Meta-analysis of Interaction (Top Secret! – for now)

Shinichi Nakagawa, Daniel Noble, et al.

25 November 2020

Plan

We will write it up as a method paper to upload to **EcoEvoRxiv** as a preprint (we may try *Ecology Letters* or *BMC Biology*). We also use effect size statistics for the meta-analysis of interaction in some on-going meta-analyses where applicable (i.e. Alfredo's meta-analysis and Kei's meta-analysis).

Background

In experimental work, it is common to have a 2x2 factorial design. In such a design, you have 3 important effects: the main effect of the first factor (factor 1), 2) the main effect of the first factor (factor 2) and 3) the interaction effect (factor 1 x factor 2). This commonality of this design increases dramatically once one realize that two groups (treatment and control) in one's experiment can be split into 4 groups, conditioned on sex, if these two original groups have the two sexes (males and females). Although a usual meta-analysis focuses on the main effect of one factor, the meta-analysis of the interaction effect as well as the two main effects is possible. For the standardized mean difference, SMD (aka Cohen's d or Hedges' g), Gurevith and colleagues (2000) proposed the method nearly two decades ago, followed by the similar method for log response ratio (lnRR) by Morris et al. (2007). However, the intake of this method seemed to have been slow. We suspect the reason for this slow uptake is that these potentially very useful methods are hidden in the appendix of these articles (cf. (Lajeunesse 2011)) (we are currently surveying this).

Indepedent Groups

Here, we derive effect size statistics for the meta-analysis of the 2x2 factorial design (i.e. 4 independent groups). We first start with reviewing the formula for SMD and lnRR. Then, we re-derive the equivalent formulas for lnRR (log response ratio; (Hedges, Gurevitch, and Curtis 1999); cf. (Morris et al. 2007)), and also we newly derive lnVR (log variability ratio) and lnCVR (log coefficient of variation ratio; (Nakagawa et al. 2015)). As discussed in Nakagawa et al. (Nakagawa et al. 2015), there are few meta-analyses simultaneously examining the mean and variance, which will bring new insights not only into a new topics but also topics, which are already meta-analysed for the mean difference. Indeed, such an combined approach has discovered new patterns across a wide range of fields such as evolution (Janicke et al. 2016), ecology (Senior et al. 2015), medicine (Senior et al. 2016), and social sciences (O'Dea et al. 2018).

SMD (Standarised Mean Difference)

The main effect of factor 1 According to Hedges et al. (1999), SMD for the main effect of factor 1 (d_{f1}) can be written as:

$$d_{f1} = \frac{\left(\frac{\bar{x}_{e1e2} + \bar{x}_{e1c2}}{2}\right) - \left(\frac{\bar{x}_{c1e2} + \bar{x}_{c1c2}}{2}\right)}{sd_{pool}}$$
$$= \frac{\left(\bar{x}_{e1e2} + \bar{x}_{e1c2}\right) - \left(\bar{x}_{c1e2} + \bar{x}_{c1c2}\right)}{2sd_{pool}},$$

where \bar{x}_{e1e2} , \bar{x}_{e1c2} , \bar{x}_{c1e2} and \bar{x}_{c1c2} are the mean of the experimental/experimental (factor1/factor2) group, the experimental/control group, the control/experimental group and the control/control group, respectively and sd_{pool} is the pool standard deviation of the four groups (see below). One can, from the first row of the formula, d_{f1} represents the standardized difference between the average of two experimental groups and that of two control groups for factor 1.

$$sd_{pool} = \sqrt{\frac{(n_{e1e2} - 1)sd_{e1e2}^2 + (n_{e1c2} - 1)sd_{e1c2}^2 + (n_{c1e2} - 1)sd_{c1e2}^2 + (n_{c1c2} - 1)sd_{c1c2}^2}{n_{e1e2} + n_{e1e2} + n_{c1e2} + n_{c1e2} - 4}},$$

where n_{e1e2} , n_{e1c2} , n_{c1e2} and n_{c1c2} are the sample size of the four groups, sd_{e1e2} , sd_{e1c2} , sd_{c1e2} , and sd_{c1c2} are the standard deviation of the four groups. The sampling variance for d_{f1} can be estimated as:

$$s^{2}(d_{f1}) = \frac{1}{4} \left[\frac{1}{n_{e1e2}} + \frac{1}{n_{e1c2}} + \frac{1}{n_{c1e2}} + \frac{1}{n_{c1c2}} + \frac{1}{2(n_{e1e2} + n_{e1e2} + n_{e1e2} + n_{c1c2})} \right],$$

Note that the 1/4 in $s^2(d_{f1})$ comes from the 1/2 in d_{f2} .

The main effect of factor 2 Similarly, SMD for factor 2 and its sampling variance can be written as:

$$d_{f2} = \frac{(\bar{x}_{e1e2} + \bar{x}_{c1e2}) - (\bar{x}_{e1c2} + \bar{x}_{c1c2})}{2sd_{pool}},$$

$$s^{2}(d_{f2}) = \frac{1}{4} \left[\frac{1}{n_{e1e2}} + \frac{1}{n_{e1c2}} + \frac{1}{n_{c1e2}} + \frac{1}{n_{c1c2}} + \frac{1}{2(n_{e1e2} + n_{e1e2} + n_{e1e2} + n_{c1c2})} \right],$$

where the symbols are as above.

The interaction effect (factor 1 x factor 2) The interaction effect and its sampling variance are:

$$d_{f1:f2} = \frac{(\bar{x}_{e1e2} - \bar{x}_{c1e2}) - (\bar{x}_{e1c2} - \bar{x}_{c1c2})}{sd_{pool}},$$

$$s^2(d_{f1:f2}) = \frac{1}{n_{e1e2}} + \frac{1}{n_{e1c2}} + \frac{1}{n_{c1e2}} + \frac{1}{n_{c1e2}} + \frac{1}{n_{c1c2}} + \frac{d_{f1:f2}^2}{2(n_{e1e2} + n_{e1e2} + n_{e1e2} + n_{c1c2})}.$$

It is notable that a positive $d_{f1:f2}$ value indicates the (experimental) effect of factor 1 is stronger in the presence of factor 2 whereas a negative value represents the effect of factor 1 is stronger in the absence of factor 2.

lnRR (log Response Ratio)

The main effect of factor 1 Morris et al. (2007) defined that the main effect of factor 1 and its sampling error variance (approximation) as:

$$\ln RR_{f1} = \ln \left(\frac{\bar{x}_{e1e2} + \bar{x}_{e1c2}}{2} \right) - \ln \left(\frac{\bar{x}_{c1e2} + \bar{x}_{c1c2}}{2} \right),$$

$$= \ln \left(\frac{\bar{x}_{e1e2} + \bar{x}_{e1c2}}{\bar{x}_{c1e2} + \bar{x}_{c1c2}} \right),$$

$$s^{2}(\ln RR_{f1}) = \left(\frac{1}{\bar{x}_{e1e2} + \bar{x}_{e1c2}} \right)^{2} \left(\frac{sd_{e1e2}^{2}}{n_{e1e2}} + \frac{sd_{e1c2}^{2}}{n_{e1e2}} \right) + \left(\frac{1}{\bar{x}_{c1e2} + \bar{x}_{c1c2}} \right)^{2} \left(\frac{sd_{c1e2}^{2}}{n_{c1e2}} + \frac{sd_{c1c2}^{2}}{n_{c1c2}} \right).$$

However, we propose a different formula for main effects (including sampling error variances). We define the main effect of factor 1 as:

$$\ln RR_{f1} = \ln \left(\frac{\sqrt{\bar{x}_{e1e2}\bar{x}_{e1c2}}}{\sqrt{\bar{x}_{c1e2}\bar{x}_{c1c2}}} \right),$$

$$= \left(\frac{\ln \bar{x}_{e1e2} + \ln \bar{x}_{e1c2}}{2} \right) - \left(\frac{\ln \bar{x}_{c1e2} + \ln \bar{x}_{c1c2}}{2} \right),$$

$$= \frac{1}{2} \ln \left(\frac{\bar{x}_{e1e2}\bar{x}_{e1c2}}{\bar{x}_{c1e2}\bar{x}_{c1c2}} \right).$$

Notice that analogous to SMD for the main effect of factor 1 (d_{f1}) , $\ln RR_{f1}$ is the difference between the average of on the natural logarithm scale (i.e. geometric mean rather than arithmetic mean seen in d_{f1}). The sampling error variance for $\ln RR_{f1}$ can be estimated as:

$$s^{2}(\ln RR_{f1}) = \frac{1}{4} \left(\frac{sd_{e1e2}^{2}}{n_{e1e2}\bar{x}_{e1e2}^{2}} + \frac{sd_{e1c2}^{2}}{n_{e1c2}\bar{x}_{e1c2}^{2}} + \frac{sd_{c1e2}^{2}}{n_{c1e2}\bar{x}_{e1e2}^{2}} + \frac{sd_{c1e2}^{2}}{n_{c1e2}\bar{x}_{e1e2}^{2}} + \frac{sd_{c1e2}^{2}}{n_{c1e2}\bar{x}_{e1e2}^{2}} \right).$$

We believe our definition of the main effect seem more comparable and analogous to that of SMD originally proposed by Gurevith et al. (2000).

The main effect of factor 2 Similarly, the main effect of factor 2 and its corresponding sampling error variance can be written as:

$$\ln RR_{f2} = \frac{1}{2} \ln \left(\frac{\bar{x}_{e1e2} \bar{x}_{c1e2}}{\bar{x}_{e1c2} \bar{x}_{c1c2}} \right),$$

$$s^2 (\ln RR_{f2}) = \frac{1}{4} \left(\frac{sd_{e1e2}^2}{n_{e1e2} \bar{x}_{e1e2}^2} + \frac{sd_{e1c2}^2}{n_{e1c2} \bar{x}_{e1c2}^2} + \frac{sd_{c1e2}^2}{n_{c1e2} \bar{x}_{c1e2}^2} + \frac{sd_{c1e2}^2}{n_{c1e2} \bar{x}_{c1e2}^2} \right).$$

Note $s^2(\ln RR_{f1})$ and $s^2(\ln RR_{f2})$ are identical.

The interaction effect (factor 1 x factor 2) As with Morris et al. (2007) (also see (Hawkes and Sullivan 2001)), the interaction effect for lnRR can be written as:

$$\ln RR_{f1:f2} = \ln \left(\frac{\bar{x}_{e1e2}/\bar{x}_{c1e2}}{\bar{x}_{e1c2}/\bar{x}_{c1c2}} \right),$$

$$= \ln \left(\frac{\bar{x}_{e1e2}}{\bar{x}_{c1e2}} \right) - \ln \left(\frac{\bar{x}_{e1c2}}{\bar{x}_{c1c2}} \right),$$

$$= (\ln \bar{x}_{e1e2} - \ln \bar{x}_{c1e2}) - (\ln \bar{x}_{e1c2} - \ln \bar{x}_{c1c2}).$$

The interpretation of is the same as for $d_{f1:f2}$. The sampling variance for $\ln RR_{f1:f2}$ can be estimated as:

$$s^{2}(\ln RR_{f1:f2}) = \frac{sd_{e1e2}^{2}}{n_{e1e2}\bar{x}_{e1e2}^{2}} + \frac{sd_{e1c2}^{2}}{n_{e1c2}\bar{x}_{e1c2}^{2}} + \frac{sd_{c1e2}^{2}}{n_{c1e2}\bar{x}_{c1e2}^{2}} + \frac{sd_{c1e2}^{2}}{n_{c1e2}\bar{x}_{c1e2}^{2}}$$

lnVR (log Variablity Ratio)

The main effect of factor 1 The effect size statistic, lnVR, introduced by Nakagawa et al. (2015), represents the difference in variability (i.e. standard deviation, sd) between the two group. The main effect of factor 1, for lnVR, can be written as:

$$\ln VR_{f1} = \frac{1}{2} \left[\ln s d_{e1e2} + \frac{1}{2(n_{e1e2} - 1)} + \ln s d_{e1c2} + \frac{1}{2(n_{e1c2} - 1)} \right]$$

$$- \frac{1}{2} \left[\ln s d_{c1e2} + \frac{1}{2(n_{c1e2} - 1)} + \ln s d_{c1c2} + \frac{1}{2(n_{c1c2} - 1)} \right],$$

$$= \frac{1}{2} \ln \left(\frac{s d_{e1e2} s d_{e1c2}}{s d_{c1e2} s d_{c1c2}} \right) + \frac{1}{2} \left[\frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{e1c2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} - \frac{1}{2(n_{c1c2} - 1)} \right].$$

The sampling error variance for $\ln \mathrm{VR}_{f1}$ can be estimated as:

$$s^{2}(\ln VR_{f1}) = \frac{1}{4} \left[\frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{e1c2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} \right].$$

The main effect of factor 2 In a similar way to that of factor 1, the main effect of factor 2 and its sampling error variance can be written as:

$$\ln VR_{f2} = \frac{1}{2} \ln \left(\frac{sd_{e1e2}sd_{c1e2}}{sd_{e1c2}sd_{c1c2}} \right) + \frac{1}{2} \left[\frac{1}{2(n_{e1e2} - 1)} - \frac{1}{2(n_{e1c2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} \right],$$

$$s^{2}(\ln VR_{f2}) = \frac{1}{4} \left[\frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{e1c2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} \right].$$

The interaction effect (factor $1 \times factor 2$) The interaction effect and its sampling error variance for lnVR can be written as:

$$\ln VR_{f1:f2} = \ln \left(\frac{sd_{e1e2}/sd_{c1e2}}{sd_{e1c2}/sd_{c1c2}} \right) + \frac{1}{2(n_{e1e2} - 1)} - \frac{1}{2(n_{e1c2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)},$$

$$s^{2}(\ln VR_{f1:f2}) = \frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)}.$$

lnCVR (log Coefficient of Variation Ratio)

The main effect of factor 1 For lnCVR (Nakagawa et al. 2015), which represents the ratio of coefficient of variation (CV) between the two groups, the main effect of factor 1 can be written as:

$$\ln \text{CVR}_{f1} = \frac{1}{2} \left[\ln \text{CV}_{e1e2} + \frac{1}{2(n_{e1e2} - 1)} + \ln \text{CV}_{e1c2} + \frac{1}{2(n_{e1c2} - 1)} \right]$$

$$- \frac{1}{2} \left[\ln \text{CV}_{c1e2} + \frac{1}{2(n_{c1e2} - 1)} + \ln \text{CV}_{c1c2} + \frac{1}{2(n_{c1c2} - 1)} \right],$$

$$= \frac{1}{2} \ln \left(\frac{\text{CV}_{e1e2} \text{CV}_{e1c2}}{\text{CV}_{c1e2} \text{CV}_{c1c2}} \right) + \frac{1}{2} \left[\frac{1}{2(n_{e1e2} - 1)} + \frac{1}{2(n_{e1e2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} \right].$$

Also, the sampling error variance can be estimated as:

$$s^{2}(\ln \text{CVR}_{f1}) = s^{2}(\ln \text{RR}_{f1}) + s^{2}(\ln \text{VR}_{f1}).$$

Note that we assume there is no correlation between the mean and variance at the level of the sampling error although Nakagawa et al. (2015) did (but see Alistair's simulation work – in prep).

The main effect of factor 2 In a similar manner, the main effect of factor 2 and its sampling error variance can be written as:

$$\ln \text{CVR}_{f2} = \frac{1}{2} \ln \left(\frac{\text{CV}_{e1e2} \text{CV}_{c1e2}}{\text{CV}_{e1c2} \text{CV}_{c1c2}} \right) + \frac{1}{2} \left[\frac{1}{2(n_{e1e2} - 1)} - \frac{1}{2(n_{e1c2} - 1)} + \frac{1}{2(n_{c1e2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} \right],$$

$$s^2(\ln \text{CVR}_{f2}) = s^2(\ln \text{RR}_{f2}) + s^2(\ln \text{VR}_{f2}).$$

The interaction effect (factor $1 \times factor 2$) As above, he interaction effect of lnCVR and the corresponding sampling error variance can be estimated as:

$$\ln \text{CVR}_{f1:f2} = \ln \left(\frac{\text{CV}_{e1e2}/\text{CV}_{c1e2}}{\text{CV}_{e1c2}/\text{CV}_{c1c2}} \right) + \frac{1}{2(n_{e1e2} - 1)} - \frac{1}{2(n_{e1c2} - 1)} - \frac{1}{2(n_{c1e2} - 1)} + \frac{1}{2(n_{c1e2} - 1)},$$

$$s^{2}(\ln \text{CVR}_{f1:f2}) = s^{2}(\ln \text{RR}_{f1:f2}) + s^{2}(\ln \text{VR}_{f1:f2}).$$

Non-indepedent Groups

Another application of the meta-analysis of interaction arise when one considers time as factor 2 in an experiment which measures subjects before (time 1) and after (during; time 2) a treatment (factor 1). Such design is very common in (bio-)medicine and clinical psychology but also found in biology. In a typical meta-analysis dealing with such designs, one may only utilize measurements from time 2. However, this does not account for potential difference between the two groups at time 1. As shown below, it turns out that the interaction effect between experimental treatment (factor) and time is the experimental effect at time 2, controlling for the difference at time 1. Here, we derive such an interaction effect for SMD, lnRR, lnVR and lnCVR, none of which has been described in the literature.

SMD (Standarised Mean Difference)

The interaction effect (factor x time) For SMD, the interaction effect can be written as:

$$\begin{split} d_{f:t} &= \frac{(\bar{x}_{et2} - \bar{x}_{ct2}) - (\bar{x}_{et1} - \bar{x}_{ct1})}{sd_{pool}}, \\ &= \frac{(\bar{x}_{et2} - \bar{x}_{et1}) - (\bar{x}_{ct2} - \bar{x}_{ct1})}{sd_{pool}}, \end{split}$$

where \bar{x}_{et1} , \bar{x}_{et2} , \bar{x}_{ct1} and \bar{x}_{ct2} are the mean of the experimental group at time 1, the experimental group at time 2, the control group at time 1 and the control group at time 2, respectively and sd_{pool} is the pool standard deviation of the four groups (see below).

$$sd_{pool} = \sqrt{\frac{(n_e - 1)sd_{et1}^2 + (n_e - 1)sd_{et2}^2 + (n_c - 1)sd_{ct1}^2 + (n_c - 1)sd_{ct2}^2}{2(n_e + n_{c2} - 2)}},$$

where n_e and n_c are the sample size of the two groups (we assume that there are not dropouts between time 1 and time 2), sd_{et1} , sd_{et2} , sd_{ct1} , and sd_{ct2} are the standard deviation of the two groups at two time points (time 1 & 2).

The sampling error variance for $d_{f:t}$ can be estimated as:

$$s^{2}(d_{f:t}) = \frac{2}{n_{e}} - \frac{2r_{et12}}{n_{e}} + \frac{2}{n_{c}} - \frac{2r_{ct12}}{n_{c}} + \frac{d_{f:t}^{2}}{2(n_{e} + n_{c})}$$
$$= \frac{2(1 - r_{et12})}{n_{e}} + \frac{2(1 - r_{ct12})}{n_{c}} + \frac{d_{f:t}^{2}}{2(n_{e} + n_{c})}.$$

where r_{et12} and r_{ct12} are correlations between x_{et1i} and x_{et2i} $(i = 1, 2, ..., n_e)$ and between x_{ct1i} and x_{ct2i} $(i = 1, 2, ..., n_c)$, respectively.

lnRR (log Response Ratio)

The interaction effect (factor x time) For lnRR, the interaction effect can be written as:

$$\ln RR_{f:t} = \ln \left(\frac{\bar{x}_{et2}/\bar{x}_{ct2}}{\bar{x}_{et1}/\bar{x}_{ct1}} \right).$$

The sampling error variance for $\ln RR_{f:t}$ can be estimated as:

$$\begin{split} s^2(\ln \mathrm{RR}_{f:t}) &= \frac{sd_{et1}^2}{n_e \bar{x}_{et1}^2} + \frac{sd_{et2}^2}{n_e \bar{x}_{et2}^2} - 2r_{et12} \frac{sd_{et1}sd_{et2}}{n_e \bar{x}_{et1}\bar{x}_{et2}} + \frac{sd_{ct1}^2}{n_c \bar{x}_{ct1}^2} + \frac{sd_{ct2}^2}{n_c \bar{x}_{ct2}^2} - 2r_{ct12} \frac{sd_{ct1}sd_{ct2}}{n_c \bar{x}_{ct1}\bar{x}_{ct2}}, \\ &= \frac{\bar{x}_{et1}^2 sd_{et2}^2 + \bar{x}_{et2}^2 sd_{et1}^2 - 2r_{et12}\bar{x}_{et1}\bar{x}_{et2}sd_{et1}sd_{et2}}{n_e \bar{x}_{et1}^2 \bar{x}_{et2}^2} + \frac{\bar{x}_{ct1}^2 sd_{ct2}^2 + \bar{x}_{ct2}^2 sd_{ct1}^2 - 2r_{ct12}\bar{x}_{ct1}\bar{x}_{ct2}sd_{ct1}sd_{ct2}}{n_c \bar{x}_{ct1}^2 \bar{x}_{ct2}^2}. \end{split}$$

lnVR (log Variablity Ratio)

The interaction effect (factor x time) For lnVR, the interaction effect can be written as:

$$\ln VR_{f:t} = \left[\ln s d_{et2} + \frac{1}{2(n_e - 1)} - \ln s d_{ct2} - \frac{1}{2(n_c - 1)}\right] - \left[\ln s d_{et1} + \frac{1}{2(n_e - 1)} - \ln s d_{ct1} - \frac{1}{2(n_c - 1)}\right],$$

$$= \ln \left(\frac{s d_{et2}/s d_{ct2}}{s d_{et1}/s d_{ct1}}\right).$$

The sampling error variance for $\ln VR_{f:t}$ can be estimated as:

$$s^{2}(\ln VR_{f:t}) = \frac{1}{2(n_{e}-1)} + \frac{1}{2(n_{e}-1)} - 2r_{et12}^{2} \frac{1}{2(n_{e}-1)} + \frac{1}{2(n_{c}-1)} + \frac{1}{2(n_{c}-1)} - 2r_{et12}^{2} \frac{1}{2(n_{e}-1)}$$
$$= \frac{1 - r_{et12}^{2}}{n_{e}-1} + \frac{1 - r_{ct12}^{2}}{n_{c}-1}.$$

Note that the correlation between two $\ln sd$ are not r_{12} but r_{12}^2 (REF)

lnCVR (log Coefficient of Variation Ratio)

The interaction effect (factor x time) For lnCVR, the interaction effect and its sampling error variance can be written as:

$$\ln \text{CVR}_{f:t} = \ln \left(\frac{\text{CV}_{et2}/\text{CV}_{ct2}}{\text{CV}_{et1}/\text{CV}_{ct1}} \right),$$

$$s^{2}(\ln \text{CVR}_{f:t}) = s^{2}(\ln \text{RR}_{f:t}) + s^{2}(\ln \text{VR}_{f:t}).$$

Note that we made the same assumption as for $\ln \text{CVR}_{f1:f2}$ above.

Extension: Carry-over Effect

If we have measurements at time 3 when subjects are not exposed to experimental treatments or some time has elapsed since time 2, we can calculate that the carry-over effect of experimental effect by comparing time 1 and time 3. For example, for lnVR, such an effect and its sampling error variance are as follows:

$$\ln VR_{c/o} = \ln \left(\frac{sd_{et3}/sd_{ct3}}{sd_{et1}/sd_{ct1}} \right),$$
$$s^{2}(\ln VR_{c/o}) = \frac{1 - r_{et13}^{2}}{n_{e} - 1} + \frac{1 - r_{ct13}^{2}}{n_{c} - 1},$$

where r_{et13} and r_{ct13} correlations between x_{et1i} and x_{et3i} ($i = 1, 2, ..., n_e$) and between x_{ct1i} and x_{ct3i} ($i = 1, 2, ..., n_c$), respectively. Note that $\ln VR_{c/o}$ and $s^2(\ln VR_{c/o})$ are identical except that we use measurements at time 3 rather than time 2. The carry-over effect for SMD, $\ln RR$ and $\ln CVR$ can be obtained accordingly.

Some notes

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