Handling Missing Covariates in Mixed-Effects Meta-Analysis with Full-Information Maximum Likelihood

Mike W.-L. Cheung
Department of Psychology
National University of Singapore

22 July 2019

Introduction

- Meta-regression (or mixed-effects meta-analysis) is a popular tool to explore the heterogeneity of effect sizes.
- A standard model for the *i*th study is:
  - y_i: an observed effect size
  - β_0: the intercept
  - β_1: the regression coefficient
  - x_i: a study characteristic (covariate)
  - $\tau^2 = Var(u_i)$: the residual variance after controlling for the covariate
  - $v_i = Var(e_i)$: the known sampling variance.

$$y_i = \beta_0 + \beta_1 x_i + u_i + e_i, \tag{1}$$

Potential issues with mixed-effects meta-analysis

- Tipton, Pustejovsky, and Ahmadi (2019a; 2019b)[1], [2] recently provided comprehensive reviews on issues related to applying meta-regression.

[1] Tipton, E., Pustejovsky, J. E., & Ahmadi, H. (2019a). A history of meta-regression: Technical, conceptual, and practical developments between 1974 and 2018. *Research Synthesis Methods*, *10*(2), 161–179.

[2] Tipton, E., Pustejovsky, J. E., & Ahmadi, H. (2019b). Current practices in meta-regression in psychology, education, and medicine. *Research Synthesis Methods*, *10*(2), 180–194.

Three key findings relevant to this presentation

1. There are missing covariates in almost half (45%) of meta-analyses published in the selected journals.
2. Ad hoc procedures, e.g., listwise deletion, are usually used to handle missing covariates (86%).

TABLE 4 Practical characteristics of systematic reviews published in 2016

Analysis		*Psychological Bulletin* (*k* = 24)	*Review of Educational Research* (*k* = 13)	*Journal of Applied Psychology* (*k* = 4)	*Cochrane Library* (*k* = 23)	Total (*k* = 64)
Missing covariates	No	15 (62%)	4 (31%)	1 (25%)	15 (65%)	35 (55%)
	Yes	9 (38%)	9 (69%)	3 (75%)	8 (35%)	29 (45%)
Missing data method[a]	Ad hoc	6 (67%)	9 (100%)	3 (100%)	7 (88%)	25 (86%)
	Multiple imputation	1 (11%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)
	Other principled methods	1 (11%)	0 (0%)	0 (0%)	1 (12%)	2 (7%)
	Not reported	1 (11%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)

Figure 1: Partial Table 4 in Tipton, Pustejovsky, and Ahmadi (2019b)

Three key findings relevant to this presentation

3. Each covariate is usually individually entered into the meta-regression.

TABLE 2 Technical characteristics of systematic reviews published in 2016

Analysis		***Psychological Bulletin* (*k* = 24)**	***Review of Educational Research* (*k* = 13)**	***Journal of Applied Psychology* (*k* = 4)**	***Cochrane Library* (*k* = 23)**	**Total (*k* = 64)**
Any moderator analysis		24 (100%)	11 (85%)	4 (100%)	20 (87%)	59 (92%)
Subgrouping[a]	One-way	4 (17%)	1 (8%)	0 (0%)	12 (52%)	17 (27%)
	Multi-way	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
ANOVA[a]	One-way	17 (71%)	9 (69%)	4 (100%)	9 (39%)	39 (61%)
	Multi-way	2 (8%)	0 (0%)	0 (0%)	0 (0%)	2 (3%)
Meta-regression[a]	Simple	17 (71%)	4 (31%)	0 (0%)	7 (30%)	28 (44%)
	Multiple	8 (33%)	3 (23%)	0 (0%)	0 (0%)	11 (17%)

Figure 2: Partial Table 2 in Tipton, Pustejovsky, and Ahmadi (2019b)

Missing data mechanisms I

- Rubin (1987)[3] provided a general framework to classify missing data mechanisms.
- Pigott (2019)[4] applied Rubin's definitions to meta-analysis and discussed common methods to handle missing data in meta-analysis.

[3] Rubin, D. B. (1987). *Multiple imputation for nonresponse in surveys*. John Wiley and Sons.

[4] Pigott, T. D. (2019). Missing data in meta-analysis. In H. Cooper, L. V. Hedges, & J. C. Valentine (Eds.), *The handbook of research synthesis and meta-analysis* (3nd ed., pp. 367–381). New York: Russell Sage Foundation.

Missing data mechanisms II

- Missing completely at random (MCAR): the missingness is not related to the missing values or other observed variables in the analysis;
- Missing at random (MAR): the missingness can be fully accounted for by the other variables in the analysis;
- Missing not at random (MNAR): the missingness is related to the values of the missing values even after controlling for other variables in the analysis.

Methods to handle missing data I

- Both multiple imputation (MI) and (full-information) maximum likelihood (FIML) are the preferred methods to handle missing data with either MCAR or MAR (e.g., Enders, 2010;[5] Graham, 2009;[6] Newman, 2014;[7] Schafer & Graham, 2002).[8]

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[5] Enders, C. K. (2010). *Applied missing data analysis*. New York: Guilford Press.

[6] Graham, J. W. (2009). Missing Data Analysis: Making it work in the real world. *Annual Review of Psychology*, *60*(1), 549–576.

[7] Newman, D. A. (2014). Missing data five practical guidelines. *Organizational Research Methods*, *17*(4), 372–411.

[8] Schafer, J. L., & Graham, J. W. (2002). Missing data: Our view of the state of the art. *Psychological Methods*, *7*(2), 147–177.

Methods to handle missing data II

Table 2. Missing Data Bias and Error Problems of Common Missing Data Techniques.

	Missingness Mechanism		
Missing Data Technique	MCAR	MAR	MNAR
Listwise Deletion	Unbiased; Large Std. Errors (Low Power)	Biased; Large Std. Errors (Low Power)	Biased; Large Std. Errors (Low Power)
Pairwise Deletion	Unbiased; Inaccurate Std. Errors	Biased; Inaccurate Std. Errors	Biased; Inaccurate Std. Errors
Single Imputation	Often Biased; Inaccurate Std. Errors	Often Biased; Inaccurate Std. Errors	Biased; Inaccurate Std. Errors
Maximum Likelihood (ML)	**Unbiased; Accurate Std. Errors**	**Unbiased; Accurate Std. Errors**	Biased; Accurate Std. Errors
Multiple Imputation (MI)	**Unbiased; Accurate Std. Errors**	**Unbiased; Accurate Std. Errors**	Biased; Accurate Std. Errors

Note. Recommended techniques are in boldface. Adapted from Newman (2009).

Figure 3: Table 2 in Newman (2014)

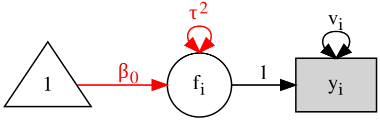
Similarities and differences between FIML and MI

- Unlike MI, FIML analyzes all available data without imputing any data.
- FIML and MI are asymptotically equivalent when the number of imputations in MI tends to infinity.
- FIML is only implemented in SEM packages such as Mplus, AMOS, lavaan (in R), and OpenMx (in R).

A random-effects model

- We introduce the SEM-based meta-analytic models with a mean structure $\mu_i(\theta_i)$ and covariance structure $\Sigma_i(\theta_i)$ (Cheung, 2015):[9]
  - Observed or measured variables: Squares or rectangles
  - Latent or unmeasured variables: Circles or ellipses
  - Means or intercepts: Triangles of one
  - Directional paths or regression coefficients: one-headed arrow
  - Variances and covariances: two-headed arrows

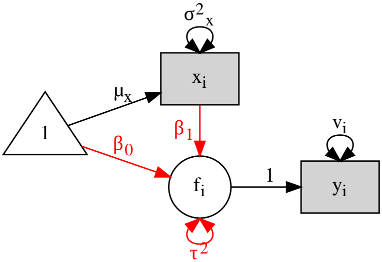
$$
\begin{aligned}
y_i &= \beta_0 + u_i + e_i, \\
\mu_i(\theta_i) &= \beta_0, \\
\Sigma_i(\theta_i) &= \tau^2 + v_i.
\end{aligned}
\tag{2}
$$

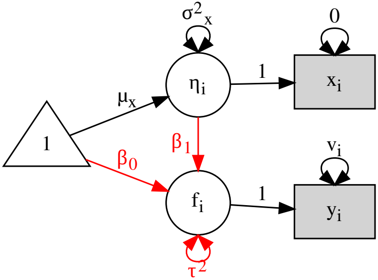


[9] Cheung, M. W.-L. (2015). *Meta-analysis: A structural equation modeling approach*. Chichester, West Sussex: John Wiley & Sons, Inc.

A meta-regression

- We may extend the random-effects meta-analysis to a meta-regression.
- *Left*: studies with missing data in x_i are dropped.
- *Right*: studies with missing data in x_i are handled with FIML .





Full-information maximum likelihood (FIML)

- The key idea of FIML is to allow each study having its own model by filtering out the missing data.[10]
- These models are combined in estimating the parameters.

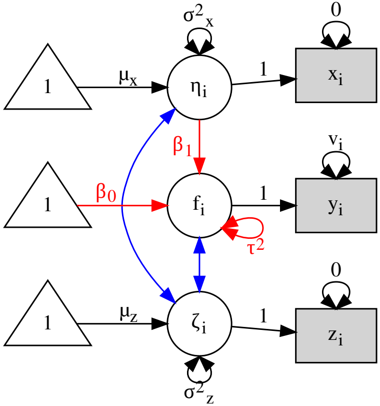
$$
\begin{aligned}
-2\log L_i &= c_i + \log|\Sigma_i(\theta_i)| + (\mathbf{y}_i - \mu_i(\theta_i))^{\mathsf{T}}\Sigma_i(\theta_i)^{-1}(\mathbf{y}_i - \mu_i(\theta_i)), \\
-2\log L &= \sum_{i=1}^{k} -2\log L_i
\end{aligned}
\tag{3}
$$

- where c_i is the number of non-missing observed variables in the ith study.

[10] https://vipbg.vcu.edu/vipbg/OpenMx2/docs//OpenMx/latest/FIML_RowFit.html

A meta-regression with an auxiliary variable

- It is useful to include *auxiliary variables* (AV) in the analysis.
- An auxiliary variable is a variable not of substantive interests but is potentially correlate of the missingness or the missing variables. It may make the missing data more likely to be MAR.



An example: Tenenbaum and Leaper (2002)[11]

- A total of 48 studies
- Effect size (r): correlation between parents' and children's gender schemas.
- Covariate: Mean age of children (months)
- Potential auxiliary variable: Year of publication

Table 1
Independent Samples Included in the Meta-Analyses

Authors	*N*	Effect size (*r*)	Publication source[a]	Author gender[b]	Parent type[c]	Parent predictor[d]	Offspring age (months)	Offspring type[e]	Offspring outcome[f]
Atkinson (1983)	334	.12	3	M	MF	S	231	DS	S
Barak et al. (1991)	99	−.08	2	W	MF	A	72	DS	W
Barry (1980)	96	−.05	2	M	MF	A	48	DS	I
Bennett (1979)	105	−.08	3	M	MF	S	51	DS	S
Blee & Tickamyer (1986)	730	.15	2	W	M	A	330	D	A, W
Bliss (1988)	24	.12	2	W	MF	A	60	DS	A, S
Bollman et al. (1988)	181	.17	2	M	MF	A	156	DS	A
Dambrot et al. (1984)	43	.34	1	W	M	A	228	D	A
Eccles et al. (1993)	494	−.01	1	W	MF	A	96	DS	A
Ex & Janssens (1998)	165	.33	2	W	M	A	228	D	A

Figure 4: Partial Table 1 in Tenenbaum and Leaper (2002)

[11] Tenenbaum, H. R., & Leaper, C. (2002). Are parents' gender schemas related to their children's gender-related cognitions? A meta-analysis. *Developmental Psychology*, *38*(4), 615–630.

An example

- As an illustration, I randomly introduced 40% of missing data in the covariate (Mean age of children).
  - MCAR: missing data were randomly introduced.
  - MAR: missing data were introduced for studies reported earlier.
- R code to run FIML:

```
## Load the library
library(metaSEM)

## y: effect size
## v: sampling variance
## x: covariate
## av: auxiliary variable
fit <- metaFIML(y=r, v=v, x=Offspring_age, av=Year_pub, data=my.MCAR)
summary(fit)
```

Results

```
##
## Call:
## metaFIML(y = r, v = v, x = Offspring_age, av = Year_pub, data = my.MCAR)
##
## 95% confidence intervals: z statistic approximation (robust=FALSE)
## Coefficients:
##                  Estimate       Std.Error          lbound          ubound z value                Pr(>|z|)
## Tau2_1_1      0.012136188     0.004531652     0.003254314     0.021018062    2.68                 0.00740 **
## CovX1_X1   4611.581284823 1207.242842911 2245.428792123 6977.733777523    3.82                 0.00013 ***
## CovX2_X1    -60.798579051   93.708103796 -244.463087550  122.865929448   -0.65                 0.51646
## CovX2_X2     57.118055708   11.659671739   34.265519027   79.970592388    4.90              0.00000096 ***
## CovX2_Y1     -0.133004840    0.160179080   -0.446950067    0.180940387   -0.83                 0.40634
## Slope1_1      0.000683188    0.000359106   -0.000020646    0.001387023    1.90                 0.05711 .
## Intercept1    0.184199248    0.021920854    0.141235164    0.227163332    8.40 < 0.0000000000000002 ***
## MeanX1        0.077301969   13.244922411  -25.882268935   26.036872872    0.01                 0.99534
## MeanX2        0.000000142    1.090515354   -2.137370676    2.137370959    0.00                 1.00000
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Q statistic on the homogeneity of effect sizes: 179.01
## Degrees of freedom of the Q statistic: 47
## P value of the Q statistic: 0
##
## Explained variances (R2):
##                           y1
## Tau2 (no predictor)     0.01
## Tau2 (with predictors) 0.01
## R2                      0.15
##
## Number of studies (or clusters): 48
## Number of observed statistics: 125
## Number of estimated parameters: 9
```

Multiple imputation

- I included MI here for comparisons.
- Wolfgang[12] also illustrates how to conduct MI with `mice` and the `metafor` package.

```
## Year_pub is not included in the imputation phase.
## m=200: 200 imputations in MI
##
## fit <- metaMI(y=r, v=v, x=Offspring_age, data=my.MCAR[, c("r", "v", "Offspring_age")], m=200)
## summary(fit)

## Year_pub is treated as an auxiliary variable and included in the imputation phase.
fit <- metaMI(y=r, v=v, x=Offspring_age, data=my.MCAR[, c("r", "v", "Offspring_age", "Year_pub")], m=200)
summary(fit)
```

```
##              estimate  std.error statistic      df   p.value
## Intercept1 0.18470878 0.02175830    8.4891 66568.7 0.0000000
## Slope1_1   0.00067569 0.00038161    1.7706  1570.1 0.0768166
## Tau2_1_1   0.01220727 0.00447368    2.7287 52489.9 0.0063609
##
## Explained variances (R2):
##                           y1
## Tau2 (no predictor)     0.01
## Tau2 (with predictors)  0.01
## R2                      0.14
```

[12] http://www.metafor-project.org/doku.php/tips:multiple_imputation_with_mice_and_metafor

Comparisons of methods in handling missing covariates

- As the results are only based on one sample, they are not conclusive.

Table 1: Estimated regression coefficients of missing covariates with MCAR

	Estimate	Std.Error	z/t value	df	P.Value
Full set (k=48)	0.000857	0.000301	2.8479	NA	0.004401
Listwise (k=21)	0.000676	0.000375	1.8021	NA	0.071524
FIML w/o AV	0.000684	0.000357	1.9151	NA	0.055474
FIML w AV	0.000683	0.000359	1.9025	NA	0.057110
MI w/o AV	0.000707	0.000392	1.8025	1202.9	0.071713
MI w AV	0.000649	0.000389	1.6667	1306.2	0.095817

Table 2: Estimated regression coefficients of missing covariates with MAR

	Estimate	Std.Error	z/t value	df	P.Value
Full set (k=48)	0.000857	0.000301	2.84789	NA	0.004401
Listwise (k=21)	0.000308	0.000264	1.16624	NA	0.243519
FIML w/o AV	0.000491	0.000490	1.00244	NA	0.316133
FIML w AV	0.000399	0.000540	0.73871	NA	0.460083
MI w/o AV	0.000338	0.000418	0.80806	802.29	0.419296
MI w AV	0.000276	0.000433	0.63752	884.83	0.523953

Future work

- Future simulation studies to explore:
  - Methods: listwise deletion, mean imputation, MI, and FIML
  - Types of missing data mechanisms: MCAR, MAR, and MNAR
  - Percentage of missing data
- An experimental version of `metaFIML` is available in Github.[13] `metaMI` will be added soon.

[13] https://github.com/mikewlcheung/metasem

Thank you for your attention!

- Questions and comments are welcome!