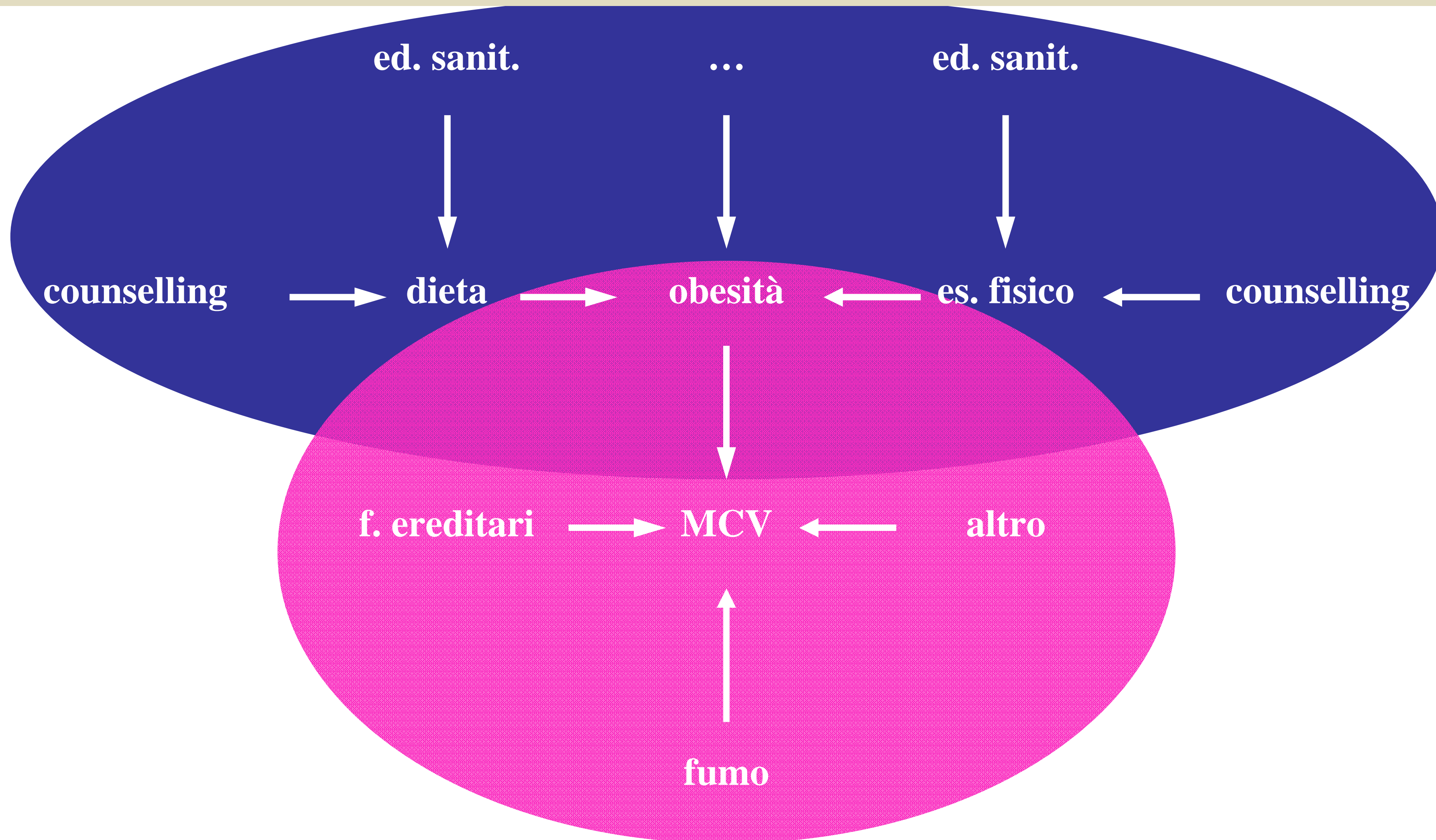
Università del Piemonte Orientale

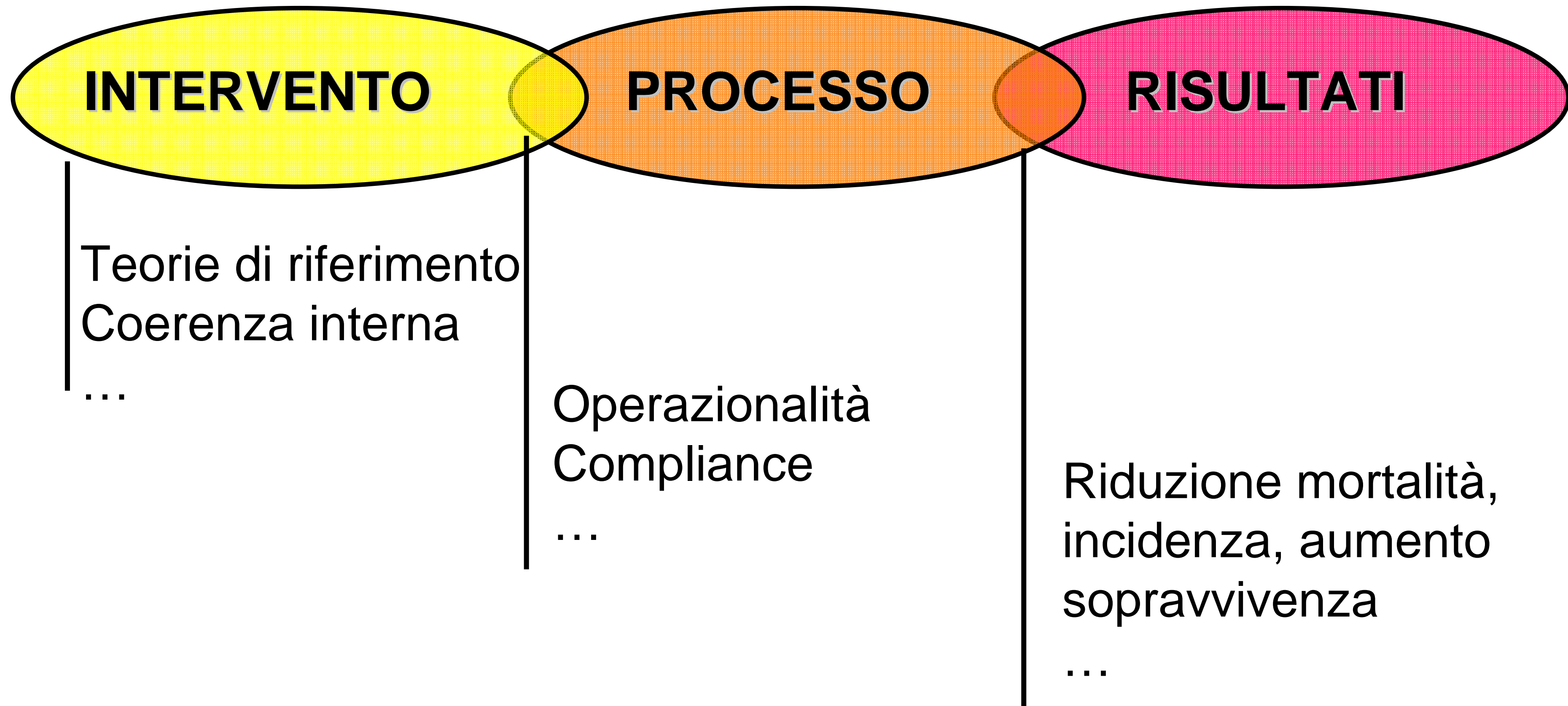
Corso di Perfezionamento in
EBM e metodologia delle revisioni sistematiche di studi di efficacia

Introduzione alla EBM

Ricerca eziologica vs ricerca di efficacia



Le dimensioni della qualità



Efficacia di Comunità

- ***Community effectiveness*** depends on:
  - efficacy of the intervention
  - diagnostic accuracy
  - provider compliance
  - patient compliance
  - coverage

Tugwell, Bennett, Sackett, Haynes.
J Chron Dis1985

Efficacia di Comunità

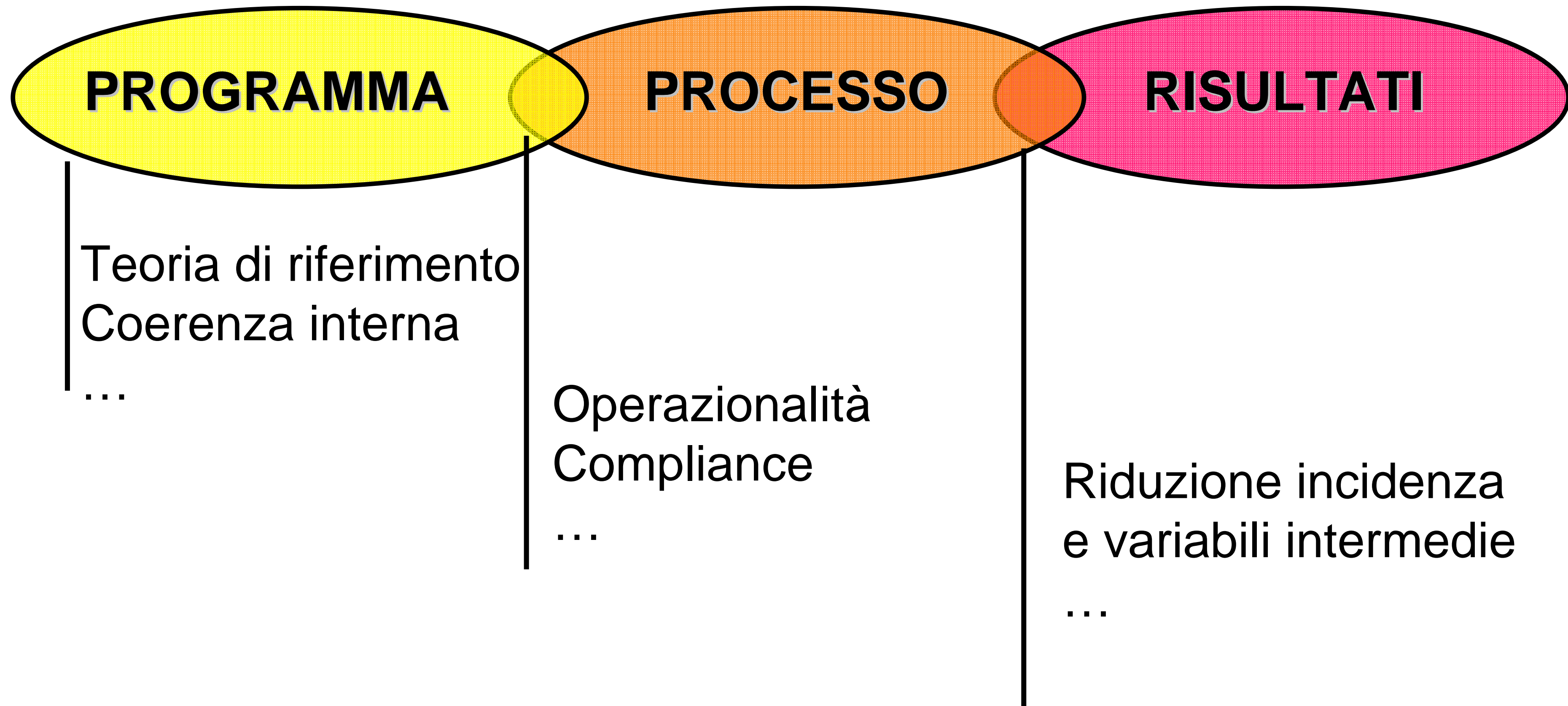
- For hypertention:
  - efficacy of the intervention 76%
  - diagnostic accuracy 95%
  - provider compliance 66%
  - patient compliance 65%
  - coverage 90%

  - community effectiveness

    (76%*95%*66%*65%*90%) = 28%

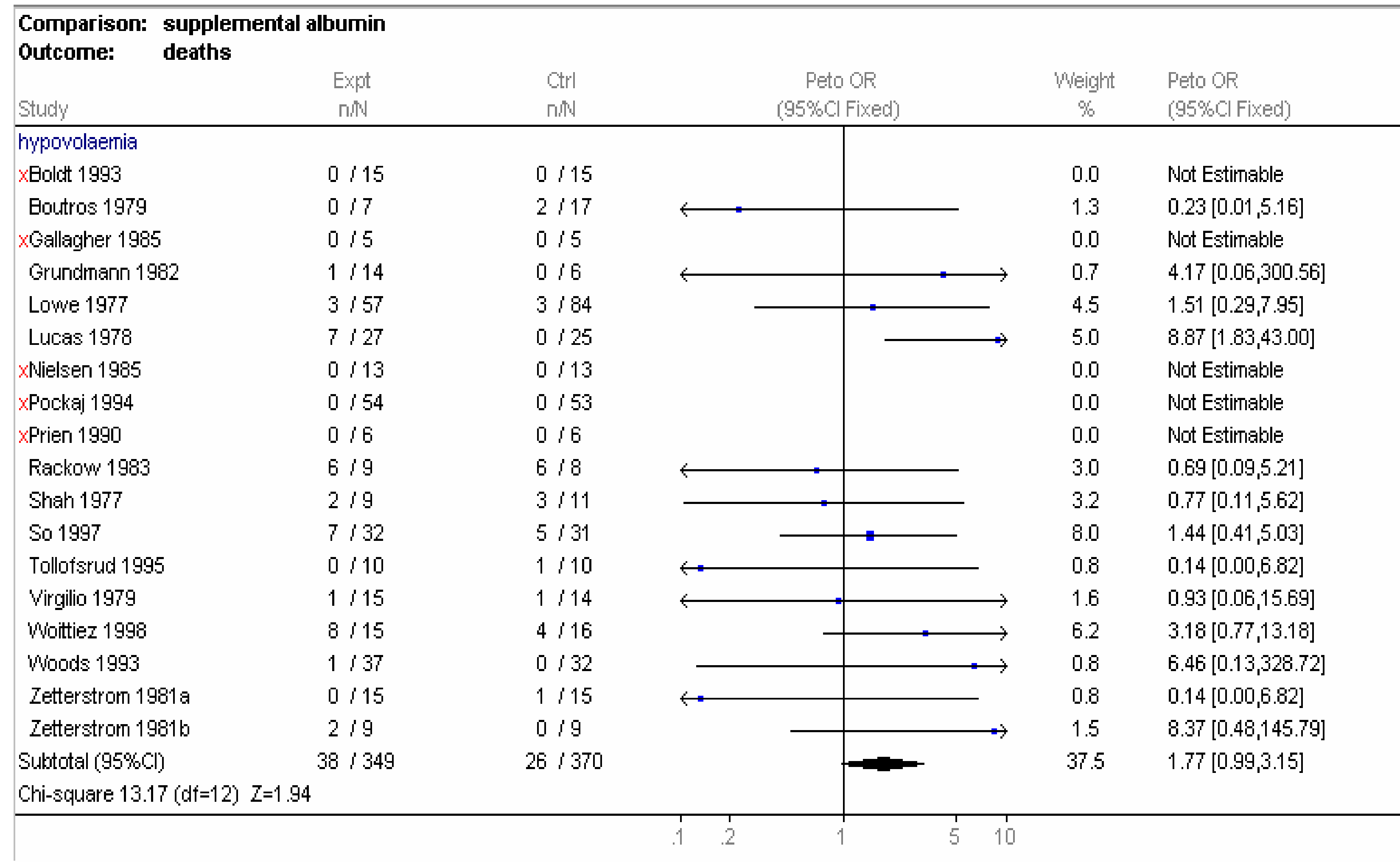
Tugwell, Bennett, Sackett, Haynes.
J Chron Dis1985

Le dimensioni della qualità



Possono il programma e il processo da soli predire i risultati?

Il caso dell'albumina (I)

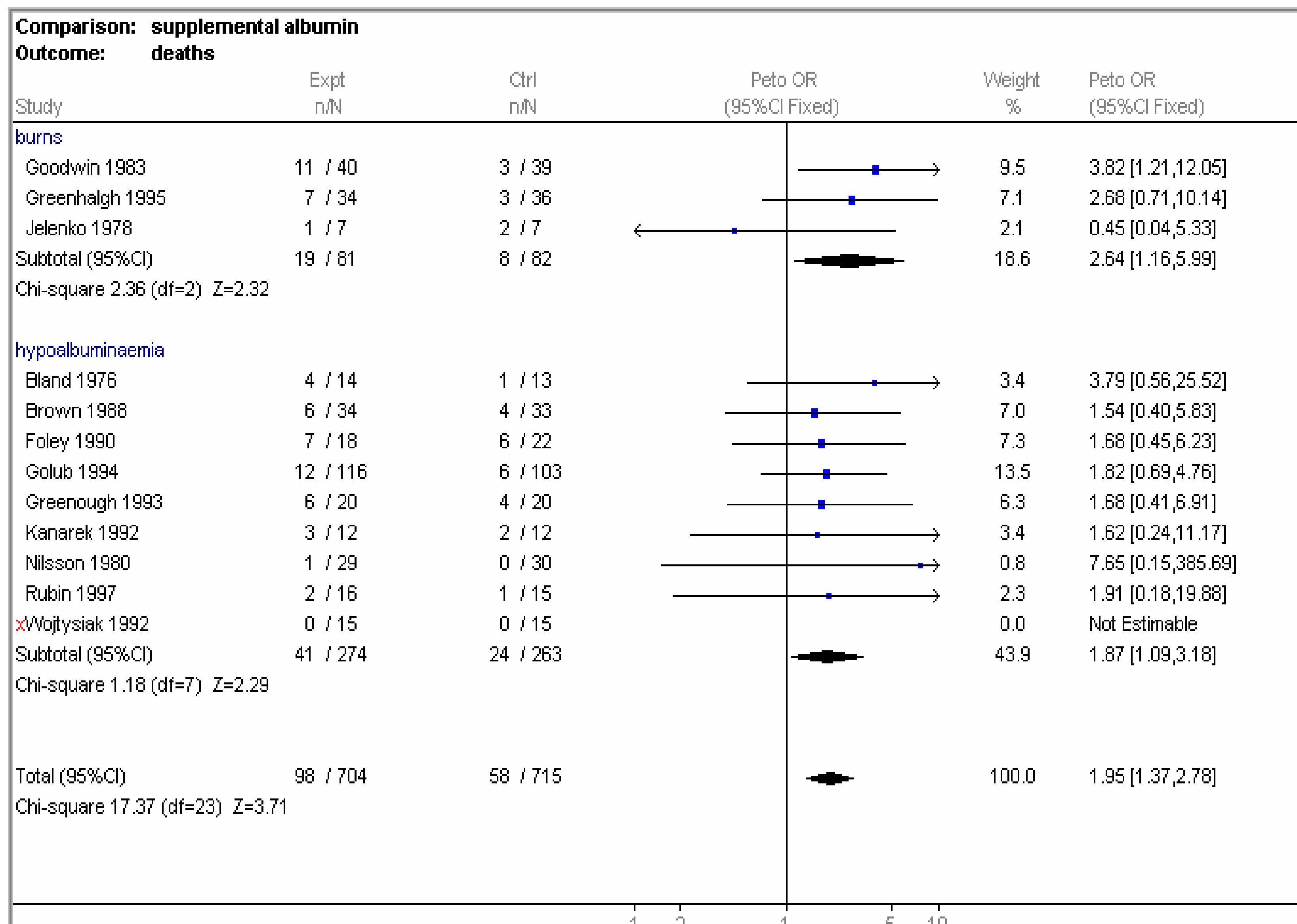


Comparison: **supplemental albumin**
Outcome: **deaths**

Study	Expt n/N	Ctrl n/N	Weight %	Peto OR (95%CI Fixed)
hypovolaemia				
xBoldt 1993	0 / 15	0 / 15	0.0	Not Estimable
Boutros 1979	0 / 7	2 / 17	1.3	0.23 [0.01,5.16]
xGallagher 1985	0 / 5	0 / 5	0.0	Not Estimable
Grundmann 1982	1 / 14	0 / 6	0.7	4.17 [0.06,300.56]
Lowe 1977	3 / 57	3 / 84	4.5	1.51 [0.29,7.95]
Lucas 1978	7 / 27	0 / 25	5.0	8.87 [1.83,43.00]
xNielsen 1985	0 / 13	0 / 13	0.0	Not Estimable
xPockaj 1994	0 / 54	0 / 53	0.0	Not Estimable
xPrien 1990	0 / 6	0 / 6	0.0	Not Estimable
Rackow 1983	6 / 9	6 / 8	3.0	0.69 [0.09,5.21]
Shah 1977	2 / 9	3 / 11	3.2	0.77 [0.11,5.62]
So 1997	7 / 32	5 / 31	8.0	1.44 [0.41,5.03]
Tollofsrud 1995	0 / 10	1 / 10	0.8	0.14 [0.00,6.82]
Virgilio 1979	1 / 15	1 / 14	1.6	0.93 [0.06,15.69]
Woittiez 1998	8 / 15	4 / 16	6.2	3.18 [0.77,13.18]
Woods 1993	1 / 37	0 / 32	0.8	6.46 [0.13,328.72]
Zetterstrom 1981a	0 / 15	1 / 15	0.8	0.14 [0.00,6.82]
Zetterstrom 1981b	2 / 9	0 / 9	1.5	8.37 [0.48,145.79]
Subtotal (95%CI)	38 / 349	26 / 370	37.5	1.77 [0.99,3.15]

Chi-square 13.17 (df=12) Z=1.94

Il caso dell’albumina (II)



Il caso dell'albumina (III)

Saturday 25 July 1998

BMJ

Excess mortality after human albumin administration in critically ill patients

Clinical and pathophysiological evidence suggests albumin is harmful

Papers p 235
Letters p 277
Science commentary p 240

Albumin is a medium weight colloid which plays an essential role in generating the colloid-osmotic pressure. It facilitates fluid retention in the intravascular space. Human albumin is often given to critically ill patients with life threatening hypo-

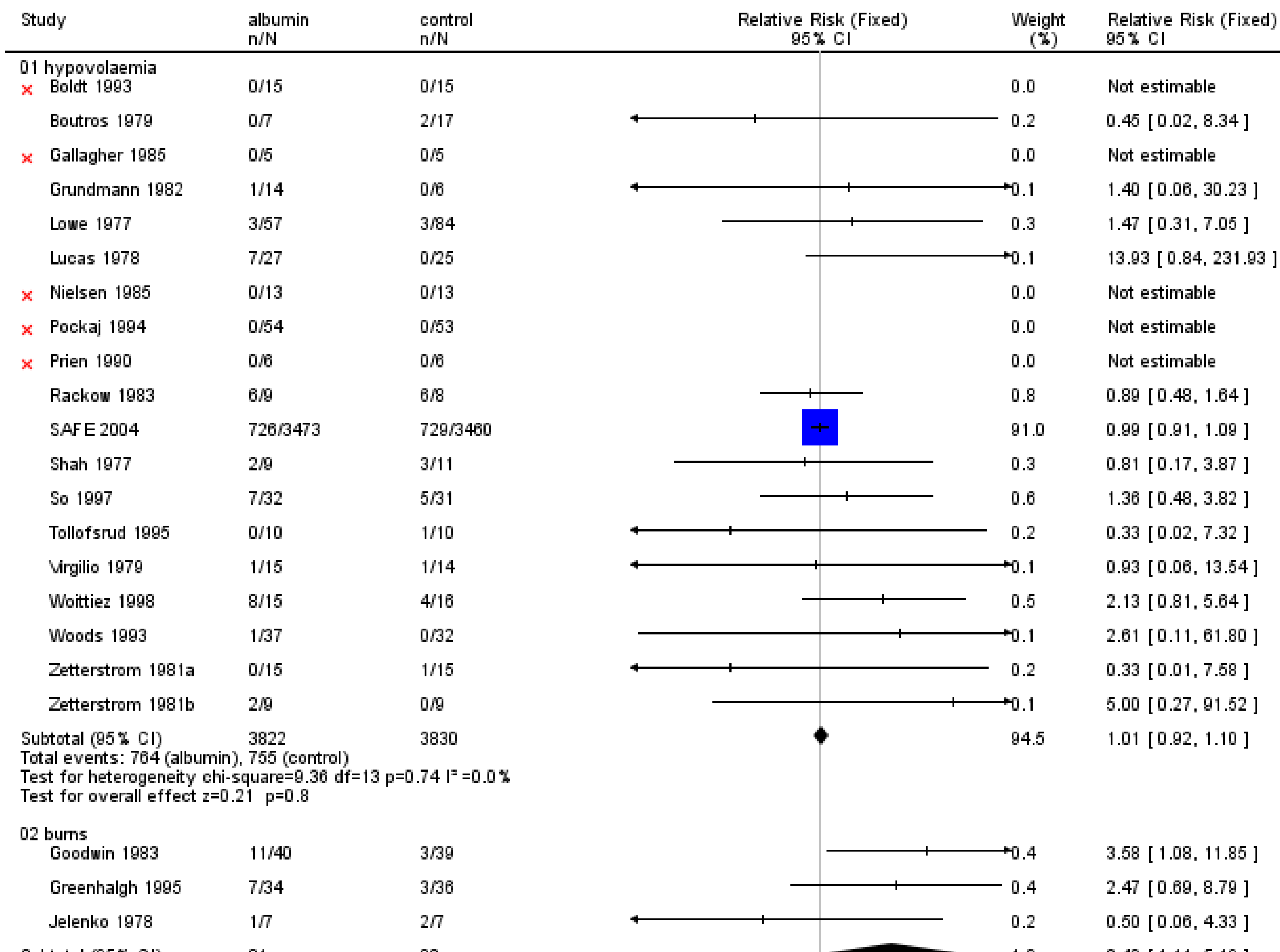
different settings: volume expansion, burns, and trea
low serum albumin. The review therefore seems t
scientifically robust. What adds to the credibility of t
results is that if results are consistent across studies
are likely to apply to this wide variety of patients.[5] H

torna

Il caso dell’albumina … continua

Versione 2

Review: Human albumin solution for resuscitation and volume expansion in critically ill patients
Comparison: 01 supplemental albumin
Outcome: 01 deaths



Cochrane Systematic Review 2004

Background

…..Volume for volume human albumin solution is twice as expensive as hydroxyethyl starch, and over thirty times more expensive than crystalloid solutions such as sodium chloride or Ringer's lactate….

Implications for practice

For patients with hypovolaemia there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline. There is no evidence that albumin reduces mortality in critically ill patients with burns and hypoalbuminaemia and a suggestion that albumin may increase the risk of death.

Implications for research

… in view of the absence of evidence of a mortality benefit from albumin and the increased cost of albumin compared to alternatives such as saline, it would seem reasonably that albumin should only be used within the context of well concealed and adequately powered randomised controlled trial.

Esempi di effetto iatrogeno

1. Hormone replacement therapy
2. Sudden Infant Death Syndrome
3. Vitamine
4. Life education
5. Campagna mass media americana

1. Hormone replacement therapy

- Rispetto all'uomo, la donna gode di una protezione importante nei confronti delle malattie cardiovascolari e dell'osteoporosi
- Questa protezione scompare dopo la menopausa, in corrispondenza del calo degli estrogeni
- Da decenni viene proposta alle donne in menopausa una terapia sostitutiva ormonale per mantenere la protezione pre-menopausale
- Gli studi di coorte hanno confermato questa teoria

torna

1. Hrt: primi studi osservazionali

Postmenopausal estrogen therapy and cardiovascular disease. Ten-year follow-up from the nurses' health study

Stampfer, NEJM 1991

- RR for major CHD = 0.56 (0.40-0.80)
- RR for total mortality = 0.89 (0.78-1.00)
- RR for mortality from CVD = 0.72 (0.55-0.95)

1. Hrt: le conferme degli scorsi anni

Postmenopausal Estrogen and Progestin Use and the Risk of Cardiovascular Disease

Grodstein Ann Int Medicine 2000

- 16 year results from the Nurses health study
- RR of CHD estrogen+progestin = 0.39 (0.19-0.78)
- RR of CHD estrogen alone = 0.60 (0.43-0.83).

1. Hrt: 2002 - risultati di WHI

Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women
Principal Results From the Women's Health Initiative Randomized Controlled Trial

Writing Group for the Women's Health Initiative Investigators

Context Despite decades of accumulated observational evidence, the balance of risks and benefits for hormone use in healthy postmenopausal women remains uncertain.

Objective To assess the major health benefits and risks of the most commonly used

- 16608 postmenopausal women aged 50-79 years

Results On May 31, 2002, after a mean of 5.2 years of follow-up, the data and safety monitoring board recommended stopping the trial of estrogen plus progestin vs placebo because the test statistic for invasive breast cancer exceeded the stopping boundary for this adverse effect and the global index statistic supported risks exceeding benefits. This report includes data on the major clinical outcomes through April 30, 2002. Estimated hazard ratios (HRs) (nominal 95% confidence intervals [CIs]) were as follows: CHD, 1.29 (1.02-1.63) with 286 cases; breast cancer, 1.26 (1.00-1.59) with 290 cases; stroke, 1.41 (1.07-1.85) with 212 cases; PE, 2.13 (1.39-3.25) with 101 cases; colorectal cancer, 0.63

Decline in breast cancer since HRT study

Although the causal link hasn't been conclusively established, US researchers say there's been a remarkable decline in breast cancer rates since fewer women began taking hormone replacement therapy (HRT) to alleviate the symptoms of menopause.

The overall incidence of breast cancer in the US declined 7% between 2002 and 2003, while the number of women aged 50–69 diagnosed with estrogen receptor positive (ER-positive) breast cancer declined 12% over the same period, when millions of women stopped taking HRT after the release of a July 2002 Women's Health Initiative study indicating HRT bore more risks than benefits.

Some 14 000 fewer women were diagnosed with breast cancer in 2003 than in 2002, when an estimated 203 500 cases were diagnosed, researchers at the University of Texas MC Anderson Cancer Center told the 29th annual San Antonio Breast Cancer Symposium last month.

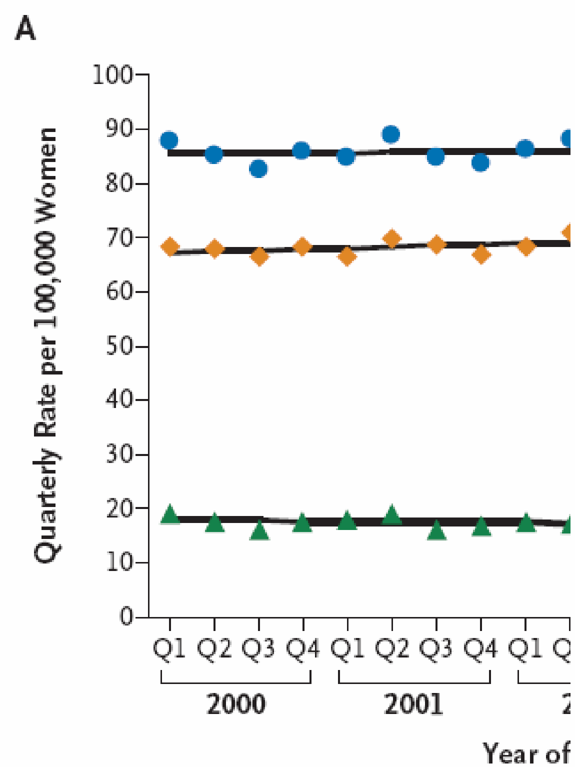
Kondro, CMAJ Feb 2007

SPECIAL REPORT

The Decrease in Breast-Cancer Incidence

d States

Ph.D., Nadia Howlader, M.S.,



age-adjusted incidence was 8.6% (95% confidence interval [CI], 6.8 to 10.4). The decrease was evident only in women who were 50 years of age or older and was more evident in cancers that were estrogen-receptor–positive than in those that were estrogen-receptor–negative. The decrease in breast-cancer incidence seems to be temporally related to the first report of the Women's Health Initiative and the ensuing drop in the use of hormone-replacement therapy among postmenopausal women in the United States. The contributions

1. HRT: cosa è successo

- Una solida ***teoria eziopatogenetica*** (sbagliata!) ha guidato le scelte
- Gli ***studi osservazionali*** erano gravati da un grave ***confondimento*** (classe sociale-istruzione)
- La ***potenza dell'industria***…. e di alcune ***corporazioni mediche***

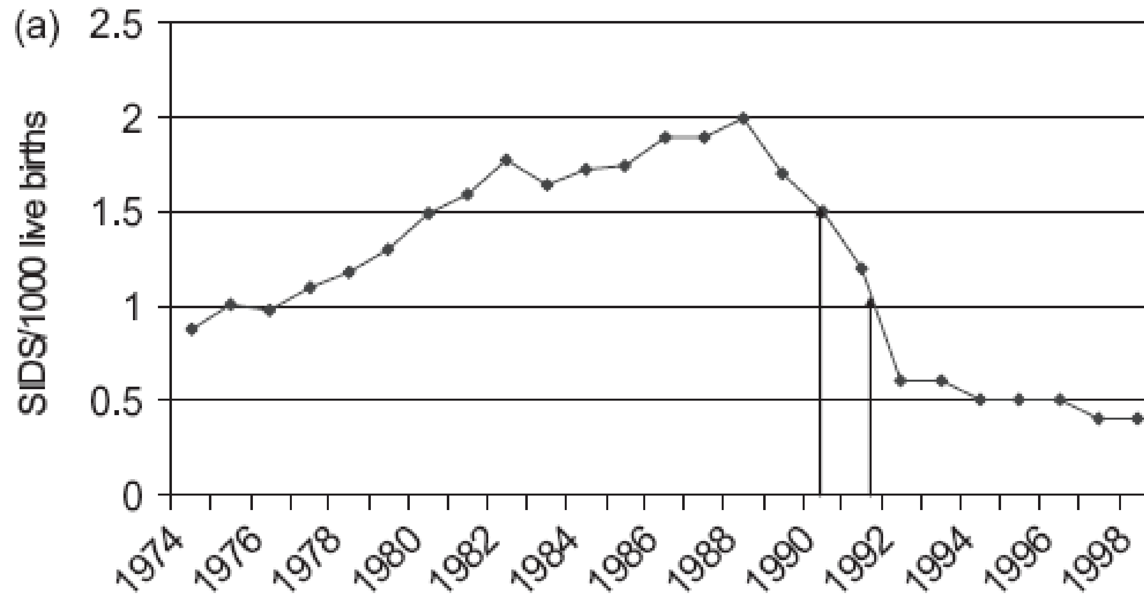
Prime conclusioni

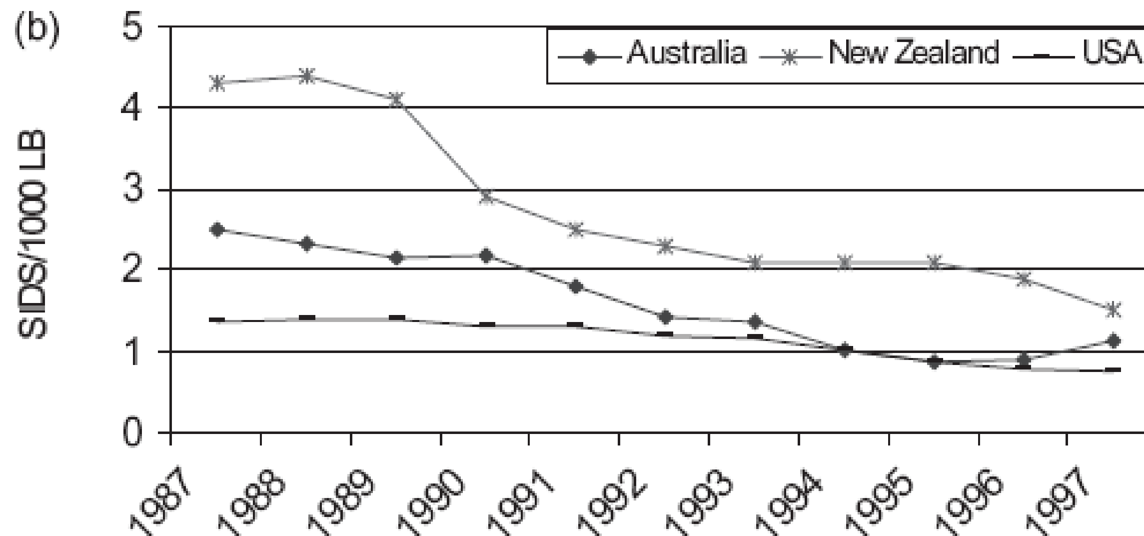
- Le teorie eziopatogenetiche, ***in assenza di prove empiriche***, determinano decisioni che possono essere sbagliate

2. Il caso della SIDS

- La *Sudden Infant Death Syndrome* era responsabile durante gli anni ’80 di 3-4 decessi ogni 1000 nati
- La posizione prona (di pancia) per il sonno dei neonati è stata raccomandata fin dal 1943 al 1988
- sulla base della teoria del rischio di soffocamento per rigurgito, vomito…
- Le prime linee guida che raccomandavano la posizione supina (sul dorso) sono state pubblicate solo nel 1992

2. Il caso della SIDS





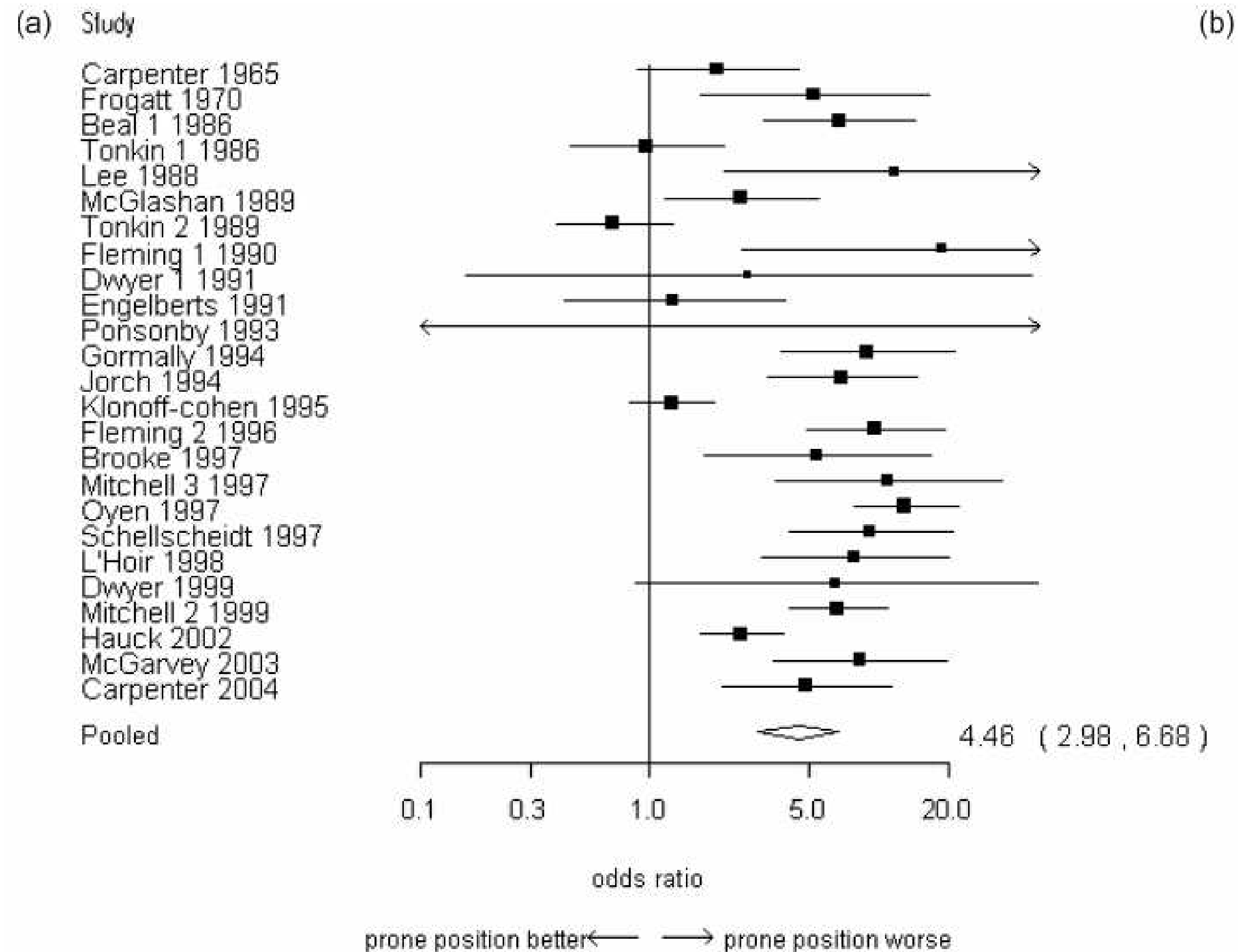
Mortalità per SIDS (Sindrome della morte improvvisa del neonato) -
(a) Svezia [1°-12° mese];
(b) AU, NZ, USA [0-12 mesi]

Jilbert, IJE 2005

2. Il caso della SIDS

…ma si poteva fare prima?

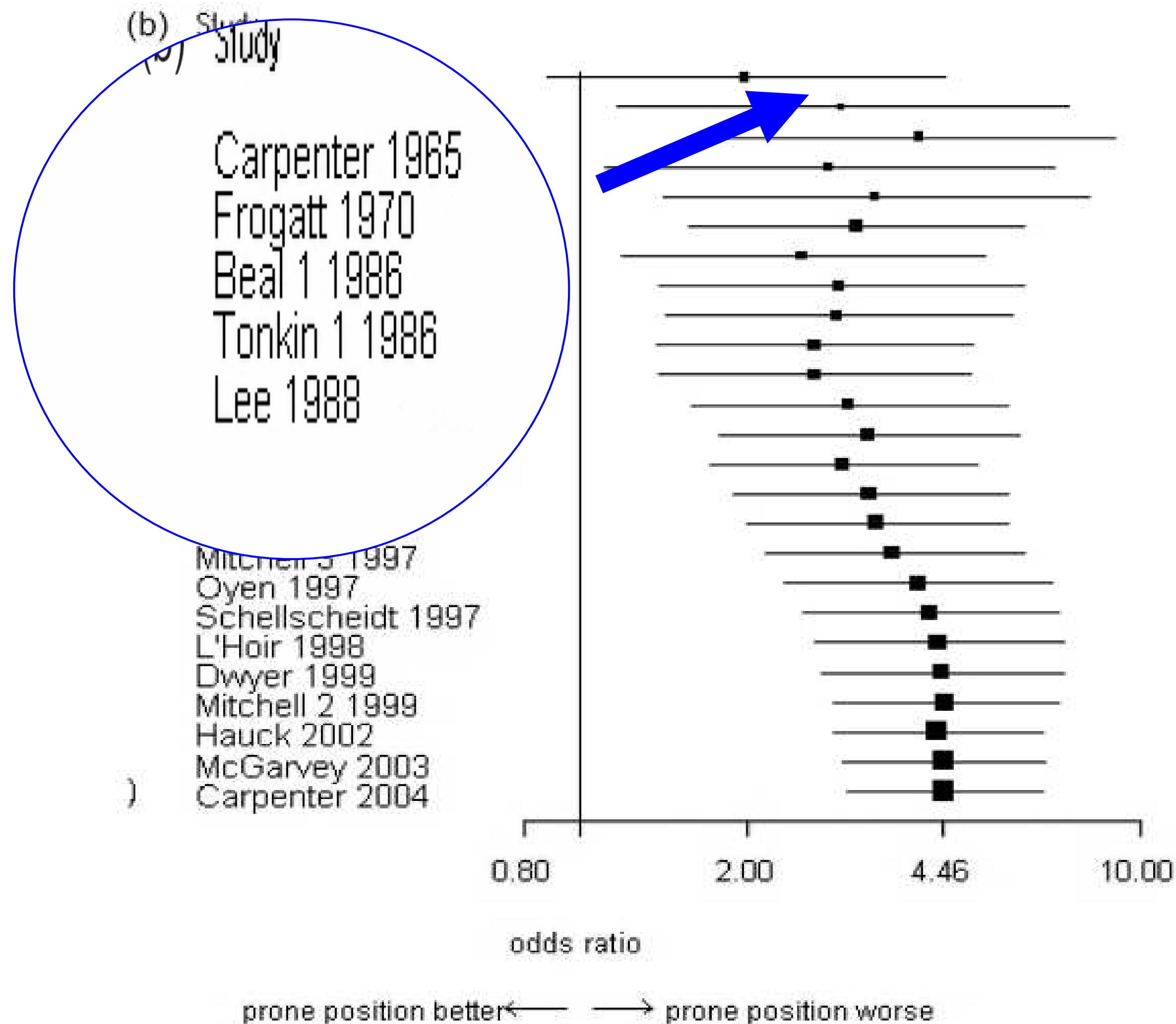
2. Il caso della SIDS



Revisione sistematica di efficacia: RR di morte per prono vs supino

Jilbert, IJE 2005

2. Il caso della SIDS



Revisione sistematica di efficacia: RR di morte per prono vs supino

Jilbert, IJE 2005

2. Il caso della SIDS

- Jilbert suggerisce che il ritardo sia da attribuire alla maggiore attrazione che i meccanismi teorici (cardiaci, cerebrali etc) della morte hanno rispetto alle evidenze di efficacia
- Dal 1970 al 1992 ***10000*** bambini USA e ***50000*** europei avrebbero potuto sopravvivere se le linee-guida fossero state emanate prima

Jilbert, IJE 2005

3. Il caso della chemioprevenzione dei tumori

- Nel 1981 Science pubblica il seguente articolo:

Peto R, Doll R et al. Can dietary beta-carotene materially reduce human cancer rates? Science 1981;290:201-8.

- Gli autori ipotizzano, a partire da una rassegna di studi, che gli alimenti contenenti retinolo e beta-carotene proteggano contro il cancro
- RR=3.0 per i bassi consumi
- Gli autori suggeriscono di studiare l'efficacia degli integratori dietetici a base di beta- carotene.

3. Il caso del ß-carotene (II)

La teoria dell'effetto protettivo era supportata da studi e esperimenti:

- con elevata concordanza
- RR=5.3 per i livelli più bassi di retinolo ematico
- provata capacità di reprimere colture cellulari malignizzate *in vitro*
- potente azione antiossidante

… dai primi anni novanta il ß-carotene è presente in molti integratori vitaminici

3. Il caso del ß-carotene (III)

Studio ATBC - Finlandia

- nel 1986: 29 133 fumatori maschi 50-69, randomizzati in 4 gruppi (combinazioni di ß-carotene e α-tocoferolo) e seguiti per 5-8 anni

Studio CARET - USA

- nel 1992: 18 314 soggetti, fumatori o esposti ad asbesto, randomizzati in 4 gruppi e seguiti fino al 1997

3. Il caso del ß-carotene (IV)

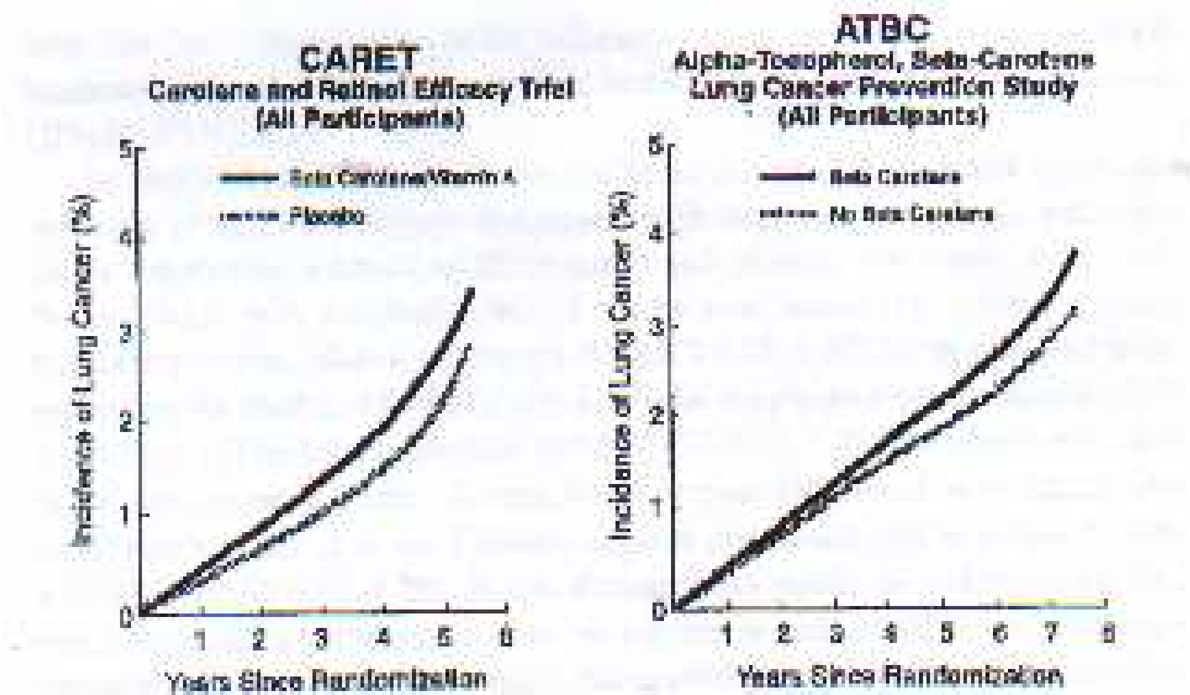


Figure 1 Kaplan-Meier curves of the cumulative incidence of lung cancer among participants receiving active vitamins and those receiving placebo. Data are shown only through 5.5 years of follow-up because of the small number of participants beyond that time.

3. Il caso del ß-carotene (V)

Annu. Rev. Public Health. 1998. 19:73–99
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CHEMOPREVENTION OF LUNG CANCER: The Rise and Demise of Beta-Carotene

Gilbert S. Omenn

Former address: School of Public Health & Community Medicine, University of Washington, Seattle, Washington 98195–7230 and Fred Hutchinson Cancer Research Center, Seattle, Washington 98109–1024; Current address: University of Michigan, Ann Arbor, Michigan 48109–0624; e-mail: gomenn@umich.edu

KEY WORDS: fruits/vegetables, carcinogenesis, vitamin-supplements, antioxidants, vitamin A

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INFORMATIO

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JAMA® The Journal of the American Medical Association

Vol. 297 No. 8, February 28, 2007

Review

Mortality in Randomized Trials of Antioxidant Supplements for Primary and Secondary Prevention

Systematic Review and Meta-analysis

Goran Bjelakovic, MD, DrMedSci; Dimitrinka Nikolova, MA; Lise Lotte Gluud, MD, DrMedSci; Rosa G. Simonetti, MD; Christian Gluud, MD, DrMedSci

JAMA. 2007;297:842-857.

Data Synthesis When all low- and high-bias risk trials of antioxidant supplements were pooled together there was no significant effect on mortality (RR, 1.02; 95% CI, 0.98-1.06). Multivariate meta-regression analyses showed that low-bias risk trials (RR, 1.16; 95% CI, 1.05-1.29) ... ow-bias trials with 180 938 pa ...). In low-bias risk trials, after exclus ... .0-1.24), and vitamin E (RR, 1.04; ... no significant effect on mortality.

Conclusior ... s of vitamin C and selenium or

beta carotene (RR, 1.07; 95% CI, 1.02-1.11),

vitamin A (RR, 1.16; 95% CI, 1.10-1.24),

and vitamin E (RR, 1.04; 95% CI, 1.01-1.07),

significantly increased mortality.

Author Affiliations: The Cochrane Hepato-Biliary Group, Copenhagen Trial Unit, Center for Clinical Intervention Research, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark (Drs Bjelakovic, L. L. Gluud, Simonetti, and C. Gluud and Ms Nikolova); Department of Internal Medicine, Gastroenterology and Hepatology, University of Nis, Nis, Serbia (Dr Bjelakovic); and Divisione di

4. Il caso della prevenzione dell'abuso di sostanze

Gli interventi di prevenzione dell'uso di fumo, alcool e droghe illegali nella scuola dovrebbe avere le seguenti caratteristiche:

1. essere basati su un approccio di ***Comprehensive Social Influence (CSI)***
2. con ***limitati contenuti di conoscenza***
3. ***Interattivi***
4. avere una ***durata importante*** nell'arco di un anno
5. essere condotti dagli insegnanti curricolari

Cochrane Systematic Reviews:

Valutazione di efficacia di "Life Education" in Australia:

- Cigarettes RR=1.6
- Alcohol RR=1.4
- Other substances RR=1.4

When the data are extrapolated to the state-wide ... estimates, ... of all smoking among year 6 schoolchildren,

25% of girls' and 19% of boys' smoking could be attributed to participation in Life Education

as could 22% of all boys' recent drinking

The program was extended to all Australia, UK, USA, … India, China, … South Africa….

The findings suggest that intervention programmes should be thoroughly evaluated prior to widespread implementation…

Hawthorne, Addiction 1995

4. Il caso della prevenzione dell’abuso di sostanze

Virtualmente in tutte le scuole italiane vengono condotti interventi per la prevenzione dell’uso di alcool, fumo e droghe.

Da una indagine in Piemonte:

- solo il 20% sono basati sui Life Skills
- più del 50% sono inferiori a 3 ore
- il 47% si basano su lezioni frontali
- il 70% sono condotte da esperti esterni

4. Il caso della prevenzione dell'abuso di sostanze: cosa è successo?

- La teoria che l'***uso*** di sostanze quali il ***tabacco o le droghe*** sia ***determinato dall'assenza di informazioni*** è ancora maggioritario
- nonostante le prime evidenze di inutilità degli interventi conoscitivi risalgano agli anni 60 (!!)

5. American National Youth Anti-drug Media Campaign

- planned by the National Drug Control Policy (ONDCP)
- funded in 1997 by the United States Congress with ***$1.5 billion dollars***
- main objective: "***to educate and enable America's youth to reject illegal drugs as well as alcohol and tobacco***"
- alcohol and tobacco were omitted from the main focus of the campaign
- focused mainly on minimizing illegal drug use among young adolescents who have not yet become "regular" users of illegal substances
- televised antidrug public service announcements (PSAs) broadcasted 1998-2004

5. American National Youth Anti-drug Media Campaign

- Evaluation provides ***no evidence of positive effect*** in relation to teen drug use, and shows some indications of a negative impact.
- Some intermediate outcomes (parents talking with children about drugs, and doing fun activities with their children) showed positive results.
- Other (parents' monitoring of their children's behaviours) were not shown to be affected

- the ***past month use of marijuana significantly increased by 2.5% among 14-18 years*** (Orwin 2006).
- post-2002 results: statistically significant ***increase in rates of marijuana use initiation among youth who were prior nonusers*** (2000 to 2004 change 2.1%)

Conclusione preliminare (I)

Because professionals sometimes do more harm than good when they intervene in the lives of other people, their policies and practices should be informed by rigorous, transparent, up-to-date evaluations.

Chalmers AAPPS 2003

Considerazioni (I)

- Alla base di questi errori vi è la ***fiducia acritica nelle teorie eziopatogenetiche***
- Le donne aumentano il rischio di CVD e osteoporosi per la caduta ormonale, e quindi, ***teoricamente*** la somministrazione di ormoni previene questo aumento
- "*Se i giovani conoscessero il rischio legato all'uso di alcool, tabacco e droga, non le userebbero*"

Considerazioni (II)

- Ma la ***complessità della biologia*** (e dell'interazione con le scienze sociali)
- ***e l'inadeguatezza degli strumenti di ricerca***
- rende ***la teorizzazione*** precaria e inaffidabile fino a che….
- ***…non sia confermata o refutata da una prova di efficacia (Popper)***

Qualche considerazione

- Il corretto uso dei risultati della ricerca sulla efficacia degli interventi per la scelta di interventi sanitari va sotto il nome di:

EVIDENCE BASED MEDICINE

- (*Evidence* in inglese significa PROVA, come quella di tribunale e quindi la migliore traduzione italiana è

MEDICINA BASATA SULLE PROVE DI EFFICACIA

- Questa “filosofia” sta pervadendo la medicina e la sanità pubblica, grazie anche a Internet ed alle basi dati che permette di raggiungere

What evidence-based medicine is:

- Evidence-based medicine is the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.

What evidence-based medicine is:

- **Individual clinical expertise: the increasing proficiency and judgement that individual clinicians acquire through clinical experience and clinical practice.**
  - reflected especially in more effective and efficient diagnosis, and
  - in the more thoughtful identification and compassionate utilisation of individual patient's predicaments, rights, and preferences in making clinical decisions about their care.

What evidence-based medicine is:

- **Best available external clinical evidence:**
  - clinically relevant research, especially patient-centred, into:
    - the accuracy and precision of diagnostic tests;
    - the power of prognostic markers;
    - the efficacy and safety of therapeutic, rehabilitative, and preventive regimens.

La pratica della *Evidence-Based Medicine*:

1. Translation to an answerable question (patient/manoeuvre/outcome). →

2. Efficient track-down of the best evidence
   – secondary (pre-appraised) sources e.g., Cochrane; E-B Journals
   – primary literature

avanti

Quesito clinico

- E’ utile per:
  - ordinare il ragionamento
  - identificare le carenze di informazione
  - ricercare dati utili a colmare le carenze (p.e in basi dati)
- Formato generale
  - paziente (diagnosi, gravità, patologie concomitanti, sesso, età…)
  - intervento (diagnostico, farmacologico, chirurgico, riabilitatico…)
  - esito (sintomi, recidive, sopravvivenza, qualità della vita…)
- P.e. quale trattamento è efficace per ridurre la disfagia nel paziente con tumore dell’esofago?
- P.e. è utile l’albumina umana per ridurre la mortalità nei pazienti critici con ipoalbuminemia

avanti

La pratica della *Evidence-Based Medicine*:

3. Critical appraisal of the evidence for its validity and clinical applicability ➔ *generation of a 1-page summary.*
4. Integration of that critical appraisal with clinical expertise and the patient’s unique biology and beliefs ➔ *action.*
5. Evaluation of one’s performance.

Three solutions

Clinical performance can keep up to date:

1 by learning how to practice evidence-based medicine ourselves. (carrello)

2 by seeking and applying evidence-based medical summaries generated by others. (RS)

3 by accepting evidence-based practice protocols developed by our colleagues.

avanti

(EBM center - Oxford, 1998)

Contents of the Dave's Cart:

- Physical diagnosis text book and reprints (JAMA Rational Clinical Exam).
- Notebook computer, computer projector, and pop-out screen.
- Rapid printer.
- 125 summaries (1-3 pp) of evidence previously appraised and summarised
- CD of *Best Evidence*
- CD of WinSPIRS (Medline)
- CD of the *Cochrane Library*

Sette alternative alla EBM:

Basis of clinical practice

Basis for clinical decisions	Marker	Measuring device	Unit of measurement
Evidence	Randomised controlled trial	Meta-analysis	Odds ratio
Eminence	Radiance of white hair	Luminometer	Optical density
Vehemence	Level of stridency	Audiometer	Decibels
Eloquence (or elegance)	Smoothness of tongue or nap of suit	Teflometer	Adhesin score
Providence	Level of religious fervour	Sextant to measure angle of genuflection	International units of piety
Diffidence	Level of gloom	Nihilometer	Sighs
Nervousness	Litigation phobia level	Every conceivable test	Bank balance
Confidence*	Bravado	Sweat test	No sweat

*Applies only to surgeons.

Isaacs D et al BMJ VOLUME 319 18-25 DECEMBER 1999 www.bmj.com