การใช้โปรแกรม R ในการวิเคราะห์อภิมานพหุด้วยข้อมูลทางทันตกรรม: บทความสอนการใช้งาน

Using R Programming to Conduct a Multivariate Meta-analysis with Dental Data: A Tutorial

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บทคัดย่อ

บทความนี้เป็นการแนะนำวิธีใช้งานโปรแกรม R มีวัตถุประสงค์เพื่อแสดงวิธีการใช้งานโปรแกรม R ในการวิเคราะห์อภิมานหลายตัวแปร โดยครอบคลุมชุดฟังก์ชันและชุดข้อมูลสำหรับ metaSEM รวมถึงการใช้ชุดของฟังก์ชันและชุดข้อมูลอื่นๆ ที่เกี่ยวข้องและจำเป็น ส่วนการวิเคราะห์แบ่งเป็นสองส่วนคือ การสาธิตการใช้โปรแกรม R สำหรับการวิเคราะห์อภิมานหลายตัวแปรในการศึกษาวิจัยทางด้านทันตกรรม และเทคนิคการใช้โปรแกรม R สำหรับการวิเคราะห์เชิงอภิมานหลายตัวแปร สำหรับผู้เริ่มต้นใช้งานใหม่จากตัวอย่างที่แสดงถึงความสามารถเต็มรูปแบบของโปรแกรม R ในการวิเคราะห์ โดยการสาธิตให้เห็นว่าโปรแกรม R สามารถใช้งานได้อย่างมีประสิทธิภาพสำหรับการวิเคราะห์อภิมาณพหุตัวแปรในการวิจัยทางทันตกรรม และการเพิ่มศักยภาพให้กับผู้เริ่มต้นใช้งานทั้งในด้าน R และการวิเคราะห์อภิมาณพหุตัวแปรเพื่อใช้เทคนิคเหล่านี้ในงานวิจัย บทความนี้จะช่วยเพิ่มทักษะที่จำเป็นสำหรับผู้เริ่มต้นใช้โปรแกรม R ในการวิเคราะห์อภิมานหลายตัวแปร ไม่เฉพาะในงานวิจัยทางด้านทันตกรรมเท่านั้นแต่ยังสามารถนำไปใช้ในศึกษาวิจัยอื่นๆ โดยไฟล์ที่ใช้ในบทความนี้เป็นไฟล์ที่เปิดให้ผู้เรียนสามารถนำไปใช้ทำซ้ำในการวิเคราะห์อภิมานหลายตัวแปรได้เอง

คำสำคัญ: ข้อมูลทันตกรรม, การวิเคราะห์อภิมาน, โรคปริทันต์, R, กลุ่มทดลอง

ABSTRACT

This manuscript presented as a guide on utilizing R program for conducting a multivariate meta-analysis (MMA) of dental data. R software has been extensively employed for meta-analysis tasks, and specific packages like metaSEM extend its capabilities to analyze MMA in health-related contexts and beyond. However, newcomers to both R and MMA might encounter challenges, given the complex nature of these analyses. Moreover, our literature review revealed a scarcity of learning resources focused on employing R for MMA, indicating a significant gap in the literature. To address this gap, we developed this tutorial paper to provide a comprehensive overview of utilizing R for MMA. The primary R package highlighted in this paper was metaSEM, chosen for its robust learning resources tailored for newcomers. While other packages were also utilized throughout the paper, they would be introduced as needed. Our aim with this paper had twofold: firstly, to bridge the practice gap by demonstrating how R could be effectively used for MMA in dental research; and secondly, to empower newcomers to R and MMA to apply these techniques in their own research endeavors. Through an illustrative example presented herein, we showcased the full capabilities of R in conducting MMA. Ultimately, we hope that this tutorial equips newcomers with the necessary skills to apply MMA techniques using R, not only in dental research but also in broader research contexts. An R file used for conducting MMA in this tutorial paper is available on the Open Science Framework (OSF), allowing learners to replicate the MMA results presented in this paper.

Key words: Dental data, Meta-analysis, Periodontal disease, R, Treatment group

Introduction

This paper introduces how to use R to conduct a multivariate meta-analysis in a dental context. R software is accepted worldwide and free. In addition, R is widely used to conduct meta-analysis (MA). However, newcomers to R may still find it challenging to use the R software. Likewise, meta-analysis is not an easy subject to grasp because MA is a topic of advanced statistics. In addition, Multivariate Meta-Analysis (MMA) is more sophisticated than the general MA topic. Furthermore, graduate courses offering MA are probably limited around the world. As a result, the number of researchers familiar with MA is also limited. However, the number of research using MA has been growing (Shin, 2017). Many Thai researchers are still not familiar with using R to conduct MMA because we do not come across Thai researchers conducting MMA using R. This can be viewed as problematic. Thus, there is a need for more learning resources (e.g., a tutorial paper) covering Multivariate Meta-Analysis (MMA) using R. But the learning resources are still limited. This can be viewed as a literature gap.

Thus, this paper attempts to fill such a gap. We hope that newcomers will apply what they learn from this paper to their research and publication in the context of dental research and beyond. This article aims to demonstrate how to use R to conduct Multivariate Meta-Analyses using health data.

Categories of meta-analyses

Based on our literature review, we came across categories of meta-analysis. These categories are captured in Figure1, which classified meta-analysis into six categories.

The first category is called a univariate meta-analysis. This is a traditional meta-analysis, dealing with one treatment and one outcome (pooled effect size).

The second category is called multivariate-meta-analysis. This category of meta-analysis deals with one treatment but multiple outcomes (pooled effect sizes). This paper is in line with this category.

The third category is called a network meta-analysis. This category deals with multiple treatments and outcomes.

The fourth category is called multilevel meta-analysis. This category integrates the concept of multilevel statistics with a meta-analysis.

The fifth category is called structural equation meta-analysis (MASEM) combining the concept of SEM into a meta-analysis.

Finally, the last category is called Bayesian meta-analysis. This category adopts Bayesian calculation methods (not the Frequentist method).

In summary, these different categories of meta-analyses require different calculation methods, interpretations, and reporting. A good introductory work on meta-analysis is called *"How to Review and Assess a Systematic Review and Meta-analysis article"*: a methodological study (Myung, 2023). Figure 1 draws upon the work of Savatsomboon *et al.* (2024). There may be other rival categorizations of meta-analysis.

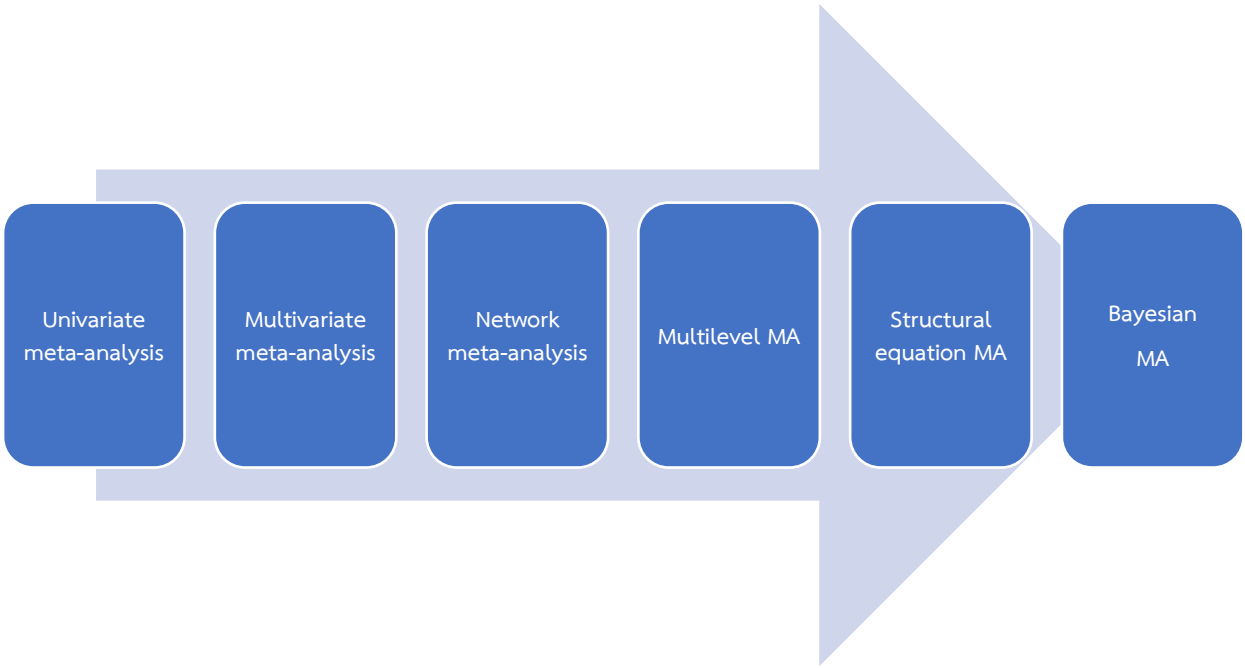

Figure 1 Categories of meta-analysis (Savatsomboon *et al.*, 2024)

Univariate vs. multivariate meta-analyses

This paper places a focus on MMA. The MMA can be viewed as an extension of a Univariate Meta-Analysis. Thus, the distinction between Univariate Meta-Analysis vs. Multivariate Meta-Analysis must be drawn before we proceed any further. Based on Figure 2, the Univariate Meta-Analysis (UMA) includes multiple (six) studies but using the same treatment (X) and each study measures the same outcome (effect size, YY). The YY effect sizes can be obtained from, for example, the mean differences between the YY effect sizes of their experiment group vs. the control group. On the other hand, MMA also includes multiple (six) studies using the same treatment (Z); but, each study measures at least two outcomes (PD (pocket depth) and AL (attachment level) effect sizes). Likewise, the effect sizes of PD and AL can be obtained from, for example, the mean differences (effect sizes) of their respective experimental groups vs. control groups.

In short, UMA is interested in pooling /combining the effect sizes (YYs) of the six studies into one effect size in a (Univariate) Meta-Analysis study (see Figure 2). Thus, the research question for UMA becomes, is the pooled/combined effect size of YYs statistically significant? However, the MMA is interested in pooling/combining the effect sizes of the two outcomes (pooled/combined effect sizes of PD and AL) of the six studies in a (Multivariate) Meta-Analysis study (see Figure 2). Thus, the research question for MMA is, are the pooled/combined effect sizes of PD and AL significant?

Study	Treatment	Effect size
1	X	YY
2	X	YY
3	X	YY
4	X	YY
5	X	YY
6	X	YY

Univariate Meta-Analysis (UMA)

Study	Treatment	Effect size	Effect size
1	Z	PD	AL
2	Z	PD	AL
3	Z	PD	AL
4	Z	PD	AL
5	Z	PD	AL
6	Z	PD	AL

Multivariate Meta-Analysis (MMA)

Figure 2 The difference between univariate meta-analysis vs. multivariate meta-analysis (PD = pocket dept, AL = attachment level)

In basic terms, pocket depth measures the distance between the gum and the teeth (see Figure 3). The left side represents the healthy gum because no gap between the gum and the teeth. On the other hand, the right side represents the diseased gum because there is a gap between the gum and the teeth. This gap is usually measured in millimeters.

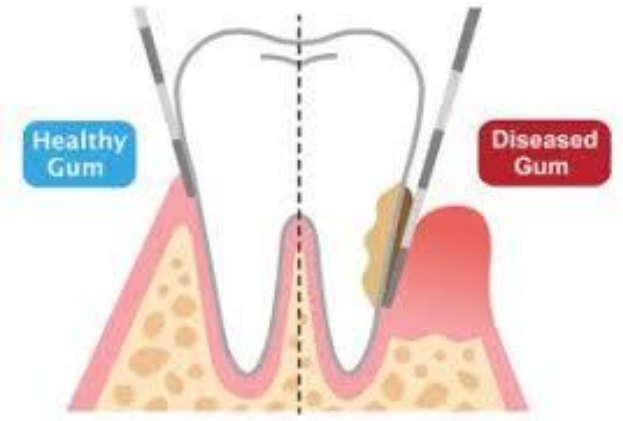

Figure 3 Pocket depth (PD) and attachment level (AL) (Ujdreams, n.d.)

Attachment level (AL) is measured by how much your gum is attached to your teeth. Based on Figure 3, the attachment level is higher on the left side of the Figure because the gum is more attached to the left side of the teeth. On the other hand, the attachment level is lower on the right side of the Figure because the gum is less attached to the right side of the teeth. Thus, the measurement values of PDs and ALs are in the opposite direction

PICO, systematic review, and PRISMA in research practice

PICO stands for participants (P), intervention (I), control (C), and outcome (O). Let's apply it to the example of this paper. Participants (P) include patients with medium-severity periodontal (gum) disease who had undergone surgery and participated in this study one year after treatment. The intervention (I) (treatment) is surgery. The control group (C) includes patients with medium-severity periodontal disease who had not undergone surgery and participated in this study one year after treatment. The outcome (O) is the research question: Are the improvements (pooled/combined effect sizes) of PD (pocket depth) and AL (attachment level) statistically significant (while accounting for the correlation between PD and AL)?

Next, a systematic review can be viewed as a prerequisite for a meta-analysis. Overall, a systematic review is a search strategy to obtain necessary studies that would help answer the two research questions of the meta-analysis study identified in the PICO session earlier. Thus, readers are recommended to study systematic reviews further on their own at other existing learning resources. Finally, PRISMA clearly explains the procedures of inclusions and exclusions of studies to be included in a meta-analysis study at hand in detail. This is usually presented in a diagrammatic form. In short, researchers need to execute PICO, systematic review, and PRISMA before moving on to a (Multivariate) Meta-analysis.

Conceptual framework and hypothesis development

It is not usual to explicitly present a conceptual framework and hypothesis development in a meta-analysis study. However, this paper covers these two important topics for clarity purposes. First, the conceptual framework includes three items (see Figure 3). The first item is treatment. In MMA, there is only one treatment (surgery) in an MMA study. The second item is the outcome (the pooled/combined effect size of PDs). The third is the outcome (the pooled/combined effect size of ALs).

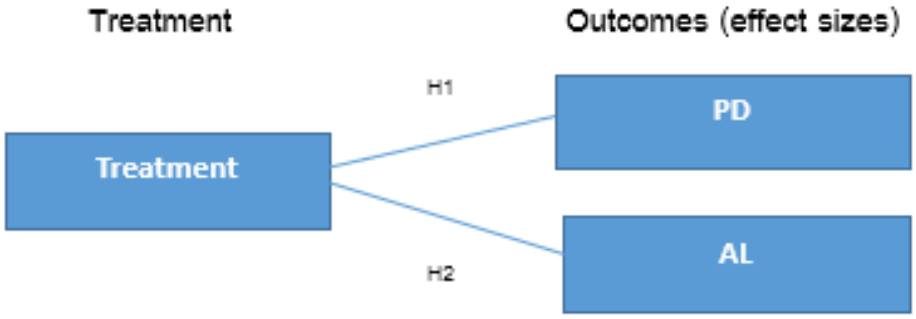

Figure 4 Multivariate meta-analysis conceptual framework and hypotheses

For hypothesis development, two basic hypotheses can be proposed. The first research hypothesis (H1) is that the pooled/combined effect size of PDs is significant. Likewise, the second research hypothesis (H2) is that the pooled/combined effect size of ALs is significant. Again, the PD and AL are assumed to be correlated because they are the two outcomes measured from the same treatment (surgery).

The dataset

The dataset can be traced back to two papers. The first paper is called Meta-Analysis of surgical versus non-surgical methods of treatment for periodontal disease (Antczak-Bouckoms *et al*., 1993). This paper offers a dataset in raw score (mean differences) forms. The second paper is called Meta-analysis of multiple outcomes using regression with random effects (Berkey *et al*., 1998). The second paper offers a dataset in (calculated) effect size forms. In fact, the second paper draws upon the first paper. Our paper draws upon the second paper because the R (software) package (called metaSEM) (Cheung, 2015) used in this paper requires effect sizes and related statistics as input data into the metaSEM package.

Based on Table 1, there are seven columns. The first column is Trial (Trial number). The second column is Year (of publication of that particular trial). The third column is n (Sample size). The fourth column is PD (millimeters (mm)). The PD values are not in favor of the experiment group at the time of the surgery. This is why the value of PD are positive for the experiment group due to wider PD values. The fifth column is AL. The values of this column are negative

because the values of AL are improving in favor of the experiment group after surgery (see Figure 3). The sixth and seventh columns are under variances which include three (not four due to redundancy) important variance-related statistics, including the sample variance of PD 0.0075, and 0.0077 for AL, and the covariance between PD and AL 0.0030, the remaining 0.0030 is redundant (see Table 1). In summary, Si includes the values of the sample variance of PD and AL, and the covariance of PD and AL. For a given trial, we would obtain the improvement in PD and AL, the sample variance of PD and AL, and the sample variance of PD and AL.

For the dataset availability, this dataset is a built-in dataset that comes with the metaSEM package and is publicly available. The dataset includes data from two groups, surgical (S) and non-surgical groups (NS) for a medium-severity periodontal disease. The data were collected one year after treatment. Thus, S can be viewed as the experimental group and NS can be viewed as the control group. The same dataset is also publicly available in other R packages, for example, Multivariate and Univariate Meta-Analysis; mvmeta (Gasparrini *et al*., 2012), and Meta-Analysis Package for R; metafor (Viechtbauer, 2010) packages. However, we strongly encourage users who would like to learn from our paper to use the dataset from the metaSEM package because we use this package as the main package to conduct our MMA in this paper.

Table 1 The dataset with PD and AL mean differences

Trial	Year	n	Improvement in		S_i	
			PD	AL	PD	AL
1	1983	14	+0.47	-0.32	0.0075	0.0030
					0.0030	0.0077
2	1982	15	+0.20	-0.60	0.0057	0.0009
					0.0009	0.0008
3	1979	78	+0.40	-0.12	0.0021	0.0007
					0.0007	0.0014
4	1987	89	+0.26	-0.31	0.0029	0.0009
					0.0009	0.0015
5	1988	16	+0.56	-0.39	0.0148	0.0072
					0.0072	0.0304

Required R packages for MMA

First, the R base (R Core Team, 2021) needs to be installed. Second, RStudio (RStudio Team, 2020) is optional, but strongly recommended. Third, the metaSEM package needs to be installed. Finally, the metafor package needs to be installed. We chose the metaSEM package because the package provides abundant information on how to conduct MMA.

Bringing the data into R

There are ways that input data can be brought into R for further MMA analyses. First, raw data (e.g. raw means) can be brought into R. Second, required pre-calculated effect sizes and related statistics can be brought into R. However, users need to check their target meta-analysis R packages to see whether the package can take raw data as input data, or if the target R package requires (pre-calculated) effect sizes and related statistics. Let's take the example data employed in this paper. The metaSEM is the main package used in this paper. This package requires the effect sizes of PD and AL, the sample variances (var) of PD and AL, and the covariances of PD and AL. Thus, the information needed requires precalculated effect sizes and related statistics. This is consistent with the input data requirements of the metaSEM package.

Finally, we strongly recommend that the data file should be prepared using Excel and instruct R to read the data from the data file (Excel), located on Drive D, for example (see Figure 6).

R codes for conducting MMA using the metaSEM package

Figure 5 captures R codes for conducting MMA, including text and graphical outputs. Line 1 instructs R to install a package called metaSEM. Line 2 the package metaSEM to be in use. Line 3 specifies the dataset (called Berkey98) to be in use. Line 4 looks at the Berkey dataset. Line 5, is intentionally left blank.

Line 6 is the comment line (no R action has taken place here). Line 7 runs MMA, analyzing two pooled-effect-size outcomes (PD and AL). In addition, the sample variances of PD and AL are required, also the covariance of PD and AL. The dataset used is Berkey98. Line 8 provides the required MMA text outputs. Line 9 is intentionally left blank

Line 10 is a comment line. Line 11 installs the metafor package. Line 12 puts the metafor package to use. Line 13 is intentionally left blank

Line 14 is a comment line. Line 15 plots a multivariate meta-analysis. Line 16 is intentionally left blank

Line 17 is a comment line. Line 18 provides a forest for PD. Line 19 provides a title for the PD forest plot. Line 20 is intentionally left blank

Line 21 is a comment line. Line 22 runs a forest plot for AL. Finally, Line 23 provides a title of AL.

```
Install.packages("metaSEM")
library(metaSEM)
data(Berkey98)
Berkey98

# Multivariate meta-analysis, (ML estimation method)
m1 <- meta(y=cbind(PD, AL), v=cbind(var_PD, cov_PD_AL, var_AL),
data=Berkey98)
summary(m1)

# Load the library for forest plots
Install.packages("metaSEM")
library(metafor)

# Create extra panels for the forest plots
plot(m1, diag.panel=TRUE, main="Multivariate meta-analysis",
axis.label=c("PD", "AL"))

# Forest plot for PD
forest( rma(yi=PD, vi=var_PD, data=Berkey98) )
title("Forest plot of PD")

# Forest plot for AL
forest( rma(yi=AL, vi=var_AL, data=Berkey98) )
title("Forest plot of AL")
```

Figure 5 R codes for executing required text and graphical outputs

Dataset storing in Excel and displaying in R

The dataset is publicly available in R packages, for example, metaSEM, mvmeta, and metafor packages. There are eight columns in the dataset. The first column is the trial number. There 5 trials in the dataset. The second column is the publication year. The years range from 1979 to 1988. The third column is the number of patients in individual trials. The fourth column contains the effect sizes of PD (pocket depth, patient improvements (mm)). The fifth column contains the effect sizes of AL (attachment level, patient improvements (mm)). The sixth column contains the sampling variance of PD. The seventh column contains the sampling covariance between PD and AL. Finally, the eighth column contains the sampling variance of AL. If users would like to use Excel as a data input file, they need to type the data as presented in Figure 6.

	A	B	C	D	E	F	G	H
1	trial	pub_year	no_of_patiens	PD	AL	var_PD	cov_PD_AL	var_AL
2	1	1983	14	0.47	-0.32	0.0075	0.0030	0.0077
3	2	1982	15	0.20	-0.60	0.0057	0.0009	0.0008
4	3	1979	78	0.40	-0.12	0.0021	0.0007	0.0014
5	4	1987	89	0.26	-0.31	0.0029	0.0009	0.0015
6	5	1988	16	0.56	-0.39	0.0148	0.0072	0.0304

Dataset storing in Excel

Berkey98 ×

Filter

	trial	pub_year	no_of_patients	PD	AL	var_PD	cov_PD_AL	var_AL
1	1	1983	14	0.47	-0.32	0.0075	0.0030	0.0077
2	2	1982	15	0.20	-0.60	0.0057	0.0009	0.0008
3	3	1979	78	0.40	-0.12	0.0021	0.0007	0.0014
4	4	1987	89	0.26	-0.31	0.0029	0.0009	0.0015
5	5	1988	16	0.56	-0.39	0.0148	0.0072	0.0304

Dataset displaying in R

Figure 6 The dataset is stored in Excel and displayed in R

Results of hypothesis testing and multivariate meta-analysis

Two research hypotheses are proposed (see Figure 3) The results of hypothesis testing are summarized as follows:

Hypothesis 1: The pooled effect size of PD is statistically significant. (Supported, $p<0.05$).

Hypothesis 2: The pooled effect size of AL is statistically significant. (Supported, $p < 0.05$).

The text outputs of the MMA are based on the multivariate random-effects model and are captured in Figure 7. The pooled effect sizes with their 95% Wald Cis based on the random-effects model for PD and AL are 0.3448 (0.2397, 0.4500), and -0.3379 (-0.4972, -0.1787), respectively. The Q statistic (df = 8) is 128.2267, (p = 0.0000). The I2 based on the Q statistic for PD and AL are 0.6021 and 0.9250, respectively. Thus, the research hypotheses are accepted. Both, the pooled effect sizes of PD and AL are significant ($p<0.05$).

```
Call:
meta(y = cbind(PD, AL), v = cbind(var_PD, cov_PD_AL, var_AL),
    data = Berkey98)

95% confidence intervals: z statistic approximation (robust=FALSE)
Coefficients:
            Estimate  Std.Error     lbound     ubound z value  Pr(>|z|)
Intercept1  0.3448392  0.0536312  0.2397239  0.4499544  6.4298 1.278e-10
***
Intercept2 -0.3379381  0.0812479 -0.4971812 -0.1786951 -4.1593 3.192e-05
***
Tau2_1_1    0.0070020  0.0090497 -0.0107351  0.0247391  0.7737    0.4391
Tau2_2_1    0.0094607  0.0099698 -0.0100797  0.0290010  0.9489    0.3427
Tau2_2_2    0.0261445  0.0177409 -0.0086270  0.0609161  1.4737    0.1406
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

Q statistic on the homogeneity of effect sizes: 128.2267
Degrees of freedom of the Q statistic: 8
P value of the Q statistic: 0

Heterogeneity indices (based on the estimated Tau2):
                          Estimate
Intercept1: I2 (Q statistic)   0.6021
Intercept2: I2 (Q statistic)   0.9250

Number of studies (or clusters): 5
Number of observed statistics: 10
Number of estimated parameters: 5
Degrees of freedom: 5
-2 log likelihood: -11.68131
OpenMx status1: 0 ("0" or "1": The optimization is considered fine.
Other values may indicate problems.)
```

Figure 7 Results of multivariate meta-analysis

Heterogeneity, text outputs

Please note that the heterogeneity values are quite high for both PD and AL. Dealing with heterogeneity is beyond the scope of this paper. Based on Figure 7, the heterogeneities of PD (0.6021) and AL (0.9250). These results are based on the multivariate random-effects model. However, users can also run the MMA using the multivariate fixed-effects model. They have to make that choice. The rationale for choosing a random- or fixed-effects model needs to be provided. Usually, the random-effects model is employed.

Plots of multivariate effect sizes and correlations among the random effects

This section provides explanations on two main topics: plots of multivariate effect sizes and correlation among the random effects. Let's start with plots of multivariate effect sizes. Figure 8 is generated by part of the R codes presented in Figure 5, starting from Line 10. Based on Figure 8, there are three graphical outputs. The first graphical output is the forest plot of PD. Here, the pooled effect size is in favor of the experiment group because the effect-size values of PD are positive (see Figure 8). The second output is the forest plot of AL. The pooled effect size is in favor of the control group because the effect-size values of AL are negative (see Figure 8). Finally, the third output presents the multivariate effect sizes (PD and AL). This is the most crucial plot in Figure 9. We capture Cheung's explanations of Figure 9 in verbatim below. He is the author of the metaSEM package.

Cheung explains that

If a multivariate meta-analysis is conducted, pairwise plots on the pooled effect sizes and their confidence ellipses can be obtained via the plot() function. This plot is a multivariate generalization of the forest plot in the univariate meta-analysis. By default, 95% confidence intervals on the average effect sizes and confidence ellipses on the random effects are plotted. Figure 9 shows the average effect sizes of the Berkey98 example. The black dots and the black dashed ellipses are the observed effect sizes and their 95% confidence ellipses in the primary studies. The blue square is the estimated average population effect sizes, while the red ellipse is the 95% confidence ellipse of estimated population average effect sizes. This is a multivariate generalization of the average effect size and its 95% confidence interval in the univariate meta-analysis. The green ellipse is the 95% confidence ellipse of the random effects. Ninety-five percent of the studies with average population effect sizes fall inside this confidence ellipse in the long run.9 (p. 21)

However, we find that the explanation above is too technical. Thus, we recommend that readers further consult his work called metaSEM: An R Package for Meta-Analysis using Structural Equation Modeling on how to interpret the graphical outputs of Figure 7 in full (Cheung, 2024).

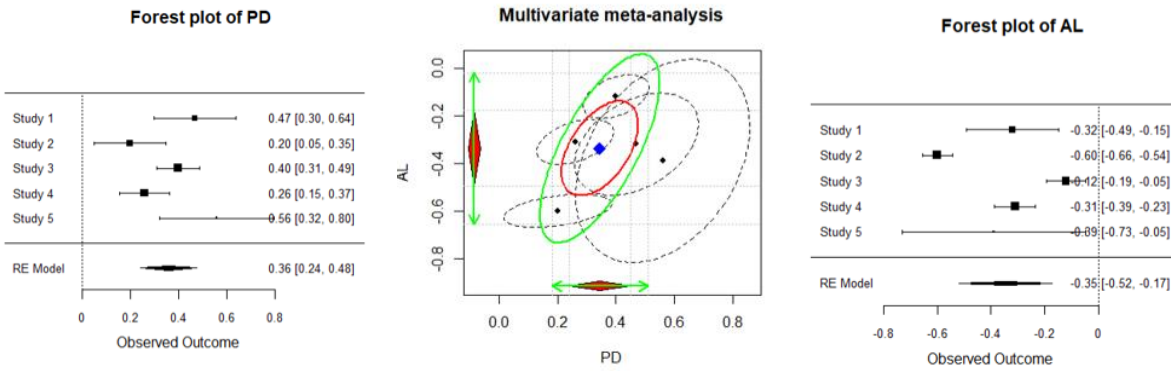

Figure 8 Forest plots of PD and AL, and multivariate meta-analysis

Thus, we provide a complementary explanation. It is assumed that in a multivariate meta-analysis, the multiple outcomes (effect sizes) are assumed to be correlated (Hattle *et al*., 2022). The outcomes in our examples are PD and AL. We think that the correlations among the random effects (PD and AL) could be used to complement previous explanations. We may also visualize these correlations using the confidence ellipses (see Figure 7). Figures 8 and 9 appear to be the same, but they are not. Based on the text output, the correlation among the random effects (PD and AL) is quite high (0.6692). A set of R codes is needed to generate the required text output and graphical output (see Figure 9). This makes sense because the multivariate outcomes from the multivariate meta-analysis are assumed to be correlated.

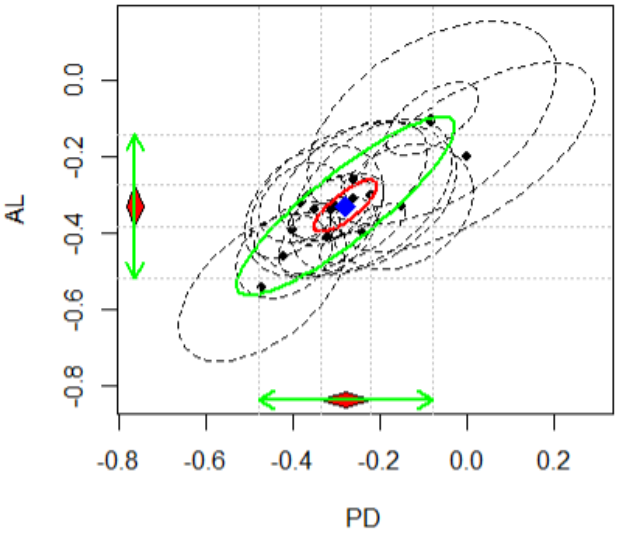

Figure 9 Correlations among random effects, PD and AL

Publication bias

Detecting small study effects in a Multivariate Meta-Analysis setting remains an untouched research area (Hong *et al*., 2020). Thus, such capability is not yet available in R. However, there are at least two pieces of work attempting to detect publication bias based on their simulation studies. The first study is called *"Testing small study effects in multivariate Meta-Analysis"* (Hong *et al*., 2020). The second study is titled "*Detecting Selection Bias in Meta-Analyses with Multiple Outcomes: A Simulation Study*" by Fernández-Castilla *et al*. (2019). This study focuses on investigating and identifying selection bias in meta-analyses that involve multiple outcomes, using simulation techniques to assess the impact and detection of such biases. Finally, we hope that the R software will be available to detect publication bias for MMA soon.

Conclusion

R is fully capable of analyzing MMA. The paper aims to help newcomers to be able to use R to conduct the MMA. This paper points out that MMA must begin with the research problem/question. The research problem/ question can be derived from PICO. A systematic review (i.e. search strategy) is needed to obtain studies that could satisfy the research problem/question. PRISMA captures the results of the search strategy which spells out the inclusion and exclusion criteria for including the MMA at hand in text and visual forms combined. The paper points out how to bring the dataset into R for further MMA analysis. R codes are included to conduct MMA. In summary, this paper teaches how to conduct MMA using R and interpret the text and graphical outputs of the MMA analyses generated by R. Thus, this paper makes R and MMA more accessible to medical and health audiences wishing to use R to conduct MMA. As demonstrated, R is capable of analyzing MMA at the basic level. Thus, we urge researchers in medical health and related fields to adopt R as an alternative software to conduct MMA. Again, R is free and accepted worldwide.

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Conflict of interest

None.

References

Antczak-Bouckoms, A., Joshipura, K., Burdick, E., & Tulloch, J. F. C. (1993). Meta-analysis of surgical versus non-surgical methods of treatment for periodontal disease. Journal of Clinical Periodontology, 20(4), 259-268. [cited 2024 January 12]; Available from: https://doi.org/10.1111/j.1600-051x.1993.tb00355.x

Berkey, C. S., Hoaglin, D. C., Antczak-Bouckoms, A., Mosteller, F., & Colditz, G. A. (1998). Meta-analysis of multiple outcomes by regression with random effects. Statistics in Medicine, 17(22), 2537-2550. [cited 2024 January 10]; Available from: https://doi.org/10.1002/(SICI)1097-0258(19981130)17:22<2537::AID-SIM953>3.0.CO;2-C

Cheung, M. W. (2015). metaSEM: an R package for meta-analysis using structural equation modeling. Frontiers in Psychology, 5. [cited 2024 January 20]; Available from: https://doi.org/10.3389/fpsyg.2014.01521

Cheung, M. W. (2024). The metaSEM package: Examples [Internet]. [cited 2024 April 15]; Available from: https://cran.r-project.org/web/packages/metaSEM/vignettes/Examples.html

Fernández-Castilla, B., Declercq, L., Jamshidi, L., Beretvas, S. N., Onghena, P., & Van Den Noortgate, W. (2019). Detecting Selection Bias in Meta-Analyses with Multiple Outcomes: A Simulation Study. The Journal of Experimental Education, 89(1), 125-144. [cited 2024 April 20]; Available from: https://doi.org/10.1080/00220973.2019.1582470

Gasparrini A, Armstrong B, Kenward MG (2012). Multivariate meta-analysis for non-linear and other multi-parameter associations. Statistics in Medicine, 31(29), 3821-3839. [cited 2024 April 20]; Available from: https://doi.org/10.1002/sim.5471

Hattle, M., Burke, D. L., Trikalinos, T. A., Schmid, C. H., Chen, Y., Jackson, D., & Riley, R. D. (2022). Multivariate meta-analysis of multiple outcomes: characteristics and predictors of borrowing of strength from Cochrane reviews. Systematic Reviews, 11(1). 149. [cited 2024 April 10]; Available from: https://doi.org/10.1186/s13643-022-01999-0

Hong, C., Salanti, G., Morton, S. C., Riley, R. D., Chu, H., Kimmel, S. E., & Chen, Y. (2020). Testing small study effects in multivariate meta-analysis. Biometrics, 76(4), 1240-1250. [cited 2024 February 5]; Available from: https://doi.org/10.1111/biom.13342

Myung, S. (2023). How to review and assess a systematic review and meta-analysis article: a methodological study (secondary publication). Journal of Educational Evaluation for Health Professions, 20, 24. [cited 2024 February 1]; Available from: https://doi.org/10.3352/jeehp.2023.20.24

R Core Team (2021). R: A language and environment for statistical computing (Version 4.0.1) [Computer software]. R Foundation for Statistical Computing, Vienna, Austria. Available from: https://www.R-project.org/.

RStudio Team (2020). RStudio: Integrated Development for R. (Version 1.3) [Computer Software]. RStudio, PBC, Boston, MA. [cited 2024 February 1]; Available from: http://www.rstudio.com/

Savatsomboon, G., Yurayat, P., Chanprasitchai, O., Narkbunnum, W., Sharma, J., & Svetsomboon, S. (2024). A proposed categorization of meta-analysis, their respective example conceptual frameworks, and applicable R packages for education research: a review. Journal of Practical Studies in Education, 5(3), 1-7. [cited 2024 April 2]; Available from: https://doi.org/10.46809/jpse.v5i3.83

Shin, I. (2017). Recent research trends in meta-analysis. Asian Nursing Research, 11(2), 79-83. [cited 2024 April 2]; Available from: https://doi.org/10.1016/j.anr.2017.05.004

Ujdreams. (n.d.). Periodontal probe. Dreamstime. [cited 2024 April 5]; Available from: https://www.dreamstime.com/illustration/periodontal-probe.html

Viechtbauer, W. (2010). Conducting meta-analyses In R with the metafor package. Journal of Statistical Software, 36(3). 1-48. [cited 2024 April 5]; Available from: https://doi.org/10.18637/jss.v036.i03