Indirect Comparisons Workshop

Some methods of Analysis

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SSAI
Statistical Society of Australia Inc.

APBG
Australian Pharmaceutical Biostatistics Group

Adjusted Indirect Comparison Random Effects

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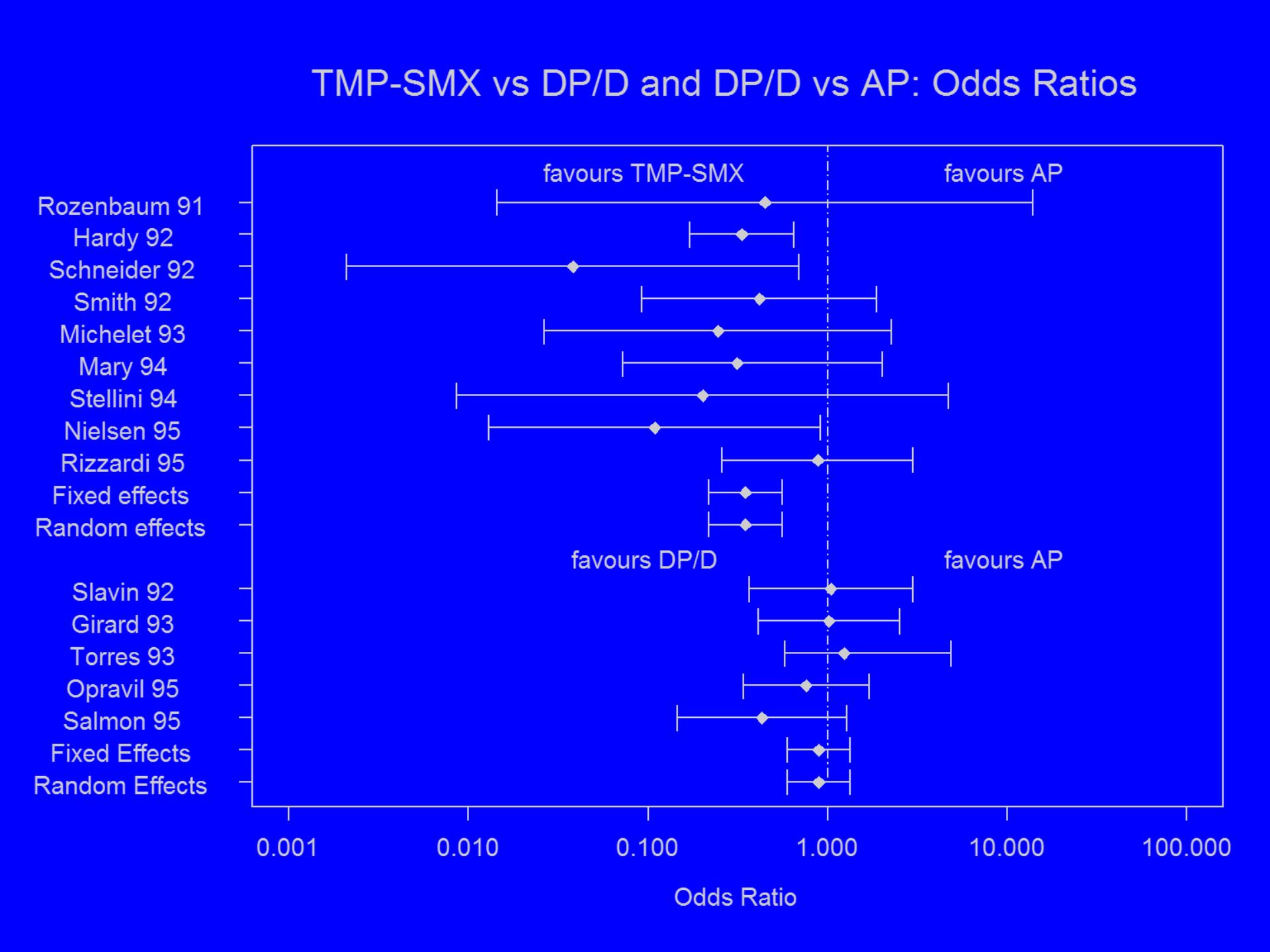
Adjusted Indirect Comparison

- Combine the results of several studies, which address the same research question
- Bucher et al (1997): two experimental, trimethoprim-sulphamethoxazole and dapsone/pyrimethamine, and one standard regimen, aerosolized pentamidine, for primary and secondary prevention of Pneumocystis carinii pneumonia in HIV infection
- Nine trials compared TMP-SMX with AP, and five with
- Primary efficacy: number of patients with Pcp


TMP-SMX vs DP/D and DP/D vs AP: Odds Ratios
favours TMP-SMX
favours AP
Rozenbaum 91
Hardy 92
Schneider 92
Smith 92
Michelet 93
Mary 94
Stellini 94
Nielsen 95
Rizzardi 95
Fixed effects
Random effects
favours DP/D
favours AP
Slavin 92
Girard 93
Torres 93
Opravil 95
Salmon 95
Fixed Effects
Random Effects
0.001
0.010
0.100
1.000
10.000
100.000
Odds Ratio

Statistical Details

- Let Y_{hi} denote the estimator of the effect in treatment *h*, study *i*; treatment h denotes direct comparisons such as A vs B and B vs C
- Let θ_{hi} denote the parameter of interest for treatment *h*, study *i;* eg odds-ratio, relative risk, hazard ratio
- The fixed effect model assumes that $\theta_{hi} = \theta_h$ for all *i*; that is the true value of the parameter of interest is constant across studies within treatment *h*

Statistical Details

- The meta-analysis estimate for θ_h is obtained with weights proportion to the reciprocal of the variance in each study

$$\hat{\theta}_h = \frac{\sum_i W_{hi} Y_{hi}}{\sum_i W_{hi}}$$

with se

$$\left(\sum_i W_{hi} \right)^{-\frac{1}{2}}$$

- Note that the estimates of θ_h and its se do not require any large sample assumptions

Testing the homogeneity

- **Cochran's Q statistic:**

$$Q_h = \sum_i W_{hi}\left(Y_{hi} - \hat{\theta}_h\right)^2$$

which follows a chi-square distribution on k_h-1 degrees of freedom

- **Then sum *Q1* and *Q2* on *k1*+*k2*-2 df to test the homogeneity over all studies**

Adjusted Indirect Comparison Bucher et al (1997)

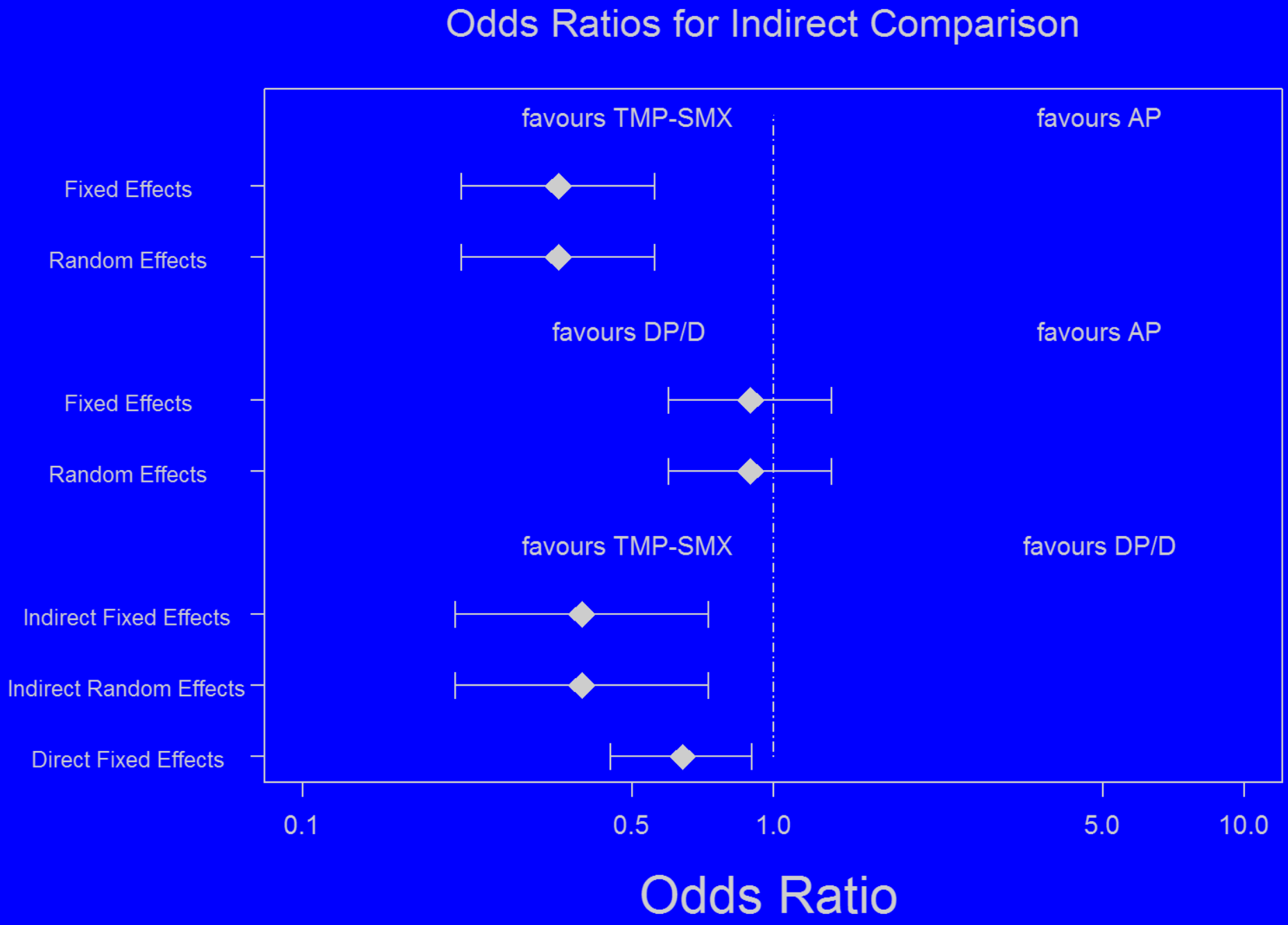
- Treatment effect of TMP-SMX versus AP with standard error, se(TMP-SMX vs AP), and Treatment effect of DP/P versus AP with standard error, se(DP/P vs AP).
- Adjusted Indirect Comparison of TMP-SMX versus DP/P is achieved by subtracting the two treatment effects, which will have a variance of the sum of var(TMP-SMX vs AP) and var(DP/P vs AP)

Adjusted Indirect Comparison Bucher et al (1997)

- TMX-SMP vs AP
  - OR = 0.349; LCL = 0.217; UCL = 0.560
  - Cochran Q_1 = 5.92 on 8 df
  - $Log(OR)_1$ = -1.053; se = 0.241
- DP/P vs AP
  - OR = 0.892; LCL = 0.598; UCL = 1.329
  - Cochran Q_2 = 2.76 on 4 df
  - $Log(OR)_2$ = -0.115; se = 0.204

Adjusted Indirect Comparison Bucher et al (1997)

- Adjusted indirect comparison
  - $Log(OR_{TMP/AP}) – log(OR_{DP/AP}) = -1.053 + 0.115$
  - Log(OR) = -0.938
  - Var(diff) = se^2 + se^2 = 0.0997
  - Se(diff) = 0.316
  - Cochran Q = 5.92 + 2.76 = 8.68 on 12 df
  - OR_{diff} = 0.39; LCL = 0.211; UCL = 0.726
- Direct comparison of TMP-SMX with DP/P
  - OR = 0.64; LCL = 0.45; UCL = 0.90


Odds Ratios for Indirect Comparison
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favours AP
Fixed Effects
Random Effects
favours DP/D
favours AP
Fixed Effects
Random Effects
favours TMP-SMX
favours DP/D
Indirect Fixed Effects
Indirect Random Effects
Direct Fixed Effects
0.1
0.5
1.0
5.0
10.0
Odds Ratio

Estimating the Random Effect

- Estimate the between studies component of variance using the method of moments proposed by DerSimonian & Laird (1986)

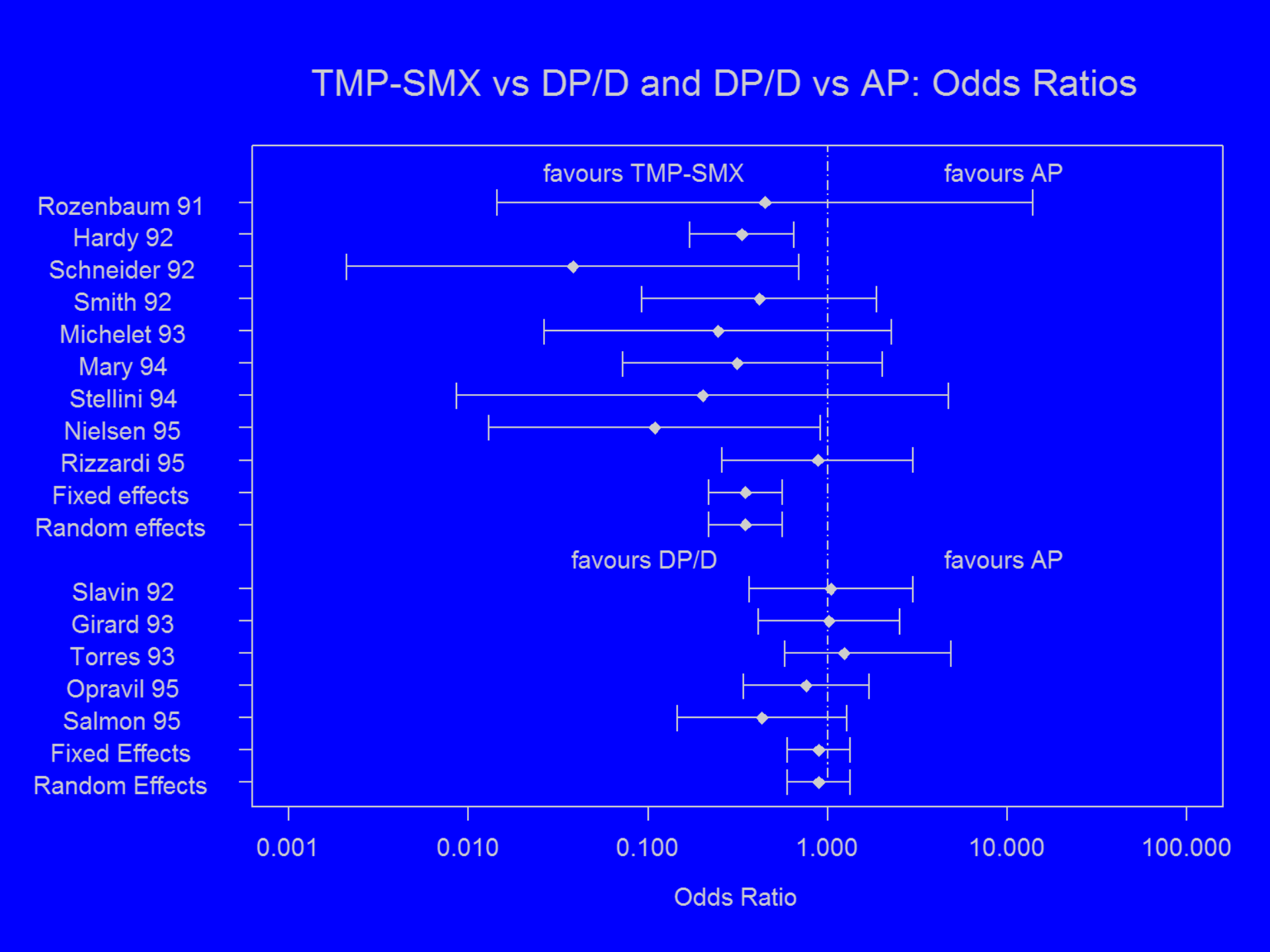
$$\tau_h^2 = \max\left(0, \frac{Q_h - (k_h - 1)}{\sum_i W_{hi} - \frac{\sum W_{hi}^2}{\sum W_{hi}}}\right)$$

Estimating the Random Effect

- Calculate the new weights for each Y_{hi}

$$W_{hi}^{*} = \frac{1}{\sigma_{hi}^{2} + \tau_{h}^{2}}$$

- Now estimate the $\hat{Y}_{h}$ and 95% CI with these new weights, and undertake the adjusted indirect comparison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Estimating a combined variance component

- If the number of studies in one arm, eg A vs B, is small then a combined estimate of the between study component of variance may be recommended

$$\tau^2 = \max\left(0, \frac{Q_1 + Q_2 - (k_1 + k_2 - 1)}{\sum_{h,i} W_{hi} - \frac{\sum_{h,i} W_{hi}^2}{\sum_{h,i} W_{hi}}}\right)$$

Estimating a combined variance component

- The new weights are:

$$W_{hi}^{*} = \frac{1}{\sigma_{hi}^{2} + \tau^{2}}$$

Other methods of analysis

- Higgins & Whitehead (Stats in Med, 1996) meta-regression (GLMM)
- Hirotsu & Yamada (Comm in Stats, 1999) inverse variance meta-analysis
- Hardy & Thompson (Stats in Med, 1996) Likelihood approach for estimating the between study variance component
- Develop the code in SAS and Splus