Assessment of Homogeneity and Consistency for Network Meta-Analysis

Joseph G. Ibrahim

Department of Biostatistics, University of North Carolina
E-Mail: ibrahim@bios.unc.edu

Joint work with Cheng Zhang, Hao Li, Ming-Hui Chen
Arvind K. Shah and Jianxin Lin

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Outline

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Network Meta-Analysis

- NMA was first termed by Thomas Lumley in 2002.
- It is known as multiple/mixed treatment comparisons (MTC).
- Extend the pairwise meta-analysis for (A, P) trials to data structures that include (A, P), (B, P), (A, B) and even (A, B, P) trials. (Lumley, 2002; Lu & Ades, 2004)
- Direct and indirect comparisons co-exist.
- NMA allows for simultaneously comparisons and even ranking of several treatments.

Key Issues in NMA

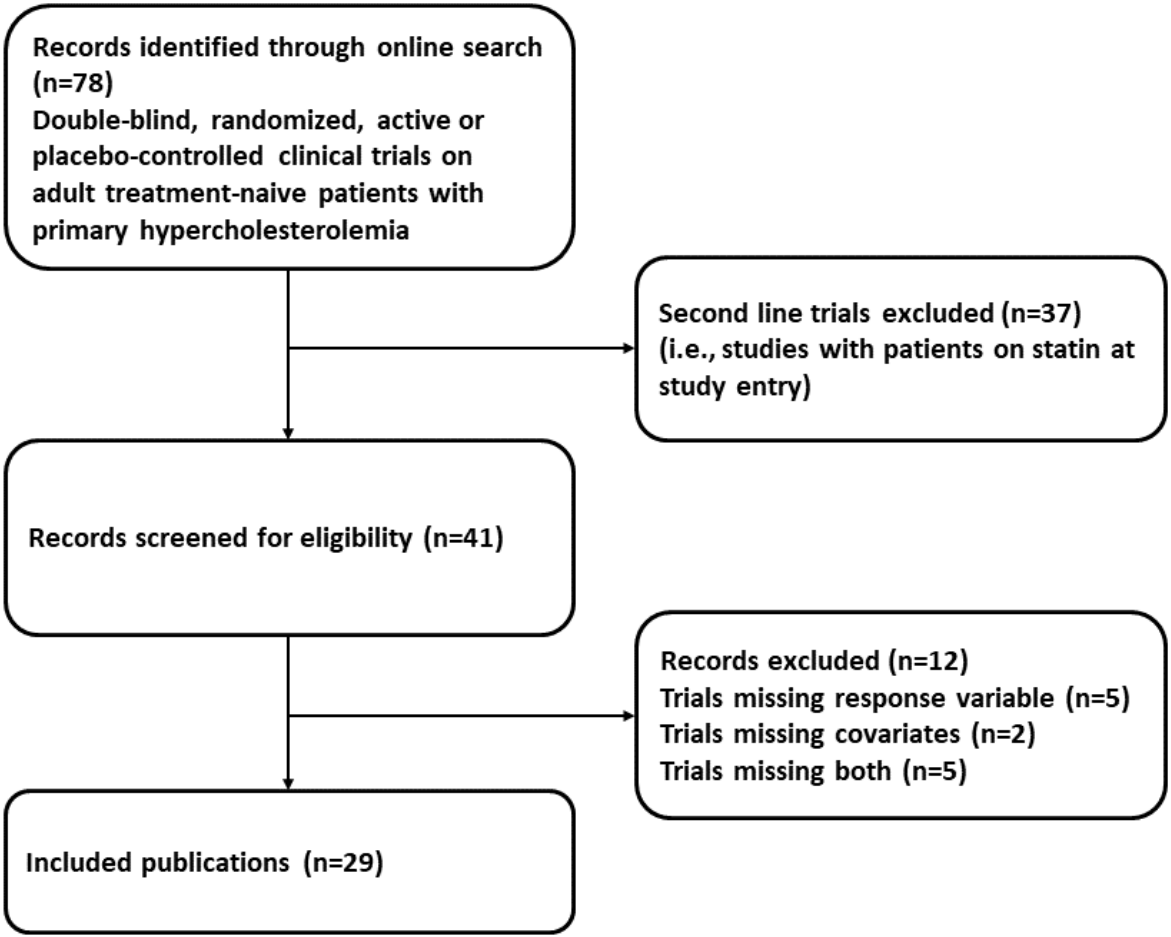
- **Arm Heterogeneity**: The effects of a treatment are different across trials.
- **Relative Treatment Effect Heterogeneity**: The relative effects of two treatments are different across trials.
- **Inconsistency**: Obvious conflict between the direct evidence and the indirect evidence.

Outline

Background of the Cholesterol-Lowering Drugs

- Cholesterol lowering medicines
  - Statins
    - positively affect the lipid profile by decreasing low density lipoprotein cholesterol (LDL-C, 'bad' cholesterol) and triglycerides (TG) and increasing high density lipoprotein cholesterol (HDL-C, 'good' cholesterol).
    - work mainly in the liver to decrease the production of cholesterol and reduce cholesterol in the bloodstream.
  - Ezetimibe (Zetia)
    - works in the digestive tract to help block absorption of cholesterol that comes from food.
    - can be given as monotherapy to lower cholesterol levels in patients who are intolerant to statins.
    - can be used in combination with statins in patients whose cholesterol levels remain elevated despite treatment with statins alone.

Trials Inclusion-Exclusion Flow Diagram

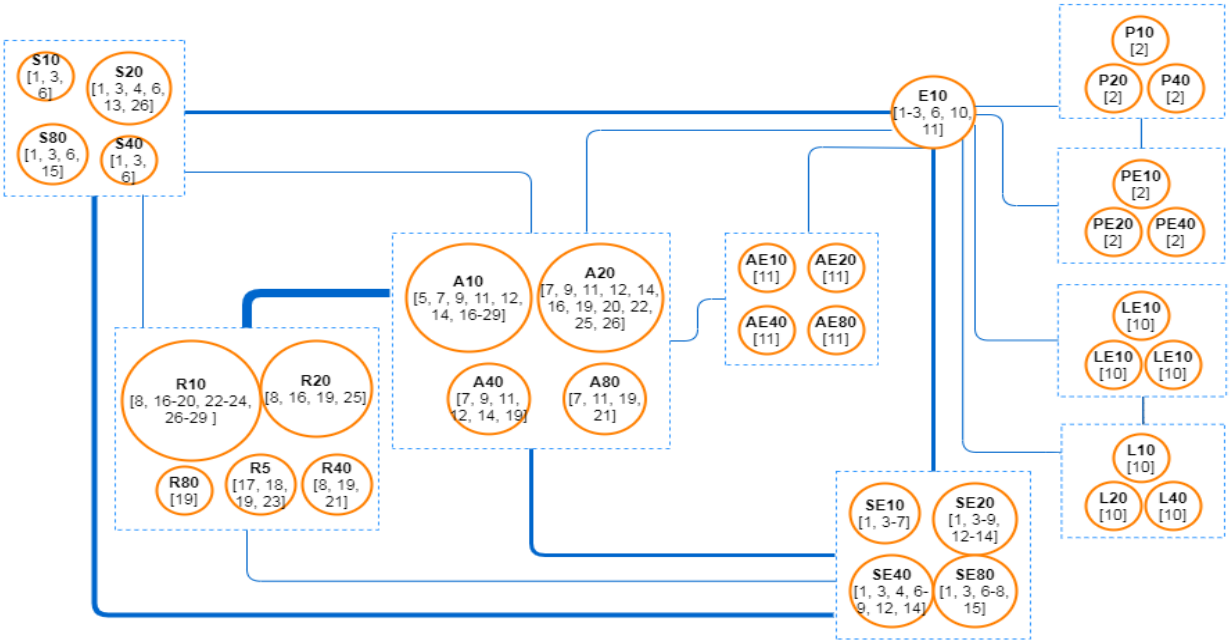


Treatments in the LNM Data

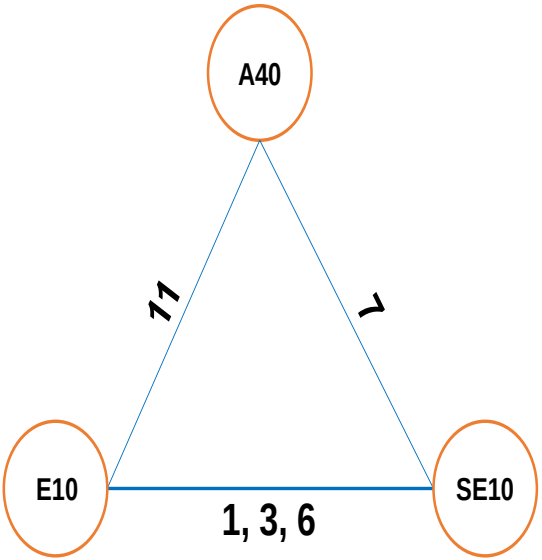
- 11 treatment arms (10 active treatments plus placebo)
  - placebo (PBO)
  - simvastatin (S), atorvastatin (A), lovastatin (L), rosuvastatin (R), pravastatin (P)
  - Ezetimibe (E)
  - the combinations of S and E (SE), A and E (AE), L and E (LE) and P and E (PE)
  - Each treatment, except for treatment E, has multiple dose levels that range from 5 milligrams to 80 milligrams (mg), whereas E only has a single dose level of 10 mg across all the trials.
  - According to Grundy et al. (2018), it is a clinical practice for doctors to prescribe Statin with different doses for different patients.
  - Thus, to investigate treatment at dose levels in network meta-analysis is of great clinical importance.

- The outcome variable: mean percent change from baseline in LDL-C.

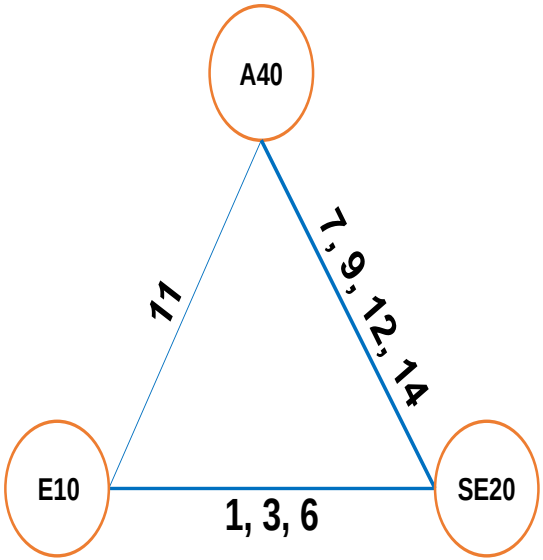
The LNM Network Diagram



The Triangle Testable Loops



(a) Loop A40-E10-SE10

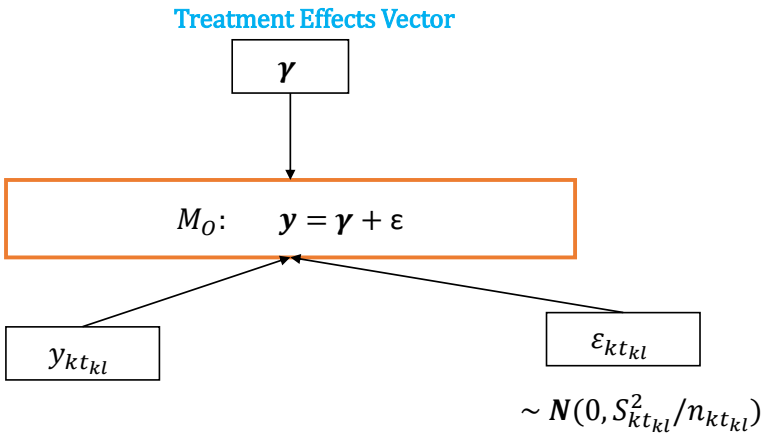


(b) Loop A40-E10-SE20

- Each node represents a treatment. Each edge represents the direct comparisons of the two treatments that are connected, with the numbers on the edge being the trials that directly comparing the two treatments.

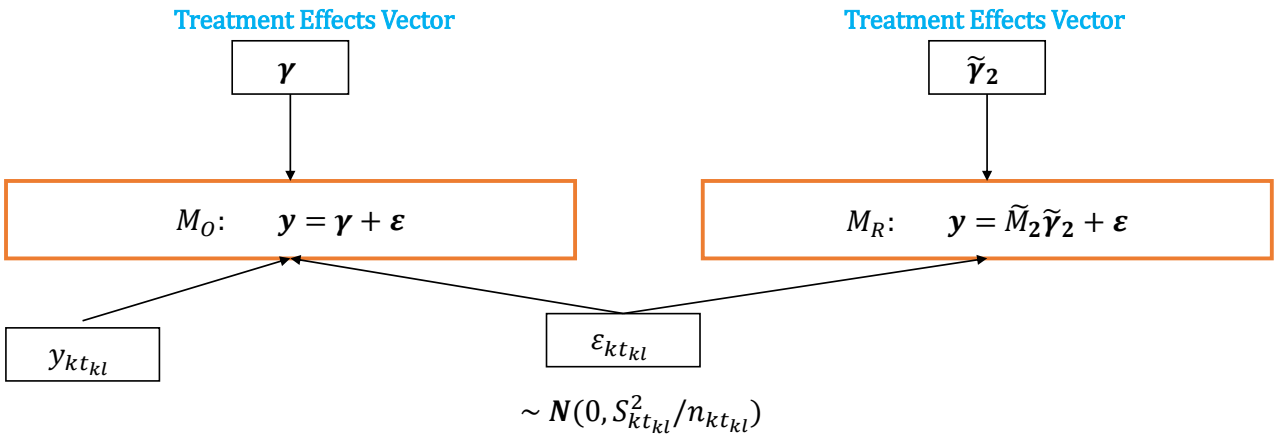
Outline

NMA Fixed Effects Model



See White et al. (2012).

NMA Fixed Effects Model



See White et al. (2012).

Linear Hypotheses for Relative Effects Homogeneity

- To illustrate our assessment of relative homogeneity, we consider two treatments, E10 and SE10, which are compared head-to-head in trials 1, 3, and 6 in the LNM data.
- Relative homogeneity of the pair E10-SE10 indicates

$$\gamma_{1E10} - \gamma_{1SE10} = \gamma_{3E10} - \gamma_{3SE10} = \gamma_{6E10} - \gamma_{6SE10}, \tag{1}$$

  where γ_{kE10} and γ_{kSE10} denote the effects of E10 and SE10 in trial k for $k = 1, 3, 6$.
- Let C_H be the contrast matrix for (1), then C_H is a $2 \times n$ matrix with full row rank equal to 2.
- Detecting heterogeneity between the pair E10-SE10 is to test the hypothesis $C_H\boldsymbol{\gamma} = 0$.

Linear Hypotheses for Loop Consistency

- An inconsistency testable triangle loop is consistent if the direct relative treatment effect of two treatments in the loop agrees with the indirect relative treatment effects obtained through the third treatment in that loop.
- Therefore, it implicitly indicates that loop consistency should be evaluated only if loop homogeneity is confirmed.
- For example, if homogeneity of the loop A40-E10-SE10 is confirmed, i.e., $\gamma_{1E10} - \gamma_{1SE10} = \gamma_{3E10} - \gamma_{3SE10} = \gamma_{6E10} - \gamma_{6SE10} = \delta_D$, we need to add an additional constraint to establish consistency,

$$\delta_D = (\gamma_{11E10} - \gamma_{11A40}) - (\gamma_{7SE10} - \gamma_{7A40}), \tag{2}$$

  where γ_{11E10} and γ_{11A40} are the effects of E10 and A40 in the trial 11 and γ_{7SE10} and γ_{7A40} denote the effects of SE10 and A40 in the trial 7. Let C_I be the contrast matrix corresponding to (2).
- Write

$$C = (C_H^\top, C_I^\top)^\top. \tag{3}$$

  Simultaneously detecting heterogeneity and inconsistency of the loop is to test $C\boldsymbol{\gamma} = 0$.

Heterogeneity and Inconsistency Detection: the Bucher Method

- $\hat{d}_1$ is the direct estimate of the relative effect of A versus P.
- $\hat{d}_2, ..., \hat{d}_K$ are the indirect estimates.
- Overall, $\hat{d}_1, ..., \hat{d}_K$ are K independent estimates with variances $V_1, ..., V_K$.
- The average treatment effect $\tilde{d} = \frac{\sum_{k=1}^{K} W_i \hat{d}_i}{\sum_{k=1}^{K} W_i}$, where $W_i = 1/V_i$.
- $T = \sum_{k=1}^{K} W_i (\hat{d}_i - \tilde{d})^2$ is the test statistic, which approximately follows a $\chi^2(K-1)$ distribution.
- Small p-value suggests that there is evidence of inconsistency.

Heterogeneity and Inconsistency Detection: the Likelihood Ratio test

- Under the NMA fixed effects model, the observed likelihood function is

$$L(\boldsymbol{\gamma}|D) = (2\pi)^{-\frac{n}{2}} |\widehat{\Sigma}|^{-\frac{1}{2}} \exp\{-\frac{1}{2}(\boldsymbol{\gamma} - \boldsymbol{y})^\top \widehat{\Sigma}^{-1}(\boldsymbol{\gamma} - \boldsymbol{y})\}, \tag{4}$$

  where $\widehat{\Sigma} = \text{Diag}\Big(\frac{S^2_{1t_{11}}}{n_{1t_{11}}}, \ldots, \frac{S^2_{1t_{1T_1}}}{n_{1t_{1T_1}}}, \ldots, \frac{S^2_{Kt_{K1}}}{n_{Kt_{K1}}}, \ldots, \frac{S^2_{Kt_{KT_K}}}{n_{Kt_{K_TK}}}\Big)$.

- By formulating appropriate null and alternative hypotheses, we can show that Bucher's test is equivalent to the likelihood ratio test (LRT) under the NMA fixed effects model.
- Theorem 1: *Under the NMA fixed effects model, the LRT statistic for testing the hypotheses*

  H_0: Consistent and Homogeneous Network *versus* H_A: Homogeneous Network

  is Bucher's test statistic.
- The significance of the result established in Theorem 1 is twofold: (i) it provides new understanding of the Bucher's method and (ii) it nicely connects the estimation-based approach to the hypothesis-based method for assessing homogeneity and consistency, which sheds light on the development of our proposed new methodology.

General Linear Hypotheses

- Given a $q \times n$ contrast matrix C, assume $r = \text{rank}(C)$ and let $C = FQ$ be a full rank decomposition of C, where F is a $q \times r$ full column rank matrix and Q is a $r \times n$ full row rank matrix. Under the homogeneity/consistency assumption, $C\boldsymbol{\gamma} = 0$ is equivalent to $Q\boldsymbol{\gamma} = 0$.
- Let $M = \begin{bmatrix} Q \\ Q^{\perp} \end{bmatrix}$, where $Q^{\perp}_{(n-r)\times n}$ is the orthogonal complement of Q in R^n.
- $\tilde{\boldsymbol{\gamma}} = M\boldsymbol{\gamma}$ be a transformation of $\boldsymbol{\gamma}$ (a vector of treatment effects).
  $\tilde{\boldsymbol{\gamma}} = \begin{bmatrix} \tilde{\boldsymbol{\gamma}}_1 \\ \tilde{\boldsymbol{\gamma}}_2 \end{bmatrix} = \begin{bmatrix} Q \\ Q^{\perp} \end{bmatrix} \boldsymbol{\gamma}.$
- Let $\tilde{M} = \begin{bmatrix} \tilde{M}_1 & \tilde{M}_2 \end{bmatrix}$ denote the inverse matrix of M.
- Under the assumption of consistency $H_0 : Q\boldsymbol{\gamma} = \mathbf{0}$,

$$\boldsymbol{\gamma} = \tilde{M}\tilde{\boldsymbol{\gamma}} = \tilde{M}_2\tilde{\boldsymbol{\gamma}}_2, \text{ since } \tilde{\boldsymbol{\gamma}}_1 = Q\boldsymbol{\gamma} = \mathbf{0}.$$

Theorem 2

Suppose that F_1Q_1 *and* F_2Q_2 *are two full rank decompositions of* C. *The corresponding orthogonal complement subspaces, transformation matrices and transformed parameters are* $Q_i^{\perp}$, $M^{(i)}$, *and* $\tilde{\gamma}^{(i)}$, $i = 1, 2$. *Write the inverse matrices of* $M^{(1)}$ *and* $M^{(2)}$ *as block matrices* $\begin{bmatrix} \tilde{M}_1^{(1)} & \tilde{M}_2^{(1)} \end{bmatrix}$ *and* $\begin{bmatrix} \tilde{M}_1^{(2)} & \tilde{M}_2^{(2)} \end{bmatrix}$, *respectively. We have*

$$\tilde{M}_2^{(1)}\tilde{\gamma}_2^{(1)} = \tilde{M}_2^{(2)}\tilde{\gamma}_2^{(2)}.$$

Theorem 3

Further, assume that FQ is a full rank decomposition of C and $Q_{(1)}^{\perp}$, $Q_{(2)}^{\perp}$ are two orthogonal complement subspaces of Q. The corresponding transformation matrices and transformed parameters are $M^{(1)}$, $M^{(2)}$ and $\tilde{\boldsymbol{\gamma}}^{(1)}$, $\tilde{\boldsymbol{\gamma}}^{(2)}$. Write the inverse matrices of $M^{(1)}$ and $M^{(2)}$ as block matrices $\begin{bmatrix} \tilde{M}_1^{(1)} & \tilde{M}_2^{(1)} \end{bmatrix}$ and $\begin{bmatrix} \tilde{M}_1^{(2)} & \tilde{M}_2^{(2)} \end{bmatrix}$, respectively. We have

$$\tilde{M}_2^{(1)} \tilde{\boldsymbol{\gamma}}_2^{(1)} = \tilde{M}_2^{(2)} \tilde{\boldsymbol{\gamma}}_2^{(2)}.$$

Computing $Q^{\perp}$

- Since the choice of Q and $Q^{\perp}$ does not impact the reverse transformation of $\tilde{M}_2\tilde{\boldsymbol{\gamma}}_2$ to $\boldsymbol{\gamma}$ when $Q\boldsymbol{\gamma} = \mathbf{0}$, we utilize singular value decomposition (SVD) to obtain Q and $Q^{\perp}$. The following proposition states how to obtain Q and $Q^{\perp}$ through SVD.
- Proposition 1: *Let $C = UBV^T$ be a singular value decomposition of C, where B is a diagonal $q \times n$ matrix with non-negative real numbers on the diagonal, U and V are $q \times q$ and $n \times n$ orthogonal matrices containing the left and right singular vectors, respectively. The columns of V corresponding to singular values of C make up a basis for Q, and the columns of V corresponding to vanishing singular values of C make up a basis for $Q^{\perp}$.*

Quantification of Evidence: Plausibility Index

- The Plausibility Index (PI) is developed in Tilki et al. (2019) within the frequentist framework to assess the evidence of equivalence for the risk of prostate cancer-specific mortality and all-cause mortality between treatments.
- In Tilki et al. (2019), PI is defined under χ^2 distribution with one degree of freedom as

$$\text{PI} = T_0 f(T_0) + (1 - F(T_0)), \tag{5}$$

  where T_0 is the observed χ^2 test statistic, and $f(t)$ and $F(t)$ denote the probability density function and the cumulative distribution function of the χ^2 distribution with one degree of freedom.
- However, this definition of PI is difficult to extend to a χ^2_d test statistic with d degrees of freedom for $d > 1$.

The General Definition of Plausibility Index

- Let $\hat{\tilde{\boldsymbol{\gamma}}}_1$ be the MLE of $\tilde{\boldsymbol{\gamma}}_1$, which is calculated as $\hat{\tilde{\boldsymbol{\gamma}}}_1 = Q\boldsymbol{y}$.
- Following the asymptotic normaility of MLE, we have

$$\hat{\tilde{\boldsymbol{\gamma}}}_1 \sim N_p(\tilde{\boldsymbol{\gamma}}_1, \mathrm{Var}(\hat{\tilde{\boldsymbol{\gamma}}}_1)), \tag{6}$$

  where $\mathrm{Var}(\hat{\tilde{\boldsymbol{\gamma}}}_1) = (Q\widehat{\Sigma}Q^\top)$.
- Let ϕ denote the pdf of $\hat{\tilde{\boldsymbol{\gamma}}}_1$ under $H_0 : \tilde{\boldsymbol{\gamma}}_1 = 0$, which is a p-dimensional multivariate normal.
- To assess the strength of evidence in favor of $H_0 : \tilde{\boldsymbol{\gamma}}_1 = 0$, we propose PI as

$$\mathrm{PI}(\tilde{\boldsymbol{\gamma}}_1 = \mathbf{0}) = \int \phi(\boldsymbol{t}) \wedge \phi(\hat{\tilde{\boldsymbol{\gamma}}}_1)\, d\boldsymbol{t}. \tag{7}$$

- By standardization of $\hat{\tilde{\boldsymbol{\gamma}}}_1$, we can rewrite (6) as

$$\mathrm{Var}(\hat{\tilde{\boldsymbol{\gamma}}}_1)^{-\frac{1}{2}}(\hat{\tilde{\boldsymbol{\gamma}}}_1 - \tilde{\boldsymbol{\gamma}}_1) \sim N_p(\mathbf{0}, \boldsymbol{I}).$$

- Define $\boldsymbol{z} = \mathrm{Var}(\hat{\tilde{\boldsymbol{\gamma}}}_1)^{-\frac{1}{2}}(\hat{\tilde{\boldsymbol{\gamma}}}_1 - \tilde{\boldsymbol{\gamma}}_1)$. An alternative definition of PI follows naturally, which is given by

$$\mathrm{PI}_{\boldsymbol{z}}(\tilde{\boldsymbol{\gamma}}_1 = \mathbf{0}) = \int \phi_0(\boldsymbol{t}) \wedge \phi_0(\boldsymbol{z})\, d\boldsymbol{t}, \tag{8}$$

  where ϕ_0 is the pdf of p-dimensional standard multivariate normal random variable.

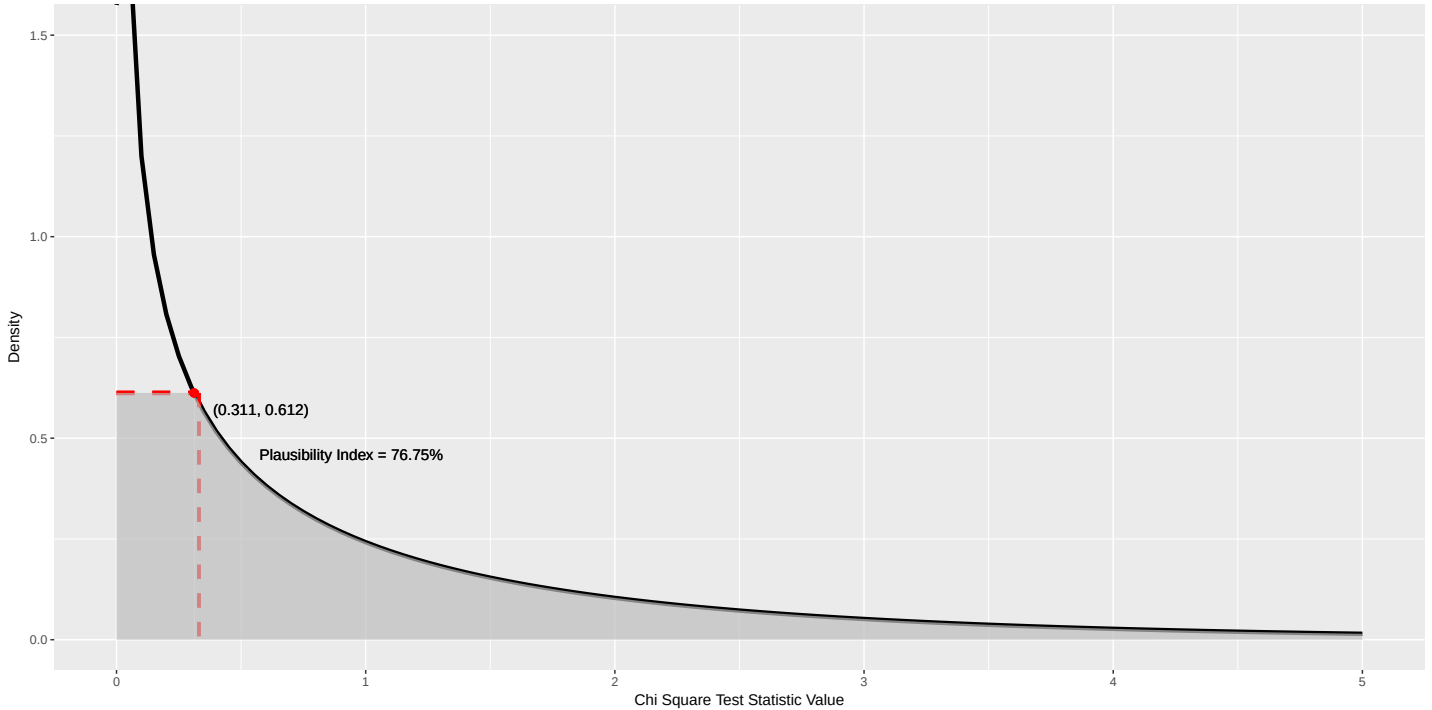


Figure 1: Graphical Illustration of How the Plausibility Index Value Is Calculated for the Comparison of Treatment With MaxRP vs MaxRT for the End Point of the Risk of PCSM

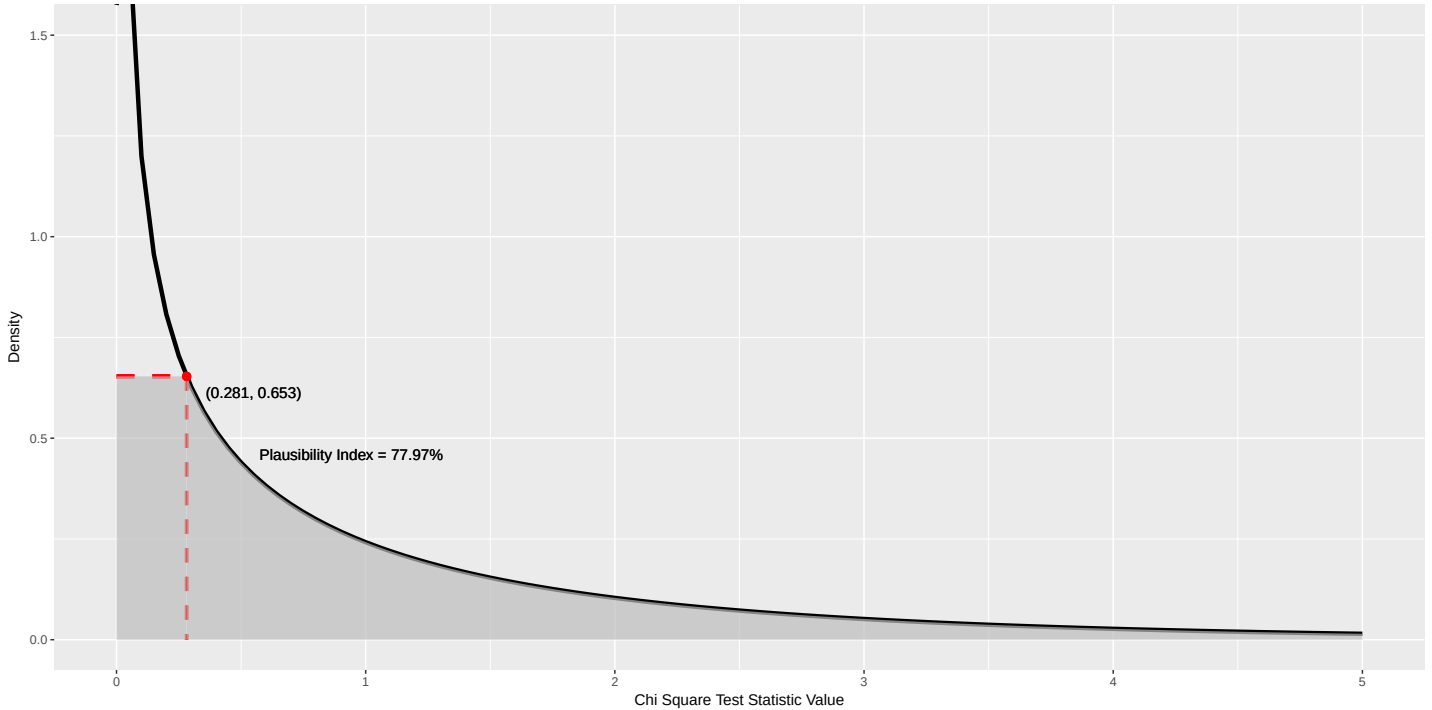


Figure 2: Graphical Illustration of How the Plausibility Index Value Is Calculated for the Comparison of Treatment With MaxRP vs MaxRT for the End Point of the Risk of ACM

Properties of Plausibility Index

- It turns out that the PI defined in (7) and (8) coincide with each other.
- Proposition 2: PI *remains unchanged under the standardization of multivariate normal distribution.*
- The PI is well calibrated since $0 \leq \text{PI} \leq 1$.
- Under $H_0 : \tilde{\boldsymbol{\gamma}}_1 = 0$, the maximum value of PI is attained when $\hat{\tilde{\boldsymbol{\gamma}}}_1 = \mathbf{0}$.
- When $\hat{\tilde{\boldsymbol{\gamma}}}_1$ is far away from the center given by $\tilde{\boldsymbol{\gamma}}_1 = \mathbf{0}$, the value of PI tends to be small.
- Thus, a PI close to 0 implies less evidence in favor of H_0, and a PI close to 1 gives more evidence in favor of H_0.

Relationship between PI and p-value

Theorem 4: *Let $p(H_0)$ denote the p-value. We have*

$$PI(H_0) = c_1(k, \boldsymbol{z}_0^\top \boldsymbol{z}_0) + p(H_0),$$

where $c_1(k, \boldsymbol{z}_0^\top \boldsymbol{z}_0) = \frac{1}{2^{\frac{k}{2}-1}\Gamma(\frac{k}{2})} \exp(-\frac{1}{2}\boldsymbol{z}_0^\top \boldsymbol{z}_0) \frac{\sqrt{\boldsymbol{z}_0^\top \boldsymbol{z}_0}^k}{k}$.

Conditional PI

- We have $\tilde{\gamma}_1 | D_0 \sim \mathcal{N}_r(Q\boldsymbol{y}, Q\Sigma Q^\top)$.
- Let $\tilde{\gamma}_1 = (\tilde{\gamma}_{10}^\top, \tilde{\gamma}_{11}^\top)^\top$, where $\tilde{\gamma}_{10}^\top \in \mathcal{R}^{r-1}$ is the vector to test heterogeneity, and $\tilde{\gamma}_{11}^\top \in \mathcal{R}$ is to test consistency. Partition $Q = \begin{bmatrix} Q_0 \\ Q_1 \end{bmatrix}$, write $Q\Sigma Q^\top = \begin{bmatrix} Q_0\Sigma Q_0^\top & Q_0\Sigma Q_1^\top \\ Q_1\Sigma Q_0^\top & Q_1\Sigma Q_1^\top \end{bmatrix} = \begin{bmatrix} \Omega_{00} & \Omega_{01} \\ \Omega_{10} & \Omega_{11} \end{bmatrix}$ in a block matrix form.
- Then we have:

$$\tilde{\gamma}_1 = \begin{bmatrix} \tilde{\gamma}_{10} \\ \tilde{\gamma}_{11} \end{bmatrix} \sim \mathcal{N}_r(\begin{bmatrix} Q_0\boldsymbol{y} \\ Q_1\boldsymbol{y} \end{bmatrix}, \begin{bmatrix} Q_0\Sigma Q_0^\top & Q_0\Sigma Q_1^\top \\ Q_1\Sigma Q_0^\top & Q_1\Sigma Q_1^\top \end{bmatrix})$$

- Thus, we have

$$\tilde{\gamma}_{11} | \tilde{\gamma}_{10} = 0 \sim \mathcal{N}_r(Q_1\boldsymbol{y} - \Omega_{10}\Omega_{00}^{-1}Q_0\boldsymbol{y}, \Omega_{11} - \Omega_{10}\Omega_{00}^{-1}\Omega_{01}).$$

- Theorem 5: *The relationship between Bucher's p value and the conditional PI is*

$$PI(\tilde{\gamma}_{11} | \tilde{\gamma}_{10} = 0) = c_1(1, z_0^\top z_0) + p_{Bucher}.$$

Outline

Test Results for Relative Treatment Effects Homogeneity

Pair	Trials	DF	p	PI	Pair	Trials	DF	p	PI
S10-SE20	[1, 3, 6]	2	0.999	1.000	A10-A20	[7, 9, 11, 12, 14, 16, 19]	6	0.424	0.647
S40-SE80	[1, 3, 6]	2	0.973	1.000	S40-SE10	[1, 3, 6]	2	0.416	0.780
S20-SE40	[1, 3, 4, 6]	3	0.935	0.994	S80-SE40	[1, 3, 6]	2	0.402	0.768
A40-SE20	[7, 9, 12, 14]	3	0.923	0.993	S40-SE40	[1, 3, 6]	2	0.389	0.755
SE10-SE40	[1, 3, 4, 6, 7]	4	0.906	0.985	A20-SE20	[7, 9, 12, 14]	3	0.376	0.683
A10-R20	[16, 19]	1	0.869	0.999	S40-S80	[1, 3, 6]	2	0.351	0.718
E10-SE10	[1, 3, 6]	2	0.869	0.991	A10-SE40	[7, 9, 12, 14]	3	0.342	0.646
E10-SE80	[1, 3, 6]	2	0.861	0.990	E10-SE20	[1, 3, 6]	2	0.326	0.691
A80-R40	[19, 21]	1	0.839	0.998	R10-R20	[8, 16, 19]	2	0.321	0.684
S20-SE10	[1, 3, 4, 6]	3	0.824	0.969	SE10-SE80	[1, 3, 6, 7]	3	0.320	0.621
SE20-SE80	[1, 3, 6, 7, 8]	4	0.775	0.938	E10-S80	[1, 3, 6]	2	0.311	0.673
E10-SE40	[1, 3, 6]	2	0.763	0.969	SE10-SE20	[1, 3, 4, 5, 6, 7]	5	0.305	0.536
A10-A80	[7, 11, 19]	2	0.760	0.968	R10-R5	[17, 18, 19, 23]	3	0.300	0.597
E10-S40	[1, 3, 6]	2	0.754	0.966	A40-A80	[7, 11, 19]	2	0.299	0.659
A20-R20	[16, 19, 25]	2	0.697	0.948	S20-SE80	[1, 3, 6]	2	0.284	0.640
A20-SE40	[7, 9, 12, 14]	3	0.689	0.916	E10-S10	[1, 3, 6]	2	0.262	0.611
A20-A40	[7, 9, 11, 12, 14, 19]	5	0.686	0.876	SE20-SE40	[1, 3, 4, 6, 7, 8, 9, 12, 14]	8	0.235	0.402
R20-R40	[8, 19]	1	0.678	0.982	A10-SE10	[5, 7]	1	0.228	0.692
S80-SE20	[1, 3, 6]	2	0.677	0.940	S20-S40	[1, 3, 6]	2	0.188	0.500
R10-R40	[8, 19]	1	0.675	0.981	S20-SE20	[1, 3, 4, 6, 13]	4	0.182	0.395
A10-SE20	[5, 7, 9, 12, 14]	4	0.663	0.878	S80-SE10	[1, 3, 6]	2	0.182	0.490
S10-S80	[1, 3, 6]	2	0.637	0.923	S10-SE40	[1, 3, 6]	2	0.148	0.428
S40-SE20	[1, 3, 6]	2	0.585	0.898	S80-SE80	[1, 3, 6, 15]	3	0.135	0.349
S10-SE80	[1, 3, 6]	2	0.585	0.898	S20-S80	[1, 3, 6]	2	0.133	0.399
A40-SE40	[7, 9, 12, 14]	3	0.571	0.847	S10-SE10	[1, 3, 6]	2	0.067	0.245
A20-A80	[7, 11, 19]	2	0.561	0.884	S10-S20	[1, 3, 6]	2	0.032	0.140
A10-R5	[17, 18, 19, 23]	3	0.556	0.837	SE40-SE80	[1, 3, 6, 7, 8]	4	0.022	0.072
E10-S20	[1, 3, 6]	2	0.548	0.877	A10-R10	[16, 17, 18, 19, 23, 24, 27, 28, 29]	8	0.016	0.041
S10-S40	[1, 3, 6]	2	0.524	0.861	A20-R10	[16, 19, 20, 22, 26]	4	0.000	0.000
A10-A40	[7, 9, 11, 12, 14, 19]	5	0.486	0.725					

List of Inconsistency Testable Loops and Test Results for Loop Consistency

Loop X-Y-Z	X-Y	X-Z	Y-Z	Bucher's p	condPI	Loop X-Y-Z	X-Y	X-Z	Y-Z	Bucher's p	condPI
A10-R10-SE20	[16, 17, 18, 19, 23, 24, 27, 28, 29]	[5, 7, 9, 12, 14]	[8]	0.972	1.000	A20-R10-SE20	[16, 19, 20, 22, 26]	[7, 9, 12, 14]	[8]	0.448	0.902
A80-E10-SE20	[11]	[7]	[1, 3, 6]	0.964	1.000	A40-R20-SE80	[19]	[7]	[8]	0.430	0.891
A10-E10-SE10	[11]	[5, 7]	[1, 3, 6]	0.955	1.000	A10-R20-SE20	[16, 19]	[5, 7, 9, 12, 14]	[8]	0.414	0.881
A10-R20-SE80	[16, 19]	[7]	[8]	0.949	1.000	A40-R40-SE40	[19]	[7, 9, 12, 14]	[8]	0.414	0.881
A10-E10-SE40	[11]	[7, 9, 12, 14]	[1, 3, 6]	0.944	1.000	A20-R40-SE40	[19]	[7, 9, 12, 14]	[8]	0.384	0.860
A20-R40-SE20	[19]	[7, 9, 12, 14]	[8]	0.938	1.000	A40-E10-SE10	[11]	[7]	[1, 3, 6]	0.376	0.854
A80-R20-SE20	[19]	[7]	[8]	0.894	0.999	A40-R40-SE80	[19]	[7]	[8]	0.294	0.777
A10-R40-SE80	[19]	[7]	[8]	0.883	0.999	A80-R10-SE40	[19]	[7]	[8]	0.285	0.767
A40-R40-SE20	[19]	[7, 9, 12, 14]	[8]	0.853	0.998	A80-R10-SE80	[19]	[7]	[8]	0.278	0.759
A40-R20-SE20	[19]	[7, 9, 12, 14]	[8]	0.848	0.998	A40-E10-SE40	[11]	[7, 9, 12, 14]	[1, 3, 6]	0.264	0.741
A10-E10-SE20	[11]	[5, 7, 9, 12, 14]	[1, 3, 6]	0.806	0.996	A80-R40-SE80	[19, 21]	[7]	[8]	0.253	0.728
R10-S20-SE40	[26]	[8]	[1, 3, 4, 6]	0.771	0.994	A40-E10-SE20	[11]	[7, 9, 12, 14]	[1, 3, 6]	0.213	0.671
A20-R20-SE20	[16, 19, 25]	[7, 9, 12, 14]	[8]	0.712	0.987	A20-R20-SE80	[16, 19, 25]	[7]	[8]	0.210	0.665
A10-R40-SE20	[19]	[5, 7, 9, 12, 14]	[8]	0.710	0.987	A40-R20-SE40	[19]	[7, 9, 12, 14]	[8]	0.207	0.661
A80-R40-SE20	[19, 21]	[7]	[8]	0.697	0.985	A20-E10-S20	[11]	[26]	[1, 3, 6]	0.198	0.646
A20-E10-SE10	[11]	[7]	[1, 3, 6]	0.686	0.983	A20-R40-SE80	[19]	[7]	[8]	0.197	0.645
A80-E10-SE80	[11]	[7]	[1, 3, 6]	0.686	0.983	A20-E10-SE80	[11]	[7]	[1, 3, 6]	0.188	0.630
A20-E10-SE40	[11]	[7, 9, 12, 14]	[1, 3, 6]	0.679	0.982	A40-R10-SE80	[19]	[7]	[8]	0.170	0.596
A40-R10-SE40	[19]	[7, 9, 12, 14]	[8]	0.669	0.980	A10-R40-SE40	[19]	[7, 9, 12, 14]	[8]	0.165	0.588
A80-R10-SE20	[19]	[7]	[8]	0.626	0.971	A80-R40-SE40	[19, 21]	[7]	[8]	0.094	0.423
A20-E10-SE20	[11]	[7, 9, 12, 14]	[1, 3, 6]	0.613	0.968	A20-R20-SE40	[16, 19, 25]	[7, 9, 12, 14]	[8]	0.090	0.411
A10-E10-SE80	[11]	[7]	[1, 3, 6]	0.605	0.966	A40-E10-SE80	[11]	[7]	[1, 3, 6]	0.083	0.391
A80-R20-SE80	[19]	[7]	[8]	0.603	0.965	A10-R10-SE40	[16, 17, 18, 19, 23, 24, 27, 28, 29]	[7, 9, 12, 14]	[8]	0.078	0.376
R10-S20-SE20	[26]	[8]	[1, 3, 4, 6, 13]	0.586	0.961	A80-R20-SE40	[19]	[7]	[8]	0.075	0.366
A80-E10-SE10	[11]	[7]	[1, 3, 6]	0.584	0.960	A10-R20-SE40	[16, 19]	[7, 9, 12, 14]	[8]	0.038	0.230
A10-R10-SE80	[16, 17, 18, 19, 23, 24, 27, 28, 29]	[7]	[8]	0.579	0.958	A20-R10-SE80	[16, 19, 20, 22, 26]	[7]	[8]	0.036	0.223
A40-R10-SE20	[19]	[7, 9, 12, 14]	[8]	0.561	0.953	A20-S20-SE10	[26]	[7]	[1, 3, 4, 6]	0.026	0.174
R10-S20-SE80	[26]	[8]	[1, 3, 6]	0.503	0.930	A20-S20-SE40	[26]	[7, 9, 12, 14]	[1, 3, 4, 6]	0.004	0.039
A80-E10-SE40	[11]	[7]	[1, 3, 6]	0.489	0.924	A20-S20-SE20	[26]	[7, 9, 12, 14]	[1, 3, 4, 6, 13]	0.002	0.020
A20-R10-SE40	[16, 19, 20, 22, 26]	[7, 9, 12, 14]	[8]	0.462	0.910	A20-S20-SE80	[26]	[7]	[1, 3, 6]	0.001	0.011

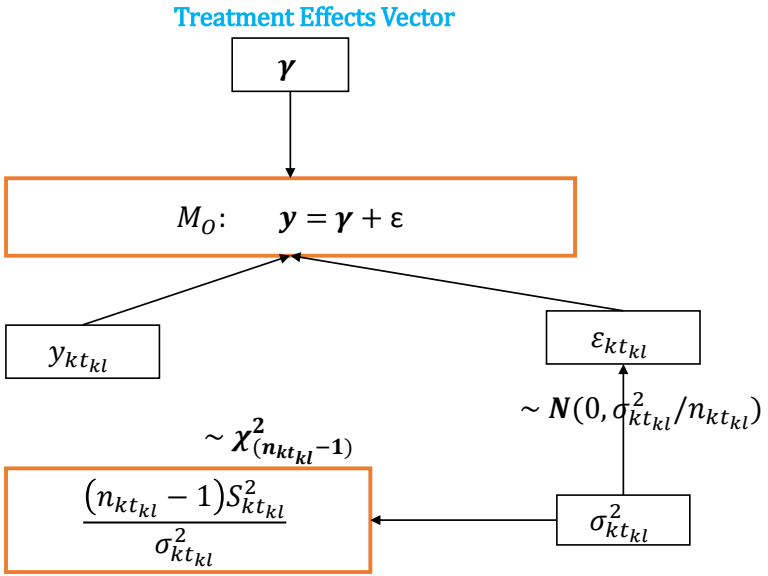
Outline

Concluding Remarks

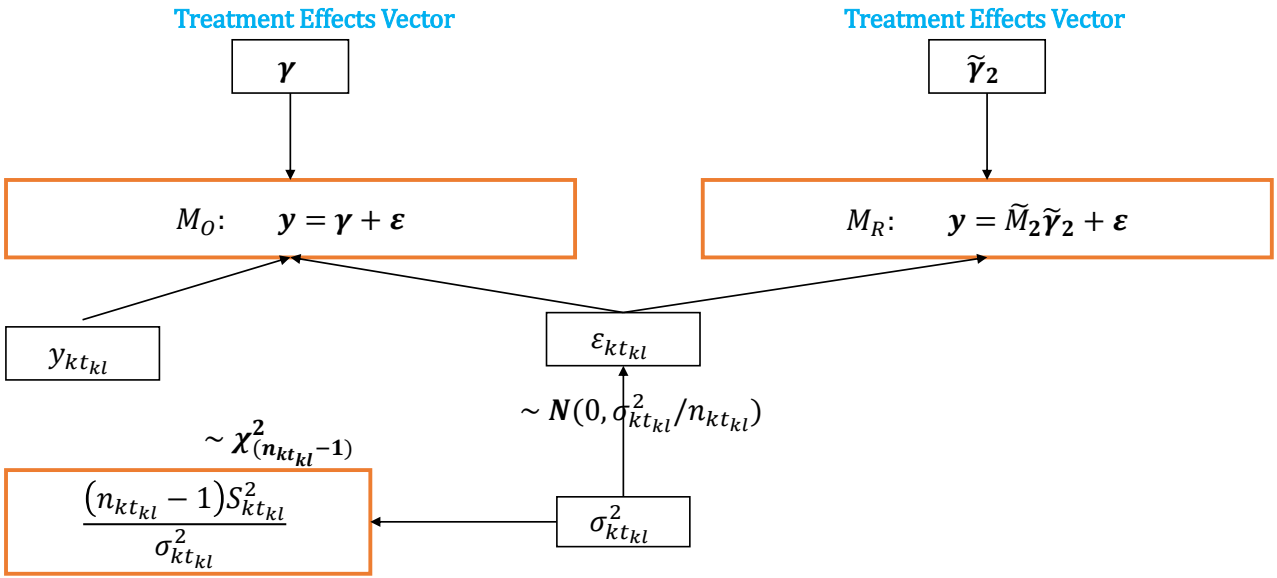
- We construct general linear hypotheses to investigate homogeneity/consistency under the saturated fixed effects model without any assumptions.
- A general algorithm is developed to compute the contrast matrix under homogeneity/consistency assumptions.
- We develop a very efficient algorithm to compute inconsistency testable loops.
- We also develop an algorithm to check if a NMA network is a connected network.
- The methods can also be extended to a more general fixed effects model and random effects regression models within the NMA framework.
- For the papers published by our group
  and software developed by us, please visit the website of our Meta-Analysis Lab:

http://merlot.stat.uconn.edu/packages/metapack/

General NMA Fixed Effects Model



General NMA Fixed Effects Model



See Li et al. (2019) and Yao et al. (2011, 2015).

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Thank you !