A new Mantel-Haenszel estimator for network meta-analysis?

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This is work in progress and joint work with

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Outline

1. **The Mantel-Haenszel estimator in pairwise meta-analysis**
2. **The Mantel-Haenszel estimator in network meta-analysis**
3. **Comparing results of different methods (examples)**
4. **Discussion**
5. **Additional material**

Binary data in pairwise meta-analysis

Data of study i $(i = 1, k)$

	Event		
	yes	no	Total
Treatment	a_i	b_i	$a_i + b_i$
Control	c_i	d_i	$c_i + d_i$
	$a_i + c_i$	$b_i + d_i$	n_i

Odds ratio of study i

$$\hat{\theta}_i = \frac{a_i d_i}{b_i c_i}$$

The Mantel-Haenszel estimator in pairwise meta-analysis

[Mantel and Haenszel, 1959]

- Estimator for common odds ratio in stratified case-control study
- Can be used in meta-analysis of RCTs
- Common effect method

Mantel-Haenszel odds ratio (OR) $\hat{\theta}_{MH}$

$$\hat{\theta}_{MH} = \frac{\sum_{i=1}^{k} \frac{a_i d_i}{n_i}}{\sum_{i=1}^{k} \frac{b_i c_i}{n_i}}$$

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with weights $w_i = \frac{b_i c_i}{n_i}$

The Mantel-Haenszel estimator in pairwise meta-analysis

- The MH estimator can be interpreted as a weighted mean of the study-specific odds ratios
- Averaging on the natural scale, not on the log scale
- (Ian White's idea:) Rewrite the condition for the true OR, θ_{MH}:

$$\theta_{MH} = \frac{\sum_{i=1}^{k} \frac{a_i d_i}{n_i}}{\sum_{i=1}^{k} \frac{b_i c_i}{n_i}}$$

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with $\theta_{MH} = \theta_T / \theta_C$ (θ_T, θ_C uniquely determined only if an additional constraint is imposed)

- We choose $\theta_T + \theta_C = 1$, that is $\theta_{MH} = \frac{\theta_T}{1-\theta_T}$

The Mantel-Haenszel estimator in network meta-analysis (NMA)

- Write similar equations for all existing treatment contrasts Y:X in an NMA:

$$\sum_{i=1}^{k} \frac{\theta_X \; a_{Yi} b_{Xi} - \theta_Y \; a_{Xi} b_{Yi}}{n_{Xi} + n_{Yi}} = 0$$

  where $\theta_{XY} = \theta_Y / \theta_X$ is the parameter of interest, the OR for comparison Y vs X, and k is the number of studies for that comparison (sum over these studies)

- Identifying assumption:

$$\sum_{t=1}^{T} \theta_t = 1$$

  (sum over all treatments in the network)

The Mantel-Haenszel estimator in network meta-analysis (NMA)

- For each existing comparison Y:X in the network we have an equation:

$$\sum_{i=1}^{k} \frac{\theta_X \, a_{Yi} b_{Xi} - \theta_Y \, a_{Xi} b_{Yi}}{n_{Xi} + n_{Yi}} = 0, \quad \sum_{t=1}^{T} \theta_t = 1$$

- For a network with T treatments, this makes up to $T(T-1)/2$ linear equations for $T-1$ parameters
- For a tree-shaped network (for example, a star) we have $T-1$ equations and the solution is unique, giving the usual MH estimator
- For general networks we propose least squares

The Mantel-Haenszel estimator in network meta-analysis (NMA)

- Set $\theta = (\theta_1, \ldots, \theta_{T-1})$ and write the system in matrix form:

$$\mathbf{X}\,\theta = \mathbf{y}$$

where $\mathbf{y}$ contains the negative coefficients of (say) the last parameter θ_T

- Least squares solution [Albert, 1972, Theorem (3.8)]

$$\hat{\theta} = \mathbf{X}^{+}\mathbf{y}$$

where $\mathbf{X}^{+}$ is the Moore-Penrose pseudoinverse of $\mathbf{X}$

- Obtain odds ratios by setting

$$\hat{\theta}_T = 1 - \sum_{t=1}^{T-1} \hat{\theta}_t \quad \text{and} \quad \hat{\theta}_{XY} = \hat{\theta}_Y / \hat{\theta}_X$$

The Mantel-Haenszel estimator in network meta-analysis (NMA)

Remarks

- It doesn't matter which parameter is made dependent (e.g., θ_T), as the condition is symmetric in all parameters
- As the equations are based on the odds $(\theta_1, \dots, \theta_T)$, the solution is consistent
- Zeros automatically handled (double zeros don't contribute, single zeros retained)
- For tree networks (star, pairwise meta-analysis) or fully consistent networks, the unique solution agrees with the solution of the standard method
- Squared distances minimized with respect to the odds (not the log odds ratios!) ⇒ the general solution differs from that obtained by the approach by Efthimiou that operates at the log odds level [Efthimiou et al., 2019] , implemented in function netmetabin() of R package **netmeta** [Rücker et al., 2025]
- This is expected – is it a reason for concern?

A consistent example - Comparison of methods

			OR estimate				
Study	group1	group2	direct	MH/ Inverse Variance	Penalized logistic regression	Non-central hypergeometric (NCH) method	Mantel-Haenszel New method
A:B	2/100	3/100	0.660	0.660	0.691	0.667	0.660
A:C	2/100	4/100	0.490	0.490	0.528	0.500	0.490
B:C	3/100	4/100	0.742	0.742	0.763	0.750	0.742

- Consistent data
- Results of IV and both MH methods agree [Efthimiou et al., 2019]
- Penalized logistic regression [Evrenoglou et al., 2022] and NCH results [Stijnen et al., 2010] deviate from MH/IV results
- Note: Implemented version of the non-central hypergeometric method (NCH) estimates the risk ratio (RR)!

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Study	group1	group2	direct	MH/ Inverse Variance	Penalized logistic regression	Non-central hypergeometric (NCH) method	Mantel-Haenszel New method
A:B	2/100	2/100	1	0.615	0.638	0.600	0.459
A:C	1/100	4/100	0.242	0.444	0.468	0.429	0.395
B:C	3/100	3/100	1	0.721	0.734	0.714	0.860

- Inconsistent data
- Results of IV and established MH method agree
- Note: Implemented version of the non-central hypergeometric method (NCH) estimates the risk ratio (RR)!
- Results of new method differ considerably!

Real data: Inhaled medications in patients with COPD

Data set `"Dong2013"` of R package **netmeta** [Dong et al., 2013]

Compared to Placebo	Inverse Variance	Mantel-Haenszel Standard	Penalized logistic regression	Non-central hypergeometric (NCH) method	Mantel-Haenszel New method
ICS	1.024	1.029	1.031	1.024	1.037
LABA	0.933	0.925	0.929	0.936	0.905
LABA-ICS	0.784	0.790	0.795	0.812	0.809
TIO-HH	0.920	0.921	0.918	0.927	0.917
TIO-SMI	1.504	1.517	1.504	1.497	1.550

- IV, Standard MH, NCH: three double-zero studies, one quadruple-zero study and one other design removed
- New method: two double-zero studies and one quadruple-zero study removed

Real data: Mortality at 60 days post liver transplantation

Data set `"Gurusamy2011"` of R package **netmeta** [Gurusamy et al., 2011]

Compared to Control/Placebo	Inverse Variance	Mantel-Haenszel Standard	Penalized logistic regression	Non-central hypergeometric (NCH) method	Mantel-Haenszel New method
Antithrombin III	0.215	–	0.215	–	0.287
Aprotonin	0.400	0.355	0.356	0.360	0.366
EACA	0.814	0.736	0.764	0.769	0.689
rFVIIa	1.538	1.538	1.324	1.509	1.660
Solvent detergent plasma	–	–	1.080	–	–
Tranexamic acid	0.905	0.767	0.776	0.806	0.567

- IV: three double-zero studies removed
- Standard MH, NCH: three double-zero studies and one other design removed (treatment arm without any event in the whole data set)
- LRP: non-convergence warning occurred
- New method: three double-zero studies and a treatment without events removed

Zero counts – Comparing frequentist methods (avoiding CC)

Problem	Standard IV	Mantel-Haenszel method	Non-central hypergeometric method	Penalized logistic regression	New method
zero count for A in a study	study removed	✓	✓	✓	✓
zero count for both treatments in a study	study removed	study removed	study removed	✓	✓
zero count for A in all A:B studies	design A:B removed	design A:B removed	design A:B removed	✓	✓
zero count for A in all studies that include A	A removed	A removed	A removed	✓	A removed
zero count for A in all A:B studies and zero count for B in all B:C studies	designs A:B, B:C removed	designs A:B, B:C removed	designs A:B, B:C removed	✓	⚡

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- Odds or log odds?
- How to obtain plausible standard errors for the θ_X?
- How to account for correlation within multi-arm trials?
- Simulation study?

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Appendix: Variance estimation

- Variance-covariance matrix of $\hat{\theta}$:

$$\operatorname{Cov}\hat{\theta} = \mathbf{X}^{+} \operatorname{Cov}\mathbf{y}\, (\mathbf{X}^{+})^{\top}$$

- What to insert for $\operatorname{Cov}\mathbf{y}$?
- Example: Pairwise meta-analysis

$$\widehat{\operatorname{Var}}\,\mathbf{y} = \operatorname{Var}\left(\sum_{i=1}^{k} \frac{a_i d_i}{n_i}\right) = \sum_{i=1}^{k} \operatorname{Var}\left(\frac{a_i d_i}{n_i}\right) = \sum_{i=1}^{k} \frac{1}{n_i^2} \operatorname{Var}(a_i d_i) = \sum_{i=1}^{k} \frac{a_i d_i}{n_i^2}\left(\frac{b_i c_i}{n_{1i}\, n_{2i}} + \frac{a_i c_i}{n_{2i}} + \frac{b_i d_i}{n_{1i}}\right)$$

Then

$$\operatorname{Var}\hat{\theta} = \sum_{i=1}^{k} \frac{a_i d_i}{n_i^2}\left(\frac{b_i c_i}{n_{1i}\, n_{2i}} + \frac{a_i c_i}{n_{2i}} + \frac{b_i d_i}{n_{1i}}\right)\left(\sum_{i=1}^{k} \frac{a_i d_i + b_i c_i}{n_i}\right)^{-2}$$

- Problem: Because of the arbitrary choice of $\mathbf{y}$ this is not symmetric in the treatments – a different naming/order of treatments leads to a different variance!

Appendix: Variance estimation

Use the delta method to derive the variances for the (log) odds ratios from the variances of the odds (if known …):

$$\mathrm{Var}\left(\log\frac{\theta_X}{\theta_Y}\right) = \frac{\mathrm{Var}\left(\theta_X\right)}{\left[\mathrm{E}\left(\theta_X\right)\right]^2} + \frac{\mathrm{Var}\left(\theta_Y\right)}{\left[\mathrm{E}\left(\theta_Y\right)\right]^2} - 2\,\frac{\mathrm{Cov}\left(\theta_X, \theta_Y\right)}{\mathrm{E}\left(\theta_X\right)\mathrm{E}\left(\theta_Y\right)}$$

- numerators ($\mathrm{Var}\left(\theta_X\right), \mathrm{Var}\left(\theta_Y\right), \mathrm{Cov}\left(\theta_X, \theta_Y\right)$) from the variance-covariance matrix $\mathrm{Cov}\,\hat{\theta}$
- denominators from observed values $\hat{\theta}_X,\ \hat{\theta}_Y$

Real data: Smoking cessation

	OR estimate					
Comparison	direct	Inverse Variance	Mantel-Haenszel Standard	Penalized logistic regression	Non-central hypergeometric (NCH) method	Mantel-Haenszel New method
A:B	0.874	0.819	0.809	0.797	0.818	0.836
A:C	0.514	0.521	0.486	0.467	0.532	0.478
A:D	0.644	0.488	0.485	0.435	0.534	0.497
B:C	1.082	0.636	0.601	0.585	0.651	0.572
B:D	0.565	0.596	0.599	0.546	0.653	0.595
C:D	1.042	0.938	0.997	0.932	1.003	1.040

- Results of all methods differ
- Splitting between direct and indirect evidence shows some inconsistency for comparison B:C (e.g., $p = 0.0357$ for standard MH method)

Real data: Smoking cessation