Níveis de Evidência, Análise de Decisão e Análise de Sensibilidade

Moysés Szklo

INTERFACE OF EPIDEMIOLOGY AND CANCER CONTROL POLICY

1. BURDEN OF CANCER

Determine health status (mortality, incidence, survival, recurrence rates)

Modified from: Tugwell et al, *J Chron Dis* 38(4)

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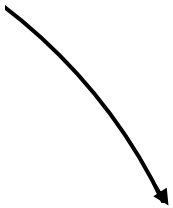

2. ETIOLOGY AND PROGNOSIS
Identify risk factors and prognostic factors

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4. EFFECTIVENESS
Assess effectiveness in the target population/patients

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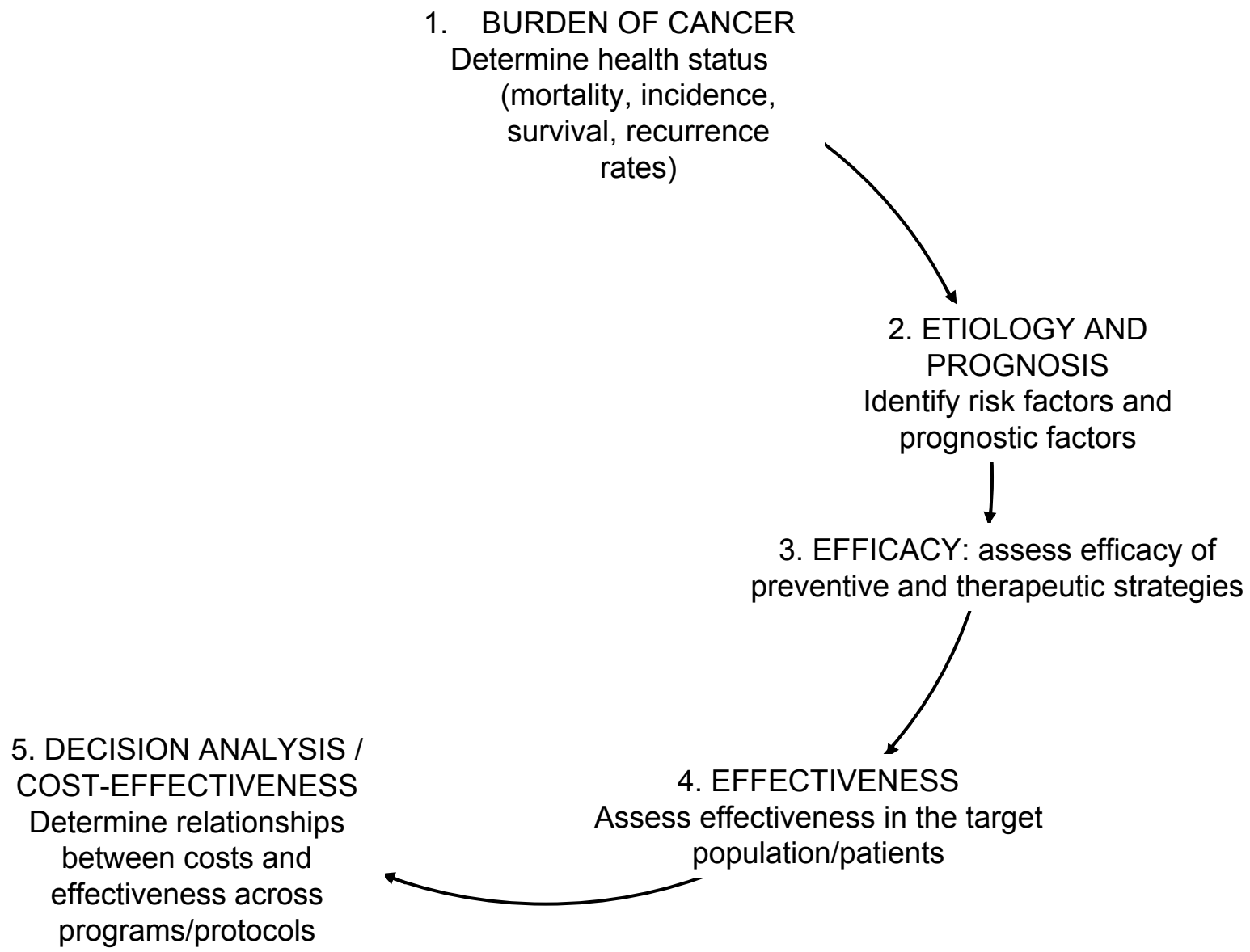

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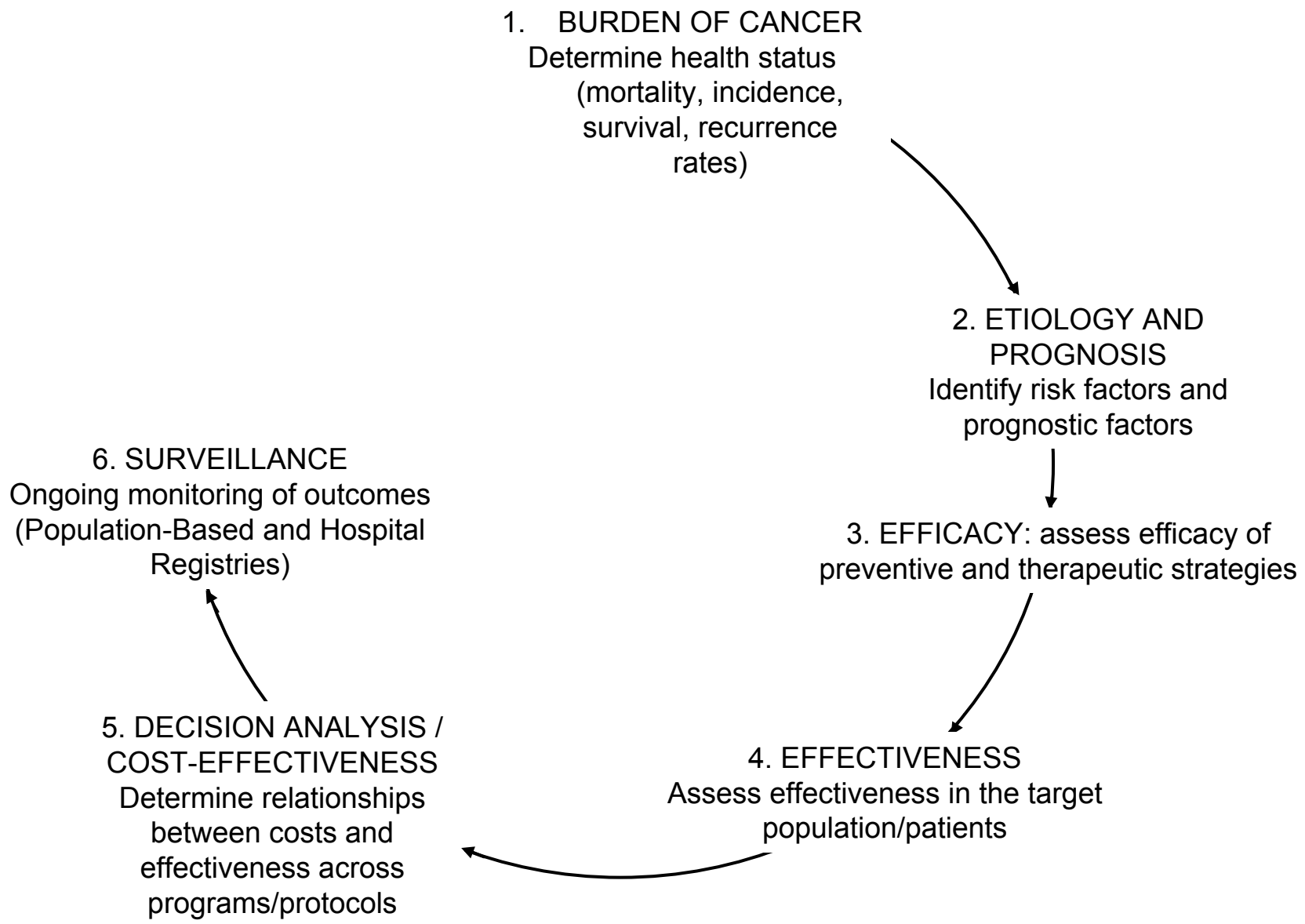

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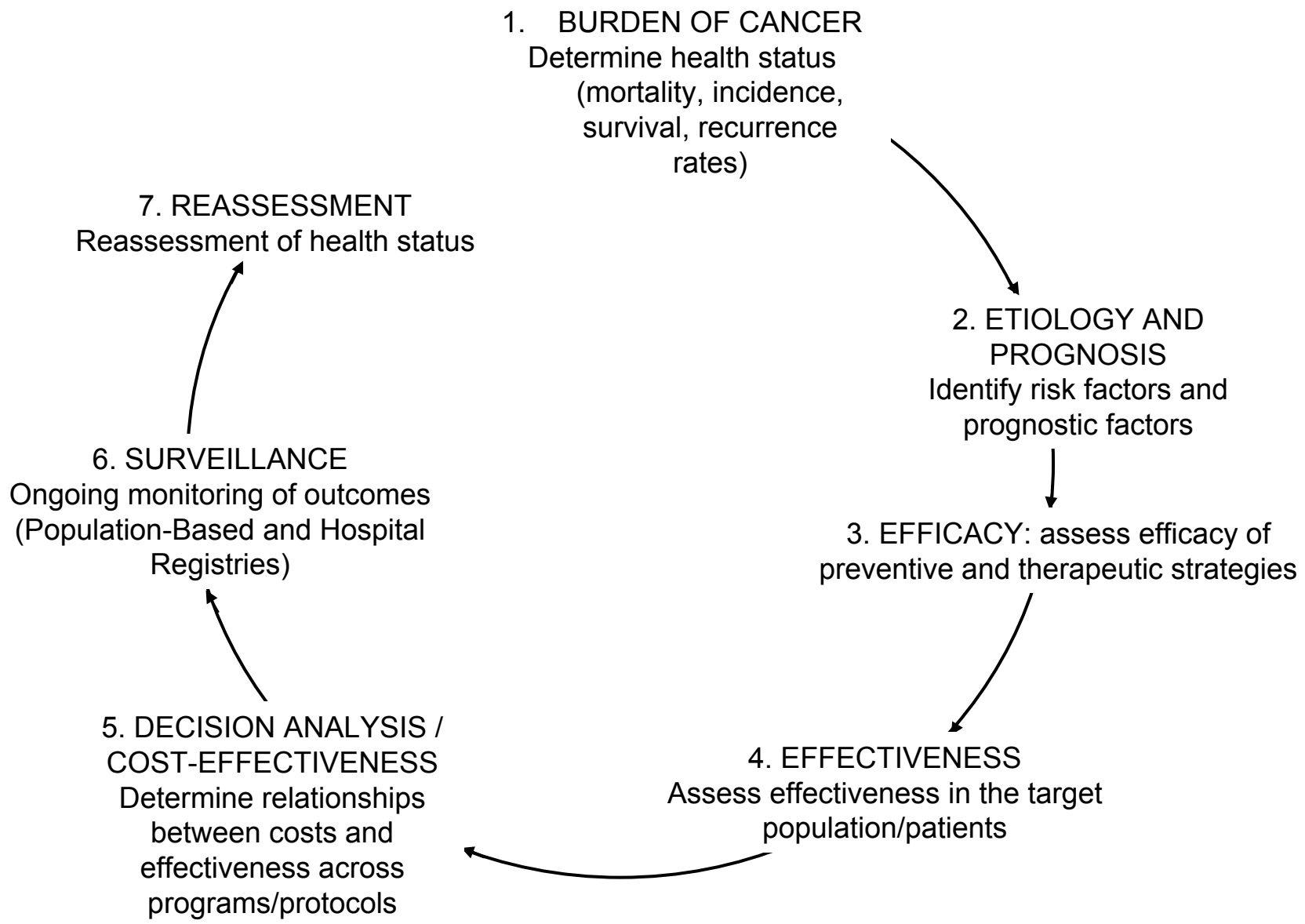

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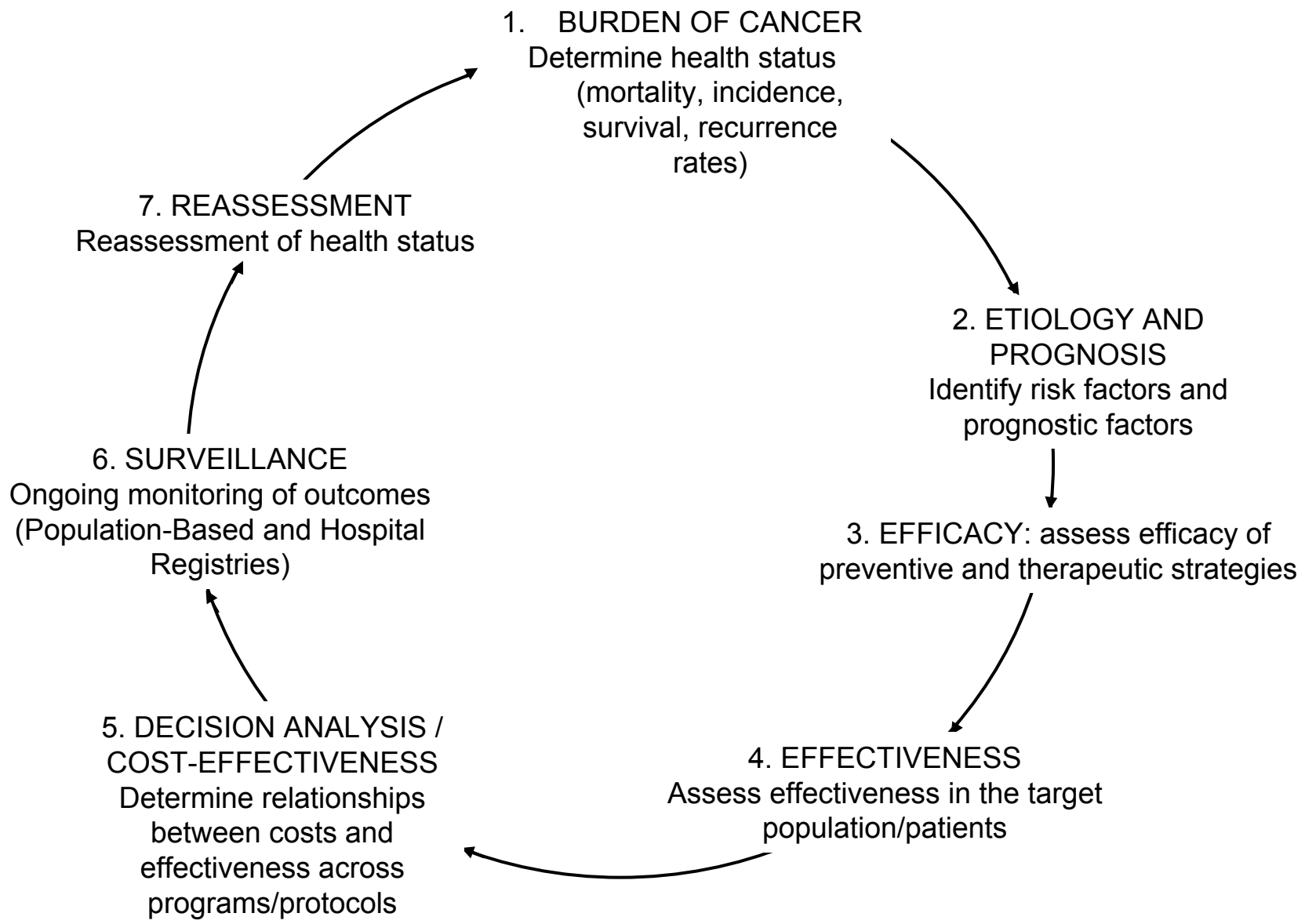
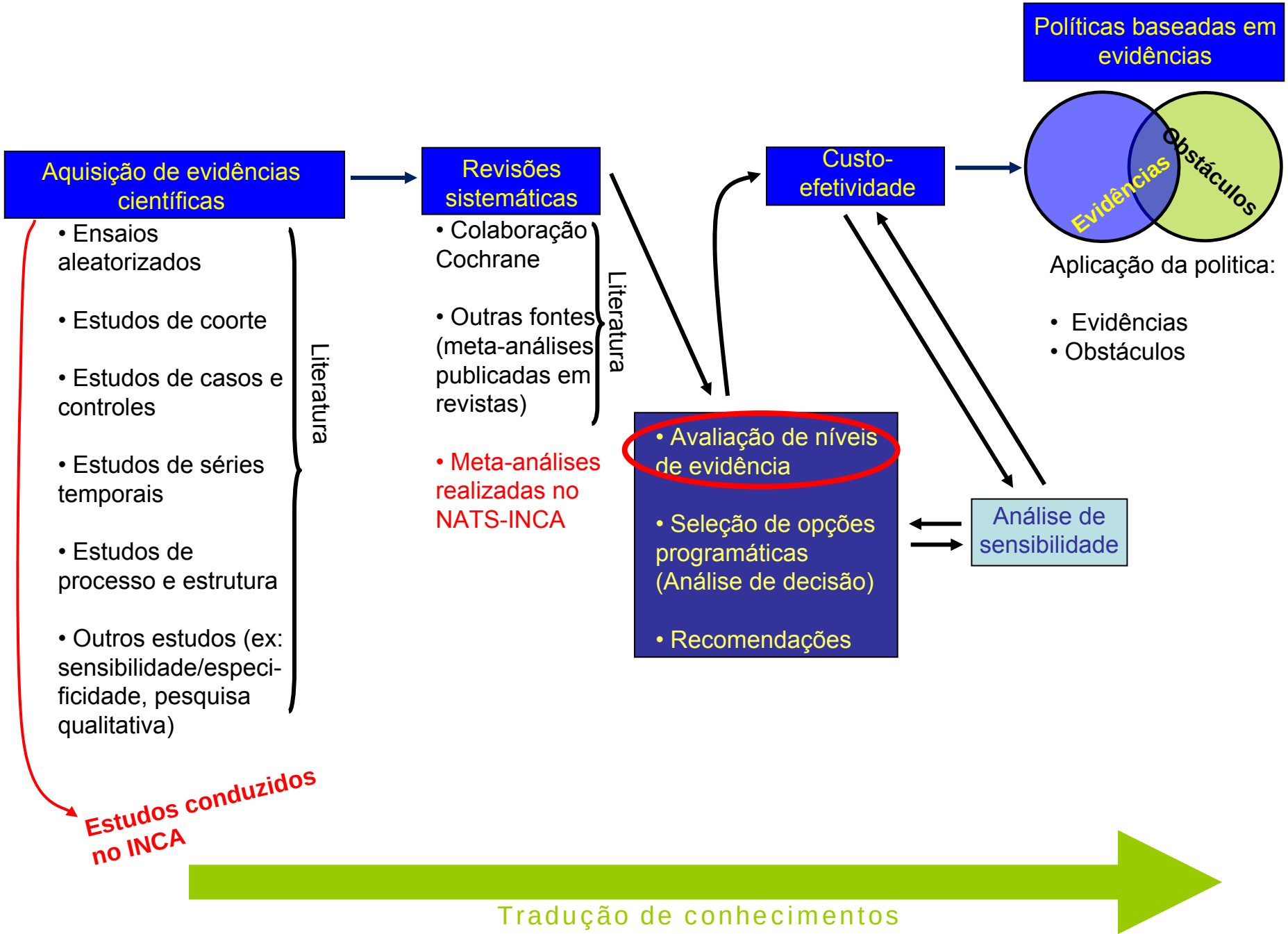


Modified from: Tugwell et al, *J Chron Dis* 38(4)

INCA/DECIT/MS: Núcleo de Avaliação de Tecnologias em Saúde -- Processo de Implementação de Politicas de Controle de Câncer Baseadas em Evidências



Políticas de Saúde Baseadas em Evidências

Critérios para julgar a eficácia e efetividade de uma intervenção (medida preventiva ou tratamento)

Classificação	Nível de evidência	Descrição do nível	
melhor A	1a	Revisão sistemática de ensaios aleatorizados com homogeneidade – inclusive meta-análise	ESTUDOS EXPERIMENTAIS
	1b	Um único ensaio aleatorizado de boa qualidade	
	1c	Experimentos “naturais” (exemplo: estreptomicina e meningite tuberculosa) e séries temporais	
	2a.	Revisão sistemática de estudos de coorte com homogeneidade – inclusive meta-análise	ESTUDOS OBSERVACIONAIS
	2b	Um único estudo de coorte (prospectivo) de boa qualidade	
B	3a	Revisão sistemática de estudos de casos e controles com homogeneidade – inclusive meta-análise	
	3b	Um único estudo de casos e controles de boa qualidade	
C	4	Série de casos	
pior D	5	Opinião de especialistas não baseada em avaliação de resultados de estudos ou dedução lógica, ou sem um critério explícito de avaliação	

(Modificado de: NHS R&D Centre for Evidence-Based Medicine. See http://www.indigojazz.co.uk/cebm/levels_of_evidence.asp)

Example of Application of Levels of Evidence Cervical Cancer – Summary (NCI)

- Evidence strongly suggests a decrease in mortality from regular screening with Pap tests in women who are sexually active or who have reached 18 years of age.

- Level of evidence for preceding statement:

  3 - Well-designed cohort/case-control studies

  4 - Evidence from multiple time series with or without intervention

  5 - Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

Screening for Breast Cancer
US Preventive Services Task Force
Recommendations for Breast Cancer Screening (Updated December 2009

- The USPSTF recommends biennial mammography for women aged 50-74 years

Grade B recommendation

- The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account including the patient's values regarding specific benefits and harms

Grade C recommendation

- The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of screening mammography in women 75 years and older

Grade I statement

- The USPSTF recommends against teaching breast self examination

Grade D recommendation

- The USPSTF concludes that the current evidence is insufficient to assess benefits and harms of clinical breast examination beyond screening mammography in women 40 years and older

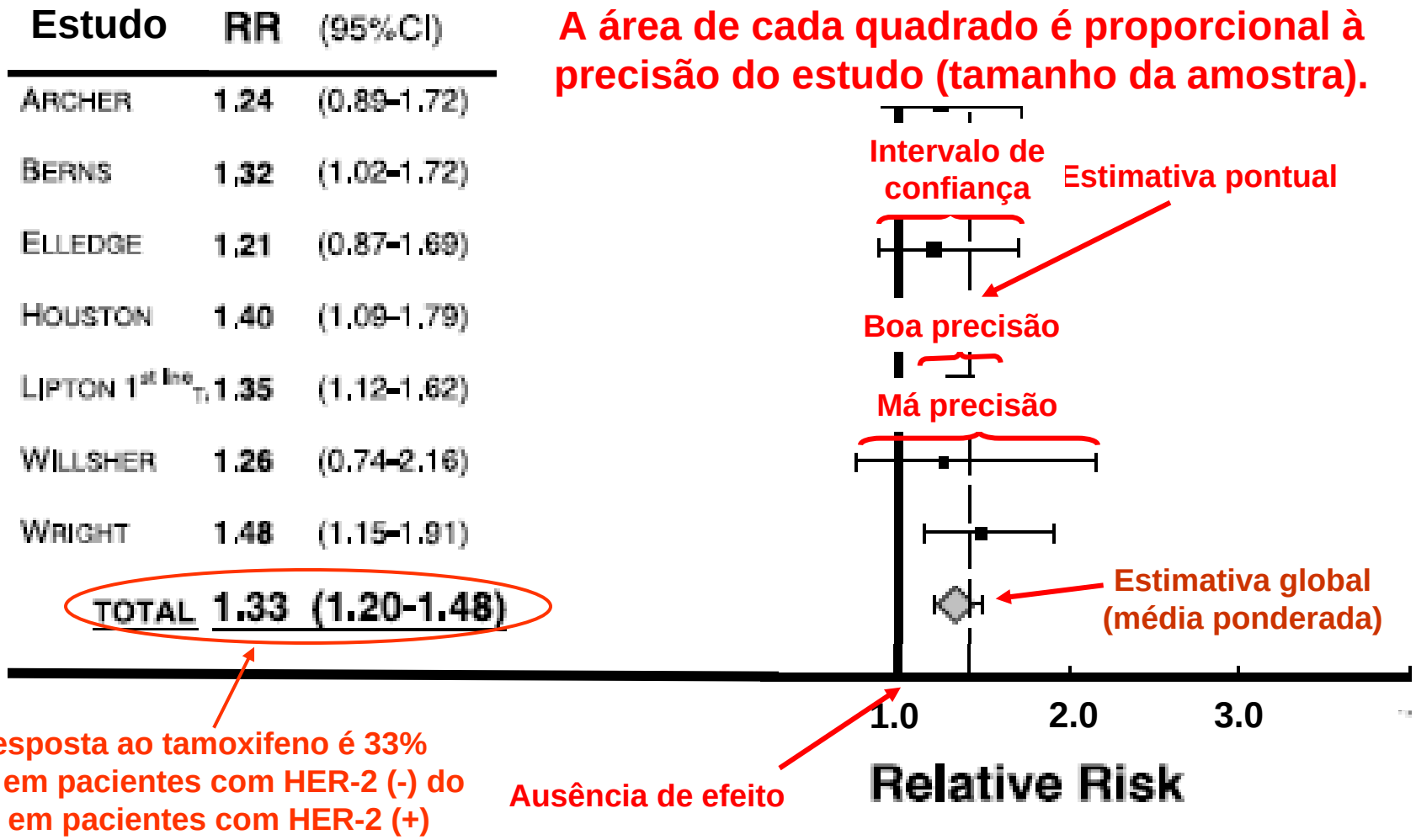
Grade I statement

- The USPSTF concludes that the current evidence is insufficient to assess the additional benefits and harms of either digital mammography or magnetic resonance imaging instead of film mammography as screening modalities for breast cancer

Grade I statement

Meta-analysis: quantitative method that aims at summarizing study results, thus, facilitating the process of inferring effectiveness of an intervention, service or program.

Meta-análise da Interação entre a Expressão do HER-2 e Resposta ao Tamoxifeno em Câncer de Mama Avançado



(De Laurentiis G, et al. *Clin Cancer Res* 2005;11:4741-8)

THE MAIN THREAT TO META-ANALYSIS

PUBLICATION BIAS: SELECTION BIAS THAT OCCURS EITHER AT THE LEVEL OF ENTIRE STUDIES (**STUDY PUBLICATION BIAS**) OR AT THE LEVEL OF ENDPOINTS WITHIN PUBLISHED STUDIES (***OUTCOME REPORTING BIAS***)

(Chan AW et al. Empirical evidence for selective reporting of outcomes in randomized trials: comparison of protocols to published articles. *JAMA* 2004;291:2457-65)

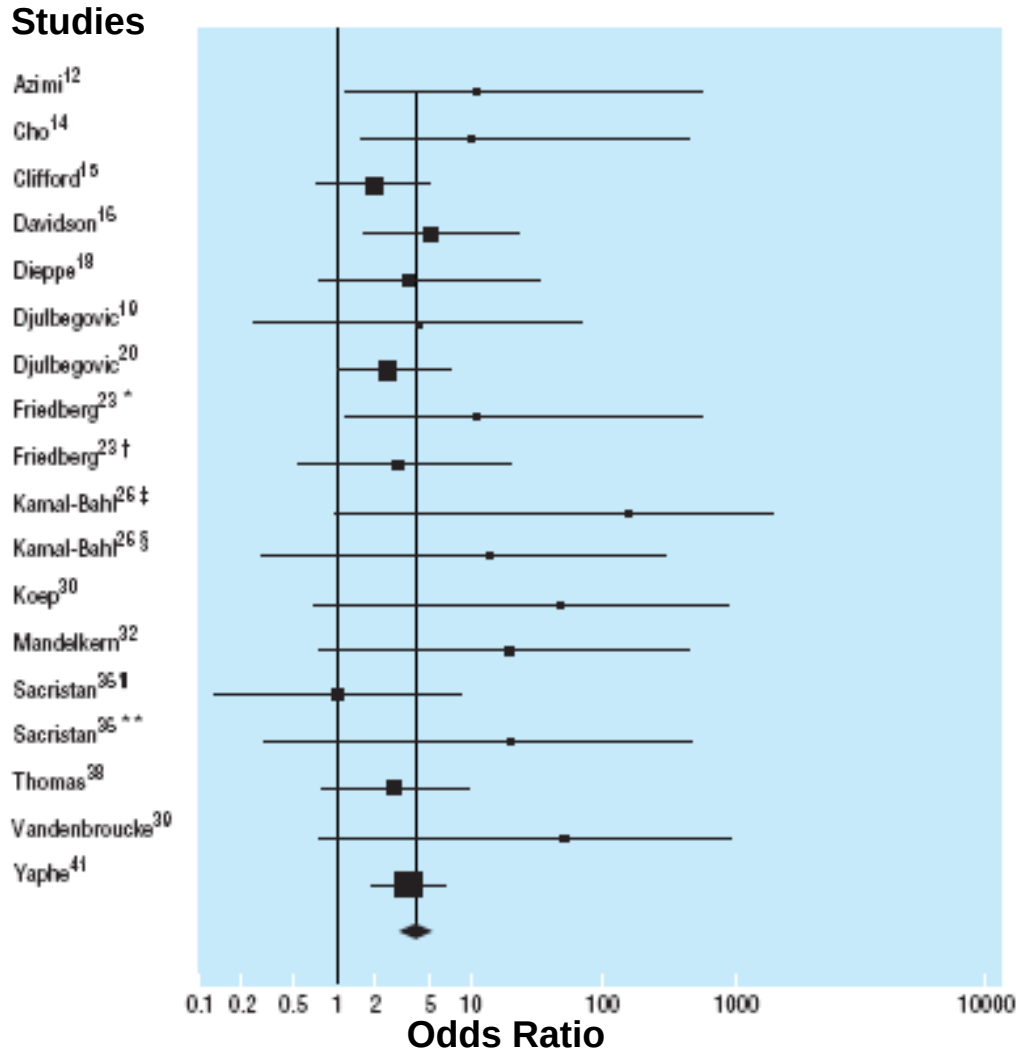
Factors Associated with Publication Odds: Multivariate Analysis (No. of studies= 285)

Factor	Odds Ratio (95% Confidence Limits)
Null result	1.00
Statistically significant at ά=0.05	2.32 (1.25, 4.28)
Perceived importance of results by author: low	1.00
Perceived importance of results by author: high	3.50 (1.45, 8.45)

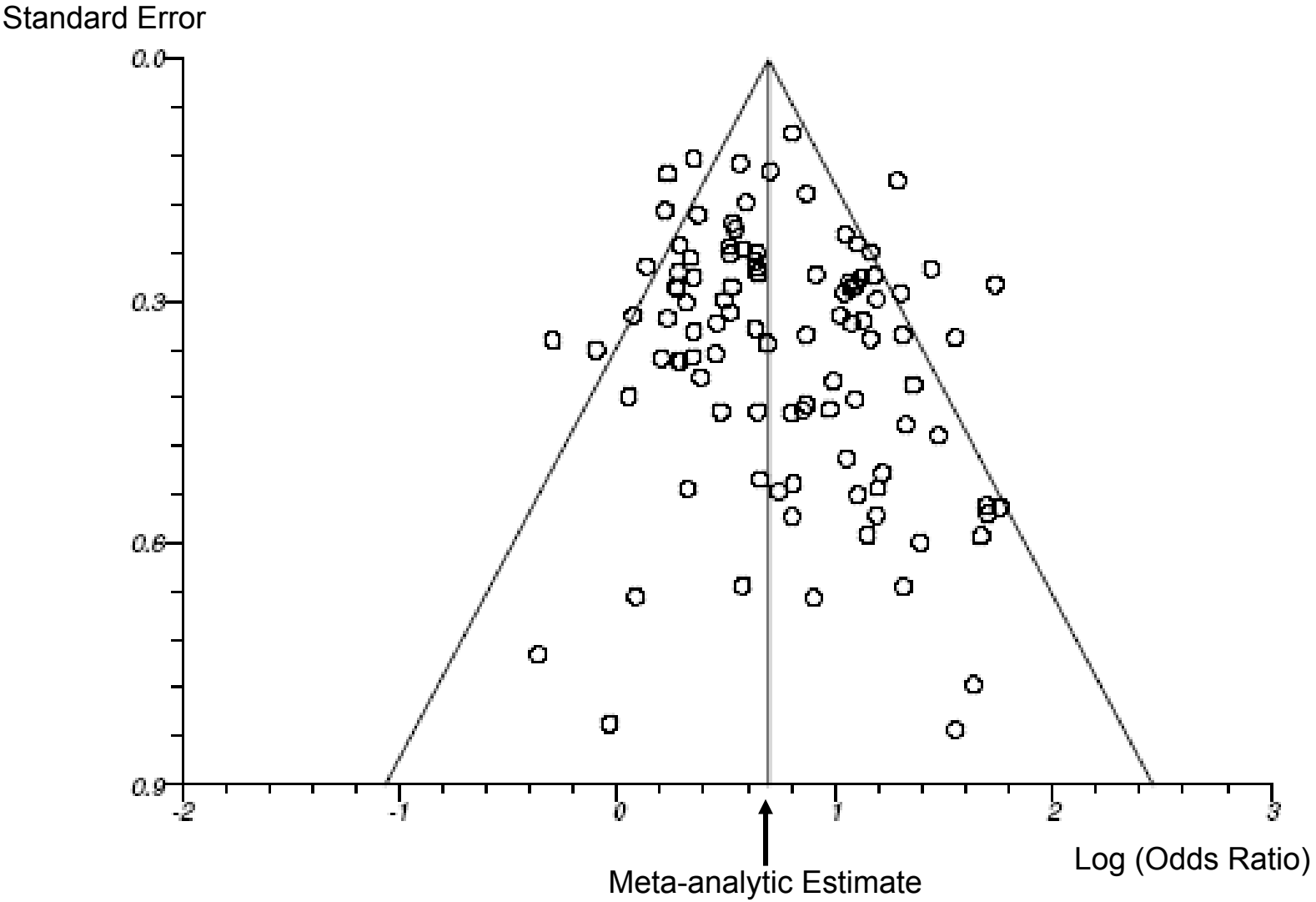
(Easterbrook et al, 1991)

Odds ratios for publication according to source of funding in meta-analyses

$$\text{Odds Ratio} = \frac{\text{Odds of Favoring the Product in Published Studies Sponsored by Drug Companies}}{\text{Odds of Favoring the Product in Published Studies Not Sponsored by Drug Companies}}$$



(Lexchin J, et al. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ* 2003;326:1167-70)

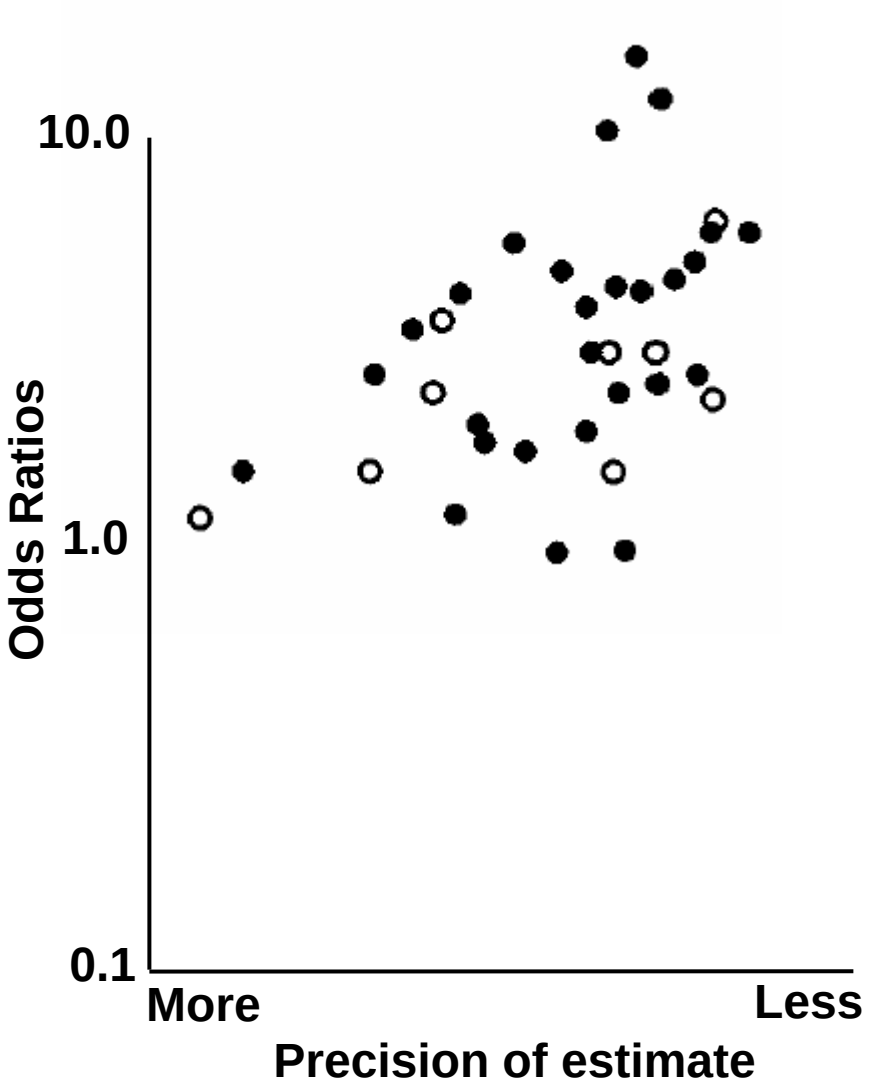


Funnel Plot Evaluating Publication Bias in Nicotine Replacement Therapy Vs. Control Event Rates at 4 Weeks Post Target Quit Date

(Mills EJ. *Harm Reduction Journal* 2009;6:25)

Funnel plot of odds ratio (OR) of family history of stroke as a risk factor for stroke vs. precision (i.e., inverse of the standard error of the OR) in case-control (full circles) and cohort studies (empty circles). Note the asymmetry of the plot due to lack of estimates when OR<1 (i.e., small negative studies).

(Source: Data from E Floβmann, UGR Schulz, PM Rothwell, Systematic review of methods and results of studies of the genetic epidemiology of ischemic stroke, *Stroke*, Vol 35, pp 212-227, © 2004.)



Relações entre meta-análise, análise de decisão e análise de custo-efetividade

Meta-Análise

Sumário da efetividade de intervenções na população

Análise de Decisão

Avaliação do valor relativo de opções programáticas baseada na efetividade de intervenções na população. É baseada na "árvore de decisão"

Análise de custo-efetividade

Avaliação do custo do programa, baseado no valor relativo das opções programáticas

Eficácia e Efetividade

- **Eficácia**: estimada em um ou mais estudos em condições ideais.

- **Efetividade**: estimada em um ou mais estudos em condições não ideais (perdas de seguimento, “cross-overs”, etc)

- **Efetividade na população (inclusive a população de pacientes)**: o que acontece quando o programa é implementado na população alvo.

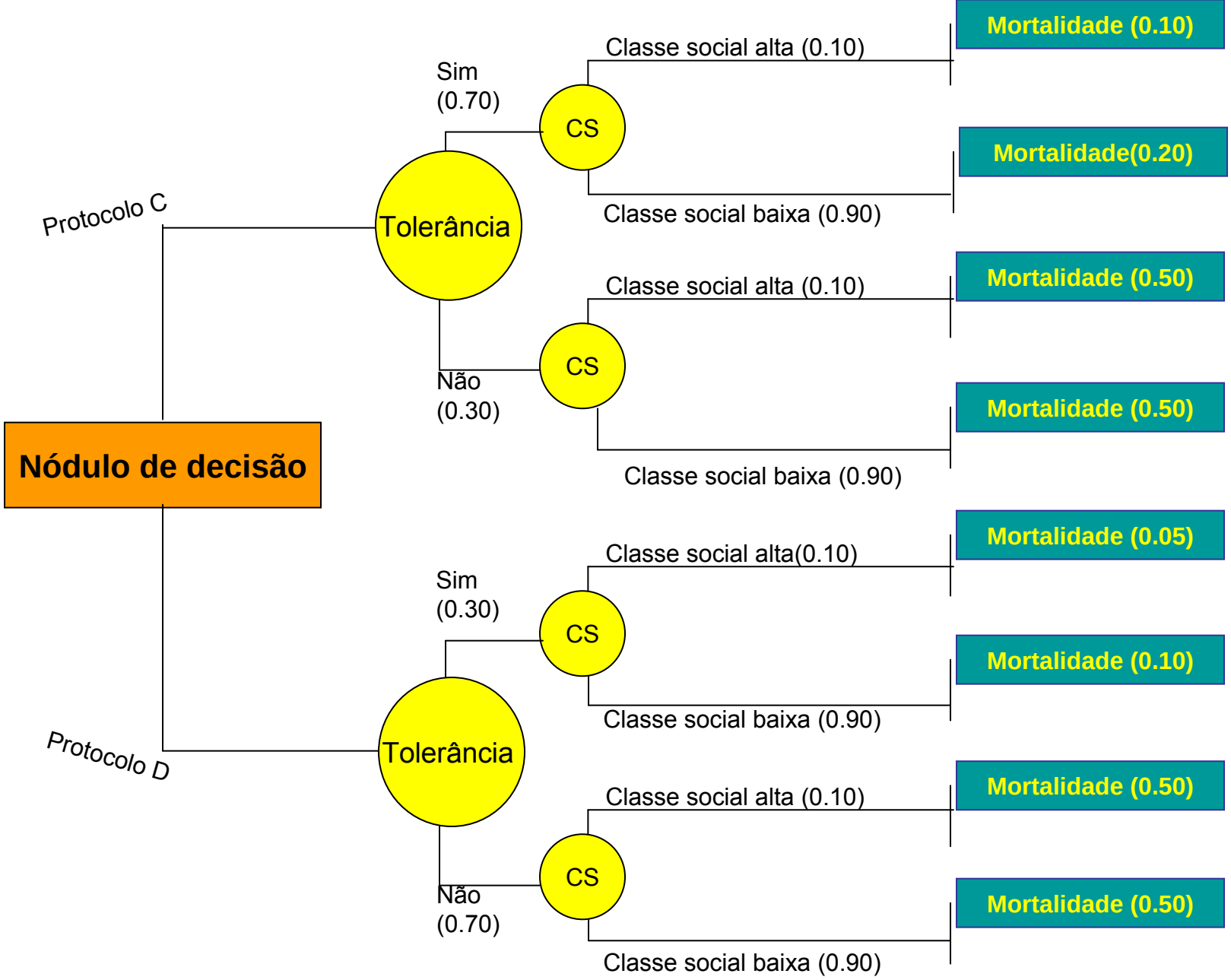
$$\text{Eficacia ou Efetividade} = \frac{\text{Incidência}_{\text{controle}} - \text{Incidência}_{\text{intervenção}}}{\text{Incidência}_{\text{controle}}} \times 100$$

Análise de decisão: Usa uma estratégia quantitativa a fim de avaliar o valor relativo de uma ou mais intervenções, programas ou serviços

Árvore de decisão

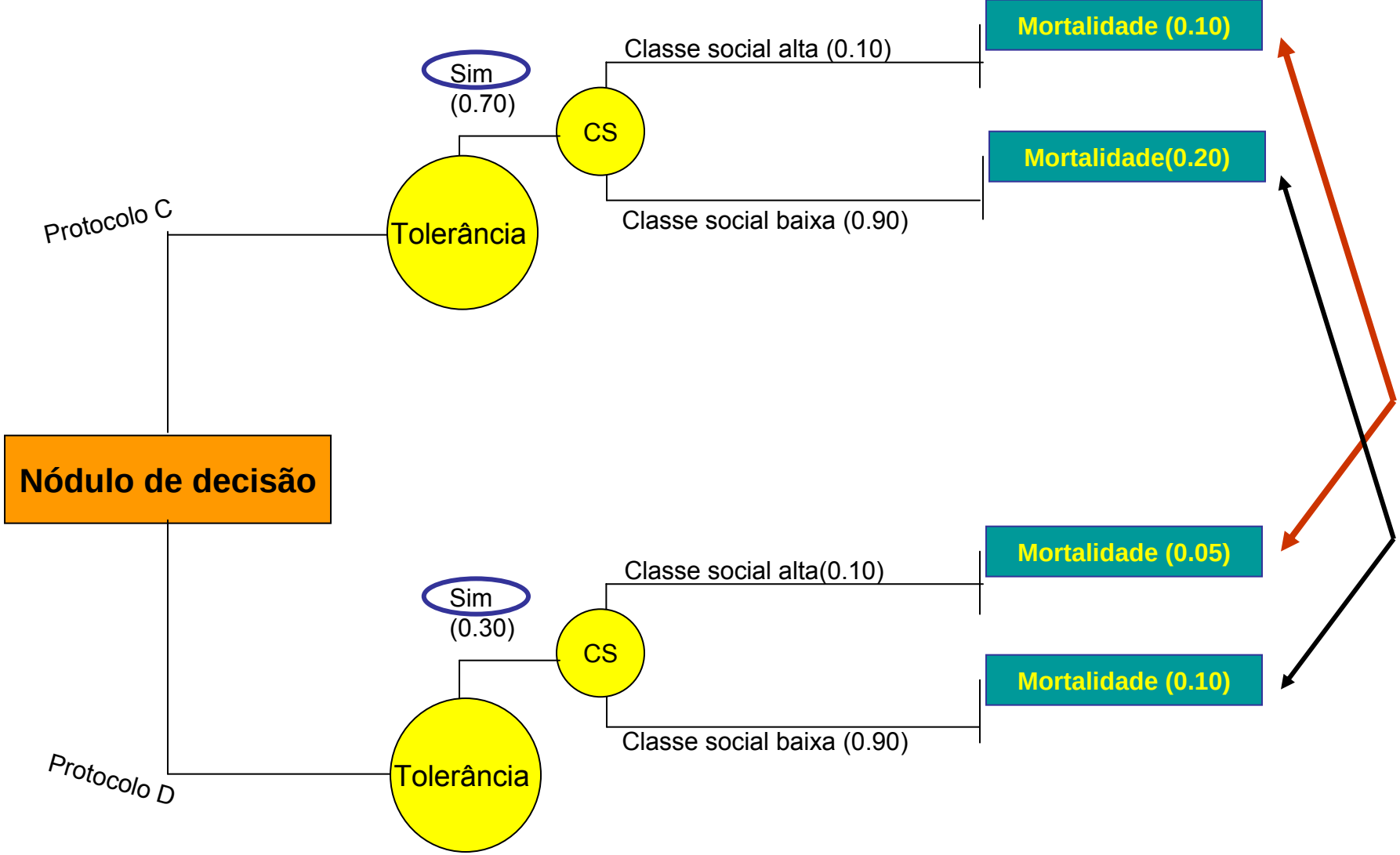
- Nódulo de decisão: sob controle do investigador

- Nódulo de probabilidade: fora do controle do investigador



Exemplo de árvore de decisão com dois nódulos de probabilidade

Para os que toleram as terapias, D tem uma mortalidade mais baixa do que C



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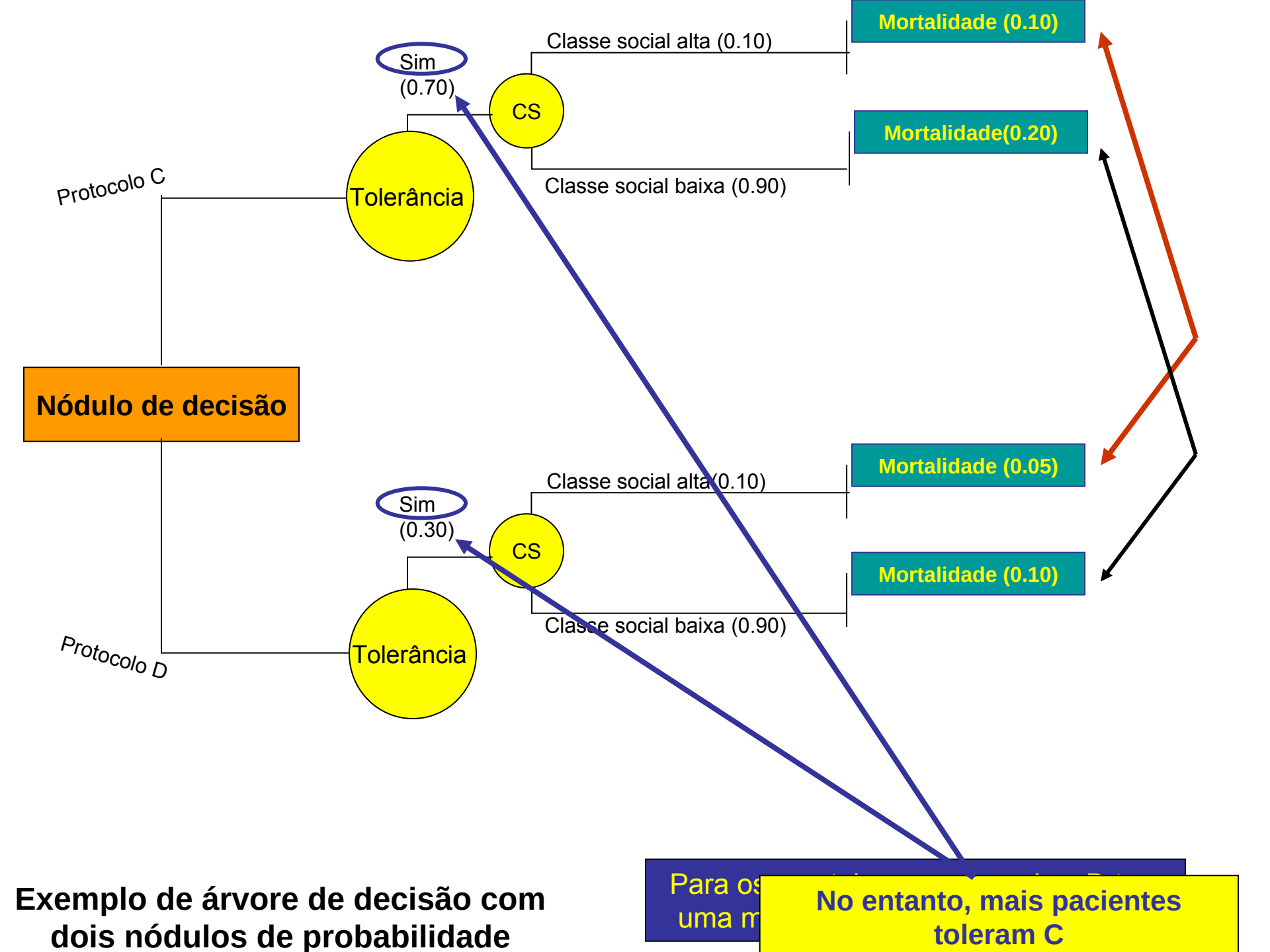

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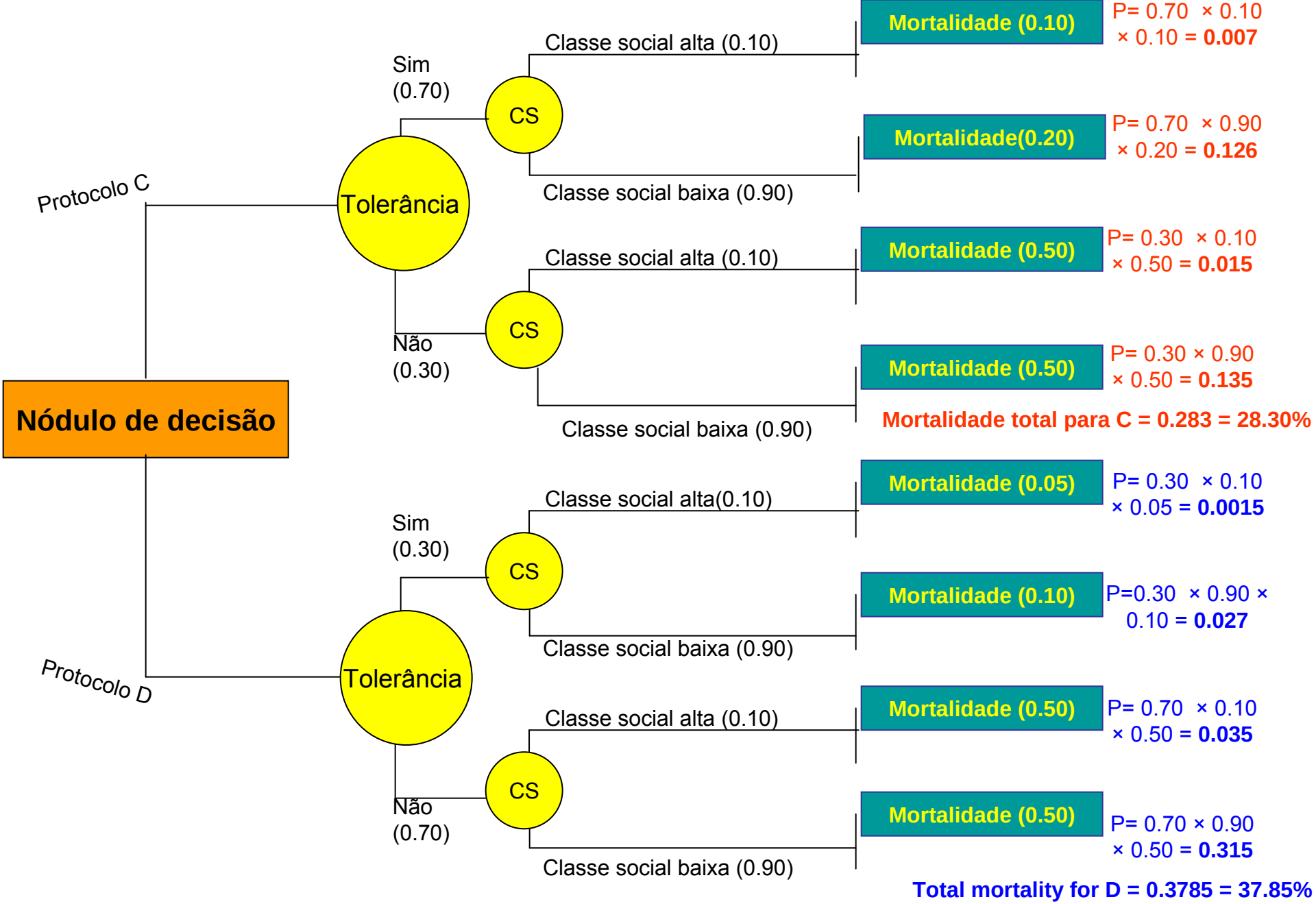
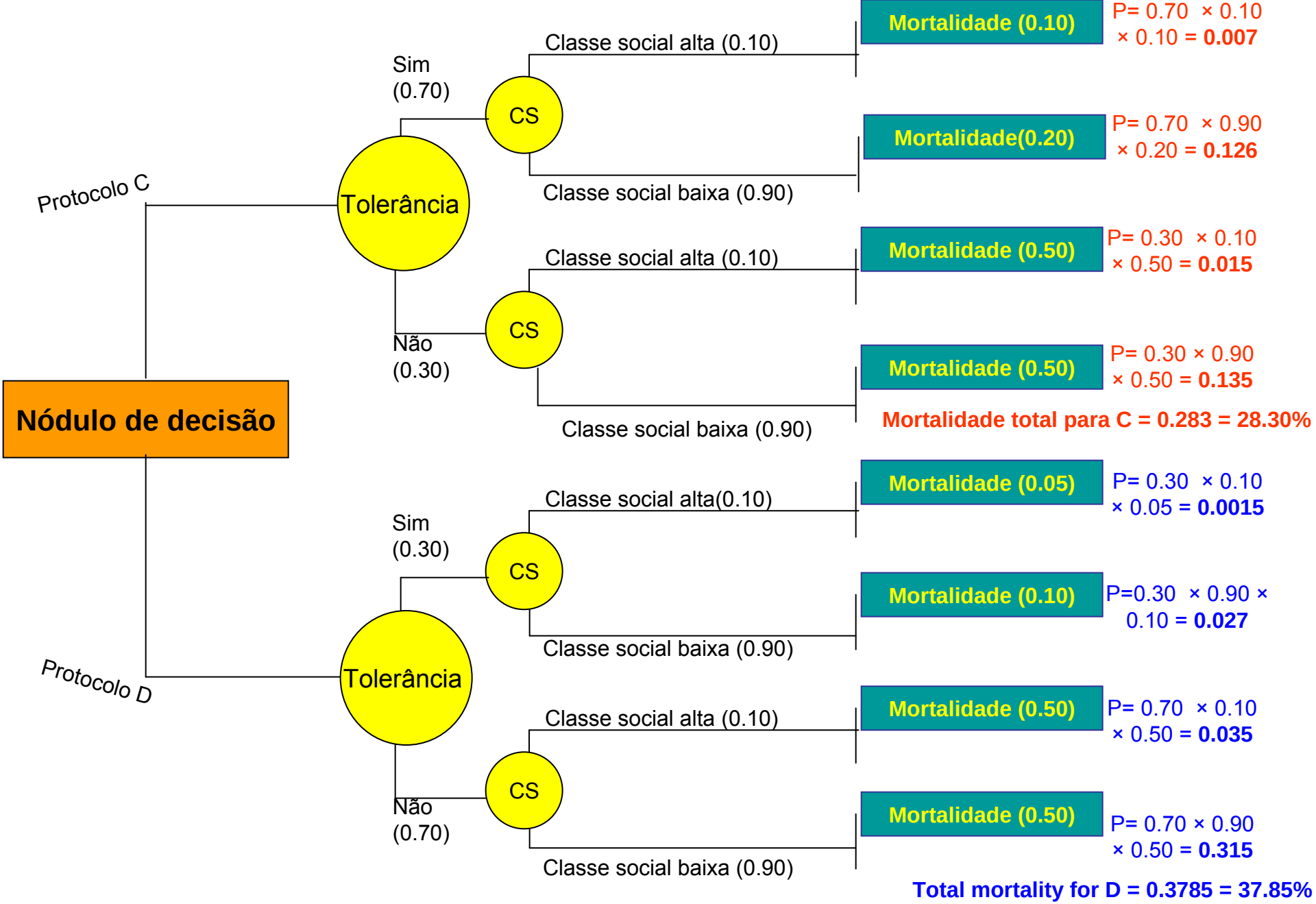


Efetividade de C nos pacientes (comparada com D)= {(37.85% - 28.30%) ÷ 37.85%} × 100= 25.20%



<u>Conclusão</u>: D é mais eficaz (isto é, os que o toleram têm uma mortalidade mais baixa do que C), mas como C tem melhor tolerância, a efetividade no total de pacientes é mais elevada

Análise de sensibilidade: um instrumento para políticas de saúde

Análise de sensibilidade é uma estratégia baseada em modificações dos *outputs* esperados de um modelo (por exemplo, mortalidade) como resultado da variação dos seus parâmetros (ou pressupostos) dentro de uma faixa razoável de valores.

(Szklo M & Nieto FJ. *Epidemiology: Beyond the Basics*. 2nd edition. Jones & Bartlett, 2006)

Análise de sensibilidade – pressuposto: tolerância ao protocolo D aumentou de 30% para 50%

Tabela 2a – C: menor eficácia, maior tolerância	
Tolerância?	Probabilidade conjunta de morte
Yes	0.70 × 0.10 × 0.10= 0.007
	0.70 × 0.90 × 0.20= 0.126
Não	0.30 × 0.10 × 0.50= 0.015
	0.30 x 0.90 x 0.50= 0.135
Mortalidade total	0.007 + 0.126 + 0.015 + 0.135= 0.283 or **28.30%**

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Tabela 2a – D: maior eficácia, menor tolerância

Tolerância?	Probabilidade conjunta de morte
Yes	**0.50** × 0.10 × 0.05= 0.0025
	0.50 × 0.90 × 0.10= 0.045
No	**0.50** × 0.10 × 0.50= 0.025
	0. 50 × 0.90 × 0.50= 0.225
Mortalidade total	0.0025 + 0.045 + 0.025 + 0.225= 0.2975 or **29.75%**

(Antes: 37.85%)

C é ainda um pouco mais efetivo do que D, mas se o custo de D for menor, a custo-efetividade de D pode ser melhor do que a de C.

Efetividade de C (vis-a-vis D)= {[29.75% - 28.30%] ÷ 29.75%} × 100= 4.90% (antes: 25.2%)

Selective Screening:

When Should Screening Be Limited to High-risk Individuals?

MOYSES SZKLO, MD, DrPH

Issues related to selective screening are discussed. The distinction between test accuracy and program accuracy is presented in the context of impact on cost/true case detection, which in turn reflects the gain in specificity and loss in sensitivity for the total target population. When two or more risk factors are combined to define high-risk subjects, a gain in program accuracy and a relative reduction in cost/true case found ensue if there is additive interaction between these risk factors. The author also discusses periodicity of screening and emphasizes the inappropriateness of using the notion of risk for disease occurrence as a criterion to define periodicity. **Key words:** *selective screening; high-risk; specificity; sensitivity; cost; periodicity.* **J GEN INTERN MED 1990; 5(suppl):S47–S49.**

Hypothetical Examples of the Effect of Selective (High Risk) Screening on Program Accuracy and Cost/True Case Detected in a Population of 2 000 Individuals

Who is screened?	% of reference population	Program sensitivity (%)		False Positive Rate		Cost/True Case (US$) (Initial screening $200/test)	
All eligible persons	100	90		45		1 850	
Participants with risk factor X1(+)	50	60		37		1 390	
		Additive interaction?		Additive interaction?		Additive interaction?	
		No	Yes	No	Yes	No	Yes
Participants with risk factors X1(+) and X2(+)	25	38	53	31	14	1 110	560

(Szklo M. *J Gen Intern Med* 1990;5(Suppl):S47-S49)

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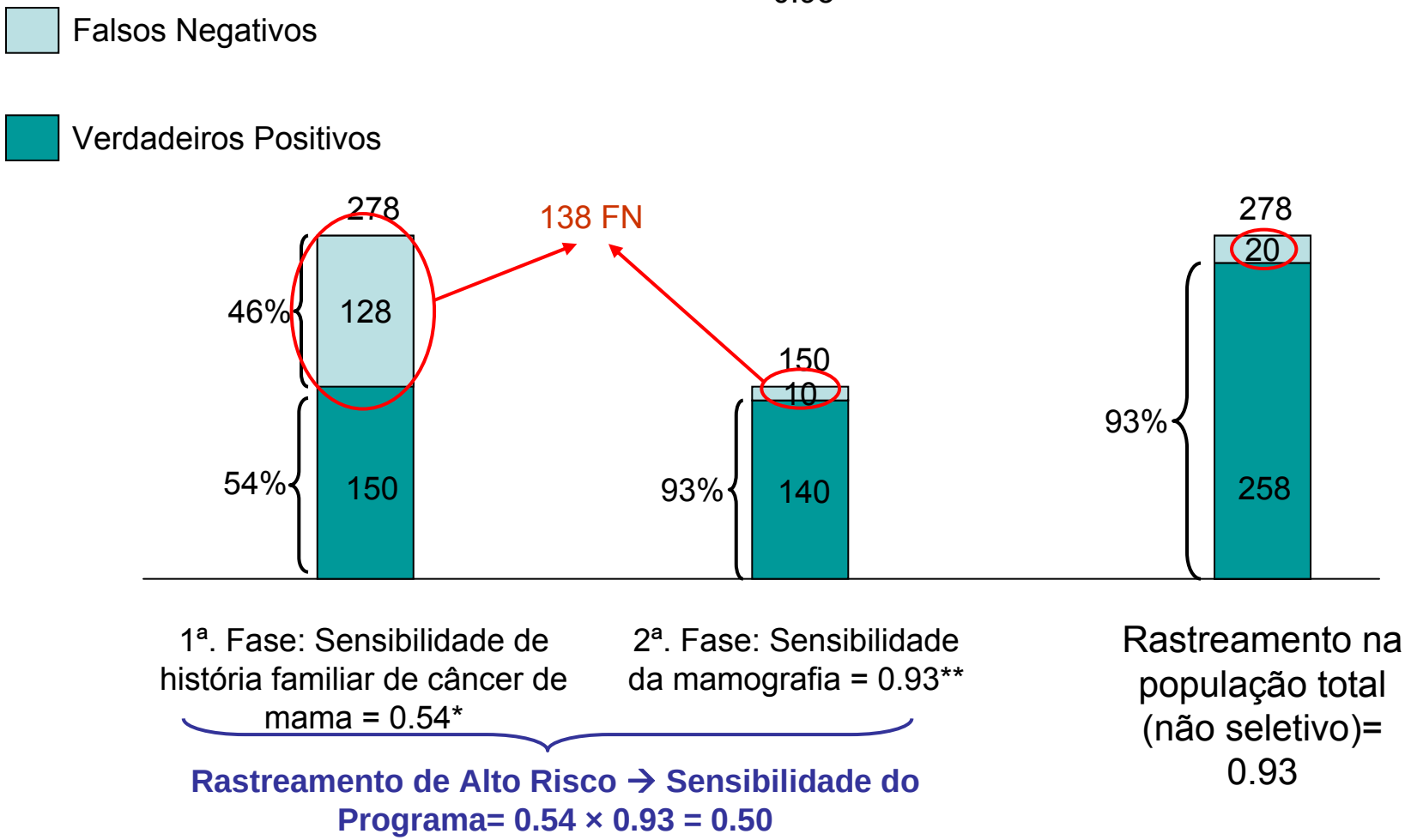
RASTREAMENTO DE ALTO RISCO (SELETIVO) PARA CASOS INCIDENTES DURANTE UM ANO EM UMA POPULAÇÃO DE 100 000 MULHERES: EFEITO SOBRE A SENSIBILIDADE¶

Incidência anual média de cancer de mama feminina em Sao Paulo, 1998-2000 ≅ 278/100 000, São Paulo§

1ª. Fase: Sensibilidade de história familiar de câncer de mama = 0.54*; 2ª. Fase: Sensibilidade da mamografia = 0.93**



§Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

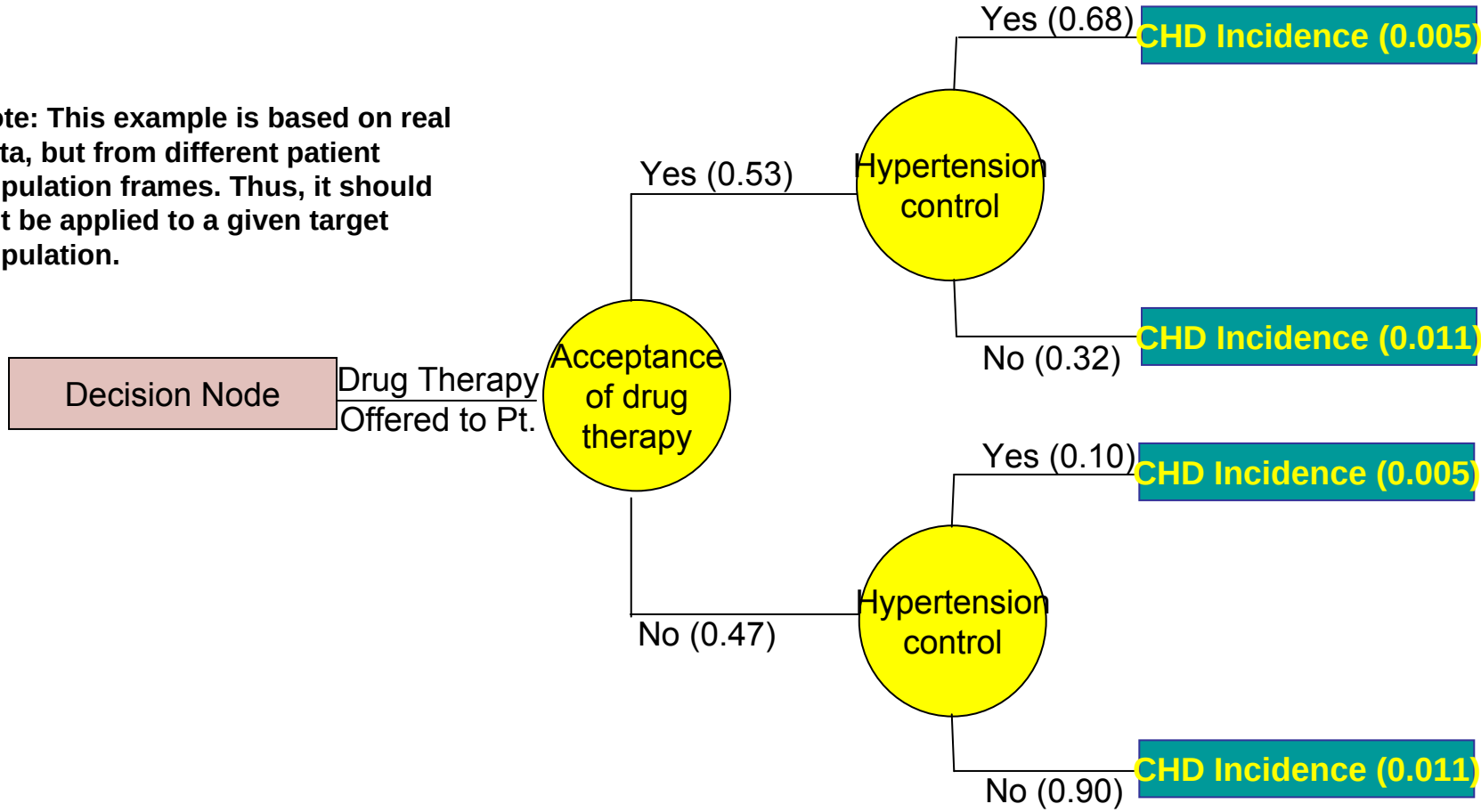
¶Szklo M. *J Gen Intern Med* 1990; 5(Suppl):S47-S49

*Hartmann et al, New Eng J Med 2005;353:229-37

**Mushlin et al, Am J Prev Med 1998;14:143-53

Decision Tree of Hypertension Medication Therapy with One Decision Node Using Average Annual Incidence of Coronary Heart Disease (CHD) as Outcome

Note: This example is based on real data, but from different patient population frames. Thus, it should not be applied to a given target population.



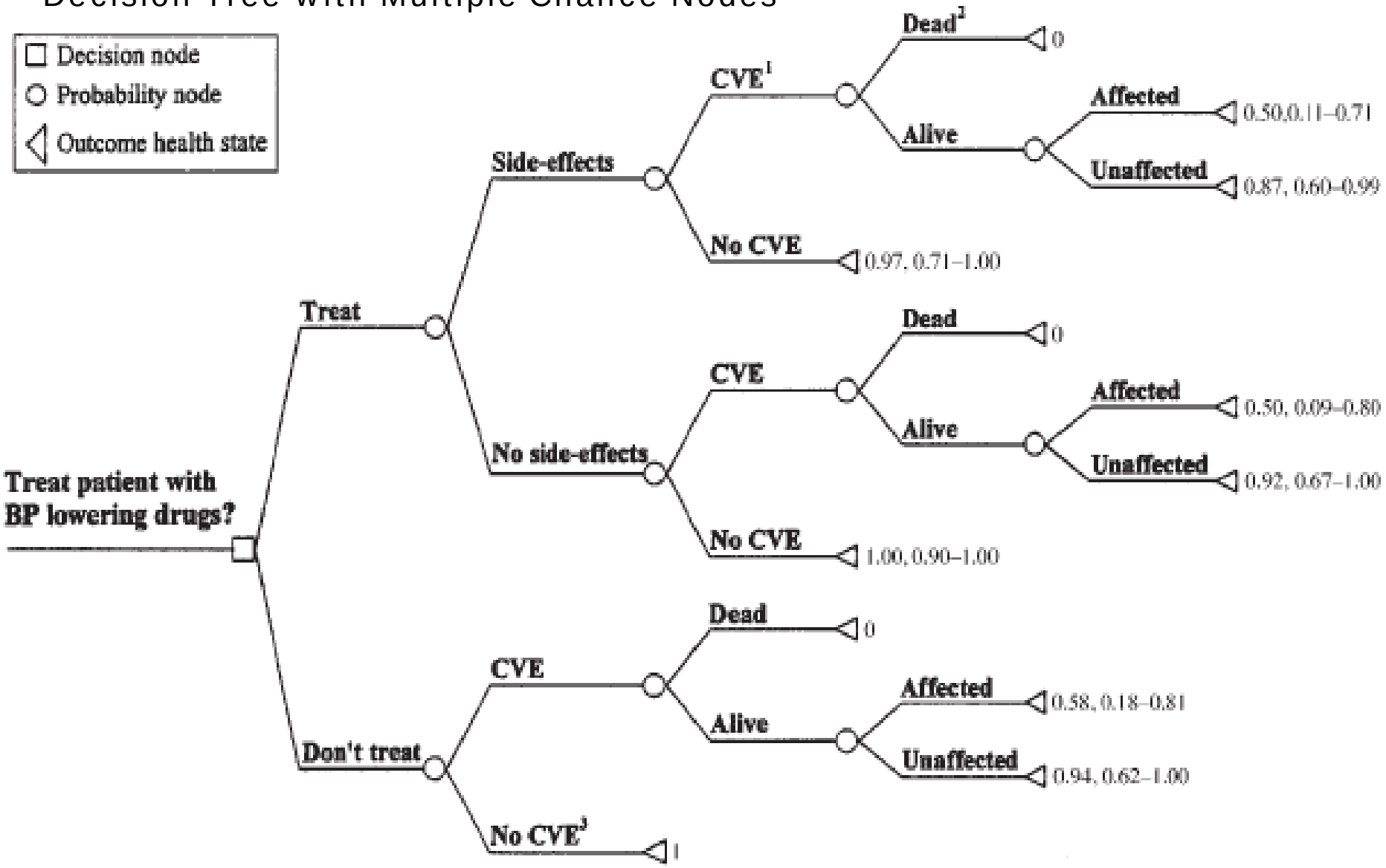
Incidence According to Acceptance of Drug Therapy

Yes: (0.53 × 0.68 × 0.005) + (0.53 × 0.32 × 0.011)= 0.0037= 3.7/1,000
No: (0.47 × 0.10 × 0.005) + (0.47 × 0.90 × 0.011)= 0.0049= 4.9/1,000

Effectiveness of Drug Therapy
[(4.9 – 3.7) ÷ 4.9] × 100= 24.5%

(Nieto FJ, et al. Population awareness and control of hypertension and hypercholesterolemia. *Arch Intern Med* 1995;155:677-684; Chambless LE, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors. *Am J Epidemiol* 1997;146:483-494; Moore J. Hypertension. Catching the Silent Killer. *The Nurse Practitioner* 2005;30:16-35)

Decision Tree with Multiple Chance Nodes



Decision tree for the treatment of high blood pressure based on 52 hypertensive patients. Values besides each outcome health state are median and inter-quartile range. CVE, cardiovascular event (newly diagnosed angina, myocardial infarction, coronary heart disease, stroke or transient ischemic attack)
(Montgomery AA, et al. Shared decision making in hypertension. *Family Practice* 2001;18:309-313).

Age-Adjusted Death Rate Ratios for Current vs. Non-smokers by Cause of Death: The Harvard Six Cities Prospective Study
(adapted from *N Eng J Med* 1993;329:1753-9)

Cause of death	Death Rate Ratio (95% CI): Current Smokers vs. Non-smokers
All	2.0 (1.5, 2.7)
Lung Cancer	8.0 (3.0, 21.6)
Cardiopulmonary Diseases	2.3 (1.6, 3.4)
All other causes	1.5 (0.9, 2.4)

"Smoking was most strongly associated with mortality due to lung cancer, significantly associated with mortality due to cardiopulmonary diseases, but not associated with mortality from (the category) other causes"

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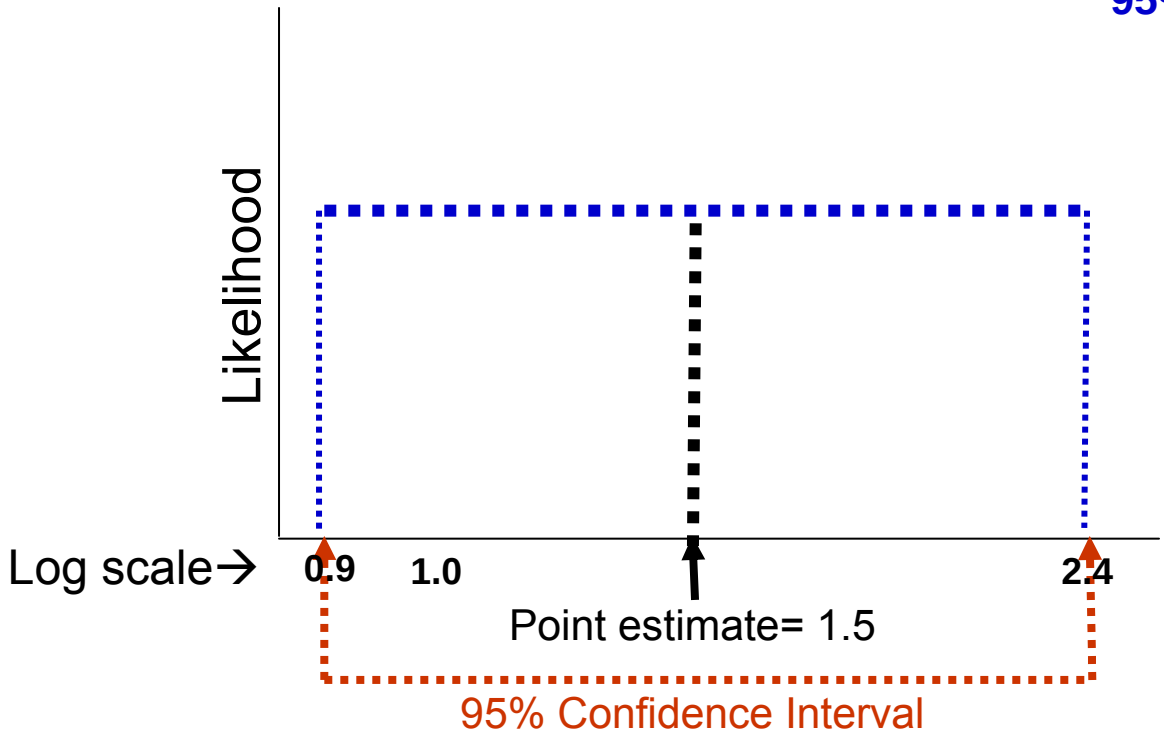
A. Incorrect Interpretation of the 95% Confidence Interval



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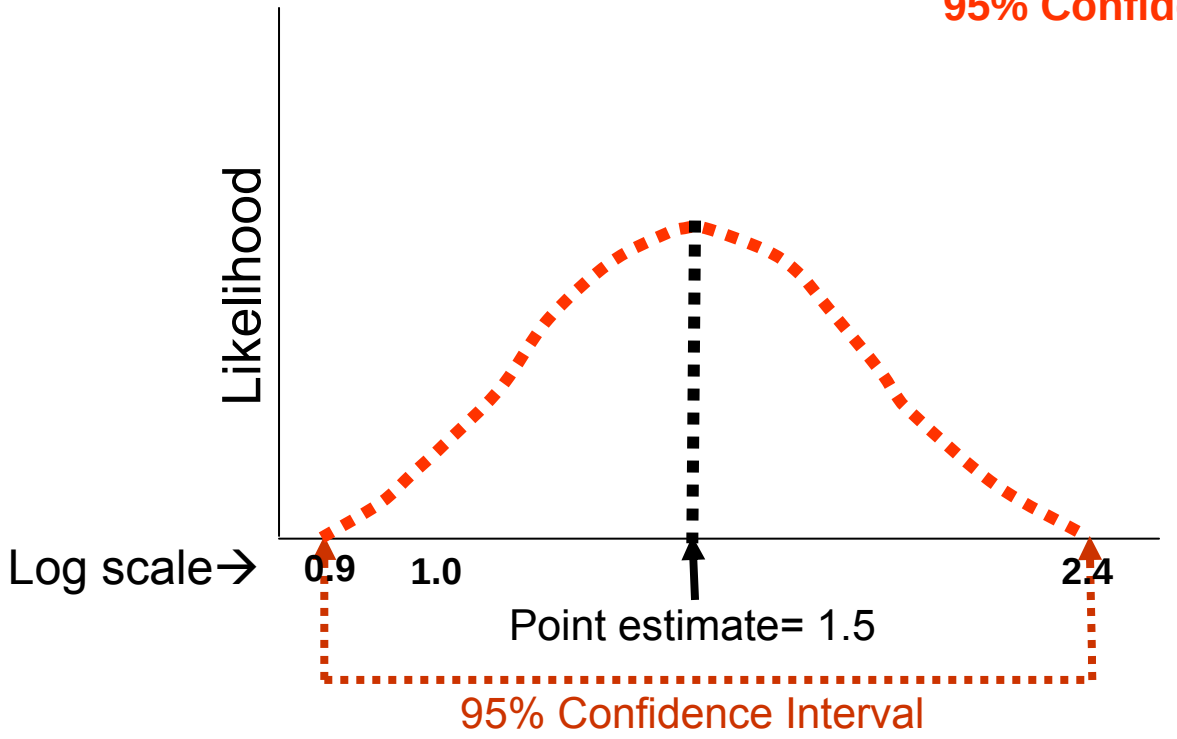
B. Correct Interpretation of the 95% Confidence Interval



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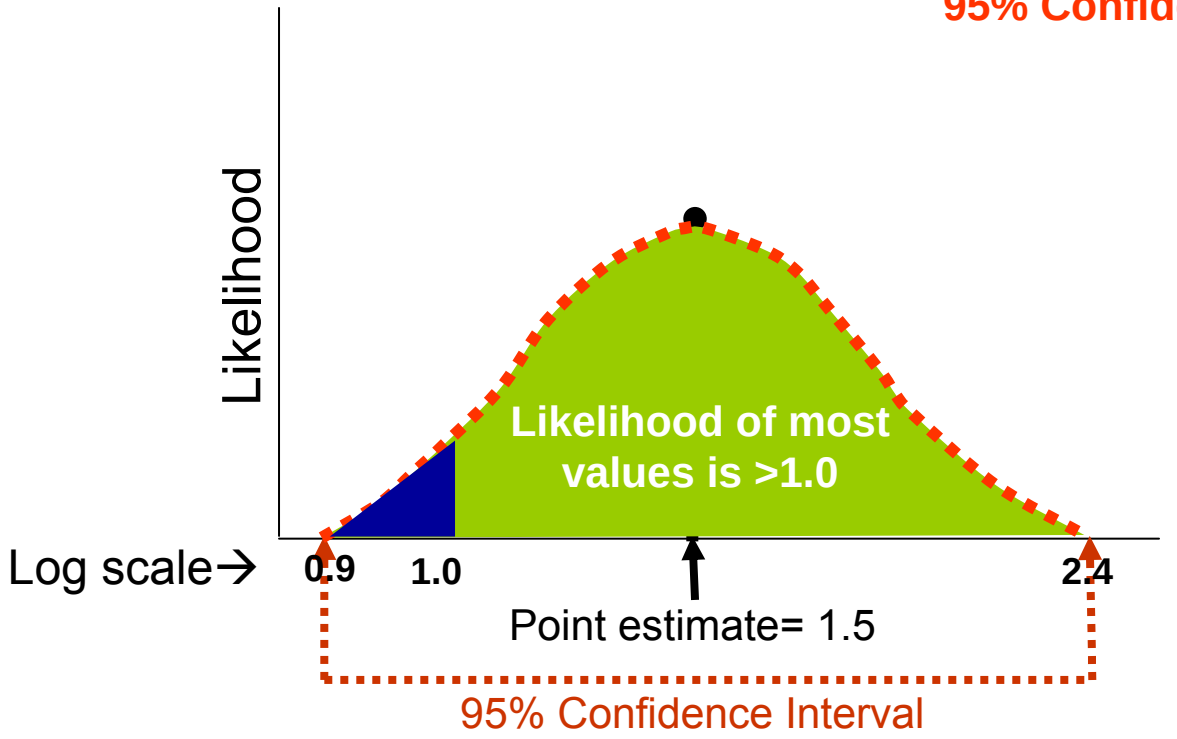
Lung Cancer	8.0 (3.0, 21.6)
Cardiopulmonary Diseases	2.3 (1.6, 3.4)
All other causes	1.5 (0.9, 2.4)

B. Correct Interpretation of the 95% Confidence Interval



What is the basic principle of meta-analysis?

Mantel-Haenszel Formula for Calculation of Adjusted Odds Ratios

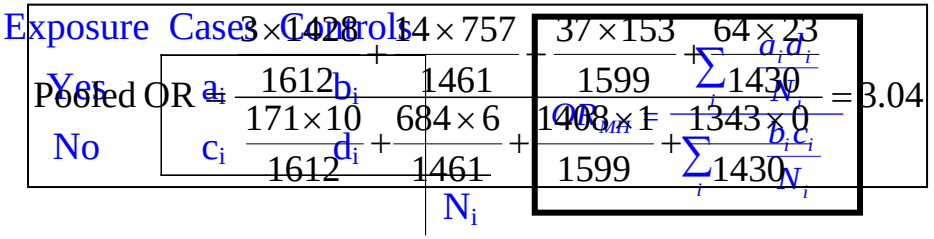
Exposure	Cases	Controls	
Yes	a_i	b_i	
No	c_i	d_i	
			N_i

$$OR_{MH} = \frac{\sum_i \frac{a_i d_i}{N_i}}{\sum_i \frac{b_i c_i}{N_i}}$$

The OR_{MH} is a weighted average of study-specific ORs (OR_i), with weights equal to each study:

$$w_i = \frac{b_i c_i}{N_i}$$

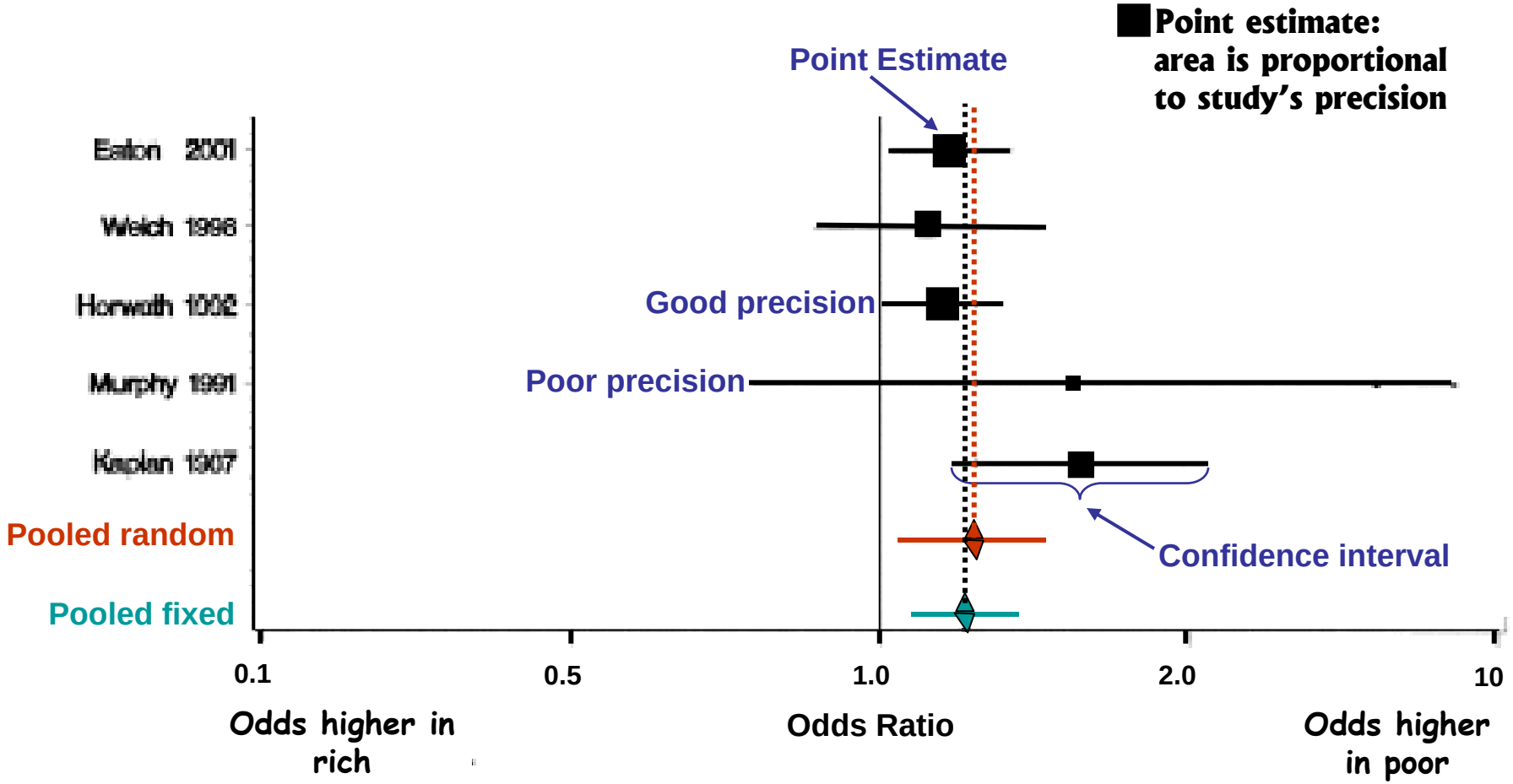
Mantel-Haenszel meta-analytic pooling strategy



HYPOTHETICAL EXAMPLE OF META-ANALYSIS OF FOUR STUDIES

Study	Menopause	Cases	Controls		Odds Ratio
1	Post	3	171		$OR_1 = 2.5$
	Pre	10	1428		
				1612	
2	Post	14	684		$OR_2 = 2.6$
	Pre	6	757		
				1461	
3	Post	37	1408		$OR_3 = 4.0$
	Pre	1	153		
				1599	
4	Post	64	1343		$OR_4 = 1.2$
	Pre	0	23		
				1430	

Meta-Analysis of Studies of Incidence of Depression and Socio-Economic Status



(Lorant et al, *Am J Epidemiol* 2003;157:98-112)

Model Choice in Meta-Analysis

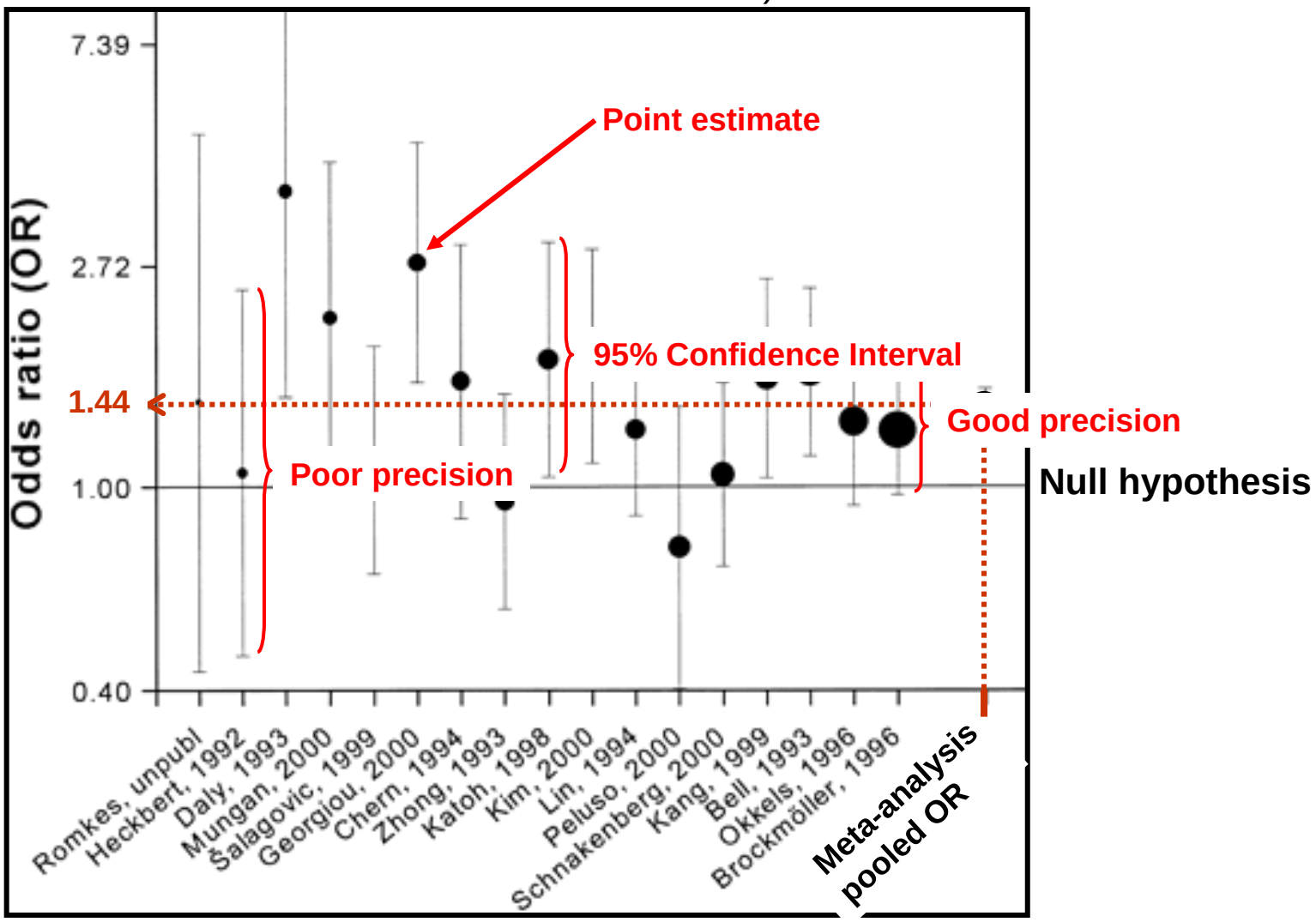
- ***Fixed-effects model***: inference is conditional on the studies actually carried out – **"Did the treatment produce benefit on the average in the studies at hand?"**
  - It incorporates only a within-study component of the variance

- ***Random-effects model***: inference is based on the assumption that the studies are a random sample of some hypothetical population of studies – **"Will the treatment produce benefit on average"?**
  - It incorporates between-study and within-study components of the variance; thus, it is more conservative

Note: When the study results are fairly homogeneous -- which is an important assumption for estimating the pooled effect -- the fixed and the random effects models will provide virtually identical results.

(Pettiti DB. *Meta-Analysis, Decision Analysis and Cost-Effectiveness Analysis*. New York, Oxford, Oxford University Press, 1994); Bailey KR. Inter-study differences: how should they influence the interpretation and analysis of results? *Stat Med* 1987;6:351-358)

Meta-Analysis of Studies of Bladder Cancer and Glutathione S-Transferase M1 (GSTM-1) Null Status (GSTM-1 is Involved in the Detoxification of Carcinogens Found in Tobacco Smoke)



Example of Application of Levels of Evidence Cervical Cancer – Summary (NCI)

- Evidence strongly suggests a decrease in mortality from regular screening with Pap tests in women who are sexually active or who have reached 18 years of age.

- Level of evidence for preceding statement:

  3 - Well-designed cohort/case-control studies

  4 - Evidence from multiple time series with or without intervention

  5 - Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees

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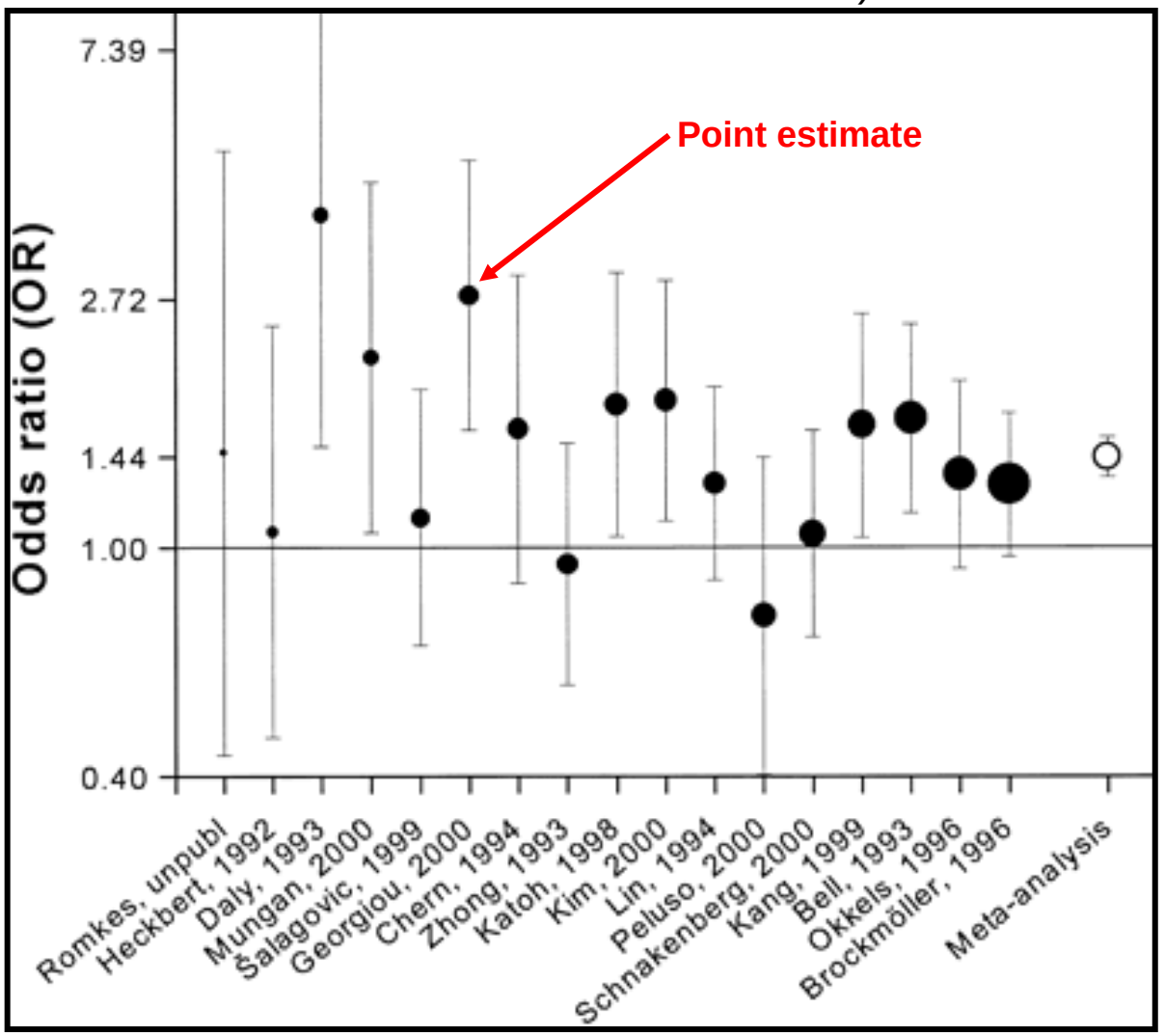

● **Point estimate: area is proportional to the study's precision (sample size)**

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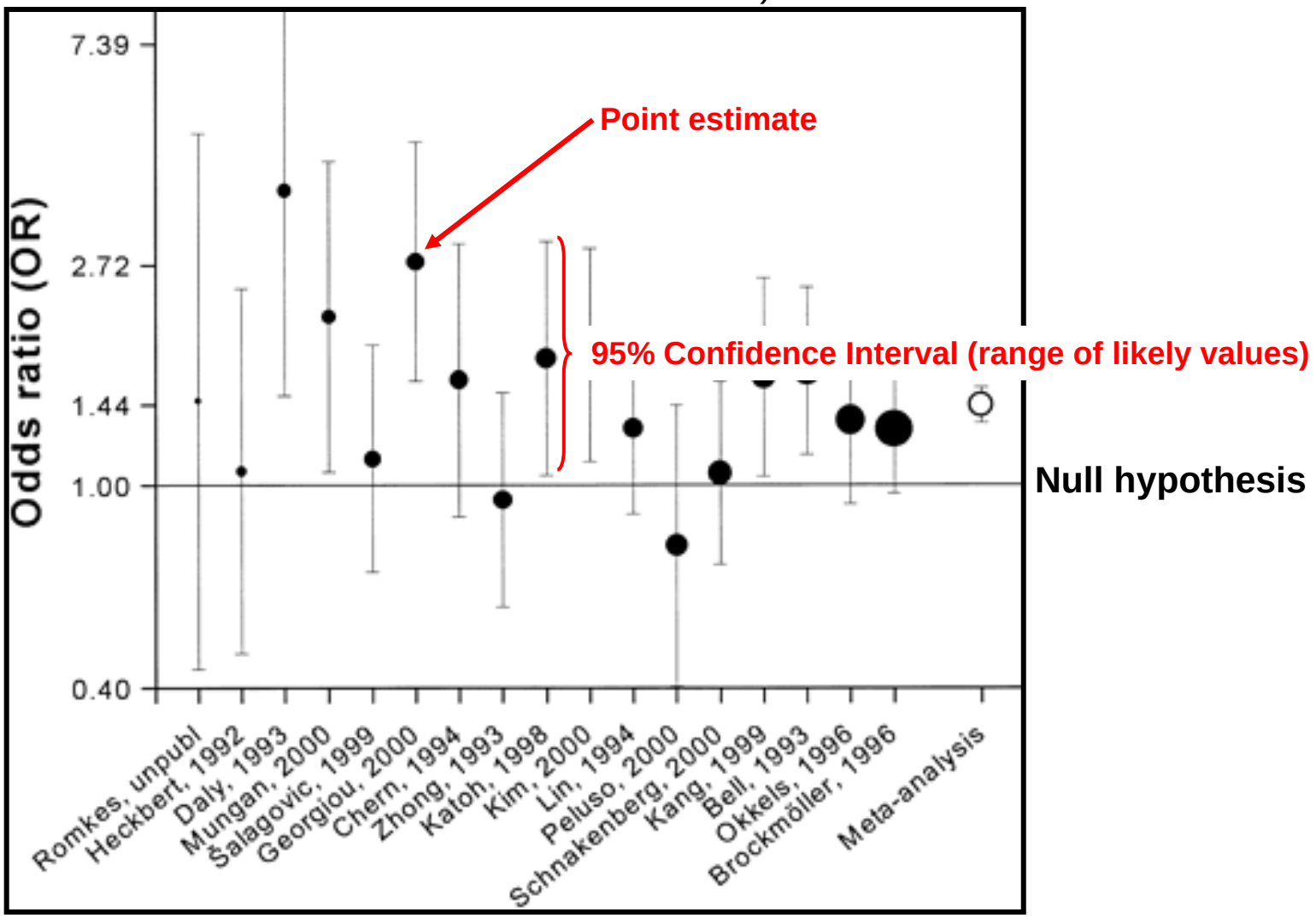

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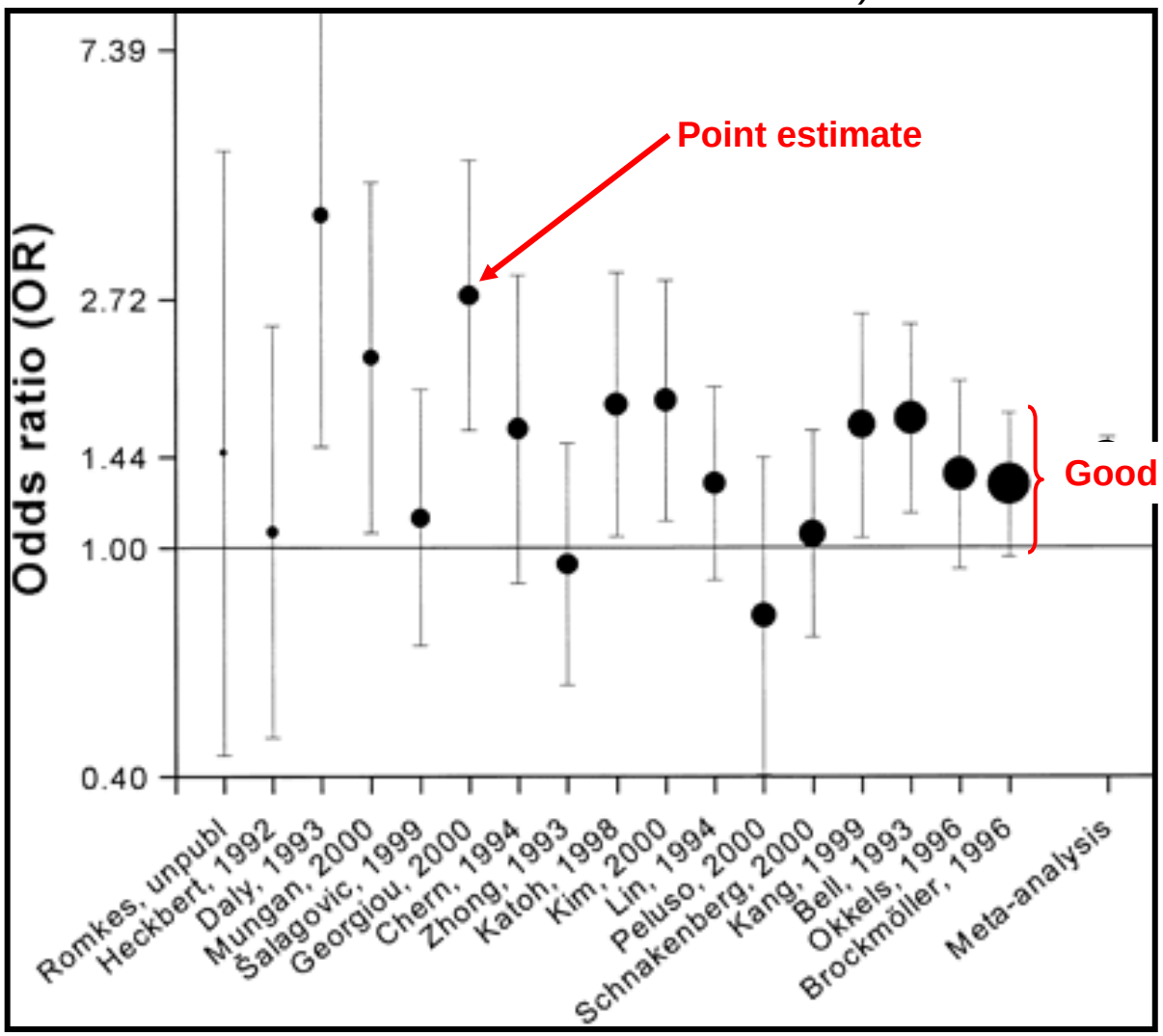

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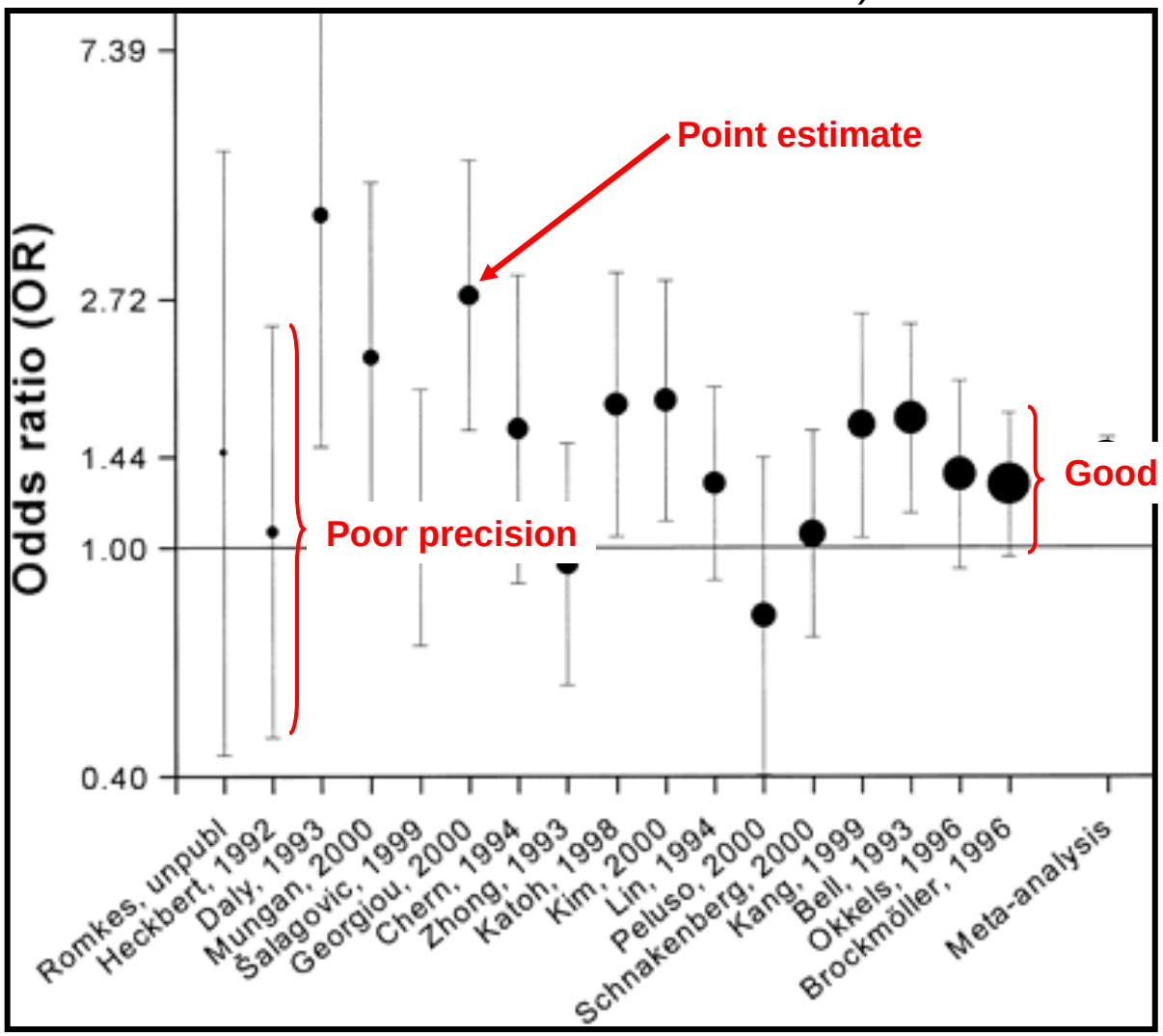

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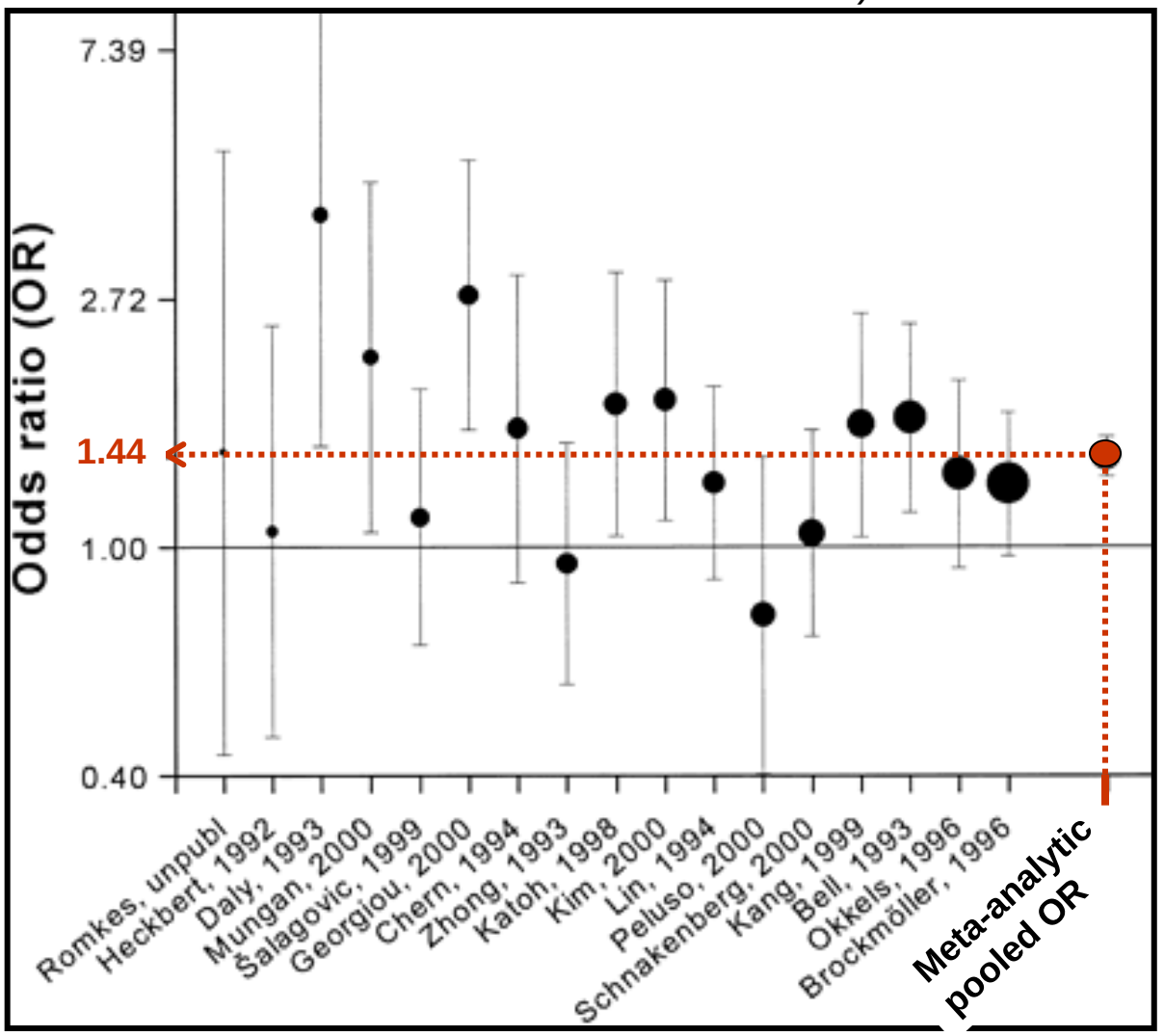

MAIN ASSUMPTION OF META-ANALYSIS: HOMOGENEITY
Most studies are consistent with a positive association (odds ratio above 1.0)

Meta-analysis: quantitative method that aims at summarizing study results, thus, facilitating the process of inferring effectiveness of an intervention, service or program.

Steps in Meta-Analysis

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- Selection of studies based on quality
- Statistical analysis

INSTEAD OF PERSON, THE ANALYTIC UNIT IS STUDY

uicc
global cancer control

Int J Cancer 2010;127:172-184

IJC
International Journal of Cancer

Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials

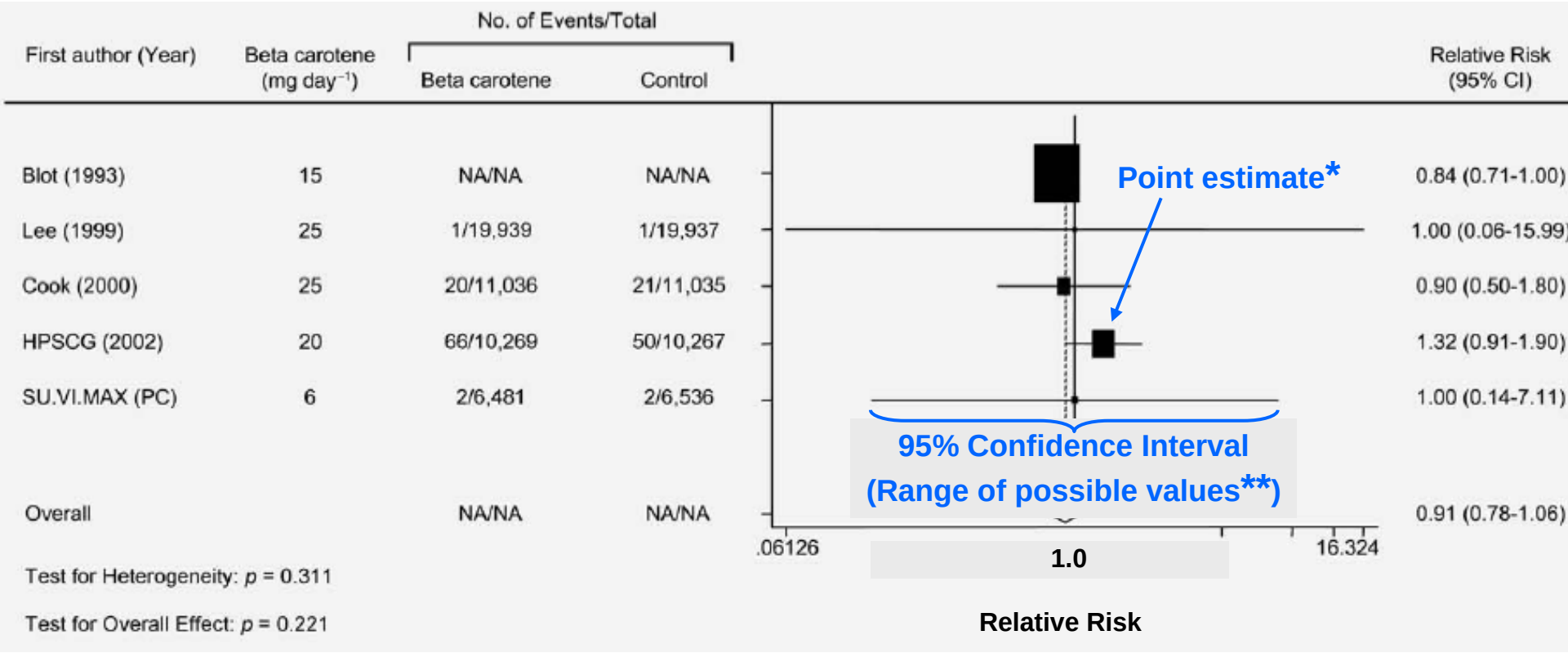
Nathalie Druesne-Pecollo[1], Paule Latino-Martel[1], Teresa Norat[2], Emilie Barrandon[1], Sandrine Bertrais[1], Pilar Galan[1] and Serge Hercberg[1,3]

[1] UMR U 557 INSERM, U 1125 INRA, CNAM, Université Paris 13, F-93017 Bobigny, France
[2] Department of Epidemiology and Public Health, Imperial College, London, United Kingdom
[3] Département de Santé Publique, Hôpital Avicenne, F-93017 Bobigny, France

The effect of beta-carotene supplementation on cancer incidence has been investigated in several randomized controlled trials. The objective was to review the effect of beta-carotene supplementation on cancer incidence in randomized trials by cancer site, beta-carotene supplementation characteristics and study population. Relevant trials were retrieved by searching PubMed (up to April 2009). Authors involved in selected studies were contacted for additional information. Thirteen publications reporting results from 9 randomized controlled trials were included. Overall, no effect of beta-carotene supplementation was observed on the incidence of all cancers combined (RR, 1.01; 95% CI, 0.98–1.04), pancreatic cancer (RR, 0.99; 95% CI, 0.73–1.36), colorectal cancer (RR, 0.96; 95% CI, 0.85–1.09), prostate cancer (RR, 0.99; 95% CI, 0.91–1.07), breast cancer (RR, 0.96; 95% CI, 0.85–1.10), melanoma (RR, 0.98; 95% CI, 0.65–1.46) and non melanoma skin cancer (RR, 0.99; 95% CI, 0.93–1.05). The incidence of lung and stomach cancers were significantly increased in individuals supplemented with beta-carotene at 20–30 mg day^{-1} (RR, 1.16; 95% CI, 1.06–1.27 and RR, 1.34; 95% CI, 1.06–1.70), in smokers and asbestos workers (RR, 1.20; 95% CI, 1.07–1.34 and RR, 1.54; 95% CI, 1.08–2.19) compared to the placebo group. Beta-carotene supplementation has not been shown to have any beneficial effect on cancer prevention. Conversely, it was associated with increased risk not only of lung cancer but also of gastric cancer at doses of 20–30 mg day^{-1}, in smokers and asbestos workers. This study adds to the evidence that nutritional prevention of cancer through beta-carotene

Beta Carotene and Gastric Cancer Incidence in Not Only Smokers or Asbestos Workers

(Druesne-Pecollo N, et al, *Int J Cancer* 2010;127:172-184)



*** The area of the rectangle (or dot) is proportional to the study's precision (sample size)**

**** The narrower the 95% CI, the better the precision**

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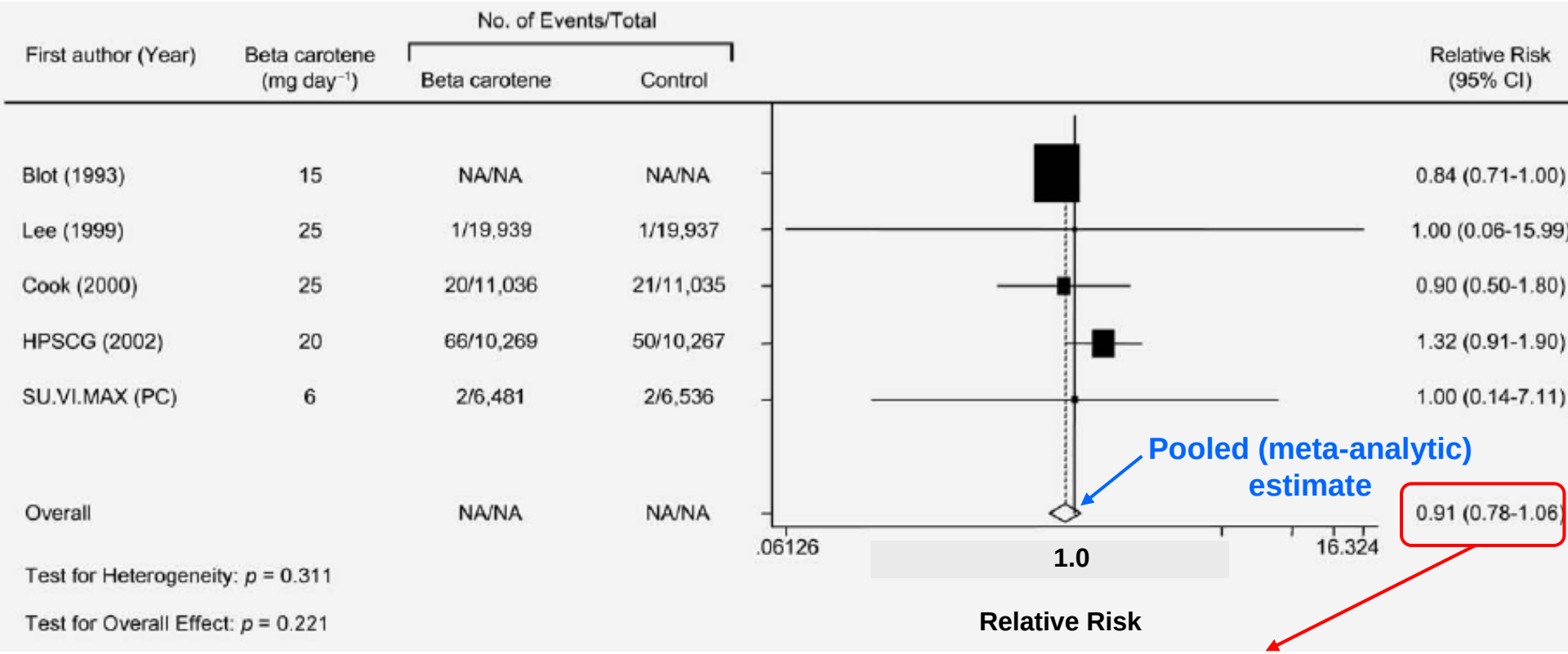

When the 95% CI includes 1.0, the association is not significant.

<u>Inference</u>: beta carotene is not effective

Políticas de Saúde Baseadas em Evidências

Critérios para julgar a eficácia e efetividade de uma intervenção (medida preventiva ou tratamento)

Classificação	Nível de evidência	Descrição do nível
melhor A	1a	Revisão sistemática de ensaios aleatorizados com homogeneidade – inclusive meta-análise
	1b	Um único ensaio aleatorizado de boa qualidade
	1c	Experimentos “naturais” (exemplo: estreptomicina e meningite tuberculosa) e séries temporais
	2a.	Revisão sistemática de estudos de coorte com homogeneidade – inclusive meta-análise
	2b	Um único estudo de coorte (prospectivo) de boa qualidade
B	3a	Revisão sistemática de estudos de casos e controles com homogeneidade – inclusive meta-análise
	3b	Um único estudo de casos e controles de boa qualidade
C	4	Série de casos
pior D	5	Opinião de especialistas não baseada em avaliação de resultados de estudos ou dedução lógica, ou sem um critério explícito de avaliação

(Modificado de: NHS R&D Centre for Evidence-Based Medicine.
See http://www.indigojazz.co.uk/cebm/levels_of_evidence.asp)

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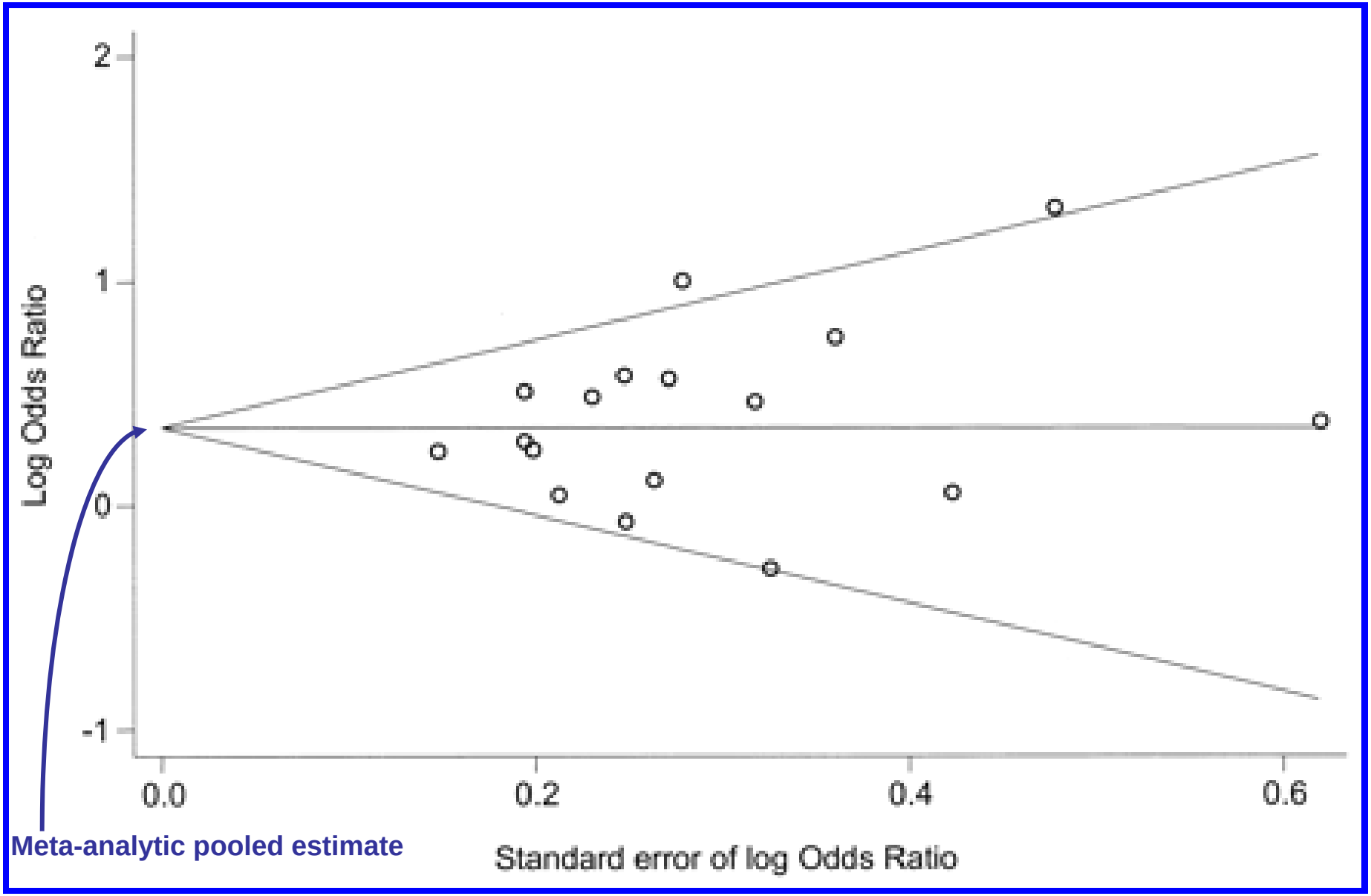
Begg's funnel plot for assessing publication bias in relation to glutathione S-transferase MI null status and bladder cancer risk

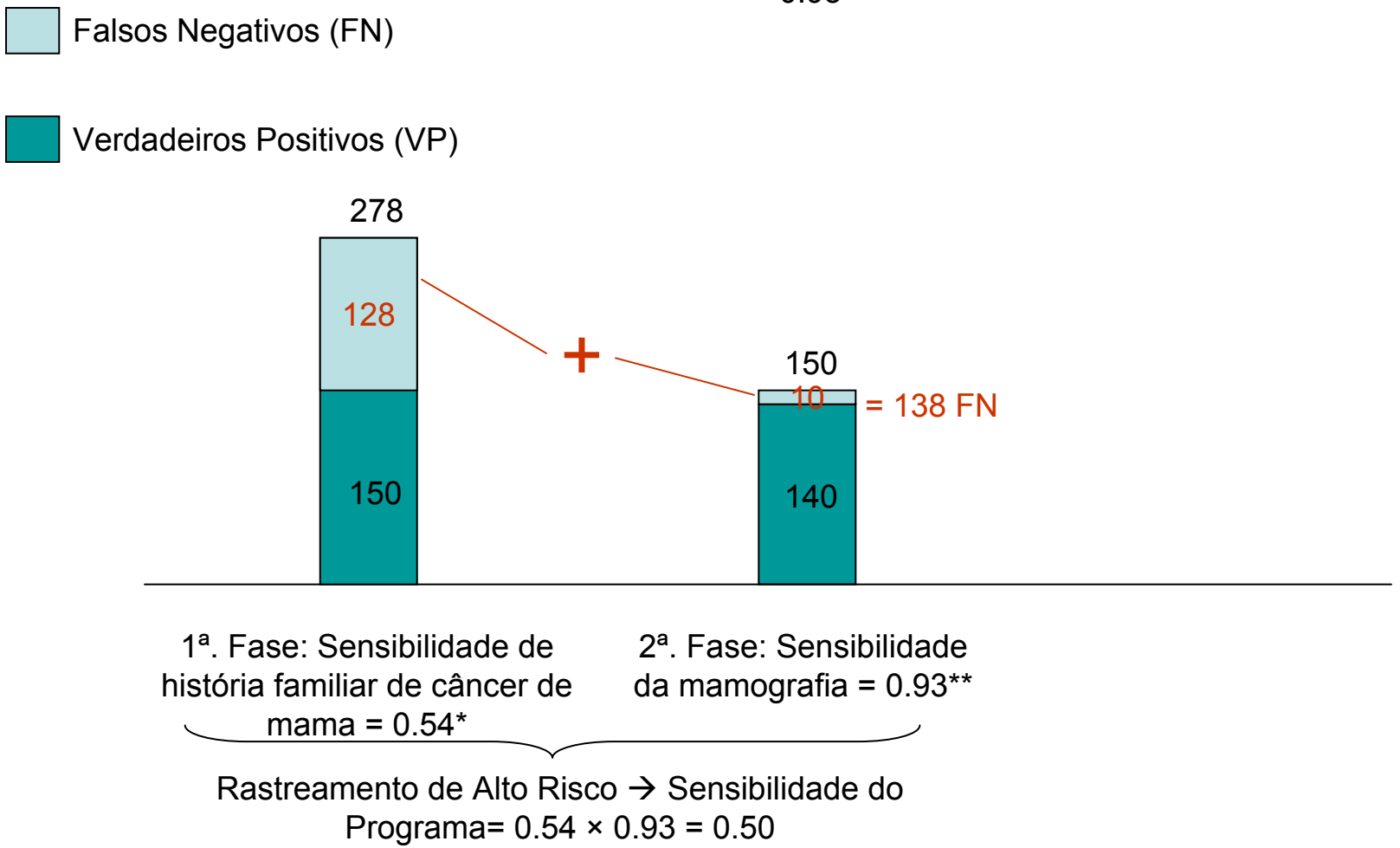


Engel LS et al. *Am J Epidemiol* 2002;156:95-109

RASTREAMENTO DE ALTO RISCO (SELETIVO) PARA CASOS INCIDENTES DURANTE UM ANO EM UMA POPULAÇÃO DE 100 000 MULHERES: EFEITO SOBRE A SENSIBILIDADE¶

Incidência anual média de cancer de mama feminina em Sao Paulo, 1998-2000 ≅ 278/100 000, São Paulo§

1ª. Fase: Sensibilidade de história familiar de câncer de mama = 0.54*; 2ª. Fase: Sensibilidade da mamografia = 0.93**



§Câncer no Brasil- Dados do Registro de Câncer de Base Populacional. Disponível em http://www.inca.gov.br/vigilancia/ CONPREV-INCA-MS e IBGE-MP

¶Szklo M. *J Gen Intern Med* 1990; 5(Suppl):S47-S49

*Hartmann et al, New Eng J Med 2005;353:229-37

**Mushlin et al, Am J Prev Med 1998;14:143-53