Healthcare Technology Engineering

Evidence Based Medicine and Meta-analysis

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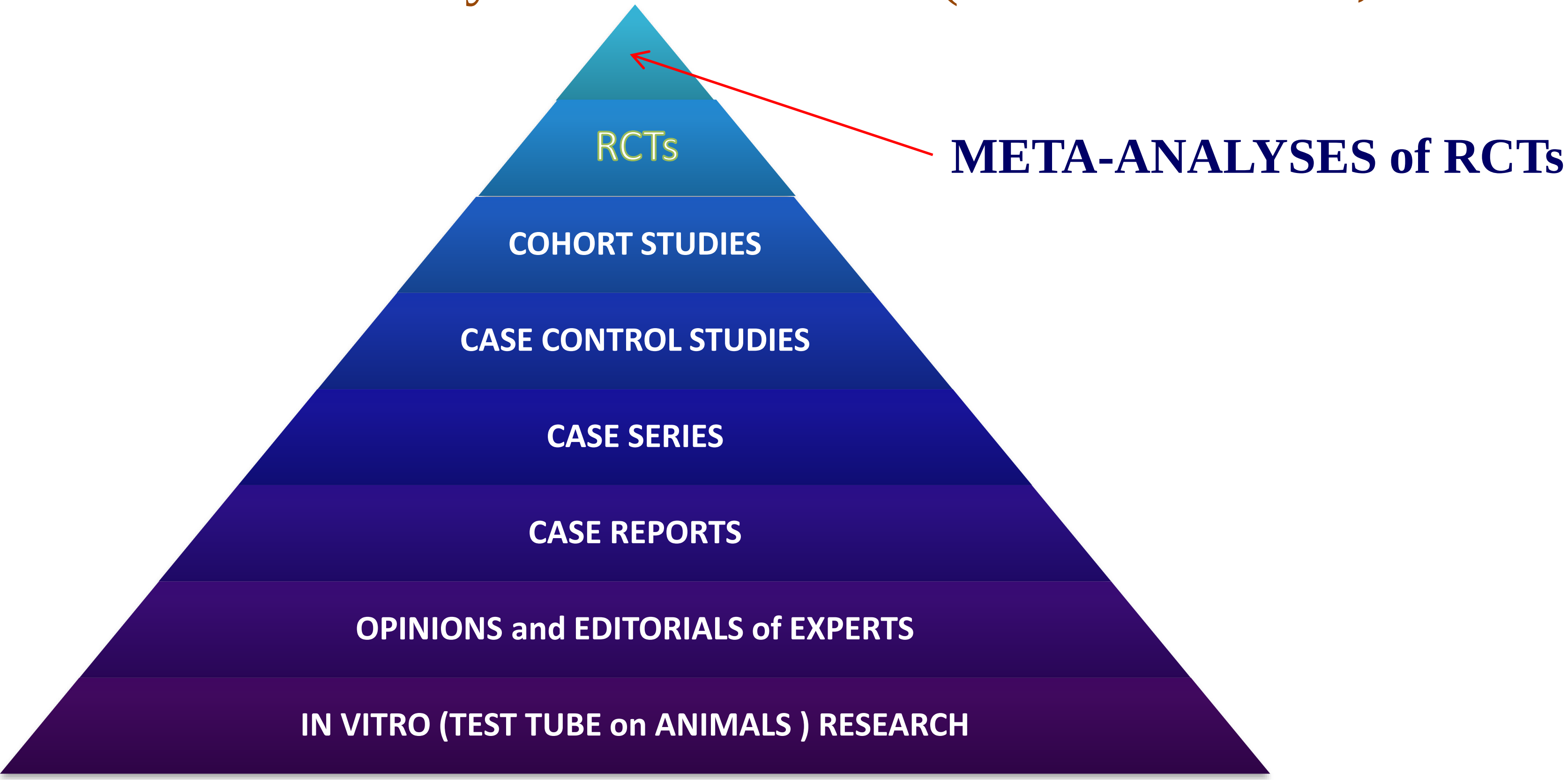
Evidence Based Medicine (EBM)

EBM is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients. The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research. (From BMJ 1996;312:71-72).



Meta-analysis: Goal

- Meta-analysis is a clinical-statistical technique that allows to assemble the results of more clinical trials on the same treatment in a single cumulative result (pooled)
- The primary goal is to put together more homogeneous studies, each on a limited number of cases, to estimate the overall effect, as if it had been conducted only one study on the total number of cases
- Ex.: I can aggregate the results of 10 studies, of a population of 50 patients each, and estimate the effect as if they had been studied 500 patients in one study.

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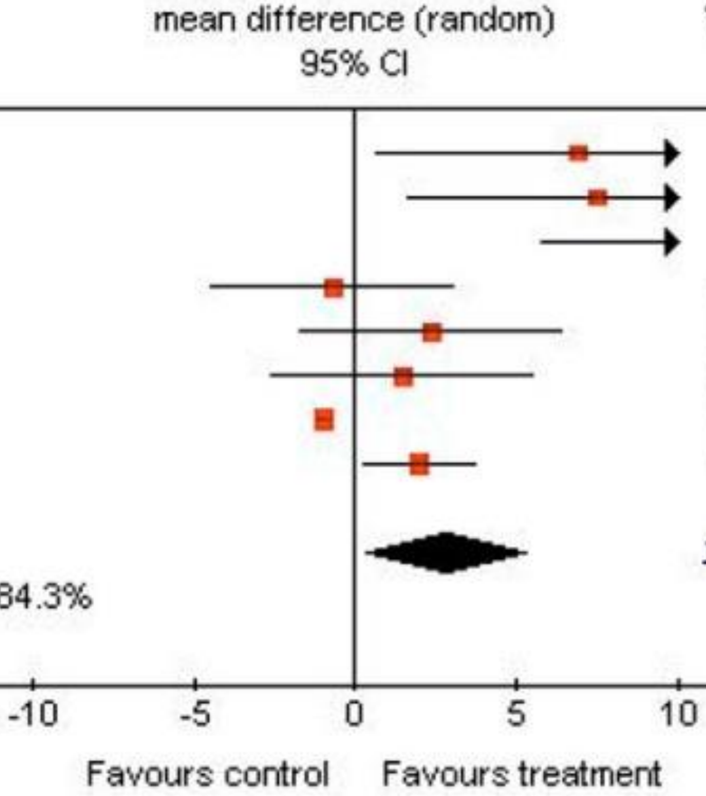
Meta-analysis: let's start from the end

Study or sub-category	mean difference (SE)	Weight %	mean difference (random) 95% CI
Silver	6.9000 (3.1900)	8.59	6.90 [0.65, 13.15]
Davas Pulse Cyc	7.5000 (3.0100)	9.13	7.50 [1.60, 13.40]
Pakas High Pred	12.4000 (3.3600)	8.10	12.40 [5.81, 18.99]
Pakas Low Pred	-0.7000 (1.9300)	13.12	-0.70 [-4.48, 3.08]
Hoyles	2.4000 (2.0800)	12.50	2.40 [-1.68, 6.48]
Nadashkevich	1.5000 (2.0800)	12.50	1.50 [-2.58, 5.58]
Tashkin	-1.0000 (0.0764)	18.86	-1.00 [-1.15, -0.85]
Airò	2.0000 (0.9100)	17.20	2.00 [0.22, 3.78]
Total (95% CI)		100.00	2.83 [0.35, 5.31]

Test for heterogeneity: $Chi^2 = 44.66$, df = 7 ($P < 0.00001$), $I^2 = 84.3\%$

Test for overall effect: $Z = 2.24$ ($P = 0.03$)



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The Evidence Based Medicine

	Pro	Contro
Traditional Reviews	- In-depht analysis on the topic - Superior Authors and Studies number - Greater case number - Easy conclusions, also if qualitative	-No standardized method -No quantitative measures of results -No measurement error -No measurement of data's heterogeneity

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Meta-analysis: method

1) Define the research question

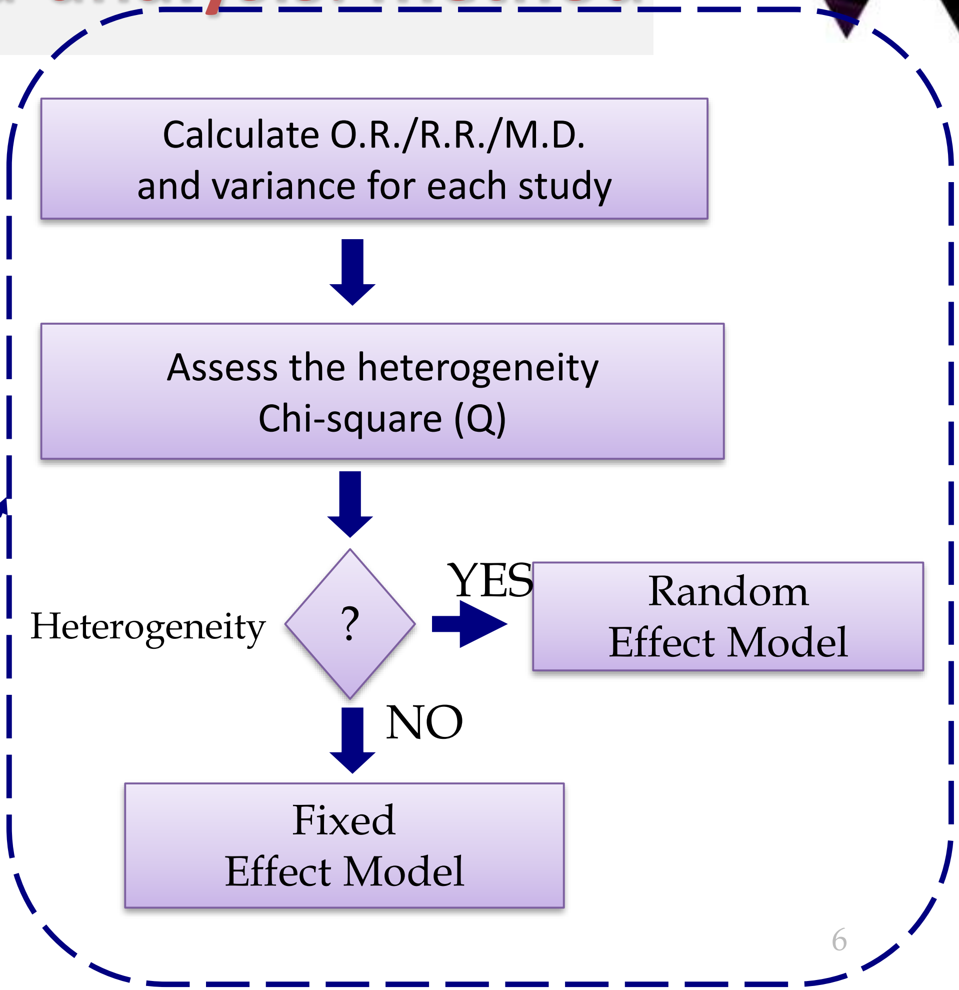
2) Search for articles relevant

3) Exclusion of non coherent, inconsistent, repeated studies

4) Calculating statistics each study

5) Data Pooling (fixed vs random effect)

6) Graphical Representation



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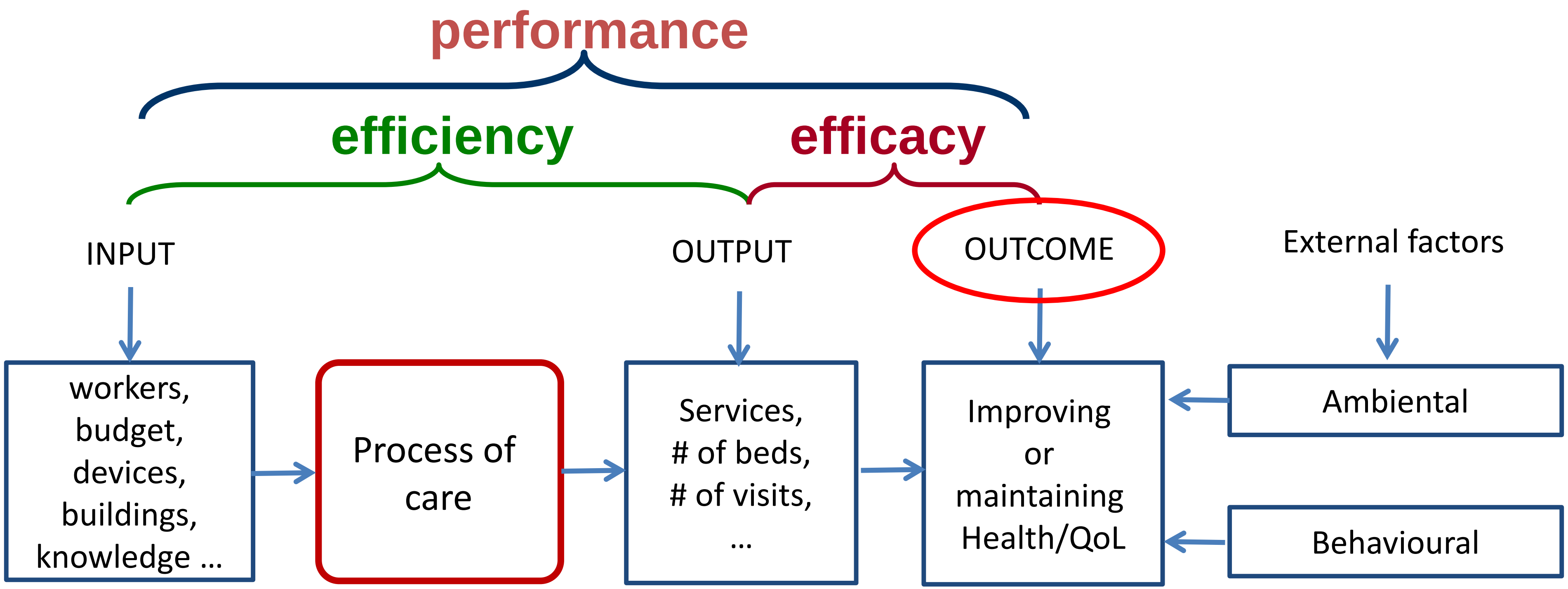
Where is this entering in HTA??



$$Efficiency = \frac{output}{input} \quad Efficacy = \frac{outcome}{output} \quad Performance = \frac{outcome}{input}$$

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Outcomes

- Outcomes (independent variabiles) can be:
  - Dichotomy (death/alive, positive/negative etc…)
  - Continue (diuresis, BP variation, etc…)

- Outcome will be called *Effect Size*

- Each selected paper we will calculate an *outcome*$_i$ (O_i) e its variance [$Var(O_i)$]:
  - discrete outcomes: Odds Ratio (OR_i) or Relative Risk (RR_i) depending from the study design;
  - conterminous outcomes: Mean Difference (MD_i)
  - 95% confidence interval ($IC_{95\%}$)

Meta-analysis: the statistics

1) Odds Ratio/ Relative Risk/ Mean Difference

2) Variance

3) 95% Confidence Interval (95%CI)

4) Chi square / P-Value

5) Pooling of results

6) Graphical representations: Forest and Funnel Plot

Meta-analysis: statistics computation

STATISTICAL INFERENCE: to investigate some parameters of a population (e.g. all the Italians) from the data achieved observing a subsample (e.g. all the Italians in this room).

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Statistical inference

1. If you have sufficient data, you could estimated PdF
2. (hypothesis on PdF) parameter estimation

- *mean*
- *variance*
- *Confidence interval*

3. Hypothesis testing
The groups are homogenous?
The differences are by chance?

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- The hypothesis expressed in terms of population parameters, such as mean and variance, is referred as stastical hypothesis. (e.g. "the two populations are statistically homogenous")

- The procedure done to refuse of accept the stastical hypothesis using the data of a sample is referred as

HYPOTHESIS TESTING

"Null hypothesis" Ho/ Alternative hypothesis H1

Statistical TEST (Chi, Student, Fisher, Anova)

You refuse Ho if the value of an aggregate statistically is higher / lower than a critical value

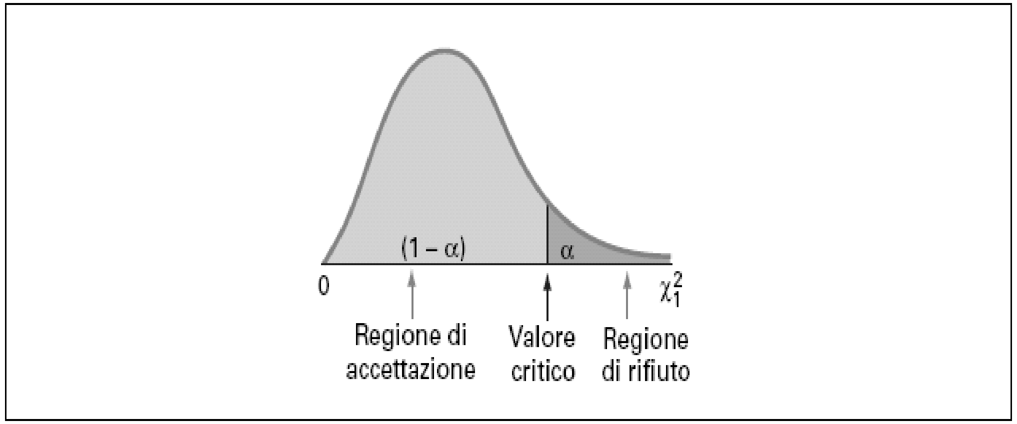
Table
-P-Value

SIGNIFICANCE OF A STATISTICAL TEST

The significance of statistical test is represented by the risk to refuse by error the null hypothesis, when this is true.

By convention two levels are adopted:

- If the probability that the null hypothesis is true is lower or equal to 5% (P<=0.05) the difference between the two populations is significant
- If the probability that the null hypothesis is true is lower or equal to 1% (P<=0.01) the difference between the two populations is extremely significant



Chi square test

In order to compare the proportions of cases in two indepedent groups, you can build a **contingency table sized 2×2** in which the number (or percentag) for each group are reported

Contingency table

	Variabile di colonna (gruppi)		
Variabile di riga	1	2	Totale
Successi	X_1	X_2	X
Insuccessi	$n_1 - X_1$	$n_2 - X_2$	$n - X$
Totale	n_1	n_2	n

dove:
- X_1 = numero di successi nel gruppo 1
- X_2 = numero di successi nel gruppo 2
- $n_1 - X_1$ = numero di insuccessi nel gruppo 1
- $n_2 - X_2$ = numero di insuccessi nel gruppo 2
- $X = X_1 + X_2$ = numero totale di successi
- $n - X = (n_1 - X_1) + (n_2 - X_2)$ = numero totale di insuccessi
- n_1 = ampiezza campionaria del gruppo 1
- n_2 = ampiezza campionaria del gruppo 2
- $n = (n_1 + n_2)$ = ampiezza campionaria totale

NB: I GdL di una tabella r * k saranno (r-1) * (k-1).

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Chi square test

In order to verify the null hypothesis, i.e. no difference between the two proportions (*H0: π1 = π2)* against the alternative hypothetis: (*H1: π1 ≠ π2), the χ2 statistics could be computed* as follows:

$$\chi^2 = \sum_{cells} \frac{(f_o - f_e)^2}{f_e}$$

The statistic χ2 is obtained by computing for each cell the squared difference betweem the observed frequency *(f0=x/no) and the estimated one (fe=X/n), divided by fe, and then summing the results for each cells*.

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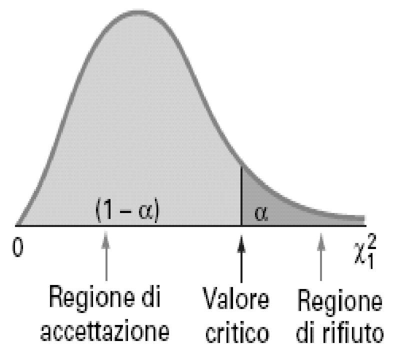
Chi square test

To computed the expceted frequency, the null hypothesis is considered true, the proportions among the groups should be the same.
To estimate the parameter, you could utilize a combination of the two frequencies, referred as p*

$$p^* = \frac{x_1 + x_2}{n_1 + n_2} = \frac{x}{n}$$

Chi Square Test

The selected statistics follows the pdf of Chi square with one degree of freedom



Given α, the null hypothesis should be rejected if the observed value of the statistic χ2 is higher than the critical value X2
of a pdf χ2 with 1 degree of freedom

Area nella coda di destra

Gradi di libertà	.995	.99	...	.05	.025	.01	.005
1			...	3.841	5.024	6.635	7.879
2	0.010	0.020	...	5.991	7.378	9.210	10.597
3	0.072	0.115	...	7.815	9.348	11.345	12.838
4	0.207	0.297	...	9.488	11.143	13.277	14.860
5	0.412	0.554	...	11.071	12.833	15.086	16.750

Fonte: Tavola E.4.

Meta-analysis: statistics computation 1/3

- Let have a study with a treatment group (T) and a control group (C), two cases could occur:

Binary variables

- You can abstract:

	Positive	Negative
Treatment	*A*	*b*
Control	*C*	*d*

- *The outcome could be*

$$OR = \frac{\frac{a}{c}}{\frac{b}{d}} = \frac{ad}{bc}$$

$$RR = \frac{\frac{a}{a+b}}{\frac{c}{c+d}}$$

- Confidence interval

$$CI_{95\%} = Outcome \pm (1.96 * SD(Outcome))$$

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Meta-analysis: statistics computation 1/3

- Let have a study with a treatment group (T) and a control group (C), two cases could occur:

Continuous variable

- You can abstract:

	Mean	SD
Treatment	μ_T	σ_T
Control	μ_C	σ_C

- *The outcome will be:*

$$\boxed{MD = \mu_t - \mu_c}$$

- Confidence interval

$$\boxed{CI_{95\%} = Outcome \pm (1.96 * SD(Outcome))}$$

Meta-analysis: statistics computation 2/3

- Variance of OR:

$$\mathrm{Var}[\mathrm{Ln}(\mathrm{OR})] = \frac{1}{a} + \frac{1}{b} + \frac{1}{c} + \frac{1}{d}$$

- Variance of RR

$$\mathrm{Var}[\mathrm{Ln}(\mathrm{RR})] = \frac{1}{a} - \frac{1}{a+b} + \frac{1}{c} - \frac{1}{c+d}$$

Meta-analysis: statistics computation 3/3

- Variance of MD

$$\boxed{\mathrm{Var}(\mathrm{MD}) = \sigma^2\left(\frac{1}{n_t} + \frac{1}{n_c}\right)}$$

- Combined standard deviation
  (Hedges and Olkin Formula)

$$\boxed{\sigma = \sqrt{\frac{(n_t - 1)(\sigma_t)^2 + (n_c - 1)(\sigma_c)^2}{n_t + n_c - 2}}}$$

WC2015, Toronto, Canada

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Meta-analysis: outcome

- Results of meta-analysis is a weighted average of the outcomes of the selected study:

$$Outcome_{Pooled} = \frac{\sum_{i=1}^{k} W_i O_i}{\sum_{i=1}^{k} W_i}$$

$$Var[O_{Pooled}] = \sqrt{\frac{1}{\sum_{i=1}^{k} W_i}}$$

… how to computed W_i?

- The results could be represented by two plots:
  - Forest Plot: to show the pooled outcome
  - Funnel Plot: to estimate eventual bias or error

- Performing a sensitivity analysis

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Meta-analysis: statistics computation 3/3

- Chi square test:

$$Q = \sum_{i=1}^{k} X_i T_i^{2} - \frac{\left(\sum_{i=1}^{K} X_i T_i\right)^2}{\sum_{i=1}^{K} X_i}$$

$$X_i = \frac{1}{Var_i}$$

- Data Pooling

P Value

Fixed Effect Model

$$W_i = X_i$$

Random Effect Model

$$W_i^{*} = \frac{1}{\left(\frac{1}{X_i} + \tau^2\right)}$$

$$\begin{cases} \tau^2 = \dfrac{(Q-(k-1))}{U} & [Q > k-1] \\ \tau^2 = 0 & [Q < k-1] \end{cases}$$

OUTCOME

$$T_{Pooled} = \frac{\sum_{i=1}^{k} W_i T_i}{\sum_{i=1}^{k} W_i}$$

$$Var[T_{Pooled}] = \sqrt{\frac{1}{\sum_{i=1}^{k} W_i}}$$

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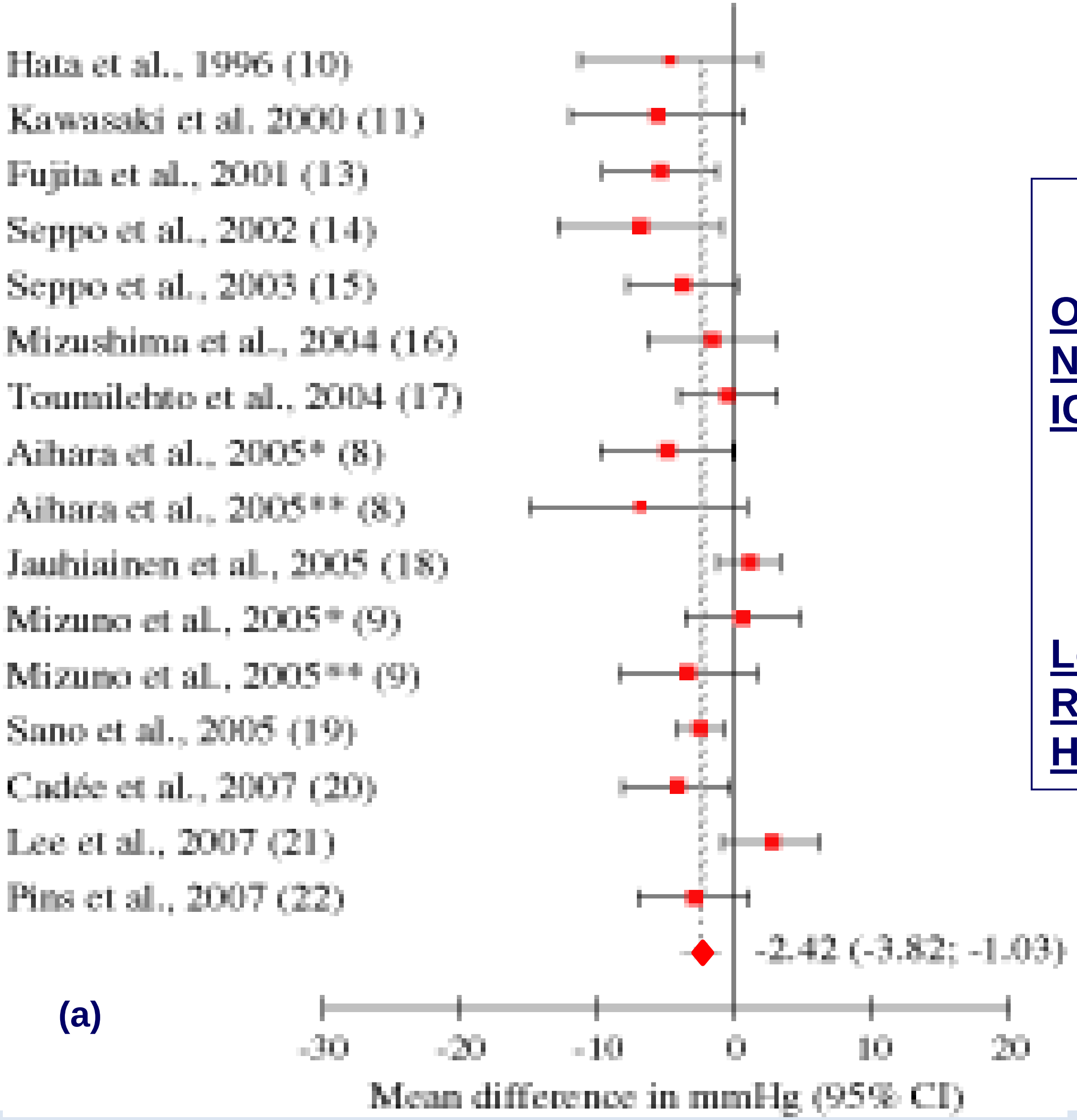
Meta-analysis: Forest Plot



Outcome

OR/RR/MD	(center of square)
Number of	(size of the square)$^{-1}$
IC	(error bar)

Line of non-significant

Left	in favor of experimental treatment
Right	in favor of control treatment
Heterogeneity	please, see following slides

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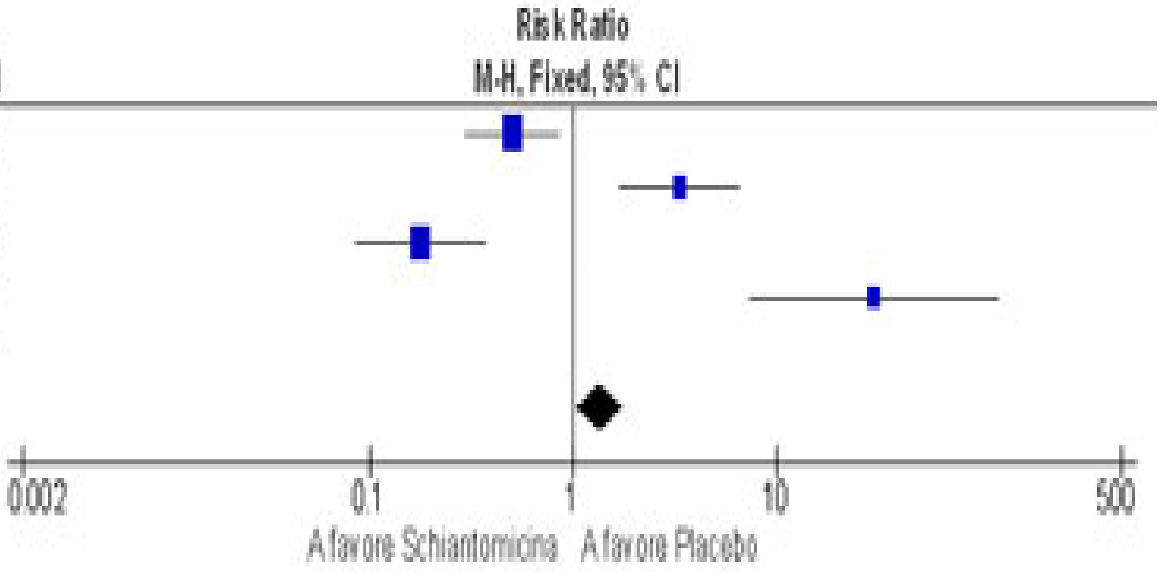
Meta-analysis: Forest Plot

Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Ubalda 1999	20	1250	40	1250	44.2%	0.50 [0.29, 0.85]
Romero 2003	40	300	10	250	12.1%	3.33 [1.70, 6.53]
Ramba 2001	9	500	30	300	41.5%	0.18 [0.09, 0.37]
Fratello Homo 2005	60	500	2	500	2.2%	30.00 [7.37, 122.06]
Total (95% CI)	**129**	**2550**	**82**	**2300**	**100.0%**	**1.36 [1.05, 1.77]**

Heterogeneity: $Chi^2 = 68.58$, $df = 3$ ($P < 0.00001$); $I^2 = 96\%$
Test for overall effect: $Z = 2.29$ ($P = 0.02$)



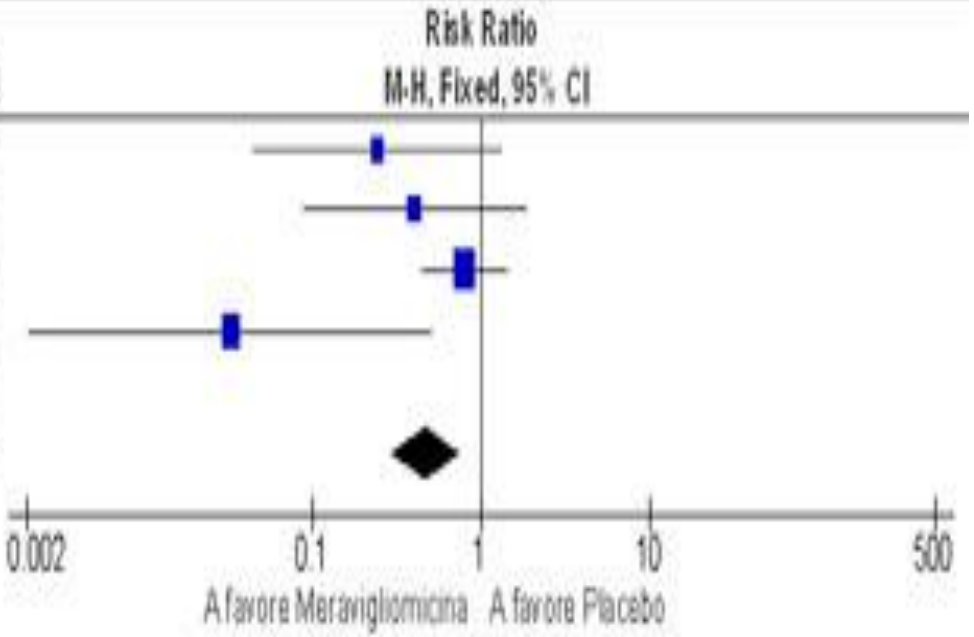
The plot shows the absence of robustness

Meta-analysis: Forest Plot

Study or Subgroup	Favore Meravigliomicina Events	Favore Meravigliomicina Total	Favore Placebo Events	Favore Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Sorella Bona 2007	2	250000	4	120000	10.6%	0.24 [0.04, 1.31]
Raul 2000	2	20	5	20	9.8%	0.40 [0.09, 1.83]
Koi 2002	20	500	25	500	49.1%	0.80 [0.45, 1.42]
Donna Lorica 1996	0	20	15	20	30.4%	0.03 [0.00, 0.50]
Total (95% CI)	**24**	**250540**	**49**	**120540**	**100.0%**	**0.47 [0.29, 0.75]**

Heterogeneity: $Chi^2 = 7.62$, $df = 3$ ($P = 0.05$); $I^2 = 81\%$

Test for overall effect: $Z = 3.17$ ($P = 0.002$)



Meta-analysis: Funnel Plot

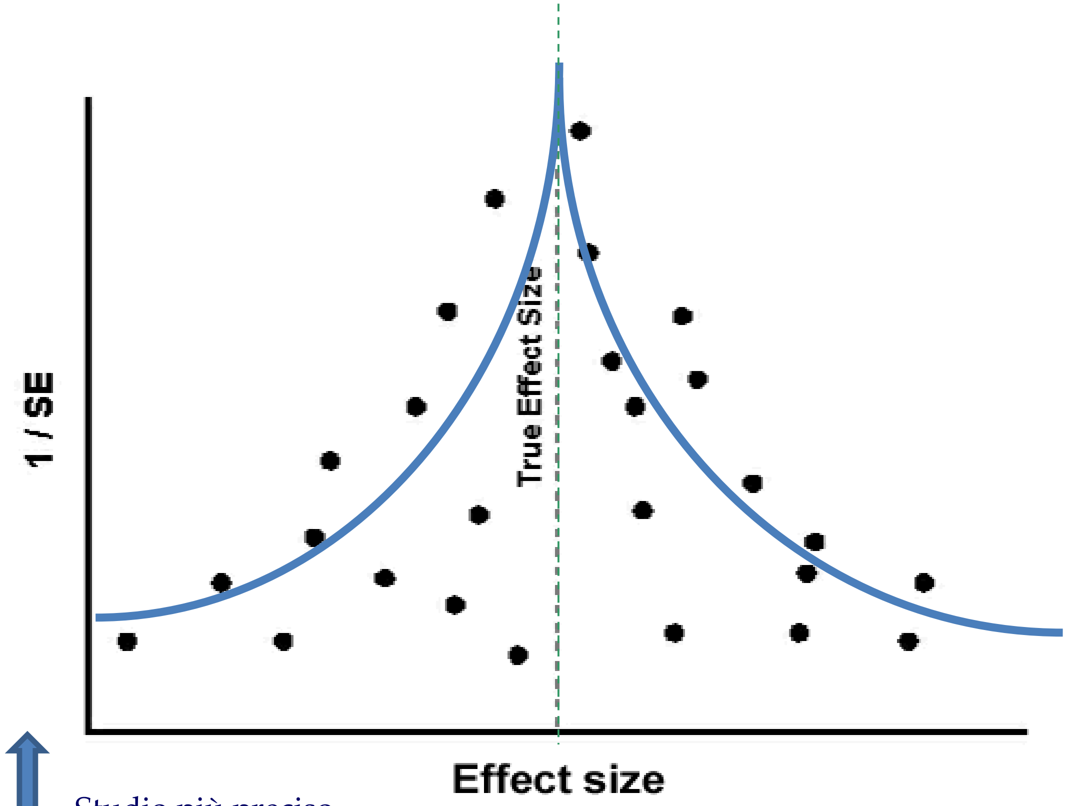


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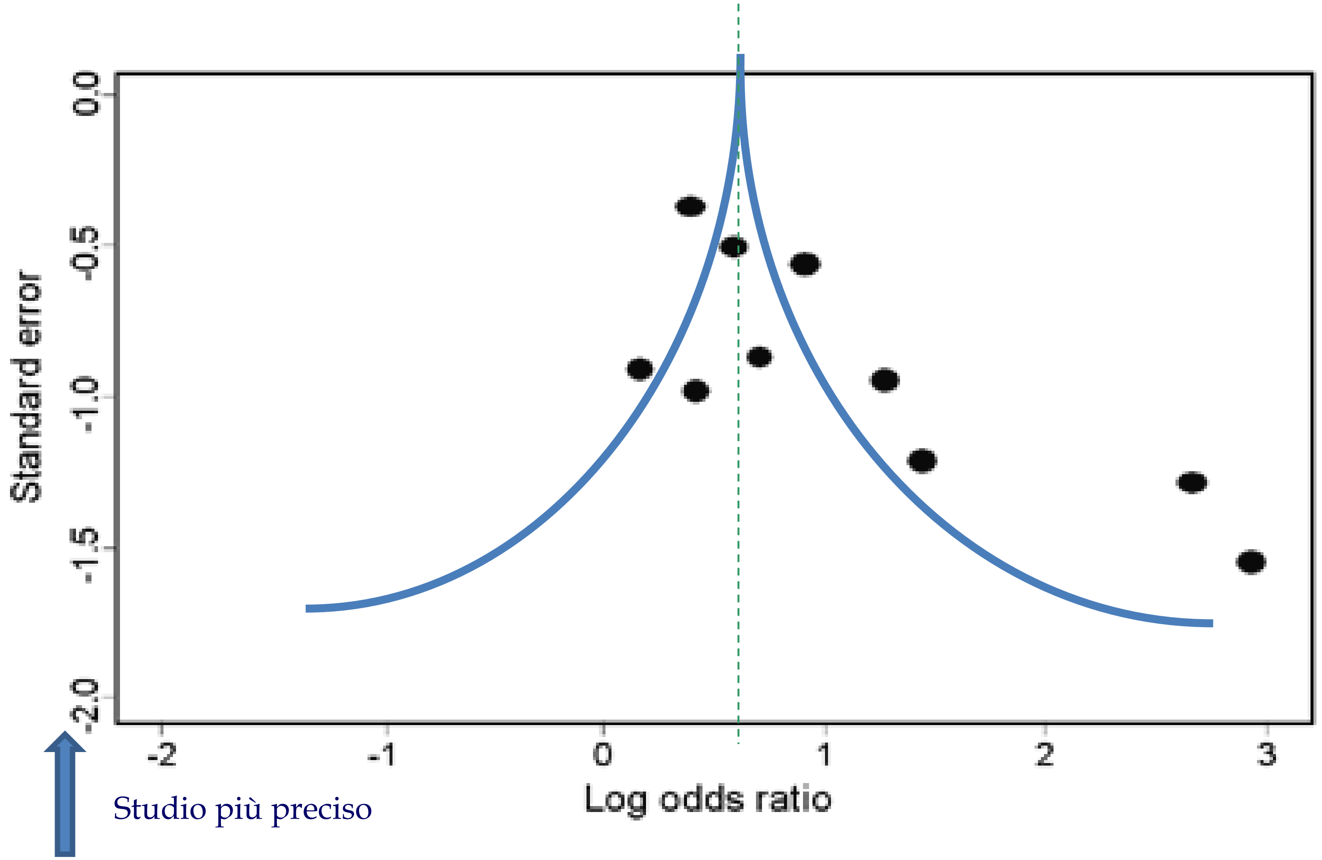
Figure 1.
A fictitious funnel plot with no publication bias

Meta-analysis: Funnel Plot



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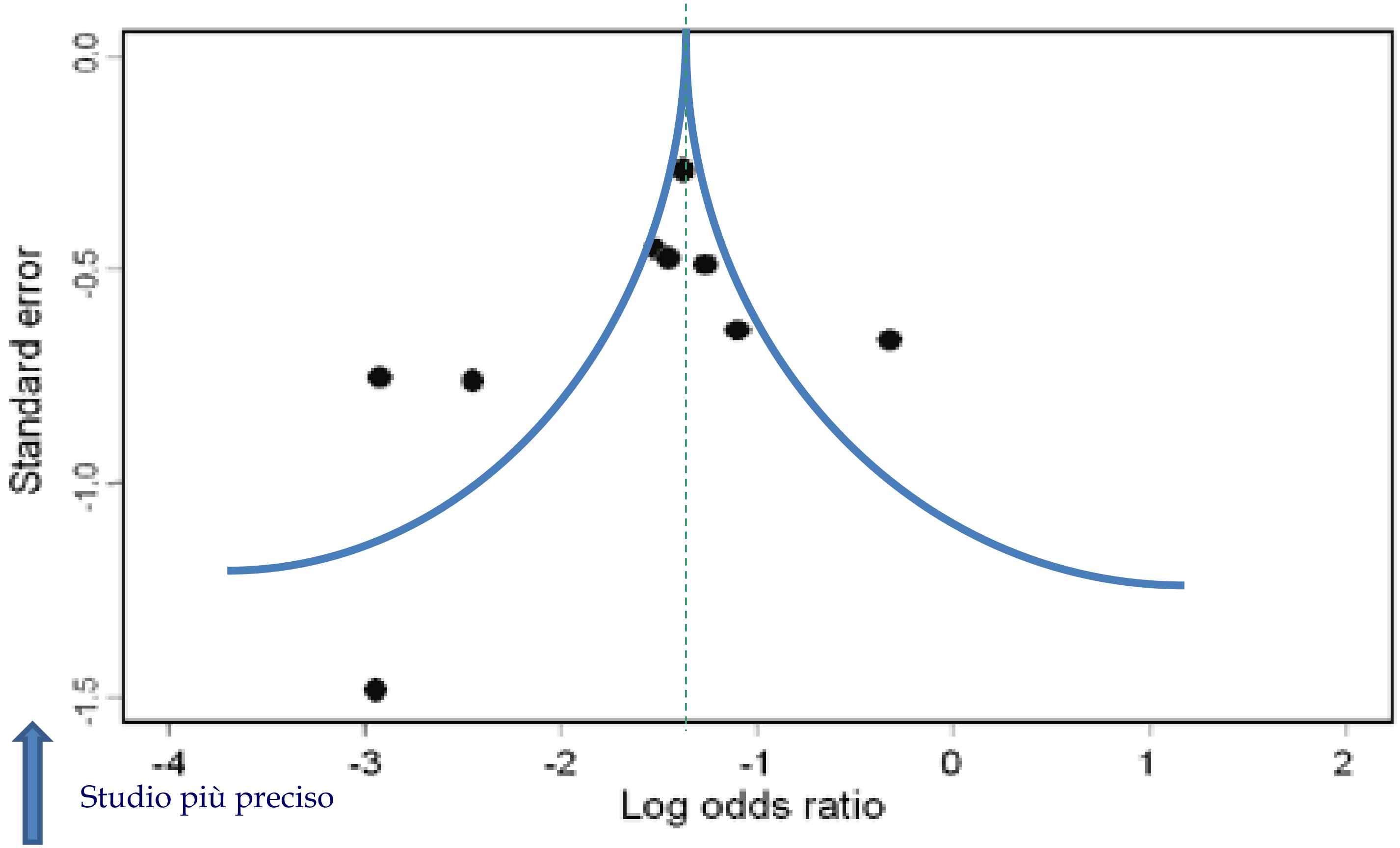
Meta-analysis: Funnel Plot



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Meta-analysis: advantages

- The advantages:

- ❑ quantitative measurement of the results, with an estimation of the uncertainty.
- ❑ higher sample size, compared to that of each clinical study

Meta-analysis: limitations

- The main limitations are:
  - ❑ related to statistical analysis (hypothesis)
  - ❑ heterogeneity among studies:
    - Sample (inclusion / exclusion criteria)
    - Health provider (e.g. university hospital versus small clinic)
    - Health management
    - Costs related to the procedures
  - ❑Time: the first included study could be published many years before the last one.

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