Medical and Pharmaceutical Statistics Research Unit

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Sequential Methods for Random Effects Meta-Analysis

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Outline

1. Cumulative meta-analysis
2. Sequential methods – monitoring boundaries
3. Sequential methods – repeated confidence intervals
4. Incorporating between study heterogeneity
5. Bayesian updating of heterogeneity variance
6. Simulation study
7. Application
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1. Cumulative meta-analysis

- **Cumulative meta-analysis is the technique of conducting a new meta-analysis when the results of new trials become available**
- **It is typically conducted without any allowance for multiple testing, so Type I error too large**
- **Some argue no need to adjust p-value as decision to stop further studies not made by meta-analyst**
- **We argue sequential methods are appropriate as meta-analysts frequently make recommendations on the need for further studies**

Fixed-effects meta-analysis

θ_i : measure of treatment advantage e.g. log-odds ratio in the ith study, i = 1,…,k

$\hat{\theta}_i$: estimate of θ_i from i^{th} study

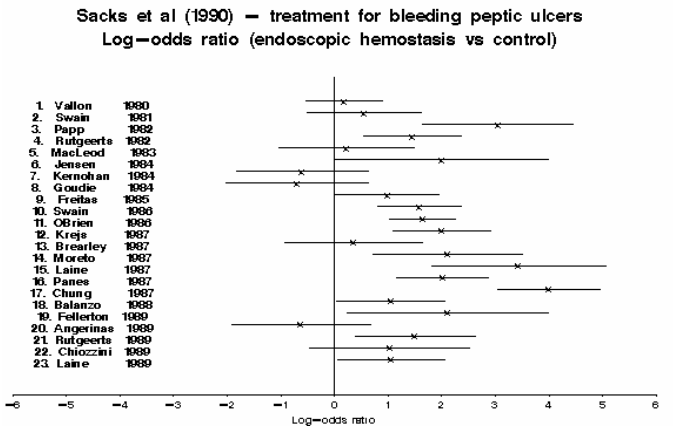
$$\hat{\theta}_i \sim N\left(\theta_i, \xi_i^2\right) \qquad \hat{\xi}_i^2 = 1/V_i$$

$$\hat{\theta}_i \sim Z_i/V_i \qquad \hat{\theta} \sim \sum V_i\hat{\theta}_i \Big/ \sum V_i$$

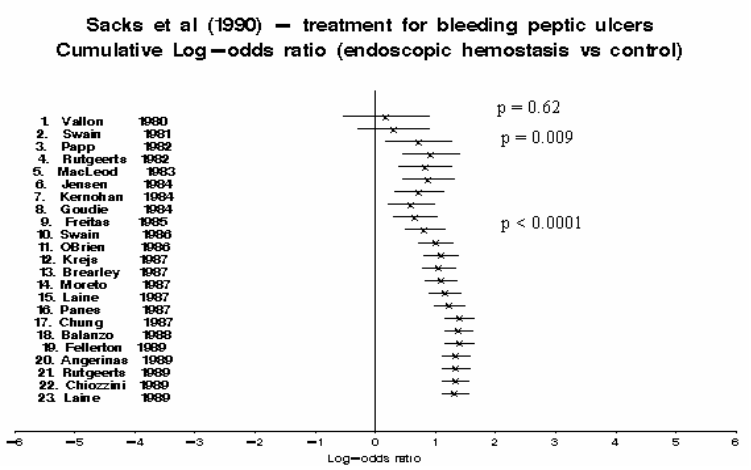
Z_i is efficient score for θ_i (evaluated at $\theta_i = 0$)

V_i is Fisher's information for θ_i (evaluated at $\theta_i = 0$)

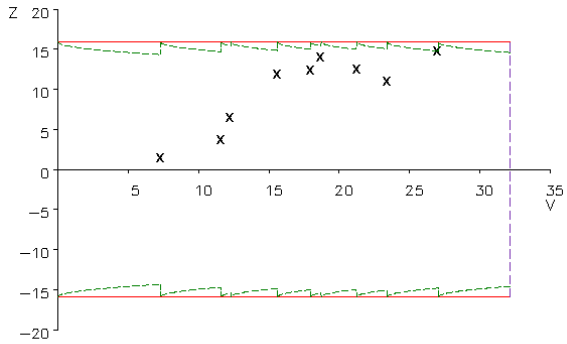
Example



Cumulative fixed-effects meta-analysis (no adjustment for repeated analyses)



2. Sequential methods – monitoring boundaries e.g. O'Brien and Fleming Design



$$Z_j \sim \sum_{i=1}^{t_j} V_i \hat{\theta}_i \qquad V_j \sim \sum_{i=1}^{t_j} V_i$$

Stopping boundaries for O'Brien and Fleming Design

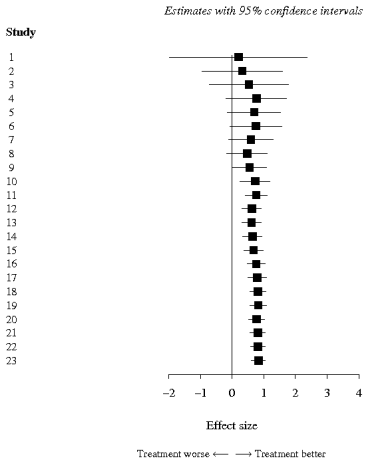
- **Rectangular stopping boundaries in (Z, V) plane**
  - *symmetric upper and lower boundaries at* $Z = \pm H$
  - *vertical boundary at* $V = V_{max}$
- **Christmas tree correction for discrete monitoring**
  - *upper boundary* $H_j = H - 0.583\sqrt{(V_j - V_{j-1})}$
  - *lower boundary* $-H_j = -H + 0.583\sqrt{(V_j - V_{j-1})}$
- **Stop if**
  - $V_j \geq H_j$ *(superiority)*
  - $V_j \leq -H_j$ *(inferiority)*
  - $V_j \geq V_{max}$ *(usually no sig diff)*

3. Repeated confidence intervals

- **Lower and upper limits of repeated confidence intervals obtained from monitoring boundaries**
  - $L_j = (Z_j - H_j)/ V_j$
  - $U_j = (Z_j + H_j)/ V_j$

- **All confidence intervals (L_j , U_j) calculated up to $V = V_{max}$ contain the true value of θ with probability $1 - \alpha$, where α is the selected two-sided significance level for the O'Brien and Fleming design**

Repeated confidence intervals



4. Incorporating between study heterogeneity

$$\hat{\theta}_i \sim N\left(\theta, \xi_i^{\,2} + \tau^2\right)$$

$$\hat{\tau}^2_{DL} = \max\left\{0, \frac{Q-(k-1)}{\sum V_i - \left(\sum V_i^2 / \sum V_i\right)}\right\}$$

$$\text{where } Q = \sum V_i \left\{\hat{\theta}_i - \left(\sum V_i \hat{\theta}_i / \sum V_i\right)\right\}^2$$

$$\hat{\theta} \sim \sum V_i^* \hat{\theta}_i \Big/ \sum V_i^* \qquad \text{where} \quad V_i^* = \left(V_i^{-1} + \hat{\tau}^2_{DL}\right)^{-1}$$

Plot $\quad Z_j \sim \sum_{i=1}^{t_j} V_i^* \hat{\theta}_i \qquad V_j \sim \sum_{i=1}^{t_j} V_i^*$

Problems with estimation of τ^2

- **Large value may lead to path moving backwards**
- **Few trials – poor estimate**
- **Underestimation of τ^2 leads to overestimation of Z and V**
- **May stop with incorrect findings**

5. Bayesian updating of heterogeneity variance

- Combine the likelihood $\hat{\theta}_i \sim N\left(\theta, V_i^{-1} + \tau^2\right)$ with a prior for τ^2 $\quad IG\left(\alpha, \beta\right)$
- Assume θ is known and equals the previous estimate
- Generate the posterior for τ^2
- Numerically integrate to obtain posterior mean $\hat{\tau}_B^2$ and use this as an estimate
- Can incorporate genuine prior information or use a suitable vague prior

Approximate Bayesian Method (avoiding integration)

- Assume θ_i is known and equals $\hat{\theta}_i$
- Set $\varphi_j = \frac{1}{t_j}\sum_{i=1}^{t_j}\left(\theta_i - \theta\right)^2$
- Combining the likelihood with an inverse gamma prior gives an inverse gamma posterior

$$IG\left(\alpha + \frac{t_j}{2}, \beta + \frac{t_j}{2}\varphi_j\right)$$

- The posterior mean of τ^2 is given by

$$\frac{2\beta + t_j\varphi_j}{2\alpha + t_j - 2}$$

Inverse gamma prior and posterior

- The prior mean of τ^2 is $\hat{\tau}^2_{AB0} = \beta/(\alpha - 1)$
- Replace φ with $\hat{\tau}^2_{DL}$
- Posterior mean: $\dfrac{2(\alpha-1)\hat{\tau}^2_{AB0}}{2(\alpha-1)+t_j} + \dfrac{t_j\hat{\tau}^2_{DL}}{2(\alpha-1)+t_j}$
  is weighted average of prior mean and usual estimate from studies in meta-analysis
- Example, prior $IG(1.5, 0.08)$ has a weight of one trial, with $\hat{\tau}^2_{AB0} = 0.16$

6. Simulation Study

- O'Brien and Fleming design
  - *two-sided α = 5% , 90% power to detect θ_R = 0.5*
- True effect $\theta = 0, 0.25, 0.5, 1$ $\tau^2 = 0, 0.0625, 0.25$
- E(trials to V_{max}) = 5, 10, 20

- 5000 simulations for each of the 36 scenarios
- Fixed effects analysis
- Random effects analysis
- Bayesian and approximate Bayesian updating
  - *Prior* $IG(1.5, 0.08)$

Results with approximately five studies

θ	τ^2	At stopping	Fixed	Random	Bayes	Approx Bayes
0	0	No. Trials	5.5	6.4	8.6	7.5
		P(superiority)	0.039	0.034	0.007	0.017
		% coverage all CIs	92.2	93.1	98.4	96.5
	0.0625	No. Trials	5.3	7.7	9.2	8.8
		P(superiority)	0.095	0.067	0.027	0.045
		% coverage all CIs	81.5	86.2	94.6	91.2
	0.25	No. Trials	4.8	13.1	12.7	14.3
		P(superiority)	0.225	0.115	0.083	0.084
		% coverage all CIs	55.6	77.7	83.9	83.7

Results with approximately five studies

θ	τ^2	At stopping	Fixed	Random	Bayes	Approx Bayes
0.5	0	No. Trials	3.7	4.3	5.9	5.2
		P(superiority)	0.948	0.958	0.974	0.968
		% coverage all CIs	91.6	92.5	98.2	95.8
	0.0625	No. Trials	3.7	5.2	6.2	6.0
		P(superiority)	0.909	0.938	0.948	0.947
		% coverage all CIs	80.9	86.7	94.6	91.3
	0.25	No. Trials	3.7	8.3	8.0	9.1
		P(superiority)	0.840	0.909	0.901	0.908
		% coverage all CIs	56.4	77.9	83.5	83.1

Results with approximately ten studies

θ	τ^2	At stopping	Fixed	Random	Bayes	Approx Bayes
0	0	No. Trials	10.5	11.9	13.9	12.5
		P(superiority)	0.032	0.028	0.015	0.023
		% coverage all CIs	93.2	93.9	96.9	95.1
	0.0625	No. Trials	10.3	13.4	14.5	14.0
		P(superiority)	0.057	0.046	0.027	0.037
		% coverage all CIs	88.5	90.9	94.5	92.5
	0.25	No. Trials	9.7	19.5	17.5	19.9
		P(superiority)	0.136	0.069	0.063	0.060
		% coverage all CIs	71.8	85.9	87.7	87.8

Results with approximately ten studies

θ	τ^2	At stopping	Fixed	Random	Bayes	Approx Bayes
0.5	0	No. Trials	7.0	7.9	9.4	8.5
		P(superiority)	0.933	0.943	0.947	0.942
		% coverage all CIs	93.6	94.6	97.4	95.5
	0.0625	No. Trials	7.0	9.0	9.7	9.5
		P(superiority)	0.903	0.922	0.932	0.926
		% coverage all CIs	87.9	90.8	94.6	92.7
	0.25	No. Trials	6.8	12.3	11.3	12.7
		P(superiority)	0.861	0.909	0.901	0.909
		% coverage all CIs	72.1	85.4	86.5	87.0

Conclusions from Simulation Study

- **Increased Type I error rate partly due to stopping with V > V_{max}. Improves as number of studies increases**
- **Type I error rate increases with increasing heterogeneity**
  - ***most noticeable for fixed effect method***
- **Incorporating random effect partly reduces this risk**
- **Bayesian methods further reduce the risk**
- **Coverage of CI worsens with increasing τ^2**
  - ***best with Bayesian methods***
- **Over-coverage in Bayesian methods when $\tau^2 = 0$**
- **Choice of prior may affect performance of Bayesian methods**

7. Application (Sacks et al. 1990)

- **Random effects meta-analysis of 23 trials**

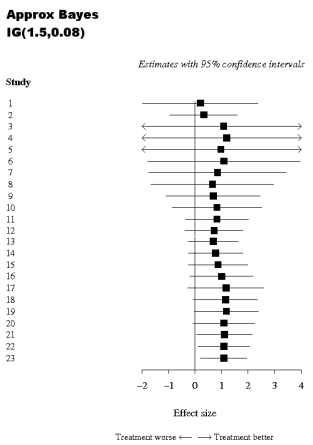
  $\hat{\theta} = 1.15$ $\hat{\tau}^2_{DL} = 1.04$

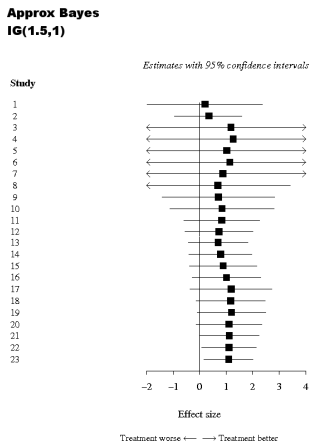
- **O'Brien and Fleming design with**
  - ***90% power***
  - ***2-sided 5% significance level***
  - ***odds ratio of 2***
  - ***$\theta = 0.693$***

Sequential meta-analysis of the Sacks Data

		Fixed effects	Random effects	Approx Bayes IG(1.5,0.08)	Approx Bayes IG(1.5,1)
At Stopping	No. Trials	9	21	21	21
	Z/V	0.55	1.11	1. 10	1.12
	CI	0.00, 1.10	0.04, 2.18	0.06, 2.15	0.00, 2.23
	τ^2	0	0.93	0.91	0.99
PEST analysis	Median unbiased estimate θ	0.54	1.10	1.09	1.11
	CI	0.16, 0.92	0.58, 1.62	0.57, 1.61	0.58, 1.65

Repeated confidence intervals –Approximate Bayes





8. Conclusions

- **Formal sequential procedures address the multiple looks problem within a cumulative meta-analysis**
- **O'Brien and Fleming sequential design with Christmas tree correction leads easily to repeated confidence intervals**
  - ***Use forest plots to present sequential meta-analyses***
- **Fixed and random effect approaches can lead to inflated Type I error and poor CI coverage**
- **The Bayesian approaches can reduce these problems**
- **The approximate Bayes method is simpler to implement**
  - ***Easy to program in standard software***
- **Careful choice of priors is needed**
- **Could consider different sequential designs and responses**