# Healthcare Technology Engineering

WARWICK

Evidence Based Medicine and Meta-analysis
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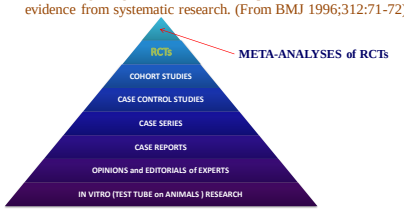
## Evidence Based Medicine (EBM)

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).

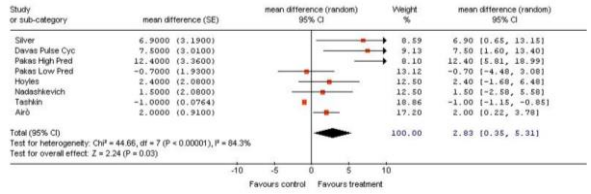





## Meta-analysis: Goal

- 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.

## Meta-analysis: let's start from the end






## The Evidence Based Medicine

| | Pro | Contro |
|---|---|---|
| ***Traditional Reviews*** | - In-dept analysis on the topic<br>- Superior Authors and Studies number<br>- Greater case number<br>- Easy conclusions, also if qualitative | -No standardized method<br>-No quantitative measures of results<br>-No measurement error<br>-No measurement of data's heterogeneity |
| ***Systematic Reviews*** | - As above<br>- Presence of an explicit method for the selection of the Studies | - No quantitative measurement of results<br>- No measurement error<br>- No measurement of data's heterogeneity |
| ***Meta-Analyses*** | - Standardized method<br>- Quantitative measurement of Results<br>- Error measurement<br>- Data's heterogeneity Measurement | -Exclusion of a large number of studies<br>-Difficulty Or potential inability to reach conclusions look |

Benchmark: RCT



## 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

Calculate O.R./R.R./M.D. and variance for each study

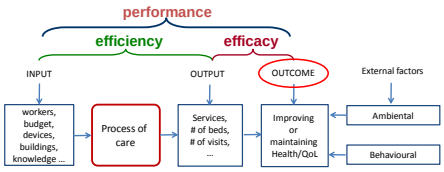
Assess the heterogeneity Chi-square (Q)

Heterogeneity ?

YES → Random Effect Model

NO → Fixed Effect Model

## Where is this entering in HTA??




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



## 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).



## 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?*



- 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)

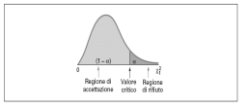
You refuse Ho if the value of an aggregate statistically is higher / lower than a critical value → Table -P-Value

## 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).



## 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.*

## Chi square test

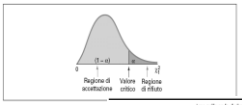
To computed the expceted frequency, the null hypothesis is considered true, the proportions among the groups should be the same.
To estimate the parameter, you could utilize a combination of the two frequencies, referred as p*

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



## 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 $\chi^2$ is higher than the critical value X2
*of a pdf $\chi^2$ 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 F.4.



## Test Chi Squared

Il test $\chi^2$ opportunamente generalizzato può essere utilizzato per confrontare le proporzioni di più popolazioni indipendenti.
Supponiamo di voler verificare l'ipotesi nulla secondo cui le proporzioni di *c popolazioni sono* uguali :

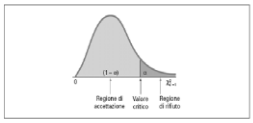
*H0: π1 = π2 = ... = πc*
*contro l'alternativa*
*H1: non tutte le πj sono uguali tra loro (con j=1,...,c)*

Per risolvere questo problema dovremo costruire una tabella di contingenza di due righe (successo e insuccesso) che avrà un numero di colonne pari a *c*.
La statistica test sarà la stessa, ma la frequenza attesa viene calcolata dalla stima di p*
*π = π1 = π2 = ... = πc che in questo caso si ottiene come*
combinazione delle *c frequenze campionarie:*

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

## Test Chi Squared

La statistica test si distribuisce approssimativamente secondo una distribuzione chiquadrato con (2−1)×(c−1)=(c−1) *gradi di libertà*
Fissato α, l'ipotesi nulla dovrà essere rifiutata se il valore osservato della statistica $\chi 2$ è maggiore del valore critico $\chi 2$ *di una distribuzione* $\chi 2$ *con (c−1) gradi di libertà*






## Test Chi Squared

| osservati | morti | sopravvissuti | totale |
|---|---|---|---|
| agente A | 22 | 48 | 70 |
| agente B | 24 | 26 | 50 |
| totale | 46 | 74 | **120** |

$$\text{frequenza attesa} = \frac{\text{totale riga} \cdot \text{totale colonna}}{\text{totale generale}}$$

| attesi | morti | sopravvissuti | totale |
|---|---|---|---|
| agente A | 26,83 | 43,17 | 70 |
| agente B | 19,17 | 30,83 | 50 |
| totale | 46 | 74 | **120** |



## Test Chi Squared

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

$$\chi^2_{2;1} = \frac{(22-26{,}83)^2}{26{,}83} + \frac{(48-43{,}17)^2}{43{,}17} + \frac{(24-19{,}17)^2}{19{,}17} + \frac{(26-30{,}83)^2}{30{,}83} =$$

$$= \frac{23{,}33}{26{,}83} + \frac{23{,}33}{43{,}17} + \frac{23{,}33}{19{,}17} + \frac{23{,}33}{30{,}83} = 0{,}87 + 0{,}55 + 1{,}24 + 0{,}76 = 3{,}42$$

Valori di $\chi^2$

| Gradi di libertà | Probabilità 5% | Probabilità 1% |
|---|---|---|
| 1 | 3.841 | 6.635 |
| 2 | 5.991 | 9.210 |
| 3 | 7.815 | 11.345 |
| 4 | 9.488 | 13.277 |
| 5 | 11.070 | 15.086 |
| 6 | 12.592 | 16.812 |
| 7 | 14.067 | 18.475 |
| ... | ... | ... |

$\chi^2 < \chi^2_s$

## 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*

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

- 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 | $\mu_T$ | $\sigma_T$ |
| Control | $\mu_C$ | $\sigma_C$ |

- *The outcome will be:*

$$MD = \mu_t - \mu_c$$

- Confidence interval

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





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## Meta-analysis: statistics computation 2/3

- Variance of OR:

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

- Variance of RR

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





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## Meta-analysis: statistics computation 3/3

- Variance of MD

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

- Combined standard deviation (Hedges and Olkin Formula)

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



## Meta-analysis: outcome

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

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

… 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



## Meta-analysis: statistics computation 3/3

- Chi square test:

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

- Data Pooling

P Value

**Fixed Effect Model**

$$W_i = X_i$$

**Random Effect Model**

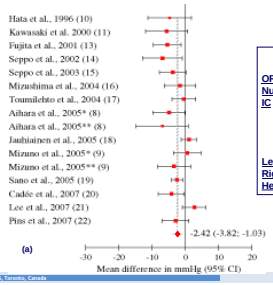
$$W_i^* = \frac{1}{\left(\frac{1}{X_i} + \tau^2\right)}$$

$$\tau^2 = \frac{(Q - (k-1))}{U} \quad [Q > k-1] \qquad \tau^2 = 0 \quad [Q < k-1]$$

OUTCOME

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

## Meta-analysis: Forest Plot




**Outcome**

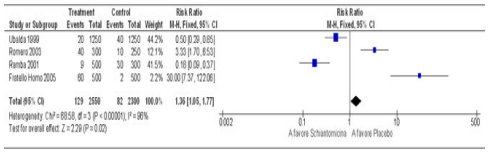
| | |
|---|---|
| **OR/RR/MD** | (center of square) |
| **Number of** | (size of the square)$^{-1}$ |
| **IC** | (error bar) |

**Line of non-significant**

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



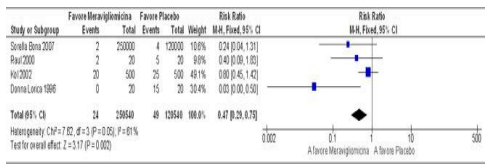
## Meta-analysis: Forest Plot




**The plot shows the absence of robustness**



## Meta-analysis: Forest Plot



## Meta-analysis: Funnel Plot

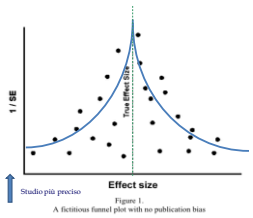
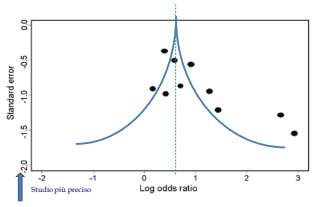



Figure 1.
A fictitious funnel plot with no publication bias

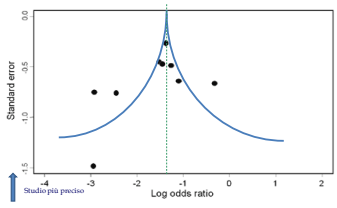


## Meta-analysis: Funnel Plot






## Meta-analysis: Funnel Plot



## 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.