Test confounding bias in exposure-response modeling for randomized concentration controlled trials

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Introduction

Confounding biases may occur in exposure-response modeling, since exposure levels are typically not randomized. Some study designs with randomized concentration controlled (RCC) trials [1] offer limited exposure control. But confounding bias may still exists, particularly when exposure is very variable. The randomization in such designs provides a tool to test potential confounding bias. We propose a test based on comparisons between the mean responses of randomized exposure ranges and the model prediction. The test does not require model assumptions. Bayesian bootstrapping is proposed to improve small sample properties. Performance of this approach is investigated by simulation and its implementation is illustrated by a hypothetical (yet realistic) scenario.

Randomized concentration controlled trial design

The issue of confounding bias in exposure-response modeling has been emphasized in the FDA guidance for exposure-response relationship (FDA,2003). Using RCC trials was recommended. In an RCC trial patients are randomized into multiple groups, each with a pre-determined concentration range. During the trial repeated concentration measures are taken from each patient and the dose is adjusted till the concentration is within the specified range. After the concentrations are in the target ranges PD is also measured as the response to the exposure in the target range.

As an example, we consider an RCC design with 2 ranges below and above 10ng/mL, with starting doses 5 and 15mg and dose adjustment step 30%. At each visit j a trough samples c_{ij} is taken and it follows the power model:

$$\log(c_{ij}) = \alpha_0 + \alpha \log(d_{ij}) + v_i + \varepsilon_{ij}, \;\; j = 1, ..., r$$

with a0=0,a=1, SD(vi)=0.5 and SD(epsi)=0.2. The PKPD model at stable concentration ci is

$$y_i = E_0 + E_{max}/(1 + EC_{50}/c_i) + Kv_i + e_i$$

where E0=1,Emax=1, EC50=10 and SD(ei)=0.2. Confounding is introduced if K is not 0. Figure 1 shows the data, fitted model and mean response of each range based on the model and randomization for K=0 (left) and K=0.3 (right)

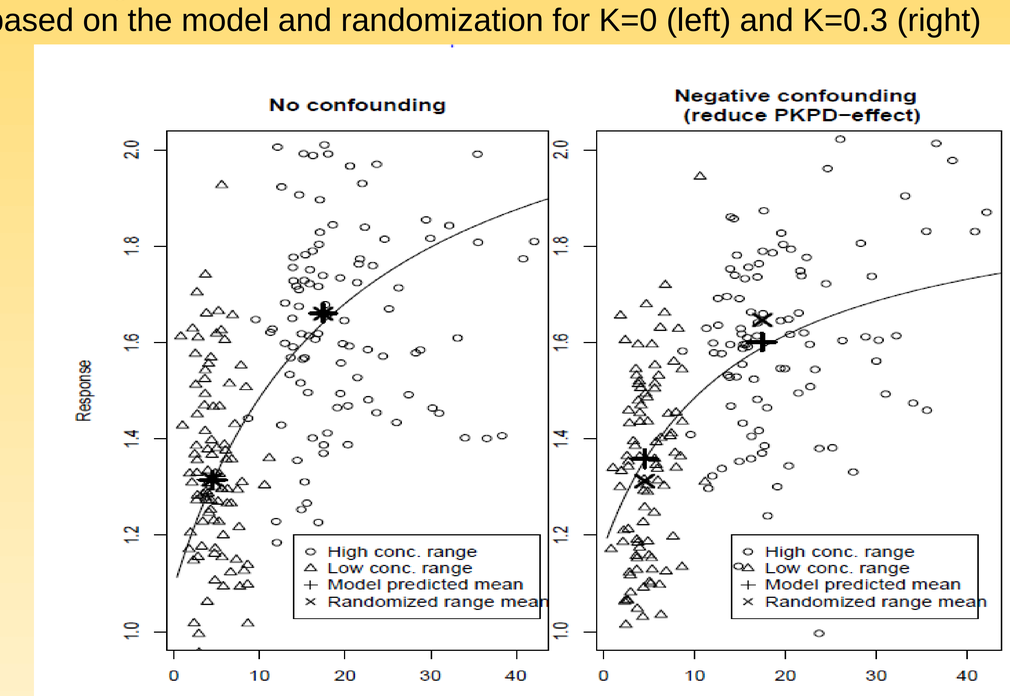

Figure 1: Concentration-response relationship generated from a Emax model with a two-range RCC design. The model based and randomization based mean responses estimates for both ranges are plotted at the expected median concentration of each range.

Randomized concentration ranges as instrumental variable

Let the PKPD model be $y_i = f(c_i, \beta) + Kv_i + e_i$

Randomization can be used as an IV to eliminate confouding bias.The ordinary least squares estimate solves equation

$$S(\beta) = \sum_{i=1}^{n} \frac{\partial f(c_i, \beta)}{\partial \beta}(y_i - f(c_i, \beta)) = 0 \qquad (1)$$

while the IV estimate {2-4] solves

$$S_{iv}(\beta) = \sum_{i=1}^{n} E_{c_i}\left(\frac{\partial f(c_i, \beta)}{\partial \beta} | R_i\right)(y_i - f(c_i, \beta)) = 0 \qquad (2)$$

where Ri is the randomization indicator, i.e., $\frac{\partial f(c_i, \beta)}{\partial \beta}$ in (1) is replaced by its average within the Ri randomization group.

Randomization based tests for confounding

The idea of randomization based text is to check if the mean responses based on model prediction and on randomization are similar. An intuitive approach is **to test randomisation effect on the residuals of a fitted model**. The following shows comparison between residuals of the two ranges in data in Figure 1

Randomization effect on residuals	Estimate	SE	P-value (t-test)
No confounding	0.023	0.032	0.484
With confounding	-0.107	0.036	0.003

Bayesian bootstrap and posterior distribution

However, the test may have low power at moderate sample sizes. The plot on the right shows that the p-values are not uniformely distributed where there is no confounding. We propose a Bayesian bootstrap approach to obtain the posterior distribution of the difference between the model and randomization based estimates of response difference between ranges. Posterior samples are generated by weighted LS with weights following the exponential distribution.

The posterior distribution can be used to test confounding as without it, the distribution should be around 0. Figure 2 shows the posterior distribution for the example with confounding, with 999 bootstrap, which suggests a significant confouding bias (the area In the negative region was 0.04)

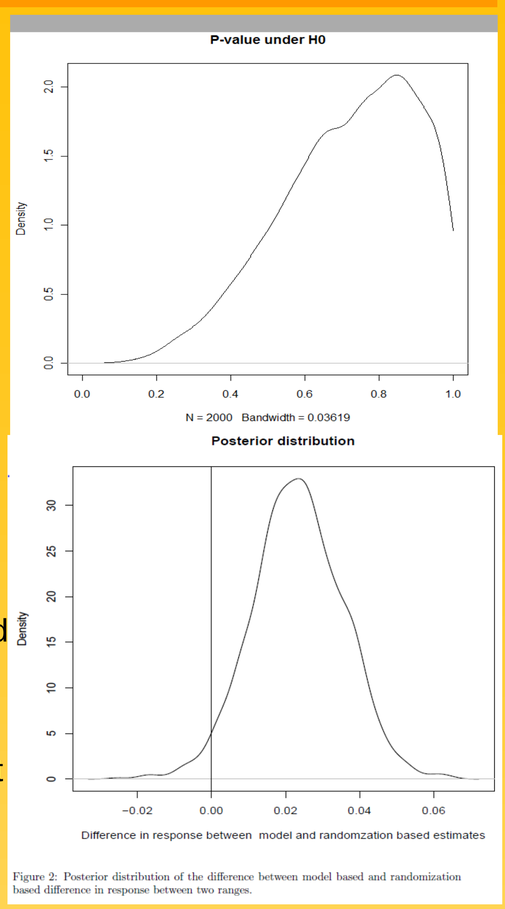

Figure 2: Posterior distribution of the difference between model based and randomization based difference in response between two ranges.

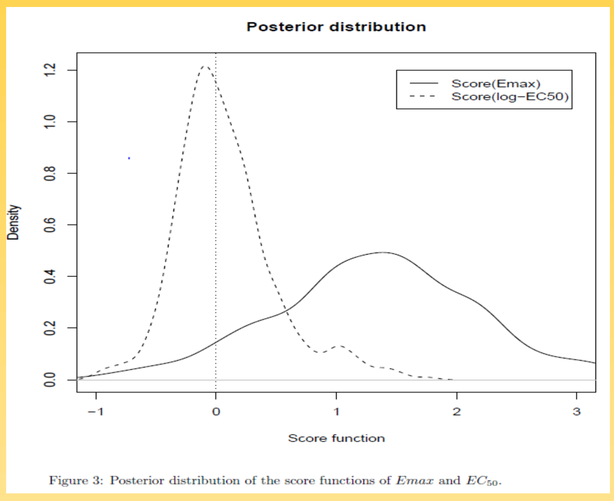

Figure 3: Posterior distribution of the score functions of $Emax$ and EC_{50}.

To investigate the impact of confounding bias in individual parameters we can use the score function 2. Without confouding, the mean of $S_{iv}(\beta)$ should be 0, when calculated at the LS estimate. Therefore, a deviation from 0 of the individual components indicates an impact of confounding on the respective parameter. Figure 3 gives the posterior distributions for Emax and log-EC50 from the example data, showing that the confounding only causes bias in Emax, not EC50.

Simulation for power comparison

We used simulations to examine the type I error and power of the residual based and the Bayesian bootstrap tests. The power of the former was calculated by 3000 simulations and that of the latter was calculated with 300 simulation each with 200 bootstraps. The table below shows the power of type I error and power for a few scenarios. The p-value plot suggests that the residual test can be very conservative. The power of the Bayesian bootstrap test is generally high even with moderate size of confounding.

Confounding coefficient K	0	0.1	0.2	0.3
Residual test	0	0.02	0.97	1.00
Bayesian bootstrap	0.04	0.63	0.25	0.88

Discussion

We proposed a randomization based approaches to test confounding factors in PKPD modeling for RCC trial. This approach can also be used in other types of models, e.g., nonlinear mixed PKPD models, by constructing appropriate comparisons between ranges. The Bayesian bootstrap approach allows more reliable assessment of the bias even for small sample sizes and different distributions. The approaches can also used to assess the impact of confounding on individual parameters, which may suggest using the IV based estimation method. With the increasing use of RCC trials [1], the proposed approach provides practical tools to investigate the presence and the impact of potential confounding factors. It can also be used in randomized dose level trials. The approach can be implemented on ordinary model fitting software.

Reference

[1] Karlsson KE, Grahnen A, Karlsson MO, Jonsson EN. (2007) Randomized exposure-controlled trials; impact of randomization and analysis strategies. *Br J Clin Pharmacol* 64: 266--77

[2] Nedelman, J.R. (2005) On some "disadvantages" of the population approach. *The AAPS Journal* 7, Article 38.

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