**Name of journal: *World Journal of Meta-Analysis***

**ESPS Manuscript NO: 16292**

**Manuscript Type: Meta-Analysis**

**How to impute study-specific standard deviations in meta-analyses of skewed continuous endpoints**

Greco T *et al.* Study-specific standard deviations imputation in meta-analysis

**Teresa Greco, Giuseppe Biondi-Zoccai, Marco Gemma, Claude Guérin, Alberto Zangrillo, Giovanni Landoni**

**Teresa Greco,** Laboratorio di Statistica Medica, Biometria ed Epidemiologia “G. A. Maccacaro”, Dipartimento di Scienze Cliniche e di Comunità, University of Milan, 20133 Milan, Italy

**Teresa Greco, Marco Gemma, Alberto Zangrillo, Giovanni Landoni,** Anaesthesia and Intensive Care Department, IRCCS San Raffaele Scientific Institute, 20132 Milan, Italy

**Giuseppe Biondi-Zoccai,** Department of Medico-Surgical Sciences and Biotechnologies, Sapienza University of Rome, 04100 Latina, Italy

**Giuseppe Biondi-Zoccai,** Eleonora Lorillard Spencer Cenci Foundation, 00185 Rome, Italy

**Giuseppe Biondi-Zoccai,** Meta-analysis and Evidence based medicine Training in Cardiology (METCARDIO), 18014 Ospedaletti, Italy

**Claude Guérin,** Medical Intensive Care, Hospital de La Croix Rousse, 69317 Lyon, France

**Author contributions:** All authors contributed equally to this work; Greco T conceived the study, participated in its design and coordination, did the analyses and revised the manuscript critically; Biondi-Zoccai G and Gemma M conceived the study, helped in interpretation of data and to draft the Manuscript; Guérin C, Zangrillo A and Landoni G conceived the study, participated in its design and coordination, drafted the manuscript; all authors read and approved the manuscript.

**Conflict-of-interest statement:** The authors declare that there are no conflicts of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. This work is part of the PhD program in Biomedical Statistics, University of Milan, Italy.

**Data sharing statement:** Technical appendix, statistical code, and dataset are available in the Supplemental Material and from the corresponding author (at greco.teresa@hotmail.it), who will provide a permanent, citable, and open-access home for the dataset.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Correspondence to: Teresa Greco, MSc,** Laboratorio di Statistica Medica, Biometria ed Epidemiologia “G. A. Maccacaro”, Dipartimento di Scienze Cliniche e di Comunità, University of Milan, Via Festa del Perdono 7, 20133 Milan, Italy. greco.teresa@hotmail.it

**Telephone:** +39-02-26436153

**Received:** January 8, 2015

**Peer-review started:** January 10, 2015

**First decision:** June 3, 2015

**Revised:** June 26, 2015

**Accepted:** July 24, 2015

**Article in press:**

**Published online:**

**Abstract**

**AIM:** To compare four methods to approximate mean and standard deviation (SD) when only median and interquartile ranges are provided.

**METHODS:** We performed simulated meta-analyses on six datasets of 15, 30, 50, 100, 500, and 1000 trials respectively. Subjects were iteratively generated from one of the following seven scenarios: five theoretical continuous distributions [Normal, Normal (0, 1), Gamma, Exponential, Bimodal] and two real-life distributions of Intensive Care Unit stay and hospital stay. For each simulation, we calculated the pooled estimates assembling the study-specific medians and SD approximations: conservative SD, less conservative SD, mean SD, or interquartile range. We provided a graphical evaluation of the standardized differences. To show which imputation method produced the best estimate, we ranked those differences and calculated the rate at which each estimate appeared as the best, second-best, third-best, or fourth-best.

**RESULTS:** Our results demonstrate that the best pooled estimate for the overall mean and SD is provided by the median and interquartile range (mean standardized estimates: 4.5 ± 2.2, *P* = 0.14) or by the median and the SD conservative estimate (mean standardized estimates: 4.5 ± 3.5, *P* = 0.13). The less conservative approximation of SD appears to be the worst method, exhibiting a significant difference from the reference method at the 90% confidence level. The method that ranked first most frequently is the interquartile range method (23/42 = 55%), particularly when data were generated according to the Standard Normal, Gamma, and Exponential distributions. The second-best is the conservative SD method (15/42 = 36%), particularly for data from a bimodal distribution and for the Intensive Care Unit stay variable.

**CONCLUSION:** Meta-analytic estimates are not significantly affected by approximating the missing values of mean and standard deviation with the correspondent values for median and interquartile range.

**Key words:** Imputation; Interquartile range; Meta-analysis; Randomized controlled trial; Standard deviation

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Meta-analyses of continuous endpoints are generally supposed to deal with normally distributed data and the pooled estimate of the treatment effect relies on means and standard deviations. However, if the outcome distribution is skewed, some authors correctly report the median together with the corresponding quartiles. In the present work, we compared methods for the approximation of means and standard deviations when only medians with quartiles are provided. Our results demonstrate that meta-analytic estimates are not significantly affected by approximating the missing values of mean and standard deviation with the correspondent values for median and interquartile range.

Greco T, Biondi-Zoccai G, Gemma M, Guérin C, Zangrillo A, Landoni G. How to impute study-specific standard deviations in meta-analyses of skewed continuous endpoints. *World J Meta-Anal* 2015; In press

**INTRODUCTION**

Meta-analysis (MA) is a powerful statistical method that merges the results of different studies considering the same outcome variables. The included studies are mainly randomized controlled trials with experimental and control arms. MA aims at assessing the treatment effect size under scrutiny, at identifying sources of heterogeneity among the included studies, at unrevealing patterns behind the available data, and sometimes at identifying new subgroup associations. Some authors believe that MA represents the highest level of evidence to provide recommendations on clinical issues.

Just as many other innovative statistical techniques, MA is still a matter of intense debate, since many of its assumptions are critical and even small violations of them can lead to misleading conclusions[1]. The appeal of MA resides also in the quick and cost-effective way it yields useful pieces of information for clinical decision making. Hence, MAs are published and quoted with an impressive increasing frequency and it seems evident that, despite their limitations, they will continue to play a crucial role in medical decision-making in the foreseeable future.

Meta-analyses of continuous outcomes exploit data with a Gaussian distribution, so that the pooled estimate computation requires the study-specific mean, standard deviation (SD), and sample size of the variable at stake. The easiest way to compare the outcomes of two treatment groups is to evaluate the difference between their means[2]. If measurements are expressed with the same unit, the mean difference between the treatment and the control group can be used. Results from trials in which the same outcome is measured with different units can be compared by using SDs units rather than absolute differences[2,3]. However, if data are reported in a limited or incomplete way, it can be difficult or impossible to obtain sufficient information to perform a correct summary of the results. Missing SD and non-compliance in reporting collected data are common limitations in MAs of continuous outcomes.

If the outcome has a skewed distribution, authors often report in the original paper the median together with the 1st and 3rd quartiles, rather than the mean with its SD. MA authors arbitrarily combine these study-specific estimates to approximate the missing SD. In addition, some authors combine together means (SD) and medians (1st and 3rd quartiles) from different studies.

In this setting, the most immediate question is whether it is legitimate to approximate study-specific means and SDs from study-specific medians and quartiles and how to do it in the most appropriate way.

In the present work we simulated MA of continuous outcomes generated from seven different distributions and we compared four methods to approximate SDs when only study-specific medians and quartiles are available. For each simulation we calculated a pooled estimate by assembling the individual medians and, in turn, all four SD approximations. Finally, we compared these results with those obtained by pooling the individual means and SDs.

To our knowledge, this is the first study on how to impute the study-specific mean and SD in meta-analyses of skewed outcomes. After a failed tentative of comparing results coming from published studies, the present paper compares the available methods making use of both simulations and real-life set-ups to identify the best and the worst SD-approximation.

**MATERIALS AND METHODS**

***Simulation algorithm***

We generated six datasets of 15, 30, 50, 100, 500, and 1000 trials respectively. Each trial is based on an equal number of treated and control subjects which is fixed at the number of trials included in the MA under examination. The distributions of the continuous endpoints for the treatment and control groups are respectively generated according to Table 1. The first five scenarios provided the basis for our analysis on simulated data. The last two scenarios of Table 1 represent our real-life data and are randomly extracted from an Italian observational study with more than 7000 patients with cardiovascular disease.

In summary, we generated 1695 (15 + 30 + 50 + 100 + 500 + 1000) trials for each of the seven distribution scenarios for a total of 11865 trials. For each trial we calculated the principal measures of position, mean and median, and variability, SD and interquartile range (IQR).

All simulations and analyses were performed using SAS (release 9.2, 2002-2008 by SAS Institute Inc., Cary, NC, United States)[4]. An example of SAS code is reported in Table 2.

***Simulated*** MA

For each of the six datasets we carried out a series of MAs differing with respect to the method of imputation of the study-specific SD[2], as described in Table 3.

For each distribution scenario, 30 MAs were therefore performed (6 datasets × 5 methods).

Each MA was carried out using a fixed effect model with the Inverse-Variance method[3].

The global estimate is the mean difference between treatment and control groups, obtained by pooling individual means and SDs.

***Comparison of estimates***

For each distribution scenario we computed four standardized estimates, $θ\_{stand\_{ijk}}$, calculated as:

$θ\_{stand\_{ijk}}=\frac{θ\_{ijk}- θ\_{reference\_{jk}}}{se\left(θ\_{ijk}\right)}$ for $i=1,2,3,4;j=15, 30, …1000 and k=1,2,…,7.$

where $θ\_{ijk}$ is the pooled mean difference resulting from the performed MA, $se\left(θ\_{ijk}\right)$ is the corresponding standard error and $θ\_{reference\_{jk}}$ is the global estimate obtained by pooling individual means and SDs for each dataset and distribution scenario.

We obtained a total of 168 standardized estimates (7 distributions × 6 dataset × 4 methods).

***Statistical model***

After blocking for dataset and distribution, we evaluated if the standardized estimates, calculated by each of the four methods, were different from zero in the framework of a repeated measures model using the MIXED PROCEDURE implemented in the SAS software. Statistical significance was set at the two-tailed 0.05 level for hypothesis testing. Adjustment for multiple comparison was performed with Tukey-Kramer, Bonferroni and Scheffé corrections[5,6].

***Ranking***

To identify which imputation method produced the pooled estimate $θ\_{ijk}$ with the minimum difference from the reference one, $θ\_{reference\_{jk}}$, we ranked each standardized estimate $θ\_{stand\_{ijk}}$ for each dataset and for each distribution scenario. According to this ranking, we calculated the rate at which each estimate appeared as the best, second-best, third-best, or fourth-best[7] and the area under the cumulative ranking curve[8].

***Literature screening***

We screened all the best published studies reported in the medical literature on critically ill patients included in the 1st web based International Consensus Conference[9] to assess which information authors of original papers provided in the case of ICU and hospital stay outcome. We contacted the corresponding authors by e-mail when one or more of the following information was missing: mean, SD, median, 1st-3rd quartiles. No manuscript provided all of the information requested and only 3 authors replied to our e-mail providing the extra information needed.

***Statistical analysis***

The statistical methods of this study were reviewed by Rosalba Lembo from San Raffaele Scientific Institute, Via Olgettina 60, 20132 Milan, Italy.

**RESULTS**

Table 4 reports the $θ\_{stand\_{ijk}}$ means and the corresponding unadjusted and adjusted *P*-values to assess the presence of a significant difference from zero. Conservative SD and IQR methods showed the lowest mean difference (with mean standardized estimates equal to 4.5 ± 3.5 for conservative SD and 4.5±2.2 for IQR methods respectively). The less conservative SD method appeared to be the worst, exhibiting the highest difference from the reference.

Table 5 shows the $θ\_{stand\_{ijk}}$ estimates for each distribution, dataset, and imputation method and some descriptive statistics. For each distribution, the number of times each standardized estimate ranked first is indicated. The method that ranked first most frequently was IQR (23/42 = 55%), particularly when the data were generated according to the Standard Normal, Gamma, and Exponential distributions. The second best is the Conservative SD method (15/42 = 36%), which was particularly suitable for data with a bimodal distribution and for the ICU stay variable. The quartiles at the bottom of Table 5 were similar for these two methods: 1.62 (0.27-4.94) and 1.40 (0.34-4.86) respectively. Figures 1 and 2 show plots of the pooled estimates for all distribution scenarios. The difference between $θ\_{stand\_{ijk}}$ and reference values increased together with the increased number of trials in each MA.

Table 6 reports the rate of occurrence as best, second-best, third-best and fourth-best, for the four imputation methods. The conservative SD and IQR methods most often appeared as best or second-best (cumulative frequencies: 35/42 and 41/42 respectively), the Less conservative SD and mean SD methods as third- or fourth-best. The less conservative SD method was identified as the worst method as it has by far the highest number of fourth positions. Even when it ranked first, the $θ\_{stand\_{ijk}}$ was very similar to the IQR method, which is consistently suitable for any distribution scenario.

Figure 3 shows the areas under the cumulative ranking curve for each imputation method. IQR method yields the largest area.

**DISCUSSION**

The aim of our work was to clarify how to best impute study-specific mean and SD when only the median and 1st and 3rd quartiles are provided.

It is notoriously good practice to report information on medians and quartiles for skewed distributions but standard meta-analytic approaches require study-specific means and SDs, so that careful evaluation of the best trade-off between these two approaches is needed.

This issue is of prominent interest when dealing with MA, but few scientific works addressed this topic. Hozo *et al*[10] described two formulas for estimating the mean from the median, range, and sample size values. Pigott[11] discussed and examined how to deal with missing data (studies, effect size, methodological information) during MA. Furukawa *et al*[12,13] reported on the imputation of the missing response rate from the mean ± SD[12] and suggested that borrowing the missing SD from other studies included in the MA may be a valid solution[13]. Thiessen Philbrook *et al*[14] compared results from MAs that either were restricted to available data or imputed the missing variance with one of four methods (*P*-values, nonparametric summaries, multiple imputation, or correlation coefficients). Robertson *et al*[15] highlighted and evaluated different ways to include in MAs studies in which the treatment effect was not provided. Weibe *et al*[16] conducted a systematic review of methods for handling missing variances in MAs of continuous outcomes and classified the relevant approaches into eight groups: algebraic recalculation, approximate algebraic recalculation, study-level imputation, study-level imputation from nonparametric summaries, study-level imputation of correlation (for change-from-baseline or crossover SD and to calculate the design effect for cluster studies), MA-level imputation of overall effect, MA-level tests, and no-imputation methods. Finally, Stevens[17] gave an overview of the Bayesian approach to deal with missing data in MA. However, authors who carry out MAs rarely adopt similar methods in their current clinical practice.

In the present study, we showed that MA pooled estimates are not significantly affected by approximating the missing study-specific mean and SD with the corresponding median and IQR, in both simulated and real-life set-ups. In comparison with the other methods, we examined, the Median-IQR method has extra advantages, since it is the simplest one and it makes no assumption on the underlying distribution of the data. Furthermore, we showed how the use of a less conservative approximation of SD can bias the meta-analytic pooled estimate when authors work with skewed data. Nevertheless, it is well known that median and mean values are very different as the data distribution is skewed[2].

Our study has several limitations. First, we did not perform a sensitivity analysis with the random effect model. However, since data were generated from the same distribution for each trial we decided to apply fixed effect models. Second, we did not analyzed mixed set-ups in which study-specific means and SDs are available for some studies and others are imputed. Third, we worked only on trials where the number of treated/control subjects was equal to the number of studies included in the MA. It follows that we did not consider set-ups with many studies and few subjects or vice-versa. Although we present several distribution scenarios, the choice of their parameters was arbitrary. However, the performance is not expected to change with different parameters.

It is not surprising that many papers report median and IQR, rather than mean and SD. Actually this is considered good practice when dealing with non-normally distributed data. As an example, since the distributions of ICU or hospital stay are skewed, it might be worth using median and IQR when setting up any MA with these end-points.

***Conclusion***

Our work supports the procedure of using study-specific medians and quartiles to impute means and standard deviations. This avoids the dangerous practice of not including in the MA studies with missing information. Nevertheless, we recognize that, in order to improve the quality of future MAs, authors of research papers should report as much information as possible at least for concerning their primary outcomes. We suggest that authors who use median and interquartile range in MAs with continuous endpoints, perform a sensitivity analysis in which trials not providing study-specific means and SDs are excluded.

**COMMENTS**

***Background***

Meta-analyses (MA) of continuous outcomes exploit data with a Gaussian distribution, so that the pooled estimate computation requires the study-specific means, standard deviations (SD), and sample sizes. However, should data be reported in a limited or incomplete way, it can be difficult or impossible to obtain sufficient information to perform a correct summary of the results. Missing standard deviations and non-compliance in reporting collected data are common limitations in meta-analyses of continuous outcomes. At the simpler level, an interest emerged as to the opportunity and the best way to approximate on study-specific means and standard deviations from study-specific medians and quartiles.

***Research frontiers***

The aim of our work was to clarify how to best impute study-specific mean and standard deviation when only the median and 1st and 3rd quartiles are provided. We compared the available methods in simulated and real-life set-ups to identify the best and the worst one.

In the present study, we showed that MA pooled estimates are not significantly affected by approximating the missing study-specific mean and SD with the corresponding median and interquartile range. Among the four methods proposed, this one has the extra advantages that it is the simplest one and that makes no assumption on the underlying distribution of the data.

***Innovations and breakthroughs***

For the first time, to our knowledge, this manuscript provides a list of four available approximation methods in MAs of skewed outcomes. The authors became aware of these methods in the clinical practice and we strongly believe in the good practice to report information on medians and quartiles when a distribution is skewed. However, standard meta-analytic approaches require study specific means and SDs and it was natural to us to find out a compromise between this two needs. This issue is important when carrying out a MA, but few scientific works addressed this topic. Authors described formulas and estimating procedures to work with missing data in a MA, in either frequentist and Bayesian approaches. However, authors who carry out MAs rarely adopt similar methods in their current clinical practice.

***Applications***

The work gives support to the procedure of using study-specific medians and quartiles to impute means and SDs in a MA of skewed outcome. This avoids the dangerous practice of not including in the MA studies with missing information.

***Terminology***

Approximation: An estimate of the value of a quantity to a desired degree of accuracy; Conservative estimate: Estimate that avoids excess in approximating the quantity or worth of the list of (potentially infinite) values identified; Distribution: List of the values in a population, or sample, with the corresponding frequency or probability of occurrence; Estimate: A value (a point estimate) or range of values (an interval estimate) to a parameter of a population on the basis of sampling statistics; Interquartile range: Measure of dispersion around the median given by the difference between the 3rd quartile and 1st quartile of the distribution; these quartiles can be clearly seen on a box-plot of the data; Study-specific: Related to a specific study included in a more comprehensive MA (*i.e.*, group of study).

***Peer-review***

The study addresses a very interesting topic and deals with a major concern for investigators who have to perform a meta-analysis from published studies.

**REFERENCES**

1 **Greco T**, Zangrillo A, Biondi-Zoccai G, Landoni G. Meta-analysis: pitfalls and hints. *Heart Lung Vessel* 2013; **5**: 219-225 [PMID: 24364016]

2 **Higgins JPT**, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. The Cochrane collaboration 2011. [accessed 2015 Jun]. Available from: URL: http://www.cochranehandbook.org/

3 **Rothstein HR**, Sutton AJ, Borenstein M. Publication Bias in Meta-Analysis: Prevention, Assessment and Adjustments. Chapter 8. The Trim and Fill Method. New York: John Wiley & Sons Ltd, 2006 [DOI: 10.1002/0470870168.ch8]

4 **Moser EB**. Repeated measures modeling with PROC MIXED. In: Proceedings of the 29th SAS Users Group International Conference. Montreal, Canada 2004. [accessed 2015 Jun]. Available from: URL: http://www2.sas.com/proceedings/sugi29/188-29.pdf

5 **Edwards D**, Berry JJ. The efficiency of simulation-based multiple comparisons. *Biometrics* 1987; **43**: 913-928 [PMID: 3427176]

6 **Rafter JA**, Abell ML, Braselton JP. Multiple Comparison Methods for Means. *SIAM Review* 2002; **44**: 259-278

7 **Dias S**, Welton NJ, Sutton AJ, Ades AE. NICE DSU Technical Support Document2: A generalised linear modelling framework for pairwise and network meta-analysis of randomised controlled trials 2011. [accessed 2015 Jun]. Available from: URL: http://www.nicedsu.org.uk

8 **Flach P**, Matsubara ET. On classification, ranking, and probability estimation. Dagstuhl Seminar Proceedings 07161. Probabilistic, Logical and Relational Learning - A Further Synthesis 2008. [accessed 2015 Jun]. Available from: URL: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.183.6043&rep=rep1&type=pdf

9 **Landoni G**, Augoustides JG, Guarracino F, Santini F, Ponschab M, Pasero D, Rodseth RN, Biondi-Zoccai G, Silvay G, Salvi L, Camporesi E, Comis M, Conte M, Bevilacqua S, Cabrini L, Cariello C, Caramelli F, De Santis V, Del Sarto P, Dini D, Forti A, Galdieri N, Giordano G, Gottin L, Greco M, Maglioni E, Mantovani L, Manzato A, Meli M, Paternoster G, Pittarello D, Rana KN, Ruggeri L, Salandin V, Sangalli F, Zambon M, Zucchetti M, Bignami E, Alfieri O, Zangrillo A. Mortality reduction in cardiac anesthesia and intensive care: results of the first International Consensus Conference. *Acta Anaesthesiol Scand* 2011; **55**: 259-266 [PMID: 21288207 DOI: 10.1111/j.1399-6576.2010.02381.x]

10 **Hozo SP**, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13 [PMID: 15840177]

11 **Pigott TD**. Missing predictors in models of effect size. *Eval Health Prof* 2001; **24**: 277-307

12 **Furukawa TA**, Cipriani A, Barbui C, Brambilla P, Watanabe N. Imputing response rates from means and standard deviations in meta-analyses. *Int Clin Psychopharmacol* 2005; **20**: 49-52 [PMID: 15602117]

13 **Furukawa TA**, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. *J Clin Epidemiol* 2006; **59**: 7-10 [PMID: 16360555]

14 **Thiessen Philbrook H**, Barrowman N, Garg AX. Imputing variance estimates do not alter the conclusions of a meta-analysis with continuous outcomes: a case study of changes in renal function after living kidney donation. *J Clin Epidemiol* 2007; **60**: 228-240 [PMID: 17292016]

15 **Robertson C**, Idris NR, Boyle P. Beyond classical meta-analysis: can inadequately reported studies be included? *Drug Discov Today* 2004; **9**: 924-931 [PMID: 15501727]

16 **Wiebe N**, Vandermeer B, Platt RW, Klassen TP, Moher D, Barrowman NJ. A systematic review identifies a lack of standardization in methods for handling missing variance data. *J Clin Epidemiol* 2006; **59**: 342-353 [PMID: 16549255]

17 **Stevens JW**. A note on dealing with missing standard errors in meta-analyses of continuous outcome measures in WinBUGS. *Pharm Stat* 2011; **10**: 374-378 [PMID: 21394888 DOI: 10.1002/pst.491]

**P-Reviewer:** Naugler C, Omboni S, Trkulja V **S-Editor:** Ji FF **L-Editor: E-Editor:**

**Table 1 Distributions of the continuous endpoint for treatment and control groups**

|  |  |
| --- | --- |
|  | **Endpoint distribution** |
| **Scenarios** | **Treatment group** | **Control group** |
| Normal | Mean = 5 and SD = 2 | Mean = 7 and SD = 2 |
| Standard Normal | Mean = 0 and SD = 1 | Mean = 0 and SD = 1 |
| Gamma | Alpha = 2 and beta = 5 | Alpha = 2 and beta = 7 |
| Exponential | Mean = 5 and lambda = 0.2 | Mean = 7 and lambda = 0.14 |
| Bimodal | 50% Normal distribution with mean = 5 and SD = 2 and 50% Standard Normal distribution | 50% Normal distribution with mean = 7 and SD = 2 and 50% Standard Normal distribution |
| ICU stay | Real-life data | Real-life data |
| Hospital stay | Real-life data | Real-life data |

ICU: Intensive care unit.

**Table 2 Example of SAS code to simulate a meta-analysis on 15 datasets with 15 records generated from a Gamma distribution (alpha = 2 and beta = 5 *vs* alpha = 2 and beta = 7 for the treatment and control group, respectively)**

\* q is the assigned library;

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;

\* SIMULATIONS;

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;

%let s=gamma;

%let ndset=15;

\* Simulation of n=15 dataset using the Gamma distributions;

**%macro** ***simul***;

%do q=**1** %to &ndset;

 %let seed=%sysevalf(1234567+&q);

 %let num\_i=%sysevalf(&ndset);

 %let v=%sysevalf(0+&q);

data s&q;

 k=&q;

 %do i=**1** %to &num\_i;

 var1=**5**\*rangam(&seed,**2**);

 var2=**7**\*rangam(&seed,**2**);

 output;

 %end;

run;

%end;

\* Dataset combining;

data simul\_&s;

 set

 %do w=**1** %to &ndset;

 s&w

 %end;

 ;

 run;

**%mend**;

%***simul***;

\* Descriptive statistics for each dataset;

 ods trace on;

 ods output summary=summary\_&s;

 **proc** **means** data=simul\_&s mean std median q1 q3;

 class k;

 var var1 var2;

 **run**;

ods trace off;

**data** summary\_&s;

 set summary\_&s;

 l1=(var1\_Median-var1\_Q1)/**0.6745**;

 l2=(var2\_Median-var2\_Q1)/**0.6745**;

 u1=(var1\_Q3-var1\_Median)/**0.6745**;

 u2=(var2\_Q3-var2\_Median)/**0.6745**;

 if l1>u1 then MeSD\_v1\_cons=l1; else MeSD\_v1\_cons=u1;

 if l2>u2 then MeSD\_v2\_cons=l2; else MeSD\_v2\_cons=u2;

 if l1>u1 then MeSD\_v1\_prec=u1; else MeSD\_v1\_prec=l1;

 if l2>u2 then MeSD\_v2\_prec=u2; else MeSD\_v2\_prec=l2;

 MeSD\_v1\_mean=(var1\_Q3-var1\_Q1)/**1.349**;

 MeSD\_v2\_mean=(var2\_Q3-var2\_Q1)/**1.349**;

\* Median difference;

 MeD=var1\_Median-var2\_Median;

 \*1 conservative estimate of standard deviation;

 a1sd=((MeSD\_v1\_cons)\*\***2**)/NObs;

 b1sd=((MeSD\_v2\_cons)\*\***2**)/NObs;

 MeSD\_cons=sqrt(a1sd+b1sd);

 \*2 less conservative estimate of standard deviation;

 a2sd=((MeSD\_v1\_prec)\*\***2**)/NObs;

 b2sd=((MeSD\_v2\_prec)\*\***2**)/NObs;

 MeSD\_prec=sqrt(a2sd+b2sd);

 \*3 mean estimate of standard deviation;

 a3sd=((MeSD\_v1\_mean)\*\***2**)/NObs;

 b3sd=((MeSD\_v2\_mean)\*\***2**)/NObs;

 MeSD\_mean=sqrt(a3sd+b3sd);

 \*4 Interquartile range;

 a4sd=((var1\_Q3-var1\_Q1)\*\***2**)/NObs;

 b4sd=((var2\_Q3-var2\_Q1)\*\***2**)/NObs;

 MeSD\_iqr=sqrt(a4sd+b4sd);

 \* Mean difference and pooled standard deviation;

 MD=var1\_Mean-var2\_Mean;

 asd=((var1\_StdDev)\*\***2**)/NObs;

 bsd=((var2\_StdDev)\*\***2**)/NObs;

 SD=sqrt(asd+bsd);

 drop l1 l2 u1 u2 asd bsd a1sd b1sd a2sd b2sd a3sd b3sd a4sd b4sd;

**run**;

\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*\*;

\* Meta-analyses;

**data** sum\_&s;

 set summary\_&s;

 keep k NObs MeD MeSD\_cons MeSD\_prec MeSD\_mean MeSD\_iqr MD SD qq;

**run**;

\*1 Median and conservative estimate of standard deviation;

**data** meta\_&s.1;

 set sum\_&s;

 model="Conservative SD";

 MDz=MeD;

 SDz=MeSD\_cons;

 w=**1**/(SDz\*\***2**);

 MDw=MDz\*w;

keep model k NObs MDz SDz w MDw;

**run**;

\*2 Median and less conservative estimate of standard deviation;

**data** meta\_&s.2;

 set sum\_&s;

 model="Less Conservative SD";

 MDz=MeD;

 SDz=MeSD\_prec;

 w=**1**/(SDz\*\***2**);

 MDw=MDz\*w;

keep model k NObs MDz SDz w MDw;

**run**;

\*3 Median and mean estimate of standard deviation;

**data** meta\_&s.3;

 set sum\_&s;

 model="Mean SD";

 MDz=MeD;

 SDz=MeSD\_mean;

 w=**1**/(SDz\*\***2**);

 MDw=MDz\*w;

keep model k NObs MDz SDz w MDw;

**run**;

\*4 Median and interquartile range;

**data** meta\_&s.4;

 set sum\_&s;

 model="IQR";

 MDz=MeD;

 SDz=MeSD\_iqr;

 w=**1**/(SDz\*\***2**);

 MDw=MDz\*w;

keep model k NObs MDz SDz w MDw;

**run**;

\* Mean and standard deviation (reference);

**data** meta\_&s.5;

 set sum\_&s;

 model="Reference";

MDz=MD;

SDz=SD;

w=**1**/(SDz\*\***2**);

MDw=MDz\*w;

keep model k NObs MDz SDz w MDw;

**run**;

**proc** **format**;

 value model

 **1**="conservative SD"

 **2**="Less Conservative SD "

 **3**="Mean SD "

 **4**="IQR"

 **5**="Reference"

 ;

**run**;

\*\*\* Fixed effect model meta-analysis – Inverse of Variance method;

**%macro** ***meta\_iv***;

%do i=**1** %to **5**;

ods output Summary=somme&i;

proc means data=meta\_&s&i sum;

 var MDw w;

run;

data somme&i;

 set somme&i;

 model=&i;

 format model model.;

 theta=MDw\_Sum/w\_Sum;

 se\_theta=**1**/(sqrt(w\_sum));

 lower=theta-(se\_theta\***1.96**);

 upper=theta+(se\_theta\***1.96**);

 mtheta=sqrt(theta\*\***2**);

 CV=se\_theta/mtheta;

 keep model theta se\_theta lower upper cv;

run;

%end;

data aaMeta\_&s;

 set

 %do w=**1** %to **5**;

 somme&w

 %end;

 ;

 run;

 title "distr=&s - k=&ndset";

 proc print; run;

**%mend**;

%***meta\_iv***;

**Table 3 Method for imputing the study-specific standard deviation**

|  |  |  |  |
| --- | --- | --- | --- |
| **Method number** | **Method name** | **Mean imputation** | **Standard Deviation imputation1** |
| 0 | Reference | Mean | SD |
| 1 | Conservative SD | Median | $$max\left[\frac{\left(3^{rd} quartile-median\right)}{0.6745};\frac{\left(median-1^{st} quartile\right)}{0.6745}\right]$$ |
| 2 | Less conservative SD | Median | $$min\left[\frac{\left(3^{rd} quartile-median\right)}{0.6745};\frac{\left(median-1^{st} quartile\right)}{0.6745}\right]$$ |
| 3 | Mean SD | Median | $$\frac{\left(3^{rd} quartile-1^{st} quartile\right)}{2\*0.6745}$$ |
| 4 | IQR | Median | $\left(3^{rd} quartile-1^{st} quartile\right)$. |

1The 0.675 is the *Z* value corresponding to an area of 75% of the Standard Normal distribution function. IQR: Interquartile range.

**Table 4 Comparison of results obtained from the four methods of approximation of study-specific means and standard deviations in a meta-analysis of a continuous outcome**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Standardized pooled estimate,** $θ\_{stand\_{ijk}}$ **(standard error)** | ***P* value1****(unadjusted)** | ***P* value1****(Tukey-Kramer adjustment)** | ***P* value1****(Bonferroni adjustment)** | ***P* value1****(Scheffé adjustment)** |
| **Conservative SD** | 4.5 (3.5) | 0.14 | 0.7 | 0.9 | 0.8 |
| **Less conservative SD** | 7.8 (2.9) | 0.01 | 0.056 | 0.07 | 0.12 |
| **Mean SD** | 6.1 (3.3) | 0.04 | 0.3 | 0.6 | 0.5 |
| **IQR** | 4.5 (2.2) | 0.13 | 0.2 | 0.4 | 0.4 |

1*P*-values were derived from a test on the “method” effect in a repeated measures model including also adjustment by “dataset” and “distribution” effects. IQR: Interquartile range.

**Table 5 Absolute differences between standardized estimates,** $θ\_{stand\_{ijk}}$**, calculated by means of one of the four methods (conservative SD, less conservative SD, mean SD and interquartile range), and the reference**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Distribution scenario** | **Dataset** | **Conservative SD** | **Less conservative SD** | **Mean SD** | **IQR** |
| Normal | 15 | -0.310 | 1.274 | 0.149 | 0.110 |
| Normal | 30 | 0.029 | -1.483 | -0.109 | -0.081 |
| Normal | 50 | -0.434 | -0.946 | -0.599 | -0.444 |
| Normal | 100 | 0.340 | 0.095 | 0.243 | 0.180 |
| Normal | 500 | -0.336 | -0.357 | -0.353 | -0.261 |
| Normal | 1000 | 0.754 | 0.989 | 0.860 | 0.638 |
| **No. of times of begin first in the ranking1** |  | **2** | **1** | **0** | **3** |
| Standard Normal | 15 | -0.335 | 1.072 | 0.062 | 0.046 |
| Standard Normal | 30 | -0.101 | -1.710 | -0.290 | -0.215 |
| Standard Normal | 50 | -0.535 | -1.013 | -0.690 | -0.511 |
| Standard Normal | 100 | 0.502 | 0.281 | 0.416 | 0.308 |
| Standard Normal | 500 | -0.306 | -0.314 | -0.317 | -0.235 |
| Standard Normal | 1000 | 0.814 | 1.054 | 0.923 | 0.684 |
| **No. of times of begin first in the ranking1** |  | **1** | **1** | **0** | **4** |
| Gamma | 15 | -0.283 | 0.054 | -0.119 | -0.088 |
| Gamma | 30 | 1.441 | 2.229 | 1.846 | 1.368 |
| Gamma | 50 | 1.795 | 2.929 | 2.218 | 1.644 |
| Gamma | 100 | 4.915 | 8.193 | 6.070 | 4.500 |
| Gamma | 500 | 24.081 | 35.799 | 28.753 | 21.314 |
| Gamma | 1000 | 49.089 | 71.072 | 58.012 | 43.002 |
| **No. of times of begin first in the ranking1** |  | **0** | **1** | **0** | **5** |
| Exponential | 15 | -0.150 | -0.163 | -0.157 | -0.116 |
| Exponential | 30 | 1.880 | 2.958 | 2.301 | 1.706 |
| Exponential | 50 | 2.948 | 4.975 | 3.707 | 2.748 |
| Exponential | 100 | 10.213 | 19.490 | 13.493 | 10.002 |
| Exponential | 500 | 39.546 | 74.955 | 51.913 | 38.481 |
| Exponential | 1000 | 80.605 | 157.083 | 106.593 | 79.016 |
| **No. of times of begin first in the ranking1** |  | **0** | **0** | **0** | **6** |
| Bimodal | 15 | 1.142 | 4.114 | 1.751 | 1.298 |
| Bimodal | 30 | 0.079 | 0.356 | 0.096 | 0.071 |
| Bimodal | 50 | 0.545 | 3.051 | 1.110 | 0.823 |
| Bimodal | 100 | 2.405 | 6.849 | 3.650 | 2.706 |
| Bimodal | 500 | 19.156 | 41.495 | 26.212 | 19.431 |
| Bimodal | 1000 | 38.825 | 81.301 | 52.527 | 38.938 |
| **No. of times of begin first in the ranking1** |  | **5** | **0** | **0** | **1** |
| ICU stay | 15 | 0.076 | -2.816 | 2.667 | 1.977 |
| ICU stay | 30 | -3.011 | -6.341 | -4.201 | -3.114 |
| ICU stay | 50 | -1.361 | -3.162 | -2.163 | -1.603 |
| ICU stay | 100 | -0.580 | -2.205 | 1.393 | 1.032 |
| ICU stay | 500 | -6.218 | -21.788 | -6.462 | -4.790 |
| ICU stay | 1000 | 3.162 | -5.020 | 6.801 | 5.042 |
| **No. of times of begin first in the ranking1** |  | **5** | **0** | **0** | **1** |
| Hospital stay | 15 | 1.437 | 8.948 | 2.777 | 2.058 |
| Hospital stay | 30 | 2.603 | -1.088 | 2.595 | 1.924 |
| Hospital stay | 50 | 0.297 | -0.839 | -0.055 | -0.041 |
| Hospital stay | 100 | -4.674 | -13.063 | -6.734 | -4.992 |
| Hospital stay | 500 | -29.239 | -55.703 | -37.170 | -27.554 |
| Hospital stay | 1000 | -52.720 | -85.673 | -63.453 | -47.038 |
| **No. of times of begin first in the ranking1** |  | **2** | **1** | **0** | **3** |
| **1st quartile** |  | 0.337 | 1.023 | 0.368 | 0.273 |
| **Median** |  | 1.399 | 2.944 | 2.190 | 1.624 |
| **3rd quartile** |  | 4.855 | 12.034 | 6.666 | 4.942 |
| **Total number of times of begin first in the ranking1** |  | **15** | **4** | **0** | **23** |

1The ranking procedure was based on differences in absolute value. Number of times that each standardized estimate ranked as for first, for each simulated distribution. Median (interquartile range) of overall standardized estimate distributions. IQR: Interquartile range.

**Table 6 Absolute and relative frequencies of occurrence of the four methods to approximate study-specific means and standard deviations in a meta-analysis of a continuous outcome**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **No. of first** **ranking (%)** | **No. of second ranking (%)** | **No. of third ranking (%)** | **No. of fourth ranking (%)** |
| **Conservative SD** | 15 (35.7) | 20 (47.6) | 3 (7.1) | 4 (9.5) |
| **Less conservative SD** | 4 (9.5) | 1 (2.4) | 1 (2.4) | 36 (85.7) |
| **Mean SD** | 0 | 3 (7.1) | 37 (88.1) | 2 (4.8) |
| **IQR** | 23 (54.8) | 18 (42.9) | 1 (2.4) | 0 |

IQR: Interquartile range.



**Figure 1 Value of each standardized estimate,** $θ\_{stand\_{ijk}}$**, for each number of dataset included in the corresponding meta-analysis simulated.** A: All distributions together; B: Normal (mean = 5 and SD = 2 for the treatment group; mean = 7 and SD = 2 for the control group); C: Standardized Normal; D: Gamma (alpha = 2 and beta = 5 for the treatment group; alpha = 2 and beta = 7 for the control group). The X-axis represents the number of studies (datasets) included in the meta-analysis. For each approximation method (blue line for the conservative estimate of SD, green line for the less conservative estimate of SD, pink line for the mean estimate of SD, and red line for the interquartile range), the Y-axis reports the difference between the standardized estimate and the reference (black line). IQR: Interquartile range.



**Figure 2 Value of each standardized estimate,** $θ\_{stand\_{ijk}}$**, for each number of dataset included in the corresponding meta-analysis simulated.** A: Exponential (mean = 5 and lambda = 0.2 for the treatment group; mean = 7 and lambda = 0.14 for the control group); B: Bimodal (50% Normal distribution (with mean = 5 and SD = 2) and 50% Standardized Normal for the treatment group; 50% Normal distribution (with mean = 7 and SD = 2) and 50% Standardized Normal for the control group); C and D: Real distribution of intensive care unit (ICU) stay and hospital stay of an Italian cardiology dataset with 7471 patients. The X-axis represents the number of studies (datasets) included in the meta-analysis. For each approximation method (blue line for the conservative estimate of SD, green line for the less conservative estimate of SD, pink line for the mean estimate of SD, and red line for the interquartile range), the Y-axis reports the difference between the standardized estimate and the reference (black line). IQR: Interquartile range.

**Figure 3 Area under the cumulative ranking curve for the four methods to approximate mean and standard deviation in a meta-analysis of continuous outcome.** IQR: Interquartile range.