Meta-analysis of Non Statistically-significant Unreported Effects (MetaNSUE), explained and revisited

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Abstract

This introduction to the R package **metansue** is a (slightly) modified version of a text submitted to the *Journal of Statistical Software*.

Published studies sometimes report that a difference or correlation was not statistically significant but do not report its effect size, or any statistic from which the latter may be derived. Unfortunately, these studies cannot be excluded from meta-analyses, because their exclusion would strongly bias the meta-analytic outcome, but can neither be included as null effect sizes because this strategy is also associated to bias. To overcome this problem we have previously developed and validated MetaNSUE, a novel method based on multiple imputations of the missing information. Here we present an updated R package with several numerical improvements to make the method more robust in extreme scenarios, as well as an easy-to-use Graphical User Interface for non-R users. We also include examples of its use.

Keywords: Meta-analysis, missing, non-reported, bias, correlation, standardized mean difference, standardized mean change, GUI, R.

1. Introduction

When conducting a meta-analysis, researchers may find that some studies report that the effect (e.g., a difference between two groups) was not statistically significant but do not report the specific value of the outcome, or any statistic from which the outcome may be derived (e.g., a t-value). These non-statistically-significant unreported effects (NSUE) cannot be excluded from the meta-analysis but can neither be included assuming them to be null. Note that they probably correspond to small effect sizes, and thus its exclusion would bias the meta-analysis upwards. However, they are not probably null, for what including them as null effect sizes would bias the meta-analysis downwards (Radua, Mataix-Cols, Phillips, El-Hage, Kronhaus, Cardoner, and Surguladze (2012)).

To correctly include studies with NSUEs into meta-analyses, we developed MetaNSUE, a novel method based on multiple imputations algorithms (Radua, Schmidt, Borgwardt, Heinz,

Schlagenhauf, McGuire, and Fusar-Poli (2015)). Briefly, the method consists in obtaining maximum likelihood estimations (MLE) of the missing outcomes (i.e., the NSUEs), adding noise to these estimations to multiply impute the NSUEs, conducting a meta-analysis for each set of imputations, and finally pooling these meta-analyses. Importantly, the bounds of statistical significance of the NSUEs are taken into account throughout the analyses.

In its empirical validation, we showed that estimations were strongly biased when conducting a standard meta-analysis without NSUEs, moderately negatively biased when converting NSUEs to zeros, and nearly unbiased when using MetaNSUE (Radua *et al.* (2015)). However, in subsequent uses we have detected that the method may be unstable in two extreme scenarios, namely in meta-analyses with seldom known data, or when studies use unconventional bounds (e.g., $9.9 < z < 10$). Relevantly, these scenarios are indeed common in some disciplines such as voxel-based neuroimaging.

The aim of this paper is two-fold. First, we detail a series of numerical modifications in the original implementation of the software to make the MLE substantially more robust in extreme scenarios. Second, we describe the **MetaNSUE** package for R as well as its new Graphical User Interface (GUI), freely available at www.metansue.com, www.sdmproject.com and at the CRAN repository.

2. Conversion of the raw statistics to effect sizes

Prior to the MLE step, known statistics (e.g., t-values) must be converted to effect sizes using standard formula (Radua *et al.* (2012)). The conversion is conducted with simple R functions, specific for each measure, that return an object of class "nsue":

- "smc_from_t" converts one-sample *t*-values into standard mean changes:

$$y_i = J\left(df_i\right) \cdot \sqrt{\frac{1}{n_i}} \cdot t_i \qquad (1)$$

  where J is the exact form of the Hedge correction factor (Hedges and 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 revisited version of the method for large degrees of freedom using the combination of the R functions "exp" and "lgamma" instead of the function "gamma".

- "smd_from_t" converts two-sample *t*-values into standard mean differences:

$$y_i = J\left(df_i\right) \cdot \sqrt{\frac{1}{n_{i,1}} + \frac{1}{n_{i,2}}} \cdot t_i \qquad (2)$$

  where $n_{i,1}$ is the size of the first group, and $n_{i,2}$ is the size of the second group.

- "z_from_r" converts r correlation coefficients into z values using the Fisher transform):

$$y_i = \operatorname{atanh}(r_i) \qquad (3)$$

  where r_i is the correlation coefficient.

Statistics in studies with NSUEs must be coded with "NA", so that the above functions know that these studies have NSUEs and use the alpha level of the studies to calculate the effect sizes corresponding to the bounds of non-statistical significance (i.e., the unknown effect-sizes must be within these bounds; otherwise, they would have reached statistical significance).

The variances of correlations only depend on sample sizes and thus can be straightforwardly derived:

$$v_i = \frac{1}{n_i - 3} \tag{4}$$

Conversely, the variances of standardized mean changes and differences depend on the effect sizes, which are unknown in NSUE studies. To overcome this problem, the formula of the variance is expressed as a function of two constants (k_1 and k_2) that only depend on the sample sizes (or the degrees of freedom) but allow a subsequent straightforward derivation of the variances:

$$v_i = k_{1,i} + k_{2,i} \cdot y_i^2$$
$$k_{1,i} = \begin{cases} \text{smc}: & \frac{1}{n_i} \\ \text{smd}: & \frac{1}{n_{i,1}} + \frac{1}{n_{i,2}} \end{cases} \tag{5}$$
$$k_{2,i} = 1 - \frac{df_i - 2}{df_i \cdot J(df_i)^2}$$

2.1. Study labels and correlation

Objects of class "nsue" also contain the labels of the studies, which beyond being useful for associating data to studies (e.g., in a forest plot), are used to indicate which studies are related (MetaNSUE understands that all studies with the same label are related). The expected correlation between dependent studies can also be specified.

2.2. Example of use

Before we start with the examples, the metansue package has to be loaded:

```
> library(metansue)
```

Then we can run the example:

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

'nsue' object description:
- Measure: standardized mean change
- Known measures: 6
- Non-statistically-significant unknown measures: 4

> str(x)
```

```
List of 8
 $ measure : chr "smc"
 $ y       : num [1:10] 0.527 NA NA NA NA ...
 $ y_lo    : num [1:10] -0.314 -0.449 -0.427 -0.408 -0.475 ...
 $ y_up    : num [1:10] 0.314 0.449 0.427 0.408 0.475 ...
 $ y2var_k1: num [1:10] 0.025 0.05 0.0455 0.0417 0.0556 ...
 $ y2var_k2: num [1:10] 0.0134 0.029 0.026 0.0235 0.0328 ...
 $ labels  : chr [1:10] "study1" "study2" "study3" "study4" ...
 $ rm      :List of 1
  ..$ r: num 0.3
 - attr(*, "class")= chr "nsue"
```

2.3. Special case: missing correlations in two-sample pre-post studies

Two-sample pre-post studies can be meta-analyzed with the R functions "smd_from_t" and "meta" (see below), i.e., imputing the unknown effect sizes of the between-group comparison of the pre-post effects. However, an alternative method consists in imputing the unknown correlations between pre and post measures, and using them, along with the reported means and standard deviations of the groups at the two time-points, to estimate the unknown effect sizes of the between-group comparison of the pre-post differences Harrison, Fernandez de la Cruz, Enander, Radua, and Mataix-Cols (2016). An advantage of this method may be that imputed data is ensured to follow the pre-post correlations. However, is inapplicable when means and standard deviations are not fully reported.

To apply this method, user can use the R function "r_in_smd_from_t_means_and_sds1", which calculates the (Fisher transform of the) pre-post correlation:

$$
\begin{aligned}
v_{pooled} &= \frac{df_1 \cdot v_1 + df_2 \cdot v_2}{df_1 + df_2} \\
&= \frac{df_1 \cdot (v_{1,pre} + v_{1,post} - 2 \cdot s_{1,pre} \cdot s_{1,post} \cdot r) + df_2 \cdot (v_{2,pre} + v_{2,post} - 2 \cdot s_{2,pre} \cdot s_{2,post} \cdot r)}{df_1 + df_2} \\
r &= \frac{df_1 \cdot (v_{1,pre} + v_{1,post} - v_{pooled}) + df_2 \cdot \left(v_{2,pre} + v_{2,post}^2 - v_{pooled}\right)}{2 \cdot (df_1 \cdot s_{1,pre} \cdot s_{1,post} + df_2 \cdot s_{2,pre} \cdot s_{2,post})}
\end{aligned}
\tag{6}
$$

where, m_j, s_j, v_j, df_j are the mean, standard deviation, variance and degrees of freedom of group j, v_{pooled} is the pooled variance (straightforwardly derived from t-values) and r is the pre-post correlation.

Correlations can be then imputed and meta-analyzed using the R function "meta". This meta-analysis is of no interest but we recommend that the user checks, e.g., that correlation values are plausible.

Finally, imputed correlations may be converted back to between-group comparisons of the pre-post differences (see (6)) using the R function "r_in_smd_from_t_means_and_sds2". This function also calls again the last part of the R function "meta", easily returning the meta-analysis of interest.

Example of use:

```
> t <- c(NA, -2.2, -3.0, -2.1, NA, -2.7, -2.6, -2.4, -3.2)
```

```
> n1 <- c(18, 15, 22, 17, 14, 23, 29, 24, 45)
> mean1.pre <- c(49.9, 49.9, 50.2, 49.8, 50.1, 50.0, 49.9, 51.0, 49.8)
> sd1.pre <- c(5.1, 5.2, 6.6, 5.3, 5.5, 3.6, 3.2, 5.9, 5.9)
> mean1.post <- c(65.6, 65.7, 66.0, 65.8, 66.6, 65.9, 66.0, 67.0, 65.9)
> sd1.post <- c(6.1, 7.3, 5.4, 6.1, 4.6, 7.1, 4.6, 2.8, 7.1)
> n2 <- c(18, 18, 23, 18, 16, 23, 27, 23, 45)
> mean2.pre <- c(50.8, 50.2, 50.0, 49.7, 49.8, 50.6, 49.8, 50.9, 49.9)
> sd2.pre <- c(5.2, 5.9, 4.0, 7.5, 5.7, 4.0, 5.8, 5.6, 5.4)
> mean2.post <- c(69.9, 70.3, 70.4, 69.8, 70.2, 70.0, 69.7, 70.8, 69.7)
> sd2.post <- c(5.2, 4.7, 4.5, 3.6, 3.7, 6.1, 4.6, 5.9, 6.2)
> r <- r_in_smd_from_t_means_and_sds1(t, n1, mean1.pre, sd1.pre,
+      mean1.post, sd1.post, n2, mean2.pre, sd2.pre, mean2.post, sd2.post)
> r


'nsue' object description:
- Measure: correlation in standardized mean difference
- Known measures: 7
- Non-statistically-significant unknown measures: 2


> mr <- meta(r)
> mr


Meta-analysis description:
- Measure: correlation in standardized mean difference
- Known measures: 7
- Non-statistically-significant unknown measures: 2
- Imputations: 500
- Model: measure ~ 1
- Hypothesis:  (Mean)=0

Residual heterogeneity (tau^2): 0.0269   I^2: 49.98%   H^2: 2.06
F-statistic (heterogeneity): 1.66 on 8 and 37816.2 df  Pr(>F): 0.1014


Model:
        Estimate  Std. Error
(Mean)    0.6270      0.0843


One-row hypothesis:
           Corr  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0  0.556   7.4395    <.0001    0.432   0.660  ***


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


> m <- r_in_smd_from_t_means_and_sds2(mr)
> m
```

```
Meta-analysis description:
- Measure: standardized mean difference
- Known measures: 7
- Non-statistically-significant unknown measures: 2
- Imputations: 500
- Model: measure ~ 1
- Hypothesis:  (Mean)=0


Residual heterogeneity (tau^2): 0.0000   I^2:  0.00%   H^2: 1.00
F-statistic (heterogeneity): 0.06 on 8 and 657883.4 df  Pr(>F): 0.9999


Model:
        Estimate  Std. Error
(Mean)   -0.7221      0.1023


One-row hypothesis:
           Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    -0.7221  -7.0565    <.0001   -0.9227  -0.5216   ***


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

3. NSUE meta-analysis

The command "meta" conducts the core steps of the analysis:

a) MLE of the unknown effect-sizes and between-study heterogeneity (Radua *et al.* (2015))

b) Multiple imputation of these unknown effect sizes based on the MLE (Rubin (1987))

c) Separate meta-analyses for each set of imputations (Viechtbauer (2010))

d) Pooling of the results of the meta-analyses (Li, Meng, Raghunathan, and Rubin (1991))

e) Hypothesis testing using the pooling statistics (Fox (2008))

3.1. Maximum likelihood estimation (MLE)

It must be highlighted that the MLE is conducted with the only aim to provide a basis for the subsequent multiple imputations of the unknown effects. Numbers resulting from this step cannot be understood as meta-analytic results, because they do not incorporate the complex body of variances involved in a meta-analysis. These variances are not only important per se, but also for the estimation of the effect sizes.

Weight for related studies

As in a general linear model, the researcher could deal with related studies by specifying the correct factors in the design matrix. However, a simpler and more convenient approach

in some meta-analyses is to combine each group of related studies into a single "combined study" with decreased variance (Alegria, Radua, and Rubia (2016)Norman, Carlisi, Lukito, Hart, Mataix-Cols, Radua, and Rubia (2016)Rubia, Alegria, Cubillo, Smith, Brammer, and Radua (2014)). To this end, MetaNSUE calculates a MLE weight for each study according to the following formula (Radua *et al.* (2015)):

$$w_i = \frac{1}{1 + (R_i - 1) \cdot r} \tag{7}$$

where R_i is the number of studies with the same label as the ith study and r is the expected correlation specified in the "nsue" object. Note that with this adjustment, the overall weight of a group of related studies is:

$$R_i \cdot w_i = \frac{R_i}{1 + (R_i - 1) \cdot r} \tag{8}$$

Note that $R_i \cdot w_i = 1$ if $r_r = 1$ (i.e., the related studies are indeed the same), $R_i \cdot w_i = R_i$ if $r_r = 0$ (i.e., the "related" studies are indeed unrelated), and $1 < R_i \cdot w_i < R_i$ if r lies between 0 and 1.

The log-likelihood

MLE is based on finding the parameters that maximize the likelihood of the data. Specifically, the likelihood to maximize is the multiplication of the likelihood of each reported effect size (obtained with the probability density function, *pdf*) and the likelihood that each unreported effect size lays within its two effect size bounds (obtained with the probability mass function, *pmf*):

$$L\left(\theta; y_i, \ldots; v_i^2, \ldots; w_i, \ldots; y_{\alpha/2,j}, y_{1-\alpha/2,j}, \ldots; v_{\alpha/2,j}^2, v_{1-\alpha/2,j}^2, \ldots; w_j, \ldots\right)$$
$$= \prod_{i=1}^{N_1} pdf\left(y_i; v_i^2|\theta\right)^{w_i} \cdot \prod_{j=1}^{N_2} pmf\left(y_{\alpha/2,j}, y_{1-\alpha/2,j}; v_{\alpha/2,j}^2, v_{1-\alpha/2,j}^2|\theta\right)^{w_j} \tag{9}$$

where θ are the parameters to be estimated, y are effect sizes, v^2 their variances, N_1 is the number of reported effect sizes, N_2 is the number of studies with NSUEs.

The parameters to estimate include not only the coefficients of interest (usually the intercept, i.e., the main outcome of a meta-analysis) but also regressors that may be used to better estimate the effect size of a study. The original version of MetaNSUE also included the between-study heterogeneity τ^2 as a parameter to estimate, but the revisited version conducts this estimation in a subsequent step due to the modifications described in the next section.

Assuming normality, the *pdf* is simply:

$$pdf\left(y_i, v_i^2|\beta\right) = \frac{1}{v_i}\phi\left(\frac{y_i - X_i \cdot \beta}{v_i}\right) = \frac{1}{v_i} \cdot \frac{1}{\sqrt{2\pi}} \cdot \exp\left(-\frac{1}{2} \cdot \left(\frac{y_i - X_i \cdot \beta}{v_i}\right)^2\right) \tag{10}$$

where X_i is the ith row of the design matrix of the model of covariates, β is the vector of coefficients of the model of covariates, and ϕ is the probability density function of the standard normal distribution.

The pmf is the difference of the cumulated distribution function evaluated at the upper and lower effect size bounds:

$$pmf\left(y_{\alpha/2,i}, y_{1-\alpha/2,i}; v^2_{\alpha/2,i}, v^2_{1-\alpha/2,i}|\beta\right) = \Phi\left(\frac{y_{1-\alpha/2,i} - X_i \cdot \beta}{v_{1-\alpha/2,i}}\right) - \Phi\left(\frac{y_{\alpha/2,i} - X_i \cdot \beta}{v_{\alpha/2,i}}\right) \quad (11)$$

where Φ is the cumulated distribution function of the standard normal distribution.

In practice it is more convenient to minimize the minus log-likelihood than to directly maximize the likelihood. Thus, the expression to minimize is the sum of the minus logarithms of the pdf or pmf of each study.

The minus logarithm of the pdf is again relatively simple:

$$
\begin{aligned}
-log\left(pdf\left(y_i, v_i^2|\beta\right)\right) &= \log(v_i) + \frac{1}{2} \cdot \log(2\pi) + \frac{1}{2} \cdot \frac{(y_i - X_i \cdot \beta)^2}{v_i^2} \\
&= \frac{1}{2} \cdot \log(2\pi) + \frac{1}{2} \cdot \log(v_i^2) + \frac{1}{2} \cdot \frac{(y_i - X_i \cdot \beta)^2}{v_i^2} \\
&= (ct.) + \frac{1}{2} \cdot \left[\log(v_i^2) + \frac{(y_i - X_i \cdot \beta)^2}{v_i^2}\right]
\end{aligned}
\quad (12)
$$

Conversely, the logarithm of the pmf may be numerically unstable in an extreme scenario when the two expressions inside the cumulated distributed are large and close. To overcome numerical errors, the revisited version of MetaNSUE includes the following transformation:

$$
\begin{aligned}
\log\left(\Phi(m) - \Phi(n)\right) &= \log\left(\Phi(m) \cdot \left(1 - \frac{\Phi(n)}{\Phi(m)}\right)\right) \\
&= \log\left(\Phi(m)\right) + \log\left(1 - \frac{\Phi(n)}{\Phi(m)}\right) \\
&= \Phi_{\log}(m) + \log\left(-\left(\frac{\Phi(n)}{\Phi(m)} - 1\right)\right) \\
&= \Phi_{\log}(m) + \log\left(-\left(\exp\left(\log\left(\frac{\Phi(n)}{\Phi(m)}\right)\right) - 1\right)\right) \\
&= \Phi_{\log}(m) + \log\left(-\left(\exp\left(\log\left(\Phi(n)\right) - \log\left(\Phi(m)\right)\right) - 1\right)\right) \\
&= \Phi_{\log}(m) + \log\left(-\left(\exp\left(\Phi_{\log}(n) - \Phi_{\log}(m)\right) - 1\right)\right) \\
&= \Phi_{\log}(m) + \log\left(-\text{expm1}\left(\Phi_{\log}(n) - \Phi_{\log}(m)\right)\right)
\end{aligned}
\quad (13)
$$

where $\text{expm1}(x)$ is equivalent to $e^x - 1$ but with increased numerical accuracy. For $m = 10$ and $n = 9.9$, the initial expression wrongly returns $-\infty$, whereas the last, equivalent expression correctly returns -52.7.

Minimization of the minus log-likelihood is conducted using the R function "optimize" when there is a single coefficient and with the R function "optim" when there are two or more coefficients. The latter function requires initial values for the parameters, which in the original version were simply the mean for the intercept and zeroes for the remaining coefficients. In the revisited version, these initial values are better estimated with a fixed-effects meta-analysis (assuming NSUEs to be the mean of their upper and lower bounds).

Leave-one-out protection

When nearly all studies of a meta-analysis are NSUEs, there is a possibility that the single or few studies with known measures drive the MLE, potentially leading to a falsely positive meta-analysis. This situation may be detected in a subsequent leave-one-out jack-knife analysis when the artifact is clearly produced by a single study. For example, this was the case for reward feedback in Radua *et al.* (2015). However, the issue could potentially be unnoticed in less extreme situations.

To minimize this possibility, the revisited version of MetaNSUE presented in this work includes a leave-one-out protection within the MLE step, which consists in iteratively discarding the study that increases the most the MLE effect size. Specifically, the MLE is first estimated with all studies but the first, then with all studies but the second, then with all studies but the third, and so on, and only the combination returning the lowest absolute MLE effect size is kept.

When the number of studies is large, this iteration may have to be repeated several times. In each iteration, one additional study is discarded. This process is repeated until the probability that the meta-analysis is falsely positive due to the issue is not higher than 0.05 even in the worst-case scenario (i.e., when all studies with not-statistically significant effect sizes are NSUEs). 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:

$$P = \sum_{k=1}^{N} p_{\text{FP studies}}(k, N) \cdot p_{\text{FP meta-analysis}}(k, N) \tag{14}$$

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:

$$p_{\text{FP meta-analysis}}(k, N) = \left(1 + \exp \left(\begin{array}{ll} 5.62 & if\, k = 1 \\ -0.82 + 0.059N & if\, k = 2 \\ 1.27 + 0.13k - 0.0075N & if\, k > 2 \end{array} \right) \right)^{-1} \tag{15}$$

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 is roughly approximated using a linear simplification.

When the user does not aim to conduct a simple, mean meta-analysis but a meta-regression or other linear models, studies in the leave-one-out iterations must be discarded according

to the effect size of the hypothesis of interest, rather than according to the effect size of the mean. For this reason, the user must specify the hypothesis to contrast before conducting the MLE, and a new MLE must be conducted for each other new hypothesis.

Estimation of heterogeneity τ^2

Once the coefficients have been estimated, a second MLE step is conducted to estimate the between-study heterogeneity parameter τ^2 using all studies. The likelihood to maximize is the same as in (9), and we have added the same numerical improvements described in (13). However, the *pdf* and *pmf* described in (10) and (11) are modified to include τ^2 (and to use $e_i = y_i - X_i \cdot \beta$ instead of y_i):

$$
\begin{aligned}
pdf\left(e_i, v_i^2 | \tau^2\right) &= \frac{1}{\sqrt{v_i^2 + \tau^2}} \phi\left(\frac{e_i}{\sqrt{v_i^2 + \tau^2}}\right) \\
&= \frac{1}{\sqrt{v_i^2 + \tau^2}} \cdot \frac{1}{\sqrt{2\pi}} \cdot \exp\left(-\frac{1}{2} \cdot \frac{e_i^2}{v_i^2 + \tau^2}\right) \\
-log\left(pdf\left(y_i, v_i^2 | \tau^2\right)\right) &= \frac{1}{2} \cdot \log\left(v_i^2 + \tau^2\right) + \frac{1}{2} \cdot \log\left(2\pi\right) + \frac{1}{2} \cdot \frac{e_i^2}{v_i^2 + \tau^2} \\
&= \frac{1}{2} \cdot \log\left(2\pi\right) + \frac{1}{2} \cdot \log\left(v_i^2 + \tau^2\right) + \frac{1}{2} \cdot \frac{e_i^2}{v_i^2 + \tau^2} \\
&= (ct.) + \frac{1}{2} \cdot \left[\log\left(v_i^2 + \tau^2\right) + \frac{e_i^2}{v_i^2 + \tau^2}\right]
\end{aligned}
\tag{16}
$$

$$
pmf\left(e_{\alpha/2,i}, e_{1-\alpha/2,i}; v_{\alpha/2,i}^2, v_{1-\alpha/2,i}^2 | \tau^2\right) = \Phi\left(\frac{e_{1-\alpha/2,i}}{\sqrt{v_{1-\alpha/2,i}^2 + \tau^2}}\right) - \Phi\left(\frac{e_{\alpha/2,i}}{\sqrt{v_{\alpha/2,i}^2 + \tau^2}}\right)
\tag{17}
$$

3.2. Multiple imputation

The multiplication of X and β returns the expected value of the effect size of each NSUE study. For example, if $\beta = (3.2, 0.2)$ and $X_i = (1, 2)$, the expected value of the effect size for this i^{th} study is $1 \times 3.2 + 2 \times 0.2 = 3.6$. Then, the multiple imputation step consists in adding Gaussian noise to the expected value in order to have realistic imputations. In the example, random noise would be added to 3.6 so that imputation 1 could be 3.3, imputation 2 could be 3.7, and etcetera. Note that imputing the NSUE studies using their *expected* value without added noise, would erroneously mean assuming that both within-study variability and between-study heterogeneity are null.

The addition of noise must meet two conditions: a) the noise must be the sum of the variance of the effect size plus τ^2; and b) the noisy imputation must be between the effect size bounds. The truncated normal distribution accommodates these conditions, and thus each imputation

is a random generation of:

$$pdf\left(y_i|\theta\right) = \frac{\frac{1}{\sqrt{v_i^2 + \hat{\tau}^2}} \cdot \phi\left(\frac{y_i - \hat{y}_i}{\sqrt{v_i^2 + \hat{\tau}^2}}\right)}{\Phi\left(\frac{y_{i,1-\alpha/2} - \hat{y}_i}{\sqrt{v_i^2 + \hat{\tau}^2}}\right) - \Phi\left(\frac{y_{i,\alpha/2} - \hat{y}_i}{\sqrt{v_i^2 + \hat{\tau}^2}}\right)}, y_i \in \left(y_{i,\alpha/2}, y_{i,1-\alpha/2}\right) \tag{18}$$

However, it must be noted that for some measures such as standardized mean differences, the variance depends on the imputed effect sizes (rather than on the sample size alone). Therefore, in those imputations in which the noise decreases the effect size, the variance is smaller and the study receives more weight. Conversely, in those imputations in which the noise increases the effect size, the variance is larger and the study receives less weight. In order to avoid this bias, the probability of a given effect size is weighted by the inverse of the weight (i.e., the variance) that the effect size would receive in a subsequent meta-analysis:

$$pdf\left(y_i|\theta\right) = \frac{\left(\hat{v}_{i,y_i}^2 + \hat{\tau}^2\right) \cdot \frac{1}{\sqrt{\hat{v}_{i,\hat{y}_i}^2 + \hat{\tau}^2}} \cdot \phi\left(\frac{y_i - \hat{y}_i}{\sqrt{\hat{v}_{i,\hat{y}_i}^2 + \hat{\tau}^2}}\right)}{\int_{x=y_{i,\alpha/2}}^{y_{i,1-\alpha/2}} \left(\left(\hat{v}_{i,x}^2 + \hat{\tau}^2\right) \cdot \frac{1}{\sqrt{\hat{v}_{i,\hat{y}_i}^2 + \hat{\tau}^2}} \cdot \phi\left(\frac{x - \hat{y}_i}{\sqrt{\hat{v}_{i,\hat{y}_i}^2 + \hat{\tau}^2}}\right)\right)}, y_i \in \left(y_{\alpha/2}, y_{1-\alpha/2}\right) \tag{19}$$

In practice, the continuum between the bounds is divided in a number of bins; the probability of each bin is calculated using the numerator of (19), and a bin is randomly selected according to its probability.

Also important, the noise for related studies is created accounting for the correlations between them. Specifically, instead of straightforwardly using the expected values and variances as in (18) or (19), these are conditioned to the observed and/or to the already imputed related studies (Radua *et al.* (2015)). For example, for two related studies, the expected value and variance of the first study are simply as in (18) or (19), whereas the expected value and variance of the second study are:

$$\begin{pmatrix} \hat{y}_{2,1}^* \\ \vdots \\ \hat{y}_{2,n_{imp}}^* \end{pmatrix} = \begin{pmatrix} y_{1,1} \\ \vdots \\ y_{1,n_{imp}} \end{pmatrix} \times \hat{\gamma} \tag{20}$$

$$\hat{v}_2^{*2} = \hat{v}_2^2 - \hat{\gamma}^\top \times \hat{\Pi}_{XX} \times \hat{\gamma}$$

where $y_{1,j}$ is the jth imputation of the study 1, n_{imp} is the number of imputations, and $\hat{\gamma}$ and $\hat{\Pi}_{XX}$ are the coefficients and covariance matrix of the linear model used to predict the expected values and variances of the study 2 from the imputations of study 1:

$$\hat{\gamma} = \hat{\Pi}_{XX}^{-1} \times \hat{\Pi}_{XY}$$
$$\hat{\Pi}_{XX} = \left(\hat{v}_1^2 + \hat{\tau}^2\right)$$
$$\hat{\Pi}_{XY} = \left(\sqrt{\hat{v}_1^2 + \hat{\tau}^2}\right) \cdot \sqrt{\hat{v}_2^2 + \hat{\tau}^2} \cdot r \tag{21}$$

3.3. Meta-analysis, pooling and hypothesis testing

After the multiple imputation step, there are several datasets of complete data. For each imputed dataset, related studies are combined so that each group of related studies is converted into a single study. The effect size of this "combined study" is simply the mean effect size of the corresponding related studies, whereas the variance of the "combined study" is the mean variance of the corresponding related studies divided by the sum of the weights calculated in (7). In other words, the variance of the "combined study" is reduced by (Alegria *et al.* (2016)Norman *et al.* (2016)Rubia *et al.* (2014)):

$$\sum_{i=1}^{R_i} w_i = \sum_{i=}^{R_i} \frac{1}{1 + (R_i - 1) \cdot r} = \frac{R_i}{1 + (R_i - 1) \cdot r} \tag{22}$$

The resulting datasets can be meta-analyzed using standard formula. As in the "metafor" package Viechtbauer (2010), MetaNSUE estimates τ^2 using restricted-maximum likelihood (REML) for its statistical advantages (Viechtbauer (2005)), and the covariates included in the MLE step are also included here in the modeling to allow testing meta-regressions or other linear models:

$$\beta = \Lambda \times X^\top \times W \times Y$$
$$\Lambda = \left(X^\top \times W \times X \right)^{-1}$$
$$H^2 = 1 + \frac{\hat{\tau}^2_{REML}}{df} \cdot trace\left(P_{FE}\right) \tag{23}$$
$$I^2 = 1 - \frac{1}{H^2}, \quad I^2 \geq 0$$
$$Q = Y^\top \times P_{FE} \times Y, \quad Q \geq 0$$

where β are the coefficients, Λ is their covariance matrix, H^2, I^2 and Q are heterogeneity statistics, and:

$$W = diag\left(1/\hat{v}_i^2 + \hat{\tau}^2_{REML}, ... \right)$$
$$P_{FE} = W_{FE} - W_{FE} \times X \times \left(X^\top \times W_{FE} \times X \right)^{-1} \times X^\top \times W_{FE} \tag{24}$$
$$W_{FE} = diag\left(1/\hat{v}_i^2, ... \right)$$

After a meta-analysis has been conducted for each imputation dataset, the resulting statistics are pooled Li *et al.* (1991) in order to have a single vector of coefficients and a single covariance matrix:

$$\beta_{pooled} = mean\left(\beta\right)$$
$$\sigma^2_{pooled} = mean\left(\sigma^2\right) + \left(1 + \frac{1}{n_{imp}}\right) \cdot var\left(\sigma^2\right) \tag{25}$$

Finally, the hypothesis specified by the user is tested using the pooled statistics:

$$\beta_H = H \times \beta_{pooled}$$
$$\sigma^2_H = H \times \Lambda_{pooled} \times H^\top \tag{26}$$
$$Z = \frac{\beta_H}{\sigma_H}$$

As commented earlier, if the user wants to test another hypothesis, the process must be repeated from the MLE step, typing the "meta" command again.

3.4. Example of use

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


Meta-analysis description:
- Measure: standardized mean change
- Known measures: 6
- Non-statistically-significant unknown measures: 4
- Imputations: 500
- Model: measure ~ 1
- Hypothesis:  (Mean)=0


Residual heterogeneity (tau^2): 0.0016   I^2:  2.63%   H^2: 1.04
F-statistic (heterogeneity): 0.30 on 9 and 8677.7 df  Pr(>F): 0.9763


Model:
       Estimate  Std. Error
(Mean)   0.4212      0.0738


One-row hypothesis:
         Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0   0.4212   5.7075    <.0001   0.2765   0.5658  ***


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


> str(m)


List of 10
 $ measure     : chr "smc"
 $ y2var_k1    : num [1:10] 0.025 0.05 0.0455 0.0417 0.0556 ...
 $ y2var_k2    : num [1:10] 0.0134 0.029 0.026 0.0235 0.0328 ...
 $ labels      : chr [1:10] "study1" "study2" "study3" "study4" ...
 $ rm          :List of 3
  ..$ r      : num 0.3
  ..$ M      : num [1:10, 1:10] 1 0 0 0 0 0 0 0 0 0 ...
  ..$ weights: num [1:10] 1 1 1 1 1 1 1 1 1 1
 $ known       :List of 2
  ..$ i: int [1:6] 1 6 7 8 9 10
```

```
  ..$ y: num [1:6] 0.527 0.498 0.407 0.551 0.475 ...
 $ unknown      :List of 2
  ..$ i: int [1:4] 2 3 4 5
  ..$ y: num [1:4, 1:500] 0.3437 0.3824 0.1041 0.0831 0.146 ...
 $ model        :List of 6
  ..$ formula: chr "~ 1"
  ..$ matrix : num [1:10, 1] 1 1 1 1 1 1 1 1 1 1
  ..$ labels : chr "(Mean)"
  ..$ coef   : num 0.421
  ..$ cov    : num [1, 1] 0.00545
  ..$ se     : num 0.0738
 $ heterogeneity:List of 4
  ..$ tau2: num 0.00161
  ..$ h2  : num 1.04
  ..$ i2  : num 0.0263
  ..$ q   :'data.frame':        1 obs. of  4 variables:
  .. ..$ f      : num 0.295
  .. ..$ df1    : int 9
  .. ..$ df2    : num 8678
  .. ..$ p.value: num 0.976
 $ hypothesis   :List of 6
  ..$ text   : chr "(Mean)=0"
  ..$ matrix : num [1, 1] 1
  ..$ coef   : num 0.421
  ..$ se     : num [1, 1] 0.0738
  ..$ z      : num [1, 1] 5.71
  ..$ p.value: num [1, 1] 1.15e-08
 - attr(*, "class")= chr "meta.nsue"
```

4. Other functions in the package

4.1. forest

This function creates a forest plot of the studies, showing their effect sizes and the 95% confidence intervals. For studies with NSUE, a light gray shadow shows the interval containing 95% of the imputations. The function also returns the optimal width and height of the plot.

Example of use

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

```
Use pdf(filename, width, height) before calling forest to save it.
The optimal width and height of this plot is ~7 x ~4 inches.
```

See an example of outcome in Figure 4

4.2. 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, a light gray shadow shows the ellipse containing 95% of the imputations.

Asymmetry in the funnel plot is usually understood as an indication of publication bias, but this might not be always the case and the researcher 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).

Example of use

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

```
Use pdf(filename) before calling funnel to save it.
```

See an example of outcome in Figure 4

4.3. 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.

Example of use

```
> t <- c(3.4, NA, NA, NA, NA, 2.8, 2.1, 3.1, 2.0, 3.4)
> n <- c(40, 20, 22, 24, 18, 30, 25, 30, 16, 22)
> x <- smc_from_t(t, n)
> summary(leave1out(x))
```

```
Meta-analysis model: smc ~ 1

Discarded study: study1
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
```

```
(Mean)=0     0.3962    4.7448     <.0001    0.2325    0.5598   ***


Discarded study: study2
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4405   5.8078    <.0001    0.2919   0.5892   ***


Discarded study: study3
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4391   5.7428    <.0001    0.2892   0.5889   ***


Discarded study: study4
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4447   5.8428    <.0001    0.2955   0.5939   ***


Discarded study: study5
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4352   5.6955    <.0001    0.2855   0.5850   ***


Discarded study: study6
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4075   5.0409    <.0001    0.2491   0.5659   ***


Discarded study: study7
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4184   5.2559    <.0001    0.2624   0.5744   ***


Discarded study: study8
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.3994   4.9297    <.0001    0.2406   0.5581   ***


Discarded study: study9
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4153   5.2563    <.0001    0.2605   0.5702   ***


Discarded study: study10
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.3895   4.9735    <.0001    0.2360   0.5430   ***
```

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

4.4. 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 researcher should take the same caution than with funnel plots.

Example of use

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

        'meta.nsue' regression test for funnel plot asymmetry

data:  m
z = -0.4166, p-value = 0.677
```

4.5. subset

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

Example of use

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

'nsue' object description:
- Measure: standardized mean change
- Known measures: 6
- Non-statistically-significant unknown measures: 4

> sx <- subset(x, n > 20)
> sx

'nsue' object description:
- Measure: standardized mean change
- Known measures: 5
- Non-statistically-significant unknown measures: 2
```

5. 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.
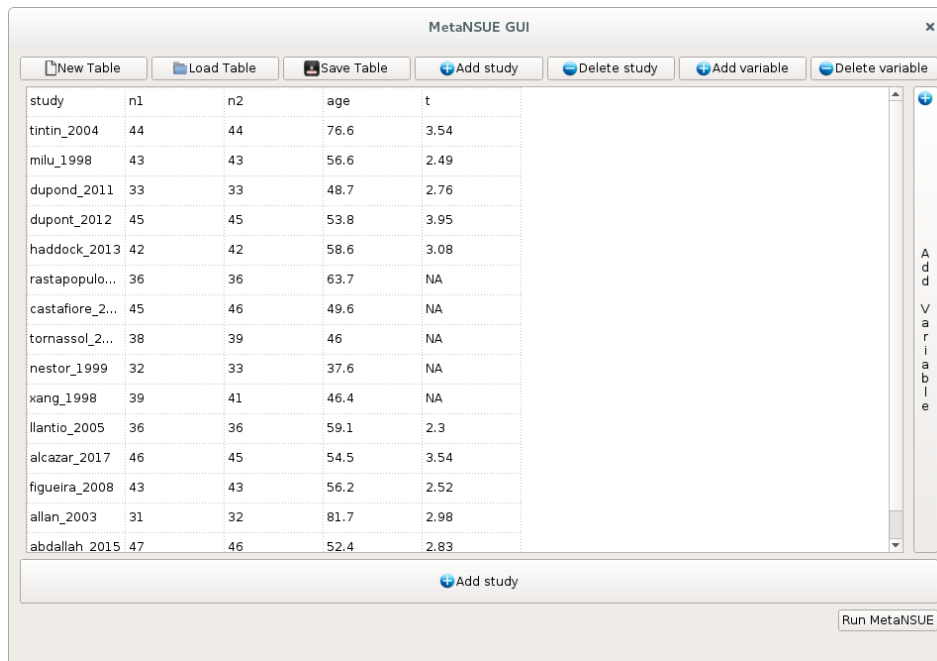

Figure 1: Main window of the GUI with an example data table loaded.

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).

After pressing the button 'Launch MetaNSUE', a webpage with the results of the meta-analysis will be automatically open (see Section 6 for examples).
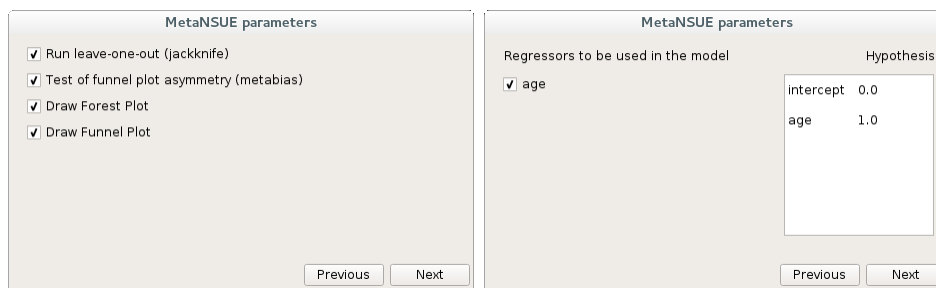
6. Worked examples

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

6.1. 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.

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

Find below the code to conduct the same analysis within R:

```
> data <- read.table("example1.txt", header = TRUE)
> y <- smd_from_t(data$t, data$n1, data$n2, labels = data$study)
> m <- meta(y)
> m

Meta-analysis description:
- Measure: standardized mean difference
```
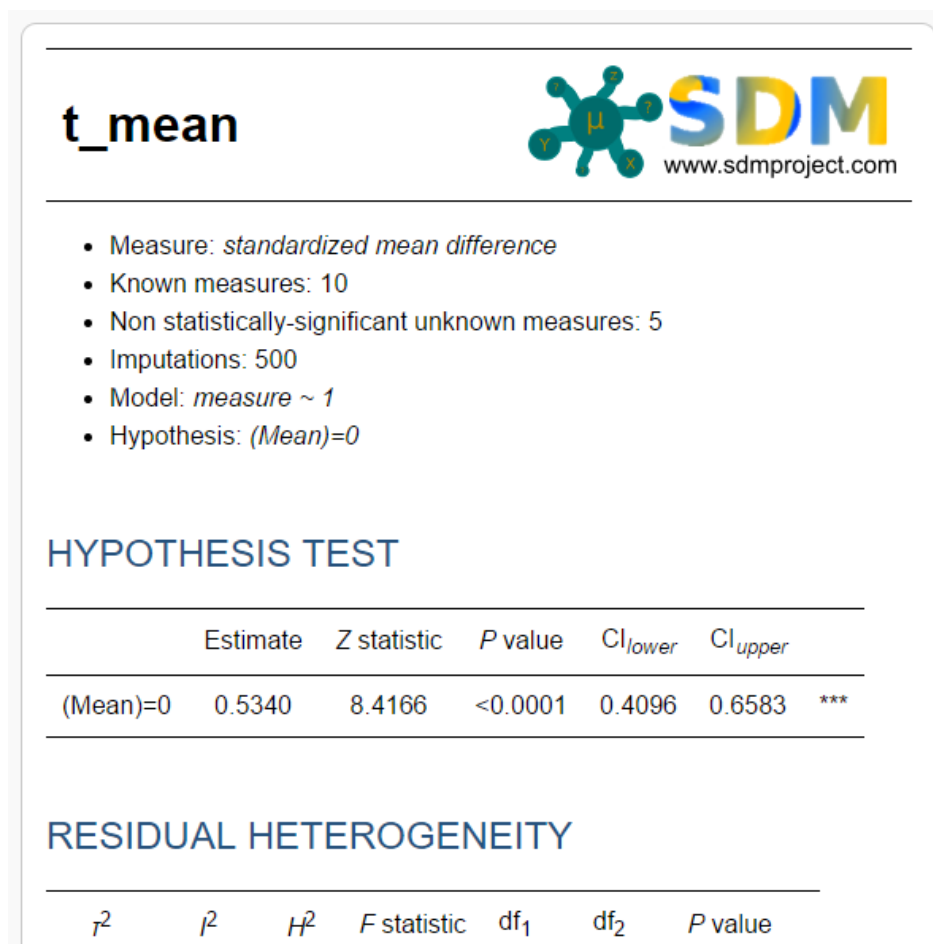
Figure 3: Results webpage for a meta-analysis of a 2-sample standard mean differences.

```
- Known measures: 11
- Non-statistically-significant unknown measures: 4
- Imputations: 500
- Model: measure ~ 1
- Hypothesis:  (Mean)=0

Residual heterogeneity (tau^2): 0.0004   I^2:  0.60%   H^2: 1.01
F-statistic (heterogeneity): 0.20 on 14 and 9549.7 df  Pr(>F): 0.9994

Model:
       Estimate  Std. Error
(Mean)   0.4568      0.0609

One-row hypothesis:
         Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0   0.4568   7.5003    <.0001   0.3374   0.5762  ***
```
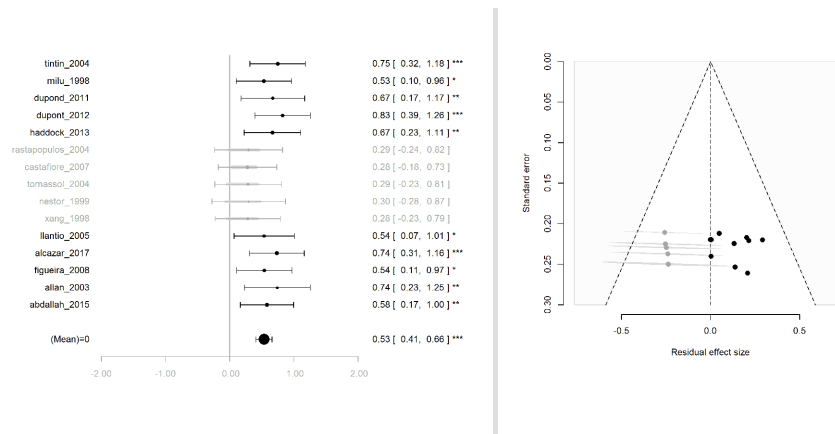
Figure 4: Forest plot (left) and funnel plot (right).

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


> summary(leave1out(y))


Meta-analysis model: smd ~ 1


Discarded study: tintin_2004
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0   0.4529   7.1292    <.0001    0.3284   0.5774  ***


Discarded study: milu_2013
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0   0.4685   7.5535    <.0001    0.3469   0.5901  ***


Discarded study: dupond_2005
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0   0.4540   7.2451    <.0001    0.3312   0.5768  ***


Discarded study: dupont_2006
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0   0.4606   7.2402    <.0001    0.3359   0.5853  ***


Discarded study: haddock_1999
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)  CI(up)
(Mean)=0   0.4345   6.8318    <.0001    0.3098   0.5592  ***
```

```
Discarded study: rastapopoulos_1997
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4729   7.5731    <.0001   0.3505   0.5953  ***


Discarded study: castafiore_2005
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4569   7.1768    <.0001   0.3321   0.5817  ***


Discarded study: tornassol_2002
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4467   7.0348    <.0001   0.3222   0.5711  ***


Discarded study: nestor_2017
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4533   7.2288    <.0001   0.3304   0.5762  ***


Discarded study: xang_2010
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4518   7.1477    <.0001   0.3279   0.5757  ***


Discarded study: llantio_2013
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4399   6.9291    <.0001   0.3155   0.5644  ***


Discarded study: alcazar_2006
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4714   7.6483    <.0001   0.3506   0.5921  ***


Discarded study: figueira_2009
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4797   7.6737    <.0001   0.3572   0.6022  ***


Discarded study: allan_2003
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4497   7.1575    <.0001   0.3266   0.5729  ***


Discarded study: abdallah_1998
```

```
One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4563   7.2237    <.0001   0.3325   0.5801  ***

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

> metabias(m)

        'meta.nsue' regression test for funnel plot asymmetry

data:  m
z = 0.34988, p-value = 0.7264

> forest(m)

Use pdf(filename, width, height) before calling forest to save it.
The optimal width and height of this plot is ~8 x ~6 inches.

> funnel(m)

Use pdf(filename) before calling funnel to save it.
```

6.2. 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.

Find below the code to conduct the same analysis within R:

```
> data <- read.table("example2.txt", header = TRUE)
> y <- smd_from_t(data$t, data$n1, data$n2, labels = data$study)
> meta(y, ~ data$age)

Meta-analysis description:
- Measure: standardized mean difference
- Known measures: 10
- Non-statistically-significant unknown measures: 5
- Imputations: 500
- Model: measure ~ data$age
```
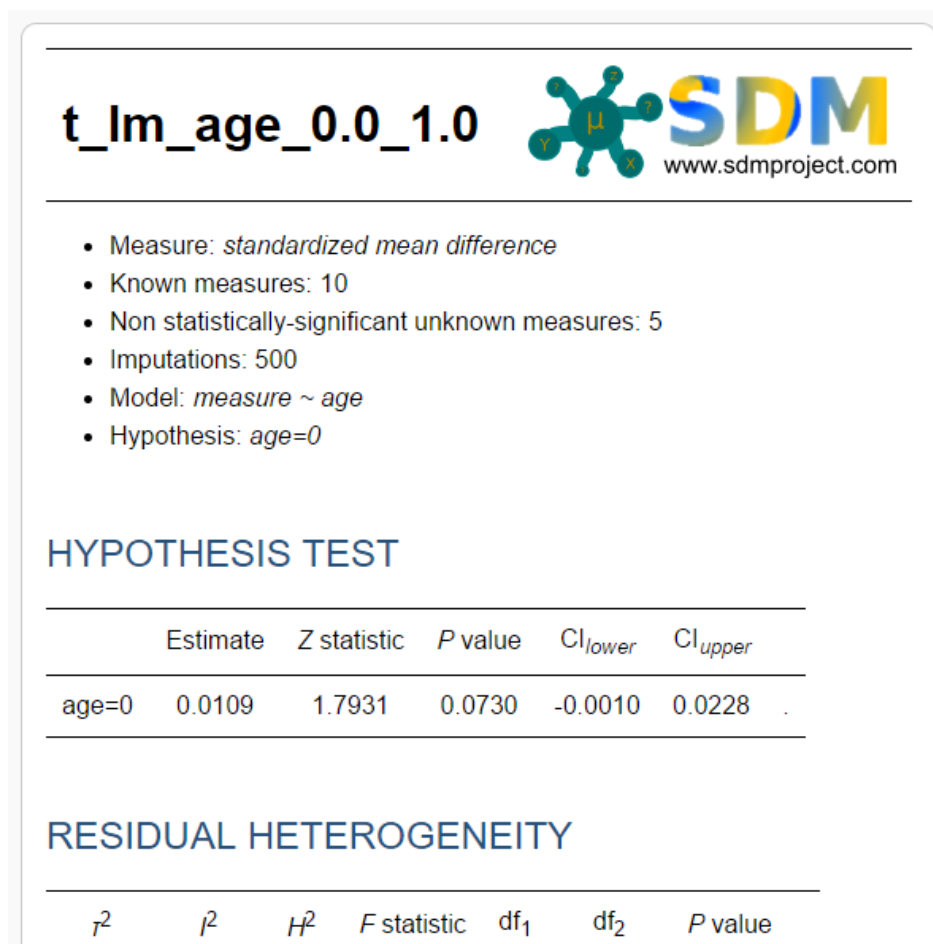
Figure 5: Results webpage for a meta-regression of a 2-sample standard mean differences using the variable "age" as a modulator.

```
- Hypothesis:  data$age=0

Residual heterogeneity (tau^2): 0.0012   I^2:  1.78%   H^2: 1.02
F-statistic (heterogeneity): 0.40 on 13 and 14371.6 df  Pr(>F): 0.9700


Model:
            Estimate  Std. Error
(Intercept)  -0.0699      0.3537
data$age      0.0107      0.0061


One-row hypothesis:
            Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
data$age=0    0.0107   1.7509    0.0800  -0.0013   0.0228   .


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

6.3. Tables without missing data

The files "example1_truth.txt" and "example2_truth.txt" contain the same data, but the NSUEs have been replaced by the actual t statistics obtained during the simulation of the studies. The user may repeat the analyses and find that the results are similar to those above, and identical to the ones obtained with the "metafor" package Viechtbauer (2010).

```
> data <- read.table("example1_truth.txt", header = TRUE)
> y <- smd_from_t(data$t, data$n1, data$n2, labels = data$study)
> meta(y)


Meta-analysis description:
- Measure: standardized mean difference
- Known measures: 15
- 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
F-statistic (heterogeneity): 0.52 on 14 and Inf df  Pr(>F): 0.9208

Model:
       Estimate  Std. Error
(Mean)   0.4572      0.0577

One-row hypothesis:
          Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
(Mean)=0    0.4572   7.9228    <.0001   0.3441   0.5703  ***

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

> library(metafor)
> n <- nrow(data)
> y <- escalc(measure = "SMD", vtype = "UB",
+           m1i = data$t * sqrt(1 / data$n1 + 1 / data$n2),
+           n1i = data$n1, n2i = data$n2,
+           m2i = rep(0, n), sd1i = rep(1, n), sd2i = rep(1, n))
> rma(y)


Random-Effects Model (k = 15; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.0187)
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 = 14) = 7.3393, p-val = 0.9208


Model Results:


estimate       se     zval     pval    ci.lb    ci.ub
  0.4572   0.0577   7.9228   <.0001   0.3441   0.5703        ***


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

> data <- read.table("example2_truth.txt", header = TRUE)
> y <- smd_from_t(data$t, data$n1, data$n2, labels = data$study)
> meta(y, ~ data$age)

Meta-analysis description:
- Measure: standardized mean difference
- Known measures: 15
- Non-statistically-significant unknown measures: 0
- Imputations: 0
- Model: measure ~ data$age
- Hypothesis:  data$age=0


Residual heterogeneity (tau^2): 0.0000   I^2:  0.00%   H^2: 1.00
F-statistic (heterogeneity): 0.58 on 13 and Inf df  Pr(>F): 0.8707


Model:
            Estimate  Std. Error
(Intercept)   -0.0909      0.3223
data$age       0.0112      0.0057


One-row hypothesis:
            Estimate  z value  Pr(>|z|)  CI(low)   CI(up)
data$age=0    0.0112   1.9717    0.0486   0.0001   0.0223 *


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

> n <- nrow(data)
> y <- escalc(measure = "SMD", vtype = "UB",
+          m1i = data$t * sqrt(1 / data$n1 + 1 / data$n2),
+          n1i = data$n1, n2i = data$n2,
+          m2i = rep(0, n), sd1i = rep(1, n), sd2i = rep(1, n))
> rma(y, mods = data$age)

Mixed-Effects Model (k = 15; tau^2 estimator: REML)
```

```
tau^2 (estimated amount of residual heterogeneity):    0 (SE = 0.0202)
tau (square root of estimated tau^2 value):            0
I^2 (residual heterogeneity / unaccounted variability): 0.00%
H^2 (unaccounted variability / sampling variability):  1.00
R^2 (amount of heterogeneity accounted for):           NA%


Test for Residual Heterogeneity:
QE(df = 13) = 7.5656, p-val = 0.8707


Test of Moderators (coefficient(s) 2):
QM(df = 1) = 3.8877, p-val = 0.0486


Model Results:

         estimate       se     zval     pval    ci.lb    ci.ub
intrcpt   -0.0909   0.3223  -0.2820   0.7779  -0.7225   0.5407
mods       0.0112   0.0057   1.9717   0.0486   0.0001   0.0223  *


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

7. Discussion

This paper presents an improved version of MetaNSUE, a novel meta-analytic software that can include studies that report that the outcome was not statistically significant but do not report the actual outcome. This version includes numerical improvements, making the software more robust in extreme scenarios, as well as a new, easy-to-use GUI. With these improvements, we hope that both R users and non-R users are able to conduct robust MetaNSUE meta-analyses rather than, incorrectly, excluding NSUE studies or assuming that they have a null effect size.

Acknowledgements

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