienti provenienti da studi indipendenti, i risultati relativi ad un singolo outcome.

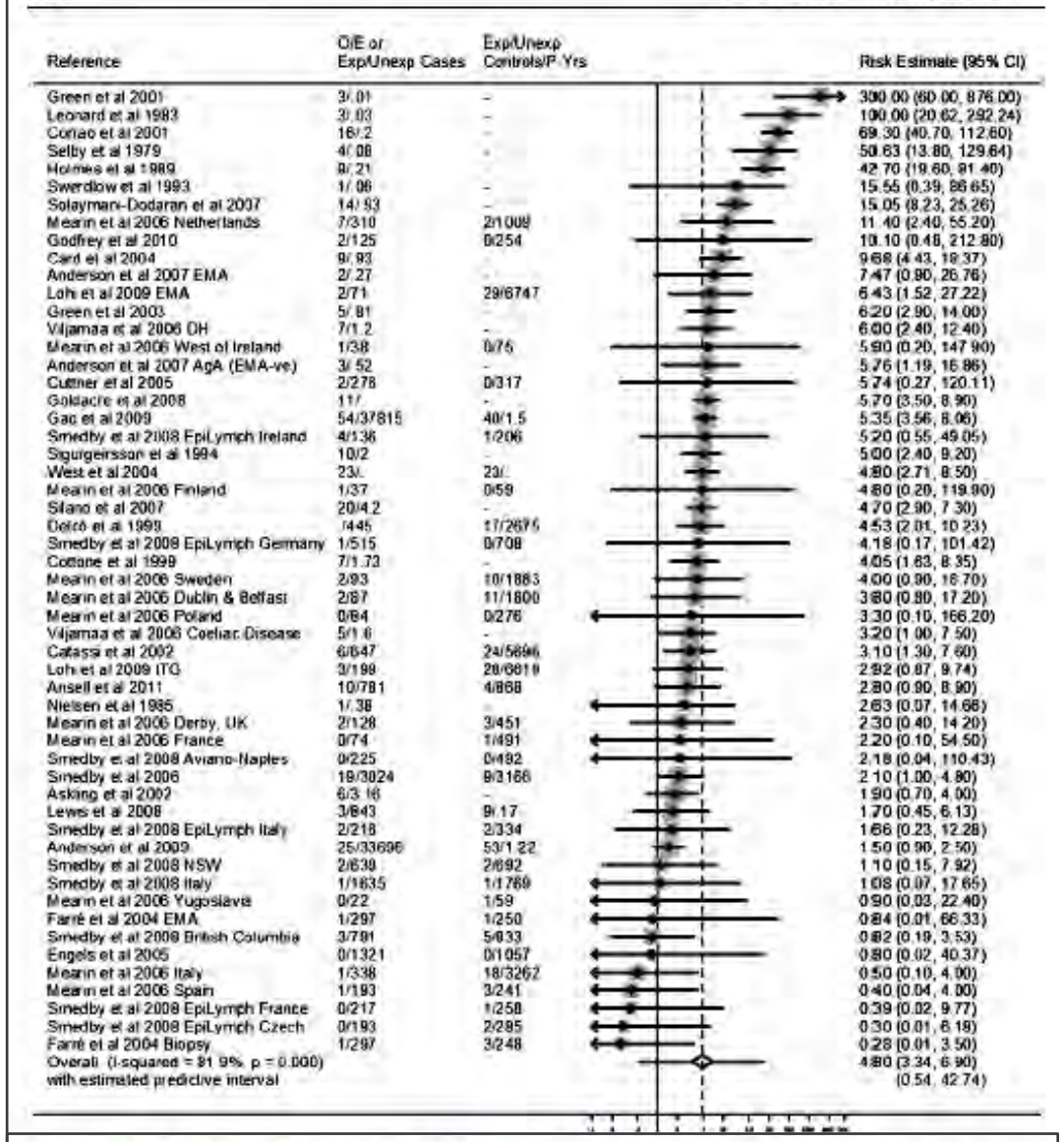


Fig. 1 Risks of non-Hodgkin lymphoma associated with gluten-sensitive enteropathy. Frequencies are observed (O) and expected (E) cases of non-Hodgkin lymphoma in cohort studies [11–17, 19–22, 24, 26, 28, 30, 33, 34]; observed cases of non-Hodgkin lymphoma and

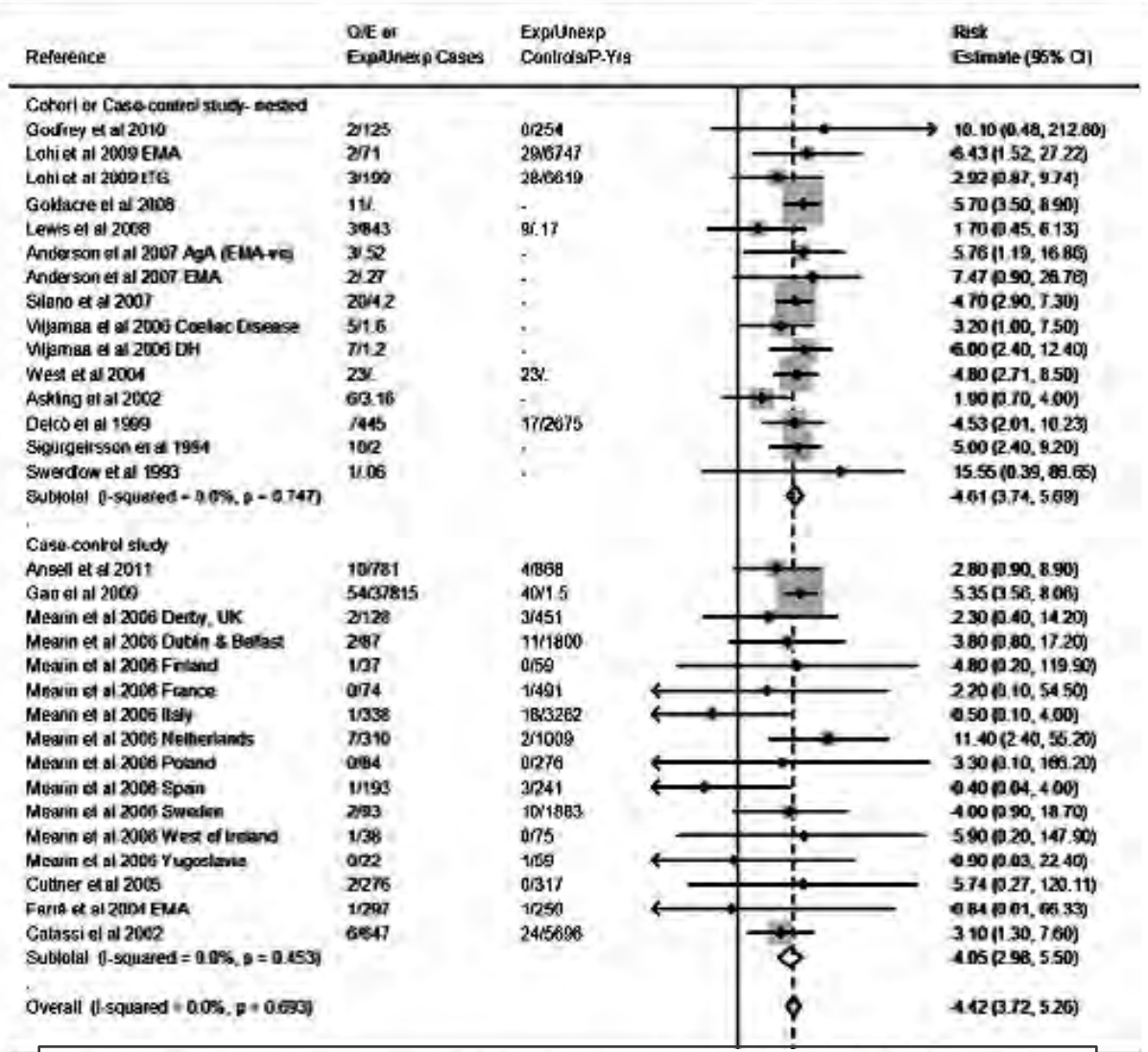
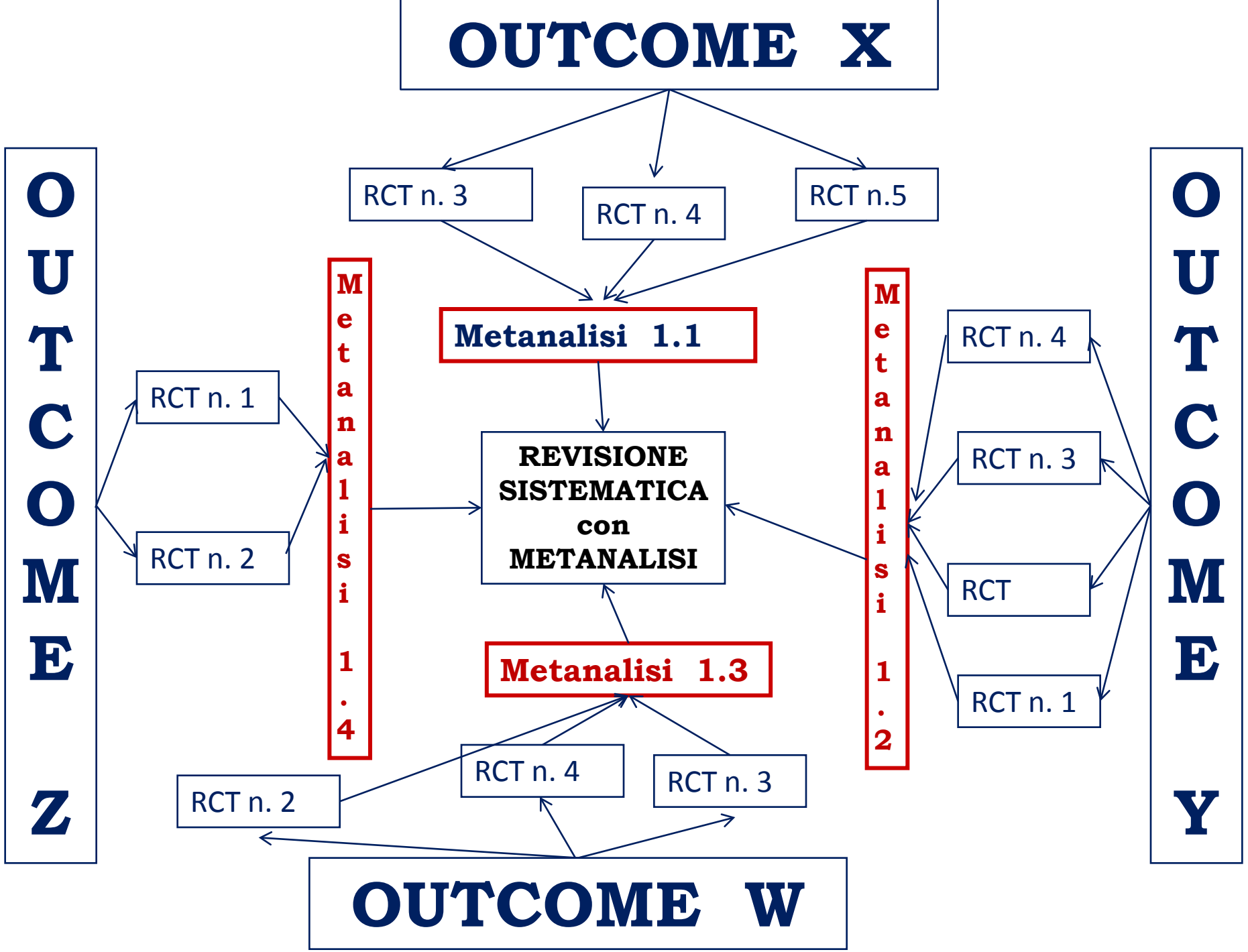


Fig. 2 Risks of non-Hodgkin lymphoma associated with gluten-sensitive enteropathy in studies where gluten-sensitive enteropathy was diagnosed using serology followed by biopsy; serology only; was noted in medical records or diagnostic methods were mixed or unclear. Frequencies are observed (O) and expected (E) cases of non-


OUTCOME X
RCT n. 3
RCT n. 4
RCT n.5
Metanalisi 1.1
OUTCOME Z
RCT n. 1
RCT n. 2
Metanalisi 1.4
REVISIONE SISTEMATICA con METANALISI
Metanalisi 1.3
RCT n. 2
RCT n. 4
RCT n. 3
Metanalisi 1.2
RCT n. 4
RCT n. 3
RCT
RCT n. 1
OUTCOME Y
OUTCOME W

La Metanalisi

- permette di chiarire meglio la **forza dell'associazione** fra l'intervento e le modificazioni dell'outcome nei vari gruppi

- permette di chiarire in modo definitivo la **direzione di tale associazione**

- permette di ottenere **stime più precise** degli effetti delle cure, rispetto a quelle derivate dagli studi individuali inclusi

- facilita le valutazioni sulla **"consistenza" delle prove di efficacia** fra i vari studi

- consente di esplorare le **differenze fra gli studi**

Quali misure utilizzano le Metanalisi?

VARIABILI DICOTOMICHE

- **Rischio Relativo** o Risk Ratio **(RR)** … la più frequente
- Rapporto fra gli Odds (probabilità) o **Odds Ratio(OR)**
- Risk Difference e il suo reciproco, il **Number Needed to Treat (NNT),** il meno frequente >>> **PERCHE'?**

Misure inserite nei Forest Plot

VARIABILI CONTINUE

- Differenze Medie **(MD)**
- Differenze Medie Pesate **(WMD)**
- Differenze Medie Standardizzate **(SMD)**

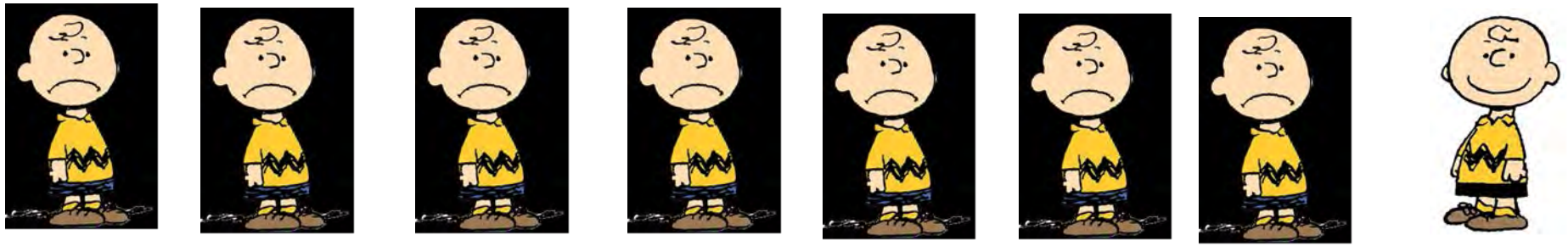
Number Needed to Treat (NNT)

E’ il N° di pazienti da trattare affinchè 1 solo ne tragga beneficio, cioè affinchè ci sia 1 successo.

Minore è il NNT, maggiore è l’efficacia del trattamento. E viceversa.

Es. 1 NNT = 3

Es. 2 NNT = 8



Rischio Relativo (RR)

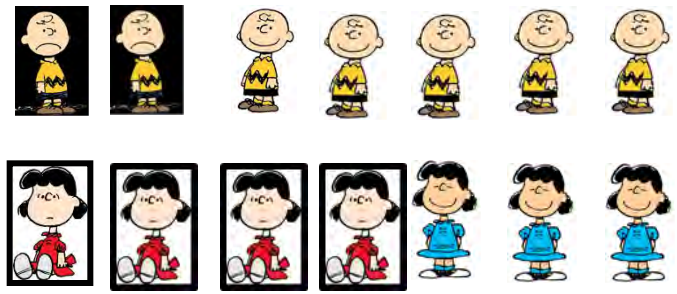
Il Rischio (o Rischio assoluto) è la probabilità che si verifichi l'evento (sviluppo della malattia) in un determinato periodo di tempo. Esso corrisponde all' *Incidenza*

Più è lungo il periodo di osservazione, più il rischio aumenta.

In genere, ma non sempre, viene utilizzato per patologie a breve periodo di latenza (es. malattie infettive).

Il Rischio Relativo (RR) valuta:

- in un RCT: il rischio del verificarsi dell'evento (es. contrarre la malattia) tra i trattati ed i controlli il rapporto tra n° di casi nei trattati e n° di casi nei controlli, nel periodo di osservazione dello studio



$$= \frac{2/7}{4/7} = \frac{0.3}{0.6} = \frac{30\%}{60\%} \qquad RR = 0.5$$

- In uno studio prospettico osservazionale: il rischio del verificarsi dell'evento (es. contrarre la malattia) tra gli esposti ed i controlli Il rapporto tra n° di casi negli esposti e n° di casi nei controlli, nel periodo di osservazione dello studio.

ES. N° casi esposti (sul N° totale e nel periodo considerato) = 20/67 = 0.30 = 30%

N° casi non esposti (sul N° totale e nel periodo considerato) = 9/72 = 0.12 = 12%

RR = 30/12 = 2.5

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E. **Vaccines for preventing influenza in healthy children**. *Cochrane Database of Systematic Reviews* 2012, Issue 8.

Vaccines for preventing influenza in healthy children (Review)

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E

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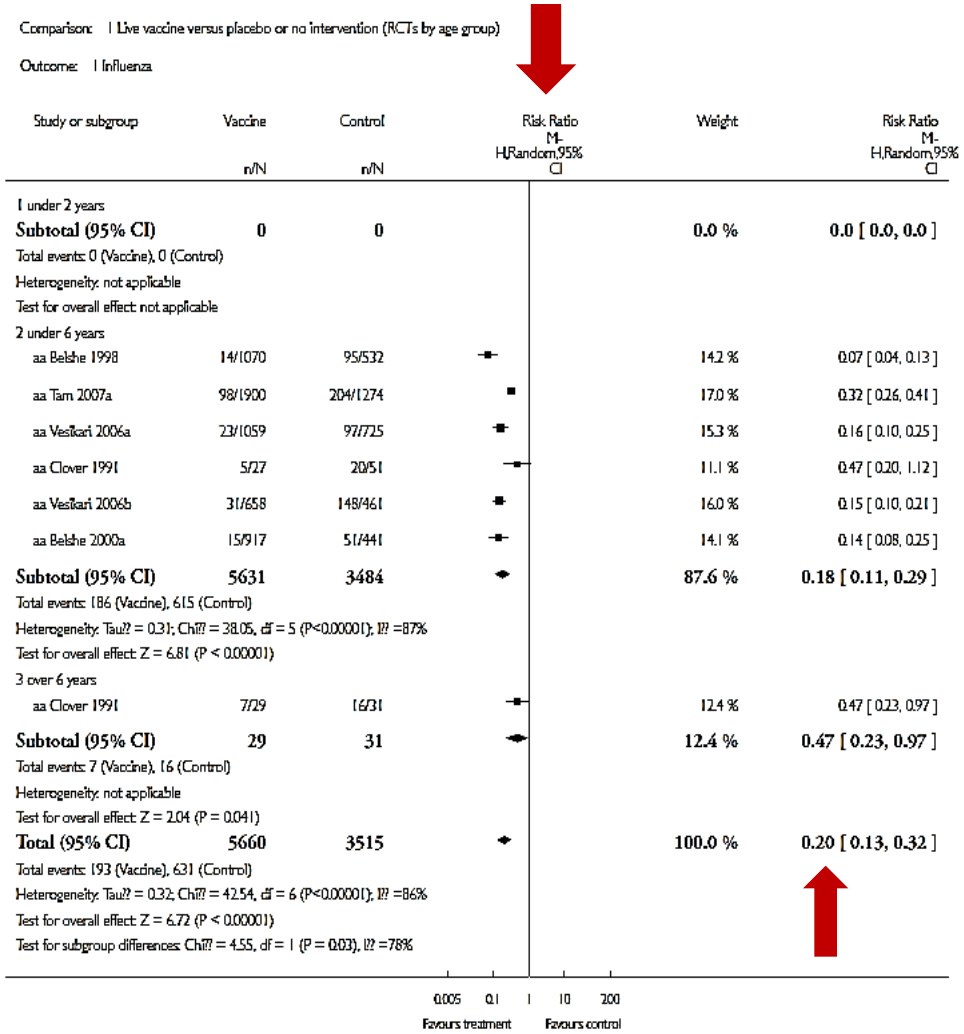
Comparison 01 (Analysis 1.1, evidence from RCTs) shows that live attenuated vaccines have **80% overall efficacy (RR 0.20; 95% CI 0.13 to 0.32)**

Analysis 1.1. Comparison 1 Live vaccine versus placebo or no intervention (RCTs by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 1 Live vaccine versus placebo or no intervention (RCTs by age group)

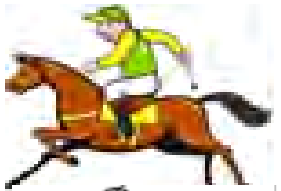
Outcome: 1 Influenza



Odds e Odds Ratio (OR)

Odds è un termine molto in uso nel mondo delle scommesse.

E' il rapporto tra la probabilità che si verifichi l'evento (sviluppo della malattia) e la probabilità che l'evento non si verifichi.



La malattia di Exposed è data 9:1 (l'Odds è 9:1)

Exposed ha 9/10 possibilità di ammalarsi e 1 /10 di non ammalarsi

La malattia di Control è data 3:7 (l'Odds è 3:7)

Control ha 3/10 possibilità di ammalarsi e 7 /10 di non ammalarsi

L'Odds Ratio è il rapporto tra l'odds degli esposti e l'odds dei controlli

Definisce **la forza dell'associazione o la non-indipendenza tra 2 dati binari** (es. successo/insuccesso), non randomizzati (negli studi osservazionali **non prospettici**) o randomizzati (nelle metanalisi delle RS)

= 9:1 = 9 = 22.5

3:7 0.4

L'Odds Ratio degli esposti è 22.5, cioè gli esposti hanno un rischio 22,5 volte maggiore di sviluppare la malattia rispetto ai non esposti

Differenza tra rischio e odds

Il Rischio è il n° di casi sul totale in un determinato periodo di tempo. E' un'incidenza ed aumenta in proporzione alla lunghezza dell'intervallo temporale. Si valuta negli studi prospettici in rapporto alla lunghezza dello studio.

RA degli esposti (in un anno)= 9/10
RA dei controlli = 3/10

L'Odds è una proporzione che, in quanto tale, rimane costante. Si valuta negli studi retrospettivi, a posteriori.

Odds degli esposti = 9:1

Exposed ha 9/10 possibilità di ammalarsi e 1 /10 di non ammalarsi

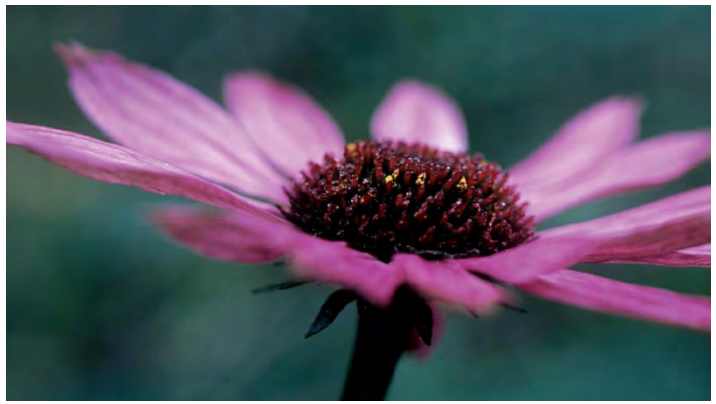
Odds dei controlli =3:7

Control ha 3/10 possibilità di ammalarsi e 7 /10 di non ammalarsi

Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis

Sachin A Shah, Stephen Sander, C Michael White, Mike Rinaldi, Craig I Coleman

Lancet Infect Dis 2007; 7: 473–80



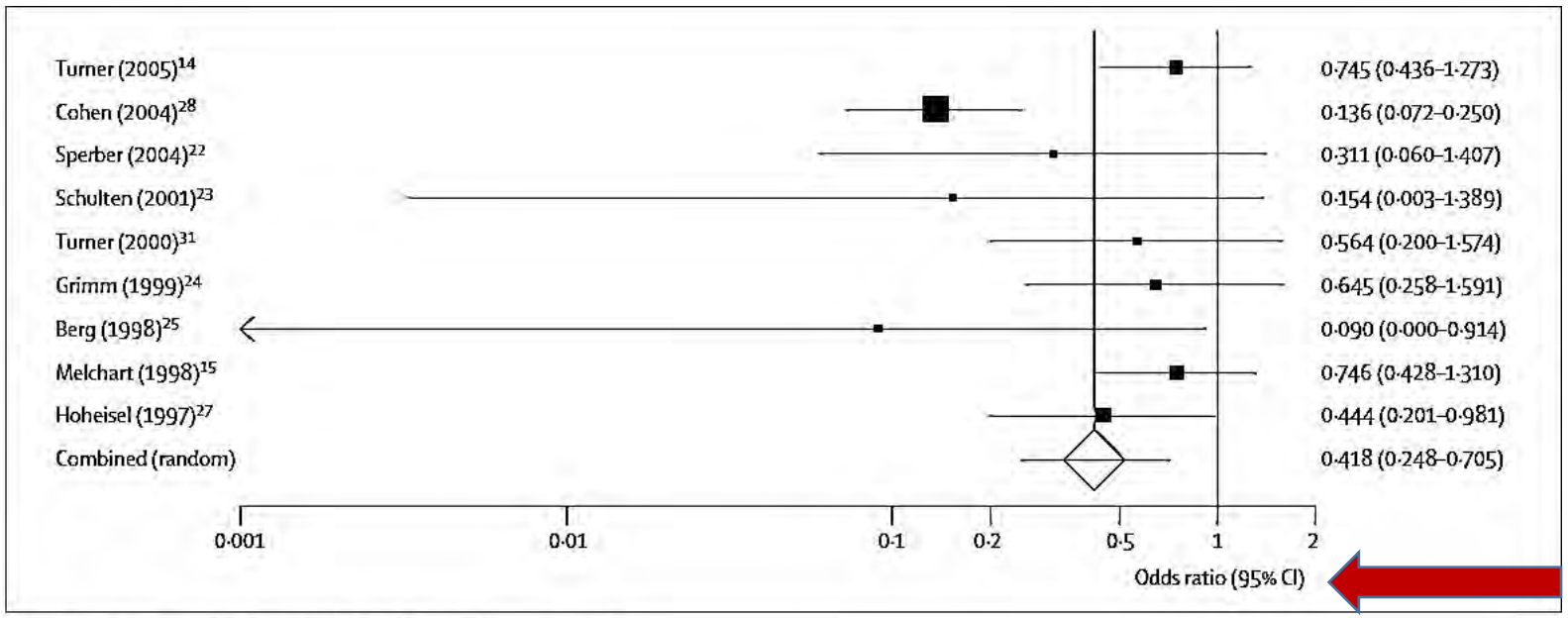


Figure 3: The effect of echinacea on incidence of common cold

Differenze Medie (MD)

La Media (aritmetica) è facile…

Studio	1		2		3	
Intervento (fisiologica o ipertonica)	3%	0.9%	3%	0.9%	3%	0.9%
N° pazienti	27	25	21	20	47	49
Variabile considerata (Indicatore d'esito)	Giorni di ricovero					
Scala o unità di misura della variabile	N° ↔					
Medie aritmetiche nei singoli gruppi	3	4	2.6	3.5	2.6	3.5
Differenza delle medie (MD)	-1		-0.9		-0-9	

Nebulized hypertonic saline solution for acute bronchiolitis in infants (Review)

Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP

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Zhang L, Mendoza-Sassi RA, Wainwright C, Klassen TP. **Nebulized hypertonic saline solution for acute bronchiolitis in infants.** *Cochrane Database of Systematic Reviews* 2008, Issue 4.

Mean Difference >>>>
il metodo di misurazione è **unico** = numero di giorni di degenza, con relativi decimali

Analysis 1.1. Comparison 1 3% saline versus 0.9% saline, Outcome 1 Length of hospital stay (days).

Review: Nebulized hypertonic saline solution for acute bronchiolitis in infants

Comparison: 1 3% saline versus 0.9% saline

Outcome: 1 Length of hospital stay (days)

Study or subgroup	3% saline N	Mean(SD)	0.9% saline N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Mandelberg 2003	27	3 (1.2)	25	4 (1.9)		38.1 %	-1.00 [-1.87, -0.13]
Tal 2006	21	2.6 (1.4)	20	3.5 (1.7)		31.6 %	-0.90 [-1.86, 0.06]
Kuzik 2007	47	2.6 (1.9)	49	3.5 (2.9)		30.3 %	-0.90 [-1.88, 0.08]
Total (95% CI)	**95**		**94**			**100.0 %**	**-0.94 [-1.48, -0.40]**

Heterogeneity: Chi² = 0.03, df = 2 (P = 0.98); I² =0.0%

Test for overall effect: Z = 3.42 (P = 0.00063)

-4 -2 0 2 4

Favors 3% saline Favors 0.9% saline

Differenze Medie Pesate (WMD)

ma che cos'è la **Media Pesata?**

Minore è la varianza, maggiore è la precisione della stima, più lo studio «pesa»

Studio	1		2		3		4	
Intervento	Alarm	Control	Alarm	Control	Alarm	Control	Alarm	Control
Variabile considerata	Notti bagnate/settimana							
Scala o unità di misura della variabile	N°							
Medie aritmetiche nei singoli gruppi (DS)	1 (1.95)	5.15 (1.50)	1.69 (2.28)	4.06 (1.63)	3.25 (2.67)	5.00 (2.26)	0.41 (1.76)	5.74 (3.00)
Peso dello studio	24.5		37.8		16.2		21.5	
Differenza delle medie (MD)	(4,15 + 2,37 + 1,75 + 5,33) /4 = 3.4							
Differenza delle medie pesate	(4.15*0.245) + (2.37*0.378) + (1.75*0.162) +(5.33*0.215) = 3.34							

Alarm interventions for nocturnal enuresis in children (Review)

Glazener CMA, Evans JHC, Peto RE

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Glazener CMA, Evans JHC, Peto RE. **Alarm interventions for nocturnal enuresis in children**. *Cochrane Database of Systematic Reviews* 2005, Issue 2.

WMD: il peso dato ad ogni studio è uguale all'inverso della Varianza (precisione della stima)

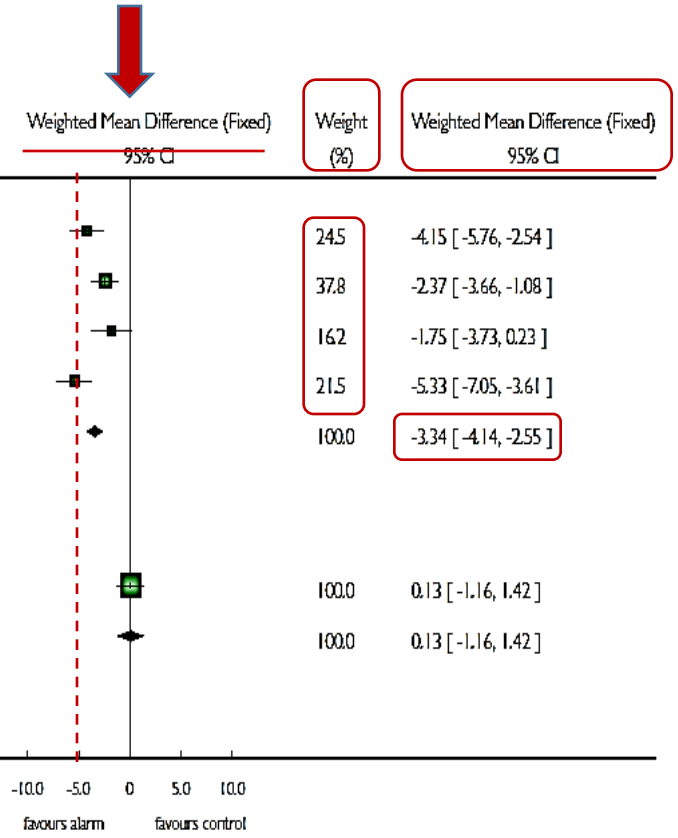
Analysis 01.01. Comparison 01 ALARM vs CONTROL, Outcome 01 Mean number of wet nights per week

Review: Alarm interventions for nocturnal enuresis in children

Comparison: 01 ALARM vs CONTROL

Outcome: 01 Mean number of wet nights per week

Study	alarm N	alarm Mean(SD)	augmented alarm N	augmented alarm Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 alarm vs control							
Bennett 1985	9	1.00 (1.95)	9	5.15 (1.50)		24.5	-4.15 [-5.76, -2.54]
Lynch 1984	18	1.69 (2.28)	18	4.06 (1.63)		37.8	-2.37 [-3.66, -1.08]
Nawaz 2002	12	3.25 (2.67)	12	5.00 (2.26)		16.2	-1.75 [-3.73, 0.23]
Ronen 1992	15	0.41 (1.76)	16	5.74 (3.00)		21.5	-5.33 [-7.05, -3.61]
Subtotal (95% CI)	54		55			100.0	-3.34 [-4.14, -2.55]
Test for heterogeneity chi-square=10.76 df=3 p=0.01 I? =72.1%							
Test for overall effect z=8.23 p<0.00001							
02 delayed alarm vs control							
Lynch 1984	18	4.19 (2.28)	18	4.06 (1.63)		100.0	0.13 [-1.16, 1.42]
Subtotal (95% CI)	18		18			100.0	0.13 [-1.16, 1.42]
Test for heterogeneity: not applicable							
Test for overall effect z=0.20 p=0.8							



Differenze Medie Standardizzate (SMD)

… e la Media Standardizzata?

Se negli studi sono stati adottati sistemi diversi per misurare l'outcome, prima di aggregare i risultati è necessario «standardizzarli» in un'unica scala.

Non sempre è possibile.

Studio	1		2		3	
Intervento	< Der. pt	Control	< Der. pt	Control	< Der. pt	Control
Variabile considerata	Score sintomi asma					
Scala o unità di misura della variabile	Diversi, negli studi					
Medie aritmetiche nei singoli gruppi	1.6	1.4	1.1	0.4	1.4	1.18
Differenza delle medie (MD)	0.2		0.7		0.22	
Differenza Medie Standardizzate	0.13		0.56		0.24	

Gøtzsche PC, Johansen HK

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Gøtzsche PC, Johansen HK. **House dust mite control measures for asthma**. *Cochrane Database of Systematic Reviews* 2008, Issue 2.

Standardized Mean Difference >>>> sistemi diversi di misurazione dell'Outcome

Analysis 1.2. Comparison 1 House dust mite reduction versus control, Outcome 2 Asthma symptoms score.

Review: House dust mite control measures for asthma

Comparison: 1 House dust mite reduction versus control

Outcome: 2 Asthma symptoms score

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Chemical methods							
Bahir 1997	13	1.6 (1.5)	17	1.4 (1.5)		2.0 %	0.13 [-0.59, 0.85]
Chang 1996	12	1.1 (1.7)	14	0.4 (0.5)		1.7 %	0.56 [-0.23, 1.35]
Dietemann 1993	11	1.4 (1.24)	12	1.18 (0.36)		1.6 %	0.24 [-0.58, 1.06]
Reiser 1990	23	5.5 (4.3)	23	3.3 (3.5)		3.0 %	0.55 [-0.04, 1.14]
Subtotal (95% CI)	**59**		**66**			**8.3 %**	**0.39 [0.04, 0.75]**

Heterogeneity: Chi^2 = 1.10, df = 3 (P = 0.78); I^2 =0.0%

Test for overall effect: Z = 2.16 (P = 0.031)

2 Physical methods - parallel-group studies

-4 -2 0 2 4

Favours treatment Favours control

La Metanalisi:

- permette di chiarire meglio la **forza dell'associazione** fra l'intervento e le modificazioni dell'outcome nei vari gruppi

- permette di chiarire in modo definitivo la **direzione di tale associazione**

- permette di ottenere **stime più precise** degli effetti delle cure, rispetto a quelle derivate dagli studi individuali inclusi

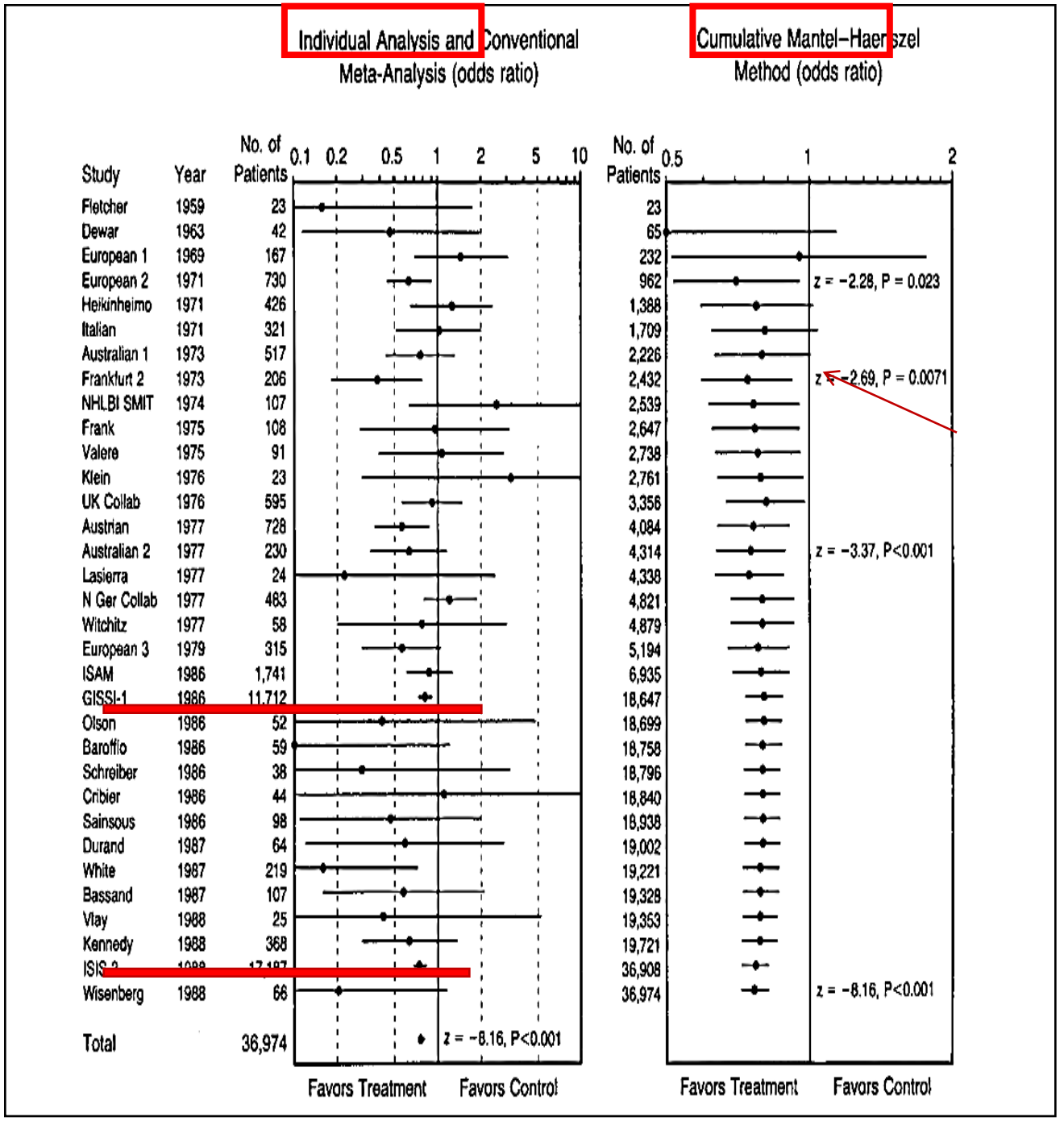
CUMULATIVE META-ANALYSIS OF THERAPEUTIC TRIALS FOR MYOCARDIAL INFARCTION

JOSEPH LAU, M.D., ELLIOTT M. ANTMAN, M.D., JEANETTE JIMENEZ-SILVA, M.D., BRUCE KUPELNICK, B.A., FREDERICK MOSTELLER, PH.D., AND THOMAS C. CHALMERS, M.D.

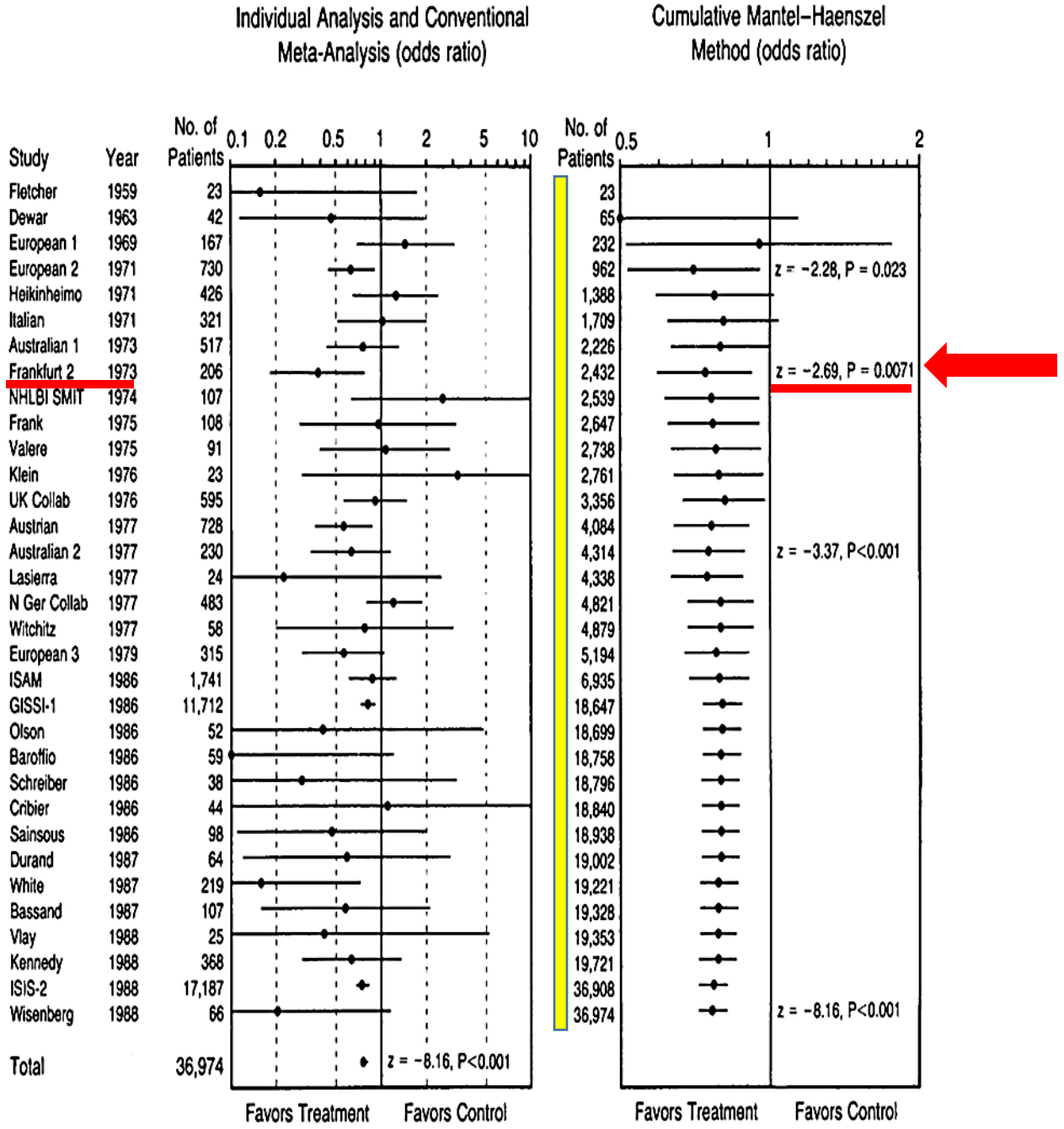
Metanalisi sull'efficacia preventiva della **Terapia Trombolitica** sull'evento **«morte»**

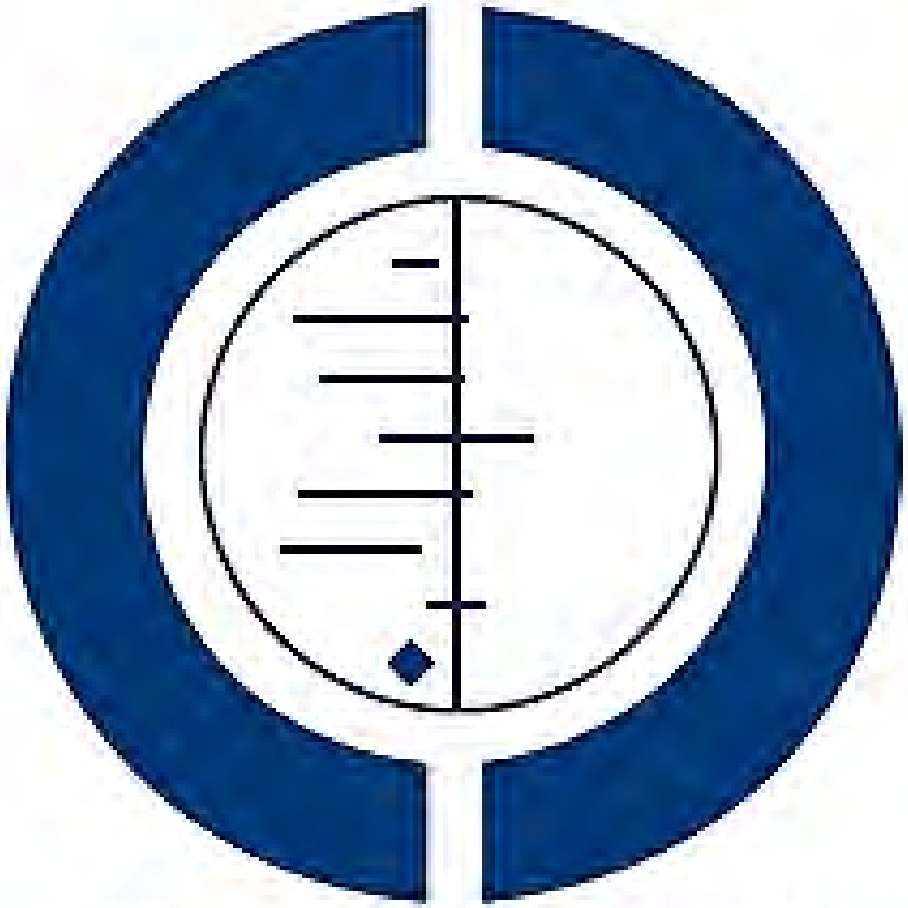
Risultati dei singoli studi anno dopo anno >>>

Solo 2 Big Trials (1986 e 1988 mostrarono risultati SS con IC molto ristretti



Risultati SS (P < 0.001) già nel 1973, 13 anni prima del primo Big Trial!





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CONCLUSIONI della RS (e discussione)

- Devono **rispondere,** se possibile, al/i quesito/i iniziale/i
- Devono considerare i difetti della RS stessa (le cosiddette **limitazioni**)
- Devono occuparsi della eventuale **trasferibilità** dei risultati

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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 Tetzlaff[1], Douglas G. Altman[5], The PRISMA Group[¶]

Guidelines and Guidance

The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of Studies That Evaluate Health Care Interventions: Explanation and Elaboration

Alessandro Liberati[1,2*], Douglas G. Altman[3], Jennifer Tetzlaff[4], Cynthia Mulrow[5], Peter C. Gøtzsche[6], John P. A. Ioannidis[7], Mike Clarke[8,9], P. J. Devereaux[10], Jos Kleijnen[11,12], David Moher[4,13]

Check-list per la conduzione e l'esposizione di una Revisione Sistematica o di una Metanalisi

27 items

Cochrane Handbook for Systematic Reviews of Interventions

Version 5.1.0

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Editors: Julian PT Higgins and Sally Green

Come si possono valutare le Revisioni Sistematiche?

BMC Medical Research Methodology

BioMed Central

Research article

Open Access

Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews

Beverley J Shea*[1,5], Jeremy M Grimshaw†[2], George A Wells[3], Maarten Boers†[4], Neil Andersson[5], Candyce Hamel†[5], Ashley C Porter[5], Peter Tugwell[2], David Moher[6] and Lex M Bouter†[1]

11 ESPERTI

Table 1: Items identified through the factor analysis

	Original Instrument (Item no)	1	2	3	4	5	6	7	8	9	10	11
1 Protocol	Sacks	.58										
2 Literature Search	Sacks				.82							
3 List of Trials Analyzed	Sacks		.75									
4 Log of Rejected Trials	Sacks								.68			
5 Treatment Assignment	Sacks		.80									
6 Ranges of Patients	Sacks											
7 Ranges of Treatment	Sacks		.88									
8 Ranges of Diagnosis	Sacks		.80									
9 Combinability Criteria	Sacks									.88		
10 Measurement	Sacks				.57							
11 Selection Bias	Sacks	.85										
12 Data abstraction	Sacks	.50										
13 Inter-observer Agreement	Sacks	.65										
14 Sources of Support	Sacks								.64			
15 Statistical Methods	Sacks			.81								
16. Statistical Errors	Sacks											
17 Confidence Intervals	Sacks			.73								
18 Subgroup Analysis	Sacks											
19 Quality Assessment	Sacks					.77						
20 Varying Methods	Sacks					.63						
21 Publication Bias 1	Sacks						.77					
22 Caveats	Sacks											
23 Economic Impact	Sacks											.84
24 Language 1	Added to Sacks							.79				
25 Search Strategy	OQAQ (1)				.81							
26 Was the search comprehensive	OQAQ (2)											
27 Criteria used for deciding which studies to include	OQAQ (3)											
28 Was bias in the selection avoided	OQAQ (4)	.81										
29 Were the criteria used for assessing the validity reported?	OQAQ (5)					.75						
30 Was the validity of all studies referred to in the text assessed using appropriate criteria	OQAQ (6)				.53						.60	
31 Were the methods used to combine the finding of the relevant studies reported	OQAQ (7)											
32 Were the findings of the relevant studies combined appropriately	OQAQ (8)			.78								
33 Were the conclusions made by the author supported by the data	OQAQ (9)			.68								
34 Overall Summary	OQAQ (10)											
35. Publication Bias 2	Additional (1)						.80					
36 Publication Status	Additional (2)							.77				
37 Language 2	Additional (3)							.63				

- **Shea e Hamel analizzano criticamente 149 RS usando i 37 items da valutare**

11 grandi esperti vengono utilizzati per selezionare un pool di items ristretto grazie ad una «*nominal group technique*» (NGT)

ELSEVIER

Journal of Clinical Epidemiology 62 (2009) 1013–1020

Journal of Clinical Epidemiology

AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews

Beverley J. Shea[a,b,c,*], Candyce Hamel[a], George A. Wells[d,e], Lex M. Bouter[b], Elizabeth Kristjansson[f], Jeremy Grimshaw[g], David A. Henry[h], Maarten Boers[c]

Conclusioni

AMSTAR è dotato di **buona concordanza, buona attendibilità, buona validità di costrutto e fattibilità**. Questi reperti devono essere confermati da un più ampio gruppo di valutatori e su di un più diverso range di Revisioni

Appendix: A measurement tool to assess systematic reviews (AMSTAR)

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
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
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 registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.[a]	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form, such as a table, data from the original studies should be provided on the participants, interventions, and outcomes. The ranges of characteristics in all the studies analyzed, e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? "A priori" methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo-controlled studies, or allocation concealment as inclusion criteria); for other types of studies, alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e., Chi-squared test for homogeneity, I^2). If heterogeneity exists, a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e., is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest included? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

OVERVIEW = REVISIONI DELLE REVISIONI SISTEMATICHE

AMSTAR items	(13)	(30)	(28)	(31)	(11)	(25)	(26)	(27)	(24)	(29)
1. Was an *'a priori'* design provided?	Yes	No	No	Yes	No	No	No	No	No	No
2. Was there duplicate study selection and data extraction?	No	Yes	Yes	No				No	No	Yes
3. Was a comprehensive literature search performed?	Yes	Yes								Yes
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Yes									
5. Was a list of studies (included and excluded) provided?	Yes									
6. Were the characteristics of the included studies provided?										
7. Was the scientific quality of the included studies assessed and documented?	Yes									
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	No									
9. Were the methods used to combine the findings of studies appropriate?	No	NA	No							NA
10. Was the likelihood of publication bias assessed?	No	No	No	No	No	No	No	No	No	No
11. Was the conflict of interest stated?	Yes	No	No	No	Yes	No	No	No	Yes	No
Total	7	5	3	5	7	1	5	1	3	6
Proportion of applicable items	7/11	5/10	3/10	5/11	7/11	1/9	5/10	1/9	3/9	6/10

NA, not applicable; AMSTAR, assessment of multiple systematic reviews.

?? Alcuni autori hanno ritenuto di classificare le RS in 3 categorie di qualità (0-4 bassa ; 5-8 moderata; 9-11 elevata)

AMSTAR

(Assessment of Multiple Systematic Reviews)

1. **E' stato descritto un disegno di studio "a priori"?**

- Il **quesito** della ricerca e i **criteri di inclusione** dovrebbero essere stabiliti prima del lavoro di revisione

2. La selezione degli studi e l'estrazione dei dati sono state eseguite "in doppio"?

Ci dovrebbero essere **almeno due revisori indipendenti** e una procedura condivisa per dirimere i disaccordi

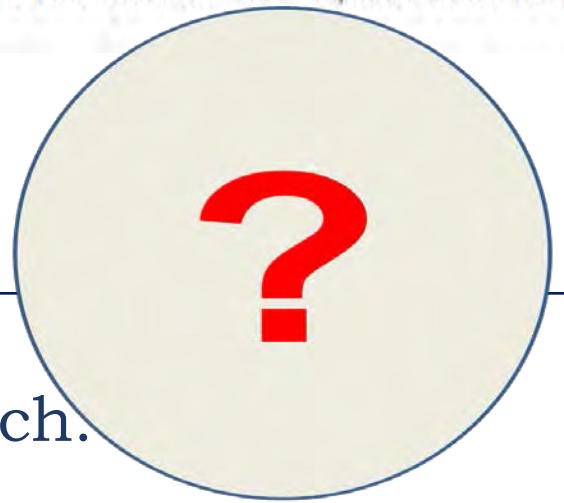
Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?

A meta-analysis of published RCTs

H R Fisher, G du Toit, G Lack

Arch Dis Child 2011;**96**:259–264. doi:10.1136/adc.2009.172460

IMPACT FACTOR = 2.616



Search strategy

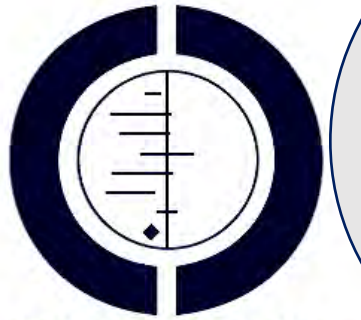
One author (HF) conducted the search.

Study type and quality criteria

One author (HF) reviewed the studies using the NIHCE quality framework

Vaccines for preventing influenza in healthy children (Review)

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E



Di più proprio non si può!

Selection of studies

Two review authors (TOJ, AR) independently excluded all studies not fulfilling the inclusion criteria of initially identified and retrieved articles. **In the case of disagreement, arbitration was carried out by VD.**

Data extraction and management

Four review authors (AR, TOJ, CDP, EF) performed data extraction using a data extraction form

Experimental studies (trials)
The review authors independently assessed the methodological quality of the included studies. In the case of disagreement in assigning quality criteria amongst the review authors (TOJ, EF, CDP, AR), **VD carried out arbitration.**

3. E’ stata sviluppata una ricerca esaustiva della letteratura?

Dovrebbero essere interrogati **almeno 2 database** elettronici**,** che devono essere esplicitati insieme alle **date della ricerca**, alle **parole chiave o i MeSH terms** nonché, dove possibile, alla **strategia di ricerca** adottata. Ogni ricerca dovrebbe essere supportata dalla consultazione di libri di testo, riviste, registri specializzati ed esperti in materia, e dalla revisione della bibliografia degli studi reperiti

4. Lo stato della pubblicazione (ad es. letteratura grigia) costituiva un criterio di inclusione?

Gli autori dovrebbero dichiarare di aver effettuato la ricerca dei reports **indipendentemente dal tipo di pubblicazione**, e se hanno escluso dalla RS qualche report in base a stato di pubblicazione, linguaggio, o altro

Specific oral tolerance induction in food allergic children: is oral desensitisation more effective than allergen avoidance?

A meta-analysis of published RCTs

H R Fisher, G du Toit, G Lack

Arch Dis Child 2011;**96**:259–264. doi:10.1136/adc.2009.172460

Nessun contatto con gli autori dei maggiori trials.

Nessun contatto con i maggiori esperti del settore

Search strategy

One author (HF) conducted the search. The Cochrane Database of Systematic Reviews was first examined using the term *food allergy*, but no relevant review was found. Using the terms detailed in table 1, a variety of additional electronic databases were searched: MEDLINE (1950 to July 2009), EMBASE (1980 to July 2009) and all EBM Reviews: Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment and NHS Economic Evaluation Database (from start date to November 2008). To further improve the sensitivity of the search, the online table of contents of three key specialty journals (*Pediatric Allergy*, the *Journal of Allergy and Clinical Immunology* and *Allergy*) were scrutinised (November 2003 to July 2009), and reference lists of retrieved articles were also examined for relevant studies.

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL

OK!

Dr Arturo Berber contacted trial authors to request unpublished data. Responses were received from 10 trial authors (Arroyave 1999; Collet 1993; Gómez-Barreto 1998; Gutiérrez-Tarango 2001; Jara-Pérez 2000; Karam-Bechara 1995; Paupe 1991; Sarachu-Weber 2001 (co-worker Vazquez-Ramos); Schaad 1986; Schaad 2002). However, no additional data were provided. A further 11 trial authors were contacted by Dr Berber without response (Aymard 1994; Careddu 1994a; Careddu 1994b; Fiocchi 1986; Fiocchi 1988; Fiocchi 1989; Fiocchi 1990; Motta 1994; Paupe 1986; Rutishauser 1998 (co-worker Grevers); Valleron 1992). Dr. Arturo Berber provided the database for OM-85 trials from Mexico. In 2010, we made attempts to contact the following authors: Joseph Bellanti, Jean Bousquet, Herman A. Cohen, Craig I Coleman, Jean Paul Collet, Alessandro Fiocchi, Sergio Marcassa, Renzo Mora, RJ Riedl-Seifert, Urs B. Schaad, Draganka Stankulova, Claudia Steurer-Stey and James A. Taylor, and manufacturers Luipold (luivac), OM Pharma (broncho-vaxom), Pierre Fabre (ribomunyl) and Polichem (adimod). Only Sergio Marcassa, Renzo Mora, RJ Riedl-Seifert, Urs B. Schaad (by himself and in name of OM Pharma) replied; no information regarding new studies was obtained.

5. E’ stato fornito un elenco degli studi inclusi ed esclusi?

Dovrebbe essere resa disponibile una lista dei lavori inclusi ed esclusi

Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis

Sachin A Shah, Stephen Sander, C Michael White, Mike Rinaldi, Craig I Coleman

Lancet Infect Dis 2007; 7: 473–80

Echinacea is one of the most commonly used herbal products, but controversy exists about its benefit in the prevention and treatment of the common cold. Thus, we did a meta-analysis evaluating the effect of echinacea on

	Patient population	*Echinacea* species	Use of Echinaguard or Echinacin	Concomitant supplement	Dose	Virus exposure	Duration	Jadad score
Turner et al (2005)[14]	Healthy volunteers	*E angustifolia*	No	No	Three times a day equivalent to 900 mg/day	Inoculation with rhinovirus 39	7 days pre and 5 days post-inoculation	4
Cohen et al (2004)[28]	Healthy volunteers, children	*E purpurea*/ *E angustifolia*	No	Vitamin C, propolis	5 mL twice a day for ages 1–3 years, 7·5 mL twice a day for ages 4–5 years. Increase to four times a day during episode flare only	Natural	12 weeks	5
Sperber et al (2004)[27]	Healthy volunteers	*E purpurea*	Echinaguard	No	2.5 mL three times a day	Inoculation with rhinovirus 39	7 days pre and 5 days post-inoculation	4
Taylor et al (2003)[32]	Active cold, children	*E purpurea*	No	No	3·75 mL twice a day for ages 2–5 years and 5 mL twice a day for ages 6–11 years	Natural	10 days	5
Barrett et al (2002)[20]	Active cold	*E purpurea*/ *E angustifolia*	No	Thyme, peppermint, citric acid	6 g on day 1 and 3 g on subsequent days	Natural	10 days	5
Schulten et al (2001)[23]	Healthy volunteers	*E purpurea*	Echinacin	No	5 mL twice a day	Natural	At first sign of cold for 10 days	5
Turner et al (2000)[31]	Healthy volunteers	Not specified	No	No	300 mg three times a day	Inoculation with rhinovirus 23	14 days pre and 5 days post-inoculation	1
Lindenmuth and Lindenmuth (2000)[29]	Active cold	*E purpurea*/ *E angustifolia*	No	Lemongrass leaf, spearmint	Five to six bags per day titrated down to one bag on day 5	Natural	12 weeks	3
Grimm and Muller (1999)[24]	Healthy volunteers	*E purpurea*	Echinacin	No	4 mL twice a day	Natural	8 weeks	5
Berg (1998)[25]	Healthy volunteers	*E purpurea*	Echinacin	No	8 mL/day	Natural	28 days	1
Melchart et al (1998)[15]	Healthy volunteers	*E purpurea*/ *E angustifolia*	No	No	50 drops twice a day for 12 weeks	Natural	12 weeks	5
Hoheisel et al (1997)[22]	Healthy volunteers	*E purpurea*	Echinaguard	No	20 drops every 2 h in water on day 1 followed by three times a day for 9 days	Natural	At first sign of cold for 10 days	5
Scaglione and Lund (1995)[30]	Active cold	*E purpurea*	No	Vitamin C, rosemary leaf, eucalyptus, fennel seed	Four tablets daily equivalent to 100 mg/day	Natural	For duration of the cold	2
Braunig and Knick (1993)[26]	Active cold	*E pallida*	No	No	90 drops equivalent to 900 mg/day	Natural	8–10 days	3

Table 1: **Characteristics of included studies**

Evaluation of echinacea for the prevention and treatment of the common cold: a meta-analysis

Sachin A Shah, Stephen Sander, C Michael White, Mike Rinaldi, Craig I Coleman

Lancet Infect Dis.
Impact Factor = 17.39 !

Echinacea is one of the most commonly used herbal products, but controversy exists about its benefit in the prevention and treatment of the common cold. Thus, we did a meta-analysis evaluating the effect of echinacea on

Lancet Infect Dis 2007; 7: 473–80

Table …. Characteristics of excluded studies ??????

Ma perché noi non possiamo verificare quali lavori hanno escluso e magari anche perché?

OK! Diamo a Cesare quel che è di Cesare. Tutte le RS Cochrane rispettano il criterio

M. CALVANI[1], V. GIORGIO[2], S. MICELI SOPO[2]

Specific oral tolerance induction for food. A systematic review

[1] Department of Paediatrics, San Camillo de Lellis Hospital, Rome
[2] Department of Pediatrics, Catholic University of Rome, Rome, Italy

Table 3 – Main characteristics and results of the studies excluded from analysis

Author	Treatment	Design	Age	Cases (n.)	Controls (n.)	Food	Adverse effect	Failure (%)
De Boissieu, 2006	SI	Open	Children (over 6 yrs)	8	–	Milk	12,5	50
Wuthrich, 1996	OD	Open	Adult	16	–	Milk	?	25
Patriarca, 2003	OD	Open controlled	Children and adult (3-55 years)	59	16	Milk (29), egg (15) fish (11) other foods (6)	67,8	16,7
Longo, 2004	OD	Open	Children (mean age 6.8 yrs)	30	–	Milk	100	10
Meglio, 2004	OD	Open	Children (median age 6 yrs)	21	–	Milk	62	14,2
Buchanan, 2007	OD	Open	Children (14-84 months)	7	–	Egg	100	43
Zapatero, 2008	OD	Open	Children (mean age 5 yrs)	18	–	Milk	68,5	11,4
Staden, 2008	OD	Open	Children (3-14 yrs)	9	–	Milk	100	33,3
Caminiti, 2009	OD	RCT (in a subgroup)	Children (mean age 8 years)	3 (+ 7 in open)	3	Milk	80	20

6. Sono state descritte le caratteristiche degli studi inclusi?

I dati relativi a partecipanti, interventi e outcomes dovrebbero essere riportati per mezzo di una forma di aggregazione come **una tabella**. Per ogni studio dovrebbe comparire l'insieme delle caratteristiche quali età, razza, sesso, dati socio-economici rilevanti, durata e stato attuale della malattia, la sua gravità, e le altre malattie eventualmente presenti.

Annals of Otology, Rhinology & Laryngology 120(2):116-122.

Systematic Review of Endoscopic Airway Findings in Children With Gastroesophageal Refl[illegible]ase

Jason Glenn May, MD; Priyanka Shah, MA; Lori Le[illegible]MS;
Jovana Koscica, DO; James M[illegible]

Molte grazie!

Però!! ☺

The result was a total of 20 articles.[3-5,7-23] Each was reviewed to determine the level of evidence, subject population, methods of evaluation, results, and conclusions.

Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children (Review)

Chauhan BF, Ducharme FM

Chauhan BF, Ducharme FM. Anti-leukotriene agents compared to inhaled corticosteroids in the management of recurrent and/or chronic asthma in adults and children. *Cochrane Database of Systematic Reviews* **2012**, Issue 5.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abadoglu 2005

Methods	DESIGN: Randomised clinical study Confirmation of methodology: Not obtained
Participants	SYMPTOMATIC PARTICIPANTS RANDOMISED: N = 24 WITHDRAWALS: Not mentioned AGE in years ± SD: 35.65 ± 10.75 GENDER (male %): 20.83% ASTHMA SEVERITY: Mild persistent asthma ASTHMA DURATION: • less than 5 years: 62.5% • 5-10 years: 27.75% • more than 10 years: 9.75% • % pred. FEV_1 (%, ± SD): 89.3 ± 14.85% MEAN (± SD) β_2-AGONIST USE (puffs/day): Not described DOSE OF inhaled corticosteroids AT STUDY ENTRY AND AT RUN-IN: Not mentioned ATOPY (% of patients): 54.16% ELIGIBILITY CRITERIA: A history of recurrent symptoms of wheezing, shortness of breath, cough; Demonstration of objective signs of reversible airway obstruction by means of at least 12 % increase in FEV_1 after 15 minutes with an inhalation of 200 µg salbutamol; A PC_{20} methacholine < 8 mg/mLas stated by the American Thoracic Society and International Asthma Guidelines. Asthma severity was determined by the frequency of asthma symptoms, pulmonary function tests EXCLUSION CRITERIA: On inhaled corticosteroids, leukotriene receptor antagonists, theophylline and long acting β_2-agonists within the preceding 12 months of the study; airway infection for at least 6 weeks before investigation
Interventions	PROTOCOL DURATION • Run-in - Not mentioned • Intervention - 4 weeks TEST GROUP: Montelukast CONTROL GROUP: Fluticasone propionate DEVICE: Not mentioned CRITERIA FOR WITHDRAWAL FROM STUDY: Not mentioned
Outcomes	ANALYSIS: Not by intention-to-treat analysis OUTCOMES: Reported at 4 weeks; Report outcomes are reported as pre- and post-values (not change from baseline) PULMONARY FUNCTION TESTS: Only pretreatment FEV_1 was reported as not difference was observed after treatment FUNCTIONAL STATUS: Not reported INFLAMMATORY MEDIATORS: Eosinophils count; Apoptotic eosinophils; Apoptotic ratio ADVERSE EVENTS: Not mentioned WITHDRAWALS: Not mentioned
Notes	Full paper (2005) Funding not available

Abadoglu 2005 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Means of randomisation: not described
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Not mentioned
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There is no report as to whether some patients withdrew from the study after randomisation
Selective reporting (reporting bias)	Low risk	All primary and secondary data are presented
Other bias	Low risk	No apparent other bias

Seguono altre 66 tabelle simili dedicate ad ognuno degli studi inclusi

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abadoglu 2005

Methods	DESIGN: Randomised clinical study Confirmation of methodology: Not obtained
Participants	SYMPTOMATIC PARTICIPANTS RANDOMISED: N = 24 WITHDRAWALS: Not mentioned AGE in years ± SD: 35.65 ± 10.75 GENDER (male %): 20.83% ASTHMA SEVERITY: Mild persistent asthma ASTHMA DURATION: • less than 5 years: 62.5% • 5-10 years: 27.75% • more than 10 years: 9.75% • % pred. FEV_1 (%, ± SD): 89.3 ± 14.85% MEAN (± SD) β_2-AGONIST USE (puffs/day): Not described DOSE OF inhaled corticosteroids AT STUDY ENTRY AND AT R tioned ATOPY (% of patients): 54.16% ELIGIBILITY CRITERIA: A history of recurrent symptoms of of breath, cough; Demonstration of objective signs of reversible a means of at least 12 % increase in FEV_1 after 15 minutes with μg salbutamol; A PC_{20} methacholine < 8 mg/mLas stated by the Society and International Asthma Guidelines. Asthma severity was frequency of asthma symptoms, pulmonary function tests EXCLUSION CRITERIA: On inhaled corticosteroids, leukotriene rece theophylline and long acting β_2-agonists within the preceding 12 month airway infection for at least 6 weeks before investigation
Interventions	PROTOCOL DURATION • Run-in = Not mentioned • Intervention = 4 weeks TEST GROUP: Montelukast CONTROL GROUP: Fluticasone propionate DEVICE: Not mentioned CRITERIA FOR WITHDRAWAL FROM STUDY: Not mentioned
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Abadoglu 2005 *(Continued)*

	totic ratio ADVERSE EVENTS: Not mentioned WITHDRAWALS: Not mentioned	
Notes	Full paper (2005) Funding not available	
Risk of bias		
	...gement	Support for judgement
		Means of randomisation: not described
		Not mentioned
		Not mentioned
		There is no report as to whether some patients withdrew from the study after randomisation
		All primary and secondary data are presented
Other bias	Low risk	No apparent other bias

Non è facile che le Cochrane abbiano tutti i dettagli riportati da Chauhan e colleghi

Seguono altre 66 Tabelle dedicate ad ognuno degli studi inclusi

7. E' stata valutata e documentata la qualità scientifica degli studi inclusi?

Dovrebbe essere stato previsto un **metodo "a priori" di valutazione** (ad esempio, per gli studi di intervento, la scelta di includere solo studi randomizzati, in doppio cieco e con randomizzazione mascherata; oppure, per altri disegni di studio, parametri alternativi di qualità)

A seconda del **quesito** cui vorrà rispondere la RS, gli autori devono aver dichiarato quale sarà il **disegno di studio da privilegiare (*criteri di inclusione*)**

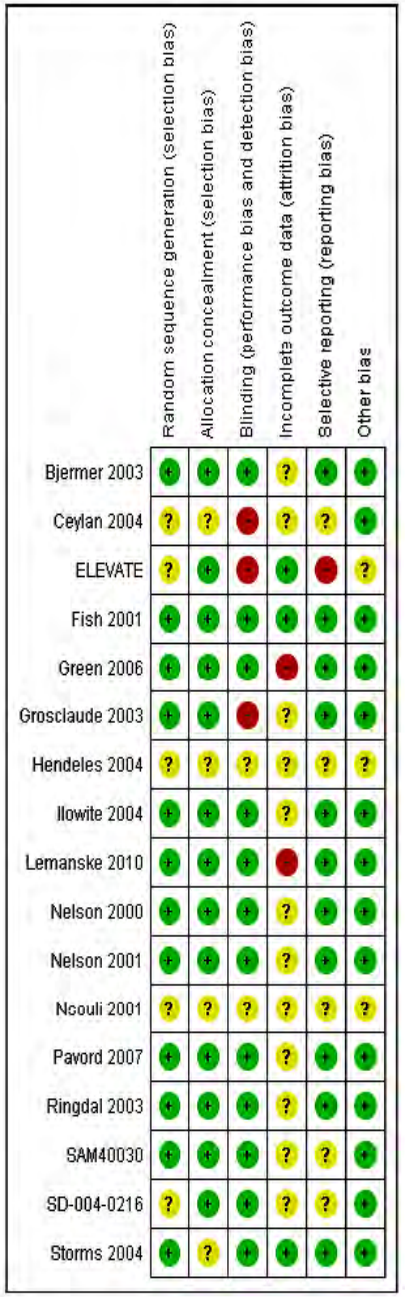
- Ma gli autori devono anche scegliere quale **metodo usare per valutare la qualità di ogni lavoro incluso**, e metterlo conseguentemente in atto

- Il metodo attualmente raccomandato per gli autori delle Revisioni Cochrane è, ormai da qualche anno, il cosiddetto «**Assessment of Risk of Bias**» che include le **cinque maggiori fonti potenziali di errori sistematici**

ASSESSMENT OF RISK OF BIAS
(strumento-tool della ***Cochrane***)

- **Bontà della randomizzazione**
- **Presenza di Mascheramento delle Liste di Random**
- **Cecità (pazienti, personale, medici valutatori)**
- **Completezza del Follow-Up**
- **Esposizione selettiva dei risultati**
- **Altri bias**

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



8. La determinazione della qualità degli studi inclusi è stata usata in modo appropriato al fine di formulare le conclusioni della RS?

I risultati relativi al rigore metodologico e alla qualità scientifica dovrebbero essere presi in considerazione nelle analisi e nelle conclusioni della revisione (ed esplicitate nel formulare eventuali raccomandazioni)

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL

THE COCHRANE COLLABORATION®

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL. Immunostimulants for preventing respiratory tract infection in children. *Cochrane Database of Systematic Reviews 2006, Issue 4.* Review content assessed as **up-to-date: 3 March 2011**.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Il Metodo GRADE

Any immunostimulant (IS) compared with placebo for preventing respiratory tract infection in children

Patient or population: children (age <18 years) susceptible to acute respiratory tract infections (ARTIs)
Settings: outpatient
Intervention: any IS
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk			
	Placebo	Any IS			
Number of ARTIs	The range of ARTIs in the control group was 0.92 to 6.2	The mean Number of ARTIs in the intervention groups was 1.24 lower (0.94 to 1.54 lower)	4060 (35 studies)	⊕⊕⊕○ **moderate**[1]	The effect depends on the number of ARTIs in the control group
Percent difference in ARTIs		The mean Percent difference in ARTIs in the intervention groups was **39 lower** (31.31 to 46.37 lower)	4060 (35 studies)	⊕⊕⊕⊖ **moderate**[1,2]	
Incidence of gastrointestinal adverse events	**21 per 1000**	**30 per 1000** (11 to 50 per 1000)	1457 (10 studies)	⊕⊕○○ **low**[1,3]	
Incidence of skin adverse events	**3 per 1000**	**7 per 1000** (-8 to 14 per 1000)	1469 (10 studies)	⊕⊕⊖⊖ **low**[1,3]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **OR:** odds ratio

BMJ

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Gordon H Guyatt, Andrew D Oxman, Gunn E Vist, Regina Kunz, Yngve Falck-Ytter, Pablo Alonso-Coello, Holger J Schünemann and for the GRADE Working Group

BMJ 2008;336;924-926
doi:10.1136/bmj.39489.470347.AD

- **E' un sistema**
- **Gradua la qualità dell'evidenza**
- **Sviluppa le raccomandazioni attraverso un approccio sistematico e trasparente**
- **Comprende l'indicazione della forza**

Livelli di Evidenza

- **Qualità elevata**
- **Qualità moderata**
- **Qualità bassa**
- **Qualità molto bassa**

Forza di una raccomandazione (livello al quale si può confidare che gli effetti desiderabili di un intervento siano prevalenti rispetto a quelli indesiderabili)

- **Forte**
- **debole o condizionale a favore o contro un intervento**

BMJ

GRADE: an emerging consensus on rating quality of evidence and strength of recommendations

Gordon H Guyatt, Andrew D Oxman, Gunn E Vist, Regina Kunz, Yngve Falck-Ytter, Pablo Alonso-Coello, Holger J Schünemann and for the GRADE Working Group

BMJ 200
doi:10

Implementato nella Cochrane da poco tempo

Tutto da studiare

Troppo «soggettivo»?

- **E' un <u>sistema</u>**
- **Gradua la qualit**
- **Sviluppa le racc**
  attraverso un ap
  trasparente
- **Comprende l'indica**

li Evidenza
tà elevata
tà moderata
ità bassa
alità molto bassa

Forza di una raccomandazione (iv [illegible] si può confidare che gli effetti desiderabili di un intervento siano prevalenti rispetto a quelli indesiderabili)

- **Forte**
- **debole o condizionale a favore o contro un intervento**

9. Sono stati utilizzati metodi appropriati per l'accorpamento dei risultati dei vari studi?

L'accorpabilità ☺

Per i risultati cumulativi dovrebbe essere stato utilizzato un test per determinare la possibilità di accorpamento degli studi, nel senso di accertare l'omogeneità fra di loro (ad es. metodo del Chi quadrato, metodo dell' I^2)

L'eterogeneità!

Metodo che descrive la percentuale di variabilità nelle stime dell'effetto che è attribuibile all'**eterogeneità fra i lavori** piuttosto che ad un errore nel campione (***caso***)

Immunostimulants for preventing respiratory tract infection in children (Review)

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL

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- **OM-85**
- **D53**
- **Pidotimod**
- **Timomodulina**
- **Levamisole**
- **Isoprinosina**

Figure 6. Forest plot of comparison: Any IS compared with placebo, outcome: 1.2 Per cent difference in ARTIs.

Study or Subgroup	Immunostimulant Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ahrens 1984	74.4	67.86	83	100	80.16	72	2.8%	-25.60 [-49.18, -2.02]
Arroyave 1999	33.33	15.48	42	100	22.62	44	3.8%	-66.67 [-74.83, -58.51]
Careddu 1994a	72.82	96.12	329	100	97.09	342	3.5%	-27.18 [-41.80, -12.56]
Clarici 1988	55.43	13.04	20	100	13.04	20	3.8%	-44.57 [-52.85, -36.49]
Cohen 2004	50	61.11	150	100	72.22	168	3.6%	-50.00 [-64.45, -35.55]
De Laure 1979	56.62	52.17	15	100	73.91	17	1.7%	-43.38 [-87.33, 0.57]
Del-Rio-Navarro 2003	53.85	26.92	20	100	28.85	20	3.4%	-46.15 [-63.44, -28.86]
Fiocchi 1986	64.63	13.41	8	100	14.63	8	3.6%	-35.37 [-49.12, -21.62]
Garabedian 1990	48.67	59	75	100	110.67	69	2.5%	-51.33 [-80.56, -22.10]
Gutiérrez-Tarango 2001	63	24.88	26	100	31.88	26	3.5%	-37.00 [-52.20, -21.80]
Gómez-Barreto 1998	70.27	69.82	26	100	106.75	30	1.6%	-29.73 [-76.42, 16.96]
Hauguenauer 1987	66.12	42.86	45	100	97.75	42	2.5%	-33.88 [-63.23, -4.53]
Hüls 1995	68	56.4	78	100	70.8	78	3.2%	-32.00 [-52.09, -11.91]
Jara-Pérez 2000	47.83	31.44	89	100	27.09	100	3.8%	-52.17 [-60.33, -44.01]
Karam-Bechara 1995	60.92	75.86	33	100	116.48	39	1.7%	-39.08 [-83.87, 5.71]
Lacomme 1985	75.09	78.07	47	100	68.77	40	2.4%	-24.91 [-55.77, 5.95]
Litzman 1999	84.62	48.72	43	100	51.28	41	3.1%	-15.38 [-36.79, 6.03]
Maestroni 1994	36.04	36.94	11	100	96.58	9	1.0%	-63.96 [-130.73, 2.81]
Molta 1994	62.82	57.69	117	100	78.53	118	3.4%	-37.18 [-54.79, -19.57]
Paupe 1988	65.15	66.39	21	100	107.47	22	1.4%	-34.85 [-87.98, 18.28]
Pech 1997	59.04	61.7	36	100	76.06	34	2.3%	-40.96 [-73.69, -8.23]
Piquett 1986	100	104.44	17	100	108.15	20	0.8%	0.00 [-68.64, 68.64]
RB10 1994	85.61	90.91	158	100	106.06	161	3.1%	-14.39 [-36.21, 7.43]
RB17 1998	32.17	23.06	15	100	54.96	15	2.5%	-67.83 [-97.99, -37.67]
RB21 1998	56.84	63.16	45	100	52.63	42	2.9%	-43.16 [-67.53, -18.79]
RB22 1990	48.39	16.13	20	100	22.58	20	3.7%	-51.61 [-63.77, -39.45]
RB24 1990	39.13	54.35	16	100	86.96	17	1.5%	-60.87 [-110.04, -11.70]
RB25 1990	40.31	6.15	13	100	18.46	12	3.8%	-59.69 [-70.66, -48.72]
Saracho-Weber 2001	111.11	47.22	135	100	44.44	117	3.8%	11.11 [-0.22, 22.44]
Schaad 1986	96.98	59.4	45	100	52.35	49	3.0%	-3.02 [-25.74, 19.70]
Schaad 2002	85.48	58.06	98	100	65.72	85	3.3%	-14.52 [-32.81, 3.57]
Van Eygen 1978	42.11	39.47	38	100	52.63	32	3.0%	-57.89 [-80.03, -35.75]
Van Eygen 1979	41.69	48.53	53	100	61.55	53	3.1%	-58.31 [-79.41, -37.21]
Vautel 1993	60.97	38.67	32	100	39.75	32	3.3%	-39.03 [-58.24, -19.82]
Zagai 1988	34.86	23.85	29	100	59.63	22	2.7%	-65.14 [-91.53, -38.75]
Total (95% CI)			2012			2018	100.0%	-38.64 [-46.37, -31.91]

Heterogeneity: Tau² = 357.14; Chi² = 195.07, df = 34 (P < 0.00001); I² = 83%
Test for overall effect: Z = 10.11 (P < 0.00001)

Mean Difference IV, Random, 95% CI

-50 -25 0 25 50
Favours immunostimulant Favours control

Immunostimulants for preventing respiratory tract infection in children (Review)

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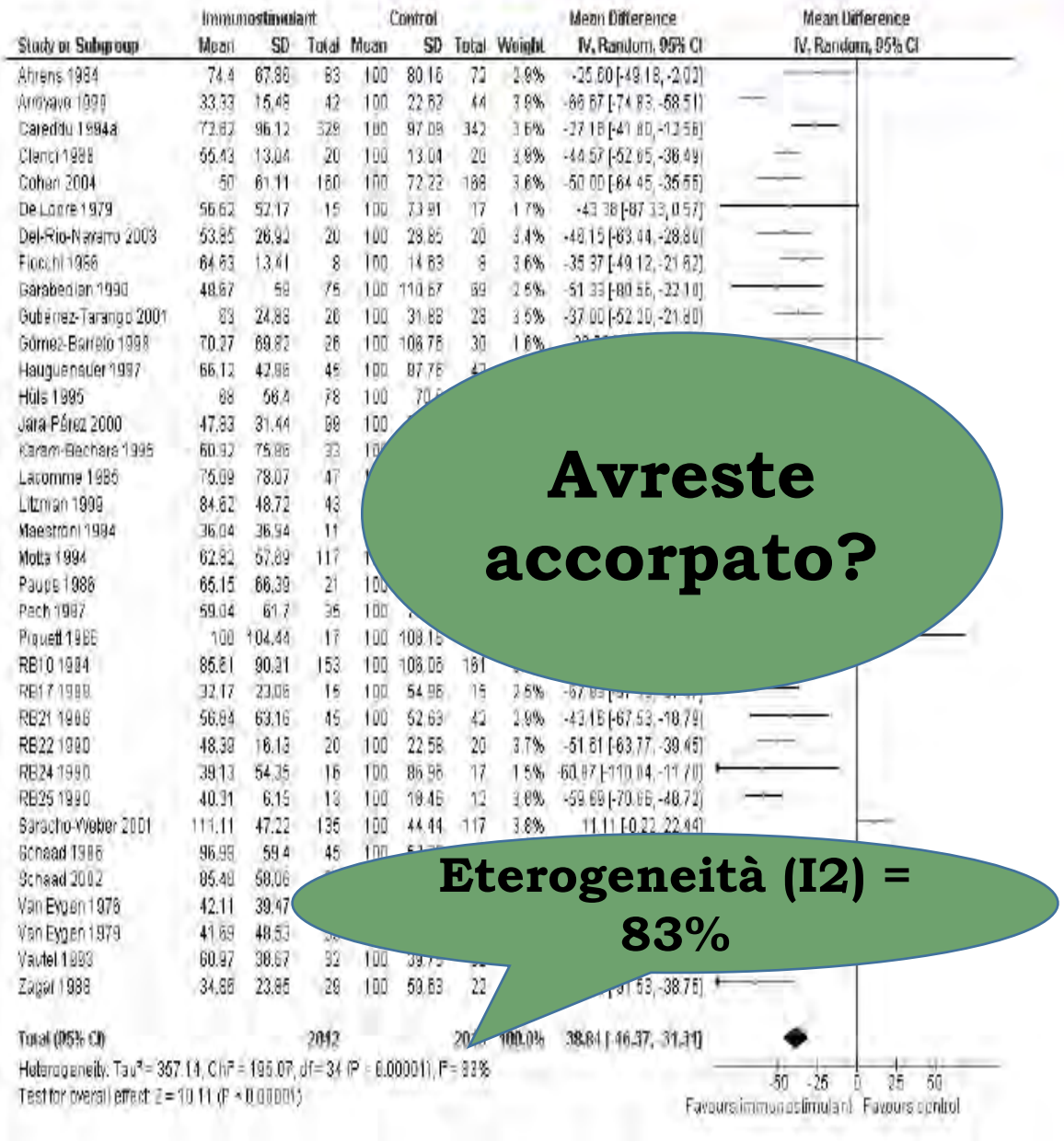
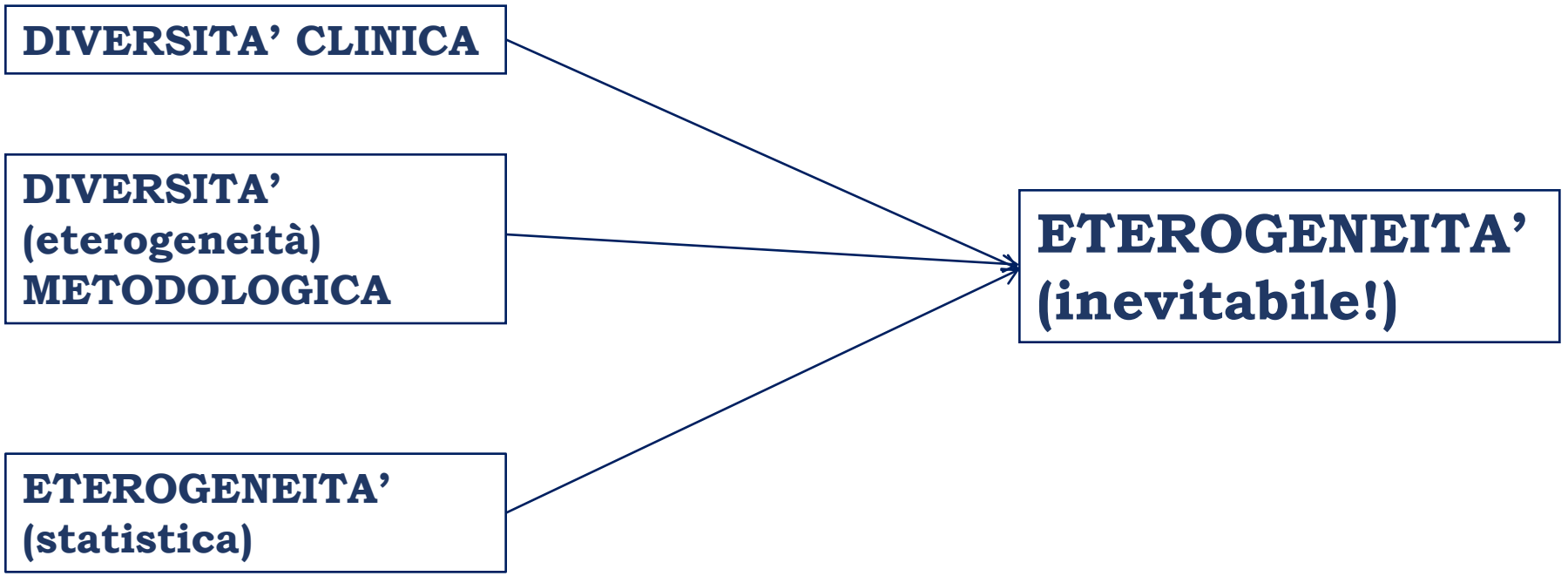
Figure 6. Forest plot of comparison: Any IS compared with placebo, outcome: 1.2 Per cent difference in ARTIs.



Avreste accorpato?

Eterogeneità (I2) = 83%



- **0% to 40%:** potrebbe non essere importante
- **30% to 60%:** moderate heterogeneity
- **50% to 90%:** substantial heterogeneity
- **75% to 100%:** considerable heterogeneity

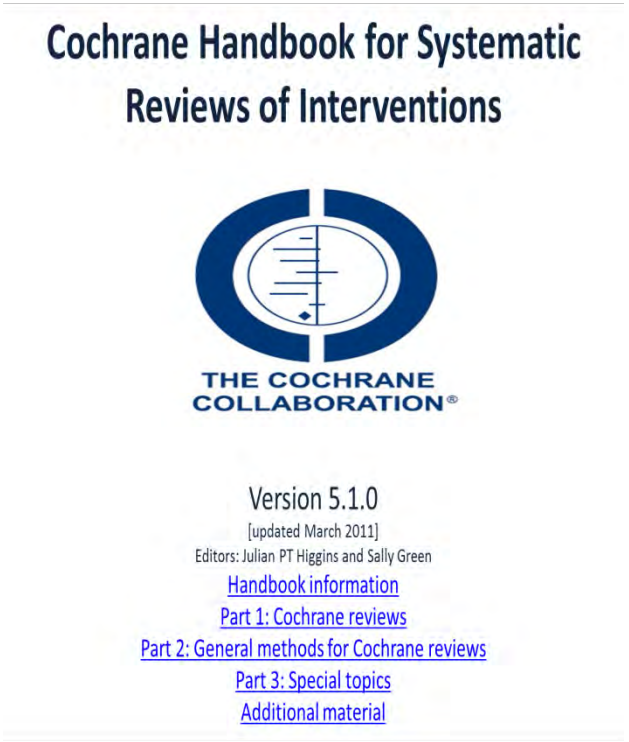
La Metanalisi NON è una necessità!

Può essere fuorviante quantificare il Valore Medio dell'effetto di un intervento quando:

1. **E' presente una considerevole diversità nei risultati**

2. **Soprattutto nel caso di direzione dei risultati opposta**

E' discutibile voler investigare l'Eterogeneità quando esiste un numero esiguo di lavori



L'Eterogeneità dovrebbe essere studiata attraverso le ANALISI DI SOTTOGRUPPO

- **di partecipanti**
- **per tipologia di studio (aree geografiche, qualità metodologica, tipo di intervento, …)**

Vaccines for preventing influenza in healthy children (Review)

Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V, Ferroni E

THE COCHRANE COLLABORATION®

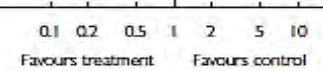
Analysis 2.1. Comparison 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 2 Inactivated vaccine versus placebo or no intervention (RCTs by age group)

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 under 2 years					
aa Hoberman 2003a	15/273	22/138		19.1 %	0.34 [0.18, 0.64]
aa Hoberman 2003b	9/252	4/123		8.1 %	1.10 [0.35, 3.50]
Subtotal (95% CI)	**525**	**261**		**27.2 %**	**0.55 [0.18, 1.69]**
Total events: 24 (Vaccine), 26 (Control)					
Heterogeneity: Tau?? = 0.45; Chi?? = 3.00, df = 1 (P = 0.08); I?? =67%					
Test for overall effect: Z = 1.04 (P = 0.30)					
2 under 6 years					
aa Gruber 1990	3/19	9/27		8.0 %	0.47 [0.15, 1.52]
aa Clover 1991	9/35	20/51		18.0 %	0.66 [0.34, 1.27]
Subtotal (95% CI)	**54**	**78**		**25.9 %**	**0.61 [0.34, 1.08]**
Total events: 12 (Vaccine), 29 (Control)					
Heterogeneity: Tau?? = 0.0; Chi?? = 0.23, df = 1 (P = 0.63); I?? =0.0%					
Test for overall effect: Z = 1.71 (P = 0.087)					
3 over 6 years					
aa Beutner 1979a	28/300	82/275		28.7 %	0.31 [0.21, 0.47]
aa Clover 1991	0/19	16/31		1.7 %	0.05 [0.00, 0.76]
aa Gruber 1990	7/35	28/50		16.5 %	0.36 [0.18, 0.72]
Subtotal (95% CI)	**354**	**356**		**46.9 %**	**0.31 [0.22, 0.45]**
Total events: 35 (Vaccine), 126 (Control)					
Heterogeneity: Tau?? = 0.00; Chi?? = 2.03, df = 2 (P = 0.36); I?? =2%					
Test for overall effect: Z = 6.46 (P < 0.00001)					
Total (95% CI)	**933**	**695**		**100.0 %**	**0.41 [0.29, 0.59]**
Total events: 71 (Vaccine), 181 (Control)					
Heterogeneity: Tau?? = 0.08; Chi?? = 9.35, df = 6 (P = 0.15); I?? =36%					
Test for overall effect: Z = 4.76 (P < 0.00001)					
Test for subgroup differences: Chi?? = 4.12, df = 2 (P = 0.13), I?? =51%					

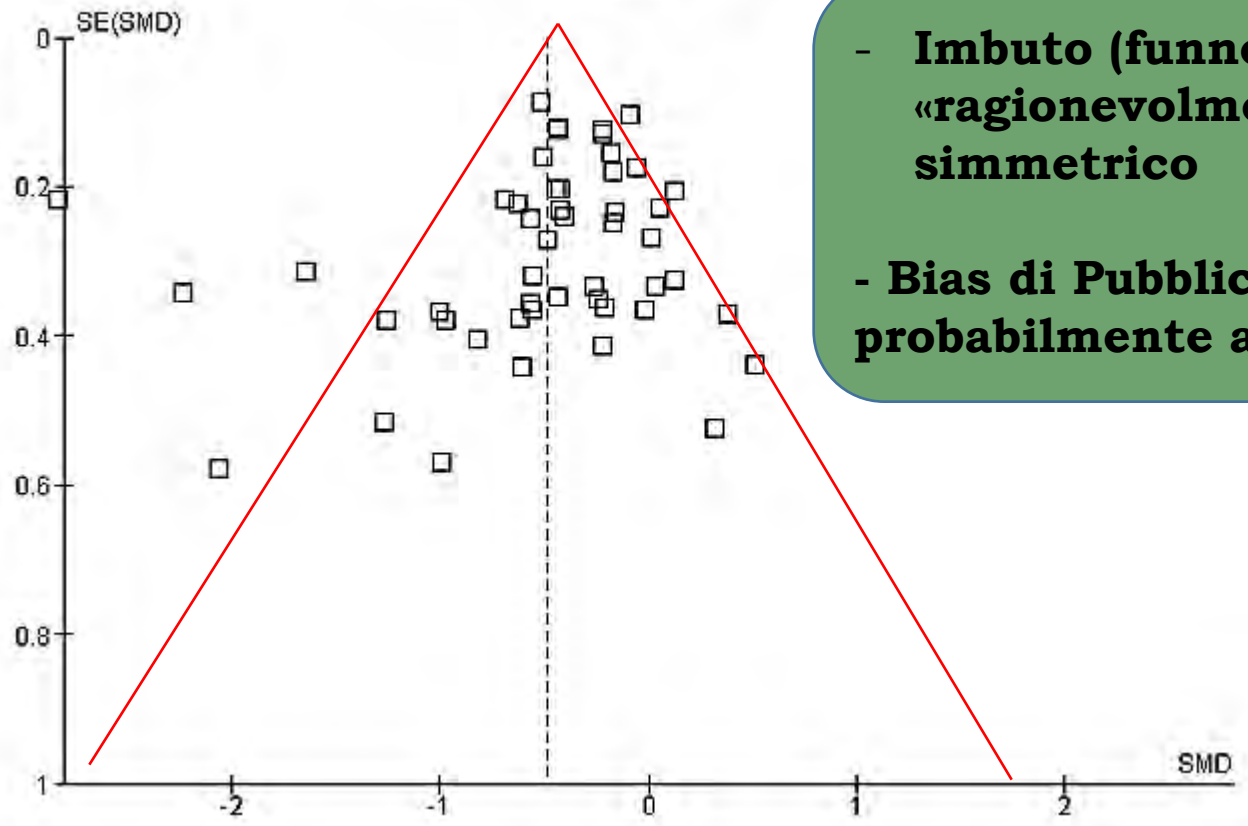


10. E' stata verificata la probabilità di bias di pubblicazione?

Una valutazione della probabilità di bias di pubblicazione dovrebbe comprendere un insieme di **strumenti grafici** (ad es. un funnel plot o altri test disponibili) e/o test statistici

Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. ***Cochrane Database of Systematic Reviews* 2010, Issue 12.**

Figure 3. Funnel plot of comparison: 1 SLIT versus placebo - all, outcome: 1.1 Allergic rhinitis symptom scores.

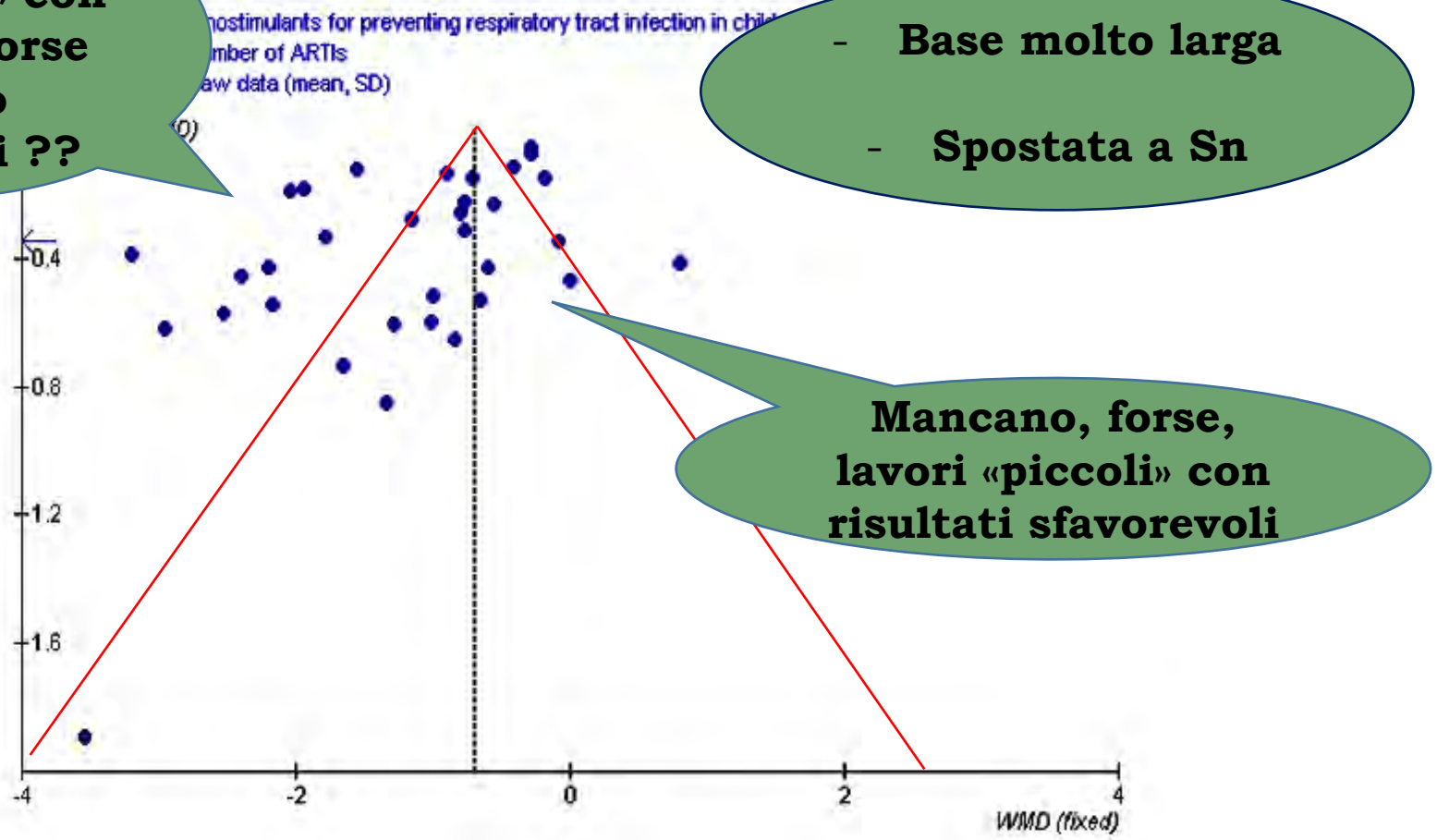


- **Imbuto (funnel) rovesciato «ragionevolmente simmetrico**

- Bias di Pubblicazione probabilmente assenti

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL. Immunostimulants for preventing respiratory tract infection in children. *Cochrane Database of Systematic Reviews 2006, Issue 4.* Review content assessed as **up-to-date: 3 March 2011**.

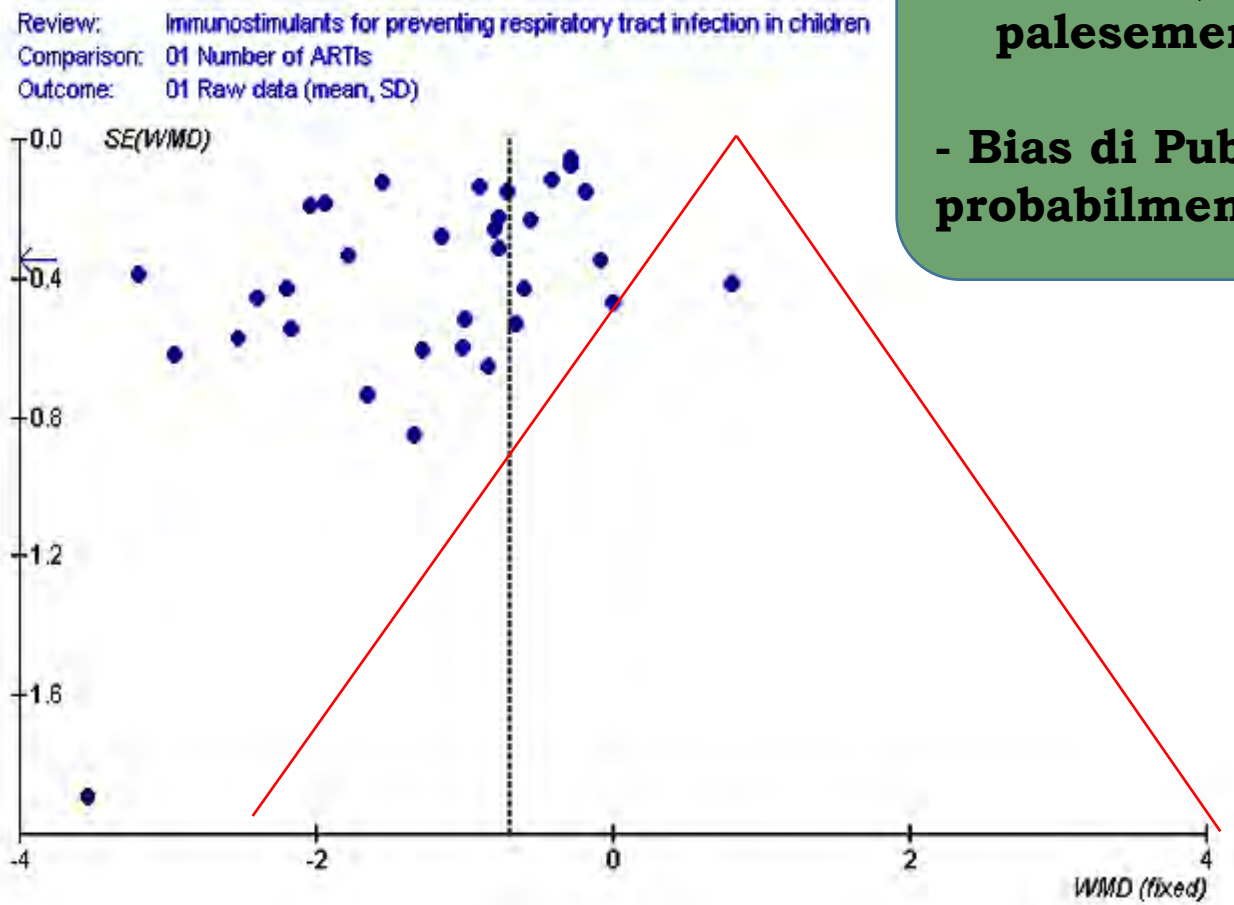
Molti lavori «numerosi» con risultati forse troppo favorevoli ??



- **Base molto larga**
- **Spostata a Sn**

Mancano, forse, lavori «piccoli» con risultati sfavorevoli

Del-Rio-Navarro BE, Espinosa-Rosales FJ, Flenady V, Sienra-Monge JJL. Immunostimulants for preventing respiratory tract infection in children. *Cochrane Database of Systematic Reviews 2006, Issue 4.* Review content assessed as **up-to-date: 3 March 2011**.



- **Imbuto (funnel) rovesciato palesemente A-SIMMETRICO**

- **Bias di Pubblicazione probabilmente PRESENTI**

In effetti sembra che, in presenza di **meno di 10** lavori in una Metanalisi**, un'eventuale asimmetria del Funnel Plot possa essere dovuta al semplice caso** e non alla presenza di bias

Altre ragioni di asimmetria del Funnel Plot

- Differenze importanti nella qualità metodologica
- Grande diversità clinica (caratteristiche di base dei partecipanti)
- Risultati inferiori nei trial più numerosi e più recenti

11. E’ stato dichiarato il conflitto di interessi?

Le potenziali sorgenti di finanziamento dovrebbero essere chiaramente descritte nella RS e negli studi inclusi

Leukotriene receptor antagonists in monotherapy or in combination with antihistamines in the treatment of chronic urticaria: a systematic review

Gabriele Di Lorenzo[1]
Alberto D'Alcamo[1]
Manfredi Rizzo[1]
Maria Stefania Leto-Barone[1]
Claudia Lo Bianco[1]
Vito Ditta[1]
Donatella Politi[1]
Francesco Castello[1]
Ilenia Pepe[1]
Gaetana Di Fede[2]
GiovamBattista Rini[1]

[1]Dipartimento di Medicina clinica e delle Patologie Emergenti; [2]Dipartimento di Discipline Chirurgiche ed Oncologiche, Università degli Studi di Palermo, Italy

Journal of Asthma and Allergy 2009:2 9–16

Disclosures

The authors have no conflicts of interest to disclose.

Nessun finanziamento per lo studio?

Mancherebbero anche le Disclosures sui pregressi rapporti degli Autori con le ditte produttrici dei farmaci studiati

Sublingual immunotherapy for allergic rhinitis (Review)

Radulovic S, Calderon MA, Wilson D, Durham S

THE COCHRANE COLLABORATION®

Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database of Systematic Reviews* 2010, Issue 12.

Forse quelli dichiarati bastano …

TABLE OF CONTENTS

Tutte le RS Cochrane contengono una dichiarazione delle fonti di finanziamento attuali e pregresse

DECLARATIONS OF INTEREST

The lead review author, Dr Suzana Radulovic, has received financial support from the ITN (Immune Tolerance Network) as an employee of the Paediatric Allergy Research Department at King's College London, UK.

The Department of Upper Respiratory Medicine, National Heart & Lung Institute, London, UK, headed by Professor Durham, has received financial support from ALK Abello, Horsholm, Denmark - manufacturers of allergen extracts.

There are no other conflicts of interest to be declared.

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL ARTICLE

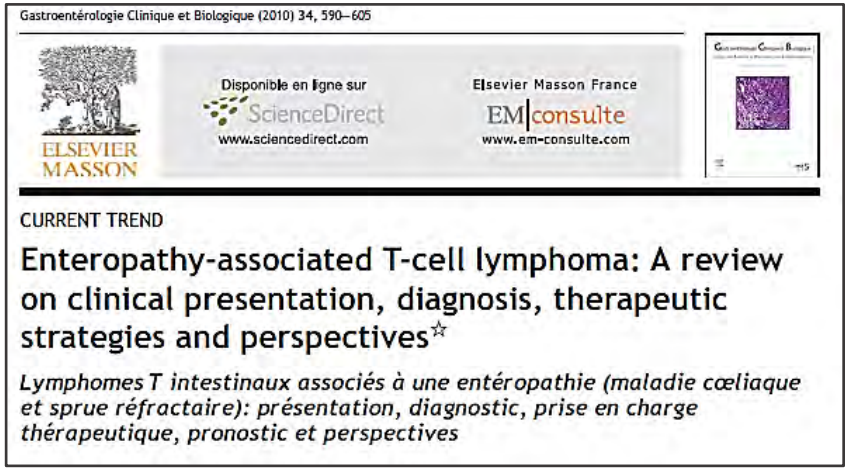
A Randomized Study of How Physicians Interpret Research Funding Disclosures

Aaron S. Kesselheim, M.D., J.D., M.P.H., Christopher T. Robertson, Ph.D., J.D., Jessica A. Myers, Ph.D., Susannah L. Rose, Ph.D., Victoria Gillet, B.A., Kathryn M. Ross, M.B.E., Robert J. Glynn, Ph.D., Steven Joffe, M.D., and Jerry Avorn, M.D.

N Engl J Med. 2012 Sep 20;367(12):1119-27.

Conclusions

Physicians discriminate among trials of varying degrees of rigor, but **industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings**, independently of the trial's quality. These effects may influence the translation of clinical research into practice.



Gastroentérologie Clinique et Biologique (2010) 34, 590–605

Disponible en ligne sur ScienceDirect www.sciencedirect.com

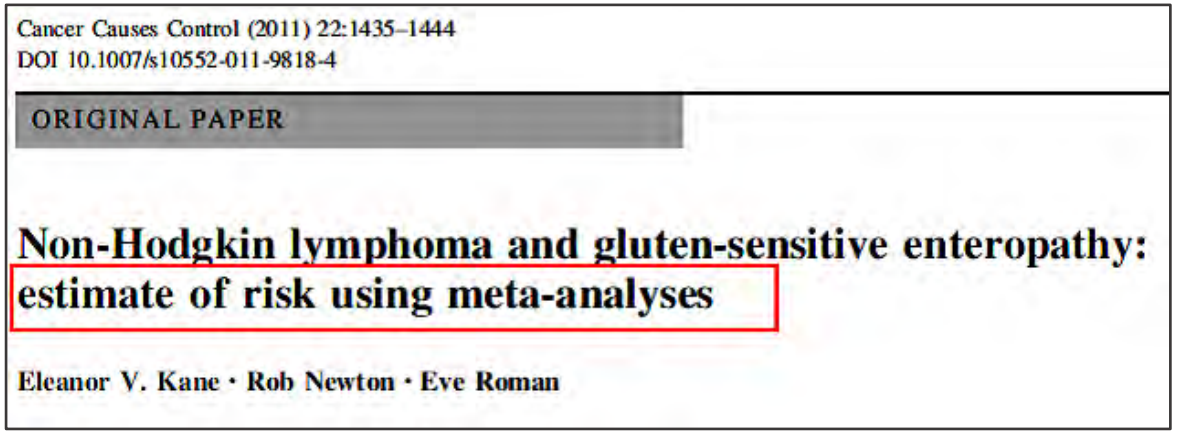
Elsevier Masson France EM|consulte www.em-consulte.com

ELSEVIER MASSON

CURRENT TREND

Enteropathy-associated T-cell lymphoma: A review on clinical presentation, diagnosis, therapeutic strategies and perspectives☆

Lymphomes T intestinaux associés à une entéropathie (maladie cœliaque et sprue réfractaire): présentation, diagnostic, prise en charge thérapeutique, pronostic et perspectives

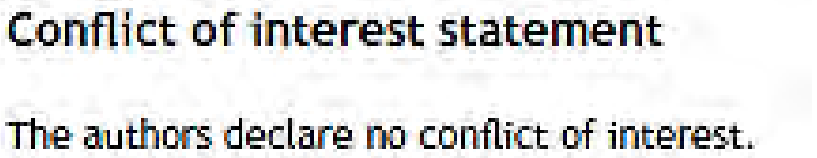


Cancer Causes Control (2011) 22:1435–1444
DOI 10.1007/s10552-011-9818-4

ORIGINAL PAPER

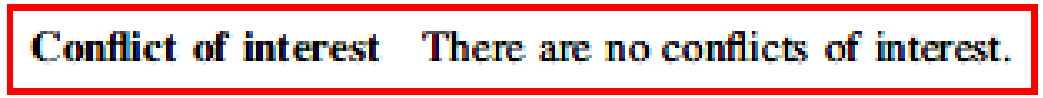
Non-Hodgkin lymphoma and gluten-sensitive enteropathy: estimate of risk using meta-analyses

Eleanor V. Kane · Rob Newton · Eve Roman



Conflict of interest statement

The authors declare no conflict of interest.

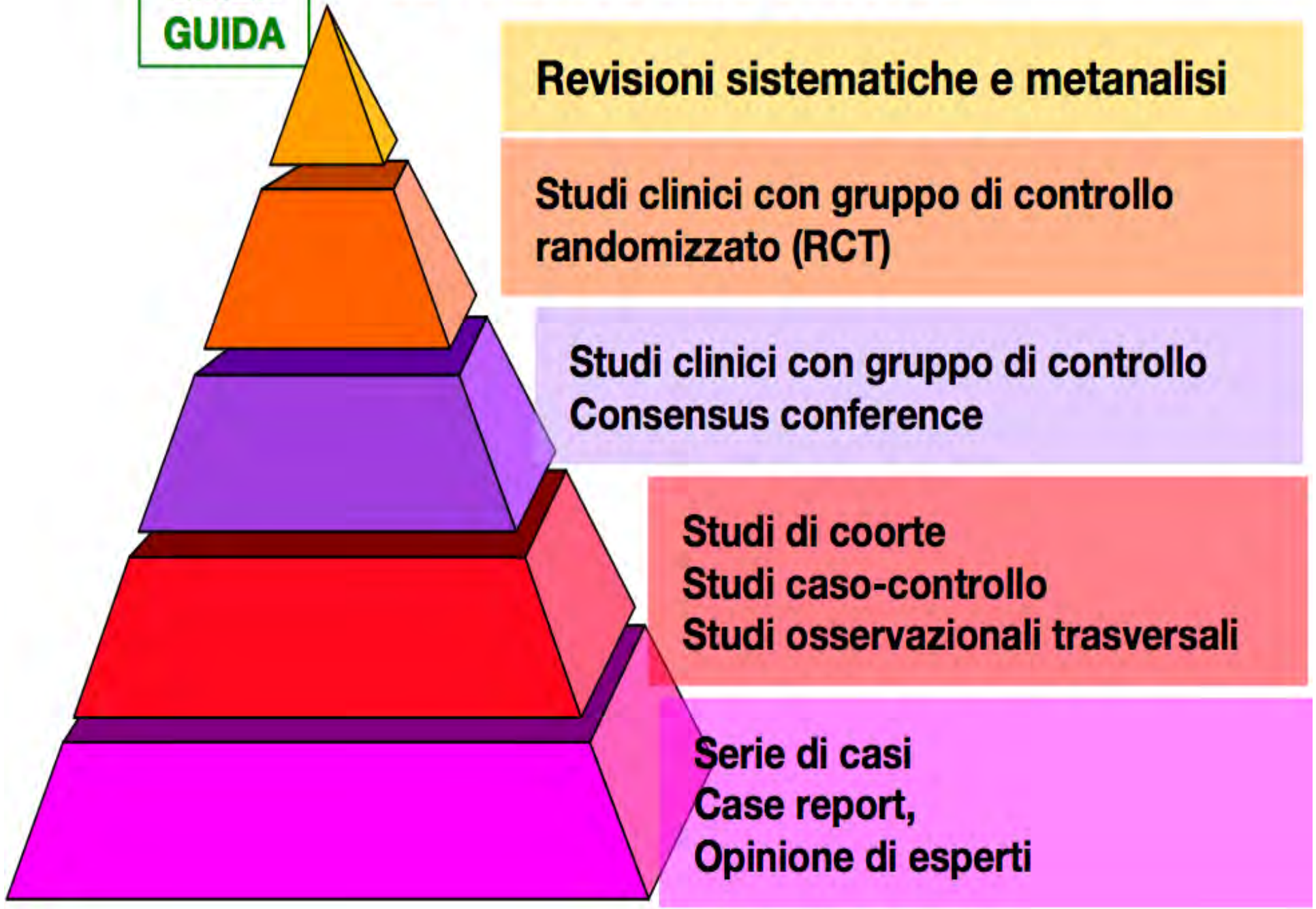


Conflict of interest There are no conflicts of interest.

Lo scopo di queste revisioni sembrerebbe non poter dare origine a conflitti d'interesse…

…anche se non dimentichiamo che esistono aziende produttrici di prodotti senza glutine, oltre ad un fiorente mercato di test diagnostici «alternativi» per le intolleranze alimentari.

La Piramide delle evidenze



Dove si possono reperire la RS
Le Banche Dati Online.

Dal sito del **GIMBE** (Gruppo Italiano di Medicina Basata sull'Evidenza)

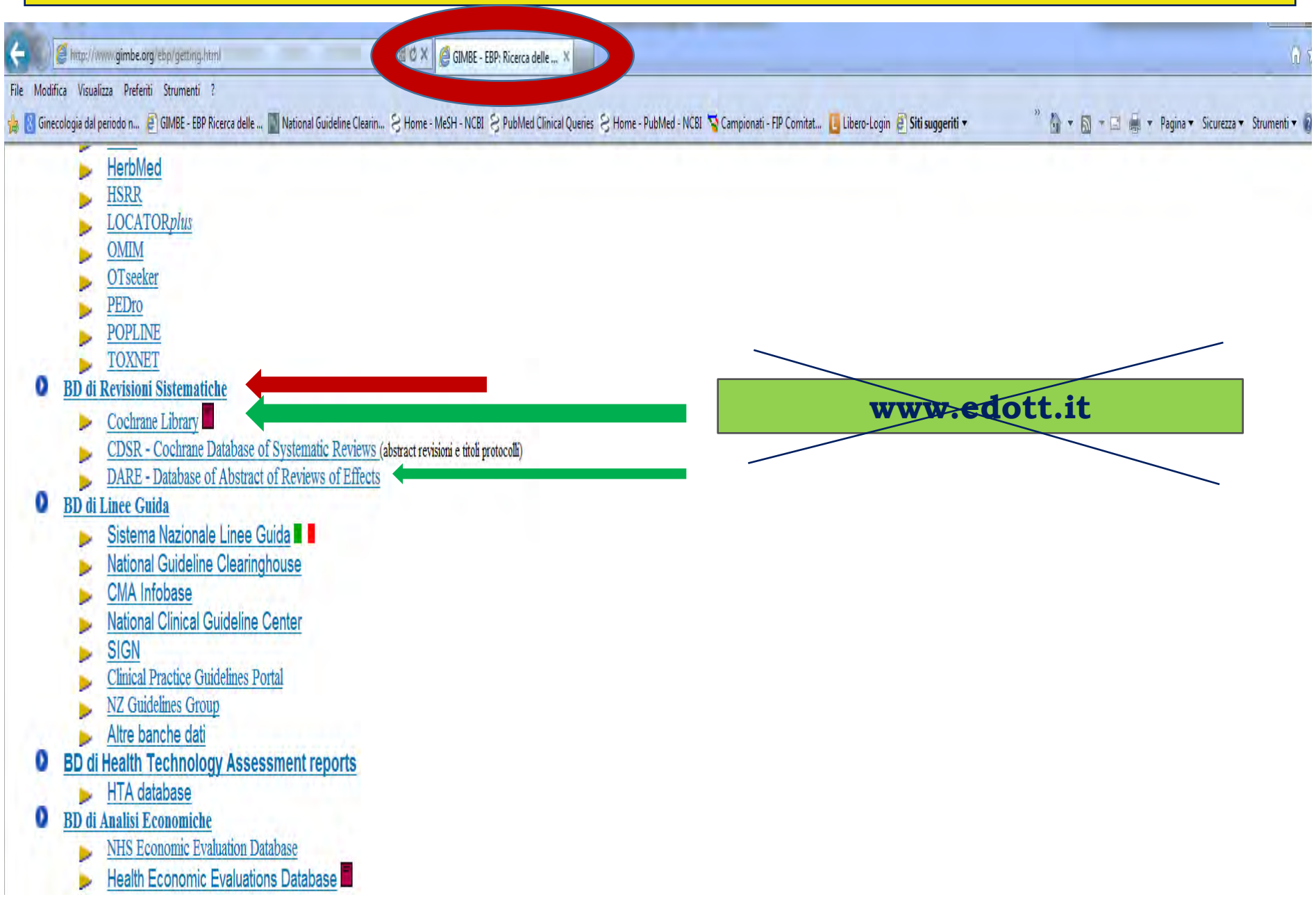
Database principali

Fanno capo alla Cochrane Collaboration:

Cochrane Library

DARE (Database of Abstract of Reviews of Effects) nel quale è possibile trovare anche le RS non-Cochrane.

Dove trovare le Revisioni Sistematiche



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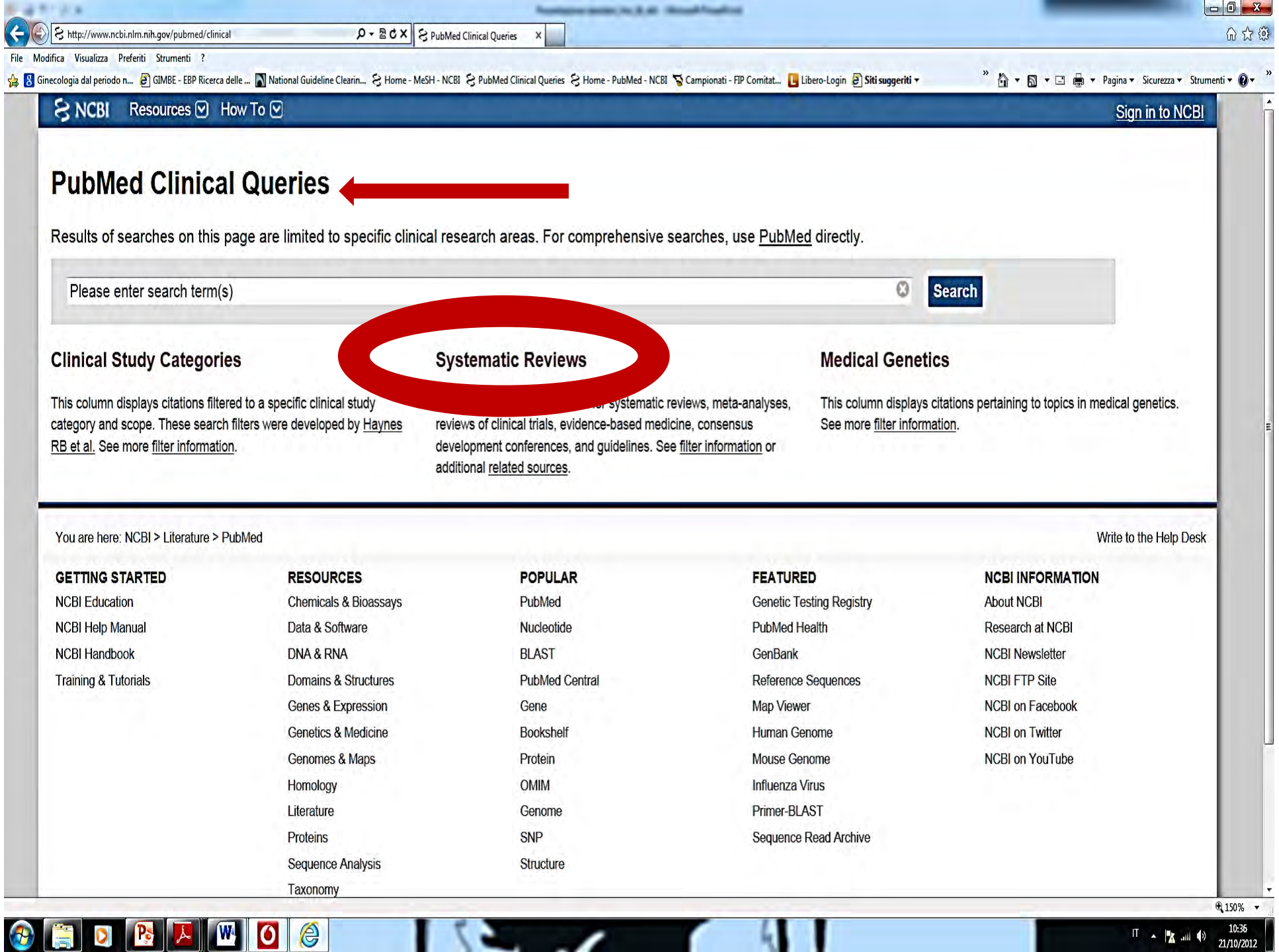
L’altra strategia, interessante in quanto può essere resa molto sensibile e/o molto specifica grazie ai filtri, è l’utilizzo della funzione **“Clinical Queries”** su **PubMed**

Qui è possibile impostare la stringa che si ritiene più idonea per la ricerca delle migliori RS che ci interessano >>> il sistema, in automatico, esplora sia gli studi clinici primari che le Revisioni Sistematiche (questa funzione raccoglie di solito anche le RS Cochrane)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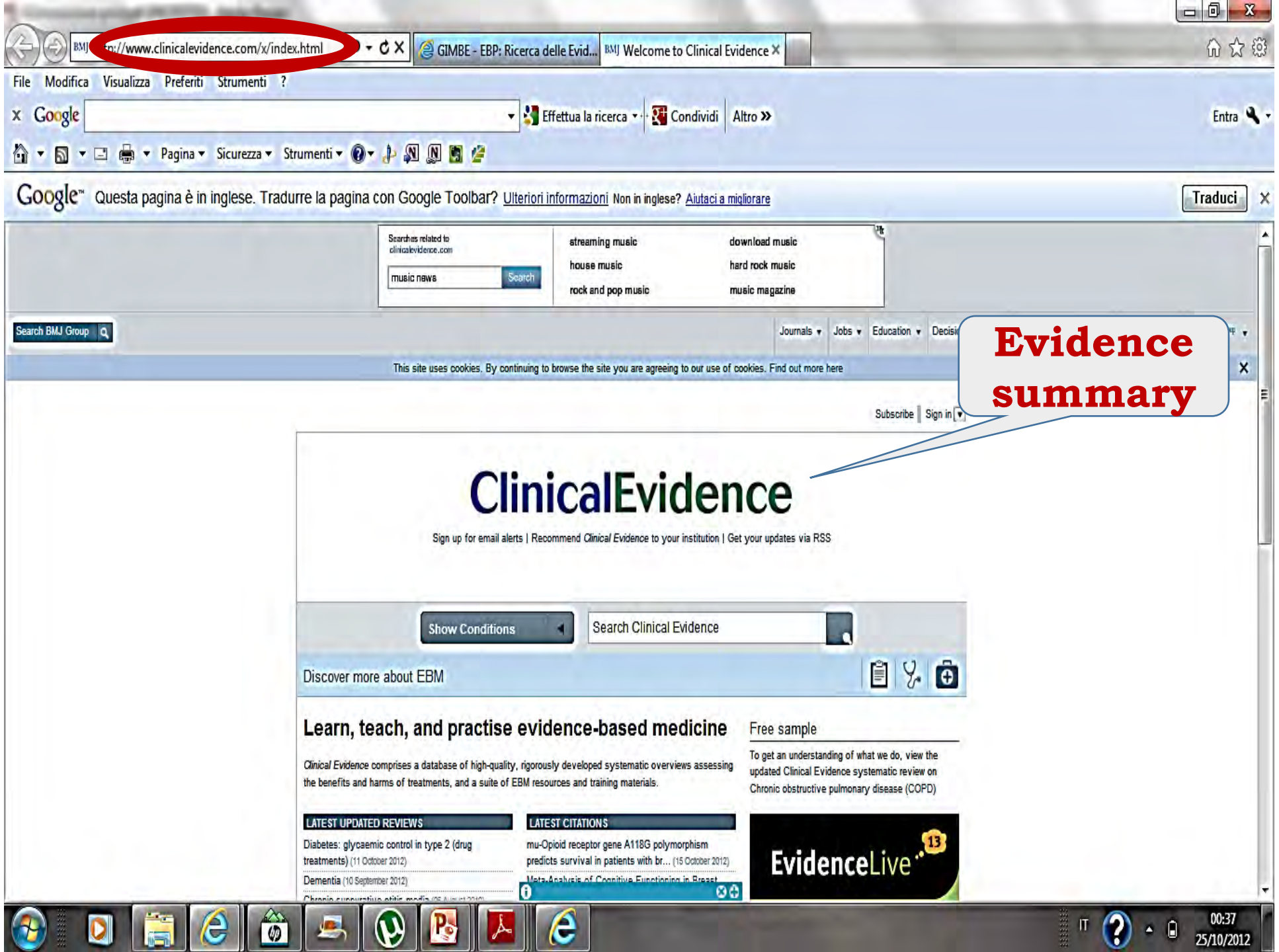
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