Bridging Meta-Analysis and Standard Statistical Methods

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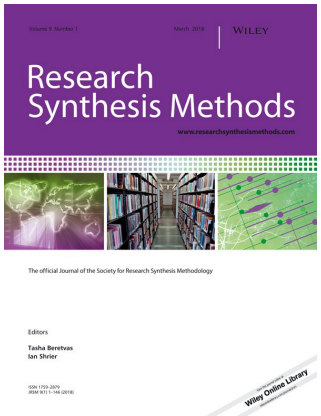
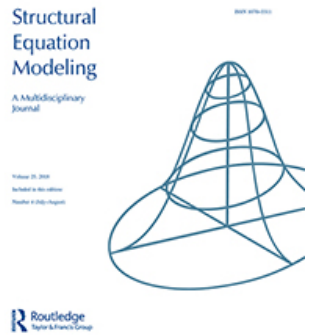
Two different research traditions and communities

- These models are treated as two separate techniques in the literature:
  - Primary research (SEM) vs. meta-analysis
- **Meta-analysis**: *Research Synthesis Methods*, the official journal of the Society of Research Synthesis Methodology
- **SEM**: *Structural Equation Modeling: A Multidisciplinary Journal*





SEM as a general modeling framework

- M*plus* and the generalized linear latent and mixed models (GLLAMM):[1], [2]
  - SEM, generalized linear models, multilevel models, mixture models, IRT models, Bayesian, etc.
- Advantages of integrating various models into a single framework:
  - A single framework can be used in data analysis;
  - Techniques developed in one model can be transferred to other models;
  - It helps to develop new techniques, e.g., MASEM (MA+SEM), multilevel SEM (multilevel model + SEM), growth mixture models (growth model + mixture model), etc.

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[1] Muthen, B. O., & Muthen, L. K. (2012). *Mplus user's guide* (7th ed.). Los Angeles, CA: Muthen & Muthen.

[2] Skrondal, A., & Rabe-Hesketh, S. (2004). *Generalized latent variable modeling: Multilevel, longitudinal, and structural equation models*. Boca Raton: Chapman & Hall/CRC.

Main goal of today's talk

- Present an overview how meta-analysis can be integrated into the SEM framework:
  - Univariate meta-analysis
  - Multivariate meta-analysis
  - Three-level meta-analysis

Univariate meta-analysis

- Let us use a classic dataset in the meta-analysis to motivate the introduction:
  - Studies on the effectiveness of the Bacillus Calmette-Guerin (BCG) vaccine in preventing tuberculosis (TB).[3]
  - We use odds ratio (OR) as the effect size in this illustration. We usually use log(OR) to normalize the sampling variance of the OR.

[3] Berkey, C. S., Hoaglin, D. C., Mosteller, F., & Colditz, G. A. (1995). A random-effects regression model for meta-analysis. *Statistics in Medicine*, *14*, 395-411.

Data

- Negative log-OR means the vaccine is effective.
  - **VD**: Vaccinated group with the disease; **VWD**: Vaccinated group without the disease
  - **NVD**: Not vaccinated group with the disease; **NVWD**: Not vaccinated group without the disease
  - **Latitude**: Geographic latitude of the place where the study was conducted

	Author	Year	VD	VWD	NVD	NVWD	Latitude	ln_OR	v_ln_OR
1	Aronson	1948	4	119	11	128	44	-0.93869414	0.357124952
2	Ferguson & Simes	1949	6	300	29	274	55	-1.66619073	0.208132394
3	Rosenthal et al	1960	3	228	11	209	42	-1.38629436	0.433413078
4	Hart & Sutherland	1977	62	13536	248	12619	52	-1.45644355	0.020314413
5	Frimodt-Moller et al	1973	33	5036	47	5761	13	-0.21914109	0.051951777
6	Stein & Aronson	1953	180	1361	372	1079	44	-0.95812204	0.009905266
7	Vandiviere et al	1973	8	2537	10	619	19	-1.63377584	0.227009675
8	TPT Madras	1980	505	87886	499	87892	13	0.01202060	0.004006962
9	Coetzee & Berjak	1968	29	7470	45	7232	27	-0.47174604	0.056977124
10	Rosenthal et al	1961	17	1699	65	1600	42	-1.40121014	0.075421726
11	Comstock et al	1974	186	50448	141	27197	18	-0.34084965	0.012525134
12	Comstock & Webster	1969	5	2493	3	2338	33	0.44663468	0.534162172
13	Comstock et al	1976	27	16886	29	17825	33	-0.01734187	0.071635117

What is a fixed-effects model?

- Conceptual issues:[4], [5]
  - Studies are direct replicates of each other;
  - Findings can only be generalized to studies with the same study characteristics.
- Statistical issues:
  - The population effect sizes are usually assumed the same for all studies (homogeneity of effect sizes), which is also known as the *common effect* model;
  - Differences in the observed effect sizes are only due to the sampling errors.

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[4] Borenstein, M., Hedges, L. V., Higgins, J. P. T., & Rothstein, H. R. (2010). A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, *1*(2), 97-111.

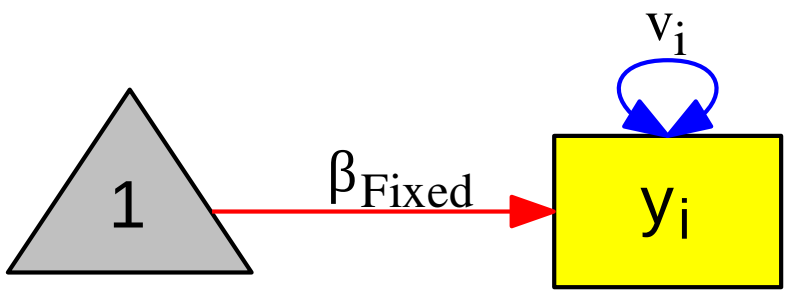
[5] Schmidt, F. L., & Hunter, J. E. (2015). *Methods of meta-analysis: Correcting error and bias in research findings* (3rd ed.). Thousand Oaks, CA: Sage.

Univariate fixed-effects meta-analysis

- $y_i = \beta_{Fixed} + e_i$ with $e_i \sim \mathcal{N}(0, v_i)$
  - β_{Fixed} is the common population effect size under a fixed-effects model.
- I use y_i to represent an observed effect size in the ith study:
  - Example: a (standardized) mean difference, correlation coefficient, or log odds ratio.
- v_i is the conditional sampling variance of y_i:
  - It is assumed known in a meta-analysis;
  - Example: $v_r = \frac{(1-r^2)^2}{n}$ is the approximate sampling variance for the correlation coefficient.

SEM approach

- We may use the following model to fit the fixed-effects meta-analysis in SEM. There is only one unknown parameter β_{Fixed}:[6]
  - **Mean structure**: $\mu_i(\theta) = \beta_{\text{Fixed}}$,
  - **Covariance structure**: $\Sigma_i(\theta) = v_i$.
- We treat *studies* in a meta-analysis as *subjects* in SEM. v_i is fixed for each *subject*.



[6] Cheung, M. W.-L. (2008). A model for integrating fixed-, random-, and mixed-effects meta-analyses into structural equation modeling. *Psychological Methods*, *13*(3), 182-202.

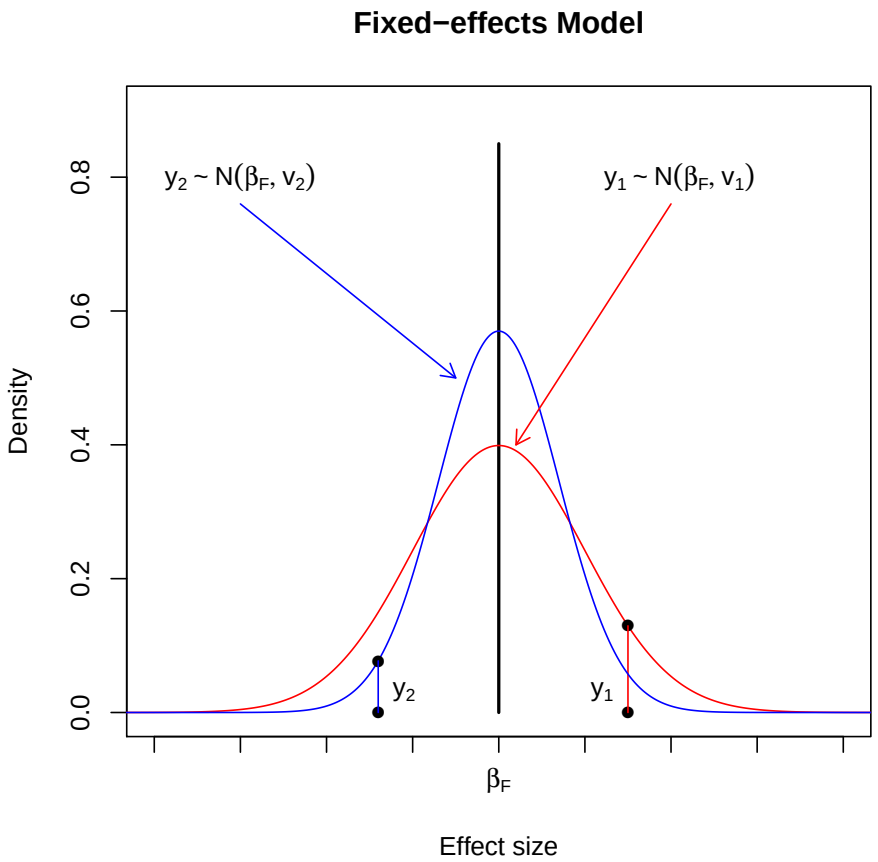
Results based on the fixed-effects model

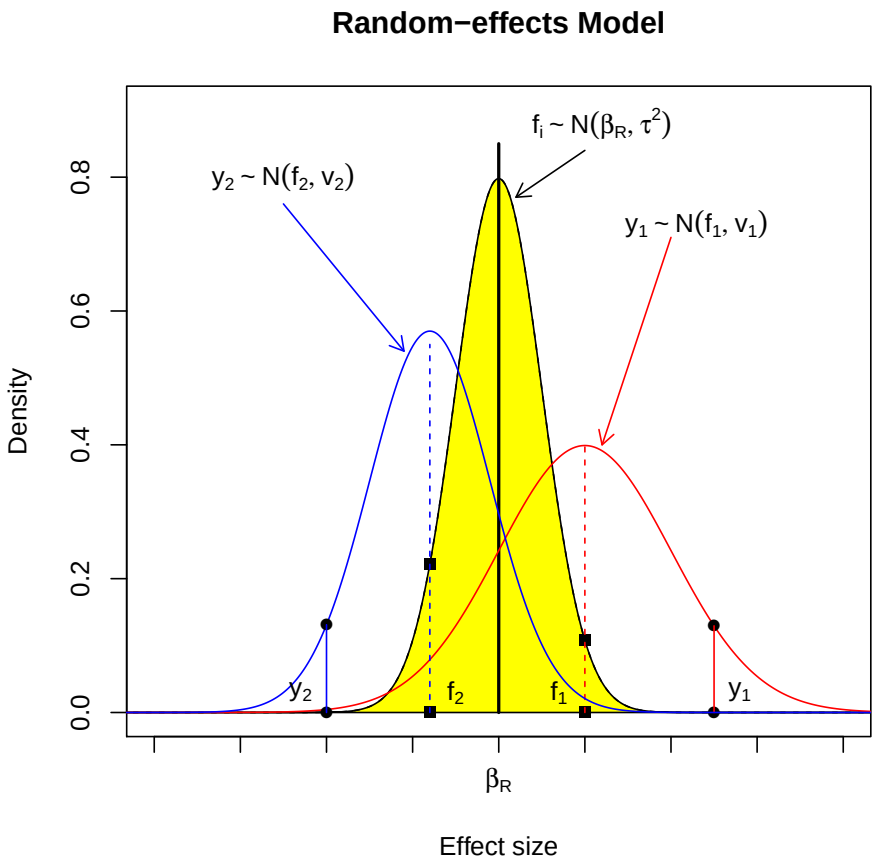
- The homogeneity test is $Q(df = 12) = 163.16, p < .0001$, suggesting that the population effect sizes are heterogeneous.
- The estimated common effect (log-OR) and its 95% confidence interval (CI) is -0.4361 (-0.5190; -0.3533).
- The fixed-effects model does not seem to be appropriate here. We should be cautious in interpreting the results.

What is a random-effects model?

- Conceptual issues:
  - Studies are randomly sampled from a pool of studies;
  - Findings can be generalized to other studies that have not been included in the meta-analysis.
- Statistical issues:
  - Each study may have its *population* (or *true*) effect size;
  - The variance of the *true* effect size (heterogeneity variance) can be estimated.

Graphical representation of fixed- vs. random-effects models



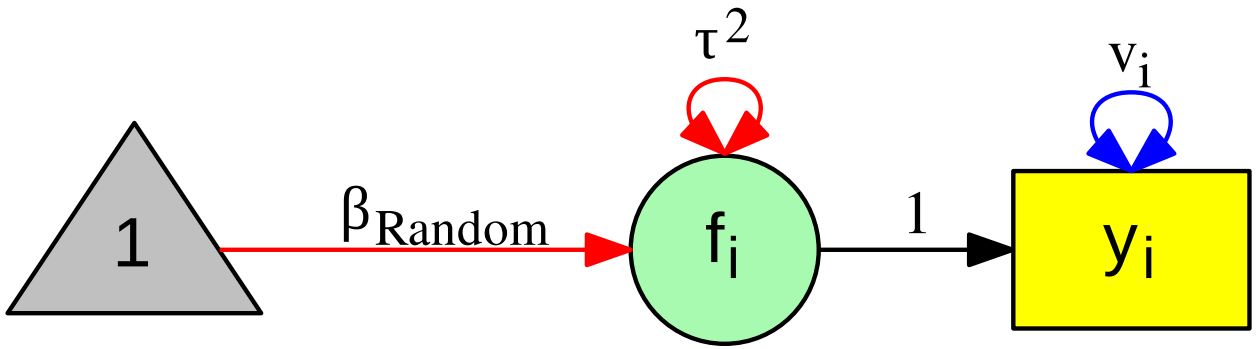


Univariate random-effects meta-analysis

- The random-effects model can be conceptualized as a two-level model with known sampling variance:
  - Level 1 (subjects): $y_i = f_i + e_i$,
  - Level 2 (studies): $f_i = \beta_{Random} + u_i$,
    - f_i is the *true* effect size in the ith study,
    - β_{Random} is the average population effect size,
    - $u_i \sim \mathcal{N}(0, \tau^2)$ and τ^2 is the heterogeneity variance of the random effects.
  - Single equation: $y_i = \beta_{Random} + u_i + e_i$.
- We may calculate $I^2 = \frac{\tau^2}{\tau^2 + \tilde{v}_i}$, where $\tilde{v}_i$ is the *typical* sampling variance. I^2 indicates the total variation on the effect size that can be explained by the between-study effect.
- The fixed-effects model is a special case of the random-effects model when $\tau^2 = 0$.

SEM approach

- Under the SEM approach, the study-specific random effect u_i is conceptualized as a latent variable f_i:
  - **Mean structure**: $\mu_i(\theta) = \beta_{\text{Random}}$,
  - **Covariance structure**: $\Sigma_i(\theta) = \tau^2 + v_i$.
- Both maximum likelihood (ML) and restricted maximum likelihood (REML) estimation can be used to fit the models. I will focus on ML estimation here.[7]



[7] Cheung, M. W.-L. (2013). Implementing restricted maximum likelihood estimation in structural equation models. *Structural Equation Modeling: A Multidisciplinary Journal*, *20*(1), 157-167.

Translation between meta-analysis and SEM

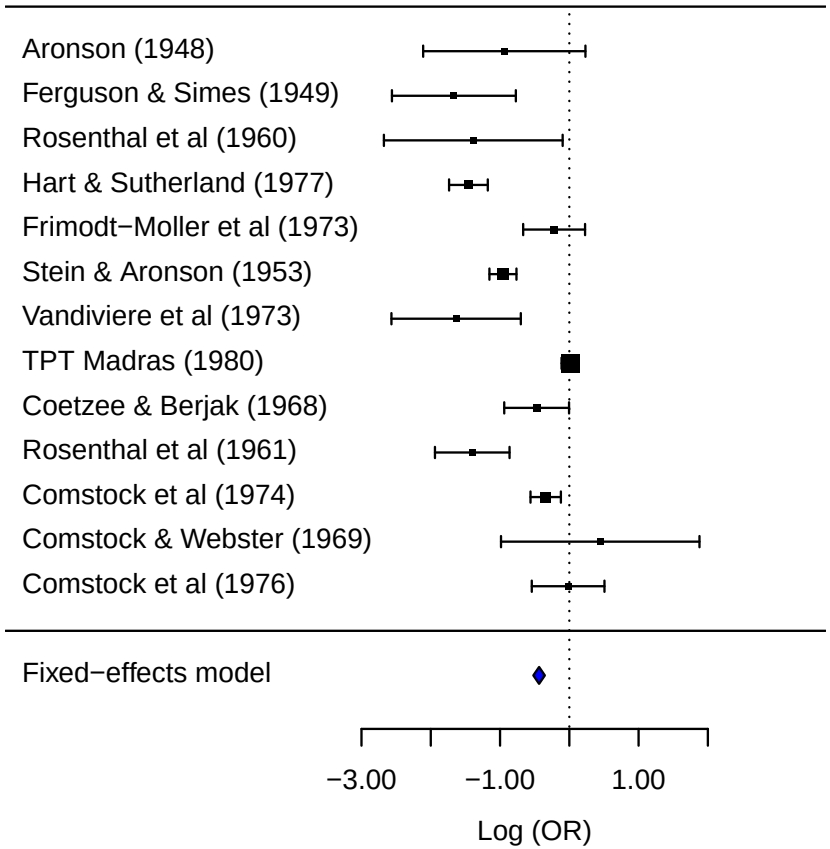
Meta-analysis	SEM
k studies	N subjects
Observed effect size y_i	Observed score y_1
Population effect size f_i	Factor score f_1
Average effect β_{Random}	Factor mean μ_{f1}
Heterogeneity variance τ^2	Factor variance ϕ_{11}
Sampling variance v_i	Variance of measurement error ψ_{11}
Moderator x_i	Predictor x

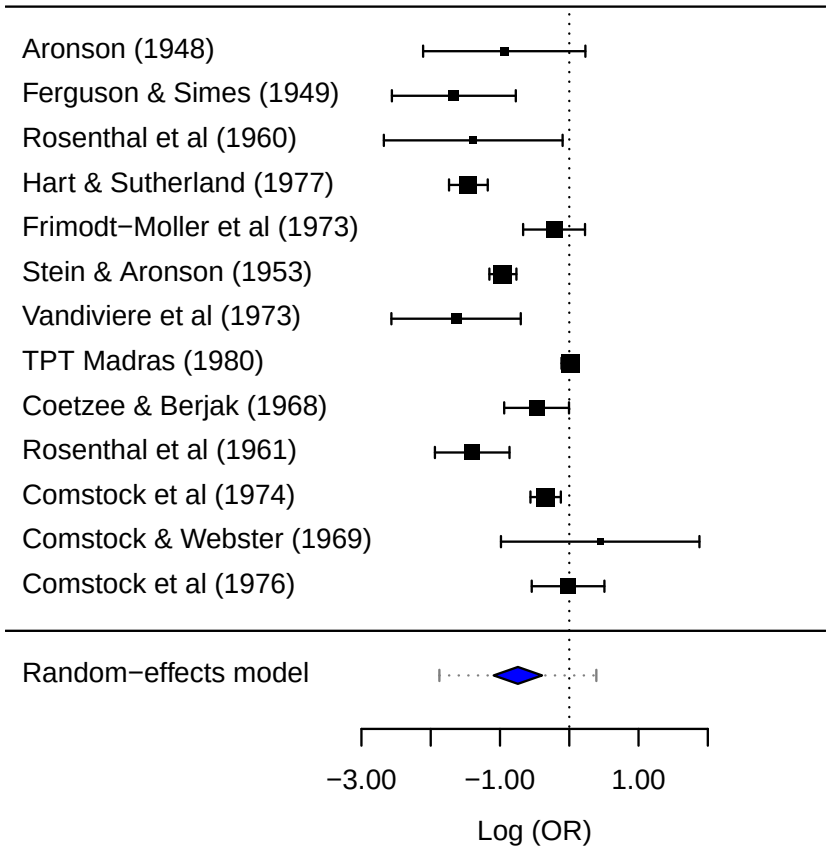
Results based on the random-effects model

- The estimated heterogeneity variance is $\hat{\tau}^2 = 0.30$ and the I^2 is .91. It indicates that about 91% of the variance can be attributed to the between-study effect.
- The average effect size (log-OR) and its 95% confidence interval (CI) is -0.7420 (-1.0907; -0.3932).

Forest plots

- By comparing the forest plots, the fixed-effects model under-estimates the CI of the average effect size.
- Fixed-effects models are rarely correct in applied settings.



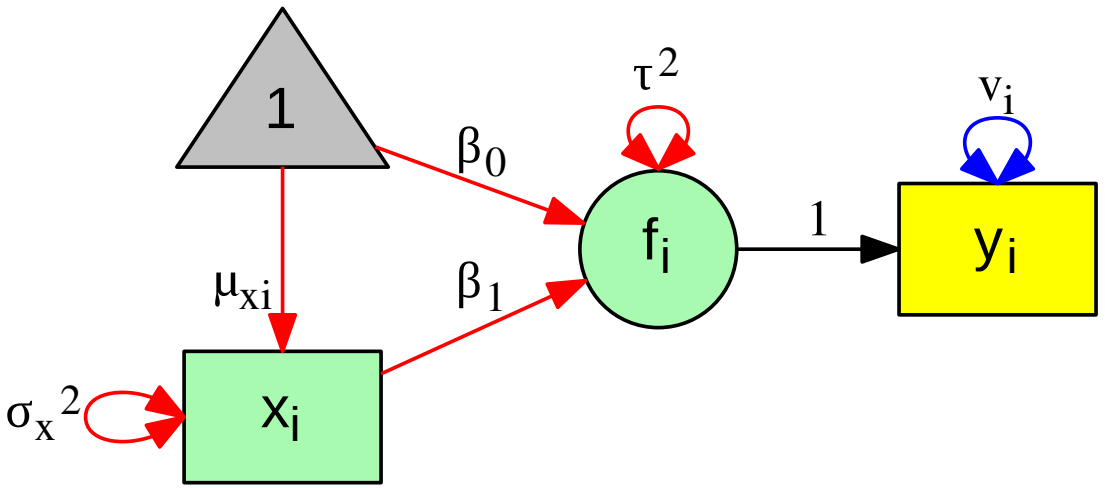


Univariate mixed-effects meta-analysis

- When there is excessive heterogeneity, we may want to explore why some studies have larger/smaller effects by using study characteristics as moderators.
- In our example, we may use the absolute `Latitude` of studies or year of publications as potential moderators.
- $y_i = \beta_0 + \beta_1 x_{1i} + u_i + e_i$ with $u_i \sim \mathcal{N}(0, \tau^2)$
  - β_0 and β_1 are the intercept, and the regression coefficient, respectively;
  - τ^2 is the residual of the random effects after controlling for x_1.

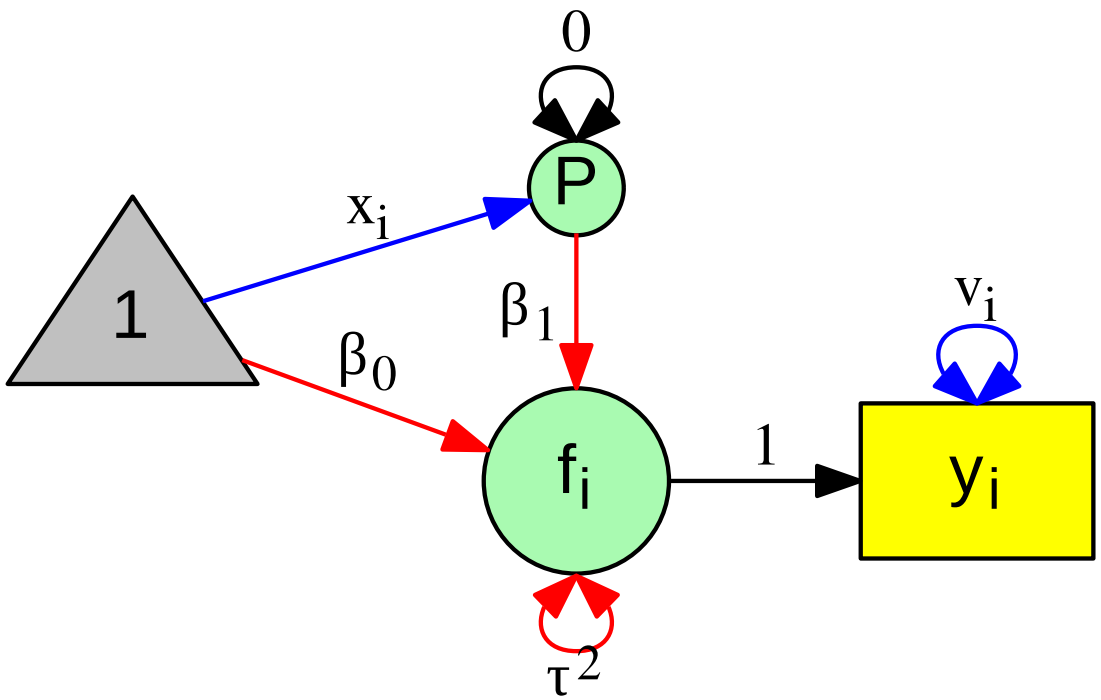
SEM approach (1)

- Under the SEM approach, we may jointly model both y_i and x_i:
  - **Mean structure**: $\mu_i(\theta) = \mathrm{E}(\begin{bmatrix} y_i \\ x_i \end{bmatrix}) = \begin{bmatrix} \beta_0 + \beta_1 \mu_x \\ \mu_x \end{bmatrix}$
  - **Covariance structure**: $\Sigma_i(\theta) = \mathrm{Cov}(\begin{bmatrix} y_i \\ x_i \end{bmatrix}) = \begin{bmatrix} \beta_1^2 \sigma_x^2 + \tau^2 + v_i & \\ \beta_1 \sigma_x^2 & \sigma_x^2 \end{bmatrix}$.



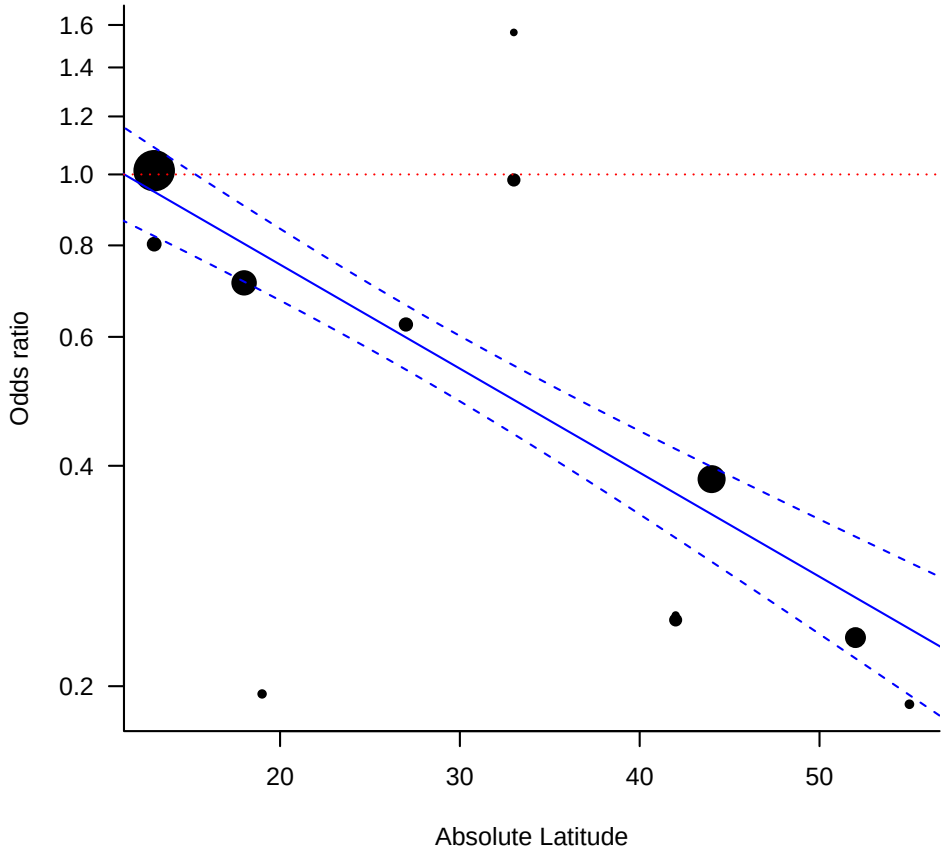
SEM approach (2)

- An alternative approach is to treat x_i as a *design matrix*. We fix x_i as a *definition variable* with the use of a *phantom variable* P.
  - **Mean structure**: $\mu_i(\theta|x_i) = \beta_0 + \beta_1 x_i$
  - **Covariance structure**: $\Sigma_i(\theta|x_i) = \tau^2 + v_i$.



Results based on the mixed-effects model

- The estimated regression coefficient is -0.0327 (-0.0393; -0.0261) with $R^2 = .9868$. The effect is stronger (more deviated from 1) for studies conducted in larger latitude.



Multivariate meta-analysis (1)

- One fundamental assumption in univariate meta-analysis is that the effect sizes are independent.
- When this assumption is violated, the test statistics are no longer correct.
- Each study may report more than one effect sizes.
- Sometimes, it is inappropriate to combine them into one single effect size as they are representing different constructs, e.g.,
    - Gender differences in mathematical achievement and language achievement.

In our BCG example

- Some researchers suggested using a bivariate meta-analysis by considering the log-odds of the treatment and the log-odds of the control as two effect sizes.[8]
- One benefit of this model is to study how the true treatment and control effects are related.

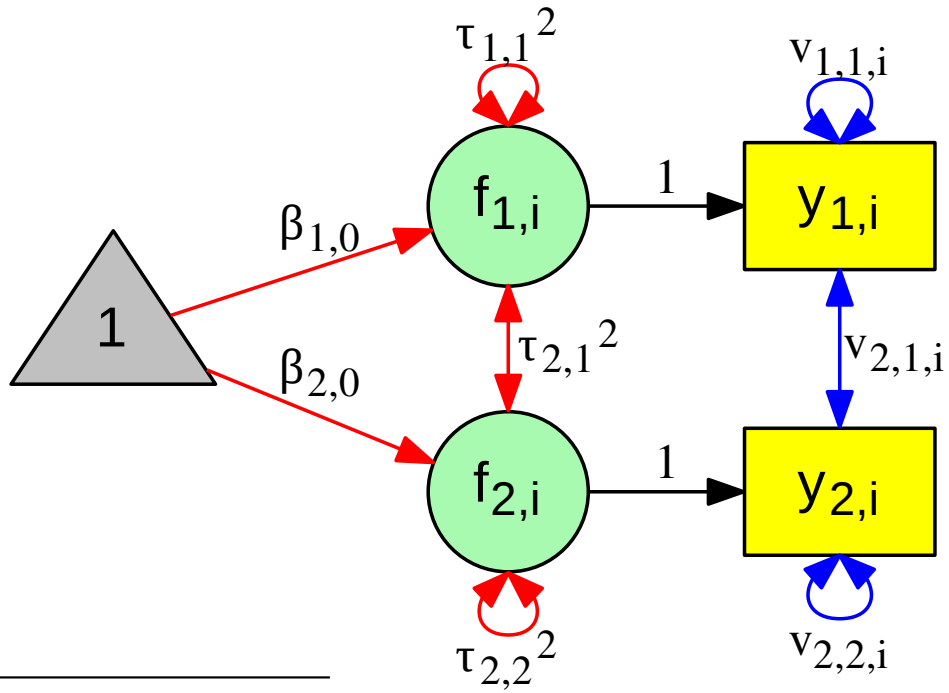
[8] van Houwelingen, H. C., Arends, L. R., & Stijnen, T. (2002). Advanced methods in meta-analysis: multivariate approach and meta-regression. *Statistics in Medicine*, *21*(4), 589-624.

Multivariate meta-analysis (2)

- $\boldsymbol{y}_i = \beta_{Random} + \boldsymbol{u}_i + \boldsymbol{e}_i$ with $\boldsymbol{e}_i \sim \mathcal{N}(0, \boldsymbol{V}_i)$ and $\boldsymbol{u}_i \sim \mathcal{N}(0, \boldsymbol{T}^2)$
  - β_{Random} is the vector of the average population effect size under a random-effects model;
  - $\boldsymbol{V}_i$ is the conditional sampling covariance matrix of $\boldsymbol{y}_i$;
  - $\boldsymbol{T}^2$ is the heterogeneity variance of the random effects.
- The fixed-effects model is a special case when $\boldsymbol{T}^2 = \boldsymbol{0}$.

SEM approach

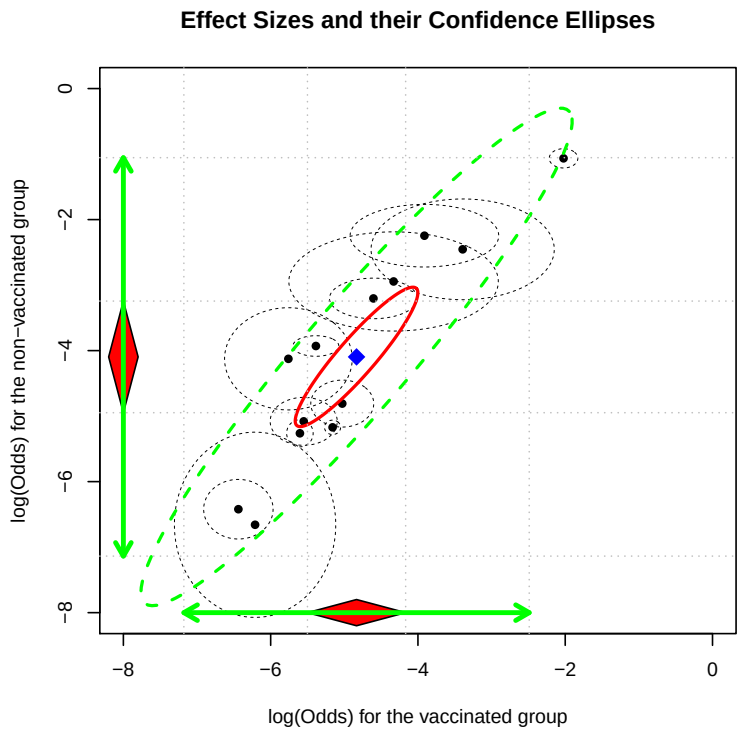
- The multivariate meta-analysis can be easily extended as a structural equation model.[9]
- Incomplete effect sizes are handled with (full information) maximum likelihood (FIML) estimation.



[9] Cheung, M. W.-L. (2013). Multivariate meta-analysis as structural equation models. *Structural Equation Modeling: A Multidisciplinary Journal*, *20*(3), 429-454.

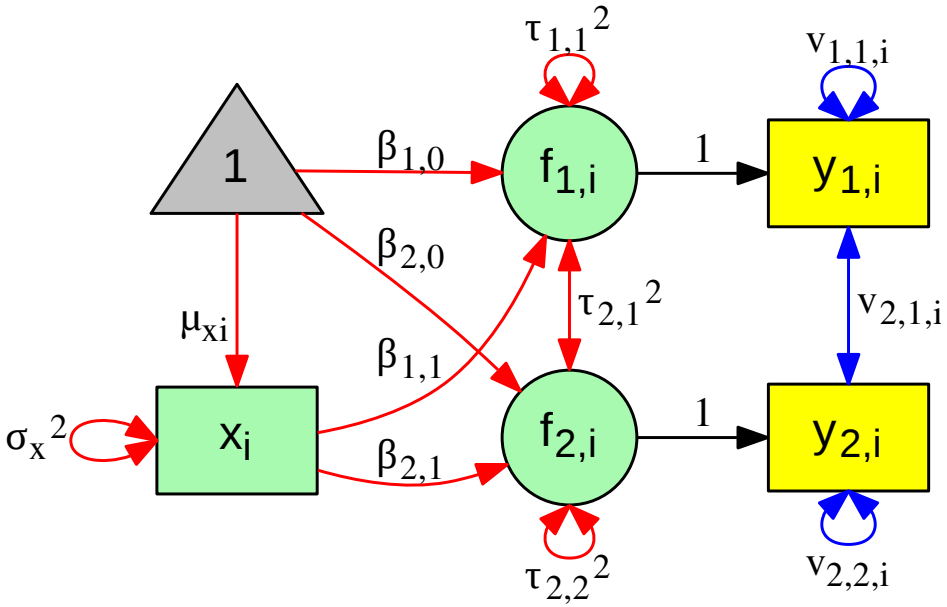
Our example

- The average log-odds are -4.8338 and -4.0960 in the vaccinated and non-vaccinated group, respectively. The difference between them is statistically significant $\chi^2(df = 1) = 77.06, p < .001$, indicating the BCG vaccine is effective.
- The correlation between the random effects is as high as 0.95!



Multivariate mixed-effects meta-analysis

- $\boldsymbol{y}_i = \beta_0 + \beta_1 x_{1i} + \boldsymbol{u}_i + \boldsymbol{e}_i$ with $\boldsymbol{u}_i \sim \mathcal{N}(0, \boldsymbol{T}^2)$
  - β_0 and β_1 are vectors of the intercepts, and the regression coefficients, respectively,
  - $\boldsymbol{T}^2$ is the residual of the random effects after controlling for the predictor x_1.



Three-level meta-analysis

- Effect sizes are non-independent within a study or cluster:
  - Multiple effect sizes reported in the same study;
  - Studies published by the same research team or authors;
  - Publications using the same datasets, e.g.,
    - the Programme for International Student Assessment (PISA);
    - the World Values Survey (WVS);
    - the International Social Survey Programme (ISSP), etc.
- The standard errors are likely under-estimated if we treat the non-independent effect sizes as independent.

Can multivariate meta-analysis be used here?

- Multivariate meta-analysis assumes that we know the sampling *covariances* among the effect sizes, which are often unknown in many settings.
- A three-level meta-analysis may be used when we do not know the sampling covariances among the effect sizes[10].

[10] Van den Noortgate, W., López-López, J. A., Marín-Martínez, F., & Sánchez-Meca, J. (2013). Three-level meta-analysis of dependent effect sizes. *Behavior Research Methods*, *45*(2), 576–594.

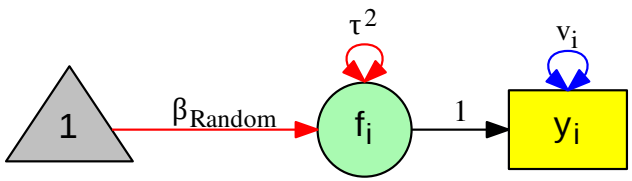
Three-level meta-analysis

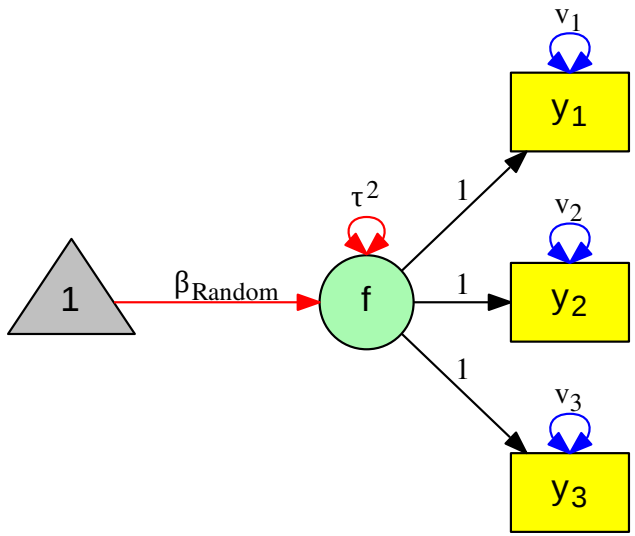
- We may extend the two-level model to a three-level model:[11]
  - Level 1 (subjects): $y_{ij} = \lambda_{ij} + e_{ij}$ with $e_{ij} \sim \mathcal{N}(0, v_{ij})$,
  - Level 2 (effect sizes): $\lambda_{ij} = f_j + u_{(2)ij}$ with $u_{(2)ij} \sim \mathcal{N}(0, \tau^2_{(2)})$,
  - Level 3 (studies): $f_j = \beta_0 + u_{(3)j}$ with $u_{(3)j} \sim \mathcal{N}(0, \tau^2_{(3)})$,
    - y_{ij} and v_{ij} are the ith effect size and the known sampling variance in the jth cluster,
    - β_0 is the average population effect,
    - $\tau^2_{(2)}$ and $\tau^2_{(3)}$ are the heterogeneity variances at (within) level-2 and (between) level-3, respectively.
  - Single equation: $y_{ij} = \beta_0 + u_{(2)ij} + u_{(3)j} + e_{ij}$.
- Example: Studies are level 3 and multiple effect sizes reported in a study are level 2.

[11] Konstantopoulos, S. (2011). Fixed effects and variance components estimation in three-level meta-analysis. *Research Synthesis Methods*, *2*(1), 61-76.

Two graphical representations of a conventional meta-analysis

- **Left** (a column of effect sizes): We usually use *one variable* to represent *k studies* (or *subjects* in SEM).
- **Right** (a row of effect sizes): An equivalent approach is to use *k variables* to represent *k* effect sizes but there is only *one subject*.[12]





[12] Mehta, P. D., & Neale, M. C. (2005). People are variables too: Multilevel structural equations modeling. *Psychological Methods*, *10*(3), 259-284.

SEM approach for the three-level meta-analysis (1)

- Suppose that the maximum no. of effect sizes per cluster is 5, the effect sizes are arranged as:

Table 6.3 Wide format data for a three-level meta-analysis.

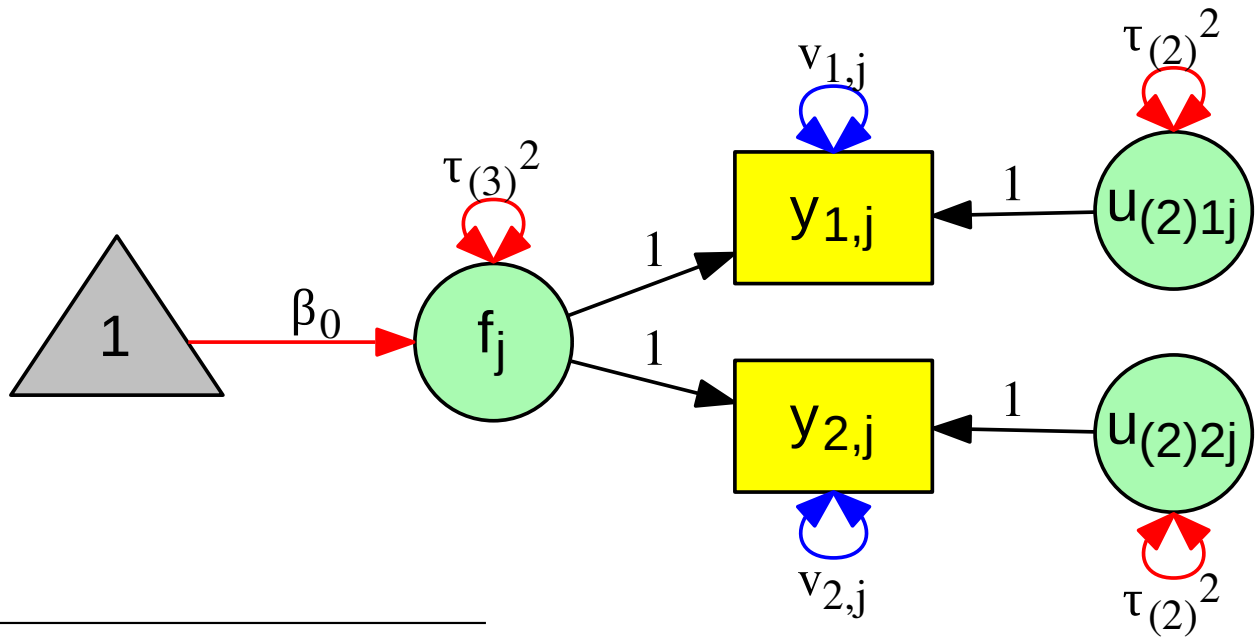
Cluster	y_1	y_2	y_3	y_4	y_5
1	$y_{1,1}$	$y_{2,1}$	NA	NA	NA
2	$y_{1,2}$	$y_{2,2}$	$y_{3,2}$	$y_{4,2}$	$y_{5,2}$
⋮	⋮	⋮	⋮	⋮	
k	$y_{1,k}$	NA	NA	NA	NA

Abbreviation: NA, not available. $y_{i,j}$ represents the ith effect size in the jth cluster.

- The incomplete effect sizes are handled by the FIML estimation.

SEM approach for the three-level meta-analysis (2)

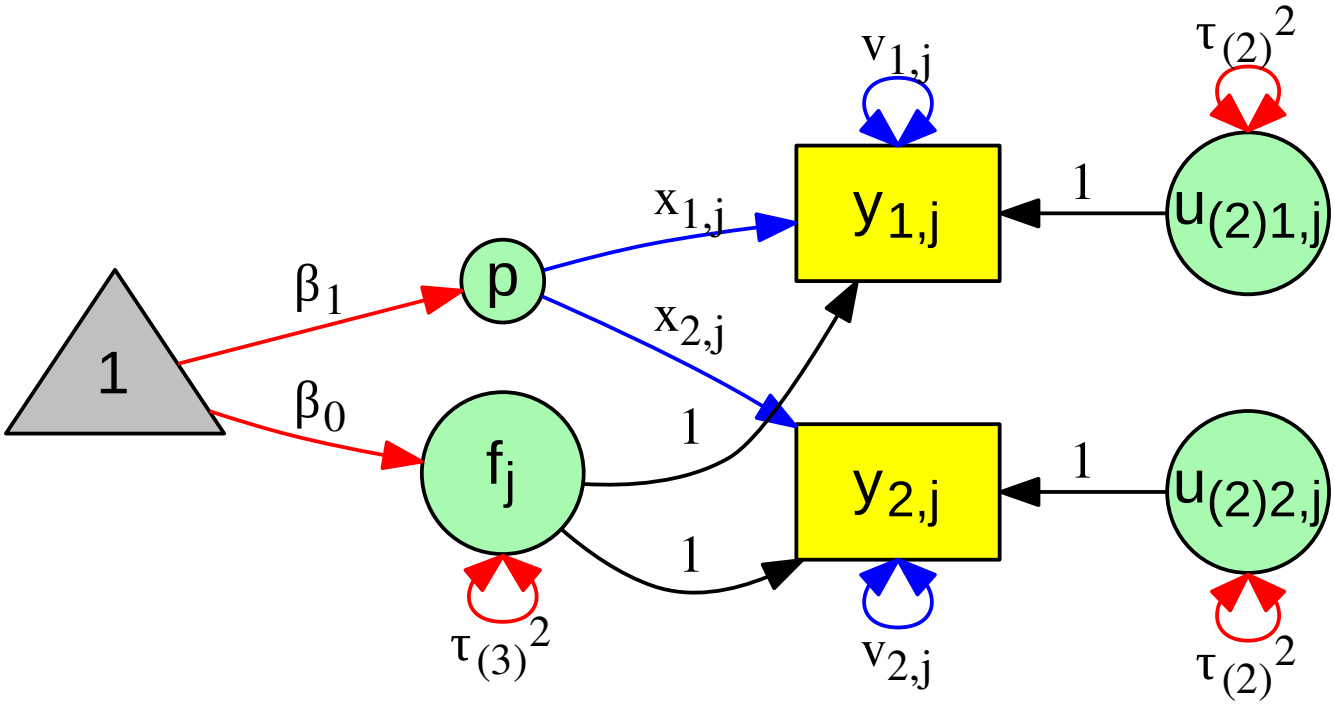
- *Studies* are the subjects and multiple effect sizes are the variables.[13]
- We may conceptualize the level-3 and level-2 random effects as *common* factor and *specific* factor in SEM.
- Example: a model with 2 effect sizes per cluster in the *j*th cluster.



[13] Cheung, M. W.-L. (2014). Modeling dependent effect sizes with three-level meta-analyses: A structural equation modeling approach. *Psychological Methods*, 19(2), 211-229.

Three-level mixed-effects meta-analysis

- Both level-2 and level-3 moderators can be included, for example,
  - Level-2 moderator: duration of treatment or the types of therapy within a study;
  - Level-3 moderator: year of publication.



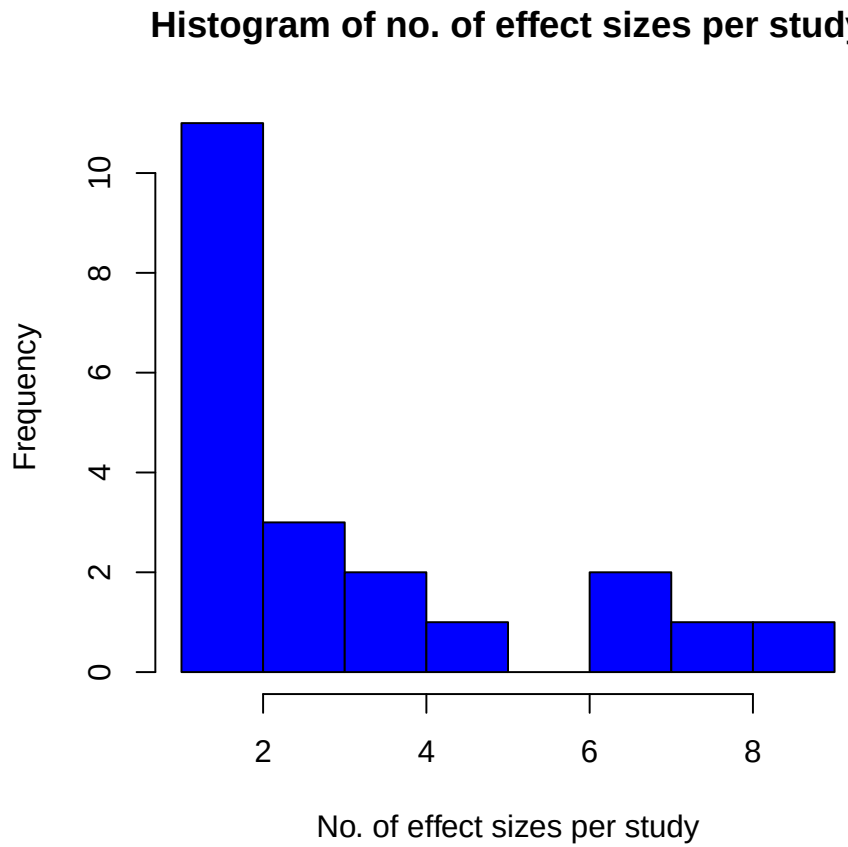
An example

- Bornmann et al. (2007) studied the gender differences in the successful rates in receiving a grant and fellowship applications.[14]
- They extracted 66 effect sizes from 21 studies.
- The effect size is log-OR that measured the odds of being approved among applicants. If it is positive, female applicants are favored to receive the grant or fellowship.

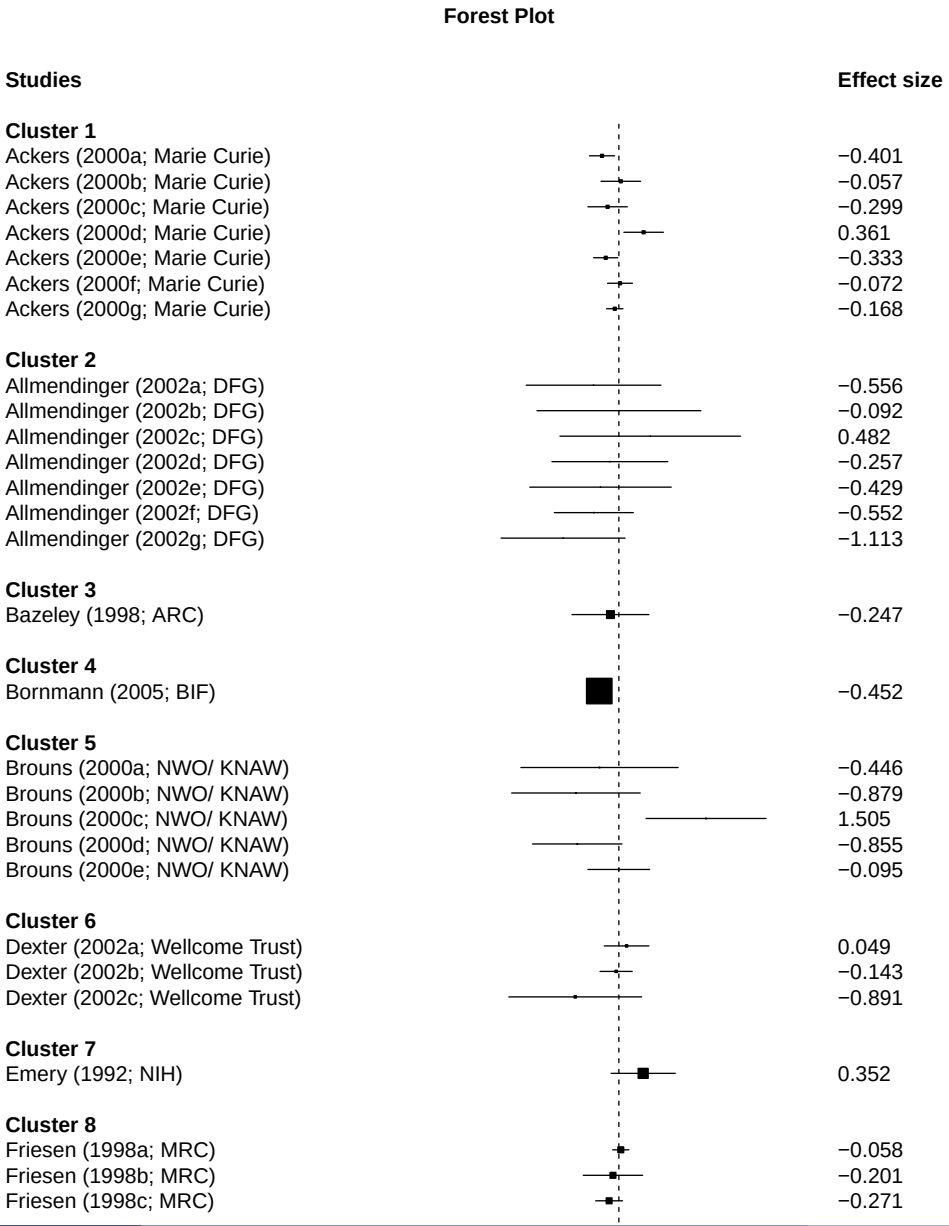
[14] Bornmann, L., Mutz, R., & Daniel, H.-D. (2007). Gender differences in grant peer review: A meta-analysis. *Journal of Informetrics*, *1*(3), 226-238

Data are nested within studies/funding programs

- Different funding programs may have different base rates. The effect sizes are not independent.
- Level 3: Studies/funding programs; Level 2: effect sizes



Partial forest plot



Results of the three-level model

- The average log-OR with its 95% CI is -0.1008 (-0.1794; -0.0221), indicating that male applicants are more likely to receive a grant and fellowship.
- The level-2 and level-3 heterogeneity variances are 0.0038 and 0.0141, respectively. The $I^2_{(2)}$ and $I^2_{(3)}$ are 0.1568 and 0.5839, respectively.

Software implementations

- One key feature of analyzing meta-analytic models as structural equation models is to fix the study-level error variances/covariances at the *subject* level via *definition* variables in SEM.
- The `metaSEM` package implements all of these models using the `OpenMx` package as the backend in `R`.[15], [16]
- M*plus* may also be used to analyze some of these models.[17]

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[15] Cheung, M. W.-L. (2015). metaSEM: an R package for meta-analysis using structural equation modeling. *Frontiers in Psychology*, *5*(1521).

[16] Neale, M. C., Hunter, M. D., Pritikin, J. N., Zahery, M., Brick, T. R., Kirkpatrick, R. M., . . . , Boker, S. M. (2016). OpenMx 2.0: Extended structural equation and statistical modeling. *Psychometrika*, *81*(2), 535-549.

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Conclusion

- Meta-analysis is an essential tool in synthesizing research findings.
- Common meta-analytic models including the univariate, multivariate, and three-level meta-analyses, can be integrated into the SEM framework.
- SEM has high potential to contribute to the statistical development of meta-analysis.

Thank you!

- Comments and questions are welcome!