PROGRAMMA DELLA GIORNATA

- **si riprendono i concetti della volta precedente**

- **"compiti" dati da fare a casa**

- **si richiama il programma del corso**

- 1.1.1.   Studi integrativi
  1.1.2.   Revisioni sistematiche

- **1.1.4.1.** **TEST DIAGNOSTICI**

- 1.1.5.   **Banche dati di revisioni sistematiche Cochrane**

- **Lettura di una revisione sistematica**

Systematic reviews

and meta-analysis

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The need for reviews

- The explosion of biomedical publishing
- Many of the studies give unclear or contradictory results
- Each trial may offer little information , the hope is that , when taken together a clearer picture will emerge

When systematic reviews are needed ?

- Systematic reviews are needed whenever there is a substantive therapeutic question , several primary studies -perhaps with disparate findings – and substantial uncertainty.

Systematic reviews

- "…in science…two processes are thus at work side by side, the reception of new material and the digestion and assimilation of the old…"

- 　　　　　Lord Rayleigh
Professor of Physics at Cambridge University 1884

Summary point

- **<u>Narrative Reviews</u>** are tools for health care workers,researchers,and policy maker who want to keep up with the evidence that is accumulating in their fields but…

- **<u>Systematic reviews</u>** allow for a more objective appraisal of the evidence than traditional narrative reviews

- **<u>Meta-analysis</u>** ,if appropriate,will enhance the precision of estimates of treatment effects,leading to reduced probability of false negative results

What's the right name

- Narrative Reviews

- Systematic Reviews. : reviews that has been prepared using a systematic approach to minimising biases and random errors which is documented in a material and methods section. With meta-analysis <u>Quantitative Systematic Reviews</u> .Without meta-analysis Qualitative Systematic reviews

- M.A. :a statistical technique for combining the results from independent studies which aims to produce a single estimate of a treatment effect
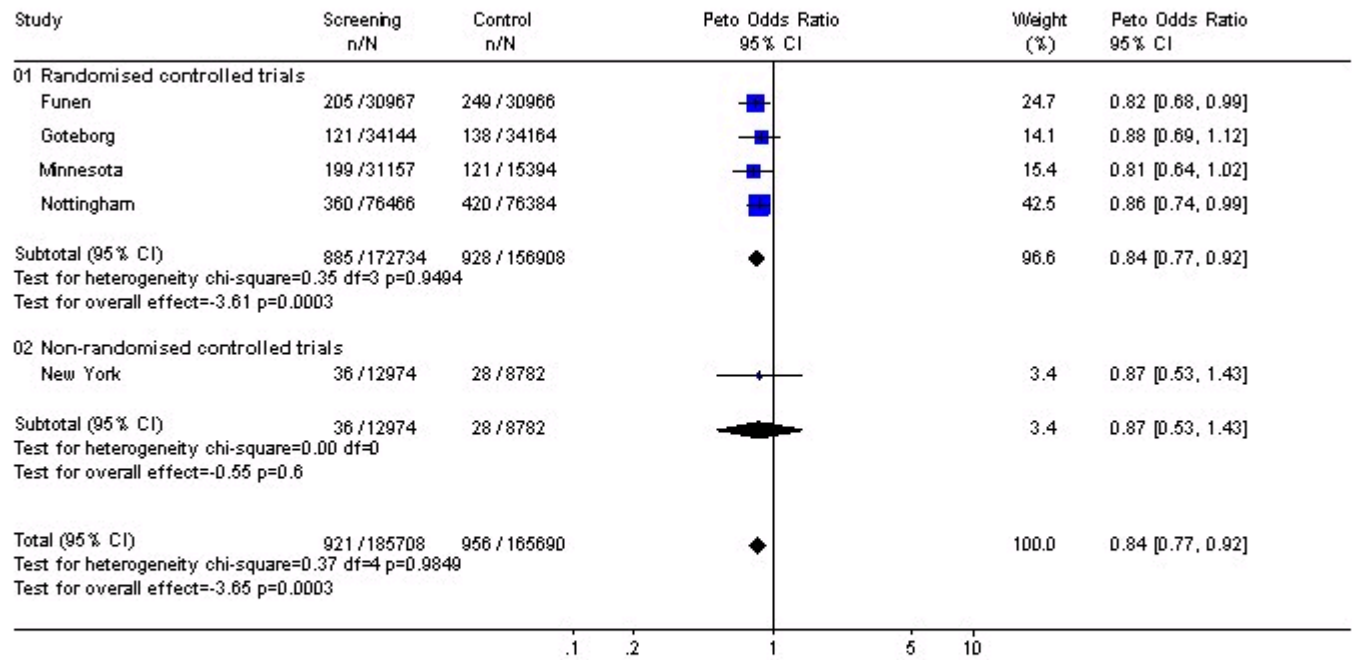
Meta-analysis

- Is most often used to assess the clinical effectiveness of healthcare interventions by combining data from two to more randomized control trials

- It provide a precise estimate of treatment effect giving due weight to the size of the different studies included

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Validity of Meta-analysis

- Depends on the quality of the systematic review on which it is based

- Good meta-analysis give complete coverage of all relevant studies,look for the presence of heterogeneity and explore the robustness of the main findings using sensitivity analysis

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Review: Screening for colorectal cancer using the faecal occult blood test, Hemoccult
Comparison: 01 All Hemoccult screening programs Vs Control
Outcome: 01 Colorectal cancer mortality

Study	Screening n/N	Control n/N	Peto Odds Ratio 95% CI	Weight (%)	Peto Odds Ratio 95% CI
01 Randomised controlled trials					
Funen	205 /30967	249 /30966		24.7	0.82 [0.68, 0.99]
Goteborg	121 /34144	138 /34164		14.1	0.88 [0.69, 1.12]
Minnesota	199 /31157	121 /15394		15.4	0.81 [0.64, 1.02]
Nottingham	360 /76466	420 /76384		42.5	0.86 [0.74, 0.99]
Subtotal (95% CI)	885 /172734	928 /156908		96.6	0.84 [0.77, 0.92]
Test for heterogeneity chi-square=0.35 df=3 p=0.9494					
Test for overall effect=-3.61 p=0.0003					
02 Non-randomised controlled trials					
New York	36 /12974	28 /8782		3.4	0.87 [0.53, 1.43]
Subtotal (95% CI)	36 /12974	28 /8782		3.4	0.87 [0.53, 1.43]
Test for heterogeneity chi-square=0.00 df=0					
Test for overall effect=-0.55 p=0.6					
Total (95% CI)	921 /185708	956 /165690		100.0	0.84 [0.77, 0.92]
Test for heterogeneity chi-square=0.37 df=4 p=0.9849					
Test for overall effect=-3.65 p=0.0003					

.1   .2   1   5   10

Author's Reply:

Contributors:
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GRAPHS

To view a graph or table, click on the outcome title of the summary table below.

To view graphs using MetaView, click on the "Show metaview" link at the top of the graph.

01 All Hemoccult screening programs Vs Control				
Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Colorectal cancer mortality	5	351398	Peto OR [95% CI]	0.84 [0.77, 0.92]

COVER SHEET

Title	**Screening for colorectal cancer using the faecal occult blood test, Hemoccult**
Reviewer(s)	**Towler BP, Irwig L, Glasziou P, Weller D, Kewenter J**

Limitations of narrative reviews

- Is subjective

- no clear the sources of informations

- no standardized methodological quality of studies

Distinction in meta-analysis

- A clear distinction should be made between meta-analysis of RCT and meta-analysis of epidemiological studies

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Limitations of a single study

- Often fails to detect ,or exclude, a difference in the effects of two therapies
- the number of patients included in trials is often inadeguate
- expl. drug < 10% mortality in IMA ; in order to detect such an effect with 90% certainty over 10000 in each treatment group are needed

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Principles of systematic reviews

- Carefully planned with a written protocol
- Formulation of a review question
- A priori definition of eligibility criteria for trials
- A comprehensive search of such trials and an assessment of their methodological quality
- There are different statistical methods for combining the data but there is not a single "correct" method

Principles of systematic reviews

- When interpreting results the reviewers should consider the importance of benefical and harmful effects and address economic implications and implications for future research

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Formulate review question

- Define inclusion and exclusion criteria
- **This require a clear statement of the intervention of interest**
- Partecipants
- interventions and comparisons
- outcomes
- study desing and methodological quality

Locate studies

- Develop a search strategy considering the following sources

  - CCTR

  - electronic databeses not covered by CCTR

  - handsearching of key journals

  - personal communication with experts in the filed

Select studies

- Have eligibility checked by more than one observer

- Develop strategy to resolve disagreement

Assess study quality

- Consider assessment by more than one observer

- Use simple score

- Always assess concealment of treatment allocation, blinding

- Consider blinding of observers to authors ,journals and institutions

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Again about quality

- Same question ?
- Same trials ?
- Same quality ?

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S.R. are the best of the best ?

- What is better for health care workers: meta-analyses of small trials or a large randomised controlled trial ?

Problems may arise

- A sistematic review may be done badly ; why ?

- -inappropriate aggregation of studies that differ in terms of intervention used or patients included

- -the findings from s.r. are not always in harmony with the findings from <u>large scale high quality single trial</u>

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Extract data

Analyse and present results

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Analyse and present results

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Interpret results

- Consider limitations and related bias
- Consider strenght of evidence
- Consider applicability
- Consider NNT and benefit/arm
- Consider economic implication
- Consider implications for future research

Type of reporting bias

- Publication bias

- Time lag bias

- Multiple publication bias

- Citation bias

- Language bias

- Outcome reporting bias

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Identifying randomized trials

- In 1993 before C.C. only 19000 reports of C.T. were identifiable in MEDLINE
- At the end of 1999 the *Cochrane Controlled Trials register* identify more than 250000 reports of controlled trials

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Sources to be searched to identify randomized trials for systematic reviews

- The Cochrane Controlled Trials Register

- MEDLINE and EMBASE

- Other database

- Journals

- Conference proceedings

- Reference lists

Quality

- Is difficult to define

- design
- conduct
- clinical relevance
- quality of reporting

Assessing the quality of randomized controlled trials

- Inadequate quality of studies may distort the results from systematic reviews and meta-analyses, evaluation of studies is routinely evaluated; this is best done using <u>sensitivity</u> analysis

- the use of summary score is problematic so:

- -concealment of treatment allocation

- -blinding

- -outcome assessment

- -handling of patient attrition

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Validity of a trial

- Internal validity

- External validity

Bias

- Any process at any stage of interference tending to produce results that differ systematically from the true values

Randomisation consists in two parts

- Generation of allocation sequences
  - Adequate
  - Inadequate

- Concealment of allocation sequences

  - Adequate

  - Inadequate

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Generation of allocation sequences

- Adequate if resulting sequences are unpredictable
  - computer generated random numbers
  - table of random numbers
  - coin tossing
  - throwing dice
- Inadequate if resulting sequences are predictable
  - according to date of birth
  - according to date of admission

Concealment of allocation sequences

- **<u>Adequate</u>** if patients and enrolling investigators cannot foresee assignment
  - central randomisation
  - a priori numbered or coded containers
- **<u>Inadequate</u>** if patients and investigators can foresee upcoming assignment
  - open allocation schedule
  - all procedures based on inadequate generation of allocation sequences

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Internal validity

- Is clearly a prerequisite for external validity; is the extent to which the results of a study are correct for the circumstances being studied; the aim is the reduction of systematic bias

  - selection bias
  - performance bias
  - detection bias
  - attrition bias

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Issues addressed by Jadad's quality assessment scale

- Randomisation
  - described as randommized ?
  - allocation sequences appropriately generated ?
- Blinding
  - described as double blind ?
  - control treatment described as hidden ?
- Patients attrition
  - described for each group(including the
  - number of patients lost or excluded) along
  - with the reasons ?

External validity

- The extent to which the results of a trial provide a correct basis for applicability to other circumstances

- Patients :age , sex , severity of disease , co-morbidity

- Treatment regimens: dosage,timing,concomitant therapies

- Settings:level of care ,experience and specialisation of care provider

- Modality of outcomes:definition of outcomes,lenght of follow up

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CONSORT

- Initiative to improve thequality of reporting of randomized controlled trials

QUOROM

- **Qu**ality

- **O**f

- **R**eporting

- **O**f

- **M**eta-analysees

- is the "gold standard " for reporting of S.R.

QUOROM

- Checklist of 18 items

- flow diagram

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Systematic reviews of observational studies

- Are as common as reviews of randomized controlled trials

- Confounding and selection bias often distort the findings of observational studies. Bigger is not necessarily better

- Meta-analyses of observational data can produce precise but spurious results so statistical combination is not a prominent component ;more is gained by examining possible sources of heterogeneity between the results from ob. studies

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Confounding and bias

- MRFIT
- ISIS-3

S.R. of prognostic variables

- Prognostic studies are difficult to search
- Prognostic variables should be evaluated in a sample ,of patients at a common point in the course of their disease
- Evaluation of study quality is essential
- A high proportion of prognostic studies are of poor methodologic quality

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Problems with S.R. of prognostic studies

- Difficulty of identifying all studies
- Inadequate reporting of methods
- Variation in study design
- Most studies are retrospective
- Variation in methods of analysis
- Lack of recognised criteria for quality assessment

Requirement for meta-analisys

- The main requirement for a worthwhile mata analisys is first and foremost a well-executed systematic review

Interpreting the main findings

- ## Blobbogram

  - Blob or square(the measured effect)
  - Horizontal line(usually 95% confidence interval)
  - The size of blob may vary to reflect the amount of information in that individual study
  - The lenght of horizontal line is the estimate of the treatment effect for that study

- ## Odds ratio (summary measure)

  - For practical purpose is similar to relative risk

Bias in meta-analysis

- **Location and selection of studies**
- " a statistical analysis which combines or integrates the results of several independent clinical trials considered by the analyst to be <u>combinable</u>"

- The key difficulty lies in deciding which set of studies are "combinable",so good meta-analysis will use explicit and objective criteria for excvlusionor rejection of studies

Heterogeneity

- Patient group
- Interventions applied
- Primary outcomes
- Different settings

Loss of information in important outcomes

- Dichotomous outcomes
  - Pain/no pain
  - Dead/alive
  - Ecc.
- Expl.
  - use of 50% reduction of pain
  - divide patients in "success" and "failure"

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Conflict with new experimental data

- Meta-analysis vs. mega trials

G.I.G.O. principle