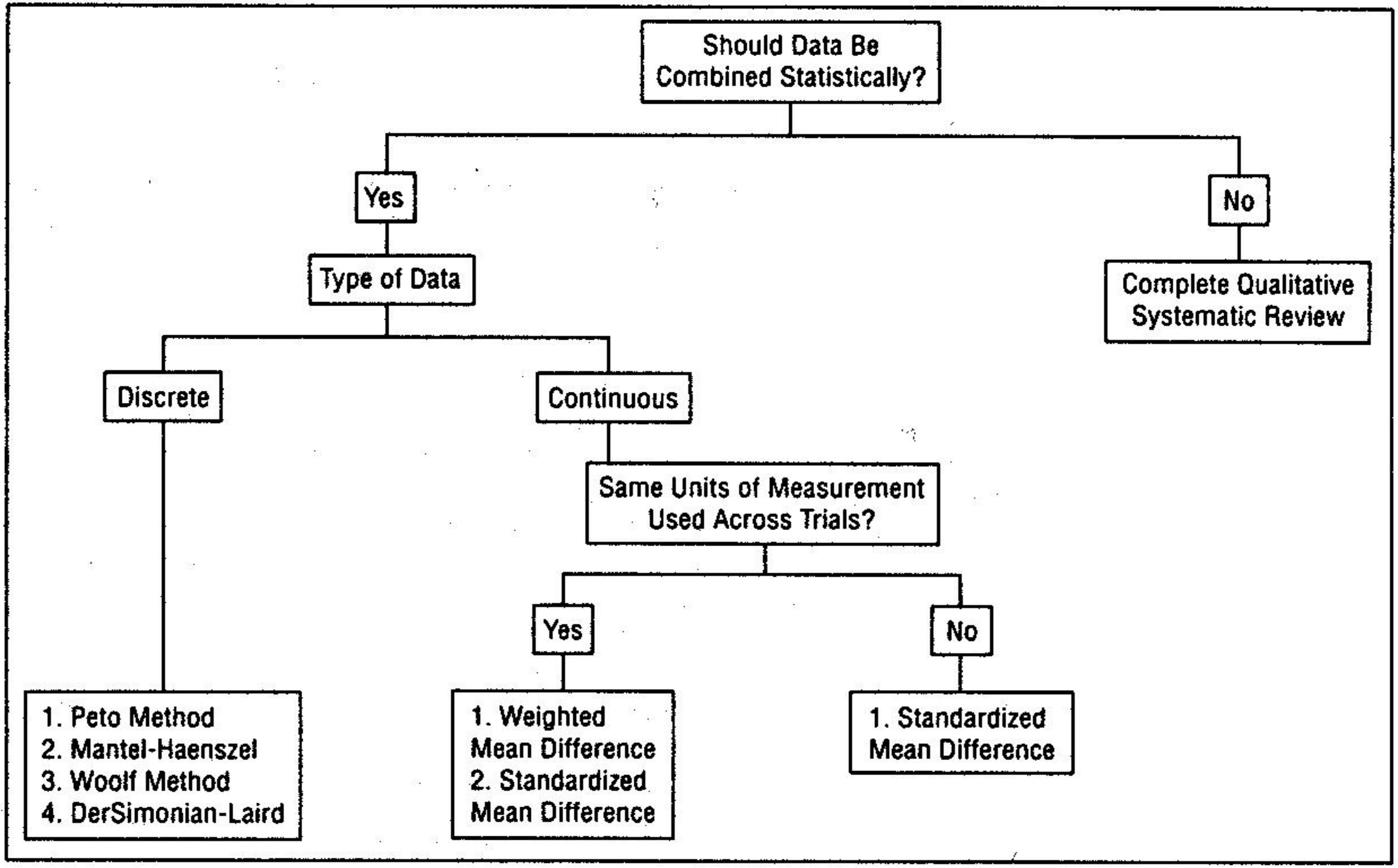
Revisão sistemática e meta-análise

Aula 4



Algorithm of statistical choices available to systematic reviewers.

Moher D et al. Arch Pediatr Adolesc Med 1998;152:915-20

Exemplo

- Ingesta de fibras e incidência de câncer do endométrio
- 7 estudos observacionais
- Compara categorias de maior consumo com as de menor consumo

Ao comparar categorias extremas

- Os extremos podem não ser similares
  - Um estudo pode comparar ingesta (0) contra a ingesta de uma certa quantia de fibra
  - Outro, compara o primeiro com o quarto quartil

O que fazer

- Se existe algum motivo para comparar o “efeito”de uma certa quantidade de exposição, devemos excluir os estudos que não se enquadram nessa categoria
- Incluímos todos estudos e as categorias comparadas entram como uma variável

Author, year	Study design	Mean age at assessment	Gender	Categorization of breastfeeding	Odds ratio of type-2 diabetes among breastfed subjects
Young, 2002	Case-control	13 years	All	Breastfed ≥ 6 months vs. Breastfed < 6 months	0.36 (0.13; 0.99)
Izadi, 2013	Cross-sectional	14 years	All	Breastfed ≥ 18 months vs. Breastfed ≤ 6 months	0.57 (0.26; 1.22)
Halipchuk, 2018	Case-control	14 years	All	Exclusively breastfed at hospital discharge vs. Formula fed at hospital discharge	0.52 (0.36; 0.74)
Mayer-Davis, 2008	Case-control	15 years	All	Ever breastfed vs. Never breastfed	0.43 (0.19; 0.99)
Evenhouse, 2005	Cross-sectional	15 years	All	Ever breastfed vs. Never breastfed	0.40 (SE: 0.24)
Fall, 2011	Cohort	25 years	All	Ever breastfed vs. Never breastfed	1.26 (0.63; 2.50)
Petit, 1997	Cohort	25 years	All	Exclusively breastfed vs. Exclusively bottle-fed at 2 months	0.41 (0.18; 0.93)
Baldassarre, 2017	Cross-sectional	26 years	All	Exclusively breastfed ≥ 6 months vs. Not exclusively breastfed < 6 months	0.63 (0.41; 0.95)
Martens, 2016	Cohort	27 years	All	Breastfed before hospital discharge vs. Not breastfed before hospital discharge	0.83 (0.69; 0.99)
Parikh, 2009	Cohort	41 years	All	Ever breastfed vs. Never breastfed	0.40 (0.09; 1.70)
Ravelli, 2000	Cohort	50 years	All	Exclusively breastfed vs. Bottle-fed during hospital stay	0.51 (0.30; 0.90)
Martin, 2005	Cross-sectional	52 years	Male	Ever breastfed vs. Never breastfed	2.89 (0.65; 12.83)
Rich-Edwards, 2004	Cohort	59 years	Female	Ever breastfed vs. Never breastfed	0.79 (0.74; 0.85)
Martin, 2005	Cohort	71 years	All	Ever breastfed vs. Never breastfed	0.97 (0.41; 2.30)

Estudo	Risco relativo	95% I C
Barbone et al.	.6	(.3, 1.1)
Potischman et al.	.7	(.4, 1.3)
Shu et al.	1.1	-
Goodman et al.	.47	(.25, .86)
⋮	⋮	⋮

- Para dados dicotômicos, entre com os dados de uma das seguintes formas:

1	No. com desfecho no grupo intervenção	No. sem o desfecho no grupo intervenção	No. com desfecho no grupo controle	No. sem o desfecho no grupo controle
2	Effect size (Transformado em logaritimo se ratio)	Limite inferior IC	Limite superior IC	
3	Effect size (Transformado em logaritimo se ratio)	Erro padrão		

- Para a opção 2, metan não aceita valor missing
- LEMBRANDO: transforma em logaritmo natural razão de odds e risco relativo

Comandos do STATA

- Excluindo estudos com valores missing
  - drop if ll==. | ul==.
- A seguir, transformação em logaritmo

```
gen lnrr = ln(rr)
gen lnll = ln(ll)
gen lnul = ln(ul)
```

meta lnrr rrll rrul, **eform**

Erro Padrão

O intervalo de confiança (95%) para o risco relativo ou odds ratio θ é calculado através da seguinte fórmula:

$$\exp\left(\ln(\theta) \quad \pm \quad 1.96 \times EP[\ln(\theta)] \right)$$

O erro padrão para ln(θ) é:

$$EP[\ln(\theta)] \quad = \quad \frac{\ln(\text{limite superior}) - \ln(\text{limite inferior})}{2 \times 1.96}$$

STATA

- gen se =(lnul - lnll) / 3.92

- Outro comando
  - meta rr se

- Meta-analysis of 6 studies
- ----------------------------
- Fixed and random effects pooled estimates, lower and upper 95% confidence limits, and asymptotic z-test for null hypothesis that true effect=0

- Fixed effects estimation

Est	Lower	Upper	z_value	p_value
0.778	0.573	0.983	7.436	0.000

- Test for heterogeneity: Q= 7.085 on 5 degrees of freedom (p= 0.214)
- Der Simonian and Laird estimate of between studies variance = 0.029

- Random effects estimation

Est	Lower	Upper	z_value	p_value
0.756	0.505	1.008	5.893	0.000

meta lnrr se, ef

- Meta-analysis of 6 studies (exponential form)
- ---
- Fixed and random effects pooled estimates, lower and upper 95% confidence limits, and
- asymptotic z-test for null hypothesis that true effect=0

- Fixed effects estimation

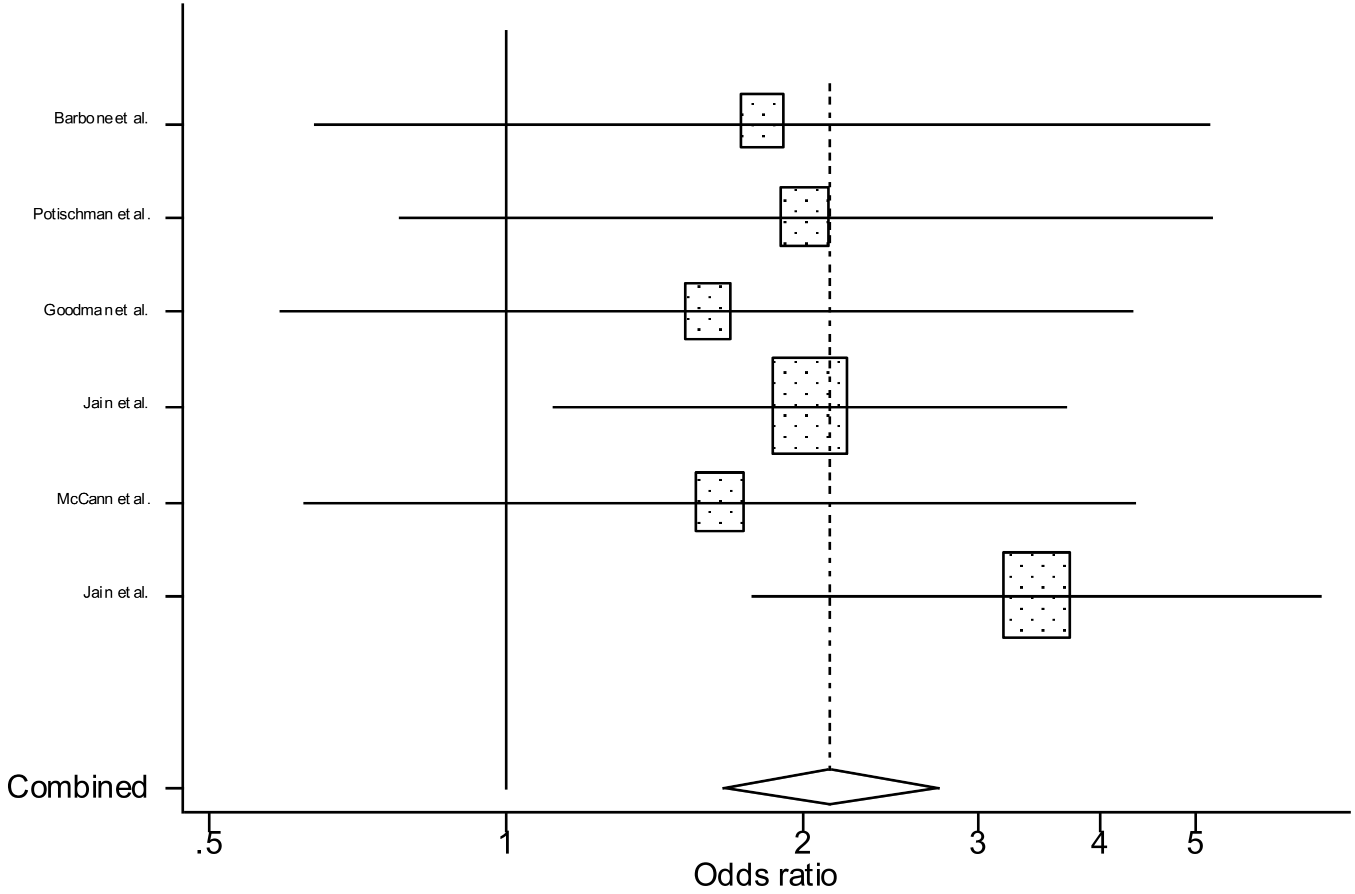
Est	Lower	Upper	z_value	p_value
2.178	1.774	2.673	7.436	0.000

- Test for heterogeneity: Q= 7.085 on 5 degrees of freedom (p= 0.214)
- Der Simonian and Laird estimate of between studies variance = 0.029

- Random effects estimation

Est	Lower	Upper	z_value	p_value
2.130	1.657	2.739	5.893	0.000

meta rr se, ef graph(r) cline xlabel (0.5,1,2,3,4,5) xline(1) id(author) b2title(Odds ratio)



- Para desfechos contínuos, escolha:

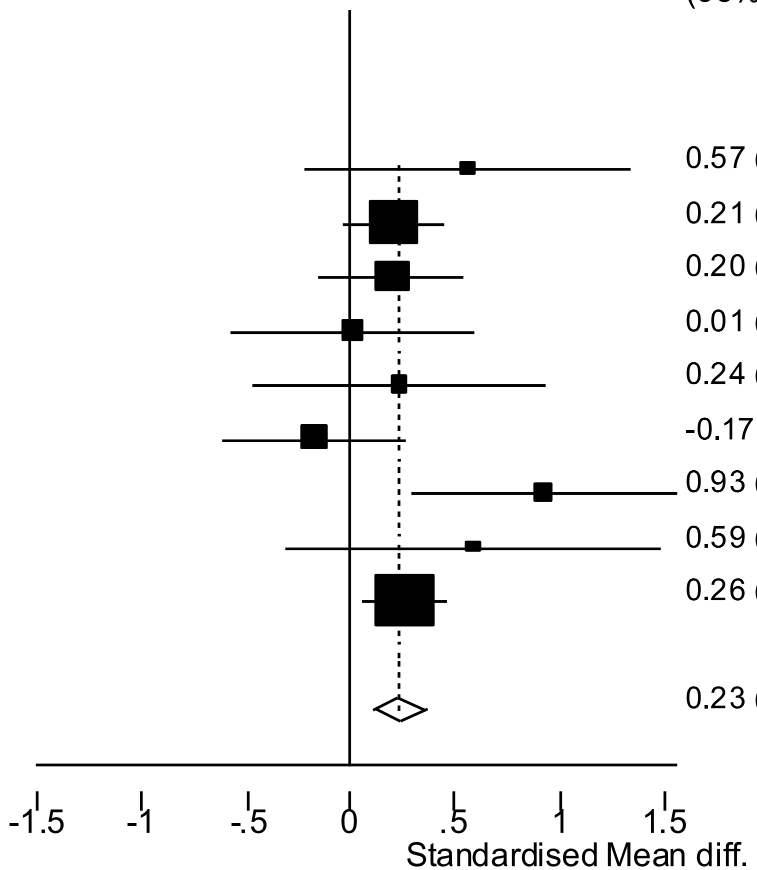
1	Grp. 1 N	Grp. 1 Média	Grp. 1 D.P.	Grp. 2 N	Grp. 2 Média	Grp. 2 D.P.
2	Effect size (Diferença entre médias)	Limite inferior I.C.	Limite superior IC			
3	Effect size (Diferença entre médias)	Erro padrão da diferença				

Comandos no Stata

```
metan n1 mean1 sd1 n2 mean2
  sd2,xlabel(-1.5,-1,-
  0.5,0,0.5,1,1.5) t1(Effect of
  antihistamines on cold
  severity)
```

Effect of antihistamines on cold severity

Study	Standardised Mean diff. (95% CI)	% Weight
1	0.57 (-0.22,1.35)	2.5
2	0.21 (-0.03,0.45)	26.0
3	0.20 (-0.15,0.55)	12.5
4	0.01 (-0.58,0.60)	4.4
5	0.24 (-0.47,0.94)	3.0
6	-0.17 (-0.61,0.27)	7.9
7	0.93 (0.30,1.57)	3.7
8	0.59 (-0.31,1.49)	1.9
9	0.26 (0.06,0.46)	38.1
Overall (95% CI)	0.23 (0.11,0.36)	



Diferença Média

Todos os desfechos são medidos na mesma escala

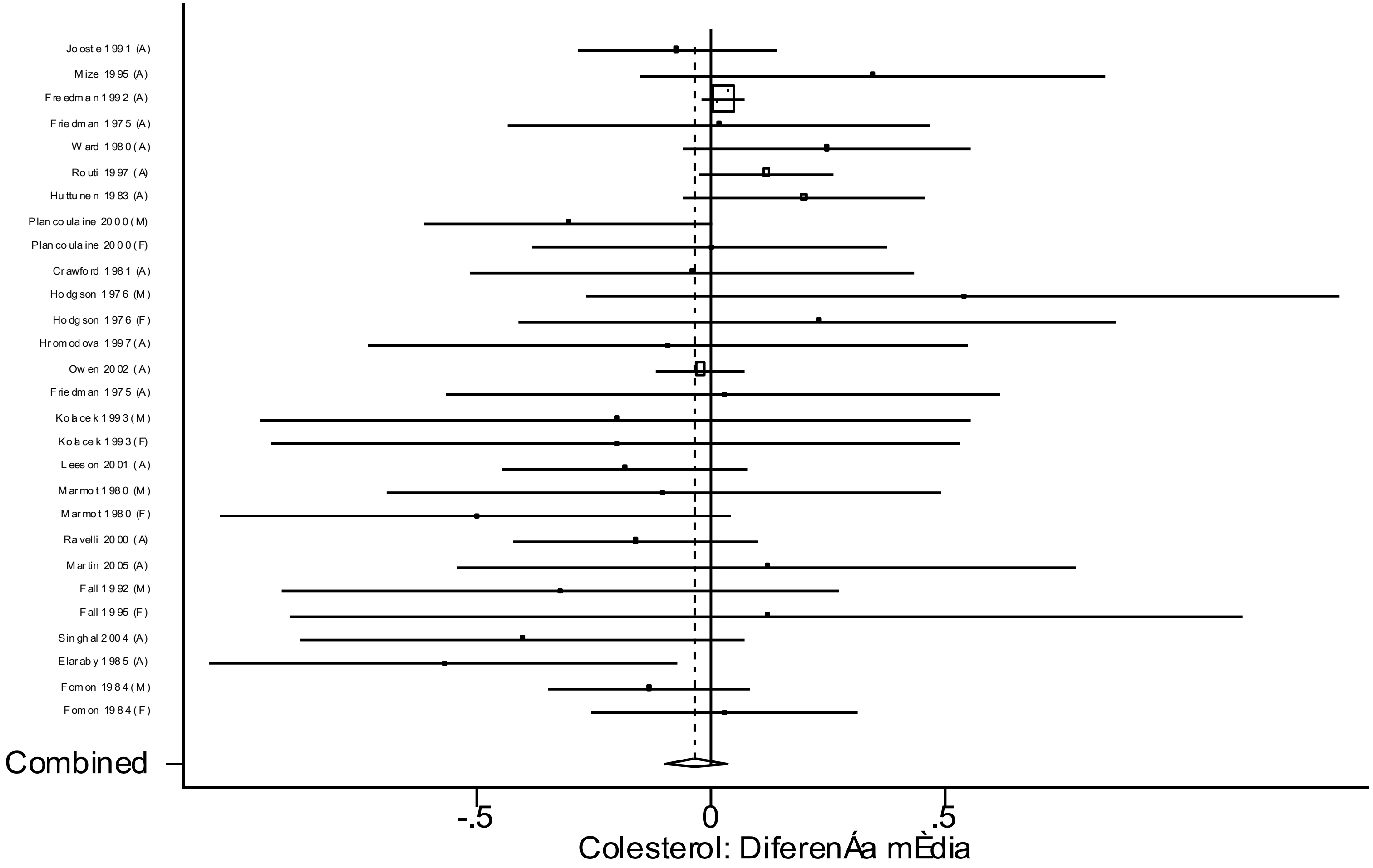
$$\boldsymbol{MD_i = m_{1i} - m_{2i}}$$

Diferença Média

Erro Padrão

$$EP(MD_i) = \sqrt{\frac{SD_{1i}^2}{n_{1i}} + \frac{SD_{2i}^2}{n_{2i}}}$$

meta Mean SD, graph(r) cline xlabel (-0.5,0, 0.5) xline(0) id(Study) b2title(Colesterol: Diferença média)



Diferença padronizada

- Quanto os desfechos são medidos em diferentes escalas ou com diferentes instrumentos
- As medidas devem ser padronizadas, permitindo comparações

Cohen's d

Diferença média

$$d_i = \frac{m_{1i} - m_{2i}}{s_i}$$

Erro padrão

$$SE(d_i) = \sqrt{\frac{N_i}{n_{1i} n_{2i}} + \frac{d_i^2}{2(N_i - 2)}}$$

- Superestima o efeito, quando o tamanho da amostra é pequeno

- Use apenas se todos os *trials* tem $N_i > 10$

Hedges' g

Diferença média

$$g_i = \frac{m_{1i} - m_{2i}}{s_i}\left(1 - \frac{3}{4N_i - 9}\right)$$

Erro padrão

$$SE(g_i) = \sqrt{\frac{N_i}{n_{1i}n_{2i}} + \frac{g_i^2}{2(N_i - 3.94)}}$$

Hedges' g é uma extensão do Cohen's d

- Usa um pequeno ajuste para produzir melhores estimativas quando o tamanho da amostra é pequeno

- Se N_i é grande, o ajuste é relativamente pequeno e a diferença entre os dois métodos é pequena.

Glass's Δ

Diferença média

$$\Delta_i = \frac{m_{1i} - m_{2i}}{SD_{2i}}$$

Erro padrão

$$SE(\Delta_i) = \sqrt{\frac{N_i}{n_{1i} n_{2i}} + \frac{\Delta_i^2}{2(N_{2i} - 1)}}$$

- Glass's Δ usa o erro padrão do grupo controle, ao invés de usar o pooled.

- Tem melhor performance quando a intervenção altera a média e o desvio-padrão.

SENSIBILIDADE E ESPECIFICIDADE

Lembrando

		Doença	
		Presente	Ausente
Teste	Positivo	Verdadeiro positivo	Falso positivo
	Negativo	Falso negativo	Verdadeiro negativo

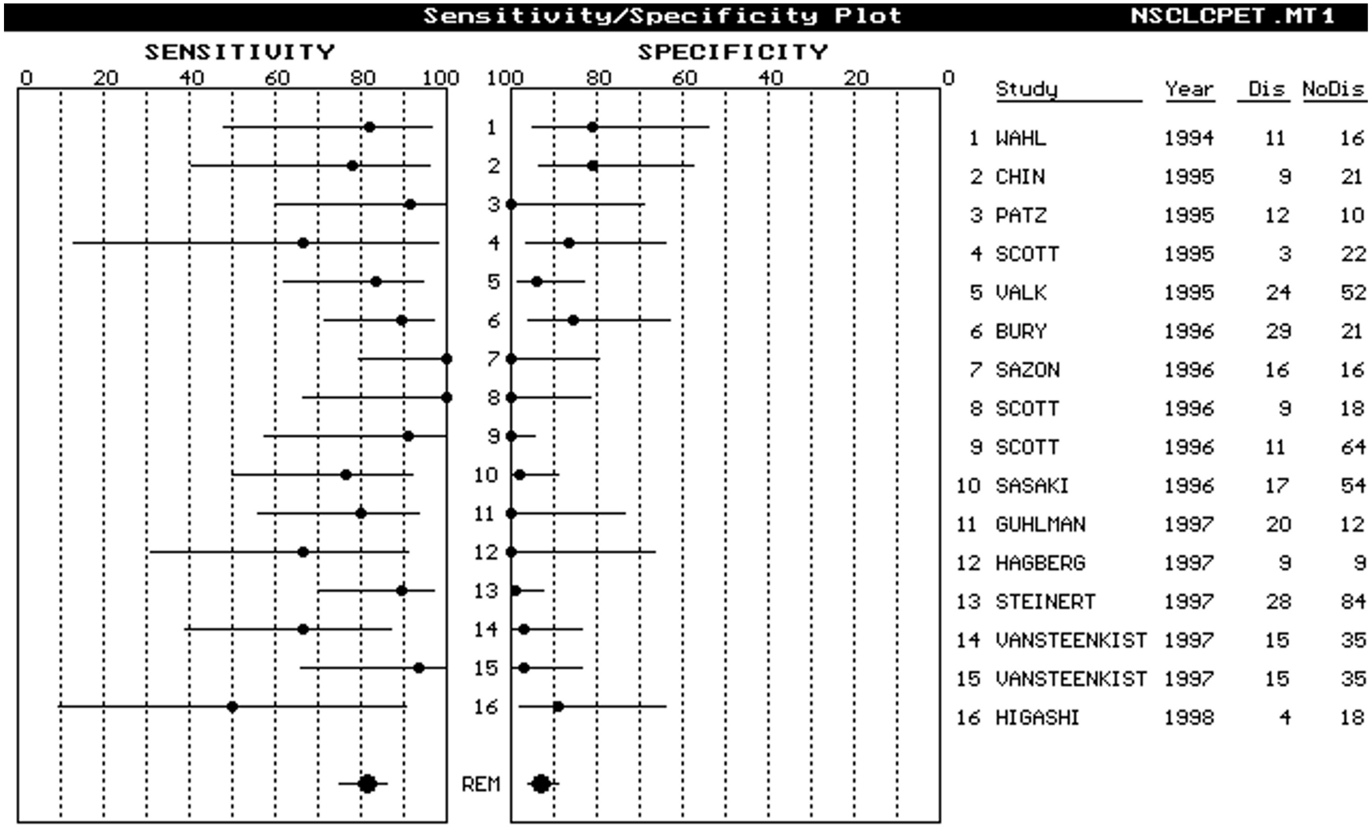
Algumas diferenças na análise

- Risco relativo no grupo intervenção{[a/(a + c)]/[b/(b+ d)]} =Likelihood Ratio – Teste Positivo.
- Risco Relativo no grupo controle= Likelihood Ratio – Teste Negativo.
- Odds Ratio (OR) (a x d)/(b x c).

Entrando os dados

FIRST AUTHOR	TP	FN	FP	TN
WAHL	9	2	3	13
CHIN	7	2	4	17
PATZ	11	1	0	10
SCOTT	2	1	3	19
VALK	20	4	3	49
BURY	26	3	3	18
SAZON	16	0	0	16
SCOTT	9	0	0	18
SCOTT	10	1	0	64
SASAKI	13	4	1	53
GUHLMAN	16	4	0	12
HAGBERG	6	3	0	9
STEINERT	25	3	1	83
VANSTEENSKISTE	10	5	1	34
VANSTEENSKISTE	14	1	1	34
HIGASHI	2	2	2	16

Apresentando os resultados



Diagnostic Odds Ratio

- Logit VP (sensibilidade) e FP (1 - especificidade).

  $D = \ln(DOR) = \text{logit}(VP) - \text{logit}(FP)$

Diagnostic odds ratio

- Descreve em quantas vezes o odds de ter um teste positivo é maior em um indivíduo doente do que não doente.

```
.  metandi tp fp fn tn

True  positives: tp                    False positives: fp
False negatives: fn                    True  negatives: tn

Refining starting values:

Iteration 0:   log likelihood = -87.369886
Iteration 1:   log likelihood = -87.286917
Iteration 2:   log likelihood =  -87.28439
Iteration 3:   log likelihood = -87.284364

Performing gradient-based optimization:

Iteration 0:   log likelihood = -87.284364
Iteration 1:   log likelihood = -87.284283
Iteration 2:   log likelihood = -87.284283

Meta-analysis of diagnostic accuracy

Log likelihood   = -87.284283                    Number of studies =       14
------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
Bivariate    |
  E(logitSe) |   1.791051   .2928671                      1.217042     2.36506
  E(logitSp) |   1.978175   .3348528                      1.321876    2.634475
Var(logitSe) |   .9840405   .4730037                       .383585    2.524436
Var(logitSp) |   1.229617   .5637082                      .5006606    3.019927
Corr(logits) |   .4370949   .2810972                     -.2092853    .8176519
-------------+----------------------------------------------------------------
HSROC        |
      Lambda |   3.764646   .5149784                      2.755307    4.773985
       Theta |   .0113157   .3219068                     -.6196101    .6422415
        beta |   .1113956   .3095365     0.36   0.719    -.4952848     .718076
     s2alpha |     3.1616   1.381317                      1.342806    7.443902
     s2theta |   .3095969   .1704515                      .1052349    .9108222
-------------+----------------------------------------------------------------
Summary pt.  |
          Se |    .857056   .0358794                      .7715425    .9141238
          Sp |   .8784865   .0357449                      .7894936    .9330476
         DOR |   43.34649   22.38929                      15.75042    119.2932
         LR+ |   7.053175   2.195976                      3.831481    12.98383
         LR- |   .1627162   .0436108                      .0962263    .2751487
       1/LR- |   6.145671   1.647146                      3.634398    10.39217
------------------------------------------------------------------------------
Covariance between estimates of E(logitSe) & E(logitSp)   .0344472
```

Meta análise com dados faltantes

- Perda de informações sobre o desfecho compromete a validade de um ensaio clínico
- Compromete a meta-análise
- Isto é sobre dados missing em estudos, não sobre estudos perdidos

Haloperidol

	Haloperidol				Placebo				
	r1	f1	m 1	n1	r2	f2	m 2	n2	% missing
Arvanitis	25	25	2	52	18	33	0	51	2%
Beasley	29	18	22	69	20	14	34	68	41%
Bechelli	12	17	1	30	2	28	1	31	3%
Borison	3	9	0	12	0	12	0	12	0%
Chouinard	10	11	0	21	3	19	0	22	0%
Durost	11	8	0	19	1	14	0	15	0%
Garry	7	18	1	26	4	21	1	26	4%
Howard	8	9	0	17	3	10	0	13	0%
Marder	19	45	2	66	14	50	2	66	3%
Nishikawa 82	1	9	0	10	0	10	0	10	0%
Nishikawa 84	11	23	3	37	0	13	0	13	6%
Reschke	20	9	0	29	2	9	0	11	0%
Selman	17	1	11	29	7	4	18	29	50%
Serafetinides	4	10	0	14	0	13	1	14	4%
Simpson	2	14	0	16	0	7	1	8	4%
Spencer	11	1	0	12	1	11	0	12	0%
Vichaiya	9	20	1	30	0	29	1	30	3%

r=success0

f=falha

m=missing

n=total

Abordagem padrão para dados faltantes

- Casos disponíveis(com informação completa): dados faltantes são excluídos
  - assume MAR: *Missing at random em cada braço do estudo*
- Assume missing=falha
  - Implausível, mas não é ruim para desfechos em saúde

Outras ideias

- Análise de sensibilidade
  - missing=falha
  - Casos com dados completos
- Análise pior e melhor cenário
- Informative missingness (IM)
  - IM: *perda é dependente do desfecho*

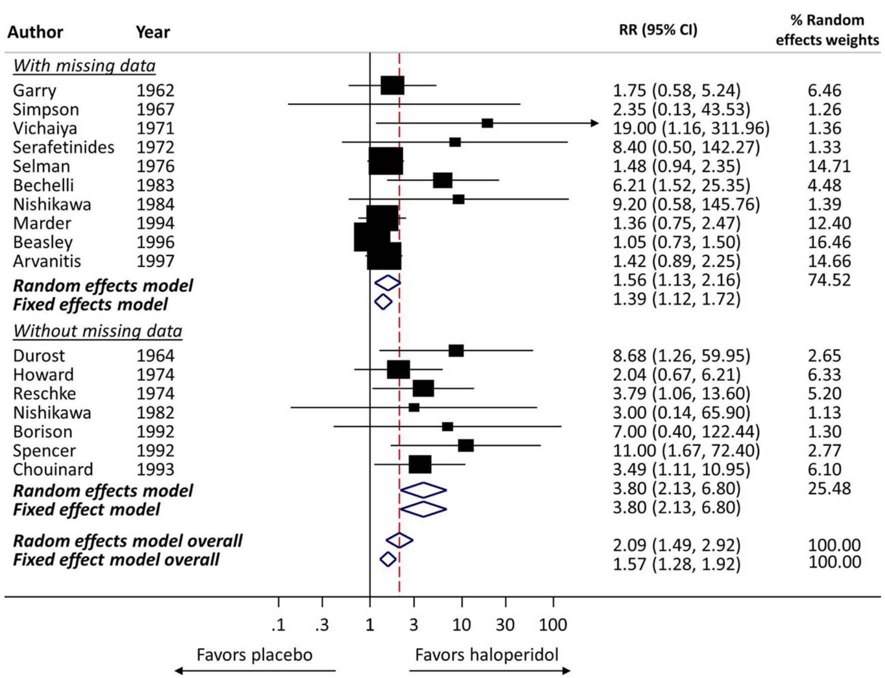
metamiss

- Análise com casos disponíveis(ACA)
- Análise com casos imputados(ICA):
  - Missing é imputado como falha: ICA-0
  - Missing é imputado como sucesso: ICA-1
  - Melhor cenário: ICA-b (missing=sucesso em E, falha em C)
  - Pior cenário: ICA-w (missing=falha em E, sucesso em C)
  - Usa a probabilidade de desfecho no controle para a imputação : ICA-pC
  - Usa a probabilidade de desfecho no grupo intervenção para a imputação : ICA-pE
  - Usa a probabilidade de cada grupo para a imputação : ICA-p(concorda com ACA)

IMORs

- Informative Missing Odds Ratio (IMOR):
  - Odds ratio entre desfecho e perdas em cada grupo
- IMOR
  - 1 – indica que as perdas são totalmente ao acaso
  - 0 – indica que todas as perdas são falha
  - ∞ - indica que todas as perdas são sucesso
- IMOR não é estimado a partir do dado, mas dado um valor de IMOR, é possível analisar os dados
- Por exemplo,
  - ICA-0 usa IMORs 0, 0
  - ICA-1 usa IMORs ∞, ∞
  - ICA-b usa IMORs ∞, 0
  - ICA-p usa IMORs 1, 1

Explorando missing



ACA

- Ignora missing
- Assume que os casos missing ocorrem ao acaso
- Resultado igual ao obtido com o comando meta, usando apenas os dados disponíveis

ACA

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) aca
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********               Available cases analysis            ********
*******************************************************************
Measure: RR.
Zero cells detected: adding 1/2 to 6 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.417       0.891     2.252        18.86
Beasley              |  1.049       0.732     1.504        31.22
Bechelli             |  6.207       1.520    25.353         2.05
Borison              |  7.000       0.400   122.442         0.49
Chouinard            |  3.492       1.113    10.955         3.10
Durost               |  8.684       1.258    59.946         1.09
Garry                |  1.750       0.585     5.238         3.37
Howard               |  2.039       0.670     6.208         3.27
Marder               |  1.357       0.747     2.466        11.37
Nishikawa_82         |  3.000       0.137    65.903         0.42
Nishikawa_84         |  9.200       0.581   145.759         0.53
Reschke              |  3.793       1.058    13.604         2.48
Selman               |  1.484       0.936     2.352        19.11
Serafetinides        |  8.400       0.496   142.271         0.51
Simpson              |  2.353       0.127    43.529         0.48
Spencer              | 11.000       1.671    72.396         1.14
Vichaiya             | 19.000       1.157   311.957         0.52
---------------------+---------------------------------------------------
I-V pooled ES        |  1.567       1.281     1.916       100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  27.29 (d.f. = 16) p = 0.038
  I-squared (variation in ES attributable to heterogeneity) =  41.4%

  Test of ES=1 : z=   4.37 p = 0.000

.
end of do-file
```

ICA-0

- Todas as perdas são consideradas como sendo falha

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) w4 ica0
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                 Simple imputation                 ********
*******************************************************************
Measure: RR.
Method: ICA-0 (impute zeros).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.362       0.854     2.172         24.38
Beasley              |  1.429       0.901     2.266         25.01
Bechelli             |  6.200       1.513    25.402          2.67
Borison              |  7.000       0.400   122.442          0.65
Chouinard            |  3.492       1.113    10.955          4.06
Durost               |  8.684       1.258    59.946          1.42
Garry                |  1.750       0.582     5.266          4.38
Howard               |  2.039       0.670     6.208          4.29
Marder               |  1.357       0.745     2.473         14.75
Nishikawa_82         |  3.000       0.137    65.903          0.56
Nishikawa_84         |  8.474       0.534   134.463          0.70
Reschke              |  3.793       1.058    13.604          3.26
Selman               |  2.429       1.189     4.960         10.42
Serafetinides        |  9.000       0.530   152.927          0.66
Simpson              |  2.647       0.142    49.419          0.62
Spencer              | 11.000       1.671    72.396          1.50
Vichaiya             | 19.000       1.156   312.417          0.68
---------------------+---------------------------------------------------
I-V pooled ES        |  1.898       1.507     2.390        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  21.56 (d.f. = 16) p = 0.158
  I-squared (variation in ES attributable to heterogeneity) =  25.8%

  Test of ES=1 : z=   5.45 p = 0.000

.
end of do-file
```

ICA-1

- Perdas são consideradas como sendo sucesso

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) w4 ica1
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                 Simple imputation                 ********
*******************************************************************
Measure: RR.
Method: ICA-1 (impute ones).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 3 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.471       0.934     2.317          5.95
Beasley              |  0.931       0.773     1.120         35.81
Bechelli             |  4.478       1.417    14.151          0.93
Borison              |  7.000       0.400   122.442          0.15
Chouinard            |  3.492       1.113    10.955          0.94
Durost               |  8.684       1.258    59.946          0.33
Garry                |  1.600       0.603     4.247          1.29
Howard               |  2.039       0.670     6.208          0.99
Marder               |  1.312       0.754     2.283          4.01
Nishikawa_82         |  3.000       0.137    65.903          0.13
Nishikawa_84         | 10.684       0.682   167.429          0.16
Reschke              |  3.793       1.058    13.604          0.75
Selman               |  1.120       0.953     1.316         47.38
Serafetinides        |  4.000       0.509    31.456          0.29
Simpson              |  1.000       0.106     9.444          0.24
Spencer              | 11.000       1.671    72.396          0.35
Vichaiya             | 10.000       1.364    73.328          0.31
---------------------+---------------------------------------------------
I-V pooled ES        |  1.156       1.035     1.292        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  40.34 (d.f. = 16) p = 0.001
  I-squared (variation in ES attributable to heterogeneity) =  60.3%

  Test of ES=1 : z=   2.57 p = 0.010

.
end of do-file
```

Melhor cenário

- missing=sucesso em E, falha em C

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) w4 icapc
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                 Simple imputation                 ********
*******************************************************************
Measure: RR.
Method: ICA-pC (impute control group risk).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.401       0.880     2.230         19.89
Beasley              |  1.033       0.718     1.486         32.56
Bechelli             |  6.033       1.475    24.682          2.17
Borison              |  7.000       0.400   122.442          0.53
Chouinard            |  3.492       1.113    10.955          3.29
Durost               |  8.684       1.258    59.946          1.15
Garry                |  1.721       0.574     5.161          3.57
Howard               |  2.039       0.670     6.208          3.47
Marder               |  1.346       0.741     2.448         12.05
Nishikawa_82         |  3.000       0.137    65.903          0.45
Nishikawa_84         |  8.553       0.539   135.713          0.56
Reschke              |  3.793       1.058    13.604          2.64
Selman               |  1.300       0.759     2.228         14.85
Serafetinides        |  8.400       0.496   142.271          0.54
Simpson              |  2.353       0.127    43.529          0.51
Spencer              | 11.000       1.671    72.396          1.21
Vichaiya             | 18.419       1.121   302.646          0.55
---------------------+---------------------------------------------------
I-V pooled ES        |  1.530       1.243     1.883        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  27.61 (d.f. = 16) p = 0.035
  I-squared (variation in ES attributable to heterogeneity) =  42.0%

  Test of ES=1 : z=   4.02 p = 0.000

.
end of do-file
```

Pior cenário

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) w4 icab
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                 Simple imputation                ********
*******************************************************************
Measure: RR.
Method: ICA-b ('best'-case [0 in exp, 1 in control]).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 6 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.471       0.934     2.317         22.59
Beasley              |  2.513       1.695     3.727         30.05
Bechelli             |  6.717       1.654    27.279          2.37
Borison              |  7.000       0.400   122.442          0.57
Chouinard            |  3.492       1.113    10.955          3.57
Durost               |  8.684       1.258    59.946          1.25
Garry                |  2.000       0.686     5.831          4.07
Howard               |  2.039       0.670     6.208          3.76
Marder               |  1.500       0.837     2.689         13.68
Nishikawa_82         |  3.000       0.137    65.903          0.49
Nishikawa_84         | 10.684       0.682   167.429          0.62
Reschke              |  3.793       1.058    13.604          2.86
Selman               |  4.000       2.091     7.654         11.08
Serafetinides        |  9.000       0.530   152.927          0.58
Simpson              |  2.647       0.142    49.419          0.54
Spencer              | 11.000       1.671    72.396          1.31
Vichaiya             | 21.000       1.286   342.934          0.60
---------------------+---------------------------------------------------
I-V pooled ES        |  2.416       1.947     2.998        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  21.60 (d.f. = 16) p = 0.156
  I-squared (variation in ES attributable to heterogeneity) =  25.9%

  Test of ES=1 : z=   8.00 p = 0.000

.
end of do-file
```

```
. metamiss r1 f1 m1 r2 f2 m2, fixed nograph id(author) w4 icaw
*******************************************************************
******** METAMISS: meta-analysis allowing for missing data ********
********                Simple imputation                  ********
*******************************************************************
Measure: RR.
Method: ICA-w ('worst'-case [1 in exp, 0 in control]).
Weighting scheme: w4.
Zero cells detected: adding 1/2 to 3 studies.

(Calling metan with options: label(namevar=author) fixed eform nograph ...)

           Study     |     ES    [95% Conf. Interval]     % Weight
---------------------+---------------------------------------------------
Arvanitis            |  1.362       0.854     2.172         13.99
Beasley              |  0.529       0.391     0.716         33.33
Bechelli             |  4.133       1.294    13.202          2.26
Borison              |  7.000       0.400   122.442          0.37
Chouinard            |  3.492       1.113    10.955          2.33
Durost               |  8.684       1.258    59.946          0.82
Garry                |  1.400       0.510     3.847          2.98
Howard               |  2.039       0.670     6.208          2.46
Marder               |  1.187       0.671     2.102          9.35
Nishikawa_82         |  3.000       0.137    65.903          0.32
Nishikawa_84         |  8.474       0.534   134.463          0.40
Reschke              |  3.793       1.058    13.604          1.87
Selman               |  0.680       0.485     0.954         26.57
Serafetinides        |  4.000       0.509    31.456          0.72
Simpson              |  1.000       0.106     9.444          0.60
Spencer              | 11.000       1.671    72.396          0.86
Vichaiya             |  9.000       1.214    66.704          0.76
---------------------+---------------------------------------------------
I-V pooled ES        |  0.944       0.793     1.124        100.00
---------------------+---------------------------------------------------

  Heterogeneity chi-squared =  62.07 (d.f. = 16) p = 0.000
  I-squared (variation in ES attributable to heterogeneity) =  74.2%

  Test of ES=1 : z=   0.64 p = 0.519

.
end of do-file
```

Meta análise em rede

- Tradicional
  - Compara dois tratamentos
- Se temos vários tratamentos
  - Estudos comparam A com B
  - Outros comparam B com C
- Meta análise tradicional
  - Compara A com B
  - B com C
  - Mas não A com C
- A com B e B com C são comparações diretas

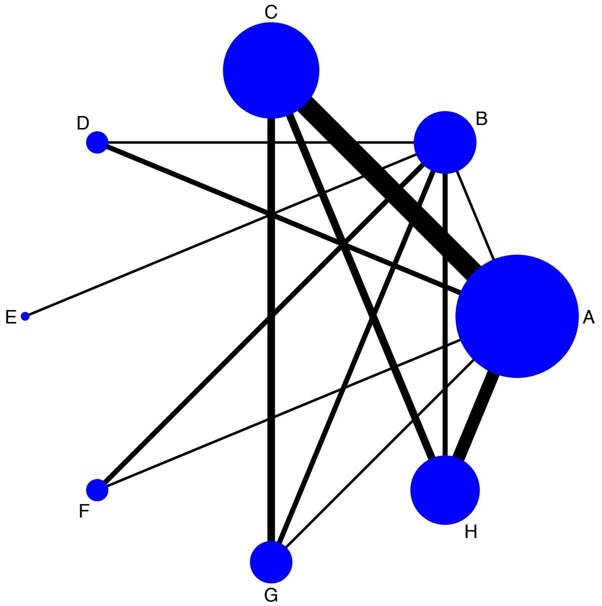
Meta-análise em rede

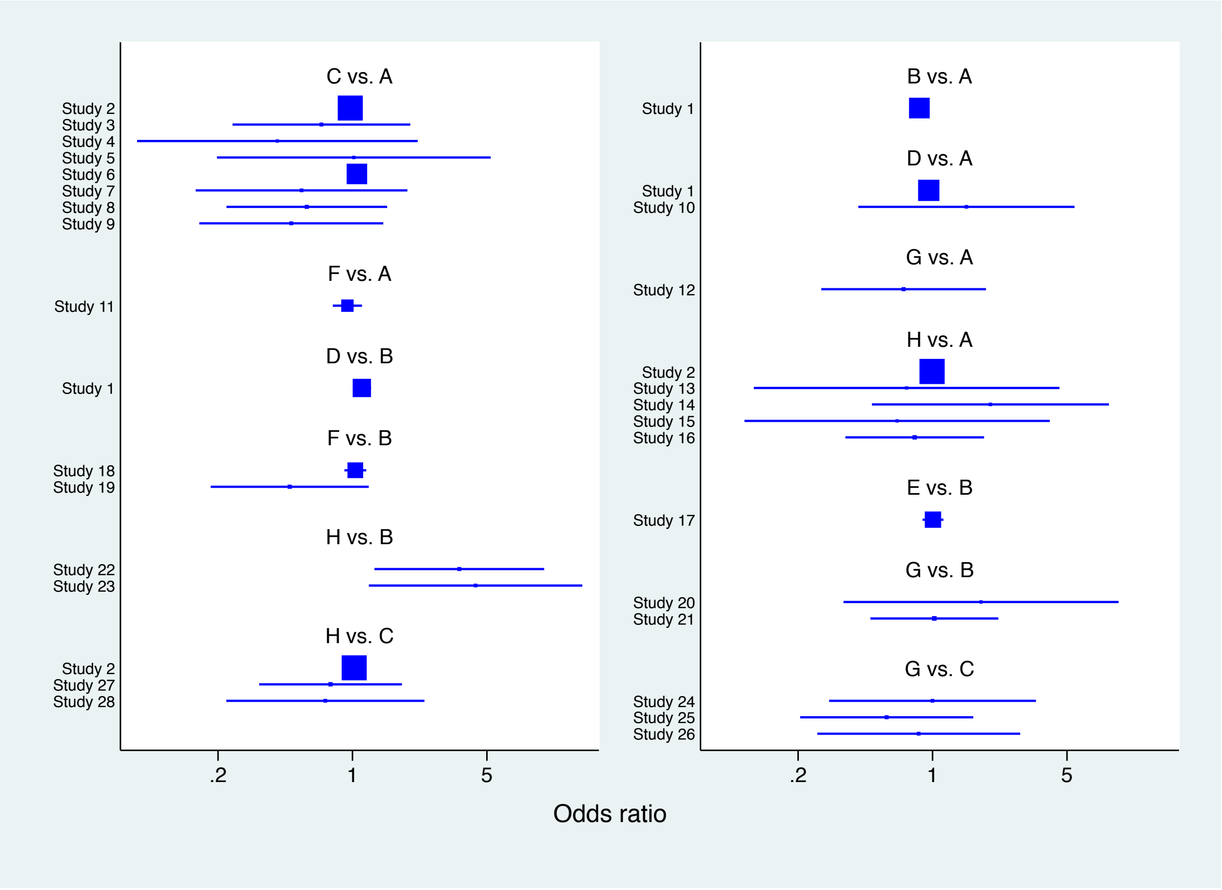
- Permite
  - Comparar A com B
  - B com C
  - Também A com C – comparação indireta

Fazer o set – up do banco

```
. network setup r n, studyvar(study) trtvar(treat)
Treatments used
   A (reference):                     A
   B:                                 B
   C:                                 C
   D:                                 D
   E:                                 E
   F:                                 F
   G:                                 G
   H:                                 H

Measure                               Log odds ratio

Studies
   ID variable:                       study
   Number used:                       28
   IDs with zero cells:               [none]
   IDs with augmented reference arm:  17 18 19 20 21 22 23 24 25 26 27 28
   - observations added:              0.001
   - mean in augmented observations:  study-specific mean

Network information
   Components:                        1 (connected)
   D.f. for inconsistency:            8
   D.f. for heterogeneity:            15

Current data
   Data format:                       augmented
   Design variable:                   _design
   Estimate variables:                _y*
   Variance variables:                _S*
   Command to list the data:          list study _y* _S*, noo sepby(_design)
```

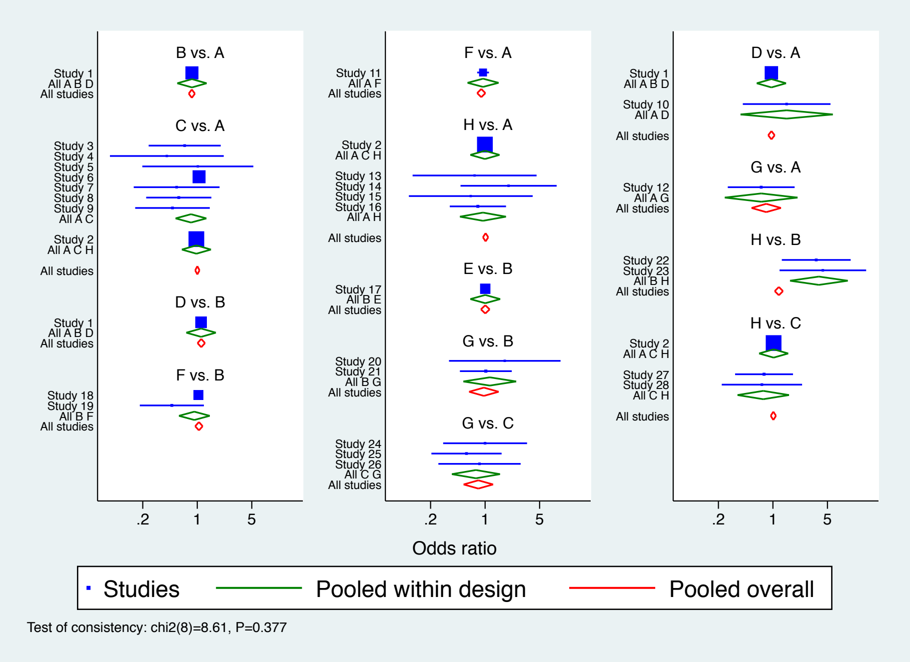
network mapgraph export thrombmap1.eps, replace





C vs. A
Study 2
Study 3
Study 4
Study 5
Study 6
Study 7
Study 8
Study 9
F vs. A
Study 11
D vs. B
Study 1
F vs. B
Study 18
Study 19
H vs. B
Study 22
Study 23
H vs. C
Study 2
Study 27
Study 28
B vs. A
Study 1
D vs. A
Study 1
Study 10
G vs. A
Study 12
H vs. A
Study 2
Study 13
Study 14
Study 15
Study 16
E vs. B
Study 17
G vs. B
Study 20
Study 21
G vs. C
Study 24
Study 25
Study 26
.2
1
5
.2
1
5
Odds ratio

Após estimar todas as comparações



```
. network sidesplit all
```

Side	Direct Coef.	Direct Std. Err.	Indirect Coef.	Indirect Std. Err.	Difference Coef.	Difference Std. Err.	P>|z|
A B	-.1575349	.062153	-.1895708	.1255688	.0320359	.1400551	0.819
A C	-.0030623	.0320637	.4616848	.3032621	-.4647471	.3049371	0.127
A D *	-.0406997	.0624884	-.1265838	.2884612	.085884	.2952869	0.771
A F	-.0603276	.0972427	-.1720842	.1135808	.1117566	.1495217	0.455
A G	-.3462582	.5035061	-.1614462	.2467496	-.184812	.5607172	0.742
A H	-.0058175	.0389527	.1694457	.1107251	-.1752632	.1173529	0.135
B D	.1122506	.0713263	.2353325	.3053638	-.1230818	.3140009	0.695
B E *	.005435	.0656528	.322518	238.4321	-.317083	238.4321	0.999
B F	.0146997	.0782736	.1264566	.1216721	-.1117568	.1495227	0.455
B G	.1212546	.3545816	-.1382147	.2860893	.2594694	.4555891	0.569
B H	1.354421	.4059271	.1496602	.0606317	1.204761	.4104342	0.003
C G	-.2756473	.339353	-.1424003	.2933971	-.1332471	.4486046	0.766
C H	-.017902	.1392018	.3408459	.3755195	-.3587479	.4313328	0.406

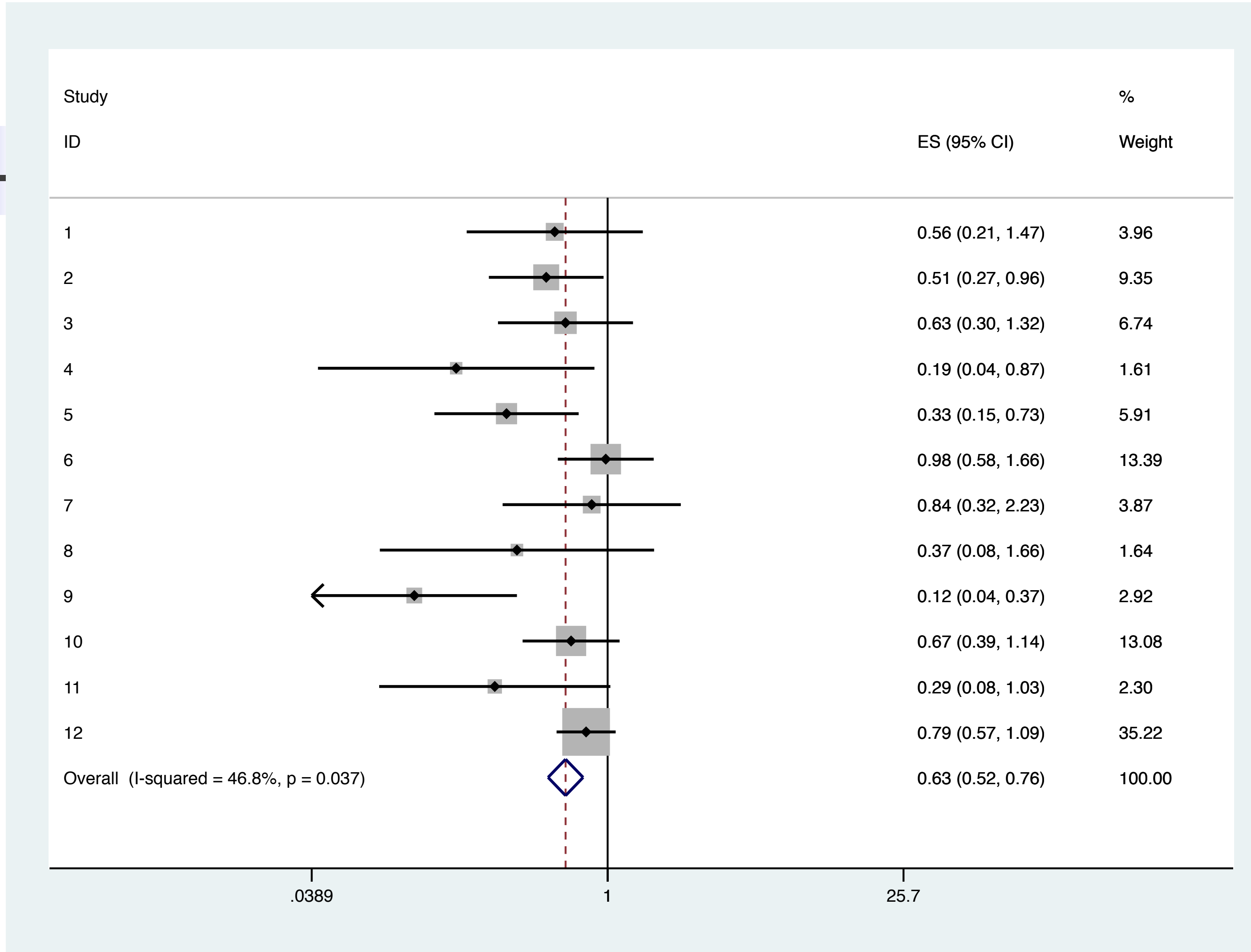
Meta p

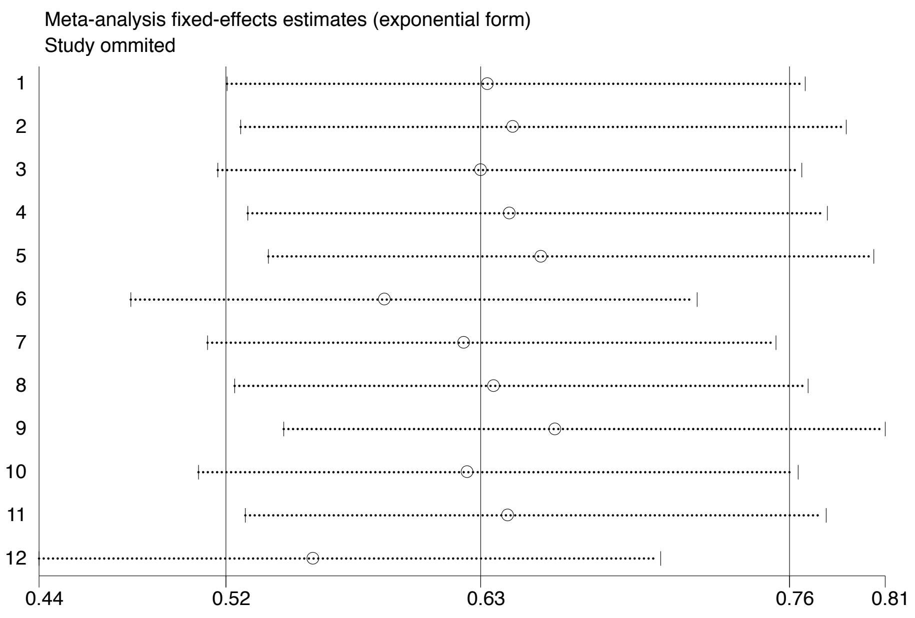
- Combina valores de p

```
. metap pvar

Meta-analysis of p-values

-------------------------------------------------------------
 Method               |   chi2         p_value      studies
----------------------+--------------------------------------
 Fisher               |   38.938246    .00037283    7
-------------------------------------------------------------

.
```

metainf

- Retira um estudo de cada vez e faz uma nova meta-análise
- Serve para avaliar se algum estudo está influenciando o pooled effect


Study
ID
ES (95% CI)
%
Weight
1
0.56 (0.21, 1.47)
3.96
2
0.51 (0.27, 0.96)
9.35
3
0.63 (0.30, 1.32)
6.74
4
0.19 (0.04, 0.87)
1.61
5
0.33 (0.15, 0.73)
5.91
6
0.98 (0.58, 1.66)
13.39
7
0.84 (0.32, 2.23)
3.87
8
0.37 (0.08, 1.66)
1.64
9
0.12 (0.04, 0.37)
2.92
10
0.67 (0.39, 1.14)
13.08
11
0.29 (0.08, 1.03)
2.30
12
0.79 (0.57, 1.09)
35.22
Overall (I-squared = 46.8%, p = 0.037)
0.63 (0.52, 0.76)
100.00
.0389
1
25.7

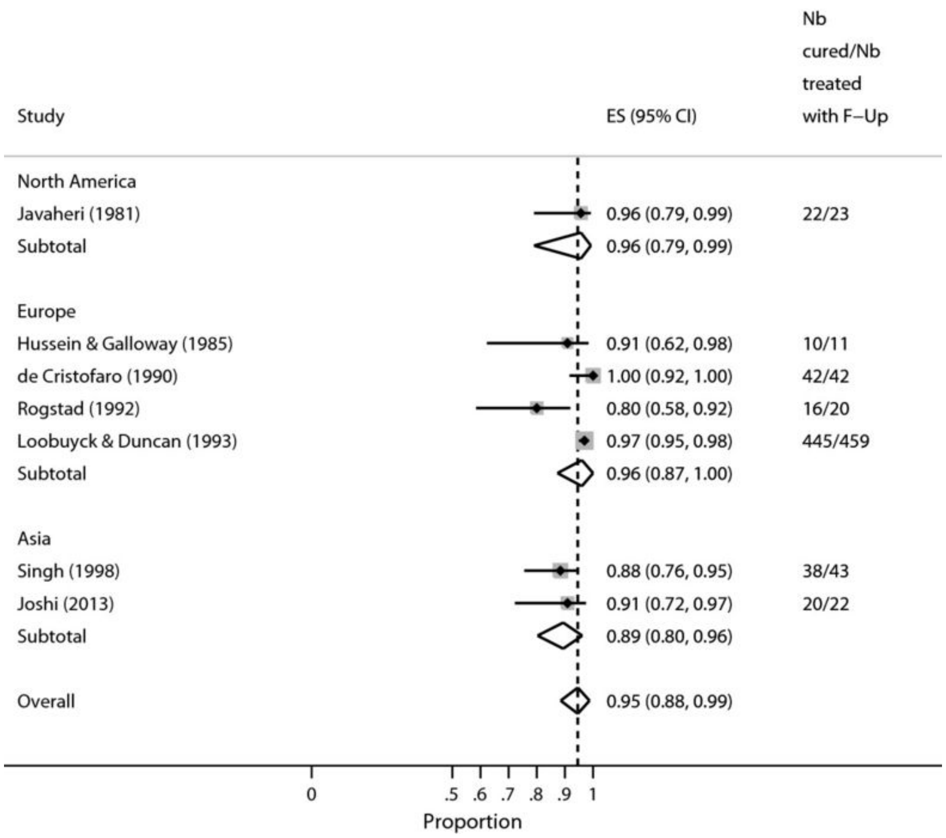


Meta-analysis fixed-effects estimates (exponential form)
Study ommited
1
2
3
4
5
6
7
8
9
10
11
12
0.44
0.52
0.63
0.76
0.81

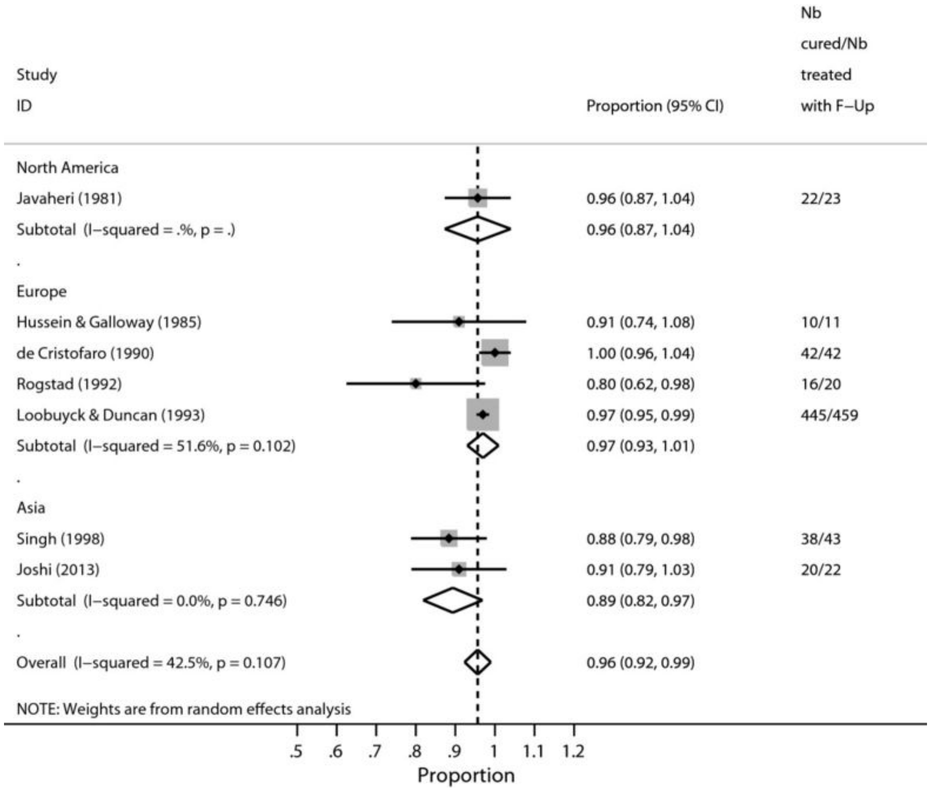
Meta análise – prevalência / incidência

- Prevalência – varia de 0 a 1
- V $\mathrm{Var}(p) = \dfrac{p(1-p)}{N}$
- Distribuição binomial

Ao usar meta ou metan, assimetria no IC



metaprop


Study
ID
Proportion (95% CI)
Nb
cured/Nb
treated
with F–Up
North America
Javaheri (1981) 0.96 (0.87, 1.04) 22/23
Subtotal (I–squared = .%, p = .) 0.96 (0.87, 1.04)
.
Europe
Hussein & Galloway (1985) 0.91 (0.74, 1.08) 10/11
de Cristofaro (1990) 1.00 (0.96, 1.04) 42/42
Rogstad (1992) 0.80 (0.62, 0.98) 16/20
Loobuyck & Duncan (1993) 0.97 (0.95, 0.99) 445/459
Subtotal (I–squared = 51.6%, p = 0.102) 0.97 (0.93, 1.01)
.
Asia
Singh (1998) 0.88 (0.79, 0.98) 38/43
Joshi (2013) 0.91 (0.79, 1.03) 20/22
Subtotal (I–squared = 0.0%, p = 0.746) 0.89 (0.82, 0.97)
.
Overall (I–squared = 42.5%, p = 0.107) 0.96 (0.92, 0.99)
NOTE: Weights are from random effects analysis
.5 .6 .7 .8 .9 1 1.1 1.2
Proportion