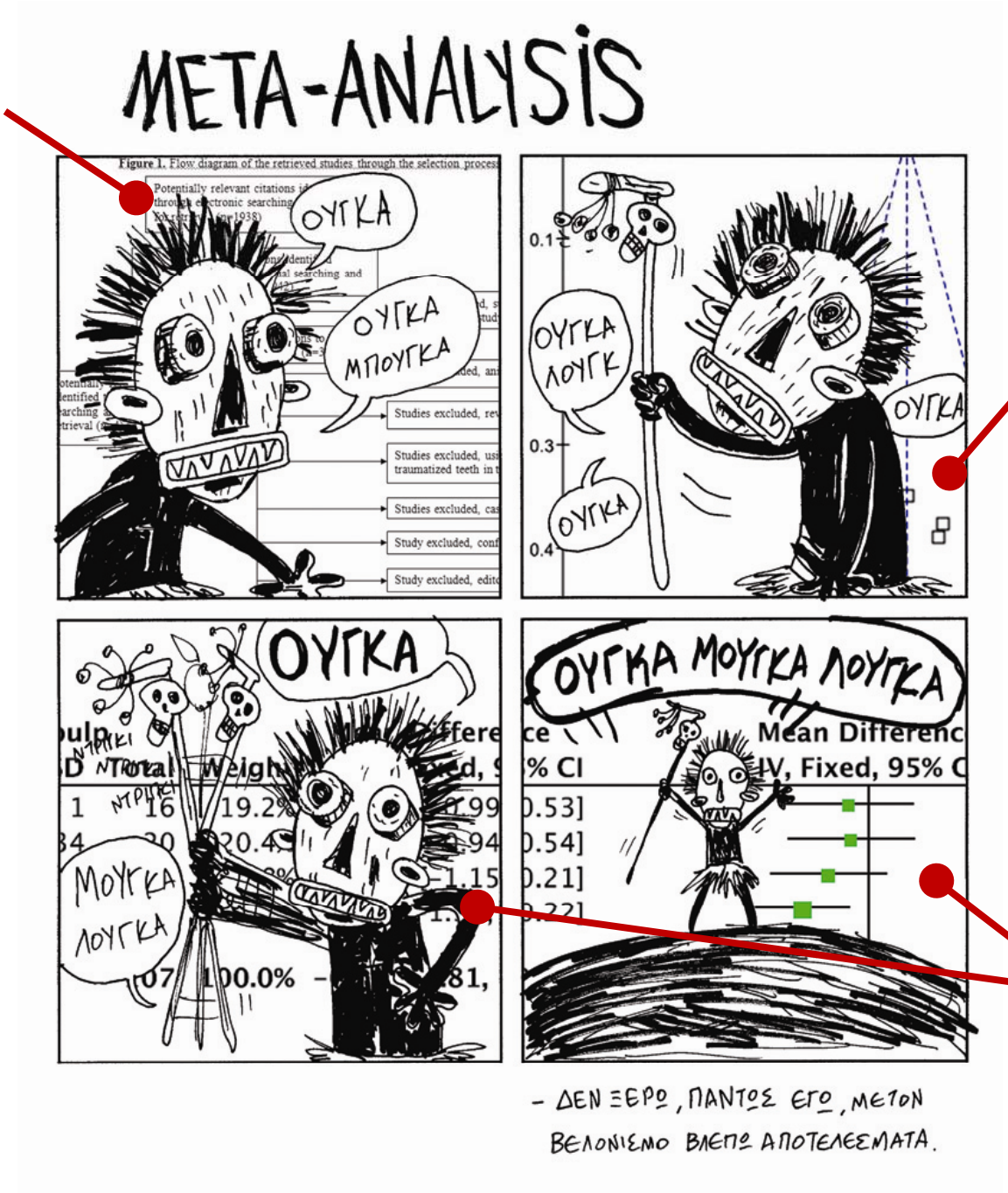
Revisione sistematica della letteratura



Valutazione della presenza di bias

Meta-analisi degli studi selezionati

Fare il punto delle conoscenze

- Revisione narrativa: sintesi soggettiva delle conoscenze su un dato argomento
- The art and science of meta-analysis, the combination of results from multiple independent studies [Sutton AJ, Higgins JP. Recent developments in meta-analysis. Stat Med. 2008;27:625-50] .

Obiettivi

- Riunire quanto è stato prodotto in termini di conoscenze scientifiche su un dato argomento
- Fornire la base per decisioni sanitarie specifiche

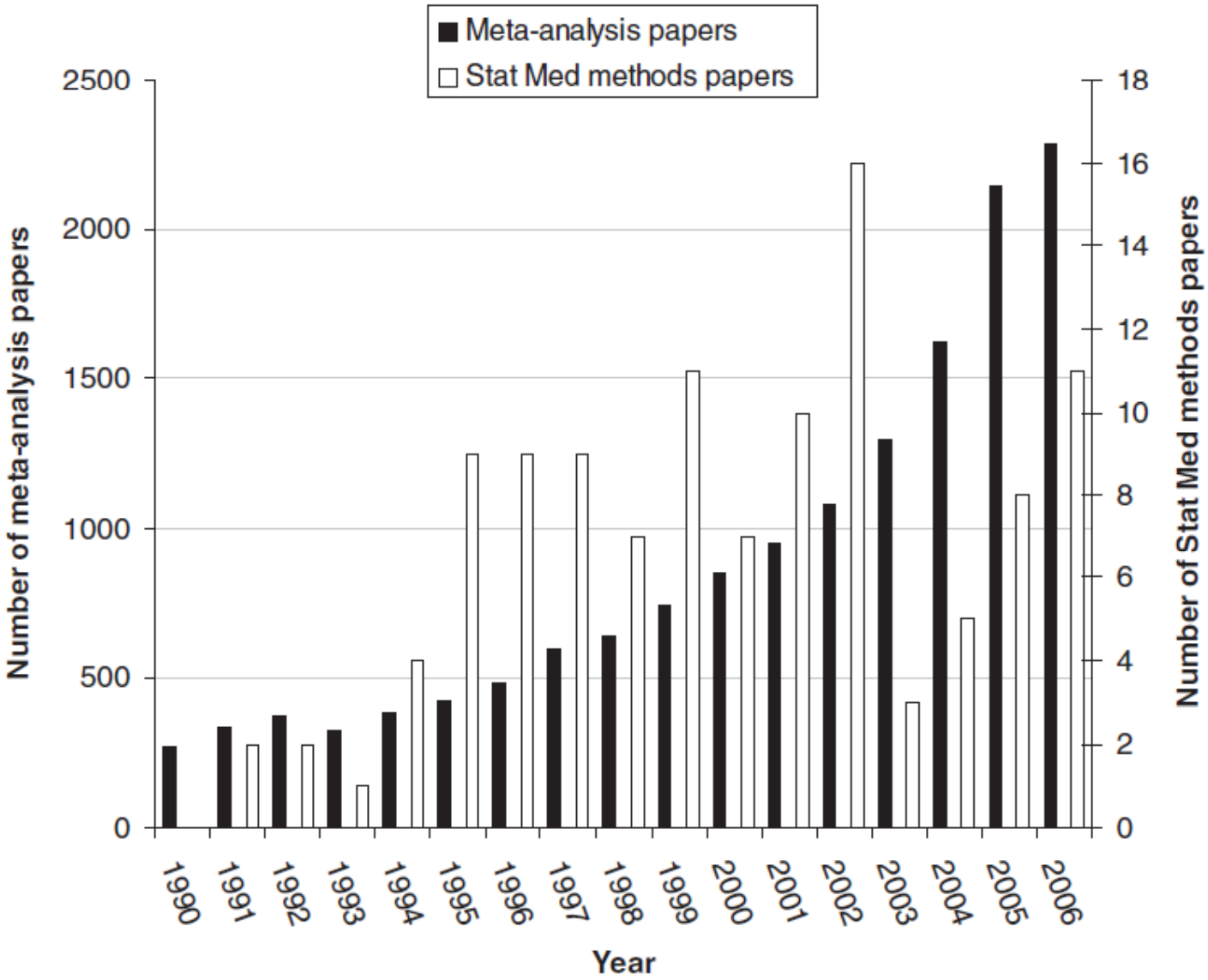


Figure 1. Graph showing crude numbers of meta-analyses as publication types in PubMed, along with numbers of methodological papers in this journal, for years 1990–2006.

Definizione

- Analisi statistica di un insieme di studi che è in grado di produrre nuove evidenze (strumento di ricerca)
- Gli studi inclusi nella meta-analisi costituiscono le unità sperimentali
- Finalità sintetica: stima di effetto complessivo o medio di una esposizione
- Finalità analitica: individuazione e quantificazione delle differenze tra i risultati degli studi

Consistenza

- Il confronto analitico consente di verificare se gli studi disponibili hanno fornito risultati consistenti tra loro, omogenei o meno
- Quindi se è appropriato combinare i risultati degli studi singoli per produrre una nuova stima sintetica di effetto
- La consistenza dei risultati rappresenta uno dei criteri di causalità nella valutazione degli studi epidemiologici

Revisione sistematica e meta analisi

- **Revisione sistematica**: a. ricerca estensiva degli studi rilevanti utilizzando criteri definiti e riproducibili; b. valutazione critica dei lavori condotta secondo schemi prestabiliti (spesso si usano scale per assegnazione di punteggi)
- Meta-analisi: analisi degli studi che soddisfano i criteri di inclusione e non presentano criteri di esclusione

Stima di effetto

- La determinazione di una stima sintetica di effetto e della relativa variabilità è appropriata se gli studi sono omogenei
- La nuova stima mette insieme le unità sperimentali dei diversi studi.
- La dimensione del nuovo studio è pari alla somma delle dimensioni degli studi individuali e ne risulta un vantaggio in termini di incertezza della stima (intervallo di confidenza più stretto)
- Se la meta-analisi utilizza studi osservazionali e i risultati degli studi divergono o se per disegno e condizioni di validità gli studi differiscono (eterogeneità), la stima sintetica prodotta dalla meta analisi presenta limiti di interpretazione e produce una maggiore confidenza unicamente apparente e fittizia

Oggetto della meta-analisi

- Esposizione
- Evento
- [Fattori confondenti]

Dominio della meta-analisi

- **Studi clinici randomizzati e controllati**

- Studi osservazionali
  - Studi di coorte
  - Studi caso-controllo

- La meta analisi dei primi pone minori difficoltà

Identificazione degli studi

- Elemento cruciale della meta-analisi: The validity of the meta-analysis depends on the **quality of the systematic review on which it is based**
- Basi dati bibliografiche (ad esempio MEDLINE)
- Strategia di ricerca

- Riferimenti bibliografici dei lavori, ricerca libera, richiesta di informazioni ad esperti del settore
- La mancata pubblicazione di lavori (ad esempio in seguito a risultati negativi) può distorcere i risultati della meta-analisi (**bias di pubblicazione**)
- Studi in lingue diverse dall'inglese debbono essere presi in considerazione (**bias della lingua di pubblicazione**)

Revisione sistematica

- Reperire tutti gli studi rilevanti (pubblicati e non pubblicati)
  - Strategia di ricerca descritta in dettaglio
  - Criteri di inclusione ed esclusione espliciti e oggettivi
- Valutare la qualità degli studi in termini di disegno ed analisi *(critical appraisal)*
  - Utilizzo di scale di valutazione (punteggio di qualità)
  - Valutazione delle conseguenze dell'esclusione di studi sul risultato della meta-analisi (*sensitivity analysis)*

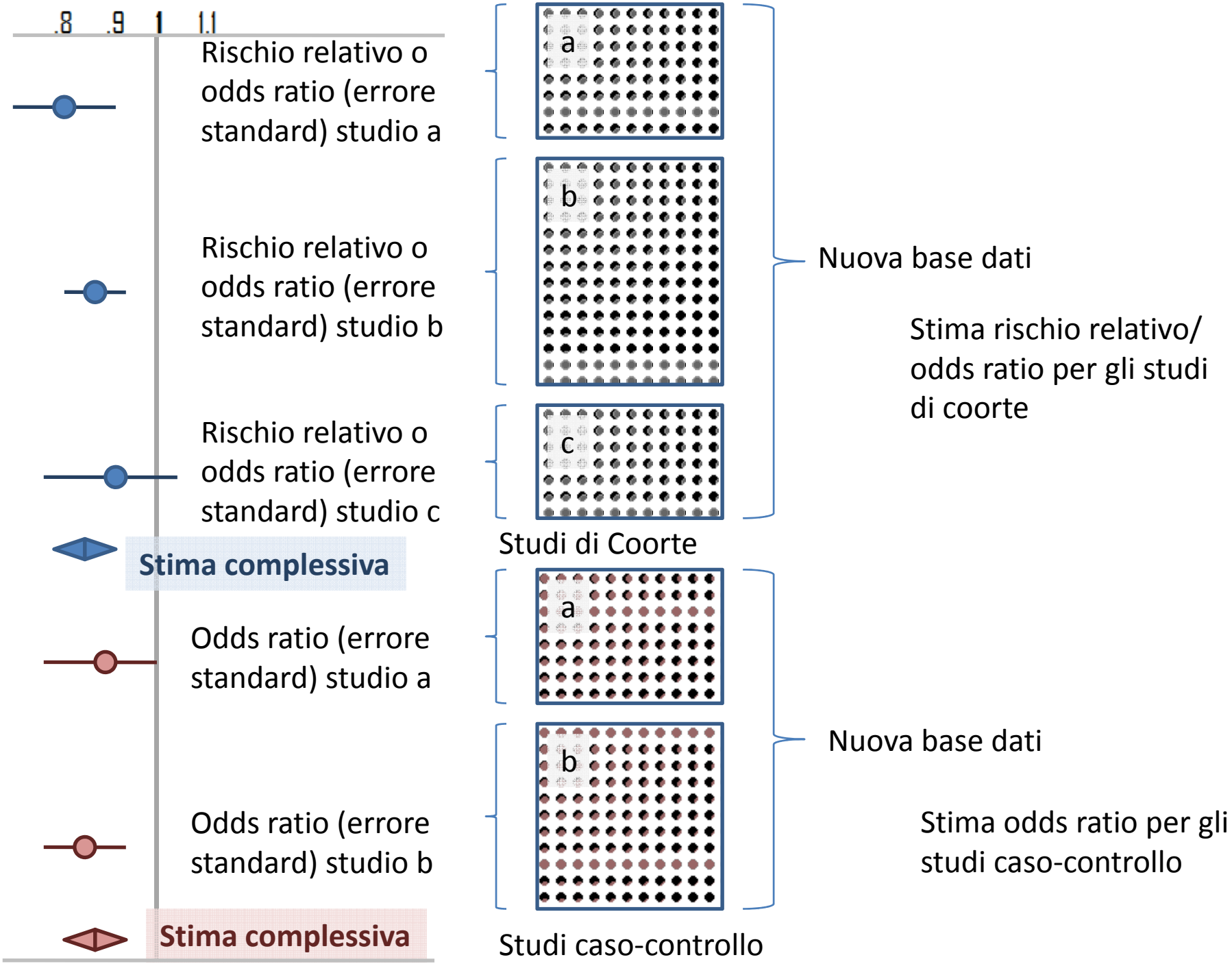
Meta-analisi

- Ri-analisi di dati individuali forniti da diversi studi

(richiede identificazione e disponibilità; ricodifica di variabili misurate in modo differente nei diversi studi)

- Analisi dei risultati degli studi

(richiede attento confronto per verificare comparabilità; può essere necessario assumere informazioni dagli autori o il ricorso a metodi più o meno raffinati di stima in caso di informazioni mancanti)


.8
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Rischio relativo o odds ratio (errore standard) studio a
Rischio relativo o odds ratio (errore standard) studio b
Rischio relativo o odds ratio (errore standard) studio c
Stima complessiva
Odds ratio (errore standard) studio a
Odds ratio (errore standard) studio b
Stima complessiva
a
b
c
Nuova base dati
Stima rischio relativo/ odds ratio per gli studi di coorte
Studi di Coorte
a
b
Nuova base dati
Stima odds ratio per gli studi caso-controllo
Studi caso-controllo

Forest plot

Forest plot displays

- the findings from **each individual study** as a **blob or square**
- with squares towards the left side indicating the new treatment to be better, whereas those on the right indicate the new treatment to be less effective.
- The **size of the blob** or square is proportional to the **precision of the study** (roughly speaking, the sample size).
- A horizontal line (usually **the 95% confidence interval**) is drawn around each of the studies' squares to represent the **uncertainty of the estimate of the treatment effect**.
- The **aggregate effect size** obtained by combining all the studies is usually displayed as a **diamond**.

Meta-analysis: formulating, evaluating, combining, and reporting. Normand SL. Stat Med. 1999;18:321-59.

Table III. Study summaries for the lidocaine example. T denotes treatment group, C denotes control group, $q_i = 1 - p_i$; n_{Ti} and n_{Ci} denote the total number of treated and control patients, respectively; and a, b, c, and d denote the number of observations in each of the cells defined by the treatment (lidocaine or control) and outcome (dead or alive) table. The confidence intervals for the relative risk and odds ratio are computed on the logarithmic scale and transformed back to the original scale

	Risk difference	Relative risk	Odds ratio
Parameter	$D = P_T - P_C$	$R = P_T / P_C$	$\Omega = \frac{P_T/(1-P_T)}{P_C/(1-P_C)}$
Estimator	$d_i = \hat{p}_{Ti} - \hat{p}_{Ci}$	$r_i = \frac{\hat{p}_{Ti}}{\hat{p}_{Ci}}$	$\omega_i = \frac{\hat{p}_{Ti}\hat{q}_{Ci}}{\hat{q}_{Ti}\hat{p}_{Ci}}$
Standard error	$s_{d_i} = \sqrt{\left(\frac{p_{Ti}q_{Ti}}{n_{Ti}} + \frac{p_{Ci}q_{Ci}}{n_{Ci}}\right)}$	$s_{\mathrm{Log}(r_i)} = \sqrt{\left(\frac{q_{Ti}}{n_{Ti}p_{Ti}} + \frac{q_{Ci}}{n_{Ci}p_{Ci}}\right)}$	$s_{\mathrm{Log}(\omega_i)} = \sqrt{\left(\frac{1}{n_a} + \frac{1}{n_b} + \frac{1}{n_c} + \frac{1}{n_d}\right)}$

Study	Sample size	d_i (%)	95% CI	r_i	95% CI	ω_i	95% CI
1	82	2·8	(−5·5, 11·1)	2·2	(0·2, 23·4)	2·3	(0·2, 26·1)
2	88	0·0	(−12·0, 12·0)	1·0	(0·3, 3·8)	1·0	(0·2, 4·3)
3	217	2·0	(−3·6, 7·6)	1·5	(0·5, 5·3)	1·6	(0·4, 5·7)
4	213	1·8	(−4·7, 8·3)	1·4	(0·4, 4·1)	1·4	(0·4, 4·5)
5	216	3·5	(−2·0, 9·1)	2·2	(0·6, 8·5)	2·3	(0·6, 9·3)
6	300	4·4	(−0·5, 9·3)	2·6	(0·8, 8·0)	2·7	(0·8, 8·8)

L’effetto complessivo

- Sintesi dei risultati dei diversi studi
- Se calcoliamo semplicemente la media degli studi implicitamente attribuiamo la stessa importanza a tutti gli studi senza considerarne le dimensioni e la qualità
- per attribuire una diversa influenza agli studi inclusi nella meta-analisi, stimiamo l’effetto come media ponderata dei risultati

Stima dell'effetto medio

$$\hat{\theta}_{pooled} = \frac{\sum w_i \hat{\theta}_i}{\sum w_i}$$

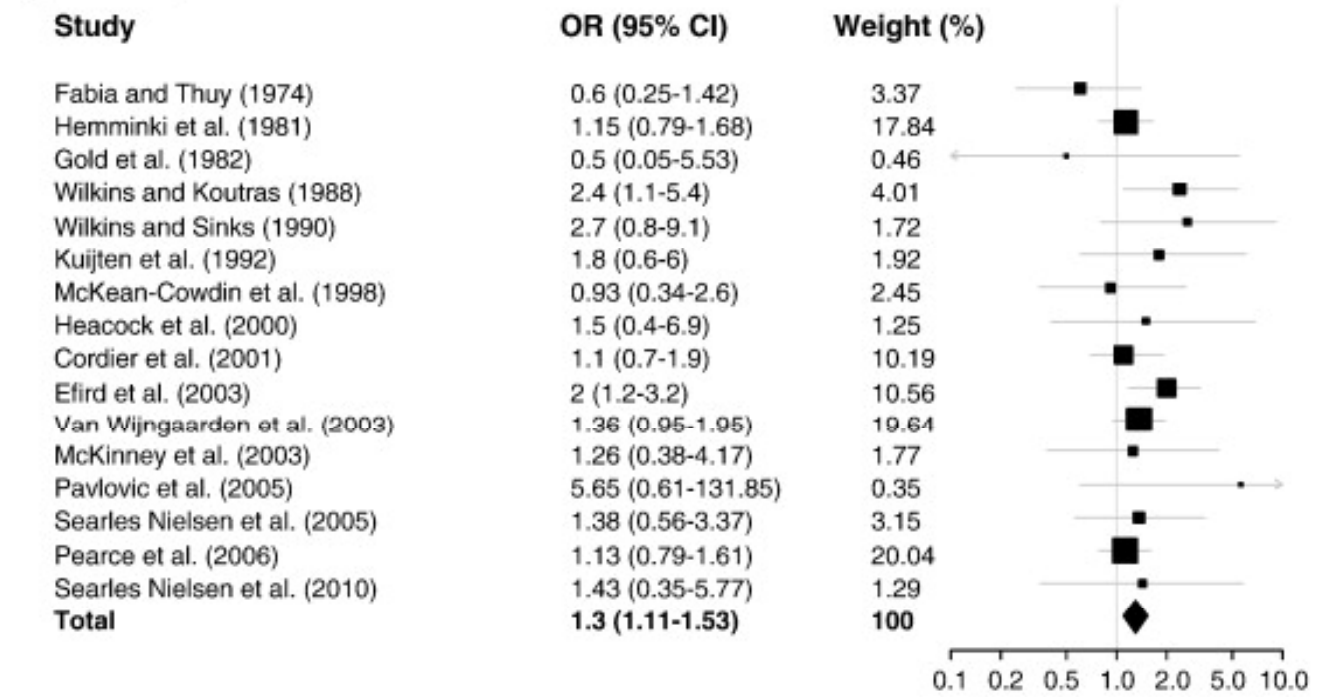
In cui θ_i è una qualche stima di effetto (RR, OR, ARR) ottenuta dagli studi inclusi nella meta analisi, e w_i è il fattore di ponderazione per lo studio *i*

$$w_i = \frac{1}{\hat{\text{var}}(\hat{\theta}_i)}$$

Il fattore di ponderazione più utilizzato è l'inverso della varianza, che tuttavia non tiene conto di differenze nella qualità degli studi inclusi

Parental occupational exposure to pesticides as risk factor for brain tumors in children and young adults: A systematic review and meta-analysis. Van Maele-Fabry G, Hoet P, Lison D. Environ Int. 2013;56:19-31.

A) Forest plot of case-control studies



B) Forest plot of cohort studies

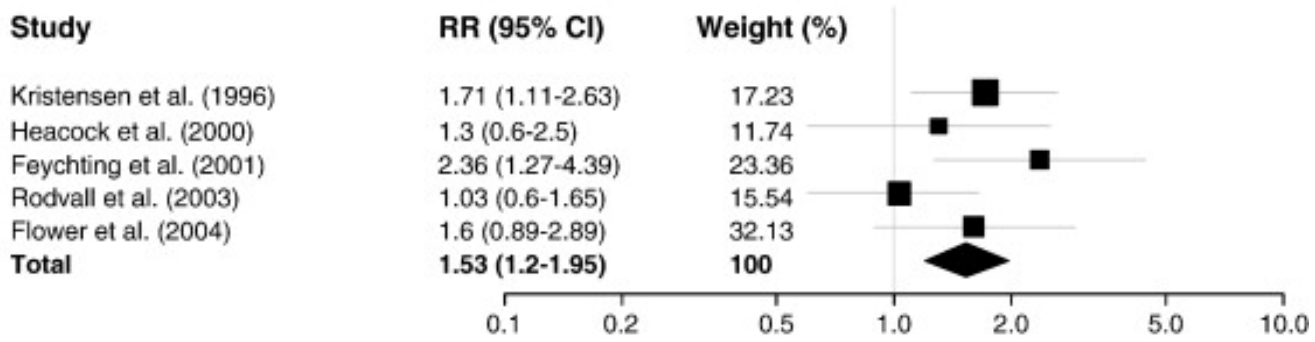


Table 2
Summary results presented for meta-analyses of the relation between parental occupational exposure to pesticides and childhood brain tumors after several stratifications.

Stratification	N.	Summary		Homogeneity			
	Studies	Ratio	95% CI	χ^2 Woolf	P-value	I^2	95% UI
A. Case–control studies							
All studies (A.0)[a,b,c]	16	**1.30**	1.11–1.53	13.752	0.554	0	0–48.0
Exposure time windows							
(A.1) Prenatal	13	**1.33**	1.10–1.60	6.538	0.887	0	0–20.3
(A.1.1) Preconception	6	1.34	0.85–2.12	4.415	0.491	0	0–71.3
(A.1.2) Pregnancy	4	1.18	0.83–1.66	0.495	0.920	0	0–7.2
(A.2) At birth[d]	3	1.19	0.63–2.22	5.441	0.066	63	0–89.5
(A.3) Postnatal	4	1.07	0.55–2.10	0.733	0.866	0	0–37.3
Exposed parent[e]							
(A.4) Mother	6	**1.39**	1.10–1.75	3.599	0.608	0	0–64.8
(A.5) Father	13	**1.19**	1.03–1.38	10.737	0.552	0	0–51.5
Exposure definition							
(A.6) Pesticides[f]	5	**1.56**	1.18–2.05	2.551	0.636	0	0–67.4
(A.6.1) Insecticides	2	1.36	0.98–1.90	0.001	0.976	0	ND
(A.6.2) Fungicides	2	1.07	0.76–1.50	0.228	0.633	0	ND
(A.7) Farming/agriculture[g]	14	**1.22**	1.04–1.43	7.619	0.868	0	0–23.3
(A.7.1) Farming	5	1.01	0.72–1.40	2.394	0.664	0	0–65.3
(A.7.2) Agriculture-occupation	7	**1.27**	1.02–1.59	3.292	0.771	0	0–46.8
(A.7.3) Agriculture-industry	6	**1.57**	1.11–2.22	4.425	0.490	0	0–71.3
Brain tumor type							
(A.8) ASTRO	5	**1.44**	1.05–1.98	1.883	0.757	0	0–55.8
(A.9) PNET	4	1.18	0.81–1.71	1.320	0.725	0	0–65.2
(A.10) other glial tumors	2	1.04	0.53–2.04	0.031	0.859	0	ND
Geographic location							
(A.11) Europe	4	1.16	0.90–1.49	1.374	0.712	0	0–66.6
(A.12) North America	10	**1.36**	1.06–1.76	8.074	0.527	0	0–58.1
(A.13) International	2	1.49	0.83–2.67	2.803	0.094	64.3	0–91.9
Age at diagnosis							
(A.14) <6 years	2	1.00	0.46–2.17	2.912	0.088	65.7	0–92.2
(A.15) <15 years	6	1.21	0.96–1.53	3.498	0.624	0	0–63.7
B. Cohort studies							
All studies (B.1)[h,i]	5	**1.53**	1.20–1.95	4.705	0.319	15.0	0–82.3
Geographic location							
(B.2) Europe	3	**1.57**	1.01–2.45	4.473	0.107	55.3	0–87.2
(B.3) North America	2	1.47	0.93–2.32	0.193	0.660	0	ND

Sensitivity analysis

- **explores the** ways in which the main findings are changed by varying the approach to aggregation.
- A good sensitivity analysis will explore, among other things, the
- effect of excluding various categories of studies; for example, unpublished studies or those of poor quality.
- It may also examine how consistent the results are across various subgroups (perhaps defined by patient group, type of intervention or setting, *period*).

Eterogeneità nel caso di studi clinici

Gli studi possono differire per vari motivi come:

- Tipo di pazienti studiati (severità della malattia, presenza di comorbosità),
- Caratteristiche della struttura sanitaria che somministra gli interventi,
- Intervento somministrato ed esito misurato (morte, evento patologico, diasbilità).

Queste differenze sistematiche tra gli studi possono influire sulla stima di efficacia dell'intervento (entità dell'effetto)

Bias di pubblicazione

- Può accadere che gli studi con risultati negativi, soprattutto se di piccole dimensioni e quindi non conclusivi, non vengano accettati per la pubblicazione con maggiore frequenza rispetto agli studi che evidenziano differenze significative
- In questo caso, la stima di effetto ottenuta mettendo insieme gli studi è distorta (bias di selezione)

Megafono: un grafico per evidenziare la presenza di bias di pubblicazione

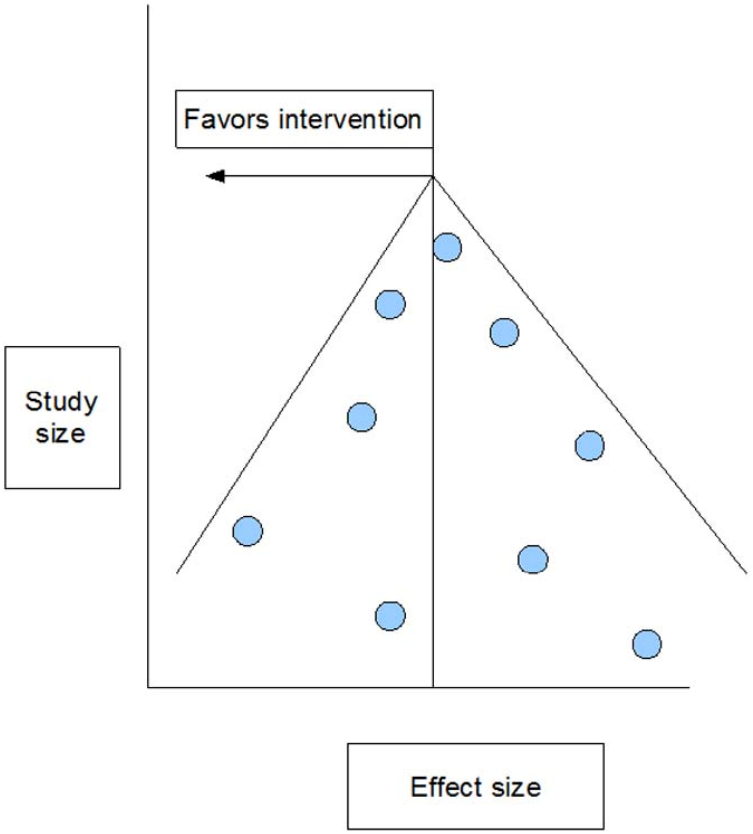
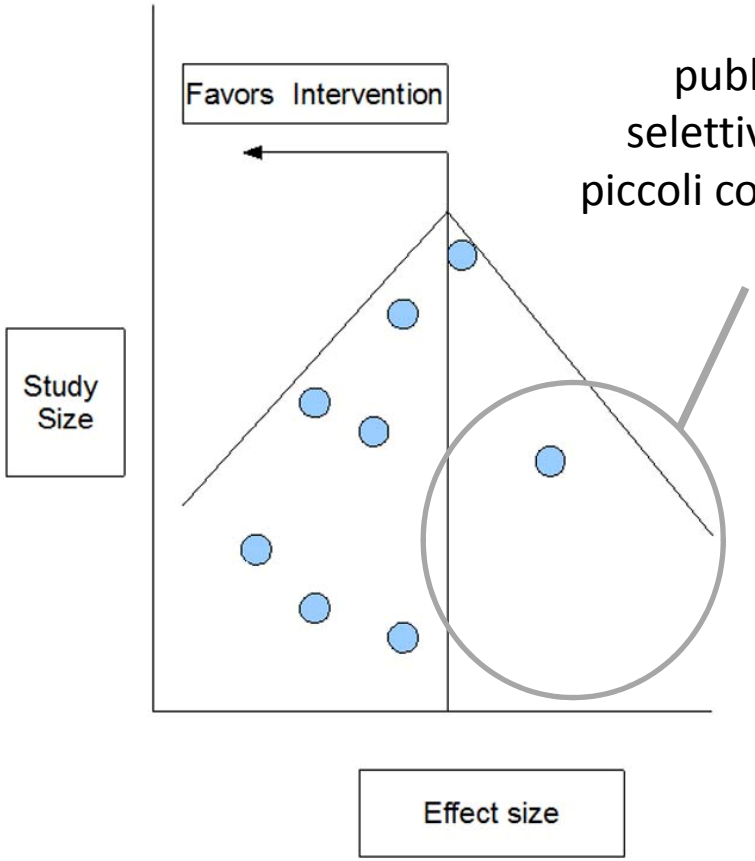


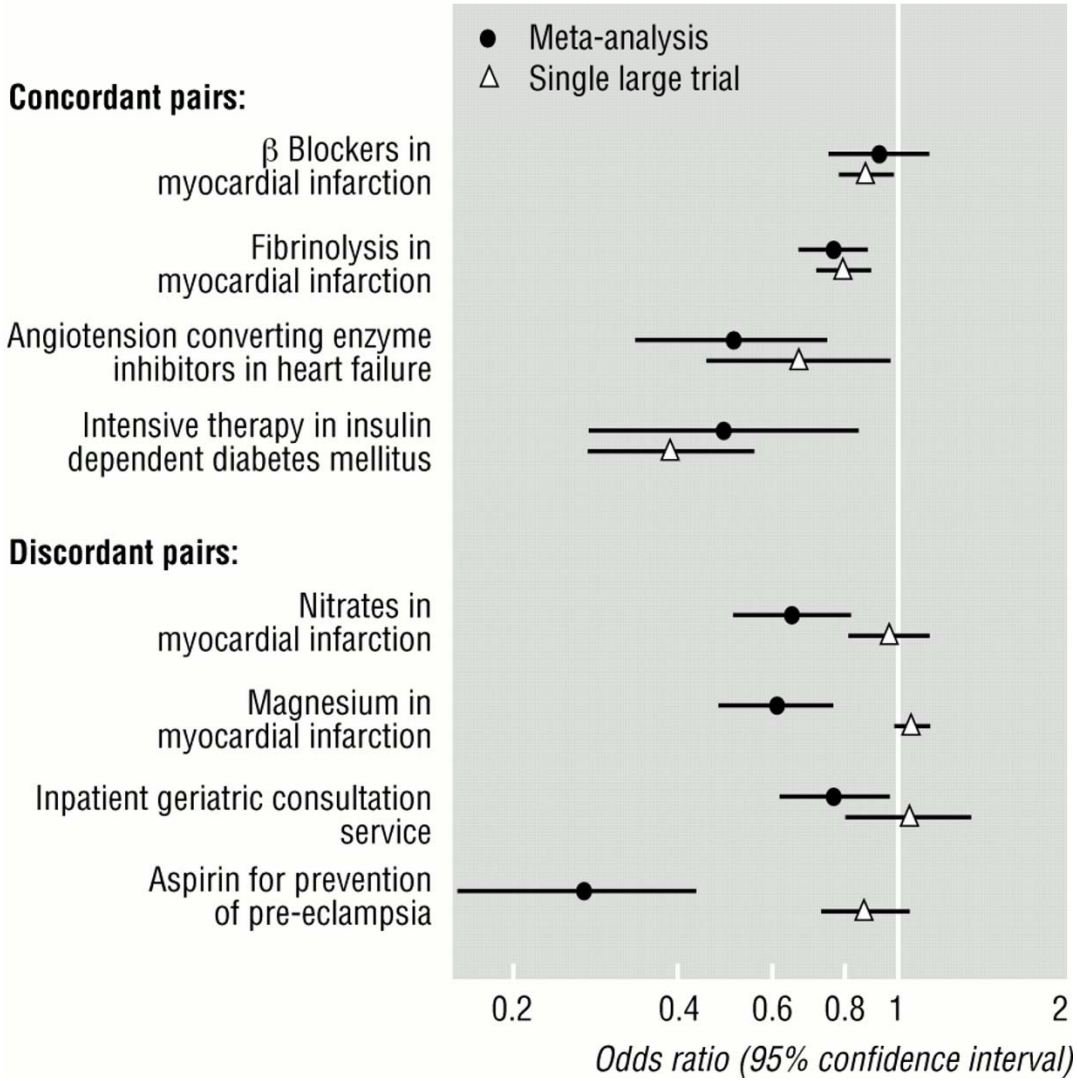
Figure 1 Hypothetical funnel plot which ***does not*** show publication bias



Mancata pubblicazione selettiva di studi piccoli con risultati negativi

Fig. 2 Hypothetical funnel plot which ***does*** show publication bias

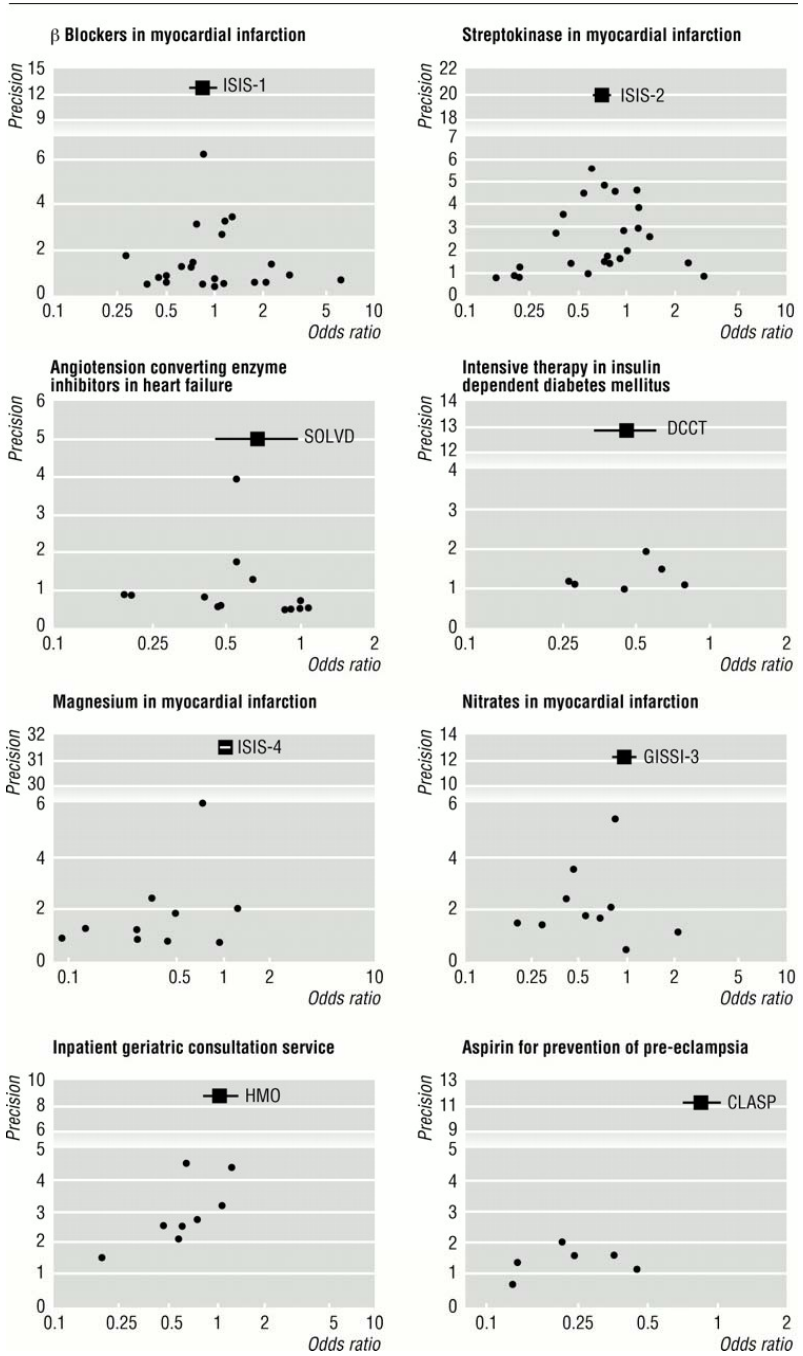
Results from four concordant and four discordant pairs of meta-analysis and large scale randomised controlled trial.



Egger M et al. BMJ 1997;315:629-634

BMJ

Funnel plots and single large trials.



Egger M et al. BMJ 1997;315:629-634

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Information for...

- Practitioners, providers & policymakers
- Patients
- Authors & researchers
- Journalists & bloggers

Abstract

Background

Jet lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world.

Objectives

To assess the effectiveness of oral melatonin taken in different dosage regimens for alleviating jet lag after air travel across several time zones.

- **Search methods.** We searched the Cochrane Controlled Trials Register, MEDLINE, EMBASE, PsychLit and Science Citation Index electronically, and the journals 'Aviation, Space and Environmental Medicine' and 'Sleep' by hand. We searched citation lists of relevant studies for other relevant trials. We asked principal authors of relevant studies to tell us about unpublished trials. Reports of adverse events linked to melatonin use outside randomised trials were searched for systematically in 'Side Effects of Drugs' (SED) and SED Annuals, 'Reactions Weekly', MEDLINE, and the adverse drug reactions databases of the WHO Uppsala Monitoring Centre (UMC) and the US Food & Drug Administration. An updating search was carried out on 12/2/2008 but no new studies were identified.
- **Selection criteria. Randomised trials** in airline passengers, airline staff or military personnel given oral melatonin, compared with placebo or other medication. Outcome measures should consist of **subjective rating of jet lag or related components**, such as subjective well being, daytime tiredness, onset and quality of sleep, psychological functioning, duration of return to normal, or indicators of circadian rhythms.
- **Data collection and analysis.** Ten trials met the inclusion criteria. All compared **melatonin with placebo**; one in addition compared it with a hypnotic, zolpidem. Nine of the trials were of adequate quality to contribute to the assessment, one had a design fault and could not be used in the assessment.
  Reports of adverse events outside trials were found through MEDLINE, 'Reactions Weekly', and in the WHO UMC database.

- **Main results.** Eight of the ten trials found that melatonin, taken close to the target bedtime at the destination (10pm to midnight), decreased jet-lag from flights crossing five or more time zones. Daily doses of melatonin between 0.5 and 5mg are similarly effective, except that people fall asleep faster and sleep better after 5mg than 0.5mg. Doses above 5mg appear to be no more effective. The relative ineffectiveness of 2mg slow-release melatonin suggests that a short-lived higher peak concentration of melatonin works better. **The estimated number needed to treat (NNT) is 2, based on the only two trials that gave the necessary data.** The benefit is likely to be greater the more time zones are crossed, and less for westward flights.
- The timing of the melatonin dose is important: if it is taken at the wrong time, early in the day, it is liable to cause sleepiness and delay adaptation to local time. The incidence of other side effects is low. Case reports suggest that people with epilepsy, and patients taking warfarin may come to harm from melatonin.

- **Authors' conclusions**
- Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.
- The pharmacology and toxicology of melatonin needs systematic study, and routine pharmaceutical quality control of melatonin products must be established.
- The effects of melatonin in people with epilepsy, and a possible interaction with warfarin, need investigation.
- **Plain language summary**
- **Melatonin for the prevention and treatment of jet lag**
- Jet lag commonly affects air travellers who cross several time zones. It results from the body's internal rhythms being out of step with the day-night cycle at the destination. Melatonin is a pineal hormone that plays a central part in regulating bodily rhythms and has been used as a drug to re-align them with the outside world. Melatonin is remarkably effective in preventing or reducing jet lag, and occasional short-term use appears to be safe. It should be recommended to adult travellers flying across five or more time zones, particularly in an easterly direction, and especially if they have experienced jet lag on previous journeys. Travellers crossing 2-4 time zones can also use it if need be.