# Dose-Response meta-analysis

Assume we meta-analyse the effect of a drug versus placebo across various studies () and each study has different number of doses; ( ). To synthesise the doses from all studies in a hierarchical model, we initially conduct a simulation data (Section 1.1) to evaluate the hierarchical model (Section 1.2) by first fit a dose-response relationship within each study (Section 1.2.1) and then pool the estimates of the dose-response associations across the studies (Section 1.2.2).

## Simulate dose-response meta-analysis datasets

We aim to compare the different approaches in estimation of the dose-response relationship in meta-analysis in a simulation study.

Consider studies where each one reports doses, . One of these doses is set to be the reference dose . We simulated a dataset of0 studies, where each study reports on 3 doses including the reference dose.

### Data-generating mechanism

We generate the data in four steps:

1. Generate the doses and their transformation.

We assume that every study involves the lowest dose which set to zero. The 2 non-referent doses are sampled from a uniform distribution,

,

LD and UD are the lowest and maximum values, respectively. Then the transformed dose, , is computed based on which dose-response transformation is assumed. For Linear transformation

.

For restricted cubic splines

,

where is the cubic spline transformation with three knots. We place the knots at the 1st, 2nd and 3rd quartiles and we use the *rcs* function to find the cubic spline transformations for the dose.

1. Generate the study-specific assumed values for the regression coefficients and implement the dose-response relationship to compute the study-specific underlying relative dose effects.

We assume that the dose-response association is characterised by the coefficient (in a linear association) and , for the restricted cubic splines with three knots. We generate the study-specific regression coefficients assuming a random-effect model based on different transformations.

* Linear transformation
* Cubic splines transformation, we generate the two regression coefficients and

Next, we compute the underlying relative effects between doses within each studyusing the study-specific coefficients

where is the dose transformation (linear or spline).

1. Generate the number of responses from a binomial distribution and estimate the relative effects.

Let the cases in the referent dose and in the non-referent dose are generated from binomial distribution

We set , and as a sample size, then

The probabilities of event in the non-referent dose are computed

For odds ratio, , we can set any value for . For risk ratios, , we need to constraint 0 < , so we set

where refers to the maximum relative risk and it is computed based on the dose-response transformation we assume.

For linear transformation, and for restricted cubic splines + .

Next, to ensure that does not drop to a value so close to zero, we set 0.05 as a lower bound for . In that we avoid (to some extent) introducing zero cases for the reference dose effect.

1. Re-estimate the study- and dose- specific relative treatment effects and the variance-covariance matrix.

Finally, we calculate the estimation of the relative effects

Where , then its corresponding variances are

### Estimands, methods and performance

Our target estimand is . We aim to compare a two-stages frequentist dose-response model (as implemented in doseresmeta package) and two Bayesian hierarchical models; with normal likelihood and with binomial likelihood. We will assume linear and cubic splines associations, RR and OR as measures of effect. The following simulation parameters will be considered fixed: HERE DESCRIBE ANY PARAMETER THAT YOU WILL NOT CHANGE SUCH AS LD, UD, N ANYTHING ELSE. All other parameters will be varied as shown in the first columns of table X (<0 HERE CITE THE RESULTS TABLE). The range of values has been chosen so that p\_0 ranges from XX to XX and the maximum possible P is XX. The four methods will be compared with respect to

* Bias = E() -
* Mean squared error (MSE) = E[
* Convergence: (I did not find it yet)
* Type 1 error () = Pr()
* Type 2 error () = Pr()
* Monte Carlo standard error for bias

## Dose-response meta-analysis hierarchical model

### Dose-Response model within each study

#### Likelihood of the observed data

In a study , we observe +1 doses , one of then is set to be the reference dose .

##### Using the normal likelihood on log-odds ratios

Assume a dose-response relationship between the relative dose effect (typically in log scale for relative effects) compared to the reference dose . The vector has length and comprises all relative effects (e.g. the logRR) of each dose compared to .

Within each study, a multivariate normal distribution is assumed for the vector of relative effects for each dose , with such a distribution the correlation between the doses can be taken into account.

The vector is ofsame dimensionas and contains the study and dose-specific underlying treatment effects .

The variance covariance matrix can be estimated simply by assuming a multinomial or poisson distribution for the counts and using the delta-method for large sample size since we have RCTs so there is no need to adjust for the covariates to consider the potential confounders. For the odds ratio , the elements of are as follow

And for the relative risk

with indicating the number of cases, the number of controls and the total number of individuals. Notice that in Rwe provide JAGS model with the inverse of variance-covariance matrix; precision matrix.

The matrix reflects association between the dose levels and the relative effects and its elements are assumed fixed and associated with a dose-transformation function (discussed in section 2.3.2)

The equation above assumes that all heterogeneity across study effects is associated with variability in , where ’s indicate the regression coefficients. An alternative model that encompasses random effects beyond the impact of the dose would be

where is the between studies variance-covariance matrix with in the diagonal and in the off-diagonal. Then, the dose transformations will be used to model so that

In this document, we will proceed with the fixed-effect assumption.

##### Using the binomial distribution

A study can in fact present the number of events per dose. Assume we have +1 doses and in each one events occur out of people exposed to dose for +1. Then

Then the probabilities of event are parametrized to give the logRR as . Then, as above. Note that the use of this approach does not require any correlations to be modelled as the study arms are independent.

#### Dose transformations and specification of the association

The relative effect quantifies the response of each dose relative to the referent dose (no exposure, zero dose or the lowest dose).

where is the dose-response transformation and ’s are the corresponding regression parameters that need to be estimated. Notice that when the reference dose is zero (that is the study compares the drug to placebo) then. Below are the three types of transformations that we consider:

1. Linear Model, is a scalar
2. Restricted Cubic Splines[[1]](#footnote-2): is the vector where is the total number of knots; . Then

where

,

for .

In R software, I simply use *rcs()* function from *rms* package to find and then input them to JAGS model to estimate .

With three knots (the default in all subsequent analyses), two dose transformations are needed: and so that the spline model still involves two regression coefficients

### Synthesise dose-response associations across studies

Each one of the regression parameters that have been estimated in the stage before can be synthesised under various assumptions.

2. Exchangeable-coefficients model: ,

3. Fixed-coefficients model:

Then prior distributions need to be set for all the parameters that should be estimated:

The heterogeneity: , i.e. refers to the zero-truncated normal distribution. Each of the pooled estimates:

NOW START THE RESULTS SECTION: SHOW BIAS, MEAN SQUARE ERROR AND COVERAGE IN THE SIMULATIONS, BOTH BAYESIAN AND FREQUENTIST.

1. Frank E. Harrell, *Regression Modelling Strategies*. [↑](#footnote-ref-2)