On Methodologies Associated with Meta-analysis

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Outline

- Systematic Evaluation
- Estimator
- Fixed Effect
- Simulation Result
- Peto method
- References
- Summary

Systematic Evaluation

- Many study design characteristics associated with a collection of studies could have a serious impact when assessing the evidence provided by the entire collection; e.g, in a meta-analysis.
- When "fundamental characteristics" are not accounted for in a valid and consistent manner, they could impinge upon the evidence provided by the studies under consideration, leading to calling into question the validity of any conclusions to be drawn from the meta-analysis

Systematic Evaluation

- Identification of these characteristics should be part of the systematic evaluation component that proceed a meta-analysis. Study design characteristics, for example, should be systematically evaluated to assess the level of "non-statistical homogeneity" associated with the studies under consideration.
- Homogeneity that can not be assessed via a statistical test

Systematic Evaluation

- A systematic evaluation is therefore key in any meta-analysis, and one of the elements from which the analyst can support a valid and meaningful assessment of the whole of the evidence.
- Any pre-analysis assessment typically involves multiple disciplines;
  - Clinical/Medical
  - Epidemiology
  - Statistical (involvement is crucial here)
- Should consider developing an assessment/analytical plan prior to conducting any meaningful assessment of the available evidence

Estimator

- Selection of an estimator should not be based solely on a computational convenience
- Rather, an estimator should be selected based on the objectives of interest
  - Association of treatment and mortality
  - Risk of liver toxicity
  - What about inclusion of covariates
- The limitations associated with any methodology should be included as part of the analytical plan; these limitations should be carefully evaluated when reporting the findings.
- Analytical Plan

Notation

- K independent studies $(K = 2, \cdots\cdots)$
- Y_i denote the observed effect size and θ_i population effect size
- Y_i is sufficient for θ_i
- Y_i differs from θ_i only due to sampling error
- Under fixed-effects: $\theta_1 = \theta_2 = \cdots\cdots = \theta_K = \theta$
- $Y_i \sim F_i$ with $E(Y_i) = \theta$ and $var(Y_i) = \sigma_i^2$

Under Fixed-effects

- Only source of uncertainty is due to sampling variation
- Conditional Model (fixed characteristics of studies associated with effect size)
  - no difference among the characteristics that could have an impact on the response
- Inference is to a "universe" of studies **similar** to those that have been conducted
- The universe consists of ensemble of studies each ensemble consistent of studies identical to those in the sample under consideration

Weighted Estimator

- $Y_i \sim F_i$ with $E(y_i) = \theta$, and $var(Y_i) = \sigma_i^2$
- $\theta_1 = \theta_2 = \cdots\cdots = \theta_K = \theta$
- Weighted estimator of θ under homogeneity
- $\hat{\theta} = \frac{\sum_i w_i y_i}{\sum_i w_i}$
- $w_i = \frac{1}{\sigma_i^2}$
- $\sigma_w^2 = var(\hat{\theta}) = \frac{1}{\sum_i w_i}$
- $\hat{se}(\hat{\theta}) = \sqrt{\frac{1}{\sum_i \hat{w}_i}}$

Weighted Estimator

- Uncertainty associated with estimating **w** was not accounted for it when estimating $se(\hat{\theta})$
- $\hat{\sigma}^2_w$ is a biased estimator (variance is under estimated, Li 1994)
- $\hat{\sigma}^2_w \leq \hat{\sigma}^2_{\text{min}} = \min_i \{\hat{\sigma}^2_i\}_{i=1}^K$ (follows directly)
- $\hat{\sigma}^2_w$ is too sensitive to the minimum of the estimated within study variance.
- $E(\hat{\theta}) < \theta$ (OR)

OR

- Let $y_i = OR_i$, and $Z_i = ln(Y_i)$
- Under fixed-effects we have a common OR across the K studies
- Assume only covariate is treatment assignment
- $z\hat{\sigma}_i^2 = \frac{1}{y_{trt}} + \frac{1}{n_{trt} - y_{trt}} + \frac{1}{y_{con}} + \frac{1}{n_{con} - y_{con}}$
- Could have issues associated with "Zero Events Problem"
- This is true in many meta-analysis examining safety, where the rareness of an event could naturally lead to empty cells

Zero Events Problem

- If you have a solution to the zero events problem, good for you, lets talk about it
- If you chose to add a quantity to accommodate for empty cells; such as 0.5
- Do this in a "robust" manner
- For example, examine the methodology under multiple values
- Your analysis should include a clear evaluation of empty cells
- Have a clear understanding of the limitations of any methodology used to account for empty cells

OR

- $s = \sum w_i$, and $s_i = \frac{w_i}{s}$, then $\sum s_i = 1$
- $\hat{\mu}_Z = \frac{\sum w_i z_i}{\sum w_i} = \sum s_i z_i$
- $\hat{\mu}_Z = ln(\prod y_i^{s_i})$
- $\hat{\mu}_Y = exp(\hat{\mu}_Z) = \prod y_i^{s_i}$
- Claim: $E(\hat{\mu}_Y) < \theta$

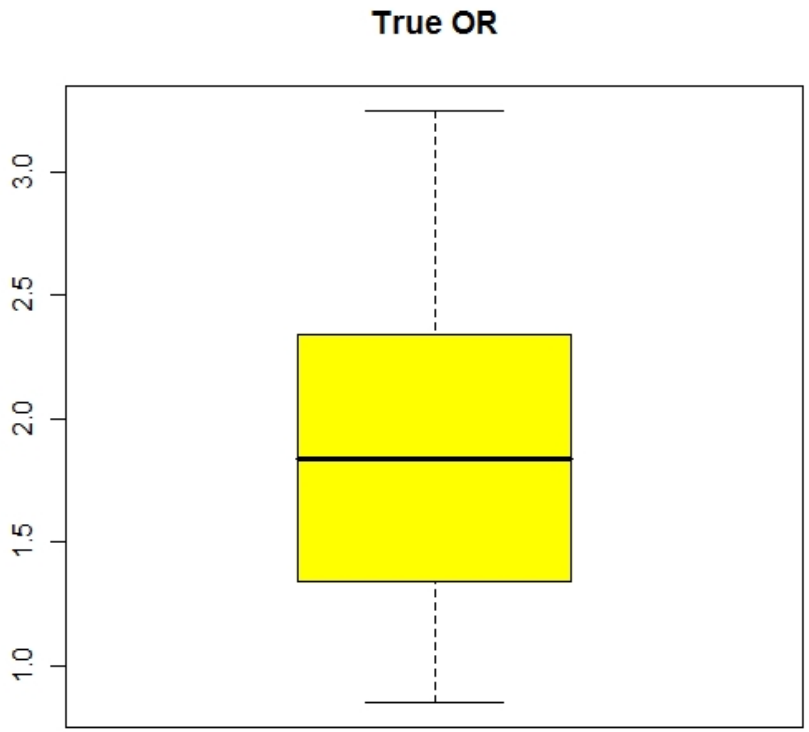
OR

- $$\begin{aligned} E(\hat{\mu}_Y) &= E(\prod_i Y_i^{s_i}) \\ &= \prod_i E(Y_i^{s_i}) < \prod_i E(Y_i)^{s_i} \\ &= \prod_i \theta^{s_i} = \theta^{\sum_i s_i} \\ &= \theta \end{aligned} \tag{1}$$

- The inequality follows by Jensen's inequality
- Biased estimator when transforming to the original scale

Simulation

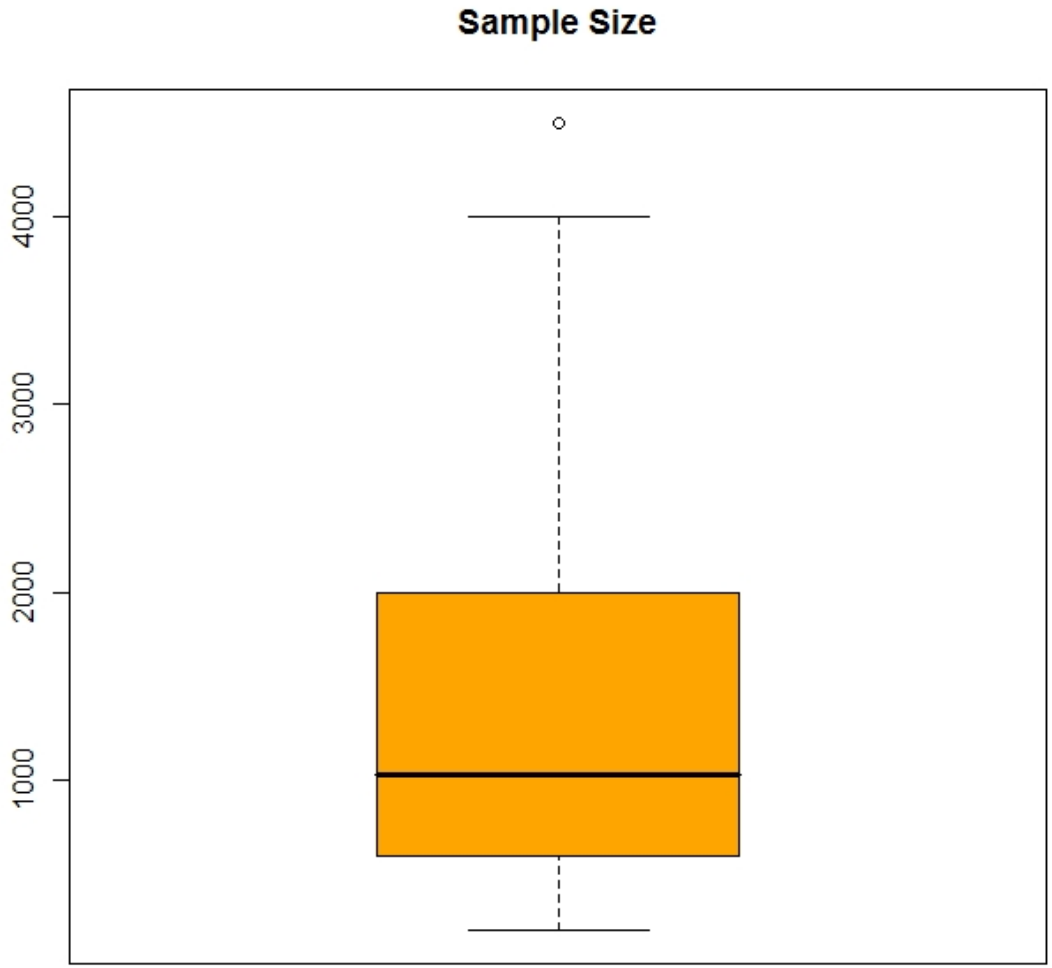
- Let $p_{con} = 0.10, 0.01$
- True OR:



Simulation

- $p_{trt} = \frac{ODDS_{con}(OR)}{1+ODDS_{con}(OR)}$
- Select total sample sizes at random from a pre-selected set of sample
- For each true value of the OR (100) generate 1000 meta-analysis
- Each meta-analysis consisted of 60 trials
- Generate the responses for each group as follows:
- $Y_{trt} \sim Bin(p_{trt}, N/2)$ and $Y_{con} \sim Bin(p_{con}, N/2)$
- We generated a total of 6000000 trials

Simulation



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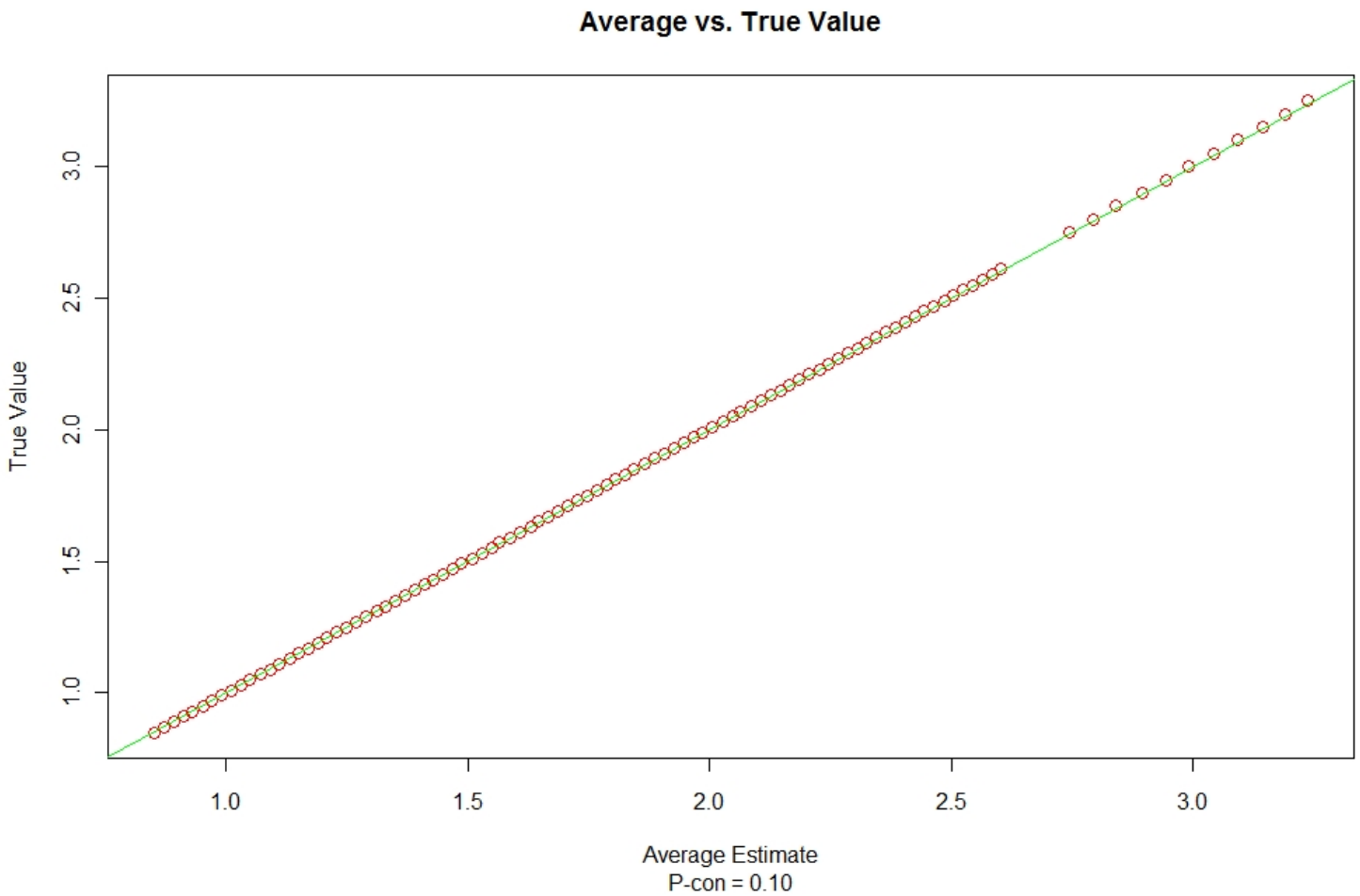

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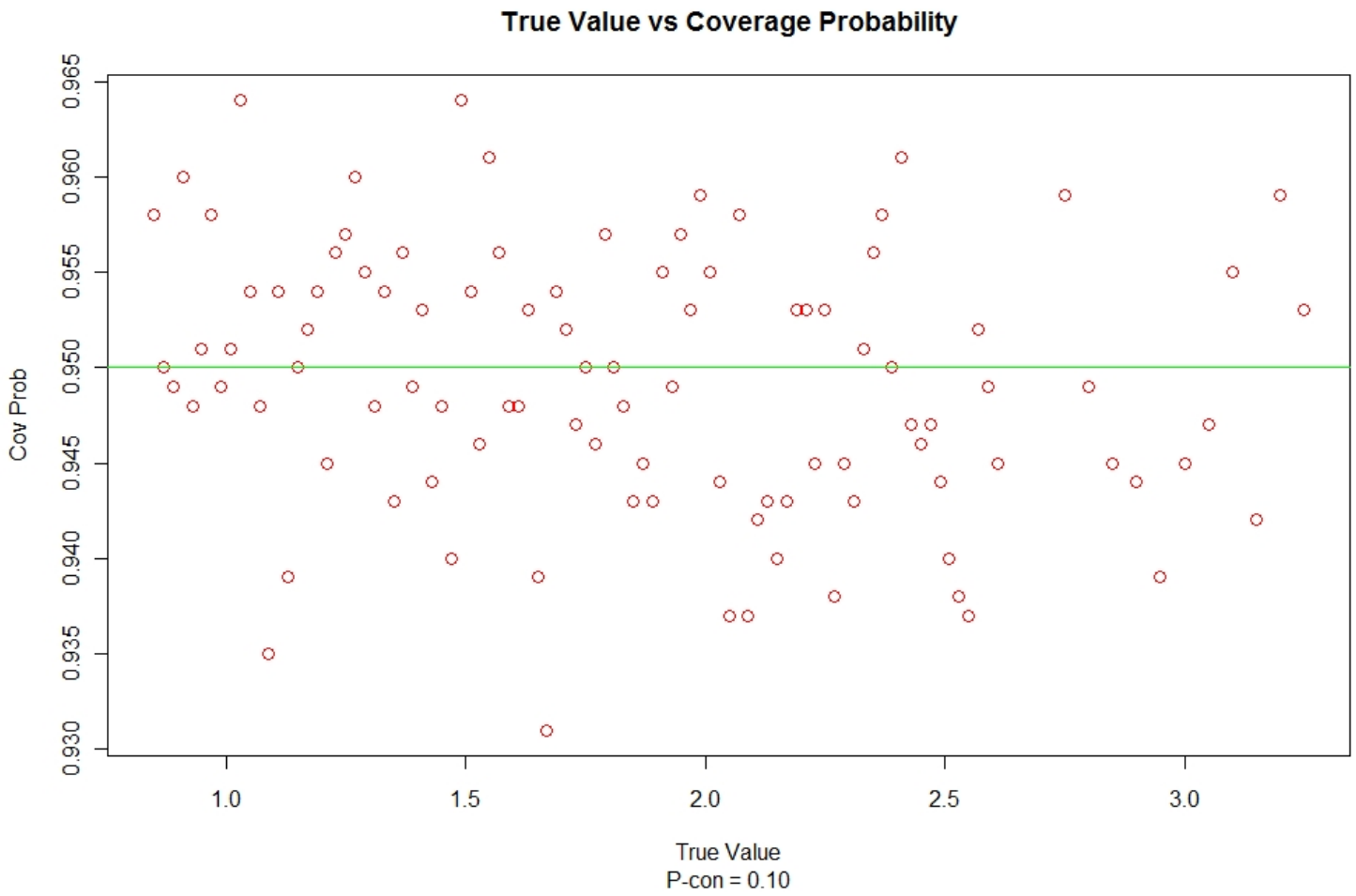

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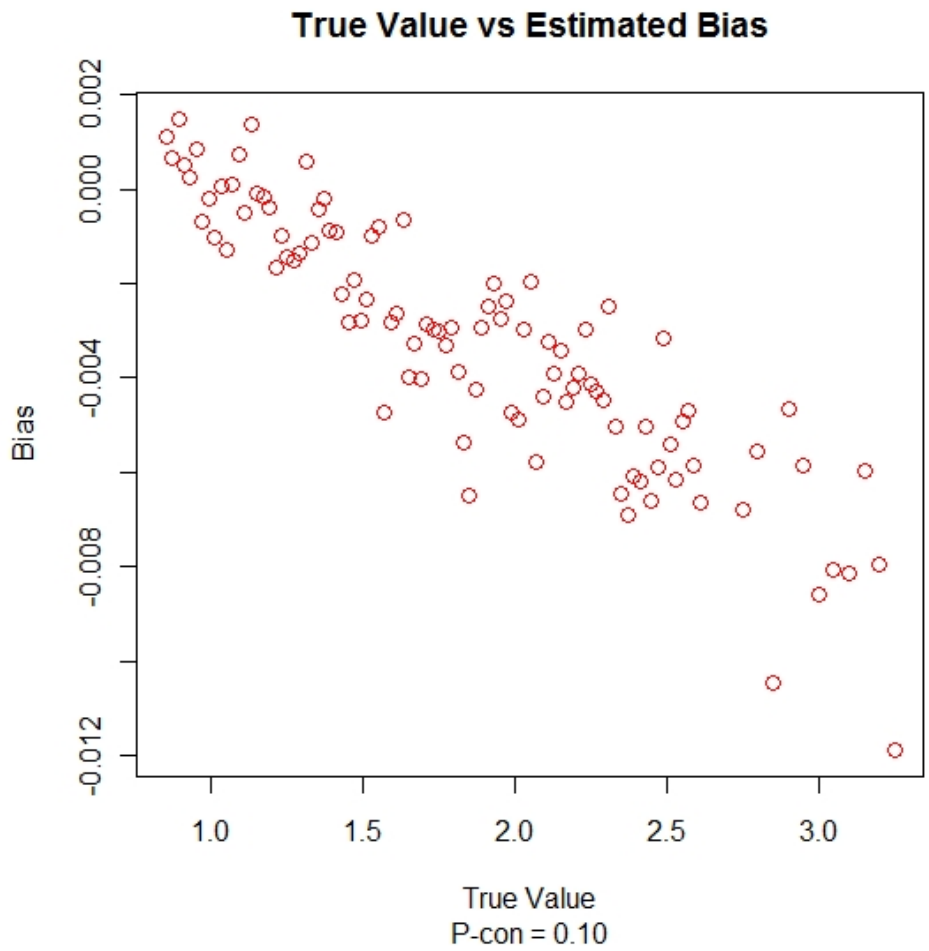

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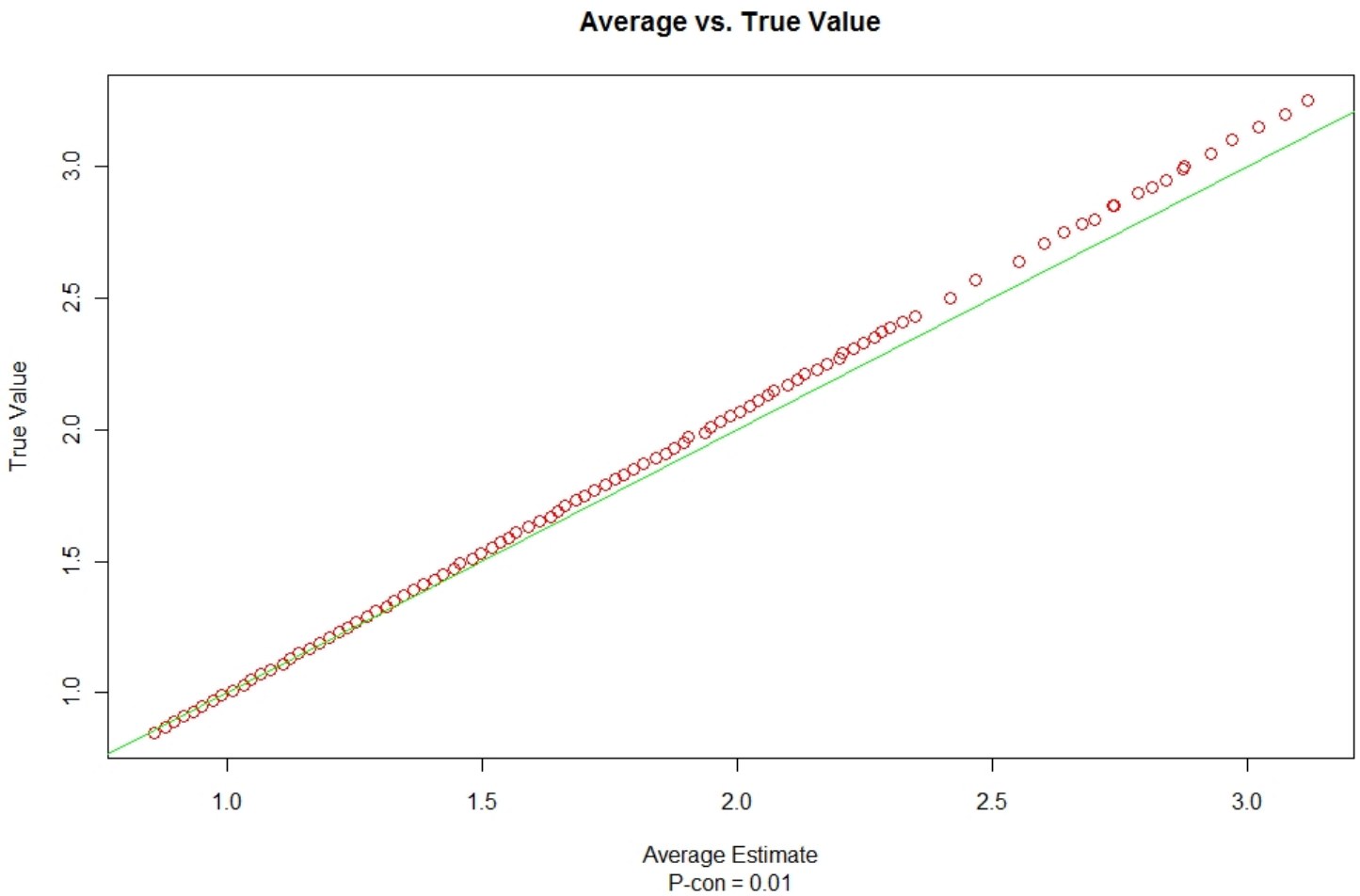

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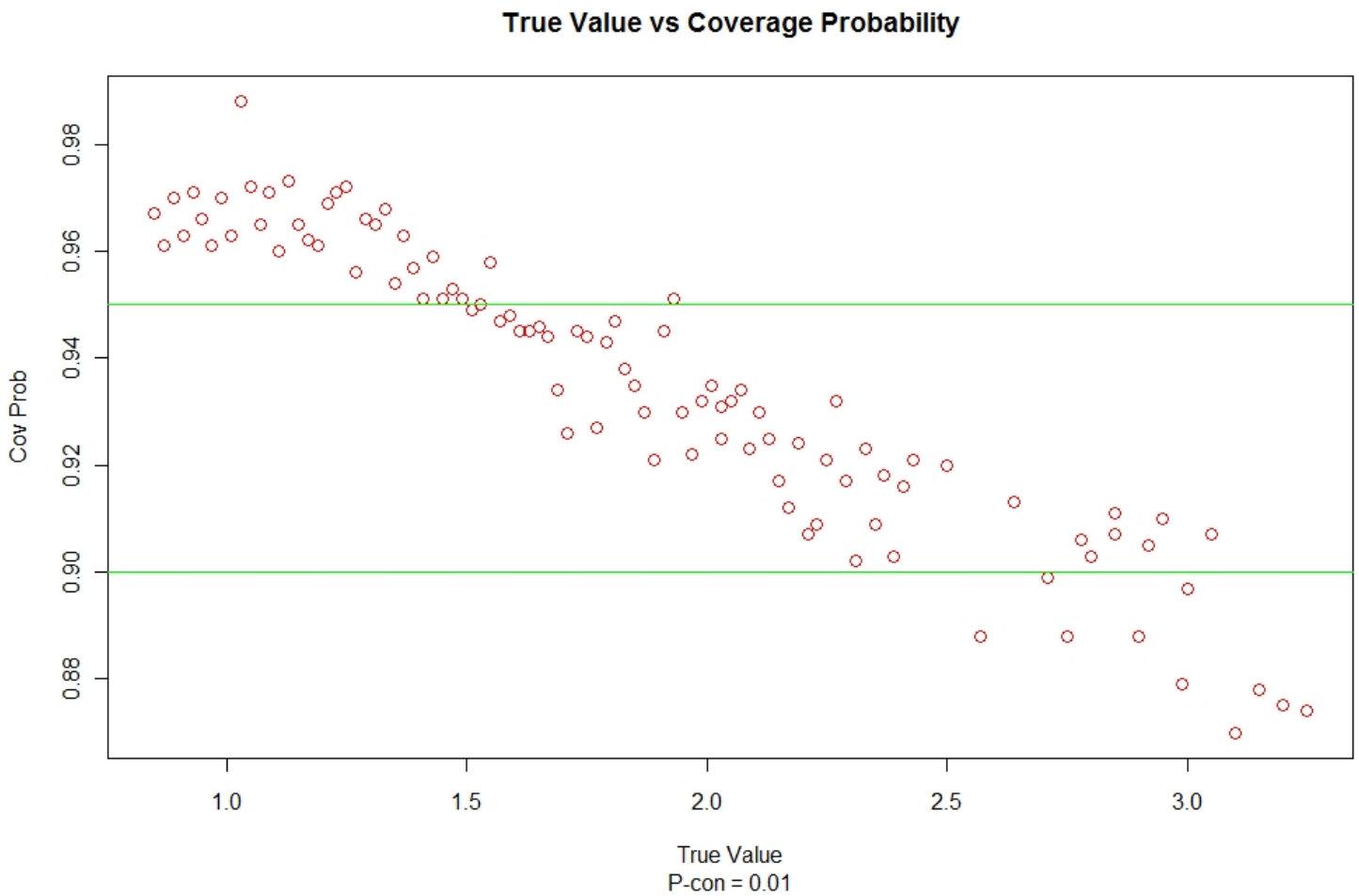

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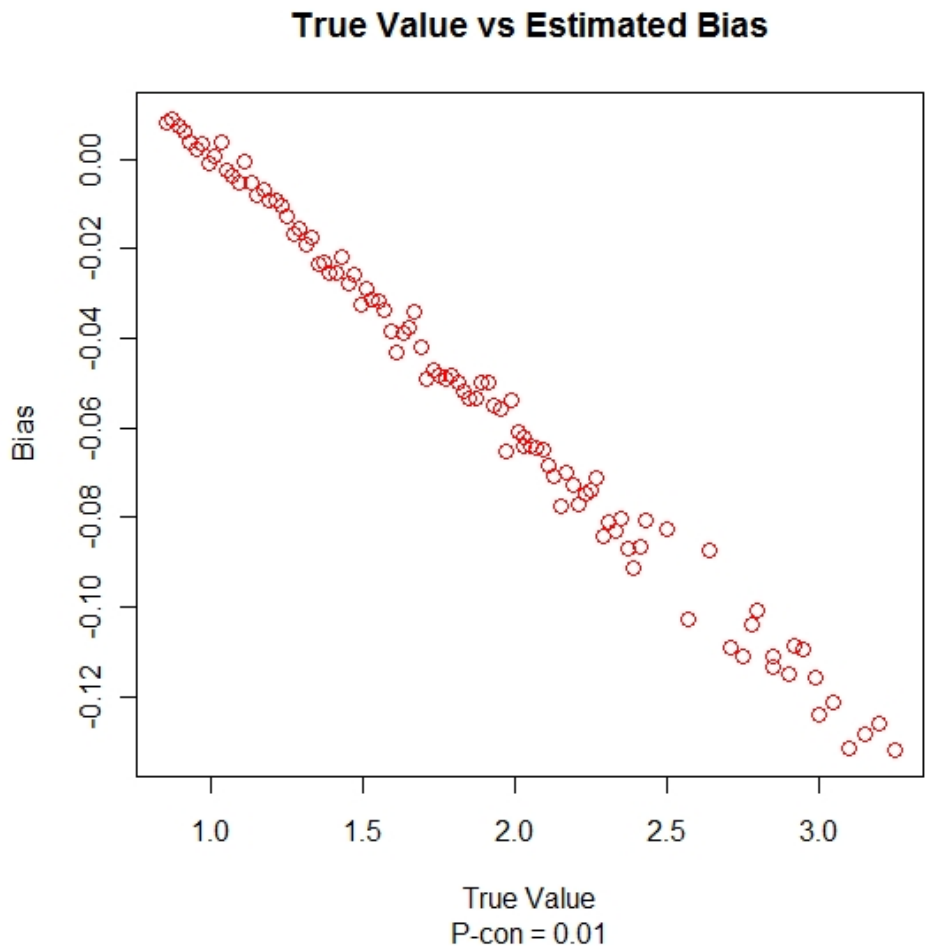


Peto Method *ORs*

- Can compute OR in the zero events case
- Can produce "high levels" of under estimation when true values are far from the null ($OR = 1$)
- Computations are conducted under the hypothesis that treatment is not different than control

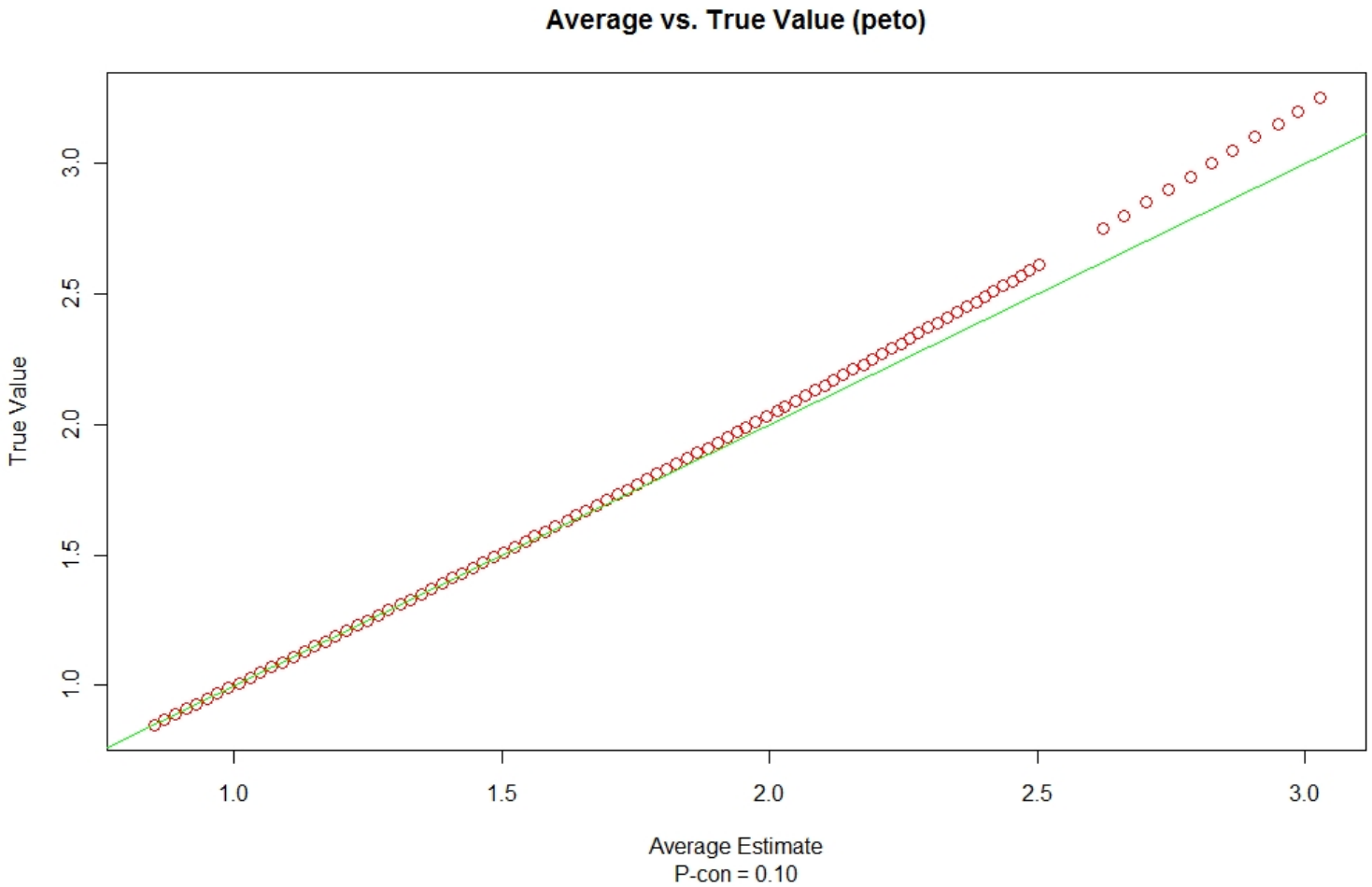
Peto Method *ORs*

- n_i = number of patients in i-th study
- n_{ti} = number of patients in treatment group
- d_i = total number of events
- O_i = number of events in treatment group
- E_i = expected number of event in trt = $\frac{n_{it}}{n_i} d_i$
- Computations are conducted under the hypothesis that treatment is not different than control

Peto Method *ORs*

- $OR_{peto} = exp\{\frac{\sum_{i=1}^{K}(O_i - E_i)}{\sum_{i=1}^{K} v_i}\}$
- $v_i = E_i(\frac{n_i - n_{ti}}{n_i})(\frac{n_i - d_i}{n_i - 1})$
- $var(Ln(OR_{peto})) = \sum_{i=1}^{K} v_i$
- $exp\{\frac{\sum_{i=1}^{K}(O_i - E_i) \pm Z_{\frac{\alpha}{2}}\sqrt{\sum_{i=1}^{K} v_i}}{\sum_{i=1}^{K} v_I}\}$

P-control = 0.10



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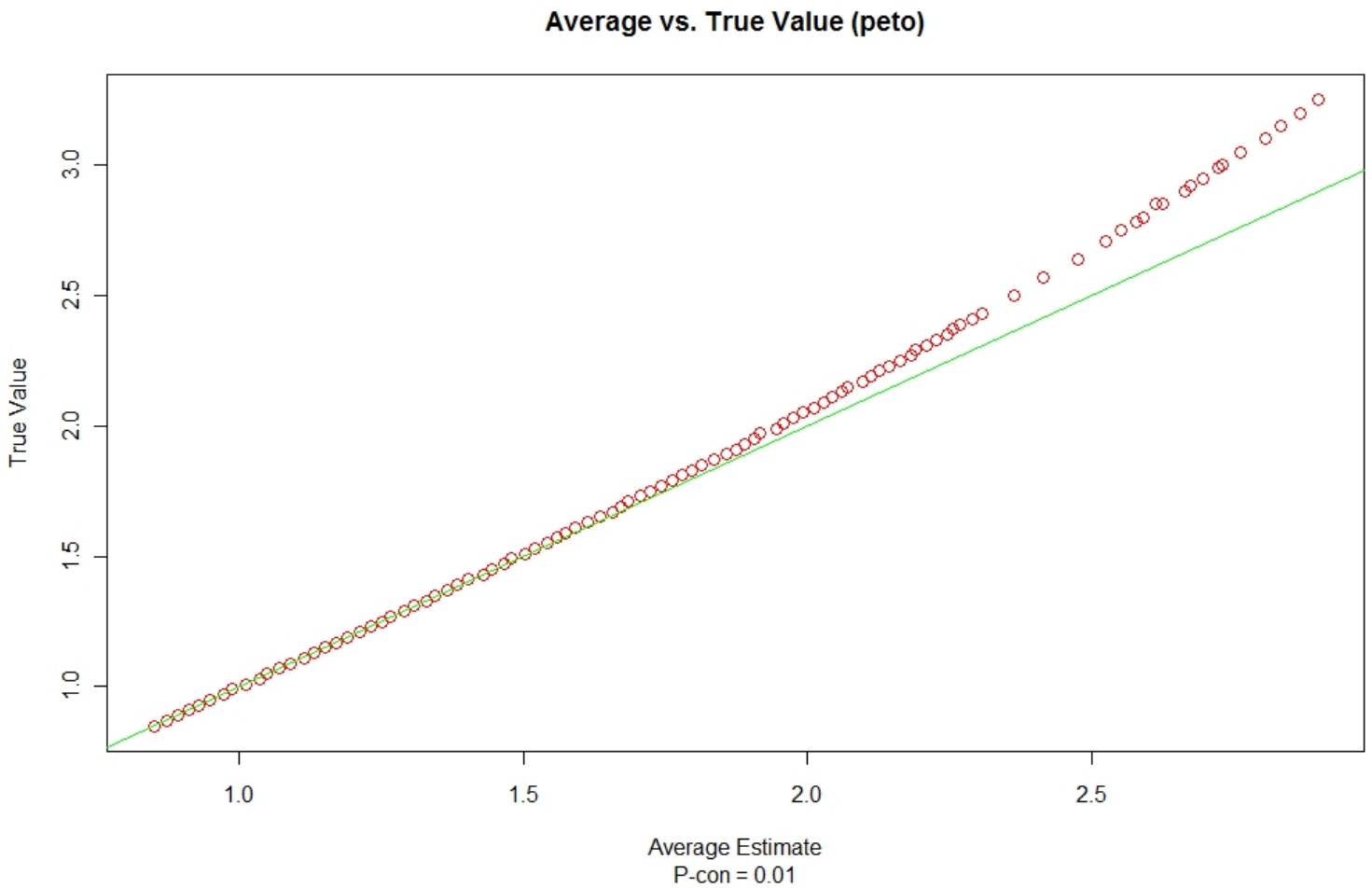

Some References

- Rebecca DerSimonia, Kaglu Kacker, Random-effects models for meta-analysis of clinical trial: An update. Contemporary Clinical trial 2007, 28: 105-14

- Alexander J Sutton, Julian P.T. Higgins, Recent developments in meta-analysis, Statistics in medicine 2008, 27: 625-650

- Yuanzhang Li, The bias of the commonly used estimate of variance in meta-analysis. Commun. Statist. Theory Method. 1994, 23 (4): 1063-1085

Summary

- Prior to conducting any assessment of the available evidence, consider developing an analytical plan ("protocol")
- A systematic evaluation of study design characteristics is a key component of any meta-analysis. A well conducted systematic evaluation is an essential component in supporting valid conclusions
- Selection of an estimator should not be based solely on a computational convenience. rather, an estimator should be selected based on a careful evaluation of the objectives of the meta-analysis

Summary

- The analytical plan should include a careful discussion on how to deal with studies with zero events
- Any statistical methodologies must be clearly supported in the analytical plan
- Note that the selected methodology might perform well in safety evaluation; however, if the the use of the methodology is not well supported in the analytical plan your conclusions call be call into question