Meta-analysis of Non Statistically-significant Unreported Effects (MetaNSUE). Supplementary material

Contents

A Worked example

As described in the text, let us imagine that we aim to conduct a meta-analysis of the drug-related change in blood pressure, and that we can include 10 studies, of which four are NSUEs. In other words, we can find or derive the t-values for six of the studies, but we only know that the change did not reach statistical significance for the other four. The data would be as follows:

```
R> t <- c(3.4, NA, NA, NA, NA, 2.8, 2.1, 3.1, 2.0, 3.4)
R> n <- c(40, 20, 22, 24, 18, 30, 25, 30, 16, 22)
```

A.1 Approach 1: discard NSUEs

We could use the following code to discard the NSUEs:

```
R> known <- which(!is.na(t))
R> t_known <- t[known]
R> n_known <- n[known]
```

Afterwards, we could conduct a standard random-effects meta-analysis of known effects with either the "metansue" package or another package such as "metafor" (Viechtbauer, 2010), obtaining identical results. For "metansue", we should first create an object of class "nsue" with the R function "smc_from_t" (standardized mean change from t-value), and then call the R function "meta" to conduct the meta-analysis. For "metafor", we should first calculate the effect size and its variance (or use other functions to do so), and then call the R function "rma" to conduct the meta-analysis.

```
R> library(metansue) # Using the metansue package
R> meta(smc_from_t(t_known, n_known))

Meta-analysis description:
- Measure: Standardized mean change (Hedges' corrected)
- Known measures: 6
- Non-statistically-significant unknown measures: 0
- Imputations: 0
- Model: measure ~ 1
- Hypothesis:  (Mean)=0

Residual heterogeneity (tau^2): 0.0000   I^2:  0.00%   H^2: 1.00
Q-statistic (heterogeneity): 0.91 on 5 df  Pr(>Q): 0.9694
Note: we strongly suggest focusing more on I^2 than on Pr(>Q)

Model:
        Estimate  Std. Error
(Mean)    0.5222      0.0842

One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0    0.5222   6.2022     <.0001   0.3572  0.6872  ***

---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

```
R> library(metafor) # Using the metafor package
R> j <- gamma((n - 1) / 2) / sqrt( (n - 1) / 2) / gamma((n - 2) / 2)
R> j_known <- j[known]
R> g_known <- j_known * t_known / sqrt(n_known)
R> var_known <- 1 / n_known + (1 - (n_known - 3) / (n_known - 1) / j_known^2)
                * g_known^2
R> rma(g_known, var_known)

Random-Effects Model (k = 6; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0265)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00

Test for Heterogeneity:
Q(df = 5) = 0.9108, p-val = 0.9694

Model Results:

estimate       se     zval     pval     ci.lb     ci.ub
  0.5222   0.0842   6.2022   <.0001   0.3572   0.6872      ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

A.2 Approach 2: assume that NSUEs are null

We could use the following code to convert NSUEs into zeroes:

```
R> t_zeroes <- sapply(t, function (x) {ifelse(is.na(x), 0, x)})
```

Afterwards, we could again conduct a standard random-effects meta-analysis of known effects with either the "metansue" package or another package such as "metafor", obtaining identical results:

```
R> meta(smc_from_t(t_zeroes, n))

Meta-analysis description:
- Measure: Standardized mean change (Hedges' corrected)
- Known measures: 10
- Non-statistically-significant unknown measures: 0
- Imputations: 0
- Model: measure ~ 1
- Hypothesis:  (Mean)=0

Residual heterogeneity (tau^2): 0.0311   I^2: 41.00%   H^2: 1.69
Q-statistic (heterogeneity): 15.27 on 9 df  Pr(>Q): 0.0839
Note: we strongly suggest focusing more on I^2 than on Pr(>Q)
```

```
Model:
        Estimate  Std. Error
(Mean)    0.3203      0.0875

One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0    0.3203   3.6604    0.0003   0.1488  0.4919  ***

---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

R> g_zeroes <- j * t_zeroes / sqrt(n)
R> var_zeroes <- 1 / n + (1 - (n - 3) / (n - 1) / j^2) * g_zeroes^2
R> rma(g_zeroes, var_zeroes)

Random-Effects Model (k = 10; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0311 (SE = 0.0359)
tau (square root of estimated tau^2 value):      0.1763
I^2 (total heterogeneity / total variability):   41.00%
H^2 (total variability / sampling variability):  1.69

Test for Heterogeneity:
Q(df = 9) = 15.2671, p-val = 0.0839

Model Results:

estimate       se     zval     pval    ci.lb    ci.ub
  0.3203   0.0875   3.6604   0.0003   0.1488   0.4919      ***

---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

A.3 Approach 3: Impute NSUEs (i.e. the strategy of MetaNSUE)

Here, we will simply leave NSUEs as NA, so that MetaNSUE software understands them as NSUEs:

```
R> meta(smc_from_t(t, n))

Meta-analysis description:
Measure: Standardized mean change (Hedges' corrected)
-        Known measures: 6
-        Non-statistically-significant unknown measures: 4
-        Imputations: 500
-        Model: measure ~ 1
-        Hypothesis: (Mean)=0
Residual heterogeneity (tau^2): 0.0003 I^2: 0.52% H^2: 1.01
Q-statistic (heterogeneity): 2.65 on 9 df Pr(>Q): 0.9767
```

```
Note: we strongly suggest focusing more on I^2 than on Pr(>Q)

Model:
Estimate Std. Error
(Mean)   0.4197   0.0744
One-row hypothesis:
Estimate z value Pr(>|z|) CI(low) CI(up)
(Mean)=0         0.4197 5.6373    <.0001 0.2738 0.5656 ***
---
Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
```

B The GUI

The main window of the GUI shows a table interface, which offers functionalities for entering and modifying the data. Rows correspond to studies and columns to variables. In a meta-analysis of one-sample studies, there must be a column called "study" with the labels of the studies, a column called "n1" with their sample sizes, and a column containing the outcome statistic (e.g., the t-value of each study). In a meta-analysis of two-sample studies, the column called "n1" must specify the sizes of the first group (e.g., the patients), and there must be another column called "n2" with the sample sizes of the second group (e.g., the controls). Figure 1 displays the main window with the buttons for managing data tables (New, Load and Save), as well as buttons for adding and deleting studies and/or variables.

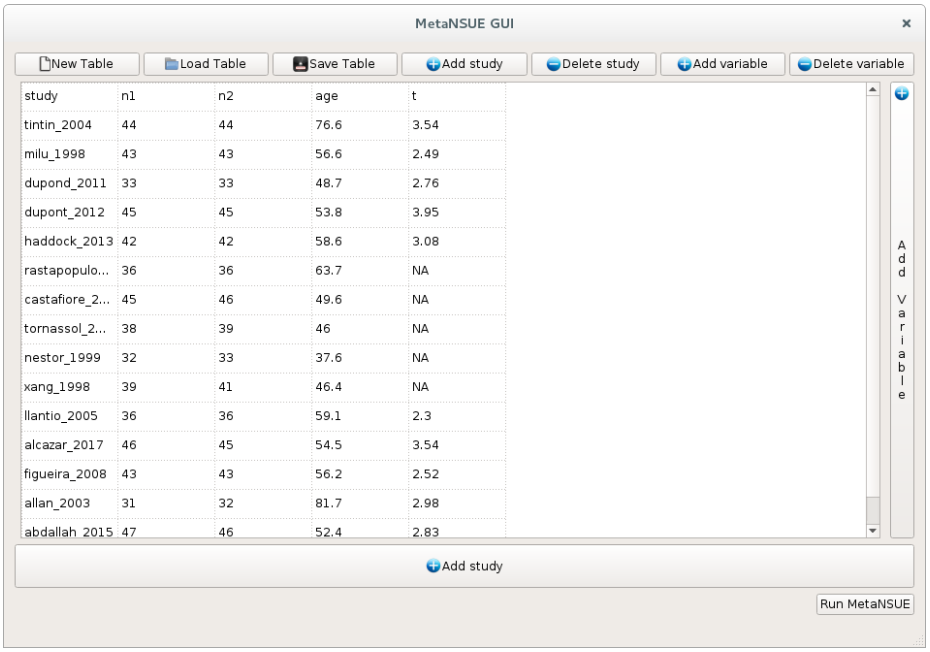


Figure 1: Main window of the GUI with an example data table loaded.

After saving the table, the user must press the button "Run MetaNSUE", at the bottom right of the main window. A dialog asks then the type of outcome (e.g., a correlation), the name of the variable specifying the outcome statistic (e.g., "t"), and whether the user wants to conduct a main analysis or a meta-regression. In case of a main analysis, a second dialog will ask which additional analyses and/or plots must be conducted. In case of a meta-regression, the user must select the modulators (and optionally specify a user-defined hypothesis matrix) (Figure 2).

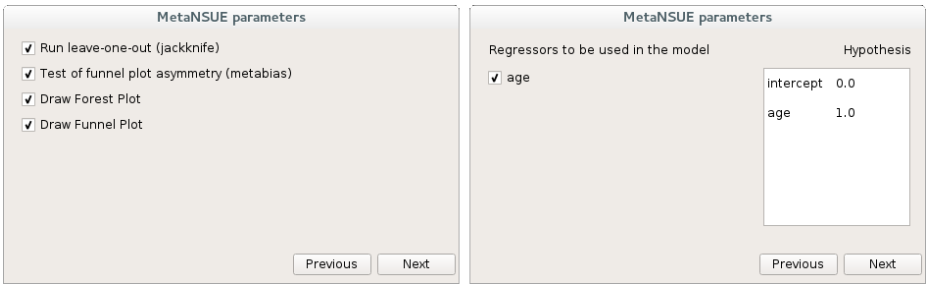


Figure 2: Dialogues for Mean (left) and Linear Model (right) analyses.

After pressing the button 'Launch MetaNSUE', a webpage with the results of the meta-analysis will be automatically open (see Section B for examples).

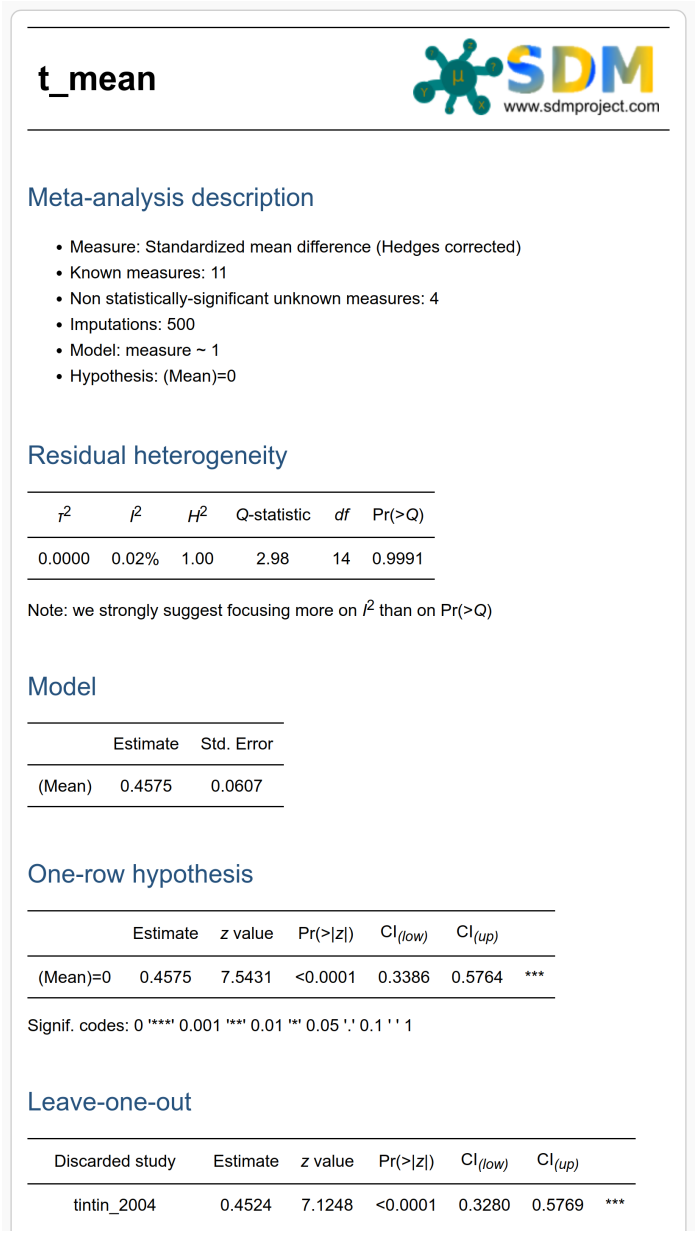
B.1 Example of main analysis

The file "example1.txt" contains simulated data of the differences in the blood levels of phosphate between patients with a given disorder and healthy controls. Within the GUI, press the button "Load table" and select the file "example1.txt" to load the data, which are organized in the following columns:

- "study": specifies a label for each study (here we used the name of the first author and the year of publication of the study),
- "n1": specifies the number of patients of each study,
- "n2": specifies the number of controls of each study,
- "t": specifies the t statistic of the t-test conducted in each study to compare the blood levels of phosphate between patients and controls.

Thus, the study in the first row was conducted by Tintin et al on 2004, included 43 patients and 44 controls, and the t statistic of its t-test was 2.35. The paper of the study in the second row, conducted by Milu et al on 2013, reports that it did not find statistically significant differences between patients and controls, but it does not report the actual value of the t statistic; this is the reason why this is coded as "NA" (Not Available).

To conduct the meta-analysis, press the button "Run MetaNSUE", select "Standard mean difference (2-sample)", "t" and "Main analysis (mean)", press the button "Next", select optional tests and plots, press the button "Next", and press the button "Launch MetaNSUE". The GUI will open the web file displayed in Figure 3.



t_mean

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Meta-analysis description

- Measure: Standardized mean difference (Hedges corrected)
- Known measures: 11
- Non statistically-significant unknown measures: 4
- Imputations: 500
- Model: measure ~ 1
- Hypothesis: (Mean)=0

Residual heterogeneity

τ^2	I^2	H^2	Q-statistic	df	Pr(>Q)
0.0000	0.02%	1.00	2.98	14	0.9991

Note: we strongly suggest focusing more on I^2 than on Pr(>Q)

Model

	Estimate	Std. Error
(Mean)	0.4575	0.0607

One-row hypothesis

	Estimate	z value	Pr(>|z|)	$CI_{(low)}$	$CI_{(up)}$	
(Mean)=0	0.4575	7.5431	<0.0001	0.3386	0.5764	***

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Leave-one-out

Discarded study	Estimate	z value	Pr(>|z|)	$CI_{(low)}$	$CI_{(up)}$	
tintin_2004	0.4524	7.1248	<0.0001	0.3280	0.5769	***

Figure 3: Results webpage for a meta-analysis of a 2-sample standard mean differences.

You can click the plots to use larger, high-resolution pictures, like the ones displayed in Figure 4.

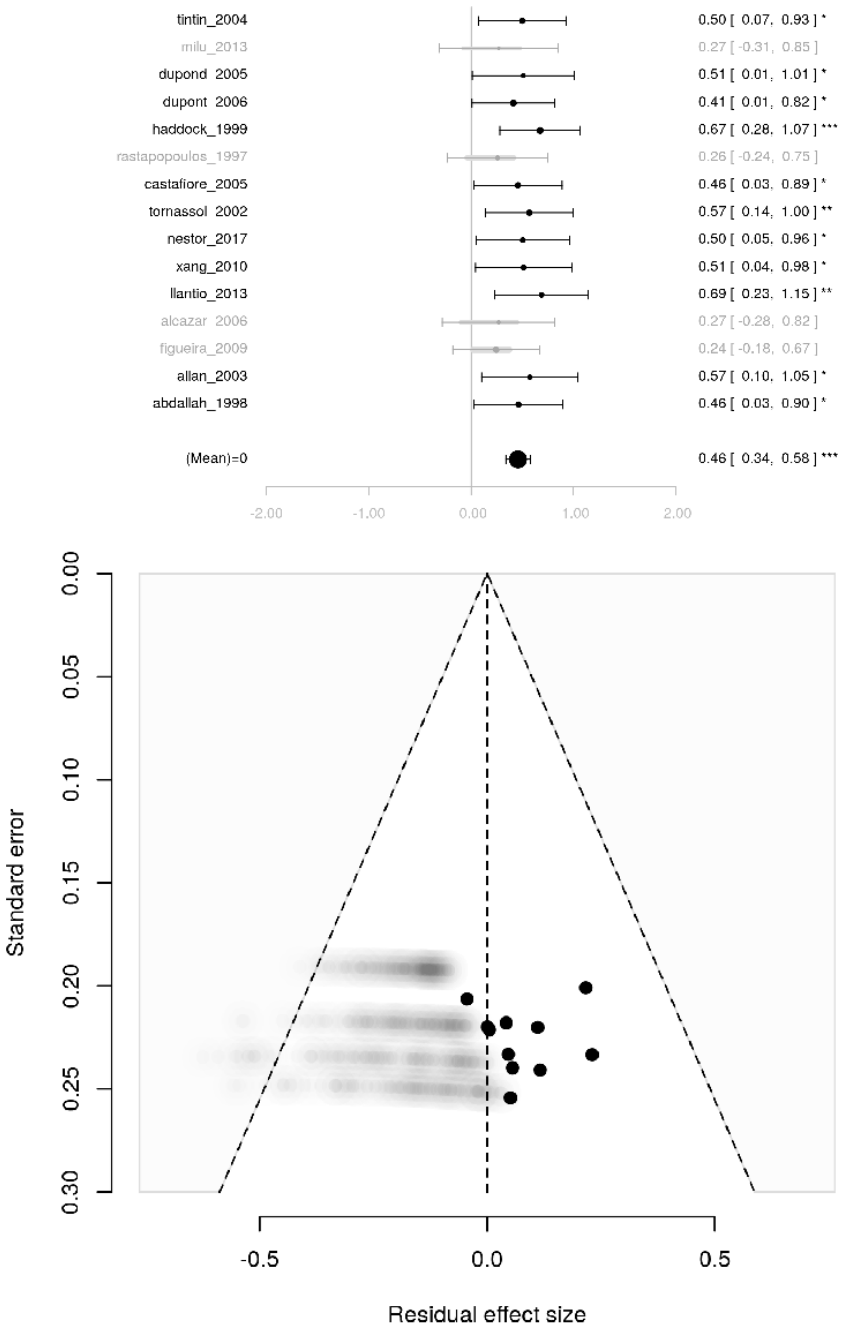

Figure 4: Forest plot (top) and funnel plot (bottom).

B.2 Example of meta-regression

The file "example2.txt"also contains simulated data of the differences in the blood levels of phosphate between patients with a given disorder and healthy controls, plus an additional column with the mean age of the participants of each study.

To know whether the differences between patients and controls are modulated by the age of the participants, press the button "Run MetaNSUE", select "Standard mean difference (2-sample)", "t" and "Meta-regression (linear model)", press the button "Next", select "age", press the button "Next", and press the button "Launch MetaNSUE". The GUI will open the web file displayed in Figure 5.

t_lm_age_0.0_1.0

Meta-analysis description

- Measure: Standardized mean difference (Hedges corrected)
- Known measures: 10
- Non statistically-significant unknown measures: 5
- Imputations: 500
- Model: measure ~ age
- Hypothesis: age=0

Residual heterogeneity

τ^2	I^2	H^2	Q-statistic	*df*	Pr(>Q)
0.0001	0.10%	1.00	5.57	13	0.9604

Note: we strongly suggest focusing more on I^2 than on Pr(>Q)

Model

	Estimate	Std. Error
(Intercept)	-0.0651	0.3522
age	0.0107	0.0061

One-row hypothesis

	Estimate	*z* value	Pr(>|z|)	$CI_{(low)}$	$CI_{(up)}$	
age=0	0.0107	1.7449	0.0810	-0.0013	0.0226	.

Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

MetaNSUE GUI is part of the SDM Project. To conduct other or more personalized analyses use MetaNSUE R package.

Figure 5: Results webpage for a meta-regression of a 2-sample standard mean differences using the variable "age" as a modulator.

C Probability of false positive meta-analyses due to single/few-study driven MLE

This probability may be estimated as follows. In a meta-analysis with N studies, the meta-analysis could be falsely positive if there was one falsely positive study and this positive study made the meta-analysis positive. However, the meta-analysis could also be falsely positive if there were two falsely positive studies and these two positive studies made the meta-analysis positive, or if there were three falsely positive studies and these three positive studies made the meta-analysis positive. In general, the meta-analysis could be falsely positive if there were k falsely positive studies and these k positive studies made the meta-analysis positive. Then, the overall probability is the sum of these probabilities:

$$P = \sum_{k=1}^{N} p_{\text{FP studies}}\left(k, N\right) \cdot p_{\text{FP meta-analysis}}\left(k, N\right) \tag{1}$$

where $p_{FPstudies}$ is the probability of having k falsely positive studies, and $p_{FPmeta-analysis}$ is the probability of having a falsely positive meta-analysis if there are k falsely positive studies. $p_{FPstudies}$ is simply the probability mass function of the binomial distribution and can be thus straightforwardly calculated. Conversely, $p_{FPmeta-analysis}$ does not have a simple expression but with simulations, we found that for $\alpha = 0.05$ can be approximated as:

$$p_{\text{FP meta-analysis}}\left(k, N\right) = \left(1 + \exp\left(\begin{array}{rl} 5.62 & if k = 1 \\ -0.82 + 0.059N & if k = 2 \\ 1.27 + 0.13k - 0.0075N & if k > 2 \end{array}\right)\right)^{-1} \tag{2}$$

Each leave-one-out iteration removes one potential falsely positive study, decreasing k, N, and the overall probability of having a falsely positive meta-analysis. The strategy to know the optimal number of studies to discard consists then in repeatedly conducting leave-one-out iterations until the overall probability of having a falsely positive meta-analysis is not higher than $\alpha = 0.05$. If the number of studies is very large, the number can be roughly derived from using a linear approximation.

D Other functions in the package

D.1 forest

This function creates a forest plot of the studies, showing the effect size of the studies on the x-axis and their standard errors on the y-axis. For studies with NSUE, a light gray shadow shows the 95% of the imputations.

D.2 funnel

This function creates a funnel plot of the studies, showing the residual effect size of the studies on the x-axis and their standard errors on the y-axis. For studies with NSUE, it plots the imputations in a light gray.

Asymmetry in the funnel plot is usually understood as an indication of publication bias, but this might not be always the case and the meta-analysts should be especially cautious because there are other causes of asymmetry, such as selective outcome reporting, poor methodological quality in the smaller studies, or true heterogeneity (i.e., effect size truly depends on study size). See an example of outcome in Figure 4

D.3 leave1out

This function is analogue to "meta" but, instead of meta-analyzing all the studies once, it meta-analyses all the studies but one n times. This is useful for exploring how each individual study affects the overall estimate of the rest of the studies.

D.4 metabias

This function conducts a meta-regression of the effect sizes of the studies by their standard errors. This aims to detect asymmetry in the funnel plot indicating potential publication bias, and consequently the meta-analysts should take the same caution than with funnel plots.

D.5 smc_from_t

This function converts one-sample t-values into standardized mean changes (smc). This is useful for studies evaluating changes in a numerical outcome (e.g. blood pressure before and after the administration of a drug), which commonly use one-sample t-tests. The conversion and its variance v are as follows:

$$y = \mathrm{J}\left(df\right) \cdot \sqrt{\frac{1}{n}} \cdot t \tag{3}$$

$$v = \frac{1}{n_i} + \left(1 - \frac{df - 2}{df \cdot \mathrm{J}(df)^2}\right) \cdot y^2 \tag{4}$$

where J is the exact form of the Hedges correction factor (Hedges & Olkin, 1985), df_i are the degrees of freedom, n_i is the sample size and t_i is the t-value. To note, J has been numerically improved for the final version of the method to accept large degrees of freedom using the combination of the R functions "exp" and "lgamma" instead of the function "gamma" (this expression should be multiplied

by -1 if $x < 1$):

$$\begin{aligned} \mathrm{J}(x) = &\exp\left[\mathrm{lgamma}\left(\frac{x}{2}\right)\right. \\ &\left.-0.5 \cdot \log\left(\frac{x}{2}\right) - \mathrm{lgamma}\left(\frac{x-1}{2}\right)\right] \end{aligned} \tag{5}$$

D.6 smd_from_t

This function converts two-sample t-values into standardized mean differences (smd). This is useful for studies evaluating differences between two groups in a numerical outcome (e.g. blood pressure in individuals treated with a drug vs. blood pressure in individuals treated with another drug), which commonly use two-sample t-tests. The conversion and its variance v are follows:

$$y = \mathrm{J}\left(df\right) \cdot \sqrt{\frac{1}{n_1} + \frac{1}{n_2}} \cdot t \tag{6}$$

$$v = \frac{1}{n_1} + \frac{1}{n_2} + \left(1 - \frac{df - 2}{df \cdot \mathrm{J}(df)^2}\right) \cdot y^2 \tag{7}$$

D.7 zcor_from_r

This function converts r correlation coefficients into z values using the Fisher transform:

$$y = \mathrm{atanh}(r) \tag{8}$$

where r is the correlation coefficient. This is useful for studies evaluating the relationship between a numerical factor and a numerical outcome (e.g. whether blood pressure depends on body mass index), which commonly use correlation tests. The variance of these z values is as follows:

$$v = \frac{1}{n - 3} \tag{9}$$

D.8 subset

This function returns a subset of the studies included in a “nsue” object, according to a logical condition.

D.9 coef, fitted, residuals

These functions extract the coefficients, fitted values or residuals of a ”meta.nsue” object.

References

Hedges, L., & Olkin, I. (1985). *Statistical methods for meta-analysis* [Book]. Orlando: Academic Press.

Viechtbauer, W. (2010). Conducting meta-analyses in r with the metafor package [Journal Article]. *Journal of Statistical Software*, *36*(3), 1-48. Retrieved from `https://www.jstatsoft.org/article/view/v036i03` doi: 10.18637/jss.v036.i03